Modelling the Human Immunodeficiency Virus

Lecture 4

Ago Merico

28 January 2020

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In this lecture we will focus on the biological insights obtained from a mathematical model developed to investigate the ecology and epidemiology of the Human Immunodeficiency Virus (HIV);

Mathematical models (1) have allowed biologists to understand otherwise hidden aspects of HIV, (2) have produced testable predictions about how HIV replicates and spreads, and (3) have generated forecasts that improve the efficacy of prevention and health care programmes.

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AIDS results from the deterioration of the immune system, which then fails to ward off various cancers (e.g. Karposi's sarcoma) and infectious agents (e.g. the protozoa that cause pneumocystis, the viruses that cause retinitis, and the bacteria that cause tuberculosis).

Human Immunodeficiency Virus (HIV)

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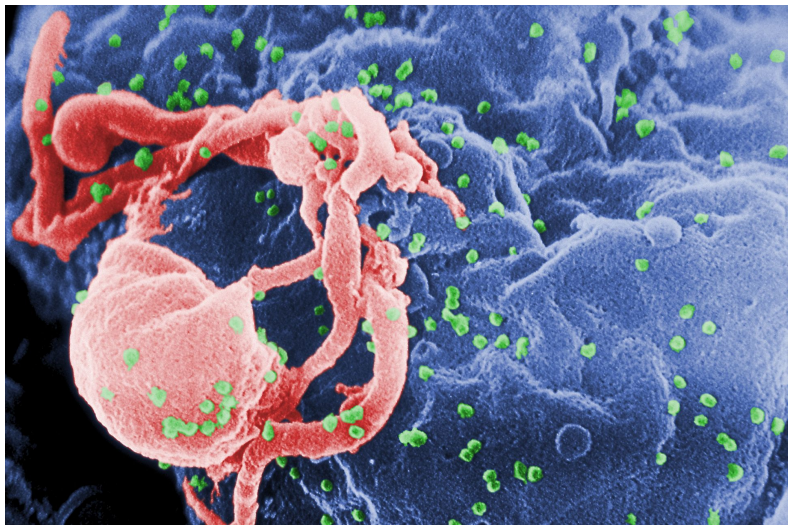

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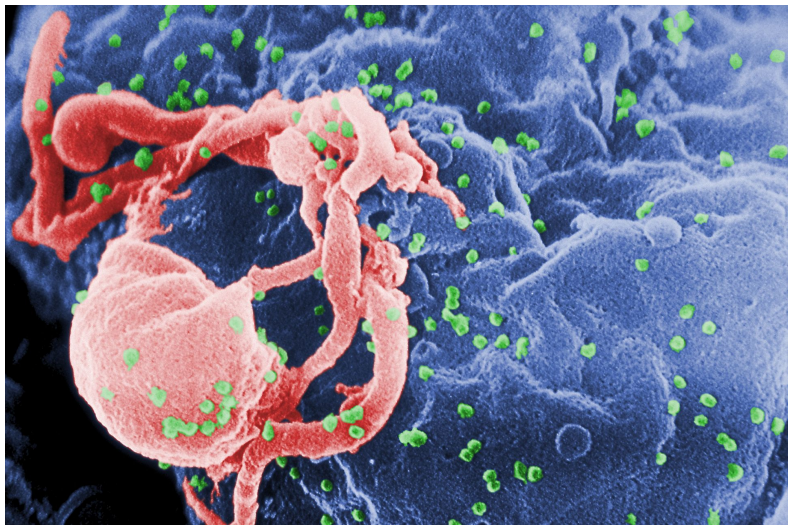

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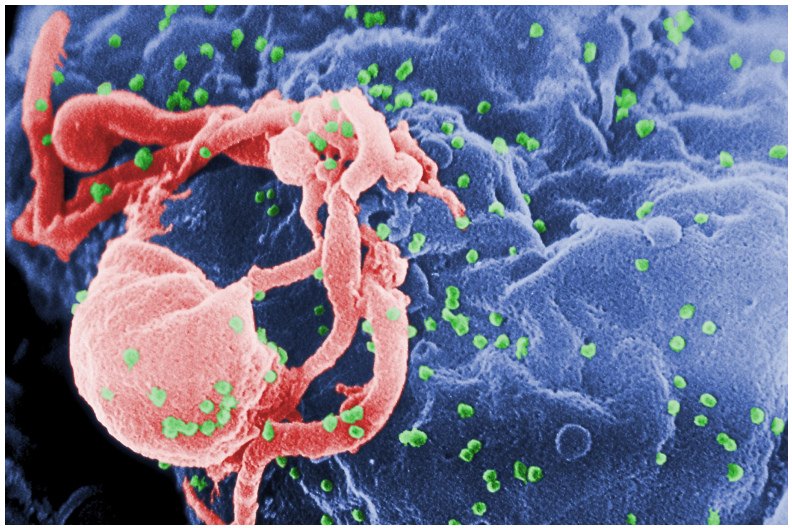
The genome of the virus, made of RNA, enters these cells and is reverse transcribed (hence also called retrovirus) into DNA, which is subsequently incorporated into the genome of the host.



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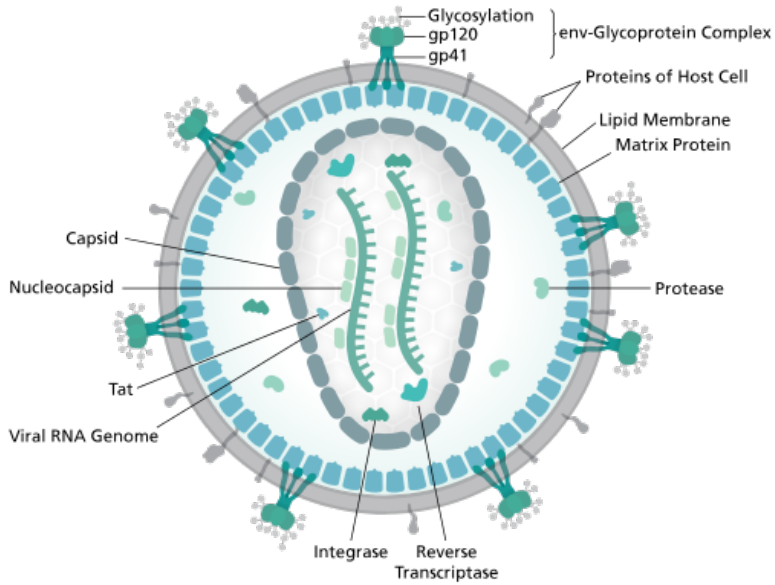

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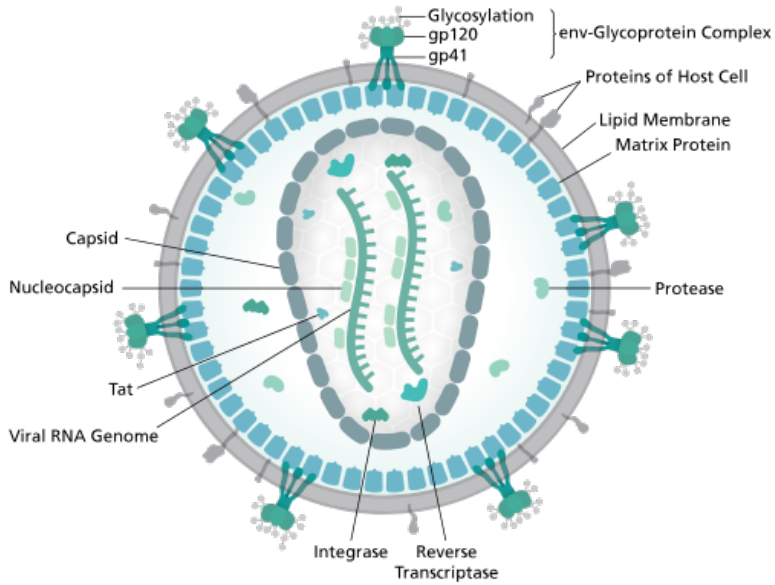

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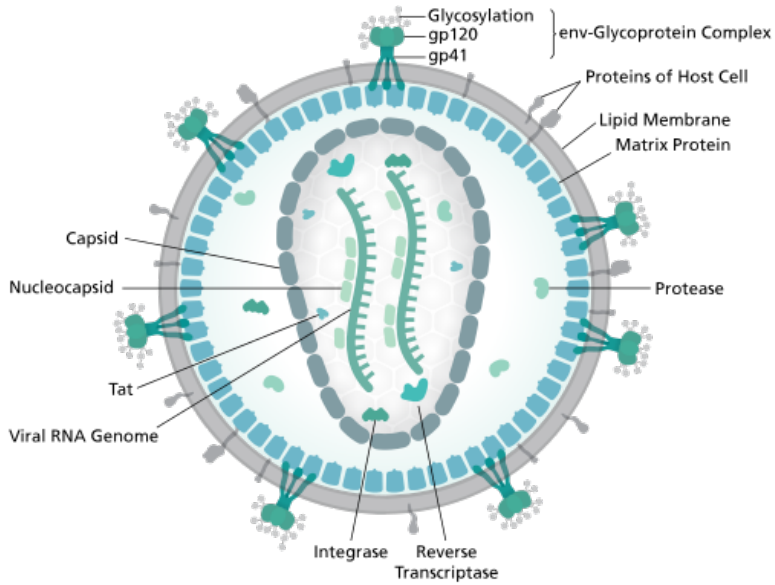
These virus particles (or virions) then go on to infect other cells.



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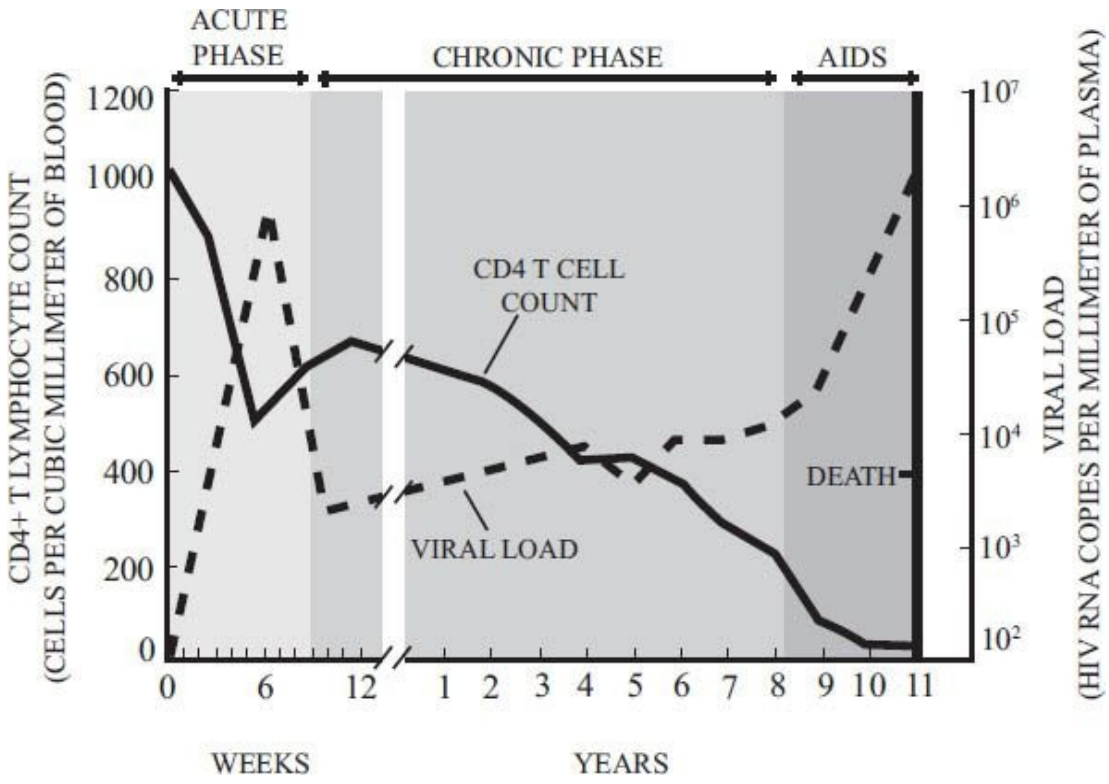
Eventually, without treatment, the population of the infected cells declines dramatically from about $1000\,\text{cells}\,\text{mm}^{-3}$ of blood to about $200\,\text{cells}\,\text{mm}^{-3}$, signaling the onset of AIDS.



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Unfortunately, modern drug therapies are extremely expensive and cannot be afforded by the majority of individuals infected with HIV worldwide.

Human Immunodeficiency Virus (HIV)

Until effective therapy or vaccines become freely available, HIV will continue to take a devastating toll...

Number of individuals living with HIV (source: Joint United Nations Programme on HIV/AIDS, 2004).

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In the following, we will explore one of these models in detail. This model was chosen because of its implication for our understanding of HIV.

Model – Dynamics of HIV after initial infection

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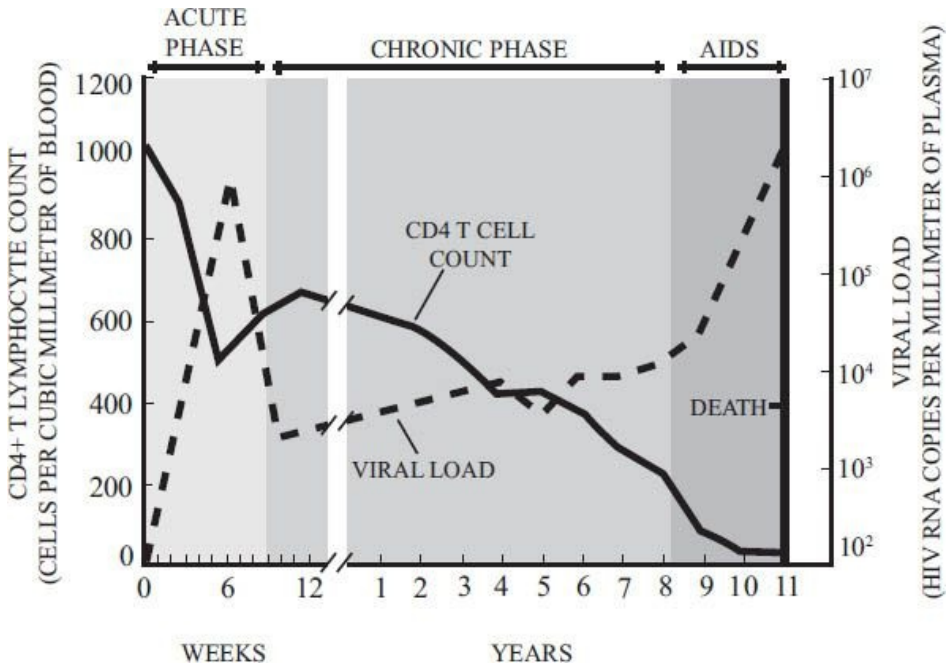

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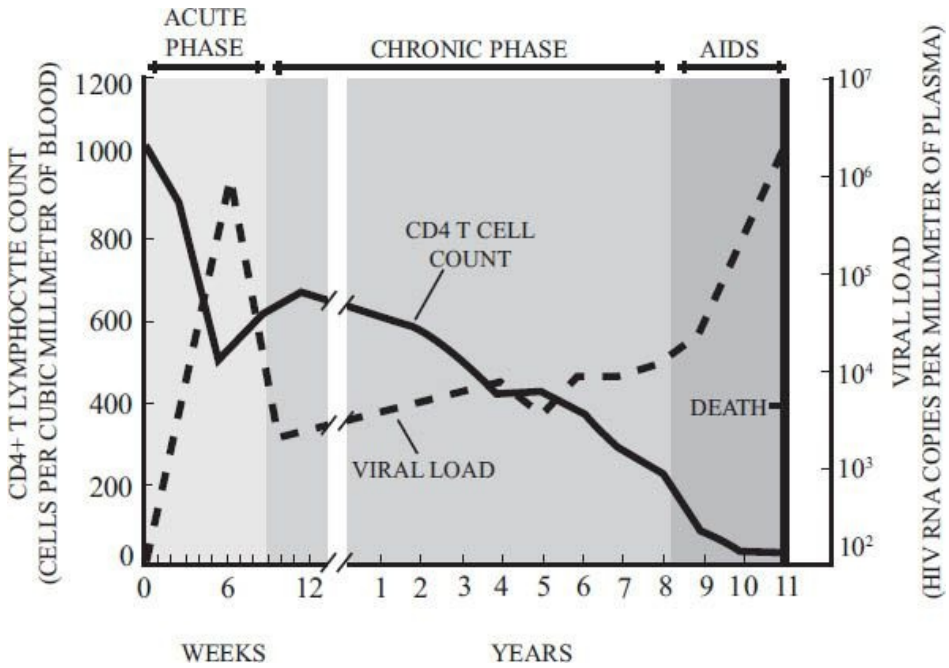

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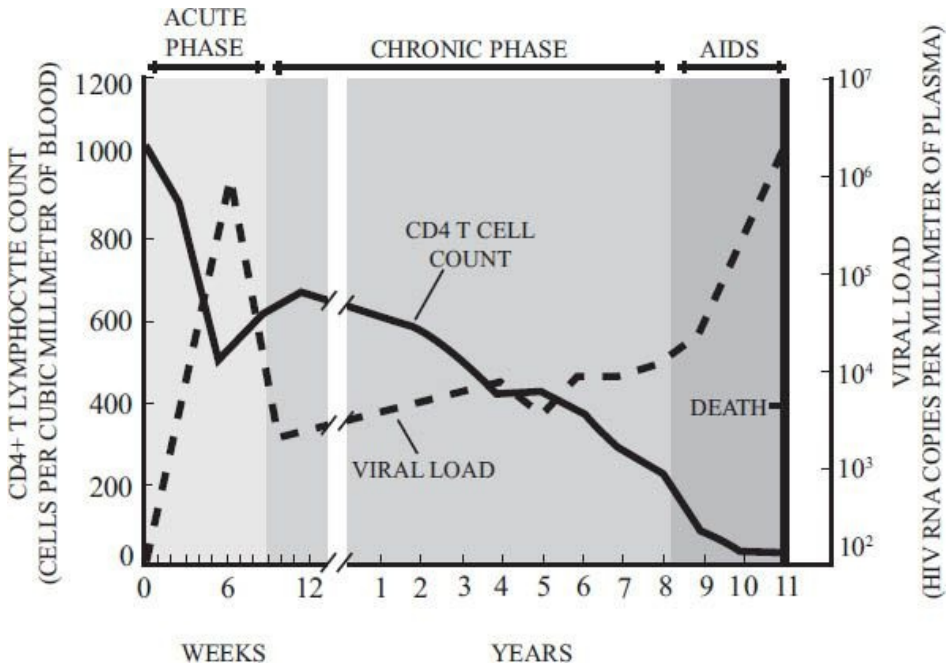

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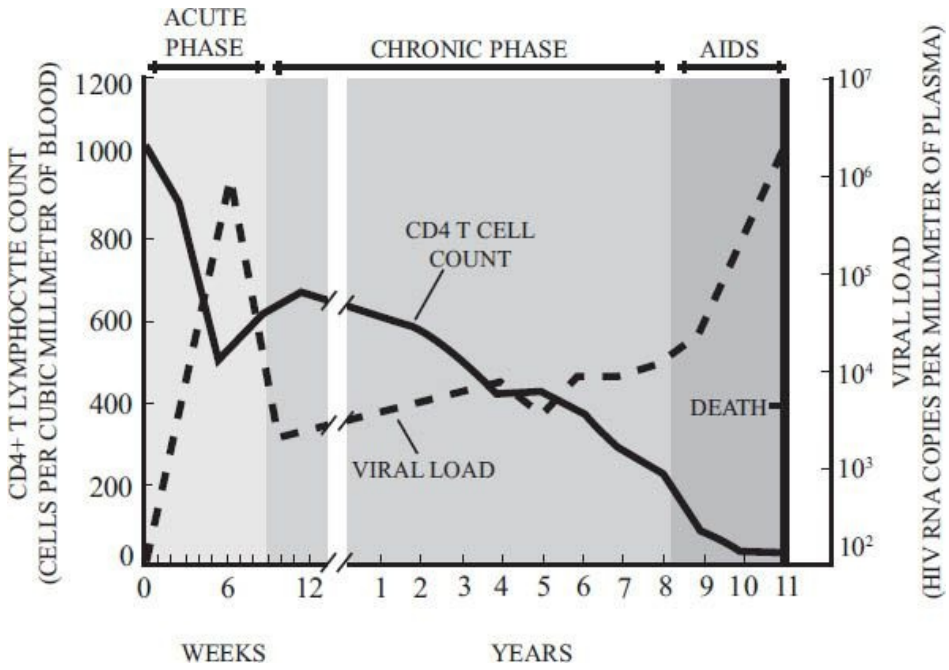
The most obvious answer is that the immune system acts to recognise and suppress the viral infection...



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The *dynamics* of each variable depends on the values of the remaining variables.

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To proceed, Phillips chose plausible values for each parameter and numerically ran the model;

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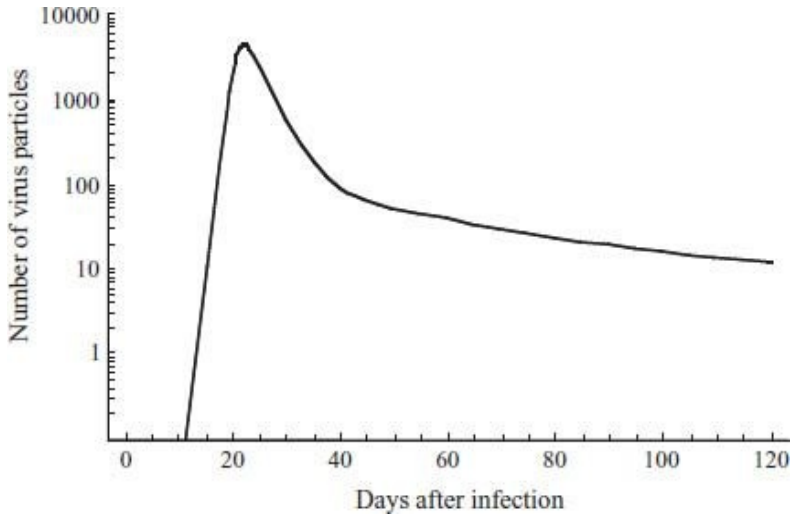
Phillip observed that the number of virus particles typically rose and then fell by several orders of magnitude over a period of a few days to weeks:



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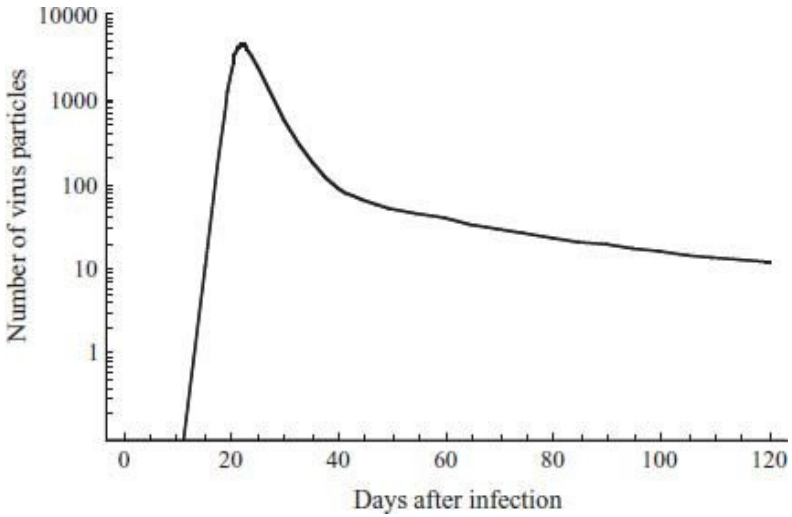

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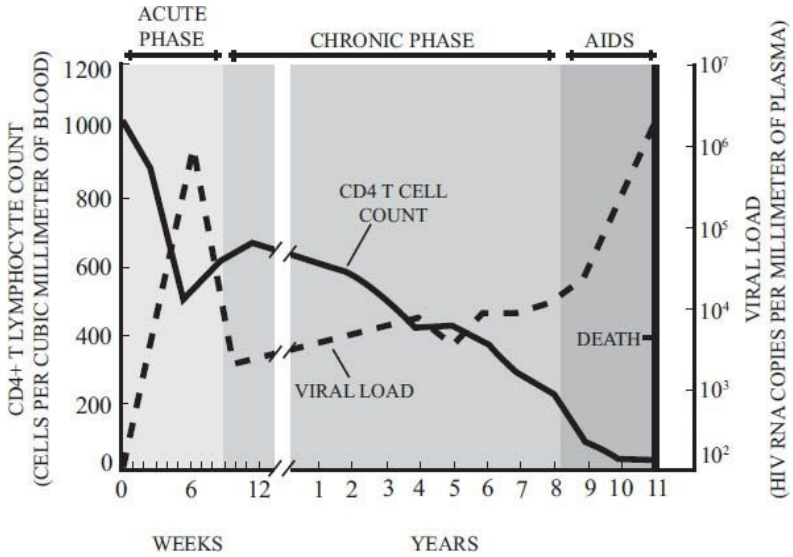

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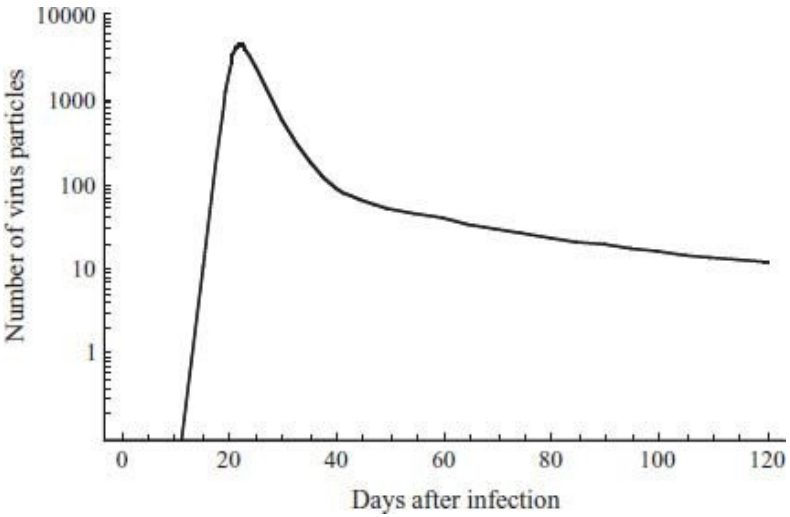

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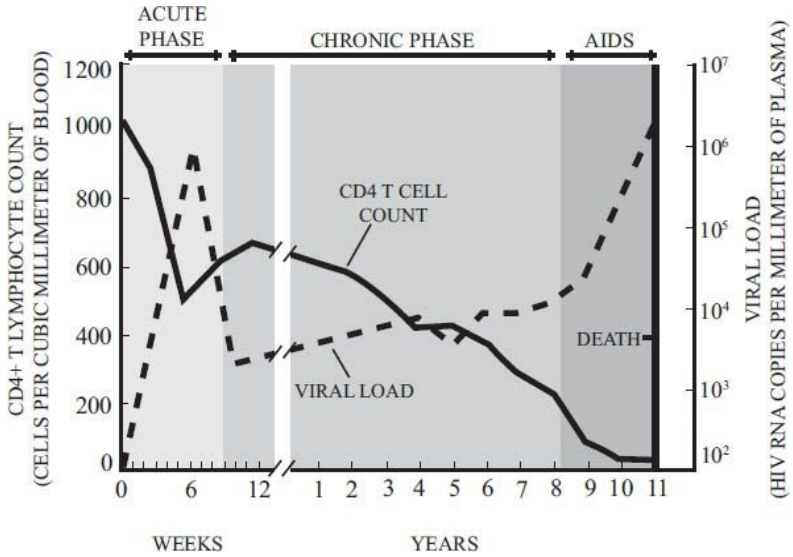

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Phillips thus came to the counter-intuitive conclusion that *"the reduction in virions during acute infection may not reflect the ability of the HIV-specific immune response to control the virus replication"*.

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3. Phillips' model generated a useful null hypothesis: viral dynamics do not reflect an immune response; this null hypothesis might be wrong, but at least it can be tested.

Phillips' model

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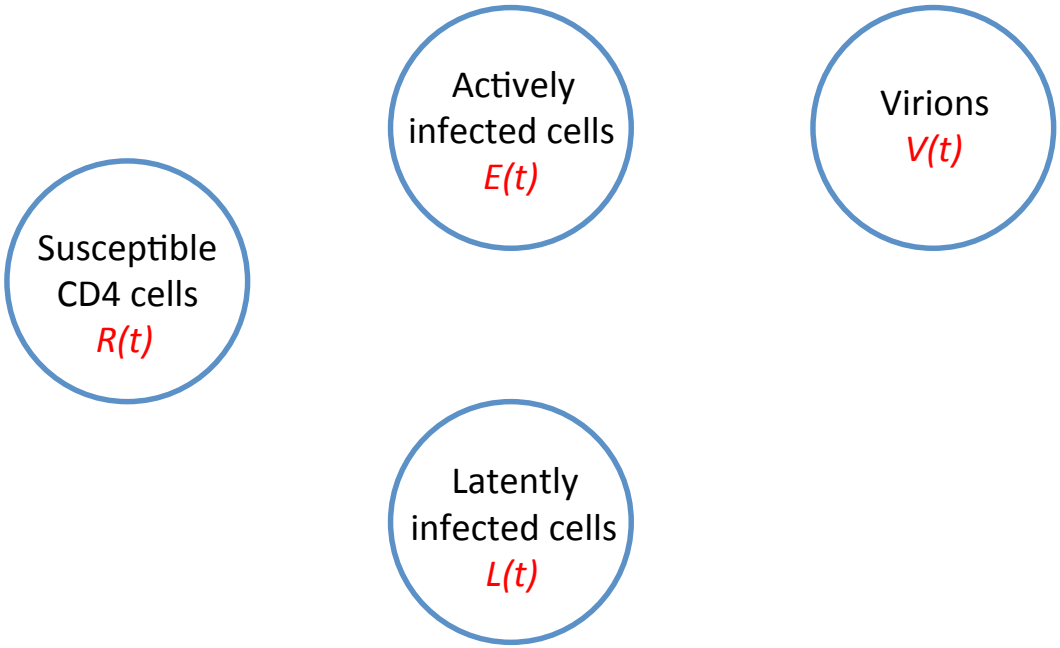
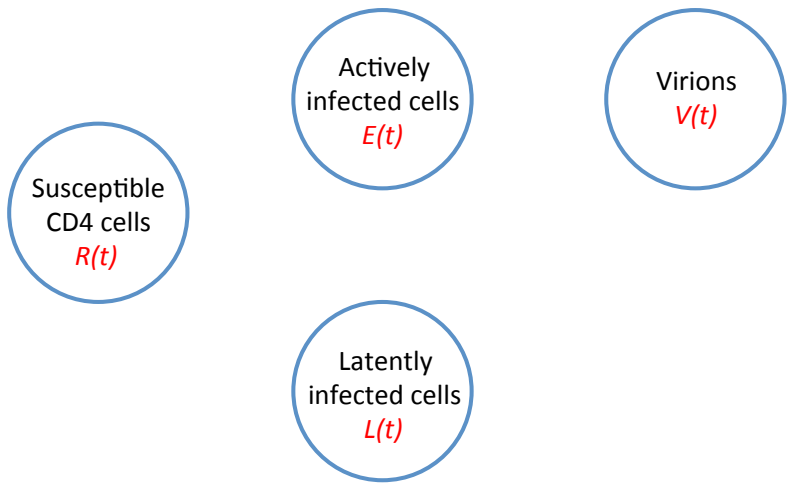
The circles represent (1) the number of susceptible CD4 cells, $R(t)$, (2) the number of latently infected CD4 cells, $L(t)$, (3) the number of actively infected CD4 cells, $E(t)$, and (4) the number of virions in the blood stream, $V(t)$.



Phillips' HIV model – flow diagram



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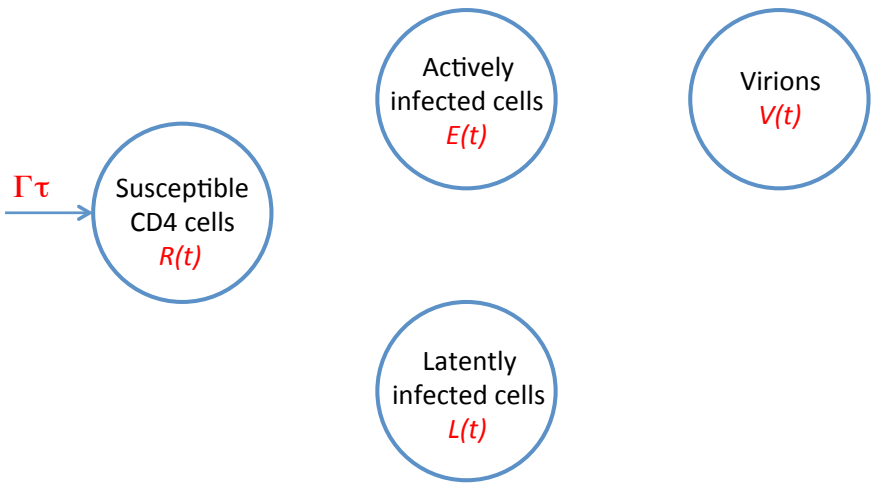

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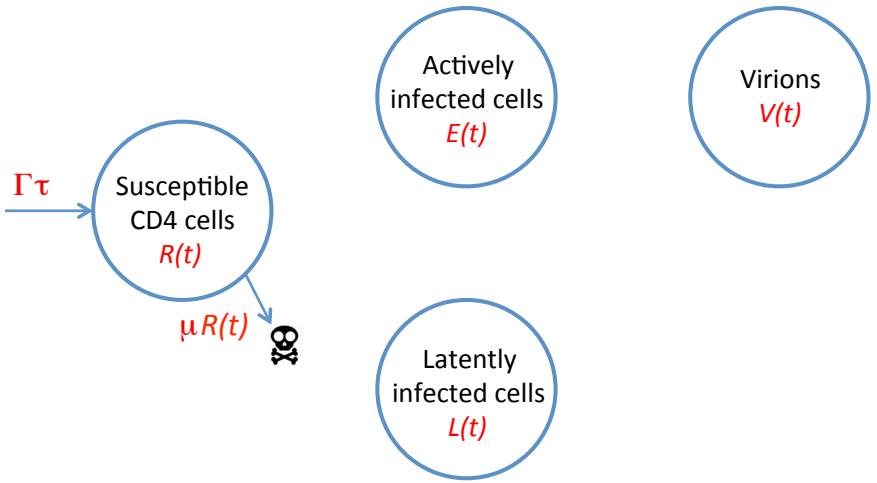

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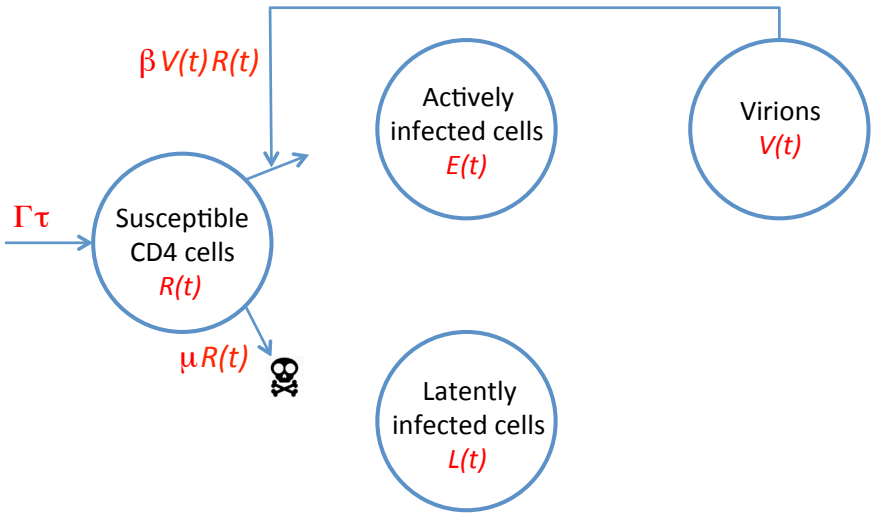

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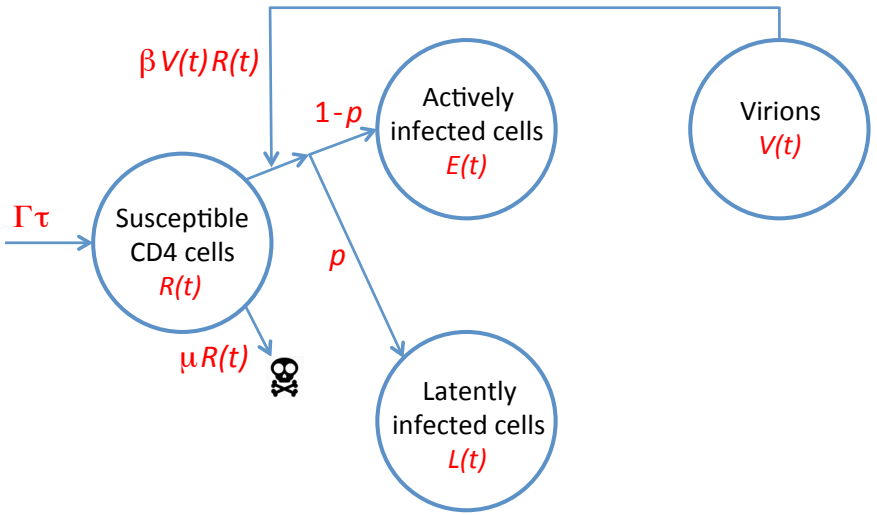
Once infected, CD4 cells may host HIV in a latent (non-replicating) state (a proportion p) or in its actively replicating state $(1 - p)$;



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Even without HIV infection, CD4 cells die at a rate μ per cell per day, leading to a total flow out of the circle of $\mu \cdot R(t)$ per day;

CD4 cells become infected if they encounter a virus; new infections are assumed to occur at a rate $\beta \cdot V(t)$ per cell per day, leading to a total flow of $\beta \cdot V(t) \cdot R(t)$ per day;

Once infected, CD4 cells may host HIV in a latent (non-replicating) state (a proportion p) or in its actively replicating state $(1 - p)$;

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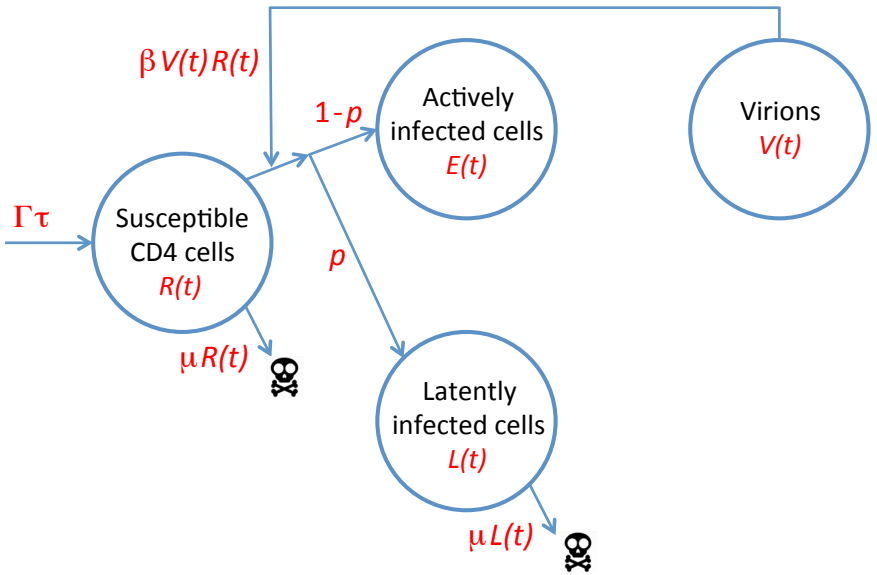

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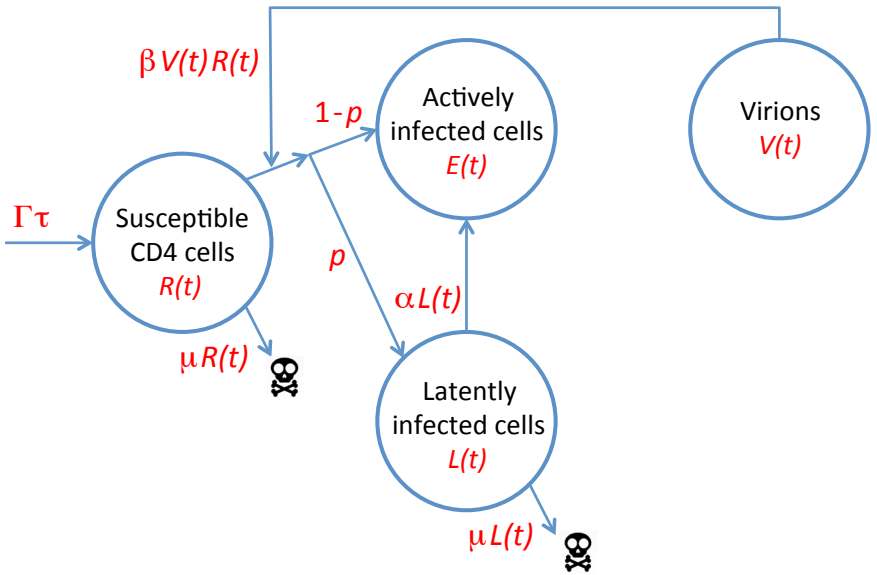
Latently infected cells may be activated at a rate α per cell per day; actively infected cells are thus produced by two means: by the infection of susceptible cells at a rate $(1 - p) \cdot \beta \cdot V(t) \cdot R(t)$ or by the conversion of latently infected cells at a rate $\alpha \cdot L(t)$;



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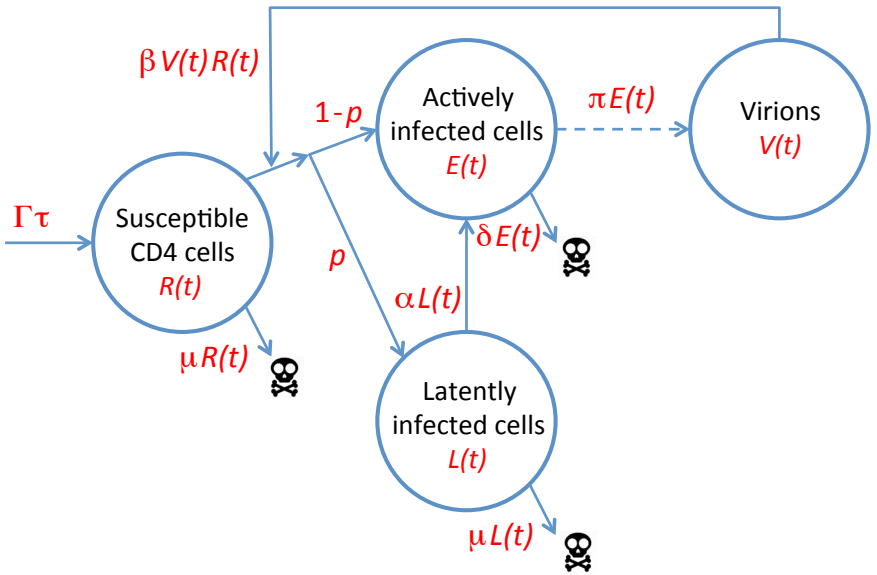
Actively infected cells die at a fast rate δ per cell per day, due to the continual budding of virus particles at a rate π per infected cell per day; a dashed arrow between actively infected cells and viruses indicates that viral production by budding, $\pi \cdot E(t)$, does not directly eliminate an infected cell;



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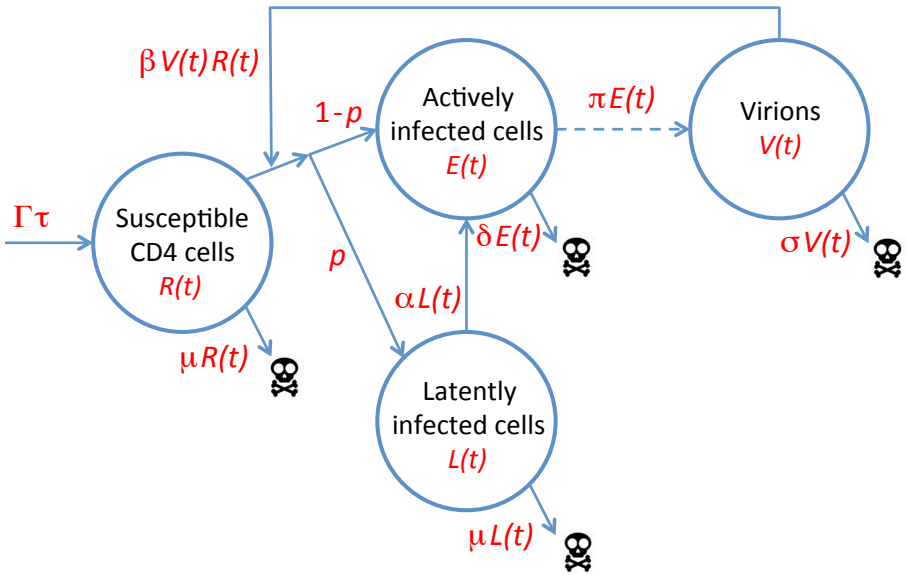
Finally, virus particles degrade or are eliminated from the body at a rate σ per virion per day.



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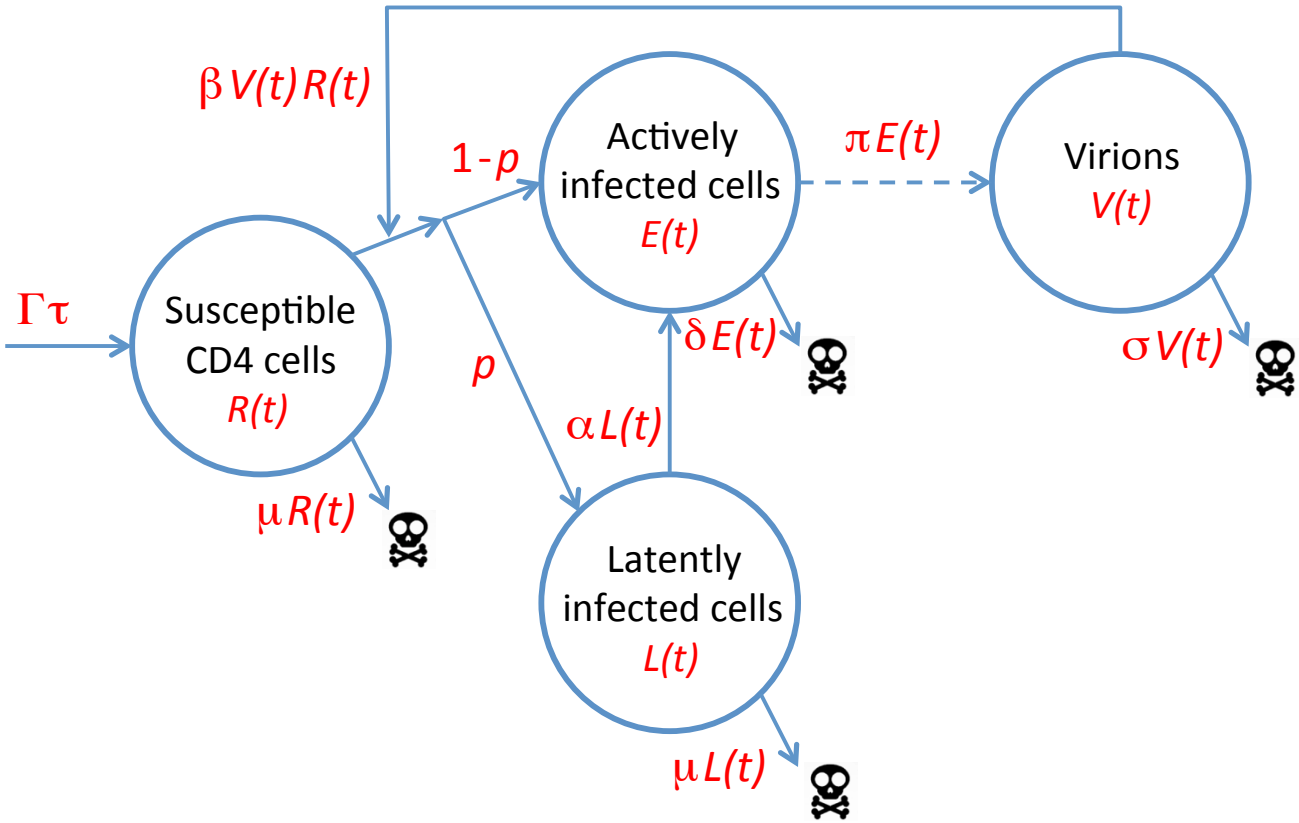

Flow diagram of Phillips' HIV model, which describes the number of viruses in the blood stream after HIV infection.

Phillips' HIV model – equations

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From the flow diagram we can write down the differential equations describing the rate of change of each variable over time (e.g. $dV(t)/dt$ for the rate of change of virus particles). Each variable represented by a circle in the flow diagram changes at a rate equal to the sum of all of the arrows entering the circle minus all of the arrows exiting the circle:

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$$\frac{dR(t)}{dt} = \Gamma\,\tau \;-\; \mu\,R(t) \;-\; \beta\,V(t)\,R(t)\,,$$

$$\frac{dL(t)}{dt} = p\,\beta\,V(t)\,R(t) \;-\; \mu\,L(t) \;-\; \alpha\,L(t)\,,$$

$$\frac{dE(t)}{dt} = (1 \;-\; p)\,\beta\,V(t)\,R(t) \;+\; \alpha\,L(t) \;-\; \delta\,E(t)\,,$$

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Technically, the rate at which virus particles infect susceptible cells, $\beta\,V(t)\,R(t)$, should also be subtracted off from $dV(t)/dt$, but this rate is assumed small relative to the large number of virus particles in the bloodstream.

Phillips' HIV model – parameter values

Symbol	Description	Value (per day)	Comments
Γ	Rate of CD4 cell production	1.36	Equivalent to 3.4×10^{8} cells per day in whole body
μ	HIV-independent death rate of susceptible CD4 cells	1.36×10^{-3}	Average life span of uninfected CD4 cells: 2 years
τ	Fraction of cells becoming susceptible of HIV attack	0.2	
β	Rate of infection of cells per virion	0.00027	Cannot be estimated directly
p	Proportion of cells becoming latently infected upon infection	0.1	
α	Activation rate of latently infected cells	3.6×10^{-2}	
σ	removal rate of cell-free virus	2.0	Average life span: 1/2 day
δ	Removal (death) rate of actively infected cells	0.33	Average life span: 3 days
π	Reate of production of virions by an actively infected cell	100.0	

- The total number of CD4 cells is: $1000 \times (1 - \tau) + R(t) + L(t) + E(t)$
- Initial conditions are: $R(t = 0) = 200$, $L(t = 0) = 0$, $E(t = 0) = 0$, $V(t = 0) = 4.0x10^{-7}$

Phillips' HIV model – results

Check the original article by Phillips (1996) [available via CampusNet]:

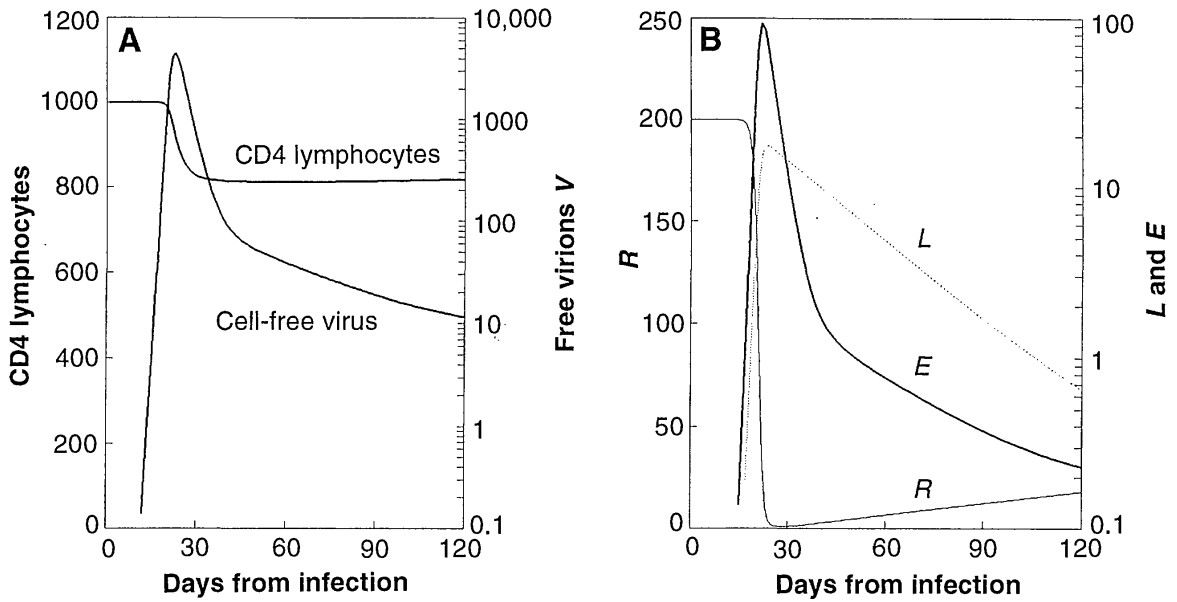

Fig. 1. Temporal changes in the number of (**A**) total CD4 lymphocytes [$1000(1-\tau)+R+L+E$] and free virions (V) and (**B**) activated, uninfected CD4 lymphocytes (R), latently infected cells (L), and actively infected cells (E) in the first 120 days after HIV infection as predicted by the model on the basis of a simulation with iterations of step length 1 hour and 20 min. The total (whole-body) inoculum of HIV was assumed to consist of 100 virions (and no infected cells); thus, there were initially 4×10^{-7} virions in the quantity being considered.

Plotting suggestions

plot using a single y-axis

```
import numpy as np
import matplotlib.pyplot as plt

t=np.linspace(0,15,100)
y=np.sin(t)
z=np.cos(t)

plt.plot(t,y, '-r', linewidth=3, label='sin(x)')
plt.plot(t,z, '-b', linewidth=3, label='cos(x)')
plt.xlim(0,15)
plt.ylim(-2,2)
plt.xlabel('x', fontsize=20)
plt.ylabel('Trigonometric function', fontsize=20)
plt.legend(loc='best')

plt.show()
```

Plotting suggestions

plot using both y-axes (with the `twinx` method)

```
import numpy as np
import matplotlib.pyplot as plt

t=np.linspace(0,15,100)

y=np.sin(t)
z=np.cos(t)

ax1 = plt.subplot(1,1,1) # create a first y-axis object
ax1.plot(t, y, '-r', linewidth=3)
ax1.set_xlim(0,15)
ax1.set_ylim(-2,2)
ax1.set_xlabel('x', fontsize=20)
ax1.set_ylabel('sin(x)', color='red', fontsize=20)
ax1.tick_params(axis='y', colors='red')

ax2 = ax1.twinx()  # create a twin y-axis object sharing the x-axis
ax2.plot(t, z, '-b', linewidth=3)
ax2.set_ylabel('cos(x)', color='blue', fontsize=20)
ax2.tick_params(axis='y', colors='blue')
ax2.set_ylim(-4,4)
ax2.set_xlim(0,15)

plt.show()
```

Plotting suggestions

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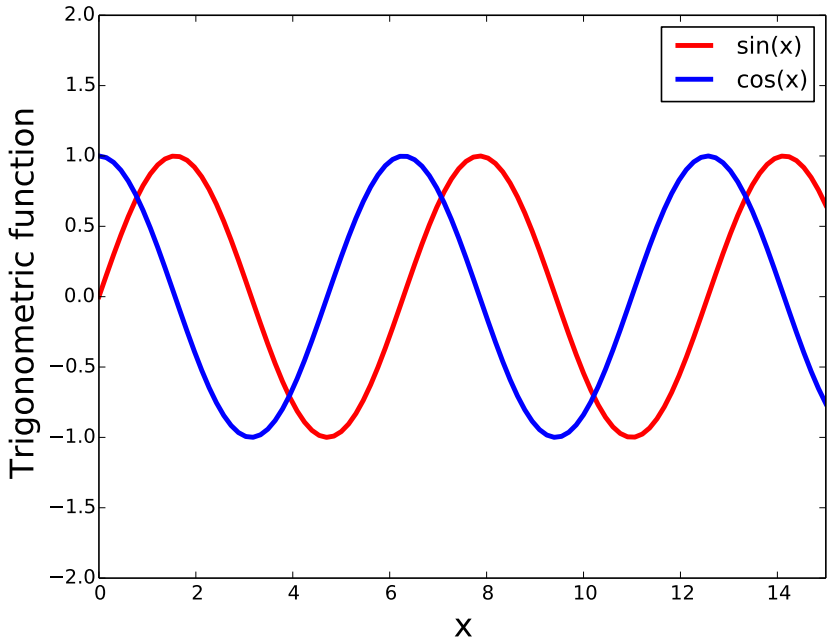

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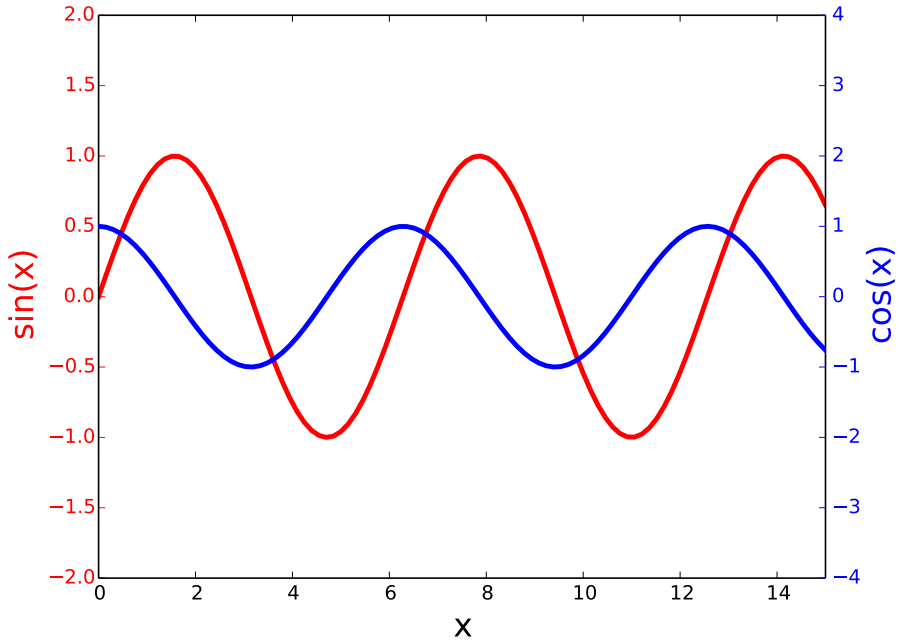

Further reading

Sarah P. Otto & Troy Day 2007
A Biologist's Guide to Mathematical Modelling in Ecology and Evolution
Princeton University Press

A. N. Phillips
Reduction of HIV concentration during acute infection: Independence from a specific immune response
Science, 271:497–499, 1996