Version AJK/1

EGT2
ENGINEERING TRIPOS PART IIA

Tuesday 4 May 2021 9.00 to 10.40

Module 3G2

MATHEMATICAL PHYSIOLOGY

ANSWER:

*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 and at the top of each answer sheet.*

STATIONERY REQUIREMENTS
Single-sided script paper

SPECIAL REQUIREMENTS TO BE SUPPLIED FOR THIS EXAM
CUED approved calculator allowed
Engineering Data Books

10 minutes reading time is allowed for this paper at the start of the exam.

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

You may not remove any stationery from the Examination Room.

1 (a) Consider the following enzymatic reaction:

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

Using a fast equilibrium assumption, find the expression of the rate V of product P formation as a function of the kinetic constants, concentration of substrate [S] and total enzyme concentration E_0.

What information can be obtained from the graph of $1/V$ as a function of 1/[S]? [30%]

Answer: Assuming fast equilibrium, we can define the constant:

$$\frac{[\mathrm{S}][\mathrm{E}]}{[\mathrm{C}]} = \frac{k_{-1}}{k_1} \equiv K$$

Assuming that the total amount of enzyme molecules is constant ([E] + [C] = E_0), we obtain the following expression:

$$\begin{aligned} \Rightarrow \quad [\mathrm{C}] &= E_0 \frac{[\mathrm{S}]}{[\mathrm{S}] + K} \\ \Rightarrow \quad V &= k_2 E_0 \frac{[\mathrm{S}]}{[\mathrm{S}] + K} \end{aligned} \tag{1}$$

$$\frac{1}{V} = \frac{1}{V_{\max}} + \frac{K}{V_{\max}} \frac{1}{[\mathrm{S}]}$$

so a plot of $1/V$ vs. $1/[\mathrm{S}]$ is a straight line with y-intercept $1/V_{\max}$ and slope $K/V_{\max}$.

(b) Consider now a situation where the enzyme is also able to react with H^+ in the solution, leading to an effect of the pH. The following enzymatic reactions capture such interactions, where the symbol H represents the ion H^+:

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

$$\mathrm{E} + \mathrm{H} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{EH}$$

$$\mathrm{EH} + \mathrm{H} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \mathrm{EH_2}$$

(i) Assuming that all reversible reactions reach their equilibrium quickly, write an expression for the rate of product formation as a function of the substrate concentration and concentration of H^+. [40%]

Answer: Let's define h and s as the concentration of H^+ and the substrate, respectively, as well as a new set of constants for this problem:

$$K_1 = \frac{s\,[\mathrm{EH}]}{[\mathrm{EHS}]}$$

$$K_3 = \frac{h\,[\mathrm{E}]}{[\mathrm{EH}]}$$

$$K_4 = \frac{h\,[\mathrm{EH}]}{[\mathrm{EH_2}]}$$

We look for the rate $V = k_2\,[\mathrm{EHS}]$. So we need to find [EHS].
The total amount of enzyme is conserved and provides a useful equation.
$[\mathrm{E}] + [\mathrm{EH}] + [\mathrm{EH_2}] + [\mathrm{EHS}] = E_0$
We now need to express all these concentrations as a function of [EHS], using the equilibrium constants defined above.
We get after some algebra:

$$[\mathrm{EHS}]\left(1 + \frac{K_1}{s}\left(1 + \frac{K_3}{h} + \frac{h}{K_4}\right)\right) = E_0$$

This leads to:

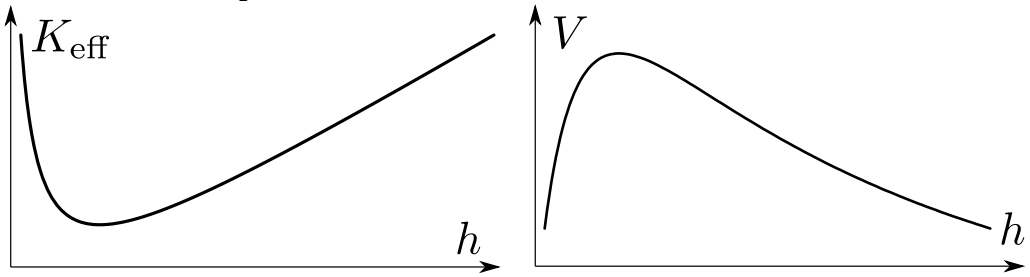
$$V = k_2 E_0 \frac{[\mathrm{S}]}{[\mathrm{S}] + K_{\mathrm{eff}}(h)} \text{ with } K_{\mathrm{eff}}(h) = K_1\left(1 + \frac{K_3}{h} + \frac{h}{K_4}\right)$$

(ii) Sketch how the rate, for a given substrate concentration, depends on the pH. If there is an optimum, find the pH of this optimum as a function of the constants involved in the problem. [30%]

Answer: The larger K_{eff}, the lower the rate. Rather than analysing the rate itself, it is equivalent to study the behaviour of K_{eff} with the pH, or here the concentration of H^+, h.
K_{eff} is the sum of a function that diverges for small of h (in $1/h$) and one that increases linearly with h. We therefore anticipate a minimum for an intermediate value of h. Let's find this minimum:

$$\frac{dK_{\mathrm{eff}}}{dh} = K_1\left(-\frac{K_3}{h^2} + \frac{1}{K_4}\right) = 0 \implies h_{\mathrm{min}}^2 = K_3 K_4$$

The optimum pH is $-\frac{1}{2}\log_{10}(K_3 K_4)$



2 (a) In deriving an ion channel's current-voltage relationship (in either the GHK or the Ohmic approximations) we assumed the system is at steady-state, *i.e.*, that the ionic concentrations and fluxes and the electric potential are everywhere time-independent, as are their boundary conditions.

(i) Explain why it is nevertheless justified to use those current-voltage relationships for studying the *time-dependent* dynamics of a neuron's membrane potential (which is the electric potential difference across the membrane's ion channels)? [10%]

Answer: This approximation is justified due to a separation of timescales between the timescales of relaxation to steady-state for ionic concentrations and fluxes inside the channel and the typical timescales of variation of a neuron's membrane potential, with the latter timescales being much larger than the former relaxation timescales. In other words, relaxation is very fast compared to the temporal dynamics of the membrane potential. Thus ionic concentrations and fluxes and the electric potential profile across the channel can be assumed to have reached or to be very near their steady-state configurations given the instantaneous value of the (relatively) slowly varying membrane potential.

(ii) Estimate the timescale of relaxation to steady-state in the ion channel electro-diffusion problem, and compare it to the timescales of variation of the membrane potential, such as the duration of an action potential. An order of magnitude estimation of each quantity is sufficient. [20%]

Here are approximate values of some quantities which may, or may not, appear in your estimations:

sodium ion channel length	10 nm
body temperature	310 K
Faraday's constant	10^5 C/mol
diffusion coefficient of sodium ion in brain tissue	10^{-3} mm^2/s
ratio of extra- to intracellular sodium concentrations	10

Answer: In the ion channel problem, the time it takes to reach steady-state is roughly given by the time it takes an ion to diffuse across the channel. During a time t an ion diffuses to a distance $L \sim \sqrt{Dt}$, so the time it takes to diffuse from one end of the channel to the other is given by $t \sim \frac{L^2}{D}$ where L is the channel length. The latter is in the same order of magnitude as the thickness of the cell membrane which is ~ 10 nm $= 10^{-5}$ mm. Taking our ion to be the sodium ion, for example, and using $D_{Na^+} \sim 10^{-3} \frac{mm^2}{s}$ for the diffusion coefficient of sodium in brain tissue, we obtain a relaxation timescale of order 10^{-7} s = 0.1 μs. The duration of an action potential or its upstroke are 1-3 milliseconds, and thus the typical timescales of variation of the membrane potential are 4 orders of magnitude slower than the timescale of relaxation to steady-state.

(b) Consider a single-compartment model of a neuron with capacitance C and n different Ohmic transmembrane conductances, $g_1, g_2, \ldots, g_n$, with reversal potentials $E_1, E_2, \ldots, E_n$. Explain what happens to the resting potential and the membrane time constant of the cell if we double all conductances, leaving all reversal potentials fixed. [20%]

Answer: The resting potential is given by $V_{\text{rest}} = \frac{\sum_i g_i E_i}{\sum_i g_i}$ while the membrane time constant is given by $\tau_m = \frac{C}{\sum_i g_i}$. (These expressions can be obtained by writing the voltage equation

$$C\frac{dV}{dt} = \sum_i g_i(E_i - V) \tag{2}$$

and dividing it by the total conductance, $\sum_i g_i$, yielding

$$\tau_m \frac{dV}{dt} = V_{\text{rest}} - V \tag{3}$$

with τ_m and V_{rest} given by the above expressions.) We thus see that doubling all g_i will halve the membrane time constant, while leaving the rest potential intact.

(c) This question is about the Hodgkin-Huxley model. Imagine molecular biologists have invented a new technology for detailed engineering of ion channel proteins, which allows you to *selectively* scale up or down the opening and closing rates of the different gates of voltage-gated sodium and potassium channels. More precisely, you can scale up or down each of the rates $\alpha_m(V)$, $\beta_m(V)$, $\alpha_h(V)$, $\beta_h(V)$, $\alpha_n(V)$, and $\beta_n(V)$ of the Hodgkin-Huxley model by (possibly different) *voltage-independent* and time-independent factors. For each of the following desired changes in properties of the action potential, answer (by providing appropriate reasoning) which rates you would scale up or scale down to affect that change, while leaving other characteristics of the action potential unchanged as much as possible:

(i) decrease the threshold potential for generation of action potential; [25%]

Answer: The action potential is initiated by triggering the positive feedback between the membrane potential and the activating gate $m(t)$ of the sodium current. The spiking threshold is thus around the voltage range over which the steady-state value, $m_\infty(V)$, of the sodium activation variable switches from 0 to 1. For concreteness, we will take the threshold to be the mid-point of this range, *i.e.*, the voltage at which $m_\infty(V) = 1/2$. Since $m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)}$, the threshold is thus the voltage at which the two curves $\alpha_m(V)$ and $\beta_m(V)$ intersect. Since $\alpha_m(V)$ is an increasing function of V and $\beta_m(V)$ is a decreasing function of V, scaling up $\alpha_m(V)$ *or* scaling down $\beta_m(V)$ will lower the V-value at which the curves intersect, and hence will lower the threshold (a simple sketch plot of these curves could also be given to support this conclusion). (Intuitively too, increasing (decreasing) the tendency of sodium channels to open (close) should make it easier to excite the cell to fire an action potential.) On the other hand, we would like to keep $\tau_m(V)$, the time constant of sodium activation (which

controls the duration of the upstroke portion of the action potential), as unperturbed as possible. Since $\tau_m(V)^{-1} = \alpha_m(V) + \beta_m(V)$, we can keep $\tau_m(V)$ approximately unchanged across the relevant voltage range (as much as possible) by appropriately scaling up $\alpha(V)$ *and* scaling down $\beta(V)$.

(ii) extend the absolute refractory period. [25%]

Answer: The duration of the absolute refractory period is governed by the timescale of sodium inactivation, $\tau_h(V)$, which is given by $1/(\alpha_h(V) + \beta_m(V))$. Scaling down either $\alpha_h(V)$ or $\beta_h(V)$ will thus extend the absolute refractory period. However, to make this perturbation as specific as possible, we will scale down both $\alpha_h(V)$ and $\beta_h(V)$ by the same factor, keeping the steady-state inactivation $h_\infty(V) = \frac{\alpha_h(V)}{\alpha_h(V)+\beta_h(V)}$ fixed.

3 (a) The stomach contributes to the digestion of food by providing a highly acidic environment. The inner surface of the stomach is lined with an epithelial layer whose cells would not survive the low pH. Cell death is prevented thanks to the secretion of a thick ($\approx$ 1mm) and insoluble mucus. The epithelial cells also produce CO_2 and the bicarbonate ion HCO_3^-, which is believed to play an important role in the protection of the epithelial tissue.

Explain how the production of HCO_3^- would help protect the epithelium from the acidic environment of the stomach. [20%]

Answer: Under an acidic environment, the bicarbonate ion would react with H^+ to produce more carbon dioxide. This contributes to the diminution of the acidity. The relevant chemical reaction is:

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

(b) To model this process, we simplify the geometry as depicted in figure 1. The epithelium is located at $x = 0$ and the stomach lumen (where food is digested) starts at $x = L$. The space in between is occupied by the mucus in which H^+, HCO_3^- and CO_2 are able to diffuse, with coefficients of diffusion D_h, D_b and D_c, respectively. Write (without solving them) reaction-diffusion equations for the concentrations of H^+, HCO_3^- and CO_2 in the mucus region, assuming a steady-state is reached. [40%]

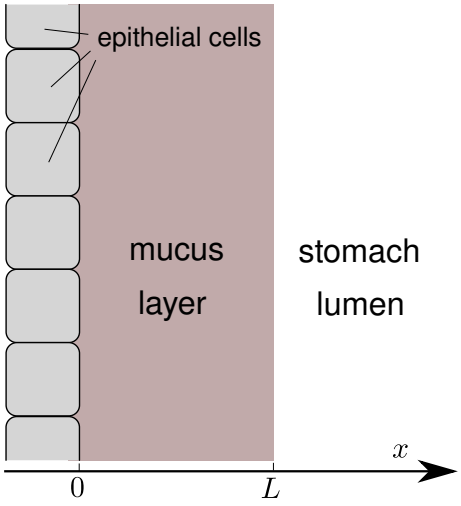


Fig. 1

Answer: Let's define the following concentration profiles: $c_h = [H^+]$, $c_b = [HCO_3^-]$ and $c_c = [CO_2]$. In the steady state, there are no time derivative in the diffusion equation, but we need to account for the relevant chemical reactions.

$$D_h \frac{d^2 c_h}{dx^2} - k^- c_h c_b + k^+ c_c = 0$$
$$D_b \frac{d^2 c_b}{dx^2} - k^- c_h c_b + k^+ c_c = 0$$
$$D_c \frac{d^2 c_c}{dx^2} + k^- c_h c_b - k^+ c_c = 0$$

(c) Figure 2 shows the sketches of six different concentration profiles. Briefly justifying your answers, indicate which one would correspond to:

(i) HCO_3^-; [10%]

(ii) H^+; [10%]

(iii) CO_2. [10%]

Answer: The bicarbonate ion is produced by the epithelial cells, and would diffuse away. (a) and (d) satisfy this constraint. Because H^+ is in large quantity, we would not expect to have any residual bicarbonate in the stomach lumen. So (a) would correspond to the bicarbonate ion.

H^+ is at its largest concentration in the stomach lumen, with a gradient leading to a flux toward the epithelial cells, so it would correspond to (e) or (f). Where the bicarbonate ion is present, it would react with it, and decrease in concentration. Considering the reaction diffusion equations, we see that the second derivatives of the concentration profiles are similar for both H^+ and bicarbonate. The bicarbonate decreases less and less with x, so H^+ would increase more and more with x. So the answer would be (e).

CO_2 is produced at the epithelium layer, and would diffuse outward. The graph (c) and (d) would lead to the right direction of diffusion. This time, the reaction diffusion equations indicate that the second derivative has the opposite sign compared to the bicarbonate ion. This is captured by the graph (c).

(d) Where on the x-axis do you expect the rate of reaction between the relevant species to be the largest? [10%]

Answer: Each profile shows two linear regions with different slopes, left and right of a transition. These correspond to the transport of the reactive species towards the place where they would primarily react. Based on the reaction diffusion equations, we expect the rate of reaction to be related to the second derivative of the concentration profiles. So the maximum reaction rate would be around the point where curvature is the largest, i.e. between the two linear domains, i.e. roughly for $x \approx 0.25L$.

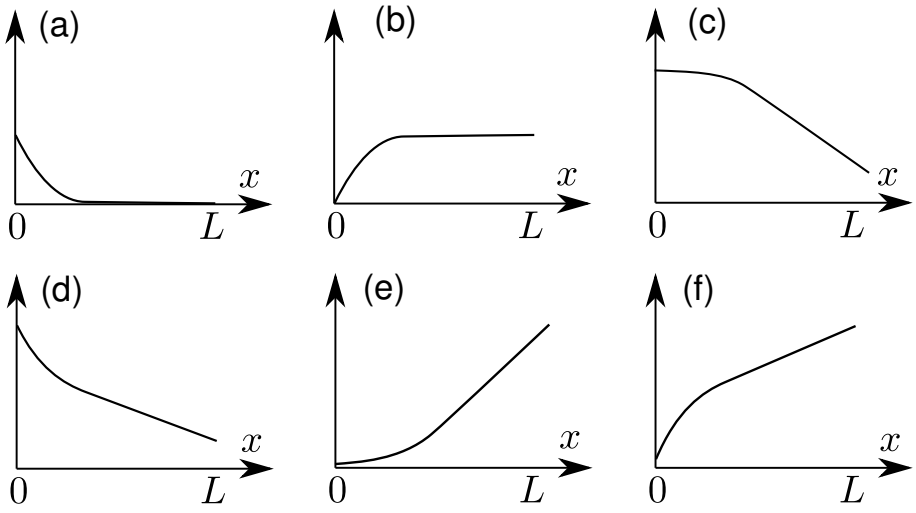


Fig. 2

4 (a) Consider a cylindrical vessel of constant radius r and length L. The vessel wall is modelled as a 2D thin material. We assume that the tension in the vessel wall along the vessel direction is negligible. Establish a relationship between the internal pressure P, external pressure P_e and tension T (force per unit length) in the circumferential direction. [20%]

Answer: Consider a small arc of the vessel of angle $d\theta$ and forces acting on it. Pressure forces contribute an outward force of magnitude $d\theta r L(P - P_e)$. Tension forces at the ends of the arc (along θ), projected along the radial direction, would balance the pressure term:

$$2T \sin(d\theta/2)L = d\theta r L(P - P_e)$$

For small angles, we get:

$$P - P_e = \frac{T}{r}$$

(b) Experimental data shows that, to the first order, the tension T is an affine function of the perimeter of the vessel cross-section:

$$T = k(2\pi r - 2\pi r_0)$$

where r_0 is the radius of the vessel in its relaxed state and k is a constant. Use this empirical expression to calculate the relationship between volume and pressure, to the first order in $r - r_0$. [15%]

Answer: We have:

$$P - P_e = \frac{k2\pi(r - r_0)}{r} = 2k\pi \frac{dr}{r_0 + dr} = 2k\pi \frac{dr}{r_0} + O(dr^2)$$

$$V = \pi r^2 L = \pi L(r_0 + dr)^2 = \pi L(r_0^2 + 2r_0 dr) + O(dr^2)$$

$$V = V_0 + 2\pi L r_0 dr + O(dr^2)$$

$$dr = r_0 \frac{P - P_e}{2k\pi}$$

$$V = V_0 + 2\pi L r_0 r_0 \frac{P - P_e}{2k\pi}$$

$$V = V_0 + L r_0^2 \frac{P - P_e}{k}$$

(c) Briefly present the experimental observations that the Windkessel model is well suited to qualitatively explain. [15%]

Answer: The Windkessel model is able to interpret the fact that the amplitude of pressure fluctuations decreases faster than the mean pressure as blood progresses along the arteries, from the heart to the capillaries.

(d) Introduce mathematically the Windkessel model and derive the relevant differential equation for the overall flow rate in the capillaries $Q_R(t)$. [25%]

Answer: The model considers arteries as a single compliant chamber of volume $V(t)$, which depend on time. The volume is assumed to be linearly related to the internal pressure $P(t)$, assumed to be uniform in the artery (i.e. no pressure waves). If C is the vessel compliance, we have $dV = CdP$. The arteries lead to the capillary beds which are modelled as a resistive component, with a flow rate Q_R proportional to the pressure difference. The pressure beyond the capillaries and pressure around the arteries are assumed to be the same (essentially atmospheric pressure) and set to 0. This leads to $P = RQ_R$, where R is a constant accounting for the hydrodynamic resistivity of the capillary network.

The change of volume per unit time of the arteries is the difference of flow rate between the input from the heart $Q(t)$ and the output to the capillaries $Q_R(t)$:

$$dV/dt = Q - Q_R$$

$$CdP/dt + Q_R = Q$$

$$RCdQ_R/dt + Q_R = Q$$

This leads to a first order linear equation, with a characteristic time RC.

(e) If the flow rate at the exit of the left heart is given by $Q(t) = Q_0(1+\sin(\omega t))$, use the Windkessel model to determine the flow rate $Q_R(t)$, and sketch it alongside $Q(t)$. How would your sketch change if the constant k introduced in part (b) was increased? [25%]

Answer: There are different ways to solve this differential equation. The simplest probably involves working with complex numbers. Take the input as $Q(t) = Q_0(1 + \exp(i\omega t))$, and look for solutions in the form $Q_R(t) = a + b\exp(i\omega t)$. (Note that we are not interested in the transient response here, which would add a decaying exponential to the solution)

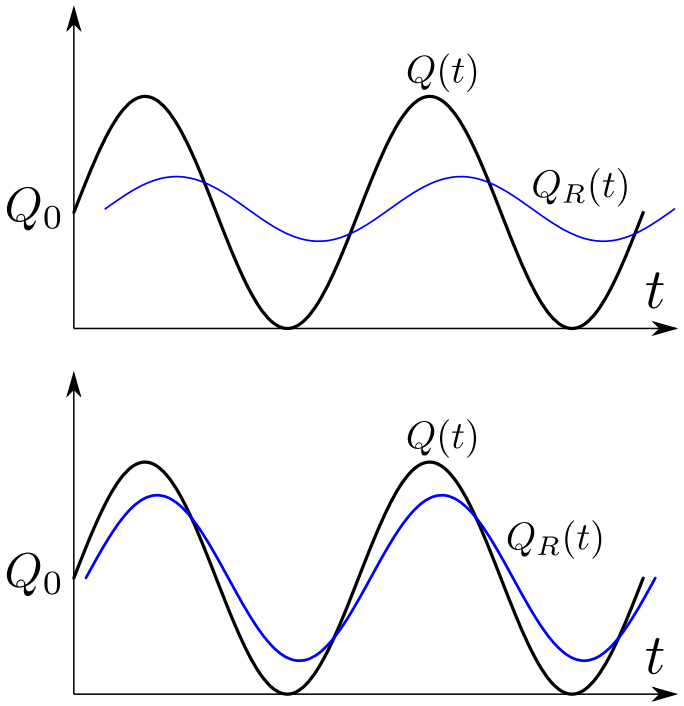
Inserting the expression for Q_R in the differential equation, we get:

$$(RCi\omega + 1)b\exp(i\omega t) + a = Q_0(1 + \exp(i\omega t))$$

This leads to $a = Q_0$ and $b = Q_0/(1 + iRC\omega)$

We see that the solution is similar to the input indeed, but the oscillating component has a decreased amplitude and a phase difference. This is what we expect since the compliance of the arteries is what causing the decrease of pressure (and flow rate) fluctuations.

The parameter k is inversely proportional to the compliance of the vessel. If k increases, the phase difference and drop in amplitude of the fluctuating component both decrease. It may then stop filtering out the pressure/flow rate fluctuations associated with the heart beat.



If k is increased significantly, the output gets closer to the original input.

END OF PAPER