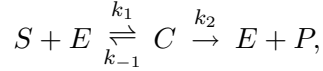


Mathematical physiology

PROBLEM SHEET 1.

1.1 Derive a suitably scaled form of the Michaelis-Menten model for the reaction

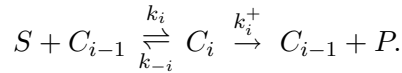


and show that it depends on the parameters

$$K = \frac{k_{-1} + k_2}{k_1 S_0}, \quad \lambda = \frac{k_2}{k_1 S_0}, \quad \varepsilon = \frac{E_0}{S_0},$$

where S_0 and E_0 are the initial values of S and E . If $\varepsilon \ll 1$, show that the solution consists of an outer layer in which $t = O(1)$, and an inner layer in which $t = O(\varepsilon)$, and find explicit approximations for these. Hence show that S decreases linearly initially, but exponentially at large times.

1.2 An enzyme has n binding sites for a substrate S . If the enzyme complexes with j bound sites are denoted as C_j , write down the rate equations for the concentrations of S , P and C_j , $j = 0, 1, \dots, n$, where $C_0 = E$, satisfying the reactions



Deduce that

$$C_0 = E_0 - \sum_1^n C_i,$$

where E_0 is the initial enzyme present. Use the quasi-steady state assumption to show that $R_i = 0$, $i = 1, \dots, n$, where

$$R_i = k_i S C_{i-1} - (k_{-i} + k_i^+) C_i,$$

and deduce that the reaction rate $r = dP/dt$ is given approximately by

$$r = \frac{E_0 \sum_{r=1}^n k_r^+ \phi_r S^r}{1 + \sum_{j=1}^n \phi_j S^j},$$

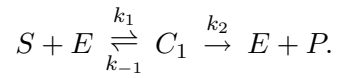
where

$$\phi_j = \prod_{i=1}^j \frac{1}{K_i}, \quad K_i = \frac{k_{-i} + k_i^+}{k_i}.$$

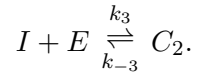
Deduce that if $k_1 \rightarrow 0$ with $k_1 k_n$ finite, the reaction rate is approximated by the Hill equation

$$r = \frac{k_n^+ E_0 S^n}{\prod_{i=1}^n K_i + S^n}.$$

1.3 A substrate S reacts with an enzyme to form a product P by the reaction scheme



An inhibitor I prevents the reaction by binding to the enzyme, as



Use the quasi-steady state hypothesis to show that the rate of reaction is approximately

$$r = \frac{k_2 E_0 S K_i}{K_m I + K_i S + K_m K_i},$$

where

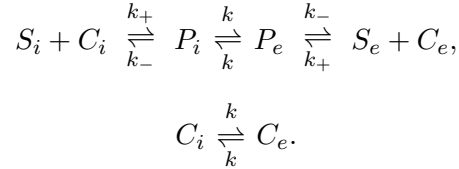
$$K_m = \frac{k_2 + k_{-1}}{k_1}, \quad K_i = \frac{k_{-3}}{k_3}.$$

If different initial values I_0, S_0 are used, can a Lineweaver-Burk plot be used to find K_m, K_i and k_2 ? Why, or why not?

Mathematical physiology

PROBLEM SHEET 2.

2.1 Carrier-mediated transport of a substrate S by a carrier protein C is modelled as the (rapid) reaction system



Explain the meaning of these reactions. If a substrate flux J is supplied to the exterior membrane surface and removed from the interior surface, use steady state kinetics to show that

$$J = \frac{K^*(S_e - S_i)}{(K_m + S_i)(K_m + S_e) - K_d^2},$$

where K^* , K_d and K_m should be defined.

2.2 (a) A membrane ion channel has two gates activated by a protein. If n denotes the fraction of open gates in a cell membrane, explain why the fraction of open channels is n^2 .

(b) An ion channel has three gates, two controlled by an activating protein A , and the other controlled by an inactivating protein B . If the density of open B gates is h , explain why the density of open channels is m^2h . How does this result generalise to r proteins controlling s gates?

2.3 Write down the Hodgkin-Huxley 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

$$g = \gamma_K(v + v_K^*)n^4 + \gamma_L(v - v_L^*) - (1 - v)(\bar{h} - n)m^3(v).$$

Give typical values of γ_K , γ_L , \bar{h} , v_L^* , v_K^* , ε . 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.

2.4 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 $\varepsilon \ll 1$. Explain the meaning of the terms in these equations, and describe where the equations come from.

Suppose $f = v(a - v)(v - 1)$, where $0 < a < 1$. Show that the system is excitable if $I^* = 0$ and γ is large enough, and that it may spontaneously oscillate if $I^* > 0$. Give an explicit criterion for such oscillations to occur, in terms of I^* , γ and a .

Mathematical physiology

PROBLEM SHEET 3.

3.1 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

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

such that v and n satisfy the dimensionless equations

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

How must l be chosen to obtain this form? What is the definition of ε ?

3.2 The Fitzhugh-Nagumo model for signal propagation in nerve cells is

$$\begin{aligned} \varepsilon v_t &= f(v) - w + \varepsilon^2 v_{xx}, \\ w_t &= \gamma v - w. \end{aligned} \tag{3}$$

Explain the origins of this model, and explain in detail why travelling waves exist if $\varepsilon \ll 1$.

3.3 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 $\alpha, \beta, \gamma, \delta, \varepsilon$.

Given $k = 10 \text{ s}^{-1}$, $K_1 = 1 \text{ } \mu\text{M}$, $K_2 = 2 \text{ } \mu\text{M}$, $K_3 = 0.9 \text{ } \mu\text{M}$, $V_1 = 65 \text{ } \mu\text{M s}^{-1}$, $V_2 = 500 \text{ } \mu\text{M s}^{-1}$, $k_s = 1 \text{ s}^{-1}$, $m = 2$, $n = 2$, $p = 4$, find approximate values of $\alpha, \beta, \gamma, \delta, \varepsilon$.

Mathematical physiology

PROBLEM SHEET 4.

4.1 Using the model of 3.3 with $\varepsilon \ll 1$, explain why $v \approx g(u)$, and derive an approximate (graphical) representation for $g(u)$, assuming $\delta \ll 1$. Hence show 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 $n > p$?

4.2 Show that the model of 3.3 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?

4.3 The dimensionless two-pool model of CICR,

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

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} .

Supposing that $f(u, v) = 0$ defines a function $v = g(u)$ with $g(0) = 0$, $g' > 0$ for $u < \mu_1$, $u > \mu_2$, and $g' < 0$ for $\mu_1 < u < \mu_2$, where $\mu_2 > \mu_1 > 0$, use phase plane analysis to show plausibly that periodic travelling wave trains will exist for $\mu_- < \mu < \mu_+$, where $g'(\mu_{\pm}) = -1/\gamma$ (assuming $\min g' < -1/\gamma$).

Will such waves exist in two or three dimensions?

Mathematical physiology

PROBLEM SHEET 5.

5.1 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.

5.2 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

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

and describe the meaning of the variables. What assumption is made about the capillary volume in writing these equations?

5.3 What is meant by *compliance*, *elastance* and *resistance* of blood vessels?

In the model of question 5.2, let p_a , p_v and p_{LV} denote the pressures in arteries, veins and left ventricle, respectively. Denoting resistances and compliances of compartment k by R_k and C_k , respectively, write down expressions for Q_{jk} , where Q_{jk} is the blood flow from compartment j to compartment k , and hence derive a model consisting of three ordinary differential equations for the three compartment pressures.

Illustrate on a diagram of p_k versus V_{LV} how you expect the pressures to oscillate during a heart beat.

5.4 What is meant by *systole* and *diastole*?

Write down a model of the circulation which describes the volumes of separate compartments representing left atrium, left ventricle, arteries, capillaries and veins. Assume that three valves (e. g., pulmonary, mitral and aortic) separate the veins, left atrium, left ventricle and arteries. By assuming compliances and resistances C_k and R_k for compartment k , write the model in the form of differential equations for the pressures in each compartment.

5.5 What are the four valves of the heart, and what is their purpose?

The blood flow rates to and from the heart (i. e., to the right atrium and from the left ventricle) are taken to be equal, and denoted by $Q(t)$. Write down a four compartment model of the pulmonary circulation for the volumes of left and right atria and ventricles, assuming that the pulmonary flow provides resistance but has no volume. Using appropriate compliances and resistances, derive equations for the pressure of each chamber of the heart.

Mathematical physiology

PROBLEM SHEET 6.

6.1 A one chamber model of the circulation having a left ventricle, arteries, veins and peripheral resistance is written in the form

$$R_c C_a \dot{p}_a = -(p_a - p_v) + \frac{R_c}{R_a} [p_{LV} - p_a]_+,$$

$$R_c C_v \dot{p}_v = (p_a - p_v) + \frac{R_c}{R_v} [p_v - p_{LV}]_+,$$

$$\left(\frac{\dot{p}_{LV}}{E_{LV}} \right) = \frac{[p_v - p_{LV}]_+}{R_v} - \frac{[p_{LV} - p_a]_+}{R_a}.$$

Describe the meaning of the terms, and explain briefly how the model is derived.

The effect of cardiac contraction on the ventricle elastance is modelled by assuming that E_{LV} jumps rapidly between a low diastolic value E_d and a high systolic value E_s . The systolic value is held for a time interval $\Delta t_F \approx 0.3$ s, and the diastolic value is held for a time interval $\Delta t_R \approx 0.5$ s.

Suppose that the end diastolic arterial pressure is p_a^+ and that the end diastolic ventricular volume is V_+ (so that $p_{LV} \ll p_a^+$). Suppose also that $R_c C_a = 1.8$ s, $R_c C_v = 60$ s, $R_c C_s = 0.4$ s, $R_c C_d = 19.2$ s, $R_c/R_v = 75$, and $R_c/R_a = 20$.

Show that during systole, where E_{LV} jumps rapidly from E_d to E_s and is maintained there for an interval of duration Δt_F , there is a period of isovolumetric contraction until p_{LV} reaches p_a^+ and the aortic valve opens, followed by a period of ejection, during which $p_{LV} \approx p_a$, and p_a rapidly jumps to the peak systolic value

$$p_a \approx \frac{C_a p_a^+ + V^+ - V_0}{C_a + C_s},$$

(V_0 is the resting ventricular volume at zero pressure), after which

$$R_c C_a \dot{p}_a + R_c \left(\frac{\dot{p}_a}{E_{LV}} \right) \approx -p_a.$$

(Assume that $p_v \ll p_a$.)

Deduce that the end systolic arterial pressure is

$$p_a = p_a^- \approx \frac{C_a p_a^+ + V^+ - V_0}{C_a + C_s} \exp \left[\frac{-\Delta t_F}{R_c(C_a + C_s)} \right],$$

and thus that the stroke volume is

$$\Delta V \approx V^+ - V_0 - \left(\frac{C_s}{C_a + C_s} \right) [C_a p_a^+ + V^+ - V_0] \exp \left[\frac{-\Delta t_F}{R_c(C_a + C_s)} \right].$$

6.2 In the model of question 6.1, suppose that the end systolic ventricular volume is V^- . Show that systole is followed by a rapid isovolumetric relaxation period, and then a filling period of duration Δt_R , in which firstly $p_{LV} \rightarrow E_d(V^- - V_0)$ rapidly, and then p_a decays

exponentially. (Assume $p_v, p_{LV} \ll p_a$, explaining why.) Deduce that if p_a^- is the end systolic arterial pressure, then the end diastolic arterial pressure is

$$p_a^{++} \approx p_a^- \exp \left[\frac{-\Delta t_R}{R_c C_a} \right].$$

If the venous pressure is p_v and is taken to be constant, show that $V_+ - V_0 \approx C_d p_v$, and deduce (using also the results of question 6.1) that

$$p_a^{++} \approx A p_a^+ + B,$$

and give definitions for A and B . Use the numerical values $V_0 = 17$ ml, $R_a = 0.06$ mm Hg s ml⁻¹, $R_v = 0.016$ mm Hg s ml⁻¹, $R_c = 1.2$ mm Hg s ml⁻¹, $C_a = 1.5$ ml mm Hg⁻¹, $C_v = 50$ ml mm Hg⁻¹, $C_d = 16$ ml mm Hg⁻¹, $C_s = 0.34$ ml mm Hg⁻¹, $p_v \approx 7$ mm Hg, to find values of A and B ; hence determine the behaviour of successive values of p_a^+ .

Mathematical physiology

PROBLEM SHEET 7.

7.1 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

$$\begin{aligned} K\dot{p} &= M - p\dot{V}, \\ \dot{V} &= \dot{V}(p_\tau); \end{aligned}$$

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

Suppose that

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

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

$$\begin{aligned} \dot{p} &= \alpha[1 - (1 + \mu p)v], \\ v &= [p_1]_+, \end{aligned}$$

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

7.2 The original Mackey-Glass model was written in the form

$$\begin{aligned} \dot{p} &= \lambda - \kappa p\dot{V}, \\ \dot{V} &= \frac{V_m p_\tau^n}{\theta^n + p_\tau^n}. \end{aligned}$$

Mackey and Glass assumed normal steady state values of $p = p^* = 40 \text{ mmHg}$, $\dot{V} = V^* = 7 \text{ l min}^{-1}$, $d\dot{V}/dp|_{p^*} = G^* = 4 \text{ l min}^{-1} \text{ mmHg}^{-1}$ and also that $\lambda = 6 \text{ mmHg min}^{-1}$ and $V_m = 80 \text{ l min}^{-1}$. Use these to infer values of κ , n and θ . Are the values of λ and κ consistent with the values of M and K in question 7.1?

7.3 The Mackey-Glass model of question 7.1 is written in the form

$$\dot{p} = \alpha[1 - (1 + \mu p)v(p_1)],$$

where v is taken to be a monotone increasing positive function of its argument, and α and μ are positive constants.

Show that there is a unique positive steady state p^* .

By linearising about this steady state, show that the steady state is unstable if $\text{Re } \sigma > 0$, where

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

and $\beta = \alpha\mu v(p^*)$, $\gamma = \alpha(1 + \mu p^*)v'(p^*)$.

Show that this equation has (two) real roots if and only if $\gamma < 1$ and $\beta < \ln(1/\gamma) - 1$, and that these are both negative.

7.4 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 $\sigma \rightarrow \infty$, then also $\text{Re } \sigma \rightarrow -\infty$.

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

Show that $\text{Re } \sigma < 0$ 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 .

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

$$\begin{aligned} K_L \dot{P}_{a\text{CO}_2} &= -\dot{V} P_{a\text{CO}_2} + 863 K_{\text{CO}_2} Q [P_{v\text{CO}_2} - P_{a\text{CO}_2}], \\ K_{\text{CO}_2} K_B \dot{P}_{B\text{CO}_2} &= MR_{B\text{CO}_2} + K_{\text{CO}_2} Q_B [P_{a\text{CO}_2}(t - \tau_{aB}) - P_{B\text{CO}_2}] \\ K_{\text{CO}_2} K_T \dot{P}_{T\text{CO}_2} &= MR_{T\text{CO}_2} + (Q - Q_B) K_{\text{CO}_2} [P_{a\text{CO}_2}(t - \tau_{aT}) - P_{T\text{CO}_2}], \end{aligned}$$

with the venous pressure being determined by

$$Q P_{v\text{CO}_2} = Q_B P_{B\text{CO}_2}(t - \tau_{vB}) + (Q - Q_B) P_{T\text{CO}_2}(t - \tau_{vT}).$$

Explain the meaning of the equations and their constituent terms.

Use values $K_L = 3 \text{ l}$, $V^* = 863 K_{\text{CO}_2} Q = 26 \text{ l min}^{-1}$, $K_B = 1 \text{ l}$, $Q = 6 \text{ l min}^{-1}$, $Q_B = 0.75 \text{ l min}^{-1}$, $K_T = 39 \text{ l}$, 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 $P_{a\text{CO}_2}$ in terms of the ventilation \dot{V} .

Mathematical physiology

VACATION SHEET.

8.1 Describe the way in which blood cells are produced, describe the different types of blood cell and explain their function. In what ways are cell numbers normally controlled?

For red blood cells, explain the rôle of hypoxia and erythropoietin in the control of differentiation.

A mathematical model of red blood cell numbers is given by the equation

$$\frac{dE}{dt} = F(E_\tau) - \gamma E,$$

where $F(E)$ is assumed to be given by the Hill function

$$F = \frac{F_0 \theta^n}{E^n + \theta^n}.$$

In what way does this represent the effect of erythropoietin control?

Non-dimensionalise the model to obtain the form

$$\dot{\xi} = \frac{\rho}{1 + \xi^n} - \delta \xi,$$

and give the definitions of ρ and δ . Use the values $\gamma = 2 \times 10^{-2} \text{ day}^{-1}$, $F_0 = 10^6 \text{ cells } \mu\text{l}^{-1}$, $n = 8$, $\theta = 3.5 \times 10^6 \text{ cells } \mu\text{l}^{-1}$, $\tau = 6 \text{ days}$, to evaluate ρ and δ .

Show that there is a unique steady state $\xi = \xi^*$, and find approximate formulae for ξ^* when $\delta \ll 1$ and $\delta \gg 1$. Draw a rough graph of ξ^* as a function of δ .

Hence show that $|f'(\xi^*)|$ varies non-monotonically with δ , where $f(\xi) = 1/(1 + \xi^n)$, and that $|f'(\xi^*)|$ is maximum when

$$\delta = \rho \left(\frac{n+1}{n-1} \right)^{1/n} \frac{n+1}{2n}.$$

8.2 What is meant by the G_0 model of stem cell proliferation? Describe the way in which a simple model for the populations P of proliferative cells and N of resting cells can be written in the form

$$\begin{aligned} \dot{P} &= -\gamma P + \beta(N)N - e^{-\gamma\tau} \beta(N_\tau)N_\tau, \\ \dot{N} &= -\beta(N)N - \delta N + 2e^{-\gamma\tau} \beta(N_\tau)N_\tau. \end{aligned}$$

Suppose that $\beta(N)$ is given by the Hill function

$$\beta(N) = \frac{\beta_0 \theta^n}{\theta^n + N^n}.$$

By suitably non-dimensionalising the model, derive the dimensionless form

$$\dot{N} = g(N_1) - g(N) + \varepsilon[\mu g(N_1) - N],$$

where

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

and give the definitions of the parameters μ , b and ε .

Use the values $\theta = 2 \times 10^3$ cells μl^{-1} , $\beta_0 = 1.8 \text{ d}^{-1}$, $\gamma = 0.2 \text{ d}^{-1}$, $\delta = 0.05 \text{ d}^{-1}$, $\tau = 2.2 \text{ d}$, to find typical values of b , μ and ε .

Show that there is a unique positive steady state if $\mu\beta > 1$, and show that it is unstable if $\text{Re } \sigma > 0$, where

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

and

$$\alpha = g' + \varepsilon, \quad \gamma = -(1 + \varepsilon\mu)g'.$$

8.3 Suppose that σ satisfies

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

where α and γ are (not necessarily positive) constants.

Show that if $\alpha > 0$, $\text{Re } \sigma < 0$ if $|\gamma| < \alpha$, and that $\sigma = 0$ if $\gamma = -\alpha$.

Show that $\sigma = \pm i\Omega \neq 0$ if $\gamma = \gamma_1(\alpha)$, where

$$\tan \Omega = -\frac{\Omega}{\alpha}, \quad \gamma_1 = \frac{\Omega}{\sin \Omega},$$

for $\Omega \in [0, \pi]$. Show that $\gamma_1(\alpha)$ is a positive monotone increasing function of α which terminates at $\alpha = -1$, where $\gamma_1 = 1$.

By consideration of the graph of $\sigma - \gamma(1 - e^{-\sigma})$, show that when $\gamma + \alpha = 0$, $\sigma = 0$ is the only real root if $\gamma < 0$, there is a second which is negative if $0 < \gamma < 1$, and a second which is positive when $\gamma > 1$.

Show that when $\gamma > 0$, the two real roots collide when $\gamma = \gamma_c(\alpha) = \exp[-(\alpha + 1)]$.

Use the above facts to show that, if σ_+ and σ_- denote the two roots $\pm i\Omega$ when $\gamma = \gamma_1$, then

σ_{\pm} are complex for $\alpha \in (\gamma_c^{-1}(\gamma), \gamma_1^{-1}(\gamma))$, and $\text{Re } \sigma_{\pm} > 0$;

σ_{\pm} are complex for $\gamma \in (\gamma_c(\alpha), \gamma_1(\alpha))$, and $\text{Re } \sigma_{\pm} < 0$;

σ_{\pm} are real for $\gamma < \gamma_c(\alpha)$, and:

$\sigma_{\pm} > 0$ for $\gamma \in (-\alpha, \gamma_c(\alpha))$ when $\alpha < -1$;

$\sigma_{\pm} < 0$ for $\gamma \in (-\alpha, \gamma_c(\alpha))$ when $\alpha > -1$;

$\sigma_+ > 0 > \sigma_-$ for $0 < \gamma < -\alpha$, $\alpha < 0$;

there is only one real root σ_+ for $\gamma < 0$, and:

$\sigma_+ > 0$ for $\gamma < -\alpha$, $\sigma_+ < 0$ for $\gamma > -\alpha$.

Hence sketch the stability regions (i. e., where $\text{Re } \sigma < 0$) in (γ, α) parameter space.

Use the definitions in question 8.2 to show that $\gamma + \alpha \geq 0$, and deduce that the positive fixed point is oscillatorily unstable for large enough μ if $0 > g' > -1 - \varepsilon$, and that it is unstable for $g' < -1 - \varepsilon$.

8.4 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

$$\begin{aligned}\frac{\partial p}{\partial t} + \frac{\partial p}{\partial m} &= -\delta p, \\ \frac{\partial e}{\partial t} + \frac{\partial e}{\partial a} &= -\gamma e,\end{aligned}$$

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 if $\sigma \sim O(1)$, then the steady state is stable if $|f'| < 1$.