MATH 495: Homework #6
Spring 2018

Due: Thursday, April 12, 2018

Solve the below questions related to cancer dynamics models. These questions require a combination of theoretical and computational analysis.

1. Consider a general cancer growth model in the presence of chemotherapy under the log-kill hypothesis:

$$\dot{N} = f(N)N - u(t)N. \tag{1}$$

Here $u(t)$ denotes the effect of any **piecewise continuous treatment** on the cancer population, and is independent of tumor size N. Furthermore, recall from class that a theoretical bolus injection of size u_m administered at time $t = T$ can be dynamically understood as the solution of the following:

$$\begin{aligned} \dot{\bar{N}} &= f(\bar{N})\bar{N}, \quad \text{for} \quad 0 < t < T \\ \bar{N}(T_+) &= \bar{N}(T_-)e^{-u_m}. \end{aligned} \tag{2}$$

The goal of this exercise is to show that a bolus injection is optimal over all treatments of size u_m, **in the case that the per-capita growth rate is decreasing** (e.g. for sigmoidal kinetics).

(a) Assume that $N(0) = \bar{N}(0) = N_0$ (both types of treatment begin with the same initial tumor mass) . For any continuous treatment strategy, show that $N(t) \leq \bar{N}(t)$, for $t \in [0, T)$.

(b) Assume that $f'(N) \leq 0$, and that $u(t)$ is any treatment regime such that $\int_0^T u(t)\,\mathrm{d}t = u_m$. That is, all treatments administer the same **total** amount of drug u_m. **Using (a), show that $\bar{\mathbf{N}}(\mathbf{T}) \leq \mathbf{N}(\mathbf{T})$.** This says that over any treatment which preserves the total administered dose, a bolus injection at the final time reduces the tumor size the most. This is the 1D analog of "bang-bang" controls, in the context of optimal control theory (which I hope to talk about soon!).
Hint: As used in the derivation in class, integrate the ODE to obtain an integro-differential equation (note: not the solution, but an equation defining the solution). From this, I claim you can make bounds to relate the two final tumor sizes.

(c) Similarly, assuming now that $f'(N) \geq 0$, show that a bolus injection **at time t = 0** is optimal in reducing the final tumor size over all administered treatments of fixed size u_m.

2. In class, we have discussed a model of tumor-immune system interactions, described via the below coupled nonlinear differential equations:

$$\begin{aligned} \frac{dE}{dt} &= s + p\frac{ET}{g+T} - mET - dE, \\ \frac{dT}{dt} &= aT(1-bT) - nET. \end{aligned} \tag{3}$$

Here E denotes the effector (immune, such as natural killer or cytotoxic T) cell concentration, and T is the tumor cell population. As with the Gyllenberg-Webb model of quiescence, we show here that the first quadrant is invariant, and that cell populations remain bounded. **Throughout the remainder of this exercise, assume that the initial conditions satisfy $\mathbf{0 < T(0) < 1/b, E(0) \geq 0}$.**

(a) Show that $T(t), E(t) \geq 0$, for all times $t \geq 0$.
Hint: What is the sign of the derivatives if one of the populations becomes zero in finite time? This is completely analogous to Gyllenberg-Webb analysis.

(b) Show that $T(t) \leq \frac{1}{b}$ for $t > 0$.

(c) Define $\lambda := \frac{p}{ng}$, and $u(t) := E(t) + \lambda T(t)$. Show that

$$\frac{du}{dt} \leq s + \lambda\frac{a+d}{b} - du(t). \tag{4}$$

(d) Using the result of part (c), conclude that $u(t)$ is bounded above, and hence as is $E(t)$.
Hint: What kind of growth is occurring on the RHS of equation (4)?

Thus, both tumor (part (b)) and effector (part (d)) cell populations remain bounded at all times.

3. Consider the non-dimensionalized version of system (3):

$$\begin{aligned} \frac{dx}{d\tau} &= \sigma + \rho\frac{xy}{\eta+y} - \mu xy - \delta x, \\ \frac{dy}{d\tau} &= \alpha y(1-\beta y) - xy. \end{aligned} \tag{5}$$

Parameter values can be obtained to fit the experimental data in the work; in Reference [12] the authors find these to be the following:

$$\sigma = 0.1181, \quad \rho = 1.131, \quad \eta = 20.19, \quad \mu = 0.00311,$$
$$\delta = 0.3743, \quad \alpha = 1.636, \quad \text{and} \quad \beta = 2.0 \times 10^{-3}.$$

(a) Using software, plot a phase portrait for the system (5). Your result should be a computer generated plot, giving a representative solution trajectory for each qualitatively distinct set of initial conditions. Note that you may use the software (*pplane2014b.m*) provided with HW #4.

(b) Verify that the two stable steady states observed in part (a) indeed have the observed type (sink, node, saddle, etc.). You may use any software to compute eigenvalues and/or determinants and traces. You may also estimate the steady states from your phase portrait numerically (e.g. you don't have to compute them by hand).

4. Provide a biological summary of the cytokine Interleukin-2 (IL-2). Namely, what cells both reproduce and respond to IL-2? What is its role in immunotherapy?

5. We now study an extension of Kuznetsov *et al.* (Resource [12]) to model immunotherapy and cell signaling. Immunotherapy usually refers to the use of cytokines (for us, assume IL-2) together with *adoptive cellular immunotherapy (ACI)*, where cultured immune cells possessing anti-tumor reactivity are injected into the tumor-bearing host.

   (a) Write a set of ODES extending the tumor-immune model presented in-class to include the signaling of IL-2. Note that there should now be three components: effector cells, tumor cells, and IL-2. Use your answer Problem #4 to include appropriate interactions.

   (b) Modify the equations in (a) to incorporate ACI as a control $u(t)$, where $u(t)$ is the injection rate of immune cells.

   (c) We may also have the ability to directly administer IL-2 into the tumor. Include a term (control) in your model representing this possibility.

   Hint: See Resource [13], which considers this extension.