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 equation and the resting potential. The current per unit area of membrane for a particular ionic species is

\[ I = -P q z a \left( \frac{N_z dV}{V_T dx} + \frac{dN}{dx} \right) \]  

(1)

where \( N \) and \( V \) are the ionic concentration and electrical potential in the bore of the transmembrane channels. Other quantities are: the membrane permeability for the ion \( P \), the absolute charge on an electron \( q \), the integer charge of the ion \( z \), the membrane thickness \( a \) and the thermal potential \( V_T \). Let \( N^i \) be the concentration in the interior \((x = 0)\) of the neuron and \( N^e \) that exterior \((x = a)\) to the neuron. The membrane voltage is \( V_m = V_i - V_e \) and varies linearly through channels, so the voltage gradient is \(-V_m/a\).

a) Explain the origin of the two derivative terms in equation (1).

b) Consider a case where the neuron is in a steady state so the ionic current \( I \) for the species of ion in question is constant. Solve equation (1) under these conditions to show that

\[ I = P q z^2 \frac{V_m}{V_T} \left( \frac{N^e - N^i e^{V_m z / V_T}}{1 - e^{V_m z / V_T}} \right). \]  

(2)

c) Use this result to derive the equation for the Nernst equilibrium voltage \( V_m = E \) at which the ionic current vanishes.

d) Consider now small deviations \( v \) of membrane voltage away from this equilibrium such that \( V_m = E + v \). Argue why for small deviations the steady-state current (Eq. 2) can be approximated by \( I \simeq g(V_m - E) \). By expanding equation (2) to leading order in \( v \) show that the conductance \( g \) takes the form

\[ g = \frac{P q z^2 V_m}{V_T} \log \left( \frac{N^e}{N^i} \right) \frac{N^e N^i}{N^e - N^i}. \]  

(3)

[HINT: Use the Nernst relation to substitute \( E \) for a function of \( N^e \) and \( N^i \).]

e) We now return to the full current equation (2). Consider a neuron that has a membrane permeable to the ions \( K^+ \), \( Na^+ \) and \( Cl^- \). By balancing the three ionic currents, demonstrate that the equilibrium voltage \( V_m^* \) is

\[ V_m^* = V_T \log \left( \frac{P_K N_{K}^e + P_{Na} N_{Na}^e + P_{Cl} N_{Cl}^i}{P_K N_{K}^i + P_{Na} N_{Na}^i + P_{Cl} N_{Cl}^e} \right). \]  

(4)

where \( P_K \) is the permeability and \( N_{K}^e, N_{K}^i \) the exterior and interior ionic concentrations for \( K^+ \) (with similar definitions for other ionic species).
2. Derivation and application of the cable equation. A cylindrical dendrite has a capacitance $C$ and membrane leak conductance $g_L$ per unit area, a radius $a$ and a resistivity $r_a$ (units: resistance × length). The leak reversal potential is $E_L$.

a) Consider the voltage on either side of a short segment of dendrite of length $\Delta$. Write down the formula for the total axial resistance $R$ and derive an equation for the axial current $I_a$ in the limit $\Delta \to 0$. [2]

b) Identify the different currents flowing into and out of a small segment of dendrite of length $\Delta$. Use the current conservation law to provide an equation linking these currents. Give the formulae for the capacitance $I_C$ and leak $I_L$ currents. Combine these with the axial currents to show that

$$\tau_L \frac{dV}{dt} = E_L - V + \lambda^2 \frac{d^2V}{dx^2}. \quad (5)$$

Give formulae for $\tau_L$ and $\lambda$ in terms of $C$, $g_L$, $r_a$ and $a$. [6]

c) What is the membrane resistance of a length $\lambda$ of cable? What is the axial resistance of the same length of cable? Use your formula for $\lambda$ from question part 2b) to show that these two resistances are identical. Call this characteristic resistance $R_\lambda$ and re-express the axial current equation in terms of $\lambda$ and $R_\lambda$. [4]

d) Measuring voltage from rest $v = V - E_L$, provide two solutions to the cable equation (5) in the steady state. [2]

e) Consider now a soma and dendrite model. The soma has total membrane resistance $R_s$ and a reversal potential $E_L$. The dendrite, of height $H$, has a length constant $\lambda$ and characteristic resistance $R_\lambda$ and is attached to the soma at a point $x = 0$. At the end of the dendrite, at $x = H$, there is an excitatory synapse of relative reversal potential $E_e = E_e - E_L$ and conductance $G_e$. The synaptic channels are kept permanently open by the action of a drug so the system is in the steady state. What is the relation between the somatic voltage $v_s$ and the dendritic voltage at $x = 0$? By considering the steady-state equation for the somatic voltage write down a second relation linking $v_s$ to the axial current in the dendrite at $x = 0$ (this expression will also involve the somatic resistance $R_s$). Write down a final relation involving the axial current in the dendrite at $x = H$ and the synaptic current (which is a function of the dendritic voltage at $x = H$). Using the general solution for the dendritic voltage in a finite cable, solve for $v_s$ to show that

$$v_s = \frac{R_\lambda G_e E_e}{(R_s/R_e + R_\lambda G_e) \cosh(H/\lambda) + (1 + R_s/R_e R_\lambda G_e) \sinh(H/\lambda)}. \quad (6)$$

[11]
3. Fluctuating voltage-gated currents. A neuron with a leak current and a noisy voltage-gated current, with reversal potentials $E_L$ and $E_N$, has a dynamics that obeys

$$C \frac{dV}{dT} = g_L(E_L - V) + g_N(N(E_N - V))$$

(7)

$$\tau_N \frac{dN}{dT} = N_\infty(V) - N + \sigma_N \sqrt{2\tau_N} \xi(t)$$

(8)

where $N$ is the gating variable of a hyperpolarization-activated depolarizing current and $\xi(t)$ is a gaussian-white-noise term with zero mean and a Dirac-delta autocorrelation $\langle \xi(T)\xi(T') \rangle = \delta(T - T')$. The voltage-dependent steady-state activation of the gating variable is $N_\infty(V)$.

a) Considering first the noise-free case where $\sigma_N = 0$, give the formula for the voltage nullcline in the form of $N$ as a function of $V$. Sketch the voltage nullcline together with the $N$ nullcline demonstrating that there is only one fixed point.

b) We now consider the noisy case ($\sigma_N \neq 0$) and introduce the variables $v = V - V^*$ and $n = (N - N^*)/\frac{dN_\infty}{dv}|_*$, where $*$ denotes a quantity evaluated at the fixed point. Show, to linear order in $v$ and $n$, that the deviations from the fixed point obey

$$\frac{dv}{dt} = -Pv + Qn$$

(9)

$$\frac{dn}{dt} = v - n + \sigma \sqrt{2} \xi(t)$$

(10)

where $t = T/\tau_n$. Give the forms for $P$, $Q$ and $\sigma$.

c) The aim for the final three parts of this question is to calculate the voltage variance around the fixed point for a system where $P = 4$ and $Q = -2$. This is complicated by the fact that equations (9,10) couple $v$ and $n$ together. We uncouple these by introducing $\phi = v + n$ and $\psi = v + 2n$. Show that $\phi$ obeys

$$\frac{d\phi}{dt} = -3\phi + \sigma \sqrt{2}\xi(t)$$

(11)

and write down a similar equation for $\psi$.

d) Assuming that the noise has been driving the system since long in the past, integrate equation (11) to provide a solution for $\phi(t)$ in terms of an integral over the history of $\xi(t)$. Also provide the corresponding solution for $\psi(t)$.

e) Noting that $v = 2\phi - \psi$, and so $\langle v^2 \rangle = 4\langle \phi^2 \rangle - 4\langle \phi \psi \rangle + \langle \psi^2 \rangle$, evaluate $\langle \psi^2 \rangle$, $\langle \psi \phi \rangle$ and $\langle \psi^2 \rangle$ using the autocorrelation rule for Gaussian white noise to show that the voltage variance is

$$\langle v^2 \rangle = \frac{2}{15} \sigma^2.$$
4. Critical exponents of the Quadratic Integrate-and-Fire model. The fluctuation-driven QIF model can be written in dimensionless form as follows

\[ \frac{dV}{dt} = V^2 + I + \sigma \sqrt{2} \xi(t) \]  

(13)

where \( I \) is a driving current and \( \sigma \) is the strength of the Gaussian white noise \( \xi(t) \). Whenever the voltage tends to \(+\infty\) it is reset to \(-\infty\) and a spike is registered.

a) For \( I > 0 \) the QIF neuron fires spontaneously with a rate \( r \) that grows with some power law of the form \( r \propto I^\alpha \). Solve equation (13) with \( \sigma = 0 \) and \( I > 0 \) to derive a formula for the period between spikes (the result \( \int_{-\infty}^{\infty} dx/(1 + x^2) = \pi \) will be useful) and thereby identify the critical exponent \( \alpha \) for the rate. [4]

b) For the rest of this question \( \sigma \neq 0 \) and \( I = 0 \). Consider an ensemble of QIF neurons defined by the probability flux \( J \) and the probability density \( P \) of finding a neuron near a voltage \( V \). For the model given in equation (13) the flux takes the form

\[ J = V^2 P - \sigma^2 \frac{dP}{dV}. \]  

(14)

Explain the origins of the two terms on the right-hand side of this equation. Using the continuity equation linking flux \( J \) and probability density \( P \), argue why the steady-state flux is independent of voltage and equal to the rate \( r \). [6]

c) Solve equation (14) to give the probability density \( P \) as a function of the unknown rate \( r \). By normalizing probability, show that

\[ \frac{1}{r} = \frac{1}{\sigma^3} \int_{-\infty}^{\infty} dx \int_{x}^{\infty} dy e^{(x^3 - y^3)/3} \]  

(15)

and identify the value of the critical exponent \( \beta \) for noise-driven firing. [7]

d) Simplify the double integral in equation (15) to show that

\[ r = \frac{\sigma^3}{\sqrt{\pi} \int_{0}^{\infty} \frac{d ze^{-z^3/12}}{\sqrt{z}}} \]  

(16)

[HINT: First change variables by substituting \( y = z + x \) and then perform a Gaussian integral over \( x \). The result \( \int_{-\infty}^{\infty} e^{-a^2/2} da = \sqrt{2\pi} \) will be useful.] [8]
5. **Dynamics of a mean-field network of inhibitory neurons.** An inhibitory neuron has a firing rate $R(t)$ that obeys the equation

$$\tau \frac{dR}{dt} = \Phi(I) - R$$  \hspace{1cm} (17)

where $\tau$ is a time constant and $\Phi$ the steady-state rate as a function of the net driving current $I$. Here $\Phi$ takes the form $\Phi(I) = I$ if $I > 0$ and $\Phi(I) = 0$ if $I \leq 0$.

a) In a mean-field network each of these neurons receives a current that is a function of the rate: $I = I_0 + \alpha R(t - d)$ where $I_0 > 0$ is a constant external drive, $\alpha < 0$ is a coupling constant and $d > 0$ is a time delay. Why is $\alpha$ negative and what might be the physical origin of the delay $d$? \[2\]

b) Write down two equations for the steady-state network rate $R^*$ where each is a function of $I$. Sketch $R^*$ versus $I$ for these two cases and thus obtain the network rate $R^*$ as a function of $I_0$ and $\alpha$ only. Is the rate lower or higher than that for an uncoupled population with the same external drive $I_0$? \[6\]

c) Consider the dynamics following a small deviation $\kappa$ from the fixed point $R = R^* + \kappa e^\lambda$. Using equation (17) and $I = I_0 + \alpha R(t - d)$ from part (5a) show that the constant $\lambda$ satisfies

$$\tau \lambda = \alpha e^{-\lambda d} - 1.$$ \hspace{1cm} (18)

\[4\]

d) Let $\lambda = \mu + i\omega$. What is the form of $\lambda$ when the network undergoes a transition to sustained oscillations? Introducing the dimensionless frequency $u = \omega d$ and dimensionless delay $\delta = d/\tau$ show that at the transition to oscillations the following two equations hold:

$$\alpha = \frac{1}{\cos(u)} \quad \text{and} \quad \alpha = -\frac{u}{\delta \sin(u)}.$$ \hspace{1cm} (19)

\[5\]

e) Sketch these two equations over the range $u = 0...\pi$ for networks; (i) with a short delay $\delta$, and (ii) with a long delay $\delta$. By examining the intersections of the two $\alpha$ curves as a function of $u$ in equation set (19) for cases (i) and (ii), show that for networks with short delays oscillations emerge at a frequency $\omega = \pi/2d$ and for networks with long delays oscillations emerge at a frequency $\omega = \pi/d$. Which of these two networks requires the strongest coupling for oscillations to emerge? \[8\]