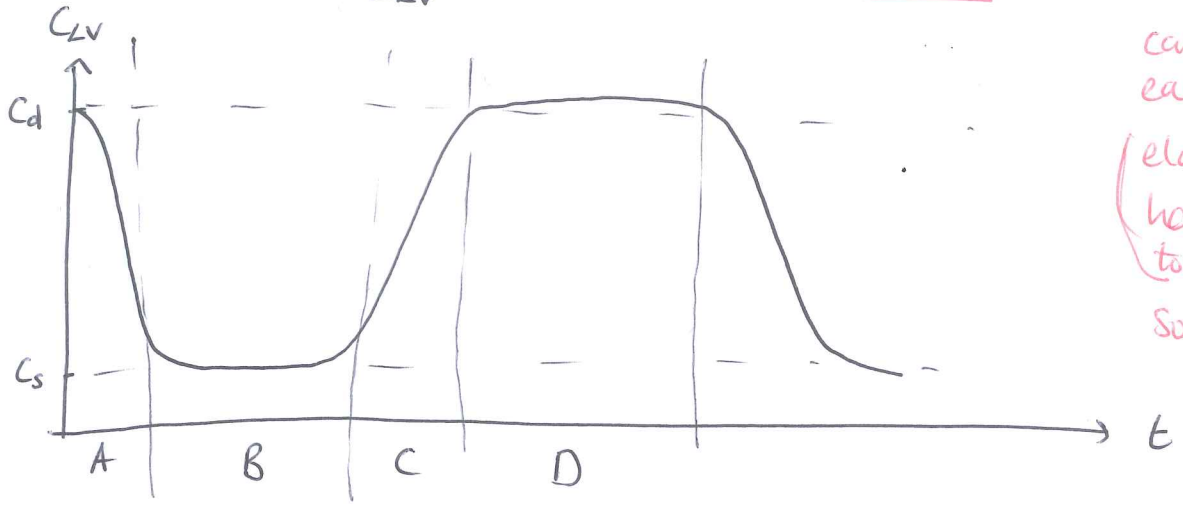
In the last lecture, Andrew discussed the pressure-volume diagram of the left ventricle. This is driven by the periodic firing / heart beat periodically changing the ventricular elastance or compliance.

The compliance can be thought of as a prescribed periodic function of time.

of the heart $C_{LV} = \frac{1}{E_{LV}}$, where E_{LV} is the elastance



compliance is how easy it is to stretch, (elastance, conversely, how resistant it is to stretching.)
So C low ⇒ tight
C high ⇒ loose

A: The systole: isovolumetric contraction.
The compliance falls as the heart tightens.

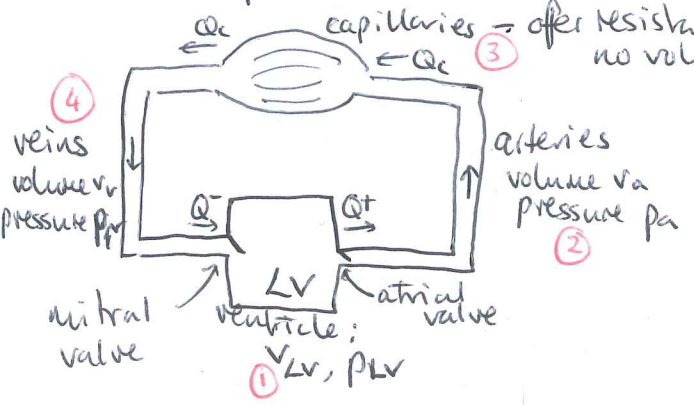
B: Ejection. constant low compliance C_s (tight) pushes blood out

C: The diastole: isovolumetric relaxation. The compliance rises as the heart loosens

D: Refilling: constant high compliance C_s (loose) allows blood in.

A simple mechanical model of the circulation

We would like to write down a mathematical model to explain the $P_{LV} - V_{LV}$ plot.



in the veins & arteries: assume no pressure lost from start to finish, so the pressure P_a or P_v is ~~constant~~ the same throughout.

Q_c, Q^-, Q^+ are blood flows
V_a, V_v, V_{LV} are volumes of compartments

Blood is incompressible but blood vessels are compliant, so blood flows at different points along the network can differ from one another and change with time.

Conservation of blood:

$$\dot{V}_a = Q_+ - Q_-$$
$$\dot{V}_v = Q_c - Q_-$$
$$\dot{V}_{LV} = Q_- - Q_+$$

Resistances:

$$Q_c = \frac{p_a - p_v}{R_c}$$
$$Q_+ = \frac{[p_{LV} - p_a]_+}{R_a}$$
$$Q_- = \frac{[p_v - p_{LV}]_+}{R_{av}}$$

positive part: there is only a flux if the ventricle pressure is higher than the artery pressure, so the atrial valve is open.

Compliance: increasing pressure distends blood vessels:

$$V_a = V_{a0} + C_a p_a$$
$$V_v = V_{v0} + C_v p_v$$
$$V_{LV} = V_{LV0} + C_{LV} p_{LV}$$

NB: C = compliance $= \frac{1}{\text{elastance}}$.

the compliance of the heart varies as discussed earlier.

Combining to write the model just in terms of the pressures:

$$\frac{dp_a}{dt} = \frac{[p_{LV} - p_a]_+}{R_a C_a} - \frac{p_a - p_v}{R_c C_a} \quad (1)$$

$$\frac{dp_v}{dt} = \frac{p_a - p_v}{R_c C_v} - \frac{[p_v - p_{LV}]_+}{R_v C_v} \quad (2)$$

$$\frac{d}{dt}(C_{LV} p_{LV}) = \frac{[p_v - p_{LV}]_+}{R_v} - \frac{[p_{LV} - p_a]_+}{R_a} \quad (3)$$

A: Isovolumetric contraction

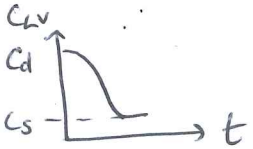
Initial conditions: $p_v < p_{LV} \ll p_a$ so both valves closed.

(1) $\Rightarrow \frac{dp_a}{dt} = -\frac{p_a}{R_c C_a}$

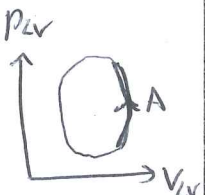
but $R_c C_a \approx 1.8$ s and time of contraction ≈ 0.05 s, so $p_a \approx$ constant

similarly (2) $\Rightarrow$ $p_v \approx$ constant

(3) $\Rightarrow \frac{d}{dt}(C_{LV} p_{LV}) = 0$.



C_{LV} falls so p_{LV} rises



B : Ejection . $C_{LV} = C_s$ is constant.

p_{LV} is now much higher, so $p_v \ll p_a < p_{LV}$

(so the atrial valve is open)

① $\Rightarrow \dfrac{dp_a}{dt} = \dfrac{p_{LV} - p_a}{R_a C_a} - \dfrac{p_a - p_v}{R_c C_a}$ ~ 1.8s

0.3s 0.089s

↑ much smaller than the other two

so $\boxed{p_{LV} \approx p_a}$

② : $\dfrac{dp_v}{dt} = \dfrac{p_a - p_v}{R_c C_v}$ $\Rightarrow \boxed{p_v = \text{constant}}$

0.3s 60s

③ : $\dfrac{d}{dt}(C_{LV} p_{LV}) = -\dfrac{p_{LV} - p_a}{R_a}$

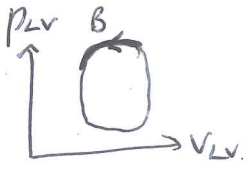
$C_{LV} \approx C_s$ is constant. Combining with ① gives :

$$\frac{dp_a}{dt} = -\frac{C_{as}}{C_a}\frac{dp_a}{dt} - \frac{p_a - p_v}{R_c C_a}$$

ie: $(C_a + C_s)\dfrac{dp_a}{dt} \approx -\dfrac{p_a}{R_c}$ (since $p_a \gg p_v$)

so $\boxed{p_a \propto \exp\left(\dfrac{-t}{R_c(C_a + C_s)}\right)}$ 0.38s 2.2s

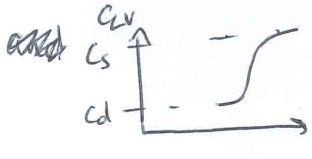
$\Rightarrow$ p_a falls by ~ 0.87 in this ejection phase.



C : Isovolumetric relaxation

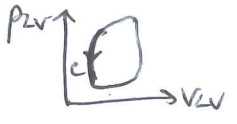
now $p_v < p_{LV} < p_a$, so both valves are closed.

and C_{LV} is rising.



①, ② $\Rightarrow$ p_a, p_v are constant

③ $\Rightarrow \dfrac{d}{dt}(C_{LV} p_{LV}) = 0$ so now p_{LV} falls (until $p_{LV} = p_v$)



D : Refilling

now $p_{LV} < p_v << p_a$ so mitral valve is open.

$C_{LV} = C_d$ is constant

① $\Rightarrow \frac{dp_a}{dt} = -\frac{p_a - p_v}{R_c C_a} \approx -\frac{p_a}{R_c C_a}$ since $p_a >> p_v$

② $\Rightarrow \frac{dp_v}{dt} = \frac{p_a - p_v}{R_c C_v} - \frac{p_v - p_{LV}}{R_v C_v} \approx -\left(\frac{p_v - p_{LV}}{R_v C_v}\right)$

$\frac{dp_v}{dt}$: 0.5s; $R_c C_v$: 60s so neglect; $R_v C_v$: 0.8s

③ $\Rightarrow \frac{dp_{LV}}{dt} = \frac{p_v - p_{LV}}{C_d R_v}$

From ① we find $\boxed{p_a \propto \exp\left(-\frac{t}{R_c C_a}\right)}$ p_a falls by ~ 0.76 in this refilling phase.

so the total fall in p_a is $0.87 \times 0.76 \simeq 0.66$

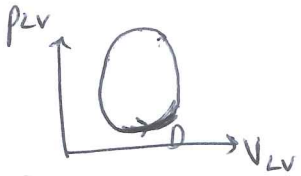
(0.87: ejection; 0.76: refilling; 120 mmHg to 80 mmHg)

② − ③ gives

$$\dot{p}_v - \dot{p}_{LV} = -\left(\frac{1}{R_v C_v} + \frac{1}{R_v C_d}\right)(p_v - p_{LV})$$

so $\boxed{p_v - p_{LV} \propto \exp\left(-\frac{1}{R_v}\left(\frac{1}{C_v} + \frac{1}{C_d}\right)t\right)}$

(Also p_v is decreasing, p_{LV} is increasing)



Thurs 24th

Nervous control of the heart

This is what controls the heart rate, stroke volume, and arterial blood pressure.

There are 2 parts of the nervous system that control cardiac output: the sympathetic and parasympathetic systems.

Nervous control is effected by
- afferent nerves (to the brain)
- efferent nerves (from the brain)

The sympathetic system releases noradrenaline and adrenaline (and other neurotransmitters). There are two parts to the sympathetic system:
- α-sympathetic (peripheral vessels): release of neurotransmitters here causes vasoconstriction which causes an increase in blood pressure
- β-sympathetic (ventricular muscle): release of neurotransmitters here causes an increase in the firing of the SA node ie: an increase in heart rate

The sympathetic system acts slowly (~10 seconds).

The parasympathetic system releases acetylcholine (another neurotransmitter) This decreases the heart rate and causes vasodilation.
This acts quickly

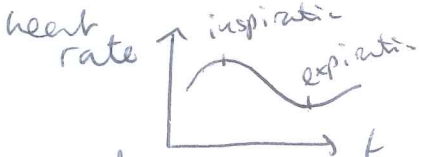
The baroreceptors control the blood flow and blood pressure. They are located in the aortic arch of the chest and the carotid sinus in the neck, and respond to high pressure in the arteries via stretching. The response of these is called the baroreflex.

Oscillatory patterns

The heart rate oscillates due to the different signals from the nervous system, in several ways.

Respiratory sinus arrythmia (RSA)

- heart rate is faster when breathing in than when breathing out. (can get a different resting heart rate depending on which you are doing when measuring it)
- inspiration (breathing in) leads to low pressure, which increases the heart rate because it is easier for blood to flow



etc.

- period $\lesssim 5$ s.

Mayer waves

- due to the sympathetic system
- period ~ 10 s (same as timescale of sympathetic system).

Mathematical models of the baroflex: the Olfesen model (1997)

Three variables: average arterial & venous pressures p_a & p_r
heart rate H

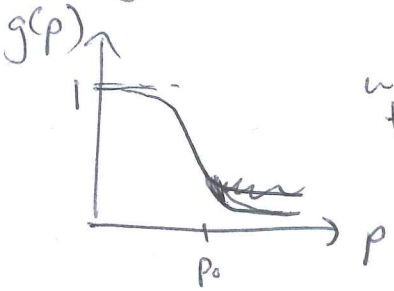
Control is effected by sympathetic and parasympathetic tones (amount of nerves firing):

- $T_S = g(p_a^\tau)$ is sympathetic tone.

  $p_a^\tau = p_a(t_4 - \tau)$ is arterial pressure at time τ ago.
  (a delay because effects are delayed).

- $T_P = 1 - g(p_a)$ is parasympathetic tone

The p^n g is $g(p) = \frac{1}{1 + \left(\frac{p}{p_0}\right)^n}$, the sigmoidal Hill function.



with $n \sim 7$ large, the transition is sharp.

The heart rate H is taken as a continuous variable, ie: the average heart rate.

$$\begin{cases} \dot{H} = \delta_H (H_0 - H) + \lambda_H T_S - \mu_H T_P \\ C_a \dot{p}_a = -\frac{p_a}{R_c} + H \Delta V \end{cases}$$

H_0: natural resting heart rate in the absence of tone

λ_H, μ_H: parameters describing the strength of the sympathetic and parasympathetic tones.

ΔV is stroke volume

C_a: compliance as before

R_c: capillary resistance as before (assumed $p_r \ll p_a$)

Nondimensionalisation:

$$H = H_0 h, \quad p_a = p_0 p, \quad t = \tau \hat{t}$$

$$\Rightarrow \begin{cases} \dot{p} = \kappa (-p + \nu h) & (1) \\ \varepsilon \dot{h} = \delta (1 - h) + \lambda g(p') - \mu (1 - g(p)) & (2) \end{cases}$$

with $\varepsilon \ll 1$ but other pars roughly $O(1)$.

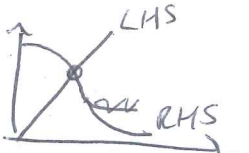
Set $\delta = 1$ (approximately correct).

For small $\varepsilon \ll 1$

(2): $h = 1 + \lambda g(p') - \mu (1 - g(p))$

so (1): $\dot{p} = \kappa \left(\nu (1 - \mu) - p + \nu \left(\lambda g(p_i) + \mu g(p) \right) \right)$

steady state: $\frac{p}{\nu} = 1 - \mu + (\lambda + \mu) g(p)$



so unique s/n

stability:

Set $p = p^* + P$, then $\dot{P} \approx \kappa \left[-P - \nu s (\lambda P_i + \mu P) \right]$

where $s = -g'(p^*) > 0$. is ~~the slope of~~ g

Look for solutions $P = e^{\sigma t}$, to find that

(*) $\boxed{\sigma = -B - G e^{-\sigma}}$ where $B = \kappa (1 + \nu s \mu)$

$G = \kappa \nu s \lambda$

Since $B, G > 0$, $\sigma < 0$ and so the steady state is stable.

(ν and real)

- There are infinitely many roots of ⊛, at most two of which are real. (Can prove this by Picards theorem in complex analysis – not the same theorem as in DEs I !)

- We have $B, G > 0$. If $G < B$ then $\mathrm{Re}(\sigma) < 0$. We can prove this by contradiction:

  if $\mathrm{Re}(\sigma) > 0$ then $\mathrm{Re}(\sigma + B) < |\sigma + B| = |1 - Ge^{-\sigma}|$

  $\mathrm{Re}(\sigma) + B \qquad \leq G < B$ ※

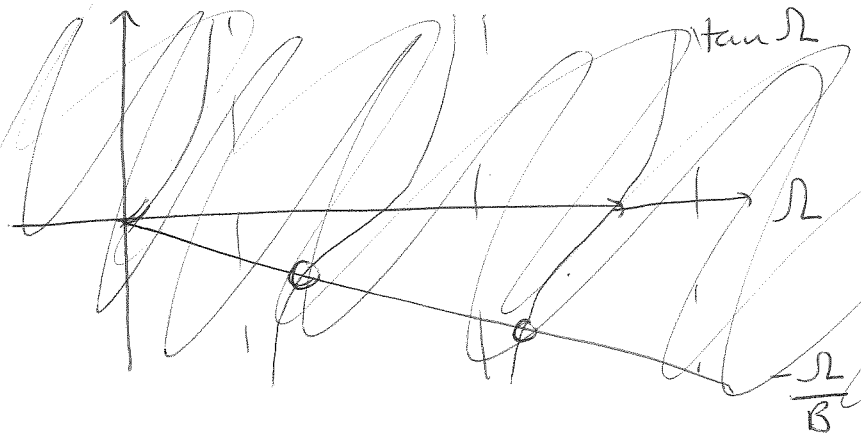
So if $G < B$ the roots of ⊛ have $\mathrm{Re}(\sigma) < 0$ and so the steady state is stable.

This is the boundary between stable & unstable.

- Let's consider $\sigma = i\Omega$ purely imaginary. If such a σ solves ⊛ we have instability.

  Then $i\Omega = -B - G\cos\Omega + iG\sin\Omega$

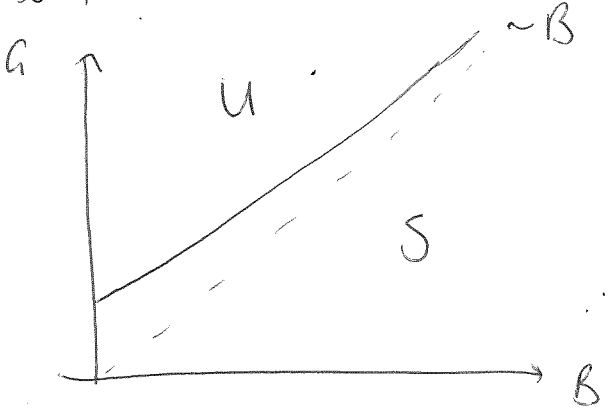
  so real part: ① $\tan\Omega = -\frac{\Omega}{B}$ imaginary part: ② $G = \frac{\Omega}{\sin\Omega}$



① has sol^{n}s $\Omega_1, \Omega_2, \cdots$ with $\Omega_n \in \left[(n-\frac{1}{2})\pi, n\pi\right]$

The corresponding sol^{n} of ② is then $G_n = G(\Omega_n)$

so ~~there are unstable~~



The sol^{n} of ①, ②, can be found. As B gets large $G(B) \sim B$.

Mon 28th

Last time heart rate: Mayer waves caused by an instab when $\tau \sim 5$ and $G \geq B$. We'll see how the instab arises by the end of this lecture. ↑s before showed. Now, for large B ↑s.

Respiratory control

Respiration provides O_2 as a nutrient to cells and removes waste CO_2. ↑s.

by gas exchange in the alveoli within the lung (with the pulmonary capillary bed)

Also:

(LATER) The ventilation $\dot{V}$ is the local time-average of the inspired volume of air per unit time. Normally $\dot{V} \approx 5\,\ell\,\text{min}^{-1}$, with ~12 breaths per minute.

~~Control of the respiratory system is effected by~~

There are 23 generations of branches in the lung with alveoli on the lower 7 branches. The surface area within the lungs is 70 m² so gas-exchange is very fast.

Control of the respiratory system is due to central (in the medulla in the brain stem) and peripheral (in the carotid artery) chemoreceptors which respond to CO_2 (mostly) and O_2.

- The central receptors in the medulla respond to H^+ but effectively to CO_2, via the reaction

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

(HCO_3^-: bicarbonate ions)

in the extracellular brain fluid.

The H^+ ions must be transported to the chemoreceptors, so this control response is slow.

- The peripheral chemoreceptors are outside the brain, mostly at the carotid arteries in the neck. They respond to CO_2 in a similar way, but the response is much faster. They also respond to reduced oxygen levels.

Normal values ~~in the blood~~:

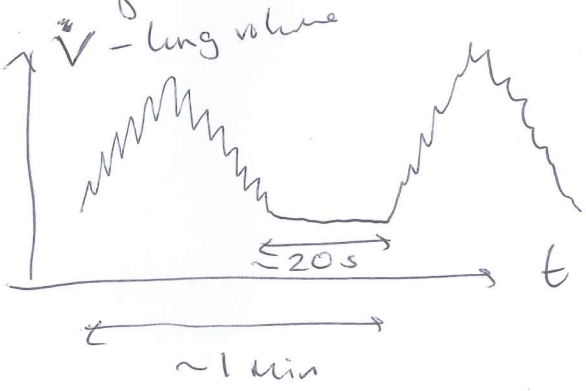
	O_2	CO_2
inspired	150	0
alveoli/arterial	100	40
venous	40	45

(partial pressures in mm Hg)

[(†) Define ventilation here (†)]

Periodic breathing is a regular waxing and waning of the amplitude of breathing (of $\dot{V}$). This occurs in infants and climbers at altitude. In extreme cases there may be an absence of breathing, called apnea, for a short period in this waxing/waning cycle.

One example is Cheyne-Stokes breathing, ~~common~~ seen in stroke ~~patients~~ and, heart-failure patients, and occasionally at high altitude:



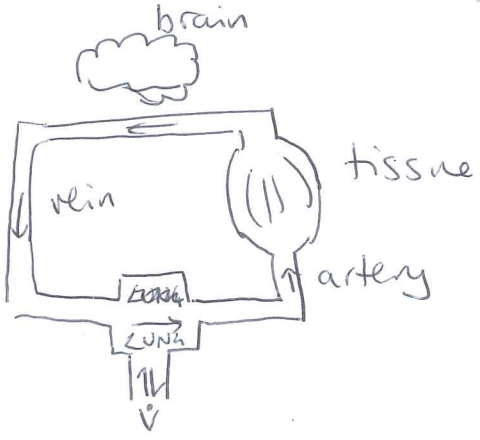
It is anticipated that these periodic breathing patterns are due to an ~~destab~~ oscillatory destabilisation of regular ($\dot{V}$=constant) breathing.

There are several models that investigate this (we'll look at two ~~of~~ over the next 2 lectures)

Mackey-Glass model: A one-compartment model (with the tissue as the compartment).

The single variable is the alveolar (or arterial) CO_2 partial pressure (equivalent to concentration).

ie: $p_{tissue} = p_{artery}$.



Model:

$$K\frac{dP}{dt} = M - P\dot{V}$$

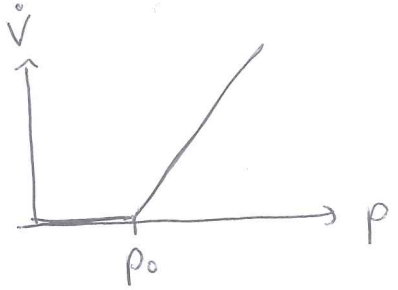
K is the effective compartment volume, P the CO_2 partial pressure. M is the rate of metabolic CO_2 production, $\dot{V}$ is ventilation rate.

By assuming the tissues are the compartment we cannot account for a delay due to the time taken for blood to reach the central controller in the brain. (a limitation of this model)

Set

$$\dot{V} = G_c\left[P(t-\tau) - P_0\right]_+$$

- G_c: gain of the central controller
- τ: delay by time τ ~12s
- P_0: apnea threshold: below this CO_2 pressure there is no breathing.



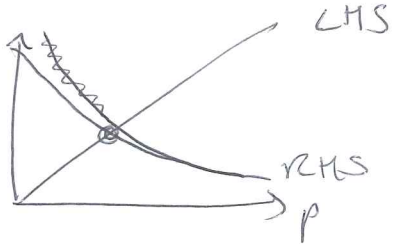
Nondimensionalisation: $t \sim \tau$, $P - P_0 \sim \Delta P = \frac{M}{G P_0}$, $\dot{V} = G\Delta P\, v$

then find

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

here $\alpha = \frac{\tau G_c P_0}{K}$, $\mu = \frac{M}{P_0^2 G_c}$.

Steady state: $p^* = \frac{1}{1+\mu p^*}$ (since $v = p$)



ie: a unique steady state solution with $p^* > 0$.

Linear stability: set $p = p^* + P$, then $\dot{P} = -\beta P - \gamma P_1$

where $\beta = \alpha\mu p^* \approx 0.02$, $\gamma = \alpha(1+\mu p^*) \approx 0.32$

↑ both terms from the $(1+\mu p)v$

Note since $p^* > 0$ $[p^* + P_1]_+ = p^* + P_1$ for sufficiently small P_1

setting $P = e^{\sigma t}$ we find $\boxed{\sigma = -\beta - \gamma e^{-\sigma}}$ (*)

We've seen this eqn before (although now β is small, not large).

Properties of the solution:

(i) $(\sigma+\beta)e^{\sigma}$ has an essential singularity at $\sigma = \infty$, and roots accumulate there.
(not a removable singularity or pole.)

(ii) As $\sigma \to \infty$, $-\left(\frac{\sigma+\beta}{\gamma}\right) = e^{-\sigma} \to \infty$ so $\mathrm{Re}(\sigma) \to -\infty$.

(roots accumulating at the essential singularity are stable)

(iii)

The instability criterion:

Instability occurs for $\gamma > \gamma_c(\beta)$ if $\begin{cases} \sigma = \pm i\Omega & \text{on } \gamma_c \\ \mathrm{Re}(\sigma'(\gamma_c)) > 0 & \text{transversality} \end{cases}$

ie: $\mathrm{Re}(\sigma)$ is increasing over the curve.

- Fixing β, we find $\sigma'(\gamma) = -e^{-\sigma} + \gamma e^{-\sigma}\sigma'$

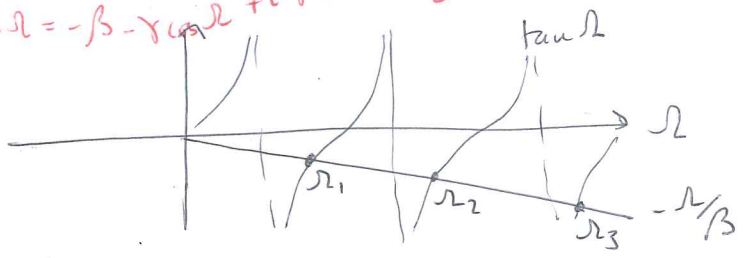
ie: $$\sigma' = \frac{-e^{-\sigma}}{1-\gamma e^{-\sigma}} = \frac{\sigma+\beta}{\gamma(1+\sigma+\beta)}$$

- as before, $\sigma = i\Omega \iff \begin{cases} \Omega = \gamma \sin\Omega \\ \beta = -\gamma\cos\Omega \end{cases}$ (suppose β fixed, then Ω solves)

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

is a root of (*)

$i\Omega = -\beta - \gamma\cos\Omega + i\gamma\sin\Omega$

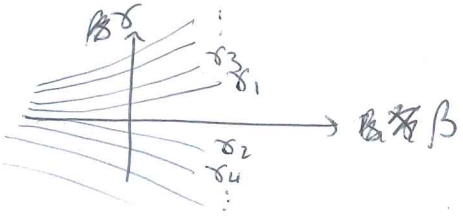


countably many solns $\Omega_n \in \left[(n-\frac{1}{2})\pi, n\pi\right]$.

and then $\gamma_n = \frac{\beta}{-\cos\Omega_n}$

The Ω_n get closer to $(n-\frac{1}{2})\pi$, so that $\cos\Omega_n \to 0$

ie: $\ldots < \gamma_4 < \gamma_2 < 0 < \gamma_1 < \gamma_3 < \ldots$

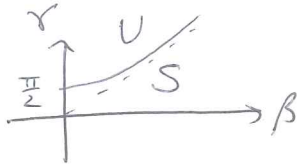


for instability we also need $Re(\sigma'(\gamma)) > 0$

$\sigma' = \dfrac{i\Omega + \beta}{\gamma[1 + i\Omega + \beta]}$ so $Re(\sigma') = \dfrac{\beta(\beta+1) + \Omega^2}{\gamma[(1+\beta)^2 + \Omega^2]}$

note $Re(\sigma'(\gamma)) > 0$ only if $\gamma > 0$

Thus $\forall\, \gamma > \gamma_1(\beta)$, the sol^{n} is unstable



We note that as $\beta \to \infty$, $\Omega \to \pi$ so $\gamma_1 \approx \beta$ (used this for the heart)

But as $\beta \to 0$, $\Omega \to \frac{\pi}{2}$, so $\gamma_1 \to \frac{\pi}{2}$

For our respiratory model, $\beta \sim 0.02$ is small, so instability occurs if $\gamma = \alpha(1 + \mu p^*) = \dfrac{\tau G_c P_0}{K}\left(\dfrac{1}{p_*}\right) \gtrsim \dfrac{\pi}{2}$.

- congestive heart failure $\longrightarrow$ decreased blood flow so τ increases
- stroke $\longrightarrow$ G_c increases
  or high altitude

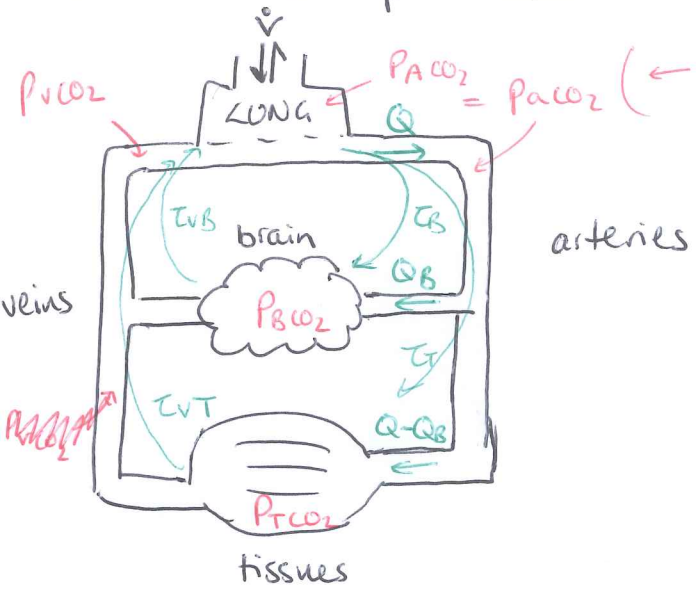
in either case this could lead to instability

The Grodins model

A problem with the Mackey-Glass model is that it confuses the tissue & artery compartments:

- what should K (compartment volume) be?
- no time-delay for blood to reach brain.

The Grodins model consists of more compartments for each of the tissues, brain, alveoli/arteries and veins, and so is more complicated but captures more biology.



($\leftarrow$ arterial CO_2 = alveolar CO_2)

- We suppose there are 4 compartments: arteries, veins, tissues, brain.
- The dependent variables are the partial pressures in each compartment

converting air pressures to blood partial pressure

Model:

conservation of CO_2 in each of arteries, brain, tissue.

vein CO_2 is a weighted average of brain/tissue CO_2, accounting for transport delays.

$$\textcircled{1}\ K_L \dot{P}_{aCO_2} = -\dot{V} P_{aCO_2} + 863\, K_{CO_2} Q \left[P_{VCO_2} - P_{aCO_2}\right]$$

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

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

$$\textcircled{4}\ Q P_{VCO_2} = Q_B P_{BCO_2}(t-\tau_{VB}) + (Q-Q_B) P_{TCO_2}(t-\tau_{VT})$$

Here $\dot{V}$ is ventilation, K are compartment volumes, Q are blood fluxes, τ are delay times, and MR are metabolic rates of CO_2 production.

NB: The Mackey-Glass model is (nearly) the tissue eqn 3

~~is the functional dependence of the ventilation~~ depends on the CO_2 pressures in ~~the system~~ at the central & peripheral controllers. This

~~There is more~~

The ventilation-~~controller~~ $\dot{V}$ may be modelled in several ways ~~depending on whether~~ like that there are more compartments in the model.

It is usually assumed that $\dot{V} = \dot{V}_c + \dot{V}_p$ has contributions from both the central controller, $\dot{V}_c$ (with dependence on ~~the~~ P_{BCO_2}) and the peripheral controller, $\dot{V}_p$ (with dependence on P_{aCO_2}).

Standard values:

delays:		
	τ_{aB}	11 s
	τ_{aT}	19 s
	τ_{vT}	35 s
	τ_{vB}	7 s

Blood fluxes: Q^* 6 l min^{-1}

Q_B^* 0.75 l min^{-1}

Nondimensionalisation:

in steady state, $\frac{①^*}{863} + ② + ③ + ④$, the fluxes all cancel.

In steady state $P_{aCO_2} = P^* = \frac{863}{V^*}\left[MR_{TCO_2} + MR_{BCO_2}\right]$

where $V^* = \dot{V}$ in steady state.

and $P_{vCO_2} = P^*(1+\varepsilon)$

$P_{BCO_2} = P^*(1+\varepsilon a)$

$P_{TCO_2} = P^*(1+\varepsilon b)$

where $\varepsilon = \frac{V^*}{863\, K_{CO_2} Q} \approx 0.2$

$a \approx 1.7$

$b \approx 0.9$.

to motivate the

Use these scalings, ie:

$P_{aCO_2} = P^*(1+\varepsilon p_a)$, $P_{BCO_2} = P^*(1+\varepsilon p_B)$, $P_{TCO_2} = P^*(1+\varepsilon p_T)$

$P_{vCO_2} = P^*(1+\varepsilon p_v)$,

and $\dot{V} = V^* v$, $\tau, t \sim \frac{K_B}{Q_B} \approx 80$s ← the timescale of interest for Cheyne-Stokes breathing

Get:

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

$$\dot{p}_B = a + p_a(t-\tau_{aB}^*) - p_B \quad ②$$

$$\dot{p}_T = s\left[b + p_a(t-\tau_{aT}^*) - p_T\right] \quad ③$$

$$p_v = p_T(t-\tau_{vT}^*) + \delta\left[p_B(t-\tau_{vB}^*) - p_T(t-\tau_{vT}^*)\right] \quad ④$$

where $\delta = \frac{Q_B}{Q} \simeq 0.13$, $\Lambda \approx 11.5$, $s \approx 0.18$

Let $\lambda >> 1$, $\varepsilon << 1$:

① $\Rightarrow$ $\boxed{p_a \approx p_v - v}$ (p_a is in Quasi-equilibrium)

$\delta << 1$: ④ $\Rightarrow$ $\boxed{p_v \approx p_T(t - \tau_{vT}^*)}$ ⋆ (most CO_2 is produced in tissues, not brain)

$\delta << 1$: so p_T varies more slowly than $O(1)$ time.

averaging ③ in time (over a local $O(1)$ time, $\int \dot{p}_T dt = 0$ as p_T indep of $O(1)$ time)

$$\boxed{p_T \approx b + \bar{p}_a}$$

where $\bar{p}_a$ is the average in time of p_a.

Since p_T varies slowly, p_v must vary slowly & the $O(1)$ delay in ④ is irrelevant $\Rightarrow p_v \approx p_T$

Combining: $p_a = p_v - v$

$= p_T - v$

$= (b + \bar{p}_a) - v$

average in time: $\bar{v} = b$

② is then $\dot{p}_B = a + p_a(t - \tau_{aB}^*) - p_B$

$= a + p_T - v(t - \tau_{aB}^*) - p_B$

averaging in time $0 = a + \bar{p}_T - \bar{v} - \bar{p}_B$

($\bar{p}_T = p_T$, $\bar{v} = b$)

so $a + p_T = b + \bar{p}_B$

Thus in ②: $\boxed{\dot{p}_B = (b + \bar{p}_B) - v(t - \tau_{aB}) - p_B}$

(A single eqn for p_B in terms of v. Similar to MG except for the long-time average $\bar{p}_B$)

This has steady state $p_B = a$ (as before).

We assume $b \approx 1$ and use $v = [1 + \gamma(p_B - a)]_+$

where $\gamma = \frac{\varepsilon p^* G}{v^*} = \frac{G p^*}{863 K_{CO_2} Q}$.

so the eqn is

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

linearise about the steady state:

$p_B = a + P$, ~~with $\bar{P} = 0$~~

so $\dot{P} = 1 + \bar{P} - P - \left[1 + \gamma P(t-\tau_{AB}^*)\right]_+$

$= \bar{P} - P - \gamma P(t-\tau_{AB}^*)$ for small enough perturbation P.

Note $\bar{P} = \frac{1}{T}\int_{t=0}^{T} P\,dt$. Setting $P = e^{\sigma t}$ we find

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

↑ we're looking for instability.

ie: even for unstable modes, growth of the average $\bar{P}$ is small, compared with growth of P

↳ reasonable for oscillatory instabilities.

and so $\dot{P} = -\bar{P} - \gamma P(t-\tau_{AB}^*)$

write $P = e^{\Sigma/\tau_{AB}^* t}$ ie $\sigma = \frac{\Sigma}{\tau_{AB}^*}$

then $\boxed{\Sigma = -\tau - \gamma\tau e^{-\Sigma}}$

"β" "γ"

As before (Mackey-Glass)

$\tau \approx 0.2$ is small, so instability for

$$\gamma\tau \gtrsim \frac{\pi}{2}$$

ie:
$$\frac{\tau_{AB} Q_B P^* G}{863\, k_{CO_2} k_B Q} \gtrsim \frac{\pi}{2}$$

Very similar to Mackey-Glass, but now we're happy with what the compartment volume is, and we've been careful in ~~ruling out~~ neglecting unnecessary ~~unrealistic~~ physical phenomena.