

MA4G4

THE UNIVERSITY OF WARWICK

FOURTH YEAR EXAMINATION: SUMMER 2012

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.

1. Goldman-Hodgkin-Katz voltage equation for multiply-charged ions.

The transmembrane current for a particular ionic species obeys the equation

$$I = -Pqza \left(\frac{Nz}{V_T} \frac{dV}{dx} + \frac{dN}{dx} \right) \quad (1)$$

where P is the permeability of the membrane, q is the magnitude of the charge on an electron, z is the integer charge number of the ion, a is the membrane thickness and V_T is the thermal voltage constant. The concentration $N(x)$ varies through the channel and takes values N^i interior ($x = 0$) and N^e exterior ($x = a$) to the neuron. The voltage is V^i interior to the cell and V^e exterior so that the membrane voltage is $V_m = V^i - V^e$. The voltage $V(x)$ varies linearly through the channel.

- a) Consider first a case where the membrane is permeable only to one ionic species. Solve equation (1) to find Nernst's formula for the membrane voltage E at which the ionic current ceases to flow. [5]
- b) Now consider the case where the current I is a non-zero constant. Derive Goldman's equation for the ionic current flowing at a membrane voltage V_m . [7]
- c) Consider first a neuron with a membrane permeable to only Na^+ and K^+ . The membrane voltage is at equilibrium so that the total current crossing the membrane is zero. Prove that the equilibrium membrane voltage V_m^* obeys

$$V_m^* = V_T \log \left(\frac{M_{\text{Na}}^e + M_{\text{K}}^e}{M_{\text{Na}}^i + M_{\text{K}}^i} \right) \quad (2)$$

where the simplifying notation $M_K^e = z_K^2 P_K N_K^e$ has been used. [5]

- d) A more complex case is now considered of a neuron with a membrane permeable to Ca^{2+} and K^+ only. For the voltage V_m^* at which the total current crossing the membrane is zero, derive a quadratic equation for $y = e^{V_m^*/V_T}$ in terms of M_{Ca}^e , M_{Ca}^i , M_{K}^e , M_{K}^i . [5]
- e) Let $M_{\text{Ca}}^e = M_{\text{K}}^i = H$ (a high concentration) and $M_{\text{Ca}}^i = M_{\text{K}}^e = L$ (a low concentration). Show that in this case

$$V_m = V_T \log \left(\frac{1}{2} \left(\sqrt{\left(\frac{H-L}{H+L} \right)^2 + 4} - \frac{H-L}{H+L} \right) \right). \quad (3)$$

[3]

2. Synaptic facilitation and depression.

Though many synapses only show use-dependent depression due to vesicle run down, some synapses strengthen with rapid use due to a process called facilitation caused by open presynaptic calcium channels. In this question the probability of release for a synapse with both facilitation and depression will be examined for a case when the presynaptic cell begins to fire regular action potentials (APs) at times $t=T, 2T, \dots$.

- a) On the arrival of an AP a fraction f of closed presynaptic calcium channels immediately open. Between APs a fraction α_F of open channels remain open while the rest close. Let f_m be the fraction of open channels just after the m th AP arrives. Derive a linear difference equation relating f_{m+1} to f_m . Without solving the equation fully for f_m , confirm that in the limit $m \rightarrow \infty$

$$f_\infty = \frac{f}{1 - \alpha_F(1 - f)}. \quad (4)$$

[5]

- b) Before the first AP arrives no calcium channels are open. What is f_1 ? Solve your difference equation with this initial condition to show that, in terms of f and f_∞

$$f_m = f_\infty \left(1 - \left(1 - \frac{f}{f_\infty} \right)^m \right). \quad (5)$$

[10]

- c) Equation (5) for f_m has a constant and an exponential component. Show that if $f/f_\infty \ll 1$ the time constant of the exponential is approximately Tf_∞/f . [2]
- d) If a vesicle is present just before the m th AP then it is released with a probability equal to the fraction of open calcium channels f_m . The probability of vesicle release p_m at the m th AP is therefore $p_m = f_m D_m$ where D_m is the probability that a vesicle is present just before the m th AP arrives. If a vesicle is released, the probability it is not restocked before the $m+1$ th AP is α_D . Derive a difference equation linking D_{m+1} to D_m in terms of f_m and α_D . Show that in the limit $m \rightarrow \infty$ the full probability of vesicle release tends to

$$p_\infty = \frac{(1 - \alpha_D)f_\infty}{1 - \alpha_D(1 - f_\infty)}. \quad (6)$$

[8]

3. Steady-state cable equation in neurons with different dendritic geometry.

The cable and axial current equations, with voltage v measured from rest, are

$$\tau \frac{\partial v}{\partial t} = -v + \lambda^2 \frac{\partial^2 v}{\partial x^2} \quad \text{and} \quad I_a = -\frac{\lambda}{R_\lambda} \frac{\partial v}{\partial x}. \quad (7)$$

This question explores steady-state and time-dependent solutions of these equations.

- a) Consider a stretch of dendrite of length L , closed at L and with a steady current I_0 injected at $x=0$. The dendrite has a length constant λ and resistance constant R_λ . What are the boundary conditions on $v(x)$ at $x=0$ and $x=L$? [2]
- b) Write down the general solutions of the steady-state cable equation in the dendrite and enforce the boundary conditions to solve for $v(x)$. Your answer will include the constants R_λ , λ and I_0 . [5]
- c) Consider a neuron composed of three dendrites in the shape of a capital Y. The dendrites are closed at their ends and have different properties: dendrite 1 has characteristic length λ_1 and resistance R_{λ_1} with similar notation for dendrites 2 and 3. A synapse is located at the vertex of the Y with channels that are kept permanently open by the action of a drug so that the synaptic current is constant. The synapse has conductance G_s and a reversal potential ϵ_s (measured from rest). Show, by adapting your result from part (3b) or otherwise, that the voltage at the vertex v_0 can be written

$$v_0 = \epsilon_s \left(1 + \frac{\tanh(L_1/\lambda_1)}{G_s R_{\lambda_1}} + \frac{\tanh(L_2/\lambda_2)}{G_s R_{\lambda_2}} + \frac{\tanh(L_3/\lambda_3)}{G_s R_{\lambda_3}} \right)^{-1}. \quad (8)$$

[6]

- d) We return to the geometry of a simple dendrite of length L that is now closed at both ends and we will consider time-dependent solutions. By writing $v(x, t) = e^{-t/\tau} X(x)T(t)$ show that X and T satisfy

$$\frac{\tau}{T} \frac{dT}{dt} = \frac{\lambda^2}{X} \frac{d^2 X}{dx^2} = -\kappa^2. \quad (9)$$

Provide the solution for $T(t)$ parameterized by τ, κ and argue why the constant of equality $-\kappa^2$ was chosen to be explicitly negative. [6]

- e) By solving for $X(t)$ and enforcing the zero-current boundary conditions find the allowed values of κ and show that the general solution for $v(x, t)$ is of the form

$$v(x, t) = \sum_{m=0}^{\infty} a_m e^{-t/\tau_m} \cos\left(\frac{m\pi x}{L}\right). \quad (10)$$

Give a formula for τ_m in terms of m, τ, L and λ . [6]

4. Voltage response in limits of weak and strong synaptic drive.

A neuron is driven by a synaptic conductance G_s and has a voltage equation

$$C \frac{dV}{dt} = G_L(E_L - V) + G_s(E_s - V) \quad (11)$$

where L refers to leak current parameters and $\tau_L = C/G_L$.

a) Consider first the case of a single active synapse with a conductance that obeys

$$\tau_s \frac{dG_s}{dt} = \tau_s \gamma \delta(t) - G_s. \quad (12)$$

Solve this equation to give $G_s(t)$ for $t > 0$. [2]

b) The single synaptic conductance is weak so $\gamma/G_L \ll 1$. By substituting your solution for $G_s(t)$ into equation (11) and making an appropriate simplifying assumption that uses the fact the synapse is weak, show that

$$V(t) \simeq E_L + \kappa (e^{-t/\tau_L} - e^{-t/\tau_s}) \quad (13)$$

and give the constant κ . [5]

c) Now consider a case of strong, fluctuating synaptic conductance

$$\tau_s \frac{dG_s}{dt} = G_{s0} - G_s + \sigma_s \sqrt{2\tau_s} \xi(t) \quad (14)$$

where G_{s0} , σ_s are constants and $\xi(t)$ is zero mean delta-correlated $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$ Gaussian white noise. Write $G_s(t) = G_{s0} + G_{sF}(t)$ and solve equation (14) to give the fluctuating component of the conductance $G_{sF}(t)$ as an integral. Verify that σ_s^2 is the variance of the synaptic conductance. [7]

d) Substitute $G_s(t) = G_{s0} + G_{sF}(t)$ into the voltage equation (11). If $G_{sF}/G_0 \ll 1$ (where $G_0 = G_L + G_{s0}$) argue why the voltage equation can be approximated by

$$\tau_0 \frac{dV}{dt} = E_0 - V + \frac{G_{sF}}{G_0} (E_s - E_0). \quad (15)$$

Give formulae for the effective time constant τ_0 and the average voltage E_0 . [5]

e) Substitute your integral solution for $G_{sF}(t)$ from part (4c) into equation (15). Simplify the equation by calling $V(t) = E_0 + V_F(t)$. Solve the equation for the fluctuating component of the voltage $V_F(t)$ and show that it is of the form

$$V_F(t) = c \int_0^\infty dt' (e^{-t'/\tau_0} - e^{-t'/\tau_s}) \xi(t - t') \quad (16)$$

and give the formula for the constant c . [6]

5. Solution of the Fokker-Planck equation for the steady-state rate.

The equation for the probability flux J for a leaky integrate-and-fire model neuron driven by Gaussian white noise can be written

$$\tau J = P(E - V) - \sigma^2 \frac{\partial P}{\partial V} \quad (17)$$

where τ is the membrane time constant, E is the resting potential and σ measures the noise strength. The probability density for the voltage is P .

- a) Consider first a leaky integrator neuron for which there is no voltage threshold and the system is in the steady state. What is the value of the flux? By taking moments of the equation or otherwise provide formula for voltage mean $\langle V \rangle$ and variance $\langle V^2 \rangle - \langle V \rangle^2$ in terms of parameters E and σ . [4]
- b) We now consider a leaky integrate-and-fire neuron with spike threshold V_{th} and reset V_{re} . Write down the continuity equation linking probability flux and density. Argue why in the steady state the flux has the form $J = r\theta(V - V_{re})$ where θ is a Heaviside step function and r is the steady-state firing rate. Why is the probability density $P(V_{th})=0$? [4]
- c) We introduce the simplifying notation $x = (V - E)/\sigma$ with $x_{th} = (V_{th} - E)/\sigma$ (and similarly for x_{re}). Rewrite the steady-state flux equation in terms of x and its probability density $p(x)$. Solve this equation to show that

$$p(x) = r\tau \int_x^{x_{th}} dy e^{(y^2 - x^2)/2} \theta(y - y_{re}). \quad (18)$$

[6]

- d) By normalizing the probability density $p(x)$, re-ordering integration variables and substituting $x = z - y$, show that the steady-state firing rate can be written

$$\frac{1}{r\tau} = \int_0^\infty \frac{dz}{z} e^{-z^2/2} (e^{zx_{th}} - e^{zx_{re}}). \quad (19)$$

[11]