UBC ISCI 422
Final Exam
December 13, 2013

Instructions:

1. Do not open this test until told to do so.
2. This test is closed book. You may NOT bring any material in with you.
3. Print your name and student number on ALL pages.
4. You may use a scratch exam booklet for workspace but enter your answers within the space provided. Do not enter answers on page-backs.
5. Electronics (calculators, computers, etc.) are NOT permitted (or needed).
6. Print or write neatly.
7. At the completion of the exam hand in your answers and all ancillary material.
8. Except where explicitly stated, you may write in paragraph or point form.
9. Point values for each question are indicated in the margins.

Marks:

Question	1	2	3	4	TOTAL
Mark					
Max	15	20	35	30	100

First Name: _____

Last Name: _____

Student Number: _____

/ 5 1. (a) In 25 words or less give a concise and complete definition of what *science* is.

/ 10 (b) Explain your definition. Why did you decide on your particular choice of words? What words do you think are most important in your definition? (If you removed them would it still define *science*?)

/ 5 2. (a) In 25 words or less give a complete definition of what a *scientific model* is.

/ 10 (b) Explain your definition. Why did you decide on your particular choice of words? What words do you think are most important in your definition? (If you removed them would it still define a *scientific model*?)

/ 5 (c) Do we need models in science? What role do they play?

3. The article listed below uses a model to investigate disease anti-viral drug treatment. You can find the first two pages of this paper appended to this exam. You will use it to help construct your own model in order to understand disease dynamics.

> M. A. Nowak, S. Bonhoeffer, G. M. Shaw, and R. M. May, "Anti-viral Drug Treatment: Dynamics of Resistance in Free Virus and Infected Cell Populations", J. Theor. Biol., 184, 203—17 (1997).

We will use the following symbols to represent the ingredients in the model:

$\varnothing$	Empty set (nothing).
X	An uninfected cell.
Y	An infected cell.
V	A virus particle.

/ 7 (a) In Section 2 the authors compile a set of rate equations; see Eqns. (1). These equations can be derived from a reaction kinetics framework. From Section 2 reconstruct the full set of reactions involved (fill in all the missing symbols) and briefly interpret what occurs in each reaction:

Reaction	Interpretation
$\varnothing \xrightarrow{\lambda} \_\_\_\_$	
$X \longrightarrow \varnothing$	
$X + V \longrightarrow \_\_\_\_$	
$\_\_\_\_ \xrightarrow{a} \varnothing$	
$V \longrightarrow \varnothing$	
$Y \xrightarrow{k} \_\_\_\_$	

/ 5

(b) At the end of Section 2 the authors give the equilibrium densities in an infected host. Derive the equilibrium densities *x*, *y*, & *v* in an uninfected host. (Show your work.)

For sub-questions (c-f) assume that the virus particles, *v*, are produced and removed much more rapidly than cells. Therefore the virus density quickly equilibrates at $v=k\,y/u$ and we can study the slower cellular processes on their own, treating the virus as always being in equilibrium:

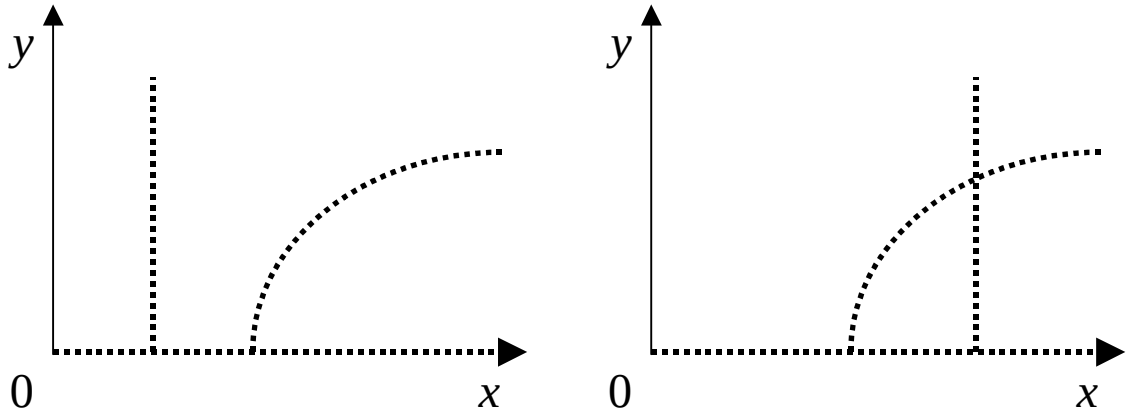
$$\frac{dx}{dt} = \lambda - d \cdot x - \frac{\beta \cdot k}{u} x \cdot y$$

$$\frac{dy}{dt} = \frac{\beta \cdot k}{u} x \cdot y - a \cdot y$$

/ 8

(c) Depending on the rate constants, there are two possible phase portraits, shown below with unlabelled isoclines (dotted lines). On each phase portrait:

- Label the *x*-isocline(s) and the *y*-isocline(s).
- Circle all equilibria.
- In each region between the isoclines, draw an arrow indicating the direction of flow.



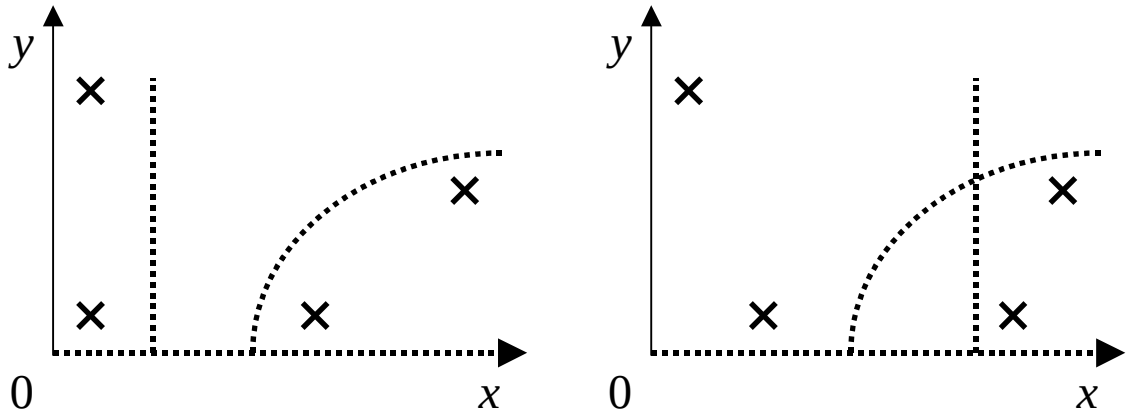
/ 5

(d) The graph on the left shows the case where the vertical isocline does not cross the curved isocline. Determine the condition on the rate constant *a* required for this to be true.

/ 5

(e) The two phase portraits are shown again below. On each phase portrait:

- Sketch the trajectory (the path or trail) from each starting point **x**.
- Based on the trajectories, circle all <u>stable</u> equilibria.



/ 5

(f) A new anti-viral treatment, T4, is discovered. The infected cell death rate, *a*, increases proportionately with the treatment dosage and T4 is found to have no other effects on the disease, but it may have toxic side effects. Determine the lowest rate of infected cell death, *a*, the treatment dosage should aim for. Explain why you chose this dosage.

4. Modeling isn't just an academic exercise—it can also be helpful in your daily life. In this problem you will construct a model to help answer a personal question you are currently or have recently struggled with.

/ 5

(a) What is the question you intend to address? Why is this question of personal interest to you? You will be graded on originality and relevance to your everyday life outside of the classroom. (Suggestion: read the remaining sub-questions before choosing your question carefully as it will be crucial to your success.)

/ 10

(b) Construct a schematic representation that clearly and simply conveys the underlying processes and/or logic of your model. (Eg. reactions, flow chart, mind map, or block diagram.) Explain your model with reference to your schematic. (Suggestion: practice in the workspace booklet provided then draw the final version here.)

/ 5 (c) What data or information will you need to collect to finalize your model?

/ 5 (d) What assumptions will you incorporate into the model? How can you justify them?

/ 5 (e) How would you employ your model to give you insights into your original question? What predictions do you anticipate your model will generate?

END OF EXAM

J. theor. Biol. (1997) **184,** 203–217

(For use with Question 3.)

Anti-viral Drug Treatment: Dynamics of Resistance in Free Virus and Infected Cell Populations

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Anti-viral drug treatment of infections with the human immunodeficiency virus type 1 (HIV-1) usually leads to a rapid decline in the abundance of plasma virus. The effect of single drug therapy, however, is often only short-lived as the virus readily develops drug-resistant mutants. In this paper we provide analytic approximations for the rate of emergence of resistant virus. We study the decline of wildtype virus and the rise of resistant mutant virus in different compartments of the virus population such as free plasma virus, cells infected with actively replicating virus, long-lived infected cells and cells carrying defective provirus. The model results are compared with data on the rise of drug-resistant virus in three HIV-1 infected patients treated with neverapine (NVP). We find that the half-life of latently infected cells is between 10 and 20 days, whereas the half-life of cells with defective provirus is about 80 days. We also provide a crude estimate for the basic reproductive ratio of HIV-1 during NVP therapy.

1. Introduction

In recent years, a number of anti-viral drugs have been developed that are potent inhibitors of HIV-1 replication *in vivo*. The two major types of anti-HIV drugs are reverse transcriptase inhibitors and protease inhibitors. Reverse transcriptase inhibitors prevent the infection of new cells by blocking the reverse transcription of the HIV RNA into DNA, which would integrate into the host cell genome. Protease inhibitors prevent already infected cells from producing infectious virus particles.

Treatment with either type of drug leads to a rapid decline in plasma virus and an increase in CD4 cells, which constitute the major target cell of HIV infection. Monitoring the rate of virus decline in the first few days of treatment leads to interesting insights into the short-term dynamics of HIV infection. Most of the plasma virus is produced by HIV-infected cells that have a half-life of about 2 days (Ho *et al*., 1995; Wei *et al*., 1995; Coffin, 1995; Nowak *et al*., 1995; Perelson *et al*., 1996). The half-life of free virus particles has been estimated to be about 6 hr and the time-span between infection of a cell and production of new virus particles to be around 0.9 days (Perelson *et al*., 1996). The latter estimates rely on a detailed kinetic understanding of the initial shoulder of virus decline within 48 hr after start of therapy and are therefore problematic (Herz *et al*., 1996).

Prolonged treatment with a single anti-HIV drug almost always results in the emergence of resistant virus (Larder *et al*., 1989, 1993, 1995; Larder & Kemp, 1989; Richman, 1990, 1994; Richman *et al*., 1994; St Clair *et al*., 1991; Ho *et al*., 1994; Loveday *et al*., 1995; Markowitz *et al*., 1995). In AZT treatment, a number of mutations have been described that render the virus more and more resistant against the drug (Boucher *et al*., 1990, 1992a, b; Mohri *et al*., 1993; de Jong *et al*., 1996). In NVP and 3TC treatment, single point mutations appear to confer high level resistance against the drug

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(Richman *et al*., 1994; Schuurman *et al*., 1995; Wei *et al*., 1995). Much hope is currently being offered by combining several different anti-HIV drugs. Simultaneous treatment with AZT and 3TC, for example, can suppress virus load about ten-fold in patients treated for up to 1 year (Eron *et al*., 1995; Staszewski, 1995). Preliminary data on treatment with AZT, 3TC and a protease inhibitor suggest that virus load can be suppressed to undetectable levels (about a 10000-fold reduction) and stays below detection limit in patients treated for several months (David Ho, Douglas Richman, personal communication).

Mathematical models have been developed to describe the population dynamics of virus replication following drug treatment and the emergence of resistant mutant. McLean *et al*. (1991) proposed that the short term effect of AZT treatment is due to the predator-prey like interaction between virus and host cells, and that the CD4 cell increase following drug treatment is responsible for the resurgence of virus even in the absence of resistant mutants. Nowak *et al*. (1991) study the effect of drug treatment on delaying progression to disease. McLean & Nowak (1992) postulate that the rise of drug-resistant virus is caused by the increase in available target cells for HIV infection. Frost & McLean (1994) and McLean & Frost (1995) describe models for the sequential emergence of resistant variants in AZT therapy. Wein *et al*. (1996) use a control theoretic approach for multidrug therapies. Kirschner & Webb (1996) study the emergence of drug resistant virus in a model with CD4 and CD8 cells. De Boer & Boucher (1996) propose that reducing CD4 cell numbers can potentially prevent the emergence of drug-resistant virus.

In this paper we develop analytic solutions for the emergence of resistant virus under single drug therapy. We will describe the rate of increase of resistant virus in the free virus population and in the infected cell population and show how the model can be used to estimate demographic parameters of virus population dynamics *in vivo*.

In Section 2 we outline the basic model of virus dynamics, in Section 3 we discuss the initial viral decline after start of therapy and in Section 4 we derive analytic approximations for the rise of resistant mutant. In Section 5 we expand the basic model to include cells that harbour latent or defective virus. We present clinical data on three patients treated with NVP in Section 6 and conclude in Section 7.

2. The Basic Model

In the basic model of viral dynamics we distinguish three variables: uninfected cells x, infected cells y, and virus particles v. Let us assume that uninfected cells are produced at a constant rate, λ, from a pool of precursor cells and die at rate dx. This is the simplest possible host cell dynamics. Later we will discuss more complex assumptions. Virus reacts with uninfected cells to produce infected cells. This happens at rate βxv. Infected cells die at rate ay. Virus is produced from infected cells at rate ky and dies at rate uv. This gives rise to the following system of ordinary differential equations:

$$\begin{aligned} dx/dt &= \lambda - dx - \beta xv \\ dy/dt &= \beta xv - ay \\ dv/dt &= ky - uv. \end{aligned} \tag{1}$$

If the basic reproductive ratio of the virus,

$$R_0 = \beta\lambda k/(adu), \tag{2}$$

is larger than one, then the system converges to the equilibrium

$$x^* = \frac{au}{\beta k} \quad v^* = \frac{\lambda k}{au} - \frac{d}{\beta} \quad y^* = \frac{\lambda}{a} - \frac{du}{\beta k}. \tag{3}$$

3. Viral Decline Under Drug Therapy

Let us assume that the virus infection is in equilibrium (steady state) as specified by eqn (3). We are interested in the decline of free virus and infected cells and the rise of uninfected cells following drug treatment. If a drug prevents the infection of new cells (i.e. $\beta = 0$) then the equations become

$$\begin{aligned} dx/dt &= \lambda - dx \\ dy/dt &= -ay \\ dv/dt &= ky - uv \end{aligned} \tag{4}$$

subject to the initial conditions x^*, y^*, and v^* at $t = 0$. This gives rise to the following solutions:

$$x(t) = \frac{\lambda}{d} - \left(\frac{\lambda}{d} - x^*\right)e^{-dt} \tag{5}$$

$$y(t) = y^* e^{-at} \tag{6}$$

$$v(t) = v^* \frac{ue^{-at} - ae^{-ut}}{u - a}. \tag{7}$$

The initial slope of the rise of uninfected cells is simply $\lambda - dx^*$. Thus for the same value of λ and d, patients with low x^* should have the higher initial decrease. The rise of uninfected cells in the absence of viral resurgence would then level out converging to the uninfected equilibrium,

(End of excerpt.)