Version CRIB v2

EGT2
ENGINEERING TRIPOS PART IIB

CRIB 2024

Module 4G7

CONTROL & COMPUTATION IN LIVING SYSTEMS

*Answer **both** questions in section A. Answer **one** question in section B.*

All questions carry the same number of marks.

*The **approximate** percentage of marks allocated to each part of a question is indicated in the right margin.*

*Write your candidate number **not** your name on the cover sheet.*

STATIONERY REQUIREMENTS
Single-sided script paper

SPECIAL REQUIREMENTS TO BE SUPPLIED FOR THIS EXAM
CUED approved calculator allowed
Attachment 1: 2011 Science paper for Question 3 (5 pages)
Attachment 2: 2000 Nature paper for Question 4 (5 pages)
Engineering Data Book

10 minutes reading time is allowed for this paper at the start of the exam.

You may not start to read the questions printed on the subsequent pages of this question paper until instructed to do so.

You may not remove any stationery from the Examination Room.

SECTION A

Answer **both** questions.

1 (a) Provide two reasons why membrane ion transport is important for sustaining life in non-excitable cells [10%]

(i) preventing swelling and membrane rupture by balancing osmotic pressure caused by high concentration of macromolecules (soluble proteins etc); (ii) using electrochemical gradient to drive metabolic processes (e.g. ATP synthase)

(b) The Hodgkin-Huxley model of the squid giant axon can be written as follows:

$$\dot{v} = -g_{Na}m^3h(v - e_{Na}) - g_K n^4(v - e_K) - g_L(v - e_L) + I_{inp} \quad (1)$$

$$\tau_m(v)\dot{m} = m_\infty(v) - m \quad (2)$$

$$\tau_h(v)\dot{h} = h_\infty(v) - h \quad (3)$$

$$\tau_n(v)\dot{n} = n_\infty(v) - n \quad (4)$$

where v denotes membrane potential, I_{inp} is injected current and the g_x, e_x are conductance densities (normalised to membrane capacitance) and reversal potentials (in mV) of the different ionic currents, Na (sodium), K (potassium) and L (leak). The functions $x_\infty(v)$ and $\tau_x(v)$ are plotted in Fig. 1.

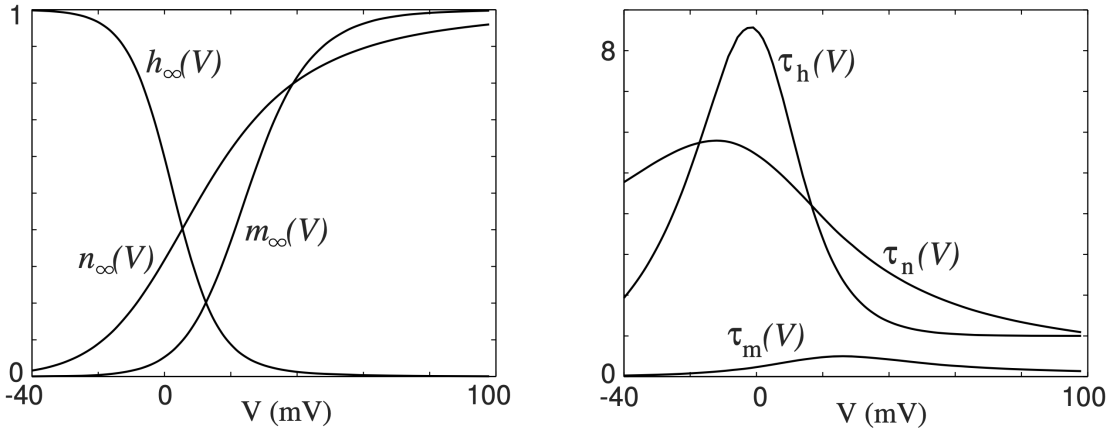


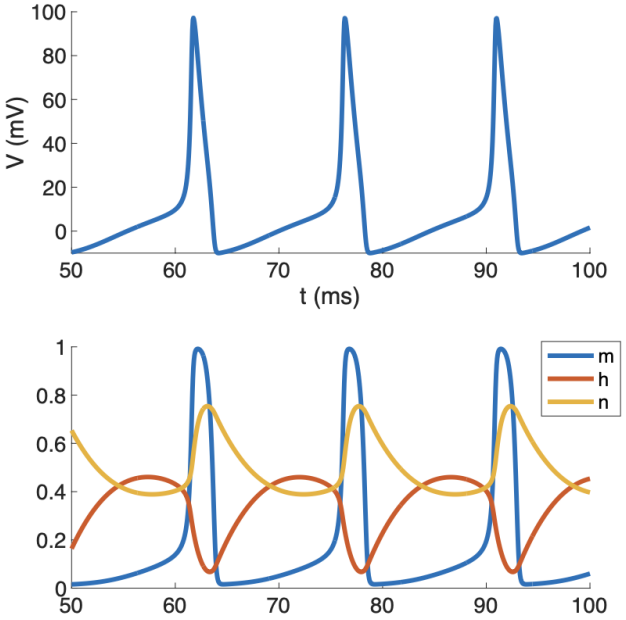
Fig. 1: plots of the voltage-dependent functions for the Hodgkin Huxley model in Question 1(b). Units of the $\tau_x(V)$ are ms.

 (cont.

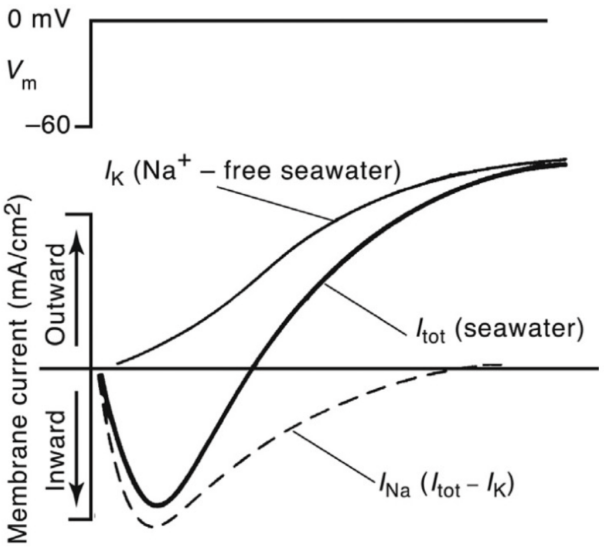
(i) Explain the significance and biological interpretation of the variables m, h and n. [5%]

m and n are dimensionless state variables describing the activation (active/open fraction) of sodium and potassium conductances/channels, respectively. h describes the inactivation of the sodium conductance.

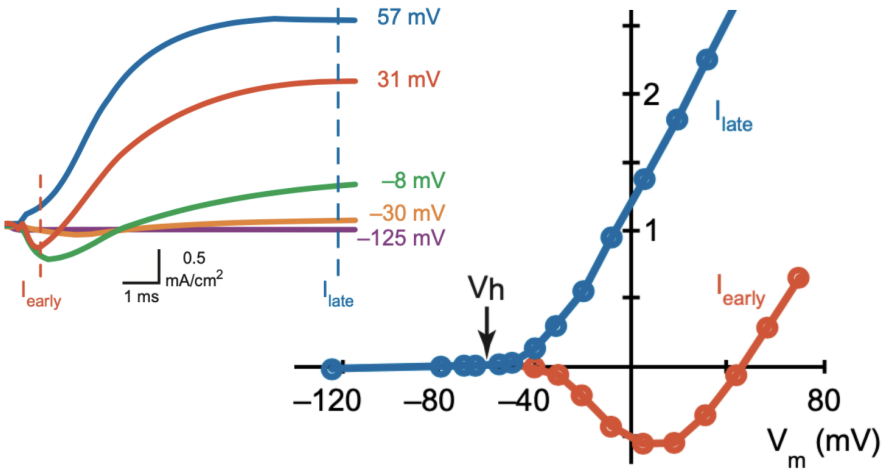
(ii) Sketch the evolution of the membrane potential and of m, h and n in response to continuous current injection of sufficient amplitude to elicit repetitive action potentials. [10%]



(iii) Sketch the response of the sodium and potassium conductance to a depolarising voltage step starting from an initial value close to the equilibrium potential of the membrane. [5%]



(iv) Referring to your sketch in (iii), plot the "early" and "late" components of the membrane current as a function of depolarising voltage steps from an initial value of −80 mV to values in the range [−80, 50] mV. [15%]



 (cont.

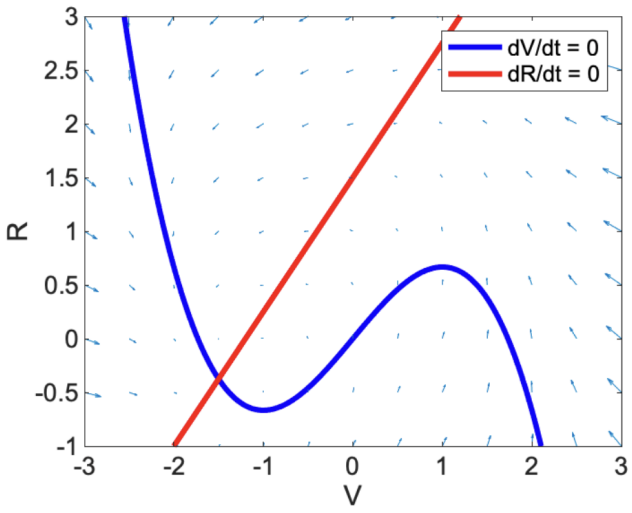
(v) Use your sketches in parts (ii-iv) to explain the form of the Fitzhugh-Nagumo model:

$$\dot{V} = 10(-V^3/3 + V - R + I_{inp}) \quad (5)$$

$$\dot{R} = 0.8(1.25V - R + 1.5) \quad (6)$$

[30%]

Inspection of the time evolution of V, m, n and h in (ii) and reference to the τ_x functions reveals a separation of timescales: V and m evolve on a fast timescale, while n and h are almost perfectly correlated on a slow timescale. Further, the "early" component of membrane current in (iv) summed with the leak conductance gives a non-monotonic dependence on membrane potential that is qualitatively similar to a cubic equation, hence the cubic equation in V for $\dot{V}$. The dependence of the late component is monotonic in V, justifying the linear dependence of $\dot{R}$ on V. These can be seen by sketching the nulclines of the FN system:



(c) Consider an *integrate and fire* model of a neuron in which membrane potential evolves according to:

$$\begin{cases} C\dot{V} = g(V_0 - V) & \text{if } V < V_{\text{thr}} \\ V_{\text{reset}} \mapsto V & \text{otherwise} \end{cases}$$

(i) Suppose the membrane potential is subjected to a train of impulses separated by a time interval T, each depolarising the membrane potential by an amplitude A. Derive a condition on A and T for the membrane to reach threshold.

Consider the membrane at rest with $V = V_0$ for $t < 0$. Following an impulse of amplitude $A < (V_{\text{thr}} - V_0)$ at time t=0, the solution is:

$$V(t) = A\exp(-t/\tau) + V_0$$

where $\tau = C/g$. After N such impulses spaced at regular intervals T:

$$V(NT) - V_0 = A(1 + \exp(-T/\tau) + \exp(-2T/\tau) + \ldots) = \frac{A}{1 - \exp(-T/\tau)}$$

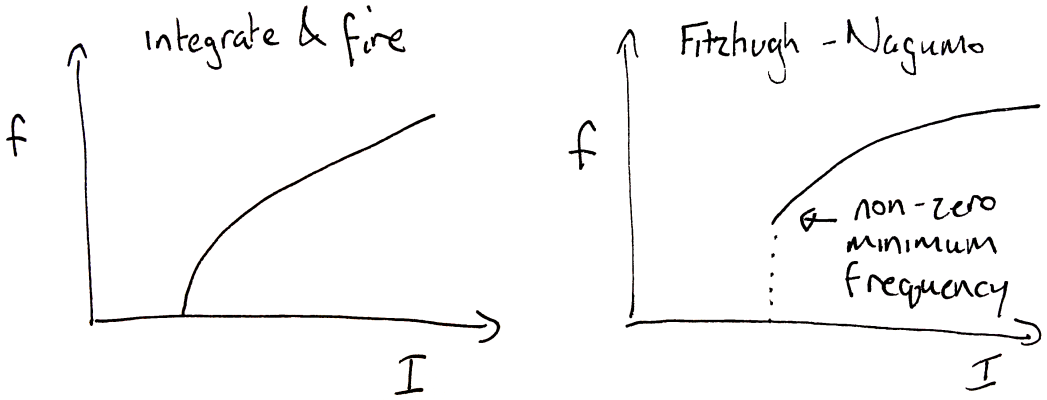
Thus the condition for reaching threshold is:

$$\frac{A}{1 - \exp(-T/\tau)} > V_{\text{thr}} - V_0$$

[15%]

(ii) Suppose instead the membrane is subjected to constant depolarising current. Sketch the firing frequency as a function of current amplitude. How does this relationship differ from that of the Fizhugh-Nagumo model in question 1b(v)? [10%]

Fitzhugh-Nagumo has a nonzero minimum frequency due to the Hopf Bifurcation:



2 (a) Consider a discrete time model of diffusion as a 1D random walk, in which a particle's position, x_n randomly and independently increments position by $\pm d$ in each timestep n.

(i) Derive expressions for the expected displacement, $\mathbb{E}(x)$ and expected squared displacement, $\mathbb{E}(x^2)$ in the general case where there may be a bias between positive and negative increments. You may state without proof formulae for the mean and variance of the Binomial distribution. [15%]

Let p be the probability per timestep of a positive increment. Then the expected displacement after T timesteps is

$$\mathbb{E}(x) = \sum_{n=1}^{T} \mathbb{E}(x_n) = T(pd - (1-p)d) = Td(2p-1)$$

using independence. Similarly,

$$\mathbb{E}(x^2) = T\mathbb{E}(x_1^2) = T(pd^2 + (1-p)d^2) = Td^2$$

(ii) Now suppose the probability of an increment of $-d, +d$ is equal and independent for each component, derive an expression for $\mathbb{E}(x_n^T x_n)$ in the case where $x \in \mathbb{R}_{\mathbb{N}}$ has N components. [10%]

By independence, mean squared displacement will sum linearly with $\mathbb{E}(x_i x_j) = 0$, thus:

$$\mathbb{E}(x_n^T x_n) = \sum_{i=1}^{N} \mathbb{E}(x_i^2) = N\mathbb{E}(x^2) = NTd^2.$$

(iii) Discuss the implications of your answer to (i) for the speed of chemical signalling within cells of different sizes. [15%]

In a fixed amount of time, the RMS displacement, x_{RMS} of a diffusing molecule scales as $\sqrt{T}$, so the time taken to traverse a fixed length grows quadratically. Thus as the linear size of a cell increases, signal delays grow rapidly and signals that may take milliseconds to cross a cell diameter can take minutes or even hours.

(b) In three dimensions the diffusion equation is:

$$\frac{\partial f}{\partial t} = D\nabla^2 f; \qquad \text{where, } \nabla^2 f = \frac{\partial^2 f}{\partial x_1^2} + \frac{\partial^2 f}{\partial x_2^2} + \frac{\partial^2 f}{\partial x_3^2}.$$

(i) Assuming a radially symmetrical solution about the origin, rewrite the three dimensional diffusion equation in terms of r, with $r^2 = x_1^2 + x_2^2 + x_3^2$. [30%]

A radially symmetric solution has the form $f = f(r,t)$. We will write $\partial/\partial x$ as $(.)_x$. By the chain rule and the definition of r,

$$f_x = f_r.r_x = (x/r)f_r$$

The second derivative is then:

$$f_{xx} = (1/r)f_r - (1/r^2)(x/r)xf_r + (x^2/r^2)f_{rr}$$

and similarly for y, z. Gathering terms and simplifying yields:

$$\nabla^2 f = (2/r)f_r + f_{rr} = (1/r^2)(r^2 f_r)_r$$

Thus the radially symmetric diffusion equation becomes:

$$(1/r^2)(r^2 f_r)_r = (1/D)f_t$$

(ii) By writing the radially symmetric solution in the form $f(r,t) = \frac{\theta(r,t)}{r}$, show that θ obeys a one dimensional diffusion equation. [30%]

Substituting the form of f suggested, the diffusion equation becomes:

$$(1/r^2)(r\theta_r - \theta)_r = 1/(Dr)\theta_t$$

$$(1/r)(\theta_r + r\theta_{rr} - \theta_r) = (1/D)\theta_t$$

This becomes

$$\theta_{rr} = (1/D)\theta_t$$

as required.

SECTION B

Answer **one** question.

3 Refer to the attached paper by Couzin et al (2011) Science.

(a) Summarise the aim, approach, findings and motivation of the paper in no more than 500 words. Provide an interpretation of the results and comment on any limitations of the study. You may use diagrams if you wish. [60%]

(b) What is meant by a *bifurcation* in the context of a dynamical system? Describe the saddle-node and pitchfork bifurcations, and any relevance they may have to Figure 2B of Couzin et al. [40%]

4 Refer to the attached paper by Elowitz & Leibler (2000) Nature.

(a) Summarise the aim, approach, findings and motivation of the paper in no more than 500 words. Provide an interpretation of the results and comment on any limitations of the study. You may use diagrams if you wish. [60%]

(b) Consider a simpler version of the system modelled in Box 1 of Elowitz & Leibler with only one mRNA/protein species:

$$\dot{m} = -m + \frac{\alpha}{1 + p^n} + \alpha_0$$
$$\dot{p} = -\beta(p - m)$$

where the symbols are defined in the paper. Would this simpler system be capable of generating oscillations, theoretically? What factors might violate your prediction if the system were experimentally implemented in a living cell? [40%]

Linearising the system at the equilibrium ($p = m$) and computing the characteristic equation gives:

$$\lambda^2 + (1 + \beta)\lambda + \beta + \frac{\alpha n p^{n-1}}{(1 + p^n)^2}$$

Due to positivity of all the parameters, the roots of this always have negative real part, therefore a sustained oscillation will not occur (there could be a decaying oscillation).

END OF PAPER