SIMULATIONAL STUDY OF CARDIAC CELL CONTRACTILITY

Bedrich Sousedik

Department of Mathematics, Faculty of Civil Engineering,
Czech Technical University,
Thakurova 7
166 29 Prague, Czech Republic

SUMMARY

This model was developed for the study of excitation-contraction coupling for single cardiac cell. The basic assumptions are following: depolarization of cellular sarkolemma (membrane) rises inward calcium current I_s, which rises the level of sarcoplasmatic calcium but also induces release of calcium from cisternal sarcoplasmic reticulum. These two basic sources increase the level of sarcoplasmic calcium so that calcium ions combine with regulatory protein troponin C and this enables combination of actin and myosin (i.e. crossbridge formation) and initiates contraction according to Huxley's sliding filament theory. Properties of muscle are modelled by Hill (Maxwell) model. The simulation was done for both types of contraction: isometric and isotonic. Formation (disjunction) of crossbridge is supposed to be an active process utilizing energy.

1. DYNAMICS OF INTRACELLULAR CALCIUM

Theory of compartments commonly used in biocybernetics was used for the modelling of intracelullar calcium dynamics. Calcium is supposed to be in homogeneous concentraction in all compartments and so modellling of calcium dynamics by the first order ordinary differential equations (ODE) is possible. Constants k in these equations are called rate constants and are reciprocal values of respective time constants. For the development of dynamic equations we used similar assumptions used by Wong (1981), Michailova (1992):

1. We did not include potassium and sodium currents in the model due to the fact that they do not affect directly development of tension.
2. The inward current I_s is supposed to be carried mainly by calcium ions.
3. The reversal potential E_R does not change appreciably, i.e. is considered to remain constant during the whole cycle of contraction.
4. Na-Ca exchanger is not included in the model although the extrusion of Ca ions out of the cell is considered.

1.1. Mathematical model

Depolarization of cellular membrane causes raise of inward calcium current (primary calcium) across membrane into the cardiac cell. This increase rises the level of sarcoplasmic calcium and induces release of much greater amount of calcium from the cisternal sarcoplasmic reticulum (called secondary calcium). The calcium ions diffund to sarcomere – contractile part of cardiac muscle cell. Ions associate with regulatory protein troponin C (TnC). TnC and another regulatory protein tropomyosin change conformation. Reaction places of actine filament are disclosed and actin-myosin combination can occur. A crossbridge can be formed. After dissociation of calcium ions from TnC the calcium ions are recirculated into the longitudinal sarcoplasmic reticulum (LSR).

In the first part of this paper we begin with description of membrane depolarization, then we describe calcium flows between compartments and finally we describe association of calcium ions with TnC. The inward calcium current is described by equation

$$I_S = g_s \, d(t) \, f(t) \, (E - E_R)$$

g_s denotes conductance of the sarcolemma to calcium ions varying with external calcium concentration Ca_o, E_R is used for reversal membrane potential. Functions $d(t)$, $f(t)$ denote the time courses of activation and inactivation (respectively) of calcium channels.
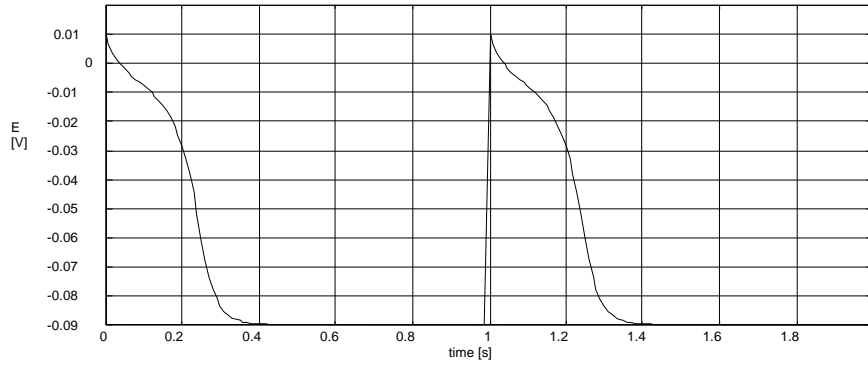
Fig.1. An artifitial action potential

The dynamic equations describing accumulation of calcium ions in compartments according to Wong (1981) are following:

$$dCa_{sp}/dt = k_1(Ca_o-Ca_{sp}) + k_2I_S + k_7d_\infty Ca_m$$
$$+ k_5d_\infty Ca_{CSR}(Ca_{sp}-Ca_{sp0})$$
$$- (k_6+k_3+k_{10}f_\infty)(Ca_{sp}-Ca_{sp0})$$
$$dCa_{CSR}/dt = - k_5d_\infty Ca_{CSR}(Ca_{sp}-Ca_{sp0})$$
$$+ k_4f_\infty (Ca_{LSR}-Ca_{LSR0}) - k_8d_\infty Ca_{CSR}$$
$$- k_9(Ca_{CSR}-Cs_{CSR0})$$
$$dCa_{LSR}/dt = (k_3+k_{10}f_\infty)(Ca_{sp}-Ca_{sp0})$$
$$- k_4f_\infty (Ca_{LSR}-Ca_{LSR0})$$
$$dCa_m/dt = k_6(Ca_{sp}-Ca_{sp0}) - k_7d_\infty Ca_m$$

The association of calcium ions with troponin C was described in Michailova et al. (1992) by equation

$$dA/dt = k_{on}Ca_{sp}(trop-A) - k_{off}A$$

This equation in fact describes amount of disclosed actin sites that are able to react with myosin and to form crossbridges. Dynamics of intracelular ion flows was simulated under rhytmically applied action potential reconstructed by Michailova et al. (1992).

2. MODEL OF CONTRACTILITY

Formation of crossbridge can be described by equations

$$A + M \xrightarrow{f} AM$$
$$AM + XP \xrightarrow{g} A + MXP$$
$$MXP \rightarrow M + X + PO_4$$
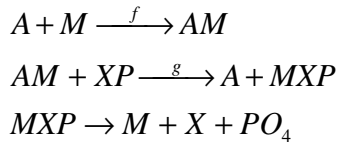
A denotes actin, M myosin, AM stands for a formed crossbridge, XP denotes high-energy phosphate molecule (ATP) and f, g denote rates of formation, dissociation (respectively) of a crossbridge.

Mechanism of crossbridge formation, which was originally proposed by Huxley (1957), is discussed in Sousedík (2001).

Functions f, g are given by relations

$u < 0$	$f(u,t) = 0$	$g(u) = g_2$
$0 \le u \le 1$	$f(u,t) = A^*(t)f_1u$	$g(u) = g_1u$
$1 < u$	$f(u,t) = 0$	$g(u) = g_1u$

u is relative distance between A and M (u = x/h), $A^*(t) = A(t)/A_{max}$ is the activation function and f_1, g_1, g_2 are given constants.

Total amount of formed crossbridges is modelled by differential equation proposed by Huxley (1957) and further used by Wong (1971), Michailova et al.(1992).

$$\partial AM(u,t)/\partial t = (1 - AM(u,t)) f(u,t) - AM(u,t) g(u)$$

The analytical solution of this equation has following form:

$-\infty < u < 0$:
$$AM_{i,j} = AM_{0i,j}exp(-g_jDt)$$

$0 \le u \le 1$:
$$AM_{i,j} = \frac{f_{i,j}}{f_{i,j}+g_j} - \frac{f_{i,j}-(f_{i,j}-g_j)AM_{0i,j}}{(f_{i,j}+g_j)\exp[(f_{i,j}+g_j)\Delta t]}$$

$1 < u < \infty$:
$$AM_{i,j} = AM_{0i,j}exp(-g_jDt)$$

In these equations $AM_{0i,j}$ denotes initial value of AM at the beginning of each time step Δt.

Energetic requirements are modelled by relation
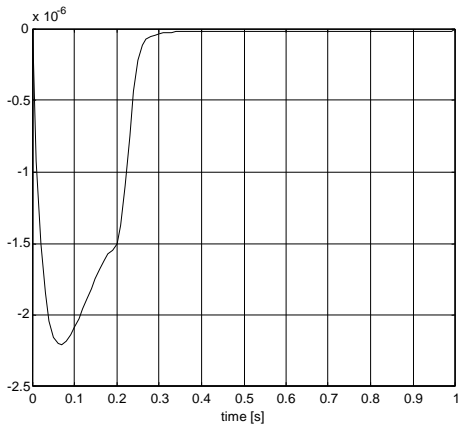
$$E_{ATP} = 1/T \int\int g(u) AM(u,t) du\, dt$$
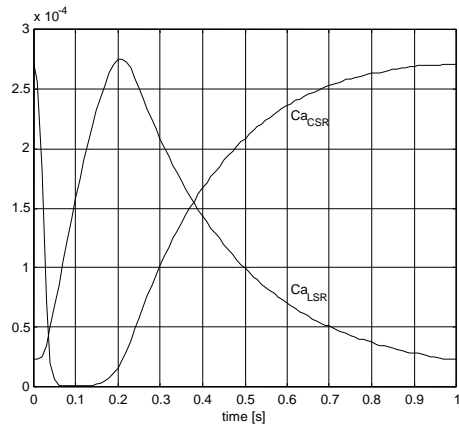
Fig. 2. Calcium current I_s across membrane.

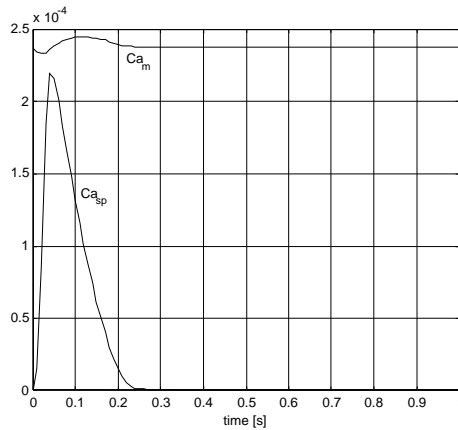Fig. 3. Amounts Ca_{CSR}, Ca_{LSR} [M].

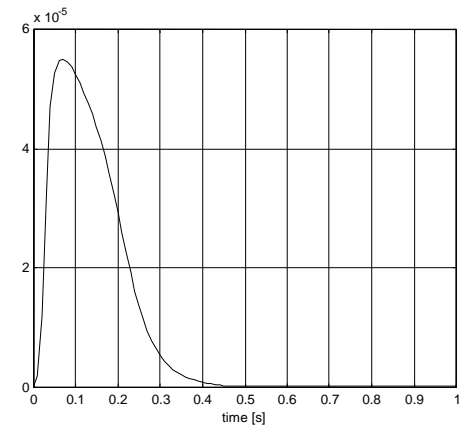Fig. 4. Amounts Ca_m, Ca_{sp} [M].

Fig. 5. Amount of disclosed actin sites A [M].

2.1. Modelling of muscle properties

Muscle properties are modelled using Hill (Maxwell) three-component model with tensions of its components given by relations

$$P_{PE} = P_0 \left(\exp \left(k_p L_{PE} \right) - 1 \right)$$
$$P_{SE} = P_L \left(\exp \left(k_s L_{SE} \right) - 1 \right)$$
$$P_{CE} = \int k_m \, AM \, u \, du$$

PE...parallel-elastic element, SE...series-elastic element, CE...contractile element.

Stiffness of CE element is given by instantaneous stiffness of all formed crossbridges

$$K_{CE} = \int k_m \, AM \, du$$

Total muscle tension

$$P = P_{PE} + P_{SE}$$

2.2. Isometric contraction

Each contraction begins with isometric part. During this type of contraction muscle develops tension but does not change its total length. Shortening of CE element equals lenghtening of SE element

$$\Delta L_{CE} = \Delta L_{SE}$$

Hence force balance must be satisfied

$$P_{CE} = P_{SE}$$

Expanding relations for tension in Taylor series with neglecting terms of second and higher orders (where $K = dP/d\Delta L$ denotes instantaneous stiffness) and substituting into the equation of force balance we finally receive a nonlinear equation for shortening (lenghtening) SE (CE) elements, respectively.
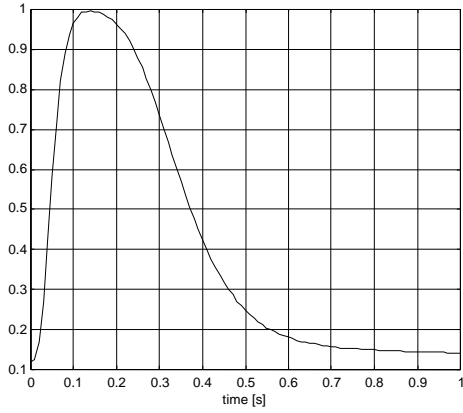
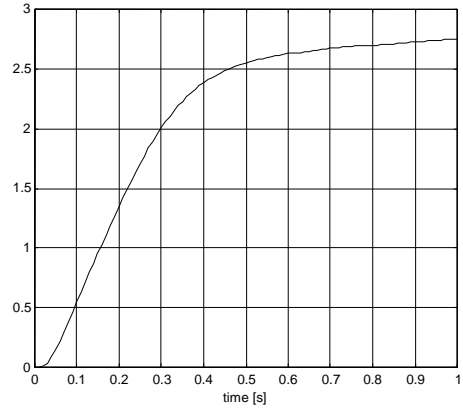Fig. 6. Tension P during isometric contraction.

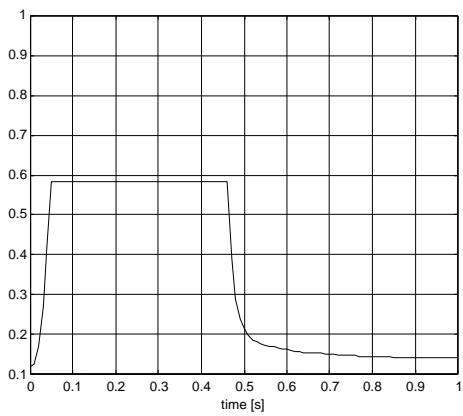Fig. 7. Energy requirements.

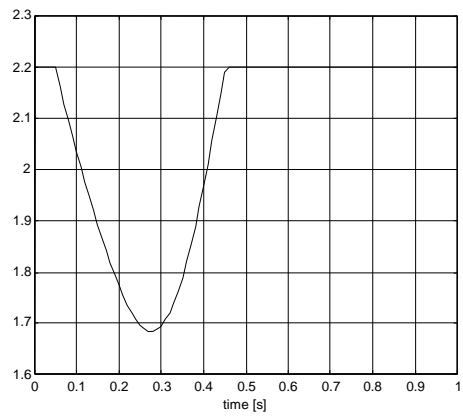

Fig. 8. Tension P during isotonic contraction.

Fig. 9. Muscle shortening during isotonic contraction.

This equation has form

$$P_{CE} - P_L(\exp(k_s L_{SE})-1) - \Delta L K_{CE}$$
$$- \Delta L k_s(P_L(\exp(k_s L_{SE})-1)+P_L) = 0$$

By numerical solution of this equation we compute ΔL and substituting back we finally compute the total muscle tension.

2.3. Isotonic contraction

Isotonic part of contraction follows isometric phase. At the moment when total muscle tension reaches

$$P_M = P_L + P_A$$

(P_L...preload, P_A...afterload),
isotonic phase of contraction begins.
Total muscle tension remains constant while the total muscle legth shortens. The equation of balance has form

$$P_{PE} + P_{SE} - P_M = 0$$

.

Elements PE, CE are shortening while element SE is further lenghtening, hence

$$- \Delta L_{PE} = - \Delta L_{CE} + \Delta L_{SE}$$

or

$$\Delta L_{CE} = \Delta L_{PE} + \Delta L_{SE}$$

Rearranging and combination of previous relations yields to

$$\Delta L_{PE} (K_{SE} + K_{PE}) = K_{SE} \Delta L_{CE}$$

After final rearrangement we obtain relation for muscle shortening

$$\Delta L_{PE} = \Delta L_{CE}/(1 + K_{PE}/K_{SE})$$

2.4. Choice of numerical constants

Computer code solving this procedure was developed in simulation environment Matlab. The system was solved with initial conditions in t=0: AM(u,0)=0, $P_{SE}(0)=0, P_{CE}(0)=0$. $AM_{0i,j}$ is the initial amount of $AM_{i,j}$ at a certain time step t_i and position u_j and is given by the final value of $AM_{i-1,j}$ of previous time step with correction ΔL_{CE}, because it is necessary to consider shortening of sarcomere (CE).

For the derivation of constants characterizing mechanical parameters of the muscle we used similar assumptions as Panerai (1980):

1. Muscle resting tension is approximately zero when muscle length is reduced by 25 % of its resting length L_{max}.
2. At peak isometric tension, sarcomere shortening amounts to 8 % of L_{max}.
3. Preload at L = L_{max} is 12 % of peak isometric tension.
4. Detailed analysis of experimental data in cardiac musle resulted in $k_s = k_p$.

First we simulated only isometric contraction during whole period of hearth muscle revolution. Then we simulated bisotonic contraction. The total muscle tensions and the total muscle shortening during isotonic contraction are on the figures on previous page

3. DISCUSSION

In the paper we showed excitation-contraction coupling for single cardiac cell. In the first part of model we simulated calcium ions flows, binding of calcium ions on the troponin C and disclosing of active sites of actin. Proposed model is a combination of Wong's model (1981) with the extension published by Michailova et. al (1992). The influence of mitochondria is considered in this model. Relative amount of dislosed actin sites is input into the second part of model. In this part we described formation of a crossbridge based on the work of Huxley (1957), computation of total amount of crossbridges and total muscle tension. We derived the constants characterizing mechanical Hill (Maxwell) model of contractile apparatus for single cardiac cell according to assumptions published in Panerai (1980). Finally we combined the model of calcium ions dynamics with mechanical model of muscle and simulated isometric and isotonic type of contraction. We confirmed basic qualitative facts observed in live tissues in vivo, but for detailed quantitative analysis it would be necessary to model longer muscle fibre in order to compare the results of our model with results obtained experimentally. Because of complicated structure of cardiac muscle (fibres are not oriented in one direction, cross each other etc.) we did not solve yet the global structure of hearth tissue.

4. BIBLIOGRAPHY

[1] G.W. Beeler, H. Reuter, "Reconstruction of action potential of ventricular myocardial fibres" *Journal of Physiology*, **268**, pp. 177-210, 1977

[2] A.F. Huxley, "Muscle structure and theories of contraction" *Prog. Biophys. Chem.,* **7**, pp. 255-318, 1957

[3] A. Michailova, V. Spassov, "Theoretical model and computer simulation of excitation-contraction coupling" *J. Moll. Cell. Cardio.,,* **74**, pp. 97-104, 1992

[4] R.B. Panerai, V. Spassov, "A model of muscle mechanics and energetics" *J. Biomechanics,* **13**, pp. 929-940, 1980

[5] Sousedik B., *Matematicky model kontraktilniho aparatu srdecni bunky*, (in czech), MSc. thesis, Faculty of Mechanical Engineering CTU, Prague, 2000.

[6] A.Y.K. Wong, "Mechanics of cardiac muscle, based on Huxley's model: mathematical simulation of isometric contraction" *J. Biomechanics,* **4**, pp. 529-540, 1971

[7] A.Y.K. Wong, "Mechanics of cardiac muscle, based on Huxley's model: simulation of active state and force-velocity relation" *J. Biomechanics,* **5**, pp. 107-117, 1972

[8] A.Y.K. Wong, "A model of excitation-contraction coupling of mammalian cardiac muscle" *J. Theoretical Biology,* **90**, pp. 37-61, 1981