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Slow-Fast Analysis of the Generation Mechanism of Bursting Oscillation in a Pancreatic β-cell Cluster

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Abstract—Pancreatic β-cells secrete insulin and adjust the blood-sugar level. In the present paper, by using two kinds of Hodgkin-Huxley-type pancreatic β-cell models with or without a calcium store, it is shown that the model which considers a calcium store can reproduce the physiological experimental result that the blockage of gap junction reduces the insulin secretion [3]. We clarify the mechanism of the difference between the two models with and without a calcium store by slow-fast decomposition analysis and 2-parameter bifurcation analysis.

1. Introduction

In response to glucose, pancreatic β-cells in the islets of Langerhans secrete insulin. This insulin facilitates the use and uptake of glucose in target tissues. In this way, insulin plays a great role in the adjustment of the blood-sugar level. On the other hand, the membrane potential of β-cell shows characteristic wave known as bursting which has two phases, active and silent one. It is believed that insulin secretion is greatly related to the bursting of pancreatic β-cell.

In this paper, two kinds of single pancreatic β-cell models which are based on [1] and [2] are used. The former considers voltage-dependent Ca^{2+} and K^+ channel, Ca^{2+}-sensitive K^+ channel and pump activity of Ca^{2+}. The latter assumes calcium stores in the cell and considers voltage-dependent Ca^{2+} and K^+ channel, cation nonselective channel, pump activity of Ca^{2+} and Ca^{2+} current from the calcium store. However the dynamical role of the calcium store in the bursting of β-cells has not been verified yet.

β-cells are connected by gap junctions and constitute a cluster. Thus we study the influence of coupling strength between β-cells on the bursting by using the two types of β-cell models with and without a calcium store. We show that the two different models produce the essentially different bursting in coupled state while they produce almost similar behavior in uncoupled or isolated state. Using slow-fast decomposition analysis and 2-parameter bifurcation analysis, we clarify the generation mechanism of the different bursting and thus clarify the effect of a calcium store on the bursting of a β-cell cluster.

2. Hodgkin-Huxley-Type Models of a Pancreatic β-cell

2.1. Model without a Calcium Store

We assume that the cluster structure is a cube and each cell is connected to nearest six cells and the boundary (edge and corner) is insulated. The pancreatic β-cell cluster model without a calcium store are described by [1]:

$$\begin{aligned} C_m \frac{dV_i}{dt} &= -g_K n_i^4 (V_i - V_K) - g_{KC}\left(\frac{C_i}{K_d + C_i}\right)(V_i - V_K) \\ &\quad -g_C m_i^3 h_i (V_i - V_C) - g_L (V_i - V_L) \\ &\quad -\sum_j g_{i,j}(V_i - V_j) \end{aligned} \tag{1}$$

$$\frac{dC_i}{dt} = f[-k_1 g_C m_i^3 h_i (V_i - V_C) - k_C C_i] \tag{2}$$

$$\frac{dy_i}{dt} = \frac{(y_{i\infty} - y_i)}{\tau_y}, \qquad y = n, m, h \tag{3}$$

where V_i is the membrane potential, C_i is the calcium concentration, and n_i, m_i, h_i are the gate variables of the i-th cell. $g_{i,j}$ is the coupling conductance between i-th cell and j-th cell, and k_C is the flow speed constant of Ca^{2+} which corresponds to the glucose level in blood.

Because the calcium concentration C_i changes slowly in comparison with other variables, we call equation (2) the slow subsystem and equations (1) and (3) the fast subsystem. The whole equations (1)-(3) are called the full system especially.

2.2. Model with a Calcium Store

In the above model, the intracellular calcium concentration oscillates slowly. However, it has been shown experimentally that the oscillation is fast. Thus the next model assumes the calcium stores in the cell and that the calcium concentration in the calcium stores changes slowly. The equations of pancreatic β-cell cluster model which considers calcium stores are

as follows [2]:

$$C_m \frac{dV_i}{dt} = -g_K n_i (V_i - V_K) - g_C d_\infty f_\infty (V_i - V_C) - g_{NS} \frac{500}{500 + C_{lum,i}} (V_i - V_{NS}) - g_L (V_i - V_L) - \sum_j g_{i,j} (V_i - V_j) \quad (4)$$

$$\frac{dC_i}{dt} = -\psi g_C d_\infty f_\infty (V_i - V_C) - k_C C_i + J_{CRC} - k_{pump} C_i \quad (5)$$

$$\frac{dC_{lum,i}}{dt} = -J_{CRC} + k_{pump} C_i \quad (6)$$

$$\frac{dn_i}{dt} = \frac{(n_{i\infty} - n_i)}{\tau_n} \quad (7)$$

where $C_{lum,i}$ is the calcium concentration in calcium stores of i-th cell, J_{CRC} is Ca^{2+} current from the calcium stores, and k_{pump} is the Ca^{2+} pump activity in calcium stores. The other parameters' meanings are the same as the former model.

Because the calcium concentration $C_{lum,i}$ in calcium stores changes slowly in comparison with other variables, we call equation (6) the slow subsystem and equations (4), (5) and (7) the fast subsystem.

3. Simulation

3.1. Typical Membrane Potential

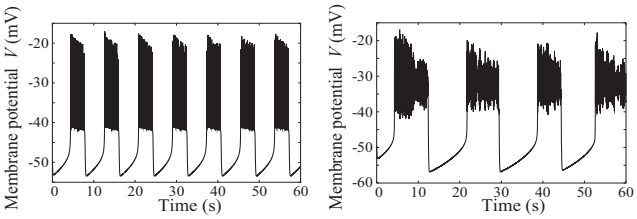
When the coupling $g_{i,j}$ is sufficiently large, the bursting of a cluster is similar to that of an uncoupled single cell and synchronous. In fact, the coupling of real pancreatic β-cells is generally strong enough to synchronize the bursting. If the coupling is too weak, the bursting is almost same for each cell without synchronization. But when it is a middle strength, the characteristics of bursting change in both models.

The typical membrane potential waveforms of the two models without and with calcium stores are shown in Figs.1 and 2, respectively. Panels (a) and (b) correspond to uncoupled cell and coupled cell, respectively. In both models, an uncoupled cell (Panel (a)) shows the same regular bursting, while a coupled cell (Panel (b)) shows different bursting between the two models when the coupling is middle strength.

A coupled β-cell without calcium stores (Fig.1b) shows a slightly messy bursting by the influence of coupling but shows the essentially same bursting as the uncoupled cell. A coupled β-cell with calcium stores (Fig.2b), however, shows a topologically different bursting from the uncoupled cell.

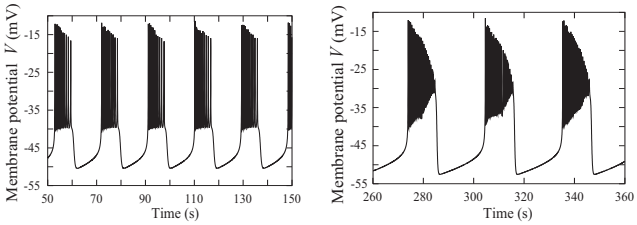
3.2. Plateau Fraction

Plateau fraction is the ratio of the active phase duration to the period of bursting (active phase is the state with high membrane potential and with high-frequency oscillation). Figure 3 shows the plateau fraction of bursting of one cell in the cluster as a function of the coupling strength in the case of several different values of k_C. Panels (a) and (b) correspond to the case without or with calcium stores, respectively. The constant k_C corresponds to the glucose level in the blood.



(a) uncoupled cell (b) coupled cell

Figure 1: Membrane potential of a β-cell without calcium stores



(a) uncoupled cell (b) coupled cell

Figure 2: Membrane potential of a β-cell considering calcium stores

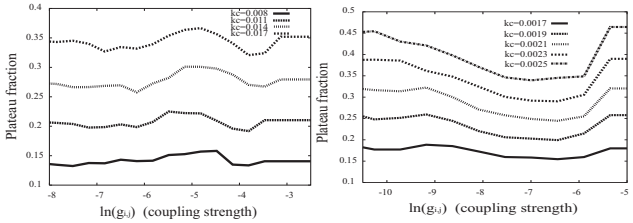
The plateau fraction in the case without calcium stores does not change much for the change of coupling strength. In the model with calcium stores, however, the plateau fraction decreases in the range of middle strength coupling. Because it is thought that insulin is secreted when the membrane potential of β-cell bursts (active phase), only the model which considers calcium stores is suitable for the explanation of physiological experiment. By the increase of k_C, the plateau fraction increases in both models. This coincides with the fact that insulin secretion increases by the addition of the glucose.

In the next section, we clarify the reason why these behaviors are different between two types of models.

4. Slow-Fast Decomposition Analysis

We show the cause of different behavior between two models from the aspect of slow-fast decomposition analysis. This is the way that treats the slow variable as a parameter approximately because its change is very slow in comparison with the fast variables.

At first, we consider the single cell model without calcium stores (Fig.4). The Z-shaped curve in Fig.4 is the equilibrium point of fast subsystem when the slow



(a) model without CS (b) model with CS

Figure 3: Plateau fraction as a function of coupling strength for both models with and without a calcium store (CS)

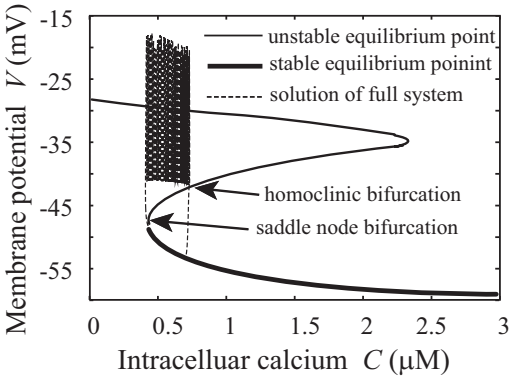


Figure 4: Slow-fast decomposition analysis (single cell model without CS)

variable C is treated as a parameter. The solution of the full system is also superimposed on it.

In the silent phase, C decreases and V increases slowly. After reaching the saddle node bifurcation of the fast subsystem, the solution of full system starts to burst while C increases slowly. When it reaches an unstable equilibrium point, homoclinic bifurcation happens and the bursting terminates. This process is repeated. In the case of the latter single cell model of which slow variable is C_{lum}, the dynamics of bursting is explained by the same mechanism (Fig.5(a)).

Because the temporal change of coupling current is very complicated and the analysis of the coupled β-cells is difficult, we consider a single β-cell and add a constant current instead of coupling current. Then different pattern of bursting appears in the latter model when constant current is positive (Fig.5(b)). In the silent phase, the behavior is similar to panel (a). But, in the active phase, there is no periodic solution of the fast subsystem because the location of Hopf bifurcation is left of the lower saddle node bifurcation, thus it converges to a stable equilibrium point with damping oscillation. When it reaches the upper saddle node bifurcation, the bursting terminates. This process is repeated.

Note that the bursting of the single cell with constant current injection in Fig.5(b) much resembles to that of the coupled cells in Fig.2(b) and thus we study the effect of the constant current injection into a single cell.

5. 2-Parameter Bifurcation Analysis

In this section, we treat both the constant current and the slow variable as parameters and study the 2-parameter bifurcation of the fast subsystem.

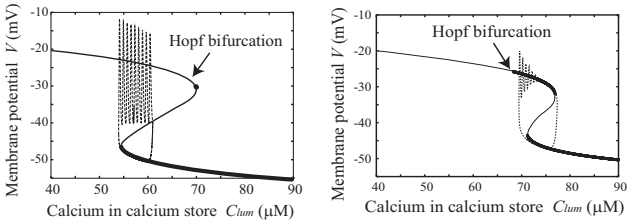
Locations of the saddle node, homoclinic and Hopf bifurcation in the former model are plotted in Fig.6. In Fig.6, we can see the relative position of the three bifurcations is unchanged for any values of the constant current. From the left, there are Hopf bifurcation, one saddle node bifurcation, homoclinic bifurcation and another saddle node bifurcation. The bursting occurs between the left saddle node bifurcation and the homoclinic bifurcation for any values of the constant current.

On the contrary, in Fig.7 that is the case of the latter model, the relative position changes greatly. If the value of the constant current is negative, the positional relationship is the same as the former one. When it is positive, the homoclinic bifurcation disappears and bursting occurs between two saddle node bifurcations. In this range, the amplitude of bursting oscillation becomes smaller in the right of Hopf bifurcation. This is the reason of the generation of the different bursting in Fig.5(b). This shape of bursting is very similar to that of the latter coupled cell model.

As a summary, this difference of 2-parameter bifurcation structure causes the difference of bursting behaviors of a coupled-cell cluster between the two models with and without calcium stores.

6. Approximation of Plateau Fraction

In both models, the slow variable increases in active phase and decreases in silent phase slowly. We consider that this slow variable dynamics mainly determines the active phase duration and period of bursting. To evaluate the plateau fraction quantitatively, we approximate the total dynamics by the slow variable dynamics. In the case of the former model, we assume that the values of the fast variables m_i, n_i and



(a) uncoupled cell (b) constant current injected

Figure 5: Slow-fast decomposition analysis (model with CS)

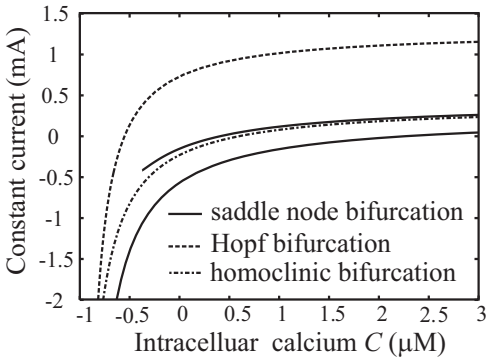


Figure 6: 2-parameter bifurcation diagrams (model without CS)

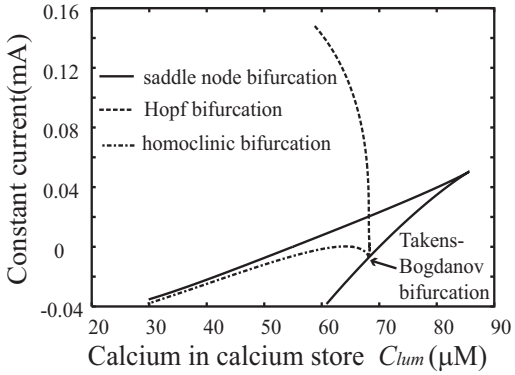


Figure 7: 2-parameter bifurcation diagrams (model with CS)

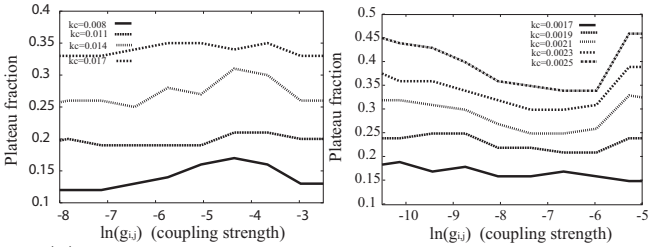
h_i are in their steady states which depend on the value of V_i and obtain the following equation (8) from equation (2):

$$T_{active} = \int_{T_1}^{T_2} dt \qquad (8)$$
$$= \int_{\underline{C}}^{\overline{C}} \frac{1}{f[-k_1 g_C m_{i\infty}^3 h_{i\infty}(\overline{V_i} - V_C) - k_C C_i]} dC_i$$

where T_{active} is the active phase duration. T_1 and T_2 is the starting and terminating time of active phase, respectively. $\underline{C}$ and $\overline{C}$ is the value of the calcium concentrations C_i at the time T_1 and T_2, respectively. $\overline{V_i}$ is the average of V_i over one spike in active phase. We can obtain the active phase duration by two variables: the slow variable C_i and average of the fast variable $\overline{V_i}$. By the same way, we obtain the silent phase duration and thus the plateau fraction as follows.

$$\text{plateau fraction} = \frac{\mathrm{T_{active}}}{\mathrm{T_{active}} + \mathrm{T_{silent}}} \qquad (9)$$

In the case of the latter model, we also obtain the durations of both phases from equation (6) by two variables: the slow variable $C_{lum,i}$ and average of the fast variable $\overline{C_i}$. We can estimate the plateau fraction by the similar way.



(a) model without CS (b) model with CS

Figure 8: The result of approximation

The plateau fraction estimated by equation (9) is shown in Fig.8 as a function of the coupling strength in the case of several different values of k_C. It is shown that these approximated values of plateau fraction are in good agreement with the simulation result (Fig.3).

7. Conclusion

We have studied the influence of coupling strength between pancreatic β-cells on the bursting behavior of a cell cluster by using two kinds of models. By examining the plateau fraction, it has been shown that the model that considers calcium stores is more suitable for the physiological experimental result.

The difference of bursting for the change of coupling strength between two kinds of models has been explained by the difference of bifurcation structures using slow-fast decomposition analysis and 2-parameter bifurcation analysis of fast subsystems.

In addition, we have approximated the total dynamics by the slow variable dynamics and clarified the reason of the plateau fraction decrease by the reduction of coupling strength also.

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