Electro-Mechanical Modeling of the Myocardium: Coupling and Feedback Mechanisms

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Abstract

Computer aided simulations of the heart provide knowledge for cardiologic diagnosis and therapy. A model of the myocardium is presented which allows the reconstruction of electrical and mechanical processes with inclusion of feedback mechanisms. The model combines detailed models of cellular electrophysiology and force development with models of the electrical current flow and the mechanical behavior of the myocardium. Results of simulations show the connection between the electrical excitation process and the following mechanical deformation in a three dimensional, anisotropic area of the myocardium.

1. Introduction

Modeling of the electro-mechanical behavior of the myocardium is of importance for the understanding of the physiology and pathophysiology of the heart. A fusion of different models allows the simulation of the electro-mechanics of the myocardium: An electrophysiological model of single myocardial cells is necessary to reconstruct the intra- and extracellular ion concentrations, ion flows through the cell membrane and gap junctions, and the transmembrane voltage. The combination with a model of the electrical conductivity allows the reconstruction of the electrical excitation propagation. A further model describes the development of forces outgoing from the cellular electrophysiological conditions. Another model is needed to specify the deformation of the myocardium under the influence of the developed forces.

In this work a three dimensional model of a myocardial area is developed, which allows the coupled simulation of electrical excitation propagation, force development and deformation. The model is derived from the Noble-Varghese-Kohl-Noble model of the electrophysiology of a ventricular cell, the Rice-Jafri-Winslow-Hunter model of force development and a continuum mechanics based deformation model. The electrical coupling of cells is achieved using the bidomain model by calculating the intercellular current source density. Therefore, Poisson's equation for electrical current fields is applied on deformable grids with the finite element technique. 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 the orientation of myocytes, which leads to an anisotropy of the electrical and mechanical properties.

The hybrid model is used to investigate the coupling mechanisms between the different basis models and the influences of feedback mechanisms.

2. Methods

2.1. Modeling of Cellular Electrophysiology

The Noble-Varghese-Kohl-Noble model describes the electrophysiology of a ventricular cell. 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 varient applied in this work is based on [1, 2, 3] neglecting ATP and ACh 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, 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.

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. In this

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Table 1. Tropomyosin and cross bridge states of Rice-Winslow-Hunter Model 3 of cardiac cells.

state	Tropomyosin	No. of cross bridges
$N0$	non permissive	0
$N1$	non permissive	1
$P0$	permissive	0
$P1$	permissive	1

Table 2. Ca^{2+} binding states of Rice-Winslow-Hunter Model 3 of cardiac cells.

state	Ca^{2+} binding to Troponin C
T	no
TCa	yes

work the bidomain model with Poisson's equation for electrical current fields is used [4, 5].

2.3. Modeling of Force Development

The Rice-Winslow-Hunter models consists of 5 models reproducing the force development in cardiac muscle [6]. As an example of the modeling a short description of the 3rd model is given.

This model consists of 6 states, $N0$, $N1$, $P0$, $P1$, T, and TCa with $N0 + N1 + P0 + P1 = 1$ and $T + TCa = 1$ (tables 1 and 2). 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 equilibrium of a body is achieved if the internal and external forces are balanced [7]. The equilibrium at time $t + \Delta t$ can be expressed using the principle of virtual displacements:

$$\int_{t+\Delta t V} {}^{t+\Delta t}\tau_{ij}\, \delta_{t+\Delta t} e_{ij}\, d^{\,t+\Delta t}V = {}^{t+\Delta t}R$$

with the volume ${}^{t+\Delta t}V$, the components of the Cauchy stress tensor ${}^{t+\Delta t}\tau_{ij}$, the strain tensor $\delta_{t+\Delta t}e_{ij}$, and the external virtual work R. The formula uses the summation convention of Einstein, where repeated subscripts become the designation for summation. The strain tensor is defined as

$$\delta_{t+\Delta t} e_{ij} = \frac{1}{2}\left(\frac{\partial \delta u_i}{\partial^{t+\delta t} x_j} + \frac{\partial \delta u_j}{\partial^{t+\delta t} x_i}\right)$$

with the components of the virtual displacement vector δu_i. The external virtual work R is sub-dived in applied force densities ${}^{t+\Delta t}f_i^B$ and surface tensions ${}^{t+\Delta t}f_i^S$:

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

with the surface ${}^{t+\Delta t}S_f$.

In a Lagrangian description, which is suitable for a numerical solution, the upper strain and Cauchy stress tensors are replaced by the Green-Lagrange strain E and 2nd Piola-Kirchhoff stress tensor T. Furthermore, the integration is performed over the volume in reference configuration.

Biological materials are often described using a hyperelastic constitutive law assuming incompressibility. A strain energy density function $W(E)$ is defined with its derivative being the 2nd Piola-Kirchhoff stress tensor T.

The strain energy density function W proposed by Hunter et al. takes the anisotropic and inhomogeneous behavior of the myocardium into account [8, 9]. The parameterization of the function W was performed by uniaxial measurements of canine ventricle in the different directions of the axes. Three microstructural, orthogonal axes are distinguished: the fiber, sheet and sheet normal axis. For each axis i a set of parameters, k_i, a_i, and β_i, describes its contribution to the strain energy density, called pole-zero law:

$$W = \sum_{i=1}^{3} \frac{k_i e_{ii}^2}{(a_i - |e_{ii}|)^{\beta_i}}$$

with the diagonal components of the Green-Lagrange strain tensor e_{ii}. The parameter k_i is set to zero, if e_{ii} is negative. The strain energy density function W is defined for $|e_{ii}| < a_i$. The function shows large values for e_{ii} approaching

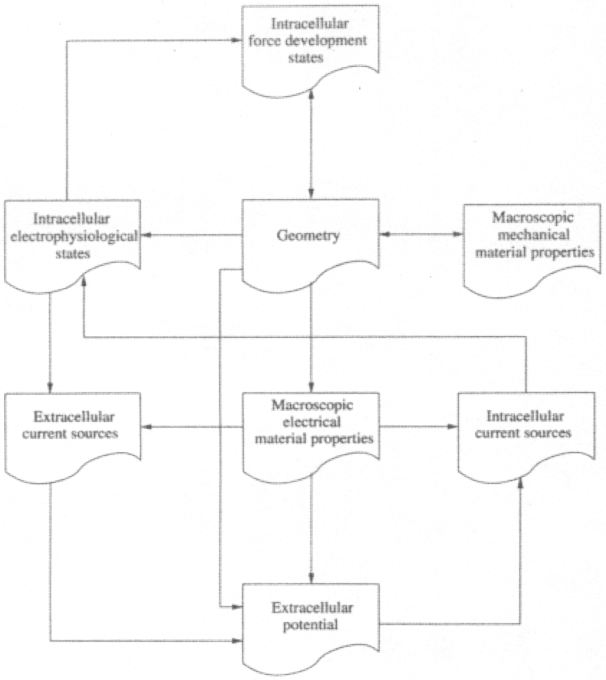


Figure 1. Modeling of cardiac electromechanics.

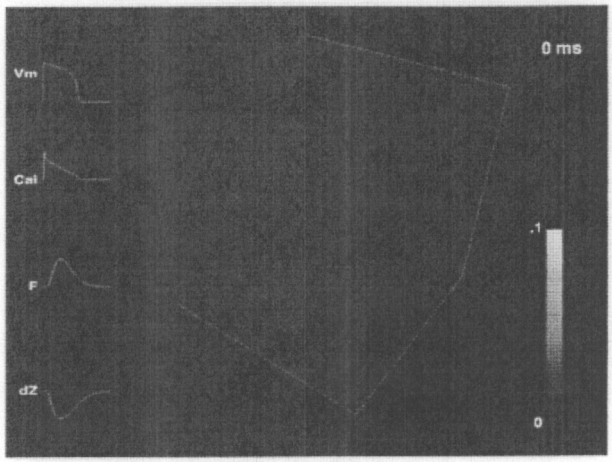
a_i, reflecting the steep rise in tension coming upon a strain limit.

The strain energy was extended by terms representing the incompressibility of the myocardium. The energy does not comprise shear and viscoelastic effects.

3. Results

The developed numerical model has the purpose to achieve knowledge concerning the cardiac deformation and its influence to the initiation and propagation of electrical excitation and to the force development. The model combines and extends the presented cellular and macroscopic models. It consists of a single cell electrophysiological model with stretch dependent behavior, a classical bidomain model, a model of the force development with inclusion of stretch effects, and an elastomechanical model. The interdependencies of the different data are depicted in figure 1, results from an exemplary simulation in figures 2 and 3.

As an electrophysiological model the modified Noble-Varghese-Kohl-Noble model was used [1], whereby stretch dependent ion channels were included [10]. The intercellular electrical coupling through the gap junctions and extracellular space was performed with the classical bidomain model. The engaged force model was the Rice-Winslow-Hunter model (type 3). The elastomechanical behavior was modeled by numerical methods of continuum mechanics [7] using the strain energy function proposed by Hunter et al.[8].



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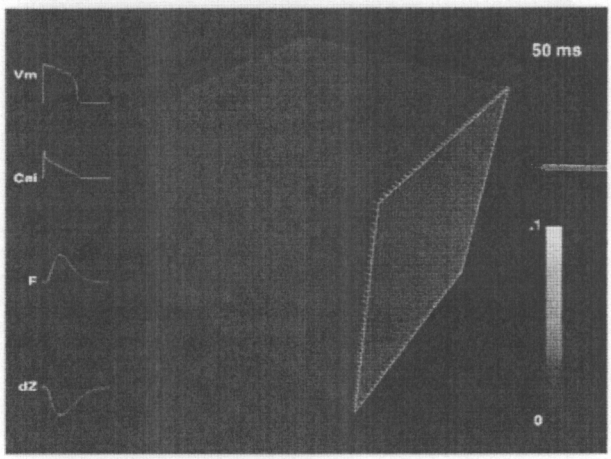

(b)

Figure 2. Normalized force and deformation at time (a) 0 ms and (b) 50 ms in an anisotropic model of myocardial area. The model consists of 40 x 40 x 40 cubic voxels with an initial size of 0.1 mm x 0.1 mm x 0.1 mm. The central position of the plane z=0 was fixed, i. e. the displacements were set to zero. The bright wire frame shows the reference configuration. At the left side the course of membrane voltage, intracellular calcium concentration, normalized force and displacement in z direction of a central voxel are shown.

The hybrid model was implemented with the programming language C++. The simulations were performed on Silicon Graphics UNIX workstations and compute servers. A parallelization of numerically expensive steps was achieved with OpenMP.

4. Conclusion

The simulations with the hybrid model show processes of different time scale. The process of excitation propagation is rapidly spreading over the myocardium. The force development and the resulting deformation follows with a significant delay. The presented model shows to be of great significance for the development of realistic models of the whole heart, e.g. for studying cardiac arrhythmias and for the computer aided planning of surgical interventions.

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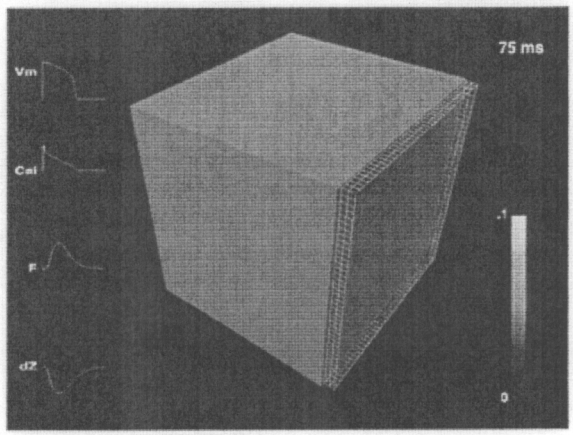

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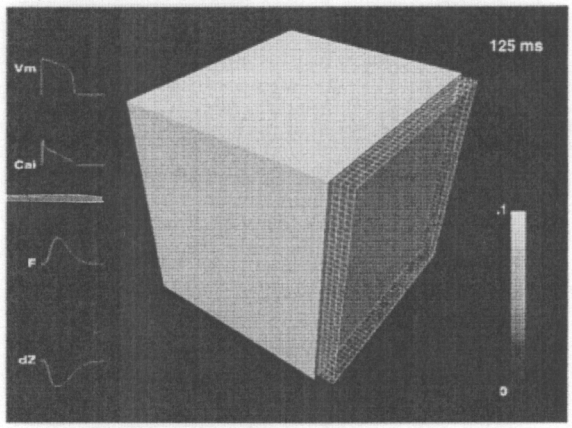

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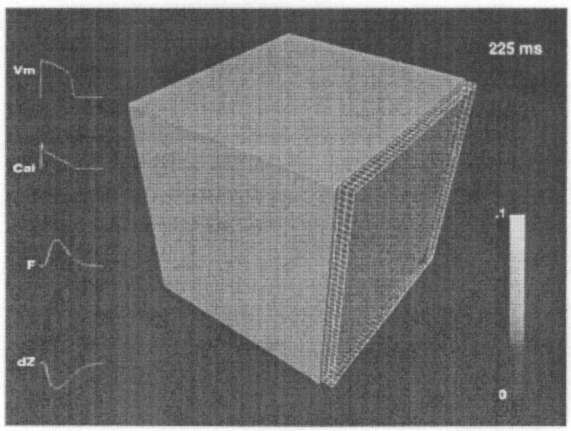

(c)

Figure 3. Normalized force and deformation at time (a) 75 ms, (b) 125 ms and (c) 225 ms in an anisotropic model of myocardial area (continued).