A 3D ELECTROMECHANICAL FEM-BASED MODEL FOR CARDIAC TISSUE

Minh Tuan Duong\textsuperscript{1,2}, Alexander Jung\textsuperscript{1}, Ralf Frotscher\textsuperscript{1} and Manfred Staat\textsuperscript{1}

\textsuperscript{1} Aachen University of Applied Sciences
Institute of Bioengineering
Heinrich-Mußmann-Str. 1, 52428 Jülich, Germany
e-mail: \{a.jung, frotscher, m.staat\}@fh-aachen.de

\textsuperscript{2} Hanoi University of Science and Technology
DaiCoViet No.1, Hanoi, Vietnam
tuan.duongminh@hust.edu.vn

\textbf{Keywords:} Cardiac Tissue, CellDrum, Cell Models, Drug Modeling, Electromechanical Coupling

\textbf{Abstract.} The CellDrum provides an experimental setup to investigate the electromechanics of a cardiac tissue construct and particularly the effect of drugs. Experimental data can be used to parametrize and validate computational electromechanical models. Until now, the experiments have been performed with a thin tissue layer of a mixture including ventricular, atrial and sinoatrial cells. Mechanically, it is modeled as a materially and geometrically nonlinear shell. For future experiments with a thick tissue layer of mixtures and single cardiac cell types the mechanical model is extended to a nonlinear 3D continuum which can be used as a step towards whole heart modeling. Comparisons with the 2D shell model are presented with and without the consideration of a chosen drug and a simulation with a model for thick cardiac tissue construct is carried out to give a first impression on how the experiments might look like.
1 INTRODUCTION

A human heart is divided into four chambers, two atria and two ventricles, connected by four valves. The right atrium receives oxygen-poor blood from the body and pumps it to the right ventricle from where it is pumped to the lungs. The left atrium receives oxygen-rich blood from the lungs and pumps it to the left ventricle from where it is pumped back to the body. Both the filling and ejection processes are controlled by electrophysiological processes. At the cellular level the main components in the heart are cardiomyocytes, cardiac fibroblasts, endothelial cells and vascular smooth muscle cells [1]. Cardiomyocytes are subdivided into two types, namely the pacemaker-conduction and the contractile cardiomyocytes. Each cardiac cycle is initiated by sinoatrial cells located in the upper wall of the right atrium. Sinoatrial cells are pacemaker cardiomyocytes that can generate spontaneous action potentials, i.e. a rapid change in the membrane potential. Over a conduction system the action potential propagates throughout the whole heart so that the contractile cardiomyocytes in the atria and ventricles are electrically excited. Cardiomyocytes are composed of myofilaments enabling the cells to contract. Even pacemaker-conduction cardiomyocytes are able to contract but by far not as strong as the contractile cardiomyocytes. In a process called excitation-contraction coupling the action potential results in a release of Ca$^{2+}$ from intracellular stores which activate the sarcomeres so that tension can be created and the cells can contract.

Computational cardiac models have been developed with the motivation to investigate the physiology and pathologies of the heart and ultimately to optimize therapies. In 1952, Hodgkin and Huxley published the first electrophysiological model of an excitable cell [2]. For a squid giant axon they linked the kinetics of ion channel conformation change with ion currents through the cell membrane and the change of the membrane potential. Ten years later, this groundbreaking work was extended by Noble to model the electrophysiology of cardiac myocytes [3]. Since then, the understanding of cellular mechanisms and the experimental potential has increased. This has led to the development and improvement of models for different human cardiomyocytes [4-7]. Since the models are already at a mature stage, they can serve as a basis to investigate the effect of various drugs on the cardiac electrophysiology [7, 8]. When these models are applied to tissues the action potential propagation from one cell to its neighboring cells needs to be taken into account. For this, the monodomain and bidomain reaction-diffusion equations are used. Bidomain equations account for the different electrical conductivities of the intracellular and extracellular spaces whereas only one conductivity is used in the monodomain equations. Differences between monodomain and bidomain results were reported to be extremely small [9] so that the monodomain equations with a much lower computational cost is widely preferred. Solving them with the Finite Element Method (FEM) gives the membrane averaged over a set of myocytes in each element.

While many questions can be addressed with electrophysiological models, others e.g. regarding the dilated cardiomyopathy necessitates a complete representation of the electromechanics. Improved computer performance has made it possible to develop FEM models where the electrophysiology is coupled with the mechanics. Electromechanical coupling is based on the relationship between the electrical activation of the tissue, the respective active tension generated by the sarcomeres and the resulting deformation [10]. Here, the electrophysiology is modeled on the cellular level [11-15] or is simplified using eikonal equations [16] or the FitzHugh-Nagumo model [17,18]. There exist a wide range of electromechanical models from the cell [10,12] over the tissue [14] to the organ level including left ventricular models [11,15], models of both ventricles [12-15,17], and whole heart models [18]. They feature a varying degree of complexity with respect to the anatomical representation, associated mesh fineness, boundary conditions, material models, underlying electrophysiological models and coupling.
models depending on the research objective. Different from the electrophysiological models electromechanical models are still in a maturing phase. Magnetic resonance imaging makes it now possible to create patient-specific highly resolved anatomical models [13], ventricle muscle fiber directions can be determined and assigned with a rule-based algorithm [19] and the orthotropic electric [20] and mechanical properties [21, 22] of the ventricular myocardium are well studied. However, there are still many tasks towards a highly sophisticated whole heart computer model. Examples include the model parametrization, verification, and validation procedures [23].

For thin cardiac tissue constructs these tasks have been addressed with a device called CellDrum [24, 25]. The CellDrum is a circular, 4 μm thin silicone membrane with a diameter of 16 mm. Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) are seeded and cultivated on top of the silicon membrane which is coated with fibronectin. The tissue monolayer has a thickness of up to 19 μm and consists of the following mixture: 60% myocardial ventricular, 35% atrial, and 5% nodal hiPSC-CM (Cor.4U, Axiogenesis AG, Germany). The cardiomyocytes live within a culture medium and beat autonomously as in the real heart. Clamped in a fixed ring the composite material can be inflated by a syringe pump and the resulting cellular contraction-dependent deflection is measured using a laser sensor. Thus, parameters for passive and coupling models can be determined [26]. Drugs have already been applied to the culture medium leading to phenomenologically observable changes in the beating frequency, deflection, contraction duration, activation time, relaxation time and resting time [25]. Frotscher et al. [14, 26, 27] developed an electromechanical model of the CellDrum which they parametrized, verified and validated using respective experiments. On the level of the electrophysiological cell models also the drug action was implemented. Until now, the effect of four drugs could be successfully simulated. Currently, the thin tissue construct is modeled as a materially and geometrically nonlinear shell whereas electrically it is viewed as a nonlinear three-dimensional continuum.

The next step is to perform experiments with thick cardiac tissue. For this, the mechanical model is modified towards a 3D continuum as well. Comparisons between the 2D shell formulation and 3D continuum formulation are presented. Furthermore, a new geometry is introduced to roughly predict the results of future experiments with thick cardiac tissue. Simulation results with and without the consideration of a chosen drug are shown.

2 ELECTROMECHANICAL MODEL

2.1 Electrophysiological model

Hodgkin-Huxley based cell models for sinoatrial [5], atrial [6] and ventricular [4] cardiomyocytes were employed, each having the general form

\[ \frac{\partial V_m}{\partial t} = \frac{1}{C_m} I_{tot} \] (1)

\[ I_{tot} = I_{stim} - \sum_{i=1}^{n} I_i(g_j) \quad (j = 1, ..., m) \] (2)

\[ \frac{\partial g_j}{\partial t} = \alpha_j^+(V_m)(1 - g_j) + \alpha_j^-(V_m) g_j \] (3)
where $V_m$ is the cell membrane potential, $C_m$ is the electrical capacitance of the cell membrane, 
$I_{tot}$ is the total current for each cell model, $I_{stim}$ is an electrical stimulus which is zero in the
sinoatrial model, $I_i$ are ionic currents related to the ion $i$ and $n$ is the number of ionic currents
in the respective cell model. Gate variables $g_j$, usually one or two, control the opening and
closure of each ion channels. Here, $\alpha_j^+$ and $\alpha_j^-$ are experimentally determined opening and
closure rates which depend on a threshold value of the membrane potential for each ion channel. Channel currents take the form

$$I_i = G_i \prod_{j=1}^{m} g_j(V_m - E_i), \quad (4)$$

where $G_i$ is the maximum conductance of channel $i$ and $E_i$ is the reversal potential for the type
of ion which flows through this channel.

Furthermore, the employed cell models provide ordinary differential equations for free intra-
cellular sodium, potassium and calcium concentrations as well as for internal calcium stores.

Cellular interaction on the micro-scale level was took into account with a simple homogeni-
zation approach. Once the total current density of the sinoatrial model falls below a threshold
$I_{tot} < -0.5 \mu A m^{-1}$, the atrial and ventricular model receive a stimulus

$$I_{stim} = -\frac{50 \mu A m^{-3} \cdot V_{cell}}{C_m \cdot A_m} \cdot V_{cell} \quad (5)$$

for 2 ms depending further on their ratio of cell volume $V_{cell}$ to cell surface area $A_m$.

Concerning the respective volume fraction and cell volume to cell surface ratio of every cell
model ($s$: sinoatrial, $a$: atrial, $v$: ventricular) the highly nonlinear source current per unit length
reads

$$I_{src} = \left( \theta_s \frac{A_s}{V_{cell}} I_{tot}^s + \theta_a \frac{A_a}{V_{cell}} I_{tot}^a + \theta_v \frac{A_v}{V_{cell}} I_{tot}^v \right) (1 - \theta_{ECM}). \quad (6)$$

Here, also the volume fraction of the extracellular matrix $\theta_{ECM}$ including fibroblasts are taken
into account. With this approach the microscopic cellular action potential are homogenized in
order to get a macroscopic action potential that propagate throughout the tissue. The
monodomain describing the action potential propagation reads

$$C \frac{\partial V}{\partial t} = \nabla (G(B) \nabla V) + I_{src}, \quad (7)$$

with the action potential $V$, capacitance $C$, isotropic conductance $G$ and the left Cauchy-Green
tensor $B$. 

2.2 Electromechanical coupling

Electromechanical coupling is described by the following two ordinary differential equations for each cell model:

$$\frac{\partial Ca_b}{\partial t} = f_1(Ca_i, Ca_b, T_0)$$  \hspace{1cm} (8)

$$\frac{\partial z}{\partial t} = f_2(z, Ca_b, B).$$  \hspace{1cm} (9)

The calcium concentration $Ca_b$ that is bound to troponin C in the myofilaments depends on the freely available calcium concentration $Ca_i$ and on the cellular stress $T_0$. The strain-dependent state of activation is expressed by the activation variable $z \in (0,1)$. Finally, the cellular stress for each cell model is computed according to Niederer and Smith [10] by

$$T_0 = T_{\text{ref}} \left( 1 + \beta_0 (\lambda - 1) \right) K \frac{z}{z_{\text{max}}},$$  \hspace{1cm} (10)

with $T_{\text{ref}}$ being the cellular reference stress, $\beta_0$ is a scalar determining the length dependence of the tension, $\lambda$ is the one-dimensional cellular stretch in fiber direction, $K$ reflects the binding velocity and $z_{\text{max}}$ is the maximally available activation level. Due to a missing cell type specific parametrization an equal parametrization was used for all cell types. For the whole tissue construct the cellular reference stress was determined to be $T_{\text{ref}} = 0.5808 \text{ kPa}$ [26] which replaced the original model parameter [10].

2.3 Drug action

Drug action can be implemented in (4) using the conductance-block formulation where the maximal conductance of the channel $i$ is reduced by the factor

$$g_i = g_{i,\text{control}} \left[ 1 + \left( \frac{D}{IC_{50_i}} \right)^n \right]^{-1}.$$  \hspace{1cm} (11)

Here, $g_{i,\text{control}}$ is the drug-free maximal conductance, $D$ is the drug concentration the $IC_{50}$ value represents the half-inhibitory value, i.e. the concentration of a given drug that will cause the current flowing through the channel $i$ to be reduced by 50%. It has been shown that drug effects at steady-state concentration can be well represented by this model [28]. In this study, Verapamil is used as an example associated with blocking effects on the hERG-, L-type calcium- and sodium-channels of the ventricular cardiomyocytes. Respective $IC_{50}$ values and effective free therapeutic plasma concentrations (EFTPC) used for $D$ can be found in [8].
2.4 Mechanical model

Derivation of the mechanical properties of cardiac muscle tissue can be performed by employing either the active strain or active stress approach. The active strain approach utilizes a multiplicative split of the deformation gradient into passive $F_p$ and active deformation $F_a$

$$F = F_p F_a,$$  \hspace{1cm} (12)

whereas in the active stress approach the total stress in the tissue is additively decomposed into the passive and active stress. Both approaches are considered to lead to comparable solutions [29].

Since the experimental parametrization was based on the level of stresses, the latter approach was used. Based on the work of Hunter et al. [30] the total Cauchy stress reads

$$\sigma = \sigma_p + \sigma_a = 2J^{-1}B \frac{\partial \psi}{\partial B} - pI + T(t, B) a \otimes a,$$  \hspace{1cm} (13)

with the strain energy function $\psi$, the determinant of the deformation gradient $J$, the hydrostatic pressure $p$, the identity tensor $I$, the active stress $T$ being a scalar, the time $t$ and the vector $a$ oriented in the direction of the cardiac muscle fiber. Global isotropy of the muscle fibers is given in the thin cardiac tissue construct on the CellDrum [26], thus

$$a \otimes a = I.$$  \hspace{1cm} (14)

is assumed. Finally, the 2nd Piola-Kirchhoff stress $S$ is given as

$$S = S_p + S_a = 2 \frac{\partial \psi}{\partial C} - pC^{-1} + T(t, C)C^{-1},$$  \hspace{1cm} (15)

in terms of the right Cauchy-Green tensor $C$. According to the experimentally measured pressure-deflection curves the quasi-incompressible hyperelastic neo-Hookean constitutive law

$$\psi = C_{10}(I_1 - 3)$$  \hspace{1cm} (16)

was used where $I_1$ is the first invariant and $C_{10} = 0.0838284$ [26].

2.5 Finite Element Models

Finite element models were created for 19 μm and 100 μm thick cardiac tissue constructs. Due to symmetry only one quarter of the CellDrum was modeled. For a 19 μm thick cardiac tissue construct two models were developed. The first model is composed of a 2D mechanical model and a 3D electrical model. Shell formulation was used for the mechanical model which consists of 120 seven-node triangular elements. The electrical model consists of 7664 ten-node quadratic tetrahedral elements. The second model is completely formulated in 3D and both the mechanical and the electrical part are computed using the same mesh which is described above.
For a 100 μm thick cardiac tissue construct another 3D model was created. Here, the mesh consists of 7639 ten-node quadratic tetrahedral elements.

Firstly, the inflation process is simulated by applying a certain pressure to the clamped mechanical mesh. X Pa is necessary to displace the central point of the 2D 19 μm model to 1.2 mm. This has been experimentally validated [14]. Displacements are then projected onto the 3D electrical mesh. Subsequently, the autonomous cell contractions is simulated using an algorithm to solve the electromechanical problem which is described in [14]. When using the same mesh for the mechanical and the electrical part, the displacements do no longer need to be projected. The open source code Code_Aster was used to solve the nonlinear mechanical and electrical problem, whereas the cellular ordinary differential equations were solved internally using a fourth-order singly-diagonally implicit Runge-Kutta method.

3 RESULTS

3.1 Comparison between 2D and 3D mechanical model

Figure 1 shows the central node deflection of two 19 μm thick cardiac tissue construct models as a function of time. Models composed of a 2D and a 3D mechanics model are compared. As it was to be expected, the difference between both models is negligibly small. The same is true when the drug Verapamil is applied to the respective ventricular cell models [4]. Simulations with a low (25 nM) and a high effective free therapeutic plasma concentration (81 nM) were carried out. The resulting membrane potentials of the respective ventricular cell models correspond to [8]: the duration of the action potential decreases with increasing drug concentration. As distinguished from pure electrophysiology models CellDrum models are capable of predicting the drug effect on the deflection. Effects on the deflection are shown in Figure 2 for the second model: the deflection decreases with increasing drug concentration.

Figure 1: Central node deflection of a 19 μm thick cardiac tissue constructs. A 2D- (solid line) and a 3D-mechanical model (dashed line) are compared.

Figure 2: Effect of Verapamil on the central node deflection of a 19 μm thick cardiac tissue construct. The second 3D model was used. Results of the control (0 nM, solid line), low EFTPC (25 nM, dashed line), and high EFTPC (81 nM, dotted line) are shown.

3.2 Comparison between a 19 μm and a 100 μm thick cardiac tissue construct model

Figure 4 shows the time function of the central node deflection of two 3D cardiac tissue construct models. Models with different tissue construct thicknesses, 19 μm and 100 μm, are compared. In order to have the same start position, x Pa more pressure is needed to inflate the 100 μm model up to the same height as the 19 μm model. The deflection of the 100 μm model is lower compared to the 19 μm model. Furthermore, the effect of Verapamil on the deflection was investigated in both models. The application of 81 nM Verapamil results in a peak deflection difference of x1 (x2) mm in the 19 (100) μm models.

Figure 3: Central node deflection of two differently thick tissue constructs. 19 μm thick (solid line) and 100 μm thick (dashed line) cardiac tissue construct models are compared. Comparisons were made with no addition of a drug.
4 OUTLOOK

In the present model the electric and passive material properties were modeled to be isotropic according to global isotropy of the cardiac tissue on the CellDrum. However, myocardial tissue of the left ventricle is orthotropic in both electrical [20] and passive mechanical properties [21] and thus, it is unsuitable for heart models. Currently, an orthotropic model is developed which is described in the following.

Myocardial tissue is organized in layers with collagen fibers between the sheets and are referred to a right-handed orthonormal coordinate system with the fiber axis \( f_0 \), the sheet axis \( s_0 \), and sheet normal axis \( n_0 \) (Figure 4).

**Figure 4**: Right-handed orthonormal coordinate system with fiber axis \( f_0 \), sheet axis \( s_0 \) and sheet-normal axis \( n_0 \) in the layered organization of myocardial tissue. The fiber direction is indicated with dashed arrows.

Orthotropic electrical behavior is considered in the monodomain equation (7). Here, an anisotropic conductance tensor \( \mathbf{G} \) is used in order to incorporate differences in the action potential propagation in all axes as has been done in [13]. Orthotropic passive material behavior is implemented using the strain energy function published Holzapfel and Ogden [21]

\[
\psi = \frac{a}{2b} \exp[b(l_1 - 3)] + \sum_{i=f,s} \frac{a_i}{2b_i} \{\exp[b_i(l_{4i} - 1)^2] - 1\} + \frac{a_{fs}}{2b_{fs}} \exp(b_{fs}l_{8fs}^2 - 1),
\]

where \( a, b, a_f, a_s, b_f, b_s, a_{fs} \) and \( b_{fs} \) are eight positive material constants which can be derived from [22]. The given strain energy function consists of an isotropic term in \( l_1 \), a transversely isotropic term in \( l_{4f} \) and \( l_{4s} \) and an orthotropic term in \( l_{8fs} \). The respective invariants read

\[
l_1 = \text{tr} \mathbf{C}, \quad l_{4f} = f_0 \cdot (f_0 \cdot \mathbf{C} f_0), \quad l_{4s} = s_0 \cdot (s_0 \cdot \mathbf{C} s_0), \quad l_{8fs} = f_0 \cdot (s_0 \cdot \mathbf{C} s_0).
\]

Using the CellDrum geometry the fiber direction will be set to be orientated radially from the center to the edge. Analogue experiments might be possible in the future using mainly myocardial ventricular cells which are cultivated in a way that they grow in the desired direction. This allows to parameterize the active stress model (10) by measuring the cell type specific reference stress having the mentioned passive stress model as basis. All in all, improved models can help to better investigate the effect of drugs *in-silico*. 

\[
\]
REFERENCES


