Research Statement

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As a mathematical biologist, my research strives to achieve the following two goals: 1) use biological applications as inspiration for the creation of new mathematical techniques, and 2) combine these new techniques with classical approaches to investigate the mechanisms driving biological processes.

During my doctoral work at the University of Utah with advisor Alla Borisyuk, my research has focused on computational neuroscience. More precisely, I have studied astrocytes, a type of cell in the brain that makes up approximately 50% of human brain volume [TY73] and are roughly as numerous as neurons [NRG03]. Conventionally, astrocytes were viewed as passive and neurons active, so a majority of studies focused solely on the dynamics of neurons to understand the way the brain functions and malfunctions. However, with the advancement of experimental technologies, studies have recently revealed that astrocytes have the ability to play an active role in the brain. For example, they have been shown to be involved in many neurological pathways (e.g., uptake of neurotransmitters [ZD13]), and have the ability to signal downstream mechanisms via calcium transients [Hay01, WSX+13]. Further, astrocytes are thought to be involved in some neurological disorders, such as epilepsy [SWFW10], Huntingtons disease [TAF+14], and Alzheimers disease [OHW+15]. However, the exact mechanisms and pathways astrocytes use to influence neighboring neurons and electrical signals in the brain are still largely unknown.

My early work focused on investigating previous experimental results and making verifiable predictions regarding the calcium transients observed in these cells. More recently, it has inspired a novel mathematical framework involving the interaction of particles with a recharging boundary. Specifically, my work thus far can be summarized in the following two projects:

1. Created and tuned, along with experimental collaborators John A. White (Boston University) and Marsa Taheri (University of Utah), a minimalistic mathematical model of **calcium dynamics** in astrocytes. The **bifurcation analysis** of this model led to a better understanding of experimental observations [HTWB17, THBW17].

2. Investigated, along with Sean Lawley (University of Utah), the statistics of **particles diffusing** in a environment with **recharging receptors** [HLB18a, HLB18b]. Motivated by the synaptic cleft, this project yielded insight into the number of molecules that can escape and activate neighboring astrocytes.

These projects required the use of various applied mathematics techniques, including bifurcation theory, mean-field approximation, asymptotic analysis, parameter estimation, and data analysis. This theory was also coupled with numerical simulations, which were completed in MATLAB, Mathematica, and C. The code for both projects is open source, and has been uploaded to ModelDB Accession: 189344 (Project 1), and GitHub (`github.com/gregoryhandy`; Project 2). Lastly, the document ends with a short description about an upcoming project investigating the role astrocytes have in modulating neuronal network dynamics.

Project #1: Mathematical investigation of IP_3-dependent calcium dynamics in astrocytes

Astrocytes are a type of cell in the brain consisting of a soma and extending processes that can wrap around neuronal synapses. These cells express a variety of functional receptors, which may be activated by neighboring neurons. Activation of these receptors leads to increases in intracellular Ca^{2+} in astrocytes, primarily through the release of inositol (1,4,5)-trisphosphate (IP_3) into the cytosol, which subsequently opens intracellular Ca^{2+} stores [Hay01] (Fig. 1). Interestingly, when our experimental collaborators applied a brief pulse of ATP near the soma and processes of an astrocyte, they observed a variety of calcium responses, with no clear classification scheme or understanding of the driving forces leading to this variability [THBW17].

While other models of astrocytic calcium dynamics exist [DGV+09, UJCB06], many are not created and verified with experimental data. Thus, we started our investigation by creating a minimalistic open-cell calcium that fitted the average experimental observation. While previous mathematical models were considered, this process involved an extensive literature review of experimental papers, in order to determine the most important calcium channels to include. Most notably, we found experimental evidence suggesting that astrocytes have store-operated calcium channels, which are channels located on the plasma membrane

that open only when the intracellular stores are depleted [MNP08]. However, this channel was not included in previous calcium models, and its influence on calcium transients was largely unknown.

Using this minimalistic mathematical model, we found the following **key results**:

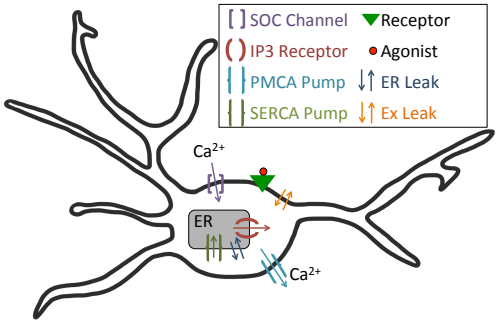

Figure 1: Simplified schematic of an astrocyte and its major calcium components. Arrows show the direction of calcium flux.

1. Using bifurcation analysis and treating the concentration of IP_3 as the bifurcation parameter, we found an oscillatory regime that was started and ended by Hopf bifurcation points. This information, when coupled with possible IP_3 time courses, yielded four possible calcium response types: Single-Peak, Multi-Peak, Plateau, and Long-Lasting.

2. Using this categorization on the experimental observations led to a systematic way to analyze the data, revealing that different regions along the astrocytes (i.e., soma vs. processes) expressed a different distribution of calcium response types. This led to the experimental prediction that channel densities were not homogeneous along astrocyte processes. Further, through two-parameter bifurcation analysis, we were able to understand the role of key channel parameters, which allowed us to make specific predictions about how the channel parameter change between astrocyte compartments.

3. Despite finding that store-operated calcium channels contributed very little to the calcium flux during a transient, we showed that these channels largely shape the underlying dynamical landscape, and predict that blocking these channels would severely limit the diversity of calcium transients and lower the frequency of calcium oscillations, underscoring the importance of considering these channels in both experimental and mathematical settings.

4. We created a database of calcium response distributions for a wide range of parameter values that can be used by experimentalists to help estimate the underlying channel distribution of their cells. In addition, all code used for this project, including the classification algorithm and numerical method for solving the mathematical model, has been uploaded to ModelDB Accession: 189344.

Thus far, this project has led to two publications: [THBW17] details the novel experimental data and the creation of the mathematical model, and [HTWB17] details the mathematical analysis. I am the co-first author on both of these publications.

Future Directions:

Using our calcium model as a starting point, we are now examining the role astrocytes have in the tripartite synapse, which consists of the pre- and post-synaptic terminal, as well as the astrocyte (Fig. 2). Mathematical models have shown that astrocytes have the ability to significantly change the firing patterns of nearby neurons [DBC+07, WMH+11], and rely on the ability of astrocytes to release vesicle-dependent neurotransmitters. However, this mechanism, known as gliotransmission, is highly controversial in the experimental literature [FM18].

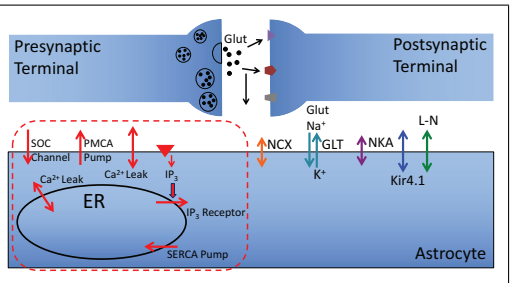

Figure 2: Schematic of the tripartite synapse. The red/dashed box highlights the completed calcium model.

In our future work, we plan on investigating the pathway proposed by [WSX+13], namely elevated intracellular calcium may drive sodium-calcium exchangers (NCX) and the sodium-potassium pumps (NKA) to pump potassium into the cell, thus decreasing the extracellular potassium concentration, and changing the resting potential for nearby neurons. Work on this project has already begun, with the help of *undergraduate REU student* Daniel Griffin, with whom I was the primary contact. We extended the calcium model by including additional ionic fluxes found on astrocytes. Specifically, we were successfully

able to tune the parameters of the model in such a way that our original results regarding the calcium model remained entirely intact. Further, we considered the situation where the extracellular space experienced a large spike in potassium, and ran the model with and without a simultaneous calcium transient in the astrocyte. We found that the calcium activity in the astrocyte returned the extracellular concentrations to baseline quicker, enabling the neighboring neuron to return to its baseline spiking rate. These preliminary results confirm astrocytes' ability to modulate spiking ability.

Project #2: Role of receptor recharge time on the statistics of captured particles

Particles moving and interacting with traps is a broad description of many biological processes. For example, in the context of neuronal synapses, particles and traps would represent molecules and receptors, while in ambush predator-prey dynamics, they are the prey and predators, respectively. Despite the vast differences between these two sample applications (e.g., scale and description of movement), the mathematical description can be very similar. Specifically, we consider a finite number of particles randomly moving in a bounded domain. The boundary is partitioned into reflecting regions which reflect particles, escape regions which absorb particles, and m-many traps, or capture regions (Fig. 3). After capturing a particle, the capture region turns reflecting for an exponentially distributed amount of time, referred to as the "recharge" time, before it can capture an additional particle. While we assume that these particles do not interact during motion, the boundary conditions depend on the paths of particles, and as a result, the particles can indirectly affect each other. Eventually, all of the particles will be removed from the domain by either escaping via an escape region, or being captured by a capture region.

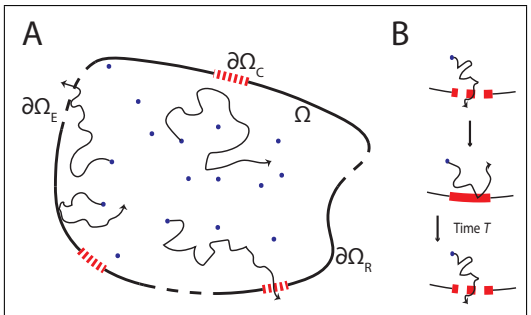

Figure 3: **Schematic of particles in a domain with traps.** A: General bounded domain, with reflecting, escape, and capture regions, B: Traps must recharge between captures.

Similar work has been done regarding the distribution of exit times when the particles are trying to find small targets [AM18, RK17, SSH07, HS14], and on studying diffusion with stochastically switching boundary conditions [BL15, Doe00, LMR15]. In these studies, the particle paths are also statistically correlated, since they are diffusing in the same random environment. However, the state of the boundary does not depend on interacting with the particles, and the particles' paths do not influence one another. We deviate from these previous studies in this work by not necessarily assuming that the capture regions are small, and by having the particles interact via the switching boundary conditions.

For this project, we are interested in the time evolution of the first and second moments of a) the number of particles remaining in the domain, b) the number of cumulative captures, and c) the number of available capture regions evolve with time. Thus far, we have the following **key results**:

1. We proved that for any nonzero recharge time, the average number of captured particles grows at most *logarithmically* in the total number of initial particles. This is a fundamental effect of recharge, as it holds under very general assumptions on particle motion and spatial domain. It is also dramatically lower than in the instantaneous recharge case, where the average number grows linearly.

2. We characterized the parameter regime in which a given recharge time will dramatically affect a system, allowing researchers to easily verify if they need to account for recharge in their specific system. Applying this characterization for parameters corresponding to neuronal synapses and ambush-predators, we found that both applications were significantly affected by the recharge time.

3. We approximated the full spatial and stochastic process with a continuous-time Markov process on a discrete state space, and as a system of ODEs in a mean-field approximation. Utilizing these approximations, we found that the mean recharge time determines the mean and variance of the clearance time, defined as the time it takes for all particles to leave the domain. Further, we find that while a finite recharge rate will always result in a lower expected number of captured particles when compared to instantaneous recharging, it can either increase or decrease the amount of variability of this random variable.

The code for this project has been posted online (github.com/gregoryhandy), and has led to two publications: [HLB18a] details the proof behind the logarithmic growth rate observed with a nonzero recharge time, and [HLB18b] outlines the approximation to the continuous-time Markov process and explores second order moments of the stochastic process.

Future Directions:

For the next phase of this project, we are returning to the specific application of the tripartite synapse. Specifically, we are interested in understanding the time-course of receptor activations and the number of neurotransmitters that are able to escape the cleft and activate the neighboring astrocyte process. Thus far, the mathematical framework resembles an idealized synaptic cleft, where the particles are neurotransmitters, the capture regions are receptors, and the neurotransmitters are broken down by enzymes after being captured by the receptors. As a first step, we have extended our model to allow for partially absorbing capture regions, since a neurotransmitter colliding to a receptor does not necessarily result in binding event [KS09]. This extension makes use of the theory for such imperfect absorption found in [EC07]. The theory and approximations can be directly used due to our general framework for this project. Our initial results yield that the size of the synaptic cleft tunes the duration of receptor activation, while the number of receptors determines the amplitude of receptor activation. Astrocytes, through their level of ensheathment (the tightness of wrapping of the synapse by astrocytes [VH99]), may be able to regulate both of these characteristics of a synapse.

Future Project #3: Astrocytes' Role on Network Dynamics

For our next project, we plan on using the results from the zoomed in perspectives of our other projects to consider the role astrocytes have on network level dynamics. Specifically, we are interested in investigating how the astrocyte's ability to ensheath, or tightly wrap around, the synapse influences network level behavior. Using the general framework of our previous projects, we plan to create a family of parameters, associated with the amount of astrocyte ensheathment at a specific synapse, that captures the effective influence astrocytes have on the properties of synaptic transmission (i.e. the ability for a synapse to propagate an electrical signal). We will then ask how the distribution of the ensheathment parameter in the network relates to its firing rate and synchronization properties. In order to perform this investigation at the network level and to relate this work to that of existing literature, we plan to use and extend the tools already used to link network structure properties with the neural firing characteristics [RSK+17]. Despite the wealth of literature on neuronal networks, it is important to note that this field of work is almost entirely devoid of any consideration of astrocytes. This next project promises to yield interesting mathematical and biological results.

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