MATH 495: Homework #4
Spring 2018

Due: Thursday, March 8, 2018

Solve the below questions related to cancer dynamics models. Most questions will require theoretical analysis, but there is also a problem of data fitting which will require the use your software of choice.

1. Many of the simple one-dimensional models that we have considered implicitly assumed a carrying capacity of some form. In-class examples (e.g. logistic growth) have had a fixed carrying capacity. However, many types of cancers demonstrate the ability to create their own blood supply to obtain nutrients via a process called *angiogenesis.* One simple way to understand this, undertaken by Hahnfeldt *et al.* (see Resource [9]), is to allow the carrying capacity to change in time. That is, a *system* of equations, coupling tumor growth and carrying capacity, are defined. For example, consider the following:

$$\frac{dN}{dt} = bN\log\left(\frac{K}{N}\right),$$
$$\frac{dK}{dt} = cN - dN^{2/3}K.$$

   Note that the carrying capacity K is no longer constant in time. All other parameters (b, c, d) are assumed positive.

   (a) Interpret the above system of ODEs. In particular, what are we assuming about the tumor growth dynamics? How do N and K interact with each other? Provide as much justification as possible for each term utilized in the above, so that you clearly understand all the underlying assumptions. Note: you may need to do some research in mentioned paper and/or online.

   (b) Find the steady-state(s) of the system. What sort of dynamics do expect (you don't need to prove, but just use intuition).

   (c) Anti-angiogenic therapy has long been thought of as a promising tool for cancer therapy. Write a new system of ODEs which incorporates this therapy into the model. Please provide justification.

2. This problem deals with finding the least-squares fit to temporal tumor growth data, **assuming that the underlying model is exponential.** Most models are nonlinear, and hence require iterative methods (this is what *fminsearch* does in MATLAB, see HW #2), but exponential data can be linearly transformed, as we see below.

   (a) Included in the ZIP file are two CSVs: one containing time data (*time.csv*), another containing the corresponding cell numbers (*N_noise.csv*). Plot this data, making sure to include labels and a title.

   (b) Assume this data can be described by an exponential function. That is, there exists $k, N_0 \in \mathbb{R}_+$ such that

   $$\frac{dN}{dt} = kN,$$
   $$N(0) = N_0.$$

   Note that the relationship between N and t is nonlinear (clearly, it is exponential). However, I claim that you can find a transformation of coordinates (here transformations must be invertible), where, in the new coordinates, a linear relationship exists. That is, if $y = f(N, t)$, the relationship between y and t is linear. **Find this transformation.** *Hint:* Use the solution to the exponential ODE.

   (c) Using your results from (b), plot the transformed data. Note that if (b) is correct, the data should now appear (roughly) linear. Noise has been added (think of this as experimental error), so that the data will not lie precisely on a line. Hence (part (d) below) why we need to minimize an error (and not solve exactly).

   (d) Find the least-squares fit for a line for the transformed data in (c). Do not use any built-in solvers (like *fminsearch*), but instead have MATLAB solve the **normal equations.** Note that you can solve linear systems in MATLAB very easily and efficiently using the backslash (\) operator: to solve $Ax = b$, simply input $x = A \setminus b$. For example, the code can be written in basically three lines:

```
% Now find the least-squares fit
% Set up the coefficient matrix F
F = ;
A =F'F;
```

```
b =;
params_least_squares = A\b;
```

All that is needed is to define the matrix F and vector b (b depends on the transformed data from (c)).

(e) Plot the computed exponential model (from (d)) on the same set of axes as the data.

(f) There is nothing for you to do here, but I just want to call your attention to a subtle point. You may think that you are solving the original least-squares problem, but actually you are not. You are solving the least-squares problem **for the transformed data**, which, in general, is not the same. That is, there is no theorem that states that they must have the same solution (e.g. parameters k, N_0 in this case).

3. Consider the Gyllenberg-Webb model introduced in class to describe the transitions from proliferation to quiescence:

$$\begin{aligned} \frac{dP}{dt} &= (\tilde{\beta} - \mu_p - r_0(N))P + r_i(N)Q, \\ \frac{dQ}{dt} &= r_0(N)P - (r_i(N) + \mu_q)Q, \end{aligned} \tag{1}$$

where $N = P + Q$ is the total cancer cell population, and r_0, r_i are the transition functions between proliferation and quiescence. Recall that we assume that $r_0, r_i \geq 0, r_0(N)$ is increasing, and $r_i(N)$ is decreasing. Note that the **net** growth rate of the dividing cells can be written as $\beta := \tilde{\beta} - \mu_p$.

(a) Suppose that we isolate a colony of *dividing cell*, and we measure a time of one day for the colony to double in size. Find β.

(b) Suppose that quiescent cells have a mean lifetime of 0.5 days. Find μ_q. *Hint:* We need a slightly different interpretation of our ODE model. Google "mean lifetime" to obtain more information.

(c) Show that solutions of (1) which begin in the first quadrant ($Q, P \geq 0$) must remain there for all time $t \geq 0$. *Hint:* You must hit one of the axes first, since $(0, 0)$ is a steady state. If you hit one of the axes, what must happen to the trajectory?

(d) Analysis of the above system will be easier in the PN plane. Transform the system to the PN plane. That is, write an equivalent set of equations to (1), which describes the evolution of P (proliferating) and N (total tumor size) in time:

$$\begin{aligned} \frac{dP}{dt} &= ..., \\ \frac{dN}{dt} &= ... \end{aligned} \tag{2}$$

Note that in your equations, the only dependent variables that should appear are P and N.

(e) Now consider your equations (2) from part (d). Suppose, for definiteness, that the transitions are given by the following:

$$\begin{aligned} r_0(N) &= kN, \\ r_i(N) &= \frac{1}{N+1}, \end{aligned}$$

where $k > 0$ is a parameter. **Perform a phase portrait analysis of this system.** Note that you only have one parameter, k, so you should study the behavior as k is varied. Find steady states, draw nullclines, perform a linearized stability analysis, etc. to understand as best as possible the dynamics of the system. You will get different behaviors for different k, so please classify carefully (i.e. where any bifurcations occur, and the corresponding dynamics). *Hint:* To help get intuition, I have included a piece of MATLAB software, *pplane2014b.m*, in the ZIP file. Note that I did not write this, but you can use it to plot phase portraits for 2×2 systems. All you need to do is run the function inside MATLAB, and then the GUI provides prompts, which are hopefully self-explanatory. I suggest using this to gain intuition about the behavior of the system (for various k's), but note that you should provide analytic justification in your solution. Feel free to include numerical plots in your write-up, but also provide sketches by hand.

4. Consider an extension of the model presented in Problem 2, where we now consider dead cells D explicitly. Assuming cells in D are removed at a constant rate d (presumably by the immune system), the model extends to

the following form:

$$\begin{aligned}\frac{dP}{dt} &= (\beta - r_0(N))P + r_i(N)Q,\\ \frac{dQ}{dt} &= r_0(N)P - (r_i(N) + \mu_q)Q, \qquad (3)\\ \frac{dD}{dt} &= \mu_q Q - dD.\end{aligned}$$

The same assumptions on $r_0(N), r_i(N)$ apply as in Problem 2 (increasing/decreasing, respectively), and all other parameters are strictly positive. Also assume that $r_0(0) = 0$ (no population implies no transition into quiescence).

(a) Assuming that there exists $\bar{N} > 0$ such that

$$\mu_q r_0(\bar{N}) > \beta(r_i(\bar{N}) + \mu_q),$$

show that system (3) has a unique positive steady state.

(b) Show that that origin of (3) is a saddle.

Hint: [6] in Resources has both of these answers, if you look carefully.