IMPERIAL COLLEGE LONDON

B.Eng. Examinations 2013–2014
Part 3

Biomedical Engineering

BE3.HMIB Modelling in Biology

14 May 2014, 2pm-4.30pm
(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 **Lakes** generally tend to be in an *oligotrophic* state or an *eutrophic* state. The oligotrophic state is characterised by clear waters and small amounts of nutrients (in particular, phosphorous) and plants. On the other hand, the eutrophic state is characterised by murky waters and large amounts of nutrients (in particular, phosphorous) and plants. Eutrophication (*i.e.* the process of driving a lake from an oligotrophic state to an eutrophic state) is often caused by excessive amounts of phosphorous entering the lake, typically as a by-product of industrial or agricultural activities occurring in the vicinity of the lake. More often than not, it is ecologically and commercially favourable for lakes to be in an oligotrophic state. In 1999, Carpenter, Ludwig and Brock proposed the following model for the amount of phosphorous in a lake:

$$\dot{x}(t) = a - \frac{1}{2\sqrt{2}}x(t) + \frac{x^2(t)}{1 + x^2(t)}. \tag{1}$$

The variable $x(t) \in [0, \infty)$ represents the amount of phosphorous (in some unspecified unit) in the lake as a function of time. The term $a \geq 0$ represents the constant rate at which phosphorous enters the lake from the surrounding lands, the term $-\frac{1}{2\sqrt{2}}x(t)$ is the rate at which phosphorous is removed from the lake by absorption from plants and sedimentation, and the term $\frac{x^2(t)}{1+x^2(t)}$ represents the rate at which phosphorous re-enters the lake from the sediments.

In all the sub-questions that follow, remember that x denotes the amount of phosphorous in the lake, and therefore we are only interested in non-negative values of x.

a) Suppose that there is no inflow of phosphorus into the lake (that is, $a = 0$). Compute all the fixed points analytically when $a = 0$. **/15**

b) Suppose that $a = 0$ and that model (1) has 3 fixed points x_1, x_2 and x_3 such that $0 \leq x_1 < x_2 < x_3$.

i) Using a graph of $\dot{x}$ vs x, find the fixed points graphically.

ii) On the x-axis of your $\dot{x}$ vs x graph draw arrows indicating the direction of the flow, *i.e.* the direction in which x is moving.

Hint: You might find it useful to sketch both $\frac{1}{2\sqrt{2}}x$ and $\frac{x^2}{1+x^2}$ versus x on the same plot and to use these two curves to find the fixed points and the direction of the flow on the x-axis. **/15**

c) Suppose that $a = 0$.

i) On your graph in part **b)** classify each of the fixed points as stable or unstable.

ii) In addition, find the region(s) of attraction of each of the fixed points.

/20

d) Suppose that $a = 0$. Does it make sense to identify any of the fixed points with the lake's oligotrophic and eutrophic states? If so, say which fixed point correspond to eutrophic or oligotrophic states and **briefly** explain.

Hint: Unstable fixed points are not observed in real life (since any small perturbation drives a system away from an unstable fixed point and small perturbations occur constantly in real life). **/15**

e) What type of bifurcation occurs as the rate of inflow of phosphorus (that is, a) increases from zero to infinity? Give a one line interpretation of what this means in terms of the lake.

Hint: You might want to think about the $\dot{x}$ vs x plot described in the hint of part **b)** and consider the effect of $a > 0$ on this plot. **/20**

f) A lake is said to be *reversible* if, by simply removing the inflow of phosphorus (*i.e.* taking a from a positive value to zero), its state automatically returns to one of low phosphorous levels. A lake is said to be *irreversible* if, once it undergoes eutrophication, cutting the inflow of phosphorous is not sufficient to drive the lake to a state of low phosphorous levels. Based on your answers to the previous parts, argue whether the lake modelled by (1) is reversible or irreversible. **/15**

The six parts carry, respectively, 15%, 15%, 20%, 15%, 20%, and 15% of the marks.

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

a) Fixed points and Jacobian matrix of a model of order 2. **/20**

Consider the following set of chemical reactions:

$$A \xrightarrow{k_1} X_1, \qquad X_1 \xrightarrow{k_2} X_2, \qquad 2X_1 + X_2 \xrightarrow{k_3} 3X_1, \qquad X_1 \xrightarrow{k_4} \emptyset \tag{2}$$

where A is some chemical species kept at a constant level and k_1, k_2, k_3 and k_4 are positive reaction constants.

Supposing that $[A] = 1$ and $k_1 = k_2 = k_3 = k_4 = 1$, and using the law of mass action the set of reactions in (2) can be modelled with the following **second order ODE model**:

$$\begin{cases} \dot{x}_1 = 1 - 2x_1 + x_1^2 x_2 \\ \dot{x}_2 = x_1 - x_1^2 x_2 \end{cases} \tag{3}$$

i) Find the analytical expression of the fixed points of the second order ODE model in (3).

ii) Give the analytical expression of the Jacobian matrix (also known as the linearisation matrix) of (3). At this stage, we only ask for the analytical expression of the Jacobian matrix for model (3), *i.e.* we do not ask to plug in the coordinates of the fixed points into the Jacobian matrix.

b) Local stability and the Hartman-Grobman Theorem (also known as the linearisation theorem). **/30**

i) Evaluate the Jacobian matrix obtained above at each fixed point of (3) and compute the corresponding eigenvalues.

ii) Using the Hartman-Grobman Theorem, what can you deduce regarding the local behaviour of each of the fixed point(s) of model (3)?

iii) If appropriate, sketch the local phase portrait around each fixed point.

c) Consider the following **biological network** **/30**

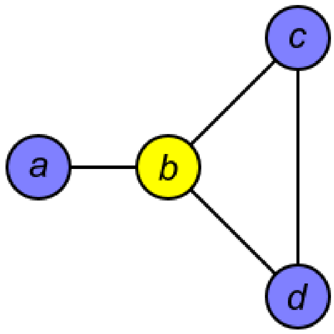

Fig. 1: A 4 node biological network

i) Determine the network's diameter.

ii) Determine the network's clustering coefficient.

iii) To assess network robustness we consider the case where each link between nodes may be deleted with equal probability. Determine the probability that a single random link deletion will produce a disconnected network (*i.e.* a network where a node becomes unreachable).

iv) What makes node b special?

d) Explain in your own words how to differentiate a **small-world** network from a **hierarchical network** using network measures. **/20**

The four parts carry, respectively, 20%, 30%, 30%, and 20% of the marks.

Question 3 **Neurons** and their action potentials are the fundamental means of representing and transmitting information in the nervous system. Characterising neuronal activity and its variability is therefore of great importance, *e.g.* for the design of any device interfacing with the nervous system. Instead of using differential equations to model neural activity we will use discrete-time, discrete-state Markov processes, as these can capture at a systems-level both the different states of a neuron and the variability of its activity.

We know that neurons undergo in sequence the 4 following states:

- State R: The neuron is at rest. When at rest the neuron may remain at rest or transition to a more active state F.
- State F: The neuron fires an action potential. Once the neuron has fired it immediately transitions into the absolute refractory state A.
- State A: The neuron is in the absolute refractory state. In this state the neuron cannot fire again, no matter how strong the stimulus driving the neuron is. Once the absolute refractory period has elapsed the neuron transitions to state L.
- State L: The neuron is in the relative refractory state (L). In this state, the neuron is less sensitive to stimuli. Weak stimuli, *i.e.* stimuli that would otherwise drive a neuron to fire a signal when at rest, do not provoke a response when the neuron is in state L. If the neuron is not driven strong enough to fire again, it transitions back to the resting state.

We want to model this 4-state Markov process and are given the following transition probabilities:

$$\begin{aligned} p_{RF} &= f \\ p_{FA} &= 1 \\ p_{AL} &= \frac{1}{2} \\ p_{LR} &= \frac{1}{2} \\ p_{LF} &= f(1 - p_{LR}) \end{aligned}$$

Note that f is a variable here, with support between 0 and 1, that represents the neuron's driving input by specifying the probability to transition to the active firing state. (If it helps your intuition you can imagine that each discrete-time step lasts milliseconds of real time.)

a) Sketch out the Markov process including all states and all possible transitions. Label the states and the transitions. **/10**

b) Write out the transition probability matrix using the Markov matrix notation, *i.e.* such that the columns of the transition matrix sum to 1. **/15**

c) Derive the percentage of time that the neuron spends in the resting state (R) as a function of f. (*Hint*: Determine the stationary distribution of the states). Is there a value of f for which the neuron is in the resting state $\frac{1}{3}$ of the time? If so what is that value? Show and briefly explain your derivation. **/40**

d) Determine the mean time between neuron firing events when the neuron operates under maximum stimulus drive, *i.e.* $f = 1$. Use first-step analysis on the Markov chain to derive this result and explain your derivation. **/35**

The four parts carry, respectively, 10%, 15%, 40%, and 35% of the marks.