Theoretical and experimental quantification of a period doubling cascade to chaos in cardiac tissue and its relation to arrhythmias.

YOUR NAME

Introduction: The heart is an excitable system through which electrical waves of depolarization propagate in a coordinated manner to initiate mechanical contraction. A fundamental characteristic of cardiac cells is a shortening of the depolarization time, known as the action potential duration (APD), with increasing electrical stimulation rates. However, at high stimulation frequencies many cardiac cells exhibit alternans, a beat-to-beat alternation in APD between long and short pulses.

Motivation: Experiments and mathematical models of the heart strongly suggest that desynchronized depolarization, such as alternans, can lead to fibrillation and sudden cardiac death (SCD)[1]. As such, understanding and characterizing the onset and stability of alternans is of great interest not only as a dynamical systems problem but also as a medical one. Clinically, APD alternans is considered one of the primary mechanisms for SCD, taking the lives of over 350,000 people, which is half of all heart disease deaths in America each year.[2] A potential pathway for the transition from alternans to fibrillation is a period doubling cascade, a well-studied phenomenon in the field of chaos and nonlinear dynamics.[3] Alternans has been proposed as the manifestation of the first period doubling bifurcation along this cascade under which the system enters a state of complex spatiotemporal dynamics (fibrillation).

Problem: Despite experimental evidence of higher order bifurcations in paced cardiac tissue (see [4] and references therein), **there exists only one proposed model to explain the observed phenomena**. This model features a simple 1D return map of a biphasic curve that describes the relationship between an APD and the immediately preceding diastolic interval (DI), known as a restitution curve (RC).[5] However, **biphasic curves are not observed experimentally during steady state pacing**.[6] Furthermore, several mathematical cell models reproduce alternans but cannot explain or produce higher order bifurcations.[7]

Approach/Tools: Cardiac cells and tissue APD can be modeled from simple two variable return maps to complex reaction diffusion systems with tens of variables.[8] To understand and predict characteristics of cardiac tissue I will use mathematical methods from nonlinear dynamics, numerical analysis of partial differential equations, as well as state-of-the-art voltage and calcium optical mapping experiments on four different animal species.

Research Plan: The discrepancy between experimentally observed phenomena and the predictions of current models suggests a higher dimensional RC in that it may depend not only on the previous DI but also retain some memory as a restitution manifold (RM).[9,10] I will begin by investigating the relevant physiological effects that drive the memory dimensionality of the RM through experiments by varying **(1)** chemicals, **(2)** electrical stimulus, and **(3)** species.

(1) I will vary concentrations of potassium, calcium, and sodium alongside drugs such as verapamil, a calcium blocker, and pinacidil, a potassium enhancer, to quantify their effects on the bifurcation dynamics as they increase or suppress them.

(2) The hearts will be electrically stimulated using different perturbative pacing protocols[11] to characterize RM dimensionality.

(3) To address and quantify known differences in tissue characteristics across species, I will use four different animal species: zebra fish, rabbit, cat, and pig.

By determining the explicit dependence of APD on all previous DIs experimentally, I can

quantify the importance of memory and determine truncation errors. After developing a more general multidimensional restitution hypothesis, I will then proceed to calculate trajectories on this RM mathematically through nonlinear dynamics and computationally through cardiomyocyte models that will be included and compared to my experimental data.

Research Goals and Milestones: My goal is to experimentally measure the higher dimensional character of this restitution manifold (RM). With a more specific understanding of this manifold and experimental data, I will then mathematically and computationally model the mechanisms giving rise to the higher order bifurcations.

Milestones	Experiment	Theory
Year 1	Quantify relevant dimensionality of the RM and truncation error.	Develop single cell memory model to predict temporal dynamics of RM.
Year 2	Categorize effects of varying chemical concentrations on RM and memory.	Model tissue with memory based on chemical changes to ionic currents.
Year 3	Specify and construct RM trajectories based on stimulation protocols.	Simulate/investigate high resolution tissues with spatial inhomogeneities.

Resources: My lab in physics at GT works with the biomedical and physiology departments to share animal research subjects. The PI also has funds available for animals to be used for this study if necessary. The lab has a fully equipped dual optical mapping system to record voltage and calcium signals from the heart's surface. For computational work there are two PCs with a K40 Nvidia Tesla each for GPU simulations in addition to an XSEDE account.

Methods: Zebra fish, rabbit, cat, and pigs will be euthanized according to approved IACUC protocols. Simultaneous voltage and calcium data will be obtained via fluorescence images over the entire surface of the heart, using a EMCCD camera at a frame rate of 511Hz (see detailed methods in [12]). Numerical simulations using GPUs will be performed using both simplified mathematical models for cardiac tissue as well as more complex ionic cell models.[8] The effects of drugs on APD and peak duration of intracellular calcium will be compared directly with these simulations to identify the bifurcation mechanisms.

Qualifications: I have been working full time in the lab participating in experiments since the beginning of the summer, and for the past two months I have been performing heart experiments all by myself (N=12), collecting preliminary data for this project. I have extensively reviewed literature from experiments and theory, and I have developed simple models of spatially coupled cardiac cells in inhomogeneous issue.

Broader Impacts: This research will lead to a much better understanding of the mechanisms that initiate arrhythmias in the heart. The mathematical models developed for this biophysical system will provide insights on methods to suppress or prevent initiation of lethal arrhythmias. As mentioned in my personal statement, I truly enjoy disseminating science to the general public. This interdisciplinary research will provide me with outreach opportunities where I may illustrate the strong connection between mathematics, physics, and biology. I intend to participate with local high schools through workshops and public talks.

References

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