

Mathematics is the language of science. It enables us to investigate scientific questions which cannot be approached or fully understood experimentally. The biological sciences are particularly interesting to me and I am intrigued by the mathematics which is inspired by and applied to these types of problems. As a graduate student at the University of Utah, I have been introduced to a wide variety of biological problems and the various mathematical techniques used to study them. I am excited about the idea of interdisciplinary research and have an interest in many different biological research topics, ranging from the microscopic to the macroscopic levels. My current research, however, is focused on the electrical coupling of cardiac cells.

Cardiac cells are electrically coupled through gap junction channels, which allow ionic current to spread intercellularly from one cell to the next. It is clear that gap junctional coupling is the primary mechanism for propagation of action potentials in cardiac tissue. However, because the extracellular junctional cleft space between neighboring cells is so narrow and tortuous, it might act as a microdomain for ionic concentrations and electric potentials. In this microdomain, ionic concentrations and electric potentials might vary drastically and rapidly enough to conduct an electrical signal from one cell to the next. Sperelakis et al. have proposed at least two possible mechanisms for this type of coupling, [2]. The first relies on a negative electric potential in the junctional cleft space, which arises due to a high resistance to current between the cleft space and the extracellular space. The second coupling mechanism is based on the accumulation of potassium ions in the junctional cleft space. According to Sperelakis, these coupling mechanisms are strong enough to support propagation in the absence of gap junction channels. His theories are quite controversial and have yet to be verified experimentally. My research is focused on mathematical analysis of these proposed coupling mechanisms.

To investigate coupling through the electric potential, we consider two neighboring cells separated by a narrow junctional cleft space, [1]. The electric potential in the junctional cleft varies due to ionic currents across the junctional membranes of the two cells. Numerically solving the resulting three variable system of nonlinear differential equations, we observe that propagation of electrical activity is possible, but that the coupling mechanism is highly parameter dependent. Propagation is successful if there is high density of sodium channels localized to the junctional membranes and if the resistance to current between the cleft space and the bulk extracellular space is high. To provide a more mathematical explanation of these parameter dependencies, we exploit the fact that there are two time scales involved in the dynamics. Using singular perturbation theory, we consider the slow subsystem and find that there are two distinct types of propagation failure. Furthermore, we are able to characterize parameter space into regions of propagation success and the two different types of propagation failure.

To study the effects of junctional potassium, we keep track of the average concentration of K^+ in the junctional cleft space. When one cell experiences an action potential, potassium accumulates in the junctional cleft space. This raises the K^+ equilibrium potential, resulting in a depolarization of the junctional membrane of the neighboring cell. If this depolarization is sig-

nificant then the neighboring cell might reach threshold and undergo an action potential. In this case, the parameters of interest are the width of the cleft and the rate of potassium leak between the junctional cleft space and the bulk extracellular space. If the cleft width is narrow then the cells are well-coupled. In addition, if the leak rate is low then the coupling resembles gap junctional coupling, but through gated K^+ channels rather than gap junction channels. For wider cleft widths we observe oscillatory behavior, where the action potential is reflected back and forth between the two coupled cells. Bifurcation analysis reveals that the oscillations arise with a constant amplitude through a saddle-node infinite period bifurcation. This analysis also reveals that there is a critical junctional potassium concentration above which the cells are coupled and below which the cells are uncoupled.

These results raise many interesting questions, some of which I hope to investigate in future work. Once I understand how the two mechanisms work independently, I hope to study how they interact. How do the parameter dependencies change when more than one coupling mechanism is present? In addition, how do these coupling mechanisms depend on spatial information, such as the geometry of the cleft or number of coupled cells? For K^+ coupling, is the oscillatory regime physiologically relevant? If so, what are the implications of these oscillations? I have been studying coupling in the context of cardiac cells, but are these coupling mechanisms present in other cell types, such as neurons or smooth muscle cells? As an extension to these questions, I am interested in trying to understand how conduction over the myocardium appears as a reliable, smooth wave front while propagation from cell to cell is discrete and saltatory in nature. Ultimately, a more complete understanding of how individual cells are electrically coupled will provide insight about electrical conduction on the macroscopic level, under both healthy and pathological conditions.

Although I have recently been studying problems in cardiac electrophysiology, I am interested in a variety of research topics and would enjoy the opportunity to work on a new project. As a member of the diverse math biology group at the University of Utah, I feel fortunate to have been introduced to many different and exciting research topics. I am particularly intrigued by questions arising in physiology, including cellular processes, electrophysiology and excitability, calcium dynamics, neuroscience, intercellular communication, and systems physiology. These types of problems often span multiple time and space scales, a feature that is mathematically challenging but at the same time can be used to obtain analytic results and develop appropriate computational algorithms. My current work utilizes dynamical system theory, bifurcation analysis, perturbation methods, partial differential equations and numerical analysis. However, I am open to learning and developing new mathematical approaches as the biology demands. Although most biological processes are extremely complicated, and may seem daunting at first glance, my approach is to "make things as simple as possible, but no simpler." My objective is to develop and analyze mathematical models that capture the essential behavior and provide insight about the biological mechanisms. My goal is to predict or explain a given biological phenomenon rather than simply reproduce it. Ideally, this type of mathematical analysis will help explain experimental results and inspire new experimental approaches.

References

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- [2] N. Sperlakis and K. McConnell. Electric field interactions between closely abutting excitable cells. *IEEE Engineering in Medicine and Biology*, pages 77–89, January/February 2002.