Calcium signaling in heart: Multi-scale modeling with instabilities

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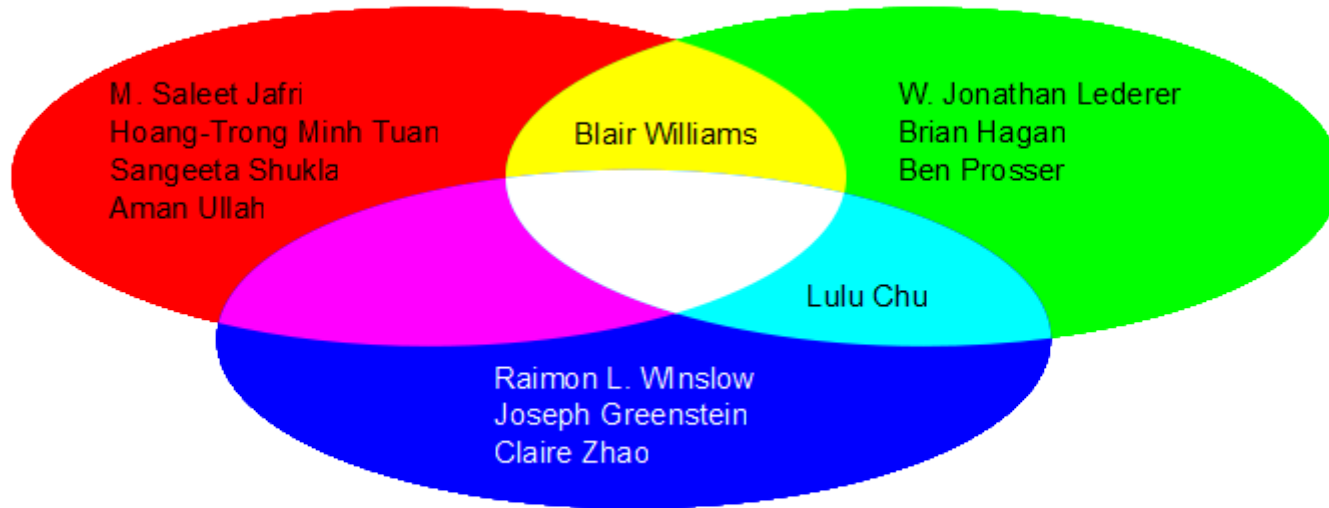University of Maryland Baltimore
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Introduction

- Heart disease is the leading cause of death worldwide.

- Cardiac arrhythmia leading to sudden cardiac death (fibrillation) is a major mechanism for this fatal disease.

- Defects in cardiac calcium dynamics underlie certain types of cardiac arrhythmias.

Cardiac Calcium Dynamics

- Calcium plays a central role in the function of the heart as it couples the electrical excitation of the heart to contraction.

- Calcium release is comprised of a large number of stochastic events called calcium sparks that are coordinated by the opening of voltage-gated calcium channels during electrical excitation.

Ca²⁺ Transient and Ca²⁺ Sparks in Ventricular Myocytes

$[Ca^{2+}]$ "sparks" are the elementary release events. They are synchronized by the electrical signal of the cell to produce the elevation of $[Ca^{2+}]$.
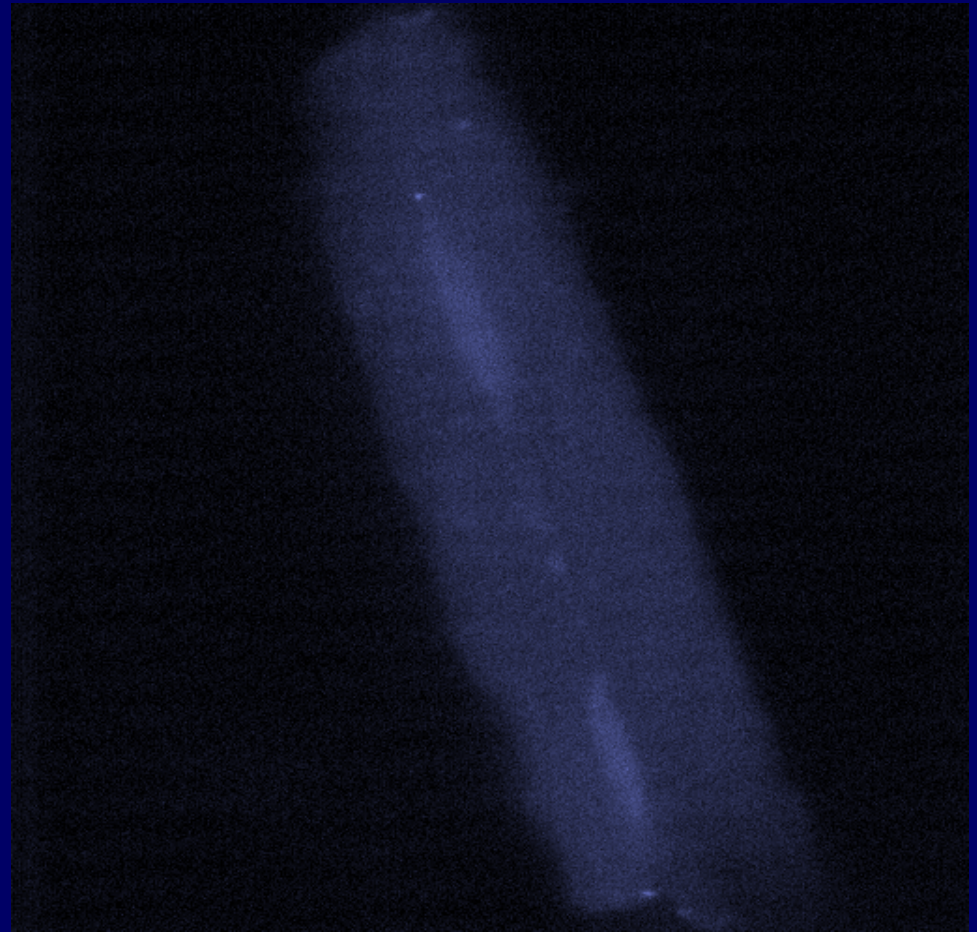
Model Schematic
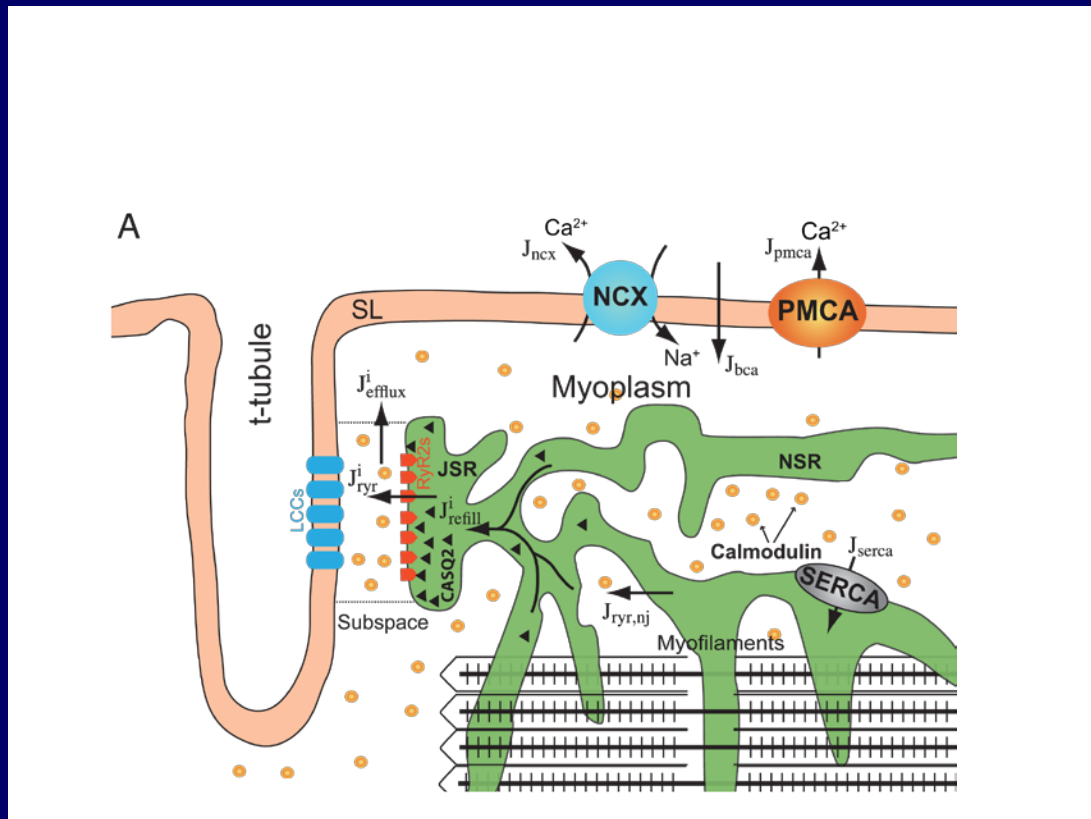
Complex Multiscale Problem

- Calcium sparks occur on the millisecond time scale involving diadic compartments that are 10's of nanometers in size and the action of the molecular entities that reside there.

- Over 1 million molecules – Ryanodine Receptors and L-type calcium channels gate rapidly with kinetics on the submicrosecond time scale.

- Cardiac myocytes (10-100 microns) beat with frequencies of approximately 1 Hz

- Arrhythmias arise of the course of many beats in cardiac tissue (cm) that is comprised of many individual myocytes

Approach

- We have developed the Ultrafast Monte Carlo Simulation Algorithm. Simulation that used to take a month take less than a minute.

- It will be used to describe stochastic cellular and multicellular calcium dynamics.

- Experiments on single cells and sections of cardiac tissue are being performed to constrain and test model predictions.
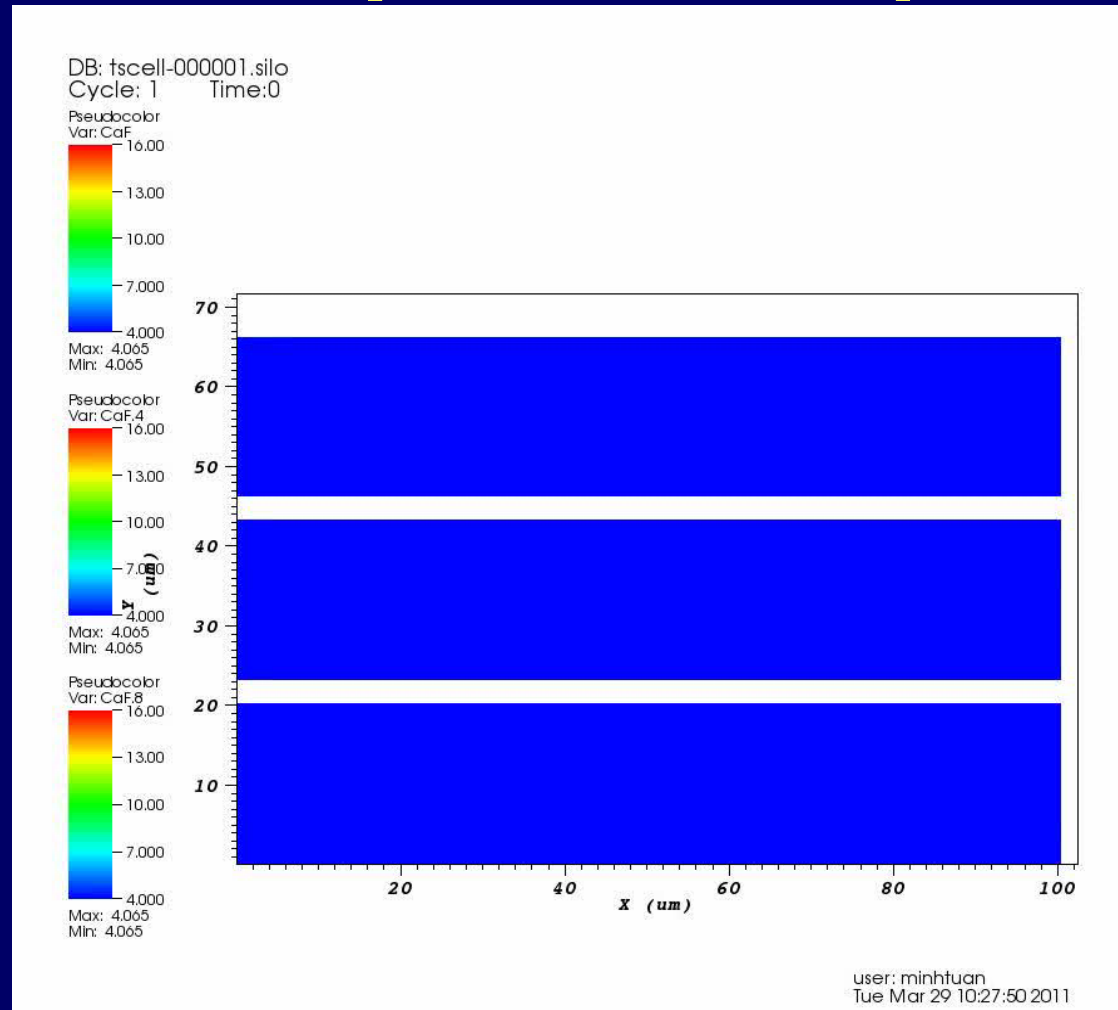
Resting Myocyte Activity
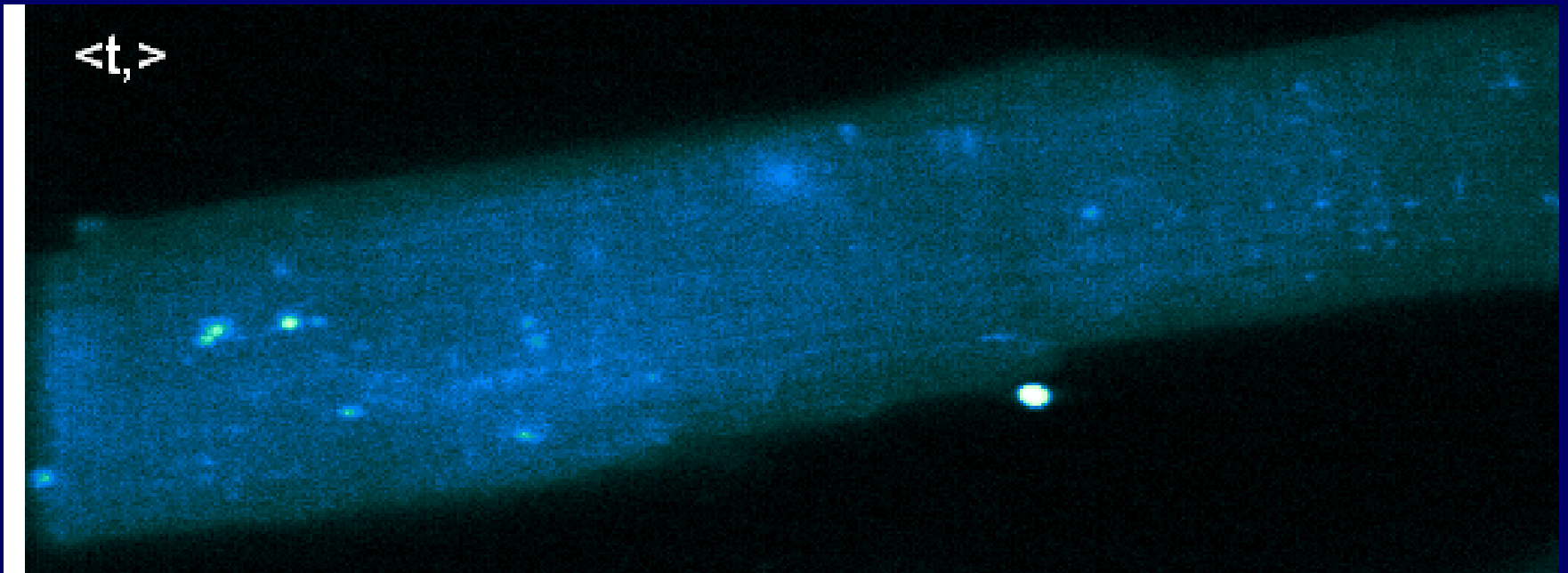
Experimental Spontaneous Calcium Sparks
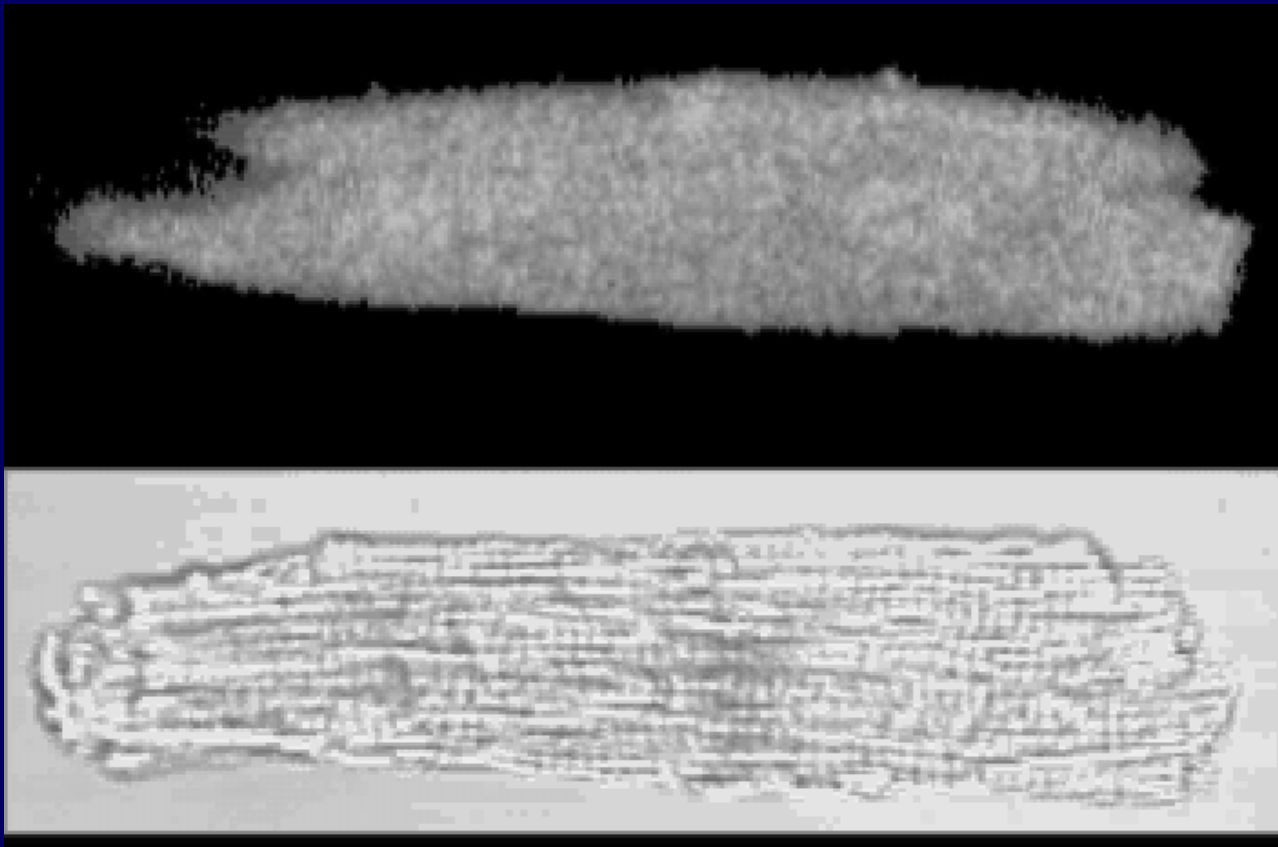
Resting Myocyte Activity

Simulated Spontaneous Calcium Sparks

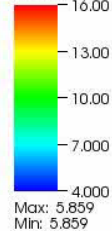# Calcium Entrained Arrhythmias

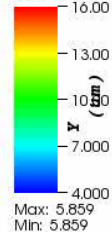Experimental Calcium overload

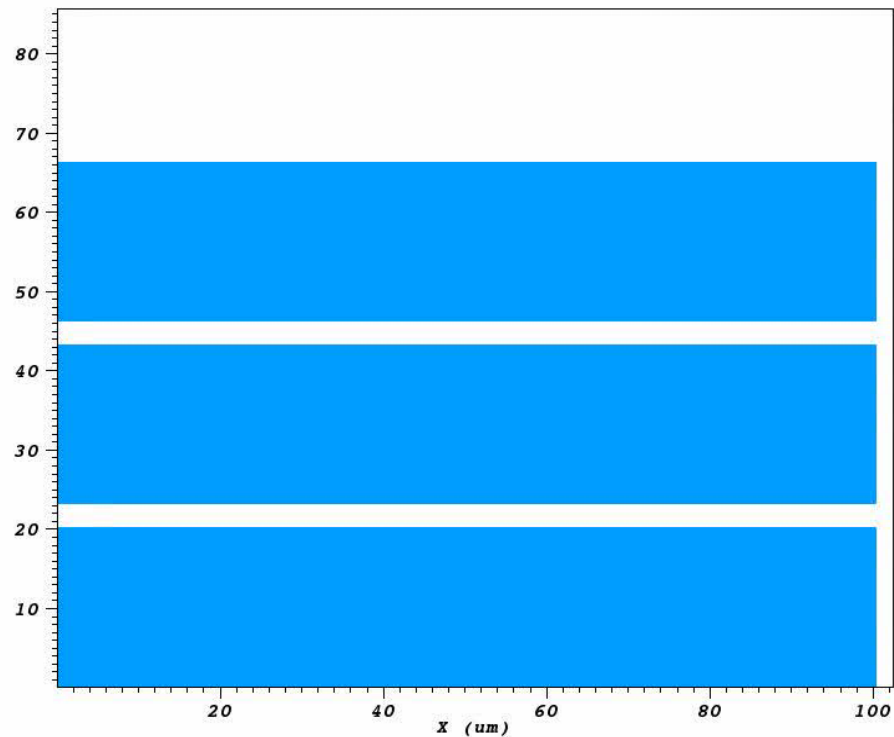# Calcium Entrained Arrhythmias

Simulated Calcium Overload
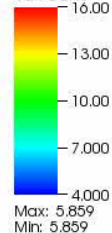
Summary

- Address multiscale problem with experimental and computational studies on different scales.

- Integration of information across scales.

- New approaches – experimental and computational