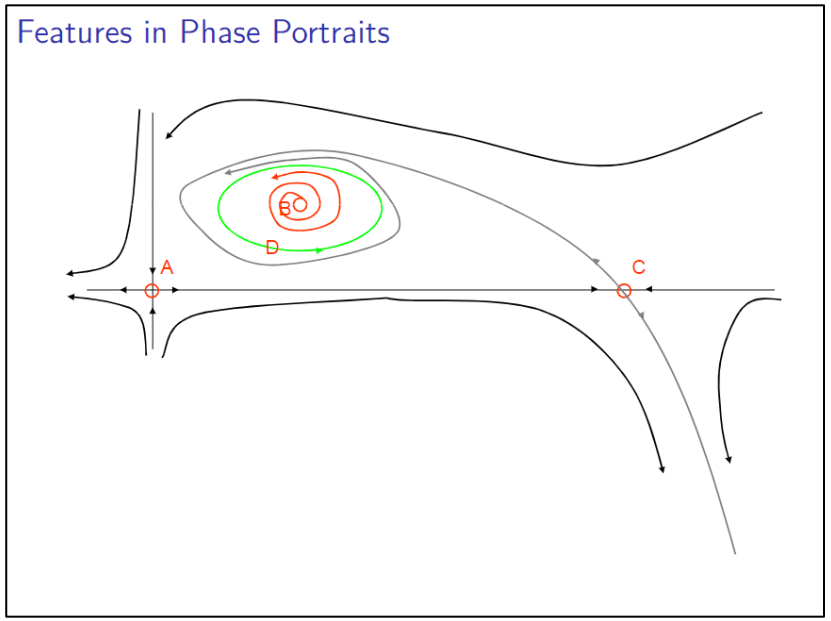
BE 175/275: Machine learning & data-driven modeling in bioengineering

Discussion 6

Topics:

- ~~Differential Equation review~~
- ~~Dynamical Systems: Solving ODEs in Python~~
- Homework: Implementation of Perelson *et al.*



Lab: Implementation of *Perelson et al.*

- Mathematical ODE model was developed to help predict HIV patient's viral loads after treatment with ritonavir, which causes infected cells to produce non-infections viruses.
- T = target cells
- T* = infected cells
- V = Concentration of viral particles in plasma
- δ = rate of loss of viral producing cells
- N = number of new virions produced per infected cell
- c = rate constant for virion clearance
- V_{NI} = virions produced in non-infection pools
- V_I = virions produced in infectious pool

HIV-1 infects target cells (T) with a rateconstantk andcauses them to becomeproductivelyinfe
Beforedrugtreatment,the dynamics ofcellinfectionandvirionproductionare representedby

$$\frac{dT^*}{dt} = kVT - \delta T^* \qquad (1)$$

$$\frac{dV}{dt} = N\delta T^* - cV \qquad (2)$$

Homework: Problem 1

$$\frac{dT^*}{dt} = kV_I T - \delta T^* \qquad (3)$$

$$\frac{dV_I}{dt} = -cV_I \qquad (4)$$

$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI} \qquad (5)$$

- (i) Equations to use

V1(t=0)=V_0

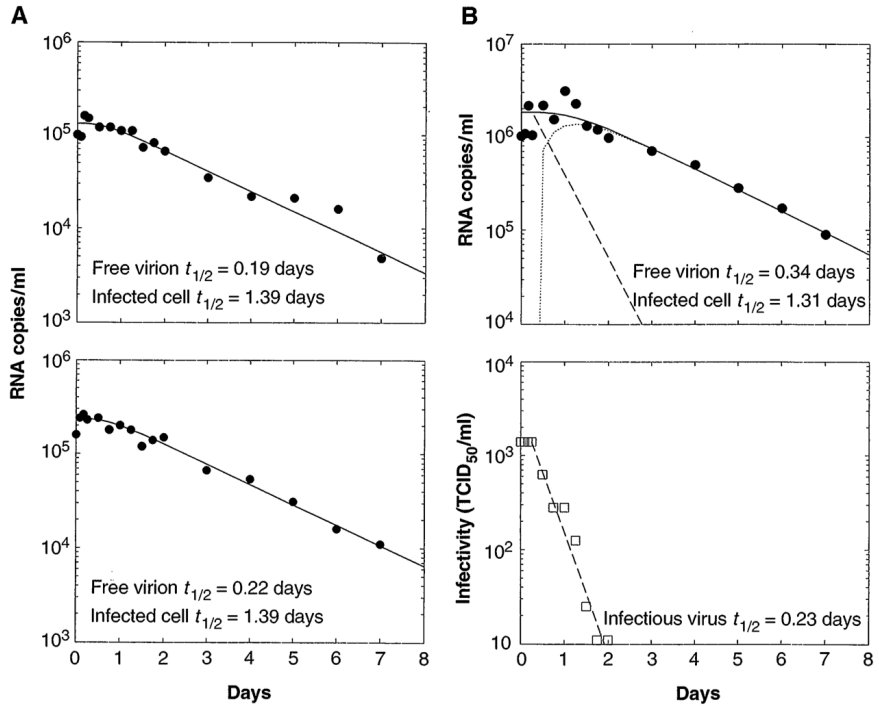
VNI(t=0)=0 (bc havent given the drug)

$$V(t) = \underbrace{V_0 \exp(-ct)}_{V_I(t)} + \underbrace{\frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}[\exp(-\delta t) - \exp(-ct)] - \delta t \exp(-ct)\right\}}_{V_{NI}(t)}$$

$V_I(t)$ from eq 4

Homework: Problem 1

- (ii) You need to recreate Figure 1
  - ***Multiply V0 or final V for each patient by 2 to exactly recreate paper figures as there are two RNA copies/virion***
  - (B, top) Plot $V(t)$, $V_I(t)$, and $V_{NI}(t)$ separately.
  - (B, bottom) conversion factor is found in question (5)



Patient	Base-line values		Pharm. delay (hours)	Estimates from fit of $V(t)$ to plasma viral load								Total virion production (10^9 per day)
				Virion clearance				Infected cell loss				
					Confidence interval				Confidence interval			
	CD4 cells (per mm^3)	Plasma virions (10^3 per ml)		c (day^{-1})	Lower	Upper	$t_{1/2}$ (days)	δ (day^{-1})	Lower	Upper	$t_{1/2}$ (days)	
102	16	294	2	3.81	1.93	7.03	0.18	0.26	0.24	0.30	2.67	12.9
103	408	12	6	2.73	2.04	3.70	0.25	0.68	0.63	0.73	1.02	0.4
104	2	52	2	3.68	2.53	6.19	0.19	0.50	0.47	0.54	1.39	2.9
105	11	643	6	2.06	1.42	3.76	0.34	0.53	0.48	0.60	1.31	32.1
107	412	77	2	3.09	2.56	4.55	0.22	0.50	0.48	0.52	1.39	3.1
Mean	170	216	3.6	3.07	2.10	5.05	0.24	0.49	0.46	0.54	1.55	10.3
±SD	196	235	2.0	0.64	0.42	1.34	0.06	0.13	0.13	0.14	0.57	11.7

Table 1 from paper. Get initial values, rates etc. from here.

Homework: Problem 2

- Determine whether oscillations are possible using Jacobian of system of equations.
- T is held constant at this point
- Type your math portion with LaTeX!
  - Write down the Jacobian Matrix
  - Show steps to calculate the eigenvalues of this matrix
  - Use math equations to show the conditions for oscillation

$$\frac{dT^*}{dt} = kVT - \delta T^* \qquad (1)$$

$$\frac{dV}{dt} = N\delta T^* - cV \qquad (2)$$

Calculate Jacobian of this system of equations.

Homework: Problem 3

- i) Define an equation which calculates and returns the derivatives of state variables.
  - def deriv(y, t, args…)
    - return dy
  - y and dy are vectors (numpy array)
  - *Remember to relax assumption that T is constant by setting* $T = T_o + T^*$
- ii) Create a new function to solve each y
  - initial values of N and T* for each patient using the steady state assumption
  - Then use this to numerically solve system of equations using odeint and return the state variables solved for at every time point.
  - from scipy.integrate import odeint
  - Solved variables = odeint(<derivFunction>, <initialvalues>, time, args = other derivefunction args)
- iii) Use this function to recreate plot 1 again.

Homework: Problem 4

Note 9 The effect of a nonperfect drug can be modeled by simply adding the term (1 - η)NδT* to Eq. 4 and multiplying the first term in Eq. 5 by the factor η, where η represents the drug's inhibitory activity [for example, il = D/(D + EC50), where D is the plasma concentration of drug and EC50 is the concentration required for 50% effectiveness].
Note 12 Because our parameter estimates are based on the assumption of complete inhibition of the production of new infectious virions and no increase in target cells, we expect our parameter estimates, to be minimal estimates. Generalizing our model to relax these two assumptions, we can show that …

- i) Solve for V_{total} for patient 105 using varying ***η*** values
  - drug effectiveness coefficient: where to add?

$$\frac{dT^*}{dt} = kV_I T - \delta T^* \qquad (3)$$

$$\frac{dV_I}{dt} = -cV_I \qquad (4)$$

$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI} \qquad (5)$$

  - Remember that lower coefficients should lead to higher virion load

Homework: Problem 4 + 5

- ii) Use least squares fitting to solve for C and δ.
  - Should be comparing your P105 V_T from question 1 as your least squares function.
  - Your function should be able to vary with gnu!
- iii) Find residual error at each time point from solved ODE result
  - Make a plot with four curves (gnu = .9, .95, .99, 1) (4b and 4c)
  - Answer the question by look for trends
- (5) Simple – find conversion factor between infectivity and V(t) for patient 105.
- ***Trick for this homework: think if you can modify previous question and reuse the code!***