Physiol. Res. 50: 425-432, 2001

Mathematical Model of the Electromechanical Heart Contractile System – Regulatory Subsystem Physiological Considerations

M. MLČEK, J. NEUMANN, O. KITTNAR, V. NOVÁK

Institute of Physiology, First Faculty of Medicine, Charles University, Prague, Czech Republic

Received October 25, 2000
Accepted January 11, 2001

Summary

The biochemical model of excitation-contraction coupling in cardiomyocyte is presented and the validity of simulations of both physiological and pathological processes is discussed. The model of regulatory and actomyosin subsystems, even if it is rather simple in its regulatory subunit, gives results well consistent with experimental data. Specifically, intracellular free calcium levels ($[Ca^{2+}]_i$) were computed under various states of sarcoendoplasmic reticular Ca^{2+}-ATPase (SERCA2) and compared to experimental findings. Computed results reproduced well both the increase in resting $[Ca^{2+}]_i$ level and the attenuation of $[Ca^{2+}]_i$ decline commonly observed in heart failure. Thus the computational simulations could help to identify core relations in studied systems by comparing results obtained using similar models of various complexities.

Key words

Myocardial contraction • Excitation-contraction coupling • Simulations

Introduction

Our article deals primarily with molecular level of electromechanical events in cardiac muscle and discusses the results obtained from computational simulations. Computational modeling in molecular cardiology is a promising trend which is believed to help in interpreting huge and ever increasing amount of experimental and clinical data. Various models simulating subsets of myocardial excitation-contraction processes are being developed. Recently, more complex models, which often integrate several elementary approaches, have been introduced.

In the past, electrophysiological processes attracted a lot of attention of both experimental and computational scientists. Recently, increasing interest has been focused upon excitation-contraction coupling (Rice *et al.* 1999, 2000) and mechanical events, in order to elucidate substantial myocardial function – the mechanics, which could further help to explain pathophysiological mechanisms of heart failure.

Sometimes there is a question to find reasonable level of complexity (Kushmerick 1999) because many situations, especially physiological ones, can be surprisingly well reproduced and interpreted by rather simple models. Complex models, on the other hand, can

© 2001 Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic
Fax+4202 24920590
E-mail physres@biomed.cas.cz http://www.biomed.cas.cz/physiolres

be difficult to interpret and/or to be used for reasonable simulations.

We have recently introduced a sophisticated model of actomyosin system accompanied by a simple regulatory subsystem (Neumann *et al.* 1999). Many simulations, especially those of mechanical properties, were performed, having proved the stability and reliability of this model. In this paper we present selected results on free intracellular calcium ($[Ca^{2+}]_i$) behavior as determined by a simple regulatory subunit of the former model and we compare these results with experimental findings.

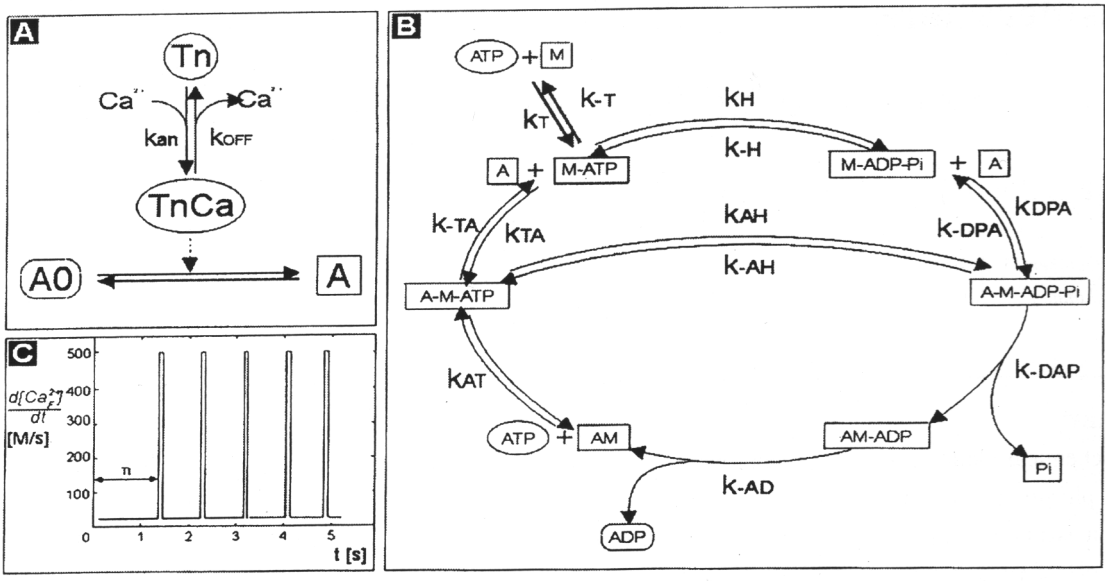

Fig. 1. *Panel A: Regulatory subsystem scheme. Tn – troponin C, AO Actin in restin, non-permissive state. A – actin available for cross-bridge interaction. k_{an} – calcium-troponin association time constant. Panel B: Actomyosin subsystem scheme. A – actin, M – myosin, A-M… – actomyosin weak cross-bridge interaction, AM – actomyosin strong cross bridge interaction (rigor state). k_{xx} – respective time constants. Panel C: The input signal curve representing the ideal time course of the rate of the calcium ions release out of JSR. Tt – transient state time*

Material and Methods

Model construction

The construction of the model involved: 1) identification of the basic reactions, 2) collection of time constants, and 3) setting of initial conditions.

Ad 1) Basic reactions of excitation-contraction coupling based on strong-weak states and filament sliding theories were considered. The model consists of two major subsystems – the regulatory one and the actomyosin one. The reactions adopted are schematically described in Fig 1A and 1B. The reaction kinetic was expressed by the system of ten ordinary non-linear first order differential equations with constant coefficients of biochemical reactions mentioned above (rare constants, denoted as "k"). The constants represent the parameters of the mathematical model (for the relevant equations see Appendix A). Numerical model was implemented in Matlab, Matworks Inc. (Neumann *et al.* 1999). $[Ca^{2+}]_i$ peaks were used as the input signal. These were obtained from a mathematical substitution of the time course of an ideal rate of intracellular calcium concentration change reported from experimental findings (Fozzard *et al.* 1986, Takamatsu and Wier 1990). Thus $d[Ca^{2+}_F]/dt$ (see Fig. 1C) was the only input signal of the model, the mathematical characteristics (e.g. amplitude) of which were chosen to fit the steady-state value of $[Ca^{2+}]_i$ and maximal $[Ca^{2+}]_i$ value (before maximal contraction) during simulation. It should also be noted, that the contribution of calcium passing through the cell membrane directly into sarcomere and other phenomena (e.g. the role of mitochondria) were neglected in this model for the time being.

Ad 2) Time constants of respective reactions were adopted from available literature. (Robertson and Johnson 1981, Eisner 1984, Fozzard *et al.* 1986, Sipido and Wier 1991) 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.

Ad 3) The crucial problem was to determine the initial conditions for the simulations as only few data about the concentrations of relevant molecules at a given instant were hitherto available. It was experimentally found, that after implementing the time constants and setting the known initial conditions, the model reached a steady state within 2 s. Therefore the input signal (defined by rectangular shape with amplitude of 480 [μM/s] and pulse duration of 100 ms) was always applied after 2 s of transient state period (Tt; Fig. 2A) after beginning of the simulation.

Simulations

Various physiological and pathological situations were simulated. All the simulations presented here were carried out under the following conditions: onset of simulation = 0 seconds, total time = 4 or 20 s, sample period = 0.00001 s, integration method Gear, tolerance = 0.0001 s. The model was simulated on a two PENTIUM III processors working station based on Windows NT and Matlab 5.

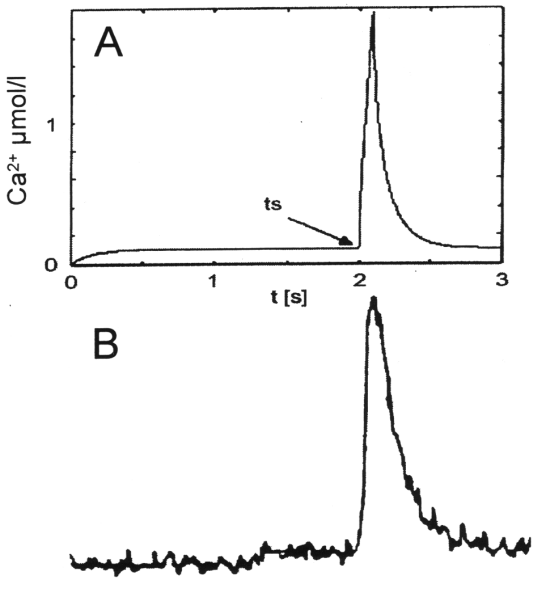

Fig. 2. *[Ca^{2+}]i transient. Panel A: simulation result. t_S – end of transient response. Panel B: experimental finding (Fozzard et al. 1986).*

Results

Physiology

The model was proved to be stable within physiologically (and most pathophysiologically) relevant ranges. Although only basic relations are considered, after reaching the steady state, all computed values reproduce well the experimental findings. As has already been mentioned above, due to the problem with defining the initial conditions, the initial 2 s of simulations were considered as transient response of the model (Fig. 2A; t_S – end of transient response). Figure 2 compares the simulated and experimentally measured intracellular $[Ca^{2+}]_i$ transients during a single cycle (Fozzard *et al.* 1986). Obviously, there is very close correspondence of the simulated data in terms of the course of the $[Ca^{2+}]_i$ transient, while the quantitative comparison, in respect to the great variability of experimental data, is less evident, depending on the species and method used (Del Nido *et al.* 1998).

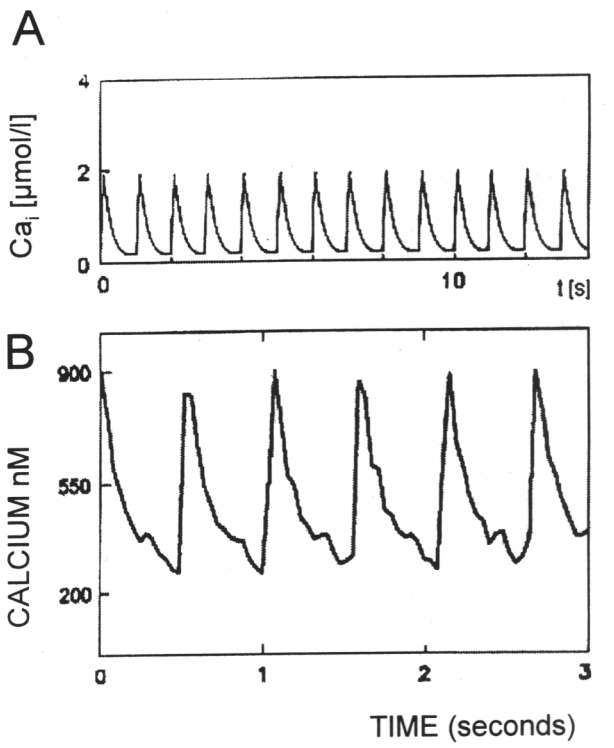

Fig. 3. *Intracellular calcium $[Ca^{2+}]_i$ during several cycles. Panel A: simulation results. Panel B: experimental results (Del Nido et al. 1998).*

Figure 3A shows the stability of our model in long-term simulations. Similar results are obtained at various stimulation frequencies (0.5-2.5 Hz). Again, good conformance with experimental data is documented by

Figure 3B (Del Nido *et al.* 1998). The relationship of frequency and diastolic $[Ca^{2+}]_i$ is also reproduced by the simulations in accordance with experimental findings (Maier *et al.* 1998).

Pathophysiology

A great deal of both physiological and pathological results is presented in our recent study (Novák and Neumann 2000). In the present report we try to discuss specific pathophysiological consequences of selected simulation. The effect of impaired function of the reticular Ca^{2+}-ATPase pump was studied. A set of simulations was performed for various states of sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) represented by the time constant adjustment (k_r = 100, 50 and 25% of reference value) (Takamatsu and Wier 1990). We have thus tried to simulate the situation reported from experimental data obtained from hypertrophied or failing hearts (Schwinger *et al.* 1995, Maier *et al.* 1998, Münch *et al.* 2000). Figure 4A demonstrates computed diastolic steady-state $[Ca^{2+}]_i$ levels (i.e. in time $t \rightarrow \infty$, no stimulation) related to calcium sequestration into the sarcoendoplasmic reticulum (SR) by SERCA2. Diastolic $[Ca^{2+}]_i$ concentrations in the beating heart are higher since the steady-state values are not reached due toi) slowed $[Ca^{2+}]_i$ transient decline and/or ii) increased frequency. Attenuated $[Ca^{2+}]_i$ decline resulting from decreased SERCA2 activity was also successfully simulated. Figure 4B demonstrates both the effect on the Ca^{2+} sequestration and resting $[Ca^{2+}]_i$ level in an overview. On the other hand, the simulation fails to reproduce correctly the amplitude of $[Ca^{2+}]_i$ transient, which is overestimated by the model. This is a consequence of limitations of this model in some calcium handling mechanisms, e.g. Na^+/Ca^{2+} exchange or exact definition of SR compartment. Figure 5A (adopted from Bueckelmann *et al.* 1992) shows experimentally obtained $[Ca^{2+}]_i$ transients from human hearts with terminally failing dilated cardiomyopathy which demonstrate increased resting $[Ca^{2+}]_i$ level, slowed $[Ca^{2+}]_i$ decline and diminished amplitude of $[Ca^{2+}]_i$ transient.

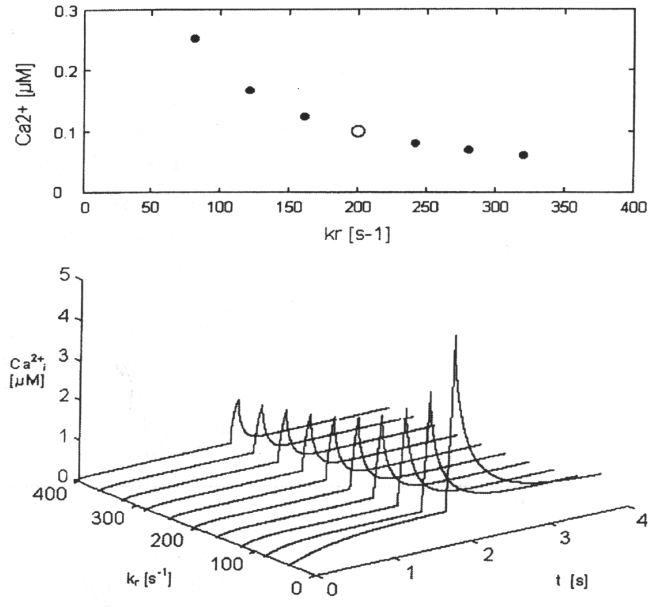

Fig. 4. *Effect of different Ca^{2+} sequestration rates into the sarcoplasmic reticulum by Ca^{2+}-ATPase (SERCA) Panel A: computed diastolic steady-state calcium intracellular concentrations $[Ca^{2+}]_i$.* o *represents reference value for normal Ca^{2+} sequestration rate. Panel B: computed $[Ca^{2+}]_i$ transients. The trend of increased diastolic $[Ca^{2+}]_i$ and slowed $[Ca^{2+}]_i$ decline are demonstrated. Reference value for normal Ca^{2+} sequestration rate is k_r=200. $[Ca^{2+}]_i$ transient peaks are overestimated due to the limits of the model (see the text).*

$[Ca^{2+}]_i$ levels during 14-s simulation, when sequestration rate by reticulum is 30 % lower compared to normal healthy hearts is shown in Figure 5B. The increase in resting $[Ca^{2+}]_i$ level under these conditions is, as stated above, greater than the computed steady-state level already during 1 Hz stimulation frequency (Figs 3 and 4).

According to the simulation results, the increased $[Ca^{2+}]_i$ reaches the level sufficient for troponin conformation change (approx. 0.26 μM) and thus cross-bridge formation in about 50 % of Ca pump activity and 1 Hz pacing. Again as was already mentioned, the peak of the $[Ca^{2+}]_i$ transient is not considered to reproduce the reality accurately enough.

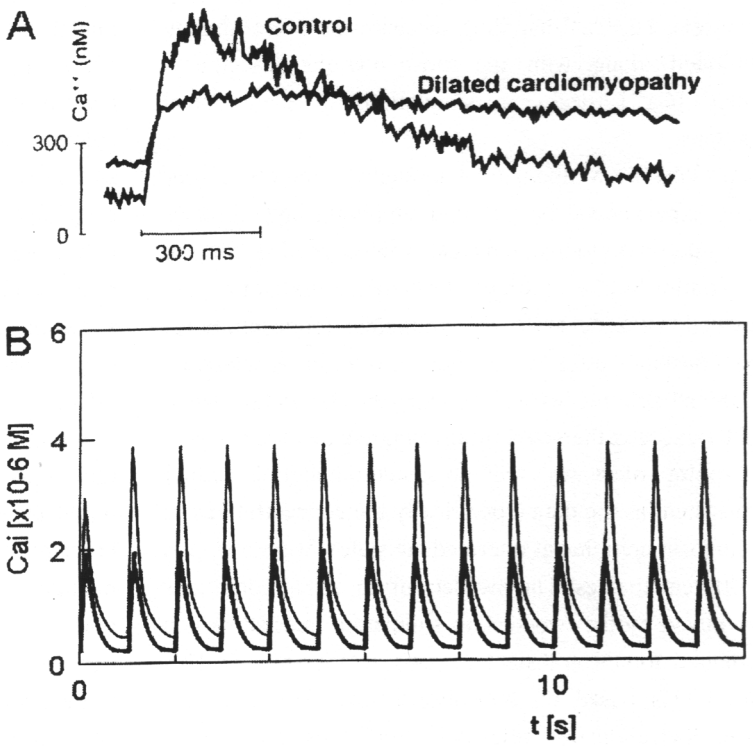

Fig. 5. *Panel A: $[Ca^{2+}]_i$ transients in healthy and failing (terminal stage of dilated cardiomyopathy) human hearts show increased diastolic $[Ca^{2+}]_i$ and decreased recovery slope in failing hearts (adopted from Bueckelmann et al. 1992). Panel B: simulated $[Ca^{2+}]_i$ transients in various Ca^{2+} sequestration rates (gray); 30 % of reference value (black). Difference in diastolic $[Ca^{2+}]_i$ and $[Ca^{2+}]_i$ decline is presented. Both simulations 60 cycles/min. Lower maximum of the first peak reflects the transient period of the model. Calcium transient maximums do not reflect the reality correctly because of the model limits.*

Discussion

Physiology

The presented biochemical model of excitation-contraction coupling has been proved to reproduce many physiologically relevant situations. The fact that only junctional sarcoplasmic reticulum (JSR) and troponin compartments of calcium metabolism were considered is thus consistent with hypothesis that under physiological conditions major part (over 90 %) of calcium intracellular metabolism is realized through the endoplasmic Ca^{2+}-ATPase.

Pathophysiology

The model exhibits limited validity even for simulations of commonly discussed pathophysiological situations related to sarcoplasmic Ca^{2+}-ATPase dysfunction. There is a very good conformity in reproducing increased diastolic $[Ca^{2+}]_i$ levels. A more detailed study has shown that there are several mechanisms contributing to this change: i) increased steady-state $[Ca^{2+}]_i$ level (Fig. 4A), ii) decreased $[Ca^{2+}]_i$ decay (Fig. 4B) and iii) increased heart rate. All of these facts were successfully simulated. According to the computed results, the reduction of Ca^{2+} sequestration rate by SERCA to 50 % (reported from experimental findings of Bueckelmann *et al.* 1992) at 1 Hz stimulation frequency produces $[Ca^{2+}]_i$ rise to 0.3 μM which is sufficient to initiate cross-bridge formation (Gao *et al.* 1994) or relaxation, respectively. These findings are consistent with the hypothesis of molecular origin of diastolic dysfunction in the terminal stages of heart failure (Bueckelmann *et al.* 1992, Schwinger *et al.* 1995, Maier *et al.* 1998, Münch *et al.* 2000,). Because of its shortcomings (Na^+/Ca^{2+} exchanger and further Ca^{2+} handling mechanisms were not implemented), this model cannot yet be temporarily used for wider conclusions. Typically Na^+/Ca^{2+} current is supposed to play an important role in $[Ca^{2+}]_i$ regulation under pathological conditions, thus helping to reduce increased $[Ca^{2+}]_i$ level. There are other pathways, not effective under physiological conditions, which are supposed to play important role in pathological states. With respect to the proposed model, we might conclude that in terminally failing heart the $[Ca^{2+}]_i$ level is crucially frequency-dependent. Thus the increased heart rate, besides detiorating the metabolic and contractility state, also promotes diastolic dysfunction.

Model limitations

Major limits of presented model are i) its simplicity in regulatory subsystem and ii) its inconsistency in experimental data used.

Ad i) The shortcomings of the regulatory subsystem, i.e. Ca^{2+} handling mechanisms, were already mentioned along with the most obvious inaccuracy, namely $[Ca^{2+}]_i$ peaks in simulations of pathological situations.

Ad ii) 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. The problem of the initial conditions was solved by the two-second simulation interval, which accounted for the transient response of our model. This approach is based on our observations that under all simulated (clinically relevant) conditions this model tended to achieve a steady state.

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 (Rice *et al.* 1999). On the other hand, there is no doubt that only extremely complex 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.

Acknowledgements

This work was supported by grant GACR 106/99/0975.

References

BUECKELMANN DJ, NÄBAUER M, ERDMANN E: Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation* **85:** 1046-55, 1992.

DEL NIDO PJ, GLYNN P, BUENAVENTURA P, SALAMA G. KORETSKY AP: Fluorescence measurement of calcium transients in perfused rabbit heart using rhod 2. *Am J Physiol* **274:** H728-H741, 1998.

EISNER DA: Control of intracellular ionized calcium concentration by sarcolemal and intracellular mechanism *J Mol Cell Cardiol* **16:** 137-146, 1984.

FOZZARD HA, HABER E, JENNINGS RB, KATZ AM, MORGAN HE: The Heart and Cardiovascular System, Raven Press, New York, 1986, pp. 1223 - 1227.

GAO WD, BLACKX PH, AZAN-BLACKX M, MARBAN E: Myofilament Ca^{2+} sensitivity in intact verus skinned rat ventricular muscle. *Circ Res* **74:** 408-415, 1994.

KUSHMERICK M: Muscle energetics: simple rules to reduce complexity, 1999 Physiome Symposium: Integrated Biology of the Heart, University of Washington, Seattle, 1999.

MAIER LS, BRANDES R, PIESKE B, BERS DM: Effects of left ventricular hypertrophy on force and Ca^{2+} handling in isolated rat myocardium. *Am J Physiol* **274:** H1361–H1370, 1998.

MÜNCH G, BÖLCK B, BRIXIUS K, REUTER H, MEHLHORN U, BLOCH, W, SCHWINGER RHG: SERCA2a activity correlates with the force-frequency relationship in human myocardium, *Am J Physiol Heart Circ Physiol* **278:** H1924–H1932, 2000.

NEUMANN J, NOVAK V, SOUKUP J: Mathematical model of electromechanical heart contractile system In: Proceedings of the 10th International DAAAM Symposium, DAAAM International, Vienna, 1999. pp. 377-378

NOVAK V, NEUMANN J: Mathematical model of the electromechanical heart contractile system - simulation results. In: CardioModel 2000, Karlsruhe, 2000, CD-ROM.

RICE JJ, JAFRI MS, WINSLOW RL: Modeling short-term interval-force relations in cardiac muscle" *Am. J. Physiol. Heart Circ Physiol* **278:** H913–H931, 2000.

RICE JJ, WINSLOW RL, HUNTER WC: Comparison of putative cooperative mechanisms in cardiac muscle: length dependence and dynamic responses, *Am J Physiol* **276:** H1734–H1754, 1999.

ROBERTSON P, JOHNSON JD: The time-course of Ca^{2+} exchange with calmodulin, troponin, parvalbumin and myosin in response to transient increases in Ca^{2+}, *Biophys J* **34:** 559-569, 1981.

SCHWINGER RHG, BÖHM M, SCHMIDT U, KARCZEWSKI P, BAVENDIEK U, FLESCH M, KRAUSE EG, ERDMANN E: Unchanged protein levels of SERCA II and phospholamban but reduced Ca^{2+} uptake and Ca^{2+}-ATPase activity of cardiac sarcoplasmic reticulum from dilated cardiomyopathy patients compared with patients with nonfailing hearts, *Circulation* **92:** 3220-3228, 1995.

SIPIDO KR, WIER WG: Flux of Ca^{2+} across the sarcoplasmic reticulum of guinea-pig cardiac cells during excitation-contraction coupling, *J. Physiol* **435:** 605-630, 1991

TAKAMATSU T, WIER WG: Calcium waves in mammalian heart, quantification of origin, magnitude, waveform, and velocity, *FASEB J.* 1990.

Reprint requests

M. Mlček, Institute of Physiology, Charles University, Albertov 5, 120 00 Prague 2, Czech Republic. E-mail: mikulas.mlcek@lf1.cuni.cz

Appendix

Units

M = mol/l

B. Mathematical Model

$$\frac{d[A]}{dt} = -k_{TA}\cdot[A]\cdot[M-ATP] + k_{-TA}\cdot[A-M-ATP] - k_{DPA}\cdot[A]\cdot[M-ADP-P_i] +$$
$$+ k_{-DPA}\cdot[A-M-ADP-P_i] + u\cdot k_{ax}\cdot[Ca^{2+}{}_i]\cdot[TnC] - k_{ab}\cdot[A]$$
$$\frac{d[M-ADP-P_i]}{dt} = -k_{DPA}\cdot[A]\cdot[M-ADP-P_i] + k_{-DPA}\cdot[A-M-ADP-P_i] + k_H\cdot[M-ATP] -$$
$$- k_{-H}\cdot[M-ADP-P_i] + w_1\cdot u\cdot k_{ax}\cdot[Ca^{2+}{}_i]\cdot[TnC] - k_{ab}\cdot[M-ADP-P_i]$$
$$\frac{d[A-M-ADP-P_i]}{dt} = -k_{DPA}\cdot[A]\cdot[M-ADP-P_i] - k_{-DPA}\cdot[A-M-ADP-P_i] -$$
$$- k_{-DAP}\cdot[A-M-ADP-P_i] + k_{AH}\cdot[A-M-ATP] - k_{-AH}\cdot[A-M-ADP-P_i]$$
$$\frac{d[AM-ADP]}{dt} = -k_{-AD}\cdot[AM-ADP] + k_{-DAP}\cdot[A-M-ADP-P_i]$$
$$\frac{d[AM]}{dt} = -k_{AT}\cdot[AM]\cdot[ATP] + k_{-AT}\cdot[A-M-ATP] + k_{-AD}\cdot[AM-ADP]$$
$$\frac{d[ATP]}{dt} = -k_{AT}\cdot[AM]\cdot[ATP] + k_{-AT}\cdot[A-M-ATP]$$

$$\frac{d[A-M-ATP]}{dt} = k_{TA}\cdot[A]\cdot[M-ATP] - k_{-TA}\cdot[A-M-ATP] + k_{AT}\cdot[AM]\cdot[ATP] -$$
$$- k_{-AT}\cdot[A-M-ATP] + k_{-AH}\cdot[A-M-ADP-P_i] - k_{AH}\cdot[A-M-ATP]$$
$$\frac{d[M-ATP]}{dt} = k_{-H}\cdot[M-ADP-P_i] - k_{H}\cdot[M-ATP] - k_{TA}\cdot[A]\cdot[M-ATP] +$$
$$+ k_{-TA}\cdot[A-M-ATP] + w_6\cdot u\cdot k_{an}\cdot[Ca^{2+}{}_i]\cdot[TnC] - k_{ab}\cdot[M-ATP]$$
$$\frac{d[TnC]}{dt} = -k_{an}\cdot[Ca^{2+}{}_i]\cdot[TnC] + \frac{1}{u}\cdot k_{ab}\cdot[A]$$
$$\frac{d[Ca^{2+}{}_i]}{dt} = -k_{an}\cdot[Ca^{2+}{}_i]\cdot[TnC] + \frac{1}{u}\cdot k_{ab}\cdot[A] - k_{\gamma}\cdot[Ca^{2+}{}_i] + \frac{d[Ca_F^{2+}]}{dt}$$