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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 ($[K^+]_o$) and calcium ($[Ca^{2+}]_o$).

$[K^+]_o$ and $[Ca^{2+}]_o$ 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.

Aiming 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

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 [7] using lead fields calculated in a 1-mm resolution finite-difference torso model. All simulations were performed on a cluster computer using the Propag-5 software [8] with provisions for the handling of lead fields [7] and recent corrections in the handling of model initialization from stored membrane states.

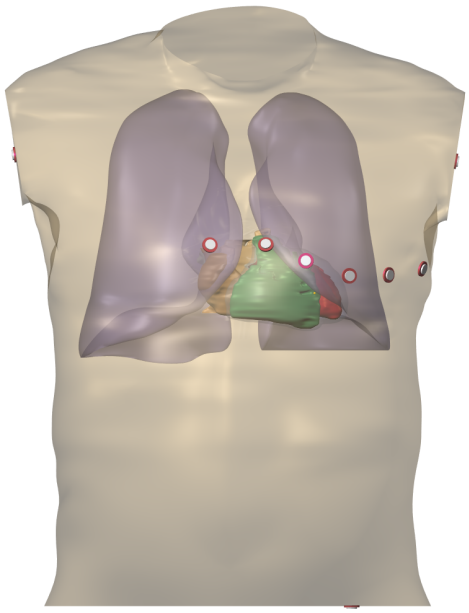

Figure 1. Human torso-heart model used for the ECG simulations.

Stabilization of the Whole-Heart Model In order to get the whole-heart model into a stable state as quickly as possible for each CL, we found initial values for all the membrane model variables that correspond to a stable state under the given CL. This was done by running single-cell simulations for all different cell types (endocardial, midmyocardial and epicardial, for LV and RV) for 1000 beats, and then the membrane state variables from the last beat were copied to the cells of the same type in the large-scale model. Then the heart model was simulated for 5 beats to see how long it takes before it reaches a stable state.

Two initialization methods were tested: freezing and non-freezing. In the freezing method, at the beginning of the whole-heart simulation, the membranes are "frozen", meaning that none of their state variables can change, except those of the activation gate of the sodium (Na) current. When the Na channel opens, 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 integrated normally throughout the whole-heart simulation.

Model stability was evaluated in terms of action potential duration at 90 % repolarization (APD_{90}), and in terms of correlation between the ECG of the last beat and the earlier beats.

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

To assess how different layers of heart (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 ($D_{M;c;a_i}$) and its sensitivity ($S_{M;c;a1,a2}$) to changes in each of the ventricular layers were computed as follows [9, 10]:

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

$$S_{M;c;a_1,a_2} = \frac{(D_{M;c;a_2} - D_{M;c;a_1})100}{a_2 - a_1}, \quad (2)$$

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

3. Results

Figure 2 shows the differences in APD_{90} with and without freezing for 1^{st} and 5^{th} 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 1^{st} to 5^{th} beats at each tested CL. The effect of freezing is more visible at shorter CL, particularly at the 1^{st} 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 5^{th} 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 1^{st}, 2^{nd} and 3^{rd} beat with freezing, respectively).

Table 1 shows the APD_{90} values at varying CL, computed for the 1^{st} to 5^{th} beats. Results show that APD_{90} values are stable from 2^{nd} or 3^{rd} beat onwards. Differences in the APD_{90} values between the 1^{st} and 5^{th} 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 (F) and without (nF) freezing, in different layers at varying CL for the 1^{st} to 5^{th} beat. The highest absolute differences in the sensitivities were obtained at the 1^{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^{rd} beat onwards in the whole-heart model.

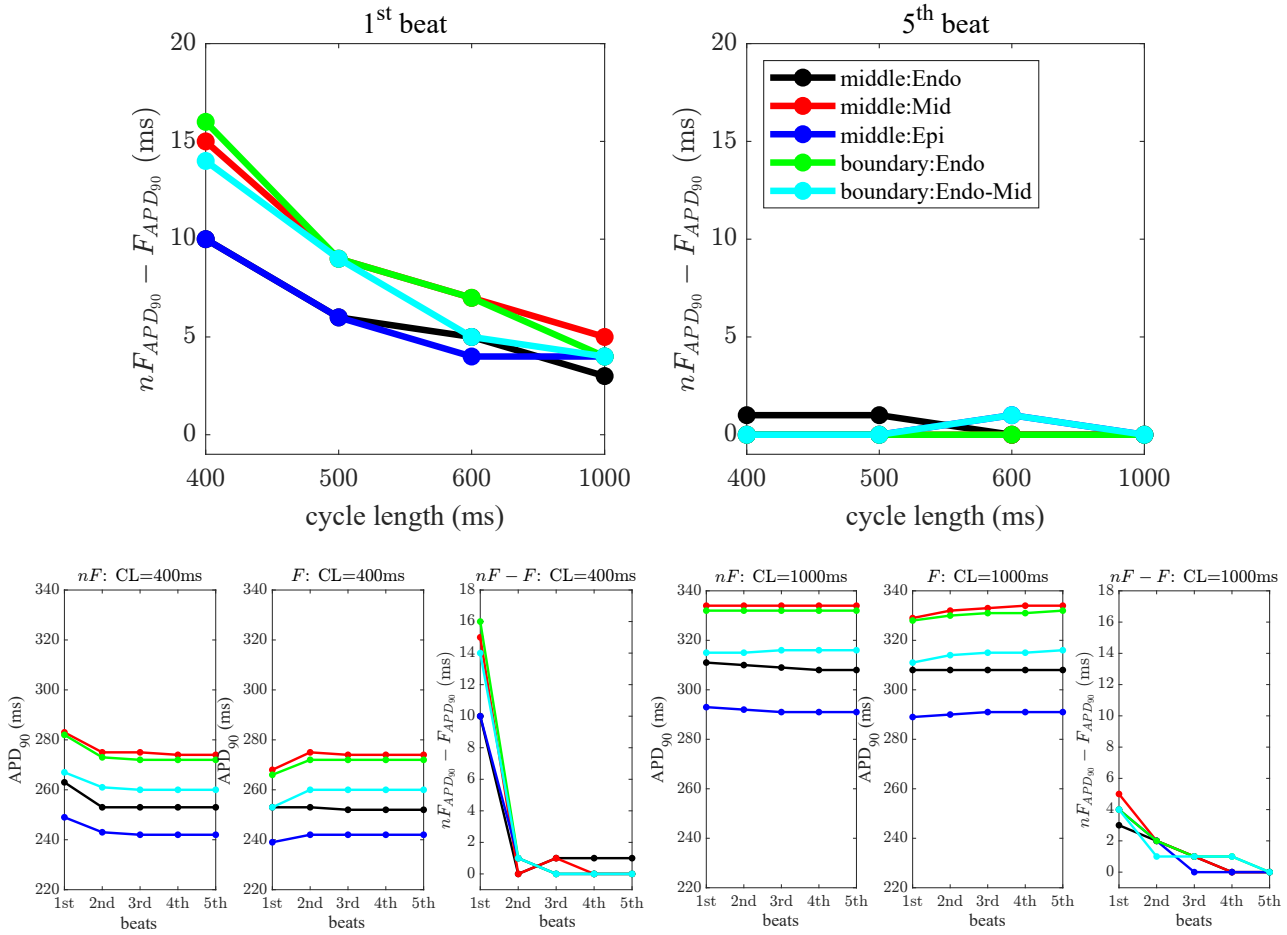

Figure 2. Top panels: Differences in APD_{90} with (F) and without (nF) freezing for 1st and 5th beat at different CL. Bottom panels: APD_{90} and its differences with (F) and without (nF) freezing for 1st to 5th beats at CL=400 ms (bottom left panels) and 1000 ms (bottom right panels).

Table 1. APD_{90} at different CL and different layers (middle of endocardial, mEndo, midmyocardial, mMid, epicardial, mEpi, the boundary of endocardial, bEndo, and the boundary of endocardial with midmyocardial, endo-mid, layers) after freezing, computed from the 1st to the 5th beat.

	mEndo				mMid				mEpi				bEndo				endo-mid			
	cycle length (ms)				cycle length (ms)				cycle length (ms)				cycle length (ms)				cycle length (ms)			
beat	400	500	600	1000	400	500	600	1000	400	500	600	1000	400	500	600	1000	400	500	600	1000
1	253	268	279	308	268	284	296	329	239	252	262	289	254	270	282	309	266	283	295	328
2	253	268	279	308	275	288	299	332	242	254	264	290	254	270	281	310	272	286	298	330
3	252	267	279	308	274	288	300	333	242	255	264	291	254	270	281	309	272	287	298	331
4	252	267	279	308	274	289	300	334	242	255	264	291	254	270	281	309	272	287	299	331
5	252	267	279	308	274	289	301	334	242	255	264	291	254	270	281	309	272	287	299	332

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 differences in apparent CL at the start of the first beat would be the most important cause of short-term drift. Although this certainly seems to be one of the causes, our results show that other factors are at least as important. One possible explanation is that when cells of different types are first coupled to each other, electrotonic interactions will change the behaviors of the cells and thus invalidate their initialization state, computed for a slightly different functional cell type. Thus, we would expect that the largest drifts occur at the interfaces between layers of different cell types.

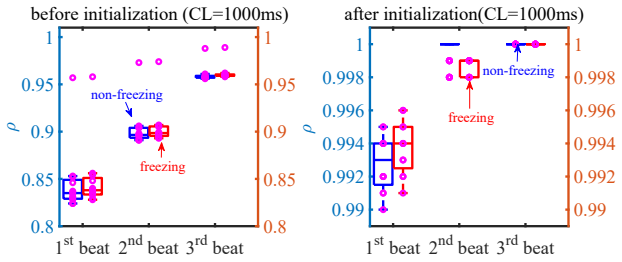

Figure 3. Median and 25^{th}/75^{th} percentiles of the correlation coefficient (ρ) between the 12-lead ECGs of the first three beats and the 5^{th} beat, without (left panel) and with (right panel) initialization for 1000 beats in the whole-heart. Blue and red boxplots show the effects with and without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

Table 2. Results of the differences in the sensitivity analysis, $S_{m;p;a_1,a_2}$, with (F) and without (nF) freezing for different values of CL, at different layers of heart in each beat from minimum CL (a_1) to maximum CL (a_2).

	$\lvert S_{nF_{\text{APD}_{90}}} - S_{F_{\text{APD}_{90}}} \rvert$				
beat	mEndo	mMid	mEpi	bEndo	endo-Mid
1	0.38	0.50	0.34	0.39	0.60
2	0.11	0.10	0.06	0.01	0.05
3	0.00	0.00	0.00	0.06	0.05
4	0.05	0.00	0.00	0.04	0.05
5	0.05	0.00	0.00	0.04	0.00

Interestingly, this turned out not to be the case either: the largest drifts occurred in the middle of the mid-myocardial layer. Nevertheless, it is possible that the freezing method delayed the stabilization by inhibiting the effects of electrotonic interactions until the first activation.

A shortcoming of our study is that we did not systematically investigate the relation between drift and activation time, the freezing method being expected to be most effective for late-activated areas which, without freezing, experience the largest deviation from the CL for which they were initialized.

We conclude that to understand and possibly prevent short-term drift in heterogeneous heart models we must better understand the effects of electrotonic coupling between cells with different intrinsic types.

Acknowledgements

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