ENGINEERING TRIPOS PART IIA

Thursday 28 April 2011 2.30 to 4

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.*

There are no attachments.

STATIONERY REQUIREMENTS
Single-sided script paper.

SPECIAL REQUIREMENTS
Engineering Data Book
CUED approved calculator allowed

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

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1 This question concerns the effect of the pH on the haemoglobin saturation curve. For simplicity, ignore the fact that each dioxygen molecule can bind independently to haemoglobin, and assume that haemoglobin exists in only four states: Hb, $Hb(H^+)$, $Hb(O_2)_4$ and $Hb(H^+)(O_2)_4$. Use the following notations in your calculations:

$C_b = [Hb]$,

$C_{bh} = [Hb(H^+)]$,

$C_{bo} = [Hb(O_2)_4]$,

$C_{bho} = [Hb(H^+)(O_2)_4]$,

$C = C_b + C_{bh} + C_{bo} + C_{bho}$,

$h = [H^+]$ and $o = [O_2]$.

(a) Define what allosteric regulation is. [15%]

(b) Describe, using a diagram, the transitions between the different haemoglobin states, introducing the relevant kinetic and thermodynamic constants. [20%]

(c) Find the analytical expression of the haemoglobin saturation curve. [40%]

(d) Figure 1 shows three different saturation curves, obtained at different pH values. What do these measurements imply concerning the relative values of the equilibrium constants? [15%]

(e) Is the hydrogen ion an allosteric inhibitor or an allosteric activator of the fixation of oxygen? Explain your answer. [10%]

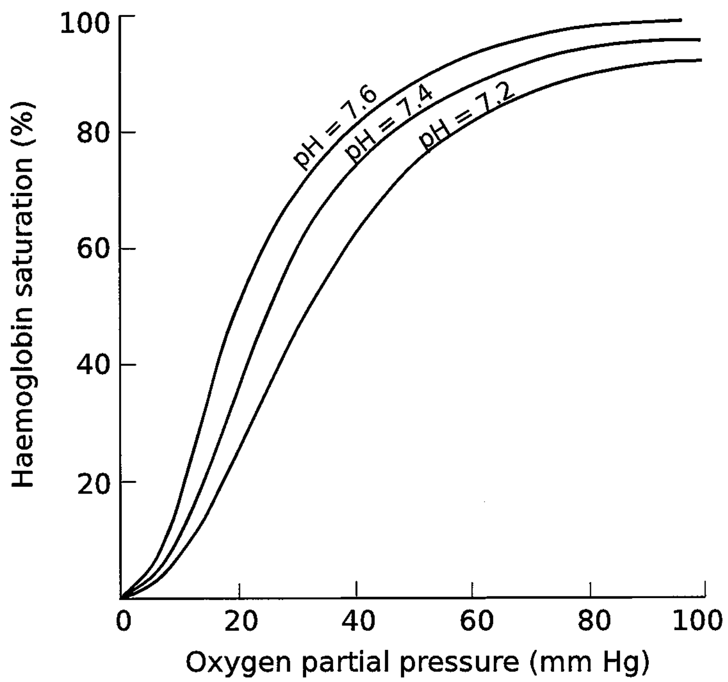
100
80
60
40
20
Haemoglobin saturation (%)
pH = 7.6
pH = 7.4
pH = 7.2
0
20
40
60
80
100
Oxygen partial pressure (mm Hg)

Fig. 1

2 (a) With regard to models of ion channels, there are two voltage levels for which all sensible models should agree on the corresponding channel currents.

(i) What are these two voltage levels? Provide either a numerical value or a formula for each of them. If providing a formula, define the meaning of all variables in words. [20%]

(ii) Explain with reasons why any model should predict the same channel current at these voltage levels. [20%]

(iii) What are the current values predicted at these two voltage levels? Provide either a numerical value or a formula for each of them. If providing a formula, define the meaning of all variables in words. [20%]

(b) With regard to reducing the Hodgkin-Huxley model to a simpler dynamical system

(i) State the number of dynamical variables in the Hodgkin-Huxley model, and for each variable, describe its biophysical meaning. [10%]

(ii) State the number of dynamical variables in the reduced dynamical system model. Explain how they relate to the original variables of the Hodgkin-Huxley model. [10%]

(iii) Explain the main logical steps in the reduction of the Hodgkin-Huxley model. [20%]

3 A solution of water is at equilibrium with a gas containing carbon dioxide at a partial pressure $P = 10^{-2}$atm= 1013 Pa.

The following thermodynamical relationships are provided:

$$CO_2 + H_2O \underset{}{\overset{K_a}{\rightleftharpoons}} H^+ + HCO_3^- \text{ with } K_a = \frac{[H^+][HCO_3^-]}{[CO_2]} = 4.30 \cdot 10^{-7}$$

$$H_2CO_3 \underset{}{\overset{K_1}{\rightleftharpoons}} H^+ + HCO_3^- \text{ with } K_1 = \frac{[H^+][HCO_3^-]}{[H_2CO_3]} = 2.5 \cdot 10^{-4}$$

$$HCO_3^- \underset{}{\overset{K_2}{\rightleftharpoons}} H^+ + CO_3^{2-} \text{ with } K_2 = \frac{[H^+][CO_3^{2-}]}{[HCO_3^-]} = 5.61 \cdot 10^{-11}$$

$$H_2O \underset{}{\overset{K_d}{\rightleftharpoons}} H^+ + OH^- \text{ with } K_d = [H^+][OH^-] = 10^{-14}$$

(a) Consider that the solution only contains the species above.

(i) Find the concentrations of CO_2 and H_2CO_3 at equilibrium. The solubility of carbon dioxide in water is $\sigma = 2.48 \cdot 10^{-7}$ Molar/Pa. [15%]

(ii) Explain why $[H^+] = [HCO_3^-] + 2\,[CO_3^{2-}] + [OH^-]$. [10%]

(iii) Find the pH and concentrations of HCO_3^- and CO_3^{2-} in the solution. [35%]

(b) A buffer is now added to the solution so that its pH is controlled and matches the typical pH of blood, which is 7.4.

(i) Are the results obtained in parts (a)(i) and (a)(ii) still valid? [10%]

(ii) Find the concentrations of CO_2, H_2CO_3, HCO_3^- and CO_3^{2-} in the solution. [15%]

(iii) How are these concentrations changed if the gas pressure is increased by a factor α? [15%]

4 This question regards the role of surface tension in the mechanical response of lung tissues. Part (a) concerns the relationship between the surface tension and the internal pressure of a liquid bubble. Parts (b) and (c) regard the case of an alveolus.

(a) Consider a spherical gas bubble of radius R at the mechanical equilibrium. Due to surface tension effects, the energy stored in the fluid layer is $E_s = \Gamma A$, where Γ is a constant corresponding to the surface tension of the water film, and A is its total surface area.

(i) If the internal pressure is P_i and external pressure is P_e, show that the energy required to slightly change the radius from R to $R + \delta R$ is:

$$\delta E = \left((P_e - P_i)A + \Gamma \frac{dA}{dr} \right) \delta R$$

[15%]

(ii) Given that the total energy is minimum at equilibrium, show that:

$$(P_i - P_e) = \frac{2\Gamma}{R}$$

[15%]

(b) The alveolus is modelled here as a perfectly spherical soft elastic shell of rest radius R_0 coated by a thin fluid film at the interface between the air and the tissue (see figure 2). The connective tissues surrounding the alveolus are ignored.

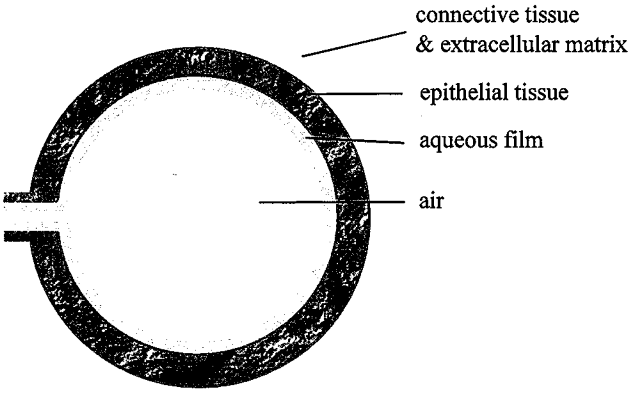

Fig. 2

(i) For small deviations from the rest radius R_0, show that the tension in the shell T and the change in volume $V - V_0$ are proportional, i.e. that $T = k(V - V_0)$, where $V_0 = \frac{4\pi}{3}R_0^3$. [15%]

(ii) Using the approach of part (a), show that:

$$(P_i - P_e) = \frac{2\Gamma_m + 2k(V - V_0)}{R}$$

where Γ_m is the surface tension of the air/aqueous film interface. [15%]

(c) Figure 3 shows experimental measurements of the relationship between the pressure difference $P_i - P_e$ and the total volume of the lungs in the adult cat. Two sets of experiments have been performed, one by inflating/deflating the lungs with air, and the other by inflating/deflating with a saline solution, removing any gas-water interface in the lungs.

What can we learn by doing these experiments with both air and a saline solution? Discuss potential agreements/inconsistencies between the graph in figure 3 and the relationship obtained in part (b)(ii). [40%]

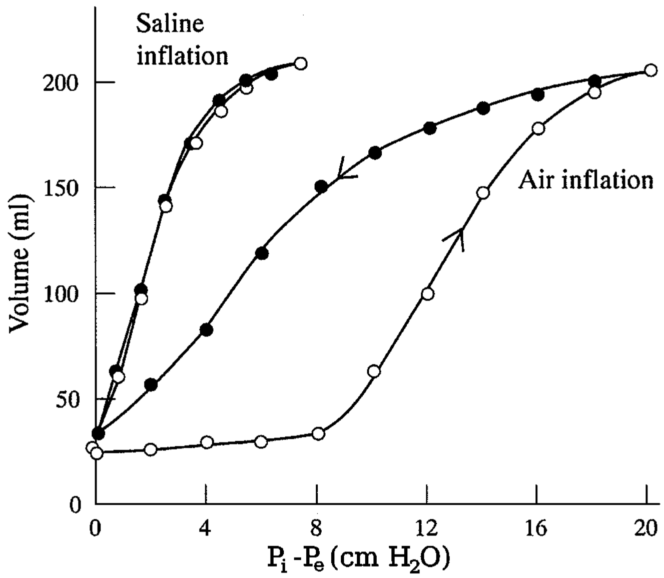

Fig. 3

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(6)

Numerical answers

1.c) $Y = \frac{o^4}{o^4 + K_1^{-1}\phi(h)}$, with $\phi(h) = \frac{(1+K_2 h)}{1+\frac{\bar{K}_1}{K_1}K_2 h}$

3.a.i) $[CO_2] = 2.51 \cdot 10^{-4}$ Molar, $[H_2CO_3] = 4.3 \cdot 10^{-7}$ Molar.

3.a.iii) $[HCO_3^-] = 1.04 \cdot 10^{-5}$ Molar, pH = 4.98, $[CO_3^{2-}] = K_2$.

3.b.ii) $[H^+] = 3.98 \cdot 10^{-8}$ Molar, $[HCO_3^-] = 2.71 \cdot 10^{-3}$ Molar, $[CO_3^{2-}] = 3.82 \cdot 10^{-6}$ Molar.