BIOMECHANICS OF LEFT VENTRICLE AND IN SILICO DRUG TESTING

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Extended Abstract:

In silico clinical trials are a new paradigm for development and testing of a new drug and medical device. SILICOFCM project [1] is multiscale modeling of familial cardiomyopathy which consider a comprehensive list of patient specific features as genetic, biological, pharmacologic, clinical, imaging and cellular aspects. Biomechanics of the heart is key part of in silico clinical platform. We have built this platform using state of the art finite element modeling for macro simulation of fluid-structure interaction with micro modeling on the molecular level for drug interaction with the cardiac cells.

The blood is considered as an incompressible homogenous viscous fluid. The fundamental laws of physics which include balance of mass and balance of linear momentum are applicable here. These laws are expressed by continuity equation and the Navier-Stokes equations [2].

We here present the final form of these equations to emphasize some specifics related to blood flow. The incremental-iterative balance equation of a finite element for a time step 'n' and equilibrium iteration 'i' has a form

$$\begin{bmatrix} \frac{1}{\Delta t}\mathbf{M} + {}^{n+1}\tilde{\mathbf{K}}_{vv}^{(i-1)} & \mathbf{K}_{vp} \\ \mathbf{K}_{vp}^{T} & \mathbf{0} \end{bmatrix} \begin{Bmatrix} \Delta\mathbf{V}^{(i)} \\ \Delta\mathbf{P}^{(i)} \end{Bmatrix}_{blood} = \begin{Bmatrix} {}^{n+1}\mathbf{F}_{ext}^{(i-1)} \\ 0 \end{Bmatrix} - \begin{bmatrix} \frac{1}{\Delta t}\mathbf{M} + {}^{n+1}\mathbf{K}^{(i-1)} & \mathbf{K}_{vp} \\ \mathbf{K}_{vp}^{T} & 0 \end{bmatrix} \begin{Bmatrix} {}^{n+1}\mathbf{V}^{(i-1)} \\ {}^{n+1}\mathbf{P}^{(i-1)} \end{Bmatrix} + \begin{Bmatrix} \frac{1}{\Delta t}\mathbf{M}\,{}^{n}\mathbf{V} \\ 0 \end{Bmatrix} \tag{1}$$

where ${}^{n+1}\mathbf{V}^{(i-1)}$ ${}^{n+1}\mathbf{P}^{(i-1)}$ are the nodal vectors of blood velocity and pressure, with the increments in time step $\Delta\mathbf{V}^{(i)}$ and $\Delta\mathbf{P}^{(i)}$ (the index 'blood' is used to emphasize that we are considering blood as the fluid); Δt is the time step size and the left upper indices 'n' and 'n+1' denote start and end of time step. Note that the vector ${}^{n+1}\mathbf{F}_{ext}^{(i-1)}$ of external forces includes the volumetric and surface forces. In the assembling of these equations, the system of equations of the form (1) is obtained, with the volumetric external forces and the surface forces acting only on the fluid domain boundary (the surface forces among the internal element boundaries cancel).

Solid domain for left ventricle was defined with nonlinear finite element equation taken into account Holzaphel and Hunter model [2]. The balance of linear momentum is derived from the fundamental differential equations of balance of forces acting at an elementary material volume. In dynamic analysis we include the inertial forces. Then, by applying the principle of virtual work

$$\mathbf{M}\ddot{\mathbf{U}} + \mathbf{B}^{w}\dot{\mathbf{U}} + \mathbf{K}\mathbf{U} = \mathbf{F}^{ext} \tag{2}$$

Here the element matrices are: $\mathbf{M}$ is mass matrix; $\mathbf{B}^{w}$ is the damping matrix, in case when the material has a viscous resistance; $\mathbf{K}$ is the stiffness matrix; and $\mathbf{F}^{ext}$ is the external nodal force vector which includes body and surface forces acting on the element.

About half of cardiomyopathies are caused by genetic malformations with mutations in sarcomeric proteins [3]. In addition to significant changes at the level of molecular mechanisms within cardiomyocytes, significant changes are also observed at the macroscopic level in terms of changes in blood pressure, left ventricular mass index, wall thickness, left ventricular diameter, left ventricular volume, fractional shortening and ejection fraction. Change in these parameters induce many other physiologically important features and finally on health status of suffering patient. Many drugs are created to counteract these changes by reducing wall thickness, increasing left ventricular volume, or increasing ejection fraction. We have presented the velocity field distribution for different part of heat cycle for parabolic Ca^{2+} concentration function for drug Entresto® action.

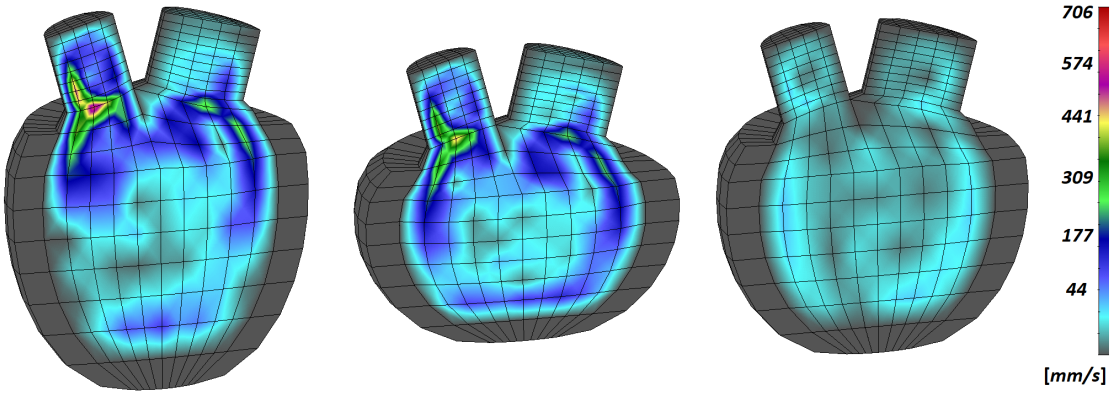

Fig. 1. Velocity field at 0.2s, 0.5s and 0.6s for parabolic Ca^{2+} concentration function

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