COMPUTER MODELLING IN CARDIAC CELL ELECTROPHYSIOLOGY

Michal Pásek*

Experimentally based models of cardiac cells have been developed since 1960. The early models were based on extension of the Hodgkin-Huxley nerve impulse equations. Including only a few membrane currents they were able to successfully reconstruct the depolarization and repolarization of cellular membrane. Since that time, the models have underwent extensive modifications and reached a high degree of physiological detail. This short review is aimed to outline the history of their development and show the importance of computer modelling for the research in cardiac cell electrophysiology.

Key words: *electrophysiology, cardiac cell, quantitative modelling*

1. History of models development

The history of modelling of electrophysiological processes in excitable cells started 50 years ago with the Hodgkin-Huxley model of the giant squid axon [1]. Hodgkin and Huxley's work (for which they were, jointly with J. C. Eccles, awarded the Nobel Prize in 1963) provided the core foundation for mechanistic description of nerve cell function. In 1962, Noble followed their basic idea that the currents are carried by ions moving down the electrochemical gradient and showed that, with certain modifications (for schematic diagram see Fig. 1), the Hodgkin-Huxley formulation may be used to describe the long-lasting action and pacemaker potentials of the Purkinje fibres of the heart [2]. Later, based on the experiments carried out by Noble and Tsien [3], a refined description of the repolarization process in cardiac Purkinje fibres was provided [4].

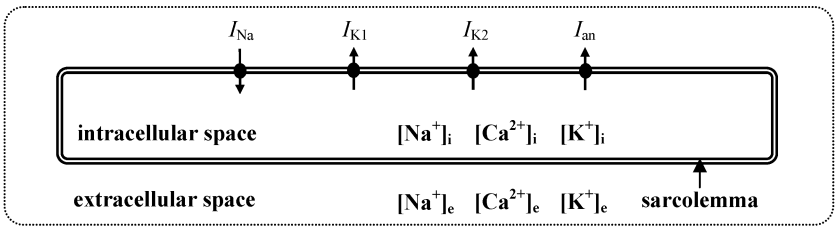

Fig.1: Schematic diagram of the first cardiac cell model (Purkinje fibre) published by Noble in 1962; the currents included in the model were: I_{Na} sodium inward current; I_{K1} time-independent inward rectifier potassium current; I_{K2} delayed rectifier potassium current; I_{an} anion current

* Ing. M. Pásek, Ph.D., Institute of Thermomechanics, Czech Academy of Science, branch Brno, Technická 2, 616 69, Brno and Department of Physiology, Faculty of Medicine, Masaryk University, Komenského nám. 2, 662 43, Brno

The development of cardiac cell models then continued by the work of McAllister et al. [5] who mathematically reconstructed action potential (AP) of Purkinje fibres using nine ionic currents. This model featured a role for Ca^{2+} current (at that time called secondary inward current – I_{si}) in the generation of the AP and introduced a novel Cl^- current (I_{qr}) activated during strong depolarization. In 1977, Beeler and Reuter created a model of ventricular cell action potential [6] that took into account the function of Ca^{2+} as a link between electrical events at the membrane and the contractile responses of the cell. The connection between the membrane potential and changes in internal Ca^{2+} ($[Ca^{2+}]_i$) was bi-directional, so that $[Ca^{2+}]_i$ also influenced Ca^{2+} current (later marked as I_{Ca}). This was an important step for modelling ionic currents not simply as functions of membrane potential but also as functions of ion concentrations which change during the AP. This concise model consisted of only four currents: I_{K1}; I_{X1}; I_{Na} and I_{Ca} plus the stimulus. Despite its simplicity, experimental phenomena like slow recovery from inactivation, frequency dependence of the AP duration, all-or-none repolarization and membrane voltage oscillations were adequately described. The Ca^{2+} ions flowed into a small distribution volume in this model, from which they were removed by an uptake mechanism which reduced $[Ca^{2+}]$ in that compartment exponentially with time constant $\tau = 14\,\text{ms}$, to achieve a resting level of 100 nM. This assumption was made despite the lack of experimental data to ascertain that intracellular ion accumulation or depletion could occur in cardiac cells. However, this initial attempt at modelling intracellular Ca^{2+} flux set the stage for inclusion of newly described mechanisms in addition to ionic currents, e.g., electrogenic pumps and buffers inside the cytoplasm. The integration of such mechanisms was first achieved by Di Francesco and Noble in 1985. At that time, they published a model of cardiac electrical activity, incorporating ionic pumps and concentration changes [7]. This model included formulations for the Na^+-K^+ pump (Na/K-ATPase) and Na^+-Ca^{2+} exchanger (NCX). The sarcoplasmic reticulum (SR) was represented by two compartments, one for Ca^{2+} uptake and another for its release back into the cytoplasm. The mechanism of Ca^{2+} release from SR [8] was described assuming intracellular free Ca^{2+} to be a trigger of the release. Extracellular and intracellular ionic concentrations ($[Na^+]_e$, $[K^+]_e$, $[Ca^{2+}]_e$ and $[Na^+]_i$, $[K^+]_i$, $[Ca^{2+}]_i$) were now variables which enabled this model to successfully reproduce experimental results including; (a) intracellular Na^+ concentration changes produced by variations in $[Na^+]_e$ or by Na^+-K^+ pump block, (b) the Na^+ dependence of the overshoot potential, (c) the shortening of AP duration and suppression of pacemaker activity at high $[K^+]_e$, (d) the increased automaticity at low $[K^+]_e$ and (e) the depolarization to the plateau range with premature depolarizations and low voltage oscillations at very low $[K^+]_e$. The modification of this model done to simulate excitation-contraction coupling and extracellular Ca^{2+} transients in rabbit atrium was subsequently published by Hilgemann and Noble in 1987 [9].

In the 1990s, Yoram Rudy produced a series of papers describing an expanded model of the guinea-pig ventricular myocyte [10, 11, 12]. Based on Beeler and Reuter's description of the mammalian ventricular myocyte, the first version of Luo and Rudy model [10] introduced the dependence of K^+ currents on $[K^+]_e$, the negative-slope characteristic of the time-independent K^+ current, a novel K^+ channel that activates at plateau potentials and a reformulation of the fast Na^+ current taking into account its fast and slow inactivation. This model enabled to simulate various phenomena that involve changes in $[K]_e$, including membrane responses to premature stimuli at different $[K]_e$ and to periodic stimulation at low $[K]_e$. The second version of the Luo and Rudy model [11] represented much more so-

phisticated description of cardiac cell electrophysiology. It included a new description of ionic currents particularly based on experiments from guinea-pig and equations calculating dynamic changes of intracellular ionic concentrations during APs. The intracellular Ca^{2+} handling was improved by a new formulation of network and junction compartment of sarcoplasmic reticulum as well as by an incorporation of intracellular Ca^{2+} buffers (troponin, calmodulin and calsequestrin). Later, the delayed rectifier K^+ current in this model was split into a rapid (I_{Kr}) and a slow component (I_{Ks}) [12], which enabled better analysis of AP repolarization and of its restitution properties.

2. Compartmentalisation of models

While the second version of Luo and Rudy's model has became a classical study used as starting point for development of variety of newer ventricular cell models (e.g. [12, 13, 14, 15, 16]) some of its drawbacks could not be further overlooked. The cytosolic space in this model was described as a single compartment with spatially uniform concentrations of ions. However, there was an increasing evidence that there exists a small restricted subsarcolemmal domain between the L-type Ca^{2+} channels and the junctional SR where Ca^{2+} concentration may transiently reach much higher levels than in the cytosol as a whole [17, 18, 19]. The first attempt to take this phenomenon into account was done in 1993 by Nordin [20] in his model of guinea-pig ventricular myocyte. The cytosolic space in this model was divided into three regions: superficial, medium and deep. Ion flux between these compartments followed a simple gradient diffusion law and the volume of each compartment was empirically adjusted. In spite of being rather a phenomenological description, this division matched experimental data related to rates of change in myoplasmic $[Ca^{2+}]$ [21]. A similar approach was adopted by Nygren et al. in their model of human atrial cell published in 1998 [22]. To simulate transient accumulation of submembrane Ca^{2+}, a small cleft subspace was used in this model. At the same time, Jafri et al. [23] published a ventricular cell model with a more specific subspace: a restricted volume located between the junctional SR and the T-tubules. It possessed a buffer (calmodulin) and was the place where the L-type Ca^{2+} channels and the ryanodine receptors (part of SR Ca^{2+} release channels) interacted. This representation allowed to explore the mutual interplay between the function of ryanodine receptors and SR load and to investigate their effect on cardiac action potential. Later, an analogous scheme was used in the models of canine, rat and mouse ventricular myocytes [24, 25, 26]. In 2004, Shannon et al. [52] modified this model conception by adding a second subsarcolemmal space to comply with new experimental observations showing that some membrane proteins sense ionic concentrations that differ from those in bulk cytosol and cleft subspace [27, 28, 29]. The architecture of this model appeared to be more suited to account for the essential macroscopic features of excitation-contraction (E-C) coupling.

3. Models incorporating local control of Ca^{2+}-induced Ca^{2+} release

A critical characteristic of the models described in the previous section is the presence of common subsarcolemmal cleft space into which the Ca^{2+}-flux through sarcolemmal L-type Ca^{2+}-channels as well as through SR Ca^{2+} release channels is directed. The result of this physical arrangement is that once the SR Ca^{2+} release is initiated by Ca^{2+} from L-type Ca^{2+} channels, the increase of its concentration in the 'common-pool' stimulates regenerative, all-or none Ca^{2+} release. However, this was in contradiction with experimental results

showing that the rate and amount of SR Ca^{2+} release is tightly controlled by the magnitude and duration of the L-type Ca^{2+} current ($I_{Ca,L}$) so that increasing $I_{Ca,L}$ produces graded Ca^{2+} release [30, 31, 32]. A way to overcome this problems associated with common-pool models was suggested already in 1992 by Stern at al. [33] who proposed that this paradox of control might be explained if the stimulus for Ca^{2+} release were actually the local nanodomains of $[Ca^{2+}]$ generated by nearby L-type channels, rather than the global cytosolic $[Ca^{2+}]$. According to this local control hypothesis, the graded control of macroscopic Ca^{2+} release from SR would actually be achieved by graded statistical recruitment of individual, autonomous, stochastic release events. The junctional space with its functional L-type and SR Ca^{2+} channels and the adjacent element of junctional SR was called Ca^{2+} release unit (CRU). The first CRU model consisting of one L-type channel and one SR release channel was able to reproduce graded release and high gain (ratio $I_{SR,peak}/I_{Ca,peak}$) with the duration of macroscopic $I_{Ca,L}$ [33]. The more recent model of Rice et al. [34] used more complex gating schemes of both channels but ignored spatial Ca^{2+} gradients in the junctional space. Furthermore, their CRUs which contained one L-type channel and eight SR release channels were uncoupled when myoplasmic and network SR Ca^{2+} concentrations were low. The first integrative model that conformed to local control theory was published by Greenstein and Winslow in 2002 [35]. This model also ignored spatial gradients within the CRU, but coupled CRUs via average cytosolic $[Ca^{2+}]$ and membrane currents. Despite the ability of these models to reliably reproduce key properties of cardiac E-C coupling, only a small number of truly integrative models of local control that relate the cellular behaviour to the ensemble properties of E-C coupling have been developed to day. The main reason remains their high complexity even if simplified [36, 37].

4. Models incorporating transverse-axial tubular system

The importance of changes of ion concentrations in the clefts between cardiac cells is well recognised [38, 39]. However, despite the experimental evidence suggesting that restricted ion diffusion coupled with ion fluxes in cardiac transverse-axial tubular system (TATS) may also produce significant changes of ion concentrations in its lumen [40, 41, 42] the possible consequences of tubular ion accumulation or depletion has only rarely been considered. The first attempt to integrate a quantitative description of the TATS with a simple model of cardiac ventricular cell was done by our group in 2001 [43]. Shortly afterwards, we incorporated TATS into a modified ventricular cell model of Jafri et al. [23] and published a pioneering study [44] pointing out that the changes of tubular ion concentrations may be sufficient enough to modulate membrane currents. This raised another question: can ion concentration changes in TATS modulate cellular function and how potent is this modulation in different species? To answer these questions we incorporated TATS into our models of rat (Fig. 2) and guinea-pig ventricular myocytes [45, 46] respecting the experimentally observed differences in these two species. The comparison of the outputs of simulations in these two models gave interesting results: in both models, the variations of tubular ion concentrations reduced the intracellular Ca^{2+} load and consequently the systolic Ca^{2+} transient. However, the magnitude of this effect and its frequency-dependence were much more prominent in the rat model. The main reason of these differences lied in the different frequency-dependence of $I_{Ca,L}$ (positive in rat, negative in guinea-pig) and in different fraction of tubular $I_{Ca,L}$ in both models (87 % in rat [47], 64 % in guinea-pig [41]). Thus, at physiological stimulation frequencies, the ion concentration changes in TATS appear to play more important role in

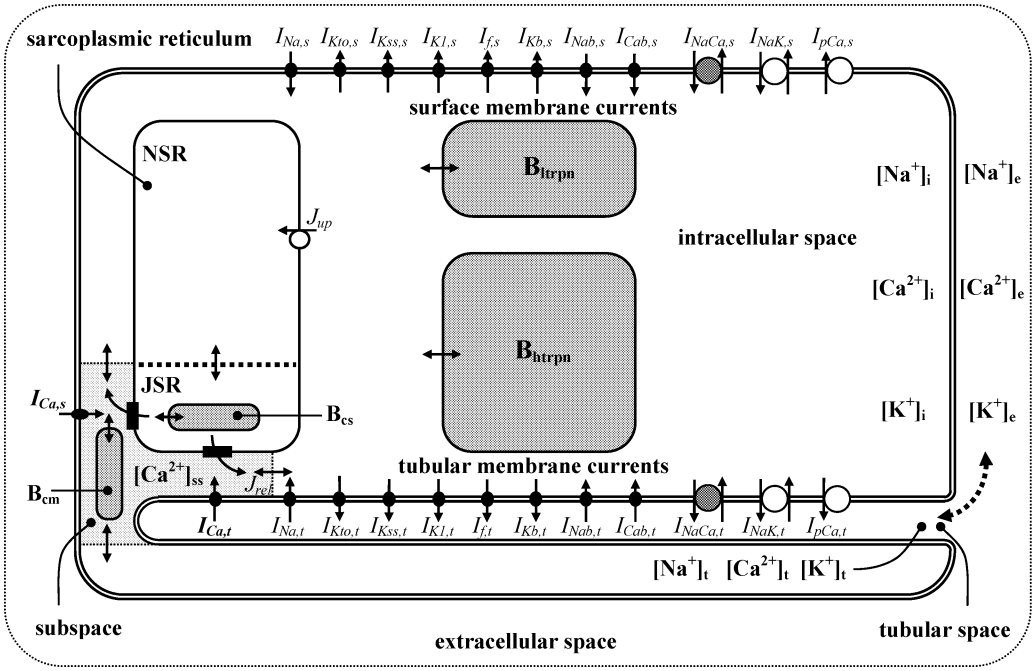

Fig.2: Schematic diagram of the rat ventricular cell model with TATS published by Pásek et al. in 2006. The description of electrical activity of surface (s) and tubular (t) membrane comprises formulation of ion transporters that are labelled in the scheme. The intracellular space contains the subspace, the Ca^{2+}-uptake and Ca^{2+}-release compartments of sarcoplasmic reticulum (NSR, JSR) and the Ca^{2+} buffers: calmodulin (B_{cm}), troponin (B_{ltrpn}, B_{htrpn}) and calsequestrin (B_{cs}). The small filled rectangles in JSR membrane represent SR Ca^{2+}-release channels. The small bi-directional arrows denote Ca^{2+} diffusion. The dashed arrow represents ionic diffusion between the tubular and the bulk space. The currents included in the model were: I_{Na}, sodium inward current; I_{Ca}, calcium inward current; I_{Kto}, time-dependent transient outward potassium current; I_{Kss}, steady-state outward potassium current; I_{K1}, time-independent inward rectifier potassium current; I_f, hyperpolarization-activated current; I_{Nab}, background sodium current; I_{Cab}, background calcium current; I_{Kb}, background potassium current; I_{NaCa}, Na^+-Ca^{2+}-exchanger current; I_{NaK}, electrogenic Na^+-K^+ pump current; I_{pCa}, Ca-pump current

rat than in guinea-pig myocytes. Despite these differences and the limitation in description of excitation-contraction coupling, both models provide strong theoretical evidence that ion concentration changes in the TATS lumen modulate the activity of ventricular myocytes (for review see [48]).

5. Conclusion

In his seminal book, *Introduction a l'étude de la médicine expérimentale* [49], Claude Bernard wrote 'Cette application des mathématiques aux phénomènes naturels est le but de toute science' (This application of mathematics to natural phenomena is the aim of all science). Nowadays, the wide use of mathematical models in medical sciences shows that we are approaching this dream. Although there is much that remains unknown, computer

models can help us to explore the role and importance of various events in such a complex system as the human body. Regarding cardiac cell electrophysiology, the way to such models and their use to explore cellular processes are given above. Current challenges are to model the consequences of the reduction of TATS in pathological conditions [50, 51], the cellular activity under genetically induced dysfunctions of membrane transporters, the effect of various drugs on cardiac cell function and the interconnection between cellular electrophysiology and bioenergetics. Moreover, this all should be particularly done using the human models. As always, new questions will appear, but the combination of experimental and computational approaches promises to be powerful way to answer them.

Acknowledgments

This study was supported by the project AV0Z 20760514 from the Institute of Thermomechanics of Czech Academy of Science. I thank Assoc. Prof. J. Šimurda and Dr. G. Christé for helpful comments on the manuscript.

References

[1] Hodgkin A.L., Huxley A.F.: A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol., Vol. 117, 1952, p. 500–544

[2] Noble D.: A modification of the Hodgkin-Huxley equations applicable to Purkinje fibre action and pacemaker potentials. J. Physiol., Vol. 160, 1962, p. 317–352

[3] Noble D., Tsien R.W.: Outward membrane currents activated in the plateau range of potentials in cardiac Purkinje fibres, J. Physiol., Vol. 200, 1969, p. 205–231

[4] Noble D., Tsien R.W.: Reconstruction of the repolarization process in cardiac Purkinje fibres based on voltage clamp measurements of membrane current, J. Physiol., Vol. 200, 1969, p. 233–254

[5] McAllister R.E., Noble D., Tsien R.W.: Reconstruction of the electrical activity of cardiac Purkinje fibres, J. Physiol., Vol. 251, 1975, p. 1–59

[6] Beeler G.W., Reuter H.: Reconstruction of the action potential of ventricular myocardial fibers, J. Physiol., Vol. 268, 1977, p. 177–210

[7] Di Francesco D., Noble D.: A model of cardiac electrical activity incorporating ionic pumps and concentration changes, Phil. Trans. Roy. Soc. London, Vol. 307, 1985, p. 353–398

[8] Fabiato A., Fabiato F.: Contractions induced by a calcium-triggered release of calcium from the sarcoplasmic reticulum of single skinned cardiac cells, J. Physiol., Vol. 249, 1975, p. 469–495

[9] Hilgemann D.W., Noble D.: Excitation-contraction coupling and extracellular calcium transients in rabbit atrium: reconstruction of basic cellular mechanisms, Proc. Roy. Soc. London B, Vol. 230, 1987, p. 163–205

[10] Luo C.H., Rudy Y.: A model of the ventricular cardiac action potential, depolarization, repolarization and their interaction, Circ. Res., Vol. 68, 1991, p. 1501–1526

[11] Luo C.H., Rudy Y.: A dynamic model of the cardiac ventricular action potential. I Simulations of ionic currents and concentrations changes, Circ. Res., Vol. 74, 1994, p. 1071–1096

[12] Zeng J., Laurita K.R., Rosenbaum D.S., Rudy Y.: Two components of the delayed rectifier K^+ current in ventricular myocytes of the guinea pig type: theoretical formulation and their role in repolarization, Circ. Res., Vol. 7, 1995, p. 140–152

[13] Priebe L., Beuckelmann D.J.: Simulation study of cellular electric properties in heart failure, Circ. Res., Vol. 82, 1988, p. 1206–1223

[14] Courtemanche M., Ramirez R.J., Nattel S.: Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model, Am. J. Physiol., Vol. 44, 1998, p. H301–H321

[15] Puglisi J.L., Bers D.M.: LabHEART: an interactive computer model of rabbit ventricular myocyte ion channels and Ca transport, Am. J. Physiol. Cell Physiol., Vol. 281, 2001, p. C2049–C2060

[16] Fox J.J., McHarg J.L., Gilmour R.F.: Ionic mechanism of electrical alternans, Am. J. Physiol. Heart Circ. Physiol., Vol. 282, 2002, p. H516–H530
[17] Bers D.M., Peskoff A.: Diffusion around a cardiac calcium channel and the role of surface bound calcium, Biophys. J., Vol. 59, 1991, p. 703–721
[18] Stern M.D., Lakatta E.G.: Excitation-contraction coupling in the heart: the state of the question, FASEB J., Vol. 6, 1992, p. 3092–3100
[19] Sun X.H., Protasi F., Takahashi M., Takeshima H., Ferguson D.G., Franzini-Armstrong C.: Molecular architecture of membranes involved in excitation-contraction coupling of cardiac muscle, J. Cell Biol., Vol. 129, 1995, p. 659–671
[20] Nordin C.: Computer model of membrane currents and intracellular Ca flux in the isolated guinea pig ventricular myocyte, Am. J. Physiol., Vol. 34, 1993, p. H2117–H2136
[21] Nordin C., Ming Z.: Computer model of current-induced early after-depolarizations in guinea pig ventricular myocytes, Am. J. Physiol., Vol. 37, 1995, p. H2440–H2459
[22] Nygren A., Fiset C., Firek L., Clark J.W., Lindblad D.S., Clark R.B., Giles W.R.: Mathematical model of an adult human atrial cell: the role of K^+ currents in repolarization, Circ. Res., Vol. 82, 1998, p. 63–81
[23] Jafri M.S., Rice J.J., Winslow R.L.: Cardiac Ca^{2+} dynamics: the roles of ryanodine receptor adaptation and sarcoplasmic reticulum load, Biophys. J., Vol. 74, 1998, p. 1149–1168
[24] Winslow R.L., Rice J., Jafri S., Marbán E., O'Rourke B.: Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, II-Model studies, Circ. Res., Vol. 84, 1999, p. 571–586
[25] Pandit S.V., Clark R.B., Giles W.R., Demir S.S.: A mathematical model of action potential heterogeneity in adult left ventricular myocytes, Biophys. J., Vol. 81, 2001, p. 3029–3051
[26] Bondarenko V.E., Szigeti G.P., Bett G.C., Kim S.J., Rasmusson R.L.: Computer model of action potential of mouse ventricular myocytes, Am. J. Physiol. Heart Circ. Physiol., Vol. 287, 2004, p. H1378–H1403
[27] Matsuoka S., Nicoll D.A., Hryshko L.V., Levitski D.O., Weiss J.N., Philipson K.D.: Regulation of the cardiac Na^+-Ca^{2+} exchanger by Ca^{2+}, J. Gen. Physiol., Vol. 105, 1995, p. 403–420
[28] Trafford A.W., Diaz M.E., O'Neill S.C., Eisner D.A.: Comparison of subsarcolemmal and bulk calcium concentration during spontaneous calcium release in rat ventricular myocytes, J. Physiol., Vol. 488, 1995, p. 577–586
[29] Weber C.R., Piacentino V., Ginsburg K.S., Houser S.R., Bers D.M.: Na^+-Ca^{2+} exchange current and submembrane $[Ca^{2+}]$ during the cardiac action potential, Circ. Res., Vol. 90, 2002, p. 182–189
[30] Lopez-Lopez J.R., Shacklock P.S., Balke C.W., Wier W.G.: Local calcium transients triggered by single L-type calcium channel currents in cardiac cells, Science, Vol. 268, 1995, p. 1042–1045
[31] Cannell M.B., Cheby H., Lederer W.J.: The control of calcium release in heart muscle, Science, Vol. 268, 1995, p. 1045–1049
[32] Rios E., Stern M.D.: Calcium in close quarters: microdomain feedback in excitation-contraction coupling and other cell biological phenomena, Annu. Rev. Biophys. Biomol. Struct., Vol. 26, 1997, p. 47–82
[33] Stern M.D.: Theory of excitation-contraction coupling in cardiac muscle. Biophys. J., Vol. 63, 1992, p. 497–517
[34] Rice J.J., Jafri M.S., Winslow R.L.: Modeling gain and gradedness of Ca^{2+} release in the functional unit of the cardiac diadic space, Biophys. J., Vol. 77, 1999, p. 1871–1884
[35] Greenstein J.L., Winslow R.L.: An integrative model of the cardiac ventricular myocyte incorporating local control of Ca^{2+} release, Biophys. J., Vol. 83, 2002, p. 2918–2945
[36] Hinch R., Greenstein J.L., Tanskanen A.J., Xu L., Winslow R.L.: A simplified local control model of calcium-induced calcium release in cardiac ventricular myocytes, Biophys. J., Vol. 87, 2004, p. 3723–3736
[37] Greenstein J.L., Hinch R., Winslow R.L.: Mechanisms of Excitation-Contraction Coupling in an Integrative Model of the Cardiac Ventricular Myocyte, Biophys. J., Vol. 90, 2006, p. 77–91
[38] McGuigan, J.A.S.: Some limitations of the double sucrose gap and its use in a study of the slow outward current in mammalian ventricular muscle, J. Physiol., Vol. 240, 1974, p. 775–806

[39] Attwell D., Cohen I., Eisner D.: Membrane potential and ion concentration stability conditions for a cell with restricted extracellular space, Proc. R. Soc. London, Vol. 206, 1979, p. 145–161
[40] Yao A., Spitzer K.W., Ito N., Zaniboni M., Lorell B.H., Barry W.H.: The restriction of diffusion of cations at the external surface of cardiac myocytes varies between species, Cell Calcium, Vol. 22, 1997, p. 431–438
[41] Shepherd N., McDonough H.B.: Ionic diffusion in transverse tubules of cardiac ventricular myocytes, Am. J. Physiol., Vol. 275, 1998, p. H852–H860
[42] Blatter L.A., Niggli E.: Confocal near-membrane detection of calcium in cardiac myocytes, Cell Calcium, Vol. 23, 1998, p. 269–279
[43] Pásek M., Christé G., Šimurda J.: Computer modelling of effect of transversal tubules on excitation – contraction coupling in cardiac cells (Basic study), In: CD of the conference Engineering Mechanics, Svratka, 2001
[44] Pásek M., Christé G., Šimurda J.: A quantitative model of cardiac ventricular cell incorporating the transverse-axial tubular system, Gen. Physiol. Biophys., Vol. 22, 2003, p. 355–368
[45] Pásek M., Šimurda J., Christé G.: The functional role of cardiac T-tubules in a model of rat ventricular myocytes, Phil. Trans. R. Soc. A, Vol. 364, 2006, p. 1187–1206
[46] Pásek M., Šimurda J., Orchard C.H., Christé G.: A model of the guinea-pig ventricular cardiac myocyte incorporating a transverse-axial tubular system, Prog. Biophys. Mol. Biol., Vol. 96, 2008, p. 258–280
[47] Brette F., Orchard C.: T-tubule function in mammalian cardiac myocytes, Circ. Res., Vol. 92, 2003, p. 1182–1192
[48] Pásek M., Šimurda J., Christé G., Orchard C.H.: Modelling the cardiac transverse-axial tubular system (review), Prog. Biophys. Mol. Biol., Vol. 96, 2008, p. 226–243
[49] Bernard C.: Introduction a l'étude de la médicine expérimentale, Flammarion, Paris, 1865.
[50] Balijepalli R.C., Lokuta A.J., Maertz N.A., Buck J.M., Haworth R.A., Valdivia H.H., Kamp T.J.: Depletion of t-tubules and specific subcellular changes in sarcolemmal proteins in tachycardia-induced heart failure, Cardiovasc. Res., Vol. 59, 2003, p. 67–77
[51] Louch W.E., Bito V., Heinzel F.R., Macianskiene R., Vanhaecke J., Flameng W., Mubagwa K., Sipido K.R.: Reduced synchrony of Ca^{2+} release with loss of T-tubules – a comparison to Ca^{2+} release in human failing cardiomyocytes, Cardiovasc. Res., Vol. 62, 2004, p. 63–67
[52] Shannon T.R., Wang F., Puglisi J., Weber C., Bers D.M.: A mathematical treatment of integrated Ca dynamics within the ventricular myocyte, Biophys. J., Vol. 87, 2004, p. 3351–71

Received in editor's office: March 13, 2008
Approved for publishing: May 20, 2008