MA4G4

THE UNIVERSITY OF WARWICK

FOURTH YEAR EXAMINATION: SUMMER 2016

INTRODUCTION TO THEORETICAL NEUROSCIENCE

Time Allowed: **3 hours**

Read carefully the instructions on the answer book and make sure that the particulars required are entered on each answer book.

Calculators are not needed and are not permitted in this examination.

ANSWER 4 QUESTIONS.

If you have answered more than the required 4 questions in this examination, you will only be given credit for your 4 best answers.

The numbers in the margin indicate approximately how many marks are available for each part of a question.

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1. Derivation of the Goldman current equation

An ionic species, of concentration N_{in} inside the neuron and N_{out} outside, diffuses through membrane channels of length a and cross-sectional area σ. Each ion carries a total charge zq where q is a constant and z an integer. The potential inside the cell is V_{in} and outside is V_{out} so the membrane potential is $V_{\mathrm{m}} = V_{\mathrm{in}} - V_{\mathrm{out}}$. The potential $V(x)$ and concentration $N(x)$ are functions of position x within the channel. Steady-state conditions are assumed so that the flux J of ions per second per unit area of open channel is constant. This flux takes the form

$$J = -\mu q V_{\mathrm{T}} \left(N \frac{z}{V_T} \frac{dV}{dx} + \frac{dN}{dx} \right) \tag{1}$$

where μ and V_{T} are constants.

a) Use equation (1) under conditions of zero flux to show that

$$E = \frac{V_{\mathrm{T}}}{z} \log \left(\frac{N_{\mathrm{out}}}{N_{\mathrm{in}}} \right) \tag{2}$$

is the equilibrium potential for this ionic species. **[5]**

b) From now on we return to the non-zero flux case. The density of channels in the cell membrane is ϱ. What is the area of open channels per unit area of membrane? Write down an equation relating the membrane current I (dimensions of charge per second per unit area of membrane) to the flux J. **[2]**

c) Assume that the potential changes linearly from the inside $x = 0$ to the outside $x = a$ of the membrane. Remember that the flux is in a steady state and therefore constant throughout the channel. Use the flux equation (1) together with the relation of J to I to show that

$$I \;=\; \gamma V_{\mathrm{m}} \left(\frac{N_{\mathrm{out}} - N_{\mathrm{in}} e^{zV_{\mathrm{m}}/V_{\mathrm{T}}}}{1 - e^{zV_{\mathrm{m}}/V_{\mathrm{T}}}} \right) \tag{3}$$

and give the proportionality constant γ in terms of membrane parameters. **[10]**

d) For weak deviations around the equilibrium potential E the voltage dependence of the current I will be approximately linear. Linearise the current equation (3) around E by substituting in the variable $v = V - E$. Show that to leading order in v the current is $I = gv$ and give the conductance g in terms of the constants γ, N_{out} and N_{in} only. You will need to use equation (2) for the equilibrium potential. **[8]**

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2. Paired-pulse synaptic correlations

An experimental protocol for probing synaptic dynamics is to examine the postsynaptic response to a pair of presynaptic action potentials (APs) separated by some time interval. This method can distinguish between depression and facilitation (when subsequent amplitudes increase due to an increasing release probability).

Let p_1 be the probability of neurotransmitter release given that a vesicle is present before the first AP, and p_2 the probability of release given that a vesicle is present before the second AP (note that these are slightly different definitions from those in the course) and let f be the probability that an empty release site is restocked during the period between the two presynaptic APs. Assume that release sites are stocked with a vesicle before the first AP. The notation $\langle X \rangle$ denotes the expectation of X.

In parts (a – c) we will consider synaptic depression with $p_1 = p_2 = p$ whereas in parts (d – e) we will consider facilitation where $p_2 > p_1$.

a) Consider a single contact that can be either occupied by a vesicle or empty. Let x be the binary variable signifying a release ($x = 1$) at the first AP, and y the binary variable signifying release at the second AP. By considering all outcomes provide the forms of $\langle(1-x)(1-y)\rangle$, $\langle(1-x)y\rangle$, $\langle x(1-y)\rangle$ and $\langle xy\rangle$ in terms of $p_1 = p_2 = p$ and f. Verify that these expectations sum to unity. **[4]**

b) Calculate $\langle x\rangle$ and $\langle y\rangle$ and demonstrate that $\langle y\rangle < \langle x\rangle$. **[4]**

c) We now consider the case of n independent release sites, each as described in part (a). The summed release events from the first AP are written $X = \sum_{m=1}^{n} x_m$ and similary for Y for the second AP. Use your results from parts (a-b) to express the correlator

$$\langle XY\rangle - \langle X\rangle\langle Y\rangle \tag{4}$$

in terms of n, p and f. Demonstrate that release events are anti-correlated. **[8]**

d) We now consider the case of facilitation where $p_2 > p_1$. Find the condition on p_2 such that $\langle y\rangle > \langle x\rangle$. Verify that $p_2 > p_1$ is not a sufficient condition for the second post-synaptic amplitude to be larger than the first. **[4]**

e) Express the correlator (Eq. 4) as a function of p_1, p_2, n and f for the case of facilitation and demonstrate that it is still negative in this case. **[5]**

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3. Soma and dendrite model with two synapses

The cable considered here has uniform radius a, and a capacitance C and conductance g per unit area. The voltage is measured from the resting potential. The resistivity of the ionic medium within the cable is r_{a} (units of resistance $\times$ length).

a) By considering a short length of cable, derive the axial current equation and the cable equation, respectively:

$$I = -\frac{\lambda}{R_\lambda}\frac{\partial v}{\partial x} \quad \text{and} \quad \tau\frac{\partial v}{\partial t} = \lambda^2\frac{\partial^2 v}{\partial x^2} - v$$

and give forms for λ, R_λ and τ in terms of the cable parameters. **[7]**

b) Provide two independent solutions of the cable equation in the steady state. **[2]**

c) Consider a dendrite of length L with a voltage that is at rest ($v = 0$) at $x = 0$. At the end ($x = L$) of the dendrite there is an excitatory synapse with a reversal potential $\mathcal{E}_e$ measured from rest and a conductance G_e. The synapse is kept permanently open by the action of a drug and so the system is in the steady state. Provide the solution for the voltage as a function of x in this dendrite and calculate the axial current flowing at $x = 0$. **[8]**

d) Now consider a neuronal model that has a soma of total membrane resistance R_{s} receiving an inhibitory synapse of reversal potential $\mathcal{E}_{\mathrm{i}}$ and conductance G_{i} that is kept permanently open by the action of a drug. Also attached to the soma is a dendrite of length L with an excitatory synapse at the end, as described in part (c). Write down an equation for the steady-state somatic voltage v_{s} in terms of the somatic parameters, the inhibitory synaptic parameters and the current I_0 flowing into the dendrite. **[3]**

e) The excitatory and inhibitory synaptic strengths are such that the somatic voltage is at rest. Show that the ratio of synaptic reversal potentials

$$-\frac{\mathcal{E}_{\mathrm{e}}}{\mathcal{E}_{\mathrm{i}}} = \frac{G_{\mathrm{i}}}{G_{\mathrm{e}}}\left(R_\lambda G_{\mathrm{e}} \sinh(L/\lambda) + \cosh(L/\lambda)\right)$$

achieves this balance. **[5]**

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4. Models of spiking neurons

In parts (a-b) of this question the quadratic integrate-and-fire model is considered which obeys the equation

$$\frac{dv}{dt} = I + qv^2 \tag{5}$$

where $q > 0$ and I is an applied current. If the voltage is sufficiently positive it will run off to infinity in finite time. A spike is then registered and the voltage is re-inserted at minus infinity, from which it will rapidly return to finite voltages.

In question parts (c – e) we imagine that a new kind of neuron has just been discovered. This can emit positive spikes, which occur if the voltage crosses some positive threshold; however, it can also emit negative spikes if the voltage crosses some negative threshold. A model is proposed that takes the following form

$$\frac{dV}{dt} = K + V(V^2 - A^2) \tag{6}$$

where K is the applied current and A is a constant. If the voltage goes to minus infinity then a negative spike is registered, if it goes to plus infinity then a positive spike is registered. After either event the voltage is reset to $V = 0$ from which the dynamics continue.

a) For $I < 0$ identify the fixed points of equation (5) and determine which are stable by linearising the equation around each fixed point. **[4]**

b) For the case $I > 0$ show that the firing rate of the neuron is

$$r = \frac{\sqrt{Iq}}{\pi}.$$

The integral $\int_{-\infty}^{\infty} dx/(1 + x^2) = \pi$ will be of use. **[6]**

c) We now consider the neuron defined by the cubic term in equation (6). For the case $K = 0$ identify the fixed points. Through linearisation identify which are stable and which are unstable. **[4]**

d) We now allow K to be non-zero. Give the lower K_- and upper K_+ bounds of the range of K for which the voltage has a stable resting potential. **[4]**

e) Consider a case where $K > K_+$ such that the neuron is unstable and fires positive spikes periodically. Using your result from part (b), or otherwise, calculate the formula for the firing rate when $K - K_+$ is small and positive. **[7]**

5. Synaptic fluctuations in a two-compartment model

A neuron with a voltage v and a time constant τ has always been subject to fluctuating synaptic drive

$$\tau \dot{v} = -v + \sigma\sqrt{2\tau}\xi(t) \qquad (7)$$

where σ is a constant and $\xi(t)$ is zero-mean, delta-autocorrelated white noise.

a) Solve equation (7) to express $v(t)$ in terms of a filter integral over $\xi(t)$. **[3]**

b) Prove that the autocorrelation $\langle v(t)v(t+T)\rangle = \sigma^2 e^{-|T|/\tau}$. HINT: consider $T > 0$ first and look for a symmetry argument for $T < 0$. **[4]**

c) This model is now generalised to account for the non-uniformity of voltage in large neurons by approximating the neuron as having two compartments at voltages v_1 and v_2. This two-compartment model obeys the equations

$$\begin{aligned} \tau \dot{v}_1 &= -v_1 + \gamma(v_2 - v_1) + \sigma\sqrt{2\tau}\xi_1(t) \\ \tau \dot{v}_2 &= -v_2 + \gamma(v_1 - v_2) + \sigma\sqrt{2\tau}\xi_2(t) \end{aligned}$$

where $\gamma > 0$ is a coupling constant between the two compartments, and $\xi_1(t)$ and $\xi_2(t)$ are independent, delta-autocorrelated white-noise processes. Write down differential equations for the voltage sum $S = v_1 + v_2$ and difference $D = v_1 - v_2$ bringing each of these equations into the form:

$$\tau_\mu \dot{\mu} = -\mu + \sigma_\mu\sqrt{2\tau_\mu}\xi_\mu(t)$$

with $\mu{=}S$ or D denoting the cases corresponding to the sum or difference variables, respectively. You will need to combine any sums of white noise processes that may arise into a single process. Identify ξ_S, ξ_D in terms of ξ_1 and ξ_2. Give τ_S, τ_D, σ_S, σ_D in terms of τ, γ and σ. **[8]**

d) Demonstrate that $\langle \xi_S(t)\xi_D(t+T)\rangle = 0$. **[2]**

e) Using the results derived in parts (a) and (b) for the one-dimensional case, or otherwise, derive the autocorrelation of the voltage sum $\langle S(t)S(t+T)\rangle$ and the autocorrelation of the difference $\langle D(t)D(t+T)\rangle$. What is $\langle S(t)D(t+T)\rangle$? **[5]**

f) Express v_1 in terms of S and D and use your results to show that the voltage autocorrelation $\langle v_1(t)v_1(t+T)\rangle$ is

$$\frac{\sigma^2}{2}\left(e^{-|T|/\tau} + \frac{1}{1+2\gamma}e^{-|T|(1+2\gamma)/\tau}\right).$$

[3]