Version ML/5 – updated crib

EGT2
ENGINEERING TRIPOS PART IIA

Friday 1 May 2026 9.30 to 11.10

Module 3G2 – CRIB

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 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.

You may not remove any stationery from the Examination Room.

1 An enzyme E catalyses the conversion of a substrate S into a product P according to the following mechanism:

$$\mathrm{S + E} \rightleftharpoons \mathrm{ES} \qquad K_1 = \frac{[\mathrm{ES}]}{[\mathrm{S}]\,[\mathrm{E}]}$$

$$\mathrm{ES} \xrightarrow{k_2} \mathrm{E + P}$$

$$\mathrm{S + ES} \rightleftharpoons \mathrm{SES} \qquad K_3 = \frac{[\mathrm{SES}]}{[\mathrm{S}]\,[\mathrm{ES}]}$$

$$\mathrm{SES} \xrightarrow{k_4} \mathrm{E + S + P}$$

All equilibrium reactions are assumed to be fast. The total enzyme concentration is E_0, and the rate of product formation is denoted by V.

Answer: For this mechanism, the rate of product formation is

$$V = \frac{\mathrm{d[P]}}{\mathrm{d}t} = k_2[\mathrm{ES}] + k_4[\mathrm{SES}]\,,$$

and the conservation of enzyme implies

$$[\mathrm{E}] + [\mathrm{ES}] + [\mathrm{SES}] = \mathrm{E}_0\,.$$

(a) Consider first the case $k_2 = 0$ and $k_4 \neq 0$, so that the product is formed only from the complex SES.

(i) Derive the following expression for the rate law:

$$\frac{V}{V_{\max}} = \frac{K_1\,K_3\,s^2}{1 + K_1\,s + K_1\,K_3\,s^2}$$

where $V_{\max} = k_4\,E_0$ and $s = [\mathrm{S}]$. [15%]

Answer: If $k_2 = 0$, then $V = k_4[\mathrm{SES}]$. From the fast equilibrium relations we obtain

$$[\mathrm{ES}] = \frac{[\mathrm{SES}]}{K_3 s} \quad \text{and} \quad [\mathrm{E}] = \frac{[\mathrm{ES}]}{K_1 s} = \frac{[\mathrm{SES}]}{K_1 K_3 s^2}\,, \quad \text{with } s = [\mathrm{S}].$$

Substituting these expressions into the enzyme conservation yields

$$\mathrm{E}_0 = \left(\frac{1}{K_1 K_3 s^2} + \frac{1}{K_3 s} + 1\right)[\mathrm{SES}]\,.$$

Hence

$$\frac{V}{k_4 \mathrm{E}_0} = \frac{[\mathrm{SES}]}{\mathrm{E}_0} = \left(\frac{1}{K_1 K_3 s^2} + \frac{1}{K_3 s} + 1\right)^{-1},$$

or equivalently

$$\frac{V}{V_{\max}} = \frac{K_1 K_3 s^2}{1 + K_1 s + K_1 K_3 s^2}\,, \quad \text{with } V_{\max} = k_4 \mathrm{E}_0.$$

 (cont.

(ii) Derive an expression for the value s_h of s at which $V = \dfrac{V_\mathrm{max}}{2}$. [10%]

Answer: The concentration s_h solves $1 + K_1 s + K_1 K_3 s^2 = 2K_1 K_3 s^2$, that is $K_1 K_3 s^2 - K_1 s - 1 = 0$. The physically relevant (positive) solution is

$$s_h = \frac{K_1 + \sqrt{K_1^2 + 4K_1 K_3}}{2K_1 K_3} = \frac{1 + \sqrt{1 + 4\frac{K_3}{K_1}}}{2K_3}\,.$$

(iii) In the limit $K_1 \gg K_3$, determine s_h and show that the rate law reduces to a standard Michaelis–Menten equation. [15%]

Answer: If $K_1 \gg K_3$, then

$$s_h = \frac{1 + \sqrt{1 + 4\frac{K_3}{K_1}}}{2K_3} \overset{K_1 \gg K_3}{=} \frac{1}{K_3}\,.$$

Writing the rate law in terms of s_h gives

$$\frac{V}{V_\mathrm{max}} = \frac{\left(\frac{s}{s_h}\right)^2}{\frac{K_3}{K_1} + \left(\frac{s}{s_h}\right) + \left(\frac{s}{s_h}\right)^2} \overset{K_1 \gg K_3}{=} \frac{\left(\frac{s}{s_h}\right)^2}{\left(\frac{s}{s_h}\right) + \left(\frac{s}{s_h}\right)^2} = \frac{\left(\frac{s}{s_h}\right)}{1 + \left(\frac{s}{s_h}\right)} = \frac{s}{s_h + s}\,,$$

which is Michaelis–Menten equation with $V_\mathrm{max} = k_4 \mathrm{E}_0$ and Michaelis constant $K_M = s_h$.
In this limit the binding is effectively non-cooperative. The formation of the bisubstrate complex SES is rate-limiting, while the complex ES is readily formed owing to the high affinity of E for S. As a result, ES behaves as the effective enzyme species, and the kinetics reduce to the standard Michaelis–Menten form.

(iv) In the limit $K_3 \gg K_1$, determine s_h and show that

$$\frac{V}{V_\mathrm{max}} = \frac{s^2}{s_\mathrm{h}^2 + s^2}$$

Sketch V as a function of s, and explain how this behaviour differs from Michaelis–Menten kinetics. [20%]

Answer: If $K_3 \gg K_1$, then

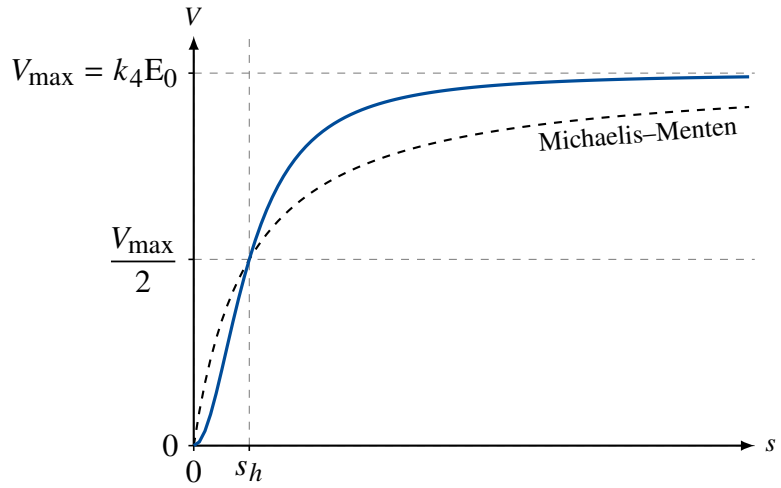
$$s_h = \frac{1 + \sqrt{1 + 4\frac{K_3}{K_1}}}{2K_3} \overset{K_3 \gg K_1}{=} \frac{1}{\sqrt{K_1 K_3}}$$

Writing the rate law in terms of s_h gives

$$\frac{V}{V_\mathrm{max}} = \frac{\left(\frac{s}{s_h}\right)^2}{1 + \sqrt{\frac{K_1}{K_3}}\left(\frac{s}{s_h}\right) + \left(\frac{s}{s_h}\right)^2} \overset{K_3 \gg K_1}{=} \frac{\left(\frac{s}{s_h}\right)^2}{1 + \left(\frac{s}{s_h}\right)^2} = \frac{s^2}{s_h^2 + s^2}$$

In the plot below, we compare this rate with a Michaelis–Menten model that has the same V_max and half-maximum concentration s_h, that is

$$\frac{V}{V_\mathrm{max}} = \frac{s}{s_h + s} \quad \text{for an equivalent Michaelis–Menten model}\,.$$



In this limit, the binding is cooperative (and homotropic), since the complex ES has higher affinity to the substrate than the enzyme by itself, hence facilitating the formation of the bisubstrate complex leading to the product. The resulting rate law is sigmoidal, where the maximum reaction rate can be reached at lower substrate concentration when compared with the non-cooperative, hyperbolic Michaelis–Menten behaviour.

(b) Next consider the case $k_4 = 0$ and $k_2 \neq 0$, so that the product is formed only from the complex ES.

(i) Derive an expression for $\dfrac{V}{k_2\, E_0}$. [20%]

Answer: If $k_4 = 0$, then $V = k_2[\mathrm{ES}]$. From the fast equilibrium relations we obtain

$$[\mathrm{E}] = \frac{[\mathrm{ES}]}{K_1 s} \quad \text{and} \quad [\mathrm{SES}] = K_3 s[\mathrm{ES}]\,, \quad \text{with } s = [\mathrm{S}].$$

Substituting these expressions into the enzyme conservation yields

$$\mathrm{E}_0 = \left(\frac{1}{K_1 s} + 1 + K_3 s\right)[\mathrm{ES}]\,.$$

Hence

$$\frac{V}{k_2 \mathrm{E}_0} = \frac{[\mathrm{ES}]}{\mathrm{E}_0} = \left(\frac{1}{K_1 s} + 1 + K_3 s\right)^{-1},$$

or equivalently

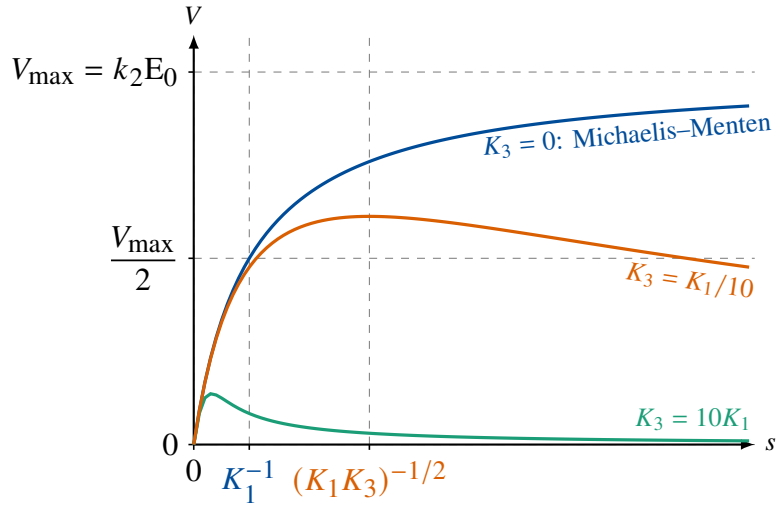
$$\frac{V}{V_{max}} = \frac{K_1 s}{1 + K_1 s + K_1 K_3 s^2}\,, \quad \text{with } V_{max} = k_2 \mathrm{E}_0.$$

(ii) On the same set of axes, sketch V as a function of s for $K_3 = 0$ (when the complex SES does not form), and for $K_3 \neq 0$. Explain why this type of enzyme kinetics is called *substrate inhibition*. [20%]

Answer: For $K_3 = 0$, we find the Michaelis–Menten equation,

$$\frac{V}{V_{max}} = \frac{s}{K_1^{-1} + s}\,.$$

For $K_3 \neq 0$, $V \to 0$ when $s \to \infty$. $\dfrac{V}{V_{\max}}$ attains a maximum value $\left(1 + 2\sqrt{\dfrac{K_3}{K_1}}\right)^{-1} < 1$ at $s = \dfrac{1}{\sqrt{K_1 K_3}}$.
This maximum rate decreases as $\dfrac{K_3}{K_1}$ increases.



[Note: Only the curve with $K_3 = 0$ and one curve with $K_3 \neq 0$ were required to obtain full marks.]

The equilibrium constant K_3 characterises the binding of substrate to the enzyme–substrate complex ES. This sequesters ES in an inactive complex and inhibits product formation. As a result, increasing the substrate concentration reduces the effective rate of product formation, which eventually tends to zero. This behaviour is known as *substrate inhibition*.

2 Blood is often modelled as a non-Newtonian fluid with a yield stress. Two commonly used constitutive laws are the Bingham and the Casson models. The Bingham model is

$$\tau = \tau_{\mathrm{y}} + \mu_{\mathrm{b}}\,\dot{\gamma}$$

where τ is the shear stress, $\dot{\gamma}$ the shear rate, τ_{y} the yield stress, and μ_{b} the viscosity. The Casson model is

$$\sqrt{\tau} = \sqrt{\tau_{\mathrm{y}}} + \sqrt{\mu_{\mathrm{c}}\,\dot{\gamma}}$$

where μ_{c} is the viscosity. For both models, $\dot{\gamma} = 0$ when $\tau \le \tau_{\mathrm{y}}$.

(a) Consider steady, fully developed flow in a cylindrical vessel of radius R, driven by a constant pressure gradient $G > 0$. Let r denote the radial coordinate. Then

$$\frac{1}{r}\frac{\partial(r\tau)}{\partial r} = G$$

(i) Show that both models predict a central plug region, and determine the plug radius R_{p} in terms of G and τ_{y}. [15%]

Answer: We solve for $\tau(r)$ by integrating the force balance:

$$\frac{1}{r}\frac{\partial(r\tau)}{\partial r} = G \quad \Rightarrow \quad \tau(r) = \frac{Gr}{2} + \frac{C}{2}.$$

Since the shear stress must vanish everywhere when $G = 0$, the integration constant is $C = 0$, and hence

$$\tau(r) = \frac{Gr}{2}.$$

Yielding occurs when $\tau(r) = \tau_y$, giving the plug radius

$$R_p = \frac{2\tau_y}{G}.$$

Hence both models predict a central plug region $0 \le r \le R_p$.

(ii) Assuming $R_{\mathrm{p}} < R$, derive expressions for $\dot{\gamma}(r)$ for each model in terms of G, R_{p}, and the relevant viscosity. [15%]

Answer: We assume $R_p < R$, so that the fluid yields within the tube.

•For the Bingham model,

$$\dot{\gamma}(r) = \frac{\tau(r) - \tau_y}{\mu_b} = \frac{G}{2\mu_b}(r - R_p).$$

Thus

$$\dot{\gamma}(r) = \frac{G}{2\mu_b}\begin{cases}(r - R_p), & R_p \le r \le R,\\ 0, & 0 \le r \le R_p.\end{cases}$$

•For the Casson model,

$$\dot{\gamma}(r) = \frac{\left(\sqrt{\tau(r)} - \sqrt{\tau_y}\right)^2}{\mu_c}. = \frac{G}{2\mu_c}\left(\sqrt{r} - \sqrt{R_p}\right)^2.$$

Thus

$$\dot{\gamma}(r) = \frac{G}{2\mu_c}\begin{cases}\left(\sqrt{r} - \sqrt{R_p}\right)^2, & R_p \le r \le R,\\ 0, & 0 \le r \le R_p.\end{cases}$$

When $R_p > R$, the fluid does not yield anywhere and there is no shearing flow.

(iii) For each model, show that

$$\dot{\gamma}(r) \propto (r - R_\mathrm{p})^n \quad \text{as } r \to R_\mathrm{p} \text{ (with } r > R_\mathrm{p})$$

and determine the exponent n in each case. Comment briefly on which model is more suitable for describing blood. [20%]

Answer:

•For the Bingham model,

$$\dot{\gamma}(r) \propto (r - R_p) \quad \text{as } r \to R_p\,.$$

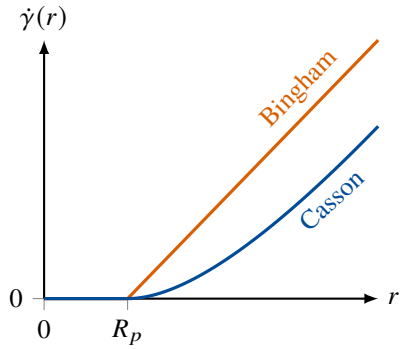
•For the Casson model, define $\rho = \dfrac{r - R_p}{R_p}$ so that $\rho \to 0$ as $r \to R_p$. Then

$$\dot{\gamma}(r) = \frac{GR_p}{2\mu_c}\left(\sqrt{1+\rho} - 1\right)^2.$$

Using the expansion $\sqrt{1+\rho} = 1 + \rho/2 + O(\rho^2)$, we find $\dot{\gamma}(r) \propto \rho^2$, and hence

$$\dot{\gamma}(r) \propto (r - R_p)^2 \quad \text{as } r \to R_p\,.$$

The yield transition is smoother for the Casson model, with zero slope at the yield surface. It is therefore more realistic for biological fluids such as blood.



(b) A yield stress τ_y and viscosity μ have been measured for blood. It is proposed to discriminate between the Bingham and Casson models by measuring the volumetric flow rate Q in the vessel of part (a). All models will now employ the measured τ_y and μ.

(i) Using integration by parts, show that Q can be written as an integral involving only $\dot{\gamma}(r)$. Verify your result by recovering Poiseuille's law,

$$Q_{\mathrm{n}} = \frac{\pi\, G\, R^4}{8\,\mu}$$

for the flow rate Q_{n} of a Newtonian fluid. [20%]

Answer: Let $u(r)$ denote the axial velocity. The volumetric flow rate is

$$Q = 2\pi \int_0^R u(r)\, r \, \mathrm{d}r.$$

Using integration by parts,

$$Q = 2\pi \left[u(r) \frac{r^2}{2} \right]_0^R - 2\pi \int_0^R \frac{\partial u}{\partial r} \frac{r^2}{2} \, \mathrm{d}r.$$

Since $u(R) = 0$ and $\dot{\gamma}(r) = -\partial u/\partial r$, this reduces to

$$Q = \pi \int_0^R \dot{\gamma}(r)\, r^2 \, \mathrm{d}r.$$

For a Newtonian fluid with viscosity μ,

$$\dot{\gamma}(r) = \frac{Gr}{2\mu},$$

and hence

$$Q_n = \frac{\pi G}{2\mu} \int_0^R r^3 \, \mathrm{d}r = \frac{\pi G R^4}{8\mu} \quad \text{(Poiseuille's law).}$$

(ii) Let $\Delta Q = |Q_{\mathrm{b}} - Q_{\mathrm{c}}|$ denote the absolute difference between the flow rates predicted by the Bingham and Casson models, respectively. Using parts (a)(ii) and (b)(i), show that

$$\frac{\Delta Q}{Q_{\mathrm{n}}} = \frac{8}{21} \left(x^4 - 7\,x + 6\,x^{1/2} \right), \quad \text{where } x = \frac{R_{\mathrm{p}}}{R} \qquad [20\%]$$

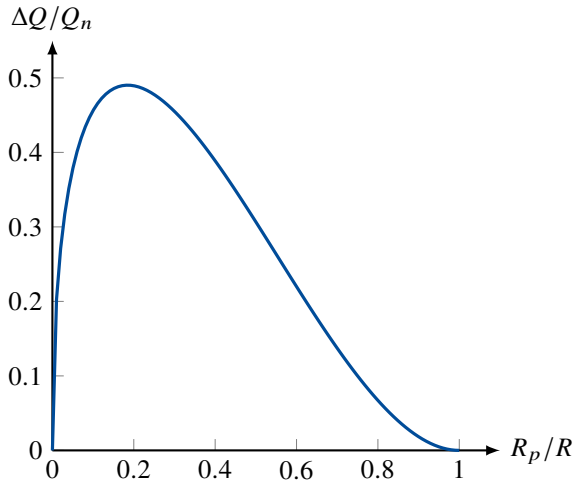
Answer: The relative difference in flow rate is

$$\begin{aligned}
\frac{\Delta Q}{Q_n} = \frac{Q_b - Q_c}{Q_n} &= \frac{8\mu}{\pi G R^4} \frac{\pi G}{2\mu} \int_{R_p}^R \left[(r - R_p) - (\sqrt{r} - \sqrt{R_p})^2 \right] r^2 \, \mathrm{d}r \\
&= \frac{8}{R^4} \int_{R_p}^R (\sqrt{r R_p} - R_p)\, r^2 \, \mathrm{d}r \\
&= \frac{8\sqrt{R_p}}{R^4} \int_{R_p}^R r^{5/2} \, \mathrm{d}r - \frac{8R_p}{R^4} \int_{R_p}^R r^2 \, \mathrm{d}r \\
&= \frac{16\sqrt{R_p}}{7R^4} (R^{7/2} - R_p^{7/2}) - \frac{8R_p}{3R^4} (R^3 - R_p^3) \\
&= \frac{8}{21} \left[\left(\frac{R_p}{R} \right)^4 - 7 \left(\frac{R_p}{R} \right) + 6 \left(\frac{R_p}{R} \right)^{1/2} \right] > 0 \quad \text{for } 0 < R_p < R.
\end{aligned}$$

 (cont.

(iii) Comment briefly on whether such measurements could reliably discriminate between the two models. [10%]

Answer: A sketch of this result is shown below.



There exists a range of $R_p/R = 2\tau_y/(GR)$ for which the difference between the flow rates predicted by the two models is of order 40–50% of the Newtonian flow rate. If the latter can be measured with sufficiently small relative uncertainty, then the difference between the two models should also be measurable. This conclusion, however, assumes that at least one of the models provides an adequate description of blood.

3 Assuming Poiseuille flow through systemic vessels, it can be shown that the flux Q of blood in the x direction, through a cylindrical vessel with a cross-section area A_0, is given by

$$Q = -\frac{A_0^2}{8\,\pi\,\mu}\,\frac{\partial P}{\partial x}$$

where μ is the viscosity and P denotes the pressure.

(a) State the assumptions required for a Poiseuille flow. [10%]

Answer: The fluid must be Newtonian, incompressible, steady, leaminar and fully developed in a circular cross-section.

(b) Assume that at each level (arteries, veins, capillaries, etc) there are N parallel vessels, each of the same radius and cross-sectional area A_0 and length L_v.

(i) Show that the pressure drop at each level is given by

$$\frac{\partial P}{\partial x}\,L_\mathrm{v} \propto \frac{L_\mathrm{v}}{A\,A_0}$$

where $A = N\,A_0$. [20%]

Answer: For each vessel,

$$Q_0 = -\frac{A_0^2}{8\pi\mu}\frac{\partial p}{\partial x}$$

Total

$$Q = NQ_0 = -\frac{NA_0^2}{8\pi\mu}\frac{\partial p}{\partial x} = -\frac{A_0 A}{8\pi\mu}\frac{\partial p}{\partial x}$$

Therefore,

$$\frac{\partial p}{\partial x} \propto \frac{Q}{A_0 A}$$

Because the flow is incompressible, Q must be a constant at each level, therefore,

$$\frac{\partial p}{\partial x} \propto \frac{1}{A_0 A}$$

$$\frac{\partial p}{\partial x} L_v \propto \frac{L_v}{A_0 A}$$

(ii) Using the data in Table 1, explain why most of the viscous dissipation occurs in the capillaries. [20%]

Answer:

$$\Delta p \propto \frac{L_v}{A_0 A}$$

Using the data in the table:

Ascending Aorta	Femoral Artery	Arteriole	Capillary	Venule
$\frac{5}{2\times2}$	$\frac{10}{0.2\times3}$	$\frac{0.15}{2\times10^{-5}\times125}$	$\frac{0.06}{3\times10^{-7}\times600}$	$\frac{0.15}{2\times10^{-5}\times570}$
1.25	17	60	333	13

This shows that most of the viscous dissipation occurs in the capillaries.

(c) A compliant vessel has length L, input pressure P_0, output pressure P_1 and zero external pressure. Assume a linear relationship between the cross-sectional area A and the internal pressure P:

$$A = A_0 + C\,P$$

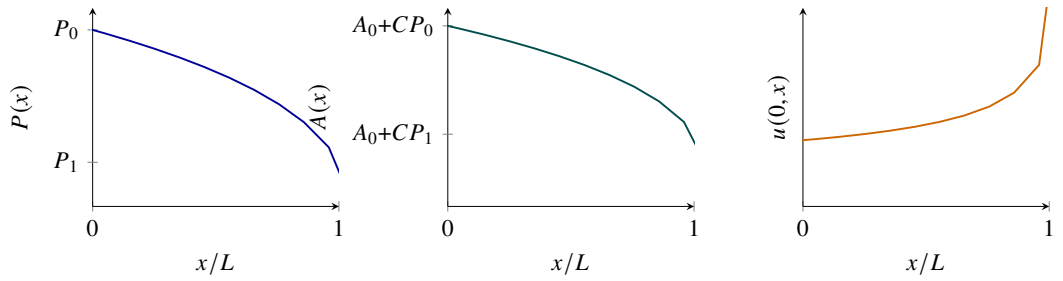
where A_0 is the cross-sectional area for zero internal pressure and C is the compliance.

(i) Sketch the pressure, cross-sectional area, and the centerline velocity along the vessel. [20%]

Answer: For a compliant vessel the local area $A(x) = A_0 + CP(x)$ varies along x, so Poiseuille's relation applies locally:

$$Q = -\frac{A^2(x)}{8\pi\mu}\frac{\mathrm{d}P}{\mathrm{d}x}, \tag{1}$$

with Q independent of x by mass conservation. Rearranging, $|\mathrm{d}P/\mathrm{d}x| = 8\pi\mu Q/A^2(x)$, so the pressure gradient is shallow where A is large (near the inlet) and steep where A is small (near the outlet). Because A is linear in P, the area profile has the same shape as the pressure profile. The centreline velocity follows from the parabolic Poiseuille profile, $u(0,x) = 2Q/A(x)$, so it rises along the vessel and accelerates fastest where A shrinks fastest. Integration of Eq. 1 gives $A^3(x)$ linear in x, which fixes the curvature of all three sketches in the figure below, showing pressure, cross-sectional area, and centreline velocity along a compliant vessel with $A = A_0 + CP$. All three profiles share the same concave shape: the curves are gentle near the inflated inlet and steepen toward the narrower outlet.



(ii) Derive an expression for the flux in the x-direction through the vessel. Use this expression to explain why compliance makes flow easier in a vessel. [30%]

Answer:

$$8\pi\mu Q = -\frac{\partial p}{\partial x}A^2(p)$$

The left hand side is a constant. Therefore,

$$\int_0^L dx = -\frac{1}{8\pi\mu Q}\int_{p_0}^{p_1} A^2(p)dp$$

$$L = -\frac{1}{8\pi\mu Q} A_0^2 \int_{p_0}^{p_1} (1+\gamma p)^2 dp$$

where $\gamma = C/A_0$.

$$\begin{aligned} \frac{8\pi\mu Q}{A_0^2} L &= \frac{1}{3\gamma} (1+\gamma p)^3 \Big|_{p_1}^{p_0} \\ &= (p_0 - p_1) \left\{ 1 + \gamma(p_0 + p_1) + \frac{\gamma^2}{3}(p_0^2 + p_0 p_1 + p_1^2) \right\} \end{aligned}$$

Because Q increases with γ ($\propto C$, the compliance), for a given pressure difference, the flow rate increases with increasing compliance, thus making flow easier in a vessel with increasing compliance.

Site		Ascending aorta		Descending aorta	Abdominal aorta	Femoral artery	Carotid artery
Internal diameter d_i	cm	1·5 1·0–2·4		1·3 0·8–1·8	0·9 0·5–1·2	0·4 0·2–0·8	0·5 0·2–0·8
Wall thickness h	cm		0·065 0·05–0·08		0·05 0·04–0·06	0·04 0·02–0·06	0·03 0·02–0·04
h/d_i			0·07 0·055–0·084		0·06 0·04–0·09	0·07 0·055–0·11	0·08 0·053–0·095
Length	cm	5		20	15	10	15 10–20
Approximate cross-sectional area	cm^2	2		1·3	0·6	0·2	0·2
Total vascular cross-sectional area at each level	cm^2	2		2	2	3	3
Peak blood velocity	$cm\ s^{-1}$	120 40–290		105 25–250	55 50–60	100 100–120	
Mean blood velocity	$cm\ s^{-1}$	20 10–40		20 10–40	15 8–20	10 10–15	
Reynolds number (peak)		4500		3400	1250	1000	
α (heart rate 2 Hz)		13·2		11·5	8	3·5	4·4
Calculated wave-speed c_0	$cm\ s^{-1}$		580		770	840	850
Measured wave-speed c	$cm\ s^{-1}$		500 400–600		700 600–750	900 800–1030	800 600–1100
Young's modulus E	$Nm^{-2} \times 10^5$		4·8 3–6		10 9–11	10 9–12	9 7–11

Site		Arteriole	Capillary	Venule	Inferior vena cava	Main pulmonary artery
Internal diameter d_i	cm	0·005 0·001–0·008	0·0006 0·0004–0·0008	0·004 0·001–0·0075	1·0 0·6–1·5	1·7 1·0–2·0
Wall thickness h	cm	0·002	0·0001	0·0002	0·015 0·01–0·02	0·02 0·01–0·03
h/d_i		0·4	0·17	0·05	0·015	0·01
Length	cm	0·15	0·06	0·15	30	3·5
Approximate cross-sectional area	cm^2	0·1–0·2 2×10^{-5}	0·02–0·1 3×10^{-7}	0·1–0·2 2×10^{-5}	20–40 0·8	3–4 2·3
Total vascular cross-sectional area at each level	cm^2	125	600	570	3·0	2·3
Peak blood velocity	$cm\ s^{-1}$	0·75 0·5–1·0	0·07 0·02–0·17	0·35 0·2–0·5	25 15–40	70
Mean blood velocity	$cm\ s^{-1}$					15 6–28
Reynolds number (peak)		0·09	0·001	0·035	700	3000
α (heart rate 2 Hz)		0·04	0·005	0·035	8·8	15
Calculated wave-speed c_0	$cm\ s^{-1}$				100	350
Measured wave-speed c	$cm\ s^{-1}$				400 100–700	250 200–330
Young's modulus E	$Nm^{-2} \times 10^5$				0·7 0·4–1·0	6 2–10

Table 1

4 This question is about the spatial average of the Cl^- flux inside a Cl^- channel.

You can assume that the intra- and extra-cellular concentrations of Cl^- do not change over time. Unless otherwise noted, the spatial average of the flux inside the channel at time t is defined as $\bar{J}(t) = \dfrac{1}{L}\displaystyle\int_0^L J(x,t)\ \mathrm{d}x$, where $J(x,t)$ is the flux at position $x \in [0, L]$ and time t, and L is the length of the channel.

Explain with reasons what is the spatial average of the Cl^- flux under each of the following conditions, or explain with reasons why it cannot be determined. Support your explanations with mathematical derivations.

(a) The membrane potential momentarily equals the Cl^- Nernst potential. [15%]

Answer: Flux is expressed by the following equation:

$$J(x,t) = -D\left(\frac{\partial}{\partial x}c(x,t) + \frac{zF}{RT}\,c(x,t)\ \frac{\partial}{\partial x}\phi(x,t)\right)$$

The membrane potential being the same as the Cl^- Nernst potential means that

$$V(t) = \frac{RT}{zF}\ln\frac{c_\mathrm{e}(t)}{c_\mathrm{i}(t)}$$

where c_e and c_i is the extra- and intracellular concentration of Cl^-, respectively. From this it follows with trivial algebraic manipulations that

$$\begin{aligned}
\phi(L,t) - \phi(0,t) &= -\frac{RT}{zF}\ [\ln c(L,t) - \ln c(0,t)] \\
\int_0^L \frac{\partial}{\partial x}\phi(x,t)\ \mathrm{d}x &= -\int_0^L \frac{RT}{zF}\ \frac{\partial}{\partial x}\ln c(x,t)\ \mathrm{d}x \\
0 &= \int_0^L \left[\frac{\partial}{\partial x}\phi(x,t) + \frac{RT}{zF}\ \frac{\frac{\partial}{\partial x}c(x,t)}{c(x,t)}\right]\mathrm{d}x \\
0 &= \int_0^L \frac{\frac{\partial}{\partial x}c(x,t) + \frac{zF}{RT}\,c(x,t)\,\frac{\partial}{\partial x}\phi(x,t)}{c(x,t)}\,\mathrm{d}x
\end{aligned}$$

By noting that the numerator of the term inside the integral in the last equation is proportional to the flux, as shown by the first equation above, we can then rewrite this as

$$0 = \int_0^L \frac{J(x,t)}{c(x,t)}\,\mathrm{d}x$$

Unfortunately, it is not possible to express $J(x,t)$ (and from that $\bar{J}(t)$) from this equation in general, as $J(x,t)$ can be positive or negative at different points inside the channel (while $c(x,t)$ must be non-negative everywhere).

(b) The membrane potential momentarily equals the Cl^- Nernst potential, and the spatial average of the flux inside the channel is defined as a weighted average, where the weighting factor for the flux at a given location is inversely proportional to the Cl^- concentration at that location. [10%]

Answer: The description of the new definition of the average flux implies the following formula:

$$\bar{J}_{\text{weighted}}(t) \propto \frac{1}{L}\int_0^L \frac{J(x,t)}{c(x,t)}\,\mathrm{d}x$$

The right hand side of this equation is proportional to what we derived to be zero in the answer to question (a) above, and so

$$\bar{J}_{\text{weighted}}(t) = 0$$

(c) The membrane potential momentarily equals the Cl^- Nernst potential, and Cl^- flux inside the channel is unidirectional (its sign is the same everywhere inside the channel). [25%]

Answer: Restating the equation derived in the answer to question (a) above

$$0 = \int_0^L \frac{J(x,t)}{c(x,t)}\,\mathrm{d}x$$

and noting again that concentration is a non-negative quantity, and knowing that the sign of $J(x,t)$ is constant as a function of x, we note that if this sign was positive than the integrand is always positive and therefore the integral is also positive (i.e. non-zero), vice versa if the sign of the flux is negative. Thus, the only way the integral can be negative is if

$$0 = J(x,t) \quad \forall x$$

From this, it follows that

$$\bar{J}(t) = \frac{1}{L}\int_0^L J(x,t)\;\mathrm{d}x = 0$$

(d) The membrane potential has been held at the Cl^- Nernst potential for a millisecond. [15%]

Answer: By maintaining the membrane potential for such a long time (at least compared to the $\sim 10^{-4}$ millisecond time scale of ionic movements inside a channel), the channel will have approached steady state. This means that normally time-dependent quantities, such as flux or concentration, don't change any more in time. Thus, the steady state concentration is a function of space but not time: $c(x,t) = c^*(x)$. In addition, because the concentration does not change in time, due to the conservation law, stating that $\frac{\partial}{\partial t}c(x,t) = -\frac{\partial}{\partial x}J(x,t)$, the spatial gradient of the steady state flux is zero, i.e. the steady state flux is constant across space. Thus, steady state flux does not depend on either time or space: $J(x,t) = J^*$. Given

these observations, we can rewrite the equation derived in the answer to question (a) above as

$$0 = \int_0^L \frac{J^*}{c^*(x)}\,\mathrm{d}x$$

Because concentration is a non-negative quantity, the equation above can only be satisfied if

$$J^* = 0$$

Because the steady-state flux is the same everywhere in the channel, its spatial average is also the same:

$$\bar{J}^* = \frac{1}{L}\int_0^L J^*\,\mathrm{d}x = J^* = 0$$

(e) The membrane potential has been held at 10 mV above the Cl^- Nernst potential for a millisecond. [5%]

Answer: Although we can once again assume that the channel is in steady state, there is no general solution to the steady state flux for arbitrary values of the membrane potential. So unless the membrane potential happens to be the Cl^- Nernst potential (in which case the flux, and the average flux is zero as we derived above, the average Cl^- flux cannot be determined.

(f) The membrane potential has been held at 10 mV above the Cl^- Nernst potential for a millisecond, the conditions for the "long channel limit" are satisfied, the conductance of the channel for Cl^- is 20 pS, and the cross-sectional area of its pore is 0.4 nm^2. [30%]

Answer: In the long channel limit, we know that the channel current in steady-state (which we can assume again, as above) is

$$I^* = g\ (V - V_{\mathrm{Nernst}})$$

where g is the conductance (per unit cross-sectional area), V is the membrane potential, and V_{Nernst} is the Nernst potential of the ion (in this case, Cl^-), and so in our case $V - V_{\mathrm{Nernst}} = 10$ mV. We note that given the information about channel conductance and cross-sectional area

$$g\ 0.4\ \mathrm{nm}^2 = 20\ \mathrm{pS}$$

and so

$$\begin{aligned} g &= \frac{20}{0.4}\,\frac{\mathrm{pS}}{\mathrm{nm}^2} \\ &= 50 \cdot \frac{10^{-12}}{10^{-18}}\,\frac{\mathrm{S}}{\mathrm{m}^2} \\ &= 50 \cdot 10^6\,\frac{\mathrm{A}}{\mathrm{V\,m}^2} \end{aligned}$$

The relationship between current and flux (here written for steady state) is

$$I^* = z\,F\,J^*$$

Faraday's constant is $F = 96\,485\ \frac{\mathrm{C}}{\mathrm{mol}}$. For the Cl^- ion $z = -1$. Thus

$$\begin{aligned} J^* &= \frac{g\ 10\ \mathrm{mV}}{z\,F} \\ &= \frac{50 \cdot 10^6\ \frac{\mathrm{A}}{\mathrm{V\,m^2}} 10 \cdot 10^{-3}\ \mathrm{V}}{(-1)\ 96\,485\ \frac{\mathrm{C}}{\mathrm{mol}}} \\ &= -\frac{500\,000\ \frac{\mathrm{A}}{\mathrm{m^2}}}{96\,485\ \frac{\mathrm{A\,s}}{\mathrm{mol}}} \\ &= -5.18\ \frac{\mathrm{mol}}{\mathrm{m^2\,s}} \approx -5\ \frac{\mathrm{mol}}{\mathrm{m^2\,s}} \end{aligned}$$

Again, because the channel is at steady state, the flux is the same everywhere in the channel, and so it's average is also the same:

$$\bar{J}^* = \frac{1}{L}\int_0^L J^*\,\mathrm{d}x = J^* = -5.18\ \frac{\mathrm{mol}}{\mathrm{m^2\,s}} \approx -5\ \frac{\mathrm{mol}}{\mathrm{m^2\,s}}$$

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