Mathematical physiology

PROBLEM SHEET 4.

1. The delayed logistic equation is

$$\dot{x} = \alpha x(1 - x_1), \quad x_1 = x(t-1).$$

Show that the steady solution $x = 1$ is oscillatorily unstable if $\alpha > \frac{1}{2}\pi$.

When α is large (a value $\alpha > 3$ is sufficient), the resulting oscillations take on the appearance of periodic isolated pulses. Find an approximation to this solution by assuming $x \approx e^{\alpha t}$ for $t < 0$, and integrating forward using the method of steps to find the solution in $0 < t < 1$, then in $1 < t < 2$ and finally in $2 < t < 3$. [*You should write the solution in terms of* $\phi = \ln x$.]

Show that, approximately,

$$\phi = \alpha t - e^{\alpha(t-1)}, \quad 0 < t < 1;$$

using this, show that

$$\phi \approx \alpha t + e^{\alpha}\left[e^{-e^{\alpha(t-2)}} - 1\right], \quad 1 < t < 2,$$

and using this, show that

$$\phi \approx \alpha t + e^{\alpha}\left[e^{-e^{\alpha(t-2)}} - 1\right], \quad t > 2,$$

where the last approximation is valid for $t < 2.5$.

Show that for $t \gtrsim 2$,

$$\phi \approx \alpha(t - P), \quad P = \frac{e^{\alpha}}{\alpha},$$

and deduce that the solution is periodic with approximate period P.

Show that the maximum and minimum values of x are

$$x_{\max} \approx e^{\alpha - 1}, \quad x_{\min} \approx \alpha e^{2\alpha - e^{\alpha}}.$$

Sketch the form of the solution for $x(t)$. Why is the approximate solution already good for $\alpha = 3$?

2. 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.

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

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

with the venous pressure being determined by

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

Explain the meaning of the equations and their constituent terms.

Use values $K_L = 3$ l, $\dot{V} \sim V^* = 5$ l min^{-1}, $863K_{\mathrm{CO_2}}Q = 26$ 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 $P_{\mathrm{aCO_2}}$ in terms of the ventilation $\dot{V}$.

4. 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 $|f'| < \frac{1}{2}$.

5. The Hopf bifurcation curve for the equation

$$\sigma = -\alpha - \Gamma e^{-\sigma}$$

is defined parametrically by

$$\Gamma_0(\alpha) = \frac{\Omega}{\sin\Omega}, \quad \alpha = -\frac{\Omega}{\tan\Omega},$$

for $\Omega \in (0, \pi)$. By expanding for small Ω, show that

$$\Gamma_0 = 1 + \tfrac{1}{6}\Omega^2 + \tfrac{7}{360}\Omega^4 + \tfrac{31}{15120}\Omega^6 + O(\Omega^8),$$

and that

$$\alpha + 1 = \tfrac{1}{3}\Omega^2 + \tfrac{1}{45}\Omega^4 + \tfrac{2}{945}\Omega^6 + O(\Omega^8).$$

Deduce that

$$\Gamma_0 = 1 + \tfrac{1}{2}(\alpha + 1) + \tfrac{3}{40}(\alpha + 1)^2 - \tfrac{9}{2800}(\alpha + 1)^3 + O[(\alpha + 1)^4],$$

i. e.,

$$\Gamma_0 \approx 1 + 0.5(\alpha+1) + 0.075(\alpha+1)^2 - 0.0032(\alpha+1)^3 + O[(\alpha+1)^4].$$

Plot Γ_0 versus α using suitable graphical software, and show that an accurate quadratic approximation for $\alpha \in (-1, 2)$ is

$$\Gamma_0 \approx 1 + 0.5(\alpha+1) + 0.058(\alpha+1)^2,$$

and that an accurate cubic approximation for $\alpha \in (-1, 5)$ is

$$\Gamma_0 \approx 1 + 0.5(\alpha+1) + 0.075(\alpha+1)^2 - 0.005(\alpha+1)^3.$$

Can you find a value of c for which

$$\Gamma_0 \approx 1 + 0.5(\alpha+1) + 0.075(\alpha+1)^2 - 0.0032(\alpha+1)^3 + c(\alpha+1)^4$$

provides an accurate approximation for larger values of α?

Show (plot it and compare with the quadratic approximation) that a better two coefficient approximation is given by

$$\Gamma_0 = \frac{1 + b(\alpha+1) + c(\alpha+1)^2}{1 + c(\alpha+1)},$$

if $b = 0.65$ and $c = 0.15$. Why would these values of b and c be chosen? Show (graphically) that an even better approximation is obtained if $b = 0.69$ and $c = 0.3$. (The maximum error for $\alpha < 100$ is less than 0.05.) How could you extend this type of approximation to larger values of α?

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 $j \gg 1$.