Bio-Systems Modeling and Control

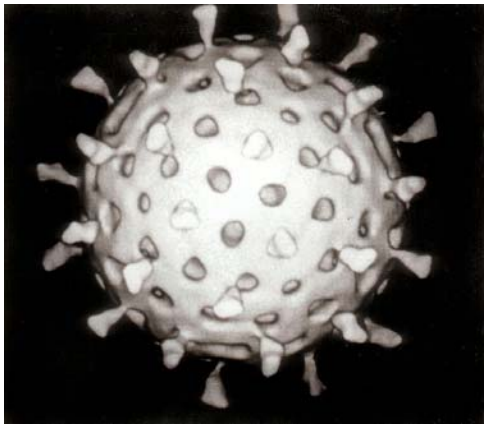
Lecture 16

Viral Dynamics

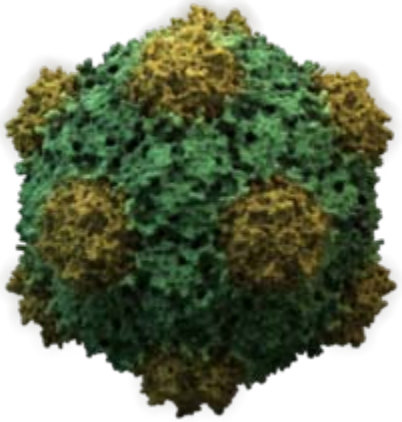
References

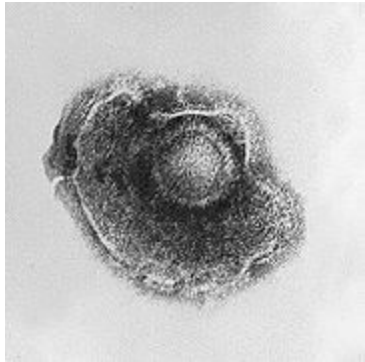
- Herz, Bonhoeffer, Anderson, May and Nowak, “Viral Dynamics in vivo: Limitations on Estimates of Intracellular Delay and Virus Decay”, Proc. Natl. Acad. Sci. USA, July 1996.
- Tuckwell and Wan, “Nature of Equilibria and Effects of Drug Treatments in Some Simple Viral Population Dynamical Models”, IMA Journal of Mathematics Applied in Medicine and Biology, 2000.

Virus



A small infectious agent that can replicate only inside the living cells of an organism.

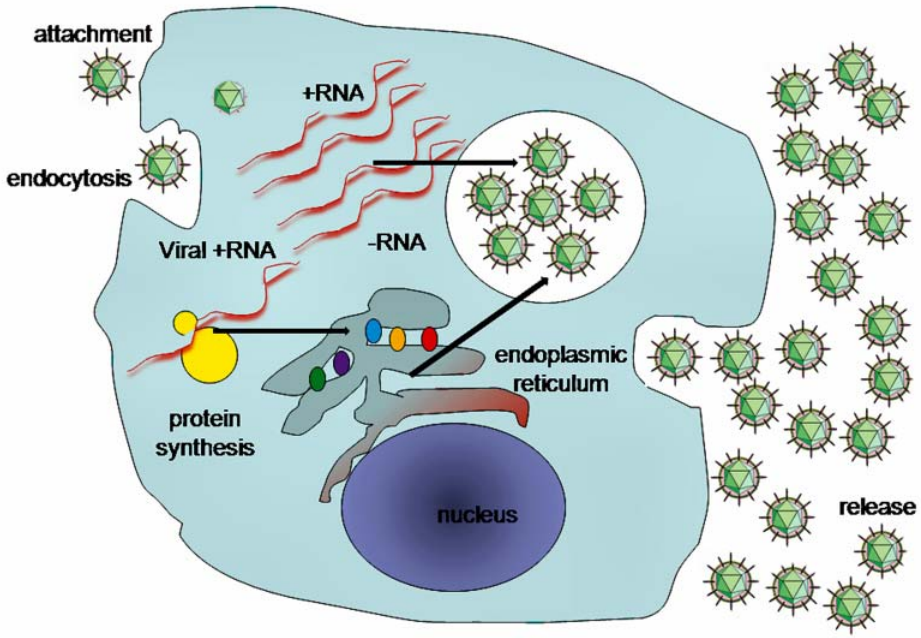




Virions (Virus Particles)

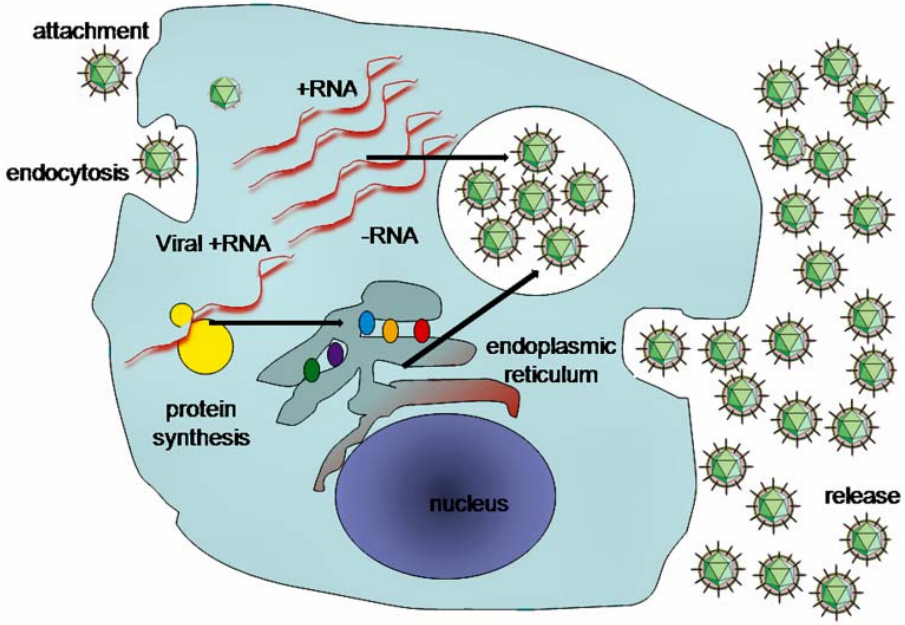
- Virus particles (known as *virions*) consist of two or three parts:
- the genetic material made from either DNA or RNA, long molecules that carry genetic information;
- a protein coat that protects these genes; and in some cases
- an envelope of lipids that surrounds the protein coat when they are outside a cell.

Replication Cycle of a Virus



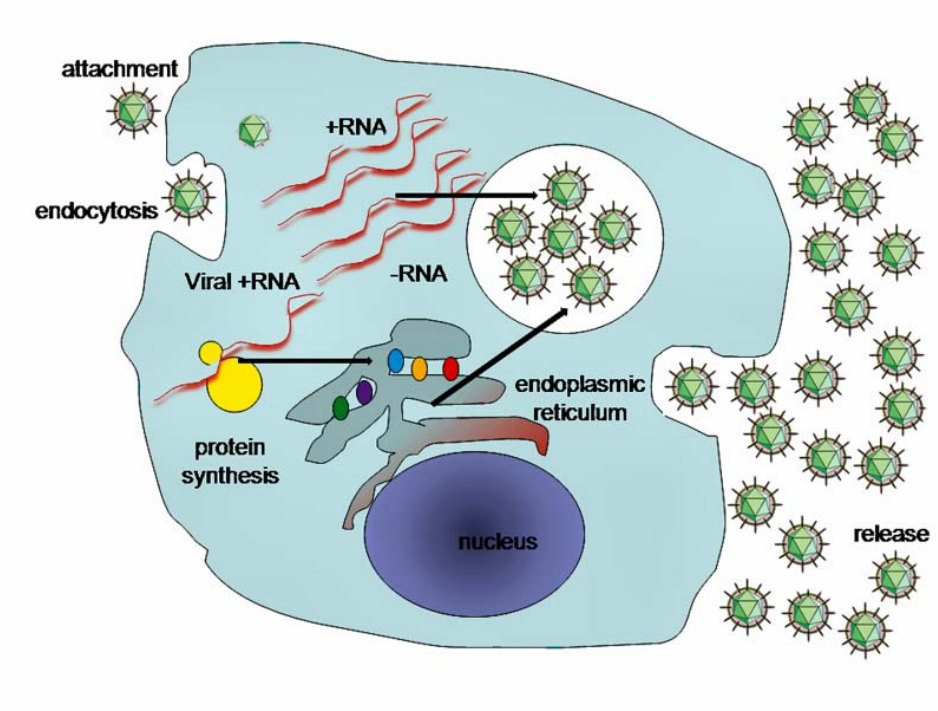
- *Attachment* is a specific binding between viral capsid proteins and specific receptors on the host cellular surface.
- *Penetration* follows attachment: Virions enter the host cell (Viral Entry)

Replication Cycle of a Virus



- *Uncoating* is a process in which the viral capsid is removed
- *Replication* of viruses involves primarily multiplication of the genome: synthesis of viral mRNA, viral protein synthesis, possible assembly of viral proteins, then viral genome replication.

Replication Cycle of a Virus



- Following the self-*assembly* of the virus particles, some modification of the proteins often occurs.
- Viruses can be *released* from the host cell by lysis, a process that kills the cell by bursting its membrane and cell wall if present

Paper by Herz et al

Summary of main ideas

Basic Three-Variable Viral Dynamic Model

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t)x(t)v(t) - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

- Where x(t)=population of uninfected cells, y(t)=population of infected cells, v(t)=plasma population of the virus
- Constant influx λ of uninfected cells; d is their death rate

Basic Three-Variable Viral Dynamic Model (Herz et al)

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t)x(t)v(t) - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

- Uninfected cells and free virus produce infected cells at a rate of β(t)x(t)v(t).
- Infected cells produce free virus particles at a rate of k(t) and die at a rate of a.
- Free virus particles are cleared at rate u.

Basic Three-Variable Viral Dynamic Model (Herz et al)

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t)x(t)v(t) - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

- Effects of various drug therapies may be modeled via time varying β(t) and k(t) coefficients.
- For constant β and k there are 2 equilibrium points.

Tuckwell's Modification to Herz Viral Dynamic Model

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t)x(t)v(t) - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t) - \beta(t)x(t)v(t)$$

- Tuckwell's little modification is to claim reduction in v(t) at the same time that x(t) decreases. Does the model behavior change drastically due to this modification?

Basic Viral Dynamic Model Equilibria if β and k are constant

$$\frac{dx_e(t)}{dt} = 0 = \lambda - dx_e - \beta x_e v_e$$

$$\frac{dy_e(t)}{dt} = 0 = \beta x_e v_e - a y_e$$

$$\frac{dv_e(t)}{dt} = 0 = k y_e - u v_e$$

How many equilibrium points are there?

Basic Viral Dynamic Model Equilibria if β and k are constant

$$0 = \lambda - dx_e - \beta x_e v_e \rightarrow 0 = \lambda - dx_e - ay_e \rightarrow y_e = \frac{\lambda - dx_e}{a}$$

$$0 = \beta x_e v_e - ay_e$$

$$0 = ky_e - uv_e \rightarrow v_e = \frac{k}{u}\frac{\lambda - dx_e}{a}$$

$$0 = \beta x_e v_e - ay_e \rightarrow \beta x_e \frac{k}{u}\frac{\lambda - dx_e}{a} = \lambda - dx_e$$

$$\rightarrow x_{e1} = \frac{\lambda}{d} \rightarrow y_{e1} = 0 \quad , v_{e1} = 0$$

An equilibrium in which viruses and infected cells are eradicated

Basic Viral Dynamic Model Equilibria if β and k are constant

$$0 = \lambda - dx_e - \beta x_e v_e \rightarrow 0 = \lambda - dx_e - ay_e \rightarrow y_e = \frac{\lambda - dx_e}{a}$$

$$0 = \beta x_e v_e - ay_e$$

$$0 = ky_e - uv_e \rightarrow v_e = \frac{k}{u}\frac{\lambda - dx_e}{a}$$

$$0 = \beta x_e v_e - ay_e \rightarrow \beta x_e \frac{k}{u}\frac{\lambda - dx_e}{a} = \lambda - dx_e$$

$$\rightarrow x_{e2} = \frac{ua}{\beta k} \rightarrow y_{e2} = \frac{\lambda}{a} - \frac{du}{\beta k} \quad , v_{e2} = \frac{k\lambda}{ua} - \frac{d}{\beta}$$

An equilibrium in which there is steady state population of viruses and infected cells.

Modified Viral Dynamic Model to Incorporate the Virus Life-Cycle

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t-\tau)x(t-\tau)v(t-\tau)e^{-\alpha\tau} - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

Virus production lags by a delay of τ behind the infection of the cell.

Modified Viral Dynamic Model to Incorporate the Virus Life-Cycle

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t-\tau)x(t-\tau)v(t-\tau)e^{-\alpha\tau} - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

Recruitment of virus-producing cells is determined by cells that got infected at time t-τ and are still alive at time t.

Modified Viral Dynamic Model to Incorporate the Virus Life-Cycle

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t-\tau)x(t-\tau)v(t-\tau)e^{-\alpha\tau} - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

A constant death rate α is assumed for infected but not yet virus-producing cells. The probability of surviving from time t-τ to time t is exp(-ατ).

Non-Trivial Equilibrium using Pre-Treatment constant β and k Rates

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t)$$

$$\frac{dy(t)}{dt} = \beta(t-\tau)x(t-\tau)v(t-\tau)e^{-\alpha\tau} - ay(t)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

$$x_0 = \frac{au}{\beta k}e^{-\alpha\tau} \qquad y_0 = \frac{\lambda}{a}e^{-\alpha\tau} - \frac{du}{\beta k} \qquad v_0 = \frac{ky_0}{u}$$

These will now serve as initial conditions for studying treatment strategies.

Example: HIV-1 Treatment by Reverse Transcriptase Inhibitors

$$\frac{dx(t)}{dt} = \lambda - dx(t) _ for _ t > 0$$

$$\frac{dy(t)}{dt} = \begin{cases} 0 _ for _ 0 < t \le \tau \\ -ay(t) _ for _ t > \tau \end{cases}$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

In HIV-1 reverse transcriptase inhibitors block the infection of uninfected cells.

Example: HIV-1 Treatment by Reverse Transcriptase Inhibitors

$$\frac{dx(t)}{dt} = \lambda - dx(t) _ for _ t > 0$$

$$\frac{dy(t)}{dt} = \begin{cases} 0 _ for _ 0 < t \le \tau \\ -ay(t) _ for _ t > \tau \end{cases}$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

In the model it means that β(t) is strongly reduced once treatment sets in at time t=0.

Example: HIV-1 Treatment by Reverse Transcriptase Inhibitors

$$\frac{dx(t)}{dt} = \lambda - dx(t) _ for _ t > 0$$

$$\frac{dy(t)}{dt} = \begin{cases} 0 _ for _ 0 < t \le \tau \\ -ay(t) _ for _ t > \tau \end{cases}$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

For simplicity the paper assumes that the drug has 100% effectiveness → β(t)=0.

Example: HIV-1 Treatment by Reverse Transcriptase Inhibitors

$$\frac{dy(t)}{dt} = \begin{cases} 0 _ for _ 0 < t \leq \tau \\ -ay(t) _ for _ t > \tau \end{cases}$$

For 0 <t≤ τ cells that are virus producing at time t were infected at time t- $\tau \leq 0$; that is, before the drug was administered.

Until t = τ both y and v remain at their pre-treatment steady-state. Thereafter the drug begins to block further infections.

Example: HIV-1 Treatment by Reverse Transcriptase Inhibitors

$$\frac{dx(t)}{dt} = \lambda - dx(t) _ for _ t > 0$$

$$\frac{dy(t)}{dt} = \begin{cases} 0 _ for _ 0 < t \le \tau \\ -ay(t) _ for _ t > \tau \end{cases}$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t)$$

$$\rightarrow v(t) = \begin{cases} v_0 _____ for _ 0 < t \le \tau \\ \frac{v_0}{a-u}[ae^{-u(t-\tau)} - ue^{-a(t-\tau)}] _ for _ t > \tau \end{cases}$$

Example: HIV-1 Treatment by Reverse Transcriptase Inhibitors

$$v(t) = \begin{cases} v_0 _____ & for_0 < t \le \tau \\ \dfrac{v_0}{a-u}[ae^{-u(t-\tau)} - ue^{-a(t-\tau)}]_ & for_t > \tau \end{cases}$$

The same time lag that exists between infection of the cell and emission of viral particles, shows up at the drug-treated response.

Measurements have confirmed that u > a.

Similar Example: HIV Treatment by Protease Inhibitors

- Protease inhibitors of HIV block the production of new infectious virus v_I from already infected cells.
- Only non-infectious virus is generated.
- One can model the treatment by using $k(t)=0$.
- For $t>0$ infectious viruses decay according to $dv_I(t)/dt=-uv_I(t)$.

Paper by Tuckwell et al

Summary of main ideas

General Two-Component Effector-Virus Model

$$\frac{da}{dt} = s - \mu a + \varepsilon a v$$

$$\frac{dv}{dt} = rv - \gamma a v$$

- Anderson & May, 1991
- Model describes the immune system attack on disease-causing particles
- a(t) = effectors (such as CD4+ T-cells), v(t) = virus population

General Two-Component Effector-Virus Model

$$\frac{da}{dt} = s - \mu a + \varepsilon a v$$

$$\frac{dv}{dt} = rv - \gamma a v$$

- Effectors production rate = s = const.
- Effectors per-capita death rate = μ
- More effectors are produced at a rate of εav by interaction with the viral population
- Virion production rate = r, virion removal rate = γav

General Two-Component Effector-Virus Model Equilibria

$$\frac{da}{dt} = s - \mu a + \varepsilon a v$$

$$\frac{dv}{dt} = rv - \gamma a v$$

$$P_1 = (\frac{s}{\mu}, 0)$$

$$P_2 = (\frac{r}{\gamma}, \frac{\mu r - s\gamma}{\varepsilon r})$$

- The eigenvalues associated with P_1 are $\lambda_1 = -\mu$ and $\lambda_2 = r-(s\gamma/\mu)$.
- If $s=0$ then P_1 is an unstable saddle point.
- If $s \neq 0$, then P_1 is an unstable saddle if $s\gamma \leq r\mu$ and an asymptotically stable node if $s\gamma > r\mu$

General Two-Component Effector-Virus Model Equilibria

$$\frac{da}{dt} = s - \mu a + \varepsilon a v _ \frac{dv}{dt} = r v - \gamma a v$$

$$P_1 = (\frac{s}{\mu}, 0) _ P_2 = (\frac{r}{\gamma}, \frac{\mu r - s\gamma}{\varepsilon r})$$

$$\lambda_{1,2} = -\frac{1}{2r}\{\gamma s \pm \sqrt{(\gamma s)^2 + 4r^2(\gamma s) - 4\mu r^3}\}$$

- The eigenvalues associated with P_2 are shown above.
- If s=0 then $\lambda_{1,2}=\pm j(\mu r)^{1/2}$ → P_2 becomes a center.
- If $s\gamma > r\mu$ then P_2 is a saddle.

General Two-Component Effector-Virus Model Equilibria

$$\frac{da}{dt} = s - \mu a + \varepsilon a v _ \frac{dv}{dt} = r v - \gamma a v$$

$$P_1 = (\frac{s}{\mu}, 0) _ P_2 = (\frac{r}{\gamma}, \frac{\mu r - s\gamma}{\varepsilon r})$$

$$\lambda_{1,2} = -\frac{1}{2r}\{\gamma s \pm \sqrt{(\gamma s)^2 + 4r^2(\gamma s) - 4\mu r^3}\}$$

- If $s\gamma < r\mu$ then P_2 is a stable node if $(4r^2/(s\gamma)^2)[\mu r - \gamma s] \leq 1$
- If $s\gamma < r\mu$ then P_2 is a stable focus if $(4r^2/(s\gamma)^2)[\mu r - \gamma s] > 1$
- If $s\gamma = r\mu$ then the nature of P_2 cannot be determined by a linearization.

General Two-Component Effector-Virus Model Equilibria

$$\frac{da}{dt} = s - \mu a + \varepsilon a v$$

$$\frac{dv}{dt} = rv - \gamma a v$$

$$P_1 = (\frac{s}{\mu}, 0)$$

$$P_2 = (\frac{r}{\gamma}, \frac{\mu r - s\gamma}{\varepsilon r})$$

- If $s\gamma > r\mu$ then P_1 is stable and P_2 does not exist. In such a case the effector annihilates the virus.
- If $s\gamma < r\mu$ then P_1 is unstable and P_2 is stable → virus becomes endemic.

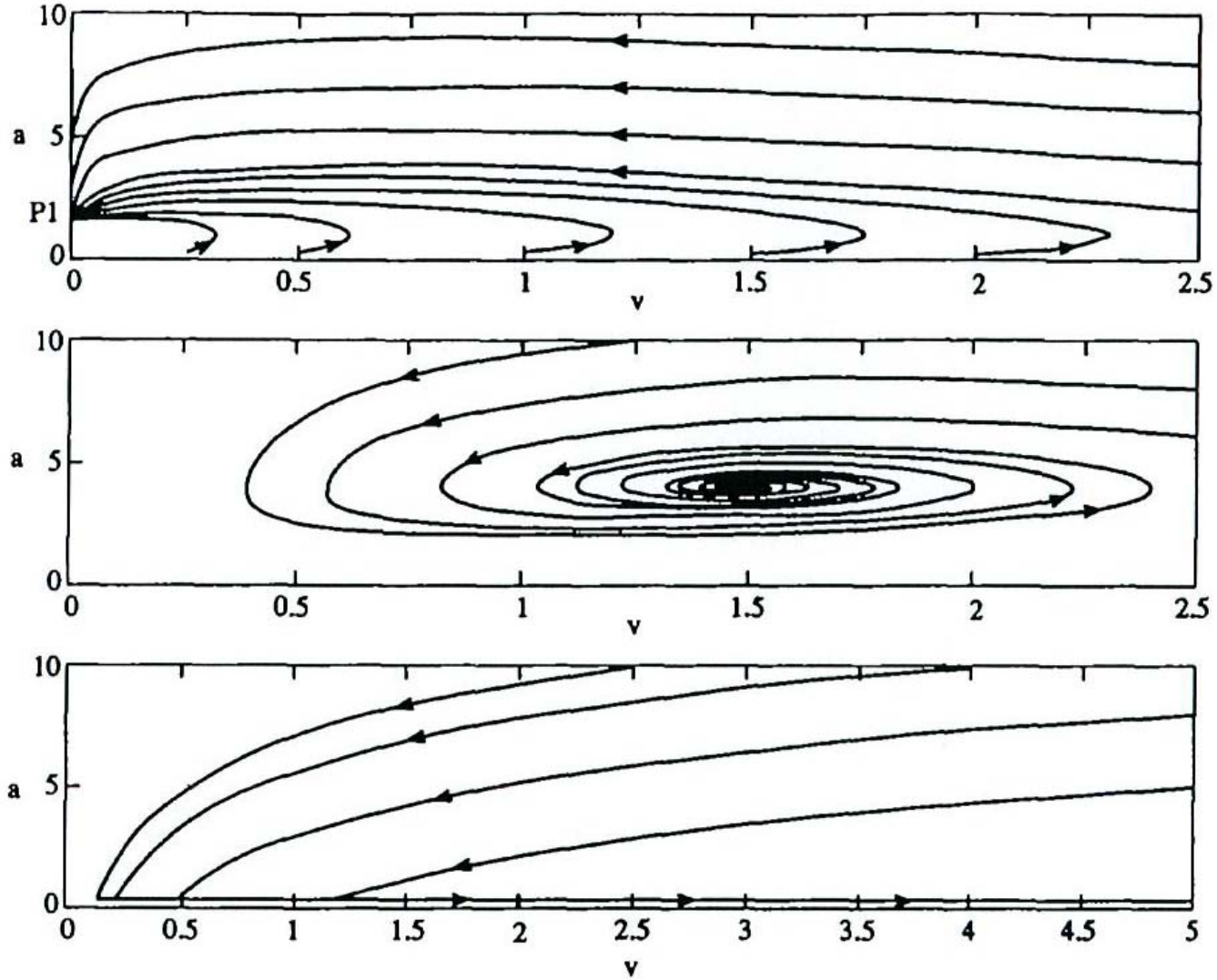


FIG. 1. Examples of phase portraits for the Anderson–May two-component model for viral–antibody dynamics. Top part. Here there is just one critical point—a stable node P_1. All solutions end up at P_1 regardless of the initial values. The viral population is driven to extinction. Parameter values: $\lambda = 1{\cdot}5, \mu = 1, \epsilon = 1, r = 1, \gamma = 1$, which puts P_1 at $(0, 3/2)$. Middle part. There are two critical points but only the one in the positive quadrant is stable and this is a spiral point. Parameter values: $\lambda = 2, \mu = 2, \epsilon = 1, r = 2, \gamma = 0{\cdot}5$, putting the two critical points at $(0, 1)$ and $(3/2, 4)$. Bottom figure. There are two critical points, but again only one is asymptotically stable and a node. Parameter values: $\lambda = 3, \mu = 10, \epsilon = 0{\cdot}2, r = 1, \gamma = 3$ with equilibrium points $(0, 0{\cdot}3)$ and $(5, 1/3)$.

Two-Component Model for HIV-1

$$\frac{dx}{dt} = s - \mu x - kxy$$

$$\frac{dy}{dt} = kxy - \alpha y$$

Similar results as in previous case

- Bonhoeffer et al, 1997
- x(t) = uninfected CD4+ T-cells, y(t) = infected CD4+ T-cells
- Rate of infection by virus = kxy
- The other parameters: s = production rate of such cells; Death rates=μ,α

Three-Component Model for HIV-1

$$\frac{dx}{dt} = s - \mu x - kvx$$

$$\frac{dy}{dt} = kvx - \alpha y$$

$$\frac{dv}{dt} = cy - \gamma v - kvx$$

- Modification of Herz's model.
- The model includes the virus population.
- It will soon turn out, using realistic numerical values, that the modification is insignificant.

HIV-1 Model Equilibria

$$\frac{dx}{dt} = s - \mu x - kvx$$

$$\frac{dy}{dt} = kvx - \alpha y$$

$$\frac{dv}{dt} = cy - \gamma v - kvx$$

- P_1=((s/μ),0,0)
- P_2=((αγ)/(k(c-α),(s/α)-(γμ)/(k(c-α)),s(c-α)/(αγ)-(μ/k))
- According to Herz model one has: P_2'=((αγ)/(kc),(s/α)-(γμ)/(kc)),(sc/(αγ))-(μ/k))

HIV-1 Model Equilibria

$$\frac{dx}{dt} = s - \mu x - kvx$$

$$\frac{dy}{dt} = kvx - \alpha y$$

$$\frac{dv}{dt} = cy - \gamma v - kvx$$

P_2=(49.21,0.6214,15.43)

P_2'=(48.89,0.6228,15.57)

- Typical coefficients (Phillips, 1996): s=0.272/day/mm^3, μ = 0.00136/day/mm^3, k=0.00027/day/(virion /mm^3), α=0.33/day/mm^3, c=50 virion/CD4/day, γ=2.0/day

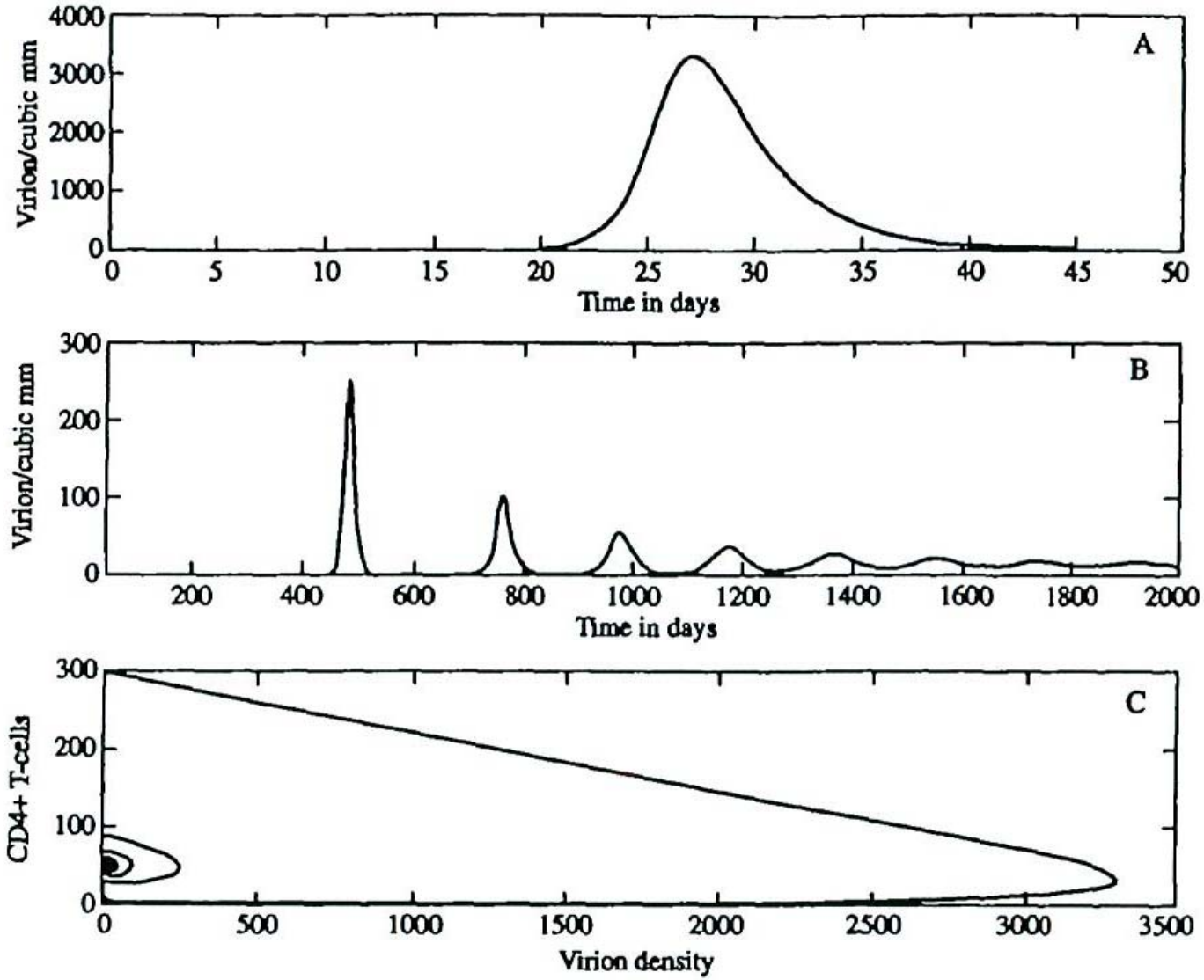


FIG. 2. Computed solutions for the 3-component HIV-1 model using the standard parameter set, $a = 0{\cdot}33$, $\lambda = 0{\cdot}272$, $\mu = 0{\cdot}00136$, $k = 0{\cdot}00027$, $\gamma = 2$, $c = 50$ and $x(0) = 200$, $y(0) = 0$ and $v(0) = 4 \times 10^{-7}$, where x, y, v are in mm^{-3}. a. The virion density for the first 50 days, showing a primary peak of about 3000 mm^{-3} at about 27 days after initial infection. b. The time course of the virion density over days 50–2000, showing peaks of diminishing amplitude as solutions approach the asymptotically spiral point P_2. c. Phase diagram of the solution in which uninfected CD4+ T-cell density is plotted against virion density for the first 2000 days.