Title: Rest, Activate, Repeat: Ionic Dynamics in Stimulated and Quiescent Cardiomyocytes in Silico

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Abstract

Numerous human atrial and ventricular cardiomyocyte (CM) *in silico* models exist, each developed with slightly different assumptions, parameter sets, and implementation details. These variations lead to subtle but important differences in simulated ion dynamics, membrane potentials, and overall electrophysiological behaviour.

Our aim was to compare ion dynamics and electrophysiological behaviour across three atrial and two ventricular *in silico* CM models with differing parametrisations. We ran simulations in atrial models by Grandi, Maleckar, and Sönmez, and ventricular models by Grandi and Tomek under quiescent and 1 Hz paced conditions. Membrane potentials, intracellular ion concentrations, and key ion currents were analysed.

The results showed distinct differences in ion dynamics and membrane behaviours across all models. The Grandi atrial model showed early pacing instability, indicating sensitivity during the transition from quiescence to active pacing. Quiescent membrane potentials varied by up to 5.3 mV in atrial models and 7.3 mV in ventricular models, with additional differences observed in calcium handling and action potential peaks.

Our conclusion is that model-specific responses to pacing transitions emphasise the importance of model selection in *in silico* CM studies. Selecting a model that aligns well with a specific research question is necessary to ensure the accuracy and reliability of *in silico* cardiac simulations. Short- and long-term adaptations using more complex protocols and *in vitro* comparisons should be further studied.