Q 1

a) $S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E$

What is V?

$V = k_2 [C]$

→ We need to find $[C]$

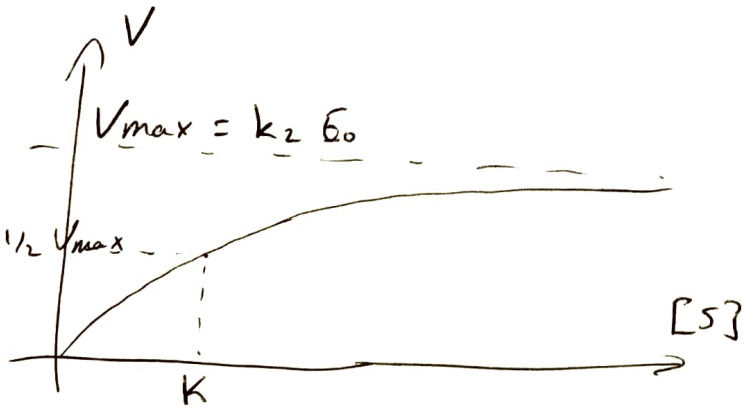
We have $E_0 = [E] + [C]$ (1)

Fast equilibrium → $\frac{[C]}{[S][E]} = \frac{k_1}{k_{-1}} = K^{-1}$

→ $[E] = K \frac{[C]}{[S]}$ (2)

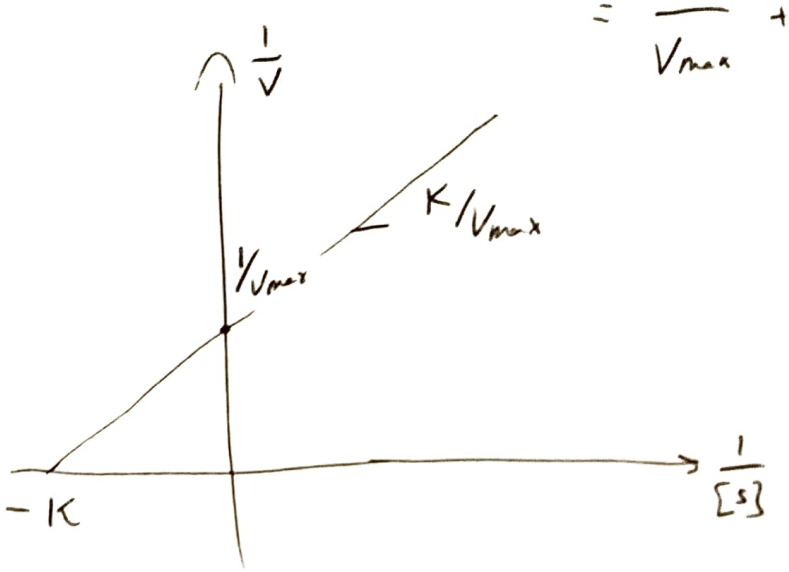
(1) + (2) → $E_0 = \frac{K}{[S]}[C] + [C] = \left(1 + \frac{K}{[S]}\right)[C]$

$V = k_2[C] = \frac{k_2 E_0}{1 + K/[S]} = \frac{k_2 E_0 [S]}{K + [S]}$



$$\frac{1}{V} = \frac{K + [S]}{k_2 E_0 [S]} = \frac{1}{k_2 E_0} + \frac{K}{k_2 E_0} \frac{1}{[S]}$$

$$= \frac{1}{V_{max}} + \frac{K}{V_{max}} \frac{1}{[S]}$$



b) i) In this case, the rate of product formation is $V = k_2 [C_1] + k_4 [C_3]$

We need to find $[C_1]$ and $[C_3]$ as a function of E_0, $[S]$, $[I]$ and other constants.

Fast equilibrium:

$$K_M = \frac{[E][S]}{[C_1]} = \frac{[C_2][S]}{[C_3]}$$

$$K_I = \frac{[E][I]}{[C_2]} = \frac{[C_1][I]}{[C_3]} \rightarrow [C_3] = \frac{[I]}{K_I}[C_1]$$

We also have $E_0 = [E] + [C_1] + [C_2] + [C_3]$

Let's focus on C_1 for now.

We have:

$$[E] = \frac{K_M}{[S]}[C_1]$$

$$[C_2] = \frac{[I]}{K_I}[E] = \frac{[I]}{K_I}\frac{K_M}{[S]}[C_1]$$

$$\rightarrow E_0 = \left(\frac{K_M}{[S]}\left(1 + \frac{[I]}{K_I}\right) + \frac{[I]}{K_1} + 1 \right)[C_1]$$

$$E_0 = \left(\frac{K_M}{[S]} + 1\right)\left(\frac{[I]}{K_1} + 1\right)[C_1]$$

$$\Rightarrow [C_1] = \frac{E_0 [S]}{(K_M + [S])\left(1 + \frac{[I]}{K_1}\right)}$$

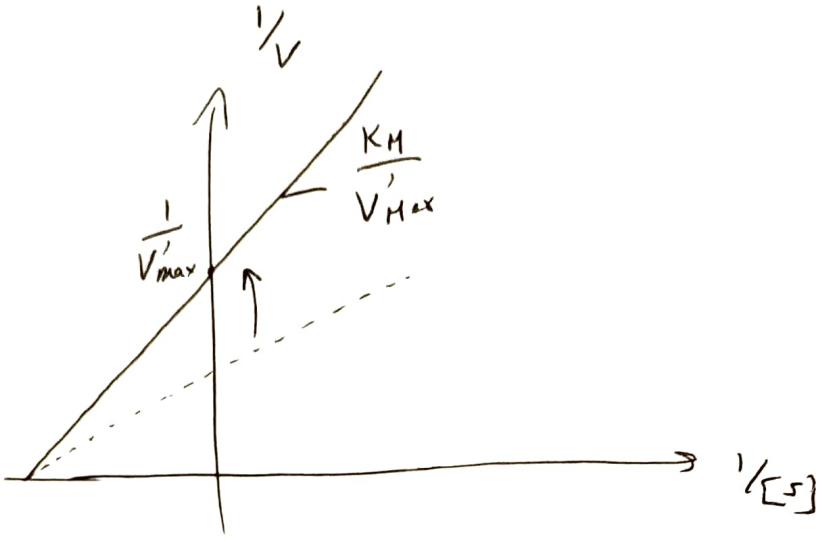
$$[C_3] = \frac{[I]}{K_1} \frac{E_0 [S]}{(K_M + [S])\left(1 + \frac{[I]}{K_I}\right)}$$

$$V = \left(k_2 + k_4 \frac{[I]}{K_1}\right) \frac{E_0 [S]}{(K_M + [S])\left(1 + \frac{[I]}{K_1}\right)}$$

Let's rewrite this to show the effect of the inhibition more clearly

$$V = \frac{1 + \frac{k_4}{k_2} \frac{[I]}{K_I}}{1 + \frac{[I]}{K_I}} \cdot \underbrace{\frac{k_2 E_0 [S]}{K_M + [S]}}_{\text{result from part (a)}}$$

$$V'_{max} = \underbrace{k_2 \, t_0}_{V_{max}} \frac{1 + \frac{k_4}{k_2}\frac{[I]}{K_I}}{1 + \frac{[I]}{K_I}}$$



b) ii) Inhibition happens when $V'_{max} < V_{max}$

$$\Rightarrow \quad 1 + \frac{k_4}{k_2}\frac{[I]}{K_I} < 1 + \frac{[I]}{K_I}$$

$$\Rightarrow \quad k_4 < k_2$$

If $k_4 > k_2$, I promotes the product formation

If $k_4 = k_2$, I has no effet on the rate V.

1 (a) (i)

Answer: The generation of an action potential depends on the positive feedback loop between the activation of the Na^+ channel and the depolarisation of the membrane. Thus, an action potential is generated when depolarisation exceeds the threshold for the activation of the m gate, which is where the step is in the sigmoid-shaped m_∞ vs. V curve is. This value is about 10 mV above the resting membrane potential.

(ii)

Answer: The absolute refractory period is caused by the inactivation of the Na^+ channel, i.e. that the h gate closes when the membrane potential becomes depolarised during the action potential. Thus, the duration of the absolute refractory period depends on the time constant of the h gate, which determines how slowly it re-opens once the membrane has repolarised (or even hyperpolarised) after (the peak of) the action potential. Its value is about 5 ms.

(iii)

Answer: The relative refractory period is caused by the fact that (the peak of) the action potential is followed by hyperpolarisation and thus it requires more current to depolarise the cell above threshold than if the membrane potential was at its resting value. During hyperpolarisation, the voltage-dependent Na^+ and K^+ channels have approximately constant conductances and so the membrane mostly behaves as a simple RC circuit. Therefore, the duration of the relative refractory period is mainly determined by two factors: 1. the peak hyperpolarisation, and 2. the membrane time constant (which sets the speed with which the cell recovers from hyperpolariation). 1. The peak hyperpolarisation is controlled by the K^+ Nernst potential (which is about 10 mV below the resting membrane potential). 2. The membrane time constant is the product of the membrane capacitance ($1.0\ \frac{\mu F}{cm^2}$) and the membrane resistance. In turn, the latter is the reciprocal of the sum of all conductances (0.01, 0.2, and 0.05 $\frac{mS}{cm^2}$ for the Na^+, K^+, and Cl^- [or "leak"] conductances respectively, making membrane time constant to be about $\tau = 4$ ms). Considering the end of the refractory period to be when the membrane potential gets to be within $V_{end} = 1$ mV of the resting membrane potential from the original $V_{hyp} = 10$ mV hyperpolarisation (see above), we can write the following equation for the membrane potential:

$$V_{end} = V_{hyp}\, e^{-\frac{t_{refr}}{\tau}} \tag{1}$$

which we can solve for the length of the refractory period, t_{refr}, giving us:

$$t_{refr} = \tau \ln \frac{V_{hyp}}{V_{end}} = 4\text{ ms} \ln \frac{10\text{ mV}}{1\text{ mV}} \approx 10\text{ ms} \tag{2}$$

(b) (i)

Answer: The time constant of the axon is the product of the membrane capacitance, C_m, and the total membrane resistance R_m, which in turn is the reciprocal of the total membrane conductance:

$$\tau = \frac{1.0\ \frac{\mu F}{cm^2}}{0.25\ \frac{mS}{cm^2}} = 4\text{ ms} \tag{3}$$

(ii)

Answer: Given the membrane resistance $R_m = 4\ k\Omega\,cm^2$, the axial resistance $R_a = 1\ k\Omega\,mm =$

0.1 kΩ cm, and the axon radius $r = 0.125$ mm $= 0.0125$ cm, the length constant is

$$\lambda = \sqrt{\frac{R_\mathrm{m}\, r}{2\, R_\mathrm{a}}} = \sqrt{\frac{4\ \mathrm{k\,\Omega\,cm^2}\ 0.0125\ \mathrm{cm}}{2 \cdot 0.1\ \mathrm{k\Omega\,cm}}} = \frac{1}{2}\ \mathrm{cm} \tag{4}$$

(iii)

Answer: As the stimulation is small enough (5 mV) that it will not make the axon generate an action potential, the membrane potential is well described by the standard cable equation. As such, peak depolarisation at location x is reached at time (relative to stimulus offset)

$$t_\mathrm{max} = \frac{\tau}{4}\left[\sqrt{1 + 4\ (x/\lambda)^2} - 1\right] \tag{5}$$

The distance of the midpoint from the location of current injection is

$$x_{1/2} = \frac{\sqrt{2}\ \mathrm{cm}}{2} = \frac{\sqrt{2}}{2}\ \mathrm{cm} \tag{6}$$

and so for $x = x_{1/2}$:

$$t_\mathrm{max} = \frac{4\ \mathrm{ms}}{4}\left[\sqrt{1 + 4\left(\frac{\frac{\sqrt{2}}{2}\ \mathrm{cm}}{\frac{1}{2}\ \mathrm{cm}}\right)^2} - 1\right] = \sqrt{1 + 4\left(\sqrt{2}\right)^2} - 1\ \mathrm{ms} = 2\ \mathrm{ms} \tag{7}$$

(iv)

Answer: The depolarisation at distance $x_{1/2}$ from the location of depolarisation and time t_max is given by

$$V\left(x_{1/2}, t_\mathrm{max}\right) = \alpha\ \frac{1}{\sqrt{2\,\pi\,\sigma^2}}\ e^{-\frac{1}{2}\frac{x_{1/2}^2}{\sigma^2}}\ e^{-\frac{t_\mathrm{max}}{\tau}} \tag{8}$$

$$\text{where } \sigma = \sqrt{2}\,\lambda\,\sqrt{t_\mathrm{max}/\tau} \tag{9}$$

Knowing the amount of depolarisation, V_0 at the location of stimulation, $x = 0$, and at $t_0 = 1$ ms, allows us to solve for α:

$$V_0 = \alpha\ \frac{1}{\sqrt{2\,\pi\,\sigma_0^2}}\ e^{-\frac{t_0}{\tau}} \tag{10}$$

$$\alpha = V_0\ \sqrt{2\,\pi\,\sigma_0^2}\ e^{\frac{t_0}{\tau}} \tag{11}$$

$$\text{where } \sigma_0 = \sqrt{2}\,\lambda\,\sqrt{t_0/\tau} \tag{12}$$

With the constants provided:

$$\sigma_0 = \sqrt{2} \cdot \frac{1}{2}\,\text{cm} \cdot \sqrt{1\,\text{ms}/4\,\text{ms}} = \sqrt{1/8}\,\text{cm} \tag{13}$$

$$\alpha = 5\,\text{mV}\,\sqrt{2\,\pi\,1/8}\,\text{cm}\,e^{\frac{1\,\text{ms}}{4\,\text{ms}}} = \sqrt{2\,\pi} \cdot 5 \cdot \sqrt{1/8} \cdot e^{1/4}\,\text{mV}\,\text{cm} \tag{14}$$

$$\sigma = \sqrt{2}\,\frac{1}{2}\,\text{cm}\,\sqrt{2\,\text{ms}/4\,\text{ms}} = 1/2\,\text{cm} \tag{15}$$

$$V\left(x_{1/2}, t_{\max}\right) = \sqrt{2\,\pi} \cdot 5 \cdot \sqrt{1/8} \cdot e^{1/4}\,\text{mV}\,\text{cm}\,\frac{1}{\sqrt{2\,\pi}\,1/2\,\text{cm}}\,e^{-\frac{1}{2}\frac{\left(\frac{\sqrt{2}}{2}\right)^2\,\text{cm}^2}{1/4\,\text{cm}^2}}\,e^{-\frac{2\,\text{ms}}{4\,\text{ms}}} \tag{16}$$

$$= \frac{5}{\sqrt{2}}\,e^{-\frac{5}{4}}\,\text{mV} \approx 1\,\text{mV} \tag{17}$$

(v)

Answer: According to cable theory, the effects of two stimuli simply add, and since we are measuring the membrane potential at exactly the midpoint, and the two stimuli are identical, the membrane potential at any time is just going to be twice as large as what it would be for either stimulus alone – which is the case we considered above. Thus, the peak depolarisation is going to be twice as large as that derived above, i.e.

$$V\left(x_{1/2}, t_{\max}\right) = \frac{10}{\sqrt{2}}\,e^{-\frac{5}{4}}\,\text{mV} \approx 2\,\text{mV} \tag{18}$$

(vi)

Answer: This is a stimulus that is strong enough to make the axon generate an action potential when Na^+ channels are not blocked. This action potential is then propagated along the axon. Thus, the peak of the membrane potential at any location along the axon, including its midpoint, will be determined by the action potential, which is about 100 mV.

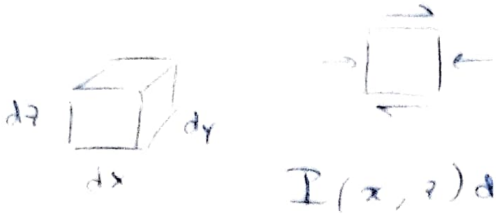
(vii)

Answer: As both ends are being stimulated, there is going to be an action potential generated and propagated from both ends. Unlike passively propagated signals, which we considered above, action potentials do not add, as their peak value is limited by the Na^+ Nernst potential. Thus the peak of the membrane potential is still going to be about 100 mV.

END OF PAPER

Q3

a) In the x direction:



$$I(x,z)\,dy\,dz - I(x+dx,z)\,dy\,dz - \tau(z)\,dx\,dy + \tau(z+dz)\,dx\,dy = 0$$

Divide by $dy\,dz\,dx$

$$\hookrightarrow -\frac{\partial P}{\partial x} + \frac{\partial \tau}{\partial z} = 0$$

In the z direction:

$$I(x,z)\,dx\,dy - I(x,z+dz)\,dx\,dy = 0$$

Divide by $dx\,dy\,dz \longrightarrow \frac{\partial I}{\partial z} = 0$

b)

$$\frac{\partial P}{\partial z} = 0 \longrightarrow P \text{ only depends on } x$$

$$\frac{\partial \tau}{\partial z} = \frac{\partial P}{\partial x} = \text{constant} \quad \text{(separation of variable)}$$

$$\longrightarrow \tau = \frac{\partial P}{\partial x} z + C$$

Placing the origin of the z-axis in the middle of the channel.

$$\tau(z=0) = 0 \quad \text{by symetry.}$$

$$\longrightarrow \tau = \frac{\partial p}{\partial x} \cdot z$$

For a Newtonian fluid. $\tau = \mu \frac{du}{dz}$

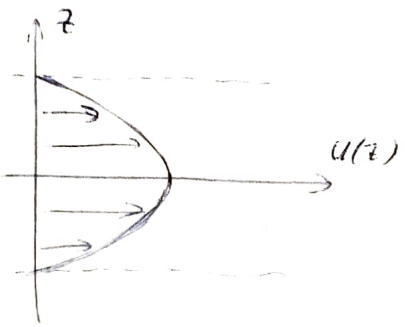
$$\frac{du}{dz} = \frac{1}{\mu} \frac{dp}{dx} \cdot z$$

$$u = \frac{1}{2\mu} \frac{dp}{dx} z^2 + D$$

$u\left(\pm \frac{h}{2}\right) = 0$ (no slip on the walls)

$$D = -\frac{1}{2\mu} \frac{dp}{dx} \frac{h^2}{4}$$

$$u = -\frac{1}{2\mu} \frac{dp}{dx} \left(\frac{h^2}{4} - z^2 \right)$$



c) We need to integrate the velocity over the cross-section.

$$Q = \iint u \, dy \, dz = w \int_{-h/2}^{h/2} u(z) \, dz$$

$$= \frac{w}{2\mu}\left(-\frac{dp}{dx}\right) \cdot 2 \int_0^{h/2} \left(\left(\frac{h}{2}\right)^2 - z^2\right) dz$$

$$\int_0^{h/2} \left(\frac{h}{2}\right)^2 - z^2 \, dz = \left[\frac{h^2}{4} z - \frac{1}{3} z^3\right]_0^{h/2} = \frac{h^3}{8} - \frac{1}{3}\frac{h^3}{8} = \frac{2}{3}\frac{h^3}{8} = \frac{h^3}{12}$$

$$Q = \frac{w\left(-dp/dx\right) h^3}{12\mu}$$

Q4 a)

$$4\,O_2 + Hb \underset{k_-}{\overset{k_+}{\rightleftharpoons}} Hb(O_2)_4$$

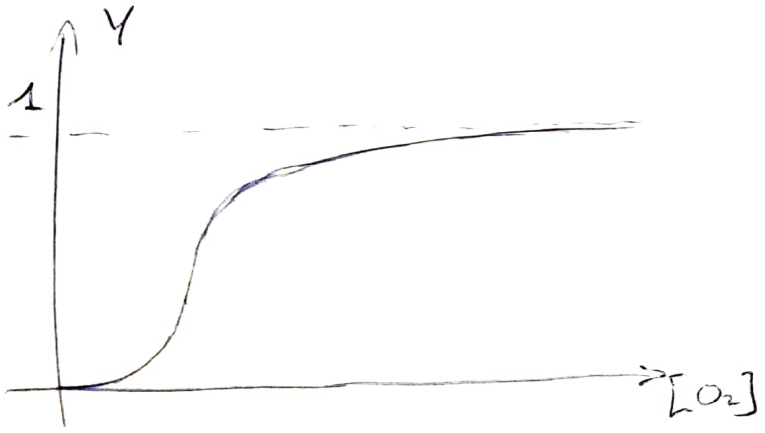
In this model, it is assumed that 4 O_2 molecules will bind at once to Hb, as an elementary reaction.

$$\frac{d[Hb(O_2)_4]}{dt} = k_+ [O_2]^4 [Hb] - k_- [Hb(O_2)_4]$$

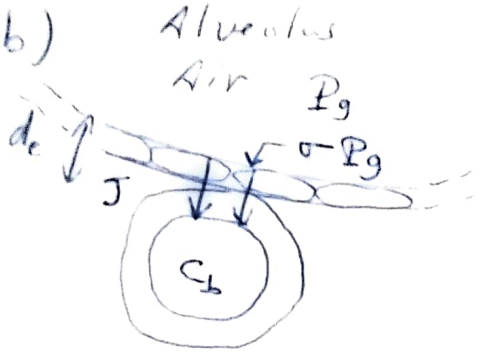
at equilibrium, the rate is 0.

$$\frac{[Hb(O_2)_4]}{[O_2]^4 [Hb]} = \frac{k_+}{k_-}$$

$$Y = \frac{[Hb(O_2)_4]}{[Hb] + [Hb(O_2)_4]} = \frac{\cancel{[Hb]} \frac{k_+}{k_-} [O_2]^4}{\cancel{[Hb]} + \cancel{[Hb]} \frac{k_+}{k_-} [O_2]^4} = \frac{[O_2]^4}{\frac{k_-}{k_+} + [O_2]^4}$$



b)



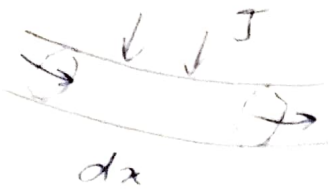
We assume that the syrtem reaches steady state for diffusion.

$$J = D_e \frac{\sigma P_g - C_b}{d_e}$$

correspond to the flux entering the capillary.

σP_g is the oxygen concentration in the tissue at the air-tissue interface.

c)



$\Longrightarrow$ Conservation of oxygen argument, taking into account the oxygen stored in Hb.

Total amount / concentration of oxygen transported C_t

$$C_t = [O_2] + 4[Hb(O_2)_4] = [O_2] + 4\,Y([O_2])\,Hb_0$$

$$C_t = C_b + 4\,Hb_0 \frac{C_b^4}{\frac{k_-}{k_+} + C_b^4}$$

Mass conservation.

$$v\,d_a^2\,dt \cdot C_t(x) + D_e \frac{\sigma P_g - C_b}{d_e} \cdot d_a dx \cdot dt = v\,d_a^2\,dt \cdot C_t(x+dx)$$

$$v\,\frac{dC_t}{dx} = D_e \frac{\sigma P_g - C_b}{d_e d_a}$$

$$\longrightarrow v\,\frac{d}{dx}\left(C_b + 4\,Hb_0 \frac{C_b^4}{\frac{k_-}{k_+} + C_b^4} \right) = \frac{D_e}{d_a d_e}(\sigma P_g - C_b)$$

$$K = k_-/k_+$$

Q1 Enzyme kinetics

This was a very popular question, selected by all students. It was a relatively straight forward application of what students had covered in the course, and students did overall very well indeed. I number of students used the quasi steady-state assumption on this questions that required a fast equilibrium to be done easily, as prompted in the question. But otherwise, students demonstrated a good understanding of this part of the course.

Q2 Electrophysiology

This question proved to be extremely unpopular (only chosen by 4 students) and even those attempting it did quite poorly on it, and were mostly unable to answer even the basic bookwork questions (solutions to a(i) and a(ii), and membrane time and length constant, b(i) and (ii)). Nobody tried to use the correct formula for transient stimulation in b(iii) and (iv) (those who tried hardest, used the formula for steady-state stimulation, despite explicit instructions in the question to the contrary “stimulated […] with a brief electrical pulse”).

Q3 Flow in rectangular channel

This was a very popular question. A majority of students demonstrated an excellent ability to balance forces on a volume element and deduce from this differential equations expressing equilibrium. This was different from the standard Poiseuille flow in a cylinder covered in lecture, and somewhat easier due to the rectangular geometry. Unfortunately, a number of students memorised the cylindrical results and started with this, which was of no use in this case.

Q4 Oxygen transport in the alveolus

The question was fairly popular, and generally well answered. The oxygen binding model was well understood by nearly all students. The diffusion across the epithelium was also generally well tackled. Many students were running out of time to cover the last section, but those who attempted it typically did well. Because this was a “show that” question, a number of students explained the origin of the different terms rather than establishing it properly. They got a few marks for insight.