Version AJK/2

EGT2
ENGINEERING TRIPOS PART IIA

Tuesday 3 May 2022 9.30 to 11.10

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 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:

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

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%]

(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^+:

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

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

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

(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%]

(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%]

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%]

(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

(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%]

(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%]

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

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%]

(b) To model this process, we simplify the geometry as depicted in Fig. 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%]

(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%]

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

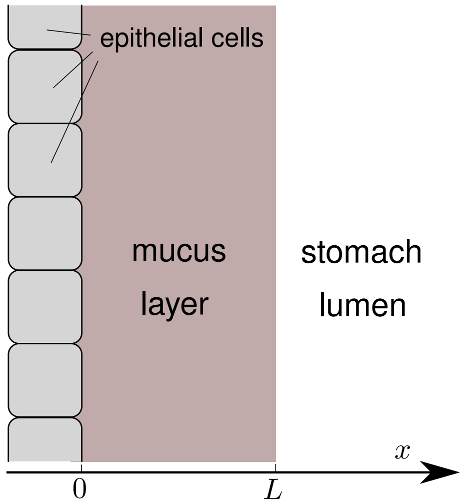

Fig. 1

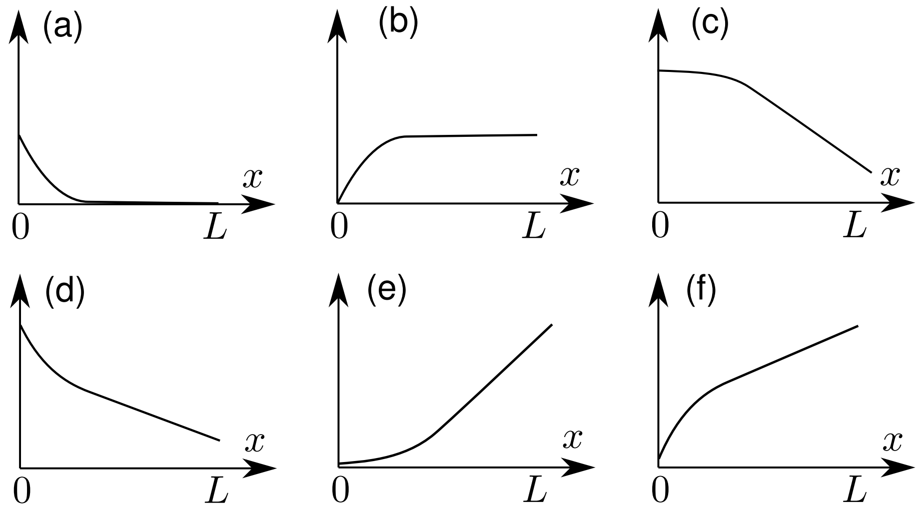

Fig. 2

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%]

(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%]

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

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

(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%]

END OF PAPER