Chapter 12

The Primary Role of the Electric Near-Field in Brain Function

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71945

Abstract

The origin and spatial-temporal structure of the endogenous (internal) electric near-fields associated with the neurological network activity of the brain are described. Recent discoveries have elevated the importance of the endogenous fields to a leading role of primary phenomena, as opposed to the traditionally thought secondary role of epiphenomena. This implies that the spatial-temporal structures of the brain's endogenous fields are rich in information that directly convey brain health. Understanding the spatial-temporal structures of the endogenous fields under healthy and unhealthy conditions coupled with the technologies needed to sense and manage these fields opens a world of possibilities for the rational design of clinically accurate, wearable neurodevices to diagnose, therapeutically treat, and manage chronic neurological dysfunctions, mental disorders, and traumatic injuries. The World Health Organization reports that more than 1 billion people worldwide, irrespective of age, sex, education, or income, suffer because of neurological disorders. Devices of the type described here will provide clarity and relief to those individuals that have an impaired neurological system.

Keywords: axon, nerve fiber, electric near-field, nerve fiber crosstalk, regenerative repeater, node of Ranvier, endogenous field, exogenous field, brain function, brain structure, neurodegenerative diseases, linear antenna array, myelin sheath, wireless neurological networking, multiple sclerosis, autism spectrum disorder, Alzheimer's disease, chronic care, wearable device, rational design

1. Introduction

It is our hope that the avenue of investigation reported here leads to new modalities for brain mapping and the non-invasive diagnosis and treatment of neurological and mental disorders. We recommend that future work in brain mapping include both the current neuroimaging

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methods and the spatial-temporal monitoring of electric near-field signatures. By doing this, we will better understand how brain structure leads to dynamic brain function and further reveal that the highly sophisticated brain network is comprised of a fixed anatomical network discovered by neuroimaging augmented by a near-field wireless network which is shown here to naturally occur at the most fundamental levels of the nervous system. The problem we treat is at the intersection of medicine, science, and electrical engineering, and further research into the ideas presented has the potential to not only meet a great many societal health needs, but also impact a variety of allied fields, including advanced materials, biosensors, fluid dynamics, near-field electromagnetics, nanotechnology, and information (Shannon) theory.

The defining framework for one of the fundamental problems in neuroscience was laid down in the seminal work presented in [1]. In relation to this work, we believe that understanding circuit functions not only encompasses the intrinsic properties of individual neurons and their synaptic connections, but also their connections to, and interactions with, other neurons. Several mechanisms for transmission of excitation from one nerve cell to another are discussed in [2]. In this work, we will discuss a new mechanism.

The plan of the chapter is as follows. Section 2 describes nerve bundles and tracts, reviews fundamental axon structure-function relationships for myelinated, or insulated, fibers, and provides the reader with a feeling for how densely fibers are packed in bundles and tracts. This section also reminds us of the concept of *tortuosity*. Although axonal tortuosity is a ubiquitous phenomenon, no mathematical models exist to describe it in the context of nerve bundles and tracts.

Section 3 casts a Node of Ranvier, a critical element of a myelinated fiber, in the role of a *dual channel (or dual port) device* having both electrochemical (EC) *and* electromagnetic (EM) signaling channels. The EC channel is well known and is generally governed by Hodgkin-Huxley dynamics; whereas, the EM channel described here is not well known and is enabled by electric near-field dynamics. In the case of the EM channel, electric near-field characteristics for approximately linear arrays of Nodes of Ranvier consecutively located along myelinated nerve fibers are simulated and discussed, as is the much larger bandwidth and speed of the EM channel vis-à-vis the EC channel. This relatively rapid ability to traverse physically different regions of the brain can account for the statistically correlated concurrent activity observed during the execution of cognitive tasks which the anatomical links of the human connectome cannot currently all account for.

Indeed, a more comprehensive story of brain function can be constructed from the *fixed network* of the human connectome augmented by the *wireless network* described here. A study of this type opens many exciting avenues of research. Of interest are those that examine the spatial-temporal signatures of the electric near-fields, the *endogenous* (internal) fields for different central nervous system neuropathies, and the subsequent design of non-invasive or minimally invasive, clinically accurate medical devices capable of delivering rationally designed spatial-temporal *exogenous* (external) fields for neurological dysfunction mitigation. No such rationally designed, clinically accurate medical devices exist today. Section 4 provides a discussion that presents several ideas that we are certain will stimulate further the world research.

Section 5 describes the continuing research and development phases conducted in our laboratories for a non-invasive, wearable neurodevice that provides clinical grade information on cognitive and behavioral states of the brain and insight into impaired central nervous neurological network dynamics. We believe that this section is a model for those desiring to develop such medical devices using an integrated clinical *in vitro* wet laboratory/computer simulation *in silico* dry laboratory environment. The reader will note that Section 5 provides additional neurobiological support for the electrical engineering investigation found in Sections 2 and 3. Section 6 presents the conclusions of this work.

2. Nerve bundles/tracts

A nerve is a grossly visible anatomic structure and is a bundle or tract of axonal processes from many different neurons wrapped in connective tissue. Axons with larger diameters are generally insulated, or myelinated. The insulation is a highly intricate lamination of plasma membrane known as a myelin sheath and forms an efficient barrier to charge leakage, signal loss, and interference.

The myelin sheath is discontinuous along the length of the axon. The "gaps" are known as the Nodes of Ranvier where the axonal membrane is exposed (uninsulated) to the extracellular space. The Nodes of Ranvier act like digital repeater stations in communications networks. These digital repeater stations contain a high density of voltage-gated Na + channels that regenerate action potentials, if incoming current exceeds a threshold and incoming rate does not violate certain refractory conditions. In the following, we briefly review some properties of myelinated fibers.

2.1. Axon structure-function in myelinated Fibers

Early work [3] discusses axon structure-function relationships. **Figure 1** defines axon structural parameters and illustrates the recent analogy with communications networks.

Using current flow arguments, we arrive at the following proportionality:

$$\frac{l}{D} \propto \left(\frac{d}{D}\right)\left[\ln\left(\frac{D}{d}\right)\right]^{1/2} \tag{1}$$

where comparison with experimental data shows that the ratio $g = d/D$ varies in a relatively tight range about $g^* = 0.6$. This highly interesting behavior gives rise to a nearly linear variation of internodal length (average distance between Nodes of Ranvier) with fiber diameter [3]. We note that the right-hand side of (1) is proportional to the length constant which also attains a maximum at g^*. The length constant is a mathematical constant used to quantify the distance that a graded electric potential travels along a fiber via passive electrical conduction. The greater the value of the length constant, the farther the potential will travel. Note that a large length constant can contribute to spatial summation, the electrical addition of one potential with potentials from adjacent areas of a cell.

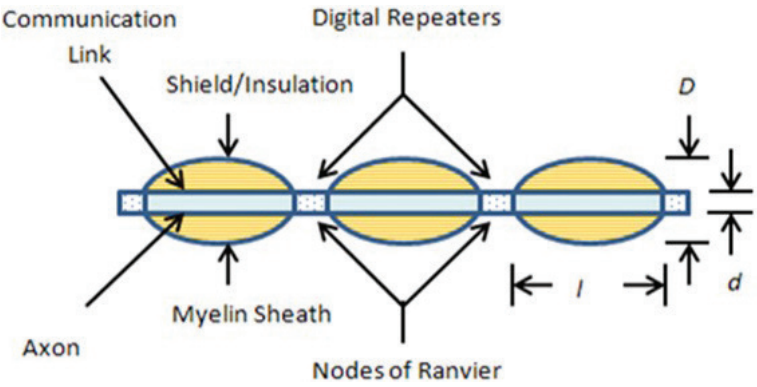

Figure 1. Elements of a Myelinated axon.

The situation with fiber conduction velocity is more complex, as pointed out in Ref. [4]. Conduction velocity is related to the delay between the times at which adjacent nodes reach threshold. There is an optimal value of g (and, therefore, myelin thickness) at which conduction velocity is maximized. It appears that nerve fibers enjoy a structural relationship which ensures that currents rapidly reach repeaters and exceed the threshold necessary for regeneration through a delicate balance of relatively costly (in terms of energy) Nodes of Ranvier and passive internode conduction.

2.2. Morphometric studies of nerve bundles/tracts

We provide two distinctly different examples. The human trigeminal nerve is composed of several bundles of primarily myelinated fibers in the motor and sensory roots. The average transverse sectional sensory (motor) nerve area is 2.147 (0.295) mm^2, into which 51.862 (5.268) axons are packed, each with an average cross-sectional area of 0.896 (2.526) μm^2 [5]. The diameter of the optic nerve increases from about 1.6 mm within the eye to 3.5 mm in the orbit to 4.5 mm within the cranial space. Within the optic nerve, there are from 0.77 to 1.7 million fibers [6].

To appreciate the complexity and elegance of nerves, we consider what are known as *packing problems*, a class of spatial optimization problems. The model we employ is that of non-overlapping congruent circular cylinders (a rough model for fibers) of aspect (fiber length/fiber diameter) much greater than unity. This would appear to be a poor model for trigeminal nerves, where the packing density for sensor (motor) nerves is 0.022 (0.045), and a much better model for the optic nerve, where the average packing density is 0.846, close to the maximum packing density of $\pi/\sqrt{12} = 0.907$.

The reason that we differentiate the applicability of the packing model in the two cases is because optic nerve fibers tend to run approximately parallel within very small spaces and, thus, achieve a high packing density; whereas, trigeminal fibers generally do not run parallel, and require considerably more nerve volume for their runs. The difference

may be described by the term *tortuosity*, which refers to the twisting, turning property of curves [7]. When we couple the concept of tortuosity to the quantum nature of the reactive near-field electromagnetic environment to be described in the sequel, it leads us to ponder the question of whether the ground-breaking results reported in [8] on entanglement and communications-assisted entanglement provide an approach to the study of axonal interaction. This is a thought to store away for future research. In this work, we stay on classical ground.

We refer to the interaction of tightly packed nerve fibers in a tract as *crosstalk*. The concept of crosstalk is well known in the discipline of electrical engineering, where it is characterized as any phenomenon by which a signal transmitted on one circuit or channel of a transmission system creates an *undesired* effect in another circuit or channel. There is a wealth of information in the electrical engineering literature on ways of mitigating the undesired effect of crosstalk. The situation may not be so clear in the current case of neurobiology, where the crosstalk may not necessarily be undesired. In fact, if we strictly apply the thinking that structure leads to function, then the fact that the Nodes of Ranvier are uninsulated, a structure which directly leads to crosstalk, we tentatively conclude that the crosstalk may serve a useful function [9].

It is instructive to provide a few remarks on the techniques for reducing crosstalk. Crosstalk in the electrical engineering context refers to interactions among wires carrying currents. With the full understanding that the nerve fiber is not a wire, we do know that it does exhibit activity which generates potential differences, current flow and electromagnetic fields that can influence the surrounding environment. Best practices in electrical engineering indicates that the following techniques can reduce crosstalk (analogies to nerve fibers are in parentheses):

- Widen spacing between signal lines (reduce packing density of fibers).
- Position signal lines as close to ground plane as possible (surround fibers by substantial amounts of extracellular material).
- Route signal lines on different layers orthogonal to each other (we see this in the cortex).
- If necessary, route signal lines in parallel, but minimize run lengths (as previously noted in the optic nerve).

Anatomy within the nervous system reflects a great variety of structural practice. In many cases, we see high fiber packing density and relatively little extracellular space, conditions which promote crosstalk. It is important to realize that, in the neurobiological context, crosstalk may be beneficial and not the problematic phenomenon it is viewed as in the electrical engineering context. Depending on where in the central nervous system we focus, we note that crosstalk may enable communication, cooperation, or competition among nerve fibers[1].

[1]The reader may wish to view the TEDx talk at https://www.youtube.com/watch?v=Jg50wEHqpas on the "Grandest Social Network" to obtain an additional perspective on how the vast population of 100 billion nerve fibers in the human brain interact in a manner similar to the way in which humans interact in much smaller social networks like Facebook.

3. The Node of Ranvier—A dual channel EC/EM device

In [10], we see that each Node of Ranvier serves two functions which may be differentiated by propagation process:

1. An element of a longitudinal EC conduction digital repeater string, as discussed earlier. This is the classical function discovered by Hodgkin and Huxley.
2. An element which provides bidirectional coupling into a transverse EM near-field channel. This is the new function described here. Note that we use the acronym EM, although the mechanism is solely an electric field.

We focus on item 2 above. Coupling, or interaction among nerve fibers, is accomplished by one or more consecutive Nodes of Ranvier which serve as elements of an approximately *linear antenna array*. **Figure 2** illustrates the dual channel nature associated with each Node of Ranvier.

3.1. Reactive near-field characteristics

To model the transverse EM propagation, we start at basic principles which describe the opening and closing of ion pores (channels) at a Node of Ranvier. Each pore opens and closes as what is called in communications systems a stochastic Pulse Position Modulation/Pulse Width Modulation (PPM/PWM) signal, i.e., the opening of a pore is rather abrupt and occurs at a stochastic position in time, the duration of pore opening is stochastic, and the closing of a pore is also rather abrupt.

Pulse position and pulse duration are assumed to be statistically independent uniformly distributed random variables with ranges established by clinical measurements. The time and frequency domain characteristics of an ensemble of such signals is shown in **Figures 3** and **4**, respectively.

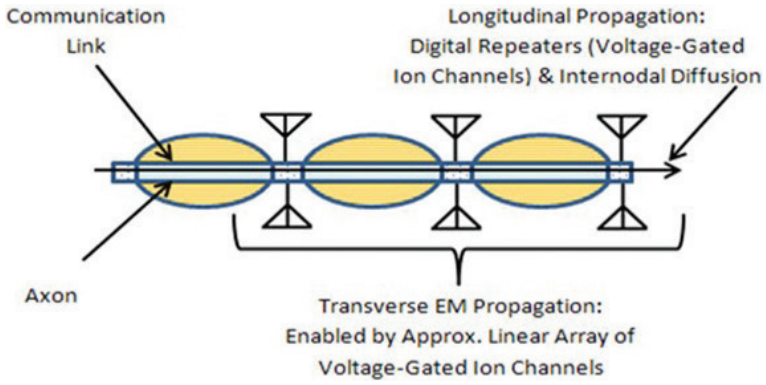

Figure 2. Axonal EC longitudinal Classical Channel and EM Transverse Channel (small triangular shapes positioned at nodes of Ranvier are symbols for antenna elements).

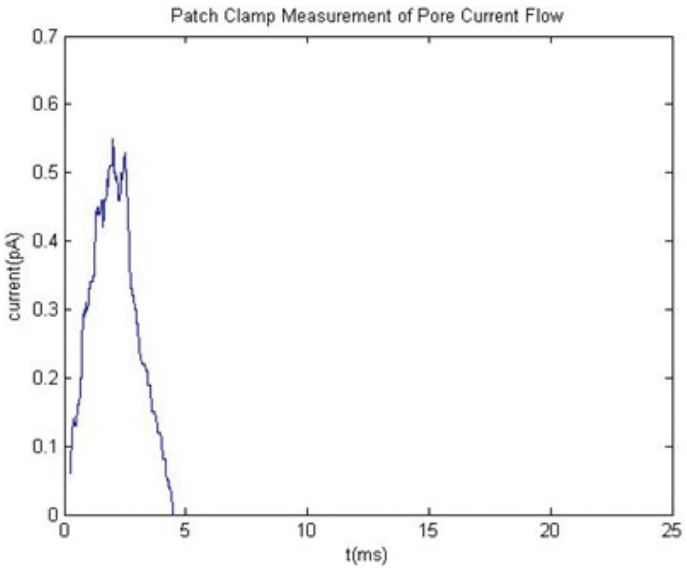

Figure 3. Typical patch clamp measurement of pore current flow.

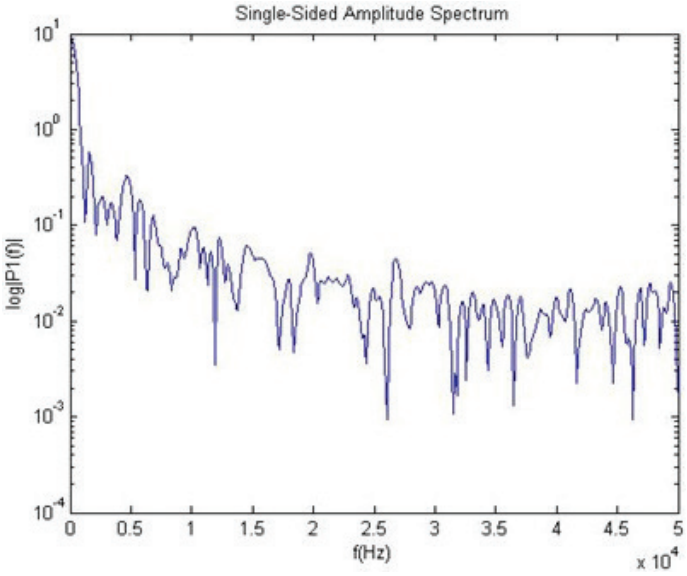

Figure 4. Fourier transform of an average of 100 patch clamp measurements.

A Node of Ranvier consists of several thousand pores per square micrometer of membrane each with diameter ≅ 0.4 nm disposed on an annulus with width ≅1–2 μm and diameter that of the nerve fiber. If we assume that the pore signals as modeled above

are statistically independent, it is then possible to obtain a comprehensive model for the transverse EM propagation at a Node of Ranvier due to the ensemble of pores, or voltage-gated ion channels.

It is important to note that the electric field generated as above is not a single frequency field, but a field consisting of many frequencies associated with the characteristics of an ensemble of pores rather abruptly opening and closing. Looking at the Fourier transform of **Figure 4** and adopting a criterion that the significant band of frequencies are those that are no more than 30 dB down from the maximum, we see that the significant band of frequencies goes up to at least 50 kHz. This is a startling result, as research on nerve fibers is commonly conducted in the much lower 1 or 2 kHz regime associated with the time domain characteristics of the EC channel action potentials. We now see that the nerve fiber operates in two widely different frequency regions, EC at low frequencies and EM at much higher frequencies.

The need to treat a wide band of frequencies in the EM case distinguishes this problem from the many problems and solutions in electromagnetics that assume a single frequency. The offshoot of this is that advanced methods that start with dyadic Green's functions and can accommodate a wide band of frequencies at the outset are used. In this work, we make certain assumptions that reasonably accurately reflect first-order effects to present some new results in as simplistic terms as possible. In any event, we note that the expected range of frequencies leads to wavelengths λ that are long relative to physical dimensions associated with axons and nerve bundles and tracts; therefore, EM interaction among Nodes of Ranvier for closely packed axons within a bundle or tract, or even among Nodes of Ranvier for physically distant tracts as occurs in the brain, is in the *reactive near-field*. For wave number $k = 2\pi/\lambda$ and interaction distance r, the near-field condition satisfies $k \cdot r \ll 1$.

As noted above, precise wide band near-field prediction of the electric field is challenging and few accurate tools are available. In the near-field region, in contrast to the far-field, absorption of radiation *does* affect the load on the source Node of Ranvier, electric and magnetic fields can exist independently of each other, and both phase and group speeds can be superluminal [11]. The speeds of potential *Shannon information* transfer from one axon to another over these transverse EM channels are slower and depend on EC channel speed.

Focusing on a single Node of Ranvier, and keeping things simple for this work, an action potential regenerates because of the transient ion flows passing through voltage-gated ion channels. Maxwell's equations show that such transient ion flows emit EM waves in the form of electrical pulses in a manner approximately like that of a pulsating dipole antenna [12]. This was the approach taken in [13, 14].

3.2. Antenna array of pulsating dipole elements

As shown in **Figure 2**, transverse EM propagation is enabled by several consecutive Nodes of Ranvier, modeled as pulsating dipole antennas. Each pulsating dipole is, in turn, derived from many filamentary currents associated with the voltage-gated ion channels. The rate and/or coding of action potentials traveling longitudinally determine whether all consecutive nodes are active or not at a given instant of time. If several nodes are active, we coherently add their

individual fields [15]. Should some consecutive nodes be active and others inactive, we refer to those that are not active as *parasitic* and the resulting array of nodes as *sparse*. Note that the pore opening times described earlier at consecutive Nodes of Ranvier are not statistically independent.

It is important to note that the rate and/or coding patterns of action potentials converts into EM near-field *spatial-temporal patterns* which impact the extracellular space of the fiber itself, and other fibers within nerve bundles and tracts. In the brain, the EM near-fields easily have reach across the span of the brain and may help to account for the activation of different regions of the brain during the execution of cognitive tasks. This type of activity is entirely missed by the fixed network studies undertaken in the Human Connectome project.

As we discuss in Section 5, the electric near-field levels measured using patch clamp techniques range from 9×10^{8} V/m at the very surface of the node of Ranvier to approximately 5×10^{3} V/m at about 1.767 millimeters from the surface. This is a field level that is measurable and biologically significant in that it can impact neighboring nerve fibers. As a rough comparison, the average electric field strength from wiring and appliances can range from 5 to 20 V/m, but is often less than 10 V/m. Let us consider near-field communication (NFC). NFC is a new short-range, standards-based wireless connectivity technology, that uses magnetic field induction to enable communication, such as Apple Pay®, between devices. Even though NFC systems operate using magnetic fields vis- à -vis electric fields, we can look at the equivalent power level, which is roughly 0.55 V/m for an NFC system. At this level, which is lower than axon interaction levels, a complex transaction between proximate devices can be completed. Further, several consecutive active Nodes of Ranvier increase the aperture and, consequently, both the reception and transmission gains and, therefore, the electric field levels, relative to a single Node of Ranvier. As discussed in Section 2, some fibers run more parallel than others because of tortuosity and other evolutionary factors; thus, we refer to the arrays as being *approximately* linear.

We have developed software for approximately linear array electric near-field modeling. The geometry for a single dipole of dimension $L \ll \lambda$ is shown in **Figure 5**. The electric field vector $\mathbf{E}(E_{\theta}, E_{r})$ is inhomogeneous. These components are not assumed to be constant over near field nerve bundle/tract fiber membranes and extracellular structures.

When $I(z)$ is the current supplied to the dipole the electric field is given by,

$$E_{\theta} = -j\frac{LI(z)\,k^{3}\sin\theta}{4\pi\omega\varepsilon}\left(\frac{1}{(kr)^{3}}+\frac{1}{(kr)^{2}}-\frac{1}{kr}\right)e^{-jkr} \tag{2}$$

$$E_{r} = -j\frac{2LI(z)\,k^{3}\cos\theta}{4\pi\omega\varepsilon}\left(\frac{1}{(kr)^{3}}+\frac{1}{(kr)^{2}}\right)e^{-jkr} \tag{3}$$

where $z = r\cos\theta$, ω is the angular frequency, and ε is the (variable) complex permittivity of the near field bundle or tract membranes and extracellular structures. Examples of values for biological tissue may be found in Ref. [16].

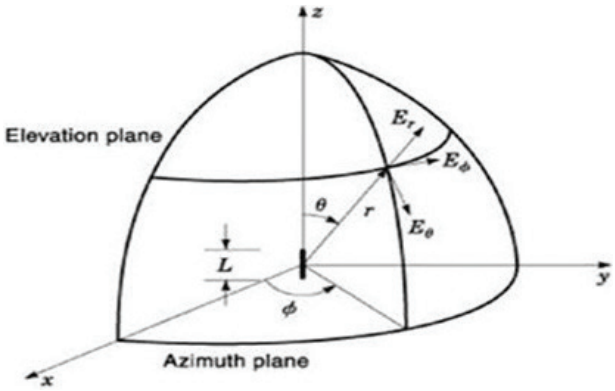

Figure 5. Electric field geometry and components.

These "biological antennae" are *electrically short*, and self and mutual impedance (coupling) effects cannot be disregarded. Note that coupling between Nodes of Ranvier is generally decreased in the tortuous case, roughly like the way crosstalk is reduced for twisted pair wires. We associate an $(N \times N)$-dimensional generalized impedance matrix $\mathbf{Z} = \mathbf{R} + j\mathbf{X}$ with an array of N Nodes of Ranvier, where the real part $\mathbf{R}$ is resistance and the imaginary part $\mathbf{X}$ is capacitive reactance.

Electrically short antennas have low radiation resistance into which it is difficult to couple significant power. On the other hand, the energy transferred to the antenna, the extracellular region, and other fibers by the reactive power flow is stored mostly in the reactive near-field. Simulations indicate that the average radiation resistance for diagonal elements of $\mathbf{R}$ is $\cong 0.02\Omega$, indicating low EM radiation efficiency, and the capacitive reactance for diagonal elements of $\mathbf{X}$ is $\cong -40\text{k}\Omega$, indicating a capacitance at a frequency of 10 kHz that is about that of closely packed fiber membrane capacitances. The fundamental research in impedance matching found in [17] helps to understand the nature of reactive power flow.

3.3. Simulation of the electric near-field

As previously mentioned, in a tightly packed bundle or tract of axons, the dimensions are such that axons are immersed in a reactive near-field. We choose an array length of $10l \cong 10\text{mm}$, where l is internode length. Our simulation therefore includes 10 Nodes of Ranvier, equally distributed over $x \in [-5, 5]$ mm, $y = 0$.

The electric field is calculated using (2) and (3) for a frequency of 10 kHz on an (x, y) axis planar rectangular surface located in the extracellular space between fibers [18]. No tortuosity is included in the simulations presented here. **Figure 6** illustrates a snapshot of the electric near-field magnitude and applies to the case where all 10 Nodes of Ranvier are concurrently active. We have also examined the phase of the near-field, the role of which is not well understood, but believed to be important in developing time synchronicity among groups of axons. This information is presented in Section 5.

Figure 7 illustrates another snapshot of the electric near-field. **Figure 7** applies to the case where 5 of the 10 Nodes of Ranvier are alternately active. As mentioned earlier, we refer to such an array of nodes as a *sparse* array. Note that **Figures 6** and **7** display substantial and clinically measurable differences in electric field signature.

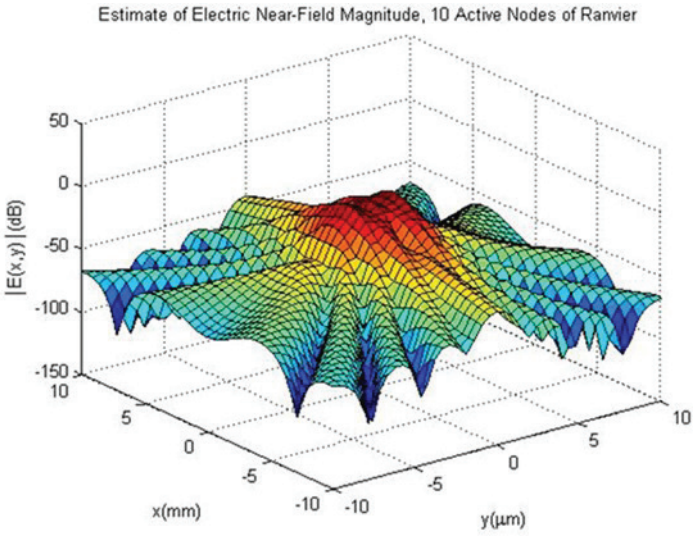

Figure 6. Extracellular region electric near-field magnitude, full Array.

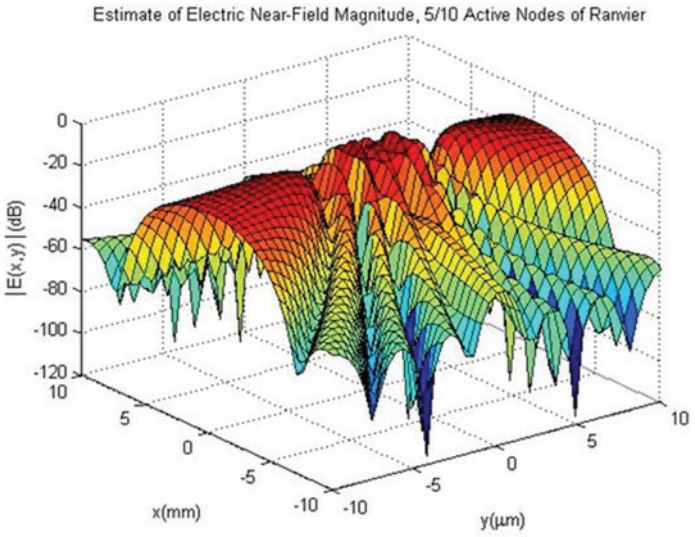

Figure 7. Extracellular region electric near-field magnitude, sparse Array.

4. Discussion of nerve fiber crosstalk modeling

Regarding the EM near-field model, if the environment consisting of tightly bundled fibers and extracellular material has any inductive properties, these can resonate out the capacitive reactance and provide a matching effect which can improve power transfer [17] for nerve fiber crosstalk. We also note that, in this case, the overall antenna array becomes more tuned or *narrowband*. Should this be the situation, the array of Nodes of Ranvier will become more sensitive to the disposition of any scattering objects in the near-field. Whether this is seen depends on the mutual impedances between the antenna and the scattering objects. Understanding these phenomena requires accurate near-field estimation methods, non-homogeneous extracellular matrix measurement and modeling, and improved understanding of electrical phenomena at biointerfaces. The random field model described in [19] is relevant here, as is the model presented in [20].

We leave the reader with several quite remarkable and game-changing thoughts regarding the potential functionality of the EM near-field. As we have been taught, the human nervous system provides extremely energy efficient, highly complex realization and control of how we sense and think. For machines designed by humans, the ideas of energy efficiency and complexity tend to be at odds, thus the question of how the nervous system *really* works has received intense scrutiny for decades. We believe that this chapter takes a first step in this understanding.

The electric near-field described in this work is generated in an energy efficient manner as the *natural by-product* of action potential generation by millions of nerve fibers. The electric near-field bathes regions of the central nervous system like the brain, optic nerves, and spinal cords, thereby enabling a wireless network that has the capability, for example, to interconnect different physical regions of the brain at instants of time as is required for the execution of many cognitive tasks. This realization leads to a change in thinking that augments the Human Connectome,[2] a fixed anatomical network, with a relatively rapid high-capacity wireless network. **Figure 8** explains this augmentation in simple terms.

On the left-half of **Figure 8** is the Human Connectome shown as a tractographic map of the nerve fiber connections in the human brain. This mapping of anatomical connections is the *fixed network* of the brain. An example of advanced work contributing to the Human Connectome is [21] which has led to a new anatomical map of the cortex based on neuroimaging. It is important to note that neuroimaging only provides indirect measurements of brain activity and that no additional modalities of measurement such as electric near-field measurements have been made in the Human Connectome project studies. On the right-half of the **Figure 8** are magnifications showing neuronal groups in two regions of the brain. There is an electric near-field between these neuronal groups, a point illustrated by the red spherical waves. These near-field waves communicate action potential activity and fine details of their regions in a bi-directional manner. This creates a wireless connection,

[2]See the Human Connectome Project, www.humanconnectomeproject.org.

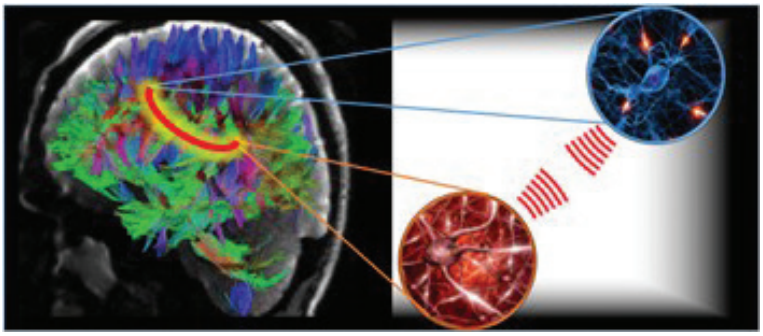

Figure 8. Electric near-field wireless network augmentation of the human Connectome.

as shown by the red loop across these brain regions in the left-half of the figure. Thus, the brain consists of a fixed network augmented by a wireless network which helps to explain how physically disparate regions of the brain connect so quickly during the execution of certain cognitive tasks.

Furthermore, as additional impetus for conducting electrical near-field measurements along with neuroimaging, neurological diseases, such as Multiple Sclerosis, Parkinson's, and Autism Spectrum Disorder, are associated with dysfunctions that are like those experienced in conventional wireless networks and electrical near-field measurements will detect neurological dysfunctions. For example, in Multiple Sclerosis, the physical change is a deterioration in the myelin sheath which insulates the nerve fiber. Damage to the myelin sheath can slow and even eliminate nerve conduction, in which case, Nodes of Ranvier do not regenerate action potentials and electric near-fields have levels that are significantly reduced, or do not occur. Our studies indicate that the electric near-field spatial-temporal signatures of healthy nerve fibers and demyelinated nerve fibers are quite different, with the radiation characteristics generally being more diffuse across both internodal and Node of Ranvier regions depending on the nature and extent of the lesions. This also suggests the possibility of a novel diagnostic tool to accompany the usual nerve conduction studies and electromyography used to assess axonal conduction speeds. This is discussed more precisely in Section 5.

Pursuing these ideas will lead to a new understanding of brain function as enabled by a highly intricate combination of fixed and wireless network connectivity [22]. This vision of brain function is indeed exciting, particularly when we recall the previous discussion that describes the EM near-field spatial directivity in terms of the data (action potentials) propagating down nerve fibers. One implication is that synchronous activity in groups of nerve fibers, which is a well-known clinically observable phenomenon, can spatially direct significant, frequency-rich electric fields toward certain target brain regions, thereby assuring that point-to-point connections are established. Thus, physically disparate brain destination regions are activated as a function of synchronous source region activity. This is a *data-driven* form of spatial connectivity.

5. Development of a wearable neurodevice

This section describes the research and development phases conducted in our laboratories for a non-invasive, wearable neurodevice that provides clinical grade information on cognitive and behavioral states of the brain and insight into impaired central nervous system neurological network dynamics. This medical device will be a game changer for the non-invasive diagnosis and treatment of a variety of neurological dysfunctions, including Multiple Sclerosis, Autism Spectrum Disorder, and Alzheimer's Disease; mental disorders; and traumatic brain and spinal cord injuries.

The material in this section provides neurobiological support for the engineering investigation presented in Section 3. To accomplish this, we model and clinically validate the origins, levels, and spatial-temporal structures of the endogenous fields under healthy and non-healthy conditions. As we have seen, the endogenous fields of the brain are characterized as low frequency electric near-fields (the electric field version of well-known NFC magnetic field technology). We believe that certain scientific and engineering challenges can be overcome because we approach this problem from a bioengineering perspective, with a team having a strong background in wireless communications; the design of "electrically short" antenna arrays; low frequency, highly sensitive receivers; and electric field transmission systems capable of a rich variety of modulation formats, along with partnerships with research laboratories, institutes and clinics dedicated to the understanding and therapeutic treatment of neurological disorders.

The overarching goals that we have set are:

1. Benchmark the Wearable Neurodevice as being clinically differentiated in both diagnostic and therapeutic efficacy and accuracy vis-à-vis fitness and lifestyle oriented wearables.[3]
2. Significantly impact chronic care management for patients with certain neurological and mental health dysfunctions.
3. Fill the enormous care gap for those with chronic neurological dysfunctions, where patients are not getting the long-term support they need and improve health outcomes for both doctors and patients.
4. Ensure patient compliance with physician treatment plans involving the Wearable Neurodevice by building useful levels of feedback into the device software.
5. As medical wearables are integrated into the chronic disease healthcare space, the biggest effect on the market will come from physicians who prescribe a Wearable Neurodevice such as that described here. Such a device will make a real difference in the lives of countless numbers of individuals afflicted with neurological dysfunctions and their families.

[3]To gauge reliability, we have run a clinical trial or benchmark against brain imaging modalities and neuromodulation devices that are the best known. Of these, there are only a small number that are US FDA-cleared and clinically-tried; therefore, the field is relatively open to the development of a device that becomes the benchmark for future device development.

5.1. Research objectives

The research objectives are as follows:

1. Conduct computer simulation of brain fiber tracts, or neurological networks, consisting of thousands of myelinated nerve fibers (axons) packed tightly together as found in several regions of the brain.
2. Establish the levels and spatial-temporal structure of the electric near-fields generated during typical physiological activity states that can be pharmacologically evoked (so that simulation and clinical data can be more easily compared).
3. Conduct a set of simulation studies for healthy conditions and for selected neurological dysfunctions. Each dysfunction will be associated with a different nerve fiber disease model, e.g., Multiple Sclerosis presents as a demyelination of the nerve fibers; this results in a change in the level and spatial-temporal structure of the resulting endogenous field.
4. Use the simulation studies, refined by the clinical data, to establish a specification for the near-field system and low frequency transceiver used to passively sense the brain's endogenous fields (diagnostic mode) and actively modulate them (therapeutic treatment mode).
5. Accomplishing these objectives requires the use of clinical data to refine simulation models. We have clinical data available to us from our partners. A carefully executed simulation study will reduce the time and risk associated with the development of a device approved for use. Future work includes the study of recommended feedback modes, personalization, and protocols for integration into existing legacy and proposed next generation healthcare systems.

5.2. Significance of the research and development

We mention three neurological dysfunctions in this chapter, because we feel that we can bring a new perspective to their diagnosis and therapeutic treatment. These diseases and their current prognoses are:

1. Multiple sclerosis (MS)—A chronic disease in which the immune system eats away at the protective coating (myelin) of nerve fibers. This disease requires a medical diagnosis. It appears that this disease cannot be cured, but treatment in the way of immunosuppressant drugs may help. These drugs have significant side effects. This disease primarily affects those in age between 14 and 60+ years.
2. Autism spectrum disorder—A chronic, serious developmental disorder that impairs the ability to communicate and interact with others. This disease requires a medical diagnosis. It appears that this disease cannot be cured, but treatment in the way of antipsychotic drugs may help. These drugs have significant side effects. This disease primarily affects those in age between 3 and 60 years.
3. Alzheimer's disease (*senile dementia*)—A chronic, progressive disease that impairs memory and other important mental functions. This disease requires a medical diagnosis. It appears

that this disease cannot be cured, but treatment in the way of cognition-enhancing medications may help. These drugs have significant side effects. This disease primarily affects those in age from 41 to 60+ years.

There are over 4 million individuals diagnosed with just these three neurological conditions each year in the US. Individuals with these diseases suffer throughout the diagnosis process, as it is many times painfully invasive, and they suffer throughout the treatment process, as the best drugs available have long lists of side effects. The significance of this research is the firm belief that a rationally designed, clinically accurate, wearable neurodevice can mitigate their suffering and allow them to take a greater role in their disease management.

We do not pretend to have cures for these neurological dysfunctions; however, we do claim to bring a new perspective to the table. This new perspective represents a paradigm shift in current thinking. Our biologically realistic preliminary *in-silico* disease models illustrate that each of the three neurological dysfunctions mentioned above is a specific impairment of the neurological networks of the brain that is reflected in specific spatial-temporal characteristics of the brain's electric near-fields. We provide a brief description and use an example to further underline the significance of the proposed research.

The most fundamental element of the neurological network is the nerve fiber, or axon. In vertebrates, many CNS nerve fibers have Oligodendrocyte derived myelin sheaths, multi-lamellar structures that wrap around the fibers, insulate them, and allow rapid information transmission over long distances with minimal energy as mentioned in Section 3. The Oligodendrocyte cells also actively promote formation of distinct membrane domains on the fiber that are not insulated. The distinct membranes of interest to us are the Nodes of Ranvier, short gaps between adjacent myelin segments as shown in **Figure 9**.

Voltage-gated ion channels are densely packed in these Nodes of Ranvier regions; key among these molecules are the Nav sodium (Na^+) channels that regenerate action potentials. Research shows that the bi-directional flow of ions through the Nav channels gives rise to electric

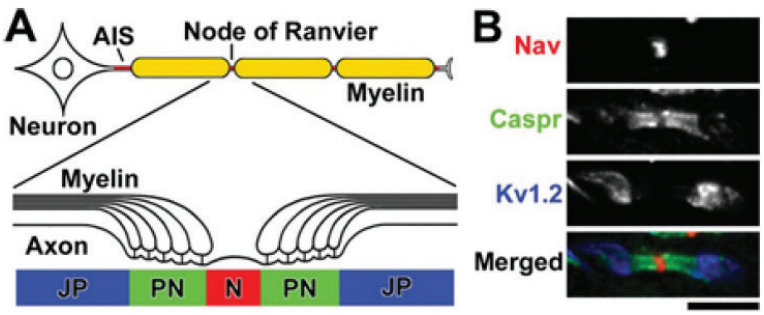

Figure 9. Molecular composition at nodes of Ranvier. (A) Diagram illustrating the structures of the myelinated nerve fiber and axonal subdomains: Axon initial segments (AIS), nodes of Ranvier (N), paranode (PN), and juxtaparanodes (JP). (B) Longitudinal sections of mouse optic nerve section immunostained with antibodies to Nav channels (nodal marker, red), Caspr (paranodal marker, green), and Kv1.2 channels (juxtaparanodal marker, blue) [23].

near-fields present in the extracellular space outside the uninsulated Nodes of Ranvier. These electric near-fields can be measured and have distinctly different spatial-temporal signatures when the Nodes of Ranvier function in healthy and unhealthy manners.

Since nodal Nav channel clusters are critical for action potential transmission, it is not surprising that changes and impairments in Nav channels are closely correlated with neurological symptoms. Furthermore, since the formation and maintenance of nodes depend on Oligodendrocyte interactions, defects in this interaction and axonal damage can disrupt nodal Nav channel clusters and consequently cause nerve conduction failure. There is a growing body of evidence for a pathogenic role of nodal dysfunction and/or disruption during neurological diseases. Dysfunction or disruption of Nodes of Ranvier are a primary focus for understanding the pathophysiology of neurological diseases. Our work is based on this evidence and our preliminary models which illustrate that the electric near-fields generated at impaired Nodes of Ranvier have spatial-temporal signatures which differ considerably from healthy profiles and that these signatures can be accurately classified as to the specific type of neurological dysfunction.

5.3. Research plan and technical approach

To fully understand our approach and the associated scientific and engineering challenges, we provide a brief introduction to the way various measurements are currently made. The study of neurological network connectivity, physiology, and pathology, is carried out using both invasive *in vivo* and *in vitro* methods and non-invasive modalities [24]. Invasive modalities range from sharp-glass and patch-clamp electrodes to planar electrodes (MEA) and FET arrays to recently developed intracellular recording nano- and micro-devices. These modalities generally measure what is known as the local field potential (LFP), an electrophysiological signal generated by the summed electric current flowing from a relatively localized population of neurons within a volume of neuronal tissue. Voltage is produced across the local extracellular space by action potentials in neurons in the volume and varies primarily because of synaptic activity.

What we would call "semi-invasive" modalities include optical imaging and stimulation technologies using either fluorescent indicators or genetically encoded molecular probes and the electrocorticogram (EcoG). Perhaps the most common non-invasive modality is the electroencephalogram (EEG). LFP signals differ from EEG and EcoG signals, principally because LFP signals are recorded in depth, from within deep brain structures, as opposed to at the surface of the scalp using macro-electrodes and at the surface of the brain using large subdural electrodes, respectively.

There are three advantages and considerations from the standpoints of diagnosis and therapeutic treatment of invasively measuring LPF signals vis-à-vis EEG signals:

1. They are representative of the activity of relatively localized populations of neurons [25], as opposed to characterizing the average activity of much larger populations [26].
2. They are not subject to the extensive filtering, diffusion, and distortion that EEG signals are because of propagation through many layers of strongly heterogeneous media [27].

3. It is believed that LFP measurements are correlated with normal and pathological excitable cell tissue operation [28–31].

From this discussion, we see that it would be desirable to develop a means of measuring LFP signals or other, even more relevant localized, non-distorted indicators, in a *non-invasive* manner for diagnostic purposes. Accomplishing this will require innovative technology for passively accessing localized populations of neurons from the level of the scalp.

Research Objective 1: Conduct computer simulation of brain fiber tracts, or neurological networks, consisting of thousands of myelinated nerve fibers (axons) packed tightly together as found in several regions of the brain.

Research Plan: There are two fundamental physical fields of the brain, the vector electric field $\mathbf{E}(\mathbf{r}, t)$(V/m) and the vector magnetic field $\mathbf{B}(\mathbf{r}, t)$(V-s/m^2). Our focus is on the vector electric field. The vector electric field can be Helmholtz decomposed into the gradient of a scalar potential $\Phi(\mathbf{r}, t)$ which can be measured with appropriate sensing technology at the spatial resolution of tissue fine structure [32, 33]. Our hypothesis is that membrane-related sources, specifically the Nodes of Ranvier, through their transmembrane currents and supporting systems of voltage-gated ion channels, act as electromagnetic field sources that contribute to the spatial-temporal structure of $\mathbf{E}(\mathbf{r}, t)$ and, consequently, $\Phi(\mathbf{r}, t)$. These fundamental fields then, in turn, mediate LFP expression, which is essentially a filtered, distorted, and spatially averaged version of $\Phi(\mathbf{r}, t)$. As described in recent work [34], in the neurological diseases involving myelinated nerve fibers (all those mentioned in this proposal and more), altered functions of nodal Nav channels and juxtaparanodal Kv channels lead to conduction failure. Indeed, the disruption of the molecular organization, altered ion channel expression, function, location, and/or density at the nodes of Ranvier are emerging as key players in the pathophysiology of neurological disorders [35].

We have developed our neurological network simulation software to accommodate thousands of myelinated nerve fibers tightly packed into fiber tracts. The simulation environment is COMSOL Multiphysics, a widely-accepted platform for coupled or Multiphysics phenomena executed within our CIRCE 6000 core computing cluster environment. Not only will this simulation be unique in its dimension (number of nerve fibers) and attention to fiber cross talk, a primary phenomenon in shaping electric field spatial-temporal structure [13], COMSOL Desktop will be used to ensure cross-disciplinary product development. Our software computing laboratory is fully integrated with the wet laboratory, so that *in vitro* model and parameter knowledge can be immediately transferred to the *in-silico* model development. This is a particularly important factor for ensuring that the biologically realistic nerve fiber functional deficit (disease) models needed for each type of neurological disorder are reflected in a biologically realistic manner in the *in-silico* model development.

In this work, we focus on deficit models associated with the Nodes of Ranvier. Dysfunction and/or disruption of the Nodes of Ranvier play significant roles in the development of neurological symptoms. Voltage-gated ion channel functions are disturbed by genetic mutations and by toxins. Autoimmunity against molecules at and near Nodes of Ranvier, myelin defects, and nerve fiber damage alter the localization and expression of ion channels and disrupt nerve fiber-Oligodendrocyte interactions. Our deficit models will be fully integrated with Hodgkin-Huxley

models to account for how disease impacts both the electrophysiological passive and active regions of nerve fibers. **Figure 10** depicts the simulation for a disease model.

Research Objective 2: Establish the levels and spatial-temporal structure of the electric near-fields generated during typical physiological activity states that can be pharmacologically evoked (so that simulation and clinical data can be more easily compared).

Research Plan: With the nerve tract geometry set up, we treat each Node of Ranvier as the initiation site of an electric near-field[4] component. As described in Section 3, we mathematically model the electric near-field generated by the ensemble of voltage-gated ion channels distributed around a Node of Ranvier and then extend our development to the consecutive Nodes of Ranvier on a single nerve fiber. If we model each Node of Ranvier as a cylindrical electrical field source, it is then natural to model several consecutive Nodes of Ranvier as an approximately linear antenna with cylindrical elements. Note that the radiation characteristics of this linear antenna will depend on which Nodes of Ranvier are active or parasitic; therefore, the radiation characteristics are said to be data driven [13].

The resulting field from a small number of neighboring nerve fibers is what we referred to earlier as the endogenous field. This field's spatial-temporal signature is representative of the health of a localized population of nerve fibers in specific regions of the brain. Using the mathematical development, we then use COMSOL Desktop to create simulation software which we refine in parallel with ongoing wet lab studies. To test the validity of this approach, we have carried out a preliminary simulation of the electric near-field generated by a ring of ion channels in a Node of Ranvier. For a single ion channel (pore), clinical patch clamp measurements provide the information shown in **Figures 3** and **4**, e.g., pore current flow lasts several milliseconds and peaks at 0.5 pA.

It is important to note that the electric field generated by the pore ion flow is not a single frequency field, but a field consisting of many frequencies associated with the pore rather abruptly opening and closing. Adopting a criterion that the significant band of frequencies are those that are no more than 30 dB down from the maximum, we see that the significant band of frequencies goes up to at least 50 kHz. This is a startling result, as research on nerve fibers is commonly conducted below 1 kHz. The electric field is characterized as a multiple frequency, reactive near-field [13, 36]. Our preliminary analysis for a ring of ion pores at a node of Ranvier partially follows the theory presented in [37] and employs the geometry shown in **Figure 5**. A snapshot of the time-varying electric field is shown in **Figure 11**.

From **Figure 11** and the associated calculations, the electric near-field level is approximately 9×10^8 V/m at the very surface of the Node of Ranvier and approximately 5×10^3 V/m at about 1.767 millimeters from the surface. This is a field level that is biologically significant in that it can

[4]More precisely, we treat each voltage-gated ion channel (pore) as the initiation site of an electric near-field component. Voltage-gated ion channels are found in greatest density along myelinated nerve fibers at the nodes of Ranvier. For example, Na + channel density is ~2000 channels/μm at the nodes of Ranvier. They directionally propagate electrical signals. Voltage-gated ion-channels specific to sodium (Na), potassium (K), calcium (Ca), and chloride (Cl) ions have been identified. The opening and closing of the channels is best modeled as a stochastic process triggered by changing ion concentration, and hence charge gradient, between the sides of the cell membrane.

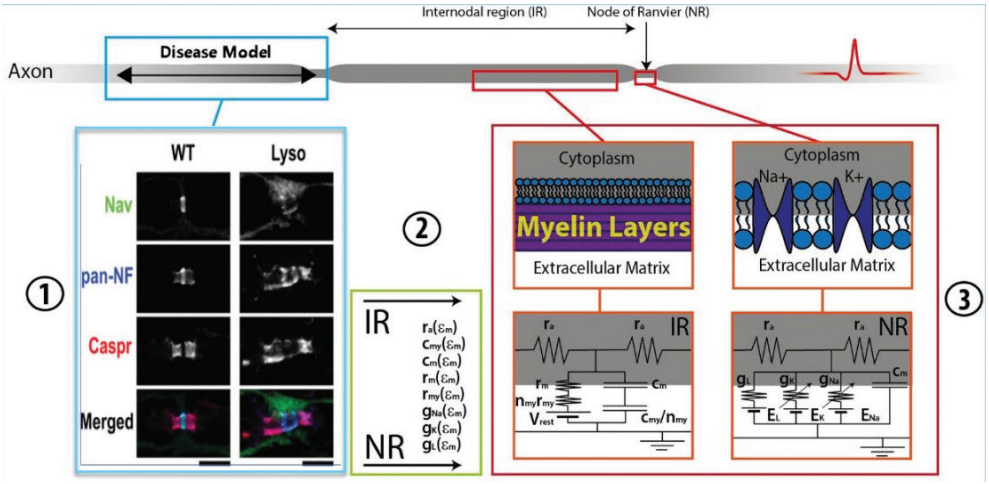

Figure 10. Schematic plan for the simulation. (1) the disease model. Shown is one example of the impact of demyelination in longitudinal sections of mouse nerves immunostained as indicated. Nerve fibers run horizontally. Scale bars = 10 microns. WT denotes wild-type; Lyso denotes lysolecithin. Note the anti-pan-NF antibodies display both nodal NF186 (strong signal colocalized with Nav channel staining) and paranodal NF155 (relatively weak signal colocalized with Caspr staining). Demyelination model induced by intraneural injection of lysolecithin (7 days after injection). Nodal cluster of Nav channel and NF186 is remarkably dispersed. (2) the coupling model reflects the disease model into the nerve fiber model as a set of altered parameters. (3) the nerve fiber model for both the Internodal regions (IR) and the nodes of Ranvier (NR) [38].

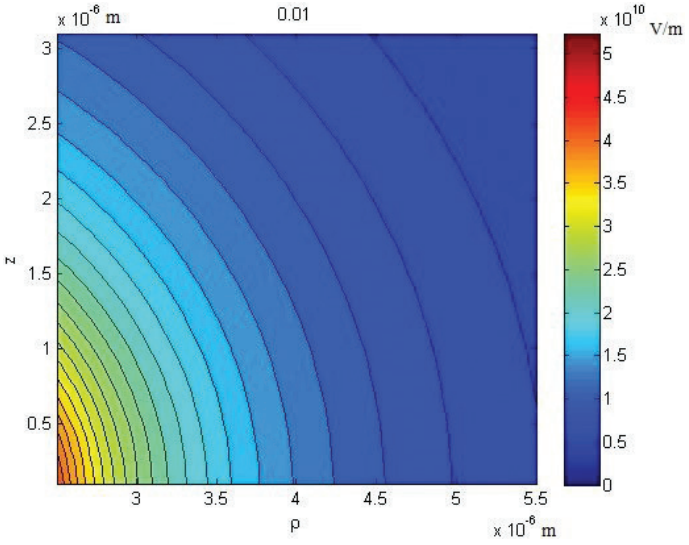

Figure 11. Snapshot of the time-varying electric near-field generated due to a ring of voltage-gated ion channels in a node of Ranvier. Video of time-varying field and clinical measurements available from the author.

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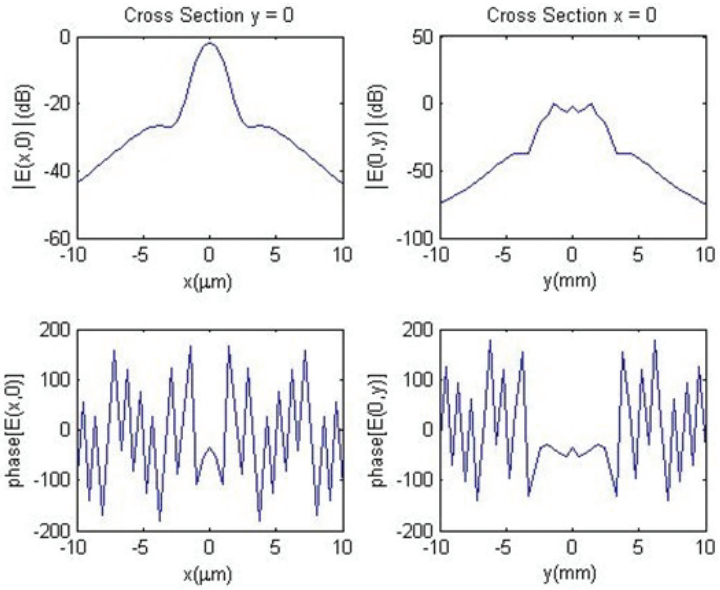

Figure 12. Cross-sectional plots of magnitude and phase of electric near-field at 10 kHz. Healthy nerve fiber with 10 active nodes of Ranvier.

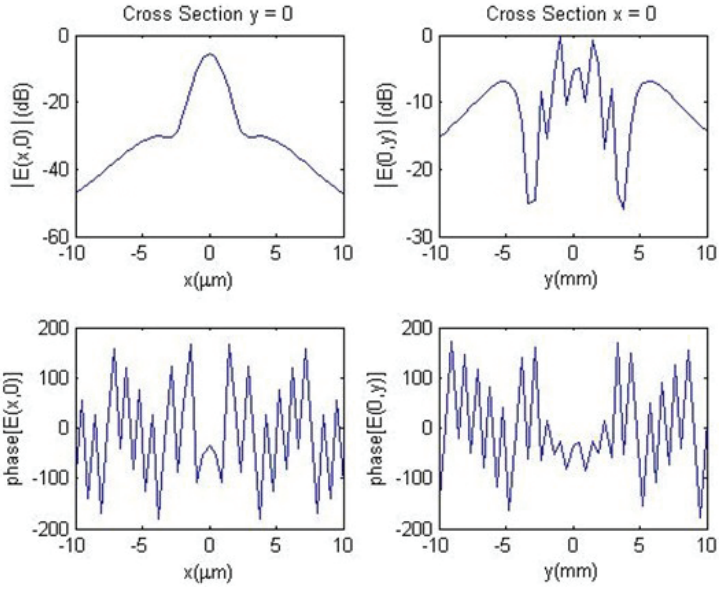

Figure 13. Cross-sectional plots of magnitude and phase of electric near-field at 10 kHz. Unhealthy nerve fiber with 50% nodal disruption. The unhealthy nerve fiber model is consistent with a progression of multiple sclerosis.

impact neighboring nerve fibers. This preliminary study indicates that this objective has merit and establishes the frequency range and range of levels expected for the electric near-field.

Research Objective 3: Conduct a set of simulation studies for healthy conditions and for selected neurological dysfunctions. Each dysfunction is associated with a different nerve fiber disease model, e.g., Multiple Sclerosis presents as a demyelination of the nerve fibers and as a change in the level and spatial-temporal structure of the resulting endogenous field.

Research Plan: Our selected neurological dysfunctions include Multiple Sclerosis (MS), Autism Spectrum Disorder (ASD), and Alzheimer's Disease, as mentioned earlier. These are dysfunctions that can be traced primarily to either the balance of excitatory and inhibitory nerve fibers or nodal demyelination in the central nervous system. Each dysfunction can be associated with a different nerve fiber disease model as described in Research Objective 1. To meet this research objective, we are concerned with the separability of spatial-temporal electric near-field signatures, or patterns, associated with healthy and non-healthy conditions. Note that the separability of patterns is exhibited by measurable differences in electric near-field signatures, which, in turn, are associated with time and frequency dynamics of localized, small nerve fiber populations. Here, frequency (up to 50 kHz, as described earlier) is a valuable parameter but unavailable to the EEG modality.[5]

Consider an experiment to demonstrate the separability of spatial-temporal electric near-field signatures when Nodes of Ranvier are disrupted [39–42]. For more detailed information about disruption of axon-Oligodendrocyte interaction in autoimmune diseases, see [43, 44]. In a tightly packed tract of nerve fibers, the dimensions are such that axons are mutually immersed in a reactive near-field. To examine the near-field characteristics, we choose an array length of $10\ell \approx 10$ mm, where ℓ is internodal length. Our simulation includes 10 nodes of Ranvier, equally distributed over $x \in [-5, 5]$ mm, $y = 0$.

The electric near-field is calculated for a frequency of 10 kHz on an (x, y) axis planar rectangular surface located in the extracellular space between fibers [18]. **Figure 12** and **13** shows two cross sections of the magnitude and phase of the electric near-field for a healthy fiber and for a fiber where 50% of the nodes of Ranvier are disrupted, respectively. Note that the healthy and unhealthy nerve fibers display significant differences in electric field magnitude and phase characteristics and spatial extent.

Clearly, diagnosis and therapeutic treatment requires both position accuracy and spatial resolution within the brain. Our vision for this is a cap of flexible electronics sensors with time-delay electronics under control of a smart phone application that can facilitate beam formation to allow for passive listening and active therapeutic treatment of specific regions within the brain.

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[5]Among the different brain imaging techniques, the EEG is classically considered as having an excellent temporal resolution, but a poor spatial one. We argue that the actual temporal resolution of conventional (scalp potentials) EEG is overestimated, and that volume conduction, the main cause of the poor spatial resolution of EEG, also distorts the recovered time course of the underlying sources at scalp level, and hence degrades the actual temporal resolution of EEG. A few facts about the temporal and spatial resolution of EEG: millisecond temporal resolution; localization of neural generators is complicated and usually not carried out; different tissues and the skull differ in their conductivity, and electric potentials do not pass through these structures undistorted; localization requires realistic head models. This last point is important and useful regarding the proposed wearable neurodevice.

Since we are dealing with near-field phenomena, resolution significantly better than $\lambda/2$ is possible by accessing the evanescent modes of the spatial spectrum. We believe that utilizing near-field properties plus a head model will provide unprecedented spatial positioning capability.

It is important to note that in addition to neurological disease, traumatic injuries in the CNS may involve disruption of nodes. In an experimental model for spinal cord compression, exposure of juxtaparanodal Kv1.2 channels with accompanying myelin retraction at the nodes contributed to the induction of conduction block [22, 45]. In an animal model of traumatic diffuse brain axonal injury produced by fluid percussion insult, calpain-mediated proteolysis of cytoskeletal and scaffolding proteins, ankyrin-G at nodes and αII-spectrin at paranodes, was associated with nodal damage, suggesting a possible contribution of nodal disruption to the complex mechanisms of traumatic brain injury [46].

These findings suggest that the wearable neurodevice can be designed to also monitor and therapeutically treat individuals that suffer insults to the spinal cord and brain. The possibilities for a device of this type are extraordinary. The Wearable Neurodevice can be a game changer in the mental health space for both diagnosis and therapeutic treatment [47, 48].

Research Objective 4: Use the simulation studies, refined by the clinical data, to establish a specification for the near-field antenna array system and low frequency transceiver used to passively sense the brain's endogenous fields and to actively modulate them.

Research Plan: The progress toward this research objective will evolve as we continue to experiment and explore and explain new concepts; however, to diagnose and therapeutically treat neurological dysfunctions of the type described in this proposal, we need a wearable neurodevice that meets exceptionally rigorous specifications. Our only interest is in non-invasive methods and technologies. We have worked on an initial set of specifications which we will detail here and refine as research progresses. The specifications include, but are not limited to, the following:

1. A passive listening capability and an active neuromodulation capability that allows recording and stimulation of small populations of neuronal targets.
2. Receiving sensitivity outside the human body consistent with neuron physiological parameters, e.g.,
   a. Transmembrane potentials in the range [−80,30] mV
   b. Subthreshold potentials in the range [±0.5,10] mV with rapid rise times (<1 ms) and slow decay times (100–1000 ms).
   c. Membrane oscillations in the range of ±5 mV at frequencies of 1–50 Hz.
3. Passive/active spatial resolution goal of 1 cubic nanometer for frequencies in the range 10 Hz to 10 kHz.

These specifications represent an unprecedented and extraordinarily exciting challenge to the fields of science and engineering.

6. Conclusions

Several conclusions can be drawn from this work:

(1) Neuroimaging principally drives current models of neurological networks through anatomical discovery, and it is known that the models are deficient in explaining all aspects of cognition and dysfunction. This deficiency is particularly acute in the cases of brain enhancement, Multiple Sclerosis and Autism Spectrum Disorder, examples where we believe that the wireless neurological networking described here plays a primary role.

(2) We have presented a wireless neurological networking model that augments current models and is based on conventional electrical engineering principles. The fundamental principle that is at play is that of crosstalk between nerve fibers. *In silico* and initial *in vivo* experiments carried out at the University of South Florida Bioengineering Laboratories and the Global Center for Neurological Networks indicates that this crosstalk may enable communication, cooperation, and/or competition among nerve fibers and that the electric near-field level is approximately 5×10^{10} V/m at the very surface of an active Node of Ranvier. This level is orders of magnitude higher than the equivalent electric field level for the NFC Apple Pay® system and other contactless smart chips and cards which clearly accomplish complex information transfers. The electric near-field level increases when several consecutive active Nodes of Ranvier are active and when neural oscillations and nerve fiber synchronicity occur.

(3) As a matter of interest, the wireless neurological networking model can be cast in the form of a massive biological multiple input multiple output (MIMO) network [49] that permeates the brain and nerve bundles/tracts and explains cognition and dysfunction in terms of local and global effects and dynamics. Defining this model in detail is the target of future research.

Note that the spatial-temporal structure of the electric near-field depends on whether healthy or unhealthy, for example, demyelinated, conditions are present and may contribute to these conditions. Healthy conditions are associated with only the unshielded Nodes of Ranvier having the capacity to create electric near-fields in extracellular space; whereas, unhealthy conditions as clinically understood in Multiple Sclerosis, for example, present as demyelinated fibers which provide many more opportunities between Nodes of Ranvier for leakage and electric near-field activity as voltage gated ion channels migrate to these positions [50].

In short, the electric near-field spatial-temporal signatures are different for healthy and unhealthy conditions, as we have verified by simulation. Understanding and measuring electric near-field signatures could serve as a diagnostic tool, on one hand, and as an endogenous field, on the other hand, which could presumably be manipulated for therapeutic purposes by the application of exogenous neurostimulation devices. At present, there exists no rational design for neurostimulation devices and emitted waveforms based on endogenous field structure. This work represents one of the first steps toward such a rational design of non-invasive devices.

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