Calcium signaling in heart: Systems biology through multi-scale modeling

M. Saleet Jafri, Raimond L. Winslow & W. J. Lederer
George Mason University, Johns Hopkins University, University of Maryland Baltimore

We have developed and implemented novel approaches to enable us to directly investigate the spatial and temporal details of local and cell-wide Ca^{2+} signaling in a cardiac ventricular myocyte with a fully stochastic mathematical model. The details of the signaling relationships in the mathematical model are highly constrained by molecular and cellular experimental information. Code has been written for graphic processor units (GPU) to enable fast large-scale computations that greatly accelerate the simulation speed. Although the cellular model computation is daunting, the five year goal is to carry out a larger multicellular, whole heart scale-up. Presumably the rapid expansion of GPU technology and the availability of large GPU clusters will keep up with our needs. As with the cellular modeling, the larger scale simulation will be constrained by new experimental findings.

The problem of calcium signaling is inherently multi-scale. The opening and closing of over one million calcium channels is stochastic and occurs on the sub-microsecond timescale and occurs in the diadic subspace which has dimensions defined in the nanometer scale. The release sites are placed fairly regularly throughout the myocyte which is a large cell 120 microns in length. Calcium transients and action potentials in myocytes are typically observed one the millisecond scale. The myocytes combine to form heart muscle which can be millimeter up to centimeters in scale with long simulation times in the order of seconds required. Hence in order to understand the system a multi-scale approach is essential.

Typically when approaching this problem models would be constructed on different scales and information from one model would used to inform the design of other models. Attempts to integrate models on different scales often have used model reduction methods, simplifying assumptions, and approximations to make the multi modeling possible. Unfortunately, while there is value in these approaches, it is possible that these methods obfuscate essential details necessary for a detailed understanding of the system. For example, model reduction might only be valid under a certain range of conditions that might be violated during pathology. Also, reduction methods might remove the stochastic element of the model which we feel is essential for a calcium-entrained cardiac arrhythmias.

Our systems approach takes advantage of recent advantages in algorithms and computational resources that makes a detailed multi-scale model that can incorporate stochastic channel dynamics into spatial model of the cardiac myocyte and heart tissue. We have developed the "Ultrafast Monte Carlo method" (with collaborators Smith and Sobie in a previous NSF funded project) that in addition to algorithmic improvements in computational efficiency exploits the recent advances in computational speed available on GPUs. Further computational resources include clusters of the GPUs which are becoming easier to access and obtain.

These issues pertain not only to models of cardiac myocytes but are ubiquitous in biological systems. There are many discrete, stochastic and local events that govern cellular behavior. For example, the calcium release events in nerve terminals that induce neurotransmitter release are a problem that parallels the type of multi-scale problem described here. Other events depend upon signaling molecules and their ligands (or receptors) that can be described as discrete signaling events. Studies have suggested that the discrete stochastic behavior can result in above threshold events that would not be observed in continuous discrete model descriptions. Hence, in some systems, it is essential to capture this discrete stochastic behavior.

One additional challenge is the coupling of experimental studies that provide data that inform and constrain the model. Often experiments use the reductionist approach that studies the system at a specific level with its inherent spatial and temporal scales The models are crucial at integrating this information to understand the system behavior. The multi-scale systems approach not only allows, bur requires that the model be validated at these different scales to be optimally meaningful. New molecular imaging methods allow the spatial and temporal observation and dissection of the behavior in living cells. New animal models (transgenic, knockout, and disease model organisms) allow pathology to be studied in living systems. These experimental advances allow the dynamics of cellular function both under normal and pathological conditions to be measure and finer spatial and temporal detail.

In summary, realistic multi-scale modeling and systems biology has become more tractable due to advances in computational and experimental methodologies. We are applying these methods to understand calcium entrained arrhythmias in the heart. The methods and insights we are using and developing can find broad application to other biological systems.