Parameter Sensitivity in a Model of the Ventricular Action Potential: Visualizing a Multi-Dimensional Conductance Space

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The electrical behavior of the cardiac myocyte depends on the coordinated action of numerous voltage-dependent ion channels in the cell membrane. With each heartbeat, the orderly opening and closing of these ion channels results in membrane depolarization, which initiates an action potential, and subsequent membrane repolarization, which allows for myocyte relaxation. Computational models serve as an important tool to link ion channel behavior to action potential morphology. With most existing models, however, our understanding of how changes in ion channel expression lead to changes in cell behavior is limited.

In this study we sought to explore thoroughly the parameter space of a mathematical model of the human ventricular myocyte. We systematically varied the nine maximal conductances that govern electrical behavior in this model and examined how changes in each conductance affected the action potential duration, an important physiological characteristic. Five values of each maximal conductance were tested, for a total of 59 = 1,953,125 action potential simulations.

In order to understand how changes in multiple parameters affect the action potential duration we used a technique called dimensional stacking. This technique allowed us to visualize multidimensional data in two dimensions. Pairs of dimensions are embedded within each other with each data point having a unique location on the resulting image. We generated five images, each displaying an eight dimensional space at a different conductance of G_{Nab}, and chose a color scale that most appropriately displays the changes in action potential duration across the multidimensional space. The order in which dimensions are stacked has a large impact on the “interpretability” of the resulting image. An optimal order is believed to be one that yields an image with a uniform distribution of solid color rather than patches of color. Furthermore, the order provides insight into which conductances have a larger affect on the action potential duration than others. The more significant parameters end up on the outer dimensions, while the less significant end up on the inner dimensions. The technique described here serves as a useful complement to PLS regression. The latter approach only provides insight into the neighborhood within a parameter space. Using dimensional stacking we can explore the parameter space more thoroughly.