Version GH/2 – CRIB

EGT2
ENGINEERING TRIPOS PART IIA

Tuesday 9 May 2023 9:30 to 11:10

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.

You may not remove any stationery from the Examination Room.

1 A neuroscientist trained a macaque monkey to perform centre-out reaching movements of length d with its right hand in a vertical plane, starting at a 'centre' position and ending on a 'target' location that could be placed at any angle θ from the horizontal (Fig. 1). During the task, the scientist simultaneously recorded the spiking activity of $N > 50$ neurons in the monkey's primary motor cortex (left hemisphere). Let r_i be the random variable that describes the observed number of action potentials emitted by neuron i per unit time during the course of a reach. The scientist performed basic statistical analysis of these noisy neural responses $\{r_1, r_2, \ldots, r_N\}$ and found them to be well modelled by a factorized Gaussian conditional density

$$p(\{r_1, \ldots, r_N\}|\theta) = \prod_{i=1}^{N} \mathcal{N}(r_i; f_i(\theta), \sigma^2). \tag{1}$$

The conditional mean $f_i(\theta)$ was found to be modulated by the reach angle θ according to $f_i(\theta) = \alpha + \beta\cos(\theta - \theta_i)$, where $0 < \beta < \alpha$ are two constants and θ_i is the 'preferred direction' of neuron i.

(a) What recording technique is likely to have been used in this experiment, and why? [10%]

Answer: Given that more than 50 neurons were recorded simultaneously, it is likely that the neuroscientist used an array of (extracellular) electrodes. Calcium imaging could have been used too, though it would have required a deconvolution step to extract "spiking activity".

(b) Explain why r_i is best modelled as a random variable, and why θ_i is called the 'preferred direction' of neuron i. [10%]

Answer: Neural responses in the cortex are known to be highly variable from trial to trial, even when one carefully constrains the animal to produce the same behaviour of interest in each trial (here, the same reach). This is because it is impossible for the experimenter to control for everything in a given trial (e.g. what the monkey is momentarily attending to, eye and face movements, internal thought processes etc). This element of stochasticity means that one cannot perfectly predict the response of a neuron during a particular behaviour, such that the response is best formalised as a random variable. The angle θ_i is called the 'preferred direction' of neuron i simply because it is the reach angle that elicits the largest firing rate response in that neuron on average (i.e. this is where $f_i(\theta)$ has its maximum).

(c) Express $f_i(\theta)$ as a function of $\vec{v}(\theta)$ and $\vec{v}(\theta_i)$, where $v(\theta) = \begin{pmatrix} \cos\theta \\ \sin\theta \end{pmatrix}$. [10%]

Answer: Since the two unit vectors $\vec{v}(\theta)$ and $\vec{v}(\theta_i)$ are separated by an angle $\theta - \theta_i$, their dot product is equal

to $\cos(\theta - \theta_i)$. Thus, $f_i(\theta) = \alpha + \beta\, \vec{v}(\theta_i)^\top \vec{v}(\theta)$.

(d) In order to decode the reach angle θ that underlies a set of responses $\{r_1, \ldots, r_N\}$, the scientist proposes to use the 'population vector' defined as

$$\vec{x}(\{r_1, \ldots, r_N\}) = \frac{1}{N} \sum_{i=1}^{N} (r_i - \alpha)\, \vec{v}(\theta_i) \tag{2}$$

with $v(\cdot)$ defined as in part (c). Assume that the neurons' preferred directions $\{\theta_1, \ldots, \theta_N\}$ are approximately uniformly distributed between 0 and 2π. Show that, on average over repeated reaches and in the limit of large N, $\vec{x}(\{r_1, \ldots, r_N\})$ is proportional to $\vec{v}(\theta)$. Briefly discuss the implications for decoding. [30%]

Answer: Averaging over repeated reaches, we get $\mathbb{E}[\vec{x}] = \frac{1}{N} \sum_i (f_i(\theta) - \alpha)\vec{v}(\theta_i)$. Using the answer to (c), we get $\mathbb{E}[\vec{x}] = \frac{1}{N} \sum_i \beta\, \vec{v}(\theta_i)^T \vec{v}(\theta)\vec{v}(\theta_i) = \beta \left(\frac{1}{N} \sum_i \vec{v}(\theta_i)\vec{v}(\theta_i)^\top \right) \vec{v}(\theta)$. In the limit of large N, the bracket is equal to the covariance of $\vec{v}(\theta_i)$ across neurons. With the assumption of a uniform distribution of preferred directions, this covariance matrix is easily shown to be $1/2$ of the 2×2 identity matrix (e.g. the first diagonal element is $\int \frac{ds}{2\pi} \cos(s)^2 = \frac{1}{2}$). Thus, $\mathbb{E}[\vec{x}] = \frac{\beta}{2} \vec{v}(\theta)$. This means that the population vector can be used as an unbiased estimator of the reach angle: on average, it points in the direction of the reach.

(e) Prove that, in the limit of large N, the population vector $\vec{x}(\{r_1, \ldots, r_N\})$ is in fact proportional to $\vec{v}(\theta)$ for *any single reach* at angle θ (as opposed to being proportional to $\vec{v}(\theta)$ *only on average* over repeated reaches, as already shown in part (d)). [30%]

Answer: For a given reach at angle θ, each neural response can be written $r_i = f_i(\theta) + \epsilon_i$ where $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$. Thus, $\vec{x} = \frac{1}{N} \sum_i (f_i(\theta) + \epsilon_i - \alpha)\vec{v}(\theta_i) = \mathbb{E}[\vec{x}] + \frac{1}{N} \sum_i \epsilon_i \vec{v}(\theta_i)$. The first term is the one that was shown in (d) to be $\propto \vec{v}(\theta)$. The second term is a noise term that converges to the expectation of $\epsilon_i \vec{v}(\theta_i)$ in the limit of large N. Since ϵ_i is independent of θ_i, the expectation of the product is equal to the product of the expectations, which is zero since ϵ_i has zero mean.

(f) Now consider the more realistic scenario in which the constants α and β are different for each neuron, and are therefore denoted by α_i and β_i. Modify the definition of $\vec{x}(\{r_1, \ldots, r_N\})$ such that the property shown in part (d) continues to hold. [10%]

Answer: From the derivation in (d), it is easy to see that the end result depends critically on the term in front of $\vec{v}(\theta_i)$ being proportional to $\vec{v}(\theta_i)^\top \vec{v}(\theta)$. Thus, a suitable modification is to define $\vec{x}(\{r_1, \ldots, r_N\}) = \frac{1}{N} \sum_{i=1}^{N} \left(\frac{r_i - \alpha_i}{\beta_i} \right) \vec{v}(\theta_i)$.

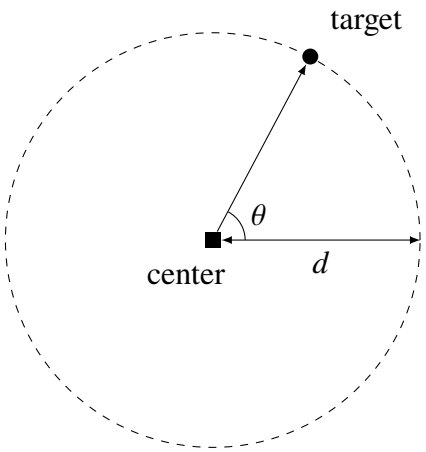


Fig. 1

2 (a) A scientist is studying a neuron *in vitro*. The membrane potential of this neuron is at rest (−70 mV).

(i) What is the net current flowing through the membrane, and why? [5%]

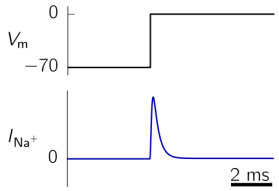
Answer: For a membrane at rest, by definition there is no net current flowing through the membrane.

(ii) A scientist wonders how the membrane current would behave if, somehow, the cell's membrane potential was suddenly brought to 0 mV and kept constant at that value. How could their curiosity be satisfied experimentally? Explain the principle underlying your proposed solution. [20%]

Answer: Following Hodgkin and Huxley, this scientist could perform a voltage clamp experiment, by setting up a high-gain negative feedback loop to inject into the cell a current directly proportional to the difference between the momentary voltage and the target voltage (here, 0mV). The current which the scientist needs to inject (known!) to maintain V_m at this target value *must* be equal and opposite to the current flowing through the membrane through natural means (the thing which the scientist wants to measure).

(iii) The scientist performs the experiment in part (a)(ii) under a pharmacological manipulation that allows them to isolate the sodium current. Sketch the timecourse of this sodium current and explain the mechanism underlying its shape. [20%]

Answer:



Just before clamping begins, the sodium channels are closed (due to the activating m gate being closed), so no sodium flows in. As V_m switches to $0mV$, the m gates open fully, and they do so much faster than the h gates close, leaving a small window of less than 1ms for a large sodium current to flow in.

(b) A monkey wears a custom headset allowing a pure tone to be played simultaneously to the left and right ears with different intensities A_L and A_R, respectively. During the presentation of such an auditory stimulus, noisy aggregate neural activity, x_L and x_R, can be measured in the primary auditory cortices of the left and right hemispheres, respectively. The neural responses x_R and x_L are positive scalar quantities that depend on the contralateral intensities A_L and A_R, respectively, and vary independently across

repeated stimulus presentations following exponential distributions

$$p(x_\mathrm{R}|A_\mathrm{L}) = \frac{1}{cA_\mathrm{L}} \exp\left(-\frac{x_\mathrm{R}}{cA_\mathrm{L}}\right) \quad \text{and} \quad p(x_\mathrm{L}|A_\mathrm{R}) = \frac{1}{cA_\mathrm{R}} \exp\left(-\frac{x_\mathrm{L}}{cA_\mathrm{R}}\right) \tag{3}$$

where $c > 0$ is a constant gain factor.

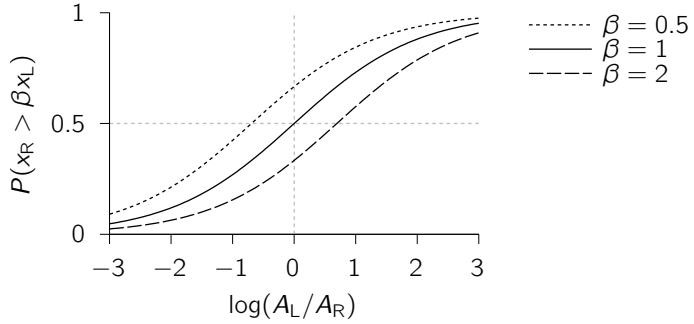
(i) For $\beta > 0$, derive an expression for the probability that x_R exceeds βx_L. Give your answer in terms of $\log(A_\mathrm{L}/A_\mathrm{R})$ and $\log\beta$ (where log denotes the natural logarithm). [30%]

Answer: In very detailed steps (all relevant integrals are simple exponential integrals):

$$\begin{aligned}
P(x_\mathrm{R} > \beta x_\mathrm{L}|A_\mathrm{L}, A_\mathrm{R}) &= \int_0^\infty dx_\mathrm{R}\, p(x_\mathrm{R}|A_\mathrm{L})\, P(x_\mathrm{L} < (x_\mathrm{R}/\beta)|A_\mathrm{R}) && (4)\\
&= \int_0^\infty dx_\mathrm{R}\, p(x_\mathrm{R}|A_\mathrm{L}) \int_0^{x_\mathrm{R}/\beta} dx_\mathrm{L}\, p(x_\mathrm{L}|A_\mathrm{R}) && (5)\\
&= \int_0^\infty \frac{dx_\mathrm{R}}{cA_\mathrm{L}} \exp\left(-\frac{x_\mathrm{R}}{cA_\mathrm{L}}\right) \int_0^{x_\mathrm{R}/\beta} \frac{dx_\mathrm{L}}{cA_\mathrm{R}} \exp\left(-\frac{x_\mathrm{L}}{cA_\mathrm{R}}\right) && (6)\\
&= \int_0^\infty \frac{dx_\mathrm{R}}{cA_\mathrm{L}} \exp\left(-\frac{x_\mathrm{R}}{cA_\mathrm{L}}\right) \left[1 - \exp\left(-\frac{x_\mathrm{R}}{\beta cA_\mathrm{R}}\right)\right] && (7)\\
&= 1 - \int_0^\infty \frac{dx_\mathrm{R}}{cA_\mathrm{L}} \exp\left[-\left(\frac{1}{cA_\mathrm{L}} + \frac{1}{\beta cA_\mathrm{R}}\right) x_\mathrm{R}\right] && (8)\\
&= 1 - \frac{1}{cA_\mathrm{L}\left(\frac{1}{cA_\mathrm{L}} + \frac{1}{c\beta A_\mathrm{R}}\right)} = 1 - \frac{1}{1 + \frac{A_\mathrm{L}}{\beta A_\mathrm{R}}} = \frac{1}{1 + \frac{\beta A_\mathrm{R}}{A_\mathrm{L}}} && (9)\\
&= \frac{1}{1 + \exp(-(\log(A_\mathrm{L}/A_\mathrm{R}) - \log\beta)} && (10)\\
&= \mathrm{sigmoid}(\log(A_\mathrm{L}/A_\mathrm{R}) - \log\beta) && (11)
\end{aligned}$$

(ii) Sketch this relationship for $\beta = 0.5$, $\beta = 1.0$ and $\beta = 2$. [10%]

Answer: This is the sigmoid function:



(iii) A scientist hypothesises that the monkey perceives a sound source to be located in the left (respectively right) hemifield when the corresponding responses in primary auditory cortex obey $x_\mathrm{R}/x_\mathrm{L} > \beta$ (respectively $x_\mathrm{R}/x_\mathrm{L} < \beta$). Based on your answers

to parts (b)(i) and (b)(ii), describe a behavioural task for the monkey to perform, based on which the scientist could corroborate their hypothesis and estimate the value of β.

[15%]

Answer: The monkey could be subjected to a two-alternative forced choice task as follows. In each trial, a different (virtual) sound source location is selected, and the stereo headset plays a tone with an intensity ratio A_L/A_R determined so as to mimick the location of the virtual sound source. The monkey must then report whether they judge the sound source to be located in the left or in the right hemifield. A psychometric curve can be plotted, showing the percentage of 'left' choices as a function of $\log(A_L/A_R)$. If the scientist is correct, then this curve should be the same as sketched in part (b).(ii), and the expression derived in part (b).(i) can be fitted to the data to yield an estimate of the monkey's bias β.

3 (a) This question is about synaptic transmission.

(i) What are the main events following the generation of a presynaptic action potential that lead to the generation of an excitatory postsynaptic potential at a glutamatergic synapse with AMPA receptors? [10%]

Answer:

1. Presynaptic action potential propagates along the axon of the presynaptic cell.
2. Presynaptic action potential arrives at the presynaptic terminal (the synaptic bouton), depolarising the membrane there.
3. Voltage-dependent Ca^{2+} channels open in the presynaptic membrane.
4. Intracellular Ca^{2+} concentration increases at the presynaptic terminal.
5. Glutamate-containing presynaptic vesicles fuse with the presynaptic membrane.
6. The glutamate content of presynaptic vesicles is released into the synaptic cleft.
7. Glutamate molecules diffuse across the synaptic cleft.
8. When reaching the postsynaptic membrane, glutamate molecules bind to postsynaptic AMPA receptors.
9. Postsynaptic AMPA receptors open ion channels in the postsynaptic membrane.
10. Na^+ ions enter and K^+ ions leave the postsynaptic cell through these ion channels, so that their intracellular concentration increases and decreases, respectively.
11. On balance, there are more Na^+ ions entering than K^+ ions leaving the postsynaptic cell, which therefore becomes depolarised.

(ii) Explain with reasons which of the events that you described in your answer to part (a)(i) directly require the cell to use energy? [30%]

Answer: Only the fusion of vesicles requires direct energy expenditure. In particular none of the steps described above involving the opening or closing of ion channels due to changes in membrane potential or the movement of ions through these ion channels use energy directly, as they involve channel molecules taking their energetically more favoured conformations (given the changed membrane potential, or the binding of transmitter molecules), and ions simply moving according to their electrochemical gradients. Action potential propagation does not directly require energy (again channel opening/closing and ions moving as described above). Diffusion does not require energy. Transmitter binding and receptor ion channel opening (see above) also does not require energy directly.

(iii) Neuronal membranes contain selective molecular pumps that expend energy to maintain differences in the concentrations of ions inside and outside the cell. (Indeed, the energy used by these pumps constitutes a major part of energy used for signalling in the brain.) Based on this, explain with reasons which of the events

you described in your answer to part (a)(i) will lead (albeit indirectly) to energy expenditure by these pumps. [30%]

Answer: These are the events that involve the crossing of ions through ion channels, as this means that ionic concentrations (and thus their differences) change on the two sides of the membrane, and it is these changes that need to be compensated for by the action of pumps. Therefore, the events that lead to energy expenditure are:

1. Presynaptic action potential propagates along the axon of the presynaptic cell – because this involves Na^+ ions entering and K^+ ions leaving the cell.
2. Presynaptic action potential arrives at the presynaptic terminal (the synaptic bouton), depolarising the membrane there – again because this involves Na^+ ions entering and K^+ ions leaving the cell.

(3-)4. Intracellular Ca^{2+} concentration increases at the presynaptic terminal.

10. Na^+ ions enter and K^+ ions leave the postsynaptic cell through these ion channels, so that their intracellular concentration increases and decreases, respectively.

(b) This question is about the *Aplysia* gill withdrawal reflex.

(i) What neurotransmitter receptor(s) do the sensory neurons have, and are they ionotropic, or metabotropic? [5%]

Answer: Serotonin. It is metabotropic.

(ii) What neurotransmitter receptor(s) do the motor neurons have, and are they ionotropic, or metabotropic? [5%]

Answer: Glutamate (both NMDA and non-NMDA). They are both ionotropic.

(iii) What secondary messengers in the sensory neurons play a role in the reflex and the forms of learning associated with it that we covered during lectures? [10%]

Answer: Ca^{2+}, cAMP (cyclic adenosine monophosphate), DAG (diacyl glycerol).

(iv) What secondary messengers in the motor neurons play a role in the reflex and the forms of learning associated with it that we covered during lectures? [10%]

Answer: Ca^{2+}.

4 (a) This question is about the hippocampus.

(i) Where in the human brain is the hippocampus? [10%]

Answer: In the medial temporal lobe.

(ii) What distinguishes it from most other parts of the cortex? [10%]

Answer: It is evolutionarily an older type of cortex, so-called 'archicortex', which only has three layers (while most of the rest of the cortex is neocortex, comprised of six layers.

(iii) What are the main regions of the hippocampus? [10%]

Answer: the dentate gyrus (DG), CA1, and CA3 (where CA stands for *cornu Ammonis*), and optionally, the subiculum.

(iv) Describe the 'trisynaptic loop', the main route of information flow through the hippocampus. In your answer, include the names of relevant brain areas, their respective principal cell types, and the pathways connecting them. [20%]

Answer: The perforant pathway arrives from the entorhinal cortex, and its axons synapse on the granule cells of the denrate gyrus. The axons of the dentate gyrus form the mossy fibres, which synapse onto CA3 pyramidal cells. The axons of CA3 pyramidal cells form the Schäffer collaterals that synapse onto CA1 pyramidal cells. The axons of CA pyramidal cells leave the hippocampus (and enter the subiculum and the entorhinal cortex).

(v) Explain with reasons what anatomical, physiological, and functional features make the hippocampus an ideal brain area to study learning and memory. [20%]

Answer: Anatomically, in rodents, (1) the hippocampus (especially the CA1 region) is close to the surface of the brain, making it relatively easy to conduct recordings in it, or selectively lesion it (this is not true in humans). Moreover, (2) it has only three layers, with all principal cells in a single, densely packed layer, which again makes it relatively easy to record their electrical activity. (3) The main dendritic trunks of the pyramidal cells are all parallel, and (4) the fibres arriving from the previous stage of the trisynaptic loop form synapses on a specific region of the dendritic tree, which together make it easier use to extracellular recordings to detect the coordinated activation of these synapses (i.e. fEPSPs). (5) Physiologically, the hippocampus shows important forms of synaptic plasticity that likely underlie hippocampal learning and memory, prominently LTP and LTD (long term potentiation and depression). (6) These forms of plasticity (especially LTP) involve receptors (NMDA) for which we have specific antagonists (AP5). Functionally, lesion and inactivation studies have shown the hippocampus to support critical forms of memory, including (7) episodic memory (the case of patient H.M.), and (8) spatial memory (Morris water maze, and plus-maze studies).

(b) Explain with reasons whether it is true that, according to the Rescorla-Wagner rule, the strength of association between a CS and a US only depends on the number of trials in which they co-occurred. Support your answer by describing suitable experimental paradigms that could be used to demonstrate the correctness of your answer. [30%]

Answer: This is not true in general because, according to the Rescorla-Wagner rule, the strength of association between a CS and a US also depends on the number of times the CS appeared alone, or the US appeared alone (in the absence of any experimentally controlled CSs), or the US has appeared together with other CSs, and it even depends on the order in which different occurrences / co-occurrences happened. For example, in the following paradigms, when the CS and US are made to co-occur on the same number of (CS+US or CS'+CS+US) trials as they would in a simple Pavlovian conditioning paradigm, the strength of CS-US association becomes different from that in the reference Pavlovian conditioning paradigm. In extinction, a number of CS-only trials are added after the CS+US trials, and the strength of the association decreases. Similarly, in partial reinforcement, a number of CS-only trials are interspersed with the CS+US trials, and the CS-US association becomes weaker. In overshadowing, CS'+US trials are interspersed with original CS+US trials, and the CS-US association also becomes weaker. In blocking, CS'+US trials precede CS'+CS+US trials, and the CS-US association also becomes weaker. In secondary conditioning, CS'+US trials precede CS+CS' trials, and the CS-US association can be strong (despite that fact that there had been no CS+US trials).

END OF PAPER

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