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HOMOGENIZATION OF A CARDIAC TISSUE CONSTRUCT

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SUMMARY

We extend the modeling of a cardiac tissue composite by proper homogenization of all the different mechanical contributions to the constitutive tensor as well as the contributions to the diffusion tensor and the electrical source current in the parabolic system. The model is applied to support the interpretation of experimental findings in drug testing being able to explain the results at the cellular level. Moreover the model can be used for the prediction of drug effects on cardiac tissue and for computational studies of cardiomyocyte and cardiac tissue electromechanics.

Key words: *cardiac tissue modeling, electromechanical coupling, homogenization*

1 INTRODUCTION

Cardiac tissue constructs or engineered heart tissues are a valuable tool for *in vitro* drug testing, for the analysis of gene expression or the investigation of diseases on both, the mechanical and electrophysiological level. Different experimental setups all over the world are created in order to assess the mechanical or electrophysiological behavior of those tissues and their parameters, e.g. [1] and [2]. As these setups provide only macroscopic results (tissue level), computational models and simulations are employed in order to resolve and elucidate experimental findings at the microscale (cellular level).

We recently reported about a computational model of a cardiac tissue construct [3] that is illustrated in fig. 1. It consists of a cardiac monolayer composed of an extracellular matrix (ECM), atrial, ventricular and nodal cardiomyocytes (CM) and fibroblasts. The tissue is cultivated on top of a circular silicone membrane. The whole composite tissue can be placed into an inflation setup (cf. fig. 2) in order to measure for instance beating force, beating frequency and cardiac throughput.

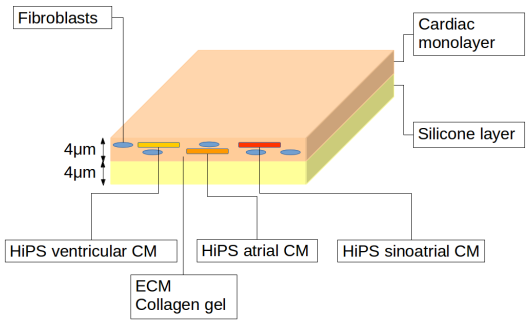

Figure 1: Schematical drawing of the investigated tissue consisting of a silicone membrane and engineered heart tissue that in turn consists of an ECM and potentially multiple cell types

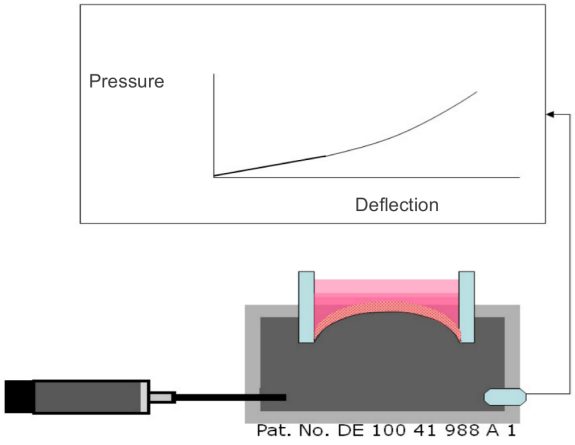

Figure 2: Bulge test in a CellDrum^{TM} [3]

Herein we extend the modeling of this composite presented in [3] by proposing a framework that properly homogenizes all the different mechanical contributions to the constitutive tensor as well as the contributions to the diffusion tensor and the electrical source current in the parabolic system.

2 HOMOGENIZATION OF MECHANICAL STRESS

The first step is to represent the Cauchy stress in the two incompressible layers in parallel by

$$\boldsymbol{\sigma^s} = 2J^{-1}\boldsymbol{B}\frac{\partial \Psi^s}{\partial \boldsymbol{B}} - p\boldsymbol{I} \tag{1}$$

$$\boldsymbol{\sigma^t} = 2J^{-1}\boldsymbol{B}\frac{\partial \Psi^t}{\partial \boldsymbol{B}} - p\boldsymbol{I}\ , \tag{2}$$

with Cauchy stress $\boldsymbol{\sigma}^*$ and strain energy Ψ^* in the respective silicone (s) or tissue (t) layer, the determinant of the deformation gradient J, the left Cauchy-Green tensor $\boldsymbol{B}$ and the hydrostatic pressure p. In Voigt's parallel model the total composite stress in the structure can be written as

$$\boldsymbol{\sigma} = \theta_s\boldsymbol{\sigma}^s + \theta_t\boldsymbol{\sigma}^t\ , \tag{3}$$

with volume fractions θ_s and θ_t, at which $\theta_s + \theta_t = 1$. Following the isostrain model, we assume equal kinematics for both layers, i.e. $\boldsymbol{\varepsilon}^s = \boldsymbol{\varepsilon}^t = \boldsymbol{\varepsilon}$.

We model the silicone layer using an incompressible neo-Hookean strain energy function Ψ^s_{nH}, such that

$$\boldsymbol{\sigma}^s = 2J^{-1}\boldsymbol{B}\frac{\partial \Psi^s_{nH}}{\partial \boldsymbol{B}} - p\boldsymbol{I}\ . \tag{4}$$

The modeling of the cardiac tissue though is more complicated due to its complex structure. Besides the neglect of viscoelastic effects and the microscopically verified assumption of global isotropy, the modeling approach is based on the one presented in [5]. Following the active stress formulation, the Cauchy stress is the sum of cellular and extracellular matrix contributions

$$\boldsymbol{\sigma}^t = \boldsymbol{\sigma}^c + \boldsymbol{\sigma}^m\ , \tag{5}$$

wherein the latter one is again modeled by a neo-Hookean material law similarly to eq. (4).

The cellular model is depicted in fig. 3 and following the derivations presented in [5] one ends up with

$$\boldsymbol{\sigma}^t = 2J^{-1}\boldsymbol{B}\frac{\partial \Psi^m_{nH}}{\partial \boldsymbol{B}} + \frac{1}{4}\omega_0 J^{-1}\boldsymbol{B}\frac{\partial \Psi^c_{nH}}{\partial \boldsymbol{B}} + \frac{1}{2}T_0(\boldsymbol{B},t)\boldsymbol{I} - p\boldsymbol{I}\ , \tag{6}$$

with $\omega_0 = Nl_0A_0$ a dimensionless constant transforming cell stress to global stress and $T_0 = Nl_0F_0(\lambda,t)$ the contractile part of the stress. N, l_0, A_0 and λ are the number of cells per unit volume, the initial cell length, its initial cross-section and the current cellular stretch, respectively. F_0, the actively generated force is determined from models of cellular electrophysiology and excitation-contraction coupling.

The investigated tissue consists of four different cell types, namely ventricular, atrial and nodal CM and fibroblasts. In the short-term experiments we are focusing at, it is realistic to assume that $\boldsymbol{\varepsilon} = \boldsymbol{\varepsilon}^m = \boldsymbol{\varepsilon}^c$, independent of the cell type thus the arithmetic average

$$\boldsymbol{\sigma}^c = \theta_v\boldsymbol{\sigma}^v + \theta_a\boldsymbol{\sigma}^a + \theta_n\boldsymbol{\sigma}^n + \theta_f\boldsymbol{\sigma}^f \tag{7}$$

for the cellular Cauchy stress can be employed with volume fractions θ_* that in sum give 1. The mechanical model can then be summarized as

$$\boldsymbol{\sigma} = 2\theta_s J^{-1}\boldsymbol{B}\frac{\partial \Psi^s_{nH}(\boldsymbol{B};C^s_{10})}{\partial \boldsymbol{B}} + \theta_t\Bigg(2J^{-1}\boldsymbol{B}\frac{\partial \Psi^m_{nH}(\boldsymbol{B};C^m_{10})}{\partial \boldsymbol{B}} \tag{8}$$

$$+ \sum_{*=v,n,a,f}\theta_*\left(\frac{1}{4}\omega^*_0 J^{-1}\boldsymbol{B}\frac{\partial \Psi^*_{nH}}{\partial \boldsymbol{B}} + \frac{1}{2}T^*_0(\boldsymbol{B},t)\boldsymbol{I}\right)\Bigg) - p\boldsymbol{I}\ , \tag{9}$$

with silicone and ECM neo-Hookean parameters C^s_{10} and C^m_{10}, respectively.

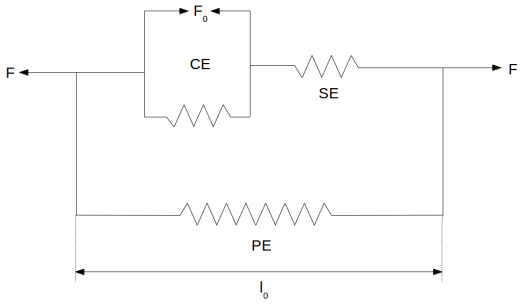

Figure 3: Modified Hill's model for a contractile cell having a series passive element (SE), a contractile element (CE) and a parallel passive element (PE) related to the intrinsic passive properties of the filaments

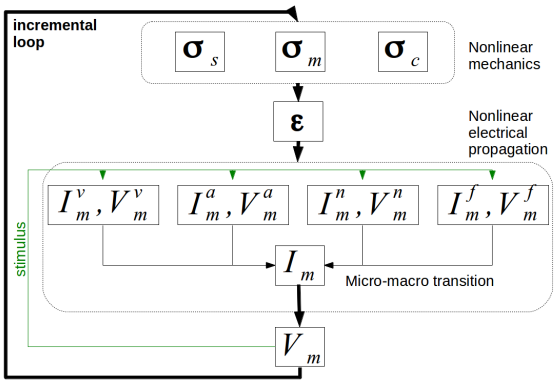

Figure 4: Flowchart of the incremental algorithm, the nonlinear mechanical and electrical model

3 HOMOGENIZATION OF ACTION POTENTIAL AND IONIC CURRENTS

Concerning the homogenization of the action potential and the whole electrophysiology of the cells we follow the framework of Keip et al. [6]. The overall parabolic system reads as

$$C_m \frac{\partial V_m}{\partial t} = \nabla \left(\boldsymbol{G}(\boldsymbol{B}) \nabla V_m \right) - I_m \ , \tag{10}$$

with action potential V_m, cell membrane capacitance C_m, conductance $\boldsymbol{G}$ and ionic membrane current I_m. Each cell type is described by an own ordinary differential equation system

$$\frac{\partial V_m^*}{\partial t} = \dot{V}_m^* = \frac{1}{C_m^*} \left(I_{stim}^* - \sum_{i=1}^{n} I_i^* (g_{x_1}^*, g_{x_2}^*, ...) \right) \tag{11}$$

$$\frac{\partial g_x^*(V_m)}{\partial t} = \alpha_x^+ (V_m^*)(1 - g_x^*) + \alpha_x^- (V_m) g_x^* \ , \tag{12}$$

that governs the cellular electrophysiology. In eq. (12), g_x are ion channel gates and α_x^+ and α_x^- are respective activation and inactivation constants. Analogously to the averaging processes of the mechanical stress, in [6] it is proposed to approximate $\dot{V}_m$ by Reuss or Voigt bounds.

In order to stay time-consistent, the chosen model of excitation-contraction coupling [7] is implemented at the level of the ordinary differential equations as well.

4 SUMMARY

The proposed modeling approach is capable of simulating separate cellular action potentials that are homogenized in order to give a global action potential that is propagated through the tissue. In the subsequent nonlinear mechanical computation the active stress contribution is computed based on the activation variable determined in the electrophysiological computation. In the next iteration the mechanical strains serve as an input to the electrophysiological problem in order to allow for a mechano-electrical feedback. The whole algorithm is depicted in fig. 4, not showing the excitation-contraction coupling that is part of the electrophysiology.

From the bulge test drawn in fig. 2 we are able to measure most of the required mechanical material parameters. Concerning the electrophysiological part of the model we rely on published literature data for the parameterization although it is already planned to measure individual currents in other experimental setups to better model specific human-induced pluripotent stem cell-derived CMs.

By using this homogenization framework we expect to be able to more accurately capture the shape of the experimentally determined deflection curve as shown in fig. 5. The asymmetry, the size,

the durance and the integral below this curve characterize the contraction behavior in many aspects. Incorporating homogenized action potential propagation and electrophysiological and mechanical inhomogeneities will lead to a more accurately simulated curve shape.

Further, fig. 5 shows that the shape of the deflection curve strongly depends on the model parameterization, e.g. here on the beating frequency that affects the deflection through the so-called *force-frequency relationship*. Thus it is also essential to adjust the cellular models.

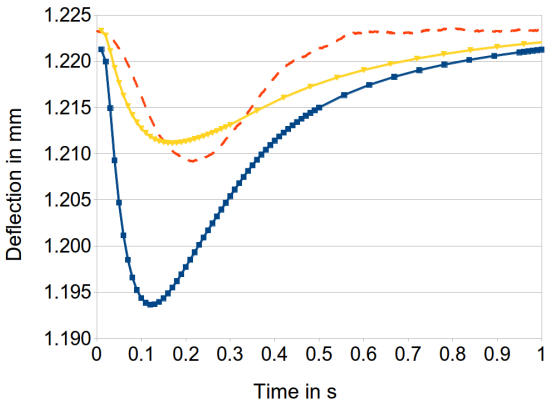

Figure 5: Comparison of deflection curves in experiment (*dashed*), simulation paced at 0.75Hz (*triangular markers*) and simulation paced at 1Hz (*rectangular markers*)

In the near future the model is intended to be used for drug prediction, for analyzing the influence of fibroblast concentration on the beating force as initiated in [8] and for the investigation of mechano-electrical and electro-mechanical feedback which currently is implemented rather phenomenologically. Another very important analysis will cover the computational costs because it is expected that the numerous and elaborate ordinary differential equation systems consume much computation time. Depending on the results this might limit the applicability of the model to small tissue samples or needs a higher degree of parallelization than currently used.

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