Research Statement

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1 Introduction

I develop dimension-reduction methods for neural network models using stochastic and deterministic **dynamical systems theory**, and in turn, use these findings to understand how biological neural networks function and how they are maintained. I also specialize in **interdisciplinary research with excellent funding potential**. My publication record demonstrates my ability to produce high-impact work with researchers of diverse backgrounds including neuroscientists [17], engineers [3, 19], mathematical neuroscientists [13, 18, 14, 15], and fluid dynamicists [16]. My research program includes the following sub-directions:

- **Coupled oscillators, Section 2**. In summary, I introduce a generalization of weakly coupled oscillator theory to strong coupling. This work will allow mathematician to include subtle but important details in reduced phase models that are often neglected by idealized models. This work opens the way for a thorough re-examination of decades of existing oscillator theory using realistic models as opposed to highly constrained or unrealistic models. There is excellent potential to sharpen general questions regarding network dynamics in physics, chemistry, and biology.
- **Molecular motors, Section 3**. In summary, I analyze a model of molecular transport, where vesicles are forced into nanometer-scale cell compartments. My work suggests that fluid dynamics forces, molecular motor forces, and the shape of the confinement play significant factors in neural maintenance. This work opens the way for detailed, tractable studies on neural maintenance and how defects in maintenance affect brain function. The long-term goal of this work is to help understand the causes and mechanisms behind brain disorders such as Alzheimer's.
- **Cortical network analysis and machine learning, Section 4**. In summary, I introduced an idealized model of the auditory cortex, which unified disparate optogenetics results in the literature. The model serves as a proof of concept that large numbers of computations in the brain may be handled efficiently by relatively simple neural circuits. This work is an excellent starting point to gain a deeper understanding into the principles underlying general sensory processing. The goal is to create biologically-inspired artificial neural networks which may learn more quickly and robustly than existing methods.
- **Undergraduate research, Section 5**. In summary, my work is accessible to a broad spectrum of skills and backgrounds in STEM (although I strongly encourage students from other backgrounds to participate in my research). My goal is to equip students with skills such as programming and scientific literacy, which they can use to enhance their lives and careers.

2 Coupled Oscillators

My work on oscillations falls within the broader work of oscillator theories oriented towards understanding pathological neural behavior such as Parkinsonian tremors, epilepsy, and cardiac alternans. Overall theoretical work in these directions has been promising, but tend to use one of three starting points: mathematically tractable but very abstract models [11], particular forms of symmetry [5], and the *weak coupling* assumption, or more generally, the *linear* approximation [4]. The weak coupling assumption has long been an invaluable theoretical tool to understand neural behavior consisting of only small deviations from a known behavior such as quiescence

or oscillatory activity. Indeed, the weak coupling assumption has driven much of my work [13, 14, 15].

While these assumptions facilitate theorists to a potent degree and were perhaps close to experimental conditions some decades ago, they are now far from modern experimental conditions. Modern experiments are often done *in vivo*, where neurons are often strongly coupled, heterogeneous, and interact nonlinearly. These properties hold in both normal and pathological neural function, so it follows that pathologies can not always be understood using abstraction, symmetry, or linearity. Therefore, my field must develop theories that directly address *strongly coupled* networks of *heterogeneous* neurons with *nonlinear* interactions at multiple scales. We must understand the brain as it is.

To this end, *I have formulated a theory of strongly coupled oscillators* [19]. I tested this theory using a realistic four-dimensional model of a thalamic neuron. Figure 1 shows how my theory predicts phase differences in two thalamic oscillators for different coupling strengths (higher order corresponds to greater accuracy). The right-hand side of the reduced ODE (labeled $-2\mathcal{H}_{\text{odd}}$) is shown in the top row. Roots and slopes correspond to existence and stability of phase-locked states. Phase differences of the full model is shown in the bottom row for 20 difference initial conditions. Coupling strength increases from weak ($g_{\text{syn}} = 0.02$, left column) to strong ($g_{\text{syn}} = 0.25$, right column). **Roots of the fourth-order reduction coincide with the steady-state phase-locked states of the full system**.

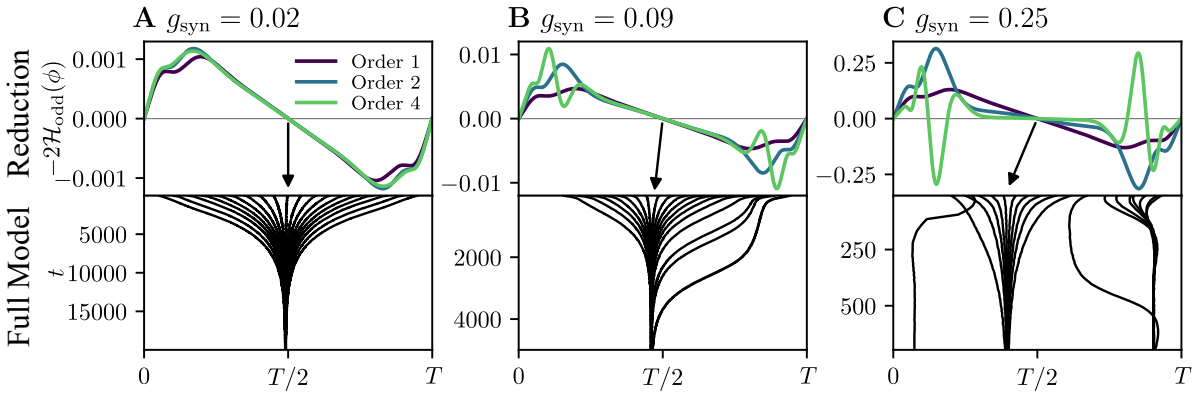

Figure 1: Performance of the strong coupling reduction compared to a full simulation of thalamic neuron models. A: Weak coupling. The right-hand side of the reduction (top) is shown for different orders (higher is more accurate) and coincides with the long-term phase difference of the full model (bottom). B: Moderate coupling. The reduction (top) coincides with the full model (bottom). C: Strong coupling. The reduction (top) only agrees with the full model (bottom) at order 4.

These results demonstrate how my theory is not specific to particular models or coupling functions. Indeed, my theory naturally applies to general coupled oscillator models including those found in physics, biology, and chemistry (the only requirement is that the vector fields of the models are sufficiently smooth).

2.1 Future Work

In the long term, I will further develop mathematical methods to analyze neural networks in several important directions. I will augment my theory to include heterogeneity (including n:m phase-locking), making my theory applicable to far more realistic neural networks. I will augment my theory to include oscillator death to understand interactions between bursting neurons in networks such as subcortical networks and central pattern generators. Finally, I will derive the mean-field equations for neural models (in contrast to existing mean-field theories

that use idealized models [11]) to understand how microscopic neural interactions influence large-scale brain activity.

This theory is not just suited to problems in neuroscience, but biology, chemistry, and physics. For example, I have started a collaboration with the Fraden lab at Brandeis University, where I am applying strong coupling theory to problems of oscillatory reactions in star networks. By using a this reduced model, I will be able to uncover the mechanisms behind transitions in phase-locked patterns and account for the heterogeneity inherent in experimental reactions.

3 Neural Maintenance: Dendritic Spines

Pyramidal neurons, the most ubiquitous type of neurons in the mammalian neocortex, feature tens of thousands of excitatory convergent synaptic inputs. Most incoming synaptic signals terminate on sub-micron bulbs known as dendritic spines [10]. Spines exhibit a significant degree of morphological plasticity [7] with pathological spine formation implicated in disorders such as Autism spectrum disorder and Alzheimer's disease [20]. How spines function and how they are maintained is therefore an important question.

Dendritic spines receive surface proteins by protein-carrying vesicles that squeeze through the neck of the spine and eventually fuse with the spine head [2]. The motion of such vesicles has been observed to not involve only translocation, where the motion is unidirectional, but includes corking, where the vesicle gets "stuck" in the spine neck, and rejection, where the vesicle initially enters the spine but eventually reverses direction and exits [12]. **How molecular motors affect changes in vesicle direction is the goal of ongoing work**.

Indeed, the importance of this problem has spurred an extensive literature on the effects of molecular motors on vesicle dynamics, including the computation of the distribution of cargo velocities [8], computing mean first passage times to transport targets on dendritic morphologies [1], and the generation of bidirectional motion despite the assumption of symmetry [21]. *However, these studies often neglect or fix drag forces which could arise from constriction effects in the unique bulbous shape of dendritic spines.*

To this end, I have reduced a fluid dynamics model of dendritic spine transport into a tractable fast-slow system:

$$\begin{aligned} \frac{dZ}{dt} &= U, \\ \varepsilon \frac{dU}{dt} &= F(U) - \zeta(Z)U. \end{aligned} \tag{1}$$

F is the net motor force, U is the vesicle velocity, Z is the vesicle center of mass, and ζ is the function that captures information about the constriction geometry at position Z.

Standard dynamical systems theorems (Fenichel theory) allows us to view the equivalent system in the limit $\varepsilon \to 0$,

$$\frac{dU}{ds} = F(U) - \zeta U,$$

where ζ is a parameter and $s = t/\varepsilon$. Using this reduced system, I proved the unique existence of unidirectional motion for sufficiently close vesicle-to-spine diameter ratios. *This result is consistent with experimental observations of vesicle trajectories in the literature [16].* Experimentally-observed vesicles traveling into thin spines with tight constrictions tend to exhibit unidirectional motion, whereas vesicles traveling into wider, stubby spines tend to exhibit bidirectional motion. The consistency suggests that fluid flow in dendritic spines combined with molecular motor forces contribute significantly to bidirectional vesicle motion. Neurons may modify spines to become wider or thinner depending on the needs of the synapse.

3.1 Future Work

While mean-field models are useful with large numbers of agents, sub-micron spines only contain a few dozen myosin motors. *The effects of noise are prominent, and we can not rely on mean-field models to fully understand how spines function.* Thus I will shift my attention to understanding how finite numbers of stochastic motors affect the probability of translocation.

Before turning to the probability of vesicle translocation, I will focus on the specific question of the mean first passage time (MFPT) to switch the direction of vesicle motion. This switching is a well-known "tug-of-war" effect [6] that has not been studied using myosin motors or with constrictions. I have developed an agent-based simulation where individual myosin motors attach and detach with position-dependent rates in order to compute MFPTs. However, agent-based simulations are computationally expensive: to obtain mean first passage times (MFPT), roughly 5-10 trials must be run in parallel over 50-100 time units with time steps on the order of 1e-6. These requirements mean dozens of hours per simulation. I will overcome the problem of long simulation times through the use of a master equation approximation.

4 Cortical Network Analysis and Machine Learning

I introduced an idealized model of the auditory cortex unifying numerous experimental results in the field of auditory neuroscience [17]. This model demonstrated that simple cortical mechanisms including synaptic facilitation and depression are sufficient to reproduce numerous types of auditory processing. The model included excitatory (pyramidal) neurons as well as the inhibitory subtypes somatostatin-positive (SOM) and parvalbumin-positive (PV) interneurons, which were necessary to reproduce optogenetic results. Many questions remain regarding robustness of the model and its similarity to real cortical networks. While we performed some parameter sweeps, the ability of the model to reproduce additional auditory phenomena was not explored in depth.

In addition, I worked with a neuroscientist who ran auditory experiments on mice. They generated many gigabytes of partially-observed calcium traces, which were generated as the mouse responded to auditory tasks. In order to generate correlations between all observed neurons, I used subspace identification to recover correlations when pairs of neurons were not observed on a given trial. The method included the use of stochastic gradient descent to estimate the optimal correlation matrix corresponding to the partial data. Once this was performed, I used hierarchical clustering and found that correlated neurons tended to be spatially clustered in the cortex (unpublished).

4.1 Future Work

Machine learning is an incredibly powerful, general tool, yet learning algorithms then to be extremely expensive in terms of trials, requiring countless iterations. In contrast, animals tend to learn with far fewer iterations. I hypothesize that there exist neural networks with biologically-inspired constraints that are capable of learning far more rapidly than a general neural network.

To this end, I will view the cortex as a large number of coupled differential equations with heterogeneous parameters. This starting point is natural from a modeling perspective because all parameters and connections are explicit. It is also general, extending beyond cortical responses to auditory inputs, indicating just how powerful this framework can be. My goal is to use automated and theoretical tools, including machine learning and inverse methods, to uncover the parameter spaces within which healthy and unhealthy cortical networks operate. This information will include connectome data as well as connectivity data in dendrites and axons in order to uncover which aspects of the physical organization in the cortex contribute

most to network performance. This information will in turn better constrain artificial neural networks and improve performance [9].

5 Undergraduate Research

Virtually any STEM student with a basic understanding of calculus and ordinary differential equations will be able to contribute to my research. My students will first learn the fundamentals of the field of their choosing. For example, a student interested in coupled oscillator theory will learn about phase response curves, return maps, and weak coupling theory, and a student interested in molecular motor dynamics and cellular transport will learn about stochastic calculus, PDEs, and numerical analysis. I will also introduce them to state-of-the-art research through journal club discussions. This process will lead them towards research questions of their choosing, and I will guide them towards tractable problems. Driven students will have the opportunity to publish first- and second-author papers in reputable journals.

My goal is to provide undergraduates many opportunities to learn important and relevant skills. They will develop the ability to extract essential features from complex problems. They will learn to program in languages of their choosing to generate figures for abstract mathematical concepts. They will learn to communicate in speech and writing by interacting with others of different STEM backgrounds. I truly hope to have a diverse lab of varying majors, e.g., biology majors who interact with and learn alongside computer science majors, who are capable of presenting their work clearly and concisely to another diverse audience, e.g., consisting of math and English majors.

Below are potential project ideas from simple to complex, to be given depending on the skill, interest, and commitment time of the student. I remark that I fully understand the potential for a relatively unskilled and uninterested student to turn into a skilled and dedicated researcher, so this list is by no means a hard rule.

- (Simple) Reproduce figures from a paper of the student's choosing and present on the main results. Generate potential research ideas based on the paper.
- (Simple) Help improve the documentation for my open source projects in coupled oscillators and molecular motor dynamics. Contribute features to these projects.
- (Moderate) Join an ongoing research project. For example, generate figures for a paper using a language and numerical integrator of their choosing. The student will be tasked with visualizing a particular problem and will be responsible for writing and debugging their own code from top to bottom.
- (Complex) Lead a research project. For example, study the effects of splay states using strong oscillator coupling theory. Determine different types of bifurcations as a network transitions from different phase-locked states as a function of a network parameter, such as coupling strength.

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