Viral dynamics via Direct Simulation: Lab

In class we looked at the direct method (Gillespie's algorithm) for simulating a branching process. In this lab you will use Matlab or the system of your choice to simulate simple branching process models for an epidemic and for a viral dynamics problem.
As a reminder, Gillespie's algorithm for a birth death process with per-capita rates b and d goes like this:

1. Initialize $N(0) = N_0$, $t = 0$.

   Main Loop:

2. Select the waiting time before the next reaction by sampling a variable τ from an exponential distribution with rate $N(b + d)$

3. Select the next reaction according to the reaction propensities: draw a uniform random number x on [0,1]. If $x < \frac{b}{b+d}$ then the event is a birth. Otherwise it is a death.

4. Update N according to the birth or death. Update $t \to t + \tau$. Store the vector $(t, N(t))$.

5. Unless t exceeds the end time for the simulation or other stopping criteria are met (e.g. populations are extinct), go to step 2.

This algorithm can be updated for many models of this general type, including models for more than one dependent variable, or models with immigration.

1. Birth-death model for latent HIV infected cells during successsful treatment

During successful treatment for HIV infection, very few new cells become infected. However, there can be a detectable viral load in the patient's blood. One hypothesis is that some cells which became infected prior to treatment might have become dormant - so-called **latent cells** – and these cells can "wake up" and begin to produce virus during treament. After they wake up, the cells will produce virus for a short period until they die. It is also believed that a latent cell may occasionally be able to divide to produce two latent cells – but without activating the production of virus. Any new viruses that are produced by latent cells will rarely be able to reproduce, due to the drug treatment.
A very simple model for the latent cell population $L(t)$ in a treated patient is as follows:

$$\frac{dL}{dt} = \rho L - aL - \mu L \qquad L(0) = L_0. \tag{1}$$

Here, ρ is the reproduction rate of latent cells due to cell division. a is the rate of activation (leading to viral production, after which the cell dies) and μ is some background death rate for the cells. L_0 is the initial number of latent cells in the patient.
• Solve this model analytically. Using the parameter estimates below, estimate the time to extinction for the latent cell population (approximate this as the time when there is a single cell remaining).
• Now consider a stochastic branching process version of this model. Use direct (Gillespie) simulation to generate several plots of $L(t)$. By running your code sufficiently many times, estimate the

mean and standard deviation of the time to latent cell extinction. How does this estimate compare to the continuous model prediction?
• Reflect on how the difference in predicted time to extinction between continuous and stochastic models comes about. How could this affect predictions for disease cure (HIV, or other diseases)? Alternatively, consider a birth-death model where the population under consideration is an endangered species. Do continuous or stochastic models give better predictions regarding time to extinction? How could this affect policy among conservation ecologists?

2. Multitype branching process model for latent HIV infected cells and productively infected cells, during successsful treatment

Let's now consider what happens when the latent cells are reactivated and become productively infected cells. Let the number of productively infected cells be $I(t)$ and suppose they have a death rate of δ where $\delta >> \mu$ reflecting the long-lived nature of latent cells. A simple differential equation model for this process could be:

$$\frac{dL}{dt} = \rho L - aL - \mu L \qquad L(0) = L_0. \tag{2}$$

$$\frac{dI}{dt} = aL - \delta I \qquad I(0) = \frac{a}{\delta} L_0. \tag{3}$$

• Solve this model analytically. Plot your solution curves ($L(t)$ and $I(t)$) for the parameters below.
• Modify your simulation code so that it now simulates a branching-process analogue of this model. Generate several simulations and plot $L(t)$ and $I(t)$.
• To a rough approximation, the viral load in the blood is believed to be proportional to the number of infected cells present in the patient at any given time. Simulate and estimate the mean first time to total viral clearance in the blood - which should happen from time to time before the infection is entirely cleared from the latent cells.

3. Latency reversing drugs (kick-and-kill strategy for HIV cure)

The reservoir of latent cells is seen as a significant barrier to achieving an HIV cure. A possible strategy is to treat the patient with drugs that will speed the reactivation (and therefore the death) of latently infected cells. Such drugs under investigation include Auranofin and Vorinostat. We can model their behaviour as giving a transient increase in the activation rate. In this spirit, let's define

$$a(t) = \begin{cases} a_0 & 0 < t < T_1 \\ a_0 + a_D & T_1 < t < T_2 \\ a_0 & T_2 < t \end{cases}$$

where a_T is an additional activation rate due to the additional drug.
• Change your simulation code to allow for this transiently changing parameter. You should give some thought as to what happens around the on- and off- times for the activatory drug, T_1 and T_2.
• Using parameters as given below, and letting $T_1 = 365$ days, [1] determine an effective duration of the latency reversing agent which allows for cure of approximately 50% of the patients by the end of the latency reversing agent therapy.

[1] It would be reasonable to make sure that the patient is on stable therapy before giving the latency reversing agent.

Parameter Estimates

	Symbol	**Estimate**
Initial number of latent cells	L_0	10^3 cells
Latent cell reproduction rate	ρ	0.0159 day^{-1}
Latent cell re-activation rate	a	0.0063 day^{-1}
Latent cell background death rate	μ	0.01 day^{-1}
Productive cell death rate	δ	1 day^{-1}
Latency reversing agent efficacy	a_D	$100a = 0.63$day^{-1}

References:

1. Siliciano JD, Kajdas J, Finzi D, Quinn TC, Chadwick K, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4(+) T cells. *Nat. Med.* 9: 727–728 (2003).

2. J.M. Conway and D. Coombs. A Stochastic Model of Latently Infected Cell Reactivation and Viral Blip Generation in Treated HIV Patients. *PLoS Comp. Biol.* 7(4): e1002033. doi:10.1371/journal.pcbi.1002033 (2011).

3. AL Hill, DIS Rosenbloom, E Goldstein, E Hanhauser, DR Kuritzkes, et al. Real-time predictions of reservoir size and rebound time during antiretroviral therapy interruption trials for HIV. *PLoS Pathogens* 12(4) e1005535 (2016).