3 The Electrolytic Theory of the Neuron/Synapse

A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that are familiar with it.

Max Planck

3.1 Introduction

This chapter presents a new theory of the neuron based fundamentally on electrolytic, rather than chemical mechanisms. Chemical mechanisms are only found in a supportive role. The Electrolytic Theory of the Neuron presented here is quite comprehensive and explains many phenomena not currently explainable based on the prior chemical theories. The Theory applies to both intraneural and interneural mechanisms. Many readers may find it difficult to rationalize their past training, and their current teaching syllabus with this new material. The author understands the assertion of Max Planck, provided above, may be the only rational solution to this problem. This work is prepared for the benefit of the next generation (born after the early 1980's).

Space in this volume will not be sufficient to explore application of the Theory completely. That will be the subject of the next book. In the meantime, more comprehensive material is available on the internet. www.sightresearch.net provides even greater detail in Chapters 8, 9 & 10 of the manuscript "Processes in Biological Vision."

This chapter will establish a framework for understanding and discussing the functional performance of all neurons. It will also link the functional performance to the morphology of the neurons. Because the available information is so extensive, the features of the visual system will frequently be used as an exemplar of the general situation. However, the physiology of the synapse is better developed within the hearing community and those sources will be used as a reference. Regardless of the source of detailed data, it must be made clear to the reader. The Electrolytic Theory differs from previous chemical theories in many ways, and provides answers that cannot even be asked based on the current state of the chemical theory. The Electrolytic Theory leads to detailed parameters and circuit diagrams for all of the neurons of the body and provides a totally different definition and description of the synapse.

This work does not support the putative chemical-gate structure of neural operation. Nor does it support the concept of a chemically based synapse between neurons. As a result, the term neurotransmitter is not used in this work except to show how that concept compares to the more rational electrolytic proposal. For those trained in the chemical approach, it is important to note that no transfer of heavy metal ions through the lemma of a neuron has ever been observed by relatively direct means. The reported observations have all relied on electronic circuitry involving the flow of electrons to support the putative flow of heavy ions. This work will rely upon two companion works, Processes in Biological Vision [PBV] and Biological Vision: A 21st Century Tutorial [BV] to provide an extensive review of the literature in these areas. As noted in Chapter 1, PBV is available on the internet.

The companion work also develops a complete physiological explanation for the operation of the synapses. This operation is also electrolytic and does not involve any chemical transport across the synaptic gap. An entirely different operating rationale is provided for the materials previously labeled neurotransmitters. They are in fact neuro-facilitators and neuro-inhibitors. However, their action relates to the electrical power supplies of the neurons and not the transfer of signals across the synapse.

If the reader finds it difficult to embrace the electrolytic character of the neural system, it may help to recall that the underlying mechanisms only became known to man during the late 1950's and 1960's. Theories developed before that time (and reiterated up to the present[1]) relied upon an inadequate technological base. While those early workers would look upon the ideas presented here as magic (just like they would the liquid-crystal-based display of a hand-held calculator or cell phone), they are well known to the current college graduate in chemistry, physics and electronics.

3.1.1 Background

It is incredible but there is virtually no published material on the internal physiology of the neuron. The generic material available describes currents flowing from the tip of the dendrites to somewhere near the nucleus, generally within the soma, and similar currents flowing from that same general area to the terminations of the axon of the neuron. Similarly, there is little published material on the internal cytology of the neuron beyond those components supporting homeostasis.

Feducci & McCrady, editing Torrey's 5th Edition, provides a brief introduction to the evolution of the sensory neurons once the fundamental neuron has already evolved[2]. The textbook by Aidley, first presented in 1971 and currently in its fourth edition, is based entirely on the chemical theory of the excitable cell[3]. It will not be relied upon or supported in this work. The neurobiological text by McGeer, Ecccles & McGeer (1987) has an interesting title but says virtually nothing about the fundamental form of the neuron. The neurobiology textbook by Shephard (1988, 2nd Ed.) is voluminous and discusses the potential physiology of the synapse but does not discuss the formation of the neuron. It assumes the neuron exists. Squire et al. (2003, 2nd Ed.) edited a large volume on the fundamentals of neuroscience. It contains no discussion of the fundamental neuron. It begins at the electron microscope level of detail.

Shepherd also provided an interpretation (pg 208) of a figure by Bodian (1967) that will be expanded upon in Section 5.2.2. The caricatures for the modalities other than vision are overly simple. They do not provide for signal processing within the neural system supporting that modality. However, it is readily shown that most individual sensory neurons are not connected to the brain by a unique and exclusive neural circuit.

This author has taken a different approach. He asked, how did the first neuron form and from what?
This chapter will begin with a brief summary of what was found in response to that question (Section 3.1.2).

After showing how the basic neuron evolved, this work describes how the basic interface between two fluid-filled electrolytic conduits can be packaged as a neuron, a synapse or a Node of Ranvier. In all cases, it will show the transfer of an electrical current across such interfaces is a totally electrolytic process. This work will then describe how the basic form was elaborated into much more complex, purpose optimized, neurons. Section 3.3.2 will end with a caricature of a fully elaborated sensory neuron. The work will then review the specialized forms of neurons employed within different stages of the hearing modality of the neurological system. Finally, it will discuss the unique way neurons are provided with electrical power. This discussion uncovers an entirely different way of understanding the effects of neuro-facilitators and neuro-inhibitors in the operation of the neuron.

3.1.1.1 The electrolytic versus ionic argument of neuron operation

From the mid 1800's until the 1930's, the neuron had been considered an electrical device of mysterious character. Following the first World War, the pharmacology community discovered a number of chemicals that had significant effects on the nervous system. During the 1930's through the early 1950's, a major argument ensued between those supporting the neuron as an electrical device and those claiming it was fundamentally chemical. The remarkable fact about these discussions was their conceptual nature. In his recent book, Valenstein described the arguments culminating in the dogmatic decision that the neural system was based on chemical neurotransmitters without using a single detailed model, diagram or schematic[4]. He also noted the alternate designation of the day for chemical neurotransmitters, neurohumoral secretions. In hindsight, the arguments on both sides appear quite conceptual and lacking in the most basic of definitions. The most damning argument against the electronic concept was that an electrical pulse could not act as an inhibiting mechanism (pg 128). Today, this seems like a ludicrous argument. The second damning argument concerned the delay associated with a synapse, with no definition of what kind of synapse (pg 127). The delay of 0.2 to 0.4 milliseconds being discussed then is now recognized as only applying to the regeneration delay associated with phasic signals. It is readily explainable, and in fact expected, within the electrolytic theory of this work.

While the argument of the 1930's centered on pharmacological molecules versus an electrical signal of unknown character crossing the synaptic gap, the framework of the argument changed during the 1950's (with a recess during the war-torn 1940's). Hodgkin & Huxley performed a major set of experiments which they could not explain. While they postulated two distinct currents operating simultaneously, and associated those currents with the concentration of heavy ions on opposite sides of a biological membrane, they avoided claiming those heavy ions actually crossed the membrane. Subsequent investigators generalized their concepts to include the flow of heavy metallic ions across the plasma lemma of cells. The mechanisms required to support these concepts were never demonstrated and we know now that the plasmalemma of neurons are impervious to such simple metallic ions. However, the accepted theory of the neuron became associated with the flow of heavy metallic ions through plasmalemma while that of the transfer of signals between neurons remained focused on the secretion of large molecules through the presynaptic lemma and into the poorly defined synaptic gap. Neither of these mechanisms appeared to operate at sufficiently high speeds to support the measured speed of neurological signaling.

Meanwhile, the technology of semiconductor physics was maturing simultaneously in a different field. It was a field where most biologists felt uncomfortable. As a result, the biological community has remained wedded to the ionic/chemical theory of neural operation until at least the mid 1990's. This posture became a strong suppressant to additional activity by electrophysiological investigators in the field. To be published, they had to accept what became the ionic/chemical neurotransmitter dogma.

An interesting situation arose in 1974. The position of Grundfest, in a book edited by Bennett, and Bennett's comments in the Preface show how antagonistic the chemical versus electronic argument remained[5]. Grundfest was objecting to Bennett addressing electrotonic synapses in the same book (Bennett's book) that Grundfest was addressing the chemical synapse. Between the 1960's and the present, semiconductor physics has caused the greatest advancements in man's knowledge, and standard of living, ever known. Meanwhile, concepts related to the neuron and synapse have remained largely stagnant in the literature.

To this day, most neuroscientists are unaware of the other mechanisms of charge transport provided by semiconductor physics and overlooked by Hodgkin & Huxley. Finally, the ideas offered by Hodgkin & Huxley only applied to neurons generating action potentials. Less than 10% of the neurons in the brain and none of the sensory neurons in the cochlea generate action potentials. The Hodgkin & Huxley hypothesis did not address the other 90% of the neurons?

3.1.1.2 A redefinition of neuro-active substances

The literature has historically assumed any exogenous material that interacts with the operation of a neuron is a neurotransmitter in the broad sense. Similarly, any material present in measurable amounts in the matrix surrounding a neuron after neural action has been considered a neurotransmitter. There has been little confirming evidence that any of these materials are actually secreted by the axolemma within a synaptic junction and reached the opposing neurolemma. The most recent data of Ottersen et al. and Matsubara et al. suggest just the opposite (Section 3.7.3).

This work replaces the single, largely conceptual, definition of a neurotransmitter supported most strongly by the pharmacology community with a new set of more specific physiologically and pharmacologically supportable definitions.

Based on the electrolytics and quantum-mechanics of the synaptic junction (as well as the Nodes of Ranvier and the active semiconductor devices within the neurons) a neurotransmitter can be defined very precisely. A neurotransmitter is defined as the signal carrying entity that traverses the seven-layer junction formed by two asymmetrical lemmas in appropriate juxtaposition and properly biased electrically. This entity is the electron.

Any material that facilitates the transfer of an electron across the above defined junction is a neuro-facilitator. Any material that inhibits such a transfer is a neuro-inhibitor. These materials need not be found within the synaptic junction, or even within the synaptic cleft (although they frequently are found within the cleft).

Neuro-facilitators and neuro-inhibitors are of two types and two sub-classes. Primary agents participate intimately in the metabotropic/electrostenolytic mechanism providing electrical power to the neurons. The primary neuro-facilitators are limited to the negatively charged dicarboxylic amino acids, glutamate and aspartate. The secondary neuro-facilitators occur in two classes. Class 1 agents participate directly in the electrostenolytic mechanism, typically suppressing the reaction of the primary agents. Class 2 agents do not participate directly in

the electrostenolytic mechanism but effect the participation of the primary and class 1 agents in such mechanism. These definitions will be explored more fully in Section 3.6.2.

These definitions are compatible with the available pharmacological and physiological data.

3.1.2 The genesis of the neuron–an introductory scenario

The neuron appears very early in the development of the animal kingdom of the phylogenic tree. It can be argued that the appearance of the neuron is what differentiated the animal kingdom from the simpler single cell animals, the fungi, and the plants. It is reasonable to assert that the neuron is a fundamental cell type in the animal kingdom. How the neuron evolved is clearly worthy of study, both from an evolutionary perspective and a physiological perspective. This analysis will begin with the simplest eukaryotic cell as a precursor.

The eukaryote is defined as a biological cell containing a nucleus (or more recently, a nucleus and mitochondria). The external boundary, the plasmalemma, of a biological cell is formed of a bilayer film of lipid material. In the simplest case, the bilayer is symmetrical. The resulting lemma is found to be a perfect insulator. Such lemmas are extremely thin, typically 90 Angstrom (nine nanometers) thick. As a result, they exhibit significant capacitance per unit area. Interestingly, such a chemical bilayer is self-forming at the molecular level and will spontaneously form a spherical shell under appropriate (but simple) conditions. This property is due to the amphiphilic character of lipid films. They have one surface that is hydrophilic and one surface that is hydrophobic. They will naturally rearrange themselves to isolate the hydrophobic surface from the water environment by forming a bilayer. To protect the exposed hydrophobic portions at the end of a bilayer film, they will seek to form a closed sphere with no ends.

To complete the creation of a biological cell, all we need to do is to introduce a nucleus into the above shell. How the nucleus is formed (within or without a suitable shell) is currently beyond science. However, it will become clear that the nucleus plays no significant role in the signaling aspect of the neuron. Therefore, an escape is available from this challenge. It will be assumed that the nucleus is created by a virus boring through the membrane and establishing itself as the nucleus, resulting in a complete cell.

As defined, the simple biological cell is not very effective. It is not able to effectively interact with its environment and is not able to grow to significant size without losing its inherent external shape. Note it contains no pores in the lemma. The simplest biological cell has evolved a variety of modifications to solve these problems.

3.1.2.1 Important features of the eukaryotic cell

What has come to be known as the neurological system of an animal has evolved from, and is based on, the simplest eukaryotic cell. The eukaryotic cell is the basic entity capable of both maintaining and reproducing itself. As the current interest in stem-cell research attests, it is also capable of evolving into other more complex types of cells. How does the eukaryotic cell maintain itself and how does it perform these evolutionary changes?

Most fundamentally, the nucleus has found a way to create mitochondria that can produce a wide variety of protein and other materials for elaboration of the cells architecture. It has also found a way to modify its (or its offsprings) lemma. The modifications will be defined in detail in subsequent sections. Fundamentally, it has found a way to create asymmetrical sections in the cell lemma. It has also found a way to pass complex chemicals (but not simple metallic ions) through other specialized sections of the cell lemma. This latter capability has led to the ability of the biological cell to maintain an electrically conductive internal environment by obtaining and dissolving electrolytes in a water environment.

The introduction of a molecularly asymmetrical section of lipid-based lemma has provided a critical new dimension to the cell. A molecularly asymmetrical biological lipid section is no longer an insulator. It is electrically asymmetrical also and forms a perfect electrical diode. A cell with an asymmetrical lemma is sensitive to the electrical environment surrounding it. If the surrounding environment is electron-rich compared to the cell, electrons will flow through the lemma and into the cell easily. On the other hand, if the environment is electron-poor, electrons will not flow out of the cell into the environment. If the cell has an excess of electrons relative to its environment, an interesting phenomenon occurs. The repulsion force between the electrons will cause them to separate as far as possible. The result is the cell will take on a spherical shape in the absence of any other forces. If the plasma lemma is longer in one dimension, the cell will take on an ellipsoidal shape. This shape can be extended into a sausage-like section that will be labeled a conduit.

Rather than just depending on the elasticity of the plasmalemma and the internal electrical charge to form the cell,

the nucleus can implement additional internal lemmas. These internal lemmas are also typically lipid bilayers and may be symmetrical or asymmetrical at the molecular level. Any single internal lemma can restrict the distance between any two points on the plasmalemma. The junction between any two lemmas is typically formed as a lap joint, although this is frequently difficult to demonstrate in electron micrographs because of the very small and complex geometries involved.

Achieving an electrically negative internal environment by depending on the surrounding environment is awkward if an alternate mechanism can be found. Such a mechanism is readily available if the surface chemistry of the external lipid layer can be modified to attract certain negatively charged amino acids. There are only two biologically prominent amino acids that are negatively charged, glutamate and aspartate. These amino acids can be used to provide an electron with sufficient energy to penetrate the asymmetrical lemma section. In the process, the amino acid is reduced. The resultant "waste products," carbon dioxide and GABA (gamma-amino butyric acid) are release into the external environment. They are released because they no longer are electrically compatible with the outer chemistry of the lipid. The process just described is called electrostenolytic chemistry. It is the method that is used to polarize all biological cells and to power the neurons.

3.1.2.2 The creation of active devices within a biological environment

The simple cell configurations defined above can be developed into two additional configurations that are particularly useful. They will be described in sequence. They result in the creation of the active device found within every neuron and between every pair of neurons. These active devices are called Activas[6].

If a cell is developed with two internal lemmas that are molecularly asymmetrical, appropriately arranged, and biased electrically as shown in Figure 3.1.2-1(A), a remarkable phenomenon is observed. The unique arrangement involves bringing the molecularly asymmetrical regions of the lemmas into physical contact at one or more points. As the two lemmas approach each other, the electrolyte between them, water plus a variety of other molecules or ions, is confined within dimensions that are smaller than a majority of the ions and molecules. As a result, the remaining electrolyte is restricted to water molecules. At a spacing of about 100 Angstrom (10 nanometers), even these molecules are restricted relative to their normal Brownian motion and they take on a semi-solid, or liquid-crystalline form. This form of water, $(H_2O)_n$, will be called a hydronium crystal in this work. In the literature, it is described as a form of room-temperature ice that is usually formed only under extreme pressure or when subject to high electrical fields. However, Zangi & Mark have recently computer-modeled its formation within a confined (non-bonding) space measured in Angstroms[7]. In the case of interest here, the molecules of water are allowed to bond to the lipids of the confining lemmas resulting in a hydronium bridge. This liquid-crystalline material effectively interconnects the two lemmas in a unique electrical configuration. The base terminals of the two diodes are joined in a single quantum-mechanical structure.

The presence of a hydronium crystal as described above has been encountered in the laboratory. Choi et al, observed such a material when confining water between two (non-bonding?) gold surfaces when using a scanning tunneling microscope (STM)[8]. While they reported the effect in the presence of an electrical field, the field was on the order of that found between neurological lemmas. They noted, "At a so-called critical gap distance–as small as the height of two water molecules, the field probably coerces the water molecules into the regimented alignment of a solid." It is suggested here that it is the combination of three effects that generate the hydronium bridge forming the Activa; the confinement by the two lemmas, the high electrical field due to the axoplasm and dendroplasm potentials and the ability of the hydronium crystal to form hydrogen bonds with the lemmas.

Water molecules are not round and seldom exist in the "free" state. Their diameter is on the order of 2-5 Angstrom depending on the measurement axis. When bringing two surfaces to within 100 Angstrom of each other, many organic molecules within any solution between them will be squeezed out. The result is a space containing only water and other small molecules.

Because of their size, most organic molecules usually thought of as neurotransmitters cannot exist within the confines of the active region of the synapse.

If an electrical current is caused to flow in the left-hand diode of both frames (A) and (C), by forward-biasing it, a current will flow out of the right-hand diode, even though it is reverse-biased and would not be expected to pass any current. This unique phenomenon is known as "transistor-action" in man-made semiconductors. In the above described biological semiconductors, the resulting structure is called an Activa. The Activa corresponds precisely to a man-made transistor of the PNP type, where the letters describe the charge density within the three regions, the input diode, the common base region and the output diode at the quantum-mechanical level.

Every biological neuron contains at least one Activa as described conceptually above.

The Activa is portrayed by the symbology used for man-made transistors. This does not imply the circuit is emulated by a transistor. The Activa is a semiconductor device in its own right. If desired, the symbol can be modified by the addition of the letter A to define an electrolytic semiconductor Activa rather than a metal semiconductor transistor.

Note, the nucleus and/or mitochondria play no role in the electrical performance of the neuron. Their presence and location are inconsequential to the electrical operation of the cell. Note also that the physical device is entirely symmetrical. It is the potentials applied to its fluids (terminals) that determine its performance. Because of this feature, the electrical performance of the simple neuron as proposed is also reversible under pathological conditions.

It should be noted that the active portion of a neuron involves three different potentials associated with three different plasmas. The input plasma will be defined as the dendroplasm. The output plasma will be defined as the axoplasm. The third plasma will be defined as the podaplasm for reasons described below.

Every biological neuron exhibits at least three electrical terminals. Contrary to the common assumption, a neuron is a three-terminal device.

To allow easier interchange of terminology between the morphological and physiological domains, the dendroplasm is electrically identical to the emitter terminal (E, point of charge injection) of the Activa, the podaplasm is electrically identical to the base terminal (B) and the axoplasm is electrically identical to the collector terminal (C, point of charge/ discharge) of the Activa. These terminologies will be used interchangeably below.

Figure 3.1.2-1 (B) shows the second lemma configuration of interest. In this case, two conduits as described above are juxtaposed as shown. The spacing between them in the gap region is reduced to the same range of dimensions as discussed above, about 100 Angstrom (10 nanometers). This configuration has historically been called a synapse. The terminology associated with this configuration is the same except the emitter terminal, E, is associated with the axoplasm of the preceding neuron and the collector terminal, C, is associated with the neuroplasm (dendroplasm or podaplasm) of the orthodromic neuron. The polarity of these terminals is the same as in the previous case, the axoplasm to base potential must forward bias the input diode and the dendroplasm to base potential must reverse bias the output diode.

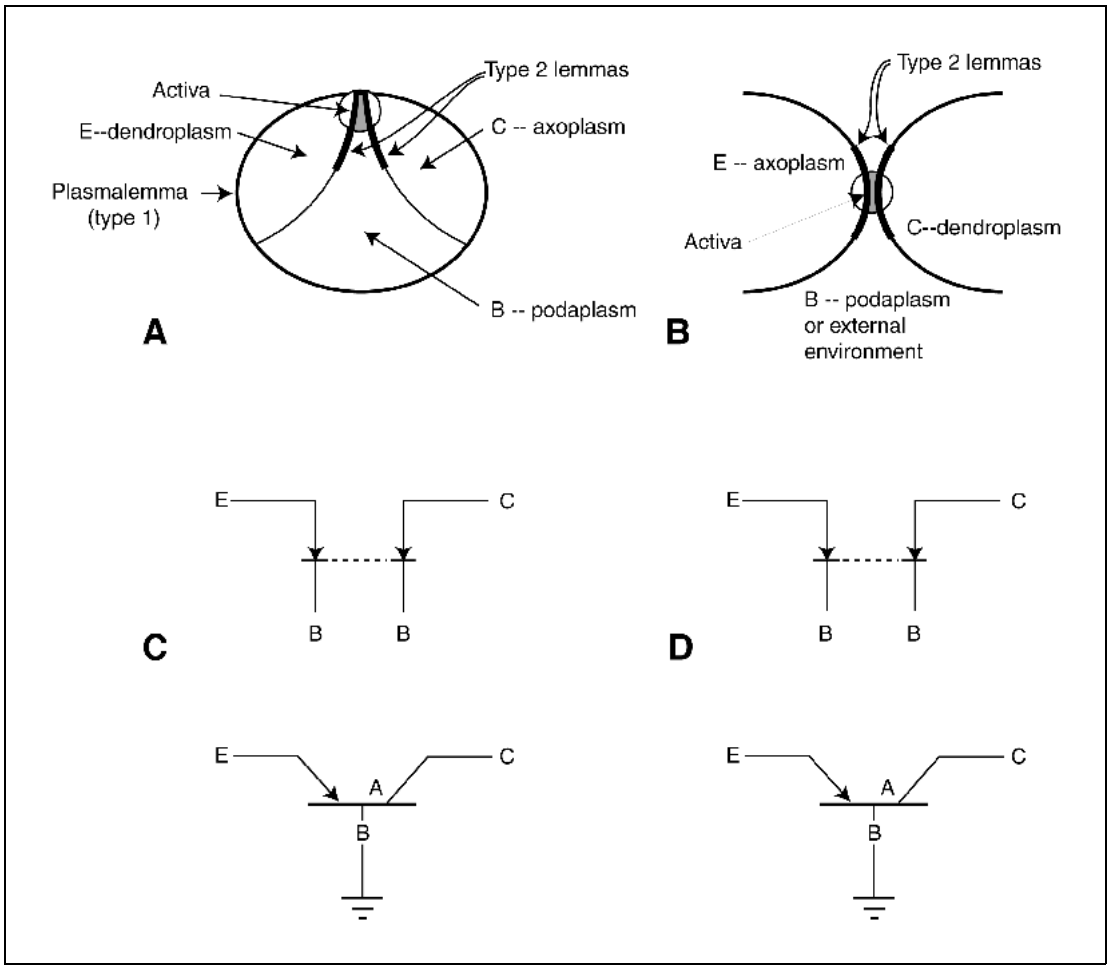

Figure 3.1.2-1 Fundamental electrolytic junctions. A; the nominal junction between the plasmas of a single simple neuron. B; the nominal junction between the plasmas of two juxtaposed simple neurons axoplasm on the left and orthodromic dendroplasm on the right. C & D; electrical representations of the type 2 lemmas before (above) and after (below) being brought within 100 Angstrom of each other. The lower symbols indicate the right diode has been reverse biased. See text.

During the 1950's, Davis and others used the term ephapse and synapse to differentiate between an electrical-based and a chemical-based biological junction. In this work, the term synapse will be used to define any junction between two electrolytic conduits originating in entirely separate neurological structures and used to convey signaling information.

Every biological synapse associated with neurological signaling contains an Activa as described conceptually above.

As in the case of the neuron described above, the nucleus and/or mitochondria play no role in the electrical performance of the junction between two neurons. Note also that the physical device, the synapse, is entirely symmetrical. It is the potentials applied to the plasmas that determine its performance. Because of this feature, the electrical performance of the simple synapse as proposed is also reversible under pathological conditions.

Note also that the lemmas forming the junction do not display any pores or other mechanisms to deliver a chemical into the junction space. Nor do they exhibit any location for specialized chemical receptors on the orthodromic lemma. In fact, the narrowness of the gap between the two lemmas forces all chemical constituents except water out of the area between them. The formal presentation will show that chemical receptor locations are located on both the pre and post synaptic lemma within the larger cleft between the neurons but now within the narrow gap of

the synapse.

No chemicals, no pores and no receptors are present within the gap region of the biological synapse.

Rand & Paregian have provided a current discussion of the forces controlling the spacing of two juxtaposed membranes[9]. Exploration in this area is a recent undertaking and the number of variables is very large. Although they show stable spacings in the tens of Angstroms area, they do not report on the type 2 membranes of primary interest here. They do note the difficulty of defining spacings between atoms and polar groups of similar intrinsic dimensions.

The synapse was defined as the junction between two electrolytic conduits originating in different neurons. There is a special case involving a junction between two electrolytic conduits that are within a more complex single neuron structure but not located within the soma of that neuron. These junctions are the same as the synapse except they are supported by a common neuron for homeostasis. These junctions are called Nodes of Ranvier. Nodes of Ranvier are typically associated with other features such as myelin covering the conduits. However, this is not a defining characteristic of a Node of Ranvier.

3.1.2.3 The Activa, the active semiconductor device of biology

Guttmann has chronicled the long search, by him and others, for an active semiconductor device within the biological system[10]. It does not appear they had adequate background to recognize such an active device when they saw it. The above scenario has described the Activa as an active device within or between neurons. It has also been mentioned that it exhibits transistor-action. A few more specific words may be helpful. The Activa of the neurological system is the exact analog of the man-made transistor. It is a liquid-crystalline structure at the quantum-mechanical level as opposed to the metal-crystalline structure of the transistor. It is a three-terminal device just like the transistor. The structure consists of two identifiable electrical diodes sharing a common (and identifiable) base material, in this case a very thin liquid-crystalline matrix of hydronium (a liquid-crystalline form of water) resulting in a hydronium bridge. In operation, the input diode must be forward biased (favorable to the flow of electrons through it) and the output diode must be reverse biased. Under these conditions, an electron current injected into the input diode creates an electron current at the terminal of the output diode. This most unexpected result is transistor-action. This simple mechanism underpins the modern world of man-made electronic equipment just as it has the biological world since the animal kingdom began.

All Activas are analog devices. However, when supported by auxiliary electrolytic circuitry these intrinsically analog devices can be made to perform in a wide variety of modes, one of which is an all-or-nothing pulse mode usually associated with action potentials.

3.1.2.4 Specialized plasmalemmas of the neuron

The outer membrane completely surrounds a cell and consists of a double wall membrane of two leaves. Each leaf usually consists of a liquid-crystalline film of biological phospho-triglycerides. The plasma membrane 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. At least three specializations are known.

> Type 1 lemma consists of a continuous molecularly symmetrical liquid-crystalline bilayer of phospholipid material that is impervious to virtually all molecular material and is an excellent electrical insulator. This type forms the bulk of the lemma of any cell, particularly where it is myelinated.
>
> Type 2 lemma consists of a molecularly *asymmetrical* continuous liquid-crystalline bilayer where the individual molecular layers are homogeneous but consist of different phospholipid materials. It is impervious to transverse molecular flow but acts as an electrical diode with respect to electron flow. 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.
>
> Type 3 lemma consists of a liquid-crystalline bilayer that is largely impervious to all materials but contains islands of protein or sterol material that are presumed to penetrate both films of the bilayer. The penetrations are thought to support the transport of selected (electrically neutral) 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[11]." While using different semantics than defined in this work, 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.

3.1.2.5 The molecular structure of the junction between two membranes

Figure 3.1.2-2 provides a cross sectional view of two membranes brought into close proximity[12]. 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 junction area is a variable *in-vitro*.

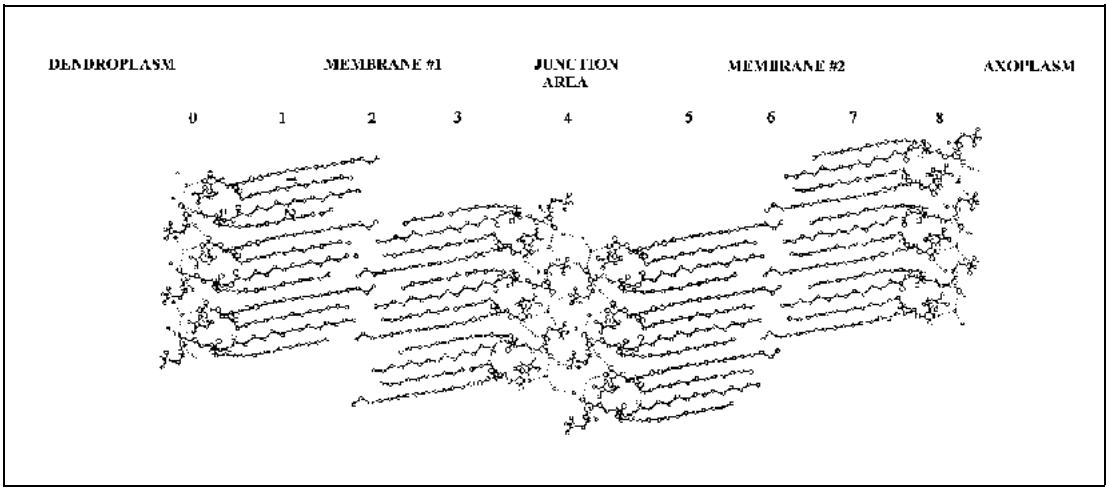

Figure 3.1.2-2 The structure of the Activa at the atomic level. In operation, the configuration consists of two bilayer membranes (BLM) in close proximity and appropriate voltages applied between the dendroplasm, the axoplasm and the material in the junction area between the two bilayers (the podaplasm). The lattice of water in the junction area forms a hydronium bridge. The lattices on the left and right form a hydronium crystal interfacing with the lemma and free water molecules nearby. Detailed atomic structure of two bridged biological lemmas 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 crystal lattice. The structure in the junction area, between the two membranes is also described in terms of hydronium crystal lattice, but this lattice hydrogen bonds to the two lemmas to form a hydronium bridge. 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 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[13]. "The present understanding of membrane structure is a reflection of how young the field 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. However, he tempers this criterion 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 discussed the proclivity of the polar head of each leaf to participate in hydrogen bonding and a state of hydration. He briefly discusses the energy considerations related to the state of hydration of lipid molecules and the energy necessary to bring the polar heads of two bilayers into juxtaposition (pp 58-66). This positioning determines the thickness of the junction area in the above figure.

The cross sectional area of each molecule in the lipid bilayer is approximately the same as that of a glutamate molecule. 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).

3.1.2.6 A preview of neuron morphologies based on the electrolytic theory

One of the simplest forms of the neuron is that most studied, the morphologically bipolar but electrolytically three-terminal signal processing neuron. In its simplest form, it shows no arborization of the dendritic structure and no bifurcation of the axonal structure. It is shown in frames A and B of Figure 3.1.2-3. As noted earlier, each neuron is a three-terminal device. The dendritic terminal on the left and the axonal terminal on the right (the pedicle) are well defined in the literature. However, the podoplasm (shown as the white bar below the internal Activa) and its external poditic terminal, have been less well defined (even though it is well represented in the electron micrographs of cytology). Frames A & B stress the triviality of the difference between morphologically defined monopolar and bipolar neurons. The nucleus, and its location, play no functional role in neural signaling.

Frames C and D introduce the first order of elaboration found in neurons. In C, the poditic structure has been expanded into a recognizable external structure. This is a very valuable form found widely in neurobiology. As will be described in Chapter 4, this configuration provides a "noninverted" pedicle output signal compared to the input signal at the dendrite. However, it provides an "inverted" pedicle output signal compared to the input signal at the podite. This feature is the basis for the signal processing performed within the neurological system. Frame D shows the beginning of the further elaboration of the neuron. Both the dendritic and poditic structures are subject to very large degrees of elaboration beginning from simple dendritic and poditic stems. By selectively synapsing with multiple antidromic neurons, the neuron is able to perform significant feats of signal summation, differencing, correlation and thresholding.

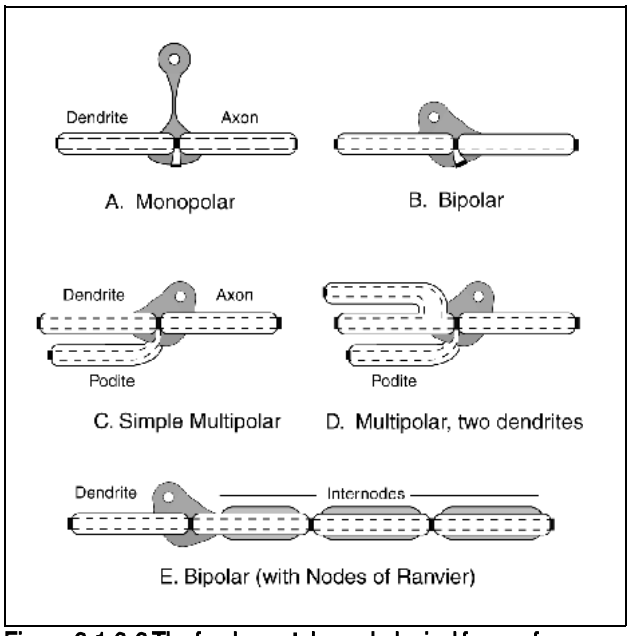

Figure 3.1.2-3 The fundamental morphological forms of neurons.

Frame E shows an additional degree of elaboration. In this case, the axon has been elaborated into a serial series of axon segments or internodes separated by Activa at each junction between the axon segments. The axon segments are shown by an outer myelin wrap. The active mechanism between each pair of conduits allows regeneration of the signal at intervals to compensate for the attenuation associated with the individual axon segment. While this process

is noisy in analog circuits, it is an ideal method of noise-free regeneration in phasic circuits. If all of the axon segments shown are supported homoeostatically by the same soma and nucleus (as shown), the junctions between the axon segments are known as Nodes of Ranvier. If the segments are supported by different soma, the junctions are called synapses.

As noted as early as 1961 by Davis[14], Nodes of Ranvier can occur between any two conduit segments at locations before or after the soma.

3.1.2.7 The neuron as an electrolytic circuit

Figure 3.1.2-4 reproduces frame C of the above figure and shows the electrolytic representation of the same cell. The circuit (lower right) displays two distinct input terminals, $V_{in}(1)$ and $V_{in}(2)$ and a common output analogous to the pedicle of the axon. $V_{in}(1)$ represents the input to the circuit associated with the dendritic structure. The signal applied to this terminal is reproduced at the axon with the same polarity. The signal waveform is not inverted. $V_{in}(2)$ represents the input to the circuit associated with the poditic structure. The signal applied to this terminal is reproduced at the axon with the opposite polarity. The signal waveform is inverted. This circuit configuration is ideally suited for taking the mathematical difference between two analog signals.

The simple circuit elements shown between each input and output terminal and the common ground symbol are more complex in the real case. They typically incorporate both an electrical impedance and a voltage source, although in some cases the voltage of the source may be zero. All of the circuit elements associated with a given Activa can be grouped into a single complete circuit (or a conexus). The designation AL refers to the type of Activa used in this lateral type neuron. Lateral neurons include both the horizontal neurons and the amercine neurons of the visual retina. They occur widely in the signal processing and signal manipulation circuits of all sensory modalities.

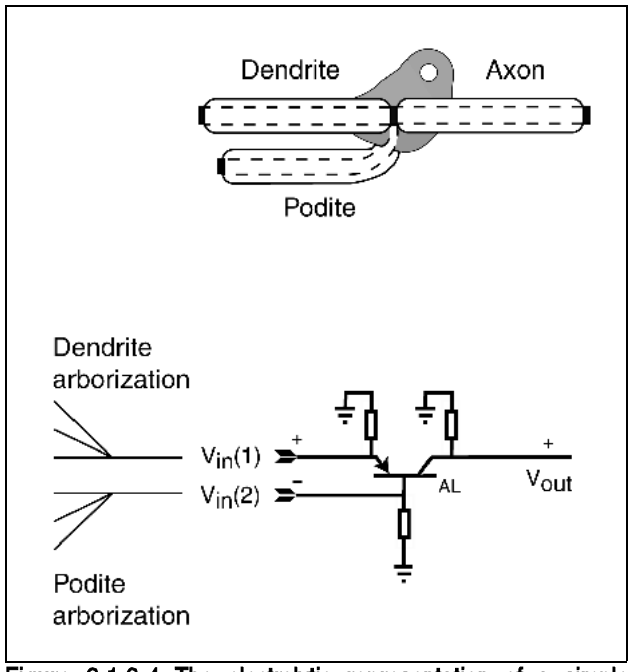

Figure 3.1.2-4 The electrolytic representation of a simple multipolar neuron. Top; generic cytology. Bottom right; basic electrolytic circuit. Bottom left; arborization of each neurite. See text.

The input structures are expanded at lower left to suggest the tree-like extensions of the basic dendritic and poditic inputs. This process is described as arborization. Dacey & Lee have provided excellent imagery of dual arborizations of the type described in this figure[15]. However, they did not recognize the physiological difference between these two input structures and described their figures as bi-stratified dendritic structures. They did recognize the capability of this neuron type to take signal differences, which they associated with "color opponency" in the visual system.

Dacey & Lee observed an important point in their 1994 introduction. "The neural mechanisms producing colour opponency are not understood." Such a mechanism is described in detail here.

The number of inputs to a specific dendritic or poditic tree is known to reach the thousands. Morphology has been unable to account for, or interpret the function of, such large numbers of inputs. The summation of such a large number of uncorrelated inputs, by either arborization, would typically lead to a constant amplitude signal as a function of time. However, physiology provides an answer. The arborizations reach out and contact antidromic neurons that are either correlated in time, in frequency, or space, depending on the sensory modality. Whenever correlated signals appear at the pedicles of these neurons, their signals sum to significant signal amplitudes in the orthodromic neurites for a nominal period of time. This correlation capability plays a major role in the information extraction

functions of the neural system.

The dendritic and poditic input circuits exhibit another major difference beside signal inversion. The signal applied to the dendritic input is always reproduced at the pedicle at nominally the same amplitude. However, the signal applied to the poditic input is both inverted and amplified. Depending on the parameters of the Activa within the neuron and the circuit elements associated with that Activa, the circuit can exhibit amplification factors of from 1.0:1 to as much as 200:1. This feature is of fundamental importance to the sensory neuron circuits. While most of the neural system operates in a nominally constant signal amplitude environment, the sensory neurons are expected to amplify the very small signals at their input up to a nominal amplitude appropriate to the neural system.

3.1.2.8 The elaboration of a eukaryotic cell into a complete neuron

The above discussion has described a variety of features that can be associated with a neuron. The most elaborate neurons are neurosecretory structures. Figure 3.1.2-5 attempts to bring those features into a single composite neuron illustrated at a very detailed level. It is divided into three distinct regions, its neurological component, its growth and homeostatic (housekeeping) component, and its secretive and/or ancillary structure generating component. All of the features of this neuron cannot be developed within the scope of this book but they are developed in the companion documents (PBV chapters 8, 9 & 10; BV chapter 4). The point to be made is that the simple prototypical cell (stem-cell) can evolve into a wide variety of cell types optimized to meet many functional requirements. Each of the stages of the neural system defined earlier place unique requirements on the neurons used in those stages. The remainder of this chapter will develop the fundamentals of the neuron in greater detail and show how they have evolved into a variety of forms.

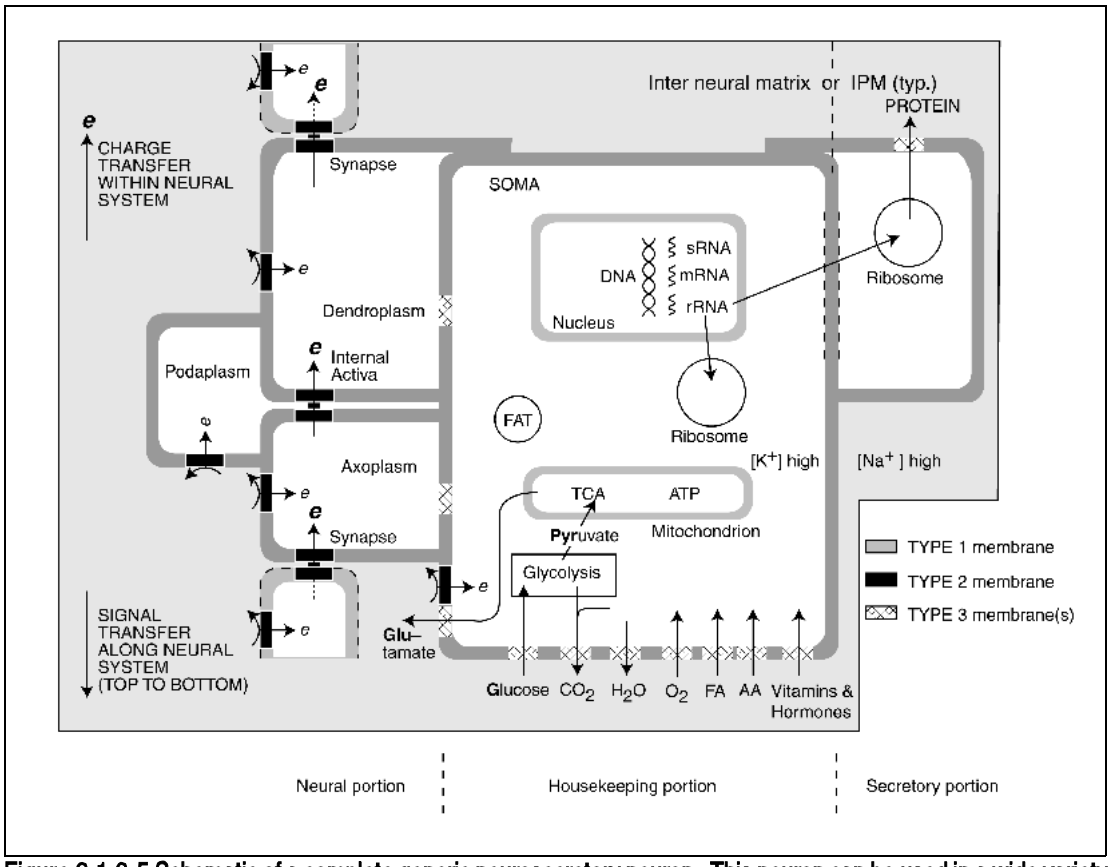

Figure 3.1.2-5 Schematic of a complete generic neurosecretory neuron. This neuron can be used in a wide variety of neural applications with a minimum number of optimizations. See text.

The lap joint character of the union between lipid bilayers is illustrated along the top edge of the figure. It is ignored in the remainder of the figure for convenience. All of the lemmas of the cell are formed of lipid bilayers. Where shown as solid gray, they are symmetrical, or type 1, bilayers that are electrical insulators. Where the lemma is shown as black, the membrane is a molecularly asymmetrical type 2 bilayer and forms an electrical diode. When shown crosshatched, the lemma is type 3 and supports the transfer of complex molecules through the membrane by an undefined mechanism.

The type 2 membranes are present in two functional situations. When juxtaposed with another type 2 membrane, it is functioning as part of an Activa providing a signaling path from one portion of the cell to another or between cells. Where the type 2 membrane stands alone between two different plasmas, it is generally associated with the electrostenolytic task of providing electrical power to the neuron. This function is highlighted by the arc with an arrowhead associated with the external surface of the membrane. This arc represents the chemical reduction process that converts glutamic acid (glutamate in pharmacological circles) to GABA and carbon dioxide.

The lemma enclosing the podaplasm on the left of the figure highlights the three-terminal character of the Activa to its right.

The secretory portion of the generic neuron is shown on the right. It is shown creating protein material and secreting that material into the exterior environment adjacent to the neuron. This is the typical case in many sensory neurons (vision, taste, touch) but it is not the situation in the sensory neurons of hearing. In the case of hearing, the protein material remains within the plasmalemma. It forms the "filling" within the cilia that are attached to the cuticular plate at the apical end of these neurons. This filling material forms a piezoelectric structure in conjunction with the cuticular plate. The formation of this complex structure is addressed later.

The middle portion of the figure addresses all of the myriad housekeeping functions required of a self-sustaining neuron. The lifetime of a neuron typically is equal to the lifetime of the animal itself. As will be shown below, this is not true of the piezoelectric filling described above. It is replaced continually with a lifetime of about one week. The high potassium ion concentration within the plasma membrane is shown in comparison to the high sodium ion concentration on the outside. These concentrations have no relevance to the signaling operation of the neuron.

3.1.3 The fundamental architectures of the neuron and nerves

This section will explore the analog neurons first and then show how they have evolved into the phasic forms where necessary and appropriate.

3.1.3.1 The fundamental neural signaling path of biological systems

By combining the circuits found within a neuron with those found between neurons, a complete fundamental signaling path is defined. A signal introduced into the first dendroplasm can be reproduced (in modified form if desired) at the last axoplasm of the circuit.

Noback provided a conventional definition of a neuron in 1967 that has been 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[16]." While this was a satisfactory introductory definition for pedagogy, it is not scientifically adequate now. Shepherd & Koch have recently taken a big step forward by describing the synapse as the basic functional unit of neural circuits[17]. 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 architectural commonality of the circuits within the soma of the neuron, within the synapses and within the Node of Ranvier. It will be shown that there is a functional unit that is frequently replicated within a single neuron, and between neurons. This replicated circuit (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 3.1.2-6(a). A signal (I_{in}) is delivered to a series of electrolytic conduits as shown. A message related to that signal is transmitted 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, a post-junction electrolytic conduit, and a set of electrolytic elements. 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). Frame (c) portrays the basic Activa as developed above.

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

3.1.3.2 Neuron/nerve architectures are stage specific

Each stage of the hearing modality places different requirements on the neuron. This and the following chapters will follow the framework of a multiple stage neural system laid out earlier in Chapter 1. Stage 1 neurons must provide a mechanism for accepting one of various forms of energy and converting that energy into an initial electrical signal. Ancillary requirements placed on the sensory neurons are to provide significant amplification of a small initial electrical signal, and to vary that gain in the presence of large initial signals. Stage 2 & 4 neurons must provide a variety of signal processing and signal manipulation functions in order to optimize the signals participating in the ultimate goal of the modality, extraction of the information associated with the signals that describe the source of the signals. Only a small variety of these types of neurons have been documented. The neurons of stages 1, 2 & 4 are all analog neurons, the predominant neuron class in biology. Stage 3 required a different class of neuron in order to provide efficient transmission of signals over long distances (distances greater than two millimeters in the biological context). The result is a class of phasic neurons processing pulse signals that are frequently described as exhibiting an "all-or-nothing" characteristic at a given instant in time. As will be seen, this is an oversimplification. The shape of these pulses shows a continuous and graded amplitude variation as a function of time. However, the information associated with these pulses can be described using a phasic code. While these stage 3 phasic neurons are a minority within the sensory modalities, they are by far the most widely studied because of their easily identified pulse characteristics. While not discussed in detail in this work, the stage 5 of neurobiology, cognition, also employs analog neurons similar to stages 1, 2 & 4.

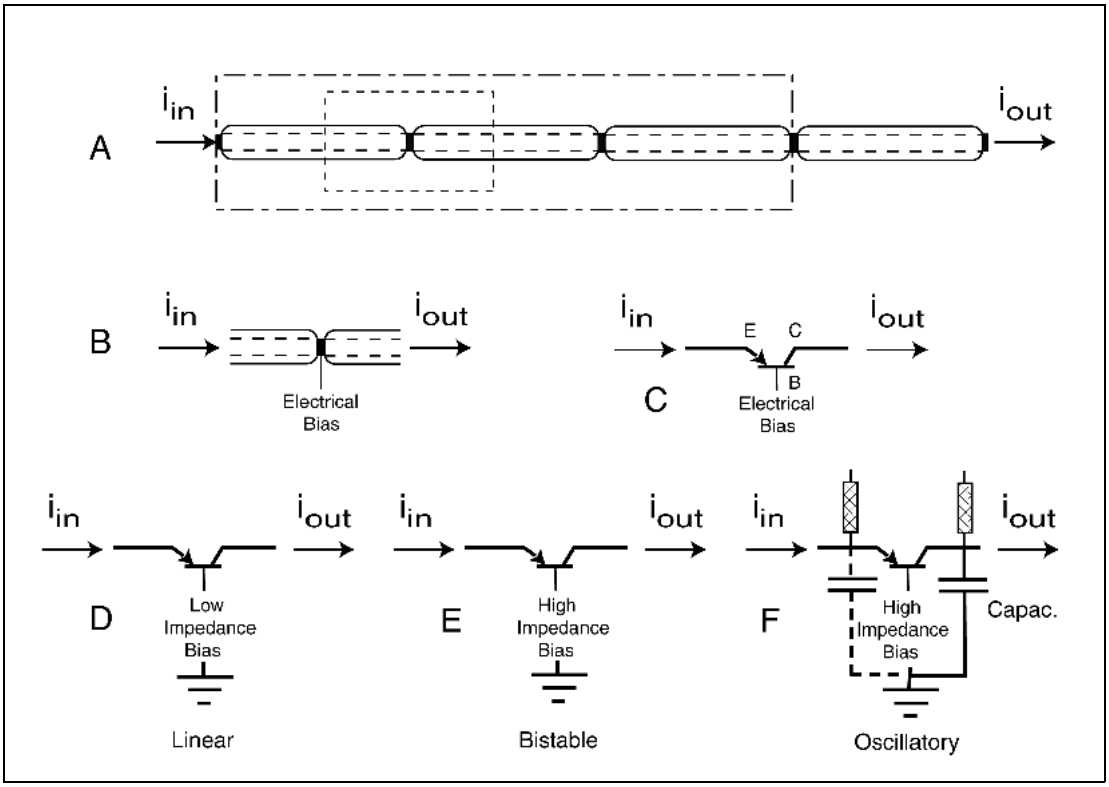

Figure 3.1.2-6 The fundamental functional form of the neuron and its electrical variations. A; the nominal signaling path of the neural system. The inner box encloses a minimal physiological unit (the conexus) of the neural system. The outer box encloses multiple conexuses as typically found within an individual signal projection neuron, a fundamental metabolic unit. B; the Activa within a conexus shown in electro-cytological form. C; the Activa within a conexus shown in standard symbolic form. Bottom frames, additional optimizations available depending on circuit requirements.

In some cases, particularly when working with simpler animals, examples have been documented where the formal separation between functions inferred by the multiple stage architecture is not found morphologically. This technique for minimizing the circuitry associated with a given signal path should not be considered typical.

3.1.4 The common cytological and morphological characteristics of neurons

The morphological naming of neurons has been largely fanciful and unproductive. This has been true ever since Cajal isolated a neuron and labeled it either a "psychic or pyramid neuron." Neither name identified the function of that neuron. Subsequent workers adopted the name pyramid cell, probably because it sounded more substantial. Few "pyramid cells" exhibit a tetrahedral shape and even fewer have a square base. More recent names, e.g., furry cells, octopus cells, etc., have been even less descriptive of their purpose or function. This section will identify a variety of neurons based on their function or their location in the overall neurological architecture. In some cases, this leads to slightly modifying the definition of the common name and in other cases, to adopting a common name to a wider group of neurons.

The pharmacological naming of neurons has been even less productive. Naming a neuron based on how it reacts to the introduction of a pharmacological agent, without defining the precise location of the topical application, is invariably ambiguous.

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 1st and 2nd 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. 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. More common than, and often mistaken for, projection neurons. 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.

This work subdivides the neuron into more elements related to signaling than the previous literature. These additional parts include:

Axon segment– A subdivision of an axon used for the propagation of signals between points of regeneration known as Nodes of Ranvier. Usually myelinated to optimize signal propagation.

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

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–A neurite and 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.

To avoid new terminology in defining the field of 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 (conversion of a steady potential into a time varying electrolytic waveform). This amplification may be exemplified by either current or voltage amplification.

All biological Activas 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.

Emitter--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.

3.2 A functional pyramid cell as an exemplar of a *type 1* (electrotonic) conexus

This section will only discuss the internal features of a neuron concerned with stage 2 signal processing and stage 4 signal manipulation.

The literature displays a "pyramid cell" in two dimensions as a triangular structure with the dendrite emanating from the apex, the axon emanating from the center of the base, and a second neuritic structure, a podite, emanating from one corner of the base. In three dimensions, the structure could be either a cone or a tetrahedron (a pyramid with a triangular base). It could also be a pyramid with a square base. Frequently, a swelling is associated with the point where the axon emerges from the base. The resulting structure appears diamond shaped in two dimensions. This swelling will be addressed in more detail in Section 3.4.

The generic features of a pyramid cell are one or more dendritic arborizations emanating from near the apex of the cell, one or more poditic arborizations emanating from the perimeter of the base of the cell and an axon emanating from the nominal center of the base.

3.2.1 The cross-section of a typical pyramid cell

The Activas found within various neurons have not been studied as entities before their discovery and definition in this work. As indicated in the previous sections of this Chapter, the Activas exist in several different configurations within the various major types of neurons. Hersch & Peters have provided a well-defined electron-micrograph of the Activa in a pyramidal cell of a rat[18]. The picture displays two separate and distinct neurites, the apical dendrite(conventional) and the basal dendrite (or podite as defined in this work). The four major elements concerning signaling are clearly shown, the apical dendrite, the basal dendrite (the podite), the Activa (within the hillock) and the axon. They are shown within the cell membrane but external to the nucleus in the area generally described as the cell body. The cell membrane and other features are not well resolved at only x5000 magnification. At higher magnification, imaging a different plane through the cell would probably be necessary to show the actual location of the "7-layer" membrane forming the actual Activa. The figure clearly shows the *location* of the podite or base region of the Activa between the apical dendrite and the axon. The Activa is in the region described as the initial segment of the axon. This is a subregion of the hillock and is not covered by myelin. The figure also shows the access of each of these areas to the external surface of the cell membrane for electrical and other purposes.

Figure 3.2.1-1 is a caricature of the Hersch & Peters figure shown with several additional synapses for purposes of discussion. Note the nucleus is shown surrounded by the dendritic conduit in this 2-dimensional view of a 3-dimensional object. For purposes of signaling, the nucleus is irrelevant and can be omitted entirely. For purposes

of growth and maintenance, the nucleus has direct access to the surrounding fluids via the third dimension. The critical area of this neuron is the space within the dotted box. This area includes the two internal membranes separating the dendroplasm and the axoplasm. Usually, the distance between these two membranes is inconsequential. However, in a small region (not shown at this scale), they are only separated by about 100 Angstrom (10 nm.). The resulting 7-layer region forms the physical location of the Activa. The Activa is only found in the region where the two bi-layer membranes are separated by less than 100 Angstrom (but more than a critical minimum amount). They are not in physical contact from the perspective of semiconductor physics.

The inset shows the detailed electrical equivalent of the Activa region of the figure. The emitter terminal is connected to the dendritic region. The base terminal is connected to the poditic region and the collector is connected to the axon region. Note carefully that the so-called axo-soma synapses are in fact conventional axo-dendritic synapses from a functional and from a plasma-to-plasma perspective. The remainder of the electrical circuit within a pyramid circuit is that shown in Figure 3.1.2-5. The non-inverting input, $V_{in}(1)$ corresponds to the dendritic input to the pyramid neuron. The inverting input, $V_{in}(2)$ corresponds to the poditic input to the pyramid neuron. This circuit operates in the linear mode amplification regime. In general the amplification factor is adjusted to be equal to one for both inputs by adjusting the resistive component of the poditic impedance.

Afifi & Bergman[19] have discussed the podite contact with the surrounding medium under the morphological designation, initial segment. They describe the base region of the Activa within this region as of 200 Angstrom (20 nm.) thickness and consisting of a dense layer of granular material. At this gap width, it is proposed that the so-called dense granular material occupying the perinodal gap is, in fact, a liquid-crystal of hydronium described earlier as a hydronium bridge.

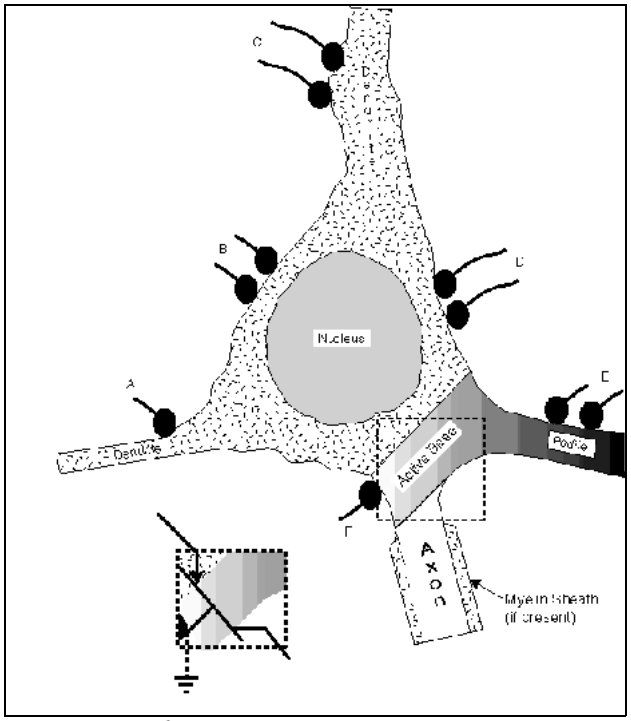

Figure 3.2.1-1 Caricature of the rat pyramidal cell based on a figure from Hersch & Peters. The apparent synapses with the soma are functionally synapses with the dendroplasm. Inset; the functional arrangement of the Activa within the soma.

Hersch & Peters show a structure in the lower left of their figure that is not labeled. It may be an additional dendritic branch that is not well represented in the slice of the cell imaged in this electron micrograph. This is the assumption made in the caricature which shows two distinct dendritic roots (both truncated for purposes of this discussion). The caricature also shows a series of synapses, labeled A through F. It provides an opportunity to simplify and rationalize the naming of synapses associated with a typical signal processing neuron. Synapses A through D all contact the dendritic plasma membrane and are by that definition axo-dendritic synapses. While synapses B and D may be labeled axo-somatic based on morphology, these designations are functionally meaningless. Synapses occur between the plasmas of electrolytic conduits. In this case, features B & D are both axo-dendritic synapses based on physiology. The synapses at E would be called axo-dendritic based on morphology but is more correctly named axo-poditic based on physiology. The synapse at F has frequently been labeled axo-axon because of its location on the morphological hillock. It also is more properly labeled axo-poditic based on physiology. These more precise definitions stress the need to replace tabulations based on morphology (such as those of Afifi & Bergman) with those based on function (physiology). The morphological description of a synapse as dendro-dendritic makes no sense within the functional architecture of the neural system.

The Law defined by Sherman & Guillery[20], and consistent with Cajal, is;

> "A functional synapse or useful and effective contact between two neurons can only be formed between the collateral or terminal axonal ramifications of one neuron and the dendrites or cell body of another neuron."

> The law can be updated to comply with modern requirements, *A functional contact between two neurons can only be formed between the axoplasm of a collateral or terminal axonal ramifications of one neuron and the neuritic plasma of another neuron, where both lemmas are of type 2 within the synaptic gap region and juxtaposed with a spacing of 10 nanometers.*

Sherman & Guillery have recognized the likelihood of two routes for inputs to the "multiplexing" by a single neuron[21].

Only a few investigators have attempted to measure the potentials within the dendrites of bipolar and horizontal cells. Copenhagen, Ashmore & Schnapf have provided point measurements reflecting the response of the photosensing system to light[22]. Guyton has provided an electrical potential mapping of a neuron of the pyramidal type[23]. A modified version of that figure is shown in Figure 3.2.1-2. Note the more negative potential in the upper (poditic) arm of the neuron than found in the bulk of the neuron. The poditic arm is normally 15-25 mV more negative than the dendrites in order for the dendritic terminal of the Activa to be forward biased relative to the base terminal. Note also the voltage gradients in the various arms. This is exactly what would be expected by the current passing through the resistive arms and creating a voltage drop. The voltage gradient is determined by both the current entering the neuron and the diameter of the arm at a given location that controls its local impedance. Although Guyton considered the various junctions shown to be either excitatory, the ones on the two left arms, or inhibitory, generally the ones on the top arm, these labels have been omitted. In this work, it is the Activa circuit within the neuron and its input circuits represented by the neurites that determines whether the output is the same or opposite polarity as the input signal. The circuit and the overall neuron constitute an analog device as illustrated by the smooth potential gradients within the neuron. The upper poditic arm is the inverting input terminal. The dendrites on the left are non-inverting input terminals. The axon potential was not provided in the original figure. It was probably near -120 mV (necessarily between -75 and -150 mV) because of the large voltage difference between the dendrites and the podite and because of the considerable current flow present.

Actual neurons can vary substantially from the generic "pyramid" form for both functional and packaging reasons. The poditic arborization can be rudimentary, as in the bipolar neuron or the axon can be missing as in the auditory, sensory neurons (Section 5.2.2).

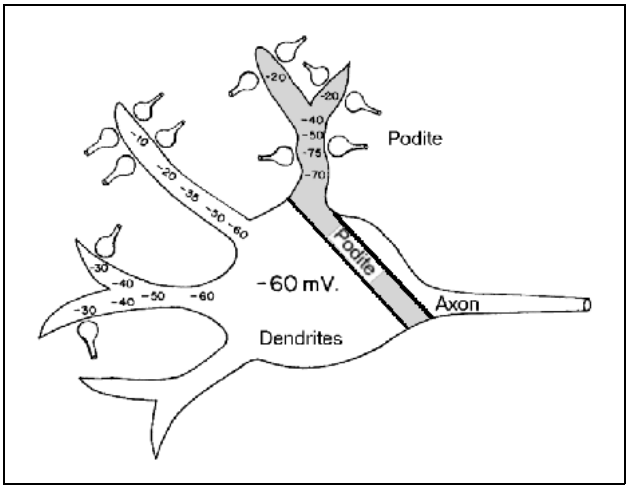

Figure 3.2.1-2 A potential map of a pyramidal type neuron showing the higher negative potential in the podite arm than in the bulk of the neuron representing the dendritic arm. Note the potential gradient along the arms due to current flowing within them. Modified from Guyton (1976).

3.2.2 Interior features of the neuron

Little attention has been paid to the internal electrical isolation of the plasmas within a neuron by membranes. These membranes are extremely thin molecular monolayers or bilayers that seldom form planes that can be easily photographed. However, the presence of electrically isolated plasmas demonstrates their presence.

3.2.2.1 The electrical conduits within the neuron

When studying the detailed structures within a cell, classifying the material found within the plasma membrane of the neurites and the axons is appropriate. At a cursory level, these are usually called the dendroplasm, podaplasm and axoplasm. However, the material is a very complex matrix that needs further definition. Such definition aids in the discussion of both the metabolic and signaling functions associated with these structures.

There are many filamentary materials within these cytoplasms that give the cell a degree of form and rigidity. These materials when embedded in the plasma, along with other elements, result in a matrix given the name cytoskeleton. The major elements are the microtubules, neurofilaments, mitochondria and frequently microfilaments. The neurofilaments are usually described as "solid." The focus here will be on the microtubules. They are known to extend to the terminal ends of the neurons, to be hollow, to consist of a well-ordered molecular wall that would be expected to be non-conducting to electricity, and to contain a fluid (or liquid-crystal) that can be expected to be a

conducting medium. Downing has recently provided new details relative to the construction of the microtubules[24]. The size of these microtubules would suggest that any material inside them would be essentially immobile. Such material might be liquid-crystalline in form.

This theory calls for an *electrically* conducting path between the synapses of the dendrites and the synapses of the axons and also a path from the base region of the internal Activa to the surface of the plasma membrane of the cell. The path need not be contiguous for diffusion. Such paths are clearly present, although in some cases in a dispersed form. The reticulum, well documented in both the neuritic structures and the axons, serves this function. A major conduit within the axonal reticulum appears to approach the synapse area and is frequently labeled the "ribbon" in morphology. The ribbon appears more visible in the area of the synapses, probably because of the electrical charge concentrated within it, even under equilibrium conditions. If the junction associated with the synapse is disturbed, it is likely that this electrical charge concentration may be disturbed. The ribbon would become harder to recognize under this condition. Smaller conduits contacting the synapse area would appear similarly.

Figure 17-13, in Waxman et al., provides a low resolution image of a rat axon injected with a dye. Unfortunately, it is truncated and does not show the location of the cell nucleus or the end of the axon conduit within the cell body. This location would identify the "hot spot," e.g. the Activa, within this neuron. A similar figure showing the nucleus and employing two different dyes in the dendritic and axonal structures would display the electrical organization of the neuron more clearly.

Note the bifurcation in the axon. Such division into collateral branches raises another variable characteristic of neurons that needs to be identified. It will be discussed in detail in the following sections on specific neuron types. This characteristic relates to whether the neuron is employed in the "current" or "voltage" mode. A simple neuron, and particularly an internode segment of a neuron, has only one synapse. All of the current flowing in the axon is available for delivery to the next neural segment. However, for most neurons, there are multiple synapses associated with one axon. If it is operated in the current mode, this current must be divided between the various synapses. Each following neuron will receive a small fraction of the original current through a low impedance Activa connection. If however, the output of the neuron is operated in the voltage mode, each connection to the subsequent neurons operates in a high impedance mode and they all sample the same voltage level. This allows for a high level of divergence in the signaling circuitry without a significant loss in signal amplitude.

Figure 3.2.1-3 provides a conventional morphological view of the fundamental neuron with additional electrical notation beyond that in Figure 3.1.2-3(A). Functionally, it differs from the electrical model in figure 9.7 of Segev & London by further differentiating their soma[25]. Practically, their axon length of only one micron compared to an 800-micron long dendrite seems unusual. It appears they misinterpreted the drawing of Rall in adopting this high value for the dendrite. In any case, the Rall model of an equivalent dendrite is not appropriate when calculating transit delay of signals. The nucleus, and the bulk of the soma, is shown separated from the juxtaposition of the dendritic and axonal conduits. The classical morphologist defines this configuration as a monopolar neuron because of the single structure emanating from the area of the nucleus. It has been expanded slightly to show the reticulum frequently shown within the dendritic and axonal conduits. When considering ionic flow within a neural conduit, most of the physical ion flow occurs within the reticulum. However, when considering electrical charge flow, most of the charge is located along the inner wall of the lemma. The area outside of the reticulum is generally of such high viscosity that ionic flow is unlikely. When considering electromagnetic signal transmission, it is the inductance and capacitance associated with the cylinder between the exterior medium and the outside of the reticulum that is important. The resistances associated with the interior of the dendrite are only important for establishing steady state electrical parameters.

In sensory neurons, the reticulum plays an additional role that will be addressed in Section 5.2.

3.2.2.2 The role of the vesicles

One of the most interesting, and relatively pervasive elements within these spaces, are the vesicles. These are poorly characterized, typically spherical structures of a nominal 40-50 nm diameter. There may be many different classes of vesicles that are performing different functions. Some of them may be mitochondria in the eyes of other investigators. Others are reported to have an electrically charged core that appears translucent (or under different circumstances, opaque) in electron-micrographs. Some of them are believed to flow significant distances within the axonal and neuritic structures. Others may be fixed, particularly in relation to the plasma membrane wall near synapses.

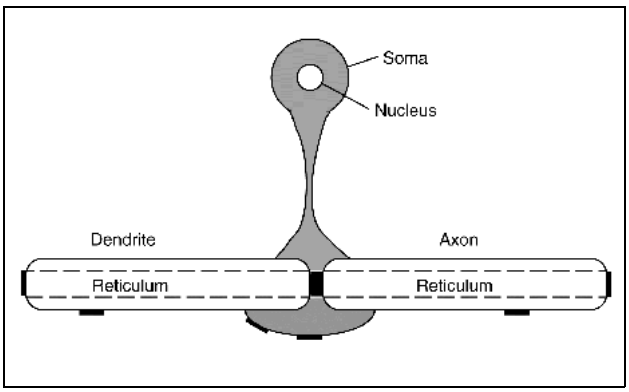

Figure 3.2.1-3 Cytological view of the fundamental neuron including the reticula within the dendrite and axon. The dendrite and axon are shown in their final juxtaposition. The space between them is greatly exaggerated for purposes of illustration. All horizontal black bars are electrostenolytic sites. Vertical and oblique bars are signaling sites (if used).

Most of the available literature is based on low resolution, less than x50,000, which does not allow detailed interpretation of boundary conditions. This has also limited the understanding of the electrostenolytic situation.

Terminology can be a problem when discussing vesicles. The literature appears inconsistent concerning the term translucent when speaking of electron microscopy. Shepherd contrasts electron-lucent and electron-dense vesicles. Synonyms might be electron-transparent and electron-opaque, with the understanding that transparent is restricted to the transmission of non-imaging energy. When speaking of electron-dense vesicles, it is frequently stated that the vesicle has an electron-dense core. Based on the available knowledge concerning the dielectrics of the vesicle, this is very unlikely. Electrons oppose each other. The discipline of electrostatics calls for the electrons to distance themselves from each other as much as possible within the electrical constraints of their environment. Barlow[26], among others, shows the more likely nature of any charge on a particle embedded in an electrolyte. The charge is spread uniformly over the inside of the dielectric membrane containing it. Size can also be a problem. Shepherd defines small (40-60 nm), medium (80-100 nm) and large (100-160 nm) vesicles. He then continues on the same page defining small vesicles (20-40 nm) as the most common size vesicles found in his Type I and Type II synapses.

Osborne provided a discussion of the role of vesicles in sensory cells as of 1977[27]. The functions described are limited to the synthesis, storage, transport & release of the putative chemical neurotransmitter. However, the imagery and caricatures are limited to about x50,000 and that limits the recognition of fine details. No evidence was presented for the existence of vesicles transporting chemicals through any membrane.

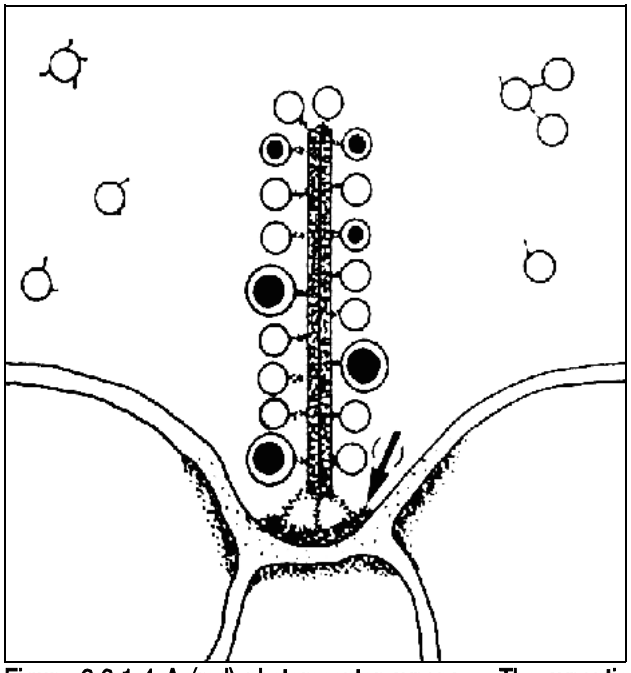

Figure 3.2.1-4 A (rod) photoreceptor synapse. The synaptic vesicles, some of which have dense cores, surround the synaptic ribbon. The ribbon is connected to the arcuate body (arrow). Figure and citation from Osborne, 1977.

He reports that vesicles may originate almost anywhere within a neuron. He also summarizes a variety of vesicle types and says at least some types exhibit a life time of 1-28 days. Although he does not take a position concerning the physiological function of the vesicles, his caricatures, particularly his Figure 4.11(E), reproduced here as Figure 3.2.1-4 has formed the basis of several subsequent caricatures by other authors discussed below. Note the conceptual description of materials along the cell surfaces. The arcuate form, below the central column, known as the ribbon and surrounded by vesicles, has frequently been described as an arcuate body. An arcuate body implies a more substantial structure than shown. As shown, the arcuate form could be considered a region of space charge at the end of the axo-reticulum.

Similar to the premise that the dense regions associated with the ribbon and arcuate form might guide or transport vesicles in the presynaptic region, this work proposes that they are part of the charge conduction conduit. They are part of the reticulum, between the Activa within the Soma and the presynaptic

region.

The class of vesicles in this discussion will be assumed to be fixed in location for significant periods of time. They are generally larger than the microtubules and could not flow through them. They also appear to be embedded in the matrix of the axoplasm in most electron-micrographs. Only more detailed experiments will rationalize the function and movement of these vesicles and determine whether the vesicles are carried along with the diffusion supported flow of the cytoplasm.

3.2.2.3 Diffusion within the plasmas & surrounding fluids

The literature and texts of neuroscience frequently discuss transport phenomena within and about neurons. These discussions frequently define multiple discrete transport velocities. It is important to remember that the diffusion laws are highly dependent on the physical state of the materials present. Ions and large molecules do not move through liquid-crystalline material (like gels) as freely as they do through low viscosity fluids.

The literature contains a variety of references to axon transport velocities. Heeding man's normal tendency, these velocities were first divided into fast and slow, and traveling in distal and proximal directions. The laws of diffusion discuss the movement of individual species in a solvent. Each species can have its own characteristic velocity. This velocity may also be affected by any electrostatic field in the area if the species is charged. There are a large variety of species in the various cytoplasms of a cell and in the fluids surrounding the cell. Each of these species may move at a different velocity. The result is a continuum, as opposed to a dichotomy, of transport velocities.

3.3 More complex analog neuron configurations

As noted above, the analog neuron exhibits three primary features. The first is the ability to aggregate signals from a large number of antidromic neurons based on their spatial or temporal characteristics. The second is the ability to subtract the signals presented at the poditic terminal from the signals presented at the dendritic terminal of the internal Activa. The third is the ability of the Activa to perform a thresholding operation on the resultant signal. It can be biased so that it generates no output unless the net signal applied to the Activa exceeds a specific value. By combining the three primary features of the analog neuron, a wide variety of signal processing circuits can be generated.

The histology of the stage 2 auditory system is much more complex than that of the visual system in all but the most primitive animals with hearing. This has made the detailed description of most of the stage 2 neurons difficult.

The simple organization of the first order signal processing in the retina, and the ease of experimental access to the retina, has led to well-defined functional characteristics for most of the neurons found there. The retina contains two obvious stage 2 neuron types. The first type consists of the summation neurons, typically called bipolar neurons (although many are monopolar based on their morphology). The second type consists of the differencing neurons. The morphological most obvious of these are the horizontal cells located in a layer immediately behind the stage 1 sensory neurons. These neurons are concerned with taking the difference between the signals of spectrally different sensory neurons in a local area of the retina. An additional layer of differencing neurons is found at slightly later in the signal processing architecture. The neurons in this layer are generally called amercine neurons. They perform differencing on signals that have already been aggregated to a degree by the horizontal and bipolar neurons. While relatively easily to isolate morphologically, the outputs of these neurons are so complex that it is difficult to describe or categorize them.

The horizontal and amercine neurons are specific implementations of the pyramid neuron described above, even though their morphology may be significantly different.

The virtual inaccessibility of the stage 2 neurons of the spiral ganglia, and the cochlear nucleus has significantly limited definition of the neural circuitry of these elements. The difficulty has been compounded by a shortage of models of the architecture of these portions of the auditory system that can suggest the appropriate experimental protocols. In many cases, the signals arriving at the cochlear nucleus are so complex that it is difficult to visualize the signal processing carried out within that element. At the current time, only fanciful names have been associated with these output waveforms. The same or similar fanciful names have been assigned to the neurons generating these waveforms.

3.3.1 The auditory sensory neurons

Like the stage 2 signal processing neurons, the stage 1 signal generating neurons of the auditory system are extremely difficult to access electrophysiologically in their *in-vivo* state. The auditory sensory neurons exist in two morphologically distinct forms, the outer hair cells (OHC) and the inner hair cells (IHC). The difference between them is primarily related to the way the neurons are mounted and arranged. The IHCs are mounted on one side of a triangular structure and lean outward relative to the modiolos of the cochlear partition. The OHCs on the other hand are mounted on the other side of the triangle and lean toward the modiolos. The OHCs are arranged in three to five parallel rows spanning the length of the cochlear partition. The IHCs are arranged in a single row spanning the length of the cochlear partition. Cytologically and functionally, the OHC and the IHC are virtually identical. However, the signals presented to them, and processed by them, are grossly different.

The internal complexity of the auditory sensory neurons, and the limited empirical base, has made their analysis difficult. However, their functional similarity to the visual sensory neurons provides an avenue for accomplishing this analysis. This avenue is addressed in Chapter 5.

The sensory neurons face a neurological requirement not shared by the other neurons, the ability to amplify very weak signals generated by the stimuli to the level required within the nervous system without encountering interference or crosstalk from nearby neurons. The arrangement of the sensory neurons within the Space of Nuel is designed specifically to satisfy this requirement. Figure 1 of Bredberg (1977) shows this arrangement clearly[28]. The individual neurons are isolated from each other and all other structures except where they penetrate the reticular lamina and where they are supported by Deiters cells at their basal end. Otherwise, each cell is totally immersed in a fluid from which they draw nutrients. The cells may also draw nutrients, particularly glutamate, from the adjacent Deiters cells. The figure also shows the cilia protruding through the reticular lamina and into the endolymph in order to interact with the tectorial membrane. Figure 2(a & b) from Zenner et al. shows individual sensory neurons in isolation. Little information was provided about the imagery[29].

3.3.2 The fully elaborated auditory sensory neuron

The sensory neurons of hearing, the OHC and IHC, are derived from the generic neuron developed in Section 3.2.1. The two major differences are shown in the upper portion of Figure 3.3.2-1. These differences are implemented because an electrical signal must be generated from a non-electrical stimulus. The generic neuron is elaborated by a modification to the dendrite of the sensory neuron and the "special protein" producing portion of the neuron is active. These are the same differences found in the visual sensory neurons.

To implement the specializations required in the neural portions of the cell, the figure highlights changes made to the internal structures of the dendritic compartment. Either the reticulum, or an additional lemma, becomes a barrier across the top of the compartment. This barrier must contains a region of type 2 membrane. This barrier, with its type 2 region, is positioned immediately adjacent to a type 2 region of the plasmalemma. The spacing must be appropriate for the creation of an additional Activa. The region occupied by hydronium as a result of this positioning (the base region of the Activa) is shown sharing an electrical conduit connecting it to the protein producing chamber on the right.

The protein producing chamber is electrically isolated from the electrical conduit by a region of piezoelectric protein material. This material fills the cilia of the neuron and much of a region known as the cuticular plate at the apex of the cell. Note the protein material is not secreted to form a protein-based hair outside the cell. The arrangement of the protein material within the cilia and the cuticular plate is very complex. As shown, the primary mechanical (acoustic) force applied to the cilia is axial. This stress results in an electrical potential transverse to the applied force. However, transverse forces can also generate a transverse electrical potential. The electrically bipolar potential generated by these stresses is shown by the horizontal line with two arrowheads.

All of the other mechanisms associated with the generic neuron remain unchanged. As a point of interest, the relative concentration of the sodium ion and the potassium ion are listed on the right. It should be noted that these two materials play no role in the operation of the neuron under the Electrolytic Theory of the Neuron. No mechanism has ever been discovered that will allow these simple metallic ions to pass through the plasmalemma of a neuron.

Two symbols are shown on the left of the figure for clarification. The upper symbol shows the direction of electron flow within a neuron. This symbol appears at multiple locations within the figure. The lower symbol is meant to be interpreted more narrowly. It is only provided to clarify that the neural signal begins at the upper left and proceeds downward through the pedicle of the neuron and into the orthodromic neuron shown by a dashed line.

The resulting neuron contains two distinct Activas. The original Activa has been labeled the distribution Activa and the new Activa can be labeled the adaptation Activa in order to describe their primary functional roles. The adaptation Activa has the electrical potential produced by the piezoelectric material applied to its base region. As discussed earlier, applying the electrical stimulus to the base region of the Activa results in significant amplification of that signal at the collector terminal of the Activa This amplified signal can be measured by probing the dendroplasm of the neuron. This amplified signal is then applied to the emitter of the distribution Activa. This Activa provides no voltage amplification at the pedicle of the neuron but it does provide a lower electrical impedance at this point. The resulting neuron contains a variety of individual chambers and their respective plasmas. When patch-clamp techniques are used in the laboratory, it is important to define what plasma is accessed.

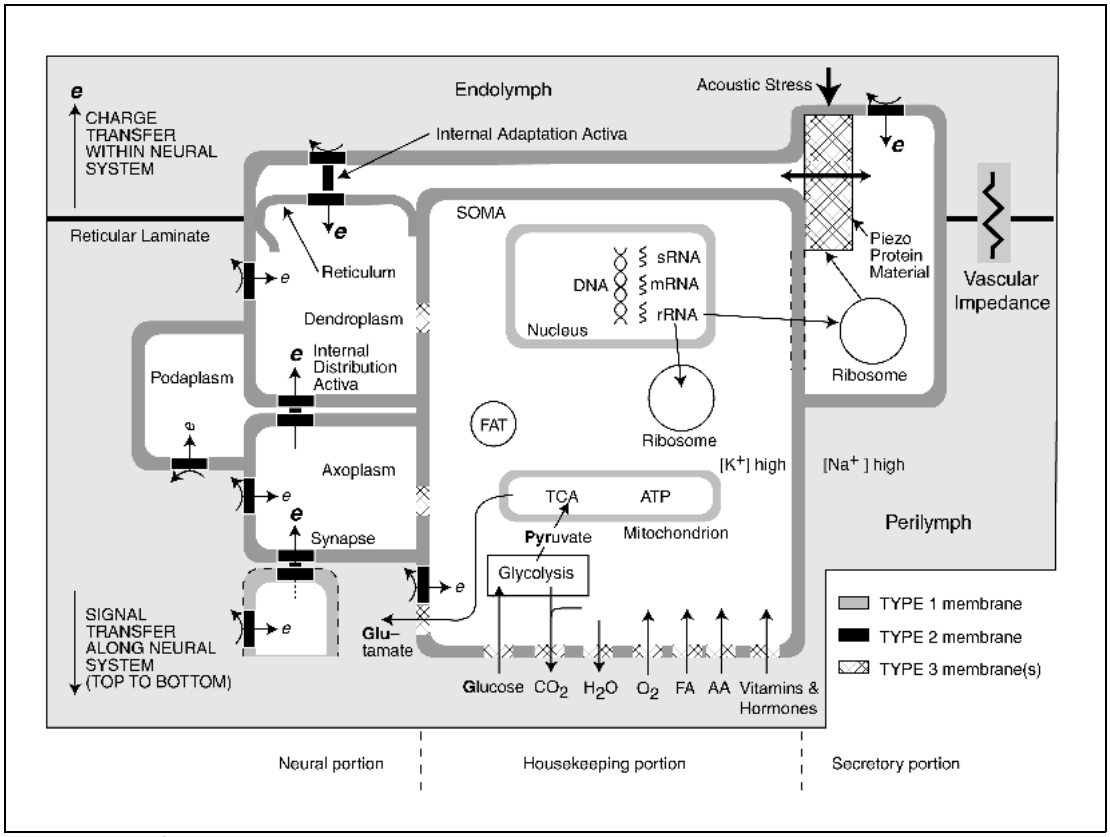

Figure 3.3.2-1 Schematic of a complete sensory neuron of hearing. The figure is similar to Figure 3.1.2-5 except for changes made along the upper edge of the neuron. The reticulum within the dendrolemma has changed character and assumed a new role. The reticulum and the dendrolemma now form an additional Activa. The base of this Activa is electrically connected to the piezo-electric material shown on the right. Part of this material is contained within the cilia (shown at upper right). The remainder is within the cuticular plate (not shown). See text.

The auditory sensory neuron is shown immersed in the perilymph of the cochlear partition except for the apical region that pierces the reticular laminate and is immersed in the endolymph. This configuration, and the vascular impedance between these two lymphs, play an important role in the operation of the sensory neurons (Section 5.2.3).

While the topology and cytology of the IHCs and OHCs are quite complex, their morphology is not. They exhibit neither neuritic arborization nor typical external axons.

3.4 A modified pyramid cell as an exemplar of a *type 2* (phasic) conexus

The phasic pyramid neuron is morphologically, cytologically and topologically identical to the electrotonic pyramid neuron (Section 3.2) except for three features. The first is the morphologically more prominent hillock at the interface between the initial axon segment and the soma. This hillock provides the additional axolemma area required to provide a larger electrical capacitance between the collector terminal of the Activa and the common electrical ground. The second is the myelination of the axon beginning a short distance from the hillock. This myelination supports the more efficient transmission of action potential by propagation over that achievable by diffusion. The concept and properties of propagation are developed in Section 7.4. The third is the interruption of the myelination at regular intervals by Nodes of Ranvier. These nodes provide the regeneration of the action potentials at full amplitude to compensate for the attenuation associated with each axon segment. The Nodes of Ranvier will be discussed in Section 3.6.

The phasic pyramid neuron has been given many different morphological names. The most common is the ganglion neuron. Even the name ganglion neuron has been differentiated into sub classes, such as the parasol ganglion neuron and the midget ganglion neuron. There are functional differences between the parasol and the midget ganglion neurons that can provide more meaningful names.

The electrical circuit within a phasic pyramid neuron is the same as that shown in Figure 3.1.2-1 except for the additional capacitance between the collector terminal and the common ground point. The non-inverting input, $V_{in}(1)$ corresponds to the dendritic input to the pyramid neuron. The inverting input, $V_{in}(2)$ corresponds to the poditic input to the pyramid neuron. The additional capacitance introduces a change in operating mode that has not been discussed previously in the hearing literature. To understand this mode, it is also necessary to understand the concept of *internal* feedback.

While feedback as a concept has frequently been discussed in the hearing literature, it is generally discussed in terms of a separate signal path proceeding back from some point to an earlier point in the flow of the signal. This path is always shown as an external one. The circuit shown in Figure 3.1.2-4 includes an internal feedback path. Note the circuit path associated with a signal applied between the non-inverting input, $V_{in}(1)$, and the common ground point. It consists of the input impedance of the emitter-to-base circuit of the Activa plus the poditic impedance. A voltage applied to the emitter will cause a change in the current in the collector circuit. However, this change in collector circuit current results in a voltage across the poditic impedance. This change in the voltage across the poditic impedance may serve to enhance or reduce the net voltage applied to the emitter-to-base terminals relative to the input, $V_{in}(1)$. The mathematical expression for this effect is the same as that for an external signal path feeding back from the collector terminal to the emitter terminal. The effect is described as *internal* feedback. Internal feedback combined with the capacitance connected between the collector and ground is very important in the operation of the phasic pyramid neuron. The effect is to introduce a region of negative impedance in the transfer characteristic of the circuit. This negative impedance region introduces an instability into the operation of the circuit. The circuit wants to drive the collector potential to either its maximum or its minimum value depending on its present state as discussed in Section 7.3. The mechanism causes the circuit to operate in the "switching mode." The result is the generation of action potentials at a pulse-to-pulse interval determined by the magnitude of the emitter-to-base potential applied to the Activa.

The three morphological changes described above introduce profound changes in the physiological performance of the type 2 (phasic) neuron. The result of each of these changes and their cumulative result is developed in detail in Chapter 7.

3.5 The metabolic and metabotropic processes supporting the neurons

As described in the illustration of the fully elaborated neuron, the neuron requires a wide assortment of chemical material to support its operation. Many of these materials support the homeostasis of the neuron. Other materials are only associated with the operation of the specialized neural portion of the cell. This work will not address the materials required in the metabolic processes supporting homeostasis. It will concentrate on a process specific to the neural portion of the cell and occasionally described as metabotropic. This is the electrostenolytic process wherein glutamate is converted to GABA with the release of an electron.

The electrostenolytic process used in the neural system is highly optimized and effectively isolated from the more general chemistry of life. It is designed to use the only two negatively charged natural amino acids to power the neural system. These are glutamic acid and aspartic acid (glutamate and aspartate respectively to the pharmacologist).

The specialized receptors found at specific (specialized) sites on the lemmas of the neurons are stereo-specific for these two amino acids. Only chemicals mimicking the stereochemistry of these materials and carrying a negative charge are effective in the electrostenolytic processes of the neurons. Such materials participate in a metabotropic, or more specifically electrostenolytic process that provides power to the electrical circuits of the neuron. Because of the compartmented character of the interior of the neuron, several independent electrostenolytic processes may be associated with individual surface areas of a single plasma lemma.

3.5.1 The basic electrostenolytic process supporting neurons

The source of the electrical bias across the plasma membrane of every cell has been sought a very long time. Based on their experiments, Hodgkin & Huxley hypothesized an ion-pump as a component of a neuron. This putative ion-pump could transfer simple metallic ions across a membrane for purposes of biasing the cell. Because of their other hypotheses, two ion-pumps were required, one for moving sodium ions into the neuron and another one for moving potassium ions out of the neuron. These conceptual pumps necessarily moved one ion in opposition to the existing electrical bias. While many researchers have sought to move this ion-pump beyond the conceptual stage, no actual, or even plausible, cytological explanation of such a mechanism has appeared during the last 50 years.

The biology community has generally adopted a narrow philosophy regarding the electrostatics of a cell. They have assumed that it requires separating the ions of an ionizable material by a membrane to create an electrical potential across that membrane. Another method exists for achieving the same potential. If the purest of deionized waters (pH =7.000) is placed on each side of a closed insulating membrane and a battery is used to inject free electrons into the interior of the membrane, the interior of the membrane will assume a negative electrical potential with respect to the outside fluid. The potential will be precisely equal to the charge injected times the capacitance of the membrane. This negative potential will be achieved regardless of the presence of any ions. If the experiment is repeated using a solution of neutral saltwater on each side of the membrane, the same result will be obtained. The fact that all of the salt in the water is fully ionized is immaterial.

It is not necessary to transfer ions through the membrane of a cell to achieve a negative electrical potential inside the cell. Any mechanism that will transfer electrons to the interior of the membrane will generate such a negative potential. These electrons need not form an ion, in association with a specific atom, inside the membrane. The simplest method of providing this potential is described in Section 3.5.2. Electrostenolysis of glutamate on the surface of a locally asymmetric plasma membrane will inject electrons into the interior of the membrane and cause a negative potential to be observed. The free charge will spread out evenly over the interior of the closed membrane (assuming it is spherical) just as it would on the surface of any capacitor. The charge cannot escape through the membrane because of the insulating properties of the membrane with respect to negative charges.

3.5.2 The Electrostenolytic Process replaces the "ion-pump"

A continuous asymmetrical bilayer membrane is an electrolytic diode. It can transport an electrical charge (but not a physical ion) across the membrane under proper bias conditions. In this configuration, the membrane can participate in an additional mechanism that is critical to the operation of all neurons. This is the electrostenolytic process, an obscure although well-documented process of physical chemistry. The subject of electrostenolysis is too complex to detail here. Eyring[30] and Marino[31] have provided texts including sections on this subject but not in the detail required below. For that level of detail, more focused material such as Finkelstein[32] and Gutmann & Keyzer[33] should be reviewed.

The electrostenolytic process involves a chemical reaction that is stereo-chemically dependent on a substrate. The reaction will not take place unless the binding group of the potential reactant is in a specific stereochemical relationship with the substrate. The electrostenolytic process of interest in neuroscience is the conversion of an unusual amino-acid in exchange for the release of CO_2 and an electron. The specific reaction is shown in Figure 3.5.2-1. Glutamic acid (glutamate) becomes attached to the surface of an asymmetrical bilayer membrane by sharing a hydrogen bond (shown by the dashed line) of a carboxyl group within the binding group. The susceptible bond of the molecule is then broken, releasing the second carbon dioxide group along with an electron. This electron can then pass to the inside of the membrane. This charge movement causes a net negative charge on the capacitor associated with the membrane. The inside of the associated cell (or a conduit of the cell) is thereby biased negatively with respect to the surrounding interneuron matrix.

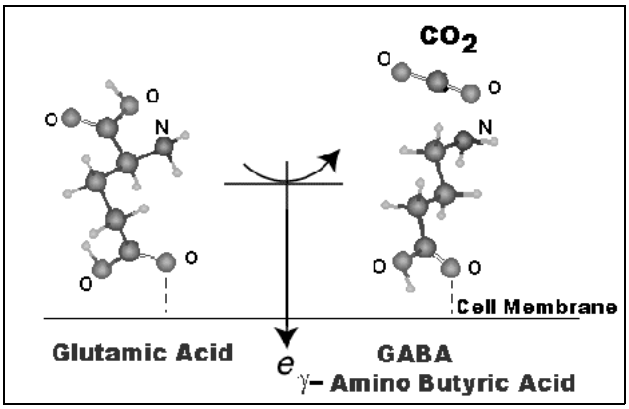

Figure 3.5.2-1 The electrostenolytic process powering the neural system. Glutamic acid becomes associated with the cell membrane in a highly selective stereo chemical relationship (dashed vertical lines). A reduction then occurs. The process releases carbon dioxide as shown. It also injects a free electron into the plasma on the other side of the cell membrane. GABA is then released from the stereo-chemical bond. The symbology in the center of the figure suggests the steps in the process.

The underlying mechanism can be explained based on earlier descriptions. It uses the polarization of the asymmetrical bilayer and requires the characteristics of a gap junction formed by two asymmetrical bilayers. Here, the single asymmetrical bilayer exhibits a net polarization. The glutamate molecule also exhibits a net polarization. The net polarization of the two constituents causes the electron to move to the interior side of the membrane. Following, or simultaneous with, that action, the CO_2 group is released. The remainder of the reactant is now described as gamma-amino-butyric acid (GABA). Notice that glutamate could just as easily be defined as gamma-amino glutaric acid except for the specific rules for naming chemicals. Under those rules, glutamate is labeled alpha-amino-glutaric acid.

The symbol in the figure is drawn to suggest that glutamate reacts to form GABA while releasing CO_2 on one side of the membrane and an electron on the other. It suggests the reaction occurs on the outside of the cell membrane. More study is required of this reaction. The reaction may occur within the cell.

The reaction of glutamate to form GABA has long been associated with the operation of neurons. By associating the reaction with the electrical biasing of the plasma associated with the process, the explanation of the putative ion-pump is provided. Noting that the ion-pump is really a charge-pump is important. Electrons are the form of charge moved (pumped) across the membrane. There is no need for heavy metallic ions to be transported (pumped) across the membrane, either into or out of the plasma, as part of the neural mechanism.

In the above context, the molecules forming the type 2 plasmalemma are also the receptors that are stereo-compatible with glutamate. There is no need for any other catalyst or enzyme. While the literature frequently defines an enzyme (a biological catalyst) conceptually as glutamic acid decarboxylase (GAD), no such enzyme is needed in the electrostenolytic conversion of glutamic acid to GABA.

3.5.3 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. 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 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.

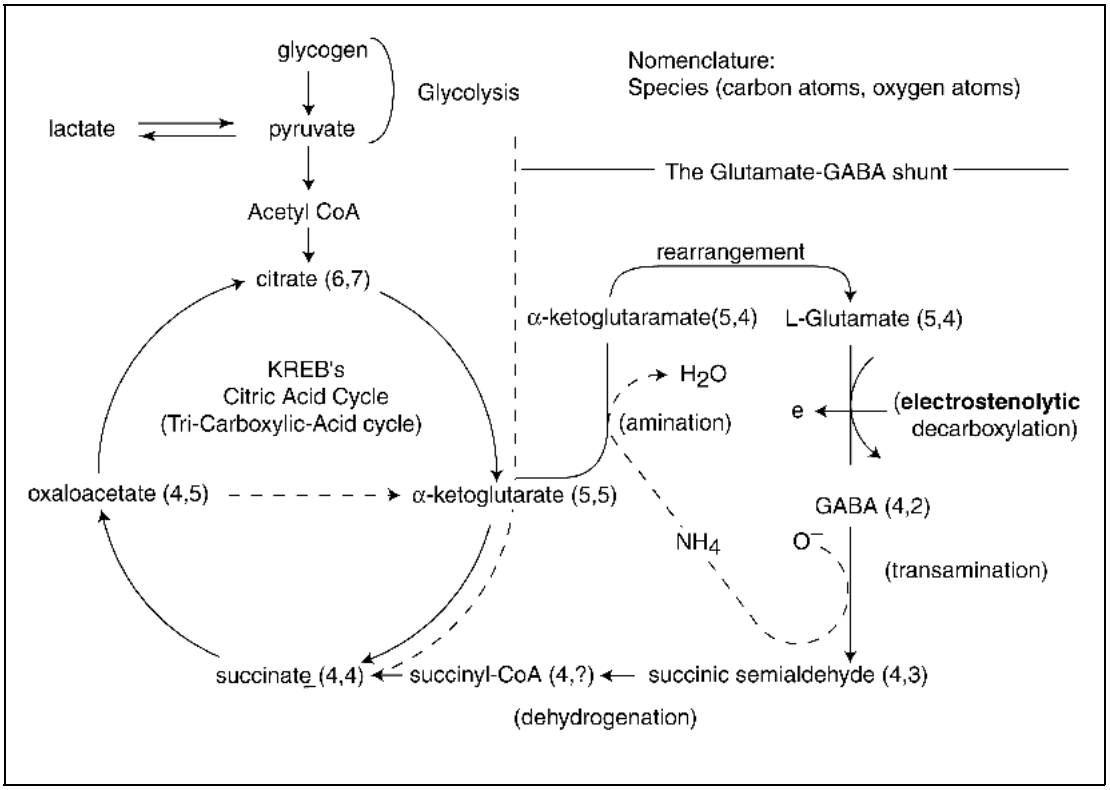

Figure 3.5.3-1 The variant of the Kreb's cycle critical to neural operation. The glutamate-GABA shunt is shown on the right using solid arrows. An available glutamate regeneration path is shown at lower right using dashed lines.

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 3.5.3-2 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.

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 3.5.3-2 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.

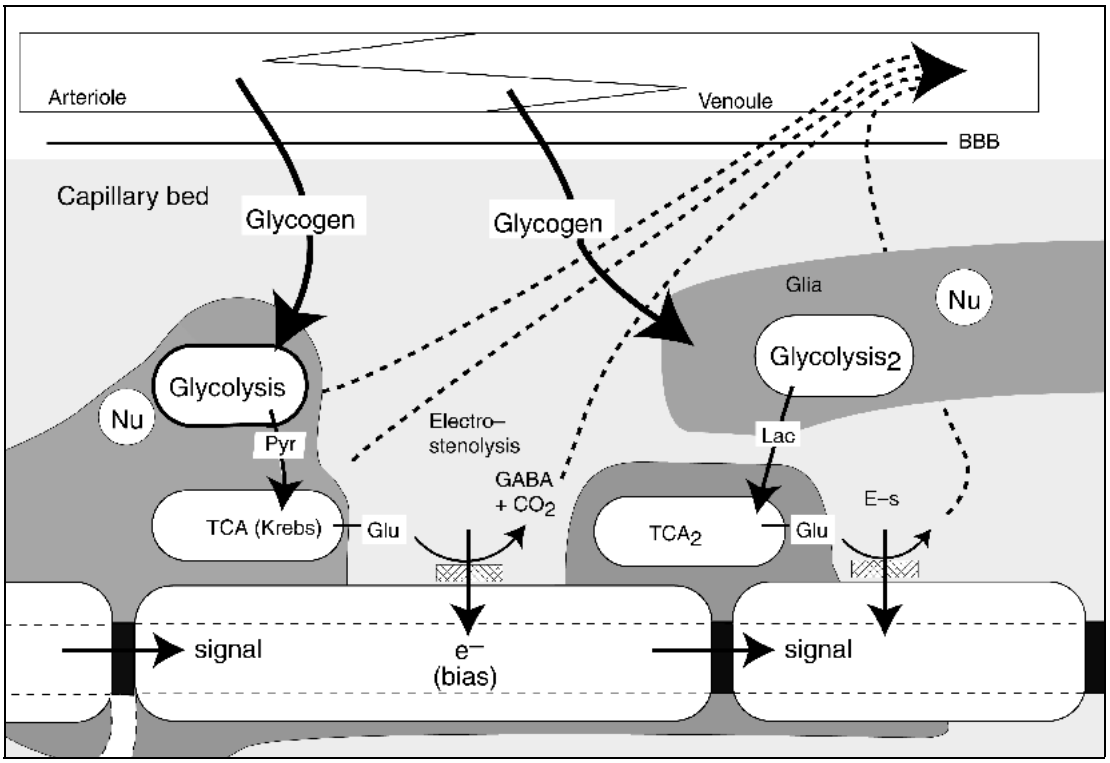

Figure 3.5.3-2 Details of the metabotropism and hydraulic flow of the neuron. It is highly likely that the glia supply lactate to the remote sites of glutamate production (TCA_2). Waste product removal is represented by the dashed arrow. The transport of glycogen, GABA and CO_2 through the capillary 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[34]. 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[35].

Sutherland et al. have recently addressed the genetic relationships that may (at least partially) control the flow of reactants in the above figure[36]. As a minimum, their paper expands the above model at the detail level.

3.5.4 The description of materials affecting 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.

3.5.4.1 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 3.5.3-3 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 3.5.3-3 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)[37]. Bobbin et al. have provided a discussion of the criteria for a neurotransmitter and an accompanying list of references as of 1984[38]. 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 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[39]. 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.

3.5.4.2 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[40], 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.

3.5.4.3 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 overall -ergic concept, based on a two-terminal concept of a neuron.[41] Sherman & Guillery have attempted to clarify the use of GABA-ergic, within the chemical neurotransmitter context, with less than the desired clarity[42]. 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[43]. 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[44]. 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.

Oertel & Young make an interesting observation that constitutes a dichotomy in their discussion of the chemical theory of the neuron, but is fully explained in the model of this work. They note, referencing Golding & Oertel[45], "Although cartwheel cells contain GABA and glutamic acid decarboxylase, they are glycinergic." Three founding premises of the Electrolytic Theory of the Neuron are:

- glutamic acid (glutamate) is found at multiple sites on the surface of all functioning neurons.
- glutamate decarboxylase is not required in neural operation because electrostenolysis performs the same function In many cases, investigators may not be able to differentiate between the presence of an electrostenolytic process and the presence of glutamate decarboxylase.
- GABA is found at multiple sites on the surface of all functioning neurons as an end product of electrostenolysis. Carbon dioxide, the other end product of electrostenolysis, rapidly diffuses into the INM.

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[46]. 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.

3.6 The synapse and Node of Ranvier

As discussed above, the synapse forms an external junction between two neural conduits. The Node of Ranvier forms a functionally similar junction. In the absence of the soma, the junction within a neuron is indistinguishable from a synapse (the junction between two neurons) or Node of Ranvier. The theoretical aspects of the synapse and Node of Ranvier have not been discussed in the neuroscience literature, particularly the question of *how* an electrical potential can cause the release of a chemical neurotransmitter. Prior to the 1950's, an argument raged as to whether the synapse involved an electrical-based or a chemical-based mechanism. During the 1950's through 1980's, the conventional wisdom expressed in text books was that, in concept, the synapse was chemically based. The chemical assumption has begun to crumble in recent time. Recent editions of Aidley's introductory physiology text have devoted more and more space to the reality of a totally electrolytic synapse[47]. Bennett has reopened the debate between the chemical theory and the electronic theory[48].

This section will present a few paragraphs regarding the subject of electrolytic versus chemical neurotransmitters. The traditionalists, including virtually all academics, remain wedded exclusively to the chemical neurotransmitter. Simultaneously, the modernist, and the evidence, takes the view that the electron is the major neurotransmitter. It should be obvious to any reader of the literature that the chemical neurotransmitter remains at the conceptual level with little material presented to describe the associated mechanisms required to justify the concept. On the other hand, the electrolytic neurotransmitter (the electron) and its mechanisms are the same as found at other locations within the neural system. The recent work in electron microscopy, documented by Pannese[49] and presented in detail by Vardi[50] and others, when combined with the physical chemistry associated with a gap of less than 10 nm between the axon and a neurite, demands the electrolytic mode of synaptic transmission be recognized.

3.6.1 Background

The chemical theory of the neuron, as applied to the synapse, has come under increased pressure due to the recent experimental work of two groups. Usami & Ottersen have shown the vesicles in the presynaptic plasma do not include high concentrations of the putative primary neurotransmitter glutamate[51,52]. Glowatzki & Fuchs have shown the direction of signal flow is entirely reversible across the synapse depending on the electrical potentials of the pre and post synaptic plasmas[53]. The measured reversible current flow introduces a major difficulty for the chemical theory. The chemical theory does not provide any mechanism for secretion of any chemical neurotransmitter by the post synaptic lemma and its collection by the presynaptic lemma. Glowatzki & Fuchs have also found difficulty in describing the performance of the synapse based on both the release of chemical neurotransmitters and the statistics conforming to a Poisson distribution. They have also questioned how continuous and initially rapid chemical transmitter release is achieved as required within the chemical neuron concept.

Stacy & Santolucito provided an introductory description of a chemical synapse based only on empirical data[54]. Their description can be extended considerably based on the synapse as a three-terminal active electrolytic device, an Activa, in its own right.

Pappas has provided information supporting the position of this work that large molecules do not cross the synapse in the gap area[55]. He performed a series of experiments using "certain marker substances–their molecular weight must be less than 200–are injected intracellularly into one of several cells connected by gap junctions." He then noted, "Immediately afterwards, the marker is seen to pass rapidly into adjacent cells but *not* into the intercellular spaces." [emphasis in the original] The next experiment injected lanthanum, which he says we know cannot cross the plasma membrane, into the fixative associated with the cells. He asserts, "it will still penetrate the gap junction insinuating itself between the 20 Å to 40 Å extracellular space or gap." He describes the gap saying, "the electron microscope reveals a hexagonally arranged mosaic of more-or-less circular areas into which the lanthanum has not penetrated. Several conclusions can be drawn from these experiments. First, molecules with a molecular weight greater than 400, such as the typical putative neurotransmitter, cannot cross the gap junction. Second, a heavy metal can diffuse into the gap region but cannot diffuse into the actual hydronium liquid-crystalline lattices forming the active electrolytic junctions critical to the operation of the Activa present and key to the electrical transmission of neural signals across the gap. Pappas concludes with the following. "Evidently, then, the gap junction consists of an array of channels, or pores, passing through the cell membrane." This work prefers the designation channels to pores and proposes the channels are electronic diodes in character and are incapable of transporting heavy ions or molecules.

Hayashi & Stuart inadvertently displayed the difficulty of explaining the operation of the synapse on chemical grounds in 1993[56]. Their specimen was a barnacle, *Balanus nubilus*. They found difficulty explaining the phenomenon they defined as synaptic adaptation using chemical models. The phenomenon is easily explained as the transient performance of an active nonlinear electrolytic circuit. Their concluding sentence falsifies their premise that Ca^{2+} is the mechanism controlling the phenomenon.

Barnes continued to display the difficulty with the chemical hypothesis in an extended commentary in 1994[57]. He chose to define a myriad of individual channels. His figure 4 is explained on entirely different electrolytic grounds than offered in this work.

Sherman & Guillery have recently reopened the discussion of the conventional wisdom related to the synapse[58]. Unfortunately, they parrot the conventional wisdom with a new twist. They focus on the putative ionotropic versus metabotropic forms of receptors. These complex explanations of the operation of a synapse are not supported here.

3.6.2 The synapse, an active electronic device at a deceptive location

If one places two of the fundamental neurons of Figure 3.1.2-3 in series, as suggested by Figure 3.1.2-6, the configuration between the axon of the first and the dendrite of the second appears remarkably similar to that between the dendritic and axonal conduits of either of the individual neurons. Except for the fact that the region between the two juxtaposed conduits is in contact with the interneural plasma instead of being enclosed by a podaplasm, they are cytologically identical. This situation suggests that if the two conduits are juxtaposed with the necessary spacing, this configuration has the potential for exhibiting "transistor action." It is only necessary to provide the necessary bias potentials. The typical synapse is an active electrolytic device biased according to the rules described below.

The conditions described above for "transistor action" does not require that the action occur within a single cell membrane. It can occur between two adjacent cells under the prescribed conditions, i. e:

+ each membrane "system" must be operational; the membrane in the contact area must be of type 2 and must be contacted 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 regardless of the polarity of the output membrane.

These conditions are easily met within the neurological system. It appears an Activa can be created at any point where a type 2 portion of cell wall enclosing a region of axoplasm is brought within the appropriate distance of a type 2 portion of cell wall enclosing a region of dendroplasm (and the above electronic bias conditions are met). The contact areas can be quite small or can be extended depending on the overall current carrying capacity required. The synapse between two neurons is the site of an active electrolytic semiconductor device, an Activa, operating as an "active diode."

> An "active diode" is formed from a three-terminal Activa. It requires the emitter of the Activa to be forward biased relative to the base and the collector to be reverse biased relative to the base. Under these conditions, the current into the device at the emitter is determined by the emitter to base input characteristic and the emitter to base potential. The same current appears as an output current at the collector terminal regardless of the potential of the collector terminal. The large signal forward transfer characteristic of the active diode is logarithmic in accordance with the emitter to base input characteristic. The small-signal forward transfer characteristic exhibits a voltage gain up to, but less than, 1.00. Its precise value depends on the large signal bias point. Both the large signal and small signal reverse transfer characteristics of the active diode are zero. The active diode is unidirectional based on the bias conditions.

Under the above conditions, it is possible for a dendrite to form synaptic, or gap, junctions exhibiting "transistor action" with as many axons as desired. It is only necessary for the type 2 dendrolemma to "grow" to within the appropriate gap spacing of each of the type 2 axolemmas of target axons. By this means, the dendrite collects a current from each axon with a magnitude proportional to the voltage difference between the emitter of the active diode and its base, and the area of the contact. The total current injected into the dendroplasm is then delivered to the emitter terminal of the post synaptic neuron.

Pannese has provided a recent description of the so-called electrotonic or gap junction that is in excellent agreement with the above description except for one point[59]. He describes (this) mode of transmission via a gap junction as distinguishable "from chemically mediated transmission since (a) it is basically reciprocal, . . ." (page 108, emphasis added). He gives no reference for this assertion that is in opposition to the position if this work. The transmission mode across an electrotonic, or gap, junction is unidirectional based on the bias potentials of the circuit.

Pannese provides a long list of the locations of gap or electrotonic junctions within various species of animals. This type of junction is obviously common (if not, as proposed here, dominant) in the neural system. Pannese also provides a caricature of the possible forms and locations of synapses between neurons based exclusively on the exterior morphology of the cells. The functional names resulting from that analyses are a bit fanciful. As discussed in Section 3.1 and this section, all of his designations are represented by a synapse between an axon conduit and a subsequent neurite conduit in the orthodromic signal path.

The electron micrograph in his figure VI.1, at about 90,000X, provides an excellent cross-section of a synapse at high resolution. It clearly demonstrates the bilayer character of each membrane, the close spacing associated with the hydronium liquid-crystal between the axon and the neurite, and the variety of inclusions found within the respective plasmas. These inclusions include the reticulum that has formed a hydraulic delta, similar to that of a river, as it approaches its termination at the surface of the conduit. His figure VI.2, at 44,000X, is more complex. It shows multiple synapses between four axons and three neurites (there being no definitive way of determining whether these structures are dendrites or podites). Some degree of darkening can be seen in the figures at locations where an accumulation of charge is to be expected based on the Electrolytic Theory of the Neuron.

The description of the fundamental connection between neurons as associated with a gap junction of electronic origin has always been a controversial one. However, the database is unequivocal. This work has developed the fact that the external coupling between neurons (the synapse) is not fundamentally different from the coupling between the various internal conduits of a neuron.

Application of the Electrolytic Theory of the Neuron to the synapse provides a viable explanation of its cytology and physiology. The proposition that the synapse is an electrical connection between two neurons does not eliminate the role of chemistry in the vicinity of the junction. Chemistry is seen to play the same role at the external Activa found at a synapse that it plays in supporting the internal Activas of the neural system. It provides the source of energy that powers the active device.

The empirical features of a synapse depend upon it being properly biased for orthodromic operation. *In-vivo*, the orthodromic terminal is always more negatively biased than its antidromic and third terminal. Like any three-terminal active device, varying its biases significantly can cause unexpected operation. When properly biased, the synapse:

1. provides unidirectional transmission across the junction,
2. exhibits a very small time delay between its input and output terminals (less than microseconds),
3. normally exhibits negligible impedance (transimpedance) between its input and output terminals (Dowling[60] gives a value of 1-3 ohms-cm^2),
4. cross-sectional area can be varied to control the transimpedance of a synapse, as an aid to stage 2 signal processing,

5. is very sensitive to the action of drugs, lack of oxygen and fatigue (Drugs normally affect the electrostenolytic power sources used to bias the synapse. Oxygen affects the soma of the adjacent cells forming the synapse).

3.6.2.1 Measured electrical performance of the synapse

Within its operating range, a synapse can be represented by an active diode. However, if its operating potentials are reversed while the base (interneural matrix connection) remains most positive, the three-terminal device will operate like an active diode in the opposite direction. This phenomenon is frequently encountered during patch-clamp experiments as reported in the literature. This is clearly represented in figure 3 of Glowatzki & Fuchs[61]. Figure 3.6.2-1 redraws their figure slightly to show this situation. The current is shown as an excitatory post-synaptic current (ESPC) measured *in-vivo* at the synapse on the surface of a rat (AF #5) auditory sensory neuron. The current resulted from a tight-seal patch-clamp configuration. The location and character of their reference potential were not specified. As a result, their holding potentials are most likely relative to the resting potential of the dendroplasm contacted. They did not report the axoplasm potential of the sensory neuron or the steady state current through the synapse associated with their holding potentials. The randomly occurring waveforms have been aligned in time, and displaced in quiescent current for purposes of presentation. The temperature of the animal was not specified. Their exploratory experiments should be repeated under more controlled conditions in order to support future applied research. The typical operating range of a synapse is 20-30 mV with its output terminal, the neuroplasm contacted in this case, more negative than its input terminal, the axon of the hair cell in this case.

Glowatzki & Fuchs chose to draw a single straight diagonal line through their data points. This line represents a transimpedance of about 230,000 Ohms (transconductance of 4 micro-mhos) for the synapse. This is a very low impedance relative to most neural circuits and explains why some of the literature describes the synapse as of zero impedance. The range of their data at zero current was large, ±11 mV (n=4). This range is suggestive of the change in mode occurring in that region.

The synapse operates very similarly to a Node of Ranvier. However, it does not go into monopulse oscillation and does not regenerate the signal presented to it. Synapses are inherently analog (electrotonic) transmission devices, although they may transfer phasic waveforms.

They noted an important fact (page 150) that can be reinterpreted more generally here. If an axon segment of a neuron is stimulated in the middle of its length, nerve impulses will travel in both directions from the point of stimulation. Thus, there is no unidirectional behavior of the axon segment. However, when the nerve impulse traveling toward the input end of the neuron reaches the internal Activa, that nerve impulse is not transmitted to the dendroplasm of the neuron. When the impulse traveling toward the output end of the neuron reaches a synapse that is properly biased (and terminated by a neurite), the impulse travels across the synapse with negligible loss in amplitude.

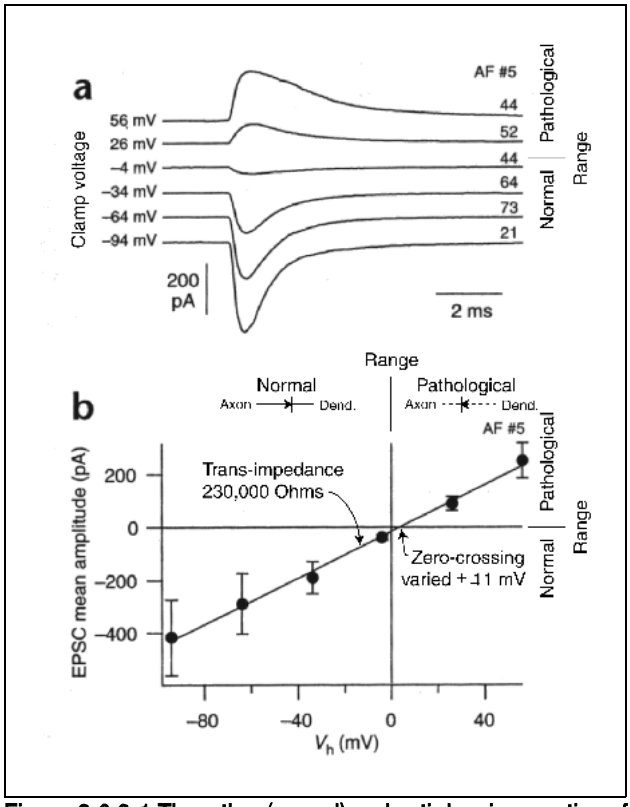

Figure 3.6.2-1 The ortho- (normal) and anti-dromic operation of a synapse. a; currents recorded at a post synaptic plasma under voltage patch-clamp conditions. Voltages are original holding potential before a step change. Numbers on right indicate number of waveforms averaged to obtain the trace. b; the transfer function of the synapse obtained by varying the collector potential of the Activa forming the synapse. Extended from Glowatzki & Fuchs, 2002.

3.6.2.2 The cytology of the synapses with the sensory neurons

It is generally recognized that there are two distinct types of synaptic junctions with the sensory neurons. The first are associated with the afferent signal path neurons. The second

are associated with efferent path neurons. Traditionally, the synapses with the sensory neurons have been shown in caricature because of the difficulty of isolating the very fine neural structures. The caricatures have usually shown a cluster of synapses engulfing the basal area of the sensory neuron. Bredberg has been able to isolate these synapses in certain rows of OHC's[62]. His graphics show the groups of synapses normally associated with the sensory neuron near the basal portion of the cell along with a distinctly separate synapse located up along the side of the neuron. This synapse appears to be an efferent neuron associated with controlling the gain of the Activa within the cell.

Little information appears in the literature about the specific purpose of the large number of efferent neurons synapsing with the sensory neurons. Engstrom has provided an electron micrograph of one of these synapses[63]. It shows a synaptic gap of about 20 nm (200 Angstrom) and some defocusing of the electron beam due to the electrical charge in the area. However, this early electron micrograph is poor by modern standards. He describes two distinct types of synapses but does not differentiate them functionally. Looking at the OHC of guinea pig, he noted that "one type of smaller and less granulated nerve endings is found under all outer hair cells, and these nerve endings are all of almost the same size and structure." However, his comments concerning the other type of synapse are more interesting. "These endings differ in size under the different hair cell rows. The first hair cell row has very large nerve endings of this second type. The second row has smaller such granulated endings and the third hair cell row very small, if any, such richly granulated endings." Engstrom closes by noting his estimate that the richly granulated type of nerve ending has a more presynaptic appearance that he would associate with the efferent nerve fibers terminating at the sensory neuron.

3.6.3 The detailed cytological structure of the synapse

The synapse, the junction between the axon of one neuron and the neurite of another has been studied for a long time via light microscopy. A large mass of literature has evolved based on this imagery and the presumed chemical nature of the signal transmission across this gap. Unfortunately, this literature has been largely limited to a conceptual foundation. This foundation has not been able to explain the most basic features of the synapse.

1. how does an electrical potential elicit the release of chemicals by the axon?
2. how does the arrival of a chemical at the dendrite elicit a current in the dendrite, or a potential between the dendrite and the surrounding medium?

The micrographs produced by the electron microscope have shown a structure for the synapse that is drastically different from that portrayed by the light microscope. It not only shows the finer structure that was never available earlier, it also shows the location of charges in these structures. The imagery shows an uncanny similarity to the imagery of man-made transistor devices. This resemblance applies both to the dimensions of the structures and to the charge distributions. This imagery provides strong support for the proposition of this work that the synapse is an active electrolytic semiconductor device based on liquid-crystal technology.

3.6.3.1 A redefinition of the physiology of a synapses

Contrary to the assertive title of Nordang et al[64]., most major articles and reviews in the current literature are cautious to conclude that glutamate is the neurotransmitter of the biological synapse. The presence of glutamate on the surface of a neuron does not confirm its role as a neurotransmitter. However, it is compatible with the neuron as described here. Before 1990, it was common to assert, without experimental evidence, that the vesicles within a neuron near the synaptic body were sources of glutamate. This glutamate could be discharged into the synaptic cleft through some form of pore in the lemma. As Usami & Ottersen have shown the vesicles in and near the presynaptic lemma do not contain a significant supply of glutamate[65].

Figure 3.6.3-1 summarizes the proposed synapse compared to a recent alternative[66]. This version is based on the transfer of electrons across the synaptic junction by electrolytic means. No ions are released through the axolemma and no ions move from the axon to the dendrite within the synaptic junction. No pores are required in the axolemma. The only glutamate found within the axoplasm is used for growth and homeostasis. The basic chemistry associated with this synapse is quite different from that generally discussed conceptually in the past literature. An electrostenolytic process is carried out at the "glutamate receptors labeled Glu R4 and Glu R2/3." The glutamate is broken down into GABA and CO_2 at these stereo-specific sites and an electron is simultaneously delivered to the inside surface of the plasma membrane. This process is carried out at both the axolemma and the dendrolemma. These actions cause the axoplasm and the dendroplasm to exhibit a negative potential relative to the fluid matrix surrounding the neurons. These potentials are not necessarily the same because of the impedances associated with the different circuits. There is no requirement that glutamate enter the sensory neurons for purposes of signaling.

It must only reach the synaptic cleft.

Following the conversion of the glutamate to GABA and CO_2, the GABA is absorbed into the nearby glia while the CO_2 is transported (as a carbonate) to the vascular system for removal. Within the glia, the GABA is regenerated into glutamate by the loop shown in Figure 3.5.3.

Besides the quotation above, the 1995 Usami & Ottersen paper makes a number of critically important observations.

• "Even though the compartmentation of glutamate and glutamine in the vestibular end organs is consistent with a transmitter role for glutamate it remains a matter of concern that no distinct enrichment of Glu-LI (glutamate-like immunoreactivity) was found in synaptic vesicles."

• "There is no direct evidence for glutamate release from the nerve chalices although they have been reported to contain synaptic-like vesicles and several neuroactive compounds."

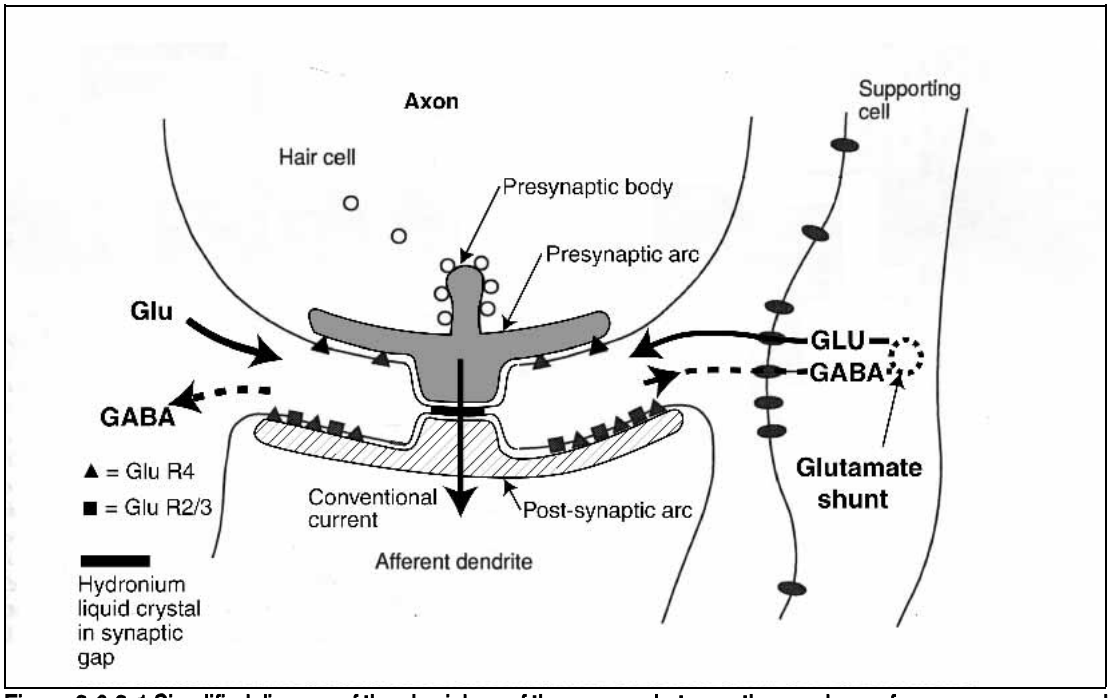

Figure 3.6.3-1 Simplified diagram of the physiology of the synapse between the axoplasm of a sensory neuron and the dendroplasm of the first afferent neuron. The curvature of the axolemma and dendrolemma are accentuated to highlight the synaptic junction within the synaptic cleft. Note the physical symmetry of the synapse and the presence of glutamate receptors on both faces of the synaptic cleft. The synaptic junction is not normally visible in light microscopy and difficult to locate for purposes of light microphotography. See text. Compare to Ottersen et al., 1998.

The 1998 Ottersen et al. paper was even more succinct concerning the presence of Glu-LI (page 142). "There is so far no evidence that metabotropic receptors are involved in synaptic transmission at afferent synapses of hair cells." Their figure 9 stressed the fact (using question marks) that no mechanism was known that could describe the movement of glutamate from the supporting cells into the hair cells.

The above conclusions support their earlier pronouncement in 1992[67];

• ". . it was clear that gold particles signaling Glu-LI were not preferentially associated with synaptic vesicles."

• "In conclusion, rather than substantiating the hypothesis that glutamate is the hair cell transmitter, several of our observations call this hypothesis into question."

The problems summarized by Usami & Ottersen and Usami et al. do not appear in the electrolytic theory of the neurons based on the glutamate-GABA reaction. However, the observation by Ottersen et al (1998, page 133) is compatible with this theory. "3.4 *Possible metabolic roles of glutamate and aspartate.* In addition to its [putative, ed.] role as a neurotransmitter, glutamate is also an important metabolite and could as such be envisaged to serve as an energy source in hair cells." Their observation on page 141 is also pertinent if modified to replace the term "receptor protein" by the term "material." "An alternative explanation of the central trough in receptor concentration is that the central part of the post-synaptic specialization is occupied primarily by another receptor protein." The material in this context is the liquid-crystalline form of water labeled hydronium. They note in the following sentences that their attempts to identify another "receptor protein" have failed. As noted below, Matsubara et al. provided similar data on the central trough.

3.6.3.2 The physical and intrinsic electrical symmetry of the synapse

Symmetry is an important feature of the synapse at a variety of levels. As shown in the above figure, the geometric synapse can be drawn as axially symmetrical about the synaptic junction and its associated presynaptic body (and the presynaptic arc). Longitudinally, the synaptic junction forms a neck that focuses the transfer of electrons through a restricted region. There are features, observable by electron microscopy, such as the pre and post synaptic arcs that are axially symmetric. The physical post synaptic arc is frequently obscured by the presence of stored electrical charge at its location. This charge causes a defocusing of the electron beam of the microscope. This stored electrical charge is easily and commonly observed in synaptic junctions[68].

The majority of the plasmalemma of a neuron is a high quality insulator because of the symmetry of the two leaves of the bilayer membrane. A symmetrical bilayer membrane is defined as a type 1 membrane in this work. Such membranes are formed of lipid materials that are highly impervious to the flow of hydrophilic materials, such as metal ions. In the vicinity of the presynaptic and post synaptic arcs, the plasmalemma is fundamentally different. This type 2 membrane is formed from two unsymmetrical (at the molecular level) leaves of lipid material. While type 2 membranes of these lipid materials remain impervious to hydrophilic materials, they do exhibit a remarkable reduction in impedance to the flow of electrons in one direction. The resulting membrane exhibits the characteristics of a high quality electrical diode.

As shown earlier, when two type 2 asymmetrical bilayer membranes are brought into juxtaposition with water in the space between them, the configuration forms an active liquid-crystalline semiconductor device called an Activa. This device is equivalent to the man-made active solid-state semiconductor device called a transistor. While formed of asymmetrical lemma material, an important property of an Activa is that it is intrinsically a symmetrical three-terminal electrolytic device. Its electrical performance depends on the magnitude and polarity of the potentials applied to the different terminals. When biased appropriately, such a device can act as a high quality active diode. The direction of current passage is reversible by changing the potentials. This feature suggests the synapse should be a reversible diode based on the potentials applied to it. This is in fact a well documented feature of a synapse. *A synapse is a physically symmetrical three-terminal biological device that forms an "active diode" that is electrically reversible.* While a conventional diode is not known to be reversible under biological conditions *in-vivo*, this active diode is easily reversed by changing the potential of the associated axoplasm or dendroplasm.

The method of establishing the potential on the electrodes of the Activa also requires a degree of asymmetry. Potentials must be supplied to both the axoplasm and the dendroplasm of the synapse. These potentials are created by the electrostenolytic processes occurring at the type 1 plasmalemma. The locations of these electrostenolytic processes are coincident with the receptor locations described in the figure for Glu R4 and Glu R2/3 (note also figure 8a of Matsubara, 1996). Note the symmetrical location of these sites on both the pre and post synaptic lemma. The presence of these sites on both membranes has been well documented by Matsubara et al[69]. The presence of symmetrical glutamate receptors is not easily explained under the chemical theory of the neuron. Matsubara et al. also established that the glutamate receptors did not occur within the central region defined by the closely spaced synaptic junction. The receptors were specifically found to be located symmetrically around the center position defined by the synaptic body.

Matsubara et al described the synaptic junction as a region only 149 Angstrom wide (based on 10 units examined). This value is compatible with the values found by other investigators (depending on how you define the edge of a membrane). This edge is near the limit of resolution of the instrumentation. More importantly, it is defined by the probabilistic energy field patterns associated with a molecule.

As described earlier, this narrow space is not able to support the presence of large molecules. They are squeezed out during the formation process. As a result, the space is normally occupied by a matrix of water molecules in a

liquid-crystalline state called hydronium. This lattice is in intimate contact with the molecular structure of the lipid molecules of the two juxtaposed asymmetrical membranes. This intimate contact is required for the operation of the Activa defined above.

Matsubara et al. noted the difficulty of preparing a longitudinal slice through a synapse that included the synaptic body. However, when this was accomplished, the glutamate receptors were found to be located symmetrically about the junction at distances on the order of 12 nm to 300 nm from the centerline of the presynaptic body. The nominal synaptic junction had a radius of seven nanometers. The concentration of the glutamate receptors was higher peripherally than centrally. They found glutamate receptors on both the presynaptic and post synaptic lemma.

Pannese[70] and Puel et al[71]. have provided excellent electron micrographs of synapses. Frame 7D in Puel et al. is particularly valuable. It shows four synaptic bodies in one image. The synaptic body with a star next to its arrow is an efferent synapse (the synaptic body/ribbon is in the efferent neuron, not in the IHC) while the other three are afferent synapses.

3.6.4 The Node of Ranvier, a specialized synapse

As noted in Section 3.1.2, the Node of Ranvier is a specialized junction between two neural segments that are supported by the same soma. In most other respects, it is identical to a synapse where the neural segments are supported by separate soma. However, there is one other frequent difference. Most Nodes of Ranvier reported in the literature have been configured as Activa capable of acting as a regenerative repeater in order to regenerate action potentials before passing them to the orthodromic neural segment, whether axon segment or neurite. The Node of Ranvier exhibits negligible cytological difference from a synapse except the post junction area is generally larger than in the analog synaptic case. This increased area provides the capacitance necessary to support regenerative action by the node. The physiology of the Node of Ranvier will be discussed in Section 7.3.

Like the synapse, the base terminal of the Activa within the Node of Ranvier is connected to the surrounding matrix. Frequently however, the base is connected to the matrix via a high impedance. Furthermore, the post-nodal axon segment presents a high capacitance to the collector terminal of the Activa. These are the conditions described above for a phasic pyramid neuron. These conditions lead to the monopulse oscillatory operation of the Node of Ranvier. The majority of Nodes of Ranvier studied have been operating as pulse driven monopulse oscillators used to regenerate action potentials generated at previous phasic pyramid neurons or previous Nodes of Ranvier.

In hearing, some Nodes of Ranvier occur before the soma of their associated afferent neuron. These nodes near the axons of the sensory neurons and in neural circuits before the habenula perforata of the cochlea, are known to receive analog signals and generate action potentials. The result is a Node of Ranvier operating as a driven monopulse oscillator that provides time-delay encoding. The basic circuit is the same as that shown in Figure 7.3.1-2 with a large capacitance between the collector and the common ground point (except input $V_{in}(2)$ is omitted).

As a result of both the phasic pyramid neuron and the Nodes of Ranvier, an action potential pulse stream is generated to its nominal 100 mV maximum amplitude and regenerated to the same amplitude every few millimeters along the parent neuron. These regenerative repeaters make it possible to transmit pulse signals over any distance required (measured in meters to tens of meters in large mammals) with negligible degradation in pulse shape or changes in the pulse-to-pulse timing.

3.6.5 A reversible synapse current challenges the chemical theory

The measured data in the previous figure from Glowatzki & Fuchs introduces a very significant problem for any chemical theory of the synapse.

The chemical theory of the synapse implicitly assumes the synapse is unidirectional with at least one chemical released by the presynaptic terminal. The chemical theory normally does not concern itself with any mechanism involved in creating a change in the electrical potential of the post synaptic terminal. The concept of the process being reversed doesn't appear. However, the experimental record is clear. The flow of current through the synapse is easily reversed by reversing the electrical biases applied to it. As expected by the Electrolytic Theory of the Neuron, the synapse is actually a three terminal device whose performance should be reversible by simply reversing the electrical potentials on the terminals. On the other hand, the chemical theory must either assume chemicals are released by the post synaptic terminal and collected by receptors at the presynaptic terminal, or postulate additional chemicals that can have the opposite effect of normal neurotransmitters when the electrolytic bias conditions are reversed. Neither of these situations is supported, or addressed, by the current chemical theory.

Pannese provides a recent, but brief, background on the synapse. It is followed by a broader discussion heavily weighted toward the chemical concept of a synapse. Fonnum provides a more systematic discussion of the requirements on a synapse[72].

The concept of a chemical neurotransmitter began in 1904 with a hypothesis by a student. McGeer et al. review the early discussions based on analogy with the action of pharmaceutical preparations[73]. It remains largely based on this analogy to this day. However, rather than the injection of a pharmaceutical, the evidence now is largely based on topical application to tissue. The fact that the presumed neurotransmitters have such a potent impact on the metabolic activity of the neuron when applied to non-synaptic areas has caused a significant problem. McGeer et al. have divided chemical neurotransmitters into two classes to meet this challenge. They speak of the metabotropic function of neurotransmitters as well as the conventional ionotropic function. They do not specifically define these terms and ionotropic does not appear in Webster's Dictionary of Medicine. The term metabotropic will be taken to describe the participation of glutamate in a metabolic function, specifically electrostenolysis on the surface of a neuron. Ionotropic will be taken as relating to the participation of glutamate (or other material) in a neural signaling function, specifically changing the potential of a neuroplasm via a receptor on the surface of a neurite within the synaptic gap of a synapse. This work shows that most materials previously labeled neurotransmitters, or neuro-inhibitors, relate exclusively to the metabotropic function. In that role they act as neuro-facilitators or neuro-inhibitors.

McGeer et al. conclude their introductory material with the statement, "It has turned out that chemical transmission is a much more complicated biological process than Dale (circa 1938) had supposed." In the following paragraph, McGeer et al. say, "These chemically transmitting synapses were designed to compensate for electrical mismatch between the presynaptic and post synaptic components of the synapse, e.g., the very small nerve terminal and the large area of the muscle fiber membrane with its high capacity." These quotations suggest that McGeer et al. have recognized the difficulties associated with their concept of chemical neurotransmitters and are open to other options. It will be shown that their "mismatch" is related to the mechanism employed by the Activa to achieve near-perfect efficiency.

McGeer et al. note the absence of good markers for glutamate and aspartate in the 1987 time period. This problem has been overcome through nuclear chemistry as discussed in a companion work [PBV, Sections 7.7.5 & 18.8.5]. Their chapter 6 describes the role of glutamate and aspartate primarily in metabotropic terms which are completely consistent with the above sections of this work. Their table of metaboloid concentrations by location within the nervous system is very useful. They also note the ubiquitous ability of glutamate and aspartate to excite multiple neural "receptors" in response to topical application.

Greenfield discussed current problems with the concept of a chemical neurotransmitter in 1998[74]. Her frustration is couched in such expressions as "I shall consider some of the principal anomalies arising from current findings, specifically why; (a) there are many diverse transmitter substances; (b) transmitters are released from sites outside of the classical synapse; (c) some well-known transmitters have surprising 'modulatory' actions; (d) synaptic mechanisms themselves have no obvious or direct one-to-one relationship with functions such as movement, mood and memory; and (e) it is difficult to extrapolate from drug-induced modification of synaptic mechanisms to the effects of those same drugs . . ." and "No doubt the forthcoming years will herald the discovery of still further surprising transmitter-like molecules that strain the accepted concept of how transmitters behave." She concludes with "We are about to enter an exciting phase in brain research, where there is a shift in emphasis away from the all-pervasive paradigm of classical synaptic transmission." This work provides the basis for that shift and provides a rationale for each of the above problems. Unfortunately, the new paradigm is completely contrary to the concept of a chemical neurotransmitter.

As shown above, the transmission of a signal across a synapse is extremely simple when the signal remains in electrical form. In this case, the physical structure of the synapse forms an active electrolytic device, an Activa, virtually identical in characteristics to the man-made transistor. When the Activa is properly biased electrically, an electron can pass from the pre-synaptic to the post-synaptic terminal of such a device with an efficiency of greater than 99%.

On the other hand, the chemical synapse requires what is generally described as the translation of the signal from an electrical form in an axoplasm to a chemical form in the synaptic gap and then a reconversion from the chemical form back to an electrical form in the post-synaptic neuroplasm. How such a translation would be achieved remains largely conceptual to this day.

PBV, Section 7.7.2 reviews the chemical characteristics of various pharmaceuticals (including their stereo-chemistry) and how these characteristics determine whether the materials are neuro-facilitators or neuro-inhibitors.

Fonnum describes "the four main criteria for the classification of a chemical as a neurotransmitter:
1. it is presynaptically localized in specific neurones;
2. it is specifically released by physiological stimuli in concentrations high enough to elicit postsynaptic response;
3. it demonstrates identity of action with the naturally occurring transmitter, including response to antagonists; and
4. mechanisms exist that will terminate transmitter action rapidly."

He then attempts to show that glutamate meets most of these requirements. He does raise one concern; "There is a poor correlation between the pharmacological activity of the agonist and antagonist and the binding to glutamate sites in several studies."

Each of these criteria is global in concept. They lack specificity with respect to the mechanisms involved in meeting these criteria. Item 3 appears to be the catchall item. It includes the requirement that the chemical neurotransmitter somehow cause the generation of a change in electrical potential within the post-synaptic neuroplasm. The mechanism used to accomplish this transition has not been described in detail in the literature.

McIlwain & Bachelard gave a similar list of five criteria[75].

The requirements on an electrolytic neurotransmitter are much simpler than those listed above. As defined in this work, an electrolytic neurotransmitter is an electron, initially present in the axoplasm of a pre-synaptic neuron, that is transferred across the synaptic gap and injected into the neuroplasm of the target neuron. By injection into the neuroplasm, it causes a change in potential of that neuroplasm defined by the electrical impedance of that plasma. The action of the electron is orthodromic *in-vivo* because the synaptic gap acts as an active diode. No translation mechanism is needed in this instance. The only mechanism associated with this transfer of charge is the properly biased Activa. The transfer characteristic between the axoplasm potential and the resulting neuroplasm potential is easily measured.

The definition of the Activa provides the ability to differentiate between the mechanisms providing power to the Activa (such as the electrostenolysis of the glutamates) and the mechanisms associated with signal transfer between neurons.

As indicated by Pannese, the subject of electrolytic versus chemical neurotransmitters was a hot topic during the 1930-40s. It was supposedly settled in favor of the chemical neurotransmitter, using the technical base available at that time. More recently, the debate has gained new life with the demonstration of electrical synapses in a long list of animals (pp 108-116). While he continues to suggest the primacy of chemical neurotransmitters, he recognizes the legitimacy of electrolytic synapses in specialized situations and the presence of both types of synapses in many animals.

Following the debate in the 1930-40s, it became necessary to isolate one or more putative neurotransmitters. Fonnum noted; "Electrophysiological studies focused early on the powerful and excitatory action of glutamate on spinal cord neurons. Since the action was widespread and effected by both the D- and L-forms, it was at first difficult to believe that glutamate could be a neurotransmitter." Fonnum provides a variety of evidence concerning glutamate as a neurotransmitter. It is largely conceptual and involves topical application of the material, generally in bulk, and not to a specific neuron or portion of a neuron. McGeer et al. say "Highly convincing evidence that L-glutamate and L-aspartate should be neurotransmitters comes from their iontophoretic actions. Both of these dicarboxylic amino acids powerfully excite virtually all neurons with which they come in contact. (Page 186)" Such topical application of a chemical does not relate to its role as a neurotransmitter. It relates to its role as a fuel source, particularly when its concentration exceeds the normal 2-5% at the site of electrostenolysis. Just prior to the above quote, McGeer et al. say "While the anatomical data at this stage must still be regarded as highly tentative, it can be said that glutamate and aspartate meet many of the generally accepted anatomical criteria for neurotransmitter status." The words "should be" and "highly tentative" are important in the above quotations.

Still earlier, McGeer et al. said the following. "Nevertheless, it must be recognized that truly definitive markers that can be applied at the cellular level do not exist for glutamate and asparate 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."

> Additional experimental effort needs to be expended on identifying the microscopic portions of a single cell that are sensitive to the topical application of so-called neurotransmitters. It is predicted that these areas will be found to be chemically asymmetrical membrane segments and the applied chemical will form a stereochemical union with the membrane at these locations.

As noted in Pannese, it has only been in recent times that the biological community would consider the possibility that the junction between two neurons might have an electrical aspect, they are now speaking more frequently of a "gap junction" which is electrical in nature. In the evolution of this work, the similarity between the structural form of the Nodes of Ranvier and the so-called gap junction cannot be ignored. Close study indicates that the gap junction involves the close juxtaposition of two cell walls in the same manner as in the Node of Ranvier. By application of appropriate voltages to the plasmas on each side of these juxtaposed cell walls relative to the fluid in the space between the walls, transistor action will occur[76]. This transistor action can be used for several purposes.

Two recent events have cause additional problems for the chemical theory of the synapse. Ottersen et al. have found a lack of glutamate (and a low ratio of glutamate to glutamine) in the vesicles associated with the synaptic body of auditory sensory neurons[77]. Siegel has also noted the growing evidence that the putative synaptic vesicle binding protein, synapsin, is absent from a number of synaptic bodies (ribbons) in the sensory neurons[78].

The simplest purpose is for the creation of a nearly lossless current path between the two conduits. Positioning the two neurons so that the axon of one is in close juxtaposition to a dendrite of the other and establishing the proper potentials between them is all that is necessary. This connection allows the transmittal of an electrical signal from one neuron to the other without significant loss and no chemical action at all with respect to the signal. The only chemical action is metabolic in nature. It involves establishing the appropriate voltages. To achieve this result, the transistor formed is employed in what is conventionally called the common-base configuration. This configuration does not normally exhibit any voltage amplification and the ratio of the output current to the input current is very close to 1.000. An Activa used in this "gap Junction" role will be defined as a Type BS with the S derived from the name synapse.

A second purpose for employing an Activa at the intersection between an axon and one or more dendrites is to act as a current amplifier and a distribution amplifier. This can be achieved by connecting the axon to the input of an amplifier capable of current amplification and then distributing the resultant current to the various dendrites as appropriate. In this case, the amplifier is usually embedded within a neuron and such a neuron in the retina is typically described morphologically as a bipolar cell.

At this point, it is important to define a synapse from a functional perspective. A synapse is a functional junction between the electrical circuits of an axon and a second neuron, a muscle or a gland. It typically consists of a common-base connected Activa and the bio-energy supplies necessary to bias the axon and input structures appropriately. The common-base connected Activa provides the signal transmission path. The bio-energy supplies are provided by means of diffusion from the surrounding medium and/or the nucleus of the respective cells.

Based on the above discussion, this work only supports the existence of an electrolytic synapse. The synapse is capable of transmitting an analog or pulse signal. However, it is not capable of signal regeneration or signal summation (addition or subtraction) except in conjunction with other circuit elements.

There is no requirement for a translation mechanism in the case of an electrolytic synapse. Nor is there any requirement for a given number of molecules, that is proportional to the change in electrical voltage generated in the neuroplasm, to successfully transverse the synaptic gap.

There is no requirement for the synapse, which is external to a neuron, to be functionally different from the junctions found between the various conduits within a neuron.

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