Version ML/2 – CRIB

EGT2
ENGINEERING TRIPOS PART IIA

Monday 27 April 2015 14.00 to 15.30

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) This question is about the Hodgkin-Huxley model for action potential generation.

(i) State and explain:

A. the differential equation that Hodgkin and Huxley used to describe the dynamics of the membrane potential; [10%]

B. the equation for the sodium current in terms of the gating variables and the membrane potential; [10%]

C. the differential equation for one of the gating variables. [10%]

Answer:

A.

$$C\frac{d}{dt}V = -I_{Na} - I_K - I_L,$$

Here, C is the capacitance of the cell membrane, V is the membrane potential, and I_{Na}, I_K and I_L are sodium, potassium and leak currents, respectively.

B.

$$I_{Na} = g_{Na}m^3h(V - V_{Na})$$

Here, g_{Na} is the maximal conductance of the sodium channels, m and h are gating variables that vary between 0 and 1, and V_{Na} is the reversal potential for sodium ions.

C.

$$\tau_m(V)\frac{d}{dt}m = m_\infty(V) - m.$$

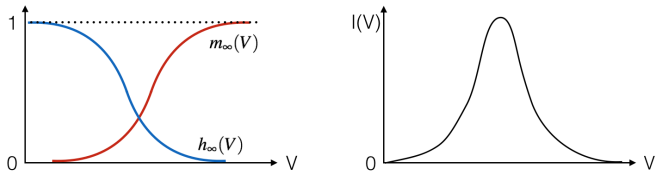
Here, τ_∞ is the time constant of the gating variable, and m_∞ is its equilibrium value. Because both depend on the current membrane potential, the dynamics of the membrane potential are highly nonlinear. Similar equations hold for the other gating variables h and n.

(ii) The membrane potential of a neuron in voltage-clamp mode is very slowly increased from −100 mV to 20 mV. Sketch and describe how:

- the two gating variables for sodium; and
- the sodium current

change as a function of the membrane potential. [15%]

Answer:



The gating variable m gradually increases from 0 to 1, while the gating variable h gradually declines

 (cont.

from 1 to 0. Because the current is the product of m^3 and h, it exposes a peak in the region of the membrane potential where the gating variables transition from 0 to 1.

(iii) Explain which of the gating variables is responsible for the positive feedback that triggers the action potential. [5%]

Answer: The positive feedback that is required for the action potential is caused by the gating variable m, because this gate opens with increasing depolarisation, leading to further current influx and hence further depolarisation.

(b) This question is about the drift-diffusion model for perceptual decision making.

(i) Name the parameters of the drift-diffusion model for perceptual decision making and explain their role. [15%]

Answer: The key parameters of the drift diffusion model are

A. the drift rate, which reflects the strength of the stimulus, i.e., the amount of evidence per time unit for either of the behavioural choices.

B. the height of the decision bound, which controls how much evidence needs to be accumulated before a decision is made.

C. the starting point of the random walk, which captures potential response biases of the subjects.

(ii) Explain the speed-accuracy trade-off within this model. [15%]

Answer: The speed-accuracy tradeoff arises from the fact that subjects have to decide at every moment whether to either make a (potentially premature) decision or collect more evidence. More evidence improves the accuracy of the decision, so the subjects can trade off a slower response for a more accurate decision.

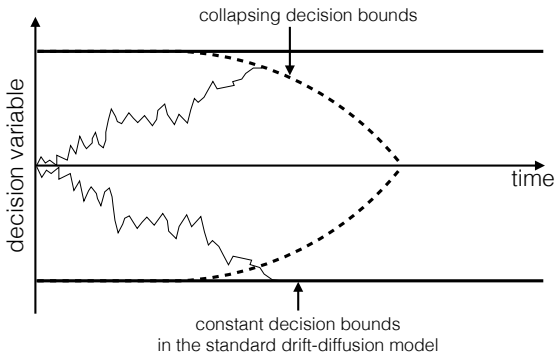


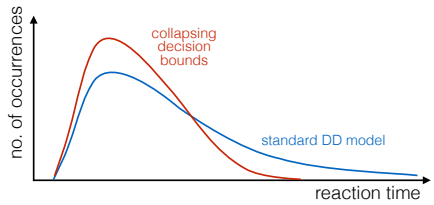
Fig. 1

(iii) In many decision making experiments, subjects are put under time pressure by requiring a response within a given time interval. To incorporate time pressure into the drift-diffusion model, a common variation of the model lets the decision bounds gradually collapse to zero over time (see Fig. 1).

- Sketch and describe the shape of the reaction time distribution for the standard drift-diffusion model with constant decision bounds.
- Sketch and explain how the reaction time distribution is altered by collapsing bounds.
- Explain with reasons whether you would expect the fraction of correct responses to increase or decrease as the decision bound approaches zero.

[20%]

Answer:



The reaction time distribution for the standard drift diffusion model starts at zero for zero reaction time and stays around low for short reaction times, because of unavoidable sensory and motor delays. It then rises to a peak and then slowly decays with a relatively long "tail" of long reaction times. Collapsing bounds reduce this tail, because all decisions are made by the time the decision bounds have collapsed to zero. Later decisions are less accurate, i.e., the fraction of correct responses decreases, because those decisions are forced by the decision bound rather than being based upon accumulated evidence.

2 (a) Write short notes on the following:

(i) functional magnetic resonance imaging and its strengths and weaknesses; [15%]

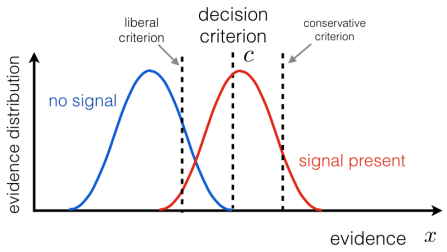
Answer: Functional magnetic resonance imaging (fMRI) uses oscillating magnetic fields to measure the oxygenation level of the blood (BOLD), which in turn reflects neural activity (in an unfortunately not fully resolved way). Usually, two experimental conditions are compared, because the oxygenation level itself is not informative per se. The core advantages of fMRI are that it is non-invasive, and can hence be applied to humans, and its relatively high spatial resolution (compared to, e.g., EEG). Its main disadvantages are the relatively low temporal resolution and the fact that the relation between the BOLD signal and neural activity is not yet fully resolved.

(ii) the Eriksen flanker task and what it teaches us about spatial attention; [15%]

Answer: In the Eriksen flanker task, subjects are asked to fixate until one of two stimuli appear in the centre of the screen flanked by two other stimuli, and then provide one of two different responses depending upon the central stimulus (they need to disregard the flanking stimuli). The flanking stimuli can either be congruent (corresponding to the same response as the stimulus at the fixation point), incongruent (corresponding to the opposite response than the stimulus at the fixation point) or neutral. Subjects are asked to respond as quickly as possible, and reaction times are measured. The main outcome of the experiment is that reaction time decreases from the incongruent to the congruent condition, while the neutral condition provides intermediate reaction times. The strength of this reaction time effect decreases with increasing distance of the flankers from the fixation point. In general, the task teaches us that our attentional focus cannot be arbitrarily small. More specifically, these results have also been interpreted in the context of the debate whether attention is an "early" or "late" selection of stimuli. The results support the late selection theory because they suggest that supposedly non-attended stimuli are nevertheless processed, because the reaction time depends on the behavioural consequence these stimuli would have had.

(iii) the assumptions of signal detection theory (provide a graphical illustration with your answer). [15%]

Answer:



Signal detection theory, as taught in the lecture, assumes that two different stimuli (which could, e.g., contain/not contain a sensory feature) cause effectively 1-dimensional and noisy sensory evidence. Given the stimulus, the evidence is drawn from a Gaussian distribution in each trial. The two Gaussian distributions for the two stimuli are both assumed to have a variance of one, and their means differ by an amount that is referred to as the sensitivity d'. Subjects are assumed to make decisions based on a fixed decision criterion c for the evidence. These assumptions allow us to calculate the sensitivity d' and the criterion c from the number of true/false positives/negatives, and thereby to disentangle the subject's sensory discrimination ability and potential response biases.

(b) A point sound source is located at an azimuthal angle θ and a distance r from a listener as shown in Fig. 2. The head width of the listener is $l = 0.2\,\mathrm{m}$ which can be assumed to be much smaller than the distance to the point source. The speed of sound is $c = 340\,\mathrm{m\,s^{-1}}$.

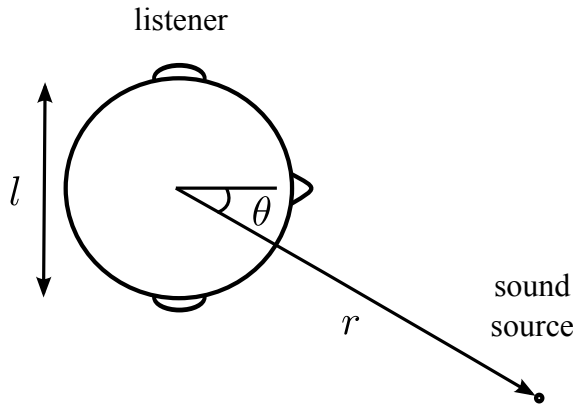
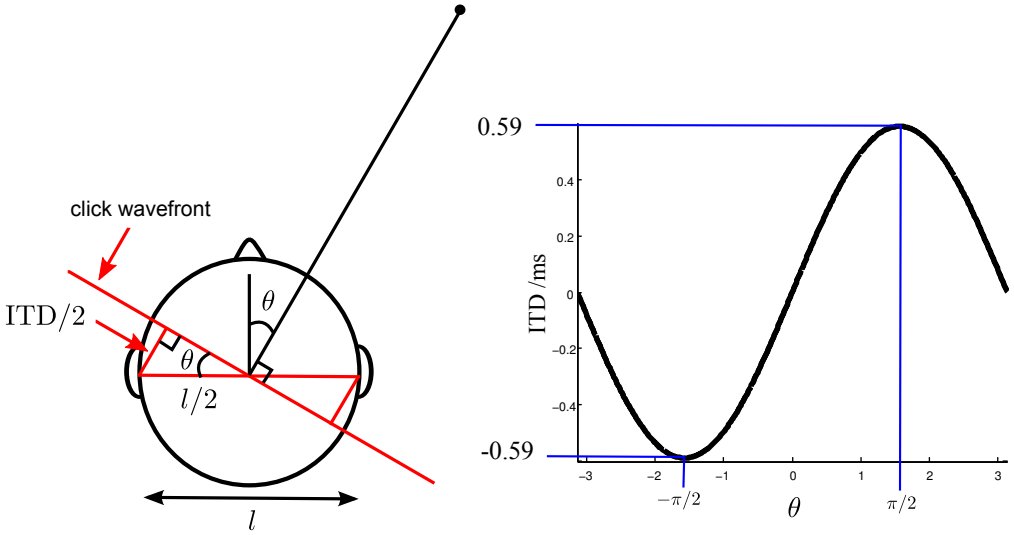


Fig. 2

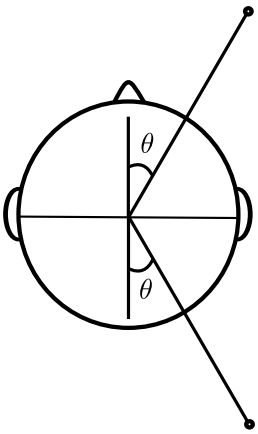
(i) The point source emits a click. Sketch how the resulting interaural time difference (ITD, using left ear minus right ear convention), varies as a function of θ over the range $-\pi \leq \theta < \pi$. Label the values of the maximum and minimum ITDs and the azimuthal angles at which they occur. [15%]

Answer: $\mathrm{ITD}(\theta) = \frac{l}{c}\sin(\theta) = 0.59\sin(\theta)$ ms

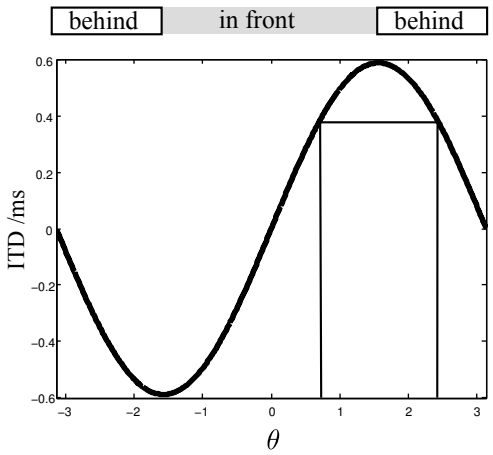


(ii) Listeners sometimes experience a so-called front-back confusion where they perceive a source that is located in front of them as being located behind them and vice versa. Explain the origin of this phenomenon using your sketch. [10%]

Answer:



ITDs from these two souces are identical

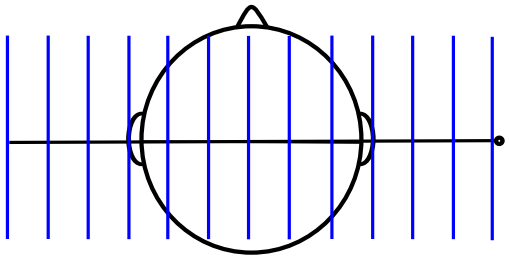


ITD is consistent with two azimuthal positions one at θ and one at $\pi - \theta$

(iii) The point source now emits a 3kHz sinusoid. Disregarding the front-back confusion, can the source be reliably localised using ITDs in this case? Explain your reasoning by considering the signals arriving at the two ears. [15%]

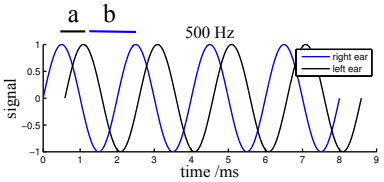
Answer: In general, ITDs are not useful in this case even disregarding the front-back confusion (e.g. at $\theta = \pi/2$ at which the front-back confusion does not exist by definition).

consider the case when $\theta = \pi/2$

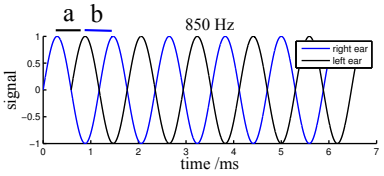


To see how ITDs might be computed for steady sinusoids, plot the signal arriving at the two ears.

For low frequency sinusoids the association is unambiguous since time delay b is too long to be generated by a 20cm head



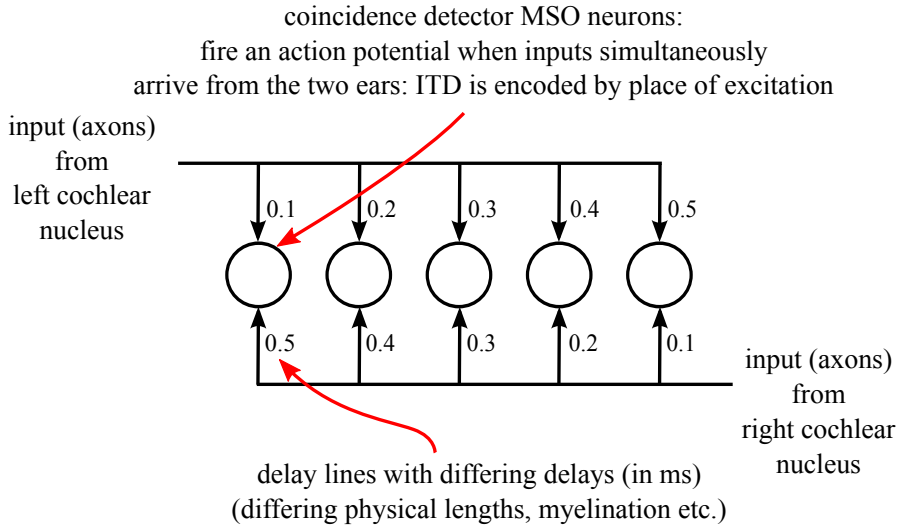
For frequencies > c/(2l) = 850 Hz ambiguities arise



3kHz is far larger than this threshold, so ITDs are not reliable for even small values of θ

(iv) Describe the Jeffress model for the neural processing of ITDs in the medial superior olive. [15%]

Answer: Under the Jeffress model the MSO forms a place code for ITD. The MSO is modelled as a set of coincidence detectors that receive inputs from both the left and right cochlear nucleus. The inputs from the two ears are passed through opposing delayed lines (see figure). In this way, sounds from the left excite the right cochlear nucleus first and therefore cause activation of the left most MSO neuron on the figure. Sounds which are directly ahead activate the central MSO neuron. The model therefore establishes a place code for ITDs.

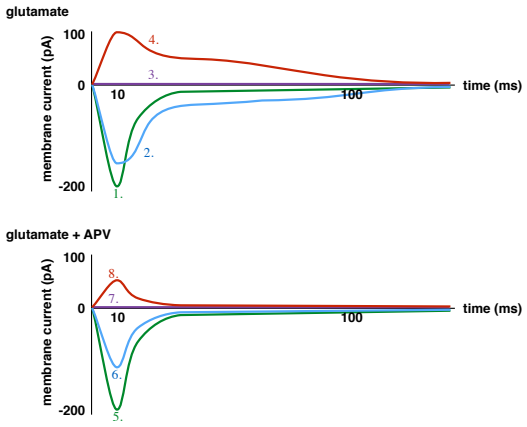

coincidence detector MSO neurons:
fire an action potential when inputs simultaneously
arrive from the two ears: ITD is encoded by place of excitation
input (axons)
from
left cochlear
nucleus
0.1
0.2
0.3
0.4
0.5
0.5
0.4
0.3
0.2
0.1
input (axons)
from
right cochlear
nucleus
delay lines with differing delays (in ms)
(differing physical lengths, myelination etc.)

3 (a) In a voltage-clamp experiment, a neuron is stimulated by local application of glutamate, and the postsynaptic current is measured. Sketch and describe in words the synaptic current as a function of time under the following eight conditions, and explain with reasons why the postsynaptic current differs across conditions:

condition	holding voltage	APV is applied together with glutamate
1.	−100 mV	no
2.	−50 mV	no
3.	0 mV	no
4.	+25 mV	no
5.	−100 mV	yes
6.	−50 mV	yes
7.	0 mV	yes
8.	+25 mV	yes

Ensure that you define units on the axes of your plots. [40%]

Answer:



In general, the traces are the sum of two components: an early component due to AMPA current, peaking around 5 ms and decaying within another 10 ms, and a late component due to NMDA current, peaking around 20 ms and decaying by 100 ms. Hence in general, the shape of the traces is a "bump" which peaks around 10 ms (between the peaks of the two components) and whose amplitude is roughly the sum of the two components, followed by a longer tail whose time scale and amplitude is determined by the late component. The magnitude of the early component grows linearly with holding voltage, such that it is roughly −200 pA at −100 mV. The magnitude of the late component is a nonlinear function of the holding voltage, due to the Mg^{2+} block of the NMDA channel which blocks the channel under −50 mV, such that the NMDA current is approximately 0 pA at −100 mV (so only the fast component contributes at this voltage), −50 pA at −50 mV, 0 pA again at 0 mV, +50 pA at +25 mV (and above that it also grows linearly). Note that the magnitudes of both components are 0 pA at 0 mV, because that is where the reversal

 (cont.

potentials of both AMPA and NMDA channels are, and therefore we expect no current whatsoever at that holding voltage. Since APV is a selective NMDA blocker, in conditions 5-8. only the fast component is visible. (This makes no difference between conditions 1. and 5. because at that voltage the NMDA channel is closed in any case, and between 3. and 7. because there is no current at all at the reversal potential under any circumstances.)

(b) Describe the main differences between massed training and spaced training for habituating the gill-withdrawal reflex in *Aplysia* in terms of:

- the stimulation pattern applied;
- their effects on habituation;
- their mechanisms.

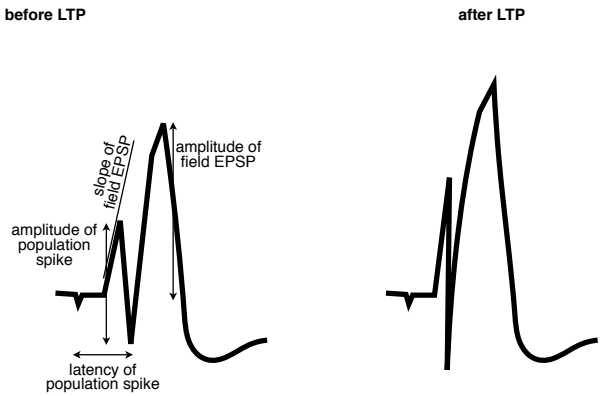
[30%]

Answer:

- Massed training consists of one session when the habituating stimulus is applied several times within a relatively short span of time, while spaced training consists of several sessions separated in time (and potentially fewer stimuli per session).
- Massed training results in strong habituation but it decays within a week, while spaced training results in habituation that lasts several week.
- Massed training only changes the amount of neurotransmitter released in already existing synapses in the gill-withdrawal pathway, while spaced training results in the decrease of the number of (excitatory) synapses between sensory and motor neurons.

(c) In an *in vitro* experiment about LTP, extracellular electrodes are used both for stimulation and recording. Sketch the extracellular potential signals that can be recorded following a stimulation before and after the induction of LTP, when the recording electrode is in the same layer where cell bodies of the postsynaptic cells are located. Describe in words the main components of the recorded signals, their electrophysiological sources, and the main differences between the "before" and "after" signals. [30%]

Answer: The recorded signals will look like:



The first very small downward deflection is a stimulation artefact which is due to direct volume conduction between the stimulating and the recording electrode. (This can be useful as it gives a reference point in the recording for when the stimulation occurred.)

The large upward deflection is the field EPSP which is the reflection of the postsynaptic depolarisation. This is recorded as a depolarisation because locally, at the synapses which are distant from the soma, intracellular depolarisation and so extracellular hyperpolarization occurs, and this gets inverted at the somata, because the circuit needs to be closed.

The sharp and large downward deflection is the population spike which is a reflection of the postsynaptic action potentials. This is recorded as a hyperpolarisation because the action potential is generated near the soma, resulting in large intracellular depolarisation and so extracellular hyperpolarization, again because the circuit needs to be closed.

The amplitude and slope of the field EPSP increases because transmission in the synapses has become more efficient (i.e. postsynaptic potentials in individual neurons have become larger). The amplitude of the population spike increases, while its latency decreases, because more cells reach the threshold for action potential generation (not because the action potentials in individual cells have become larger), and the threshold is reached faster, due to the larger postsynaptic potentials, which also means that they reach this threshold more synchronously.

4 (a) You are to design an experiment in which you can use a neurotransmitter antagonist to attempt to distinguish between the contributions of hippocampal LTP to at least three different navigational strategies during spatial navigation. Include the following details, and explain your choices in all cases:

(i) What receptor would you block with your antagonist? At what point(s) during the course of the experiment would you apply your antagonist? [10%]

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

(iii) What results would you expect from your experiment? [10%]

(iv) If you had the opportunity to do *in vivo* electrophysiological recordings, how would you do them to give further support to your results? [20%]

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

(i) I would use rats, and use an NMDA receptor antagonist (eg. AP5), injecting it to the hippocampus, thereby selectively preventing the induction of LTP there. I would also have a control group in which only saline is injected into the hippocampus. AP5 / saline would be applied throughout training, but not during testing.

(ii) I would use three versions of the Morris water maze test (in three different groups of animals): (1) one in which the rat is always started from a different position, and a clear and near visual cue identifies the location of the escape platform (eg. a beacon hanging above it) , (2) one in which the rat is always started from the same position, but the location of the escape platform cannot be identified by visual cues, (3) one in which the rat is always started from a different position, and no visual cue identifies the location of the escape platform. Version (1) tests whether the rat can learn to swim towards the platform based on the visual cue (taxic strategy, or stimulus-response learning). Version (2) tests whether the rat can learn the sequence of actions needed to reach the platform from the fixed starting position (praxic strategy, or procedural learning). Version (3) tests whether the rat has done proper spatial learning, when no taxic or praxic strategy would be sufficient. Performance in all cases would be measured by time spent in the target quadrant in catch trials (without a platform), or escape time (in trials with a platform).

(iii) I expect that AP5 and saline injected animals will perform similarly in the first two groups, but not the third, as praxic and taxic strategies do not depend on the hippocampus, while spatial learning does.

(iv) I would conduct standard LTP-experiments in anaesthetised animals. I would try to induce LTP in their hippocampus, to demonstrate that LTP cannot be induced in animals injected with AP5 but can be induced in control animals (injected with saline).

(b) In a classical conditioning experiment, three different conditioned stimuli (CS), CS_1 (a light), CS_2 (a tone), and CS_3 (a click), are used to signal the same US (unconditioned stimulus, e.g. the delivery of food). Before training, none of the CSs evoked a response.

Describe how strong a response (if any) you would expect for each of the CSs presented in separation after the following training protocols:

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

where e.g. CS_1+CS_2 stands for sequential presentation of stimuli, and (CS_1,CS_2) means simultaneous presentation of stimuli. [40%]

Answer:

- CS_1: moderately strong, because it is only a secondary conditioner in phase 1 (by being conditioned to CS_2, though the Rescorla-Wagner rule does not account for it), and extinction in phase 2, CS_2: stronger, because of primary conditioner in phase 1 and no extinction in phase 2, CS_3: very weak, because of secondary conditioning to an already only moderately strong cue (CS_1), and eventually extinction in phase 2 (again, the Rescorla-Wagner does not account for it)
- CS_1: strong, because although it is only a secondary conditioner in phase 1, there is additional conditioning to the US with weak overshadowing (by CS_3) in phase 2, CS_2: moderately strong, because although primary conditioner in phase 1, US is presented without it in phase 2, CS_3: weaker, because of partial blocking due to phase 1 and overshadowing in phase 2 (by CS_1)
- CS_1: moderately strong, because only secondary conditioner in phase 1 and overshadowing in phase 2 (by CS_2 and CS_3); CS_2: stronger, because primary conditioner in phase 1, and additional training (though with overshadowing by CS_1, and CS_3) in phase 2; CS_3: none (or very weak), because of complete blocking due to training in phase 1 (by CS_2, and to a lesser degree CS_1)

END OF PAPER

Version ML/2 – CRIB

Comments on Questions

Q1 Hodgkin-Huxley and drift-diffusion models

A popular question, well-answered by many candidates. The main difficulty was in being able to distinguish between parameters and variables of a model (here: drift-diffusion) and to realise that reaction time distributions cannot possible be Gaussian distributed and are instead heavy tailed.

Q2 General questions and auditory processing

A popular question, quite well answered by many candidates. Most errors were due to not considering that signal detection theory assumes two (rather than just one) distributions to be Gaussian Ñ one in the presence and one in the absence of the signal Ñ, and a failure to identify dÕ as a central quantity in it.

Q3 Learning and memory: cellular and molecular processes

A relatively less popular question. In response to a request by the External Examiner, part a was made more challenging by going beyond textbook material. Most candidates struggled with putting together known facts about maximal conductances and time constants (covered in lectures) to predict time courses, and failed to realise that in a voltage clamp experiment voltage sensitive conductances to not change their conductances (and there cannot be action potentials).

Q4 Learning and memory: systems and cognitive processes

A very popular question. Each part was well answered by at least some of the candidates. Many failed to realise the importance of proper control experiments and provide explicit notes on how to distinguish between the contributions of LTP to each of three navigational processes (and instead focussed on only one: cognitive map), despite explicit instructions in the paper.

M.L.