A12214W1

SECOND PUBLIC EXAMINATION

Honour School of Mathematics Part C: Paper C5.12
Honour School of Mathematics and Statistics Part C: Paper C5.12
Master of Science in Mathematical Sciences: Paper C5.12

Mathematical Physiology

TRINITY TERM 2024

Thursday 30 May, 09:30am to 11:15am

You may submit answers to as many questions as you wish but only the best two will count for the total mark. All questions are worth 25 marks.

You should ensure that you observe the following points:

- start a new answer booklet for each question which you attempt.
- indicate on the front page of the answer booklet which question you have attempted in that booklet.
- cross out all rough working and any working you do not want to be marked. If you have used separate answer booklets for rough work please cross through the front of each such booklet and attach these answer booklets at the back of your work.
- hand in your answers in numerical order.

If you do not attempt any questions, you should still hand in an answer booklet with the front sheet completed.

Do not turn this page until you are told that you may do so

1. (a) A dimensionless version of the Fitzhugh–Nagumo equations for nerve action potentials is

$$\epsilon \frac{\mathrm{d}v}{\mathrm{d}t} = f(v) - w, \qquad \frac{\mathrm{d}w}{\mathrm{d}t} = v, \tag{1}$$

where $f(v) = -v(v-\alpha)(v-1)$, where ϵ and α are constants, with $0 < \epsilon \ll 1$ and $0 < \alpha < 1$.

(i) [2 marks] Outline what v and w represent physically.

(ii) [6 marks] Draw the nullclines on the (v, w) phase plane and show that the only equilibrium point is $(0, 0)$. Use the phase plane to show that a trajectory starting from $(v, w) = (v^*, 0)$, where v^* is a constant, is linearly stable for $0 < v^* < v_0$ and displays excitable dynamics for $v_0 < v^* < 1$ for some v_0 to be specified. Indicate the fast and slow parts of the excitable trajectory, and sketch a graph of $v(t)$ in both the linearly stable and excitable cases.

(b) Now consider the spatial version of equation (1):

$$\epsilon \frac{\partial v}{\partial t} = \epsilon^2 \frac{\partial^2 v}{\partial x^2} + f(v) - w, \qquad \frac{\partial w}{\partial t} = v. \tag{2}$$

Additionally, assume v, w tend to zero as $x \to \pm\infty$.

(i) [6 marks] Consider the travelling wave solution $v(y)$ where $y = (x - ct)/\epsilon$ and c is a positive constant. Show that, to leading order in ϵ, the behaviour is governed by the first-order system

$$\frac{\mathrm{d}v}{\mathrm{d}y} = p, \qquad \frac{\mathrm{d}p}{\mathrm{d}y} = -cp - f(v), \tag{3a,b}$$

where (3a) corresponds to the definition of p. Hence show that

$$\frac{\mathrm{d}p}{\mathrm{d}v} = \frac{-cp - f(v)}{p}, \tag{4}$$

with $v \to 0$ as $y \to \infty$ and $v \to 1$ as $y \to -\infty$.

(ii) [6 marks] By imposing the ansatz $p = Av(1-v)$ for some constant A, find the required value of the constant A and the wave speed c that satisfies (4). Hence find the solution $v(y)$.

(iii) [5 marks] After the fast phase described by the travelling wave, found in part (b)(i), the trajectory in (v, w) phase space will follow the v nullcline closely, moving in the direction of increasing w. Assume that the trajectory departs from the v nullcline at $w = w^*$, where w^* is a constant, and then enters a second fast phase. By taking a similar approach to part (b)(i), derive an analogous equation to (4) for the behaviour in this second fast phase and state the boundary conditions. Explain how the value of w^* is determined.

2. Consider the following enzyme reaction scheme:

$$\xrightarrow{k_1} S_1 \tag{1a}$$

$$2S_2 + E \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ES_2^2 \tag{1b}$$

$$S_1 + ES_2^2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} S_1ES_2^2 \overset{k_4}{\rightarrow} ES_2^2 + S_2 \tag{1c}$$

$$S_2 \overset{k_5}{\rightarrow} \tag{1d}$$

where S_1 and S_2 are different species, E is an enzyme, and k_i, $1 \leqslant i \leqslant 5$, k_{-2} and k_{-3} are all constants. Reaction (1a) corresponds to creation of species S_1 at a rate k_1 while reaction (1d) corresponds to removal of species S_2 at a rate k_5.

(a) [5 marks] Explain the physical processes that reactions (1b) and (1c) describe.

(b) [6 marks] Write down a system of ordinary differential equations that describe the time evolution of the concentrations of the species S_1, S_2 and the complexes $X_1 \equiv ES_2^2$ and $X_2 \equiv S_1ES_2^2$ and state a conservation law for the amount of enzyme.

(c) [4 marks] Consider now a simplified dimensionless version of the reaction scheme (1):

$$\frac{\mathrm{d}s_1}{\mathrm{d}t} = \alpha - 2x_1s_1 + x_2, \tag{2a}$$

$$\frac{\mathrm{d}s_2}{\mathrm{d}t} = s_2^2(1 - x_1 - x_2) - x_1 + x_2 - s_2, \tag{2b}$$

$$\epsilon\frac{\mathrm{d}x_1}{\mathrm{d}t} = x_2 - s_1x_1 + \frac{1}{2}\left[s_2^2(1 - x_1 - x_2) - x_1\right], \tag{2c}$$

$$\epsilon\frac{\mathrm{d}x_2}{\mathrm{d}t} = s_1x_1 - x_2, \tag{2d}$$

where $\alpha > 0$ and $0 < \epsilon \ll 1$ are constants.

Find expressions for $x_1(s_1, s_2)$ and $x_2(s_1, s_2)$ in the quasistatic limit $\epsilon \ll 1$ and show that s_1 and s_2 satisfy the following ordinary differential equations:

$$\frac{\mathrm{d}s_1}{\mathrm{d}t} = \alpha - f, \tag{3a}$$

$$\frac{\mathrm{d}s_2}{\mathrm{d}t} = f - s_2, \tag{3b}$$

where

$$f = f(s_1, s_2) = \frac{s_1s_2^2}{1 + s_1s_2^2 + s_2^2}. \tag{4}$$

(d) [3 marks] Find any physically realistic equilibrium points (s_1^*, s_2^*) and comment on how their existence depends on α.

(e) [3 marks] By considering a linearization of the equations about the equilibrium point, via $s_1 = s_1^* + \delta\tilde{s}_1$, $s_2 = s_2^* + \delta\tilde{s}_2$, where $0 < \delta \ll 1$, show that the stability of the equilibrium point is determined by the sign of $g(\alpha) = h(s_1^*(\alpha), s_2^*(\alpha))$ where

$$h(s_1, s_2) = \frac{\partial f}{\partial s_1} - \frac{\partial f}{\partial s_2} + 1. \tag{5}$$

(f) [4 marks] By calculating $h(s_1, s_2)$ and using this to consider $g(\alpha)$ when $\alpha \to 0$ and $\alpha \to 1$, show that the stability of the equilibrium point must change nature at some value $\alpha^\dagger \in (0, 1)$. (You do not need to find the specific value of $\alpha^\dagger$.)

3. (a) [4 marks] Draw a schematic of the pressure–volume cycle of the left ventricle (p_{LV}, V_{LV}) indicating the systole, ejection, diastole, and refilling phases. Your diagram should include the places when: (A) the mitral valve closes; (B) the aortic valve opens; (C) the aortic valve closes; and (D) the mitral valve opens. You should also label the stroke volume and any phases in which V_{LV} is approximately constant and explain why this is the case.

(b) [3 marks] What is meant by the compliance of the component vessels of the circulation? During ventricular contraction, the compliance C_{LV} jumps from a high value C_d to a low value C_s, while during relaxation it jumps back. Draw a graph of how the compliance C_{LV} varies with time t and label the points A, B, C and D that correspond to those in part (a).

(c) [6 marks] A simple model of the circulation consists of a left ventricle (with mitral and aortic valves), arteries, veins and capillaries. Show that a simple compartment model for this system which describes the volumes of the arteries, veins and ventricle can be written in the form

$$\frac{\mathrm{d}V_a}{\mathrm{d}t} = Q_+ - Q_c, \qquad \frac{\mathrm{d}V_v}{\mathrm{d}t} = Q_c - Q_-, \qquad \frac{\mathrm{d}V_{LV}}{\mathrm{d}t} = Q_- - Q_+,$$

where

$$Q_c = \frac{p_a - p_v}{R_c}, \qquad Q_+ = \frac{[p_{LV} - p_a]_+}{R_a}, \qquad Q_- = \frac{[p_v - p_{LV}]_+}{R_v},$$

and

$$V_a = V_a^* + C_a p_a, \qquad V_v = V_v^* + C_v p_v, \qquad V_{LV} = V_{LV}^* + C_{LV} p_{LV},$$

and describe the meaning of the variables.

(d) [3 marks] Consider a dimensionless, scaled version of the model of the circulation:

$$\delta \frac{\mathrm{d}p_a}{\mathrm{d}t} = -\delta\,(p_a - \delta p_v) + [p_{LV} - p_a]_+\,, \tag{1a}$$

$$\delta \frac{\mathrm{d}p_v}{\mathrm{d}t} = \delta\,(p_a - \delta p_v) - [\delta p_v - p_{LV}]_+\,, \tag{1b}$$

$$\delta \frac{\mathrm{d}}{\mathrm{d}t}\,(C_{LV} p_{LV}) = \delta\,[\delta p_v - p_{LV}]_+ - [p_{LV} - p_a]_+\,, \tag{1c}$$

where $0 < \delta \ll 1$, and all other variables are treated as order one, with initial conditions

$$p_a(0) = p_a^0, \qquad p_v(0) = p_v^0 \qquad p_{LV}(0) = p_{LV}^0, \qquad C_{LV}(0) = C_d, \tag{2}$$

where p_a^0, p_v^0, p_{LV}^0 and C_d are all order-one constants.

Consider the isovolumetric contraction (systole) phase. By scaling $t = \delta^2 T$ and supposing that this phase takes place over a time $T = T_1$, find the values of the pressures at the end of this phase, say p_a^1 and p_v^1 and p_{LV}^1, in terms of the values at the beginning of the phase, p_a^0, p_v^0 and p_{LV}^0.

(e) [5 marks] Now consider the ejection phase, where $C_{LV} = C_s$. Assuming that $p_{LV} > p_a$ for the duration of this phase, show that

$$(1 + C_s)\frac{\mathrm{d}p_a}{\mathrm{d}t} = -p_a, \tag{3}$$

to leading order in δ. By using this result along with the system (1) at leading order in δ, solve for p_a, p_v and p_{LV} in this phase, subject to the initial conditions $p_a(0) = p_a^1$, $p_v(0) = p_v^1$ and $p_{LV}(0) = p_{LV}^1$. Use the result to state a condition relating p_a^0 to p_{LV}^0.

(f) [4 marks] If the ejection phase lasts for a time t_2, use the results from part (d) to write down the total volume ejected from the left ventricle. Explain why we might expect the compliance to fall with age. Suppose that $C_s = 1/n$, where n is a measure of the age of the person, and suppose that $p_a^0 = (1 - \exp(-n))/n$. Show that this leads to an age at which the volume of blood ejected from the left ventricle is a maximum. (You do not need to find the location or value of this maximum.)