CELLULAR AND SYSTEMS MODELING - HW1

Student: Shu-Ting Cho (shc167@pitt.edu)

HIV infection modeling

(10 points) PMLS2, problem 1.4.

1.4 *Model action of antiviral drug*

Finish the analysis of the time course of HIV infection after administering an antiviral drug. For this problem, you may assume that virus clearance is faster than T cell death (though not necessarily much faster). That is, assume $k_V > k_I$.

a. Follow Section 1.2.4 (page 11) to write down the trial solution for $N_V(t)$ in terms of the initial value N_{V0} and three unknown constants k_I, k_V, and β.

trial solution for $N_V(t)$, N_{V0}, k_I, k_V, β

(1.4)

$$N_V(t) = Xe^{-k_I t} + (N_{V0} - X)e^{-k_V t}$$

from (1.3)

$$\frac{dN_V}{dt} = -k_V N_V + \gamma N_{I0} e^{-k_I t}$$

derivative 1.4

$$\frac{dN_V(t)}{dt} = (Xe^{-k_I t})(-k_I) + (N_{V0} - X)e^{-k_V t}(-k_V)$$

1.3=1.4 $\Rightarrow -k_V(Xe^{-k_I t}) - k_V(N_{V0} - X)e^{-k_V t} + \gamma N_{I0} e^{-k_I t}$

$$= -k_I(Xe^{-k_I t}) - k_V(N_{V0} - X)e^{-k_V t}$$

$$\Rightarrow -k_V X + \gamma N_{I0} = -k_I X \Rightarrow X(k_V - k_I) = \gamma N_{I0} = \beta$$

$$\Rightarrow X = \frac{\beta}{k_V - k_I}$$

$$N_V(t) = \left(\frac{\beta}{k_V - k_I}\right) e^{-k_I t} + \left(N_{V0} - \left(\frac{\beta}{k_V - k_I}\right)\right) e^{-k_V t}$$

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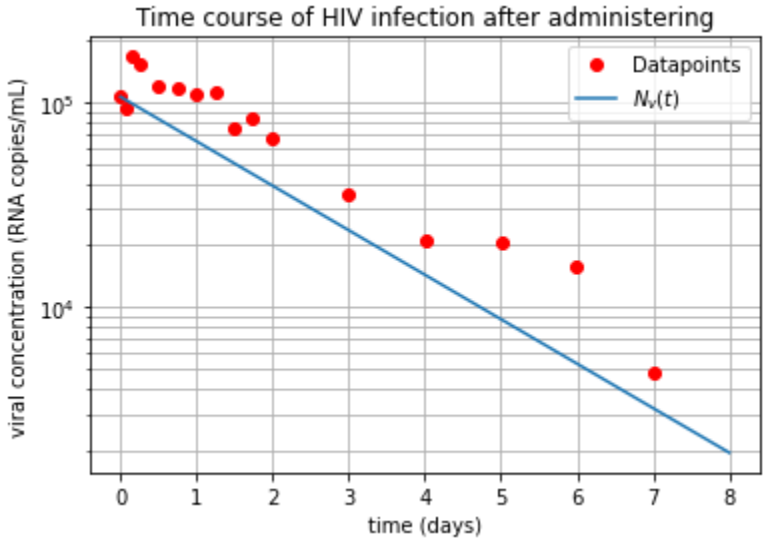
b. Obtain Dataset 1,[12] and use a computer to make a semilog plot. Don't join the points by line segments; make each point a symbol, for example, a small circle or plus sign. Label the axes of your plot. Give it a title, too. Superimpose a graph of the trial solution, with some arbitrary values of k_I, k_V, and β, on your graph of the actual data. Then try to fit the trial solution to the data, by choosing better values of the parameters.



See code and values in the .ipynb.

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c. You may quickly discover that it's difficult to find the right parameter values just by guessing. Rather than resort to some black-box software to perform the search, however, try to choose parameter values that make certain features of your graph coincide with the data, as follows. First, note that the experimental data approach a straight line on a semilog plot at long times (apart from some experimental scatter). The trial solution Equation 1.4 also approaches such a line, namely, the graph of the function $N_{V,asymp}(t) = Xe^{-k_I t}$, so you can match that function to the data. Lay a ruler or other straightedge along the data, adjust it until it seems to match the long-time trend of the data, and find two points on that straight line. From this information, find values of k_I and X that make $N_{V,asymp}(t)$ match the data.

P1 $(1, 10^5)$
P2 $(6, 10^4)$

$\log N_V = \log X + \log e^{-k_I t}$

$\begin{cases} 5 = \log X + \log e^{-k_I} \\ 4 = \log X + 6\log e^{-k_I} \end{cases}$

$30 = 6\log X + 6\log e^{-k_I}$

$4 = \log X + 6\log e^{-k_I}$

$1 = -5 \cdot \log e^{-k_I}$

$\log e^{-k_I} = -\frac{1}{5}$

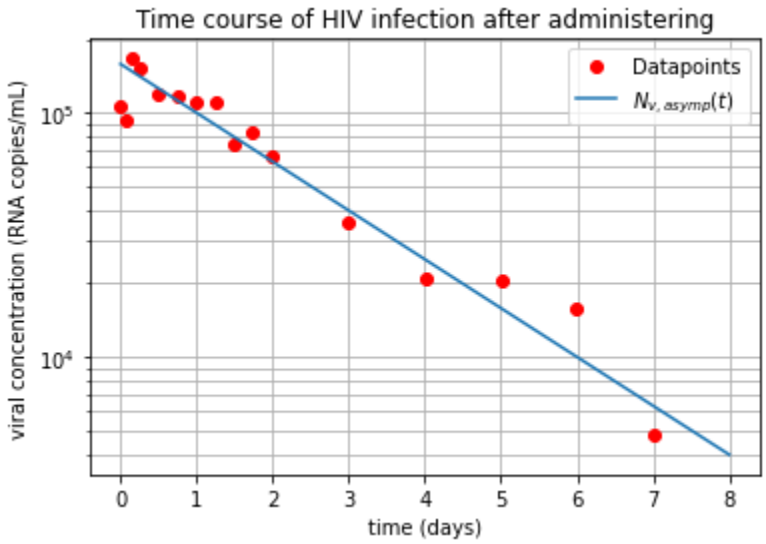
$\log e = \frac{1}{5 \cdot k_I}$

$k_I = \frac{1}{5 \cdot \log e}$

$5\log X = 26$

$\log X = \frac{26}{5}$

$X = 10^{\frac{26}{5}}$



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d. Substitute your values of k_I and X into Equation 1.4 (page 13) to get a trial solution with the right initial value N_{V0} and the right long-time behavior. This is still not quite enough to give you the value of k_V needed to specify a unique solution. However, the model suggests another constraint. Immediately after administering the drug, the number of infected T cells has not yet had a chance to begin falling. Thus, in this model both viral production and clearance are the same as they were prior to time zero, so the solution is initially still quasi-steady:

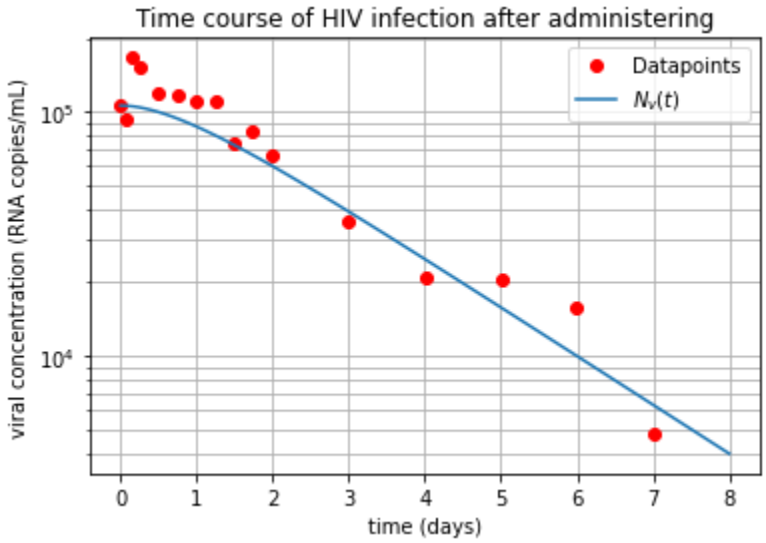
$$\left.\frac{dN_V}{dt}\right|_{t=0} = 0.$$

Use this constraint to determine all parameters of the trial solution from your answer to (c), and plot the result along with the data. (You may want to tweak the approximate values you used for N_{V0}, and other parameters, in order to make the fit look better.)

$$N_V(t) = Xe^{-k_I t} + (N_{V0} - X)e^{-k_V t}$$

$$\frac{dN_V}{dt} = (Xe^{-k_I t})(-k_I) + (N_{V0} - X)e^{-k_V t}(-k_V)$$

$$\text{At } t=0 \rightarrow \quad -k_I X + (N_{V0} - X)(-k_V) = 0 \quad \Rightarrow \quad k_V = \frac{-k_I X}{N_{V0} - X} = \frac{k_I X}{X - N_{V0}}$$



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e. We have been exploring the hypothesis that the reciprocal of the T cell infection rate is much shorter than the typical latency period for the infection, or in other words that

$(1/k_I)$ is much smaller than 10 years.

Do the data support this claim?

$k_I = 0.460517$

$1/k_I = 1/0.460517 = 2.171472409516259$

Yes, 2.17 days is much shorter than 10 years.

f. Use your result from Problem 1.3 to convert your answers to (d) into half-life values for virions and infected T cells. (They can be interpreted as half-lives in a hypothetical system with clearance, but no new virion production nor new infections.)

$\frac{dN_I}{dt} = -k_I N_I$

$\Rightarrow \frac{dN_I}{N_I} = -k_I dt$

$\Rightarrow \ln N_I = -k_I t + C$

$\Rightarrow N_I(t) = e^{-k_I t + C} = N_{I0} e^{-k_I t}$

$N_0 \times e^{-k_I t} = \frac{1}{2} N_0$

$\Rightarrow e^{-k_I t} = \frac{1}{2} \Rightarrow -k_I t = \ln \frac{1}{2}$

$t = \frac{\ln \frac{1}{2}}{-k}$

half-like for virions = 1.505150 days
half-like for infected T cells = 0.497534 day

See code and values in the .ipynb

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(10 points) PMLS2, problem 1.8.

1.8 **T2** *Infected cell count*

First, work Problem 1.4. Then continue as follows to get an estimate of the population of infected T cells in the quasi-steady state. (Chapter 3 will argue that this number is needed in order to evaluate the hypothesis of viral evolution in individual patients.)

a. The human body contains about 5 L of blood. Each HIV virion carries two copies of its RNA genome. Thus, the total virion population is about $2.5 \cdot 10^3$ mL times the quantity plotted in Figure 0.3b. Express the values of N_{v0} and X that you found in Problem 1.4 in terms of total virion population.

$2.5 \times 10^3 mL \times N_V = \text{Total virion population (TVP)}$

$\Rightarrow N_V = \frac{TVP}{2.5} \times 10^{-3} = TVP \times 4 \times 10^{-4}$

(eq 1.4)

$N_V = X e^{-k_I t} + (N_{V0} - X) e^{-k_V t}$

$\Rightarrow \frac{N_V - X e^{-k_I t}}{e^{-k_V t}} + X = N_{V0} \Rightarrow N_{V0} = \frac{TVP \times 4 \times 10^{-4} - X e^{-k_I t}}{e^{-k_V t}} + X$

$= TVP \times \frac{4 \times 10^{-4}}{e^{-k_V t}} - X e^{(k_V - k_I)t} + X$

$\Rightarrow N_V - N_{V0} e^{-k_V t} = X(e^{-k_I t} - e^{-k_V t})$

$N_{V0} = TVP \times 4 \times 10^{-4} \times 0.25^t - 158489 \times 2.5^t + 158489$

$\Rightarrow X = \frac{N_V - N_{V0} e^{-k_V t}}{e^{-k_I t} - e^{-k_V t}} = \frac{TVP \times 4 \times 10^{-4} - N_{V0} e^{-k_V t}}{e^{-k_I t} - e^{-k_V t}}$

$X = \frac{TVP \times 4 \times 10^{-4} - 10^5 \times 0.25^t}{0.63^t - 0.25^t}$

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b. Obtain a numerical estimate for β from your fit. (You found the value of k_I in Problem 1.4.)

$X = 158489.319246$

$k_V = 1.393166$

$k_I = 0.460517$

$\beta = X(k_V - k_I) = 158489.319246(1.393166 - 0.460517) = 147814.9337476635$

c. The symbol β is an abbreviation for the product γN_{I0}, where $\gamma \approx 100k_I$ is the rate of virion release by an infected T cell and N_{I0} is the quantity we want to find. Turn your results from (a) and (b) into an estimate of N_{I0}.

$\beta = \gamma N_{I0}$

$\Rightarrow 147814.9337476635 = 100k_I N_{I0}$

$\Rightarrow N_{I0} = \beta/\gamma = \frac{147814.9337476635}{100 \times k_I} = \frac{147814.9337476635}{100 \times 0.460517} = 3209.760503475251$

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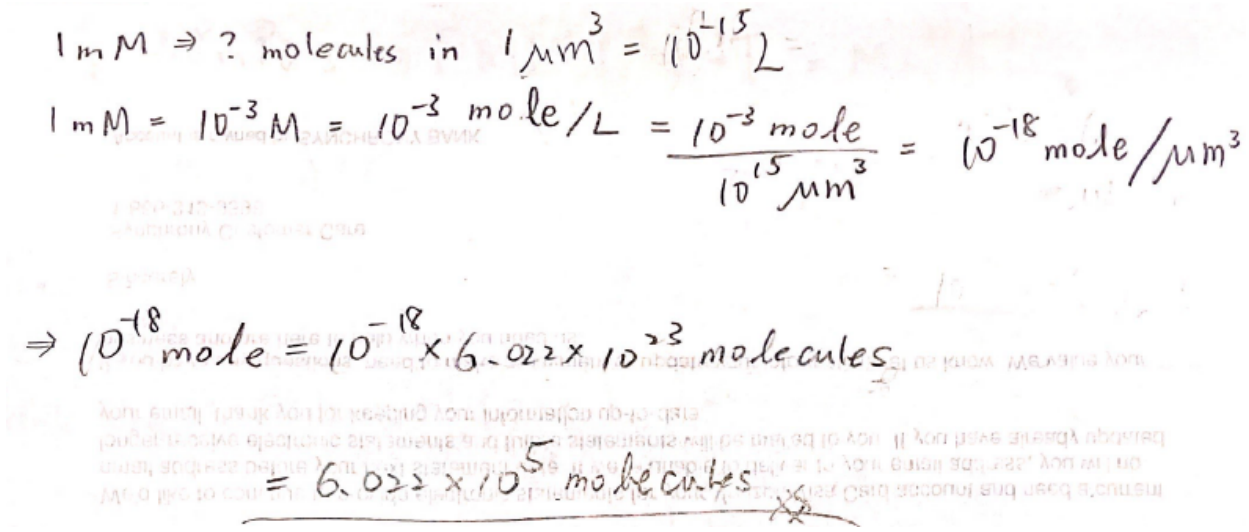
Dimensional analysis and units

(5 points) PMLS2, problem 2.6.

2.6 *Concentration units*

Appendix B introduces a unit for concentration called "molar," abbreviated M. To practice dimensional analysis, consider a sugar solution with concentration 1 mM. Find the average number of sugar molecules in one cubic micrometer of such a solution.

$6.022 \times 10^{5} molecules$



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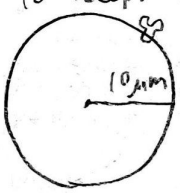
(5 points). Consider a typical eukaryotic cell with a diameter of 20 μm that has 10^4 copies of a surface receptor R. What is the concentration of receptors distributed over the total volume contained by the cell? What is the concentration of receptors contained in a volume made up of a 10 nm thick layer adjacent to the cell membrane?

$2.3873241463784303\ receptors/\mu m^3$

$796.5710209567719\ receptors/\mu m^3$

Q4

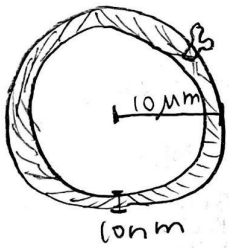


$V = \frac{4}{3}\pi r^3 = \frac{4}{3}\pi (10\mu m)^3$

$= \frac{4}{3} \times 10^3 \pi\ \mu m^3$

$\Rightarrow conc. = \frac{10^4}{\frac{4}{3}\times 10^3 \times \pi\ \mu m^3} = \frac{10^{4\times\frac{-3}{4}} \times 10^{-3}}{\pi}$ per $\mu m^3 = \frac{30}{4\pi}$

$\simeq 2.39$ receptors/μm^3 ※



$V = \frac{4\pi}{3} \times 10^3\ \mu m^3 - \left[\frac{4}{3}\pi (10\mu m - 10nm)^3\right]$

$10nm \rightarrow 0.01\mu m$

$= \frac{4\pi}{3}\left[10^3 - 9.99^3\right] \simeq 12.55\ \mu m^3$

$\Rightarrow conc. = \frac{10^4}{12.55}\ \mu m^{-3} = 796.57$ receptors/μm^3 ※

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(5 points) PMLS2, problem 2.7.

2.7 *Atomic energy scale*

Read Appendix B.

a. Using the same logic as in Section B.6, try to construct an *energy* scale as a combination of the force constant k_e defined there, the electron mass m_e, and Planck's constant $\hbar$. Get a numerical answer in joules. What are the values of the exponents a, b, and c analogous to Equation B.1 (page 441)?

$a = 2,\ b = 1,\ c = -2$

$4.366349206349205 \times 10^{-18} J$

Q2.7 $2.3 \cdot 10^{-28}\ J\,m$, $9.1 \cdot 10^{-31}\ kg$, $1.05 \cdot 10^{-34}\ kg\,m^2/s$

a. k_e, m_e, $\hbar \Rightarrow J$

(B.1) $\frac{\hbar^2}{k_e m_e} \approx 0.5 \times 10^{-10}\ m$

$(k_e)^a (m_e)^b (\hbar)^c = J = (M^1 L^2 T^{-2})$

$(J\,m)^a (kg)^b (kg \cdot m^2/s)^c$

$(ML^3/T^2)^a M^b (ML^2/T)^c = M^1 L^2 T^{-2}$

$M: a + b + c = 1$

$L: 3a + 2c = 2$

$T: -2a - c = -2$

$3a + 2c = 2$

$-4a - 2c = -4$

$-a = -2 \Rightarrow a = 2$

$\Rightarrow c = -2$

$\Rightarrow b = 1$

$(2.3 \times 10^{-28}\ J\,m)^2 \times (9.1 \times 10^{-31}\ kg)^1 \times (1.05 \times 10^{-34}\ kg\,m^2/s)^{-2} \cong 4.4 \times 10^{-18}\ J$

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b. We know that chemical reactions involve a certain amount of energy per molecule, which is generally a few eV, where the **electron volt** unit is 1.6×10^{-19} J. (For example, the energy needed to remove the electron from a hydrogen atom is about 14 eV.) How well does your estimate in (a) work?

Conver 14eV to J:

$$14\,eV = 14 \times 1.6 \times 10^{-19} J = 2.24 \times 10^{-18} J$$

The energy scale we construct in (a) is about the same scale as 14eV. My estimate in (a) work well.

(5 points) PMLS2, problem 2.8

2.8 *Blood flow*

Review Appendix B.

When fluid flows through a pipe, it sometimes does so in a stately, organized fashion called **laminar flow**: In contrast to "turbulent flow," each fluid element moves at constant velocity (without acceleration). For example, blood flow through small and medium size vessels is laminar. Because there is no acceleration, the mass density of the fluid is irrelevant to finding the resistance. Another material parameter of the fluid, called **viscosity**, is relevant, however. Suppose that you look up this quantity, η, finding that it's about 2.8 mPa s for blood at body temperature. The symbol Pa represents the SI unit of pressure (force per area).

a. Convert the unit mPa (millipascals) to SI base units.

An infinite pipe is characterized by a single number: its diameter a. Resistance to flow depends on the fluid, and also on the total volume flow rate (volume per time), which we'll call Q.

$\eta = 2.8\,mPa\cdot s \Rightarrow (ML^{-1}T^{-2})\cdot T = ML^{-1}T^{-1}$

a. $1\,mPa = 10^{-3}\,Pa$

$2.8\,mPa\,s = 2.8\times 10^{-3}\,Pa\cdot s$

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b. Viscous drag (friction) results in a continuous pressure drop as we move down the pipe, that is, a quantity with units ~(pressure)/(distance). Use dimensional analysis to propose an approximate formula for this quantity in terms of η, a, and Q.

b. (a)

a (L)

Q $(\text{Vol}/\text{Time}) = (L^3/T)$

η $(ML^{-1}T^{-1})$

Viscous drag $\Rightarrow$ pressure / distance

$$\Rightarrow \frac{ML^{-1}T^{-2}}{L} = ML^{-2}T^{-2}$$

$$\eta^a a^b Q^c = (ML^{-1}T^{-1})^a (L)^b (L^3T^{-1})^c = ML^{-2}T^{-2}$$

$$\begin{cases} M: a = 1 & c = 1 \\ L: -a+b+3c = -2 & b = -4 \\ T: -a-c = -2 \end{cases}$$

$$\Rightarrow \eta^1 a^{-4} Q^1$$

c. Suppose that arterial plaque reduces the pipe diameter to one half its normal value, but Q is unchanged. Use your answer to (b) to predict the change in pressure drop.

Pressure drop 16 times.

$a \Rightarrow \frac{1}{2}a$

Q unchange

$\rightarrow \left(\frac{1}{2}\right)^{-4} = 16$ ✗