Mathematical physiology

Problem sheet 2.

1. 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 $g_{\mathrm{Na}} = 120$ mS cm^{-2}, $g_{\mathrm{K}} = 36$ mS cm^{-2}, $g_{\mathrm{L}} = 0.3$ mS cm^{-2}, $v_{\mathrm{Na}} = 115$ mV, $v_{\mathrm{K}} = -12$ mV, $v_{\mathrm{L}} = 10.6$ mV, $C_m = 1$ μF cm^{-2}, $\tau_n = 5$ 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, $g = 0$. Hence deduce that (if n'_∞ is large enough) the membrane is *excitable*, defining also what this means.

2. The Fitzhugh-Nagumo model for an action potential is

$$\begin{aligned}\varepsilon\dot{v} &= I^* + f(v) - w,\\ \dot{w} &= \gamma v - w,\end{aligned} \tag{1}$$

and you may assume $\varepsilon \ll 1$.

Suppose $f = v(a-v)(v-1)$, where $0 < a < 1$. Show that if

$$\gamma > \tfrac{1}{3}(a^2 - a + 1)^{1/2},$$

there is a unique steady state for any I^*. In this case show that the system is excitable if $I^* = 0$. Show that it may spontaneously oscillate if $I^* > 0$. Give an explicit criterion for such oscillations to occur, and show that the approximate criterion for oscillations is that

$$I_- < I^* < I_+,$$

where

$$I_\pm = \gamma v_\pm - f(v_\pm), \quad v_\pm = \tfrac{1}{3}[(a+1) \pm (a^2 - a + 1)^{1/2}].$$

3. If the membrane potential of an axon is V and the transverse membrane current is $I_\perp$, derive the cable equation

$$C\frac{\partial V}{\partial t} = -I_\perp + \frac{1}{R}\frac{\partial^2 V}{\partial x^2},$$

explaining also the meaning of the terms. What is meant by the resting potential V_{eq}?

Suppose that the gate variable n satisfies $\tau_n \dot{n} = n_\infty - n$, and that

$$V - V_{\mathrm{eq}} = v_{\mathrm{Na}} v, \quad t \sim \tau_n, \quad x \sim l, \quad I_\perp = p g_{\mathrm{Na}} v_{\mathrm{Na}} g(n, v),$$

where p is the axon circumference, and $C = pC_m$, $R = R_c/A$, where C_m is the membrane capacitance per unit area, R_c is the intracellular fluid resistance, and A is the axon cross-sectional area. Show that v and n satisfy the dimensionless equations

$$\begin{aligned} \varepsilon v_t &= -g(n, v) + \varepsilon^2 v_{xx}, \\ n_t &= n_\infty(v) - n. \end{aligned}$$

How must l be chosen to obtain this form? What is the definition of ε? Use the values $g_{\mathrm{Na}} = 120$ mS cm^{-2}, $v_{\mathrm{Na}} = 115$ mV, $C_m = 1$ μF cm^{-2}, $R_c = 35$ Ω cm, $\tau_n = 5$ ms and axon diameter $d = 0.05$ cm to estimate the values of ε and l. Is the latter value of concern?

4. Describe the basic cell physiology of intracellular calcium exchange which is used in the two pool model:

$$\begin{aligned} \frac{dc}{dt} &= r - kc - [J_+ - J_- - k_s c_s], \\ \frac{dc_s}{dt} &= J_+ - J_- - k_s c_s, \\ J_+ &= \frac{V_1 c^n}{K_1^n + c^n}, \\ J_- &= \left(\frac{V_2 c_s^m}{K_2^m + c_s^m}\right)\left(\frac{c^p}{K_3^p + c^p}\right). \end{aligned}$$

Non-dimensionalise the model to obtain the equations

$$\begin{aligned} \dot{u} &= \mu - u - \gamma \dot{v}, \\ \varepsilon \dot{v} &= f(u, v), \\ f &= \beta\left(\frac{u^n}{1 + u^n}\right) - \left(\frac{v^m}{1 + v^m}\right)\left(\frac{u^p}{\alpha^p + u^p}\right) - \delta v, \end{aligned}$$

and define α, β, γ, δ, ε.

Given $k = 10\ \mathrm{s}^{-1}$, $K_1 = 1\ \mu\mathrm{M}$, $K_2 = 2\ \mu\mathrm{M}$, $K_3 = 0.9\ \mu\mathrm{M}$, $V_1 = 65\ \mu\mathrm{M\ s}^{-1}$, $V_2 = 500\ \mu\mathrm{M\ s}^{-1}$, $k_s = 1\ \mathrm{s}^{-1}$, $m = 2$, $n = 2$, $p = 4$, find approximate values of α, β, γ, δ, ε.

Denoting the nullcline of v as $v = g(u)$, derive an approximate (graphical) representation for $g(u)$, assuming $\delta \ll 1$. If also $\varepsilon \ll 1$, deduce that there is a range of values of μ for which periodic solutions are obtained, and give approximate characterisations of the form of the oscillations of the cytosolic Ca^{2+} concentration u; in particular, explain the spikiness of the oscillation, and show that the amplitude is approximately independent of μ, but that the period decreases as μ increases.

What happens if $n > p$?