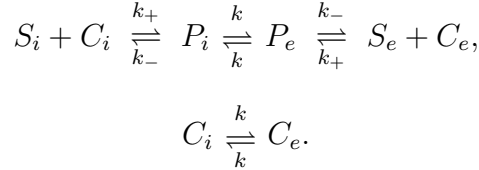


Mathematical physiology

PROBLEM SHEET 1.

1. Carrier-mediated transport of a substrate S by a carrier protein C is modelled as the (rapid) reaction system



Explain the meaning of these reactions. If a substrate flux J is supplied to the extra-cellular fluid and thus also (in a steady state) to the intra-cellular fluid, use steady state kinetics to show that

$$J = \frac{K^*(S_e - S_i)}{(K_m + S_i)(K_m + S_e) - K_d^2}, \quad K_m = \frac{k_- + k}{k_+}, \quad K_d = \frac{k}{k_+},$$

where K^* should be defined.

2. A membrane channel has N identical gates. If S_i is the proportion of channels with i open gates, write down rate equations for S_i in terms of the overall reaction rates R_i of $S_{i-1} \rightleftharpoons S_i$, $i = 1, 2, \dots, N$. Derive a conservation law expressing the conservation of the total number of channels.

Suppose that

$$S_j = {}^N C_j n^j (1 - n)^{N-j},$$

where ${}^N C_j$ is the binomial coefficient. Show that the equations are satisfied if

$$\dot{n} = \alpha(1 - n) - \beta n, \quad (*)$$

where α and β are the gate opening and closing rates.

For the case $N = 2$, show that all initial states tend to this solution (*put* $S_0 = (1 - n)^2 + y_0$, $S_2 = n^2 + y_2$, where n satisfies $(*)$, and show that $y_0, y_2 \rightarrow 0$.)

3. Suppose a membrane channel has three gates, two of which are controlled by a protein M , and the other is controlled by a protein H . Suppose that the fractions of open M and H gates are m and h respectively. By letting S_{ij} denote the density of channels with i open M -gates and j open H -gates, write down the rate equations for S_{ij} , assuming that the rates of M -gate opening and closing are α and β , and the rates of H -gate opening and closing are γ and δ , respectively.

Explain why the density of open channels is $m^2 h$, and show that the equations have solutions in which $S_{00} = (1 - m)^2(1 - h)$, etc., providing m and h satisfy equations which you should find. [*There is no need to be exhaustive.*] How do you expect this result to generalise to r proteins controlling s gates?

4. Write down the Hodgkin-Huxley space-clamped model of trans-membrane conduction, and explain its derivation. Non-dimensionalise the model, and show that with certain parametric assumptions (which you should explain) it reduces to

$$\begin{aligned}\dot{n} &= n_\infty(v) - n, \\ \varepsilon\dot{v} &= I^* - g(v, n),\end{aligned}$$

where v is membrane potential and n is a gating variable, and show that g can be written as

$$g = \gamma_K(v + v_K^*)n^4 + \gamma_L(v - v_L^*) - (1 - v)(\bar{h} - n)m^3(v).$$

Use typical values $g_{\text{Na}} = 120 \text{ mS cm}^{-2}$, $g_K = 36 \text{ mS cm}^{-2}$, $g_L = 0.3 \text{ mS cm}^{-2}$, $v_{\text{Na}} = 115 \text{ mV}$, $v_K = -12 \text{ mV}$, $v_L = 10.6 \text{ mV}$, $C_m = 1 \text{ } \mu\text{F cm}^{-2}$, $\tau_n = 5 \text{ ms}$, to estimate the values of γ_K , γ_L , v_L^* , v_K^* and ε . [*You may assume that $m_\infty(v)$ is a sigmoidal function (in fact it is rather well approximated by $[1 + \exp\{-12.5(v - 0.22)\}]^{-1}$)]. Giving reasons, derive the graphical form of the v nullcline, $g = 0$, assuming that $I^* = 0$. Hence deduce that (if n'_∞ is large enough) the membrane is *excitable*, defining also what this means.*