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 %]

(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%]

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

(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%]

(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%]

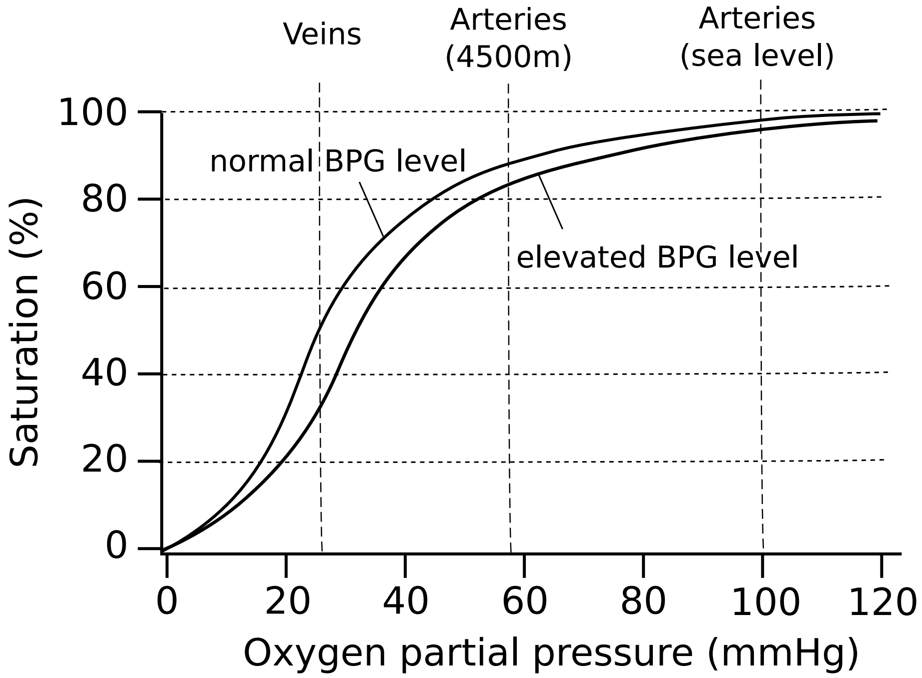
Veins
Arteries
(4500m)
Arteries
(sea level)
100
80
60
40
20
0
Saturation (%)
normal BPG level
elevated BPG level
0
20
40
60
80
100
120
Oxygen partial pressure (mmHg)

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%]

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

(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%]

(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%]

(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%]

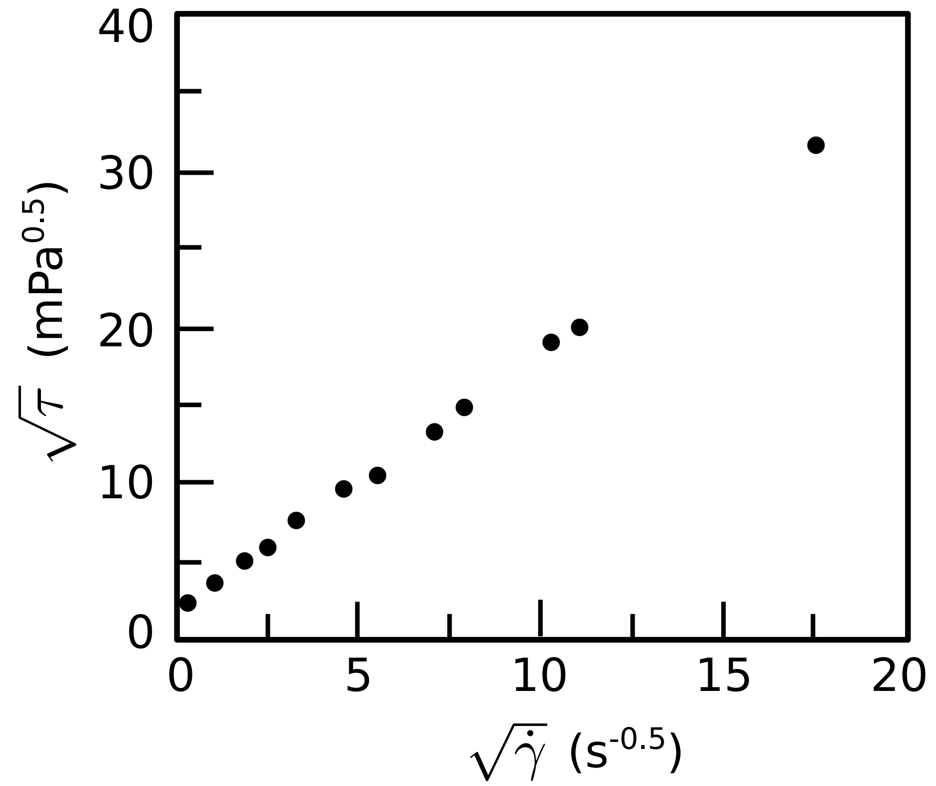

Fig. 2

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%]

(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%]

(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%]

(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%]

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

(cont.

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

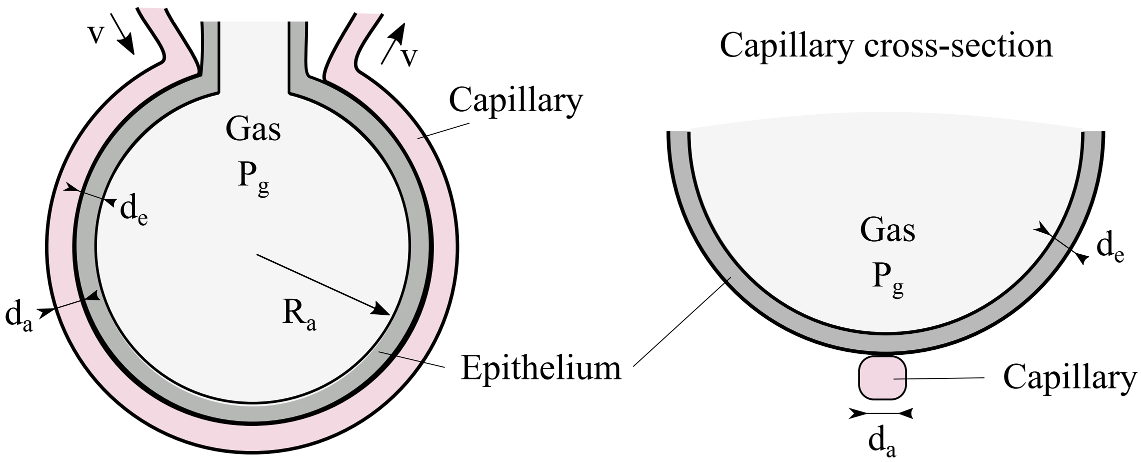

Fig. 3

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%]

(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%]

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

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

(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%]

(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%]

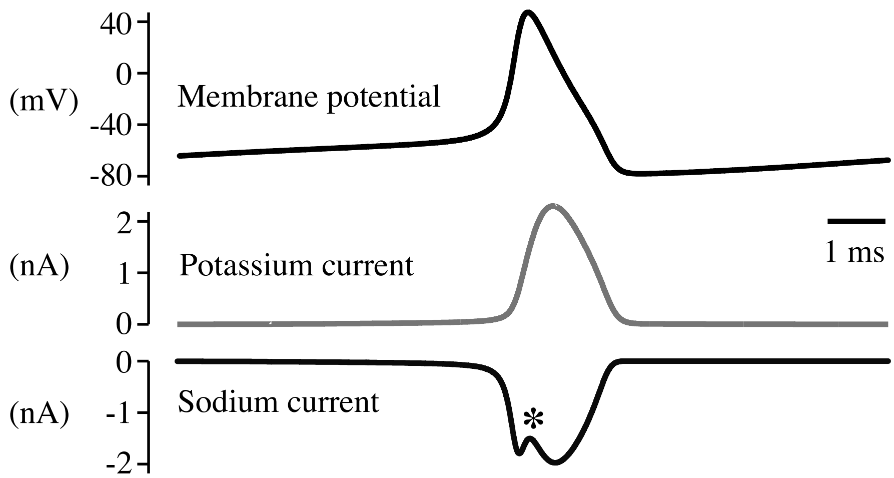

Fig. 4

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

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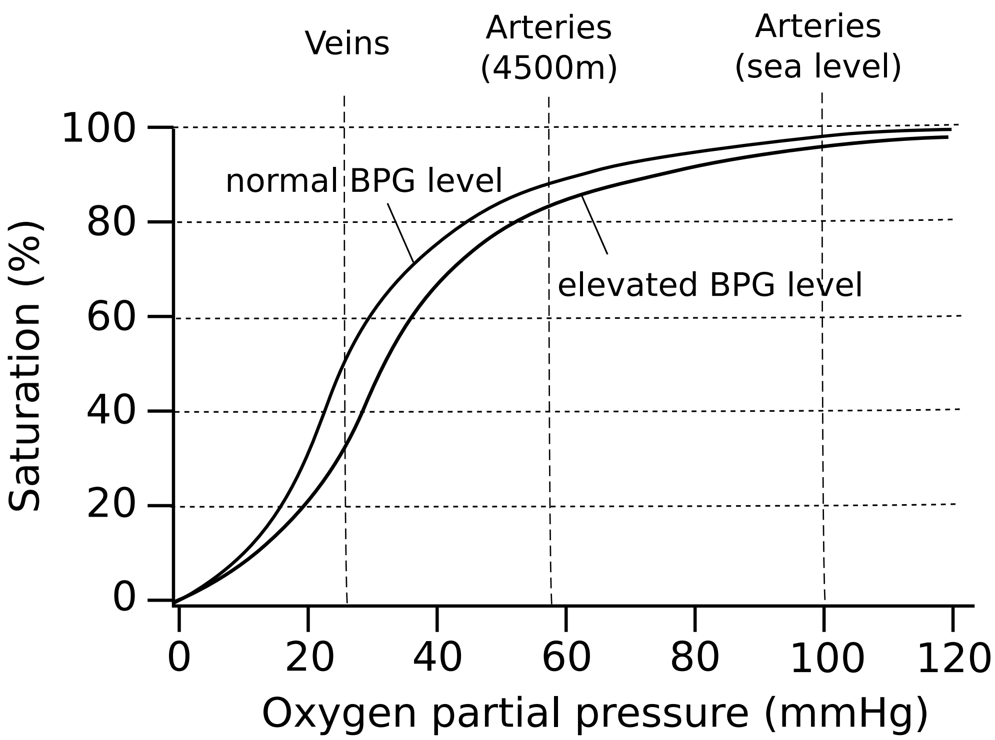

Extra copy of Fig. 1: Haemoglobin saturation curves for Question 1.

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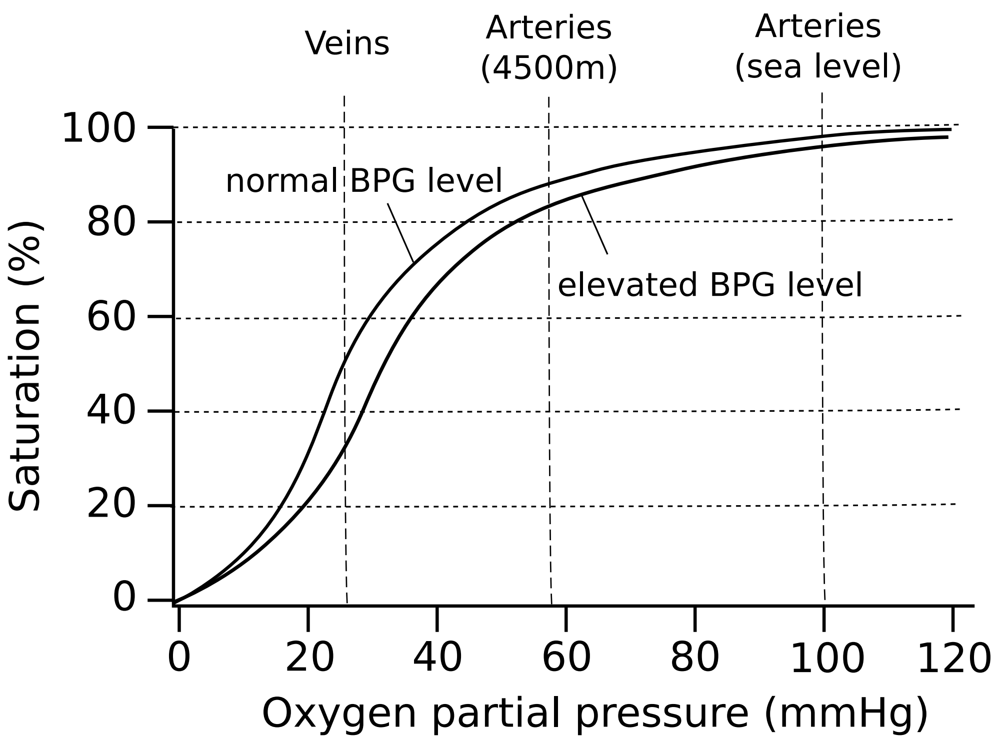

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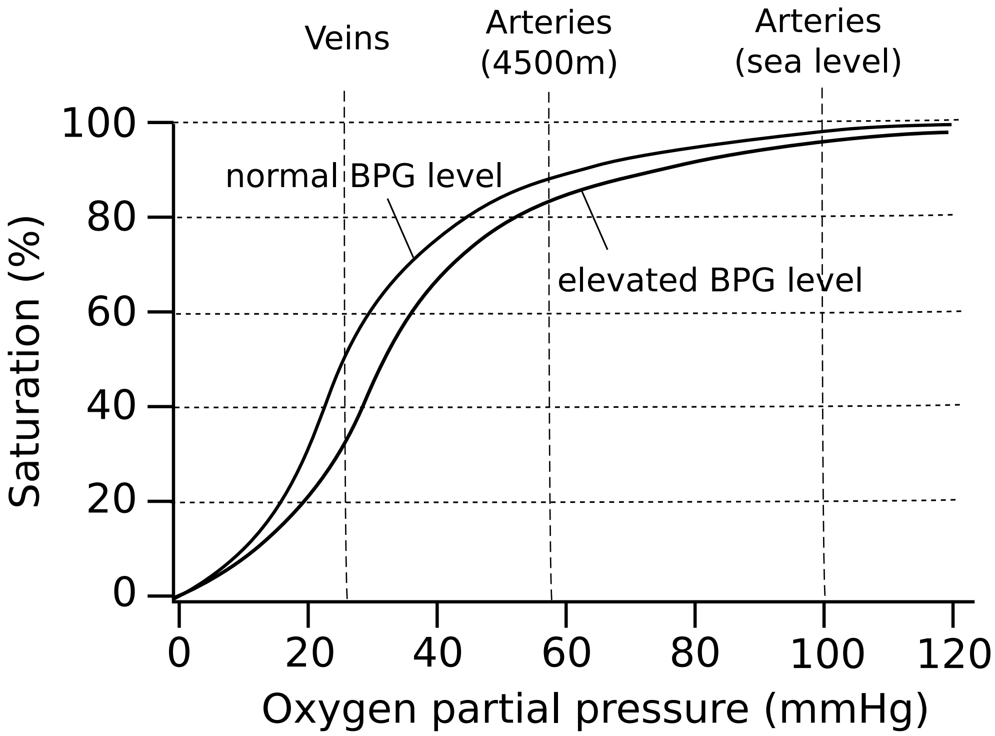

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