Version AJK/2

EGT2
ENGINEERING TRIPOS PART IIA

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27 April 2018 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
Supplementary page: one extra copy of Fig. 3 (Question 4)
Engineering Data Book

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.

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 quasi steady state assumption, find the expression of the rate V of product P formation as a function of the kinetic constants and concentrations of substrate S and enzyme E.

Explain how these parameters could be extracted from a graph of $1/V$ as a function of 1/[S]. [30%]

(b) Explain what an enzyme inhibitor is. Describe qualitatively two different types of enzyme inhibition. [15%]

(c) The liver produces an enzyme called alcohol dehydrogenase (ADH) responsible for the first step of the degradation and elimination of alcohol in the body. Unfortunately, the enzyme reacts in the same way with ethylene glycol (EG), a common chemical used in anti-freeze fluids. This reaction initiates the formation of a toxic product, oxalic acid. The crucial reaction to limit is:

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

The Michaelis Menten constant characterising this reaction is $K_M = 10^{-4}$ M.

(i) Fomepizole (F) currently is the most effective treatment for EG poisoning. Its key biochemical property is to react with ADH in the following manner:

$$\mathrm{F} + \mathrm{ADH} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{D} \qquad\qquad K = \frac{k_3}{k_{-3}} = 10^6 \ \mathrm{M}^{-1}$$

What should be the concentration of Fomepizole in the body to reduce the rate of production of oxalic acid by 95% if the concentration of ethylene glycol is 5×10^{-5} M? [40%]

(ii) On 31 December 2002, the BBC reported the following news item (slightly reworded for the exam paper):

Mrs Middleton, from Forfar in Angus, drank antifreeze left on a table by a relative who she was helping decorate her house.
"There was a four to five hour waiting time at the accident and emergency department, but I got taken in after about 30 seconds. The doctors say about 100 millilitres of antifreeze is sufficient to kill you - I had between half a cupful and a cupful of the stuff. I think it's all the more dangerous because it doesn't taste bad - I thought it was particularly strongly-flavoured water. It didn't taste bitter."
She added: "The medical staff at Ninewells were concerned about me because they previously had a patient who died 22 hours after taking it. I was thinking that I was all right and that I had more important things to do but the doctor was saying to me 'you could die here, woman, you must stay'."

Doctors at Ninewells Hospital in Dundee gave her a choice of gin, vodka or whisky. She chose whisky - known as the "water of life" - and was given two cupfuls to drink immediately.

Explain why the doctors made such an unusual offer to a patient in a critical condition. [15%]

2 Consider a simple 1D diffusion model where cells move at constant velocity v either in the (+) or (-) direction along the x axis, with a probability per unit time p_+ to switch from + to -, and p_- to switch from - to +. The 1D density of cells at a particular location x and time t is $n(x,t)$.

(a) Write conservation equations for the cell density functions $n_+(x,t)$ and $n_-(x,t)$ of the (+) and (-) cell populations respectively. [20%]

(b) Use the result above to derive the following differential equation for the cell flux J defined as $J = v\,(n_+ - n_-)$.

$$\frac{\partial J}{\partial t} = -2\,Jp - v^2\,\frac{\partial (n)}{\partial x} - v\,\Delta p\,n$$

where $2p = p_+ + p_-$ and $\Delta p = p_+ - p_-$. You may use the following identity in your answer:

$$(n_+ - n_-)(p_+ + p_-) + (n_+ + n_-)(p_+ - p_-) = 2(p_+ n_+ - p_- n_-)$$

[30%]

(c) Making a suitable assumption, show that the cell density n satisfies Fick's law, with an additional drift term. Find the expression of the effective coefficient of diffusion of the cells, as well as the mean speed of the cells due to the drift term. [30%]

(d) Explain how this analysis could be exploited to model chemotaxis. [20%]

3 Consider blood flowing in an artery. The mean blood velocity at a location x along the artery is $u(x,t)$. The vessel has a homogeneous compliance c. The density of blood is ρ. We define along the vessel the cross-sectional area $A(x,t) = A_0 + cP(x,t)$ where $P(x,t)$ is the blood pressure.

(a) Explain why blood velocity can be assumed to be independent of the radial distance r in the vessel. State the physical principles used in the course to derive the equations below.

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

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

[30%]

(b) Derive a second order linear partial differential equation (the wave equation) from the equations above, making suitable assumptions in your derivation. [30%]

(c) Check that functions of the form $P(x,t) = f(x - vt)$ are solution of the wave equation derived above. Explain what v represents and find its analytical expression as a function of the physical parameters involved in this problem. [20%]

(d) Use the data available on Fig. 1 and Fig. 2 to comment on the suitability of this model. [20%]

Site		Ascending aorta	Descending aorta	Abdominal aorta	Femoral artery	Carotid artery	Arteriole	Capillary	Venule	Inferior vena cava	Main pulmonary artery
Internal diameter d_i	cm	1·5	1·3	0·9	0·4	0·5	0·005	0·0006	0·004	1·0	1·7
		1·0–2·4	0·8–1·8	0·5–1·2	0·2–0·8	0·2–0·8	0·001–0·008	0·0004–0·0008	0·001–0·0075	0·6–1·5	1·0–2·0
Wall thickness h	cm	0·065		0·05	0·04	0·03	0·002	0·0001	0·0002	0·015	0·02
		0·05–0·08		0·04–0·06	0·02–0·06	0·02–0·04				0·01–0·02	0·01–0·03
h/d_i		0·07		0·06	0·07	0·08	0·4	0·17	0·05	0·015	0·01
		0·055–0·084		0·04–0·09	0·055–0·11	0·053–0·095					
Length	cm	5	20	15	10	15	0·15	0·06	0·15	30	3·5
						10–20	0·1–0·2	0·02–0·1	0·1–0·2	20–40	3–4
Approximate cross-sectional area	cm^2	2	1·3	0·6	0·2	0·2	2×10^{-5}	3×10^{-7}	2×10^{-5}	0·8	2·3
Total vascular cross-sectional area at each level	cm^2	2	2	2	3	3	125	600	570	3·0	2·3
Peak blood velocity	$cm\,s^{-1}$	120	105	55	100		0·75	0·07	0·35	25	70
		40–290	25–250	50–60	100–120		0·5–1·0	0·02–0·17	0·2–0·5	15–40	
Mean blood velocity	$cm\,s^{-1}$	20	20	15	10						15
		10–40	10–40	8–20	10–15						6–28
Reynolds number (peak)		4500	3400	1250	1000		0·09	0·001	0·035	700	3000
α (heart rate 2 Hz)		13·2	11·5	8	3·5	4·4	0·04	0·005	0·035	8·8	15
Calculated wave-speed c_0	$cm\,s^{-1}$	580		770	840	850				100	350
Measured wave-speed c	$cm\,s^{-1}$	500		700	900	800				400	250
		400–600		600–750	800–1030	600–1100				100–700	200–330
Young's modulus E	$Nm^{-2}\times10^5$	4·8		10	10	9				0·7	6
		3–6		9–11	9–12	7–11				0·4–1·0	2–10

Fig. 1

(cont.

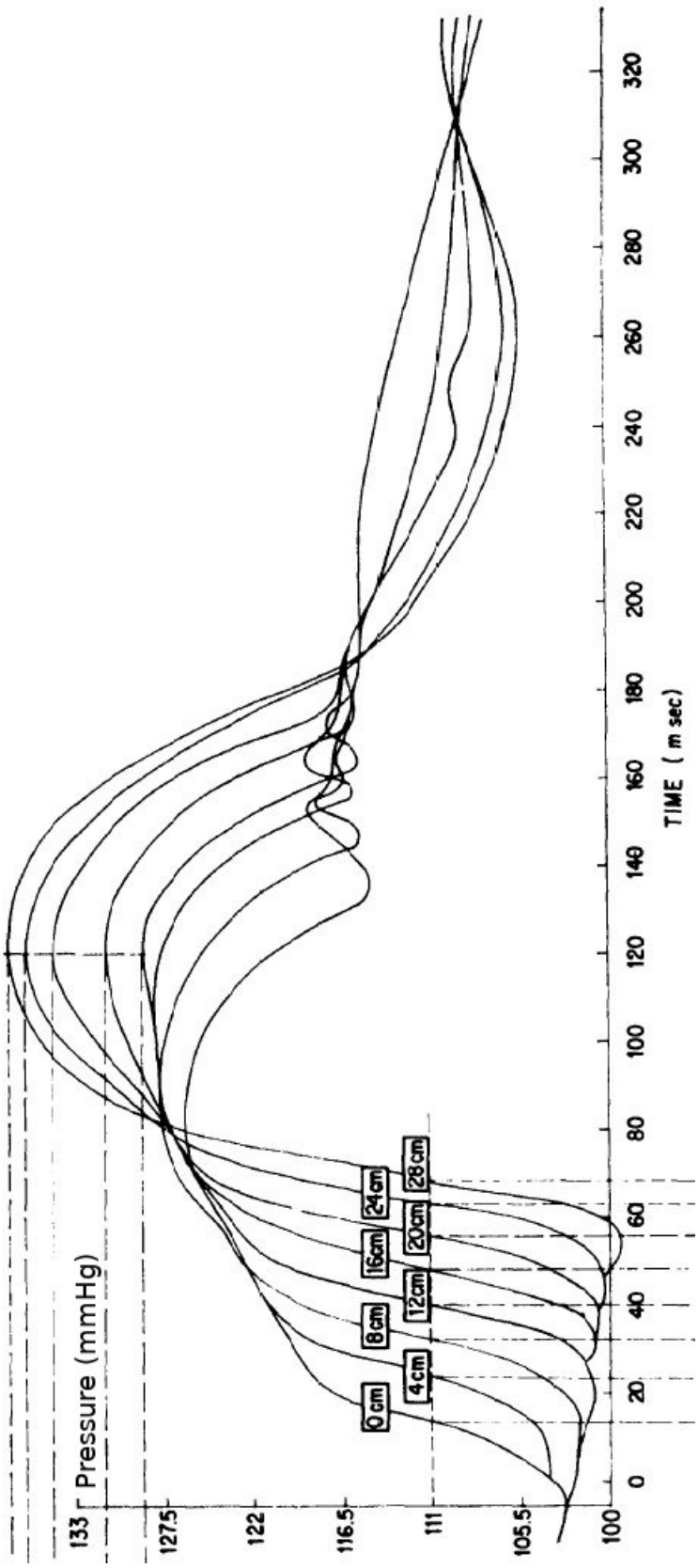

Fig. 2

(TURN OVER

4 (a) What ions carry the main currents that contribute to action potential generation in the Hodgkin-Huxley model? [10%]

(b) Imagine you want to design a drug that accelerates the upstroke of the action potential, but leaves other characteristics of the action potential unchanged as much as possible. Which rate constants would be its ideal targets and how should they be affected? [30%]

(c) The time-evolution of the four variables in the Hodgkin-Huxley model during an action potential evoked by a brief current pulse (denoted by I) is given in Fig. 3. Sketch on the additional copy of Fig. 3 how the dynamics of the system will change qualitatively for the same stimulation if the inactivating gate is blocked ($h = 1$ at all times), and all other variables start from the same initial condition as in the normal case. Describe in words the changes you expect before, during, and after the upstroke of the action potential and explain why you expect them. [60%]

An additional copy of Fig. 3 is attached to the back of this paper. It should be detached and handed in with your answers.

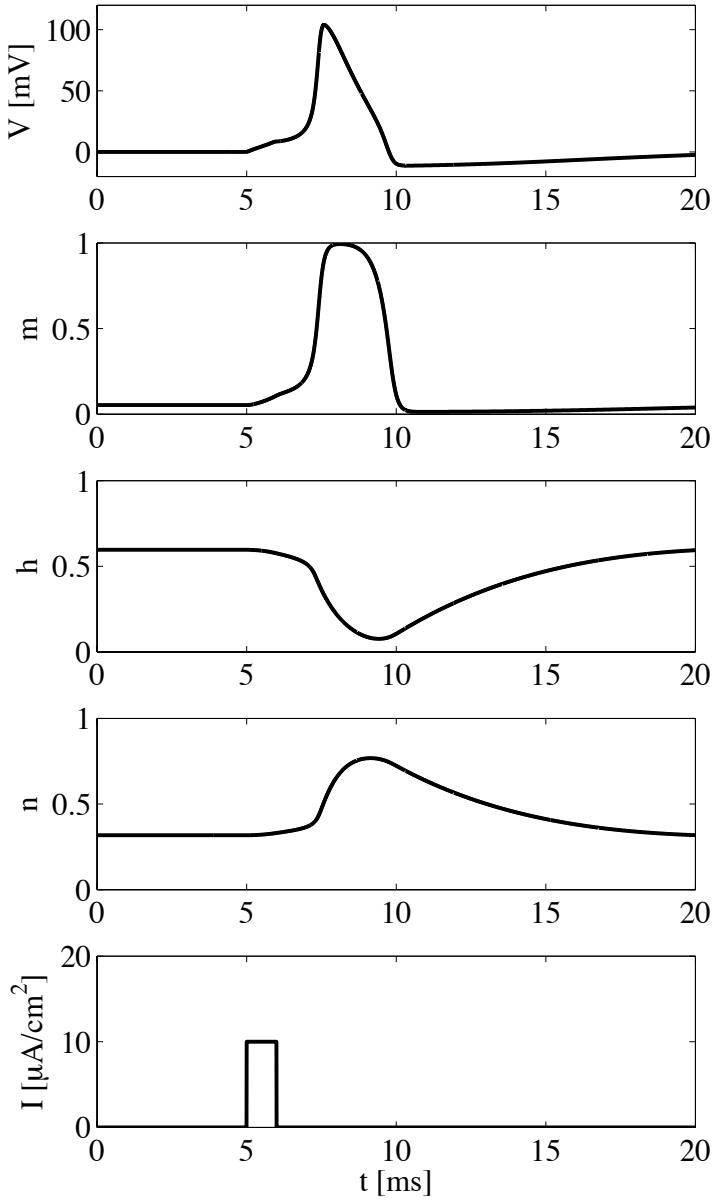

Fig. 3

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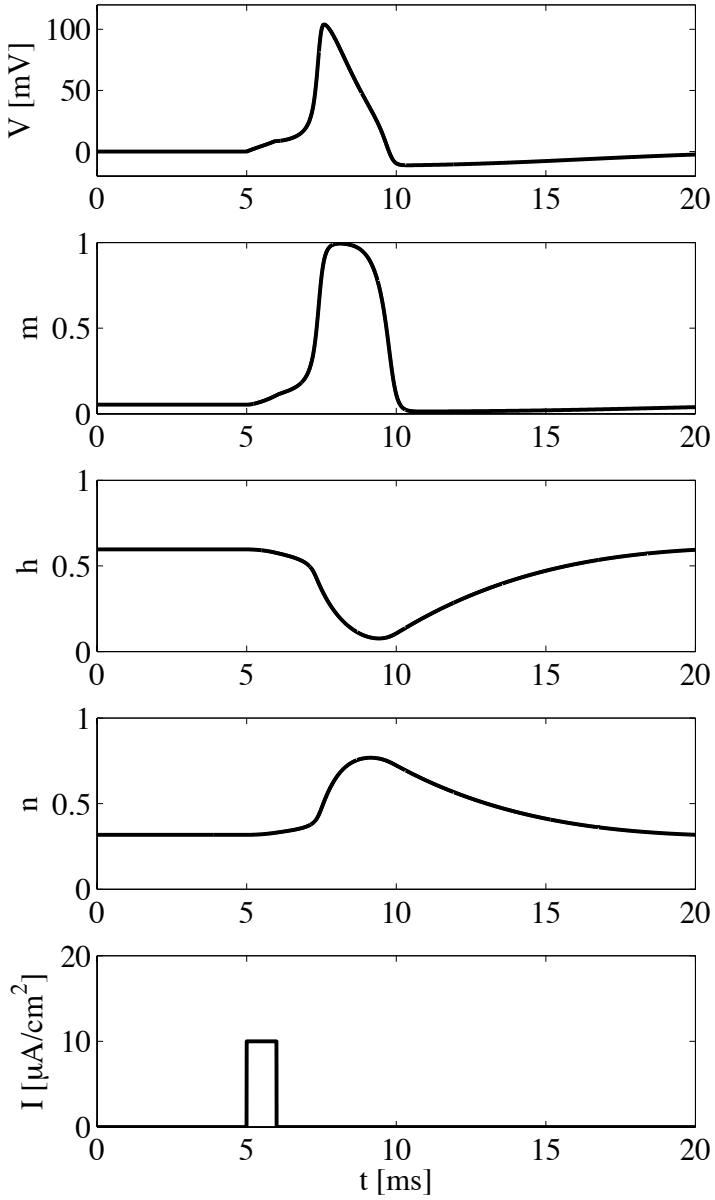
Version AJK/2 Candidate Number:

EGT3
ENGINEERING TRIPOS PART IIA
27 April 2018, Module 3G2, Question 4.



Extra copy of Fig. 3: Action potential for Question 4.