Excerpts from

PROCESSES IN BIOLOGICAL VISION:

including,

ELECTROCHEMISTRY OF THE NEURON

This material is excerpted from the full β-version of the text. The final printed version will be more concise due to further editing and economical constraints. A Table of Contents is at the end of this paper.

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8 The Basic Configuration of the Neuron [1]

> Drawing is the Education of the Eye. It is more interesting than words. The language of the tongue is often used to disguise our thoughts, whereas the language of the pencil is clear and explicit. *James Nasmyth, 1808-1890.*

[xxx consolidate material concerning pnp transistors]

8.1 Introduction

The following theoretical exposition of the operation of the neuron and neural systems is based on a new unconstrained analysis of the potential mechanisms involved and the empirical database. The empirical database provides the critical winnowing of potential mechanisms into the shorter list of actual mechanisms. The winnowing process is multidimensional and therefore difficult to illustrate. **Figure 8.1.1-1** attempts to illustrate the procedure by selecting only two dimensions of the overall matrix examined. A selected set of options for these two dimensions is shown along each axes. The abscissa describes the major potential mediums of signal generation. The ordinate describes the major potential locations of the active mechanism generating the signal. As the winnowing process unfolded, the most likely explanation for the overall process became more obvious.

The unconstrained analysis leads to the overall Electrolytic Theory to be developed here. In brief, it states the operation of the neural system is based on a quantum-mechanical process employing the transfer of electrons through a complex electrolytic medium centered on the "junctional-tissue" associated with a series of neural conduits.

The Electrolytic Theory differs fundamentally from the Dual Alkali-ion Theory proposed in the 1950's and prevalent in the literature to date. The Dual Alkali-ion Theory (involving sodium and potassium) was proposed by Hodgkin & Huxley in their series of papers culminating in 1952. As noted by Hodgkin in an introductory paper[2], their approach did not involve the use of the optimal "scientific method." It was highly constrained.

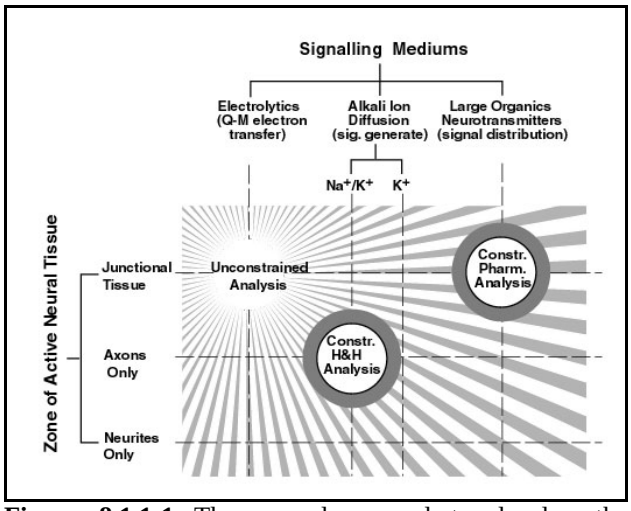

Figure 8.1.1-1 The procedure used to develop the electrolytic theory of neuron operation. All of the data converges on the electrolytics of junctional-tissue. Only the constrained analysis of Hodgkin & Huxley converges on the Dual Alkali Theory to explain the axon only hypothesis.

"In order to restrict the field, the review has been confined to the problem of conduction in single fibres, and any consideration of junctional-tissue or the central nervous system has been omitted. Wherever possible, experiments will be discussed in terms of a general hypothesis, which may be regarded as the modern counterpart of the membrane theory of Bernstein (1912) and Lillie (1923). Briefly, the hypothesis is that the action potential depends on a rapid sequence of changes in the permeability to the sodium and potassium ions. It makes use of the observation that potassium is concentrated inside most excitable cells, whereas sodium and chloride are relatively dilute."

Their constrained analysis led to the isolated region of this two dimensional figure. It was a derivative of an earlier conceptual analysis (based on only the potassium ion) dating from 1912. Although not explicitly stated in the above quotation, their analysis contained other implicit and explicit constraints. The Alkali-ion Theory only applies to the neurons that generate "action potentials." Less than 5% of the neurons in a given organism generate action potentials

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[1]Released: April 30, 2017

[2]Hodgkin, A. (1951) The ionic basis of electrical activity in nerve and muscle *Biol Rev*. Vol. 26, pp 339-409

(operate in the phasic domain). Most of this 5% consists of *transition* circuits that accept electrotonic (analog) signals and generate phasic signals at their output. The remainder of this 5% consists of circuits that reproduce phasic signals following stimulation by preceding phasic signals. It is this latter small group that was the subject of Hodgkin & Huxley's attention. Thus, their analyses applied to much less than 5% of the neurons in a typical organism. The rest of the neurons operate exclusively in, or form a bridge to, the electrotonic (analog) domain. The Alkali-ion Diffusion Theory has never attempted to explain the operation of the *transition* neurons (typically ganglion cells) or the totally electrotonic cells (typically sensory cells, bipolar cells and lateral cells).

The Hodgkin & Huxley exposition contained another major constraint. In their laboratory investigations they denuded their neuron (and axon) significantly to focus on the axolemma of that neuron. This action changed the operational mode of the *in-vitro* giant axon compared with its *in-vivo* operation.

By concentrating on the axolemma of a neuron, they necessarily constrained their concept to a two-terminal device. A more general exploration in the area of "junctional-tissue" would have allowed them to consider a more general three-terminal device. The three-terminal device of the Electrolytic Theory overcomes many problems remaining in the Dual Alkali-ion Theory.

The Dual Alkali-ion Theory is based on an explanation of neural operation derived from an understanding of the conventional chemistry of the first half of the 20th Century. It did not consider the quantum-mechanical mechanisms revolutionizing the world of science outside biology at that time. By analogy, the constrained analysis of Hodgkin & Huxley left them attempting to explain the heat source of the stars before the discovery of atomic energy.

Because of these shortcomings, the Dual Alkali-ion Theory has not led to a significant increase in knowledge regarding the detailed operation of the neuron. Many investigators have noted the slow progress in understanding the neuron while relying upon the Dual Alkali-ion Diffusion Theory. They have claimed future progress will require a paradigm shift in the basic concept of a neuron. The growing understanding of the amphipathic nature of the axolemma has caused serious problems with that theory. One approach to overcoming these shortcomings has been the conceptual introduction of pores and gates into the membrane forming the lemma. This approach is clearly a crutch designed to support an inadequate model. No explicit evidence or theoretical mechanism has appeared to support this crutch.

This work presents an alternate theory defining an electrolytically based neuron. It provides a paradigm shift in approach that explains the operation of both phasic and electrotonic neurons. Furthermore, it provides a consistent analytical framework and explanation of the detailed operation of all types of neurons. The level of detail goes beyond even the level of questions that can be posed under the above diffusion-based theory.

> **No legitimate method of comparing the Electrolytic Theory of the Neuron (and neural system) with the Dual Alkali-ion Diffusion Theory** exists due to the artificial constraints introduced into the latter. The Electrolytic Theory focuses on the "junctional-tissue" occurring within and between neurons. This "junctional-tissue" was dismissed as irrelevant in the Dual Alkali approach. **The Electrolytic Theory also addresses quantum-mechanical mechanisms largely unknown at the time of the Dual Alkali approach.** These same quantum-mechanical mechanisms also provide a precise explanation of the photo chemical mechanisms leading to the spectral sensitivity of vision.

The neuron has traditionally been a morphologically defined biological cell associated with the signaling function in an animal. It has developed a unique physiological capability through evolutionary specialization from a generic biological cell. This generic cell can be considered a neurogen. The steps in this evolution are substantial and one is particularly significant. This involves the creation of an active electrolytic semiconducting device, the Activa, within the cell. The Activa is also found in the synapse between neural cells.

Understanding the neuron without understanding its dynamic characteristics is impossible. However, addressing the dynamic characteristics is difficult until the static characteristics have been grasped. This chapter will survey the minimal functional characteristics of the neuron under static conditions and then introduce some additional characteristics found under dynamic conditions. The discussion will form the foundation of more specific descriptions of specific morphologically recognized types of neurons in the following chapters.

Experimentally evaluating the neuron has been difficult in the past because of the extremely high impedance levels involved. The equivalent resistance associated with a square micron of biological membrane frequently falls in the

region between 500 megohms and 5000 megohms. Shepherd says that "The generation of ionic currents useful for the propagation of action potentials requires the movement of significant numbers of ions across the membrane in a relatively short period of time.[3]" The statement is correct from a physiological perspective if the word ionic is deleted and the word ions is replaced with charges. However, it is misleading from an instrumentation perspective. The currents associated with the typical neuron at operational voltages are quite small compared with the capability of normal instrumentation. A saturation current of 25 pA current (which is relatively large) calculates to only 16×10^7 charges per second passing a given surface plane. For a more common 2.5 pA current lasting only one millisecond, only 16,000 charges need pass through a given surface. When compared with Avogadro's Number, this is an extremely small value. This number of charges remains far below the measurement threshold of current techniques of physical chemistry. Therefore, confirmation of many proposed ionic currents in neurology by chemical means remains elusive. 16,000 charges is less than one micro-micro-micro-mole.

On a related subject, Puil has given estimates of the amount of glutamate needed to excite a functional spinal neuron[4]. "Using several assumptions, the threshold amount of S-glutamate which is sufficient to excite a cerebral cortical neuron is believed to be about 10^{-14} mole and this may serve as a first approximation of the amount of S-glutamate require to excite a spinal neuron." 10^{-14} mole is 10,000 micro-micro-micro moles. This is clearly the amount required to excite an *in-vivo* nerve parametrically by "forcing the electrostenolytic process" and overriding the normal cell bias conditions rather than introducing a smaller signal charge at the neurite. Threshold amount estimates based on experiment are usually in the micro-mole or larger range. These appear to be based more on the instrumentation and dexterity of the investigator than on the actual sensitivity of the neuron.

Considerable care is required if such small currents are to be measured at such high impedance levels using electrical instrumentation. The capacitance of the test probes frequently affects the measurements severely. In at least one paper published from a prestigious institution, a figure reproduces the transient response of the test probe rather than the target element of a neuron.

This Chapter will focus on the underlying physical chemistry and cytology that leads to the formation of the active element at the heart of every neurological circuit, the Activa. It will be shown that the performance of these Activas can vary depending on their physical dimensions. The Chapter will also characterize a variety of Activas based on their functional use. The actual operation of the functional circuits containing the Activa will be addressed in the following Chapter. The relationship between the morphology (cytology) of various neurons and their operation will be examined in detail in the Chapter after that one.

Ignoring the individual concepts involved in the Alkali-ion Diffusion Theory will frequently be necessary in the development of this work. If the reader finds this procedure difficult to accept, Appendix XXX provides a summary of the problems underlying the Alkali-ion Diffusion Theory. These problems are frequently overlooked in abstractions from the original papers. Such problems are not encountered in this work.

8.1.1 Historical problems in neuroscience

Understanding of the neural system remains hampered by the breadth of many investigators background. The remarks of Whittaker appear to be due to this condition[5]. He comments that "electrical neurotransmission, though speedy, is also unselective. It is an all-or-nothing affair, incapable of being quantitatively modified or integrated with other afferent impulses." His position appears to be based strictly on his familiarity with action potentials, not the analog signals found so widely in the neural system and retina.

Similarly in 1992, Hille uses the interesting bold headline, "Ohm's law is central" and presents an entire book on excitable membranes that relies heavily on kinetic models and never introduces the integral calculus or differential equations[6]. This work shows that his headline is frivolous. Ohm's Law is not only not central, but it is largely inappropriate. Ohm's Law, usually introduced to non-electrical engineering students in a brief overview course, applies

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[3]Shepherd, G. (1998) Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 45

[4]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res Rev* vol. 3, pp 229-332

[5]Whittaker, V. (1975) Membranes in synaptic function. *In* Weissmann,G. & Claiborne, R. *ed*. Cell Membranes: Biochemistry, Cell Biology & Pathology. NY: HP Publishing Co. Chap 9, pg 167

[6]Hille, B. (1992) Ionic channels of excitable membranes. Sunderland, MA: Sinauer Associates.

only to linear (and passive) impedances. In its conventional form, it cannot be used to evaluate circuits containing diodes and/or batteries. It must be replaced by Kirchoff's Laws in the analysis of neural systems. The only mention of Kirchoff's Laws found in the vision and neurological literature was a passing one by Eckert & Randall[7].

> **Ohm's Law** is defined in the ISO Definition of Electrical Terms. "The voltage across any part of a circuit is equal to the product of the current in amperes and the resistance in ohms, *provided that the current is steady and that there are no sources of emf within this part of the circuit.*"
>
> If the current is not steady, the more general Kirchoff's Laws must be used to evaluate the circuit.

Discussion of the electrical regionalization of the interior of a cell is largely absent from the literature. Discussion of the electrical properties of the resulting individual membrane enclosed plasmas of a neuron is also largely absent from the literature. Failure to cross these intellectual bridges has restricted understanding of the neuron.

A particular problem in the neuroscience (and vision) literature occurs in the introduction to many papers. The authors casually recapitulate the conclusions drawn by others. These conclusions are frequently based on conventional wisdom, and intuitive conclusions following an analysis of limited empirical evidence. This leads to an ever-expanding database of limited theoretical consequence. The literature applicable to the putative neurotransmitters is an excellent example.

Terminology is a major problem in the neurosciences. Workers in different disciplines have adopted a variety of terms for identical or similar morphological features and functional notions. Minimizing the introduction of new terminology is important in a field where so much interdisciplinary science is needed. This work will rely heavily on the nomenclature used by Shepherd[8] in the neurobiological area and the definitions and symbols standardized by the IEEE in the electronics area. However, recognition of the three-terminal nature of the Activa will necessarily affect and require expansion of Shepherd's contribution. As will be seen below, his definition of a dendrite has been assigned to the more general term neurite. It will also require expansion of the four chief functional compartments defined most recently by Kandel, Schwartz & Jessell[9], to an expanded list. Added to the list of the cell body, dendrites, axons and terminals are an internal Activa and several other elements. These include a proliferation of external Activas, a second class of neurite defined as a podite, and multiple electrostenolytic sites critical to the operation of the neuron.

A recurring problem has been the repeated attempts to use the most elementary possible electrical engineering and mathematical tools to explain complex bio-electro-chemical processes. As a few examples;

> + Ohm's Law is frequently invoked to quantify impedances which are clearly not independent of the current passing through them--a linearity requirement fundamental to Ohm's Law. See above and Starzak[10].
>
> + Ohm's Law is frequently invoked to quantify impedances in networks containing current and/or voltage sources. These sources must be eliminated from the computations if correct impedance values are to be obtained. Otherwise only effective (not real) impedances are measured. These effective parameters become functions of the test set used.
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> + Attempts are still being made in the community to measure resistances and conductances in the neuron not only in the presence of voltage/current sources and active devices, but also in the presence of internal feedback mechanisms (See **Section 9.3.1**).

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[7]Eckert, R. & Randall, D. (1978) Animal Physiology San Francisco, CA: W. H. Freeman, pg 118

[8]Shepherd, G. (1988) Neurobiology. NY: Oxford Univ. Press, pg 63- 71

[9]Kandel, E. Schwartz, J. & Jessell, T. (2000) Principles of Neural Science, 4th Ed. NY: McGraw-Hill, Pg. 67

[10]Starzak, M. (1984) The Physical Chemistry of Membranes. NY: Academic Press pg. 309

+ No discussion of internal feedback within a neuron has been found in the vision literature.

+The Goldman, Donnan and Nernst Equations all assume a constant electrical field gradient within a membrane separating two dilute electrolytes. These conditions are not met in biological membranes. A more comprehensive variable field theory must be used to describe biological membranes separating high concentration solutes.

+ The bio-electro-chemistry community has failed to accept the fact that active electrolytic devices are present within the neuron, although their presence is obvious. It is obvious because measured output voltages are frequently higher than the applied stimulus voltages and no transformer is involved. An active mechanism must be present to cause this amplification.

+ The most important recent foundation work, by Hodgkin & Huxley, culminated in the 1950's almost coincident with the discovery of the transistor. They did not incorporate elements of Semiconductor Theory developed around the discovery of the transistor in their work.

+ The waveforms used by Hodgkin & Huxley as the foundations of their mathematical analyses were not action potentials. They were the impulse responses of their axon material combined with their test set.

Because of these procedural difficulties, integrating most of the relevant discussions in the literature into this work is very difficult. The models and concepts proposed in the literature are not adequately founded. On the other hand, some data reported in the literature can be used effectively if care is taken to learn what the specific, and important, conditions and parameters of measurement were.

8.1.1.1 Problems with the biological membrane literature

To understand the operation of the neuron, the characteristics of the plasma membrane enclosing the neuron must be well understood. Unfortunately, the theoretical, and even conceptual, activity in this field has lagged behind the empirical effort. This has led to many conceptual models of membranes based on inadequate floating models.

The literature before 1950 is sparse and was based almost exclusively on a very simple concept. Lacking the investigative power of the electron microscope, the biological membrane was considered a symmetrical semipermeable membrane separating two aqueous (low concentration) solutions. The semipermeability was initially based only on particle size. Later investigators also suggested the permeability could vary with the electrical charge on the particles.

Following the publication of the work of Hodgkin, Huxley and Katz in the 1950's, there was a massive renewal of interest in biological membranes. Many books were published on the subject in the 1960's. However, these remained based on the above conceptual model of the semipermeable membrane separating two dilute solutions. These materials were not consistent. Troshin published a book in 1966 highlighting the problems with the various conceptual treatments and the theories (largely notions) extant at that time[11]. His comments highlight the condition of the literature then.

"The problem has been studied for more than seventy years. . . . To date, however, research workers have sharply divergent opinions about the fundamental questions of cell permeability."

The conception ruling at the present time is the membrane theory; as is well known, the basis of this is the idea that any animal and plant cell behaves like an osmometer. Advocates of the old (classical) membrane theory assert that almost all the water in the protoplasm does not differ in its physico-chemical characteristics from the water of the surrounding medium and is an ordinary solvent and that all the fundamental mineral substances forming part of the composition of the protoplasm in it are in the dissolved state and are completely ionized.

After the formulation of the fundamental proposition of the membrane theory, it quickly grew into a conception of wide application in general biology.

Soon however, the membrane theory encountered difficulties which it was unable to overcome. Already at the beginning of this century, several distinguished physiologists came out against this

[11]Troshin, A (1966) Problems of Cell Permeability. NY: Pergamon Press. Translated by Hell, M. & Widdas, W.

> theory, pointing out that its fundamental propositions were erroneous.
>
> Comparison of the facts relating to cell permeability with the material characterising other facets of the activity of cells demonstrates convincingly that the present need is not for the improvement of some or other link in the membrane theory, but for its complete revision."

The reader should note the use of such theological terms as Dogma and Doctrine in some of the following material. The appearance of these terms in the scientific literature outside Neuroscience is rare. They are a sign of the deviation from the scientific method found in this field. The need for a completely new theory, not a revision, will continue to emerge within this section. The new theory will be addressed initially in **Section 8.1.3** and be expanded in **Section 10.8.1**.

8.1.1.2 Bibliography of the biological membrane literature

The work of Hodgkin, Huxley & Katz is appropriately recognized as monumental in their time. It was monumental in relation to the scope and perseverance shown in so many areas. However, like a tombstone in an unkempt cemetery, the monument is showing considerable wear. The problems with their work in the current time are reviewed in Appendix X xxx. Scientific American has been circulating a series of papers by Nobel Prize Winners as a subscription enticement during the first decade of the 21st Century. It includes a 1952 paper by Katz[12] that clearly shows the naivete of Katz, as well as Hodgkin and Huxley during that period relative to the present state of the art. The picture of their test configuration, along with a prewar oscilloscope lacking a sophisticated time base generator (a product of WW II radar and sonar research) is illustrative.

This work will offer an alternative theoretical foundation for the complete neuron to replace the empirically derived description of just the axon presented by Hodgkin & Huxley.

Troshin provides a bibliography of the work between 1907 and 1959 exploring alternate theories related to the neuron. He quotes a key finding according to Fischer was "there is absolutely no free water in the protoplasm–all the water molecules form part of special complex organic compound of which the live substance is composed." He also notes the attempts of the conservatives to salvage the classical theory by redefining the meaning of permeability to meet the needs of the concept (pgs 3, 7, 20-21, 28-29, 352-353). This is a common technique in biology that leads to mass confusion. Take a common word in the language and give it a unique technical meaning. Then fail to define the unique meaning upon first use of the term in ones writings. After about the third reference to the writing in the literature, all specificity associated with the unique definition is lost.

An example of the above methodology is the so-called "activated diffusion" theory of Danielli. It moved from a conventional symmetrical non-crystalline semipermeable membrane to a membrane consisting of a continuous lipoid (liquid-crystalline) film completely without pores. His concept called for the penetration into the cell of a substance by passage via the interstices between the molecules of the lipoid film. This penetration was independent of the solubility of the material in lipoids. The permeating substance "punches" its way through, pushing apart the lipoid molecules in the membrane. The source of the energy behind the punch was not defined.

An alternate approach was supported by Michaelis based on dried colloidal membranes with a pore diameter sufficiently large to pass glucose molecules. He proposed the pores of his materials had a negative charge and were therefore impermeable to similarly charged particles–anions. A caveat frequently lost in subsequent discussions was that the Michaelis membranes were permeable to urea molecules although impermeable to monosaccharides. The fact that many living membranes are also permeable to disaccharides and other large molecules further undermines the simple Michaelis idea.

Troshin went on to focus on the protoplasm as a colloidal system incorporating a new concept for the membrane. Initially, he labeled this the "new membrane theory." However, he gravitated to the label "phase theory" based on the

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[12]Katz, B. (1952) The Nerve Impulse *in* Nobel Prize Winners in Scientific American NY: Scientific American supple. copyright 2012. pp 26-36

proposals of Nasanov[13]. The term relates to the states of matter in the phase diagram as known then.

Nasanov was investigating the electrical properties of the biological membrane. His phase theory of bioelectric potentials is based on the idea that the disperse medium of the protoplasm behaves as a phase with respect to the surrounding solution of substances. Most of the electrolytes in the protoplasm (normally found in the state of rest) are in the bound and not the dissociated state.

After presenting sections on how various chemical agents passed through a cell membrane, Troshin summarized as follows. "According to the new membrane theory, the penetration into a cell of substances in most cases follows the scheme; substance A, dissolved in the medium, is converted in the cell membrane into substance B and in this form passes into the cell; in the cell this substance is reconverted into substance A (Ussing, 1949). This position concurs with many others (referenced later) that sodium and potassium ions cannot pass through a cell wall in a timely manner as simple ions. He also addresses the problem, that has remained such until now, concerning the asymmetrical distribution of substances between cell and medium. He describes "physiological permeability" as a mechanism relating to two simultaneous conditions. The mechanism operates when the passage of a substance into or out of a cell is accomplished against the concentration gradient and when its distribution between cell and medium cannot be explained by Donnan equilibrium. He notes, "In explaining these phenomena within the framework of the membrane theory writers have had to resort to postulating the existence in the cell of mechanisms for the 'expelling' or continuously 'pumping out' of the cell of some substances and of the 'active transport' into the cell of others."

Cole was a major player in the study of neural mechanisms in the middle of the last century. He probably had the strongest mathematical background of any researcher during that period. He addresses many of the same problems as Troshin but from a more mathematically precise perspective[14]. His work addresses the subject of signal propagation along a neuron in considerable detail and shows that an inductance is required to achieve a reasonable attenuation rate, in opposition to the Hermann Cable hypothesis (see **Section 10.3.4**). He noted, "The suggestion of an inductive reactance anywhere in the system was shocking to the point of being unbelievable. It seems to be certainly a property of the axon." He supports this assertion by providing a Smith Chart showing the complex longitudinal impedance of a squid axon (his figure 1:40).

> A **Smith Chart** plots the reactive component of a complex impedance on the vertical axis and the resistive component on the horizontal axis, both parametrically as a function of frequency. A positive reactance indicates an inductive component. A negative reactance indicates a capacitive component. A negative resistive component implies the presence of an active device in the circuit.

His report of discussions concerning inductance within the community is quite revealing (pp 78-87 & 103). Cole was not able to explain the source of the large inductances his calculations required (0.1 Henry per square centimeter of axon surface). The problem can be explained by two facts. First was his use of the average (or group) velocity of neural signals, about four meters per second (pg 118), over distances containing multiple synapses and/or Nodes of Ranvier. By using the phase velocity of the signals between points associated with only one axon segment, about 4400 meters per second, his required inductance values would be reduced by 1000:1. His misinterpretation (or lack of an adequately differentiated model) is highlighted in his calculation of the attenuation constant of his "standard squid axon." He calculated an order of magnitude loss at less than three centimeters of propagation. This is a reasonable attenuation for the very large diameter of the axon of *Mollusca* that does not employ action potentials. The vast majority of neural signals in *Mollusca* (and other organisms) are usually propagated as electrotonic signals and by diffusion (pp 118-121). Clearly, his calculations did not include any Nodes of Ranvier at two millimeter intervals as normally found in the neurons of *Chordata* propagating action potentials. His discussion on page 119-120 references Brink and introduces superficially the separation between the electrotonic and the phasic transmission modes. Speaking of the period before 1968 on page 128, Cole notes, "The abstract consolidation of the facts of the conduction of a nerve impulse had also not been impressive."

His second problem related to his assumption that the inductance was in shunt across the membrane, rather than in series and related to the coaxial nature of the conduit. Circuit realization theory shows that the element values between a series and shunt representation of a given circuit are quite different. While he discussed the coaxial nature of the axon, he apparently was not familiar with the equations associated with the propagation of signals over a coaxial transmission line. He notes several investigators abhorrence of the term inductance as applied to the surface area of a membrane.

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[13]Nasanov, D. (1959) Local reaction of the protoplasm and propagation excitation. *Izd Akad. Nauk SSSR*, Moscow-Leningrad, pp 1-434

[14]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press

As shown by the coaxial equations, the inductance of an axon is not associated with the surface area of a membrane, it is associated with the configuration of the conductors and the insulating dielectric. The inductance is independent of the nature of the dielectric.

As an indication of his frustration with the state of the art in the 1960's, Cole begins his Part III with the theme "Taming the Axon" and begins with a section title of "Cable Frustrations and Limitations." He also makes an interesting statement on page 475. "The expression of the clamp data in the system of equations conveniently called the HH axon, is admittedly purely empirical, only approximate, and of limited scope. It has no necessary connection with the mechanisms of ion permeability. It may represent the mean of widespread data and may depart from this noticeably. . . . Nonetheless, the HH axon is a remarkable feat both as curve fitting and as an instrument of prediction." Unfortunately, it does not offer any insight into the operation of the neuron and its axon. This work will offer alternate, and more satisfying models, of the entire neuron, the axon and the cable properties of such an axon.

Cole presents a massive amount of raw experimental data related to the *in-vitro* squid giant axon. The axon is typically 0.5 mm in diameter in animals about eight inches long. [These numbers highlight the fact it is a giant axon within a small squid rather than an axon within a giant squid.] The emphasis is generally on the changing of the parameters of the axolemma to induce a change in charge location. This is contrary to the more orthodox circuit configuration where the circuit parameters remain fixed and the amount of charge changes. In current engineering, this mechanism is described as parametric excitation. A major problem with the Cole material, which it shares with the work of Hodgkin, Huxley & Katz, is it does not represent the operational configuration of the squid neuron. **This author has searched the literature and not found a single recording of an action potential recorded under *in-vivo* conditions for squid, a member of *Mollusca*.** The waveforms generally labeled action potentials are actually more complex signals recorded from an isolated axon following parametric excitation of that axon using a pulse generated in the test set. The early recordings, such as those in Cole are recorded using a fixed frequency oscillator to generated the excitation and simplify the oscilloscope recording process (pg 135).

Cole documents the diode characteristic of the axolemma of squid well. However, rather than accept the membrane as a diode, he continues efforts to describe the membrane as a voltage controlled variable resistance. He then provides a broad perspective of his knowledge and participation in the activities of Hodgkin, Huxley & Katz. Surprisingly, Cole has provided the only known equivalent circuit of the axon membrane that shows mechanisms for controlling the variable resistors so commonly found in the works of Hodgkin & Huxley and subsequent discussions of their work (pg 272). He briefly describes two conceptual control systems labeled Kal and Nat that modulate the conductances g_K and g_{NA} respectively, as required to achieve the desired ion currents through the conductances. The modulation is both in amplitude and with respect to time (figure 3:25, pg 272). On page 520, Cole notes; "I see no present, definite, and certain indications of the nature of the mechanism by which the ion permeabilities of a membrane are controlled. There is no dearth of proposals. Some of these have been made to describe a single phenomenon and tested only rather casually." No physical mechanism has been demonstrated that can perform these separate modulations.

In all seriousness, Cole suggested an alternate title to the formal "Sodium Theory" of Hodgkin & Huxley. He suggests the alternate title:

> "A Theory that a Sodium Ion Permeability, Controlled by the Membrane Potential, is Responsible for the Impulse Excitation and Propagation of the Squid Axon in Its Normal Environment and Under Normal Conditions, with the Hope and Expectation that the Theory Will Apply to Some Other Excitable Cells and Under Some Other Conditions."

His suggestion is not entirely facetious, as discussed further beginning in **Section 8.1.2**.

Cole presents considerable data (similar to less data presented by Hodgkin & Huxley in the Journal of Physiology) on the unique output impedance of the squid axon. This output impedance data is strong evidence supporting the three-terminal configuration of the neuron to be presented below. It is largely unexplainable using the two-terminal configuration of the axon supported by Hodgkin & Huxley and by Cole.

Cole addresses medullated axons (axons containing Nodes of Ranvier) but does not address the possibility that the Nodes are sophisticated monopulse regeneration oscillator circuits (pg 375+). With apparent reference to the axons of squid, he notes "The myelinated axons are in a separate category of excitable cells." His remarks do not delve into the significance of these types of axons except to note "it is this system that made it possible for man to exist and to dominate

in his world." Cole, as in Hodgkin & Huxley, relied exclusively on linear passive circuit theory in their circuit models, although they recognized the necessity for and presence of negative resistive impedances in their models (pp 378-392). Cole repeated the tabulation of the electrical properties of a myelinated fiber of a frog from Hodgkin (1964). Both groups relied upon the passive assumption in spite of the presence of Nodes of Ranvier at intervals of 2 mm. Cole also noted the investigations of Frankenhaeuser & Huxley of 1964 where they noted fifteen uncertainties concerning the available data related to axons of the toad, *Xenopus*. "They then produced 'standard data' in the form of the HH axon, . . ."

Cole summarized his understanding of the situation regarding medullated axons (pg 398). "The conclusion that the node is qualitatively the same as the squid membrane and only an order of magnitude or so different quantitatively is impressive." This author finds such a statement difficult to accept. Much of Cole's data related to the Node of Ranvier and medullated neurons. The operation of these elements will be explained in this and subsequent chapters using a much more sophisticated and precise model. A precision of 10–20% is easily achievable in this area.

Cole was one of the first investigators to include an electron micrograph of a cell wall in his publication. He also provided some observations he deduced from that image. He also introduced data supporting the nearly zero impedance between two cell membranes in close proximity (pg 517). He states; "The idea that a pair of unit membranes might have a negligible resistance–perhaps less than that of a micron thickness of electrolyte was so contrary to past experience as to be quite unbelievable. Yet in a flurry of a few years of intense competition and cooperation, electrophysiolgy and electron microscopy forced us to believe that two membranes not only can but frequently do join to become essentially perfectly ion-permeable connections between cells." This work will show the only problem with this statement is its use of the term ion-permeable instead of charge (electron or hole) permeable.

In discussing membrane junctions, Cole described another recognized fact that will be exploited in this work. He noted; "From all of the lines of physical and chemical evidence we are led to a bimolecular membrane model with a hydrocarbon central layer about 25-50 Angstrom thick and a polar and protein layer of about the same thickness or less on each side, substantially supporting the Fricke, Gorter and Grendel, and Danielli suggestions." This work will show the hydrocarbon is hydronium and each bilayer is polar based on its asymmetrical lipid structure (See **Section 8.1.3.2.3**). It will also show specific bias potentials must be present to achieve the efficient transfer of charge across such a junction.

Writing in 1968, Cole closes with an interesting statement (pg 506). "The new challenge in the new era is to find what happens inside the membrane, the black box of the past."

Troshin and Cole, along with more recent results obtained with the electron microscope, are mandatory reading for any serious investigator of biological membranes. They form an essential base for separating the third person accounts (hear-say) found in many subsequent papers, books and textbooks purporting to explain the operation of the neuron.

The above discussion shows the slow advance of the membrane concept from a homogeneous semipermeable membrane between two dilute solvents in the direction of the current knowledge. The system involves a highly in-homogeneous bilayer membrane (with many unique electrical properties) separating two largely colloidal solutions where the protoplasm generally lacks ions free to physically move through the liquid medium via diffusion.

> In hindsight, the removal of a highly gelatinous material from the giant axon of the squid and its replacement with a dilute saline solution should have raised red flags in conjunction with the work of Hodgkin & Huxley. Their work is discussed in Appendix xxx.

Even the above advances overlook at least three additional features that are critically important. First is the significantly different chemical and electronic properties of various portions of the differentiated biological membrane. Second are the unique chemical and electronic properties of parts of the differentiated biological bilayer membrane as it is known today. Third is the further division of the colloidal state into the various forms of colloids and gels and the more critical state now known as the liquid crystalline state. This latter liquid crystalline state plays a critical role in the neural aspects of the cell that has evolved (differentiated) into the neuron.

The only valid conclusion is that nearly all of the literature before 1970 (and all subsequent textbooks based on that work–generally those published before 1995) should be discounted when studying the electrical parameters of the biological membrane system. The system actually consists of differentiated sections of membrane within a colloidal matrix. Each of the differentiated types of biological membrane, and their interaction with the colloidal matrix, must be analyzed based on its unique character.

Starzak published a treatise on membranes in 1984[15]. While introducing many individual aspects of the electrical properties of the biological bilayer membrane, it suffers from a lack of continuity. This is apparently due to a lack of a consistent framework describing the membrane. In this respect, the author displayed little familiarity with the details of biological membranes and appears to rely upon much of the conceptual background (hear-say) discussed above. Little actual data from biological membranes appears in the book. The caption for his figure 4.4 lacks details and is not supported by a reference. It is proposed that the figure is not an action potential from an *in-vivo* squid neuron but a parametrically driven response using an axon prepared in the manner of Hodgkin & Huxley. Chapter 12 of the work focuses on the opposing ionic currents theory of Hodgkin & Huxley. He makes the interesting statement that "This may appear to be adequate information, because it does explain the transient behavior of the excitation process. However, on closer examination, it raises more questions than it answers." This work will show that the Hodgkin & Huxley conceptualization is only one of many available, and an inadequate choice among the options. Starzak also surfaces the many problems associated with the earlier Donnan and Nernst theories based as they were on dilute solutions on opposite sides of a symmetrical semipermeable membrane (pg 253+). **Section 8.3.2** will address the character of the biological membrane of a cell in detail.

Mueller & Rudin published a large volume of work in the 1960's attempting to document the properties of synthetic bilayer membranes ascribed to the axolemma of Hodgkin & Huxley[16]. Being organic chemists, their exploratory focus was largely on the kinetics of the processes while adhering to the fundamental concept of the continuous bilayer biological membrane as the wall of a cell. On the other hand, they appear to be the first in the community to recognize the concept of a negative resistive impedance associated with their data. The magnification of the electron microscope available to this team was limited due to the time period. Their cross-sections of membranes were marginal for their purpose. As part of their work, they published a large collection of references and many measured parameters from various membranes[17]. The breakdown potential of 0.15 to 1.0 x 10^6 V/cm is of particular interest when discussing the gain associated with the adaptation amplifier of Chapter 12. Their material on permeability is extensive. It introduces the name translocators for modified (Type 3 in this work) membranes containing elements that can transport miscellaneous molecules and species across the membrane boundary. They constructed a potentially useful framework to describe these translocator materials. However, they noted that in 1969, "The molecular mechanisms of translocation and gating are unresolved." While their work did result in demonstration of a nonlinear and negative resistance characteristic in certain synthetic membranes, the characteristics were not those of the axolemma as proposed by Hodgkin & Huxley. In particular, the current density levels achieved were about 0.1% of those measured in biological samples and the current levels when the interior potential was positive with respect to the exterior did not remain at a low level until breakdown. Their portrayal of an action potential will be discussed in **Section 8.1.6**. While the authors offered no theoretical explanation for their results, there is little doubt they did achieve the quantum-mechanical process (tunneling) exhibited by a tunnel diode in a single synthetic bilayer membrane[18,19]. Their test configuration is described in an associated paper[20]. The papers should be considered simultaneously. The waveforms in that paper compare favorably with a typical tunnel diode oscillator with a resistive load. The oscillatory waveforms exhibit time constants appropriate to the parameters of the test set, including the expected membrane capacitance, of the circuit. They also noted the liquid crystalline properties of their synthetic bilayer membranes.

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[15]Starzak, M. (1984) The Physical Chemistry of Membranes. NY: Academic Press

[16]Mueller, P. & Rudin, D. (1968) Resting and action potentials in experimental bimolecular lipid membranes *J Theor Biol* vol. 18, pp 222-258

[17]Mueller, P. & Rudin, D. (1969) Translocators in biomolecular lipid membranes: their role in dissipative and conservative bioenergy transductions *Cur Topics Bioenergetics* vol 3, pp 157-249

[18]Millman, J. & Halkias, C. (1972) Integrated Circuits: Analog and Digital Circuits & Systems. NY: McGraw-Hill pp 77-79, fig 3-18

[19]Mueller, P. & Rudin, D. (1968) Op. Cit. *Nature* vol. 217, pg 715

[20]Mueller, P. & Rudin, D. (1968) Resting and action potentials in experimental bimolecular lipid membranes *J Theor Biol* vol. 18, pp 222-258

A problem with the theoretical framework assumed by Mueller & Rudin is their assumption that all neurons generated action potentials. In fact, less than 5% of the neurons in Chordata generate action potentials. The other 95% of the neurons exhibit the current-voltage characteristic expected of an analog circuit. These circuits do not exhibit the negative resistance feature they concentrated on creating. The second paper also says, with references but little discussion, oscillatory waveforms are also encountered in plant cells. Mueller & Rudin do provide a specific set of values (page 210) for the proposed electrical equivalent circuit of the axolemma proposed by Hodgkin & Huxley. They also address their interpretation of the theoretical status of the action potential on their page 214. This material will be addressed in **Section 8.1.6**.

The analysis on page 246 of the paper in the Journal of Theoretical Biology relating to Ohm's Law should be reinterpreted based on the discussion at the beginning of this section. The correct laws are Kirchoff's Laws. The discussion of methods in their section 4.6 should be of value to the active researcher.

Adelman edited a large textbook in 1971[21]. While containing considerable data, the work is totally in line with the conventional assumptions concerning the operation of a biological membrane, based on chemistry and ionic diffusion through the membrane.

Yeagle edited a large compendium on the biological membrane in 1992[22]. Noting that the Yeagle work did not address the electrical properties of the asymmetrical biological bilayer membrane is important. It did not address the electrolytic properties of membranes associated with the neurological class of cells at all. It remained focused on the chemical aspects of the biological membrane, although it did address the predominance of non-covalent bonding (generally hydrogen bonding) holding the individual molecules together in their unique liquid crystalline configuration. Yeagle is the first comprehensive work to recognize the liquid crystalline nature of the biological membrane. While Chapter one of Yeagle does recognize the liquid crystalline character of some differentiated portions of the biological bilayer membrane, and does develop the stereochemistry of the molecular structure associated with the bilayer, it does not delve into the electronic consequences of these arrangements. A comprehensive classification of lipids appears in **Table 1-1**. Chapter two addresses the liquid crystalline characteristics of the biological membrane further. However, it also does not address the electronic properties of such membranes. While the second half of the book focuses on ionic transport through the biological membrane, it never addresses the transport of elementary charges (instead of heavy ions) through the membrane.

The latter chapters in Yeagle are worthy of review. Chapter sixteen, entitled structural motifs for ion channels in membranes is unique. It is characterized by the predominance of caricatures of potential transport scenarios (with an absence of pictures, actual structural models or schematic models of membranes). Ionophoric agents (ionophores) are defined as organic molecules that can induce or facilitate ion transport across membranes (pg 722). The chapter contains several significant quotes. "Ionophores are classified either as ion carriers or channel-forming entities." "It should be stated that most ionophores are extremely toxic at the concentrations at which they are effective and are at present therapeutically useless (pg 722)." Ion carriers include the putative transport vesicle. The operation of these vesicles remains largely unresolved. The methods of material transport across the cell boundary (in either direction) are poorly understood at this time.

During the 1990's, Rapp and his associates undertook a major modeling effort related to the neuron[23]. It concentrated on passive modeling and the Hodgkin & Huxley characterization of the axon. Their models appear to assume all neurons within the major engines of the central nervous system operate in a phasic mode. They appear to extend this characterization to the dendrites and prepare dimensionally equivalent models of a neuron based on the earlier modeling of Rall. While Rapp et. al. note the two separate neurite trees (apical and basal) of the pyramid cell of the rat, they treat them as one. Their dimensionally equivalent models does not recognize the sensitivity of the properties of the axon to its physical form. Neither their lumped parameter (compartmented) models or their distributed parameter (cable) models recognize the inductance associated with their extended neural elements. They appear to rely upon a Hermann type of

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[21]Adelman, W. *ed.* Biophysics and Physiology of Excitable Membranes NY: Van Nostrand Reinhold

[22]Yeagle, P. (1992) The Structure of Biological Membranes. Boca Raton, FL: CRC Press

[23]Rapp,M. Yarom, Y. & Segev, I. (1996) Modeling back propagation action potential in weakly excitable dendrites of neocortical pyramid cells *Proc Natl Acad Sci USA* vol. 93, pp 11985-11990

cable exclusively[24,25]. While their laboratory investigations noted the source of the action potential as within the hillock or axon itself, they were unable to explain how it was generated. They relied upon the two-terminal excitable membrane model where no effort was made to differentiate the membrane into distinct regions. They did note the reflection of the action potential back along the dendritic tree as well as forward along the axon.

The important work of other authors will be introduced during the development of the theory of the electrolytic liquid crystalline semiconducting neuron in this chapter.

This work will introduce a new electrolytic theory of the biological membrane that defines three unique regions of that membrane. These regions are defined at the level of their molecular structure. The type one region will be defined by the presence of two molecularly-symmetrical uninterrupted lipid (liquid crystalline) films forming a bilayer. This type forms the bulk of the axolemma, particularly where it is myelinated (**Section 8.2.3.5.1**). The type two region will be similar structurally but the two films will consist of different lipids. This is the region of primary interest in this work. It is the backbone of the neurological system and supports both neural signaling and electrostenolysis. It will be discussed in many following sections. The type three region is structurally more complex. The membranes in this region may include protein and other materials embedded in, and facilitating the transfer of other materials through, the membrane. As noted by Cole in 1966, "Several experiments suggest strongly that ion permeability at least does not involve more than a few per cent of the membrane volume, so most of the molecular structure is passive and quiet if not completely inert[26]." While using different semantics than defined in **Section8.2**, his comment is certainly relevant. The limited area of the type 3 membrane is different from the type 1 and 2 regions that are inert to molecular transport. The type 3 membrane is of little interest to neural signaling. Its purpose is primarily homeostasis. It will be discussed briefly in **Section 8.2.5**.

Some biologists have written about symmetrical and asymmetrical membranes in a different context. They discussed a biological membrane with coatings on the two hydrophilic surfaces that were asymmetrical. This is not the context used here. Here, it is the two lipid layers that are symmetrical or asymmetrical.

In the neuron, one of the most important types of differentiated biological membrane is the asymmetrical lipid bilayer and its associated electrostenolytic constituents when immersed in a colloidal matrix. Several variants of this combination will be studied in detail in this Chapter. Most of the variants require at least some materials present to be in the liquid crystalline state of matter.

8.1.2. Archaic notions found in current neuroscience literature

Many archaic concepts continue to appear in the neuroscience literature designed for pedagogy. They are generally presented based on floating models and cannot be justified based on more comprehensive model. They are products of an earlier time.

8.1.2.1 The archaic chemical theory of the Neuron

The neuron has been studied intensely since medieval times. Its electrochemical aspects have been studied in parallel with electricity itself beginning in the 18th century. These studies have consistently suffered from one aspect that is excessively common in the biological fields. The empirical investigators of a given time have sought to solve problems with inadequate theoretical and/or mathematical tools. Tasaki[27] stated the situation succinctly: "We see repeatedly that

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[24]Rapp, M. Segev, I. & Yarom, Y. (1994) Physiology, morphology and detailed passive models of guinea-pig cerebellar Purkinje cells *J Physiol* vol. 474.1, pp 101-118

[25]Segev, I. & London, M. (1999) A theoretical view of passive and active dendrites *In* Stuart, G. Spruston, N. & Hausser, M., *Ed*, Dendrites, Oxford: Oxford University Press pg 209

[26]Cole, K. (1966) The melding of membrane models Ann NY Acad Sci pp 405-408

[27]Tasaki, I. (1982) Physiology and electrochemistry of nerve fibers. NY: Academic Press

physiologists prefer mathematically formulated theories of excitation, even when the quantities which are treated in their theories are of dubious physicochemical significance." These comments are obviously the words of investigators looking back in time. They are intended to provide a current evaluation but may lack adequate reverence for the work of others outside their narrow field. Workers from outside look upon the work Tasaki is discussing with similar lack of reverence, particularly when chemical kinetics is used to support broad physiological hypotheses by physicochemists. Tasaki has provided an excellent synopsis of the history of the electrochemistry of the neuron up through 1982. No significant change has occurred at the foundation level since then (except for the greater recognition of the salutatory aspect of action potential propagation along the axon).

> In 1987, McGeer, Eccles & McGeer presented an entire textbook on molecular neurobiology that hardly addressed the electrolytic nature of the neural system. It dismissed the idea of an electrolytic (electronic) synapse within the neural system out of hand on page 14 of 770 pages[28]. It is worth quoting the opening and closing sentences of their paragraph. They open with "Only brief reference need be made to electrical synapses, where transmission is by electric currents flowing from the presynaptic to the postsynaptic component." After discussing a variety of alternatives, and later devoting whole chapters to chemical synapses, they close with a clear statement. "It is well to keep in mind, therefore, that the classical descriptions presented here fall far short of telling the complete story of how neurons communicate by chemical messengers." The natural conclusion is that they were unable to confirm their ideological position.
>
> One of the classic descriptions that fall short is given in their Chapter 5, Principles of Synaptic Chemistry. The opening sentence of this chapter says "Unfortunately, the (chemical) transmitters are not known for the vast majority of the neurons in the central nervous system (CNS)." It then provides a series of criteria for determining if a compound is a neurotransmitter based on anatomical, chemical, physiological and pharmacological grounds only. No mention is made of the impact of such a compound on signaling or cognitive functions.

The chemical theory of the neuron has gone nowhere during the last 100 years (excluding pedagogical circles where it has been expressed repeatedly *ad infinitum*). Fortunately, other later investigators still accept at least the possibility that electrolytic synapses occur[29].

8.1.2.2 The archaic Neuron Doctrine

Cajal originally promulgated what became the Neuron Doctrine, at the end of the 1800's. It was based entirely on morphology and has been revered by morphologists ever since. However, beginning in the last quarter of the 20th Century, the underlying concept began to wear thin due to the work of electrophysiologists. This matter is reviewed by Bennett[30].

Shepherd presented a largely philosophical and historical review of the Neuron Doctrine as of 1991[31]. He looked at the neuron from the perspective of an anatomical unit, a physiological unit, as a genetic unit, and as a metabolic unit. Finding an explicit statement of the Doctrine in his book is difficult. His chapter and section titles include (in the following order), The Neuron Doctrine, Modern Revisions of the Neuron Doctrine, and Revising the Neuron Doctrine. However, these headings do not lead to an explicit statement. He draws a revealing conclusion after 292 pages reviewing the historical record. "Despite the 50 years of work that led to the classical neuron doctrine, the progress over the past 100 years, and the accelerated pace of recent research, our understanding of the neuron is still at an early stage."

The review shows that the initial Doctrine was based entirely on morphology. As time progressed, a set of putative chemical processes was defined that supported the morphological conclusions. Only in the 1950's were the electrical potentials associated with (at least) the axon confirmed. Simultaneously, the ability of an electrical current to transfer across a "gap junction" was demonstrated. These findings caused two unresolved problems. The operation of the

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[28]McGeer, P. Eccles, J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain. NY: Plenum Press. pg 14.

[29]Brown, A. (1991) Nerve Cells and Nervous Systems. NY: Springer Verlag Chapter 5

[30]Bennett, M. (1997) Gap junctions as electrical synapses. J. Neurocytol. vol 26, pp 349-366

[31]Shepherd, G. (1991) Foundations of the Neuron Doctrine. NY: Oxford university Press

synapse conflicted with the idea that the neuron (as a cell) was the basic physiological unit. The ability of a current to spread across a gap junction caused a problem with the notion of a chemical "neurotransmitter" mediating signaling across the gap. These problems have not been explained within the ideology that has arisen around the Neuron Doctrine.

Wandell made his view clear in 1995[32]. "The used of the neuron doctrine to interpret brain function is very widespreqad, but thre is very little evidence in directs support of the doctrine. The main virtue of the hypothesis is the absence of an articulated alternative."

8.1.2.3 The archaic Central Dogma of Neuroscience

More recently, Dowling developed what he described as the Central Dogma of Neuroscience[33]. He described the Dogma by use of a highly conceptual sketch that was not supported by any morphological or electrophysiological model. Furthermore, it invoked the concept of a synaptic potential generated by mechanisms at the post synaptic terminal. The Dogma does not differentiate clearly between electrotonic and pulse signals. The sketch also introduces external feedback without any demonstration of its actual occurrence within the neural system. It further confuses the concepts of encoding and modulation by associating electrotonic signals with the RF signals of an AM band radio. This approach will not be supported by this work.

8.1.2.4 The Archaic Notion of the Standalone Axon

[xxx shorten this section to include only the following brief remarks, move the rest to Appendix X]

Hodgkin & Huxley performed an extensive laboratory investigation on the large neuron of the squid, *Loligo* during the 1940's culminating in an extensive series of papers in 1952. Their published results relating to the non-myelinated neuron of a member of *Mollusca* have been widely interpreted as applying to the myelinated projection neurons of *Chordata*. This has come true in spite of the extensive work of Tasaki and others, both before and after that of Hodgkin & Huxley, showing quite contrary results.

It is important to distinguish carefully, when reviewing a body of work, between the experimental findings and the conceptual picture on which the study is based, or which emerges from the given study. As noted in the introduction, the analyses of Hodgkin & Huxley were highly constrained and did not address many other physical mechanism available to explain their measured data. They did not investigate, eliminate or accept the possibility that the putative action potential of *Loligo* originated in junctional tissue. Their final set of equations contains an exceedingly high number of arbitrary constants and independent variables that can be used to match virtually any set of initial conditions. The equations defining *m, h, n* & *p* used by Hodgkin & Huxley, and reproduced in Frankenhaueser & Huxley, also suffer from inconsistency in the units associated with the variables.

The merging of the so-called cable equation (for a lossy cable) with the wave equation (that only applies to a loss-free cable) appears undefendable. Their assumption of a real number (as opposed to a complex number) for their "conduction velocity" is completely incompatible with their assumed lossy cable. Such a cable always exhibits a complex "conduction velocity" where the phase shift component, β, is always a function of frequency (wavelength).

They were unable to solve their differential equations describing the putative action potential of *Loligo*. As a result, they were unable to define the transient and steady state components of the predicted waveform and confirm that their assumed initial condition were correct. They proceeded by using an arduous series of mathematical tabulations based only on the proposed set of differential equations. No one is known to have reproduced their mathematical procedures.

As Cole noted on page 476, "As to curve-fitting, the procedure and the results of Hodgkin & Huxley (1952b) are entirely unorthodox and are looked at with both amazement and admiration by trained mathematicians." An alternate expression

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[32]Wandell, B. (1995) Foundations of Vision. Sunderland, Mass: Sinauer Associates pg 190

[33]Dowling, J. (1992) Neurons and Networks. Cambridge, MA: Harvard University Press, pp 56-57

might be “courteous consternation” or simple “courteous disbelief.” The orthodox goal of a mathematician is to derive a set of mathematically consistent equations that provide incite into the underlying mechanism being studied. It is difficult to comprehend the goals of Hodgkin & Huxley when all they have prepared is a very complex mathematical procedure for creating a template approximating a poorly characterized response intimately related to their test configuration. As noted in statement (15) of Frankenhaueser & Huxley, the resulting template does not describe any specific fibre but only an undocumented ensemble of fibers.

Other problems related to their mathematical manipulations are summarized in Appendix X.

The reader is cautioned that exception is not taken to any of the data presented by Hodgkin & Huxley, or Cole. It is the interpretation and the calculated waveforms (as a function of time), that fail to satisfy the operational requirements of a valid theory/model, that are questioned. Most readers are not aware that their widely reproduced figure 17 (page 530) does not represent the ionic currents flowing through a membrane but only the variations in conductance proposed by them *ad hoc*. Figure 18 (page 531) showing their predicted currents is seldom reproduced because it is so difficult to justify.

Briefly addressing the work of the team of Hodgkin, Huxley and Katz is important before proceeding. The work was done at Cambridge University during the 1940's and 1950's. This work is addressed in greater detail in Appendix X. As noted above, the work has taken its place as a monument in the field on neuroscience. The work has become a cornerstone in all pedagogy related to neuroscience. However, the work has not stood the test of time as well in the research environment. Their truncation of the scientific method (**Section 8.1**) as they applied it to the overall problem of the neural system has introduced a variety of unstated limitations. This truncation has also prevented the introduction of a broad array of scientific and mathematical tools to the challenge of understanding the operation of the neuron (and the axon).

This work will not dwell on the problems with what has become widely known as the Hodgkin-Huxley axon, and by casual extension the underlying foundation of the common wisdom concerning the operation of the neuron. Instead, this work will present a totally different hypothesis. This hypothesis answers many questions not even addressed in the Hodgkin-Huxley idea. However, because of its pervasive presence in the background, certain features of their work need to be introduced here. The book by Cole, referenced above, provides a useful scenario of the work under way on both sides of the Atlantic at that time.

The Hodgkin team was apparently looking for improved methods of exploring the electrophysiology of the neuron when they were introduced to the very large neuron of the squid, *Loligo*, by J. Z. Young. The hind-most stellar axon of this neuron was particularly large (giant) and one of the few axons compatible with the physical lab equipment available at that time. The denuded axons had a typical diameter of 500-700 microns (0.5-0.7 mm). For the ideological reasons stated clearly by Hodgkin (**Section 8.1**), the team focused exclusively on this axon, to the exclusion of any attention to the dendrites and other morphological/electrophysiological structures of the neuron. In fact, they note their extensive effort to prevent instability in their experiments by physically removing the dendritic material from the neuron. It also appears they removed all of the structure associated with the minor neurons tightly enclosing the giant axon. In hindsight, this was done without realizing the significant role these structures played in reducing the capacitance between the axoplasm of the giant axon and the surrounding environment. Thus, their activity did not attempt to evaluate a complete operational neuron (or axon), either *in-vivo* or *in-vitro*. They also removed all of the smaller axons closely packed about the stellar axon (**Section 10.8.2.1**) without completely accounting for the convergent evolution exhibited by this organization. This close packing is the technique adopted by *Mollusca* to achieve the same result as myelination in *Chordata*. Removing these smaller axons significantly changes the operational performance (including the transient response) of the stellar neuron.

As noted above, to the best of this author’s knowledge, they never reported (with graphic documentation) any waveform recorded from the *in-vivo* giant neuron of *Loligo*. The response they characterized as an action potential is highly temperature dependent. A recording of an action potential in *Mollusca* at room temperature can be expected to differ considerably from a similar recording of an endothermic member of *Chordata*. They, and Cole, have provided multiple waveforms resulting from their electrical stimulation of the isolated axon. However, these waveforms show distinctly different characteristics from those associated with the typical chordate action potential. A modern analysis of their test configuration strongly suggests that their recorded transient waveforms consisted of three components. First, the parametric excitation provided by their test set. Second, a finite delay not associated with the subsequent action Potential. Third, the actual monopulse response to the stimulation. Note the delay of approximately 0.5 ms between the end of the excitation and the beginning of the rise of the main response in their recordings. Typical *in-vivo*

recordings of action potentials from *Chordata* do not show such a delay. Note also the fact that the excitation in Hodgkin & Huxley, 1949, fig 3 is of opposite polarity to the main response. This situation is also portrayed in Hodgkin, 1951, fig 2. These waveforms differ markedly from what is typical in *Chordata* (see **Section 10.8.3** and Schwarz & Eikhof). The latter Hodgkin figure also highlights the difference between the actual measured response and the "traced" waveforms frequently appearing in their papers. Figure 2(E) shows considerable valuable detail concerning the rate of the rise in the waveform versus time compared with the rate of fall. Such detail is usually lost in tracings. This frame of the figure also shows what may be the rise of the axolemma potential (from –85 mV to –77 mV) before excitation has reached the threshold level. Unfortunately, the duration of this waveform is 500 times longer than a typical action potential.

Hodgkin & Huxley were properly circumspect when they proposed how the observed waveforms were generated. Although they were working in the electrical domain, they apparently did not review the laws of electrolytics as known at that time. It also appears they were not conversant with the laws of electrostatics as applied to a membrane that was a potential electrical insulator. Although they were aware of the capacitance per unit area of a membrane, they may not have been aware of the fact this capacitance was a variable. It is sensitive to the magnitude and polarization of the applied potential because of the quantum-mechanical properties of the membrane. Electrolytic rectifiers and (polarization-sensitive) capacitors were in wide use at the time. Most common polarization-sensitive capacitors are now known to be based on an underlying diode. It would be at least a leaky rectifier in the terminology of their day. They anguished over how to explain the electrical properties of the membrane. In the end, they dismissed any possibilities related to electrons, or even negative ions such as chlorine, moving through the membrane. In the end, they proposed that the waveforms were due to the diffusion of the ions of sodium and potassium moving in opposite directions (in spite of the presence of an electrical field of constant direction) through the membrane. This premise was based primarily on the relative molar concentrations of these ions in the solutions on opposite sides of the *in-vivo* membrane. While it appears they began with the concept of a simple semipermeable membrane of the day that changed. They soon introduced two batteries into the proposed membrane that acted independently with respect to the counter positive ion flow. They also introduced two variable resistors into their equivalent circuit, one controlling the flow of the current associated with sodium (in conjunction with one of the batteries) and one associated with the flow of potassium.

They did not explain the physics or electrical mechanisms underlying their model, yet, the community accepted their proposals with great enthusiasm. This enthusiasm has continued in the academic community to this day.

Based on their conceptual model, they drew up a large set of differential equations that they did not solve. However, they did define a set of boundary conditions for each equation (using an iterative procedure until the desired graphic results were obtained). These equations, with minor modifications in the coefficients, exist today in the pedagogical computer emulation program called Neuron.

The differential equations were based on the important premise that the flow of sodium ions in one direction and potassium ions in the opposite direction continued over the duration of the waveforms they recorded. However, they allowed the initiation of the potassium flow to be delayed to make it easier to fit the equations to the data. This was in contradiction to the 1951 paper that described the two current flows as being separate in time. It appears they discarded the possibility that the pulse waveform was formed by a switching action similar to that found in conventional switching type electronic oscillators of the day. There is now ample evidence that a majority of the surface area of an axolemma of a neuron is impermeable to free ions. The lack of permeability of the lemmas of a neuron to heavy inorganic ions will be alluded to many times in **Section 8.1** before it is addressed directly and defended in **Section 8.2**.

It is a mystery to an investigator with an electronics background why they did not discuss in their papers the more conventional electronic explanation of their waveforms. The reason can only be associated with their truncated approach to the analyses involved.

The conventional explanation would consider the membrane between the axoplasm and the surrounding matrix a conventional electrical "load" and an active electronic element within the neuron (nominally between the axolemma and the neurolemma) as the "pull-down element." In this scenario, the axoplasm potential would be at a resting potential until the pull-down switch became a short circuit and drained electrons from the axoplasm into the neuroplasm. This would cause the axoplasm to become more positive. When the pull-down element returned to an open circuit condition, the axoplasm would return to its original resting potential as electrons moved through the "load" from the power supply. Under this mode of operation, the transient voltage-current characteristic of the axoplasm exhibits a very recognizable shape. It is precisely the shape presented by Hodgkin & Huxley in their figure (H&H, pg 481) and in figures 4:16 and

4:52 of the section of Cole entitled “Other Membranes, New Techniques and More Data.”

The previous paragraph, those preceding it in this section, and the many other detailed problems with the Hodgkin & Huxley model summarized in the literature support the need for a new functional model of the complete neuron. Frankenhaeuser & Huxley summarized, in 1964, many problems with the H & H model of the axon (and its extension to the neuron)[34]. Those authors explore fifteen distinct aspects of the previously proposed differential equations (A primary equation with approximately 16 auxiliary equations). As an example: “(15) It has not been possible to carry out a complete analysis on one single fibre; different parts of the data refer to different fibres.” They go on to say “The equations and the quantitative data obtained in the voltage clamp analysis must to a large extent be considered as approximations. A fair amount of scatter appears especially between values from different fibres. The equation system is so involved that it is impossible in most cases to get even a fair idea of the effect of a change of a single value without going through a complete computation.” These aspects plus others in the more recent literature show why the H & H model is untenable following the advances of the last fifty.

The same previous paragraph also summarized the method of operation of the complete neuron as proposed in this work.

A mathematician would suggest that any set of differential equations with more than 10 variables can be made to match any arbitrary waveform that can be drawn on paper. This is particularly in this case where Frankenhauser & Huxley note at least six of which “are arbitrary and of uncertain origin” (pg 304). It is also noteworthy in hindsight that the delay as a function of temperature between the stimulus and the beginning of the response does not appear explicitly in the equations. This delay is intrinsic to four of the “variables of uncertain origin,” the unmeasured, and hence undocumented, variations in the permeability of the membrane to different ionic species, *m, h, n* & *p*. These variables are defined by differential equations that have no intrinsic relationship to the permeability of the membrane or the temperature. They are defined only with respect to time and a series of arbitrary constants. However, these “constants” have been shown to also be variables with respect to the peak response amplitude by Frankenhaeuser & Huxley. It can be shown they are also variables with respect to temperature. The equations defining *m, h, n* & *p,* in Hodgkin & Huxley and reproduced in Frankenhaeuser & Huxley, also suffer from inconsistency in the units associated with the variables.

As Cole noted on page 476, “As to curve-fitting, the procedure and the results of Hodgkin & Huxley (1952b) are entirely unorthodox and are looked at with both amazement and admiration by trained mathematicians.” An alternate expression might be “courteous consternation” or simple “courteous disbelief.” The orthodox goal of a mathematician is to derive a set of mathematically consistent equations that provide incite into the underlying mechanism being studied. It is difficult to comprehend the short-term goals of Hodgkin & Huxley from three perspectives. They prepared a very complex mathematical procedure for creating a template. The template was not well characterized by modern standards and appears to include artifacts associated with their test instrumentation. As noted above in statement (15) of Frankenhaueser & Huxley, the resulting template and equations do not describe any specific fibre. They only describe a few characteristics of some undefined ensemble of fibers.

The reader is cautioned that exception is not taken to any of the data presented by Hodgkin & Huxley, or Cole. It is the interpretation and the calculated waveforms (as a function of time) that fail to satisfy the operational requirements of a valid theory/model that are questioned. Two important notes should be made about this situation.

1. Frankenhaeuser & Huxley based their work on a myelinated axon from *Chordata* not an unmyelinated axon from *Mollusca*. Specifically, they were studying the frog, *Xenopus,* not the squid *Loligo*.

2. The leading and trailing edges (and the absolute delay) of the action potential are affected differently by temperature. The computer emulation program, Neuron, purports to replicate the equations of Hodgkin & Huxley. An investigator should be sure this program properly reflects these differences in actual neurons as shown in **Section 10.8.3** and documented by Hodgkin in 1951 and by Schwarz & Eikhof in 1987.

Further consideration of the sodium ion-based Dual Alkali-ion Diffusion Theory of the axon or neuron will be postponed until after an alternate theory is presented. The alternative provides a theoretical framework with which to evaluate the propositions developed by Hodgkin & Huxley (which were based entirely on curve-fitting to empirical data).

8.1.2.5 Lack of the concept of impedance in physical chemistry

The operation of complete neurons are critically dependent on the transfer of electrical signals between components of

[34]Frankenhaeuser, B. & Huxley, A. (1964) The action potential in the myelinated nerve fibre of Xenopus laevis as computed on the basis of voltage clamp data *J. Physiol.* vol. 171, pp 302-315

the neuron. The mode of transfer and the efficiency of transfer are dependent on the characteristic electrical impedance of these components. Physical chemistry in general and the Chemical Theory of the Neuron in particular do not include a concept of impedance.

The concept of impedance plays a major role in electrical and mechanical systems, especially those that contain an elastic element. The elastic element is typically represented by an inductance in any electrical circuit or electrical analog of a physical circuit. In the form of interest here, impedance is a measure of the response of a second physical mechanism due to time-varying stimulation by a first mechanism. For most systems, the impedance depends on the frequency of the stimulus. The impedance of most mechanisms describes a combination of resistive and reactive elements described by lumped parameters. Mathematically, the reactive components are in quadrature with respect to the resistive elements. As a result, an impedance is typically described using complex algebra (of the form, $x + j \bullet y$).

The concept of impedance is found primarily in engineering, as opposed to science. It plays a crucial role in many aspects of signal transmission. The International Dictionary of Physics and Electronics devotes nearly six pages just to defining subsidiary relationships related to impedance[35].

In the absence of a concept of impedance, the description of the neuron using chemical principles is fundamentally constrained. This fact will become obvious in **Chapter 10**.

8.1.3 The Electrolytic Theory of the Neuron

Piccolino made an interesting observation in 1998[36]. "The voltage-dependence of the ion permeability changes involved in the discharge of the nervous impulse links electricity in a fundamental way to this event (the activation of the phasic neuron), and makes unlikely any hypothesis that considers the electrical phenomenon only as one of the many possible functional expressions of nerve excitation." While discussing his thesis in a broader discussion of the work of Hodgkin and Huxley, he did not discuss the ground rules of his thesis. Piccolino's thesis is heavily dependent on the constraints introduced by Hodgkin & Huxley. He does not even discuss the role of the dendritic and other neuritic structures in the generation of the action potential and fails to review the operation of the 95% of all chordate neurons that do not involve the generation of action potentials **at all**. Piccolino did note; "The questions left largely unresolved by the Hodgkin-Huxley studies concerned the mechanism of ion permeation through the membrane." This question remains unresolved today.

It is proposed that the theory developed here involves a paradigm shift that was outside of the purview of Piccolino and circumvents his assertion. The Electrolytic Theory of the Neuron dismisses the concept of ions passing through the biological membranes for purposes of signaling in favor of a junctional tissue concept. In this concept, an entirely different mechanism is proposed that relies upon quantum-mechanics occurring in the junctional tissue between axonal and neuritic tissue to explain the operation of the neuron. The junctional tissue model is a three-terminal model as opposed to the two-terminal model of Hodgkin & Huxley. This model does not require the putative, and undemonstrated, Independence Principle of Hodgkin & Huxley, or the unexplained variation in the permeability of the plasmalemma to ions of sodium or potassium for purposes of signaling.

To understand the operation of the neuron, and the neural system, a major review of the literature was performed. The conflicts found within that literature led to special attention being placed on the fundamentals underlying the empirically observed and intuitively explained material. Of particular importance was a review of the protocols and test sets used by Hodgkin & Huxley in their seminal experiments of the early 1950's. A careful analysis of this material, based on modern electrical engineering principles surfaced two important facts. First, many waveforms they observed and reported did not have the characteristics of action potentials. Second, the waveforms they observed and reported did not relate to an active mechanism associated with the plasma membrane of an axon (although they may have involved the electrical asymmetry of such a membrane). Often, the same results can be obtained using the same test set and a totally

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[35]Michels, W. et. al. (1961) International Dictionary of Physics and Electronics, 2nd ed. NY: Van Nostrand, Inc. pp 586-591

[36]Piccolino, M. (1998) Animal electricity and the birth of electrophysiology: the legacy of Luigi Galvani *Brain Res Bull* vol. 46, no. 5, pp 394-396, pg 400

passive axon membrane. The differences between their interpretation and an interpretation based on parametric stimulation of a passive electrolytic circuit are discussed in detail in **Section 10.8.3** & **10.8.4**.

Simultaneously, a large amount of data was reviewed concerning the electrical and physical characteristics of the Node of Ranvier. The examination of physical parameters exposed the presence of a crystalline form of water (hydronium) within the narrowest region of the structure formed by the pre and post nodal membranes (See **Section 8.1.3.2.3**). The low permeability of this material is not compatible with the movement of various heavy ions across this gap. However, it is compatible with the movement of electrons across such a gap. The examination of the electrical characteristics of this Node showed it to be capable of generating an action potential. This action potential exhibited much more power than the excitation required to initiate it. This characteristic is the hallmark of an underlying active mechanism. The challenge was to find this mechanism.

The above activity led to the discovery and documentation of a new active element, the Activa, within the neural system. This discovery led to a reexamination of the neural system and the detailing of a new theory of its operation. The new Electrolytic Theory of the Neuron will be summarized here, before the development of the Activa and neural system are addressed in detail.

8.1.3.1 *The Electrolytic Theory of the Neuron in axiomatic form*

A new Electrolytic Theory of the Neuron has emerged that answers many questions left unanswered by the previous chemical theory. The Electrolytic Theory is also able to answer questions that have not even been formulated under the chemical theory.

The Electrolytic Theory begins with a basic axiom.

> **The neural system of any organism consists of a series of electrolytic conduits interconnecting a series of fundamental physiological units of the neural system. Each fundamental physiological unit is a conexus. A conexus consists of an Activa, an active electrolytic liquid-crystalline semiconducting device, and its associated electrical components.**

The conexus (and its Activa) are found within individual neurons and between neurons. Every neuron contains at least one Activa, but may contain many. A neuron containing multiple Activas cannot be considered the fundamental physiological element of the neural system.

The Electrolytic Theory contains several Corollaries to the basic axiom.

#1 **Signaling within the neural system is by electronic means. Signaling is accomplished by transferring electrons (fundamental electrical charges) into and out of electrolytic conduits, and between conduits. The Activas control the flow of charge out of and between conduits.**

The lemma of each conduit is subdivided into regions optimized for each of the above functions. As a group, these regions remain impervious to hydrophilic ions.

#2 **Each Activa is a three-terminal electrolytic device interconnecting three electrolytic conduits.**

#3 **The Activa is equivalent to a man-made pnp transistor. It is an analog (tonic) device.**

#4 **The Activa can be made to oscillate (generate action potentials) by introducing positive feedback into its associated circuitry. Less than 5% of all neurons generate action potentials.**

#5 **Electrons (electrical charges) are supplied to each conduit of the neural system by an electrostenolytic process on the lemma of the conduit. The electrostenolytic process converts glutamic acid (glutamate) into GABA (gamma amino butyric acid). The process releases one molecule of CO_2 and injects one electron into the interior of the conduit for each molecular conversion.**

#6 **All chemicals previously known as neurotransmitters are actually neuro-facilitators or neuro-inhibitors depending on how they affect the basic electrostenolytic process.**

#7 **The conduits of extended length, typically described as axons, are properly modeled as coaxial transmission lines. Inductance and capacitance play major roles in their operation.**

#8 **Signal Propagation over a coaxial axon is by electromagnetic means (not chemical diffusion). Delay, due to a finite signal propagation velocity, is a significant factor in the neural signaling system.**

A paradigm shift to the Electrolytic Theory of the Neuron is justified based on at least four major factors.

1. The experimental fact that the most common symmetrical biological bilayer membranes are impervious to ions[37].

2. The recognition of the experimental fact that the biological membranes of interest are electrical diodes.

3. The understanding of the internal structure of the neuron and the variety of membranes employed within it. This is due primarily to recent improvements in high magnification electron-microscopy.

4. The discovery of the Activa, a device critically dependent on the semipermeability of a membrane to fundamental electrical charges.

Accepting the above paradigm shift requires that much of the neurological literature of 1950-2000 be reexamined for relevance. While most of the data remains relevant, much of the discussion does not. Accepting the above paradigm shift also leads to the complete description of the neural system contained in the following chapters.

> **Fortunately, this work finds no need to issue such a sweeping caveat to the Electrolytic Theory of the neuron as that by McGeer, et. al. for the chemical theory. It provides a very comprehensive description of how neurons communicate electrolytically without invoking any chemical messengers. It also shows that the purported chemical messengers actually affect the power supply to the neurons. They are not directly involved in signaling. Obviously, the Electrolytic Theory of the Neuron does not suffer from the problem of defining neurotransmitters highlighted in their Chapter 5. It provides precise mathematical descriptions of the performance of each and every synapse and neuron.**

If one abandons the chemically based Neuron Doctrine, and embraces a totally electrolytic framework, our understanding of the neuron and the neurological system can move forward very rapidly. It is the electrolytic theory of the neuron and neural system that is the basis of this work.

The long-sought, but never cytologically defined, ion-pump required by the chemical theory of the neuron is replaced by the electrostenolytic process, acting as an electron-pump, in the Electrolytic Theory of the Neuron.

8.1.3.2 Theoretical aspects of electrolytics

8.1.3.2.1 Background

The concept of in-rushing and out-rushing ionic currents, as used in neurology, will forever be associated with the names Hodgkin and Huxley. However, it is important to appreciate two situations. First, how they arrived at the media implementing these currents and second, what alternate implementations are available. This section will take a moment to discuss the state of the art of their day and their concept of electronic circuits. It will then present an entirely different concept based on more generally accepted electrolytics, as used throughout industry and semiconductor physics [xxx edit out].

8.1.3.2.2 Organization of the field of electrolytics

[37]Finkelstein, A. (1987) Op. Cit. pg. 94

[xxx condense 8.1.3.2.2 and 8.1.3.2.3]

The field of electrolytics (or electro-osmotic chemistry of solutions) evolved very rapidly during the 20th Century. Early in that time period, the field began with coarse studies of the electrical properties of ionizable materials in solvents. This led to extensive studies of the osmotic properties of these materials in the presence of externally applied electrical potentials. This led to the recognition that the nature of the interface between the metallic electrodes used to introduce the potential, and the electrolytes was complex. At that point, the field of electrolytics evolved into the study of electrolysis (of solutions) and the study of electrodics (of metal-solution interfaces). This was the state of the art in the late 1930's to early 1950's. In the mid 1950's (after the principal work of Hodgkin & Huxley and their school had been completed) the field of semiconductor physics came to the fore with the discovery of the transistor. This discovery opened a new field of electronic processes within semiconductors. Although these materials were conceptually located between insulators and metals, they exhibited entirely different properties than either of these states of matter. These materials were found to employ the laws of osmosis in a new and different way, particularly with regard to the unusual field potentials found within the materials. These fields were a result of the laws of quantum-mechanics. Soon thereafter, in the 1960's, a new state of matter was documented for the first time as the liquid crystalline state. This state of matter was positioned between liquids and crystals in much the same way that solid-state semiconductors were positioned between (normally non-crystalline) metals and (typically insulating) crystals. The laws of osmosis also helped understand this state of matter when the unique quantum-mechanical aspects of the material were recognized.

With the advent of these new fields, the overall field of electolytics could be further subdivided into at least four lower level fields, electrodics, electrolysis, solid state electronics and liquid-crystalline-state electronics.

Whereas the field of electrolysis involved the movement of charged particles in the form of positive and negative ions, the new fields of solid state and liquid crystalline state semiconductor physics were different. They involved the movement of charged particles in the form of electrons and holes. Holes in this context were lattice positions exhibiting the absence of an electron compared with a neutral crystalline lattice (in contrast to other positions in the lattice showing the presence of an extra electron). This concept should not be confused with that used by some cell biologists who have conceptualized the physical movement of actual ions within a lattice[38]. While the latter is known to happen at glacial speeds (months to years in forming whiskers on surfaces) in metallic semiconductors under operating bias conditions, it is not of concern here.

It was the transition from ionic current flow in a liquid solution to fundamental charge current flow in a metal that was the essence of the study of electrodics. Similarly, the transition from ionic current flow in a liquid solution to fundamental charge current flow in a semiconductor (whether solid-state or liquid-crystalline state) is the essence of the study (unnamed) of interest here. Within liquid-crystalline materials, the currents are in the form of fundamental particles and the laws of quantum-mechanics apply. The study of phenomena within these materials is called semiconductor physics.

8.1.3.2.3 Solutions, solvation and liquid crystalline water

Neither the biological or neurological literature have addressed the role of water in the neurological systems of animals in detail. The role of water as a solvent in biological systems is generally different than the text book cases that describe solutions at infinite dilution. In general, biological fluids are found to have a molarity of greater than 0.5 moles. At these concentrations, the mobility of the ionic constituents are not the textbook values. Further, many ions and molecules of interest in biology aggregate with multiple molecules of water to form solvated molecular structures exhibiting their own unique properties. The diffusibility of these larger aggregations, while in the electrically neutral state, within a given solution are more restricted than for the simple molecule. When ionized, the mobility of these materials are also reduced.

Water itself exhibits drastically different properties as a function of temperature and state of confinement. The properties of water change significantly in the temperature range below four degrees centigrade as it becomes liquid crystalline in character prior to freezing into a true crystal. In both the liquid crystalline and crystalline state, as well as in the liquid state, water exhibits the properties of a semiconductor. In fact the definition of pH is based on the semiconducting properties of water. One molecule in 10^7 becomes ionized even under conditions of perfect purity. This is a significant ionization rate per unit volume compared to other common semiconductors .

Figure 8.1.3-1 illustrates the properties of the water molecule. It is a highly asymmetric molecule containing two pairs of non-bonded electrons associated with the oxygen atom. This asymmetry makes the molecule highly polar electrically.

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[38]Stein, W. (1967) The Movement of Molecules across Cell Membranes. NY: Academic Press pg 66

This dipole moment is one of the highest found in chemistry and suggests the materials ability to dissolve other polar materials. In the dilute state, the bond angle and spacing between the atoms are shown on the right.

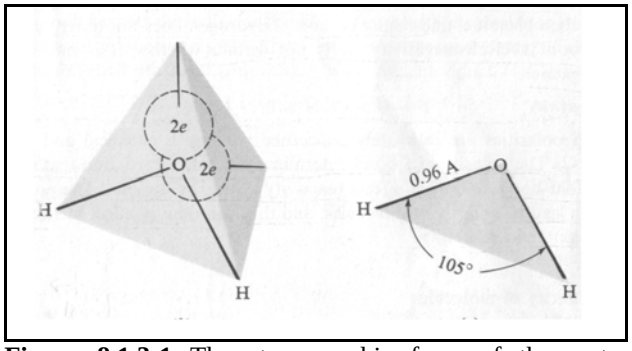

Figure 8.1.3-1 The stereographic form of the water molecule. Note the significant polar character of the molecule due to the two pairs of non-bonding electrons arranged asymmetrically with respect to the hydrogen atoms.

Water has a tendency to assume the liquid crystalline state even at temperatures above four degrees when in contact with other materials or when forced into a very narrow space (measured in tens to hundreds of molecules in thickness). Under these conditions, water is frequently described as a liquid crystalline material called hydronium[39]. This designation describes an electrically neutral structure that is distinctly separate from the individual hydronium ion, H_3O^+ found elsewhere in the literature.

In the liquid crystalline and crystalline state, water exhibits electrical properties that differ significantly from those taught in lower university courses. Bockris & Reddy have struggled to describe and explain these properties[40]. Their discussion is not satisfying to this investigator. Specifically, their crystalline model of figure 5-11 is that of $(H_1O)_n$ instead of $(H_2O)_n$. It describes a planar crystal with rectangular lattice faces instead of the correct model with hexagonal lattice faces and significant out of plane structures shown in **Figure 8.1.3-2**. The upper part of this figure shows the planar hexagonal lattice formed by water when in the form of hydronium or ice. Note the first order asymmetry within each hexagonal ring. The atoms shown at positions 1, 3 & 5 are bound to their neighboring hydrogens within the hexagon by ionic bonds (two-tone solid links). However, the atoms at positions 2, 4 and 6 are bound to the adjacent hydrogens within the ring by hydrogen bonds (dotted link). Note also the unpaired (non-bonding) electrons that remain associated with the oxygen atoms. These are shown as free along the bottom of the crystal in the lower frame. Six oxygen atoms are shown associating with an adjacent crystal lattice along the top of the frame through a covalent bond arrangement. These weak hydrogen and covalent bonds account for the tendency of hydronium and ice to exhibit significant ionization. This ionization results in free electrons in the conduction band of the material and holes (the absence of electrons) in the valence band of the material. Such conduction band electrons and valence band holes exhibit different mobilities that can be measured using the Hall Effect.

Individual sheets of liquid crystalline and crystalline water connect to adjacent sheets in a complex arrangement. The bonds to a sheet above tend to occur at every other oxygen. The bonds to a sheet below occur at the interdigitated oxygen atoms. The bonds to adjacent sheets is even more complicated. Note each of the two oxygen atoms in each pair along the top of the bottom frame bond to two lattice rings in separate layers. As a result, *two* layers in one "row" of the crystal bond to *three* layers in the adjacent "row." These combinations of bonding techniques and locations provide a variety of unique properties to the overall liquid crystalline or crystalline forms of water. Bockris & Reddy provide many parameters describing these properties.

[39]Merali, Z. (2005) As hot as ice *New Scientist* pp 38-39

[40]Bockris, J. & Reddy, A. (1970) Modern Bioelectrochemistry. NY: Plenum Press Chapter 5, pp 461-488

8.1.3.2.3X The special case of hydronium and the definition of a hole

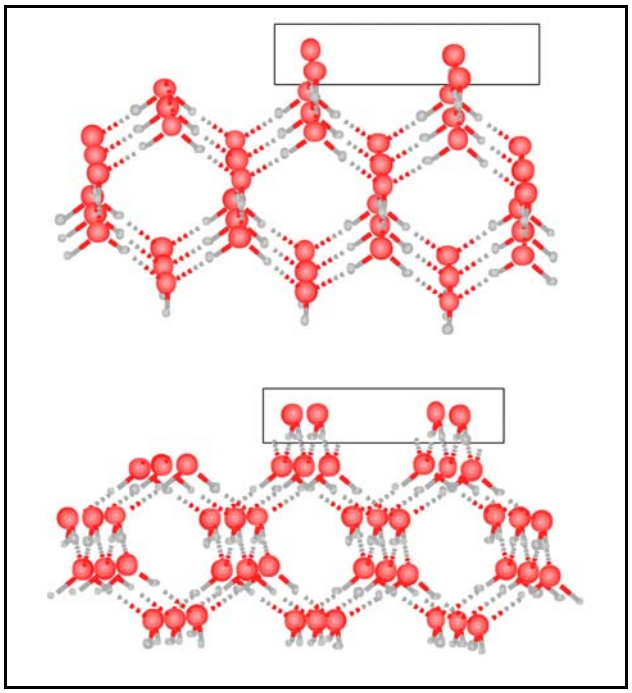

Figure 8.1.3-2 The crystalline form of hydronium and ice. The top three pairs of oxygen atoms shown in both frames are part of an adjacent lattice. Note, all of the oxygen atoms exhibit unpaired electrons with which they can form hydrogen bonds (dotted lines). The two-tone solid lines represent ionic bonds between hydrogen and oxygen. See text.

Although it will not be pursued in this section, pointing out that water can act in a very unusual way is important. Under certain conditions, it will form a liquid crystal known as hydronium. The evidence is unmistakable that as some of the water ionizes, the hydrogen ion may become associated with an un-ionized molecule. The proton is said to become (possibly highly) hydrated, $H^{+}(H_2O)_n$. The evidence also suggests that this hydrated structure exists in a matrix of other water hydrates, $H^{+}(H_2O)_n + (H_2O)_m$. The result, as m and/or n become large, is a contiguous liquid crystal of hydrogen and oxygen ions. Furthermore, the evidence suggests that the electric charge associated with the original proton (a hydrogen ion) may be transferred through the matrix without physical movement of individual protons.[41] This apparent motion of a positive charge in a crystalline matrix also occurs in the "solid state." The positive charge is given the name "hole" to distinguish it from a specific positive ion and suggest its true character, a missing electron. If an electron associated with an OH^{--} radical and a "hole" associated with a hydrated proton combine at the surface of such a liquid crystal, a molecule of water is reformed with little impact on the overall liquid crystal. The importance of this possible action revolves around the mobility of the "hole" within a potential field applied to an electrolyte. This mobility may be drastically different from that of a minimally hydrated proton in a dilute solution. If this action can be confirmed, a one-to-one correlation between the electronic nature of water based liquid crystals and the solid state of semiconductor-based metal crystals can be recognized. This method of charge transfer in a hydronium liquid crystal is in stark contrast to the mechanism discussed by Conway[42] in 1964 and reproduced in Eyring[43] in 1970. He speaks of proton transport in a hydronium crystal as involving two activities. First, the physical movement of the proton in conjunction and second, a rotation of an associated water dipole within the crystal lattice. This work will adopt an alternate model from solid state physics. The apparent motion of a proton in an electrical field applied to a crystal is the result of a hole, a lack of an electron, being sequentially filled by an electron jumping from a filled site to the empty site. This explanation is compatible with the writing of Gerischer in the same volume of Eyring, (pg 488). The very high electrical mobility of the positive charge recognized but not explained by Conway should be confirmable by Hall effect measurements on Hydronium. Rattee & Breuer present a table comparing the electrical properties of water and ice and note the very high "mobility" of H^{+} ions (holes) in ice[44].

The very high mobility of holes in hydronium is largely responsible for the temporal frequency response of the typical neuron. Holes are known to move through lattices of hydronium in times smaller than 10^{-13} seconds per step.

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[41] Adamson, A. (1973) A text book of Physical Chemistry NY: Academic Press pp. 321-322 & 507-509

[42]Conway, B. (1964) Modern aspects of electrochemistry. (Bockris & Conway editors) NY: Butterworths Chapter 2

[43]Eyring, H. (1970) Physical Chemistry: an advanced treatise. NY: Academic Press pp. 150-155

[44]Rattee, I. & Breuer, M. (1974) The physical chemistry of dye adsorption. NY: John Wiley & Sons. pg. 20

The high mobility of holes in hydronium, the base material of an Activa, defines the basic parameters of the electrolytic liquid crystalline semiconductor known as an Activa.

The complex nature of water is reviewed in Dowben[45] but answers concerning its nature, especially in high concentration solutions, are still elusive. Several candidate structures have diameters of 5-20 Angstrom.

Revel and Karnovsky have documented the porosity of the material in the 20–40 Angstrom gap of a gap junction to lanthanum hydroxide[46]. This porosity to the proposed hydronium crystal filling this gap is probably due to the substitution of lanthanum ions for hydrogen ions in the lattice. [xxx other statements in R & K?]

8.1.3.2.4 The putative ionic theory as an extension of electrolysis

The Hodgkin & Huxley school attempted to explain the operation of the axon of a neuron based on a very limited model of the complete neuron. Based on the state of the art of that day, they assumed the remainder of the neuron was essentially passive and only the axon played an active role. They also decided to treat the lemma of the axon as a semipermeable membrane based on the osmotic chemistry of that day. By ignoring the electrical properties of the termini of the axon, they found it necessary to account for the potential of the axoplasm because of currents flowing through the largely uncharacterized lemma of the axon. At that point, they incorporated their knowledge of the field of electrochemistry as it stood at that time. The field only included the sub-field of electrolysis. Therefore, they based their work on the known electro-osmotic properties of common materials separating electrolytes. They were unable to address the actual physics of the virtually unknown molecular structure and size of the lemma. From this point forward, their analyses depended upon the application of the laws of electrolysis to the actual problem of semiconductor physics. This application was inappropriate. It led to the concept of two positive ions traversing the lemma in opposite directions under the influence of a single electrical field during the same time interval. The implausibility of this phenomenon was explained through the adoption of an "independence principle" that has yet to obtain a theoretical foundation. Because of their relative abundance on the two sides of the lemma, the inward flowing current was associated with the sodium ion concentration. The outward flowing current was associated with the potassium ion concentration. No role was assigned to the free flow of electrons or holes through the membrane.

The in-rushing current was labeled the sodium current. In the 1951 Hodgkin paper, it was related to the rising phase of the action potential. The out-rushing current was labeled the potassium current. In the same paper, it was associated with the falling phase of the action potential. These labels became more directly related with the flow of these ions through the axolemma of a neuron as the years have gone by. However, in the 1952 Hodgkin & Huxley paper, these currents took on more euphemistic properties. They were unable to correlate these currents with their mathematical framework that called for the currents to travel in opposite directions simultaneously in a single electro-diffusion situation. Therefore, they invoked an "independence principle." It introduced entirely separate scenarios for the currents responding to the difference in concentration of each metal ion. Under this scenario, the currents were unaffected by the presence of other ionic species (and probably other applied potentials). This principle allowed them to define a specific conductance and variable resistance applicable to each current. A foundation for their independence principle has never been developed. They also stated a fundamental fact related to their studies. They state the following In their summary paper. "At present the thickness and composition of the excitable membrane are unknown." It is now known that the membranes of neural conduits are impervious to ions and their thickness is so thin that quantum-mechanical effects must be considered in describing their electronic characteristics.

Hille has provided an important discussion of how ionic channels have come to be named[47]. He pointed out, "The naming of ionic channels has not been systematic. . . . Finally, it is tacitly assumed that each component of the model corresponds to a type of channel, and the putative channels are given the same names as the permeability components

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[45]Dowben, R. (1969) General physiology: a molecular approach. NY: Harper & Row pp. 96-96-112

[46]Revel, J. & Karnovsky, M. (1967) *J Cell Biol* vol. 33, pp C7-C12

[47]Hille, B. (1984) Op. Cit. pp. 5-6

in the original analysis." He then provides a back of the envelope calculation that the required change in the ionic concentration required to generate a 110 mV action potential in the giant squid axon as only one part in 10^5. He points out that these minute changes are much below the changes in concentration that can be measured using available instrumentation. Dowling[48] made a similar calculation and determined the change in concentration was only two parts in 10^8. A change that he notes in not measurable with current techniques. No measurements have been made to date relating action potential generation to a change in chemical concentration within a neuron. [xxx relate to other calculations in this area, including mine.]

In what appears to be convoluted logic, the role of charge collecting on the surfaces of the lemma, acting as the dielectric of a capacitor, was largely discounted. *In hind-sight*, it is possible to see how this position could be adopted based on the above state of the art. It would be due primarily to the limited experimental design effort and the poor performance of their test instrumentation (See **Section 10.8.4.5.2**) and their inappropriate reliance upon Ohm's Law.

By limiting their analyses to ions as charge transporters, Hodgkin & Huxley required an ion-pump to maintain the average potential between the inside and outside of the plasma membrane of an axon. This pump (or pumps) was responsible for the active transport of Na+ out of the axon and the simultaneous transport of K+ into the axoplasm. It had to operate on a time scale of hundredths of a second. They characterized this ion-pump as a mechanism imbedded in the plasma membrane. Their pump was apparently adopted from a much earlier proposal by Ostwald and by Bernstein in the 19th Century[49]. From the 1950's until the present, no confirmation of the existence of such an ion-pump related to the signaling operation of a neuron has appeared. This statement does not reflect on the use of an ion-pump in the metabolic aspects of the cell. Such a pump was recently discussed by Stein[50].

In a recent book heralded as one of the first comprehensive works on bioelectrochemistry, Ling found many problems with the original ion-pump thesis[51]. Problems were even found that related to kinetics. This work does not require, nor does it support an ion-pump as a participant in the neural signaling function.

The work of Hodgkin & Huxley using the voltage clamp technique did not record actual action potentials, only the current changes in response to an artificial stimulus. In fact, they were careful to remove any dendritic and poditic tissue from their samples. This action prevented the neuron from operating in its normal mode.

The professed irritability of the axolemma according to the ionic theory does not appear to be applicable to electrotonic neurons (the vast majority of neurons). These neurons are routinely called upon to respond to either positive going or negative going pulses, associated with bipolar signals, without generating an action potential.

8.1.3.2.5 A more comprehensive electrolytic theory

This work takes a quite different view of the overall neuron (and the operation of the entire neural system) from that of Hodgkin & Huxley. Most prominently, this work considers the axon as only a typical section of conduit within the neural system. In that role, it is a passive medium. All active properties of the neural system are associated with the unique juxtaposition of the terminal elements of these conduits to form active electrolytic liquid crystalline semiconductor devices, Activas.

In this context, each minimal neural conduit consists of at least two terminal structures and a cylindrical section connecting these structures. Furthermore, to achieve the unique properties associated with the Activas, additional sources of electrical potential must be provided. In toto, currents can enter and leave each individual conduit by a variety of paths not considered by Hodgkin & Huxley. To understand the potential of the axoplasm, or any other plasma, under these conditions requires the consideration of all the ionic and electronic currents applicable to the complete conduit surrounding the plasma. This accounting requires the use of Kirchoff's Laws (Ohm's Law is a special simplified

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[48]Dowling, J. (1992) Neurons and Networks. Cambridge, MA: Harvard University Press pg 75

[49]Ling, G. (1986) The origin of cellular electrical potentials. *In*, Gutmann, F. & Keyzer, H. Modern Bioelectrochemistry. NY: Plenum Press pg 47

[50]Stein, W. (1991) Carrier kinetics show how the sodium pump uses ATP to render pumping of both sodium and potassium effective. *In* Yudilevich, D. Deves, R. et. al. Cell Membrane Transport. NY: Plenum Press Chap. 2, pp 21-38

[51]Ling, G. (1986) Op. Cit.

case of Kirchoff's Laws). The conclusion from this accounting, based on our more complete knowledge of the nature of the biological membranes involved in lemmas, is that no ionic currents pass through the lemma in time spans short enough to affect signaling. The lemma of an axon or other conduit is an amphipathic membrane subdivided into regions with unique electrical properties. All currents through such a membrane consist of fundamental electrical charges, electrons and/or holes.

Individual regions of the lemma are found to represent very high quality electrical insulators or very high quality semiconductor diodes. These properties are stable with respect to time. There are no uncontrolled variations in the conductivity of these membranes. Their variation in conductivity is directly related to their unique electrical properties. Within each conduit, the plasma exhibits the properties representative of an electrolyte of its concentration. Where the plasma assumes the concentration and structure of a liquid crystalline material, its electrical properties are represented by the appropriate laws of semiconductor physics (charge transfer is by electrons and holes). Where the plasma is less concentrated, its electrical properties are represented by the laws of electrolysis (charge transfer is by positive and negative ions). There is no theoretical conflict between electrons and holes traveling in opposite directions, simultaneously and at different velocities, within a semiconductor. There is a significant theoretical prohibition between positive ions traveling in opposite direction within the same electrostatic field lacking another definable mechanism. Such an active mechanism has been labeled an ion-pump within the ionic theory, but such a mechanism with the necessary temporal properties has never been isolated.

In general, the electrolyte within a biological membrane conduit can be treated as completely electrically isolated from any other electrolyte surrounding the lemma. In most cases where the interior electrolyte is of low concentration, the laws of electrostatics treat the interior electrolyte as a conducting medium with a uniform potential gradient. If the conduit is exceptionally long and the electrolyte is of particularly high concentration, ionic flow may be restricted and a nonuniform potential field may be sustainable along its length.

This work holds that the change in potential of a membrane enclosed plasma is caused by the injection or removal of fundamental charges from within the membrane and that the membrane is static in its electrical characteristics. Thus, an in-rush of electrons will cause the potential within the membrane to become more negative relative to the surrounding matrix. Removal of charge will cause the potential to become less negative.

Hodgkin & Huxley wrote in terms of "conventional currents" and not electrons[52]. In this work, the in-rush of conventional current corresponds to an out-rush of electrons, and vice versa.

> **Polarization involves the injection, or in-rush, of electrons into (out-rush of conventional current from) the plasma within a conduit by electrostenolysis using the glutamate cycle. Depolarization involves the removal, or out-rush of electrons from within (in-rush of conventional current to) the plasma by passage through a reverse biased membrane operating as part of an Activa (exhibiting transistor action).**
>
> **Hyperpolarization is an observational aspect related to polarization. It does not involve any unique physical mechanism. It merely represents an enhancement of the nominal negative potential associated with a plasma.**
>
> **There is no need for ions of sodium or potassium to pass through the membrane. There is no need for an ion-pump or independence principle. There is no need for the axon membrane to change electrical properties.**

8.1.3.2.6 Additional perspective

As elsewhere in this work, the observable portion (although not necessarily the total) of the discharge current within a regenerator circuit can be equated to the "inward current" of Hodgkin & Huxley. The observable portion of the

[52]Hodgkin, A. Huxley, A. & Katz, B. (1952) Measurement of current-voltage relations in the membrane of the giant axon of *Loligo. J. Physiol*. vol 116, pp. 424-448

recharging current can be equated to the "outward current." **NO** overlap in the time history of the discharging and recharging currents occurs at the gross level based on this Theory. However, at the more detailed level, the recharging current exists throughout the discharging portion of the action potential. The apparent discharging current is the net of the discharging current through the Activa and the charging current due to electrostenolysis plus the displacement current associated with the axolemma capacitance. Under this definition, the majority of the inward conduction current is an electron current passing out through the Activa. The majority of the outward conduction current is an electron recharging current flowing inward through the electrostenolytic process supporting the axoplasm. No need exists for an ionic current to flow through the axolemma.

8.1.4 The plan of presentation

This is the first publication of the electrolytic theory of the neuron and the operation of the Activa based thereon. Because of the difficulty of presenting the cognitive and assimilative process used during this work to discover the electronic nature of the neuron, an alternate pedagogical approach will be followed below. A fundamental neuron will be synthesized on paper to highlight its most important electrical properties. This pedagogical presentation will familiarize all readers with the many interdisciplinary features found within the neuron. Those with a stronger background can skip over familiar material.

After presenting a functional framework (**Section 8.1.5**) and defining many terms (**Section 8.1.6** & **8.1.7**) required before proceeding, the presentation will begin with a discussion of the physical chemistry applicable to the biological membrane (**Section 8.2** & **8.3**). This discussion will be followed by a discussion of the differentiation of a single membrane enclosing a protocell into many localized and specialized regions (**Section 8.4**). These regions will be shown to support different types of biochemical operations. Many of these operations are foreign to the conventional biochemical curriculum. They are borrowed from the more esoteric corners of physical chemistry.

> During the remainder of this Chapter, a natural biological bilayer membrane will be described as a BLM. Where appropriate, the expression BLM will be preceded by one or more descriptive adjectives.

While differentiating and elaborating the membrane of a single cell, two uniquely important situations will be discussed. The first will discuss the elaboration of the cell membrane to form more than one electrolytically isolated chamber within the cell. It will then show that each of these chambers may develop a different internal potential compared with an external reference. Next, a situation will be examined where two membranes are brought into juxtaposition (**Section 8.5**). When the potentials within different plasma are appropriate and the membranes separating the plasmas are juxtaposed appropriately, a remarkable situation occurs. The configuration exhibits all of the electrical properties found in a man-made transistor. More specifically and scientifically, the configuration exhibits "transistor action."

Chapter 9 will continue the pedagogical presentation by developing the topology of the more complex forms of neurons found in the neural system. Each type of neuron found in the visual system will be discussed in detail. Additional discussion of the topology of the synapse will also be presented. Finally a set of initial "Activa data sheets" will be presented. Like man-made transistors, biological Activas exhibit a range of parameters depending on their application. These data sheets will define the electrolytic parameters of each type of Activa, based on its application within a specific type of neuron.

After discussing the features of a variety of neurons, the chapter will discuss another remarkable configuration. It will be shown that a synapse can also exhibit "transistor action" when it is configured appropriately (**Section 9.4**). This finding forces the inescapable conclusion that the morphological neuron is not the fundamental physiological unit of the neural system. *Activas are found outside neurons*. It can be shown that the neuron is the fundamental morphological and genetic unit but not the fundamental physiological unit. As will be developed in later chapters, a question arises whether the neuron can be considered the fundamental metabolic unit. It appears the projection neuron often relies upon nearby glia to provide critical chemical reaction products for use in the remote portions of its axon. This may also be true of the photoreceptor cells.

Chapter 10 will continue the pedagogical presentation into the area of the morphology and electrophysiology of each type of neuron based on its application. By comparing the morphology and the topology of each type of neuron, it will become obvious that "Form follows Function" in biological neurons.

After completing the discussions of **Chapters 8, 9** & **10**, **PART D** will continue with the development of the visual system. It will explore the unique character of each type of neuron used in each stage of the visual system. These stages will extend from the photoreceptors of the retina to the major cells of the central nervous system.

8.1.4.1 Major discoveries and ground rules in the following analyses

Many major surprises were uncovered during the initial exploration of the characteristics of the neuron. The most important was the discovery of the nature of the basic mechanism that powers the neural system. It is the same mechanism that created the recent explosive growth in electronics and communication, "transistor action." The second profound discovery was that each morphologically simple synapse was in fact a complex active electrolytic device. The third discovery was the fact that the Outer Segment of the photoreceptor cell was actually outside the external membrane of the cell. The fourth discovery was the critical role of the glutamate cycle in the operation of the neural system. This discovery explains the ubiquitous presence of the constituents of the glutamate cycle along the neural pathways of the body. The fifth was the recognition of the fact that the electro-osmotic laws of dilute solutions do not apply to the neural membranes. These laws all assume a condition not achieved in BLMs, a constant potential field gradient within a semipermeable membrane. Each of these discoveries will be explored at length in the following material.

The metabolic functions of the neuron associated with genesis and growth will be largely ignored in the following discussions. The signaling functions of the neuron are of paramount importance. Failure to differentiate between these roles can lead to considerable confusion.

The neurosecretory functions associated with the photoreceptor cells will be shown to be of critical importance. This is the only area where the neurosecretory capabilities of neurons will be explored. This function is distinctly separate from the signaling function. This function is explored in depth in **Chapters 4** & **7**. Smith has also discussed it from a more general perspective[53].

8.1.4.2 Other significant findings

This work has uncovered a variety of unique operating elements and operating mechanisms that relate to the neuron. Some of these are foreign to the historical literature. However, they are critical to an understanding of the neural system of a biological system. This makes them critical to the operation of the visual system.
As discussed in detail below and in other sections, this work accepts the following facts as fundamental:

+ The individual Activas found within the neural system, even within a single neuron, vary considerably in performance. This performance is tailored to the specific function required.

+ nearly every neuron contains at least one Activa employed in a feedback loop that is ***internal*** to the neuron. Internal feedback has not been discussed previously in the neurological literature.

+ the electrical signaling system in the animal uses the diode as the fundamental resistive impedance--not the resistor.

+ the diode associated with the single membrane wall of a neuron has a resistive component described by an electrolytic resistance that has unusual properties of its own.

+ the electrical properties of a membrane vary with the environment on each side of it. They also vary with the temperature and other internal characteristics of the membrane itself. Isolation of the membrane, or significantly changing its electrical environment, will significantly change its performance.

+ the fluid environment surrounding a neuron is an integral part of the functional neuron--disturbing this environment (as by careful washing) significantly affects the performance of the neuron. A neuron should never be washed with distilled water or any detergent.

+ the transient overshoot frequently encountered when discussing the action potential of a neuron

[53]Smith, C. (1989) The Neuron as a secretory cell, Chapter 14 of Elements of Molecular Neurobiology. NY: John Wiley & Sons

needs to be discussed more completely. The intrinsic feature is a normal result of the active circuitry employed internal to the neuron and does not involve any external feedback mechanism. It is more appropriately labeled the after-hyperpolarization[54]. On the other hand, the recorded overshoot is frequently caused or emphasized by the parameters of a poorly designed test set.

+ a single membrane wall of a neuron does not satisfy the normal definition of an active electronic device. **A single biological membrane is not excitable**. It is a passive electrical circuit that can generally be represented by a battery and a diode in series. More complex representations may be required if significant capacitance is present or if unusual large signal conditions are forced upon the membrane.

Based on these premises, the reader can clearly see why this work and the discussions and conclusions appearing in the previous literature are not compatible in most respects. On the other hand, most of the data in the literature is completely compatible with the theory developed here.

8.1.5 Preview--Functional framework of the neural system

Neuroscience has traditionally defined the neural system from a morphological perspective. The tendency under this perspective has been to think "function follows form." Such a portrayal has provided little insight into the operation of the neural system. This work adopts a functional perspective and adopts the contrary motto, "form follows function." The primary roles of the neural system are two. The first responsibility is to transport information from one location in the organism to another. The second responsibility is to evaluate and generate responses based on that information. The first role is the subject of PART C of this work. The second role will be developed in Chapter 15 of PART D.

8.1.5.1 Differentiation of neurons from a stem-cell

Figure 8.1.5-1 provides a roadmap for the differentiation of a proto-cell (stem-cell) into one of a variety of neurons. A stem cell can differentiate into one of at least four different cell families. The family of most interest here is the neuro-secretory family, B. This family is primarily involved in signaling within the organism. Several potential signaling modalities are summarized in the figure. These will be addressed individually in the following paragraphs.

The neural system is used to transmit time-critical signals throughout the organism using a dedicated and optimized network.

[54]Ganong, (1975) Medical Physiology, 7th Ed. Los Altos, CA: Lange Publishing pg 22

8.1.5.2 The conventional view of communications and signaling

The biological community has defined communications within the organism very broadly. It is critically important that this term be clearly defined in this work. Signaling in the broad biological sense will be addressed first. Some of the signaling tasks relate to long time frames and are easily accomplished using the endocrine (hormonal) system, #1, in conjunction with the vascular system. The Paracrine and autocrine modalities operate over short ranges that rely more upon diffusion within the local region rather than rely upon the vascular system. The neural system, #3, is implemented specifically to support the more time sensitive signaling requirements. This type of signaling will be addressed in the next and subsequent sections.

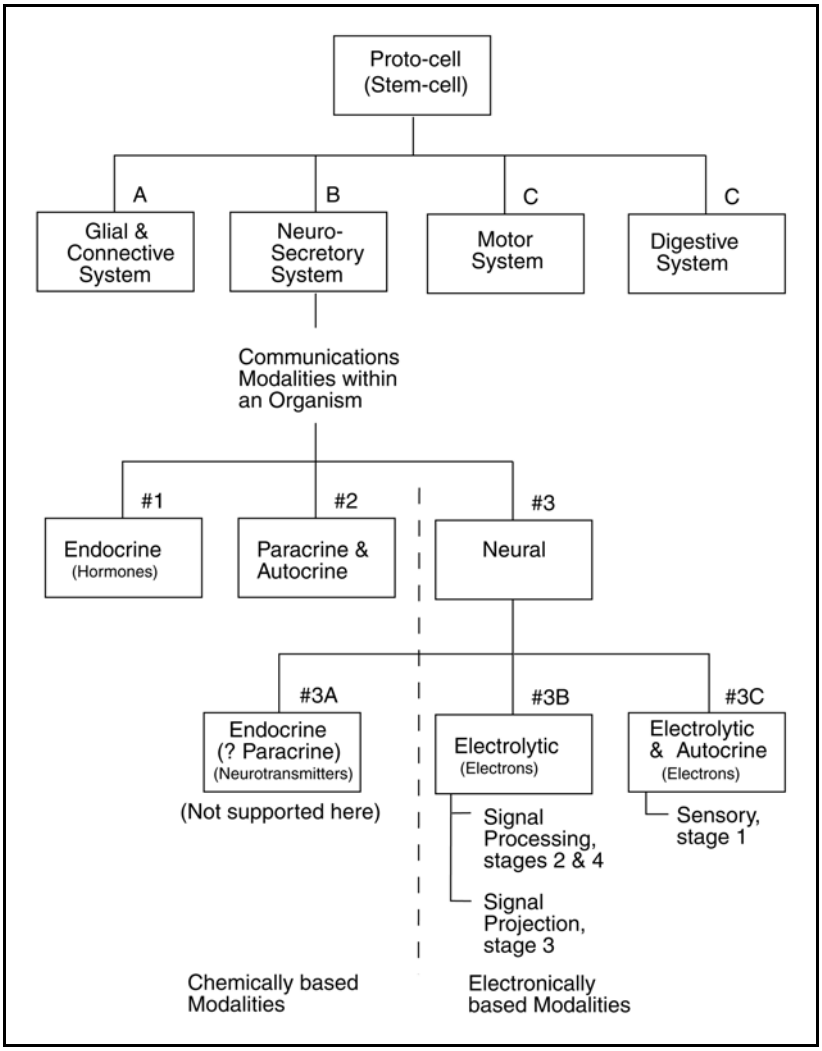

Figure 8.1.5-1 The differentiation of a stem-cell into a variety of neurons. Other cell types are shown for orientation and discussion purposes. See text.

Spaargaren, et. al. explored the subject of biological communications recently from the conventional perspective[55]. They did not recognize the existence of electrolytic signaling throughout the neural system. Their introduction can be used as a starting point. "Optimal functioning of an organism is only possible if the individual cells that make up the different tissues and organs are able to communicate with one another in order to coordinate their growth, division, development, differentiation, and organization." They go on. "In general, cells are able to communicate in three ways: (1) by small molecules (e.g., ions or metabolites, smaller than +/– 1 kDa) that can pass gap junctions, which connect the cytoplasm of two cells; or by signalling (*sic*) molecules (e.g., hormones, Gfs and neurotransmitters) that are either (2) cell-surface-localized, or (3) secreted. The first two mechanisms are only available to adjacent cells, whereas the latter can act over some distance." They conclude: "Cellular communication via secreted signalling molecules can be classified in three categories, based on the distance over which the signal acts. The first category, denoted endocrine signalling, occurs if the distance between the signal producing cell and the target cell is relatively large, the signalling molecules (hormones) being secreted by endocrine cells, usually organized in specific glands, and transported by the bloodstream to the target cells. . . . The second category, paracrine and autocrine

[55]Spaargaren, M. Delaat, S. & Boonstra, J. (1993) General mechanistic patterns of signal transduction across membranes, *Chapter 1 in* Shinitzky, M. *ed*. Biomembranes: Signal Transduction Across Membranes. NY: Balaban Publishers

signalling occurs if the signal producing cell is in the immediate environment of the target cell (paracrine), or if the signal producing cell itself is the target cell (autocrine). . . . The third category is employed by neurotransmitters, acting in the synaptic signalling of the nervous system. Although this type of signalling occurs in a paracrine fashion, it is regarded as a different category because of the extremely short distance between the signal producing cell and the target cell, which are only separated by the synaptic cleft (*sic* gap)."

The concepts of Spaargaren, et. al. have been diagramed in the middle of the figure. Their neural signaling mode labeled #3 is not adequate for the purposes of this work. The figure has been extended to subdivide this mode. Modality #3A is not supported in this work. It will be shown that the classical neurotransmitters of 20th Century biology are not related to signaling within the neural system. They play a significantly different role. This role for the neurotransmitters is defined in detail (**Section 8.6**). Modes #3B and #3C are added to reintroduce the, long dismissed, electronic mode of signaling between neurons. This modality is developed in the next section. The understanding of the operation of the neural system is greatly extended by adopting the modalities of #3B and #3C.

8.1.5.3 Reintroduction of electronic signaling in neurology

The lower right portion of **Figure 8.1.5-1** summarizes the communications modalities available within an organism based on the Electrolytic Theory of the Neuron. During the first half of the 20th Century, there was a spirited debate concerning the modality employed by the neural system. A chemical-based interpretation of the operation of the neural system (mode #3A) has been dominant during the last 50 years, following a bone-crushing debate based more on desires than data. This domination was due primarily to the overwhelming numbers of chemically trained (heavily academically oriented) members in the debate. Subsequently, the data has provided clear evidence. The neural system is electronically based (mode #3B & #3C). This will be proven conclusively in the remainder of this document.

Neural signaling, modality #3, has been separated into a modality #3B and a modality #3C. This is done to recognize the crucial role autocrine secretion plays in the operation of the photoreceptor cells of vision and many other sensory neurons. The further delineations under these modalities aid in describing the various types of neurons found in the neural system and the functional stage wherein they are found.

While accepting the concept of electronic (in place of chemical) signaling is difficult for many chemically trained biological researchers, it is inescapable. After more than 50 years, the chemical-based ideology has been unable to explain even the most basic properties of the system theoretically. Many examples of the failure of the chemical-based ideology are available. Most involve situations not even addressed by that ideology. The operation of the ganglion cell is a good example. No chemically based explanation has been presented as to how an action potential is generated in response to an electrotonic signal within a ganglion cell. Similarly, no theoretical explanation has been presented explaining how a Node of Ranvier regenerates the action potential applied to its dendritic terminal. There is no theoretical explanation of how a horizontal or amercine cell forms an output signal that is the algebraic difference between two electrotonic input signals.

The evidence in the literature is overwhelming that the neural system is electronically based. Theoretical explanations of each of the above examples are readily available under the Electrolytic Theory of the Neuron. While communications between conventional cells is clearly dominated by chemical processes, neurons are highly specialized to convey information by a different mechanism. The information conveyed within an organism by chemical means is primarily for command and control purposes (growth, differentiation, etc.) The response time related to these commands is typically long (several seconds to weeks). Assigning a signaling bandwidth to such slow signaling systems is difficult. The bandwidth does not exceed one Hertz.

The information conveyed within the neural system of an organism by electronic means is primarily related to interaction with the environment surrounding the organism. The response time, within the visual system, to these signals is typically within tens of milliseconds (following extensive internal computation). To support these response times, the actual communications bandwidths associated with these signals is generally above 100 Hertz.

The reintroduction of the electronic basis for the operation of the neural system requires a careful examination of the literature. As noted in **Section 8.1.1**, many concepts found in the literature date from the first half of the 20th Century or earlier. Many of these are no longer defendable based on the detailed experimental data acquired more recently through the use of spectacularly more capable instrumentation. As an example, it is now abundantly clear that the BLM is not amenable to the mathematical modeling of Nernst, Planck, Donnan, Goldsmith, Hodgkin & Huxley and most recently Starzak. The BLM of interest to neurology is not a symmetrical non-crystalline ionically semipermeable element. The BLM of interest is an asymmetrical liquid-crystalline semiconducting (quantum-mechanical) element essentially impervious to ions and semipermeable to electrons (**Section 8.3.2**).

Under the electronic hypothesis of neural operation, the neurotransmitters of the chemical ideology take their proper chemical place as neuro-facilitators and neuro-inhibitors of the system but do not participate in neural signaling. Although this assertion flies in the face of many (highly ornate) caricatures in the recent literature, the results of electron microscopy do not support the role of any chemicals in neural signaling. No framework has evolved under the chemical ideology to explain the detailed operation of a wide range of putative neurotransmitters. On the other hand, the Electrolytic Theory of the Neuron provides a simple and unique framework for explaining the pharmacological operation of these materials. The unique and detailed mechanisms related to the amino acids (glutamate, aspartate and GABA) provided under the electronic hypothesis are beautiful in their simplicity (**Section 8.6**). These mechanisms are completely compatible with the recent language of Stephenson & Strange[56], but they require a different interpretation of the location of various "neurotransmitter" receptors. The receptors are found outside the synaptic gap. With only the most minor semantic changes, their words are quite compatible with the theory presented in **Section 8.6**. "From biochemical studies it became apparent that neurotransmitter *(primary neuro-facilitator*) receptors are integral membrane proteins with binding sites for the neurotransmitter; these binding sites are available extracellularly (synaptically, *but outside the synaptic gap*), and the receptor also has the ability to signal to the inside of the cell." An open question remains concerning the "integral membrane protein." No protein or protein mechanism has been identified except conceptually. A more satisfactory situation replaces the term "integral membrane protein" with the polar portion of a lipoid integral to the underlying asymmetrical (type 2) BLM.

8.1.5.4 The fundamental neural signaling mode of biological systems

The following preview is not designed to convince the skeptical reader. It is designed only as a preview of the following material to provide the reader a contextual framework.

Noback has provided the conventional definition of a neuron shared by many authors. "The neuron is the keystone; it is the *morphologic unit*, the *functional* unit, and the *ontogenetic* unit of the nervous system[57]." While this is a satisfactory introductory definition for pedagogy, it is not scientifically adequate. Shepherd & Koch have recently taken a big step forward by describing the synapse as the basic functional unit of neural circuits[58]. However, their discussion is based entirely on the conventional chemical view of the synapse that is not supported here. They also remain unaware of the Activa within each neuron and the commonality of the conexuses within the soma of the neuron, within the synapses and within the Node of Ranvier. These relationships will be discussed thoroughly in **Chapter 10**. It will be shown that there is a functional unit that is frequently replicated within a single neuron, and between neurons. This replicated conexus is properly defined as the *functional* unit of the neural system, and within the neuron itself. It is the Activa, and its supporting plasma conduits and electrolytic elements, that form the fundamental functional unit, the conexus, of the neural system.

The signal transport role supporting the collection of sensory information and distribution of commands can be described functionally by **Figure 8.1.5-2(a)**. A signal (I_{in}) is delivered to a series of electrolytic conduits as shown. A message related to that signal is propagated along the neural system until it emerges at the output as a signal, I_{out}. This figure highlights the fundamental functional unit enclosed by the small dashed box. This unit includes a junction plus a pre-junction electrolytic conduit and a post junction electrolytic conduit. The following material will show that this fundamental unit can be described as in (b). In this figure, the junction between the two electrolytic conduits may be connected to an additional source of electrical bias. Under the appropriate conditions, the circuit of (b) can be portrayed as in (c). In (c), the junction is portrayed as an electrolytic transistor, known as an Activa, that operates exactly like a man-made transistor.

The configuration of the fundamental functional unit of the neural system in (c) exhibits great flexibility. By varying

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[56]Stephenson, F. & Strange, P. (1993) Receptors for neurotransmitters, *Chapter 2 in* Shinitzky, M. Biomembranes. NY: Balaban Publishers

[57]Noback, C. (1967 The Human Nervous System. NY: McGraw-Hill pg 28

[58]Shepherd, G. (1998) The Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 3

the associated components and biases, the circuit can be made to operate in a variety of electrically functional modes as suggested by (d), (e) and (f). **Chapters 8** & **9** will develop these capabilities in detail.

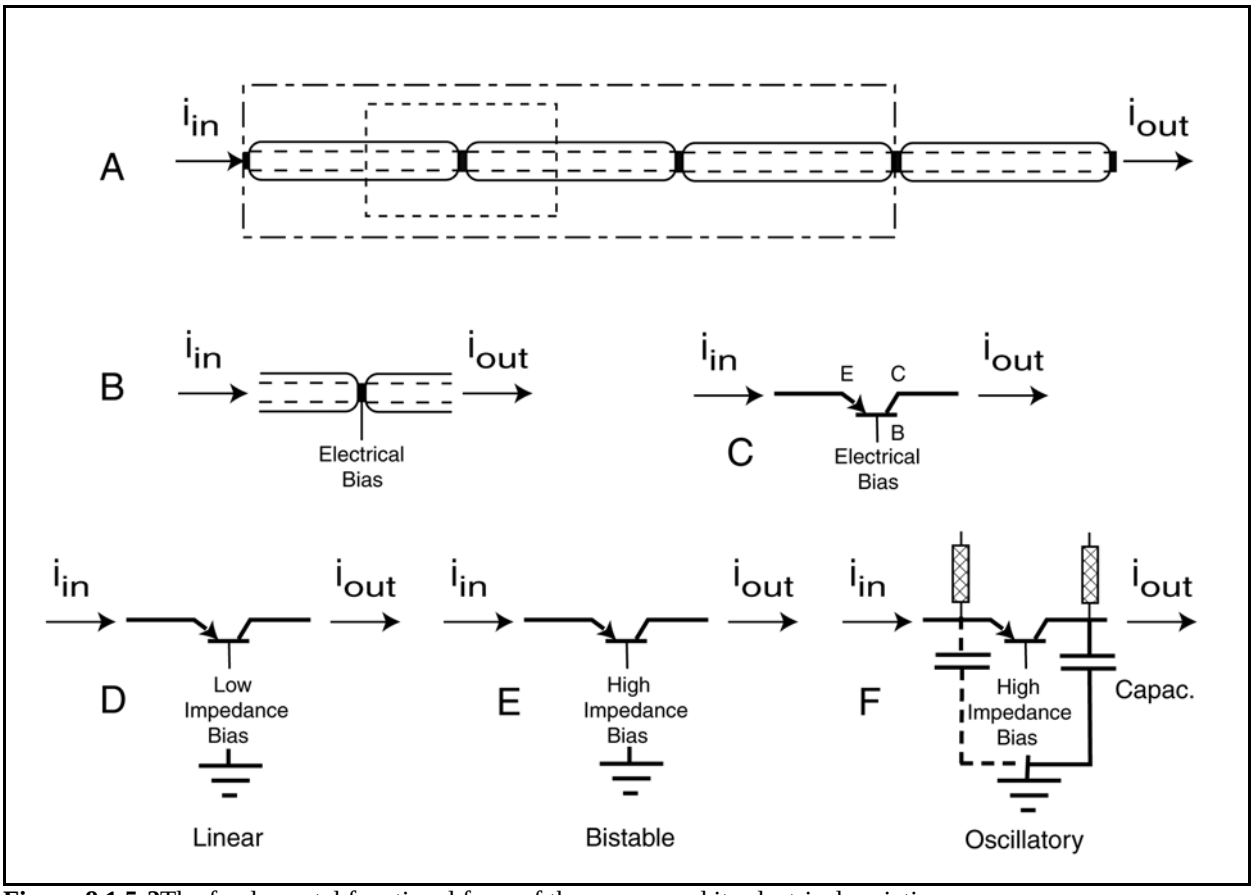

Figure 8.1.5-2 The fundamental functional form of the neuron and its electrical variations.

Chapter 10 will review the details of the electrolytic model of the neuron and neural system in both morphological and electrophysiological contexts. **Figure 8.1.5-3** previews how the fundamental functional unit can be packaged within the traditional morphological envelopes of the literature. The shaded parts of each figure are associated with the metabolic and homeostatic aspects of the neuron. The other features are associated with the primary task of neural signaling. These caricatures highlight a variety of important facts.

First, the original morphological designation, monopolar neuron is seen to be unfortunate. Both the morphologically described monopolar and bipolar neurons are functionally identical.

Second, every fundamental functional unit within the neural system consists of a three terminal circuit consisting of a dendrite, an axon, and a third terminal known as a podite. The podite need not be visible using light microscopy. It may only exist as a specialized area of plasmalemma associated with the soma of the cell. This configuration accounts for the frequent description of axo-soma junctions in the literature. When the podite terminal is more highly developed, it can exhibit a tree-like structure not unlike a conventional dendrite. The references in the literature to a bilayer dendritic tree frequently refers to a combination of a single dendritic tree and a poditic tree. These structures can be distinguished by their geometrical arrangement where they merge with the soma.

Third, a single soma can support many fundamental functional units as shown in (e). Each conduit receives metabolic and homeostatic support from the single nucleus and soma. The functional units can be difficult to recognize under light microscopy. The junction completely enclosed within the soma, and labeled a conexus, can only be identified by electron microscopy. It is generally found within the “hillock” of the soma leading to the axon. The junctions along the

axon between the conexus and the terminal junction (known as a synapse) are known as Nodes of Ranvier. These nodes are also difficult to study when they are largely enclosed by the soma. The form shown in (e) is labeled bipolar for consistency. In fact, this form is the only form shown that is exclusively associated with action potentials. Forms (a) through (d) are typically associated with tonic signals unless they are transition types. Using the circuit modifications of (d), (e) and (f) of the previous figure, transition types can be adopted to other functions. When configured as a tonic-to-phasic converter, the neuron is known as a ganglion cell. When configured as a phasic-to-tonic converter, the neuron is known as a stellate cell.

8.1.6 Glossary

The following definitions will be used in this work;

Communications– The transfer of instructions, sensory information and skeleto-muscular commands within the biological organism

Conductance–The ratio of total net charge transported through a two-terminal substance per unit time divided by the potential applied to that substance. The conductance must frequently be further specified with respect to steady state versus dynamic conditions. It frequently shows variation when operating under small-signal versus large-signal conditions. Within the substance, it is frequently useful to differentiate between the various types of charge transport found. This differentiation can lead to the description of (specific) ion conductance, electron conductance and hole conductance.

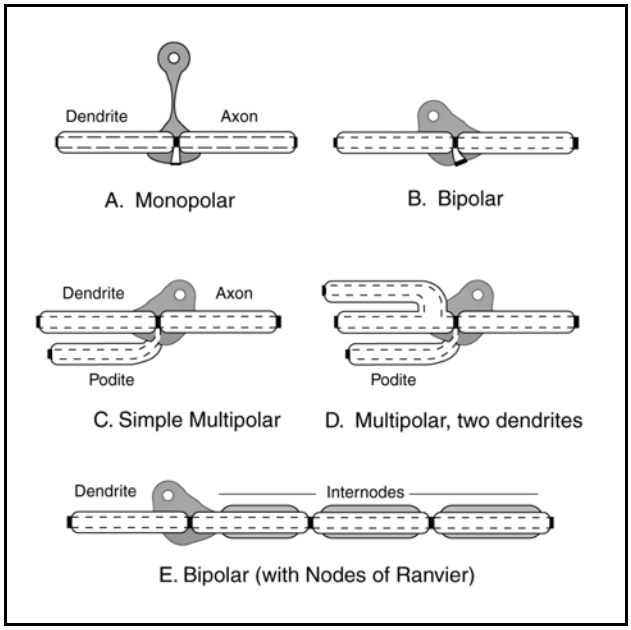

Figure 8.1.5-3 The fundamental functional units of the neuron within a morphological context.

Electrostenolysis– The generation of an electrical potential across a BLM as part of a chemical reaction. The reaction occurs on one surface of the membrane acting as a catalytic substrate. The potential is a response to the movement of fundamental electrical charges through the membrane.

Fundamental charges–The electron and the proton (and the emulation of a proton known as a hole–literally the absence of an electron).

Hole–The idea of a location in an otherwise neutral crystalline molecular lattice where an electron is missing.

Hole transport–The apparent motion of positive charges through the valance band of a liquid or metallic crystalline material by electrons jumping from one electronic void in the lattice to another. The average velocity of this motion of electrons described the apparent mobility of the holes. See **Section 8.1.3.2.3**.

Interneural matrix (INM)–The electrolyte surrounding one or more neurons.

Intra-axon–A segments of axon connecting two Nodes of Ranvier.

Intrinsic battery– A representation of a quantum-mechanical junction in a crystalline material where the charge distribution is not uniform. This “intrinsic battery” is not capable of supporting an external current in the performance of thermodynamic work (the generation of heat).

Ion-pump– A conceptual mechanism for causing the transfer of ions from one side of a cell membrane to the other. Such a conceptual mechanism is redefined in this work based on the underlying mechanisms. It is considered a type of

charge-pump. See also electrostenolysis and electron-pump.

Neuron–A specialized organic cell used to communicate information from one portion of the animal to another. The definition of the neuron is frequently extended to neuro-secretory cell. This is because of the propensity of the terminal cells in a signal path to exhibit a distinct secretory function. The elementary neuron is characterized by three signal carrying electrical structures converging on an active electrolytic device within the cell, the Activa. The neuron contains internal electrically-insulating partitions. It is also characterized by a group of specialized regions of the plasma membrane associated each of these partitions.

Permeability–A term synonymous with conductivity but usually restricted to the bulk conduction of ions, uncharged particles and other molecules through a bulk material. The term has been subject to reinterpretation to satisfy various theories of the BLM (Troshin, 1966, pg 3)

Resistivity-- A measure of the bulk electrical properties of a material. It is typically proportional to the thickness of the material and inversely proportional to the cross sectional area that a current passes through traversing the material. Thus, it has the units of Ohm-cm in the CGS system. See also thin-film resistivity.

Signal transduction–

1. (with respect to the hormonal system) An intracellular cascade of biochemical events that follow the interaction between extracellular growth factors and their membrane receptors, ending in the switch of nuclear mechanisms controlling the proper biological responses. (Battistini, et. al. 1993 in Papa & Tager)

2. (with respect to the sensory mechanisms of the neural system) The transfer of acoustic energy, electromagnetic energy or tactile motion by quantum-mechanical sensors into free electrons that can be further processed by the neural system.

Signaling–The transfer of sensory information, and skeleto-muscular instructions and commands over the neural system of the biological organism. Does not include the communications carried out by the hormonal system.

Thin-film resistivity– A measure of the electrical properties of a material having a characteristic (largely invariant) thickness such as a bilayer membrane. Defined as the resistivity of the "bulk" material multiplied by the nominal thickness of the film. Units are Ohms-cm^2. See also resistivity.

8.1.6.1 Types of neurons

Five functionally distinct classes of neurons are known. These are the signal detection neurons, the signal manipulation neurons, the hybrid neurons, the signal projection neurons and the motor activation (or mylo-) neurons. Those of importance here include;

Projection neurons--Neurons optimized to transmit information over long distances within the animal. The distances are longer than one mm. Frequently described as principal neurons or relay neurons. They accept action potentials at their input and produce action potentials at their output. They are found in the stage 3 circuits of this work.

Interneurons--Neurons optimized to process information within a local area (one mm.) prior to transmission. Frequently described as intrinsic neurons. Exhibit electrotonic (analog) waveforms at both their input and output. Bipolar and lateral neurons are members of this group. These neurons are found in the stage 2 and stage 4 circuits of this work.

Lateral neurons–Neurons recognized morphologically as connecting parallel neural signaling paths generally within the 1^{st} and 2^{nd} lateral processing matrices of the retina. This group includes the horizontal neurons and the amercine neurons of stage 2 circuits.

Amercine neurons--A special type of interneuron in which the axon and one neurite are next to each other and are surrounded by a common section of plasma membrane. The structure of this type cannot be discovered by morphological techniques except using electron microscopy. An electron-micrograph can image the interior membrane wall between the two structures. Alternately, careful electrophysiological measurements can identify the different electrical potentials between the axon and the neurite. This type of neuron is found in stage 2 circuits.

Encoding neurons--Also known as ganglion cells in vision. Hybrid neuron cells that generate "action

potentials" at their output in response to electrotonic input signals. Used in stage 3 circuits.

Decoding neurons–Hybrid neurons used to receive "action potentials" and to generate electrotonic waveforms in support of further signal processing within the brain or to control muscle tissue. The stellate cells of the cortex are typical examples. Used in stage 3 circuits.

8.1.6.2 Cytological parts of a neuron

Nucleus--That portion of a neuron concerned with the control of growth and maintenance of the neuron. It is responsible for producing messenger DNA.

Activa--The functional portion of the neuron, an active three-terminal electrolytic semiconductor device found (1) within the cell body and (2) at the junction of the neuritic (dendritic and poditic) and axonal structures. It is recognizable by electro-physiological probing or high magnification electron microscopy.

Cell body--That region of a cell surrounding the Nucleus, and portions of the conduits of the signaling mechanism in neurons. It supports the manufacture of many chemicals used to support the signaling function. Also called the Soma.

Plasma membrane--The outer membrane completely surrounding a cell and consisting of a double wall membrane of two leaves. Each leaf usually consists of a liquid crystalline film of biological phospho-triglycerides. The cell is usually divided by internal membranes into at least three distinct functional sections in neurons. These sections are associated with the morphologically defined axons, dendrites and podites. These sections of the membrane may show further specialization. The character of the membrane is also divided into three functional types.

> The **type 1 plasmalemma** consists of a molecularly symmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular and electron flow (it is a very good insulator).
>
> The **type 2 plasmalemma** consists of a molecularly asymmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular flow but acts as an electrical diode with respect to electron flow.
>
> The **type 3 plasmalemma** consists of a liquid crystalline bilayer with many embedded proteins providing a transport path through the membrane.

Plasmas–The high concentration, high viscosity, heterogeneous, hydrophilic materials found within the water based solute of cells. The material is frequently present as a gel or a liquid crystal. Typically of four distinct types; cytoplasm, dendroplasm, podaplasm & axoplasm. The last three of these are functional with respect to signaling.

Nuclear membrane--The membrane separating the nucleus from the cell body of a neuron.

Soma--See cell body.

8.1.6.3 Functional parts of a neuron

Activa within the hillock–The fundamental active device providing "transistor action" within the body of a projection (stage 3) neuron.

Axon–The output conduit of a neuron. It usually lacking the extensive arborization associated with the neurites. Contains an inner core, labeled the reticulum. It is filled with a conducting plasma, the axoplasm, connecting the Activa collector to the electrostenolytic supply and the pedicle of the neuron.

Conexus– A cytologically/morphologically recognizable electrical circuit complex within a neuron. The combination of an Activa combined with a few other electrolytic components defines the conexus within the neuron.

Neurite–A global name for the functional input structures of a neuron. It includes the dendrites and the podites. Each neurite contains at least one reticulum filled with a conducting plasma that terminates at the Activa within the neuron.

Dendrite–The input to the non-inverting terminal of the Activa within a neuron. It is frequently a highly complex tree-like structure. Contains at least one reticulum filled with a conducting plasma. This reticulum contacts the emitter of the Activa of the neuron.

Podite– The third signaling structure of a neuron. Occurs in two applications.

(1) Frequently the connection between the surrounding plasma and the base terminal of the Activa within a neuron. Frequently represented by a specialized region of the plasma membrane in contact with the surrounding plasma.

(2) The input to the inverting terminal of the Activa within a neuron. It is frequently a highly complex tree-like structure similar to a dendritic tree.

(3) Culminates in at least one reticulum filled with a conducting plasma. This reticulum contacts the base of the Activa of the neuron.

Node of Ranvier– Functionally, a point of signal regeneration between the axoplasm of axon segment #n and axon segment #n+1.

(1) Cytologically, the location of a three terminal Activa with terminals contacting the above two axon segments and the surrounding plasma.

(2) Morphologically, a discontinuity in the myelin coating of an axon that allows (a) electrical access between the base of the signal regenerating Activa and the surrounding interneural plasma and (b) electrical access between the surrounding interneural plasma and the regions of both axon segment #1 and axon segment #2 involved in power generation. May also provide chemical access between the axons and the nearby glia.

Specialized regions of the plasma membrane are used to create power sources in the neuron. By employing various bio-energetic materials coating the inner and/or outer surface of these regions, obtaining the appropriate amplitude and polarity of bias voltage within each plasma of a neuron is possible. The mechanism involved is known as electrostenolysis. It is believed that all of the materials are amino acids participating in a metabolic process known as the glutamate cycle. These bio-energetic materials are replaced upon consumption via diffusion. Two distinct diffusion rates have been defined for the material found within the reticulum of an axon. *Slow transport* at rates of about one mm. per day and *fast* (rapid) *transport* at rates of several hundred mm. per day. Neither of these rates is compatible with signaling.

Power sources--Unnamed specialized regions on the surface of the plasma membrane where electrostenolytic processes employ bio-energetic materials to establish electrical potentials supporting the signal handling properties of the neuron. These sources can be represented by an electrical current source in parallel with an electrical diode or as electrical voltage sources in series with a diode.

Autoradiography has been successfully used to image the above structures within a neuron.

8.1.6.4 Functional parts between neurons

Synapses--(1) Functionally, a point of low loss signal transmission between the axoplasm of an axon, or axon segment, and a neurite of a following neuron.

(2) Cytologically, the location of a three terminal Activa with terminals contacting the preceding axoplasm, the postsynaptic neurite and the surrounding INM matrix.

(2) Morphologically, a discontinuity in the neural signaling chain caused by the architecture of the neural system. Generally described as the space between two serial neurons. Typically less than 100 Angstrom long

within the active gap region.

8.1.6.5 Functional parts of an Activa

To avoid new terminology in electrolytics, the names used for analogous solid state structures will be used. The Activa is a "pnp" type of sandwich (or junction) structure at the molecular level. When properly biased electrically, it exhibits "transistor action." By exhibiting this capability, it becomes an active device characterized by power amplification. This amplification may be exemplified by either current or voltage amplification.

All biological Activa are believed to be of the "pnp" type. Holes are the majority electrical carrier in "pnp" type active devices. To achieve transistor action in an active biological, electrolytic semiconductor device of the "pnp" type, it is necessary that the emitter be biased positively with respect to the base. Similarly, the collector must be biased negatively with respect to the base.

E**mitter**--The input structure of the Activa. The emitter function may involve several independent emitter substructures.

Collector--The output structure of the Activa.

Base--The middle structure of the Activa, represented by "n" in the designation "pnp." The critical area of the Activa in which "transistor action" is achieved.

Biological junction--(1)At the molecular level, the nominal location of the interface between the emitter and the base or the base and the collector of an Activa. Useful in establishing the location of the space charge layer in an Activa.

(2) At the molecular level, the nominal location of the interface between the "p" and the "n" type material found in the plasma membrane, or any "three layer" membrane (using the morphological expression), of a cell. Useful in establishing the location of the space charge layer in the diode associated with a power source in the membrane wall.

(3) At the morphological level, the common name for the structure at the signaling interface between two neurons.

There has been occasional discussion in the literature attempting to conceptually associated "gates" in biological membranes with the properties of a field effect transistor[59]. These discussions have not led to the detailed description of the mechanisms involved. Using a term from patent law, these concepts have not been reduced to practice.

8.2 The physical chemistry of biological membranes

Developing the physical chemistry of the BLM without recognizing the quantum-mechanical conditions that are involved is impossible. These will be addressed below in detail.

Stein noted a problem in 1967 when discussing biological membranes[60]. "The very definition of the term 'cell membrane' is a matter of contention. In fact, we cell biologists use the term 'cell membrane' or 'plasma membrane'—we shall use these terms interchangeably— in at least three quite different senses. In the anatomical sense, the cell membrane is the external limiting region of the cell. . . ." "In the biochemical sense, the cell membrane is a 'fraction' of the cell prepared by the now classical techniques of selective disintegration of the whole cell, followed by differential centrifugation." "Finally, in the physiological sense, the 'cell membrane' is a hypothetical structure invented to explain

[59]Sigworth, F. (2003) Life's transistors *Nature* vol. 423, pp 21-22

[60]Stein, W. (1967) Op. Cit. pp1-2

certain data on the 'permeability of cells' and to explain other data on the distribution of metabolites and other molecules between the cell and the fluid in which the cell is immersed." It is time to prohibit such license among investigators. Only real plasma membranes are of interest in this work. Any "hypothetical structure" must conform entirely with reproducible experimental facts.

The focus of this section will be on the properties of a simple BLM in an electrolytic environment. Such a membrane is associated with the fundamental lemma of a cell. It is differentiated from a "mosaic membrane" that may contain inclusions, and a "skin" that consists of multiple cells and/or other structures. The mosaic membrane is defined as a type 3 membrane in this work. Skins are significantly different from plasmalemma. Skins normally exhibit a potential between their two surfaces under unbiased conditions while a membrane does not. The polarity of a skin is normally positive on the inside[61] whereas the plasmalemma is normally negative on the inside under operating conditions.

Mueller & Rudin addressed the natural evolution of cellular membranes in considerable technical detail[62]. They show why the conventional wisdom of their time (based on protein walled cells) was most probably wrong. Both Mueller & Rudin and Ehrenstein note the appearance of the liquid crystalline molecular bilayer membrane under the electron microscope. Mueller & Rudin describe it as palisade like. Ehrenstein in Adelman describes the appearance as railroad tracks.

Goldman, writing in Adelman, presents a good discussion of a scientific model[63]. He couches his material within his view of a model. However, his perspective might be considered too narrow. His assumption is that substantial size particles must move through the membrane but does not recognize a difference between the signaling and other metabolic functions. He does provide a series of lists describing (or questioning) the characteristics of an axon membrane from that perspective.

The fundamental BLM, or protomembrane, is a continuous (void free) liquid crystalline structure. It is a symmetrical liquid crystalline material that is largely impervious to any molecules or ions but is semipermeable to electrons. It consists of two mono-molecular bilayers of the same polarized phospholipid material arranged with their two hydrophobic surfaces in close proximity. In many regions of the membrane, the two layers may be made from different polarized phospholipid materials. Such a proto-membrane has limited utility in application. Practical BLMs have evolved to incorporate a variety of specialized regions. These regions are highly tailored to their individual purpose. The initial requirement is to evolve a method of controlling the electrical potential of the protoplasm relative to its surrounding. This is accomplished by causing the two phospholipid materials forming the bilayer to be asymmetrical at the molecular level and instituting an electrostenolytic process to transfer electrical charge through the membrane. The potential generated by this mechanism is quantum-mechanically controlled by the energy of a CO_2 ligand separating from a molecule of an amino acid. A second requirement is to transfer metabolic supplies into the cell from the surrounding matrix and discharge waste products. A separate region of the BLM is tailored to support this task. Since the task is multifaceted, it is of immense experimental interest. However, to date no single theoretical framework has evolved to explain the myriad experimental results available. The tailored region probably contains proteins embedded in the membrane. A brief review of this area that is peripheral to the neural process appears in **Section 8.2.5**.

The neuron, as a cell, has evolved from the initial cell described above to include additional internal partitions beyond those associated with the nucleus and other chemical processing areas. In the following discussions, the membrane region supporting the metabolic health and growth of the cell are of little interest. This region will be discussed in **Section 8.2.5** along with discussions concerning ion-pumps. The regions of primary interest to neurology are the symmetrical lipid bilayer regions and the asymmetrical lipid bilayer regions. The symmetrical regions make up most of the walls of dendrites, podites and axons. These regions are passive in nature and provide very high quality electrical isolation. They are electrical insulators and impervious to ions. The asymmetrical lipid bilayer regions are small areas associated with the electrical polarization of the various plasmas within the cell. The asymmetrical regions perform a variety of critically important tasks as defined below.

Although, the following analysis does not concentrate on the detailed molecular, and sub-molecular properties, of the BLM, it does depend on those fundamental properties. Yeagle has provided a comprehensive work assembling material

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[61]Armstrong, W. W. (1971) The cell membrane and biological transport *in* Selkurt, E. *Ed*. Physiology, 3rd ed. Boston, MA: Little Brown pg 33

[62]Mueller, P. & Rudin, D. (1969) Op. Cit. pp 237-240

[63]Goldman, D. (1971) Excitability models, *in* Adelman, W. *ed.* Biophysics and Physiology of Excitable Membranes NY: Van Nostrand Reinhold pp 337-356

on both the theoretical molecular chemistry of these membranes and their measured properties[64]. That work differentiates between many meso-states of matter and explores the family relationships between the fatty-acids. Subtle differences are discussed between liquid crystals and gels. Yeagle's work is limited primarily to the study of symmetrical bilayers (page 141). Houslay & Stanley have provided a discussion of modeling BLMs[65]. It is mostly conceptual but includes many properties of membranes.

Three principal theories of the biological membrane have been used during the last century:

A. A chemically undefined membrane with an internally homogeneous structure. The structure is semipermeable to the flow of various ions and molecules. Little or no consideration is given to its permeability to the elementary electron.

B. A lipid based bilayer membrane as an internally asymmetrical structure. The structure is semipermeable to the flow of electrons but impermeable to ions and other molecules.

C. A lipid membrane with protein inclusions. The inclusions provide an array of putative pores or channels. These devices support the passage of various ions or molecules through the membrane.

The type A membrane dominated from its initial description in the third quarter of the 19th Century until the membrane was shown to be impermeable to ions during the second half of the 20th Century.

The type B membrane was defined both chemically and electrically during the second half of the 20th Century and provides the theoretical foundation of this chapter.

The type C membrane was defined conceptually during the second half of the 20th Century. It was defined by those who recognized the inadequacies of the type A membrane but were not ready to accept the electronic nature of the neuron associated with the type B membrane. Shepherd drew a conclusion without considering a type B membrane. "The rapid rate of ionic flow occurring during the generation of an action potential is far too high to be achieved by an active transport mechanism, but rather results from the opening of ion channels[66]." This statement was speculative and based on limited visibility. While many caricatures of this type of membrane exist, little or no data from the electron microscope exists to support the association of this type of membrane with the neural signaling process. It is surprising how little discussion appears related to the inclusions of cholesterol in the type C membrane. This material is well known for its binding power relative to water. It provides a candidate substrate for a water transport mechanism.

The tentative nature of the present state of the putative pores and channels is reflected in the summary by Unwin. This review paper will be examined more closely in **Section 8.2.5.1**.

Sections 8.2.1 & **8.2.2** will review a broad range of basic physics and biochemistry before characterizing a BLM further and developing the premises of this work in **Sections 8.2.3** through **8.2.5**.

The above alphabetical categories are not totally independent and failed to provide a distinct framework for discussing BLMs. An alternate set of numeric categories will be used henceforth. They are all based on two liquid-crystalline molecular films of amphipathic organic material formed into a bilayer. The bilayer is hydrophilic on its outside but contains a lipophilic core region. At least three distinct types of membrane can be distinguished.

Type 1. A continuous liquid-crystalline bilayer structure where each layer is homogeneous and the two layers consist of the same phospholipid material. The structure is largely impervious to all materials and is an insulator relative to electrical charges.

Type 2. A continuous liquid-crystalline bilayer structure where the individual molecular layers are homogeneous but

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[64]Yeagle, P. (1992) The structure of biological membranes. Boca Raton, FL: CRC Press.

[65]Houslay, M. & Stanley, K. (1982) Dynamics of Biological Membranes. NY: John Wiley & Sons

[66]Shepherd, G. (1998) Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 45

consist of different phospholipid materials. The structure is largely impervious to all materials other than electrons. It is electrically asymmetrical and forms a diode.

Type 3. A liquid-crystalline bilayer structure that is largely impervious to all materials but contains islands of protein or sterol material penetrating both films of the bilayer. The penetrations are thought to support the transport of selected materials through the membrane.

Using a caricature that will be introduced later, these membrane types can be illustrated in **Figure 8.2.1-1**. The role of the dashed lines will be discussed later. The left cylinder describes the dendritic input to the cell. The right cylinder represents the axon output of the cell. The white disk defines the nucleus of the cell within the soma or body of the cell. In this caricature, large portions of the external lemma are shown as type 1 membrane. These areas are impervious to the diffusion of materials or electrons. The axon is frequently enclosed in a multilayer lipid wrapping (myelination) that further impedes the flow of material (and electrons) from the surrounding matrix through the membrane. The areas shown in heavy black along the periphery of the membrane represent regions of type 2 material that remain impervious to materials other than electrons. Under the appropriate electrical conditions, these areas act as electrical diodes. The remaining periphery is shown shaded and represents type 3 membrane. Individual regions of this membrane are permeable to a variety of materials required by the cell to maintain homeostasis and growth.

Because it is pertinent to research in the current literature, the electrostenolytic site powering the dendritic conduit is shown explicitly. Recent literature[67] has asserted that the protein mGluR6 is a receptor for glutamate participating as a neurotransmitter at the dendritic input at the tip of the dendrite or one of its spines (not shown). However, Vardi et al. have recently completed a search for the location of this receptor material[68]. They found it at a site between 400 and 800 nm from the tip of the dendrite (**Section 8.6.5.2**). This location is not compatible with synaptic action but is precisely the location expected according to the Electrolytic Theory of the Neuron developed here (**Section 8.3**).

8.2.1 The environment of the neuron

Although it is well established that the neurons of vision involve a variety of electrical signals, their classification for purposes of this work must be much more precise. Electrical signaling can be accomplished in a variety of environments:

+ the electromagnetic environment of free space,

+ the electro-metallic environment of vacuum tube electronics,

+ the electro-semi-metallic or solid-state environment of semiconductor electronics,

+ the electro-liquid (electrolytic) environment of aqueous electronics, such as batteries,

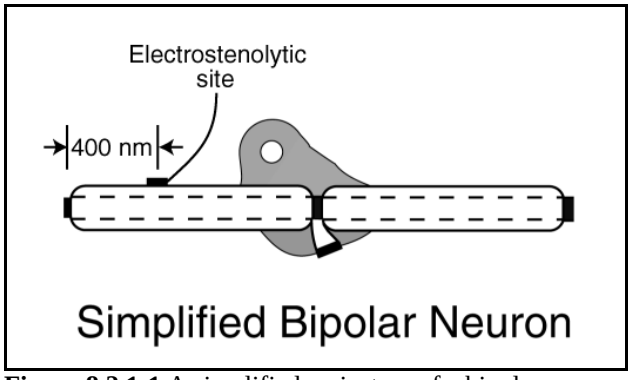

Figure 8.2.1-1 A simplified caricature of a bipolar neuron. The bulk of the plasmalemma consists of type 1 bilayer membrane. The solid black areas along the periphery of the cell are proposed regions of type 2 membrane material. The shaded area can accommodate type 3 membrane material. Type 3 membrane is optimized for transporting material through the membrane to the nucleus (white disk).

and as shown below,

+ the electro-semi-liquid or **liquid crystalline environment of the neuron**.

The neuron exists in and is controlled by the laws of electrolytic electrochemistry expanded to include the liquid crystalline state of the BLMs. Although various aspects of these fields have been studied and documented extensively, no work could be found that focused on the aspects of the science needed to support a clear understanding of the functional characteristics of the neuron. A brief summary of the necessary technology will be given in this section and

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[67]Duvoisin, R. Morgans, C. & Taylor, W. (2005) the mGluR6 receptors in the retina: analysis of a unique G-protein signaling pathway [on line journal, *Cell Sci Rev*] vol 2(2), pp 225-236

[68]Vardi, N. Duvoisin, R. Wu, G. & Sterling, P. (2000) Localization of mGluR6 to dendrites of ON bipolar cells in primate retina *J Comp Neurol* vol 423, pp 402-412

below.

Briefly, the neuron is an electrolytic system involving multiple electrolytes associated with a variety of liquid crystalline membranes (or more precisely regions of one or more liquid crystalline membranes). By creating structures within this electrolytic environment, the animal can create a signaling system that we call the nervous system. The system typically consists of a variety of neural types that are all electrolytically based. It will be shown, however, that a very simple underlying type of neuron can be easily expanded topologically to satisfy a wide range of requirements. In this work, this proto-neuron (neurogen) will be described initially as a fundamental cell leading to a fundamental neuron.

8.2.1.1 The nature of the electrolytes of the neuron

The general literature of cytology defines the material within the external cell wall of a neuron as (1) the *ground substance* or *cytoplasmic matrix*, and (2) the organelles and other inclusions suspended in it. This definition fits the cytoplasm within the soma of the simple cell. However, it is not sufficiently explicit to support additional internal membrane structures. The presence of the word ground will also cause problems where it conflicts with conventional electronic terminology. For purposes of this work, a more detailed and specific set of definitions is needed. First, the term ground substance will be dropped and the definition of the cytoplasmic matrix will be expanded. The cytoplasmic matrix will be redefined as including all of the plasmas, organelles, *internal cell membranes* and other inclusion within the plasma (or outer) cell membrane. The cytoplasmic matrix will be further divided into least four separate matrices;

+ the dendroplasm found within the dendrite(s), or input structure of the neuron, and separated from most of the soma by an internal membrane

+ the axoplasm found within the axon(s), or output structure of the neuron, and separated from most of the soma by an internal membrane. Several areas may be defined within the axon. These areas are isolated by their own lemma and contain their own axoplasm; i. e., the regions between the Nodes of Ranvier known as intra-axons.

+ the podaplasm found within the poda or third terminal area of the neuron. This podaplasm may be separated from most of the soma by an internal membrane.

+ the common cytoplasm found associated with the nucleus and other housekeeping structures of the neuron and restricted to the area of the soma not defined above.

Although the electron microscope has provided new details and allowed considerable discussion of the inclusions in the above plasmas, it has not provided information about the plasmas themselves. The literature in this area is based mainly on physical contact and chemical analysis with some tests involving optical techniques. The only area large enough to support most of these observations is the cytoplasm as defined above. The other plasmas are quite limited in volume and difficult to concentrate without contamination. It will be assumed that all these plasmas have the same bulk electrical properties and largely the same hydraulic properties.

Because of its importance in the overall function of a neuron, the interneuron matrix (INM) surrounding the neuron must also be referenced here. This material can also be considered a plasma based on its content. It is crucial to the operation of the neuron. It is also significantly different in composition from the other plasmas. Loewy & Siekevitz[69] provide some numbers in this area.

[69]Loewy, A. & Siekevitz, P. (1969) Cell structure and function. NY: Holt, Rinehart & Winston pp. 54-62

TABLE 8.2.1
Ionic concentrations in the Squid axon and the surrounding body fluid

	Concentration in milliequivalents per liter			
	K^+	Na^+	Cl^-	Organic anions
Squid axon (axoplasm)	400	50	40-100	345
Body fluid (interneuron plasma)	10	460	540	----
Sea water[70]	19.4	415	486	

The difference in concentration of sodium and potassium led Hodgkin and Huxley to assume (incorrectly) these materials must play a role in neural signaling. The differences between these ionic concentrations play an important part in the homeostasis of the neuron but no part in the signaling function.

8.2.1.2 The liquid crystalline materials of the neuron

Loewy & Siekevitz also provide a brief but readable summary of the nature of these plasmas. "The ground substance has the unusual property of being capable of both viscous flow like a liquid and of elastic deformation like a solid . . . Generally, the cytoplasmic matrix near the outer membrane, often referred to as the ectoplasm, tends to be more like a solid whereas the interior of the cell, or endoplasm, is generally in a more fluid state . . . Most workers agreed that although the ground substance appeared optically homogeneous in the light microscope, it must nevertheless contain a submicroscopic skeleton responsible for its elastic properties." These observations relate to the properties of what is now called a liquid crystal. These comments serve to focus attention in two areas:

+ the electrolytes of the neuron are not dilute solutions, they are highly concentrated solutions

+ the electronic state of the solvent, water, is quite complex--more so when combined in a matrix exhibiting liquid crystalline properties.

Usually, the electrolytes of the neuron are nematic liquid crystals while the plasma membrane is a smectic liquid crystal. This arrangement agrees with Wolken's model of a fundamental cell[71]. The endoplasm will be associated with the reticulum. The reticulum is a central region within a neurite or axon that is frequently identified using electron microscopy. Determining whether it is a separate membrane is difficult unless very high magnification techniques are used.

8.2.1.3 The molecular structure of the plasmalemma of the neuron EDIT

The membranes of a neuron are closely related to the membranes of any other type of cell. However, they do possess many specialized regions that are specific to neurons. It appears the most complex neurons are of the neuro-secretory type such as the photoreceptor cells. Many authors have presented simple definitions of a model membrane. As Houslay & Stanley have pointed out: "No single published model of membrane structure embodies all the features of a biological membrane[72]." These authors also discuss the state of experiments to reconstitute the "defined membrane ***functions***" using material mined from previously vital biological membranes. Their work was at an early stage in the 1980's.

With the availability of high resolution electron microscopy, the intricate internal structure of cells has become evident. This intricacy extends to the membranes forming the boundaries, both internal and external, of a cell. There are many types of physical junctions occurring between cell membranes. Many appear to be lap joints between two bilayer membranes. Historically, the axolemma of a cell has been defined from a morphological perspective as the outer plasma

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[70]interpolated values from Lehninger, A. (1970) Biochemistry. Worth Publishers, Inc. pp. 608-609

[71]Wolken, J. (1986) Light and life processes, photoreceptors and evolution. NY: Van Nostrand Reinhold. pg. 54

[72]Houslay, M. & Stanley, K. (1982) Dynamics of biological membranes. NY: John Wiley & Sons, pg. 9-26 & Chapter 5

membrane associated with that part of the cell between the cell body and the output structure of the cell. However, this definition may include other components within the axolemma that are not appropriate. This is particularly true for the Node of Ranvier. A more appropriate definition from a functional perspective would be that bilayer membrane of a cell enclosing the axonal reticulum of the cell. In this context, the primary definition of the axolemma is the outer wall of an electrolytic conduit between the Activa typically found within the soma and the Activa associated with the output terminal of the neuron or a Node of Ranvier. In the region of the Node of Ranvier particularly, there may be additional plasma membrane found externally to the axolemma and bridging the space between the two axolemmas. These portions of membrane are similar to the initial segment of the hillock of a pyramidal cell. The initial segment also encloses and is critical to the biasing of the Activa in the pyramid cell.

It is generally accepted that the morphological membranes of a cell are not uniform in composition over their length. However, this need not imply heterogeneous composition, only regions of different homogeneous material.
This theory does not support the view that there are inclusions within the membranes involved in neural processes or that these inclusions can actually penetrate the membrane without causing serious functional complications.

10.2.5.1 The molecular structure of a membrane

Goodsell has presented a beautiful stereographic caricature of a lipid bilayer at a scale of 10,000,000:1[73]. It models each atom of each molecule of the liquid crystal lipid making up each of the two bilayer. The two layers appear to be symmetrical. The result is a model exhibiting a well defined hydrophobic region between the layers but no effort was made to model the content of this region. Unfortunately, it is difficult to describe the variability in the structure of membranes in a single figure. Unsymmetrical membranes necessarily cause variability in this region.

All neural cells employ an external cell wall (not to be confused with the cellulose-based outer "cell wall" of plants) that can be described as a typical biological membrane. Such a typical membrane consists of two films of molecules separated by an extremely small space. It is frequently described as a three-layer structure. The two physical films are known as leaflets. Each layer consists of a liquid crystalline film of a phosphoglyceride. The hydrophobic ends of these molecules form one surface of each leaflet. The hydrophobic surfaces of the two leaflets are next to each other. The resulting membrane is hydrophilic but impervious to water. Its porosity to other materials may be highly specialized, depending on the specific phosphoglycerides involved. Although the two films appear identical under the electron microscope, a critical difference exists between the phosphatidyl groups. The difference may involve only one atom in each molecule.

The preparation of artificial bilayers of lipid material has been studied intensely by Mueller, et. al. Their methods allow the fabrication of asymmetric bilayers[74]. The data they collected on membranes formed in the absence of a hydrocarbon solvent is excellent. Unfortunately, they did not use PC or PE to form their bilayer membranes and produced thinner membranes than generally found in biological membranes. Siddiqi & Tien also discuss asymmetrical bilayers and provide a more explicit variant of the Montal & Mueller fabrication cell[75].

An asymmetrical biological membrane separating two different solutions may cause the solutions to exhibit a difference in potential. This potential difference is the foundation for the electrical operation of the neuron. By proper selection of the phosphoglycerides and solutes, different potentials can be obtained. By proper adjustment of the area of the membrane formed from a specific phosphoglyceride(s), the power handling capabilities of this source can be determined. If external test equipment is attached to the two solutions, the impedance of the configuration will be seen to be highly asymmetrical and therefore nonlinear. In fact, the impedance is that of a perfect diode at low currents. The

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[73]Goodsell, xxx (1993) in Rodieck 1998, pg 91

[74]Montal, M. & Mueller, P. (1972) Formation of bimolecular membranes from lipid monolayers and a study of their electrical properties *Proc Nat Acad Sci USA* vol. 69, pg 3561

[75]Siddiqi, F. & Tien, H. (1983) Electrochemistry of bilayer lipid membranes in Milazzo, G. ed, Topics in Bioelectrochemistry and Bioenergetics, vol. 5 NY: John Wiley & Sons pp 157-221

electrochemistry of such configurations is well understood[76] and is reviewed in Appendix B. However, little emphasis has been placed on the dynamic characteristics of these configurations. In addition, it has seldom been recognized that additional charge carrying mechanisms exist besides electrons and ions. The most important is the "hole" of conventional semiconductor physics.

The semiconductor properties of BLM configurations are poorly understood. **Figure 8.2.1-2** illustrates the fundamental situation. (a) shows the conventional electrochemical description of a single BLM immersed between two different solutions. (b) shows the same situation but with the BLM described at the molecular level.

(a) shows that no ions actually pass through the membrane. Instead, all reduction and oxidation occur at the respective surfaces with only charge actually passing through the BLM (shown by the horizontal lines). This charge is composed of two components, electrons and "+" charges or holes. The net charge transfer is the algebraic sum of these two components. The ratio between these two components is an important characteristic of a semiconductor. In BLM's of interest to neuroscience, the hole current dominates in one part of the membrane cross section and that material is described as "p" (positive) type material. The dominant current in another part of the cross section is dominated by electrons. It is described as "n" type material. The overall material is described as a "pn" junction and exhibits a perfect diode impedance characteristic under low charge flow conditions.

(b) shows how this "pn" type material operates at the molecular level. The BLM consists of two phosphoglycerides arranged in two liquid crystalline films and a region of hydronium liquid crystal material associated with the hydrophilic (outer) surfaces of each film. Oxidation or reduction occurs at the respective exterior surfaces. The charge generated within the BLM is then transported within the BLM in the valence band of the liquid crystals by holes. These are empty electron sites in the crystalline lattice that are continually filled by electrons jumping from a filled site to the empty site. It is tempting to think of the holes moving along the fatty acid chain of each molecule. However, this is a poor analogy. Each molecule occupies a lattice site in the liquid crystal. The charge appears to move from site to site, not from atom to atom.

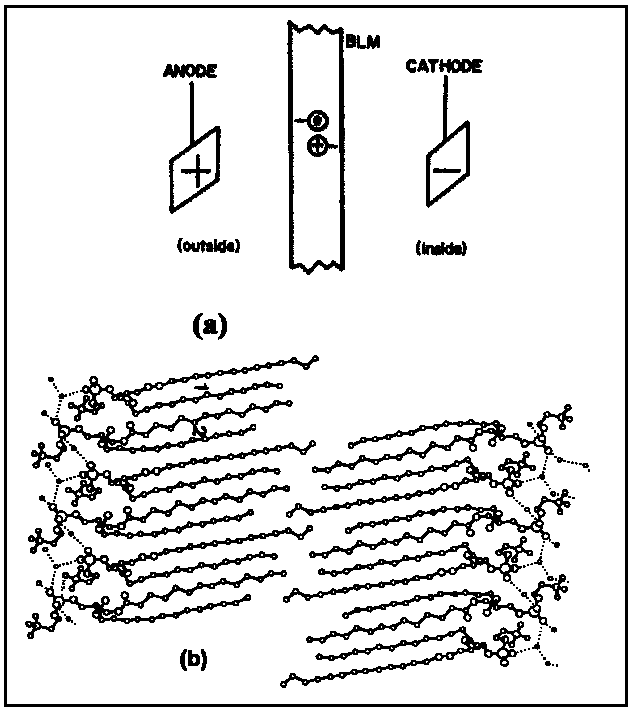

Figure 8.2.1-2 Bilayer lipid membrane configurations. (a) Conventional electrochemical model of a BLM separating two solutions. (b) Molecular level model of same BLM showing liquid crystalline structures.

The electrical properties of the asymmetrical bilayer membrane are becoming clearer. Xxx, writing in Yeagle[77], has discussed the interface between the hydrophobic components of the two molecular films in detail. He defines two major physical states. In the first, the two phospholipid films exhibit a clear bilayer midplane. In the second, the fatty acid chains of the phospholipids are of unequal length and interdigitation occurs between the two films. Three levels of interdigitation are defined. These levels of interdigitation probably account for the diode properties of the resultant membrane (See **Sections 8.2.4** & **8.3**). Further discussion of the chemical properties of these interdigitated membranes is found in Slater & Huang[78].

The electrical characteristic of this configuration is that of a perfect diode in series with a battery. The operating characteristics of the diode and of the battery are determined by the area of the ***active portion*** of the BLM. Although cell walls may appear uniform under the electron microscope, detailed study would show they have a very spotted

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[76]Tien, H. (1974) Bilayer lipid membranes. NY: Dekker

[77]XXX (1992) Lipid bilayer interdigitation *In* Yeagle, P. The Structure of Biological Membranes. Boca Raton, FL: CRC Press pp 175-180

[78]Slater, J. & Huang, C. (1988) xxx *Prog Lipid Res* vol. 27, pp 328+

appearance at the functional level--different regions providing different capabilities.

The BLM making up an exterior cell wall is oriented in such a way that the interior of the cell can sustain a negative potential, i.e., the diode associated with the BLM is reverse biased. This condition is obtained by having the "n " type material of the junction in contact with the fluid surrounding the cell.

8.2.2 Background of Electrolysis and the electronics of electrolytic chemistry

A basic premise, that no metallic conductors are found in the visual system, is probably not a surprise. However, its consequences may be a surprise. First, as any laboratory investigator knows, *a very large gulf exists between the electrolytic and the metallic worlds of electronics*; as typified by the unusual techniques used to interconnect these two worlds, salt bridges, glass electrodes, silver chloride contacts, etc. A similar situation exists between the solid state and the metallic worlds of electronics.

In this work, the field of electrolytic chemistry/physics will be divided into four main areas:

1. electrodics – the electrical interactions between metals and electrolytes
2. (unnamed) – the interactions between semiconductors and electrolytes
3. (unnamed) – the interaction between BLMs and electrolytes
4. electrolysis – the interaction of solutes and solvents with electrical currents
5. electrostenolytics – the reaction of solutes dissolved in electrolytes at the surface of a biological substrate.

The first three types of electrolytic chemistry involve interfaces responding to or generating external electrical potentials. The specific definition of electrodics from Bockris & Reddy is quite adequate. Electrodics is the study of processes that occur at the surface of an electronic conductor in contact with a liquid phase[79]. Their definition does not describe the interactions of the 2nd and 3rd type adequately. The fourth type does not actually involve non-electrolytes except in the implementation of a complete electrolytic cell. The fifth type does not involve any impressed external electrical potential although it may generate an external current. In the inorganic world, it is frequently associated with the rapid corrosion of metals in sea-water. [xxx edit paragraph]

Just as in the solid state world, the electrolytic world does not use free electrons moving along metallic wires.

> In solid state devices, metallic wires are only used for making convenient interconnections. These wires are passive.

Both semiconducting worlds employ charges of a more complex nature and *existing in two complementary forms*. In solid state electronics, the charges consist of electrons in the conduction band of a semiconducting crystal and "holes" in the valence band of the same crystal.

Electrolytics involves two distinctly separate situations. In the first situation, the ions in the solvent are free to physically move subject to the laws of diffusion and electrical fields. Here, the charges consist of negative and positively charged ions moving in a generally low physical and electrical impedance solvent. In the second, the ions are unable to move physically due to the liquid crystalline nature of the solution. Here, the movement of electrical charge is distinctly separate from the physical movement of individual charged atoms (ions). Protons do not move through the lattice of a liquid crystal. Only holes, the absence of a negative charge, move through a liquid crystalline lattice.

Water has many unique properties. It is clearly a semiconductor by the normal electrical definition; it is far more conducting than typical organics and far less conducting than solutions of inorganic salts.

A key feature of both the solid state and liquid state worlds is that the different charges in each of these worlds have different mobilities within their respective environments. This leads to concentration, and necessarily related potential, gradients within the medium. If these gradients are properly exploited, what is known as *"transistor action" can be achieved in an electrolytic medium* as well as in a solid state medium. The basic requirement for transistor action is that

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[79]Bockris, J. & Reddy, A. (1970) Modern Bioelectrochemistry. NY: Plenum Press

these gradients be manipulated under the force of an external electrical potential.

8.2.2.1 Classical membrane Electrolysis

> This section is provided primarily for background. It will be shown that most of the classical theories of diffusion (Nernst, Donnan, Goldman) do not apply to a membrane as complex as a BLM. They definitely do not apply to the combination of an electrostenolytic process, found on the surface of a neural membrane, and the membrane itself.

Many investigators have used the term semipermeable membrane without providing a precise definition. The new knowledge available calls for defining the term "semipermeable" more completely. It also calls for a review of the relevance of the Principle of Electrical Neutrality.

> The Principle of Electrical Neutrality is used in an entirely different sense in the electrolytics of a semipermeable membrane than it is in the electrostatics of a real BLM separating two electrolytes (See **Section 8.2.3.4**).

In Modern Physics, a semipermeable membrane may be semipermeable in terms of what species it will pass. It may also be semipermeable as to in which direction it will pass a species. This later characteristic is much more important for BLMs that are frequently asymmetrical at the molecular level. Such membranes are represented electrically by diodes.

Realizing there are membranes that are semipermeable to different classes of materials is important. Some are semipermeable to rocks, such as the screens used in a concrete manufacturing plant. Others are semipermeable to large molecules, to specific simple ions or to fundamental electrical charges. The field of neurology has suffered from a lack of precision in this area.

The basic electrochemical situation is illustrated in **Figure 8.2.2-1**. A Leyden jar is shown with a semipermeable membrane dividing a solvent into two compartments and containing an electrode in each compartment. The membrane is shown as a biological bilayer of phosphoglyceride materials. The individual phosphoglyceride layers may be uniform or made up of regions of different molecular composition. Similarly, the two layers may be of the same composition or they may be of different molecular composition. If the two layers are of the same material, the impedance between the two electrolytes will be symmetrical. If the two layers are of different material, the impedance may be asymmetrical (a diode).

For the simple case of the same electrolyte on both sides of the septum, identical electrode and electrolyte geometries, and the same type of electrodes, the entire cell is symmetrical except for the membrane. As a result, a voltage-current characteristic can be obtained that is representative of the membrane when measured in this geometry. However, there is no effective way to precisely separate the impedance of the test cell from that of the membrane.

Figure 8.2.2-2 shows a more complex configuration designed to isolate only the impedance of the membrane. It is called a Ussing chamber due to the work of Ussing

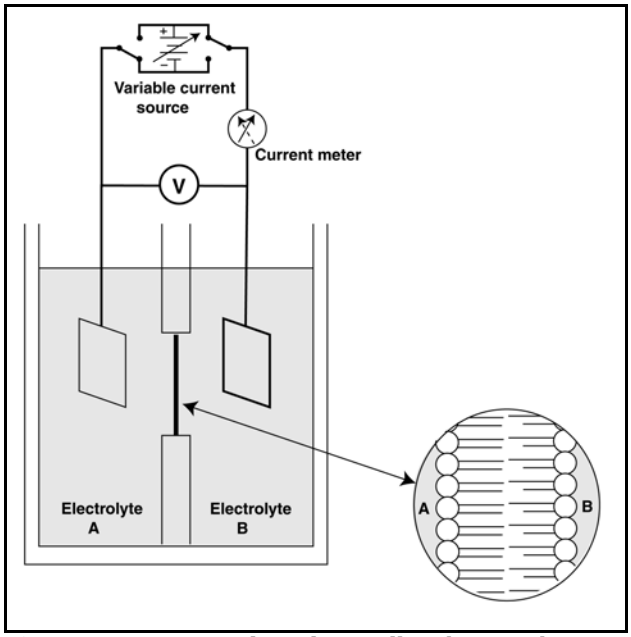

Figure 8.2.2-1 Basic electrolytic cell with a membrane in aperture separating two electrolytes. In blow-up, membrane is shown as a biological bilayer. Each layer is shown as a phosphoglyceride.

in the 1930-50's[80]. Note that it contains two sets of electrodes and frequently involves equipment for the continual oxygenation of the electrolytes. Ussing's work generally involved complex multiple layer membranes (skins) using artificial electrolytic conditions (same electrolytes on each side of a skin). Although not expressed in the caption, this configuration is susceptible to many errors if the two electrolytes are different and the correct procedures are not followed. His papers should be studied carefully (see next footnote) before adopting this configuration. The physical dimensions (sizes and positions of all of the elements) should be measured and recorded. The nature of the electrodes should be carefully chosen and their ½ cell potential recorded. Finally, the nominal conductivity of each electrolyte should be determined. Absent these precautions, the intrinsic potential of the membrane cannot be accounted for properly. Being able to change the location of the inner electrodes along the horizontal axis is also useful. This allows the more precise determination of the impedance of the bulk electrolytes. It also supports the detection of any charge density changes near the specimen, due to surface effects.

A more practical Ussing Chamber is presented in Ussing & Zerahn[81]. Their work involved skins rather than membranes. Their figure also highlights the greater complexity encountered if an oxidation or reduction reaction occurs near the surfaces of the membrane.

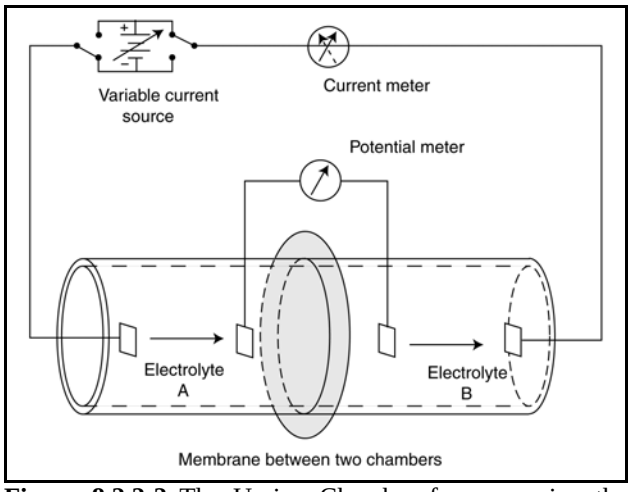

Figure 8.2.2-2 The Ussing Chamber for measuring the impedance of biological membranes. Note the reversible bias source. Neural membranes are typically not electrically symmetrical.

[80]Ussing, H. (1954) Ion transport across biological membranes. *In* Clarke, H. & Nachmansohn, D. *eds*., Ion transport across membranes. NY: Academic Press

[81]Ussing, H. & Zerahn, K. (1951) Active transport of sodium as the source of electric current in the short-circuited isolated frog skin *Acta Physiol Scand* vol. 23, pp 110-127 *Also in* figure 1-9 of Armstrong, W. writing in Selkurt, E. *Ed*. Physiology, 3rd ed. Boston, MA: Little Brown

Figure 8.2.2-3 illustrates the value of the Ussing cell over the Leyden Jar when evaluating BLMs. Note the small amplitude of the voltages associated with the forward biased BLM compared with the other voltages. Often the potentials associated with the anodic and cathodic terminals are larger than the total potential across the membrane. The potentials associated with the two electrolytes are also larger than the total membrane potential. The potentials associated with the terminals are usually not straight lines because of the boundary layers found between materials of different states. Using the Leyden Jar approach, only the average impedance of the entire cell can be found directly. By using the auxiliary probes of the Ussing apparatus in an open loop configuration, the potential between two locations within the electrolyte can be determined while current is flowing through the overall cell. By physically moving these probes and using a little algebra, the impedance per unit distance of the electrolytes can be measured and the absolute membrane potential and impedance can be calculated with precision. This potential plot also provides the background for understanding and partitioning the data of Eliasof presented in **Section 8.3.2.1.2.** Note how this figure can be used to separate the various concepts of electrolytic chemistry listed above. Electrodic chemistry is found near the two metallic terminals while the electrolytic chemistry of membranes in solution is found near the center of the cell. If a metabolic material reacts on the surface of the membrane, it also occurs in an environment distinctly separate from the electrodic environment.

Limiting the discussion to water as the solvent, two interesting cases are found, that of the solvent by itself and that of a solvent with a dissolved solute. In the first case, the water will ionize slightly. Two charged species will be formed, the hydroxyl ion and the proton (normally hydrated and called the hydronium ion). Because of the semipermeable character of the membrane, these ions will be partly separated resulting in a potential difference between the two sides of the membrane. This potential can be measured via the electrodes. It should be noted that the mobilities of the two ions within the solvent are not equal.

It should also be noted that there is no requirement that hydroxyl ions actually pass through the membrane. A three-step process involving the transfer of a "hole" through the membrane will create the desired hydroxyl ion on one side and a hydronium ion on the other side of the membrane.

If an additional solute that is highly ionized is added to the solvent, the situation changes in two ways. First, the potential difference between the two compartments takes on a character indicative of the separation of the two ions of the more highly ionized solute. Second, the cell can sustain a much larger current through an external circuit, such as the voltmeter.

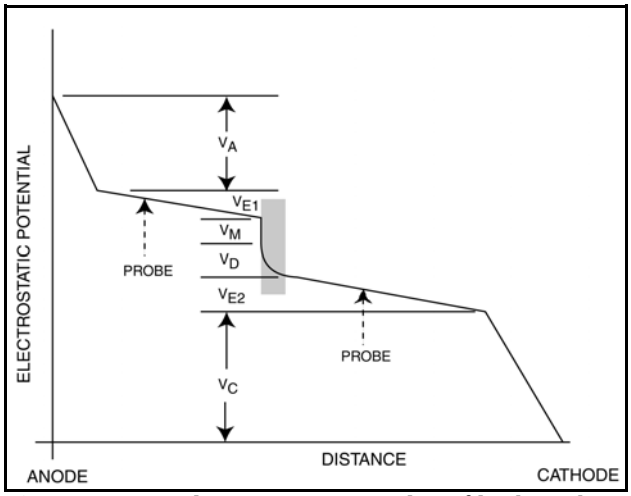

Figure 8.2.2-3 Electrostatic potential profile through an electrolytic cell. V_A, voltage across the Helmholtz layer near the anode terminal. V_{E1}, the potential drop across the bulk of the anodic electrolyte. V_C, voltage across the Helmholtz layer near the cathode. V_{E2}, the potential drop across the bulk of the cathodic electrolyte. V_D, the voltage across the diode of the membrane. V_M, the intrinsic membrane potential. The area of primary interest is shaded.

The names of three investigators appear repeatedly in the literature of osmotic diffusion in the presence of an electrical potential, Nernst (1890's), Donnan (1900's) and Goldman (1940's). Each addressed a more complex situation than his predecessor. Nernst only addressed the open circuit or zero current situation due to a single ion-pair in the electrolyte. Donnan addressed the equilibrium condition for two ion-pairs and Goldman provided the general solution for any number of simple well-behaved ions. All these mathematical solutions for the equilibrium condition were based on an electrically symmetrical membrane that resulted in a constant potential field gradient within the membrane. They also applied to dilute solutions of electrolytes. These conditions are not compatible with biological membranes supporting the neural signaling process. Starzak dedicates considerable space to developing each of these equations and discussing their limitations[82]. Matthews reviewed the applicability of the work of each of the above investigators in a briefer format at an introductory level[83].

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[82]Starzak, M. (1984) The physical chemistry of membranes. NY: Academic Press. pp. 44-83 & 218-223

[83]Matthews, G. (1991) Cellular physiology of nerve and muscle. Boston, MA: Blackwell Scientific Publications, pp. 27-50

8.2.2.1.1 Previous application of classical membrane theory to the neuron

Ling, writing in Gutmann & Keyzer, reviewed in detail the subject of colloidal chemistry as it applies to bioelectrochemistry[84]. He describes the development of the lipoidal membrane theory based on totally hydrophobic thin films. He also develops the chronology of the work of Hodgkin & Huxley in electrolytics of membranes. A major step in their work was the modification of the Hodgkin-Huxley variant of the Goldman equation by Hodgkin & Huxley themselves. This ionic theory of cell potentials originally called for the permeability of the membranes they studied to chlorine ions. In their modification, the permeability of chlorine was omitted in order to more adequately match their data. However, dropping this factor without any theoretical justification has been criticized. Their modified equation led to the development of their "independence principle" regarding the movement of ions through a cell membrane. They assumed the membrane was a homogeneous isotropic medium and that no other ions were present. That treatment required unique gates in the membrane for the passage of each ion type.

8.2.2.1.2 The demise of ionic transport through biological membranes

Habib & Bockris, writing on page 72 in Gutmann & Keyzer, stress that although examples of compliance with the Nernst-Planck equation certainly exist in the laboratory, they are rare. That equation and the subsequent Goldman and Hodgkin-Huxley equations are not consistent with most of the data concerning the BLM. Cole said in 1968: "Since Goldman, there have been extensive developments of the electrodiffusion theory that are almost entirely without an anchor in experiments on artificial or living membranes[85]." This situation appears to remain true today. [xxx provide more from appendix] Anderson & Fuchs have provided a particularly relevant paper[86]. They discuss the necessary changes to the Nernst-Planck model needed to represent a lipid bilayer. They also show that little or no ionic permeability exists on a steady state basis. There finding that the smaller the ion the less likely its permeability through a lipid bilayer is particularly interesting (page 797). This finding may suggest how large molecules can be transported across a type 3 biological membrane while the membrane remains largely impervious to small ions. Their potential barrier calculations are compatible with others. Gavach & Sandeaux also explored artificial bilayer membranes and provided an interesting quotation[87]. The small values for the membrane resistance obtained with hydrophobic ions, as compared to those where inorganic ions are present in the aqueous solutions indicate that only the former ions can penetrate into the membrane. This fact is corroborated by the sign of the Nernstian transmembrane potential under zero current conditions." In summary, since the intense work of the 1970's, it has been clear that biological bilayer membranes show negligible permeability to ions of sodium or potassium, even under pathological conditions.

Ling also addressed the subject of ion-pumps as they relate to the BLM. He did this because of the considerable confusion over the laboratory results related to this putative phenomena obtained during the 1980's. He provides some brief remarks on pages 49-62 of Gutmann & Keyzer and a thorough exposition in his own monograph.[88] He shows that the ion-pump is far from an accepted and verified solution to the ionic equilibrium problem of biological cells. Unfortunately on page 62 of Gutmann & Keyzer, he repeats the mantra that the action potential is the result of two sequential events. The first is an inward surge of positive charge of Na^+ into the cell. The second is a similar rush of K^+ ions out of the same cell in the presence of the same external potential fields but through separate "gates." Habib & Bockris address the subject of the chicken and the egg on page 75 concerning the ion-pump. Relying on their interpretation of electrodics, they suggest another view. The concentration of alkali metal ions on the two sides of a membrane may be the result of the electrical potential across a membrane rather than the cause of that potential. ***This***

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[84]Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press. pp 45-49

[85]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press pg 200

[86]Anderson, O. & Fuchs, M. (1975) Potential energy barriers to ion transport within lipid bilayers. *Biophysic J* vol. 15, pp 795-829

[87]Gavach, C. & Sandeaux, R. (1975) Non-mediated zero voltage conductance of hydrophobic ions through bilayer lipid memberanes *Biochim Biophys Acta* vol. 413, pp 33-44

[88]Ling, G. (1984) In search of the physical basis of life. NY: Plenum Press

is a profound difference of view from the conventional wisdom. They further suggest the initial potential may be due to anodic or cathodic processes that are "(different for membranes of varying function)."

Recently, Finkelstein crossed the intellectual bridge by emphatically and publicly noting the virtual impermeability of lipid bilayer membranes to small ions such as Na^+, K^+ and Cl^-.[89] However, he did not address the subject of the asymmetrical bilayer as a semiconductor. Wanting to accept the transport of ions through a membrane, he assigned this capability to proteinaceous pathways inserted into and through the membrane. In this position, he appears to be supporting the complex caricature of a BLM presented by Mackowski[90]. This caricature does not assign any quantum-mechanical properties to the membrane. Such gate structures are not seen at the molecular level in electron micrographs (or from x-ray scatter analyses) of conduit membranes.

In summary, most of the neuroscience literature presents a picture of a fundamental BLM that is permeable to the ions of sodium and potassium, and generally chlorine, in spite of significant data to the contrary. The literature also assumes the membrane is an electrically symmetrical material with a uniform potential field gradient within it when subjected to an electrical bias. The most recent comprehensive books discussing the electrolysis of BLMs do not go beyond these two assumptions[91,92]. Possibly for pedagogical reasons, Habib & Bockris also stop with the consideration of paired redox reactions on the opposite sides of an undefined membrane. That membrane is apparently symmetrically conductive to electrons and/or holes. An alternate approach, involving a single redox reaction on one surface of an electrically asymmetrical membrane, was not addressed.

8.2.2.2 The test configuration problem

The biological neuron operates at a very high impedance level compared with most man-made circuitry. This makes interfacing the test set with the neuron challenging. The impedance level led to several difficulties in the (vacuum tube-based) test set of Hodgkin & Huxley. Later figures have appeared in the literature that represent the characteristics of the test set only. No feature of the figure can be assigned to the specimen under test. The primary problem is the high capacitance (low impedance) of the probe compared with the impedance of the neural circuit under test. Furthermore, interfacing the neuron to a test set involves making electrical contact between the metallic and electrolytic domains of electronics. This is a well-known area of difficulty. Considerable experience in circuit design is needed to insure reliable results.

8.2.2.2.1 The electrode problem

In interfacing a neuron to a test set, a problem arises just as it does in solid state electronics. The transition at the electrodes of a free electron in a metallic conductor to or from an ionized particle (in solution or the solid state) is frequently a difficult one. In solid state physics, it resulted in the development of a sub-discipline focused on achieving ohmic contact to semiconductors. The same situation exists in electro-physiology. Release of an electron by a negative ion frequently results in the formation of an un-ionized atom of a gas that tends to escape from the Leyden jar. Similarly, the injection of an electron into the fluid in the jar frequently results in the release of a unionized atom of a gas at that electrode. In biology, the release of these gases is very detrimental to cell integrity. Hence, a sub-discipline has emerged that is concerned with biologically acceptable electrodes[93].

Fortunately, no metallic circuits are found within a biological organism. These transitions from ionized carriers to free electrons within a metallic conductor do not occur. It is only in the laboratory that this problem arises. In the animal, multiple containers can be formed with membranes between them and the various carriers can travel from one region to another without this conflict.

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[89]Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. Volume 4 of the Distinguished Lecture Series of the Society of General Physiologists. NY: John Wiley & Sons. Chapter 6.

[90]Mackowski, L. Casper, L. Phillips, W. & Goodenough, D. (1977) Gap junction structure II: Analysis of x-ray diffraction data *J. Cell Biol*. vol. 74, pp 629-645

[91]Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press.

[92]Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker

[93]Starzak, M. (1984) The Physical Chemistry of Membranes. NY: Academic Press pp. 91-97

The equivalent impedance of the transition between a metallic electrode and an electrolyte is also quite complex. It frequently involves a potential source due to quantum-mechanical processes. This source is frequently overlooked when exploratory results are presented describing the potential of a plasma as a function of time.

8.2.2.3 A common pedagogical figure

Figure 8.2.2-4 is presented to orient the reader. It will be discussed in an entirely different context than in the past. In principle, it does not apply to the electrolytics of a membrane for two reasons. First, BLMs are not linear impedances to the flow of either electrons or ions. Second, no significant channels exist in a typical bilayer BLM to support physical transport of ions in an electrolytic environment.

The top left frame of the figure repeats a frequently used caricature. It shows the concentration gradient between the two compartments of the Leyden jar with a homogeneous non-crystalline semipermeable hydrophilic membrane in the aperture. Both the concentration and electrical potential gradients are shown as fixed within the membrane. The dashed lines passing through the membrane need not be straight lines. However, if they are, the configuration is susceptible to analyses by one or more of the constant field gradient theories of electrolytic physics (Nernst, Donnan or Goldman).

The BLM is not homogeneous at the molecular level and this fact has significant quantum-mechanical consequences as discussed in the next paragraph. Although externally hydrophilic, the membrane has a lipophilic core. Because of this feature, most of the BLM is impermeable to most ions that dissociate when dissolved in water. The detailed discussion of the regions of a BLM will begin in **Section 8.2.3.5**.

The top right frame shows the situation for a typical asymmetrical phospholipid bilayer membrane. An important difference exists, however, regarding the concentration gradient. Two distinct situations must be addressed. The ionic concentration gradient of a BLM between two electrolytes is discontinuous and undefined within the membrane. On the other hand, the concentration gradient of the fundamental charges within the membrane is continuous but not generally a straight line. The intrinsic potential with a molecularly asymmetrical BLM is shown. It is shown without a potential across the cell and in the presence of an external electrical bias. In both cases, the potential gradient is not constant within the cell. This situation is not amenable to the constant potential (gradient) theories of electrolytic physics.

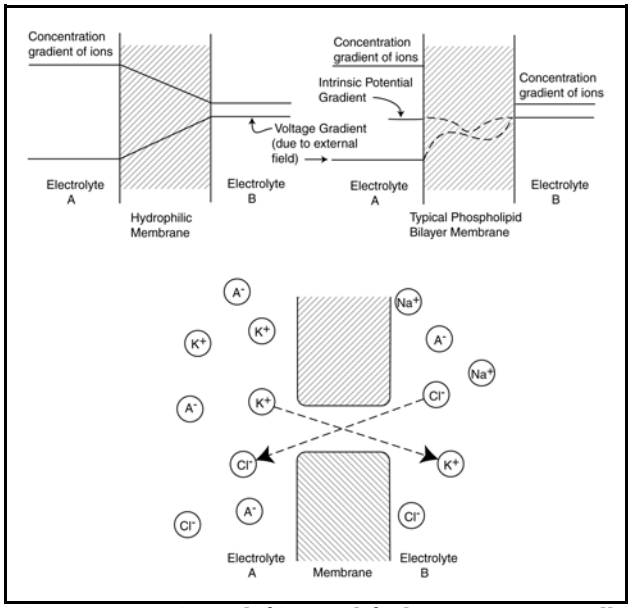

Figure 8.2.2-4 (Top, left) Simplified caricature typically used to suggest the concentration and voltage gradient across a hydrophilic membrane. (Top right) More appropriate caricature of an asymmetrical phospholipid bilayer membrane. There is no concentration gradient for ions within the membrane. (Bottom) A simplification of the top left frame frequently used for pedagogical purposes. The caricature suggests the existence of physical channels through the membrane. It **does not apply** to fundamental neural membranes such as at the top right.

Many authors have used a figure like that at the bottom of the figure to represent a BLM separating two electrolytes. Whereas, this caricature may apply to many non-BLMs and may apply to some BLMs related to metabolism, it does not apply to membranes involved in neural signaling. Most recent investigators have found that free ions cannot pass through the BLM. The process should only be represented this way for introductory pedagogical purposes. The following discussion will make the following crucial point. Signaling does not require physical holes in the membrane large enough to pass ions.

Most BLMs, and particularly neural membranes, consist of a liquid crystalline structure consisting of a two-dimensional

linear molecular array. The structural and electrical integrity of the membrane calls for it to be free of voids. To maintain this integrity while allowing ions to flow through on a temporally non-uniform basis, many authors have proposed the adoption of a complex gate structure at the molecular level.

A liquid crystalline molecular array may be conductive to both electrons and "holes" but not the physically larger ions.

8.2.2.4 Electrostenolytics

As its name implies, electrostenolytics is the study of catalytic electronic processes occurring on a surface in an electrolytic environment. The field is relatively narrow in its application to man-made systems and its literature is therefore immature. Fuel cells are the dominant man-made application at this time. The process involves a redox reaction and can involve the transfer of fundamental charges to or from the substrate. Electrostenolytics also has a commercial application in the technique of electrodeless electroplating. The result of the process is also of interest in diagnosis of pathological conditions of the retina (See **Chapter 18**).

Whereas caricatures of the process frequently show external electrodes contacting two electrolytes separated by a substrate[94], this is not the simplest form of electrostenolysis. In its simplest form, no external electrical circuit is required and only one electrolyte is involved. The process frequently involves only a local electrolytic current loop similar to that employed in the rusting of metal in sea water. The "classical form" of electrostenolytics defined by Tien, Karvaly & Shieh is based on descriptions dating from the 1860's and represents a much more complex set of reactions[95]. These reactions involve both currents through the electrolytic cell and redox reactions at the membrane surfaces. Habib & Bockris provide a more comprehensive discussion of the process, including the static condition where no current flows through an external circuit[96]. They also make comparisons to the field of electrolytics involving fuel cells. Their discussion and figure 5 also show that only one redox process needs to be present at a time. Siddiqi & Tien readdressed the subject of electrostenolysis in 1983 and provide references[97].

When the process produces free atoms at one surface of the substrate, these materials may be deposited on the surface depending on their solubility in the electrolyte. Discolored or mirrored surfaces may be formed depending on the surface texture of the substrate.

The electrostenolytic process is critical to the operation of the neural signaling system. It converts chemical energy into electrical energy in the form of an electrical potential across a membrane. The chemical reaction involves the conversion of glutamic acid (glutamate) into GABA with the release of CO_2 and an electron. This electron appears on the inner surface of the neurolemma. There, it generates a potential in conjunction with the capacitance of the lemma. The electrostenolytic process is detailed in **Section 8.6**.

The electrostenolytic process is well recognized in the studies of metabolism. However, it is normally described using a different terminology specific to that field. Berry, honoring the 80th birthday of the patriarch of that field, Sir Hans Krebs, has provided an extensive article that includes most of the elements of electrostenolytics found associated with the neural system[98]. In that context, they describe the redox reactions on a membrane surface as causing the transfer of electrons across the membrane. The transfer occurs in opposition to a previously present electrostatic potential. They describe this process as "reverse electron transfer" and treat it as a unique situation instead of recognizing that it is the normal situation in any electromotive source. The fact is that the metabolites are acting as a battery in generating the electrostatic potential from the flow of electrons. They also note the reversibility of the reaction by discussing redox cycles. The reversibility is limited by the tendency of the glutamate and CO_2 to diffuse away from the site.

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[94]Tien, H. (1974) Bilayer lipid membranes. (*also in* Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker, Chap 7 written by Zon & Tien, pg 191)

[95]Tien, H. Karvaly, B. & Shieh, P. (1977) Electrostenolytics in bilayer lipid membranes. J. Coll. Inter. Sci. vol. 62, no. 1, pp. 185-188

[96]Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press. pp. 73-89

[97]Siddiqi, F. & Tien, H. (1983) Electrochemistry of bilayer lipid membranes in Milazzo, G. ed, Topics in Bioelectrochemistry and Bioenergetics, vol. 5 NY: John Wiley & Sons pp 157-221

[98]Berry, M. (1980) The function of energy-dependent redox reactions in cell metabolism. FEBS Letters, vol. 117, supplement, pp. K106-K119

When all is said, Berry offers an important statement: “It is concluded that energy-dependent reversed electron transfer is a fundamental feature of the living state. It provides a mechanism for the reversal of thermodynamically unfavorable redox reactions by energy coupled steps, distinct from the forward reactions.” Paraphrasing, he continues, these redox reactions maintain the cell in a state removed from chemical equilibrium and helps support a balance between degradative and synthetic processes. Finally, “It would appear that living systems can conserve energy derived from degradation of foodstuffs, not only by synthesizing new chemical bonds, but also by storing separated charge. The energy conserved in the electric field so created can be used to drive . . . reversed electron transfer . . . This interaction of chemical and electrical energy within the cell makes living systems highly efficient units operating close to equilibrium.”

8.2.2.4.1 Methods of establishing a potential across a membrane

The biological community settled on the transfer of ions through the cell membrane, as a method of polarizing a neuron, based primarily on the work of Hodgkin & Huxley. These early authors were initially seeking an explanation for their results, not proposing a new mechanism. However, they were forced to adopt several new (and speculative) concepts. Unfortunately, they did not consider all of the possible methods of polarizing a cell, only the ones they were familiar with from their training. The beginning of the semiconductor revolution occurred at that very time. It would have been fortunate if they had looked into other fields for additional potential solutions to their dilemma.

Ohki has said; “Until recently the possibility of electron conduction in living systems was not seriously considered, with perhaps a few notable exceptions to be mentioned below. Traditionally, the origin of electrical potentials observed in liviing systems has been attributed almost exclusively to ionic permeability.” He goes on to discuss the electron transfer now assumed in photosynthesis[99].

Applying the laws of both electrostatics and electrodynamics carefully to the biological plasmalemma is important. It exists in several optimized regions that may operate differently. Hodgkin & Huxley did not differentiate between the potential types of plasmalemma. Their concept is not compatible with either type 1 (symmetrical) or type 2 (asymmetrical) membrane. Whatever its type, each region of a membrane exhibits an electrical capacitance. This capacitance is defined by the potential produced across the membrane per unit of (net) charge deposited on one side of a unit area of the membrane. For asymmetrical (type 2) membranes, the measured capacitance may be a strong function of the polarity and magnitude of the applied potential.

For a closed membrane, several potential sources of the above charge exist. First, individual electrons may cross the membrane and create a net charge imbalance. Second, at least theoretically, heavy ions can cross the membrane and create a net charge imbalance.

Note that a net electrical charge cannot exist within the volume of a closed membrane. The laws of electrostatics say that all of the individual charges will repel each other. This will cause all of the net charge to be deposited on the wall of the membrane. The plasma within the membrane will remain neutral under any steady state conditions. Similarly, the net charge on the plasma outside the membrane will accumulate on the surface of the membrane. The bulk of the surrounding plasma must remain electrically neutral.

At least two methods exist to move electrons across a BLM. The first involves the transfer of electrons through the membrane by conventional chemical processes. The study of the movement of electrons across a BLM by chemical means is known as electrostenolytics. While not well known in the biological community, it is well documented and understood in the organic chemistry community. The second method of transfer involves the movement of electrons into (or out of) a closed membrane by “transistor action.” Organic chemists have been attempting to achieve this type of transfer for at least the last 25 years. However, they have needed an invention. The Activa is the embodiment of the invention they have sought. It will be shown that the operation of a neuron depends on the transfer of electrons through a BLM by two separate methods, electrostenolytics and transistor action.

To be complete, another form of electron motion can exist within a crystalline (or semi-crystalline)

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[99]Ohki, S. (1985) The origin of electrical potential in biological systems *in* Srinivasan, S. et. al. Comprehensive Treatise of Electrochemistry, vol. 10, Bioelectrochemistry. NY: Plenum Press pg 83+

material like a membrane. It involves the motion of voids in the electronic states associated with individual atoms in the crystalline lattice. Only a minuscule number of voids are required to support a significant current. If a void (known technically as a hole) occurs, it represents a positive equivalent charge at that location. An electron can jump from a nearby atom to the location of the hole. It thereby neutralizes that hole but creates a new void at its previous location. This action will occur randomly within the lattice unless a potential exists across the membrane. In that case, the electric field within the membrane will influence the motion of electrons. The result will be the apparent flow of holes from the positive to the negative surface of the membrane. In many semiconductors, the hole current is the dominant form of charge transport.

The process of electrostenolysis can cause a potential between two electrolytes. It does this by depositing an electron onto the p-type surface of an asymmetrical BLM.

The study of the movement of ions across a BLM is more complex than the study of electron movement. While extensive studies of the movement of ions through various non-biological (and generally non-polarized) membranes have been well documented, substantive reports of the transfer of ions across a uniform BLM are rare. The hydrophobic core of such membranes essentially prohibit the transfer of water soluble ions across a BLM. To get around this problem, the literature frequently introduces other putative mechanisms. It speaks of the movement of ions across a BLM through "gates" or enclosed in specialized mobile vesicles. The gates are conceived of as channels in a membrane that are able to selectively isolate and allow ions to pass through a membrane. Similarly, many authors have suggested that vesicles can isolate a net charge (as ions of like charge) and move that charge across a heterogeneous membrane while enclosed in such a vesicle. Collectively, these gates and vesicles have been described under the label ion-pumps. To overcome the laws of electrostatics, these ion-pumps require a source of energy. To date, no such source of energy has been documented in the literature. Only various hypotheses based on chemical kinetics have appeared.

Note that the movement of non-ionized material (or a quantity of ionized materials with a net charge of zero) across a membrane requires much less energy. It only requires the energy needed to open and close the putative gate in the membrane or move the putative vesicle through the membrane. The existence of a transport mechanism for purposes of metabolism and cytogenesis is not disputed. Stein has recently discussed the kinetics of such a transport mechanism in the context of metabolism[100]. He notes the number of conflicts in the literature (page 25) and then makes a comment. "It is thermodynamics that determines whether or not pumping will occur, not kinetics." Note that chemical kinetics is a global technique. It cannot be used to determine the specific constituents of a reaction from among a large ensemble. Other techniques must be used to identify the actual materials involved in a reaction. Stein develops the possibility that the ions are transferred in an "occluded state." His analysis also suggests it may only be protons (rather than heavy ions) that move across the membrane barrier (page 32). If the quantum-mechanical concept of "holes" is adopted, the transport of a proton is replaced with the transport of a hole. The effective transport of a hole is actually due to the physical movement of electrons in the opposite direction.

Hodgkin & Huxley did not demonstrate the movement of any ions (sodium or potassium) across the axolemma of the squid giant axon. The amounts of charge required to polarize a typical neuron plasma is far below the minimum number of ions (less than a micro-micro-micro mole) currently measurable by man. No reports have been found that claim to have measured a quantity of ions of this size moving through a BLM. **Section 8.6** describes in detail the movement of electrons across the neural membrane due to the electrostenolysis of glutamic acid (glutamate) into GABA.

8.2.3 Characterizing the electrolytic environment of a biological membrane

A more precise understanding of the mechanisms at work at a neural membrane-electrolyte interface is needed. No significant experimental activity related to a BLM separating two electrolytes has occurred since the efforts of Goodman in the 1950's. Stein prepared a book in 1967 that provides some excellent data on synthetic biological membranes[101]. Adelman edited an extensive review in 1971designed for pedagogy[102]. Finkelstein, writing for a general audience within

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[100]Stein, W. (1991) Carrier kinetics show how the sodium pump uses ATP to render pumping of both sodium and potassium effective. . . . *In* Yudilevich, D. et. al. *ed*. Cell Membrane Transport: Experimental Approaches and Methodologies. NY: Plenum Press. Chapter 2

[101]Stein, W. (1976) Op. Cit. Chapter 1

[102]Adelman, W. (1971) Biophysics and Physiology of Excitabel Membranes. NY: Van Nostrand Reinhold

his discipline, oversimplified the mechanisms involved[103]. His assertion that by squeezing a hydrocarbon film down to a thickness of 50 Angstrom, the permeability properties of a lipid bilayer would be emulated appears simplistic. It overlooks the quantum-mechanical facts related to such a thin lipid bilayer. He noted a reluctance by the community to accept his assertion. This is particularly true with respect to his assertion that "ordinary" olive oil has the same permeability characteristics as a plasma membrane. It does not! To circumvent this fact, he then fell back on the idea that significant proteinaceous intrusions into the integrity of the bilayer lipid accounted for its actual properties. Finkelstein & Cass, writing in the above volume, showed that their reconstituted bilayer membranes did not contain pores suitable for transporting water molecules.

This work will review the situation related to BLMs from three perspectives. The first will review the new knowledge available concerning the molecular nature of these membranes. The second will examine the quantum-mechanical conditions associated with the structure of the membranes. The third will examine the boundary layers associated with the interface between a membrane and electrolytes of significantly different molecular structure. These are frequently called Helmholtz layers or the double layer in electrochemistry (see **Section 10.1.3**).

This discussion will be limited to simple BLMs as opposed to complex structures such as skins. Skins, such as those of humans and the experimentally popular frogs, contain a variety of macromolecular structural features not found in neural membranes and not relevant to this work. In this work, the primary interest is in BLMs that consist of two bilayers that are semipermeable to electrons and holes due to their asymmetry at the molecular level.

From this time forward, a neural membrane cannot be considered from a global perspective. It must be recognized that it consists of multiple specialized regions. The properties of these regions must be addressed individually.

Before proceeding, it is important to review the comprehensive texts of Starzak[104] and of Eckert[105] in the light of the previous material in **Section 8.2.** Unfortunately, Starzak frequently falls into the situation described in the second paragraph of **Section 8.1.** His work must be read *in-toto* because he frequently changes position as the subject is presented in more detail (compare his figures 5.19 and 8.1). These problems are undoubtedly related to his focus on pedagogy. The details of his work will be discussed in more detail in [**Section 10.10.4.2.** Xxx] He presents many figures which relate to the phenomenon of "transistor action." However he, like many others, did not have the background to recognize the presence of an Activa. Eckert discusses many aspects of permeability and transport. However, it is not always easy for the reader to decide what material applies to simple membranes and what applies to more complex multiple cell structures such as skins. His comments on pages 67-71 are particularly relevant to the following discussion of simple bilayer membranes. Subsequently, he discusses more complex membranes that he labels fluid mosaic models and finally multiple cellular membranes (labeled here as skins). The potential methods of ion transport through these more complex structures are addressed on page 80.

When discussing neural signaling, beginning with the discussion of fundamental BLMs is important. Introducing the more complicated areas of fluid mosaic models and skins should be avoided. The transition into these areas should only be undertaken explicitly and when appropriate. For purposes of this work, the fluid mosaic model is a type 3 membrane. It will only be associated with the genesis and metastasis of individual cells. These are long term processes and do not involve time scales related to neural signaling.

Limiting the discussion to fundamental BLMs still leaves a large arena to cover. As earlier, morphology can help up to a point. Beyond that point, biochemistry and molecular topology become important disciplines. These are followed by the very important discipline of electrolytic chemistry. The morphologist is generally limited to structures larger than one micron by light microscopy. In neurobiology, the more important characteristics are at the molecular level.

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[103]Finkelstein, A. (1987) Water movement through lipid bilayers, pores, and plasma membranes. NY: John Wiley & Sons. pg 94.

[104]Starzak, M. (1984) The physical chemistry of membranes. NY: Academic Press

[105]Eckert, R. (1988) Animal Physiology. 3rd ed. NY: W. H. Freeman Chapter 4.

8.2.3.1 The molecular constituents of biological membranes

The fundamental BLM consists of two liquid crystalline layers of phospholipid material arranged with their hydrophobic (non-polar) surfaces next to each other. Their precise liquid crystalline geometry is described by the smectic phase[106]. The resulting sandwich is less than 100 Angstrom thick. The precise definition of the boundaries of the individual layers becomes difficult in this quantum-mechanical size range. The chemical constituents of the membrane are typically multiple regions formed by different members of the phosphatidyl ethanolamine (PE) family in one bilayer and a member of the phosphatidyl choline (PC) family in the other layer.

Historically, PE was known as Cephalin and PC was known as Lecithin. However, as suggested above, and stressed by Chapman, PE and PC are not complete chemical names, they are family names[107]. Both PE and PC exist in a variety of species depending on the exact fatty acids incorporated at each of the two positions in the nonpolar tail[108]. **Figure 8.2.3-1** shows their basic polar structure. A similar figure tailored for spectroscopic studies appears on page 310 of Yeagle. A figure by Finean in Stein highlights the problem in displaying these materials[109]. Every author's version is stereometrically different.

> **As pointed out by Lehninger**[110] and illustrated by Stryer[111], these molecules are so complex that they are usually shown in a standardized form in which all the fatty acids are shown as palmitic acid for convenience. This obscures several points of significance here:
>
> + PE and PC are large families containing many species,
> + The two fatty acid components need not be the same,
> + The fatty acid in the 2-position is usually unsaturated,
> + The fatty acids may be in isomeric forms other than all-*trans*.
> + As many as 100 different members of the PE and PC family may be present in a single membrane, probably congregating in different regions.
>
> These materials can have different physical lengths (affecting their dielectric properties), different geometric spacings (affecting their permeabilities) and possibly different stereochemistry. The length is typically equal to 1.25 Angstroms per CH_2 group in the chain. The cross-sectional area of each chain is between 20 and 26 sq. Angstrom[112].

Chapman has provided a broader discussion of the structure of the triglycerides and phospholipids.

The term phosphotriglyceride will frequently be replaced with the more general term phospholipid below for convenience.

The two layers can also be symmetrical or asymmetrical with respect to each other. The asymmetrical type is quite common[113].

Sphingomyelin is another phospholipid material quite closely related to PC (while it contains phosphocholine as its

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[106]Blumstein, A. (1978) Liquid crystalline order in polymers. NY: Academic Press, pgs. 7 & 265

[107]Chapman, D. (1975) The bilayer hypothesis of membrane structure. *In* Weissmann, G. & Claiborne, R. *ed.* Cell Membranes; Biochemistry, Cell Biology & Pathology. NY: HP Publishing Co. pg 15

[108]Yeagle, P. (1992) The Structure of Biological Membranes. Boca Raton FL: CRC Press pg. 17

[109]Stein, W. (1967) Op. Cit. pg 10

[110]Lehninger A. (1970) Biochemistry. Worth Publishers, Inc. pg 196.

[111]Stryer, L. (1981) Biochemistry. 2nd. ed. NY: W. H. Freeman Chapter 12, pp 283-312

[112]Barrow, Gordon (1961) Physical Chemistry. NY: McGraw-Hill pp 755-757

[113]Miljanich, G. et. al. (1979) Disaturated and dipolyunsaturated phospholipids in the bovine retinal outer segment disk membrane. *Biochim. Biophysic. Acta*. vol. 552, pp 294-306

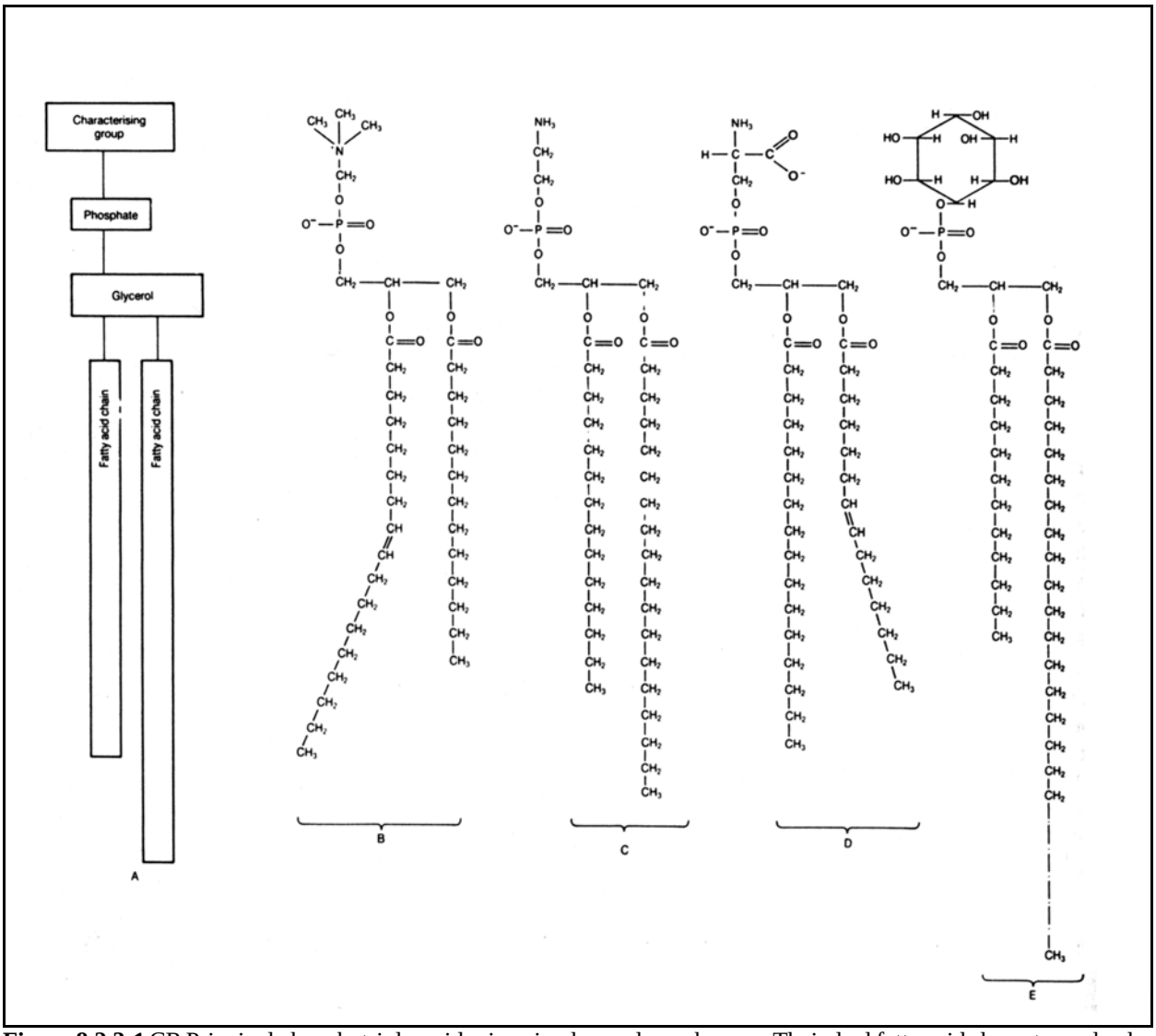

Figure 8.2.3-1 CR Principal phosphotriglycerides in animal neural membranes. Their dual fatty acid character and polar nature are shown. A; schematic diagram. B; phosphatidyl choline (lecithin). C; phosphatidyl ethanolamine (cephalin). D; phosphatidyl serine. E; phosphatidyl inositol. From Smith, 1989.

"head," it differs stereochemically from PC). This material is found primarily in brain and nerve tissue. It is a primary candidate for one of the asymmetrical bilayers forming the diode regions of neurolemma.
When membranes are formed of two sheets of different phosphotriglycerides with their hydrophobic ends next to each other, the resulting structure is impervious to ions and large particles.

Simultaneously, the above structure forms a pn junction with a higher charge density within the phosphatidyl ethanolamine portion of the membrane. It is semipermeable to fundamental electrical charges. This semipermeability is recognized when the membrane is placed between two electrolytes at different electrical potentials. Typically, the membrane will be conductive to electricity when the hydrophilic surface of the PE is made more negative than the hydrophilic PC surface. When the applied potential is reversed, the membrane acts as an insulator.

When examined in detail, the change from a conductor to an insulator is described by a simple exponential function. However, the transition from an insulator to a conductor may not occur at zero applied voltage. This fact suggests that the membrane may exhibit an intrinsic electrical potential. Such a potential will be defined as the intrinsic membrane potential. Note that this potential is not directly related to any plasma potential associated with a neuron.

When reverse biased, the insulating properties of the membrane can be defined in terms of its capacitance per unit area. When forward biased, this capacitance is of less importance at high bias potentials due to the high conductance of the membrane. The membrane may exhibit a variable capacitance at low applied potentials due to space-charge effects.

As will be discussed below, the biological bilayer membrane when immersed in electrolytes has been shown experimentally to be the equivalent of a diode and battery in series, the combination shunted by a capacitance.

> **Note: The characteristics described here are those of a simple electrolytic system. They are not those of a membrane standing alone. The *system* consists of the membrane and the electrolyte on each side of the membrane. The electrolytes need not be different. To determine the characteristics of the membrane, an external source of electrical polarization must be provided.**

Three different generic BLM configurations can be developed based on the above chemistry plus one other optional condition. These generic forms are developed below.

8.2.3.2 Candidate situations for describing the electrolytics of membranes

Many models exist describing the electrolytic situation associated with an in-vivo membrane system. They rest on a variety of foundations. Most of them only address putative membranes that are permeable to ions.

Knowledge concerning real biological membranes has advanced considerably in the last 50 years. This knowledge must be integrated into an overall view of the electrolytics of the biological membrane.

Figure 8.2.3-2 illustrates several potential situations that may occur at the neural membrane-electrolyte interface. The figure is applicable to several of the discussion to follow in this chapter. The membranes are assumed to be without voids. Each electrolyte is complex. They contain single and multiple-valence simple ions, more complex ions and both ionized and unionized metabolites supporting the glutamate cycle. This figure does not address the boundary layers associated with the external electrodes.

The upper half of the figure involve electrolytic cells with an external potential applied. The lower half does not involve any external potential. A potential is generated at the membrane surface regardless of the character and concentration of the electrolytes.

8.2.3.2.1 Regions of membrane subject to external potentials

The upper third of the figure addresses the conventional wisdom of a membrane as a homogeneous bulk material that is semipermeable to a variety of solutes. The material is void free. This is the conventional model addressed by Nernst, Donnan, Goldman and finally Hodgkin & Huxley. The permeability of this material to fundamental electrical charges, electrons and holes, is generally not addressed in the neuron, or basic cell, literature. It is this configuration that was applied to the lemmas of the neuron until recently. It is the configuration addressed in most of the literature referenced

in **Section 8.1**. This configuration shares little commonality with the nature of biological bilayer membranes, BLMs, as currently understood.

The middle third of the figure is applicable to actual biological bilayer membranes , BLMs, when investigated in the laboratory. The material is void free. Such membranes are essentially impervious to ions and large molecules due to their hydrophobic core. It is also immersed between two electrolytes and an electrical potential is applied via the electrodes. The specific nature of the electrolytes is immaterial. However, electrons and positive charges, in the form of holes, can pass through such a membrane under appropriate electrical conditions.

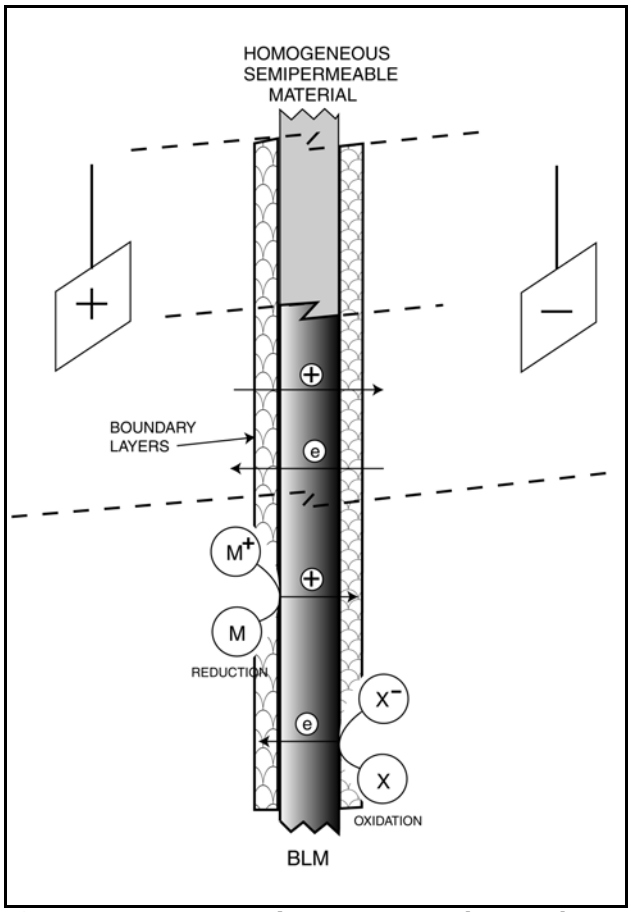

Figure 8.2.3-2 Potential situations at the membrane-electrolyte interface. The grey section of membrane represents the classical homogeneous semipermeable case. The remainder of the membrane represents a proposed biological bilayer membrane, BLM. See text.

1. When the membrane is a molecularly symmetrical BLM, the liquid-crystalline interface between the two bilayers is not conducive to the transmission of electrons or holes. The symmetrical BLM acts as a very high quality insulator, conducting neither electrons or holes. The membrane acts as a pair of ideal electrical diodes wired back-to-back. The overall membrane configuration exhibits the reverse bias breakdown characteristic expected of such a configuration. This configuration will be defined as a type 1 BLM.

2. When the membrane is a molecularly asymmetrical BLM, the liquid-crystalline interface between the two bilayers is more flexible. Depending on the details of the asymmetry, the BLM is found to exhibit asymmetrical electrical performance from two perspectives. First, the BLM exhibits the electrical impedance characteristics of a high quality electrical diode. The electrical characteristic exhibits a finite reverse bias breakdown potential to be expected of such a configuration. The intrinsic value of the diode is determined by the mobility of both the electrons and holes moving through the membrane. Second, the BLM may exhibit an "intrinsic battery" that acts exactly like a conventional battery in the presence of an external polarization. In the absence of an external polarization, this "intrinsic battery" disappears. It cannot provide energy to an external load or perform work. in the thermodynamic sense. This configuration will be defined as a type 2 BLM.

Both of these configurations exhibit a capacitance in parallel with the conductive components due to the intrinsic dielectric properties of the membrane. However, the value of this capacitance must be calculated based on quantum-mechanical principles. The distance between the charges stored near the surfaces of the membrane is a function of the potential across the membrane.

The type 1 and type 2 designations can also be applied to synthetic BLMs prepared in the laboratory without inclusions.

8.2.3.2.2 Regions of membrane generating their own potentials

The bottom third of the figure shows a situation similar to the middle third. However, no external bias is required to cause electrons and holes to pass through the BLM. It represents the typical oxidation and/or reduction reactions that can occur at the surface of a BLM based on the mechanism of electrostenolysis. This model is key to understanding the

means by which cells and neurons self bias themselves. It is also key to understanding a variety of clinical situations where films of free atoms are deposited on the surface of many biological membranes. Application of this configuration using a symmetrical (type 1) BLM is trivial since the membrane does not support the passage of current. However, application of this configuration to an asymmetrical (type 2) BLM is key to the operation of the entire neural system in animals.

Depending on the nature of the metabolic materials in the solutions on each side of the membrane, an electrostenolytic reaction can occur at the surface of the membrane as shown. This is commonly called a catalytic reaction in general chemistry with the membrane described as a substrate. However, in biochemistry, the reactant is frequently described as the substrate.

The rate of this electrostenolytic reaction depends on many characteristics of the membrane and the potential reactants. This reaction can cause an electron or hole to transit the membrane and thereby generate a potential between the two electrolytes independent of any other potentials present. Two potential electrostenolytic reactions are shown. A simple reduction reaction of the ionic species, M^+, forming the unionized species, M, is shown on the left. A similar but unrelated oxidation process is shown on the right for completeness. It is proposed that the actual process taking place at the surface of many specialized regions of plasma membranes involves the glutamate cycle. This cycle involves the reduction of glutamate to GABA through a rearrangement. No unionized form is created in this situation.

[xxx leave here?] The role of glutamate has long been a mystery in metabolism. This material has generally been associated with metabolism in the non-signaling portion of neural cells and in all other types of cells. This process is normally found occurring on the outside of cells where the required reactants are readily available from the blood stream and the local vascular matrix. The process appears to be the main source of the potential between the various plasmas of a cell and the surrounding environment. This reaction will be studied in detail in **Section 8.xxx.**

When these reactions occur on the surfaces of the BLM as shown, charge will be transferred across the membrane. Whether the charge is transferred as an electron or as a hole is determined by the mobility of these species within the BLM. Since no electrical path exists through the electrolytes to an external circuit, the transferred charges will accumulate in a boundary layer associated with the BLM-electrolyte interface. Note the asymmetry of this situation. An electrical potential can exist across the BLM only if the electrostenolytic process reverse biases the diode characteristic of the BLM. Otherwise, the diode will be forward biased and the charge would be able to pass back through the BLM. Due to the electrical asymmetry of the type 2 BLM, the reduction reaction and the oxidation reaction can only be effective if they occur on the appropriate side of the membrane.

The charge transferred through the BLM is not able to flow freely into the electrolyte. That is not allowed by Gauss's Law of electrostatics. However, it can collect on the surface of the membrane and form an electrically charged boundary layer. Under steady state conditions, it is this electrostenolytic mechanism that provides the electrical potential of each plasma of the neural signaling system. It is also the source of potential in other chambers of neurons as well as other cells. Note that this electrostenolytic potential is not directly related to the "intrinsic battery" associated with the membrane and discussed in **Section 8.2.3.2.1.**

This configuration has been produced in the clinical research laboratory but without the investigator being completely aware of the precise situation. Tien discussed a combination of the above situations that included the electrostenolytic effect, an external potential bias and a BLM[114]. Tien describes that situation as involving a BLM that is electron conducting but highly resistive to the transport of ions. He did not address its electrical symmetry. Habib & Bockris describe an electrostenolytic situation (they call it an electrodic model) involving a pair of redox processes[115]. By eliminating one of these reactions, a potential is found to exist across the membrane as discussed above.

8.2.3.2.3 Regions where material transport dominates over electrolytics

The membranes described in earlier parts of **Section 8.2.3.2** do not contain voids and the BLMs are virtually impermeable to ions and other large molecules. However, it is obvious that some of these types of materials must be able to transit a cell membrane. To accommodate this requirement, the community has conceptuallized a transfer mechanism involving two potential mechanisms, the formation of permanent inclusion penetrating the membrane and

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[114]Tien, H. (1974) Bilayer lipid membranes. (*also in* Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker, Chap 7 written by Zon & Tien, pg 191)

[115]Habib, M. & Bockris, J. *In* Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press. pp. 82-83

acting as selective channels through the membrane. To date, electron microscopy has not been able to confirm the existence of any channels having this capability. Alternately, a family of vesicles have been conceptualized that can selectively capture material on one side of a membrane and transport the material through the membrane prior to releasing it unchanged. To date, electron microscopy has not been able to confirm the existence of any vesicles having this capability. While the mechanism is not currently known, a type 3 BLM will be defined that supports this capability. For purposes of discussion, the type 3 BLM will be defined as a modified type 1 BLM. Under this assumption, the three types of BLM have independent, non-overlapping properties.

8.2.3.2.4 Regions of membrane pertinent to the neuron

When considering the operation of the neurons, only the two lower portions of the figure need be considered. Due to their hydrophobic core, the BLMs in these portions are impervious to the flow of hydrophilic ions. Due to their impermeability to ions, **the diffusion analyses of Nernst, Donnan, Goldman, and Hodgkin & Huxley do not apply to actual BLMs.** These investigators all relied upon the assumption of a homogeneous material exhibiting an internal electrical potential field gradient that was uniform. Neither the type 1 or type 2 BLM meet this criteria. **The electrical field gradient within such membranes are not uniform.**

The quantum-mechanical characteristics of symmetrical (type 1) BLMs make them impervious to electrical charges as well as most hydrophilic solutes. However, the quantum-mechanical properties of the asymmetrical (type 2) BLM do support the flow of fundamental charges through the BLM. More complex analyses, based on quantum-mechanics and available from semi-metallic semiconductor physics can be used to address this situation. Some of these techniques were introduced above and will continue to be used below.

The boundary conditions related to the types of BLMs defined above must be addressed. The boundary conditions applicable to the homogeneous membrane are irrelevant to the neuron. The more complex problem related to “skins” of animals need not be addressed here. Skins contain a variety of individual zones performing a myriad of functions beyond neurological signaling.

To be relevant to the membrane situation related to neural activity, any model of an *in-situ* BLM must address questions related to both the BLM and the associated electrolytes. The model must meet a number of conditions:

+ It should separate the housekeeping, i. e. metabolic functions of the membrane(s) from their electrical signal handling characteristics.

+ It must recognize, and/or account for, the liquid-crystalline nature of the very concentrated gel-like plasma. It should explain the part water plays in this liquid crystal.

+ It must explain the transport mechanism involved in positive charge transfer within a matrix of water molecules under both gel-like (found within the plasmas) and liquid-crystalline conditions (found within the BLM).

+ It must be able to explain what negative ionic species and what positive ionic species have the highest mobility in the cytoplasm(s) of the neuron

+ It should allow the determination of which of the highest mobility species is the dominant species within the environment in terms of its charge carrying capacity.

The answers to these questions may vary with location within the membrane system.

8.2.3.3 The chemical and electrical characteristics of a simple membrane *system*

The typical neuron has regions of membrane, both external and internal, which are different. Each region is composed of two layers of frequently different phospholipids. A single membrane may contain up to 100 different members of the PE and PC family, probably congregating in different regions**.**

Figure 8.2.3-3 illustrates the situation; (a) shows the chemical arrangement of the material forming the fundamental membrane, (b) shows the elementary electrical circuit applicable to the membrane, (c) shows a fundamental cell in topological form, both chemically and electrically. Also shown is the boundary layer between the wall and the enclosed electrolyte. This boundary layer was discussed earlier. Its significance will be discussed more fully in **Sections 8.2.6**, **9.3.5** and **10.1.3**.

(a) emphasizes the geometric arrangement of the two phospholipids. The total thickness of the membrane is usually less than 100 Angstrom. The dots represent the polar heads of each molecular film and the two short lines represent the two hydrocarbon chains of the molecule. The inner core of the bilayer membrane is highly hydrophobic while the external surfaces are hydrophilic. As a result, the fundamental BLM is essentially impervious to ions. The case shown is asymmetrical with the outer layer containing PC and the inner layer containing PE.

(b) illustrates the equivalent electrical circuit of a molecularly asymmetrical bilayer membrane. As indicated above, the membrane is impervious to ionic charges. However, it is semipermeable to fundamental electrical charges. The diode allows a conventional current to flow easily from the inside the membrane to the outside. Thus, an enclosed membrane cannot support a positive potential on its inside surface. However, if the membrane is subjected to a bias such that the inside is negative, the diode is reverse-biased and no significant current will flow through it. A battery is shown in series with the diode. Based on experimental data, this battery is usually of less than 50 mV static potential and of either polarity depending on the particular phospholipids present. This battery represents the intrinsic membrane potential of a bilayer sandwich. This battery is due to a quantum-mechanical mechanism and is part of an *equivalent circuit*. *It does not exist alone or in the absence of a polarizing bias across the membrane*. Because of the thinness of the membrane, it exhibits a significant capacitance per unit area.

Kinnunen & Virtanen have described their concept for the transfer of electrons along properly arranged ethylenic double bonds of unsaturated nerve membrane lipids forming liquid crystalline films[116]. Their configuration appears compatible with that defined above. However, no need for double bonds is apparent when other mechanisms (such as hydrogen bonding and possibly tunneling (see **Section xxx**), are available.

If the two bilayers of the membrane are molecularly symmetrical, the single diode is replaced by two back to back diodes. As a result, the circuit will not pass significant current in either direction. It is a very high quality electrical insulator. Here, the potential of the battery is irrelevant.

(c) illustrates a cross-section of an electrical conduit formed of a BLM. The left and right quadrants are drawn to show how the phospholipids form a hollow cylinder. This cylinder contains a barrier to the

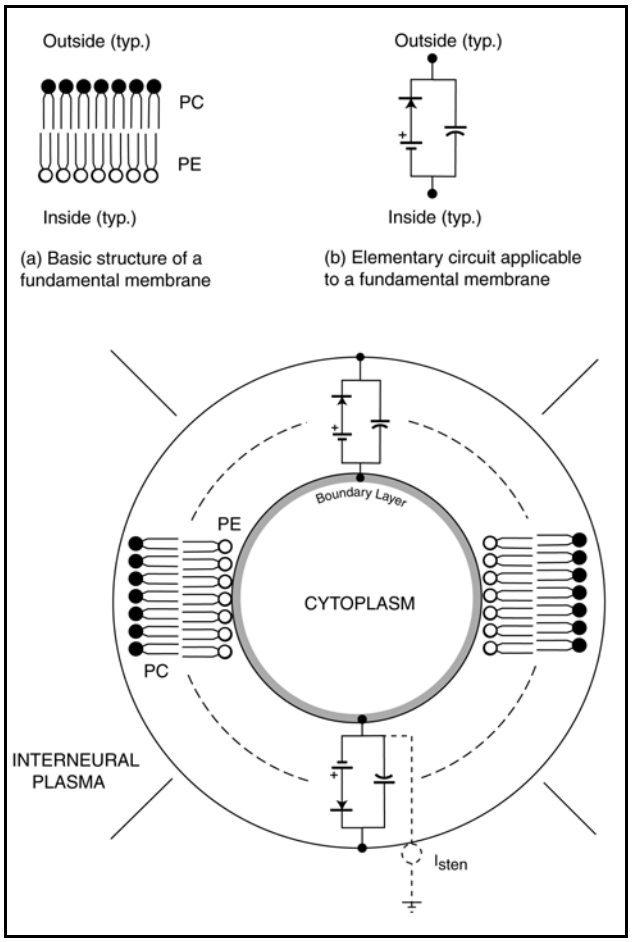

Figure 8.2.3-3 The physical and electrical structure of a typical cell conduit. (a) Basic molecular structure of the membrane. In asymmetrical membranes (type 2), the two phospholipids are different. When they are the same (type 1), the material is typically an electrical insulator. In either case, the hydrophobic core of the membrane is impervious to ions. Only type 2 membranes are shown in the figure. (b) Basic electrical network of membrane. (c) Caricature of conduit showing both molecular and electrical characteristics and the boundary layer between the wall and the electrolyte. The electrostenolytic process is shown dotted.

[116]Kinnunen, K. & Virtanen, J. (1986) *in* Gutmann, F. & Keyzer, H. Modern Bioelectrochemistry. NY: Plenum Press, pg 459

movement of ionized particles as shown by the dashed line. The molecules are also in a closely packed liquid crystalline arrangement that makes a formidable barrier to the flow of any large particles.

For the molecularly asymmetrical bilayer shown, the electrical equivalent circuit shown in the top and bottom quadrants of the figure are appropriate. This configuration is electrically neutral in the absence of an externally applied potential. Because of the impermeability of the membrane, the introduction of an electrically neutral electrolyte, both inside and outside the membrane, does not affect the electrical performance of the system. Either or both electrolytes may contain highly ionized material. However, the net charge within either electrolyte is zero. The constant field diffusion laws do not apply to this situation.

An electrostenolytic process is shown by dotted lines in the lower quadrant of the frame. It effectively connects the interior electrolyte of the system to the external electrolyte. By proper choice of reactants, an electrical charge can be injected through the membrane and into the space labeled the boundary layer. If this charge consists of electrons, the interior of the membrane will develop a negative electrical potential compared with the interneural matrix, INM. Since the equivalent diode of the membrane is reverse biased, this potential will only decay slowly in the absence of continued electrostenolytic action. However, as Matthews postulated, a finite amount of electrostenolytic activity is required to maintain the interior cytoplasm at a quiescent potential compared with the INM[117]. The precise value of this intrinsic cytoplasm potential is given by the solution of the electrochemical equation for the current through the electrostenolytic process and the equivalent batteries and diodes as given by Kirchoff's Laws.

> **This frame illustrates the fundamental BLM conduit of the neural system. It describes a quiescent system exhibiting an internal plasma potential. The membrane is impervious to ionic charges. The potential of the interior of the membrane is due to an electrostenolytic process that can be described as an electron-pump. This electron-pump replaces the ion-pump previously proposed in the literature. The potential of the cytoplasm is electrically uniform due to the conductivity of the medium. The actual potential of the cytoplasm compared with the INM is determined by the charge within the boundary layer surrounding this cytoplasm and forming one plate of a capacitor.**

8.2.3.4 Electrostatics and the Principle of Electrical Neutrality

The principle of electrical neutrality plays a major role in the study of both chemistry and electricity. **Unfortunately, the name is used for two distinctly different concepts**.

The electro-chemist uses the Principle of Electrical Neutrality to describe the electrical potential established between two solutes that are allowed to equilibrate on opposite sides of a semipermeable membrane. It is based on the equilibrium potential or Nernst Potential[118]. The solutes may contain only one ionizable species or many ionizable species. However, Matthews makes the important caveat. "The Nernst equation only applies to one ion at a time and only to ions that can cross the barrier." The problem with this definition when discussing neurons is that the biological bilayer membrane is not semipermeable to ions. This diffusion based version of the Principle of Electrical Neutrality does not apply to BLMs separating two solutes regardless of the electrolytes present.

In electricity, the Principle of Electrical Neutrality is used entirely differently. The electromagnetics based version of the Principle of Electrical Neutrality applies in all cases regardless of the nature of any individual material within the region being examined. It also applies when part(s) of the region is filled with an ionized plasma(s) (whether a gas or a liquid). Two concepts are involved.

Gauss's Law for Electric Fields plays an important role in describing any electrical field. It is most easily applied to

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[117]Matthews, G. (1991) Op. Cit.

[118]Matthews, G. (1991) Op. Cit. pp 27-29

static electrical fields. The subject is treated thoroughly in Kraus[119]. The proper application of this principle to the neural conduit requires careful analysis. The formulation stated by Matthews, and noted above, is needlessly narrow. The situation under discussion involves a conductive electrolyte within an insulating or quasi-insulating membrane. Of necessity, a boundary layer separates these materials. There are two separate principles that must be applied to this situation. The first concept is based on one of Maxwell's Equations of Electromagnetics. These laws are usually presented in differential form. When presented in integral form, the first law is known as Gauss's Law for Electric Fields; *the surface integral of the normal component of the electric flux density vector, **D**, over any closed surface equals the charge enclosed, Q* (using the rationalized mksc system of units). The second concept is based on another interpretation of one of Maxwell's Laws. *The total net charge **within** any complete conductive or semi-conductive system must be zero*[120].

> Note that the first concept applies to any closed surface, whether it contains conductive material or not. The second only applies to a conductive volume.

Based on the above two concepts, the potential between the inside of the membrane and the outside of the membrane is given by the total net charge enclosed by the membrane. The first concept does not concern itself with how the charge is distributed within the membrane. The second concept calls for the total net charge within the conducting electrolyte to be equal to zero. This concept does not concern itself with the total charge within the membrane, only that within the bulk electrolyte. Any excess electronic charges within the boundary of the electrolyte cannot exist there in the steady state. The individual electrons will repel each other. The result is that these electrons will form a shell at the boundary layer between the electrolyte and the insulating membrane. Thus, the charge within a membrane surrounding a conductive electrolyte need not be zero. Excess free electrons can be present, and potentially move, along the surface of the boundary layer between the membrane and the electrolyte. However, they cannot move through the electrolyte without an exchange of charge between the constituents of the solution.

In the configuration at hand, it is Gauss's Law of Electric Fields that is important.

No requirement exists for the net charge within a conduit membrane to equal zero.

On the other hand,

A requirement does exist for the net charge within any equilibrated electrolyte to equal zero.

The net charge within a conduit can be changed by mechanisms independent of the ionic particles present.

Finally, the specific types of charges within the electrolyte are of no importance in this situation. It is imperative that the experimentalist recognize the possibility of charge within a closed fundamental membrane that is not related to the level of ionization within the electrolyte. This charge is found in the boundary layer between the dielectric membrane and the electrolyte.

8.2.3.4.1 The local boundary conditions for biological membranes

In solid state semiconductors, it is normal to have a positive (p) species dominant on one side of a cell and the negative (n) species to be dominant on the other. This results in a unique situation called a pn junction. This junction is characterized by a ***potential barrier*** discussed below. As will be seen below, *this appears to be the situation in a portion of a neural membrane system,* **Figure 8.2.3-4(top)**. Compare this figure to figure 5-9 of Eckert. Both halves of this figure are compromises in that they are trying to illustrate details at both the macro and micro level. The presentation will be further refined in the following section.

The bottom portion of the figure shows a situation that will be important later. It shows a closely juxtaposed sandwich of two asymmetrical bilayer membranes. *It appears that the two surfaces nearest the electrolytes are dominated by the p- species and the region between the two membranes is dominated by the n- species. The result is a biological transistor of the pnp type,* **Figure 8.2.3-4(bottom)**. This is determined from the polarity of the voltages involved in the operation of all neurons of various types. What is not known at present is the exact nature of the two electrically dominant species within the BLM and within the two closely juxtaposed BLMs. The next section will suggest, based on mobility grounds, they are the positive charge or "hole" and the negative charge associated with the electron. This

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[119]Kraus, J. (1953) Electromagnetics. NY: McGraw-Hill. Chapters 1 & 2.

[120]Kraus, J. (1953) Op. Cit. pp 68-70

situation would give the highest net charge transport velocity with the BLMs of the neuron. *The mobility ratio between these most likely species is known to be 3:1 in dilute solution.* Analyses in later sections will show this mobility ratio is an important parameter in the overall operation of the eye.

A key feature of both of these figures relates to the amount of charge within a given region. The detailed rules differ between the electrolytes and the BLMs (because of the quantum-mechanical conditions within the BLMs). However, the general rules of electrostatics apply. Under equilibrium conditions, the net amount of charge enclosed by any finite size closed figure drawn over either of these two frames must equal zero. A "conductive" electrolyte cannot sustain a charge gradient within its volume. Similarly, a BLM cannot sustain a charge imbalance within its volume under equilibrium conditions.

If a steady external potential is placed across the BLM-electrolyte combination, the equilibrium conditions become more complex. However, the charge balance must still be observed within the electrolytes. These situations will be addressed in **Sections 8.4** & **8.5**.

8.2.3.4.2 The global boundary conditions for a membrane in electrolytes

The above figure, and that of Eckert, are inadequate in describing the overall boundary conditions applicable to one or more BLMs separating two electrolytic solutions. It is also important to review the premises of Matthews and others related to the stability of BLM systems. They have relied upon the basic assumption that the BLM is semipermeable to a range of ions. If the alternate position is taken that the BLM (at least of type 1 and 2) are impervious to ions, a completely different analysis is required. The conclusions relative to equilibrium are quite different.

It is appropriate to review the global situation within the laws of electrostatics.

8.2.3.5 Equilibrium conditions for a biological membrane between two electrolytes

Any discussion of equilibrium should differentiate between static equilibrium and dynamic equilibrium. These are fundamentally different situations in neuroscience. Static, or quasi-static equilibrium, is most often encountered in the laboratory under *in-vitro* conditions. The term quasi-static equilibrium is introduced here to account for the fact that most *in-vitro* experiments cannot be maintained for very long because of the consumption of unknown documented metabolic supplies. Dynamic equilibrium is encountered whenever *in-vivo* experiments are performed.

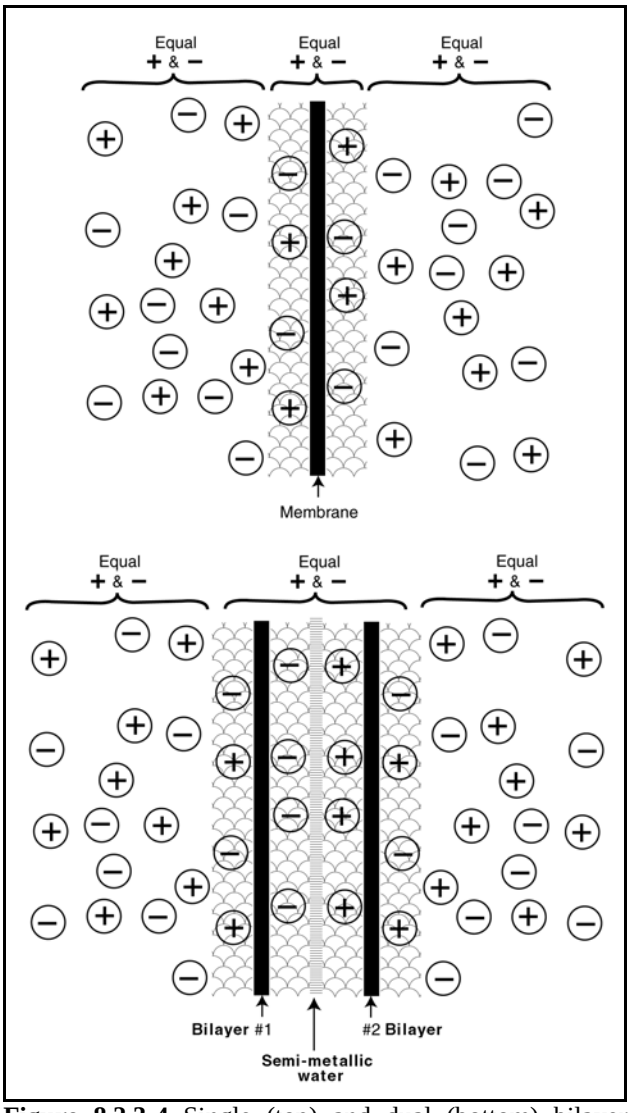

Figure 8.2.3-4 Single (top) and dual (bottom) bilayer membranes separating two electrolytes (in the absence of an external bias). Note the electrical gradient between the two membranes as symbolized by the paired charges in the median of the lower frame. See text.

Some experimenters have attempted to move from quasi-static to dynamic *in-vitro* conditions through continuous oxygenation of their electrolytes. While this practice may have an observable effect, it probably has little direct effect on the anaerobic nature of the neural signaling process (**Section 8.3.4.xxx**).

The dynamic equilibrium between a neuron and its environment will be addressed in **Section 10.xxx**.
[xxx define further before addressing Matthews]

The premise of Mathews must be carefully considered when discussing BLM systems[121]. His summary position is that animal cells are not at equilibrium because their ionic concentrations are not at equilibrium with their surroundings. Therefore, metabolic energy must be continually expended to maintain the quiescent condition. While his position is rational based on the conventional wisdom related to membranes porous to ions, it is irrelevant to neural conduits formed of fundamental BLMs that are impervious to ions. If the membrane is impervious to ions, the concept of osmotic equilibrium between the interior and exterior of a conduit does not apply.

However, a fundamental BLM is semipermeable to fundamental electrical charges. This condition could lead to a continuous lack of electrical equilibrium and a continuous requirement for the expenditure of energy to maintain a status quo. This condition is avoided by keeping the interior of the asymmetrical membrane at a negative potential. Such a condition requires no continuous expenditure of energy.

This situation justifies the need for a charge-pump but discounts the need for an ion-pump. In a non-neural cell, the need for a charge-pump is minimal. However, in a neuron, the continuous action of the Activa requires a more active charge-pump.

8.2.3.5.1 Affect of diffusion on the electrochemistry at the membrane-electrolyte boundary

The long term diffusion of ions and particles across selected regions of the neural membrane obviously occurs. Such movement supports cell genesis and metastasis. It is proposed that this process is found only in more specialized and complex regions of type 3 membrane described by others as "fluid mosaic zones" or using subunit models[122]. This diffusion generally occurs slowly and has no significant impact on neural signaling. It is believed to involve the association of the ions with other molecular structures to achieve passage through the membrane. Some authors have suggested that only lipophilic molecules can pass through a membrane. This is probably an oversimplification. To reach the interior of a BLM, the molecule must be transportable in a water-based solvent and be able to pass through a lipophilic region as well. Achieving these goals may require at least an electronic rearrangement during the journey. [xxx edit]

Here again, the applicability of the constant field diffusion laws is brought into question.

8.2.3.5.2 The complexity of the diffusion environment near the neuron

The complexity of the diffusion environments internal to and external to the membrane conduit and their ability to support the various electrostenolytic processes is closely tied to the morphology of the local neural structures. This subject will be addressed in detail in [**Section 10.10** xxx] following the discussion of a variety of individual neural morphologies.

8.2.3.5.3 The mathematics of electrical equilibrium for a real membrane

The mathematics of electrical equilibrium related to a real membrane between two electrolytes can be quite complex. The equilibrium associated with each type of charged species must be considered. However, the putative fundamental BLM, whether symmetrical or not, is impervious to ions and other charged particles. The resulting problem resolves down to the solution of the equilibrium condition associated with the flow of fundamental charged particles, electrons and holes.

For a fundamental BLM that is not a complete insulator to the flow of electrical charges, a quantum-mechanical potential

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[121]Matthews, G. (1991) Cellular physiology of nerve and muscle. Boston, MA: Blackwell Scientific Pulbications, pg. 1

[122]Eckert, R. (1988) Op. Cit. pp. 69-71

barrier exists within the membrane. The potential within the membrane is not constant with respect to position within the membrane. Written in differential calculus form, $dV/dx \neq V/a$ where V is the total potential across the membrane of thickness a. This potential barrier results in an asymmetrical porosity with respect to charges that is not addressed by a constant field equation such as that of Goldman or Hodgkin & Huxley. The resulting variable field theory proposed here is based on this condition. It is not new. It is used throughout semiconductor physics.

This alternate theory related to fundamental charged particles can be summarized by comparing it with the derivation of the constant field theory of Goldman. Either the material of Starzak or a more concise presentation provided by Matthews can be applied to fundamental charges as easily as to ions[123]. The above inequality is taken as an equality in his equation B-4. Therefore, equation B-5 does not follow from equation B-3 and the appropriate differential equation is of a higher order than assumed by Goldman. In solving the equation of B-5, Goldman employed definite integrals. The limits he chose are appropriate but do not allow for the presence of an electrostenolytic process on one surface of the membrane. Such a process would introduce another fixed potential into the earlier equation B-1. Although this addition would not add significant complexity to the mathematics, it does change the form of his equation B-1. This changes the form of the equation following B-11 and after factoring results in a new variable field equation describing a real asymmetrical membrane. The precise solution of this equation depends on the profile of dV/dx and will be left to others to define.

Ignoring the genesis and routine metabolic phases of activity, most of the BLM associated with the conduits of a neuron is inherently an insulator to the flow of ions. The primary concern of the variable field theory, particularly within the time span associated with neural signaling, is with the transit of electrons and holes and ***not ions***.

8.2.3.5.4 How do you feed an in-vitro neuron MOVE

It is important to recognize that there are two distinct metabolic parts to a neuron. The non-signaling portion of the cell is a conventional cell. Its normal operation is described as aerobic. It has two primary requirements, oxygen and glucose, that it must get from the vascular system. The primary waste product of this part of the cell is CO_2.

The signaling part of the neural cell is quite different. It normally operates in a anaerobic mode (Section xxx) and uses an electrostenolytic reduction process to provide electrical power to the neuron. It has one primary requirement, glutamic acid (glutamate) and can operate on a backup, aspartic acid (apartate) if necessary. These two amino acids are the only negatively charged amino acids. Hence, they are the only amino acids capable of supporting the electrostenolytic process required to polarize the plasmas of the neuron negatively with respect to the surrounding matrix. An obvious waste product of this part of the cell is CO_2. A second waste product is gamma-amino butyric acid (GABA). When operating in backup mode, this second waste product is beta-amino propionic acid. These amino acid waste products are in the same family with glycine (*alpha*-amino acetic acid). They are all aminated carboxylic acids.

In brief, a typical Ringer's solution cannot support a neuron *in-vitro*. The solution must be augmented to and maintained at a 2-4% solution of glutamate along with sufficient glucose and oxygen. Without glucose and oxygen, the homeostasis of the cell cannot be maintained. Without glutamate (or its backup), the neural signaling capability of the cell cannot be maintained. Both situations require the continual removal of waste products to avoid neuro-inhibition.

> It is noted that Gibco, in the U.K., sells a Ringer's solution augmented with vitamins and amino acids. It is known as Eagle's Minimal Essential Medium. The name suggests this solution might contain a mixture of the essential amino acids. However, glutamate and asparte are specifically defined as non-essential amino acids because the body can create them from other readily available food stocks. These mediums are designed for culturing non-neural cells. Some variants of Eagles MEM contain L-glutamine but none were found that contained glutamate, the critical ingredient for sustained neural operation in culture.

8.2.4 Extended descriptions of neural membrane regions

For neural membrane, it must **not** be assumed that all of the surfaces of an axolemma exhibit the same uniform electrical

[123]Matthews, G. (1991) Op. Cit. Appendix B

properties. The properties of any neural lemma should be determined on a micron by micron basis. These properties should be determined for the isolated membrane and for the membrane with its surfaces in their *in-vivo* condition.

> **Recall that an isolated membrane will not exhibit its true electrical characteristics without an external electrical potential applied between its two surfaces (e. g., the intrinsic battery is a quantum-mechanical device. It will only add to or oppose an externally applied potential bias)**.
>
> **The following descriptions will use the term capacitance. Recall that the reactive properties of a membrane depends on its configuration. The properties of a cylindrical membrane involve both capacitance and inductance that cannot be calculated from their equivalent flat surface area**.

Three primary types of external membrane have been identified as associated with the conduits of a neuron and required to support signaling. These types were initially introduced in the caricature of **Section 8.2.1**. The major features of these types will be discussed in this section.

10.3.3.2 The electrical circuit of the plasma membrane MELD

There are at least three specialized zones of the neuron membrane associated with each dendrolemma, podalemma, axolemma and nodal-lemma. The prototypical zone consists of a bilayer of molecularly symmetrical phosphotriglyceride material. This zone is intrinsically a high quality electrical insulator that is also impervious to the flow of ions and other particles. The second type of zone consists of a bilayer of molecularly asymmetrical phosphotriglyceride material. This zone exhibits the electrical characteristics of a high quality diode in series with a battery. It is still impervious to the flow of ions and large particles. The third type of zone consists of a bilayer of unspecified molecular properties. Ions or large particles are capable of passing through this type of membrane. Whether individual ions are capable of passing through the membrane is still speculative. It may be that they must be combined with larger molecules during this passage. It is also speculative as to whether this membrane type contains inclusions in its structure that provide passageways through the membrane. In this case, it has been given the name fluid mosaic membrane. This third type of membrane is primarily concerned with the genesis and metastasis of the cell or conduit. The processes involved are temporally slow and do not significantly impact the signaling function of the neuron. This third type of membrane will not be discussed further herein.

Certain areas on the surface of the conduit membrane are known to be coated with a bioenergetic material. It is not clear whether this coating only occurs on one of the above membrane types. The combination of a bioenergetic material coating an asymmetrical membrane immersed in an electrolyte creates a configuration that constitutes an electrostenolytic power source. The detailed electrical configuration of this process was addressed in Chapter 8. The combination can be represented by a battery and diode in series, the combination shunted by a capacitor. However, the resulting battery is representative of the intrinsic electrostenolytic potential of the process and not the intrinsic membrane potential which is generally lower. In biological systems, the negative electrical terminal of this power source is always the inside of the membrane. The intrinsic electrostenolytic potential is a major factor in establishing the quiescent plasma potential of the conduit formed by the membrane.

By analyzing the individual zones of a given lemma, it is possible to define the overall electrical circuit of that lemma. For the axon, this electrical circuit is fundamentally different from that found in the literature[124] for the last 50 years for three principle reasons. *First*, because of the realization that the lemma is a liquid crystalline substance capable of supporting the flow of fundamental electrical charges (electrons and holes) through the membrane wall. This electron flow is the dominant form of charge transfer through the cell wall in the neuron. *Second*, because of the realization of the passive nature of the individual membrane (until it is properly juxtaposed with a second membrane and provided with certain biases in order to create the Activa). *Third*, because of the realization that the axon does not support the physical flow of ions through it (at least in a timely manner required for signaling). This realization makes the discussion of the flow of individual ions through the lemma, based on the various constant field theories and the so-called independence principle, irrelevant.

There have been a few experiments designed to show the permeability of biological membranes to radioactive sodium ions. Hille summarized this activity in 1977[125]. His references should be reviewed to obtain important experimental

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[124]Shepherd, G. (1988) Neurobiology, 2nd Ed. NY: Oxford University Press pg. 114

[125]Hille, B. (1977) Ionic basis of resting and action potentials, Chapter 4 *In* Handbook of Physiology, Section 1, Vol. I, Kandel, E. *ed*. pg. 111

details. [XXX WHERE DOES THIS BELONG]

The electrical model of the neural membrane is somewhat more complex than generally described in the literature. Rather than consisting of a resistive material in parallel with a capacitance as shown in frame **A** of **Figure 8.2.4-1**, it is more appropriately shown as in **B** or **C**. B shows the preferred electrical description of a type 1 BLM and C shows the preferred description of a type 2 BLM. In **B**, the membrane will exhibit an extremely high resistance due to the back to back diodes but may exhibit a voltage sensitive capacitance due to space charge within the diode structure in addition to the conventional or average capacitance of the membrane. In **C**, the series impedance of the single equivalent diode will be much lower but the voltage sensitive space charge may actually be higher since it is no longer balanced as in **B**. G_s and C_s represent the conductance and capacitance of the solution and C_p represents any stray capacitance associated with the test set. G_m represents the equivalent conductance of the membrane in the simple model. In **B** and **C**, the resistive element has been replaced by either of two diode elements to more accurately reflect the membrane. Since the diode may exhibit a voltage sensitive capacitance due to the space charge effect, the total capacitance is shown as consisting of an average capacitance, C_m and a voltage sensitive component, C_{sc}.

When measurements are made on type 2 BLM, it is important to note the character of the overall electrical circuit. Particularly when making AC measurements, the overall circuit of C, without considering the properties of the metal-electrolyte interfaces, can act as a clamp circuit. This action can cause the measured capacitance, $C_m + C_{sc}$, to be a function of the frequency of the AC waveform. A similar situation is encountered in most measurements where a DC path is maintained through the test configuration.

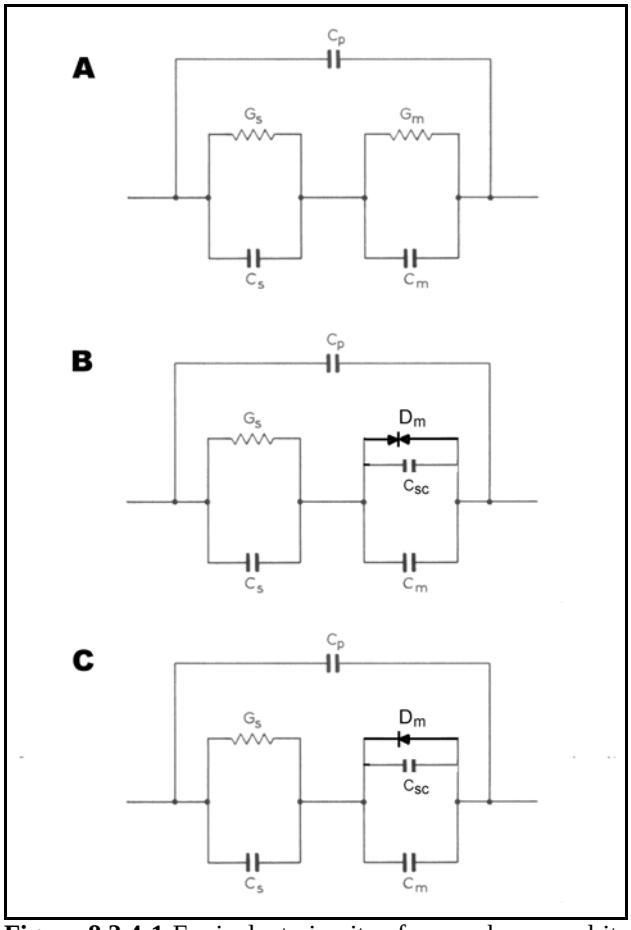

Figure 8.2.4-1 Equivalent circuits of a membrane and its adjacent solution. A; the simple circuit of many texts. B; the more detailed circuit of a type 1 BLM. C; the detailed circuit of a type 2 BLM. See text.

8.2.4.1 Type 1 regions of molecularly symmetrical membrane

The easiest specialized region of a BLM to discuss, is the type 1 region. This type appears to occupy the largest surface area of a given neuron, particularly in the case of stage 3 projection neurons. Type 1 regions are characterized by a *molecularly symmetrical bilayer lipid membrane (BLM)*. It appears this type of membrane is also characterized by a minimum amount of interdigitation between the molecules on opposite sides of the hydrophobic interface between the two lipoid layers.

The type 1 membrane exhibits two hydrophilic surfaces and is quite compatible with the electrolytes. However, it contains a hydrophobic core that does not support the transport of hydrophilic ions through the membrane. These regions of membrane are almost totally passive, both chemically and electrically.

The continuous symmetrical liquid crystalline biological membrane is highly impervious to ions and large molecules, and is an electrical insulator. It offers few opportunities to support any ionic diffusion. However, the symmetrical BLM has very complicated electrical properties because of its quantum-mechanical nature. These properties will be addressed below. The membrane configuration represents a capacitor unless

it is formed into a tube. In the case of a tubular liquid crystalline BLM, it exhibits both a capacitance and an inductance.

Type 1 membrane forms the extended portion of the axons. Its primary role is to act as the insulating component in a coaxial transmission line. When myelinated, the electrical insulation and chemical impermeability of the axon membrane is enhanced.

8.2.4.2 Type 3 membrane supports homeostasis & growth

The metabolic requirement to transfer a wide variety of organic materials, inorganic materials and water through the cell wall is well recognized in biological chemistry. The need is to support both homeostasis and growth. Although much research has been accomplished, the details related to the method of transfer of water molecules, large organic molecules, and potentially ions, through the plasmalemma of any cell (much less a neuron) remains largely speculative. Most of the information has been obtained in one of two ways. First, by observation of a living organism *in-vivo* following ingestion or injection of the material. Second, by topical application of the individual chemical to a neuron *in-vitro*.

No general framework has evolved yet for correlating the observed results with the individual chemicals interacting with the neuron. The type 3 BLM is proposed as the generic type of membrane involved in homeostasis and growth. The majority of the type 3 regions of membrane are associated with the soma (as opposed to the membranes forming the conduits of the neuron). The chemical transfer properties of the membrane dominate over any potential electrical properties. To simplify the understanding of the type 3 BLM, it is defined as a type 1 membrane (electrically and chemically inert) that has been modified to change its transport properties only. Any requirements associated with electrical performance are assigned to adjacent areas of type 1 or type 2 membrane. Under this proposal, the two bilayers of the membrane are assumed to exhibit little molecular interdigitation in the hydrophobic area. It is also assumed that the overall membrane is penetrated in multiple individual areas by a variety of complexes containing protein or sterol materials. Such a type 3 membrane has been described as a "mosaic membrane."

In attempting to characterize the individual transfer mechanisms, two schools have developed in the literature. The first supports the notion that these regions exhibit a variety of subregions where various *proteins* are embedded in the membrane. These embedded proteins are assumed to support the transport of molecular material through the membrane. Whether this process relies upon a vesicle able to access both sides of the membrane or a selective pore through the membrane is not known. The second school supports the notion that these regions contain embedded *sterols* (particularly cholesterol) believed to support the absorption and release of water molecules (thereby supporting the transport of water through the membrane).

The mechanisms associated with the transfer of materials by these individual areas of protein or sterol material are often spoken of as pumps in the vernacular. Both molecular-pumps and ion-pumps have been defined in this manner using a large and conflicting array of caricatures (of which there is an infinite supply). Little substantive information has been obtained concerning these pumps at the structural or molecular level.

While extremely important to the homeostasis of the cell over the long term, these pumps are not involved in neural signaling or neural power generation. As Shepherd noted generically: "Ionic pumps are essential and important constituents of neurons and neuronal membranes. Their time scale of action is seconds to minutes and they are therefore thought of as being more involved in long-term rather than short-term neuronal processing[126]."

The faster putative ion-pumps of Hodgkin & Huxley fame have been addressed in **Section xxx** and are not considered important to this section. During most of the 20th Century, it was taken as an article of faith that ions could be readily transferred across the BLM. At the midpoint of the century, Hodgkin & Huxley postulated that free ions, particularly sodium and potassium, could pass rapidly through the axolemma. Subsequent experiments, during the latter quarter of that century, have failed to show such permeability. The generally accepted position now is that these ionic materials can only move through a type 3 BLM (associated with the soma) when in the "undissociated state" or when complexed with another material. Armstrong addressed this change in ideology beginning in 1971[127]. However, Armstrong was not aware of the complex quantum-mechanical nature of the BLM when he discusses its electrical characteristics.

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[126]Shepherd, G. (1998) Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 46

[127]Armstrong, W. (1971) The cell membrane and biological transport *in* Selkurt, E. *Ed*. Physiology, 3rd ed. Boston, MA: Little Brown pp 1-3

8.2.4.2.1 The generic transmembrane material pump

It is likely that water molecules are transferred through the plasmalemma of a cell by embedded cholesterol, and potentially other sterols.

With the immense powers of the nucleus of a cell, and surrounding regions within the soma, to manufacture individual proteins and perform glycolysis, it is only necessary to transfer a small number of chemicals through the plasmalemma of a neuron. These include;

1. Oxygen, glycogen, H_2O, CO_2,

2. Either a variety of amino acids or a source of ammonia suitable for building amino acids,

3. A source of phosphoric acid or a variety of phospho-triglycerides.

4. And a variety of materials providing trace amounts of other critical atoms.

Most theories associate the transfer of this limited list of chemicals to the formation of protein based areas as discussed above. Many additional chemical reactions can occur on the external surface of the plasmalemma in support of neural operation. Only those additional chemical transformations occurring within the cell require the transport of additional reactants through the plasmalemma.

Lacking an adequate electron microscope image of a transmembrane material transfer mechanism, the community has been free to speculate on the mechanism. This speculation has spawned an endless variety of block diagrams and caricatures. Each variant has been supported primarily by kinetic evidence, frequently drawn from experiments on a different but chemically related species. Some evidence has been obtained from gross measurements of concentration changes, usually under *in-vitro* conditions. Such approaches are awkward. The proposed hypothetical mechanisms are frequently labeled pumps in the vernacular as a convenience. A generic kinase is frequently associated with the mechanism in the absence of any additional understanding. This is the case in **Figure 8.2.4-2** with apologies to Mullins who presented a similar block diagram in 1971[128]. The labels have been made more generic than in the original as the diagram seems compatible with almost any chemical species. Several additional arrows were provided in the original drawing. These suggested a variety of other materials might augment the basic machinery. The arrows associated with the rightmost pump are reproduced as in the original. The two pumps on the left can be considered as independent or as coupled depending on the argument to be made. If they are coupled, it is frequently proposed that the coupling is complicated and not representative of a one-to-one transfer process.

[128]Mullins, L. (1971) *in* Bolis, C. et. al. *ed*. Permeability and function of biological membranes. Amsterdam, North-Holland Pub. Co, pg 200.

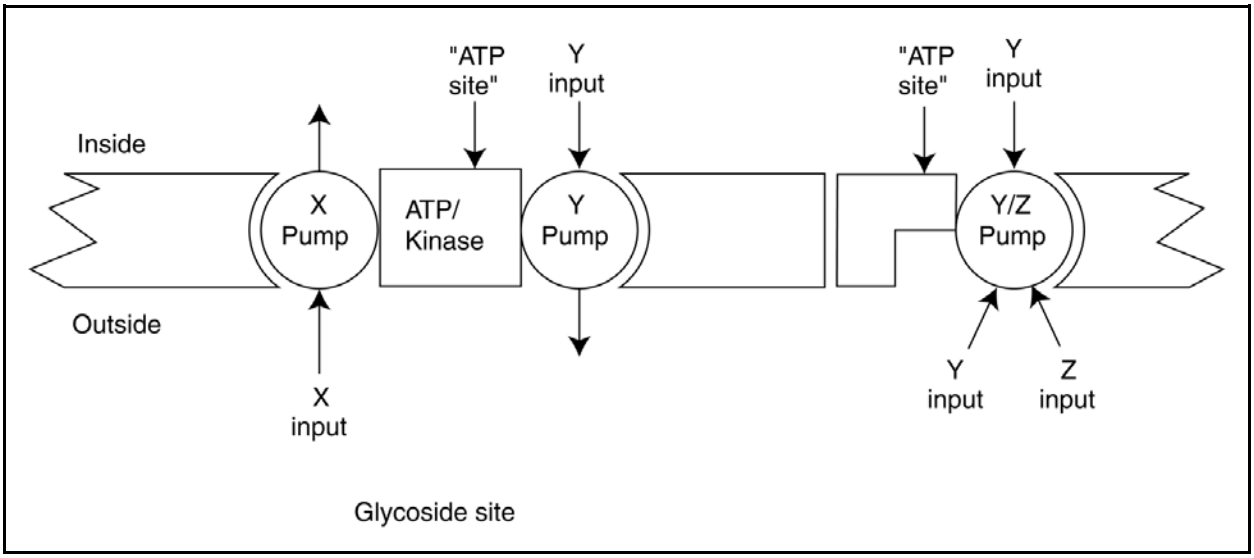

Figure 8.2.4-2 A generic transmembrane material transfer system. See text.

The description of this type of block diagram in caricature is where the fun begins. Are individual pumps provided for each species? If the pumps are coupled, how are they coupled and with respect to what species? In the chemical domain? In the physical domain? In the electronic domain? In the neural domain? Does one kinase support the transfer of two distinctly different materials in opposite direction? Virtually all of the above approaches have been proposed in the literature of biological transmembrane transfer.

Do the pumps represent a vesicle type structure that can either penetrate the membrane or do they represent an embedded vesicle that can access both the internal and external plasmas? If the pumps represent a pore, how is control of the species to be transferred accomplished? In either case, can the mechanism transfer a free ion or only complete (electrostatically neutral) molecules?

A fundamental framework that explains the transmembrane transfer of a variety of materials is desperately needed at this time.

8.2.4.2.2 Common detailed caricatures of a membrane pore

Caricatures of a pore composed of a protein material forming a cylindrical aperture passing through a BLM have been common for a very long time. Some X-ray crystallography has been interpreted as supporting such a configuration. Unfortunately, no electron micrograph of such a pore has appeared. Unwin has carried the caricature of the acetylcholine receptor (pore) the farthest. His data was gathered from the post synaptic membranes of the electric organ of the torpedo ray, *Squaliformes Torpedo nobiliana*. The Order defines the sharks. He assumes this data is generic to all synapses of other animals. No details were provided about where within the post synaptic membrane (inside or outside the gap junction) the proposed pores were located. His 1993 review provided proposed dimensions based on calculated sizes of various proteins[129]. The proposed pore is 80 Angstrom in diameter and 110 Angstrom long with about 55 Angstrom extending into the extracellular space. This latter dimension causes a problem. If the pore was present within the gap junction, the pore would extend across the entire width of the gap. Unwin does define a separate structure, a porin, as occurring within the gap junction. Based on this, it can be assumed his ligand-gated pores do not occur within the gap junction.

The review clearly defines the exploratory and conceptual nature of the field. The paper highlights the wide variety of purported neurotransmitters and the leading caricature of a pore. The description relies heavily on words like may, must, is likely to be, thought to be, despite, do not know, it is possible and another possibility. The review also defines two separate classes of pores, putative voltage-gated ion channels and putative ligand-gated ion channels.

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[129]Unwin, N. (1993) Neurotransmitter action: opening of ligand-gated ion channels *Neuron* vol. 10 (suppl) pp 31-41

Stephenson & Strange have provided a slightly modified version of Unwin's conceptual drawing of a pore[130].

The largely conceptual framework for the pore as a physical mechanism associated with neural signaling does not compete with the measured data associated with the BLM as an electrical diode. If operated as a gate, the pore continues to rely upon a difference in concentration density for the driving force behind the transfer of ions. The "three-dimensional image" in Unwin's figure 4 may be a caricature based on computer modeling with artificial surface reflectance added to provide detail not available in an electron micrograph.

The comments of Unwin on page 32 concerning the receptor sites of glutamate are encouraging. However, he is unable to associate these sites with a pore or channel. No references were provided for these comments.

8.2.4.2.3 The location of the material transfer mechanism

Before the introduction of the electron microscope, no way was available to image the BLM in detail. Since then, new images appear regularly. However, most images have centered on the synaptic region and the Nodes of Ranvier. These images have shown the unique electronic configuration of these regions along with a nearly uniform bilayer biological membrane (**Sections 10.6.3** & **10.7.1**). Little or no sign of vesicles or other pores in the membrane have been recorded. This is probably understandable for two reasons. First, little functional reason exists for such metabolic material transfer mechanisms to be found in these regions. Second, if they occurred in these regions, their highly transient nature (required if they are to support a 100-1000 Hertz bandwidth signaling function) would be difficult to record. The problem would be aggravated by the sample preparation procedures required in current electron microscopy.

A more extensive examination of the regions of the plasmalemma of a neuron may expose the location of regions dedicated to the transport of metabolic materials. However, examining the total surface area of a neuron at the required resolution is a time-consuming process.

8.2.4.3 Type 2 regions of membrane– *key to understanding the operational neuron*

Type 2 biological bilayer membrane is defined by its *molecularly asymmetrical structure*. The overall membrane remains impervious to the flow of ions. However, its electrical properties are affected by the molecular asymmetry. This asymmetry at the molecular level has quantum-mechanical implications. The type 2 membrane appears to exhibit a significant amount of interdigitation, at the molecular level, between the lipid materials facing each other in the hydrophobic core area of the membrane. This feature has a profound effect on the quantum-mechanical properties of the membrane and provides it unique set of electrical characteristics. The basic electrical characteristic is that of an electrical diode in series with an "intrinsic battery." Frequently, the intrinsic battery can be ignored. This quantum-mechanical configuration is used in two distinctly different mechanisms within the neural system. When used in the electrostenolytic process, these two properties are essentially passive in character. This usage is addressed initially in **Section 8.3.3**. It is addressed in greater detail in **Section 8.6.2**. When used in the mechanism of transistor-action (discussed beginning in **Section 8.4**), these properties are involved in an active mechanism of larger scope.

> The continuous molecularly asymmetrical liquid crystalline BLM is highly impervious to ions but it is a semiconductor with respect to fundamental charges and sensitive to its electrical potential environment. Such a membrane is of crucial importance to the operation of the neural system.

While requiring conductive electrolytes on both sides of the type 2 membrane for circuit continuity, the properties and operation of the type 2 BLM is independent of the chemical nature of the electrolytes. The primary property of any electrolyte is its electrical conductivity. The diode characteristic of the membrane is key to the transfer of electrical charge along the neural signaling path.

Ritchie and Rogart have provided a calibration for the difference between type 2 and type 1 BLM based on their

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[130]Stephenson, F. & Strange, P. (1993) Receptors for neurotransmitters, *Chapter 2 in* Shinitzky, M. Biomembranes. NY: Balaban Publishers

pharmacological experiments[131]. They measured the relative binding of tritiated saxitoxin to rabbit sciatic nerve membrane. They note the physiological in homogeneity of myelinated neuron, even when demyelinated. Speaking of an axon segment, they say that nodal membrane has an electrical conductivity per square micron 500 times higher than internodal membrane based on this relative binding. While they associate this phenomenon with a difference in putative density, 12,000 vs 25 channels per square micron, of sodium channels (in accordance with the chemical theory of the neuron), it is more easily described by one of two quite different situations.

1. The relative ability of the saxitoxin to bind to sites associated with the asymmetrical molecular structure of the type 2 BLM, and particularly sites of electrostenolytic activity.

2. The relative ability of the saxitoxin to bind to sites associated with type 3 BLM involved in molecular transport through the membrane.

Their extended discussion of the potential areas of the putative gates compared to the total size of the available membrane and the precision of their calculations (factors of two or larger) testify to the tentativeness of their conclusions.

Type 2 membrane is associated with providing the electrical potential to each isolated region of plasma within a neuron. In this role, a region of type 2 membrane is found on the surface of every lemma associated with a neurite, an axon, and the soma. Type 2 membrane is also involved in the transfer of signal information along and between neurons. In this role, areas of type 2 membrane are found within the gap region of every conexus, whether located within the soma of a neuron, at a Node of Ranvier, or at a synapse.

8.2.4.3.1 The properties of electrically conducting organic molecules

The recent work on conductive polymers (awarded a 2000 Nobel Prize) has not been introduced into the field of neural research up to 2007. It is particularly relevant to the theory of neural lemmas and adds to the material addressed in **Section 8.2.3.1** above. The work has been particularly important to the explosive development of organic light emitting diodes in recent years leading to organic flat screen television displays and other display devices.

> ***Any bioengineer or biochemist who does not recognize the importance of electrically conductive organic molecules should not be working in neuroscience.***

The materials used in these organic conducting devices are typically conjugated long chain hydrocarbons similar to those found in the long chain portions of the lipids of biological membranes. The materials used in conducting polymers have been described as polyacetylenes based on their initial preparation from the vapor deposition of acetylene. IUPAC has described this class of conjugated hydrocarbon chains as polyethynes (where only hydrogens are associated with the backbone carbons. IUPAC has noted that more complex families may involve alkyl groups replacing the hydrogens. Elsewhere in this material, these materials have been described as polydienes (**Section xxx**).

The discovery of man-made conductive polymers[132] was a momentous event during the 1970's and resulted in a Nobel Prize in 2000 to Heeger, MacDiarmid & Shirakawa[133].

The name polyacetylene fell into disuse quickly because the material contained no triple bonds (the hallmark of that family). **Figure 8.2.4-3** shows the fundamental conjugated structure of the polyethynes. This structure is a common one in organics and biologicals. When various hydrogens are replaced by other alkyls, the resulting chains form the long chain components of the Rhodonines as well as the terpenes. The p-bond orbitals overlap forming a conductive cloud extending the length of the material. Charges can move along this pathway very efficiently as they do in both photoexcitation in the retina and in the type 2 lemma structures.

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[131]Ritchie, J. & Rogart, R. (1977) Density of sodium channels in mammalian myelinated neerve fibers and nature of the axonal membrane under the myelin sheath *Proc Natl Acad Sci USA* vol. 74, no. 1, pp 211-215

[132]Fincher, C. Park, Y. Heeger, A. & Shirakawa, E. (1977) Electrical Conductivity in Doped Polyacetylene - *Phys Rev Letters* vol 39, pp 1098-1101

[133]Heeger, A. MacDiarmid, A. & Shirakawa, H. (2002) Conductive polymers Nobel Prize Lecture, http://www.kva.se

The type 2 lemma of biological cells can be described well by the theory of conductive polymers.

A vast amount of work has been performed adopting the polyethynes to use creating light emitting diodes for use in visual displays. To achieve the required objectives, high light output density yet long operating life, ever more complex molecular structures have been adopted. Although they still exhibit the conjugated double bond structure (where some or all of the double bonds may be replaced by their Kekule equivalent structures), dendromeres have recently become very popular in this application.

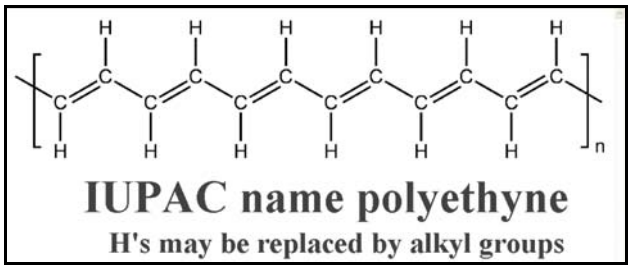

Figure 8.2.4-3 The polyethyne family (trivial name polyacetylene).

Important texts have appeared describing these materials[134,135]. Much of the reported work has employed isotropic, unaligned molecules. However, Steiger & Weder have reviewed work involving aligned (uniaxially oriented) molecules producing polarized light[136]. Heeger, MacDiarmid Shirakawa went considerably farther in their 2002 Nobel lecture. Their description of the mechanisms of conduction in a variety of organic materials are discussed in **Section 8.2.4.3.4**.

8.2.4.3.2 Glossary of terms used in LED technology

A specialized terminology is evolving rapidly in the field of conductive polymers, spawned particularly by the field of light emitting diodes. They following terms are from Nguyen & Destruel[137].

Bipolaron– a doubly charged polaron without spin, designated P^{++} or P^{--}.

Bound polaron pairs– adjacent oppositely charged polarons. Alternately, interchain charge transfer excitons.

Distant polaron pairs– polarons of opposite charge at a distance from each other. See bound polaron pairs.

Eximer– Two identical molecules, which are attracted when one of them is excited but which are mutually repulsive in the ground state

Geminate– A polaron pair originating from ionizing radiation.

Polaron–an electrically charged polymer molecule.

1. A positively charged polymer is a **radical cation** or a positive polaron.
2. A negatively charged polymer is a **radical anion** or a negative polaron.

Polaron pair– a pair of polarons of opposite charges, P^+ and P^- which interact with each other. They can be in the singlet or triplet state. See bipolaron.

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[134]Li, Z. & Meng, H. (2007) Organic light-emitting materials and devices. NY: Taylor & Francis

[135]Nalwa, H. *ed*, (2008) Handbook of Organic Electronics and Photonics, Volume 1-3. Los Angeles: American Scientific Publishers ISBN 1-58883-095-0.

[136]Steiger, D. & Weder, C. (2007) Polarized light emission from organic light-emitting diodes *In* Li, Z. & Meng, H. *eds*. Op. Cit. Chapter 5

[137]Nguyen, T. & Destruel, P. (2008) Electroluminescent devices based on organic materials and conjugated polymers *In* Nalwa, H. *ed*, (2008) Op. Cit. Vol 1, pg 42

The term doping is used in a somewhat different context than in solid state electronics.

The halogen doping that transforms polyacetylene to a good conductor of electricity is oxidation (or pdoping). Reductive doping (called n-doping) is also possible using, e.g., an alkali metal.

$[CH]_n + 3x/2\ I_2 \longrightarrow [CH]_n^{x+} + xI_3^-$ oxidative doping

$[CH]_n + xNa \longrightarrow [CH]_n^{x-} + xNa^+$ reductive doping

The doped polymer is thus a salt. However, it is not the counter ions, I_3^- or Na+, but the charges on the polymer that are the mobile charge carriers. By applying an electric field perpendicular to the film, the counter ions can be made to diffuse from or into the structure, causing the doping reaction to proceed backwards or forwards. In this way the conductivity can be switched off or on. [xxx This may be a key capability in the operation of the neuro-affectors discussed currently in **Sections 16.2 & 16.4** of Neuron. It is discussed further on the Nobel website.]

In the case of doping of long chain polymers, the dopants are not present as replacements in the three-dimensional lattice. They do not necessarily form acceptor or donor levels as in the solid state.

8.2.4.3.3 Operating principle of an OLED !!!

[xxx also appears in section 12.5.2.4. copied into the neuron book after the definition of type 2 lemma]

[xxx the following figures are trivial versions adopted from solid state physics While it is the cloud of excited electrons that is most important, the underlying structured materials are formed of long chain lipids and not three-dimensional crystalline material. See **Figure 5.4.5-1**.]

The organic light emitting diode is an organic diode not drastically different from the liquid crystalline material of the chromophores and the lipids of the biological lemma. **Figure 8.2.4-4** shows the relevant structure at the liquid crystalline lattice level.

Working principle
An OLED is composed of an emissive layer, a conductive layer, a substrate, and anode and cathode terminals. The layers are made of special organic polymer molecules that conduct electricity. Their levels of conductivity range from those of insulators to those of conductors, and so they are called organic semiconductors.

OLED schematic: 1. Cathode (-), 2. Emissive Layer, 3. Emission of radiation, 4. Conductive Layer, 5. Anode (+)
A voltage is applied across the OLED such that the anode is positive with respect to the cathode. This causes a current of electrons to flow through the device from cathode to anode. Thus, the cathode gives electrons to the emissive layer and the anode withdraws electrons from the conductive layer; in other words, the anode gives electron holes to the conductive layer.

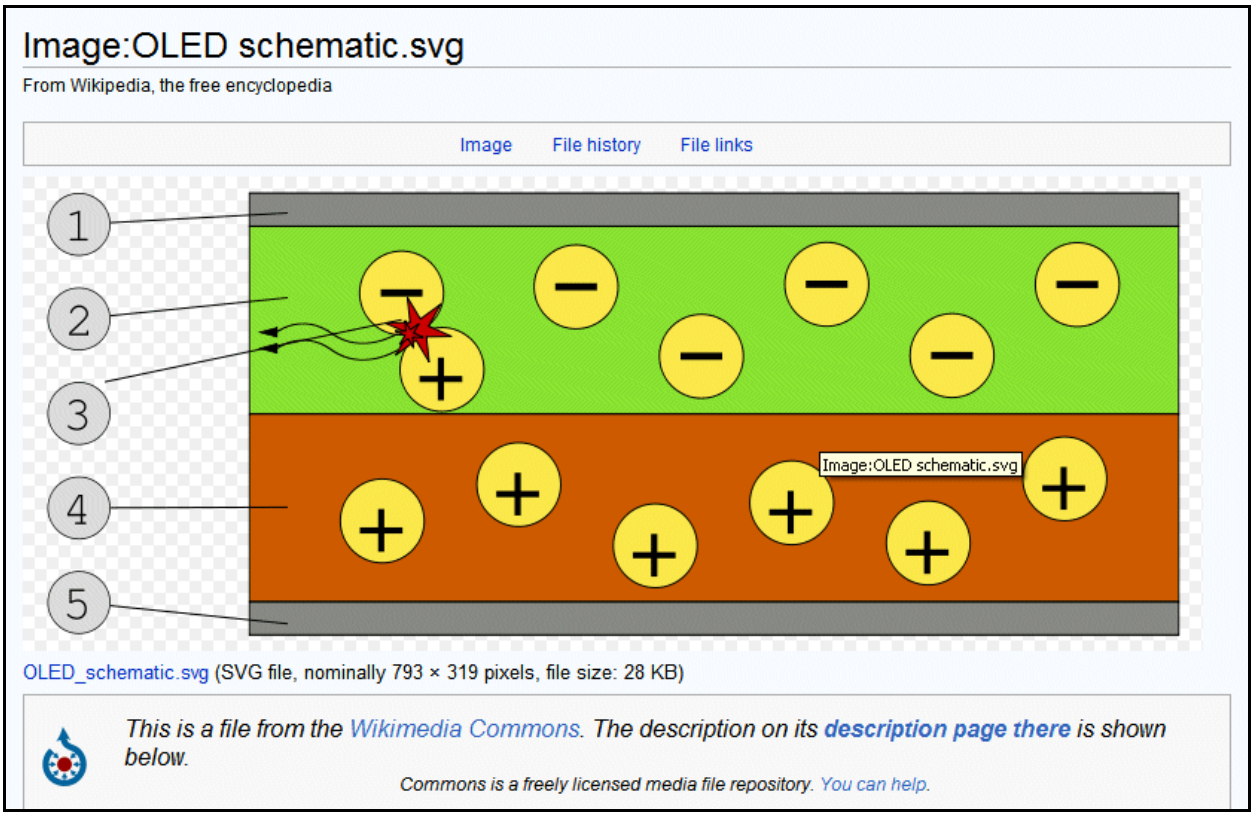

Figure 8.2.4-4 The structure of an OLED. 1. Cathode (-), 2. Emissive Layer, 3. Emission of radiation, 4. Conductive Layer, 5. Anode (+)

Soon, the emissive layer becomes negatively charged, while the conductive layer becomes rich in positively charged holes. Electrostatic forces bring the electrons and the holes towards each other and recombine. This happens closer to the emissive layer, because in organic semiconductors holes are more mobile than electrons (unlike in inorganic semiconductors). The recombination causes a drop in the energy levels of electrons, accompanied by an emission of radiation whose frequency is in the visible region. That is why this layer is called emissive.

The device does not work when the anode is put at a negative potential with respect to the cathode. In this condition, holes move to the anode and electrons to the cathode, so they are moving away from each other and do not recombine.

Figure 8.2.4-5 shows a diagrammatic representation.

Unfortunately, neither of these figures describes the orientation of the actual molecules of the polymers.

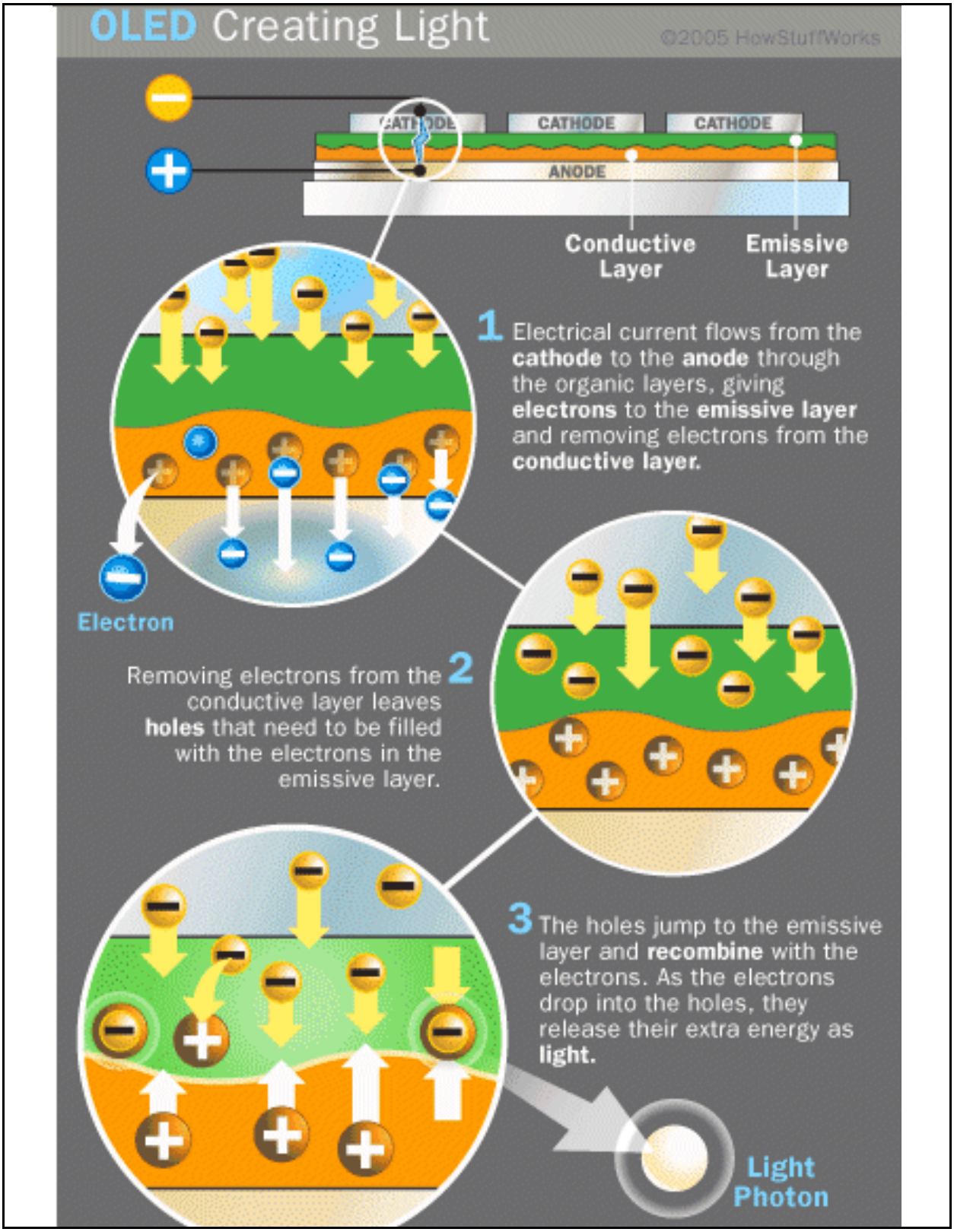

Figure 8.2.4-5 Steps in OLED operation.

Further reading
Shinar, Joseph (Ed.), Organic Light-Emitting Devices: A Survey. NY: Springer-Verlag (2004). ISBN 0-387-95343-4.
Hari Singh Nalwa (Ed.), Handbook of Luminescence, Display Materials and Devices, Volume 1-3. American Scientific Publishers, Los Angeles (2003). ISBN 1-58883-010-1. Volume 1: Organic Light-Emitting Diodes

Yersin, Hartmut (Ed.), Highly Efficient OLEDs with Phosphorescent Materials. Wiley-VCH (2007). ISBN 3-527-40594-1

8.2.4.3.4 Conduction in organic materials–Nobel Prize Lecture (2000)

The operation of OLED's is based on the flow of charges through relatively conductive organics. The discovery of man-made conductive polymers was a momentous event during the 1970's and resulted in a Nobel Prize in 2000. The type 2 lemma of biological cells can be described well by the theory of conductive polymers.

The operation of conductive polymeres (particularly polyacetylene) is described in the report on the 2000 Nobel Prize in Chemistry, http://nobelprize.org/nobel_prizes/chemistry/laureates/2000/public.html and http://nobelprize.org/nobel_prizes/chemistry/laureates/2000/chemadv.pdf . The first report contains a nice animation of charge moving along a conjugated molecule that has been "doped." **Figure 8.2.4-6** reproduces a frame of this animation showing its operational similarity to the child's toy known as Jacob's Ladder or "Click-Clack-Blocks."

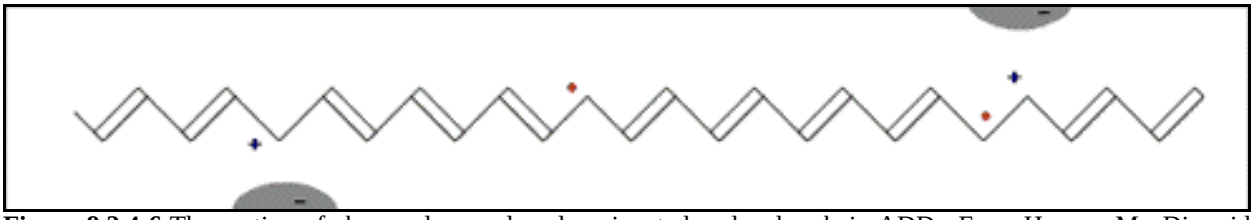

Figure 8.2.4-6 The motion of charge along a doped conjugated molecular chain ADD. From Heeger, MacDiarmid Shirakawa, 2000.

Figure 8.2.4-7 shows the arrangement of Jacob's Ladder.

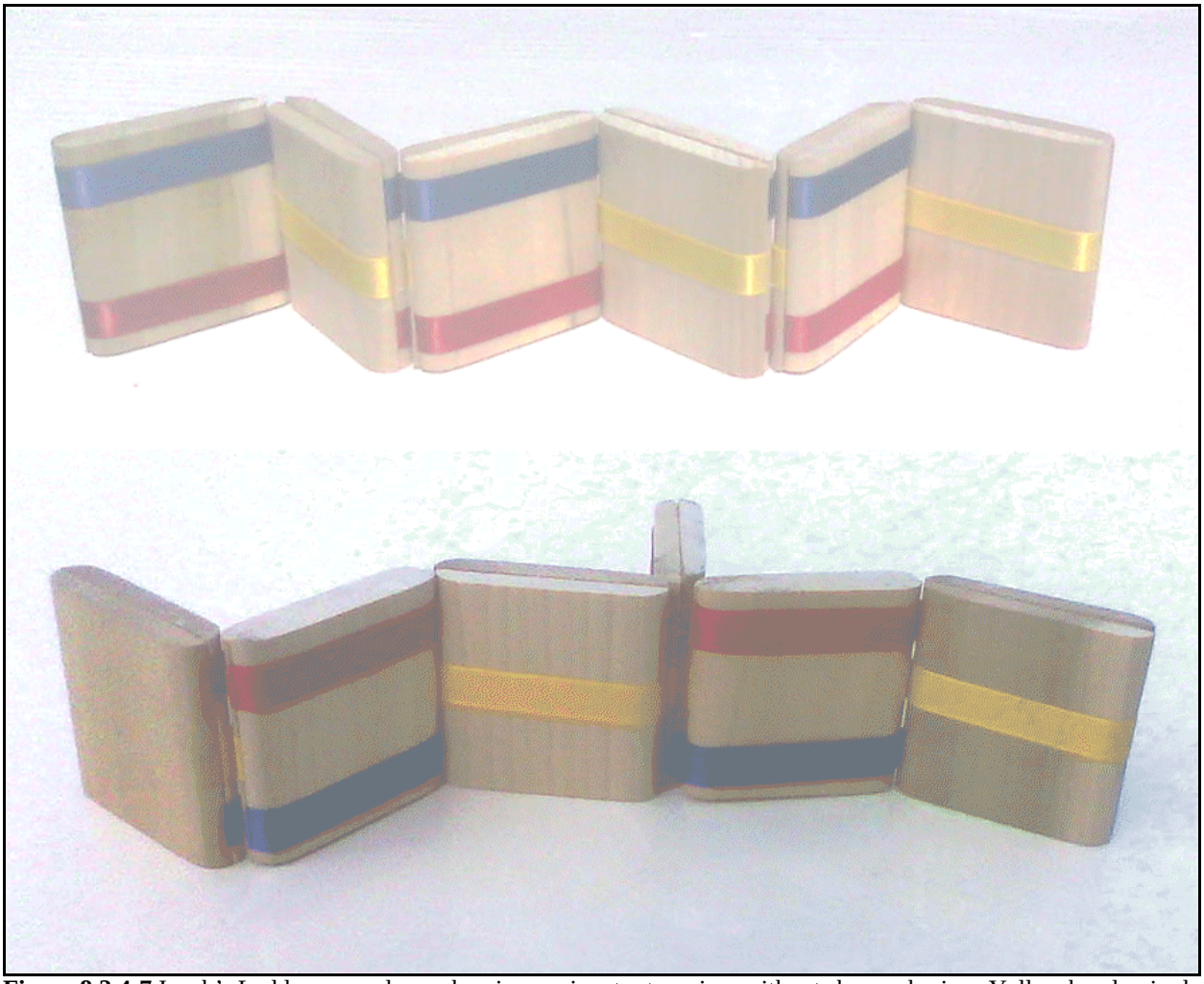

Figure 8.2.4-7 Jacob's Ladder, an analogy, showing conjugate strapping, without charge sharing. Yellow bands; single bonds. Red & blue; double bonds, one color represents sigma bonds. The other color represents pi bonds. Top; ladder in static condition. Bottom; ladder in transition with one conjugate link in motion and proceeding left to right along the ladder. Note, conjugation is maintained along the ladder during the transition.

As pointed out by Heeger, MacDiarmid Shirakawa, the situation in arrays of molecules becomes much more complex due to the expanded possibilities for doping and/or temporary charge positioning.

8.2.4.4 Measured electrical data for real bilayer membranes

The large variety of individual BLM types associated with neural signaling are widely dispersed within a neuron and it is difficult to identify their properties at the molecular level. A model can aid in the identification of these types as they appear in different regions of a membrane. Such a model has not been used in the past. One is presented in **Section 8.2.4.2.** [? Old section on electron pump]

Because of the above situation, the literature examining real biologically relevant membranes is in need of careful reexamination as noted by Finkelstein & Cass[138]. While the use of the patch clamp technique offers the potential of

[138]Finkelstein, A. & Cass, A. Permeability and electrical properties of thin lipid membranes. *In* Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. Volume 4 of the Distinguished Lecture Series of the Society of General Physiologists. NY: John Wiley & Sons. pg. 147s-172s

measuring carefully differentiated areas of plasmalemma, the detailed characteristics of generic samples of natural neural membrane presented in the literature have been inconsistent. More careful comparison to the differentiated areas of membrane suggested by this work should be used by investigators in the laboratory.

Caution is required in the analysis of the available data because of the susceptibility of membranes of liquid crystalline material to rupture or change by external agents. Precisely quantifying both the values and circumstances associated with the values are important. The values of Zon & Tien for example are prefaced by the words "typical" and "greater than" when speaking of a mixed group of bilayer membranes[139]. They do not specify the area of the membrane used to determine the capacitance and resistance.

Equally important are the criteria for determining the impedances within a complex circuit. The Laws of Kirchoff and Ohm require explicit conditions if accurate results are to be obtained. All voltage (and current) sources within the circuit must be removed before impedance measurements can be attempted using Kirchoff's Laws. If Ohm's Law is to be used, all diodes and other nonlinear elements must also be removed from the circuit.

Most of the conductivity changes reported in the biological literature are due to the presence of diodes (not variable resistors) and voltage sources within the circuits examined.

Pethig has provided one of the few descriptions of the permittivity of biological tissue as a function of frequency[140]. However, it is described as "typical" and suggests the sample has a permittivity extending over six orders of magnitude corresponding to a frequency range of eleven orders of magnitude. Little additional description and no additional references were provided. The reader should review this data considering the possibility that the data represents several capacitive element in series of drastically different size. See Pethig, pages 15-17. This condition may separate the individual components on a plot of this type without actually requiring changes of permittivity of such extreme values. As an example, most investigators of myelin report relative permittivity values of only 2-3.

His page 139 provides the complex permittivity of both water and ice. In this context, the real part of the permittivity corresponds to the capacitative effect and the imaginary corresponds to the loss component. The data shows the real portion of the permittivity of ice to be about 96 up to a frequency of about 1000 Hz compared to about 80 for water up to a frequency of over 1000 mHz. Mohilner gives the relative permittivity of water as 78.49 at 25 C[141].

8.2.4.4.1 Analogs of fundamental membranes using synthetics

In the early 1960's, Mueller, et. al. prepared bilayer membranes of phospholipid material plus hydrocarbon additives designed to represent prototypical biological membranes. In the late 1960's, Finkelstein & Cass reported detailed information on their synthesis of artificial bilayer membranes based on the methods of Mueller, et. al. The work involved a complicated protocol. It was designed to measure the permeability of these prototypical biological membranes to a variety of particles (water, neutral solutes, ions, ions in the presence of their unionized atoms). It was also designed to make measurement of the electrical characteristics of the membranes in the presence of various solutions containing the above materials. Lecithin (PC) based membranes were prepared in the presence of a variety of hydrocarbons, including cholesterol. Their primary finding was stated unequivocally in their abstract; **"The unmodified membrane is virtually impermeable to ions and small 'hydrophilic' solutes, but relatively permeable to water and 'lipophilic' molecules."**[142] They found the rate of ion movement to be immeasurably small through the prototypical membrane because of the extreme insolubility of ions in the hydrophobic region. They presented electrical resistivities per unit membrane thickness of 10^6-10^9 Ohms–cm^2. These membranes had a typical thickness of less than 100

[139]Zon, J. & Tien, H. Electronic properties of natural and modeled bilayer membranes. In Marino, A. (1988) Modern bioelectricity. Chapter 7, pg. 208

[140]Pethig, R. (1979) Dielectric and Electronic Properties of Biological Materials. NY: John Wiley pg 226

[141]Mohilner, D. (1966) The electrical double layer *In* Bard, A. *ed.* Electroanalytical Chemistry, vol 1 pg 313

[142]Finkelstein, A. & Cass, A. (1987) Op. Cit., pg. 145s

Angstrom.

They also present an interesting sidebar. They found the "permeability" of ionized iodine was enhanced in the presence of unionized iodine. This fact would suggest the presence of an electrostenolytic mechanism. This explanation is enhanced by their footnote concerning the appearance of "'black' regions" in the film. Could these regions have been the result of electroplating through electrostenolysis on the surface of the film? They found the thinness of the hydrocarbon region crucial to the transport of ionized iodine and introduced the fact that space charge becomes significant and electro-neutrality becomes less significant as controlling factors. They also found that the electrical resistance of the prototypical membrane was reduced by 1000:1 in the presence of iodine ions at concentrations greater than one millimole. Further, a 10:1 concentration ratio across the membrane resulted in a 60 mV potential across the membrane with the high concentration side positive. This result was obtained even in the presence of chlorine ions at 100 times higher concentration. [xxx sidebar can be eliminated]

Finally, they established that these prototypical membranes, and most of those prepared earlier by others from extracts of natural samples, did not exhibit "pores" through which particles could pass.

When they prepared a membrane in the presence of cholesterol, they found the filtration (osmotic) permeability coefficient, P_f, for water to be a significant function of the molar concentration of the constituents.

Ehrenstein, writing in Adelman, reviewed the properties of synthetic lipid membranes versus real axon membranes[143]. It appears from the electrical resistance measurement given that the artificial lipid membrane was probably symmetrical (type 1) and therefore an electrical insulator five orders of magnitude higher than the real membrane (of unknown and probably mixed type).

8.2.4.4.2 Analogs of <u>modified</u> fundamental membranes using synthetics

Finkelstein & Cass also explored the modification of fundamental membranes after their formation by various materials, mostly complex organics. However, their methods were more likely to introduce inclusion between the two bilayers or penetrations of only one bilayer than they were to emulate a natural membrane. Little reason exists to suggest their penetrations of the total membrane, if any, had the complexity of real penetrations at the molecular level.

They noted that many detergents simply disrupt the membrane structure and destroy the film. Many other organics lowered the apparent ion permeability of the membranes, frequently accompanied by the appearance of "black regions" within or on the surface of the films (pg 163s). [The appearance of a black film is a very strong indication of electrostenolytic activity at the surface of the membrane.] These changes in permeability were significant, varying by the sixth to tenth power of the concentration of the additional constituent. Because of these changes, the membranes showed a typical leaky diode current-voltage characteristic at 32 degree centigrade and major, repeatable changes in conductance as a function of temperature. Their work suggests the high sensitivity of the permeability to ions of prototypical and real membranes to the presence of complex organics.

8.3 The detailed electronic characteristics of a <u>type 2</u> membrane and membrane systems

It is important to differentiate between a complete multi-segment BLM system immersed in its *in-vivo* electrolytic environment and an isolated fundamental BLM *in-vitro*. The reason is the difference in complexity of the equivalent electrical circuits for these situations. For type 1 and type 2 membranes, each situation is completely analyzable using Kirchoff's Laws. However, without isolating a specific type of membrane, the integrity of the recorded data is affected. Understanding the data acquired from "pure" samples of each type of membrane makes interpretation of more complex situations possible. It is also important to address two matters frequently confused by investigators trained in biology.

> **The biological community has frequently and apparently unknowingly applied Kirchoff's Laws of electricity incorrectly. This has generally been due to attempts to use Ohm's Law (a special case of Kirchoff's Laws) outside its range of applicability. The result has been the description of variable impedances that are in fact composites of simpler impedances combined with other unrecognized mechanisms (voltage or current sources)**.
>
> **Ohm's Law only applies to totally passive linear circuits, wherein all voltage or current sources have been accounted for** (See **Section 8.1.1**)**.**

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[143]Ehrenstein, G. (1971) Excitability in lipid bilayer membranes *in* Adelman, W. Biophysics and Physiology of Excitabel Membranes. NY: Van Nostrand Reinhold Chapter 21

Benjamin Franklin is credited with a serious mistake. He defined a current as passing through an external circuit from a positive terminal of a battery to the negative terminal. Unfortunately, we now know it is the electron that actually moves in such a circuit. It travels from the negative terminal to the positive terminal.

As noted in **Section 8.2**, the electrical characteristics of type 1 membrane (and type 3 membrane) are easily understood. They operate as electrical insulators under normal conditions. It is the type 2 membrane that is key to the electrical performance of the neuron and the neural system. The following sections will address the type 2 membrane as it participates in two distinct mechanisms. Section 8.3 will address the type 2 membrane associated with the electrostenolytic process in detail. The more complex situation, where two type 2 BLMs are brought into juxtaposition and appropriately biased, will be deferred until **Sections 8.4** & **8.5**.

8.3.1 The unique quantum-mechanical characteristics of a membrane

Finkelstein & Cass were probably the first to raise the following question[144]. "Does the very thinness of the membrane, irrespective of its organization, necessitate the consideration of physical phenomena that can generally be ignored in the discussion of 'macroscopic' membranes (such as ion exchange membranes or dialysis tubing)?" The following material (and the papers of Mueller & Rudin–see **Section 8.1.1.2**) will confirm the answer is yes.

Section 8.2.1.3 developed the detailed molecular arrangements found in BLMs. When these physical arrangements are explored within a quantum-mechanical context, the diode characteristic of the asymmetric membrane becomes understandable.

The molecularly asymmetrical BLM can be represented by three electrical elements, an "intrinsic" battery in series with a diode and a capacitor shunting that pair of elements. As indicated earlier, the combination of the battery and a diode is an equivalent circuit resulting from quantum-mechanical mechanisms. They do not exist without an external potential across the membrane. **This combination of circuit elements cannot perform thermodynamic work when connected to an external circuit**.

A simple application of "the law of electrical neutrality based on electrostatics" shows that the membrane cannot perform thermodynamic work unless it was to chemically consume itself in the process. The fact that this does not occur in practice proves that the battery symbol does not represent a conventional battery. It represents an equivalent battery as discussed in the following section.

The following section will also prove that the voltage-current characteristic of a type 2 membrane, in the presence of an external potential, is most appropriately represented by a circuit *equivalent* to that of a battery and a diode in series. The BLM has traditionally been represented in the physiological literature by a battery and a variable resistor in series. This representation has not lead to a satisfactory explanation of the operation of a membrane.

8.3.2 The characteristics of an isolated biological membrane

The steps in applying Kirchoff's Laws will not be addressed here. The general procedure requires that all batteries and other sources of a potential within the electrical network be short circuited or removed. This allows the remaining impedance network to be quantified precisely. For a fundamental membrane, the three expected equivalent circuit elements are integrated and the measurements require greater care. By starting at a sufficiently simple circuit level, examining the performance of the circuit graphically is possible. From this examination, the characteristics of the individual components can be measured with considerable precision. No unusual postulates to accepted electrical circuit theory are required.

Noting the parameters of a BLM depend on the geometry of that membrane is important. A significant difference exists between the values of capacitance, and other parameters, calculated assuming an equivalent flat surface for the membrane and the values calculated for a cylindrical membrane. This difference is addressed in **Section 10.3.4**.

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[144]Finkelstein, A. & Cass, A. (1987) *in* Finkelstein, A. Water movement through lipid bilayers, pores and plasma membranes. NY: John Wiley & Sons. pg 145

The impedance associated with an electrical element consists of two parts, a resistive part and a reactive part. These are the usual terms used in electrical engineering. They are used to separate the "resistive" (normally dissipative) component of the impedance from the energy storage (or non-dissipative) component of the impedance. The latter consist of capacitances and inductances. These parts can be isolated by applying an alternating potential across the element, or network of elements. The resistive part is characterized by the fact the current flowing through it is in phase with the applied voltage. The reactive part is characterized by the fact the current flowing through it is in quadrature with the applied voltage. The total current flowing through an arbitrary network of more than two passive electrical elements can exhibit any phase angle between –90 and +90 degrees (first and fourth quadrants) relative to the applied voltage. With the addition of active components, the phase angle can move into the second and third quadrants. This section will discuss the "resistive" part of the impedance and then the "reactive" part.

As will be shown below, the typical *in-vivo* axolemma cannot be described using only resistive and capacitive elements. It also exhibits inductance, a diode characteristic and a current source associated with electrostenolysis.

8.3.2.1 The resistive characteristics of the fundamental membrane in electrolyte

Terminology is a problem in the literature concerning the impedances of membranes. Many authors have been inconsistent in the units they associated with the terms resistance, conductance and resistivity. The terms resistance and conductance are associated with a parameter measured between two discreet points in a circuit. They are reciprocal. The resistance is defined with units of Ohms. These terms are normally associated with fixed values associated with electrically linear and bilateral materials.

Resistivity is a measure of the bulk electrical properties of a material. It is typically proportional to the thickness of the material and inversely proportional to the cross sectional area that a current passes through traversing the material. Thus, it has the units of Ohms per unit length times the unit cross section, or typically Ohm-cm in the CGS system. The conductivity is the reciprocal of the resistivity. A problem can arise when discussing a BLM with a nominally fixed thickness. In this case, several experimenters have used resistivity with the units of Ohms times the unit cross section without including the unit length term. As a result, they use the expression Ohms-cm^2 to indicate resistivity. This is an incorrect (shorthand) expression prevalent during the 1930–1960's. The expression Ohms-cm^2 refers to an alternate parameter, the resistivity per membrane thickness. The resistivity per membrane thickness can be given the name "thin-film resistivity." With a typical membrane thickness of 100 Angstrom, the thin-film resistivity, or resistivity per membrane thickness (with units of Ohm-cm^2) is typically 10^6 smaller than the true resistivity of an equivalent bulk material (with units of Ohm-cm).

Cole provided an elementary discussion of the properties of a single membrane versus sea water in 1968[145]. It highlights the above problem with units. The terms in parentheses have been added for clarity. "Membrane conductances range from very small values beyond the negative resting potential (in cutoff) to much larger maximum values at positive potentials (in conduction). The nominal value of 1000 Ohm-cm^2 (resistivity per membrane thickness) at rest corresponds to a column of sea water 50 cm long. A maximum conductance equivalent to 5 Ohm–cm^2 (resistivity per membrane thickness) is approached in a number of membranes under positive voltage clamp, and 0.1 Ohm-cm^2 (or less, see **Section 9.4**) has been found for a node (electrotonic synapse). A nominal value of 1 Ohm-cm^2 (resistivity per membrane thickness) is then equivalent to a 0.5 mm of sea water." This last value shows the synapse (a pair of uniquely juxtaposed BLMs) can have a conductance 10,000 times greater than for a single BLM.

Cole also considered the operating and breakdown potentials of a membrane. "The values of the average (high forward bias) and the breakdown (reverse bias) field strengths in the membrane are of the order of 10^5 V/cm. This average value for the normal operations of the membrane is certainly striking. It may well be highly significant as more becomes known of the behavior of other systems under such conditions." Cole was entirely correct. The high field strength under reverse biased conditions plays a key role in the adaptation amplifier within the photoreceptor cell (**Section 12.5**). The fact that the breakdown potential is about +150 mV is also important when exciting the membrane artificially in the laboratory.

Cole concludes: "Considerable effort was devoted to the expression of membrane parameters in terms of centimeters and seconds but we have reached a stage at which molecular units may be more immediately significant." This work will return to that theme after the next paragraph.

The biological literature has long represented the equivalent electrical circuit of a BLM by a battery in series with a variable resistor (sometimes shunted by a capacitor). This representation is an oversimplification. To compensate for

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[145]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press pp 520-522

this difficulty, authors have frequently resorted to using multiple current paths with each path represented by a battery and a variable resistor in series. Justification for this representation has relied upon the "independence principle" introduced by Hodgkin & Huxley. This principle is not found in electrical engineering. It is merely an attempt to introduce a mechanism justifying their hypothesis concerning the axon. The correct representation for a single region of a type 2 membrane is a single intrinsic battery in series with a single diode with the combination shunted by a single capacitor.

8.3.2.1.1 The electrical characteristics of a theoretical diode

The literature contains an immense amount of data showing that the fundamental impedances found in vision research are inherently nonlinear and are symbolized by a perfect diode. This is also true of the fundamental BLM. The perfect diode is characterized by a very simple algebraic equation, $I = f(e^{v})$ or more specifically, $I = I_o(\exp((V - V\gamma)/\eta V_T) - 1)$. The terms in this equation are discussed below.

Others could argue that the nonlinear characteristics found in the literature are not those of diodes. Historically, the impedance has been described as a variable resistor (using a symbol with a sweeper but no hand to control the sweep)[146]. However, the evidence is overwhelming. There is a critical test that the exponential hypothesis passes with flying colors. The natural base e has a unique property in the calculus in that it is its own derivative. Therefore, if the current-voltage characteristic of an impedance is described by the above equation, its derivative will also be described by an equation of the same form. No other simple mathematical function exhibits this property. Figure 6 and 7 of paper number III of Millecchia & Mauro[147] provide just such results. Their plots of the differential, $\Delta I/\Delta V$ versus V are identical in form to the original I versus V plots.

Figure 8.3.2-1 displays the current-voltage characteristic of a diode. The frame on the left shows the exponential characteristic on a single set of linear scales. The frame on the right is frequently used to highlight the features of the diode. The lower portion is at a much finer current scale than the top. The general equation for this function contains three parameters, the offset parameter, $V\gamma$, the thermal parameter, ηV_T, and the scaling parameter, I_o. By using a split scale, the reverse current value (I_o) can be illustrated on the same graph with the much more prominent offset parameter and the forward current value. It also makes a more convenient graph for illustrating the reverse voltage breakdown characteristic of the diode, usually labeled V_Z. These four parameters, and the capacitance of the device, completely characterize any diode. In many situations, the static impedance, shown by the line labeled Z(static) is of interest. In other situations, the dynamic impedance, shown by the line labeled Z(dynamic) is of interest. Note the dynamic impedance is normally lower than the static impedance.

The offset parameter, $V\gamma$, is the potential of the intrinsic battery associated with a membrane.

Comparing these figures with that of a simple resistor is useful. The current-voltage characteristic of any resistor is a straight line through the origin on these graphs. The line describes the voltage across the resistor divided by the current through the resistor and given by the relationship V/I. There is no reason to use an expanded scale with a resistor. A high value of resistance is shown by a nearly horizontal line in the left frame while a low value of resistance is shown by a nearly vertical line.

Defining a fixed resistance for the resistive component of a diode is not possible since the equation cannot be written in the form V/I. However, it is possible to define an effective resistance (actually two) at a given voltage (or current). The first, the static resistance (also known as the large signal resistance) can be defined as (V-V(0))/(I-I(0)) where V(0) and I(0)are defined as equal to the zero point on the graph of I versus V (or any other point if desired). The second can be defined as the small signal (also known as the small signal or dynamic) resistance given by the slope of the graph of V versus I at a given voltage (current), $\Delta V/\Delta I = K \bullet e^{-v}$. Alternately, the small signal conductance is, at a given voltage, $\Delta I/\Delta V = (1/K) \bullet e^{v}$. Both the static and dynamic impedances of the diode play important roles in the neural system.

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[146]Eckert, R. & Randall, D. (1978) Op. Cit. pg 118

[147]Millecchia, R. & Mauro, A. (1969) The ventral photoreceptor cells of Limulus. J. Gen. Physiol. vol. 54, paper II-pp. 310-330 and paper III-331-351

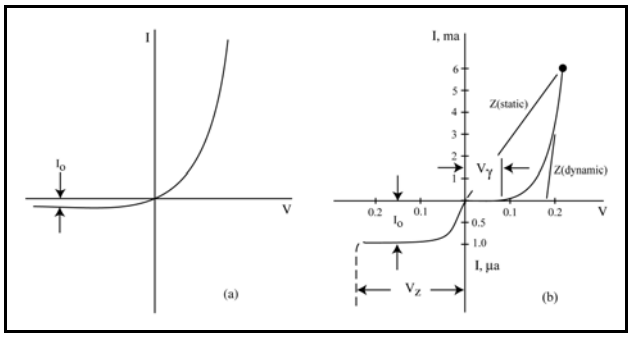

Figure 8.3.2-1 The current-voltage characteristic of a diode. The left frame employs linear axes. The right frame has a break in the scale of the vertical axis to highlight the reverse current through the diode. See text for other features of the graphs.

Occasional discussions appear in the literature as to whether a particular biological impedance is a function of the current through it or of the voltage across it. Clearly, such a distinction is meaningless.

The diode is seen to represent a very high resistive impedance when it is reverse biased (that is defined by the reverse current, I_0, for any large value of voltage). Alternately, it exhibits a very low resistive impedance (approaching an asymptotic value) when it is forward biased. The limitation of the current to I_0 says the diode is not equivalent to a fixed resistor at high reverse voltages. Up to the point of breakdown, the calculated resistance will be proportional to the voltage applied.

8.3.2.1.2 Measured characteristics of a fundamental biological membrane

8.3.2.1.2 Measured resistive impedance of a real BLM

The goal of this section is to determine whether the fundamental BLM can be defined using a Donnan–Nernst symmetrical but semipermeable membrane or is more properly defined using an asymmetrical semiconducting membrane that is impermeable to ions. In the Donnan–Nernst context, the membrane is electrically symmetrical and the asymmetrical electrical properties are due to the difference in concentrations and permeabilities of the two electrolytes. In the semiconducting membrane approach, the membrane itself is electrically asymmetrical to the flow of electrons regardless of the adjacent electrolytes. It need not be conductive to any ions present in the solutes.

While performing experiments with a different purpose, Eliasof, et. al. have provided a useful set of voltage-current characteristics for a simple membrane-electrolyte system[148]. The data was captured using a special voltage clamp technique known as the patch clamp technique. This technique allows the analysis of very small areas of a BLM. The details of their test configuration were not provided. Their figure 4 is reproduced in **Figure 8.3.2-2** with the addition of several curves to the frame labeled sEAAT2B. These will be discussed below. Their figures 5 through 7 are also instructive. The membrane is the plasmalemma of an oocyte of salamander, *Xenopus*, and not that of a neuron. However, it is a premise of this work that the plasmalemma of all animal cells share a common structure whether the cell has evolved into a neuron or not. The electrolyte associated with the electrical contact was KCl at a concentration of 3 M. This configuration gave an electrode resistance of "less than one K-Ohm." The initial interior plasma was native to the cloned oocyte.

[148]Eliasof, S. et. al. (1998) Localization and function of five glutamate transporters cloned from the salamander retina. *Vision Res*. vol. 38, pp 1443-1454

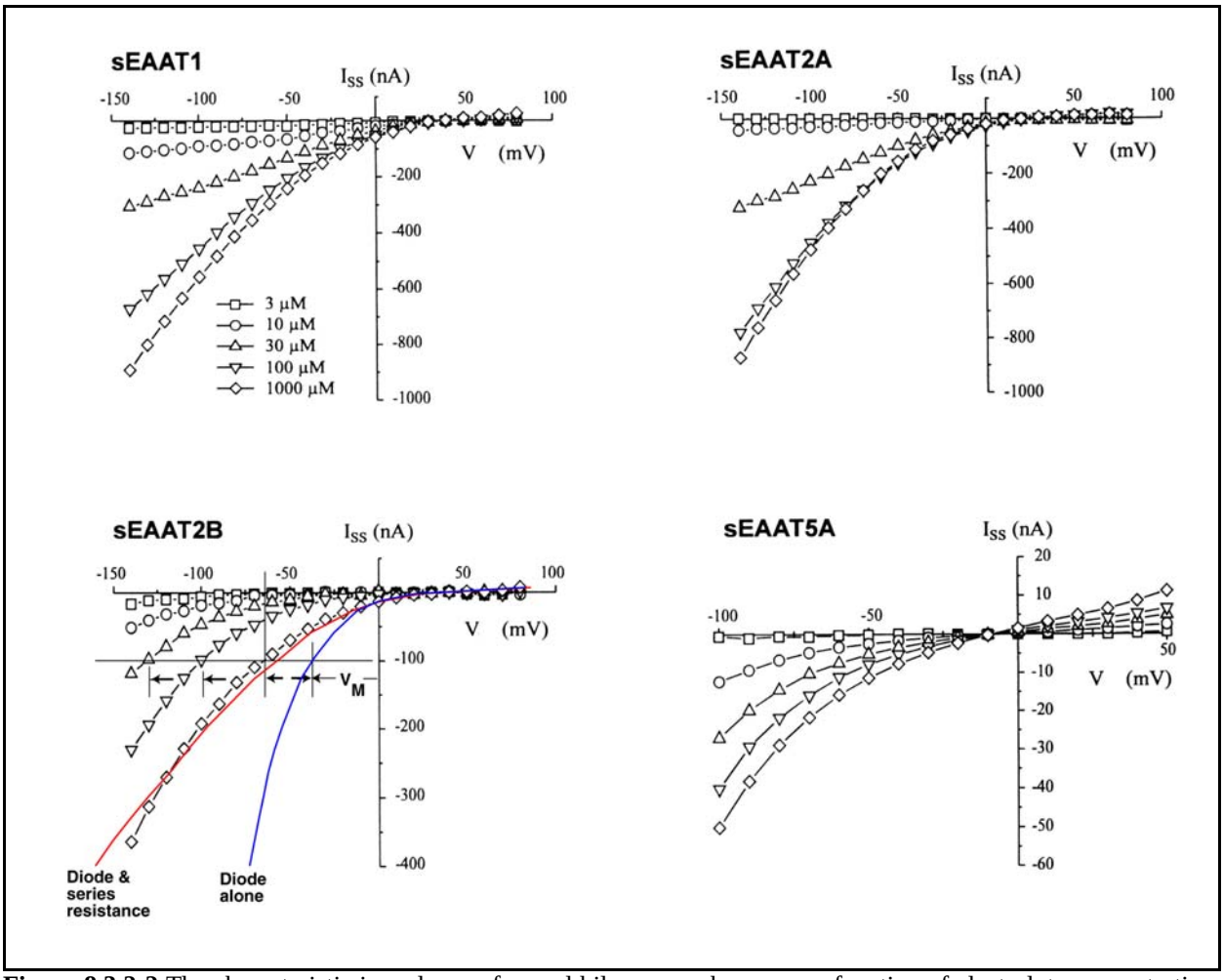

Figure 8.3.2-2 The characteristic impedance of neural bilayer membranes as a function of electrolyte concentration. A reinterpretation of Eliasof (1998). One electrolyte was modified to contain L-glutamate at the concentrations shown. Note the distinct crossover at minus 10 millivolts for the lower right sample. The labels of the voltage scales have been changed and labeling added to the lower left quadrant. The "series resistance" is the resistance attributable to the two bulk electrolytes and the electrodes.

Unfortunately, at least two problems relate to this data. First, Eliasof, et. al. used a patch clamp approach. This approach is a variant of the simple Leyden Jar technique and similar to those suggested in Kotyk & Janacek[149]. A better approach would use a Ussing apparatus discussed in **Section 8.2.2.** The Leyden Jar approach results in the total recorded voltage being a function of three elements, the conductivity of the sample membrane, the conductivity of the electrolytes employed and the ½ potentials (and conductances) of the test set electrodes. Because of these unknowns, it is not possible to ascertain the exact impedance characteristic of just the membrane. Following this rationale, the data can be interpreted as the result of a combination of an electrical diode (the membrane), a conductance (the bulk electrolyte plus the electrode electrolyte) and one or more batteries (the electrodes and any intrinsic membrane potential) in series.

[149]Kotyk, A. & Janacek, K. (1975) Cell membrane transport, 2nd ed. NY: Plenum Press pp. 303-304

The second problem relates to the electrolyte used. It appears the concentrations given refer to the concentration of L-glutamate in an undefined solvent, probably distilled water. If this is the case, no sodium was present on either side of the membranes. The quality (pH) of the water could be significant in precise measurements. This author was unable to determine unequivocally from the paper how the solution was applied to the oocytes, topically or by injection. Because of the participation of L-glutamate in the electrostenolytic process of a typical cell, it was a poor choice for purposes of this analysis. However, the experimental goal of Eliasof, et. al. and their protocol assumed the role of L-glutamate was that of a neurotransmitter, not a neuro-facilitator. For the immediate purpose, it is only necessary that L-glutamate (glutamic acid) is highly ionized at the concentrations used. The analysis below confirms this is the case.

In spite of these problems, the data appears to provide good relative data regarding the plasma membrane of the oocytes of salamander. The individual frames published all show a common underlying mechanism except for sample sEAAT5A. Note the scale change for this sample. Eliasof, et. al. discussed the problems with their experiments involving sample sEAA5A. The curves for this sample show a symmetry between the first and third quadrants about the value –10 mV. They also show a total impedance 10-25 times higher than for the other frames. The data suggests the portion of membrane captured within the voltage clamp apparatus was dominated by type 1 membrane and not type 2 membrane like in the other frames.

Omitting sEAAT5A for the moment, the question is whether the data supports the symmetrical membrane proposition based on Donnan and Nernst or the semiconductor diode proposition of this work. Starzak has recently reproduced the mathematics of the Goldman constant field equations (pg 220-223) that reflect the Donnan and Nernst models. He notes that the symmetrical membrane model can act as a "rectifier" due to the difference in permeabilities and concentrations of the electrolytes. Unfortunately, the models of Starzak, Donnan, Nernst and others have not included the resistive impedance associated with the electrolytes acting as conduits to the test set electrodes.

Starzak has provided a theoretical description of the current-voltage characteristic of a putative BLM based on the hypothesis that the membrane is a symmetrical semipermeable material[150]. He developed a complete equation for his symmetrical membrane configuration (eq. 9.98) but did not plot it explicitly (with data points), preferring to discuss its asymptotic limits. This was probably because his equations are discontinuous at zero potential. A discontinuity in a mathematical analog of a continuous process is not a desirable feature, particularly when small values of the independent variable are particularly important. Such a discontinuity says the equation, while describing the data, is not that used in the underlying mechanism.

The results of Starzak's analysis shows that the impedance of the cell absent the electrolytes becomes a fixed resistance represented by a straight line passing through the origin for equal electrolyte concentrations on each side of the membrane. His analysis did not include any finite resistances due to the current paths between the surfaces of the membrane and the electrodes. He recognized the need for this in more complicated models found in practice.

Starzak used the term rectifier in its generic form by saying it exhibits a different asymptotic resistance in opposing quadrants of the voltage-current characteristic. This definition is similar to the large signal approximation used in industrial rectifiers, Z(static) in the earlier paragraph. This definition is significantly different from the definition of a diode (acting as a rectifier) as used in low voltage circuits. The diode exhibits an asymptotic resistance when passing current in the forward direction. However, it exhibits a limiting absolute current, I_0, when opposing the flow of current. It also exhibits a characteristic exponential curvature in the area of low applied potential. These conditions are significantly different from the "rectifier" defined by Starzak.

It is useful to consider the asymptotes related to the data of Eliasof, et. al. as they help define the boundary conditions of the underlying mechanisms. By evaluating each frame of the figure graphically, it is possible to discern the contribution of the membrane, the electrolyte and the electrodes. Assuming the electrolyte and the electrodes used to introduce the electrical potential into the cell are symmetrical with respect to polarity (a questionable assumption), the impedance associated with the test set alone is symmetrical with respect to the current and no extraneous potential source is introduced at zero current through the cell.

It is clear from the upper and left frames of the figure that the test configuration does not exhibit the detailed properties of a Starzak (Goldman–Donnan–Nernst) rectifier. The curves in the first quadrant exhibit an asymptote at a current, I_0 rather than an asymptote described by a constant resistance passing through the origin. The asymptotes of each curve do not appear to pass through the origin. This feature is a characteristic of a diode rectifier.

Looking at the third quadrant of the frames is also instructive. The sets of curves are consistent with part of the

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[150]Starzak, M. (1984) The physical chemistry of membranes. NY: Academic Press, pg. 223

asymptotic condition defined by Starzak for a "rectifier" however, the asymptotes do not pass through the origin. They appear to converge near -70 mV.

The curves are amenable to further analysis. It is proposed that the overall characteristic of a BLM separated by two electrolytes of finite path length is that of a diode rectifier in series with a finite resistance due to the electrolytes. Under these condition, the equation describing the curves in the figure would be given by:

$V - V\gamma = I(Z + R)$ or $V - V\gamma = IZ + IR$ or $V - V\gamma = V_m + V_e$

where Z is a perfect diode with an exponential impedance representing the membrane. R represents the resistive impedance associated with the electrodes and the electrolytes. $V\gamma$ is the offset parameter associated with a semiconducting diode. V_m and V_e represent the voltages across the membrane and the electrolyte and electrodes respectively. The last relationship has been plotted on the lower left frame of the figure. The total voltage, at a given current, between the copper wire terminals of the test set is given by the sum of the voltage across the membrane, V_m, and the voltage V_e representing the appropriate concentration for the test electrolytes. For the asymmetrical membrane (that is impervious to ions) assumption, the current is less than I_0 for any potential that is opposed by the diode. Significant current through the test set should only be found in the lower left quadrant of each frame.

For a very dilute electrolyte, the resistivity of the electrolyte is high. For R>>Z, the curve is a straight line given by $V - V\gamma = IR = V_e$. Such a line approaches horizontal in this graphical presentation.

As the electrolyte concentration rises, its electrical conductivity also rises and its resistivity drops. As the concentration continues to rise the voltage drop across the electrolyte becomes negligible and the curve becomes representative of only the membrane and the electrode potentials. The curve is an exponential given by $V - V\gamma = IZ = V_m$. This function is described by the line marked "diode alone" in the lower left frame of the figure.

The lower left frame has been overlaid by the response of a perfect semiconductor diode and a perfect semiconductor diode in series with a resistance. The diode limits the reverse current in quadrant one to its reverse current parameter, I_0 regardless of the resistive impedance present. This value appears to be on the order of 10 nA or less (see figure 6 in Eliasof, et. al.). The current in the forward direction is limited by the effective resistance of the diode (that varies with applied voltage) and the resistance of the electrolytes in series. While this configuration does exhibit an asymptote as described for a "rectifier," it does exhibit a specific shape defined by the current-voltage characteristics of the diode and resistor combination. The curve labeled diode & series resistance corresponds to the condition for a diode in series with a resistance calculated at –100 nA of 650 Ohms. This number is in excellent agreement with the "less than one K-Ohm" value given by Eliasof, et. al. for their test set. It also suggests that the curve marked 1000 μM is in fact the asymptotic value for this test configuration. At this concentration, the resistance of the test set is dominated by the resistances of the electrodes. Further increasing the concentration of the L-gluamate electrolyte would have negligible effect.

The curve marked diode & series resistance is within 10% of the measured response for 1000 μM over the entire range of measurement. The equation of this curve is not discontinuous at any point until it reaches the asymptotic value for I_0.

> **The data of Eliasof, et. al. is highly supportive of the fact that the BLM is an electrically asymmetrical diode element that is independent of the ionic environment external to the membrane (except that it be ionizable in order to provide an electrical path to the electrodes of the test set). The BLM need not be (and generally is not) permeable to ions!** The equations of Donnan, Nernst, Goldman and Starzak do not apply to the real *in-vivo* BLM. They do not exhibit an absolute asymptote limiting the reverse current through the system. The asymptotes applicable to the BLM are those illustrated in **Figure 8.3.2-1**.

The individual frames suggest the diode characteristic is accompanied by an offset parameter, $V\gamma$, but the data is not consistent enough to clearly define this parameter. Yau, et. al. presented data that leads to a more explicit definition of

the offset parameter, Vγ. They employed different solutions on the two sides of the membrane[151]. With "Normal Ringer's solution" on one side and a pseudo intracellular solution on the other side, they measured a very precise +10 mV for the offset parameter, regardless of the amount of Ca^{2+} or Mg^{2+} added during the experiment. When the same complex solution was provided on both sides of a different membrane of larger size, the offset parameter was found to be zero (and the currents were much larger). This stresses the importance of evaluating the diode equation of a membrane under *in-vivo* conditions and in specifying the physical dimensions of the sample.

> The data of Yau, et. al. was all obtained under Leyden jar conditions. Pending better data based on experiments using a Ussing apparatus, the offset parameter (intrinsic battery potential) of the in-vivo biological diode will be taken as +10 mV at 300 Kelvin, much less than the values in conventional germanium or silicon diodes. (See **Section 8.5.4** or **Appendix B.6.2** xxx)

Starzak proceeded to present several additional scenarios based on the symmetrical semipermeable membrane assumption. These appear to be totally academic with regard to the electrically asymmetrical ionically impermeable nature of the BLM.

Neither the analysis by Starzak nor the graph by Eliasof, et. al. address the second order process of dielectric breakdown in a diode at high reverse voltage leading to the parameter V_Z. However, Mueller & Rudin[152] have provided the complete electrical characteristic of a "biomolecular lipid membrane."

Figure 8.3.2-3 documents the findings of Mueller & Rudin for a bilayer membrane made from synthetic sphingomyelin (a family name not a specific molecular formula) using the method of Yeda. The tocopherol was also synthetic. The membrane potential describes the inside potential minus the outside potential. A positive current is "outward."Thus, the third quadrant would be the operational quadrant in a biological cell. The characteristic in the third quadrant shows dielectric breakdown at –170 mV occurring before the diode current becomes significant because of the symmetry of the bilayers. The first quadrant shows the material biased to prevent current flow. The rapid rise in this quadrant near 76 mV is due to dielectric breakdown in this membrane. The wording in their text is a bit brief as to whether this sample contained alamethicin or was the reference sample. Alamethicin is a cyclopeptide antibiotic containing a variety of amino-acids and at least one carboxyl group. It may attack the sphingomyelin or associate with it stereochemically like glutamate does. Note the very small currents per square cm through this membrane. These currents are about 0.1% of those reported for the average current through a large piece of the lemma of the giant axon of *Loligo*. The (thin film) resistivity for this synthetic material is about 2×10^5 Ohms-cm^2. The low current level, and linear current change, for potentials between +76 and –170 mV strongly suggests the bilayer membrane consisted only of sphingomyelin and was therefore symmetrical. The membrane is a very high quality Type I BLM (a near perfect insulator). The asymmetry of breakdown potential may be due to the presence of alamethicin in one of the electrolytes.

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[151]Yau, K-W. Haynes, L & Nakatani, K. (1986) Roles of calcium and cyclic GMP in visual transduction. *In* Luttgau, H. *ed*. Membrane Control of Cellular Activity. Stuttgart: Gustav Fischer pp 343-366 *Reported in* Yau, K. (1994) Phototransduction mechanism in retinal rods and cones, *Invest. Ophthal. & Vis. Sci*. Vol. 35, no. 1, pp 9-32

[152]Mueller, P. & Rudin, D. (1968) Action potentials induced in biomolecular lipid membranes *Nature* vol. 217, pp 713-719

Mueller & Rudin also reported "Membranes made from purified lecithin (PC) dissolved in decane are not suitable for the study of the action potentials reported here, the EIM gating mechanism being poorly developed." They describe a variety of Excitation Inducing Materials (EIM's). The reader is cautioned concerning their definition of an action potential and of the EIM gating mechanism that are discussed elsewhere in this work. [xxx add section #'s](See **Sections xxx & 9.3**)

Additional research using two distinctly different molecules in the two bilayers to ascertain the properties of a Type 2 (asymmetrical) synthetic membrane is still needed.

Figure 8.3.2-4 shows the best available estimate of the diode characteristic of biological membranes in comparison to the characteristics of common man-made diodes. From this curve and the above data, the cut-in voltage for the biological diode is actually negative at –0.02 Volts.

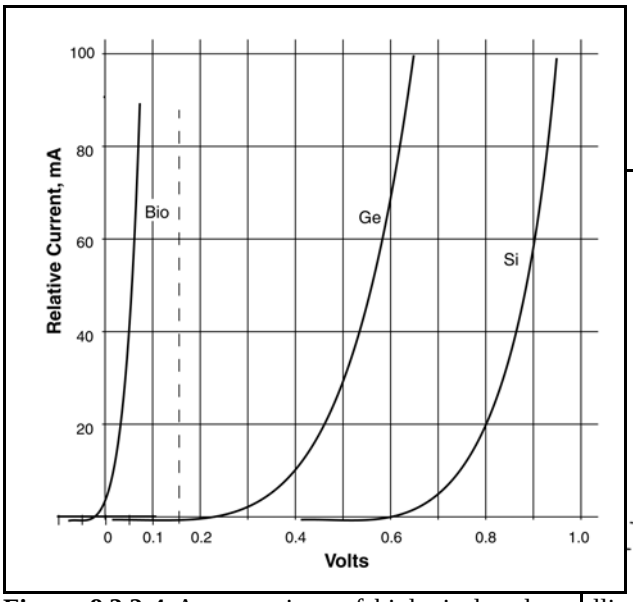

Figure 8.3.2-4 A comparison of biological and metallic semiconductor diode characteristics. The dashed vertical line shows the typical collector to base (axon to podite) potential of a biological circuit.

A common practice in preliminary design of circuits is to use a piecewise linear characterization of a semiconductor diode. This approximation replaces the curved diode characteristic with a constant slope beginning at the cut-in voltage with a slope approximating the current vs voltage characteristic of the diode in the area of interest.

This figure suggests that emulations of analog biological circuits using silicon-based device parameters should use voltages approximately 12 times those of the biological circuit if similar cutoff characteristics are desired.

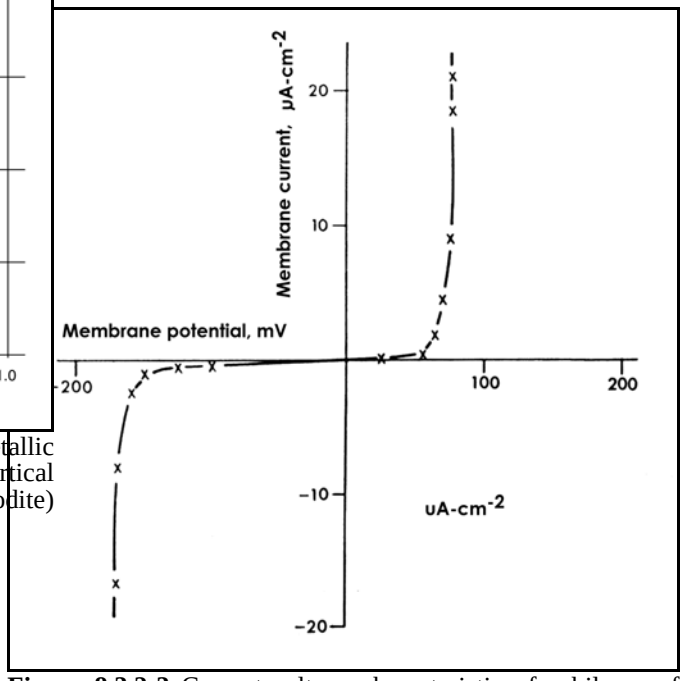

Figure 8.3.2-3 Current-voltage characteristic of a bilayer of sphingomyelin prepared from a bath of 2.5% sphingomyelin dissolved in tocopherol:chloroform:methanol::5:3:2. 0.1 M sodium chloride as the electrolyte on both sides. The asymmetry is purported to be due to the addition of 10^{-7} g/ml of alamethicin to one of the electrolytes. From Mueller & Rudin, 1968.

8.3.2.2 The reactive characteristic of the fundamental membrane in electrolyte

The reactive component of the total impedance of a membrane depends critically on its geometry. While an artificial

membrane prepared as a planar layer on a fluid surface may exhibit negligible inductance, it will exhibit a significant capacitance because of its thinness and its quantum-mechanical properties. If that same membrane is formed into a cylindrical tube, its capacitance will change due to its new geometry and the membrane will exhibit a significant inductance per unit length of the tube. Only planar films will be addressed in this section.

8.3.2.2.1 The capacitive characteristic of the fundamental membrane in electrolyte

The capacitive impedance found in a neuron is calculated conventionally (based on the actual geometry involved). It can vary between regions of the membrane and varies significantly if the INM is separated from the membrane by a myelin sheath. Typical values found in the literature for unmyelinated membrane range from 1 to 3 $\mu F/cm^2$. The measured values reported in the literature varies between 10% and 1000% of these values (See pg 13 in Troshin for early references). The wide range could be due to the primitive methods of measuring the thickness of the BLMs and the lack of good values for their dielectric constants. There are also significant charge density variations associated with the calculation of the capacitance of a membrane. These variations are found within the membrane at the quantum-mechanical levels associated with a diode. They are also found in the adjacent electrolytes where they are generally described as Maxwellian layers. These variations are bias-potential sensitive.

In spite of the above range, the nominal value is very large. It is due primarily to the extreme thinness of a single membrane, typically 100-150 Angstroms[153] or less. In terms more appropriate to a neuron, the capacitance is about 10^{-8} $\mu F/micron^2$. The effective capacitance of a region of membrane is frequently reduced by a factor of more than 100 if a myelin sheath is present.

The capacitance of type 1 and type 2 regions of membrane are significantly different. In type 1 regions, the symmetrical bilayer represents a very high quality capacitor that is largely unaffected by the voltage across it up to the point of dielectric breakdown. Type 2 regions are significantly different. The asymmetric bilayer forms an electrical diode. Such a diode exhibits a change in capacitance as a function of the reverse potential across the diode[154]. This change is known to be incremental in character. This transition region capacitance is given by the equation: $C_T = |dQ/dV|$ and not the conventional $C = Q/V$. As a result, there is a displacement current $i = C_T(dV/dt)$ that is proportional to the rate of change of the applied potential. The transition region capacitance is a function of the applied reverse potential. The total capacitance associated with a membrane is therefore C_M (the DC capacitance) plus C_T (the displacement capacitance). This may account for some of the variation in values in the literature. The literature does not normally specify the potential (or the method) used to measure the capacitance. Precise values must specify both the potential and whether a DC (relaxation) or an AC (steady state) technique was used in the determination.

The transition capacitance can dominate the DC capacitance in specially prepared man-made diodes. Those devices are known as varactor diodes or varicaps.

For purposes of this section, the capacitance will be taken as 1.0 microfarad per square centimeter, the nominal value found to describe a range of about 0.5 to 3.0 $\mu F/cm^2$ found throughout the literature.

8.3.2.2.2 The intrinsic RC time constant of a typical membrane

The concept of a time constant is drawn from the simple exponential response exhibited by a two-element electrical circuit involving linear components. Such linear components exhibit impedance properties that are independent of the voltages applied to them. Type 1 BLM can be evaluated using this simple concept. Type 2 BLM is an electrical diode. A diode is not a linear component and this simple concept does not apply to a circuit containing a diode. To accommodate circuits containing a diode, various re-definitions of the term time constant have been used. They generally fall into two categories, the large scale or DC approximation and the small scale or AC approximation.

Finkelstein has measured ohmic resistivities as high as 10^{12}–10^{13} Ohm/cm^2 for membranes that appear to be of type 1. When combined with the nominal capacitance of such a membrane (1.0 $\mu F/cm^2$), the resulting intrinsic time constant is on the order of 10^6–10^7 seconds (10^5 minutes, 3000 hours or 100 days). Such a free-standing membrane has little significance to the operation of a neural system.

Finkelstein & Cass have reported resistivities of 10^6–10^9 Ohm/cm^2 for membranes that appear to be of type 2. When

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[153]Eckert, R. & Randall, D. (1978) Animal Physiology San Francisco CA: W. H. Freeman pg. 114

[154]Millman, J. & Halkias, C. (1972) Op. Cit. pg 63-67

combined with the nominal capacitance of a membrane, the resulting intrinsic time constant of this type of membrane is on the order of one second to a millisecond. This is a significant value when considering the operation of a neural circuit.

The mechanisms associated with physical transport of material through a type 3 region of membrane make the capacitance of such a region less important than for the type 1 and type 2 regions.

8.3.2.2.3 The inductive characteristic of the fundamental membrane in electrolyte

As noted in **Section 8.3.2**, the inductance of a fundamental membrane is a function of the geometry of the membrane. In the case of the long cylindrical axon, the inductance is a significant parameter. For the neurites, the inductance is much smaller and very difficult to calculate due to their complex geometry. The inductance of an axon is primarily an operational concern. It will be addressed in detail in **Section 10.3.4**.

8.3.3 Combining the type 2 membrane with electrostenolysis–*powering the neural system*

By repeating the work of Eliasof using a Ussing apparatus, it is relatively straight forward to continue the experiments to determine the quiescent electrical potential of a membrane in combination with its native electrostenolytic process (See **Section 8.6** on electrostenolysis). The equivalent circuit diagram is still relatively simple as shown in **Figure 8.3.3-1**. Assuming a saturated solution of the electrostenolytic reactants in the INM, a finite circulating current will be found within the loop formed by the electrostenolytic source and the membrane. It may be extremely small for a small conduit. By measuring the quiescent potential of the the terminal shown in the upper electrolyte relative to the INM using a finite and controlled impedance voltmeter, and knowing the diode characteristic and equivalent battery potential of the membrane, it is possible to compute the electrostenolytic source voltage and impedance. The electrostenolytic impedance is assumed to be a simple resistance in the absence of any other data.

It should be noted that the electrostenolytic potential is generally higher than the intrinsic membrane potential. When making the above measurement with a high impedance voltmeter relative to any circuit element, it is important to specify that a quiescent voltage is being measured not the intrinsic membrane potential or the intrinsic electrostenolytic potential.

The available evidence suggests electrostenolysis occurs at sites on the external surface of type 2 BLM occupied by phosphatidyl choline (PC).

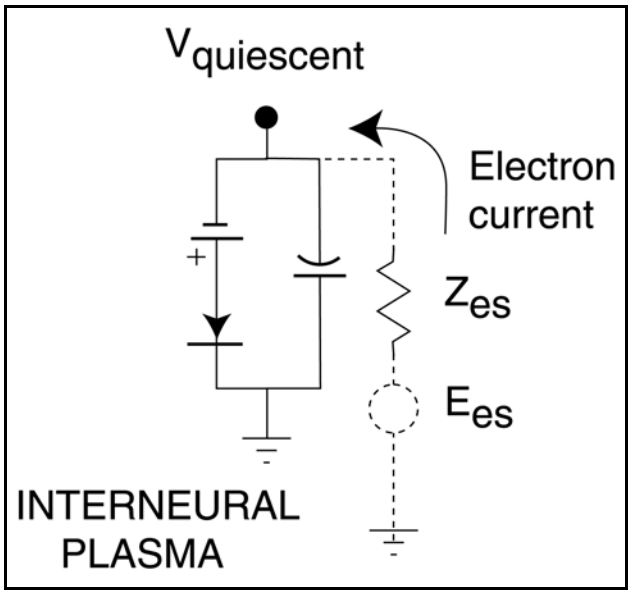

Figure 8.3.3-1 Fundamental membrane with electrostenolysis support. The capacitance shown consists of both the bulk capacitance and the displacement capacitance of the diode.

8.3.3.1 The apparent intrinsic potential and impedance of a biological membrane combined with electrostenolysis

Many experiments have been carried out treating the circuit in the above figure as a lumped circuit. The voltage at the upper terminal has been measured as a function of an external load impedance between that point and the INM (or as the case of one variant of the voltage clamp experiment, a current has been introduced into the circuit via this terminal while holding the voltage constant). The resulting voltage-current characteristic has been used to compute a single voltage and impedance representative of the combined membrane and electrostenolytic system. The result may be interesting but it lacks precision. It blatantly conflicts with the requirements of Kirchoff's Laws.

8.3.3.2 The nature of the impedance measured by the voltage clamp technique

The type of resistances found in the neuron are not normally found in man made devices and circuits. They are unique. Whereas man-made resistors are usually dissipative, i. e. they generate heat as a result of electrical current passing through them; the principle resistive component found in neurons does not!

A problem associated with this fact is exacerbated in the two-terminal experiment described in the previous paragraph.

The resistances found in a neuron are primarily of three types:

+ usually relatively small resistive components related to the finite conductivity of simple electrolytes, i. e. the resistivity of the various (bulk) plasmas. These resistances are dissipative and do result in energy being transformed into heat and being lost from the process. *It should be noted these resistance involve a significant transit delay that should be taken into account.*

+ the more important resistive component related to the equivalent diode associated with the membrane.

+ the impedance of the electrostenolytic supply discussed above.

It is important to note that the impedance of the electrostenolytic supply is usually lower than that of the membrane and it is not represented by a conventional dissipative resistance. It is an equivalent resistance representing the reversible electrostenolytic process. Thus, in the experiment described, the measured impedance is not that of the membrane but is dominated by the impedance associated with the electrostenolytic process. In addition, the voltage measured is not the intrinsic potential of anything! In general, the energy introduced into this circuit by the test configuration is not dissipated as heat but is converted back into chemical energy to the extent possible by the available chemical reactants. This is a very key feature; <u>neurons and their membranes do not normally dissipate electrical energy as heat!</u>

Because of the above fact, the "load impedance" used in the electrical circuits of the neuron cannot be correctly described as a passive resistance. The load is an active resistance, or more descriptively, an electrolytic resistance. The characteristic voltage versus current curve of the active resistance remains that of a diode; however, the electrical energy is not dissipated.

The description of the load impedance of the neuron as an electrolytic, non-dissipative, impedance has some very important consequences.

First, *it explains why calorimetric measurements have failed to give meaningful values* for the amount of energy consumed by the billions of neurons in the typical brain. In general, they do not "consume" significant power by generating heat. They merely relocate electrons and other ionic species in relation to a gradient. Similarly in the retina, power consumption measurements have been fruitless. The few measurements that have been found meaningful have been indirect in nature.[155,156] The major power consumption of the neural system is measurable in terms of the difference in entropy of the reactants flowing in the vascular system..

Second, it provides a clearer understanding of *why it has been so difficult to measure the net ionic flow of Na^+, K^+ and Ca^{++} ions through the membranes of a neuron.* There is no net flow of these ions through the ionically impervious membranes of a neuron related to the signaling function.

Third (and beyond the scope of this work and to be considered speculative in terms of rigorous science), in all interneural regions known as synapses, a variety of ionic species may be found. However, *in general it is the flow of electrons that constitutes the primary signal path.* The most important flow in this region, besides that of electrons, is the flow of reactants associated with the

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[155]Kageyama, G. & Wong-Riley, M. (1984) The histochemical localization of cytochrome oxidase in the retina and lateral geniculate nucleus of the ferret, cat, and monkey... J. Neuroscience, vol. 4, #10, pp. 2445-2459

[156] "total blood flow to the brain = 16% of cardiac output" in Tower, D. (1975) The basic neurosciences, vol. 1 NY: Raven Press pg. 201

glutamate cycle and employed in electrostenolysis. The flow of ions in this region, if any, is incidental to the neural signaling function. These ions are required primarily to provide low conductivity electrolytes for use as both plasmas and the INM.

8.2.4.3.y The nature of the electron-pump powering the neural system

Many authors have attempted to define the mechanism powering the neural system. They have explored a variety of mechanisms familiar to the physiology of nutrition. This area of physiology normally concentrates on chemical energy stored as ATP and similar materials. It does not normally focus on the creation of an electrical potential. However, many of the same materials can participate in an electrostenolytic process producing free electrons. These electrons can traverse the substrate.

This work proposes that a portion or portions of the glutamate cycle of nutrition can take place at an appropriate reaction site on the surface of a membrane conduit. This reaction is of the electrostenolytic type and provides electrical bias to the conduit.

It is proposed that the nominal reaction involves the transformation of the simple amino acid, glutamic acid (that is commonly called glutamate in the pharmacology literature) into GABA (gamma-amino butyric acid). The desired potential can be maintained indefinitely with minimal continuous consumption of energy. Only the presence of glutamate on the exterior surface of the type 2 membrane is required.

No singly ionized heavy atoms are required to cross the membrane barrier to support the polarization of the membrane. **No requirement exists for an ion-pump to support the neural signaling function**. Details of the participation of the glutamates in electrostenolysis are presented in [**Section 8.6.2**].

8.2.4.3.x The electron-pump replaces the putative ion-pump in charging a biological membrane

[xxx include electron-pump supporting the soma and individual plasmas of the neuron]
By broadening the designation ion-pump, to charge-pump, the processes of electrostenolytics and transistor action provide demonstrable solutions to the charge-pump problem associated with the polarization of neuron plasmas.

The transfer of electrons across a membrane by electrostenolytics is analogous to and is in fact the solution to the long quest for an ion-pump that could polarize the interior of a neurite or axon structure. This finding is even more profound than the earlier one of Habib & Bockris. **No requirement exists for an ion-pump to polarize the interior of a cell. Neither is there a requirement for the polarization of the interior of a cell to pump ions through the cell membrane for signaling purposes.**

The potential established on the interior surface of the BLM is a function of the materials used in the electrostenolytic process. It is not directly related to any characteristic of the membrane except for its electrical asymmetry. This potential of the interior plasma is specifically not related to the properties of the membrane and is entirely separate from any intrinsic membrane potential to be discussed below.

Besides the above region designed to polarize the interior of a BLM conduit, additional regions of similar specialized nature can be added to the membrane to support signal injection into and signal ejection from the interior of the membrane. **It is the formulation of a neural membrane discussed above that will be addressed in this work. It will be considered the fundamental conduit of a neural signal path**.

According to this formulation, no requirement exists for the transfer of ions or large particles across the BLM of the fundamental biological conduit to support neural signaling. Although such transfer obviously occurs during some phase of the genesis and metastasis of the conduit, it will not be addressed further in the context of neural signaling.

The simplest forms of this formulation are of academic interest and the most complex formulations provide a distinctly broader interpretation of the results of the voltage clamp experiments of Hodgkin, Huxley (& Katz). The scope of these

experiments on the above formulation will be addressed in detail in **Section 10.10.**

While a continuous symmetrical BLM forms a very high quality insulator, an asymmetrical membrane forms an electrical diode. When associated with a charge-pump and the capacitance of the membrane, this diode can sustain a potential between the two sides of the membrane of one polarity but not the other. The simple non-neurological cell incorporates this feature to insure its interior is always polarized negatively with respect to the surrounding electrolytes. In a neuron, additional care is required to insure the potential of each isolated plasma is negative with respect to the electrolyte on the opposite side of its containment membrane. In cases where the polarity is reversed, it can be expected that charge will flow out of the containment membrane. Fortunately, this is the specific feature used to achieve transistor action.

8.3.4 Conclusions to be drawn concerning a biological membrane before proceeding

Up until now, the neurological literature has focused on an elementary concept of the BLM enclosing a cell that has not been sufficiently compartmentalized. As a result, most discussions of the BLM in a chemical context are archaic. They assume a set of conditions not found in real neurons.

Efforts in the neurological community have continued to focus on a chemical explanation for signaling within the neural system. These efforts have not resulted in a framework that can guide future investigations.

When different investigators attempt to explain the operation of a cell membrane based on their data, they have generally assumed a simplified membrane that conflicts with those of other investigators. No satisfactory generic membrane has appeared to date.

To avoid the increasing evidence that free ions cannot move across a majority of the plasmalemma of a cell, efforts have been increased to find a pore structure adequate to the task. Improvements in electron microscopy have failed to support such proposals, particularly in the areas (the junctional-tissue) separating two or more neurons.

It is time to move on to a biological bilayer membrane that is regionalized where each region serves a different purpose. To achieve these purposes, the molecular character of the regions vary.

The most complex models found in the current literature do not do justice to the BLM. Specifically, they do not address the subject of hydrophobic membranes or membranes containing a hydrophobic phase, such as BLMs. Nor did they allow for the presence of complex organic ions, within the solvents, capable of resonance among their ionic states. Nor did they address the presence of ions such as calcium that can exhibit two different valences. Finally, they do not address the two fundamental and crucial conditions. They do not consider the presence of electrostenolytic processes which could skew their electrochemical equations and they do not address the quantum-mechanical properties of such thin membranes. In neurons, these last two conditions are the most crucial.

Two facts must be accepted to understand the operation of the neural membrane. First, quantum-mechanical principles apply to these membranes. Second, the permeability of these membranes to electrons and holes is far more important than their permeability to ions and large uncharged particles. It is their quantum-mechanical distribution of charge that accounts for both their asymmetrical electrical properties and their non-uniform potential field gradient as a function of transverse distance.

> The result is a membrane structure that is not directly addressed by the Nernst-Donnan-Goldman theories, or the Hodgkin-Huxley modifications to those equations (due to their underlying constant field assumption). Adjustments to the lipoidal membrane theory are required as well (due the quantum-mechanical characteristics of a membrane).

The last two conditions lead to two key facts. First, each of the cited authors derivations, related to diffusion through a membrane, assumed a constant potential field gradient within the membrane. This condition requires an electrically symmetrical membrane. Such a constant gradient is only found in relatively uniform heterogeneous material. Second, none of the authors allowed for the presence of a chemical source of electrons on the surface of the operational membrane.

It is now time to rationalize the above materials and to recognize that bilayer membranes of two phosphoglyceride leaves form a special class. They consist of hydrophilic surfaces with a hydrophobic interior. When the two bilayers are symmetrical, the material is an exceptionally good insulator and it is impervious to the movement of both heavy ions and fundamental charged particles. When the two bilayers are asymmetrical, they remain impervious to heavy ions. Electrically, membranes are liquid crystalline and are so thin that they are subject to quantum-mechanical effects. Such membranes are susceptible to the transport of fundamental charges and exhibit a non uniform potential gradient between

their two surfaces. In fact the gradient is a characteristic of an electrical diode.

The thinness and electrical asymmetry of membranes also place them in a special category with respect to electrolytic chemistry. Employing a pair of redox equations to explain the transfer of charge through a membrane is not necessary. If it did electrodeless electroplating onto the surface of a substrate would be impossible. Such electroplating is frequently observed in retinas and is an important industrial process.

A single reaction can generate free electrons, transport those electrons through the membrane (by quantum-mechanical tunneling or otherwise) and leave them on the surface of the membrane in an isolated state. Due to the extremely high impedance of the now reverse biased electrical diode character of the membrane, these isolated charges can maintain a potential across the capacitance of the membrane for a long time. The result is a non-equilibrium electrical condition that is not dependent on any chemical or diffusion related condition involving heavy ions.

Recognizing that a continuous symmetrical bilayer membrane of phospholipid material is impervious to virtually all ions and an extremely good insulator (10^{12}-10^{13} Ohms/cm^2 based on some extremely difficult measurements) **is necessary.** Asymmetrical bilayer membranes are also impervious to ions. Only when the membranes are asymmetrical do they exhibit a lower *and asymmetrical* electrical impedance. Recognizing the great sensitivity of bilayer membranes of liquid crystalline materials to attack by a wide range of chemicals is also necessary. A wide variety of both ionic and non-ionic detergents can disrupt them. Even micro-molar amounts of many organic compounds will disturb their electrical characteristics by many orders of magnitude.[157] This sensitivity, and electron microscopy, suggest that real BLMs do not include significant proteinaceous pathways. Finally, noting the likelihood that different regions of a given membrane may be optimized, at the molecular level, for specific functions is appropriate.

Based on the above, one can describe a membrane in much greater detail than previously done in the terminology of the 1950's. It appears that type 1 and type 2 membranes form a majority of the conduits associated with neural signaling and type 3 membranes are found primarily in regions of the plasmalemma associated with the homeostasis of the overall cell.

8.3.4.y The characteristics of the total impedance

[xxx address as the sum of several impedances when measured indiscriminately]
The treatment of the total impedance of a conduit formed of a biological membrane is complex if it involves multiple regions with different electrical properties. The treatment is also different depending on the type of signal being considered. Cole has provided extensive information on the individual components of the total impedance, including the reactive component associated with an inductance[158]. The more complex treatments will be found in **Section 9.3.5 and 10.4.**

8.3.4.x The electrical efficiency of neural circuits

The neural system is uniquely optimized for its tasks from an efficiency perspective. As recently confirmed in the development of central processing chips for computers, operating at higher impedances and lower voltages over shorter distances (all related to using smaller circuit elements) results in higher overall efficiency. In addition, the neural system has essentially eliminated the use of current continuously passing through resistive impedances. This is a trick similar to that used in man-made CMOS (complementary metal oxide on silicon) circuits. These design approaches greatly reduce the energy employed in processes subject to the Second Law of Thermodynamics.
Many processes used in the neural system are not subject to the Second Law and are reversible. [xxx explain difference between a closed and open system] These processes greatly reduce the consumption of power in the system. Thus, a fundamental difference exists between the electronics of charges flowing in metallic (and semi-metallic) circuits and the

[157]Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. NY: John Wiley & Sons. pp. 109

[158]Cole, K. (1968) Op. Cit.

charges flowing in electrolytic circuits.

As recently found in the development of the magnetic resonance imaging techniques (MRI & fMRI) the consumption of oxygen is not a good indicator of brain activity. The original technique given the catchy acronym BOLD for Blood Oxygenization Level Dependent contrast, was based on the concept of the direct utilization of oxygen in the brain. However, it was quickly found this was an inappropriate criteria and the measurement of oxygen flow was related to the total blood flow to the brain (which was more indicative of the state of the brain). The problem with the original BOLD concept relates to the neural, as opposed to the homeostatic, operation of the brain. The neural portion of the brain operates anaerobically using a process based primarily on fermentation. Its primary fuel is glycogen from the blood stream. This material is broken down anaerobically through a series of steps releasing CO_2 but not consuming any oxygen from the blood stream. The first major step is the glycolysis of glycogen into either pyruvate or lactate and the consumption of ATP. The resulting chemicals contain approximately 93% of the energy in the original glycogen. They are then converted into glutamic acid in one version of the Krebs Cycle and used to power the neurons. In the process, the glutamic acid is converted to GABA with the release of CO_2. However, GABA continues to contain considerable chemical energy. It is recycled back through a variant of the Krebs Cycle to produce more glutamic acid at the expense of ATP. Because of these steps, **the operation of the signaling portion of the neural system is completely anaerobic although the production of CO_2 is indicative of the energy consumed**. There is no net oxidation of the fuel molecule. Instead, an internal oxidoreduction occurs. The net oxidation state of the fermentation products is the same as that of the fuel.

> Hodgkin noted the extremely low level of Joule heat produced in individual neurons[159]. He noted the generation of heat during neural activity for the frog nerve was only about twice as high as for the resting state. The increase was measured at less than 10% for the giant neuron of Loligo. The range in these values suggests the difficulty of measuring this quantity.

By employing many processes that are both anaerobic and not subject to the Second Law, the animal nervous system can achieve remarkably high thermal efficiency, compared with conventional metallic based man-made electronic circuitry. Through this process, the entire brain can consume considerable energy while dissipating less energy as heat than a flashlight bulb. Gutmann & Keyzer state that the entire body only consumes 20 Watts of power[160]. They are apparently referring to the thermal power consumption of a resting body. They do not estimate how much chemical energy is consumed by that same body. Most investigators have failed to account for the chemical energy difference between the food ingested and the waste products excreted (both as gas and solids) by the specimen.

Although of immense importance, the subject of total energy consumption by the organism, or its nervous system, is peripheral to the scope of this work. Starzak addresses the subject briefly at the theoretical level[161]. Two main points should be stressed. **The electrical energy used in the neural system is generated by an electrostenolytic process on the surface of membranes.** This process is associated with glycolysis and the Krebs Cycle. **Many steps in these processes are theoretically and practically reversible, both chemically and thermodynamically**.

8.2.3.5.x.1 Unique metabolic conditions in neural tissue

A surprising situation arises based on the above review, the discussion on the reconstitution of glutamate in **Section 8.6.3.3**, and the discussion related to the development of MRI techniques in **Section 7.7**. During the development of the inappropriately named (in hindsight) BOLD technique, it was found that the level of brain activity was largely independent of the consumption of oxygen. On the other hand, lack of oxygen is known to be catastrophic for the brain. Taken as a group, this material strongly suggests discussions of the metabolic operation of the neural system (including the brain) must be divided into two categories at the cellular level. The first concerns the operation of the non-neural portions of neurons concerned with homeostasis. This portion appears to operate aerobically and be critically dependent on oxygen. The second concerns the operation of the neural portion concerned with signaling. This portion appears to operate anaerobically and rely on the availability of glycogen, and its successful processing into the neuro-facilitator glutamate.

> **The catastrophic failure of the brain and neural system can be caused in two distinct ways.** A

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[159]Hodgkin, A. (1951) The ionic basis of electrical activity in nerve and muscle *Biol Rev*. Vol. 26, pp 339-409

[160]Gutmann, F. & Keyzer, H. (1986) Op. Cit. pg. 78

[161]Starzak, M. (1984) The physical chemistry of membranes. NY: Academic Press, pp 238-242

lack of oxygen leads to significant damage or death to the homeostatic portions of the brain cells. A lack of glycogen leads to significant interference with or the death of the neural (signaling) portions of the brain cells. Failure achieve electrostenolytic reduction of glutamate can result in a vegetative state. This failure may be a key to understanding Alzheimer's Disease.

8.3.4.x.2 Unique transmission mode for the projection neurons EMPTY

8.4 The electrical characteristics of the static neuron

The neuron and the neural system are very special in that their electrical performance is determined by the repetitive use of a single circuit group. At the heart of this group is an electrical conduit formed by the enclosure of an electrically conductive electrolyte within an insulator formed of a BLM that is itself surrounded by an electrolyte. Electrically, a simple conformal transformation can be used to show that this configuration is identical to that of a single hollow electrical conductor filled and surrounded by an insulator. Morphologically, the result is a series of conduits connecting a source of information to a consumer of that information. These conduits exhibit a variety of surface characteristics associated with their chemical composition at the molecular level. Chemically, the result is a series of regions, associated with each conduit, formed of bilayers of various phospholipid molecules. Electrically, the result is a set of circuit elements representative of the electrical characteristics of each region of the membrane. These sets of circuit elements form the electrical barriers between the various plasmas inside and outside the cell. **With one crucial exception to be discussed below**, the values of the circuit elements of a given region are fixed. No variable elements controlled by external or unspecified forces are involved.

The crucial exception involves the following fact. Under conditions where the cathodes of two semiconductor diodes are formed on a common crystalline substrate, the two diodes can exhibit "transistor action." Transistor action causes a current to flow in the second diode in spite of the diode being reverse biased. This activity will be introduced in **Section 8.4.2** and be explored extensively in **Section 8.5**.

The operation of the fundamental neuron is best understood by proceeding to examine a generic biological cell before it becomes a neuron. This will be done in steps. In the following sections, three degrees of complexity will be explored. Initially, only the fundamental cell membrane will be examined. A basic, or ***first order***, fundamental cell will then be examined as an operating entity without regard to the physical arrangement providing electrical bias to the circuit. Finally, a ***second order*** fundamental cell will be considered as a complete operational entity. This second order cell consists of multiple individual membrane isolated conduits within a single external membrane. The surface of the membrane surrounding each of these compartments is usually differentiated into regions at the molecular level. At this point, the importance of the electrolytic and metabolic matrix surrounding the cell is found to be critically important to its static characteristics. *In-vitro* experiments must observe these requirements of the surrounding interneural matrix if the results are to be meaningful.

8.4.1 The fundamental cell membrane

Danielli has provided a brief overview of the evolution of the bilayer hypothesis of membrane structure[162]. It is based on his long involvement in the field, includes many of the early caricatures of cell walls and stresses the conceptual nature of these early ideas.

The fundamental cell membrane is defined here as a bilayer lipid membrane (BLM) where each layer is a continuous liquid crystalline film of phospho-triglyceride material. The BLM is nominally 90 Angstrom in thickness. There are no inclusions within the BLM and no disruption of either film above the molecular level.

From an electro-chemical perspective, a BLM is a surface of finite thickness composed of a highly structured material exhibiting a characteristic electrical impedance and a characteristic voltage potential between its two surfaces. The

[162]Danielli, J. (1975) The bilayer hypothesis of membrane structure. *In* Weissmann, G. & Claiborne, R. *ed.* Cell Membranes; Biochemistry, Cell Biology & Pathology. NY: HP Publishing Co. Chapter 1

electrical equivalent circuit of the BLM may contain both a variable resistive component (characteristic of a diode) and a battery in series with the combination shunted by a capacitive component. These properties are directly related to the molecular structure of the membrane, the thickness of the membrane, the temperature and to other properties to be defined below. These electrical properties are independent of the properties of any more complex regions of a membrane separating two electrolytes that are used for genesis or metastasis. The combination of the membrane separating two electrolytes will be discussed more fully below.

Both the intrinsic voltage of the battery and the impedance of the BLM are highly dependent on the degree of symmetry between the two bilayers of the membrane. For a symmetrical membrane, the impedance is exceedingly high and the material acts as an insulator. For more asymmetrical arrangements, the impedance per unit surface area is also asymmetrical. It can be defined by the reverse cutoff current of the diode. For these asymmetrical BLMs, the intrinsic voltage of the battery is usually in the range of 0.00 +/- 50 mV.

The highly structured nature of the phospholipids in the membrane and the large amount of oxygen in the polar components of these molecules supports the position that the materials are in the form of a "liquid crystal" when at biological temperatures. It is quite possible that this structure, of polar components exhibiting a large amount of oxygen, may exhibit unusual electrical conductivity in the plane of the oxygen ions.

There have been many caricatures of the fundamental membrane. Pannese discusses the history of this research[163]. Discounting his comments concerning excitability of the membrane, he points out that "The study of neuronal plasma membrane is beset with particular problems." He also points out that most of the common wisdom concerning neural membranes has been obtained by inference from data on non-neural cells and by inference from experiments prior to the development of the electron microscope. Most of the resulting caricatures, including those of Danielli & Davson (1935) and of Robertson (1959) assemble the various constituents known to be associated with a membrane into a single structure. In the above two cases, protein "skins" are shown on each side of the bilayer. Although such protein layers are undoubtedly present, and are proposed to be key to the electrostenolytic support to the operation of the neuron, they are not believed to be intrinsic to the membrane.

There has been no way for the above investigators to know when they were dealing with a fundamental membrane or a highly differentiated segment of neural membrane. Pannese also addresses this problem due to the fact that a neural membrane does not show uniform properties over its whole surface.

There have only been a few attempts to create a synthetic BLM. These have generally involved attempts to grow a single layer and then fold it over on itself to create a symmetrical membrane. They have resulted in high quality electrical insulators.

8.4.1.1 Local (cytological) uniformity of the neuron membranes.

Many authors invoke caricatures of neural membranes containing a variety of inclusions and/or voids in the membranes. The voids are frequently described as gates for the passage of (simple or complex) ions through the membrane under controlled or controllable conditions. Proposals for such gates are especially common when describing the synaptic region between two neurons. Some authors become quite fanciful and indicate a separate void (gate) for each ion participating in the proposed process along with a wide variety of other inclusions in the membrane surface. These caricatures are usually proposed based on interpretations of electron micrographs made at around 50,000 x. Shepherd reviews a number of these concepts[164].

The description of the membrane face as containing a large number of "gates" seems highly unlikely since a great many different tailored holes would be needed per unit surface. **Figure 8.4.1-1** from Gilula[165], supports this position. It shows an *en face* view of a gap junction at 360,000x. There are no signs of either inclusions or physical holes in the area shown (about 6000 x 3000 Angstrom or 0.6 x 0.3 microns). On the contrary, the uniformity of the para-crystalline lattice strongly supports the idea that the cell wall is a continuous liquid crystalline structure devoid of gates.

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[163]Pannese, E. (1994) Neurocytology. NY: Thieme Medical Pulbishers. Pg. 74

[164]Shepherd, G. (1991) Foundations of Neuron Doctrine. Pg. 277

[165]Gilula, N. (1975) Junctional membrane structure. in The Nervous System, Tower, D. ed. vol. 1, The basic neurosciences. NY: Raven Press pg. 6

At the molecular scale, the change of molecular species within one or both bilayers with position along the surface of the BLM is well accepted. Although such changes do not support a major change in the permeability of the membrane to large particles and ions, it can have a significant impact on the permeability of the membrane to fundamental electrical charges.

8.4.1.2 Local molecular level uniformity of the fundamental membrane

As explored earlier, the fundamental membrane is typically subdivided into a series of application oriented regions. These regions of material differ primarily at the molecular level. **Section 8.2.3** has introduced the molecular characteristics and resulting electrical characteristics of these regions.

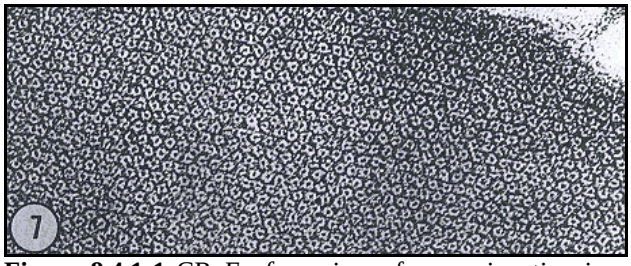

Figure 8.4.1-1 CR *En face* view of a gap junction in a neuron found in the liver of a rat. Negative stain was used. The central region of each "particle" is penetrated by the stain to produce a 15-20 Angstrom electron dense spot. Lattice spacing is approximately 80-85 Angstrom. From Gilula (1975)

8.4.2 Development of the functional structure of the neuron

Figure 8.4.2-1 provides a caricature of the development of a functional neuron from a simple cell, a neurogen. In the current vernacular, the neurogen is called, or is derived from, a stem-cell. The process is straight forward but sophisticated. The metabolic and growth aspects of the cell will not be addressed here. Each frame of this figure is discussed below.

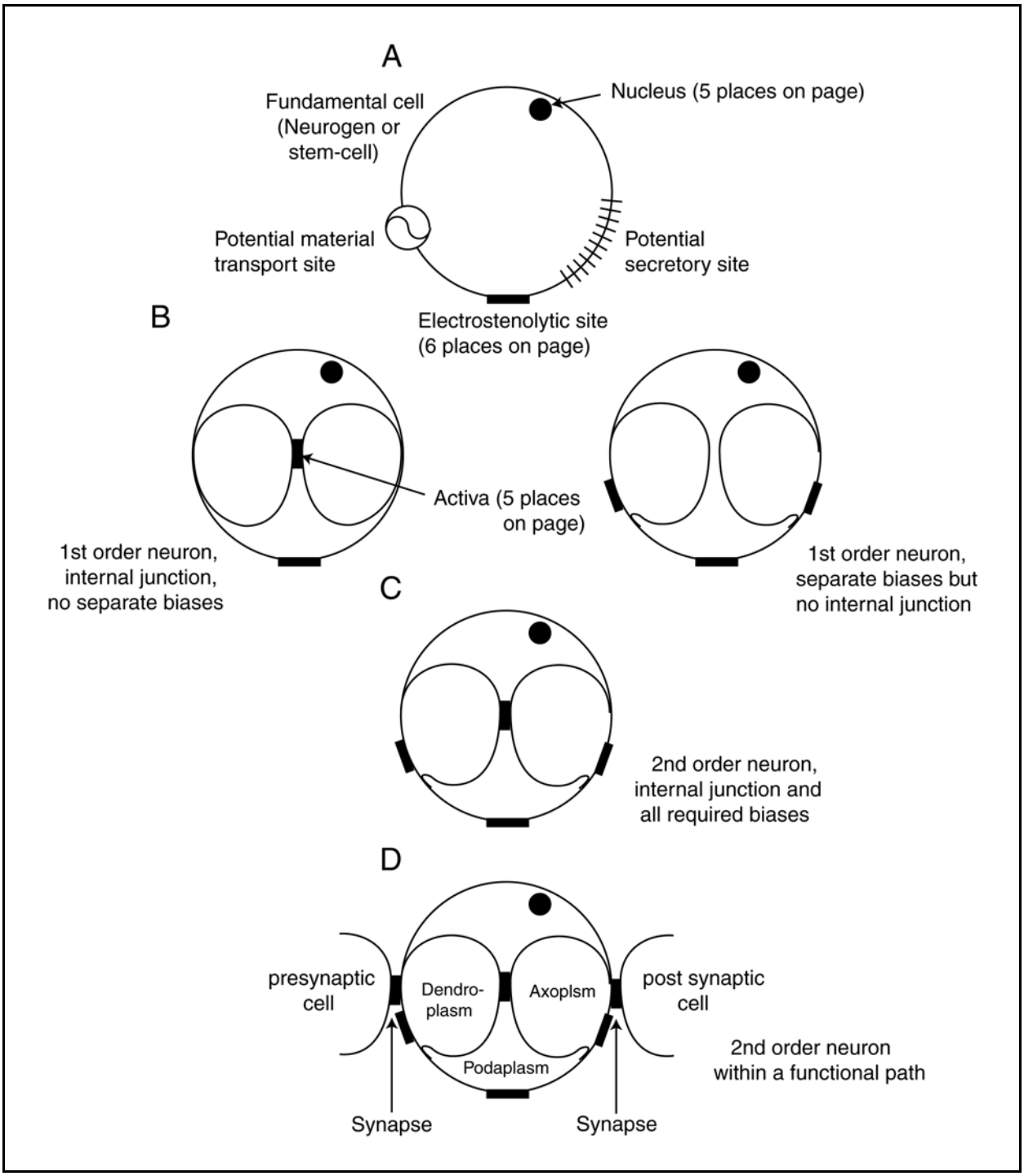

Figure 8.4.2-1 Cytological evolution of a neuron. (A), a simple cell or neurogen, a stem-cell in the current vernacular. The nucleus, a potential secretory site and a potential material transfer mechanism are shown. (B), two variants of the 1st order neuron. (C), a second order neuron. (D), a fully functional neuron within a neural signaling path. See text.

8.4.2.1 The *first order* fundamental cell

In order to provide a foundation for the following paragraphs, it is useful to define a reference situation which will be called a fundamental cell: i. e. a living organism consisting of a continuous, single outer membrane enclosing a variety of cytological elements. The outer membrane is more commonly called the plasma membrane, and is recognized to be a bilayer consisting of two leaflets as described earlier. This situation is represented in frame (**A**). The outer membrane necessarily contains a site for exchanging materials between the interior of the cell and the surrounding electrolytic matrix and potentially contains a secretory site. Sensory neurons, those originating afferent neural signals generally contain secretory sites. Similarly, a variety of neurons terminating efferent paths are characterized by their secretory capability.

From an electrochemical perspective, the fundamental cell is a region enclosed by a plasma membrane. The inside of the cell is filled with a heterogeneous electrolyte of finite conductivity. The cell is surrounded by an electrolyte of finite conductivity containing bioenergetic materials capable of supporting a glutamate cycle as part of an electrostenolytic process. Both of these electrolytes may be more completely described as to their viscosity and ionic content. The electrolyte within the cell is generally gelatinous and may be in a true liquid crystalline form. The external matrix may also be gelatinous or a liquid crystalline material.

Somewhere on the surface of the membrane is an area of type 2 membrane supporting an electrostenolytic process (indicated by the rectangular bar at the bottom of the cell in frame (**A**). Because of this electrostenolytic activity, the cytoplasm of the cell exhibits a negative electrical potential with respect to the external electrolyte under quiescent conditions. Little or no energy is required to maintain this quiescent condition because *a majority of the plasma membrane is an electrical insulator and impervious to the flow of both ionized atoms and fundamental electrical charges.*

As the neurogen evolves into more specialized forms, a variety of internal membranes may be formed within the cell and multiple electrostenolytic sites may be formed on the surface of the cell.

8.4.2.2 The *first order* neuron

(**B**) illustrates the 1st order neuron at two separate stages of development. There is no data to define which occurs first. On the left, the cell is seen to have formed three separate plasma enclosures through the development of interior membranes connected to the plasma membrane by lap joints. At the center of the cell, the two interior membranes have become juxtaposed so as to form a potential Activa (shown by the vertical black bar). However, all of the plasmas remain at essentially the same electrical potential. On the right, an alternate first step is shown where the cell has formed the same three separate plasma enclosures through the development of the same lap joints. It has then proceeded to create two more areas of specialized plasma membrane supporting additional electrostenolytic activity. The three plasmas are now capable of sustaining different electrical potentials depending on the precise nature of the electrostenolytic activity at each site on the surface of the plasma membrane. However, no electrically active junction has formed within the cell.

8.4.2.3 The fully functional *second order* neuron

(**C**) in the above figure shows the cell continuing to evolve. It now exhibits three separate internal plasmas, each of which exhibits a different electrical potential compared to the surrounding electrolyte. There is a fully formed Activa at the juxtaposition of the left and right-hand internal membranes. The cell remains in overall electrochemical equilibrium. However, the Activa is fully functional and it influences the potential between the various plasmas. The relationships between the potentials of these plasmas will be discussed further in **Section 8.5** following the development of additional background material.

8.4.2.4 Preview of the fully functional neuron in a neural signal path

(**D**) shows the fully functional neuron interfaced with two adjacent cells to form a continuous neural signal path. These intefaces, or synapses, are also Activas and are represented by the two vertical black bars. If the electrostenolytic processes have provided the correct biases to the internal Activa and a charge is injected into the dendroplasm of the neuron from the axoplasm of the neuron shown in partial view on the left, the Activa will cause a charge to appear in its axoplasm. This charge will change the potential of the axoplasm. A change in this potential will cause charge to be transferred to the dendroplasm of the neuron shown in partial view on the right via the synapse shown. Thus, signaling will have been achieved. This signaling is inherently analog in character. However, if the neuron has evolved farther and significant electrical capacitances have become associated with the dendroplasm and/or axoplasm, the circuit may

be prone to monopulse oscillation depending on the impedance between the podaplasm and the surrounding electrolyte. In this case, action potentials will be observed in both the axoplasm and the dendroplasm. The neuron will now be operating in a pulse mode with respect to its output.

> For the remainder of this Chapter, the elements of the cell related to housekeeping, growth, glandular and other functions will not be considered; as an example, the nucleus is not of significance to this discussion. They will be assumed to be walled off from the electrical signal carrying portions of the cell by the internal membranes, dendrolemma and axolemma of the neuron. Thus, in a general sense, the discussion will center on the poor but widely used morphological concept of a morphologically monopolar neuron without concern for the nucleus portion of that neuron.

8.4.2.5 Features of the *second order* fundamental cell

If a cell commonly labeled a neuron is examined very carefully, it will be seen to include a variety of internal membranes in addition to the enclosing membrane. Furthermore, the enclosing membrane may consist of more than one layer of membrane (each a bilayer by themselves) at some locations. These membranes may provide a variety of functions beyond those of interest here. From the electrochemical perspective, these membrane configurations provide at least the following functions:

+ partitioning the cell electrically from the exterior environment

+ partitioning the cell electrically into internal regions containing different heterogeneous materials.

+ providing an electrical potential between the above regions and/or the external environment.

+ controlling the impedance between the above regions.

+ **provide an active device "based on transistor action**" between some of the above regions and/or the exterior of the cell.

The presence of a single type 2 region of membrane between two plasmas, supported by electrostenlytics, can provide both an impedance between these two regions and a change in potential between these regions--two very useful mechanisms in electrical circuits. As mentioned previously, the impedance is not resistive. Using Thevinen's Theorem, the impedance can be represented by a diode in parallel with a capacitance.

> Here again, it is important to point out that Thevinen's Theorem does not apply to more complicated circuits which include a variable impedance unless the voltage or current level is specified. Specifying these levels complicates the application of Thevinen's Theorem greatly.

The presence of two very closely spaced membranes can provide even greater electrical complexity and opportunity. The scope of these complexities and opportunities is directly related to the distance between the two membranes. Here again, the literature is not well focused. For this work, three classes of juxtaposed membrane pairs will be defined based on the distance between the edges of the two membranes:

+ Tight junctions, spacing typically zero Angstrom

+ Gap junctions, spacing typically 20-50 Angstrom

+ Chemical junctions, spacing typically greater than 200 Angstrom

The tight junction by definition does not allow for the presence of any independent electrolyte to exist between the two membranes. On the other hand, the gap and chemical junctions can support an independent electrolyte in this region which can be either extracellular or associated with a different enclosed region of the cell. These last two junctions are those generally related to neural signaling processes. The gap junction is used in internal Activa, in Nodes of Ranvier and in synapses.

Figure 8.4.2-2 is significantly modified from Pappas to illustrate the typical gap junction based on the above terminology and this work[166]. A comparison between the two variants (and their extension justifying physical channels between the two plasmas) is instructive. The labels have been changed to allow the figure to represent a broader range of situations. In the case of the Activa within a given neuron, the two plasmas are both internal to a given neuron (cell). The space marked interplasma space may also be internal or external to a given neuron (and may in fact be a third plasma space within the same neuron).

The typical gap junction involves a space between two membranes that is so narrow that large molecules can not persist there. They are essentially eliminated during the formative process due to Brownian Motion. The remaining material is generally hydronium, a liquid crystalline matrix of water molecules. While membranes are frequently made up of back-to-back arrangements of the same lipids (resulting in a highly effective electrical insulator), this need not be the case. In the gap region, each membrane is made up of two asymmetrical lipid layers. This is indicated in the figure by filling the heads of some of the lipid molecules. The resulting configuration consists of two electrical diodes connected back-to-back via a single liquid crystalline, and conductive layer of hydronium. This configuration is critically important to the operation of the neural system as shown in **Section 8.5** and following.

The conventional explanation of how electrical charge is transferred from plasma #1 to plasma #2 is to conceptualize large channels traversing the gap capable of transporting large ions across the barrier. If the alternate case (the transfer of charge by the flow of electrons) is examined, the materials present can support the flow of this current without the need for any physical channels. The channels for electron flow within the hydronium material are quantum-mechanical and not "physical."

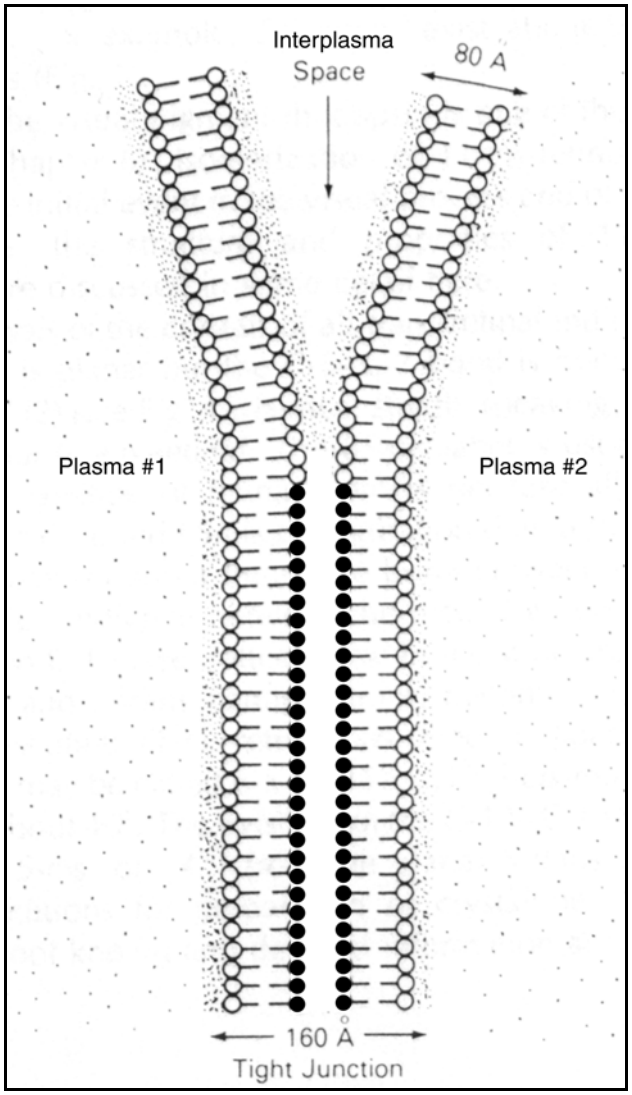

Figure 8.4.2-2 A gap junction as it appears in the neurological system. Two type 1 membranes are shown at the top of the figure (symmetrical lipid layers). Two type 2 membranes are shown at the bottom (asymmetrical lipid layers). Modified from Pappas, 1975.

[166]Pappas, G. (1975) Junction between cells. *In* Weissmann,G. & Claiborne, R. *ed.* Cell Membranes: Biochemistry, Cell Biology & Pathology. NY: HP Publishing Co. Chap 9, pp 87-94

Eckert[167], in 1988, said "Membranes are never seen to terminate with free ends; they always form enclosed compartments." There is some question about this statement based on **Figure 8.4.2-3** at a magnification of 204,000x taken from the work of Gilula[168] and the work of many others. Although drawing conclusions about three-dimensional structures from two-dimensional images is always dangerous, it would appear that Eckert's statement should be broadened to at least allow for lap joints between membranes. Because of the bi-leaf structure of individual membranes, it appears that individual membranes cannot end by tapering away to zero thickness. They can and in fact do end abruptly. Thus, lap joints involve free ends but appear to always involve gap or tight junctions. This would insure that there is no electrolytic communication among the three electrolytic chambers involved in a typical structural junction.

In the left of **Figure 8.4.2-3**, there is a piece of membrane which appears to be of finite length, to end abruptly on each end and to be sandwiched in between two separate membranes. On the right of this figure, there is a membrane forming a complete loop. Although the original caption by Gulila, speaks of this non-junctional membrane as contaminating the fraction; this author would take a different view and ascribe to this loop an electrical function. Specifically, the left side of the loop forms a separate membrane system (a membrane separating two different electrolytes) which in turn can generate a voltage and exhibit an impedance that may form a voltage supply or a load impedance for the Activa created by the gap junction on the right side of the loop. Thus, a revised caption might read: "Arrow points to a membrane providing an electrical potential and load impedance in support of the (two) Activas on the opposite side of the enclosed electrolyte."

It is interesting to note the preponderance of three membrane sandwiches in this figure. It is also interesting to note the significant defocusing of the image of the membrane in the center of the figure and at lower left. This defocusing suggests significant electron charge concentration exists in these regions.

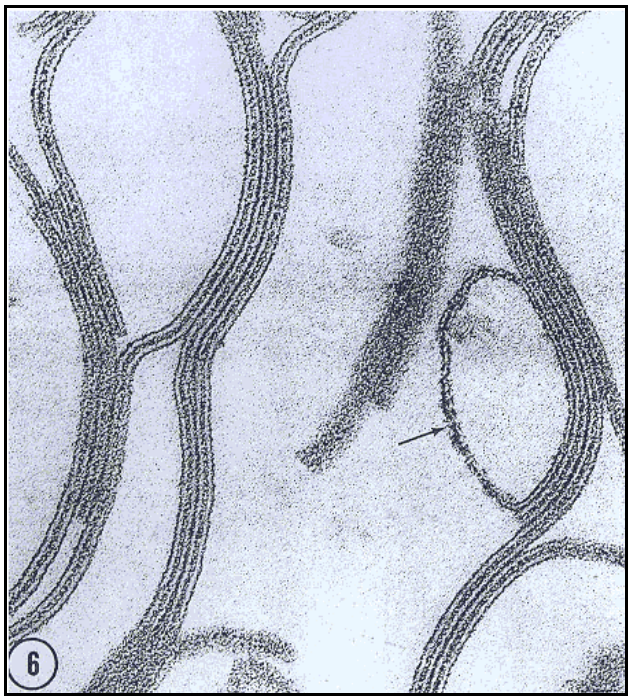

Figure 8.4.2-3 CR Subcellular fraction of gap junctions isolated from rat liver. (X204,000) See text. From Gilula (1975).

8.4.2.3 The molecular structure of the junction between two membranes

Figure 8.4.2-4 provides a cross sectional view of two membranes brought into close proximity[169]. Pearson & Pascher provide many parameters related to lipid bilayers. Each membrane is the same as that shown in **Section 8.2.1.3** The two solutes are labeled the dendroplasm and the axoplasm. The numbers 1 through 7 are those assigned by a cytologist to a seven-layer junction between two bilayer membrane walls. Note they usually see layers 1, 3, 5 & 7 as dark lines and assign 2, 4 & 6 to the light spaces between these lines. It is seen from this figure that the characters of these spaces are different. Whereas 2 & 6 appear empty, 4 has a distinct character. In fact, the material represented by 4 is critical to the operation of the neurons. A similar material that is performing a different function is found between layers 1 & 7 and their respective plasmas. It would be advisable to number these regions 0 & 8 when speaking of the functional performance of such a sandwich. The thickness of the

[167]Eckert, R. (1988) ibid. pg. 65

[168]Gulila, N. *ibid.*, figure 6

[169]Pearson, R. & Pascher, I. (1979) The molecular structure of lecithin dihydrate *Nature* vol 281, pp 499-501

junction area is a variable *in-vitro*.

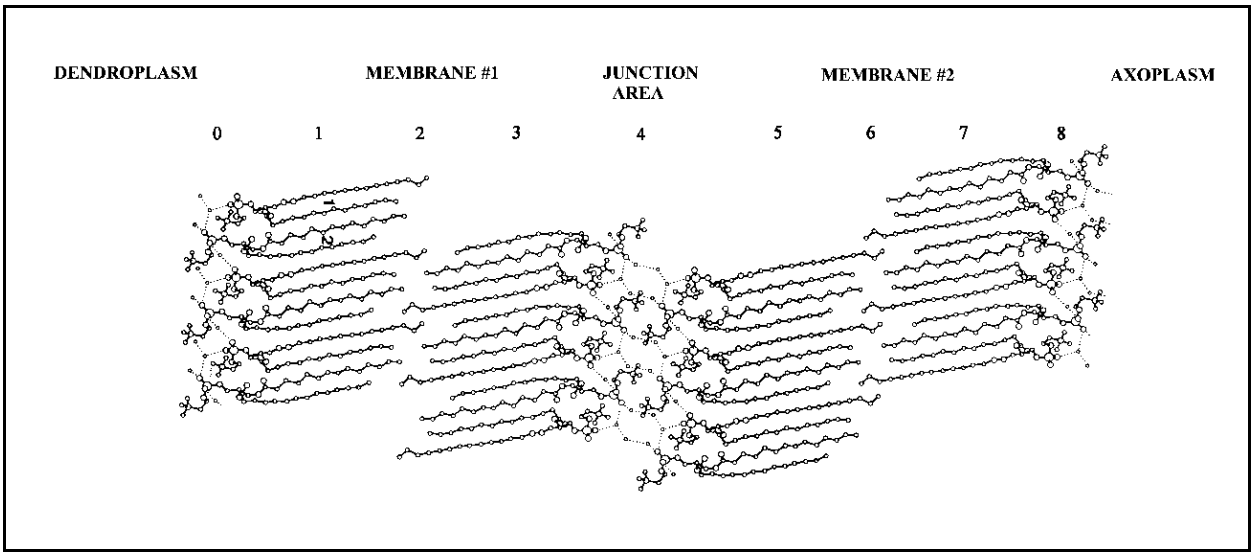

Figure 8.4.2-4 The structure of the Activa at the atomic level. In operation, the configuration consists of two bilayer membranes (BLM) in close proximity and appropriate voltages applied between the dendroplasm, the axoplasm and the material in the junction area between the two bilayers (the podaplasm). The lattices in the junction area and on the extreme left and right surfaces are hydronium. Detailed atomic structure of an individual membrane from Pearson & Pascher, 1979.

Note the complex molecular structure at the interface between each plasma and the corresponding membrane. These areas are described in terms of hydronium ions. The structure in the junction area, between the two membranes is also described in terms of hydronium. In this case, the material constitutes a hydronium crystal. There is no physical movement of ions within this overall structure at biological temperatures. No ions move through either the hydrophobic liquid crystalline lipids or through the hydronium liquid crystal. This is true even under the influence of external voltages.

When configured as shown, the areas marked 3, 4 & 5 exhibit unique quantum-mechanical properties. These properties result in a unique electrical feature as well. This feature is defined as an Activa. The unique electrical feature of the Activa and the overall structure will be explored further in **Section 8.5**.

It is still an early day in the field of biological membrane research. Yeagle has published a 2nd edition that is quite different from the first but is still focused on exploratory research[170]. "The present understanding of membrane structure is a reflection of how young the filed of membrane studies is (pg 65)." A majority of the literature focuses on bilayers of phosphatidyl choline variants. Yeagle briefly discusses the energy situation relative to the spacing between two membranes and introduces the subject of asymmetric lipids. He asserts that transition of a given lipid or lipid species between layers of a membrane is remote. However, during membrane biogenesis, he notes the clear tendency for the outer leaf to be PC and the inner leaf to be PE (pg 131 & chap. 12). He also notes the high concentrations of carbohydrate (CO_2) often found on the surface of plasma membranes (pg 6).

Yeagle makes a distinction between the liquid crystalline state of bilayer membranes as a function of temperature. He describes the liquid crystalline state of these materials as a gel at temperatures below 42 C based on the reduced lateral diffusion of the molecules within the individual layers of a membrane but tempers this criteria based on the location of double bonds along the nonpolar chains (pp 87-96). The transition *in-vitro* occurs between -20 and +42 C. He reverts to general concepts when discussing the transport of materials through a membrane.

Yeagle also discusses the energy considerations related to the state of hydration of lipid molecules and the energy necessary to bring two bilayers into juxtaposition (pp 58-66). This positioning determines the thickness of the junction area in the above figure.

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[170]Yeagle, P. (1993) The Membranes of Cells, 2nd Ed. NY: Academic Press

The cross sectional area of each molecule in the lipid bilayer is approximately the same as that of glutamate. The fact that PC is polar positive and glutamate is polar negative suggests these two materials may come together in a stereographic arrangement independent of any other catalyst such as GAD (glutamic acid decarboxylase).

8.4.3. Transition from an axon-only to a junctional-tissue model

The initial goal of this work was to model the neural system in sufficient detail as to define its input parameters relative to the photoreceptor cells of the visual system. The intent was to model the photoreceptor cells more intensively based on the findings related to the simpler neurons of the neural system. The analytical and system analysis tools used will be discussed in **Chapter 11** were employed. The procedure was to look closely at the database and attempt to define the basic functional stages of the neural system. Particular emphasis was placed on the data available concerning the S-plane (see Section xxx), the neurons immediately behind the photoreceptor cells in the signaling chain. It became clear that the so-called bipolar neurons of the retina were one of the simplest types of neurons. Effort was concentrated on modeling this type of neuron. Initially, the neuron was assumed to contain a generic operational amplifier. A variety of different types of operational amplifiers were examined to determine which type exhibited characteristics most closely matching the bipolar neuron. The input and output impedance levels appeared to rule out amplifiers based on field-gate technology. They were more compatible with junction-gate technology. The voltage levels involved also appeared more compatible with junction-gate technology. Although there was little precise data available concerning the input or transfer impedance of the cells, there was good data on the output impedance. This data showed the amplifier to have an output impedance identical to that of a diode. Combining the output impedance data and the voltage normally associated with the output strongly suggested the output amplifier of the bipolar neuron could be modeled by a PNP type junction transistor operating in the common base mode. The challenge was to define the rest of the circuitry within the bipolar neuron. The key feature was the recognition that the bipolar neuron acted as an impedance changing device but did not exhibit significant voltage amplification. Such performance could be achieved using only a single PNP type semiconductor device combined with a few other electrical components. This combination of an Activa combined with a few other electrolytic components defines the conexus within the neuron.

> Sigworth has recently published a brief philosophical discussion suggesting field-effect type of transistors occur within the neural system[171]. He describes himself as a member of the ion-channel field. His thesis was all-encompassing when he says the putative "Voltage gated ion channels control electrical activity in nerve, muscle and many other cell types." No quantitative performance data is provided that shows how such a field effect device actually works in the electrolytic environment of the neural system. He does present an interesting rhetorical question. "What structural design would allow so many charges to move so far, crossing the 30 Angstrom thick, electrostatically hostile interior of a cell membrane?" While potentially hostile to the transfer of ions, the membrane is well known to form a diode that is quite amenable to electron transport–in one direction. Sigworth concludes with a list of fundamental questions that need to be answered before the concept of an ion gate can be described as a field-effect transistor.

The above analysis led further. It showed, as illustrated in [**Figure 8.4.2-1**], that the configuration of the junctional-tissue between two neurons was largely indistinguishable from the configuration of the junctional-tissue between the dendrite and the axon within a neuron. As a result of further analysis, to be presented in **Chapter 9**, a stunning conclusion appeared. It became clear that the synapse was another form of conexus built using the three-terminal Activa defined above. **All synapses are in fact active semiconducting devices acting as low loss current transfer devices** (see **Section xxx**).

> **The discovery that all neurons and all synapses contained at least one active electrolytic semiconductor device provided an entirely new foundation on which to build a broader understanding of the neural system**.

8.4.3.1 Rationalizing the axon-only versus the junctional-tissue models

[171]Sigworth, F. (2003) Life's transistors *Nature* vol. 423 pp 21-22

Since the constrained analyses of Hodgkin & Huxley in the 1950's, the axolemma of a neuron has been considered the key active element in the neurological system. This axolemma has been modeled as a two-terminal electrical network of varying degrees of complexity. However, these axon-only models have not proven satisfactory and have not explained the roles of the other neurites of the neuron. A large cadre of investigators have not been able to explicitly define the mechanism controlling the variable impedance(s) shown in these axon-only models. Finally, the two-terminal axon concept has not led to progress in understanding the overall operation of the neural system. It has been unable to explain the signaling mechanism found between neurons. This has led other authors to question the adequacy of the basic two-terminal assumption associated with the axon only ideology.

It has also been common for authors to attempt to explain the operation of the neural system based entirely on chemical processes. This appears to be primarily due to the academic training of the authors and the ubiquity of certain chemicals near elements of the neural system. However, this ubiquity has not provided insight into the mechanisms employing these chemicals. The concept of neurotransmitters is a particularly awkward one that can be questioned on many grounds.

An alternate unconstrained analysis, summarized above and diagramed in **Figure 8.1.1-1**, has led to a fundamentally different "junctional-tissue" ideology. At a top level, this ideology focuses on the junctional-tissue between conduits within a neuron as the location of the active mechanism within the neuron. At the next lower level, the ideology focuses on the junctional-tissue as forming a unique three-terminal electronic component. At a functional level, this single three-terminal device is seen to be ubiquitous throughout the neural system. This three-terminal device can be shown to be the biological equivalent of the man-made transistor. It is a PNP type electrolytic liquid-crystalline semiconductor devices named an Activa. This ideology expands to describe three-terminal Activas located at multiple locations along each neural signal path. These locations are both within and between (outside) individual neurons.

The three-terminal junctional-tissue ideology leads to radically different interpretation of the chemicals found in and adjacent to the neurons. Many of them are bio-energetic materials associated with metabolism in other parts of the body. They are particularly associated with the well-known glutamate cycle of metabolism. These materials are well suited to participation in an electrostenolytic process at the surface of the neurons designed to provide electrical power for signaling instead of chemical based signaling. **Section 8.6** will expand the chemical mechanisms available under the junctional-tissue ideology that lead to a complete understanding of the synapse as presented in **Section xxx**.

The following sections will proceed to define the detailed features and proposed operation of the fundamental neuron containing an Activa. **Chapter 9** will address neurons of greater functional complexity. **Chapter 10** will address the morphological packaging and physiological operation of complete neurons based on the junctional-tissue ideology and the Activa hypothesis. Following these chapters, the reader can make an independent judgement concerning the competitive merits between the axon-only and the junctional-tissue ideologies. The material of **Chapters 11** through **15** will describe the operation of the entire neural system based on the junction tissue ideology and Activa hypothesis.

8.4.3.2 The junctional tissue as the conexus within a neuron

As developed above and expanded upon in **Section 8.5**, the performance of the individual bipolar neurons suggests they contain a very simple electrical circuit (a conexus) that contains a single active semiconductor device (an Activa) as its centerpiece. This assumption has proved to be entirely satisfactory in the case of all signal manipulation neurons and has led to a detailed understanding of the more complex types of neurons. Such semiconductor devices are described as three-terminal devices. The fact they are three-terminal devices suggests the internal construction of the neuron is more complex than previously recognized. Two of these terminals are connected to a dendritic conduit and an axon conduit respectively. The third terminal is connected to a newly defined element, a poditic conduit. The nature and characteristics of this conduit will be discussed briefly in [**Section 8.4.4.1**] and presented in detail in **Chapter 10**.

Both projection neurons and many signal detection neurons are found to contain multiple active devices. All of the Activas found within these neurons are found in areas composed of junctional tissue.

8.4.3.3 The junctional tissue as the conexus between neurons–the synapse

As suggested by [**Figure 8.4.2-1(D)**], the synapse between two neurons appears cytologically identical to the conexus within a neuron. They both occur in areas of junctional-tissue. While there is a functional difference between an internal conexus and the synapse, the difference is defined primarily by the electrical biases supplied to the three terminals of the Activa within each conexus. The operation of the synapse is described in detail in **Section 9.xxx**.

8.4.4 Defining the static conexus found within and between neurons

8.4.4.1 Defining the electrical circuits of a neuron

The fact that the neurons operate in a nonlinear impedance environment, at least in the second order, has been recognized since at least 1949[172]. In those early days, the term "anomalous rectification" and "inward rectification" were found in the literature. Recently, the expression has frequently been shortened to just rectifying channels. It is important to understand the theoretical and practical voltage-current characteristic of a diode or Activa. This characteristic is fundamental to the operation of all neurons. It plays a primary role in all experimental investigations and the proper interpretation of all test results.

The fundamental voltage-current characteristic of all diodes and active semiconductor devices is a simple exponential function as shown in [**Figure 8.3.1-1**]. Two facts are important in experiment design. A diode in the absence of any other electrical component is useless, especially for signaling purposes. Whether a diode is considered a linear element in practice, a logarithmic signal compressor, or a rectifier depends on the voltage level applied to it and the other circuit elements present. Under small signal conditions, a diode can be considered a fixed impedance. If the signal is larger but its instantaneous value is always either significantly larger or smaller than ηV_T, the circuit is valuable as a signal compressor or expander. This is the primary role of the diodes in the neural system. If very large signals are applied to the circuit containing a diode and the instantaneous amplitude of the signal straddles the voltage ηV_T, the signal appearing across the diode will be significantly changed in shape. The diode will be acting as a rectifier. In the neural system under *in-vivo* conditions, the absolute potential of all of the signals (which may include a bias component) applied to the diodes are larger than ηV_T. The resulting circuits operate as signal compressors or expanders. It is only under artificial conditions created by man (or unfortunate lightning strikes), either *in-vivo* or *in-vitro*, that the diodes may be driven into the "rectifying" region. In the laboratory, it is important to recognize two facts:

+ that nonlinear amplification, either signal compression or expansion as a function of the applied parameter is the normal condition. This nonlinear amplification can be further described as exponential in most cases.

+ that rectification in the neural system (except in stellate neurons, Section 8.5.4.5.5) is due to poor experiment design. Application of test stimuli of more than 100 mV do not emulate actual neural signals and are frequently destructive of the tissue under test.

For those interested, the recent figures of Baker, et. al.[173] can be interpreted much differently under these ground rules than they were by the authors. They were apparently attempting to evaluate the performance of myelinated projection neurons under electrotonic (unusual and forced) conditions on the assumption that the axon was represented by a linear circuit model with variable resistors. In the positive portion of their figure 1(C), the waveforms are the normal exponential transient characteristics of an amplifier employing logarithmic compression. Similarly in figure 2(A) and (B). Their figure 3 is the predictable case of low-level excitation that does not cause generation of an action potential. Row (C) in that figure clearly shows the effect of a temporary (low frequency) shift of the signal operating point. The gain parameter is reduced for the high frequency waveform. In the majority of their figures, the negative signal excursion is an atypical response due to human intervention. [drop this paragraph in published text xxx]

Figure 8.4.4-1 provides a conventional morphological view of the fundamental neuron. It is basically a redrawing of the figure in **Section 8.4.2**. Functionally, it differs from the electrical model in figure 9.7 of Segev & London by further differentiating their soma and differentiating between the signal and power terminals associated with the axon and neurites[174]. Practically, their axon length of only one micron compared to an 800 micron long (0.8 mm) dendrite seems

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[172]Katz, B. (1949) Les constantes electriques de la membrane du muscle. Archived des Sciences Physiologiques, vol. 3, pp. 285-299

[173]Baker, M. Bostock, H. Grafe, P. & Martius, P. (1987) Function and distribution of three types of rectifying channel in rat spinal root myelinated axons. J. Physiol. (London) vol. 383, pp. 45-67

[174]Segev, I. & London, M. (1999) A theoretical view of passive and active dendrites *In* Stuart, G. Spruston, N. & Hausser, M., *Ed*, Dendrites, Oxford: Oxford University Press pg 225

unusual. It appears they misinterpreted the drawing of Rall in adopting this high value for the dendrite.

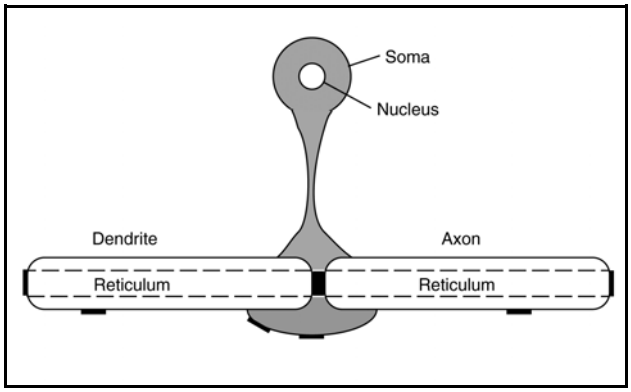

Figure 8.4.4-1 Cytological view of the fundamental neuron including the reticulums within the dendrite and axon. The dendrite and axon are shown in their final juxtaposition. The space between them is greatly exaggerated for purposes of illustration. All horizontal black bars are electrostenolytic sites. Vertical and oblique bars are signaling sites (if used).

This figure can serve as a model for all more complicated neurons based on the fact that it shows all six electrical terminals associated with the typical neuron. In this figure, the terminals providing power to the neuron through electrostenolytic processes are symbolized by the three horizontal black bars (including the one on the soma associated with the poditic terminal). The terminals associated with the signaling process are symbolized by the two vertical bars (representing conventional synapses) and the angles bar at the bottom of the soma symbolizing a potential additional signaling input via the poditic terminal to be discussed later.

A further discussion of the electrical circuits of a neuron related to their morphology and operational electrophysiology will be presented in **Chapter 10**.

8.4.4.2 The quiescent operational potentials found in axons of different neurons

In electrophysiological investigations to date, it has been common to measure the absolute potential of various axons, and occasionally other neurites and the soma, relative to a "surrounding matrix." As in the case of using the Leyden Jar approach versus the Ussing Apparatus approach, the potential of the surrounding matrix is a variable with location. Analysis of the available data would suggest a typical difference of 10 mV between the potential of the circuit ground in the experiment and the local ground at the poditic terminal of the neuron. This variability has led to a great deal of confusion in the literature. Future measurements must account for the impedance of the inter-neuron matrix (INM) surrounding the *in-vivo* neuron. For *in-vitro* experiments, similar precautions should be taken. To minimize this confusion, many authors have attempted to use a nominal axon potential in their discussions. The following table will show that a nominal potential is an elusive concept.

In the absence of an adequate electrical model of a neuron, the biology community has also adopted the "resting membrane potential" as a reference when discussing the neuron. **Chapters 9** and **10** will make it clear that the resting membrane potential is actually the plasma resting potential and that the resting plasma potential varies with the application of the neuron. This convention has made it difficult for many to comprehend the additional circuit elements present in a neuron. As developed in [**Figure 8.5.4-2(c)**], there is frequently a considerable difference between the intrinsic plasma potential (provided by the power source when the Activa is cutoff) and the resting axoplasm potential. The resting axoplasm potential is actually a function of the intrinsic electrostenolytic potential, the biases applied to the Activa, and the impedances of these elements within the neuron. The resting axoplasm potential bears no relationship to the intrinsic battery associated with the membrane alone.

Figure 8.4.4-2 provides the correlation between the historical electrophysiological terminology and a broader terminology consistent with the actual situation and normal electronic circuitry. Frame D of the figure is based on a figure from Ottoson[175]. It is clearly a composite figure. The left-hand scale of this frame makes it clear that it is the voltage of the surrounding interneural matrix, INM, that is actually used as the reference in most physiological work. The most frequent nomenclature is defined in terms of the commonly defined "resting membrane potential." This potential is actually the quiescent plasma potential. The most negative potential associated with a cell is actually the intrinsic electrostenolytic potential. While this potential is closely associated with the membrane, it is distinctly different from the intrinsic potential of the membrane. This intrinsic electrostenolytic potential is usually considerably higher than the intrinsic membrane potential. It is also generally higher than the quiescent plasma potential unless the Activa associated with the plasma is in the cutoff condition.

[175]Ottoson, D. (1983) Physiology of the nervous system NY: Oxford University Press. pg.. 56

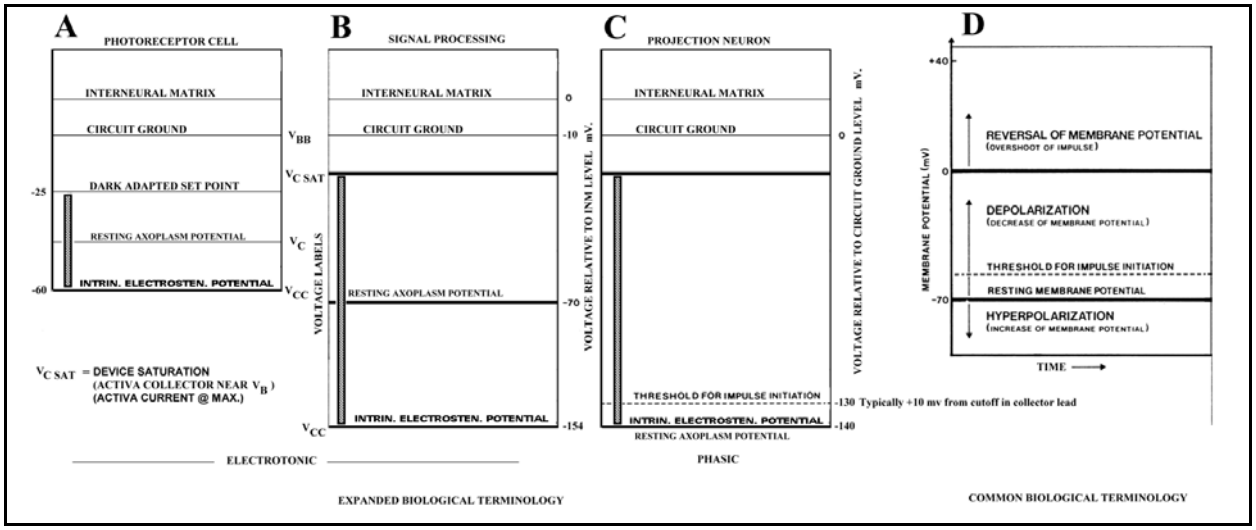

Figure 8.4.4-2 Static electrical terminology in electrophysiology. The conventional biological terminology is shown in frame (D) on the right. It represents a composite neuron. This conventional terminology is expanded and differentiated into three specific cases on the left. Frames (A) and (B) represent electrotonic neurons. Frame (C) represents a phasic neuron. (A); this frame shows the potentials associated with the axon of the typical photoreceptor cells. (B); this frame shows the typical potentials associated with signal processing neurons. (C); this frame shows th potentials associated with typical signal projection neurons These neurons spend a majority of their time in the cotoff condition with the axoplasm at –142 to –154 mV relative to the INM. See text.

The resting axoplasm potential of a neuron need not be at or near -70 mV. It can vary significantly determined by three circuit parameters. The intrinsic electrostenolytic potential is determined by the reactants participating in the electrostenolytic process on the surface of the axolemma. The quiescent or resting axoplasm potential is reduced by the currents flowing in the circuit. This reduction is due to these currents flowing through the source impedance of the electrostenolytic process. The magnitude of these currents is determined primarily by the collector current of the Activa associated with this plasma. It is also a function of any current being injected into the next dendrite at the synapse.

Frames A, B & C of the figure present an expanded terminology and nominal potential profile applicable to the different types of functional neurons. These three profiles discriminate between the ground potential of the INM and the circuit ground of the individual type of neuron. In many cases, the circuit ground is a few millivolts more negative than the INM ground due to the intrinsic membrane potential of the poditic membrane and the impedance of the INM. Frame A represents the typical photoreceptor cell. This type of cell exhibits a lower intrinsic membrane potential than the other types. Its dynamic range, of only about 35 millivolts, is less than most other cells. The distribution Activa of the cell has a quiescent current in the dark which is defined as the dark adapted set point. It also exhibits an average current in response to illumination that is shown as the resting axoplasm potential. Frame B describes the potentials found in the signal processing type of neuron. It exhibits a more negative intrinsic electrostenolytic potential than the photoreceptor cell. The resting axoplasm potential is near the intrinsic electrostenolytic potential of the photoreceptor cells. The large signal voltage swing capability of the signal processing cell is shown by the vertical bar.

Frame C represents the typical signal projection neuron (including the hybrid neurons such as the ganglion cells). These cells have a high intrinsic electrostenolytic potential. Under resting conditions, the Activa within these cells is in cutoff. The resting axoplasm potential closely approaches the intrinsic electrostenolytic potential under the cutoff condition. The critical threshold condition of the emitter circuit is shown transposed to the output circuit and labeled the threshold for impulse initiation. The large signal voltage swing associated with action potential generation is shown by the vertical bar. The collector current of the Activa reaches saturation at the peak of the action potential. This can cause the axoplasm potential to become positive for a short interval during action potential generation. However, the intrinsic electrostenolytic potential and the smaller intrinsic membrane potential remain negative at all times.

The intrinsic electrostenolytic potential for the signal processing and signal projection neurons is normally in the region of -142 to -154 mV relative to the interneural matrix. The intrinsic membrane potential is usually much smaller. It is typically less than 50 mV. A broader discussion of this figure will be found in [**Section 10.10**]. As an side, the resting plasma potential in a cell from the algae, *Nitella*, was measured as –138 mV at 20 C. This value would suggest the intrinsic potential of a wide variety of animal and plant cells was in the –138 to –150 mV range at 20 C. The variation is more likely due to experimental technique than differences in the actual intrinsic value.

The data in the literature requires careful interpretation. It is not normally associated with a specific type of neuron and it generally uses the old, less precise, terminology. Neumcke et. al. have provided a number of potentials with respect to temperature. The resting axoplasmic potential in myelinated frog neuron is given as -71 mV @ 17 C and -50 mV @ 21 C[176]. In a separate paper, a resting potential of -78 mV was assumed and used as a clamp voltage. The so-called Na equilibrium potential is given as -152 mV @ 20 C and -144 mV @ 37 C[177]. These latter values are clearly the intrinsic electrostenolytic potential of the axolemma of a neuron biased for action potential generation. Schwarz & Eikhof[178] have provided additional numerical data concerning the transient performance of such neurons. However the *model* used to explain their *data* is in conflict with the model of this work. They discuss the "run down" that occurred within a period of 30-50 minutes. This run-down is to be expected if the reactants required by the electrostenolytic process (see **Section 8.6**) are not supplied by diffusion within the cardiovascular system supporting the neurons.

By comparing these frames, it is seen that only the signal processing neurons exhibit hyperpolarization, the movement of the axoplasm potential to a more negative voltage than its quiescent or resting value. Depolarization is a common occurrence in all three neuron types. The reversal of the axolemma potential relative to the INM is unusual. Its observation is usually caused by the capacitance introduced by the test set rather than by the *in-vivo* neuron.

The voltage of the dendroplasm and podaplasm must also be addressed briefly although very little data appears in the literature. Segev & London have recently provided data related to the potentials of the dendrites and the soma (?) that will be addressed more fully in **Chapter 10**. The instantaneous difference in potential between the dendroplasm and the podaplasm (both measured at the Activa) se two voltages determines the emitter to base voltage of the Activa within the neuron. The quiescent value of this difference determines the operating mode of the Activa, whether it operates electrotonically or generates action potentials. If operating electrotonically, this difference can determine the gain coefficients for the signals applied to the dendrite and the podite.

8.4.4 Equivalent circuits of the differentiated conduits of the static neuron MOVE to Chap 10

What appears to be a continuous membrane at the cytological level may in fact exhibit different electrical properties at different locations because of changes in its molecular parameters as discussed in **Section 8.4.1.** Whereas a given membrane may exhibit a specific impedance and a specific voltage potential at a given location, either of these characteristics may effectively vanish or be significantly different at a second location.

Electron microscopy invariably shows that the single bilayer membrane is about 90 Angstrom thick and composed of two distinct surfaces which appear dark separated by a space appearing lighter. This sandwich is usually defined as consisting of two phosphoglyceride layers, the hydrophobic tail of the two layers facing each other and the two hydrophilic heads facing outward. Frequently, the sandwich is not symmetrical. The head group facing "outward" in a cell wall is normally *mostly* choline related (typically phosphatidyl choline or PC) and the head group facing "inward" is composed *mostly* of amino acids (typically phosphatidyl ethanolamine or PE). See the earlier **[Figure 8.2.5-1(a)]**.

At each location, the equivalent circuit of the membrane is characterized by the cathode of the diode being in contact with the "exterior" of the cell, the anode being connected to the positive terminal of the battery, and the negative terminal of the battery being connected to the "interior" of the cell as illustrated in the earlier **Figure 8.2.5-1(b)**. Words are in quotation marks in the above sentence because, it is necessary to also consider membranes that are entirely within a single cell--more succinct terminology is clearly required.

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[176]Neumcke, B. (1983) The myelinated nerve: Some unsolved problems, Experientia, vol. 39, pp. 976-979

[177]Neumcke, B.& Stampfli, R. (1982) Sodium currents and sodium-dependent fluctuations in rat myelinated nerve fibres. J. Physiol. vol. 329, pp. 163-184

[178]Schwarz, J. & Eikhof, G. (1987) Na currents and action potentials in rat myelinated nerve fibres at 20 and 37 C. Pflugers Archive--European Journal of Physiology. vol. 409, pp. 569-577

Because of the significantly different properties of symmetrical and asymmetrical BLMs, it is important to go beyond the description of the cell membrane using averages. The topology of the individual phospholipids may need to be mapped. As a minimum, the degree of electrical asymmetry of each region of the membrane needs to be specified.

8.4.4.3 Equivalent circuit of the axon element

The electrical characteristics of the axon have been studied the most. This has been due primarily to the ease of access to axons. The dendrites are generally very small structures and the poditic structures have not generally been identifiable through morphology. These structures will be addressed independently in this section.

Over the years, a series of ever more complex two-terminal networks have been presented in the literature that purport to represent the active characteristics of "the axon" or of "the axon membrane." From an analyst's perspective, the proposed networks have gotten out of hand. The original two-terminal network of Huxley et. al. consisted of three current paths and one capacitive path in parallel, each connecting to the "inside" and the "outside" of the plasma membrane. Shepherd shows a total of seven paths[179]. Each current path consisted of a battery and a "variable resistor" in series. The polarity of the two batteries frequently varied in subsequent transcriptions, analyses, and expansions of these simple circuits. The original network is shown in **Figure 8.4.5-1(A).** The circuit was highly conceptual at the time and no reason was given for the battery in series with the load resistance, R_L. In the original paper, the authors were careful to specify that they were reporting on a membrane. They did not claim to be reporting on a functional axon, or an operating axon, in that paper. The variable resistors were seldom discussed in detail. There has been no discussion of what is controlling the variation although Raymond & Lettvin[180] offer the important observation: "It is obvious that g_{Na} and g_K are not two-terminal elements but three-terminal elements; they are governable conductances in much the same way as is any junction transistor . . ."

Figure 8.4.5-1(B) shows a more precise representation of a portion of neural membrane using the style of Huxley, et. al. The membrane is represented between the two dashed lines as consisting of a single conductive path and a single capacitive path. The conductive path consists of a diode and a battery in series. In this representation, a current is being introduced into the axoplasm inside the membrane from an external source on the left. The load impedance is shown on the right as external to the equivalent circuit of the membrane alone. There are problems with both of these representations. In (**A**), no means is provided to determining the value of the resistances although it is stated that they vary with time and the membrane potential. This statement implies that there must be other elements to the circuit.

(**B**) is more explicit in defining the membrane as an impedance, Z_m, in series with a voltage, E_m. These are intrinsic parameters of the bilayer membrane. There are no undefined variable impedances. However, it does not explain the intrinsic potential associated with the axoplasm in the typical axon. This potential is normally much higher than the intrinsic potential, E_m, of the membrane.

The above problems can be overcome by looking at the more complex model shown in (**C**). This frame segregates the membrane of an axon into four identifiable regions shown here as quadrants. Two of the regions are normally in contact with the interneural plasma. The other two are not. In the latter case, each of the regions is in intimate contact with another conduit of the neural path. There performance will be discussed in **Section 8.5.** Hodgkin and Huxley were careful to remove any "dendritic material" associated with their test specimens, thereby changing the electrical configuration of the left region. It can only be assumed that they similarly cleaned away any material associated with the following conduit on the right. They then immersed the entire axon (if not the entire neuron) in an artificial interneural matrix.

It is important to note the nature of the battery and diode in the upper region. A majority of the membrane of any conduit is not designed to pass a conductive current. Wherever the membrane is designed to be an insulator, it is likely that its bilayer will be formed of two leaflets of symmetrical phospholipids. The result is a region of membrane represented by two high quality diodes back to back. This configuration is highlighted by the asterisk in the figure. Such a

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[179]Shepherd, G. (1988) Neurobiology, 2nd ed. NY: Oxford Press Pg. 114

[180]Raymond, S. & Lettvin, J. (1978) Aftereffects of activity in peripheral axons as a clue to nervous coding. In Physiology and Pathobiology of Axons, Waxman, S. Ed. NY: Raven Press pp. 203-225

configuration is a nearly perfect insulator. No current will flow through this path and the voltage, E_m, will be insignificant in the operation of the conduit.

The lower region represents a key element of the overall conduit. Although the membrane itself appears much the same cytologically as that in the upper region, it is intrinsically different and similar to that in the left and right region. Its two bileaves are asymmetric at the molecular level. As a result, the membrane exhibits a finite impedance and an intrinsic membrane potential as shown. This portion of the membrane, when coated with an electrostenolytic material, can introduce a current into the axoplasm by electrostenolytic action. This current is shown by the dotted source and current path. This current will generate a voltage across the combination of all of the current paths represented by the various diodes associated with the complete conduit. There is a source impedance associated with this current. The relationship between this source impedance and the net impedance of the diodes in parallel determines the quiescent potential, or resting potential, of the axoplasm. To a large extent, it is this axoplasm potential that is measured in experiments where the electrolytes within and outside of the membrane are slowly varied. In each case, a net conductance (or impedance) for the diode network is established that can be described as the static current through an equivalent single reverse biased diode in response to an axoplasm potential, E. This is the quiescent current, I_{diff} , in frame (B) in the absence of any external stimulus or loading.

The left and right quadrants of frame (C) represent the signaling portions of the axon. By juxtaposing other neural conduits approopriately, electrons can be introduced into or removed from within the membrane without the curring passing through the INM. At any time, the instantaneous axoplasm potential is determined by the solution of Kirchoff's Laws in the presence of all of these currents. The detailed operation of the circuits in these quadrants will be discussed in **Section 8.5.**

If the overall circuit in (C) is disturbed by connection to a test set, I_{diff} is impacted by the test set. Hodgkin and Huxley reported that the impedances, which they showed as resistances in frame (**A**), varied with the potential of the plasma just as expected by a diode network. In their early papers, they did not address the question of whether their calculated impedances were due to the static or dynamic characteristics of the equivalent diode.

It becomes obvious from frame (C) that the method of sample preparation plays a large role in the measured characteristics of a single section of neural conduit, whether it is called an axon, a dendrite or a podite.

The equivalent circuits of various neurons will be discussed more fully in later sections.

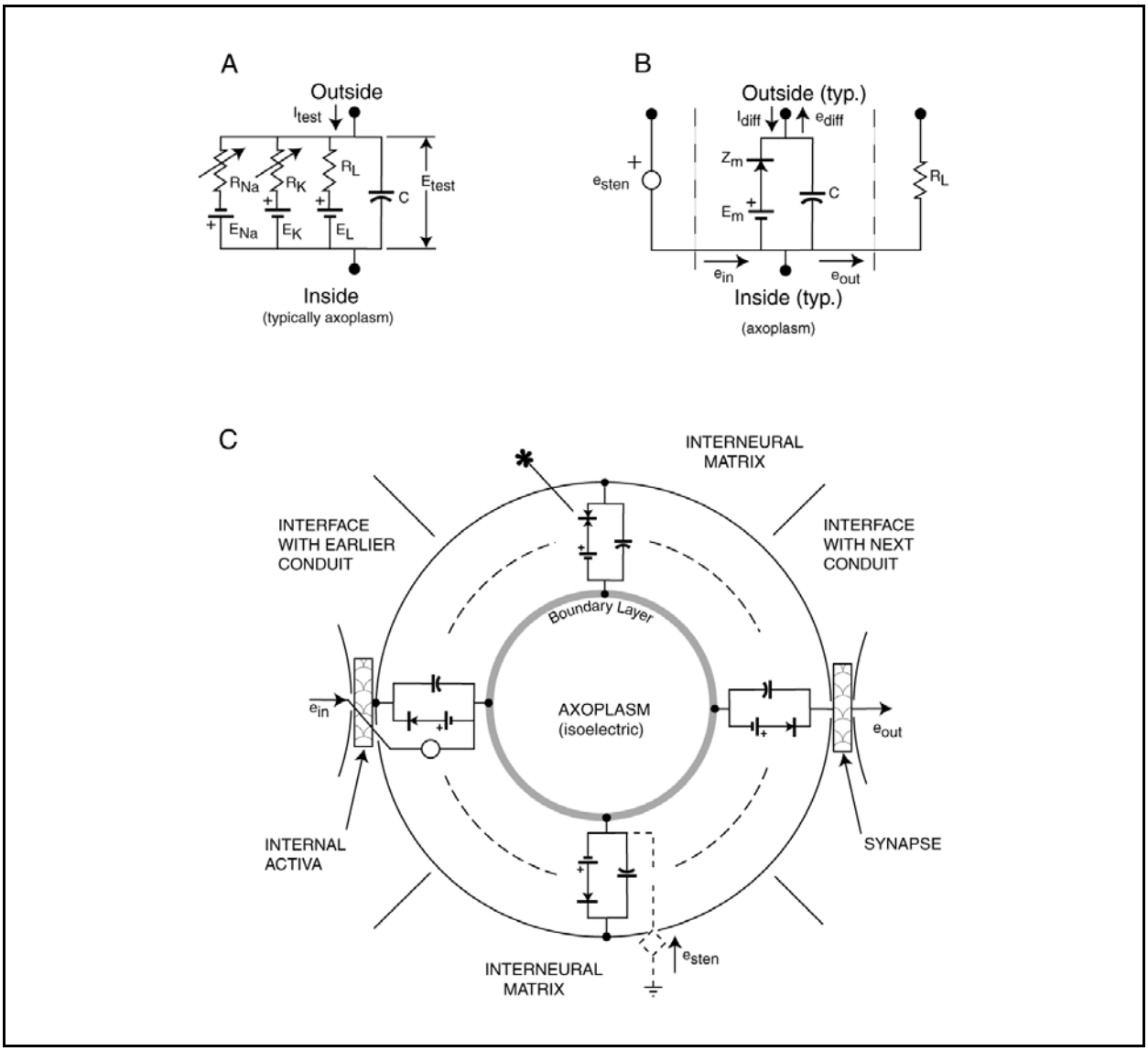

Figure 8.4.5-1 Illustration of the various electrical equivalent circuits representing individual specialized regions of the axolemma. A; the 2-terminal equivalent circuit of the isolated axolemma based on the constrained analysis of Hodgkin & Huxley and others. B; the more general network associated with the axolemma that can be used in several specific applications. C; a composite representing a longitudinal cross section of an axon before it has become extended horizontally. The boundary layer between the axolemma and the axoplasm is needed to properly understand the operation of the conduit. The conexus on the left represents the internal connection with a dendrite. This region of the axolemma is of type 2. Conventional current is injected into (electrons actually leave) the boundary layer by transistor action. The conexus on the right represents the connection with an orthodromic axon segment or dendrite. This region of the axolemma is of type 2. Conventional current leaves (electrons actually enter) the boundary layer by transistor action. The network at the top represents the type 1 membrane used for a majority of the axolemma surface. This network prevents any current from entering or leaving the axoplasm until the applied potential exceeds the breakdown potential of the membrane. The network at the bottom represents the type 2 membrane region used to polarize the axoplasm via electrostenolysis. Electrons are injected into the boundary layer at this site. Note that all of the diodes shown are reverse biased when the interior of the membrane is negative.

8.4.4.4 Equivalent circuit of the dendritic element

8.4.4.4.1 Background literature

Describing the electrical circuit of the dendrite is complicated by the extreme variation in its topography. Stuart, et. al. have recently edited a broad discussion of the dendrite[181]. It continues the policy of discussing the morphology and chemical functions of the dendrite while only discussing its signaling function from the most global perspective. This work takes exception to their basic premise on page 232 that "The action potential is the final output signal of most neurons." As will be discussed in Chapter 11, less than 10% and probably less than 1% of all neurons have action potentials as outputs. Only projection neurons in **stage 3** generate action potentials.

The complex topography of the dendrites, and frequently the podites as well, leads to difficulty in determining the electrical topology that best describes the element. For the longer uniform stretches of dendrite, it can be modeled as a distributed transmission line similar to equivalent structures of an axon. Where branching is prevalent, it is more useful to represent each branch as a lumped equivalent of the distributed parameters. These approaches are reviewed by Segev & London in Chapter 9 of Stuart, et. al. However, it must be noted that these structures cannot be treated as only RC circuits. At the impedance levels involved, the inductance plays a significant role in these circuits. Segev & London have (possibly without realizing it) omitted the inductance following the approach of Rall[182]. Rall adopted the approach used from 1900-60. The dendrite is modeled as a cylinder but it is studied by a patch approach where only the resistive and capacitive parameters of the cylinder wall are recognized. The second order Euler (alternately Cauchy) equation is reduced to a first order differential equation with constant coefficients. The result is an infinite series solution to a wave equation instead of a closed form solution based on sinusoids. It is suggested that a more conventional electrical circuit theory approach to this problem would provide better results in a closed form. This would be particularly true with regard to the excessively long time delays predicted by their approach. At the impedance levels involved, the impedance of the various inductances is much smaller than the resistances they shunt. This alternate approach is employed in **Chapter 10** with excellent results. The "kind of digital code" used in neuron signaling will be defined precisely in **Chapters 10** & **11**.

In the absence of a complete circuit model for the neuron, Segev & London struggle with the mechanism of signal amplification in the neuron. Although they do not define the soma specifically, they appear to be treating it morphologically as the portion of the cell other than the dendrites and axons. They do speak of the source of the action potential as occurring at generally unspecified locations internal to the soma.

Segev & London have made considerable progress in recording the steady state electrical properties of the dendrites, and sometimes relative to the associated axon. However, the asymmetrical waveforms shown for the response to a simple pulse in their dynamic signal experiments all suggest significant impedance problems in their test configuration due to the high impedance levels.

The above assumptions have a major impact on the seven insights, based on the passive (RC) cable model, presented in their paper. By recognizing the presence of inductance in the dendritic circuits, time constants at least one or two orders of magnitude lower would be calculated. Similarly, the voltage attenuation for dynamic signals would be considerably lower. Finally, the time delays based on an RLC circuit, where the R is usually negligible would lead to much lower time delays within the dendrites. By recognizing the presence of an Activa within their soma, operating in the current summation mode, their comments about window duration for signal summation take on a different meaning.

8.4.4.4.2 Equivalent circuit in this work

Because of the much higher transit velocity for dendritic signals deduced from other works, typically 40 times higher than in Segev & London, and the short physical distances involved, the dendrite can usually be considered a lumped constant electrical network derived from a complex of smaller distributed constant sections. However, to understand the mechanisms involved, it is best to consider the fundamental dendrite as a coaxial cylinder. The intrinsic inductance and capacitance of such a structure is easy to calculate.
The dendritic conduit element of the neuron can be represented by the same equivalent circuits as those for the axon.

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[181]Stuart, G. Nelson, S. & Hausser, M. (1999) Dendrites. NY: Oxford Press

[182]Rall, W. et. al. (1959-92) Extensive bibliography in Stuart, et. al. Op. Cit. pg 228-229

The only major difference relates to the value of the current and equivalent voltages associated with the electrostenolytic mechanism and the details of how the current from the previous conduit is injected into the conduit. This subject is explored fully in the next Chapter.

8.4.4.5 Equivalent circuit of the poditic element

As seen in the above figure, the cytological structure of the poditic conduit is somewhat different from that of the dendrite and axon. The podaplasm occupies the remainder of the plasma within the exterior membrane that is not isolated within the dendritic or axonal conduits and not isolated as part of the nuclear system. As shown, there is a specialized region of the podalemma for purposes of the electrostenolytic process. It is shown as the horizontal black bar similar to the horizontal black bars associated with the electrostenolytic terminals of the dendrite and the axon. The diagonal black bar on the surface of the podalemma indicates a potential specialized zone for purposes of receiving a neural signal. This site will be discussed in **Chapter 9**. Prior to complete genesis of the cell, the podaplasm occupies the space between the dendritic and axonal conduits. As these two conduits become juxtaposed, the space between these two structures becomes very small, typically 50-100 Angstrom. The majority of the chemical species of the podaplasm are forced out of this area by the rules of Brownian Motion. The remaining species is believed to be water in the form of a liquid crystal of hydronium.

Figure 8.4.5-2 describes the cytology and individual electrical equivalent circuit of the poditic portion of the neuron. The input and electrostenolytic interfaces are the same as for the dendrite and the axon. However, the output configuration is different. The podaplasm is in direct contact with the base region of the Activa to be defined below. If there is a boundary layer between the podaplasm and the base region, it appears to provide an Ohmic electrical contact (a finite and symmetrical resistance) between the two. This allows electrons to flow from inside the podalemma into the base region of the Activa to be defined more fully below. This flow is shown by the arrow with the asterisk for a point.

8.5 The electrical characteristics of the dynamic neuron

When the independent electrical conduits of the neuron are brought into a unique structural arrangement and electrically biased in a specific way, they exhibit properties uniquely related to their juxtaposition. The resulting inter-coupled structures exhibit "transistor action." Through this mechanism, the neuron is found to contain an active electrolytic semiconductor device, named an Activa. It is this Activa that is key to the dynamic operation of the entire neural system.

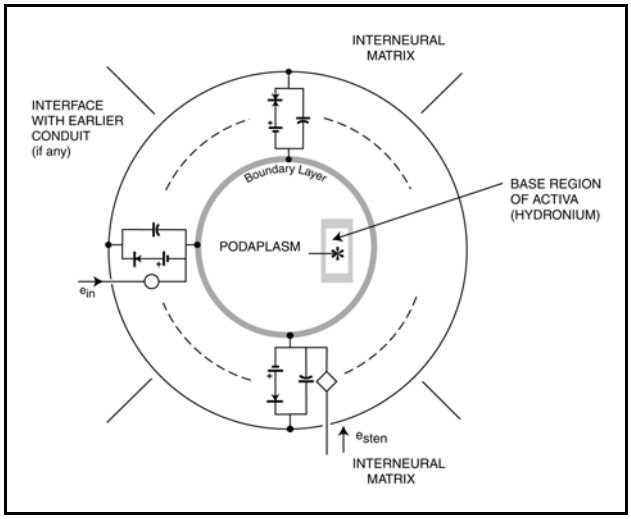

Figure 8.4.5-2 Electrical equivalent circuit of the poditic conduit. The base region of the Activa is typically surrounded by the podaplasm. Other contacts to the base region are out of plane. Any boundary layer surrounding the base region is Ohmic.

8.5.1 The phenomenology of a *second order* neuron with "Transistor action"

The importance of the liquid crystalline state of matter in biology has not gained wide acceptance in the biological community. Liquid crystalline materials exhibit unexpected electrical properties. Basically, they exhibit unusual electrical conductivity--frequently in asymmetric ways and in only certain planes. These properties are due to the semi-crystalline structure of the membranes and the presence of specific electrical species within these structures. Such structures can be described as biological semiconductors and bring to biology much of the flexibility found in Solid State Theory--specifically, "transistor action." "Transistor action" was first described in the 1950's to explain some unexpected effects measured in unusual configurations of a semi-conducting material, specifically "doped" germanium. Adding minute amounts (parts per billion) of a dopant to a part of a crystalline structure of germanium created these quantum-mechanical properties in an otherwise molecularly symmetrical material.

It came to be realized that a semiconducting material exhibited unusual conductivity characteristics which could not be explained simply by electrons moving through the conduction band of the material; it was necessary to also consider the movement of "holes" located in the valence band. These holes were locations in the crystal lattice where electrons were missing. The total current through the bulk material was the summation of the current due to movement of both the electrons and the holes. It was found that, if two pieces of this material containing different levels of dopant were brought into very intimate contact, the electrons and holes were subject to the conflicting pressures of the laws of diffusion and electrical potential. These realizations provided the explanation of the *rectifying characteristic* of these materials (and other materials that had been used for years without a clear knowledge of how they worked). The active process was described as occurring at **a junction** between two such materials and the resulting device was described as **a junction diode**. It exhibited a conductance which was asymmetrical and described by the diode equation, $I = I_o(\exp((V/Vo) - 1)$.

Further work led to the understanding of how two such junction diodes worked when they were brought into intimate contact. If two of these junctions were manufactured such that the cathode area was very thin and shared by the two diodes, the resultant device consisted of two junctions in intimate contact in a back-to-back configuration. Depending on what voltages were applied to these devices, very strange things happened. If one diode was forward biased, it was easy to inject a current into the device from the emitter into the common base. If simultaneously, the third terminal was *reverse* biased with respect to the base, a current would appear at the collector essentially equal to the current injected at the emitter. This current is directly proportional to the current injected into the input diode and exhibits no relationship to the impedance of the output diode.

This "transistor action" was accounted for based on the action of the electrons and holes in the material responding to the laws of quantum-mechanics in addition to the requirements of the laws of diffusion and electrical fields. "Transistor action" resulted in spite of the presence of opposing electrical potentials. Significant power amplification was possible through this process since the input current was at a low impedance level and the output current was at a high impedance level.

It is proposed here that certain BLMs when brought into intimate juxtaposition exhibit "transistor action" and provide the nonlinear current-voltage relationships observed in neurons. This capability has not been defined previously in the literature. It is entirely independent of any ions moving through any membranes associated with the neuron.

8.5.1.1 The three terminal biological transistor

If it were possible to bring into intimate contact, two *asymmetrical* membranes such that their cathodic terminals merged quantum-mechanically and it were possible to vary the voltages on the two outer surfaces with respect to the voltage associated with the central region between them, transistor action would result. The resultant device, called an Activa, would exhibit near electrical autonomy between the two external surfaces, *except for the common current appearing to flow between the two surfaces*[*]. **Figure 8.5.1-1(A)** and **(B)** illustrate this extremely useful configuration. Frame (B) introduces the conventional transistor symbol modified to include an "A," to designate an active biological semiconductor device, the Activa.

The configuration shown in (**A**) was introduced incrementally in earlier parts of this chapter. In this frame, the arrows indicate the direction of conventional current flow. The direction of actual electron flow is in the opposite direction. The space between the two membranes is labeled B and is shown as an extremely thin region of different composition than the two membranes. It is defined as the base. The base is conductive to electrons and holes but not ions. The left-most surface is labeled E, for emitter and the right-most surface is labeled, C, for collector. These labels correspond to the language of the solid state physicist. Conventional current is introduced into the base region from the emitter. A nearly identical conventional current originates in the base and emerges at the collector. Frame (**B**) shows the shorthand notation corresponding to the physical conditions of frame (**A**). The arrowhead highlights the emitting (or injection) of conventional current into the base region. This arrowhead also suggests the low electrical impedance of this input structure when properly biased. The lack of an arrowhead on the collector lead is suggestive of the high electrical impedance of this circuit when properly biased.

The Activa in this three-terminal form is the basis for the operation of the signal handling characteristics of all neurons. Note the back-to-back connection of the two *pn* diodes in frame (A). This orientation leads to the designation *pnp* for a structure of this type. In the absence of transistor action, no current will flow between the emitter and the collector sides of this structure.

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[*]In man-made transistors, the output current as a function of the input current is given by $I(out) = I(in)*(1 - \alpha)$ where α is usually 0.01-0.02 depending on the quality of the manufacturing process.

To achieve "transistor action," three conditions must be met:

+ each membrane "system" must be operational; that is the membrane must be of the right constituency and be bathed on each side by an appropriate electrolyte.

+ the input membrane must be forward biased so as to conduct current relatively easily and the output membrane must be reverse biased so that it does not easily conduct current.

+ the distance between the adjacent membrane walls must be less than the distance required for transistor action, i.e., a charge passing through the input membrane will continue on and pass through the output membrane in spite of the opposing polarity of the output membrane. The required distance is less than 10 nm.

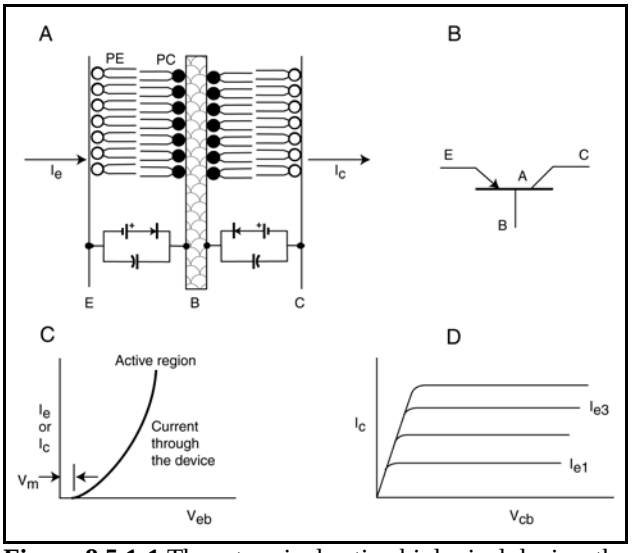

Figure 8.5.1-1 Three terminal active biological device, the Activa. (A) A cross section of the junction between two membranes. Equivalent chemical and electrical schematics are shown. (B) Equivalent circuit of (A) if the two bases are intimately related quantum-mechanically. Note the "A" above the base region in (B). The conventional currents are positive for a positive voltage V_{eb}. (D) Output current Ic versus the collector potential V_{cb} where V_{cb} is negative.

The electrical characteristics of the Activa under these conditions are relatively simple. The input impedance of the device is relatively low and the output impedance of the device is quite high. The input characteristic is that of a forward biased diode in series with a battery as developed earlier. The output characteristic is represented by a very high impedance as expected from a reverse biased diode in series with a small battery. No current flows in the output circuit in spite of the external bias supplied to the device. However, a current will flow in the output circuit equal to the current in the input circuit due to "transistor action." Since the output current is essentially the same as the input current, the transfer characteristic, i. e. the output current as a function of the input voltage, is also given by the diode equation plotted against different coordinates. These characteristics are illustrated in **Figure 8.5.1-1(C) & (D).**

Frame (**C**) displays the input, or emitter, current as a function of emitter-to-base potential within the operating range of the device. Since the collector current is essentially the same as the emitter current, the vertical axis shows both labels. For the pnp type of device found in all neurons, the current increases with a positive increase in emitter-to-base potential. Therefore, the flow of electrons also increases but in a negative direction. The diode characteristic is offset by the presence of the intrinsic membrane potential, V_m, of the emitter-to-base membrane. This parameter is usually symbolized by V_γ in electrical engineering texts.

Frame (**D**) displays the output current of the Activa as a function of the collector-to-base potential. As long as the collector potential is more negative than required to reverse bias the collector, the output current is directly proportional to the input current and is independent of the collector potential as shown. The size of the intrinsic membrane potential of the collector-to-base membrane is usually too small to be plotted on this graph.

The symbol for the biological transistor does not show the internal voltages implied by the symbol "A." However, they are shown explicitly in the conventional equivalent circuit for a biological transistor. This notation will be developed further in **Section 8.5.3.2.**

8.5.1.2 The two-terminal biological transistor of the photoreceptor cell

In the absence of electrical access to the region between the membranes, the two-membrane laminate has limited (*but very important*) application as an amplifier. **Figure 8.5.1-2(A) and (B)** illustrate this situation. Here again, the symbol "A" above the base region signifies an active biological semiconductor device. Note that if the collector is made negative with respect to the emitter, the bias requirements for "transistor action" is still obtained. The emitter to base region is forward biased and the collector to base region is reverse biased.

If the Activa is fabricated without explicit electrical contact to the base, it is still possible to obtain transistor action by exciting the Activa by other means. If quantum-mechanical energy of sufficient strength (not intensity) is applied to the region of the device near the emitter-base junction, free charges of opposite sign can be generated in the base region. The charge of higher mobility will impact the operation of the device more significantly. Solving the equations applying to the current in such a device, it can be shown that the base current must be equated to the collector current minus the emitter current. Solving for the collector current, I(out) = I(free)/α or the output current is typically 50-100 times the current generated by the incident energy. In specially produced man-made transistors, this amplification factor can be as high as 5,000. Devices of this type are excellent photon detectors and can also be used as mechanical impact detectors, ionization gauges, etc.

Frame (**C**) shows the output current as a function of a fictional input potential that cannot be measured, $V_{e\text{-}c}$. The input current remains equal to the output current.

The transfer characteristic of such an Activa to energetic stimulation is given by the equation above and is independent of the collector-to-emitter potential.

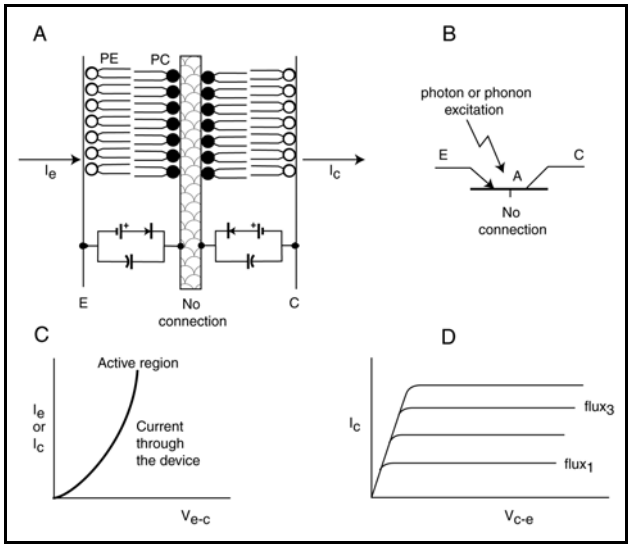

Figure 8.5.1-2 The three-terminal active biological device, the Activa, with an open terminal. This is the configuration used in the initial circuits of the photoreceptor cell. Charges created in the base region are treated as if the came from the emitter.

8.5.2 The intrinsic properties of the Activa

To aid in the modeling of neural circuits, it is important to define the fundamental properties of the Activa. As in the case of man-made transistors, the Activas can vary in gross properties based on their construction. However, their fundamental properties vary only with temperature.

There are two distinct types of man-made transistors, those described as junction transistors and those described as field effect transistors. Junction transistors show a continuity between the current into the emitter terminal and the current out of the collector terminal. Field effect transistors (FET) exhibit a current that is proportional to the potential on a gate but no current flows through that gate (at low frequencies). Only junction devices have been found among biological semiconductor devices, Activas.

One of the common methods of creating man-made junction transistors capable of handling high power levels is to use replication techniques and then wire the various devices in parallel. As will be shown in Chapter 10, biological devices also use this technique frequently. Individual devices, defined here as a unit Activa, are formed into a two-dimensional array and connected to a common reticulum via vesicles and minor branches of the larger reticulum.

There are two fundamental forms of man-made junction transistors, those with a base material that is a single element, such as silicon or germanium, and those with a base material that is a compound, such as gallium arsenide, mercury cadmium telluride, etc. The compounds offer lower band gaps in their electronic structures than do the elements. The n-type material forming the base in the Activa consists of the liquid crystalline compound hydronium. This name is given to a specific phase of water.

The band gaps of silicon and germanium have led to offset parameters for diodes made of these materials of 0.6 and 0.2 volts respectively. These values are considerably higher than the 10 mV values found in biological semiconductors. This difference will lead to a challenge when trying to use man-made transistors to emulate biological Activas.

There are also two fundamental classes of man-made junction transistors, those with an n-type base material and those with a p-type base material. To date, all known biological transistors have hydronium as a base material. This material is of the n-type. Therefore, all known biological transistors are of the pnp class.

The following sections will define the principle fundamental parameters and performance parameters of the Activa. The physical dimensions will only be discussed briefly. **Section 10.xxx** will explore these parameters in detail. These dimensions describe the performance of the "unit Activa." Groups of unit Activas are frequently observed forming disk shaped arrays within the gap junctions of synapses. They should not be confused with vesicles or gates forming pores in either of the membranes. It is the total current carrying capacity of these "synaptic disk" that describes the electrical performance of a specific synapse.

8.5.2.1 The physical dimensions of the unit Activa

When examining the face of one membrane of a gap junction, an orderly pattern is frequently discerned. This pattern is generally described as a close packed hexagonal arrangement of domains of about 150 Angstrom across[32]. **Figure 8.4.1-1** shows a similar organization but for a "gap junction" found in the liver of a rat. The total diameter of the individual disks of Activas found within the neural system are indicative of their current carrying capacity in support of a particular application. Specific sizes for various Activas will be developed in **Chapters 9** & **10**.

8.5.2.1.1 The collector capacitance of the unit Activa

The intrinsic collector capacitances of an Activa depends on the size of the Activa. They are very small and difficult to measure. The collector to base and collector to INM capacitances are most important. The bulk of the capacitance associated with the collector is due to the extended area of the unmyelinated portion of the axolemma.

It appears the collector-to-base capacitance has played an important role in the parametric stimulation of the neuron employed by Hodgkin & Huxley. Under some circumstances, it appears the collector-to-emitter capacitance played a significant role in the Hodgkin & Huxley experiments.

It is generally necessary to make a distinction between the capacitances associated with the collector alone and with the overall axon.

8.5.2.2 The Ebers-Moll model and the Early Effect

Versions of the Ebers-Moll model of a transistor have appeared in many textbooks. However, they do not always appear in the same form. Some of the versions are simplified to meet the authors goals. This is particularly true in texts for non-electronics majors[33]. Millman & Halkias develop the concept in two different chapters of their book and lean upon a simplified equation (3-9) in a third chapter[34]. They provide a pair of equations related to the model whereas many authors only present one. In their presentation in Section 5-12, they rely upon the diode equation with the offset potential (or cutin potential), $V\gamma$, equal to zero. This is acceptable when dealing with collector saturation potentials that are many times higher than $V\gamma$. However, this is not the case in most biological circuits. An even more complete presentation than that in Millman & Halkais is required under these conditions. This more complete presentation replaces V_{EB} by $V_{EB} - V\gamma$.

When evaluating a biological transistor, an Activa, it is also important to be aware of the Early Effect. This Effect, discussed in Section 5-5 of Millman & Halkias, documents the reduction in output signal as a function of input signal due to the reduction in the space charge within the base region. Although evidence of this Effect was not found in the biological literature, the literature does not exhibit the precision required to recognize this Effect explicitly.

8.5.2.3 The fundamental electrical parameters of the unit Activa

Attempting to specify the fundamental electrical parameters of a unit Activa or of a given Activa array is difficult based

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[32]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press pg 515

[33]Horowitz, P. & Hill, W. (1989) The Art of Electronics, 2nd ed. NY: Cambridge University Press, pg 80

[34]Millman, J. & Halkias, C. (1972) Integrated electronics, NY: Mc Graw-Hill, chapters 3, 5, & 19

on the available literature. The diameter of the membrane area under test has generally been set by the size of the electrical probe. This value has been used under the assumption that the membrane is uniform throughout the area being examined. This assumption is not valid. The test protocol should determine the size of the active region of membrane under test. The most critical parameters are those found in the diode equation discussed previously. The best available sources of current-voltage data applicable to an Activa appear to be Luttgau (Yau) and Eliasof (**Section 8.3.2.1.2**).

8.5.2.3.1 The offset parameter

Only limited data is available in the literature concerning the diode characteristic of the Activa. The data of Eliasof discussed in **Section 8.3.3** can be used. However, that data was not collected under the desired conditions. It was collected using a Leyden jar rather than a Ussing apparatus. Therefore, the current-voltage characteristics include a resistive impedance due to the electrolytes on each side of the membrane. These impedances obscure the underlying diode characteristic associated with the membrane. By looking at the data as an ensemble, a trained eye can estimate the diode characteristic to a first approximation. The data appears to converge to a value very similar to the current-voltage characteristic provided by Luttgau[35] and reproduced by Yau[36]. Luttgau presented a characteristic obtained with a pseudointracellular solution on one side of an asymmetrical membrane and a "Normal" Ringer's solution on the other. He then introduced variable amounts of Ca^{2+} and Mg^{2+} into the pseudointracellular solution. By using the characteristic for zero amounts of added cation, a very good approximation to the desired diode characteristic is obtained.

Assuming his Normal Ringer's solution does not disturb the Helmholtz layer of hydronium immediately adjacent to the plasma membrane, the data of Luttgau provides the best available estimate of the offset parameter of the in-vivo membrane generally associated with an Activa of a synapse. This configuration consists of a cytoplasm on the internal side of a membrane and a hydronium crystal on the external side. The parameter has a value of 10 mV at 300 Kelvin. Data has not been found that unambiguously defines the offset parameter for the Activa formed within a cell. The offset parameter of these Activas may have a value of near zero because of the similar composition of the fluids on each side of the membrane.

8.5.2.3.2 The thermal parameter

The thermal parameter, V_T, is given in several papers in the literature as equal to 25 mV or 26 mV. 26 mV is the theoretical value for a device operating at 300 Kelvin. 26.7 is the equivalent value at 310 Kelvin (98.6 F) and a value of 25 mV could be expected in cold blooded animals at laboratory temperatures. Thus, the theoretical value of this parameter only varies by about 1.7 mV over the biological range. Obviously, greater care will be required in the laboratory to measure this parameter accurately.

8.5.2.3.3 The reverse saturation parameter

The reverse saturation current parameter, I_0, can be determined from a variety of diode characteristics in the literature. However, determining the reverse saturation current density, I_0/unit area, is more difficult. Most authors have not given the precise area of the membrane under test and most authors have not made measurements up to a voltage of -150 mV which would give the most precise value. Most of the available data suggests a reverse saturation current, I_0, between 18 and 25 picoamperes for the typical biological diode.

The estimated reverse saturation current density of the giant axon of squid is less than 0.01 ma/cm^2 based on Cole[37]. It is difficult to determine from Cole what area was assumed in his measurements. It may have been larger than the actual type 2 region of membrane.

8.5.3 The electrical characteristics of a *second order* neuron with *"Transistor Action"*

By combining the properties discussed in **Sections 8.5.1** & **8.5.2**, the operational characteristics of a complete neuron begin to emerge. However, two major classes of neurons need to be distinguished based on the complexity of the electrical network forming the conexus around the Activa. These classes differ in the relative value of the impedance

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[35]Luttgau, H. *ed*. (1986) Membrane Control of Cellular Activity. Stuttgart: Gustav Fischer, pp 343-366

[36]Yau, K. (1994) Phototransduction mechanism in retinal rods and cones. *Invest. Ophthal. Vis. Sci*. vol. 35, pp 9-32

[37]Cole, K. (1968) Op. Cit. fig 4:52

found between the base terminal of the internal Activa and the surrounding INM. If this impedance is negligible, the resulting neuron forms a simple impedance type amplifier. The amplitude of the signaling component of its output signal is essentially a linear copy of the signal applied to its input. However, if the value of this impedance is significant, a world of new opportunities arises. These opportunities include the option of introducing a second signal into the circuit via the poditic terminal. It also includes the opportunity to convert the circuit into an oscillator.

Arranging the conexus to support oscillation requires introducing a new concept not previously found in the neurological literature, "internal feedback." Internal feedback performs the same function as the frequently diagramed external feedback. It takes a sample of the signal at the output of an amplifier and returns it to the input circuit of the same amplifier. However, this same mechanism, feedback, can be accomplished within the conexus and without any obvious feedback path. The feedback is accomplished by sharing an impedance between the input and output circuits of the conexus. This results in the mechanism of internal feedback.

Internal feedback can be obtained using only simple resistive elements or using reactive elements. While the use of resistive internal feedback can cause distortion in the amplitude of the transfer characteristic of the conexus, the use of reactive internal feedback is required to achieve oscillation.

To understand how negative internal feedback occurs within a conexus, a short introduction to the morphology of the neuron will be required prior to Chapter 10.

8.5.3.1 The morphology of a *second order* neuron with *"Transistor Action"*

Figure 8.5.3-1(a) illustrates the important features of the fundamental neuron. It is drawn as a three-chamber electrical device (cell) wherein each chamber is isolated from the other chambers and the exterior by an electrical barrier (membrane). Each of these membranes, and different regions of the same membrane as discussed in section 8.2, may have different electrical characteristics as will be noted below. By drawing the cell in this manner, the spacing between the left and right internal membranes is a variable. The spacing passes through a region corresponding to the spacing of a gap junction, nominally less than 10 nm, on its way to a region with the spacing of a tight junction.

The INM is considered the common ground in this configuration. An impedance is shown between the base contact of the Activa and the poda contact at the external plasma membrane of the cell. This is to highlight the fact that such an impedance is shared between the emitter-to-ground and the collector-to-ground circuits. Such a shared impedance is a source of internal feedback in any circuit.

Figure 8.5.3-1(b) shows an alternate configuration where the base region is essentially outside of the cell perimeter. The symbols on the right are the standard symbols for a transistor (of the pnp type to be discussed below) modified to include the large A, for Activa (or biological transistor), located above the horizontal line. In the (b) set of figures, the base connection is made directly to the inter-neural plasma.

In both (a) and (b), each membrane wall can be described in electrical terms by the circuit developed earlier, a diode in series with a battery (the pair shunted by a capacitor in some circumstances). The characteristics of the diode are related primarily to the physical dimensions of the membrane and the material from which it is fabricated. The battery is similarly characterized by its intrinsic material.

> It is seen by inspection that the cell in **Figure 8.5.3-1(b)** involves a different offset potential with regard to its emitter-to-ground circuit than the cell in **Figure 8.5.3-1(a)** due to the different potentials developed by the different combination of membranes.

Figure 8.5.3-1(c) takes the configuration one step further and introduces impedances in each of the circuits due to the dimensions and limited conductivity of the electrolytes in each plasma of the cell. The net conductance of each plasma frequently plays a significant role in the operation of the overall circuit. Although not shown explicitly, both the emitter and the collector leads must be connected to the common ground terminal through external circuit elements if the overall circuit is to function properly. The INM provides the common connection among the three symbols.

8.5.3.2 Circuit diagrams of a *second order* neuron with *"Transistor Action"*

The mathematical treatment of the Activa of a fundamental cell is slightly different from that frequently used for that of a non-biological transistor in that the source of the individual intrinsic membrane potentials is more obvious than in solid-state physics. Thus the simplest basic Activa, corresponding to [**Figure 8.5.3-1(b**)], is represented by a back-to-back pair of diodes plus a pair of voltage sources as shown in **Figure 8.5.3-2(a**). The input current, i_e, and the output current, i_c, are also shown with the arrowheads drawn to illustrate the direction of the currents under a given set of conditions.

> In standard electronic nomenclature, the two conventional currents are both defined as going into the device toward the base and the direction of the actual currents is determined by whether the device is of the npn or pnp type.

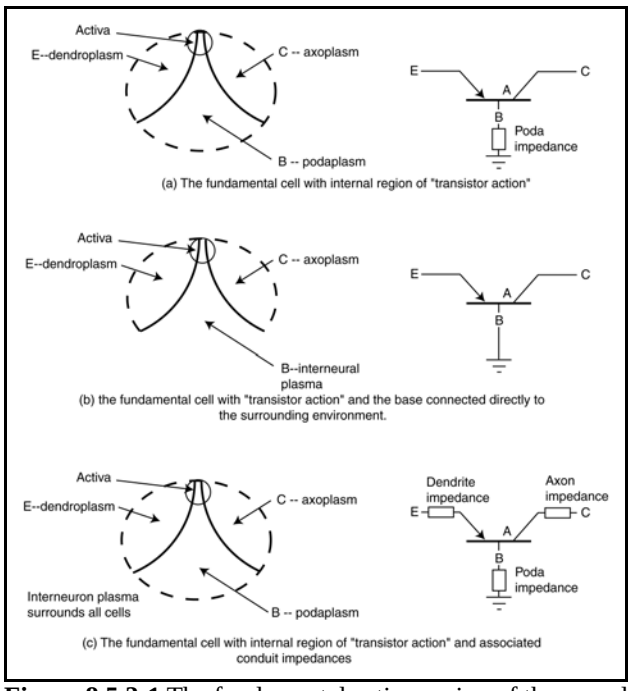

Figure 8.5.3-1 The fundamental active region of the neural portion of a cell. See text.

Figure 8.5.3-2(b) shows the Activa with the impedances associated with each of the plasmas connecting the device to the neural system. Recall that these impedances are electrolytic and frequently present a significant time delay associated with ion transport through a viscous electrolyte. This time delay may be more important than any associated resistance. The device is still not operational since the terminals are not properly biased relative to each other. The impedances shown in this figure are the lumped parameter values associated with the dendroplasm, podaplasm and axoplasm in the immediate vicinity of the Activa. The lumped parameters are sometimes defined in terms of a "compartmental model" of a simplified neuron. In the case of the complete neuron, and particularly the axon of a complete neuron, the distributed parameters associated with these elongated structures must be introduced separately. These distributed parameters are frequently associated with a "cable model."

Figure 8.5.3-2(c) shows the general situation for a complete fundamental neuron incorporating an Activa and all of the required support circuitry. The frame on the left shows how the circuit is typically drawn for convenience. The frame on the right provides a more detailed circuit. Looking first at the frame on the right, the symbols at the bottom of the figure represent the extreme ends of each plasma conduit at the point where each is in contact with the INM. The diamonds represent the electrostenolytic process providing electrical bias potential to each plasma. These bias sources are all polarized so as to insure a negative potential across each specialized region of membrane. However, they are not of equal magnitude. Each bias source relies upon specific reactants within the glutamate cycle to create the desired electrostatic potential.

In real circuits, the intrinsic membrane potentials associated with the regions of membrane forming the Activa and those in parallel with the electrostenolytic sources should not be ignored. Using Kirchoff's Laws, all of the batteries shown in the right frame can be combined into the three individual batteries shown in the left frame. However, before doing this, it is important to note that all of the plasmas must be negatively biased relative to the INM to maintain the integrity of the cell. For this purpose, it is the relative sizes of the batteries associated with each electrostenolytic source that is important.

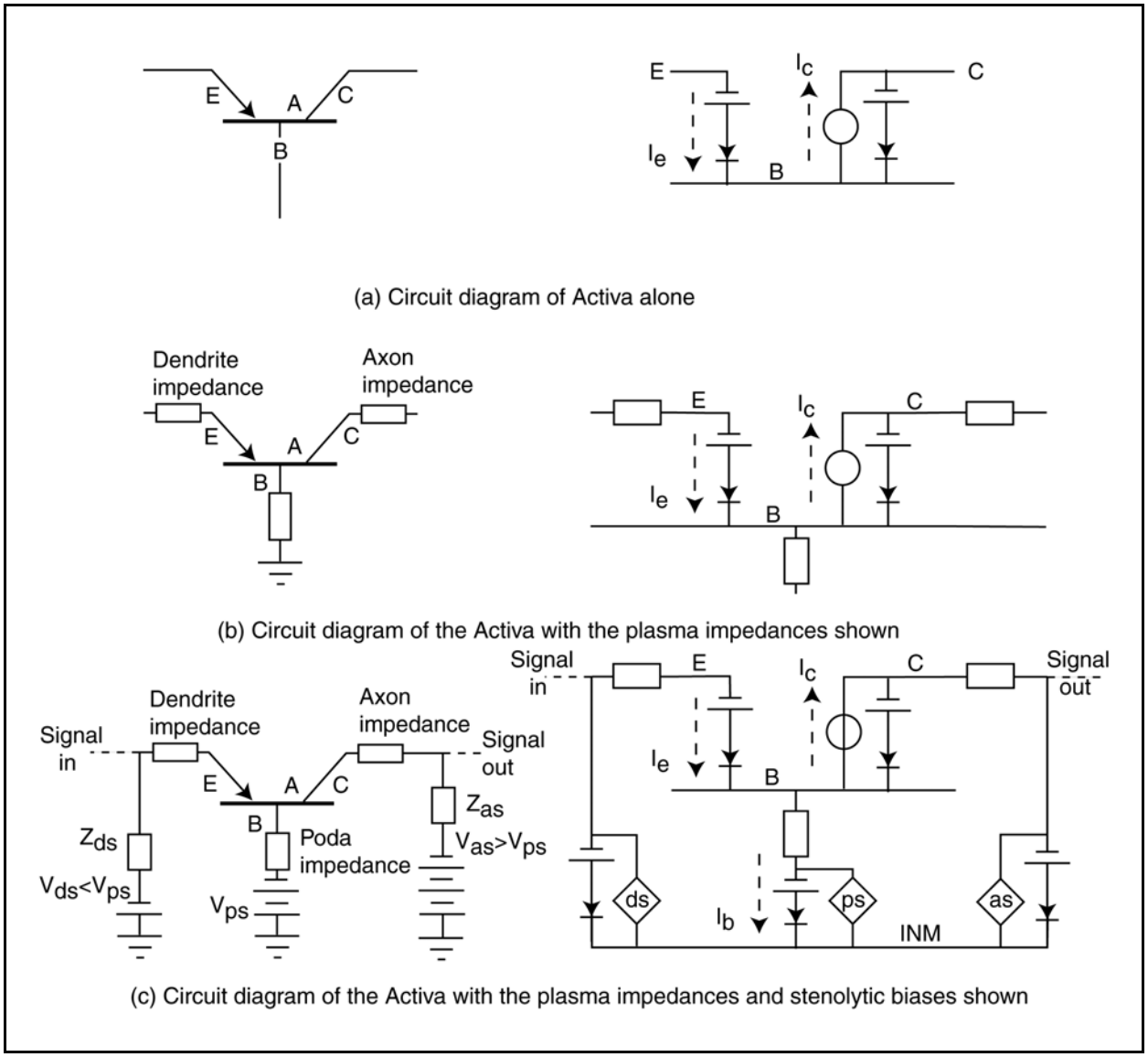

Figure 8.5.3-2 The equivalent electrical circuits of the conexus within a neuron. The dendrite, poda and axon impedances shown are the lumped parameter values associated with the Activa. They do not include the distributed values associated with an extended axon. See text for details.

By insuring the dendritic supply, V_{ds}, is of lower potential than the poditic supply, V_{ps}, the relative voltage between the emitter and the base will be positive and a conventional current will tend to flow into the base of the Activa. By insuring that the axonal supply, V_{as}, is of higher potential than the poditic supply, the collector-to-base potential will reverse bias the diode and no current will flow in this circuit due to the bias.

The circuit now represents a fully functional neuron.

8.5.4 Operation of a *second order* neuron with "*Transistor Action*" w & w/o feedback

The above second order cell can perform in a variety of modes depending on the value of the circuit elements associated with the Activa. Many of these modes are used in both man-made and biological circuits. The operation of the circuit with finite values for the poda impedance will be deferred to the next section. The special case of no electrical source associated with the base of the Activa will be addressed in **Section 8.6.3.**

8.5.4.1 Simple operation of a second order neuron with "transistor action"

8.5.4.1.1 Monopolar amplification

Assume initially that there is no input signal to the circuit, that the poda impedance is equal to zero, and that V_{as} is larger than V_{ps}. Let the dendritic supply be such that $V_{ds} = V_{ps}$. Under this condition, no current will flow in either the emitter or the collector of the Activa. If a small positive signal should be applied to the input terminal, a current will flow from the emitter to the base of the Activa. This will cause a similar current to flow from the base to the collector and through the axon impedance and the source impedance, Z_{as}. This current will cause an incremental rise in the voltage across Z_{as} in response to the incremental rise in the input signal. The ratio of the incremental rise in output to the incremental rise in input voltage equals the voltage gain of the circuit. This is the characteristic of a monopolar amplifier.

8.5.4.1.2 Bipolar amplification

If $V_{ds} < V_{ps}$, the emitter will be positive relative to the base. Under this condition, current will pass through the emitter-to-base circuit and current will flow in the collector circuit. The collector potential will be at a quiescent potential that is incrementally less than the intrinsic electrostenolytic potential of the axon. Under this condition, the circuit can respond to either a positive going or a negative going input signal. The result will be a similarly positive or negative going signal at the pedicel of the neuron. This is the characteristic of a bipolar amplifier.

8.5.4.1.3 Thresholding circuit

If $V_{ds} > V_{ps}$, no current will flow in the emitter circuit and no current will flow in the collector circuit. The collector potential will be at the intrinsic electrostenolytic potential. To obtain current flow in the emitter circuit will require a positive input signal greater than the $V_{ds} - V_{ps}$. Only under this condition will current flow in the emitter and collector circuits and a signal proportional to the signal minus the difference, $V_{ds} - V_{ps}$, appear at the pedicel of the neuron. Such a thresholding circuit can be used to eliminate extraneous low level noise from the signal path.

8.5.4.1.4 Frequency pre-emphasis circuit

A unique frequency response capability can be achieved by placing a capacitor in parallel with the dendrite impedance. Because of the time delay inherent in an electrolytic impedance, this combination can provide an emphasis on the higher frequency components of the signal. This capability of frequency response shaping in the time domain explains one of the ways the visual system achieves frequency response shaping in the absence of multiple stage RC filter stages. This capability is easily achieved by adjusting the topography of the dendrite at the cytological level.

8.5.4.1.5 Pulse integration circuit

If a large capacitor is connected between the collector and the INM, the circuit is biased as a monopolar amplifier, and action potentials are applied to the input of the circuit, the pulses of current occurring in the collector circuit will be integrated on the capacitor. As a result of the combination of this integration process and the time constant of the combination of the capacitor and the source impedance, the collector potential will represent the time average of the current through the Activa for pulse intervals of less than a critical value related to the time constant of the circuit. This is the fundamental capability of a pulse to analog decoder such as found in the stellate cells of the brain. The required value of the capacitor is easily obtained by increasing the unmyelinated surface area of the axon.

A circuit operating in this pulse integration mode is commonly identified as a rectifier in the biological literature. This type of circuit is generally found in the stellate cells of the neural system operating as decoders of information encoded by an associated ganglion cells of the system.

8.5.4.1.6 General operating characteristics of a fundamental neuron

Figure 8.5.4-1(a) presents two versions of the same input current to input voltage characteristic of the Activa alone. The two versions represent the same data. The left frame plots the input current as a function of the applied voltage. The right frame plots voltage as a function of the input current. Both demonstrate that the input characteristic is that of a diode. The transfer characteristic showing the current out as a function of the current in is usually not plotted for a transistor since the relationship is very nearly 1:1. The output current to input voltage transfer characteristic is of interest here and is seen to be essentially the same as the input characteristic shown in the left frame with more specific labels on the scales. Note that the external voltage applied to the collector lead of the Activa must remain high enough to maintain the junction in a state of reverse bias.

Figure 8.5.4-1(b) illustrates the output characteristic of an Activa with no impedance in the circuit between the base and the ground point. The output load is due to the combination of the electrostenolytic supply impednace and any impedance connected to the output signal terminal of the circuit. In typical man-made electronic circuits, the load consists of a resistor and a battery; the corresponding load line is a straight line (shown dashed). However, in the biological case, the load is normally a forward biased diode representing the input circuit of the next neuron. The corresponding graphical representation is exponential(also shown dashed). The output current and the output voltage are both shown as negative quantities. This is the convention for active devices of the PNP type. The straight load line represents a real resistor of 1.5 megohms. The curved load line represents a diode input characteristic. It exhibits an effective impedance of about 3.0 megohms at 30 pA current.

> It is very important to note that the axoplasm is always biased to a negative value with respect to the INM when the circuit is functional. This means that the potential of the axoplasm causes negligible leakage of current into the INM through the reverse biased axolemma wall.
>
> If the connection to the subsequent neuron is removed in a laboratory experiment, the load impedance of the circuit is profoundly affected. This modified e circuit tends to operate in the mode of a pulse integration circuit due to the combined stray capacitance associated with the axon and the capacitance of the test probe. This situation significantly affects the recorded waveforms.

It is important to analyze these graphs more fully and determine the relationships between the quiescent operating point of the neuron and its operating points in the presence of an input signal. If the input conditions are such that the total input voltage generates no current in the input circuit, the output circuit current will also be essentially zero and the output voltage will be approximately, -75 mV which is assumed to be the net voltage applied to the collector of the Activa by the electrostenolytic supply. This is spoken of as the cutoff condition, no current flows in the Activa. If the input conditions are adjusted to cause a current of 20 pA, the output circuit will now operate with an output current of -20 pA and an output voltage of -33 mV. These three values are spoken of as the quiescent values of the circuit. If an additional input current of 5 pA is applied, the output will move to the point of -25 pA and -30 mV. Similarly if the input current is reduced by 5 pA relative to the quiescent condition, the output circuit will be at -15 pA and -37 mV. Notice that if the input current is increased by more than 7 pA, the saturation limit of the Activa will be reached. The output will remain at -26 mV regardless of further increases in input current. If the input current is reduced to zero, the operating point of the output circuit will be at 0 pA and -77 mV. **Figure 8.5.4-1(c)** illustrates these conditions along with the notation common in the biology community. Depolarization is a movement along the curve toward saturation. Hyperpolarization is a movement along the curve toward cutoff. Both terms are usually used with reference to the quiescent point, Q. In the case of this fundamental neuron, an increase in input current from its quiescent value will result in depolarization in the output circuit until saturation is reached. Reducing the input current will hyperpolarize the output until cutoff is reached at zero output current. The output voltage will be maximum under this condition.

8.5.4.2 Operation of a *second order* cell with *"Transistor Action"* and feedback

Figure 8.5.4-2(a) carries the analysis of (**b**) in the above figure one step farther and introduces the effect of the feedback impedance in the poda circuit connected to the base. The poda impedance between the base and the common ground terminal (n) may be the purely resistive component of a diode or it may be this impedance shunted by a capacitance. Note that any current passing through the collector-base circuit path induces a voltage into the emitter to ground circuit. This inducement of a change in the input circuit due to a change in the output circuit is a fundamental definition of electrical feedback. This circuit configuration forms the heart of all hybrid and projection neurons associated with the generation and regeneration of action potentials.

8.5.4.2.1 The nature of feedback

A clear distinction is required between the concept of inhibition of psychology and the concept of feedback in signaling. The building blocks used in the neural system of animals are analog electrical circuits. They can be modified to provide a variety of amplifier, comparator and pulse generating functions. However, they are inherently analog. If, as outlined above, a sample of a change in the output of a circuit is introduced into the input of that same circuit, the effect is known as feedback. The method of introducing this sample need not involve a separate and distinct (external) signal path. It may involve a shared impedance between the two circuits. The sample of the output returned to the input is normally not sufficient to block or inhibit the operation of the circuit. Its effect is determined by the amplitude and phase of the sample. The sample need not be "in" or "out" of phase with the output signal. The sample may have any phase relationship with the output signal. If the poda impedance has a complex value defined by the resistive and capacitive components of the impedance, its phase angle will be intermediate between the above values.

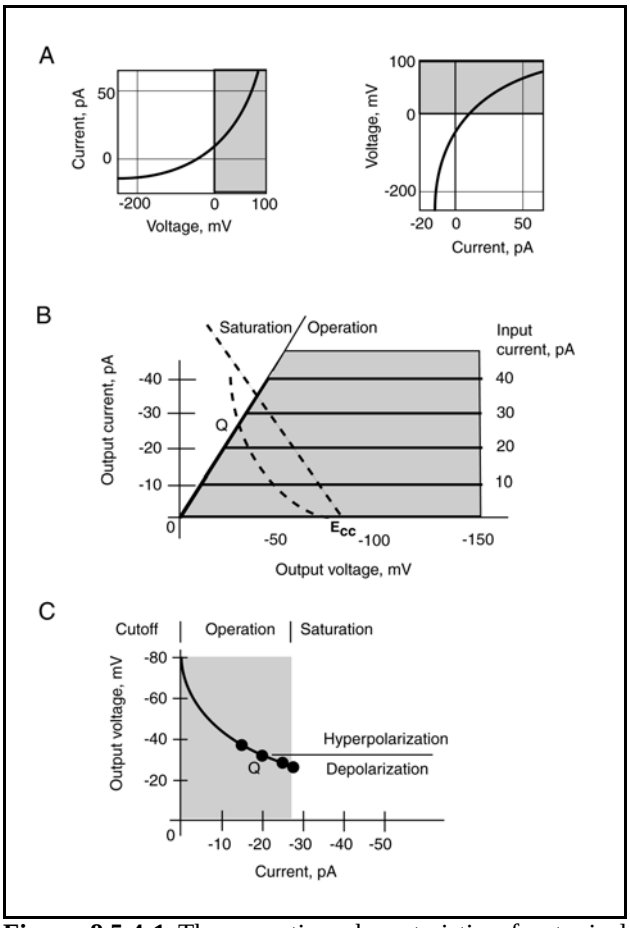

Figure 8.5.4-1 The operating characteristic of a typical Activa. A, two presentations of the same input characteristic of the Activa. B, the output characteristic of the Activa in electrical terms. C, the output characteristic of an Activa showing the output voltage relative to the INM and the nomenclature of biology. See text.

Because of the importance of the phase angle of the sample returned to the input circuit, it is not appropriate to speak of positive or negative feedback except in the general sense.

Figure 8.5.4-2(b) illustrates the effect on the collector voltage of an Activa as a function of the collector current for different values of the common impedance, Z_P. Assuming the potential due to the poda membrane does not disturb the basic biasing of the overall Activa so that the Activa remains in the transistor mode, the input current to voltage characteristic of the Activa becomes distorted due to the feedback process as the value of the poda impedance increases as indicated. Since the output circuit shares the same poda impedance, the output current to voltage characteristic is similarly distorted. The degree of distortion is shown relative to a nominal poda impedance.

Note the effect of changing the value of the poda impedance; for low values of resistance only, the circuit operates as a common (well behaved)amplifier but with reduced gain. If the load impedance includes a shunt capacitance, it will operate with some distortion compared to a circuit with a resistor load but no instability. As the poda impedance rises, the amplification varies with signal level until the point is reached where the output current is bistable as a function of the input voltage.

The distortion in these two characteristics is unusual and extremely important. The portion of the input characteristic sloping downward to the right represents an area of negative resistance. Such a negative dynamic resistance over even a limited region is indicative of instability and leads to two stable states (or an oscillatory condition if a reactive element is present such as a capacitor).

8.5.4.2.2 Internal feedback in the circuit of a fundamental neuron

The explanation of internal feedback as found in frame (**b**) needs expansion. The mathematics of this process involve complex algebra if the capacitances of the circuit are considered. Even for pure resistances, the mathematics are relatively difficult. This is because of the mode switching that is involved in the operation of the circuit. Mode switching typically occurs whenever a given current can be associated with two different voltages in the same circuit. Which voltage is assumed by the circuit frequently depends on secondary or parasitic circuit elements within the circuit. These are most often capacitances.

To alleviate this problem, a graphical analysis or computer program is usually used to determine the overall characteristic. However, the typical result can be shown here.

Figure 8.5.4-2(c) illustrates the input characteristic and the output characteristic for a simple conexus containing an Activa and an impedance connected to its base terminal. A; the basic circuit. B; the general input transfer impedance of this circuit as a function of the load impedance size. C; The operation of this circuit with a given level of internal feedback and a specified load line labeled $V_{en}(I_s)$. The symbol n is used here as a synonym for the common electrical ground point of the circuit. The figure is in the form of a two-quadrant nomograph with the sloping line used to connect the common current axis of the two sets of axes. The lower left set represents the emitter voltage versus the emitter current of the Activa. The right-hand set represents the collector current versus the collector voltage for the Activa where the two currents are identical in the absence of any capacitance in the circuit. Baker & Wood have presented a measured response similar to the right portion of C[38]. However, they did not discuss it or even cite it in the same paper.

The operation of this circuit is best understood by following the numbers next to the curves. Begin at point 1. At this point, the operating curve labeled $V_{en}(I_e)$ intersects the static load line, $V_{en}(I_s)$. However, at this point the operating curve has a negative slope. It represents a negative impedance. This causes the circuit to be unstable as shown on the right by the fact that two voltages on the collector can satisfy the collector current. As a result, the operating point will proceed to point 2. At this point, the voltage $V_{en}(I_e)$ is compatible with two different emitter currents. The circuit will jump to point 3 and then proceed in an orderly way to point 4. At point 4, the operating curve can support two different emitter currents. The operating point will jump to point 5. At point 5, the operating point will proceed toward point 2. When it reaches point 2, the cycle will begin again.

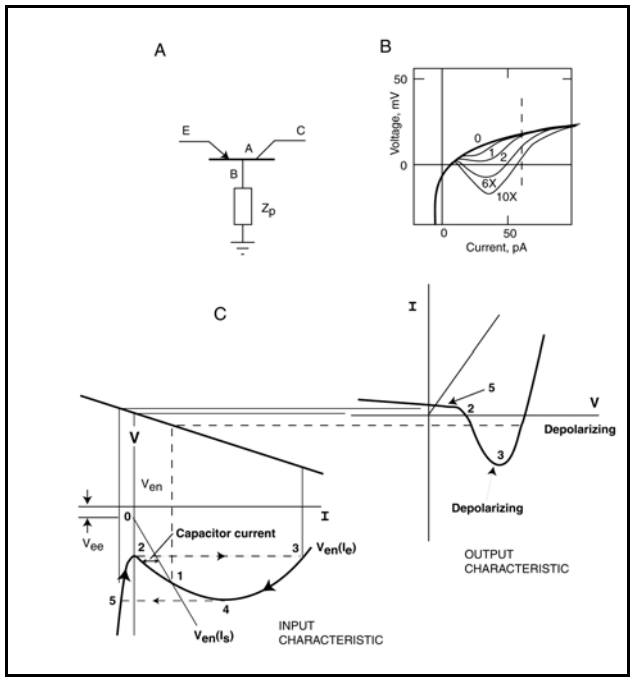

Figure 8.5.4-2 Transfer characteristics of the Activa with internal feedback. A; the Activa with a significant poda impedance. B; the effective input characteristic based on the value of this impedance. C; the overall operating characteristic of the conexus based on this impedance. See text.

[38]Baker, M. & Wood, J. (2001) Involvement of Na^+ channels in pain pathways *Trends Pharma Sci* vol. 22, no. 1, pp 27-31

The operation of the above circuit will be erratic unless the capacitance associated with the circuit is well defined and stable. This capacitance can be between either the emitter or collector terminals and the ground point (in this case, poda ground).

The value of this capacitance and the internal impedance of the Activa at different times during the operating cycle determines the pulse rate of the output action potential very precisely.

A key to the operation of the circuit is seen to be the voltage at which the emitter is set by the operating biases of the circuit. V_{ee} is the intrinsic membrane potential for the emmiter side of the Activa. If V_{en} is more negative than V_{ee}, the operating curve will not intersect the load line while it is negative and the circuit will not oscillate. This is the condition found in the parasol ganglion cells of the luminance channels and in all Nodes of Ranvier. No action potential will be produced until the external input signal causes the net potential between the emitter and base terminals exceeds V_{ee}. This is the same condition as for the emitter-to-base potential to become positive with respect to the bias point, V_{ds} - V_{ps}. Action potentials will be produced as long as the input signal is larger than the above difference. While the input signal is larger that the quiescent emitter-to-base bias, the period between these pulses will be determined by the difference between the input signal and the quiescent bias. This period is used to signal the relative brightness in the luminance channel.

If the bias value of is positive, the circuit will oscillate continuously at a pulse interval determined by the instantaneous value of V_{ds} - V_{ps}. This is the condition found in the midget ganglion cells of the chrominance channels. In the absence of a P or Q signal, the circuit will generate action potentials with a nominal time interval between pulses. The time interval between these pulses will vary in a bipolar manner as a function of the difference between the instantaneous emitter-to-base voltage and its quiescent value.

This process will find application in **Section 9.5 and/or 10.10** where it will be explored more fully. Burke, et. al. have described the clinical characteristics described in the above figure in section 6 of their paper[39]. It is interesting how closely their description of the refractory portion of the operating cycle agrees with the intervals associated with the paths between points defined above.

8.5.4.2.3 The refractory period of 2nd order neurons with positive feedback

When the output waveform of the above figure jumps from point 4 to point 5, the Activa returns to its cutoff condition, no current flows through it. Simultaneously, the coupling of the capacitances and other impedances of the circuit are separated into individual input and output circuits. If point 5 is not the normal quiescent point of the input circuit determined by the poditic and dendritic biases, the circuit will exhibit a specific refractory period. During this period, the circuit will respond, either by delay or by early initiation of a response to a subsequent excitation. Although it is a real option and almost certainly occurs, the second option is not normally reported in the literature.

8.5.5 Transition from a dual-alkali to an electron-based model

The previous sections have portrayed the neuron in an entirely different light than that proposed by the Dual Alkali-ion Diffusion Theory. Under the junctional-tissue ideology, the operation of the neuron is based entirely on the flow of electrons into and out of a variety of enclosed plasma conduits. These conduits are impervious to the sodium and potassium ions of the Dual Alkali-ion Diffusion Theory. Under this Electrolytic Theory based on the junctional-tissue ideology, the neuron is fundamentally an electrolytic device (or circuit) capable of performing a variety of electrical signal manipulations similar to man-made transistor circuits. This performance is achieved by exploiting the conexus (combined Activa and other electrolytic circuit elements) within the neuron. It is the exploitation of the analog device, the Activa, within the fundamental neuron that gives the neural system its great flexibility and overall capacity.

The Dual Alkali-ion Diffusion Theory is unsustainable in the presence of the superior Electrolytic Theory.

The Electrolytic Theory has explained the operation of a neuron in ways the Dual Alkali-ion Diffusion Theory cannot even address. The following sections of this Chapter and **Chapter 9** will exploit the Electrolytic Theory even further to explain additional details of the operation of individual neurons. Chapters 11 through 15 will exploit the Electrolytic Theory even further to explain the operation of the entire neural system at a very detailed level.

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[39]Burke, D. Kiernan, M. & Bostock, H. (2001) Excitability of human axons *Clin Neurophysiol* vol. 112, pp 1575-1585

8.5.6 Changes in perspective relative to the equivalent circuits of neurons

8.5.6.1 Absence of resistors in biological circuits

It is important to reflect on the fact that the above equivalent circuits of neural activity have completely avoided the symbol for a variable resistor with its implied external control mechanism. By replacing these symbols by the more appropriate diode symbol, the element is recognized for its variable but completely programmed change in impedance as a function of applied voltage.

It is also important to note that the electrical potential of the plasma enclosed by a membrane has been changed relative to the matrix without any change in the permeability of, or the transport of any ions across, the conduit membrane.

A change in plasma potential within a membrane to a more negative value with respect to its quiescent value is seen to be caused by transistor action and not by the "excitability of the membrane." The instantaneous potential returns to its quiescent value through either of two processes. Current can be injected into the subsequent conduit through a synapse or it can be used to reverse the electrostenolytic process and regenerate the reactants used to power the neuron. A corollary to this situation is that the ionic concentration of the plasmas within and adjacent to a neural conduit do not change in the short term and play no role in the signaling function.

No conventional, power dissipating, resistors are found within the neural system. The transport delays associated with diffusion of charge through an electrolyte play a role similar to that of a resistor in more conventional (non-electrolytic) circuits.

As noted by Yau[40] based on the data he presented from Luttgau, changes in the concentration of Ca^{2+} and Mg^{2+} within the intracellular medium do not affect the current versus voltage characteristic of the typical plasma membrane *in-vivo*. Such changes would have negligible impact on the operation of the reverse biased axonal plasma membrane. However, his analysis was incomplete. Such changes could have a significant impact on the performance of the forward biased emitter to base portion of the neural circuit. By impacting the dendroplasm to intracellular potential, such a change would significantly impact the current injected into the axoplasm by the Activa.

The electrical potential of the plasma within a membrane conduit can be adjusted by changing a number of circuit parameters, including the intrinsic electrostenolytic potential. The intrinsic electrostenolytic potential can be changed by using different members of the glutamate metabolic cycle as reactants in the electrostenolytic process on the surface of a given membrane.

8.5.6.2 Electrochemical support by region

The division of the external membrane of a conduit into regions with distinctly different electrical characteristics appears to be a fundamental design parameter of the neural system. By making adjustments in the molecular makeup of the individual bilayers of the regions of a membrane, unique electrical parameters may be easily obtained for these regions.

Although the literature does not provide sufficient detail, it appears that the electrostenolytic support to the individual conduits of a neuron occurs at regions of type 2 membrane specifically tailored to optimize this support.

8.5.6.3 The lack of requirement for ions to pass through the cell membrane

A totally unexpected result of the analysis in this work is the lack of a requirement for ions to pass through the exterior membranes (generally type 1 and type 2) of the conduits of a neuron for signal related purposes. It appears that the movement of ions through type 3 membranes is entirely for the purposes of genesis and metastasis. The hydrophobic core of the type 1 and type 2 BLMs completely blocks the short term flow of ions through the membrane. **No ionic currents are required for the signaling operation of the neurons.**

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[40]Yau, K. (1994) Phototransduction mechanism in retinal rods and cones, *Invest. Ophthal. & Vis. Sci*. Vol. 35, no. 1, pp 9-32

8.5.6.4 Confirmation of the switching characteristic of the oscillating neuron

[xxx consistent with notion in 1951 Hodgkin paper but inconsistent with their unsolved differential equations]

8.5.7 Emulation and simulation of Activa and Activa circuits

In this section, emulation will refer to the use of physical circuit elements to represent the electrical performance of another physical element or elements. Simulation, on the other hand will refer to the use of a mathematical construct (frequently via a digital computer) to represent the electrical performance of a physical element or circuit.

Care must be taken in both emulations and simulations to recognize the significant impact of temperature on the neuron. The sensitivity to temperature is much higher in electrolytic circuits and BLMs than in metallic circuits.

The Activas of the neural system vary in size and capacity according to their function. They are all made up of a large number of unit Activas arranged within a finite area (the synapse disk in the case of a synapse). The characteristics of many Activas are catalogued in **Section 9.6**.

Emulation of the adaptation amplifier within the photoreceptor cell is more complex than for other Activa and neurons. The unique characteristics of the adaptation amplifier Activa developed in **Chapter 12** must be introduced into the emulation or simulation of this component.

8.5.7.1 Emulations

This section will differentiate between the emulation of an Activa alone, the simpler task, and the emulation of a complete Activa circuit (including its electrical circuit configuration, associated components, output load and input signal).

Selection of a man-made transistor to emulate a biological Activa requires close attention to detail. Similarly, simulation by digital computer, using a variant of SPICE or similar programs, also requires close attention to the selection of a template from the available library.

8.5.7.1.1 Emulation of the first order Activa

Biological semiconductors operate in a current-voltage regime much different than current man-made devices. This will change in the near future as man-made devices leave the realm of silicon and germanium and move to substrates of binary chemical composition. However, at this time, the current-voltage characteristic of an Activa cannot be approximated by a man-made transistor without employing parameter scaling.

To emulate an Activa using silicon or germanium transistors, it is necessary to scale the currents and voltages properly to account for this difference in operating range. In general, this scaling requires that the voltages used reflect the ratio between the offset parameters of the two technologies.

> The offset parameter of the biological Activa is known with considerable precision from the graph of Yau . The offset parameter of transistors is less well known and was originally derived empirically from test data. Under those conditions, it became common to use the values of 0.2 volts for germanium and 0.6 volts for silicon. Looking more closely at these materials, the so-called photovoltaic potential is given as 0.1 volts for germanium and 0.5 volts for silicon. An alternate example for silicon is the parameter called the base cutoff parameter by Motorola[41]. The value of this parameter is very close to 0.31 volts at 298 Kelvin and a collector to emitter voltage of 30 volts. It appears that this last value best represents the theoretical offset parameter of silicon.

Using 0.31 Volts as the offset parameter of Silicon, an Activa operating with a collector potential of -150 mV would be emulated by a silicon pnp transistor with a collector potential of minus 4.5 volts. If a germanium transistor is used, a collector potential of about minus 3.1 volts would be appropriate.

> If it is prefered to use a npn type of man-made transistor, the investigator must remember to reverse

[41]Motorola (1974) Semiconductor Data Library, Series A, Volume 1. Figure 13 on pg 2-399

> the polarity of all potentials applied to the circuit relative to those in the biological circuit (and note this fact carefully in any published report of the investigation).

Similarly, scaling of the current regime requires scaling the impedance level of the emulation circuit to reflect the ratio between the reverse current saturation parameters of the two technologies. The reverse saturation current of man-made devices vary significantly between silicon and germanium. Those of silicon are generally in the nanoampere range and those of germanium are in the microampere range. The reverse saturation current of most biological Activas appear to be in the range of picoamperes or lower. The data of Luttgau discussed above, indicates a reverse saturation current of 18-25 picoamperes for a biological diode of unspecified (but undoubtedly large) cross-sectional area.

> In the case of the typical photoreceptor cell, the in-vivo output Activa is only capable of a forward collector current on the order of 25 picoamperes, the reverse saturation current under this condition is probably measured in tenths to hundredths of a picoampere.

The result of the scaling process requires the emulation circuit to operate at very high impedance levels. At these levels, the shunt capacitances of the emulation circuit become quite important. They may control the bandwidth of the resultant circuit. The investigator should evaluate the desirability of using germanium versus silicon in emulations because of this impact.

> While it is formally correct to base the above scaling on the reverse saturation current of the Activa and the selected man-made component, the low values for the reverse saturation current associated with silicon are frequently not documented in conventional transistor data sheets because they are trivial in many applications. Similarly, biological researchers seldom record the reverse saturation currents associated with the conduits of a neuron. This complicates the scaling process. The alternative is to employ a totally empirical method of scaling. In this method, the collector voltage is chosen first to properly emulate the biological collector potential based on the ration of offset parameters as described above. The emitter current is then scaled by overlaying the current-voltage characteristics of the Activa and the chosen emulation transistor to determine the current scaling factor. These scalings will determine the scaling factor applicable to the current on the collector current to collector voltage characteristic of the emulation device.

8.5.7.1.2 Emulation of the second order Activa, the complete circuit

After developing the proper emulation of the desired Activa at the basic or first order level, it is possible to emulate the entire circuit for a given neuron. Most of the circuits within neurons employ Activa in the common base (or grounded base) configuration. However, the adaptation amplifier of the photoreceptor cell employs the common emitter (or grounded emitter) configuration and the lateral cells (horizontal and apparently most amercine cells) employ a hybrid circuit where input signals are applied to both the emitter and base signal leads.

After the configuration to be emulated is chosen, the appropriate load line can be drawn on the output characteristic of the circuit based on the scaling parameters developed above. This output characteristic is usually the collector current versus collector to ground voltage characteristic. This characteristic varies considerably depending on whether the common base or common emitter configuration is used.

While a resistive impedance may be used to approximate the load line over a limited range, it should be remembered that the load is generally a diode and the Activa circuit is operated under large signal conditions. The use of a resistive load may be deceiving under these conditions and mask non linearities that occur in the real circuit.

8.5.7.2 Simulations

Simulations via digital computer can be performed by implementing a set of differential equations or by calling upon a library of preprogramed transistor characteristics. The later approach generally involves more parameters and provides a more accurate result. However, the choice of a template from the library of available transistors should follow the procedure described in the previous section. In the selection of a preprogramed template, it is important to confirm that the offset parameter appropriate to the base material has been included in the template, and the program is capable of

operating at the impedance levels required.

Before using the simulation program known as NEURON, the investigator should assure himself that the program properly reflects the effect of temperature on the operation of the neuron.

8.6 Electrostenolytic metabolism powers the neurons REORDER

Sections 8.4 and 8.5 discussed the functional neuron from an operational perspective. This section will address the molecular and electrostenolytic mechanisms supporting the operation of such cells. These are the mechanisms that provide the electrical power required to operate the electrolytic circuits of the neurons. This discussion builds on the previous detailed discussion of the biological bilayer membranes (BLM's) of the neuron on a region by region basis.

The electrostenolytic process introduces a new area of metabolism not covered in the current literature. Previous discussions of metabolism related to the neural system has focused on the metabolism associated with cell development and cell homeostasis, not neural signaling. Conventional metabolism has focused on the utilization of various chemical forms, lipids, carbohydrates, proteins etc. Recent studies have delved deeper into the metabolism associated with the tricarboxylic acid cycle (TCA)[42,43]. Some of these studies have differentiated between the neuronal and astrocyte variations of these cycles. Bachelard (1997, pg 32-33) addressed the intracellular compartmentation of metabolism within a cell. It is the stereo-specific in-vivo metabolism occurring on the surface of the neuron and associated with the glutamate shunt that is defined here as electrostenolytic metabolism.

It is important to differentiate between the glutamate shunt converting glutamate to GABA (used for electrostenolytic metabolism) and the alternate process converting glutamate to glutamine (used for other metabolic functions). This differentiation requires careful reading of the literature. It is the neuronal variant that employs the "glutamate shunt to convert glutamate to GABA instead of glutamine. The schematics in figures 4(b) and 5(b) on pages 18 & 19 of Bachelard appear to be the only TCA cycles of interest in neural signaling. Figure 4(b) occurs naturally while 5(b) is artificial. Figure 5(b) does highlight an idiosyncracy introduced by the IUPAC naming rules. The same carbon atoms in glutamate and GABA are numbered differently. As noted in the footnote to **TABLE 8.6.2-1**, the carbon atoms of glutamate are numbered as if it were α-amino glutaric acid. If it were defined as γ-amino glutaric acid (in parallel with γ-amino butyric acid or GABA), the same carbon atom would have the same number in both formulas.

The schematic TCA cycle described in Ross, Lin, et. al. only applies to astrocyte cell metabolism. If the neuronal metabolism schematic of figure 4(b) of Bachelard is used to interpret figure 8 of Ross, Lin, et. al., a possibly significant difference surfaces. Ross, Lin, et. al. show the presence of glutamate with a labeled ^{13}C at position 2 is significantly reduced in patients with Hepatic Encephalopathy (HE). This condition would suggest glutamate is formed normally within the brain from glucose (via pyruvate, et. al.) but it is not regenerated within the brain from GABA (via succinic acid, et. al.).

The powering of the neural system is dependent on many features of the vascular system for resources. In this sense, the power supply of the neural system operates in parallel with the metabolic systems supporting cell growth and homeostasis. Only the critical aspects of the vascular system will be discussed in this section.

As earlier, it is proposed that the passage of large particles through the type 3 plasma membrane for purposes of genesis and growth are outside of the scope of this work. In addition, the type 1 membrane is not only impervious to ions and molecules, it is a near perfect electrical insulator. The passive nature of the type 1 membrane prevents it from participating in the electrostenolytic process powering the neurons. The subject of this section will be the passage of fundamental charges through type 2 regions of the BLM and the inducement for such passage by the electrostenolytic processes. As noted in **Section 8.1.3.2.3**, it is the high mobility of holes in the hydronium lattice forming the base of each Activa that defines the electrical requirements of the neuron. For analog circuit operation, the collector must be biased negatively with respect to the base region. When this requirement is met, the injection of holes (extraction of electrons) from the emitter (due to a positive change in emitter to base potential) will cause a proportional number of electrons to pass from the collector to the base region of the Activa. This loss of charge on the capacitance associated with the collector causes the collector voltage to become more positive.

As a result of this method of operation, it is necessary to provide a set of biases to the terminals of the Activa that will sustain the above operation. These biases are established by an electrostenolytic process associated with regions of type

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[42]Bachelard, H. (1997) Magnetic Resonance Spectroscopy and Imaging in Neurochemistry. NY: Plenum Press

[43]Ross, B. Lin, A. et. al. (2003) Clinical experience with ^{13}C MRS in vivo NMR Biomed vol. 16, pp 358-369

2 BLM dedicated to this task.

This section will address the operation of the neural system without regard to its homoeostatic and growth functions. The emphasis is on the unique requirements of the neurons to achieve different electrical potentials within the different electrical conduits of the neuron. These conduits are usually described as the lemmas of the cell. The dendrolemma, podalemma and axolemma are physically distinct from each other.

McIlwain & Bachelard have provided a comprehensive description of the Biochemistry of the Central Nervous System[44]. However, it is interesting to note they do not discuss the stereochemistry or electrostenolytic chemistry so crucial to the provision of power to the neurons. Otherwise, their coverage of the biochemistry of the CNS is very broad.

Ruscak & Ruscakova have provided very valuable data on the presence of glutamic acid and GABA in the brains of mice under a very broad range of experimental conditions[45]. Although addressed from a different perspective, it is proposed that their findings are in total agreement with the expected results based on the theory presented below.
Ross, Lin, et. al. have extended the work of Ruscak & Ruscakova considerably. They have begun to consider improper operation of the TCA as potentially related to Alzheimer's Disease (which they associate with a mitochondrial disorder). They propose that "Alzheimer's may represent a failure of glutamine-glutamate cycling and glutamate neurotransmission". However, they did not address the glutamate-GABA shunt per se, and the consequences of a malfunction of the electrostenolytic metabolism associated with this shunt. Their discussions did not include the role of GABA. This work would suggest the problem focuses on the availability of glutamate and its electrostenolytic conversion to GABA while powering the neurons.

8.6.1 Electrical power requirements of the neural system

It is the hydraulic and nutritional properties of the eye and optic nerve that support the operation of, and control the adaptation characteristics of, the visual system. This section will illustrate the role played by these portions of the overall biological system in supporting the neural system, especially regarding vision.

8.6.1.1 The power requirements presented symbolically

The hydraulic and metabolic systems play a very important role in determining the state of adaptation of the visual system. Because of this fact, a description of this role is illustrative of the general requirement. **Figure 8.6.2-1** illustrates the relevant elements of the system. The amplifiers shown in symbolic form are the adaptation amplifiers of the individual photoreceptor cells. They receive excitation from their respective spectrally selective Outer Segments. They deliver their output to their respective distribution amplifiers also contained within the photoreceptor cells. The amplifiers normally employ internal negative feedback. However, they are drawn as if they used negative external feedback to highlight this function. The capacitances, C_A, are shunted across the nodes shown by the black dots and no external path back to the input of the amplifiers exists.

The crosshatched blocks are the electrostenolytic supplies to each amplifier. These supplies are connected in parallel to the vascular system as shown at the top of the figure. The vascular system is shown by an electrical analog where the capacitors represent hydraulic reservoirs and the resistances represent the impedances of the vascular channels. The symbols, V_x, represent the energy potential of the vascular system at a given point. The relative values of these elements are not currently known. However, the multistage character of this network is the source of the dark adaptation characteristic of the visual system. The differential equation describing this situation is third order. Its solution results in the exponential sinewave that is characteristic of the dark adaptation function. See **Section 12.5.3** and **17.6.1**.

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[44]McIlwain, H. & Bachelard, H. (1985) Biochemistry and the Central Nervous System. NY: Churchill & Livingstone.

[45]Ruscak, M. & Ruscakova, D. (1971) Metabolism of the nerve tissue in relation to ion movements in vitro and in situ Baltimore, MD: University Park Press pp 85-98

The supply of electrostenolytic materials to the neurons of the visual system is a responsibility of the vascular system. The adequacy of the vascular system in meeting this requirement is represented most clearly by the variation in sensitivity of the photoreceptors as a function of their position in the retina. Although addressing the subject from a different perspective, Spillmann & Fuld[46] and Wooten, et. al[47]. have provided valuable information in this area. They test a concept that attempts to account for the variation in sensitivity with position in the retina by a single function that can be described as an equivalent illumination (a dark light?). Their results showed that each location followed its own time course. The process was obviously more complex than they suspected. However, their data is good. It allows one to determine the relative impedance and time constant of the vascular supply system serving each photoreceptor (or each zone) of the retina. This is particularly useful in calculating the adaptation characteristic as a function of position in the retina. It also provides a method of specifying the magnitude of the Halo Effect seen in conjunction with high contrast edges in the field of view.

8.6.1.2 The power requirements presented at the circuit level

The above paragraph establishes the need for a power source of about -150 to -154 mV. As discussed in **Chapters 8 & 9**, the Activas of any neural circuit must normally be biased such that the emitter terminal (the dendroplasm) is negative with respect to the base terminal (the podaplasm). To satisfy the variety of bias requirements required in different circuit configurations, a potential source of -25 to -30 mV is needed. While such a potential can be derived from the higher potential, it would be more efficient if a lower electrostenolytic voltage source were available.

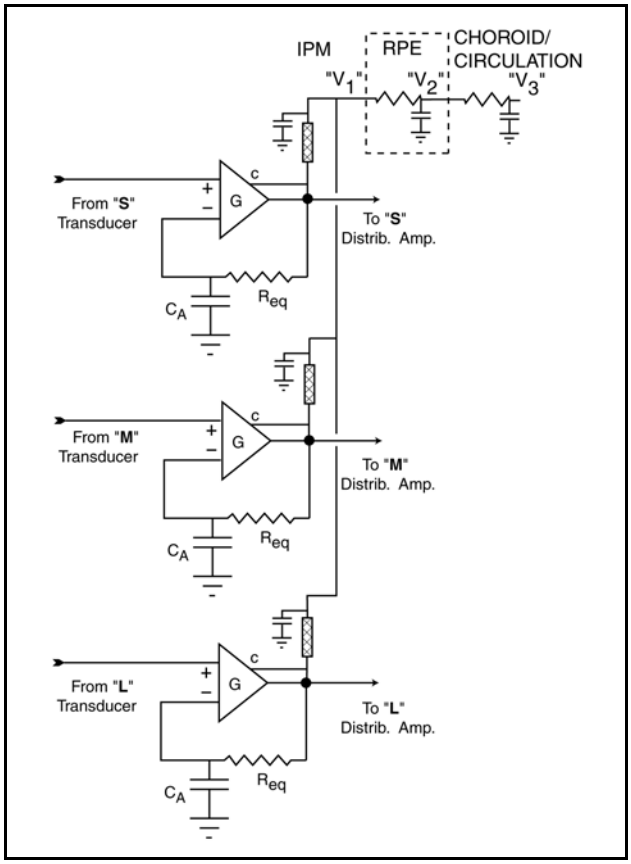

Figure 8.6.2-1 The adaptation amplifiers share a common power supply. The adaptation amplifiers are shown symbolically to highlight what is normally an internal feedback mechanism (C_A & R_{eq}). The gain of each amplifier is controlled by the voltage applied to the collector terminal, c.

8.6.2 Use of Glutamic acid in neural respiration, specifically electrostenolysis

There is a dichotomy in the biological literature. Two amino acids have gained the distinction of being labeled "nonessential amino acids," aspartic and glutamic acids. This label was apparently bestowed because researchers could find no use for these amino acids in normal cell development. However, they are the only two amino acids with two carboxyl acid groups. This makes them polar and negatively charged (acidic)[48]. Tyrosine, while acidic, does not have two carboxyl groups (a critical factor in the stereochemistry of electrostenolysis). These unique features are critically important to neural cells and the operation of the neural system of an organism. The neural literature is well aware of the importance of glutamic acid (generally glutamate in pharmacology) in the operation of the neural system and vision. Unfortunately, their precise role in the neural process has not been recognized.

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[46]Spillmann, L, & Fuld, K. (1979) The equivalent background and retinal eccentricity. Vision Res. vol. 19, pp. 117-122

[47]Wooten, B. Fuld, K. & Spillmann, L. (1975) Photopic spectral sensitivity of the peripheral retina. J. O. S. A. vol. 65, pp. 334-342

[48]Pethig, R. (1979) Op. Cit. pp 36-39

Glutamic acid (glutamate) has been given the label neurotransmitter based primarily on the fact that its presence enhances neural activity. On the other hand, the presence of GABA appears to depress neural activity. It was therefore labeled a neurotransmitter blocker. McGeer said in 1987 "Nevertheless, it must be recognized that truly definitive markers that can be applied at the cellular level do not exist for glutamate and aspartate as they do for several other neurotransmitters. Therefore, evidence for neuronal identification and for pathways involving these amino acids must in all cases be considered as tentative."[49] This work holds that glutamate is a neuro-facilitator, and GABA is a neuro-inhibitor due to their roles in the electrostenolytic process providing electrical power to the neurons. Neither material plays any direct role in signal transmission across a gap junction.

Hirsch & Ortel made another important observation in 1988 while investigating individual mice neurons in-vitro[50]. "Glutamate excited all eleven neurons tested." This excitation, occurring in the absence of any functional synapse, shows the topically applied material was not acting as a neurotransmitter but as a neurofacilitator. It was changing the intrinsic operational parameters of the neuron.

The more recent work of Ross and others may have changed the situation with respect to markers[51]. They report N-acetyl aspartate is a marker for neurons, axons and dendrites (presumably all neurites).

The roles of glutamate as a neuro-facilitator and GABA as a neuro-inhibitor have gained attention recently due to a recently uncovered anachronism in fMRI investigations. While the use of glycogen in ultimately fueling the neural system is easily measured, the lack of an equivalent absorption of oxygen from the blood during a similar time period has come as a surprise. This subject will be explored in depth in **Section 8.6.6**.

Glutamic acid is present in abundance in the CNS. It is used in protein and peptide formation, fatty acid synthesis, control of ammonia levels and many other functions. This paragraph will concentrate on the role of glutamate as the principal reactant in the mechanism providing power to the neural system. As in nearly all biological systems, alternate manufacturing paths are provided to satisfying a requirement that is critical to the organism. Here, aspartic acid can play such a backup role. Other backup materials may also exist.

With respect to neurology, the vascular system is primarily involved in the transport of the reaction products supporting the electrostenolytic process common to the power supplies of all neurons. This is the metabolic reaction of the glutamates at the various surfaces of individual neurons. The glutamates participate in a "glutamate cycle" but not a glutamate cascade. The vascular system must bring the appropriate materials to each site and carry away the waste products. It must also support the storage of the reaction materials near the reaction sites in sufficient quantity to meet the variable demand under operational conditions. Fortunately, because of the location of the adaptation amplifiers at the very front of the electrical signal chain in the visual system, the variation in the consumption of electrostenolytics is small. Unfortunately, this has made it difficult to explain the ubiquitous presence of the glutamate cycle materials near neurons. Their consumption does not correspond to areas of high signal activity (as discovered by Wong-Riley).

An important aspect of glutamate utilization is its inability to cross the blood-brain-barrier[52]. This requires that all of the glutamate used within the brain be created from glycogen within the brain enclosure.

Many references to the concentration of materials related to glutamate cycle along the neurons of the body appear in the

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[49]McGeer, P. Eccles, Sir John. & McGeer, E. (1987) Op. Cit. pg 176

[50]Hirsch, J. & Oertel, D (1988) Intrinsic properties of neurones in the dorsal cochlear nucleus of mice, *in vitro J Physiol* vol 396, pp 535-548

[51]Ross, B. (or other source) Magnetic Resonance Spectroscopy - - - -

[52]Mc Geer, P. Eccles, Sir John. & Mc Geer, E. (1987) Molecular Neurobiology of the Mammalian Brain, 2nd Ed.. NY: Plenum Press pg 176

literature. Lolley, et. al[53]., referencing Blanks & Johnson[54], say that the individual photoreceptor cells are "coated with a mixture of glycoproteins and glycolipids which may play important roles in maintaining the unique structural and/or functional organization of the cell." They did not further define the chemical nature of these materials. Korschen, et. al. have provided a more detailed mapping of materials in intimate contact with the photoreceptors[55]. Similar statements appear concerning other types of neurons. Whereas, glutamate is frequently as ligands in short glycolipids, the properties of these lipids are not of significance here.

Berman has presented considerable information on the metabolism employed by the visual system. However, She did not explore any electrostenolytic systems[56]. She shows two versions of the tricarboxylic acid cycle including a variety of associated cycles (fig. 7.2 & 7.20). Her notation uses that of the nutritionist, glutamic acid is called glutamate. These cycles show glutamate involved in many individual reactions occurring at a great many locations. Table 7.2 shows the concentration of free amino acids in a variety of retinas. There is no discussion of more complex molecules such as the GARPs, glutamatic acid rich proteins, that have been proposed to support the overall metabolic process.

Most works on physiological chemistry employ the glutamates along with other simple amino acid groups in the energy cycles supplying individual cells and the elements interior to these cells. Overall, these processes do not involve the constant and rapid flow of these materials through cell membranes. Usually, the materials are found on both sides of the membrane and only electrons (and/or holes [H^+depending on the terminology used]) actually transverse the membranes. (The biological community seems to prefer the concept of transporting protons through membranes instead of electrons. In fact, protons almost never transit material with a crystalline lattice and it is doubtful that they actually transit liquid crystalline lattices. Electrons have much higher mobility within lattices and the net result is the same.)

Most of the biological system is powered by reactions involving a series of amino acids and their derivatives. These reactions have been categorized and grouped into a series of cycles by those studying metabolism and nutrition. One of these major cycles is the glutamate cycle. It is normally shown as generating energy by creating glutamic acid and NAD^+. These reactions are characterized by the movement of hydrogen ions (or conversely electrons) between various species in the reactions. These reactions are usually discussed as if they were taking place in solution. However, many of them can take place equally well on a substrate. In this electrostenolytic case, the electron or proton freed or absorbed can be transferred to the substrate and ultimately across the substrate to its opposite surface. This electrostenolytic case is the foundation of the electrical power generation system used to support the electrolytic operations of the neural system.

A broad review of all of the possible sources of energy to support the neural system of an animal could not be found in the literature. Gutmann & Keyzer have addressed selected potential sources and referred to reviews by Kell and by Berry[57]. Their attention appears to be drawn to the potentials and differences between concentration gradient sources and fuel cell sources. Both of these sources involve ion transfer across a membrane.

8.6.2.1 Background

The basic premise to be developed here is; there is an electrostenolytic energy loop occurring at selected locations on the surface lemmas of neurons. At these locations, two members of the glutamate family, glutamic acid in a primary role and aspartic acid in a backup role, are reduced to provide electrical energy to the neuron conduits. The ultimate process may result in the formation of GABA. However, there are a variety of intermediate processes and many terminate with glutamic acid. In the immediate process, energy is released that is realized as a voltage potential across the lemma of the neuron. Other simple waste products are also released into the surrounding matrix. It is proposed that this is the mechanism used to power all animal neurons. This premise does not require the physical transport of ***any*** ions through

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[53]Lolley, R. Lee, R. Chase, D. L& Racz, E. (1986) Rod photoreceptor cells dissociated from mature mice retinas. Invest. Ophthal. Visual Sci. Vol. 27, no. 3, pp 285-295

[54]Blanks, J & Johnson, L (1983) Selective lectin binding of the developing mouse retina. J Comp. Neurol. vol 221, pp 31

[55]Korschen, H. et. al. (1999) Interaction of glutamic-acid-rich-proteins with the cGMP signaling pathway in rod photoreceptors *Nature*, vol. 400, pp 761-766

[56]Berman, E. (1991) Biochemistry of the Eye, NY: Plenum Chap. 1 & 7

[57]Gutmann, F. & Keyzer, H. (1986) Modern Bioelectrochemistry. NY: Plenum Press, pg 90

the plasma membrane of the neuron for purposes of powering the neuron. Such transport may occur for other purposes.

The subject of electrostenolysis is too complex to detail here. Eyring[58] and Marino[59] have provided texts including sections on this subject but not in the detail required below. For that, more focused material such as Finkelstein[60] and Gutmann & Keyzer[61] should be reviewed.

8.6.2.1.1 Background related to architecture

The neurons of the visual system are each supported by multiple, individual, limited capacity power sources based on electrostenolytic principles. This reminds one of the old battery radio days when the A battery heated the filaments, the B battery supplied the high voltage and the C battery provided the bias voltage required. To reduce the number of batteries required, the circuits were AC coupled. This allowed certain batteries to be shared. It also avoided another problem associated with DC coupled circuits, supply voltage creep. It is very difficult in DC coupled circuits to avoid a step-wise rise (or fall) in the output circuit voltage of each amplifier stage. This is because of the need to maintain the appropriate voltage difference between the output and input circuits of a given stage. This problem can be overcome in semiconductor circuits by using a combination of PNP and NPN type active devices. To date, no NPN type devices have been found in the neural literature.

In a long string of amplifiers, only two practical solutions to the voltage creep problem exist. One is to introduce at least one stage of AC coupling. The other is to use saturable switching circuits. The last solution is the one used in the vision process. A certain amount of voltage creep is accepted in the analog (electrotonic) signal processing circuits of the retina before the ganglion cells. The ganglion cells encode the previously analog signals to binary pulses in order to avoid additional voltage creep. Subsequent transmission amplifiers operate in a saturation mode until the decoding circuits of the brain are reached.

8.6.2.1.2 The role of glutamate and GABA in retinal metabolism

The clinical science course of the American Academy of Ophthalmology has provided a succinct discussion of the metabolism of the retina[62]. It is too general for the purposes of this work. However, it notes the potent role of glutamic acid and GABA on retinal operation. They specifically note the ability of "millimolar concentrations of the compounds to cause an excitation block of the retina, rendering all cells except photoreceptor cells non-responsive to light stimulation." This is clearly due to the presence of the outer limiting membrane that isolates the electrolytic source of the a-wave within the inter photoreceptor matrix from attack by these materials. The article also notes the following with regard to neurotransmitters. "In spite of the data for putative glutamate receptors, there is no clear demonstration of release of glutamate or aspartate from photoreceptors in the dark. Therefore, this identification as photoreceptor cell transmitters is tentative." As noted in this work, the receptors are actually electrostenolytic sites that are not involved in signaling.

The paper also discusses the excess capacity of the retina to produce lactate relative to its metabolic needs, even in the absence of oxygen. It gives the production as 1.12 μmoles/mg dry wt/hr in the presence of oxygen and 80% higher in

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[58]Eyring, H. (1970) Physical Chemistry: An advanced treatise. Vol IXA/ Electrochemistry NY: Academic Press.

[59]Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker

[60]Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. NY: John Wiley & Sons. pp-94-114

[61]Gutmann, F. & Keyzer, H. (1986) Modern bioelectrochemistry. NY: Plenum Press, Chapters 2 & 3

[62]— (1992) Fundamentals and Principles of Ophthalmology, section 2 *in* Basic and Clinical Science Course. San Francisco, CA: American Academy of Ophthalmology pp 191-198

the absence of oxygen. Although it suggests the excess is removed by diffusion, it indicates the mechanism is unknown. In this work, it is converted into glutamic acid and eventually it is GABA that is removed or recycled.

8.6.2.1.3 The search to define materials used in neural electrostenolytics

Although amino acids are often described as functioning primarily as precursors of proteins and other biomolecules, they are often used as a source of energy. Lehninger[63] devotes two chapters to the oxidation of fatty acids and the oxidative degradation of amino acids. These categories include the glutamates, glycine and GABA. He says that higher animals actively oxidize both exogenous and endogenous amino acids obtained from the metabolic turnover of body proteins. He also says that free amino acids are readily absorbed through cell plasma membranes. It appears this sentence is too broad and should probably be interpreted as at least one region of the plasma membrane is capable of supporting such absorption. Lehninger indicates there are 20 different flow sheets for amino acid oxidation. Several of these sheets include the glutamates, glycine and GABA. Many terminate with the formation of glutamic acid. This material is then transported to the kidney in the form of glutamine, to aid in the excretion of ammonia. Lehninger also devotes a chapter to the biogenesis of the same fatty acids. In essence, these materials are used over and over again within the body through a series of metabolic cycles.

Many of the above bio-energetic processes were being annotated during the 1930-50 time period. That involving the glutamate cycle appears to be involved in powering the neurons of the neural system [xxx english]. The presence of the glutamates on the surface of neurons would be expected and is well known. In general, the presence of these materials near the plasma membrane walls of neurons was determined during this same period and prior to the introduction of the electron microscope.

Because of the cyclic uses of many amino acids within the animal system, it is difficult to differentiate between the consumption and the generation of a particular constituent at a given location.

Whereas most of the discussion in Biochemistry, concerns the interaction of the above compounds and the release of energy via the conventional agents (ATP, ADP and $NAD^{+)}$, electrostenolysis provides another path to the release of energy. This release is in the form of electrons stored on a capacitor. The result is an electrical potential that is used to bias the Activas of the neurons.

The extensive 1981 review by Puil is of great value in describing the impact of electrostenolytics on the neuron[64]. However, his basic model was of a dynamically porous membrane wall along the lines of Huxley, Hodgkin & Katz (See **Sections 10.8.3 & 10.8.4**). Because of this, he does not differentiate carefully between probing (or stimulating) the individual dendroplasm, the podaplasm and the axoplasm of a given neuron. The paper has a considerable number of 'however," "on the other hand" and "alternately" expressions when discussing the effect of a given chemical on a neuron. This is at least partly due to the wide variety of investigators referenced. Techniques and interpretations varied widely. The use of a three-terminal neural model eliminates many of these ambiguities and inconsistencies.

Puil observed that the topical application of glutamate to a neuron resulted in a hyperpolarization of the associated plasma inside the neuron (pg 234), "an indication of enhanced excitability of these terminals in the frog and the cat." He goes on to note, In the isolated amphibian spinal cord, either super-perfusion by bath application or intra-arterial perfusion of S-glutamate produces a negative DC-potential shift which may be measured with pairs of non-polarizable Ag-AgCl electrodes, and also by the sucrose-gap method, on dorsal as well as ventral roots " (accompanied by a long list of references). He further notes, "The responses are relatively constant, usually showing no evidence of fade or tachyphylaxis and they completely disappear within a few seconds after withdrawing glutamate." Puil also investigated iontophoretic response over a range of concentrations of glutamate, ultimately resulting in toxicity. This demonstrates the care required in discussing the effect of glutamate concentration on the neural system.

It is important to note that in much of Puil's subsequent discussion, he speaks of the hyperpolarization or depolarization of the axon associated with a neuron. There is no one-to-one correlation between the hyperpolarization of a plasma adjacent to an electrostenolytic site and the change in polarization of the distinctly separate axoplasm. The impact on

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[63]Lehninger, A. (1972) Biochemistry, 6th printing NY: Worth Publishers Chap. 19 & 20

[64]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res Rev* vol. 3, pp 229-332

the axoplasm depends on whether the dendroplasm or the podaplasm was hyperpolarized.

Puil performed microiontophoretic experiments to determine the point of action of glutamate on a neuron. While, he discussed a range of difficulties associated with delivering a precise amount of glutamate within a specific volume associated with the surface of a neuron, he did draw several conclusions with respect to motoneurons. He noted, "(1) evidence that the dendritic regions of feline motoneurons are more sensitive to S-glutamate than the soma, (2) the possible diversity or variations in the sites and extent of uptake of glutamate and its analogues by neurons or glia. . . ." And, "Axons of motoneurons have been found to be relatively insensitive to S-glutamate." These observations are easy to rationalize based on the three-terminal model of the Activa and the neuron.

Puil also noted, "The discharges evoked by S-glutamate can be blocked by microiontophoretic applications of procaine to the same cell."

Puil was working with micropipettes having short, <150 microns, and longer, 150-350 micron, intertip distances. These are very large numbers relative to most neurons. His Section 3.1 is also based strictly on a dynamic and porous membrane model.

Puil noted the similar action of aspartic acid to that of glutamic acid. He also noted that the chirality of these two acids had little effect on their actions.

Finally, Puil noted the impact of various analogs of glutamic and aspartic acid on the neurons. "When applied microiontophoretically to spinal neurons only a few amino acids other than the closely related homologues of S-glutamate have been found to produce excitation with exactly the same characterestics as those of S-glutamate." Many of the materials they investigated exhibited a reduction in the root potentials in a reversible manner. However, the rate of recovery following application of these materials was frequently very slow. These materials appear to operate similarly to L-Dopa, the current drug of choice in Parkinson's Disease (See **Section 18.8.5.3**).

> Puil has provided an extensive list of analogs and chemicals closely associated with the glutamates (pp 304-6).

Puil's paper appears to be highly compatible with the thesis of this work that the electrostenolytic process occurs at specific locations on the surface of the individual lemma of a neuron by stereospecific electrostenolysis. To accomplish this, the portion of the lemma must be electronically asymmetrical and the reactant must be stereochemically compatible with the polar (positive) portion of the phosphoglyceride forming the outer layer of the lemma. To accomplish this, it appears the reactant must be a dicarboxylic compound of specific stereochemistry. Puil stated this requirement somewhat more loosely based only on chemistry and a list of references, "initial studies quickly established the minimal requirements for the excitatory property: one basic and two acidic groups with α-decarboxylation of the parent molecule leading to a substance with depressant action (e.g. α-decarboxylation of glutamate yields GABA, a neutral, inhibitory amino acid. (pg 266)" Only one compound listed by Puil was not dicarboxylic in form (excepting a class where sulphur was substituted for carbon in the radical). When the one carboxylic group was replaced by a tetrazolic group, the resulting chemical showed no neural effect.

The above ground rules limit the primary electrostenolytic reactants to the two dicarboxylic (and negatively charged when in ionic form) amino acids, glutamic and aspartic acid, and there dicarboxylic analogs. Within the current wisdom, these materials are inappropriately labeled neurotransmitters. Within the context of this work, they are neuro-facilitators.

A broad range of other compounds may impact the rate of reaction at the electrostenolytic surface. These have generally been classed as false neurotransmitters in the current common wisdom.

While the proposed electrostenolytic process involves stereochemistry, it only requires a loose interpretation of the "lock and key" model usually used to explain the mechanism. The critical portion of the reactant molecule appears to be limited largely to the area close to the carboxylic group farthest from the amino group.

Polarity is important when discussing the impact of a chemical on a neuron. Except at toxic levels, application of glutamatic and/or aspartic acid to an electrostenolytic site lead to a higher negative potential within the associated plasma. This is generally described as hyperpolarization. The change in potential associated with a subsequent action potential may be greater. Such a change is generally described as involving a larger positive going amplitude. This is because, the underlying DC level became more negative. Action potentials do not normally become more positive than the potential of the matrix surrounding a cell. However, determining this local potential is experimentally difficult if the matrix has a significant resistivity. The reference potential, measured at a remote location in the INM, may not reflect the local potential.

Aspartic acid appears to be a minor player in the electrostenolytic process at this time. Subsequent discussion will center on the role of glutamic acid.

As of 1986, Gutmann & Keyzer had not explored the roles of all of the metabolic materials found in the IPM and the interneural matrix of the eye. They do provide relevant material concerning Na^+, Ca^+, ATP and other related materials. Similarly, they were not aware of the active device within the neuron. Their Chapter 17[65] provides a qualitative attempt to explain the action potential based on simple fields and some very complex chemistry. These attempts are not required when the presence of an active device is accepted.

In the current literature, many authors are attempting to relate the metabolites present on the surfaces of the external neural membranes to the signal transmission task instead of the electrical power generation task. These metabolites are extremely important to the operation of the nervous system but not as signal amplification and transmitting mechanisms. Further, the metabolites on one or both sides of the membrane control the actual potential produced by the power source. These metabolites are not found concentrated at the synapses. They appear all along the length of many types of neurons.

It is true that the consumption of the metabolites may be approximately related to the signal intensity at the adaptation amplifier. However, this is a very indirect and complex relationship of little theoretical or practical importance. Because of the high degree of negative feedback within the adaptation amplifier, the consumption of metabolites at later points in the signal chain is essentially independent of the signal intensity.

Each metabolic power source can be represented by a three-element electrical network, a perfect rechargeable battery in series with a perfect diode and the combination shunted by a capacitor. The current capability of the battery is dependent on three parameters. First, it depends on the electrical characteristics of the membrane. Second, it depends on the area of the available membrane wall. Third, it depends on the metabolic diffusion rates in the vicinity of the membrane and the sources of additional metabolites. The only available source is the vascular system. Similarly, the capability of both the diode and the capacitor are determined by (other) characteristics of the membrane and the available area of the membrane wall.

Only detailed experimentation can determine the exact parameters of these power supplies. The data would suggest that most of them are tailored to meet the operational requirement with little impact on the operating characteristics. A major exception occurs in the photoreceptor cells. These cells employ a variety of electrostenolytic sources to provide different potentials at different sites. Some of these potentials may only be used at these particular sites. The potential provided to the adaptation amplifier is of particular interest. The impedance associated with this power source has been tailored to provide the extremely wide acceptable signal amplitude range found in vision. The potential sources associated with the distribution amplifier of the photoreceptor cell are also specialized. Genetic errors in the establishment of these potentials appears to play a major role in achromatopsia (See **Section 18.8**).

8.6.2.1.4 GABA as a byproduct of electrostenolysis

Considerable data is available in the literature concerning GABA (gamma amino-butyric acid), Glycine and Glutamine in their various forms. Most of the data is the result of exploratory research. Unfortunately, much of the literature does not address the chemical role of GABA, where it is produced and where it goes. Mize et al. have edited an entire volume that never addresses the chemistry of the material[66].

All three of these chemicals are closely related structurally and appear to concentrate in areas associated with neurons after exogenous intake. The functional role played by these materials has never been developed in detail. Recently, it has been proposed that a “glutamate cascade” is present in the signaling function related to vision. The proposal has been that such a conceptual mechanism provides an explanation for the high initial signal amplification process found

[65]Prepared by Kinnunen, K. & Virtanen, J.

[66]Mize, R. Marc, R. & Sillito, A. (1992) GABA in the Retina and Central Nervous System. NY: Elsevier

in dark adapted vision. This work takes an entirely different view.

It is proposed that these materials are bio-energetic sources that participate along with other materials in powering the electrical operation of the neural system in animals. In this role, they are the most common materials involved in electrostenolysis at various specific locations along the outer membrane of the neuron. These sites tend to be grouped in areas designated as manifolds.

Lake et. al[67]. have demonstrated the metabolism of GABA and glutamine in the retina of various mammals. However, the quality of instrumentation available in their era limited the precision with which the location of these materials could be determined. It is proposed by this theory that their compartments are now known as (terminal) manifolds of the vascular system and these manifolds contain glia next to the specialized surfaces of all neurons. By performing uptake experiments, the conclusion was drawn that GABA accumulates in retinas more than in other areas of high neuron density. *If this is true, it would suggest that GABA plays a preferred role to other bioenergetics in the operation of neurons*. However, additional experiments are probably required to show that GABA did not accumulate similarly in the brain, and the inner ear. Besides uptake experiments involving autoradiography, they showed that GABA reacted to form glutamine that they describe as a non-neuroactive compound. They also showed that the glutamine found in glia transferred to neurons, "where it is subsequently metabolized to GABA via glutamate, thus completing the cycle of GABA uptake by glia following neuronal release." They did not address the energy balance in these transitions or if electrostenolysis was involved. Their investigations suggest that these materials are found on the exterior surface of the axolemma in the area exposed to the interneural matrix. The reversible nature of the reactions involved makes the statement by Lake quite reasonable as part of the metabolic process. It appears the dominant reaction within the neuron, that generates electrons, is carboxylation[68].

More recently, Benson, et. al. have studied the role of glutamic acid in the nervous system[69]. Their concentration was on tracking an enzyme they describe as GAD (glutamic acid decarboxylase). However, they do not describe the reaction chemistry as a result of GAD, e. g. why a carboxyl group should be removed from glutamic acid?

Glutamine, in one form or another is an end product in a variety of bioenergetic reactions. Many of these reactions are very complex, include many steps, and are critical to the metabolism of the animal. As a result, many of these reactions are sufficiently well studies to have specific names. By providing energy to the animal, these reactions are ideal candidates to provide electrical energy to the neural system as well. By releasing energy in small steps, these materials are well suited to the requirement to supply electrical energy at approximately 150 mV to the neural system. The determination of what individual chemical reactions might be employed in the electrostenolytic process at the cell membrane to provide energy at this voltage level is beyond the scope of this work. However, the α-Ketoglutarate pathway is a likely analog. In such a case, the GABA would be transformed into glutamic acid with the release of an electron. The electron released by the reaction would be transferred through the wall of the membrane instead of being transferred to a molecule of nicotinamide adenine dinucleotide, NAD^+.

More recent investigations approach the electrostenolytic process from a different perspective. Steriade, et. al. state, "there is reason to believe, mainly from neurochemical studies, that GABA may be released by afferent pathways. . . ."[70] They also say, "All of the reticular nucleus cells appear to produce gamma-aminobutyric acid (GABA). . . ." This theory proposes that the glutamate-GABA reaction is the source of electrical power for the neural system and *neither* of these chemicals participates directly in the signaling function. In this context, the materials are present primarily in specialized regions on the external surfaces of neurons devoted to the creation and sustenance of the intrinsic membrane potential associated with a given plasma compartment within a neuron. The materials are delivered to the specialized regions from the blood stream by the interneural matrix following ingestion. This electrostenolytic process is the key to the very high thermal efficiency of the neural system. Normally, the material is converted in a reaction cycle. However, the crucial step of supplying electrons to the plasma within a cell by electrostenolysis is reversible. Glutamic acid is well known

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[67]Lake, N. Marshall, J. & Voaden, M. (1977) Metabolic compartmentation and the metabolism of GABA and glutamine in retina pg. 354 *in Synapse, Cottrell & Usherwood* Op. Cit.

[68]Lehninger, A. (1972) Biochemistry NY: Worth Publishers pg. 446

[69]Benson, D. Isackson, P. Gall, C. & Jones, E. (1992) Contrasting patterns in the localization of glutamic acid decarboxylase and Ca2+/calmodulin protein kinase gene expression in the rat central nervous system *Neurosci*. vol. 46, no. 4, pp 825-849

[70]Steriade, M. Jones, E. & Llinas, R. (1990) Thalamic oscillations and signaling. NY: John Wiley, pg 62 & 84

for its importance in reactions providing energy[71].

8.6.2.1.5 Relation of glutamic acid and GABA to photodetection

Whereas the notion of a glutamate cascade requires a mechanism for controlling the level and termination of such a cascade, this theory does not. To interpret the role of this chemical complex in the operation of the photoreceptors of vision, separating the photoexcitation/de-excitation role from the photo-translation role is appropriate as done earlier. Both processes have been explained without relying upon the presence of the glutamic acid-GABA electrostenolytic reaction explicitly. However, it does support the power requirements of the adaptation amplifier within the photoreceptor cell. This requirement is unusual due to the voltage breakdown and resulting variable gain characteristic of this amplifier.

+ At very low excitation levels, the gain of this amplifier is about 4000:1. Approximately 4000 electrons flow in the collector lead of the Activa within this amplifier for every electron-hole pair created in its base region. As shown earlier, a direct and linear (except in the L-channel) relationship exists between the number of photons incident on the chromophores of the disks and the number of electron-hole pairs created in the base region. Under this very low current level through the adaptation amplifier, the voltage between the collector and base is high. This causes any electrons formed in the base region to be swept out of the region at high speed. This speed is high enough that any collision with other electrons in the lattice can cause their excitation into the valence state. The result is current multiplication by what is known as the avalanche effect. [The term is analogous to the putative molecular "cascade" of the glutamate cascade theory.]

+ as the excitation level rises, one electron-hole pair is still created for every photon absorbed. However, the electrical power supply to the adaptation amplifier is not stiff. It cannot meet the current demands of the amplifier and the collector to base voltage drops. As this voltage drops, the number of electrons generated by the avalanche effect drops, and the overall current gain of the amplifier drops below 4000:1. It eventually reaches 1:1 under high levels of excitation. This level corresponds roughly to the photopic illumination level in vision.

All of the current flowing through the collector of the adaptation amplifier must be supplied from the electrical power supply. The voltage supplied to the collector varies with both the time constant of the power supply and previous consumption levels. The performance of the power supply is best described using a state variable approach. The current supplied at a given instant is a strong function of the current instantaneous level of excitation and the earlier excitation level and its impact on the performance of the power supply.

Assuming each electron flowing in the adaptation amplifier collector must come from an individual bioenergetic reaction, the consumption of bioenergetic material is a variable that can be computed precisely as in every other active semiconductor circuit employing the avalanche effect. The instantaneous consumption, in terms of electrical charges flowing per incident photon, is very high at low excitation levels following dark adaptation. As the adaptation is changed, the instantaneous consumption for the same amount of excitation will decrease. Upon reaching the photopic level of adaptation, the instantaneous current consumption will now reach a level approximating one electron per photon absorbed.

It is interesting that the effect of the avalanche effect is to reduce the current consumption as a function of the photo-excitation level. This is not the image provided by the notion of a cascade. The avalanche effect provides a large amount of negative feedback in the adaptation amplifier circuit. This is done to stabilize the output level of the photoreceptor cell and not overload the remainder of the neural system of vision at high illumination levels. The role of the bioenergetic materials is to provide the current called for by the performance of the overall circuit. No additional governing mechanism is required to control how much bioenergetic material consumed at this location.

8.6.2.1.6 Unique stereochemical characteristics of glutamic and aspartic acids

By reviewing the pharmacological performance of glutamic and aspartic acid in **Section 18.8.5.3** and the fundamental structures of the common amino acids, an interesting feature appears. These two amino acids are the only dicarboxylic

[71]Lehninger, A. (1972) Op. Cit. Chap. 20, Oxidative degradation of amino acids

amino acids. Because of this feature, they can be described as acidic amino acids. They are the only amino acids exhibiting a negative charge in ionic form. These materials also exhibit an ability to engage in a stereochemical relationship with the phosphoglycerides of the membrane walls. They also show a propensity to lose one of their carboxylic groups through the release of carbon dioxide. The aggregate of these properties shows why these two materials play a unique role in the electrostenolytic powering of the neural system..

Figure 8.6.2-2 shows the detailed stereo-molecular configuration of these materials[72]. Akoev & Andrianov also report on the significant affects on the auditory system of perfusion of the scala tympani with L-glutamic acid and L-aspartic acid at concentrations of 10^{-2} to 10^{-3} M.

8.6.2.2 Underlying physical chemistry of electrostenolytic conversion

The molecular chemistry involved in creating electrical power from metabolites will not be discussed here. However, the concept of "hole" transfer, as an alternative to hydrogen ion transfer, through a membrane is critical to understanding electrostenolytics.

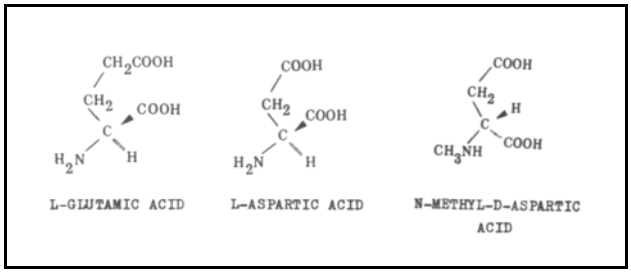

Figure 8.6.2-2 The molecular configuration of glutamic and aspartic acid. From Akoev & Andrianov, 1993.

Gutmann & Keyzer[73] have prepared a comprehensive work on the general subject of bioelectrochemistry but have not addressed the more specific field of electrostenolytics. The most important point is that the use of the electrostenolytic effect, or electrodics in the vocabulary of the above authors, can lead to very high operating efficiencies. The second most important point is that ***the electrodic model of gates in a membrane is a caricature.*** **No physical gates controlling the flow of ions exist in the biological membranes corresponding to this caricature.** The caricature is used to represent the actual chemiosmotic situation for a continuous membrane immersed between two different solutes and porous to electrons and/or holes.

> A hole, if discussed at all in biology, is usually thought of as ionized hydrogen atom moving through a membrane. It is actually the site of a missing electron in a crystalline lattice. This hole is continually filled by an electron at a nearby site jumping into the empty site. The result is the apparent movement of an empty site, a hole, in the opposite direction to normal electron flow. At the terminal surface of the lattice, an electron from a neutral hydrogen or other atom may contribute an electron to fill the hole now on the lattice surface. Similarly, at the other surface, an electron may leave the lattice and become associated with a positively ionized atom, thereby neutralizing it. The net result from an external perspective is the apparent movement of a positive ion through the lattice.

8.6.2.3 The specific energy sources of the neural power supplies

A neuron under cutoff conditions exhibits a high negative axoplasm potential. It also exhibits the highest potential differences between plasmas. The high axoplasm potential suggests that an electrical source of about 150-154 mV (measured at 37° Celsius) is a primary requirement. If necessary, all other potentials can be obtained from this source. Alternately, a lower potential source of about 25-30 mV would be useful in supporting the needs of the neurites of a particular neuron. In both cases, the source must provide a negative potential to the plasma compared with the surrounding matrix.

The glutamate family plays a large role in providing energy for use in animal system. However, the actual chemical reactions involved in powering the neurological system have not been defined previously.

The generic name glutamate is frequently used in pharmacology but is not found in formal biochemistry, except with an anion partner. Although used as a specific term in most discussions of the glutamate cascade theory, it is usually used as a shorthand notation for glutamic acid in other disciplines.

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[72]Akoev, G. & Andranov, Y. (1993) Sensory Hair Cells: Synaptic Transmission. NY: Springer-Verlag pp 98-99

[73]Gutmann, F. & Keyzer, H. (1986) Modern Bioelectrochemistry. NY: Plenum Press

The glutamate family, as defined below, contains a variety of members. They are all obtained ultimately from glucose by using a variety of citrate (Kreb) cycles. The glutamates appear to be derived locally along the neural pathways of the PNS. This ubiquitousness along the peripheral nervous system led to the unfortunate conclusion that it must be a major neurotransmitter of neurology. Later, it was found to be not only ubiquitous, but dominant among the amino acids within the brain cavity of the CNS. However, the literature remains committed to its role as a neurotransmitter. This work recognizes the role of glutamate as a neuro-facilitator and not a neurotransmitter. GABA is the reactive product of electrostenolysis of glutamate. Since its presence tends to inhibit the glutamate/GABA reaction, GABA has frequently been called a neuro-inhibitor. This subject is discussed more completely in **Section 9.4**.

Within the CNS, its presence is so general that determining its origin is difficult. It may be manufactured locally with respect to each neuron, in association with a nearby glia, or more generally within the volume of the CNS. One author has chosen to speak about one or more pools of glutamate within the CNS. However, he does not arrive at a location for such a physical pool.

Finding anything in the literature providing a concise comparison of the physiological metabolism of the neuron with other cell types is virtually impossible. Cantarow & Schepartz has provided a comparison of a variety of cell types (with the notable exception of the neuron)[74]. **Figure 8.6.2-3** places the neuron in perspective with respect to these other types of cells. The neuron exhibits a unique capability associated with the glutamate shunt. This shunt is the source of power for the neural portion of the cell. It is the analog of the putative ion-pump of Hodgkin & Huxley. In the operation of the neuron, most of the activity associated with the Krebs cycle is devoted to supplying power to the signaling function. This activity is so intense that it has been suggested that the typical neuron cannot provide sufficient pyruvate via the glycolysis mechanism beginning with glycogen. The suggestion is that additional lactate is acquired from adjacent glial cells. See **Section 8.6.6.2.3**.

[74]Cantarow, A. & Schepartz, B. (1967) Biochemistry, 4th Ed. London: W. B. Saunders. pg 422

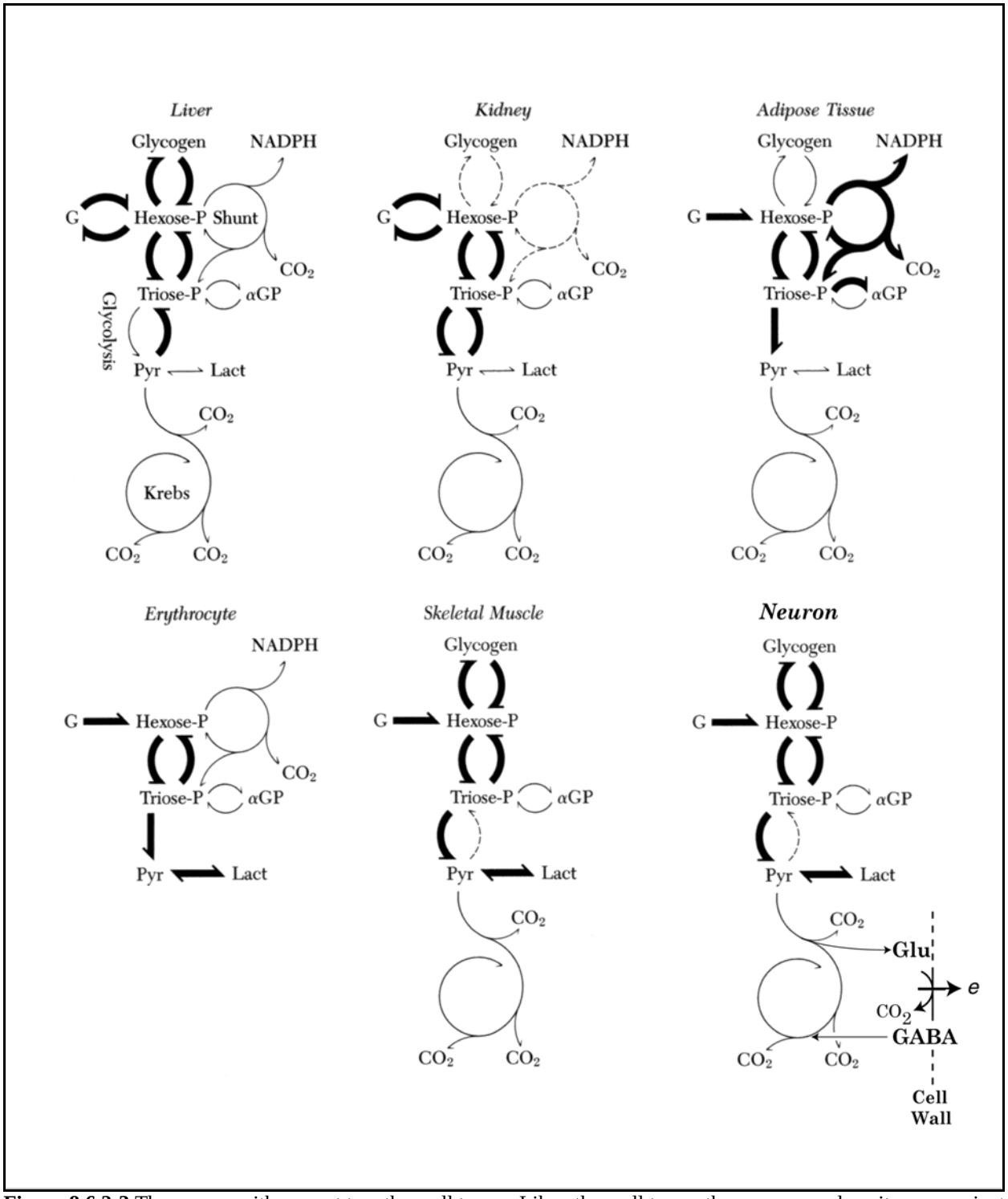

Figure 8.6.2-3 The neuron with respect to other cell types. Like other cell types, the neuron employs its own variant of the nominal glycolysis and tri-carboxylic-acid (Krebs) cycle. The glutamate shunt provides free electrons required to power the signaling capability of the neuron. Modified from Cantarow & Schepartz, 1967.

8.6.2.3.1 Background

White, et. al[75]. provide a variety of electrochemical information related to the energy sources of biochemistry. It includes a table of the free energies of hydrolysis for many compounds of biological interest. Glutamine is shown as releasing 3,400 calories/mole at pH = 7. They also provide a series of electrode potentials of some reduction-oxidation systems. Two values of particular interest are the α–ketoglutaric acid + NH_4^+/glutamic acid system at -140 mV (pH=7) and the α–ketoglutaric acid/ succinic acid + CO_2 system at -670 mV. The first system suggests that changes of about 140 mV are available within the glutamate shunt. The two together suggest that the glutamate to GABA conversion might provide the desired -154 to -140 mV potential.

White, et. al. also provide a flow chart of amino acid metabolism in the brain (pg. 973). The glutamates and GABA play a major role in this flow diagram.

The conversion of glutamic acid into GABA with the release of CO_2 is diagramed in Harper, but no numerical data is provided on the available energy[76]. Pyridoxal phosphate is given as a coenzyme but no other details are given. Harper discusses a variety of reactions involving the glutamates. This aspect of the tricarboxylic acid cycle is described in Hertz using the designation GABA shunt[77]. The ionization constants and pH values at the isoelectric point of glutamic and aparatic acids are given in Pethig[78]. Their isoelectric points are significantly lower than the other amino acids listed. He shows how easy it is to isolate glutamic and asparitic acid in the laboratory based on this factor. He also presents the hydration number for these amino acids and their residues. For the acids, their hydration number is two. Interestingly, the residue of glutamic acid, GABA, is shown as non-polar and without a hydration number.

Puil has provided a massive, well referenced and invaluable paper published in an obscure review[79].

Dowling provides a useful pedagogical description of glutamate and its potential conversion into GABA, aspartate and glycine[80]. No discussion of the mechanisms or energy required to perform these changes is given.

Recently, Korschen has proposed an alternate source of glutamic acid. He has proposed that the glutamates are provided by glutamic acid rich proteins (GARP) that presumably could cross the BBB. This approach is discussed briefly below.

While the treatment of the glutamates in the literature is large, little attention appears to have been placed on the stereochemistry of the family. In this work, this is a key mechanism that appears to eliminate the need for enzymatic mechanisms in the process of providing electrical power.

8.6.2.3.2 The potential reactants in neural electrostenolytics

Having a ready reference to the chemical structure of the material important to this section is helpful. **Table 8.6.2-1** presents several equations and formula, taken mostly from Lehninger, that should be helpful.

> Puil has provided an extensive list of analogs and chemicals closely associated with the glutamates (pp 304-6). His discussion of their actions is extensive. See **Section 8.7.3**.

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[75]White, A. Handler, P & Smith, E. (1973) Principles of Biochemistry, 5th ed. McGraw-Hill Chapters 14, 15, 23, & 25 [my library]

[76]Harper, H. (1975) Review of Physiological Chemistry, 15th ed. Los Altos, CA: Lange Medical Publications. pg 377

[77]Hertz, L. (1969) The biochemistry of brain tissue *in* Bittar, E. & Bittar, N. *eds*. The Biological Basis of Medicine NY: Academic Press pp 20

[78]Pethig, R. (1979) Op. Cit. pg 73

[79]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res. Rev*. vol. 3, pp 229-332

[80]Dowling, J. (1992) Neurons and Networks. Cambridge, MA: Harvard University Press, pg 143

The transition from the simple blood sugar, glucose to the glutamates is described conceptually in McGeer, Eccles & McGeer as a variant of the tricarboxylic acid cycle[81]. Their paragraph on page 177 is quite enlightening. Although they are discussing glutamate from the perspective of a known neurotransmitter, they note its unusual characteristic in that it is not exclusively a neurotransmitter and appears to be used for other functions.

McGeer, Eccles & McGeer have provided considerably material on the glutamates and GABA. They note that "Glutamate and aspartate are nonessential amino acids that do not cross the blood-brain barrier (BBB); therefore, they are not supplied to the brain by the blood. Instead, they are synthesized from glucose and other precursors by several routes." These routes have been described by many authors, usually using top-level block diagrams because of their complexity. These diagrams are frequently accompanied by considerable text to describe all of the enzymatic activity involved. They suggest that GABA is also prepared from glucose and that its location of highest concentration within the retina is near the ganglion cells. It could be prepared by virtually the same process as glutamic acid. A feature of glutamate generation is that all of the steps involve carbohydrates up to the point where α-keto-glutaric acid is converted to L-keto-glutamic acid (α-amino glutaric acid) by the introduction of an amine group. Their findings would suggest that the glutamates may also be formed within the retina and along the neural pathways throughout the body rather than being supplied by the blood.

[81]McGeer, P. Eccles, J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain. NY: Plenum Press. pg 177

TABLE 8.6.2-1
Bio-energetic compounds of interest

Abbrev.	Name	Formula	Comment
GABA	γ-Aminobutyric acid	$CH_2CH_2CH_2COOH$ $\vert$ NH_2	See note *
	Glutamic acid	$COOH\text{-}CHCH_2CH_2COOH$ $\vert$ NH_2	α-amino glutaric acid. Also known as glutamate in pharmacology **
L-Dopa	L-Dopa	$COOH\text{-}CHCH_2(C_6H_3\text{-}(OH)_2)$ $\vert$ NH_2	3,4-dihydroxyphenylalanine (See other names in text)
MSG	Sodium glutamate	$COOH\text{-}CHCH_2CH_2COONa$ $\vert$ NH_2	
	Glycogen	$(C_6H_{10}O_5)_n$	Ultimate source of glutamates
	Glycine	$HCHCOOH$ $\vert$ NH_2 or $HCH\text{-}COO^-$ $\vert$ NH_3^+	
	Glutamine(1)	$O{=}C\text{-}CH_2CH_2CHCOOH$ $\vert \quad\quad \vert$ $NH_2 \quad NH_2$ or $CH\text{-}COO^-$ $\vert$ NH_3^+	
	Glutamine(2)	$NH_2\text{-}C\text{-}CH_2CH_2CHCOOH$ $\Vert \quad\quad\quad \vert$ $O \quad\quad NH_2$	
AKGmA	α-Ketoglutaramic Acid	$NH_2\text{-}C\text{-}CH_2CH_2CCOOH$ $\Vert \quad\quad \Vert$ $O \quad\quad O$	Amide of AKGA, one NH_2
AKGA	α-Ketoglutaric Acid	$COOH\text{-}CH_2CH_2CCOOH$ $\Vert$ O	
	Glutaraldehyde	$OHC\text{-}CH_2CH_2CCOOH$ $\Vert$ O	?? $OHC\ (CH_2)_3COOH$

Glutaric Acid	$COOH\text{-}(CH_2)_3COOH$
Succinic Acid	$COOH\text{-}CH_2CH_2COOH$
Succinic semialdehyde	$OHCH_2CH_2COOH$
Citric Acid	$COOHCH_2C(OH)(COOH)CH_2COOH$

* "$GABA_A$ receptor" refers to a "GABA Receptor" of type A. The receptors are putative proteins on the surface of neurites that are intimately related to GABA. This work does not recognize such sites as necessary.
** Technically a glutamate is a salt or ester of glutamic acid. Glutamate without a prefix is a historical name that describes the radical of glutamic acid. It generally refers to glutamic acid in the biological sciences and pharmacology.[82] Glutamic acid can be described as α-amino glutaric acid under the IUPAC rules. Bending the rules slightly would suggest the name γ-amino glutaric acid is equally representative.

GABA is not a true amino acid. It does not exhibit an amino acid group. Nor does it exhibit the properties of an amino acid. The word amino in its name refers to the amine group associated with the gamma carbon. At best, it can only be considered a stereoisomer of aspartic acid, a true amino acid. GABA is not believed to occur as a constituent of proteins. Glutamine is easily formed from glutamic acid. The two forms of Glutamine shown are merely to adapt to two-dimensional paper. They are the same compounds. Glutamine is easily hydrolyzed to produce glutamic acid (glutamate) and NH_4^+. AKGA is an intermediate form frequently mentioned in discussions of the other materials. These materials are all complex enough to support many different electronic configurations and participate in reactions involving transitions between their different electronic isomers.

The formation of many of these compounds from GABA, a natural amino acid, is quite straightforward and documented in many texts dealing with the nutritional aspects of biochemistry. The consumption of these materials as a part of metabolism is less widely discussed. Their metabolism plays a key role in the operation of the neural system through the electrostenolytic process.

When employed in an electrostenolytic process, the above materials can be used to create an electrical potential. The hydrolysis of Glutamic acid to form GABA releases one molecule of CO_2 and energy. The energy is expressed as an electrical potential across a cell wall. The cell is said to be polarized. This polarization can cause the migration of simple ions or fundamental charges through the cell wall to alleviate the degree of polarization.

Whether ions are actually able to pass through the bilayer-membrane forming the plasma membrane, at a given location, is yet to be demonstrated. Where the membrane is enclosed within myelin, the subject is largely academic. The continual presence of the reactants on one side of the cell wall will result in a continuous polarization of the cell.

[
The key portion of the above equation, with regard to the neurological system, is the conversion of glutamate to GABA with the concurrent release of a free electron at the inner surface of one of the external walls of an individual neuron (an electrostenolytic mechanism). The rate of the production of free electrons is directly related to the concentration of glutamate and GABA at the surface of such a electrostenolytic mechanism. Under normal conditions, the above percentages are typical. The presence of 5-5% glutamate and 1.5-3% GABA result in a typical neural axon potential, under cutoff conditions, of between 150 and 154 mV. Variations in these concentrations can be looked upon as an impedance to the progress of the reaction **OR** a reason to reverse the reaction.
]

8.6.2.3.3 Fundamental reaction of the electrostenolytic process

Providing the electrical power required by an individual plasma of a neuron appears to involve three steps. First, the reactant material must be transported to the appropriate specialized site of the neurolemma and allowed to unite with that site (substrate) stereo-chemically. Second, the reactant must react, releasing carbon dioxide and injecting an electron

[82]Dowling, J. (1992) Pg. 143

through the electrically asymmetrical lemma into the adjoining plasma. Third, the reaction product must be released from its stereochemical relationship with the substrate and removed from the site.

The basic electrostenolytic reaction supporting the supply of electrical power to each plasma of each neuron is shown in **Figure 8.6.2-4** The reaction occurs on the surface of the lemma, surrounding the plasma, acting as a substrate. It appears that the glutamic acid molecule attaches itself stereo-chemically to the substrate via the carboxyl group farthest from the amine group. Although McIlwain & Bachelard speak of an enzyme (decarboxylase, pg 167) catalyzing the glutamate to GABA reaction, it is not clear any enzymatic support is required in the presence of a substrate. The process releases one molecule of carbon dioxide for each molecule of glutamic acid converted to GABA. Simultaneously, the process injects a free electron into the plasma on the opposite side of the lemma forming the substrate. The GABA is then released from the substrate. As discussed in **Section 18.8.5.3**, this reaction may operate with aspartic acid as the initial reactant. While CO_2 is still released, the other residue changes accordingly. Selinsky noted the close relationship formed between aspartic acid and the choline headgroup of the membrane[83]. "These interactions range in strength from several kcal/mol for charge-charge interactions, as might occur between a charged amine headgroup such as choline with a negatively charged amino acid side chain such as aspartic acid, . . ." It is proposed the same relationship exists between BLMs and the "other" negatively charged amino acid, glutamate. The introduction of L-Dopa into the blood stream is found to have beneficial results in Parkinson's Disease and possibly in nystagmus. It appears it replaces, or blocks the participation of, glutamic acid (and aspartic acid) in at least some of the electrostenolytic reactions supporting the neural system.

8.6.3 The sources of glutamic acid

The "blood/brain" barrier plays a crucial role in understanding the potential sources of the glutamates. The glutamates must be available to neurons both within the CNS and along the length of the PNS. Because the literature says the glutamates cannot cross the blood/brain barrier, the above requirement suggests that it must be synthesized within the immediate vicinity of each neuron.

At least three alternate sources of the glutamates have been proposed in the literature. One involves the synthesis of glutamic acid from glycogen, via a Kreb cycle. The second would create the glutamates from other complex molecules via a variant of the Krebs cycle. This method is particularly awkward because of the multiple variations presented in the literature. The third involves the local decomposition of proteins. This section will rationalize some of this material.

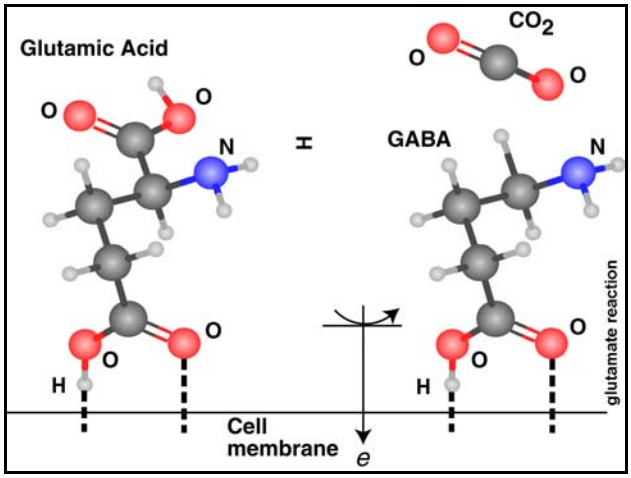

Figure 8.6.2-4 The fundamental electrostenolytic process powering the neural system. Glutamic acid becomes associated with the cell membrane in a highly selective stereo chemical relationship (dashed vertical lines). A reduction then occurs. The process releases carbon dioxide as shown. It also injects a free electron into the plasma on the other side of the cell membrane. GABA is then released from the stereo-chemical bond.

8.6.3.1 Glycogen as the principal source of glutamate

Fonnum provided a comprehensive review of potential sources of glutamate in 1984[84]. Unfortunately, his discussion was limited to text. He defines two different "compartments" for the processing of glucose. The compartments appear to process glucose through two different versions of a citrate (Krebs) cycle. Under normal conditions, the glucose metabolized in the large glutamate

[83]Selinsky, B. (1992) Protein-lipid interactions and membrane function *In* Yeagle, P. Op. Cit. pg 607

[84]Fonnum, F. (1984) Glutamate: a neurotransmitter in mammalian brain *J. Neurochem.* Vol. 42, no. 1, pp 1-11

"compartment" results in large amounts of glutamate and lesser amounts of glutamine. Alternately, the glucose metabolized in the small glutamate "compartment" results in a higher percentage of glutamine. He references other work that states the large compartment contains 85-90% of the total glutamate pool in brain.

Defining the above compartments becomes another matter. Fonnum speaks of two sub-compartments supporting the production of glutamate. One is for glutamate as a neurotransmitter. The second is for glutamate destined to react and form GABA. McGeer, et. al. comment that, "Unfortunately, it has not yet been possible to associate definitively any of these metabolic pools [compartments] with anatomical structures such as neurons, or glia or with distinct glutamate or aspartate neuronal systems."[85] Fonnum closes with the observation that "the relative contribution of glutamine or glucose to transmitter glutamate in-vivo remains an open question." In this work, based on the electrolytic model of the neural system, glutamate as a neurotransmitter is not necessary. The processing of glutamate into GABA occurs in the normal electrostenolytic process of powering the neural system.

Recalling that glutamate and GABA are ubiquitous in the peripheral nervous system is important. Conceptualizing unique compartments where glutamate is found may not be necessary. It is also important to note Fonnum's comment that until about 15 years ago, ". . . it was at first difficult to believe that glutamate could be a neurotransmitter." This work will show glutamate is not a neurotransmitter as defined within the chemical theory of the neuron. It is more appropriately described as a neuro-facilitator within the electrolytic theory of the neuron.

Fonnum briefly addresses the formation of glutamate from glutamine, possibly from that formed via the small compartment defined above. In that case, the original source would still be glucose, despite the citrate cycle used.

McGeer, et. al. note that glutamic acid is the precursor of GABA and that glutamic acid can be formed from either glutamine or α-ketoglutarate (pg 198). These are only two of the potential precursors of glutamate. The literature contains many "Krebs Cycles" which could be used to create glutamate from glucose. Fonnum lists three routes[86]. The paths of Fonnum and of McGeer, et. al. typically suggest 8-10 precursors between glucose and glutamate and a large variety of accompanying enzymes facilitating the individual reactions. Lehninger illustrates about a dozen paths from various amino acids or intermediaries to glutamate.[87] Enumerating the ways of forming glutamate appears to be primarily an intellectual exercise.

The best description of the method of forming glutamate, and eventually GABA, appears to be that shown in McIlwain & Bachelard. They injected radio-nucleotide labeled glucose into cerebral tissue and observed the distribution of the nucleotides in various compounds after one hour. Their figure 4.7 is reproduced as **Figure 8.6.3-1**. Although this is a transient measurement, it can be compared with their table 8.1 of steady state concentrations. The concentrations are consistent between the two data sets. Paul notes the concentration of GABA in vertebrate CNS can reach millimolar levels[88]. The figure supports the first claim in the following quotation from Hertz[89]. "This concept is in agreement with the finding that pyruvate and lactate is almost as effective a substrate as glucose in the maintenance of not only the resting and the stimulated respiration, but also of a reasonably high concentration of energy-rich phosphates." Ruscak & Ruscakova have provided compatible data from a variety of investigators on the ratios found in rat brains for glutamic acid, GABA and glutamine[90]. They have also commented more positively on the relative permeability of the blood-brain-barrier by glutamic acid.

Lehninger lists nine steps, in two stages, in the conversion of glucose into pyruvate (pg 316). The reversible reaction to form lactate is a major method of intermediary storage. Only a few steps are needed to go from pyruvate to citrate

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[85]McGeer, P. Eccles, Sir J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain, 2nd ed. NY: Plenum, pg 177

[86]Fonnum, F. (1984) Op. Cit. pg 1

[87]Lehninger, A. (1970) Biochemistry. NY: Worth Publishers, pp 445-452

[88]Paul, S. (1995) GABA and glycine *Chapter 8 In* Bloom, F. & Kupfer, D. *ed*. Psychopharmacology: the Fourth Generation of Progress. NY: Raven Press pg 87

[89]Hertz, L. (1969) Op. Cit. pg 21

[90]Ruscak, M. & Ruscakova, D. (1971) Metabolism of the nerve tissue in relation to ion movements in vitro and in situ. Baltimore, MD: University Park Press pp 85-98

via the Kreb cycle. Typical descriptions of this cycle begin with citrate at the top of the loop and rely upon an extension to glutamate. This glutamate shunt is shown in Figure 6.1 of McGeer, et. al. Nomenclature remains a problem in this area. McIlwain & Bachelard use the designation α-oxoglutarate while McGeer, et. al. use α-ketoglutarate and Fonnum uses 2-oxoglutarate for the same material. The reaction of glutamate to GABA is not addressed in Lehninger since it is not a metabolic step in his context. However, it is the fundamental step in powering all neurons.

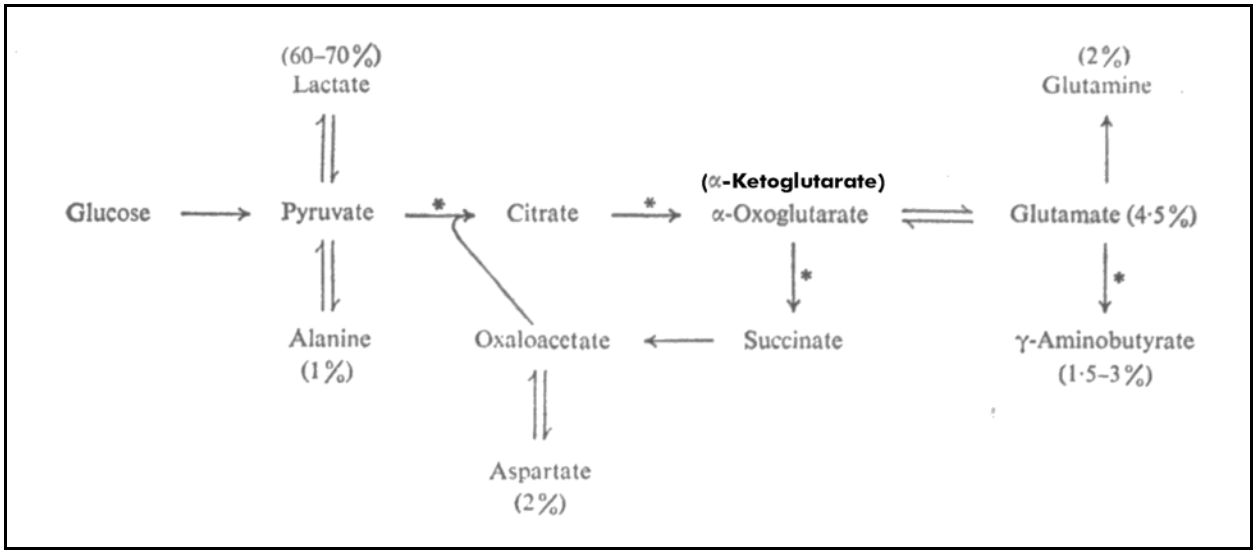

Figure 8.6.3-1 Distribution of nucleotide labeled material one hour after labeled glucose was introduced into cerebral tissue. The asterisks indicate the release of carbon dioxide (in total, about 20% of the labeled material). From McIlwain & Bachelard, 1985.

In brief, the general plan begins with conversion of glucose into pyruvate and then a citrate leading to α-ketoglutarate. The α-ketoglutarate is then converted to glutamate. The electrostenolytic reaction converts this glutamate into GABA and carbon dioxide. Any enzyme or other chemical impacting (either positively or negatively) on the supply of glutamate or the removal of the reaction product GABA, relative to their normal concentration near a neuron, can be considered an important neuro-facilitator or neuro-inhibitor. Such a facilitator or inhibitor indirectly affects the operation of the neural system.

8.6.3.1.1 Fundamental steps leading from glucose to glutamic acid

While glutamic acid can be obtained from nearly any simple sugar, it is usually obtained from glucose, or glucose stored as the polysaccharide glycogen. Obtaining glutamic acid from glucose involves three and one-half major stages of biological chemical processing.

Stage one involves the collection of the simple sugars and their conversion into glyceraldehyde. Glucose, the formal name for the dominant constituent being α-D glucopyranose, is converted to glucose 6-phosphate by hexokinase and then to fructose 6-phosphate. The fructose 6-phosphate is then converted to D-glyceraldehyde-3-phosphate.

Stage two requires six steps to convert the D-glyceraldehyde-3-phosphate into pyruvate and then into acetyl CoA, a very complex thioester of acetic acid and a very complex enzyme known as coenzyme A.

Stage three introduces acetyl CoA into a tri-carboxylic-acid cycle (alternately citrate cycle or Kreb cycle) that can produce a variety of biochemicals including α-ketoglutarate. A shunt associated with this cycle, and labeled stage 3.5 here, is used to produce glutamic acid. The steady-state compositions of these materials found in the brain are shown

in the above figure.

A more detailed discussion of these chemical processes appears in **Section 15.1.8**.

8.6.3.2 Protein as a potential source of glutamate–the GARPS

A protein-based source of the glutamic acid supporting the above reactions has recently been proposed by Korschen, et. al[91]. While their configuration (based on the existence of a lemma surrounding the outer segment of the photoreceptor) and their concept of the gated cGMP channel are not supported in this work, their physical chemistry deserves review. They define "an unusual set of glutamic-acid-rich-proteins (GARPs) of unknown function." Because their starting assumptions are so different, interpretation of their data may be difficult. However, several features of their work standout. First, the materials were found to congregate intimately with the outer segments of the "rod photoreceptors" and were not found close to "cones." This would be consistent with the premise of this work that the so-called cone is a non-functional or immature photoreceptor.

Second, the materials were found within the notches along the periphery of the outer segment, the precise location of the microtubules (neural dendrites) of the inner segment. Korschen, et. al. state: (the italics have been added)

+ The (*morphological*) rod photoreceptors in eyes contain an unusual set of glutamic-acid-rich proteins (GARPs).

+ No similar material was found near the (*morphological*) cones.

+ The GARPs are found along the rim and in the furrows of the disks. (*micrographs provided*)

+ The GARPs contain many GLU residues.

Third, the GARPs were found in two forms, "GARP2 lacks the carboxyl-terminal glutamic-acid-rich region." This feature and the proposition that electrostenolysis of glutamate acid to GABA is key to neuronal activity, would suggest that GARP1 is in fact a glutamic-acid-rich-material. However, GARP2, without a carboxyl group attached to each glutamate, would be more appropriately described as a GABA-rich-material (GABARP). This proposition would lead to the question of whether the GARPs are actually proteins or other large molecular complexes. Such complexes would have a ratio of molecular weights of 147:103 just due to glutamate in the former and GABA in the latter. Korschen, et. al. report a ratio of GARP1 to GARP2 of 130K:62K.

Korschen, et. al. also note the materials are highly soluble in hypotonic solution. Soluble GARPs reassociate completely with membrane, and GARPs are tightly bound to a membrane under physiological conditions.

They conclude their extensive paper with a question, "What is the function of GARPs?"

Their analysis focuses more clearly on the submicroscopic location of the reactants associated with the neural power system than earlier studies. However, they obviously have not determined the role of the material in these locations.

If the GARPs are the source of the glutamates, it is proposed that the GARPs are the source of energy for the neural system in general. They would be broken down as required and the residues would react electrostenolytically to produce GABA and carbon dioxide. In this process, they create an electrical potential across the plasma membrane acting as a substrate. In this interpretation, the GARPs should be found located along the furrows of the disks since that is where the dendrites (microtubules) of the neural portion of the photoreceptor cells are found. The fact that the material is found in these regions is documented in figure 4 of Korschen, et. al. They show a caricature in figure 5 that suggests the GARP material is located near a putative plasma membrane surrounding the disks. However, their electron micrographs do not support the presence of a surrounding plasma membrane, either directly by resolving them or indirectly by an accumulation of GARP where the membrane would be found. An alternate caricature is shown in [**Figure 4.3.5-6**] based on the discussions in **Section 4.3.5**. In that figure, the GARP is associated with the specialized electrostenolytic surface of the dendrites. Based on figure 1 of Korschen, et. al., it appears that GARP1 reacts to release glutamate, the glutamate reacts electrostenolytically with the membrane acting as a substrate, and the residue of GABA is reincorporated into GARP2 (GABARP) and carbon dioxide is released into the surrounding matrix.

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[91]Korschen, H. et. al. (1999) Interaction of glutamic-acid-rich-proteins with the cGMP signaling pathway in rod photoreceptors *Nature*, vol. 400, pp 761-766

Under the above scenario, the GARPs may consist of a protein moiety capable of binding a large fixed number of glutamate or GABA molecules in a loose stereochemical relationship. This material might act as an intermediate substrate for collecting the material required for electrostenolysis and providing local storage. They might also contribute to the regeneration of glutamic acid from GABA. **Section 15.1.8** addresses this subject further.

8.6.3.3 Probable reconstitution of glutamic acid

McIlwain & Bachelard provide an additional discussion of potential Kreb cycle operations that could regenerate glutamic acid[92]. GABA is easily converted to succinic semialdehyde through transamination. This chemical is a participant in the Kreb cycle originally used to create α-ketoglutarate and then glutamic acid (see **Section 8.6.3.1** and **Section 8.6.6**).

Lake, Marshall & Voaden[93] have discussed a "glutamate pool" within the retina and shown, using radioactive labeling, that GABA is converted into glutamine within this pool. They indicate the initial site of uptake of exogenous GABA varied by species. It was the Muller fibers (glial cells) within the retina of mammals, e.g., rat and cat. The site was the actual neuron of the retina in the non-mammalian frog and pigeon. However, these results from autoradiography are not as specific as could be obtained via more modern techniques. They also introduced labeled glutamine into retinal tissue. They found it was converted to 30% glutamate, 30% GABA and 30% glutamine after 25 minutes. After 55 minutes, the material was 60% GABA and 10% glutamine with 30% unaccounted for. These experiments disturb the normal concentrations of these chemicals. Thus, they do not necessarily represent the normal conditions in the specimen. It is interesting that all of the above animals are chordates. Further study is needed to determine whether GABA is actually absorbed into these cells or is merely accumulated on or near the surface of the cells.

There is every likelihood that glutamic acid is consumed in electrostenolysis and reconstituted by a short loop near the point of electrostenolysis. It may proceed as suggested by Lake, et. al:

glutamic acid –>GABA–>glutamine–>α-ketoglutaramic acid–>glutamic acid

Glutamine contains two NH_2 groups. It may be unnecessary to go to this point in the reconstitution of glutamic acid. An alternative approach would eliminate the glutamine step with the re-carboxylation of the GABA to α-ketoglutaramic acid followed by hydrogenation to glutamic acid. Any glutamine produced from GABA would then be incidental to the reconstitution process.

Either process probably remains totally anaerobic.

8.6.4 Metabolic processes related to the operation of the neuron

The creation and delivery of glutamate (glutamic acid) to the site of electrostenolysis, and the removal of the waste products, are key to the polarization of all living cells. These processes are generally grouped under the label metabotropic processes. The production of glutamate is a complex process performed in glia cells, and to a limited extent in neural cells, throughout the animal organism in support of the neural system. The production process involves a variant of the Kreb Cycle generally described as the glutamate shunt. The process begins with glycogen and produces glutamic acid (glutamate). This process requires the availability of, or the creation of, many intermediaries.

Glycogen is the primary source of energy for the cell. The complete degradation of a single molecule of glucose, the basic unit of the glycogen polymer, to CO_2 and H_2O releases a great deal of energy (686 kcalories). The energy associated with glucose and the quantized method of its release are key to the efficient operation of the neuron. The energy is usually released in units of 7.3 kcal through reactions involving ATP and other enzymes. The reaction of interest here, the electrostenolysis of glutamate to CO_2 and GABA involves an energy change of about 14.6 kcal. This value generates a maximum negative potential of 154 mV across the lemma of a cell (or a conduit). This is also the

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[92]McIlwain, H. & Bachelard, H. (1985) Op. Cit. pp 168-180

[93]Lake, N. Marshall, J. & Voaden, M. (1977) Metabolic compartmentation and the metabolism of GABA and glutamine in retina: A species comparison. *In* Synapse, Cottrell & Usherwood ed. London: Blackie pg.354

observed cutoff potential associated with individual axoplasms of the neural system.

A special variant of the citric acid cycle is used by the neural system to create smaller units of chemical energy than normally associated with ATP and similar units of chemical energy. This variant is called the glutamate shunt. Its purpose is to generate glutamic acid (glutamate) efficiently beginning with the precursor glucose and using GABA as an alternate source when it is readily available. The details of the glutamate shunt are discussed in **Section 8.6.2.3**.

To obtain glutamate from glucose involves the glycolysis of glucose to either pyruvate or lactate followed by two additional steps. The first involves the tri-carboxylic-acid (Krebs) cycle (abbreviated TCA) and the creation of alpha-ketoglutarate. This material can be readily converted into glutamate by amination. The process is carried out in the glutamate shunt to the TCA cycle. **Figure 8.6.4-1** illustrates this little known variant of the Krebs cycle. Also shown is an available glutamate regeneration path. The literature also describes a process for generating glutamate from glutamine. A broad discussion of this cycle appears in the website documentation.

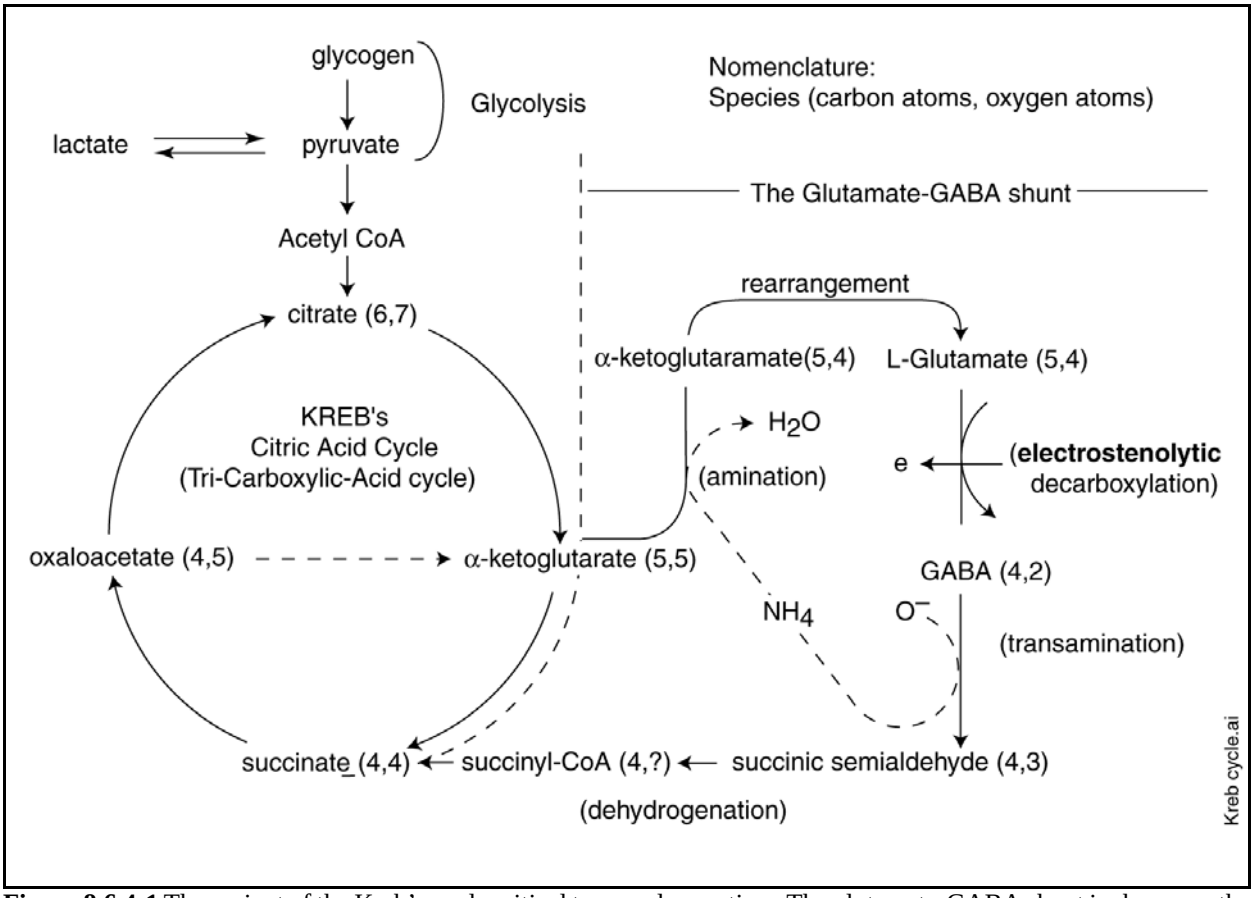

Figure 8.6.4-1 The variant of the Kreb's cycle critical to neural operation. The glutamate-GABA shunt is shown on the right. An available glutamate regeneration path is shown at lower right.

The reason both pyruvate and lactate are mentioned is because of their different properties. While they are easily interconverted, lactate moves easily through cell walls whereas pyruvate does not. There are suggestions in the literature that some neurons have limited capacity to prepare pyruvate and deliver it to the point of use along the axon. It is suggested that glia may generate excess lactate that can easily be transferred through the necessary cell walls to support the axon segments found far from the soma of a propagation neuron. In large animals like humans, individual stage 3 neurons may be one to a few meters long. The supply of lactate by glia cells could substantially reduce the axoplasmic transport of pyruvate and other materials from the soma to the remote axon segments of the neuron.

Figure 8.6.4-2 shows an expanded view of the area surrounding a stage 3 neuron, including the Activa embedded within the soma (the solid black rectangle on the left) and the Node of Ranvier (the solid black rectangle in the center). The

metabotropic steps of primary interest in neuron signaling, discussed above, are illustrated in this figure.

The solid arrows show the absorption of glycogen from the bloodstream by a neuron and a glial cell. Glycolysis is shown taking place in both cells. The process proceeds to pyruvate in the soma of the neuron. This material is transferred within the cell to the ribosomes. The ribosomes use the TCA cycle to prepare glutamate that can be used to support the electrical power generating electrostenolytic process. These ribosomes are found near every electrolytic conduit of the neuron. To reduce the need to transport pyruvate along the length of the axon, glia cells are shown preparing lactate that can be diffused into the capillary bed and across into the neural cell. Once within the cell, this lactate can participate in the TCA cycle and contribute additional glutamate to the electrostenolytic process. The glutamate passes freely through selected regions of type 3 lemma of the neuron. The glutamate participates in electrostenolysis at regions of type 2 lemma on the external surface of the conduits of the neuron. The electrostenolytic process will seek to maintain a constant electrical potential within the conduit it is supporting compared with the outside of the conduit.

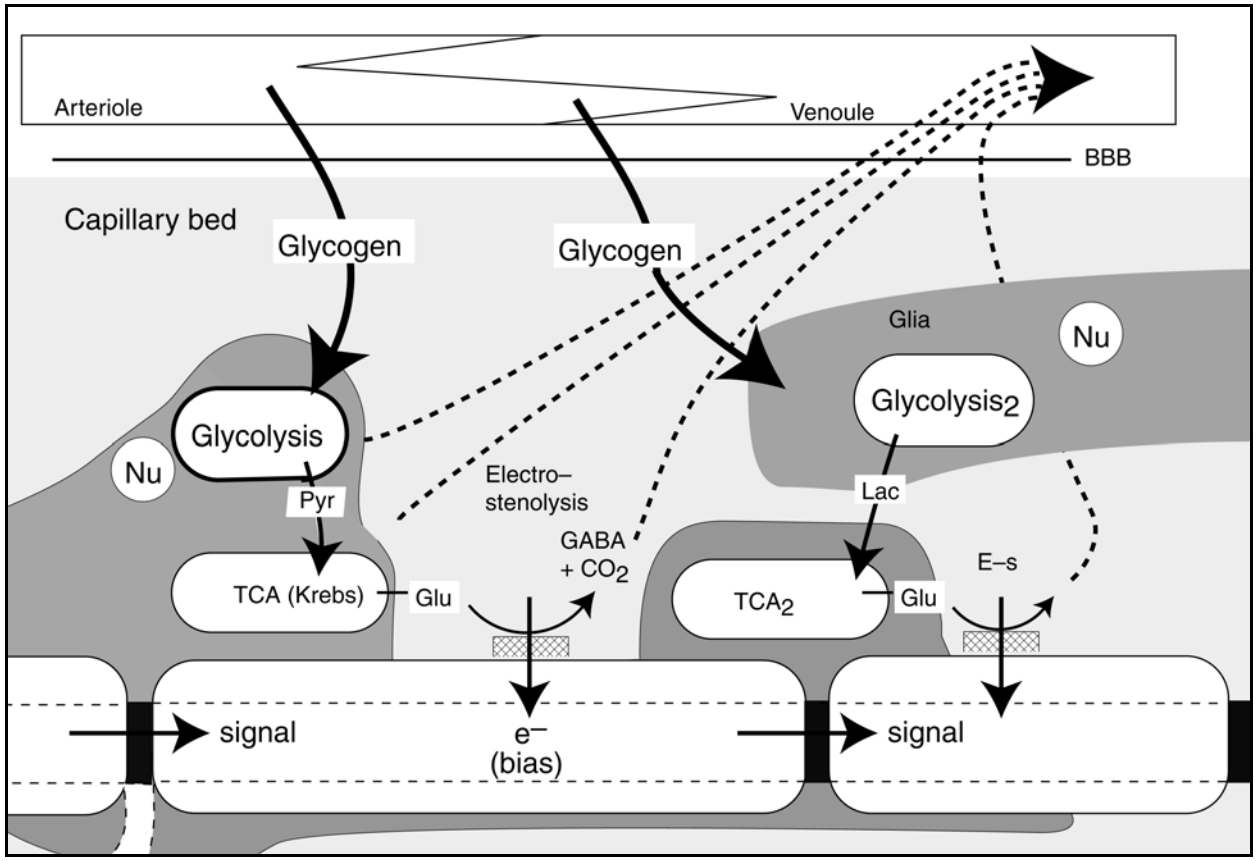

Figure 8.6.4-2 Details of the metabotropism and hydraulic flow of the neuron. It is highly likely that the glia supply lactate to the remote sites of glutamate production (TCA_2). Waste product removal is represented by the dashed arrow. The transport of glycogen, GABA and CO_2 through the capillary bed and INM can be affected by many neuro-facilitators and neuro-inhibitors.

Electrostenolysis of glutamate produces CO_2 and GABA. These materials must be removed from the immediate vicinity of the electrostenolytic process to avoid interfering with the ongoing process. The CO_2 is diffused to the venule system as part of the respiration process. GABA may be removed in a similar way. However, GABA can be reused as indicated above.

The most extensive information on the presence of L-glutamate and GABA in and near the neural system is provided in Chapters 2 & 3 of Hockman & Bieger[94]. Johnston, writing in Chapter 2, found it difficult to explain how GABA is chemically formed within the CNS in order to participate as a neuro-inhibitor. He did discuss the "glutamate shunt" discussed here under the label "GABA shunt." While not appreciating its significance he did note the major known path of GABA formation. "GABA appears to be synthesized essentially by only one enzymatic activity, glutamine decarboxylase which catalyzes the irreversible decarboxylation of L-glutamate to GABA." He clearly did not consider that the major source of GABA might be a reaction product of L-glutamate electrostenolysis. Usherwood, writing in Chapter 3, provides extensive data on the presence of amino acids within the animal system. He distinguishes between the metabolic and metabotropic role of glutamate and also notes the neuro-facilitating action of topical application of L-glutamate to neurons.

Godfrey et al. have provided data on the concentrations of glutamate, aspartate and GABA in the cochlea of the guinea-pig[95].

Sutherland et al. have recently addressed the genetic relationships that may (at least partially) control the flow of reactants in the above figure[96]. As a minimum, their paper expands the above model at the detail level.

8.6.4.1 The crystallography of the glutamate receptor, mGluR

The field of crystallography provides very useful information confirming the Electrolytic Theory of the Neuron. It can describe mechanisms operating at the molecular and enzymatic level on the surface of neural tissue.

Kunishima et al. have provided very detailed information concerning the molecular structure of the principle glutamate receptor, now known as mGluR1. It is used to support the operation of this amino acid in its role as the primary neuro-facilitator of neuron operation, although Kunishima et al. label glutamate using the less descriptive and archaic label of neurotransmitter.

Figure 8.6.4-3 illustrates the functional role of mGluR at the histological and molecular level in its metabotropic and electrostenolytic roles supporting the electrical polarization of the neuron. Based on their crystallography perspective, Kunishima et al. describe the asymmetric unit of their crystal forms as consisting of a dimer containing two identical protomers. They are connected by a disulfide bond in their asymmetric unit. LB1 and LB2 represent the amino-terminal and the carboxy-terminal of each protomer. The numbers in (a) relate to the peptide positions in the primary structure of the protein. In frame (b), the two yellow regions represent individual glutamate molecules initially. While the mGluR molecules may form a liquid crystalline structure on the surface of the neural lemma, it is not clear that a pseudo-twofold axis is present in this functional configuration. The precise structure of the dotted regions is not developed in the paper.

The cysteine associated with the cysteine-rich area of the molecule, is rich in sulfur. While sulfur has many unpaired electrons, even when paired with hydrogen and combined with the peptide core elements of the molecule, its role in the electrolytic operation of the molecule has not been explored in this work. Similarly, the portion of the receptor molecule between peptide 599 and 1199 has not been evaluated based on its crystallographic representation. Whether this portion of the receptor is compatible with a transmembrane role relative to the lemma of a neuron is unknown.

Their figures 1c, 1d and 2, are of considerable value in understanding the detailed secondary structure of mGluR and in the comparison of mGluR with other members of the mGluR family[97]. However, it is not relevant to this discussion.

The Nakanishi paper is also largely irrelevant to this work. It does define three categories of glutamate receptors potentially used throughout the body. The third of these categories can be divided into ionotropic and

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[94]Hockman, C. & Bieger, D. eds. (1976) Chemical transmission in the mammalian central nervous system. London: University Park Press

[95]Godfrey, D. Wiet, G. & Ross, C. (1986) Quantitative histochemistry of the cochlea *In* Altschuler, R. Bobbin, R. & Hoffman, D. *eds*. Neurobiology of Hearing: the cochlea. NY: Raven Press pp 149-160

[96]Sutherland, M. Delaney, T. & Noebels, J. (1996) Glutamate transporter mRNA expression in proliferative zones of the developing and adult *murine* CNS *J Neurosci* vol 16(7), pp 2191-2207

[97]Nakanishi, S. (1992) Molecular diversity of glutamate receptors and implications for brain function *Science* vol 258, pp597-603

metabotropic branches. He divides the metabtropic branch into six receptors and merely sketches their characteristics and applications. He used the term functional in the limited teleological sense of chemistry, chemicals having similar traits or purposes. He does not use functional in the more important sense of its role within a process or mechanism of biology. He does make the following very significant assertion, "The six mGluRs are considerably larger than the other members of the G protein-coupled receptor family but show a common structural architecture with a large extracellular NH_2-terminal domain that precedes seven transmembrane segments. However, no sequence homology is observed with any other members of the G protein-coupled receptor family. He goes on, "The mGluRs thus represent a novel subfamily of the G protein-coupled receptor family." In fact, they may not be associated with the G protein-coupled receptor family in any way based on the Kunishima et al. paper. Kunishima et al. also demonstrate negligible homology between the primary structure sequence of this "family" of receptors. mGluR1 and mGluR5 show the most homology with a commonality of only about 75%. Nakanishi summarizes his position at the end of his discussion in 1992, "The physiological role of mGluRs is not well understood, but recent evidence has indicated many potential regulatory functions of mGluRs in the CNS." His subsequent "Conclusions" are largely speculative.

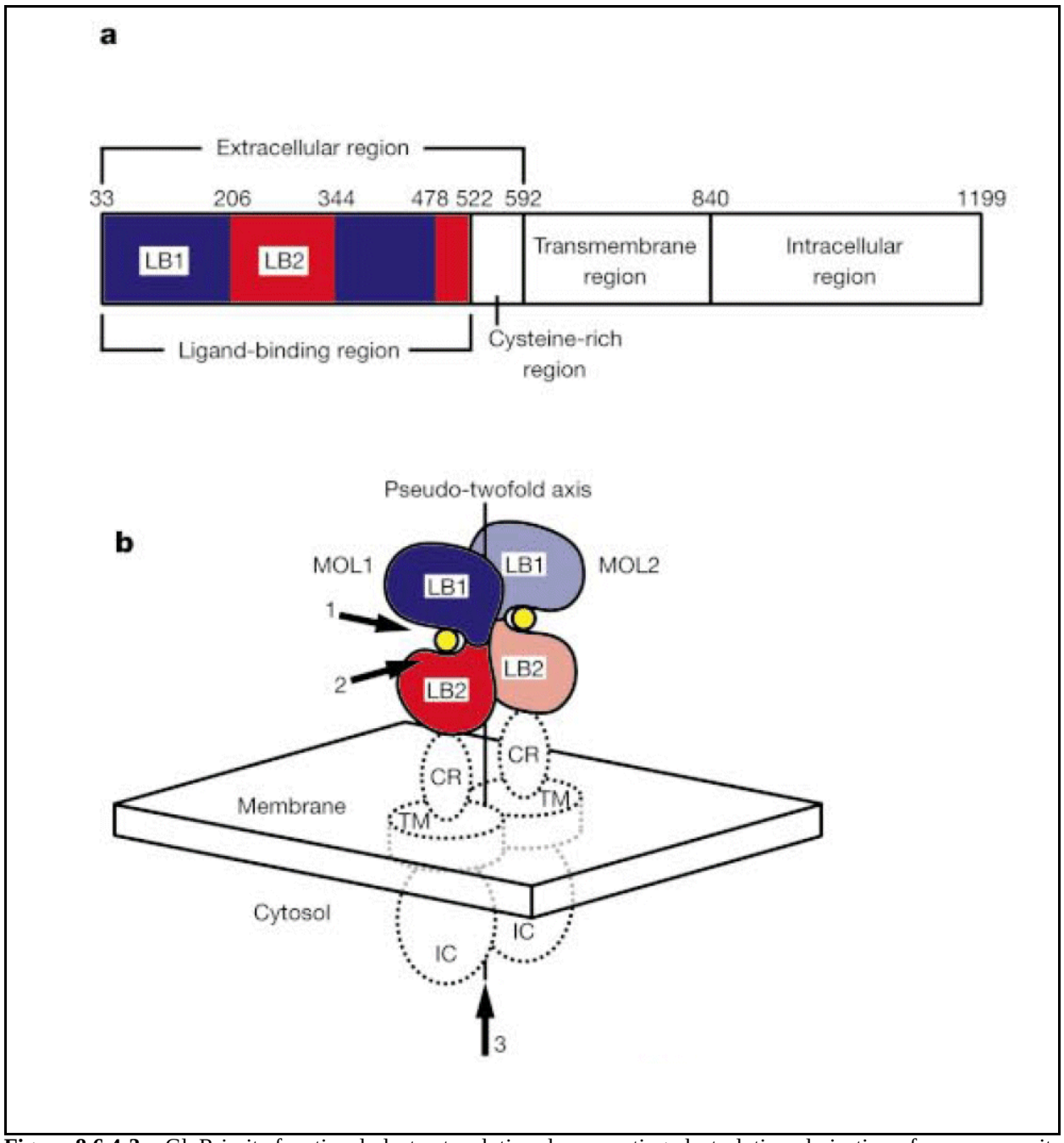

Figure 8.6.4-3 mGluR in its functional electrostenolytic role supporting electrolytic polarization of neurons. a; its proportional location related to the lemma of a cell and b; drawing of the spatial arrangements of mGluR1 domains, and their more detailed relationship to the external lemma of the neuron. "The MOL1 and MOL2 molecules of the m1-LBR dimer are distinguished by dark and light coloring, respectively. The ligand, glutamate, is shown as yellow spheres. CR, cysteine-rich region; IC, intracellular region; TM, transmembrane region." The arrows relate to projections expanded upon in the other areas of the original image. The pseudo-twofold axis is important in crystallography but may be extraneous from the operational perspective in this figure. See text. From Kunishima et al., 2000.

Kaupmann et al. addressed a set of proposed $GABA_B$ receptors in 1997[98]. They noted a similarity between the proposed $GABA_B$ receptors and the glutamate receptors. They apparently did not consider the possibility that $GABA_B$ might actually be a residue created by the metabotropic glutamate receptor mGluR1 discussed above. The Electrolytic Theory of the Neuron considers glutamate the primary neuro facilitator of the neural system and GABA as the primary residue of the decomposition of glutamate, along with CO2, in the establishing the electrical polarization of the individual neuron (rather than the historical conceptual role as a neuro inhibitor. The result is much the same but the operational (functional) situation is totally different. Kaupmann et al. begin their introduction with three important statements; "Molecular cloning has revealed that the ionotropic receptors for L-glutamate and GABA belong to two separate gene families. The metabotropic receptors for L-glutamate (mGluRs) differ structurally from other 7TM G-protein-coupled neurotransmitter receptors and constitute a new gene family." followed by "The molecular structure of metabotropic $GABA_B$ receptors, first reported in 1981, has remained elusive." They did not develop the difference between $GABA_A$, $GABA_B$ or $GABA_C$ in their paper, relying upon citations to the work of others. They did not further, " Given the physiological and clinical importance, many attempts to characterize $GABA_B$ receptors at the molecular level have been made, but as yet have met with only limited success." They made no significant effort to establish the roles of the variants of GABA mentioned in their paper. Until the character of $GABA_B$ is resolved, their research can only be described as basic research accomplished in an applied research environment.

Kaupmann et al. close with a discussion containing at least one important statement, "Except for the $GABA_B$ receptors, the receptors fo the major known neurotransmitters have been cloned." They do not further delineate their list of neurotransmitters or how they function within the neural system. There is no need, *or even definition of how*, to clone an electron, the actual neurotransmitter of biology.

Figure 8.6.4-4 illustrates two forms of mGluR from Kunishima et al. Kunishima et al. describe the host-guest relationship between mGluR1 and glutamate as that of a clam-shell opening and closing to accept glutamate and/or expel residues of the electrostenolytic process. Glutamate is nearly planar and appears correctly in these overlay representations. Kunishima et al. describe m1-LBR as the ligand-binding region of the molecule, mGluR1. They describe glutamate as "bound in an interdomain crevice, as found in iGlrR or PBP (periplasmic binding proteins). In common with these proteins, m1-LBR shows an open-closed conformation characterized by the different spatial arrangements between the LB1 and LB2 domains. We designate the relatively closed subunit of the m1-LBR dimer as MOL1 and the other as MOL2." Note the location of the nitrogen atom along the lower surface of the glutamate in both MOL1 and MOL2 for purposes of orientation.

Kunishima also introduces several other terms to describe the state of the conformers of mGluR(1) at a given time. He describes an "active" and "resting" conformations . He asserts these conformations are modulated through the dimeric interface by a packed α-helical structure (presumably when in the in-vitro condition). He claims, "The bi-lobed protomer architectures flexibly change their domain arrangements to form an 'open' or 'closed conformation." He goes on, "The structures imply that glutamate binding stabilizes both the 'active' dimer and the 'closed' protomer in dynamic equilibrium." His figure 5 suggests the resting state involves the open (receptive) conformation and the active state involves a closed clam-shell configuration. However, his cartoon may be questioned. It appears to be based on the asymmetrical unit assumed throughout his analyses and based on his original crystallographic configuration employing a "pseudo-twofold axis" of symmetry between two protomers. His LB2-LB2 spacing in Angstrom may not be relevant to a larger region of protomers in a liquid crystalline configuration.

The hypothesis of this work is that the CO_2 most remote from the nitrogen is cleaved from the remainder of the glutamate molecule (i.e., the GABA portion) in accordance with **Section 8.6.2.3.3**. The energy resulting from this cleavage is transported through the external lemma of the neuron in the electrostenolytic mechanism in conjunction with the expulsion of the two residues from the receptor. The transport of this energy by an electron through the lemma of the neuron results in the negative polarization of the interior of the neuron compared to the surrounding matrix. The vertical arrow in (b) labeled 3 in the previous figure can be considered to represent an equivalent positive charged particle moving outward through the lemma of the neuron.

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[98]Kaupmann, K. Huggl, K. Heid, J. et al. (1997) Expression cloning of GABAB receptors uncovers similarity to metabotropic glutamate receptors *Nature* vol 386, pp 239-246

Their section on "Ligand recognition" involves considerable speculation regarding the stabilization of the ligand-host relationship rather than any discussion of the purpose of capturing the ligand for further processing. *The purpose of the capture is to provide electrical power to the neuron in accordance with* ***Section 8.6.2.3.3***. A reinterpretation of their section in the context of this work. Quoting Kunishima et al., "The most characteristic feature of m1-LBR is the striking different dimer configurations, which are dependent on the dimer interface construction."

Continuing to quote Kunishima et al., "In the complex form, both MOL1 and MOL2 bind glutamate at similar sites (as shown). A large cleft formed by the bi-lobed architecture involves two interfaces that contact the glutamate: one lies in the LB1 domain (LB1 interface) and the other in the LB2 domain (LB2 interface). The structures of the LB1 interface are essentially identical between MOL1 and MOL2, except for the positions of a few bound water molecules. By contrast the LB2 interface with the open conformation is not used for glutamate binding by MOL2." An alternate interpretation would suggest the MOL2 interface might contribute to the cleaving of the glutamate into the residues, GABA and CO_2. What they describe as "a predominant role for the LB1 domain in achoring the ligand" might be a temporary condition before the GABA is also released due to its inability to remain bound to LB1. Their comments concerning stabilizing the host-guest relationship is not warranted if the purpose of the relationship is to transfer energy to the neuron via the lemma interface and then discard the residues.

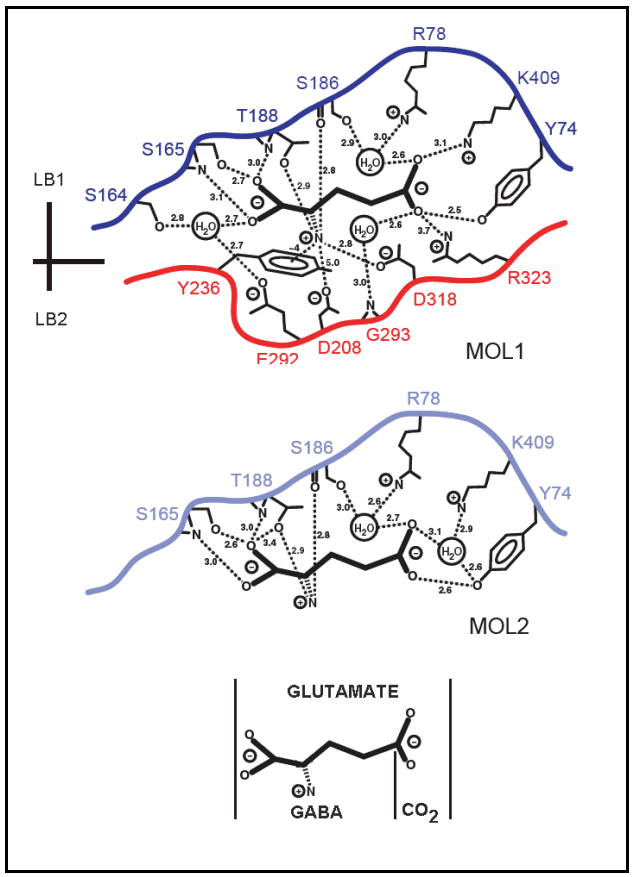

Figure 8.6.4-4 Representations of glutamate binding. "Polar interactions of glutamate with MOL1 and MOL2 are denoted by dotted lines with distances. Domain colouring is as in figure 1b." The upper representation involves domains LB1 above the line and LB2 below. In the middle representation, LB2 is not relevant. The lower frame shows the cleaving of glutamate into GABA and CO_2. See text. Modified from Kunishima et al., 2000.

Their discussion of "Interdomain movement" and subsequent discussions are highly dependent on the purpose of the host-guest relationship and needs to be recast. They do note, "The free form II maintains the same dimer conformations as those of the complex form, even in the absence of ligand." Their discussion continues under the heading, "Relocation of dimer interfaces" and beyond. It is largely irrelevant if the *purpose* of the receptor is changed. They close with, "In conclusion, we have shown that the dimeric ligand-binding region of mGluR adopts multiple conformations, where the activated domain arrangements of the dimer are in equilibrium with other states and are selectively stabilized by glutamate binding."

Bettler et al[99]. provided an extensive followup to the Kaupmann paper that extends well into the field of clinical medicine. It continues to assert the role of GABA as a nuerotransmitter based on several citations but no independent investigations. "The cloning of the first $GABA_B$ receptor cDNAs in 1997 revived interest in these receptors and their potential as therapeutic targets." "GABA research, because of its medical relevance, has always attracted a great deal of attention in academia and industry. Over the years pharmaceutical companies successfully exploited the GABA system and introduced a number of drugs to the market. However, despite considerable drug-discovery efforts, baclofen (β-chlorophenyl-GABA, Lioresal) currently remains the only available $GABA_B$ medication."

The isolation of mGlu1 and mGlu5 from the rest of the mGlu family is illustrated in their figure 1. Figures 6 & 7 provide caricatures of putative GABA capture by a receptor that are strikingly similar to those of Kunishima et al reproduced above. However, Bettler et al. do not introduce any discussion of glutamate. They also fail to provide any evidence of

[99]Bettler, B. Kaupmann, K. Mosbacher, J. & Gassmann, M. (2004) Molecular Structure and Physiological Functions of GABAB Receptors *Physiol Rev* vol 84(3), pp 835-867 DOI: 10.1152/physrev.00036.2003

a transmembrane capability for the receptor relative to the lemma of a neuron beyond citations to the general literature.

In the Electrolytic Theory of the Neuron presented here, the mGluR1 receptors of Kunishima et al. and of Bettler et al. are the same *in-vivo*, The "resting" and "active" states of their two receptor molecules are compatible but their operations need to be expanded into a single contiguous time sequence. Glutamate is captured by the receptors and GABA, along with CO_2, are released from the same receptors after cleavage. After release of the residues, the receptor returns to the resting (receptive or open) state and is available for the capture of another glutamate molecule. Bettler et al. do introduce the concept of a "Venus flytrap" module (VFTM) into their caricatures. The paper does not contribute significantly to the academic research relating to the neural system outside of the development. of new drugs.

8.6.4.2 Remaining analyses regarding operation of the mGluR1-glutamate complex

The work of Kunishima et al. provides very useful confirmation of the role of mGluR1 in the Electrolytic Theory of the Neuron. It is now appropriate to move ahead, based on the Electrolytic Theory of the Neuron, and explore the details related to the powering of the neurons via the decomposition of glutamate with the resultant transfer of about 154 milli-electron volts to the plasma (cytosol) of a neuron for each glutamate molecule cleaved. Kunishima et al. did not describe in detail the morphology of the areas shown dotted in [**Figure 8.6.4-3**]. He did not demonstrate in any way that the mGluR1 molecule actually penetrated the neural lemma. The remaining work is focused on the *in-vivo* functional role of the elements mediating this energy transfer, as contrasted with the *in-vitro* effort to date of the mGluR1-glutamate complex. The questions include;

1. Is the outer bilayer of the liquid crystalline external lemma of the neuron modified to provide electrical conductivity between the liquid crystalline monolayer of mGluR1 and the cytoplasm of the neuron?
2. Is mGluR1 attracted to a specific surface area of the outer layer of the neural lemma, or is it grown there under genetic direction?
3. Do individual molecules of mGluR1 penetrate the lemma of a neuron as suggested by the Kunishima et al. cartoon or is MGluR1 present on the surface of the lemma in a larger liquid crystalline array?
4. What are the actual conformations of mGluR1 and its complex with glutamate as a function of time during the formation of the residues, GABA and CO_2, and their presumed orderly and prompt release from the complex.
5. What is the time line for the above changes in conformation of mGluR1 and its restoration to what Kunishima et al. call its resting (or void of any glutamate) condition.

Kunishima et al. describe mGluR1 as having a transmembrane region in their cartoon based on there conceptual similarity to other G-proteins. However, Kaupmann et al. note mGluR1 and its family members differ significantly from the G-proteins usually described as exhibiting this capability. Electrolytic impedance considerations related to the signaling capability of the neuron strongly suggest that mGluR1 molecules are not present individually *in-vivo* but are grouped into an area that can provide a large number of electrons to the plasma of the neuron in a minimum time interval and on a continuous basis. This supply function must be a continuing one to support the analog signaling capability of the neuron over time.

Kunishima et al. speaks of an equilibrium condition between his resting and active states. However, this long term average *in-vitro* condition probably does not exist under *in-vivo* conditions. The goal of the electrostenolytic process is to actively support the electrical biasing of each neuron under dynamic conditions. In the absence of glutamate, the *in-vivo* receptor probably remains in its resting state indefinitely. The arrival of a glutamate molecule probably does not stabilize the complex as Kunishima et al. assert in their conclusion. Instead, it initiates the process of cleaving the glutamate into GABA and CO_2 and the delivery of electrical power to the associated neuron. Subsequently, the mGluR(1) molecule is restored to its resting condition in preparation for receiving another glutamate molecule.

8.6.5 The description of materials affecting normal neural operation

The proposed use of electrons as the only means of electrolytic signal transfer between neural conduits, including the synaptic junction, requires a redefinition of terms. This redefinition is made more useful by the inclusion of the various materials known to facilitate or inhibit normal neural activity.

The basic change is the recognition that the electron is the only neurotransmitter of the biological system; it is the only carrier of information within and between neurons of the biological system. A wide variety of materials can enhance

or inhibit the transmission and signal processing of information carried by this neurotransmitter. Where these materials enhance operations, they are labeled neuro-facilitators. Where they interfere with the process, they are described as neuro-inhibitors.

Only two natural amino acids exist that are acidic. Interestingly, they are both considered nutritionally nonessential amino acids. The reason for this designation is simple. They can both be fabricated within the body. Of even more interest, they can both be fabricated within the blood-brain-barrier protecting the brain. They are both dicarboxylic and both exhibit a net negative charge (polarization). These are glutamic acid (glutamate) and aspartic acid (aspartate). These materials are the primary sources of electrical potential for the neurons when they participate in an electrostenolytic reaction. It is the net charge, the specific stereo-chemistry, and the ability to release carbon dioxide easily that makes these materials unique participants in the electrostenolytic reaction. They are the primary neuro-facilitators of the neural system.

The neural system employs a delicate balance in the concentration of the primary neuro-facilitators (nominally glutamate) and the waste products of the electrostenolytic reaction, namely the primary neuro-inhibitors (nominally GABA and CO_2), in order to provide flexibility. This balance is further adjusted (buffered) through the presence of other neuro-facilitators and neuro-inhibitors. Higher or lower than normal concentrations of these materials lead to a variety of diseases associated with hearing. As a result of the above balancing and buffering, it should be no surprise that excessive amounts of glutamate, GABA or CO_2 can be toxic to the neural system. Many studies have demonstrated this toxicity.

8.6.5.1 The redefinition of neuro-facilitators and neuro-inhibitors

The Electrolytic Theory of the Neuron provides a simple hierarchy of neuro-facilitators and neuro-inhibitors. The primary (and natural) neuro-facilitator is glutamate with a primary alternate in aspartate. The primary (and natural) neuro-inhibitor is GABA with a primary alternate in alanine. These are the intrinsic participants in the electrostenolytic potential generating process. Any material that aids or interferes directly with this process can be considered class 1 secondary facilitators or inhibitors. The most important and effective secondary inhibitor is L-dopa. L-dopa has a stereo configuration that is accepted by the metabotropic, or glutamate, receptors on the surface of neurons. When L-dopa is embraced by the receptors, it occupies the stereo site for an interval long enough to reduce the average rate of the normal glutamate reaction. Materials having an extended period of effectiveness are sometimes defined as neuro-modulators. Class 2 secondary *inhibitors* typically interfere with the ability of glutamate to reach the metabotropic sites or prevent the clearance of GABA from the immediate environment of the sites. Class 2 secondary *facilitators* typically enhance the ability of glutamate to reach the metabotropic sites or enhance the clearance of GABA from the sites. These classifications are exclusive when discussing the topical application of materials to particular areas of a neuron. However, their effect on the output of a group of neurons when applied globally is difficult to predict. The same problem arises when the material is provided by ingestion or otherwise reaches the brain via the bloodstream.

Figure 8.6.5-1 compares the new designations of a group of common materials compared to their historical designations. The framework recognizes the electron as the only true neurotransmitter and a series of materials as neuro-facilitators and neuro-inhibitors. The neuro-facilitators can be further divided into primary and secondary classes depending on whether they participate directly in the above reactions or act only as necessary enzymes or cofactors. The secondary neuro-facilitators and neuro-inhibitors can be divided into two classes. Class 1 materials directly affect the site of the electrostenolytic process. Class 2 materials affect the ability of other chemicals (primarily class 1 materials) to reach (or be removed from) those sites. This framework leads to a much simpler interpretation of the psychological results from varying the concentration of one or more of the above materials.

Those Class 1 neuro-inhibitors that actually occupy a receptor site on the surface of the plasmalemma are defined as antagonists in pharmacology. They interfere with the primary neuro-inhibitors which are considered agonists in that community. The Class 2 neuro-inhibitors exhibit greater variety. Some have astringent properties that affect the porosity of the matrix surrounding the neurons. Others, like acetylcholine, act as an alternate receptor site for the primary neuro-facilitators. They effectively impound the available primary neuro-facilitators and prevent their participation in the electrostenolytic process.

Theory	Chemical	Electrolytic	
Material	Historical designation	New designation	Comment
Electron	~	Neurotransmitter	Can act as "hole"
Glutamate	Neurotransmitter	Primary neuro-facilatator	Primary energy source
GABA	Neurotrans. (freq.)	Primary neuro-inhibitor	Pri. reaction product
Aspartate		Alt. pri. neuro-facilitator	A dicarboxylic acid
Alanine		Alt. pri. neuron-inhibitor	Alt. reaction product
L-dopa		Class 1 neuro-inhibitor	Can occupy glutamate site and react (slowly)
Glycine		Class 1 neuro-inhibitor	Can occupy glu. site
Dopamine	Neurotransmitter	Class 1 neuro-inhibitor	Can occupy glu. site
Acetylcholine	Neurotransmitter	Class 2 neuro-inhibitor	No amino group
Histamine	Neurotransmitter	Class 2 neuro-inhibitor	- - -
Norepinephrine	Neurotransmitter	Class 2 neuro-inhibitor	vasopressor
Serotonin	Neurotransmitter	Class 2 neuro-inhibitor	strong vasoconstrictor

Figure 8.6.5-1 Framework for materials impacting neural operations. L-dopa can participate in electrostenolysis but can be considered "sticky." Dopamine can occupy metabotropic sites but cannot react. Vasopressor is synonymous with vasoconstrictor. See text.

In the quantum physics of semiconductors, two mechanisms of charge transport are found. In th obvious case, an electron excess to the fundamental semiconductor lattice can move through the lattice from atom to atom, stepping stone fashion. Alternately, a void (defined as a "hole") in the electrical configuration of the lattice can be filled by an electron moving to that location from a nearby site, thereby creating a new void. In the presence of an electrical field, the resulting hole appears to move across the lattice in the opposite direction to that of an electron.

The figure can be compared with a similar listing by McCormick (note how the same material appears at multiple locations in his table)[100]. Bobbin et al. have provided a discussion of the criteria for a neurotransmitter and an accompanying list of references as of 1984[101]. They note that up to that date, most investigators have followed the ideas of Werman (1966). "At some point a guess as to the nature of the transmitter must be made and the criteria can then be used to challenge the guess." Their discussion was based on the chemical theory of the neuron. However, it provides

[100]McCormick, D. (1998) Membrane properties and neurotransmitter actions In Shepherd, G. ed. The Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 61

[101]Bobbin, R. Bledsoe Jr, S. & Jenison, G. (1984) Neurotransmitters of the cochlea and lateral line organ *In* Berlin, C. Hearing Science. Philadelphia, Pa: Taylor & Francis Chapter 4, pp 159-180

excellent data compatible with the Electrolytic Theory of the Neuron. The discussions of Wenthold & Martin in the same volume also provide good data compatible with the Electrolytic Theory of the Neuron. Guth et al. have provided a set of data that should be reviewed[102]. The experiments describe the cursory character of most experiments dealing with putative (chemical) neurotransmitters. Based on the model proposed here, the data from Guth et al. can be interpreted as supporting the role of glutamate as a power source, a primary neuro-facilitator, rather than a signal-related neurotransmitter.

It may be worth noting that the chemical structure of acetylcholine, a class 2 neuro-inhibitor, is not stereo-graphically compatible with the metabotropic/electrostenolytic process. It is not a negatively charged dicarboxylic amino acid. In fact, it is positively charged and contains no carboxylic acid or amino group. It is more likely that acetylcholine replaces or interferes with the polar head of the lipid forming the outer leaf of the type 2 lemma. This lipid is believed to be phosphatidyl choline. Because the two materials exhibit the same positive polar head, they both may be attractive to negatively charged glutamate and aspartate. Acetylcholine may even act as a receptor of free glutamate, thereby depriving the electrostenolytic process of its primary reaction agent.

8.6.5.2 Other putative glutamate receptors found on the plasmalemma

The above discussion makes the case that the phosphatidyl choline lipid of the plasmalemma is itself a receptor site for glutamate. There does not appear to be any need to find other receptor materials to support the same function. However, the literature is full of such endeavors. It should be noted that one of the prime candidates for a receptor[103], α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) is in fact alanine (or a variant of alanine), a reaction product of aspartate electrostenolysis. The citation will lead to other investigations in this area.

The studies of Matsubara et al. were not inclusive. Glutamate receptors are actually found on both pre synaptic and post synaptic lemmas, and on pre junction and post junction lemmas of the Nodes of Ranvier. Matsubara et al. did not demonstrate the receptors were not the terminal portions of the lipid molecules forming the outer leaf of the asymmetrical type 2 lemma.

Another school of pharmacology has focused on the conceptually developed and descriptively named metabatropic glutamate receptors (mGluR).

> Duvoisin et al. have reviewed the work of this scheool[104] The paper forms a good source. However, its hypotheses are largely conceptually based and without a physiological model. The approach of this school leads to very complex process loops based primarily on chemical kinetics. The introductory section labeled “Parallel processing in the retina” should be ignored from both a conceptual and functional perspective. The paper is liberally sprinkled with the terms “unique”, “probable” and “it is thought.” Their one figure contains a variety of question marks at key locations and lacks any reference source. The focus in their review is ON-bipolar neurons under the assumption there are OFF-bipolar neurons in the retina. This assumption fails to recognize the electrical bipolar character of the histologically defined bipolar neurons. They propose the ON-bipolar neurons express metabotropic receptors and the OFF-bipolar neurons express ionotropic receptors as developed below. Their hypothesis suggest complimentary circuits described as push-pull in the electrical disciplines. Since the bipolar neurons are electrically bipolar under the Electrolytic Theory of the Neuron, and this characteristic is easily demonstrated in the laboratory, there is no need for a separate ionotropic OFF-bipolar neuron and no need for any conceptual push-pull circuitry. The designation ON-bipolar is not needed. All histologically bipolar neurons in the retina are non-inverting electrolytically bipolar amplifiers that sum signals from multiple photoreceptors.

They are alternately described by the name glutamate receptors of the metabotropic type (GRM) by the Human Gene Nomenclature Committee where they are subdivided into three classes according to their amino acid sequence, assumed

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[102]Guth, P. Norris, C. & Barron, S. (1988) Three tests of the hypothesis that glutamate is the sensory hair cell transmitter in the frog semicircular canal *Hear Res* vol. 33, pp 223-228

[103]Matsubara, A. Laake, J. Davanger5, S Usami, S & Ottersen, O. (1996) Organization of AMPA receptor subunits at a glutamate synapse: a quantitative immunogold analysis of hair cell synapses in the rat organ of Corti *J Neurosci* vol 16, pp 4457-4467

[104]Duvoisin, R. Morgans, C. & Taylor, W. (2005) the mGluR6 receptors in the retina: analysis of a unique G-protein signaling pathway [on line journal, *Cell Sci Rev*] vol 2(2), pp 225-236

signal transduction mechanism, and pharmacological profiles. The GRM's have not been isolated and chemically described although they apparently have been cloned. Duvoisin et al. suggest they are dimers. In both cases, a large family of mGluR receptor proteins have been identified. Only the first class appears to be reasonably well understood from the perspective of Duvoisin et al. Interestingly, it is mGluR6, a member of the less well understood third class, that is the focus of the paper. It is hypothesized to be the receptor protein most closely associated with the dendritic tips of ON-bipolar neurons in the retina[105]. Work with knockout mice does suggest an important role for mGluR6 at the dendritic structure of the retinal bipolar neurons.

Vardi et al. of 1993 tried to isolate the glutamate receptor of "depolarizing bipolar cells" associated with what was called at the time the APB gultamate receptor[106]. The effort provided new information but was apparently unsuccessful.

This work proposes the mGluR family of proteins participates in the formation of the glutamate receptors forming the electrostenolytic mechanism powering the neural system. It is further proposed that mGluR6 is closely associated with, and may be specific to, the dendrites of retinal bipolar neurons. Other members of the family may play key roles at other neural locations in powering both the dendritic and axonal electrical conduits and effectively biasing the Activa into their operating regime.

Duvoisin et al. assert a single photon, presumably under dark adapted conditions, can generate a hyperpolarizing signal of 100 micro-volts at the photoreceptor pedicle. No specific references were provided. Photons (light) usually depolarizes photoreceptors (**Section 12.5.2**). They assert that over 10^6 cGMP molecules are hydrolyzed and an unspecified number of cGMP-gated channels are closed to generate this signal i the photoreceptor. They do not specify whether this condition applies to a "cone" or "rod" photoreceptor. Under the Electrolytic Theory, no cytological gate closings, and no chemical reactions are required (except for the conversion of glutamate to GABA in the electrostenolytic process of electrolytically powering the neuron. There is only one class of photoreceptor neurons although they are supported by different chromophores.

The potential role of the mGluR family in supporting electrostenolysis remains unclear. It could support the stereographic bonding of glutamate to the phosphoglycerides of the lemma, it could affect the porosity of the neuromatrix to elements of the electrostenolytic operation, or it could act as an antagonist to the normal electrostenolytic operation.

8.6.5.3 The redefinition of -ergic chemicals and neurons

The confusion in the literature, concerning the -ergic properties of various chemicals, speaks for itself. The term appears to have arisen primarily in a clinical context and is used as a suffix in a variety of situations. The most relevant meaning here is "Causing a psychological response or symptom similar to [the root name to which it is attached]." The -ergic properties of a chemical can be addressed in two distinct arenas. The first describes the results of topical application of the chemical to an individual neuron. The second describes the results of global application of a chemical to the organism, usually via ingestion or injection. When the material is applied topically to a neuron, the response depends strongly on where, and in what concentration, the chemical is applied. Thus, the material can be described as a neuro-facilitator or neuro-inhibitor based on its point of topical application.

There are at least three sources of information relative to the -ergic materials although the accompanying discussions are based on a chemical theory of the neuron and are inconsistent. Cucchiaro et al. reflect on the inadequacy of the

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[105]Vardi, N. Duvoisin, R. Wu, G. & Sterling, P. (2000) Localization of mGluR6 to dendrites of ON bipolar cells in primate retina *J Comp Neurol* vol 423, pp 402-412

[106]Vardi, N. Matesic, D. Manning, D. Liebman, P. & Sterling, P. (1993) Identification of a G-protein in depolarizing rod bipolar cells *Vis Neurosci* vol 10(3), pp 473-478

overall -ergic concept, based on a two-terminal concept of a neuron.[107] Sherman & Guillery have attempted to clarify the use of GABA-ergic, within the chemical neurotransmitter context, with less than the desired clarity[108]. To minimize the confusion, they suggest that; "Transmitters should no longer be classified as excitatory or inhibitory, because it is known that the same neurotransmitter can be both excitatory and inhibitory depending on the post synaptic receptor." Puil has provided a detailed report on the response of neurons to a wide variety of excitatory and inhibitory pharmacological agents in his Section 4.2.1[109]. However, his Section 3.1 must be read with care since it assumes a two-terminal neuron. His discussion frequently reflects on the inconsistency in the use of the terms polarization and hyperpolarization. Fuster has provided a guide to the literature of neurotransmitters based on the chemical neuron theory[110]. Except for one figure, the presentation is in prose. This presentation style is susceptible to misunderstanding. The acceptance of a three-terminal neuron with both an inverting and a non-inverting input and three identifiable plasmas simplifies the above presentations considerably.

A major problem with the above discussions of -ergic materials is the lack of a common precise definition of each type of -ergic material and the differences between the types. The chemical theory of the neuron does not provide a framework in this area.

When the concentration of GABA within neural tissue is increased globally, the result is indeterminate in three ways. It is indeterminate with respect to its effect on a single neuron and it is indeterminate with regard to multiple neurons in series. The effect on the output of an engine consisting of millions of neurons is similarly indeterminate. This is the source of the problem in using the expression GABA-ergic in pharmacology. A global application may cause multiple observable events. As a caricature, the observed effect following global application of GABA may be a slowing of the heart rate accompanied by an opening of the iris and a tingling feeling in the left toe. What the investigator reports depends on what characteristic(s) he has chosen to observe.

The effect of topical application of the neuro-facilitator glutamate tends to be the opposite of GABA since it drives the individual electrostenolytic processes toward completion. Aspartate, in its role as a secondary neuro-facilitator, acts similarly. The roles of other class 1 neuro-facilitators and neuro-inhibitors can be described similarly because they act to disturb the electrostenolytic process by occupying stereo-specific sites on the substrate. The role of class 2 neuro-facilitators and neuro-inhibitors are more difficult to predict because they tend to change the diffusion coefficients of the inter-neural matrix (INM) and the walls of the capillaries. These actions affect the concentrations of many individual materials within the INM.

In summary, the effect of a given chemical, whether a glutamate or other pharmacological agent, on a neural circuit depends on where and in what concentration it is applied topically. If it is applied globally to a neuron, the impact depends on at least three factors. First, the relative concentrations applied to different electrostenolytic areas of the plasma wall. Second, the relative porosity of the local environment to the topical agent. Third, the ability of reaction byproducts to exit the immediate area of electrostenolytics.

As noted above, the effect of an individual neuro-facilitator or neuro-inhibitor is highly dependent on how it is applied and what outcomes are observed. While a designation such as GABA-ergic can be used in a stylized clinical setting, it is imprecise and largely meaningless in a scientific setting. The same conclusion can be drawn concerning many other pharmaceuticals[111]. Their action can only be defined precisely when topically applied to a specific portion of a specific neuron. When ingested, or injected, their effect cannot be specified precisely and many unrelated effects are to be expected. The suffix -ergic appears to have no place in applied neurological research.

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[107]Cucchiaro, J. Uhlrich, D. & Sherman, S. (1993) Ultrastructure of synapses from the pretectum in the A-Laminae of the cat's lateral geniculate nucleus. J. Comp. Neurobiol. vol. 334, pp 618-630

[108]Sherman, M. & Guillery, R. (1996) Functional organization of thalamocortical relays *J. Neurophysiol*. vol. 96, no. 3, pp 1367-1395

[109]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res Rev* vol. 3, pp 229-332

[110]Fuster, J. (1998) The Prefrontal Cortex, 3rd Ed. NY: Lippincott-Raven, Chapter 3

[111]Baker, M. & Wood, J. (2001) Op. Cit.

8.6.6 Pharmacological impact of the glutamate family on the neural system

This work will not attempt to address the pharmacy related to the neural system. The literature is vast, primarily exploratory, and difficult to rationalize. McGeer, et. al. devote considerable space to this subject.[112] McIlwain & Bachelard have also devoted much space to the subject.[113] Their page 413 provides a generic list of the various chemical classes associated with putative neurotransmitters.

Puil has provided a massive, well referenced and invaluable paper published in an obscure review[114]. It describes the many roles of glutamate in the neural system, particularly before the heavy emphasis put on its putative neurotransmitter role in the 1970's. He noted that "in spite of the wealth of information concerning its effects and its interaction with other neurotransmitter candidates and drugs, . .there is not yet a great deal of understanding about the mode of action of S-glutamate in the central nervous system." As he also notes, he uses the Caln-Ingold-Prelog system of describing the configuration of a complex hydrocarbon. The notation S-glutamate, which he uses, is identical to L-glutamate.

Puil describes the use of glutamate in the neural system when applied both topically and micro-topically, technically described as microiontophoresis.

In the context of glutamate as a neurotransmitter, it is interesting to note the comment and references of Puil. "It has been known for a long time that intracellular injections of S-glutamate into spinal neurons produce no response" (pg 265). This fact seems unlikely if glutamate was playing the role of a neurotransmitter originating in the axoplasm of a neuron. He closes with "The physiological effects of S-glutamate thus appear to be the result of its interaction with chemical groups (receptors) on the external surface of neurons."

In 1992, Dowling provided a table of neuroactive substances and a discussion[115]. He listed glutamate, aspartate, GABA and glycine as all neurotransmitters. However, he made an interesting observation. "It is also possible for one transmitter to have an excitatory effect on one neuron and an inhibitory effect on another neuron." He offered no explanation of the mechanism(s) supporting this activity.

In 1998, Greenfield addressed the current confusion related to the putative chemical synapse. She focused on the confusion about whether a given chemical in a given situation is inhibitive or excitatory[116]. Some of her major themes are; "Why are there so many different neurotransmitters" and "How can familiar transmitters have unpredictable actions?" These questions attack the fundamental understanding of the method of signal transfer across a synapse. Greenfield has elucidated five nominal properties required of a neurotransmitter.

Because of the limited ability of the current technology to measure the progress of micro-mol quantities of chemicals in less than one second intervals, no actual data exists definitively supporting the concept of a chemical synapse.

From the perspective of this work, these authors have not separated the relevant pharmacological agents into the three

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[112]McGeer, P. Eccles, J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain, 2nd ed. NY: Plenum Press. Chapters 6 through 12

[113]McIlwain, H. & Bachelard, H. (1985) Biochemistry and the Central Nervous System. NY: Churchill & Livingstone. Chapters 14 through 18

[114]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res. Rev*. vol. 3, pp 229-332

[115]Dowling, J. (1992) Op. Cit. pg 141

[116]Greenfield, S. (1998) Future Developments, in Higgins, S. *ed*. *Essays Biochem*. vol. 33, Chap. 14

most important classes. It is proposed that these classes are;

1. those chemicals that act directly as signal transmitters between an axon and a neurite (or vice versa),

2. those chemicals that directly affect the electrostenolytic mechanism at the cell surface and

3. those that indirectly affect the mechanism by affecting the availability of the above agents.

As discussed in **Sections 8.7 and 9.4**, the minute crystal of hydronium present in the extremely narrow synapse area precludes any molecules from passing from the axon side to the neurite side of an actual synapse junction. This physical model of the synapse precludes the conceptual model found in most textbooks (McGeer, et. al. pg 414) The space between the pre- and post synaptic surfaces is too narrow to accommodate any molecule significantly larger than water. The porosity of the hydronium crystal (a liquid crystal closely related to ice) to complex chemicals is essentially zero. Therefore, no chemicals meet the requirements of item 1 above.

The physical impossibility of a large molecule passing from a vesicle of an axon to a receptor site of a neurite within the narrow confines of the hydronium filled synaptic gap, forces a re-evaluation of the above materials. It means most of the materials defined as neurotransmitters in the literature must be looked upon as facilitators or inhibitors of the electrostenolytic process, items 2 and 3 in the above list (**Section 15.1.8**). Those materials that only participate in, or affect the electrostenolytic process have been labeled "false neurotransmitters" by McGeer, et. al. (page 306 & 312).

8.6.6.1 Definition of neurotransmitter and excitatory/inhibitory agents

The neurosciences have not developed a clear and precise functional definition of neurotransmitter. Neither have they developed a precise description of an excitatory agent or inhibitory agent. Their working definitions depend on the response of an organism to the change in concentration of various pharmaceutical agents, frequently at long physiological distances from where the agent was applied. From these working definitions, they have developed a conceptual definition similar to that of Gangong (referenced in the next section). It is based on the presence of "specialized neuronal mechanisms for storage, release, and postsynaptic action of a particular substance." This definition does not localize these mechanisms with respect to the neuron nor does it specify the substances involved.

Providing a precise definition for an excitatory agent is difficult. Does such an agent,

• Result in an increased feeling of pleasure in the subject?

• Result in a specific movement by the subject?

• Involve an increase in an electrophysiologically observable parameter?

• Involve an increase in the frequency of a stream of action potential?

• Involve a depolarization (or hyper-polarization) of an axon potential?

What is the criterion for an excitatory agent under the chemical theory of the neuron?

In 1987, McGeer, et. al. referred the reader to a paper more than 20 years old for a general reference on excitatory synaptic action. They then used a generic neuron to discuss the excitation with respect to the observed depolarization (positive going change in voltage) of "intracellularly recorded potentials produced by synaptic excitatory action." They do not differentiate between the depolarization of the axoplasm and any depolarization of an associated dendroplasm (or podaplasm). From this situation, they define "excitatory postsynaptic potentials (EPSPs)." This definition places the excitatory function at the neurite plasma level but its observation at the axoplasm level. While this definition is unique under a two-terminal neuron concept, it becomes awkward when a three-terminal neuron concept is accepted. Under the three-terminal concept, the change in potential applied to the dendroplasm has the same polarity as the resulting change in axoplasm potential. However, the change in potential applied to the podaplasm has a polarity opposite to that of the change in potential of the associated axoplasm. In general, a change induced at the dendrite terminal has the opposite effect of a change at the podite terminal. The definition of an EPSP fails under the three-terminal concept of a neuron.

McGeer, et. al. do address, in one paragraph, the role of a very different synapse, the inhibitory synapse on the Mauthner cell in the fish spinal cord. Although they do not carry their discussion very far, this type of synapse would correspond to excitation of the neuron at the poditic terminal and could be labeled an inhibitory postsynaptic potential (ISPS), with

respect to the axoplasm. With respect to the podoplasm, the excitation still causes a positive going change in plasma potential, but a negative-going axoplasm potential.

McGeer, et. al. appear to have defined the EPSP based on earlier work involving the end-plate potential (EPP) of a motor neuron. In a projection type (stage 3) neuron, the role of the poditic terminal may be less important than for the generic neuron. Finding the poditic terminal with the technology of the 1960's was virtually impossible.

The definition of an excitatory agent based on the depolarization of the axoplasm of a neuron is not very useful for most psychophysical researchers. It is also foreign to the typical pharmacologist. They would prefer a definition based on parameters available based on chemical content of a specimen or observed changes in behavior of the subject. Therefore, a more expansive definition is needed that can apply to a wide range of investigations.

Based on the subdivision of the previous section, and dismissing chemical neurotransmitters operating within the synaptic gap, an excitatory agent can be defined. Excitatory agents are those that, in some way, participate directly in the electrostenolytic mechanism that provides power to the neuron **OR** affects the availability of those chemicals required in the above electrostenolytic mechanism. The first class is a small one. The second is endless.

8.6.6.2 Agents directly involved in the electrostenolytic process

The agents involved in the basic electrostenolytic process are two: glutamate (the pharmacological name for glutamic acid) and GABA. Glutamate is converted to GABA with the release of CO_2 and the transfer of an electron across the lemma forming the substrate. Within the context of the neural system, all other reactions are incidental to this reaction. Ganong has defined the role of glutamate and GABA in the electrostenolytic process most succinctly[117]. He says, "Gamma-aminobutyric-acid (GABA) has been proved to be the synaptic transmitter at the inhibitory neuromuscular junctions in crustaceans. In mammals, it appears to be the mediator for presynaptic inhibition in the spinal cord and an inhibitory mediator in the brain and in the retina." He continues, "Glutamic acid (glutamate) has been shown to be the excitatory mediator at myoneural junctions in certain insects. Glutamic acid and aspartic acid (aspartate) depolarize mammalian neurons when placed directly on their membranes by microelectrophoresis, but they have not been proved to be transmitters at any specific location in mammals." The latter clause is based on his chemical definition of a neurotransmitter. It is based on the presence of "specialized neuronal mechanisms for storage, release, and postsynaptic action of a particular substance." This is the common chemical definition of a neurotransmitter. However, Ganong describes a common problem with this definition as "the fact that these amino acids probably occur not only in neurons but in most if not all living cells." It is proposed that glutamate and GABA are the primary reactants, along with the release of CO_2, in the electrostenolytic process electrically biasing all cells (and individual conduits) of the animal organism. The electrostenolytic process can be affected by many other chemical agents. The next paragraph will highlight the wide variety of agents that can impact the routine progress of this reaction at the concentrations described in **Sections 8.6.2** & **8.6.3**.

The sites of the electrostenolytic mechanism have been found via electron microscopy. They stand out as zones of high electron density along the surface of the various lemmas of the neuron (see **Sections 9.4, 10.6** and **10.7**). They are generally near but external to the "tight gap junction," the actual synapse of neurology.

Significantly changing the concentration of either glutamate or GABA at the site of the electrostenolytic mechanisms is clearly the most effective way to change the performance of the neuron. Steriade, et. al. note this when they point out the role of glutamate (and aspartate) in stimulating neurons[118]. Benson, et. al. also note this when they say "It is well

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[117]Ganong, W. (1975) Review of Medical Physiology, 7th Ed. Los Altos, CA:Lange Medical Publishers pg 185-186

[118]Steriade, M. Jones, E. & Llinas, R. (1990) Thalamic oscillations and signaling NY: John Wiley pg 87-88

established that GABA is probably the major inhibitory neurotransmitter in the central nervous system. . . .[119]" While these materials can facilitate or inhibit the operation of the neural system, they are not a neurotransmitter found within signaling confines of the synapse.

Steriade, et. al. further note that glutamate is concentrated in nerve terminals by a high-affinity uptake system. However, the resolution of the techniques they relied upon cannot determine the location of the putative terminals. It is proposed that the terminals they speak of are not signaling terminals but the electrostenolytic terminals associated with the power supplies.

[Xxx need to focus and sequence material re: glutamate-GABA reaction.]
Sloane & York, discussing the brain, say that glutamic acid decarboxylase is found only in the brain[120]. This statement is probably too strong. To be more specific requires further definition of the material involved. McGeer, et. al. associate three different names with this coenzyme[121]. Benson, et. al. have also explored this enzyme. This work proposes the appropriate coenzyme is only found in PNS and CNS neural tissue.

According to the model of this work, changing the concentration of either glutamate or GABA at an electrostenolytic site associated with an axon may change the resting potential (and the resultant height of any action potential generated). However, it will not change the pulse interval between any action potentials. Changing the concentration of either glutamate or GABA at a neurite terminal can change the potential difference between the emitter and base terminals of the Activa within the cell. Changing the concentrations at the poditic supply terminal will cause one action while changing it at the dendritic supply terminal will cause the opposite action.

Controlling the concentration of these materials primarily depends on the hydraulic environment of the matrix surrounding the neurons. Therefore, calling a neural path GABA-ergic is more a description of the nearby chemical matrix than it is of a specific neuron or neurons. The current model removes glutamate and GABA from discussion as a neurotransmitter. The same thing can be said concerning acetylcholine and a host of other chemicals that can affect the neural power system. These will be discussed below.

8.6.6.3 Agents independent of but affecting the electrostenolytic process

Agents, other than glutamate and GABA, that impact the neurological state of a neuron are frequently described as "false neurotransmitters."[122]

Section 8.6.6.2 leads to a formal restatement of the role of "chemical neurotransmitters" within the neural system. Materials previously labeled neurotransmitters are in fact neuro-facilitators or neuro-inhibitors. They play no direct role in neural signaling. The neuro-facilitators and neuro-inhibitors play an important role in all neurons, whether their output is phasic or tonic. The primary neuro-facilitators are the source of electrical energy to each and every neuron. **Section 8.6.2** shows stereochemistry plays a major role in categorizing the putative neurotransmitters. It also shows how the unique chemical structure of glutamate and aspartate lead them to play a primary role in the electrostenolytic process. They are the only negatively charged amino acids. They are the only amino acids that are dicarboxylic and exhibit a stereochemistry uniquely compatible with the electrostenolytic substrate.

As defined above, the primary electrostenolytic process in neurology is the conversion of glutamate into GABA with the release of CO_2 and the injection of an electron into the plasma within the lemma supporting the process. In this context, glutamate and GABA are the primary neuro-facilitators and neuro-inhibitors respectively. All other materials previously labeled neurotransmitters can be considered secondary neuro-facilitators or neuro-inhibitors within the context developed in **Section 15.1.8**.

Based on the above framework, an excitatory agent independent of the electrostenolytic process, will fall into one of two

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[119]Benson, D. Isackson, P. Hendry, S. & Jones, E. (1991) Differential gene expression for glutamic acid decarboxylase and Type II calcium-calmodulin-dependent protein kinase - - *J. Neursci*. vol. 11, no. 6, pp 1540-1564

[120]Sloane, N. & York, J. (1969) Review of Biochemistry London: Macmillan. pg 229

[121]McGeer, P. et. al. (1987) Op Cit. fig 6.1 and text

[122]McGeer, P. et. al. (1987) Op. Cit. pg 306 (compare with page 312)

categories. The short list contains those (class 1 in **Section 15.1.8**) chemicals that expedite the removal of GABA from the immediate proximity of the many electrostenolytic processes. Only a few steps are involved between the formation of GABA and its re-conversion into glutamate or its elimination from the body as urea. The longer list contains all of those (class 2) materials affecting the availability of glutamate at the required locations. Alternately, an inhibitory agent is one that inhibits the removal of GABA from an electrostenolytic site or interferes with the access of glutamate to the site.

8.6.6.3.1 Other agents with a positive impact on electrostenolysis

The word putative is used here in consort with McGeer, et. al. They focus on aspartate as a potentially positive agent in the neural system. Aspartate differs from glutamate is having one less CH_2 group. Otherwise, they are structurally identical. While it can participate in the electrostenolytic process, the reaction product is not GABA but a simpler member of its chemical family.

McGeer, et. al. address the subject of excitotoxicity (pp 189-196). They point out that excessive concentrations of glutamate, aspartate and many structurally related amino acids are powerful neural stimulants and they can have destructive effects if administered in sufficient excess.

8.6.6.3.2 Other agents with a negative impact on electrostenolysis

Several groups of chemicals that significantly degrade the performance of the neural system at the cellular level are known. Like the positive case, one chemical closely related to GABA is known to have a significant negative impact, glycine. Others in the same chemical class include taurine, proline, serine and β-alanine. The presence of these chemicals near the electrostenolytic substrate probably suppresses the normal electrostenolytic reaction at the site. The effect would be to lower the individual potentials supplied to the plasmas of a neuron. McGeer, et. al. point out that "GABA and, to a lesser extent, glycine probably accounts for most of the inhibitory action in the central nervous system. . . ." (pg 197).

Pharmacologically, members of the choline family were initially found to exert a negative effect on the operation of the neural system. Based on the use of acetylcholine in electrophysiological experiments, it appears this chemical effectively occupies the electrostenolytic sites normally occupied by glutamate but does not react to form GABA. Thus, this chemical has a major deleterious impact on the neural system. It degrades the voltage supply to the various plasmas significantly. While normally considered a negative agent in neurology, McGeer, et. al. show the overall operational impact of the cholines is not consistent. It is so inconsistent that two subclasses have been identified, those that have a positive impact and those that have a negative impact. (pg 253-260). This finding is consistent with application of the material to either the dendrite or the podite terminals.

An even more powerful chemical family is the catecholamines. They are looked upon primarily as hormones. These materials couple an amine side chain with a catechol ring. In fact, the structural similarity is greater than that. One of the pharmacologically most important catecholines, L-dopa, has a side chain structure, including part of the catechol ring that is nearly identical to that of glutamate itself. [Consider forming a ring between the β– and γ– carbons of glutamate.] It is quite possible this structure allows some catecholines to occupy electrostenolytic sites normally occupied by glutamate. This action would reduce the electrical potential applied to the various plasmas. Such action could change the firing rate of ganglion cells found in stage 3 projection neurons significantly. The same action would change the quiescent axoplasm potential of tonic neurons. The potential pharmaceutical alternates to L-Dopa in neurology are explored further in the next section.

When L-Dopa participates in the electrostenolytic process, the residue is dopamine. Dopamine can also be used as a neuro-inhibitor since its presence slows the electrostenolytic reaction rate.

8.6.6.3.3 Other potentially more important neurological agents related to L-Dopa

L-Dopa has been used medicinally since the 1930's. Its absolute configuration has been known since at least 1913 and its name reflects this history. The Merck index of the 1960's provided three different scientific names for the chemical. Today, it would be described differently still, based on more recent chemical and pharmaceutical knowledge. It would not be described as a phenol at all. Such a material would now be described as a catecholamine, specifically catechol-L-

alanine. The importance of this alternate designation relates to many of its properties compared to a phenol. However, even this designation is misleading. Alanine is not a participant in, nor a precursor, of, the electrostenolytic process of neurology. It is aspartic acid that is the first member of the family of interest here. Glutamic acid is the second, and most important, member of the family. It is the catechol (or a related aromatic or aliphatic ring) embedded in the stereochemical structure of glutamic acid that gives it its importance in neurology. Of primary interest in neurology is the presence of two oxygen atoms on the ring opposite to the alanine with its own carboxyl group. This material mimics the two carboxyl groups (and the resultant stereochemistry) of glutamic acid and aspartic acid, the primary sources of electrical power in the neural system. It is this stereochemistry that allows L-Dopa to substitute for glutamic acid in the electrostenolytic process.

Figure 8.6.6-1 shows the structure and proposed reaction of L-dopa at the electrostenolytic site normally employed by glutamate in its reaction to form GABA and provide electrical power to the neural system (as in [**Figure 8..6.2-4**]). L-Dopa is quite amenable to hydrogen bonding to appropriate areas of the cell membrane. If the reaction occured slower than that of glutamate to GABA, it would have an inhibiting affect on the associated neuron by lowering one or more of the plasma potentials of the neuron.

It is conceivable that other pharmaceuticals can be developed based on the stereochemical requirements developed in this work. These preparations could take several forms.

1. The ring structure could be moved one carbon closer to the amino group resulting in two true carboxyl groups at essentially the same stereochemical locations as in glutamic acid.

2. The catechol ring could be modified to an aliphatic ring with an oxygen and a hydroxy-group both connected to a single carbon of the ring para to the amino acid structure (like the arrangement in many isoprenes). The result would be an alternate cyclic compound mimicking glutamic acid.

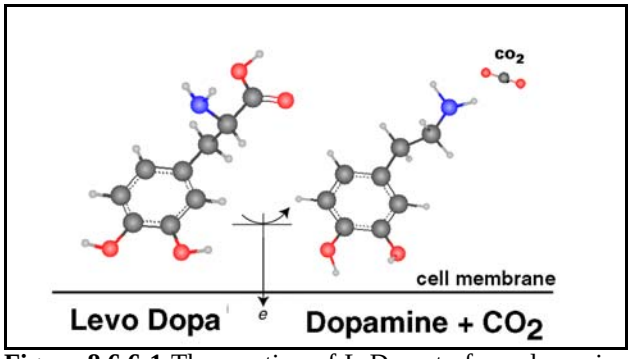

Figure 8.6.6-1 The reaction of L-Dopa to form dopamine and CO_2 at an electrostenolytic site designed for glutamic acid. The reaction and/or CO_2 release is slower at this site.

3. Replacement of the ring altogether while retaining the two carboxyl groups in an effort to obtain a material that could cross the blood-brain-barrier while still mimicking glutamic acid in its electrostenolytic role.

Only laboratory evaluation can determine if these materials would be useful weapons in neural pharmacology.

Like L-Dopa, Dopamine has been given a series of names over the years. Its primary property is its stereochemical similarity to GABA and glycine. It is this stereochemistry that makes it an active neuro-inhibitor. This role is addressed in the next section.

8.6.6.4 Re framing the pharmacology of neurotransmitters

8.6.6.4.1 Background

The confusion in the literature concerning the -ergic properties of various chemicals speaks for itself.

Cucchiaro, et. al. attempt to extend the specific nature of a these -ergic processes by stating; “That is, cholinergic inputs to interneurons and perigeniculate cells seem to hyperpolarize them.”[123] They then reflect the inadequacy of the overall -ergic concept, based on a two-terminal concept of a neuron. In a long sentence, including many references, they end with “by operating through different cholinergic postsynaptic receptors that can *either* hyperpolarize or depolarize the cell. [Emphasis added]” As the discussion proceeds, they introduce the concept of disinhibition. This convolution is

[123]Cucchiaro, J. Uhlrich, D. & Sherman, S. (1993) Ultrastructure of synapses from the pretectum in the A-Laminae of the cat’s lateral geniculate nucleus. J. Comp. Neurobiol. vol. 334, pp 618-630

apparently distinct from excitation.

Sherman & Guillery have attempted to clarify the use of GABA-ergic, within the chemical neurotransmitter context, with less than the desired clarity[124]. To minimize the confusion, they suggest that; "Transmitters should no longer be classified as excitatory or inhibitory, because it is known that the same neurotransmitter can be both excitatory and inhibitory depending on the post synaptic receptor." They then focus on two putative post synaptic receptors, $GABA_A$ & $GABA_B$. Their claim is that $GABA_A$ is ionotropic and its action inhibits the host cell, while $GABA_B$ is metabotropic and it hyperpolarizes the cell (unstated but apparently the axoplasm of the cell). Their definitions of ionotrpic and metabotropic appear to lack precision as to their actual function.

This work dismisses the idea that chemical receptors within the synaptic gap are involved. Instead, the role of chemicals in affecting the output of various neural circuits are the cause of changes at subsequent orthodromic neurons. **Figure 8.6.6-2** shows the potential effects of the application of neuro-facilitators and neuro-inhibitors to a given neural signaling chain. Consider two possibilities defined as applying a pharmaceutical to the electrostenolytic process at the axon at either point A or point B. The two bipolar cells are both noninverting and reproduce the positive going signals shown on the right. Let the positive going signal at $V_{in}(1)$ cause an increase in the action potential pulse rate at the axon of the ganglion cell. The same positive going signal applied to the inverting input at Vin(2) will decrease the action potential pulse rate.

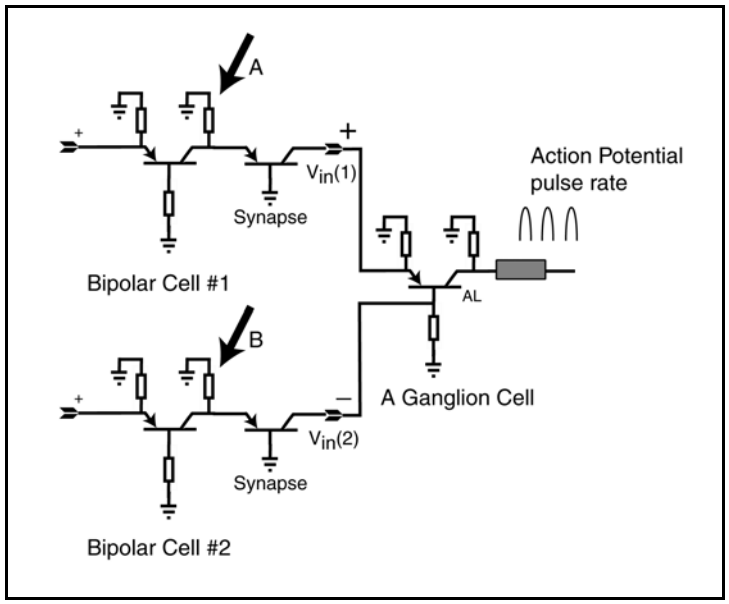

Figure 8.6.6-2 The potential effects of neuro-facilitators and neuro-inhibitors on neural activity. See text.

If a neuro-facilitator (such as glutamate) is applied to the electrostenolytic process at point A, the positive going signal generated by bipolar cell #1 will be enhanced and the action potential pulse rate will be increased. If a neuro-inhibitor (such as GABA) is applied at the same point A, the positive going signal generated by bipolar cell #1 will be suppressed and the action potential pulse rate will also be suppressed.

Repeat the same experiment only at point B. In this case, the neuro-facilitator will enhance the signal applied to the inverting terminal, Vin(2), but the action potential pulse rate will be suppressed. Alternately, applying the neuro-inhibitor (such as GABA) to point B will decrease the signal voltage at the synapse but this action will cause the action potential pulse rate to rise.

Note: The effect of any neuro-facilitator or neuro-inhibitor at an orthodromic location depends on the topology of the intervening circuitry. The application of the same pharmaceutical at the same relative location on either of two neurons may cause an increase in action potential pulse rate (or a hyperpolarization) or a decrease in the action potential pulse rate (or a depolarization) at a subsequent neuron depending entirely on the topology of the circuitry.

Puil has provided a detailed report on the response of neurons to a wide variety of excitatory and inhibitory

[124]Sherman, M. & Guillery, R. (1996) Functional organization of thalamocortical relays *J. Neurophysiol*. vol. 96, no. 3, pp 1367-1395

pharmacological agents in his Section 4.2.1. However, his Section 3.1 must be read with care since it assumes a two-terminal neuron. His discussion frequently reflects on the inconsistency of polarization or hyperpolarization. The acceptance of a three-terminal neuron with both an inverting and a non-inverting input and three identifiable plasmas solves these problems.

Fuster has provided a guide to the literature of neurotransmitters based on the chemical neuron theory (the conventional wisdom)[125]. The material is focused on the frontal lobe of the cerebral cortex and is tied to the role of neurotransmitters in relation to the "action potential." His figure 3.1 goes farther than most other authors in defining six different -ergic forms that may involve as many as thirty different neurotransmitter materials. These are presented in caricature form suggesting six different types of synapses. Fuster has provided a discussion that hints at an underlying neurosecretory system that can influence the effectiveness of various neuro-facilitators and neuro-inhibitors. It is suggested that this system (or systems) originates in the brainstem. As Fuster notes, these materials have been studied only empirically. No theoretical studies are reported or referenced. No discussion of the stereochemistry of the materials is offered. Except the above figure, the presentation of Fuster is in prose. This presentation style is susceptible to misunderstanding. The following are a few examples.

1. He makes several definitive statements on page 58. "GABA is . . . the most abundant of all neurotransmitters thus far identified in the central nervous system. The brain content of GABA is between 200 and 1,000 times greater than that of any of the four transmitters reviewed so far." The four are presumably norepinephrine, dopamine, serotonin and acetylcholine. Unfortunately, he did not address the role of glutamate to the same degree in the discussion. McIlwain & Bachelard ([**Figure 8.6.3-1**]) suggest that glutamate is 50% higher in concentration than GABA. Glutamate is clearly a neurotransmitter, according to both Fuster and many others.

2. He states that neurotransmitters are produced within the body of the nerve cell for transport along the axon to the terminal synaptic vesicles (pg 43). In another context, he says several neurotransmitter distribution pathways originate in the brainstem (pg 45). He also discusses the variation in concentration of different neurotransmitters within different portions of the cerebral cortex. The discussion suggests there may be one or more neurosecretory signal paths between the brainstem and the prefrontal cortex that control the concentration of different neuro-facilitators and neuro-inhibitors. This suggestion, along with the experiments of McIlwain & Bachelard, support the conclusion that the various neuro-facilitators and neuro-inhibitors may be fabricated outside of the neurons themselves. This is particularly true of the vasoconstrictors and other secondary facilitators and inhibitors. It also appears to be true of lactate, a precursor of glutamate (**Section 15.1.8**).

3. He describes "Dopamine is also a neurotransmitter in its own right; accordingly, there are in the brain dopamine-specific terminals and receptors. Dopaminergic systems, like norenipherinergic systems, originate in the brainstem." These statements appear to conflict with his view that "neurotransmitters are produced within the body of the nerve cell. . . ." (Page 43). As shown in **Section 15.1.8**, dopamine is a class 1 neuro-inhibitor because of its ability to occupy an electrostenolytic site.

8.6.6.4.2 Characterizing GABA-ergic, cholin-ergic and similar reactions

A major problem with the above discussions and categories is the lack of a precise definition of each type of -ergic material and the differences between the types. The chemical theory of the neuron does not provide a framework in this area and is not supported here (**Section 8.1.2**). Instead, a framework of neuro-facilitators and neuro-inhibitors will be described that explains the theoretical action of each of these materials. This description is based on the Electrolytic Theory of the Neuron (**Section 8.1.3**). These explanations are consistent with the observed pharmacological effects of these materials. The organization of these materials into a functional framework is provided in **Section 15.1.8**.

The -ergic properties of a chemical can be addressed in two distinct arenas. The first describes the results of topical application of the chemical to an individual neuron. The second describes the results of global application of a chemical to the organism, usually via injection into the bloodstream.

To frame the discussion of topical application, consider first the Node of Ranvier as shown in Section xxx. At each Node, the electrostenolytic processes associated with the pre-nodal, nodal and post nodal elements are in very close proximity. These morphological elements are closely identified with the input, base and output terminals of the Activa at the heart of the Node. Consider the topical application of GABA to each of these elements. The result is an increase in the concentration of GABA at these sites. Such an increase has a retarding effect on the normal electrostenolytic

[125]Fuster, J. (1998) The Prefrontal Cortex, 3rd Ed. NY: Lippincott-Raven, Chapter 3

reaction. When applied to the post-nodal element, GABA tends to reduce the collector potential of the Activa. This tends to reduce the amplitude of the action potential generated, and this reduction reduces the probability that the next Node will be excited sufficiently to regenerate the action potential. Regarding the propagation of the neural signal, the result is clearly inhibitory. If GABA is applied topically to the pre-nodal element, the result is generally similar but for a different reason. By lowering the negative potential at the non-inverting input of the Activa, the probability that the Activa will regenerate any action potential received from the previous Node is reduced. Thus, this application is also inhibitory. However, the topical application of GABA to the inverting input to the Activa has the opposite effect. Lowering this negative potential increases the forward bias between the emitter and base of the Activa. This action increases the likelihood that any action potential received from the preceding Node will be regenerated. Thus, this application of GABA is excitatory.

The above discussion used probabilities to describe the effect on signal propagation related to action potentials. When discussing tonic neurons (the vast majority of neurons), the effects are deterministic but slightly different. The topical application of small amounts of GABA to the site of electrostenolytics of the axon will have little effect on signal amplitude. Application of GABA in excessive amounts will cause the Activa to shut down for lack of reverse bias between the axon and the poditic terminal. Similarly, topical application of small amounts of GABA to the poditic electrostenolytic site will cause a reduction in negative potential at this site. This change in bias will cause an increase in axon potential (an increase in the signal amplitude relative to the quiescent condition). The effect is therefore excitatory. A similar application to the dendritic electrostenolytic site will have an inhibitory
effect on the output at the axon. The application of large amounts of GABA to the dendritic or poditic sites will tend to change the biases on the Activa sufficiently to cause shutdown of the circuit. GABA is the prototypical neuro-inhibitor.

The effect of other pharmacological agents is similar. If the topical application of the agent increases the measured parameter relative to the neuron, it is considered excitatory (whatever the ultimate result on the complete neural entity). If the topical application results in a decrease in the measured parameter, the agent is considered inhibitory (regardless of the ultimate result on the complete neural entity).

Once initiated, the actions described above tend to propagate through the remainder of the system until a stage 3 stellate circuit is reached. The output of a stellate circuit is applied to an engine consisting of thousands to millions of neurons performing Boolean Logic and generating many individual output signals. Whether these individual outputs reflect the original character of the excitatory (or positive) or inhibitory (or negative) input is impossible to say.

When the concentration of GABA within neural tissue is increased globally, the result is indeterminate in three ways. It is indeterminate with respect to its effect on a single neuron and it is indeterminate with regard to multiple neurons in series. The effect on the output of an engine consisting of many neurons is similarly indeterminate. This is the source of the problem in using the expression GABA-ergic in pharmacology. A global application may cause multiple observable events. As a caricature, the observed effect following global application of GABA may be a slowing of the heart rate accompanied by an opening of the iris and a tingling feeling in the left toe. What the investigator reports depends on what characteristic(s) he has chosen to observe.

The effect of topical application of the neuro-facilitator glutamate tends to be the opposite of GABA since it drives the individual electrostenolytic processes toward completion. Aspartate, in its role as a secondary neuro-facilitator, acts similarly. The roles of other class 1 neuro-facilitators and neuro-inhibitors can be described similarly because they act to disturb the electrostenolytic process by occupying stereo-specific sites on the substrate. The role of class 2 neuro-facilitators and neuro-inhibitors are more difficult to predict because they tend to change the diffusion coefficients of the inter-neural matrix (INM) and the walls of the capillaries. These actions affect the concentrations of many individual materials within the INM.

The roles of other Class 1 and Class 2 neuro-facilitators and neuro-inhibitors are more difficult to predict.

The effect of various neuro-facilitators and neuro-inhibitors, when applied topically, depends on where they are applied and in what concentrations. In this regard, each active region of the neuron must be looked at separately. This is particularly important regarding long axons containing Nodes of Ranvier. Besides each Synapse and each Activa placed within the soma of a neuron, each of these Nodes represents a separate active circuit. Exploring tonic and phasic neurons separately, regarding their sensitivity to pharmacological changes, is also important.

In summary, the effect of a given chemical, whether a glutamate or other pharmacological agent, on a neural circuit depends on where it is applied topically. If it is applied globally to a neuron, the impact depends on at least three factors. First, the relative concentrations applied to different electrostenolytic areas of the plasma wall. Second, the relative porosity of the local environment to the topical agent. Third, the ability of reaction byproducts to exit the immediate area of electrostenolytics. Finally, the toxicity of neuro-facilitators and neuro-inhibitors suggests excessive dosages can lead to neural shutdown and coma in the subject.

8.6.6.4.3 2 GABA-ergic is a clinical, not scientific, designation

As noted above, the effect of an individual neuro-facilitator or neuro-inhibitor is highly dependent on how it is applied and what outcomes are observed. While a designation such as GABA-ergic can be used in a stylized clinical setting, it is imprecise and largely meaningless in a scientific setting. This is illustrated in the caveats in a paper by a psychologist[126]. "If some degree of error can be tolerated in the identification of these neurons, there is considerable evidence that one class of GABAergic interneurons can be identified with some confidence using extracellular methods." The same conclusion can be drawn concerning many other pharmaceuticals[127]. Their action can only be defined precisely when topically applied to a specific portion of a neuron. When ingested, or injected, generally their effect can not be specified precisely and many side effects are to be expected.

Golding & Oertel have recently highlighted the inconsistencies in using the terminology glycinergic and GABAergic[128].

8.6.6 The description of materials affecting neural operation abnormally

The major group of non-natural substances impacting the neural system, particularly of the CNS are the barbiturates. The barbiturates are a large family of natural and manufactured hypnotics, derivatives of barbituric acid Clinically, their "Most likely site of action: gamma-aminobutyric acid (GABA) receptor complex, $GABA_A$. This site is the same as the electrostenolytic site proposed in this work.

Figure 8.6.7-1 shows the structure of the most prominent members of this family. It is not clear how these materials would stereo-couple to the electrostenolytic sites designed for glutamate and GABA. They do not contain two oxygen atoms attached to a common carbon or two oxygen atoms attached to adjacent carbons in a ring structure.

8.8 CHAPTER SUMMARY

This chapter has presented the neuron as viewed from the perspective of "Modern Physics." Modern Physics introduces the fields of quantum-mechanical physics, semiconductor physics, the liquid-crystalline state of matter and the static and dynamic areas of conventional electricity to the field of neurobiology. Based on these disciplines, this chapter has presented an electrolytic theory of the neural system as an alternate to the previous ionic permeability theory. The additional understanding provided by the new theory is impressive. The electrolytic theory shows that;

+ it is important to define the individual regions of the external membranes associated with the neuron much more precisely than ever before in

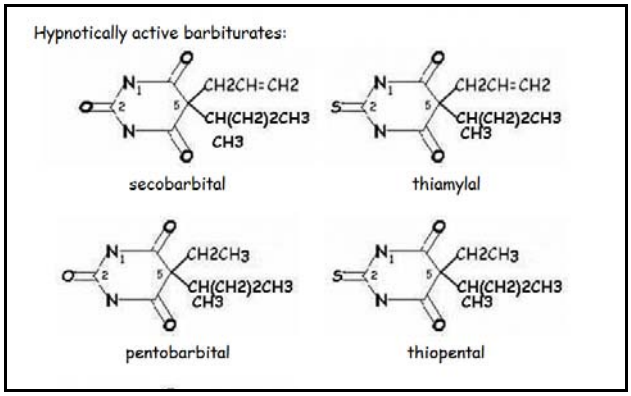

Figure 8.6.7-1 Important members of the barbiturate family of hypnotic drugs and anaesthetics.

[126]Swadlow, H. (2003) Fast-spike interneurons and feedforward inhibition in awake sensory neocortex *Cerebral Cortex* vol 13, pp 25-32

[127]Baker, M. & Wood, J. (2001) Op. Cit.

[128]Golding, N. & Oertel, D. (1996) Context-dependent synaptic action of glycinergic and GABAergic inputs in the dorsal cochlear nucleus *J Neurosci* vol 16(7), pp 2208-2219

order to understand the function of each differentiated region of the membrane.

+ the neuron is a specialized neuro-secretory cell of the animal. Neurons are grouped into signaling paths in support of the overall sensory and motor functions of the animal.

+ the fundamental neuron consists of a series of electrical conduits supported by a variety of metabolic processes grouped around the nucleus.

+ the nucleus plays no role in the signaling function of a neuron.

+ each conduit of the neuron represents a closed membrane filled with a heterogeneous electrolyte.

+ the functional performance of the fundamental neuron can be explained in terms of an active electrolytic semiconductor device called an Activa. It is formed by the precise juxtaposition of two conduits within a neuron or at the junction of two neurons. In the latter case, the Activa is known under the morphological name of a synapse.

+ The membrane of a conduit of a neuron, including the axolemma, is not an "excitable" structure. It is a passive structure consisting of a highly insulating bilayer of phosphoglyceride material. The membrane may consist of two symmetrical bilayers in which case it is an excellent insulator impervious to virtually all matter, including molecules, atoms, ions and electrical charges such as electrons and holes. The membrane may exhibit regions of asymmetrical bilayers in which case it shows a significant permeability to electrons and/or holes but remains essentially impervious to molecules, atoms and ions. In this case, it acts as a very high impedance but imperfect insulator when biased with the inner surface negative relative to the outer surface.

+ the membrane of a conduit may also exhibit a region that can be made permeable to neutral molecules, and possibly to neutral ion pairs, under specific circumstances.

+ the electrical characteristics of a conduit are dominated by the electrostenolytic and transistor processes related to it.

+ the charge injected into a conduit by transistor action need not become associated with an atom to form an ion. It may exist as a free electron on the interior surface of the membrane, as in any capacitor.

+ the overall electrolytic potentials and currents associated with a conduit and its surrounding matrix are defined in terms of a variable field equation and the principles of conventional electrostatics. The proper application of the variable field equation requires recognition of both the transistor interface at the Activa and one or more electrostenolytic interfaces on the surface of the membrane.

+ the Activa formed within a fundamental neuron is a typical three-terminal semiconductor device employing the principles of electrolytics within a liquid-crystalline environment.

+ the Activa can perform as a two terminal device (third terminal is identifiable but electrically unconnected) when it is stimulated by non-electrical means.

+ the power source for each conduit of a neuron is an electrostenolytic process on the surface of the conduit membrane employing a glutamate cycle which is reversible.

Based on the analysis, the following additional conclusions can be drawn. Much to the expected surprise of some readers, these conclusions are compatible with the position of Hodgkin and Huxley on page 541 of their final paper of

1952[129].

+ there is no requirement for ions to traverse the exterior membrane of a conduit associated with a neuron for the purpose of signaling.

+ the ions within the conduit are there primarily to provide a low impedance electrical path as far as signaling is concerned.

+ there is no requirement that the total ionic charge within the electrolyte confined by an insulating membrane be equal to the total charge on the surface of that same membrane.

+ the experiments of the 1950's did not demonstrate a direct relationship between the measured changes in interior plasma and the transit of ions through the membrane of the axon.

+ no theoretical foundation has been found for the differentiation of the putative current through the axolemma wall into an inrushing and an outrushing current.

+ no theoretical foundation has been found for the putative separation of the total current through the axolemma of a neuron in response to a putative action potential into two separate currents associated with the transfer of positive ions through that same axolemma.

+ no theoretical foundation has been found for the "certain simple assumptions" used to separate the above putative currents into currents associated with a specific type of positive ion. The independence principle cannot be supported.

Finally, a new representation of the plasmalemma of a cell can be defined that greatly aids in the discussion of neuron function. The plasmalemma can be divided into three primary types of membrane, each optimized for a different functional role.

The type 1 plasmalemma consists of a molecularly symmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular and electron flow (it is a very good insulator). This region is essentially inert with respect to cell operations.

The type 2 plasmalemma consists of a molecularly asymmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular but acts as an electrical diode with respect to electron flow . It is the primary participant in both the signaling and electrical biasing of the cell.

The type 3 plasmalemma consists of a liquid crystalline bilayer with many embedded proteins providing a transport path through the membrane. To avoid disturbing the electrical balance of the cell, this type of membrane transports electrically neutral (although frequently polarized) molecules through the cell wall. While some of these molecules may go into solution within the cell, the resulting ions are generally immobilized by the gelatinous nature of the plasma.

It is likely that much of the type 3 membrane associated with an axon is found buried within the neuron. There it would support the transfer of complex molecules from the region of the nucleus to the axoplasm. Some type 3 membrane may be exposed to the neural matrix to facilitate the transfer of lactate from adjacent glia cells to the axon.

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[129]Hodgkin, A. & Huxley, A. (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* Vol 117, pp. 500-544

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