A Bayesian Filtering methodology to identify key drivers of ventricular repolarization variability

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1. Background

Beat-to-beat variability of repolarization (BVR) has shown value to evaluate cardio-toxic effects of drugs and to identify diseased patients [1]. Computational approaches have been proposed to reproduce experimental BVR measures and identify underlying mechanisms. However, these approaches do not commonly fit experimental BVR distributions and/or need a large amount of data for proper characterization. In this work, a methodology is presented that integrates experimental action potential (AP) measurements into stochastic computational models and applies Bayesian filtering to improve BVR characterization while simultaneously allowing determination of its underlying mechanisms.

2. Materials and Methods

A statistical framework was developed in which stochastic human ventricular models were combined with available voltage measurements by means of nonlinear state-space systems. By using Bayesian filtering techniques [2], cell characteristics, such as current conductances, were estimated for each available AP trace and a fitting stochastic model was obtained.

The proposed methodology was tested over a population of 123 physiologically feasible AP traces generated by varying ionic conductances of a stochastic version of the human ventricular O'Hara *et al*. model [3,4]. BVR was evaluated by short-term variability (STV), quantifying average distance to the line of identity of 30 AP duration points in a Poincaré plot.

3. Results

As illustrated in Fig 1, the proposed methodology was able to correctly estimate ionic current conductances and to provide an accurate representation of BVR measures in the studied population of virtual cells. The median relative parameter estimation error was below 14%, while median absolute STV error was 0.52 ms.

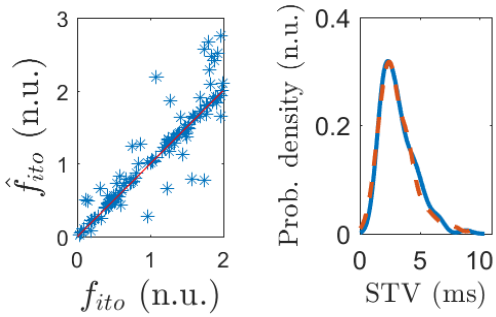

Figure 1: Left: Relation between input and estimated I_{ito} conductance factor, with red line indicating zero-error solution. Right: Probability density of input (blue) and estimated (dashed red) STV values.

4. Discussion and Conclusions

Our approach was validated in providing a one-to-one correspondence between input AP traces and cell parameter values of a stochastic AP model generating them. The distributions of input and estimated BVR measures matched very well, thus rendering this approach suitable to identify key ionic drivers of BVR at different conditions. This can be very useful in the screening of drug-induced cardiotoxicity.

5. References

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