IMPERIAL COLLEGE LONDON

B.Eng. Examinations 2014–2015
Part 3

Biomedical Engineering

BE3-HMIB Modelling in Biology

13 May 2015, 1pm-3.30pm
(duration: 150 minutes)

YOU MUST ANSWER ALL QUESTIONS

Marks are shown next to each question.
The marks for questions (and parts thereof) are indicative and may be slightly moderated at the discretion of the Examiner.

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Question 1 **1D model of gene auto-activation.** Consider a self-activated gene, *i.e.* a gene encoding for a protein which can bind to the promoter region of this same gene to enhance its transcription. The dynamics of this self-activated gene can be represented by the following ODE model of order 2:

$$\dot{m} = k_1 \frac{p}{K+p} - d_1 m \tag{1}$$

$$\dot{p} = k_2 m - d_2 p \tag{2}$$

where $m(t) \geq 0$ represents the mRNA concentration at time t, $p(t) \geq 0$ represents the protein concentration at time t, and the short-hand notation $\dot{x}$ stands for $\frac{dx}{dt}$. The parameters appearing in this model are defined as follows: $k_1 \geq 0$ represents maximal transcription rate, $K \geq 0$ the activation coefficient, $k_2 \geq 0$ the translation rate, $d_1 \geq 0$ the mRNA degradation rate, and $d_2 \geq 0$ the protein degradation rate.

It can be shown that the second order model (1)-(2) can be reduced to a **first order model** of the form:

$$\boxed{\dot{p} = \alpha \frac{p}{K+p} - d_2 p} \tag{3}$$

a) First order model (3) **and its fixed point(s) analysis** **/50**

i) Using the quasi-steady state approximation $\dot{m} = 0$, show how the model (1)-(2) can be reduced to the first order model (3) and give the analytical expression of $\alpha \geq 0$ in terms of the parameters in (1)-(2).

ii) Find the *analytical expression* of the fixed point(s) of (3). Based on this, determine how many fixed points the model described in (3) can have depending on the parameter $d_2 \geq 0$. (Remember that the concentration, p, is a non-negative quantity by definition).

b) Stability and bifurcation analysis of the first order model (3) **/50**

i) Using a graphical approach perform a stability analysis of (3). In particular, determine the direction of the flow on the p axis and, using this, determine the stability of each fixed point for the model given in (3).

ii) Considering d_2 as the bifurcation parameter, draw a bifurcation diagram of (3). Clearly indicate on the bifurcation diagram the critical value of d_2 at which a bifurcation occurs.

The two parts carry equal marks.

Question 2 **Short answer questions from both parts of the course**

a) Consider a continuous-time, nonlinear Ordinary Differential Equation (ODE) model of the form $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$. Give the different attractors that this ODE model can have when: **/15**

i) $\boldsymbol{x} \in \mathbb{R}$, *i.e.* the ODE model is 1D

ii) $\boldsymbol{x} \in \mathbb{R}^2$, *i.e.* the ODE model is 2D

iii) $\boldsymbol{x} \in \mathbb{R}^n$, with $n \geq 3$, *i.e.* the ODE model is 3D or higher

b) Consider the second order linear dynamical system:

$$\dot{\boldsymbol{x}} = A\boldsymbol{x}, \quad \text{with} \quad A = \begin{pmatrix} -k & k \\ -k & 1 \end{pmatrix}, \quad \text{and} \quad \boldsymbol{x} \in \mathbb{R}^2,$$

where $k \in \mathbb{R}$ is an unknown, real (not complex or imaginary) parameter.

Show that for $-\frac{1}{3} \leq k \leq 1$, trajectories of the phase plane will approach or escape the origin exponentially, without any spiralling (*i.e.* without any rotation). *Hint: This is linked to a property of the eigenvalues of A.* **/35**

c) **i)** Draw a social network where everybody has exactly a node degree of 3 and the *global* clustering coefficient is exactly $\frac{1}{4}$. **/25**

ii) Explain the difference between null-recurrent and positive recurrent Markov process states. Illustrate your explanation with a suitable example. **/25**

The three parts carry, respectively, 15%, 35%, and 50% of the marks.

Question 3 **Fungi** are complex eukaryotic organisms that can undergo reproduction in more than one way. The life-cycle of fungi can be represented as a Markov Process with state transitions occurring about every week. The following 6 states are known: (G) Germination, (R) Rest, (H) Heterokaryotic, (M) Meiosis, (S) Sporing, (D) Death. All fungi are "born" in the Germination state. Here we model a species of fungi that has two reproductive strategies: **1.** Sporing, that is asexual reproduction through spores (S); and **2.** Sexual reproduction through mating (H, M). The transition probabilities to other states are given as follows:

$$
\begin{aligned}
p_{GR} &= \frac{1}{2} \quad p_{RH} = \tfrac{1}{4} \quad p_{RD} = \frac{1}{8} \\
p_{RS} &= \frac{1}{4} \quad p_{SR} = \tfrac{1}{2} \quad p_{SG} = \frac{1}{2} \\
p_{HM} &= \frac{1}{2} \quad p_{MR} = \tfrac{1}{2} \quad p_{MG} = \frac{1}{2}
\end{aligned}
$$

All calculations should be doable using fractions.

a) Sketch out the Markov process including all states and all possible transitions. Label the states and transitions. Mark the absorbing states. Then, write out the transition probability matrix using the Markov matrix notation used in the course. **/30**

b) Derive the mean life time in weeks of this species of fungi based on the Markov Process model. Use first-step analysis on the Markov chain to derive this result and explain your derivation. **/35**

c) Derive the mean number of weeks these fungi are in a reproductive state. Use first-step analysis on the Markov chain to derive this result and explain your derivation. **/35**

The three parts carry, respectively, 30%, 35%, and 35% of the marks.