Centre for Biosystems Science and Engineering

S E M I N A R

at 12:00 noon on November 4, 2015

MRDG Seminar Hall

The Diversity and Complexity of Calcium Signaling in Cardiac Muscle

Prof. Raimond Winslow

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The calcium (Ca2+) ion is a ubiquitous signaling molecule in cardiac muscle cells. It regulates many cellular processes including mechanical contraction, electrical behavior, energy production, and gene expression. Ca2+ signaling begins with the process of excitation-contraction coupling (ECC). In ECC, electrical depolarization of the sarcolemma causes L-Type Ca2+ channels (LCCs) to open. Ca2+ ions entering the cell through LCCs bind to ryanodine-sensitive Ca2+ release channels (RyRs) in the junctional sarcoplasmic reticulum (JSR) membrane causing them to open, leading to a large flux of Ca2+ into the cytosol that triggers muscle contraction. Negative feedback interactions mediated by Ca2+ binding to calmodulin (CaM) molecules tethered to LCCs also influence electrical behavior of the myocyte by modulating action potential shape. A number of intracellular signaling pathways modulate ECC. We will present results on modeling these pathways in an effort to better understand their function. Using a recently published model of localized Ca2+ release events we will describe new insights into how RyR-mediated Ca2+-release is controlled by both structural and functional factors. We will present a model of the Ca2+/CaM-dependent protein kinase II pathway and its regulation by reactive oxygen species. Activation of this pathway, as occurs in heart failure, is known to be pro-arrhythmic. We will apply the models to explore mechanisms underlying these arrhythmias. The β-adrenergic and nitric oxide (NO) signaling pathways exert excitatory and inhibitory influences on ECC, respectively. These pathways are coupled through cyclic nucleotide-dependence of phosphodiesterase (PDE) activity. We will use a computational model of the coupled β-adrenergic/NO pathways to explore the dependence of this coupling on various PDEs. Finally, we will present a model in which Ca2+ and CaM binding to calcineurin promotes the de-phosphorylation of sub-sarcolemmal nuclear factor of activated T-cells and its translocation to the nucleus to regulate transcriptional events. We apply this model to understand how the same Ca2+ signal which underlies ECC also functions as a hypertrophic signal, and implications of these findings for treatment of cardiac hypertrophy.

About the speaker:

Dr. Raimond L. Winslow is a professor of biomedical engineering at the Johns Hopkins University School of Medicine. He holds an additional appointment in the Whiting School of Engineering at Johns Hopkins, through which he serves as Director of the Institute for Computational Medicine and Director of the Center for Cardiovascular Bioinformatics and Modeling. Dr. Winslow holds a B.S. in electrical engineering from Worcester Polytechnic Institute and a Ph.D. in biomedical engineering from the Johns Hopkins University. He concluded his training at the Institute for Biomedical Computing and Department of Neurology within Washington University in St. Louis. He joined the faculty of Johns Hopkins in 1991 as an assistant professor, became an associate professor in 1994 and a full professor in 2000. Dr. Winslow is a fellow of the Biomedical Engineering Society, American Heart Association and American Institute for Medical and Biological Engineering. He serves as Specialty Editor in Chief for the journal Frontiers in Computational Physiology and Medicine, and as a member of the editorial boards of Circulation Research, The Journal of Molecular and Cellular Cardiology, IET Systems Biology and the International Journal of Computational Medicine and Healthcare. He has authored or co-authored over 130 peer-reviewed articles and 12 book chapters, received numerous grants and awards and holds one patent.