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Simulating Beating Cardiomyocytes with Electromechanical Coupling

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Human-induced pluripotent stem-cell derived cardiomyocytes (hiPSc-CM, Cor.4U, Axiogenesis AG, Germany) were tested mechanically in the CellDrum, a drug testing device with a clamped circular 4μm thin silicone membrane with $\emptyset = 16000\mu$m, Fig. 1. On top of the membrane hiPSc-CM are cultivated in a collagen monolayer that has also a thickness of about 4μm. Medication applied to the culture medium changes the autonomous beating frequency and contraction force both measured by the deflection of the membrane [1].

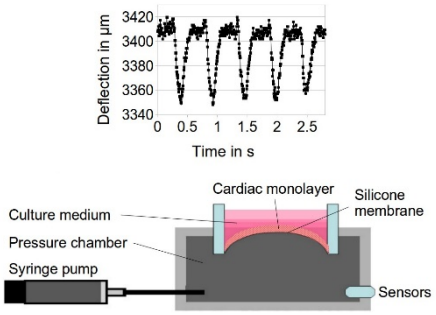

Figure 1: CellDrum™ setup and deflection over time due to autonomous contraction [1]

Experimental results depend on diffuse influences like the experimental setup, the cell type, the species, the cell production batch, the maturity of the cells and their health condition. The active stress approach characterizes the total stress as

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{\mathrm{p}} + \boldsymbol{\sigma}_{a} = 2J^{-1}\mathbf{B}\frac{\partial \Psi}{\partial \mathbf{B}} - p\mathbf{I} + T\left(\mathbf{B}, z\right)\mathbf{I}\,, \tag{1}$$

where $\boldsymbol{\sigma}_{\mathrm{p}}$ and $\boldsymbol{\sigma}_{a}$ are the passive and active stress contributions, respectively, Ψ is the strain energy density, J the Jacobian, $\mathbf{B}$ the left Cauchy-Green tensor, T the scalar factor of the spherical active stress tensor, and z an activation parameter that drives the contractibility of the cardiac tissue [1].

The tensile membrane stress results from the so-called excitation-contraction coupling as formulated in [2],

$$C_{a_b} = f_3\left(C_{a_i}, T, C_{a_b}\right), \tag{2}$$

$$z = f_2\left(z, \mathbf{B}, C_{a_b}\right), \tag{3}$$

$$T = f_1\left(\mathbf{B}, z\right), \tag{4}$$

where the ODE (2) determines the ion concentration C_{a_b} of calcium which binds to troponin C based on the freely inner calcium ion concentration C_{a_i}. C_{a_b} determines the cellular activation measured by the activation parameter z in ODE (3). Eq. (4) finally determines the active stress.

The cellular excitation model determines the variation of C_{a_i} in time. Here we employ the sinoatrial model in [3] and the ventricular model in [4] with the Hodgkin-Huxley structure given as

$$\frac{\partial V_m}{\partial t} = \frac{1}{C_m}\left(I_{stim} - \sum_{i=1}^{N} I_i \left(g_{x_1}, g_{x_1}, \ldots \right) \right), \tag{5}$$

$$\frac{\partial g_x}{\partial t} = \alpha_x^+ \left(V_m \right)\left(1 - g_x \right) + \alpha_x^- \left(V_m \right) g_x, \quad \left(x = x_1, x_2, \ldots \right), \tag{6}$$

which describes the time course of the membrane or action potential V_m and the ionic open gates g_x.

Figure 2 shows simulation results for the application of the local anesthetic drug lidocaine with negative chronotropy and negative inotropy mainly by inhibition of fast sodium channels. For alternative tests and simulations for the application of lidocaine and other drugs see [5].

If the ventricular model is paced at 1Hz for which is parameterized, the simulation is close to the experimental result. The cells in the experiment, however show beating frequencies of 0.5Hz and below in the control group and for lidocaine application. Although the force-frequency relationship (FFR) actually occurs in cardiomyocytes, the model overreacts with respect to the pacing.

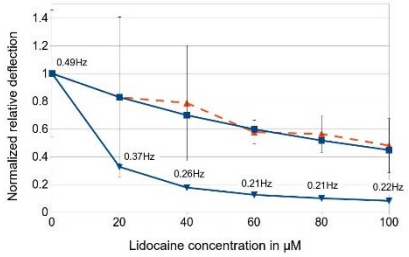

Figure 2: Inotropic effect: experiment: (dashed), simulation paced at 1Hz and paced at measured beating frequencies (continuous)

The model needs to be modified by means of cell communication by coupling of the parabolic electric "diffusion" with the mechanic equations in the open source FEM software *Code_Aster*.

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