Characterization of Temporal Repolarization Variability in the Long QT1 Syndrome under β-Adrenergic Stimulation by Dimension Reduction and Adaptive Filtering

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Background: Enhanced temporal repolarization variability has been reported to contribute to ventricular arrhythmias in the long QT1 (LQT1) syndrome, particularly under β-adrenergic stimulation (β-AS). To investigate the underlying mechanisms, methods able to estimate parameters and state variables of in silico action potential (AP) models from experimentally measured voltage traces would be of major relevance. We propose one such method and test its performance to reproduce AP duration and short-term variability (STV) measures in a human ventricular LQT1 population before and after β-AS.

Methods: From each input voltage trace, the reduction variable method Double Greedy Dimension Reduction (DGDR) was used to estimate the ionic conductances in the O'Hara-Rudy AP model at baseline as well as the phosphorylation levels of cellular substrates in the Xie model of β-AS. The obtained estimates were subsequently used for initialization and update of a second estimation method based on the Unscented Kalman Filter (UKF). The proposed methodology was tested over stochastic AP traces from an experimentally-calibrated population of LQT1 virtual cells at baseline and in response to β-AS.

Results: The combined DGDR-UKF method rendered accurate estimates of ionic current conductances and phosphorylation levels, with mean absolute errors below 0.135. This represents a remarkable improvement with respect to individual DGDR and UKF methods, for which mean errors were of 0.1806 and 0.1775, respectively. Additionally, an important reduction in the estimation uncertainty and convergence time were achieved. The combined DGDR-UKF method reliably replicated the statistical distributions of APD and STV from the LQT1 population (see figure), both at baseline and under β-AS.

Conclusion: We demonstrate the ability of a method for characterization of ventricular repolarization and its variability in the LQT1 syndrome. Our proposed method can be used to uncover the relationship between increased variability and arrhythmogenesis in LQT1 following β-AS.