The Pancreatic Beta Cell

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Introduction

The pancreatic β-cells play a vital role in controlling blood sugar insulin levels by secreting insulin. β-cells are endocrine cells in which secretion is controlled by $\left[Ca^{2+}\right]$, and this is regulated to a large extent by bursting electrical activity, which we assume here is driven by the membrane potential. In the pancreas, β-cells are organised into electrically-coupled populations called the islets of Langerhans: we may neglect this as it is known that cells in an islet are synchronised, so a one-cell model will suffice.

The Chay-Keizer Model

This model assumes that bursting occurs in response to glucose, giving spiking effects in the active phase which may be explained by the Morris-Lecar model[1], to which must be added a slow negative-feedback current. Chay and Keizer[2] proposed a model in which the concentration of calcium ions would build up until the inhibitory effect of the increased potassium current terminated the spike. Figure 1 from Fall *et al.*[3] shows typical behaviours.

The current $I_{K(Ca)}$ which represents the current of potassium ions K^+ controlled by the concentration of calcium ions $\left[Ca^{2+}\right]$ is

$$I_{K(Ca)} = g_{K(Ca)} \frac{\left[Ca^{2+}\right]_i}{K_{K(Ca)} + \left[Ca^{2+}\right]_i} (V - V_K),$$

and the modified Morris-Lecar equations for the membrane potential V, the proportion of open channels, w, and the free calcium concentration $\left[Ca^{2+}\right]_i$ are

$$C_m \frac{dV}{dt} = -I_{Ca} - I_K - I_L - I_{K(Ca)}, \tag{1}$$

$$\frac{dw}{dt} = \phi \frac{w_\infty - w}{\tau}, \tag{2}$$

$$\frac{d\left[Ca^{2+}\right]_i}{dt} = f_i \left(-\alpha I_{Ca} - \nu_{LPM} \left[Ca^{2+}\right]_i\right). \tag{3}$$

Here f_i is the fraction of free $\left[Ca^{2+}\right]_i$, C_m is the membrane capacitance, ϕ is a relaxation rate, $\alpha = 10^3/(2F\overline{\nu_I})$ converts current in fA to μM/ms. The currents are

$$I_{Ca} = g_{Ca} m_\infty (V - V_{Ca}), \tag{4}$$

$$I_K = g_K w (V - V_K), \tag{5}$$

$$I_L = g_L (V - V_L). \tag{6}$$

[1] C Morris and H Lecar. Voltage oscillations in the barnacle giant muscle fiber. *Biophysical Journal*, 35(1):193 – 213, 1 July 1981

[2] TR Chay and J Keizer. Minimal model for membrane oscillations in the pancreatic beta-cell. *Biophysics Journal*, 42(2):181–190, May 1983

[3] Christopher P Fall, Eric S Marland, John M Wagner, and John J Tyson. *Computational Cell Biology*. Springer Verlag, 2002

Finally,

$$m_\infty = 0.5\,[1 + \tanh((V - \nu_1)/\nu_2)]\,, \tag{7}$$

$$w_\infty = 0.5\,[1 + \tanh((V - \nu_3)/\nu_4)]\,, \tag{8}$$

$$\tau = 1/\cosh((V - \nu_3)/(2\nu_4)). \tag{9}$$

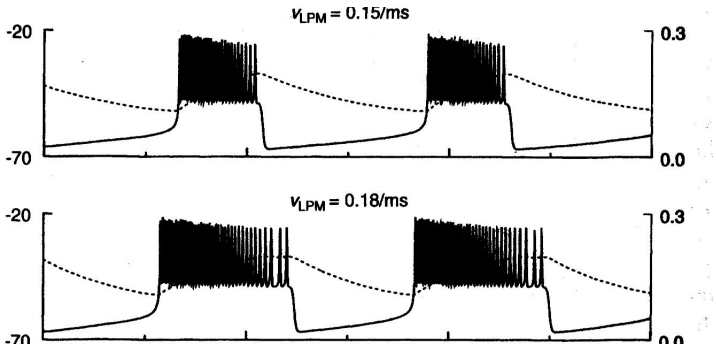

Figure 1: Bursting and glucose sensing in the Chay-Keizer model: the solid line is the membrane potential and the dotted line is the glucose concentration.

Investigate the behaviour of this model. Suggested parameters are $C_m = 5300\,\text{fF}$, $g_{Ca} = 1000\,\text{pS}$, $V_{Ca} = 25\,\text{mV}$, $g_K = 2700\,\text{pS}$, $V_K = -75\,\text{mV}$, $\nu_1 = -20\,\text{mV}$, $\nu_2 = 24\,\text{mV}$, $\nu_3 = -16\,\text{mV}$, $\nu_4 = 11.2\,\text{mV}$, $\phi = 0.035/\text{ms}$, $g_L = 150\,\text{pS}$, $V_L = -75\,\text{mV}$, $g_{K(Ca)} = 2000\,\text{pS}$, $K_{K(Ca)} = 5\,\mu\text{M}$, $f_i = 0.001$, $\alpha = 4.5 \times 10^{-6}\,\mu\text{M}/(\text{fA ms})$, and investigate values of ν_{LPM} between 0 and 1. Describe the behaviour of the free calcium concentration.

Endoplasmic Reticulum

The system in the pancreas is more complicated than we have depicted above. The endoplasmic reticulum (ER) is an intracellular compartment that serves, amongst other things, as a calcium reservoir. Calcium release is triggered by the phospholipid membrane metabolite inositol 1,4,5-trisphosphate (IP_3). As this can alter the kinetics of calcium concentration, we modify the equations as follows:

$$C_m \frac{dV}{dt} = -I_{Ca} - I_K - I_{ATP} - I_{K(Ca)}, \tag{10}$$

$$\frac{dw}{dt} = \phi \frac{w_\infty - w}{\tau}, \tag{11}$$

$$\frac{d\left[Ca^{2+}\right]_i}{dt} = f_i\left(-\alpha I_{Ca} - \nu_{LPM}\left[Ca^{2+}\right]_i\right] + \frac{f_i}{\lambda}\left(P_{IP_3R}\left(\left[Ca^{2+}\right]_{ER} - \left[Ca^{2+}\right]_i\right) - \nu_{LSP}\left[Ca^{2+}\right]_i\right) \tag{12}$$

$$\frac{d\left[Ca^{2+}\right]_{ER}}{dt} = \frac{f_i}{\sigma\lambda}\left(-P_{IP_3R}\left(\left[Ca^{2+}\right]_i - \left[Ca^{2+}\right]_i\right) + \nu_{LSP}\left[Ca^{2+}\right]_i\right), \tag{13}$$

where the ATP-sensitive Potassium current is

$$I_{ATP} = g_{ATP}(V - V_K.$$

Investigate how this model compares with the previous one. Use the same parameters as before, except for a larger $f_i = 0.01$ and

with $P_{IP_3R} = 0.0008\,/\text{ms}$, $\lambda = 2$, $\sigma = 0.032$, $g_{ATP} = 800\,\text{pS}$ and $\nu_{LSP} = 0.6\,/\text{ms}$.

Also consider the period of bursts in the model with these parameters but without the $\left[Ca^{2+}\right]_{ER}$. How does it compare with the previous case with smaller f_i? Why does $\left[Ca^{2+}\right]_{ER}$ affect it the way it does?

Possible Extensions

It is possible to construct bifurcation diagrams for the two models, using the calcium concentrations as parameters, and then to see how the time traces project onto the bifurcation diagrams.

References

[1] TR Chay and J Keizer. Minimal model for membrane oscillations in the pancreatic beta-cell. *Biophysics Journal*, 42(2):181–190, May 1983.

[2] Christopher P Fall, Eric S Marland, John M Wagner, and John J Tyson. *Computational Cell Biology*. Springer Verlag, 2002.

[3] C Morris and H Lecar. Voltage oscillations in the barnacle giant muscle fiber. *Biophysical Journal*, 35(1):193 – 213, 1 July 1981.

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