Answer THREE question.

ALL questions carry equal marks.

General Instructions

Write your CANDIDATE NUMBER clearly on each of the THREE answer books provided.

If an electronic calculator is used, write its serial number in the box at the top right hand corner of the front cover of each answer book.

USE ONE ANSWER BOOK FOR EACH QUESTION.

Enter the number of each question attempted in the horizontal box on the front cover of its corresponding answer book.

Hand in THREE answer books even if they have not all been used.

You are reminded that the Examiners attach great importance to legibility, accuracy and clarity of expression.
\[ R = 8.314 \text{ J K}^{-1}\text{mol}^{-1} \text{ and } F = 96,500 \text{ C mol}^{-1} \]

The distributions of sodium, potassium and chloride ions across the membrane of a nerve cell can be taken to be:

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside</th>
<th>Outside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>14 mM</td>
<td>125 mM</td>
</tr>
<tr>
<td>Potassium</td>
<td>124 mM</td>
<td>5 mM</td>
</tr>
<tr>
<td>Chloride</td>
<td>6 mM</td>
<td>77 mM</td>
</tr>
</tbody>
</table>
1. (i) Hodgkin and Huxley described the sodium current across the axonal membrane of the squid giant axon in terms of the following equation

\[ I_{Na} = m^3h \overline{g}_{Na}(V_m - V_{Na}) \]

What do the various parameters in this equation represent and what are the main assumptions made in its derivation?

Show that the time course of \( h \) and \( m \) are given by the following equations:

\[ h = h_\infty - (h_\infty - h_0) \exp \left( -\frac{t}{\tau_h} \right) \]

\[ m = m_\infty - (m_\infty - m_0) \exp \left( -\frac{t}{\tau_m} \right) \]  

[8 marks]

(ii) Describe voltage-clamp experiments that would determine the voltage-dependence of the parameters \( h_\infty \) and \( m_\infty \). Draw sketches of the voltage dependence of \( h_\infty \) and \( m_\infty \).

[6 marks]

(iii) Consider a voltage-clamp experiment in which the membrane is clamped at a holding potential of -100 mV and then stepped to a series of test potentials (ranging from -40 mV to +60 mV). Sketch the peak sodium current as a function of potential. How, and why, would this graph change if the initial holding potential was -60 mV?

[3 marks]

(iv) Sketch the time course of the sodium channel conductance as a function of time following a depolarising voltage step to 0 mV under voltage clamp (assume an initial holding potential of -100 mV). How would the time course change if the sodium channel was mutated such that the time constant for channel inactivation was doubled?

[3 marks]

[Total 20 marks]
2. (i) What fundamental limitations of the extracellular recording technique necessitated the development of the voltage-clamp method? [6 marks]

(ii) Explain the principle behind the voltage-clamp method for studying the electrical properties of nerve membranes. What information does the method provide that cannot be obtained by simply measuring the membrane potential? [6 marks]

(iii) What technical advances were required in order to adapt the voltage clamp technique to measure the properties of single ion channels? [4 marks]

(iv) During a voltage-clamp experiment a neuronal membrane is held at -100 mV and a single ion channel opens to an amplitude of 10 pA. The current voltage relationship for this channel is linear with a reversal potential at -10 mV. Calculate the single channel conductance of this channel and comment on its ionic permeability. [4 marks]

[Total 20 marks]

3. For a channel that obeys the constant field equation, the current through the channel for a particular ion is given by

\[
I = \frac{z^2 V_m F^2 P_c (c_{in} - c_{out} \exp\left(\frac{-zV_m F}{RT}\right))}{RT \left[1 - \exp\left(\frac{-zV_m F}{RT}\right)\right]}
\]

(i) Explain the meaning of each of the parameters in the equation. Derive an expression for the reversal potential assuming that the channel is permeable to only sodium and potassium ions. [7 marks]

(ii) If the relative permeabilities of the channel for potassium and sodium are in the ratio 2:1, calculate the reversal potential assuming the ionic concentrations are those given in the Table above (assume T=310K). Sketch the I-V curves for the individual ions and the total channel current. [7 marks]

(iii) Would the channel be excitatory or inhibitory? Explain your reasoning [2 marks]

(iv) By what factor would the potassium permeability have to increase before the resting potential of the channel was more negative than the threshold potential for firing an action potential (-43 mV)? [4 marks]

[Total 20 marks]
4. Are the following statements true or false? Explain your reasoning (N.B. no reasoning, no marks).

(i) Neurons are in a state of equilibrium with their environment. [2 marks]

(ii) GABAA receptor channel opening is always inhibitory. [2 marks]

(iii) In the Hodgkin and Huxley model the kinetics of the sodium conductance is dictated by the state of a single gating particle. [2 marks]

(iv) Myelination reduces the total membrane capacitance of the nerve fibre. [2 marks]

(v) The affinities of neurotransmitter-gated ion channels for their agonists are influenced by subunit-composition. [2 marks]

(vi) The time-course of an excitatory postsynaptic potential is different to that of the underlying conductance change. [2 marks]

(vii) When the local anaesthetic lidocaine is positively charged it exhibits voltage-dependent binding to sodium channels. [2 marks]

(viii) Inactivation of voltage-gated sodium channels reduces action potential duration. [2 marks]

(ix) The electroencephalogram reflects extracellular current flow in populations of neurons. [2 marks]

(x) Vesicle fusion occurs in response to depolarisation of the dendrite. [2 marks]

[Total 20 marks]
5. (i) With reference to the figure below, describe the key morphological features of a neuron (A, B, C, D & E) and discuss the functional significance of these five structural elements. [8 marks]

(ii) Chemical synaptic transmission enables fast communication between neurons. Describe this process and discuss the source of the synaptic delay. [8 marks]

(iii) What parameters determine the size of the postsynaptic conductance? [4 marks]

6. Write short notes on three of the following four topics:

(i) The role of the sodium pump in neuronal excitability

(ii) Mechanisms of general anaesthesia

(iii) Human brain imaging

(iv) The molecular structure of neuronal ion channels

[Total 20 marks]