Curriculum Units by Fellows of the National Initiative
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The Brain Desynchronized

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Overview

It has been claimed that the brain is the most complex system in the universe because there are more neuron connections in the brain than stars in our galaxy. Although this may be overly anthropocentric, the more than one trillion connections between neurons certainly is a compelling argument for the nearly inconceivable versatility, computational capacity, and memory retention of the human brain. In addition, the complexity of the synapses, which are the separations between neurons that convert the electrical signal to a chemical signal and back using neurotransmitters, further magnifies the potential power of the brain. The brain is a remarkable organ and the advances in knowledge pertaining to it over the past few decades have increased exponentially. Attempting to convey the scope of this knowledge is difficult, especially within the context of a unit intended for high school physics students. Therefore, focus on a particular, important element is necessary. In this unit, the creation, generation, and transmission of signals within a single neuron are discussed, to illustrate the implications of groups of neurons that do not fire properly, become synchronized, and result in epileptic seizures.

It is my goal to explain the requisite physics and chemistry to my students so that they can appreciate the awesome nature of neuron activity (not to mention the incredible nature of the intricate processes required to read this sentence!). I will describe the process of the transmission of a single impulse down a neuron and, to further engage the students, I will consider the broader context of groups of neurons and some of the implications when they do not fire as they are supposed to. Specifically, I will discuss the fact that the neuronal activity in the brain must be desynchronized and that synchronization of neurons can result in a seizure: chronic seizures are the condition known as epilepsy. Synchronization in brain signals (also referred to as entrainment) is the state when the neurons are firing systematically together, which is a malfunction of the brain that manifests as a loss of mental and/or physical control. This state is often witnessed as violent convulsions known as a seizure. Therefore, it is essential for normal brain function that the signals be desynchronized, or out of sync, otherwise, the recurrent condition can be debilitating and even deadly.

This unit is intended for mathematically advanced physics students. I will teach it to my first year gifted students as well as my second year, AP B physics students. This unit is challenging both at the conceptual and mathematical levels. However, I believe that these concepts can be simplified to teach it to all levels of physics students; perhaps, it would be of interest to chemistry teachers who would like to teach about the molecules involved in firing of a neuron.

My high school has approximately 1500 students with 450 of them being designated as gifted. The school is roughly 55% Caucasian and 40% African American and 5% other. There is a range of socioeconomic backgrounds as well, with approximately 30% of the students receiving free or reduced lunch. My classes are more homogeneous with a majority of Caucasian students, a lower percentage of African-American students and fewer economically disadvantaged students. However, next year all students will be required to take physics and all juniors are encouraged to consider taking a second year of physics.

Rationale

Most Physics curricula spend a significant amount of time exploring electricity. This usually involves an extensive study of electrostatics and current flow. Often, the teaching of these topics lacks specific relevancy even though our modern society is heavily dependent on electrical energy to power devices. It is difficult to give the students the experiential knowledge and comprehension that is inherent in the study of physical Newtonian Mechanics. There always seems to be a disconnect with the study of electricity because of the lack of tangibility and relevancy for the students. Certainly, electricity is pervasive around us, but students do not have a "physical" sense of its presence. I currently utilize static electricity to try to present my students with the physical nature of electricity by letting them feel the shock of the Van de Graff generator and less dramatic examples. Later, we explore the properties of current with batteries and light bulbs. The students can see that the light bulb is lit when properly connected to the battery and they are able to understand the applicability of electricity but I sense that there is a lack of appreciation for the generation of electrical currents and its relevance.

In this seminar, "The Brain in Health and Disease," I recognize the powerful relevancy for my students that the brain itself functions by generating electrical impulses! These electrical impulses are created by interactions of chemical ion gradients that create electric potentials that are utilized by specific brain cells, called neurons (Figure 1), to generate a signal. An "all or none" signal, known as an action potential, which is propagated along the neuron's membrane, has the special property of continual regeneration and consequently being constant over distance. The signal is sent along the length of the neuron where it meets a synapse, which is a gap between neurons. There, the signal is converted into a chemical message, carried by a chemical called a neurotransmitter, that then stimulates the next neuron and allows movement of messages throughout the body, and if the conditions are favorable the process is continued. These synaptic connections are believed to store the information that we know as memory!

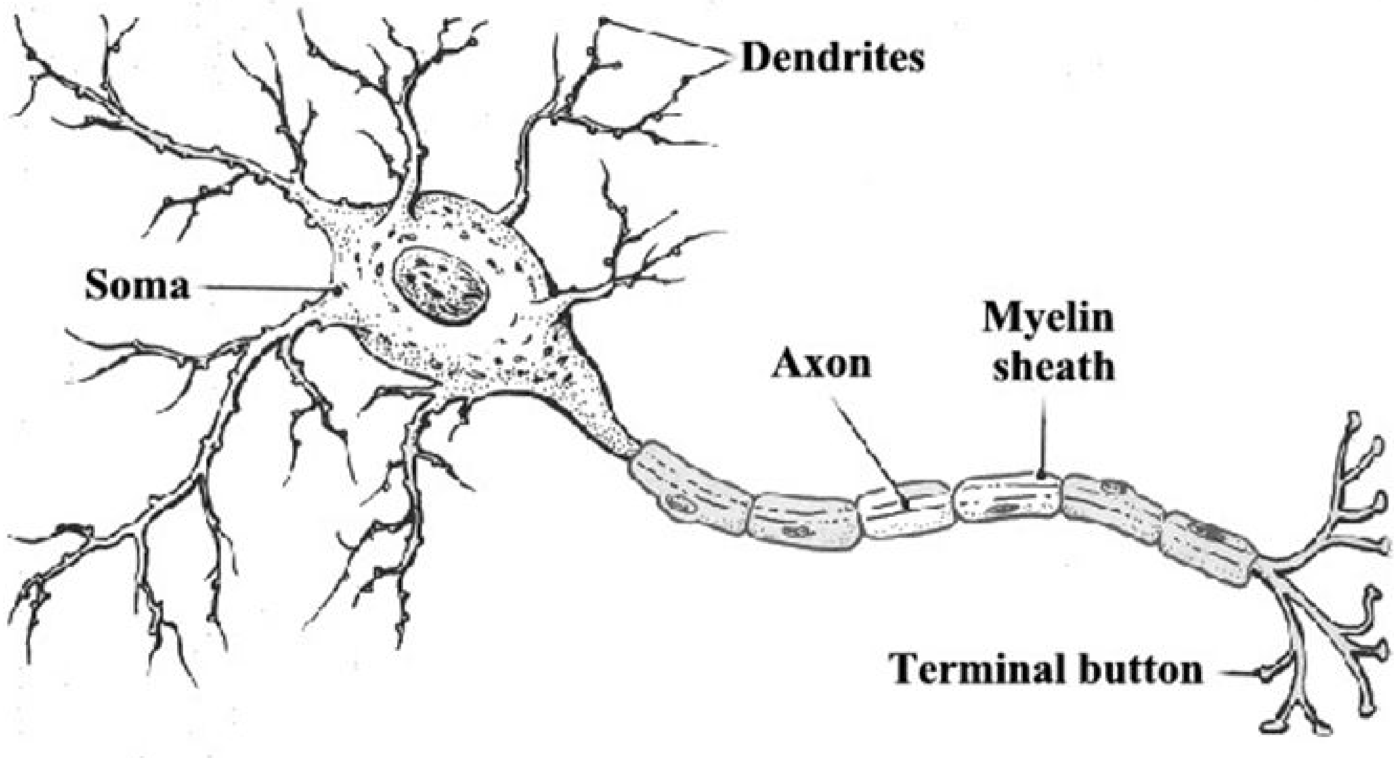


Diagram 1 - The neuron

When the brain is functioning normally we are relatively oblivious to these incredible processes; however, there are cases when exchange of electrical activity does not occur normally in the brain. One example is a seizure. My students are aware of the existence of seizures and usually know someone who has had one, since they are more common in children, but they do not know that seizures are the result of electrical activity in the brain gone awry. Seizures actually result when the electrical signals in the brain become synchronized! This is surprising, because it turns out that the brain must maintain a chaotic pattern of signals for brain health. I recently received a patent for a Radio-Frequency powered vagus nerve stimulator to help minimize epileptic seizures and will demonstrate my device and explain how introducing an intermittent electrical impulse into the brain can reduce the frequency of epileptic seizures.

I believe that this unit will provide relevance to the study of electricity, explain biochemical generation of a signal using ions, reinforce the significance of electric potential, motivate electrical-physical models of neuronal membranes, introduce mathematical models of systems, explore the implications of abnormal electrical activity, and stimulate appreciation for the scientific pursuit of knowledge acquisition. My intention in this unit is to concentrate on the specific functioning of a single neuronal axon and then to utilize that knowledge to comprehend the electrical malfunction of a group of neurons. I am confident that this will stimulate my students to relate their understanding of chemistry to electrical phenomenon, apply the combination of complex electrical elements to develop mathematical equations for membrane potentials, which can then be solved, and appreciate the impressive "normal" electrical functioning of their own brain. This curriculum unit will explore how a signal is transmitted along a neuron and as the unit develops I will create labs that will reinforce the knowledge of electrical signal generation and transmission. Lastly, we will explore the ramifications of a disorder of signal functioning that manifests in epileptic seizures.

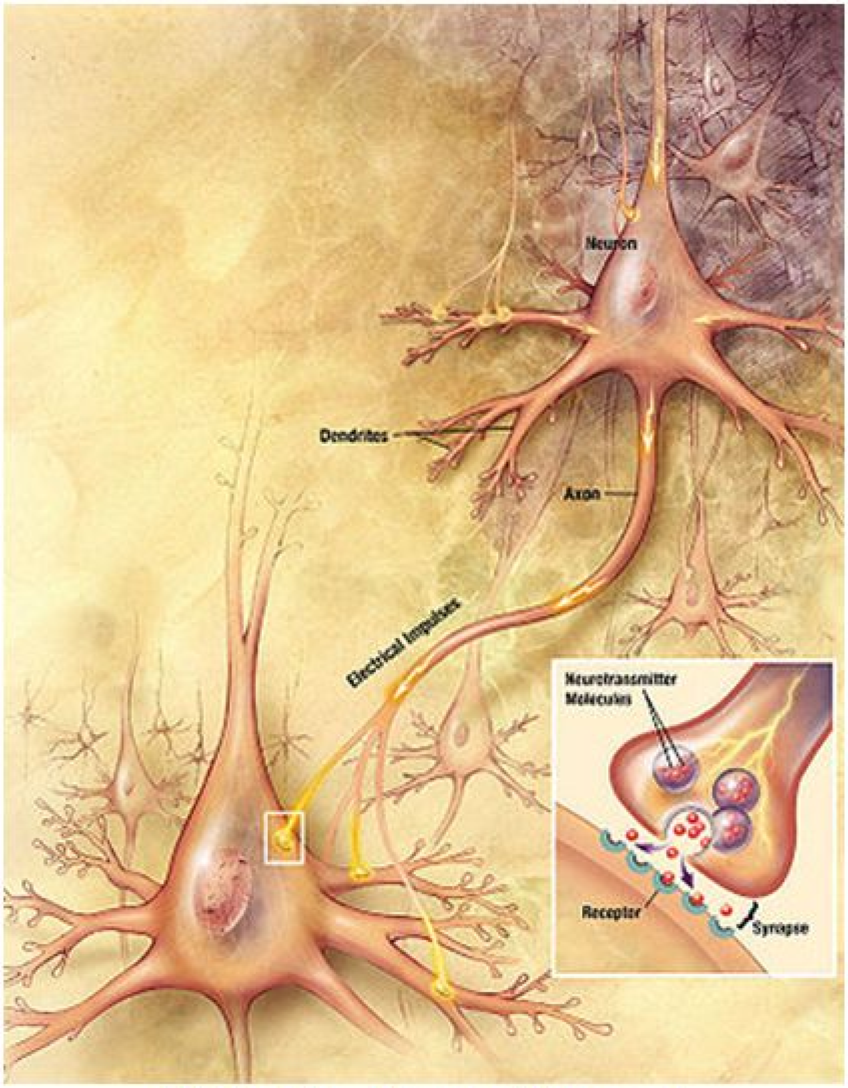
Strategies

This unit involves the introduction of conceptual knowledge that integrates student understanding of electrical physics, chemistry, biology, and mathematics. It is my belief that the best way to teach students is to provide them with engaging material that they will embrace because it captivates their imagination. Obviously, study of the brain is a compelling topic. We will explore the relevancy of electrical phenomenon by making the students the subjects of their own study. It is unusual that scientific learning at the high school level is interdisciplinary but this will draw on my students' previous knowledge and relate it to the new physics concept of electricity. In the spirit of constructivist learning, I will create the zone of proximal learning, where the student is most ready to transform their experience, by creating the desire to learn but with a sense of unease about the scope of the project. I will scaffold the students so that their varied background knowledge is reinforced. We will proceed with our learning by stimulating as many questions as answers. The labs that we do will be inquiry based, in which we manipulate simple electrical elements to create parallel circuits that simulate the electrical potential across the cell membrane. We will investigate mathematical relationships that will enable my students to derive the Nernst equation and quantitative solve previously problems related to signal generation in neurons. The hands-on activities will continue with the electrical simulation of the action potential and the graphical realization that the action potential is a pulse.

Building on this knowledge of neuron function, the students will pursue their own interests in macroscopic brain issues by researching topics of their choice in how the brain works. Our current understanding of brain functioning provides a wealth of avenues for further research on this subject. This is an opportunity for a student-centered creative pursuit of the current scientific literature. I will inquire as to whether or not anyone is familiar with seizures and encourage some of the students to explore epilepsy as a topic. The students will present this information to the class to further own their work. As a culmination activity and to enhance the students' conviction that scientific knowledge is an active process of accumulation, I will present my patented prototype and have the students test the properties of electrical stimulation that the RF vagus nerve stimulator produces using an oscilloscope. The students will write a paper summarizing their experiences of the electrical unit.

General Neuronal Background information

Electrical impulses are sent along neurons (see Diagram 1). The neuron is a cell composed of dendrites, a cell body and an axon with its pre-synaptic structure (see Diagram 2). The synapse is a specialized space between neurons, in which information is transferred from one neuron to the next. At the synapse the electrical signal is converted into a chemical signal, in the form of a neurotransmitter. The post-synaptic structure contains receptors that bind the neurotransmitter, and convert the chemical signal back into an electrical signal (either by activating ion channels or metabolic processes) in the post-synaptic dendrite. The resting state, or "equilibrium" condition, of the neuron is a negative voltage potential (the inside is negative compared to the outside), which is created and maintained by ion channels and pumps that create a greater concentration of positive ions outside of the cell. The primary ions of concern in the creation of the differential are sodium (Na^+) and potassium (K^+). Throughout the body, sodium has a much higher concentration outside of cells and potassium has a much greater concentration inside cells. The cell membrane is made up of two layers of phospolipids, which have hydrophilic ends facing outward and hydrophobic ends facing inward. This creates a membrane barrier that is impermeable to most substances. To allow selected substances to pass, the membrane is imbedded with specific membrane channels that allow these substances to cross the membrane barrier.



(Wikipidea, Chemical Synapse)
Diagram 2 -The Synapse

The neuronal impulse is only sent in one direction, from the dendrites to the cell body to the axon. The dendrites are projections from the cell body that receive electrical stimulation from other cells. The stimulation of the dendrites results in the generation of changes in chemical concentrations along the membrane; these changes are produced by the activity of ion channels that result in graduated electrical signals that are either excitatory or inhibitory. The transmission of these signals through dendrites attenuates because the low resistance interiors are surrounded by very "leaky" high resistive membranes. The increase in diameter of the neuron increases the speed of transmission of the signal. Although as many as a thousand dendrites come into the cell body only one process, the axon, sends a signal out.

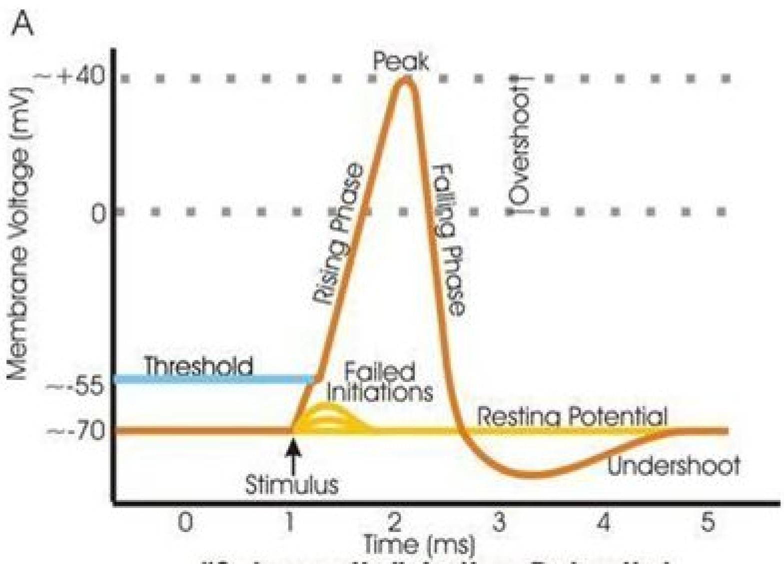
I will explain the electrochemical properties of the cell membrane that enable the interior of the neurons to be maintained at a voltage of approximately -60 mV. This is the result of the ion pumps and channels, which pump out Na^+ and pump in K^+ . The pumping process, which occurs continuously, results in three Na^+ being pumped out for every two K^+ that are brought into the cell. This results in the creation of ion gradients (K^+ high in, Na^+ high out). The continuous leakage of these ions down the gradients that are created leads to the negative potential.

There are also ion channels that allow for the selective transfer of ions through diffusion when the channels are open. Many of these ion channels are voltage dependant. This means that when an electrical signal is generated in the neuron, these ion channels can be activated to open or close thereby "transmitting" the signal along the neuron. This is the primary method of transmission of electrical signals. The cell membrane has a high resistivity, on the order of 10,000 ohms, whereas the cells interior has a resistivity of only a few hundred ohms. The problem is that there are many "holes" in the cell membrane, which are either ion channels or other protein-based pores that allow the electrical charge to be dissipated. Consequently, signals that are generated in the dendrites are not efficiently transmitted along the neuron. The distance that a signal can be transmitted is proportional to the radius of the neuron. The dendrites are the location where signals are generated. These appendages of the neuron cell body can be hundreds of "processes". Each dendrite will carry the signal that it receives from other neurons towards the cell body.

These electrical-chemical signals are graded, which means that they vary in strength depending on the strength of the input, unlike an action potential which is a fixed amplitude signal that is only sent when a certain threshold is reached. These graded potential signals from the dendrites can also be either excitatory or inhibitory, which means that they can be positive or negative and either contribute to the creation or suppression of an action potential in the neuron. All of the dendrites send their signals to the neuron cell body which then continue to the axon which is a single appendage. [1]

The Action Potential and Transmission of a Signal

The initial segment of the axon, known as the "axon hillock", has an extremely high density of voltage-gated Na^+ channels. When the dendrites collectively generate a signal of sufficient strength, which exceeds the threshold for that neuron, this axon hillock generates an action potential. An action potential is an all or nothing event. As a result of the generation of an action potential at the hillock, an electrical signal is sent down the length of the axon. An action potential provides a sustainable signal that can travel as far as a meter or two.



"Schematic" Action Potential

(Wikipedia, Action Potential)

Diagram 3

Speed of Transmission

In addition to an increase in diameter of the neuron, the signal speed is also improved if the neuron is myelinated. Myelination is the coating of axons with "highly resistive" Schwann cells in as many as one hundred layers that acts like electrical tape to reduce the "leakiness" of the neuron. It results in improvement of speed of signal transmission by fifty times. There is also a complex advantage, known as saltatory signal transmission, through myelinated axons that causes the electrical signal to jump between the "Nodes of Ranvier," which are the areas between the myelinated segments of a neuron (see Diagram 1). Saltatory transmission is an extremely fast and efficient method. The Nodes of Ranvier are the intermittent areas of the neuron that are unmyelinated because myelination occurs in segments. The Nodes of Ranvier contain ion channels and the saltatory signal transmission allows the electrical signal to propagate from node to node without having to transverse the myelinated areas thus significantly increasing the speed of the signal (see Diagram 1). The myelination is white and consequently the areas of the brain referred to as white matter contain high densities of myelinated fibers, whereas the areas referred to as grey matter are enriched in unmyelinated cell bodies.

The Synapse

When the signal reaches the end of the axon it triggers an influx of Ca^{+2} ions. This flux activates the release of vesicles filled with neurotransmitters through the presynaptic membrane. These neurotransmitters carry the signal across the gap of the synapse and allow for the recreation of the signal in the new neuron. In fact, the neurotransmitters can assist in the sustainability or even increase in the signal in the new neuron by triggering the opening of ion channels in the postsynaptic cell. This is the incredible system of signal transmission, which allows for cells to transmit signals efficiently over distances.

Transmission of Information

On the most basic level it is the capacity to transmit information over distances that enables cells to communicate, respond to their environment, and exist in complex arrangements. However, the brain is able to do far more with these signals. The capacity to send signals enables the encoding of information within those signals as different frequencies or spikes of action potentials. The capacity to encode information in the action potential spikes leads to the ability for more complex signal generation and eventually the deciphering of that information. Much is unknown about how this cognitive process occurs, but it is clear that it does. Mathematical models have been proposed to explain these phenomena, but they simplify the neural networks and do not adequately explain how the signals are in fact a computation or a transfer of information. [2]

An Advanced Explanation of the Electrical Impulse

The information that follows is a more specific and advanced explanation of the firing of an action potential. In this section, I have followed the formulation and utilized the circuit equivalents of cell membranes in the book Physical Biology of the Cell, Chapter 17, "Biological Electricity and the Hodgkin-Huxley Model."

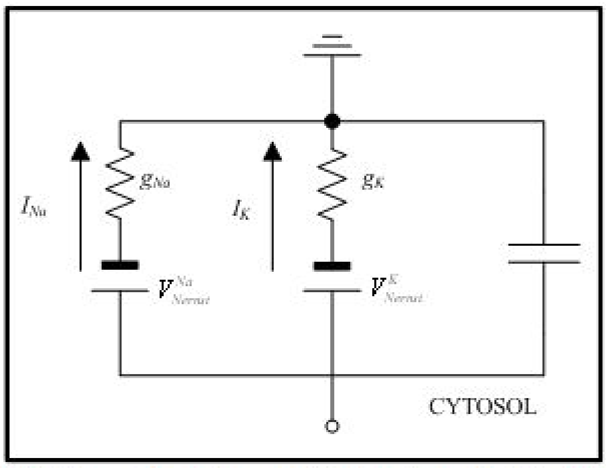
Electrical Potential Creation and Use in Signal Creation

Cell membranes separate charge by the function of ion channels and ion-exchange pumps. Energy is consumed in this process, and stored in the form of electric potential: this is similar to our experience with batteries on the macroscopic level. The cells utilize this charge separation produced across their membrane by ion channels and pumps to keep the cell from returning to equilibrium. In addition to providing a necessary element for the survival of the cell, the cell membrane has the remarkable ability to propagate a signal along its length without the attenuation of the signal, in the form of an action potential. The voltage difference across the cell membrane is the physical basis for the creation of an action potential, which is the resulting disturbance caused by altering the polarity of membrane by a chemical, electrical or mechanical stimulus, which then propagates down the cell membrane (see Diagram 3). This mechanism is the fundamental basis for an animal to sense its environment and to communicate that information over a distance. In the broadest sense, it is the capacity for neurons to transmit a signal that enables the transfer and encoding of information that eventually results in the nearly inconceivable volume of information processing of the human brain.

Explanation of Biological Current

In the study of physics, we mostly discuss electricity as electrons flowing along conductors. Conventional current flow occurs in the positive direction, primarily because the original work done with batteries by Volta and Daniell in the late 1700s and early 1800s relied on the flow of positive ions such as Zn^{2+}, Cu^{2+}, and Ag^{+}. In cells, there are a few cases in cells of electron transport directly producing charge separation, such as in photosynthesis in chloroplasts and electron transport in mitochondria. Usually, though, cells create and manipulate gradients of positive ions across the membrane. The most important ions in this process are Na^{+}, K^{+}, and Ca^{2+}. This makes sense because many of the large molecules in the cell, particularly nucleic acids, are intrinsically negatively charged and consequently, small positive ions are utilized in the creation of the cell's electrical state. Of the small negative ions, chlorine ions, Cl^{-}, are the only monatomic ions exploited by cells processes. Bicarbonate, HCO_3^{-}, is another important anion in cell function.

The electrical potential in cells is predominantly created by the nonequilibrium of sodium and potassium. The creation of electric potentials and currents requires cellular mechanisms that can separate and concentrate ions and control the flow of these ions through selected conduits. The cell membrane is a key component because its phospholipid bilayer contains many different ion-selective channels and pumps and is an effective thin insulator. The electrochemical properties of the cell membrane makes it equivalent to a circuit with a set of resistors (which are voltage-dependent), batteries (whose voltage is set by the ion concentration difference), and a capacitor which are all connected in parallel (Diagram 4). By selectively opening and closing the ion channels, which can only allow the transport of a specific ion, the cell can adjust its membrane electrical potential. This process is the key to electrical signaling in excitable cells. The neuron acts like a parallel RC circuit powered by the electric potential. We will create this model of a cell membrane in our classroom.



(Phillips, Kondev and Theriot 2009, 661)
Diagram 4 - The equivalent electrical circuit of a cell membrane

The Nernst Equation

The Nernst Equation enables us to quantify the electrical potential provided by the ionic gradient. In this case it is the cell membrane that we will consider. We can calculate the electrical energy mathematically by multiplying the ionic unit charge and the potential difference. We can also calculate the probability of finding an ion in a given region using the Boltzmann distribution for electrical energies. Although these formulas look complicated, setting up a proportion of concentrations allows us to take the logarithm of both sides of the equation and derive the famous Nernst equation,

$$V_2 - V_1 = \frac{KBT}{e} \, ln \frac{c_1}{c_2} \qquad : Equation\, 1$$

which will enable us to understand how cells utilize charge to create electric potentials. [3] We will consider this in more detail in the First Lesson Plan at the end of the unit where the students will learn how to use their knowledge of electrical physics equations and chemical ionic information to derive this powerful formula.

Speed of Propagation of Nerve Cells

The electrical signal propagation of neurons is a remarkable process that allows animals with nervous systems to respond to their environment fast enough to be able to survive. For animals, it is essential to be able to respond to stimuli in their environment rapidly, to avoid harm, elude predators, or catch prey. Chemical diffusion is a very slow process, as we know by the time it takes for perfume to diffuse to us in a room without drafts, and is insufficient for important signal conduction. The electrical conduction of a signal is an ingenious evolutionary adaptation. Action potentials transmit information 9-10 orders of magnitude faster than it would take molecules to diffuse over the length of a typical axon, and about 7 orders of magnitude more rapidly than motor-driven transport could send a signal the same distance. [4] The signal propagates through a single neuron at a rate of 10-100 m/s. The evolution of the action potential allowed for the survival of complex animals and eventually led to the development of the cortex (which is the outer, convoluted section of the brain responsible for higher level reasoning). The cortex enables the advanced critical thinking of the human brain.

Voltage-gated Ion Channels

Ion channels are proteins that allow the selective passage of ions through a membrane. When channels are voltage-gated that means that the state of the channel is dependent on the potential difference across the membrane. Voltage-gated ion channels are essential for the cell's control of the charge differential that enables the polarization of the membrane that is a signal spike, or action potential. Ion channels are able to detect stimuli such as a particular voltage change, permit the flow of select ions through the channel. The natural state of the ion channel is to be open, however, the negative normal potential that exists causes the protein of the ion channel to be closed. [5] Only when the threshold is reached, resulting in an action potential, the firing of which momentarily makes the membrane positive, do the voltage-gated ion channels open and depolarize the neighboring membrane, thereby propagating an electrical signal down the axon.

Membrane Depolarization and the Membrane as a Switch

The change of sign of the membrane potential is known as depolarization. The voltage-gated ion channels are essential as a switch for a signal to be created. The specialization of excitable cells to conduct an action potential occurs if the cells have selective ion channels that can be opened in response to a change in membrane voltage. When this happens, a local and temporary depolarization of the membrane can be amplified and propagated to travel across the entire length of the neuron. This propagated signal occurs quickly and without attenuation as indicated previously. These features are essential to the neurons ability to achieve its purpose.

The Electrical Circuit Model of the Membrane

The membrane can be idealized as an electric circuit. In terms of biological electricity, the system can be demonstrated as a collection of resistors, batteries, and capacitors, as shown in Diagram 4. The essential aspect is that the presence of the thin insulating membrane creates a capacitance to the system of membrane and channels, while the existence of ion channels makes the membrane behave like a series of resistors connected in parallel. The conductance of each channel type is different. The battery elements in Diagram 4 arise from the Nernst potentials that result from the concentration difference of ions across the cell membrane. The Nernst electrical potential for each ion can be represented as a battery because the voltage is additive and will have to be overcome or act in concert with the electrical potential across the membrane. [6]

Mathematical Models of the Current

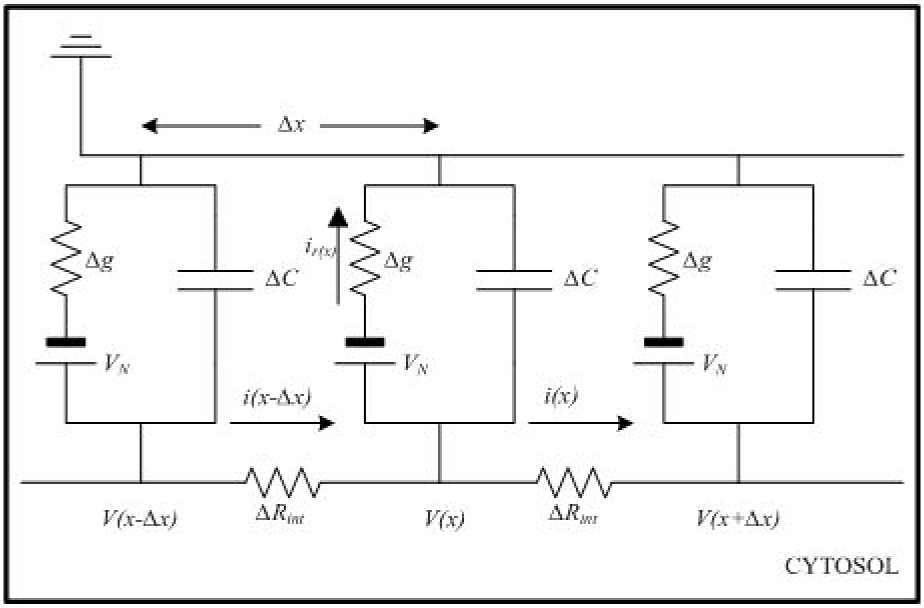
The difference between the potential of the membrane and the Nernst potential gives the driving force for ion movement or current: $I=g(V_{mem}-V_{Nernst})$ Equation 2. The Nernst potential plays the role of a battery in series, which is additive, with a resistor of conductance g, as depicted in Figure 4. In this equation, a linear relation between the current and the voltage is assumed; this relation is known as Ohm's law. Ohm's Law as stated in physics is V=IR or I=V/R, which will be familiar to physics students.

In reality though, like much of the idealized physics equations, the voltage-gated channels actually result in a much more complicated, nonlinear current-voltage relationship across the cell membrane. The consequence of this is that when the potential of the cell changes so as to allow voltage dependent channel gating, the membrane permeability changes, due to the newly open channels. In the open state, the channels allow for current to flow in a fashion that is predicted by the I-V curve. A simple model for the ionic current through the membrane presented in Equation 2 above demonstrates a linear relationship between the membrane potential and the curve. Therefore, the ionic conductance, g, as defined above must be voltage-dependent. [7]

Action Potentials and the Hodgkin-Huxley Model

Signals in cells are often mediated by the presence of electrical spikes called action potentials. At this point our interdisciplinary study enables us to quantitatively describe an action potential. The study of action potentials culminated in one of the most successful models for the integration of biology, chemistry, and physics in the history of science, the Hodgkin-Huxley (HH) model. The HH model depicts action potentials and predicts the nonlinear affect on the membrane model of alterations in the membrane voltage; it is a widely accepted explanation of neuron functioning. Through this model the action potential is described and its properties can be graphed.

The action potential is an all-or-nothing event. If a charge stimulus raises the membrane voltage above a threshold (V~-40mV-depending on the cell), the membrane potential jumps up to a value roughly given by the Nernst potential of sodium, $V_{Nernst(Na)}$ ~50mV (see Diagram 3). The drastic increase in electrical potential of a small section of the cell membrane causes the adjacent small section of membrane to go above the voltage-gated threshold, causing it to be depolarized. This effect then influences the next section of membrane to exceed its threshold, resulting in a wave of signal propagation known as an action potential. The HH model is the mathematical equation that governs the propagation of an action potential and it provides an indication of how electrical signals can be propagated over long distances at constant speed and without dissipation. One other consequence of the electrical stimulation exceeding the voltage-gated threshold is that the membrane is temporarily desensitized and is incapable of further depolarization. This effectively allows the signal to only propagate in one direction, which is essential for the proper functioning of a neuron. [8]



(Phillips, Kondev and Theriot 2009, 668)

Diagram 5 - A circuit of the voltage variation of an action potential

We can utilize the diagram above (Diagram 5) to simulate the action potential voltage variability over distance. Cell membranes and their ion channels can be modeled as a collection of resistors, capacitors, and batteries. Excitable membranes behave as bistable switches. The interaction between voltage-gated potassium and sodium ion channels mediates the response. The Hodgkin-Huxley model of the propagation of action potentials shows how cells can produce propagating pulses, or action potential spikes, that serve as the key information carrier in complex organisms. [9] This is meant to demonstrate the usefulness of the Hodgkin-Huxley model, to explain the electrical aspects of the neuron in physical terms, and to suggest lab possibilities and potential mathematical and graphical problems. I believe this physical knowledge justifies the pursuit of the HH model in the explanation of vagus nerve stimulation treatment, which is related to my patent and helps to illuminate the potential reasons for the onset of epileptic seizures.

Macroscopic Brain Function and Malfunction

Normal brain functioning is remarkably complex and involves the firing of the billions of neurons via electrochemical processes. Although more is known about the brain all the time, many of the mechanisms by which these few pounds of matter are able to produce the intricate processes of the human mind are still mysterious. The brain's evolution, evidenced by its anatomical structure and functioning, has culminated in the large cortical region in humans, which is responsible for higher level reasoning. Many models of neural and cognitive modeling have been proposed, such as the Hodgkin-Huxley model, but these mathematical non-linear models cannot replicate completely the firing of a single neuron, much less achieve the functional magnitude of the human brain. This is partly the consequence of the brain being a chaotic system, which is the mathematical state of apparent randomness that is highly structured and oscillates around strange attractors or values. The importance of this is that normal brain functioning does not produce a regular electrical brain pattern. In fact, regular brain patterns manifest in the malfunction of the brain known as seizures. Repeated seizures are known as epilepsy. Although the mathematical models are too difficult to understand, my students will be able to appreciate the fact that ordered brain signaling or synchronization, called entrainment, can help explain the normal, desynchronized electrical brain activity that enables normal macroscopic brain functioning and processing. This will add to the relevancy of this electrical brain unit.

In May, 2009, I received a patent for a Radio Frequency (RF) powered vagus nerve stimulator. [10] The RF vagus nerve stimulator utilizes radio waves to power the VNS device without the need for an implanted battery. The patent is titled "Vagus Nerve Stimulation Apparatus, and Associated Methods." The VNS has been approved for treatment of epileptic patients who do not respond to drug treatment and for the treatment of severe pharmacologically resistant depression. My interest in this unit is to explain the normal state of brain patterns, the entrainment of neuronal signaling, that manifests in epileptic seizures and the means by which the VNS can help the brain to retain its unsynchronized signal pattern. It is another goal to indicate that scientific pursuit and application of knowledge can add to the understanding of previously unexplained diseases, to the development of technologies that may be applied to the improvement of treating disease, and hopefully to the scientific understanding of biological or physical systems like the amazing brain.

An Explanation of Epileptic Seizures

Epilepsy results from the synchronization of neuronal signaling that results in an entrainment. When the brain is in its normal state, the global signal is desynchronized and chaotic. This means that, for the most part, neurons are not firing action potentials in rhythm. In epilepsy, neuronal signaling becomes rhythmic in parts of the brain, which is an unnatural state, and results in a seizure. According to Iasemidis et al. the seizure is actually not the result of entrainment but instead is the brain's attempt to reset the neuronal firing pattern and desynchronize the EEG pattern. Seizures occur after a period of sustained dynamical entrainment of the epileptic brain. It is suggested that seizures actually occur in order to reset the entrainment. [11] This theory—in conjunction with the observation that there is a period after the seizure that inhibits further seizures—helps to explain why the vagus nerve electrical stimulation prevents epileptic seizures by actually causing miniature, localized seizures! It is possible that electromagnetic stimulation by the vagus nerve stimulator intervenes in entrainment of brain signals by periodically disentraining entrained critical sites and thereby may alleviate the need for a seizure to occur because the brain is reset. [12] This sentiment is supported by Bewernitz et al. and the efficacy of the VNS is explained, indicating that there is evidence that electrical stimulation mimics the electroencephalographic resetting effect of a seizure. Therefore it is reasonable to consider that VNS therapy mimics the effect of a seizure. [13] This explanation leads to the only explanation that I am aware of as to how and why the VNS works. The molecular mechanism was further clarified in a 2007 study which indicated that VNS triggers neurochemical and molecular changes in the rat brain involving the neurotransmitters and growth factors that play a crucial role in neuronal health. [14] This explanation of the neurochemical affect adds to the electrical understanding of the VNS's mediation of seizure activity.

There have been recent efforts to use the Hodgkin-Huxley mathematical model of the neuron to explain how VNS can be tuned to maximize the reduction in epileptic seizures. [15] Although these efforts are in their early stages, I believe that an understanding of the onset of seizures and the ability to improve the tuning of the VNS for individuals would greatly improve our comprehension of brain function. Before fMRI and PET scans, neuroscientists utilized the existence of imperfections in brain functioning, caused by lesions and or brain damage to understand the brain's underlying anatomical structure and how it worked. I believe that seizures may well enable an equivalent insight into the electrical-chemical functioning of the brain using EEG and mathematical modeling. I hope that this research will lead to a greater comprehension of the working of the human brain.

Classroom Activities

Lesson Plan 1: Simulating the Electric Potential Across the Cell Membrane Physically and Electronically and Simulating the Firing of an Action Potential.

I will begin by placing basins containing different colored dyes and membranes around the room. I will ask the students what they expect to happen? Why does this happen. We will discuss the concept of passive diffusion. Why do some of the dyes diffuse and others do not? We will discuss the properties of molecules and membranes. What would happen if these molecules where charged ions? What would happen to the environment around the "cell membrane?" Would there be a charge differential?

The students will be encouraged to explore the relationship of their chemical understanding to electricity. What happens when the ions flow? We call this current. Are there other ways to increase or decrease the amount of charge diffusion or flow? Are there active ways to move the dyes, or ions, from one side of the membrane to the other?

What are they? Could we make holes? Could we take some of the dye and dump it into the other side? What are the correlations that we can make with the cell membrane regarding the flow of ions? How could we increase and decrease the amount of charge (or dye) on one side of the membrane or the other? This is exactly what the cell does to create a charge differential across the membrane using ion pumps and channels.

To get a better understanding of the way that a cell works, we will interact with an excellent animation of the creation of the charge differential across the cell membrane and the propagation of the action potential at the website, http://outreach.mcb.harvard.edu/animations/actionpotential.swf. This will give us a better sense of cell function and will introduce us to the ingenious means by which the cell utilizes this charge difference to create action potentials. Action potentials are fundamental signals sent by the neurons that result from the localized depolarizations of regions of the cell membrane. In short, the cell harnesses the potential difference across the membrane to rapidly change its polarity (positive to negative and vise versa) and return it to its resting state. Like a line of dominos, this process, once started, propagates a signal along the length of the axon. Once we have examined the nature that the cells harness this latent potential we will be ready to investigate these concepts in electronic circuits.

I will provide the students with electrical components and the circuit diagram in Diagram 4. The students will be encouraged to attempt to create the circuit. Once they have succeeded, we will discuss the significance of the hypothesis that a biological membrane can be modeled by an electronic circuit. We will discuss the different components and what their corollary is in the cell.

Lastly, I will ask the students what an action potential is and begin a discussion on the significance of the observation that the electrical signal does not attenuate, or dissipate over distance. To explore this concept we will construct the circuit demonstrated in Diagram 5, which shows the effect of signal propagation over distance in a neuron. This will complete the electronic labs that model the biological cell with electronic circuits.

Lesson Plan 2: The Action Potential, a Mathematical Derivation of the Nernst Equation (and For My Mathematically Advanced Students - Mathematically Solving a Simplified HH Model)

At this point we are prepared to begin quantifying our understanding of the concepts that we have so far been discussing qualitatively. We will derive the famous Nernst Equation using tables in the Phillips book, Physical Biology of the Cell, on page 151 and Chapter 17.

We will begin this mathematical solution of the multiple equations by taking them one at a time. The electrical energy of an ion of unit charge e, when placed in a region of potential V_1, is eV_1. For an ion whose valence is z the corresponding charge is ze and the energy is zeV_1. The potential is V_1 and the concentration of positive ions is c_1, while in the other we have V_2 and c_2 for the potential and the concentration. In equilibrium there is a probability of finding a positive ion in the region 1 or 2. The formula for P_1 is

$P_{1,2}=1/Z\ e^{-eV1,2/kgT}$:Equation 2

This results from application of the Boltzmann distribution to this problem when the energies are electrical. The subscript 1,2 on p and V means the subscript should be either 1 or 2 which results in a distinct equation for each area, 1 and 2. The ratio of the two probabilities is equal to the ratio of the number of ions in region 1 and the number in region 2, which in turn are proportional to the ion concentrations in the two regions. We can use this proportionality to write the ratio of concentrations as:

$$\frac{c_1}{c_2} = \frac{p_1}{p_2} = \frac{e^{-eV_1/kBT}}{e^{-V_2/kBT}}$$

Equation 3

If we take the logarithm of both sides of this equation, we are left with the famous Nernst equation which relates the difference of electrical potentials to the ratio of concentrations of ions and is given by

$$V_2 - V_1 = \frac{KBT}{e} ln \frac{c_1}{c_2}$$

The Nernst equation allows us to specifically and mathematically comprehend how the cell membranes utilize differences in ion concentrations to create electrical potentials. [16]

For my students who are familiar with calculus I will introduce them to the simplified version of the HH model. I will encourage them to explore the Phillips book equation on page 675. This will be a challenge for my mathematically advanced students who are familiar with derivatives and will introduce them to simplified differential equations.

Lesson Plan 3: Demonstration of My Patented RF Vagus Nerve Stimulator Prototype

I have the prototype of my RF vagus nerve stimulatior. I will introduce this demonstration as an example of creating electrical current using an unusual powering device. At this point the students have not yet studied waves (except for my second year AP physics students), so they will not be familiar with the significance of utilizing radio waves to power a device over a distance. However, I anticipate that we will have a lively inquiry discussion about how this device might work!

I will have the Radio Frequency vagus nerve stimulator set up with the two one inch "chips" set up about one centimeter apart. The "chips" are two silica squares imbedded on both sides with minute electronic wiring and "populated" with tiny electronic elements, such as microprocessors, resistors, diodes, capacitors, etc. One chip has a battery to power it. The other chip (both of which have antennas build into their circuitry) does not have a power source and is connected to an oscilloscope, which is an electronic device for converting electrical impulses into visible wave patterns. The oscilloscope will demonstrate that the chip without the battery is actually receiving energy through the air! The radio waves transmit enough energy at this distance to power the RF vagus nerve stimulator device. The oscilloscope will demonstrate the frequency, pulse width, voltage, and duration of the electrical pulse generated by the device. These electrical parameters can be tuned for each patient. The device without the battery would be implanted under the skin and the generated electrical signal would be transmitted to an electrode wrapped around the vagus nerve in the neck of the patient.

I will explore with the students how this energy could be transferred through the air, what the "implanted" chip does to convert this energy into a signal, what the function of the different electrical components of the chips are, how the electrical pulse can stimulate the nerve in the neck, and lastly, the hardest question of all, why stimulating a nerve in the neck might help to prevent seizures? These are the fundamental questions of the unit. This is a culminating activity that will allow my students to creatively explore their understanding of the relevant electrical issues and to identify areas with which they are not familiar.

This exercise will lead to students choosing topics for further independent research that will result in students presenting their findings to the class.

Resources

Annotated Bibliography

Baev, Konstantin V. Biological Neural Networks: The Hierarchical Concept of Brain Function. Boston: Birkhauser, 1998.

Useful for the global concept of neural networks.

Bewernitz, Michael, Georges Ghacibeh, Onur Seref, Panos M. Pardalos, Chang-Chia Liu, and Basim Uthman. "Quantification of the impact of vagus nerve stimulation parameters on electroencephalographic measures." AIP Conference Proceedings. 2007. 206-219.

Extremely significant article that demonstrated mathematical modeling related to the VNS treatment.

Bloom, Floyd E., M. Flint Beal, and David J. Kupfer, . The Dana Guide to Brain Health. New York: Dana Press, 2006.

An excellent, comprehensive book for background brain information.

Boom, Floyd, E., ed. Best of the Brain From Scientific American. New York: Dana Press, 2007.

Contains relatively current articles including one on VNS.

Boron, Walter F. and Emile L. Boulpaep, ed. Medical Physiology. Philadelphia: Elsevier Saunders, 2005.

An essential textbook on brain physiological for background information.

Casado, Jose Manuel. "Synchronization of two Hodgkin-Huxley neurons due to internal noise." 2003: 1-7.

An article that initiated the quantification of neural connections using the HH model.

Chauvet, G.A., and T.W. Berger. "Hierarchical Model of the Population Dynamics of Hippocampal Dentate Granule Cells." Hippocampus, 12 2002: 698-712.

A marginally useful article.

Cronin, Jane. Mathematical aspects of Hodgkin-Huxley neural theory. New York: Cambridge University Press, 1987.

A more comprehensive approach to mathematical modeling of neural theory using the HH model.

Doidge, Norman. The Brain That Changes Itself: Stories of Personal Triumph from the Frontiers of Brain Science. London: Penguin Books, 2007.

An excellent, accessible book about the plasticity of the brain.

Follesa, Paolo, et al. "Vagus nerve stimulation increases norepinephrine concentration and the gen expression of BDNF and bFGF in the rat brain." 2007: 1-9.

A specific article relating VNS to chemical impacts in the rat brain.

Hoppensteadt, Frank C. An Introduction to the Mathematics of Neurons. second edition. New York: Cambridge University Press, 1997.

An early approach to linking mathematics in the study of neurons.

Iasemidis, Leon D., Deng-Shan Shiau, J. Chris Sackellares, Panos M. Pardalos, and Awadhesh Prasad. "Dynamical Resetting of the Human Brain at Epileptic Seizures: Application of Nonlinear Dynamics and Global Optimization Techniques." IEEE Transaction on Biomedical Engineering , March 2004: 504-505.

Quintessential article explaining the mechanism of VNS treatment.

Levine, Daniel S. Introduction to Neural and Cognitive Modeling. second edition. Mahwah, New Jersey: Lawrence Erlbaum Associates, Publishers, 2000.

A book introducing neural and cognitive modeling.

Li, Yan-Long, Zhao-Yang Chen, Jun Ma, and Yu-Hong Chen. "Simulation study of stimulation parameters in desynchronisation based on the Hodgkin-Huxley small-world neuralnetworks and its possible implications for vagus nerve stimulation." Acta Neuropsychiatrica, 2008: 25-30.

A key article in my linking VNS and the HH model.

Mickle, Marlin H., et al. "Patent title: Vagus Nerve Stimulation Apparatus, and Associated Methods." Patent, 2009.

My patent from this May for work done in 2005.

Piccinini, Gualtiero, and Andrea Scarantino. "Computation vs. Information Processing: Why Their Difference Matters to Cognitive Science." Studies in the History and Philosophy of Science, Forthcoming.

Interesting article on the nature of digital computation and cognitive science.

Phillips, Rob, Jane Kondev, and Julie Theriot. Physical Biology of the Cell. New York: Garland Science, 2009.

An invaluable, discernible resource book on biophysics and the mathematical derivations of useful equations.

Strogatz, Stephen. Sync: The Emerging Science of Spontaneous Order. New York: Hyperion Books, 2003.

A book that examines the natural occurrence of synchronicity.

Appendix- Standards

Pennsylvania Standards

3.2.12.B Evaluate experimental information for appropriateness and adherence to relevant science processes.

3.2.12.C Apply the elements of scientific inquiry to solve multi-step problems.

3.4.10.A Explain concepts about the structure and properties of matter.

3.4.10.B Analyze energy sources and transfers of heat.

3.4.12.A Apply concepts about the structure and properties of matter.

3.4.12.B Apply and analyze energy sources and conversions and their relationship to heat and temperature.

3.4.12.C Apply the principles of motion and force.@SH:Notes

1 Bloom, Beal and Kupfer 2006

2 Piccinini Forthcoming

3 Phillips, Kondev and Theriot 2009, 650

4 Phillips, Kondev and Theriot 2009, 647

5 Phillips, Kondev and Theriot 2009, 654-5

6 Phillips, Kondev and Theriot 2009, 661-2

7 Phillips, Kondev and Theriot 2009, 663-4

[8] Phillips, Kondev and Theriot 2009, 674

[9] Phillips, Kondev and Theriot 2009, 676

[10] Mickle, Marlin H., et al., 2009, Patent

[11] Iasemidis, et al. 2004, 503

[12] Iasemidis, et al. 2004, 504

[13] Bewernitz, et al. 2007, 209

[14] Follesa, et al. 2007, 1

[15] Li, et al. 2008

[16] Phillips, Kondev and Theriot 2009, 650