MATH 495: Homework #3
Spring 2018

Due: Tuesday, February 20, 2018

Solve the below questions related to basic cancer growth models. Most questions will require theoretical analysis of growth models. There is also a problem of data fitting, that will require the use of your preferred software.

1. If a cancer cell population is growing exponentially, by definition the number of cells (or equivalently, the tumor volume) satisfies the differential equation
$$\dot{N} = kN, \tag{1}$$
for some constant k. Experimentally, we measure the growth rate by measuring the time it takes for a population to grow.
Assuming $N(t)$ satisfies (1), show that the doubling time τ of the population is constant (i.e. independent of time), and find a relation between τ and k.

2. Tumor cell sizes can vary, but for an estimate, assume in a particular disease they are all **solid spheres** with diameter 20 μm. Furthermore (again, this is overly simplistic), assume each cell divides regularly after 24 hours, i.e. that the growth is exponential. If this exponential growth continues unabated, how long will it take for the tumor to reach the size of a 60 m^3 room? What does this tell you about the growth dynamics of tumors (and cells in general)?

3. Consider the well-known model of Gompertzian growth, frequently utilized in modeling cancer modeling. We saw in class that it takes the form of exponential growth, where the growth constant $G(t)$ is itself exponentially decreasing:
$$\dot{N} = G(t)N(t),$$
$$\dot{G} = -\alpha G(t).$$
   (a) Show that this can be written equivalently as a one-dimensional autonomous equation of the form
$$\dot{N} = a\left(1 - b\log N\right)N.$$

Relate the parameters a and b to the parameters in the original model: $\alpha, N(0)$, and $G(0)$.

(b) Find the carrying capacity of the equation found in part (a).

4. In Problem 3, you showed that the Gompertz growth rate takes the form

$$F(N) = a\,(1 - b \log N)\,N.$$

(a) What is the maximum growth rate for this tumor, and for what size does it occur?

(b) Provide a sketch of $F(N)$ vs. N. Be as precise as possible, for all physical tumor sizes.

(c) Using (a) and (b), plot all qualitatively distinct solution trajectories ($N(t)$ vs t).

5. The "classical" von Bertalanffy model a division rate proportional to the **surface area**, and a death rate proportional to the **mass** (and hence the volume).

(a) Using these assumptions, provide justification for the corresponding mathematical model describing the evolution of the number of cancer cells $N(t)$:

$$\dot{N} = \alpha N^{\frac{2}{3}} - \beta N. \tag{2}$$

(b) Although equation (2) can be solved analytically, it is easier if we assume that tissue does not change shape as the tumor grows. That is, if we can write

$$N(t) = \gamma S(t)^3,$$

for some constant γ, where S represents a length in one dimension. Using (2) and the above definition for $S(t)$, derive a **linear** first-order equation for $S(t)$. Feel free to relabel constants to make notation simpler, but please keep track of all parameter definitions.

(c) Solve the obtained ODE in part (b), and find the limits $\lim_{t\to\infty} S(t)$ and $\lim_{t\to\infty} N(t)$.

6. In this problem, we investigate different growth models on a set of experimental data. In the attached csv files (*mass.csv, times.csv, samples.csv,*

and *stdevs.csv*), growth kinetics of Fortner Plasmacytoma 1 tumors from tumorigeneic mouse models are provided. The four data sets represent temporal data (days) of mean tumor mass (mgs) over a number of different mice (the number of mice at each data point is contained in *samples.csv*, with corresponding standard deviation in *stdevs.csv*).

(a) Plot the data, including errors bars representing the sample standard deviation:

$$\tilde{\sigma} := \frac{\sigma}{\sqrt{n}}.$$

The following (incomplete) code may be useful:

```
clear all; close all;

% Read in the data
times = csvread('times.csv');
mass = ;
stdevs = ;
samples = ;

% Standard error
error = ;

% Plot with error bars
figure(1)
errorbar(times, mass, error,'ok');
hold on;
xlabel('time (days)');
ylabel('tumor mass (mg)');
```

(b) Now, fit a Gompertz growth equation to the data set. That is, find parameters a and b, with

$$\frac{dN}{dt} = a\left(1 - b\log N\right)N,$$

which (locally) minimize the residual

$$E(a,b) = \sum_{i=1}^{N} \left(\frac{N(t_i; a, b) - N_i}{\sigma_i}\right)^2,$$

where N_i represents the experimental data measured at $t = t_i$, and $N(t; a, b)$ is the model (i.e. the solution of the ODE at time t with parameters a and b). Note the σ_i in the denominator to weight terms according to their overall variance (large σ contributes less to the minimization).

This can be accomplished relatively easily in MATLAB, in a number of different ways. One way is to utilize the built-in function *fminsearch*. You will probably need to construct **three** *m-files*:

(i) One with ODE right-hand side, i.e. vector field (say *gompertz.m*, a function),

(ii) one which evaluates the error between the model and the data, given by $E(a, b)$ above (say *errorGompertz.m*, a function),

(iii) and a driver, which which call the minimization procedure *fminsearch*.

For the driver (part (iii)), the following can be used to solve for the parameters and plot the model:

```
%Now fit the data
%Include initial guess
a0 = 1;
b0 = 0.5;
params0 = [a0,b0];

% Call MATLAB minimization fminsearch
% min is the optimized parameters (vector [a,b])
% err is the difference in E between data and model at optimized parameters min
[min,err] = fminsearch(@(params)error_gompertz(params,times,mass,error),params0,optimset('TolX
a_opt = min(1);
b_opt = min(2);

% Solve Gompertz equation with computed parameters
[T_opt,N_opt] = ode23s(@gompertz,times,mass(1),[],a_opt,b_opt);
plot(T_opt,N_opt,'-b','LineWidth',2);
```

I am not including everything here, but most can be accomplished in a short amount of code. (i) involves just writing the vector field, as in HW #1, and (ii) requires you to solve the ODE on the time interval indicated in *times.csv*, and then find the net error $E(a, b)$ (it should return this). **Plot the experimental data together with the Gompertz fit obtained.** Indicate your values for a and b.

(c) Do the same, but for exponential growth. That is, repeat the analysis from (b), except assuming here that N satisfies the ODE

$$\frac{dN}{dt} = kN.$$

Note here you will want to find **one parameter**, k.

(d) What are the respective errors for each of the two models? Which does better?

(e) What do they each predict for the tumor size at 30 days?