Imperial College London

19 October 2023

Department of Bioengineering

BIOE60024 – Modelling in Biology I (MiB.1), Dr Thomas Ouldridge

Autumn Term Coursework

To be returned by **Monday 15th January, 2023, 1pm**

Your coursework should contain: calculations if appropriate, annotated Matlab graphs and figures, *well-commented* code to back up any answers obtained with computational support, and *succinct* answers to the questions **with clear explanations and derivations**. Do not forget to include a title in your plots and to label *all* the axes. The document should be submitted in **PDF format**. Note that the solutions to exercises are available via the link to the Mobius gradebook in Blackboard.

Please note that unreadable documents or illegible hand writing will make it very difficult to mark your coursework and will lead to points being deducted.

Your answers should be *yours*, i.e. written by you, in your own words, showing your own understanding. You must produce your own code and submit it when appropriate.

Deterministic Nonlinear Dynamics (/100)

Question 1: Phase plane analysis of a gene network (/60)

A line of stem cells is observed to differentiate into two types of daughter cells. This differentiation is driven by 4 genes, G_1, G_2, G_3 and G_4. In the first type of differentiated cell, it is observed that the concentrations of proteins coded by the relvant genes are $[G_1] \gg [G_2]$ and $[G_3] \ll [G_4]$; in the other type, $[G_1] \ll [G_2]$ and $[G_3] \gg [G_4]$. Initially, the undifferentiated cell is stable with low concentrations of all proteins. Differentiation is triggered by an increase in the production rate of G_4 above a critical value. When this happens, cells evolve to one or the other differentiated state, where they maintain stable concentrations of G_1, G_2, G_3 and G_4. Whether the cells transition to one differentiated state or the other depends on the concentrations of the genes when the consititutive production of G_4 exceeds its critical value.

A model is proposed for the gene network of the form:

$$\begin{aligned}
\frac{\mathrm{d}[G_1]}{\mathrm{d}t} &= \alpha[G_1] + \beta[G_4] - \gamma[G_1][G_2], \\
\frac{\mathrm{d}[G_2]}{\mathrm{d}t} &= \alpha[G_2] + \beta[G_3] - \gamma[G_1][G_2], \\
\frac{\mathrm{d}[G_3]}{\mathrm{d}t} &= \delta([G_1] - [G_2])^2 - \epsilon[G_3][G_4], \\
\frac{\mathrm{d}[G_4]}{\mathrm{d}t} &= \eta - \epsilon[G_3][G_4].
\end{aligned} \tag{1}$$

Here, terms $\alpha[G_i]$ and $\beta[G_i]$ are gene expression due to G_i acting as a simple transcription factor. η represents constitutive production of G_4, without the need for a transcription factor, and $\delta([G_1] - [G_2])^2$ represents pairs of either G_1 or G_2 acting as transcription factor, depending on which one is in excess. The remaining terms represent mutually destructive interactions between the proteins encoded by the genes. All parameters are assumed to be positive.

(a) Using the substitutions

$$t = \frac{\tau}{\alpha}; \quad [G_1] = \frac{\alpha^2}{\beta\delta}g_1; \quad [G_2] = \frac{\alpha^2}{\beta\delta}g_2; \quad [G_3] = \frac{\alpha^3}{\beta^2\delta}g_3; \quad [G_4] = \frac{\alpha^3}{\beta^2\delta}g_4, \tag{2}$$

verify that the model can be written in non-dimensionalized form

$$\begin{aligned}
\dot{g_1} &= g_1 + g_4 - \mu g_1 g_2, \\
\dot{g_2} &= g_2 + g_3 - \mu g_1 g_2, \\
\dot{g_3} &= (g_1 - g_2)^2 - \nu g_3 g_4, \\
\dot{g_4} &= \rho - \nu g_3 g_4,
\end{aligned} \tag{3}$$

where $\dot{g_i} = \frac{\mathrm{d}g_i}{\mathrm{d}\tau}$, where μ, ν, and ρ are parameters. How are μ, ν and ρ related to the original parameters?

(b) Show that $x = g_1 - g_2$ and $y = g_3 - g_4$ obey the coupled ODEs

$$\begin{aligned}
\dot{x} &= x - y, \\
\dot{y} &= x^2 - \rho.
\end{aligned} \tag{4}$$

(c) Identify the fixed points of the x^*, y^* system for $\rho > 0$.

(d) By considering the eigenvalues of the Jacobian matrix near each fixed point, determine the nature of the fixed points for $\rho > 0$.

(e) Sketch the phase-plane (x-y) for $\rho = 1$. Your sketch should include the location of fixed points, nullclines, and trajectories in the vicinity of the fixed points. You do not have to indicate system behaviour far from the fixed points, or trajectories that go between the fixed points. Give your reasoning.

(f) Using the ode45 solver in Matlab, or otherwise, show the evolution of trajectories over the time interval $0 \leq \tau < 6$ for $\rho = 1$ and using the following initial conditions (overlay all trajectories on the same graph):

$$\begin{gathered}
(x(0), y(0)) = (-2, -4), \quad (x(0), y(0)) = (0.9, 0.9), \quad (x(0), y(0)) = (-3, -5.5), \\
(x(0), y(0)) = (0, 0.5), \quad (x(0), y(0)) = (-0.9, -1.1), \quad (x(0), y(0)) = (-0.5, 0.1).
\end{gathered} \tag{5}$$

It is recommended that you specify the scale of the axes (eg. -15 to 15) and also plot the nullclines to make the behaviour more clear.

(g) Comment on whether the model studied is capable of reproducing the behaviour of this system described at the start of the question. Is it a "good" model for the system in question?

Question 2: Bifurcations in a chemical system(/40)

The following equations are a non-dimensionalized model of a chemical reaction system; $v \geq 0$ and $w \geq 0$ represent concentrations; $b > 0$ is a parameter.

$$\begin{aligned}
\dot{v} &= 25 - v - \frac{4vw}{1 + v^2}, \\
\dot{w} &= bv\left(1 - \frac{w}{1 + v^2}\right).
\end{aligned} \tag{6}$$

(a) Solve for the fixed point (v^*, w^*).

(b) Show that the fixed point is stable if and only if $b > 14$.

(c) By considering the flow of trajectories across the lines $v = 0$, $w = 0$, $v = 25$ and $w = 626$, show that the system contains a limit cycle for $b < 14$. Be explicit about your reasoning.

(d) What kind of bifurcation occurs at $b = 14$? What behaviour would be observed in the chemical system as the system goes through the bifurcation by decreasing b?