

ECG SIMULATION WITH IMPROVED MODEL OF CELL ACTION POTENTIALS

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Keywords: ECG, action potential, repolarization, myocardium, computer simulation.

Abstract: An improved model of action potentials (AP) is proposed to increase the accuracy of simulated electrocardiograms (ECGs). ECG simulator is based on a spatial model of a left ventricle, composed of cubic cells. Three distinct APs, modeled with functions proposed by Wohlfart, have been assigned to the cells, forming epicardial, mid, and endocardial layers. Identification of exact parameter values for AP models has been done through optimization of the simulated ECGs. Results have shown that only through an introduction of a minor extension to the AP model, simulator is able to produce realistic ECGs. The same extension also proves essential for achieving a good fit between the measured and modeled APs.

1 INTRODUCTION

The standard 12-lead electrocardiogram (ECG) is a diagnostic tool in cardiology for more than 60 years. It is a view on the electrical heart activity from the body surface that results from differences between potentials of myocardium cells. These in turn are a consequence of different times in which cells excite (excitation sequence) and the differences in cells themselves. The mechanisms for ECG generation are still not fully understood. In our research, we tackle the problem of ECG genesis on the cellular level, more precisely, through the shape of the action potentials (APs). Focus of this paper is on the shape of the repolarization phase of modeled APs and on the increase of its fidelity.

Modeling of APs on the cell level is quite complex, because a system of non-linear time-dependant differential equations has to be solved (Ten Tusscher et al., 2004). Simpler method, proposed by Wohlfart (Wohlfart, 1987), models APs as a product of two sigmoidal functions (A and C) and one exponential function (B):

$$\begin{aligned} A(t) &= \frac{1}{1+e^{-k_1 t}} \\ B(t) &= k_2((1-k_3)e^{-k_4 t} + k_3)e^{-k_5 t} \\ C(t) &= \frac{1}{1+e^{k_6(t-k_7)}} \\ AP(t) &= A(t) \times B(t) \times C(t), \end{aligned} \quad (1)$$

where component $A(t)$ controls the initial upstroke (phase 0), $B(t)$ the immediate fast repolarization and

the AP plateau (phases 1 and 2, respectively), and $C(t)$ the repolarization part (phase 3). Because of the characteristics of exponential functions, however, the whole AP curve is influenced to some extent by all the components.

A model of AP curve with four phases is shown in Figure 1. Activation time (AT) represents delay between the myocardium excitation start and individual cell activation, which is defined by the excitation sequence (both are shown on the spatial model in Figure 2). Repolarization time (RT) is a sum of AT and action potential duration (APD) and is a measure of the delay between the myocardium excitation start and individual cell repolarization end.

The mechanisms forming the repolarization phase of ECG are still under investigations. For example, the shape of the T wave, its width and its slopes have not been elucidated yet in all details. Even more mysterious is the genesis of the U wave (Surawicz, 1998).

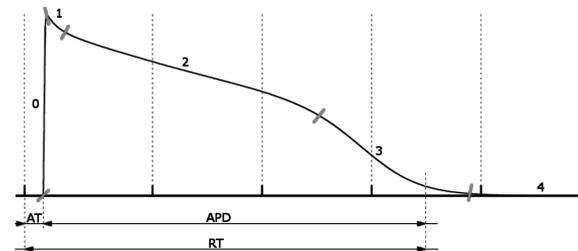


Figure 1: An example of AP with corresponding phases 0 – 4. AT, APD, and RT are shown at 90% repolarization.

Several hypotheses are frequently quoted: U wave genesis is a consequence of the late repolarization of Purkinje fibers (Watanabe, 1975); U wave is generated because of mechano-electrical feedback (Franz, 1996); U wave is a residual of the late repolarization of cells in mid-myocardium (Druin et al., 1995).

A new view of the mid-myocardium hypothesis was presented in (Ritsema van Eck et al., 2005) that suggests that the end of the T wave is taken as the residual of cancellation of opposing potential contributions throughout the myocardium during the repolarization while the U wave arises because of imbalance of potentials in the late repolarization because of the prolonged repolarization of mid-myocardium. Recently, it was shown that there are other alternatives for T and U wave genesis (Depolli et al., 2008). U waves can be generated even if the repolarization of the mid-myocardium is not prolonged.

Leaving physiological causes aside and looking on the problem purely mathematically, we experienced drawbacks of the Wohlfart's AP model in two ways. First, we were unable to get a good fit between the Wohlfart model and the measured APs from the intact heart. Second, we identified the inability to control AP phases 2 and 3 independently, to be the limiting factor in our simulator's abilities to produce properly shaped ECGs. This comes about because the slopes in these phases determine the shape and duration of the T wave and the time of its appearance. We propose an extension of the Wohlfart model in terms of changing the repolarization part $C(t)$ in the Equation 1, as a solution for the problems mentioned above.

The rest of the paper is organized as follows. In Methods, the spatial model of the left ventricle and the simulation procedure are described. The simulation results obtained with the Wohlfart model are compared with a measured ECG. In section 3, the proposed model extension is introduced together with an example of an improved AP curve fit and measured ECG fidelity. The paper concludes with an overview of the obtained results and further work.

2 METHODS

2.1 Model of the Left Ventricle

We constructed a three-dimensional model from 65628 cubic cells with a volume of 1 mm^3 , stylized in a cup-like shape, shown in Figure 2. The model is onion-like composition of twelve layers, which enables different APs to be assigned to each layer. Results presented in this paper were obtained by com-

posing three thicker layers: epi, mid and endo, each of them composed of four identical thinner layers.

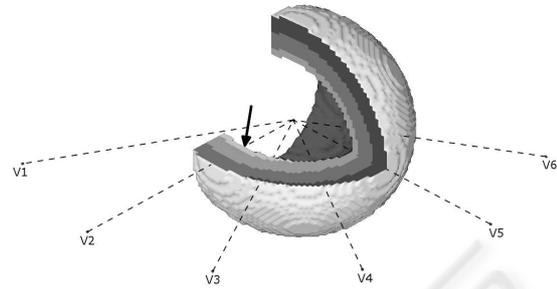


Figure 2: Spatial model of the left ventricle. ECG lead positions are shown with dashed lines. Arrow points to the excitation trigger area. The excitation time is shown on the cutout of the myocardial wall; each level of gray representing 10 ms.

Implementation of faster longitudinal conduction between cells of the same layer (along the wall) than transversal conduction between cells of different layers (across the wall) emulates faster conduction paths of the Purkinje fibers .

2.2 Simulation Method

ECG is simulated by first calculating the excitation sequence for all the cells and then projecting the sum of differences in cell potentials on approximate positions of ECG leads. Simulation procedure is integrated into a simulator, that takes parameters of Equation 1 as input and generates ECGs on predefined positions as output. This simulator is then used in simulation based optimization that solves the inverse problem of identification of AP parameters.

The ECG simulator works with cell APs and a simple rule for each cell. Excited cells behave as sources of electrical potential determined by their AP functions. Every excited cell stimulates its neighboring non-excited cells to become excited with a small delay, which depends on the layer of the neighboring cell and its position relative to the excited cell. Because of the onion-like layering, cell neighbors along the wall will be of the same layer while neighbors perpendicular to the wall will be of different layers. If neighbors are from different layers, the delay of 2 ms results in transversal conduction velocity of 0.5 m/s. On the other hand, if neighbors belong to the same layer, the delay of 1/3 ms results in longitudinal conduction velocity of 3 m/s. Both velocities are in accordance with measured values on myocardial tissue (Macfarlane and Lawrie, 1989).

Six observation points were selected around the model, 4 cm away from the epicardial layer, at an-

gles -120° (V1) to 30° (V6), in increments of 30° , as in a real ECG precordial leads placing (see Figure 2). For each observation point, an ECG is simulated with the following procedure. We assume formation of a dipole between cell i and its immediate neighborhood Ω (caused by cells having different prescribed APs and different ATs), in the same way as in (Miller and Geselowitz, 1978). This includes only neighbors with coincident faces, i.e., 6 neighbors for the spatial model. Dipole moment \mathbf{D}_i is proportional to the vector sum of differences in potentials V :

$$\mathbf{D}_i(t) \propto \sum_{j \in \Omega(i)} (V_i(t) - V_j(t)). \quad (2)$$

ECG leads are simulated as a sum of dipole potential contributions at the observation point P from all N cells:

$$V_P(t) \propto \sum_{i=1}^N \frac{|\mathbf{D}_i(t)| \cdot \cos \phi}{|\mathbf{R}_{i,P}|^2}, \quad (3)$$

where $\mathbf{R}_{i,P}$ is a directional vector from the cell i to P , and ϕ is the angle between \mathbf{D}_i and $\mathbf{R}_{i,P}$.

Simulator based optimization with evolutionary algorithm works on top of the above simulation procedure. It deduces optimal parameters for three AP groups from a predefined target ECG on a predefined location. Currently, a measured ECG on V2 is used as the target. The evaluation algorithm starts with a number of random inputs for the simulator and generates ECGs on target location for each input. Then it combines and modifies inputs in an evolution-like procedure, resulting in inputs that produce ECGs very similar to target ECG. Finally, the result of the optimization is the input that produces the most similar ECG.

2.3 Simulation Results – Wohlart AP Model

APs for epicardium, mid, and endocardium have been generated with Wohlart model, using coefficients from Table 1. Resulting APs are shown in the upper part of Figure 3. The repolarization phase of the simulated and measured ECGs on V_2 are shown in the lower part of Figure 3. The simulated ECG fits well the measured signal, however, some details around the T and U waves are still inadequate.

Table 1: Coefficients of Equation 1 used for modeling APs from Figure 3.

layer	k_1	k_2	k_3	k_4	k_5	k_6	k_7
endo	2.5	100	0.9	0.1	0.00194	0.0755	326
mid	2.5	100	0.9	0.1	0.00260	0.0345	339
epi	2.5	100	0.9	0.1	0.00228	0.0376	296

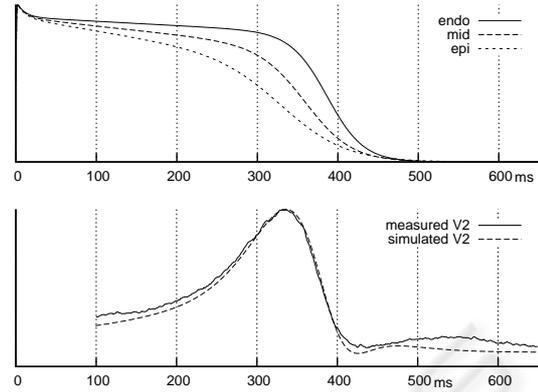


Figure 3: Wohlart APs for epicardial, mid and endocardial layer (top), simulated and measured ECG repolarization phase on the lead V_2 (bottom). Note that the ECG on the lower part of the figure is generated through Equation 3, where besides the APs (upper part of the figure), also the shape of the heart model plays an important role.

3 MODIFIED AP MODEL

In the Wohlart model, used in the previous section, AP phases 2 and 3, and the transition between them cannot be independently controlled. Shape of the transition between phases 2 and 3 is defined by the shape of the transition between phases 3 and 4, and to some extent by the shape of phase 2. This dependence constraints possible shapes of resulting T and U waves and consequently limits the usability of our simulator. Therefore, we propose a modification of the factor $C(t)$, which controls the repolarization part of the ECG. Instead of using a simple sigmoid we introduce an asymmetric sigmoidal function, which requires an additional parameter k_8 :

$$C(t) = 1 - \left(1 + e^{-k_6(t-k_7) + \ln(2^{k_6/k_8} - 1)}\right)^{-\frac{k_8}{k_6}} \quad (4)$$

Incorporating the extended AP model, the simulator immediately shows improvements. The results of simulation based optimization on the same target ECG as before are shown on Figure 4. The ECG fidelity is increased while the APs remain similar to previous ones. The newly introduced asymmetry of their phase 3 is barely noticeable.

The confirmation that proposed modification of the AP model does not reflect a quirk of our simulator but is an actual improvement of the model can be found through examination of the measured APs. Trying to fit both modified and unmodified Wohlart AP model (searching for parameters that would result in the most similar shape) to measured APs published by Druin et al. (Druin et al., 1995), difference

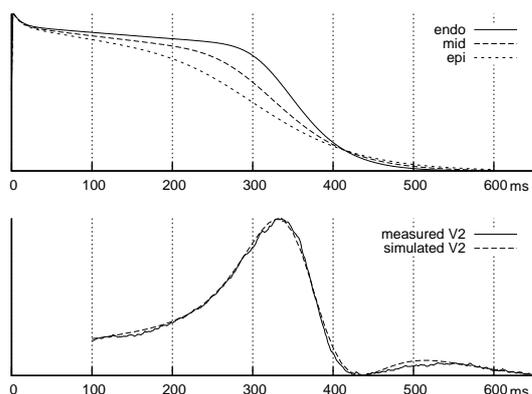


Figure 4: Extended Wohlart APs for epicardial, mid and endocardial layer (top), simulated and measured ECG repolarization phase on the lead V_2 (bottom).

in model fidelity can be observed. An example is shown in Figure 5, where the modified model, using coefficients (1.0, 145.6, 0.8, 0.374, 0.00130, 0.0160, 0.244, 225) for k_1 to k_8 , respectively, fits the target AP more accurately than does the unmodified model. Both models were fitted to measured APs using the same optimization method, based on an evolutionary algorithm.

4 CONCLUSIONS

We have created a simple three-dimensional model of a left ventricle for a computer simulation of ECGs. The simulation is based on a variety of different AP sets based on the Wohlart AP model, which were shown to have some limitations in the simulation of known phenomena in the myocardial wall. Examining the AP model closer, problem with its fidelity was discovered and identified as the most probable cause of the mentioned simulator limitations. The problem was solved through addition of another degree of freedom to the AP model.

We are preparing new simulations of ECGs with the modified AP model and improvements of the op-

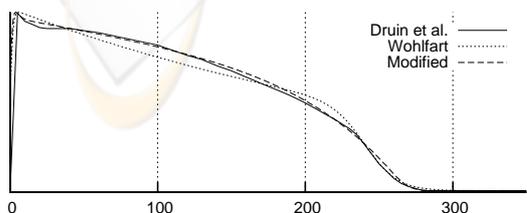


Figure 5: Endo AP published by Druin et al. (Druin et al., 1995) (solid line), fitted with the Wohlart model (dotted line) and proposed modified model (dashed line).

timization. Currently, only one ECG lead can be targeted at a time, which leads to inaccuracies of other ECG leads. Although the modified AP model both increases fidelity of simulated ECGs and enables better approximation of measured APs, there are still differences between measured APs and APs acquired through our simulation based optimization. If we succeed in reconciling these differences, we expect that the simulator will provide helpful in explaining some of the complex phenomena of the repolarization phase.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the Slovenian Research Agency under grant P2-0095.

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