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Influence of ionic currents on a simple model for pancreatic β cells

Hiroyasu Ando† and Kantaro Fujiwara‡

†Division of Policy and Planning Sciences,
Faculty of Engineering, Information and Systems, University of Tsukuba
1–1–1 Ten-noudai, Tsukuba, 305-8573, Japan
‡Department of Management Science, Tokyo University of Science
1–3 Kagurazaka, Shinjuku-ku, Tokyo 162–8601 , Japan
Email: ando@sk.tsukuba.ac.jp, kantaro@ms.kagu.tus.ac.jp

Abstract—Pancreatic β cells exhibit bursting electrical activity, which is correlated with insulin secretion. It has been reported that several ionic channels may contribute to their characteristic electrical activity, but the mechanism of electrical activity in pancreatic β cells is still unclear. In this study, we investigate the influence of ionic currents on a simple model for pancreatic β cells. Our findings from mathematical modeling imply that the difference of activity patterns in β cells can be explained by the difference of ionic currents which produce bursting activity.

1. Introduction

Pancreatic β-cells are the cells in the islet of Langerhans. These cells secrete insulin which is a hormone for glucose homeostasis to maintain blood glucose level. They exhibit bursting electrical activity, which is correlated with the insulin secretion. In both mice [1] and humans [2], insulin secretion is controlled by calcium oscillations. Calcium oscillations are driven by bursts of action potentials with periods ranging from tens of seconds to several minutes. However, it is still unknown how such bursts arise, and how they are modulated by glucose and other signals.

In pancreatic β-cells in a cluster or in an intact islet, it is reported that they exhibit regular bursting [3]. On the other hand, isolated single β-cells in rats show continuous spikes with decreasing amplitude [4]. To explain the difference between isolated cell and intact islet behaviors, Atwater et al. proposed the channel-sharing hypothesis [6], where current fluctuations caused by individual channel openings prevent bursting. There are several experimental evidences which indicate that β-cells' bursting activity depends on gap junctional couplings [5]. Although channel-sharing hypothesis and gap junctional couplings obviously contribute to explain β-cell bursting in islets, it is still unclear how continuous spikes with decreasing amplitude in isolated cells occur.

In Ref.[4], membrane potential of β cell is recorded in glucose-stimulated condition. At the low glucose concentration level, the membrane potential is in a resting potential, approximately -70mV. By increasing the glucose concentration level, the membrane potential gradually increases and finally emits burst-like spikes. Its spike has three characteristics: continuous spikes, decreasing amplitude, and oscillation with small amplitude. One may recall neuronal adaptation in which neurons show a reduction in their spike response, adapting to the stimulus [8]. However, the spike frequency is reduced in neuronal adaptation, while the spike frequency is almost constant in β cells and only the amplitude shows an adapting behavior to the stimulus.

In this study, we examine how such characteristic spiking of isolated β cells occur. We show the effects of ionic conductances to the continuous spiking in the isolated β-cell using simple mathematical model. In Sec. 2, we introduce a mathematical model which is used in this study. In Sec. 3, we show that characteristic spiking of β-cells can be explained by the modulation of the ionic conductances with noise. In Sec. 4, physiological interpretation is discussed.

2. Model

As a simple example of bursting activity in β cells, we consider the model proposed by Chay, which is a conductance-based model of a membrane potential with three variables as follows [9]:

$$\begin{aligned}\dot{V} &= g_{\mathrm{I}}^* m_\infty^3 h_\infty (V_{\mathrm{I}} - V) + g_{\mathrm{K,V}}^* n^4 (V_{\mathrm{K}} - V) \\ &\quad + g_{\mathrm{K,C}}^* \frac{C}{1+C}(V_{\mathrm{K}} - V) + g_{\mathrm{L}}^*(V_{\mathrm{L}} - V) \quad (1)\\ \dot{n} &= (n_\infty - n)/\tau_n, \quad (2)\\ \dot{C} &= \rho[m_\infty^3 h_\infty (V_{\mathrm{C}} - V) - k_{\mathrm{C}} C]. \quad (3)\end{aligned}$$

Equation (1) represents the dynamics of the membrane potential V, where V_{I}, V_{K} and V_{L} are the reversal potentials for mixed Na^+ and Ca^{2+}, K^+ and leakage ions, respectively. The C is the concentration of intracellular Ca^{2+} ions divided by its dissociation constant from the receptor. The g_{I}^*, $g_{\mathrm{K,V}}^*$, $g_{\mathrm{K,C}}^*$ and g_{L}^* are the maximal conductances divided by the membrane capacitance, where the subscripts (I), (K, V),

(K, C) and (L) refer to the voltage-sensitive mixed ion channel, the voltage-sensitive K^+ channel, the Ca $^+$-sensitive K^+ channel and the leakage channel, respectively. Then, m_∞ and h_∞ are the probabilities of activation and inactivation of the mixed channel.

In Equation (2), the dynamical variable n is the probability of opening in the voltage-sensitive K^+-channel, where τ_n is the relaxation time, and n_∞ is the steady state value of n.

Note that the variables m_∞, h_∞ and n_∞ are replaced by the steady states described by $y_\infty = \alpha_y/(\alpha_y + \beta_y)$, where y stands for m, n or h with

$$\begin{aligned}
\alpha_m &= 0.1(25+V)/[1-\exp(-0.1V-2.5)],\\
\beta_m &= 4\exp[-(V+50)/18],\\
\alpha_h &= 0.07\exp(-0.05V-2.5),\\
\beta_h &= 1/[1+\exp(-0.1V-2)],\\
\alpha_n &= 0.01(20+V)/[1-\exp(-0.1V-2)],\\
\beta_n &= 0.125\exp[-(V+30)/80].
\end{aligned}$$

Also, τ_n is defined as,

$$\tau_n = [230(\alpha_n + \beta_n)]^{-1}.$$

In Equation (3), the dynamics of C is described, where k_C, ρ and V_C are the rate constant for the efflux of intracellular Ca^{2+} ions, a proportionality constant and the reversal potential for Ca^{2+} ions, respectively. In Table 1, we show the values of the parameters.

Table 1: Parameters used in the numerical simulations.

Parameter	Value	Unit
V_K	-75	mV
V_I	100	mV
V_L	-40	mV
V_C	100	mV
$g^*_{K,C}$	11	mV
g^*_L	7	s^{-1}
k_C	3.3/18	mV

3. Simulations

In this section, we demonstrate numerical simulations of the model introduced in the previous section. Specifically, we try to reproduce the experimental results by Yoshida *et al.* [4] qualitatively by using the model with varying the parameter g^*_I and ρ. In the following simulations, we fix the parameter $g^*_{K,V} = 1200$.

First, we show results without noise in the model. Figures 1 ($g^*_I = 1100$) and 2 ($g^*_I = 1150$) show periodic bursts in which the amplitude of the spikes in each bursting period is shrinking. This shrinking property in the bursting spikes is observed in the experiment [4]. Moreover, the amplitude of the spikes finally vanishes in each bursting period. On the other hand, the amplitude does not vanish in each bursting period when $g^*_I = 1150$ as shown in Figure 3. Then, as increasing the value of g^*_I, the shrinking property changes as the amplitude in each bursting period shrinks first then remains almost constant in the rest of the bursting period (See Figure 4). Finally, at the value of $g^*_I = 1300$, the amplitude of the oscillation shrinks and expands in each bursting period as shown in Figure 5.

Next, we consider the case with noise in Equation (1) as follows,

$$\begin{aligned}
\dot{V} &= g^*_I m^3_\infty h_\infty (V_I - V) + g^*_{K,V} n^4 (V_K - V)\\
&\quad + g^*_{K,C}\frac{C}{1+C}(V_K - V) + g^*_L(V_L - V) + D\xi,
\end{aligned}$$

where D is the strength of noise and ξ is white Gaussian noise following $N(0,\ 1)$. We change the value of ρ as 0.03 which is smaller than that in the previous simulations. Figure 6 shows time series of V with regards to $D = 10$ and $g^*_I = 1100$, $g^*_{K,V} = 1200$. As can be seen in the figure, the bursting period is prolonged compared to that in Figure 1. Note that the vanished spikes (or oscillations) in the case without noise reappear due to noise as shown in Figure 6 bottom.

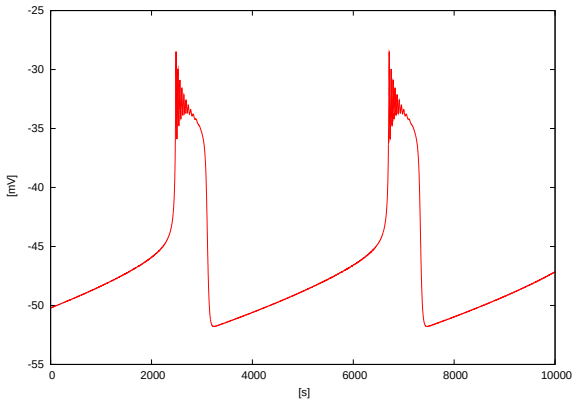


Figure 1: Time series of V in the model with the parameters as $g^*_I = 1100$, $g^*_{K,V} = 1200$, $\rho = 0.27$.

4. Discussion

In isolated pancreatic β-cells of rats, continuous spikes with decreasing amplitude are observed [4], but its mechanism is still unknown. Our result implies that such characteristic spiking can be reproduced by modulating parameter values of the conductances of the voltage-sensitive mixed ion channel and the voltage-sensitive potassium channel. When their values are

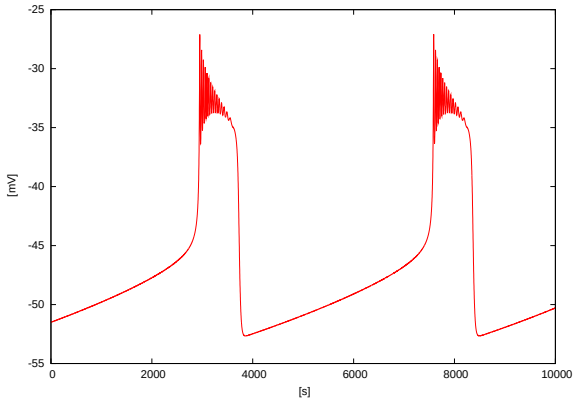


Figure 2: Time series of V in the model with the parameters as $g_{\mathrm{I}}^{*} = 1150$, $g_{\mathrm{K,V}}^{*} = 1200$, $\rho = 0.27$.

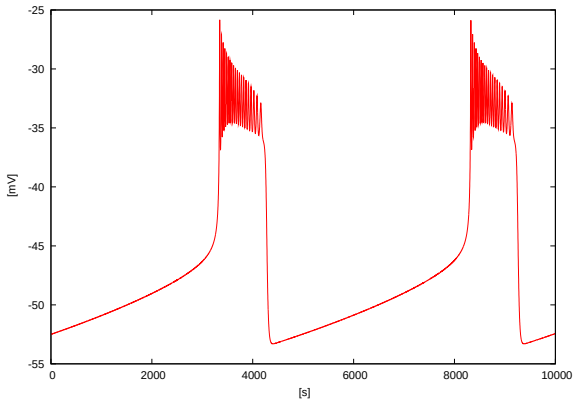


Figure 3: Time series of V in the model with the parameters as $g_{\mathrm{I}}^{*} = 1200$, $g_{\mathrm{K,V}}^{*} = 1200$, $\rho = 0.27$.

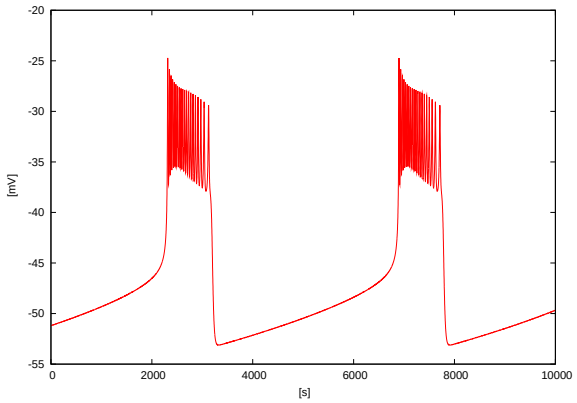


Figure 4: Time series of V in the model with the parameters as $g_{\mathrm{I}}^{*} = 1250$, $g_{\mathrm{K,V}}^{*} = 1200$, $\rho = 0.27$.

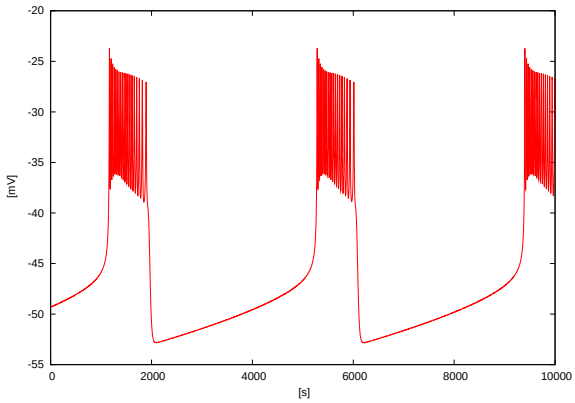
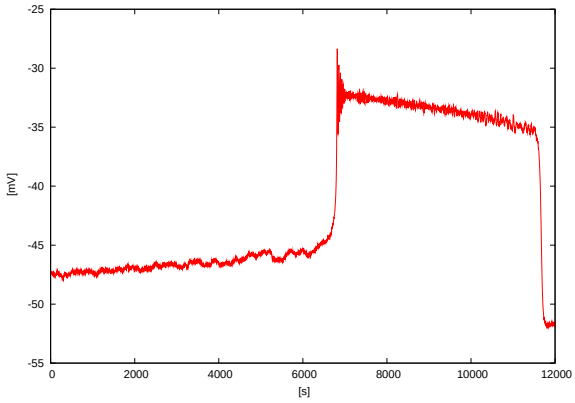


Figure 5: Time series of V in the model with the parameters as $g_{\mathrm{I}}^{*} = 1300$, $g_{\mathrm{K,V}}^{*} = 1200$, $\rho = 0.27$.



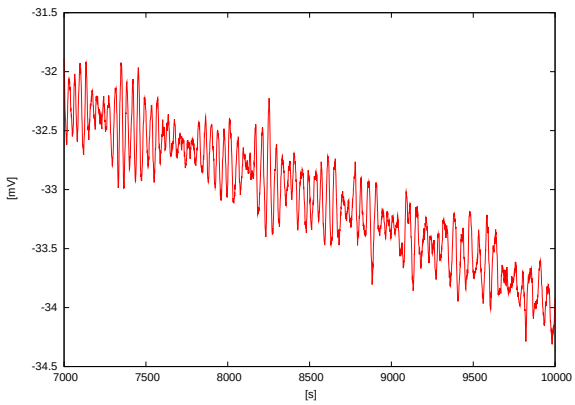


Figure 6: (Top)Time series of V in the model with the parameters as $g_{\mathrm{I}}^{*} = 1100$, $g_{\mathrm{K,V}}^{*} = 1200$, $\rho = 0.03$ with noise $D = 10$. (Bottom) Enlarged view of the top figure.

in a certain range, characteristic spiking in [4] can be observed. By decreasing the proportionally constant of the calcium concentration, the time-scale of the spiking is adjusted. In addition, with a existence of additive noise, the bursting period was prolonged. These findings indicate that the modulation of conductance values of the voltage-sensitive mixed ion channel, the voltage-sensitive potassium channel and the proportionally constant of the calcium concentration in a noisy situation explains the characteristic bursting in an isolated pancreatic β-cell.

Acknowledgments

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