Viral dynamics: Lecture 1 problems

1. **Reverse Transcriptase (RT) Inhibitors** We will consider two classes of HIV drugs: reverse transcriptase inhibitors and protease inhibitors, within the simplest model for HIV dynamics. The simplest model is (as given in class)

$$\frac{dT}{dt} = \lambda - dT - kVT \tag{1}$$

$$\frac{dT^*}{dt} = kVT - \mu T^* \tag{2}$$

$$\frac{dV}{dt} = pT^* - cV \tag{3}$$

RT inhibitors prevent productive infection of cells by HIV.

a. Suppose that a RT inhibitor that is 100% effective is introduced to a patient at infected steady state. Ignore the dynamics of uninfected T cells, which should happen on a slower time scale. Solve the resulting model for $T^*(t)$ and $V(t)$. Given that the clearance rate of virus c is greater than the death rate of infected cells μ, show that $V(t)$ decays exponentially after a short phase of slower-than-exponential decay. Which parameter of the model governs the asymptotic phase of decay?

b. The drug nevirapine leads to a decay of free virus by a factor of 10-100 during the first two weeks of therapy. Use this fact to estimate an important parameter of the model using the result of part a.

c. It's unrealistic to think that any RT inhibitor is 100% effective. Therefore, write $k_T = sk$ as the infectivity parameter in the basic model, where s controls the efficiency of the drug. If we also suppose that the timescale for turnover of T cells is long compared to that for viral decay and so approximate $T = \hat{T}$, a routine calculation shows that the viral load is governed by

$$V(t) \sim \frac{\gamma_2}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} \qquad \text{where} \tag{4}$$

$$\gamma_{1,2} = \frac{c+\mu}{2} \mp \frac{1}{2}\sqrt{(c-\mu)^2 + 4s\mu c} \tag{5}$$

Sketch $V(t)$ for $c >> \mu$ using different values of s between 0 and 1.

d. Supposing again that c is greater than μ, approximate the decay rate γ_1 to first order in μ/c.

e. Describe how the efficacy of the drug affects the estimate you made in part b, and suggest an experiment that could help estimate the efficacy of the drug.

2. **Protease Inhibitors** Protease inhibitors prevent infected cells from producing infectious virions. Free virus particles that are around when treatment begins will continue to infect new cells, but infected cells will produce non-infectious virions (called $W(t)$). For a 100% effective protease inhibitor (proteases are actually very effective so this is a fair approximation), the equations become

$$\frac{dT}{dt} = \lambda - dT - kVT \tag{6}$$
$$\frac{dT^*}{dt} = kVT - \mu T^* \tag{7}$$
$$\frac{dV}{dt} = -cV \tag{8}$$
$$\frac{dW}{dt} = pT^* - cW \tag{9}$$

a. Assume again that T remains constant during the treatment and solve for T^*, V and W.
b. In simple experiments, it is possible to measure $V(t) + W(t)$. How does this quantity behave asymptotically?

Hints:
The solution of

$$X'(t) + aX(t) = f(t) \qquad X(0) = X_0$$

is (by integrating factor method)

$$X(t) = e^{-at}\left(X_0 + \int_0^t f(t')e^{at'}\,dt'\right)$$

The infected steady solution of the basic viral dynamics model

$$\frac{dT}{dt} = \lambda - dT - kVT \tag{10}$$
$$\frac{dT^*}{dt} = kVT - \mu T^* \tag{11}$$
$$\frac{dV}{dt} = pT^* - cV \tag{12}$$

is

$$T_{ss} = \frac{c\mu}{kp} \tag{13}$$
$$T^*_{ss} = \frac{\lambda}{\mu} - \frac{cd}{kp} \tag{14}$$
$$V_{ss} = \frac{\lambda}{\mu}\frac{kp}{ck} - \frac{d}{k} \tag{15}$$