膵β細胞からのスパイク列に対する統計的解析と数理モデリング

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1 Introduction

Glucose is monosaccharide that provides a body with its primary source of energy. Glucose comes from digesting carbohydrates into a chemical easily converted to energy. When glucose levels in the blood stream are not properly regulated, one might suffer from a serious condition, such as diabetes [1]. One of the most important hormones for glucose metabolism is insulin, because it is used to treat diabetes. Insulin is secreted when β-cells fire in the islets of Langerhans in the pancreas when the level of glucose in blood rises [2]. It means that firing patterns of the β-cells can predict the secretion of insulin. Namely, we can effectively treat diabetes if we analyze the firing patterns of the β-cells.

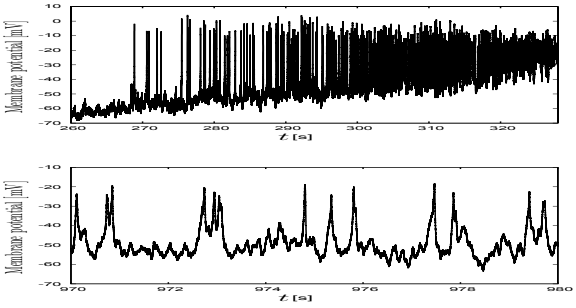


Figure 1: Two characteristic firing patterns observed from the same β-cell of a mouse. (a) Pattern I (The amplitude of the membrane potential slowly decreases with time.) (b) Pattern II (tonic bursting).

In this project, we propose a simple mathematical model to reproduce the firing patterns of the β-cells. From the β-cells, two major firing patterns are observed. Figure1 shows these two examples observed from the same β-cell of a mouse. In the experiment, the glucose level is controlled at 5.6[mM]. The first pattern (Fig.1(a)) shows that the amplitudes of membrane potential slowly decrease with time. The second pattern (Fig.1(b)) is called tonic bursting.

In the following, we show that the proposed model with three differential equations can effectively reproduce these two characteristic firing patterns observed from the pancreatic β-cells.

2 Methods

Neurons in the brain and β-cells in the pancreas have similar properties in voltage oscillation. Thus, bifurcation analysis plays an important role in both systems. In a two-dimensional dynamical system, two nullclines are defined by correspoinding differential equations. The bifurcations involving fixed points and limit cycles are controlled by the shapes of nullclines. The limit cycle decides the amplitude of the membrane potential.

The Morris-Lecar neuron model[4] is one of the popular neuron model that is widely used. It is described by a set of two nonlinear differential equations. The Morris-Lecar model has the following form:

$$C_M\dot{V} = -\bar{g}_{\rm L}(V - V_{\rm L}) - \bar{g}_{\rm Ca}M_\infty(V - V_{\rm Ca}) - \bar{g}_{\rm K}N(V - V_{\rm K}) + I \quad (1)$$

$$\dot{N} = \frac{N_\infty - N}{\tau_N} \quad (2)$$

$$M_\infty = 0.5(1 + \tanh((V - V_1)/V_2)) \quad (3)$$

$$N_\infty = 0.5(1 + \tanh((V - V_3)/V_4)) \quad (4)$$

$$\tau_N = 1/(\cosh((V - V_3)/2V_4)) \quad (5)$$

where V is the membrane potential; $N \in [0,1]$ is the activation variable for K^+; and I is the current; the parameters $V_{\rm Ca}$, $V_{\rm K}$, and $V_{\rm L}$ represent equilibrium potentials of Ca^{2+}, K^+ and leak currents; $\bar{g}_{\rm L}$, $\bar{g}_{\rm Ca}$ and $\bar{g}_{\rm K}$ denote the maximum conductance of corresponding ionic currents; N_∞ and M_∞ are steady-state activation; V_1, V_2, V_3 and V_4 are parameters.

Action potential and repolarization of the β-cell also depend on the Ca^{2+} channels and K^+ channels[5]. For this reason, it is very natural to expect that we can obtain a possible model for reproducing firing patterns of β-cells. However, it is not so easy to treat the nullclines of the Morris-Lecar mode. Then, we simply replaced the nullclines of Morris-Lecar model by a qubic polynomial and an exponential function to reproduce the firing patterns observed from the β-cell. The nullclines of the Morris-Lecar model are shown in Fig.2(a) and (b).

In our model, we first used an approximation form of the nullclines of the original Morris-Lecar model. Namely, we used qubic polynomial and exponential functions as shown in Eqs.(6) and (7). The nullclines of the proposed model are shown in Fig. 2(c) and (d).

To reproduce the two patterns shown in Fig.1, we also introduced movement of the nullclines with time to control the amplitude of the limit cycle. To realize this property automatically, we introduced the third differential equation to move the second (or u-) nullcline:

$$\dot{v} = a_1(v + a_2)^3 + a_3(v + a_2)^2 + a_4(v + a_2) + a_5 - u, \quad (6)$$

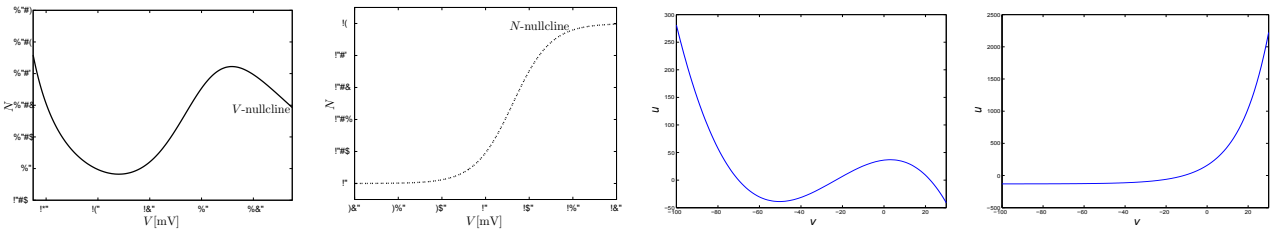
$$\dot{u} = 0.7{\rm e}^{0.07(v-w+86)} - 130 - u, \quad (7)$$

$$\dot{w} = c_1 v - c_2 u - c_3 w, \quad (8)$$

where u, v and w are dimensionless variables, and $a_1, a_2, a_3, a_4, a_5, c_1, c_2$ and c_3 are also dimensionless parameters. The variable v represents the membrane potential of the β-cell. The role of w is to move the u-nullcline in the u-v phase plane. We tried several parameters and choose the most proper parameters for the u-nullcline to perform the two firing patterns of β-cells.

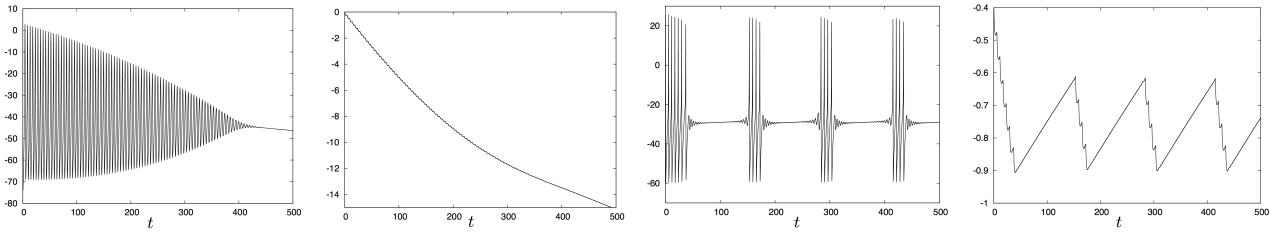
2.1 Pattern I

As shown in Fig.1(a), the amplitude of the membrane potential slowly decreases with time.To realize this feature, we set parameters for the variable w in Eq.(8) to make the value of w decrease slowly with time, which means that the u-nullcline moves slowly



(a) (b) (c) (d)

Figure 2: The nullclines of the Morris-Lecar neuron model. (a) V-nullcline shows the membrane potential and (b) N-nullcline shows the fraction of open channel. (c) v-nullcline and (d) u-nullcline of the proposed model.



(a) v for Pattern I (b) w for Pattern I (c) v for Pattern II (d) w for Pattern II

Figure 3: Reproduced time series of v for (a) Pattern I and (c) Pattern II. The variable w (b) for Pattern I decreases gradually in time, and (d) for Pattern II is changed periodically.

to the leftward in the u-v phase plane. Then, the limit cycle will slowly shrink to an equilibrium point. We set $a_1 = -0.001$, $a_2 = 7$, $a_3 = -0.05$, $a_4 = 1.3$, $a_5 = 30$, $c_1 = 0.0025$, $c_2 = 0.0007$ and $c_3 = 0.002$ for Pattern I.

2.2 Pattern II

The feature of the pattern shown in Fig. 1(b) is that the membrane potential of a β-cell exhibits periodic bursting. To realize this feature, we set $a_1 = -0.003375, a_2 = -5, a_3 = -0.1, a_4 = 6, a_5 = 100, c_1 = 1/2000, c_2 = 1/5500$ and $c_3 = 1/500$ for this pattern. In this pattern the value of variable w changes repeatedly in a limited range. It means that the u-nullcline moves leftwards and rightwards repeatedly to make the state of equilibrium point periodically changed and to generate a limit cycle. Then, the model automatically performs the Hopf bifurcation repeatedly.

2.3 Results

Simulation results to reproduce the pattern I is shown in Fig.3(a) and (b). As the value of w changes (Fig.3(b)), the amplitude of membrane potential(v) gradually decreases with time as in Fig.3(a). This result indicates that the proposed model can automatically perform the Hopf bifurcation.

In the case of the pattern II, the simulation results are shown in Fig.3(c) and (d). In this pattern, the value of w changes in a limited range (Fig.3(c)). Due to this prperty, the u-nullcline moves leftwards and rightwards repeatedly. Figure 3(c) shows that the membrane potential exhibit tonic bursting.

3 Conclusions

In this report, we proposed a simple mathematical model of the pancreatic β-cell. In particular, we emphasize how to reproduce two characteristic firing patterns of β-cells. The basic part of the proposed model consists of the Morris-Lecar neuron model. In the conventional mathematical models, the value of a parameter is changed to perform bifurcation. However, in our model, to automatically change parameters, we control the movement of the u-nullcline. As a result, the proposed model automatically performs bifurcation, and reproduces two major firing patterns of the pancreatic β-cell.

Our model is a simple mathematical model that can reproduce the two major firing patterns observed from the β-cells. It consists only three differential equations and has eight parameters. Namely, the proposed model can reduce the computational costs when simulating a β-cell mass comparing to conventional models. The point of this research is that an extra differential equation realize the movement of the u-nullcline to perform Hopf bifurcation automatically. This point can be used in other mathematical model. Finally, we analyzed the bifurcation for several parameters that decide the movement of nullcline. In particular, the parameter c_1, c_2 and c_3 in the third differential equation are parameters which control the movement of u-nullicne. We can modulate the firing patterns using this bifurcation analysis in our model.

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