UNIVERSITY OF CAMBRIDGE

MAMA/356, NST3AS/356, MAAS/356

MAT3
MATHEMATICAL TRIPOS Part III

Friday 7 June 2024 1:30 pm to 3:30 pm

PAPER 356

STOCHASTIC PROCESSES IN BIOLOGY

Before you begin please read these instructions carefully

Candidates have TWO HOURS to complete the written examination.

Attempt **BOTH** questions.
There are **TWO** 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 four chemical species X_1, X_2, X_3 and X_4 in a reactor of volume V which are subject to the following seven chemical reactions:

$$2X_1 \xrightarrow{\alpha_1} \varnothing, \qquad X_1 \xrightarrow{\alpha_2} X_1 + X_2, \qquad 2X_2 \xrightarrow{\alpha_3} X_2, \qquad \varnothing \xrightarrow{\alpha_4} X_3,$$
$$X_3 + X_4 \xrightarrow{\alpha_5} \varnothing, \qquad X_2 \xrightarrow{\alpha_6} X_2 + X_4, \qquad X_2 + X_4 \xrightarrow{\alpha_7} X_4,$$

where $\alpha_1, \alpha_2, \ldots, \alpha_7$ are non-negative dimensionless rate coefficients.

Assume that there is initially 5 molecules of X_1 and no molecules of X_2, X_3 and X_4 in the reactor, i.e. $X_1(0) = 5$ and $X_2(0) = X_3(0) = X_4(0) = 0$. Let $p(x_1, x_2, x_3, x_4, t)$ be the probability that $X_1(t) = x_1$, $X_2(t) = x_2$, $X_3(t) = x_3$ and $X_4(t) = x_4$, where x_1, x_2, x_3 and x_4 are non-negative integers.

a) State the *Gillespie stochastic simulation algorithm* for this chemical system.

b) The *chemical master equation* for $p(x_1, x_2, x_3, x_4, t)$ can be written in the form

$$\frac{\partial}{\partial t} p(x_1, x_2, x_3, x_4, t) = \mathcal{L}^* p(x_1, x_2, x_3, x_4, t).$$

State the forward operator $\mathcal{L}^*$ and the backward (adjoint) operator $\mathcal{L}$.

In the remainder of this question, assume that $V = 1$.

c) Assume that $\alpha_1 = 1$ and let $g(t)$ be the probability that there is one molecule of X_1 in the reactor at time t. Find $g(t)$ as a function of time.

d) Let the mean of a suitable function f be denoted by

$$\langle f(x_1(t), x_2(t), x_3(t), x_4(t)) \rangle = \sum_{x_1=0}^{\infty} \sum_{x_2=0}^{\infty} \sum_{x_3=0}^{\infty} \sum_{x_4=0}^{\infty} f(x_1, x_2, x_3, x_4) p(x_1, x_2, x_3, x_4, t),$$

and its stationary mean by $\langle f(x_1^*, x_2^*, x_3^*, x_4^*) \rangle = \lim_{t\to\infty} \langle f(x_1(t), x_2(t), x_3(t), x_4(t)) \rangle$.

(i) Assume that $\alpha_7 = 0$. Derive differential equations for $\langle x_2(t) \rangle$ and $\langle x_2^2(t) \rangle$. Briefly explain why solving for the stationary mean $\langle x_2^* \rangle$ requires solving an infinite system of equations.

By neglecting the equations for $\langle x_2^n(t) \rangle$ with $n \geqslant 3$, and assuming that

$$\langle (x_2^* - \langle x_2^* \rangle)^n \rangle = 0 \quad \text{for all } n \geqslant 3,$$

show that $\langle x_2^* \rangle$ is a root of a cubic polynomial, which you should specify in terms of the rate coefficients. You do not have to solve for $\langle x_2^* \rangle$.

(ii) Disregard the assumptions from part (i) and assume instead that $\alpha_7 > 0$. Assume also that there exists a unique stationary mean $\langle x_i^* \rangle$ for all $i = 1, 2, 3, 4$. Compute $\langle x_2^* \rangle$ in terms of the rate coefficients.

e) Consider now arbitrary positive coefficients $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6, \alpha_7 > 0$. Assume that

$$\frac{\alpha_3 \alpha_4}{\alpha_2 \alpha_6} > 1.$$

Show that the mean copy number of some species tends to infinity in the long run, i.e., that $\lim_{t\to\infty} \langle x_i(t) \rangle = \infty$ for some i. Identify the species index i.

2 Consider a particle described by its position $(X(t), Y(t))$ in the square domain

$$\Omega = \left\{(x, y) \in \mathbb{R}^2 : \ -1 \leqslant x \leqslant 1, -1 \leqslant y \leqslant 1\right\},$$

evolving according to the diffusion process

$$\begin{aligned} \mathrm{d}X(t) &= a_1 \mathrm{d}t + \sqrt{2}\mathrm{d}W_1(t), \\ \mathrm{d}Y(t) &= a_2(X, Y)\mathrm{d}t + \sigma(Y)\mathrm{d}W_2(t), \end{aligned}$$

where W_1, W_2 are independent one-dimensional Brownian motions, a_1 is a constant and $a_2(x, y)$ and $\sigma(y)$ are functions. The particle has initial condition $(X(0), Y(0)) = (0, 0)$ and reflecting boundary conditions on $\partial\Omega$.

a) State the Fokker–Planck equation for the probability density $p(x, y, t)$ in Ω, together with the initial and boundary conditions.

b) Let (X_n, Y_n) be the Milstein scheme approximation to $(X(t_n), Y(t_n))$, where $t_n = n\Delta t$ for $\Delta t > 0$ and $n = 0, 1, \ldots, N$. Write the scheme (including boundary conditions) and comment on its weak and strong order of convergence.

For the rest of the question, we replace the boundary condition on $x = \pm 1$ with a partially reflecting/adsorbing boundary condition

$$J \cdot n = \kappa p, \quad \text{on} \quad x = \pm 1,$$

where J is the probability flux associated to the Fokker–Planck equation in (a), n is the outward normal to $\partial\Omega$ and $\kappa > 0$ is the reactivity. The reflecting boundary conditions on $y = \pm 1$ remain unchanged.

c) For $a_1 = \kappa = 1$, calculate the mean time τ for the particle to be adsorbed on $\partial\Omega$. [*Hint: you must consider how the boundary conditions on p transform for τ.*]

d) Now set $\kappa = \infty$ (fully adsorbing boundary). What is the probability $g(a_1)$ that the particle is absorbed on the left boundary, i.e., with final value $X(T) = -1$? Comment on the behaviour of $g(a_1)$ for large positive and negative values of a_1.

END OF PAPER