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Oscillations, bistabilities and bifurcations in a cardiac pacemaker cell model

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Abstract—Heartbeats are controlled by electrical signals, which are generated by sinoatrial node cells. The temporal variation of the signals is described by nonlinear ordinary differential equations, and the Zhang model is one of the most well-known models of the cardiac pacemaker cell. However, the model exhibits bistability so that the model is not adequate for a model of pacemaker cells. In this paper, we perform bifurcation analysis of the Zhang model by varying various conductances of ion channels in order to improve the model suitably. These results suggest that ion currents which can modify the model are L-type calcium current, T-type calcium current, and background sodium current.

1. Introduction

The sinoatrial node is a cardiac pacemaker. The sinoatrial node cells periodically generate electrical signals, and conduct the signals to other cardiac tissues. These electrical signals are called action potentials, which are mainly related to ion channels in cell membranes. When the ion channels open, the specific ions pass through them. This process changes the membrane potential, which is a difference of electrical potential between the inside and outside of cell membrane. However, if the process becomes abnormal, it causes heart disease.

The action potential of sinoatrial node cells are described by Hodgkin–Huxley-type models [1, 2, 3]. The Zhang model is composed of the nonlinear ordinary differential equations with fifteen variables [2, 3]. In addition, the model enables us to take account of differences between center and periphery cells, which compose the sinoatrial node. Therefore, we can analyze the pacemaker activities of sinoatrial node cells in detail. However, the model exhibits bistabilities in the normal condition so that the model is not adequate for a model of pacemaker cells [4, 5]. This means that the model cannot simulate the action potentials accurately. For example, cardiac cells actually receive stimuli so that cardiac pacemaker cell models need to take account of them. In the case of cardiac cell models which exhibits bistability, generation or annihilation of action potentials is changed by each external stimulus. Due to this, the model cannot take account of sudden external stimuli.

In this paper, we focus on single center cell activities of the one-dimensional(1D)-capable model [3]. This cell model is commonly used to explore activities of coupled cells [6, 7]. Many kinds of parameters for the model have different values from those for isolated cell model. We investigate the bifurcation structure of the model by varying conductances of ion channels in order to modify the model.

2. Zhang model

The Zhang model is a rabbit sinoatrial node cell model described by the Hodgkin–Huxley-type equation with fifteen variables. The variation of membrane potential V (mV) is described by

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{1}{C} I_{\mathrm{total}}, \tag{1}$$

$$I_{\mathrm{total}} = I_{\mathrm{Na}} + I_{\mathrm{CaL}} + I_{\mathrm{CaT}} + I_{\mathrm{Kr}} + I_{\mathrm{Ks}} + I_{\mathrm{to}} + I_{\mathrm{sus}} + I_{\mathrm{f}} + I_{\mathrm{bNa}} + I_{\mathrm{bCa}} + I_{\mathrm{bK}} + I_{\mathrm{NaCa}} + I_{\mathrm{p}}, \tag{2}$$

where C_{m}(pF) is the membrane capacitance, $I_{\mathrm{Na}}, I_{\mathrm{CaL}}, I_{\mathrm{CaT}}, I_{\mathrm{Kr}}, I_{\mathrm{Ks}}, I_{\mathrm{to}}, I_{\mathrm{sus}}, I_{\mathrm{f}}, I_{\mathrm{bNa}}, I_{\mathrm{bCa}}, I_{\mathrm{bK}}, I_{\mathrm{NaCa}}, I_{\mathrm{p}}$ (pA) are the ionic currents. These currents are given by the following equations:

$$I_{\mathrm{ion}} = c_{\mathrm{ion}} G_{\mathrm{ion}} f(V, \chi)(V - E_{\mathrm{ion}}) \tag{3}$$

(ion=Na, CaL, CaT, Kr, Ks, to, sus, f, bNa, bCa, bK, NaCa, p),

where G_{ion} (μS) is the maximum conductance of ion channels. For the simplicity of bifurcation analyses, we have introduced the coefficient of the maximum conductance c_{ion} whose standard value is 1.0. χ is the gating variable, which expresses opening and closing dynamics of ion channels. Temporal variations of gating variables are described by

$$\frac{\mathrm{d}\chi}{\mathrm{d}t} = \alpha_\chi(V)(1-\chi) - \beta_\chi(V)\chi \tag{4}$$

$(\chi = m, h_1, h_2, d_L, f_L, d_T, f_T, y, r, q, p_{\mathrm{a,f}}, p_{\mathrm{a,s}}, p_{\mathrm{i}}, x_{\mathrm{s}})$,

where $\alpha_\chi(V)$ and $\beta_\chi(V)$ are the (voltage-dependent) rate constants of the transition between open and closed states of the gate. For more details, see the reference [2, 3]. We analyzed the center cell model.

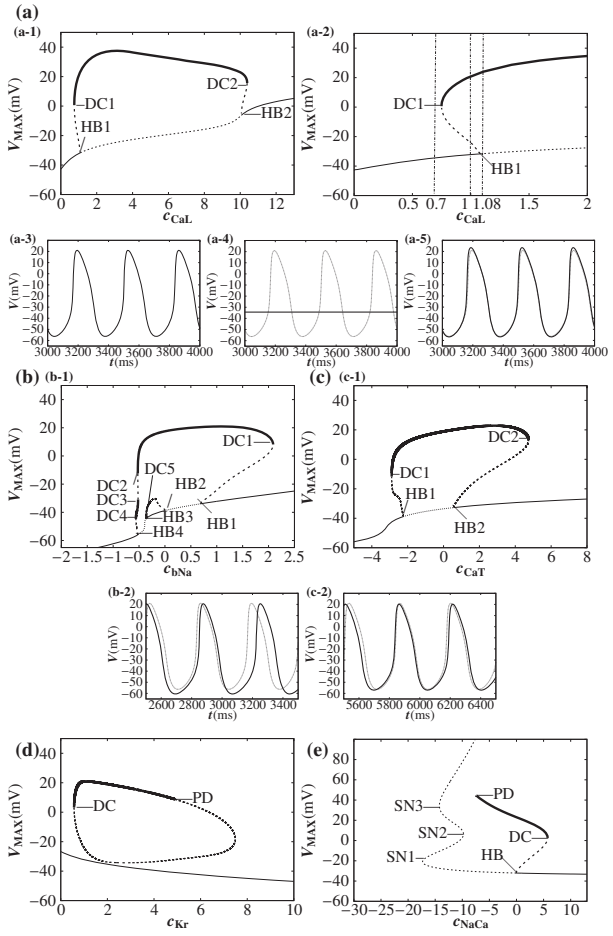

Figure 1: One-parameter bifurcation diagrams as for (a-1)c_{CaL}, (a-2)c_{CaL}(the enlarged view of (a-1)), (b-1)c_{bNa}, (c-1)c_{CaT}, (d)c_{Kr} , (e)c_{NaCa}, and results of the simulation at (a-3)c_{CaL} = 1.00, (a-4)c_{CaL} = 0.70, (a-5)c_{CaL} = 1.08, (b-2)c_{bNa} = 0.69, (c-2)c_{CaT} = 0.59.

3. One-parameter bifurcation analysis in order to modify the Zhang model

As discussed in the introduction, the Zhang model exhibits bistabilities. This means that stable equilibrium points and periodic solutions coexist in normal conditions. Therefore, this model can't take account of sudden external stimulus. In this section, we analyze the bifurcation structures of the model as for each conductance coefficient of ionic currents in order to modify the model. Each ion current plays an important role in action potential activities of a cardiac cell. The method to analyze bifurcations as for a conductance coefficient of a ion current is useful to investigate the stabilities of equilibrium points and periodic solutions [8]. This paper uses the bifurcation analysis software AUTO [9].

3.1. Effective parameters

Stabilities of equilibrium points and periodic solutions don't always depend on large ion currents. For example, hyperpolarization-activated current I_{f} has an important effect upon the automaticity of cardiac pacemaker cells although the maximum value of I_{f} is very small. Therefore, we analyze the model as for all currents even if some of them are small.

3.1.1. The L-type calcium current I_{CaL}

L-type calcium current I_{CaL} is large current in a center cell, and plays a main role in the depolarization of action potential. Figure 1(a-1) shows the bifurcation diagram as for c_{CaL}. The membrane potential V in the steady state is plotted for each value of c_{CaL} in the diagram. The solid and broken curves show stable and unstable solutions, respectively. The thick and thin curves present periodic solutions and equilibrium points, and HB, SN, PD denote the bifurcation points of Hopf, saddle-node, Period-doubling bifurcation.

When c_{CaL} is increased from 0.00, a equilibrium point is unstable at HB1 (c_{CaL} = 1.08), and the unstable periodic solutions are generated. Periodic solutions become stable at DC1 (c_{CaL} = 0.74), and become unstable at DC2 (c_{CaL} = 10.39). Eventually, periodic solutions disappear at HB2 (c_{CaL} = 10.06), so that stable periodic orbits coexist with stable equilibrium points within the range $0.74 < c_{\mathrm{CaL}} < 1.08$, $10.06 < c_{\mathrm{CaL}} < 10.39$. Therefore, the Zhang model is suitable as a cardiac pacemaker cell model in the condition of $1.08 < c_{\mathrm{CaL}} < 10.06$.

If membrane potentials are abnormal, the change of a model parameter is not adequate. Therefore, we evaluate the maximum systoilc potential and the period of the Zhang model based on Fig. 1(a-2). The result of the simulation in normal conditions is Fig. 1(a-3), and the maximum systoilc potential is 20.9 mV and the period is 336.3 ms. Furthermore, the membrane potential converges to a fixed value at c_{CaL} = 0.70 (Fig. 1(a-4)). In this figure, the solid curve is action potential waveform in the modified condition, and the broken curve is that in the normal condition. When c_{CaL} is 1.08, the maximum systoilc potential is 23.1 mV and the period is 338.0 ms (Fig. 1(a-5)). The maximum value of the action potential needs to be larger than 0.0 mV, so that the difference of the values is permissible. The difference of periods are also allowable.

3.1.2. The background sodium current I_{bNa}

Unlike I_{CaL}, I_{bNa} is so small that it seems that I_{bNa} will not affect cardiac pacemaker activities. However, as can be seen from Fig. 1(b-1), this expectation is not correct. Stable periodic orbits coexist with stable equilibrium points within the range $-0.56 < c_{\mathrm{bNa}} < -0.53$,

$-0.36 < c_{\mathrm{bNa}} < 0.00$, $0.69 < c_{\mathrm{bNa}} < 2.09$. Accordingly, periodic solutions are monostable when c_{bNa} decrease from 1.0.

As c_{CaL}, we compare the differences between the normal condition and the modified condition. The the maximum systoilc potential is 20.4 mV and the period is 378.0 ms in the condition of $c_{\mathrm{bNa}} = 0.69$ (Fig. 1(b-2)). The difference between the values of the maximum systoilc potential at $c_{\mathrm{bNa}} = 1.00$ and at $c_{\mathrm{bNa}} = 0.69$ is smaller than c_{CaL}, but the period at $c_{\mathrm{bNa}} = 0.69$ is larger than at $c_{\mathrm{bNa}} = 1.00$. This means that the heart rate per minute at $c_{\mathrm{bNa}} = 0.69$ is 20 less than that at $c_{\mathrm{bNa}} = 1.00$, but this model describes a rabbit sinoatrial node cell activity so that it may not be a problem. This is the reason why c_{bNa} is inferior to c_{CaL} to modify the model.

3.1.3. The T-type calcium current I_{CaT}

I_{CaT} is smaller than I_{bNa}, but c_{CaT} is an effective parameter to modify the model. Figure 1(c-1) shows that stable periodic orbits coexist with stable equilibrium points within the range $-4.00 < c_{\mathrm{CaT}} < -2.23$, $0.58 < c_{\mathrm{CaT}} < 4.75$. Therefore, the model is suitable as a cardiac pacemaker cell model in the condition of $0.00 < c_{\mathrm{CaT}} < 0.58$ ($c_{\mathrm{CaT}} < 0.00$ is physiologically impossible).

When c_{CaT} is 0.58, the maximum systoilc potential is 20.1 mV and the period is 355.2 ms (Fig. 1(c-2)). The change of the value of c_{CaT} hardly affects the maximum value of action potentials. Thus, compared with $c_{\mathrm{CaL}} = 1.08$, the maximum value of action potentials is closer to the value in the normal condition. On the other hand, the period at $c_{\mathrm{CaT}} = 0.58$ is larger than at $c_{\mathrm{CaT}} = 1.00$ so that the heart rate per minute at $c_{\mathrm{CaT}} = 0.58$ is 10 less than in the normal condition. The influence on the period of action potentials by decreasing the value of c_{CaT} is smaller than that by decreasing the value of c_{bNa}. Therefore, from a viewpoint of the difference of periods, the parameter c_{CaT} is more suitable than c_{bNa}, but c_{CaL} is more appropriate than these.

3.2. Non-effective parameters

In this section, we introduce the parameters which are not adequate to modify the model. We show two representative examples as follows.

3.2.1. The rapid delayed rectifying potassium current I_{Kr}

The potassium currents have an effect on repolarization of the pacemaker activity, and I_{Kr} is a larger current than I_{Ks}. However, the model isn't suitable as a cardiac pacemaker cell model as c_{Kr} is any value. Figure 1(d) shows that a equilibrium point is stable with any value of c_{Kr} when c_{Kr} is increased from 0.00. On the other hand, a stable periodic solution exists between DC ($c_{\mathrm{Kr}} = 0.48$) and PD ($c_{\mathrm{Kr}} = 4.92$). Consequently, changing the value of c_{Kr} can't improve the model.

3.2.2. The sodium–calcium exchanger current I_{NaCa}

I_{NaCa} connects with sodium ion and calcium ion movements. As can be seen from Figure 1(e), although equilibrium points become unstable and periodic solutions become stable by varying the value of c_{NaCa}, this condition is physiologically impossible. Owing to this, c_{NaCa} is not suitable to improve the model.

We investigated other conductance coefficients. However, pacemaker activities are abnormal conditions as a cardiac pacemaker cell model although $c_{\mathrm{Ks}}, c_{\mathrm{to}}, c_{\mathrm{sus}}, c_{\mathrm{f}}, c_{\mathrm{bK}}, c_{\mathrm{p}}$ are any value.

4. Interrelation between two conductance coefficients of ionic currents

In the above section, we analyzed bistabilities of the Zhang model on each conductance coefficient of ion channels. This results indicate that $c_{\mathrm{CaL}}, c_{\mathrm{bNa}}, c_{\mathrm{CaT}}$ are important to modify the model. However, the larger the value of parameter changes, the greater difference between the waveform in normal conditions and in modified conditions becomes. Thus the change of the value needs to be smaller. For this reason, we explore the adequate values of parameters to modify the model when two parameters change.

4.1. The L-type calcium current I_{CaL} and the background sodium current I_{bNa}

In the previous section, increasing c_{CaL} is to make the amplitude of membrane potentials larger. Furthermore, the period of the pacemaker activities become larger because of decreasing c_{bNa}. Thus, we expect that the shapes of action potential in modified conditions resemble those in the normal conditions when c_{CaL} and c_{bNa} are varied simultaneously. This section shows the range of parameters which makes the model adequate. Future work is needed to evaluate the shapes of membrane potentials.

Figure 2(a) shows the two-parameter bifurcation diagrams as for c_{CaL} and c_{bNa}. The shaded area indicate that the model is adequate as a pacemaker cell model (oscillations are stable and equilibrium points are unstable). When c_{bNa} is increased from 0.00, the range between HB1 and DC1 becomes wider. Accordinigly, the changes of the value of parameters are smaller to modify this model when c_{CaL} increases and c_{bNa} decreases from 1.00.

4.2. The L-type calcium current I_{CaL} and the T-type calcium current I_{CaT}

As can be seen from Fig. 2(b), when c_{CaT} is increased from 1.00, the range between HB1 and DC1 becomes

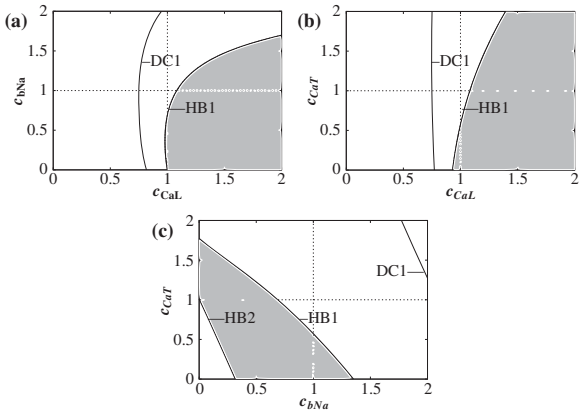

Figure 2: Two-parameter bifurcation diagram as for (a)c_{CaL}–c_{bNa}, (b)c_{CaL}–c_{CaT}, (c)c_{bNa}–c_{CaT}.

wider. DC1 curve is parallel to the c_{CaT}-axis so that the change of c_{CaT} hardly affects the contour lines of DC1 within the range $0.00 < c_{\mathrm{CaT}} < 2.00$. On the other hand, HB1 curve runs to the upper right of the figure. Therefore, the range of c_{CaL} between HB1 and DC1 becomes wider as c_{CaT} is increased.

4.3. The background sodium current I_{bNa} and the T-type calcium current I_{CaT}

Unlike I_{CaL}, I_{bNa} and I_{CaT} hardly affect the amplitude of pacemaker activities. Therefore, Fig. 2(c) is also expected to be useful to modify the model.

Fig. 2(c) shows that HB1, HB2, and DC1 curves run to the upper left of the figure. This means that the value of c_{bNa} affect loci of bifurcations much the same as that of c_{CaT}.

5. Conclusion

In this paper, we analyzed the bifurcation structure of the Zhang model, which exhibits bistabilities in normal conditions. As a result, bifurcation structures for the single conductance coefficient of ionic currents revealed that oscillations are stable and equilibrium points are unstable by varying c_{CaL}, c_{CaT}, or c_{bNa}. Therefore, in this study we showed that these conductance coefficients are important for the improvement of the model.

Furthermore, we have examined two-parameter bifurcation diagram, where the bifurcation parameters are c_{CaL}–c_{bNa}, c_{CaL}–c_{CaT} and c_{bNa}–c_{CaT}. These show that two-parameter bifurcation analysis makes the amounts of change of the bifurcation parameters smaller than the one-parameter bifurcation analyses to make the model adequate as a cardiac pacemaker cell model. These two results are key to the modification of the model.

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