Mathematical physiology

PROBLEM SHEET 2.

1. 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

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

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

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

2. 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

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

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 $g_{\text{Na}} = 120$ mS cm^{-2}, $v_{\text{Na}} = 115$ 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?

3. 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 $k = 10$ s^{-1}, $K_1 = 1$ μM, $K_2 = 2$ μM, $K_3 = 0.9$ μM, $V_1 = 65$ μM s^{-1}, $V_2 = 500$ μM s^{-1}, $k_s = 1$ 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 $n > p$?

4. The CICR model is given by

$$\begin{aligned}
u_t + \gamma v_t &= \mu - u, \\
\varepsilon v_t &= f(u, v),
\end{aligned}$$

where

$$f = \beta\left(\frac{u^n}{1 + u^n}\right) - \left(\frac{v^m}{1 + v^m}\right)\left(\frac{u^p}{\alpha^p + u^p}\right) - \delta v.$$

Show that it has a unique steady state (with $u, v > 0$). Show that it is oscillatorily unstable if

$$\varepsilon - f_v < -\gamma f_u$$

at the fixed point, and deduce that if $g(u)$ is defined by $f[u, g(u)] = 0$, and $\varepsilon \ll 1$, then this criterion is approximately

$$g'(\mu) < -1/\gamma.$$

Deduce from the form of the graph of $g(u)$ that periodic solutions will exist in a range $\mu_- < \mu < \mu_+$.

What might the instability region be in the (μ, δ) plane?

5. The dimensionless two-pool model of CICR,

$$\begin{aligned} u_t &= \mu - u - \frac{\gamma f(u,v)}{\varepsilon}, \\ \varepsilon v_t &= f(u,v), \end{aligned}$$

is considered in a one-dimensional spatial domain. Explain why the model may be modified by a diffusion term in u but not in v, and explain also why the natural length scale to choose is such that the scaled term is εu_{xx}.

Suppose that $f(u,v) = 0$ defines a function $v = g(u)$ with $g(0) = 0$, that g first increases to a large maximum, decreases to a positive minimum, and then increases to an asymptote as $u \to \infty$, and that $g' < -1/\gamma$ for $\mu_- < u < \mu_+$, where $\mu_+ > \mu_- > 0$. Use phase plane analysis to show plausibly that periodic travelling wave trains will exist for $\mu_- < \mu < \mu_+$, where also $g'(\mu_\pm) = -1/\gamma$ (assuming $\min g' < -1/\gamma$).