IMPERIAL COLLEGE LONDON

B.Eng. Examinations 2012-2013
Part 3

Biomedical Engineering

BE3.HMIB Modelling in Biology

17 May 2013, 10am-12.30pm
(duration: 150 minutes)

YOU MUST ANSWER ALL 3 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 **Model of order 1 for the prevalence of Heterochromia**

Heterochromia of the eye (also known as heterochromia iridis or heterochromia iridum) refers to a difference in the colouration of the iris of the two eyes in humans.

The prevalence in time of heterochromia in the world-wide human population can be modelled as

$$\dot{x} = \frac{dx}{dt} = x\,(1-x)\,(x-p)\,, \qquad x(0) = x_0 \in [0,1] \tag{1}$$

where $x(t) \in [0,1]$ denotes the fraction of the population with heterochromia at time t, and x_0 denotes the initial fraction of the population with heterochromia. $p \in (0,1)$ is a parameter whose value denotes the probability that a child does not inherit heterochromia from its parents if at least one of them has it (we assume this probability is neither 0 nor 1).

In all the sub-questions that follow, remember that x denotes the fraction of the human population that has heterochromia, thus we are only interested in values of x between 0 and 1.

a) Fixed point(s) and phase line analysis of model (1)

i) Find all the fixed points of model (1).

ii) Roughly, sketch the phase line, i.e., $\dot{x}$ vs x. On it label the fixed points, and draw on the x-axis arrows indicating the direction of the flow, i.e., the direction in which x is moving.

/40

b) Stability, basin(s) of attraction and interpretation

i) Using your phase line sketch and the direction of the flow, classify each of the fixed points as locally stable or unstable. In addition, find the region of attraction of each of the fixed points.

ii) Using your answers to the above, what does the model predict about the long-term prevalence of heterochromia (i.e., what are the attractors of (1))? How do the parameter $p \in (0,1)$ and the initial condition $x_0 \in [0,1]$ influence the long-term prevalence of heterochromia? Does this make sense with regards to the meaning of p?

iii) The fraction of the population with heterochromia is currently estimated at $x_0 = 0.0067$. In addition, the probability that a child does not inherit heterochromia form its parents is estimated at $p = 0.27$. Based on your

answers to the previous parts, what is your prediction to the long-term (i.e., time asymptotic) prevalence of heterochromia in the population for the values of x_0 and p considered here?

/40

c) Bifurcation analysis Consider model (1) abstractly, that is assume that x and p have no physical meaning and thus are not constrained to be non-negative. Vary p between $-\frac{1}{2}$ and $\frac{1}{2}$. ⟶ REGION OF INTEREST.

i) Does a bifurcation occur? If so what kind of bifurcation is it?

ii) At what value of p does it occur?

iii) Draw the corresponding bifurcation diagram.

/20

The three parts carry, respectively, 40%, 40%, and 20% of the marks.

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

a) **Fixed point(s) and Jacobian matrix of a model of order 2** Consider the following 2^{nd} order model:

$$\begin{cases} \dot{x} = x - x\,y, \\ \dot{y} = x\,y - y. \end{cases} \tag{2}$$

In what follows, **do not assume that $x(t)$ and $y(t)$ have to be non-negative.**

i) Find all the fixed points of model (2).

ii) Compute the analytical expression of the Jacobian matrix (also known as the linearisation matrix) of model (2). At this stage, we only ask for the analytical expression of the Jacobian matrix for model (2), i.e., we **do not** ask to plug in the coordinates of the fixed points into the Jacobian matrix.

/30

b) **Local stability and the Hartman-Grobman Theorem (also known as the linearisation theorem)** Evaluate the Jacobian matrix obtained above at each fixed point. Using the Hartman-Grobman Theorem, what can you deduce regarding the local behaviour of each of the fixed point(s) of model (2)? If appropriate, sketch the local phase portrait around each fixed point. **/20**

c) **Biological network analysis** Draw a network of 4 nodes such that each node is at least connected to another node and simultaneously so that each node has a local clustering coefficient of 1. Please label each node with the local clustering coefficient and node degree. **/12**

d) **Biological network analysis** Draw a network of 4 nodes such that the average node degree is 2 and the average clustering coefficient of the network is 0. Please label each node with the local clustering coefficient and node degree. **/12**

e) **Biological network synthesis** What class of networks does the model by Barabasi-Alberts capture and how? **/12**

f) **Biological network synthesis** What generative features renders the Barabasi-Alberts model attractive in the context of protein-networks. **/14**

The six parts carry, respectively, 30%, 20%, 12%, 12%, 12%, and 14% of the marks.

Question 3 **Markov processes of cell cycles in healthy and mutant cells**

The life cycle of a healthy (**wild-type**) cell undergoes a sequence of discrete phases **Q**uiescent, **I**nterphase and **M**itosis (cell division). Experimentally, we can monitor the state of individual cells in a Petri dish on an hourly basis and determine the probability that a cell transits from one state to the next between each observation period. Note, if a self-transition occurs (e.g., from Mitosis to Mitosis) we assume that it means that the stage continues on (instead of having re-started a new). We can write down a labelled transition probability matrix for the life cycle of the wild-type cell as follows:

$$\mathbf{P}_{\text{wild-type}} = \begin{array}{c} \\ Q \\ I \\ M \end{array} \begin{array}{c} \begin{array}{ccc} Q & I & M \end{array} \\ \begin{pmatrix} 1/2 & 1/2 & 0 \\ 1/2 & 0 & 1/2 \\ 0 & 1/2 & 1/2 \end{pmatrix} \end{array}$$

An environmentally induced **mutation** of the cell's genome affects the cell cycle in a fundamental manner, altering the state transitions of these mutant cells. The mutant cell state transition graph is depicted in Fig. 1.

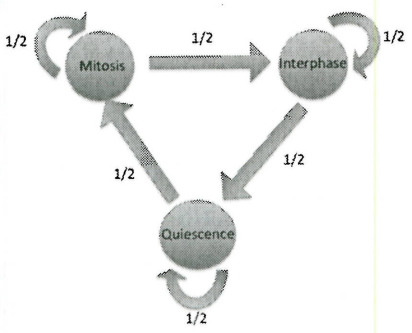

Fig. 1: Markov process model of the life-cycle of a mutant cell.

a) Markov Process basics

i) Sketch out the labelled directed Markov process diagram for the transition probability matrix of the wild- type cell's three states Q, I, M and their state transitions.

ii) Write out the labelled Markov transition probability matrix of the mutant cell cycle based on the sketch depicted in Fig. 1.

iii) In modelling cell behaviour as a Markov process, we assumed that the Markov property holds. Briefly, state the Markov property and explain the meaning of this assumption in the context of these cells and their life-cycle.

/30

b) Steady states of Markov Processes

i) In the long run what proportion of time does a wild-type cell spend in each state? Show your derivation.

ii) In the long run what proportion of time does a mutant cell spend in each state? Show your derivation.

/30

c) First-step analysis of Markov Processes

Cancerous cell mutations are often characterised by more frequent cell divisions in comparison to the non-mutant ("wild-type") cell (among other factors). Does the mutant cell cycle suggest more frequent cell divisions than the wild-type cell?

i) Calculate using first-step analysis the average number of hours it takes to go *around the cycle* from when a cell leaves Mitosis to when it returns to Mitosis (self-transitions do not count for departures and arrivals in the Mitosis state) for the wild-type cell.

ii) Calculate using first-step analysis the average number of hours it takes to go *around the cycle* from when a cell leaves Mitosis to when it returns to Mitosis (self-transitions do not count for departures and arrivals in the Mitosis state) for the the mutant cell.

(Hint: Mitosis as absorbing state). /40

The three parts carry, respectively, 30%, 30%, and 40% of the marks.