Version AJK/2

EGT2
ENGINEERING TRIPOS PART IIA

Monday 5 May 2014 9.30 to 11

Module 3G2

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

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

1 Consider the following mechanism of enzyme activity, where the enzyme is E, the substrate S and the product P.

$$\mathrm{S}+\mathrm{E} \rightleftharpoons \mathrm{ES} \qquad \mathrm{K}_1 = \frac{[\mathrm{ES}]}{[\mathrm{S}][\mathrm{E}]}$$

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

$$\mathrm{S}+\mathrm{ES} \rightleftharpoons \mathrm{SES} \qquad \mathrm{K}_3 = \frac{[\mathrm{SES}]}{[\mathrm{S}][\mathrm{ES}]}$$

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

The equilibrium reactions are all supposed to be fast. The total concentration of enzyme is E_0 and the product creation rate is V.

(a) (i) In the limit where k_4=0, show that

$$\frac{V}{E_0} = \frac{k_2 s}{K_1^{-1} + s + K_3 s^2} \text{ , where } s = [\mathrm{S}].$$

[20%]

Answer: If k_4=0, V simply equals k_2 [ES]. The general strategy here is to express the concentrations of E and SES as a function of [ES] (using the equilibrium constants), and substitute in the expression of the total enzyme concentration: E_0=[E]+[ES]+[SES]. We get:

$$E_0 = \left(\frac{1}{K_1 s} + 1 + K_3 s\right)[ES]$$

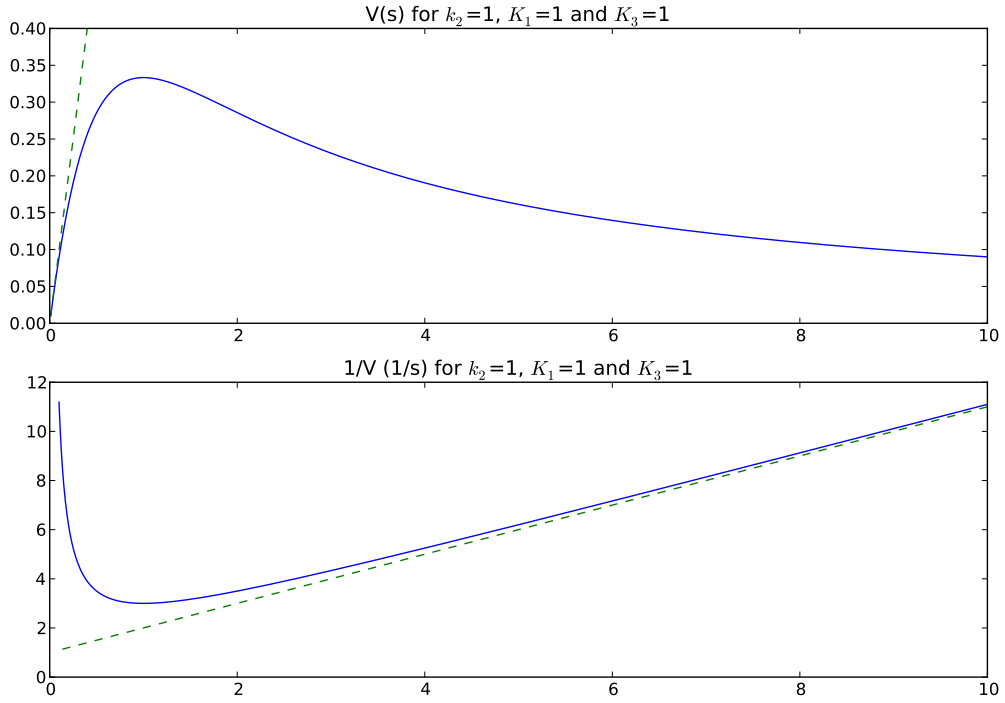
$$\frac{V}{E_0} = k_2[ES] = \frac{k_2}{\frac{1}{K_1 s} + 1 + K_3 s}$$

The expression requested can be easily derived by multiplying numerator and denominator by s.

(ii) Sketch the graphs of V as a function of s, and $1/V$ as a function of $1/s$. How do these graphs qualitatively differ from the standard Michaelis Menten case. [20%]

Answer: There is a strong qualitative difference between the current situation and Michaelis Menten case. Here, the product creation rate has a maximum for a finite substrate concentration, whereas in Michaelis Menten, the rate is monotonically increasing with s, although it saturates at a finite value.

The plot of $1/V$ as a function of $1/s$ is therefore not a straight line any more, but has a minimum.



(iii) This type of enzyme kinetics is called substrate inhibition. Explain why. [10%]

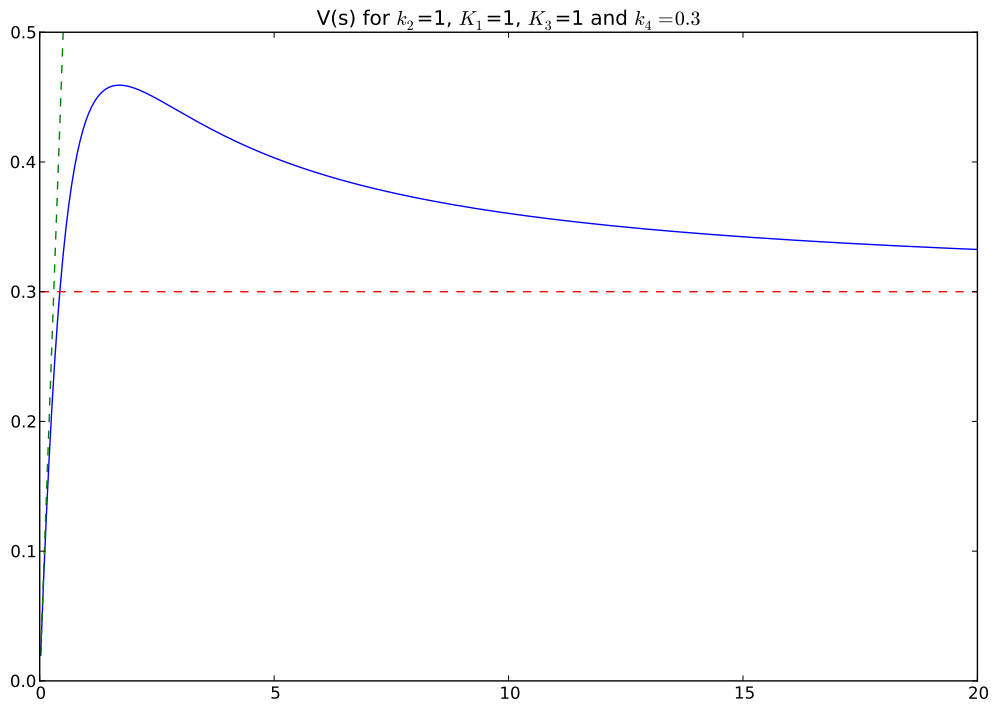
Answer: The equilibrium K_3 means that the substrate is able to sequester the Enzyme-substrate complex ES and block the formation of the product. The substrate therefore acts as an inhibitor. This is why as the substrate concentration increases, the product formation slows down and eventually its rate vanishes.

(b) (i) Derive an expression for $\frac{V}{E_0}$ in the general case, where k_4 is non-zero. Sketch the curve of $V(s)$. [30%]

Answer: In this case, the product creation rate is V = k_2 [ES] + k_4 [SES] = (k_2 + k_4 K_3 [S])[ES] . Following the same approach as in question (a)(i), we find:

$$\frac{V}{E_0} = \frac{k_2 s + k_4 K_3 s^2}{K_1^{-1} + s + K_3 s^2} \text{ , where } s = [S].$$

The main difference in the graph comes from the the new s^2 term in the numerator. When s is large, V tends to k_4 E_0 (red dashed line on the figure), as opposed to k_2 E_0 in the usual Michaelis Menten equation.



(ii) What condition on the kinetic and equilibrium constants must be satisfied for this inhibition mechanism to enhance the product creation rate at large substrate concentrations? [20%]

Answer: As explained above, the mechanism proposed for substrate inhibition changes to product creation rate from k_2 E_0 to k_4 E_0 at large values of the substrate concentration. If $k_4 > k_2$, substrate inhibition actually increases the product creation rate.

2 This question is about the Nernst potential.

(a) What is the formula for the Nernst potential? In your answer:

- explain the meaning of each symbol in the formula you provide,
- for each quantity, specify the units in which it is measured such that the formula is dimensionally consistent,
- for physical constants also provide their approximate value in the units you chose, for the other quantities state their typical values (or ranges) in living cells (such as neurons) in the units you chose. [20%]

Answer:

$$V_{\text{Nernst}} = \frac{RT}{zF} \ln\left(\frac{c_{\text{e}}}{c_{\text{i}}}\right)$$

where V_{Nernst} (typically in the range $-0.1 - 0.1$ V) is the Nernst potential of the ion, R ($8.314 \approx 10$ J/(mol K)) is the universal gas constant expressing the amount of energy needed to heat up a mole of ideal gas by 1 K, T is the temperature (room temperature: $293 \approx 300$ K), z is the valence of the ion (unitless, typically -1, $+1$ or $+2$), F is the Faraday constant ($96485 \approx 100000$ C/mol) expressing the electric charge carried by a mole of electrons, and c_{e} and c_{i} are the concentrations of the ion inside and outside the cell (typically in the range $10 - 1000$ mM, where $\text{M} = \text{mol}/\text{dm}^3$).

(b) Under what condition are the following two statements equivalent: (1) the membrane potential in a neuron is at the Nernst potential of ion X, and, (2) the channel current for ion X is zero. [30%]

Answer:

Whenever the channel current is zero everywhere inside the channel, the membrane potential must equal the Nernst potential. However, the converse is not necessarily true in principle: when the the membrane potential equals the Nernst potential, the channel current may not be zero everywhere inside the channel. However, in steady state, when ionic concentrations inside the channel don't change any more, the flux (and thus the current) inside the channel becomes a constant (both in space and time), and therefore the membrane potential being at the Nernst potential in steady state implies that this constant is zero, i.e. that the channel current is zero. Concentrations in the channel reach steady-state on the order of μs, so in practice, on the time scales that the membrane potential of a neuron varies (mV), whenever the membrane potential reaches the Nernst potential, the channel current is going to be zero.

(c) In the Hodgkin-Huxley model, the Nernst potentials of ions are assumed to be constant in time, while the model is based on ionic currents. This seems an apparent

contradiction. Explain with reasons what this contradiction is, and why in practice the assumption of fixed Nernst potentials may still be valid. [15%]

Answer:

The apparent contradiction stems from the fact that the Nernst potential is a function of the intra- and extracellular concentrations of an ion (see answer above), while the ionic currents in the Hodgkin-Huxley model will inevitably change these concentrations thereby changing the Nernst potential of the corresponding ions, which in turn seems to violate the assumption that Nernst potentials are constant over time. However, in practice, the amount of ions crossing the membrane during an action potential is very small, so that they don't measurably change the ionic concentrations (especially not the extracellular concentrations, as the extracellular volume is relatively large), and hence the Nernst potential remains constant. The effects of subsequent action potentials do not cumulate because there are special ion pumps in place in the membrane restoring ionic concentrations over time.

(d) In a very thin axon, 20 ms after a large number of action potentials have been fired at a very high rate, it is observed that no further action potentials can be elicited even with large current injections. Explain what mechanism can account for this observation. [35%]

Answer:

The inability to elicit action potentials cannot be explained by a simple refractory period, because the absolute refractory period is usually shorter than 10 ms. However, the long and high frequency action potential train must have resulted in a large amount of ions crossing the membrane that could not be compensated by the operation of ion pumps thus leading to accumulated changes in ionic concentrations inside and outside the cell. Intracellular concentration changes became particularly acute because the axon is very thin which means its volume (for a unit length) is small, so the same number of ions crossing the membrane led to large changes in concentration (which is the number of ions divided by volume). These concentration changes led to changes in Nernst potentials, such that the Na^+ Nernst potential decreased and the K^+ Nernst potential increased. Due to these changes, the resting membrane potential increased (because it is more influenced by the K^+ than the Na^+ Nernst potential), which inactivated the Na^+ channels even at rest (due to the h gate inactivating at high membrane potentials), preventing the generation of further action potentials (which need a deinactivated h gate at rest).

3 A range of pressure-volume cycles in the left heart are presented in Fig. 1. The data has been collected on the same individual (dog) under various exercise conditions and under epinephrine treatment for some of them.

(a) (i) We consider first the greyed cycle on Fig. 1. For each of the segments 1-2, 2-3, 3-4 and 4-1, indicate the state of the mitral and aortic heart valves and estimate its typical duration. Provide values for the artery pressure P_a and pulmonary vein pressure P_v. [25%]

Answer: Segment 1-2 marks the transition from diastole to systole. The mitral valve closes in 1, and the aortic valve opens in 2. This is a very short event, about 1/50 sec. During 2-3, the heart muscle pushes out blood. This lasts about 1/4 of a sec. Segment 3-4 marks the transition from systole to diastole. The aortic valve closes in 3 and the mitral valve opens at 4. This is again very short, about 1/50 sec. During 4-1, the left heart is filled up by blood, this lasts between 1/4 and 1/2 of a second. P_v is around 5-10 mmHg, and P_a is around 100-110 mmHg.

(ii) Explain the meaning of the dashed and solid straight lines on Fig. 1 for the epinephrine and control cases. What properties of the heart tissue can be measured from these lines? Estimate their value. [20%]

Answer: The solid lines represents the relationship between pressure and volume of the contracted heart muscle once it has essentially reached equilibrium. The slope is therefore a measure of heart stiffness in the contracted state. The graph allows us to express the stiffness in mmHg/ml - note that this is not a material property and also depends on the geometry of the heart. The compliance of the tissue is the inverse of the stiffness. The control data provides 9 mmHg/mL, whereas the epinephrine data is stiffer, at 12-13 mmHg/mL. Epinephrine is therefore a hormone that can enhance muscle stiffness and contractility.

(iii) Establish a simplified quantitative model of the heart cycle and provide an expression for the cardiac output as a function of heart beat frequency. [25%]

Answer: If C_d and C_s are the heart muscle compliance in the relaxed (end diastole) and contracted (end systole) state, we can relate the end of diastol and end of systole volumes to the pressures in the veins and arteries:
End systolic volume:

$$V_{ES} = V_{min} + C_s P_a$$

End diastolic volume:

$$V_{ED} = V_{max} + C_d P_v$$

The stroke volume is therefore:

$$V_{stroke} = V_{ED} - V_{ES}$$

Combining this with the cardiac beat frequency F, we can calculate the cardiac output:

$$Q = F V_{stroke}$$

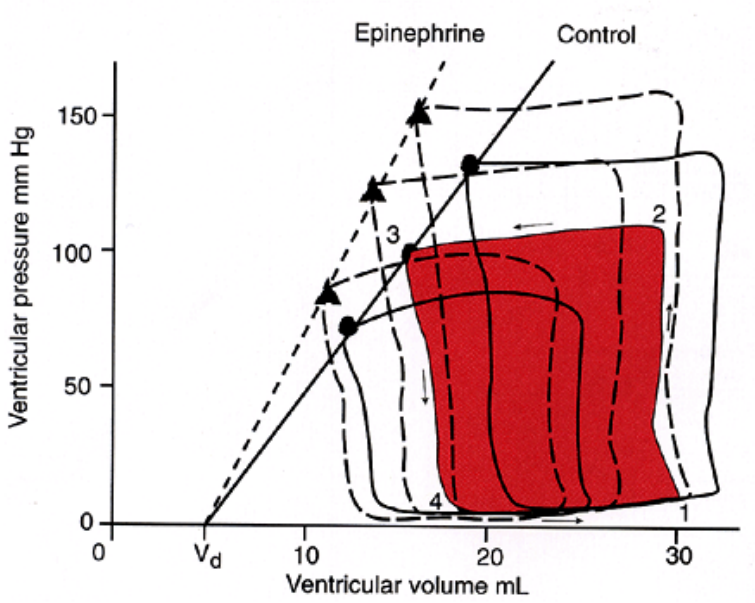


Fig. 1

(b) Velocity measurements in the circulatory system show that blood flow is pulsatile in the aorta but steady in capillaries. Explain how this is possible using a simple analytical model. [30%]

Answer: Compliant vessels behave as low pass filters on pulsatile pressure profiles. the Windkessel model illustrates well this question. We consider an artery as a finite compliant vessel. The capillary vessels are accounted for by a hydrodynamics resistance R. The volume variation of the artery is (mass conservation + blood incompressibility):

$$dV = Qdt - (P/R)dt$$

Where P is the chamber pressure and Q the incoming flow rate (from the heart). The vessel elasticity writes:

$$dV = CdP$$

The differential equation then writes:

$$Q = C\frac{dP}{dt} + P/R$$

This is the typical first order equation of low pass filters. Pulsatile pressure variations are damped whereas continuous pressure persists, protecting as a result the fragile network of blood capillaries.

4 (a) In blood, dissolved carbon dioxide is largely transformed into bicarbonate ions through the following reaction:

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^- \qquad K = 4.30 \cdot 10^{-7}$$

Assuming that blood pH is approximately 7.4, determine the value of $\lambda = [HCO_3^-]/[CO_2]$ at the chemical equilibrium. [20%]

Answer: At equilibrium, we have $K = \frac{[H^+][HCO_3^-]}{[CO_2]}$. Hence, $\kappa = [HCO_3^-]/[CO_2] = \frac{K}{[H^+]} \approx 10.8$

(b) We study in this question the balance between ventilation and perfusion of a gas in the lungs. The volume of air renewed in the lung per unit of time is $\dot{V}$ and the total blood flow rate is Q. Show that:

$$\frac{\dot{V}}{Q} = \frac{c_L - c_0}{c_i - c_a}$$

where c_i and c_a are the gas concentrations in the air entering and leaving the lungs respectively. c_0 and c_L are the gas concentrations in blood entering and exiting the lungs, respectively. [30%]

Answer: The flux of gas entering the circulatory system must the difference of the fluxes in and out: $\dot{V}(c_i - c_a)$. This must be equal to the difference of gas flux in blood between in the entry and exit of the lung capillaries: $Q(c_L - c_0)$. This identity provides the requested relationship.

(c) In the case of carbon dioxide, show that the ventilation perfusion ratio takes the following form:

$$\frac{\dot{V}}{Q} = \sigma RT(1+\lambda)\frac{P_0 - P_a}{P_a}$$

where σ is the solubility of carbon dioxide in plasma, R the ideal gas constant and T the temperature. P_a and P_0 are the carbon dioxide partial pressures in the air exiting the lungs and in the blood entering alveoli capillaries, respectively. [50%]

Answer: The concentration in the gas is related with the partial pressures by the ideal gas law: $P_i = RTc_i$ and $P_a = RTc_a$. Expressing blood concentrations in terms of partial pressures, the ventilation-perfusion ratio therefore writes:

$$\frac{\dot{V}}{Q} = \sigma RT(1+K)\frac{P_L - P_0}{P_i - P_a}$$

The factor (1+K) is due to the fact that the concentrations c_0 and c_L in blood correspond to the total concentration in carbon dioxide. It includes the dissolved CO_2, as well as the bicarbonate ions.

Since the gas exchange is complete when blood leaves the capillary, the carbon dioxide dissolved in blood ends up being at the same partial pressure that the gas in the alveolus. We therefore assume that $P_L = P_a$. We further neglect the amount of carbon dioxide coming from the atmosphere as the natural concentration is low: $P_i = 0$.

$$\frac{\dot{V}}{Q} = \sigma RT(1+K)\frac{P_0 - P_a}{P_a}$$

END OF PAPER

Examiners comments

Q1: Very popular question, 20/22 selected it. Min 4, Max 20.

Part (a) was generally very well addressed. The comparison with the Michaelis Menten case was often too qualitative and based on memory, instead of considering the limit where K3=0 and drawing the curve on the same graph. Part b.i was more technical but most students managed to get the right expression. Part b.ii was however rarely handled properly. Stating that a parameter âĂIJmust be largeâĂİ is insufficient; it must be large in comparison with something else.

Q2: Very popular question, 21/22 students selected it. Min 6, Max 17.

It was answered generally well. Each part of the question was answered perfectly by at least one student.

Q3: Unpopular question, 8/22 students selected it. Min 7, Max 17.

The style of this question seemed to confuse a few students. It is slightly more descriptive than usual, although still highly related to the course content. Part (a) was handled well in general. Part (b) was however rarely answered properly, with a number of students unable to see how to tackle the question.

Q4: Fairly popular question, 17/22 students selected it. Min 4, Max 20.

Parts (a) and (b) were relatively easy and most students managed to answer them properly. Part (c) was more difficult as students also had to recapitulate the assumptions needed to establish this result from the course. A few students managed however to give perfect answers demonstrating an excellent understanding of the course.