

EGT2  
ENGINEERING TRIPOS PART IIA

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Monday 24 April 2017 14:00 to 15:30

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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) David Marr's three levels of understanding.

Answer: Marr proposed to study vision on three different levels:

- Computational.** What is vision about? How can we formalise the problem that our visual systems is solving? What is the mathematical nature of the problem at hand?
- Algorithmic/Representational.** What is the algorithm (e.g., recipe) that our brain uses for vision? What data representations does it use?
- Implementation.** How is the algorithm implemented in the dynamics of brain networks?

These levels of analysis are applicable more broadly to neuroscience research.

(ii) The two-alternative forced choice detection task-design and the associated psychometric function.

Answer: In a 2AFC detection task, the subject is presented with two stimuli either simultaneously or in sequence, only one of which contains a salient item to be detected. The subject must report whether the salient item occurred in the first stimulus, or in the second. The experimenter will vary the intensity of the salient item, and plot the percentage of correct responses against stimulus intensity. This is called the psychometric curve; it has a sigmoid-like shape, starting at 50% correct for very low intensities (chance level), and increasing smoothly to near 100% correct for very high intensities. The detection threshold is usually defined as the intensity that yields 75% of correct answers. [30%]

(b) This question is about the action potential.

(i) Explain why, in the Hodgkin-Huxley model, voltage-gated ion channels are necessary for the generation of an action potential by injection of a step current. [20%]

Answer: Without voltage-dependence in the ion channels, the dynamics of the membrane potential  $V$  would be purely linear, with the following effective form:

$$C \frac{dV}{dt} = -g_{\text{eff}}(V - V_{\text{rest}}) + I_{\text{input}}.$$

This means that the dynamics of the voltage implements a simple low-pass filter of the step input, and therefore cannot generate an action potential.

(ii) Describe the key stages responsible for the action potential upstroke. [25%]

Answer: The input current starts to depolarize the cell (increase the membrane potential  $V$ ), which begins to open the “n” (potassium) and “m” (sodium) gates. Because the voltage is initially much closer to the resting potential for potassium than it is to the resting potential of sodium, sodium ions flow and cause further increase in  $V$ . This activates both channels even more, but sodium is much faster than potassium, leading for further, steep growth of  $V$ . This is the positive feedback underlying the action potential upstroke.

(iii) Figure 1 below shows the membrane potential of a neuron modelled with Hodgkin & Huxley's equations, in response to a pair of consecutive, 2 ms-long pulses of input current, separated by either 3 ms (CASE A, top), or 1 ms (CASE B, bottom; the membrane potential shown in A is reproduced in B as a dashed line to allow comparison). Explain why only one action potential is elicited in CASE B, and why the membrane potential eventually decays more slowly towards rest in CASE B compared to CASE A, in spite of the fact that the input is withdrawn earlier.

[25%]

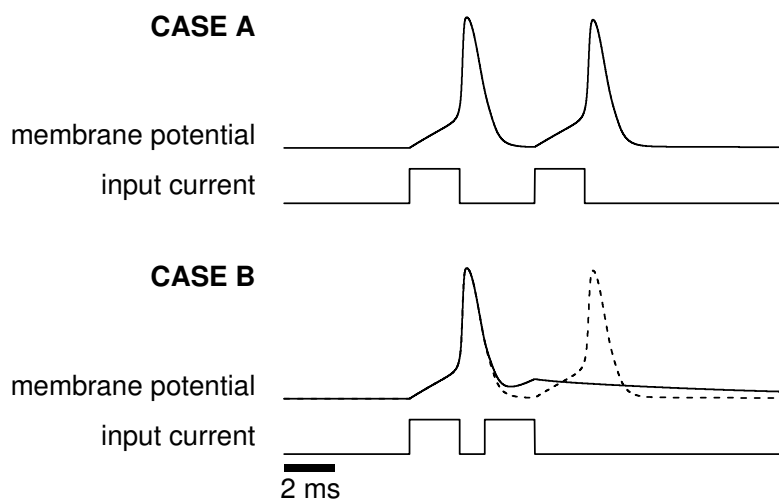


Fig. 1

Answer: The first action potential is terminated by the inactivation of the sodium channels as  $V$  becomes closer to the reversal potential for sodium (the “h” gate). The net input current is then dominated by a strong potassium current, so  $V$  is quickly repolarized near the resting potential for potassium. In CASE A, an other attempt at eliciting an action potential is made *after* the  $h$  gate has had time to de-inactivate, and is therefore successful (at the onset of the second current pulse, all dynamic variables are back to where they were at the beginning of the first action potential). In CASE B, the attempt is made while the sodium channels are still inactivated, which annihilates the opening of the “m” sodium gates and therefore prevents the upstroke – hence the absolute refractory period seen here. Moreover, in case A the return to rest following the second action potential is sped up by the potassium current; in case B, potassium channels have not had a chance to open completely (because  $V$  remained too low), and so the return to rest occurs “passively” on the timescale of the resting membrane time constant.

- 2 (a) Explain why perception is fundamentally different from sensation and support your argument with one example. [20%]

Answer: Sensation is merely the relaying of information about the environment through sensors (e.g. photoreceptors). Perception, on the contrary, is an active process of constructing interpretations of those sensory inputs. In essence, it is an inference problem, whereby the brain infers the state of the world based on noisy and ambiguous observations. For example, two people of the same size standing at the two far corners of the “Ames room” are strongly perceived as being of very different sizes. This shows that our brain makes up percepts that are not real, and indeed percepts that may even conflict with information gathered from stereoscopic vision in this case.

- (b) Outline the formalisation of perception as probabilistic inference, carefully explaining the various mathematical quantities involved. [20%]

Answer: If we denote by  $s$  the particular set of inputs that the sensory periphery sends to the brain, and by  $x$  the state of the world, then perception can be formalised as computing the posterior distribution  $p(x|s)$ . This can be done by combining information about the senses (e.g. the physical laws of transduction that they obey, and their reliability), formalised as the likelihood function  $p(s|x)$ , and expectations (what could be said about the state of the world before even observing anything), formalised as a prior distribution  $p(x)$ . Bayes’ theorem then dictates  $p(x|s) \propto p(s|x)p(x)$ .

- (c) Look at Fig. 2 below. Although the drawing is entirely flat, the first three disks are commonly perceived as bulging outwards, and the last three disks look as if they have been carved. Explain why we perceive depth where there really is none, and why the perception of depth is different in the two cases. [20%]



Fig. 2

Answer: This illusion comes from various priors, namely i) flat objects are rare, ii) light usually comes from above, and iii) light has a different, specific impact on surface luminance gradients in objects that are either convex or concave w.r.t. the light source. If the circular objects shown here were hanging on a wall, with a light source on the ceiling, protruding disks would show a luminance gradient similar to that of the first 3 disks, while carved-in disks would show the opposite gradient. Stereoscopic vision is

ambiguous/noisy enough that, although it does indicate that the drawing is flat, it does not really rule out other 3D interpretations that have higher prior probability.

(d) An experimenter discovers a new type of sensory neuron under the skin. They record its membrane potential  $V(t)$  in a variety of conditions, and find that its temporal average  $\bar{V} = \langle V(t) \rangle_t$  exactly encodes the room temperature  $\theta$  according to

$$\theta = k \times (\bar{V} + 80 \text{ mV})$$

with a gain  $k = 2 \text{ }^\circ\text{C/mV}$ . Here, the notation  $\langle x(t) \rangle_t$  denotes temporal averaging, i.e.

$$\langle x(t) \rangle_t = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T x(t) dt.$$

(i) What recording technique do you think the experimenter may have used? [10%]

Answer: To record membrane potential fluctuations, they must have performed an intracellular recording, e.g. by inserting a sharp glass microelectrode into the cell with minimum damage to the membrane.

(ii) The experimenter records  $V(t)$  over a very long time period, at constant room temperature. They compute its autocovariance function  $A(\tau)$  defined as

$$A(\tau) = \langle (V(t) - \bar{V})(V(t + \tau) - \bar{V}) \rangle_t$$

This is plotted in Fig. 3 as a function of the time lag  $\tau$ . Did this sensory neuron fire action potentials in this recording? Explain your reasoning. [5%]

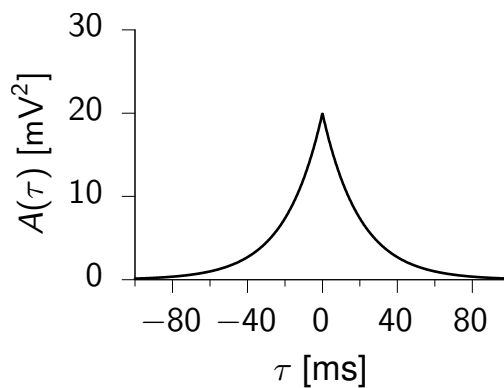


Fig. 3

Answer: No. If this sensory neuron did fire action potentials, there would be a very sharp peak in the autocovariance function around  $\tau = 0$ , due to the occurrence of brief and large depolarisations. There is no such peak in the graph.

(iii) Based on Figure 3, derive an approximation of the duration over which you would need to observe the membrane potential of this neuron to be able to estimate the room temperature with an expected squared error less than  $0.25 \text{ }^\circ\text{C}^2$ .

Hint: you may start by approximating the time lag  $\tau$  at which successive values  $V(t)$  and  $V(t + \tau)$  are effectively uncorrelated, and approximate the fluctuations of  $V$  by a staircase-like signal with steps of duration  $\tau$ . [25%]

Answer: Let  $\theta$  denote the true room temperature. Consider a recording of duration  $T$ . To form an estimate  $\hat{\theta}$  of  $\theta$ , we need an estimate  $\hat{V}$  of the true mean membrane potential  $\bar{V}$ . We obtain this estimate through sample averaging:

$$\hat{V} = \frac{1}{T} \int_0^T V(t) dt$$

Note that, due to the gain  $k = 2$ , the expected squared error we make with our estimate of  $\theta$  is  $k^2$  times the expected squared error in the estimation of  $\bar{V}$ . We now seek to compute the latter error. According to the measured autocovariance function shown in the graph, membrane potential fluctuations have variance  $\sigma_V^2 \approx 20 \text{ mV}^2$  (the peak of the autocovariance function), and samples separated by more than  $\tau = 60 \text{ ms}$  are approximately uncorrelated. One can approximate the fluctuations of  $V$  by a staircase-like signal which changes only every  $\tau$ . Thus, one can estimate  $\bar{V}$  based on  $N$  samples gathered over a duration  $T = N\tau$  by:

$$\hat{V} = \frac{1}{N} \sum_{\ell=1}^N V_\ell$$

with  $V_\ell \equiv V(\ell\tau)$ . The expected squared error is:

$$\begin{aligned} E(N) &= \left\langle \left( \hat{V} - \bar{V} \right)^2 \right\rangle \\ &= \left\langle \left[ \frac{1}{N} \sum_{\ell=1}^N (V_\ell - \bar{V}) \right] \cdot \left[ \frac{1}{N} \sum_{\ell'=1}^N (V_{\ell'} - \bar{V}) \right] \right\rangle \\ &= \frac{1}{N^2} \sum_{\ell} \sum_{\ell'} \langle (V_\ell - \bar{V})(V_{\ell'} - \bar{V}) \rangle \\ &= \frac{1}{N^2} \sum_{\ell} \sum_{\ell'} \sigma_V^2 \delta_{\ell\ell'} \\ &= \frac{\sigma_V^2}{N} \end{aligned}$$

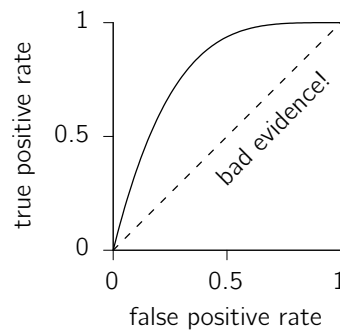
For this error to be smaller than  $0.25/4 \text{ }^\circ\text{C}^2$ ,  $N$  must be larger than 320, meaning that one must observe the membrane potential fluctuations over  $320 \times 60 \text{ ms} \approx 20 \text{ s}$ .

3 (a) Explain, with the help of one concrete example, why optimal decision-making often requires taking into account one’s uncertainty. In particular, what kinds of uncertainty must be considered? [20%]

Answer: Imagine the following game. A gold coin is hidden in one of my two closed hands. You have two choices: i) pick one of my hands – if it holds the coin, the coin is yours, but if it’s empty, you must give me 3 gold coins instead – or ii) opt out of the game and nothing happens. Which would you choose? You *might* get *some* information as to which hand holds the coin by comparing their sizes. If this clue is weak, your uncertainty about the winning hand is so great that you have near-equal probability of winning and losing, i.e. an expected negative return of -2 coins if you choose to play. You should therefore opt out. If, on the other hand, you estimate that the gold coin is 90% more likely to be in my left hand, then your return is  $0.9 - 3 \times 0.1 = 0.6$  gold coins and you might want to play. More generally, optimal decision making requires incorporating uncertainty about both the state of the environment and the way motor actions affect it.

(b) Describe the Receiver Operating Characteristic (ROC) curve. [20%]

Answer:



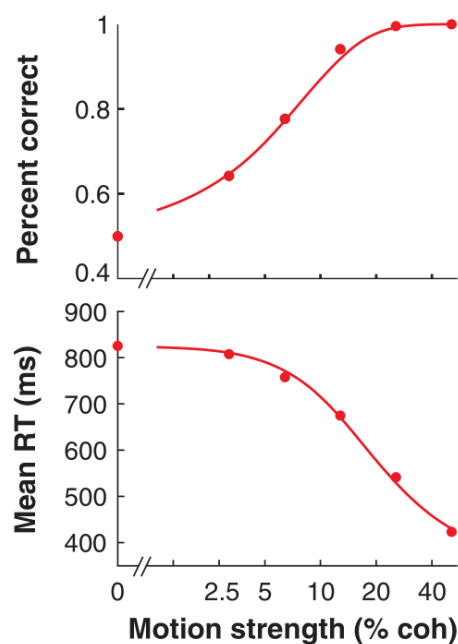
The ROC curve is a way of plotting performance in a binary classification task, a paradigmatic example of simple decision making. Scalar evidence  $s$  is provided for either of two alternatives, and a decision is made as to which class the evidence belongs to by setting a threshold  $\theta$ , attributing the evidence to class 1 if  $s > \theta$ , or to class 2 otherwise. The ROC curve (solid line) plots the “true-positive rate” (y-axis) against the “false-positive rate” (x-axis; also called “false-alarm” rate) for different values of the threshold  $\theta$ . The curve varies smoothly as  $\theta$  changes, increasing above the main diagonal from the bottom-left corner up to the top-right corner. Detection performance is usually measured as the area between the curve and the main diagonal (dashed line).

(c) A monkey engages in the classical random dot motion discrimination task. A

circular field of moving dots is presented on the display, with a fraction  $c$  of the dots moving coherently either to the left or to the right (this direction is set randomly with equal probability at the beginning of each trial). The remaining  $(1 - c)$  fraction of the dots move in random, incoherent directions. The monkey must decide whether coherent motion occurs to the left or to the right, and report its decision whenever ready.

- (i) Sketch the percentage of correct answers, as well as the mean reaction time, both as a function of  $c$ , for a typical monkey in this task. [20%]

Answer:



- (ii) What behavioural evidence exists in support of monkeys temporally accumulating and integrating evidence about motion direction? [20%]

Answer: Evidence has been gleaned from a variant of this task in which the monkey is forced to stare at the dots for a set amount of time  $t$ , which is varied across trials. Performance increases with  $t$ , which suggests evidence accumulation. More specifically, the discrimination threshold, defined here as the motion coherence level that yields 82% correct, has been shown to decrease as  $1/\sqrt{t}$ . This is the same relationship as that predicted by models involving accumulation of independent samples of noisy evidence obtained in each successive moment (e.g. the drift-diffusion model for continuous time, or the sequential probability ratio test for discrete time).

- (iii) Explain the drift-diffusion formalism typically employed to model the behaviour of monkeys in this task. Your answer should include:

- an equation describing the dynamics of the decision variable, with a



description of each term and other model parameters,

- how this equation is used to model decision making,
- a description of the behavioural quantities that this model can predict.

[20%]

Answer: The dynamics of a decision variable  $x$  follows a drift-diffusion equation

$$dx = \mu dt + dW$$

where  $\mu = kc$  is linearly related to the coherence level  $c$ , and  $dW$  is a Wiener process (or Brownian motion). The model then “decides” for alternative 1 as soon as  $x$  crosses some threshold (or “bound”)  $+B$  from below, or decides for alternative 2 as soon as  $x$  crosses  $-B$  from above. The initial condition  $x(t = 0)$  is set to some constant  $D$  which models the subject’s bias towards either choice 1 ( $D > 0$ ) or choice 2 ( $D < 0$ ). The model’s free parameters are  $k$ ,  $B$  and  $D$ . The model can be simulated (or theoretically analysed) to predict decision probabilities (left and right choices), the whole psychometric curve, and the distributions of reaction times.

- 4 (a) Using an evolutionary argument, explain why learning and adaptation are important for an animal species. [20%]

Answer: Without learning or adaptation, an organism's genome would entirely determine its behavioural repertoire (i.e. the mapping from sensory inputs to motor outputs), which itself determines the organism's fitness (the ability to pass one's genome on to the next generation). In a non-stationary environment, the fitness associated with the population's behavioural repertoire might quickly deteriorate, resulting in the death of the whole population, i.e. the loss of the species. With learning, the same genome can give rise to a large space of behaviours, and moreover this behaviour can be searched and optima can be found within a lifetime, i.e. much faster than evolutionary timescales. Thus, non-stationary environment can be adapted to quickly through learning, and more slowly thereafter through classical genetic evolution.

- (b) Explain how calcium ions are involved in the process of synaptic transmission. [20%]

Answer: When an action potential arrives at the axonal bouton, the resulting depolarisation causes voltage-gated calcium channels to open, and calcium ions to flow in on the presynaptic side. Calcium entry causes the fusion of neurotransmitter vesicles. Then, by a series of other events in which calcium no longer plays any role, postsynaptic depolarisation (or hyperpolarisation) occurs.

- (c) Figure 4 below shows the current-voltage (I-V) relationships in two types of ion channels, one bearing NMDA ionotropic glutamate receptors, the other bearing non-NMDA receptors.

- (i) Which of the two curves corresponds to NMDA receptors? What are the reversal potentials of these two ion channels? [10%]

Answer: The dashed one corresponds to NMDA. The reversal potential of a channel is the voltage at which no current flows – the graph indicates that the reversal potential is 0 mV in both cases.

- (ii) The dashed curve is strongly nonlinear for negative membrane potentials. Explain the molecular mechanism that gives rise to such a nonlinearity. [10%]

Answer: The nonlinearity arises due to magnesium ions from the extracellular space blocking the passage of other cations through the ion channel, yielding near-zero channel current when the membrane potential is near its resting value. Only when the membrane potential increases do  $Mg^{2+}$  ions get dislodged, allowing the flow of sodium, calcium and potassium ions in and out of the cell, and yielding a current which is near-linear in the voltage.

- (iii) Explain how NMDA receptors can be used as pre- and postsynaptic coincidence detectors. [20%]

Answer: NMDA receptors will only let  $\text{Ca}^{2+}$  ions into the cell provided i) glutamate has bound onto those receptors, opening the channel, and ii) concurrently, the postsynaptic membrane potential has increased sufficiently such to stop blockage by  $\text{Mg}^{2+}$  ions. Thus, the influx of  $\text{Ca}^{2+}$  through NMDA channels signals the coincidence of a presynaptic action potential and a strong postsynaptic depolarization (which may be due to a backpropagating action potential, or a synchronous volley of excitatory postsynaptic potentials in nearby synapses).

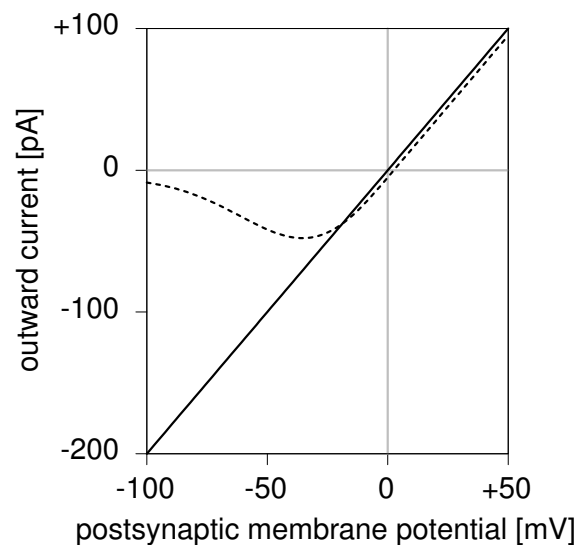


Fig. 4

(d) List three types of preparations that can be used to study synaptic plasticity in the hippocampus. For each, give one of the main limitations. [10%]

Answer: 1. Slices *in-vitro*: neurons die rapidly, inputs are trimmed. 2. Tissue culture *in-vitro*: the network keeps transforming, different extracellular environment. 3. *In-vivo*: often necessitates anaesthesia which alters brain dynamics, and otherwise difficult to record intracellularly in a behaving animal.

(e) List one pre-synaptic and one post-synaptic biophysical properties of a synapse that determine its transmission efficacy and are altered by long-term potentiation. [10%]

Answer: 1. Probability of presynaptic neurotransmitter release; 2. Density of receptors on the postsynaptic side.

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## Comments on Questions

### Q1 General questions and the Hodgkin-Huxley model

Most popular question: attempted by 52/54 candidates (mean 14/20, min 7/20, max 19/20).

David Marr's "three levels of understanding" (a.i) were generally well discussed (with a couple of rather entertaining answers). In (a.ii), many described the 2AFC *discrimination* task, as opposed to the 2AFC *detection* task, or failed to realise that "chance level" is not at 0% correct but at 50% correct. The rest of the question was mostly about the action potential. Most candidates failed to explain the necessity of voltage-gated ion channels for the generation of action potentials (b.i); instead, they explained sufficiency. The key stages of the action potential upstroke were generally well explained (b.ii), although many omitted to discuss why sodium wins over potassium initially.

### Q2 Perception

Least popular question: attempted by 25/54 candidates (mean 14/20, min 9/20, max 20/20).

Parts (a-c) posed no real problem. In (d), many candidates erroneously concluded that the neuron had fired action potentials, concluding on the basis that the membrane potential ( $V_m$ ) showed some temporal variability, but neglecting the fact that i) nothing in the question suggested that  $V_m$  should be temporally constant at constant temperature, and the fact that if action potentials were the only source of  $V_m$  variance, the decay time of the  $V_m$  autocovariance (provided) would have been much shorter. The more quantitative aspect of the question (part d.iii) was attempted by few, and correctly answered by even fewer.

### Q3 Decision making

Attempted by 36/54 candidates (mean 14/20, min 9/20, max 19/20).

In (a), many gave an example that was more about explaining why there *is* uncertainty, rather than *why this uncertainty must be taken into account* for optimal decision making. The receiver operating characteristic curve was mostly well described, though some candidates failed to indicate that different points correspond to different decision thresholds. In (c.i), most omitted to give even a rough scale for the mean reaction time as a function of the stimulus coherence. In (c.ii), some gave physiological evidence (i.e.

evidence from neural recordings), as opposed to behavioural evidence. In (c.iii), too many candidates omitted to mention the behavioural quantities captured by the drift-diffusion model.

#### **Q4** Synaptic transmission and plasticity

Very popular, and very well answered, question: attempted by 49/54 candidates (mean 15/20, min 9/20, max 20/20).

Surprisingly, part (a) turned out to be the least well-answered sub-question. Many candidates gave rather hand-wavy arguments about how learning can help a species survive, but there was no rigorous logic. Part (c.i) gave rise to a few curious answers regarding the reversal potentials. Part (d) posed no problem. In (e), a few listed phenomena (e.g. “increased EPSP size”) rather than biophysical properties (e.g. density/number of postsynaptic AMPA receptors).