Mathematical physiology

PROBLEM SHEET 4.

1. The Ottesen model for the baroreflex is written in the form

$$\begin{aligned}\dot{H} &= \delta_H(H_0 - H) + \lambda_H T_s - \mu_H T_p,\\ C_a\dot{p}_a &= -\frac{(p_a - p_v)}{R_c} + H\Delta V,\\ C_v\dot{p}_v &= \frac{p_a - p_v}{R_c} - \frac{p_v}{R_v},\end{aligned}$$

where the sympathetic and parasympathetic tonic functions are given by

$$T_s = g[p_a(t-\tau)], \quad T_p = 1 - g(p_a),$$

and g is the Hill function

$$g(p) = \frac{1}{\left(1 + \dfrac{p^n}{p_0^n}\right)}.$$

Non-dimensionalise by scaling the variables as

$$H = H_0 g, \quad p_a = p_0 p, \quad t \sim \tau, \quad p_v = \frac{R_v p_0}{R_c} q,$$

and deduce the dimensionless form of the model as

$$\begin{aligned}\varepsilon\dot{h} &= 1 - h + \lambda g(p_1) - \mu(1-g),\\ \dot{p} &= \kappa[-(p - \delta q) + \sigma h],\\ \dot{q} &= \omega[p - (1+\delta)q],\end{aligned}$$

where

$$g(p) = \frac{1}{1+p^n},$$

and give the definitions of the dimensionless parameters.

Using the values $\delta_H = 1.7\ \mathrm{s}^{-1}$, $\tau = 10$ s, $\lambda_H = 0.84\ \mathrm{s}^{-2}$, $\mu_H = 1.17\ \mathrm{s}^{-2}$, $H_0 = 1.7\ \mathrm{s}^{-1}$, $R_v = 0.06$ mmHg s ml^{-1}, $R_c = 1.2$ mmHg s ml^{-1}, $p_0 = 77$ mmHg, $C_a = 1.5$ ml mmHg^{-1}, $C_v = 50$ ml mmHg^{-1}, $\Delta V = 70$ ml, find estimates for the dimensionless parameters. Hence show that the equation for the venous pressure approximately uncouples from those for h and p.

Show that in the steady state,

$$p \approx \phi(p) = A + \frac{B}{1+p^n},$$

and give the approximate numerical values of A and B. Show that this has a unique positive solution, and find an approximate value for this by iterating one of the maps $p \to \phi(p)$, $p \to \phi^{-1}(p)$, assuming $n = 7$. Which one works? Why?

Suppose instead that the steady state ought to be (dimensionally) 100 mmHg. Find the value of n which is consistent with this.

2. Picard's theorem states that a holomorphic function $f(z)$ having an isolated essential singularity at $z = z_0$ takes on every possible complex value in any neighbourhood of z_0, with at most one exception. Use this to show that the equation for σ,

$$\sigma = -\beta - \gamma e^{-\sigma},$$

where β and γ are positive constants, has an infinite number of complex roots in a neighbourhood of ∞.

Show that if $\sigma \to \infty$, then also $\operatorname{Re} \sigma \to -\infty$.

Show that the complex roots vary continuously with γ (for example show that $\partial\sigma/\partial\gamma$ exists for complex σ).

Show that $\operatorname{Re} \sigma < 0$ for all roots if γ is sufficiently small.

Deduce that instability occurs for $\gamma > \gamma_c$, where

$$\gamma_c = \frac{\Omega}{\sin \Omega},$$

and Ω is the smallest (positive) root of

$$\tan \Omega = -\frac{\Omega}{\beta}.$$

Use `Maple` or some other graphical software to plot γ_c as a function of β.

3. In respiratory physiology, what is meant by the *minute ventilation*? Describe the way in which respiration is controlled by the blood gas concentrations at the central and peripheral chemoreceptors.

The Mackey-Glass model is a one compartment model of respiratory control, and can be represented by the equations

$$K\dot{p} = M - p\dot{V},$$

$$\dot{V} = \dot{V}(p_\tau);$$

explain what the various terms represent, and their physiological interpretation.

Suppose that

$$\dot{V} = G[p - p_0]_+,$$

and that $M = 200$ mm Hg l(BTPS) min^{-1}, $p_0 = 35$ mm Hg, $K = 40$ l(BTPS), $G = 2$ l(BTPS) min^{-1} mm Hg^{-1}, $\tau = 0.2$ min. Show how to non-dimensionalise the equations to obtain the dimensionless form

$$\dot{p} = \alpha[1 - (1 + \mu p)v],$$

$$v = [p_1]_+,$$

and give the definitions of α and μ. Check that they are dimensionless, and find their values.

4. A simplified version of the Grodins model describes CO_2 partial pressures in arteries, veins, brain and tissues by the equations

$$\begin{aligned} K_{\rm L}\dot{P}_{\rm aCO_2} &= -\dot{V}P_{\rm aCO_2} + 863K_{\rm CO_2}Q[P_{\rm vCO_2} - P_{\rm aCO_2}], \\ K_{\rm CO_2}K_{\rm B}\dot{P}_{\rm BCO_2} &= MR_{\rm BCO_2} + K_{\rm CO_2}Q_{\rm B}[P_{\rm aCO_2}(t-\tau_{\rm aB}) - P_{\rm BCO_2}] \\ K_{\rm CO_2}K_{\rm T}\dot{P}_{\rm TCO_2} &= MR_{\rm TCO_2} + (Q - Q_B)K_{\rm CO_2}[P_{\rm aCO_2}(t-\tau_{aT}) - P_{\rm TCO_2}], \end{aligned}$$

with the venous pressure being determined by

$$QP_{\rm vCO_2} = Q_{\rm B}P_{\rm BCO_2}(t-\tau_{\rm vB}) + (Q - Q_{\rm B})P_{\rm TCO_2}(t-\tau_{\rm vT}).$$

Explain the meaning of the equations and their constituent terms.

Use values $K_L = 3$ l, $\dot{V} \sim V^* = 5$ l min^{-1}, $863K_{\rm CO_2}Q = 26$ l min^{-1}, $K_B = 1$ l, $Q = 6$ l min^{-1}, $Q_B = 0.75$ l min^{-1}, $K_T = 39$ l, to evaluate response time scales for arterial, brain and tissue CO_2 partial pressures.

Deduce that for oscillations on a time scale of a minute, one can assume that the arterial pressure is in quasi-equilibrium, and that the tissue (and thus also venous) partial pressures are approximately constant.

Hence derive an approximate expression for $P_{\rm aCO_2}$ in terms of the ventilation $\dot{V}$.

5. Red blood cell precursors are produced from pluripotential stem cells in the bone marrow at a rate F. They mature for a period of τ days before being released into the blood, where they circulate for a further A days. If the apoptotic rates in bone marrow and blood are δ and γ, respectively, show that the developing cell density p and circulating RBC density e satisfy the equations

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial m} = -\delta p,$$

$$\frac{\partial e}{\partial t} + \frac{\partial e}{\partial a} = -\gamma e,$$

for $0 < m < \tau$ and $0 < a < A$, where

$$p(t,0) = F[E(t)], \quad e(t,0) = p(t,\tau),$$

and we assume F depends on the total circulating blood cell population,

$$E = \int_0^A e\, da.$$

Solve the equations using the method of characteristics, and hence show that for $t > \tau + A$, E satisfies

$$\dot{E} = F[E_\tau]e^{-\delta\tau} - F[E_{A+\tau}]e^{-\delta\tau-\gamma A} - \gamma E, \quad t > \tau + A.$$

Compare this model to that which assumes no age limit to the circulating RBC. Under what circumstances does the model reduce to the no age limit model?

Suppose that $F = F_0 f$, where f is $O(1)$ and is a positive monotone decreasing function. Show how to non-dimensionalise the model to the form

$$\dot{E} = \mu[f(E_1) - f(E_{\Lambda+1})e^{-\mu\Lambda} - E],$$

where $\mu = \gamma\tau$ and $\Lambda = A/\tau$. Supposing that $A = 120$ days and $\tau = 6$ days, explain why you might expect μ to be small.

Write down an equation for the exponent σ in solutions $\propto \exp(\sigma t)$ describing small perturbations about the steady state, and show that the steady state is stable if $|f'| < \frac{1}{2}$.

6. In a model for the evolution of the resting phase cells in a blood cell maturation model, the cell density M is given by

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial \xi} = -RM + Q,$$

where ξ is the maturation variable,

$$Q = \begin{cases} 2e^{-\gamma\tau}R[t-\tau, \xi-\tau]M[t-\tau, \xi-\tau], & \xi > \tau, \quad t > \tau, \\ 2e^{-(\gamma_0+V_0)\tau}e^{(\gamma_0+V_0-\gamma)\xi}V_0 R_0(t-\tau)N_0(t-\tau), & \xi < \tau, \quad t > \xi, \end{cases}$$

If $R = (1+\lambda)R_0$, $\lambda = 2e^{-\gamma\tau} - 1$, $\gamma_0 + V_0 = \gamma$, and all these quantities and also N_0 are constant, then the equation for M can be written as

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial \xi} = -RM + (1+\lambda)RM_{\tau,\tau},$$

with initial data being

$$M = M_0 = N_0 V_0 \quad \text{on} \quad \xi = 0 \quad \text{and} \quad t > \xi.$$

By careful consideration of how the characteristic equations are solved, show that for $t > \xi$, $M = M(\xi) \equiv M_0 u[(\xi - \tau)/\tau]$, where $u(s)$ satisfies

$$\frac{du}{ds} = -\alpha u - \Gamma u_1,$$

and $\alpha = R\tau$, $\Gamma = -(1+\lambda)R\tau$, and $u = 1$ for $s \in [-1, 0)$.

By taking the Laplace transform of the equation (exercising due care with the delayed term), show that the Laplace transform $U(p)$ of u is given by

$$U(p) = \frac{h(p)}{f(p)},$$

where

$$f(p) = p + \alpha + \Gamma e^{-p}$$

and

$$h(p) = 1 - \Gamma\left(\frac{1 - e^{-p}}{p}\right).$$

Deduce that U can also be written as

$$U(p) = \frac{\Lambda e^{p}}{p\left[(p+\alpha)e^{p} + \Gamma\right]} + \frac{1}{p},$$

where

$$\Lambda = \lambda R\tau.$$

Hence show that if the inversion contour for U is completed as a square with upper and lower sides at $\operatorname{Im} p = \pm(n + \frac{1}{2})\pi$, with n even for $\Gamma < 0$, as here, then by taking the limit as $n \to \infty$, u can be found as

$$u = \sum_{j=-\infty}^{\infty} c_j \exp\left(p_j s\right),$$

where p_j are the zeros of $f(p)$ (p_0 is the real root, and p_{-j} is the copmplex conjugate of p_j). Write down the definition of the constants c_j in terms of p_j, and show that they can be expressed as

$$c_j = \frac{\Lambda}{p_j\left(1 + \alpha + p_j\right)},$$

so that $c_j = O(1/j^2)$ for $j \gg 1$.