MA4G4

THE UNIVERSITY OF WARWICK

FOURTH YEAR EXAMINATION: SUMMER 2014

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. GHK current equation

An ionic species, with concentration N_i interior to and N_e exterior to the neuron, diffuses through membrane-spanning channels each of which has length a and cross-sectional area σ. The ions carry a charge zq where q is a constant and z an integer. The voltages interior and exterior to the neuron are V_i and V_e, respectively, so that the membrane voltage is $V_m = V_i - V_e$. It can be assumed that the voltage varies linearly through the channel. The quantities μ and V_T are constants. The ionic flux through a channel may be written

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

and has units of ions per unit area of open channel per unit time. The density of channels in the cell membrane is ϱ.

a) Solve equation (1) under conditions of zero flux to derive Nernst's equation for the ionic equilibrium voltage E. **[4]**

b) Now consider a case where the flux is non-zero. Give the proportionality relation for the membrane current I (units: charge per second per unit area of membrane) and the flux J. Using this relation between J and I and under the assumption of voltage linearity described in the question preamble, solve equation (1) to derive the Goldmann current equation

$$I = Pqz^2 \frac{V_m}{V_T} \left(\frac{N_e - N_i e^{zV_m/V_T}}{1 - e^{zV_m/V_T}} \right) \tag{2}$$

and give an equation for the permeability P in terms of other constants. **[6]**

c) Consider a scenario where the neuron is permeable to Na^+, K^+ and Cl^- ions with permeabilities P_{Na}, P_K and P_{Cl}. By considering the voltage at which no net ionic current flows, derive the GHK equation for the resting voltage. **[7]**

d) We now return the current equation (2) and consider a scenario where the voltage is close to the reversal potential E given by Nernst's equation, so that we can write $V_m = E + v$ where v is small. In this limit the Goldmann current equation behaves approximately as $I \simeq g(V_m - E)$ with corrections of order v^2. By expanding the current equation to first order in v, and using Nernst's equation, provide a formula for g in terms of the quantities P, q, z, V_T, N_e and N_i only. **[8]**

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2. Cable theory

A neuron is modelled as a cylindrical cable of length L and uniform radius a that is closed at both ends. It has capacitance C and leak conductance g_L, both per unit area, and the resting potential of the leak current is E_L. The resistivity of the ionic medium within the cell 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

$$I = -\frac{\lambda}{R_\lambda}\frac{\partial V}{\partial x}, \qquad \tau\frac{\partial V}{\partial t} = E_L - V + \lambda^2\frac{\partial^2 V}{\partial x^2} \tag{3}$$

and give equations for λ, R_λ and τ in terms of the neuronal parameters. **[6]**

b) Show that the membrane resistance and axial resistance of a stretch of membrane of length λ are equivalent and equal to R_λ. Also, provide the general solutions of the steady-state cable equation for the voltage measured from rest $v = V - E_L$. **[5]**

c) We now consider a scenario where the neuron described above has two synapses: an excitatory synapse at $x = 0$ and an inhibitory synapse at $x = L$. These synapses have conductances G_e and G_i, respectively, and reversal potentials measured from E_L of $\mathcal{E}_e > 0$ and $\mathcal{E}_i < 0$. The synaptic channels are kept permanently open by the action of a drug. Measuring the voltage v from rest, provide the boundary conditions at $x = 0$ and $x = L$ linking the axial currents I_0 and I_L to the synaptic currents at these positions. **[4]**

d) For a particular case of part (c) the conductances and reversal potentials of the synapses are such that the voltage at $x = L$ is at rest. Apply the boundary conditions and solve the system to provide an equation for the voltage at any position x along the neuron. Provide a formula for the ratio of reversal potentials $-\mathcal{E}_e/\mathcal{E}_i$ for this particular circumstance (where $V = E_L$ at $x = L$) to hold. **[10]**

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3. Neuron with voltage-gated currents

A neuron with a voltage-gated current with a fraction n of open channels obeys

$$C\frac{dV}{dt} = g_L(E_L - V) + g_n n(E_n - V) \tag{4}$$

$$\tau_n \frac{dn}{dt} = n_\infty(V) - n \tag{5}$$

where the parameters have their conventional meanings.

a) The neuron is near a fixed point (V^*, n^*). By substituting $V = V^* + v$ and $n = n^*_\infty + (dn_\infty/dV)|_* y$, linearising the equations in the small parameters v and y and suitably rescaling time $t = \kappa s$, show that the equations can be brought into the form

$$\frac{dv}{ds} = -Pv + Qy \tag{6}$$

$$\frac{dy}{ds} = y - v \tag{7}$$

and give formulae for P, Q and κ. **[5]**

b) Derive a quadratic formula for the eigenvalues of the linearised equations in part (a) and identify the region of the $(P,\ Q)$ plane where there are damped oscillations. When they exist, what is the frequency of the damped oscillations? **[5]**

c) Consider now a one-variable neuron model with a driving term $\mu(t)$

$$\frac{dv}{ds} = -Pv + \mu(s). \tag{8}$$

For sinusoidal drive the voltage response will also be sinusoidal, but with a frequency-dependent amplitude and phase shift. Derive the voltage amplitude when $\mu(s) = \sin(\omega s)$ and show that its maximum is at zero frequency. NOTE: It is convenient to write $\mu(s) = e^{i\omega s}$ and use a trial solution for the voltage $v = \hat{v}e^{i\omega s}$ where $|\hat{v}|$ is the required voltage amplitude. **[5]**

d) We now return to the linearised equations (6,7) but include the sinusoidal drive term in the voltage equation as in part (c). Show that the voltage amplitude $|\hat{v}|$ for this case satisfies

$$|\hat{v}|^2 = \frac{1+\omega^2}{(P-Q-\omega^2) + \omega^2(1+P)^2}. \tag{9}$$

Find and equality involving P and Q for the conditions under which the voltage amplitude has a maximum at a non-zero frequency. Provide a formula for the frequency of this maximum, when it exists. **[10]**

4. Synaptic depression and fluctuations

A presynaptic neuron starts to fire action potentials at constant intervals. A vesicle-release site at the neuron's axon terminal can be either occupied $D_k = 1$ or unoccupied $D_k = 0$ just before the kth spike. If a vesicle is present, it is released on the arrival of a presynaptic spike with probability p. An empty site is restocked with probability f between spikes. The notation $\langle X \rangle$ denotes the expectation of the quantity X.

a) Prove that the expectation of D_k satisfies the difference equation

$$\langle D_{k+1} \rangle = \alpha + \beta \langle D_k \rangle \tag{10}$$

and provide formulae for α and β in terms of p and f. **[5]**

b) Give, in terms of α and β, the expected occupancy $\langle D_\infty \rangle$ in the long-time limit, i.e. when $k \to \infty$. Two different cases are now considered. For case (i) the initial condition is $D_1 = 1$, solve the difference equation for $\langle D_k \rangle$. For case (ii) the initial condition is $D_1 = 0$. Show that the solution for case (ii) is

$$\langle D_k \rangle = \langle D_\infty \rangle (1 - \beta^{k-1}). \tag{11}$$

[5]

c) Use the results from case (i) of the previous question to derive the autocorrelation function $\langle D_{n+m} D_n \rangle - \langle D_{n+m} \rangle \langle D_n \rangle$, where $m \geq 1$ in the limit $n \to \infty$. Show that the autocorrelation is

$$\langle D_\infty \rangle (1 - \langle D_\infty \rangle) \beta^m. \tag{12}$$

NOTE: the conditional probability rule $P(A\&B) = P(A|B)P(B)$ is of use. **[6]**

d) Let the binary variable $R_n = 1$ if a vesicle was released at pulse n, with $R_n = 0$ if no vesicle is released. What is $\langle R_n \rangle$ in the limit $n \to \infty$? The autocorrelation for R is defined as

$$\langle R_{n+m} R_n \rangle - \langle R_{n+m} \rangle \langle R_n \rangle, \tag{13}$$

where the limit $n \to \infty$ is taken and it is assumed that $m \geq 1$. Using the result for case (ii) from part (b) and the rule for conditional probability suggested in part (c), show that

$$-p^2 \langle D_\infty \rangle^2 \beta^m. \tag{14}$$

[9]

5. Firing rate of the leaky integrate-and-fire neuron

A neuron receiving stochastic synaptic drive has a voltage v that obeys

$$\tau\frac{dv}{dt} = \mu - v + \sigma\sqrt{2\tau}\xi(t) \tag{15}$$

where τ is the membrane time constant, μ the voltage mean and σ^2 the voltage variance in the absence of threshold. ξ is a zero-mean, delta-correlated Gaussian white-noise process. These dynamics are supplemented by an integrate-and-fire threshold-reset mechanism: if ever $v \geq v_{th}$ then the voltage is reset $v \to v_{re}$, where $v_{th} > v_{re}$.

a) Write-down the continuity equation linking the probability density P and probability flux J. For the dynamics given by equation (15) the flux equation is

$$\tau J = (\mu - v)P - \alpha^2\frac{\partial P}{\partial v}. \tag{16}$$

Argue why, in the absence of the threshold and reset mechanism, the flux $J = 0$. Under these conditions show that $\alpha^2 = \sigma^2$ is the voltage variance. **[5]**

b) We now consider the case with a threshold and reset and introduce the scaled voltage $x=(v-\mu)/\sigma$. For this spiking case the flux can be written $J=r\theta(x-x_{re})$ where θ is a Heaviside step function. With this form of the flux, rewrite the flux equation (16) in terms of x and derive forms for the voltage mean and variance in terms of r, τ, x_{th} and x_{re}. Under what condition is the voltage variance with the spike threshold present greater than σ^2 (its value without threshold)? **[6]**

c) Derive the formula for the firing rate r of this leaky integrate-and-fire neuron and show that it takes the form

$$\frac{1}{\tau r} = \int_0^\infty \frac{dz}{z}e^{-z^2/2}\left(e^{zx_{th}} - e^{zx_{re}}\right). \tag{17}$$

[6]

d) Derive first the low-noise high-rate limit of the rate equation (17) for the case when $x_{th} \ll 0$ and $x_{re} \ll 0$. Now derive the low-rate limit of equation (17) for the noise-driven firing case where $\mu < v_{th}$, such that $x_{th} \gg 0$. Show that the rate in this second limit can be interpreted as the absolute value of the deterministic component of the flux at $v = v_{th}$ in the absence of a threshold mechanism. NOTE: the integral $\int_{-\infty}^{\infty} ds e^{-s^2/2} = \sqrt{2\pi}$ is useful for the second derivation. **[8]**
