Virus Dynamics Problem Set

This problem set is based on the virus dynamics system presented in Chapter 10 and the infectious dynamics system presented in Chapter 11. Feel free to use/modify the Mathematica notebooks from the course website.

Created by Daniel Rosenbloom and Ivana Bozic for Harvard Math 153, fall 2009. Use, modify, distribute with attribution.

Please show all work and represent your answers in simplest possible form. Submit Mathematica/other code for questions 1a and 1b.

Question #1 (50 points)

Consider the following one-strain model of virus dynamics, which is presented on p. 171 of the text:

$$\dot{v} = rv - pxv$$

$$\dot{x} = cv - bx$$

This is a simple, phenomenological model, but for concreteness, we can assign the following units to the variables:

- v denotes number of virions per μL of blood.
- x denotes number of CD4 immune cells per nL of blood.
- r is the replication rate of virus (per day)
- d is the death rate of immune cells (per day)
- p is the "predation rate" – the effectiveness of the immune response in clearing the virus (nL per cell, per day)
- c is the activation rate of the immune response (cells per 1000 virions, per day)

1a. (9 points) Use the parameter values $r = 2.5$, $p = 1$, $c = 0.1$, $b = 0.1$. (That is, the typical virus doubles about every 7 hours, and the typical immune cell has a lifespan of about 10 days.)

The severity of the patient's symptoms during the *acute viremic stage* depends in part on the maximum virus load.

To the nearest tenth of a virion per μL, what is the maximum viral load that occurs if the initial conditions are:

i) $v(0) = 50$, $x(0) = 0$
ii) $v(0) = 3$, $x(0) = 0$
iii) $v(0) = 0.3$, $x(0) = 0$
iv) $v(0) = 0.001$, $x(0) = 0$
v) $v(0) = 0.00001$, $x(0) = 0$
vi) $v(0) = 0.00001$, $x(0) = 1$

Hint: The Mathematica function *NMaximize*$[f[t], t]$ will search for the maximum value of the function $f[t]$, varying argument t. (The function *FindMaximum* searches for local maxima, using hill-climbing algorithms. *NMaximize* is probably better for this problem set.)

Another hint, for those using the "HIV Scenario #1" tutorial notebook: Note that if you simply add the line of code "NMaximize[v1[t], [t]]" to the end of this notebook, you will get an error message. That's because the function v1[t] is not defined in the notebook. You'll notice that every time the expression "v1[t]" is used to create a plot or get a numerical result, it is evaluated using a particular solution to the ODE. For example, the line, "Plot[Evaluate[v1[t] /. solution1], {t, 0, 100}]" tells Mathematica, "Plot the function v1[t], as defined by solution1." If you didn't invoke solution1, then you'd get a blank plot – because the function v1[t] is not defined.

1b. Assume that a patient is infected by a small amount of virus (say ≈ 50 virions in 5L of blood, or $v(0) \approx 10^{-5}$) and has had no prior exposure to this virus (so the initial immune reaction is zero).

Investigate how both the *maximum virus load* and the *equilibrium virus load* depend on the four parameters r, p, c, b:

i) (24 points) For each of the parameters, produce a graph that shows how changing that parameter affects both maximum and equilibrium virus load. While varying one parameter, you can hold the other parameters constant, using the default values $r = 2.5$, $p = 1$, $c = 0.1$, $b = 0.1$.

ii) (10 points) Briefly describe your results. Describe how each parameter affects max. and equilibrium virus load. (More specifically, describe qualitatively how virus load appears to increase/decrease with each parameter – linearly, quadratically, exponentially, logarithmically, etc. etc.?)

1c. (7 points) Again, assume that the initial virus load is small, and the initial immune reaction is zero. Prove the following:

If $b < 4r$, then when the maximum virus load is reached, the immune reaction is still increasing.

(Hint: Based on the Mathematica tutorial worksheet, we know that $b < 4r$ ensures that virus load will oscillate.)

Question #2 (50 points)

The basic epidemiological dynamics of a host-parasite interaction can be described by the following system of differential equations (see p. 192 of the text)

$$\dot{x} = k - ux - \beta xy$$

$$\dot{y} = y(\beta x - u - v)$$

Numbers of uninfected and infected hosts are denoted by x and y, respectively. In the absence of the parasite, the host population is regulated by a simple immigration-death process, with k specifying the constant immigration rate of uninfected hosts and u their natural death rate. β is the rate constant characterizing the parasite's infectivity. Infected hosts die at an increased rate $u + v$.

Please assume that all parameters are positive.

2a. (20 points) The basic reproductive ratio R_0 of the parasite is defined as the number of new infections caused by a single infected host if introduced in a population of uninfected hosts. Here we calculate the basic reproductive ratio. We use the fact that infected hosts die at rate $u + v$; in other words, in a small time interval Δt, an infected host can die with probability $(u + v)\Delta t$.

i) Suppose that we have one infected host (at time $t = 0$). Let $p(t)$ denote the probability that this one infected host is alive at time t. In terms of $p(t)$, u, v, and Δt, calculate $p(t + \Delta t)$.

ii) Calculate $p(t)$, in terms of u, v, and t.

iii) Let T denote the time of death of the one infected host from i). Let $F(t)$ denote the probability that $T \leq t$ (F is the cumulative distribution function for T). Calculate $F(t)$. What is the probability density function for T?

iv) Calculate the average lifetime of an infected host (expected value of T).

v) Calculate the basic reproductive ratio of a parasite in this model. Assume that the population of uninfected hosts is large and at an equilibrium prior to the introduction of the parasite.

2b. (30 points) Here we discuss the significance of the basic reproductive ratio.

i) (5 points) Calculate all equilibrium points of the above system of differential equations.

ii) (15 points) What conditions guarantee the stability of each equilibrium point?

iii) (10 points) Based on your above answers, explain the importance of the basic reproductive ratio in determining the fate of an infection.