MATH 495: Homework #7
Spring 2018

Due: Monday, April 30, 2018

Solve the below questions related to cancer dynamics models. The first studies the tumor-immune model (Resource [12]), the second an optimal control problem (Resource [14]-[15]), and the third a stochastic model of carcinogenesis (Resource [16]).

1. Consider the non-dimensionalized version of the system of equations describing tumor-immune interactions from Resource [12]:

$$\begin{aligned} \frac{dx}{dt} &= \sigma + \rho\frac{xy}{\eta + y} - \mu xy - \delta x, \\ \frac{dy}{dt} &= \alpha y(1 - \beta y) - xy. \end{aligned} \tag{1}$$

   Show that for all positive parameter values, the system cannot exhibit any periodic orbits.
   Hint: Use Bendixson's Criterion (i.e. the Bendixson-Dulac theorem), with auxilliary function $\phi(x, y) = \frac{1}{xy}$.

2. This problem is not exactly related to optimal control, but instead is designed to help you become familiar with different (possibly time-dependent) treatment strategies as **controls**. In particular, we will consider two idealizations of clinical procedures: **constant and pulsed therapies**:

$$u_{\text{const}}(t) \equiv u_c \tag{2}$$

$$u_{\text{pulse}}(t) = \begin{cases} u_{\text{on}}, & t \bmod T \leq \Delta t_{\text{on}} \\ 0, & \Delta t_{\text{on}} < t \bmod T \leq T, \end{cases} \tag{3}$$

   where $T := \Delta t_{\text{on}} + \Delta t_{\text{off}}$ is the total pulsed cycle length. Note that the pulsed treatment (3) is simply a piecewise constant function which alternates between **constant** values u_{on} and 0 for time intervals of lengths Δt_{on} and Δt_{off}, respectively.

   (a) Suppose that the tumor is growing **logistically**, and that chemotherapy follows the **log-kill hypothesis**. In terms of intrinsic growth rate

a and carrying capacity K, write down an ODE describing the dynamics of the number of tumor cells under an arbitrary treatment regiment $u(t)$.

(b) Measure time in days. Suppose that the small population (think for a very small tumor, e.g. a few cells) doubling time is one day. Also, the carrying capacity is 10^8 cells. Note that both of these are measured in the absence of treatment. Modify your ODE in part (a) to include this data.

(c) The applied dosage for the constant therapy (2) has an induced cell-kill rate of 0.25/day. Furthermore, the pulsed therapy is applied for 0.5 days, with a rest period of 3 days (this tells you about Δt_{on} and Δt_{off}). If we want to apply the **same total amount of drug** between therapies (2) and (3) during one pulsed cycle, what value should u_{on} take? *Hint:* Remember, total amount of drug corresponds to an **integral** of $u(t)$.

(d) Assuming that at the beginning of treatment, the disease consists of 100 cells, simulate both therapies (2) and (3) for 40 days. Your answer should contain two figures: one containing $N(t)$ for **both** treatments, and the other plotting the applied treatments $u_{\text{const}}(t)$ and $u_{\text{pulse}}(t)$. Note that both m-files are provided (*solve_constant.m* and *solve_pulsed.m*), and are extensively commented, you just need to call them with appropriate arguments and plot the results. All necessary output is returned by the provided functions.

(e) Which therapy produces the smaller tumor size at the end of therapy? This should be clear from your plots in (d).

(f) Does your answer in (e) immediately tell you which therapy is better? What else do you observe in the plots that might be clinically relevant?

3. Find the optimal control $u^*(t)$ and corresponding state $x^*(t)$ that minimizes the objective functional

$$J(u) := \int_1^2 \left(tu^2(t) + t^2 x(t)\right)\, \mathrm{d}t,$$

subject to the IVP

$$\begin{aligned} \dot{x} &= -u(t), \\ x(1) &= 1. \end{aligned}$$

Hint: First form the corresponding Hamiltonian $H(t, x, u, \lambda)$ (λ is the **adjoint**), and form the necessary conditions (i.e. the Pontryagin Maximum Principle). What boundary-value problem does the state-adjoint system satisfy?

4. Assuming a two-stage disease (i.e. two mutations are required for malignancy), a system of three differential equations describing the probability of a cell being in each stage ($i = 0, 1, 2$) at time t can be derived (in class) as below:

$$\begin{aligned} \dot{p}_0 &= -\lambda_0 p_0, \\ \dot{p}_1 &= \lambda_0 p_0 - \lambda_1 p_1, \\ \dot{p}_2 &= \lambda_1 p_1. \end{aligned} \tag{4}$$

More precisely, $p_i(t)$ denotes the probability that a **single** cell is in stage i at time t. Here stage 0 denotes a normal (healthy) cell, and stage 2 a fully malignant cell. Assume, for simplicity, that the λ_i are **constant and distinct.**

(a) Assuming the cell is healthy at time $t = 0$, write down a set of initial conditions for the system (4).

(b) Solve the IVP described by equations (4) with initial conditions as in part (a).
Hint: Start with the p_0 equation, and work down from there.

(c) The hazard function $h(t)$ represents the instantaneous rate of developing the disease, i.e. the incidence rate for a random event. If we assume a population of N cells acting independently, it can be shown (again, in class), that $h(t)$ is given by

$$h(t) = N \frac{\dot{p}_2(t)}{1 - p_2(t)}.$$

Assuming that $p_2(t) \approx 0$, show that $h(t)$ is, to first order, a line. Find its slope. For more details, see Resource [14].