5 Delayed Dynamical Systems in Physiology

For a very nice introduction to respiration, see Extended notes for reference which are available online at `http://www0.maths.ox.ac.uk/courses/course/26323`.

5.1 Example I: Respiration

Respiration is the transport of the oxygen from the air to cell mitochondria and the transport of carbon dioxide from cells in the opposite direction. Oxygen and carbon dioxide are transferred between air and blood in the huge surface area of the lung alveolar sacs (approximately the area of a tennis court on counting both lungs). Within the body, blood transfers oxygen and carbon dioxide between tissues and the lungs.

The control of respiration, and in particular breathing, is through the interaction of O_2 and CO_2 with two sets of chemoreceptors.

Central receptors are located in the medulla of the brain and induce an increased rate of breathing in response to an increased level of H^+ (hydrogen ions). This is a surrogate for the level of CO_2 as CO_2 acidifies water via the reversible reaction

$$CO_2 + H_2O \quad \rightleftharpoons \quad H^+ \; + \; HCO_3^- .$$

Peripheral receptors are located outside the brain in various sites and respond in a similar manner to central receptors, though on a faster timescale and with an amplitude of response that is much smaller.

5.1.1 Periodic breathing

- 12-14 breaths per minute (adult)
- Each breath has a volume of 500 ml.
- Alveolar ventilation: there is about 150ml of dead space and hence 350ml is involved in gas exchange per breath.
- $\dot{V} \approx 5$ litres/minute on taking a (crude) average, accounting for dead space.

Cheyne Stokes breathing: this occurs as the heart is failing and during a stroke. It is characterised by an oscillation in the depth of breathing over 30 seconds, and then breathing arrest, for about 30 seconds, before starting over again.

For a failing heart, low blood flow leads to an increased delay in response to arterial carbon dioxide concentrations. For a stroke, brain damage is thought to increase the sensitivity of the

central receptors to carbon dioxide. Thus it is interesting to consider respiration dynamics, to see if periodic solutions, with a period of the order of one minute, can emerge.

The Mackay-Glass Model (1977)
Let p be the partial pressure of carbon dioxide; this is generally proportional to the concentration of carbon dioxide at fixed temperature, as in the body. Look up Henry's law for details.

Consider tissue as a single compartment. The Mackay Glass model is:

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

where

- K is a constant of proportionality (containing the compartment volume and conversion factors between partial pressures and concentrations)
- M is the metabolic production rate
- $\dot{V}$ is the ventilation rate, which is a delayed function of the partial pressure of carbon dioxide, to allow for response delays.

In a more realistic deviation from the original Mackay and Glass model, we consider

$$\dot{V} = G[p_\tau - p_0]_+$$

where p_0 is a constant, known as the apnea threshold, G is the gain of the central controller and

$$p_\tau \stackrel{def}{=} p(t-\tau)$$

and

$$[Q]_+ \stackrel{def}{=} \left\{ \begin{array}{ll} Q & Q > 0 \\ 0 & Q \leq 0 \end{array} \right\}.$$

Note that here **Gain** refers to the sensitivity in the dependence of ventilation on CO_2 levels, and is modelled via the parameter G. Typical values are

$$\dot{V} \sim 5 \text{ litres per minute}, \quad \tau \sim 12 \text{ seconds}, \quad p_0 = 35 \text{ [mmHg]}, \quad p \sim 40 \text{ [mmHg]},$$

$$G \sim 2 \text{ litres minute}^{-1} \text{ [mmHg]}^{-1}, \quad M = 170 \text{ [mmHg] litres minute}^{-1}, \quad K \sim 39 \text{ litres}.$$

Non-dimensionalising with

$$t = \tau\tilde{t}, \quad p = p_0 + \Delta p\tilde{p}, \quad \dot{V} = G\Delta p\tilde{v}$$

and choosing the pressure scale to be

$$\Delta p = \frac{M}{p_0 G},$$

we have, on dropping tildes,

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

with

$$v = [p_1]_+, \quad p_1 = p(t-1), \quad \alpha = \frac{\tau G p_0}{K} \approx 0.36, \quad \mu = \frac{M}{p_0^2 G} \approx 0.07.$$

We will exploit the fact that $\mu \ll 1$ in the analysis that follows. **A linear stability analysis of the steady state**

The delays are not important at the steady state, which is therefore given by

$$p^* = \frac{1}{1 + \mu p^*}.$$

Hence, at steady state p^* satisfies the quadratic equation

$$\mu p^{*2} + p^* + 1 = 0,$$

and for $\mu \ll 1$, we see that the positive root corresponds to

$$p^* = 1 - \mu + \cdots.$$

Note that we select the positive root so that $[p^*]_+ = p^*$. Linearising via

$$p = p^* + \tilde{p}$$

we have the delayed pressure is given by

$$p_1 = p^* + \tilde{p}_1,$$

and hence

$$v(p_1) = v(p^*) + \tilde{p}_1 v'(p^*) + \ldots.$$

Thus

$$\begin{aligned} \frac{d\tilde{p}}{dt} &= \alpha\,[1 - (1 + \mu p^* + \mu\tilde{p})(p^* + \tilde{p}_1] \\ &= \alpha\left[\underbrace{1 - (1 + \mu p^*)p^*}_{=0} - \mu p^* \tilde{p} - (1 + \mu p^*)\tilde{p}_1\right] + \text{higher order terms} \end{aligned} \tag{1}$$

noting that $p_1 = p^* + \tilde{p}_1 > 0$ so that $[p_1]_+ = p_1$. Hence, retaining leading-order (in μ) terms

$$\frac{d\tilde{p}}{dt} = -\beta\tilde{p} - \gamma\tilde{p}_1 \tag{2}$$

where

$$\beta = \frac{\tau M}{K p_0} \approx 0.07 \times 0.36 \ll 1, \quad \gamma \approx \alpha(1+\mu) = \tau\left[\frac{G p_0}{K} + \frac{M}{K p_0}\right]. \tag{3}$$

We seek a solution to equation 2 of the form $\tilde{p} \propto \exp\lambda t$ and find that

$$\lambda \exp(\lambda t) = -\beta \exp(\lambda t) - \gamma \exp(\lambda(t-1)) \;\text{ as }\; \tilde{p}_1 = \tilde{p}(t-1), \tag{4}$$

so that

$$\lambda = -\beta - \gamma \exp(-\lambda). \tag{5}$$

Now, if λ is real, we must have $\gamma \exp(-\lambda) = -(\lambda+\beta)$ and hence any root we obtain is negative (see figure 1). Alternatively, if λ is complex, given by $\lambda = \sigma + i\omega$, $\omega \neq 0$ we find the roots correspond to

$$\sigma = -\beta - \gamma \exp(-\gamma)\cos\omega, \quad \omega = -\gamma \exp(-\sigma)\sin\omega. \tag{6}$$

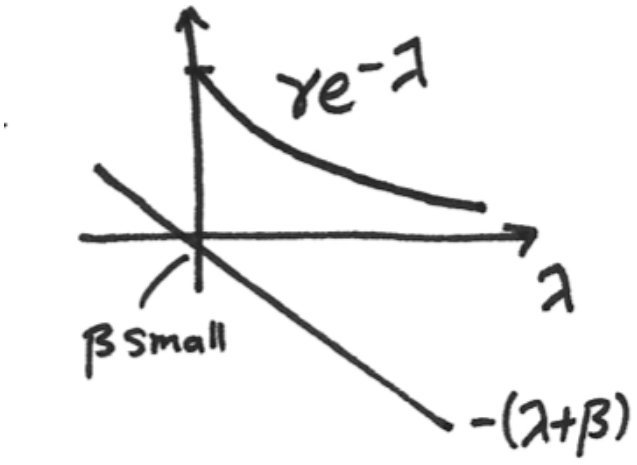


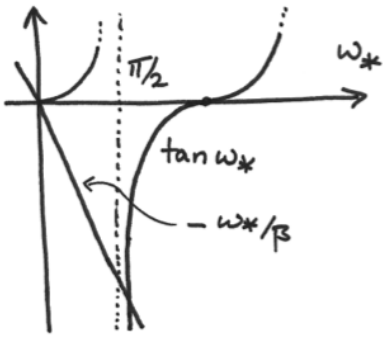
Figure 1: Obtaining the root of 5.

At bifurcation to instability $\sigma = 0$, $\omega = \omega_* \neq 0$.

$\therefore\ 0 = \beta + \gamma\cos\omega_*$ and $\omega_* = -\gamma\sin\omega_*$.

$\therefore\ 1 = \cos^2\omega_* + \sin^2\omega_* = \beta^2/\gamma^2 + \omega_*^2/\gamma^2 \ \therefore\ \boxed{\omega_*^2 = \gamma^2 - \beta^2}$ ①

$$\frac{\sin\omega_*}{\cos\omega_*} = -\frac{\omega_*}{\beta} = \tan\omega_* \quad ②$$



Note $\beta \ll 1$ $\therefore$ From ②

$\omega_* \simeq \pm\left(\pi/2 + n\pi\right)$, n integer.

From ① $\pi^2/4\,(1+2n)^2 = \gamma^2 - \beta^2 = \alpha^2\left(1 + \frac{2\mu}{(1+\mu)^2}\right) \approx \alpha^2$ at bifurcation.

For typical parameter values, $\gamma^2 - \beta^2 < \pi^2/4$ and we have no instability.

Stroke Gain $\uparrow$ $\therefore$ $G\uparrow$ $\therefore$ $\mu\downarrow$ $\therefore$ $\mu < 0.07$ $\alpha\uparrow$ too.

Hence for a sufficient increase in G, a bifurcation occurs.

The period of the resulting oscillation is $2\pi/\omega_* \approx \frac{2\pi}{\pi/2} = 4$

In dimensional terms, the period is $4\tau \simeq 48$ seconds (about right).

Heart Failure $\tau\uparrow$ $\therefore$ μ fixed, $\mu \sim 0.07 \ll 1$. $\alpha\uparrow$.

Bifurcation occurs when τ increased by a factor of $\simeq \sqrt{\left(\frac{\pi^2}{4}\right)\frac{1}{(0.36)^2}}$;

This is approximately by a factor of 4. The dimensional period is $(2\pi/\omega^*)\tau \approx 4\tau \approx 3$minutes. This is too longer. We can therefore consider (if we wish!) a model with fewer simplifications, such as Grodin's model.

5.2 Example II. The Haematopoietic System: Blood Cell Production

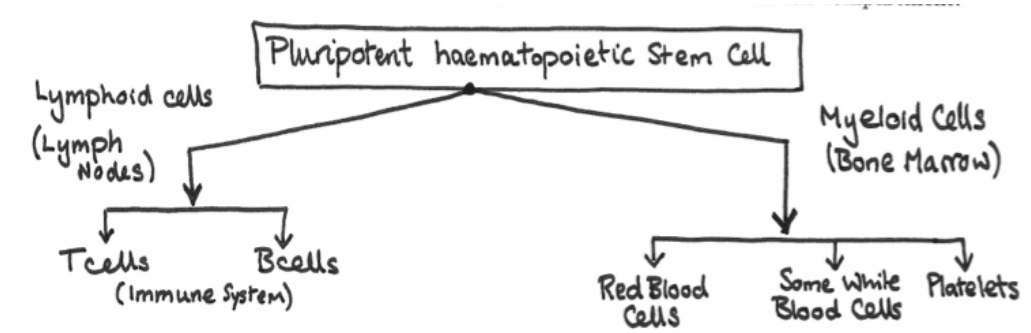
One quarter of the $\approx 8 \times 10^{13}$ cells in an adult human body are *red blood cells*, also known as *erythrocytes*, and there are $\approx 3 \times 10^{12}$ of these cells in each litre of blood. They are rich in oxygen binding haemoglobin and transport oxygen from the lungs to tissue and are continually recycled,

with a lifetime of ≈ 100 days.

Each litre of blood contains $\approx 7 \times 10^9$ *white blood cells*, also known as *leukocytes*, which form part of the immune system and have many types, e.g. T lymphocytes, neutrophils, ... These have a lifetime of about 6 hours in blood or 5 days in tissue, after release from storage in the bone marrow.

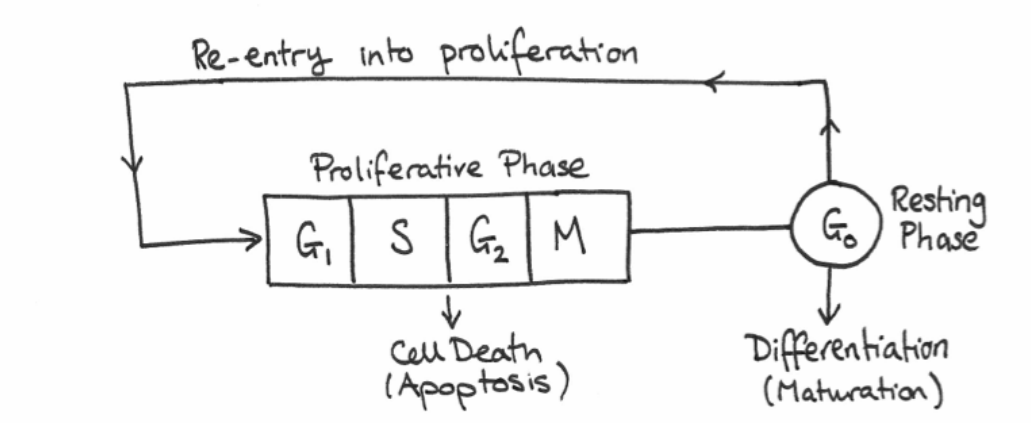
Blood also contains $\approx 7 \times 10^9$ *platelets* per litre; these are small cell fragments produced by megakaryocytes and utilised for clotting.

All blood cell types are derived from primitive cells known as *pluripotent haematopoietic stem cells* via a process of differentiation and maturation. Differentiation refers to cells changing type, maturation in particular describes the process by which cells move from the stem cell compartment to their terminally differentiated compartment, for instance the red blood cell compartment.



5.2.1 The Cell Cycle

To proliferate a cell needs to progress through the cell cycle, where it doubles its size and copies its genetic material in preparation for division. A schematic of the cell cycle is as follows:



The cell cycle duration is approximately 2 days, and this process is highly regulated for blood cells. For instance, the excessive proliferation of white blood cells induces *leukaemia*.

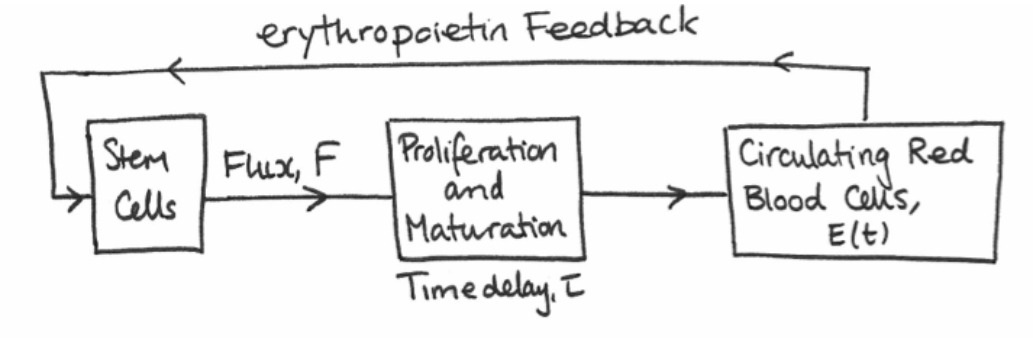
The cell cycle is generally controlled by numerous factors such as interleukin-3 (IL-3) and, in particular, the glycoprotein erythropoietin is important in regulating red blood cell levels inducing an increase in red blood cell numbers if blood oxygen levels drop.

Similarly, on infection, *granulocyte colony stimulating factor*, GCSF, stimulates the production of white blood cells.

5.2.2 Blood Diseases

- *Periodic haematopoietic diseases* These are characterised by oscillations in blood cell types.
- *Cyclical Neutropenia* Neutropenia means decreased levels of neutrophil levels. Cyclical neutropenia describes neutrophil levels that rise and fall to very low levels, with other blood cell types oscillating too.
- *Chronic Myelogeneous Leukaemia (CML)* Leukaemia is characterised by excessive white blood cell production, and also by the release of immature white blood cells. CML in particular is additionally characterised by oscillations in white blood cell numbers (with concomitant oscillations in red blood cells and platelets).
- *Anaemia* A deficiency in haemoglobin levels and/or number of red blood cells.
- *Polycythemia* Elevated levels of red blood cells.

5.2.3 A model of blood cell production



A model based on the above schematic, similar in approach to the Mackey-Glass model of respiration, is given by

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

Here $E(t)$ is the number of red blood cells per unit blood volume, $E_\tau = E(t-\tau)$, $\gamma \sim 2.3 \times 10^{-2}$ day^{-1} is the removal rate of red blood cells and the function F is the flux of new red blood cells into the circulation. In particular, the number of circulating red blood cells affects the blood oxygen level, which in turn controls the release of erythropoietin, which controls the level of pluripotent haematopoietic stem cell commitment to the red blood cell line.

Thus the flux, F, is taken to be a decreasing function, which is represented by

$$F(E) = \frac{F_0 \theta^n}{\theta^n + E^n},$$

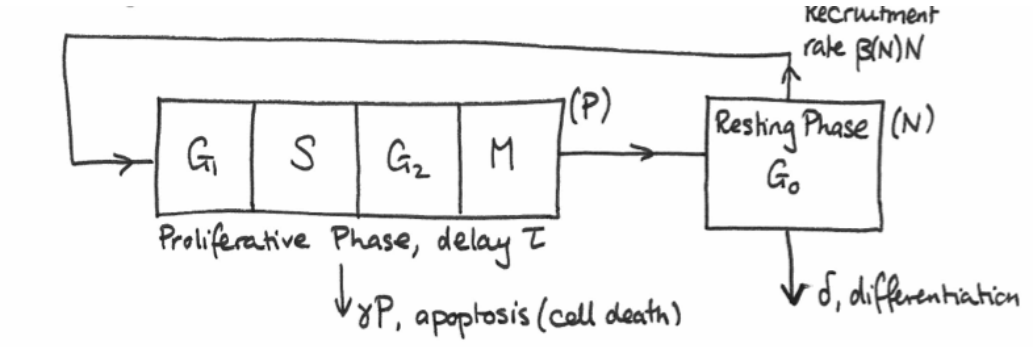
with typical parameter values $F_0 = 10^6$ cells μlitre^{-1} day^{-1}, $n = 8$ and $\theta = 3.5 \times 10^6$ cells μlitre^{-1}.

However, this regulation is delayed due to the time taken for differentiation and maturation in the production of red blood cells, which is represented by $\tau \sim 6$ days in the above equation.

A non-dimensionalisation of the above equation, a demonstration that there is a unique steady sate that is unstable if γ is increased sufficiently is explored in the problem sheet 4, Q4.4. The resulting Hopf bifurcation can be observed in auto-immune haemolytic anaemia.

5.2.4 A simple model of stem cell control

Let P denote the number of cells in the proliferative phase, and N denote the number of cells in the resting phase, G_0, and thus non-proliferating. A simple model of stem cell control is summarised in the following schematic:



Here τ is the duration of the proliferative phase, γ is the rate of apoptosis (i.e cell death) during the proliferative phase and δ is the rate of loss of cells from the non-proliferating phase into other compartments by differentiation. In addition, the function $\beta(N)$ regulates the proportion of the non-proliferating cells that enter the proliferative phase.

Note that the number of cells leaving the proliferative phase per unit time is therefore given by

$$\underbrace{\beta(N_\tau)N_\tau}_{\substack{\text{Number of cells that enter the} \\ \text{proliferative phase at time } t-\tau}} \times \underbrace{\exp\left[-\gamma\tau\right]}_{\substack{\text{Fraction of cells that survive, given} \\ \text{an apoptotic (death) rate of } \gamma}} .$$

Hence the number of cells in the proliferating and non-proliferating compartments are governed by the following equations

$$\frac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau, \qquad \frac{dN}{dt} = -\beta(N)N - \delta N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau.$$

Note that the factor of $\times 2$ in the $2e^{-\gamma\tau}\beta(N_\tau)N_\tau$ term for the flux into the non-proliferating compartment arises as cells divide to produce two daughter cells on leaving the proliferating compartment.

Note that the equation for N is uncoupled.

The function β is taken to be monotonic decreasing, for instance

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

With the non-dimensionalisation $N^* = N/\theta$, $t^* = t/\tau$ one finds the equation for the non-dimensionalised number of cells in the non-proliferating compartment $N^* = N/\theta$ becomes

$$\frac{dN^*}{dt^*} = g(N_1^*) - g(N^*) + \epsilon\left[\mu g(N_1^*) - N^*\right]$$

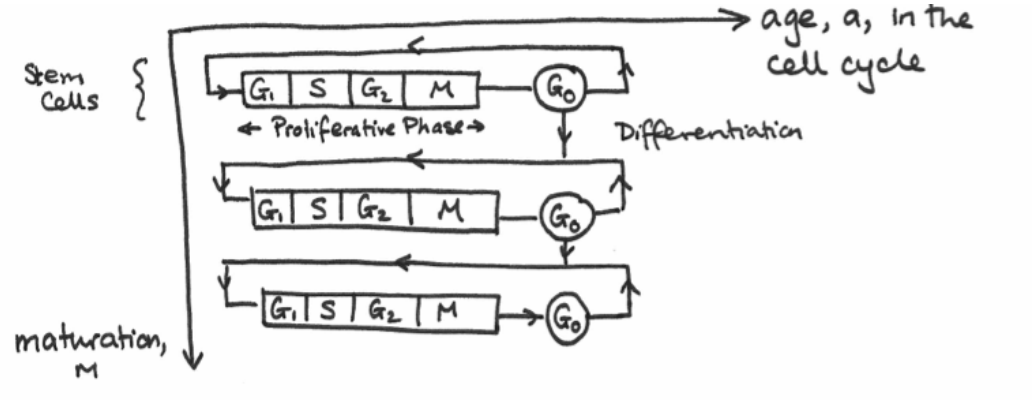
where

$$N_1^* = N^*(t^* - 1), \quad \epsilon = \delta\tau \sim 0.11, \quad \mu = \frac{2e^{-\gamma\tau} - 1}{\delta\tau} \sim 2.6, \quad g(N^*) = \beta_0\tau\frac{N^*}{1 + [N^*]^n},$$

with $\beta_0\tau \sim 3.9$. The existence of a steady state, its stability and the prospect of a Hopf bifurcation are explored in example Sheet 4, question 4.5.

5.2.5 Maturation

In modelling maturation we consider the cell cycle for multiple compartments, with a maturation index, m, which labels the compartments. In simpler models, as presented below, m is treated as a continuous index. A schematic is Here, we explicitly consider the age-distribution of cells, with



age explicitly denoting the duration since the start of the proliferative phase (and only resetting once proliferation starts once more). In particular, for time t, let

$$p(t,a,m)\delta m\delta a, \quad a\in[0,\tau] \qquad n(t,a,m)\delta m\delta a \quad a\in[\tau,\infty)$$

respectively denote the number of proliferating cells and non-proliferating cells with a maturation index in the interval $[m, m+\delta m]$ and an age in the interval $[a, a+\delta a]$.

Thus at maturation $m=0$, we have $p=p_0(t,a),\ n=n_0(t,a)$, which are assigned as the numbers of the pluripotent haematopoietic stem cells undergoing proliferation and resting, respectively. [1] A balance at any given $t,\ a,\ m$ for the proliferating cells gives

$$\frac{\partial p}{\partial t}+\frac{\partial p}{\partial a}+\frac{\partial}{\partial m}[Vp]=-\gamma p$$

where V denotes the maturation rate and γ denotes the apoptosis rate. Similarly, for the non-proliferating cells,

$$\frac{\partial n}{\partial t}+\frac{\partial n}{\partial a}+\frac{\partial}{\partial m}[Vn]=-R(t,m)n$$

where $R(t,m)$ is the rate of recruitment into proliferation.

At $a=0$ we have

$$p(t,0,m)=R(t,m)N(t,m), \qquad \text{where} \quad N(t,m)=\int_\tau^\infty n(t,a,m), \tag{7}$$

[1] This equation is derived by letting $p(t,a,m)$ be the population density at time t of proliferating cells in the age range m to $m+dm$ and age range a to $a+da$, We let γ denote the death rate. Then in a small increment of time the number of the population that dies is $\gamma p(t,a,m)dt$. The equation then follows from $dp(t,a,m)=-\gamma p(t,a,m)dt$. Note that $da/dt=1$ since a is chronological age, and $dm/dt=V$.

due to recruitment, while at $a = \tau$ we have

$$n(t, \tau, m) = 2p(t, \tau, m)$$

by cell division. Further we take it that $n \to 0$ as $a \to \infty$. Note that integrating the equation for $n(t, a, m)$ over age gives

$$\frac{\partial N}{\partial t} - 2p(t, \tau, m) + \frac{\partial}{\partial m}[NV] = -R(t, m)N.$$

Investigation with V constant Assuming the maturation rate is constant we have

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + V\frac{\partial p}{\partial m} = -\gamma p.$$

with equation (7) giving a set of Cauchy data at $a = 0$. For the above characteristic problem let A parameterise a characteristic and let (s, μ) parameterise the two-dimensional set of Cauchy data. We have the characteristic equations

$$\frac{dt}{dA} = 1, \quad \frac{da}{dA} = 1, \quad \frac{dm}{dA} = V, \quad \frac{dp}{dA} = -\gamma p,$$

with

$$t(A = 0, s, \mu) = s, \quad a(A = 0, s, \mu) = 0, \quad m(A = 0, s, \mu) = \mu, \quad p(A = 0, s, \mu) = R(s, \mu)N(s, \mu).$$

Solving we find

$$t = A + s, \quad a = A, \quad m = \mu + VA, \quad p = R(s, \mu)N(s, \mu)e^{-\gamma A}.$$

Thus we can immediately eliminate to find $A = a$, $s = t - a$ and $\mu = m - Va$. Hence

$$p(t, \tau, m) \quad = \quad R(t - \tau, m - V\tau)N(t - \tau, m - V\tau)e^{-\gamma\tau}$$

and thus with $\zeta \stackrel{def}{=} m/V$, $r(t, \zeta) \stackrel{def}{=} R(t, m)$, $y(t, \zeta) \stackrel{def}{=} N(t, m)$ we have

$$\frac{\partial y}{\partial t} + \frac{\partial y}{\partial \zeta} = -r(t, \zeta)y + 2r(t - \tau, \zeta - \tau)y(t - \tau, \zeta - \tau)e^{-\gamma\tau}.$$

For a constant recruitment rate, r is constant and we have

$$\frac{\partial y}{\partial t} + \frac{\partial y}{\partial \zeta} = -ry + 2re^{-\gamma\tau}y(t - \tau, \zeta - \tau).$$

With T parameterising characteristics, we have

$$\frac{dt}{dT} = \frac{d\zeta}{dT} = 1.$$

and hence $(t-\tau, \zeta-\tau)$ is on the same characteristic as (t, ζ) and the equation for y on a characteristic becomes

$$\frac{dy}{dT} = -ry + 2re^{-\gamma\tau}y(T-\tau).$$

This is linear, so consider $y \sim e^{\lambda T}$. Hence, one can determine whether the total number of non-proliferating cells exhibits oscillatory behaviour by considering the roots of

$$\lambda = -r + 2re^{-\gamma\tau}e^{-\lambda\tau}.$$