1. "The asymptomatic phase of HIV-1 infections is characterized by a stable set-point viral load (SPVL) within patients. The SPVL is a strong predictor of disease progression and shows considerable variation of multiple orders of magnitude between patients." This problem will explore the relation between the exponential growth rate of virus during the first week after infection and the SPVL.

(a) Assume that the target cell population remains at its equilibrium value \( \lambda / d \) during the first week and show that \( V(t) \approx V(0) \exp(qt) \), where \( q \) is the positive root of the quadratic equation \( x^2 + (a + u)x + au(1 - R_0) = 0 \).

(b) Rewrite the quadratic equation as

\[
R_0 = \left( 1 + \frac{q}{a} \right) \left( 1 + \frac{q}{u} \right). 
\]

Assume that \( q \) is considerably smaller than \( u \). Then \( R_0 \approx \left( 1 + \frac{q}{a} \right) \) or equivalently, \( q \approx a(R_0 - 1) \).

Finally, if \( R_0 \) is large, then \( q \approx aR_0 \), and thus, \( V(t) \approx V(0) \exp(aR_0t) \) for small \( t \).

Note - the formula \( R_0 \approx 1 + q/a \) provides a method for directly estimating \( R_0 \) from initial viral load data and \( a \). If you are interested see Ribeiro, Ruy M., et al. "Estimation of the initial viral growth rate and basic reproductive number during acute HIV-1 infection." Journal of virology 84.12 (2010): 6096-6102.

(c) We showed that the equilibrium value \( V^* = (\lambda k)/(au) \). This is theoretically the SPVL. Assume that \( d, \beta, \) and \( a \) are fixed. Show that \( V^* \) is proportional to \( aR_0(\approx q) \).

2. Recall the modification of the in-host ODE model of virus infection that takes in account the time lag between when a virus enters a cell and when new virions leave the cell (HW 3: Problem 3).

(a) Find formulas for the endemic equilibrium point and the analog of \( R_0 \) for this system?

(b) Evaluate these using parameters for HIV from Figure 3.3 of Nowak and May and a two-hour delay.

(c) Use ODE45 to numerically simulate the modified system for two weeks using ICs \( T(0) = 1e6, I(0) = 1, E(0) = 0, V(0) = 0 \).

(d) Compare your theoretical prediction with the simulation results.

(e) Now re-run your model with 1 minute delay and compare with the output from the classical model with no delay.

3. Begin with the classical in-host infection model and modify it to include mutation of sensitive cells to a new class of resistant cells which can not be infected by virions.

4. Begin with the SIR model and modify it to account for natural (disease un-related) births and deaths. Find the equilibrium points and determine their stability.