Modelling of cardiac cross-bridge cycling during ischemia

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Introduction

Metabolic changes caused by sudden oxygen delivery cutt-off are followed by accumulation of specific metabolites affecting force of heart muscle contraction. To closely evaluate those effects, we modified and extended the cardiac myofilament model proposed by Rice [1]. The presented results of sensitivity analysis identified parameters with significant impact on contractile force during ischemia.

Theory

The key players in heart muscle contraction cycle are the two proteins, the thin (actin) and thick (myosin) filaments, together with Ca^{2+} and ATP.

The launch of the cycle depends on concentration of Ca^{2+} in intracellular space. Action potential triggers massive elevation of Ca^{2+} in cell, which causes change of conformation of actin, enabling its contact with myosin. The influx of Ca^{2+} thus results in connection of actin and myosin and forming the cross-bridge.

During ischemia, the accumulation of H^+ and phosphates occurs. The H^+ is binding on the neck of myosin head, altering its conformation, resulting in weakening of the power-stroke. Phosphate, if present in hight concentration, is rebinding on myosin head, thus preventing the formation of strong bound between actin and myosin.

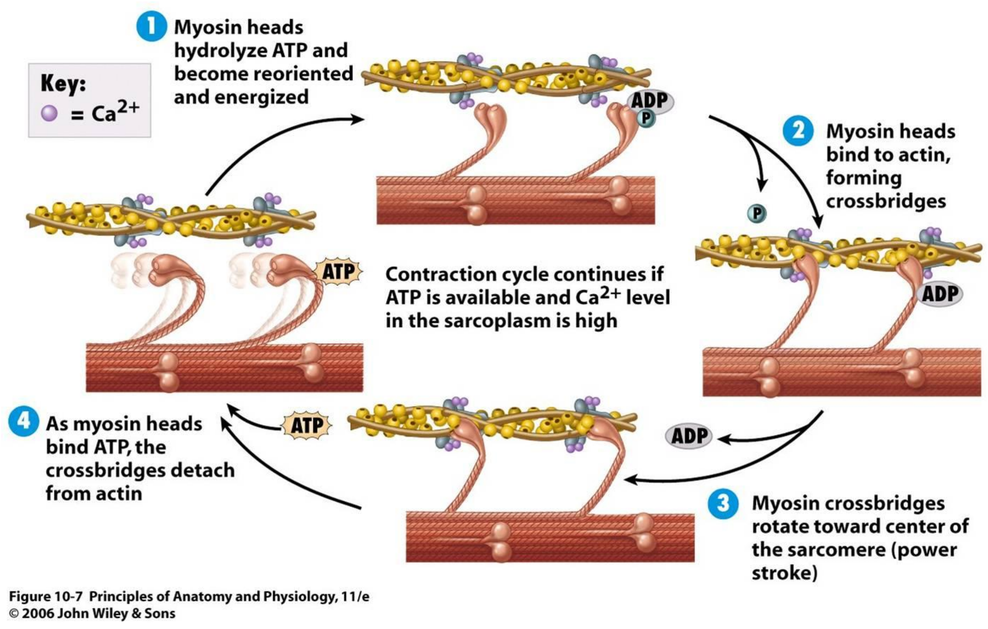

Figure 1: Physiology of the cross-bridge cycling. (Figure reproduced, with generous consent of copyright holder, for educational and noncommercial use only).

Implementation

Mechanistic behavior of contraction cycle can be well captured into mathematical model. The scheme below illustrates four underlying states of cross-bridge cycle model.

States N_{XB} and P_{XB} represent nonpermissive and permissive conformations of the regulatory proteins, respectively. The next transition is to the XB_{PreR} state, short for prerotated, that is strongly bound with the myosin head extended. The transition to the post-rotated force-generating state in dotted ellipse, represents the isomerization inducing strain in the extensible myosin head's neck region. The AM1 and AM2 are two strongly-bound rapid-equilibrium states, where the virtual power-stroke occurs. After the powerstroke, the ATP binds on myosin head, leading to disconection of cross-bridge and shift of cycle to P_{XB} state.

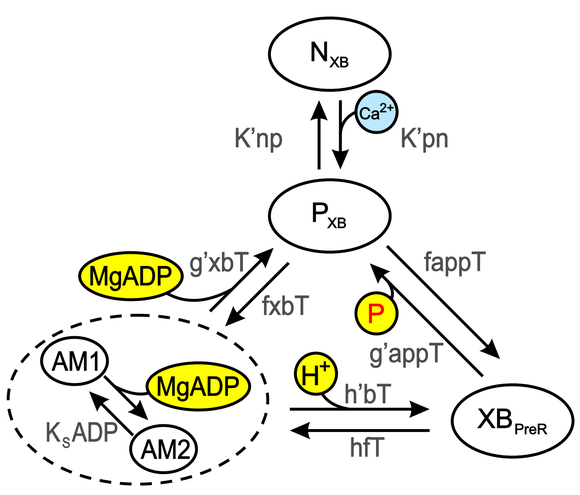

Figure 2: Model construction. Scheme redrawn and modified after Tran [2].

Methods

Basic model [2] in CellML was exported and further revised in Python programming language. Our model is using the mean-field approximations implemented as set of ODEs. Sensitivity analysis was performed using VODE integrator with BDF method from the Python SciPy package. Resulting data were visualised with the ggplot2 plotting system supplied in R programming language distribution.

Our workflow was greatly facilitated by endorsing IPython, a rich architecture for interactive scientific computing.

Results

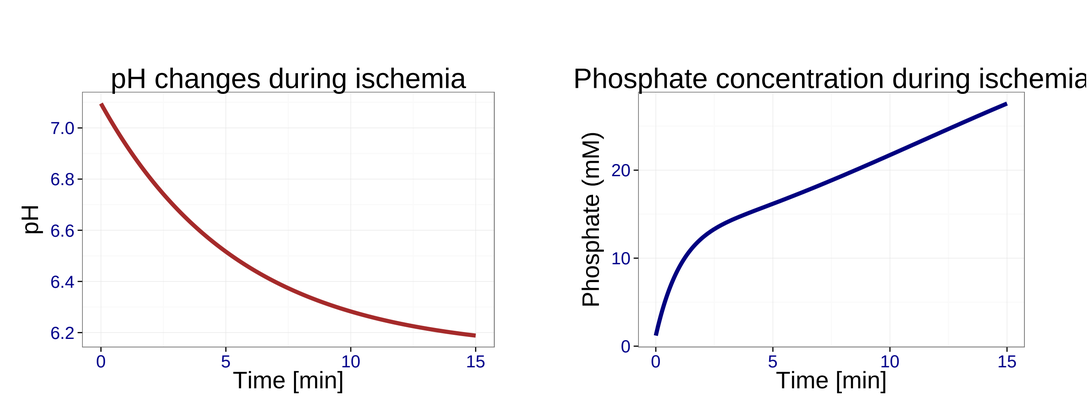

Figure 3: Simulation of ischemia. In sudden oxygen delivery cut-off, the metabolical changes occurs, which have direct impact on cycle of heart muscle contraction. The concentrations of ATP and creatine-phosphate are quickly decreasing and cumulation of ADP, phospates and protons occurs. The cell metabolism decreases and switches to anaerobic regime.

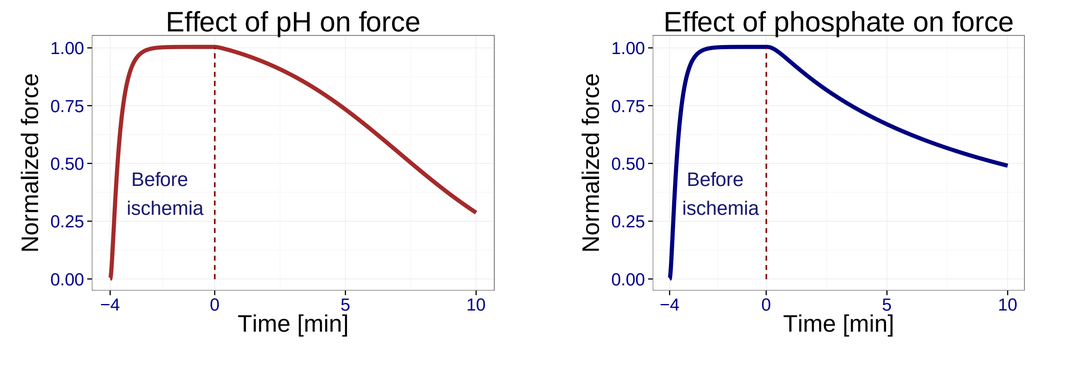

Figure 4: Effect of metabolites selected by sensitivity analysis on contraction force of cross-bridge. Build-up of protons and inorganic phosphate is characteristic for ischemia. These metabolites are directly interferring with phases of the cross-bridge cycle, resulting in drop in contractile force of heart muscle.

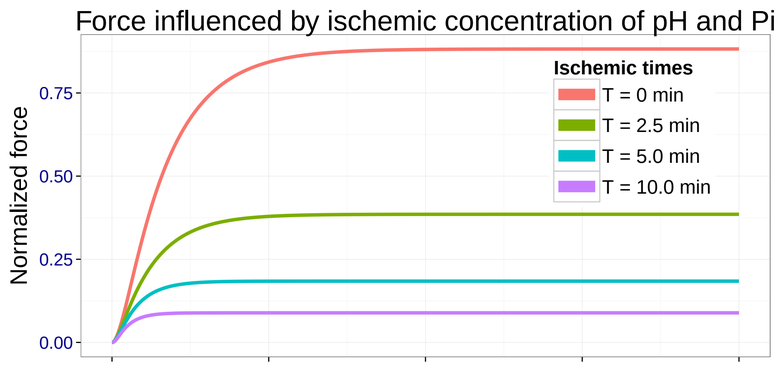

Figure 5: Influence on contractile force by ischemic concentrations of H^+ and P_i in time. Concentration values are the same as in Fig.3. The concentration of H^+ and P_i during every choosen timecourse remains constant during simulation.

Conclusions

- Sensitivity analysis identified the pH and phosphate as strongest factors participating on decrease of contractile force
- The 90% drop in contractile force observed after 10 minutes of simulated ischemia correlates with in vivo experimental data obtained by Telkirdsen [3]

Forthcoming Research

The follow-up research will be focused on extending the model with new parameters relating with mitochondrial dysfunction. Such pathologic conditions are related with hypoxia and subtler changes of metabolites in time. Aditionally, we are planning to adapt the Ca^{2+} regulation facilitated by ion channels and ryanodine receptors into our model.

References

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