MATH 495: Homework #6

Spring 2019

Due: Tuesday, April 30, 2019

Solve the below questions related to cancer dynamics models, both deterministic and stochastic.

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 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. Consider two **independent** exponential random variables X and Y, with parameters μ and λ, respectively. Find the probability that $X < Y$.

4. The following is an extension of the birth process discussed in class. Consider a continuous-time Markov chain representing birth and death. That is, there is one population of (say) cells, which can divide and die. Each cell divides and dies independently of one another, and the processes of division and death are assumed independent. Note that this looks like a continuous-time stochastic model of exponential growth which also includes death.

   The process can then be described by $\{N(t)\}$ for $t \geq 0$, where $N(t)$ represents the number of (alive) cells at time t.

(a) Describe the state space of the model. That is, what values can $N(t)$ take?

(b) Describe the transition probabilities. That is, what values of $p_{i,j}$ are non-zero? Recall that

$$p_{i,j} = \mathbb{P}(N(t_+) = j \mid N(t_-) = i, N(t_+) \neq N(t_-)),$$

i.e. given that the value of N has changed, how likely are the new values N may take?

(c) Suppose that a given cell divides with rate λ and dies with rate μ. Recall that this means that the time until division and death are exponentially distributed with parameters λ and μ, respectively. What is the random variable describing a division **OR** death in the **entire** cellular population of size n? Describe it precisely; you should be able to specify the distribution exactly. Note that this describes the event of $N(t)$ changing, and is thus fundamental in updating the stochastic process.

(d) Utilize the same assumptions as in part (c). Compute the transition probabilities in part (b). Note that the result of Problem #4 will be useful here.