Research Statement

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1 Introduction

I develop dimension-reduction methods for neural network models using **dynamical systems theory**, and in turn, use these findings to understand how biological neural networks function and how they are maintained. I specialize in **oscillator coupling theory**, **numerical bifurcation theory**, **perturbation methods**, **stochastic dynamical systems**, and **non-local integro-differential equations**. My independent research program includes the following directions:

- **Coupled oscillators, Section 2**. In summary, I introduced a generalization of coupled oscillator theory, allowing mathematicians 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 that assume either idealized oscillators with strong coupling or general oscillators with weak coupling. There is excellent potential to sharpen questions in problems of diseases such as Parkinsonian tremors.

- **Molecular motors, Section 3**. In summary, I reduced the dimension of a vesicle transport model in confined spaces and analyzed its bifurcations. The model behavior was consistent with experimental observations, suggesting 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. There is great potential for experimental collaboration. 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.

2 Neural Oscillations

My work on neural 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 [4], and the *weak coupling* assumption, or more generally, the *linear* approximation [3]. 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* [18]. Consider the coupled system of N ODEs,

$$\dot{X}_i = F(X_i) + \varepsilon \sum_{j=1}^{N} a_{ij} G(X_i, X_j), \quad i = 1, \ldots, N, \tag{1}$$

where each system admits a T-periodic limit cycle $Y(t)$ when $\varepsilon = 0$. We allow $\varepsilon > 0$ not necessarily small and assume general smooth vector fields $F : \mathbb{R}^n \to \mathbb{R}^n$ and a smooth coupling function $G : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$. The scalars a_{ij} modulate the strength of coupling between pairs of oscillators, whereas ε modulates the overall coupling strength of the network.

Let θ_i be the phase of limit cycle Y_i and define the phase difference $\phi_i = \theta_i - \theta_1$ for $i = 2, \ldots, N$. Under general conditions, it is possible to derive a phase reduction of $N - 1$ equations,

$$\begin{aligned}\dot{\phi}_i =& \varepsilon \sum_{j=1}^{N} a_{ij} \mathcal{H}(-\phi_i, \phi_2 - \phi_i, \ldots, \phi_N - \phi_i, \phi_j - \phi_i) \\ & - \varepsilon \sum_{j=1}^{N} a_{ij} \mathcal{H}(0, \phi_2, \ldots, \phi_N, \phi_j), \quad i = 2, \ldots, N,\end{aligned}$$

where

$$\mathcal{H}(\eta_1, \ldots, \eta_N, \xi) = \frac{1}{T} \int_0^T \mathcal{Z}(\eta_1 + s, \ldots, \eta_N + s) \cdot G(s, \xi + s) ds,$$

and $\mathcal{Z}$ is the higher-order phase response curve from [21]. My theory produces Taylor truncations of the function $\mathcal{H}$. The higher the truncated order, the more accurately my theory reproduces phase-locked states of N oscillators.

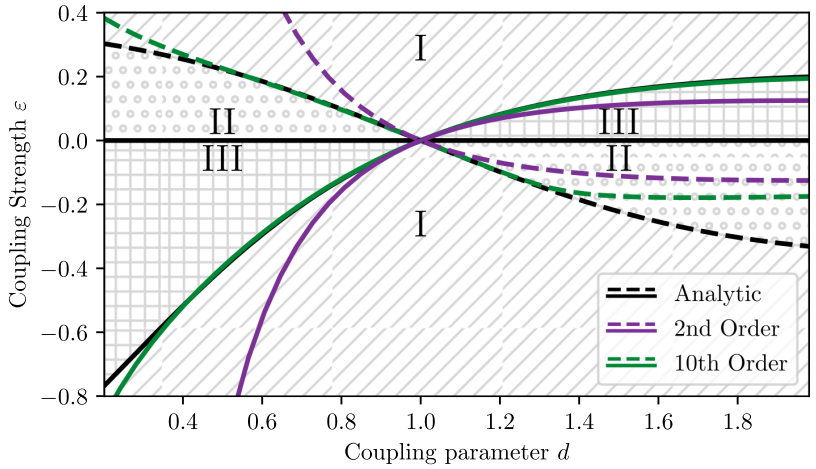

Figure 1: Validation of strong coupling theory using diffusively coupled complex Ginzburg-Landau (CGL) models. The plot is a two-parameter bifurcation diagram in coupling parameters ε and d. Synchrony is only stable in regions I and II, whereas antiphase is only stable in regions I and III. Black solid lines denote boundaries where the system switches between stable and unstable synchrony (ε_s). Black dashed lines denote boundaries where the system switches between stable and unstable antiphase (ε_a). Purple solid, dashed: bifurcations detected using 2nd order interaction functions from [22]. Green solid, dashed: bifurcations detected using 10th order interaction functions. **This result shows that my strong coupling theory substantially outperforms existing coupling theory.**

As a first step, I verified my theory using the mathematically tractable complex Ginzburg-Landau (CGL) model with diffusive coupling. The coupling function has two parameters: ε for the coupling strength, and d for the degree to which opposing species affect coupling. Both parameters significantly affect the phase-locking properties of the coupled CGL models. I show the accuracy of the theory in the left panel of Fig. 1, where the strong coupling theory (green, tenth-order) coincides strongly with the ground-truth (black) relative to existing coupling theory (purple, second-order) [22].

Next, I tested this theory using a realistic four-dimensional model of a thalamic neuron. Figure 2 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**.

These results demonstrate how my theory is not specific to particular models or

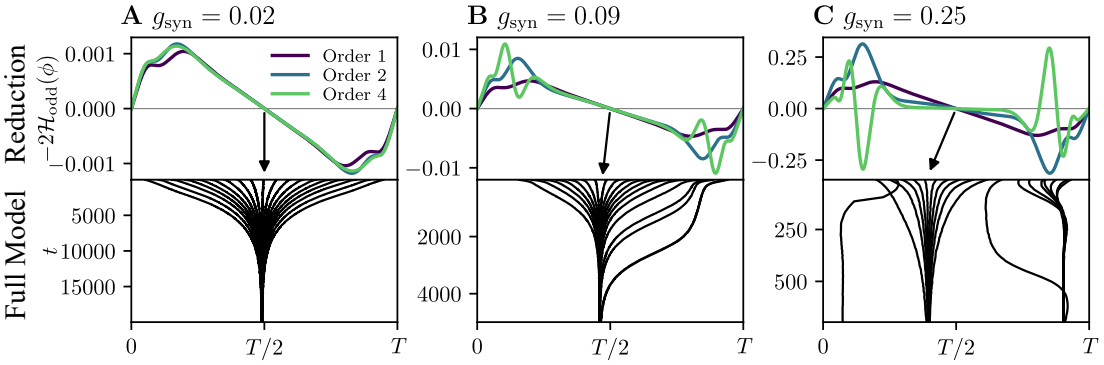

Figure 2: Performance of the strong coupling reduction compared to a full simulation of thalamic neuron models. A: Weak coupling. The right-hand side of the reduction (top) is shown for different orders (higher is more accurate) and coincides with the long-term phase difference of the full model (bottom). 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.

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.

3 Neural Maintenance: Dendritic Spines

While neural interactions are an important part of understanding how brains function, questions of neural maintenance are equally important. Seemingly minor defects at the nanometer-to-micrometer scale can result in serious disorders at the scale of the whole brain. For example, deficits in molecular motor transport in axons are implicated in neurodegenerative diseases such as Parkinson's disease [9]. Another example involves pyramidal neurons, the most ubiquitous type of neurons in the mammalian neocortex. They feature tens of thousands of excitatory convergent synaptic inputs, where most

incoming synaptic signals terminate on sub-micron bulbs known as dendritic spines [10]. Spines exhibit a significant degree of morphological plasticity [6] with pathological spine formation implicated in disorders such as Autism spectrum disorder and Alzheimer's disease [19]. 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 [7], computing mean first passage times to transport targets on dendritic morphologies [1], and the generation of bidirectional motion despite the assumption of symmetry [20]. *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:

$$\begin{aligned} \frac{dZ}{dt} &= U, \\ \varepsilon \frac{dU}{dt} &= F(U) - \zeta(Z)U. \end{aligned} \tag{2}$$

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. The two-parameter diagram in the confinement factor ζ and the ratio or up- and down-motors ϕ is shown in Figure 3. In summary, the two-parameter diagram (panel D) predicts that smaller ζ (wider constrictions) tend to show bidirectional motion, whereas larger ζ (tighter constrictions) predict unidirectional motion.

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

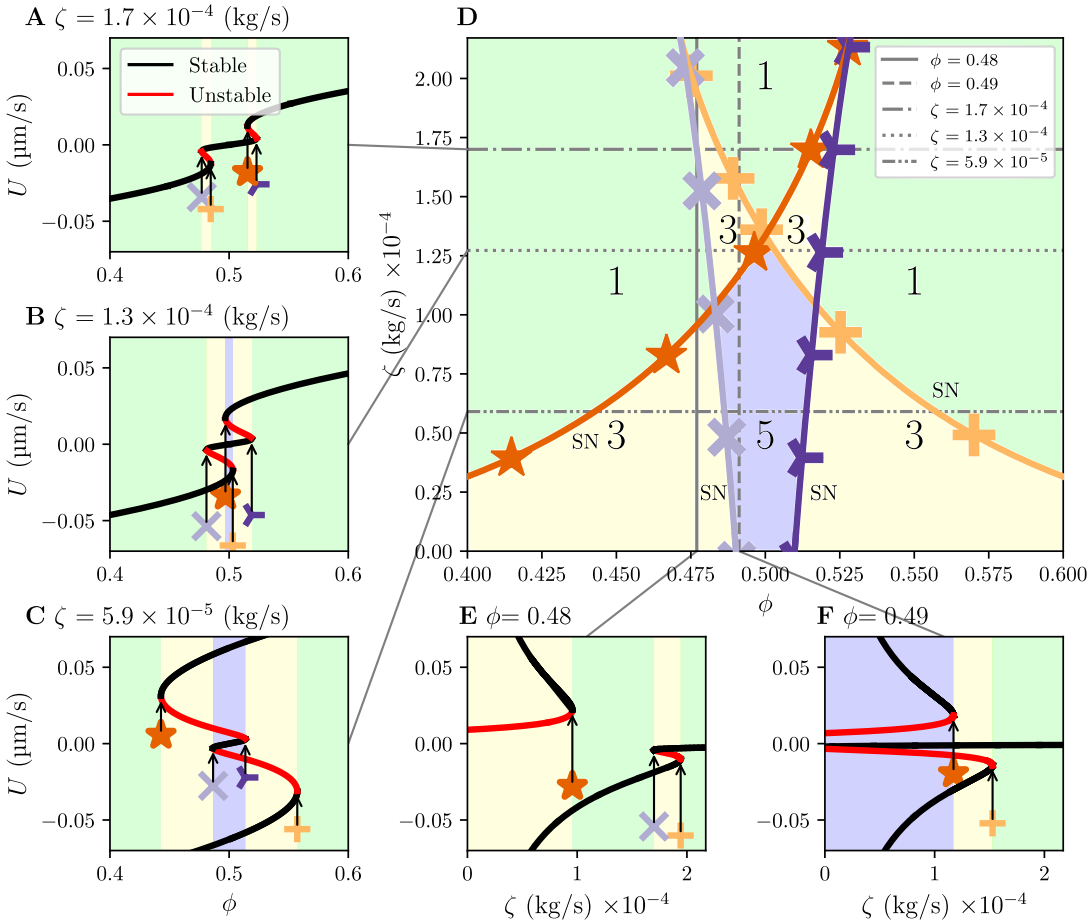

Figure 3: Two parameter bifurcation diagram in ϕ and ζ. Saddle-node (SN) bifurcations are shown in (D) as colored branches with a unique color and symbol. Numbers in (D) indicate the total number of fixed points in the corresponding region of parameter space. Subplots A, B, C, E, F, show one-parameter slices of the two-parameter diagram. Saddle-nodes are labeled with the corresponding branch color and symbol. The critical vesicle-to-spine diameter ratio at the cusps is roughly 2 µm/3 µm.

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 [5] 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. While we performed some parameter sweeps, the ability of the model to reproduce additional auditory phenomena was not explored in depth. Many questions remain regarding robustness of the model and its similarity to real cortical networks.

In addition, I worked with a neuroscientist at the Geffen lab 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. This problem is general, and machine learning researchers are working on adding physical constraints to weather prediction algorithms.

The simplest starting point is to 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 while including known synaptic dynamics such as facilitation, depression, and STDP [8]. I will include physical constraints about the network such as the physical and statistical properties of dendrites and axons.

The objective function will include real cortical responses from different auditory experiments, and the system will be trained to satisfy all the results of the experiments simultaneously. While taking care to avoid overtraining and sloppy modeling, the goal will be to determine which physical constraints and synaptic dynamics contribute most to network performance. This information will in turn better constrain cortical network models in general, and contribute to improvements in the performance of artificial neural networks.

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