

MAT3

**MATHEMATICAL TRIPOS**      **Part III**

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

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**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

<p><b>You may not start to read the questions printed on the subsequent pages until instructed to do so by the Invigilator.</b></p>
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1 Consider a bacterium with position  $X(t)$  evolving according to the stochastic differential equation

$$dX(t) = \alpha dt + \sqrt{2D}dW(t), \quad (1)$$

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  $X(0) = y \in \Omega$ :

$$T(y) = \inf\{t \geq 0 : X(t) = 0 \mid X(0) = y\}.$$

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

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

$$dX(t) = V(t)dt, \quad (2)$$

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  $x = L$ ).

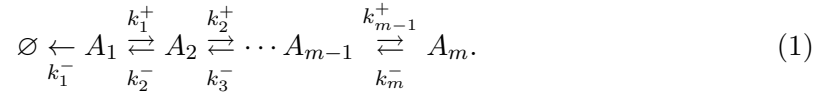
- c) Denote by  $Q^\pm(y, t)$  the probability that the bacterium has not yet found the target by time  $t$ , given that  $X(0) = y \in \Omega$  and  $V(0) = \pm s$ . Write down the system of equations and boundary conditions satisfied by  $Q^+$  and  $Q^-$ .
- d) Denote by  $T^\pm(y)$  the time it takes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

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

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

- e) Consider the scaling  $s \rightarrow \infty$ ,  $\lambda \rightarrow \infty$  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  $\tau_0$  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  $i$ th compartment centered at  $x_i = hi - h/2$  for  $i = 1, 2, \dots, m$ . Consider a compartment-based model for the movement of the molecules given as the following system of chemical reactions



a) Let  $p(\mathbf{a}, t)$ , with  $\mathbf{a} = (a_1, a_2, \dots, a_m) \in \mathbb{Z}_{\geq 0}^m$ , 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  $i$ th compartment at time  $t$  as

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

Show that

$$\frac{dM_i}{dt} = k_{i-1}^+ M_{i-1} - (k_i^+ + k_i^-) M_i + k_{i+1}^- M_{i+1}, \quad \text{for } i = 2, \dots, m-1,$$

and derive the equations satisfied by  $M_1$  and  $M_m$ .

c) Consider the limit  $h \rightarrow 0, x_i \rightarrow x$ , such that  $M_i(t) \rightarrow c(x, t)$ , 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

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

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  $\Omega$  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

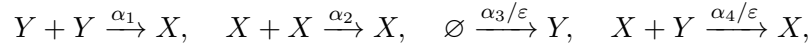
$$\tilde{k}_i^+ = (1 - a_{i+1})k_i^+, \quad \tilde{k}_i^- = (1 - a_{i-1})k_i^-,$$

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,  $\mathbb{E}[A_i(t)(1 - A_{i\pm 1}(t))] = \mathbb{E}A_i(t)[1 - \mathbb{E}A_{i\pm 1}(t)]$ . Show that the resulting partial differential equation for  $c(x, t)$  is

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

(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:



where  $0 < \varepsilon \ll 1$  is a small real number, and  $\alpha_1, \alpha_2, \alpha_3$  and  $\alpha_4$  are independent of  $\varepsilon$ . Let  $X(t) \in \mathbb{Z}_{\geq}$  and  $Y(t) \in \mathbb{Z}_{\geq}$  be respectively the number of molecules of  $X$  and  $Y$  at time  $t$ , where  $\mathbb{Z}_{\geq}$  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

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

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  $\alpha_1, \alpha_2, \alpha_3, \alpha_4$  and  $V$  such that the chemical master equation for  $p_0(x, t)$  can be written as

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

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

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

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  $V \rightarrow \infty$  with  $\lim_{V \rightarrow \infty} m(t)/V = \bar{x}(t)$ . Determine  $\lim_{t \rightarrow \infty} \bar{x}(t)$ .

- 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**