ENGINEERING TRIPOS   PART IIA

22 April 2010   2.30 to 4

Module 3G2

MATHEMATICAL PHYSIOLOGY - CRIBS

STATIONERY REQUIREMENTS   SPECIAL REQUIREMENTS

You may not start to read the questions printed on the subsequent pages of this question paper until instructed that you may do so by the Invigilator

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1   (a)   (i)   triangle: h, cross: n, circle: m [20%]

           (ii) h: Na^+, n: K^+, m: Na^+ [10%]

           (iii) Na^+: $+115\,mV$, K^+: $-15\,mV$ [15%]

       (b)   During prolonged hyperpolarisation, the h gate is more deinactivated (while the m gate is more deactivated) than at resting membrane potential. When hyperpolarisation is suddenly released, the m gate activates (to a level corresponding to normal resting membrane potential), and the h gate inactivates. However, the m gate is much faster than the h gate, so there is a time window when the m gate is already at its resting activation, but the h gate is still deinactivated compared to rest. This results in a larger Na^+ conductance, and thus current, than normally produced at resting membrane potential. This extra amount of Na^+ current may be sufficient to initiate an action potential through the usual membrane potential–Na^+ current positive feedback loop.   [40%]

       (c)   For each of the following changes in the membrane properties of a neuron, decide if it increases / decreases / does not affect the membrane time constant and the membrane space constant (assuming that all other properties are unchanged):

           (i)   Increasing membrane resistance, R_m: membrane time constant is increased, membrane space constant is increased.

           (ii)   Increasing axial resistance, R_a: membrane time constant is not affected, membrane space constant is decreased.

           (iii)   Decreasing membrane capacitance, C_m: membrane time constant is decreased, membrane space constant is not affected .

       [15%]

2   (a)   (i)   The pH of pure water is 7, which is the negative log of the concentration of H^+ ions in moles/litre. The equilibrium constant is defined by $K_{eq} = [H^+][OH^-]/[H_2O]$. The denominator is essentially unchanged at 55.6 (1 mole of water ia 18 g, 1 litre has therefore 1000/18=55.6 moles in it), so $K_{eq} = 10^{-7} \cdot 10^{-7}/55.6 = 1.8 \cdot 10^{-16}$. Alternatively, the equilibrium constant can be defined with different units as $K_{eq} = [H^+][OH^-] = 10^{-14}$.

(ii)   The dissociated fraction is $10^{-7}/55.6 = 1.8 \times 10^{-8}$.

(b)   (i)   Denoting the organic radical by A^-, the equilibrium constant is $K_{eq} = [A^-][H^+]/[AH]$. For large concentrations (like the ones in this question), the amount of H^+ produced by the dissociation of the acid is much larger than the amount due to the dissociation of water, and so the latter reaction can be neglected. Denoting the nominal concentration of the solution by c and the concentration of dissociated molecules by x, we have $x^2/(c-x) = K$. Hence $x = (-K + \sqrt{K^2 + 4cK})/2$. For $c = \{1, 0.1, 0.01\}$ the concentrations of the dissociated molecules are $x \approx \{0.01, 0.003, 0.001\}$, and hence the pHs are $1.93, 2.44, 2.95$.

(ii)   Now the concentration of H^+ is fixed to 0.01, so $0.01x = (c-x)K$, so $x = cK/(0.01 + K)$. Since $K \ll 0.01$, x and c are proportional, and for all three concentrations the dissociation fraction is about 1.4%.

(c)   (i)   The equilibrium constant of the combined reaction is $[OH^-][H^+]/[H_2O] \times [AH]/[A^-][H^+] = 1.8 \cdot 10^{-16}/1.4 \cdot 10^{-4} = 1.28 \cdot 10^{-12}$.

(ii)   This is the reverse situation to part b). We now assume that the amount of OH^- produced by the combined reaction is so large, that the *removal* of OH^- by the reverse water reaction (part a) is negligible. Suppose x is the concentration of OH^- and [AH], then, as before, $x^2/(1-x) = 55.6\,K = 7.15 \cdot 10^{-11}$. Therefore $x = 8.45 \cdot 10^{-6}$, the $-\log$ of which is 5.07, so the pH is $14 - 5.07 = 8.93$. The assumption that the solution was basic is therefore verified.

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3　(a)　(i)　　　We consider a small volume element located in (r,θ,x), with dimensions along these directions dr, $rd\theta$ and dx. Since u only depends on r, shear forces are only in the x direction. Considering first force balance in the x direction, we get:

$$p(r,x)(dr\cdot r\,d\theta) - p(r,x+dx)(dr\cdot r\,d\theta) - \tau(r)(dx\cdot r\,d\theta) + \tau(r+dr)(dx\cdot(r+dr)\,d\theta) = 0$$

This can be rewritten as:

$$-\frac{\partial p}{\partial x}(dx\cdot dr\cdot r\,d\theta) + \frac{\partial(r\tau)}{\partial r}(dx\cdot dr\cdot d\theta) = 0$$

leading to:

$$-\frac{\partial p}{\partial x} + \frac{1}{r}\frac{\partial(r\tau)}{\partial r} = 0 \qquad (1)$$

Force balance along the radial direction provides the next equation:

$$p(r,x)(dx\cdot r\,d\theta) - p(r+dr,x)(dx\cdot(r+dr)\,d\theta) + p(r,t)\underbrace{(dx\cdot dr\cdot 2\sin(d\theta/2))}_{\text{from the lateral sides}} = 0$$

This can be rewritten as:

$$-\frac{\partial(pr)}{\partial r}(dx\cdot dr\cdot d\theta) + p(r,t)(dx\cdot dr\cdot d\theta) = 0$$

Using the product rule on the first term, we get after simplification:

$$-\frac{\partial p}{\partial r} = 0 \qquad (2)$$

(ii)　The equation 2 shows that p is only a function x. Since τ is only a function of r, the equation 1 implies additionally that $\frac{dp}{dx}$ is constant.

We can now integrate Equ 1 with respect to r, and get:

$$\frac{\partial(r\tau)}{\partial r} = r\frac{dp}{dx} \Rightarrow \tau = \frac{r}{2}\frac{dp}{dx} + K/r$$

In the absence of a pressure gradient, the shear stress must be null everywhere, and therefore the integration constant K is zero. Hence the result.

$$\tau = \frac{r}{2}\frac{dp}{dx} \qquad (3)$$

(b)   We can now substitute equ. 3 in the Casson equation, isolate the velocity gradient on one side, and take the square on both sides:

$$-\mu\frac{du}{dr} = \left(\sqrt{-\frac{r}{2}\frac{dp}{dx}} - \sqrt{\tau_y}\right)^2 = -\frac{r}{2}\frac{dp}{dx} + \tau_y - 2\sqrt{\tau_y}\sqrt{-\frac{r}{2}\frac{dp}{dx}}$$

Comparing with the expression proposed in the exam paper, we find that

$$R_c = -2\tau_y\frac{dp}{dx}^{-1}.$$

For $r < R_c$, the fluid is below its yield stress and behaves as a solid; this is a plug flow. If $R_c > R$, then r is always smaller than R_c, and no flow is possible. There is not enough pressure drop to trigger a flow.

(c)   By direct integration of the differential equation (just a sum of power laws...), we get:

$$u(r) = \frac{1}{2\mu}\frac{dp}{dx}\left(\frac{r^2}{2} - 2\sqrt{R_c}\frac{2}{3}r^{\frac{3}{2}} + R_c r\right) + K$$

We constant K can be determined by the boundary condition: no flow at $r = R$, i.e. $u(R) = 0$.

$$K = -\frac{1}{2\mu}\frac{dp}{dx}\left(\frac{R^2}{2} - \frac{4}{3}\sqrt{R_c}R^{\frac{3}{2}} + R_c R\right)$$

Hence,

$$u(r) = -\frac{1}{2\mu}\frac{dp}{dx}\left(\frac{R^2 - r^2}{2} - \frac{4}{3}\sqrt{R_c}\left(R^{\frac{3}{2}} - r^{\frac{3}{2}}\right) + R_c(R - r)\right)$$

But this solution is only valid as long as $r > R_c$, where $du/dr < 0$. Note that in this flow, dp/dx is negative, as the pressure has to decrease as we move along the pipe. Since u is positive and maximum at the center of the pipe, du/dr is necessarily negative as well.

Where $r < R_c$, we have a plug flow, and $u(r) = u(R_c)$. By continuity of the velocity profile, $u(R_c)$ can be calculated from the expression above. It is worth pointing that when r tends to R_c from above, or when τ tends to τ_y, du/dr tends to zero, so the velocity profile is smooth.

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(d)　Flow starts if the pressure drop is high enough to ensure that R_c is smaller than the tube radius. If L_0 is the tube length, we have $-\frac{dp}{dx} = \frac{\Delta p}{L_0} = \frac{2\tau_y}{R_c}$. The condition for the flow is then:

$$R > \frac{2\tau_y L_0}{\Delta p} \text{ or } \Delta p > \frac{2\tau_y L_0}{R} = \Delta p_0$$

Using the values provided, we get $\Delta p_0 = 7 Pa$.

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4   (a)   The variation of the amount of oxygen in any volume V corresponds to the amount of oxygen consumed in that volume, plus the amount of oxygen that moved across its surface S. This leads to the following equation:

$$\iiint_V \frac{\partial c}{\partial t} dV = -\oiint_S \Phi dA - \iiint_V \rho dV$$

Using Gauss theorem, we get:

$$\iiint_V \frac{\partial c}{\partial t} dV = -\iiint_V \nabla \Phi dV - \iiint_V \rho dV$$

If we now take the limit of a small volume element δV, we get:

$$\frac{\partial c}{\partial t} \delta V = \nabla \Phi \delta V - \rho \delta V$$

Since $\Phi = -D\nabla c$, we finally obtain: $\frac{\partial c}{\partial t} = D\Delta c - \rho$

We have kept here for generality the time derivative, although this was not required in the question, and could have been set to zero from the beginning. In a stationary case, we therefore get: $D\Delta c - \rho = 0$

(b)   The boundary condition is the value of the concentration at the surface of the tumor: $c(R_T) = c_0$. We use cylindrical polar coordinates to study this problem. The math databook provides the expression of the Laplacian.

In the steady state, the differential equation becomes:

$$\frac{D}{r^2} \frac{d}{dr} \left(r^2 \frac{dc}{dr} \right) = \rho$$

After a first integration, we get:

$$r^2 \frac{dc}{dr} = \frac{\rho r^3}{3D} + K_1 \text{ or } \frac{dc}{dr} = \frac{\rho r}{3D} + \frac{K_1}{r^2}$$

A second integration provides:

$$c(r) = \frac{\rho r^2}{6D} - \frac{K_1}{r} + K_2$$

Because the concentration must be finite at $r = 0$, $K_1 = 0$. Since $c(R_T) = c_0$, $K_2 = c_0 - \frac{\rho R_T^2}{6D}$. The full solution is therefore:

$$c(r) = c_o - \frac{\rho}{6D}(R_T^2 - r^2)$$

(c)   The tumor gets necrosed when the minimum of the concentration, at $r = 0$, becomes negative. This occurs when:

$$\frac{\rho}{6D}R_T^2 > c_0 \text{ or } R_T > \sqrt{\frac{6Dc_0}{\rho}}$$

The numerical value is $R_T > \sqrt{0.1}$ cm ≈ 3 mm.

(d)   The total amount of oxygen consumed by the tumor per unit time is simply ρ times the total volume, i.e. $\frac{4\pi R_T^3 \rho}{3}$

(e)   The flux of blood arriving through the vessel is au_a. The flux of oxygen is $au_a c_0$. For the tumor to be properly oxygenated, we then also need:

$$\frac{4\pi R_T^3 \rho}{3} < au_a c_0 \text{ or } R_T^3 < \frac{3au_a c_0}{4\pi\rho}$$

Numerically, we obtain approximately $R_T < 1.5$ mm. In this model, the tumor size is therefore limited by the incoming blow flow, and not the diffusion. In practice, both values are of the same order of magnitude.

(f)   The previous results imply that, for a tumor to grow larger than a couple of millimeter, it has to trigger the formation of a large number of new vessels. Based on this simple model, it would need at least 5 to 10 new arterioles to reach the size at which growth is limited by diffusion. Additionally, tumors usually become vascularised in their volume, and not only surface so that they can grow up to several centimeters.

Tumors are in fact known to release chemicals that stimulate the vascularisation of tissues. Compromising the efficiency of these signals can ensure that tumors do not grow more than a couple of microns in diameter.

END OF PAPER

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