

Blood Physiology

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1. Blood physiology

* Blood composition

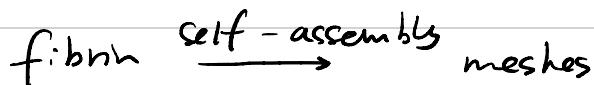
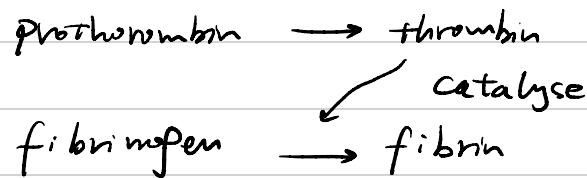
Whole blood consists of several types of cells suspended in plasma.

Blood transports mostly three cell types:

- Red blood cells (erythrocytes) : carry gases (45% in volume in blood)
- White blood cells (leukocytes) : immunological function
- Platelets (thrombocytes) : involved in blood clotting

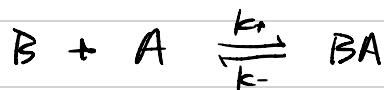
* Blood clotting

When a wound is detected:



* Leukocyte chemotaxis

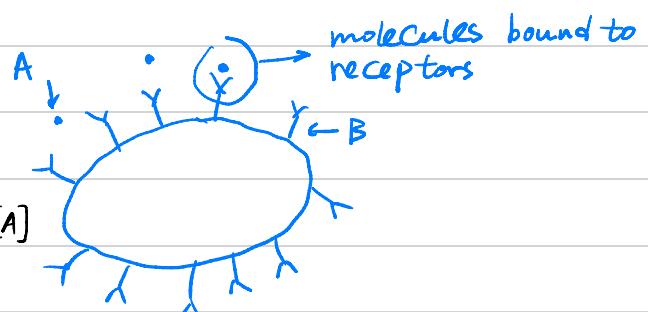
Detecting chemo-attractant through membrane binding sites



B: binding membrane protein

A: chemo-attractant, conc. $\alpha(x) = [A]$

BA: bound membrane protein



Assuming equilibrium:

$$K = \frac{k_+}{k_-} = \frac{[BA]}{[B][A]}$$

Fraction of bound protein:

$$Y = \frac{[BA]}{[B] + [BA]} = \frac{K[A][B]}{[B] + K[A][B]} = \boxed{\frac{a}{K^{-1} + a}}$$

Sensing gradient

The variation of the concentration of bound receptor over the cell size:

$$S = \frac{dR}{dx} R = \frac{dR}{da} \frac{da}{dx} R$$

Cell motility model

$$J_C = J_+ + J_- = v(n_+ - n_-)$$

$$\frac{\partial J_C}{\partial t} = -2J_C p - v^2 \frac{d(n_+ - n_-)}{dx}$$

Assume quasi-steady state:

$$J_C = -\frac{v^2}{2p} \frac{dn}{dx} \quad n = n_+ + n_-$$

Diffusion equation:

$$\frac{dn}{dt} = -\frac{\partial J_C}{\partial x} = \frac{v^2}{2p} \frac{\partial^2 n}{\partial x^2}$$

Biased diffusion model

Turning rates:

$$P_+ = P + \kappa S = P + \chi \frac{da}{dx}$$

$$P_- = P - \kappa S = P - \chi \frac{da}{dx} \quad \chi \text{ is an a priori function of } a$$

$$\Rightarrow \frac{\partial J_C}{\partial t} = -2J_C p - v^2 \frac{dn}{dx} - 2vn\chi \frac{da}{dx}$$

$$\Rightarrow J_C = -\frac{v^2}{2p} \frac{dn}{dx} - \frac{v\chi}{p} \frac{da}{dx} n$$

Additional advection term:

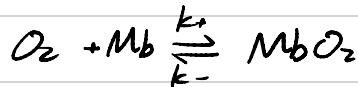
$$U_m = -\frac{v\chi}{p} \frac{da}{dx}$$

The sign of χ controls the behaviour of the cells w.r.t. the gradient

2. Gas transport

* Myoglobin

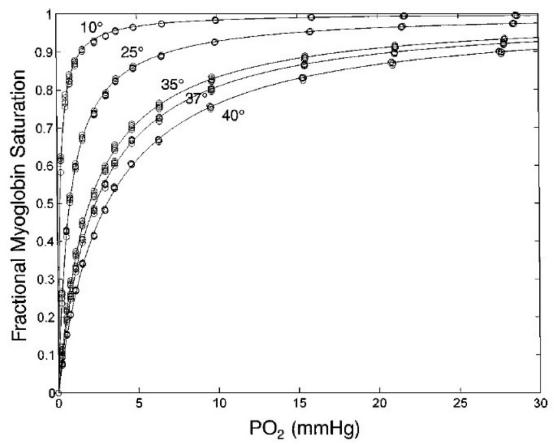
Equilibrium with the bound state



At equilibrium:

$$K(T) = \frac{k_+}{k_-} = \frac{[MbO_2]}{[Mb][O_2]}$$

Myoglobin Saturation Curve



Proportion of bound myoglobin:

$$\gamma = \frac{[MbO_2]}{[Mb] + [MbO_2]} = \frac{[O_2]}{k^{-1} + [O_2]}$$

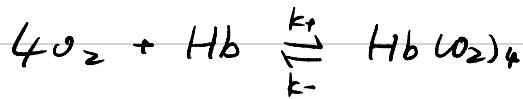
In terms of partial pressure $[O_2] = \alpha P[O_2]$

$$\gamma = \frac{P[O_2]}{K_p^{-1} + P[O_2]}, \quad K_p = \alpha k$$

* Haemoglobin

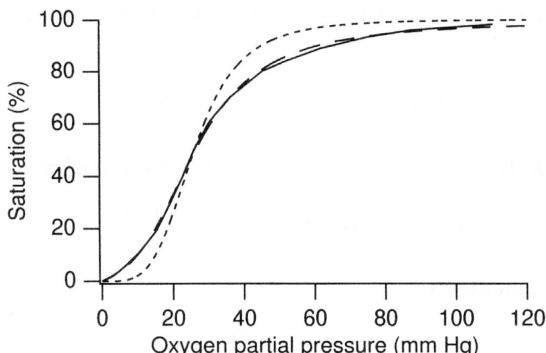
Each haemoglobin can store up to 4 oxygen molecules.

Naive model



At equilibrium:

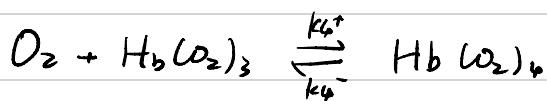
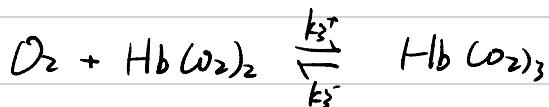
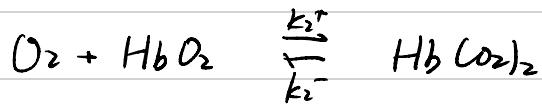
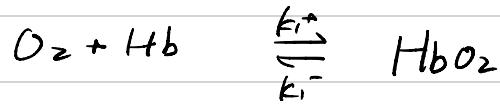
$$K(T) = \frac{k_+}{k_-} = \frac{[Hb(O_2)_4]}{[Hb] + [Hb(O_2)_4]} = \frac{[O_2]^4}{k^{-1} + [O_2]^4}$$



'S' shaped curve

Cooperativity

The affinity to haemoglobin to oxygen depends on the number of sites already occupied:



$$\Rightarrow K_i = \frac{[H_i]}{[H_{i-1}][Hb]} \quad H_i = Hb(O_2)_i, \quad H_0 = Hb$$

$$K_i = \frac{k_i^+}{k_i^-}$$

$$\begin{aligned} \Rightarrow [H_i] &= K_i [H_{i-1}] [O_2] \\ &= \underbrace{\left(\prod_{j=1}^i k_j \right) [Hb] [O_2]^i}_{\alpha_i = 1} = \alpha_i [Hb] [O_2]^i \end{aligned}$$

Total number of sites:

$$N_t = 4 \sum_{i=0}^{i=4} [H_i] = 4 \sum_{i=0}^{i=4} \alpha_i [Hb] [O_2]^i$$

Total number of occupied sites:

$$N_o = \sum_{i=0}^{i=4} i [H_i] = \sum_{i=0}^{i=4} i \alpha_i [Hb] [O_2]^i$$

Saturation function:

$$Y = \frac{N_o}{N_t} = \frac{\sum_{i=0}^{i=4} i \alpha_i [O_2]^i}{4 \sum_{i=0}^{i=4} \alpha_i [O_2]^i}$$

K_4 is much larger than $K_1, K_2, K_3 \rightarrow$ binding to the fourth oxygen molecule is much easier than the binding of the first three ones

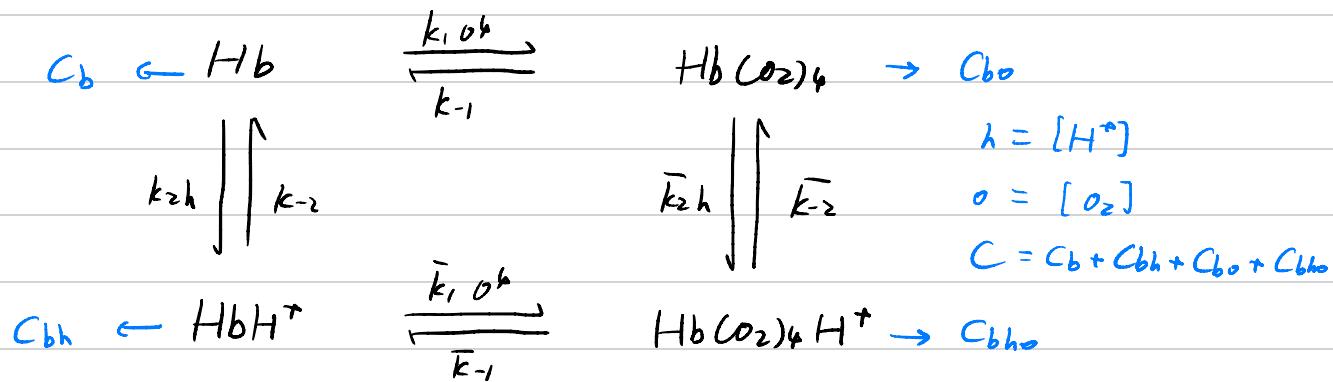
Carbon dioxide poisoning

Haemoglobin has an affinity for carbon dioxide which is 200 times larger than for oxygen \rightarrow even low conc. of CO leads to intoxication by preventing a proper oxygen supply

* Haemoglobin saturation shift due to pH

Allosteric regulation

— the regulation of an enzyme or protein activity on its main site by bonding to another molecule (the effector) on a secondary allosteric site.



$$C_{bo} = K_1 \cdot \sigma^4 C_b$$

$$C_{bh} = K_2 h C_b$$

$$C_{bho} = \bar{K}_1 \cdot \sigma^4 C_{bh} = \bar{K}_1 K_2 \sigma^4 h C_b$$

$$C = (1 + K_2 h + (\bar{K}_1 + \bar{K}_1 K_2 h) \sigma^4) C_b$$

Saturation function:

$$\gamma = \frac{C_{bo} + C_{bho}}{C} = \frac{\sigma^4}{\sigma^4 + K_1 \phi(h)}, \quad \phi(h) = \frac{1 + K_2 h}{1 + \frac{\bar{K}_1}{K_1} K_2 h}$$

- ϕ large \rightarrow late saturation \rightarrow allosteric inhibitor
- ϕ small \rightarrow early saturation \rightarrow allosteric activator

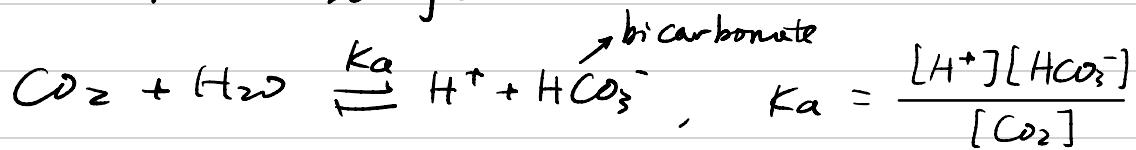
$$\phi(\gamma) = \frac{1 + \gamma}{1 + K\gamma}$$

$$\gamma = K_2 h \quad K = \bar{K}_1 / K_1$$

$K_1 < \bar{K}_1 \rightarrow$ hydrogen is an allosteric inhibitor

\rightarrow CO_2 is the waste product of cell metabolism

* Carbon dioxide storage



Carbon dioxide stored in the blood plasma as bicarbonate ions.

$$= 4.30 \times 10^{-7} \text{ mol L}^{-1}$$

Most of the carbon dioxide stored in RBCs

\rightarrow they contain carbonic anhydrase that accelerates the formation of HCO_3^-

Concentration of CO_2 decreases the pH since it is an acid.

3. Blood rheology

* Rheology introduction

Newtonian fluid: $\tau = \eta \dot{\gamma}$

Elastic: $\tau = G\dot{\gamma}$

τ : shear

$\dot{\gamma}$: shear flow

τ : shear stress

η : viscosity

G : shear modulus

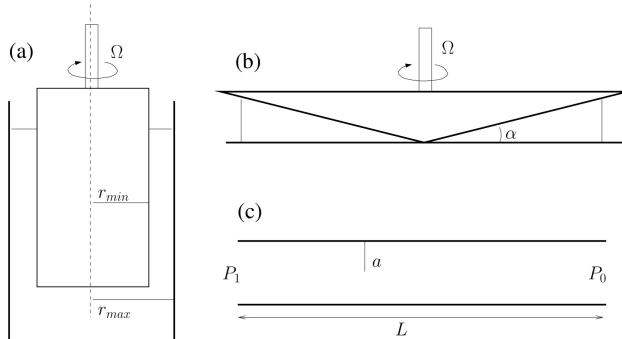
Bingham plastic: $\tau = \tau_0 + \mu \dot{\gamma}$

Power law fluid: $\tau = C\dot{\gamma}^n$

* Rheometry

Couette rheometer

$$\dot{\gamma} = \frac{\Omega r_{max}}{r_{max} - r_{min}}$$



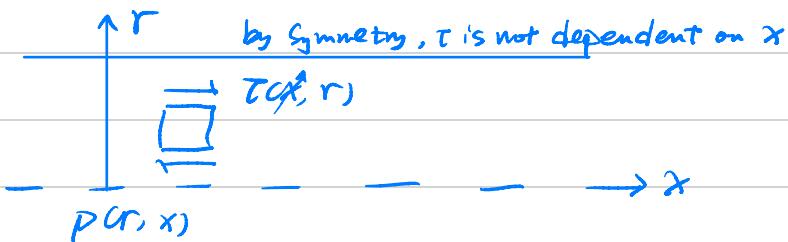
Cone-plate rheometer

$$\dot{\gamma} = \frac{\Omega r}{\alpha r} = \Omega/\alpha$$

Pipe flow rheometer

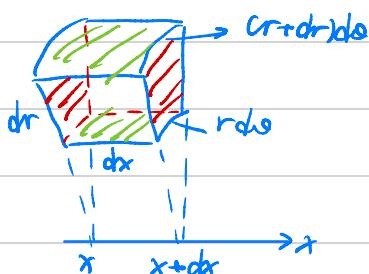
- analysis can be found below

* Pipe flow



$$\cancel{\sum F} = 0$$

$\leftarrow x$ direction

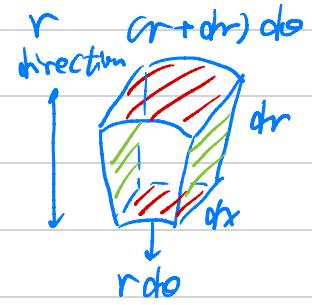


$$* p(x, r) dr r d\theta - p(x+dx, r) dr r d\theta$$

$$* -\tau(x, r) dr r d\theta + \tau(x, r+dr) dx (r+dr) d\theta = 0$$

Dividing by $dr dr d\theta$

$$\Rightarrow -\frac{dp}{dx} r + \frac{d(\tau r)}{dr} = 0$$



$$* P(r, r) r dr - P(r, r+dr) (r+dr) dr \approx 0$$

$$* + P(r, r) dr dr \sin\left(\frac{\theta}{2}\right) \times 2 \approx 0$$

Dividing by $dr \sin\theta$

$$-\frac{d(P_r)}{dr} + P = 0$$

$$-P \frac{dr}{dr} - r \frac{dP}{dr} + P = 0$$

$$\Rightarrow \boxed{\frac{dP}{dr} = 0}$$

For Newtonian fluid: $\tau = \mu \frac{du}{dr}$

$$\frac{dP}{dr} = \mu \frac{1}{r} \frac{d}{dr} \left(r \frac{du}{dr} \right)$$

$$\frac{d}{dr} \left(r \frac{du}{dr} \right) = \frac{1}{\mu} \frac{dp}{dr} r$$

$$r \frac{du}{dr} = \frac{1}{\mu} \frac{dp}{dr} \frac{1}{2} r^2 + C$$

$$u = \frac{1}{\mu} \frac{dp}{dr} \frac{1}{4} r^2 + C \ln r + D$$

* No-slip boundary condition $u(a) = 0$

$$u(r) = \frac{r^2 - a^2}{4\mu} \frac{dp}{dr} \quad \text{and} \quad \tau(r) = \mu \frac{du}{dr} = \frac{r}{2} \frac{dp}{dr}$$

$$Q = \int_0^a 2\pi r c u dr = \frac{\pi a^4}{8\mu} \frac{P(a) - P(L)}{L}$$

$$Q = \frac{A^2}{8\pi\mu} \frac{P(a) - P(L)}{L} \quad \text{with } A = \pi a^2$$

* Plasma rheology



Rigid particle suspended in a fluid cause an increase of the viscosity.

$$\dot{\gamma}_{\text{eff}} = \frac{v}{L_{\text{fluid}}} = \frac{v}{L(1-\phi)} = \dot{\gamma}/(1-\phi) \approx \dot{\gamma}(1+\phi)$$

$$\tau = \mu_0 \dot{\gamma}_{\text{eff}} = \mu_{\text{eff}} \dot{\gamma}, \quad \mu_{\text{eff}} = (1+\phi) \mu_0$$

μ_0 : water viscosity

ϕ : volume fraction occupied by the particles ($\phi \ll 1$)

$\dot{\gamma} = v/L$: imposed shear rate

Einstein relationship: $\mu = \mu_0 (1 + 2.5\phi)$

(valid for conc. up to 20%)

* Whole blood rheology

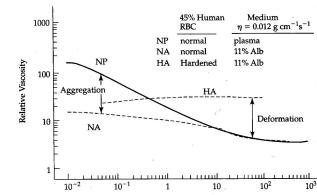
Hematocrit: proportion of blood volume that is occupied by red blood cells, noted Hct. (normal value $\sim 40 \pm 5\%$)

* Red blood cell deformation/aggregation

Red blood cells are soft and have the ability to adhere to each other.

- Aggregation takes a time of the order of a second to be significant
→ occurs at low shear rates
- Deformations requires large shear stress to be significant
→ dominant at large shear rates

Blood is shear-thinning



* Flow in large vessels

$$T_g \approx C_{fg}^2 (Hct - Hct_c)^3$$

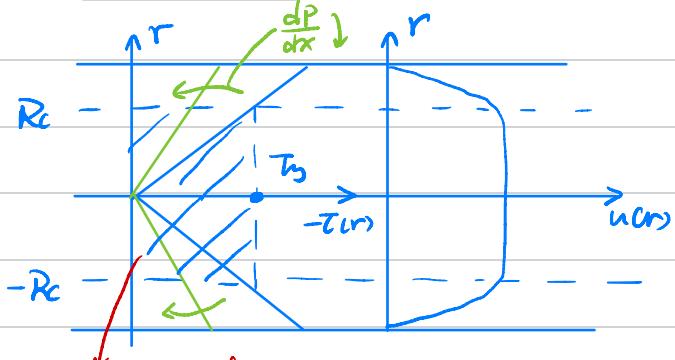
↓ ↓
a Constant the critical value of the RBC concentration
influenced by conc. at which shear stress appears
of multiple components

Casson equation:

$$|\tau|^k = T_g^k + \mu^{1/2} |\dot{\gamma}|^{1/2}$$

μ is the effective viscosity
→ depends on Hct

Derivation



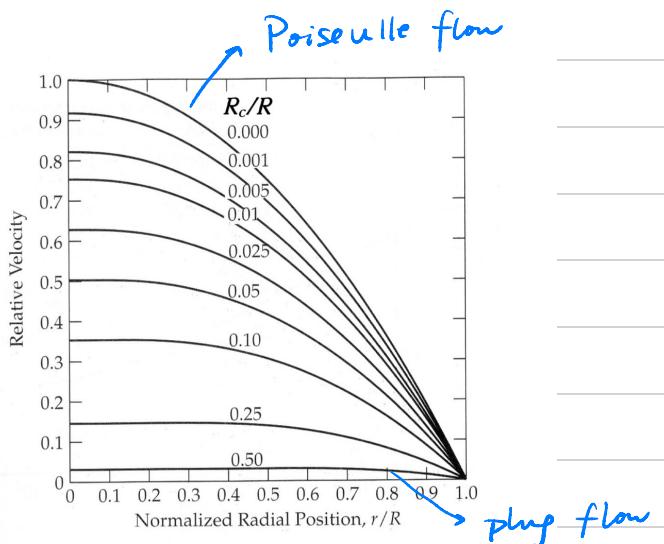
no shear flow in this region

$$\frac{1}{r} \frac{d(r\tau)}{dr} = \frac{dp}{dx}$$

$$\frac{d(r\tau)}{dr} = \frac{dp}{dx} r$$

$$r\tau = \frac{1}{2} \frac{dp}{dx} r^2 + C$$

$$\Rightarrow \tau = \frac{1}{2} \frac{dp}{dx} r$$



From Casson equation $\dot{\gamma} = 0$ if $|\tau| < T_g$

→ shear flow is only possible in the region $r > R_c$

critical radius $R_c = -2T_g \left(\frac{dp}{dx} \right)^{-1}$

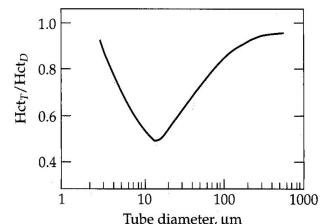
- At low flow rates (low shear stress), $\dot{\gamma}$ strongly influence flow profile
→ flow concentration near the vessel walls → \approx plug flow
- At high flow rates (high shear stress) → Poisenille flow

* Small vessels and Capillaries

Fahrems effect

— mismatch between two different measurements of the hematocrit of a blood sample flowing through a capillary.

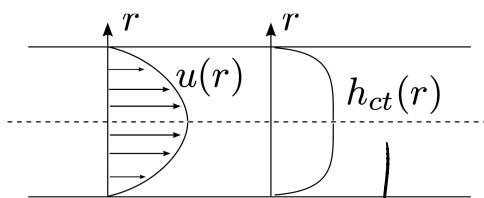
Tube hematocrit Hct_T vs discharge hematocrit Hct_D



Expressions for Hct_T and Hct_D

$$Hct_T = \frac{\int_0^a 2\pi r hct(r) dr}{\pi a^2}$$

$$= \langle hct(r) \rangle$$



local hematocrit

near the vessel wall hct is lower

$$Hct_D = \frac{\int_0^a 2\pi r hct(r) u(r) dr}{\int_0^a 2\pi r u(r) dr}$$

$$= \frac{\text{flux of RBC}}{\text{flux of fluid}}$$

Fahrems - Lindquist effect

- Depletion of RBC near the vessel wall decrease locally the viscosity and concentrates the shearing
→ apparent decrease in effective viscosity as vessel diameter decreases
- However, when vessel diameter gets closer to the RBC size, the apparent viscosity increases again
→ the RBCs have to line up in the tube and get deformed during progression

