ENGINEERING TRIPOS PART IIA

Friday, 26th April 2013 9.30 to 11am

Module 3G3

Answer: 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.*

There are no attachments.

STATIONERY REQUIREMENTS	SPECIAL REQUIREMENTS
Single-sided script paper	Engineering Data Book
	CUED approved calculator allowed

You may not start to read the questions printed on the subsequent pages of this question paper until instructed that you may do so by the Invigilator

Version: Final

1 (a) Write short notes on:

(i) Coarse coding;

Answer: Coarse coding involves receptive fields for adjacent parts of space that are large and overlapping. This allows a single location to be coded by the activity of multiple neurons and allows the precise point to be determined better than by having the same number of non-overlapping receptive fields. It is a good trade off between accuracy and resolution.

(ii) Labelled line codes;

Answer: The receptors and initial neural channels for the different senses are independent in the axon that initially carrying the signal. Therefore each sensory neuron responds to only one modality. We can therefore"label" each sensory neuron ("line") by the modality it codes.

(iii) The benefits of multisensory integration. [20%]

Answer: Multisensory integration can be used to i) bring a stimulus above threshold when each would individually be below threshold, ii) reduce the variance of a sensory estimate that arise through processes such as noise.

(b) The following questions are about the action potential.

(i) Explain the mechanisms that give rise to, and sustain, the resting potential of a neuron.

Answer: At rest the neuron has channels that are permeable to both Sodium (low conductance) and Potassium (high conductance). Sodium is concentrated outside the cell and Potassium within the cell. The resting potential reflects a dynamic balance between the diffusion of the ions under a concentration gradient which is opposed by a potential difference electromotive force in the opposite direction. The resting potential is closer to the reversal potential for Potassium as the conductance is higher. An ATP driven Na-K pump maintains the concentration gradient in the long term.

(ii) Explain the channel mechanisms that give rise to the absolute and relative refractory periods.

Answer: The absolute refractory period is the interval after an action potential during which a second action potential absolutely cannot be initiated, no matter how large a stimulus is applied. It is caused by the closure and inactivation of the Na^+ channels that

originally opened to depolarize the membrane. The h gate remains closed until the membrane repolarizes, after which they regain their ability to open in response to stimulus.The relative refractory period is the interval following the absolute refractory period during which initiation of a second action potential is inhibited but not impossible. It is caused by the residual opening of K^+ channels that make it harder to depolarize the membrane.

(iii) Explain how the voltage clamp technique works and why it is useful for studying the mechanisms underlying the action potential. [30%]

Answer: The voltage clamp is used to measure the ion currents across a neuronal membrane while holding the membrane voltage at a fixed level. It acts as a feedback controller sensing the voltage across the membrane and applying current to keep the membrane at a reference value. Neuronal membranes contain many different kinds of ion channels, some of which are voltage gated. The benefit of the voltage clamp is that it allows the membrane voltage to be manipulated independently of the ionic currents, allowing the current-voltage relationships of membrane channels to be studied. Normally voltage changes cause channels to change the conductance which itself causes voltage changes. The voltage clamp can fix the voltage and allow study the time course of the conductance change.

(c) The following questions are about hearing.

(i) Low frequency sounds are used by many species to communicate over long distances because they are less likely to be degraded by the environment. Explain why small animals that use low frequency communication sounds may find it hard to localise one another. Take care to describe the different localisation cues in your answer.

Answer: Sound localisation is possible due to the geometry of an animals head and external ears (pinna). The physical separation of the pinna causes a difference in path-length which results in an interaural time difference (ITD). Moreover, sounds are filtered by the head and pinna in a frequency dependent manner described by the head related transfer function. These effects can cause differences in the intensity of the sound at the two ears called interaural level differences (ILDs) as well as monaural spectral cues. ILDs and monaural spectra cues are small at low frequencies because sounds with long wavelengths propagate around the head without interference. ITDs are therefore the major localisation cue for low frequency sounds. This presents a difficulty for small animals since their pinna will be close together, meaning that the ITD cues will be small and therefore hard to detect.

(ii) What is auditory scene analysis? Describe the cues which are utilised by the auditory system to perform auditory scene analysis. [50%]

Answer: The first stage of auditory processing reveals the spectro-temporal energy content of a sound. Auditory scene analysis is the subsequent process by which the auditory system binds together spectro-temporal energy arising from a single underlying auditory source and separates it from that arising from other sources. Cues which are believed to be used to group activity arising from a single source are: Common onset – simultaneous co-activation of neurons at different positions along the tonotopic axis. Common offset – simultaneous deactivation of neurons at different positions along the tonotopic axis. Amplitude comodulation – coordinated changes in activation of neurons in different frequency channels. Harmonicity – activation of neurons which are harmonically related. Continuity – smooth changes in neural activity over time are indicative of a single source.

2 (a) There are an infinite number of arm movements which could move the hand from one point in space to another, yet such movements in humans are stereotypical.

(i) What are the stereotypical features of these arm movements?

Answer: Movements of the hand tend to be roughly a straight line with a bell shaped velocity profile.

(ii) Describe a computational principle that can account for the stereotypical features of arm movements.

Answer: The movements can be ranked based on a cost associated with each and the one with the lower cost enacted. For example, signal-dependent noise (SDN) corrupts the commands and leads to variability of the movement. Choosing different ways to move produced different motor command and different noise leading to different variability of the movement. By tailoring the statistics of the outcome to a particular task an optimal way of movement can be chosen because the motor system is highly redundant. Such a model has been used to predict goal-directed movements such as movement of the eye or arm. Energy conservation can also affect the optimal movement.

(iii) Given this computational principle, why might one person be more skilled in their actions than another? [50%]

Answer: Peoples might i) have lower noise i.e. a reduced coefficient of variance ii) be better at finding the optimal commands iii) have different body dynamics which affect the way noise alters the trajectory.

(b) Humans can adapt their reaching movements to a wide variety of externally imposed dynamic perturbations (e.g. tools or force fields).

(i) Briefly describe the difference between forward and inverse model learning under such perturbations.

Answer: The forward model learns to predict the consequences of the motor command on the movement of the arm in the force field whereas an inverse model learns to generate an appropriate motor command given a desired movement.

(ii) Describe the two different strategies people can employ when adapting to predictable dynamic perturbations (such as reaching while holding a tool) and unpredictable dynamic perturbations (such as when holding the string of

a kite on a gusty day).

Answer: There are two distinct strategies people employ when learning novel dynamic tasks. First, learning the forces required to compensate for an externally imposed perturbation (with an inverse model) people can directly counteract the perturbing influence. Alternatively, by co-contracting muscles, people can increase the stiffness of their arm and thereby reduce the displacement caused by an external force. With predictable dynamics people tend to employ a low-stiffness strategy whereas for unpredictable forces a stiffness strategy is used.

(iii) A robot is used to perturb a person's arm and after adaptation their arm movements become similar to the movements they made prior to the perturbation. How could you experimentally assess which of the two strategies in (b)(ii) the person has used? [50%]

Answer: Two mechanisms can be used to distinguish between stiffness (co-contraction) and compensation. First if the perturbation is unexpectedly turned off the change in movement path (after-effect) can be assessed. If there is no change this suggests that a stiffness control strategy is being used, whereas a large after-effect suggests a compensation strategy. Alternatively the electromyogram (EMG) from the muscle can be recorded and co-contraction assessed by determining to what extent opposing muscles are active.

3 This question is about the interplay of dendritic signal propagation and LTP induction in glutamatergic synapses.

(a) Just as axons, dendrites can have voltage-gated conductances, such as sodium and potassium channels, that allow the active propagation of electrical signals. Describe, for the cases when dendritic propagation is either active or passive, how the voltage spreads in time in the three main parts of a neuron (cell body, axon, and dendrite) following the generation of an action potential at the cell body. Assume the axon is unmyelinated. [10%]

Answer: The action potential appears as a large and rapid peak in the membrane potential at the site of its generation, the soma, or more precisely the axon initial segment, followed by smaller and slower hyperpolarization. This signal propagates smoothly along the axon as a travelling wave, such that roughly the same wave form appears at increasingly larger delays at successive points along the axon. Similar spreading of the action potential occurs in an active dendrite from the soma towards the tips of the dendrite. In a passive dendrite, the originally peaky wave form quickly becomes smeared out such that at successive points along the dendrite we see increasingly delayed and elongated responses with decreasing amplitude.

(b) An experiment is performed in which a single presynaptic cell is stimulated so that it fires an action potential. No other presynaptic cells fire at the same time. The experimenter controls whether the postsynaptic cell fires or not and whether signal propagation in the dendrite is passive or active (by blocking or unblocking sodium channels). When the postsynaptic cell fires, it happens at around the same time as when the presynaptic cell fires. The synapse between the pre- and postsynaptic cell is close to the tip of the dendrite (far from the soma). In each of the cases in Table 1 explain why LTP did or did not occur. Support your answer by describing the sequence of cellular-molecular events that happen at the stimulated synapse, and how the membrane potential changes in the postsynaptic cell at the synapse. [30%]

	presynaptic cell fires	**postsynaptic cell fires**	**dendritic signal propagation**	**LTP induced**
case 1	yes	no	passive	no
case 2	yes	yes	passive	no
case 3	yes	yes	active	yes

Table 1

(TURN OVER for continuation of Question 3

Answer: In all three cases, glutamate was released into the synapse by the presynaptic cell, it bound to AMPA and NMDA receptors on the postsynaptic cell. Glutamate binding to AMPA receptors opened the associated sodium channel and caused a small local depolarisation (an EPSP) there. However, this small depolarisation which is due to only a single presynaptic cell firing is insufficient to remove the Mg^{2+} block in NMDA receptors by itself. Thus, in case 1, no LTP induction occurs.

In case 2, the postsynaptic cell also fires, but because dendritic propagation is passive, the action potential does not reach the synapse in its original form, only as a very low-amplitude and sluggish response, and therefore the membrane potential at the synapse is still not sufficiently high to remove the Mg^{2+} block in NMDA receptors. Thus, in case 2, no LTP induction occurs.

In case 3, the actively backpropagating action potential causes a large enough depolarisation at the synapse such that the Mg^{2+} block is removed in the NMDA receptors, and since this is near-simultaneous with the presynaptic cell releasing glutamate, the NMDA receptors open and let Ca^{2+} into the cell which then initiates the cascade leading to LTP induction.

(c) In a different experiment, dendritic propagation is active in the postsynaptic cell, the cell's firing is not controlled by the experimenter but by the synaptic inputs it receives, and we record whether it fired or not. Two groups of presynaptic cells, A and B, that have synapses at two distinct dendritic sites on the postsynaptic cell, are stimulated. The locations of group A and B synapses are shown in Fig. 1. Group B synapses are stimulated shortly after group A synapses (if at all). No other presynaptic cells fire.

Fig. 1

In each of the cases in Table 2 explain why LTP did or did not occur. Support your answer by describing the sequence of cellular-molecular events at group A and B synapses, and how the membrane potential changes in the postsynaptic cell at each dendritic site. [60%]

	% of cells in group A stimulated	% of cells in group B stimulated	post-synaptic cell fires	LTP induced for group A	LTP induced for group B
case 1	10	0	no	no	no
case 2	50	0	no	yes	no
case 3	100	0	yes	yes	no
case 4	10	10	no	no	no
case 5	50	10	no	yes	no
case 6	100	10	yes	yes	yes

Table 2

Answer: In all cases, whichever cells are stimulated, glutamate is released in the corresponding synapses and binds to AMPA and NMDA receptors at the corresponding dendritic sites on the postsynaptic cell.

In case 1, the local depolarisation at site A is small because only very few cells have been activated and thus it does not exceed the threshold for removing the Mg^{2+} block from the NMDA receptors there, hence no LTP occurs there. As the depolarisation from site A propagates (actively) to the soma, it also does not reach the threshold for action potential generation there, so no action potential is generated. Group B synapses are not stimulated, so no local depolarisation happens there, glutamate is also not released, so there is no reason for NMDA receptors to open, and thus no LTP occurs there either.

In case 2, the local depolarisation at site A exceeds the threshold for removing the Mg^{2+} block from the NMDA receptors there, hence LTP occurs there. However, as the depolarisation from site A propagates to the soma it still does not reach the threshold for action potential generation there, so everything else is unchanged (no LTP at site B).

In case 3, even more depolarisation happens at site A, this exceeds the threshold for removing the Mg^{2+} block from the NMDA receptors there, hence LTP occurs there. In this case as the depolarisation from site A propagates to the soma it exceeds the threshold for action potential generation there, so an action potential is generated which propagates back to site B. However, no glutamate was released there, so NMDA receptors can't open, and so no LTP occurs there.

Case 4 is like case 1, the same thing happens at both site A and B, depolarisation remains subthreshold for removing the Mg^{2+} block and no LTP occurs at either site.

Case 5 is like case 2, LTP occurs at site A for the same reason, and although glutamate is released at site B, the local depolarisation still remains subthreshold (as in case 4), so for removing the Mg^{2+} block

and no LTP occurs there.

In case 6, LTP occurs at site A for the same reason as in cases 2,3, and 5, an action potential is generated as in case 3, and propagates back along both dendritic branches. Because glutamate is released in group B synapses, this together with the depolarisation caused by the backpropagating action potential which is sufficient to remove the Mg^{2+} block of the NMDA synapses, NMDA receptor-gated channels open, let Ca^{2+} into the cell there and LTP is induced.

4 This question refers to a modified secondary conditioning experiment in an animal. In this experiment, training involves two conditional stimuli (CS1 and CS2) and one unconditional stimulus (US). In phase 1, CS1 is paired with the US such that in each trial CS1 is followed by the US, after a short delay. In phase 2, CS2 is paired with CS1 such that in each trial CS2 is followed by CS1, after a short delay, which in turn is followed by the US, after another short delay.

(a) How is this paradigm different from a standard secondary conditioning paradigm? [5%]

Answer: In a standard secondary conditioning paradigm the US is not presented in phase 2.

(b) Describe how the animal responds to CS1 and CS2 presented separately, before phase 1, after phase 1, and after phase 2. [10%]

Answer: Before phase 1, the animal only responds to the US, but not to CS1 and CS2. After phase 1 it also responds to CS1 but still not to CS2. After phase 2, it also responds to CS2.

(c) Describe the time course of the activation of dopamine cells within a trial, according to the temporal difference learning rule, before phase 1, during phase 1, after phase 1, during phase 2, and after phase 2. [25%]

Answer: Before phase 1, dopamine cells fire at the presentation of the US. During phase 1, dopamine cells gradually shift their firing to the time of CS1 presentation. After phase 1 (and thus before phase 2), dopamine cells fire at the presentation of CS1. During phase 2, dopamine cells gradually shift their firing to the time of CS2 presentation. After phase 2, dopamine cells fire at the presentation of CS2.

(d) A new type of "value" neuron is discovered in the brain, that fires proportionally to the predicted total future reward within a trial, as computed by the temporal difference learning rule. Describe the time course of the activation of such a neuron within a trial before phase 1, during phase 1, after phase 1, during phase 2, and after phase 2. [30%]

Answer: Before phase 1, value neurons don't fire. During phase 1, value neurons fire in a sustained manner between the time of dopamine cell firing (which now happens before the US) and the presentation

of the US. After phase 1 (and thus before phase 2), value neurons fire in a sustained manner between the presentation of CS1 and the presentation of the US. During phase 2, value neurons fire in a sustained manner between the time of dopamine cell firing (which now happens before CS1) and the presentation of the US. After phase 2, value neurons fire in a sustained manner between the presentation of CS2 and the presentation of the US.

(e) In simple classical conditioning experiments, catch trials can be used after training is finished, to demonstrate negative prediction errors in neural signals. Using catch trials, how would you demonstrate negative prediction errors in this modified secondary conditioning experiment, and what is the time course of the activity of dopamine and value-representing neurons in these trials? [30%]

Answer: After training, either CS1 or US, or both could be omitted to obtain negative prediction errors.

When the US is omitted, dopamine neurons will change their firing such that their firing will be suppressed (drops below baseline) at the time the US should have occurred. Value neurons will not change their firing from their normal behaviour: they will fire in a sustained manner between the presentation of CS2 and when the presentation of the US should happen.

When CS1 is omitted (but the US isn't), dopamine neurons will change their firing such that firing will be suppressed (drops below baseline) at the time CS1 should have occurred, and then will have a peak in their firing at the time the US occurs (because the absence of CS1 signals the absence of the US so there is a positive surprise that the US still arrives). Value neurons will fire in a sustained manner between the presentation of CS2 and CS1, but not between CS1 and US.

When both CS1 and US are omitted, dopamine neurons will change their firing such that firing will be suppressed (drops below baseline) at the time CS1 should have occurred. There will be no change in their firing at the time of the US (because the absence of the US is predicted by the absence of CS1). Value neurons will fire as in the previous case: they will fire in a sustained manner between the presentation of CS2 and CS1, but not between CS1 and US.

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