UNIVERSITY OF CAMBRIDGE

MAMA/356, NST3AS/356, MAAS/356

MAT3

MATHEMATICAL TRIPOS Part III

Thursday, 8 June, 2023 9:00 am to 11:00 am

PAPER 356

STOCHASTIC PROCESSES IN BIOLOGY

Before you begin please read these instructions carefully

Candidates have TWO HOURS to complete the written examination.

Attempt no more than **TWO** questions.
There are **THREE** questions in total.
The questions carry equal weight.

STATIONERY REQUIREMENTS
Cover sheet
Treasury tag
Script paper
Rough paper

SPECIAL REQUIREMENTS
None

You may not start to read the questions printed on the subsequent pages until instructed to do so by the Invigilator.

1 Consider a bacterium with position $X(t)$ evolving according to the stochastic differential equation

$$\mathrm{d}X(t) = \alpha \mathrm{d}t + \sqrt{2D}\mathrm{d}W(t), \tag{1}$$

in a domain $\Omega = (0, L)$ with a reflecting boundary at $x = L$ and a target that the bacterium wishes to find at $x = 0$. The constant $\alpha \in [-\bar{\alpha}, \bar{\alpha}]$ regulates the search strategy.

a) Denote by $Q(y, t)$ the probability that the bacterium has not yet found the target by time t, given that $X(0) = y \in \Omega$. What initial boundary value problem does Q satisfy?

b) Denote by $T(y)$ the time it takes for the bacterium to find the target, given that $X(0) = y \in \Omega$:

$$T(y) = \inf\{t \geqslant 0 : X(t) = 0 \,|\, X(0) = y\}.$$

What is the expected time $\tau(y) = \mathbb{E}[T(y)]$? Find the value of α that minimises $\tau(L)$ and compute $\tau_0 := \lim_{\alpha \to 0} \tau(L)$.

For the rest of the question, consider a different model for the motion of the bacterium, where its position $X(t) \in \Omega$ evolves as

$$\mathrm{d}X(t) = V(t)\mathrm{d}t, \tag{2}$$

and $V(t) \in \{-s, s\}$ is its velocity, which changes sign according to a Poisson process with rate $\lambda > 0$. We still consider the same target at $x = 0$ and a reflecting boundary at $x = L$ (that is, the bacterium reflects its velocity at $x = L$).

c) Denote by $Q^{\pm}(y, t)$ the probability that the bacterium has not yet found the target by time t, given that $X(0) = y \in \Omega$ and $V(0) = \pm s$. Write down the system of equations and boundary conditions satisfied by Q^+ and Q^-.

d) Denote by $T^{\pm}(y)$ the time it takes for the bacterium to find the target:

$$T^{\pm}(y) = \inf\{t \geqslant 0 : X(t) = 0, V(t) = -s \,|\, X(0) = y, V(0) = \pm s\}.$$

What are the expected times $\tau^{\pm}(y) = \mathbb{E}[T^{\pm}(y)]$?

e) Consider the scaling $s \to \infty$, $\lambda \to \infty$ of (2) with $\frac{s^2}{2\lambda} = D$ fixed. Assume that $V(0) = \pm s$ with equal probability. Show that, in this limit, $\tau^{\pm}(L) = \tau_0$, with τ_0 from (b). Comment on why this is the case.

f) Write a stochastic simulation algorithm of (2) with a fixed timestep $\Delta t > 0$ to estimate $\tau^+(y)$.

2 Consider N molecules of chemical species A in the one-dimensional domain $\Omega = [0, L]$. Divide the domain into m compartments of length $h = L/m$. Let $A_i(t)$ be the number of molecules of A at time t in the ith compartment centered at $x_i = hi - h/2$ for $i = 1, 2, \ldots, m$. Consider a compartment-based model for the movement of the molecules given as the following system of chemical reactions

$$\varnothing \underset{k_1^-}{\leftarrow} A_1 \underset{k_2^-}{\overset{k_1^+}{\rightleftarrows}} A_2 \underset{k_3^-}{\overset{k_2^+}{\rightleftarrows}} \cdots A_{m-1} \underset{k_m^-}{\overset{k_{m-1}^+}{\rightleftarrows}} A_m. \tag{1}$$

a) Let $p(\mathbf{a}, t)$, with $\mathbf{a} = (a_1, a_2, \ldots, a_m) \in \mathbb{Z}^m_{\geqslant}$, be the probability that $A_i(t) = a_i$. Write the chemical master equation for $p(\mathbf{a}, t)$.

b) Define the mean number of molecules in the ith compartment at time t as

$$M_i(t) = \langle a_i, p(\mathbf{a}, t)\rangle_{\mathbf{a}} = \sum_{a_1=0}^{\infty} \sum_{a_2=0}^{\infty} \cdots \sum_{a_m=0}^{\infty} a_i p(\mathbf{a}, t), \qquad \text{for } i = 1, 2, \ldots, m.$$

Show that

$$\frac{\mathrm{d}M_i}{\mathrm{d}t} = k_{i-1}^+ M_{i-1} - (k_i^+ + k_i^-) M_i + k_{i+1}^- M_{i+1}, \qquad \text{for } i = 2, \ldots, m-1,$$

and derive the equations satisfied by M_1 and M_m.

c) Consider the limit $h \to 0, x_i \to x$, such that $M_i(t) \to c(x, t)$, where $c(x, t)$ is a continuous function defined for all $x \in \Omega$. Determine the rates $k_i^\pm$ that lead to the following partial differential equation

$$\frac{\partial c}{\partial t}(x, t) = D \frac{\partial^2 c}{\partial x^2}(x, t) - \frac{\partial}{\partial x}\left[v(x) c(x, t)\right], \tag{2}$$

where $D > 0$ and $v(x)$ is a smooth function of x. Derive the boundary conditions for (2) at $x = 0, L$.

d) Let $X(t) \in \Omega$ be the position of one molecule of A at time t. Interpreting $c(x, t)$ in (2) as the probability density of $X(t)$, what Itô stochastic differential equation does $X(t)$ satisfy?

Write down a numerical scheme for the time evolution of $X(t)$ when $v(x) = x$, which takes into account the probability of $X(t)$ leaving Ω through $x = 0$ between $[t, t + \Delta t)$.

e) Now suppose that we modify (1) such that only one molecule of A at most is allowed per compartment, that is, $A_i(t)$ can only take values 0 or 1. If one molecule attempts to jump to an already occupied compartment, the jump is aborted. Hence the rates found in (c) are modified to

$$\tilde{k}_i^+ = (1 - a_{i+1}) k_i^+, \quad \tilde{k}_i^- = (1 - a_{i-1}) k_i^-,$$

with the convention that $a_0 = 0$. Make the simplifying assumption that the probabilities of two adjacent sites being occupied are independent of each other, that is, $\mathbb{E}[A_i(t)(1 - A_{i\pm1}(t))] = \mathbb{E}A_i(t)[1 - \mathbb{E}A_{i\pm1}(t)]$. Show that the resulting partial differential equation for $c(x, t)$ is

$$\frac{\partial c}{\partial t}(x, t) = D \frac{\partial^2 c}{\partial x^2}(x, t) - \frac{\partial}{\partial x}\left[v(x) c(x, t)(1 - c(x, t))\right]. \tag{3}$$

(You are not required to derive boundary conditions in this case.)

3 Consider two chemical species X and Y in a reactor of volume V, which are subject to the following system of four chemical reactions:

$$Y + Y \xrightarrow{\alpha_1} X, \quad X + X \xrightarrow{\alpha_2} X, \quad \varnothing \xrightarrow{\alpha_3/\varepsilon} Y, \quad X + Y \xrightarrow{\alpha_4/\varepsilon} X,$$

where $0 < \varepsilon \ll 1$ is a small real number, and $\alpha_1, \alpha_2, \alpha_3$ and α_4 are independent of ε. Let $X(t) \in \mathbb{Z}_\geqslant$ and $Y(t) \in \mathbb{Z}_\geqslant$ be respectively the number of molecules of X and Y at time t, where $\mathbb{Z}_\geqslant$ is the set of non-negative integers. Assume that $X(0) \neq 0$. Let $p(x, y, t)$ be the probability that $X(t) = x$ and that $Y(t) = y$.

a) Write down the operators $\mathcal{L}_0^*$ and $\mathcal{L}_1^*$ such that the chemical master equation for $p(x, y, t)$ can be written as

$$\frac{\partial}{\partial t} p(x, y, t) = \left(\frac{1}{\varepsilon} \mathcal{L}_0^* + \mathcal{L}_1^* \right) p(x, y, t).$$

Identify the slow chemical reactions and the slow chemical species.

b) Expand the probability into the perturbation series

$$p(x, y, t) = p_0(y|x) p_0(x, t) + \varepsilon p_1(x, y, t) + \cdots ,$$

where $p_0(y|x)$ is the probability that $Y(t) = y$ given that $X(t) = x$, and $p_0(x, t)$ is the probability that $X(t) = x$.

Determine the difference equation that $p_0(y|x)$ satisfies.

Determine the mean $\langle y, p_0(y|x) \rangle_y = \sum_{y=0}^{\infty} y p_0(y|x)$, and discuss whether this quantity is well-defined. You may use adjoint operators of $\mathcal{L}_0^*$ or $\mathcal{L}_1^*$ without proof.

c) Determine $\lambda_1(x)$ and $\lambda_2(x)$ in terms of $\alpha_1, \alpha_2, \alpha_3$, α_4 and V such that the chemical master equation for $p_0(x, t)$ can be written as

$$\frac{\partial}{\partial t} p_0(x, t) = \Big([E_x^{-1} - 1] \lambda_1(x) + [E_x^{+1} - 1] \lambda_2(x) \Big) p_0(x, t),$$

where $E_x^{\Delta x}$ is defined by $E_x^{\Delta x} f(x) = f(x + \Delta x)$ for any function f. You may use adjoint operators of $\mathcal{L}_0^*$ or $\mathcal{L}_1^*$ without proof.

d) Let

$$m(t) = \Big\langle x, p_0(x, t) \Big\rangle_x = \sum_{x=0}^{\infty} x p_0(x, t).$$

Determine the ordinary differential equation that $m(t)$ satisfies.

In this differential equation, assume that $\langle f(x), p_0(x, t) \rangle_x = f(\langle x, p_0(x, t) \rangle_x)$ for any function f. Then, take the limit $V \to \infty$ with $\lim_{V \to \infty} m(t)/V = \bar{x}(t)$. Determine $\lim_{t \to \infty} \bar{x}(t)$.

e) Write down a stochastic simulation algorithm that can be used to calculate the time-evolution of the slow species without simulating the fast reactions.

END OF PAPER