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Armin Müller*, Ekaterina Kovacheva, Steffen Schuler, Olaf Dössel and Lukas Baron

Effects of local activation times on the tension development of human cardiomyocytes in a computational model

Abstract: The human heart is an organ of high complexity and hence, very challenging to simulate. To calculate the force developed by the human heart and therefore the tension of the muscle fibers, accurate models are necessary. The force generated by the cardiac muscle has physiologically imposed limits and depends on various characteristics such as the length, strain and the contraction velocity of the cardiomyocytes. Another characteristic is the activation time of each cardiomyocyte, which is a wave and not a static value for all cardiomyocytes. To simulate a physiologically correct excitation, the functionality of the cardiac simulation framework CardioMechanics was extended to incorporate inhomogeneous activation times. The functionality was then used to evaluate the effects of local activation times with two different tension models. The active stress generated by the cardiomyocytes was calculated by (i) an explicit function and (ii) an ode-based model. The results of the simulations showed that the maximum pressure in the left ventricle dropped by 2.3% for the DoubleHill model and by 5.3% for the Lumens model. In the right ventricle the simulations showed similar results. The maximum pressure in both the left and the right atrium increased using both models. Given that the simulation of the inhomogeneously activated cardiomyocytes increases the simulation time when used with the more precise Lumens model, the small drop in maximum pressure seems to be negligible in favor of a simpler simulation model.

Keywords: Local activation time, LAT, tension development, active stress, human cardiomyocytes, computational model, whole heart simulation.

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***Corresponding author: Armin Müller:** Institute of Biomedical Engineering, Karlsruhe Institute of Technology (KIT), Kaiserstr. 12, 76131 Karlsruhe, Germany, e-mail: publications@ibt.kit.edu
Ekaterina Kovacheva, Steffen Schuler, Olaf Dössel, Lukas Baron: Institute of Biomedical Engineering, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany

1 Introduction

Studying the human heart and its potential diseases as well as possible therapeutic approaches are challenging tasks which often require high-precision computational models. From these simulations, valuable information can be gathered for developing new treatment options. Simulations of high-precision computational models are very complex and therefore require a lot of computing power. Adding a new feature to such a computational model, which improves the simulation's precision, might result in higher complexity. For this study a new feature was added to involve the local activation times of human cardiomyocytes. Without this, all cardiomyocytes contract homogeneously resulting in a larger tension development. By applying local activation times to the model, we create an inhomogeneous and thus physiologically more correct excitation that increases the precision of the simulation results at the expense of computational complexity.

2 Methods

2.1 Tension models

The passive material properties of the atria were provided by the model described by Mooney and Rivlin [1]. For the passive material properties of the ventricles the model proposed by Guccione was applied [2].

To simulate the active myocardial tension during the contraction of the heart, two different tension models were combined with local activation times (LAT). The first model is the double Hill model (DHM) which uses a function to define the active tension as proposed by Stergiopulos et al. [3]:

$$\mathbf{E(t)} = \frac{\boldsymbol{P(t)}}{\boldsymbol{V(t)-V_d}} \tag{1}$$

$$\boldsymbol{e(t)} = \frac{\boldsymbol{E(t)-E_{min}}}{\boldsymbol{E_{max}-E_{min}}} = \frac{\mathbf{1}}{\boldsymbol{k}} \cdot \left(\frac{\boldsymbol{g_c}}{\mathbf{1+}\boldsymbol{g_c}}\right) \cdot \left(\frac{\mathbf{1}}{\mathbf{1+}\boldsymbol{g_r}}\right), \tag{2}$$

with $g_c = (t'/\tau_c)^{m_c}$, $g_r = (t'/\tau_r)^{m_r}$, $t' = mod(t - t_0, T)$ and $k = \max\{k, e(t)\}$.

The time course of the active stress is assumed to be equal to the chamber elasticity $\boldsymbol{E(t)}$, $\boldsymbol{V(t)}$ is the ventricular volume and $\boldsymbol{V_d}$ is the unloaded (unpressurized) ventricular volume. $\boldsymbol{E(t)}$ can also be approximated by Eq. 2 as proposed by Stergiopulos et al. [3]. The parameters $\boldsymbol{m_c}$, $\boldsymbol{m_r}$, $\boldsymbol{\tau_c}$ and $\boldsymbol{\tau_r}$ represent contraction rate, relaxation rate, contraction time offset and relaxation time offset respectively in accordance to measurements from Mynard and Senzaki [4, 5]. The time $\boldsymbol{T}$ equals the length of the heartbeat. The atria's active tension was simulated with the DHM.

The second model is the Lumens model (LM) which uses the myofiber mechanics proposed by Lumens et al. [6]. There the active tension is calculated using two differential equations:

$$\frac{dL_{sc}}{dt} = \left(\frac{L_s - L_{sc}}{L_{se,iso}} - \mathbf{1}\right) \cdot \boldsymbol{v_{max}}\,, \tag{3}$$

$$\frac{dC}{dt} = \frac{1}{\tau_R} \cdot \boldsymbol{C_L(L_{sc})} \cdot \boldsymbol{F_{rise}(t)} + \frac{1}{\tau_D} \cdot \frac{C_{rest} - C}{1 + e^{(T(L_{sc}) - t)/\tau_D}}\,, \tag{4}$$

$$\boldsymbol{\sigma_{f,act}} = \boldsymbol{\sigma_{act}} \cdot \boldsymbol{C} \cdot (\boldsymbol{L_{sc}} - \boldsymbol{L_{sc0}}) \cdot \frac{L_s - L_{sc}}{L_{se,iso}}\,. \tag{5}$$

$\boldsymbol{L_{sc}}$ is the length of the contractile cardiomyocyte part, $\mathbf{L_s}$ is the sarcomere length, $\boldsymbol{L_{se,iso}}$ is the length of the isometric stressed elastic cardiomyocyte part, $\boldsymbol{v_{max}}$ is the sarcomere shortening velocity with zero load, $\boldsymbol{C}$ describes the time course of mechanical activation, parameters $\boldsymbol{\tau_R}$ and $\boldsymbol{\tau_D}$ are scaling the rise and decay time, $\boldsymbol{t}$ is the time and $\boldsymbol{C_{rest}}$ is the diastolic resting level of the activation. Functions $\boldsymbol{C_L}$, $\boldsymbol{F_{rise}}$ and $\boldsymbol{T}$ describe the increase of activation with sarcomere length, the rise of mechanical activation, and the decrease of activation duration with the decrease of sarcomere length respectively and were defined according to [3]. $\boldsymbol{L_{sc0}}$ is the length of the contractile cardiomyocyte part without load and $\boldsymbol{\sigma_{act}}$ is a scaling factor.

In contrast to DHM, the LM uses an ODE-based formulation and is able to dynamically react on pre-stretch and a changing fiber length. It respects the physiologically imposed maximum sarcomere shortening length, which is at 84% of the sarcomere resting length [7, 8]. This length dependency results in a spatially heterogeneous tension distribution, whereas the DHM a uniform tension distribution provides.

2.2 Computational model

The heart geometry was created from MRI data of a healthy 28 year old volunteer and was kindly provided by the Universitätsklinik Heidelberg. The resulting mesh consists of 39 k nodes and 61 k tetrahedral ten-node-cells and contains the left and right ventricles (LV, RV) as well as the left and right atria (LA, RA), the left and right atrioventricular rings and the left and right atrioventricular planes.

2.3 Simulation settings

To evaluate the effects of the LAT on the active tension, four simulation settings were created. The first two settings used the DHM. One was activated homogeneously, the other heterogeneously. The two settings using the LM were created analogously.

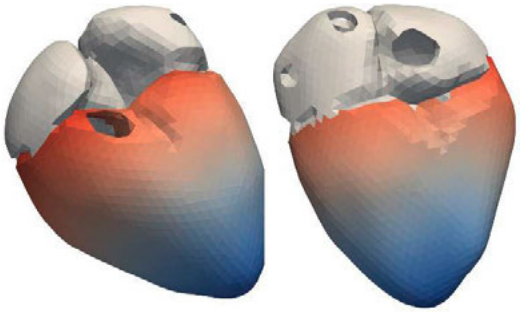

Figure 1: The used LATs from 0 ms (blue, at the hearts apex) to 120 ms (red, at the hearts base).

In Figure 1 the activation time for each cell is visualized. These were obtained with the fast marching method. The excitation starts at the apex and moves upwards to the base over a time of 120 ms, resembling the QRS-Complex length.

To create an additional average pre-stretch of about 15% of the sarcomere resting length, both ventricles were inflated to their end-diastolic pressures before the contraction began.

3 Results

Each setting was simulated for the duration of five heartbeats à 800 ms. The atrial contraction reached a maximum tension of 35 kPa.

The simulations with the DHM resulted in a maximum tension of 80 kPa in the left ventricle, with and without using LAT. The values were reached every 800 ms due to the periodicity of the DHM.

Since the right ventricle has a physiologically imposed lower tension development than the left ventricle and therefore a lower maximum tension, different scalings for the ventricles were used. Thus the right ventricular tension reached only 60 kPa. This resulted in the tension distribution seen in Figure 2.

The simulations with the Lumens model without LATs reached a maximum active tension of 104.3 kPa in the left ventricle. Using LATs, the maximum tension of the left ventricle dropped by 0.5% to 103.8 kPa in the first heartbeat.

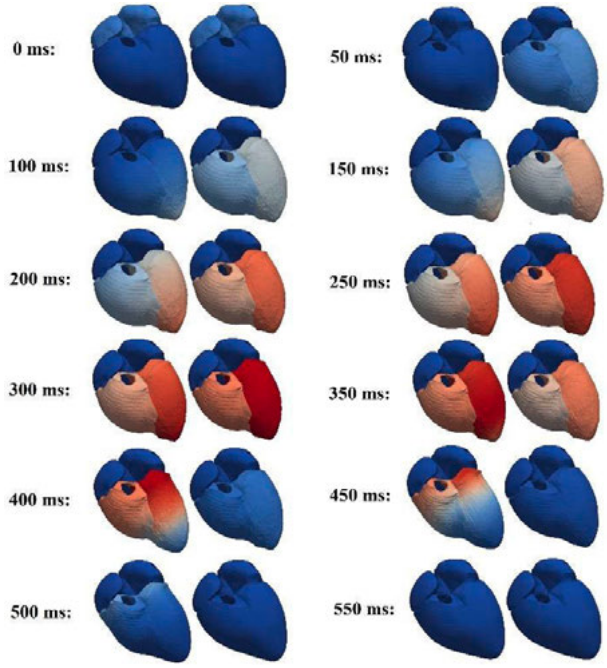

Figure 2: Changes of the active tension for the DHM. In the first and third column with, in the second and fourth column without LATs. The active tension ranged between 0 Pa (dark blue) and 80 kPa (red).

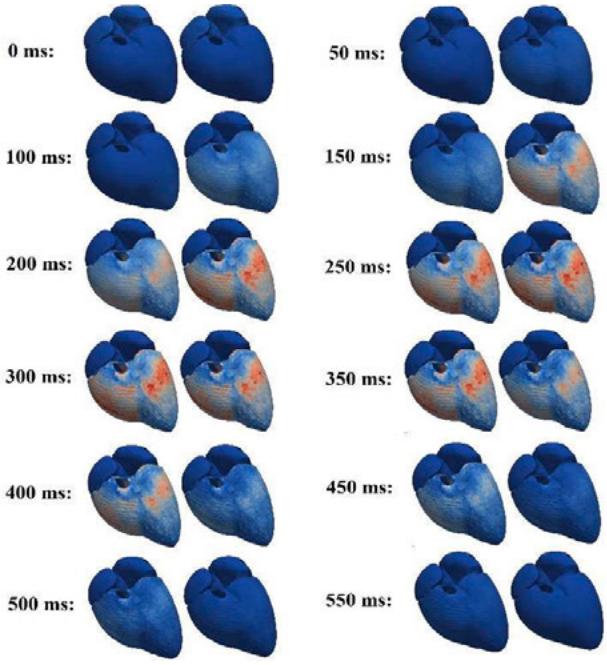

Figure 3: Changes of the active tension for the LM In the first and third column with, in the second and fourth column without LATs. The active tension ranged between 0 Pa (dark blue) and 100 kPa (red).

In Figure 3 we can also clearly see the spatially heterogeneous distributed tension of the LM.

The blood volumes and the pressures generated from the different settings can be seen in Table 1.

	DHM without local activation time	DHM with local activation time	LM without local activation time	LM with local activation time
LV Stroke Volume	76.98	74.44	59.88	55.75
LV Ejection Fraction	21.01%	21.21%	16.80%	16.02%
RV Stroke Volume	65.81	59.91	50.01	45.21
RV Ejection Fraction	33.96%	32.11%	18.25%	16.77%
Total Stroke Volume	142.79	134.36	109.89	100.96
Total Ejection Fraction	25.49%	24.99%	17.43%	16.65%
Maximum LV Pressure	133.97	130.86	100.69	95.27
Minimum LV Pressure	2.69	2.46	2.92	2.87
Maximum RV Pressure	23.96	23.25	19.80	19.25
Minimum RV Pressure	-0.19	-0.18	0.71	0.73

Table 1: Pressure and volume data. The values were extracted from each simulation's last heartbeat. Pressures are given in mmHg and volumes are given in ml.

4 Discussion and Outlook

When using cell activation delayed by a local activation time, the cells reached their tension maximum one after another and not simultaneously, which led to a drop in the maximum pressure in the ventricles for both tension models. The pressure drop in the left ventricle was 2.3% for the DHM and 5.4% for the LM compared to the homogeneous case. The right ventricle maximum pressure dropped by 3% and 2.8% respectively. Also the volumes decreased in both ventricles using LATs.

Due to the lower volumes the overall ejection fraction was also decreased and dropped to 16.7% when the more precise LM was used. This is well below the physiological values for the ejection fraction, however ejection volumes are normal or even slightly above the normal range. One problem might be the limited resolution of the mesh, which allows only a coarse representation of the real geometry. For instance the papillary muscles and the trabeculae weren't modelled. Their volume contributes to the blood volume instead, which reduces the computed ejection fractions.

We also inflated our mesh for the initial tension calculation to a better a pre-stretch. Therefore the volume of the whole heart is expanded which additionally decreases the ejection fractions.

Since the drop in maximum pressure is not particularly high, LATs might be neglected in favor of a simpler model.

The DHM is not capable of respecting the limits of physiological myocardial fibers or incorporating effects like an increased tension due to pre-stretch. A tension model like the LM might be more suitable to reproduce not only a correct global ventricular elasticity, but also respect the tension-length-dependency.

For more sophisticated modeling one can consider using other models such as the model proposed by Sander Land in 2017 [9]. The measurements of the cardiomyocytes used to create this model were made at body temperature rather than at the often used room temperature. Additionally the created model is designed for a four chamber model. A simulation of an inhomogeneous activation while using the Land model could show the effects of local activation times more precisely. Then it might be possible to obtain a different result regarding the importance of inhomogeneous activation times.

Author Statement

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