

VIRUS POPULATION DYNAMICS

Introduction: The basic epidemic model

The classical model for epidemics is described in [1] and [Chapter 10 of 2].

Consider a population of uninfected individuals who wander randomly about a city. When they encounter someone infected with a virus, there is a certain probability that they will become infected. Infected people get sick for a while, then recover, where after they are immune to the virus. We would like to construct a model the could predict the conditions for an epidemic to break out.

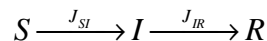
There are three reservoirs of individuals:

$S(t)$ = number of uninfected, but susceptible people at time t .

$I(t)$ = number of infected people at time t .

$R(t)$ = number of recovered people at time t .

The number of people in the city, N , is considered constant, $S + I + R = N$, at all times. Therefore we can connect Flows between S and I , and between I and R . Call the Flow between S and I J_{SI} = InfectionRate, and the Flow between I and R J_{IR} = RecoveryRate.¹



Now we must describe how the flows are controlled using Functions. First, what influences the flow from $S \rightarrow I$? Suppose that the city is small and the people mill about at random in the town square every day. Then encounters between susceptible and infected individuals occur at random, and we can define an average infection rate by assuming random encounters similar to that used in chemistry: $S + I \xrightarrow{\beta} I$; that is, random collisions between uninfected and infected individuals create new infections at a rate β (with units [1/time], so that the flow between S and I is:

$$J_{SI} = \beta \cdot S \cdot I.$$

Thus the InfectionRate flow depends on S , I , and β , as shown by the arcs in Figure 1.

To model the flow from I to R , we assume that the average time an infected takes to recover is $1/a$ [1/days]. Thus the Flow between I and R is

$$J_{IR} = a \cdot I,$$

where a is the rate constant (= the inverse of the mean lifetime in reservoir I).

The complete model is shown in Figure 1; all that is left is to assign numerical values to the reservoir initial conditions and the two parameters, β and a . In Figure 1 we have chosen to move

¹ If the recovers lost their immunity and became susceptible to re-infection, then we would have to connect a flow from R back to S ; but we ignore this possibility here.

the initial condition for the susceptibles outside the reservoir so that we can treat it as an adjustable parameter, S_0 .

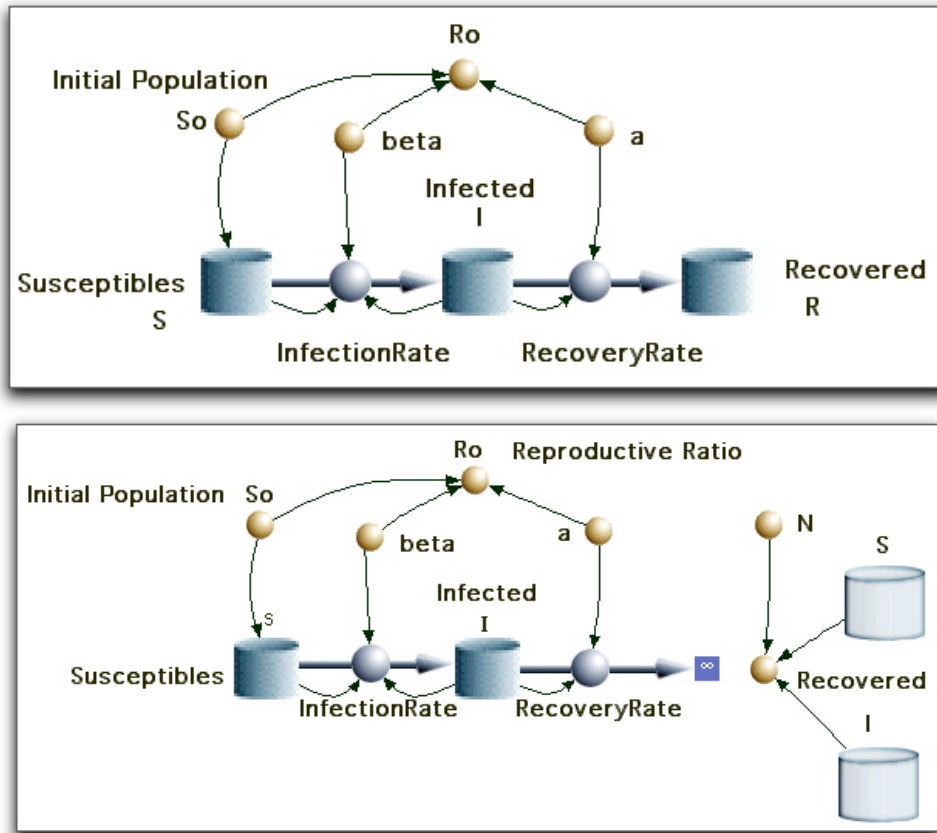


Figure 1. The basic epidemic model. (a) The reservoirs S, I, and R are the state variables. (b) Since $S + I + R = N$, the reservoir R can be replaced by a Function: $R = N - S - I$. Berkeley Madonna automatically keeps track of conserved flows, so this explicit reduction is not strictly necessary for numerical calculations.

The Equation window gives the model equations can then be written directly in conventional notation as follows: $S \xrightarrow{\beta} I \xrightarrow{a} R$

Equation 1	$\frac{dS}{dt} = -\beta SI$, $S(0) = S_0$	Susceptible
Equation 2	$\frac{dI}{dt} = \beta SI - aI$, $I(0) = 1$	Infected
Equation 3	$\frac{dR}{dt} = aI$, $R(0) = 0$	Recovered

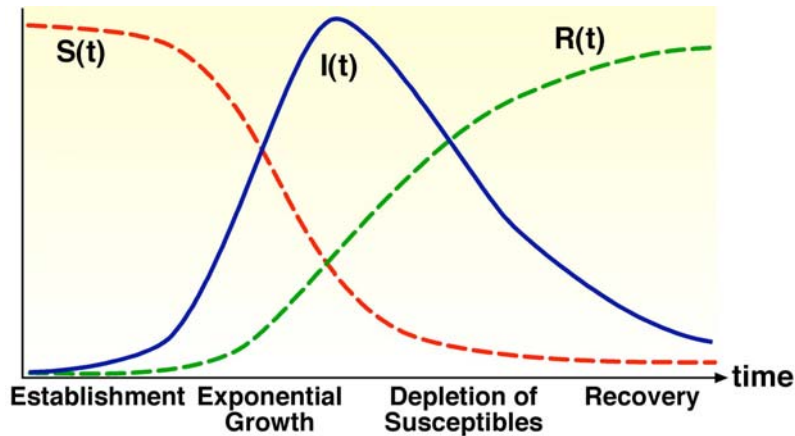


Figure 2. The phases of an epidemic [1, 3]. Early on in the trajectory of the Infected population, $I(t)$, the Establishment phase, stochastic effects dominate and determine whether the epidemic ‘breaks out’. Once $R_0 > 1$, the epidemic enters an exponential growth phase. As the supply susceptibles decreases, so does the infective population, until all have recovered. This assumes a closed system where the total population is constant.

Exercise. Run the model for a few parameter values and reproduce Figure 2.

The net reproductive ratio, R_0 , detects the onset of an epidemic

The three parameters, S_0 , β , and a can be combined into a single *dimensionless* measure of the ability of the virus to propagate itself in the population. It is conventional to ask whether the infection will grow if we introduce a single infected individual into the population. To do this, we set $I(t = 0) = \text{INIT } I = 1$, and $R(t = 0) = \text{INIT } R = 0$, and compute the ratio of the inflow to the outflow from the infected reservoir:

$$\text{InfectionRate/RecoveryRate} = J_{SI}/J_{IR} = (\beta SI/aI)|_{t=0} = \beta \cdot S_0/a \equiv R_0.$$

$R_0 = \beta S_0/a$ is the virus *net reproductive ratio*; if $R_0 > 1$, the infected population will grow, otherwise it will die out. In **Box 1** we show how this quantity arises naturally when we renormalize the equations so that they are dimensionless.

The course of an epidemic is described schematically in Figure 2 [1, 3]. In the following exercise, you can reproduce these curves using experimental data on a closed infected population.

Exercise. The table in Figure 3 shows actual data on flu infections over the course of two weeks. Use Berkeley Madonna’s Curve Fit routine to fit the data to the model using the parameter a as the fitting parameter, and $N = 763$, $\beta = 0.002$.

Box 1. Setting the time scale defines R_0

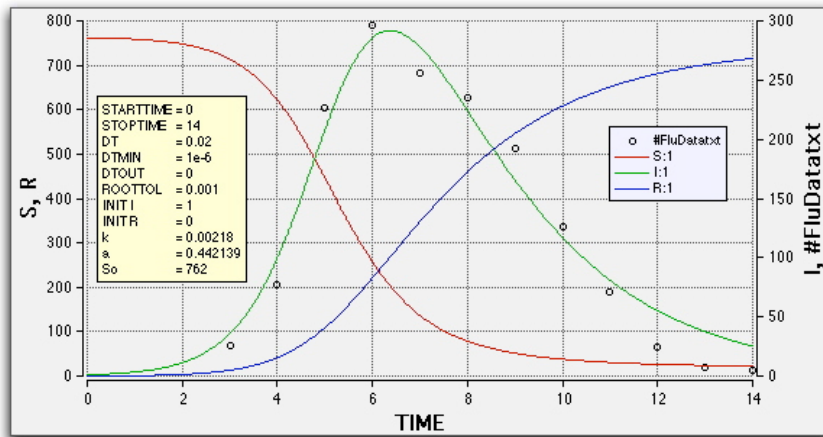
It is often a good idea to cast the equations the following form so that the various time scales can be distinguished:

$$\text{Equation 5} \quad \tau \frac{du}{dt} = f(u, p),$$

where u is any of the reservoir variables, p represents the parameters and τ is the time constant.¹ Since we are most interested in the time scale of the infected population, we divide the equations by the parameter a , so that the time constant for the infecteds is $\tau_i = 1/a$. Then the equations have the form

$$\text{Equation 5} \quad \underbrace{\frac{1}{a}}_{\tau} \frac{dS}{dt} = -\frac{\beta}{a} SI, \quad \frac{1}{a} \frac{dI}{dt} = \underbrace{\left(\frac{\beta}{a} S_0 \right)}_{\text{Basic Reproductive Ratio}} \left(\frac{S}{S_0} \right) I - I, \quad \frac{1}{a} \frac{dR}{dt} = I$$

It is sensible to measure time in units of $\tau_i = 1/a$; i.e. $t \rightarrow t/a$, and to measure the populations S and I as a fraction of their initial value: $S \rightarrow S/S_0$, $I \rightarrow I/1$. Of course, we cannot measure R this way since its initial value is zero; however, since we know that $R = N - S - I$, $R \rightarrow R/(N - S_0 - 1)$. If we substitute these renormalized variables into Equation 5, we see that the dimensionless parameter $R_0 = \beta S_0/a$ controls the dynamics of the system. This shows that the variable R is not really a variable since it can be eliminated by using the conservation relation $S + I + R = N$. Therefore, we could replace the Reservoir R by a Function. This is not necessary in Berkeley Madonna since the Flowchart automatically keeps track of conserved flows.



Time[days]	Infected
3	2.58E1
4	7.66E1
5	2.26E2
6	2.96E2
7	2.56E2
8	2.35E2
9	1.92E2
10	1.26E2
11	7.15E1
12	2.49E1
13	7.31E0
14	5.12E0

Figure 3. Fitting the model to influenza data. The table gives the number of infecteds measured over two weeks at a boys school. The outbreak began with a single student from an initial population of 763. The infection rate, β , was independently estimated as $\beta = 0.00218$.

Population dynamics of a virus in the body

The demography of viruses inside a single organism is modeled very much like that of the organisms themselves. In describing the basic model for virus dynamics we follow the treatment

found in Nowak and May’s classic text, which should be consulted for a more detailed treatment [4].

The simplest model assumes that the body can be modeled as a ‘well stirred’ chemostat containing the virus, $V(t)$, and two kinds of cells: uninfected but susceptible cells, $S(t)$, and cells infected by virus, $I(t)$. The life cycle of the virus is shown diagrammatically in Figure 4a. Susceptible cells are produced by cell proliferation at a constant rate S_0 , live for an average lifetime $\tau_s = 1/\delta_s$, and die. Thus the *deathrate* of uninfected cells is their number divided by their average lifetime S/τ_s . Virus infects cells to produce infected cells, I , with an ‘efficiency’, β . Since cells are infected by contact with virus, we model the infection rate as a simple mass action reaction: $S + V \xrightarrow{\beta} I$. Infected cells die and release new viruses at a rate k ; these viruses are cleared from the system at rate c . Therefore, the model consists of three Reservoirs, denoted S , I , and V .

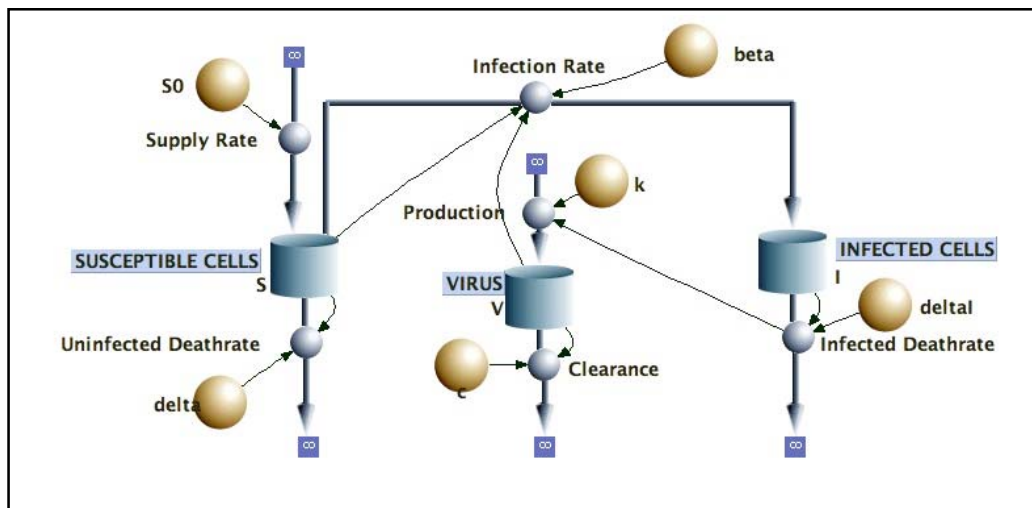


Figure 4. (a) The virus life cycle. Susceptible cells (S) are supplied at a rate S_0 and die at a rate $\delta_s = 1/\tau_s$. Virus (V) infects cells by a mass action rate: βSV , where β is the efficiency of infection. Infected cells die at rate δ_i ; and release virus particles at rate k . Viruses are cleared by the immune system at a rate c . (b) Flowchart for viral dynamics.

The Flowchart shown in Figure 4b assigns reservoirs to the susceptible (S), infected (I) and virus (V) compartments. The Flowchart produces the following set of equations in conventional mathematical notation:

Equation 6	$\frac{dS}{dt} = \underset{\text{Supply rate}}{S_0} - \underset{\text{Death rate}}{\delta_s S} - \underset{\text{Infection rate}}{\beta SV}$	Susceptible Cells
Equation 7	$\frac{dI}{dt} = \underset{\text{Infection rate}}{\beta SV} - \underset{\text{Death rate}}{\delta_i I}$	Infected Cells

Equation 8
$$\frac{dV}{dt} = \underset{\substack{\text{Virus} \\ \text{production}}}{\delta_I I} - \underset{\substack{\text{Virus} \\ \text{clearance}}}{cV} \quad \text{Virus}$$

The reproductive rate for a virus introduced into an uninfected population

We use the subscript $(\cdot)_{ss}$ to denote steady state quantities. Before infection, $V = I = 0$, and the steady state population of uninfected cells is given by Equation 6 when $dS/dt = 0 = S_0 - \delta_S \cdot S_{ss}$, or $S_{ss} = S_0/\delta_S$. Let $V_0 = V(t = 0)$ be the number of viruses introduced at $t = 0$. The graph in Figure 5 shows the ‘impulse response’ of the system to the introduction of a single virus for the parameters values shown in the figure.

Exercise: Make a slider to investigate the effect of varying the number of viruses introduced at $t = 0$, and the virus amplification factor, β . Find the value of β at which the virus becomes self-sustaining.

The rate of virus production (k) by one infected cell over its lifetime is called the ‘burst size’, k/δ_I . If the net virus production exceeds the rate at which they can be cleared from the system, then the virus will ‘win’ in its competition with the immune system. So an important quantity determining the outcome of this competition should be ratio [Production/Clearance]. In fact, we can define a dimensionless ‘virus reproductive ratio’:

R_0 = the number of infected cells generated by one uninfected cell (at the beginning of the process, when there is not yet any infected cells) [1, 5]:

Equation 9
$$R_0 \equiv \left(\frac{\beta S_0}{c} \right) \left(\frac{k}{\delta_S \delta_I} \right) \quad \text{Virus reproductive ratio}$$

If $R_0 < 1$, then the infection cannot establish itself because the virus does not infect cells as rapidly as they are cleared from the system. This can be seen from the steady state solution to equations 1-3 found by setting the rates $dS/dt = dI/dt = dV/dt = 0$ and solving for (S_{ss}, I_{ss}, V_{ss}) . A bit of algebra shows that the steady state can be written as:

Equation 10
$$S_{ss} = \frac{S_0}{\delta R_0}, \quad I_{ss} = (R_0 - 1) \frac{\delta_I c}{k\beta}, \quad V_{ss} = (R_0 - 1) \frac{\delta_S}{k} \quad \text{Steady state}$$

Since the steady state values must be positive, *only when $R_0 > 1$ can the virus establish itself.*

Exercise. Make a parameter plot of the uninfected cells and virus as the infectivity, β , increases. There is a sudden drop in the number of uninfected cells at a critical value of β (Figure 6). Investigate this transition as β and a vary to show that the epidemic (as defined by a maximum in the infected cell population) occurs when $R_0 > 1$.

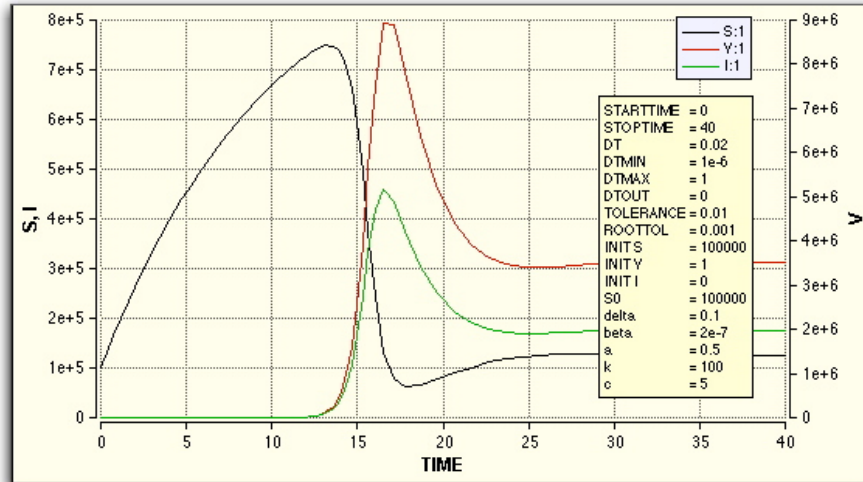


Figure 5. Population dynamics of susceptible cells (S), infected cells (I), and virus (V) when a single virus is introduced into an uninfected population using the parameters given.

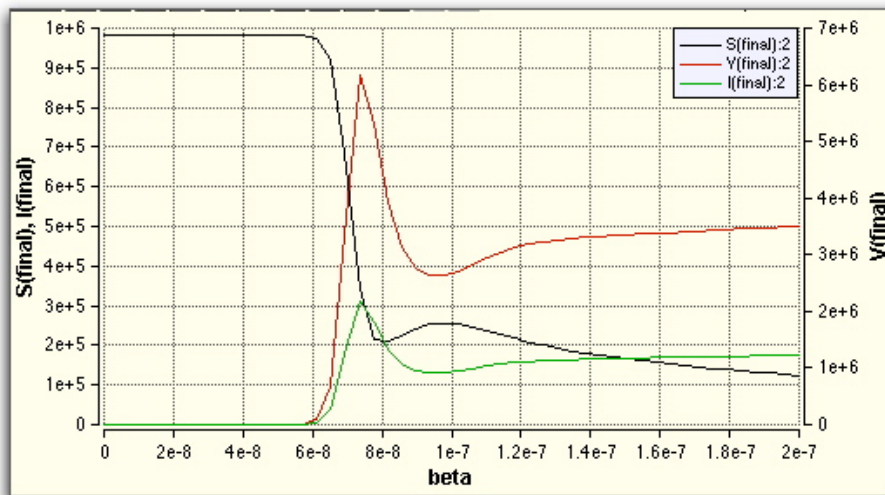


Figure 6. Long time cell and virus populations as the infectivity, β , increases.

HIV chemotherapy model

Perelson, *et al.* formulated a simple model to describe the effect of an anti-viral drug on HIV infected patients [6]. The model is shown in Figure 7a. Here the ‘target’ cells (T) for the drug are modeled as a constant supply rate (e.g. from cell proliferation elsewhere), and the infected cells are denoted by I. The target cell deathrate is δ , and each cell death releases N virus particles. The corresponding flowchart is shown in Figure 7b, from which the equations describing the populations of virus and infected cells are:

Equation 11 $\frac{dI}{dt} = \beta VT - \delta_I I, \quad I(0) = 0$ **Infected cells**

Equation 12 $\frac{dV}{dt} = N\delta_I I - cV, \quad V(0) = V_0$ **Virus**

where V_0 is the initial viral load.

Exercise. Using the same parameters as the previous model, compute the steady state (V_{ss}, I_{ss}), and $V(t)$ for various target cell populations, T .

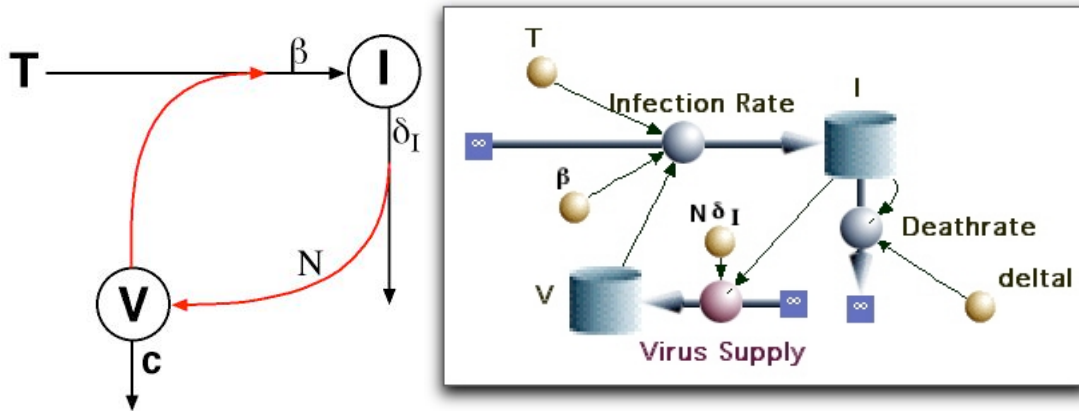


Figure 7. The Perelson *et al.* model. (a) Target cells, T , are infected by virus, V , to produce infected target cells T^*

The antiviral drug inactivates the newly produced viruses, so that there are now two virus populations: those still infective, V_I , and noninfective viruses, V_{NI} , both of which are cleared at the same rate, c .

Exercise. From the life cycle diagram in Figure 8a construct the Flowchart in Figure 8b, to obtain the population equations:

Equation 13. $\frac{dI}{dt} = \beta VT - \delta_I I, \quad I(0) = I_0$ **Infected target cells**

Equation 14 $\frac{dV_I}{dt} = cV_I, \quad V_I(0) = V_0$ **Infective Virus**

Equation 15 $\frac{dV_{NI}}{dt} = N\delta_I I - cV_{NI}, \quad V_{NI}(0) = 0$ **Non-infective Virus**

Because patients were treated with the viral drug at time $t = 0$, the initial condition for the infected target cells must be set to the steady state value for the model with no drug (Equation 11, 7): $I_0 = kV_0T/\delta_I$.

Exercise. Table 1 shows data taken from [6] giving the total viral load as a function of time after administering an antiviral drug. Use Berkeley Madonna curve fitting option to fit this data to the model, using as fitting parameters δ , c , and V_0 . (The data can be loaded directly into Berkeley Madonna from a file.)

This model has been used to rationalize treatment of HIV infections; in particular, why it is desirable to treat patients with antiviral drugs as aggressively as possible at the early stages of infection [5].

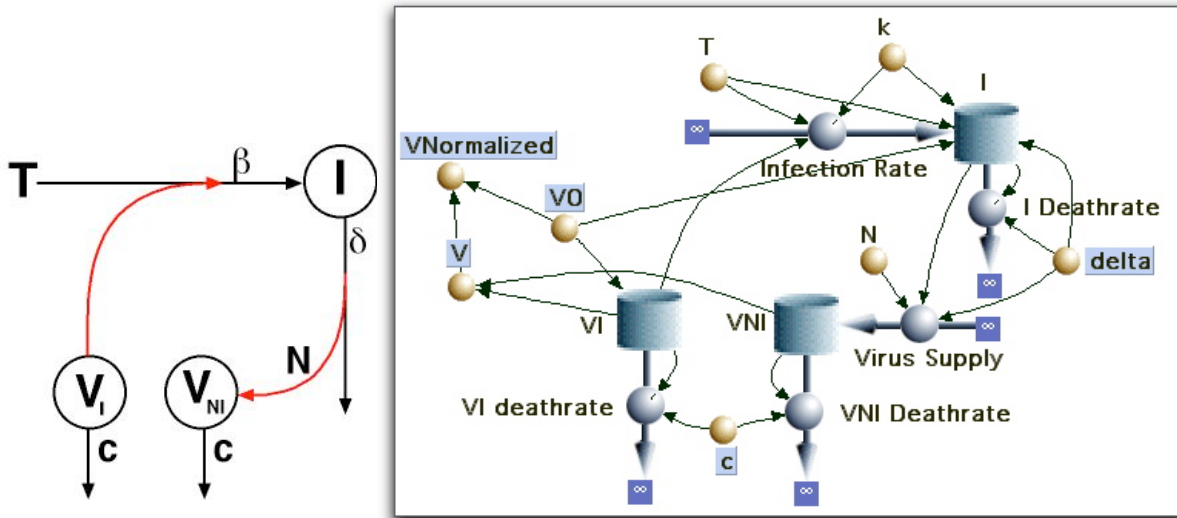


Figure 8. (a) Virus life cycle after administering antiviral drug. V_{NI} is the population of noninfective viruses which are cleared along with the still infective viruses, V_I . (b) Flowchart for the population dynamics of total virus, $V + V_I + V_{NI}$.

Time [days]	V
2.80×10^{-2}	1.00×10^5
1.26×10^{-1}	9.66×10^4
1.68×10^{-1}	1.64×10^5
2.52×10^{-1}	1.55×10^5
5.17×10^{-1}	1.22×10^5
7.69×10^{-1}	1.22×10^5
1.01×10^0	1.14×10^5
1.26×10^0	1.14×10^5
1.51×10^0	7.42×10^4
1.77×10^0	8.48×10^4
2.03×10^0	6.90×10^4
3.01×10^0	3.55×10^4
4.04×10^0	2.22×10^4
5.00×10^0	2.15×10^4
6.01×10^0	1.63×10^4
7.02×10^0	4.78×10^3

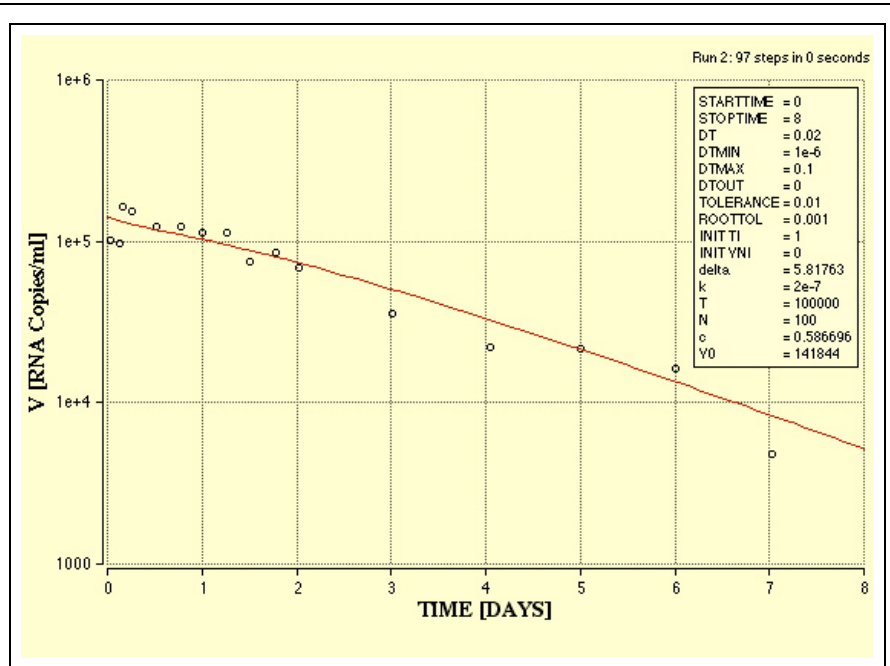


Table 1. Total virus load vs. time (from [6]).

References

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