ELEC ENG 3BB3:

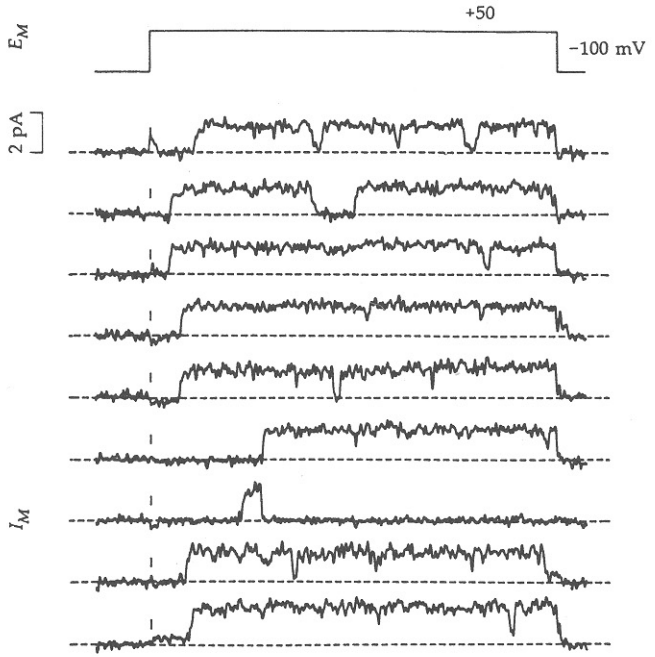
Cellular Bioelectricity

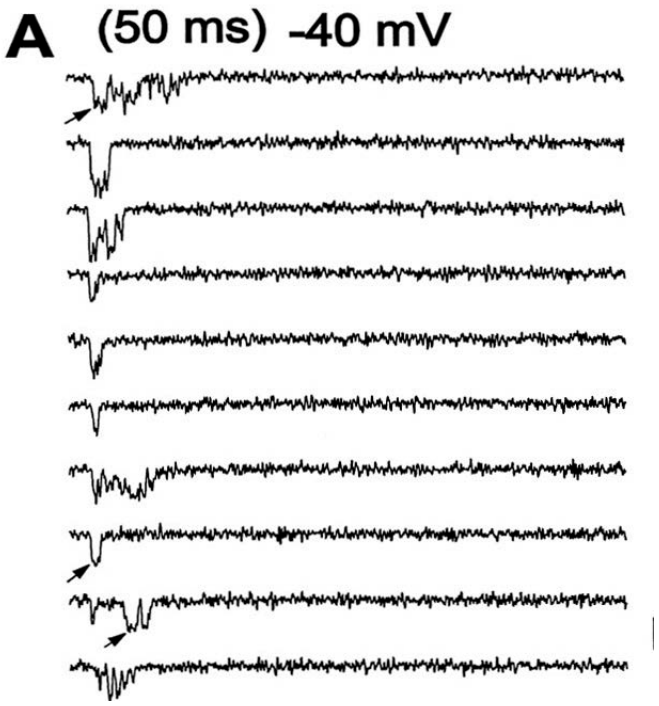
Notes for Lecture 8

Monday, January 20, 2014

Channel gating (cont.):

The stochastic nature of ion channel gating arises from thermal energy affecting the movement of the gating sections of the channel protein.





Channel gating (cont.):

Assuming that the energy required to open a closed channel is supplied through the movement of a charge $Q_g = z_q q_e$ through a transmembrane potential V_m, then *Boltzmann's equation* expresses the ratio of open to closed channels as:

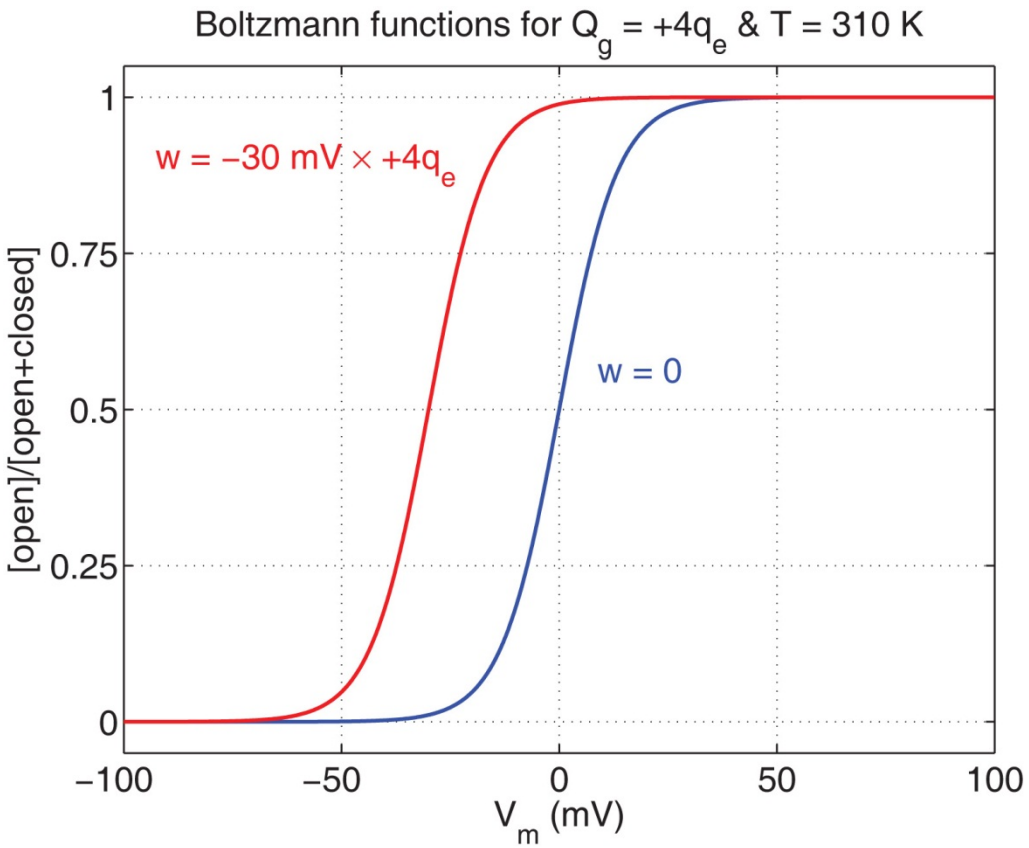
$$\frac{[\text{open}]}{[\text{closed}]} = \exp\left(-\frac{w - z_q q_e V_m}{kT}\right), \qquad (4.4)$$

where Boltzmann's constant k = 1.38 £ $10^{i\ 23}$ J/ K and w is the energy required to open the channel when the membrane potential is zero, i.e., with $V_m = 0$.

Channel gating (cont.):

Consequently, the fraction of open channels is:

$$\frac{[\text{open}]}{[\text{open}+\text{closed}]} = \frac{1}{1+\exp\left(\frac{w - z_g q_e V_m}{kT}\right)}. \quad (4.5)$$



Macroscopic channel kinetics:

Consider a large membrane patch containing N channels of a particular ion species.

We assume that each channel is either in an open or closed state and that the transition between these states is stochastic.

If the number of closed and open channels at any instant be $N_c(t)$ and $N_o(t)$, respectively, where N_c and N_o are random variables, then:

$$N = N_c(t) + N_o(t)\,. \qquad (4.6)$$

Macroscopic channel kinetics (cont.):

We assume state transitions to follow first-order kinetics. (We will check this assumption later!)

Assuming the rate constant for switching from a closed to an open state is α while that for switching from an open state to a close state is β, then the *average behaviour* is described by:

$$N_c \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} N_o. \qquad (4.7)$$

(Note: From empirical data and our understanding of the structure of voltage-sensitive gating particles, we expect α and β to depend on the transmembrane potential.)

Macroscopic channel kinetics (cont.):

From Eqn. (4.7) we have:

$$\frac{\mathrm{d}N_c}{\mathrm{d}t} = \beta N_o - \alpha N_c \qquad (4.8)$$

and:

$$\frac{\mathrm{d}N_o}{\mathrm{d}t} = \alpha N_c - \beta N_o. \qquad (4.9)$$

Combining Eqns. (4.6) and (4.9) gives:

$$\frac{\mathrm{d}N_o}{\mathrm{d}t} + (\alpha + \beta)\, N_o = \alpha N. \qquad (4.10)$$

Macroscopic channel kinetics (cont.):

The solution of Eqn. (4.10) for t ¸ 0 in the case of constant α and β is:

$$N_o(t) = A\mathrm{e}^{-(\alpha+\beta)t} + \frac{\alpha}{\alpha+\beta}N. \qquad (4.11)$$

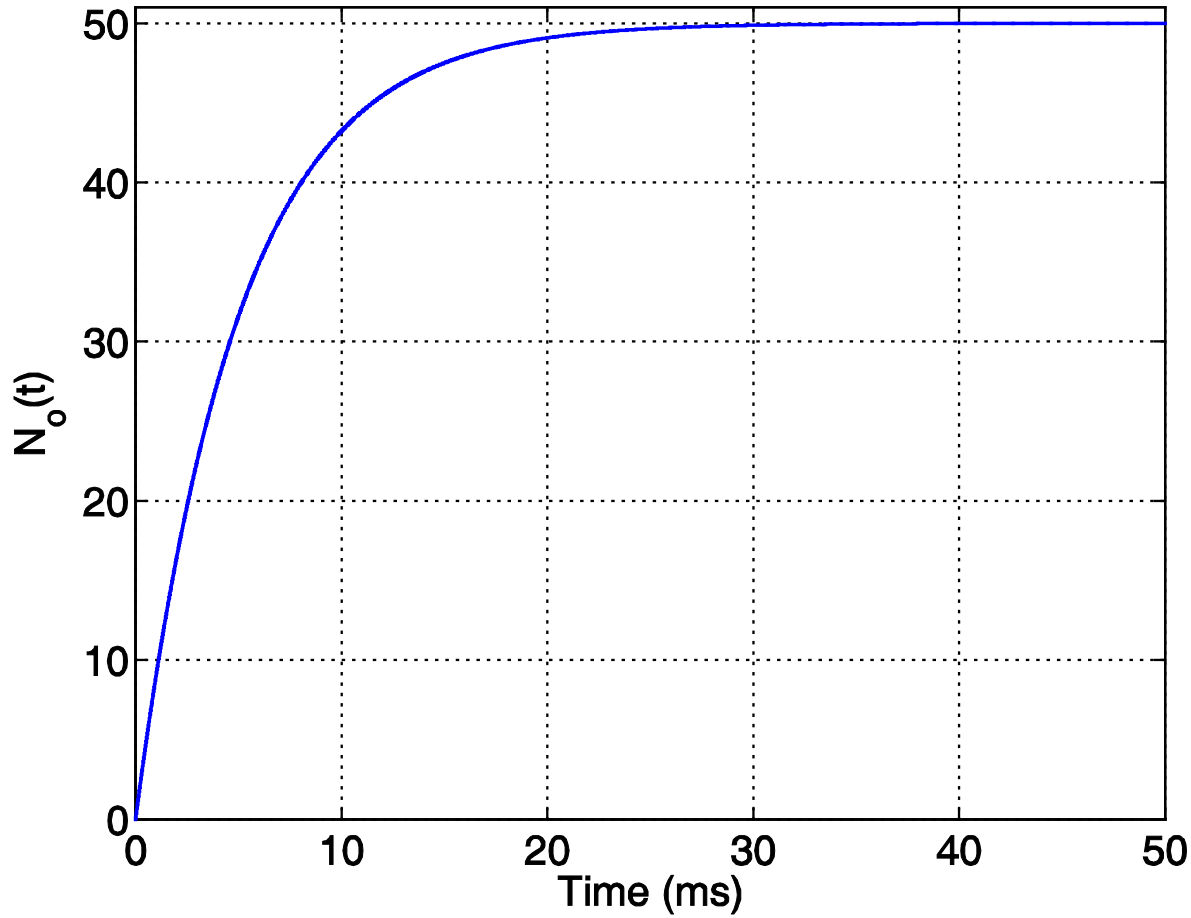
Note:-

- The parameter A is determined by the initial conditions.
- $\mathrm{N_o(t)}$ decays with a time constant of $1/(\alpha+\beta)$.
- The steady-state value is:

$$N_o(t \to \infty) = \frac{\alpha}{\alpha+\beta}N. \qquad (4.13)$$

Macroscopic channel kinetics (cont.):

For example, if N = 100, $N_o(0) = 0$ and $\alpha = \beta = 100\ s^{-1}$ for $t \geq 0$, then the following time-course for $N_o(t)$ results.



Channel statistics:

Under steady-state conditions, with an average number $< N_o >$ channels open and an average number $< N_c >$ channels closed, the *probability of a single channel being open* is:

$$p = \frac{\langle N_o \rangle}{N}, \qquad (4.15)$$

and the *probability of a single channel being closed* is:

$$q = \frac{\langle N_c \rangle}{N}. \qquad (4.16)$$

Channel statistics (cont.):

The probability of a channel being either open *or* closed must be unity, i.e.:

$$p + q = 1. \qquad (4.17)$$

For N channels, the probability of exactly N_o channels being open is described by the *Bernoulli distribution*:

$$B_N(N_o) = \frac{N!}{N_o!\,(N - N_o)!} p^{N_o} q^{N - N_o}. \qquad (4.18)$$

Channel statistics (cont.):

The *mean number of open channels* is:

$$\langle N_o \rangle = Np, \qquad (4.22)$$

and the *variance in the number of open channels* is also proportional to N.

Consequently, the relative noise level (the square-root of the variance divided by the mean) is proportional to $N^{-1/2}$. Thus, patches of membrane with a small number of channels (e.g., nodes of Ranvier) exhibit relatively more noise.

Channel statistics (cont.):

Consider N potassium channels, each with the single-channel current:

$$i_{\mathrm{K}} = \gamma_{\mathrm{K}} \left(V_m - E_{\mathrm{K}} \right) . \qquad (4.27)$$

The *mean macroscopic current* is then:

$$\langle I_{\mathrm{K}} \rangle = N p \, \gamma_{\mathrm{K}} \left(V_m - E_{\mathrm{K}} \right) , \qquad (4.28)$$

such that the *mean macroscopic conductance* is:

$$\langle G_{\mathrm{K}} \rangle = N p \, \gamma_{\mathrm{K}} . \qquad (4.29)$$

Introduction to the Hodgkin-Huxley membrane model:

The derivation of equation (4.11) — the differential equation for number of open channels — assumed that the channel opening/closing kinetics are first-order. However, many ion channels have multiple gating "particles" within the channel protein, each with their own independent voltage sensor. Consequently, the opening/closing kinetics for the entire channel may not be so simple. In 1952, Hodgkin and Huxley published mathematical expressions for channel kinetics that fit channel conductance data from squid giant axons.

Introduction to the Hodgkin-Huxley membrane model (cont.):

Consider a potassium channel with:-

- four independent gating “particles”
- the probability of a particle being open is n)
- the probability p of a potassium gate being open is n^4

The dynamics of each potassium gating particle can be described by:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n (1 - n) - \beta_n n. \qquad (4.31)$$

Introduction to the Hodgkin-Huxley membrane model (cont.):

The maximum conductance of N potassium channels is then:

$$\bar{g}_{\mathrm{K}} = N\gamma_{\mathrm{K}}. \tag{4.34}$$

For large N, where expected values can be assumed:

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 = N\gamma_{\mathrm{K}} n^4. \tag{4.35}$$

Introduction to the Hodgkin-Huxley membrane model (cont.):

The solution of Eqn. (4.31) for t ¸ 0 in the case of constant α_n and β_n is:

$$n(t) = n_\infty - (n_\infty - n_o)\, e^{-t/\tau_n}, \qquad (4.36)$$

where n_o is the initial probability of an open particle and the time constant and asymptotic values are, respectively:

$$\tau_n = \frac{1}{\alpha_n + \beta_n}, \qquad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}. \qquad (4.37)$$