Research Statement

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Introduction

My research interests lie in the field of Mathematical Biology and, more specifically, in the study of the electrical activity of neurons. The mathematical techniques I most often use in my research come from dynamical systems, perturbation methods, bifurcation theory, and numerical methods. The main goal of my research is to provide insight into how dendritic properties affect the dynamics of single and coupled neuronal oscillators. More specifically, I look to elucidate the mechanisms by which dendrites modulate neuronal firing frequency and firing dynamics. I am also interested in understanding the relationship between a neuron's intrinsic biophysical properties and its computational properties. Knowledge of this relationship will allow one to utilize techniques from the fields of neural dynamics and neural coding to build up an understanding of the dynamics of neurons in response to coupling or external input.

Current Research

Neurons can have extensive spatial geometries, but they are often modeled as single-compartment objects that ignore the spatial anatomy of the cell. This simplification is made for mathematical tractability and computational efficiency. However, many neurons are not electrotonically compact, and single-compartment models cannot be expected to fully capture their behavior. Dendritic properties can have substantial effects on the dynamics of single neurons, as well as the activity in neuronal networks [25, 27, 8, 11, 30]. As such, much of my research is focused on understanding how dendritic properties affect the dynamics of neuronal oscillators.

The Effects of Dendritic Load on the Firing Frequency of Oscillating Neurons

In collaboration with Dr. Timothy Lewis, I am examining the effects of passive dendritic properties on the dynamics of an oscillating neuron. This was prompted by the modeling work of Kepler et al. [24] and the experimental work of Sharp et al. [38] where they examine the influence of electrical coupling between a neuronal oscillator and a passive cell, which is analogous to a two-compartment model of a soma with a passive dendrite [30]. Kepler et al. find that the addition of a hyperpolarized passive compartment can cause the oscillator frequency to either increase or decrease as the strength of the electrical coupling is increased. They determine that this is dependent upon the shape of the oscillator's membrane potential wave form.

In our paper [37], we model the neuron as an isopotential soma connected to a thin passive dendritic cable, i.e. a "ball-and-stick" model, and as an isopotential soma electrically coupled to a smaller passive compartment. We use the theory of weak coupling [33, 13, 26, 22] to derive an analytical expression that relates the change in frequency of the models to the phase response properties of the model somatic oscillator and the properties of the thin dendrite. The expression reveals that if the average value of the oscillator's phase response curve is negative (positive), then the addition of the hyperpolarized dendrite will cause an increase (decrease) in firing frequency, which we confirm with numerical simulations of the full models. Thus, we are able to elucidate the mechanisms underlying counter-intuitive increases in firing frequency that can occur due to a hyperpolarizing dendritic load. Furthermore, we show that the average value the neuron's phase response curve is equal to the slope of its frequency-applied current ($f - I$) curve. As some experimentalists may not be familiar with measuring phase response curves from neurons, this relationship leads to an alternate interpretation of our result in terms of a more experimentally familiar quantity: if the instantaneous slope of the oscillator's $f - I$ curve is negative (positive), then the addition of the hyperpolarized dendrite will cause an increase (decrease) in firing frequency. This work has been submitted to Physical Review E for publication and is currently under review.

Bistability in a Leaky Integrate-and-Fire Model Neuronal Oscillator Coupled to a Passive Dendritic Cable

The above analysis utilizing the theory of weak coupling is valid in the limit of a thin dendrite attached to an oscillatory soma with general dynamics. We can relax the assumption of the thin dendrite by idealizing the somatic dynamics. In this way, we examine the influence of general dendritic perturbations on the dynamics of a leaky-integrate-and-fire-type somatic oscillator that includes spike effects [36]. We obtain an exact

analytical solution to the ball-and-stick model using a non-orthogonal basis expansion technique [12, 9]. We use this solution to derive a firing-time map for the system which reveals that, for certain spike parameters, there is a region of bistability between periodic firing and quiescence. The periodic behavior arises from a "ping-pong" effect [7] between the somatic and proximal dendritic membrane potentials. This ping-pong effect was previously only described in models that contain active dendritic conductances [7]. By examining the bifurcation structure of the system under various parameter variations, we show that the influence of the passive dendrite can either induce periodic firing or silence the oscillations for certain somatic spike parameters. We then demonstrate that the same qualitative behavior is captured in a two-compartment model with a leaky-integrate-and-fire compartment electrically coupled to a passive compartment. These results have been written into a manuscript that will be submitted to SIAM Journal of Applied Math for publication.

Effects of Passive Dendritic Properties on the Dynamics of Electrically Coupled Neuronal Networks

Networks of inhibitory neurons are thought to play a fundamental role in generating cortical oscillations [4]. Many Inhibitory neurons in the cortex are coupled electrically, via gap junctions, and/or chemically, via inhibitory synapses [17]. As a result, synchronization in inhibitory networks is a topic of much theoretical and experimental research [31]. These studies reveal that electrical coupling aides in the synchronization of inhibitory interneurons [39, 29, 10, 18]. Furthermore, these interneurons can be electrically coupled at large distances from their cell bodies [3]. This implies that dendro-dendritic electrical coupling exists in the neocortex. Therefore, dendrites are important the flow of electrical activity between inhibitory neurons in the neocortex. In addition, theoretical studies [11, 8] reveal that for neurons coupled via chemical synapses, the synchronous solution can lose stability as the location of the dendritic synapse moves further away from the soma. I am working with Dr. Lewis to examine the role that dendritic properties play in the phase-locking behavior of neuronal networks. Understanding how dendritic properties affect the phase-locking dynamics of neuronal networks will be a step towards uncovering the biophysical mechanisms that underlie synchronous oscillatory electrical activity in the brain. Our preliminary results for two neurons coupled with gap junctions at the distal end of their dendrites reveal that the stability of the synchronous solution also depends upon the distance of the electrical synapse from the cell body. That is, the synchronous solution can alternate between being stable and unstable as the length of the dendrite becomes larger. Furthermore, the rate of this alternation of stability of the synchronous solution with increasing dendritic length becomes faster as the frequency of the somatic oscillations is increased. Our network simulations reveal the emergence of stable target pattern phase-locked solutions. These patterns arise from the fact that neurons close to each other are coupled with shorter dendrites than those that are further away. As such, closer neurons tend to synchronize while farther neurons fire in anti-phase. We are currently examining how network topology affects the type of phase-locking patterns that arise in the network.

Experimental Methods to Measure Infinitesimal Phase Response Curves

Synchrony in oscillatory systems is observed in a wide variety of biological, physical, and chemical systems, and is a well studied phenomenon in these fields. Determining the phase-locking behavior that occurs, be it either synchronous or asynchronous, clustering, or a traveling oscillatory wave is of practical importance in a variety of biological fields [13, 14, 22, 29, 23, 21, 20]. The infinitesimal phase response curve (iPRC) of an oscillator measures its sensitivity to infinitesimally small perturbations at every point along its period. Knowing the iPRC enables the prediction of phase-locked behavior that will occur resulting from either coupling, or external forcing. Finding the iPRC of an oscillator is the subject of many theoretical and experimental studies because it allows for a greater understanding of the phase-locking dynamics for a variety of systems. In collaboration with Dr. Lewis, Dr. Eli Goldwyn (University of Chicago), and the experimental laboratory of Dr. Theoden Netoff (University of Minnesota), I am developing and assessing experimental techniques to measure iPRCs from neurons in order to find the optimal method. Our main method relies on the fact that the iPRC is the impulse response function of the system and quantifies the linear response of the neuron to small-amplitude perturbations. The method involves stimulating the neuron with discretely sampled small-amplitude zero-mean gaussian white noise current and measuring the corresponding change in phase due to that input. The estimation of the iPRC is then reduced to a linear algebra problem by repeatedly stimulating the neuron and recording the vector of resulting phase shifts and the corresponding

matrix of stimuli (the stimuli are averaged over a certain number of bins in order to keep phase constant). The stimuli matrix can then be inverted and multiplied against the vector or phase shifts to obtain an estimate for the iPRC. A practical issue that arises with this method is that the amplitude of the random stimulus must be large enough to overcome the intrinsic noise in the neuron, and yet be small enough so that the neuron still responds linearly. Since the iPRC's for model neurons can be found numerically by the adjoint method [16], we have implemented our technique on model neurons and have found that our estimated iPRCs fit well with the iPRC computed from the adjoint method. We are currently working on obtaining experimental data for the method and quantifying the accuracy of our method in comparison to the "standard" method. The details of our method are outlined in the book chapter [32], and we are also working towards a manuscript.

Future Work

Extensions of Previous Work

While the passive description of dendrites that I utilize in my research is not completely accurate, the results that I have obtained do provide useful insight into how dendritic properties affect the dynamics of neuronal oscillators. It is well-known that dendrites in real neurons contain active ionic channels, and, as such, I will examine how the addition of dendritic nonlinearities affect my results.

An alternative way to examine the behavior of the electrically coupled ball-and-stick neuronal network would be to use the so-called master stability function [34]. This method allows one to examine the stability of the synchronous solution only. An advantage to using this method is that it does not require the assumption that dendritic effects are weak that was needed to employ the theory of weak coupling. Furthermore, the ionic currents in the dendritic compartments can include nonlinear terms. However, the method does require that all oscillators in the network are identical and that the same function is used to couple every oscillator. I will utilize the master stability function technique to examine how dendritic nonlinearities affect the stability of the synchronous solution of electrically coupled ball-and-stick neuronal networks.

I am also very interested in extending my work with neuronal networks to examine the dysfunctions of neuronal networks such as Schizophrenia. It is known that the GABA, an inhibitory neurotransmitter, concentrations are reduced in the dorsolateral prefrontal cortices of patients with Schizophrenia. This reduction of GABA is thought to disrupt working memory by causing a decrease in the synchronization of pyramidal neurons [28, 19]. I plan to add inhibitory and excitatory synapses to my networks with dendritic structure and examine how this affects the phase-locking behavior of the network when GABA is reduced as in Schizophrenia.

Linking Neuronal Dynamics to Information Coding in Oscillatory Neurons

The complex behavior of neurons often necessitates the use of high dimensional, nonlinear biophysical models to describe their dynamics. Although these models can reproduce the observed behavior, their output in response to coupling or external input is difficult to interpret. To understand how neurons transform their inputs into a spiking output, statistical methods can be used to empirically reduce such a model to a functional description of neural coding that captures the input-output relationship of the neuron in response to time-varying stimuli [35, 1, 2]. Understanding the mapping between the functional and full dynamical descriptions provides insight into the computational properties generated by neuronal dynamics. However, this mapping is very high dimensional. An alternative reduction technique exists for neurons that are intrinsically active, firing regularly and responding to inputs through perturbations to otherwise regular spike times [6, 5]. The dimensionality of such systems can be reduced through so-called phase models using the theory of weak coupling [33, 13, 26, 22]. Recent work has shown that the properties of the phase model are related to functional characterizations up to first order [15]. However, second-order statistical methods provide more complete and accurate descriptions of neural function. These second-order statistical methods involve the spike-triggered covariance (STC) matrix, which is the covariance of stimuli that elicit spikes from a neuron. Thus, if the phase model is extended to incorporate second order effects, it is highly likely that the second order phase resetting terms will be related to the STC matrix, which is a simple quantity to measure experimentally and computationally. In the future, I will derive the second order phase model and relate the obtained second order phase resetting terms to the STC matrix, thereby strengthening the link between a neurons computational and biophysical properties.

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