IMPERIAL COLLEGE LONDON

B.Eng. Examinations 2011-2012
Part 3

Biomedical Engineering

BE3.HMIB Modelling in Biology

Monday 14 May, 2.30pm - 5pm
(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 they may be slightly moderated at the discretion of the Examiner.

DO NOT TURN THIS PAGE UNTIL YOU ARE TOLD TO DO SO.

Question 1 **Markov processes in Cancer treatment models**

In Small Cell Lung cancer treatment, cells are thought of as being in one of two discrete states, namely either "Growing" tumor cells or "Quiescent" cells. Experimentally the following observations were made by studying Small Cell Lung cancer samples in the Petri Dish on a day by day basis. Half of the growing cells turn quiescent overnight; two out of five quiescent cells turn into growing cells overnight; the other cells remain in their respective state. We can assume that these transition probabilities do not change over time.

a) **i)** Sketch out the labelled directed Markov process diagram of the cell states G, Q and their state transitions.

ii) Write out the state transition probability matrix $\mathbf{P}$ for the above 2-state Markov process.

iii) In the long run what proportion of cells will be in each state? Briefly explain your approach and show your derivation.

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b) A new cancer drug targets the quiescent cancer cells. The effect of the drug was quantified: Instead of three out of five cells remaining overnight in the quiescent state without the drug, with the drug now one third of these cells "Die" instead of remaining quiescent overnight.

i) Sketch out the labelled directed Markov process diagram of the 3 cell states $\{G, Q, D\}$ and their state transitions.

ii) Write out the state transition probability matrix $\mathbf{P}$ for this 3-state Markov process.

iii) Does this Markov process have a stationary distribution π? Justify your answer briefly.

iv) Calculate the average number of days it takes for a quiescent and a growing cell to die with the new drug treatment.

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The two parts carry, respectively, 40%, and 60% of the marks.

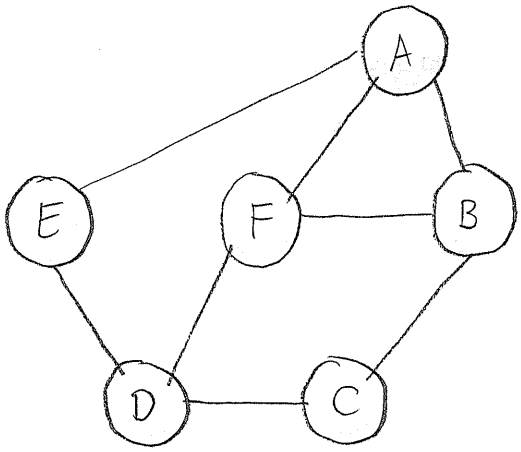

Fig. 1: (Question 2.a) Social Network of 6 friends A, B, C, D, E, F and their mutual interactions.

Question 2 Short answer questions from both parts of the course

a) **i)** Write out the adjacency matrix for the social network depicted in Fig. 1.

ii) What are the clustering coefficients for nodes A,D,F and E?

iii) What is the diameter of the social network in Fig. 1?

iv) Explain briefly in words how to create a Watts-Strogatz network.

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b) **i)** Consider a continuous-time, nonlinear Ordinary Differential Equation (ODE) model of the form $\dot{x} = f(x)$. List the different attractors that this ODE model can have when x is

A) 1D

B) 2D

C) 3D and higher

ii) Briefly explain the concept of *bifurcation* of a dynamical system.

iii) Briefly explain the following types of bifurcations:

A) Transcritical bifurcation

B) Saddle-node bifurcation

C) Pitchfork bifurcation

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The two parts carry equal marks.

Question 3 **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 model composed of two Ordinary Differential Equations:

$$\dot{m} = k_1 \frac{p^2}{K^2 + p^2} - d_1 m \tag{1}$$

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

where $m(t) \geq 0$ represents the mRNA concentration at time t and $p(t) \geq 0$ 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 threshold, $k_2 \geq 0$ 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:

$$\boxed{\dot{p} = \alpha \frac{p^2}{K^2 + p^2} - d_2 p} \tag{3}$$

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

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 identify $\alpha \geq 0$ with respect to the parameters in (1)-(2).

ii) Find the analytical expression of the fixed points of (3). Based on this, show how many fixed points the model described in (3) can have depending on the parameter $d_2 \geq 0$.

iii) For the model in (3), show that a bifurcation occurs when d_2 becomes larger than a certain critical value. Calculate, in terms of the parameters of (3), the critical value of d_2 at which the bifurcation occurs.

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

i) Using a graphical approach (nullcline) explain the stability of each fixed point for the model given in (3) and represent the flow on the p axis around each fixed point.

ii) Name and briefly explain the type of bifurcation that occurs when d_2 becomes larger than the critical bifurcation value.

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The two parts carry, respectively, 60%, and 40% of the marks.