MATH 495: Homework #6
Spring 2017

Due: Monday, May 1, 2017

Solve the below questions related to cancer dynamics models. The first studies the tumor-immune model (Resource [10]), the second an optimal control problem (Resource [12]), and the third a stochastic model of carcinogenesis (Resource [14]).

1. Consider the non-dimensionalized version of the system of equations describing tumor-immune interactions from Resource [10]:

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

   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. 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?

3. 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:

$$\begin{aligned} \dot{p}_0 &= -\lambda_0 p_0, \\ \dot{p}_1 &= \lambda_0 p_0 - \lambda_1 p_1, \\ \dot{p}_2 &= \lambda_1 p_1. \end{aligned} \tag{2}$$

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 (2).

(b) Solve the IVP described by equations (2) 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].