EGT2
ENGINEERING TRIPOS PART IIA

Thursday 2 May 2024   9:30 to 11:10

Module 3G3

INTRODUCTION TO NEUROSCIENCE

*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   A neuroscientist performs an *in vitro* study of a specific type of cortical neuron. They inject a current step, $I_{ext}(t)$, into a neuron of this type, and simultaneously record the cell's membrane potential, $V(t)$. The resulting voltage time course is shown in Fig. 1.

(a)   Briefly explain why, during the initial period when $I_{ext} = 0$, the recorded membrane potential is not zero; what biophysical factors determine the non-zero value of this resting potential?   [10%]

(b)   Explain why the electrophysiological behaviour of this neuron, as probed by this simple step current injection, cannot be fully captured by the standard Hodgkin-Huxley (HH) model presented in lectures.   [15%]

(c)   The scientist proposes to rescue the HH model by including an additional current, I_A, mediated by slow, voltage-dependent, high-threshold potassium channels. This current takes the following form:

$$I_A(t) = -\bar{g}_A\, w(t)\, \left[V(t) - E_{K^+}\right] \tag{1}$$

$$\text{with} \quad \tau_A \frac{dw}{dt} = -w(t) + w_\infty(V(t)) \tag{2}$$

$$\text{and} \quad w_\infty(V) = \frac{1}{1 + \exp\left(-\frac{(V+35)}{10}\right)} \quad (V \text{ measured in mV}) \tag{3}$$

It is estimated that $\tau_A = 200$ ms.

(i)   State the biophysical interpretations of $\bar{g}_A$, E_{K^+} and $w(t)$.   [15%]

(ii)   Sketch the temporal evolution that you expect $w(t)$ to exhibit during a voltage clamp experiment whereby the membrane voltage, having been at rest for a long time, is suddenly clamped at 0 mV for 500 ms.   [10%]

(iii)   Sketch the temporal evolution that you expect $w(t)$ to exhibit during the 150 ms-long current injection experiment of Fig. 1, assuming that $V(t)$ in this model is indeed as shown on that figure. You may approximate each action potential by a square pulse of duration 0.5 ms.   [15%]

(iv)   Based on your answer to part (c)(iii), explain how the inclusion of $I_A(t)$ makes the HH model a better model for this neuron.   [15%]

(v)   Suppose that, during the injection of a steady current of some value $I_{ext} = a$, the neuron settles into a regime of regular firing, and the conductance due to the slow potassium channels never exceeds 2% of its theoretical maximum. Derive an upper bound for the steady-state firing rate of the neuron. You may use the same

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square pulse approximation to the AP as in part (c)(iii), and indeed your may find your answer to that question a helpful starting point. [20%]

Fig. 1

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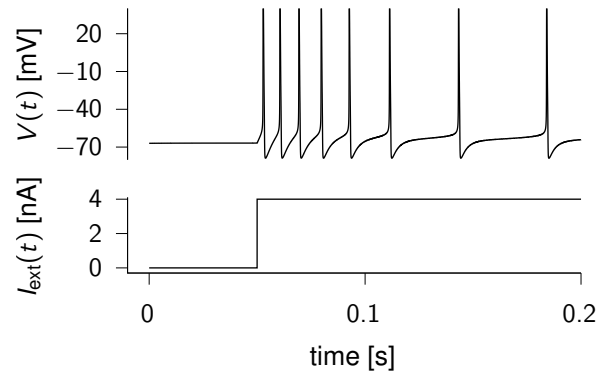
2 (a) Briefly describe the intracellular and extracellular neuronal recording techniques. State two advantages and two limitations of extracellular recordings, relative to intracellular recordings. [15%]

(b) Urn 'A' contains 6 yellow balls and 3 green balls. Urn 'B' contains 3 yellow and 3 green balls. An urn is chosen at random, and a ball drawn at random from that urn. Which of the following two questions constitutes the best illustration of the Bayesian perception framework, and why? Note: you are NOT required to solve these problems!

   (i) "What is the probability that the ball is red?"

   (ii) "The ball is red. What is the probability that it came from Urn 'A'?"

   [15%]

(c) This question is about a variant of the motion discrimination task discussed in lectures in the context of decision making. A monkey is trained to make a perceptual judgement about the net direction of motion (left or right) in a dynamic random-dot display exhibiting a certain degree of motion coherence c, presented for some limited duration T. After a short post-stimulus delay, the monkey has to indicate its direction choice by making an eye movement to one of the two direction-choice targets, and is subsequently rewarded for a correct decision with R mL of fruit juice. On a random half of the trials, the monkey is also given the option to instead choose a smaller ($0.8R$) but certain reward by making a saccade to a third target. This "sure target" is shown during the delay period, at least 500 ms after the random-dot motion is extinguished. During motion viewing, the monkey does not know whether the sure-bet option will arise.

   (i) Assume that, in each trial, the monkey does not only estimate the most likely motion direction given the sensory evidence but also the probability p of being correct about it ("confidence"), and that its decision maximises the expected reward given p. How large must the monkey's estimate of p be, for it to forgo the sure-bet option? [15%]

   (ii) For $c = 5\%$ and $c = 50\%$, *qualitatively* sketch the frequency (fraction of trials) with which you would expect to see the monkey choose the sure-bet option, as a function of T. Provide brief justifications. [15%]

   (iii) Consider 100 trials with constant c and T. State two factors that could cause variability in the monkey's internal confidence estimate across those trials. [15%]

   (iv) For any fixed c and T, the monkey's left-vs-right decisions are found to be better on average when it is offered the sure-bet option but opts out, compared to

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when it is not offered the choice. Does this speaks in favour of, or against, the assumptions of part (c)(i)? Why? [15%]

(v)   Based on what you know about the behaviour of certain LIP neurons in the standard version of this task, explain why, in the variant discussed here, it is reasonable here to expect the same LIP neurons to be somewhat predictive of whether or not the monkey will choose the sure-bet option (in trials where it is offered the choice). [10%]

3   This question is about synaptic transmission in the frog's nerve-muscle synapse (the so-called neuromuscular junction, NMJ). The NMJ works very much like an ordinary synapse between two neurons, and it has the following specifics:

     • The NMJ uses acetylcholine (ACh) as the neurotransmitter, and mainly ionotropic receptors (so-called nicotinic ACh receptors) that are permeable to Na^+, K^+, and Ca^{2+} ions.

     • Postsynaptic potentials in the NMJ are excitatory and they are called "end-plate potentials" (EPP).

(a)   Describe the main events in the NMJ following the generation of an action potential in the presynaptic (motor) neuron that lead to the generation of an EPP in the muscle.   [5%]

(b)   ACh molecules in the synaptic cleft are normally broken down by an enzyme called acetylcholinesterase. Prostigmine is a drug that blocks acetylcholinesterase. Describe how the shape of EPPs changes qualitatively when prostigmine is applied in the NMJ.   [10%]

(c)   Some snake venoms contain α-neurotoxins, which are nicotinic ACh receptor antagonists. Describe how EPPs change when an α-neurotoxin is applied to the NMJ.   [5%]

(d)   In the NMJ, so-called spontaneous miniature EPPs (mEPPs) can be recorded without stimulation, in the absence of any action potential being generated in the presynaptic neuron. Fig. 3A shows the distribution of the amplitude of these mEPPs. The histogram shows the empirical distribution, the solid line shows a smooth distribution fit to the data. For answering the questions below, you may find the following additional information useful:

     • The time course of mEPPs is indistinguishable from that of ordinary (action potential-induced) EPPs, but the amplitude of EPPs is much larger (around 70 mV).

     • Prostigmine and α-neurotoxins have the same effect on mEPPs as on EPPs.

     • The frequency, but not the amplitude, of mEPPs can be increased by a small depolarisation of the presynaptic terminal (which still does not lead to the generation of action potentials).

     • The voltage response to the elementary current through a single ACh receptor-channel is approximately 0.3 μV.

Given these facts, answer the following questions

     (i)   Describe how the mechanism responsible for generating mEPPs is different from what you described in response to question part (a).   [15%]

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(ii)   Explain with reasons why mEPPs are much smaller than EPPs and what determines the spread in their amplitude as shown in Fig. 3A.   [10%]

(e)   Fig. 3B shows the amplitude distribution of ordinary, action potential-induced EPPs in the NMJ when intracellular Ca^{2+} concentration in the motor neuron is lowered. The histogram shows the empirical distribution, the solid line shows a fit to the part of the data above 0. For answering the questions below, note the following observations about this distribution (you may find it useful to consider these in comparison to Fig. 3A):

  • The distribution has multiple peaks.
  • The first peak is at 0 mV and it is very narrow (dark grey).
  • Successive peaks are at integral multiples of cca. 0.4 mV and they widen progressively.

Given these observations, and your knowledge of the mechanism of synaptic transmission, answer the following questions:

(i)   What happens on those occasions that result in a 0 mV EPP?   [5%]

(ii)   Why does synaptic transmission appear to be "quantal": why are EPP amplitudes (approximately) integral multiples of the same value?   [20%]

(iii)   What causes the spread in EPP amplitudes around the quantal values (the peaks of the distribution), and why do the peaks become wider?   [10%]

(iv)   How does this distribution change if the intracellular Ca^{2+} concentration in the motor neuron is increased?   [20%]
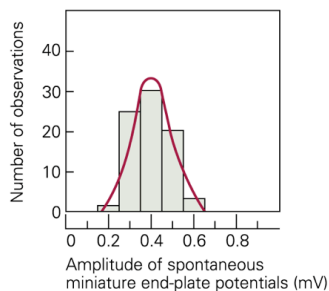

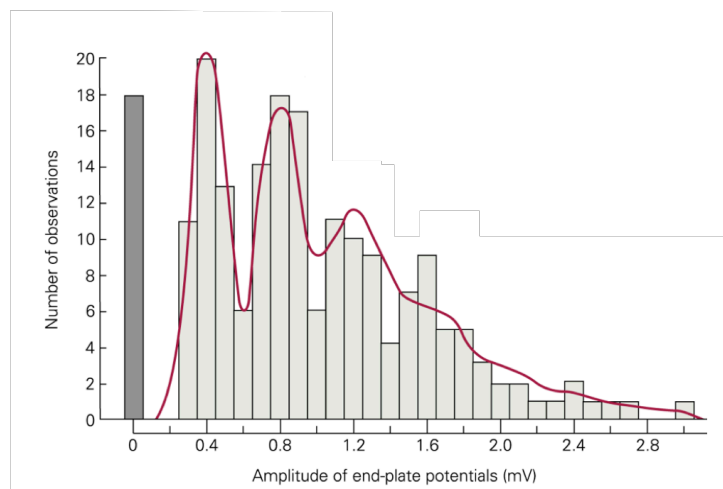Fig. 3A   Fig. 3B

4   In the lectures, we discussed an experiment in which the contributions of the hippocampus to spatial learning have been studied at different stages of learning. Answer the following questions regarding this experiment.

(a)   What species and experimental apparatus was used?   [10%]

(b)   What was the behavioural task animals had to perform? What was the protocol for training and testing animals?   [10%]

(c)   What kind of behavioural strategies might animals use to solve this task, and how can we tell which strategy they are using by observing their behaviour?   [10%]

(d)   What brain regions were blocked in this experiment?   [5%]

(e)   What pharmacological manipulations were used for perturbing the operation of these brain regions, when were these used in the experiment, and what is the mechanism of their action?   [10%]

(f)   What was the control pharmacological manipulation used, when and where was it used, and what does it control for?   [5%]

(g)   How many experimental groups were used in the experiment, and approximately how many animals were used in each group?   [10%]

(h)   What was the pattern of results observed in the experiment for each experimental group?   [10%]

(i)   What was the interpretations of these results in terms of how behaviour changes over the course of spatial learning, and how different brain regions contribute to navigation?   [10%]

(j)   A strategy that was not explicitly considered in the original experiment is that animals might use distinctive visual cues to guide them to the reward. How would you distinguish this strategy from those you described in your answer to question (c)?   [20%]

END OF PAPER