Imperial College London

24 January 2024

Department of Bioengineering

BIOE60024 – Modelling in Biology II (MiB.2), Dr Thomas Ouldridge

Spring Term Coursework

To be returned by **Monday 25th March, 2024, 4pm**

Your coursework should contain: calculations if appropriate, annotated graphs and figures, *well-commented* code to back up any answers obtained with computational support, and *succinct* answers to the questions **with clear explanations and derivations**. Please note that instructions to *sketch* a graph are asking for you to draw an illustrative diagram by hand, supported by reasoning; instructions to *plot* a graph are asking you to produce an accurate graph of the data, by hand or computationally. Do not forget to include a title in your plots and to label *all* the axes. The document should be submitted in **PDF format**.

Please note that unreadable documents or illegible hand writing will make it very difficult to mark your coursework and will lead to points being deducted.

Your answers should be *yours*, i.e. written by you, in your own words, showing your own understanding. You must produce your own code and submit it when appropriate.

Please note that this coursework comprises 3 questions.

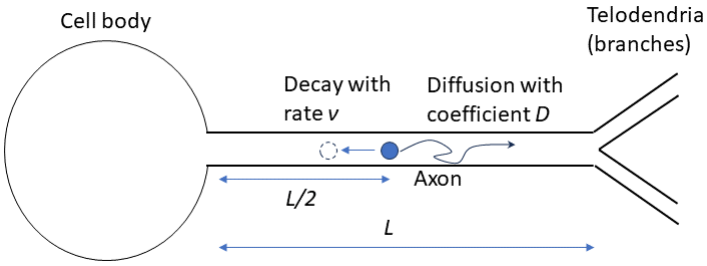

Figure 1: Simple model of a protein undergoing diffusion and decay within the axon of a nerve cell.

Stochastic processes and networks (/100)

We consider the diffusion and decay of a protein molecule in an axon of a nerve cell (Fig. 1). The main body of the axon is modelled as a 1-dimensional space of length L; the position of the protein within the axon is denoted by x ($0 \leq x \leq L$ while the protein is inside the axon). The protein undergoes free diffusion with diffusion coefficient D, and can also decay to a denatured state at a rate ν, independently from its diffusive motion. At time $t = 0$, the protein is found at $x = L/2$ and has not yet decayed; we are interested in whether the protein reaches either end of the main body of the axon before it decays. To answer this question, we can first analyse the distribution of decay times (ignoring diffusion), then analyse the distribution of times required to diffuse to the end of the axon body (ignoring decay), and finally compare the two.

Question 1: Unimolecular decay (/30)

We model the decay process as a two-state, continuous-time process with state 1 corresponding to the undecayed protein and state 0 corresponding to the decayed protein. Transitions from state 1 to state 0, an absorbing state, occur at a rate ν.

(a) Represent the decay process as a graph and give the rate matrix, indexing states in numerical order.

(b) Write down the ODE obeyed by $p_0(t)$, the probability of being in the decayed state, eliminating any dependence on $p_1(t)$. Solve the ODE to obtain $p_0(t)$.

(c) Let T_{dec} be the random variable giving the time of decay. We are interested in the distribution of decay times, $p(t_{\text{dec}})$, where $p(t_{\text{dec}})\delta t_{\text{dec}}$ is the number of decays during the time interval $T_{\text{dec}} = t_{\text{dec}}$ to $t_{\text{dec}} + \delta t_{\text{dec}}$. Explain why

$$p(t_{\text{dec}}) = \frac{\mathrm{d}p_0(t_{\text{dec}})}{\mathrm{d}t_{\text{dec}}}, \tag{1}$$

where $p_0(t_{\text{dec}})$ is the probability of being in the decayed state at time t_{dec}. Thus show that

$$p(t_{\text{dec}}) = \nu \exp(-\nu t_{\text{dec}}). \tag{2}$$

(d) Calculate the mean decay time $\langle T_{\text{dec}} \rangle$ and the variance of the decay time $\text{VAR}(T_{\text{dec}})$. *Note: please derive the answer, rather than writing it down by inspection.*

Please continue to the next page for the next question.

Question 2: Diffusion (/40)

If we ignore decay and the finite length of the axon (*i.e.*, we allow the position x to take any real value), the probability distribution $q(x,t)$ for the position x of the protein at time t obeys the free diffusion equation

$$\frac{\partial q(x,t)}{\partial t} = D\frac{\partial^2}{\partial x^2}q(x,t). \tag{3}$$

Note, we use q rather than p simply to distinguish from the quantities considered in question 1.

(a) Verify that

$$q(x,t) = \sqrt{\frac{1}{4\pi Dt}}\exp\left(-\frac{(x-L/2)^2}{4Dt}\right) \tag{4}$$

Is the correct solution for free diffusion in an infinite system, given an initial condition that the protein is at $x = L/2$. *Note: you may assume normalisation and that the boundary conditions in x (that $p(x,t) \to 0$ sufficiently fast as $x \to \pm\infty$) are satisfied.*

(b) Write down the integral(s) you would perform to calculate the probability that x is outside the region $0 \leq x \leq L$ at time t for a particle diffusing in an infite domain. Let us call this quantity $Q^\infty(t)$ *Note: you do not need to perform these integrals.*

(c) Which of the following is true:

- $Q^\infty(t)$ is less than the probability that the protein diffusing within the body of the axon of length L reaches $x = 0$ or $x = L$ by time t.
- $Q^\infty(t)$ is an accurate estimate of the probability that the protein diffusing within the body of the axon of length L reaches $x = 0$ or $x = L$ by time t.
- $Q^\infty(t)$ is more than the probability that the protein diffusing within the body of the axon of length L reaches $x = 0$ or $x = L$ by time t.

Explain your reasoning.

(d) We will use simulation to estimate the probability that the protein diffusing within the body of axon of length L has reached $x = 0$ or $x = L$ at least once by time t. Numerically integrate the Langevin equation for free diffusion,

$$\Delta x = \sqrt{2D\Delta t}\delta w \tag{5}$$

where δw is a Gaussian random variable of mean zero and variance 1. Use $L = 1\text{mm}$, $D = 10^{-4}\text{mm}^2\text{s}^{-1}$, and a time step $\Delta t = 1\text{s}$. Generate 10000 trajectories, and record the time at which each trajectory reaches $x = 0$ or $x = L$. Use the results to plot a probability density $q(t_{\text{diff}})$ for the time T_{diff} required to diffuse to the end of the axon. *Hint: you will need to form a histogram of observed diffusion times – I recommend a bin size of 50s.*

(e) Use your data to calculate estimates of $\langle T_{\text{diff}}\rangle$ and $\text{VAR}(T_{\text{diff}})$.

Please continue to the next page for the next question.

Question 3: Comparing decay and diffusion (/30)

(a) Identify a value of ν such that $\langle T_{\text{diff}} \rangle = \langle T_{\text{dec}} \rangle$. Plot $p(t_{\text{dec}})$ for this ν on the same axes as $q(t_{\text{diff}})$. Which distribution has the larger variance for this value of ν?

(b) An event is observed at $\langle T_{\text{diff}} \rangle / 10 = \langle T_{\text{dec}} \rangle / 10$. Is it more likely to be diffusion out of the main body of the axon or decay? Why, physically, do the two probability densities look so different at short times even though $\langle T_{\text{diff}} \rangle = \langle T_{\text{dec}} \rangle$?

(c) Estimate the probability that decay occurs before diffusion out of the main body of the axon, using the same values of $\langle T_{\text{diff}} \rangle = \langle T_{\text{dec}} \rangle$ obtained above. *Hint: one way to do this is to compare a list of sampled decay times to the list of sampled diffusion times you already have. For each pair of times, the event that happens is the one that corresponds to the smaller time (the other event doesn't happen).*

(d) $\langle T_{\text{diff}} \rangle$ and $\langle T_{\text{dec}} \rangle$ have been calculated in isolation, ignoring either the possibility of decay or diffusion out of the main body of the axon, respectively. Now consider only decay events that happen before diffusion out of the axon, or diffusion events that happen before decay. Without detailed calculation, describe how the average times for these events would compare to the previously calculated $\langle T_{\text{diff}} \rangle$ and $\langle T_{\text{dec}} \rangle$?