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SEMINAR

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304 Whitehead Hall  
Refreshments: 3:30 p.m.  
Seminar: 4:00 p.m.

CALCIUM SIGNALING IN THE CARDIAC DYAD

ABSTRACT

In cardiac ventricular myocytes, events crucial to excitation-contraction (EC) coupling take place in spatially restricted microdomains known as dyads. The length-scale over which this  $\text{Ca}^{2+}$  signaling occurs is a few tens of nanometers and the time-scale of these events spans the range of  $\mu\text{secs}$  to  $\text{msecs}$ . Quantitative understanding of the functional consequences of these signaling events therefore requires development of models that are applicable over a range of spatio-temporal scales. We will present several new approaches for developing such multi-scale models of EC coupling.

We will begin our analyses at the nano-scale level by presenting a model of dyad  $\text{Ca}^{2+}$  dynamics in which the Fokker–Planck equation is solved for the probability  $P(x, t)$  that a  $\text{Ca}^{2+}$  ion is located at position  $x$  at time  $t$  (Tanskanen et al., *Biophys. J.*, Feb. 27 2007; Tanskanen et al., *SIAM J. MMS*, 5(4):1280). The model will describe: (a) dyad geometry; (b) membrane surface charges; (c) geometry and space-filling properties of the calcium-binding calcium release channels (known as RyRs and measured using cryo-em), L-Type  $\text{Ca}^{2+}$  channel (LCC), and calmodulin proteins (measured using x-ray crystallography); (d) stochastic gating of and  $\text{Ca}^{2+}$  flux through LCCs; and (e)  $\text{Ca}^{2+}$  binding to RyR activation/inactivation sites, stochastic gating, and  $\text{Ca}^{2+}$  flux through RyRs. Using this model, we will demonstrate that: (a)  $\text{Ca}^{2+}$  signaling in the dyad is mediated by  $\sim$  tens of  $\text{Ca}^{2+}$  ions; (b) these signaling events are noisy due to the small number of ions involved; and (c) the geometry of the RyR protein may function to restrict the diffusion of  $\text{Ca}^{2+}$  ions, funneling  $\text{Ca}^{2+}$  ions to activation sites on the RyR, thus increasing RyR open probability and EC coupling gain.

The computational complexity of the above model prevents its incorporation into integrative models of the myocyte. Simplification of this model to one in which the dyadic space is represented using a single compartment yields what we have referred to previously as the stochastic local-control model of EC coupling (*Biophys. J.* 83:2918). We will show that this model captures the fundamental EC coupling properties of graded release and voltage-dependent gain, may be integrated within a model of the myocyte, and may be simulated in reasonable times using a combination of efficient numerical methods and parallel computing, but that in general it is not well suited for single-cell simulations. To address this problem, we will show how “separation of time-scales” may be used to formulate what we refer to as the coupled LCC–RyR gating model (*Biophys. J.* 87:3723). In this model, nearby LCCs and RyRs function gate as a coupled system that may be described using low-dimensional systems of ordinary differential equations, thus reducing computational complexity dramatically while still capturing fundamentally important EC coupling properties. The simplified model may be solved many orders of magnitude faster than can the stochastic model, thus enabling incorporation into tissue-level simulations (*Biophys. J.* 90:77).

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