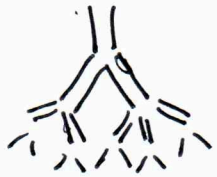
MP Lecture 13 : Respiratory Control

Respiration provides oxygen O_2 as a nutrient to cells and disposes of waste CO_2 by gas exchange at the alveoli in the lung with the pulmonary capillary bed.



∴ 23 branches

alveoli

Ventilation

The (minute) ventilation $\dot{V}$ is the average rate of volume exchange per unit time [if V is lung volume $\dot{V} = \left[\frac{dV}{dt}\right]_+$]

Normal $\dot{V} \sim 5\ \ell\ min^{-1}$, 12 breaths per minute.

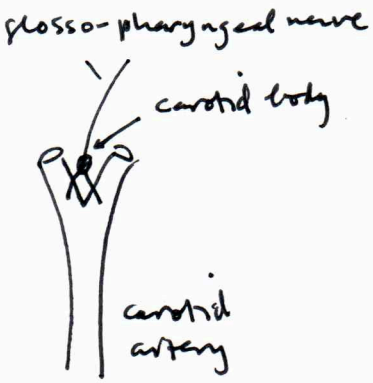
Control

Due to central (in the brainstem) and peripheral (in the carotid artery) chemoreceptors which respond to CO_2 (mostly) & O_2

Central chemoreceptors in the medulla respond to H^+ ($pH := -\log_{10}[H^+]$)
(neutral 7, acid < 7)

but effectively to CO_2 via $H_2O + CO_2 \rightleftharpoons H^+ + HCO_3^-$
(bicarbonate buffering)

- the central response is slow



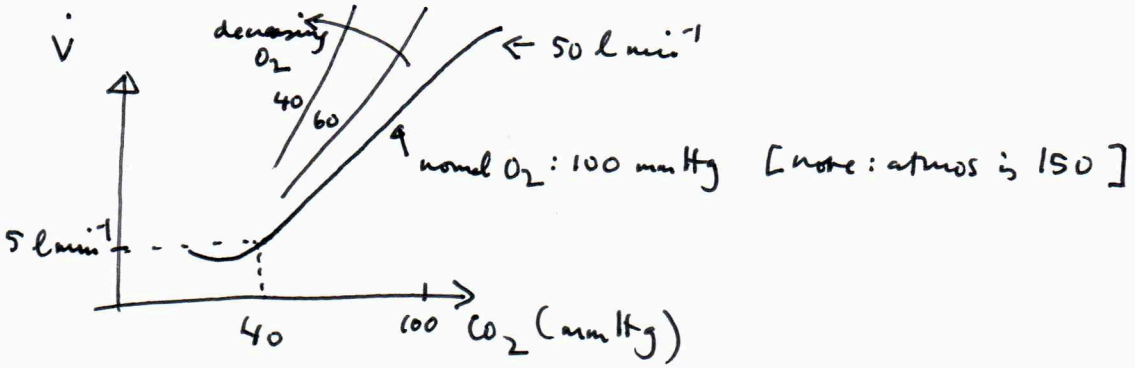
Peripheral chemoreceptors

Responds to O_2 variation, modulated by CO_2

(the Oxford Jam)

- the peripheral chemoreceptor is fast

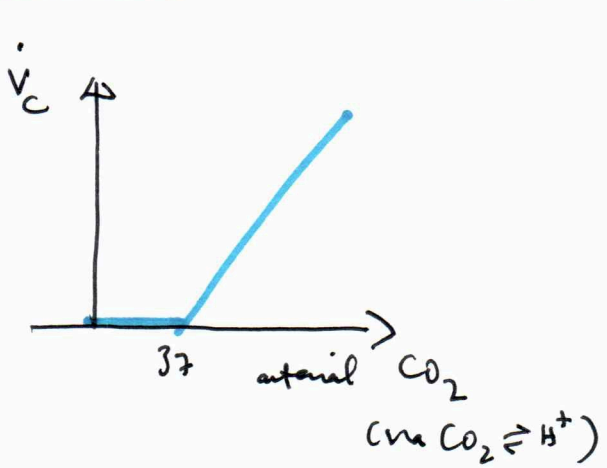
Ventilatory response to CO_2 & O_2

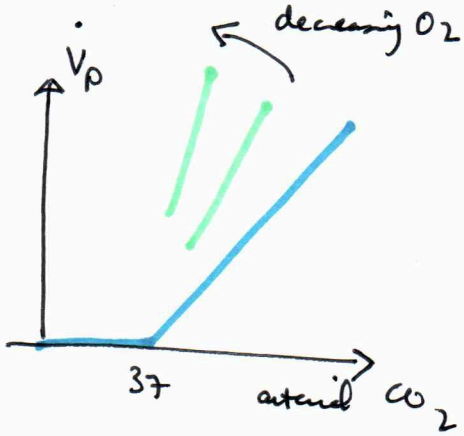


Normal values in blood (partial pressure, mm Hg)

	O_2	CO_2
inspired	150	0
alveolar/arterial	100	40
venous	40	45

Instantaneous ventilatory response





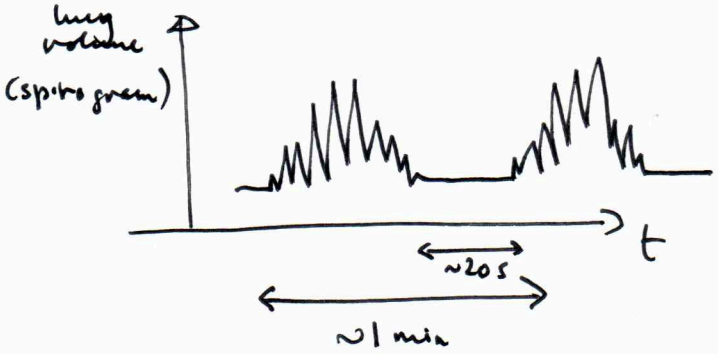
Periodic breathing

is a regular waxing and waning of the amplitude of breathing:

in extreme forms apnea occurs: absence of breathing

Cheyne-Stokes breathing is associated with congestive heart failure,

- stroke
- high altitude



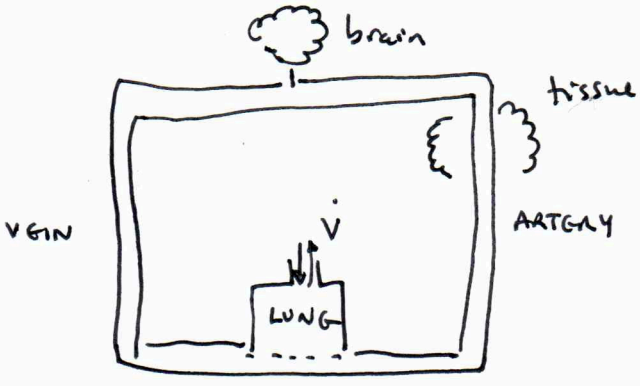
The Mackey-Glass model

This is a one-compartment model. The only variable is the alveolar (or arterial) CO_2 concentration c; or we use its partial pressure p (these are related via $c = K_{CO_2} p$)

↑
Henry's law

$K_{CO_2} = 0.005\ l\ (STPD)\ l^{-1}\ mmHg^{-1}$

STPD = standard temperature and pressure, dry



Mackey-Glass assumes tacitly that

$$p|_{tissue} = p|_{arterial}$$

- because the compartment is the tissues

Mackey-Glass model

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

K = compartment volume

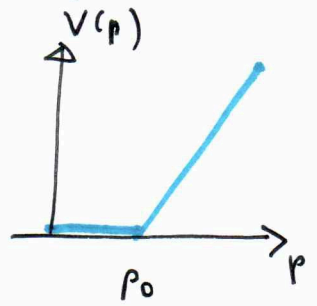
M = metabolic CO_2 production

$\dot{V}$ = ventilation

Controller

take $\dot{V} = \dot{V}(p_\tau)$, $p = p(t-\tau)$

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



(Mackey-Glass use Hill function)

τ = delay ~ 12 s

G gain

Non-dimensionalise

$t \sim \tau$, $p - p_0 \sim \Delta p$, $\dot{V} = G \Delta p \, v$, where $\Delta p = \frac{M}{G p_0}$

This leads to

$$\begin{cases} \dot{p} = \alpha\left[1 - (1+\mu p)v\right] \\ v = v(p_1) = [p_1]_+ \end{cases}$$

$\alpha = \frac{\tau p_0 G}{K} \sim 0.3$

$\mu = \frac{M}{p_0^2 G} \sim 0.06$

Steady state $p = \frac{1}{1+\mu p} \approx 1 - \mu p \approx 1 - \mu$

Linear stability

$p = p^* + \rho$, $p^* \approx 1 - \mu \ldots$

$\Rightarrow \dot{\rho} = -\beta\rho - \gamma\rho_1$

$\beta = \alpha\mu p^* \approx \alpha\mu$

$\gamma = \alpha(1+\mu p^*) \approx \alpha(1+\mu)$

$\rho = e^{\sigma t} \Rightarrow \boxed{\sigma = -\beta - \gamma e^{-\sigma}}$

We have seen this before

i $(\sigma+\beta)e^{\sigma}$ has essential singularity at $\sigma=\infty$ ($\mathbb{C}$)

Picard $\Rightarrow \infty$ roots, $\sigma \to \infty$

ii As $\sigma\to\infty$, $e^{-\sigma}\to\infty \Rightarrow \mathrm{Re}\,\sigma \to -\infty$

iii $e^{\sigma} = -\frac{(\sigma+\beta)}{\gamma}$ $\quad -\sigma = +i\bar{\pi} - \ln\gamma + \ln(\sigma+\beta)$

$$\sigma = \ln\gamma - i\bar{\pi} - \ln\sigma - \left[\frac{\beta}{\sigma}\cdots\right]$$

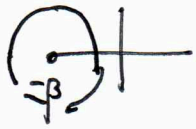
$$\sigma \simeq -(2n+1)i\bar{\pi} - \ln|\sigma| + \ln\gamma - \frac{\beta}{\sigma}\cdots$$

$$\sigma \simeq -(2n+1)i\bar{\pi} - \ln\{(2n+1)\bar{\pi}\} + \ldots \qquad n\to\infty$$

iv $\beta,\gamma>0$: fix β, $\sigma(\gamma)$ is analytic

(in fact $\sigma' = -e^{-\sigma} + \gamma e^{-\sigma}\sigma' \Rightarrow \sigma' = \frac{-e^{-\sigma}}{1-\gamma e^{-\sigma}}$

v If $\mathrm{Re}\,\sigma>0$ then $|\sigma+\beta| = \gamma e^{-\mathrm{Re}\,\sigma} < \gamma$ i.e. if $\gamma<\beta$



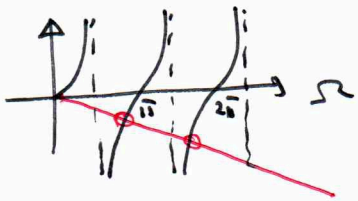
$\Rightarrow \mathrm{Re}\,\sigma<0$ for $\gamma<\beta$.

vi Instability can occur for $\gamma>\gamma_c$ if $\sigma = \pm i\Omega$ at $\gamma=\gamma_c$

and $\mathrm{Re}\,\sigma'(\gamma_c)>0$ (transversality)

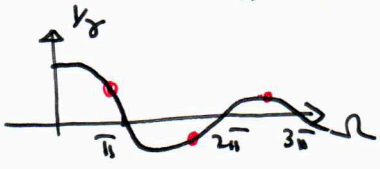
$\sigma = i\Omega \Rightarrow i\Omega = -\beta - \gamma[\cos\Omega - i\sin\Omega]$

$\Rightarrow \Omega = \gamma\sin\Omega \Rightarrow \tan\Omega = -\frac{\Omega}{\beta}$



$\Rightarrow \Omega = \Omega_1, \Omega_2 \cdots \quad \Omega_n \in (n\bar{\pi} - \frac{\pi}{2}, n\bar{\pi})$

& $\gamma = \frac{\Omega}{\sin\Omega}$



$\gamma_1, \gamma_3, \gamma_5 > 0$

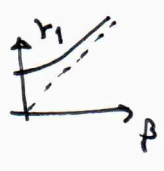
$\gamma_1 < \gamma_3 < \gamma_5 \cdots$

vii $\sigma' = \frac{-e^{-\sigma}}{1-\gamma e^{-\sigma}}$ at $\sigma+\beta = -\gamma e^{-\sigma} \Rightarrow \sigma' = \frac{\sigma+\beta}{\gamma(1+\sigma+\beta)} = \frac{(i\Omega+\beta)(\beta+1-i\Omega)}{\gamma[(\beta+1)^2+\Omega^2]}$

$\Rightarrow \mathrm{Re}\,\sigma'\big|_{i\Omega} = \frac{\beta(\beta+1)+\Omega^2}{\gamma[(\beta+1)^2+\Omega^2]} > 0$ ✓.

$\Rightarrow$ Unstable for $\gamma > \gamma_1(\beta)$

viii $\beta\to 0$, $\Omega\to\frac{\pi}{2}$, $\gamma_1\to\frac{\pi}{2}$; $\beta\to\infty$, $\Omega\to\bar{\pi}$, $\gamma_1 = \frac{-\beta}{\cos\Omega} \simeq \beta$



In the present case

$\beta = \alpha\mu$ is small so

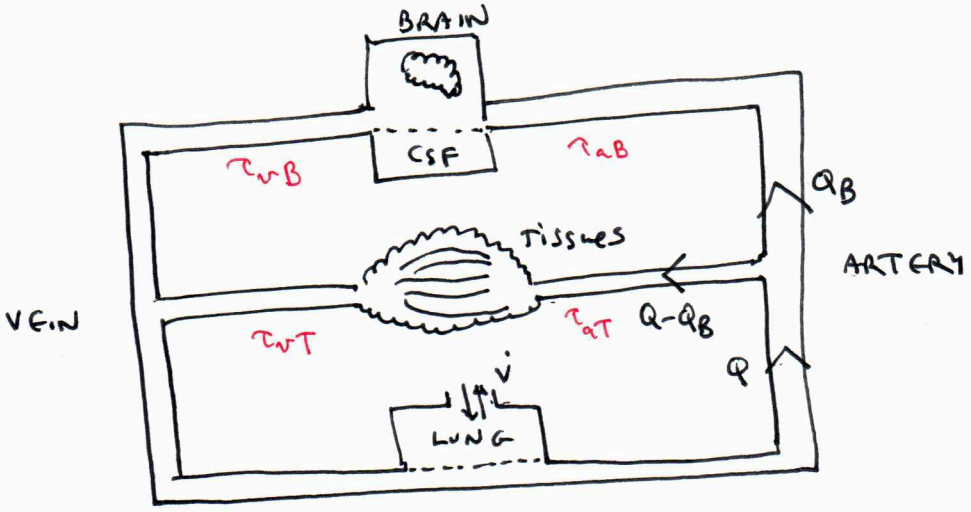
instability occurs if $\gamma \simeq \alpha = \dfrac{\tau \rho_0 G}{K} \gtrsim \pi/2$

- Congestive heart failure → decreased blood flow
  → $\tau \uparrow$
- stroke → $G \uparrow$
- high altitude → $\uparrow$
  (Oxford fan)

MP Lecture 14: The Grodins model [Grodins Buell Bart 1967]

The problem with Mackay-Glass is it confuses the compartments - tissues & arteries.

The Grodins model avoids this by having tissues, brain, alveoli as separate compartments.



Cerebro-spinal fluid

In total there are 6 compartments: [lung], arteries, veins, tissues, brain, [CSF]

we'll neglect alveolar/pulmonary bed barrier & blood/brain barrier (CSF)

Model

$= 760 \times \frac{310}{273}$: conversion factor STPD → BTPS

$$K_L \dot{P}_{aCO_2} = -\dot{V} P_{aCO_2} + 863 K_{CO_2} Q \left[P_{vCO_2} - P_{aCO_2} \right] \quad (1)$$

$$K_{CO_2} K_B \dot{P}_{BCO_2} = MR_{BCO_2} + K_{CO_2} Q_B \left[P_{aCO_2}(t-\tau_{aB}) - P_{BCO_2} \right] \quad (2)$$

[Mackay-Glass]

$$K_{CO_2} K_T \dot{P}_{TCO_2} = MR_{TCO_2} + K_{CO_2} (Q-Q_B) \left[P_{aCO_2}(t-\tau_{aT}) - P_{TCO_2} \right] \quad (3)$$

$$Q P_{vCO_2} = Q_B P_{BCO_2}(t-\tau_{vB}) + (Q-Q_B) P_{TCO_2}(t-\tau_{vT}) \quad (4)$$

Delays

	min	s
τ_{aB}	0.18	11
τ_{aT}	0.32	19
τ_{vT}	0.59	35
τ_{vB}	0.11	7

Blood flow total Q 6 l min^{-1}

to brain Q_B 0.75 l min^{-1}

Approximations

$Q_B \ll Q$ in (4) $\Rightarrow$

$$P_{vCO_2} \simeq P_{TCO_2}\,(1 - \tau_{VT}) \qquad (5)$$

Time scales [use $K_L \sim 3\,l$, $K_B \sim 1\,l$, $K_T \sim 39\,l$]

a: $\dfrac{K_L}{863\,K_{CO_2}\,Q} \sim 7\,s$

B: $\dfrac{K_B}{Q_B} \sim 80\,s$

T: $\dfrac{K_T}{Q} \sim 6.5\,min$

Periodic breathing on time scale ~ 1 min suggests

(1) in quasi-equilibrium

$$P_{aCO_2} \simeq \left(\frac{863\,K_{CO_2}\,Q}{863\,K_{CO_2}\,Q + \dot{V}} \right) P_{vCO_2} \qquad (6)$$

(3): P_{TCO_2} is slowly varying, therefore

$$P_{TCO_2} \simeq \frac{MR_{TCO_2}}{Q\,K_{CO_2}} + \overline{P_{aCO_2}} \qquad (7)$$

($\overline{}$: time average)

Combine (5), (6), (7) gives

$$P_{aCO_2} \simeq \frac{1}{1 + \frac{\dot{V}}{863\, K_{CO_2} Q}} \qquad P_{TCO_2} = \xi\, P_{TCO_2}{}_{lag}$$

$$\xi = \frac{1}{1 + \frac{\dot{V}}{863\, K_{CO_2} Q}}$$

$$\Rightarrow \quad \overline{P_{aCO_2}} = \overline{\xi}\, P_{TCO_2}$$

& (7) gives $P_{TCO_2} = \frac{MR_{TCO_2}}{Q K_{CO_2}} + \overline{\xi}\, P_{TCO_2} \Rightarrow P_{TCO_2} = \frac{MR_{TCO_2}}{Q K_{CO_2}(1-\overline{\xi})}$

and thus

$$P_{aCO_2} \simeq \frac{MR_{TCO_2}\,\xi}{Q K_{CO_2}(1-\overline{\xi})} = \frac{863\, MR_{TCO_2}}{863 K_{CO_2} Q + \dot{V}} \left[\frac{1}{1 - \left\{ \frac{1}{1 + \frac{\dot{V}}{863 K_{CO_2} Q}} \right\}} \right]$$

and then on the brain time scale

$$\frac{K_B}{Q_B} \dot{P}_{BCO_2} = \frac{MR_{BCO_2}}{K_{CO_2} Q} + P_{aCO_2}(t - \tau_{aB}) - P_{BCO_2}$$

A single delay-differential equation for P_{BCO_2} if $\dot{V} = \dot{V}[P_{BCO_2}]$

Now $863\, K_{CO_2} Q \sim 26\ \ell\ (BTPS)\ min^{-1}$

suppose $\dot{V} \ll 863\, K_{CO_2} Q$ normally

$$\Rightarrow \quad 1 - \left\{ \frac{1}{1 + \frac{\dot{V}}{863 K_{CO_2} Q}} \right\} = \frac{\left(\frac{\dot{V}}{863 K_{CO_2} Q} \right)}{1 + \frac{\dot{V}}{863 K_{CO_2} Q}} \simeq \frac{\dot{V}}{863 K_{CO_2} Q}$$

$$\Rightarrow P_{aCO_2} \simeq \frac{863\, MRT_{CO_2}}{\dot{V}} \Rightarrow \text{stability} \quad [?]$$

Back to full model, non-dimensionalise

(ex.) There is a steady state $p_{aCO_2} = p^* = \frac{863}{V^*}\left[MR_{TCO_2} + MR_{BCO_2}\right]$

where $\dot{V} = V^*$.

Define (in the steady state)
$p_{vCO_2} = p^*(1+\varepsilon)$
$p_{BCO_2} = p^*(1+\varepsilon a)$
$p_{TCO_2} = p^*(1+\varepsilon b)$

$\varepsilon = \frac{V^*}{863\, k_{CO_2} q} \sim 0.2$

$(a \sim 1.7,\ b \sim 0.9)$

So non-dimensionalise as

$t \sim \frac{k_B}{Q_B}$, $p_{aCO_2} = p^*(1+\varepsilon p_a)$, $p_{BCO_2} = p^*(1+\varepsilon p_B)$, $p_{TCO_2} = p^*(1+\varepsilon p_T)$

$\dot{V} = V^* v$

ex. $\Rightarrow$

$$\dot{p}_a = \Lambda\left[p_v - p_a - (1+\varepsilon p_a)v\right]$$

$$\dot{p}_B = a + p_a(t-\tau^*_{aB}) - p_B$$

$$\dot{p}_T = s\left[b + p_a(t-\tau^*_{aT}) - p_T\right]$$

$$p_v = p_T(t-\tau^*_{vT}) + \delta\left[p_B(t-\tau^*_{vB}) - p_T(t-\tau^*_{vT})\right]$$

$\delta \sim 0.13$, $\Lambda \sim 11.5$, $s \sim 0.18$ and controller $v = v(p_B)$; $\tau^*_k \lesssim 1$

And as earlier $\Lambda \gg 1 \Rightarrow p_a \approx p_v - v$ $\quad \varepsilon \ll 1$

$\delta \ll 1$ $\quad p_v \approx p_T(t-\tau^*_{vT})$ $\quad$ [also $b = 1-\delta(a-b) \Rightarrow b \approx 1$]

[Method of averaging] $\rightsquigarrow s \ll 1$, $\dot{p}_T = O(s)$ long time scale $\tau = st$

$$\frac{dp_T}{d\tau} \approx b + \overline{p_a} - p_T \Rightarrow p_T \approx b + \overline{p_a}$$

So $p_T \approx b + \bar{p}_a = b + \bar{p}_v - \bar{v} \approx b + p_T - \bar{v} \Rightarrow \bar{v} \approx b$

and finally

$$\dot{p}_B = a + p_a(t-\tau_{aB}^*) - p_B$$
$$= a + p_v(t-\tau_{aB}^*) - v[p_B(t-\tau_{aB}^*)] - p_B$$
$$= a + p_T - v[p_B(t-\tau_{aB}^*)] - p_B$$

p_T is indeterminate! but averaging this

$$\Rightarrow \quad 0 = a + p_T - \bar{v} - \bar{p}_B \quad \Rightarrow \quad p_T = b - a + \bar{p}_B$$

and finally $\dot{p}_B = a + b - a + \bar{p}_B - v[p_B(t-\tau_{aB}^*)] - p_B$

i.e. $\dot{p}_B = b + \bar{p}_B - p_B - v[p_B(t-\tau_{aB}^*)]$

[Note $b = 1 - \delta(a-b)$ so take $b \approx 1$.]

$\tau_{aB}^* = \frac{\tau_{aB} Q_B}{K_B}$

Stability

Steady state $p_B = a$, $v = [1 + \gamma(p_B - a)]_+$ $\gamma = \frac{\varepsilon \rho^* G}{v^*}$

(as $\bar{v} \approx 1$) $= \frac{\rho^* G}{863 K_{CO_2} Q}$

$$\Rightarrow \dot{p}_B \approx \bar{p}_B - p_B + 1 - \left[1 + \gamma\{p_B(t-\tau_{aB}^*) - a\}\right]_+$$

Linearize $p_B = a + \rho$ write $\tau = \tau_{aB}^*$

$\dot{\rho} = \bar{\rho} - \rho - \gamma \rho_T$. We might take $\bar{\rho} = \frac{1}{T}\int_{t-T}^{t} \rho \, dt$

$\rho = e^{\sigma t} \Rightarrow \bar{\rho} = \frac{e^{\sigma t}(1 - e^{-\sigma T})}{\sigma T} \approx 0$ for large T & $\mathrm{Re}\,\sigma > 0$

$\Rightarrow \sigma = \frac{\Sigma}{\tau} \Rightarrow \Sigma = -\tau - \gamma\tau e^{-\Sigma}$ again, unstable (τ small)

for $\gamma\tau = \frac{\tau_{aB} Q_B \rho^* G}{863 K_{CO_2} K_B Q} \gtrsim \frac{\pi}{2}$

C5.12 Lecture 15 : Blood cell production

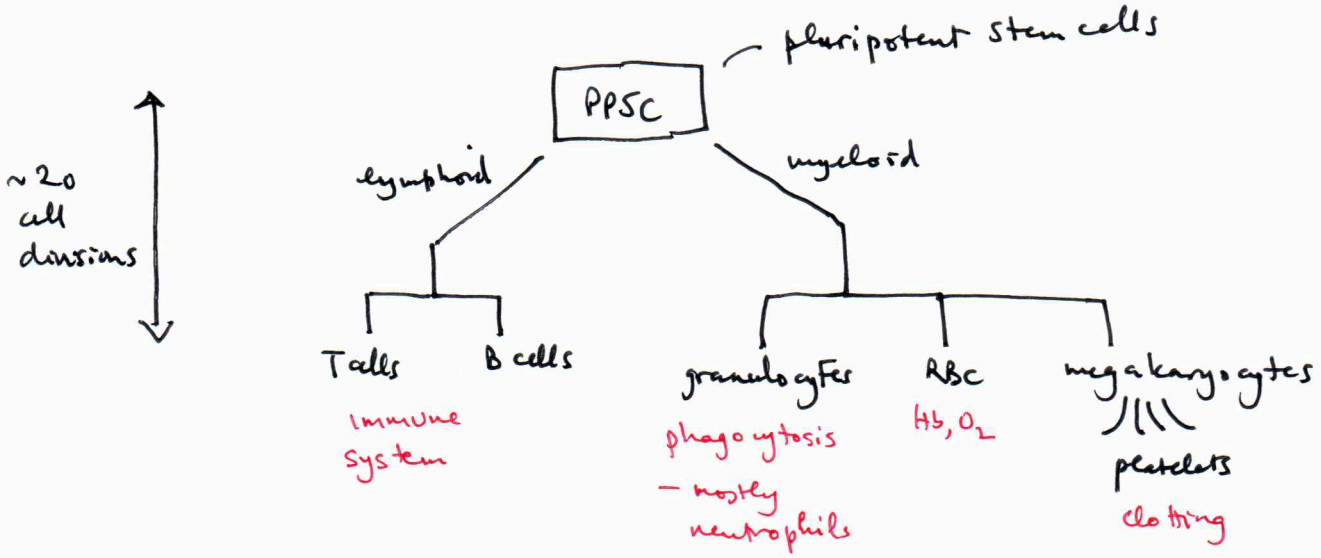
3 different types of blood cells

- red blood cells (erythrocytes) RBC 5×10^{12} cells l^{-1} (5×10^{6} μl^{-1})
  O_2 transporters via binding to haemoglobin Hb
  CO_2 buffering agent via carbonic anhydrase $\Rightarrow H_2O + CO_2 \rightleftharpoons HCO_3^- + H^+$
- white blood cells (leukocytes) 7×10^{9} cells l^{-1} (7×10^{3} μl^{-1})
  including neutrophils, T lymphocytes, phagocytes, etc.
- platelets for blood clotting 3×10^{11} cells l^{-1} (3×10^{5} μl^{-1})
  - cell fragments produced from megakaryocytes

Haematopoiesis

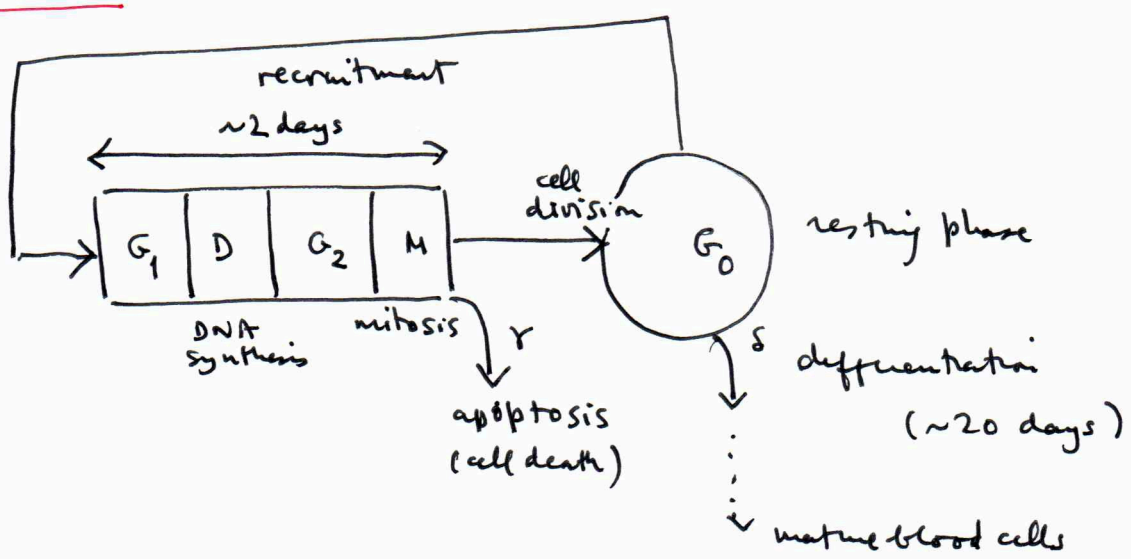
Blood cells are produced through differentiation of

Stem cells in the bone marrow & lymph tissue



Stem cells are hard to identify (!)

The cell cycle



Control of blood cell production

Growth and reproduction are controlled by proteins called growth inducers, e.g. IL-3 (interleukin-3) controls all stem cells – others are specific.

Differentiation is controlled by differentiation inducers

e.g. erythropoietin (EPO) for red blood cells

or G-CSF (granulocyte colony stimulating factor)

GM-CSF
M-CSF
IL-1
TNF tumour necrotic factor
⋮

→ white blood cells

and are effected by external events,

e.g. low O_2 → EPO → RBC

infection → G-CSF → WBC

Blood diseases

Anaemias – deficiency of Hb or # RBC

e.g. Aplastic anaemia **AA** – non-functioning bone marrow

Hemolytic anaemia – RBC short life span

Blood viscosity (normal is $3\times \eta_{H_2O}$) depends on RBC

Anaemia lowers η_{BLOOD} → decreased peripheral resistance → HR etc.

↓

hypoxia (low O_2) → vessel dilation ↑

Polycythemia

Tissue hypoxia → increased RBC production

Polycythemia Vera **PV** due to a stem cell mutation

→ PPSC control is diminished → uncontrolled cell proliferation (of all types)

Leukopenia

Bone marrow produces very few WBC

Cyclical neutropenia **CN** oscillations in neutrophil numbers

– endemic in grey collies

Leukaemias

Uncontrolled production of WBC due to cancerous mutation of stem cells. Differentation is slowed → immature WBC are released.

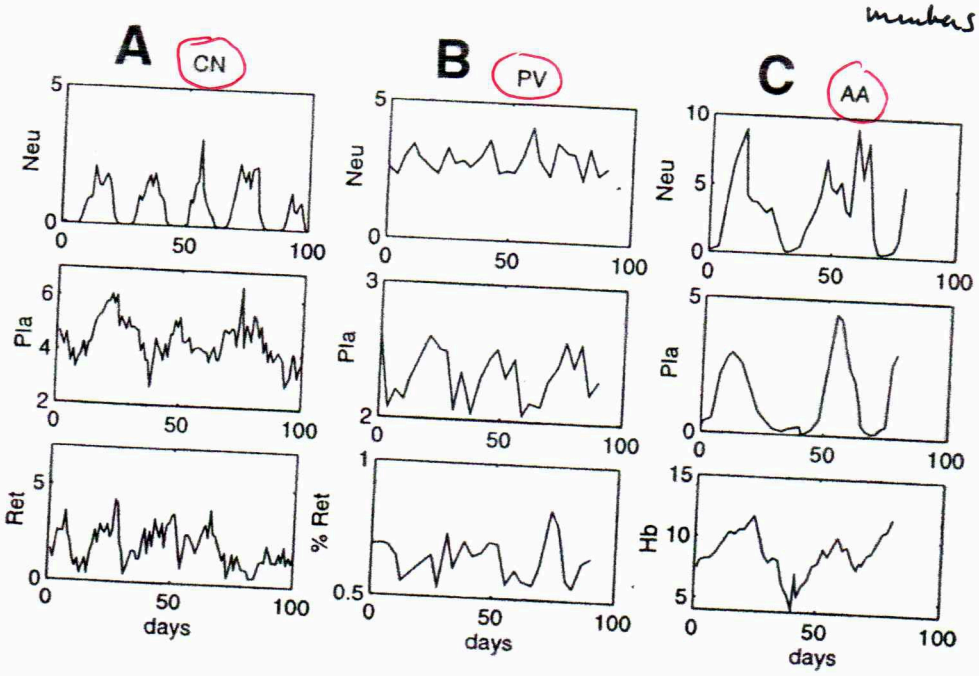
CML or Chronic Myelogenous Leukaemia **CML**

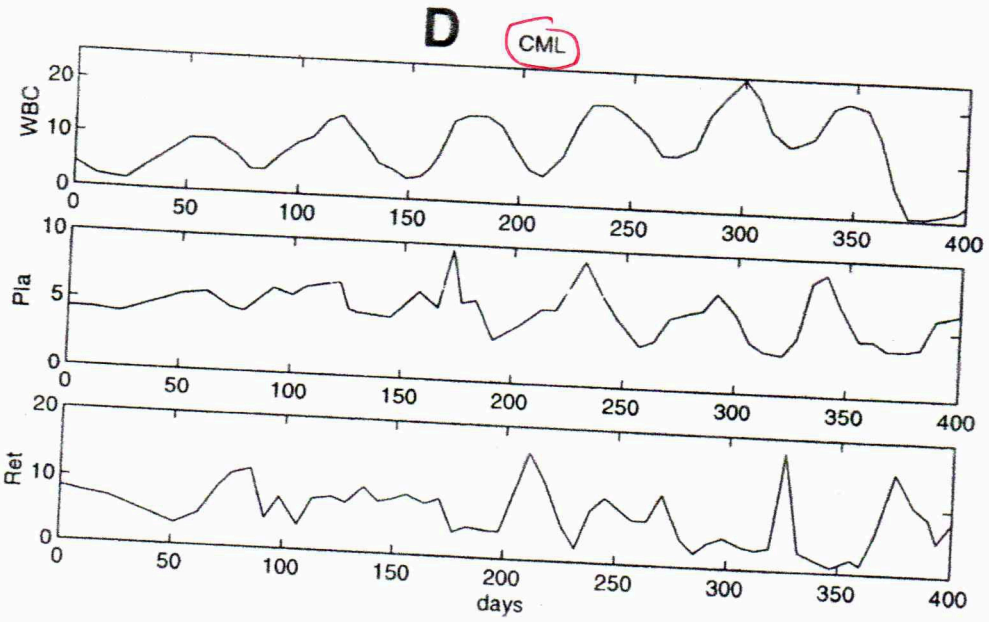
– oscillations in WBC (also platelets + reticulocytes)

Dynamical diseases

In many of these diseases, oscillations in cell numbers occur

period ~20 d

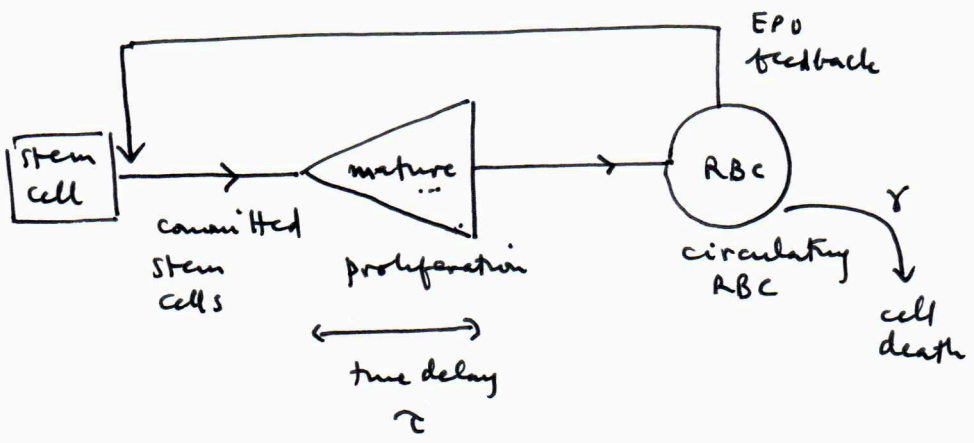




period ~60 d

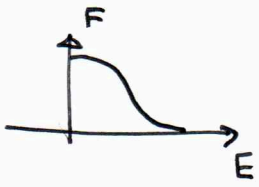
Fig 2. Representative patterns of circulating cell levels in four periodic hematological disorders considered in this review. (A) CN,[54] (B) PV,[55] (C) AA,[56] and (D) periodic CML.[57] The density scales are neutrophils, 10^3 cells/μL; white blood cells, 10^4 cells/μL; platelets, 10^5 cells/μL; reticulocytes, 10^4 cells/μL; and Hb, g/dL.

A mathematical model of blood cell production [RBC]



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

$E(t-\tau)$



Hill function $F(E) = \dfrac{F_0 \theta^n}{\theta^n + E^n}$

$\gamma = 2.3 \times 10^{-2}\ d^{-1}$

$F_0 = 10^6$ cells $\mu l^{-1}\ d^{-1}$

$n = 8$

$\theta = 3.5 \times 10^6$ cells μl^{-1}

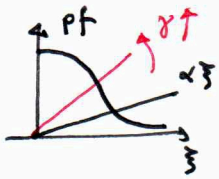
$\tau = 6$ d

(Ex.) Non-dimensionalise $t \sim \tau$, $E \sim \theta$ $\Rightarrow \dot{\xi} = \rho f(\xi_1) - \alpha \xi$ $\quad \rho = \frac{F_0 \tau}{\theta} \sim 1.7$, $\alpha = \gamma\tau \sim 0.14$

Unique steady state ξ^*

Linearise $\xi = \xi^* + \Xi$, $\Xi = e^{\sigma t}$

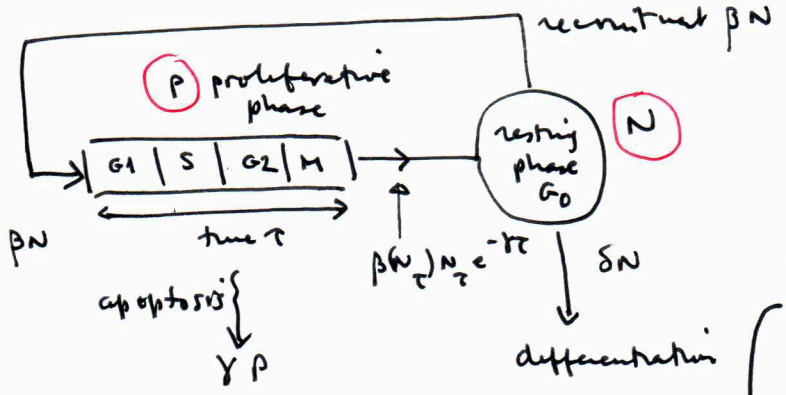
$\Rightarrow \sigma = -\alpha - \Gamma e^{-\sigma}$ $\quad \Gamma = \rho |f'(\xi^*)|$



unstable (α small) for $\Gamma \gtrsim 1/2$

– goes unstable for increasing γ ($\rightarrow \alpha \uparrow \rightarrow \xi^* \downarrow \rightarrow |f'| \uparrow$

A simple model of stem cell control



Derived via

$p_t + p_a = -\gamma p$

$P = \int_0^\tau p\,da$

$\Rightarrow \dot{P} = -\gamma P + p|_{a=0} - p|_{a=\tau}$

input b.c. $p = \beta N$ at $a = 0$

characteristics

$\dot{p} = -\gamma p$, $\dot{a} = 1$

i.c. $p = \beta N(s)$, $a = 0$, $t = s$

$\Rightarrow a = t - s$

$p = \beta N(s) e^{-\gamma(t-s)}$

$\Rightarrow p = \beta N(t-a) e^{-\gamma a}$

$\Rightarrow p|_{a=\tau} = e^{-\gamma\tau} \beta N(t-\tau)$

model

$$\dot{P} = -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau$$

$$\dot{N} = -\beta(N)N - \delta N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau$$

(2 ↑ cell mitosis)

Hill function $\beta = \dfrac{\beta_0 \theta^n}{\theta^n + N^n}$

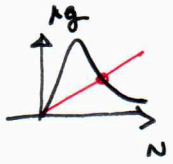
Non-dimensionalise $N \sim \theta$, $t \sim \tau$

$$g(N) \equiv bN\beta(N)$$

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

$b = \beta_0\tau$, $\varepsilon = \delta\tau$, $\mu = \dfrac{2e^{-\gamma\tau} - 1}{\delta\tau}$

eg $b \sim 3.9$, $\mu \sim 2.6$, $\varepsilon \sim 0.11$



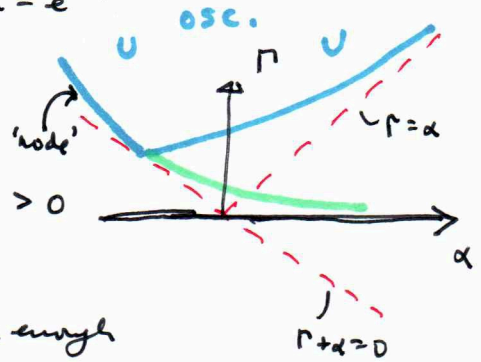
- Unique steady state ($\mu > 1$) $N = \mu g(N)$
- Linear stability $N = N^* + u$, $u = e^{\sigma t}$

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

where $\alpha = g' + \varepsilon < 0$

$$\Gamma = -(1 + \varepsilon\mu)g' > 0$$

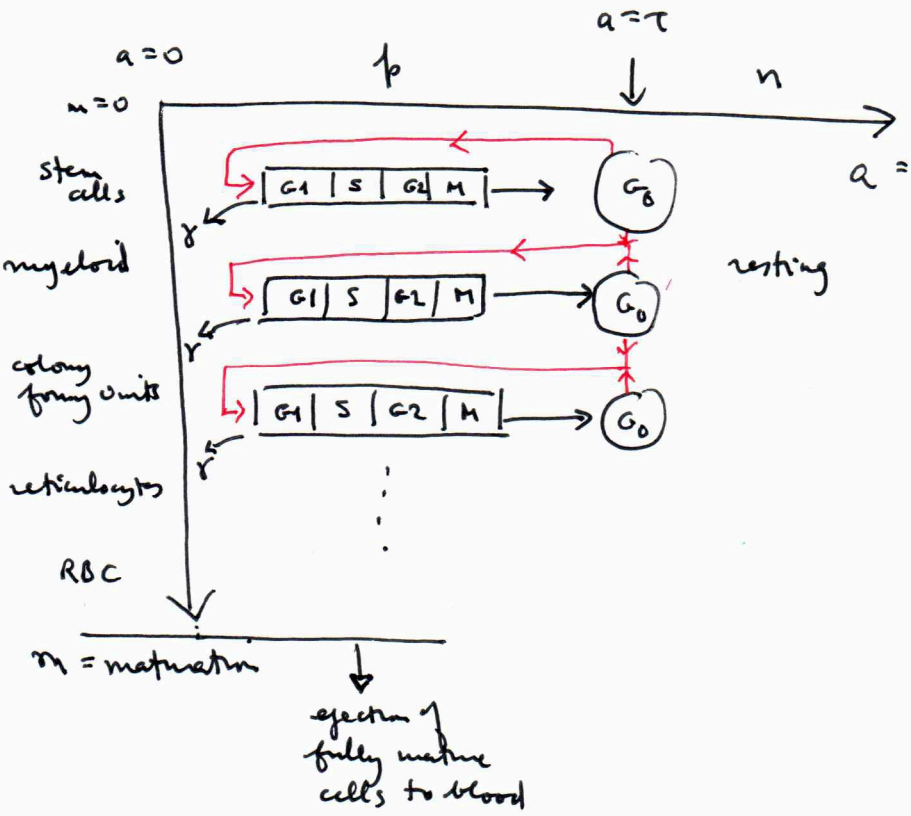
(note $\Gamma + \alpha > 0$)



- Periodic oscillations if Γ large enough
- Relaxation oscillations if $\varepsilon \ll 1$.

CS·12 Lecture 16: Blood cell maturation model

Cells proliferate through the cell cycle, but also mature through the process of differentiation



We have cell densities $p(t,m,a)$ (proliferating) & $n(t,m,a)$ (resting)

AND $p_0(t,a)$, $n_0(t,a)$ (stem cells at $m=0$) (note different units)

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial}{\partial m}(Vp) = -\gamma p$$

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \frac{\partial}{\partial m}(Vn) = -Rn$$

V = maturation rate $= V(m)$

R = recruitment

[note: the model assumes (unknowingly) that cells mature even in the proliferative phase] (!)

At $a=\tau$, $n(t,m,\tau) = 2p(t,m,\tau)$ cell division

At $a=0$, $p(t,m,0) = RN(t,m)$, $N = \int_\tau^\infty n\,da$ recruitment rate [via $\frac{\partial P}{\partial t}$, $P = \int_0^\tau p\,da$]

As $a \to \infty$ $n \to 0$

Integrate w.r.t. a : $\tau \to \infty$

$$\Rightarrow \frac{\partial N}{\partial t} + \frac{\partial}{\partial m}(VN) = -RN + 2\rho(t,m,\tau)$$

Characteristics for ρ equation ($V' = \frac{\partial V}{\partial m}$)

$$\dot{a} = 1 \quad \dot{m} = V, \quad \dot{\rho} = -(\gamma + V')\rho \qquad (' = \frac{d}{dt})$$

Initial condition at $a = 0$:

$$t = s, \ m = \mu, \ a = 0, \ \rho = R(s,\mu)N(s,\mu), \quad s,\mu > 0$$

$$\Rightarrow a = t - s, \quad \int_{\mu}^{m} \frac{d\rho}{V(\rho)} = t - s \quad \text{with } V = V(m)$$

Define $\nu(m,a)$ by $\int_{\nu}^{m} \frac{d\rho}{V(\rho)} = a \Rightarrow \mu = \nu(m,a)$

On characteristics $dt = \frac{dm}{V(m)}$

$$\Rightarrow \rho(t,m,\tau) = R\left[t-\tau, \nu(m,\tau)\right] N\left[t-\tau, \nu(m,\tau)\right] \times \exp\left[-\int_{\nu(m,\tau)}^{m} \frac{\gamma\, d\rho}{V(\rho)}\right] \frac{V\left[\nu(m,\tau)\right]}{V(m)}$$

(ρ: at $a=\tau$; s: $t-\tau$; μ: $\nu(m,\tau)$; ρ feeds into N equation.)

Let us assume γ = constant, V = constant $\Rightarrow \nu = m - Va$:

define $M = NV$, $\xi = \frac{m}{V}$ (ξ: new maturation variable) $\rightsquigarrow M\,d\xi = N\,dm$

$$\hookrightarrow \frac{\partial M}{\partial t} + \frac{\partial M}{\partial \xi} = -RM + 2e^{-\gamma\tau} R_{\tau,\tau} M_{\tau,\tau}$$

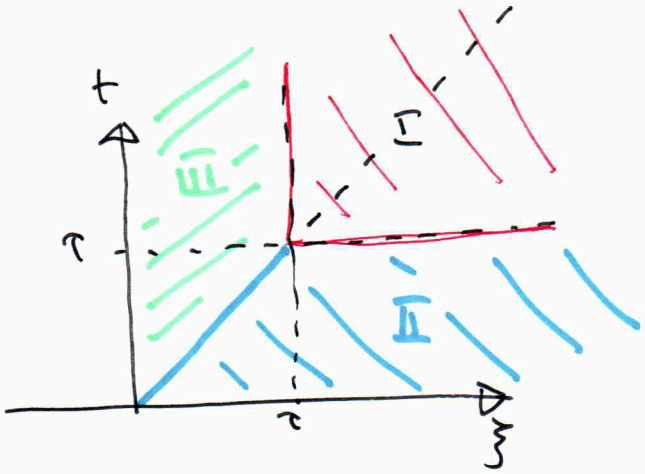
$R = R(t,\xi)$

$R_{\tau,\tau} = R(t-\tau, \xi-\tau)$

$M_{\tau,\tau} = M(t-\tau, \xi-\tau)$

Δ generally $R = R(M)$

This gives the resting cell density as a function of t and maturation ξ. : for $t > \tau$, $\xi > \tau$: ($s, \mu > 0$)



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

where in I $(t > \tau, \xi > \tau)$ $Q = 2e^{-\gamma\tau} R_{\tau,\tau} M_{\tau,\tau}$

in II $(t < \tau, \xi > t)$ $Q = 2Ve^{-\gamma t} p_I(\xi - t, \tau - t)$

where $p = p_I(\xi, a)$ at $t = 0$

in III $(t > \xi, \xi < \tau)$ $Q = 2Ve^{-\gamma\xi} p_0(t - \xi, \tau - \xi)$

where $pV = p_0(t, a)$ at $x = 0$

Note: we are only really interested in the long-time behaviour for $t > \xi$ so can ignore region II. Region III then provides the initial function for M: we solve the ordinary differential delay equation $\dot{M} = -RM + 2e^{-\gamma\tau} R_\tau M_\tau$ on $\xi = 1$

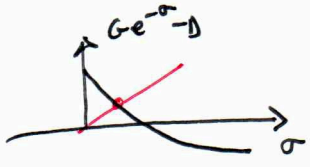
- Steady solution, R = constant

$M = M_0 e^{\alpha\xi}$, $\alpha = R\left[-1 + 2e^{-(\alpha+\gamma)\tau}\right]$

note $\sigma = \alpha\tau$, $D = R\tau$, $G = 2R\tau e^{-\gamma\tau}$

note $G > 0$, positive again.

$\Rightarrow \sigma = -D + Ge^{-\sigma}$, $G > D$



There is one real positive root

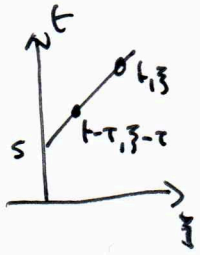
There are ∞ complex roots – decay with ξ if G small

grow if G large enough.

General solution, R constant

Characteristics, start with $t=s$, $\xi=0$, $M=M_0(s)$

$\dot{\xi}=1 \Rightarrow \xi = t-s$, $\quad \dot{M} = -RM + 2e^{-\gamma\tau} R\, M(t-\tau, \xi-\tau)$



$\Delta\ M(t-\tau, \xi-\tau) = M(t-\tau, s)$ a same characteristic

$\dot{M} = -RM + 2e^{-\gamma\tau} R M_\tau$

(Note actually need data on $[-\tau, 0]$)

General solution is $M = \sum_k M_k(s)\, e^{\sigma_k (t-s)}$

where σ_k satisfies $\sigma = -R + 2e^{-\gamma\tau} e^{-\sigma\tau}$ as before

Periodic solutions

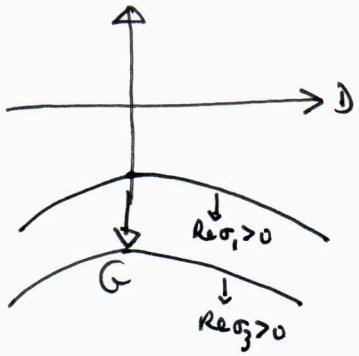
Suppose $M_0(s)$ is periodic, $M_0 = \sum c_k e^{ik\omega s}$ period $\frac{2\pi}{\omega}$

[due to stem cell oscillations]

The solution is $M = \sum_{k,\ell} b_{k\ell}\, e^{\sigma_\ell (t-s) + ik\omega s}$

where $\sum_\ell b_{k,\ell} = c_k$

and $\sigma_\ell = \frac{\Sigma}{\tau}$, $\quad \Sigma = -D + Ge^{-\Sigma}$ as before



- Oscillations can grow in ξ
  $\rightsquigarrow$ cyclical neutropenia?
- Oscillations propagate as travelling waves