Accelerating Stabilization of Whole-heart Models after Changes in Cycle Length

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Abstract

Parameter changes can cause long-term drift in membrane models. To reduce the cost of whole-heart simulations with such changes the stabilization can be performed in isolated-cell models, but it can then still take many beats to stabilize the full model. We hypothesized that differences in activation time leading to cycle length (CL) variability before the first beat contribute to this. To remove this variability we froze most state variables of the model until the sodium current activated.

Simulations were performed with CL 400, 500, 600 and 1000 ms and modified Ten Tusscher-Panfilov 2006 dynamics. Isolated endocardial, mid-myocardial, and epicardial cells were simulated for 1000 beats. Their final states were then copied to a model of the whole human ventricles, which was run for 5 beats, with and without freezing.

Stabilization of the full model took three to four beats. Freezing of the membrane state accelerated stabilization in some cell types but caused opposite drifts in others. Drifts were largest in the epicardial and mid-myocardial layers, and not in particular at their interfaces.

Freezing of membrane state may help to accelerate stabilization but in our scenarios other types of drift dominate and may be aggravated by freezing, as it inhibits electrotonic interactions.

1. Introduction

Changes in the parameters of cardiac membrane models can cause drift in model variables that lasts for hundreds of beats. This is true in particular for changes in the extracellular concentrations of potassium ([K⁺]₀) and calcium ([Ca²⁺]₀).

[K⁺]₀ and [Ca²⁺]₀ outside normal ranges increase the risk for life-threatening arrhythmia and sudden cardiac death and they have also been shown to affect depolarization and repolarization features of the electrocardiogram (ECG) [1–3]. This means that simulations of chronic kidney disease, in which these concentrations are abnormal, require long stabilization periods. This is problematic for large-scale models, for which such long periods are costly. Therefore stabilization is often performed in models of isolated cells, and then the membrane state variables are copied to the large-scale model. However, the model can then still take a few beats to reach a stable behavior, which can still cause high computational cost.

To further reduce this cost, we tested a method to reach a stable behavior faster. We hypothesized that part of the drift is caused by the different cycle lengths (CL) experienced by the cells at the start of the first beat in the whole-heart model: the cells are all initialized identically, but they activate at different times, and thus experience different CL. When the CL is short, this could lead to significant perturbations in the behavior of the cells during the first beat and possibly during subsequent beats as well. To prevent this, we froze the state variables of the cells in the whole-heart model until their first activation. Only the activation gate of the sodium channel was not frozen, as it is required for activation.

2. Methods

2.1. Computational Modeling

Cardiac electrical activity was simulated using isolated cells as well as a model of the whole human ventricles created from computed tomography data of a single patient [4]. Cellular electrophysiology was represented by the human ventricular membrane model of Ten Tusscher and Panfilov [5], as modified by Severi et al. [6]. The ventricular model was simulated with a monodomain reaction-diffusion model with 200 µm resolution and a time step of 0.01 ms. Simulations were run for CL of 400, 500, 600 and 1000 ms.

12-lead ECGs were computed with a lead-field method
ables are integrated normally throughout the whole-heart activation times. In the non-freezing method, all variables are reactivated. This serves to let all model nodes experience the same CL, despite their different activation times. When the transmembrane potential first exceeds $-50 \text{ mV}$, the other variables are reactivated. Concepts such as the activation gate of the sodium (Na) current. Furthermore, all variables are reactivated, meaning that none of their state variables can change, except those of the activation gate of the sodium (Na) current. When the transmembrane potential first exceeds $-50 \text{ mV}$, the other variables are reactivated. This serves to let all model nodes experience the same CL, despite their different activation times. In the non-freezing method, all variables are reactivated. For simplicity, we refer to each CL as the CL of the current beat, even though it represents the CL at the time of the actual beat. The effect of freezing is more visible at shorter CL, particularly at the endocardial and epicardial layers, and in the endocardial and epicardial layers, but in the endocardial and epicardial layers, it produced an opposite drift in the midmyocardial layer and its sensitivity. To assess how different layers of myocardium (middle of endocardial, midmyocardial, epicardial layers and the boundaries of the layers) modulated APD$_{90}$ at different CL with and without freezing, a sensitivity analysis was performed. For APD$_{90}$, the percentage of change ($D_{M:c,a}$) and its sensitivity ($S_{M:c,a1,a2}$) to changes in each of the ventricular layers were computed as

$$D_{M:c,a} = \left( \frac{M_{c1,a} - M_{\text{control}}}{M_{\text{control}}} \right) \cdot 100, \quad i \in \{1, 2\} \quad (1)$$

$$S_{M:c,a1,a2} = \left( \frac{D_{M:c,a2} - D_{M:c,a1})100}{a_2 - a_1} \right), \quad (2)$$

where $M_{c1,a}$ is the value of APD$_{90}$ marker $M$ under different levels of CL ($a$) in each beat ($c$) calculated at CL $a_1$ and $a_2$ [9, 10]. The values of $a_1$ and $a_2$ were taken as the minimum and maximum value of CL in each beat, respectively. $M_{\text{control}}$ is the value of APD$_{90}$ at a CL of 1000 ms, for the 5th beat.

### 2.3. Statistical Analysis

Pearson correlation coefficients ($\rho$) were computed to assess the strength and the effects of different beats in each of the 12-lead ECGs at different CL.

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and

$$S_{M:c,a1,a2} = \left( \frac{D_{M:c,a2} - D_{M:c,a1})100}{a_2 - a_1} \right), \quad (2)$$

where $M_{c1,a}$ is the value of APD$_{90}$ marker $M$ under different levels of CL ($a$) in each beat ($c$) calculated at CL $a_1$ and $a_2$ [9, 10]. The values of $a_1$ and $a_2$ were taken as the minimum and maximum value of CL in each beat, respectively. $M_{\text{control}}$ is the value of APD$_{90}$ at a CL of 1000 ms, for the 5th beat.

### 3. Results

Figure 2 shows the differences in APD$_{90}$ between the freezing and non-freezing methods for the 1st and 5th beat at different layers of the heart, with varying CL (top panels). The bottom panels show APD$_{90}$ and its differences with and without freezing for 1st to 5th beats at each tested CL. The effect of freezing is more visible at shorter CL, particularly at the 1st beat. Freezing accelerated the stabilization in the endocardial and epicardial layers, but induced an opposite drift in the midmyocardial layer and its boundaries.

Figure 3 illustrates the correlation coefficient between the 12-lead ECGs of first three beats and the 5th beat, with (right panel) and without (left panel) initialization for 1000 beats as well as with and without freezing. Higher correlation was obtained (median correlation coefficients of 0.994, 0.999 and 1.000) with initialization than without initialization (0.838, 0.899 and 0.960 for the 1st, 2nd and 3rd beat with freezing, respectively).

Table 1 shows the APD$_{90}$ values at varying CL, computed for the 1st to 5th beats. Results show that APD$_{90}$ values are stable from the 2nd or 3rd beat onwards. Differences in the APD$_{90}$ values between the 1st and 5th beat...
were larger at shorter CL, particularly for the middle of the midmyocardial layer and its interface with the endocardial layer. Therefore, drifts could be largest in these layers at shorter CL. Freezing effects are more prominent in endocardial than in other layers.

Table 2 shows the differences in the sensitivities of APD$_{90}$ with and without freezing, in different layers at varying CL for the 1$^{\text{st}}$ to the 5$^{\text{th}}$ beat. The highest absolute differences in the sensitivities were obtained at the 1$^{\text{st}}$ beat, particularly for the middle of the midmyocardial layer and its boundary with the endocardial layer. However, sensitivity differences were almost negligible from the 3$^{\text{rd}}$ beat onwards in the whole-heart model.

4. Discussion

We investigated a “membrane freezing” method to accelerate the stabilization of whole-heart models after initialization with membrane states that were pre-stabilized with isolated-cell simulations. We found that freezing of the membrane state accelerated stabilization in some cell types but caused opposite drifts in others and did not significantly accelerate stabilization.

The idea behind the freezing method was that differ-
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References


Acknowledgements

Figure 3. Median and 25th/75th percentiles of the correlation coefficient ($\rho$) between the 12-lead ECGs of the first three beats and the 5th beat, without (left panel) and with (right panel) initialization for 1000 beats in isolated cells. Blue and red boxplots show the effects with and without freezing, respectively. Each purple dot represents an individual ECG lead.

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Table 2. Results of the differences in the sensitivity analysis, $S_{mF_1\theta_1,mF_2\theta_2}$ with (F) and without (nF) freezing for different values of CL, at different layers of heart in each beat from minimum CL ($\theta_1$) to maximum CL ($\theta_2$).