Version ML/4 – CRIB

EGT2
ENGINEERING TRIPOS PART IIA

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Monday 18 April 2016 9.30 to 11.00

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**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.

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

1 (a) Write short notes on the following:

(i) differences between the brain and the central processing units (CPUs) commonly found in modern-day computers;

Answer: Brains work with slow and unreliable components (synaptic transmission is noisy and conduction in salty water is slower than in copper), and are very robust to damage. In contrast, a CPU will cease to function as soon as damage occurs at even a single location along its 100 km of copper wire. Computations with CPUs rely on an external, lossless, and random-access memory device, whereas brains implement computation and content-addressable memory simultaneously. Currently, brains have better engineering solutions for many tasks (object recognition, motor control, vision, ...), but CPUs outperform brains in others (e.g. information search, calculus, ...).

(ii) the components and properties of the neuronal membrane that contribute to establishing the resting potential;

Answer: The resting potential is the result of an interplay between different types of *ion channels* inserted in the cell's membrane, which allow charges to flow in an out of the cell (mainly potassium and sodium). The fact that the cell can hold a potential difference in the first place is due to the *capacitive property* of its membrane (a lipid bilayer that acts as an insulator). Finally, *ion pumps* also contribute to the value of the resting potential, by ensuring near-constant intracellular concentrations of ions, which in turn determine the Nernst potential of each ion channel type.

(iii) the two-alternative forced choice discrimination task-design and the associated psychometric function.

Answer: In a 2AFC discrimination task, the subject is presented with two stimuli either simultaneously or in sequence, and is asked to make a relative judgment about some feature of those stimuli (e.g. to tell which of the two stimuli is larger). The experimenter will vary e.g. the difference $\Delta$ in the size of the two stimuli, and plot the probability of the subject reporting the first stimulus to be the largest. For large negative $\Delta$, this probability is zero as the first stimulus is very clearly smaller than the second one. For large positive $\Delta$, this probability is 100%, for a similar reason. For $\Delta = 0$, this probability is 50%, because there is no evidence for either of the two stimuli to be larger than the other (thus, subjects can only guess). The psychometric function otherwise has a smooth sigmoidal shape that interpolates between these 3 limit cases, and its steepness can be used to infer the amount of noise in the sensory processes that take place in the task.

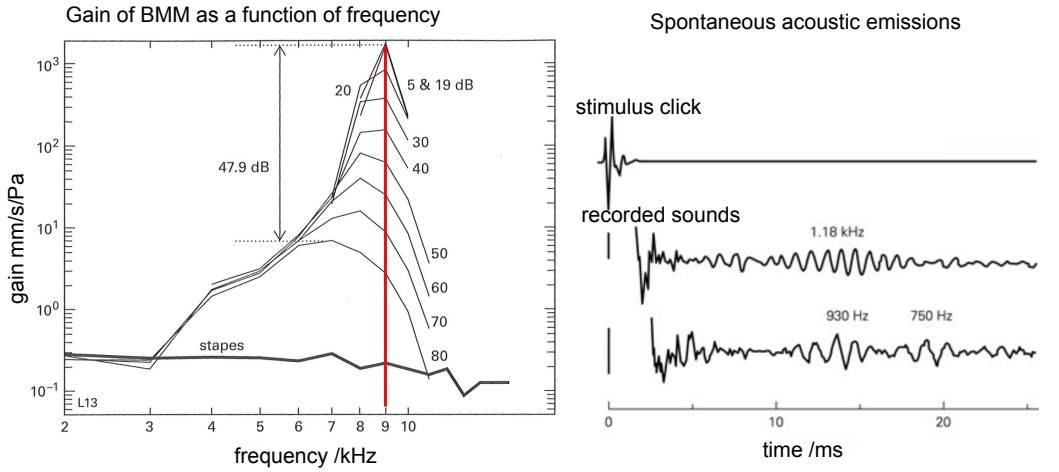
[30%]

(b) In the auditory system, it is widely believed that the inner ear carries out active amplification of incoming sounds.

(i) Describe two pieces of evidence that support this hypothesis. [25%]

Answer:

- gain of the basilar membrane motion is **level dependent**. (In order to explain what this means, a good answer might sketch the left hand figure below which shows the gain in the basilar membrane motion at different locations along the cochlear to sinusoids of 9kHz at different intensities. A linear system would exhibit a fixed gain, but here there is a compressive non-linearity.)
- **spontaneous acoustical emissions** (or otoacoustic emissions) are emitted from the ear after click sounds are presented (a good answer might sketch the right hand figure below)
- The answer might also mention **distortion products**: an input comprising a pair of sinusoids of differing frequencies $f_1 < f_2$ can result in acoustical emissions at $f_1 + N(f_2 - f_1)$ which is a sign of a non-linear system by definition




(ii) Describe what is believed to be the physiological mechanism responsible for active amplification in the inner ear. [30%]

Answer:

- **Outer hair cells**: the basilar membrane has a single row of outer hair cells along its length which are believed to mediate active amplification.
- **Outer hair cells exhibit electromotility**: Outer hair cells contain a motor protein called prestin. When the cell is depolarised the prestin contracts and when it is hyperpolarised the prestin lengthens. Prestin is one of the fastest acting motor proteins. IHCs can contract by roughly 4% 70,000 times a second.
- **Positive feedback**: these contractions set up a feedback loop, whereby an incoming sound causes deflection of the basilar membrane, and this in turn causes changes in IHC length. These length changes causes further deflection of the basilar membrane and so on. This feedback loop is thought to establish the active amplification of sounds in the cochlear, but little is known about how this feedback is stabilised.

(iii) How might an audiologist determine whether the inner ear's active

amplification mechanism is damaged? [15%]

Answer:

- a simple non-invasive test checks to see whether there is **suppression of spontaneous acoustical emissions**
- **audiogram insufficient**: damage to the outer hair cells reduces the amplification of low intensity sounds significantly increasing the detection threshold measured in the audiogram. However, there are many reasons for a threshold increase (e.g. inner hair cell death).

2 This question is about vision.

Consider performing the following experiment shown in Figure 1. A subject sits in front of a large display, and initiates a trial by fixating their gaze on a small cross, centred horizontally on the display. A dot is then presented briefly at some horizontal position $x$ chosen randomly from some distribution $p(x)$ within the grey-shaded ruler of width $w$. After the dot disappears, the subject is asked to provide an estimate $\hat{x}$ of the dot's position.

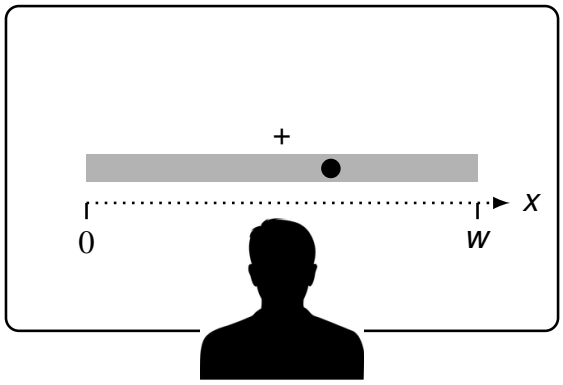



Figure 1

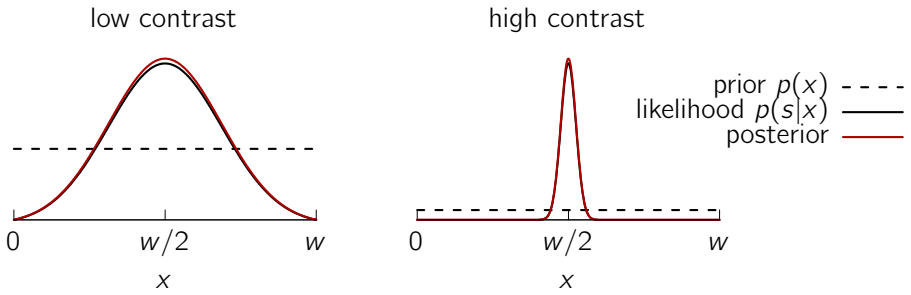
(a) Describe the algorithm that a "Bayesian observer" would use to report the most probable dot position. [30%]

Answer: A Bayesian observer would combine knowledge of how the experimenter chooses the dot position in every trial (the prior distribution $p(x)$) with knowledge about the quality of information conveyed by the retina (i.e. the likelihood function $p(s|x)$, which says how likely it is that the particular signal $s$ received from the eyes in the current trial came from a dot at location $x$). The right way of combining these two sources of information is by computing the posterior distribution $p(x|s) \propto p(s|x)p(x)$. To report the most probable dot position, the "Bayesian observer" would simply choose the $x$ that maximises $p(x|s)$.

(b) Consider the case when the distribution $p(x)$ from which dot positions are drawn is uniform across the ruler. Following intensive training on this task, we present the subject repeatedly with a dot in the centre of the ruler, and construct a histogram of the subject's estimates $\hat{x}$. Draw a sketch of this histogram, and explain your reasoning. In your answer, consider two scenarios: when the dot is high-contrast (black), and when it is low contrast (only slightly darker than the grey ruler). [30%]

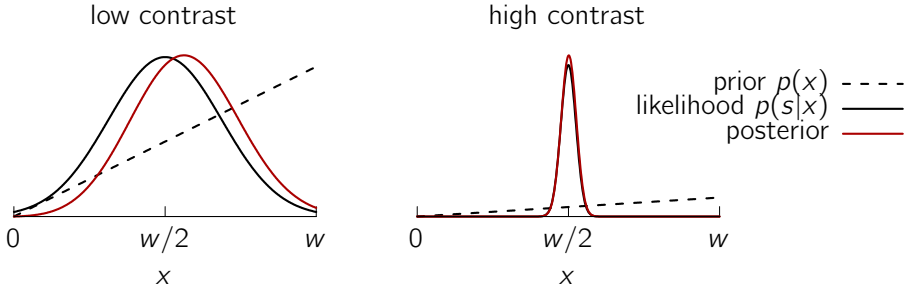
Answer: For a uniform prior, $p(x) = 1/w$, and assuming a Gaussian-shaped likelihood function, $p(s|x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-(s-x)^2/2\sigma^2\right)$, the posterior distribution is proportional to $\exp\left(-(s-x)^2/2\sigma^2\right)$ which has its maximum at $x = s$. Thus, the distribution of a Bayesian subject's $\hat{x}$ across trials with identical dot positions

$x = w/2$ will be a bell-shaped distribution centred around $w/2$ and with width $\sigma$. Here $\sigma$ controls the quality of the evidence: it will be small for high contrast dots, and large for low-contrast dots. In the figure below, note that the low-contrast posterior (red, left) is made slightly larger than the likelihood function so they can be visually distinguished.




(c) Repeat question (b) with the following prior distribution over dot positions: $p(x) = 2x/w^2$ for $x \in [0, w]$, and $p(x) = 0$ otherwise. [40%]

Answer: Now, the prior favors dot positions on the right of the ruler. The posterior distribution becomes proportional to $x \exp\left(-(s-x)^2/2\sigma^2\right)$, which is a slightly shifted version of the likelihood function (cf. figure below). The maximum a posteriori estimate can be found by differentiation (solving the equation $\mathrm{d}p(x|s)/\mathrm{d}x = 0$ for $x$), and is located at $\hat{x} = (\sqrt{s^2+4\sigma^2}+s)/2$. Thus, at high contrast (small $\sigma$), the sensory evidence dominates the estimate and the prior does not shift the distribution of subject's estimates as much as it does at low contrast (large $\sigma$).



3 (a) Describe the experimental procedure for habituating the gill-withdrawal reflex in the Aplysia. State for each of the following quantities whether they increase / decrease / or do not change in response to stimulating the siphon over the course of habituation:

(i) activity of sensory neurons;

(ii) amount of transmitter released by sensory neurons;

(iii) activity of interneurons;

(iv) amount of transmitter released by interneurons;

(v) activity of motor neurons;

(vi) amount of transmitter released by motor neurons. [10%]

Answer: Habituation can be achieved by repeatedly stimulating the siphon of the animal with an innocuous stimulus (eg. by touching it with a brush). In response to stimulating the siphon over the course of habituation:

(i) activity of sensory neurons: does not change;

(ii) amount of transmitter released by sensory neurons: decreases;

(iii) activity of interneurons: decreases;

(iv) amount of transmitter released by interneurons: decreases;

(v) activity of motor neurons: decreases;

(vi) amount of transmitter released by motor neurons: decreases.

(b) Describe four different kinds of neural preparations used for electrophysiological experiments, together with their advantages and disadvantages. [30%]

Answer:

- ***in vitro* slice:** A small and thin piece of nervous tissue is cut out from the brain and put in a special chamber in which recordings can start as soon as possible, and supplied with oxygen and nutrients so that it survives. Advantages: preserves original circuit structure within the slice, individual cells are easily identifiable and accessible (both for recording and pharmacological manipulations). Disadvantages: input and output connections are cut, survival time is limited to a couple of hours, activity patterns may not be representative of the *in vivo* situation.
- ***in vitro* tissue culture:** A small and thin piece of nervous tissue is cut out from the brain and then supplied with nutrients, etc. such that its cells transform and survive. Advantage: can survive for long periods (even months), and individual cells are easily accessable (both for recording and pharmacological manipulations). Disadvantage: individual cells as well as circuit structure transforms, so behaviour of cells and circuit may not be representative of the *in vivo* situation.
- ***in vivo* anaesthetised:** The animal is administered drugs such that it becomes anaesthetised, a 'window' is opened on its skull, and electrodes are inserted into its brain. Advantage: the nervous

tissue remains essentially intact, the animal is stationary so control over electrode placement is greater, recordings are more stable, so that intracellular recordings are still possible. Disadvantage: pharmacologically induced changes in nervous activity may mask natural neural activity, no task-related neural activity can be recorded, individual cells are difficult to access and identify.

- ***in vivo* awake:** The animal undergoes surgery under anaesthesia for placement of electrodes but is than woken up so that recordings are carried out while it is awake and behaving. Advantage: neural activity under normal conditions can be studied, such as that related to solving a behavioural task, learning, etc. Disadvantage: Individual cells are difficult to access and identify, intracellular recordings are impossible or extremely challenging technically.

(c) In a classical conditioning experiment, two different conditional stimuli (CS), $CS_1$ (a light), and $CS_2$ (a tone) are used to signal the same unconditional stimulus (US, delivery of food). Before training, neither CS evokes a response. During training, three kinds of trials are intermixed:

- $CS_1$ followed by US;
- $CS_2$ followed by US;
- $CS_1$ and $CS_2$ presented simultaneously, without US following.

After training, the following responses (salivation) are observed in response to the CSs:

- $CS_1 \longrightarrow$ response
- $CS_2 \longrightarrow$ response
- $CS_1 + CS_2 \longrightarrow$ no response

(i) Explain whether the Rescorla-Wagner rule can account for these results. [20%]

Answer: These results cannot be accounted for by the Rescorla-Wagner rule, because there the strength of response for a combination of stimuli is always the sum of the response strengths for the individual stimuli. Therefore, the rule either predicts that the two stimuli individually cause a response, and together they also lead to a (greater) response, or it predicts that neither the two stimuli individually nor their combination elicits a response. In fact, this paradigm is analogous to partial reinforcement from the perspective of the Rescorla-Wagner rule, where each cue is reinforced half the time (assuming three trial types are mixed with equal probability) so the corresponding weights will be about $1/2$ each, predicting a weak response for individual stimuli, and a strong response for the compound stimulus.

(ii) Someone proposes a new theory to describe animal learning in this experiment. The new theory starts from assuming that an animal's response to a combination of CSs reflects how much it predicts the occurrence of a US, and that in the case of two CSs this prediction, $r$, is given by the following equation:

$$r = w_1 s_1 + w_2 s_2 + w_3 s_1 s_2$$

where $s_1$ and $s_2$ are the presence (= 1) or absence (= 0) of $CS_1$ and $CS_2$ in a trial, respectively, and $w_1$, $w_2$, and $w_3$ are prediction strength parameters. Just like the Rescorla-Wagner theory, the new theory also assumes that, during learning, the prediction strength parameters are gradually changed over trials such that the average squared prediction error $E = (u-r)^2$ is minimised (where $u$ is the presence (= 1) or absence (= 0) of the US in a trial).

A. Write down the equations describing how each of the prediction strength parameters should change in a trial, based on $u$, $s_1$, $s_2$, and $r$, according to this new theory. [20%]

Answer: To minimise squared error, the change in a prediction strength parameter, $w$, should be negatively proportional to the (partial) derivative of the squared error, $E$, with respect to that parameter:

$$\frac{dw}{dt} \propto -\frac{\partial E}{\partial w}$$

This results in the following update rules for the three parameters:

$$w_1 \rightarrow w_1 + \varepsilon\,(u-r)\,s_1, \quad w_2 \rightarrow w_2 + \varepsilon\,(u-r)\,s_2, \quad w_3 \rightarrow w_3 + \varepsilon\,(u-r)\,s_1\,s_2$$

B. Explain if this new theory can account for the experimental results described above. [20%]

Answer: This new theory can account for the experimental results as it will eventually set $w_1$ and $w_2$ to have values near +1, while setting $w_3$ to have a value at -2 ($w_3 = -(w_1 + w_2)$).

4 (a) Sketch the amount of postsynaptic current as a function of the postsynaptic membrane potential for an AMPA and an NMDA receptor. For both receptors, sketch the current under four different conditions:

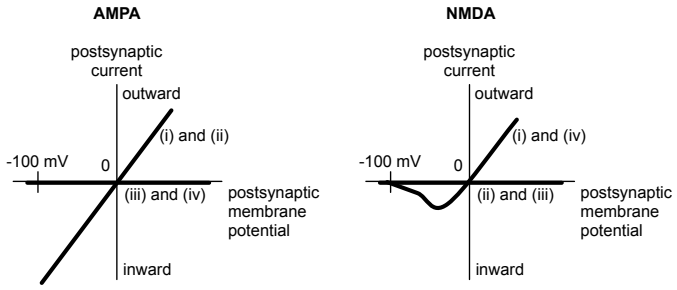
(i) when only glutamate is present in the synaptic cleft; [10%]

(ii) when glutamate and AP5 are present in the synaptic cleft; [10%]

(iii) when only AP5 is present in the synaptic cleft; [10%]

(iv) when only NMDA is present in the synaptic cleft. [10%]

Answer: The postsynaptic currents will look like:




When the AMPA receptor opens due to ligand binding, the current is a linear function of voltage (increasing outward current for increasing voltage, reversal potential around $\sim 0$ mV), because the conductance does not depend on voltage. When the NMDA receptor opens, its current is a linear function of voltage for high enough voltages (above $\sim 0$ mV), as for the AMPA receptor, but decreases back to zero for lower voltages (below $\sim -50$ mV) because its conductance is decreased due to the $Mg^{2+}$ block. These receptors open and close in the four conditions as follows:

(i) When glutamate is available in the synaptic cleft: both receptors are glutamate receptors, so both will be open.

(ii) When glutamate and AP5 is available in the synaptic cleft: AP5 is a selective NMDA antagonist, so only the AMPA receptor is open.

(iii) When AP5 is available in the synaptic cleft: neither receptor opens.

(iv) When NMDA is available in the synaptic cleft: NMDA is a selective NMDA agonist, so only the NMDA receptor is open.

(b) Describe how the Morris water maze is used in learning experiments. Include the following in your answer:

- what is the apparatus like;
- what is the animals' task;
- what aspects of behavioural performance are measured to quantify learning;
- what variants of the Morris water maze can be used to show that some treatment

specifically impairs spatial learning as opposed to other factors contributing to performance in the task?

[40%]

Answer:

- The Morris water maze is a circular tank of diameter $\sim$ 1 m filled with opaque (eg. milky) water used to measure spatial learning.
- On each trial, the animal (usually a rat) is started from some position close to the wall of the tank and has to swim to find a platform hidden under the surface of water. (There is a natural motivation for performing this task, because rats don't like being in water.) On consecutive trials, the rat is started from different (random) positions, but the platform remains in the same place (relative to some external reference frame, eg. the experimental room), so the rat needs to remember the location of the platform to be able to improve its performance over trials.
- Performance measures include escape time (time from start until the rat fins the platform), path length (overall distance taken until finding the platform), time spent in target quadrant or near the location of the platform (on catch trials, when the platform is not in its usual place).
- Starting a rat from the same position across trials will allow procedural learning (or praxic strategies) to be effective (learning the sequence of actions needed to reach the platform). Making the water non-opaque will allow the rat to see where the platform is and use taxic strategies, thereby also (partially) reducing the need for spatial memory for solving the task. If a treatment impairs performance in the original Morris water maze but not in these modified tasks, then it specifically affects spatial learning.

(c) Describe the sequence of cellular-molecular events at the synapse, including the main steps of synaptic transmission that leads to the induction of LTP. [20%]

Answer:

•presynaptic action potential arrives at the presynaptic terminal

•$Ca^{2+}$ influx to the axon terminal

•vesicles dock to the presynaptic membrane and release transmitter (glutamate) to the synaptic cleft

•glutamate diffuses across the synaptic cleft

•glumate molecules bind to AMPA and NMDA receptors on the postsynaptic surface

•AMPA receptors open $Na^{+}$ channels in the postsynaptic membrane

•NMDA receptors don't open because $Mg^{2+}$ ions still block them

•$Na^{+}$ influx to the postsynaptic cell

•postsynaptic cell depolarises

•postsynaptic depolarisation relieves the $Mg^{2+}$ block in the NMDA channels

•NMDA receptors open $Ca^{2+}$ channels in the postsynaptic membrane

•$Ca^{2+}$ influx to the postsynaptic cell

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## Comments on Questions

**Q1** General questions and auditory processing

A popular question. General questions (a) were answered well by most candidates, except for (iii) in which most candidates erroneously described a 2AFC *detection* task, as opposed to a discrimination task; the associated psychometric curve often lacked the right axis labels, showing lack of understanding. Students did rather well in the questions on auditory processing (b), although the description of the mechanism believed to underlie active amplification in the inner ear was often too shallow (often lacked one or more of the key arguments).

**Q2** Bayesian inference in vision

Only few students attempted this question, but then most answers were very good. A couple of students thought of approaching (c) more quantitatively, i.e. thought of differentiating the posterior density to find its peak – but none got it right. Qualitative answers were all good, though some were a little too “handwavy".

**Q3** Title

A popular question. All parts were generally well answered, with many students missing some of the details in part (b), very few misunderstanding what the question was referring to (despite the wording of the question clearly referring to a specific slide in the lecture handouts), and most having a harder time with the last part which required generalisation beyond the material covered during lectures,

**Q4** Title

A very popular question, chosen by every candidate. All parts were generally well answered. Many students failed to clearly indicate units on at least the x-axis of their sketch, and the sign (outward or inward) of the current on the y-axis, also many were unable to clearly articulate how using different variants of the Morris water maze can rule out factors other than spatial learning contributing to improvement in task performance, and some spending too much detail on the expression of LTP, which was not part of the questions, and missed out some important steps of the induction process.

M. L.