Viral evolution

Study the dynamics of infection within an individual in the following scenario

Infection → Treatment → Resistance

Consider a person infected by a virus. Use the basic model of virus dynamics to simulate the initial stages of the infection with parameters

- $\lambda = 10^5$ → cell replication rate
- d=0.1 → natural cell death rate
- a=0.5 → infected cell death rate
- $\beta = 2 \cdot 10^{-7}$ → infective parameter
- k=100 → production of free viruses rate
- u=5 → free viruses clearance rate

$$\begin{aligned} dx &= \lambda - dx - \beta xv \\ dy &= \beta xv - ay \\ dv &= ky - uv \end{aligned}$$

When the viral load reaches 10^6, this person starts to be treated with an antiviral drug that inhibits viral replication in a 99% (meaning k → k'=1 now). The virus, which is quite homogeneous phenotypically during this period, can generate a mutant variant resistant to the antiviral drug (this means it replicates at the original value of k) with probability 10^{-9}. (This means that the rate of mutant production upon virus replication is 10^{-9} k')

When a new strain of the virus appears, a new equation for the dynamics of that strain is added. There are also two new parameters:

- $p = 10^{-9}$ → generation rate of the mutant variant
- r = 1 → viral replication rate when drug is administered

The new set of equations would be:

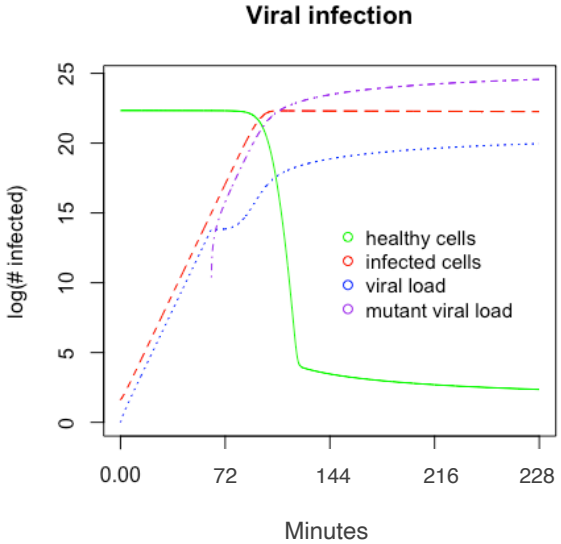
$$\begin{aligned} dx &= \lambda - dx - \beta x(v+w) \\ dy &= \beta x(v+w) - ay \\ dv &= ry - ryp - uv \\ dw &= ryp + ky - uw \end{aligned}$$

Implement and simulate the dynamics of the process. Discuss how would the generation of mutants occur in a finite population (where stochastic effects are important and mean-field descriptions may fail). How long could it take for a mutant to appear?

In this graph we see the result of the simulation, where the number of cells or viral particles is represented using a logarithmic scale in the *y* axis. The *x* axis is the time scale and it's represented in minutes.

The virus replication and infection rates are high, and the viral load of 10^6 is reached after 70 minutes (approx.). At this point is when the antiviral drug is administered and the selection pressure favors the emergence of a mutant variant that we call 'w' and that is represented in purple.

The number of healthy cells drops abruptly, unaffected by the administration of the drug, because the mutant viruses rapidly pick up the same growth curve the

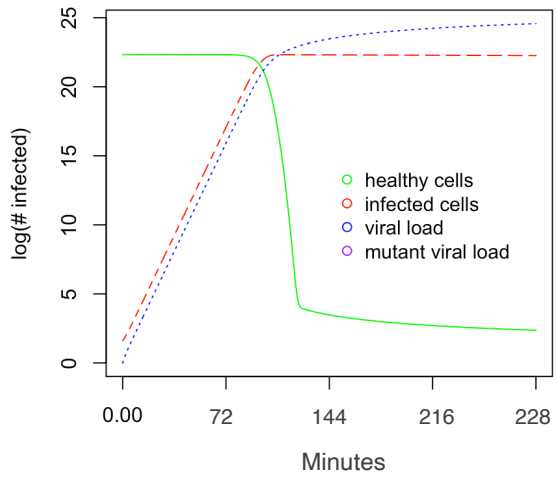


original virus had. Interestingly, the original virus persists in the system despite the drug. This is because the drug is only reducing its replication rate, but the viral load is already high and after the drug administration, the viral load has a sigmoid-like growth, reaching a plateau phase at around minute 100. At this point the whole system seems to have reached an equilibrium state with the following values:

Healthy cells	Infected cells	Original v. viral load	Mutant v. viral load
0.57269	4 644 370 114	468 925 571	46 846 853 839

Even though technically the number of healthy cells never reaches 0, the value is so low that it is as if it was and we could say that the individual would be totally infected after approximately one hour and a half.

This results leaded me to ask myself: does delivering the drug make any difference? Is it worth it? To answer this I decided to plot the simulation of the same case but without ever administrating the drug and the result is:



If the drug was never administered and we assume that no mutant with different replication and/or infection rates emerges, then the system reaches an equilibrium after approximately 80 minutes. The resulting states are:

Healthy cells	Infected cells	Original v. viral load
10.67933	4 644 354 032	46 843 535 660

The final number of infected cells is almost the same, and the number of healthy cells is actually slightly higher, meaning that actually the system would be better off never taking that drug.

Of course, this simulation is not considering how the immune system would fight the virus, and how the virus infection and replication rate would variate if its mutation rate during replication was taken into consideration. This is a very simplistic representation of the viral dynamics and it is not very trustworthy regarding how a real system would evolve with a viral infection.

Discuss possible situations where the infection could be eradicated (joint action of the immune system, an additional drug, or others).

The infection could possibly be eradicated combining different types of antiviral drugs. In this case, virus can still reproduce even if at a very small ratio and therefore they never disappear. However, if this was complemented with another drug that affected, for example, to the virus capability of encapsulating or the liberation of free viral particles, maybe the virus would reduce its spreading over the system. Moreover, if the immune system was considered, probably the initial virus replication and infection rate would be smaller.