Synchronization in FitzHugh-Nagumo Neuronal Networks

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Abstract

Some of the most interesting neuroscience problems, fundamental to the field, are inherently mathematical. Central problems include understanding how cellular and network level mechanics of the peripheral and central nervous system coordinate to encode, process, and learn information, as well as how the Central Nervous System (CNS) is able to synchronize brain-wide neural activity. Answering these questions requires understanding how neuronal circuits react to stimuli and interact with one another to process information specific to their roles within a network. To simulate these intercellular dynamics, FitzHugh-Nagumo neurons were connected through incoming and outgoing voltage currents to form dynamic networks. External stimuli consisting of both excitatory and inhibitory signals were sent through these networks. As a network's connectivity coefficient increased, neurons began to synchronize. In some cases, neuronal activity segregated and competed so that neither signal was able to dominate the artificial network – underlining the importance of the relationship between signal and architecture in functional, biological circuits. Biological components which have been implicated in network synchronization, and how they could be mathematically implemented in future network simulations, were discussed.

Introduction

A Biological Background to Mathematical Methods

The neuron is a type of electrically excitable cell common to the CNS, which includes the brain, spinal cord, and the peripheral nervous system (PNS). As seen in Figure 1 below, neurons consist of a cell body from which neuro-transmitter receptive terminals called dendrites protrude. A large tail-like structure called the axon trails off the cell body and eventually splits off into multiple, fine endings called axon terminals. A preceding neuron's axon terminal will connect up to the dendrites of multiple neighboring neurons. The individual connections that form between the axon terminals and dendrites make up what is known as the synaptic cleft. The synaptic cleft is essentially a small gap junction through which chemical signals called neuro-transmitters flow from the presynaptic neuron's terminal to the receiving post synaptic neuron's dendrite.[21]

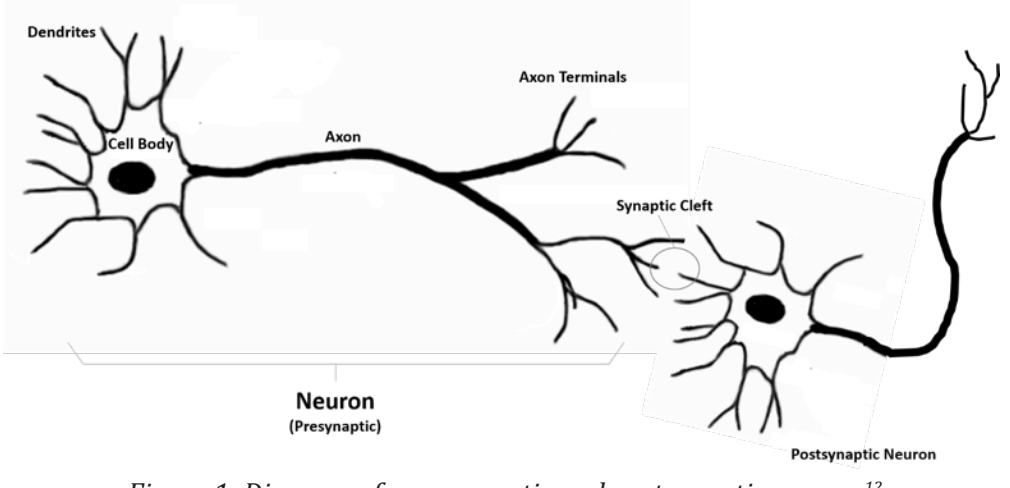

Figure 1: Diagram of a presynaptic and postsynaptic neuron.[12]

A neuron becomes "excited," or "activated," when it receives incoming neuro-transmitters from other activated neurons connected to its dendrites. The excited cell's membrane will depolarize and cause an electrical signal called an action potential to travel down the length of its axon to the axonal terminals. Once activated by the electrical signal, mechanisms in the axonal terminals will release neuro-transmitters into the synaptic clefts formed with other neurons, thereby, exciting the

neuron's neighbors as well.[21 3]

In this way, neurons connect and form an active and dynamic network amongst themselves. Neuronal networks encode and process information, such as external stimuli from an animal's environment, which can ultimately incite a motor response from the animal. Alternatively, some neurons, known as inhibitory neurons, release neurotransmitters which compete with excitatory neuro-transmitter signals from other neurons. At times, such inhibitory signals will prevent the post synaptic receiving neuron from firing. This competition between inhibitory and excitatory signals is crucial to the network's ability to encode and distribute such information carrying signals to areas of the network meant to receive and process them.[3 16 17]

As the CNS develops, synaptic connections between neurons are selectively pruned to improve efficiency. Synaptic pruning is vital to developing distinctive neural circuits which process very specific kinds of information.[15] Neural circuits are essentially substructures of the neuronal network, comprised of neurons that form specialized architectures designed to process very specific types of information. The startle circuit, for example, has been studied across a sweeping range of diverse animal species and is responsible for fast motor response in the presence of an external threat. Stimulation of these circuits in organisms with smaller, more tractable neuron connectomes are known to lead to very predictable responses such as omega turns in the Caenorhabditis Elegans, a species of nematode.[4]

One can easily extrapolate that larger, more sophisticated neuron connectomes, such as the human CNS, would exhibit a broader range of circuitry roles, such as visual processing, object recognition, and the experience of conscious thought. When an animal possessing a connectome of such magnitude, such as a vertebrate, receives an external stimuli, the neuron connectome is able to compress such high dimensional information coming in from sensory neurons throughout the body into the spinal cord. The compressed information then fans out into the vertebrate cortex for processing, ultimately eliciting a motor response signal which is compressed back into the spinal cord and fanned back out into the animal's body, activating it's muscles in a coordinated response. The nervous system's impressive feat of dimensionality reduction is key to its information processing abilities. Such

properties in combination with the electrical and chemical dynamics of connected neurons make the nervous system a mathematically interesting subject to study. Importantly, integration of Mathematics and Neuroscience are necessary to illuminating how biological components of the nervous system process information in tandem. More specifically, understanding the functionality of, and the dynamics between, neuronal circuits is key to understanding the brain's functionality and has since inspired collaborations between mathematicians and scientists, leading to mathematical neuron models and studies on the dynamics of their respective networks.[2 17]

Mathematical Models of Neurons

In 1963 Alan Lloyd Hodgkin and Andrew Fielding Huxley received the Nobel Prize in Physiology and Medicine for a series of papers they published on the ionic mechanism underlying the excitation and inhibition of neuron membranes. Their work, considered one of the great achievements of 20th century biophysics, culminated in a biophysical model, which captures action potential dynamics in neurons and has since transformed the field of mathematical and computational neuroscience. The action potential captured in their neuron model, a 4x4 system of nonlinear differential equations, is driven by the flow of ions (neuro-transmitters) across ion gates in the cell's membrane. These ion gates, known as voltage gated channels, select for specific ions: sodium (Na+), potassium (K+), and chloride anions (Cl-). It should be noted that chloride anions influence the voltage dynamics of potassium and sodium, but do not actually pass through the cell's membrane themselves. The specific alpha and beta functions in the equations of the 4x4 system were derived from experimental data the team collected on ion dynamics which generated action potentials that propagated down large nerve axons in a deceased giant squid. Applying an external stimulus I0 to the model elicits characteristic spiking behavior consistent with what was observed in the giant squid axons.[10 19]

FITZHUGH-NAGUMO NEURONAL NETWORKS

$$C_M \frac{dV}{dt} = -\bar{g}_K N^4 (V - V_K) - \bar{g}_{Na} M^3 H (V - V_{Na}) - \bar{g}_L (V - V_L) + I_0$$

$$\frac{dM}{dt} = \alpha_M (1 - M) - \beta_M M$$

$$\frac{dN}{dt} = \alpha_N (1 - N) - \beta_N N$$

$$\frac{dH}{dt} = \alpha_H (1 - H) - \beta_H H$$

V(t) is the voltage of the action potential.
Voltage gated variables potassium, N(t), and sodum, M(t) and H(t) drive the action potential.
I(0) is an externally applied current to the cell.

Parameters for the first equation are: g Na = 120, g K = 36, g L = 0.3, VNa = 115, VK = -12, and VL = 10.6

$$\alpha_M = 0.1 \frac{25 - V}{\exp\left(\frac{25 - V}{10}\right) - 1} \qquad \beta_M = 4 \exp\left(\frac{-V}{18}\right)$$

$$\alpha_H = 0.7 \exp\left(\frac{-V}{20}\right) \qquad \beta_H = \frac{1}{\exp\left(\frac{30 - V}{10}\right) + 1}$$

$$\alpha_N = 0.1 \frac{10 - V}{\exp\left(\frac{10 - V}{10}\right) - 1} \qquad \beta_N = 0.125 \exp\left(\frac{-V}{80}\right)$$

The Hodgkin-Huxley model established neuron dynamics, giving way to the meteoric expansion of the fields of mathematical and computational neuroscience. Since its advent, a number of additional models have been developed from the Hodgkin-Huxley model, including the addition of slower calcium dynamics, which allows for multiple timescales and reductions such as the FitzHugh-Nagumo Model.[10 19]

Richard FitzHugh was able to capture neuron dynamics in the Hodgkin-Huxley model while eliminating dependence on the driving electrochemical properties of calcium and potassium ion flows by modifying the Van der Pol model, an oscillator with nonlinear damping. This simplification allowed him to reduce his model to a two dimensional system. The lower dimensionality of the FitzHugh-Nagumo system, in comparison to the 4x4 Hodgkin-Huxley model, eases observation of the

$$\frac{dV}{dt} = V(a - V)(V - 1) - W + I_0$$

$$\frac{dW}{dt} = bV - cW$$

$$0 < a < 1$$

V(t) is the voltage dynamics
W(t) models the refractory period of the neuron
I(0) is an externally applied current to the cell. I(0) represents stimulus/action potential(s) of any connected presynaptic neuron(s).

system's solution and as a result, facilitates the study of dynamics of networks of neurons.[6 10]

Figure 2, shown below, depicts the action potentials of a presynaptic FItzHugh-Nagumo neuron driving the action potentials of a second, post synaptic FitzHugh-Nagumo neuron. When the neuron spike train passes above the threshold 0.8V, the neuron is considered to have spiked, or activated.

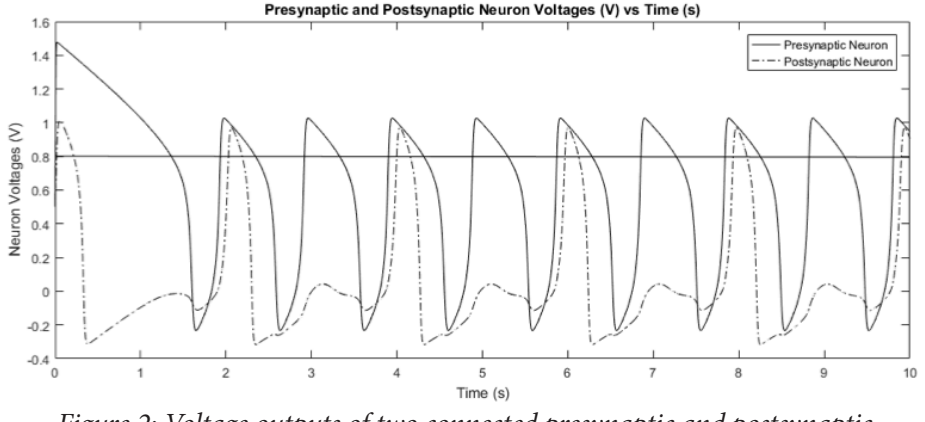

Figure 2: Voltage outputs of two connected presynaptic and postsynaptic FitzHugh-Nagumo Neurons

Methods

FitzHugh-Nagumo neurons were connected together to form a

network of ten neurons in total. Two of these neurons received external input signals. In the first experiment, the two input signals were identical and excitatory (non-negative). In the second experiment, the signals were identical in magnitude, however, one signal was inhibitory (non-positive), while the other was excitatory (non-negative).

[1 0 1 0]

Figure 3: Example of a vector of four nonnegative elements in total

External input stimuli (input signals) were implemented by shifting left-to-right through the elements of a vector. The duration of the total neuron firing for a given simulation was divided into equal intervals of time. As each time interval passed, the input signal value changed to the next element in the vector. As an example using the vector above, the input signal value during the first time interval was 1, during the second time interval the signal value would have been 0, and so on. This changing input signal value is represented by the *I(0)* term in the first FitzHugh-Nagumo equation.

In addition to containing the signal value (if the neuron was one of two receiving an external input signal), the *I(0)* term also serves as a means to connect neurons together into a network. Recall that the *I(0)* term represents all currents coming into a particular neuron – this includes possible external input stimuli and the output of all presynaptic neurons connecting to its dendrites. The total input to a neuron from its neighbors can be thought of as a weighted sum.

Each presynaptic neuron is represented as the product of its voltage output V(t) and its respective "connectivity strength". The sum of these products is a scalar representation of all currents flowing into the post synaptic neuron. Therefore, *I(0)* is the sum of any present external input signals and the incoming weighted voltages from its neighboring presynaptic neurons.

An adjacency matrix, or connectivity matrix, was used to keep

Sending Neuron (presynaptic)

Receiving Neuron (postsynaptic)

	1	2	3
1	0	−0.2700	0
2	0.2145	0	−3.668
3	0	0	0

Figure 4: Example of connectivity matrix A

Figure 5: Graph illustrating neuron connectivity given by the above example matrix

track of the connectivity strengths between all ten of the neurons in the network. An example of a connectivity matrix and its physical interpretation is given above for three neurons. Each grey circle represents a neuron, whereas the arrows represent connections, and thereby communication, between the neurons. Notice that neuron 3 connects to neuron 2, but neuron 2 does not connect to neuron 3. In this case, communication is one-directional, and only flows from neuron 3 to 2. Likewise, neurons 1 and 2 both connect to one another. As a final example, neurons 3 and 1 do not communicate at all. Neurons are not considered to communicate with themselves. In the connectivity matrix A, each column is associated with a particular neuron and the elements of each column represent its outgoing-connections to every other neuron in the network. The rows represent each neuron and their respective incoming connections. Notice that the entry in row 1, column 1 is zero. This is because neuron 1 does not connect to itself. In a similar fashion, all entries down the diagonal are also zero. As an example, the connectivity strength of the connection from neuron 1 to neuron 2 is 0.2145. The connectivity strength from neuron 2 to neuron 1 is -0.27.[11]

The dot product is taken between a vector containing output voltages (V(t)) from each of the neurons and a particular neuron's row in the adjacency matrix to obtain the weighted sum mentioned earlier. The 10x10 adjacency matrix in this experiment was randomized and had zeros as its diagonal entries. In both experiments, the connectivity matrix was scaled by a connectivity coefficient, c, set for the first run at 0.05 and the second at 0.2. Increasing c in the second run represents increasing the connectivity strengths of neurons in the matrix.

A Runge-Kutta based solver with variable time step was implemented to approximate the voltages V(t). Runge-Kutta methods are a special variation of Euler's method, popularized for their improved accuracy and stability. Euler's Method uses the definition of a derivative to approximate a function's slope and subsequent values as its trajectory

changes through time. It essentially starts with an initial function value at time t=0 and bootstraps its way to the next value, and subsequent values of a function. A subsequent function value is obtained by adding the product of the function's slope approximation and magnitude of the time step to the currently known function value, i.e. the initial value in the case of t=0. Runge-Kutta methods vary from Euler's in that they employ several approximations of a function's slope during a single time step, rather than only one.[1 10]

Results and Discussion

As the matrix connectivity coefficient, c, increases, network neurons begin to synchronize with one another and the external input signals. Neurons lose their traditional post-synaptic spiking pattern shape seen in Figure 2 and Figure 6, and more closely resemble the non-organic shapes of the artificial external input signal as demonstrated in Figure 7. As the neurons synchronize with one another, distinctive bands of synchronized spiking begin to occur throughout the spike trains in Figure 7. When a spike train passes the threshold of 0.8V, the column corresponding to the activated neuron lights up in figures 7 and 8. As long as the spike train remains above the threshold of 0.8V, the column will remain lit. Figures 7 and 8 provide an alternative means of observing synchronization between all ten neurons in the network. In

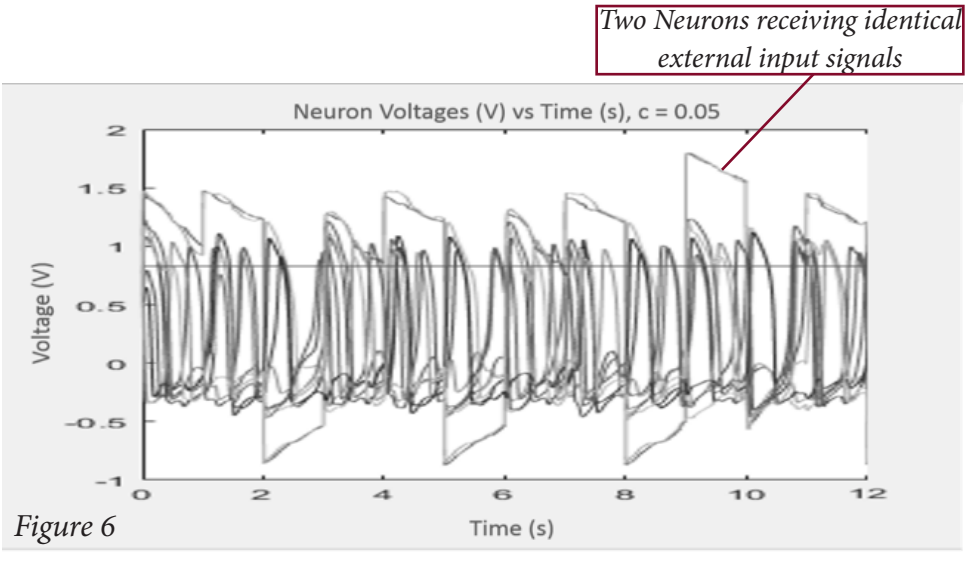

Figure 6

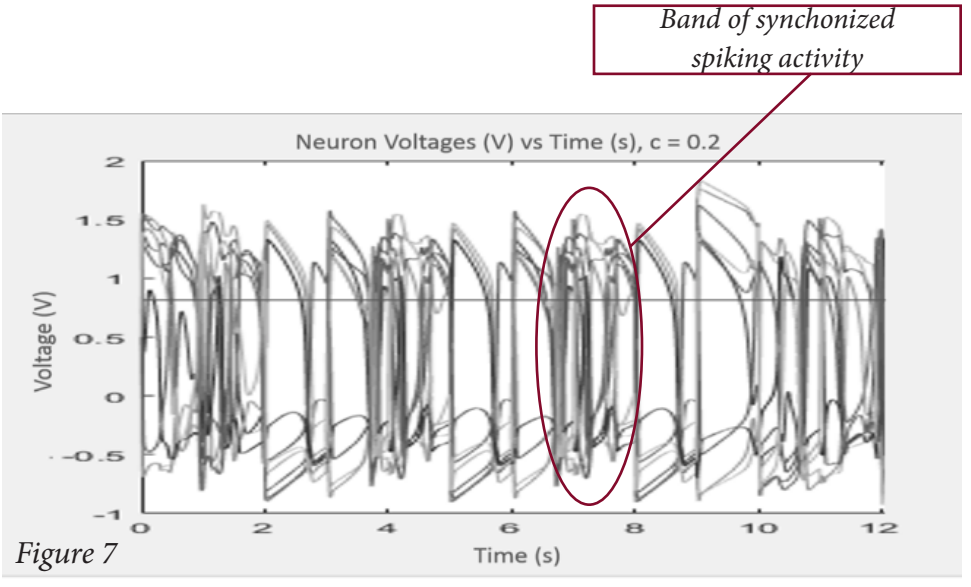

Figure 7

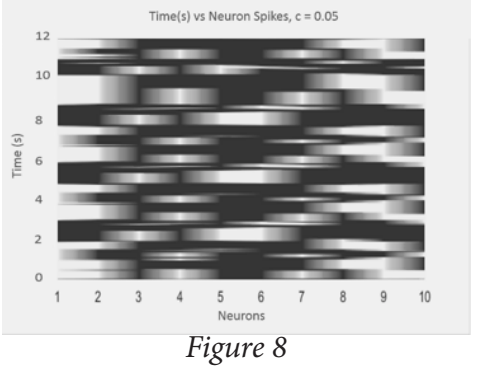

Figure 8

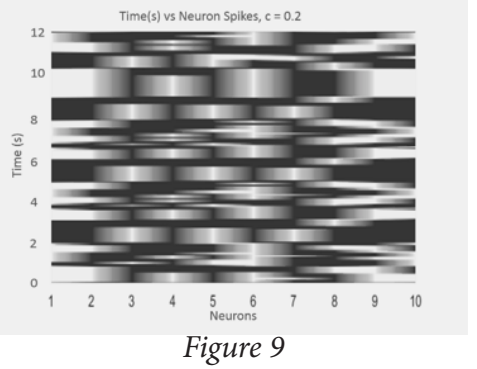

Figure 9

these, and the following illustrations, neurons 1 and 6 are receiving the external stimuli.

When neurons receiving external stimuli are fed opposing signals of equal magnitude but opposite sign, two things take place. Like figure 7, bands of synchronization begin to emerge, however, in the case of figure 10, the combination of the network's particular connectivity and opposing signals will force synchronous activity to bifurcate. In figure 7, roughly half of the neurons follow the external darker input signal and the other half follow the lighter one as though the signals are battling to dominate the networks activity. The underlying connectivity matrix determines which of the two opposing driving signals a neuron

will most closely convey, and the degree to which it is both directly and vicariously influenced by the two opposing inputs.

In naturally occurring networks, such as the nervous systems of animals, "battling" behavior is a natural result of the network's dependency on combinations of inhibitory and excitatory neurons and signals to encode specific information.[16 17] However, in biological networks, circuit architectures are formed to receive a set of signals partic-

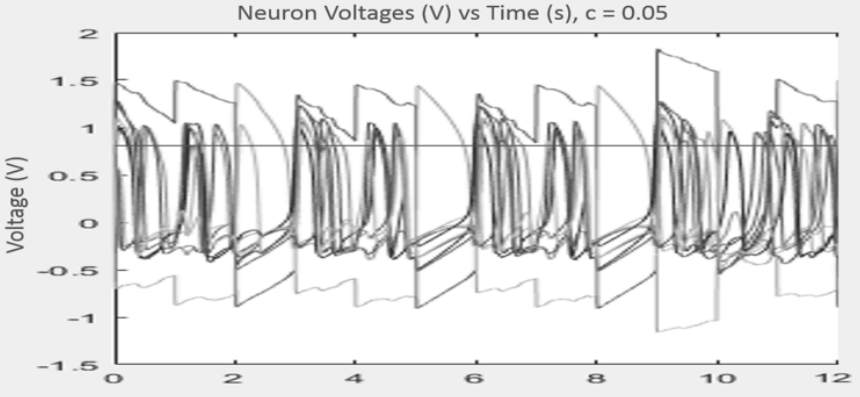

Figure 10a

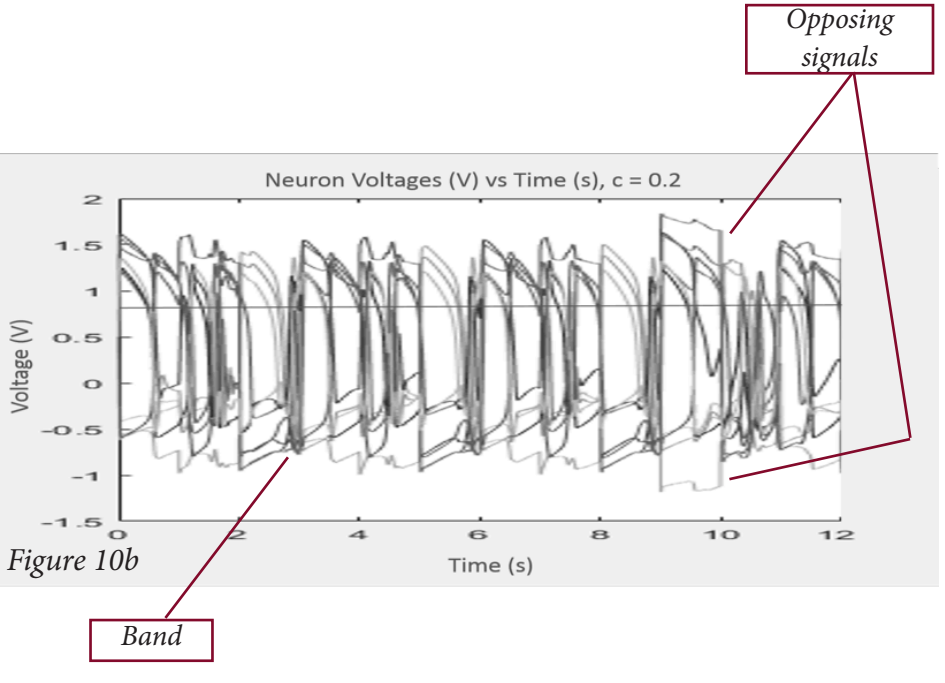

Figure 10b

ular to it, so that when this "battling" does occur, either one or the other signal will dominate and pass on to subsequent circuits.

Interestingly, the architecture of such circuits can change over time under the influence of incoming signals to reflect and incorporate new kinds of encoded information. In a way, architecture and signals inform and change one another as signals filter through dynamic networks of circuits. In some sense, these networks transform input information into output commands. As an example, imagine reading a sentence written on a chalk board; visual information is being taken in and transformed into neural activity. Now imagine copying the sentence below it and gradually increasing the size of your letters as you write. Not only is your brain taking in visual information about letter shapes as external stimuli, but it's also transforming this information into a motor function that encodes these very shapes and relative ratios. As you write larger and larger, these networks are able to temporarily modify their functionality to adjust your motor output while you compare your current movements to the size of your prior writing and prior movements.

Further Research

Synchronization is key to network functionality and coherence. It largely arises out of the network's ability to organize into structures that convey meaningful information. Such architectures have to switch between promoting and inhibiting varying sets of input stimuli to achieve different functions, much like stoplights directing traffic. A network's ability to incorporate the ability to process new information into its architecture by altering its complex, dynamic connectivities can be expressly summarized as its ability to learn.[7 20]

Glial cells, namely astrocytes and oligodendrocytes, tile the brain, forming networks and connecting to neurons, which lie in their respective domains. Previously regarded only as physical and physiological support to neurons, recent findings have implicated these cells in information processing roles comparable to their neuron counterparts: most strikingly, the ability to synchronize neuronal activity and modify network connectivity.[13] However, to gain insight into how these cells and their respective networks modulate neuronal networks, mod-

els of naturally occurring architectures and stimuli must first be established.

Recall that in Figure 10 the network's activity is somewhat incoherent. The networks in these experiments are randomized and do not reflect any particular architectures one might find in an animal's brain. The output of the networks in this experiment do not encode any kind of particularly meaningful information, thus leading to incoherent output seen in Figure 10. Further study of model neurons organized into more organic architecture with appropriate corresponding stimuli is warranted. A particular network or circuit's functionality should first be clarified before trying to understand how cells such as glia might influence and alter them. Simulating signals running through architectures in well documented circuits and connectomes such as those of the optical cortex of mice, or the nematode Caenorhabditis elegans, is an ideal starting point.[8 9]

Because glia modulate grey matter via neurotransmitters and white matter by manipulating an axon's conduction velocity, alternative neuron models to the FitzHugh-Nagumo model should be considered.[12 13] Unlike FitzHugh-Nagumo, alternate models might incorporate dynamics driven by electrochemical activity and delayed differential equations for the neuron's voltage. These additions may obstruct observation and analysis of large network dynamics, but on some level of detail may need to be addressed to capture characteristics key to a heterogeneous, neuronal-glial network's functionality in information processing and learning. Finally, because of the spatio-temporal complexity of neuronal networks, let alone neuronal-glial, mode decomposition methods may be necessary to glean information on glial functionality from data derived from organic networks, and to analyze glial functionality in simulations of heterogeneous networks.[2]

Conclusion

Understanding how dynamic networks in nature encode and process information requires an understanding of the relationship between network architecture and signal and how these architectures are modified during learning or under the influence of novel stimuli. Such architectures are complex, containing alternate modes of functionality

and feedback loops. Inherently, such a problem requires a mathematical approach. This study outlines mathematical tools fundamental to analyzing neuronal network dynamics and underlines the importance of the relationship between architecture and stimuli. To gain deeper insight into the information processing roles of neuronal networks, simulation of organic architectures and stimuli are necessary. Such information would facilitate future research of how glial cells modulate neuronal networks and perhaps offer insight into their synchronization, varying modes of functionality, and the cellular and network level mechanics of learning and information processing.

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