Version ML/2

EGT2
ENGINEERING TRIPOS PART IIA

Friday 1 May 2015 9.30 to 11.00

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
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) Determine if each statement below is universally true at steady-state inside an ion channel.

- The flux of the permeable ion is zero everywhere.
- The concentration of the permeable ion is constant in space.
- The electric potential is constant in space.
- The electric potential difference between the two ends of the channel is the Nernst potential of the permeable ion.
- The second spatial derivative of the electric field is proportional to the concentration of the permeable ion.

[25%]

(b) The membrane resistance of a neuron is $4\,\mathrm{k\Omega\,cm^2}$, its membrane capacitance is $1\,\mu\mathrm{F/cm^2}$, and its resting membrane potential is at $-68.84\,\mathrm{mV}$. The Nernst potential of the ions for which there are permeable channels in the membrane are as follows:

$$V_{\mathrm{Na}^+} = +55\,\mathrm{mV}$$
$$V_{\mathrm{K}^+} = -75\,\mathrm{mV}$$
$$V_{\mathrm{Cl}^-} = -69\,\mathrm{mV}$$

and the Cl^- conductance is

$$g_{\mathrm{Cl}^-} = 0.04\,\mathrm{mS/cm^2}$$

(i) What are the membrane conductances for Na^+ and K^+ at the resting membrane potential? [15%]

(ii) The membrane is depolarised to $-60\,\mathrm{mV}$. Assuming the steady-state conductances of the ion channels are essentially constant between -69 and $-60\,\mathrm{mV}$, what is the time taken for the membrane potential to return to within $0.1\,\mathrm{mV}$ of the resting membrane potential? [25%]

(cont.

(iii) How does your answer to part (b)(ii) change if the conductance of the K^+ channel is instead approximated as a linear function of the membrane potential, v, between $v = -69\,\text{mV}$ and $-60\,\text{mV}$, where $g_{K^+}(v) = \left[\frac{v}{25\,\text{mV}} + 2.9536\right]\,\text{mS/cm}^2$?

[35%]

You may need the solution to the differential equation:

$$\frac{dy}{dt} = Ay^2 + By + C$$

which is:

$$y(t) = \alpha \tan(\beta t + \gamma) + \delta$$

with

$$\alpha = \frac{\sqrt{4AC - B^2}}{2A}$$
$$\beta = \frac{\sqrt{4AC - B^2}}{2}$$
$$\gamma = \arctan\left(\frac{2Ay(0) + B}{\sqrt{4AC - B^2}}\right)$$
$$\delta = -\frac{B}{2A}$$

In your calculations, you may also need the following identities:

$$\arctan(0 + bi) = k\pi/2 + \left[\frac{1}{2}\ln\left((1+b)^2\right) - \frac{1}{4}\ln\left(\left(1-b^2\right)^2\right)\right] i, \qquad \text{with}$$

$$k = \begin{cases} 0 & \text{for } |b| < 1 \\ 1 & \text{for } |b| > 1 \end{cases}$$

where $i = \sqrt{-1}$ is the imaginary number,

and

$$\tan(x \pm y) = \frac{\tan x \pm \tan y}{1 \mp \tan x \cdot \tan y}$$

2 (a) Consider the following enzyme reaction:

$$\mathrm{S}+\mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k_2} \mathrm{P}+\mathrm{E}$$

(i) Assuming the equilibrium is fast, show that the speed of product creation V takes the form $V = V_{max}\frac{[\mathrm{S}]}{[\mathrm{S}]+K}$. Express V_{max} and K as a function of the other constants involved in the problem. [15%]

(ii) Sketch $1/V$ as a function of $1/[\mathrm{S}]$ and explain how the values of V_{max} and K can be obtained from this graph. [15%]

(b) Consider the following mechanism of enzyme activity, where the enzyme is E, A and B are two different substrates, and P and Q are two products. The equilibrium reactions are all supposed to be fast.

$$\mathrm{A}+\mathrm{E} \rightleftharpoons \mathrm{EA} \qquad \mathrm{K}_1 = \frac{[\mathrm{EA}]}{[\mathrm{A}][\mathrm{E}]} \qquad (1)$$

$$\mathrm{B}+\mathrm{EA} \rightleftharpoons \mathrm{EAB} \qquad \mathrm{K}_2 = \frac{[\mathrm{EAB}]}{[\mathrm{B}][\mathrm{EA}]} \qquad (2)$$

$$\mathrm{EAB} \rightleftharpoons \mathrm{EPQ} \qquad \mathrm{K}_3 = \frac{[\mathrm{EPQ}]}{[\mathrm{EAB}]} \qquad (3)$$

$$\mathrm{EPQ} \xrightarrow{k_4} \mathrm{E}+\mathrm{P}+\mathrm{Q} \qquad (4)$$

(i) Express the product creation speed, V, as a function of the kinetic and thermodynamic constants, the total enzyme concentration E_0 and the concentrations of A and B. [25%]

(ii) Assume that [B] is constant. Show that the speed of product creation from part (b)(i) takes the form obtained in part (a)(i), with A being the substrate. How would an increase of [B] change the graph of $1/V$ as a function of $1/[\mathrm{A}]$? Explain with reasons whether B can be considered an inhibitor or activator. [15%]

(iii) Assume instead that [A] is constant. Show that the speed of product creation from part (b)(i) takes the form obtained in part (a)(i), with B being the substrate. How would an increase of [A] change the graph of $1/V$ as a function of $1/[\mathrm{B}]$? Explain with reasons whether A can be considered an inhibitor or activator. [15%]

(iv) Two substrates X and Y are known to react according to this mechanism, but the order in which they bind to the enzyme is unknown. Experimentally, it is found that doubling [X] while halving [Y] decreases the rate of product creation. Deduce from this whether X binds first or second. [15%]

3 Consider a cylindrical blood vessel of radius R and length L subjected to a constant pressure difference Δp between the two ends. Let x denote the longitudinal, and r denote the radial position in the vessel. Blood pressure is represented by the function $p(r,x)$, blood velocity, which is aligned with the vessel axis, by the function $u(r)$, and blood shear stress by the function $\tau(r)$. The x-axis is oriented so that $u(r)$ is positive.

(a) By considering force balance on a fluid element, show that:

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

and

$$\frac{\partial p}{\partial r}=0$$

[30%]

(b) Assuming blood is Newtonian, derive the analytical expression of the flow profile $u(r)$. Discuss the validity of all the assumptions made to obtain this result. [30%]

(c) Derive the relationship between fluid flux Q and pressure drop Δp. [20%]

(d) Use the expression obtained in part (c) to calculate the flow rate passing through the circulatory network pictured in Fig. 1 as a function of the vessels' geometry (see parameters in the figure), pressure drop, and blood viscosity. [20%]

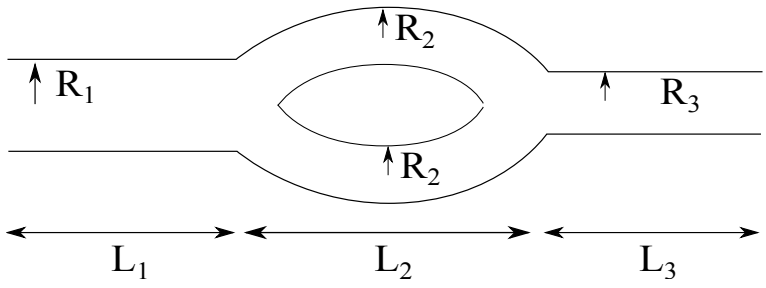

Fig. 1

4 (a) Explain the aim of the Krogh cylinder model and list the assumptions underlying the model. [30%]

(b) Prove that the oxygen concentration profile within a Krogh cylinder of radius R_0 has the following form:

$$\frac{c(r)}{c_c} = 1 + \frac{\rho R_0^2}{4 c_c D}\left(\frac{r^2}{R_0^2} - \frac{R_c^2}{R_0^2} - 2\ln\left(r/R_c\right)\right)$$

where $c(r)$ is the concentration of oxygen at radial position r, R_c is the capillary radius, c_c is the oxygen concentration in blood, D is the coefficient of diffusion of oxygen in the tissue, and ρ is the rate at which oxygen is consumed per unit volume in healthy tissue. [35%]

(c) Use this model to explain the role of capillary sphincters in capillary beds. [35%]

END OF PAPER

Answers

1(a)

For all statements: not true.

1(b)(i)

$g_{\mathrm{K}^+} = 0.20\,\mathrm{mS/cm^2}$, $g_{\mathrm{Na}^+} = 0.01\,\mathrm{mS/cm^2}$

1(b)(ii)

$t = -4 \ln \frac{0.1}{8.84}\,\mathrm{ms} \simeq 18\,\mathrm{ms}$

1(b)(iii)

$t \simeq 8\,\mathrm{ms}$

2(a)(i)

$V_{max} = k_2 E_0$ and $K = K_1^{-1} = k_{-1}/k_1$

2(a)(ii)

A plot of $1/V$ vs. $1/[S]$ is a straight line with y-intercept $1/V_{\max}$ and slope $K/V_{\max}$ (Lineweaver-Burke plot).

2(b)(i)

$V = \frac{E_0 k_4 K_3 K_2 K_1 [B][A]}{1+K_1[A](1+K_2[B](1+K_3))}$

2(b)(ii)

B acts as an activator.

2(b)(iii)

A acts as an activator.

2(b)(iv)

X binds first to the enzyme.

3(b)

$u(r) = \frac{r^2 - R^2}{4\mu} \frac{dp}{dx}$

3(c)

$Q = \int_0^R 2\pi r u(r) dr = \frac{\pi R^4}{8\mu} \frac{\Delta p}{L}$

3(d)

$$Q = \frac{\pi \Delta p}{8\mu} \left(\frac{L_1}{R_1^4} + \frac{L_2}{2R_2^4} + \frac{L_3}{R_3^4} \right)^{-1}$$

M.L.