Imperial College London

9 November 2007

Department of Bioengineering
MEng/BEng in Biomedical Engineering

BE3-H36/BE4-H36 – Modelling in Biology (MiB)

Assignment 2: *One- and two-dimensional systems of differential equations*

Instructions: To be returned to the General Office by **Wednesday, 28 November 2007**. Same rules as for the previous assignment: OK to discuss with other students and to use the MATLAB Help, but you must write your own answers. These should consist of calculations, explanations plus MATLAB plots.

Note: In the first two (longer) exercises we will follow a guided, step-by-step approach to exemplify how to approach the analysis of dynamical systems. In the following problems, fewer indications will be given.

Question 1: A one-dimensional model from population dynamics

Consider the following non-dimensionalized version of an ecological model of an insect population in a forest:

$$\dot{x} = r\,x\left(1 - \frac{x}{k}\right) - \frac{x^2}{1 + x^2}, \tag{1}$$

where x is the population of insects subject to logistic growth (the first term on the right hand side) and under depletion caused by predators (the second term on the RHS). The positive real numbers r and k are the parameters of the problem: the growth rate and the limiting value of the population in the absence of predators, respectively. We wish to explore the bifurcations of this system as a function of these parameters.

1. Consider first the case with no predators (i.e., under pure logistic growth) $\dot{x} = r\,x\,(1 - x/k)$ and review some of our calculations in class:
   (a) Find the fixed points of this system, draw the flow of trajectories on the line and deduce the stability of the fixed points. All initial conditions (except one) converge to a certain value of the population of insects. If $r = 0.9$ and $k = 3$, which value is this? What are the attractors for this system?
2. Consider now the complete system (1):
   (a) Show that $x = 0$ is always a fixed point. What is its stability?
   (b) The other fixed points of the system can be calculated as the intersections of the line $h(x) = r(1-x/k)$ and the curve $g(x) = x/(1 + x^2)$. For $r = 0.9$ and $k = 3$, plot $h(x)$ and $g(x)$ on the same graph and use the zoom in MATLAB to find the fixed points of the system with three digits accuracy.
   (c) Instead of doing it graphically, read in the MATLAB Help how to use the command `fsolve` to solve the nonlinear algebraic equation $f(x) = h(x) - g(x) = 0$ for $r = 0.9$ and $k = 3$. Find the fixed points of the system for these parameters and their stability. To what value of the population do *almost all* initial conditions tend? Compare this value to the one obtained in the absence of predators, in 1a above.
   (d) As explained in class, a drift in the values of r and k can *qualitatively* change the behavior of the system. To see this, consider three examples with $k = 10$ and $r = \{0.2, 0.4, 0.6\}$ and plot $h(x)$ for each of them on the same graph as $g(x)$. What is the number of fixed points for each of the three cases? Sketch the flows on the line and their stability.
   (e) Use `fsolve` to calculate numerically the fixed points for $r = 0.2$ and $r = 0.6$. How would the behavior of the system change if r is increased from 0.2 to 0.6? Explain your answer in terms of the population of insects.

3. The final part of this exercise is to implement a parameter sweep to obtain the *bifurcation diagram* and to study an important nonlinear effect: *hysteresis*. Consider the full system (1) and fix $k = 10$.

   (a) We now wish to simulate a slow drift of the growth rate r that might take place in the population. To do this, write a MATLAB program which implements a loop in which you use `fsolve` (as you did in ref3.1) to calculate stable fixed points for `r=[0.05:0.01:0.7]`. Your program should start from $r = 0.05$ upwards, and (*this is important*) it should use the solution found for a given r as the *initial guess* for `fsolve` to calculate the new fixed point at $r + 0.05$. Plot the calculated value of the fixed point as a function of r, as long as `fsolve` finds a **convergent solution**.

   (b) Run again the program you developed in 3a but this time starting from $r = 0.7$ downwards and calculate the fixed points in the interval `r=[0.7:-0.05:0.05]`. Plot the fixed points on the same graph as 3a, again for the instances where `fsolve` finds a **convergent solution**.

      i. Explain what you observe in connection with the following (quasi-Confucian) statement: ”In nonlinear systems, it matters which path one follows.”

      ii. Two bifurcations take place in the interval `r=[0.05:0.05:0.7]`. At what values of r do the bifurcations approximately occur? Classify the bifurcations that are observed. *[Hint: Count the number of fixed points]*

   (c) Interpret the results observed in 3a and 3b in terms of the population of insects. Use your results to explain the experimental observation that *insect outbreaks are relatively rare but once an outbreak takes place, it takes long to disappear.*

Question 2: A two-dimensional (two-species) population model

In a managed farm in Australia two species compete for the same food resource: an unwanted species (rabbits) and a profitable one (sheep) compete for grass. In isolation, each species would grow logistically. However, competition in the same environment introduces additional constraints that reduce the growth rate. This can be modelled as:

$$\begin{aligned} \dot{x} &= 3x\left(1 - \frac{x}{3}\right) - 2xy \\ \dot{y} &= 2y\left(1 - \frac{y}{2}\right) - xy, \end{aligned} \tag{2}$$

where x is the population of rabbits and y is the population of sheep. The competition between species is modelled by the cross-terms “xy” of the equations.

1. First, some qualitative understanding of the model (2):

   (a) Which species reproduces faster and by how much?

   (b) In the absence of competition, which of the two populations would be larger and by how much?

   (c) Which of the two species is more affected by the presence of the other and by how much?

2. Let us proceed now with the linear analysis of this system:

   (a) Find *all* the fixed points of the system.

   (b) Perform the linear analysis of the problem: for all fixed points, find the Jacobian matrix for (2) together with its eigenvectors and eigenvalues. Characterize the linear stability of all fixed points.

3. We now wish to *infer* the global behavior from the local analysis. To do this, draw the flow of trajectories on the phase plane (x, y), using your information about the fixed points, the calculated local eigenvectors at each of them, the fact that trajectories do **not** cross, and the obvious constraint that populations cannot be negative.

4. Check that the phase portrait obtained in 3 is correct by producing a MATLAB program that numerically integrates the system (2) with `ode45`. Run it for a variety of initial conditions and plot all the trajectories on the same plot.

5. Interpret your results in ecological terms. Can you explain why this is a model for the ecological principle of *competitive exclusion*? Can you derive any guidelines that you could apply in the management of the farm?

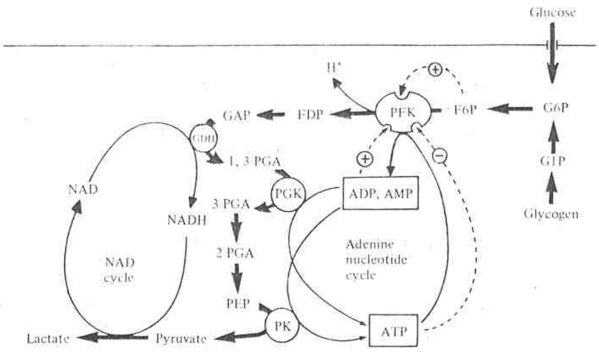
6. Use the code you produced in 4 to obtain the phase portrait of a very similar system, where some of the parameters have changed:

$$\begin{aligned} \dot{x} &= 3x\left(1 - \frac{2x}{3}\right) - xy \\ \dot{y} &= 2y\left(1 - \frac{y}{2}\right) - xy, \end{aligned} \tag{3}$$

Compare the phase portrait of this system to that of system 2 and explain the differences in ecological terms.

Question 3: The production of energy in yeast: a model for glycolysis

The energy that cells need to function is obtained mainly from glycolysis, that is, the chemical breaking of glucose (elementary sugar). This cellular process involves several biochemical reactions, some of them enzymatic, which have been summarized in the figure:



Don't panic: we will not be analyzing the full system. Using biochemical knowledge, several researchers have identified the key steps in the puzzle. If we define $X = \mathrm{ADP}$ and $Y = \mathrm{F6P}$, the main set of reactions is:

$$\begin{aligned} B &\xrightarrow{k_1} Y \\ C + Y &\xrightarrow{k_2} X + D \\ 2X + Y &\xrightarrow{k_3} 3X \\ X &\xrightarrow{k_3} E, \end{aligned} \tag{4}$$

where B, C, D, E are other metabolites that are kept *constant* by the cell, and k_1, k_2, k_3 are kinetic rate constants.

1. Brush up your 'Chemistry' and "Heat and Mass Transport" and use the *Law of Mass Action* to obtain the differential equations for system (4). *[Remember that the only two variables in the problem are X and Y.]*

Through rescaling, it can be shown that the biochemical system you obtained in 1 can be simplified to give:

$$\begin{aligned} \dot{x} &= -x + ay + x^2 y \\ \dot{y} &= b - ay - x^2 y \end{aligned} \tag{5}$$

2. Show how to obtain (5) from your result in 1.

3. Write MATLAB code to numerically integrate (`ode45`) the system (5). Now fix $b = 1/2$ and obtain trajectories for four values of $a = \{0.2, 0.11, 0.05, 0.01\}$. Plot the trajectories both as a function of time and on the phase plane. Explain the behavior as the parameter a decreases.

4. What you saw numerically in 3 is a Hopf bifurcation, a type of bifurcation that only appears in dimensions larger than 1. For $b = 1/2$, calculate the value of a at which this bifurcation takes place.

[Hint: You could do this the 'hard' way (numerically sweeping values of a and checking the dynamical behavior), or the 'elegant' way (finding when the fixed point becomes unstable). Follow the latter route and you will be able to find the condition for the bifurcation to occur for any value of b (not just for $b = 1/2$). Find where the bifurcation occurs in the parameter space (a, b).]

Question 4: Compartmental models in biology and physiology

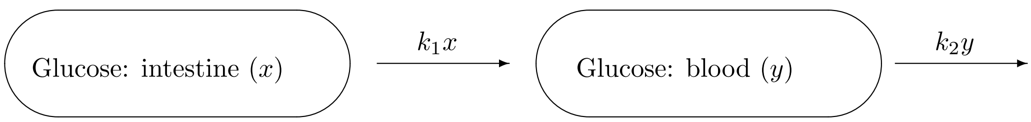
[As a respite in this nonlinear onslaught, a short exercise on a linear model, again.]

'Compartmental models' is a generic term for models where we monitor the flow between interconnected compartments. These compartments can represent almost anything: from concentrations of hormones that get degraded in the body, to oil tanks, to populations of distinct groups. They are extensively used in Engineering, Biology, Physiology and Economics. The key aspect is that they are **linear**: the flows are linearly dependent on the state variable in each compartment. We will see two examples:

Professor Parker and co-workers at St. Mary's Hospital recently published a paper on gestational diabetes. This is their first paragraph: "GESTATIONAL DIABETES (GDM) is carbohydrate intolerance first recognized during pregnancy. Although most women with GDM return to normal glucose tolerance following delivery, they remain at substantially increased risk of type 2 diabetes in later life. GDM may therefore be considered a forerunner of type 2 diabetes, and women with previous GDM provide a valuable model for detection of early metabolic abnormalities associated with the development of type 2 diabetes."

In that paper, they used a simple compartmental model to fit the experimental data obtained at St. Mary's. The experiments measured the amount of CO_2 exhaled by women subjects after a controlled meal. This measurement is in direct relation to the amount of glucose in the blood. After applying the model to ~ 80 women, they concluded that one of the parameters in the model can serve to distinguish between women with GDM and healthy women.

Consider the following compartmental model for this system:

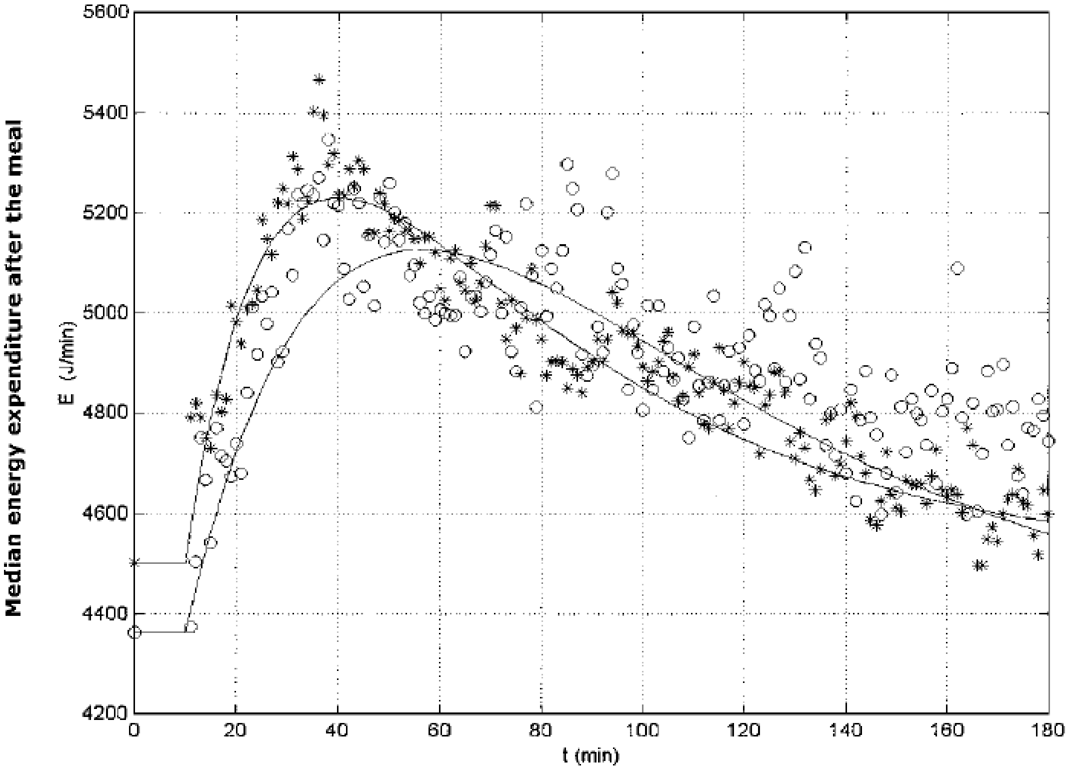


where k_1 and k_2 are positive rate constants. In particular, k_2 is the rate at which insulin moves glucose from the blood into tissue cells. When analyzing the experimental data, it was found that both rate constants are very similar in almost all subjects. Henceforth, assume : $k_1 = k_2 \equiv k$.

1. Write down the system of ODEs for the compartmental model of the figure. Solve for the value of glucose in the blood as a function of time $y(t)$ and fix one integration constant with the initial condition $y(0) = 0$.

2. In the Intranet you will find two files with data (`[t,y]`) for two subjects (`subject1.dat`, `subject2.dat`). Import them into MATLAB and find a way to estimate k from the data for both cases. Explain your answer and methodology with figures and calculations. *[Hint: This can be done in several ways but you will have to rely on your knowledge of the solution for $y(t)$. Two suggestions: (i) try to find a linear relationship in the data and fit a line (MATLAB can give you the best fit with the command* `polyfit`*); (ii) relate the maximum of $y(t)$ with k.]*

3. The real datasets (see figure below) do not look as good as the files I provided. However, the results do show that there is a clear separation between the twenty-nine GDM women and the thirty-seven healthy women: the characteristic time constant is $T_{\mathrm{GDM}} = 1/k_{\mathrm{GDM}} = 58 \pm 6\, min$ as compared to $T_{\mathrm{healthy}} = 1/k_{\mathrm{healthy}} = 42 \pm 4\, min$. Which of the two datafiles you analyzed in 2 corresponds to a GDM subject?


Median energy expenditure after the meal
E (J/min)
t (min)
5600
5400
5200
5000
4800
4600
4400
4200
0
20
40
60
80
100
120
140
160
180