UNIVERSITY OF CAMBRIDGE

MATHEMATICAL TRIPOS Part III

Tuesday 12 June 2007 1.30 to 3.30

PAPER 74

SYSTEMS BIOLOGY

*Attempt **ALL** questions.*

*There are **THREE** questions in total.*

The questions carry equal weight.

STATIONERY REQUIREMENTS
Cover sheet
Treasury Tag
Script 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 mutually repressive system in which concentrations $x(t)$ and $y(t)$ follow:

$$\frac{dx}{dt} = f(y) - x \,, \quad \frac{dy}{dt} = g(x) - y \,.$$

(a) Assume that functions f and g are positive, decreasing and bounded. Sketch the phase plane and derive a condition for multi-stability. Formulate the condition in terms of $\partial \text{In } f/\partial \text{In } y$ and $\partial \text{In } g/\partial \text{In } x$.

(b) Let $f(y) = \lambda \left(\frac{1}{1+y}\right)^n$ and $g(x) = \lambda \left(\frac{1}{1+x}\right)^m$ where m, n and λ are positive constants. For what parameter combinations of m and n will the system not display multi-stability for any values of λ?

2 Consider a system with stochastic reaction events

$$x \xrightarrow{\lambda} x + 3 \quad \text{and} \quad x \xrightarrow{\beta\sqrt{x}} x - 1 \,,$$

where λ and β are (positive) rate constants.

(a) Approximating the average death rate by $\langle \beta\sqrt{x}\rangle \approx \beta\sqrt{\langle x\rangle}$, calculate the steady state values of $\langle x\rangle$, the elasticity H, the average lifetime τ and the average chemical event size $\langle s\rangle$.

(b) State the normalised stationary Fluctuation Dissipation Theorem and demonstrate that the normalized variance follows $\eta = \sigma^2/\langle x\rangle^2 \approx 4\langle x\rangle^{-1}$.

(c) Formulate the Gillespie algorithm for simulating exact sample paths for the system above. It is sufficient to write the algorithm specifically for the example, without motivating the underlying assumptions of the algorithm.

3 Consider a metabolic system with stochastic reaction events

$$x_1 \xrightarrow{\lambda} x_1 + 1 \quad \text{and} \quad x_1 \xrightarrow{\beta x_1} x_1 - 1\,,$$

$$x_2 \xrightarrow{\lambda} x_2 + 1 \quad \text{and} \quad x_2 \xrightarrow{\beta x_2} x_2 - 1\,,$$

$$\{x_1, x_2\} \overset{C_{x_1 x_2}}{\longrightarrow} \{x_1 - 1, x_2 - 1\}\ .$$

Both components are thus made at constant rates, decay exponentially, and join to form a complex.

(a) Write down *exact* equations for changes in the averages. Also write down an approximate equation for the averages, assuming that fluctations around the average are small. Use the approximate equations when solving (b)–(d) below.

(b) Sketch the phase planes for the following three cases: (i) $C = 0$, (ii) $\beta = 0$ and (iii) the general case.

(c) Let E be the average fraction of molecules that are eliminated through complex formation,

$$E = \frac{C\langle x_1\rangle\langle x_2\rangle}{\beta\langle x_2\rangle + C\langle x_1\rangle\langle x_2\rangle} = \frac{C\langle x_1\rangle\langle x_2\rangle}{\beta\langle x_1\rangle + C\langle x_1\rangle\langle x_2\rangle}\,.$$

Show that the stationary normalised Jacobian M and diffusion matrix D of the normalised Fluctuation Dissipation Theorem can be written as

$$M = \frac{1}{\tau}\begin{bmatrix} 1 & E \\ E & 1 \end{bmatrix} \quad \text{and} \quad D = \frac{1}{\tau}\frac{1}{\langle x\rangle}\begin{bmatrix} 2 & E \\ E & 2 \end{bmatrix}\,,$$

where the parameter $\tau = \tau_1 = \tau_2$ is the average lifetime of either component, and $\langle x\rangle = \langle x_1\rangle = \langle x_2\rangle$ is the average number of molecules of either component.

[Hint: as a starting point, use the definitions

$$M_{ij} = \frac{H_{ij}}{\tau_i}\,,\ D_{ii} = \frac{2\langle r_i\rangle}{\tau_i\langle x_i\rangle}\,, \quad \text{and} \quad D_{12} = D_{21} = \frac{(-1)^2 C\langle x_1\rangle\langle x_2\rangle}{\langle x_1\rangle\langle x_2\rangle} = C\,,$$

where the H_{ij} are the elasticities and the $\langle r_i\rangle$ are the average event sizes.]

(d) Solve the stationary normalised Fluctuation Dissipation Theorem for the covariance matrix η. Simplify the results as far as possible. To reduce notational complexity, use the fact that the system is symmetric and introduce $V = \eta_{11} = \eta_{22}$ and $W = \eta_{12} = \eta_{21}$. Discuss what happens with the variance and the covariance as $E \to 1$, and relate it to the phase plane analysis in (b).

END OF PAPER