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.

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PART C.
ELECTROCHEMISTRY OF THE VISUAL NEURON

Form follows Function (& available topography)

To understand the overall operation of the biological eye, understanding the operation of the neurons of the eye is necessary. The next three chapters will provide this foundation. These chapters were not envisioned at the start of this work. However, they became crucial to the understanding of the visual system as a whole. The concepts to be presented may appear foreign and radical to the visual science and neuroscience communities. A few words of introduction are appropriate. Because of the unexpected importance of this **PART C** to the overall work, these "few words" will be more extensive than in the Introduction to other parts of this work. They more closely represent an Introduction to a separate text. Ultimately, the material presented in **PARTS C** & **D** will be published as a separate volume. Following this introduction, an overview of the **PART C** will be given as usual.

C.1 INTRODUCTION

Initially, it was expected that this introduction would need to develop the justification for embarking on a theoretical construction that was not based on the ionic-transport theory embedded in the common wisdom concerning the operation of the neuron. However, examining the applicable theoretical framework showed that the so-called ion-transport theory (associated with the names Hodgkin, Huxley and Katz) was not defendable. It was a conceptual theory melding two independent processes related to transport mechanisms in a less than precise way. The first was the transport of (largely neutral or polar but not ionized) molecules through the membrane of a cell by vesicles. The second was the transport of charged particles through the membrane wall by the process of electrostenolytics.

By delineating the electrostatic and electrolytic rules applicable to the membranes of the neuron, the problems with the ionic-transport theory can be developed in detail. Alternately, the laws of charge transport as they apply to a membrane can be developed in detail. These laws have led to such a successful charge-transport theory for explaining the operation of the neuron and neural systems operation that attempting to defend them appears largely unnecessary. The material in the following chapters speaks for itself.

> **The ion-transport theory remains to this day incapable of explaining in detail how an action potential is generated. Similarly, the ion-transport theory has not explained how the horizontal cell performs a differencing operation. The ion-transport theory has not even attempted to explain the highly complex operation of the photoreceptor cell.**
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> **The electrolytic theory of neuron operation based on the charge-transport theory is so successful, and extends so far beyond the capability of the ion-transport theory, that to debate the merits of the two approaches seems wasteful. The following material, based on the charge-transport theory, answers questions at a detailed level that have never even been formulated within the ionic-transport theory.**

Section C.4 addresses the difficulties with the ionic transport theory more completely for those interested.

C.1.1 Difficulties with the Neuron Doctrine and the Independence Principle

2 Processes in Animal Vision

The ion-transport theory relied upon by Hodgkin, Huxley and Katz depended on the permeability of the membrane wall of neurons to ions, and an "independence principle" related to the flow of positive ions through that membrane. Those authors were unable to differentiate the axon membrane into distinct regions with the tools of the day. Current data shows that the intrinsic cell membrane is totally impervious to ions because of its hydrophobic core and the independence principle has never been confirmed. However, the current data from electron microscopy also shows the membrane wall to be differentiated into distinct regions. Even within specialized regions, the transfer of material in solution through the membrane using vesicles has never been shown to involve electrically unbalanced charges. Such a concept is unlikely under the laws of electrostatic electricity.

This work presents a functional description of the neuron that provides a foundation underneath the current morphological descriptions of the literature. The morphological description is limited primarily to the histology of the neuron, as exemplified by the Neuron Doctrine originally propagated by Cajal.

> This Neuron Doctrine says that the neuron is the structural (cellular) and functional unit of the nervous system. Based on this proposition, Cajal went on to infer the Law of Dynamic Polarization. This Law says all neurons are dynamically polarized such that excitation can only be transmitted from the axon of one neuron to the dendrites or soma of another. It also says that within a neuron, this excitation travels from the dendritic pole to the axonal pole. This framework assumes the neuron is a two-terminal device with an input and an output. The framework is unnecessarily narrow.

As will be shown in considerable detail, **the above Neuron Doctrine and its corollary Law of Dynamic Polarization are no longer adequate** and must be abandoned or extensively rewritten. As suggested by Brown, these principles began to break down under careful experiment during the last quarter of the 1900's[1]. **Chapter 10** will show that they require considerable modification when the true role of the Activa and the Node of Ranvier are understood. **Section 10.8** describes a more fundamental physiological unit of the neural system than the morphological neuron. **Chapter 12** shows that the morphological neuron known as a photoreceptor cell contains multiple fundamental physiological units within one morphological cell. **Chapter 13** shows the three-terminal characteristics of the typical neuron and how this leads to signal subtraction within a single neuron. Similarly, **Chapter 14** will show that the typical ganglion cell, labeled based on morphology, contains multiple electrophysiological units.

In line with Cajal, all previous theories of neural operation have considered the neuron to be a two-terminal device. The new electrolytic theory supports the definition of a biological equivalent of the transistor, the Activa. The Activa is an active electrolytic semiconductor device with a liquid crystalline structure. Such a structure is a three-terminal device. The definition of the Activa leads to a detailed description of the entire neural system that extends far beyond that of the current literature. The definition of the Activa, combined with the detailed description of the neuron at the molecular level, leads to a paradigm shift in the fields of neurology and vision research. A comprehensive and precise all-electrolytic description of the neural system is the subject of **PART C** & **D**.

This **PART C** introduces a new charge-transport theory of the neural system based on electrolytics. It replaces the previous ionic theory in use for the last 50 years.

The functional description in this work assimilates the cytological (internal morphology), electrical, topological, and relevant metabolic data related to the neurological system in order to provide the first comprehensive description of the operational neurological system. A major result of this replacement of the simple morphological

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[1]Brown, A (1991) Nerve Cells and Nervous Systems. NY: Springer-Verlag, Intro to Chap. 10

description is the relegation of the Soma to a primarily housekeeping role. The principle functional role becomes that of the Activa, the active electrolytic semiconductor device(s) defining the performance of the individual neuron, and ultimately the entire system. With the recognition of the Activa, found at all interfaces between neurites and axons, as the primary component of the neurological system, the performance of the overall system is explained in a more direct and detailed manner.

The entire family of neuron types presented in Chapter 9 is seen to evolve, in an orderly manner, from a simple original (non-neural) cell.

Scope of the analysis in PARTS C & D

Initially, the scope of this material was limited to the neurons of the retina. However, the basic approach clearly led to an understanding of other neural types not found in the retina. The theory and framework also made it possible to describe the operation of nearly all elements of the visual system in unprecedented detail. As a result, the first chapter led to new avenues of exploration and documentation. The work now ends following the initial neurons (the stellate cells) within the very core of the individual engines of the cerebral cortex.

Neurons, like everything else in physiology, can be viewed from several perspectives and be divided into separate categories based on each perspective. To bound this work, neurons will be divided into five major classes.

1. **Sensory neurons** accept energy directly, or from an associated extracellular input structure, and convert it into an electrolytic neural signal.

2. **Interneurons** are designed to process information before or after transmission. They are generally involved with electrotonic signaling, involving continuous analog waveforms. These neurons are sometimes described, inappropriately, as operating in a sub-threshold regime.

3. **Hybrid neurons** interface between interneurons and projection neurons and provide the transition between pulse and electrotonic signaling (and vice versa). They are typically involved in functions such as encoding/decoding, thresholding and “sample and hold.”

4. **Projection neurons** are designed to transmit signals over significant distances within the organism. These neurons use pulse signaling techniques and generate “action potentials.” They are sometimes described as operating in a super-threshold regime.

5. **Mylo-neurons** are those that receive phasic signals (action potentials), normally from projection neurons, and deliver stimuli to the muscles of the organism.

Usually, a complete signal path passes through the sequence: #1, #2, #3, #4, (#3, #2, #3), #4, #5 where the bracketed group of neurons are located within the brain. Except for the neurons propagating action potentials, the above neurons invariably have lengths of less than one millimeter.

One result of this work has been the elucidation of a possible morphological evolution of all neurons from a basic non-neural cell. The evolution is based primarily on electrophysiological requirements and the putative primacy of electrical signaling in the neural system. The figures in the text show how individual simple modifications to each form of neuron lead to a more sophisticated and functionally useful form. From a system analysts perspective, the proposed evolution is truly beautiful and verging on the miraculous.

The initial intent was to separate synapses into two types, those communicating by chemical means and those communicating by electrolytic (largely quantum mechanical) means. The terminology used in the neuroscience literature is quite primitive in this area. It is based primarily on light microscopy and a large amount of chemically

oriented intuition. It is also contradictory and overlapping between authors. The terminology of individual authors is generally less precise than needed[2].

Most investigators and educators will grudgingly accept a simple dichotomy in this area between the chemically transmitting synapse and the electrically transmitting synapse. Electrical rather than electrotonic is used here intentionally. Electrotonic implies a restriction to a continuous, i. e. non-pulse signal; a distinction that is not desired at this point. While the above dichotomy may be useful for pedagogical reasons for some years, it is unnecessary based on function. All synapses associated with neural signaling are electrolytic, not chemical, in character.

It should also be pointed out that some investigators speak of signals that excite a neuron (implying that a signal that does not cause an action potential type of response is not important). In vision, this is patently untrue. The interneuron as defined above does not generate an action potential; however, it supports the primary signal processing functions in the eye. Similarly, the interneuron does not accept action potentials as an input. It is generally estimated that 90% of all neurons do not generate action potentials. These neurons are entirely electrotonic in operation.

Looking at the interface between two neurons, most investigators will accept the division of this interface into at least two groups. One group is based on the distance between the membranes of the two juxtaposed neurons. For reasons that will become obvious, this division will be made at a distance of 75-100 Angstrom in this work. This division is comfortably between the typical putative chemical synapse spacing of around 200 Angstrom and the commonly reported typical electrical synapse spacing of 20 Angstrom.[3] The narrowness of the electrical synapse has led to the assignment of the less than specific name, "gap junction," to both putative chemical and electrical synapses. Dobbin[4] makes a further distinction among the putative chemical synapses into those with a width (perpendicular to the axis of the junction) of around 200 Angstrom and those between 500-1000 Angstrom that appear most frequently with mylo-neurons.

To go further in the subdivision of classes of neurons is quite difficult and frequently misleading. Many attempts have been made to pursue the subject further on morphological grounds. However, as will be seen below, morphological categorization is fruitless unless the electrolytic topology of the neuron is brought into the discussion. Topology provides a clear indication of what are input structures and what are output structures--plus other types of structures--without depending on physical characteristics. The case of the amercine (Greek: no axon) cell is a good example; by simple topological arrangement, the input and output structures share parts of a common external cell wall. This arrangement gives the appearance of a neuron with an input structure but without an output structure. Only analysis via electron microscopy can confirm that the cytological structures along this external wall look much like normal input and output terminal structures.

Three important points can be derived from the above discussion.

> **1. Based on the above discussion, this work will focus on electrical (signal carrying) synapses using a spacing of less than 75-100 Angstrom between the membranes of juxtaposed neurons. Furthermore, it will be limited to a discussion of sensory neurons, interneurons, hybrid neurons, projection neurons and their synapses. It will specifically exclude the discussion of mylo-neurons and their interfaces with the muscles.**

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[2]Bennett, M. (1997) Gap junctions as electrical synapses. J. Neurocytology vol. 26, pp. 349-366
[3]Pappas, G. & Purpura, D. (1972) Structure and function of synapses. NY: Raven Press pp. 1-44
[4]Dowben, R. (1969) General Physiology: a molecular approach. NY: Harper & Row pg. 414

2. Many of the widely-spaced interfaces between neurons are not for the purpose of signaling but exist to support the electrostenolytic process powering the neurons.

3. Because of its apparent electrical nature and importance, a new functional class of synapse will be discussed. This is the intra-cellular synapse. Although the well-known Node of Ranvier is a member of this class, every neuron contains at least one additional intra-cellular synapse.

In the following chapters, it is shown that a neuron contains one or more internal sites that can be described as "active devices" in the terminology of the electrical engineer. These sites exhibit the phenomena known as "transistor action." They are therefore defined and described as "Activas," i.e., biological transistors. It will also be shown that transistor action can occur at the junction between any two membranes, whether external or internal to a given neuron, if the spacing requirement and other conditions are met. Thus, transistor action can occur between two neurons, and potentially more generally, between any two cells, i.e., a motor nerve cell and its associated muscle cells.

The specific location of these Activas is defined for each type of neuron discussed here. The structure supporting this "transistor action" is also defined along with the resulting operating characteristics to the level required to understand the vision process. Much of the material needed to understand the fundamental operation of the biological transistor will be found in **Appendix B**.

C.2 RELEVANT PHYSICAL CHEMISTRY OF THE NEURON

The material in the following chapters may be difficult to follow for those without any significant training in electronics. One course in how to wire a circuit and providing an algebraic explanation of Ohm's Law will not be enough background. Even electrochemistry is not generally taught to chemistry majors at the bachelor level. The finer points of quantum chemistry, which blends with quantum physics, are probably omitted in most bachelor programs. To aid the lay reader, a large Glossary is provided as part of this work. In addition, many references are provided to basic works associated with less well known subjects as they are addressed.

C.2.1 The biological organism is based on liquid crystalline chemistry

While not generally recognized, the membranes of the biological organism are liquid crystalline in character. The liquid crystalline state of matter is particularly temperature sensitive. This sensitivity defines the biologically viable temperature range. Within its operating range, the liquid crystalline state of matter exhibits unique properties. The crystalline characteristics associated with that state contribute to the quantum physical characteristics of these membranes. On the other hand, the liquid characteristics associated with that state provide a high degree of physical plasticity. Membranes do not normally support discontinuities in their structure (or inclusion) without losing some valuable properties of the liquid crystalline state. Only highly differentiated regions of membrane supporting the transport of molecules through the membrane wall support vesicles designed to support such transport. Most of the caricatures in the literature showing inclusions of protein molecules and various gate structures in membranes are not supported by electron microscope evidence. They remain largely caricatures.

C.2.2 Achieving "transistor action" between cell membranes

Presenting a comprehensive treatise on the detailed nature of the neural membranes of interest here is not appropriate. Only the pertinent parameters and general features will be discussed to provide the necessary structure to the overall vision process. The key fact is that the typical neural membrane consists of two leaves or bilayers of phospholipid material. The overall membrane consists of at least three distinct regions. In one region,

the two bilayers are symmetrical at the molecular level. The resulting structure is highly insulating electrically and is passive. One region of the membrane is asymmetrical at the molecular level, forms an electrical diode and supports an active stereo-chemically specific process known as electrostenolysis. The third region is also asymmetrical at the molecular level, forms a diode when standing alone, and under that condition is passive. However, when brought into juxtaposition with a similar region of membrane from another neuron, and electrically biased appropriately, the resulting structure exhibits unique (startling) properties. It becomes an active electrolytic device exhibiting "transistor action." This structure is called an Activa. It can be formed within a neuron or between neurons. It is the key to signal propagation within the neural system. The details of this structure, and its unique performance characteristics will be developed in **Chapter 8**.

The presence of a diode in the membrane of a cell is critically important. The role of a diode in an electrical circuit cannot be rigorously addressed using Ohm's Law. Kirchoff's Laws must be used. Of equal or greater importance, the diode does a logarithmic conversion between the current through the diode and the electrical potential across the membrane. This conversion introduces a variety of unique properties into the visual system. It also negates all of Grasslands Laws describing the putative linearity of the visual system.

To understand the neuron from this perspective, the physical chemistry of intimate asymmetric membrane pairs immersed in three different high concentration electrolytes operating under non-equilibrium conditions must be considered.

If the physical chemistry framework is broadened to consider these possibilities, the nature of a neuron is changed. The external membrane of a single axon or dendrite is seen to take on the role of a simple single layer asymmetrical membrane separating two high concentration electrolytes under non-equilibrium conditions (and it is passive!). This non-equilibrium electrolytic condition provides a framework for explaining the non-linear impedance characteristic and also the various ion pumps frequently proposed for incorporation in this "membrane system." This electrolytic cell approach also provides the explanation for the non-dissipative, and potentially reversible, thermodynamics of the neuron that accounts for its remarkable thermal efficiency. No significant energy is lost as heat!!!

C.2.3 Achieving an internal electrical potential without an ion-pump

The electrophysiologists of the middle of the 20th Century depended heavily on their physical chemistry background to hypothesize an ion-pump for transferring charge through a membrane. Simultaneously, biochemists working in metabolism were focusing more on the movement of electrons among molecules during stereo-chemical rearrangements. Also, organic chemists were exploring the transfer of electrons across artificial biological membranes. These studies confirmed many facts. The most important was that charged ions were not easily moved through biological membranes. No mechanism was ever defined and demonstrated that allowed membranes or vesicles within membranes to transport heavy ions across a membrane. A second was the fact that free electrons could be introduced into the interior of a closed plasma membrane easily. These charges resulted in a potential across the capacitance of the membrane in accordance with the laws of electrostatics. Whether ionized molecules were included in the solution filling the membrane was inconsequential. The mechanism for transporting this charge are well documented in the electrostenolytic process.

Thus, a charge-transport mechanism based on electrostenolytics can charge the interior of a closed plasma membrane negatively without the transport of any ions through the membrane (or the presence of any ions within the membrane).

C.2.4 The importance of non-equilibrium and non-steady state conditions within neurons

The literature of electrochemistry, particularly that portion found in textbooks, is highly inconsistent in both concepts and terminology. Furthermore, many if not most mathematical analyses invoke a variety of assumptions to make the mathematics more tractable. These assumptions are frequently not highlighted. A specific area of concern is the differences between the Nernst, Donnan, and Goldman equations (the latter sometimes modified and described as the Hodgkin-Huxley-Goldman equation). The serious investigator should be sure he understands the specific conditions that apply to the generation of each of these equations. As a starting point, the fact that the membrane involved is semipermeable to at least one, but not all, ionic species present should be recognized. Gutmann and Keyzer[5] provide a brief comparison and site the appropriate references. To scope the situation, keep in mind that Nernst and Donnan investigated *equilibrium conditions* whereas the later investigators were investigating *steady state conditions*. A big difference exists between the two conditions when discussing neurons. For purposes of this work, a third condition will be introduced, **non-equilibrium and non-steady state conditions**.

All of the equations developed by the above authors were developed for low concentration solutions. The plasmas associated with neurons are so concentrated as to be at least very viscous if not actually in the liquid crystalline state. Understanding the operation of the neuron requires an understanding of the liquid crystalline state of matter.

C.2.5 Neurotransmitters versus the neural signaling medium

Neuroscience has relied upon the pharmacology community to define the operation of the neuron. This community has generally relied upon psychophysical observations of the organism to learn the effect of various chemicals on the neural system. *In-vivo*, the approach has been to inject the pharmacological agent and observe the effect. *In-vitro*, the approach has generally been to apply the agent topically. Neither of these approaches directly addresses the medium employed to transfer information across the gap junction between two neurons. The assumption has been made that agents applied as described above were also the information carrying mediums. The physiology and quantum physics of the very narrow gap associated with juxtaposed neurons is not compatible with the size of the above molecules. More important, transistor action demonstrates that the information carrying medium consists of electrons.

The use of the designation neurotransmitter involves a poor choice of words. The materials involved are not involved in neural signal transmission. They are used in neuro-facilitation and neuro-inhibition based on their effect on the electrostenolytic process powering the neurons. The only neurotransmitter from a signaling perspective is the “free” electron passing through an Activa.

C.2.6 Unusual and reversible thermodynamics support the neuron

The electrostenolytic mechanism of the neuron is closely associated with the tricarboxylic acid (Krebs) cycle. In fact, the electrostenolytic mechanism can be described as the glutamate-GABA shunt in the context of the Krebs cycle. The electrostenolytic mechanism occupies an interesting place within the field of thermodynamics. In theory, the process is reversible unless the reaction products are removed from the electrostenolytic site. In addition, the process is quantum mechanical. This puts it in a special area of thermodynamics. Quantum mechanical processes are frequently carried out without the generation of any heat.

The Third Law of Thermodynamics is based on the production of heat in a non-reversible process. It is more properly named the third law of irreversible thermodynamics. In electrostenolytics, the potential exists to operate largely outside the Third Law of Irreversible Thermodynamics. By transferring electrical charges across diodes instead of resistors, the generation of heat is theoretically avoidable. This capability helps account for the very high thermal efficiency of the neural system (particularly within the skull cavity of humans where it is so obvious).

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[5]Gutmann, F. & Keyzer, H. (1986) Modern Bioelectrochemistry. NY: Plenum Press. pp. 70-72

between reversible and irreversible thermodynamic processes, and how to recognize them, is also very important. In a reversible electrolytic process, an impedance may be specified which is related to a chemically reversible

electrical energy when a current passes through it. The result is the generation of heat. This action is at the root of the Carnot Cycle and it involves an irreversible process. The impedance involved in a chemically reversible

generate heat. This impedance represents the conversion of electrical energy into retrievable chemical energy. To distinguish this type of reversible impedance, that is not a resistor (or a reactance) in electrical terms, it is

alphabet, yau, and represented by the symbol Я. This allows one to write an equation of the form:

$$V = iR + iЯ$$

where the iR term is resistive and thermodynamically irreversible while the iЯ term is thermodynamically reversible and therefore Я does not represent a resistor within the terms of Ohm's Law. Specifically, the above equation is a proper description within Kirchoff's Laws but it is not a proper description within Ohm's Laws. The power *dissipated* in the above equation is $P_d = i^2*R$ and not $i^2*(R + Я)$. The power *stored in chemical form* in the above equation is $P_s = i^2* Я$. Note however, the current related to the stored energy is not in quadrature with the current related to the resistor.

This author will undoubtedly be accused of trying to circumvent the Second Law of Thermodynamics. As noted above, the Law normally referred to is more properly named the Second Law of Irreversible Thermodynamics.

As will be seen in the following chapters, the dominant impedances involved in neurons are of the non-dissipative type. In the Activas and the electrostenolytic processes, they are not linear devices but diodes. For the long axons, the impedances are not resistors and capacitors but inductances and capacitors. This distinction must be pointed out in any equations developed to describe neural processes from the electrical perspective.

The discovery of the non-dissipative nature of the electrical signaling in the nervous system is a major, but totally unexpected result of this work. It is now possible to understand how so much information transfer can occur within the human cranium without causing excessive heat to be dissipated. In fact, virtually no heat is dissipated within the animal nervous system. The necessary change in entropy is carried out via chemical transformations.

As might be expected from the foregoing, this work will only be concerned with synapses and intra-cellular synapses relying on electrical transport of charge (current). Chemically mediated synapses are not considered or discussed. The author leans strongly toward the position that chemical synapses related to signaling do not exist.

By integrating the electrical and morphological characteristics of the neural system, the physiology of the neuron can be presented in a new, complete, compatible and satisfying framework.

C.3 OVERVIEW OF PART C BY CHAPTER

PART C is divided into three Chapters to differentiate between the basic elements and concepts involved, the basic circuits that can be formed from these elements, and how these elements and circuits are used in an actual neural circuit. **PART D** goes further to discuss the applications of the basic elements into the neurons of each stage of the visual system.

Chapter 8 focuses on the basic sciences and the functional elements associated with a fundamental neuron. Even this fundamental neuron is subdivided for discussion into a basic and a second order neuron. Both transistor action within the neural system and the need for explicit electrical power supplies to support this action are introduced. The proposition that a conventional synapse is actually an active electrolytic device is introduced.

Chapter 9 discusses the characteristics and properties of individual classes of neurons. It begins with the simplest, the bipolar neuron, and proceeds to the horizontal and amercine cells, the photoreceptor cells and the ganglion cells. The Chapter includes a preliminary "data sheet" describing the electrical performance characteristics of each type of Activa involved in the visual process. These data sheets are works in progress and subject to expansion based on the results of additional laboratory investigation.

Chapter 10 assembles the material from the first two chapters and develops the more complex relationships within and between neurons. It also develops the morphology of a given type of neuron based on its underlying functional requirements and resulting functional elements. A major section develops the electrical characteristics of various neurons as typically observed through electro-physiological experiments. It is shown that much of the inconsistency encountered in these experiments can be removed by more careful definition of the experiment and the experimental conditions employed. The putative "ion-pump" of conventional wisdom is replaced by an electrostenolytic process (a charge-pump). The relationship between this electrostenolytic process and the non-dissipative resistance discussed above is demonstrated.

The chapter addresses the morphological characteristics and the functional performance of the Node of Ranvier in considerable detail. It can be used as an example of a complete neural circuit. It shows that the action potential is formed by a switching oscillator and exhibits a discontinuity at a time near the peak in the response. This discontinuity is not explained in the Hodgkin & Huxley model of the action potential.

It also reviews the protocol and measurements of Hodgkin & Huxley in a more modern context. This review highlights the limitations on their procedures and claims. It addresses their early version of the voltage clamp procedure in detail.

Significant problems with the original voltage clamp test set of Hodgkin & Huxley are presented. With the advent of transistorized electronics in the 1960's, these shortcomings were overcome. Unfortunately, the earlier work is still widely quoted. It is shown that the critical constant voltage condition across the specimen was not achieved in the Hodgkin & Huxley tests. As a result, their putative potassium currents (where potassium was used as a presumptive label) were primarily an artifact of their test set. Without a putative potassium current in opposition to the putative sodium current, the putative independence principle is no longer needed. The unexplained “notches” in their test data are fully explained using the model of this work. The need to reexamine all of the prior data obtained for Nodes of Ranvier using voltage-clamp techniques is shown by the success of the technique when using the underlying electronic model of the Node presented in this work.

This material in these three chapters provides an alternate hypothesis to the operation of the neuron compared with that found in the current literature. Its claim to authenticity is based on its ability to describe properly and adequately the operation of a wide variety of actual neurons. Its fundamental proposition is that the neuron incorporates at least one active three terminal device, as opposed to a two terminal device such as a single membrane. The corollary to this proposition is that: failure to control this third terminal leads to spurious results experimentally. The result is frequent reports of “Spontaneous” neuron output[6]. A second proposition is that the transfer of charge is the basic signaling mechanism between neurons. A corollary to that proposition is that the measured potentials associated with that charge transfer may be misinterpreted by untrained investigators. This

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[6]Nam, S. & Hockberger, P. (1997) Analysis of spontaneous electrical activity in cerebellar Purkinje Cells acutely isolated from postnatal rats. J. Neurobiology. vol. 33, #1, pp. 18-32

can occur if the nature of the associated impedances is not understood.

This approach is consistent with the cautious statement by Gutmann, Keyzer & Lyons: "Solid state events involving conduction are evident in animate aggregations and may well be an essential characteristic of life, which may be an electromagnetic phenomena. A growing body of reviews and texts is available to support these views."[7] Amen. This approach also solves one of the major problems they associate with organic semiconductors. The biological materials of the neurological system are all transparent liquid-crystals and easy to characterize compared with the generally amorphous organic semiconductors on which the above authors have concentrated.

The circuit diagrams presented in these chapters are of actual neurons (to the level of detail required by the discussion). *These circuit diagrams should not be considered "equivalent circuits*." The symbology used is man made; but the circuits these symbols describe are those of the actual neurons in actual animals.

[7]Gutmann, Keyzer & Lyons (1983) Op. Cit. pp. 319-xxx

C.4 AN EXTERNAL ANALYSTS VIEW OF NEUROSCIENCE TODAY

The Don's of the academic community have long stressed the empirical approach and denigrated theory in biology. As discussed in the preface, this has been a major disservice to the community. Progress is most rapid when theory and experiment move forward in tandem. The problem has been exacerbated by the limited theoretical background of most people moving into the biology field. Even the advent of Bio-engineering has seen large numbers of inadequately trained bachelor level engineers moving into the biological field. In one case, a well prepared PhD level engineer moved over but found it difficult to find the theoretical underpinning needed to exploit his technical background fully.

As suggested in the previous discussion, the Neuroscience community has paid little attention to the basic laws of electrostatics when developing their technical framework for the neural system. Moreover, they have basically ignored the rules of quantum physics as they apply to complex molecules. Equally important, they have not updated or added precision to the working definitions they have used for the last 50-100 years. The above factors leave both their technical framework and their literature in a state of immaturity and inconsistency.

C.4.1 An analysts view of the current framework of Neuroscience

Since the visual system consists primarily of neurons, understanding the neuron is necessary to provide a complete explanation of the visual system in animals. The literature of Neuroscience presents an unusual picture from a variety of perspectives. These will be highlighted briefly below.

Reviewing the most prominent and comprehensive research and pedagogical works in the field at the end of the Twentieth Century is enlightening. This literature is heavily weighted toward the morphological aspects of the neuron as opposed to the physiological (functional) aspects. This has been true for a very long time. An exploratory breakthrough occurred in the 1950's that cannot be denied. The work of Huxley, Hodgkin and Katz was pivotal. However, it does not appear to have been exploited by later work. While it should have encouraged additional exploration by younger investigators, it did not. Nearly 25 years later, in 1976, a major work appeared entitled "The Synapses" edited by Cottrell & Usherwood[8]. It opened with a major chapter by Sir Katz that was mostly oriented toward the work up to the 1950's. The introductory chapter in a more recent major work[9], "The Axon" by Waxman, Kocsis & Stys (1995) is devoted to the work in the field up to the 1950's and was prepared by Sir Huxley. This is remarkable. Even 50 years later, the work of the above team is still considered one of the latest major breakthroughs in Neuroscience. This was true although these men appear to have had no training in electrolytics, electrostatics or quantum level physics. Their thesis was based entirely on observational evidence and their own intuition. Shepherd has played the role of dean of the neuroscience community for a long time. His Neurobiology has appeared in three editions up through 1994 but all based primarily on the original 1988 release. 1998 saw the publication of the text and atlas, Functional Neuroanatomy by Afifi & Bergman[10]. Although profusely illustrated, it is based on the same dated material as the above works. It contains virtually no current information on signaling as an important function of the neurons. The work to be presented here conflicts with many of the "Key Concepts" shown in the call-out boxes of that work. 1999 saw publication of the Dendrites by Stuart, Spruston & Hausser[11]. This book continues to stress the morphology and the metabolic functions of the

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[8]Cottrell, G. & Usherwood, P. (1977) Synapses. London: Blackie & Sons
[9]Waxman, S. Kocsis, J. & Stys, P. (1995) The Axon. NY: Oxford University Press
[10]Afifi, A. & Bergman, R. (1998) Functional Neuroanatomy NY: McGraw-Hill
[11]Stuart, G. Spruston, N. & Hausser, M. (1999) Dendrites. Oxford: Oxford University Press

dendrite with virtually nothing concerning its role in signaling. Even the text, Nerve Cells & Nervous Systems by Brown does not recognize the dominance of analog signaling and the statistically minor role played by phasic neurons and action potentials in the nervous system[12]. Few other fields of Science and no fields of Engineering exhibit the lack of growth of ideas *at the fundamental level* found in the Neurosciences.

Part of this slow growth of ideas at the fundamental level can be explained by the nature of electrolytic chemistry, the principal foundation of the functional aspects of the neuron. Examining the curricula of any major university shows that Electrochemistry is a stepchild of Chemistry. Similarly, Electrochemistry is a stepchild of Electrical Engineering. Electrochemistry is a niche field commercially. The Electrochemistry of the even more obscure area of the liquid-crystalline state of matter is even less well known (although it has come into its own recently in high-tech consumer electronics). Understanding the functional aspects of the neuron and the nervous system without an appreciation of the field of electrolytic chemistry, as it applies to liquid crystals, is impossible.

Another major part of the phenomena can be explained by the fact that the laws of 20th Century Quantum Physics have yet to be embraced by the neuroscience community. The community generally speaks of Gaussian (Normal) statistics when most biological processes are controlled by Log-Normal statistics. When speaking of submicroscopic particle oriented events, it generally speaks in terms based on *Boltzmann-Maxwell distribution law* when the *Fermi-Dirac distribution law* is more appropriate when discussing the interaction of photons with matter. The “hole” of semiconductor physics is a concept that has found no natural home in the literature of the neurosciences.

The above difficulties appear related to the minimal mathematical training provided to biological students at least up through the 1980's. Without understanding the concepts of differential equations, it is virtually impossible to attack, or even comprehend, the dynamic aspects of the neuron. Without such a capability, the community generally falls back on simple pedagogical explanations of more complex concepts. The adoption of physical gates in the wall of a continuous cell membrane is such a crutch. The ion gate was originally a crutch to help mid-level biology students cope with the apparent transmission of ions through a membrane. The actual electrostenolytic processes when applied to semiconductor materials do not require the physical transport of ions through a membrane. The transport of electrons and holes provides the same chemical results.

Finding a major work in Neurosciences that recognizes the fundamentally analog nature of the neuron is still rare. The field is dominated by the view that most if not all neurons operate in the pulse mode, generating “Action Potentials” through a chemical process. This position seems to have evolved for two reasons. The larger and most accessible neurons are projection neurons found in the peripheral nervous system (PNS) and associated with motor activity. Motor neurons are overwhelmingly of the pulse signaling type.

However, from a functional perspective, an entirely different view emerges. As discussed in Waxman, et. al., the plurality of neurons in any animal is associated with the central nervous system (CNS) and not the PNS. They give the ratio as 99.9% to 0.1%. The neurons of the CNS, which includes the retinas of the visual sensors, are fundamentally analog devices. Further more, many of the PNS nerves associated with sensory paths are in fact not of the pulse type. Only the projection neurons used to transmit signals beyond a few millimeters are of the pulse type. All other neurons involve analog signals represented by electrotonic potentials. The literature estimates the ratio of tonic to phasic neurons at 90% to 10%. Some hybrid neurons exist that the above authors define as PNS-CNS compound axons.

A similar situation has evolved with respect to the interconnection of neurons. Because essentially all biologists are trained in chemistry and a biochemist is by definition a chemist, biological research has been built on a

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[12]Brown, A. (1991) Nerve Cells and Nervous Systems. NY: Springer-Verlag

foundation of Chemistry, and emphatically not on Electrochemistry. As above, it is remarkable that the Neurosciences still rely on relatively simple chemical reactions to explain the operation of neurons, even in the face of the lament by Sir Katz in 1977[13]: "...but I must confess that I am sometimes worried about whether, on our present evidence, we are justified in telling our students that chemical synapses are the predominant type in our central nervous system."

Although Huxley, Hodgkin and Katz were very careful in their original papers to circumscribe their work to the membrane wall of an axon, the community quickly generalized the work to relate to the total axon and then the total neuron. Whereas, they showed the electrical parameters of the membrane to be virtually identical to those of the newly discovered (at that time) semiconductor diode, they did not explore, or introduce, the relevant technology. They and the neuroscience community continued to develop *very simple* electrical models to represent the membrane. These models are still in use today. Only weak attempts have been made to explain the controlling mechanism for the various ionic currents that putatively flow through the membrane wall of an axon.

To this day, the neuroscience community still employs passive electrical analogs to explain the operation of the neuron. Virtually no work has been reported that explains the operation of the neuron based on an active device. No work has been accepted that includes any active device within a neuron. Waxman, et. al. show an entirely passive network in their explanation for the operation of a mammalian myelinated axon, including the Node of Ranvier in 1995[14]. This model is interesting only in that it is <u>not</u> a "minimal network" from a circuit synthesis perspective. In Circuit Theory, usually associated with electronics, a minimal network is required to explain the true characteristics of a network. The principal problem here is in the lack of definition of the variable resistors. How do they vary? What causes them to vary? Where is the governing mechanism?

Bio-energetic materials are ubiquitous near neurons. However, all of the recent literature attempts to link these materials to the signal transmission function. Almost no material has appeared that would even suggest these materials play an electrostenolytic role in providing electrical power for an active electronic device within a neuron (or between neurons). This is unfortunate. When the concepts of electrostenolysis are applied to cytology, these bio-energetic materials are seen to take on an entirely different role.

The term PNS-CNS compound axon introduced above highlights another unusual feature of the Neurosciences. Shepherd[15] has written a complete book on the "Foundations of the Neuron Doctrine" discussing the evolution of the concept of the neuron as an independent physiological unit. Apparently that battle rages on. Waxman, et. al. clearly consider the Axon as a fundamental physiological unit and Cottrell & Usherwood present the Synapse as a fundamental physiological entity. At some time, these different schools must come together with a satisfactory description of the signaling function provided by neurons that can be defended by the morphology (physiology). After all, *neurons exist to provide signaling*. That is their only reason to exist. Neuroscience needs an integrated view of the integrity of the fundamental physiological unit and the intimacy of the junction between such units.

It appears that the development of the current literature of neurons at the membrane level has been seriously restricted by the ground rules set by the physical chemists in their analyses. To maintain a tractable mathematical environment, they have generally restricted their analyses to electrolytic environments consisting of a single, symmetrical membrane separating two similar low concentration electrolytes (with a minimum number of ionizable species in each) under equilibrium conditions. These are not the conditions found in a neuron. Furthermore, the biophysicists have chosen to continue (since the 1950's) to treat the neuron as electrically passive device except for the outer membrane of the axon. The axon has been considered a two-terminal circuit incorporating many inadequately defined circuit elements. From a system electro-physiologists perspective, this is

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[13]Cottrell & Usherwood, Op. Cit. Pg. 1
[14]Waxman, Kocsis, & Stys (1995) Op. Cit. Pg. 81
[15]Shepherd, G. (1991) Foundations of the Neuron Doctrine NY: Oxford University Press

quite limiting. It does not allow a broad enough view of the overall neuron. By broadening this perspective and treating the overall neuron as containing one or more active devices, which are typically three-terminal devices, a much more attractive (and functional) model of the neuron appears.

This author believes the time has come to replace the above framework entirely. The operation of the neural system relies upon an active three-terminal electrolytic semiconductor device found within, and between, all neurons associated with an individual signaling path. This device is known as an Activa. It is the electrolytic equivalent of the transistor. As Gutman et. al.[16,17] have shown in both 1981 and in 1983, a great deal of effort has gone into the search for such a transistor type of device in the non-biological portion of the organic chemistry community. However, nothing of the kind appeared. It has now appeared and been patented.

C.4.2 An analysts view of the recent literature

The literature of the neuron falls in two major categories, academic and clinical. The clinical literature depends on the academic for most of its discussion of fundamental mechanisms associated with neurology[18]. The academic literature has developed by building on early concepts that are now out of date in many critical aspects.
The academic literature of the neuron contains a great amount of experimental data and many discussions of how to interpret this data from a morphological perspective but no comprehensive model of the neuron at the fundamental functional level. Only recently, the view of the community has changed regarding the projection neurons. Previously, the entire axon was viewed as a dissipative cable made up of distributed resistances and capacitances. More recently, it has been viewed as discontinuous with sections of lumped resistance and capacitances and sections with distributed resistances and capacitances. Regeneration of the action potential has been noted at “hot spots” near hillocks of ganglion cells and each Node of Ranvier. This regeneration has led to the notion of salutatory signal transmission. Similarly, “hot spots” have been reported as occurring at various locations in the body of some neurons that are not associated with the nucleus. Recent references even report “hot spots” in the dendritic tree. This work will call on conventional (modern) electronic cable theory and demonstrate that the axon is primarily a non-dissipative cable consisting primarily of a coaxial cable. This cable exhibits significant capacitance and inductance but negligible resistance. In the coaxial cable, the various plasmas are the electrical conductors and the axolemma is the insulator.

A significant part of this problem has been the failure of the physiology community to provide a fundamental framework for the neural system to which the morphologist can relate. While maintaining an almost exclusively chemical perspective, the physiologist has not accounted for the vast array of morphological features involving measurable electrical characteristics. Specifically, the role of the electronically lucent and opaque regions have not been explained.

Extensive conceptual discussions have been held attempting to relate the nervous system to a computer. This has frequently introduced the hypothesis that the overall neural system of an animal involves digital and/or binary signaling. Stacy & Santolucito[19] have placed this discussion in context; “In summary, although the all-or-none nature of action potentials would suggest that information transfer in the nervous system is digital in nature, it actually is almost entirely, if not entirely analog in nature.” However, this description remains superficial. It does not distinguish between binary and digital. It does not distinguish between projection and local signaling.

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[16]Gutmann, F. & Lyons, L. (1981) Organic semiconductors: Part A. Malabar, FL: R. E. Krieger Publishing Co. pg. 633
[17]Gutmann, F. Keyzer, H. & Lyons, L. (1983) Organic semiconductors: Part B. Malabar, FL: R. E. Krieger Publishing Co. pg. 460
[18]Kandel, E. Schwartz, J. & Jessell, T. (2000) Principles of Neural Science, 4th Ed. NY: McGraw-Hill, Part II.
[19]Stacy, R. & Santolucito, J. (1966) Modern college physiology. St. Louis: C. V. Mosby pg. 80

Kandel[20], writing in Kandel, Schwartz & Jessell repeats the conventional wisdom, based on morphology, that the neuron consists of four chief functional compartments–the cell body, dendrites, axons, and terminals. These would not normally be considered functional descriptors in other technologies. They are more rationally described as topographic, i.e., morphological, descriptors. He also continues the tradition of considering the cell wall of a neuron to be "excitable" although our knowledge is continuing to detail the cell wall as a simple liquid crystalline film of triglyceride material without significant inclusions. Finally, He continues to explain the polarization of the cell as due to a mechanical pump that transfers ions across the cell wall. These aspects of the conventional wisdom are not supported by this work. He also continues to describe the velocity of action potentials along an axon without differentiating between phase velocity and group velocity. His assertion that: "As far as is known, glia are not directly involved in information processing, . . ." is supported. However, their role in providing electrical power to the neurons is becoming better documented every day.

His statement that all nerve cells share the same basic architecture is an oversimplification. He also claims that nerve cells differ most at the molecular level. This work will show that the photoreceptor cell exhibits a significantly different functional architecture and topology than most neurons, and that all neurons share the same detailed structures at the molecular level. It is also ironic that he supports the original assertion of Cajal (1900) that the feature that most distinguishes one neuron from another is *shape*. This feature may provide a simple, but misleading, classification of neurons. However, many other classifications exist based on more useful criterions.

He also expresses an intent to focus on four basic features of the nervous system, including the mechanisms by which neurons produce signals and the patterns of connections between nerve cells. The discussion of the mechanism of signal generation is clearly superficial.

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[20]Kandel, E. (2000) Nerve cells and behavior, in Kandel, Schwartz & Jessell, Op. Cit. Pp. 19-36