Version AK/2

EGT2
ENGINEERING TRIPOS PART IIA

Friday 28 April 2017 9.30 to 11

Module 3G2

MATHEMATICAL PHYSIOLOGY

*Answer not more than **three** questions.*

All questions carry the same number of marks.

*The **approximate** percentage of marks allocated to each part of a question is indicated in the right margin.*

*Write your candidate number **not** your name on the cover sheet.*

STATIONERY REQUIREMENTS
Single-sided script paper

SPECIAL REQUIREMENTS TO BE SUPPLIED FOR THIS EXAM
CUED approved calculator allowed
Supplementary pages: Three copies of Figure 1 (Question 1)
Engineering Data Book

10 minutes reading time is allowed for this paper.

You may not start to read the questions printed on the subsequent pages of this question paper until instructed to do so.

1 (a) Consider the following model for oxygen binding to haemoglobin:

$$4O_2 + Hb \underset{k_-}{\overset{k_+}{\rightleftharpoons}} Hb(O_2)_4$$

Find an analytical expression for the haemoglobin saturation curve. Sketch its graph as a function of the concentration of oxygen. What are the limitations of this model? [35 %]

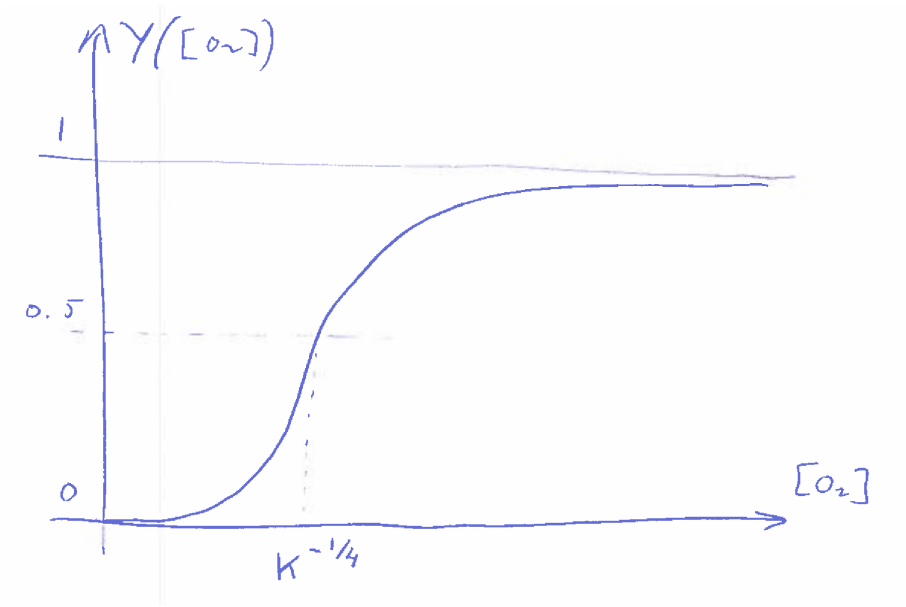
Answer: At the equilibrium, we have the following relationship:

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

The saturation curve is defined by:

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

The curve should show the "S" shape of the curve, with a slope 0 at low oxygen concentration as $Y([O_2]) \propto [O_2]^4$ in this regime. The asymptote should be $Y = 1$ for large oxygen concentrations, and ideally indicate that the curve intercepts 0.5 when $[O_2] = K^{-1/4}$.



The model assumes that all four oxygen molecules bind haemoglobin at the same time, which is not correct, but qualitatively the s-shape curve that is observed experimentally. It might be a suitable approximation to study the effect of other parameters on the saturation curves. Accounting for cooperativity effects is however required to get a close match with the data.

(b) We now consider the role of 2,3-bisphosphoglycerate (BPG), a small molecule that is a by-product of the metabolic activity of the cells, on the binding of oxygen to

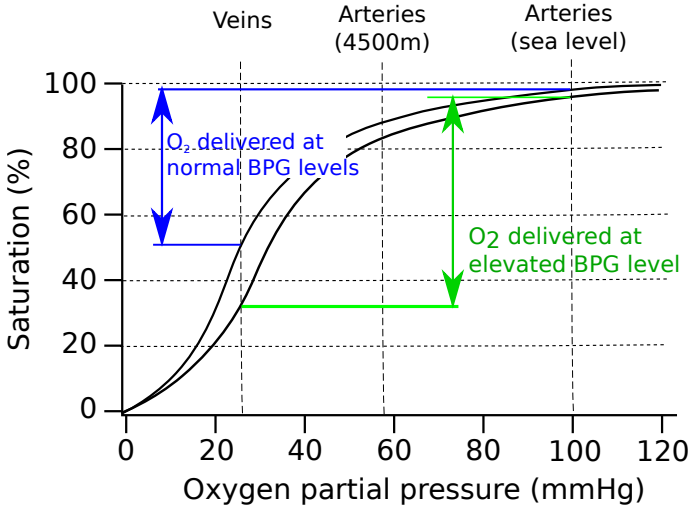
haemoglobin. Figure 1 shows the saturation curves of haemoglobin under normal and elevated BPG levels. Typical values of the oxygen partial pressure in veins and arteries are indicated on the graph. Additional copies of figure 1 are attached to the exam paper. Students may use them to support their answers to the following questions.

(i) Determine if BPG is an activator or inhibitor of oxygen binding. Using the model introduced in part (a), provide an estimate of $\frac{k_+}{k_-}$ for normal and elevated levels of BPG. The solubility of oxygen in blood at body temperature is: $\sigma = 1.36 \cdot 10^{-6}$ Molar / mmHg. [20%]

Answer: For a given partial pressure of oxygen, less is bound to haemoglogin under elevated levels of BPG. It is therefore an inhibitor of oxygen binding.
Using the model of part (a), we have $Y([O_2] = 0.5$ when $K = \frac{k_+}{k_-} = [O_2]^{-4} = (\sigma P(O_2))^{-4}$
For normal levels of BPG, we have $Y([O_2] = 0.5$ for $P(O_2) \approx 25$mmHg, i.e. $[O_2] \approx 3.5 \cdot 10^{-5}$ Molar.
Hence $K \approx 6 \pm 1 \cdot 10^{17}$.
For elevated levels of BPG, we have $Y([O_2] = 0.5$ for $P(O_2) \approx 30 - 35$mmHg. We can take $[O_2] \approx 4.5 \cdot 10^{-5}$ Molar as an approximate value. Hence $K \approx 2.5 \pm 1 \cdot 10^{17}$.

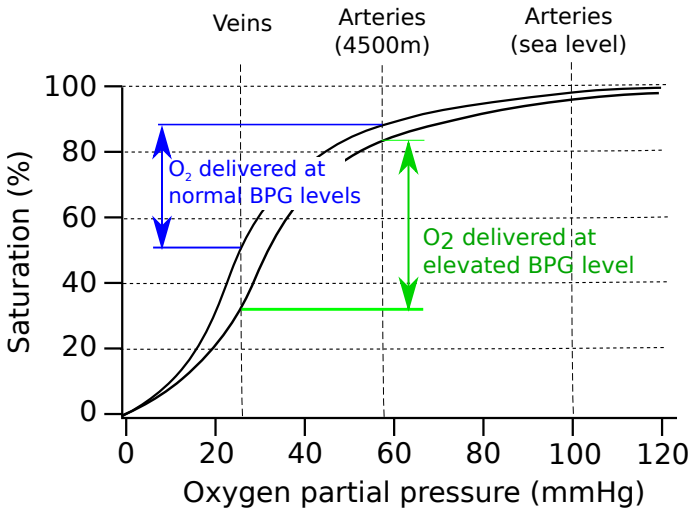
(ii) During intense exercise, BPG is naturally produced by the tissues. How would this affect the release of oxygen in the tissues? [15%]

Answer: The figure below shows how much oxygen is released to the tissues under normal and elevated levels of BPG. Elevated BPG levels increase the release from 50% to 65-70%, which is beneficial in case of intense exercise.



(iii) People who live at high altitude, where the partial pressure of oxygen is reduced, tend to produce higher levels of BPG. Explain how this contributes to the proper oxygenation of the tissues. [15%]

Answer: The figure below shows that at normal BPG level the amount of oxygen captured in altitude is diminished by about 10%. Higher BPG levels allow the body to recover the 50% obtained at normal altitude and BPG levels.



(iv) Pregnant women tend to have higher levels of BPG while foetal haemoglobin has a limited response to BPG. Is this beneficial for the developing foetus and/or the mother? Explain your answer. [15%]

Answer: In the placenta, oxygen needs to be transferred from the mother's haemoglobin to the foetus' haemoglobin. Elevated BPG levels improve this transfer by about 20%, which is beneficial for the foetus. This is also beneficial for the mother at it improves oxygen release in other tissues. Overall, elevated BPG levels increase the oxygen capacity to compensate for the increased demand in the mother's body.

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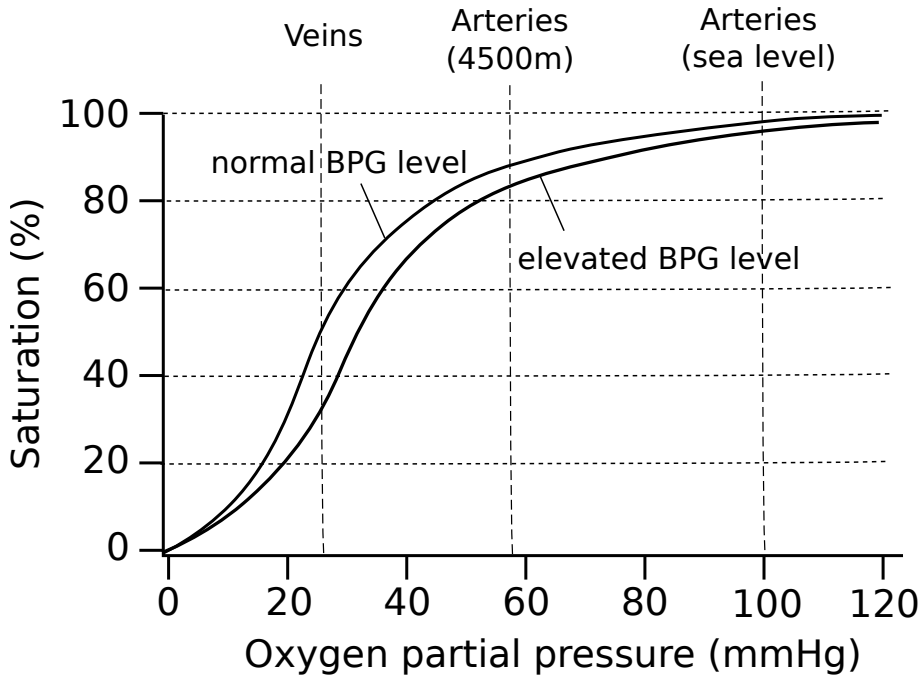

Veins
Arteries
(4500m)
Arteries
(sea level)
100
80
60
40
20
0
Saturation (%)
normal BPG level
elevated BPG level
0
20
40
60
80
100
120
Oxygen partial pressure (mmHg)

Fig. 1

2 A cylindrical vessel of radius R and length L is subjected to a constant pressure difference ΔP between entrance and exit points ($\Delta P > 0$). The position along the vessel is x, increasing in the direction of the flow. The radial distance is r. $p(r,x)$ is the blood hydrostatic pressure. $u(r)$ is the blood velocity. $\tau(r)$ is the blood shear stress.

Force balance on a fluid element provides the following equations:

$$-\frac{\partial p}{\partial x} + \frac{1}{r}\frac{\partial (r\tau)}{\partial r} = 0$$

$$\text{and} \quad \frac{\partial p}{\partial r} = 0$$

(a) We consider a non-Newtonian fluid that has a yield stress τ_y.

(i) Express the shear stress $\tau(r)$ as a function of ΔP, L and r. [15%]

Answer: $\frac{\partial p}{\partial r} = 0$ implies that p is a function of x only. The first equation can therefore be solved by separation of variables:

$$\frac{\partial p}{\partial x} = \frac{1}{r}\frac{\partial (r\tau)}{\partial r}$$

where $\frac{\partial p}{\partial x}$ is a constant, $\frac{\partial p}{\partial x} = -\frac{\Delta P}{L}$, taking as requested $\Delta P > 0$, i.e. pressure at the start - pressure at the end.

$$\frac{\partial (r\tau)}{\partial r} = -r\frac{\Delta P}{L}$$

$$r\tau = -\frac{1}{2}r^2\frac{\Delta P}{L} + C$$

$$\tau = -\frac{1}{2}r\frac{\Delta P}{L} + \frac{C}{r}$$

Because the shear stress must be finite at the centre of the vessel, we have $C = 0$.

$$\tau = -\frac{1}{2}r\frac{\Delta P}{L}$$

(ii) Find an expression for the pressure difference ΔP_c required to start a flow in the vessel. [15%]

Answer: Flow starts when the shear stress reaches the yield shear stress somewhere in the vessel. Due to the form of the shear stress profile, this would happen here on the boundary.

$$|\tau(R)| = \tau_y \implies \frac{1}{2}R\frac{\Delta P_c}{L} = \tau_y$$

$$\Delta P_c = \frac{2\tau_y L}{R}$$

(b) Figure 2 shows the rheological data for blood in physiological conditions, where $\dot{\gamma}$ represents the shear rate. Establish a phenomenological relationship between the shear

stress and the shear rate that is consistent with these data. Explain the physical meaning of any constant introduced in the relationship and provide their approximative values. [15%]

Answer: $\sqrt{\tau}$ is an affine function of $\sqrt{\dot{\gamma}}$. Since both quantities are defined in the positive domain, we have:

$$\sqrt{\tau} = A + B\sqrt{\dot{\gamma}}$$

If $\sqrt{\tau} < A$, no flow can occur, therefore A^2 is essentially the yield stress τ_y of the fluid.
When $\dot{\gamma}$ is very large, we have $\sqrt{\tau} \approx B\sqrt{\dot{\gamma}}$. Hence, B^2 acts as the effective viscosity μ of the material at large shear rate.
In summary, we could write the relationship as:

$$\sqrt{|\tau|} = \sqrt{\tau_y} + \sqrt{\mu}\sqrt{|\dot{\gamma}|}$$

We read on the graph that $A \approx 2$ mPa$^{0.5}$. Hence $\tau_y \approx 4$ mPa.
Likewise, $B \approx (33 \pm 2/20$ (mPa s)$^{0.5}$. Hence $\eta \approx 2.7 \pm 0.3$ mPa s.

(c) Show that the velocity profile $u(r)$ satisfies the following differential equation in any region where $\frac{du}{dr} \neq 0$:

$$\frac{du}{dr} = K\left(r - 2\sqrt{R_c r} + R_c\right)$$

Find the expressions of K and R_c in the above equation. What happens if $R_c > R$? [40%]

Answer:
We start from the constitutive equation of the fluid, valid in the case where $\tau > \tau_y$:

$$\sqrt{|\tau|} = \sqrt{\tau_y} + \sqrt{\mu}\sqrt{|\dot{\gamma}|}$$

and the expression of the shear stress:

$$\tau = -\frac{1}{2} r \frac{\Delta P}{L}$$

Since τ and $\dot{\gamma} = \frac{du}{dr}$ negative here, we have

$$\sqrt{-\tau} = \sqrt{\tau_y} + \sqrt{\mu}\sqrt{-\frac{du}{dr}}$$

which can also be rearranged to isolate the term we care about, $\frac{du}{dr}$.

$$\sqrt{\mu}\sqrt{-\frac{du}{dr}} = \sqrt{-\tau} - \sqrt{\tau_y}$$

We can then square the whole expression:

$$-\mu\frac{du}{dr} = -\tau + \tau_y - 2\sqrt{-\tau\tau_y}$$

$$\mu \frac{du}{dr} = -\frac{1}{2} r \frac{\Delta P}{L} - \tau_y + 2\sqrt{\frac{1}{2} r \frac{\Delta P}{L} \tau_y}$$

By analogy with the expression to obtain, we see that K must be equal to:

$$K = -\frac{1}{2\mu} \frac{\Delta P}{L}$$

Factorising K in the expression for $\frac{du}{dr}$, we get:

$$\frac{du}{dr} = K \left(r + \frac{-\tau_y}{-\frac{\Delta P}{2L}} + 2\sqrt{r} \frac{\sqrt{\frac{1}{2}\frac{\Delta P}{L}\tau_y}}{-\frac{\Delta P}{2L}} \right)$$

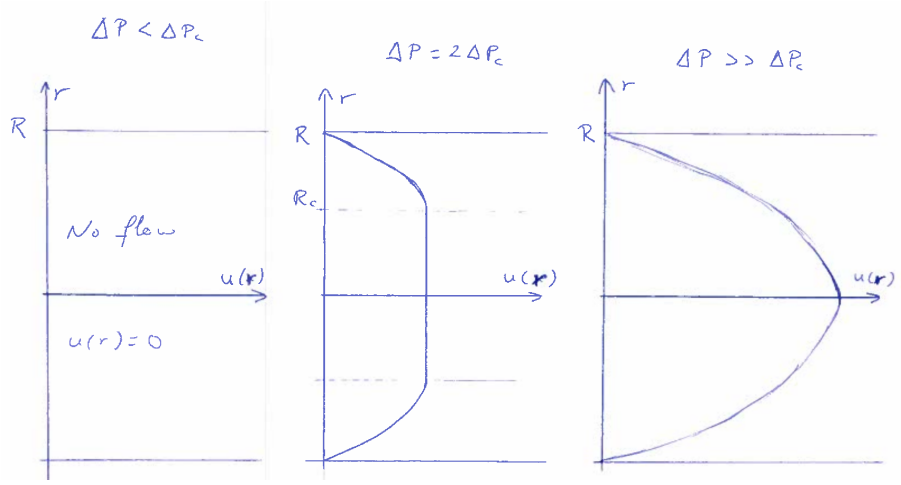
This allows us to find $R_c = \frac{2\tau_y L}{\Delta P}$

If $R_c > R$, then the shear stress at the wall is less than the yield stress and no flow occurs.

(d) Sketch the flow profiles for the following cases:

- $\Delta P < \Delta P_c$,
- $\Delta P = 2\Delta P_c$,
- $\Delta P \gg \Delta P_c$. [15%]

Answer:



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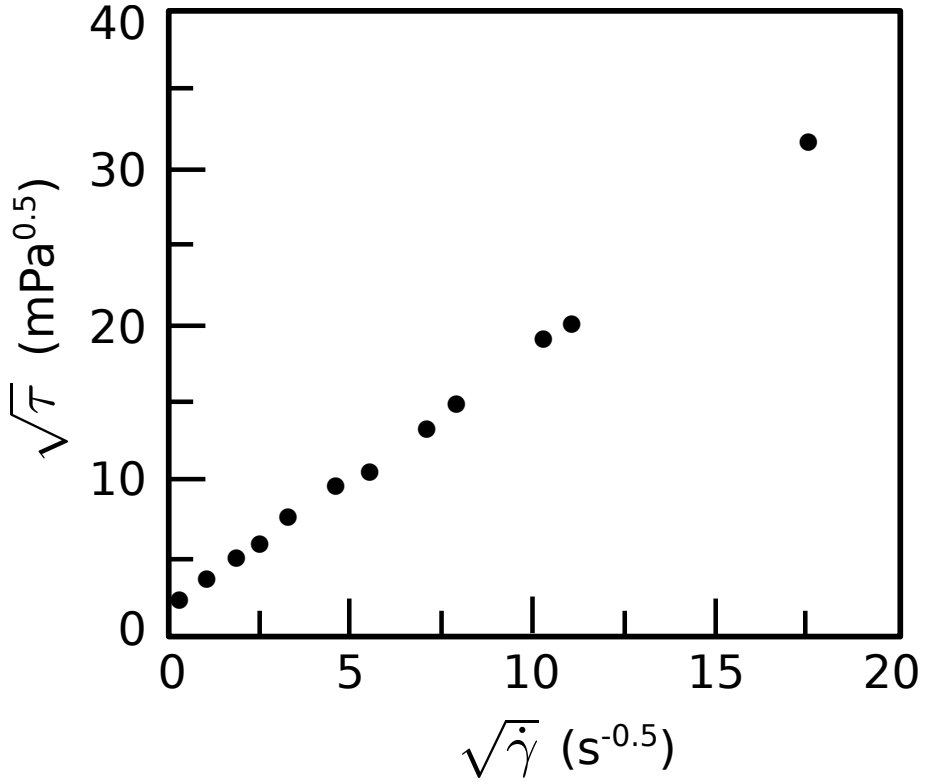

Fig. 2

3 Figure 3 represents a single alveolus and a blood capillary in contact with it. Numerical values relevant to the question are given above the figure.

(a) What is the concentration c_b^0 of carbon dioxide (CO_2) in the blood arriving in the lungs? What is the concentration c_g of CO_2 in the blood after it equilibrates with the CO_2 partial pressure in the alveolus P_g? [10%]

Answer: We just need to use the solubility σ to relate these quantities: $c_b^0 = \sigma P_i = 1.5mM$ and $c_g = \sigma P_g = 1.3mM$.

(b) In blood, pH is roughly constant and equal to 7.4. Consider the equilibrium between CO_2 and the bicarbonate ion HCO_3^-:

$$CO_2 + H_2O \underset{k_-}{\overset{k_+}{\rightleftharpoons}} H^+ + HCO_3^-$$

Show that the concentration c_d of bicarbonate is proportional to the concentration c_b of CO_2. Find the expression of $K = c_d/c_b$ as a function of the constants k_+, k_- and $[H^+]$. [20%]

Answer: At the equilibrium, we have:

$$\frac{k_+}{k_-} = \frac{[H^+][HCO_3^-]}{[CO_2]}$$

Hence: $K = \frac{k_+}{[H^+]k_-}$

(c) Find an expression for the flux per unit area of CO_2 through the alveolar epithelium as a function of the concentration of CO_2 in the blood (c_b), the partial pressure in the alveolus (P_g), the thickness of the epithelium (d_e), the solubility of CO_2 (σ), and the diffusion constant of CO_2 in the epithelium (D_e). [20%]

Answer: We consider first the flux through the layer is (Fick's law):

$$\phi = \frac{D_e}{d_e}(c_g - c_b)$$

where c_g is the concentration of CO_2 at the interface between the alveolus epithelium and the gas. The concentration at the interface is at equilibrium with the gas, so $c_g = \sigma P_g$

$$\phi = \frac{D_e}{d_e}(\sigma P_g - c_b)$$

(d) The distance along the capillary is x, taking as the origin the location where the capillary comes in contact with the alveolar epithelium (see figure 3). The capillary cross-sectional area is uniform and can be approximated by d_a^2. The arc length of the capillary cross-section that is in contact with the epithelium is about d_a. Show that the concentration of CO_2 along the capillary satisfies the following differential equation:

$$v(1+K)\frac{dc_b}{dx} = \frac{D_e}{d_a d_e}(\sigma P_g - c_b)$$

[35%]

Answer:

This question may in answered in different ways, either (i) following a lump of blood over time, finding $c_b(t)$, and then expressing it as a function of x, or (ii) using CO_2 conservation for a small length dx, accounting for all possible forms of CO_2 dissolved. We present here the former.

Following a lump of blood moving along the capillary, we have:

$$\frac{dc_b}{dt} = \frac{D_e}{d_a d_e}(\sigma P_g - c_b) + k_- h c_d - k_+ c_b$$

$$\frac{dc_d}{dt} = k_+ c_b - k_- h c_d$$

$$\frac{d}{dt}(c_b + c_d) = \frac{D_e}{d_a d_e}(\sigma P_g - c_b)$$

$$(1+K)\frac{dc_b}{dt} = \frac{D_e}{d_a d_e}(\sigma P_g - c_b)$$

Expressed now in the frame of the blood vessel ($\frac{dc_b}{dt} = v\frac{dc_b}{dx}$):

$$v(1+K)\frac{dc_b}{dx} = \frac{D_e}{d_a d_e}(\sigma P_g - c_b)$$

(e) Sketch $c_b(x)$. Using the fact that at 37°C, $k_+/k_- = 8 \cdot 10^{-7}$ mol L^{-1} and pH = 7.4, determine if gas exchange is complete by the time blood leaves the alveolus. [15%]

Answer: The solution of the equation is a simple exponential, starting at c_b^0 and reaching asymptotically c_g:

$$c_b = c_g + (c_b^0 - c_g)\exp(-x/\lambda)$$

The decay length λ is:

$$\lambda = \frac{d_a d_e}{D_e} v(1+K)$$

Numerically, we get $\lambda \approx 125$ μm, which is slightly less than $2\pi R_a$.

The relevant parameters are:

Average alveolus radius	R_a	50 μm
Epithelium thickness	d_e	1 μm
Diffusion coefficient of CO_2 in the epithelium	D_e	$2.5 \cdot 10^{-5}$ cm^2 s^{-1}
Partial pressure of CO_2 in blood arriving in the lung	P_i	45 mmHg
Solubility of CO_2	σ	$3.3 \cdot 10^{-5}$ Molar / mmHg
Partial pressure of CO_2 in the alveolus	P_g	40 mmHg
Average blood speed in the capillary	v	3 mm s^{-1}
Capillary diameter	d_a	5 μm

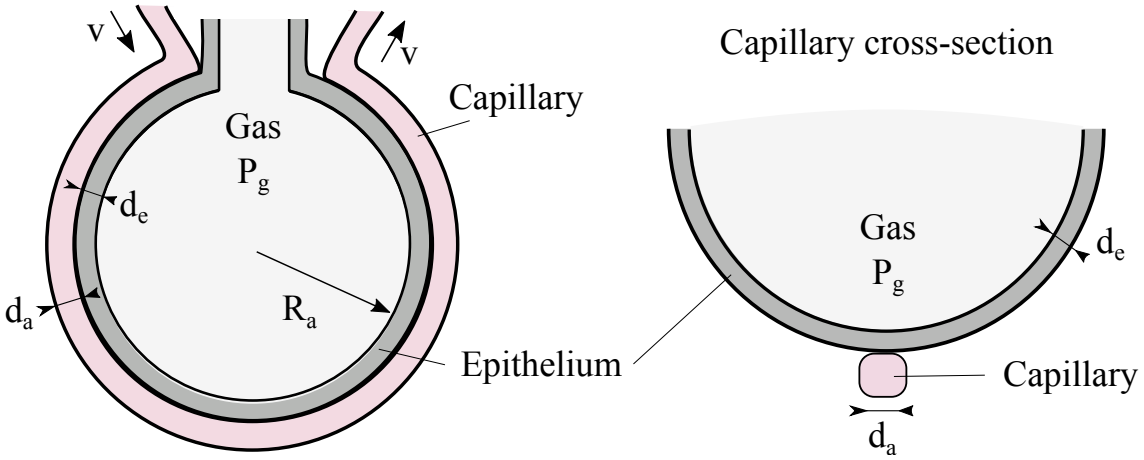

Fig. 3

4 (a) Consider a single-compartment model of a cell with capacitance C and three Ohmic transmembrane conductances, g_1, g_2, g_3 with reversal potentials E_1, E_2, E_3. Derive expressions for the membrane time-constant and the resting membrane potential of the cell. [30%]

Answer: The membrane equation for a single compartment is:

$$C\frac{dV}{dt} = \sum_i g_i(E_i - V) = -V\sum_i g_i + \sum_i g_i E_i$$

Therefore

$$\frac{C}{\sum_i g_i}\frac{dV}{dt} = -V + \frac{\sum_i g_i E_i}{\sum_i g_i}$$

Thus the membrane time constant is $\frac{C}{\sum_i g_i}$. Setting $\frac{dV}{dt} = 0$ gives the resting membrane potential:

$$V_{rest} = \frac{\sum_i g_i E_i}{\sum_i g_i}$$

(b) *Cortical spreading depression* (CSD) is a pathological condition in which sustained neuronal depolarization spreads across a large population of neurons in the brain. The mechanism is thought to involve accumulation of extracellular potassium, followed by subsequent release of additional potassium from neurons in nearby tissue.

(i) With reference to relevant terms in the Nernst Equation, explain why extracellular potassium accumulation would lead to neuronal depolarization. [20%]

Answer: The Nernst equation shows how the reversal potential of an ion species depends on its relative intracellular and extracellular concentrations:

$$E_{ion} = \frac{RT}{zF}\ln(\frac{c_e}{c_i})$$

where c_e, c_i are the extracellular and intracellular concentrations of the ion species and z is the valence. For K^+, $z = 1$ and $c_i >> c_e$, so $E_K < 0$ (typically $E_K \approx -90$ mV). An increase in c_e will *depolarize* E_K. Since *the resting potential of a neuron is dominated by* E_K, an increase in extracellular K^+ will depolarise the resting potential.

(ii) Suggest why membrane depolarization might result in further release of potassium from neurons. [10%]

Answer: Much of the potassium conductance in a neuron is *voltage-gated* (depolarization-activated) and *non-inactivating*. *Depolarization* results in *opening* of potassium channels, leading to an *outward* potassium current, which, if sufficiently large and sustained will *increase* the extracellular potassium.

(iii) CSD results in a transient *loss* of action potential activity in the affected region. What mechanism might explain this? [10%]

Answer: Action potentials depend on sodium currents which *inactivate* when subjected to continuous depolarization. Thus, CSD could cause widespread sodium channel inactivation and loss of spiking activity.

(c) (i) *Retrograde* action potentials travel in the opposite direction along axons to normal action potentials (i.e. toward the cell body). Explain what would happen if a normal action potential were to collide with a retrograde action potential. [10%]

Answer: Action potential propagation depends on sodium channels being in a *de-inactivated* state (i.e. system is not in absolute refractory period). As the action potential moves along an axon, it transiently inactivates sodium channels in its wake. Thus, if two action potentials were to collide, they would *annihilate*.

(ii) Figure 4 shows an action potential waveform and the accompanying sodium and potassium currents in the Hodgkin-Huxley squid giant axon model. Currents are plotted with the usual sign convention (negative = inward). Explain the origin of the kink (*) in the sodium current waveform. [20%]

Answer: The upward phase of the kink is due to the fact that *the membrane potential approaches the sodium reversal potential*, leading to a decrease in driving force and a transient *decrease in sodium current*. The downward phase coincides with the repolarizing effect of the *delayed* (slower-activating) potassium current (as can be seen in the action potential waveform), which evidently occurs before substantial sodium channel inactivation.

For parts (b) and (c) the following table may be useful.

Typical intracellular and extracellular ionic concentrations		
Ion	Intracellular concentration (mM)	Extracellular concentration (mM)
Na^+	10	150
K^+	145	5
Cl^-	4	110

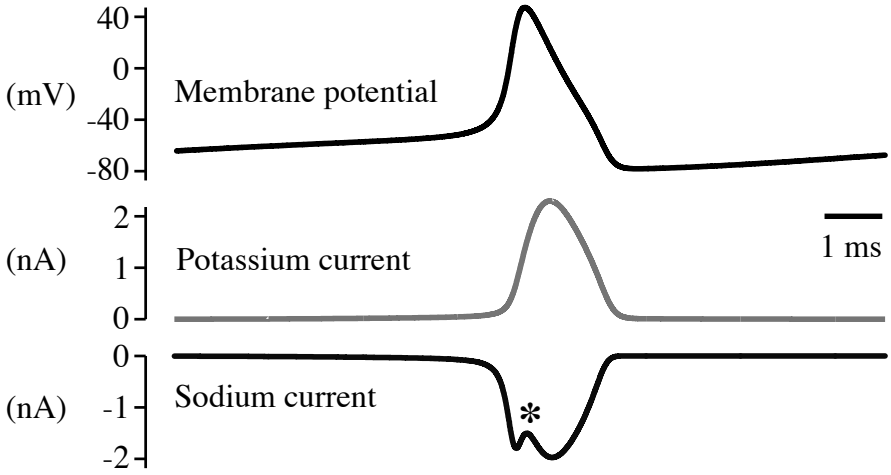

Fig. 4

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Comments on Questions

Q1 A very popular question, chosen by 27 of the 29 students taking exam.

The first part of the question was generally well answered. Students understand well the simple model of oxygen binding, can write the equilibrium and saturation curve. Nearly all students identified properly the inhibiting effect of BPG. Most students managed to get sensible values for the equilibrium constants, which is very encouraging. Overall, the basic concepts are well understood.

The three qualitative questions about the benefits of high levels of BPG were most often only partly addressed; conclusions were only rarely justified, making use of the data available. A large number of answers simply stated that higher levels of BPG help release oxygen in the tissues, for all three questions. This is correct, but misses the point. For instance, on question b(iii), answering properly the question involves comparing ball park figures for the oxygen transport at high altitude with normal and elevated levels on PBG with oxygen transport at normal altitude and normal BPG levels (as reference value for physiological needs).

Q2 A popular question, 23/29 students chose this question.

The question was overall well answered by those who took the time to tackle it. The most common issue was the handling of the signs for the shear stress and velocity gradient. Otherwise it was nice to see that most students understood properly the basic steps to extract and use rheological data to calculate a flow profile.

Q3 A popular question, selected by 23/29 students.

Many students provided excellent answers to this question. Parts a-c were well addressed and demonstrated basic understanding of equilibrium and diffusion. Part d was more challenging. There are several ways to address it, and reverse engineering the answer rarely provided a satisfactory answer. Part e was rarely answered correctly. Surprisingly, a significant number of students failed to sketch correctly the curve, with a number of answers indicating that the amount of CO2 in blood increases as a result of traversing the lungs.

Q4 Half of the students answered question 4. Part (a) was almost universally answered correctly, with one or two students loosing marks because they rushed the calculation.

Part (b) divided the students somewhat; most could outline the basic relationships between membrane polarisation and potassium ion flux, but around half failed to connect potassium efflux to voltage-gated potassium channels. The final part of the question distinguished class I from class II.1. Most students were unable to explain the origin of the kink in the Na current, but one or two students correctly identified the mechanism. Reasonable answers that were not strictly correct were awarded class I if they demonstrated sound reasoning and knowledge of channel gating mechanisms. Overall the question seemed to classify students appropriately.