Modeling of Electro-Mechanics in Left Ventricle

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Abstract

Modeling of cardiac electro-mechanics can enhance the understanding of the physiology and pathophysiology of the heart. A model of the left ventricle is presented, which allows the reconstruction of electrical and mechanical processes with inclusion of feedback mechanisms. The model combines a three-dimensional model of left ventricular anatomy with electrophysiological and force development models of cardiac myocytes as well as models of the electrical current flow and the passive mechanics of the myocardium. Results of simulations are the temporal distribution of electrical propagation and mechanical deformation, which show the connection between cellular electrophysiology, electrical excitation propagation, force development, and mechanical deformation.

1. Introduction

Mathematical modeling and computer-aided simulation of the heart give insight into basic mechanisms and phenomena, which is partly not available by measurements due to technical limitations and ethical objection [1]. This insight can be applied to improve clinical cardiologic diagnosis and therapy.

A simulation of several aspects of cardiac electro-mechanics necessitates a combination of different models [2], i.e. anatomical, electrophysiological, electrical, and mechanical models. An anatomical model defines the tissue distribution. An electrophysiological model of single myocytes reconstructs e.g. transmembrane voltage, intra- and extracellular ion concentrations, and ion flows through the cell membrane. The combination with a model of electrical current flow allows the reconstruction of electrical excitation propagation. A further model describes the development of forces outgoing from the cellular electrophysiologic and mechanic states. Another model is needed to specify the deformation of the myocardium under the influence of the developed forces.

In this work a hybrid, three-dimensional model of a left ventricle was developed, which allows the coupled simulation of electrical excitation propagation, force development and deformation. The model was derived from the Noble-Varghese-Kohl-Noble model of the electrophysiology of a ventricular myocyte [3], an adapted Rice-Winslow-Hunter model of force development [4] and the strain energy density function of Guccione-McCulloch-Waldman for passive myocardium [5]. Intercellular current flow is calculated with the bidomain model.

The force development is controlled by the concentration of intracellular calcium. The calculation of the deformation is performed in an incremental Lagrangian formulation with displacement-based isoparametric finite elements. The simulation takes into account a realistic ventricular geometry with locally varying orientations of myocytes. The orientation leads to an anisotropy of the electrical and mechanical properties.

The hybrid model is used to investigate the distribution of displacements in the left ventricle. The results of simulations, i.e. patterns of electrical propagation and mechanical deformation, are analyzed and compared with measurement data.

2. Methods

2.1. Modeling of cellular electrophysiology

The Noble-Varghese-Kohl-Noble model describes the electrophysiology of a ventricular myocyte of guinea-pig. The model includes effects on ionic channels by the concentration of adenosine triphosphate (ATP) and acetylcholine (ACh) as well as by stretching. Furthermore, a force generation model is included. A description of the diadic space is incorporated. Different variants and configurations of the model exist. The variant applied in this work is based on [3, 6, 7] neglecting ATP and ACh activated ionic channels as well as using only the electrophysiological part of the model.

The model includes dependencies of electrophysiological parameters on the length or tension of the sarcomere. The mechano-electric feedback is realized by introducing stretch-activated ion conductances, a modulation of calcium binding to troponin C, and a modulation of sarcoplasmic leak current. The usage of the mechanisms in the hybrid model presented in this work is restricted to the incorporation of length dependencies of the electrophysiological parameters.

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2.2. Modeling of excitation propagation

Different modeling approaches of the electrical excitation propagation in the myocardium can be distinguished depending on the representation of the microscopic and macroscopic anatomy as well as depending on the approximation of the cellular electrophysiology [1]. In this work a bidomain model was used [8, 2], which describes the electrical current flow in the intra- and extracellular domain by the generalized Poisson's equation. The domains are coupled by the definition of the transmembrane voltage V_m:

$$V_m = \phi_i - \phi_e$$

with the intra- and extracellular potential, ϕ_i and ϕ_e, respectively. The hereby arising 2nd order differential equations were solved on deformable grids with the finite element method. A deformation dependent transformation of the intracellular conductivity tensor was performed [9].

2.3. Modeling of force development

Rice et al. described 5 models reproducing the force development in cardiac muscle [4]. In this work the 3rd model is applied, which uses 6 states, $N0$, $N1$, $P0$, $P1$, T, and TCa with $N0 + N1 + P0 + P1 = 1$ and $T + TCa = 1$. The states $N0$, $N1$, $P0$, and $P1$ describe the cross-bridge cycling, the states T and TCa the binding of intracellular calcium Ca^{2+} to troponin C and the resulting interaction between the troponin complex and tropomyosin. The interaction between the states of the model is described by a system of 1st order differential equations:

$$\frac{\partial}{\partial t}\begin{pmatrix} N0 \\ N1 \\ P0 \\ P1 \\ T \\ TCa \end{pmatrix} = R \begin{pmatrix} N0 \\ N1 \\ P0 \\ P1 \\ T \\ TCa \end{pmatrix}$$

with the 6×6 matrix R consisting of rate coefficients. Partly, the rate coefficients are dependent on the sarcomere length SL and the concentration of intracellular calcium $[Ca^{2+}]_i$. The normalized force F is determined by

$$F = \frac{\alpha(P1 + N1)}{F_{max}}$$

with the sarcomere overlap function $\alpha = \alpha(SL)$ and the maximal force F_{max}. The states $P1$ and $N1$ are the force generating states.

2.4. Elastomechanical modeling

The principle of virtual displacements states, that the equilibrium of a body is achieved if a small virtual displacement leads to an equality of the total internal virtual work and the total external virtual work [10]. The internal work results from strains and stresses in the medium. The external work is given by forces and displacements at the surface and inside of the medium.

In the Lagrangian incremental formulation of the principle of virtual displacements the second Piola-Kirchhoff stress tensor ${}^{t+\Delta t}_{0}\boldsymbol{S}$ and the Green-Lagrange strain tensor ${}^{t+\Delta t}_{0}\boldsymbol{E}$ are applied. The Lagrangian description is suitable for a numerical solution. The equilibrium at time $t + \Delta t$ can be defined by [10]:

$$\int_{{}^0V} {}^{t+\Delta t}_{0}S_{ij}\, \delta\, {}^{t+\Delta t}_{0}E_{ij}\, d^0V = {}^{t+\Delta t}R$$

with the external virtual work ${}^{t+\Delta t}R$. The integration is performed over the volume ${}^0V$ at time $t = 0$, to which all quantities are referred. The external virtual work ${}^{t+\Delta t}R$ is decomposed in applied force densities ${}^{t+\Delta t}_{0}f_i^B$ and surface tensions ${}^{t+\Delta t}_{0}f_i^S$:

$${}^{t+\Delta t}R = \int_{{}^0V} {}^{t+\Delta t}_{0}f_i^B\, \delta\, u_i\, d^0V + \int_{{}^0S_f} {}^{t+\Delta t}_{0}f_i^S\, \delta\, u_i^S\, d^0S_f$$

with the surface ${}^0S_f$.

The interdependency between strain and stress in biological materials is frequently described by a hyperelastic constitutive law assuming incompressibility. Commonly, a strain energy density function $W = W(\boldsymbol{E})$ of the Green-Langrage strain tensor $\boldsymbol{E}$ is defined with its derivative being the 2nd Piola-Kirchhoff stress tensor $\boldsymbol{T}$.

A strain energy density function W for ventricular myocardium was proposed by Guccione et al. [5]. The function was constructed on the base of constitutive laws for arteries assuming orthotrophic material properties. The function is exponential:

$$W = \frac{C}{2}\left(e^Q - 1\right)$$

with the parameter C and the function Q, depending on the Green-Lagrange strain tensor $\boldsymbol{E}$. Two variants of the function Q were investigated: an isotropic function Q_{iso} and an anisotropic, transversal isotropic function Q_{aniso} with respect to the fiber orientation:

$$\begin{aligned} Q_{iso} &= 2b_1(E_{RR} + E_{FF} + E_{CC}) \\ Q_{aniso} &= 2b_1(E_{RR} + E_{FF} + E_{CC}) \\ &+ b_2E_{FF}^2 + b_3(E_{CC}^2 + E_{RR}^2 + E_{CR}^2 + E_{RC}^2) \\ &+ b_4(E_{RF}^2 + E_{FR}^2 + E_{FC}^2 + E_{FC}^2) \end{aligned}$$

with the parameters b_1, b_2, b_3, b_4, and the components of the Green-Lagrange strain tensor $\boldsymbol{E}$. The indices F, C, and R depict the fiber axis, cross-fiber in-plane axis, and the radial direction, respectively.

The strain energy density function was parameterized by comparison of measurements performed with canine ventricles and results of numerical simulation. The measurements delivered epicardial strains and left ventricular volumes in dependence of ventricular pressure. A thick-walled cylindrical model was used to describe the equatorial ventricular geometry. In the isotropic case the parameter C was set to $0.765\ kPa$ and the parameter b_1 to 4.24. For the anisotropic case the parameter b_3 was set to 0. Different parameterizations were determined depending on the assumption of transmural distribution of fiber orientation and residual stress in the ventricular wall.

2.5. Implementation

The hybrid model was implemented with the programming languages C++ and Perl. The simulations were performed on a Silicon Graphics Origin 2000 compute servers with 8 processors of type R10000/200 MHz and 3.8 GB of main memory. A parallelization of numerically expensive steps was achieved with OpenMP. The visualizations were carried out on Silicon Graphics unix workstations using OpenGL and Inventor.

3. Results and conclusions

The hybrid model combined and extended the presented cellular and macroscopic models. It consisted of a single cell electrophysiological model with stretch dependent behavior, a bidomain model, a model of the force development with inclusion of stretch effects, and an elastomechanical model.

The properties of the model were investigated by exemplary simulations. A hollow half ellipsoid approximated the left ventricle's shape. Two different resolutions were chosen for the electrophysiological and mechanical model. The electrophysiological model consisted of 40 x 40 x 40 cubic voxels with an initial size of $0.2\ mm$ x $0.2\ mm$ x $0.2\ mm$. The mechanical model consisted of 20 x 20 x 20 cubic voxels with an initial size of $0.4\ mm$ x $0.4\ mm$ x $0.4\ mm$. The positions in the valve plane ($z = 0$) was fixed, i.e. the displacements were set to zero. The fiber orientation in both models varied from subepicardial $-75°$, midwall $0°$, and endocardial $75°$.

An exemplary simulation started by applying an electrical stimulus at the apex at time $t = 0\ ms$. The simulation had a duration of $500\ ms$. The displacements were determined every $2.5\ ms$. Every $20\ \mu s$ a calculation of each voxel was performed in the electrophysiological, excitation and force development model. Results of this simulation are shown in figures 1 and 2.

The simulations with the hybrid model showed a rapid spread of electrical excitation and delayed force development. The simulations lead to an inhomogeneous force development and deformation, which is characterized by the fiber orientation. Significant torsions were appearing in regions near to the apex. Particularly, the simulations showed in an early stage an sub-endocardial torsion and a reverse sub-epicardial torsion, which was previously not reported.

The endocardial volume was decreased during the contraction to 75 % of its reference volume. A larger volume change would be found, if the boundary conditions ($z = 0$) were chosen conveniently. Nevertheless, while a significant decrease of the endocardial volume can be

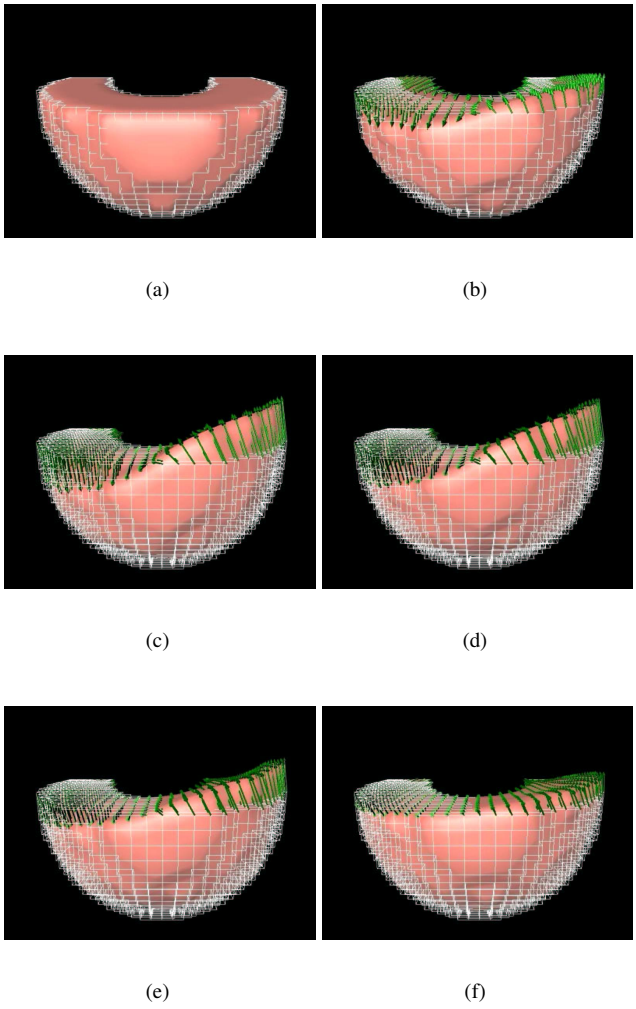
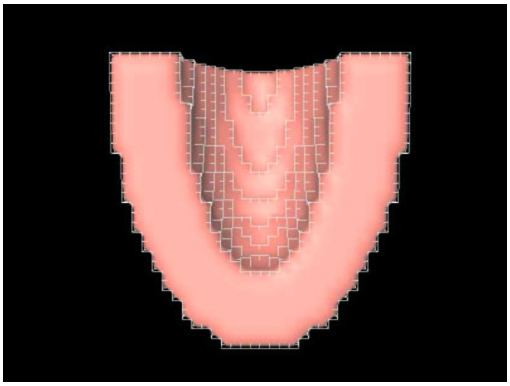
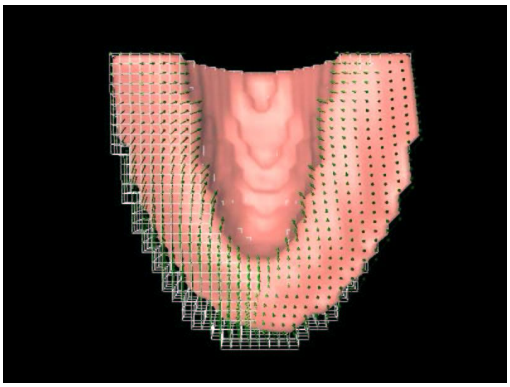


Figure 1. Apical view on deformation at time (a) $0\ ms$, (b) $70\ ms$, (c) $140\ ms$, (d) $210\ ms$, (e) $285\ ms$, and (f) $360\ ms$ in an anisotropic electro-mechanical model of left ventricle. A half of the ventricle's model is shown with a bright wire-frame as reference configuration and arrows indicating displacements.



(a)



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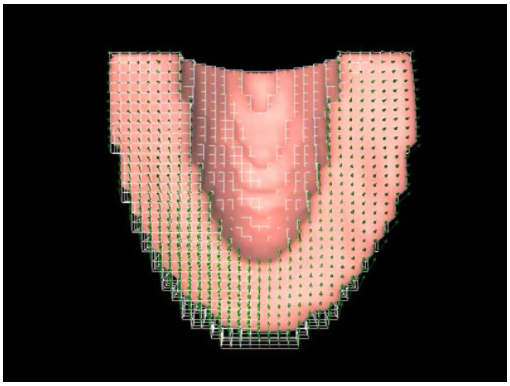

(c)

Figure 2. Lateral view on deformation at time (a) 0 ms, (b) 140 ms, and (c) 285 ms in an anisotropic electro-mechanical model of left ventricle. A half of the ventricle's model is shown with a bright wire-frame as reference configuration and arrows indicating displacements.

found, the changes in epicardial shape were small.

The presented model can be utilized for development of realistic models of whole heart. The model can improve studies of cardiac arrhythmias and computer aided planning of surgical interventions.

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