Towards the Prediction of Therapeutic Targets for Plateau-Induced Arrhythmias Using a Dominant Scale Analysis of a Computational Model of Mouse Myocyte Action Potentials

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THERE is an ever-increasing diversity and complexity of cardiac single-cell models addressing action potential dynamics [1], but our understanding of the biophysical mechanisms underlying different phenotypes is still limited. The complexity of nonlinear interactions between molecular behaviors and ionic currents can make it difficult to identify causal mechanisms using simulation or lab experimentation alone. Our novel strategy for locally-applied model reduction and analysis provides a valuable bridge between biophysically detailed and highly abstract models [2]. Our tools are applicable to the elucidation of complex mechanisms in problems across neuroscience and systems biology.

I. Model Analysis and Reduction

In a model of a mouse myocyte action potential [3], 43 dynamic variables represent 15 experimentally determined currents. This model reproduces observed phenotypes of both wild-type action potentials and genetic mutants where altered potassium channels result in arrhythmia-inducing plateau potentials [4]. Using a dominant scale analysis technique [5], we quantify the contributions of the ionic currents to the behavior of the system. We divide the action potential into distinct temporal regimes that are each characterized by a small number of dynamic variables having the greatest local influence [6]. This reduced the model to 6 active dynamic variables within the region of the plateau, with the relation between the resulting reduced models acting as a hypothesis for the mechanism of plateau potentials. Our analysis formally characterizes a mechanism underpinning the mutant phenotype model that is driven by an imbalance between sodium and potassium currents, which causes over-activation of an inward L-type calcium current during repolarization. This result is in line with experimental data.

II. Predictions of Therapeutic Targets

Our approach to elucidating dysfunctional mechanisms has the potential to tightly focus the experimental exploration of therapeutic targets. Here, we use our identification of the influence of L-type calcium on sodium dynamics during repolarization to gain insight into combinations of parameter changes that reduce plateau duration in the detailed model. Calcium channel blockade is a common therapy used in treating arrhythmias [7], but undesired side effects affecting other ion channels or non-cardiac cells may also occur. The mechanism underlying its efficacy is poorly understood. Our study of the plateau potential involves new computational tools to quantify the effects and inter-relations of pharmacological and genetic changes to other channels. We leverage dynamical systems techniques to visualize and quantify the complex interaction between the inactivation of sodium channels and the transient K+ and L-type calcium channels to identify novel therapy targets. For example, our analysis led us to try a combination of a genetic calcium channel blocker with upregulated delayed K+ rectifier current density, which dramatically reduces action potential duration in our mutant myocyte model.

References

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