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Alternans in a Crustacean Cardiac Model

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Abstract—Alternans is a kind of arrhythmia, which shows the alternation of the action potential duration (APD) or the amplitude of the action potential, and is a sign of future cardiac arrest in animal experiments. In this paper, we investigated the parameter dependence of the alternans using a mathematical crustacean cardiac model. We determined that the conductance of the calcium-dependent potassium current for the small cell is a key to generating alternans.

1. Introduction

Alternans is a beat-to-beat alternation in the action potential duration for a cardiac cell and may cause sudden cardiac death [1, 2, 3, 4]. Thus, studies of alternans using mathematical models are important to reduce the risk of sudden death. We investigated the Luo-Rudy (LR) model [5] with an external synaptic current and clarified that the alternans is generated by the period-doubling bifurcation due to increasing the value of [K]o (extracellular potassium ion concentration) [6]. [K]o affects the conductivity and the reversal potentials of several potassium currents. We were able to determine that increasing the reversal potential (E_{K1}) of the time-independent potassium current is important for the occurrence of alternans [7]. Our results showed that even though the rhythm from the pacemaker cell is normal, the alternans occurs due to the problem of the ventricular muscle.

As a next step, we have to investigate the system of making rhythmic signals, which stimulate the ventricular muscle. Here, we use a mathematical model of the crustacean heart. Because the crustacean cardiac pacemaker cells consist of a small number of neurons (four small cells (SC) and five large cells (LC), which drive muscle cells (MC)). Moreover, the network structure of the heart and the central nervous system, and the types of synapses between the SCs and LCs, the LCs and MCs, were clarified through an experiment on American lobsters [8]. Ball et al. proposed a mathematical model of the crustacean cardiac motor neurons composed of the LC and SC [9], which make signals to the cardiac muscle cells. The SCs and LCs are synchronized in each group, thus only one pair is considered. In [10], we modified some parameter values of this model to reproduce more accurate waveforms of the membrane potentials of the SC and LC. Then, we clarified that decreasing the G_{Kd} (conductance of delayed potassium current) triggers the alternans. However, the reproducibility of the experiment was limited, because the waveforms of the membrane potential for the alternans between the experiment and simulation were quite different. In particular, a long burst corresponding to the alternans for the SC was not observed in the simulation.

In this paper, we studied all combinations of the parameters (conductances of all ionic currents) and determined that a key parameter of generating a long burst is G_{KCa} (conductance of calcium-dependent potassium current). By decreasing the value of G_{KCa} for both the SC and LC, we can reproduce the firing patterns of an experiment on a hermit club.

2. Model Equation

A schematic diagram of the model proposed by Ball [9] is shown in Fig. 1. This is a two-compartment model divided by the soma and the axon. The excitatory synapses of the axon of the LC (it is not shown in Fig. 1) are connected to the cardiac muscle cells. Therefore the output in this model is the membrane potential of the axon of the LC.

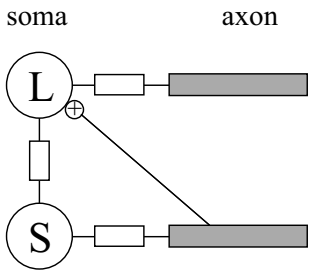


Figure 1: Schematic diagram of the model. S and L are small cell and large cell, respectively. White rectangle and circle with plus sign represent the electrical synapse or gap junction and the excitatory synapse, respectively.

We summarize the model equations described in [9]. The membrane potentials of the LC is described by:

$$C_s \frac{dV_s}{dt} = - g_{Ls}(V_s - E_{Ls}) - g_c(V_s - V_a) - \sum I_{i,s} - I_{syn} - I_{gap}$$

$$C_a \frac{dV_a}{dt} = - g_{La}(V_a - E_{La}) - g_c(V_a - V_s) - \sum I_{i,a}$$

where V_s and V_a are the membrane potential for the soma and the axon, respectively. C_s/C_a, g_{Ls}/g_{La} and E_{Ls}/E_{La} are the membrane capacitances, the leak conductances and the reversal potentials for the soma/axon compartment. g_c is the coupling conductance between the soma and the axon. Here, g_c with two connexons is given by

$$g_c = (s_1 + s_2)g_{min} + s_0 g_{max},$$

where $s_i (i = 0, 1, 2)$ is the fraction of channels in state S_i:

- S_0: gate 1 open, gate 2 open,
- S_1: gate 1 open, gate 2 close,
- S_2: gate 1 close, gate 2 open.

Note that there is little evidence for the case of both gates being closed. Using the constraint $s_0 + s_1 + s_2 = 1$, the gate kinetics is described by

$$\frac{ds_1}{dt} = \beta(u) - [\alpha(u) + \beta(u)]s_1 - \beta(u)s_2$$
$$\frac{ds_2}{dt} = \beta(-u) - [\alpha(-u) + \beta(-u)]s_2 - \beta(-u)s_1$$

where $u = V_s - V_a$ and

$$\alpha(u) = \lambda \exp[-A_\alpha(u - v_0)]$$
$$\beta(u) = \lambda \exp[-A_\beta(u - v_0)].$$

The parameter values are $\lambda = 0.68, A_\alpha = A_\beta = 0.10[\mathrm{mV}^{-1}]$, $g_{max} = 0.05$, $g_{mix} = 0.01$ and $u_0 = 4.0$ [mV] [11].

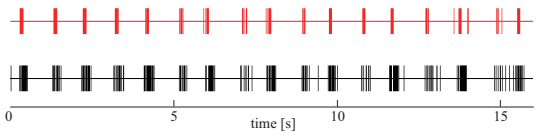
The synaptic and gap currents from the SC to LC are given by I_{syn} and I_{gap}, respectively. $I_{(i,s)}/I_{(i,a)}$ are ionic currents for the soma/axon described by

$$I_{i,(s \text{ or } a)} = G_i m^p h^q (V - E_i)$$

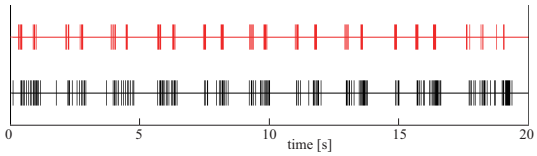
where G_i is the maximum conductance, m is the activation variable with exponent p, h is the inactivation variable with exponent q. Ionic currents are i = CaT (transient calcium current), Cas (persistent calcium current), A (early outward potassium current), Kd (delayed outward potassium current), KCa (calcium-dependent potassium current), leak (leak current) for $I_{(i,s)}$, and i = Na (transient sodium current), Kd (delayed outward potassium current), leak (leak current) for $I_{(i,a)}$. The dynamics of the gating variables x (m or h) is given by

$$\frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)}$$

where x_∞ is the steady state value and τ is its time constant. The membrane potentials of the SC are also expressed by the similar equations, but the kind of the ionic currents is different. For detailed explanation and the values of the parameters, see [9].



(a) normal pulse train



(b) abnormal pulse train

Figure 2: Pulse trains corresponding to contraction of cardiac muscle cell for hermit club. Red and black indicate pulses of LC and SC, respectively.

3. Results

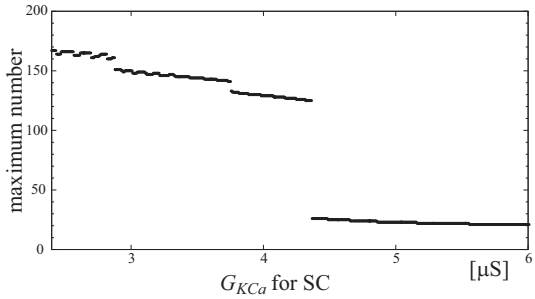
3.1. Experiment

Figure 2 shows firing patterns of an isolated cardiac ganglion cells of a hermit club. From the observed data, we separate the firing patterns of the SC and LC. Red and black lines indicate firing timing of the LC and SC, respectively. In Fig. 2(a), bursts of the SC and LC have one to one relationship, which corresponds to a normal state. On the other hand, we observe a long burst of the SC in Fig. 2(b) and the almost two (red) to one (black) relationship appears. This state corresponds to alternans.

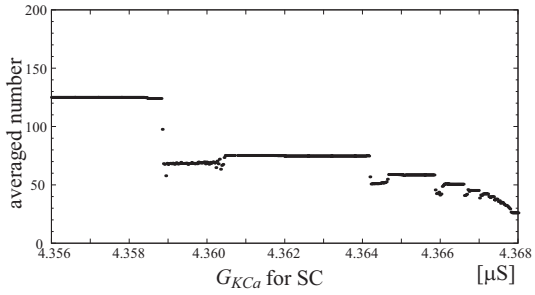
3.2. Simulation

We studied the occurrence of a long burst of the SC for 91 ($_{14}C_2$) parameter planes of 14 conductances of ionic currents. We determined that a key parameter of generating a long burst is G_{KCa}. Figure 3(a) shows a number of spikes in one burst when changing the value of G_{KCa} for the SC. The vertical axis indicates a maximum number of spikes in one burst after a transient period. If this number is large, we observed a long burst. From Fig. 3(a), we can see that a long burst occurs at $G_{KCa} \simeq 4.3$. An enlarged diagram of Fig. 3(a) around this point is shown in Fig. 3(b). The vertical axis shows an averaged number of spikes in 200 bursts. Figure 4 indicates waveforms of the membrane potentials of the axon for the SC and LC. At $G_{KCa} = 4.368$ we observed persistent normal bursts as shown in Fig. 4(a). Decreasing the value of G_{KCa}, a long burst suddenly appeared among the normal burst. Further decreasing G_{KCa} triggered increase the appearance of a long burst and the alternate firing pattern of the normal and long busts was observed between $G_{KCa} \simeq 4.359$ and 4.364. Finally, persistent long bursts as shown in Fig. 4(b) appeared for $G_{KCa} < 4.359$.

However, we could not observe the second burst of the axon for the LC in one burst for the SC. We investigated burst activity for changing other parameters' values and

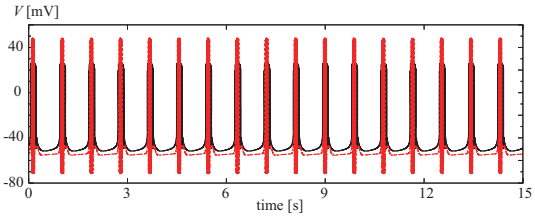


(a) Maximum number

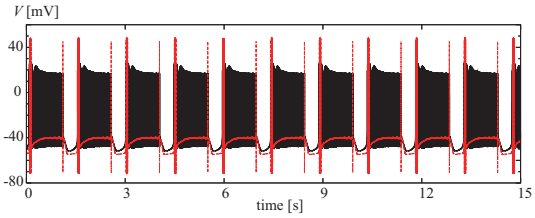


(b) Averaged number in a part of (a)

Figure 3: Number of spikes in one burst as a function of G_{KCa}



(a) G_{KCa} for SC is 4.368.



(b) G_{KCa} for SC is 4.356.

Figure 4: Waveforms of membrane potential for SC(black) and LC(red) axon

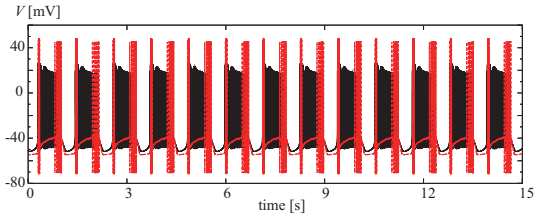


Figure 5: Waveforms of membrane potential for SC and LC axon. G_{KCa} for SC and LC are 4.356 and 35.5, respectively.

we determined that G_{KCa} for the LC is important to reproduce the experimental results. Figure 5 shows waveforms of membrane potentials for the SC and LC axon. Comparing it with Fig. 2(b) we could reproduce the experimental waveforms. Thus, we conclude that one of causes of generating alternans is G_{KCa}; decreasing this conductance triggers alternans. Note that the time scale was changed to $\tau = \omega t$, where $\omega = 2.0$ and $\omega = 4.0$ in Fig. 4(a) and, Figs. 4(b) and 5, respectively. Thus, we have to obtain these figures at the same time scale as one of our open problems.

4. Conclusion

We investigated the parameter dependence of the alternans in a mathematical crustacean cardiac model. 91 parameter planes of conductances of all ionic currents were carefully checked. As a result, we determined that the conductance of calcium-dependent potassium current for the small cell is a key to generating alternans which had been shown in an experiment on a hermit club. Thus, we can reproduce the waveforms of the alternans by changing the value of the conductances. We are now trying to clarify bifurcation structure in the parameter plane. It is said that crustacean hearts and human hearts are fundamentally the same in terms of morphology and physiology [12, 13]; thus, our result could be applicable to the human heart system.

Recently, it is reported that calcium dynamics is important for the occurrence of the alternans [14, 15, 16, 17, 18, 19, 20, 21]. Thus, studying the detailed model for calcium dynamics is also one of our open problems.

Acknowledgment

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