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Analysis of Bifurcations and Variabilities of Rhythm in a Cardiac Pacemaker Cell Model

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Abstract—A heart generates electrical signals (action potentials) in the sinoatrial node (cardiac pacemaker) and propagates them to the whole heart. Since the electrical signals control contraction and relaxation of the heart, the abnormalities of rhythm (frequency of action potential generation) in the sinoatrial node cause serious arrhythmia such as sinus tachycardia. In order to analyze variabilities of rhythm, we use the Yanagihara-Noma-Irisawa (YNI) model of sinoatrial-node cells, which is described by the Hodgkin-Huxley-type equations with seven variables. In this paper, we focus mainly on the variabilities of rhythm and analyze the global bifurcation structure of the YNI model by varying various conductances of ion channels.

1. Introduction

A heart pumps blood to the whole body by repeating contractions and relaxations regularly. These motions are related to the generation and propagation of electrical signals (action potentials). The electrical signals are generated in the sinoatrial node (cardiac pacemaker), and are propagated to the atrial muscle, the atrioventricular node, the bundle of His, the Purkinje fiber and the ventricular muscle. Since the rhythm (frequency of action potential generation) in the sinoatrial node decides the heart rate, the abnormalities of rhythm cause serious arrhythmia such as sinus tachycardia.

In biological cells, the difference of ionic concentration between the inside and the outside of cell membrane generates an electrical potential difference (membrane potential). In the cell membrane, there are various ion channels which open and close dynamically. When the ion channels open, specific ions pass through them, and the membrane potential changes. As a result, the action potential is generated. Thus, the ion channels play an important role in the action potential generation.

The abnormalities of ion channels cause diseases such as arrhythmia or diabetes. These diseases, which are called channelopathies, are usually treated by applying drugs which have effect on ion channels. Since it is difficult to analyze the drug sensitivity of ion channels only by physiological experiments, various models, which describe the relation between membrane potential and ion channels in cells, are applied to analyze the drug sensitivity.

This paper uses the Yanagihara-Noma-Irisawa (YNI) model [1] of cardiac pacemaker cells, which is a Hodgkin-Huxley-type (HH-type) model. The HH-type models are based on the famous Hodgkin-Huxley model of a squid nerve, which is described by nonlinear ordinary differential equations with four variables [2]. So far, it has been shown that the bifurcation analysis of various cardiac models (models of ventricular myocardial cells, in particular) is very useful in the treatment of arrhythmia [3, 4, 5, 6]. In this paper, we focus mainly on the variabilities of rhythm generation of cardiac pacemaker cells and analyze the global bifurcation structure of the YNI model by varying various conductances of ion channels. The results are also expected to be useful in the treatment of arrhythmia.

2. Yanagihara-Noma-Irisawa Model

The YNI model is described by the HH-type equations with seven variables. The variation of membrane potential V (mV) is described by

$$\frac{dV}{dt} = -\frac{1}{C}(I_{\mathrm{Na}} + I_{\mathrm{s}} + I_{\mathrm{h}} + I_{\mathrm{K}} + I_{\mathrm{l}}) \tag{1}$$

where C (μF/cm^2) is the membrane capacitance, I_{Na}, I_{s}, I_{h}, I_{K} and I_{l} (μA/cm^2) are the sodium current, the slow inward current, the hyperpolarization-activated current, the potassium current and the leak current, respectively. These ionic currents are described by

$$I_{\mathrm{Na}} = c_{\mathrm{Na}} G_{\mathrm{Na}} m^3 h (V - 30),\ G_{\mathrm{Na}} = 0.5 \tag{2}$$

$$I_{\mathrm{s}} = c_{\mathrm{s}} G_{\mathrm{s}} (0.95d + 0.05)(0.95f + 0.05)\left(\exp\left(\frac{V - 30}{15}\right) - 1\right),\quad G_{\mathrm{s}} = 12.5 \tag{3}$$

$$I_{\mathrm{h}} = c_{\mathrm{h}} G_{\mathrm{h}} q (V + 45),\ G_{\mathrm{h}} = 0.4 \tag{4}$$

$$I_{\mathrm{K}} = c_{\mathrm{K}} G_{\mathrm{K}} p \frac{\exp(0.0277(V + 90)) - 1}{\exp(0.0277(V + 40))},\ G_{\mathrm{K}} = 0.7 \tag{5}$$

$$I_{\mathrm{l}} = c_{\mathrm{l}} G_{\mathrm{l}} \left(1 - \exp\left(-\frac{V + 60}{20}\right)\right),\ G_{\mathrm{l}} = 0.8 \tag{6}$$

where G_{Na}, G_{s}, G_{h}, G_{K}, G_{l} (mS/cm^2) are the maximum conductances of ion channels. c_{Na}, c_{s}, c_{h}, c_{K}, c_{l} are coefficients of the maximum conductances, and their standard

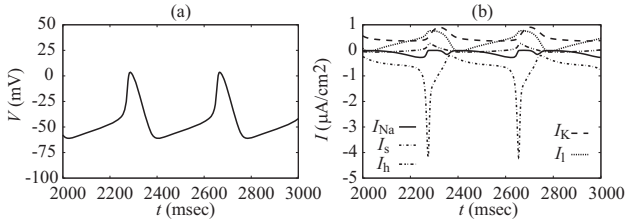

Figure 1: Temporal variations of membrane potential and ionic currents in normal condition.

values are 1.0. The gating variables m, h, d, f, q, p express the effects of opening and closing of ion channels. Temporal variations of these gating variables are described by

$$\frac{dx}{dt} = \alpha_x(V)(1-x) - \beta_x(V)x, \ (x = m, h, d, f, q, p) \quad (7)$$

where $\alpha_x(V)$ and $\beta_x(V)$ are the (voltage-dependent) rate constants of the transition between open and closed states of gates. All details can be found in the reference [1].

Figure 1(a) and (b) show temporal variations of membrane potential and ionic currents in normal condition ($c_{\rm Na}$, $c_{\rm s}$, $c_{\rm h}$, $c_{\rm K}$, $c_{\rm l}$ = 1.0), respectively. The YNI model is a sinoatrial node cell model of rabbit, and the normal period of action potential generation is about 380 (msec). As a cardiac pacemaker, the sinoatrial node generates action potentials repeatedly without external electrical signals. The inward currents (denoted by negative values in Fig. 1(b)) and outward currents (positive values) cause the membrane potential to increase and decrease, respectively. In the five ionic currents, the slow inward current $I_{\rm s}$ plays the most important role in the action potential generation, and the hyperpolarization-activated current $I_{\rm h}$ has little effect on changing the membrane potential.

3. One-parameter Bifurcation Analysis

This paper uses the bifurcation analysis software AUTO [7] for the analysis of the YNI model. Since the effects of drugs acting on ion channels can be partially expressed by varying the values of conductances, the conductance coefficients $c_{\rm Na}$, $c_{\rm s}$, $c_{\rm h}$, $c_{\rm K}$ and $c_{\rm l}$ are selected as bifurcation parameters.

3.1. The Sodium Current $I_{\rm Na}$

The one-parameter bifurcation diagram of the YNI model, where the bifurcation parameter is the conductance coefficient $c_{\rm Na}$, is shown in Fig. 2, in which V in the steady state was plotted for each value of $c_{\rm Na}$. The solid and broken curves show stable and unstable equilibrium points, respectively. The symbols • and ○ show the maximum values of V of stable and unstable periodic solutions, respectively. The bifurcation points of Hopf, saddle-node, double-cycle, period-doubling and homoclinic bifurcations are denoted by HB, SN, DC, PD and HC, respectively. Periods of periodic solutions are also shown in the diagram. In normal condition ($c_{\rm Na}$ = 1.0), a stable periodic solution whose period is about 380 (msec) exists, and Fig. 2(c) shows the corresponding waveform of membrane potential.

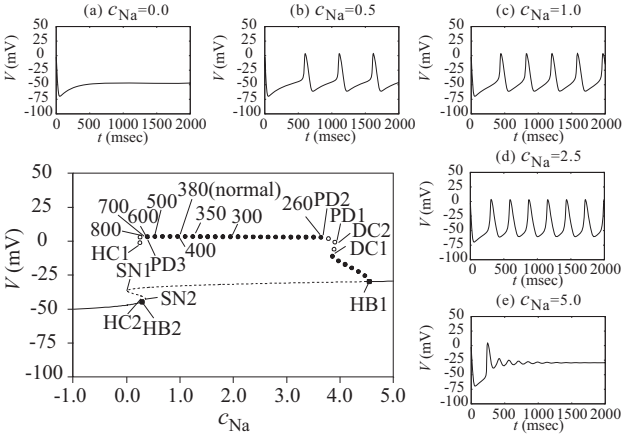

Figure 2: One-parameter bifurcation diagram as for the bifurcation parameter $c_{\rm Na}$ obtained by AUTO [7].

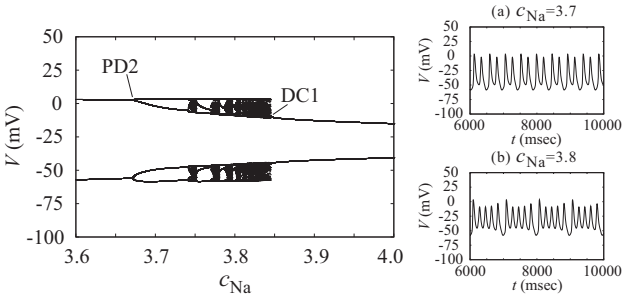

Figure 3: One-parameter bifurcation diagram obtained by numerical simulations.

For each value of $c_{\rm Na}$ between HB1 and HB2, a periodic solution (stable or unstable) exists. The period of periodic solution varies with $c_{\rm Na}$. When $c_{\rm Na}$ is increased, the period decreases, and thus the heart rate increases. In general, a very big heart rate (>325 beats/min) corresponds to sinus tachycardia, and a very small heart rate (<130 beats/min) corresponds to sinus bradycardia. Figure 2(b) and (d) show two typical waveforms of membrane potentials, whose periods are big and small, respectively. For the treatment of arrhythmia, it is important to consider the drug sensitivity of ion channels. In Fig. 2, the variation of period is small when $c_{\rm Na}$ is increased from 1.0 (normal value), and it is big when $c_{\rm Na}$ is decreased from 1.0. Especially when $c_{\rm Na}$ takes a value near 0.25, the period changes drastically. These results show that the drug sensitivity in the case of a small value of $c_{\rm Na}$ is stronger than that in the case of a big value of $c_{\rm Na}$.

In both the left side of HB2 and the right side of HB1, only equilibrium points exist. Because of the abnormality of Na^+ channel there ($c_{\rm Na}$ is too small or too big), it is difficult to generate action potentials periodically and continuously. The typical waveforms of membrane potentials in the two cases are shown in Fig. 2(a) and (e), respectively. Both of the membrane potentials converge to the equilibrium points, but the values of equilibrium points are

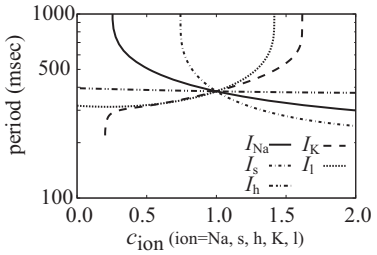

Figure 4: Comparison of the effects of various ionic currents on rhythm.

different in the two cases.

Since only unstable periodic solutions and unstable equilibrium points were detected by AUTO for the values of c_{Na} between PD2 and DC1 in Fig. 2, we also computed the one-parameter bifurcation diagram by numerical simulations (Fig. 3) for the parameter values of c_{Na} between 3.6 and 4.0. In this diagram, both the local maximum and minimum values of V for each value of c_{Na} were plotted. The waveforms of membrane potentials when $c_{\mathrm{Na}} = 3.7$ and 3.8 are shown in Fig. 3(a) and (b), respectively. In both cases, the amplitude of membrane potential varies, which shows abnormalities in action potential generation.

3.2. Comparison of the Effects of Various Ionic Currents on Rhythm

Figure 4 compares the effects of various ionic currents on the period of periodic solutions, in which the periods of stable periodic solutions are plotted when each conductance coefficient is varied. As for I_{h}, the variation of c_{h} does not make a big change of period, which means that the drug sensitivity of ion channels of I_{h} is very weak. For other four ionic currents, the period significantly changes with the variation of each conductance coefficient, particularly in the range of long period. Moreover, for the inward currents I_{Na} and I_{s}, the period decreases when c_{Na} or c_{s} increases. For the outward currents I_{K} and I_{l}, the period increases when c_{K} or c_{l} increases. These results show that the drug sensitivity of ion channels of the above four ionic currents is very high.

4. Two-parameter Bifurcation Analysis

The bifurcation points shown in one-parameter bifurcation diagrams may change when another conductance coefficient is varied. A two-parameter bifurcation diagram shows the loci of various bifurcation points (bifurcation curves) when two conductance coefficients are varied. The contour lines of various periods of stable periodic solutions are also plotted in the diagram to compare the variabilities of rhythm.

4.1. The Sodium Current I_{Na} and the Potassium Current I_{K}

Figure 5 is the two-parameter bifurcation diagram as for the two bifurcation parameters c_{Na} and c_{K}. The curve labeled with "normal" denotes the contour curve of period

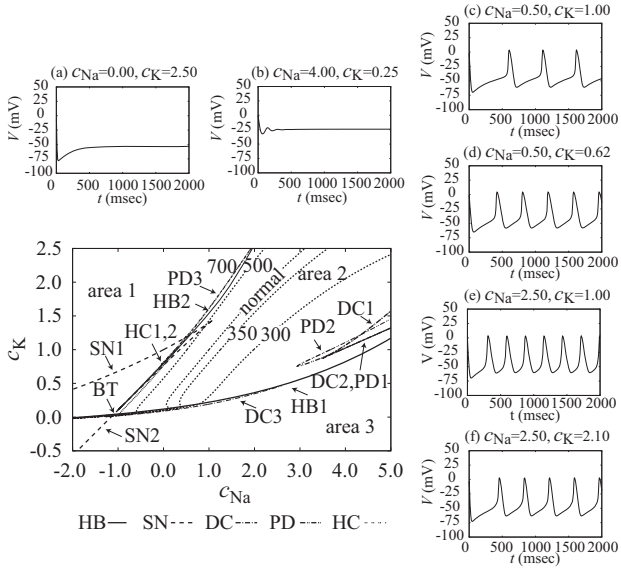

Figure 5: Two-parameter bifurcation diagram as for the two bifurcation parameters c_{Na} and c_{K}.

380 (msec), and the point labeled with BT denotes the Bogdanov-Takens bifurcation point. When c_{K} is fixed to 1.0 and c_{Na} is varied, the "one-parameter" bifurcation diagram of Fig. 2 can be obtained.

The bifurcation curves of HB1 and HB2 separate Fig. 5 into three areas. In area 2, various periodic solutions exist. When (c_{Na}, c_{K}) takes the values near (-1.0, 0.0), only periodic solutions with long period exist, and these cases correspond to sinus bradycardia. The period becomes small when c_{Na} is increased, and it becomes big when c_{K} is increased. Figure 5(c) and (e) show two abnormal waveforms of membrane potentials when c_{Na} take a small and a big value (c_{K} is fixed to 1.0), respectively. If we want to get the normal period 380 (msec) in such abnormal cases of c_{Na}, c_{K} should be adjusted as Fig. 5(d) and (f).

Figure 5(a) and (b) show the typical waveforms in area 1 and area 3, respectively. Both of the membrane potentials converge to the equilibrium points eventually and cannot show repetitive action potentials.

4.2. The Potassium Current I_{K} and the Slow Inward Current I_{s}

The two-parameter bifurcation diagram as for the two bifurcation parameters c_{K} and c_{s} is shown in Fig. 6(a). The result in Fig. 6(a) is similar to that in Fig. 5. That is, for small values of c_{K} and c_{s}, periodic solutions do not exist, thus it is difficult to generate action potentials continuously and periodically.

Figure 6(b) shows the periods of periodic solutions (stable or unstable) as a function of c_{K} along the Hopf bifurcation curves HB1 and HB2 of Fig. 6(a). The solid and broken curves correspond to stable and unstable periodic solutions (bifurcated from the Hopf bifurcation), respectively. The stability of periodic solution changes at nHB1 and nHB2. It is obvious that for small values of both c_{K} and c_{s}, the period of periodic solution at Hopf bifurcation

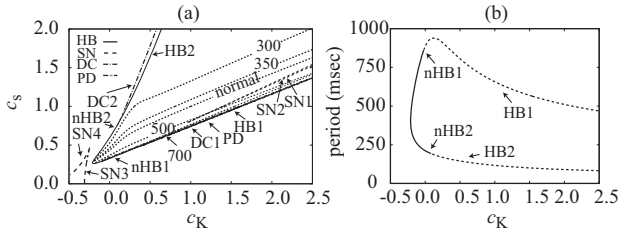

Figure 6: (a) Two-parameter bifurcation diagram as for two bifurcation parameters c_K and c_s (b) Variabilities of period along the Hopf bifurcation curves HB1 and HB2 of (a).

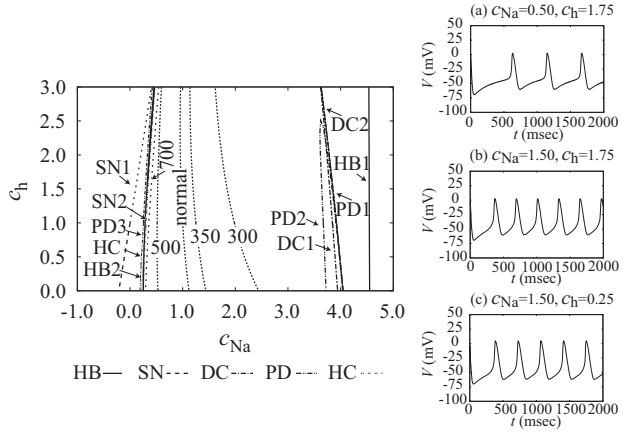

Figure 7: Two-parameter bifurcation diagram as for the two bifurcation parameters c_{Na} and c_h.

varies drastically, and the drug sensitivity of ion channels is very high.

4.3. The Potassium Current I_{Na} and the Hyperpolarization-activated Current I_h

Figure 7 is the two-parameter bifurcation diagram where c_{Na} and c_h are bifurcation parameters. The bifurcation points and periodic solutions, which appeared in the one-parameter bifurcation diagram of Fig. 2, change little when c_h is varied. From the waveform in Fig. 7(a), (b) and (c), we can also see that the period changes greatly when c_{Na} is varied, but it changes little when c_h is varied. We have also examined other two-parameter bifurcation diagrams as for the parameters: c_h and c_s, c_h and c_K, c_h and c_l, which are not shown in this paper. The similar results to Fig. 7 are obtained in all of these diagrams, that is, all the bifurcation points and periodic solutions change little when c_h is varied. It shows that I_h has little effect on changing the period of periodic solution, and the corresponding ion channels play a minor role in rhythmic action potential generation.

5. Conclusion

This paper focused mainly on the variabilities of rhythmic action potential generation and analyzed the global bifurcation structure of the YNI model, which is a cardiac pacemaker cell model.

The YNI model considers five ionic currents I_{Na}, I_s, I_h, I_K and I_l. At first, we have examined the one-parameter bifurcation structures and the variabilities of rhythm for each conductance coefficient. For I_{Na} and I_s, the increase of conductance coefficient causes the period of action potential generation to decrease. For I_K and I_l, the increase of conductance coefficient causes the period to increase. Since drugs acting on ion channels have the effects of conductance change, these results show that the drug sensitivity of ion channels of the above four ionic currents is very high. For I_h, the period changes little when its conductance coefficient is varied. It shows that the drug sensitivity is very low.

Second, two conductance coefficients are simultaneously varied to analyze the relation between two ionic currents. There are strong correlation between I_{Na} and I_K, I_K and I_s, and weak correlation between I_{Na} and I_h. For the treatment of arrhythmia, the drugs which act on sensitive ion channels are considered to be effective.

Since the YNI model is a very simple model of cardiac pacemaker, the analysis of more detailed models and the comparison of these models are necessary as a future work.

Acknowledgments

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