Lecture 3: In-Host Models for Viral Infections of Cells and Backward Bifurcation

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Outline

Part I: General In-Host Models

- Replication process of retro-viruses
- Infection process of HIV-1 and HTLV-1 viruses
- Cell-to-cell transmission of viruses v.s. virus-to-cell transmission
- Differences between HIV-1 and HTLV-1

Part II: A Simple Model For HTLV-1 Infection and Immune Responses

- Assumptions and model
- Preliminary analysis
- Possibility of multiple positive equilibria
- Basic reproduction number and backward bifurcaton
- Bi-stability and global dynamics

Outline

Part III: Proofs

- Local stability by linearization
- Global stability by phase-plane analysis

Part I: In-Host Models for Viral Infections of Cells

- The same modeling approach for epidemics in human populations can also be applied to disease processes at a microscopic level, e.g. the spread of a viral infection among a population of target cells, and the associated immune responses.
- This results in a large class of in-host models.
- In-host models have been applied to study viral persistence and clearance for HIV-1, HBV, HCV, HTLV-1, SIV-1, etc.
- In-host models can provide insights to medical researchers as to why some people can control viral replications and why others can not and develop diseases.
- For HIV, there are patients who have been infected for decades, and can control the HIV viral load in the body without having to take ART drugs. These patients are called "elite controllers". In-host models are being applied to understand their immune functions

In-Host Modeling and Background Knowledge

- As for any other biological modeling, to be able to model the viral infection and immune responses, one needs to acquire sufficient knowledge and general principles in virology and immunology.
- To understand the infection and immune response of a particular virus (or other types of pathogens, protozoa for Malaria, bacteria for TB, etc.), one can learn the most current medical understanding from the most recent medical review papers. Try not to learn biological background from mathematical modeling papers.
- The key for modeling is understand significant biological questions and challenges, in this case, medical questions and challenges.
- The modeling process begins with a translation of the key biological questions to mathematical questions. Then suitable models can be constructed.
- Always keep in mind that, a model is only good for the questions one wants to study.
- Always keep in mind what mathematics tells us about the biological questions we set out to understand.

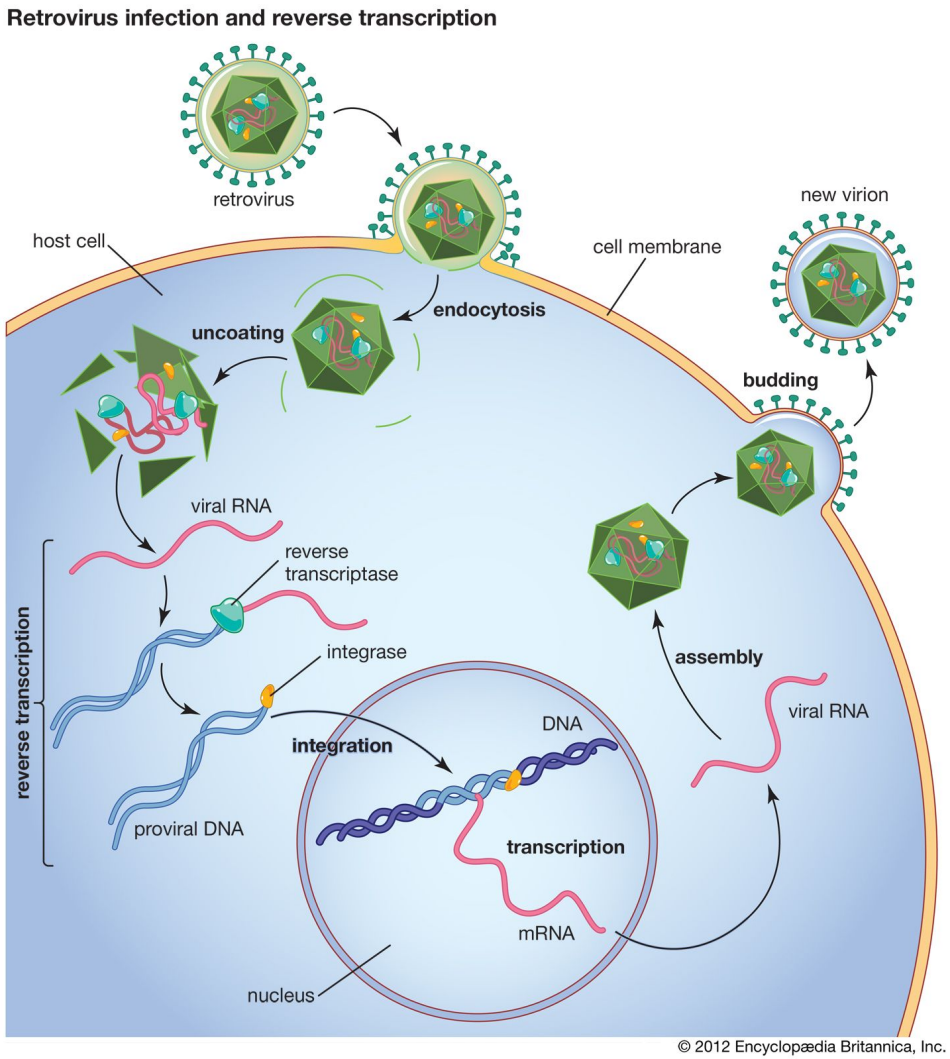
HTLV-1 Viruses and Associated Diseases

- HTLV-1 stands for Human T-cell Lymphotropic Virus type 1.
- It is the first oncogenic human (RNA) retrovirus to be discovered, when the Adult T-Cell Leukemia (ATL) were discovered and studied in 1977.
- Besides ATL, HTLV-1 also causes a type of chronic diseases on the spinal cord - HTLV-1 Associated Myelopathy (HAM), and tropical spastic paraparesis (TSP).
- Among individuals, HTLV-1 infection spreads from bodily fluids, and mother-to-child through breastfeeding.
- Most of the infected individuals remain asymptomatic (called asymptomatic carriers), only less than 5% of infected people develop diseases.
- Key medical questions are why some infected people develop disease while most don't, and what are the risk factors associated with the disease development.

Retroviruses and Their Replication Inside a Cell

Stages of infection:

- Cell entry
- Reverse Transcription
- Integration
- Transcription of viral RNA
- splicing, packaging and budding



Similarities and Differences Between HTLV-1 and HIV-1

- Both HTLV-1 and HIV-1 are retroviruses, namely, can replicate through reverse transcription
- They both preferentially infect the same type of T cells, $CD4^+$ helper T cells.
- Free HIV-1 viruses can infect T cells, while free HTLV-1 viruses are not viable to infect T cells
- Both HIV-1 and and HTLV-1 can be transmitted through cell-to-cell contact of infected T cells, the cell-to-cell contact transmission is the main route of transmission for the HTLV-1 virus
- HIV-1 is highly mutative, and HTLV-1 is genetically very stable.
- Quantity of HIV-1 viruses is measured by viral load (free viruses), and HTLV-1 is measured by proviral load (integrated viral DNA, called proviruses)
- Virologists have theoreticized that HTLV-1 viruses persist in the cell population through both horizontal cell-to-cell transmission and mother-to-daughter mitosis (cell divisions).
- Both HIV-1 and HTLV-1 infections face strong responses from all levels of the immune system.

Virus Cell-to-Cell Transmission via Virological Synapse

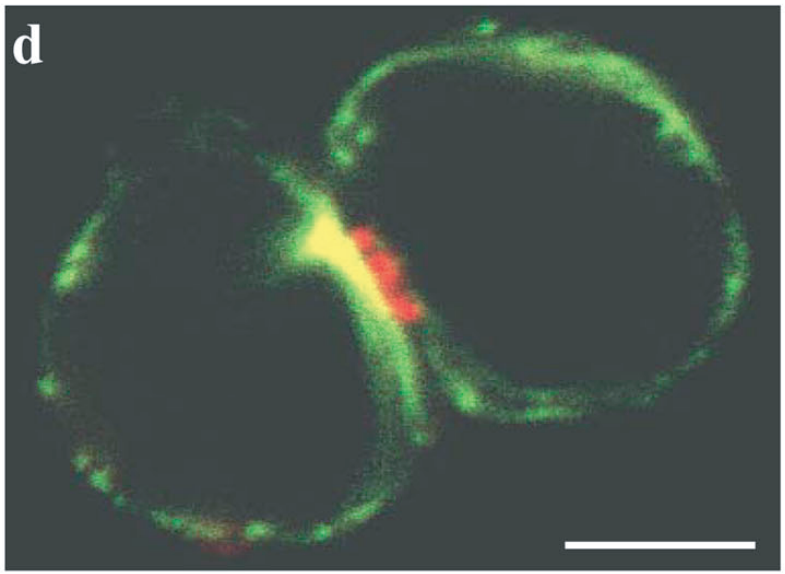


Figure: (a) HTLV-1 viral synapse

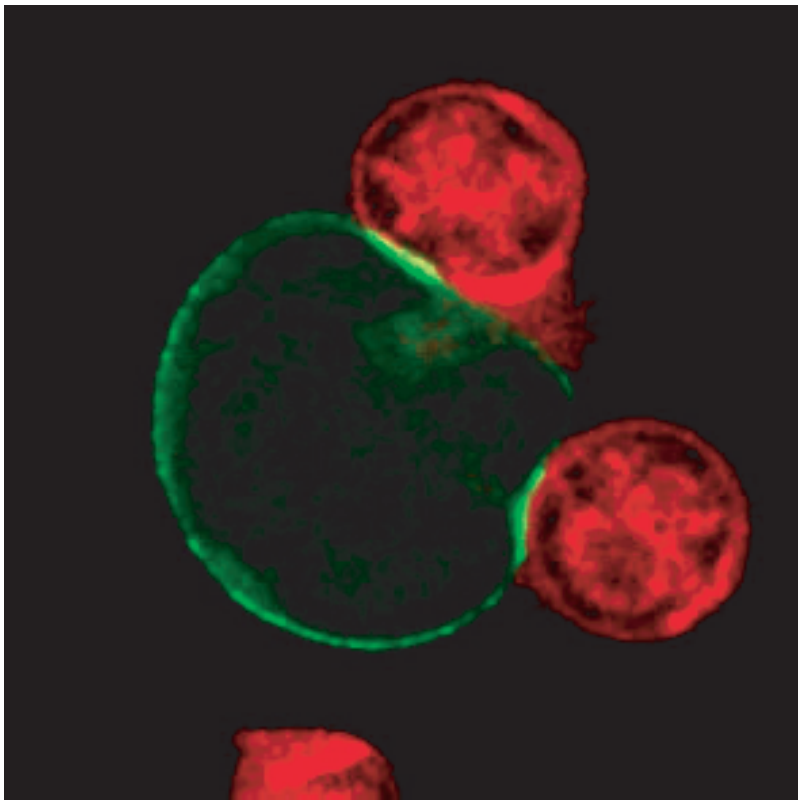


Figure: (b) HIV-1 viral synapse

Sources: (a) Igakura et al., Science 299 (2003),
(b) Hubner et al., Science, 323 (2009).

Part II: A Simple Model for HTLV-1

Mathematical Question: Can HTLV-1 maintain a stable population of infected cell through mitotic transmission?

Model Assumptions:

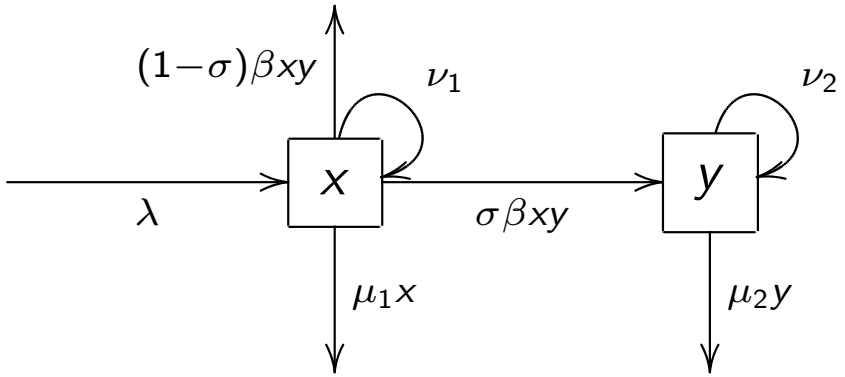
- The horizontal transmission is modelled by βxy, where x and y are healthy and infected T cells, respectively.
- T cells replicate (mitosis) is described by a logistic terms

$$\nu_1 x\left(1-\frac{x+y}{K}\right), \quad \text{and} \quad \nu_2 y\left(1-\frac{x+y}{K}\right)$$

  where K is the maximum number of $CD4^+$ T cells in the body, and ν_1 and ν_2 are replication rates for x and y, respectively.
- $CD4^+$ T cells are produced at a constant rate λ, and both x and y cells die at rates μ_1 and μ_2, respectively.
- Only a fraction $0 < \sigma < 1$ of newly infected cells survive the immune response.

Transfer Diagram and Equations

Transfer Diagram:



Equations:

$$\begin{aligned} x' &= \lambda + \nu_1 x\left(1 - \frac{x+y}{K}\right) - \mu_1 x - \beta xy, \\ y' &= \sigma\beta xy + \nu_2 y\left(1 - \frac{x+y}{K}\right) - \mu_2 y. \end{aligned} \tag{1}$$

Feasible Region

Adding the two equations and using $N = x + y$, we obtain

$$(x+y)' \leq \lambda + \nu(x+y)\left(1 - \frac{x+y}{K}\right) - \mu(x+y),$$

where $\nu = \max\{\nu_1, \nu_2\}$ and $\mu = \min\{\mu_1, \mu_2\}$. It follows that

$$\limsup_{t\to\infty}(x(t) + y(t)) \leq \overline{N},$$

where $N = \overline{N}$ is the positive root of the quadratic equation

$$\lambda + (\nu - \mu)N - \frac{\nu}{K}N^2 = 0.$$

A feasible region for (1) is

$$\Gamma = \{(x, y) \in \mathbb{R}^2_+ \mid x + y \leq \overline{N}\}, \tag{2}$$

which can be shown to be positively invariant with respect to (1).

Equilibria

An equilibrium (x, y) of model (1) satisfies

$$\begin{aligned} 0 &= \lambda + \nu_1 x \left(1 - \frac{x+y}{K}\right) - \mu_1 x - \beta xy \\ 0 &= \sigma\beta xy + \nu_2 y \left(1 - \frac{x+y}{K}\right) - \mu_2 y. \end{aligned} \tag{3}$$

The *infection-free equilibrium* $P_0 = (x_0, 0)$ exists for all parameter values, where $x_0 > 0$ is the positive root of the polynomial

$$f_1(x) = \lambda + (\nu_1 - \mu_1)x - \frac{\nu_1}{K}x^2. \tag{4}$$

A *chronic-infection equilibrium* $\overline{P} = (\overline{x}, \overline{y})$ satisfies (3) with $\overline{y} > 0$.

From the second equation of (3) we obtain

$$\overline{y} = \frac{K}{\nu_2}\left[(\sigma\beta - \frac{\nu_2}{K})\overline{x} + (\nu_2 - \mu_2)\right]. \tag{5}$$

Number of Positive Equilibria

From the previous slide, substituting (5) into the first equation of (3), we obtain an equation for $\overline{x}$:

$$f_1(\overline{x}) = f_2(\overline{x}), \tag{6}$$

where f_1 is defined in (4)

$$f_1(x) = \lambda + (\nu_1 - \mu_1)x - \frac{\nu_1}{K}x^2.$$

and

$$f_2(x) = \frac{1}{\nu_2}\left(\frac{\nu_1}{K} + \beta\right)\left[(\sigma K\beta - \nu_2)\, x + K(\nu_2 - \mu_2)\right] x. \tag{7}$$

We want to know if equation (6) can have more than one positive roots.

More Than One Positive Equilibria

- Equation (6) has more than two positive roots only if f_2 is concave down.
- This happens if and only if the following condition holds:

$$\sigma K \beta < \nu_2 \quad \text{and} \quad \mu_2 < \nu_2. \tag{8}$$

- The parameter range defined by (8) is biologically sound from the medical literature.

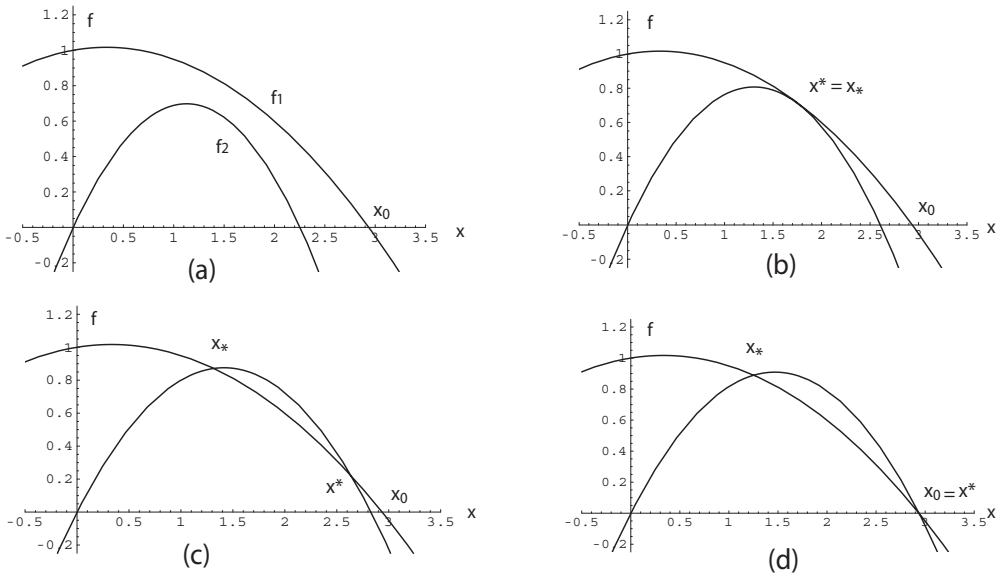


Figure: Graphical illustration of changes in the number of equilibria as σ is varied. (a) $0 < \sigma < \sigma_0$, (b) $\sigma = \sigma_0$, (c) $\sigma_0 < \sigma < \sigma_c$, and (d) $\sigma = \sigma_c$.

A Graphical Proof

To ensure that the graphs of f_1 and f_2 intersect, we require the following technical condition:

$$(\nu_1 + \beta K)^2 \left(1 - \frac{\mu_2}{\nu_2}\right)^2 > (\nu_1 - \mu_1)^2 + 4\lambda \frac{\nu_1}{K}, \tag{9}$$

which is derived from the condition $f_2'(x_0) > f_1'(x_0)$.

Define

$$\sigma_0 = \frac{4\lambda\beta\nu_2^2 - [(\nu_1 - \mu_1)\nu_2 - (\nu_1 + K\beta)(\nu_2 - \mu_2)]^2}{4\lambda\beta\nu_2(\nu_1 + K\beta)} \tag{10}$$

and

$$\sigma_c = \frac{\nu_2}{K\beta} - \frac{(\nu_2 - \mu_2)}{\beta x_0}. \tag{11}$$

How the Number of Equilibria Changes

As parameter σ varies, the number of chronic equilibria changes and the changes can be summarized in the following four cases (Figure 3):

(1) If $0 < \sigma < \sigma_0$, the graphs of f_1 and f_2 do not intersect and there is no chronic-infection equilibrium.

(2) If $\sigma = \sigma_0$, the graphs of f_1 and f_2 are tangent and there is a unique chronic-infection equilibrium.

(3) If $\sigma_0 < \sigma < \sigma_c$, there are two chronic-infection equilibria, $P_* = (x_*, y_*)$ and $P^* = (x^*, y^*)$, $x_* < x^*$. These are the two intersections of graphs of f_1 and f_2 in the first quadrant.

(4) If $\sigma \geq \sigma_c$ there is a unique chronic-infection equilibrium $P_* = (x_*, y_*)$ in the feasible region Γ. In this case, graphs of f_1 and f_2 have only one intersection in the first quadrant. The value σ_c is such that $x^* = x_0$. Also the condition (9) implies that $|f_1'(x_0)| < |f_2'(x_0)|$ when $\sigma = \sigma_c$, so that the graph of f_2 is above that of f_1 to the left of and close to x_0.

Summary of the Number of Equilibria

Theorem System (1) always has the infection-free equilibrium $P_0 = (x_0, 0)$. Assume that conditions (8) and (9) are satisfied. Then the number of chronic-infection equilibria is determined by σ. More specifically,

(1) If $0 < \sigma < \sigma_0$, there are no chronic-infection equilibria.

(2) If $\sigma = \sigma_0$, there is a unique chronic-infection equilibrium.

(3) If $\sigma_0 < \sigma < \sigma_c$, there are two chronic-infection equilibria P_* and P^*.

(4) If $\sigma \geq \sigma_c$, there is a unique chronic-infection equilibrium P_*.

Basic Reproduction Number and Backward Bifurcation

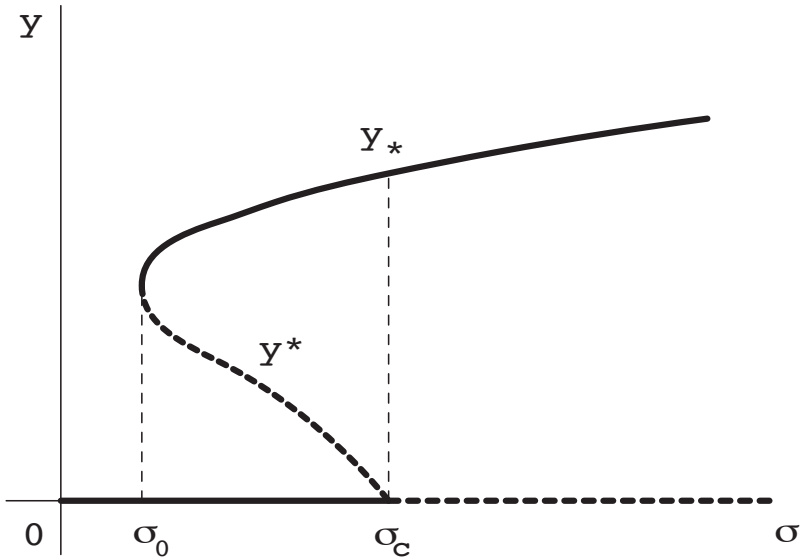
For model (1), the basic reproduction number $\mathcal{R}_0$ is:

$$\mathcal{R}_0 = \mathcal{R}_0(\sigma) = \frac{\sigma}{\mu_2}\beta x_0 + \frac{\nu_2}{\mu_2}\left(1 - \frac{x_0}{K}\right). \tag{12}$$

- We emphasize the dependence of $\mathcal{R}_0(\sigma)$ on the parameter σ.
- The first term in the brackets describes the per-unit-time secondary infections through cell-to-cell contact
- The second term those through mitotic division.
- From its definition, we see that $\mathcal{R}_0(\sigma)$ is increasing with σ.
- Furthermore, $\mathcal{R}_0(\sigma_c) = 1$ by (11) and (12).

The existence of two positive equilibria when $\mathcal{R}_0 < 1$ ($\sigma < \sigma_c$) leads to a different type of bifurcation diagram - backward bifurcation.

Bifurcation Diagram for Backward Bifurcation



Special features of a *backward bifurcation*:

- Multiple chronic-infection equilibria exist when $\mathcal{R}_0 < 1$.
- Multi-stability when $\mathcal{R}_0 < 1$: both P_0 and P^* are stable!
- Multi-stability implies that outcomes depend on initial conditions.
- Backward bifurcation indicates that the system can have catastrophic behaviours:

Comparison between Forward and Backward Bifurcations

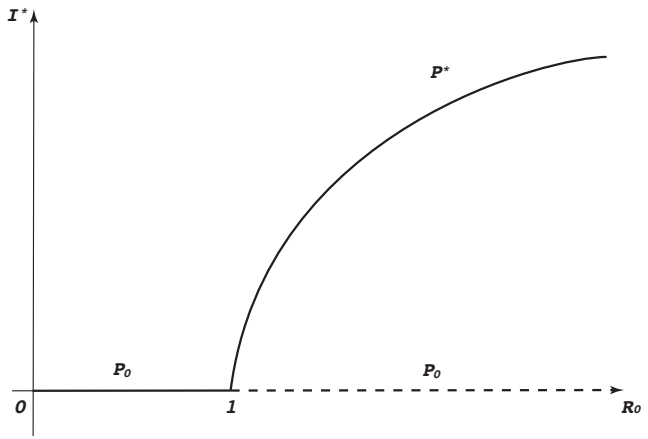


Figure: (a) Forward Bifurcation

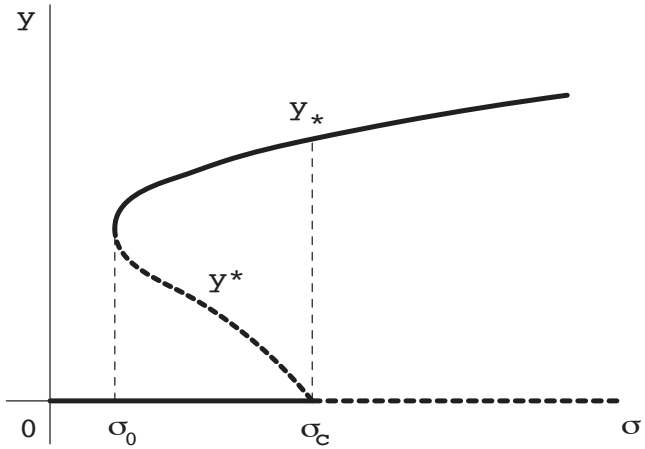
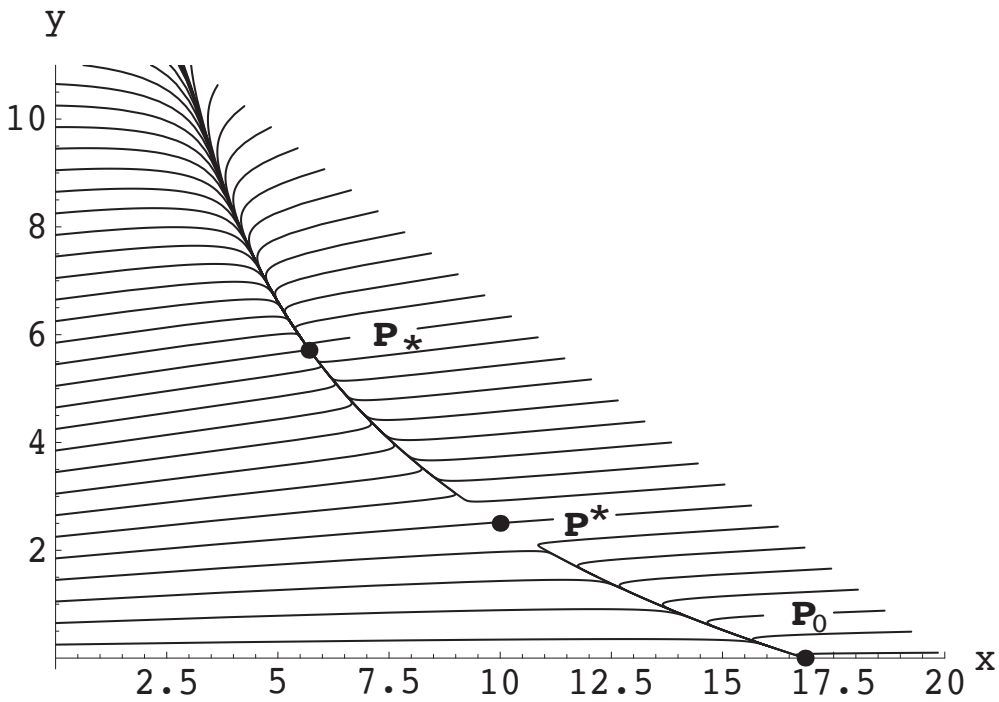


Figure: (b) Backward Bifurcation

(1) When $\mathcal{R}_0$ increases through 1, the number of infected cells has a sudden jump. This may result in a sudden explosion of the infected cell population.

(2) When $\mathcal{R}_0$ decreases through 1, the level of chronic-infection remains high. This makes the viral clearance by reducing $\mathcal{R}_0 < 1$ much more difficult.

Global Dynamics



To establish the global dynamics, we need to complete the following:

- Local stability of P_0 when $\mathcal{R}_0 < 1$. (standard)
- Local instability of P_* and stability of P^* when $\mathcal{R}_0 < 1$. (tricky)
- Local stability of P^* when $\mathcal{R}_0 > 1$ (standard)
- Global stability of P^* when $\mathcal{R}_0 > 1$. (Poincaré - Bendixson)

Part III: Proofs

1. **Local stability of the infection-free equilibrium** P_0. The infection-free equilibrium $P_0 = (x_0, 0)$ is locally asymptotically stable if $\mathcal{R}_0(\sigma) < 1$, and is unstable if $\mathcal{R}_0(\sigma) > 1$.

Proof. The Jacobian matrix of the model at $P_0 = (x_0, 0)$ is

$$J(P_0) = \begin{pmatrix} \nu_1\left(1 - \frac{x_0}{K}\right) - \frac{\nu_1 x_0}{K} - \mu_1 & -\frac{\nu_1 x_0}{K} - \beta x_0 \\ 0 & \mu_2(R_0(\sigma) - 1) \end{pmatrix}.$$

One of the eigenvalues is $\nu_1\left(1 - \frac{x_0}{K}\right) - \frac{\nu_1 x_0}{K} - \mu_1 = f_1'(x_0) < 0$, by (4) and the graph of f_1.

The other is $\mu_2(\mathcal{R}_0(\sigma) - 1)$, which has the same sign as $\mathcal{R}_0(\sigma) - 1$.

This establishes the result.

Part III: Proofs

2. **Stability of chronic-infection equilibria P_* and P^***

(1) If $\sigma_0 < \sigma < \sigma_c$, then P_* is locally asymptotically stable whereas P^* is a saddle.

(2) If $\sigma > \sigma_c$, then P_* is locally asymptotically stable.

Proof. The Jacobian matrix $J(\overline{P})$ of the model at a chronic-infection equilibrium $\overline{P} = (\overline{x}, \overline{y})$ is

$$\begin{pmatrix} \nu_1(1 - \frac{\overline{x}+\overline{y}}{K}) - \frac{\nu_1\overline{x}}{K} - \mu_1 - \beta\overline{y} & -\frac{\nu_1\overline{x}}{K} - \beta\overline{x} \\ (\sigma\beta - \frac{\nu_2}{K})\overline{y} & \sigma\beta\overline{x} + \nu_2(1 - \frac{\overline{x}+\overline{y}}{K}) - \frac{\nu_2\overline{y}}{K} - \mu_2 \end{pmatrix}.$$

By the equilibrium equation (3),

$$\begin{aligned} \operatorname{tr} J(\overline{P}) &= \nu_1\left(1 - \tfrac{\overline{x}+\overline{y}}{K}\right) - \tfrac{\nu_1\overline{x}}{K} - \mu_1 - \beta\overline{y} \\ &\quad + \sigma\beta\overline{x} + \nu_2\left(1 - \tfrac{\overline{x}+\overline{y}}{K}\right) - \tfrac{\nu_2\overline{y}}{K} - \mu_2 = -\tfrac{\lambda}{\overline{x}} - \tfrac{\nu_1\overline{x}}{K} - \tfrac{\nu_2\overline{y}}{K} < 0. \end{aligned}$$

Thus $\operatorname{tr} J(\overline{P}) < 0$ for both $\overline{P} = P_*$ and $\overline{P} = P^*$.
Why is one of them is stable and the other is unstable? The $\det J(\overline{P})$ must have a different sign.

Part III: Proofs

Using the definition of f_1 and f_2, respectively, we obtain

$$\begin{aligned}
\det J(\overline{P}) &= \left(f_1'(\overline{x}) - \left(\tfrac{\nu_1}{K} + \beta\right)\overline{y}\right)\left(-\tfrac{\nu_2 \overline{y}}{K}\right) + \left(\tfrac{\nu_1}{K} + \beta\right)\left(\sigma\beta - \tfrac{\nu_2}{K}\right)\overline{xy} \\
&= \overline{y}\left[-\tfrac{\nu_2}{K} f_1(\overline{x}) + \tfrac{\nu_2}{K}\left(\tfrac{\nu_1}{K} + \beta\right)\overline{y} + \left(\tfrac{\nu_1}{K} + \beta\right)\left(\sigma\beta - \tfrac{\nu_2}{K}\right)\overline{x}\right] \\
&= \overline{y}\left[\tfrac{\nu_2}{K} f_1'(\overline{x}) + \left(\tfrac{\nu_1}{K} + \beta\right)(\nu_2 - \mu_2) + 2\left(\tfrac{\nu_1}{K} + \beta\right)\left(\sigma\beta - \tfrac{\nu_2}{K}\right)\overline{x}\right] \\
&= \overline{y}\tfrac{\nu_2}{K}\left(f_2'(\overline{x}) - f_1'(\overline{x})\right).
\end{aligned}$$

Note that $f_2'(x) - f_1'(x) > 0$ when $x = x_*$ and $f_2'(x) - f_1'(x) < 0$ when $x = x^*$. We know that P_* is locally asymptotically stable whenever it exists, and P^* is a saddle whenever it exists. This establishes the stability results.

Part III: Proofs

We try to establish the following:

Theorem

Assume that conditions (8) *and* (9) *are satisfied. Then*

(1) *When* $0 < \mathcal{R}_0 < \mathcal{R}_0(\sigma_0)$, *the infection-free equilibrium* P_0 *is globally asymptotically stable in* $\overline{\Gamma}$;

(2) *When* $R_0(\sigma_0) < \mathcal{R}_0 < 1$, *system* (1) *has two attractors in* $\overline{\Gamma}$, *the infection-free equilibrium* P_0 *and the chronic-infection* P_*. *Their basins of attraction in* $\overset{\circ}{\Gamma}$ *are separated by the stable manifolds of the saddle point* P^*;

(3) *When* $\mathcal{R}_0 > 1$, *the unique chronic-infection equilibrium* P_* *is globally asymptotically stable in* $\overset{\circ}{\Gamma}$.

Proof. We first rule out periodic orbits in $\overset{\circ}{\Gamma}$ using Dulac's criteria (Corollary **??** in Chapter 3). We choose a Dulac multiplier $\alpha(x, y) = 1/xy$. Let $(P(x, y), Q(x, y))$ denote the right-hand-side of (1). We have

$$\frac{\partial(\alpha P)}{\partial x} + \frac{\partial(\alpha Q)}{\partial y} = -\left(\frac{\lambda}{x^2 y} + \frac{\nu_1}{Ky} + \frac{\nu_2}{Kx}\right) < 0,$$