Exercises for Tumor Dynamics Module *

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Exercises for Equation Development Module

1. **Purpose:** To interpret model equations biologically and to go through the preliminary steps of qualitative analysis.
   This model is derived from the paper by Panetta ([Pan96]). It is developed further in the Projects.

   Exercise: Another simple model of tumor/host interaction describes the growth of two populations, each growing according to a logistic law and competing with each other for resources. In this model, we lump together all non-tumor cells which are at the tumor site, including normal tissue as well as immune cells. We do *not* assume a constant source of immune cells.

   Let $X(t)$ denote the normal cell population at time t, (including immune cells), and let $Y(t)$ denote the tumor cell population at time t. The system of differential equations which describes the model is:

$$\begin{aligned} \frac{dX}{dt} &= a_1X(1-b_1X) - c_1XY \\ \frac{dY}{dt} &= a_2Y(1-b_2Y) - c_2XY \end{aligned}$$

   (a) What is the biological interpretation of each of the parameters a_1, a_2, b_1, b_2, c_1, and c_2? Are they all necessarily positive or negative?

   (b) Describe hypothetical experiments which would allow the determination of these parameters.

   (c) Determine the nullclines of this system. Use these nullclines to sketch a few representative phase portraits. Find and label all of the equilibria.

   (d) What condition must the parameters satisfy in order that the tumor-free equilibrium be stable?

2. **Purpose:** To explore another model equation using a more complicated tumor growth function, in an attempt to include the effects of angiogenesis.
   The comparison of tumor growth curves is, continued in the Projects, using published data. See also Exercise 3. Research on tumor angiogenesis is a hot topic, and a literature search on current theories and proposed mechanisms would be an interesting research project.

   Exercise: It has been observed both *in vivo* and *in vitro* that solid tumors experience an initial period of quick growth,followed by a period when growth slows or stops, follwed by another period of growth. It has been suggested that the first period of growth is during the 'avascular' phase, when the tumor has not yet developed any internal vasculature, so that the cells must acquire nutrients through diffusion from outside the tumor. Once the tumor reaches a certain size, the tumor cells release 'angiogenic growth factors', which stimulate the growth of blood vessels towards the tumor, and finally reaching into the interior of the tumor. After the tumor has been 'vascularized', another period of growth occurs.

   In this exercise, the angiogenic process will be modelled by a drastic *slowing* in the growth rate when the tumor reaches a certain size, denoted by T_a.

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(a) Sketch a graph of a possible growth function, $F(T) = \frac{dT}{dt}$, which is positive for $0 < T < T_{\text{MAX}}$, and is very small for T near $T_a < T_{\text{MAX}}$. In the spirit of generating tractable models, the function should be as simple as possible, within the prescribed constraints.

(b) Write a differfential equation for $T(t)$, after writing an equation for the function $F(T)$ you graphed in 2a.

(c) Solve the differential equation in part 2b, and compare the result to logisitc tumor growth by plotting solution curves for the two types of growth, using the same initial conditions. (Depending on the form of $F(T)$, you may or may not be able to find an *explicit* solution for the differential equation. If an explicit solution is not available, use a numeric solver.) The comparison will be most meaningful if the same initial growth rates (when T is close to zero), and the same carrying capacity are used.

Comment on the effect of varying the tumor size during vascularization, i.e. T_{MAX}.

3. **Purpose:** To come up with a model equation using a different tumor growth function. The solutions are compared with those derived from the logistic growth law.
The comparison of tumor growth curves is, continued in the Projects, using published data. See also Exercise 2

Exercise: It has been observed that in certain tumors grown *in vitro* only a thin layer of cells on the tumor's surface are actually proliferating.

Consider a perfectly spherical tumor, and let $T(t)$ denote the tumor population at time t.

(a) Write a differential equation for $T(t)$, assuming that only the cells on the surface of the sphere proliferate. (Assume that the number of cells, T, is proportional to volume, but that the number of proliferating cells is proportional to the surface area of the sphere. You'll need to express the number of proliferating cells as a function of T.) This is known as "Von Bertalanffy" growth.

(b) Solve the differential equation in part 3a, and compare the result to exponential tumor growth by plotting solution curves for the two types of growth, using the same initial conditions.

(c) Add a growth-limiting term to the differential equation in part 3a, analagous to the overcrowding term in the logistic growth equation. Again, compare numerical simulations of the two systems for, using the same initial conditions, the same proliferation rate, and the same initial conditions.

4. **Purpose:** Compare the tumor-immune model using Von Bertalanffy growth to the one presented in class using a qualitative analysis.
See Exercise 3

Exercise: Use the Von Bertalanffy model of tumor growth in the absence of an immune response:

$$\frac{dT}{dt} = aT^{2/3}(1 - bT).$$

Add the immune population, with competition and response terms identical to those used in the model presented in class. Draw nullclines, determine the number of possible equilibria and their stability. Does the qualitative behavior differ from that of the model presented in class? If so, how?

Recall the system of equations presented in class: T denotes tumor cells, and E denotes effector (cytotoxic immune) cells. The equations are

$$\begin{aligned} \frac{dE}{dt} &= s + \frac{pET}{g+T} - dE - mET \\ \frac{dT}{dt} &= aT(1 - bT) - cET \end{aligned}$$

Exercises for Qualitative Analysis Module

1. **Purpose:** To study non-linear centers.
   Notes: Define a **reversible system** to be any second-order system that is invariant under $t \to -t$ and $y \to -y$. For example, any system ofthe form

$$\begin{aligned} \dot{x} &= f(x,y) \\ \dot{y} &= g(x,y), \end{aligned}$$

   where f is odd in y and g is even in y(i.e., $f(x,-y) = -f(x,y)$ and $g(x,-y) = g(x,y)$) is reversible.

   Theorem: (Nonlinear centers for reversible systems) Suppose the origin $\mathbf{x}* = \mathbf{0}$ is a linear center for the continously differentiable system

$$\begin{aligned} \dot{x} &= f(x,y) \\ \dot{y} &= g(x,y), \end{aligned}$$

   and suppose that the system is reversible. Then sufficiently close to the origin, all trajectories are closed curves. from[Str94], Example 6.6.1

   Exercise: Show that the system

$$\begin{aligned} \dot{x} &= y - y^3 \\ \dot{y} &= -x - y^2 \end{aligned}$$

   has a nonlinear center at the origin, and plot the phase portrait.

2. **Purpose:** To study fixed points and linearizations. From [Str94], 6.3.

   Excercise: For each of the following systems, find the fixed points, classify them, sketch the neighboring trajectories, and try to fill in the rest of the phase portrait.

   (a) $\dot{x} = x - y, \dot{y} = x^2 - 4$
   (b) $\dot{x} = \sin y, \dot{y} = x - x^3$
   (c) $\dot{x} = 1 + y - e^{-x}, \dot{y} = x^3 - y$
   (d) $\dot{x} = y + x - x^3, \dot{y} = -y$
   (e) $\dot{x} = \sin y, \dot{y} = \cos x$
   (f) $\dot{x} = xy - 1, \dot{y} = x - y^3$

3. **Purpose:** To compare computer generated phase portratis with initial sketches.

   Exercise: For each of the nonlinear systems in Exercise 2, plot a computer-generated phase portrait and compare to your approximate sketch.

4. **Purpose:** To use qualitative arguments to deduce the phase portrait of a system. From [Str94], Problem 6.6.6

   Exercise: Consider the reversible system $\dot{x} = y(1 - x^2), \dot{y} = 1 - y^2$.

   (a) Plot the nullclines $\dot{x} = 0$ and $\dot{y} = 0$.
   (b) Find the sign of $\dot{x}, \dot{y}$ in different regions of the plane.
   (c) Calculate the eigenvalues and eigenvectors of the saddle points at $(-1, \pm 1)$.
   (d) Consider the unstable manifold of $(-1,-1)$. By making an argument about the signs of $\dot{x}, \dot{y}$, prove that this unstable manifold intersects the negative x-axis. Then use reversibility to prove the existence of a heteroclini trajectory connecting $(-1,-1)$ to $(-1,1)$.
   (e) Using similar arguments, prove that another heteroclinis trajectory exists, and sketch several other trajectories to fill in thephase portrait.

Exercises for Numerics Module

1. **Purpose:** Determining whether an IVP is well-posed.

   Exercise: For each of the following IVPs,determine whether or not it is well-posed, and explain why.

   (a) $y' = -5y$
   $y(0) = 1$ and $0 < t < 5$.

   (b) $y' = 2y^{1/2}$
   $y(0) = 0$ and $0 < t < 2$.

2. **Purpose:** Understanding stability of solutions, stability of a numerical method, computing solutions for Forward and Backward Euler methods.

   Note to Instructor: If you have chosen not to present the slides on stability of an ODE solution, you may wish to skip part (a) of this exercise. From [Hea02, p.417,#9.4].

   Exercise: Consider the ODE with $y' = -5y$ with initial condition $y(0) = 1$. We will solve this ODE numerically using a step-size of $h = 0.5$.

   (a) Are solutions to this ODE stable?
   (b) Is Euler's method stable for this ODE using this step-size?
   (c) Compute the numerical value for the approximate solution at $t = 0.5$ given by Euler's method.
   (d) Is the backward Euler (BE) method stable for this ODE using this step-size?
   (e) Compute the numerical value for the approximate solution at $t = 0.5$ given by the backward Euler method.

3. **Purpose:** Comparing results for Forward Euler versus Backward Euler. From [Hea02, p.417,#9.5].

   Exercise: With the initial value of $y_0 = 1$ at $t_0 = 0$ and a time step of $h = 1$, compute the approximate solution value y_1 at time $t_1 = 1$ for the ODE $y' = -y$ using each of the following two numerical methods. (Your answers should be numbers, not formulas.)

   (a) Euler's method
   (b) Backward Euler method

4. **Purpose:** Converting a second order ODE to a first order system, determining stability of solutions and stability of Euler's method and Backward Euler method on this system.

   Note to Instructor: If you have chosen not to present the slides on stability of an ODE solution, you may wish to skip part (c) of this exercise. From [Hea02, p.417,#9.7]. **Exercise:** Consider the IVP $y'' = y$ for $t \geq 0$ with initial values $y(0) = 1$ and $y'(0) = 2$.

   (a) Express this second-order ODE as an equivalent system of two first-order ODEs.
   (b) What are the corresponding intial conditions for the system of ODEs in part (a)?
   (c) Are solutions of this system stable?
   (d) Perform one step of Euler's method for this ODE system using a step size of $h = 0.5$.
   (e) Is Euler's method stable for this problem using this step size?
   (f) Is the backward Euler method stable for this problem using this step size?

5. **Purpose:** Identifying properties of methods. From [Hea02, pp.417–418,#9.9]. **Exercise:** For each property listed below, state which of the following two ODE methods has or have the given property:

$$y_{k+1} = y_k + \frac{h}{2}(3f(t_k, y_k) - f(t_{k-1}, y_{k-1})) \tag{1}$$

$$y_{k+1} = y_k + \frac{h}{2}(f(t_k, y_k) - f(t_{k+1}, y_{k+1})) \tag{2}$$

   Properties:

(a) Second-order accurate
(b) Single-step method
(c) Implicit method
(d) Unconditionally stable
(e) Good for solving stiff ODEs

6. **Purpose**: Determining the accuracy of a method through Taylor expansions. Note to Instructor: You may need to help the students by giving them a bit more background on how to Taylor expand about points other than t_{n+1}. For example,

$$y(t_{n-1}) = y(t_n) - hy'(t_n) + \frac{h^2}{2}y''(t_n) - \frac{h^3}{3!}h'''(t_n) + \mathcal{O}(h^4)$$

From [Hea02, pp.418,#9.12].

Exercise: The centered difference approximation

$$y' \equiv \frac{y_{k+1} - y_{k-1}}{2h}$$

leads to the two-step *leapfrog method*

$$y_{k+1} = y_{k-1} + 2hf(t_k, y_k)$$

for solving the ODE $y' = f(t, y)$. Determine the order of accuracy for this method.

7. **Purpose**: Computing project. Using packaged software to compute the solution to a system of ODEs representing an SIR epidemic model. Understanding the meaning of the model and experimenting with parameter values to determine different outcomes.

From [Hea02, pp.418–419,#9.2]. **Exercise:** The *Kermack-McKendrick model* for the course of an epidemic in a population is given by the system of ODEs

$$\begin{aligned} y_1' &= -cy_1y_2 \\ y_2' &= cy_1y_2 - dy_2 \\ y_3' &= dy_2 \end{aligned}$$

where y_1 represents susceptibles, y_2 represents infectives in circulation, and y_3 respresents infectives removed by isolation, death, or recovery and immunity. The parameters c and d represent the infection rate and removal rate, respectively. Use a library routine to solve this system numerically, with the parameter values $c = 1$ and $d = 5$, and initial values $y_1(0) = 95$, $y_2(0) = 5$, and $y_3(0) = 0$. Integrate from $t = 0$ to $t = 1$. Plot each solution component on the same graph as a function of t. As expected with an epidemic, you should see the number of infectives grow at first, then diminish to zero. Experiment with other values for the parameters and initial conditions. Can you find values for which the epidemic does not grow, or for which the entire population is wiped out?

8. **Purpose**: Computing project. Using packaged software to compare efficiency of various library routines. Note to Instructor: You may ask the students first to catalog the ODE solving routines available in whichever numerical package you choose to have them use. Or you may wish to specify a particular set of ODE solvers the students should implement. From [Hea02, p.419,#9.3].

Exercise: Experiment with several different library routines having automatic step-size selection to solve the ODE

$$y' = -200ty^2$$

numerically. Consider two different initial conditions, $y(0) = 1$ and $y(-3) = 1/901$, and in each case compute the solution until $t = 1$. Monitor the step size used by the routines and discuss how and why it changes as the solution progresses. Explain the difference in behavior for the two intial conditions. Compare the different routines with respect to efficiency for a given accuracy requirement.

9. **Purpose**: Computing project. Using packaged or self-written software to compare stiff and non-stiff numerical solution methods. Note to Instructor: You may choose to ask the students to compare forward Euler with backward Euler, in addition to comparing the packaged routines. From [Hea02, p.419,#9.5]. **Exercise:** The following system of ODEs models nonlinear chemical reactions

$$\begin{aligned} y_1' &= -\alpha y_1 + \beta y_2 y_3 \\ y_2' &= \alpha y_1 - \beta y_2 y_3 - \gamma {y_2}^2 \\ y_3' &= \gamma {y_2}^2 \end{aligned}$$

where $\alpha = 4 \times 10^{-2}$, $\beta = 10^4$, and $\gamma = 3 \times 10^7$. Starting with initial conditions $y_1(0) = 1$ and $y_2(0) = y_3(0) = 0$, integrate this ODE from $t = 0$ to $t = 3$. You may use either a library routine or an ODE solver of your own design. Try both stiff and non-stiff methods, and experiment with various error tolerances. Compare the efficiencies of the stiff and non-stiff methods as a function of error tolerance.

Exercises for Bifurcation Module

1. **Purpose:** To study saddle node bifurcations in a model. From [Str94], Example 8.1.1.

   Exercise: The following system has been discussed by [Gri71] as a model for a genetic control system. The activity of a certain gene is assumed to be directly induced by two copies of the protein for which it codes. In other words, the gene is stimulated by its own product, potentially leading to an autocatalytic feedback process. In dimensionless form, the equations are

$$\begin{aligned} \dot{x} &= -ax + y \\ \dot{y} &= \frac{x^2}{1 + x^2} - by \end{aligned}$$

   where x and y are proportional tothe concentrations of the protein and the messenger RNA from which it is translated, respectively, and $a, b > 0$ are parameters that govern the rate of degradation of x and y. Show that the system has three fixed points when $a < a_c$, where a_c is to be determined. Show that two of these fixed points coalesce in a saddle-node bifurcation when $a = a_c$. Then sketch the phase portrait for $a < a_c$, and give a biological interpretation.

2. **Purpose:** To study homoclinic bifurcations. From [Str94], pp 262-263
   Notes: This is similar to a heteroclinic bifurcation, in that it involves the unstable manifold of a saddle point.

   Exercise: Consider the system

$$\begin{aligned} \dot{x} &= y \\ \dot{y} &= \mu y + x - x^2 + xy \end{aligned}$$

   (a) Show that the origin is a saddle point for all values of μ.

   (b) Find any other equilibria and determine their stability.

   (c) Numerically plot phase portraits for values of μ between -1 and -0.5. What happens to the unstable manifold through the origin as μ is varied?

   (d) Numerically find the critical μ-value at which the stable and unstable manifolds through the origin intersect. (This is called a *homoclinic connection* or *homoclinic orbit.*)

   (e) Plot a few phase portraits for μ-values above and below this critical value and describe what happens to the unstable manifold through the origin.

   This type of bifurcation is called a *homoclinic bifurcation.*

3. **Purpose:** To determine the type of bifurcation. From [Str94], Problem 8.1.6.

   Exercise: Consider the system $\dot{x} = y - 2x, \dot{y} = \mu + x^2 - y$.

   (a) Sketch the nullclines.

   (b) Find and classify the bifurcations that occur as μ varies.

   (c) Sketch the phase portrait as a function of μ.

References

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[Pan96] John Carl Panetta. A mathematical model of periodically pulsed chemotherapy: Tumor recurrence and metastasis in a competitive environment. *Bulletin of Mathematical Biology*, 58(3):425–227, 1996.

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