A12214W1

SECOND PUBLIC EXAMINATION

Honour School of Mathematics Part C: Paper C5.12

MATHEMATICAL PHYSIOLOGY

Exam date

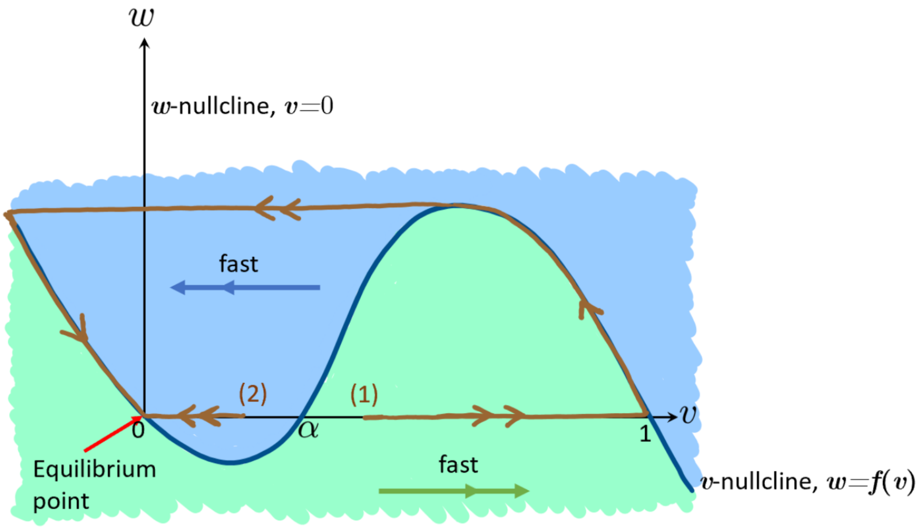
You may submit answers to as many questions as you wish but only the best two will count for the total mark.

You must start a new booklet for each question which you attempt. Indicate on the front sheet the numbers of the questions attempted. A booklet with the front sheet completed must be handed in even if no question has been attempted.

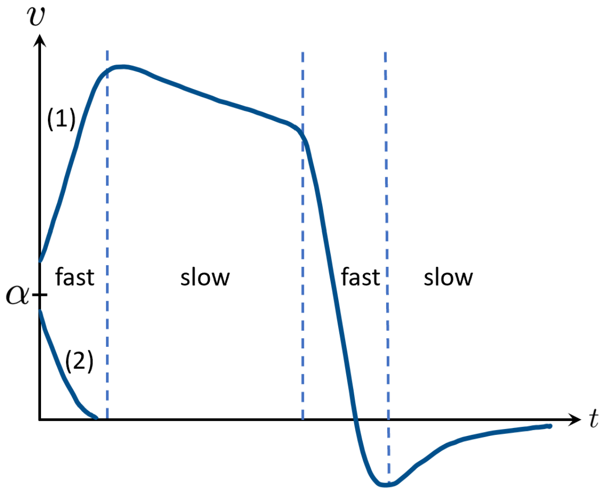
Do not turn this page until you are told that you may do so

1. (a) (i) [2 marks] [Bookwork]
v represents the membrane action potential. [1 mark]
w represents the gating potential. [1 mark]

(ii) [6 marks] [Bookwork]



[2 marks] Equilibrium points occur when $\mathrm{d}v/\mathrm{d}t = \mathrm{d}w/\mathrm{d}t = 0$, which gives $v = 0$ and $w = f(0) = 0$, so $(v, w) = (0, 0)$ is the unique equilibrium point. [1 mark]
If $0 < v^* < v_0$ and $v_0 = \alpha$ then v decays to zero and is linearly stable. (Case (2) on figure). [1 mark]
If $v_0 < v^* < 1$ and $v_0 = \alpha$ then v undergoes an excursion as indicated on the phase plane (Case (1) on figure). [1 mark]



[1 mark]

(b) (i) [6 marks] [Similar ideas to lectures]
[Equations highlighted in red correspond to the numbers used in the question, to distinguish from the numbering in the solution.]

Setting $y = (x - ct)/\epsilon$ gives

$$\frac{\partial}{\partial x} = \frac{1}{\epsilon}\frac{\mathrm{d}}{\mathrm{d}y}, \qquad \frac{\partial}{\partial t} = -\frac{c}{\epsilon}\frac{\mathrm{d}}{\mathrm{d}y}.$$

Substituting this into equation (1) gives

$$\frac{\mathrm{d}^2 v}{\mathrm{d}y^2} + c\frac{\mathrm{d}v}{\mathrm{d}y} + f(v) - w = 0, \qquad \frac{\mathrm{d}w}{\mathrm{d}y} = -\frac{\epsilon v}{c}. \tag{1a,b}$$

[2 marks]

Equation (1b) gives $w =$constant to leading order in ϵ and so $w = 0$ since $w \to 0$ as $y \to \infty$ since $w = 0$ ahead of the wavefront. [1 mark]
Equation (1a) then gives

$$\frac{\mathrm{d}^2 v}{\mathrm{d}y^2} + c\frac{\mathrm{d}v}{\mathrm{d}y} + f(v) = 0. \tag{2}$$

If we define

$$p = \frac{\mathrm{d}v}{\mathrm{d}y} \tag{3}$$

then (2) becomes

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

[1 mark]

If we divide (3) by (4) this gives

$$\frac{\mathrm{d}p}{\mathrm{d}v} = \frac{-cp - f(v)}{p}, \tag{5}$$

as required. [1 mark]
The travelling wave must have $v \to 0$ as $y \to \infty$ and $v \to 1$ as $y \to -\infty$ to take it from the fixed point $(v, w) = (0, 0)$ to $(v, w) = (1, 0)$. [1 mark]

(ii) [6 marks] [New material]
Try $p = Av(1 - v)$. Substituting into (5) gives

$$(2A^2 - 1)v^2 + (1 - 3A^2 - Ac + \alpha)v + (A^2 + Ac - \alpha) = 0.$$

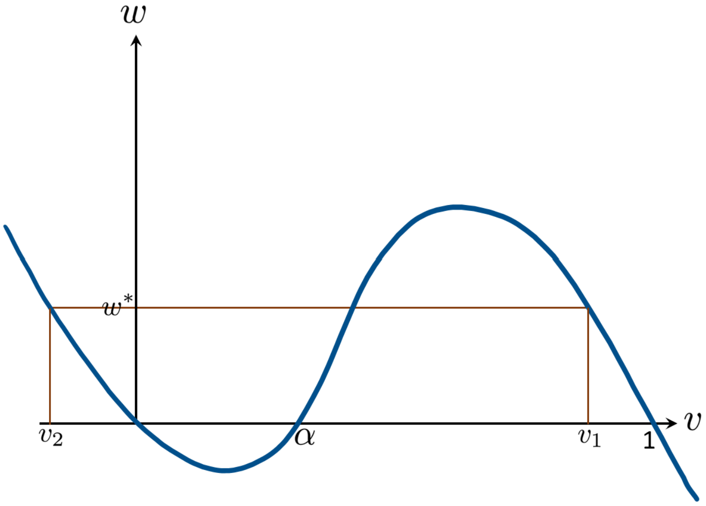
Equating coefficients of v^2 gives $A = \pm 1/\sqrt{2}$. [1 mark]
We take the negative root to satisfy the boundary conditions (see later in this part). [1 mark]
Equating coefficients of v gives $c = -\sqrt{2}(\alpha - 1/2)$. [1 mark]
The constant terms are then identically satisfied. [1 mark]
So $p = -v(1-v)/\sqrt{2}$. Since $p = \mathrm{d}v/\mathrm{d}y =$ by definition, we may separate the variables and integrate to obtain

$$v = \frac{1}{D + \exp\left(y/\sqrt{2}\right)},$$

for some constant D. [2 marks]
We see that $v \to 0$ as $y \to \infty$ and $v \to 1$ as $y \to -\infty$ as required by the boundary conditions. We note that if we had taken the positive root $A = 1/\sqrt{2}$ then these boundary conditions would have been reversed.
We can set $D = 1$ without loss of generality, so that $v(0) = 1/2$. This just corresponds to removing the translational invariance in the travelling wave solution. This gives

$$v = \frac{1}{1 + \exp\left(y/\sqrt{2}\right)}.$$

(iii) [5 marks] [New material]



Now we suppose that the trajectory departs the w-nullcline when $w = w^*$. From (1b), $\mathrm{d}w/\mathrm{d}y = 0$ to leading order in ϵ, so $w =$ constant $= w^*$ on the second travelling wave solution [1 mark] .
In (1a) this gives

$$\frac{\mathrm{d}^2 v}{\mathrm{d}y^2} - c\frac{\mathrm{d}v}{\mathrm{d}y} + f(v) - w^* = 0,$$

where we have chosen the wave speed $-c = \sqrt{2}(\alpha - 1/2)$ for the reverse wave. There is a unique value of w^* for each corresponding wave speed so this sets w^*. [1 mark]
This is subject to the boundary conditions

$$v \to v_1 \quad \text{as} \quad y \to \infty, \quad \text{and} \quad v \to v_2 \quad \text{as} \quad y \to -\infty.$$

[1 mark]
We note that once w^* is specified, v_1 and v_2 are also determined. In an analogous fashion to the front wave, in this case it is now w^* rather than the wave speed c that we determine. [2 marks]

2. (a) [5 marks] [Bookwork]

Reaction (1a): S_1 is created at a rate k_1. This is a one-way reaction. (Given in question).
Reaction (1b): Two molecules of S_2 combine with enzyme E to form a product $X_1 = ES_2^2$ at a rate k_2. The reverse reaction of dissociation of X_1 into two molecules of S_2 and enzyme E takes place at a rate k_{-2}. [2 marks]
Reaction (1c): The complex X_1 combines with one molecule of S_1 to form a product $X_2 = S_1 E S_2^2$ at a rate k_3. The reverse reaction takes place at a rate k_{-3}. [2 marks]
The species X_2 dissociates, after undergoing the enzyme reaction, into X_1 and S_2 at a rate k_4. This is a one-way reaction. [1 mark]
Reaction (1d): S_2 is removed from the system at a rate k_5. This is a one-way reaction. (Given in question.)

(b) [6 marks] [Application of ideas in lectures to a new example]

The following system of ordinary differential equations describes the reaction scheme (1):

$$\frac{\mathrm{d}\hat{s}_1}{\mathrm{d}\hat{t}} = k_1 - k_3\hat{s}_1\hat{x}_1 + k_{-3}\hat{x}_2, \qquad \text{[1 mark]} \tag{6}$$

$$\frac{\mathrm{d}\hat{s}_2}{\mathrm{d}\hat{t}} = -k_2\hat{s}_2^2\hat{e} + k_{-2}\hat{x}_1 + k_4\hat{x}_2 - k_5\hat{s}_2, \qquad \text{[1 mark]} \tag{7}$$

$$\frac{\mathrm{d}\hat{x}_1}{\mathrm{d}\hat{t}} = k_2\hat{s}_2^2\hat{e} - k_{-2}\hat{x}_1 - k_3\hat{s}_1\hat{x}_1 + k_{-3}\hat{x}_2 + \hat{k}_4\hat{x}_2, \qquad \text{[1 mark]} \tag{8}$$

$$\frac{\mathrm{d}\hat{x}_2}{\mathrm{d}\hat{t}} = k_3\hat{s}_1\hat{x}_1 - k_{-3}\hat{x}_2 - \hat{k}_4\hat{x}_2, \qquad \text{[1 mark]} \tag{9}$$

where $\hat{s}_i$ and $\hat{x}_i$ denote, respectively, the concentrations of species S_i and X_i for $i = 1, 2$, $\hat{e}$ denotes the concentration of enzyme, and $\hat{t}$ denotes time. [1 mark] (Note the hats have been added to distinguish from their dimensionless counterparts used later in this question.) Conservation of enzyme leads to the relationship $\hat{e} + \hat{x}_1 + \hat{x}_2 =$constant. [1 mark]

(c) [4 marks] [Standard calculation]

[Equations highlighted in red correspond to the numbers used in the question, to distinguish from the numbering in the solution.]
Setting $\epsilon = 0$ in equation (2d) gives

$$x_2 = s_1 x_1. \tag{10}$$

Recognizing that equation (2d) means that the terms in the square brackets of equation (2c) must equal zero, substituting for x_2 using (10) gives

$$x_1 = \frac{f(s_1, s_2)}{s_1}, \qquad \text{[1 mark]} \tag{11}$$

$$x_2 = f(s_1, s_2), \qquad \text{[1 mark]} \tag{12}$$

where

$$f = \frac{s_1 s_2^2}{1 + s_1 s_2^2 + s_2^2}. \tag{13}$$

Equations (2a,b) then become the required expressions (3) in the question. [2 marks]

(d) [3 marks] [Standard calculation]

In equilibrium, setting time derivatives to zero, gives

$$\alpha = f(s_1^*, s_2^*), \qquad f(s_1^*, s_2^*) = s_2^*. \tag{14}$$

Rearranging these equations gives

$$s_1^* = \frac{(1+\alpha^2)}{(1-\alpha)\alpha}, \qquad\qquad s_2^* = \alpha. \qquad\qquad \text{[2 marks]} \tag{15}$$

When $\alpha > 1$, $s_1 < 0$ and so the solution is non-physical. When $\alpha < 0$, $s_2 < 0$ and the solution is non-physical. This can also be seen from the definition of f, which indicates that $0 \leqslant f < 1$ and so equilibria exist only for $0 \leqslant \alpha < 1$. [1 mark]

(e) [4 marks] [New idea]
Linearization of the equations about the equilibrium state via $s_i = s_i^* + \delta \tilde{s}_i$, $i = 1, 2$ where $\delta \ll 1$ gives

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix}\tilde{s}_1\\ \tilde{s}_2\end{pmatrix} = \begin{pmatrix}-F_1 & -F_2\\ F_1 & F_2-1\end{pmatrix}\begin{pmatrix}\tilde{s}_1\\ \tilde{s}_2\end{pmatrix}, \tag{16}$$

where

$$F_i = \left.\frac{\partial f}{\partial s_i}\right|_{(s_1^*, s_2^*)} \qquad\qquad \text{for} \quad i = 1, 2. \tag{17}$$

[1 mark]
Eigenvalues λ satisfy

$$\begin{vmatrix}-F_1-\lambda & -F_2\\ F_1 & F_2-1-\lambda\end{vmatrix} = 0, \tag{18}$$

and so

$$\lambda_\pm = \frac{-(F_1-F_2+1) \pm \sqrt{(F_1-F_2+1)^2 - 4F_1}}{2}. \tag{19}$$

[1 mark]
Thus, if we define

$$h(s_1, s_2) = \frac{\partial f}{\partial s_1} - \frac{\partial f}{\partial s_2} + 1. \tag{20}$$

and $g(\alpha) = h(s_1^*(\alpha), s_2^*(\alpha))$ then the equilibrium point is stable if $g(\alpha) > 0$, provided $F_1(s_1^*(\alpha), s_2^*(\alpha)) > 0$, which can straightforwardly be shown to be true since

$$F_1(s_1, s_2) = \frac{s_2^2(1+s_2^2)}{\left(1+(1+s_1)s_2^2\right)^2} > 0 \qquad\qquad \text{for all } s_1 \text{ and } s_2.$$

[1 mark]

(f) [4 marks] Consider $h(s_1, s_2)$:

$$h(s_1, s_2) = \frac{s_2\left(s_2 - 2s_1 + s_2^3\right)}{\left(1 + s_1 s_2^2 + s_2^2\right)^2} + 1. \tag{21}$$

We may examine the behaviour near $\alpha = 0$ by considering $\alpha = \mu$ with $\mu \ll 1$. Here,

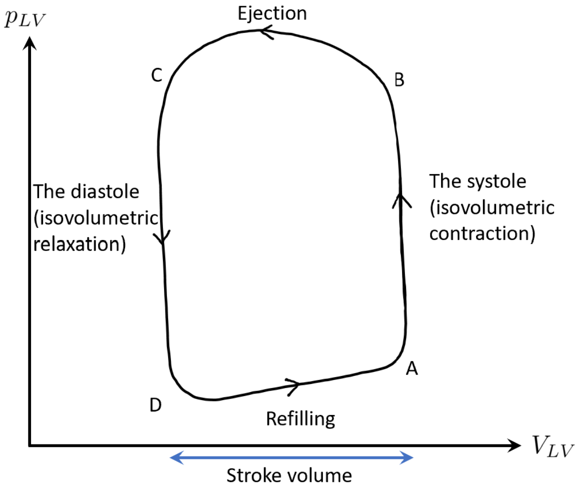
$$s_2^* = \mu, \qquad\qquad s_1^* \sim \frac{1}{\mu}, \tag{22}$$

so $g \to -1$ as $\alpha \to 0^+$. [2 marks]
We may examine the behaviour near $\alpha = 1$ by considering $\alpha = 1 - \mu$ with $\mu \ll 1$. Here,

$$s_2^* \sim 1, \qquad\qquad s_1^* \sim \frac{2}{\mu}, \tag{23}$$

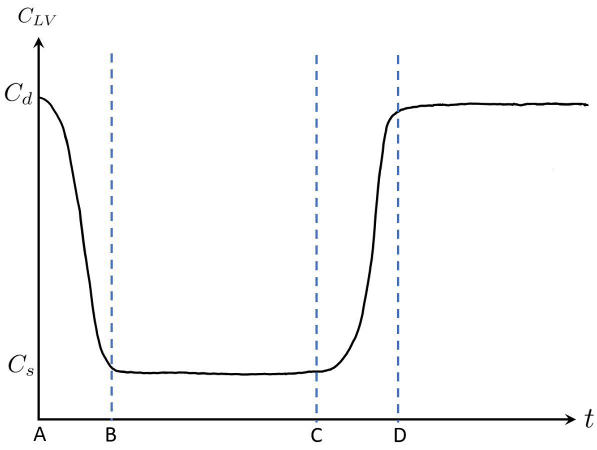
so $g \to 1$ as $\alpha \to 1^-$. [1 mark]
Thus, since $g(\alpha)$ changes sign between 0 and 1, the stability of the equilibrium must change at some $\alpha = \alpha^\dagger$, with the fixed point stable for $0 < \alpha < \alpha^\dagger$ and unstable for $\alpha^\dagger < \alpha < 1$; $\alpha^\dagger$ is given by the implicit relation $g(\alpha^\dagger) = 1$. [1 mark]

3. (a) [4 marks] [Bookwork]



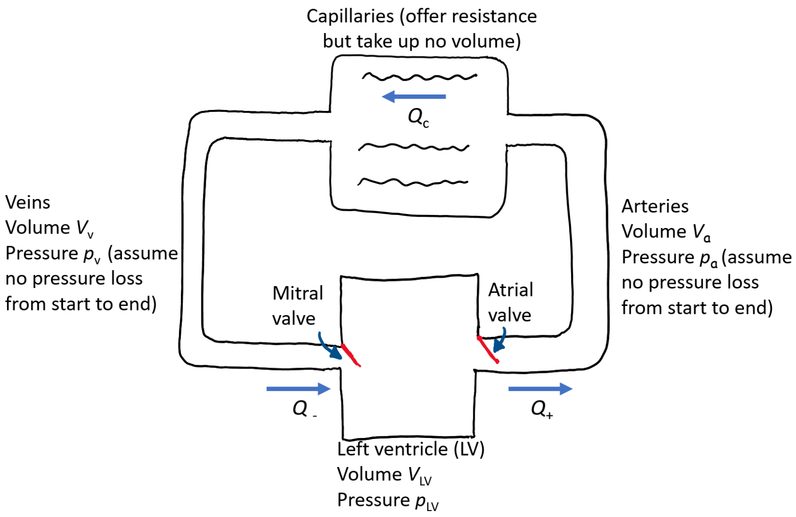
(A) the mitral valve closes; (B) the aortic valve opens; (C) the aortic valve closes; and (D) the mitral valve opens. [3 marks] V_{LV} is approximately constant between A and B and between C and D because here both valves are closed. [1 mark]

(b) [3 marks] [Bookwork]
The compliance is the balloon-like property of the blood vessel walls that allows for their distension under increased internal pressure. [1 mark]



[2 marks]

(c) [6 marks] [Bookwork]



[2 marks]

Blood is incompressible but the blood vessels are compliant so the pressure and volume in different parts of the network can change with time.

Conservation of blood in the arteries, veins and left ventricle give, respectively,

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

where Q_-, Q_+ and Q_c are, respectively, the flow rate into and out of the left ventricle and the flow rate in the capillaries. The flow rate in each compartment is proportional to the pressure drop, with the constant of proportionality being the inverse resistance of that compartment. This gives

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

Here, p_a, p_v and p_{LV} are the pressures in the arteries, veins and left ventricle, respectively, and R_c, R_a and R_v are the resistances offered by the capillaries, arteries and veins, respectively; $[f]_+ = f$ if $f > 0$ and $[f]_+ = 0$ if $f \leqslant 0$. This ensures that blood flow only occurs in directions of decreasing pressures. The volume occupied by the blood in the arteries, V_a, veins, V_v and left ventricle, V_{LV} are related to the pressures via

$$V_a = V_a^* + C_a p_a, \qquad V_v = V_v^* + C_v p_v, \qquad V_{LV} = V_{LV}^* + C_{LV} p_{LV}, \tag{1a–c}$$

where C_a, C_v and C_{LV} are the compliances of the arteries, veins and left ventricle, respectively, and V_a^*, V_v^* and V_{LV}^* all denote baseline volumes when the pressures are zero. The compliance is equal to the inverse of the elastance. A low value of compliance corresponds to vessels that are tight and resist changes in volume. A high value of compliance corresponds to vessels that are loose and permit appreciable changes in volume. [4 marks]

(d) [3 marks] [Generalization of ideas discussed in lectures]

Scaling $t = \delta^2 T$ gives, to leading order in δ,

$$\frac{\mathrm{d}p_a}{\mathrm{d}T} = 0 \qquad \frac{\mathrm{d}p_v}{\mathrm{d}T} = 0, \qquad \frac{\mathrm{d}}{\mathrm{d}T}(C_{LV} p_{LV}) = 0,$$

and so p_a, p_v and $C_{LV}p_{LV}$ all remain constant and equal to their initial values over the duration of the systole. [2 marks] Since C_{LV} goes from C_d to C_s over the systole, this gives

$$p_a^1 = p_a^0, \qquad p_v^1 = p_v^0, \qquad p_{LV}^1 = \frac{C_d p_{LV}^0}{Cs}.$$

[1 mark]

(e) [5 marks] [New material]

[Equations highlighted in red correspond to the numbers used in the question, to distinguish from the numbering in the solution.]

Equations (1a) and (1c) from the question at leading order both give $p_a = p_{LV}$. Hence $C_s p_a^0 = C_d p_{LV}^0$ applying the initial conditions. [1 mark] Equation (1b) from the question at leading order gives

$$\frac{\mathrm{d}p_v}{\mathrm{d}t} = p_a. \tag{2}$$

Considering equations (1a)+(1c) from the question at leading order gives

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

as required. [1 mark] Solving (3) subject to the initial condition $p_a(0) = p_a^0$ gives

$$p_a = p_a^0 \exp\left(-\frac{t}{1 + C_s}\right)$$

and so

$$p_{LV} = p_a^0 \exp\left(-\frac{t}{1 + C_s}\right).$$

[1 mark] Solving (2) gives

$$p_v = p_v^0 - \frac{p_a^0}{1 + C_s}\left[\exp\left(-\frac{t}{1 + C_s}\right) - 1\right].$$

[2 marks]

(f) [4 marks] [New material]

The volume ejected from the left ventricle (in similarly scaled terms) is given by

$$\Delta V_{LV}(t_2) = C_s p_{LV}(t_2) = C_s p_a^0 \exp\left(-\frac{t_2}{1 + C_s}\right).$$

using (1c). [1 mark] We expect the compliance to fall with age as the blood vessels become less flexible. [1 mark] Since $p_a^0 = n(1 - \exp(-n))$ and $C_s = 1/n$, this gives

$$V_{LV} = (1 - \exp(-n)) \exp\left(-\frac{t_2}{1 + 1/n}\right).$$

Differentiating with respect to n and setting the result equal to zero gives

$$1 + 2n + n^2 + t_2(1 - \exp(n)) = 0.$$

Since $V_{LV} = 0$ when $n = 0$ and $V_{LV} \to \exp(-t_2)$ as $n \to \infty$, this optimum is a maximum and corresponds to a measure of the age at which the volume of blood pumped in one stroke is maximized. This can also be shown to be a maximum graphically or by taking the second derivative of V_{LV}. [2 marks]