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Arrhythmia models: *in vivo*, *in vitro* and *in silico*

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Remodeling of ion channel and/or intracellular calcium handling properties lies at the heart of numerous congenital and acquired cardiovascular disorders that culminate in lethal arrhythmias. Typically pathophysiological remodeling is caused by a complex interplay between electrical, mechanical, structural, metabolic, and genetic alterations which disrupt normal excitation-contraction coupling and predispose to arrhythmic triggers. Therefore, a comprehensive understanding of arrhythmia mechanisms requires a multi-faceted approach that involves studies performed at multiple levels of integration. Specifically, the development of appropriate *in vivo*, *in vitro*, and *in silico* models that simulate key aspects of human disease is required to dissect the complex regulatory pathways and feedback mechanisms that ultimately dictate ion channel function in both health and disease.

In this section of *Drug Discovery Today: Disease Models*, several review articles by experts in the field are presented to illustrate the importance of using complimentary approaches for investigating arrhythmia mechanisms. As will become evident, state-of-the-art experimental and computational tools can be effectively exploited in a synergistic manner to better understand the role of altered ion channel and calcium handling properties in the genesis of complex and clinically relevant arrhythmias.

The article by Sobie and Wehrens is a perfect illustration of how *in vitro*, *in vivo*, and *in silico* approaches have recently improved our understanding of calcium mediated arrhythmias, in general, and catecholaminergic polymorphic ventricular tachycardia, in particular. Specifically, these studies have revealed how certain mutations targeting calcium regulatory proteins can enhance diastolic calcium leak from the sarcoplasmic reticulum and generate afterdepolarization mediated triggers at the intact organ level.

Calcium is a central signaling molecule, which along with its associated proteins, calmodulin, and calcium-calmodulin kinase II couple subcellular processes, modulate protein function and alter cellular electrophysiology by participating in microdomains that are coordinated by macromolecular signaling complexes. The article by Kline and Mohler highlights the role of anchoring proteins in cardiac pathophysiology. As will be revealed, these anchoring subunits not only regulate functional activities by coordinating structural interactions within large macromolecular complexes, but also exert direct effects on ion channel gating, which have been causally linked to cardiac arrhythmia phenotypes. Mechanisms by which altered subcellular function by anchoring proteins result in abnormal electrical behavior at the tissue

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level is perhaps best probed using multi-scale computational modeling approaches which can combine molecular details on the one hand and network properties on the other.

This concept is also highlighted by Moreno and Clancy, who discuss the challenges associated with determining the relationships between subcellular perturbations and arrhythmias - since the cardiac system is so extraordinarily complex. In order to attribute an arrhythmia to a specific parameter, individual perturbations can be studied in isolation and combination, which is only possible using computational approaches, which reveal behavior in systems throughout large parameter spaces and lead to elucidation of general mechanisms. This, in fact, is the strong suit of computational approaches. The results of model simulations can also suggest predicted outcomes that can be tested *in vitro* and ultimately *in vivo*. Consistent feedback between computer based predictions and experimental outcomes allows for targeted hypothesis testing.

Trayanova and Tice review anatomically based computational approaches in whole heart *in silico* models. The approach they describe is the complement to computer simulations aimed at discovering general mechanisms, and rather aspires to *individualized* model reconstructions that have the potential to revolutionize patient treatment options. Heart-specific reconstructions can be used to specifically identify pathological tissues and simulations may reveal appropriate ablation and even appropriate drug interventions on a case-by-case basis.

A combined *in vivo*, *in vitro* and *in silico* approach can even be used to design cardiac devices, such as a biological pacemaker described in the paper by Robinson. The biological pacemaker may someday take the place of widely used implantable devices to maintain normal cardiac rhythms. The development of a biopacemaker relies on the interplay and feedback between complementary approaches to define specific biophysical traits of the ideal pacemaker and make predictions about outcomes in increasingly complex cardiac systems. *ug Discovery Today: Disease Models | Cardiovascular diseases Vol. 4, No. 4 2007*

It has become increasingly clear that elucidation of arrhythmia mechanisms is best accomplished by a multifaceted approach that includes *in vivo*, *in vitro* and *in silico* models. Continuous feedback between distinct approaches to arrhythmias allow for revelation of the physiological mechanisms that underlie emergent arrhythmias that are observed in tissues and organs. As experimental and computational model approaches become progressively more refined and increasingly sophisticated, improved understanding of what causes arrhythmias should lead to improved treatment strategies for millions of affected patients worldwide.

Biographies

Fadi G. Akar is currently an Assistant Professor of Medicine at the Mount Sinai School of Medicine in New York and an adjunct Assistant Professor in the Division of Cardiology and Computational Medicine at Johns Hopkins University in Baltimore. Dr. Akar received a Bachelors of Science degree in Electrical Engineering from The Pennsylvania State University, and Masters and PhD degrees in Biomedical Engineering from Case Western Reserve University in Cleveland. Dr. Akar was then a Post-doctoral research fellow, a Research Associate, and an Assistant Professor in Medicine at Johns Hopkins University from 2002 to 2007. Specific areas of active research in Dr. Akar's lab include mechanisms of mechano-electrical feedback, the electrophysiology of mechanical dyssynchrony and resynchronization therapy, the interaction of myocardial energetics and electrical function in post-ischemic remodeling and reperfusion related arrhythmias, and the role of altered gene expression and targeted gene delivery on ion channel function and arrhythmogenesis in cardiovascular diseases.

Colleen E. Clancy is currently an Associate Professor of Pharmacology at the University of California, Davis. Dr. Clancy received a Bachelors of Science degree in Mathematics and Biology from Union College and the PhD degree in Physiology and Biophysics from Case Western Reserve University in Cleveland. Dr. Clancy then completed her post-doctoral training at Columbia University. She was then an Associate Research Scientist at Columbia University and an Assistant Professor in Physiology and Biophysics at Weill Medical College of Cornell University from 2004 to 2009. To achieve an integrative understanding of complex systems, The Clancy Lab uses mathematics and high performance computing to construct quantitative representations of the heart and hippocampus brain region. The general approach used in the laboratory is to design detailed models of ion channel activity that can be used to study perturbations, such as those caused by effects of drugs, mutations or phosphorylation. Ion channel models are then incorporated into virtual excitable cells and connected to form functional models of tissues, which allows us to follow perturbations across multiple scales, from the modified proteins to altered cellular states to the propagation of the perturbation in cell networks.