MATH 495: Homework #4

Spring 2017

Due: Tuesday, March 28, 2017

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. This is the problem from the quiz, which I now realize may have been to difficult (for a quiz). Please complete it here.

   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. Consider now the full the Gyllenberg-Webb model (see Resource [8]):

   $$\begin{aligned} \dot{P} &= (\beta - \mu_p - r_0(N))\, P + r_i(N)Q, \\ \dot{Q} &= r_0(N)P - (r_i(N) + \mu_q)Q. \end{aligned} \tag{2}$$

Suppose that $r_0(N) < \beta - \mu_p$ for all $N \geq 0$ (equivalently, $\ell_0 < \beta - \mu_p$). Show that the cell population diverges: $N(t) \xrightarrow{t\to\infty} \infty$.
Hint: You can bound $\dot{P}$ below by growth terms whose behavior you understand.

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:

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

   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.