Adaptive Modeling of Ionic Membrane Currents Improves Models of Cardiac Electromechanics

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Abstract
A change in activation sequence by means of pacing induces changes in action potential (AP) morphology and duration. These changes are caused by electrical remodeling of ionic membrane currents and are reflected in the T wave in the electrocardiogram (ECG). Also the calcium transient is affected, which leads to changes in cardiomechanics. By modeling the cardiac muscle as a single fiber, we investigated whether electrical remodeling may be triggered by changes in mechanical load. A homogeneous distribution of electrophysiology in our model resulted in an inhomogeneous distribution of stroke work. After remodeling of the ionic membrane currents, contraction was more homogeneous and the repolarization wave was reversed. These results are in agreement with experimentally observed homogeneity in mechanics and heterogeneity in electrophysiology. In conclusion, adaptive modeling of electrophysiology may improve current models of cardiac electromechanics.

1. Introduction
Regional variation in action potential (AP) duration and morphology is related to regional differences in ionic membrane currents. Transmural heterogeneity in electrophysiology is related to differences in excitation-contraction coupling (ECC) and is believed to help synchronize contraction of the heart muscle [1]. In models of cardiac electromechanics, heterogeneity in electrophysiology and ECC should be incorporated to obtain a more homogeneous mechanical behavior as observed in experiments [2, 3].

In 1982, Rosenbaum et al. [4] observed that longer lasting epicardial pacing leads to a change in the T wave of the ECG. With normal sinus rhythm, concordance of the T wave reappears after some time. Since it appears that the cardiac myocytes somehow "remember" their original state, this phenomenon is known as "cardiac memory" [4]. The observed changes in the T wave are related to remodeling of ionic membrane currents. Since electrical remodeling also involves the calcium transient, it is expected that the mechanical behavior of the heart muscle is affected.

Recent experimental observations indicate that electrical remodeling is triggered by changes in mechanical load (mechanoelectric feedback) [5, 6]. In this paper, we hypothesize that electrical remodeling is a way to obtain a more homogeneous contraction of the heart muscle. Based on this hypothesis, we propose an adaptive modeling method in which ionic membrane currents adapt to changes in mechanical load such that a more homogeneous distribution of stroke work is obtained.

2. Methods
Cardiac electrophysiology and mechanics is modeled by the Cellular Bidomain Model [7–9]. The heart muscle is represented as a string of segments that are electrically and mechanically coupled.

2.1. Cardiac electrophysiology
The electrophysiological state of each segment is defined by the intracellular potential ($V_{\text{int}}$), the extracellular potential ($V_{\text{ext}}$), and the state of the cell membrane, which is expressed in gating variables and ion concentrations. The membrane potential ($V_{\text{mem}}$) is defined by $V_{\text{mem}} = V_{\text{int}} - V_{\text{ext}}$.

Exchange of current between the intracellular and extracellular domains occurs as transmembrane current ($I_{\text{trans}}$), which depends on ionic current ($I_{\text{ion}}$) and capacitive current according to

$$I_{\text{trans}} = \chi \left( C_{\text{mem}} \frac{dV_{\text{mem}}}{dt} + I_{\text{ion}} \right),$$

where $\chi = 2000 \text{ cm}^{-1}$ is the ratio of membrane area to tissue volume and $C_{\text{mem}} = 1.0 \mu F/cm^2$ represents membrane capacitance per unit membrane surface.

To model $I_{\text{ion}}$, we apply the Courtemanche-Ramirez-Nattel model [10]. The total ionic current is given by

$$I_{\text{ion}} = I_{Na} + I_{K1} + I_{o} + I_{Ko} + I_{Na} + I_{Ca,L} + I_{Na,Ca} + I_{K1Na} + I_{K1Ca},$$

where $I_{Na}$, $I_{K1}$, and $I_{o}$ are the sodium, potassium, and leak currents, respectively. $I_{Ca,L}$ is the calcium current through the L-type channel, and $I_{Na,Ca}$ and $I_{K1Na}$ are the sodium-calcium and potassium-sodium currents, respectively.
where $I_{Na}$ is fast inward Na$^+$ current, $I_{Ki}$ is inward rectifier K$^+$ current, $I_c$ is transient outward K$^+$ current, $I_{s).on}$ is ultra-rapid delayed rectifier K$^+$ current, $I_{st}$ is rapid delayed rectifier K$^+$ current, $I_{k}$ is slow delayed rectifier K$^+$ current, $I_{Ca, L}$ is L-type Ca$^{2+}$ current, $I_{Ca, P}$ is Ca$^{2+}$ pump current, $I_{NaK}$ is Na$^+$-K$^+$ pump current, $I_{Na,K}$ is Na$^+$/Ca$^{2+}$ exchanger current, and $I_{Na}$ and $I_{Ca}$ are background Na$^+$ and Ca$^{2+}$ currents [10]. The model also describes Ca$^{2+}$ handling by the sarcoplasmic reticulum (SR) and Ca$^{2+}$ buffering mediated by troponin, calmodulin, and calsequestrin [10].

### 2.2. Cardiac mechanics

The mechanical behavior of a single segment is modeled by a series elastic, a contractile, and a parallel elastic element. In the undeformed state, all segments have the same length (0.1 mm) and cross-sectional area (0.01 mm$^2$). Active force generated by the contractile element is described by Model 4 of Rice et al. [11] and is related to intracellular Ca$^{2+}$ concentration and sarcomere length [7, 9]. It follows from mechanical equilibrium that the tension generated by each segment must be equal to the tension applied to the fiber.

To simulate the cardiac cycle, we distinguish five phases as indicated in Figure 1. During filling, ejection, and isovolumic relaxation, the load applied to the cardiac fiber ($T_{preload}$) is set as a boundary condition, whereas during isovolumic contraction and isovolumic relaxation, the stretch ratio of the fiber ($\lambda_{preload}$) is a boundary condition. To initiate contraction, the first segment is electrically stimulated at the beginning of isovolumic contraction.

#### 2.3. Electrical remodeling of $I_{Ca,L}$

After three weeks of epicardial pacing, Plotnikov et al. [12] observed a more positive activation and slower inactivation of $I_{Ca,L}$ in epicardial myocytes. To incorporate these observations in our model, $I_{Ca,L}$ kinetics are adapted by shifting the voltage-dependency of the activation gating variable with at most 10 mV. Adaptation of $I_{Ca,L}$ is represented with parameter $\rho$, which ranges between $-1.0$ ($-10$ mV shift) and $1.0$ ($+10$ mV shift). The reference situation is represented by $\rho = 0.0$ (no shift). A positive value of $\rho$ results in a slower decrease of $I_{Ca,L}$ during the plateau phase of the AP and leads to an increased APD and Ca$^{2+}$ transient. A negative value of $\rho$ results in a faster decrease of $I_{Ca,L}$ and a decreased APD and Ca$^{2+}$ transient [9].

Based on the assumption that electrical remodeling is triggered by changes in mechanical load, we use stroke work per unit of tissue volume as a feedback signal to determine the remodeling parameter $\rho$. We distinguish between external stroke work density ($W_{ext}$) and total stroke work density ($W_{tot}$). $W_{ext}$ is defined as the area enclosed by the stress-strain loop during the cardiac cycle and $W_{tot}$ is $W_{ext}$ extended with potential stroke work density ($W_{pot}$) (Figure 1).

For each segment $n$, the remodeling parameter is denoted by $\rho_n$. The parameters $\rho_n$ are determined such that stroke work is homogeneously distributed over the fiber. As reference, we use stroke work generated by the segment in the center of a homogeneous fiber ($\rho_{n=0}$ for all segments). The $\rho_n$ are then found by iteratively computing stroke work for each segment followed by adapting the $\rho_n$ until the $\rho_n$ no longer change. Initially, $\rho_n = 0.0$ for each segment $n$. Each time a new cardiac cycle starts, $\rho_n$ is adapted by

$$\rho_n \rightarrow \begin{cases} 
\rho_n + 0.01 & \text{if } W_n < 0.99 \cdot W_{tot} \text{ and } \rho_n < 1.0 \\
\rho_n - 0.01 & \text{if } W_n > 1.01 \cdot W_{tot} \text{ and } \rho_n > -1.0 \\
\rho_n & \text{otherwise}
\end{cases}$$

where, $W_n$ represents either $W_{ext}$ or $W_{tot}$ of segment $n$, and $W_{tot}$ represents the reference value of $W_{ext}$ or $W_{tot}$.

#### 2.4. Simulation set-up

Electrical remodeling was simulated using a cardiac fiber with a reference length of 1 cm. With stimulation
rate 1 Hz, a depolarization wave was generated by electrical stimulation of the first segment. Depolarization of the entire fiber took 32 ms (conduction velocity 0.32 m/s). The cardiac cycle was simulated with $T_{\text{rest}} = 0.5$ kPa, $T_{\text{preload}} = 1$ kPa, and $T_{\text{afterload}} = 10$ kPa. Electrical remodeling was controlled either by $W_{\text{ext}}$ ($W_{\text{ext,ref}} = 0.93$ kJ/m$^3$) or $W_{\text{int}}$ ($W_{\text{int,ref}} = 1.43$ kJ/m$^3$). In both cases, a final distribution of the $\rho$ was reached in at most 140 cardiac cycles. By simulating 150 cardiac cycles, it was ensured that steady-state was reached.

3. Results

In Figure 2, $W_{\text{ext}}$, $W_{\text{int}}$, parameter $\rho$, time of depolarization ($t_{\text{dep}}$), APD$_{-60mV}$, and time of repolarization ($t_{\text{rep}}$) are presented for each location along the fiber with and without remodeling. Here, APD$_{-60mV} = t_{\text{rep}} - t_{\text{dep}}$ is defined as the time during which $V_{\text{mem}}$ is larger than $-60$ mV. Without remodeling, $W_{\text{ext}}$ and $W_{\text{int}}$ are small for early-activated segments and larger for later-activated segments. With remodeling, both $W_{\text{ext}}$ and $W_{\text{int}}$ are increased for early-activated segments and decreased for later-activated segments, such that a more homogeneous distribution is obtained. In the case that remodeling is controlled by $W_{\text{ext}}$, the reference value ($W_{\text{ext,ref}} = 1.43$ kJ/m$^3$) is not reached for early-activated segments, while parameter $\rho$ reaches its maximum value of 1.0. Electrical remodeling has no effect on $t_{\text{dep}}$, i.e., the conduction velocity is not affected. On the other hand, $t_{\text{rep}}$ is significantly changed with remodeling due to the increase in APD$_{-60mV}$ for early-activated segments and the decrease for later-activated segments. A consequence of these changes is that the repolarization wave is reversed.

In Figure 3, the effect of electrical remodeling on the membrane potential ($V_{\text{mem}}$), intracellular Ca$^{2+}$ concentration ([Ca$^{2+}$]), and normalized contractile force ($F_{\text{norm}}$) is illustrated for the segments located at 0.1, 0.5, and 0.9 cm. Without remodeling, the APs and Ca$^{2+}$ transients have similar morphology and duration. With remodeling, the AP and Ca$^{2+}$ transient of the segment at 0.1 cm envelops the APs and Ca$^{2+}$ transients of the other two segments. In addition, $F_{\text{norm}}$ is increased for the early-activated segment and decreased for the later-activated segment, which is related to the more homogeneous distribution of stroke work (Figure 2).

In Figure 4, the effect of electrical remodeling on stress, strain, and the stress-strain loop is illustrated for the segments located at 0.1, 0.5, and 0.9 cm. With remodeling, shortening increases for early-activated segments and decreases for later-activated segments. The overall effect is a more homogeneous shortening of the fiber during ejection. The more homogeneous distribution of $W_{\text{int}}$ with remodeling is reflected by the fact that the areas enclosed by the stress-strain loops are about the same size with remodeling.
Figure 4. Effect of electrical remodeling of $I_{Ca,L}$ on the stress-strain loop for individual segments. Stress, strain, and stress-strain loops are plotted for segments located at 0.1, 0.5, and 0.9 cm. Left: without remodeling. Center: remodeling controlled by $W_{rest}$ ($W_{rest} = 0.93 \text{ kJ/m}^2$). Right: remodeling controlled by $W_{ext}$ ($W_{ext} = 1.43 \text{ kJ/m}^2$). A stimulus current was applied to the segment at 0 ms. Begin and end of ejection are indicated with be and ee, respectively.

4. Discussion and conclusions

With homogeneous electrophysiology, stroke work was small in early-activated segments and large in later-activated segments. By adapting $I_{Ca,L}$ to homogenize stroke work, a more homogeneous muscle contraction was obtained. In addition, AP duration was increased in early-activated and decreased in later-activated segments, which lead to a reversed repolarization wave. These results are in agreement with experimental observations in animals with long-term asynchronous activation [3, 12]. Our findings suggest that the abnormal electromechanics in paced ventricles leads to adaptation through mechanoelectric feedback. An effect of this adaptation is the reversal of the repolarization wave, which affects the T wave in the ECG and is consistent with experimental findings [4]. In addition, the large regional differences in mechanical workload are somewhat reduced.

In conclusion, adaptive modeling of electrophysiology may lead to better predictions of cardiac electrophysiology and mechanics in coupled models of cardiac electromechanics. As the Ca$^{2+}$ transient and the plateau phase of the AP are determined by a balance between the depolarizing $I_{Ca,L}$ and the repolarizing K$^+$ currents, a possible improvement of our model is to take the effect of electrical remodeling of the K$^+$ currents into account.

References


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