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The influences of the ionic channel conductances and kinetics on the phase-locking behaviors of modeled sinoatrial node cells and tissue

Xiaodong Huang *, Zhikun Chu, Keming Li

Department of Physics, South China University of Technology, Guangzhou, 510640, China

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ABSTRACT

Sinoatrial node (SAN) is the leading pacemaker of the heart, whose pathologies are closely associated to certain kinds of arrhythmias. Phase-locking is a characteristic behavior of the self-oscillatory SAN system, which is relevant to the heart rate modulation. It is known that the SAN phase-locking properties are influenced by the stimulating magnitude, the stimulated site in the tissue, the intercellular coupling strength and even the couplings from the atrial cells. Besides the above knowledge, a practical problem remains undiscussed, i.e., the influences of the channel conductances and kinetics on the phase-locking property. In the present paper a detailed electrophysiological SAN model is investigated. The effects of several major parameters modulating the channels' conductances and the time constants are illustrated. We find that the phase-locking ranges depend on the automaticity of the system. Any parameter variation slowing down the intrinsic oscillating rate may increase the phase-locking ranges, while that speeding up the rate may shrink them. The well known phase resetting property is applied to explain the phenomena, founding on which the analytical formulas for estimating the phase-locking ranges are derived.

1. Introduction

The sinoatrial node (SAN) is a piece of tissue embed in the right atrium. It consists of self-oscillatory cells, whose membrane voltages oscillate periodically with time. Because of coupling the membrane voltage pulses could propagate out to the atria and the ventricles, resulting in contraction of the whole heart. Thus the SAN is the leading pacemaker of the heart. In clinical studies it is known that some arrhythmogenesis are closely related to the SAN dynamics, e.g., the sick sinus syndrome, sinus node arrest, and the supraventricular tachycardia [1–4]. It is known that the SAN's dynamics is modulated by various internal and external factors [5], so that the normal heart may adjust its rate to adapt to the body demanding. How the SAN system adjusts its beating rate in the presence of environmental changes is the central problem of the research on SAN dynamics.

In physical studies, an SAN cell is usually treated as a nonlinear oscillator, which could be described by a set of nonlinear ordinary differential equations [6–10]. For the nonlinear oscillators, the characteristic dynamical behavior is called phase-locking or entrainment, which means in the presence of external periodic stimulations the frequency of the oscillator may be locked on a certain ratio to the stimulating frequency. Hence the phase-locking behavior could be regarded as one of the fundamental mechanisms for the modulation of the heart rate. The physical pictures universally occurring in the entrained systems is the so-called devil's stairs and Arnol'd tongues, which reveals the fundamental characteristics of the phase-locking behaviors [11]. For the periodically stimulated system, if one scans the stimulating period T_{sti}, a quantity called rotation number will appear to be a function of T_{sti} which looks like the stairs. The stairs have infinite self similarity and are thus called the devil's stairs. The rotation number is defined as

$$\rho = \lim_{M\to\infty} \frac{MT_{sti}}{\sum_{i=1}^{M} T_i}, \tag{1}$$

where T_i is the time span of the ith cycle of oscillation. Hence the rational $\rho = \frac{M}{N}$ (we call it N:M phase-locking) means the entrained behavior is periodic, i.e., the time span of M times of oscillation equals to N times of stimulation, and the irrational ρ means the behavior is quasi-periodic. As the stimulating magnitude is increased, the appearance of the devil's stairs would be varied. In the T_{sti}-magnitude plane the rational phase-locking regimes may look like some tongues growing from the bottom, which are called the Arnol'd tongues.

The phase-locking behaviors in biological oscillators have been well studied by the scholars such as Winfree, Glass, Keener, Gue-

* Corresponding author.
E-mail address: schuangxd@scut.edu.cn (X. Huang).

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vara, Jalife and so on. The prior studies have revealed the universality of the phase-locking in kinds of in vitro cardiac cells and models [12–25,8,26–29], illustrated the phase-locking mechanism by the phase-resetting map (a circle map) [13–15,18–20,22,28,29], and applied the theories to explain the synchronization of the SAN tissue and the heart rate modulations [30,23,31,32,24,9,33]. In our previous works, we investigated in detail the phase-locking behaviors of a heterogeneous rabbit SAN model [34,35]. The characteristics of the phase-locking in such a model influenced by the stimulating magnitude, the stimulated site in the tissue, the intercellular coupling strength and the couplings from the atrial cells are revealed, which may provide more complete and deeper knowledge for the SAN dynamics.

Besides the previous works, an interesting and practical problem remains undiscussed, i.e., the influences of the ionic channel parameters on the phase-locking behaviors of the SAN cells and tissue. It is well known physically the phase-locking property closely depends on the stimulating magnitude exerted to the system. However, how the intrinsic dynamical parameters modulate the behavior, and the relevant physical mechanism are not clearly studied. The relationship between the intrinsic dynamics and the resulted phase-locking structure, and how to predict the phase-locking ranges are not yet known. In the present work, we numerically simulate an electrophysiologically modeled heterogeneous rabbit SAN model to investigate its phase-locking behaviors influenced by the ionic channel parameters. The channel conductances and time constants are varied to simulate the changes of the channels. The bifurcation analyses are carried out, founding on which the analytical formulas are proposed to estimate the ranges of specific phase-locking regions. Our work may provide common knowledge for interpreting and analyzing the fundamental phase-locking characteristics of the nonlinear oscillators. Thus it is of interest of theoretical physics. On the other hand in the words of biological science, since it is physiologically and pharmacologically known that some drugs may influence the ionic channel conductances and kinetics [36], we believe our work may provide potentially applicable treatments for specific SAN arrhythmias. Therefore, the present study may be both physically and physiologically relevant.

2. Model an methods

The model used in the present paper is the revised version of Zhang et al.'s rabbit SAN model [34]. This model was developed founding on the in vitro experimental data from the rabbit heart. Its simulated electrophysiological properties agree with the known experimental results. Moreover, this model takes into account the heterogeneity of the cells from the central to peripheral region in the SAN tissue, which has been validated by experiments [37]. Hence the model is generic for the SAN type oscillators.

The differential equation governing the membrane voltage dynamics of a single cell reads:

$$\frac{dV}{dt} = -\frac{I_{ion}}{C_m} + I_{st}(t), \tag{2}$$

where V is the membrane voltage, C_m is the membrane capacitance, I_{st} is the external stimulus if applied, and I_{ion} is the total transmembrane ionic current, which is a summary of thirteen currents:

$$I_{ion} = I_{Na} + I_{Ca,L} + I_{Ca,T} + I_{to} + I_{sus} + I_{K,r} + I_{K,s} + I_f + I_{b,Na} + I_{b,Ca} + I_{b,K} + I_{NaCa} + I_p.$$

Each one of the thirteen currents can be expressed as

$$I_z = G_z f_z(\mathbf{y}, V)(V - E_z), \tag{3}$$

where G_z is the conductance of the channel, E_z is the Nernst potential, and $f_z(\mathbf{y}, V)$ is a function of V and $\mathbf{y}$ is a collection of the gating variables, i.e.,

$$\mathbf{y} = (m, h_1, h_2, f_L, d_L, f_T, d_T, q, r, p_{a,f}, p_{a,s}, p_i, x_s, y).$$

For example, the L type calcium current is

$$I_{CaL} = G_{CaL}[f_L d_L + \frac{0.006}{1 + e^{-(V+14.1)/6}}](V - E_{CaL}),$$

where $f_z(\mathbf{y}, V) = [f_L d_L + \frac{0.006}{1+e^{-(V+14.1)/6}}]$ here. Each gating variable y (any element in $\mathbf{y}$ as indicated above) is governed by

$$\frac{dy}{dt} = \frac{y_\infty(V) - y}{\tau_y(V)}, \tag{4}$$

where $\tau_y(V)$ and $y_\infty(V)$ are the time constant and the steady state of y, respectively, which are functions of V. The details of the functions could be found in Refs. [10,34].

In respect of the tissue model, a 1D cable is simulated. The 1D heterogeneity is expressed by the spatial variations of the capacitance and ionic conductance from the center to periphery of the tissue, which is proposed by Zhang et al. [10]. On position x from the central end, the capacitance of the cell is

$$C_m(x) = 20 + \frac{1.07x}{L[1 + 0.7745e^{-(x-1.95)/0.295}]}(65 - 20), \tag{5}$$

where L is the length of the cable. Thus on the central end ($x = 0$) the capacitance is 20 pF and on the peripheral end ($x = L$) it is approximately 65 pF. Then the conductance of a certain channel is

$$g_z(x) = \frac{[65 - C_m(x)]g_{zc} + [C_m(x) - 20]g_{zp}}{65 - 20}. \tag{6}$$

g_{zc} and g_{zp} represent the conductances of the channel z on the central end and peripheral end, respectively. In the presence of such heterogeneity, the differential equation for the 1D cable reads [10]

$$\frac{\partial V(x,t)}{\partial t} = -\frac{I_{ion} + D\nabla^2 V(x,t)}{C_m(x)} + I_{st}(x,t). \tag{7}$$

The diffusion constant D is fixed as 0.002 cm^2/ms unless specified otherwise, which is strong enough for the synchronization of the whole cable.

In the present model, six conductance parameters are explored, they are G_{CaL} for the L type calcium current, G_{CaT} for the T type calcium current, G_{Ks} for the slow rectified potassium current, G_{Kr} for the rapid rectified potassium current, G_{to} for the transient outward potassium current and G_f for the hyperpolarized activated current. These six currents are regarded as the major currents generally existing in the SAN cells. As for the time constants for the gating variables, τ_{f_L} for f_L gate (the inactivation gate of the L type calcium channel) and τ_{pa_f} for the fast component pa_f of I_{Kr} (the activation gate of I_{Kr}) are investigated since they have the most significant effects on the phase-locking structures in the time constants, while the others have little effect. The reason for the choice of the time constants are in the supplementary information (SI), see Fig. S1 and the relevant discussion. In the present paper the six conductances mentioned above and the two time constants τ_{f_L} and τ_{pa_f} are our target parameters, which are varied to simulate the ionic channel variations. When a specific ionic channel is modulated, a factor α is multiplied to the conductance or the kinetics, i.e., $I_z = \alpha G_z f_z(\mathbf{y}, V)(V - E_z)$ or $\frac{dy}{dt} = \frac{y_\infty(V) - y}{\alpha \tau_y(V)}$. The control values of the target parameters are set as the published ones [10], detailed as follows:

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