MATHEMATICAL MODEL OF CARDIOMYOCYTE ION CHANNELS SYSTEM

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Abstract: The computational model of ion channels, ion transportation, flow through ion channels between extracellular and intracellular space and excitation-contraction coupling in cardiomyocyte is presented in this paper. The validity of the model is discussed and the results are compared to physiological experimental findings. Although only calcium ions are involved in this moment, the model gives results well consistent with experimental data. Thus this simulation can be useful for studying ion channel attributes and their impact on sarcomere function and could further help to explain pathophysiological mechanisms of heart failure.

Introduction

Calcium ions distribution in cardiomyocyte can be described as a flow through ion channels among extracellular and intracellular space, sarcoplasmic reticulum, sarcomere and mitochondry (Fig.1).

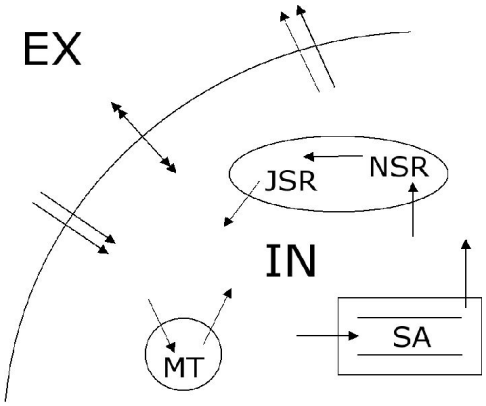

Figure 1: Ca^{2+} ions distribution (EX – extracellular space, IN – intracellular space, MT – mitochondry, SA – sarcomere, NSR – network / longitudinal portion of sarcoplasmic reticulum, JSR – junctional / cisternal portion of sarcoplasmic reticulum)

Permeability of these channels can be changed by action potential, concentration gradient and electrochemical potential during heart cycle period [1]. Opening and closing of channels is controled by either critical concentration exceeding or gating processes [2] – activation and inactivation (Fig.2) – that are dependent on action potential input (Fig.3) too. [3]

Only L-type calcium ion channels are present in this model in this moment. Sodium and potassium channels are not included yet because the complex of nonlinear differential equations representing ions transportation is stable only with specific boundary conditions now and every other channel can destabilize the simulation or cause some singularity in solution.

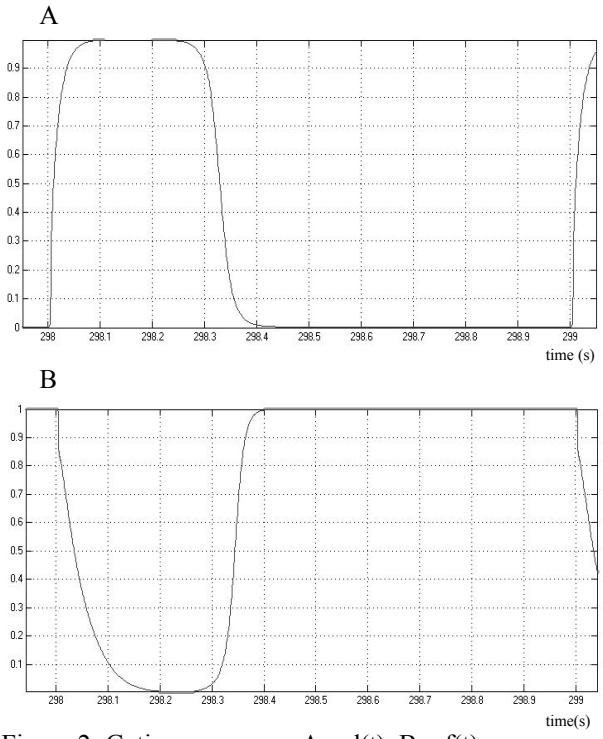

Figure 2: Gating processes. A – d(t), B – f(t)

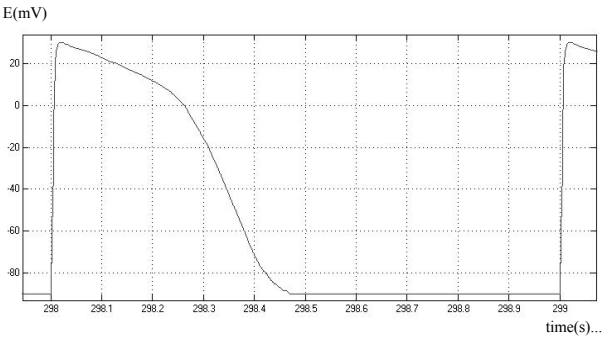

Figure 3: Action potential E(t) – simulation input signal

Materials and Methods

The construction of the model involved: contractile (actomysin) subsystem, regulatory (troponin) subsystem and intracellular calcium flow dynamics subsystem. [4]

The contractile subsystem reactions are schematically described in Fig.5. Basic reactions of

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excitation-contraction coupling based on strong-weak states and filament sliding theories were considered. [5] The reaction kinetic was expressed by the system of ten ordinary non-linear first order differential equations with constant coefficients. The constants represent the parameters of the mathematical model.

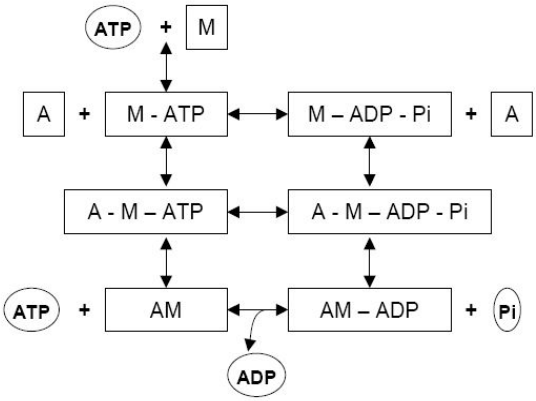

Figure 5: Actomyosin subsystem scheme (A – actin, M – myosin, A-M… – actomyosin weak cross-bridge interaction, AM – actomyosin strong cross bridge interaction (rigor state))

The regulatory subsystem is schematically described in Fig.6.

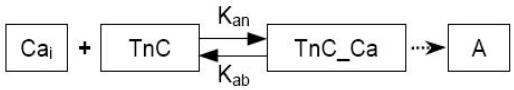

Figure 6: Regulatory subsystem scheme (TnC – troponin, A – actin, TnC_Ca – troponin-calcium complex with no inhibition influence on A)

The calcium flow dynamics subsystem is schematically described in Fig.7. Compartment method was used for the computer modelling and simulations. Each ion flow from one compartment to another was described by linear or nonlinear differential equation including current compartment ion concentrations and channel permeability. [6]

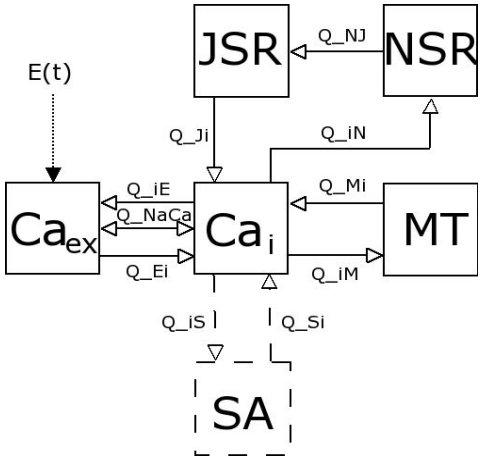

Figure 7: calcium flow dynamics subsystem scheme

This subsystem is in detail defined with following equations.

$$\frac{dCa_i}{dt} = Q_{Ei} + Q_{Ji} + Q_{Mi} + Q_{Si} + Q_{NaCa} - \\ - Q_{iN} - Q_{iM} - Q_{iS} - Q_{iE} \tag{1}$$

Eq.1 describes intracellular concentration changes in time calculated from Ca^{2+} ion flows among compartments (mol l^{-1} s^{-1}; M s^{-1}). Calcium transportation from extracellular space into the cell contains of diffusion (leak) flow and voltage controlled channel dynamics (Eq.2).

$$Q_{Ei} = (Ca_{ex0} - Ca_i) \cdot k_{dif} + \\ + (E(t) - E_{Ca}) \cdot g_{Ca} \cdot f \cdot d \cdot k_{Ei} \tag{2}$$

Q_{Ji} describes the flow from sarcoplasmic reticulum to cytoplasma that depends on intracellular Ca^{2+} concentration, concentrations inside the reticulum compartments and membrane potential changes (d(t)).

$$Q_{Ji} = (Ca_i - Ca_{i0}) \cdot Ca_J \cdot d_\infty \cdot k_{Ji} \tag{3}$$

$$\frac{dCa_J}{dt} = Q_{NJ} - Q_{Ji} \tag{4}$$

$$Q_{NJ} = (Ca_N - Ca_{N0}) \cdot f_\infty \cdot k_{NJ} \tag{5}$$

Ion flows from mitochondria to intracellular space can be described with Eq.6 and Eq.7.

$$Q_{Mi} = Ca_M \cdot d_\infty \cdot k_{Mi} \tag{6}$$

$$\frac{dCa_M}{dt} = Q_{iM} - Q_{Mi} \tag{7}$$

Eq.8 belongs to regulatory subsystem. Influx to intracellular space from contractile subsystem is calculated

$$Q_{Si} = \frac{1}{u} \cdot A \cdot k_{ab} \tag{8}$$

Transportation through the Na-Ca exchanger (Eq.9) mainly depends on activation potential, intracellular and extracellular concentrations of Ca^{2+} and Na^+ and cell volume. [7] [8] [9] [10] [11] [12] In the Fig.8 Na-Ca exchanger current is shown.

$$Q_{NaCa} = \frac{k_{NaCa}}{z \cdot F \cdot V_i} \cdot \frac{1}{1 + k_{sat} \cdot e^{\frac{(r-1) \cdot F}{R \cdot T} \cdot E(t)}} \cdot \\ \cdot (Na_i^3 \cdot Ca_e \cdot e^{\frac{r \cdot F}{R \cdot T} \cdot E(t)} - Na_e^3 \cdot Ca_i \cdot e^{\frac{(r-1) \cdot F}{R \cdot T} \cdot E(t)}) \tag{9}$$

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Ca^{2+} ion flows from intracellular space to reticulum and mitochondria are described with Eq.10 and Eq.11, to regulatory subsystem with Eq.12 and to extracellular space with Eq.13.

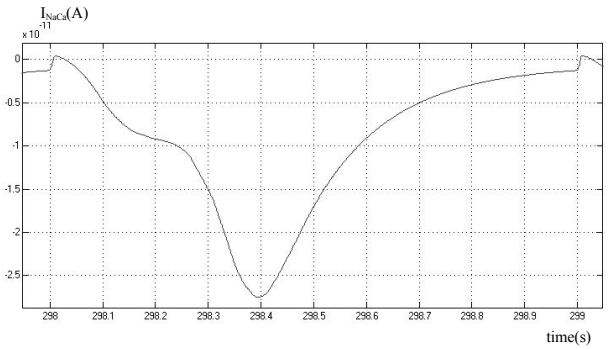

Figure 8: Na-Ca exchager current

$$Q_{iN} = (Ca_i - Ca_{i0}) \cdot k_{iN} \quad (10)$$

$$Q_{iM} = (Ca_i - Ca_{i0}) \cdot k_{iM} \quad (11)$$

$$Q_{iS} = Ca_i \cdot TnC \cdot k_{an} \quad (12)$$

$$Q_{iE} = (Ca_i - Ca_{i0}) \cdot k_{iE} \quad (13)$$

These 13 formulas can completely express ion concentration dynamic changes in compartments during the heart period.

Time constants of reactions were adopted from available literature. [13] [14] [15] [16] Naturally, all the values were not measured during a single physiological experiment and thus these values show some variance with respect to definition of laboratory conditions (temperature, pH) and to animal species. With respect to the difficulty of laboratory experiments and thus of obtaining corresponding measuring results we had to admit this non-uniformity in the model.

All the simulations presented here were carried out under the following conditions: onset of simulation = 0 seconds, total time = 300 s, sample period – variable step (max 0.001 s), integration method ode15s (stiff/NDF), tolerance = 0.0001 s. The model was simulated on a PENTIUM IV processor working station based on Windows XP and Matlab 6 (Simulink 12).

Results

The model was proved to be stable within physiologically relevant ranges. Although only basic relations are considered, after reaching the steady state, all computed values reproduce well the experimental findings. Figure 9 compares the simulated and experimentally measured intracellular Ca_i concentration during a single cycle. Obviously, there is very close correspondence of the simulated data in terms of the course of the Ca_i concentration, while the quantitative comparison, in respect to the great variability of experimental data, is less evident, depending on the species and method used.

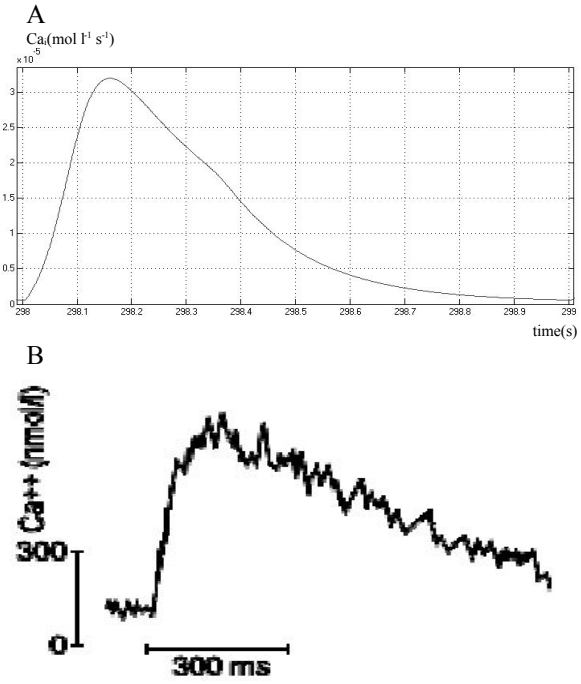

Figure 9: Ca_i concentration during heart cycle (A – simulation results, B – experimental findigs) [17]

Discussion

Major limits of presented model are its simplicity in calcium flow dynamics subsystem and its inconsistency in experimental data used.

Mathematical modeling requires a very strong experimental background supplying both theories for model definitions and real values needed for the computation. The problem often occurs when an extended, consistent set of parameters (concentrations, time constants etc.) is required. Even for a relatively simple model, the extent of experimental data needed usually exceeds the goals of any single experiment. From this point of view, the presented model is rather inconsistent as the data (specifically the concentrations of actomyosin complex at intermediate states) were obtained in different species. [18]

A scientific approach should always attempt to reduce complex phenomena to elementary relations. We have tried to identify a reasonable approach in the definition of complexity-validity relationship. A simple model can represent a real situation to a certain extent, although it may not take into account all known mechanisms. Thus the construction of models of various complexities and subsequent comparison of their simulation results can help in identifying the role of particular pathways and regulatory mechanisms involved in the whole functional system and thereby to reveal the basic mechanisms responsible for the general regulation at various levels. Another advantage of relatively simple models is the practical use, interactivity and easy interpretation. [19] On the other hand, there is no doubt that only extremely complex

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simulators, not limited to a narrow set of carefully described conditions, might finally be suitable for routine clinical work. In order to achieve this complexity, but at the same time to maintain rationally simplifying level of simulations, we have tried to stick to modular approach where elementary, "stand-alone" models will be combined into more complex systems, still with good control, understanding and interactivity.

Conclusions

The model gives result consistent with experimental data. It can provide results reflecting current ion channels and sarcomere state during heart cycle period. Then ion channels attributes impact on sarcomere contractility can be studied. Major limits of this model are shortcomings and inconsistency in experimental data used. It is sometimes almost impossible to gain real values needed for the computation (for example concentrations data and time constants were obtained in different species).

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