MATH 495: Homework #4
Spring 2019

Due: Thursday, March 28, 2019

Solve the below questions related to cancer dynamics models. Most questions will require theoretical analysis, but there is also a problem that involves simulation.

1. Consider the basic model of the cell-cycle describing proliferating and quiescent (really senescent) cells, where transitions to proliferation are prohibited, **but quiescent cells undergo apoptosis (i.e. death) at a constant rate μ_q**:

$$\begin{aligned} \dot{P} &= (\beta - \mu_p - r_0(N))\, P, \\ \dot{Q} &= r_0(N)P - \mu_q Q. \end{aligned} \tag{1}$$

   As usual, all parameters are positive, and $r_0(N)$ is an increasing function of the total cellular population N.

   (a) Transform the system (1) to the PN plane, i.e. to a closed system of equations describing the proliferating and total cell populations only.

   (b) Now assume that $\beta - \mu_p < \ell_0$, where ℓ_0 is the (well-defined) limit of $r_0(N)$. Show that your system in part (a) has a **unique steady state with positive components**, say $(\bar{P}, \bar{N})$.
   Hint: How many solutions does $\dot{P} = 0$ have?

   (c) Show that the steady state $(\bar{P}, \bar{N})$ found in part (b) is locally stable. Note that you may not have an exact formula for $(\bar{P}, \bar{N})$, but I claim you can still make an argument based on the equations it satisfies.

2. We consider a variation on the question of sequencing chemotherapy and surgery, but for an **exponentially growing tumor**, as opposed to one possessing Gompertz kinetics, as discussed in class. Note that the log-kill and Norton-Simon hypotheses are identical in this case.

   (a) Write the two mathematical models for each scenario: one describing the adjuvant case (surgery then chemotherapy), and other describing the neoadjuvant case (chemtherapy then surgery). That is, reformulate the in-class comparisons using exponential growth.

(b) Assuming the same amount of drug is administered in both cases (if t_f denotes the comparison time, then we fix $\int_0^{t_f} u(t)\,\mathrm{d}t$ as equal for both therapies), can you conclude one is better than the other? Are they equal? Is one always better, or do certain conditions related to treatment have to be met? Try and characterize the problem completely. *Hint:* It should be easier than in-class, as exponential dynamics are much simpler than Gompertzian.

3. In this problem, we numerically demonstrate the log-kill hypothesis in reducing the tumor cell burden a fixed fractional amount, dependent only on the drug dosage.

   (a) Suppose that a tumor can be described by "classical" von Bertalanaffy kinetics (see HW #2). For definiteness, assume parameters $\alpha = 1, \beta = 0.5$. Also assume that treatment is applied, which can be described via a function $u(t)$. Write an ODE describing the dynamics of tumor growth under treatment, **assuming the log-kill hypothesis**.

   (b) Assume a specific treatment of the following form:

$$u(t) = \begin{cases} 0, & 0 \le t < 4 - \epsilon, \\ 5/\epsilon, & 4 - \epsilon \le t \le 4 \end{cases}$$

   for $0 < \epsilon < 1$. If $u(t)$ is a proxy for the dosage given, show that for all such ϵ, the total amount of drug administered is constant.

   (c) As ϵ is decreased, $u(t)$ approaches a theoretical bolus injection: a maximal single dosage. Numerically investigate the dependence of the final tumor size, $N(4)$, on the value of ϵ. That is, plot $N(4)$ as a function of the treatment window ϵ. Most of the code can be found below:

```
clear all; close all;

% Solve von Bertalanffy model with chemotherapy
% Assume log-kill, and investigate (numerically) behavior of
% a bolus response

% Parameters
alpha = 1;
beta = 0.5;
t0 = 0;
tF = 4;
N0 = 1;
```

```
% Total amount of drug to apply
um = 5;
% Range to turn bolus on
% As eps gets smaller, approaches instantaneous dose
eps_vec = 1:-0.01:0.001;

% Store final tumor sizes after treatment
N_tF = zeros(1,length(eps_vec));

% Loop over eps_vec to obtain final tumor size variation at time tF
for i_eps = 1:length(eps_vec)
    % First solve prior to treatment
    u_pre = 0;
    t_switch = ;
    [T_pre,N_pre] = ode45(@(t,N)vB_rhs(t,N,alpha,beta,u_pre),[t0 t_switch],N0);

    % Now solve with new RHS as treatment is turned on
    u_treat = ;
    N0_pre = N_pre(end);
    [T_treat,N_treat] = ode45(@(t,N)vB_rhs(t,N,alpha,beta,u_treat),[t_switch tF],N0_pre);
    N_tF(i_eps) = N_treat(end);
end

% Expected theoretical result for infinitely small epsilon
[~,N_bolus] = ode45(@(t,N)vB_rhs(t,N,alpha,beta,0),[t0 tF],N0);
N_bolus_tF = ;

figure
plot(eps_vec,N_tF,'-k','LineWidth',2);
hold on;
plot(0,N_bolus_tF,'xr','LineWidth',7);
xlabel('\epsilon');
title('Effect of bolus therapy as treatment window decreases');
```

You will need to fill in some pieces of the above, as well as define the vector field describing governing ODE (this is represented by *vB_rhs*) in a separate m-file.

(d) Include a plot of the temporal tumor profile, $N(t)$ vs t, for $\epsilon = 0.5$.

(e) In the limit as $\epsilon \to 0$, what value do you expect $N(4)$ to approach? You should be able to theoretically compute this (using class notes). Also add it to the numerical plot in the appropriate location in the above.