ENGINEERING TRIPOS PART IIA

Thursday XX April 2012 2.30 to 4

Module 3G2

MATHEMATICAL PHYSIOLOGY - SOLUTIONS

*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.*

No attachment.

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

Version: 1

1 (a) Considering the reactions:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

(i) The differential equations controlling the evolution of the concentrations are:

$$\frac{d[A]}{dt} = -k_1[A]$$
$$\frac{d[B]}{dt} = k_1[A] - k_2[B]$$
$$\frac{d[C]}{dt} = k_2[B]$$

(ii) If $k_2 \gg k_1$, one can use the steady state assumption for the concentration of B.

$$\frac{d[A]}{dt} = -k_1[A]$$
$$\frac{d[B]}{dt} = k_1[A] - k_2[B] = 0 \Longrightarrow [B] = \frac{k_1}{k_2}[A]$$
$$\frac{d[C]}{dt} = k_2[B] = k_1[A]$$

(iii) The leads to:

$$[A] = [A]_0 e^{-k_1 t}$$
$$[B] = \frac{k_1}{k_2}[A]$$
$$[C] = [A]_0 \left(1 - e^{-k_1 t}\right)$$

Notice that the approximated expression for [B] does not satisfy the initial condition. This is because the steady state assumption is only valid after a short transient, during which [B] goes from 0 to $\frac{k_1}{k_2}[A](0)$.

(b) Considering the following reactions:

$$\mathrm{S} + \mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C_1} \xrightarrow{k_2} \mathrm{P} + \mathrm{E}$$

$$\mathrm{C_1} + \mathrm{I} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{C_2}$$

(i) This corresponds to the case of uncompetitive inhibition, where the inhibitor sequester a fraction of the substrate-enzyme complex C_1 and prevent it to form the product.

(ii) We use the following notations: e=[E], i=[I], s=[S], c_1=[C_1], c_2=[C_2].

$$\begin{aligned}
\frac{dc_1}{dt} &= k_1 se - k_{-1}c_1 - k_3 c_1 i + k_{-3}c_2 - k_2 c_1 \\
\frac{dc_2}{dt} &= k_3 c_1 i - k_{-3}c_2 \\
\frac{ds}{dt} &= -k_1 se + k_{-1}c_1 \\
\frac{de}{dt} &= -k_1 se + k_{-1}c_1 + k_2 c_1 \\
\frac{di}{dt} &= -k_3 c_1 i + k_{-3}c_2
\end{aligned}$$

(iii) The rate is $V = k_2 c_1$. We therefore need to have an expression of c_1 as a function of s and the total enzyme concentration E_0.

From the steady state assumption, we get:

$$\begin{aligned}
\frac{dc_1}{dt} &= 0 = k_1 se - k_{-1}c_1 - k_3 c_1 i + k_{-3}c_2 - k_2 c_1 \\
\frac{dc_2}{dt} &= 0 = k_3 c_1 i - k_{-3}c_2
\end{aligned}$$

This leads to $c_2 = K_I i c_1$, and as a result a relationship between e and c_1:

$$k_1 se = k_{-1}c_1 + k_3 c_1 i - k_{-3}c_2 + k_2 c_1 = (k_{-1} + k_3 i - k_{-3}K_I i + k_2)c_1 = (k_{-1} + k_2)c_1$$

$$e = c_1 K_M / s$$

The total enzyme concentration E_0 is $e + c_1 + c_2$. Hence:

$$E_0 = (K_M/s + 1 + K_I i)c_1$$

The expression of the rate of product creation V therefore becomes:

$$\begin{aligned}
V &= \frac{k_2 E_0 [\mathrm{S}]}{[\mathrm{S}](1 + [\mathrm{I}]/K_I) + K_M} \\
V &= \frac{V'_{\max}[\mathrm{S}]}{[\mathrm{S}] + K'_M}
\end{aligned}$$

$$\text{with } K'_M = \frac{K_M}{1 + [\mathrm{I}]/K_I} \text{ and } V'_{\max} = \frac{V_{\max}}{1 + [\mathrm{I}]/K_I}$$

(TURN OVER for continuation of Question 1

(iv) We have $1/V = 1/V'_{max} + (K'_M/V'_{max})1/[S]$. The graph therefore corresponds to a straight line. If the inhibitor concentration is increased, K'_M and V'_{max} decrease in the same proportions and the slope of the line is therefore constant. The line is simply shifted upward on the graph as the inhibitor concentration increases.

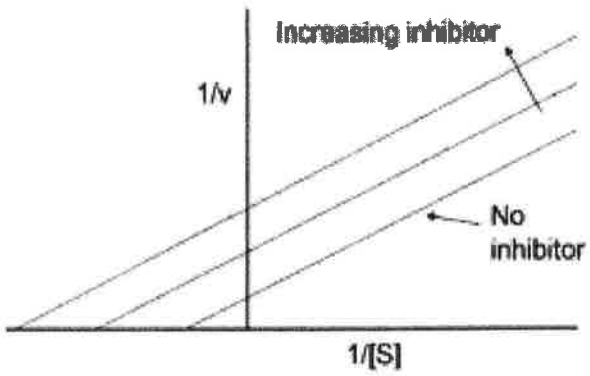

Fig. 1

2 (a) We measure the electrophysiological properties of two axons that have different radii but are otherwise identical. The radius of the thinner axon is $r_{\text{thin}} = 2\ \mu\text{m}$, the radius of thicker one is $r_{\text{thick}} = 5\ \mu\text{m}$. Provide formulæ for the following quantities:

(i) the ratio of the time constants in the two axons, $\frac{\tau_{\text{thick}}}{\tau_{\text{thin}}}$, when both axons are unmyelinated;

Answer: $\frac{\tau_{\text{thick}}}{\tau_{\text{thin}}} = 1$

(ii) the ratio of the space constants in the two axons, $\frac{\lambda_{\text{thick}}}{\lambda_{\text{thin}}}$, when both axons are unmyelinated;

Answer: $\frac{\lambda_{\text{thick}}}{\lambda_{\text{thin}}} = \sqrt{\frac{r_{\text{thick}}}{r_{\text{thin}}}} = \sqrt{\frac{5}{2}} \approx 1.58$

(iii) the ratio of the time constants in the two axons, $\frac{\tau_{\text{thick}}}{\tau_{\text{thin}}}$, when both axons are myelinated, and the thickness of the myelin layer in both axons is optimal for high propagation speed;

Answer: $\frac{\tau_{\text{thick}}}{\tau_{\text{thin}}} = 1$

(iv) the ratio of the space constants in the two axons, $\frac{\lambda_{\text{thick}}}{\lambda_{\text{thin}}}$, when both axons are myelinated, and the thickness of the myelin layer in both axons is optimal for high propagation speed.

Answer: $\frac{\lambda_{\text{thick}}}{\lambda_{\text{thin}}} = \frac{r_{\text{thick}}}{r_{\text{thin}}} = \frac{5}{2} = 2.5$

[40%]

(b) With regard to the absolute and relative refractory period in the Hodgkin-Huxley model:

(i) describe the experimental protocol by which the duration of these refractory periods can be measured;

Answer: For demonstrating the relative refractory period, the cell needs to be stimulated by brief ($\sim$ 1 ms) current injection impulses that have the minimal amplitude that is sufficient for eliciting an action potential. Pairs of this stimulus needs to be delivered into the cell, varying the inter-stimulus interval. For long enough intervals, both stimuli in a pair will elicit an action potential. For short intervals, only the first stimulus results in an action potential, the second does not. The length of the maximal interval for which the cell only fires a single action potential is the duration of the relative refractory period.

For demonstrating the absolute refractory period, the same protocol must be followed, but at inter-stimulus intervals shorter than the relative refractory period, the amplitude of the 2nd stimulus can be increased to the level necessary to elicit a 2nd action potential even at these short intervals. However, at really short intervals no matter how large the 2nd

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stimulation amplitude is, there will be no regenerative action potential elicited. The length of the longest such interval for which no stimulus amplitude results in an action potential for the 2nd stimulus is the duration of the absolute refractory period.

[30%]

(ii) explain how the behaviour of the different dynamical variables of the model accounts for these phenomena.

Answer: The relative refractory period arises because after the 1st action potential the cell is hyperpolarised, plus the potassium channels are still open. This means that the membrane potential is further from the firing threshold and the membrane resistance is smaller than before the 1st action potential. Hence, a larger current injection is needed to achieve a larger voltage change against a smaller resistance. This means that the same minimal stimulation that was sufficient for eliciting the 1st action potential will not be sufficient to elicit a 2nd action potential.

The absolute refractory period arises because shortly after the 1st action potential the h gate is still inactivated (by the high voltage during the action potential, and because it has slow dynamics). This means that the sodium channel is closed. The brief depolarisation by the 2nd stimulus impulse only activates the m gate (because it has fast dynamics) but does not deinactivate the h gate (because the duration of the impulse is too short for the slow h gate to be able to react to it) and so the sodium channels remain closed. As a result, there will be no sodium current, and so the positive feedback loop between the membrane potential and the sodium current necessary for the initiation of an action potential cannot kick in, and the cell only passively follows the depolarisation resulting from the large-amplitude 2nd current injection pulse. [30%]

3 (a) Globular proteins play an important role in regulating the osmotic pressure of blood. As blood vessels are at a higher hydrostatic pressure than tissues, the osmotic pressure is important to avoid systematic leakage of water in to the tissue while allowing for exchange of oxygen, nutrients and waste material. Blood filtration in capillary beds is an example.

(b) Kidney physiology

(i) Because the globular proteins do not flow through the porous epithelium, their flux in the arteriole must remain constant. This flux at any point along the arteriole is:

$$q_1(x)c(x) = q_1(0)c(0) = Q_i c_0$$

The osmotic pressure is related to the solute concentrations by $\pi = RTc$. We therefore have:

$$\pi = RTc = RT\frac{Q_i c_0}{q_1}$$

(ii) The flux leaving the arteriole per unit length is

$$\phi = K_f\,(P_1 - \pi - P_2)$$

Over a small distance dx, the flux filtrating out ϕdx must be equal to the change in flow rate in the arteriole $q_1(x+dx) - q_1(x)$. Hence:

$$\frac{dq_1}{dx} = -K_f\,(P_1 - \pi - P_2)$$

(iii) π can now be expressed as a function of q_1: $\pi = RTc = RTQ_i c_0/q_1$. Substituting in the equation above, we get:

$$\frac{dq_1}{dx} = K_f\,(P_2 - P_1 - \frac{RTQ_i c_0}{q_1})$$

The boundary condition is $q_1(0) = Q_i$, and $\pi(0) = RTc_0$. q_1 will decay with x and π will increase. As π increases, $P_1 - \pi - P_2$ gets smaller and could eventually reach zero if L is large enough, hence $\pi(\infty) = P_1 - P_2$. There is at that point a limit value for q_1 satisfying:

$$q_1(\infty) = Q_i\frac{RTc_0}{P_1 - P_2}$$

by mass conservation, q_2 is simply $Q_i - q_1$.

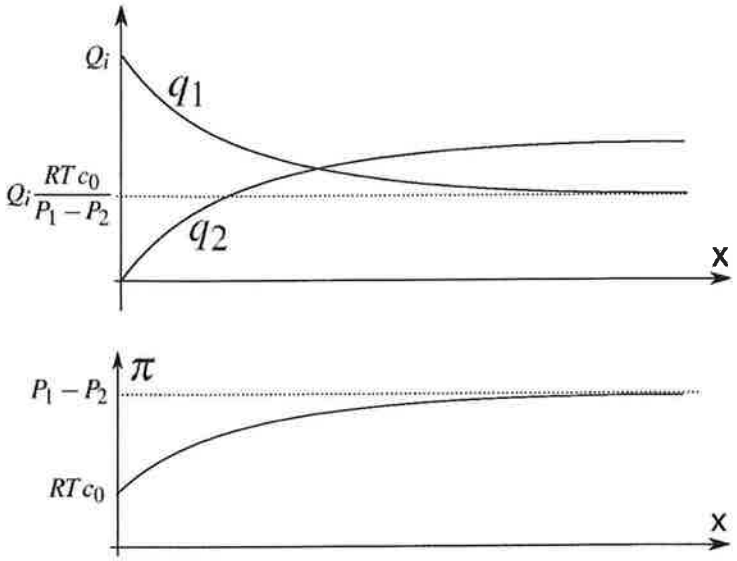

Fig. 2

4 (a) In arteries, the Womersley number is relatively high (between 5 and 10). This implies that the flow is dominated by inertial effects. Viscosity is not important. In such a situation, the flow profile looks like a plug flow as boundary layers do not have time to develop. Hence the assumption of a uniform blood velocity in a cross-section.

(b) As ρ is constant, mass and volume conservation are equivalent. Consider a small element dx of volume $A(x)dx$. The volume variation during dt corresponds to what came in from the left, minus what left on the right. Hence:

$$dAdx = A(x)u(x)dt - A(x+dx)u(x+dx)dt$$

Dividing by $dxdt$, we get:

$$\frac{\partial A}{\partial t} + \frac{\partial (Au)}{\partial x} = 0 \tag{1}$$

(c) Momentum conservation is more complex. The momentum in a small element of size dx is $u\,dm = u\,(\rho A dx)$. The variation of momentum will be due to input of material from the left, loss from the right, but also to pressure forces acting on it. We therefore get:

$$\rho d(Au)dx = \underbrace{\rho A(x)u^2(x)dt}_{in} - \underbrace{\rho A(x+dx)u^2(x+dx)dt}_{out} + \underbrace{P(x)A(x)dt}_{left\ side} - \underbrace{P(x+dx)A(x+dx)dt}_{right\ side} + \underbrace{P(x)\frac{\partial A}{\partial x}dxdt}_{vessel\ walls}$$

$$\frac{\partial(Au)}{\partial t} + \frac{\partial(Au^2)}{\partial x} = -\frac{1}{\rho}\frac{\partial PA}{\partial x} + \frac{1}{\rho}P\frac{\partial A}{\partial x} = -\frac{1}{\rho}A\frac{\partial P}{\partial x} \tag{2}$$

One can now use the product rule on $A \cdot u$ and $Au \cdot u$ and simplify this expression using the mass conservation equation.

$$\rho\left(\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x}\right) = -\frac{\partial P}{\partial x} \tag{3}$$

(d) We have so far two equations for three functions, A, u and P. We need to eliminate one of these using the compliance relationship: $A(x,t) = A_0 + cP(x,t)$. The mass conservation then becomes:

$$c\left(\frac{\partial P}{\partial t} + u\frac{\partial P}{\partial x}\right) + A\frac{\partial u}{\partial x} = 0 \tag{4}$$

To the first order in u and P, we get:

$$\rho\frac{\partial u}{\partial t} + \frac{\partial P}{\partial x} = 0 \quad \text{and} \quad c\frac{\partial P}{\partial t} + A_0\frac{\partial u}{\partial x} = 0 \tag{5}$$

Eliminating u then directly gives:

$$\frac{\partial^2 P}{\partial t^2} = \frac{A_0}{c\rho}\frac{\partial^2 P}{\partial x^2}$$

Hence $v_w = \sqrt{\frac{A_0}{c\rho}}$

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