Version GH/3 – CRIB

EGT2
ENGINEERING TRIPOS PART IIA

Monday 23 April 2018 14:00 to 15:40

Module 3G3 – CRIB

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.

1 (a) Describe the method of extracellular action potential recordings. Give one advantage and one disadvantage over intracellular recordings. [20%]

Answer: To perform an extracellular recording of action potential, an electrode is inserted in the neural tissue, but not meant to penetrate the membrane of a cell. It is kept in the extracellular environment, but close enough to a cell as to pick up large and brief potential flucutations (caused by action potentials) that rise above background noise level. Advantages over intracellular recordings include:

- much easier technique – no need to patch the cell
- because the cell is left intact, it is possible to record for longer
- using tetrodes and clustering techniques, it is even possible to record action potentials from multiple cells at the same time
- this method "scales" up: whole arrays of 50-100 electrodes can be inserted to record action potentials from large populations

Disadvantages include:

- no access to (subthreshold) membrane potential timecourse
- signals from multiple neighbouring cells tend to mix, and it is often impossible to isolate them perfectly (e.g. using clustering, "spike sorting" techniques)

(b) In the standard Hodgkin-Huxley model, the dynamics of the membrane potential V are given by:

$$C_{\mathrm{m}}\frac{\mathrm{d}V}{\mathrm{d}t} = -\bar{g}_{\mathrm{Na}}m^3h(V-E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}n^4(V-E_{\mathrm{K}}) - \bar{g}_L(V-E_{\mathrm{L}}) + I_{\mathrm{ext}}$$

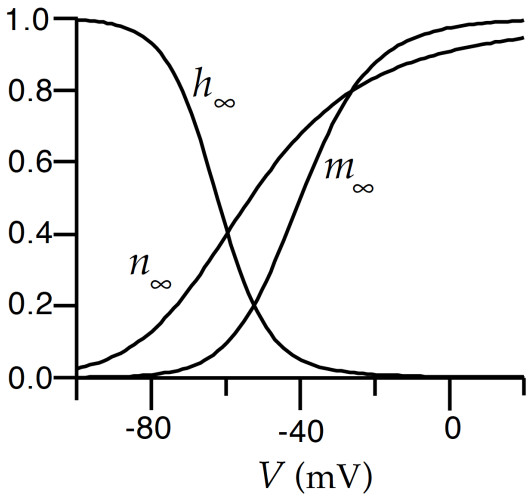
where C_{m} is the specific membrane capacitance and I_{ext} is an externally applied current.

(i) Explain the meaning of the variables $\{m,h,n\}$ as well as $\{\bar{g}_{\mathrm{Na}},\bar{g}_{\mathrm{K}}\}$. [20%]

Answer: The m, n and h variables are so-called "gate variables"; they evolve between 0 and 1. m denotes the proportion of sodium channels open; h is the proportion of sodium channels in the inactivated, closed state; and n is the fraction of potassium channels in the activated state. The momentary conductance for one of these two ion species is given by a product of the associated gate variables (as shown in the equation) – which is also between 0 and 1 – further multiplied by the corresponding "peak conductance" $\bar{g}_{\mathrm{Na}}$ or $\bar{g}_{\mathrm{K}}$.

(ii) Sketch the steady-state dependence of m, h, and n on voltage. [20%]

Answer: The steady state dependence for each of the three gate variables is sketched below:



(iii) Figure 1 shows the time evolution of the state variables V, m, n and h in the Hodgkin-Huxley model. Unfortunately the y-axes of the plots have not been labelled. Identify which plot (a, b, c, or d) corresponds to each state variable and give the approximate range used on the y-axes, giving a brief justification for each choice. [30%]

Answer: (a) m variable. Reason: fast rise that coincides with V (panel c) and sustains high value beyond peak of the action potential. (b) h variable. Reason: prior to action potential this will be at high value as sodium channels must start in de-inactivated state; only variable that is anticorrelated with all the others. (c) V, membrane potential. Reason: peak is shortest lived due to potassium activation and sodium inactivation which generate net outward current even though m has high value. (d) n variable. Reason: slower than m and activated by increase in V.

The gate variables m, n, and h vary between 0 and 1; during an action potential, V covers a range going roughly from -80 to 10 mV.

(iv) Is there a maximum achievable firing rate for the Hodgkin-Huxley model subjected to constant current input? Justify your answer briefly. [10%]

Answer: Yes. For example, the absolute refractory period when sodium channels are inactivated places a minimum period between successive action potentials and thus imposes and upper bound on firing rate.

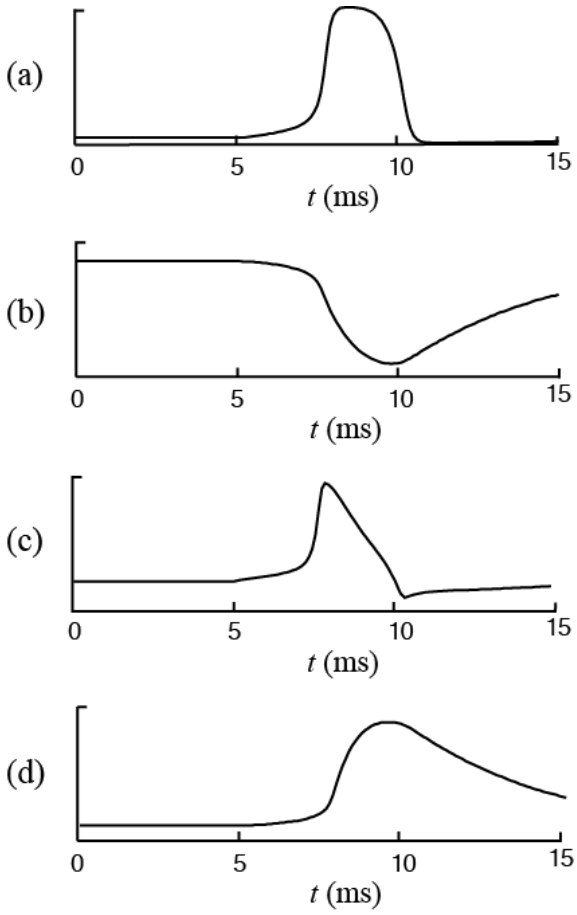


Fig. 1

2 (a) Write short notes on the following:

(i) the four dimensions that characterize any sensory input to the brain;

Answer: A sensory input has four main dimensions: modality, location, intensity and timing. Modality refers to the nature of the transducer that converts the physical stimulus into action potentials sent to the brain (e.g. visual, auditory, gustatory, tactile, ...). Location usual refers to the location of the sensory stimulus in physical space, but can also refer to the location of the sensory stimulus in a more abstract space of stimulus features (e.g. angle at which pressure is being exerted on a small patch of skin). Intensity and timing are self-explanatory.

(ii) coarse ensemble (or population) coding in the context of sensation.

Answer: Coarse ensemble coding refers to the encoding of a stimulus variable (e.g. location in physical or feature space) by a large number of neurons with largely overlapping receptive fields. Thus, a given stimulus will typically activate a large number of neurons simultaneously, though some neurons will be activated more than others. Due to the large number of neurons that respond, noise in single-neuron responses can typically be averaged out to yield a very reliable estimate of the stimulus feature; this increases the encoding resolution.

[30%]

(b) A scientist sets out to test the hypothesis that the brain optimally combines sensory evidence with prior expectations, in a task involving visual perception. In this task, a subject sits in front of a large display (Fig. 2), and initiates a trial by fixating their gaze on a small cross, centred horizontally on the display. A dot is presented briefly at some horizontal position x chosen randomly (and independently in each trial) from some distribution $p(x)$ within the grey-shaded ruler. After the dot disappears, the subject is asked to report an estimate $\hat{x}$ of the dot's position.

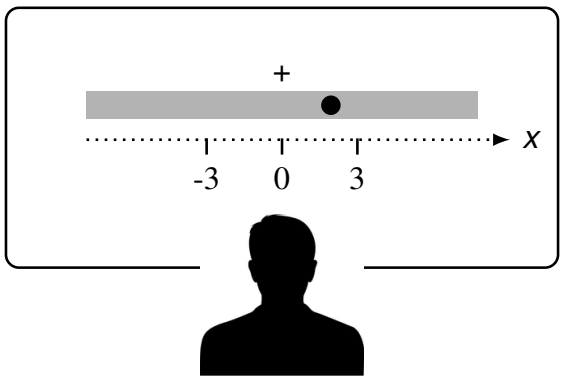


Fig. 2

(i) Optimal inference of the dot's position requires computing the posterior

distribution $p(x|s) \propto p(s|x)p(x)$, where s denotes sensory evidence. Explain what the two terms on the right of this equation represent, and in particular how they relate to the task design. [20%]

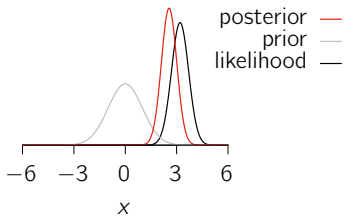
Answer: $p(x)$ is the prior, i.e. the probability density from which the true dot location x is drawn on each trial. This is controlled by the experimenter, and will be learned by the subject as they experience several hundred trials. $p(s|x)$ is the likelihood function, which reflect sensory noise (or signal to noise ratio), and quantifies the extent to which any x is compatible with the sensory evidence s experienced in a given trial. The experimenter cannot make this function any sharper (there's a limit imposed by brain-intrinsic sensory noise), but can certainly make it wider by decreasing the signal to noise ratio (e.g. modifying visual contrast).

(ii) Assume $p(x)$ is Gaussian with zero mean and unit standard deviation. Make a reasonable assumption for the form of the likelihood function, and sketch the prior distribution, likelihood function, and posterior distribution (on a single graph), when the *true* position of the dot is $x = 3$. [20%]

Answer: Due to sensory evidence typically involving many independent receptors in the periphery, the likelihood function can be reasonably assumed to be bell-shaped, i.e. of the form

$$p(s|x) \propto \exp(-(x-\mu(s))^2/2\sigma_s^2)$$

with $\mu(s)$ fluctuating on a trial-by-trial basis around the true x. The required sketch:



(iii) Assuming Bayesian estimation, how would the subject's estimate of x depend on the visual contrast of the black dot against the grey ruler? Based on your observation, explain how you would extend this experiment to directly test the implications of Bayesian inference in this task. [30%]

Answer: As the contrast decreases, the reliability of visual evidence decreases, resulting in a wider likelihood function. This causes the posterior mode to shift towards the prior mode by more than it does at high contrast. This shift can be measured (e.g. by averaging the subject's reported estimates of x over many trials when e.g. the true x falls in a small bin around 3), for various settings of the visual contrast from high to low. Of course, there is no reason to check this dependence only for x near 3, so one can more generally group the trials by binned values of true x, and perform the same analysis in each bin (cf. Körding and Wolpert, 2004).

3 (a) In the *Aplysia* gill withdrawal reflex, describe the sequence of cellular-molecular events during normal synaptic transmission between a sensory and a motor neuron, before and after sensitisation. [30%]

Answer: Before sensitisation:

(i) presynaptic action potential arrives at the synapse

(ii) voltage-gated calcium channels open causing calcium influx

(iii) calcium influx makes vesicles in the active zone fuse with the presynaptic membrane

(iv) glutamate is released to the synaptic cleft from the vesicles

(v) glutamate diffuses through synaptic cleft

(vi) glutamate binds to postsynaptic ionotropic receptors

(vii) receptor channels open ion channels in the postsynaptic membrane

(viii) ion influx through open channels depolarises postsynaptic cell

After sensitisation:

(i) presynaptic action potential arrives at the synapse, and is longer than before sensitisation because the potassium current is decreased

(ii) voltage-gated calcium channels open for a longer time due to elongated action potential, and calcium current is also amplified by itself, so extra amounts of calcium enter the cell

(iii) extra calcium influx makes more vesicles in the active zone fuse with the presynaptic membrane, this is possible because there are also more vesicles in the active zone than before sensitisation

(iv) more glutamate is released to the synaptic cleft from the increased number of fusing vesicles

(v) more glutamate diffuses through synaptic cleft

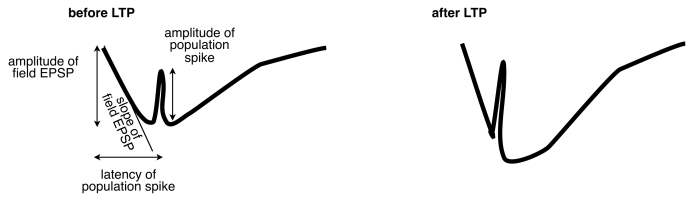
(vi) more glutamate binds to postsynaptic ionotropic receptors

(vii) more receptor channels open more ion channels, and for a longer time, in the postsynaptic membrane

(viii) more ion influx through open channels depolarises postsynaptic cell better

(b) In an *in vitro* experiment about LTP, extracellular electrodes are used both for stimulation and recording. Assume the recording electrode is in the same layer where axons of the stimulated pathway form synapses with the postsynaptic cells. Sketch the extracellular potential signals that can be recorded following a stimulation, before and after the induction of potentiation. Describe in words the main differences between the "before" and "after" signals. [30%]

Answer: The recorded signals will look like:



The amplitude (and/or slope) of the field EPSP increases, the amplitude of the population spike increases, and the latency of the population spike decreases.

(c) In a classical conditioning experiment, three different conditioned stimuli, CS_1 (a light), CS_2 (a tone), and CS_3 (a click), are used to signal the same unconditioned stimulus (US; delivery of food). Before training, none of the CSs evoked a response. Describe how strong a response (if any) you expect for each of the CSs presented in separation after the following training protocols:

(i) phase 1: (CS_1, CS_2) + US; phase 2: CS_3 + CS_1

(ii) phase 1: (CS_1, CS_2) + US; phase 2: (CS_3, CS_1) + US

(iii) phase 1: (CS_1, CS_2) + US; phase 2: (CS_3, CS_1, CS_2) + US

In these expressions, the shorthand notation X+Y stands for sequential presentation of the stimuli X and Y, while (X,Y) denotes their simultaneous presentation. [40%]

Answer:

(i) CS_1: moderately strong, because of overshadowing in phase 1 (by CS_2), and extinction in phase 2, CS_2: slightly stronger, because of overshadowing in phase 1 (by CS_1) but no extinction in phase 2, CS_3: weak, because of secondary conditioning to an already only moderately strong cue (CS_1)) in phase 2 (though the Rescorla-Wagner does not account for it)

(ii) CS_1: strong, because of overshadowing in phase 1 (by CS_2) but only weak overshadowing in phase 2 (by CS_3), CS_2: weak, because of overshadowing in phase 1 (by CS_1) (and because US is presented without it in phase 2 – even though the Rescorla-Wagner does not account for it), CS_3: weaker, because of partial blocking in phase 1 and overshadowing in phase 2 (by CS_1)

(iii) CS_1: moderately strong, because of overshadowing in both phase 1 and 2 (by CS_2); CS_2: moderately strong, because of overshadowing in both phase 1 and 2 (by CS_1); CS_3: none (or very weak), because of complete blocking in phase 1 (by CS_1, CS_2)

4 (a) Explain what determines whether a synapse is excitatory or inhibitory. [15%]

Answer: It is the reversal potential of the ion channel controlled by the receptor in the postsynaptic cell (either directly, in the case of an ionotropic receptor, or indirectly for a metabotropic receptor). A synapse is excitatory if this reversal potential is above the threshold for action potential generation. Otherwise it is an inhibitory synapse. Note that even if the reversal potential is above the resting membrane potential but below the threshold (i.e. it can depolarise the cell at rest), it is still an inhibitory synapse, because this channel will act as a "shunt", increasing total membrane conductance, and making it harder for the postsynaptic cell to exceed firing threshold, thus ultimately decreasing its propensity to generate action potentials.

(b) Describe the sequence of events during the expression of late LTP in the hippocampus. [25%]

Answer:

(i) Following Ca^{2+} influx to the cell at the synapse

(ii) molecular signals (transmitted e.g. by cAMP activated kinases) reach the nucleus of the cell

(iii) where new receptors and other molecules are synthesised for new synapses

(iv) these building blocks are transported back to where the new synapse is created

(v) a new synapse is created

(c) You are to design an experiment making use of a neurotransmitter antagonist to distinguish between the contributions of hippocampal and striatal LTP to the learning of different navigational strategies. You may assume that striatal LTP is based on the same mechanism as hippocampal LTP.

(i) What kind of behavioural task would you use to assess the performance of animals, and how would you measure their performance? [20%]

(ii) What receptor would you block with your antagonist? At what point(s) during the course of the experiment would you apply your antagonist? [15%]

(iii) What results do you expect from your experiment? [15%]

(iv) If you had the opportunity to do *in vivo* electrophysiological recordings, how would you do them to give further support to your results? [10%]

In all cases, explain your choices.

Answer: *(Many different answers can be accepted here.)*

(i) I would use a version of the Morris water maze test in which the rat is always started from the same location during training. Testing would be done with the platform not being in place and

the rat being started from a novel location that was never used during training (eg. opposite the usual location). Animals would be tested either after moderate amounts of training, or after long training. This together with the pharmacological manipulation gives a 2 (AP5 or saline injected) x 2 (injection to hippocampus or striatum) x 2 (moderate or long training) design, which means that 8 groups of animals would be used. Performance would be measured by time spent in the correct quadrant where the platform used to be ('place' choice) and time spent in the quadrant that is in the same relative location from the new starting location as the correct quadrant is from the old starting location ('response' choice).

(ii) I would use rats, and use an NMDA receptor antagonist (eg. AP5), injecting it either to the hippocampus (hippocampus) or the striatum (striatum), thereby selectively preventing the induction of LTP in one of these brain areas. I would also have two control groups into which only saline is injected (to the hippocampus or to the striatum). AP5 would be applied throughout training, but not during testing.

(iii) I expect that saline injected control animals (regardless whether it was injected to the hippocampus or the striatum) will make more 'place' choices after moderate amount of training and more 'response' choices after long training. I expect that animals with AP5 injected to their hippocampi will make less 'place' choices after moderate amount of training, but will not be different from control animals after long training. I expect that animals with AP5 injected to their striatum will make less 'response' choices after long training, but will largely be unaffected after moderate training. If standard consolidation theory also applies to striatal memories, then I may find that animals with hippocampal AP5 injection never switch to a 'response' strategy, ie. both after moderate and long training they search in random locations.

(iv) I would conduct standard LTP-experiments in anaesthetised animals. I would try to induce LTP both in their striatum and their hippocampus, to demonstrate that LTP cannot be induced in animals injected with AP5 specifically in the brain area to which AP5 was injected, but it can be induced in the other area, and that LTP induction is also unimpaired in both brain areas of control animals.

END OF PAPER