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Bifurcation Analysis of Human Ventricular Myocyte Model and its Quantitative Evaluation towards the Creation of Biological Pacemakers

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Abstract—In ventricular myocytes, pacemaker activity is induced by changing ionic currents across the cell membrane, although these cells are intrinsically quiescent non-pacemaking cells. These artificial pacemaker cells created from quiescent cardiomyocytes are called biological pacemaker, which is expected as an alternative to electronic pacemaker. Since it is necessary for biological pacemaker engineering (creation of biological pacemaker cells) to understand the dynamics of various ion channels comprehensively, we use the mathematical cell model. In this paper, we reveal that pacemaker activity is generated by changing inward rectifier potassium current I_{K1} and hyperpolarization-activated current I_f based on the bifurcation analysis of a mathematical model of human ventricular myocytes.

1. Introduction

A heart plays an important physiological role as the pump for the blood circulation by repeating contractions and relaxations regularly. These periodic motions are controlled by electrical signals (action potentials) generated in the sinoatrial node, which is a physiological pacemaker of the heart. If the rhythm of sinoatrial node is disrupted by aging or cardiovascular disorder, the heartbeat can become too slow (bradyarrhythmia).

Electronic cardiac pacemaker is extensively utilized for treatment of bradyarrhythmia, although those devices have some problems such as infection or mechanical life time. Recently, it has been reported that pacemaker activity is generated in ventricular myocytes by changing ionic current on cell membrane, although those are intrinsically quiescent non-pacemaking cells [1]. These artificial pacemaker cells are called biological pacemaker, which is expected as an alternative to electronic pacemaker. Various strategies to create a biological pacemaker have been examined [2], however, almost all these studies have used animal cells.

It is necessary for biological pacemaker engineering to understand the interaction between membrane potential and various ionic currents, which is difficult only by physiological experiments. In this paper, we use a mathematical model of human ventricular myocytes which is described by the nonlinear ordinary differential equations. We explore the bifurcation structure of the model changing the conductances of ion channels and investigate the methods to create the biological pacemaker from human ventricular myocytes. Furthermore, we examine the adequateness of "ventricular pacemaker" for cardiac pacemaker by comparing the pacemaker activities of ventricular pacemaker with those of the human sinoatrial node.

2. Mathematical model of human ventricular myocytes

Action potential is the temporal variation of the membrane potential (difference of electric potential between inside and outside of the cell membrane) caused by ion transfer through ion channels on the membrane according to electrochemical potential. Ion channels open and close depending on the membrane potential. Ions move inwards or outwards the cell membrane through the ion channels, as a result, action potential is generated. Various mathematical cell models describing the electrical characteristics of cardiac myocytes were proposed for various species or types of cells [4]. In this paper, we use the reduced ten Tusscher–Noble–Noble–Panfilov (TNNP) model [5], which is a human ventricular myocyte model developed from Hodgkin–Huxley equations [3]. The reduced TNNP model is given by the following equations:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{1}{C_\mathrm{m}}(I_\mathrm{stim} + I_\mathrm{Na} + I_\mathrm{CaL} + I_\mathrm{to} + I_\mathrm{Kr} + I_\mathrm{Ks} + I_\mathrm{K1} + I_\mathrm{NaCa} + I_\mathrm{NaK} + I_\mathrm{pCa} + I_\mathrm{pK} + I_\mathrm{bNa} + I_\mathrm{bCa}) \quad (1)$$

$$\frac{\mathrm{d}\chi}{\mathrm{d}t} = \frac{\chi_\infty(V) - \chi}{\tau_\chi(V)}, \quad (\chi = m, h, j, f_1, f_2, x_{r1}, x_s, s) \quad (2)$$

where V (mV) is the membrane potential, m, h, j, f_1, f_2, x_{r1}, x_s and s are the gating variables which express opening and closing dynamics of ion channels. C_m (μF/cm^2) is the membrane capacitance, I_stim (pA/pF) is the externally applied stimulus current, I_Na, I_CaL, I_to, I_Kr, I_Ks, I_K1, I_NaCa, I_NaK, I_pCa, I_pK, I_bNa and I_bCa (pA/pF) are the ionic currents which express the flow of ions through the ion channels. $\tau_\chi(V)$ and $\chi_\infty(V)$ are the time constant and the steady-state value of the gating variables, both of which are the functions depending on the membrane potential. General form of the ionic currents is given by the following equation:

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

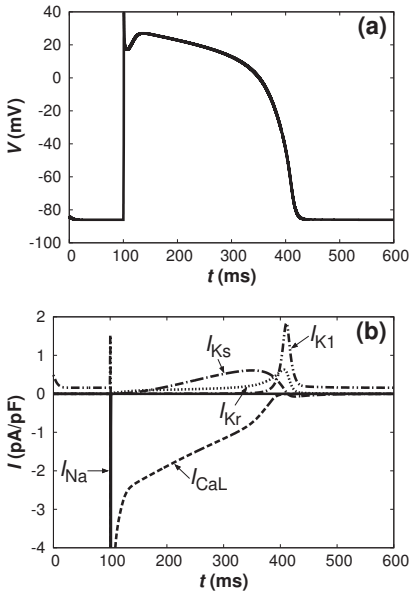

Figure 1: Action potential simulated by the reduced TNNP model, (a) membrane potential, (b) ionic current (negative current denotes inward current).

where G_{ion} (mS/cm^2) is the maximum conductance of ion channels, E_{ion} (mV) is the equilibrium potential. For the simplicity of bifurcation analysis, we included the additional coefficients c_{ion} (standard values are 1.0) in the model. For more details of the model, see the reference [5, 6].

Figure 1 shows the action potential simulated by the reduced TNNP model in the standard condition. The values of I_{Na} and I_{CaL} are (negatively) large and not shown in the range of in Fig. 1(b). In the standard condition, ventricular myocytes are electrically quiescent and keep a constant membrane potential (resting potential). When the ventricular myocytes receive the signals (pulse stimulus is applied at $t = 100$ (ms)), inward sodium current I_{Na} and subsequent inward calcium current I_{CaL} increase sharply and contribute to the upstroke of the action potential (depolarization). After the depolarization, since the outward currents cancel out the inward currents, the membrane potential keeps constant. Because the inward I_{CaL} gradually decreases and the outward potassium currents $I_{\mathrm{Ks}}, I_{\mathrm{Kr}}, I_{\mathrm{K1}}$ are activated, the membrane potential decreases (repolarization).

3. Methods of creating the biological pacemaker based on the bifurcation analysis

The pacemaker activity corresponds to the periodic oscillation of the membrane potential. In this section, we reveal the bifurcation structure of the reduced TNNP model and examine the method to initiate the pacemaking activity. We use the software AUTO [7] for the bifurcation analysis of the reduced TNNP model.

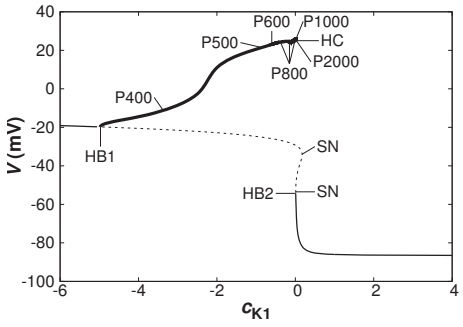

Figure 2: One-parameter bifurcation diagram as to c_{K1}. Solid and broken curves denote stable and unstable solution, respectively. Thick and thin curves denote the maximum value of periodic solution and equilibrium points, respectively.

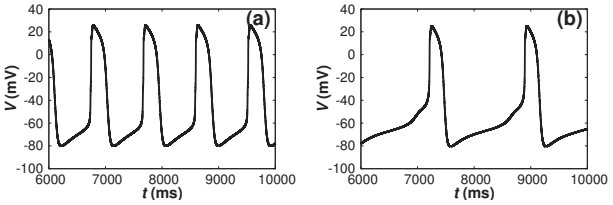

Figure 3: Time variation of the membrane potential, (a) $c_{\mathrm{K1}} = 0.01$, (b) $c_{\mathrm{K1}} = 0.025$.

3.1. Suppression of inward rectifier potassium current

Figure 2 shows the one-parameter bifurcation diagram, where the coefficient of the inward rectifier potassium current I_{K1} is a bifurcation parameter. The membrane potential V in the steady state is plotted for each value of c_{K1} in the diagram. HB, SN and HC denote the bifurcation points of Hopf, saddle-node, and homoclinic bifurcations, respectively. Periods of several periodic solutions are also labeled in the figure.

In the standard condition ($c_{\mathrm{K1}} = 1.0$), only a stable equilibrium point corresponding to the resting potential exists. The stability of equilibrium points changes at HB1, and the stable periodic solutions are generated. Period of periodic solution is increased as c_{K1} is increased, and eventually disappear with an infinitely large period at HC ($c_{\mathrm{K1}} = 0.025$). For each value of c_{K1} between HB1 and HC, a stable periodic solution exists. Figure 3 shows typical waveforms of the membrane potential corresponding to the stable periodic solution. The membrane potential spontaneously oscillates without extrinsic stimulus.

Figure 2 indicates that the spontaneous action potentials are generated by suppressing the inward rectifier potassium current I_{K1}. The pacemaker activity, however, is generated only within the range $0 \leq c_{\mathrm{K1}} \leq 0.025$ ($c_{\mathrm{K1}} < 0$ is physiologically impossible). Therefore, we need to keep c_{K1} less than 0.025 to induce continual pacemaker activity, which is difficult to implement in a cell. Although we have exam-

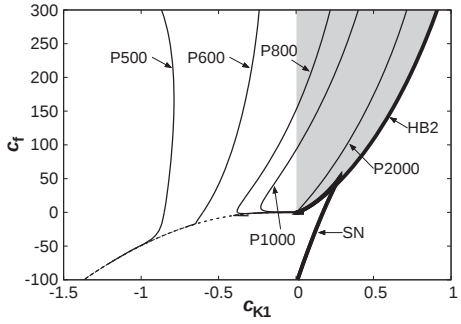

Figure 4: Two-parameter bifurcation diagram as to the two bifurcation parameters c_{K1} and c_f. Solid and broken curves denote stable and unstable solution, respectively.

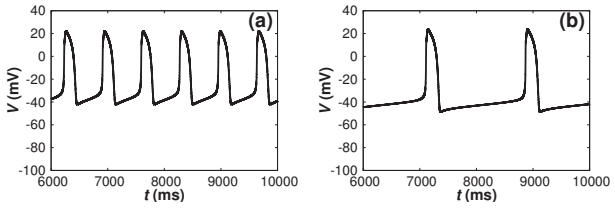

Figure 5: Time variation of the membrane potential, (a) $c_{K1} = 0.01, c_f = 300$, (b) $c_{K1} = 0.4, c_f = 150$.

ined cases of other potassium currents such as I_{Kr}, I_{Ks} and I_{to}, pacemaker activity have not appeared.

3.2. Induction of hyperpolarization-activated current with suppression of inward rectifier potassium current

Pacemaker activity is caused by the net inward current during the diastolic depolarization (slow depolarization phase subsequent to the repolarization), which increases the membrane potential to the threshold of the next action potential. Hyperpolarization-activated current I_f, principally present in the sinoatrial node (pacemaker cells), is activated by hyperpolarized membrane potential and flows inwardly during the diastolic depolarization. Because of these properties, I_f is considered to an important current for pacemaker activity of the sinoatrial node [8]. Since there is little I_f in normal ventricular myocytes (model), we use Verkerk model [9] which is a I_f model for human sinoatrial node cell. Verkerk model is described as follows:

$$I_f = c_f G_f y (V - E_f) \tag{4}$$

$$\frac{dy}{dt} = \frac{y_\infty(V) - y}{\tau_y(V)} \tag{5}$$

where y is the gating variable, and c_f is the conductance coefficient (standard value is 0.0).

Figure 4 shows the two-parameter bifurcation diagram as for c_{K1} and c_f. Curves denote the loci of the bifurcation points, and periodic solution with specific periods which are shown in Fig. 2. SN curve bents sharply at $(0.28, 52)$

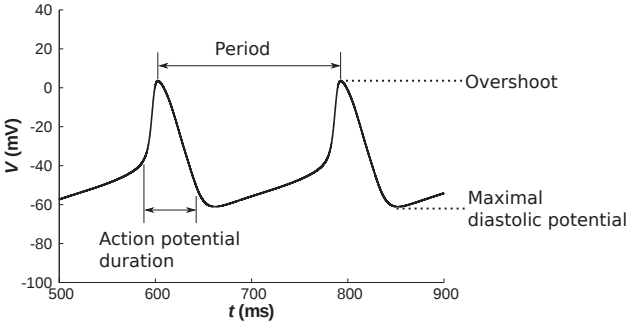

Figure 6: Feature values of pacemaker activity in the sinoatrial node.

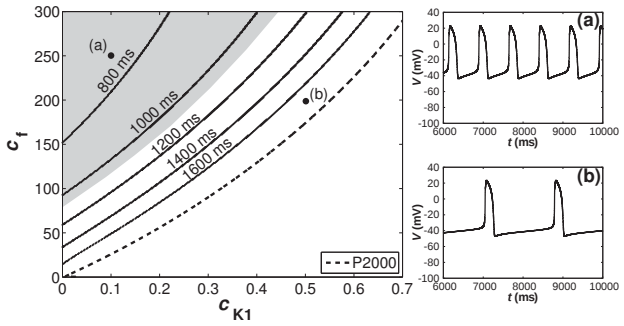

Figure 7: Contour curves of period.

(cusp point). HB2 emerges from SN at $(0, -4.0)$, and runs to the upper right of the figure. The contour lines of the periods run to the upper right as c_f is increased. The periodic solution of the membrane potential is generated in the shaded area of Fig. 4. Figure 5 shows typical time course of stable periodic orbits in the shaded area. The shaded area is broadened to the upper right as c_f is increased, which indicates the range of c_{K1} generating the pacemaker activity is extended by the induction of I_f. However, we change c_f much larger than c_{K1} in Fig. 4, which may be physiologically impossible. This is a future work.

4. Quantitative evaluation of the biological pacemaker

The biological pacemaker generated by the variation of the ionic currents in human ventricular myocytes is not always suitable for the cardiac pacemaker. In this section, we investigate the adequateness of the ventricular pacemaker for the cardiac pacemaker based on the quantitative comparison with the pacemaker activity of the human sinoatrial node as for the four characteristics: period, action potential duration at 90% repolarization (APD_{90}), overshoot, and maximal diastolic potential (MDP) (illustrated in Fig. 6). Figures 7–10 respectively show the contour curves of the four feature values plotted on a c_{K1}–c_f plane. The parameter values are limited within the range of $c_f < 300$ and the period of corresponding periodic solution is less than 2000 ms. The shaded areas of Fig. 7–10 denote neighbor-

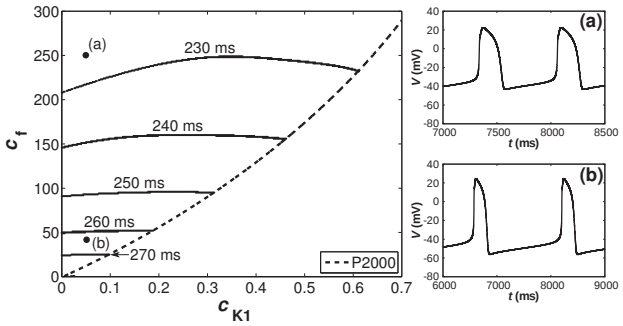

Figure 8: Contour curves of action potential duration.

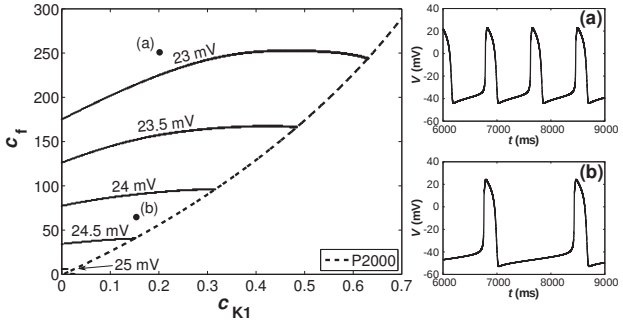

Figure 9: Contour curves of overshoot.

hood (±30%) of the feature values in a sinoatrial node cell [8]. Period and MDP can be controlled within the proper range by setting the parameters in shaded area. However, APD_{90} and overshoot in ventricular myocytes are very different from those in sinoatrial node cells. These results indicate the pacemaker activity induced by changing the ionic currents I_{K1} and I_f in ventricular myocytes may be inadequate for the cardiac pacemaker.

5. Conclusion

We have investigated the method to create the biological pacemaker from human ventricular myocytes by exploring the bifurcation structure of the mathematical cell model. Bifurcation analysis as for the conductance of ionic currents revealed that the pacemaker activity is induced by changing the inward rectifier potassium current I_{K1}. Moreover, incorporating hyperpolarization-activated current I_f increased the critical value of I_{K1} conductance for pacemaker activity to emerge. These results indicate the ventricular pacemaker can be created by changing I_{K1} and I_f simultaneously, although the action potantial waveform of the ventricular pacemaker differs from that of the sinoatrial node in some respects. However, the biological pacemaker may function adequately as a pacemaker, even if its waveform is slightly different from the sinoatrial node. Therefore, we will consider the ventricular pacemaker ability to propagate the action potential to non-pacemaking cells us-

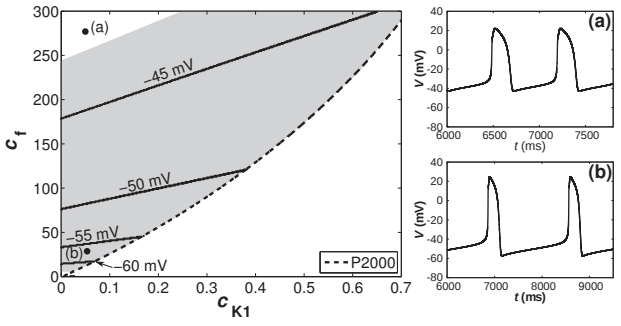

Figure 10: Contour curves of maximal diastolic potential.

ing coubled cell model as the future work.

Acknowledgments

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