Beat-to-Beat Variability in Computational hv-CM and hiPSC-CM Models

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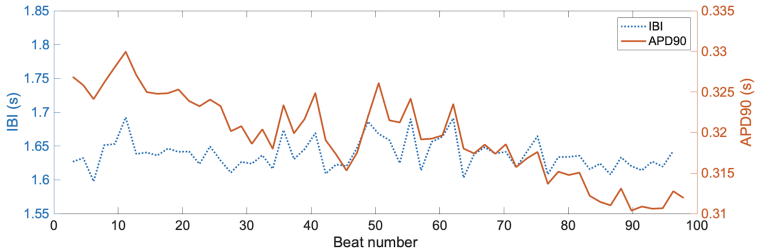
Aims: Heart rate variability (HRV) has become an important clinical marker, and the dynamic changes are becoming increasingly crucial for example in ECG analysis. Beat-to-beat variability (B2BV) in electrical activation of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) has also been previously demonstrated in vitro studies. Here, we study whether those dynamic phenomena are recapitulated in computational CM models, and how B2BV – possibly offering a novel biomarker for the models – could be achieved.

Methods: Interbeat interval (IBI) and action potential duration at 90 % repolarization (APD90) are used as input and output of the dynamic behaviour of the models by calculating the cross-correlations with different lags. We used two human ventricular cardiomyocyte (hv-CM) models, BPS2020 and MBR2021, and a hiPSC-CM model, Paci2020. The BPS2020 and MBR2021 models are studied with in vivo HRV data as the basic cycle length (BCL) to the model, and then obtaining APD90 from the simulation. With the Paci2020 model, we investigate B2BV in the spontaneous mode of activation in the hiPSC-CMs.

Results: The hv-CM models did not predict realistic B2BV. Instead, they adapted to the BCL variation almost instantaneously, with zero lag. In the Paci2020 model, the correlation between IBI and APD90 was negative. This dubious result was fixed by enhancing calcium-dependent inactivation of the L-type calcium channel and by adjusting the calcium re-circulation to be more sarcoplasmic reticulum (SR)-driven. By adding pink ($1/f$) noise to the parameter values of the SR calcium release flux ($g_{Irel_{max}}$) and the funny current conductance (g_f), we were able to create realistic B2BV. In conclusion, this work demonstrates the necessity for further development of computational CM models to accurately capture the variability and memory in B2B dynamics observed in vivo and in vitro.



IBI and APD90 values with pink noise added in simulation and changing the parameter $g_{Irel_{max}}$ values.