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COMPUTER MODELLING OF EFFECT OF TRANSVERSAL TUBULES ON EXCITATION-CONTRACTION COUPLING IN CARDIAC CELLS (BASIC STUDY)

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Summary: ***The transverse tubular system (T-system) of cardiac muscle is a structure that allows rapid propagation of excitation into the cell interior. As suggested in many resent experimental works it could have a significant effect on cardiac cell function induced by the accumulation or the depletion of ions in restricted tubular space. The aim of our work was to design a mathematical model of electrical activity of cardiac cell including a quantitative description of T-system function and to explore the physiological significance of T-system in excitation-contraction coupling quantitatively.***

1. INTRODUCTION

The transverse tubular system (T-system) is a spatial structure that penetrates deeply inside cardiac muscle cell (Fig. 1- as adopted from [1]). It provides both a rapid inward spread of electrical excitation and the calcium influx that triggers calcium release from sarcoplasmic reticulum [2]. As follows from resent experimental studies [3, 4, 5] the accumulation and depletion of ions in restricted tubular spaces (average diameter of rat T-tubules is 255 nm [1]) may play a significant role in modulation of cellular electrical activity.

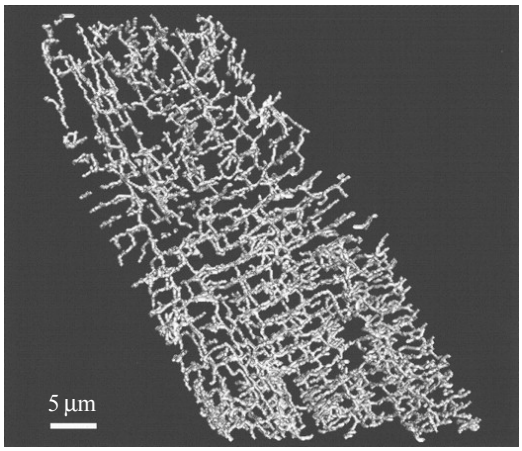

Figure 1*: Three-dimensional skeleton of the tubular system in a rat ventricular myocytes*

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To study the effect of T-system on electrical activity of cardiac cell, we have designed a model of ventricular action potential including the description of T-system function. The preliminary simulations performed on a simplified version of the model clearly indicated the origin of cardiac rhythm irregularities as due to the variations of tubular ion concentrations.

2. METHODS

Generally, the approach is based on a numerical reconstruction of ventricular action potentials using Hodgkin-Huxley formalism. To make preliminary simulations, simple models of the surface membrane electrical activity and the T-system electrical activity were designed, both based on the quantitative description of Luo and Rudy 1991 [6] with modified description of I_{Na}-channel gating [7]. The both models were subsequently interconnected according to the scheme in Fig. 2 where the R_{st} and R_{spipe} denote the total series resistance of T-tubules and the series resistance of the microelectrode, respectively.

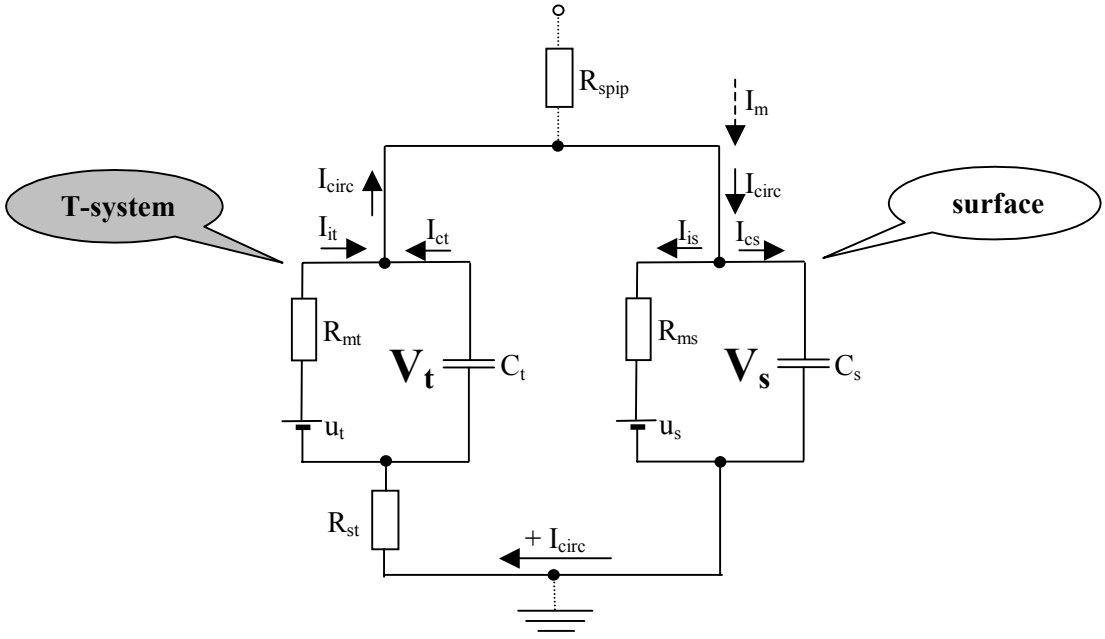

Figure 2: *The scheme representing the electrical interaction between the surface membrane and T-system*

As follows from Fig. 2, the magnitude of surface membrane voltage (V_s) and tubular membrane voltage (V_t) can be computed by solving the following differential equations:

$$\frac{dV_s}{dt} = \frac{I_{c_s}(V_s,t)}{C_s} = \frac{I_m + I_{circ}(V_s,V_t) - I_{i_s}(V_s,t)}{C_s},$$

and $$\frac{dV_t}{dt} = \frac{-I_{c_t}(V_t,t)}{C_t} = \frac{-I_{circ}(V_s,V_t) + I_{i_s}(V_t,t)}{C_t},$$

where I_{circ} is the circulation current ($I_{circ}=(V_s - V_t)/R_{st}$) and I_m is stimulation depolarizing current.

The diffusion of ions between the bulk solution and the T-system ($J_{i,bt}$) is described by the Fick's diffusion equations in the form:

$$J_{i,bt} = \frac{V_t}{\tau_i} \cdot \Delta X_{i,tb},$$

where V_t is effective total tubular volume, τ_i is the time constant of exchange of ion i between tubule lumen and bulk external solution (for these simulations τ_i was set to 65 ms [8]) and $\Delta X_{i,tb}$ denotes the concentration difference between bulk and T-system.

An important part of the model design is the choice of the parameters of the T-system governing its electrical activity.

The total series resistance of the T-system (R_{st}) was calculated from the equation:

$$R_{st} = R_{ext} \cdot \frac{0.5 \cdot l_t}{\pi \cdot r_t^2 \cdot n_t},$$

taking into account the specific resistivity of extracellular solution R_{ext} (for the Tyrode solution $R_{ext} \approx 83{,}33\ \Omega{\cdot}cm$), average radius of T-tubule r_t (for rat myocytes $r_t \approx 127 \cdot 10^{-7}\ cm$ [1]), the effective length of T-tubule l_t and finally the number of T-tubules n_t for the given area of surface membrane.

According to the model of Luo and Rudy 1991 [6] this simple model was related to $1\ cm^2$ of membrane area. As suggested in [1] this area contains approximately $2.78 \cdot 10^7$ tubules. The effective length of T-tubule was preliminary set to 4.493 μm and thus the effective total tubular volume was *6.374 nl* (approximately *1.2 %* of the total intracellular volume) and effective total tubular area was $1\ cm^2$ (equal value as the area of surface membrane). Consequently, the total capacity of the T-system as well as capacity of the surface membrane was $1 \mu F$.

The density of ionic channels in the T-system versus the surface membrane was proposed to be:

- equal for I_{Na}-channels [9, 10],
- 2 times higher for I_{Ca}-channels [10],
- 4 times lower for I_K-channels [11],
- 4 times higher for I_{to}-channels [3, 12],
- equal for plateau (I_{Kp}) and background (I_{Kb}) potassium currents (localization is unknown).

Assuming the above distribution of ionic channels in surface and tubular membrane and the total channel conductances as proposed in Luo and Rudy model [6] for $K_e = 5.4\ mM$ (Tab. 1) the partial surface and tubular membrane conductances were determined (Tab. 1).

***Table 1**: Conductivities of the surface and the tubular membrane used in the model*

	Luo and Rudy model	surface membrane	tubular membrane
G_{Na} [mS/cm^2]	23	23	23
G_{Ca} [mS/cm^2]	**0.09**	**0.06**	**0.12**
G_K [mS/cm^2]	**0.282**	**0.452**	**0.113**
G_{K1} [mS/cm^2]	**0.6047**	**0.242**	**0.968**
G_{Kp} [mS/cm^2]	0.0183	0.0183	0.0183
G_{Kb} [mS/cm^2]	0.03921	0.03921	0.03921

The model of ventricular cell was implemented in the program system MATLAB 5.3 and the numerical computation of 16 differential equation was performed using the solver for stiff systems ODE-15s with a maximal step size of $3 \cdot 10^{-4}\ ms$.

3. RESULTS OF QUANTITATIVE MODELLING

To explore the functional consequences of T-system, the preliminary simulations were performed on both the model including T-system and the model without T-system. Striking differences were observed at low bulk potassium concentration (K_b). For example the decrease of K_b by *68 %* (physiological K_b is *5.4 mM*) induced spontaneous activity in the model without T-system (Fig. 3B) in contrast to the model including T-system (Fig. 3A).

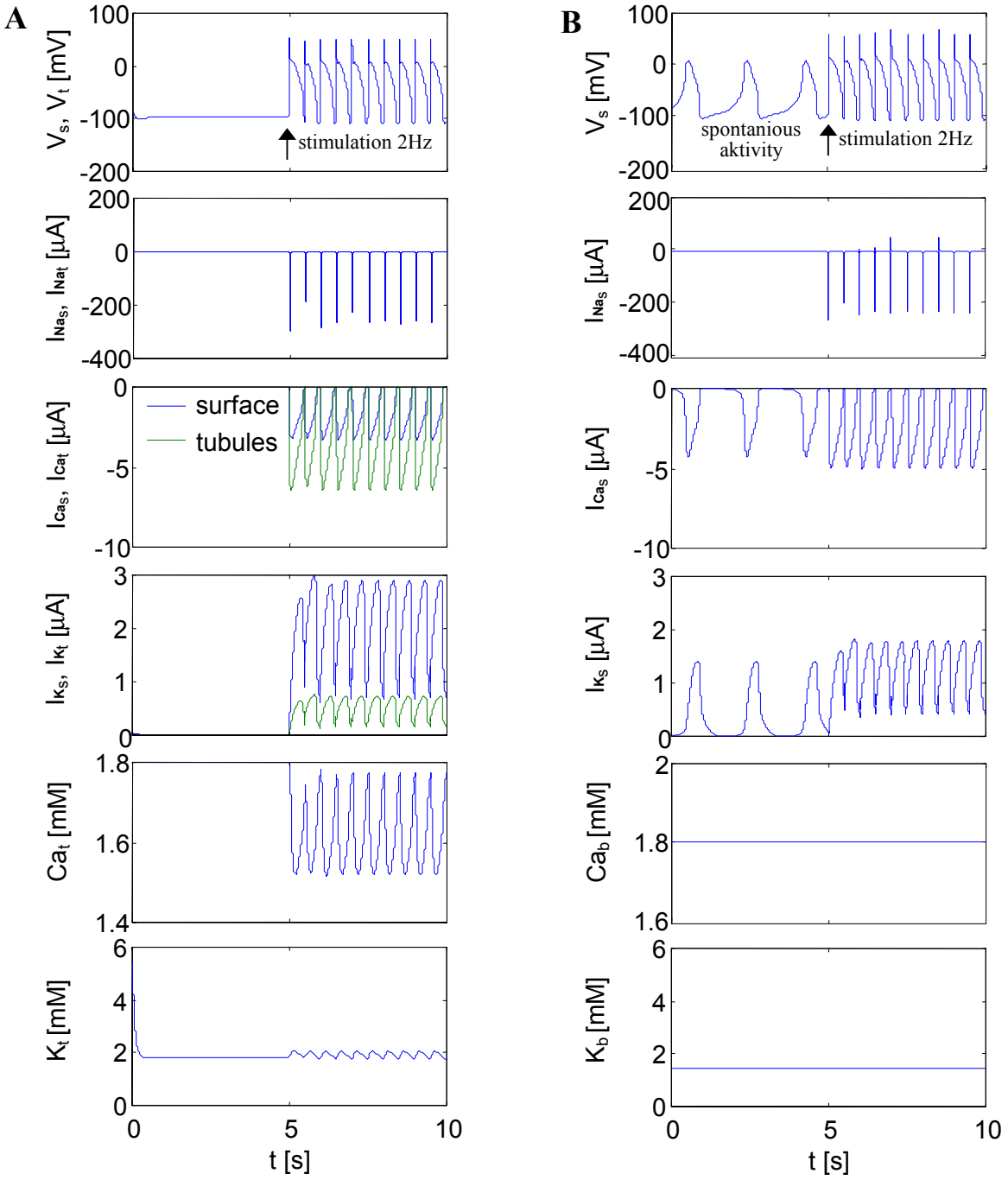

Figure 3: *Comparison of the simulations of electrical activity of ventricular cell at K_b=1.7 mM. The symbols denote the surface and the tubular membrane action voltages (V_s,V_t), inward currents (I_{Na_s} ,I_{Na_t},I_{Ca_s} I_{Ca_t}), outward currents (I_{K_s} ,I_{K_t}, I_{K1_s} I_{K1_t}), tubular and bulk concentrations (K_t,Ca_t K_b,Ca_b) A: Simulation on the model including the T-system. B: Simulations on the model without the T-system.*

The decrease of bulk potassium concentration by *81 %* at the stimulation frequency *2 Hz* led to the development of action potential irregularities only in the model including T-system (Fig. 4A). As followed from the analyses of the phenomenon observed in Fig. 4A, action potential irregularities resulted from initial conditions of membrane voltage and I_{Na}-channel gating. For example at *1.5 s* the I_{Na}-channels are not completely recovered and membrane voltage is more negative so that the stimulating pulse doesn't supply charge enough to reach the threshold for channel activation ($I_{Na} \approx 0$). At *2 s* the I_{Na}-channels are unavailable because of previous spontaneous depolarisation due to decreased conductivity of K_e-dependent potassium channels.

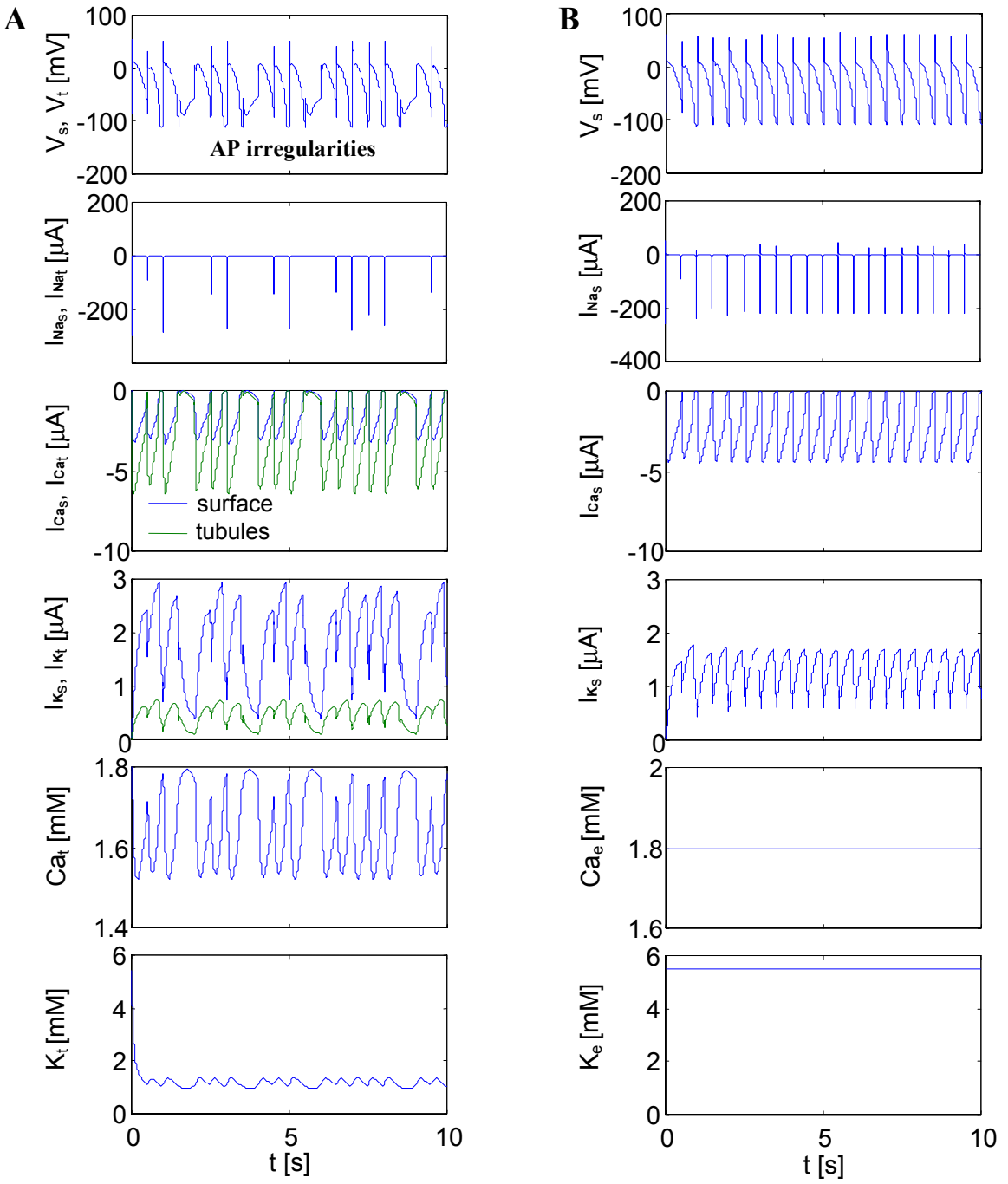

Figure 4: *Comparison of the simulations of electrical activity of ventricular cell at K_b=1 mM and stimulation frequency 2 Hz. The description of displayed quantities is the same as in Fig. 3. A: Simulation on the model including the T-system. B: Simulations on the model without the T-system.*

4. CONCLUSION

It appears clearly that both K^+ and Ca^{2+} tubular concentrations change during activity, leading to depletion of luminal Ca^{2+} ions and accumulation of luminal K^+ ions. Simulation of decreased bulk external K^+ concentration (as encountered in hypokalaemia in clinical settings) suggests that the T-tubule network may play a stabilizing role (preventing spontaneous depolarization) or a arrhythmogenic role under further lowering external K^+. In-depth analysis of such phenomena might contribute to explain hitherto poorly understood focal ventricular arrhythmogenesis. The present results already suggest that the T-tubule itself may be the site of origin of certain arrhythmias.

5. ACKNOWLEDGMENTS

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6. REFERENCES

[1] Soeller C., Cannell M. B.: Examination of the transverse tubular system in living cardiac rat myocytes by 2-photon microscopy and digital image-processing techniques*, Circ. Res*., 1999, 19;84(3):266-75.

[2] Cheng H., Cannell M. B., Lederer W. J.: Propagation of excitation-contraction coupling into ventricular myocytes, *Pflügers Arch*., 1994, 428:415-417.

[3] Christé G. Localization of K^+ channels in the T-tubules of cardiomyocytes as suggested by the parallel decay of membrane capacitance, IK_1, and IK_{ATP} during culture and by delayed IK_1 response to barium, *J.Mol.Cell.Cardiol*, 1999, 31:2207-2213.

[4] Amsellem J., Delorme R., Souchier C., Ojeda C.: Transverse-axial tubular system in guinea pig ventricular cardiomyocyte: 3D reconstruction, quantification and its possible role in K^+ accumulation-depletion phenomenon in single cells*, Biol. Cell*., 1995; 85:43-54.

[5] Yasui K., Anno T., Kamiya K., Boyett M. R., Kodama I. and Toyama J.: Contribution of potassium accumulation in narrow extracellular spaces to the genesis of nicorandil-induced large inward tail current in guinea-pig ventricular cells*, Pflügers Archiv*,, 1993, 422:371-379.

[6] Luo C., Rudy Y.: A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction, *Circ. Res*., 1991, 68:1501-1526.

[7] Pásek M.: Quantitative modelling of physiological processes in cardiac cells: block of membrane channels (in Czech), *PhD. thesis*, 2000, Technical University of Brno.

[8] Yao A., Spitzer K. W., Ito N., Zaniboni M., Lorell B. H. and Barry W. H.: The restriction of diffusion of cations at the external surface of cardiac myocytes varies between species, *Cell Calcium,* 1997, 22:431-438.

[9] Petrecca K., Amellal F., Larid D. W., Cohen S. A., Shrier A.: Sodium channel distribution within the rabbit atrioventricular node as analysed by confocal microscopy*, J. Physiol*., 1997, 2:263-274.

[10] Shepherd N and McDonough H. B.: Ionic diffusion in transverse tubules of cardiac ventricular myocytes, *Am. J. Physiol.,* 1998, 275:H852-H860.

[11] Mays D.J., Foose J.M., Philipson L.H., Tamkun M.M. : Localization of the Kv1.5 K+ channel protein in explanted cardiac tissue, *J. Clin. Invest.,* 1995, 96:282-292.

[12] Takeuchi S., Takagishi Y., Yasui K., Murata Y., Toyama J. and Kodama I.: Voltage-gated K(+)Channel, Kv4.2, localizes predominantly to the transverse-axial tubular system of the rat myocytes, *J. .Mol. Cell. Cardio*l., 2000, 32:1361-1369.