

## MATHEMATICAL MODEL OF ELECTRICAL AND MECHANICAL ACTIVITY IN HEART MUSCLE

We have developed the mathematical model of electromechanical coupling in heart muscle [11]. The model describes the generation of the action potential (AP) created by ionic currents via sarcolemma, as well as  $\text{Ca}^{2+}$ ,  $\text{Na}^+$ ,  $\text{K}^+$  ion kinetics in cardiomyocytes. Along with electrochemical processes, the model describes the time variation in length and force, which are generated by sarcomeres and the muscle as a whole.

**The description of electric activity** is borrowed from the well-verified model Noble'98 [9], which is widely used by electrophysiologists.

The rate of change of the membrane potential  $E$  is defined by the sum of ionic currents  $i_k$  (see **A.1(a)**):

$$\frac{dE}{dt} = -\frac{I}{C_m} \cdot \sum_k i_k. \quad (1)$$

The value of the current  $i_k$  transferring ions  $X$  via the specific membrane channels is determined by the difference between the membrane potential  $E$  and the equilibrium electrochemical potential  $E_X$  for ions  $X$ :

$$i_k = g_k \cdot (E - E_X), \quad (2)$$

where  $g_k$  is conductance of channels for ions  $X$ . Note that in electrophysiology the current is commonly taken to be positive,  $i_k > 0$ , if it induces a flux of positive charges from a cell outward and vice versa. See **A.1(f)-A.1(k)**, **A.1(n)**, **A.1(o)**, **A.1(q)**, **A.1(r)**.

The reversal potential  $E_X$  such that the electromotive force is balanced by the ion concentration difference gradient is described by the classical Nernst equation:

$$E_X = \frac{R \cdot T}{z \cdot F} \ln \frac{[X]_o}{[X]_i}, \quad (3)$$

where  $R$  is the gas constant,  $T$  is the absolute temperature,  $F$  is the Faraday number,  $z$  is the ion valence,  $[X]_o$  and  $[X]_i$  are ion concentrations of a given kind outside and inside a cell. See **A.1(b)**.

The conductance of the ion channels  $g_k$ , as a rule, depends in a complicated way on the potential  $E$ , the concentrations  $[X]_o$  and  $[X]_i$ , and on the probability  $P_k$  for the channels to be in an open state, which can vary with time, i.e.

$$g_k = g_k(E; [X]_i; [X]_o; P_k).$$

For example, in our model the value of a fast inward current via the sodium channels  $i_{\text{Na}}$  is defined by the relation (see **A.1(o)**):

$$i_{\text{Na}} = P_{\text{Na}} \cdot \bar{g}_{\text{Na}} \cdot (E - E_{\text{Na}}), \quad P_{\text{Na}} = m^3 \cdot h, \quad (4)$$

similar to that used in Hodgkin-Huxley model [4].

Here  $\bar{g}_{\text{Na}}$  is the peak conductance and  $P_{\text{Na}}$  is the probability of opening of the channels. The channel opening is supposed to be possible only for a certain combination of the state of three 'activating' and one 'inactivating' control particles. The probability of this combination is  $P_{\text{Na}} = m^3 \cdot h$ , where  $m$  and  $h$  are the probabilities for the corresponding particles to be in the state favourable for the channel opening. The change in the probabilities  $m$  and  $h$  is described by the conventional kinetic equation of the form:

$$\begin{aligned}\frac{dm}{dt} &= \alpha_m - (\alpha_m + \beta_m) \cdot m, \\ \frac{dh}{dt} &= \alpha_h - (\alpha_h + \beta_h) \cdot h,\end{aligned}\tag{5}$$

where the parameters  $\alpha_m, \beta_m, \alpha_h, \beta_h$  depend on  $E, [X]_{\text{out}}$ , and  $[X]_{\text{in}}$ .

In particular, the model takes into account the currents via the mechanosensitive channels  $i_{\text{MSC}}$  [12] that are directly activated by mechanical perturbations, for example, the heart preparation stretch [8] (see **A.1(r)**):

$$i_{\text{MSC}} = g_{\text{MSC}} \cdot (E - E_{\text{MSC}}) / (1 + K_{\text{MSC}} \cdot e^{-\gamma_{\text{MSC}} \cdot \Delta L}),\tag{6}$$

where  $E_{\text{MSC}}$  is the reversal potential for  $i_{\text{MSC}}$ ,  $g_{\text{MSC}}$  is the peak conductivity for mechanosensitive membrane channels,  $\Delta L$  is the deviation in the current preparation length from some fixed length,  $K_{\text{MSC}}$  and  $\gamma_{\text{MSC}}$  are the parameters defining the ‘length dependence’ of the current.

Along with the ion transport over the concentration gradient via the membrane channels, there are also cell currents that are induced by molecular pumps translocating ions against concentration gradients. The active ion transport is possible due to either exchange with other ions (for example,  $\text{Na}^+ - \text{Ca}^{2+}$  exchange current) or the energy consumption of ATP (for example,  $\text{Na}^+$  and  $\text{K}^+$  currents via  $\text{Na}^+ - \text{K}^+$  ATPase). In order to describe the active ion transport in the model, we use quasistationary equations for interaction between ions and proteins, their conformation changes provide ion translocation via the membrane (see **A.1(l)**, **A.1(m)**):

$$i_{\text{NaCa}} = k_{\text{NaCa}} \cdot \frac{e^{\frac{2\gamma_{\text{NaCa}} EF}{2RT}} [\text{Na}^+]_i^3 [\text{Ca}^{2+}]_o - e^{-\frac{2(1-\gamma_{\text{NaCa}}) EF}{2RT}} [\text{Na}^+]_o^3 [\text{Ca}^{2+}]_i}{1 + [\text{Ca}^{2+}]_i / K_{\text{NaCa}}},\tag{7}$$

where  $k_{\text{NaCa}}$  is a parameter defining the exchange current amplitude and the parameters  $K_{\text{NaCa}}$  and  $\gamma_{\text{NaCa}}$  define the exchange mechanism sensitivity to the change in  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ion concentrations.

The  $[\text{Ca}^{2+}]_o$ , and  $[\text{Na}^+]_o$  concentrations are assumed to be constant. At the same time, the transmembrane ion fluxes result in a substantial change in  $[\text{Na}^+]_i$ ,  $[\text{K}^+]_o$ ,  $[\text{K}^+]_i$  and especially  $[\text{Ca}^{2+}]_i$  concentrations. The change in the  $[\text{Ca}^{2+}]_i$  concentration in a cell also essentially depends on intracellular processes, in particular, on interaction between  $\text{Ca}^{2+}$  ions and intracellular ligands  $L_i$  and on exchange with intracellular  $\text{Ca}^{2+}$  sources. The change in the above concentrations is described by the equations (see **A.1(c)**, **A.1(d)**, **A.1(e)**, **A.2(a)**):

$$\begin{aligned}\frac{d[\text{Ca}^{2+}]_i}{dt} &= \sum_{k_1} F_{k_1, \text{Ca}^{2+}} - \sum_i \frac{d[\text{Ca} - L_i]}{dt} + F_{\text{SR,rel}} - F_{\text{SR,pump}}, \\ \frac{d[\text{Na}^+]_i}{dt} &= \sum_{k_2} F_{k_2, \text{Na}^+}, \quad \frac{d[\text{K}^+]_i}{dt} = \sum_{k_3} F_{k_3, \text{K}^+}, \quad \frac{d[\text{K}^+]_o}{dt} = \sum_{k_4} F_{k_4, \text{K}^+} - D_{\text{K}^+}.\end{aligned}\tag{8}$$

Here  $F_{k,X} = \pm |i_k| / (zV \cdot F)$  is the transmembrane ion flux  $X$  with current  $i_k$ , where the sign of flux is defined by the direction of ion motion,  $V$  is the cytosol volume for intracellular concentrations and extracellular volume for extracellular concentrations;  $[\text{Ca} - L_i]$  is the concentration of  $\text{Ca}^{2+}$  complexes with intracellular ligands;  $F_{\text{rel}}$  and  $F_{\text{pump}}$  are  $\text{Ca}^{2+}$  fluxes between intracellular compartments (see below);  $D_{\text{K}^+}$  is  $\text{K}^+$  diffusion in an extracellular medium.

The constant membrane potential at rest, which is called a resting potential, is defined by a number of differently directed background currents via the channels and exchangers sustaining cellular homeostasis. The resting potential is close to the equilibrium  $K^+$  potential  $E_K = -94.5$  mV because the membrane permeability at rest for other ions is low.

During the cardiac cell excitation (due to a stimulating signal from the conducting system of the heart or the artificial electrical stimulation of heart preparation in a physiological experiment) the membrane potential increases to a threshold level and thus the ion channels and the exchangers become activated. In the model, the prethreshold perturbation of the membrane potential, which initiates the cell excitation, is prescribed by the short-time stimulating depolarizing current  $i_{stim} < 0$ . Ionic currents that occur after threshold depolarization provide the characteristic cyclic change in the membrane potential, which is called an action potential. In particular, the fast sodium current via  $Na^+$  channels,  $i_{Na}$ , is responsible for fast upstroke. The slow inward calcium current via  $L$ -channels,  $i_{CaL}$ , mostly provides the phase of AP plateau. Outward currents via  $K^+$  channels: delayed outward  $K^+$  current,  $i_K$ , and the inward rectifier  $K^+$  current,  $i_{K1}$ , define the membrane repolarization up to the resting potential level. The above currents,  $i_{NaCa}$  and  $i_{MSC}$ , also substantially affect the AP configuration.

**Model description of the mechanical activity of heart muscle** is based on the classical three-element scheme of a contractile unit (see fig. 1), which consists of a contractile element (CE) or sarcomere as well as associated serial (SE) and parallel (PE) nonlinear elastic elements. According to the scheme the muscle length,  $L$ , is taken to be proportional to the parallel element length, whereas the tension  $T$  produced by the muscle is proportional to the sum of tensions in elastic

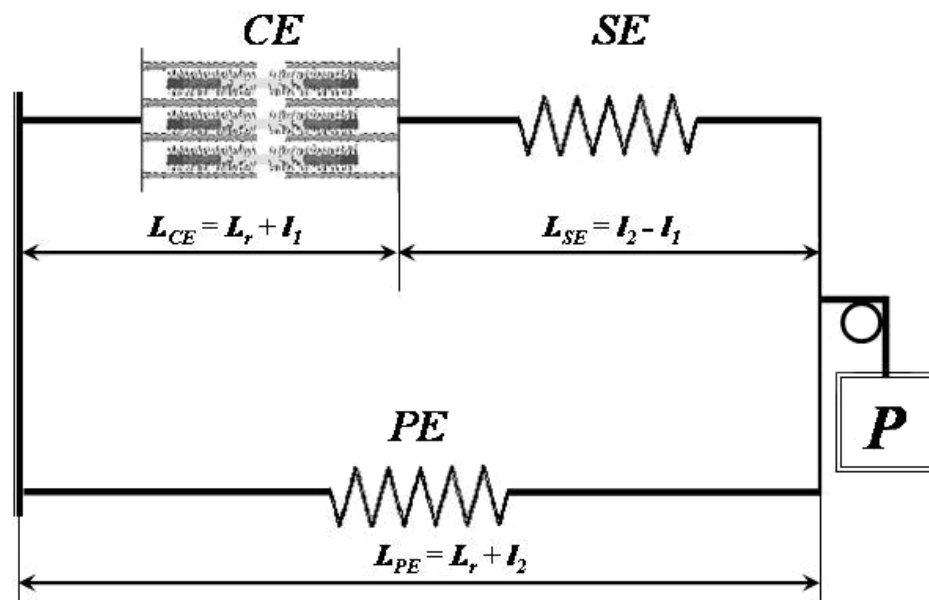


Figure 1

elements  $T_{SE} + T_{PE}$ .

In the framework of the model, we describe dynamic changes in the muscle

length  $L$  and the tension  $T$  under various contraction conditions. For example, the model can generate either the change in the tension  $T$ , given the change in the muscle length  $L = \varphi(t)$  (in particular, in the isometric regime at the fixed length  $L \equiv \text{const}$ ), or the change in the length  $L$ , given the change in the load  $T = \psi(t)$  (for example, in the isotonic regime at the fixed load  $T \equiv \text{const}$ ).

Suppose  $l_1$  is the CE deformation, i.e. the deviation in the sarcomere length from the resting length,  $L_r$ , during of contraction (relaxation),  $l_2$  is the PE deformation. These two variables are basic phase variables in the mechanical model block.

It is obvious that the SE deformation is equal to the difference between the PE and CE deformations, i.e. to  $l_2 - l_1$ . The deformation-tension coupling for elastic elements is fitted to the experimental data and represented as the parametric functions (see **A.3(a)**):

$$T_{SE} = T_{SE}(l_2 - l_1), T_{PE} = T_{PE}(l_2). \quad (9)$$

The force  $T_{CE}$  generated by sarcomere that results from to interaction between crossbridges of myosin molecules and the active centers of actin molecules and depends on the sarcomere length and the velocity of its shortening/lengthening in the model, as well as the calcium activation process of thin filaments.

It is set as (see **A.3(a)**):

$$T_{CE} = \lambda \cdot f \cdot N. \quad (10)$$

Here  $f$  is the force generated by an averaged force-generating bridge,  $N$  is the fraction of force-generating bridges per sarcomere,  $\lambda$  is a proportionality coefficient.

It is assumed that  $f$  depends on the shortening/lengthening velocity of sarcomere  $v = dl_1 / dt$ , i.e.  $f = f(v)$ . The function  $f(v)$  is given in explicit form (by the experimental data) and allows us to find the velocity  $f$  in explicit form, given the bridge load  $v = v(f)$ . In view of this and the fact that the tensions of the series connected sarcomere CE and the elastic element SE are equal,  $T_{CE} = T_{SE}$ , we derive from (9)–(10) the equation for  $l_1$  (see **A.3(c)**):

$$\frac{dl_1}{dt} = v\left(\frac{T_{SE}(l_2 - l_1)}{\lambda \cdot N}\right). \quad (11)$$

The kinetics of the force-generating bridges is described by the equation (see also **A.3(b)**):

$$\frac{dN}{dt} = k_+(l_1, \frac{dl_1}{dt}, [CaTrop]) \cdot (1 - N) - k_- \cdot N \quad (12)$$

The change in  $[CaTrop]$  is described by the kinetic equation (see **A.2(b)**):

$$\frac{d[CaTrop]}{dt} = k_{on} \cdot (TnC_{tot} - [CaTrop]) \cdot [Ca^{2+}]_{in} - \beta_{Trop}(N, [CaTrop]) \cdot [CaTrop] \quad (13)$$

One of the most important features of our model is that it takes into account in equations (12)–(13) the cooperative mechanisms in the process of calcium activation of contractile proteins, which are found experimentally earlier [1-3]. The probability of binding the bridges cooperatively increases due to conformational transformations of regulator actin proteins, which are caused by the formation of calcium complexes with troponin C. This mechanism is formalized as a power dependence of the rate of binding the bridges  $k^+$  on the value of  $[CaTrop]$  (see equa-

tion (12)). On the other hand, the affinity of troponin for calcium increases, first, as the concentration of strongly bound crossbridges,  $N$ , increases and, second, with increasing  $[CaTrop]$ . These links are formalized as a decreasing dependence of the constant of the decay rate  $\beta_{Trop}$  on the values of  $N$  and  $[CaTrop]$  (see equation (13)).

Taking into account the above mechanisms in the model allowed us to reproduce and explain quite a number of sophisticated mechanical and mechanochemical phenomena observed in the active myocardium [11, 5, 7, 10].

Finally, the final equation in the mechanical model block is the equation for finding  $l_2$ . Given the change in the muscle length  $l_2$  is specified in the explicit form:  $l_2 = \varphi(t)$ . For example,  $l_2 \equiv \text{const}$  in the isometric regime. Given the change in the muscle load,  $l_2$  is found from the identity  $T_{SE}(l_2 - l_1) + T_{PE}(l_2) = \psi(t)$ . For example,

$$\frac{dl_2}{dt} = \begin{cases} \dot{\varphi} & \text{if length control} \\ (\psi - (T_{SE})'_{l_1} \cdot \frac{dl_1}{dt}) / (T_{SE} + T_{PE})'_{l_2} & \text{if load control} \end{cases} \quad (14)$$

See also **A.3(d)**.

**The free intracellular calcium kinetics** is a “connecting link” between electrical and mechanical activities of a cardiac cell because it is closely related to transmembrane potential-dependent  $Ca^{2+}$  fluxes (see equation (8)) and directly included in the regulation of a contractile response of heart muscle (see equation (13)). As mentioned above, exchange with intracellular structures, in particular, exchange with intracellular calcium sources, i.e. sarcoplasmic reticulum (SR) (the terms  $F_{rel}$  and  $F_{up}$  in equation (8)) plays an important role in the  $[Ca^{2+}]_{in}$  kinetics. An increase in  $[Ca^{2+}]_{in}$  by an order of magnitude (from  $10^{-7}M$  in diastole to  $10^{-6}M$  in systole), which is needed for contractile cell activity during a cardiac cycle, is not mainly due to  $Ca^{2+}$  entry from the outside of a cell, but to calcium induced calcium release from SR. The  $Ca^{2+}$  flux via the release channels of the SR membrane

$$F_{rel} = \eta(i_{CaL}, [Ca^{2+}]_{JSR}) \quad (15)$$

depends in a complicated way on the current  $i_{CaL}$ , which is a trigger of  $Ca^{2+}$  release from SR, and nonlinearly depends on the calcium concentration in junctional SR,  $[Ca^{2+}]_{JSR}$ .

The process of the heart muscle relaxation is mainly due to the pumping  $Ca^{2+}$  from cytosol back to SR by calcium ATPase pumps on the SR membrane. The  $Ca^{2+}$  flux produced by these pumps (see **A.2(e)**)

$$F_{up} = Fr_{up} \cdot \alpha_{up} \cdot \frac{1}{1 + [Ca^{2+}]_{NSR} / K_{NSR}} - Fr_{back} \cdot \beta_{up} \quad (16)$$

depends on both  $[Ca^{2+}]_{in}$  and the calcium concentration in net SR,  $[Ca^{2+}]_{NSR}$ . The parameter  $Fr_{up}$  is the fraction of  $Ca^{2+}$  uptake sites,  $Fr_{back}$  is the fraction of  $Ca^{2+}$  back SR sites,  $\alpha_{up}$  and  $\beta_{up}$  is sarcoplasmic reticulum uptake flux forward and backward rates, and  $K_{NSR}$  is the degree of the pump inhibition with increasing  $[Ca^{2+}]_{NSR}$ .

Finally, cytosol  $Ca^{2+}$  forms complexes with calcium-binding ligands, in particular, with troponin C (see equation (13)). The  $Ca^{2+}$  consumption for the formation of these complexes is represented in equation (8) by the terms

$$\frac{d[CaTrop]}{dt} + \frac{d[B_1]}{dt} + \frac{d[B_2]}{dt}$$

Thus, the model of mechanical and electrical phenomena in myocardium is the system of 28 ordinary differential equations. The electrophysiological model block comprises an equation for the membrane potential  $E$  (equation (1) with relations in the right-hand side of the form (2) or (7)) and an equation for dynamic parameters that specify the probabilities  $P_k$  for the ionic channels to be in an open state (the equations of the form (5)). The mechanical model block supplements equations (11)-(14) for the deformations  $l_1$ ,  $l_2$  and the concentration of the force generating bridges  $N$ , and the control calcium complex with troponin  $C$ ,  $[CaTrop]$ . The ‘chemical’ block of the system comprises the equations for  $[Ca^{2+}]_i$ ,  $[Na^+]_i$ ,  $[K^+]_i$  and  $[K^+]_o$  (equations (8) with relations (15), (16) in the right-hand side), the equations for  $[CaTrop]$ ,  $[B_1]$ ,  $[B_2]$  and finally the equations for the  $[Ca^{2+}]_{JSR}$  and  $[Ca^{2+}]_{NSR}$  kinetics in the release and absorption compartments of SR (analogous to equation (13)).

In the framework of the described model we took into account both direct coupling and feedback between electrical and mechanical phenomena in cardiac cells. Indeed, due to the effect of the membrane potential on  $Ca^{2+}$  currents and hence on  $[Ca^{2+}]_i$  the excitation-contraction coupling is realized. On the other hand, the effect of the kinetics of the force-generating bridges on the  $[CaTrop]$  kinetics and hence on  $[Ca^{2+}]_i$  and the calcium-dependent currents ensures feedback between the contraction and electric activity of cardiomyocytes, which is called the mechanoelectric feedback. In addition to this mechanism, currents via the mechanosensitive channels (see (6)), which are directly activated by mechanical perturbations, can also contribute to the mechanically caused modulation of electric activity.

Most of the parameters in the model equations are taken from the experimental works, where these parameters were thoroughly determined. The other model parameters were chosen to achieve qualitative agreement between the model results and the values recorded in the physiological experiments.

The model system of ordinary differential equations belongs to the class of stiff systems. For the numerical integration, we first used the Runge-Kutta fourth-order method with a small step to obtain as the more exact numerical solution as possible. Then we compared the numerical solutions obtained by the Euler method with the obtained solution. We found the numerical integration step such that the two solutions are sufficiently close. We also used the combined explicit-implicit Euler method for the calculation of part of the variables explicitly and solved the system of algebraic equations for finding the other variables. This method allows us to increase the integration step as compared to that in the explicit method without loss of the solution quality. For the experiments with the model we developed a program that allows us to simulate various experimental conditions for muscle contraction, specify different initial conditions in the system, and change the free parameters.

The combined electromechanical model describes the mechanical and electrical behaviour of cardiomyocytes both in isometric and isotonic mode of contraction/relaxation cycles and in the series of contractions of various stimulation fre-

quencies. The model successfully reproduces numerous effects that demonstrate the influence of the mechanical contraction conditions on the AP generation in cardiac cells. In particular, in the framework of the model we correctly reproduced both the effect of the muscle length on the APD in the isometric regime and the effect of the muscle load on the APD in the isotonic regime [10]. The inclusion of the mechanosensitive channels in the model allowed us to describe a number of phenomena that are irreproducible without considering the channels, for example, the repolarization crossover phenomenon after the cell stretch as compared to the control one [6, 13].

## A.1. Electrical part of the model

### A.1(a) Membrane potential

$$\frac{dE_m}{dt}(t) = -\frac{1}{C_m} \cdot (i_K + i_{K1} + i_{to} + i_{Na} + i_{bNa} + i_{pNa} + i_{CaL} + i_{bCa} + i_{NaCa} + i_p + i_{MSC} + i_{stim}) ,$$

$$i_{stim} ([0.06 \text{ s}; 0.0625 \text{ s}]) = -3.0 \text{ nA}.$$

### A.1(b) Reversal potentials

$$E_{Na} = \frac{R \cdot T}{F} \cdot \ln \frac{[Na^+]_o}{[Na^+]_i}, \quad E_K = \frac{R \cdot T}{F} \cdot \ln \frac{[K^+]_o}{[K^+]_i},$$

$$E_{Ca} = \frac{R \cdot T}{2 \cdot F} \cdot \ln \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i},$$

$$E_{Ks} = \frac{R \cdot T}{F} \cdot \ln \frac{([K^+]_o + P_{KNa} \cdot [Na^+]_o)}{([K^+]_i + P_{KNa} \cdot [Na^+]_i)},$$

$$E_{mh} = \frac{R \cdot T}{F} \cdot \ln \frac{([Na^+]_o + 0.12 \cdot [K^+]_o)}{([Na^+]_i + 0.12 \cdot [K^+]_i)}.$$

### A.1(c) Intracellular $Na^+$ concentration, $[Na^+]_i$

$$\frac{d[Na^+]_i}{dt} = -\frac{1}{V_i F} \cdot (i_{Na} + i_{pNa} + i_{CaL,Na} + i_{bNa} + 3 \cdot i_p + 2 \cdot i_{NaCa}).$$

### A.1(d) Extracellular $K^+$ concentration, $[K^+]_o$

$$\frac{d[K^+]_o}{dt} = \frac{1}{V_e F} \cdot (i_K + i_{K1} + i_{CaL,K} - 2 \cdot i_p + i_{to}) - 0.7 \cdot ([K^+]_o - [K^+]_b).$$

### A.1(e) Intracellular $K^+$ concentration, $[K^+]_i$

$$\frac{d[K^+]_i}{dt} = -\frac{1}{V_i F} \cdot (i_K + i_{K1} + i_{CaL,K} - 2 \cdot i_p + i_{to}).$$

### A.1(f) Time-dependent (delayed) $K^+$ current, $I_{Kr1}$

$$i_{Kr1} = P_{Kr1} \cdot \bar{g}_{Kr1} \cdot (E_m - E_K),$$

$$P_{Kr1} = x_{r1} \cdot \frac{1}{(1 + e^{(E_m+9)/22.4})},$$

$$\frac{dx_{Kr1}}{dt} = \alpha_{xr1} - (\alpha_{xr1} + \beta_{xr1}) \cdot x_{r1},$$

$$\alpha_{xr1} = \frac{50}{1 + e^{\frac{E_m-5}{9}}}, \quad \beta_{xr1} = 0.05 \cdot e^{\frac{E_m-20}{15}}.$$

**A.1(g) Time-dependent (delayed)  $K^+$  current,  $i_{Kr2}$**

$$i_{Kr2} = P_{Kr2} \cdot \bar{g}_{Kr2} \cdot (E_m - E_K),$$

$$P_{Kr2} = x_{r2} \cdot \frac{1}{(1 + e^{(E_m+9)/22.4})},$$

$$\frac{dx_{Kr2}}{dt} = \alpha_{xr2} - (\alpha_{xr2} + \beta_{xr2}) \cdot x_{r2},$$

$$\alpha_{xr2} = \frac{50}{1 + e^{\frac{E_m-5}{9}}}, \quad \beta_{xr2} = 0.4 \cdot e^{-\left(\frac{E_m+30}{30}\right)^3}.$$

**A.1(h) Time dependent (delayed)  $K^+$  current,  $i_{Ks}$**

$$i_{Ks} = P_{Ks} \cdot \bar{g}_{Ks} \cdot (E_m - E_{Ks}),$$

$$P_{Ks} = x_s^2,$$

$$\frac{dx_{Ks}}{dt} = \alpha_{xs} - (\alpha_{xs} + \beta_{xs}) \cdot x_s,$$

$$\alpha_{xs} = \frac{14}{1 + e^{\frac{E_m-40}{9}}}, \quad \beta_{xs} = e^{\frac{E_m}{45}}.$$

$$i_K = i_{Kr1} + i_{Kr2} + i_{Ks}.$$

**A.1(i) Inward rectifier  $K^+$  current,  $i_{K1}$**

$$i_{K1} = P_{K1} \cdot \bar{g}_{K1} \cdot (E_m - E_K),$$

$$P_{K1} = \frac{[K^+]_o}{[K^+]_o + K_{m,K1}} \cdot \frac{1}{1 + e^{\frac{1.25F}{RT}(E_m - E_K - 10)}}.$$

**A.1(j) Transient outward  $K^+$  current,  $i_{to}$**

$$i_{to} = P_{to} \cdot \bar{g}_{to} \cdot (E_m - E_K),$$

$$P_{to} = s \cdot r,$$

$$\frac{dr}{dt} = 333 \cdot (r_{ss} - r),$$

$$\frac{ds}{dt} = \alpha_s - (\alpha_s + \beta_s) \cdot s,$$

$$r_{ss} = \frac{1}{1 + e^{-0.2(E_m+4)}},$$

$$\alpha_s = 0.033 \cdot e^{-\frac{E_m}{17}}, \quad \beta_s = \frac{33}{1 + e^{-0.125 \cdot (E_m + 10)}}.$$

**A.1(k) Background Na<sup>+</sup> current,  $i_{bNa}$**

$$i_{bNa} = \bar{g}_{bNa} \cdot (E_m - E_{Na}).$$

**A.1(l) Na<sup>+</sup>-K<sup>+</sup> pump,  $i_p$**

$$i_p = \hat{i}_p \cdot \frac{[K^+]_o}{[K^+]_o + K_{m,K}} \cdot \frac{[Na^+]_i}{[Na^+]_i + K_{m,Na}}.$$

**A.1(m) Na<sup>+</sup>-Ca<sup>2+</sup> exchange current,  $i_{NaCa}$**

$$i_{NaCa,cyt} = k_{NaCa} \frac{e^{\frac{2\gamma E_m F}{2RT}} [Na^+]_i^3 [Ca^{2+}]_o - e^{-\frac{2(1-\gamma) E_m F}{2RT}} [Na^+]_o^3 [Ca^{2+}]_i}{1 + [Ca^{2+}]_i / K_{NaCa}},$$

$$i_{NaCa,DS} = k_{NaCa} \frac{e^{\frac{2\gamma E_m F}{2RT}} [Na^+]_i^3 [Ca^{2+}]_o - e^{-\frac{2(1-\gamma) E_m F}{2RT}} [Na^+]_o^3 [Ca^{2+}]_{DS}}{1 + [Ca^{2+}]_i / K_{NaCa}},$$

$$i_{NaCa} = FracNaCa_{cyt} \cdot i_{NaCa,cyt} + (1 - FracNaCa_{cyt}) \cdot i_{NaCa,DS}.$$

**A.1(n) Background Ca<sup>2+</sup> current,  $i_{bCa}$**

$$i_{bCa} = \bar{g}_{bCa} \cdot (E_m - E_{Ca}).$$

**A.1(o) Fast Na<sup>+</sup> current,  $i_{Na}$**

$$i_{Na} = P_{Na} \cdot \bar{g}_{Na} \cdot (E_m - E_{mh}),$$

$$P_{Na} = m^3 \cdot h,$$

$$\frac{dm}{dt} = \alpha_m - (\alpha_m + \beta_m) \cdot m,$$

$$\frac{dh}{dt} = \alpha_h - (\alpha_h + \beta_h) \cdot h,$$

$$\alpha_m = 200 \cdot \frac{E_m + 41}{1 + e^{-0.1 \cdot (E_m + 41)}}, \quad \alpha_m \big|_{|E_m + 41| < 0.00001} = 2000,$$

$$\beta_m = 8000 \cdot e^{-0.056 \cdot (E_m + 66)},$$

$$\alpha_h = 20 \cdot e^{-0.125 \cdot (E_m + 75)},$$

$$\beta_h = 2000 \cdot \frac{1}{1 + 320 \cdot e^{-0.1 \cdot (E_m + 75)}}.$$

**A.1(p) L̃ type Ca<sup>2+</sup> current,  $i_{CaL}$**

$$i_{CaL} = FracL_{cyt} \cdot i_{CaL,cyt} + (1 - FracL_{cyt}) \cdot i_{CaL,DS},$$

$$i_{CaL,cyt} = d \cdot f \cdot f_{2,cyt} \cdot \sum i_{CaL,X},$$

$$i_{CaL,DS} = d \cdot f \cdot f_{2,DS} \cdot \sum i_{CaL,X},$$

$$\frac{df_{2,cyt}}{dt} = 1 - \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,cytInact}} - f_{2,cyt},$$

$$\frac{df_{2,DS}}{dt} = RateDSInact \cdot \left( 1 - \frac{[Ca^{2+}]_{DS}}{[Ca^{2+}]_{DS} + K_{m,cytInact}} - f_{2,DS} \right),$$

$$i_{CaL,Ca} = 4P_{Ca} \frac{(E_m - E_{surf}) \frac{F}{RT}}{(1 - e^{-\frac{(E_m - E_{surf}) \frac{2F}{RT}}})} ([Ca^{2+}]_i e^{\frac{E_{surf} \frac{2F}{RT}} - [Ca^{2+}]_o e^{-\frac{(E_m - E_{surf}) \frac{2F}{RT}}})$$

$$i_{CaL,Na} = P_{Na} P_{Ca} \frac{(E_m - E_{surf}) \frac{F}{RT}}{(1 - e^{-\frac{(E_m - E_{surf}) \frac{F}{RT}}})} ([Na^+]_i e^{\frac{E_{surf} \frac{F}{RT}} - [Na^+]_o e^{-\frac{(E_m - E_{surf}) \frac{F}{RT}}}),$$

$$i_{CaL,K} = P_K P_{Ca} \frac{(E_m - V_{surf}) \frac{F}{RT}}{(1 - e^{-\frac{(E_m - V_{surf}) \frac{F}{RT}}})} ([K^+]_i e^{\frac{V_{surf} \frac{F}{RT}} - [K^+]_o e^{-\frac{(E_m - V_{surf}) \frac{F}{RT}}}),$$

$$\frac{dd}{dt} = \alpha_d - (\alpha_d + \beta_d) \cdot d, \quad \frac{df}{dt} = \alpha_f - (\alpha_f + \beta_f) \cdot f,$$

$$\alpha_d = 90 \cdot \frac{E_m + 24 - E_{shift}}{1 - e^{-0.25 \cdot (E_m + 24 - E_{shift})}}, \quad \alpha_d \mid_{|E_m + 24 - E_{shift}| < 0.00001} = 360,$$

$$\beta_d = -36 \cdot \frac{E_m + 24 - E_{shift}}{1 - e^{-0.1 \cdot (E_m + 24 - E_{shift})}}, \quad \beta_d \mid_{|E_m + 24 - E_{shift}| < 0.00001} = 360,$$

$$\alpha_f = 1.875 \cdot \frac{E_m + 34}{e^{0.25 \cdot (E_m + 34)} - 1}, \quad \alpha_f \mid_{|E_m + 34| < 0.00001} = 7.5,$$

$$\beta_f = 3.6 \cdot \frac{1}{1 + e^{-0.25 \cdot (E_m + 34)}}.$$

### A.1(q) Persistent Na<sup>+</sup> current, $i_{pNa}$

$$i_{pNa} = P_{pNa} \cdot \bar{g}_{pNa} \cdot (E_m - E_{Na}),$$

$$P_{pNa} = \frac{1}{1 + e^{-\frac{(E_m + 52)}{8}}}.$$

### A.1(r) currents via mechanosensitive channels, $i_{MSC}$

$$i_{MSC} = P_{MSC} \cdot \bar{g}_{MSC} \cdot (E_m - E_{MSC}),$$

$$P_{MSC} = \frac{1}{1 + K_{MSC} \cdot e^{-\gamma_{MSC} \cdot (L - L_{ref})}}.$$

## A.2. Equations for the Calcium handling

### A.2(a) Ca<sup>2+</sup> concentration within the cytosol and the diadic space

$$\begin{aligned} \frac{d[Ca^{2+}]_i}{dt} &= -\frac{1}{2V_i F} \cdot (i_{CaL,CA,cyt} + i_{bCa} - 2 \cdot i_{NaCa,cyt}) + F_{rel} \cdot \frac{V_{rel}}{V_i} - F_{up} - \\ &\quad - \frac{d[CaTrop]}{dt} - \frac{d[B_1]}{dt} - \frac{d[B_2]}{dt} + [Ca^{2+}]_{DS} \cdot \text{frac}_{V_{DS}} \cdot k_{decay} \\ \frac{d[Ca^{2+}]_{DS}}{dt} &= -\frac{1}{2 \cdot \text{frac}_{V_{DS}} \cdot V_i \cdot F} \cdot (i_{CaL,DS} - 2 \cdot i_{NaCa,DS}) - \\ &\quad - k_{decay} \cdot [Ca^{2+}]_{DS} \end{aligned}$$

### A.2(b) Cytosolic $Ca^{2+}$ buffering system

$$\begin{aligned} \frac{d[B_1]}{dt} &= \alpha_{B1} \cdot (B_{1tot} - [B_1]) \cdot [Ca^{2+}]_i - \beta_{B1} \cdot [B_1], \\ \frac{d[B_2]}{dt} &= \alpha_{B2} \cdot (B_{2tot} - [B_2]) \cdot [Ca^{2+}]_i - \beta_{B2} \cdot [B_2], \\ \frac{d[CaTrop]}{dt} &= (CaTrop_{tot} - [CaTrop]) \cdot [Ca^{2+}]_i \cdot \alpha_{Trop} - [CaTrop] \cdot \beta_{Trop}, \\ \beta_{Trop} &= \beta_{Trop,0} \cdot e^{\frac{[CaTrop]}{q_{Trop}}} \cdot \Pi(n), \\ \Pi(n) &= \Pi_{max} \cdot \frac{(\Pi_{max} - \Pi_{min})}{1 + (\frac{K_{\Pi}}{n})^{k_{\Pi}}}. \end{aligned}$$

### A.2(c) $Ca^{2+}$ concentration within the SR compartments

$$\begin{aligned} \frac{d[Ca^{2+}]_{rel}}{dt} &= -F_{rel} - \frac{d[CaS]}{dt} + \frac{V_{up}}{V_{rel}} \cdot F_{tr}, \\ \frac{d[Ca^{2+}]_{up}}{dt} &= \frac{V_i}{V_{up}} \cdot F_{up} - F_{tr}. \end{aligned}$$

### A.2(d) Calcium release from the SR

$$\begin{aligned} F_{rel} &= (Fr_{OpenRelCh} \cdot K_{mRel} + LeakRate) \cdot [Ca^{2+}]_{rel}, \\ Fr_{Pre c} &= 1 - Fr_{Act} - Fr_{Prod}, \\ K_{act} &= K_{RegBind} \cdot RegBindSite, \\ K_{inact} &= 60.0 + (K_{RegBind} \cdot RegBindSite), \\ RegBindSite &= \left( \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,Cacyt}} + \right. \\ &\quad \left. + \left( 1 - \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,Cacyt}} \right) \cdot \frac{[Ca^{2+}]_{DS}}{[Ca^{2+}]_{DS} + K_{m,CaDS}} \right)^2, \end{aligned}$$

$$\frac{dFr_{Act}}{dt} = Fr_{Prec} \cdot K_{act} - Fr_{Act} \cdot K_{inact},$$

$$\frac{dFr_{Prod}}{dt} = Fr_{Act} \cdot K_{inact} - Fr_{Prod} \cdot K_{close},$$

$$\text{if } E_m < -50 \quad \frac{dFr_{Act}}{dt} = 5 \cdot \frac{dFr_{Act}}{dt}, \quad \frac{dFr_{Prod}}{dt} = 5 \cdot \frac{dFr_{Prod}}{dt},$$

$$Fr_{OpenRelCh} = \left( \frac{Fr_{Act}}{Fr_{Act} + 0.25} \right)^2.$$

### A.2(e) $Ca^{2+}$ uptake by the SRpump

$$F_{up} = Fr_{UptakeCalciumSites} \cdot \alpha_{up} \cdot \frac{1}{1 + [Ca^{2+}]_{up} / K_{inh}} - Fr_{BackSRSites} \cdot \beta_{up},$$

$$Fr_{UptakeCalciumSites} = \frac{[Ca^{2+}]_i}{K_2},$$

$$Fr_{BackSRSites} = [Ca^{2+}]_{up} \cdot \frac{K_1}{K_2},$$

$$K_1 = k_{cyca} \cdot \frac{k_{xcs}}{k_{srca}},$$

$$K_2 = [Ca^{2+}]_i + [Ca^{2+}]_{up} \cdot K_1 + k_{cyca} \cdot k_{xcs} + k_{cyca}.$$

### A.2(f) $Ca^{2+}$ translocation within the SR and buffering by calsequestrin

$$F_{tr} = \alpha_{tr} \cdot ([Ca^{2+}]_{up} - [Ca^{2+}]_{rel}),$$

$$\frac{d[CaS]}{dt} = \alpha_{CaS} \cdot (CaS_{tot} - [CaS]) \cdot [Ca^{2+}]_{rel} - \beta_{CaS} \cdot [CaS].$$

## A.3. Mechanical part of the model

### A.3(a) Force generation

$$T_{PE} = \beta_2 \cdot (e^{\alpha_2 \cdot l_2} - 1),$$

$$T_{SE} = \beta_1 \cdot (e^{\alpha_1 \cdot (l_2 - l_1)} - 1)$$

$$T_{CE} = \lambda \cdot f \cdot N$$

### A.3(b) Fraction of the force generating the cross-bridges

$$N = ([CaTrop])^\mu \cdot n \cdot (l_1 + s_0),$$

$$n = n_1 \cdot n_2, \quad \frac{dn_2}{dt} = \delta \cdot q_n(v) \cdot (G(v) \cdot n_{2(ss)} - n_2),$$

$$n_l(l_1) = \begin{cases} 0, & w(l_1) < 0; \\ w(l_1), & 0 \leq w(l_1) < l; \text{ where } w(l_1) = g_1 \cdot l_1 + g_2. \\ 1, & w(l_1) \geq l, \end{cases}$$

$$q_n(v) = \begin{cases} q_1 - q_2 \cdot \left(\frac{v}{v_{max}}\right), & v \leq 0 \\ \frac{(q_4 - q_3) \cdot v}{v_{st}} + q_3, & 0 < v \leq v_{st} \\ \frac{q_4}{\left(1 + \frac{v - v_{st}}{\beta_q}\right)^{\alpha_q}}, & v > v_{st} \end{cases},$$

### A.3(c) Sarcomere length ( $l_1$ - lengthening over the slack sarcomere length)

$$f = \frac{T_{SE}}{\lambda \cdot N}, \text{ due to } T_{CE} = T_{SE}.$$

$$\frac{dl_1}{dt} = v, \text{ where } v \text{ is obtained by explicitly solving the equation } \frac{P^*(v)}{G^*(v)} = \frac{T_{SE}}{\lambda N},$$

$$P^*(v) = \begin{cases} \frac{a \cdot (1 + v/v_{max})}{a - v/v_{max}} & -v_{max} \leq v \leq 0 \\ (\tau_1 \cdot v/v_{max} + 1) \cdot G^*(v) & 0 \leq v \leq v_l \\ \tau_2 \cdot (v_0 - v)^{\mu_P} & v_l \leq v \leq v_0 \\ 0 & v > v_0 \end{cases},$$

Coefficient  $\tau_1$  in equation is determined providing continuity of  $P(v)$ .

$$G^*(v) = \begin{cases} 0.6 \cdot v/v_{max} + 1 & , -v_{max} \leq v \leq v_l, v_l > 0 \\ (0.6 \cdot v_l/v_{max} + 1) \cdot \left[ \frac{v_0 - v}{v_0 - v_l} \right] & , v_l \leq v \leq v_0, \\ 0 & , v > v_0 \end{cases}.$$

### A.3(d) Muscle length ( $l_2$ - lengthening over the slack muscle length)

$$\frac{dl_2}{dt} = \begin{cases} \dot{\varphi} & \text{if } l_2 = \varphi(t), \\ \frac{\dot{\psi} - (T_{SE})'_{l_1} \cdot \frac{dl_1}{dt}}{(T_{SE} + T_{PE})'_{l_2}} & \text{if } T = \psi(t). \end{cases}$$

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