Mathematical physiology

PROBLEM SHEET 3.

1. A Noble-type model for excitable heart cells is given in dimensionless form by

$$\begin{aligned}\dot{n} &= \varepsilon[n_\infty(V) - n],\\ \dot{h} &= h_\infty(V) - h,\\ \dot{V} &= \gamma\left[h - h_0(V)\right],\end{aligned}$$

where n and h are gate variables and V is the electric potential. The range of interest of V is $(-1, v_{\rm Na})$, and the gate variables $n, h \in (0,1)$; $v_{\rm Na} \approx 0.4$.

The parameters are $\varepsilon \ll 1$ and $\gamma \gg 1$. Describe the qualitative behaviour of solutions in terms of the three nullcline surfaces in the phase space.

The function $h_\infty(V)$ is monotonically decreasing, with $h_\infty(-\infty) = 1$ and $h_\infty(\infty) = 0$, and $n_\infty(V)$ is monotonically increasing, with $n_\infty(-\infty) = 0$ and $n_\infty(\infty) = 1$. The function h_0 is given as

$$h_0(V) = (1+\lambda)\Psi(V)h_\infty(V),$$

where

$$\Psi = \frac{1 - e^{-(V+1)/\delta}}{1 - e^{-(v_{\rm Na}-V)/\delta}},$$

and $\delta \ll 1$. Plot the function $\Psi(V)$ over the range of interest.

Suppose that λ is constant, and that $0 < \lambda \ll 1$. Show that there is a unique steady state, find its approximate value, and by analysing the behaviour in the (V, h) phase plane, show that it is stable but excitable, stating any assumptions you make about the size of δ. Plot the shape of the action potential, describing the slow and fast regions in terms of the phase plane trajectories.

Now suppose that h_∞ changes rapidly, such that $h_\infty \approx 1$ for $V \lesssim -0.9$, and

$$h_\infty \approx \nu e^{-\alpha V} \quad \text{for} \quad V \gtrsim -\frac{1}{\alpha}\ln\frac{1}{\nu},$$

where ν is small and $\alpha \gtrsim O(1)$. Assuming that $\delta\alpha \ll 1$ and $\alpha\gamma\lambda\nu \ll 1$, show that the fast recovery phase (repolarisation) of the action potential is drawn out over a longer period, and draw the shape of the action potential in this case.

How would these results be affected by a dependence of λ on n ?

2. The equation

$$v_t = f(v) + \nabla^2 v$$

admits a travelling wave solution in one dimension of the form

$$v = V(\xi), \quad \xi = ct - x, \quad c > 0, \quad V(\infty) = 1, \quad V(-\infty) = 0.$$

Write down the ordinary differential equation satisfied by V.

Suppose now that we seek a solution in two dimensions which is slowly varying in the direction transverse to the direction of propagation. By seeking a solution in the form $v = V[\psi(\mathbf{x}, t)]$, show that

$$V'(\psi_t - \nabla^2\psi) = f(V) + V''|\boldsymbol{\nabla}\psi|^2,$$

where $V' = \dfrac{dV}{d\psi}$.

Suppose $\psi < 0$ ahead of the wavefront. Let ξ be a (curvilinear) coordinate orthogonal to the wavefront, taken to be $\psi(\mathbf{x}, t) = 0$, such that ξ increases with ψ (thus ξ points behind the wave). Show that

$$\frac{\partial \psi}{\partial \xi} = |\boldsymbol{\nabla}\psi|,$$

that the normal velocity of the interface in the direction of the unit normal $\mathbf{n} = -\dfrac{\boldsymbol{\nabla}\psi}{|\boldsymbol{\nabla}\psi|}$ pointing in front of the wave is

$$v_n = \frac{\psi_t}{|\boldsymbol{\nabla}\psi|},$$

and that the curvature is

$$\boldsymbol{\nabla}.\,\mathbf{n} = -\frac{1}{|\boldsymbol{\nabla}\psi|}\left[\nabla^2\psi + \frac{\partial|\boldsymbol{\nabla}\psi|}{\partial n}\right].$$

Hence show that

$$V_{\xi\xi} + \frac{V_\xi}{|\boldsymbol{\nabla}\psi|}\left\{-\frac{\partial|\boldsymbol{\nabla}\psi|}{\partial \xi} + \nabla^2\psi - \psi_t\right\} + f(V) = 0,$$

and deduce that

$$v_n = c - \boldsymbol{\nabla}.\,\mathbf{n}.$$

Find a solution of this equation which describes a target wave. [*Hint: seek a solution* $\psi = ct - f(r)$.]

3. The curved front equation for the motion of a wavefront $\psi(\mathbf{x}, t) = 0$ is given by

$$v_n = c - \boldsymbol{\nabla}.\,\mathbf{n},$$

where

$$v_n = \frac{\psi_t}{|\boldsymbol{\nabla}\psi|}, \quad \mathbf{n} = -\frac{\boldsymbol{\nabla}\psi}{|\boldsymbol{\nabla}\psi|}.$$

Suppose, in two-dimensional polar coordinates (r, θ), that $\psi = R(\theta, t) - r$. Find expressions for v_n and $\mathbf{n}$, and hence show that

$$R_t = \frac{c\,(R^2 + R_\theta^2)^{1/2}}{R} - \frac{(R^2 + 2R_\theta^2 - RR_{\theta\theta})}{R\,(R^2 + R_\theta^2)}.$$

Find a solution $R = \bar{R}(t)$, and describe its behaviour. In this context, describe what curvature blocking means.

Now write $R = \bar{R} + \rho$, and linearise for small ρ. Show that the target pattern is stable, but that one mode is neutrally stable. What does this mean, why does it occur?

Still writing $R = \bar{R}(t) + \rho$, but now assuming that R is large, show that, with a suitable definition of a new time variable τ,

$$\rho_\tau = \rho_{\theta\theta} + \tfrac{1}{2}c\rho_\theta^2 + \rho.$$

Seek steady solutions and describe the trajectory directions in the $(\rho, \sigma = \rho')$ phase plane. Find a first integral of the system and hence complete the determination of the phase plane. Show that non-circular target patterns are possible, if the conserved quantity, E, is negative, but that spiral waves are not.

Now look for solutions $\rho(\eta)$, $\eta = \omega\tau - \theta$, $\omega \ll 1$. Repeat the phase plane analysis, and by considering the evolution of E with θ, show that spiral waves are possible to some extent.

4. Describe the sequence of events which occurs in the human circulatory system during a single heart beat. Your description should include a schematic illustration of the circulatory system, how filling and emptying of the atria and ventricles is effected by valve opening and closing, and how this affects the pressure and volume of the left ventricle.

   What is meant by *stroke volume* and *heart rate*? How does the cardiac output depend on these?

   A simple model of the circulation consists of a (left) ventricle (with mitral and aortic valves), arteries, veins and capillaries. Show that a simple compartment model for this system which describes the volumes of the arteries, veins and ventricle can be written in the form

$$\begin{aligned}
\dot{V}_a &= Q_+ - Q_c,\\
\dot{V}_v &= Q_c - Q_-,\\
\dot{V}_{\rm LV} &= Q_- - Q_+,
\end{aligned}$$

   and describe the meaning of the variables. What assumption is made about the capillary volume in writing these equations? How should the variables Q_k be determined in terms of arterial, venous, and ventricular pressures?

5. The single ventricle model of the heartbeat is given by

$$\begin{aligned}
\dot{p}_a &= -\frac{(p_a - p_v)}{R_c C_a} + \frac{[p_{\rm LV} - p_a]_+}{R_a C_a},\\
\dot{p}_v &= \frac{(p_a - p_v)}{R_c C_v} - \frac{[p_v - p_{\rm LV}]_+}{R_v C_v},\\
\dot{V}_{\rm LV} &= \frac{[p_v - p_{\rm LV}]_+}{R_v} - \frac{[p_{\rm LV} - p_a]_+}{R_a}, \qquad V_{\rm LV} = V_0 + C_{\rm LV} p_{\rm LV}.
\end{aligned}$$

The ventricular compliance oscillates periodically between low values C_s and high values C_d of durations $\Delta t_F \approx 0.3$ s and $\Delta t_R \approx 0.5$ s, respectively, with rapid transitions (~ 0.05 s) between these values. The parameter values imply the following: $R_c C_a \sim 1.8$ s, $R_a C_a \sim 0.09$ s, $R_c C_v \sim 60$ s, $R_v C_v \sim 0.8$ s, $R_a C_s \sim 0.02$ s, $R_v C_d \sim 0.25$ s.

The heartbeat consists of four phases: contraction, ejection, relaxation, refilling. Explain how these are controlled (in the left heart) by the mitral and aortic valves.

Suppose that at the beginning of the contraction phase, $p_{\rm LV} = p^0_{\rm LV}$, $p_v = p^0_v$, $p_a = p^0_a$, and $C_{\rm LV} = C_d$. Explain why contraction is isovolumetric, and why p_a and p_v remain constant.

In the ejection phase, explain why $p_{\rm LV} \approx p_a$, and why

$$\frac{d}{dt}(C_{\rm LV} p_{\rm LV} + C_a p_a) \approx -\frac{p_a}{R_c},$$

and deduce that p_a first jumps rapidly to

$$p^* = \frac{C_d p^0_{\rm LV} + C_a p^0_a}{C_a + C_s},$$

and is thereafter given by

$$p_a = p^* e^{-\lambda_1 t}, \quad \lambda_1 = \frac{1}{R_c(C_a + C_s)}.$$

Show that

$$p_v \approx p^0_v + \frac{p^*}{\lambda_1 R_c C_v}\left[1 - e^{-\lambda_1 t}\right].$$

Deduce that at the end of the ejection phase,

$$p_a = p^1_a = \Delta_1 p^*, \quad \Delta_1 = e^{-\lambda_1 \Delta t_F},$$

$$p_v = p^1_v = p^0_v + \frac{(C_a + C_s)(1 - \Delta_1)p^*}{C_v}.$$

Show that p_a and p_v are constant in the relaxation phase, and that $p_{\rm LV}$ decreases to

$$p^1_{\rm LV} = \frac{C_s p^1_a}{C_d}.$$

In the refilling phase, show that

$$p_a = p^1_a e^{-\lambda_2 t}, \quad \lambda_2 = \frac{1}{R_c C_a},$$

that

$$C_a p_a + C_v p_v + C_d p_{\rm LV} = (C_a + C_s) p^1_a + C_v p^1_v,$$

and that

$$p_v - p_{\text{LV}} = \mu p_a^1 \left[e^{-\lambda_2 t} - e^{-\lambda_3 t}\right] + (p_v^1 - p_{\text{LV}}^1) e^{-\lambda_3 t},$$

where

$$\mu = \frac{1}{R_c C_v \left\{ \dfrac{1}{R_v}\left(\dfrac{1}{C_v} + \dfrac{1}{C_d}\right) - \dfrac{1}{R_c C_a} \right\}}, \quad \lambda_3 = \frac{1}{R_v}\left(\frac{1}{C_v} + \frac{1}{C_d}\right).$$

Deduce that the values of p_a, p_v and p_{LV} at the beginning of the next contraction phase are given by

$$p_a^2 = \Delta_2 p_a^1, \quad \Delta_2 = e^{-\lambda_2 \Delta t_R},$$

$$p_v^2 = \frac{C_d \Delta + (C_a + C_s) p_a^1 + C_v p_v^1 - C_a p_a^2}{C_v + C_d},$$

$$p_{\text{LV}}^2 = p_v^2 - \Delta,$$

where

$$\Delta = \mu p_a^1 (\Delta_2 - \Delta_3) + \Delta_3 (p_v^1 - p_{\text{LV}}^1), \quad \Delta_3 = e^{-\lambda_3 \Delta t_R},$$

Define $\boldsymbol{\psi} = (p_a^0, p_v^0, p_{\text{LV}}^0)^T$ and show that the map from $\boldsymbol{\psi}^0$ to $\boldsymbol{\psi}^2$ is linear and homogeneous. Why, nevertheless, must there be a unique solution?