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Modified Luo-Rudy model and its bifurcation analysis for suppressing alternans

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Abstract—Electrical alternans is alternating amplitude from beat to beat in the action potential for the cardiac cell. It has been associated with ventricular arrhythmias in many clinical studies, however, its dynamical mechanisms remain unknown. The reason is that we do not have simple network models of the heart system. Recently, Yazawa clarified network structure of the heart and the central nerve system. In this study, we construct a simple model of the heart system based on Yazawa's experimental data. Using this model, we clarify that the reversal potential for the time-independent potassium current plays a key role of generating alternans. This result indicates that if the cardiac cell has some problems such as channelopathies, then there is great risk of occurring alternans.

1. Introduction

Electrical alternans is beat to beat alternation in the action potential duration or amplitude for the cardiac cell. It is well known that the alternans triggers cardiac electrical instability (ventricular arrhythmias) and causes sudden cardiac death [1]. Thus, studies of alternans using mathematical models are important for reducing the risk of sudden death. Most of them are using difference equations for modeling alternans [2, 3]. The dynamics is very simple and it is easy to analyze. As the results, it is shown that generation of alternans is related with the period-doubling bifurcation or the border-collision bifurcation[4]. More realistic models using partial differential equations are proposed. Arce clarified the dependency of $[K]_o$ (extracellular concentrations of potassium) [5] and Bauer investigated influence of ionic conductances on alternans[6]. Usually, ventricular muscle cells receive signals from pacemaker cells. However, in these studies, the stimulus is a rectangular wave, because the coupling scheme from the pacemaker cell to the ventricular cell is unknown.

Recently, Yazawa clarified network structure of the heart and central nerve systems (CNS) by the experiment on American lobsters[7]. He identified the types of the synapses between small and large, large and muscle cells. In the previous study, we constructed a simple mathematical model of the heart system based on Yazawa's experimental data[8]. In this paper, we propose a simpler model. By numerical analysis of our model we obtain that two parameters (the conductance of the sodium ion and free concentration of the potassium ion in the extracellular compartment) play key roles of generating alternans. Our model is based on the data from the experiment on lobsters, however, it is said that all animals have almost the same DNA information to control the heart, thus our result could be applicable to the human heart system.

2. Systems

2.1. LR model with synaptic current

In [8], we only considered the subnetwork of the large cell to the muscle cell as the first step of our study. For the large and muscle cell we used the YNI (Yanagihara-Noma-Irisawa) [9] and LR(Luo-Rudy I) [10] model, respectively. We treated the large cell as the pacemaker cell. Considering the synaptic current from the pacemaker cell to the muscle cell, the dynamics of the pacemaker cell do not affect that of the muscle cell. Thus in this study we only consider the muscle cell with a periodic force. The period of the external force (usually called BCL: basic cycle length) is assumed to be 380[msec]. The membrane potential V of the LR model with the synaptic input is described by

$$C\frac{dV}{dt} = -(I_{Na} + I_{Ca} + I_K + I_{K_1} + I_{Kp} + I_b + I_{syn}) \qquad (1)$$

where the meaning and the equations for each current is given in Appendix. The synaptic current I_{syn} from the large cells to the muscle cells is given by

$$I_{syn} = G_{syn}(V - V_{syn})s(t^*) \qquad (2)$$

where G_{syn} is the maximum synaptic conductance, V_{syn} is the reversal potential and $s(t^*)$ is given by

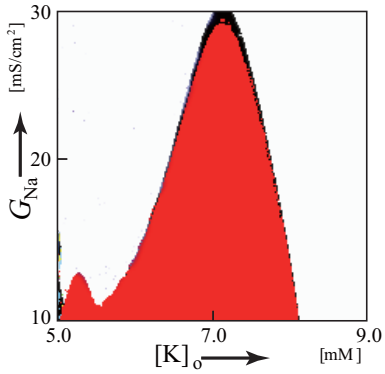
$$s(t^*) = \frac{\tau_1}{\tau_2 - \tau_1}\left(-\exp\left(-\frac{t^*}{\tau_1}\right) + \exp\left(-\frac{t^*}{\tau_2}\right)\right) \qquad (3)$$

where τ_1 and τ_2 are the raise and the decay time of the synapse, respectively. We identify these values ($\tau_1 = 5.5$ and $\tau_2 = 90.0$[msec]) from the experimental data[7]. t^* is the time which is reseted at every nT (n is an integer and T is BCL).

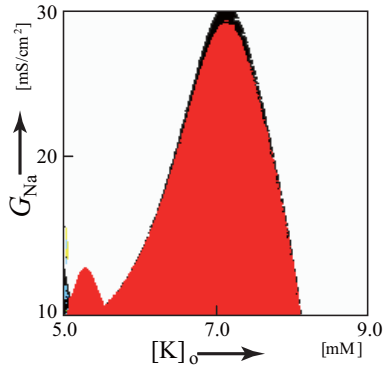
2.2. Approximation of discontinuous functions

In Eq. (1), I_{Na} and I_K are given by

$$I_{Na} = G_{Na}m^3hj(V - E_{Na}), \quad I_K = G_K XX_i(V - E_K)$$



(a) Original model (discontinuous functions)



(b) Modified model (continuous functions)

Figure 1: Parameter plane ($[K]_o$, G_{Na}) colored by its attractor. White: period 1, red: period 2, black: non-period(quasi-period or chaos).

where E_{Na} and E_K are the reversal potential, G_{Na} and G_K are the maximum ionic conductance for sodium(Na) and potassium(K) current, respectively, and m, h, j and X are given by

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y}, \quad (y = m, h, j, X) \tag{4}$$

$$\tau_y = \frac{1}{\alpha_y + \beta_y}, \quad y_\infty = \frac{\alpha_y}{\alpha_y + \beta_y}. \tag{5}$$

Here, α_j, β_j, α_h, β_h and X_i are described by discontinuous functions. For example, β_j and X_i are given by

for $V \geq -40$

$$\beta_j(V) = \frac{0.3 \cdot \exp(2.535 \cdot 10^{-7} V)}{1 + \exp\{-0.1(V + 32)\}} \tag{6}$$

for $V < -40$

$$\beta_j(V) = \frac{0.1212 \cdot \exp(-0.01052V)}{1 + \exp\{-0.1378(V + 40.14)\}}, \tag{7}$$

for $V > -100$

$$X_i(V) = \frac{2.837 \cdot (\exp\{0.04(V + 77)\} - 1)}{(V + 77) \cdot \exp\{0.04(V + 35)\}} \tag{8}$$

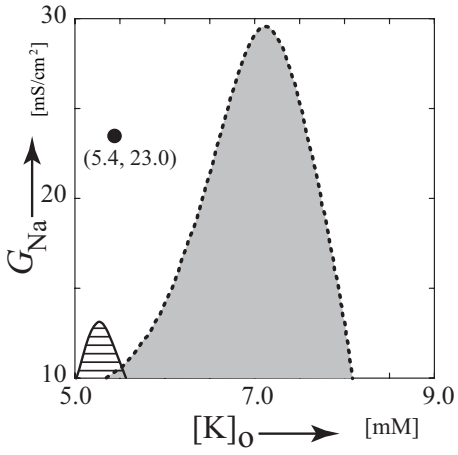


Figure 2: Bifurcation diagram. Alternans is observed in the shaded region. The boundaries indicate the period-doubling bifurcation(dashed) and saddle-node bifurcation(solid). The closed circle indicates the original values of these parameters.

for $V \leq -100$

$$X_i(V) = 1.0. \tag{9}$$

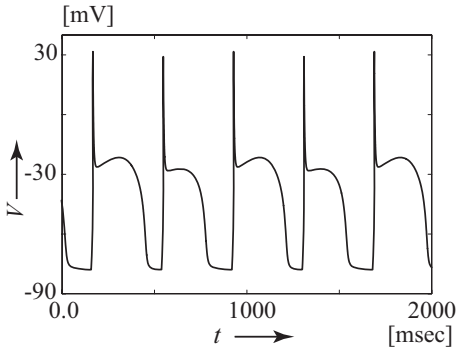
Considering a large number of neurons, discontinuous functions switched by some threshold values are not suitable for bifurcation analysis, because the algorithm becomes very complicated. We propose the continuous functions version of the Luo-Rudy model using sigmoidal functions. For example, $\beta_j(V)$ in Eqs. (6) and (7) are combined into one equation

$$\beta_j(V) = \text{Eq.(6)} \cdot 0.5(1 + \tanh\{100 * (V + 40)\}) + \text{Eq.(7)} \cdot 0.5(1 + \tanh\{-100 * (V + 40)\}). \tag{10}$$

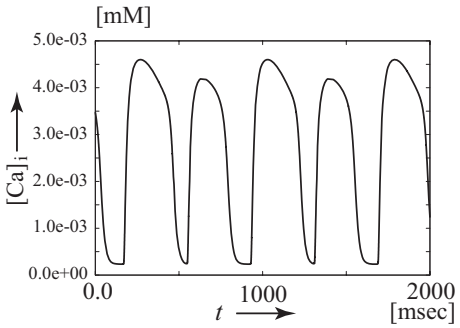
3. Results

We show the effectiveness of the approximation (e.g. Eq. (10)) in Fig. 1(a) and (b). Both figures are obtained by the brute-force method. Comparing both figures, we can see that the approximation works very well. In both figures, we observe 2-periodic solutions in the parameter region colored by red. We study bifurcation phenomena correlated to alternans in the modified model. The values of the parameters related with the synapse are fixed as $G_{syn} = 4.0$, $V_{syn} = -29$.

Figure 2 indicates a two-parameter bifurcation diagram on the parameter plane $[K]_o$ (extracellular concentrations of potassium) and G_{Na} (the conductance for the sodium current). In this parameter region we observe two types of two-periodic solutions. However, one of them observed in the hatched region is not alternans. Figure 3(a) shows a waveform of the membrane potential at $G_{Na} = 23$ and $[K]_o = 7.0$(in the shaded region). In Fig. 3(a) it is hard to recognize alternating amplitude, however, the action potential duration surely shows alternans. Figure 3(b) shows



(a) Membrane potential.

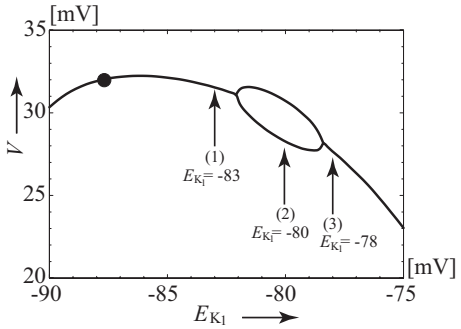


(b) Intracellular concentrations of calcium.

Figure 3: Waveforms of alternans observed at $G_{Na} = 23$ and $[K]_o = 7.0$.

a waveform of $[Ca]_i$ (intracellular concentrations of calcium). The strength of the contraction of muscles is proportional to an amount of the calcium ion in the intracellular compartment. From this figure, we can see that the contraction of the cardiac muscle shows alternation.

The parameter $[K]_o$ affects the values of other parameters (G_K, G_{K_1}, E_K and E_{K_1}). Each equation as a function of $[K]_o$ is shown in Appendix. We study bifurcations depending on these parameters and obtain that the essential parameter of generating alternans is E_{K_1} (the reversal potential for the time-independent potassium current). Figure 4(a) shows a one-parameter bifurcation diagram. From this figure we can see existence of the period-doubling bifurcation. The peak of V is decreased as the E_{K_1} is increased. At the points marked by (1) to (3) waveforms of V and I_{K_1} are shown in Fig. 4(b) and (c), respectively. In the waveforms of V (Fig. 4(b)) alternans is observed for $E_{K_1} = -80$. Considering I_{K_1} (the outward potassium current from the cell), the current for case (3) comes to the peak rapidly at $t \simeq 300$ compared with case (1); deceasing of the membrane potential V for case (3) is faster than that for case (1). On the other hand, in case (2) the current comes to the peak alternately (slowly and rapidly) as shown in Fig. 4(c); this generates alternating oscillations for V. Further decreasing of E_{K_1} leads to a cardiac arrest. The clarification of reasons why only the change of E_{K_1} leads to alternans is one of our open problems.



(a) One-parameter bifurcation diagram. The vertical axis indicates the maximum value of the membrane potential for the muscle cell.

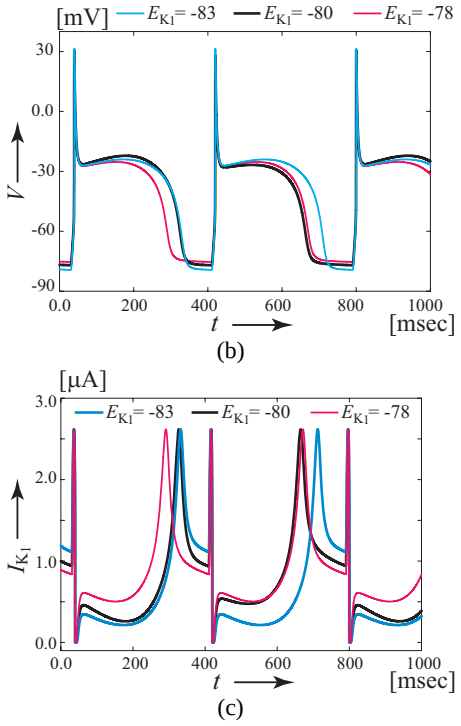


Figure 4: (a)One-parameter bifurcation diagram changing E_{K_1} and waveforms of (b)V and (c) I_{K_1}.

4. Discussion

In this paper we have investigated the mechanism of generating alternans in the single model with the synaptic current.

In most of previous studies the control parameter for generating alternans was period of an external stimulus modeled by an ideal pulse wave[12]. It is thought that its ideal pulse corresponds to the signal from the pacemaker cell to the muscle cell in the real heart. However, in the real system input signals to the muscle cell change from time to time. In our proposed model based on Yazawa's experiment the input to the muscle cell is realized by the synapse from the pacemaker cell. Thus, the timing and the amplitude of synaptic inputs depend on the membrane potential of the pacemaker cell and the muscle cell, respectively.

In our model, we obtained alternans even though the period of stimulus is unchanged; the pacemaker cell is normal. We chose the several ionic conductances as control parameters. Thus, we could study the mechanism of generating alternans caused by problems such as channelopathies in the muscle cell. We found that free concentration of the potassium ion in the extracellular compartment ($[K]_o$) and the sodium ionic conductance are key parameters to generate alternans. $[K]_o$ affects several other parameters. We studied all of them and found that E_{K_1} (the reversal potential for the time-independent potassium current) is the most important parameter correlated with $[K]_o$. Usually the change of E_{K_1} only affects the value of the resting membrane potential. However, in this study, we found that the alternating oscillations suddenly appear by a slight increase of E_{K_1}.

It was the first observation of alternans when the value of the sodium ionic conductance was decreased. From this result we saw that a decrease in influx of sodium ionic currents increases the risk of alternans. From the biological aspect, an amount of the sodium ion is controlled by the kidneys. If there are problems in the kidneys, it becomes a less amount of the sodium ions and some diseases such as hyponatremia occur. Our result suggests that decreasing the sodium current also triggers alternans as a sign of sudden death.

Our open problems are as follows:(1) study the whole network, (2) investigate more detailed model such as the Shannon model [13] describing the calcium dynamics[14, 15] and (3) develop more effective control methods of generating alternans than those in references such as [16].

Acknowledgments

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References

[1] D.S. Rosenbaum, L.E. Jackson, J.M. Smith, H. Garan, J.N. Ruskin and R.J. Cohen, *Electrical alternans and vulnerability to ventricular Arrhythmias*, N. Engl. J. Med., **330** (1994), 235–241.

[2] J.B. Nolasco, and R.W. Dahlen, *A graphic method for the study of alternation in cardiac action potentials*, J. Appl. Physiol., **25** (1968), 191–196.

[3] M.L. Kuller, M.L. Riccio and R.F. Gilmour, *Dynamic restitution of action potential duration during electrical alternans and ventricular fibrillation*, Am. J. Physiol. Heart Circ. Physiol., **275** (1998), 1635–1642.

[4] C.M.Berger, X. Zhao, D.G. Schaeffer, H.M. Dobrovolny, W. Krassowska and D.J. Gauthier, *Period-doubling bifurcation to alternans in paced cardiac tissue: crossover from smooth to border-collision characteristics*, Phys. Rev. Lett., **99** (2007), 058101.

[5] H. Arce, A. Lopéz and M.R. Guevara, *Triggered alternans in an ionic model of ischemic cardiac ventricular muscle*, Chaos, **12** (2002), 807–818.

[6] S. Bauer, G. Röder and M. Bär, *Alternans and the influence of ionic channel modifications: Cardiac three-dimensional simulations and one-dimensional numerical bifurcation analysis*, Chaos, **17** (2007), 015104.

[7] T. Yazawa, J.L. Wilkens, H.E.D.J. ter Keurs, M.J. Cavey, *Structure and contractile properties of the ostial muscle (musculus orbicularis ostii) in the heart of the American lobster*, J. Comp. Physiol. B, **169** (1999), 529–537.

[8] H. Kitajima and T. Yazawa, *Analysis of a cardiac mathematical model for suppressing alternans*, IEICE Tech. Repo. NLP2010-123, (2010), 61–64.

[9] K. Yanagihara, A. Noma and H. Irisawa, *Reconstruction of sinoatrial node pacemaker potential based on the voltage clamp experiments*, Jpn. J. Physiol., **30** (1980), 841–857.

[10] C.H. Luo and Y. Rudy, *A model of the ventricular cardiac action potential. Demoralization, repolarization, and their interaction.*, Circ. Res., **68** (1991), 1501–1526.

[11] B. Pfeuty, G. Mato, D. Golomb and D. Hansel, *The combined effects of inhibitory and electrical synapses in synchrony*, Neural Computation, **17**(2005), 633–670.

[12] R. Thul and S. Coombes, *Understanding cardiac alternans: A piecewise linear modeling framework*, Chaos, **20** (2010), 045102.

[13] T.R. Shannon, F. Wang, J. Puglisi, C. Weber and D.M. Bers, *A mathematical treatment of integrated Ca dynamics within the ventricular myocyte*, Biophysical Journal, **87** (2004), 3351–3371.

[14] K.R. Laurita and D.S. Rosenbaum, *Cellular mechanisms of arrhythmogenic cardiac alternans*, Prog. Biophysics and Molecular Biology, **97** (2008), 332–347.

[15] J.G. Restrepo and A. Karma, *Spatiotemporal intracellular calcium dynamics during cardiac alternans*, Chaos, **19** (2009), 037115.

[16] B. Echebarria and A. Karma, *Spatiotemporal control of cardiac alternans*, Chaos, **12** (2002), 923–930.

Appendix

Ionic currents in Eq. (1) are given by

$$
\begin{aligned}
I_{Si} &= G_{Si} d f (V - E_{Si}), \quad \text{(slow inward current)},\\
I_K &= G_K X X_i (V - E_K), G_K = 0.282\sqrt{[K]_o/5.4},\\
&\quad E_K = \frac{RT}{F}\ln\left(\frac{[K]_o + PR_{NaK}[Na]_o}{[K]_i + PR_{Nak}[Na]_i}\right),\\
&\quad \text{(time-dependent potassium current)},\\
I_{K_1} &= G_{K_1} K_{1_\infty}(V - E_{K_1}), G_{K_1} = 0.6047\sqrt{[K]_o/5.4},\\
&\quad E_{K_1} = \frac{RT}{F}\ln\left(\frac{[K]_o}{[K]_i}\right),\\
&\quad \text{(time-independent potassium current)},\\
I_{Kp} &= 0.0183 K p (V - E_{Kp}), \quad \text{(plateau potassium current)},\\
I_b &= 0.03921(V + 59.87), \quad \text{(background current)}.
\end{aligned}
$$

Detailed explanation of these equations is written in [10].