

MA4G4

THE UNIVERSITY OF WARWICK

FOURTH YEAR EXAMINATION: SUMMER 2013

INTRODUCTION TO THEORETICAL NEUROSCIENCE

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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. Synaptic integration and synaptic depression**

The postsynaptic voltage for a neuron driven by a synaptic conductance  $g_S$  obeys

$$C \frac{dV}{dt} = g_L(E_L - V) + g_S(E_S - V).$$

The leak time constant is  $\tau_L = C/g_L$ . For parts (1a-1b)  $g_S = 0$  for  $t < 0$ .

- a) A single synapse features  $N$  postsynaptic ion channels that are either open, each with conductance  $\gamma$ , or closed. The maximal conductance is therefore  $g_0 = N\gamma$ . A presynaptic action potential (AP) opens all channels at  $t = 0$ , after which they close at rate  $1/\tau_S$ . Prove that the average synaptic conductance is

$$g_S(t) = g_0 e^{-t/\tau_S} \tag{1}$$

for  $t > 0$ . For fast synapses  $\tau_S \rightarrow 0$  with  $g_0\tau_S$  constant: show that  $g_S \rightarrow g_0\tau_S\delta(t)$  where  $\delta(t)$  is the Dirac-delta function. [5]

- b) Show, to leading order in  $g_0/g_L$ , that  $g_S(t)$  in Eq. (1) yields the voltage response

$$V = E_L + \frac{g_0}{g_L}(E_S - E_L) \frac{\tau_S}{\tau_L - \tau_S} (e^{-t/\tau_L} - e^{-t/\tau_S}).$$

Show that for fast synapses  $V = E_L + Ae^{-t/\tau_L}$  and give the form of  $A$ . [5]

- c) We now consider a connection with  $n$  synapses and presynaptic APs at times  $t = mT$  where  $m = 1, 2, 3$  etc. Synapses have a vesicle-release probability  $p$  and restock rate  $1/\tau_D$ . Let  $D_m$  be the probability of synaptic vesicle occupancy just before the  $m$ th AP. What is  $D_1$ ? Derive the equation linking  $D_{m+1}$  to  $D_m$  in terms of  $q = 1 - p$  and the probability a vesicle is not restocked  $\alpha = e^{-T/\tau_D}$ . Verify that

$$D_\infty = \frac{1 - \alpha}{1 - q\alpha}$$

is the expected vesicle occupancy in the limit  $m \rightarrow \infty$  and solve for  $D_m$ . [5]

- d) On the arrival of the  $m$ th AP the average postsynaptic voltage jumps by  $A_m = anpD_m$  where  $a$  is a constant. Between APs the voltage decays exponentially to  $E_L$  with time constant  $\tau_L$ . Show that the voltage just after the  $m$ th AP is

$$V_m = E_L + anp \left( D_\infty \frac{1 - \beta^m}{1 - \beta} + (1 - D_\infty) \frac{\beta^m - (q\alpha)^m}{\beta - q\alpha} \right) \quad \text{where } \beta = e^{-t/\tau_L}$$

Hint: derive a difference equation for  $V_m$  and use your  $D_m$  from part (1c). [10]

## 2. Cable theory applied to a semi-infinite dendrite

A neuron is approximated as a semi-infinite cylindrical cable of radius  $a$ , with capacitance  $C$  and conductance  $g$  per unit area of membrane, and axial resistivity  $r_a$  (dimensions of resistance $\times$ length). The variable  $x \geq 0$  measures the distance from the end of the cable at  $x=0$ . The voltage  $v$  is measured from rest.

- a) What is the membrane resistance  $R_m$  of a length  $L$  of cable? What is the axial resistance of a length  $L$  cable? Give the length constant  $L = \lambda$  for which these two resistances are equal. We will call this characteristic resistance  $R_\lambda$ . Derive the equation for the axial current  $I_a$  and show that it can be written

$$I_a = -\frac{\lambda}{R_\lambda} \frac{\partial v}{\partial x}.$$

[5]

- b) By considering all the currents at the boundaries of a short stretch of dendrite, derive the cable equation parameterized by a time constant  $\tau$  and length constant  $\lambda$ . Verify that  $v$  has steady-state solutions proportional to  $e^{\pm x/\lambda}$ .

[5]

- c) The cable has a synapse at  $x=d$  with a conductance  $G_s$  and a reversal potential measured from rest of  $\mathcal{E}_s$ . The synapse is kept permanently open by the action of a drug. Write down the form of the synaptic current  $I_s$  in terms of these parameters and the voltage  $v_d$  at  $x=d$ . An additional steady current  $I_0$  is injected into the neuron at  $x=0$ . Write down expressions for the voltage in regions  $x=0 \rightarrow d$  and  $x=d \rightarrow \infty$  in terms of three unknown constants. Provide three (in total) boundary conditions at  $x=0$  and at  $x=d$  (one involves  $I_s$ ).

[5]

- d) Match the solutions with the boundary conditions to show that, in terms of the synaptic current  $I_s$ , the voltage for  $x > 0$  can be written as

$$v = I_0 R_\lambda e^{-x/\lambda} + \frac{I_s R_\lambda}{2} e^{-(x+d)/\lambda} + \frac{I_s R_\lambda}{2} e^{-|x-d|/\lambda}. \quad (2)$$

Now substitute your voltage-dependent form of  $I_s$  from question part (2c) and solve to find the voltage  $v_d$  at the synapse.

[10]

**3. A neuron with a voltage-gated current subject to white noise**

A neuron with a hyperpolarization-activated depolarizing current obeys the equations

$$\begin{aligned} C \frac{dV}{dt} &= g_L(E_L - V) + g_n n(E_n - V) \\ \tau_n \frac{dn}{dt} &= n_\infty - n \end{aligned}$$

where  $n_\infty$  is a function of the voltage  $V$ , and  $n$  is the fraction of open gated channels.

- a) Provide a formula for the voltage nullcline and sketch this, together with the  $n$  nullcline for the type of current described in the question, on the  $V, n$  plane. Mark distinct directions of flow on the nullclines (4 arrows required). [5]

- b) A linearized system with voltage variable  $x$  and current variable  $y$  obeys

$$\begin{aligned} \tau \frac{dx}{dt} &= -x - \omega \tau y + \mu(t) \\ \tau \frac{dy}{dt} &= \omega \tau x - y \end{aligned}$$

where  $\tau$  and  $\omega$  are positive constants and  $\mu(t)$  is a time-dependent input current. Solve the differential equation satisfied by  $z = x + iy$  to show that

$$z(t) = \int_0^\infty \frac{ds}{\tau} e^{-\alpha s} \mu(t - s) \tag{3}$$

where  $\alpha = 1/\tau - i\omega$ . [5]

- c) The input current is now specified as the white-noise process  $\mu(t) = \sqrt{2\tau} \xi(t)$  where  $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$  and  $\langle \xi(t) \rangle = 0$ . Use equation (3) to calculate  $\langle zz \rangle$ ,  $\langle zz^* \rangle$  and  $\langle z^* z^* \rangle$  where  $z^*$  is the complex conjugate of  $z$ , and so prove that

$$\langle x^2 \rangle = \frac{1}{2} \left( 1 + \frac{1}{1 + \omega^2 \tau^2} \right)$$

is the voltage variance using the relation  $x = (z + z^*)/2$ . (Note that  $\langle x \rangle = 0$ .) [5]

- d) An input current is now considered featuring two cross-correlated white-noise terms with a delay  $T > 0$  such that now  $\mu(t) = \sqrt{2\tau}(\xi(t) - \xi(t - T))$ . Use the result of part (3c) to find the voltage variance  $\langle x^2 \rangle_\infty$  in the limit  $T \rightarrow \infty$ . For finite  $T$  the general form is  $\langle x^2 \rangle = \langle x^2 \rangle_\infty + \langle x^2 \rangle_T$  where the second term is the  $T$ -dependent component of the voltage variance. Show that

$$\langle x^2 \rangle_T = -e^{-T/\tau} \left( \cos(\omega T) + \frac{\cos(\omega T) - \omega \tau \sin(\omega T)}{1 + \omega^2 \tau^2} \right).$$

[10]

#### 4. Dynamics of a non-linear integrate-and-fire neuron

A non-dimensionalised, non-linear integrate-and-fire neuron has a voltage dynamics that obeys

$$\frac{dV}{dt} = F(V) + I \quad (4)$$

where  $I$  is a constant input current. Whenever the voltage ever diverges to  $+\infty$  a spike is registered and the voltage reinserted at  $-\infty$ .

The following integral will be of use in this question

$$\int_0^\infty \frac{q^{\gamma-1}}{1+q} dq = \frac{\pi}{\sin \pi\gamma}.$$

- a) We first consider  $F(V) = (V^2 - A^2)^2$  where  $A$  is a positive constant. Sketch  $F(V)$  and describe how the fixed-point structure depends on  $I$ . Give equations for the fixed points  $V^*$  for each distinct scenario. Do not consider marginal cases where fixed points coincide. [5]

- b) By linearising the equation for the voltage measured from a fixed point  $v = V - V^*$  derive the eigenvalues for each fixed point and hence state which ones are stable. [5]

- c) We now consider the case where  $I > 0$  but  $I \ll 1$  so that the dynamics are very slow near the two minima of  $F(V) + I$ . Consider an expansion in  $v = V - A$  of  $F(V)$  to second order in  $v$  at the minimum  $V = A$ . Show that by rescaling voltage  $v = \alpha x$  and time  $t = \beta s$  the scaled dynamics can be approximated by

$$\frac{dx}{ds} = 1 + x^2 \quad (5)$$

and give  $\alpha$  and  $\beta$ . Show that a similar expansion at  $V = -A$  would also give equation (5) with the same  $\alpha$  and  $\beta$ . [5]

- d) Use the result from part (4c) to calculate the firing rate of the model introduced in part (4a) when  $I$  is small and positive. Finally, consider a more general power-law model of neuronal firing where  $F(V) = V^{2m}$  and  $m$  is a positive integer. Calculate the firing-rate for this general class of model as a function of  $m$  and  $I$ . Verify that in the limit  $m \rightarrow \infty$  the firing rate tends to  $I/2$  for  $I > 0$ . [10]

### 5. Firing-rate of a leak-less neuron subject to stochastic synaptic drive

We consider a population of neurons that each obeys the voltage equation

$$\tau \frac{dv}{dt} = \mu + \sigma \sqrt{2\tau} \xi(t) \quad (6)$$

where  $v$  is measured from rest,  $\tau$  is the membrane time constant,  $\mu$  and  $\sigma$  positive constants and  $\xi(t)$  is a zero-mean, delta-correlated gaussian white noise process that is independent for each neuron. A standard spike mechanism is assumed: if the voltage reaches  $v_{th} > 0$  it is reset to  $v = 0$ .

- a) Derive the continuity equation linking probability density  $p$  and probability flux  $j$  from first principles by considering neuronal voltage trajectories entering and leaving a small voltage range  $v \rightarrow v + dv$  during a time  $t \rightarrow t + dt$ . [5]

- b) The flux equation for the population of leakless-neurons is

$$\tau j = \mu p - \sigma^2 \frac{dp}{dv}. \quad (7)$$

In the steady-state, what is the formula for  $j$  in terms of the firing rate  $r$ ? What is the probability density at threshold? By using these results and solving the flux equation, show that for  $v > 0$  the probability density is

$$p(v) = \frac{r\tau}{\mu} \left( 1 - e^{\mu(v-v_{th})/\sigma^2} \right)$$

and provide the corresponding expression for  $v < 0$ . [5]

- c) Calculate the firing rate for this model and show that it is independent of the synaptic noise strength  $\sigma$ . [5]

- d) A new kind of neuron is discovered that obeys the dynamics given in (6) and (7) but has two thresholds: one at  $v_1 > 0$  and another at  $v_2 < 0$ . If the neuron fires by hitting either threshold it is reset to  $v = 0$ . Provide the probability density for  $v > 0$  in terms of the unknown rate  $r_1$  that the neuron hits the  $v_1$  threshold, as well as the density for  $v < 0$  in terms of the unknown rate  $r_2$  that the neuron hits the  $v_2$  threshold. Find the ratio of the firing rates  $r_1/r_2$ . For the particular case where  $\mu = 0$  solve for  $r_1$  and  $r_2$ . [10]