Preface

This issue of *Journal of Critical Reviews in Biomedical Engineering* contains 5 review articles about the current state-of-the-art modeling of signal transduction at different scales in cardiovascular systems. The field of cardiovascular modeling is wide. The role and importance of modeling and the simulation of cardiovascular systems are now being recognized because of the complexity of the cardiovascular system and of cardiovascular diseases. Immense potential exists for our improved understanding of cardiovascular systems using the tools from emerging discipline of Systems Biology. Both cardiovascular systems modeling and systems biology approaches have translational value in meaningful hypothesis-driven modeling and in providing a framework for the development and evaluation of pharmacological treatments. In this special issue, the focus has been on nitric oxide (NO), calcium, adenosine triphosphate (ATP), and oxidative stress in cellular and microcirculation models.

Schmitz et al.[1] reviews computational models of mitochondrial energy transduction. One of the important questions these modeling efforts are attempting to answer is, What controls the rate of mitochondrial ATP synthesis? In addition, application of these models to address longstanding biological questions including mitochondrial respiratory control, the interaction of mitochondrial calcium buffering function with the ATP synthesis function of the organelle, mitochondrial swelling during active respiration, and paradoxical elevated reactive oxygen species (ROS) production during reperfusion are presented. The authors highlight the fact that the rate at which the experimental database supporting model parameterization and validation has not kept pace with the rate at which the molecular detail and complexity of mitochondrial energy transduction models has been expanding recently. They discuss both inductive (large-scale modeling approaches) and hypothesis-driven models (the simplest model capturing the key features of a system). A major challenge in developing mechanistic mitochondrial energy transduction models is identified as model parameterization because large mechanistic models can include upward of few hundred parameters obtained from diverse sources.

Amanfu and Saucerman[2] discuss how cellular models of electrophysiology, cell signaling, and metabolism have been used to investigate pharmacological therapies for cardiac diseases. Their article presents modeling efforts for three cardiac diseases, namely arrhythmia, ischemia, and heart failure. The models of cardiac action potential, and Markov models that can simulate the molecular basis of arrhythmias caused by mutations in ion channels and the effect of pharmaceutical compounds, are reviewed for arrhythmia. For myocardial ischemia and heart failure, models describing the metabolic state of a myocyte during pathologic conditions and its effect on cardiac electrophysiology are presented. In addition, models for signaling pathways for cellular processes such as cell growth and contractility and calcium as a second messenger are discussed. Systems-based approaches such as this will play an important role in elucidating the complex interactions in cardiac electrophysiology and will have translational value in providing the development of pharmacological treatments in diseases such as atherosclerosis, cardiac hypertrophy, heart failure, and arrhythmias.

Buerk et al.[3] reviewed model predictions and relevant experimental data with respect to several signaling pathways in the microcirculation that involve NO. The articles provides a diverse and comprehensive review of the modeling of calcium kinetics in endothelial cells, endothelial nitric-oxide synthase activation, wall shear stress and NO production, and NO and coupled NO and oxygen biotransport. In addition, this review also examines the modeling of secondary targets of NO including soluble guanylate cyclase and cytochrome oxidase. The article also provides current state of NO measurements and its interaction with red blood cells.

Kapela el al.[4] present models of calcium signaling in the microcirculation with a focus on intercellular communication and vasoreactivity. They describe calcium dynamics models for vascular cells including endothelial and smooth muscle cells. Modeling of myoendothelial communication, conducted responses, and vasomotion also are presented.

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Kavdia[5] reviews kinetic models of superoxide dismutase and tyrosine nitration and biotransport models of NO, superoxide, and peroxynitrite in the microcirculation. In addition, integrated experimental and computational models of dynamics of NO/superoxide/peroxynitrite in diverse systems are evaluated. The causes and consequences of oxidative and nitrosative stresses depend on a delicate balance among many processes. A better understanding of NO, ROS, and reactive nitrogen species in biological systems will require quantitative assessment of biochemical interactions and transport of these species from a systems perspective. Computational modeling approaches can help to elucidate behavior of these interactions for a particular system and will be important for our understanding of cardiovascular diseases and therapeutic interventions.

In conclusion, these articles highlight the contribution of computational modeling to our understanding of cardiovascular systems, from molecules to the whole organ and in physiology, pathophysiology, and therapeutic approaches. We have assembled a collection of articles that will provide the reader with a comprehensive view of challenges and opportunities in modeling in cardiovascular systems. Each article in this issue will provide greater insight in understanding specific mechanisms involved related to a specific model.

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