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

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Abstract

Beat-to-beat variability (B2BV) in the electrical activation of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) has been previously demonstrated in in vitro studies. Here, we study how B2BV is recapitulated in computational CM models.

We studied the dynamic properties of two human ventricular (hv) CM models, Bartolucci et al. (BPS2020) and Margara et al. (MBR2021), and one hiPSC-CM model from Paci et al. (PHS2020). The interbeat intervals (IBIs) were used as inputs and the action potential duration at 90 % repolarization (APD90) values as outputs in the models. The cross-correlation between the IBI and APD90 time series was calculated with different lags. In the PHS2020 model, the simulation was extended with randomly modulatable J_{rel} and I_f parameters to create B2BV in the model.

The most realistic variability was created by modulating I_f the parameter, with pink noise applied to mimic the biological variability and memory effects. The results show that it is possible to add B2BV to the models. As heart rate variability (HRV) serves as an important clinical marker, B2BV could offer a new biomarker for computational CM models.

1. Introduction

Heart rate variability (HRV), which measures dynamic changes in the intervals between successive heartbeats [1], has become an important clinical marker. Analogous to HRV, beat-to-beat variability (B2BV) in the electrical activation of cardiomyocytes (CMs) has been previously studied using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) [2]. The results showed that the B2BV dynamics of spontaneously beating hiPSC-CMs were remarkably similar to HRV in the human heart. These observations prompted us to explore how this dynamic phenomenon appears *in silico* in the computational CM models.

Computational versions of hiPSC-CMs have been developed to enhance the understanding and characterization of the hiPSC-CMs, and can be used to study cardiac electrophysiology and arrhythmogenesis. This advancement is crucial for future transitions to more patient-specific care. [3]

Here, we studied the memory and variability of the beating dynamics of two human ventricular (hv) CM models, Bartolucci et al. (BPS2020) [4] and Margara et al. (MBR2021) [5], and a hiPSC-CM model, Paci et al. (PHS2020) [6]. The BPS2020 and MBR2021 hv-CM models represent the state-of-the-art, with improved physiological accuracy compared to the O'Hara et al. (2011) parent model. The two models differ in the description of calcium dynamics, which presents a potentially interesting setting for comparing memory effects. Specifically, we investigate, whether dynamic properties are recapitulated in computational CM models and how B2BV could be achieved *in silico*.

2. Materials and methods

The interbeat intervals (IBIs), also known as peak-to-peak intervals, are defined as the time interval from the previous action potential (AP) peak to the present AP peak and are used as an input to the computational CM models. Action potential duration (APD) at 90 % repolarization (APD90) is then obtained as an output from the models.

First, we analyzed the dynamic behavior of the BPS2020 and MBR2021 with APD restitution, a common biomarker for IBI-APD adaptation in CM models. The APD restitution curve represents the adaptation properties of the AP to the cell's beating rate and is commonly used as a biomarker for these models. When the pacing frequency of the model decreases, the APD lengthens. The models are run to a steady state with a basic cycle length (BCL) of 1500 ms. After that, the pacing cycle duration is shortened in increments of 50 milliseconds. 50 action potentials are simulated in each cycle, and APD90 is obtained from the last action potential of each cycle.

HRV data from healthy subjects are used to study the dynamic behaviour of the hv-CM models. HRV time series from the PhysioNet database [7–9] from Holter monitoring are implemented into the hv-CM models as input BCL. The first 10 subjects and the first 1000 data points from each subject are used. The models are run to the

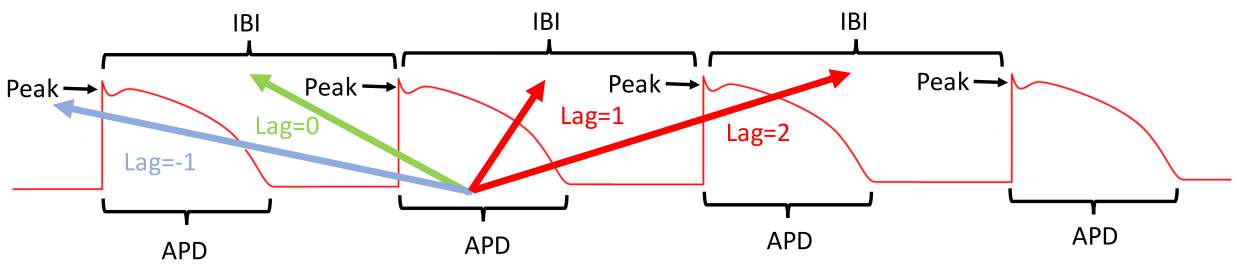

Figure 1. Definition of lag values in the IBI-APD cross-correlation analysis.

steady state using the mean of the first 10 IBI values from the data as BCL value.

To measure the similarity and history effects between the two time series, IBI and APD90, we performed a time-lagged cross-correlation (TLCC) analysis. The definition of the lag values is presented in the Figure 1. Essentially, the IBI and APD are at the same time point when the lag is 1. For each hv-CM model, we calculated the TLCC to assess the realism of the B2BV. Specifically, we examined whether the models exhibit a physiologically plausible relationship between IBI and APD90.

First, both IBI and APD90 time series were detrended using smoothness prior method [10]. Then, the TLCC analysis was conducted by shifting the IBI time series relative to the APD90 time series and computing the correlation coefficient at each lag ranging from -5 to 5. This approach allows us to identify the correlation and history effects, providing insights into the temporal relationship between IBI and APD90. Subsequently, we utilized the PHS2020 model to investigate B2BV in *in silico* hiPSC-CMs in the spontaneous mode of activation. The same TLCC analysis was applied to the PHS2020 model to compare its performance with the hv-CM models.

3. Results and discussion

3.1. Dynamic action potential duration restitution with hv-CM models

The dynamic APD restitution protocol was performed with the hv-CM models, BPS2020 and MBR2021, to study how the APD90 adapted to the changing BCL. Figure 2 (the simulation results are read from right to left) shows the APD90 value adaptation to the BCL, when the steady state is first at 1500 ms. We find a difference between the hv-CM model APD restitution as the APD90 from MBR2021 is slightly longer in the steady state than APD90 from the BPS2020. The APD90 difference decreases as the BCL becomes shorter.

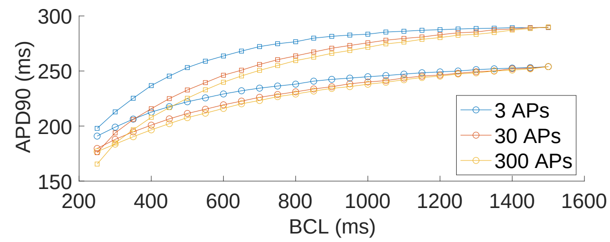

Figure 2. Dynamic APD restitution in the BPS2020 (o) and MBR2021 (□) hv-CM models.

3.2. Cross-correlation analysis with hv-CM models

The IBI time series from *in vivo* HRV data was implemented into the hv-CM models as input BCL. The APD90 values were obtained from the simulations. The boxplot distribution of the correlation coefficient values with different lags is presented in Fig. 3 A) from BPS2020 and B) from MBR2021. The boxplots from both hv-CM models show the highest correlation coefficient at lag 0, indicating a strong correspondence between APD90 and the previous IBI value. The distribution shape is similar in both models. The second highest correlation occurs at lag -1 in both cases; however, the third highest correlation differs: in BPS2020, it is at lag -2, while in MBR2021, it appears at lag 1. Notably, the magnitude of the correlation coefficients is exceptionally high in both models, which does not align with expectations for realistic beating dynamics.

3.3. Studies with *in silico* hiPSC-CM

The PHS2020 model was employed in the hiPSC-CM studies with the aim of introducing more realistic randomness to replicate the beating dynamics observed in real hiPSC-CMs [2].

Two parameters, J_{rel}, which represents the maximum calcium release from the sarcoplasmic reticulum (SR), and the funny current I_{f}, were modified separately by adding noise to the simulations, as these paramaters trigger the electrical activity in the model. Initially, J_{rel} produced a

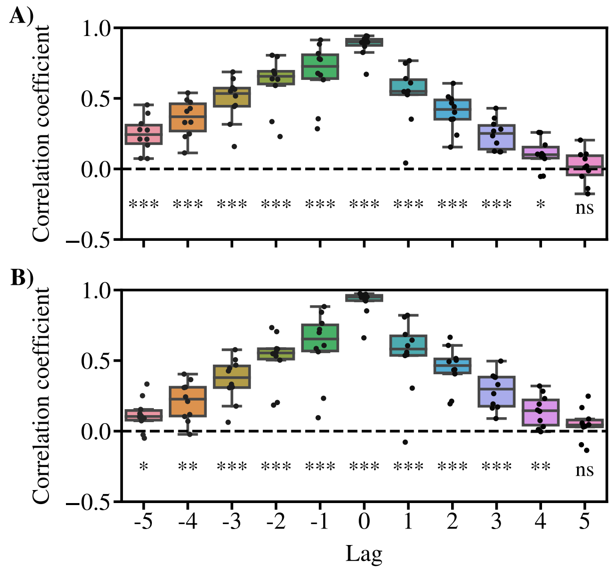

Figure 3. Results of the IBI-APD cross-correlation analysis from A) Bartolucci et al. and B) Margara et al. hv-CM models. The statistical significance is indicated as follows: ns (not significant): $P > 0.05$, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$

counterintuitive result: instead of shortening the AP, increasing the parameter value prolonged it, leading to a negative correlation between IBI and APD90. This issue was resolved by enhancing the calcium-dependent inactivation of the L-type calcium channel and adjusting calcium recirculation to be more SR-driven, which resulted in positive correlation outcomes.

To create randomness, pink noise ($1/f$) was added to the model's vector element values g_f and $g_{\mathrm{irel_{max}}}$. Pink noise is a common type of noise in biological systems [11]. The vector element values were changed in range [0.75, 1.75], based on calibrated scale for the maximum values of calcium flux released from SR in database simulations [6]. The simulation was made continuous, so that the update interval of the g_f or $g_{\mathrm{irel_{max}}}$ could be adjusted, as it affects the correlation coefficient. A wide range of update interval values was tested, but the most realistic correlations were obtained with g_f update interval of 0.1 s.

An example of a single $g_{\mathrm{irel_{max}}}$ simulation is presented in Fig. 4, and an example of a single g_f simulation is presented in Fig. 5. In both figures, the upper panel presents the vector element value changes containing pink noise. The lower panel shows the varying IBI and APD90 values. In the $g_{\mathrm{irel_{max}}}$ simulation, the APD90 values seem to follow the IBI values rather precisely, whereas in the g_f simulation the APD90 values do not significantly adapt to the variation of the IBI, although there is a visible correlation between the IBI and APD90. The correlation coefficient values present in the figures correspond to lag 0. In $g_{\mathrm{irel_{max}}}$ simulations, the values were overall higher than in the g_f simulations. Modulating g_f produced better results, so the

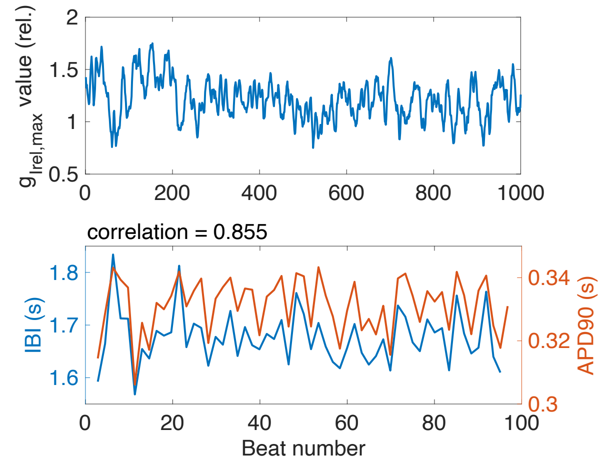

Figure 4. Example of varying maximum rate of SR Ca2+ release flux, $g_{\mathrm{irel_{max}}}$, parameter values and the resulting IBI-APD variability in the hiPSC-CM model.

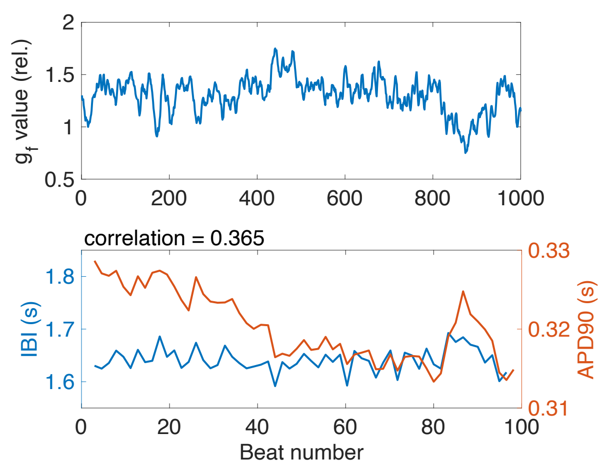

Figure 5. Example of varying funny current conductance, g_f, parameter values and the resulting IBI-APD variability in the hiPSC-CM model.

simulation was run 100 times, followed by a TLCC analysis. The resulting boxplots are presented in Fig. 6. The highest correlation coefficients are observed at lag 0, lag 1 and lag -1, and the distribution appears relatively realistic. Memory effects are evident, as positive correlations persist at larger lags, indicating that past states continue to affect the current state. However, the strength of these correlations gradually decreases as the lag increases. This rather simple method to produce B2BV to the model by only modulating the parameter I_f shows that it is possible to add variability and memory in the models.

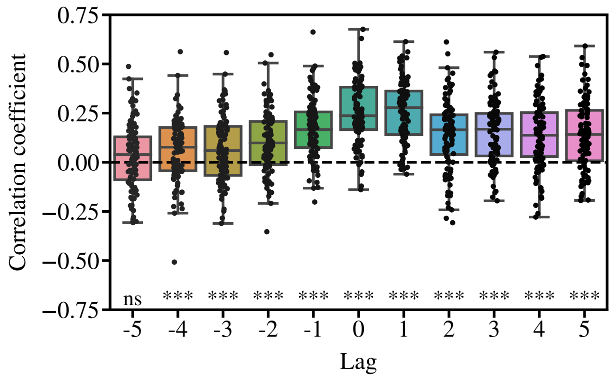

Figure 6. Results of IBI-APD cross-correlation analysis from in silico hiPSC-CMs with 0.1s g_f parameter update interval.

4. Conclusions

The adaptation properties of the two hv-CM models were studied using a standard APD restitution protocol, demonstrating how APD90 values adjusted to changes in BCL. However, this does not directly indicate the presence of B2BV in the models, particularly in the short term.

This TLCC analysis of the IBI and APD90 time series reveals that the computational hv-CM models do not recapitulate realistic B2BV, when *in vivo* IBI data is used as the input BCL. This limitation is also observed in the hiPSC-CM model, but by introducing variability to key parameters, similar B2BV patterns to those seen in real hiPSC-CMs can be achieved. The most realistic variability was obtained by modulating the I_f parameter, with pink noise added to the parameter values to reflect biological variability.

A key finding of this study is that to accurately represent the biophysical behavior of hiPSC-CMs, the model must incorporate more realistic memory and variability effects. This was evident in the PHS2020 model, where initial variation of J_{rel} led to unrealistic results, including negative correlations between IBI and APD90. After correcting this by enhancing calcium-dependent inactivation of the L-type calcium channel and adjusting calcium recirculation to be more SR-driven, the results improved significantly. Future model development should focus on better integrating B2BV to enhance the accuracy of these models. Moreover, B2BV could serve as a novel biomarker for computational models.

Acknowledgments

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