What are the Odds? Stochastic Reactions

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Introduction

There are significant differences between measurements which monitor the average behaviour of a large number of objects (be they molecules, ion channels, or cells) and those which investigate individual objects. An example given by Hille (2001)[1] shows the use of patch-clamp techniques to monitor calcium currents in individual ion channels.

[1] B Hille. *Ionic Channels of Excitable Membranes*. Sinauer Associates Inc., Sunderland, 3rd edition, 2001

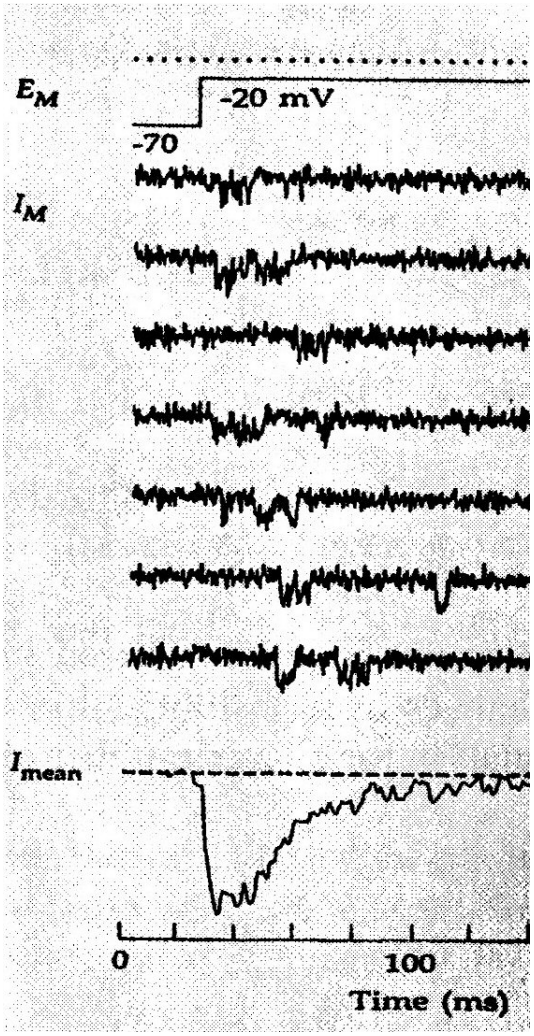

Figure 1: The upper traces show on-cell patch clamp measurements of calcium currents in guinea pig cardiac ventricular myocytes. The upper traces are from one or a few channels, whereas the lower plot is the average of several hundred such records. From Hille (2001).

T-type Calcium Channels

The data from Figure 1 suggest that an individual on channel has two states – a closed state with no current flowing and an open state with a current of about 1 pA. The transitions between these states occur at random times, but the effect of averaging over a

large number of channels shows that *on average* the channel activates and then inactivates with time constants of about 5 ms and 50 ms respectively.

The single-channel process can be modelled as

$$C(\text{closed}) \underset{k^+}{\overset{k^-}{\rightleftharpoons}} O(\text{open}).$$

Now suppose that $P_C(t)$ is the probability that the channel is closed at time t, $P_O(t)$ the probability that it is open (and, of course, $P_C + P_O = 1$). Then the probabilities evolve according to these equations, showing the difference between the opening and closing rates,

$$\frac{dP_C}{dt} = -k^+ P_C + k^- P_O, \tag{1}$$

$$\frac{dP_O}{dt} = +k^+ P_C - k^- P_O. \tag{2}$$

Another way of writing this is in terms of the *transition probability matrix* Q for a time interval Δt

$$Q = \begin{pmatrix} 1 - k^+\Delta t & k^-\Delta t \\ k^+\Delta t & 1 - k^-\Delta t \end{pmatrix}$$

operating on the probability vector

$$\begin{pmatrix} P_C(t) \\ P_O(t) \end{pmatrix}.$$

A simulation method involves choosing time intervals, in each of which the state may or may not change. We then choose a random number s from the interval $0 \leq s \leq 1$ and decide whether or not to change the state: for example, if the current state is open, a transition to closed will occur if $0 \leq s \leq k^-\Delta t$.

Set up a Monte Carlo model of this system, and consider how its behaviour depends on the parameters. Useful ranges are from $k^+ = 0.1/\text{ms}$, $k^- = 1.5/\text{ms}$ to $k^+ = 0.5/\text{ms}$, $k^- = 0.1/\text{ms}$. Characterise your results by computing the average probabilities, and also the average length of time for which the channel remains open. Analytically (you should show this) it is expected that the average closed time should be $1/k^+$.

Now consider the extension to several channels. In the first instance, do this by an extension of the method just used. Thus, in an ensemble of N two-state channels there are $N + 1$ possible numbers of open channels (that is, 0, 1,...N channels may be open), and so one must set up an $(N + 1) \times (N + 1)$ transition matrix. Follow this process through, to derive the resulting transition matrix (which will be tridiagonal). Use this scheme to simulate a number of channels.

If the transition matrix becomes very large, this explicit method of simulation becomes cumbersome. In this case a method suggested by Gillespie[2] may be used. Here we recognise that as there is a constant probability per unit time that a channel changes state,

[2] D Gillespie. Exact stochastic simulation of coupled chemical reactions. *Journal of Chemical Physics*, 81:2340–2361, 1977

the probability that a channel which is closed at time t remains closed until time $t + \tau$ is an exponentially decreasing function of τ (show this). So we can simulate an assembly of two-state ion channels by using an exponentially distributed random variable. Implement this method, and compare the results with those from a moderate number of individually modelled channels.

Possible Extension

The passive glucose transporter (GLUT) may be thought of as a system with four states: an empty pore facing the exterior of a cell; a pore with glucose bound in it but near the exterior of the cell; a pore with glucose bound close to the inside of the cell; an empty open pore facing the inside of the cell having released the glucose into the cell. Show that this can be simulated with a transition probability matrix

$$\begin{pmatrix} D_1 & k_{21}\Delta t & 0 & k_{41}\Delta t \\ k_{12}[G]_{out}\Delta t & D_2 & k_{32}\Delta t & 0 \\ 0 & k_{23}\Delta t & D_3 & k_{43}\Delta t \\ k_{14}\Delta t & 0 & k_{34}[G]_{in}\Delta t & D_4 \end{pmatrix},$$

where the diagonal elements are arranged to conserve probability, so that the sum of each column is 1, and implement a computation using this scheme.

References

[1] D Gillespie. Exact stochastic simulation of coupled chemical reactions. *Journal of Chemical Physics*, 81:2340–2361, 1977.

[2] B Hille. *Ionic Channels of Excitable Membranes*. Sinauer Associates Inc., Sunderland, 3rd edition, 2001.

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