

الجمهورية الجزائرية الديمقراطية الشعبية
République algérienne démocratique et populaire
وزارة التعليم العالي والبحث العلمي
Ministère de l'enseignement supérieur et de la recherche scientifique
جامعة عين تموشنت بلحاج بوشعيب
Université –Ain Temouchent- Belhadj Bouchaib
Faculté des Sciences et de Technologie
Département de Mathématiques et Informatique



Projet de Fin d'Etudes
Pour l'obtention du diplôme de Master en : Mathématiques

Domaine : Mathématiques et Informatique
Filière : Mathématiques
Spécialité : Biomathématique

Thème

**Global Dynamics of a Nonlocal Delayed Viral Infection Model in
Heterogeneous Environments**

Présenté Par :

M BELHADRI Mohammed Abdelmalek

Devant le jury composé de :

Dr BOUKHARI Boumediene	MCB	UAT.B.B (Ain Temouchent)	Président
Dr GAOUAR Soumia	MCB	UAT.B.B (Ain Temouchent)	Examineur
Dr BENTOUT Soufiane	MCA	UAT.B.B (Ain Temouchent)	Encadrant

Année Universitaire 2025/2026

Remerciements

*En premier lieu, nous remercions **Allah** le Tout-Puissant de nous avoir accordé la santé, la volonté et le courage nécessaires pour accomplir ce travail.*

*Nous tenons à exprimer notre profonde gratitude à notre directeur de mémoire, **DR. BENTOUT**, pour sa disponibilité, ses précieux conseils et sa rigueur scientifique tout au long de l'élaboration de ce travail.*

*Nous remercions **DR. BOUKHARI**, président du jury, d'avoir accepté de présider cette soutenance et de lui consacrer son temps et son expertise.*

*Nos sincères remerciements vont également à **DR. GAOUAR**, examinateur, pour avoir accepté d'évaluer ce travail et pour l'intérêt qu'il lui a porté.*

*Je remercie également au fond de mon cœur **Mr HAMMOUDI.A** pour ces précieux conseils et pour son aide continue.*

J'adresse mes chaleureux remerciements à tous les enseignants du département de mathématiques qui m'ont accompagnés et aidés à m'améliorer durant mon cursus de formation.

Dédicaces

Je dédie ce modeste travail...

*À mes très chers parents,
pour leur amour inconditionnel, leur soutien
et leurs sacrifices tout au long de ma vie.
Aucune dédicace ne saurait exprimer
ma profonde gratitude envers vous.*

*À mon cher frère,
Belhadri Younes,
pour sa présence et ses encouragements.*

*À mes chers amis,
**Anes Benabi, Nemiche Nasro,
Bakhti Manel et Said,**
pour tous les moments partagés
et leur soutien indéfectible.*

À tous ceux qui me sont chers.

Abstract

This work is devoted to the mathematical analysis of within-host viral infection dynamics, with particular emphasis on the hepatitis B virus. We first review three classical models that progressively incorporate spatial structure: the foundational ODE model of Nowak *et al* [23], the local diffusion model of Wang and Wang [29], and the nonlocal dispersal framework of Wang *et al* [30]. We then conduct a rigorous study of the spatially heterogeneous model proposed by Liu *et al* [17], which simultaneously incorporates nonlocal diffusion of free virions governed by a probability kernel J , an intracellular delay $\tau > 0$ reflecting the latency between viral entry and viral production, and position-dependent biological parameters. The analysis is carried out in an infinite-dimensional functional framework. We establish the global well-posedness and positivity of solutions via semigroup theory and the Banach fixed point theorem, and prove that the semiflow is bounded dissipative. Asymptotic smoothness of the semiflow and the existence of a compact global attractor are obtained through a Kuratowski measure argument. Finally, the global asymptotic stability of the infection-free steady state P_0 is established when $\mathcal{R}_0 \leq 1$, via an explicit Lyapunov functional whose integral kernel is the positive eigenfunction of the linearised problem around P_0 .

Keywords: Viral infection model, nonlocal diffusion, intracellular delay, spatial heterogeneity, semigroup theory, Lyapunov functional, basic reproduction number, global asymptotic stability.

Résumé

Ce travail est consacré à l'analyse mathématique de la dynamique de l'infection virale intra-hôte — c'est-à-dire la réplication et la propagation du virus à l'échelle d'un seul organisme infecté — avec un intérêt particulier pour le virus de l'hépatite. Nous étudions d'abord trois modèles classiques qui incorporent progressivement la structure spatiale : le modèle fondateur en équations différentielles ordinaires de Nowak et al [23], le modèle à diffusion locale de Wang *et al* [29], et le cadre à dispersion non locale de Wang *et al* [30]. Nous conduisons ensuite une étude rigoureuse du modèle spatialement hétérogène proposé par Liu *et al* [17], qui intègre simultanément la diffusion non locale des virions libres via un noyau de probabilité J , un délai intracellulaire $\tau > 0$ traduisant la latence entre l'entrée du virus et le début de la production virale, et des paramètres biologiques dépendant de la position spatiale. L'analyse est menée dans un cadre fonctionnel de dimension infinie. Nous établissons le bon positionnement global et la positivité des solutions via la théorie des semi-groupes et le théorème du point fixe de Banach, et montrons que le semi-flot est dissipatif borné. La régularité asymptotique du semi-flot et l'existence d'un attracteur global compact sont obtenues par un argument de mesure de Kuratowski. Enfin, la stabilité asymptotique globale de l'état d'équilibre sans infection P_0 est établie lorsque $\mathcal{R}_0 \leq 1$, via une fonctionnelle de Lyapunov explicite dont le noyau intégral est la fonction propre positive du problème linéarisé autour de P_0 .

Mots-clés : Modèle d'infection virale, diffusion non locale, délai intracellulaire, hétérogénéité spatiale, théorie des semi-groupes, fonctionnelle de Lyapunov, nombre de reproduction de base, stabilité asymptotique globale.

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Glossary of Terms

- **HBV (Hepatitis B Virus):** A DNA virus that infects liver cells (hepatocytes), causing acute and chronic hepatitis. HBV replication involves reverse transcription of pregenomic RNA into viral DNA by the viral polymerase [23].
- **Lamivudine:** A nucleoside analogue reverse transcriptase inhibitor used in the treatment of chronic hepatitis B. It blocks the HBV DNA polymerase, thereby inhibiting viral replication [23].
- **Nucleoside Analogue:** A synthetic compound that mimics natural nucleosides and competitively inhibits viral polymerases or reverse transcriptases, preventing viral genome replication [23].
- **Viral Polymerase:** An enzyme encoded by HBV that catalyses the reverse transcription of pregenomic RNA into viral DNA. Lamivudine inhibits this enzyme, blocking viral replication [23].
- **Inhibitor:** A substance that blocks or suppresses the activity of a specific enzyme or biological process. Lamivudine acts as a reverse transcriptase inhibitor, preventing HBV DNA polymerase from synthesising viral DNA [23].
- **Hepatocytes (Liver Cells):** The primary functional cells of the liver, representing the target cell compartment $T(t, x)$ in the model. Hepatocytes are typically immobile under normal conditions [29].
- **Sessile:** Describes cells that are permanently attached to a substrate and do not move. In the liver, hepatocytes (target cells T and infected cells I) are sessile, meaning only free virions V are capable of spatial movement [29].
- **Inflow/Outflow:** In compartmental models, *inflow* denotes the rate at which individuals or particles enter a given compartment (e.g., production of new target cells), while *outflow* denotes the rate at which they leave (e.g., death, infection, or recovery) [5].
- **Mixed Cells (Well-Mixed):** In the classical ODE framework, the assumption that target cells, infected cells, and free virions are uniformly distributed and instantly

accessible to one another, corresponding to a spatially homogeneous environment [23].

- **Intracellular Delay τ :** The latency period between viral entry into a target cell and the onset of viral production by that cell. This delay reflects the time required for viral replication and assembly within the host cell [17].
- **Heterogeneous (Spatially Heterogeneous):** Refers to biological parameters (e.g., cell production rate, death rate, infection rate) that vary with spatial position, reflecting the non-uniform structure of liver tissue [17].
- **Inhomogeneous:** Synonymous with *heterogeneous*, describes systems where properties vary with spatial position, as opposed to spatially uniform (homogeneous) systems [17].
- **Interstitial Fluid:** The fluid that surrounds cells within tissues, allowing the transport of nutrients, waste products, and free virions between different regions of the liver [21].
- **Random Motion:** The irregular, non-directed movement of particles (such as free virions) resulting from thermal agitation and collisions with surrounding molecules. This underlies both Fickian diffusion and nonlocal dispersal mechanisms [21].
- **Basic Reproduction Number ($\mathcal{R}_0$):** Biologically, the average number of secondary infections produced by a single infected cell during its entire infectious period, when introduced into a completely susceptible compartment. When $\mathcal{R}_0 \leq 1$, the infection dies out, when $\mathcal{R}_0 > 1$, the infection can persist [5, 17].
- **Threshold:** A critical value of a parameter (typically $\mathcal{R}_0$) that determines a qualitative change in the dynamical behaviour of the system, such as the transition from disease extinction to persistence [5].
- **Infection-Free Steady State P_0 :** The equilibrium state of the system where the infection has been eradicated, characterised by the absence of infected cells and free virions, with target cells at their natural carrying capacity [17].
- **Endemic Equilibrium:** A steady state where infected compartments are strictly positive, representing persistent viral infection in the host [23].
- **Disease-Free Equilibrium (DFE):** A steady state where all infected compartments vanish, representing the absence of infection in the population [5].
- **Travelling Wave:** A solution propagating with constant speed without changing shape, representing the spatial spread of infection through liver tissue as a moving front [22].

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- **Fickian Diffusion:** Local spatial movement of free virions described by the Laplacian operator, where particles move gradually from regions of high concentration to low concentration through neighbouring tissue, following Fick’s law [29].
 - **Nonlocal Dispersal:** A spatial movement mechanism where free virions can jump directly to distant positions within the tissue, governed by a probability kernel, allowing long-range transport through blood sinusoids or interstitial fluid rather than gradual local diffusion [30].
 - **Semiflow:** In contrast to a flow (where time can move both forward and backward), a semiflow describes evolution only for forward time. In viral infection dynamics, the presence of the intracellular delay $\tau > 0$ means that the system remembers the past but cannot anticipate the future, this irreversibility makes the semiflow framework the natural mathematical setting [27].
 - **In vivo:** A Latin term meaning “within the living”. It refers to biological processes occurring inside a living organism, as opposed to *in vitro* experiments performed outside the organism under laboratory conditions [23].
 - **Half-life:** The time required for the concentration of a biological entity — such as free virions or infected cells — to decrease by half its initial value. In the context of HBV infection, Nowak et al. estimated the half-life of free virions to be approximately one day, and that of infected hepatocytes to range from ten to one hundred days [23].

Introduction

Viral infectious diseases remain among the most significant challenges in modern medicine, owing to their long infectious periods, complex replication mechanisms, and capacity for long-term persistence within the host despite antiviral intervention. To investigate the mechanisms and dynamical behaviours of the viral infection process *in vivo*, mathematical modelling has emerged as a powerful and indispensable tool, capable of complementing clinical observation by providing rigorous quantitative predictions on the course of infection and the effectiveness of treatment.

The first within-host model, introduced by Nowak *et al* in 1996 [23], describes the interactions among three compartments, uninfected target cells, infected cells, and free virions, through a system of ordinary differential equations. Despite its simplicity, this model successfully fit clinical data from patients treated with lamivudine and yielded fundamental estimates of viral dynamics in hepatitis B virus (HBV) infection, including a viral half-life of approximately one day and an infected cell half-life ranging from ten to one hundred days [23]. Its mathematical simplicity and biological relevance made it the point of departure for an extensive later literature.

A central feature of viral infection that the original model does not capture is the spatial structure of the host tissue. In reality, the liver is a spatially organised organ, hepatocytes occupy fixed positions within a complex lobular architecture, and free virions must physically travel through the interstitial fluid to reach susceptible cells [29]. Wang *et al* [29] addressed this limitation by adding Fickian diffusion for the virus compartment, described by the Laplacian operator, and demonstrated the existence of travelling infection waves with a well-defined minimum speed. This spatial extension was later extended by Wang *et al* [30], who replaced local diffusion by a nonlocal dispersal operator governed by a kernel J , allowing virions to jump directly to distant positions, a mechanism more true to the physics of viral transport in tissue than the purely local diffusion approximation.

Two further biological realities motivate the model studied in this work. First, after a virion enters a target cell, a latency period of duration $\tau > 0$ passes before the cell begins producing new virions. This intracellular delay has been shown to reduce the chronic

viral load and to rule out sustained oscillations in within-host models. Second, biological parameters such as the cell production rate, the death rate, and the infection rate are not uniform throughout liver tissue but depend on the spatial position x , reflecting the real heterogeneity of the organ [17].

This work studies the model proposed by Liu *et al* [17], which combines the principal biological mechanisms discussed above, the classical within-host infection dynamics, nonlocal diffusion of free virions, intracellular delay, and spatial heterogeneity of parameters. The resulting model is a system of nonlocal delay integro-differential equations, whose rigorous analysis requires tools from semigroup theory, spectral theory for nonlocal operators, the theory of infinite-dimensional dynamical systems, and the construction of Lyapunov functionals adapted to the spatially heterogeneous setting.

The dissertation is organised as follows:

- **Chapter 1** collects the mathematical preliminaries required for the analysis, including the theory of C_0 -semigroups, Fréchet differentiability, the Kuratowski measure of noncompactness, and the relevant stability notions.
- **Chapter 2** presents the classical models that motivate and explain the main study, the original ODE model of Nowak *et al* [23], its extension with local diffusion by Wang *et al*, and the nonlocal dispersal framework of Wang, Li and Sun.
- **Chapter 3** is focused on the analysis of the spatially heterogeneous viral infection model with intracellular delay and nonlocal diffusion proposed by Liu, Xu and Jin [17]. This model incorporates nonlocal diffusion of free virions through a kernel J , allowing virions to interact across distant spatial locations, which local diffusion cannot capture, together with intracellular delay $\tau > 0$ and spatially heterogeneous parameters. The main results established are: global well-posedness, positivity, and dissipativity of the system (Section 3.2), asymptotic smoothness and existence of a compact global attractor (Section 3.3), and global threshold dynamics governed by the basic reproduction number $\mathcal{R}_0$ (Section 3.4). More precisely, the infection-free steady state P_0 is shown to be globally asymptotically stable when $\mathcal{R}_0 \leq 1$.

Chapter 1

Preliminaries

In this chapter, we present the basic mathematical tools that will be used in the rest of this dissertation. These tools are important for understanding the models and the results that will be discussed later.

1.1 Differential Equations

Definition 1.1.1: Ordinary Differential Equation

An ordinary differential equation (ODE) is an equation with a function and its derivatives. The function has one variable (often time t). A system of ODEs looks like this:

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}), \quad \mathbf{x} \in \Omega \subset \mathbb{R}^n, \quad (1.1)$$

where:

- $\mathbf{x}(t) \in \Omega$ is the state vector,
- $\mathbf{f} : \Omega \rightarrow \mathbb{R}^n$ is a function with continuous derivatives,
- Ω is an open set in $\mathbb{R}^n$.

ODEs show how the state changes with time. In this work, we study autonomous systems. In these systems, $\mathbf{f}$ does not use t directly.

1.2 Cauchy–Lipschitz Theorem (Picard–Lindelöf)

Consider the initial value problem:

$$\begin{cases} \frac{d\mathbf{x}}{dt} = \mathbf{f}(t, \mathbf{x}), \\ \mathbf{x}(t_0) = \mathbf{x}_0, \end{cases} \quad (1.2)$$

where $D \subset \mathbb{R} \times \mathbb{R}^n$ is an open domain containing $(t_0, \mathbf{x}_0)$, and $\mathbf{f} : D \rightarrow \mathbb{R}^n$ is a vector field.

Definition 1.2.1: Lipschitz Condition [25]

Let $\mathbf{f} : D \subset \mathbb{R} \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ and $S \subset D$.

1. **Locally Lipschitz in $\mathbf{x}$:** For every compact $K \subset D$, there exists $L_K > 0$ such that

$$\|\mathbf{f}(t, \mathbf{x}_1) - \mathbf{f}(t, \mathbf{x}_2)\| \leq L_K \|\mathbf{x}_1 - \mathbf{x}_2\|$$

for all $(t, \mathbf{x}_1), (t, \mathbf{x}_2) \in K$. The constant L_K may depend on K .

2. **Uniformly Lipschitz in $\mathbf{x}$ on S :** There exists $L > 0$ such that

$$\|\mathbf{f}(t, \mathbf{x}_1) - \mathbf{f}(t, \mathbf{x}_2)\| \leq L \|\mathbf{x}_1 - \mathbf{x}_2\|$$

for all $(t, \mathbf{x}_1), (t, \mathbf{x}_2) \in S$. The constant L is **independent of t** .

3. **Globally Lipschitz in $\mathbf{x}$:** The function is uniformly Lipschitz on all of D with the same constant L .

Theorem 1.2.1: Local Existence and Uniqueness [4, 25]

Let $\mathbf{f} : D \rightarrow \mathbb{R}^n$ satisfy:

1. **Continuity:** $\mathbf{f}$ is continuous on D ,
2. **Local Lipschitz condition:** $\mathbf{f}$ is locally Lipschitz in $\mathbf{x}$ on D .

Then there exists $\delta > 0$ such that the IVP (1.2) has a unique solution $\mathbf{x}(t)$ defined on the interval $[t_0 - \delta, t_0 + \delta]$.

Theorem 1.2.2: Global Existence and Uniqueness [3]

If $\mathbf{f}$ is continuous on D and **globally Lipschitz in $\mathbf{x}$** on D , then the unique solution exists on the entire interval of definition of $\mathbf{f}$.

Theorem 1.2.3: Existence without Uniqueness [11]

If $\mathbf{f}$ is continuous on D (without any Lipschitz condition), then there exists at least one solution to the initial value problem (1.2) on some interval $[t_0 - \delta, t_0 + \delta]$. However, this solution may not be unique.

Remark 1.2.1. • If $\mathbf{f}$ is only continuous: solution exists but may not be unique.

- If $\mathbf{f}$ is globally Lipschitz: solution exists for all time.

1.3 Equilibrium Points

Definition 1.3.1: Equilibrium Point [13]

An equilibrium point of system (1.1) is a point $\mathbf{x}^*$ where

$$\mathbf{f}(\mathbf{x}^*) = \mathbf{0}.$$

At this point, the system does not change: $\frac{d\mathbf{x}}{dt} = \mathbf{0}$.

To find equilibrium points, we solve the algebraic system:

$$\mathbf{f}(\mathbf{x}) = \mathbf{0}.$$

This gives the long-term behaviour of the system. In general, epidemiological models admit two types of equilibria:

- **Disease-free equilibrium (DFE):** all infected variables are zero.
- **Endemic equilibrium (EE):** infected variables are positive, representing persistent infection.

Definition 1.3.2: Jacobian Matrix [25]

The Jacobian matrix of $\mathbf{f}$ at point $\mathbf{x}$ is the matrix of all first-order partial derivatives:

$$J(\mathbf{x}) = \frac{\partial \mathbf{f}}{\partial \mathbf{x}} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \dots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \dots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}.$$

This matrix gives the linear approximation of $\mathbf{f}$ near $\mathbf{x}$.

1.4 Spectral Theory and Positive Matrices

Definition 1.4.1: Irreducible Matrix [12]

A nonnegative matrix $A \in \mathbb{R}^{n \times n}$ is called **irreducible** if no permutation of rows and columns can reduce it to block upper-triangular form. Equivalently, for every pair (i, j) , there exists $k \in \mathbb{N}$ such that $(A^k)_{ij} > 0$.

Remark 1.4.1. *In epidemiological models, irreducibility means every compartment can affect every other compartment through some path.*

Definition 1.4.2: Spectral Radius [12]

Let $A \in \mathbb{R}^{n \times n}$ be a square matrix with eigenvalues $\lambda_1, \lambda_2, \dots, \lambda_n$. The **spectral radius** of A , denoted by $\rho(A)$, is the largest absolute value of its eigenvalues:

$$\rho(A) = \max_{1 \leq i \leq n} |\lambda_i| = \max\{|\lambda| : \lambda \text{ is an eigenvalue of } A\}.$$

Definition 1.4.3: Spectral Bound [28]

Let $A \in \mathbb{R}^{n \times n}$ be a square matrix with spectrum $\sigma(A)$. The **spectral bound** of A , denoted by $s(A)$, is defined as the largest real part of an eigenvalue of A :

$$s(A) = \sup\{\Re \lambda : \lambda \in \sigma(A)\}. \quad (1.3)$$

The spectral bound plays a fundamental role in the stability analysis of differential equations, as the sign of $s(A)$ determines the asymptotic growth or decay of solutions generated by A .

Definition 1.4.4: Connected Set [20]

A subset $S \subset \mathbb{R}^n$ is said to be **connected** if there do not exist two non-empty open sets $U_1, U_2 \subset \mathbb{R}^n$ such that:

1. $S \subset U_1 \cup U_2$,
2. $U_1 \cap U_2 = \emptyset$,
3. $S \cap U_1 \neq \emptyset$ and $S \cap U_2 \neq \emptyset$.

Equivalently, S is connected if it cannot be partitioned into two non-empty disjoint open subsets.

Theorem 1.4.1: Perron–Frobenius [12]

Let $A \in \mathbb{R}^{n \times n}$ be an irreducible nonnegative matrix. Then:

1. **(Existence of Perron root)** A has a real positive eigenvalue $\lambda_{\max} = \rho(A) > 0$, called the **Perron root**.
2. **(Simplicity)** The Perron root is algebraically and geometrically simple: $\text{mult}(\lambda_{\max}) = 1$.

3. (**Positive eigenvector**) There exists an eigenvector $\mathbf{v} > \mathbf{0}$ (strictly positive entries) such that $A\mathbf{v} = \rho(A)\mathbf{v}$.
4. (**Collatz-Wielandt formula**) The Perron root satisfies:

$$\rho(A) = \max_{\mathbf{x} \geq \mathbf{0}, \mathbf{x} \neq \mathbf{0}} \min_{x_i > 0} \frac{(A\mathbf{x})_i}{x_i}.$$

5. (**Monotonicity**) If $A \leq B$ (entrywise) with $A \neq B$, then $\rho(A) < \rho(B)$.

Remark 1.4.2. This result is important for epidemiological models. The spectral radius of the **Next-Generation Matrix** K in Section (1.6) is always a positive real number. So $\mathcal{R}_0 = \rho(K)$ is a useful threshold parameter.

1.5 Reproduction Number in Epidemiology

Definition 1.5.1: The Basic Reproduction Number $\mathcal{R}_0$

The basic reproduction number, denoted $\mathcal{R}_0$, is a central concept in epidemiology. Biologically, it represents the average number of secondary infections produced by a single infected individual during their entire infectious period, when introduced into a completely susceptible compartment.

In general, the value of $\mathcal{R}_0$ determines the dynamics of an infection:

- If $\mathcal{R}_0 < 1$, the infection dies out.
- If $\mathcal{R}_0 > 1$, the infection can establish itself and persist.

A rigorous method to compute $\mathcal{R}_0$ for compartmental models is presented in the next section (1.6).

1.6 The Next-Generation Matrix Method

Definition 1.6.1: Next-Generation Matrix [5]

Consider a model with n compartments, of which m are **infected compartments** (i.e., compartments containing infected individuals or pathogens). Write the equations for these infected variables as

$$\frac{d\mathbf{x}}{dt} = \mathcal{F}(\mathbf{x}) - \mathcal{V}(\mathbf{x}),$$

where:

- $\mathcal{F}(\mathbf{x})$ is the vector of rates of **new infections** appearing in each infected compartment,
- $\mathcal{V}(\mathbf{x})$ is the vector of rates of **transfer out** of each infected compartment (due to death, recovery, etc.), with all terms in $\mathcal{V}$ being non-negative and representing outflow.

Let F and $\mathbb{V}$ be the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$, respectively, evaluated at the disease-free equilibrium (DFE). Then the **Next-Generation Matrix** is defined as

$$K = F\mathbb{V}^{-1}.$$

Theorem 1.6.1: Computation of $\mathcal{R}_0$ [5]

The basic reproduction number $\mathcal{R}_0$ is given by the **spectral radius** (largest absolute eigenvalue) of the **Next-Generation Matrix** K :

$$\mathcal{R}_0 = \rho(K) = \max\{|\lambda| : \lambda \text{ is an eigenvalue of } K\}.$$

1.7 Traveling Waves and Spread Dynamics

Definition 1.7.1: Traveling Wave [22]

A **traveling wave** is a solution that moves with constant speed without changing its shape. Mathematically, it has the form:

$$u(t, x) = U(x - ct) \quad \text{or} \quad u(t, x) = U(x + ct),$$

where $c > 0$ is the wave speed and U is the wave profile.

This representation transforms the PDE into an ODE. In the phase space:

- A **wave front** is a heteroclinic orbit linking two steady states,
- A **pulse** is a homoclinic orbit returning to the same equilibrium.

Remark 1.7.1 (Existence of Traveling Waves [22]). Consider an epidemiological model with basic reproduction number $\mathcal{R}_0 > 1$. Then there exists a minimal wave speed $c^* > 0$ such that:

1. For all $c \geq c^*$, traveling wave solutions exist,

2. For $c < c^*$, no non-negative traveling wave solutions exist.

This shows that disease spread has a minimum wave speed when $\mathcal{R}_0 > 1$. The infection cannot propagate slower than c^* . Importantly, the epidemic can be controlled by c^* and $\mathcal{R}_0$. Indeed, if $\mathcal{R}_0 \leq 1$, the disease dies out and no traveling wave exists.

To illustrate this result, consider the classical reaction-diffusion SIR model

$$\begin{cases} \frac{\partial S}{\partial t} = d_1 \frac{\partial^2 S}{\partial x^2} - \beta SI, \\ \frac{\partial I}{\partial t} = d_2 \frac{\partial^2 I}{\partial x^2} + \beta SI - \gamma I, \\ \frac{\partial R}{\partial t} = d_3 \frac{\partial^2 R}{\partial x^2} + \gamma I, \end{cases} \quad (1.4)$$

where $S(x, t)$, $I(x, t)$, and $R(x, t)$ denote the densities of susceptible, infected, and recovered individuals at position x and time t , respectively, $d_1, d_2, d_3 > 0$ are diffusion coefficients, $\beta > 0$ is the transmission rate, and $\gamma > 0$ is the recovery rate. For this system, the basic reproduction number is $\mathcal{R}_0 = \beta S_0 / \gamma$, with S_0 the initial density of susceptible individuals. Traveling wave solutions of the form $(S(x - ct), I(x - ct))$ connecting the disease-free equilibrium $(S_0, 0)$ to an endemic state have been widely studied. It is known that, if $\mathcal{R}_0 > 1$, there exists a minimum wave speed $c^* = 2\sqrt{d_2(\beta S_0 - \gamma)}$ such that non-negative traveling waves exist precisely for every $c \geq c^*$, whereas no such wave exists for $c < c^*$. Conversely, if $\mathcal{R}_0 \leq 1$, the disease cannot propagate via traveling waves and the infection dies out, which is in full agreement with the theorem above.

1.8 Limit Cycles and Bendixson–Poincaré Theorem

The Poincaré–Bendixson theory describes the long-term behavior of solutions in two dimensions. It limits the possible dynamics to three cases.

Definition 1.8.1: Limit Cycle [25]

A **limit cycle** is an isolated periodic orbit. Nearby trajectories approach it or leave it as $t \rightarrow \infty$.

Theorem 1.8.1: Poincaré–Bendixson [25]

Consider a system $\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x})$ in $\mathbb{R}^2$. Let R be a bounded region with no equilibria on its boundary. If a trajectory enters R and stays in R , then one of the following holds:

1. The trajectory approaches a stable equilibrium,

2. The trajectory approaches a heteroclinic (linking two steady states) or homoclinic (returning to one steady state) orbit,
3. The trajectory approaches a limit cycle.

Remark 1.8.1. This theorem applies only to continuous systems in $\mathbb{R}^2$. It excludes chaos and ensures that oscillations in epidemiological models are periodic, not irregular.

1.9 Notions of Stability and Equilibrium Points

Consider the autonomous system

$$\frac{dx}{dt} = f(x), \quad (1.5)$$

where $f : \Omega \subset \mathbb{R}^n \rightarrow \mathbb{R}^n$ is a C^1 function. A point $x^* \in \Omega$ is called an **equilibrium point** of (1.5) if $f(x^*) = 0$.

1.9.1 Types of Stability

Definition 1.9.1: Stability in the sense of Lyapunov [18]

The equilibrium x^* of (1.5) is said to be **stable** if for every $\varepsilon > 0$, there exists $\eta > 0$ such that for any solution $x(t)$ with $\|x(0) - x^*\| < \eta$:

$$\|x(t) - x^*\| < \varepsilon, \quad \forall t \geq 0.$$

Theorem 1.9.1: Lyapunov's Direct Method [18]

Let x^* be an equilibrium of (1.5) and let $V : \mathbb{R}^n \rightarrow \mathbb{R}$ be a continuously differentiable function such that $V(x^*) = 0$ and $V(x) > 0$ for all $x \neq x^*$ in a neighborhood of x^* . Then the following hold:

- (i) If $\dot{V}(x) \leq 0$ for all x near x^* , then x^* is **stable**.
- (ii) If $\dot{V}(x) < 0$ for all $x \neq x^*$ near x^* , then x^* is **asymptotically stable**.
- (iii) If $\dot{V}(x) > 0$ for all $x \neq x^*$ near x^* , then x^* is **unstable**.

Definition 1.9.2: Asymptotic Stability [3]

The equilibrium x^* is **asymptotically stable** if it is stable and there exists $\delta > 0$ such that:

$$\|x(0) - x^*\| < \delta \implies \lim_{t \rightarrow +\infty} \|x(t) - x^*\| = 0.$$

Definition 1.9.3: Global Asymptotic Stability [13]

The equilibrium x^* is **globally asymptotically stable** if it is stable and for **all** initial conditions $x(0) \in \Omega$:

$$\lim_{t \rightarrow +\infty} x(t) = x^*.$$

Definition 1.9.4: Instability [11]

The equilibrium x^* is **unstable** if it is not stable, i.e., there exists $\varepsilon > 0$ such that for any $\eta > 0$, there is a solution with $\|x(0) - x^*\| < \eta$ but $\|x(t) - x^*\| \geq \varepsilon$ for some $t > 0$.

1.9.2 Linearization Method

Let $J_f(x^*) = \frac{\partial f}{\partial x}(x^*)$ be the Jacobian matrix of f at x^* . The linearized system at x^* is:

$$\dot{y} = J_f(x^*)y.$$

Theorem 1.9.2: Hartman-Grobman [8, 10]

Let x^* be an equilibrium of (1.5) and let λ_i be the eigenvalues of $J_f(x^*)$.

1. If $\text{Re}(\lambda_i) < 0$ for all i , then x^* is **locally asymptotically stable**,
2. If $\text{Re}(\lambda_i) > 0$ for some i , then x^* is **unstable**,
3. If $\text{Re}(\lambda_i) \leq 0$ with some $\text{Re}(\lambda_i) = 0$, the linearization is **inconclusive**.

1.10 Semigroup Theory

Definition 1.10.1: Banach Space [14, Definition 2.1-1]

A normed vector space $(X, \|\cdot\|_X)$ is called a Banach space if it is complete. More precisely, a sequence $(u_n)_{n \geq 1} \subset X$ is called a Cauchy sequence if:

$$\forall \varepsilon > 0, \quad \exists N \in \mathbb{N} : m, n \geq N \implies \|u_m - u_n\|_X < \varepsilon.$$

The space X is complete if every Cauchy sequence $(u_n)_{n \geq 1} \subset X$ converges to an element of X , that is, there exists $u \in X$ such that:

$$\lim_{n \rightarrow +\infty} \|u_n - u\|_X = 0.$$

Definition 1.10.2: C_0 -Semigroup [6, Definition I.5.1]

A family $\{e^{At}\}_{t \geq 0}$ of bounded linear operators on a Banach space Y is called a strongly continuous semigroup (or C_0 -semigroup) if:

- (i) $e^{A \cdot 0} = \text{Id}_Y$,
- (ii) $e^{A(t+s)} = e^{At} \circ e^{As}$ for all $t, s \geq 0$,
- (iii) $\|e^{At}u - u\|_Y \rightarrow 0$ as $t \rightarrow 0^+$, for all $u \in Y$.

The operator A defined by:

$$Au = \lim_{t \rightarrow 0^+} \frac{e^{At}u - u}{t}$$

is called the infinitesimal generator of the semigroup.

Definition 1.10.3: Uniformly Continuous Semigroup [6]

A C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on Y is called uniformly continuous if:

$$\lim_{|t-s| \rightarrow 0} \|e^{At} - e^{As}\|_{\mathcal{L}(Y)} = 0.$$

Equivalently, the map $t \mapsto e^{At}$ is continuous in the operator norm topology on $\mathcal{L}(Y)$.

Definition 1.10.4: Strictly Contractive Semigroup

A C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on Y is called strictly contractive if there exists $\omega > 0$ such that:

$$\|e^{At}\|_{\mathcal{L}(Y)} \leq e^{-\omega t} < 1 \quad \forall t > 0.$$

Definition 1.10.5: Positive Semigroup [6, Definition VI.1.1]

A C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on an ordered Banach space (Y, Y_+) is called positive if:

$$e^{At}Y_+ \subset Y_+ \quad \forall t \geq 0.$$

That is, the semigroup preserves the non-negativity of the initial data.

Theorem 1.10.1: Bounded Perturbation Theorem [6]

Let A_0 be the infinitesimal generator of a C_0 -semigroup $\{e^{A_0 t}\}_{t \geq 0}$ on a Banach space Y , and let $\tilde{A} : Y \rightarrow Y$ be a bounded linear operator. Then $A = A_0 + \tilde{A}$ is also the generator of a C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on Y .

Theorem 1.10.2: Positivity Preservation [24, Theorem 1.2]

Let (Y, Y_+) be an ordered Banach space. If $\{e^{A_0 t}\}_{t \geq 0}$ is a positive C_0 -semigroup on Y and $\tilde{A} : Y \rightarrow Y$ is a bounded linear operator satisfying $\tilde{A}Y_+ \subset Y_+$, then the semigroup $\{e^{At}\}_{t \geq 0}$ generated by $A = A_0 + \tilde{A}$ is also positive:

$$e^{At}Y_+ \subset Y_+ \quad \forall t \geq 0.$$

1.11 Functional Analysis

Definition 1.11.1: Fréchet Derivative [2, Definition 8.1]

Let X and Y be Banach spaces and $F : X \rightarrow Y$. The operator F is Fréchet differentiable at $\psi \in X$ if there exists a bounded linear operator $F'[\psi] : X \rightarrow Y$ such that:

$$\lim_{\|u - \psi\|_X \rightarrow 0} \frac{\|F(u) - F(\psi) - F'[\psi](u - \psi)\|_Y}{\|u - \psi\|_X} = 0.$$

The operator $F'[\psi]$ is called the Fréchet derivative of F at ψ . If the map $\psi \mapsto F'[\psi]$ is continuous in $\mathcal{L}(X, Y)$, then F is said to be continuously Fréchet differentiable on X .

Theorem 1.11.1: Banach Fixed Point Theorem [14]

Let $(X, \|\cdot\|)$ be a Banach space and $\Phi : X \rightarrow X$ a contraction mapping, i.e. there exists $k \in [0, 1)$ such that:

$$\|\Phi(u) - \Phi(v)\| \leq k \|u - v\| \quad \forall u, v \in X.$$

Then Φ has a unique fixed point $u^* \in X$ satisfying $\Phi(u^*) = u^*$.

1.12 Semiflows and Asymptotically Smooth

Definition 1.12.1: Semiflow [27]

Let X be a metric space. A semiflow on X is a continuous mapping:

$$\Sigma : \mathbb{R}_+ \times X \longrightarrow X, \quad (t, u_0) \longmapsto \Sigma(t, u_0),$$

satisfying the following three conditions:

(i) Identity at $t = 0$:

$$\Sigma(0, u_0) = u_0 \quad \forall u_0 \in X,$$

(ii) Semigroup property:

$$\Sigma(t + s, u_0) = \Sigma(t, \Sigma(s, u_0)) \quad \forall t, s \geq 0, u_0 \in X,$$

For a fixed $u_0 \in X$, the set $\{\Sigma(t, u_0) : t \geq 0\}$ is called the positive orbit of u_0 under the semiflow $\{\Sigma(t)\}_{t \geq 0}$.

Definition 1.12.2: Positively Invariant Set [27, Definition 1.8]

A set $B \subset X$ is called positively invariant for a semiflow $\{\Sigma(t)\}_{t \geq 0}$ if:

$$\Sigma(t)B \subset B \quad \forall t \geq 0.$$

If equality holds ($\Sigma(t)B = B$), the set B is called invariant.

Theorem 1.12.1: LaSalle's Invariance Principle [16]

Let $\{\Sigma(t)\}_{t \geq 0}$ be a continuous semiflow on a metric space (X, d) . Suppose that:

1. There exists a continuous Lyapunov function $U : X \rightarrow \mathbb{R}$ such that $\dot{U}(u) \leq 0$ for all $u \in X$, where $\dot{U}$ denotes the derivative of U along the trajectories of the semiflow.
2. The semiflow has a compact global attractor in X .

Let $\mathcal{M}$ be the largest invariant subset of the set $\{u \in X : \dot{U}(u) = 0\}$. Then for any bounded trajectory, its ω -limit set is contained in $\mathcal{M}$. In particular, if $\mathcal{M} = \{u^*\}$ for some equilibrium u^* , then u^* is globally asymptotically stable.

Definition 1.12.3: Asymptotically Smooth Semiflow [27]

A semiflow $\{\Sigma(t)\}_{t \geq 0}$ on a metric space X is called asymptotically smooth if for any nonempty closed, bounded, and positively invariant set $B \subset X$, there exists a compact set $\hat{B} \subset X$ such that:

$$\lim_{t \rightarrow +\infty} d(\Sigma(t, B), \hat{B}) = 0,$$

where $d(A, \hat{B}) = \sup_{u \in A} \inf_{v \in \hat{B}} \|u - v\|$ denotes the Hausdorff semi-distance.

1.13 Measure of Noncompactness and Condensing Operators

Definition 1.13.1: Kuratowski Measure of Noncompactness [34]

Let X be a Banach space and $B \subset X$ a bounded set. The Kuratowski measure of noncompactness of B is defined by:

$$\kappa(B) := \inf\{r > 0 : B \text{ has a finite cover of diameter } < r\}.$$

The following properties hold:

- (i) $\kappa(B) = 0$ if and only if $\overline{B}$ is compact (i.e. B is precompact),
- (ii) $B_1 \subset B_2 \implies \kappa(B_1) \leq \kappa(B_2)$ (monotonicity),
- (iii) $\kappa(B_1 \cup B_2) \leq \max\{\kappa(B_1), \kappa(B_2)\}$,
- (iv) $\kappa(B_1 + B_2) \leq \kappa(B_1) + \kappa(B_2)$ (subadditivity).

Definition 1.13.2: Precompact Set [14, Definition 2.1]

Let X be a metric space. A subset $B \subset X$ is called precompact (or relatively compact) if its closure $\overline{B}$ is compact in X .

Remark 1.13.1. In view of Definition 1.13.1, a bounded set B is precompact if and only if $\kappa(B) = 0$.

Definition 1.13.3: κ -Condensing Map [34]

A continuous mapping $f : X \rightarrow X$ is said to be κ -condensing (κ -contraction of order l , $0 \leq l < 1$) if f maps bounded sets to bounded sets and:

$$\kappa(f(B)) < \kappa(B) \quad (\text{resp. } \kappa(f(B)) < l \kappa(B))$$

for any nonempty closed bounded set $B \subset X$ with $\kappa(B) > 0$, where $\kappa(B)$ denotes the Kuratowski measure (Definition 1.13.1).

Lemma 1.13.1 ([9]). Let $\{\Sigma(t)\}_{t \geq 0}$ be a semiflow on a Banach space Y . If $\{\Sigma(t)\}_{t \geq 0}$ is κ -condensing, that is, if there exists $l \in [0, 1)$ such that:

$$\kappa(\Sigma(t, B)) \leq l \kappa(B)$$

for any nonempty closed bounded set $B \subset Y$ with $\kappa(B) > 0$, then the semiflow $\{\Sigma(t)\}_{t \geq 0}$ is asymptotically smooth.

1.14 Classical Analysis Results

Theorem 1.14.1: Heine–Borel [26, Theorem 2.41]

A subset $K \subset \mathbb{R}^n$ is compact if and only if it is closed and bounded.

Theorem 1.14.2: Arzelà–Ascoli [26]

Let K be a compact metric space. A family $\mathcal{F} \subset C(K, \mathbb{R})$ is relatively compact in $C(K, \mathbb{R})$ if and only if it is:

- (i) *uniformly bounded: there exists $M > 0$ such that $|f(x)| \leq M$ for all $f \in \mathcal{F}$ and $x \in K$,*
- (ii) *equicontinuous: for every $\varepsilon > 0$, there exists $\delta > 0$ such that:*

$$d(x_1, x_2) < \delta \implies |f(x_1) - f(x_2)| < \varepsilon \quad \forall f \in \mathcal{F}.$$

Proposition 1.14.1: Mean Value Inequality [2]

Let X be a Banach space and let $f : [a, b] \rightarrow X$ be continuous on $[a, b]$ and differentiable on (a, b) . Then:

$$\|f(b) - f(a)\|_X \leq (b - a) \cdot \sup_{t \in (a, b)} \|f'(t)\|_X.$$

In particular, if there exists $M > 0$ such that $\|f'(t)\|_X \leq M$ for all $t \in (a, b)$, then:

$$\|f(b) - f(a)\|_X \leq M |b - a|.$$

Proposition 1.14.2: Variation of Constants Formula [31]

Let A be the infinitesimal generator of a C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on a Banach space Y , and let $F : Y \rightarrow Y$ be locally Lipschitz. Then the abstract Cauchy problem:

$$\frac{du}{dt} = Au + F(u), \quad u(0) = u_0 \in Y,$$

is equivalent to the integral equation:

$$u(t) = e^{At}u_0 + \int_0^t e^{A(t-\sigma)} F(u(\sigma)) d\sigma.$$

Chapter 2

Classical of Viral Infection models

2.1 Viral Dynamics of HBV [23]

The first quantitative framework for describing within-host hepatitis B virus (HBV) dynamics was introduced by Martin A. Nowak and his colleagues in 1996 [23]. Their model, based on a system of ordinary differential equations (ODEs) describing within-host viral dynamics, captures the interactions among three compartments: uninfected hepatocytes (target cells), infected hepatocytes, and free virus. A fundamental assumption of this model is that these compartments are homogeneously mixed, thereby neglecting any spatial structure. By fitting the model to clinical data from patients treated with lamivudine—a nucleoside analog that inhibits viral replication by blocking reverse transcription—the authors were able to estimate essential kinetic parameters of HBV infection. Notably, they found that the half-life of free virus is approximately one day, whereas infected hepatocytes have a much longer half-life, ranging from 10 to 100 days [23]. These findings highlighted the potential for long-term viral persistence even under antiviral therapy.

The system of ordinary differential equations (ODEs) proposed in [23] is given by:

$$\begin{cases} \frac{dT}{dt} = \Lambda - dT - bTV, \\ \frac{dI}{dt} = bTV - aI, \\ \frac{dV}{dt} = kI - uV. \end{cases} \quad (2.1)$$

In this model, the biological system is divided into three compartments: target cells $T(t)$, infected cells $I(t)$, and free virus $V(t)$. The model describes how infection spreads at the cellular level and how virus is produced and cleared over time. It is assumed that cells and virus particles are uniformly mixed and that infection occurs through contact between target cells and free virus.

The target cell compartment is continuously produced and naturally removed. When

a target cell encounters a virus particle, it can become infected and moves to the infected class. Infected cells produce new virus particles and are removed by natural death or immune response. Free virus particles are cleared at a constant rate. Antiviral treatment can be represented by reducing the viral production from infected cells.

The infection term bTV is bilinear and represents the incidence of new infections generated by contact between target cells and free virus. The parameters of the system are positive constants, which ensures biological consistency of the solutions, such that:

- Λ : production rate of new hepatocytes (target cells),
- d : death rate of target cells,
- b : infection rate,
- a : death rate of infected cells,
- k : viral production rate per infected liver cell,
- u : death rate of free virus.

The model is compartmental, where each equation describes the variation of one compartment through inflow and outflow terms. Production, infection, and death processes appear explicitly in the model equations (2.1). Under antiviral therapy, the structure of the system remains the same, but the viral production parameter can be reduced or set to zero, modifying the qualitative behavior of the solutions.

2.1.1 Basic Reproduction Number $\mathcal{R}_0$

We first determine the disease-free equilibrium (DFE) of system (2.1) proposed by Nowak et al. [23]. The DFE corresponds to the absence of infection, i.e. $I = 0$ and $V = 0$. Setting the right-hand sides of system (2.1) to zero gives:

$$\begin{cases} \Lambda - dT - bTV = 0, \\ bTV - aI = 0, \\ kI - uV = 0. \end{cases} \quad (2.2)$$

With $I = 0$ and $V = 0$, the second and third equations of (2.2) are automatically satisfied. From the first equation of (2.2) we obtain:

$$\Lambda - dT = 0 \implies T_0 = \frac{\Lambda}{d}.$$

Hence the DFE is

$$E_0 = (T_0, I_0, V_0) = \left(\frac{\Lambda}{d}, 0, 0 \right).$$

To compute the basic reproduction number we use the next-generation matrix method (1.6) developed by van den Driessche and Watmough [5]. From model (2.2), it is easy to check that the infected compartments are I and V . Therefore, the equations for these two compartments are given by:

$$\frac{d}{dt} \begin{pmatrix} I \\ V \end{pmatrix} = \mathcal{F} - \mathcal{V},$$

where

$$\mathcal{F} = \begin{pmatrix} bTV \\ kI \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} aI \\ uV \end{pmatrix}.$$

Here $\mathcal{F}$ contains the rates of new infections (or production of virus), and $\mathcal{V}$ contains the rates of transfer out of the infected compartments.

Computing the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at the DFE yields

$$F = \left. \frac{\partial \mathcal{F}}{\partial (I, V)} \right|_{E_0} = \begin{pmatrix} 0 & bT_0 \\ k & 0 \end{pmatrix} = \begin{pmatrix} 0 & \frac{b\Lambda}{d} \\ k & 0 \end{pmatrix},$$

$$\mathbb{V} = \left. \frac{\partial \mathcal{V}}{\partial (I, V)} \right|_{E_0} = \begin{pmatrix} a & 0 \\ 0 & u \end{pmatrix}.$$

Since $\mathbb{V}$ is diagonal, its inverse is simply

$$\mathbb{V}^{-1} = \begin{pmatrix} 1/a & 0 \\ 0 & 1/u \end{pmatrix}.$$

The next-generation matrix is then $K = F\mathbb{V}^{-1}$:

$$K = F\mathbb{V}^{-1} = \begin{pmatrix} 0 & \frac{b\Lambda}{d} \\ k & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{a} & 0 \\ 0 & \frac{1}{u} \end{pmatrix} = \begin{pmatrix} 0 & \frac{b\Lambda}{d} \frac{1}{u} \\ \frac{k}{a} & 0 \end{pmatrix}.$$

The basic reproduction number R_0 is defined as the spectral radius of K :

$$R_0 = \rho(K) = \max\{|\lambda| : \lambda \text{ is an eigenvalue of } K\}.$$

Since the next-generation matrix K is non-negative and irreducible, the Perron-Frobenius theorem (1.4.1) guarantees that $\rho(K)$ is a positive eigenvalue, which ensures that R_0 is

biologically realistic. We now compute the eigenvalues of K :

$$\det(K - \lambda I) = \det \begin{pmatrix} -\lambda & \frac{b\Lambda}{du} \\ \frac{k}{a} & -\lambda \end{pmatrix} = \lambda^2 - \frac{b\Lambda k}{da} = 0,$$

so that,

$$\lambda = \pm \sqrt{\frac{b\Lambda k}{da}}.$$

Therefore,

$$R_0 = \sqrt{\frac{b\Lambda k}{da}}.$$

2.1.2 Case 1: Without Treatment

We consider system (2.1) with $k > 0$ (no antiviral therapy). The basic reproduction number is

$$\mathcal{R}_0 = \sqrt{\frac{b\Lambda k}{da}}.$$

Lemma 2.1.1 (Existence of Equilibria). *System (2.2) satisfies:*

- If $\mathcal{R}_0 \leq 1$, the only nonnegative equilibrium is the disease-free equilibrium $E_0 = (\frac{\Lambda}{d}, 0, 0)$,
- If $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium $E^* = (T^*, I^*, V^*)$ given by

$$T^* = \frac{au}{bk}, \quad I^* = \frac{\Lambda}{a} \left(1 - \frac{1}{\mathcal{R}_0^2}\right), \quad V^* = \frac{k\Lambda}{au} \left(1 - \frac{1}{\mathcal{R}_0^2}\right).$$

Proof. From the third equation of this system, we obtain:

$$I = \frac{u}{k}V.$$

Substituting this expression into the second equation of system (2.2) gives:

$$V \left(bT - \frac{au}{k} \right) = 0.$$

We consider two cases:

Case 1: $V = 0$.

Since $I = \frac{u}{k}V$, we immediately obtain

$$I = 0.$$

From the first equation of system (2.2), we obtain

$$\Lambda - dT = 0,$$

so $T = \frac{\Lambda}{d}$. This corresponds to the disease-free equilibrium

$$E_0 = \left(\frac{\Lambda}{d}, 0, 0 \right).$$

Case 2: $V \neq 0$, which implies

$$T^* = \frac{au}{bk}.$$

Substituting this value into the first equation of system (2.2), we solve for V^* :

$$\Lambda - dT^* - bT^*V^* = 0.$$

Rearranging terms gives

$$V^* = \frac{k\Lambda}{au} - \frac{d}{b} = \frac{k\Lambda}{au} \left(1 - \frac{1}{\mathcal{R}_0^2} \right),$$

where we define $\mathcal{R}_0^2$ as follows

$$\mathcal{R}_0^2 = \frac{b\Lambda k}{dau}.$$

Finally, since $I^* = \frac{u}{k}V^*$, the positivity of both I^* and V^* requires $\mathcal{R}_0 > 1$. □

2.1.3 Case 2: With Treatment (Lamivudine)

Lamivudine is a nucleoside analogue used in the treatment of chronic hepatitis B (CHB). It inhibits the HBV DNA polymerase, thereby blocking the reverse transcription of pre-genomic RNA into viral DNA. In this model, we incorporate the effect of lamivudine treatment by setting $k = 0$, which represents the inhibition of viral production from infected cells. However, infection of target cells may still occur, so we keep $b \neq 0$. The reduced system is:

$$\begin{cases} \frac{dT}{dt} = \Lambda - dT - bTV, \\ \frac{dI}{dt} = bTV - aI, \\ \frac{dV}{dt} = -uV. \end{cases} \quad (2.3)$$

Lemma 2.1.2 (Infection Eradication Under Therapy). *For system (2.3), the only non-negative equilibrium is the disease-free equilibrium $E_0 = (\frac{\Lambda}{d}, 0, 0)$. Moreover, for any*

nonnegative initial conditions,

$$\lim_{t \rightarrow \infty} V(t) = 0, \quad \lim_{t \rightarrow \infty} I(t) = 0, \quad \lim_{t \rightarrow \infty} T(t) = \frac{\Lambda}{d},$$

Proof. The third equation of system (2.3) is independent and can be solved directly, giving $V(t) = V_0 e^{-ut}$ with $V_0 = V(0)$, thus $V(t) \rightarrow 0$ exponentially.

Substituting this expression into the second equation of system (2.3) gives a linear inhomogeneous differential equation:

$$\frac{dI}{dt} + aI = bT(t)V_0 e^{-ut}.$$

Using the integrating factor e^{at} , the solution can be written exactly as

$$I(t) = I_0 e^{-at} + e^{-at} \int_0^t bT(s)V_0 e^{-us} e^{as} ds.$$

We first examine the first equation of system (2.3):

$$\frac{dT}{dt} = \Lambda - dT - bTV(t).$$

Since $V(t) \rightarrow 0$ exponentially, the nonlinear term $-bTV$ becomes negligible for large t . A standard perturbation argument shows that

$$\lim_{t \rightarrow \infty} T(t) = \frac{\Lambda}{d}.$$

In the long-time limit, the function $T(s)$ in the integral is close to its limit Λ/d , replacing $T(s)$ by this constant introduces an error that is exponentially small. Hence we obtain the asymptotic approximation

$$I(t) \approx I_0 e^{-at} + \frac{b\Lambda V_0}{d} e^{-at} \int_0^t e^{(a-u)s} ds.$$

The evaluation of the integral depends on whether a equals u .

We distinguish two cases:

Case 1: $a \neq u$.

$$\int_0^t e^{(a-u)s} ds = \frac{1}{a-u} (e^{(a-u)t} - 1),$$

so that

$$I(t) \approx I_0 e^{-at} + \frac{b\Lambda V_0}{d(a-u)} (e^{-ut} - e^{-at}).$$

Case 2: $a = u$. The integral simplifies to t , giving

$$I(t) \approx I_0 e^{-at} + \frac{b\Lambda V_0}{d} t e^{-at}.$$

In both cases every term decays to zero as $t \rightarrow \infty$. Therefore $\lim_{t \rightarrow \infty} I(t) = 0$.

Thus, together with the limit $T(t) \rightarrow \Lambda/d$, we have shown that the disease-free equilibrium is globally attractive. $\square$

2.2 Spatial HBV dynamics with Local Diffusion[29]

The Nowak model [23] assumes spatial homogeneity, meaning that cells and viruses are well-mixed. While mathematically convenient, this assumption overlooks a key biological fact: the liver is a spatially structured organ, and virus particles do not reach all target cells instantaneously. In reality, hepatocytes (both target cells T and infected cells I) are sessile under normal conditions, they do not move. Free virus particles V , however, can diffuse through the interstitial fluid, spreading from regions of high concentration to low concentration [21]. Consequently, the Nowak model cannot capture spatial phenomena such as the propagation of infection fronts or the influence of local viral gradients.

To address these limitations, Wang and Wang [29] improved the Nowak model by introducing local diffusion for the free virus compartment. They assumed that the random motion of virus follows Fickian diffusion, described mathematically by the Laplacian operator Δ acting on the virus density. This spatial extension allows the study of **traveling waves** (1.7), propagating fronts of infection that move through liver tissue with a characteristic speed. The existence and properties of these waves can be analyzed using geometric singular perturbation theory [7], and the minimal wave speed c^* is related to the basic reproduction number R_0 and the diffusion coefficient D [29].

The proposed model is written as follows:

$$\begin{cases} \frac{\partial T}{\partial t} = \Lambda - dT - bTV, \\ \frac{\partial I}{\partial t} = bTV - aI, \\ \frac{\partial V}{\partial t} = D \Delta V + kI - uV, \end{cases} \quad (2.4)$$

where $T(t, x)$, $I(t, x)$ and $V(t, x)$ denote the densities of target cells, infected cells and free virus at position x and time t . The parameters have the following biological meanings:

- Λ : production rate of new hepatocytes,

- d : death rate of target cells,
- b : infection rate constant,
- a : death rate of infected cells,
- k : viral production rate per infected liver cell,
- u : death rate of free virus.

The new element is the diffusion term $D \Delta V$, with $D > 0$ the diffusion coefficient of the virus. The Laplacian Δ is defined as $\Delta V = \sum_{i=1}^n \frac{\partial^2 V}{\partial x_i^2}$, where $n = 1, 2$ or 3 depending on the spatial dimension, in one dimension this reduces to $\Delta V = \frac{\partial^2 V}{\partial x^2}$, which describes the local spatial spread of virus from regions of higher concentration to lower concentration. Importantly, **no diffusion terms appear for T and I** because hepatocytes are assumed immobile [29].

Biologically, the diffusion term represents the random motion of virus particles in the interstitial fluid of the liver [21]. This motion allows the virus to reach target cells that are not immediately adjacent to an infected cell, enabling spatial spread of the infection. The diffusion coefficient D reflects viral mobility: larger D means faster spread. Thus, the Wang model (2.4) captures the **spatial propagation** of HBV within the liver, predicting that the infection advances as a traveling wave with a well-defined front speed [29].

When the solution is spatially uniform ($\Delta V = 0$) or when $D = 0$, system (2.4) reduces exactly to the Nowak ODE model (2.1). Hence, the Wang model (2.4) generalises the classical framework by embedding it into a spatially explicit setting, while retaining the original dynamics as a special case.

2.3 Nonlocal Dispersal in Periodic Habitats [30]

The classical diffusion model [29] describes local movement through the Laplacian operator, where particles can only migrate to neighbouring locations. This framework cannot capture long-range dispersal mechanisms where individuals may jump directly to distant locations.

To overcome this limitation, Wang, Li and Sun [30] developed a theoretical framework for nonlocal dispersal in spatially periodic environments. Their general model for two interacting species reads:

$$\begin{cases} \frac{\partial u}{\partial t} = \int_{\mathbb{R}} J(x-y)u(t,y) dy - u(t,x) + f(x, u(t,x), v(t,x)), \\ \frac{\partial v}{\partial t} = g(x, u(t,x), v(t,x)), \end{cases} \quad (2.5)$$

where $u(t, x)$ and $v(t, x)$ denote the densities of two interacting species at time t and location x . The domain is assumed to be L -periodic, meaning that all coefficients and the kernel are invariant under translation by L , this captures repetitive spatial structures such as layered tissues or patterned environments. The functions f and g describe local reactions and satisfy $f(x, 0, 0) = g(x, 0, 0) = 0$, so that the zero state corresponds to the absence of both species.

The key novelty lies in the nonlocal dispersal operator for u :

$$\mathcal{N}[u](t, x) = \int_{\mathbb{R}} J(x - y)u(t, y) dy - u(t, x),$$

which allows individuals at position y to directly influence position x , weighted by the dispersal kernel J . Unlike the Laplacian, this operator permits long-range interactions. The kernel $J : \mathbb{R} \rightarrow \mathbb{R}_+$ satisfies the following:

Assumption 2.3.1. :

- **Normalisation:** $\int_{\mathbb{R}} J(z) dz = 1$, which ensures conservation of mass in the absence of reactions.
- **Symmetry:** often $J(z) = J(-z)$, however, asymmetry can be allowed to model directional drift (e.g., due to blood flow).
- **Compact support or fast decay:** typically J is zero outside a bounded interval, or decays rapidly, reflecting that very long jumps are improbable.
- **Positivity:** $J(z) > 0$ for small $|z|$ guarantees that nearby locations always interact.

This nonlocal framework generalises the previous models: if the kernel J is taken as a highly concentrated function approximating a Dirac delta, the nonlocal operator reduces formally to the local Laplacian, so that the Wang (2007) model [29] becomes a limiting case. Moreover, when the solution is spatially uniform, the nonlocal term vanishes and we recover a system of ordinary differential equations similar to the Nowak model [23]. Thus, the Wang (2018) model provides a unifying mathematical framework that incorporates both local and nonlocal dispersal while explicitly accounting for spatial periodicity.

Chapter 3

The viral infection model with nonlocal dispersal

Within-host viral infection models have progressively incorporated spatial structure to better capture the dynamics of infection in heterogeneous tissue environments. This chapter studies the model proposed by Liu et al [17], which fills this gap by combining nonlocal diffusion of free virus, an intracellular delay $\tau > 0$ reflecting the latency between viral entry and the onset of viral production, and position-dependent parameters throughout. This combination places the analysis in the framework of infinite-dimensional dynamical systems and requires tools from semigroup theory and functional analysis.

3.1 The Model with Nonlocal Dispersal versus Local Diffusion

The spatially structured viral infection model studied in (2.2), following Wang et al [29], represented an important advance over the classical ODE framework by introducing local Fickian diffusion for free virus. Governed by the Laplacian operator ΔV , that framework captures short-range viral spread but rests on three simplifying assumptions that limit its biological fidelity.

First, the Laplacian framework cannot represent long-range transport mechanisms. In reality, free virus in the liver may travel through blood sinusoids or interstitial fluid, allowing them to jump directly between distant lobules rather than diffusing gradually through tissue. Second, the model neglects the intracellular delay between viral entry into a target cell and the subsequent release of newly assembled virions.

Motivated by these considerations, Liu et al [17] introduced a within-host viral infection model that simultaneously incorporates nonlocal diffusion of free virus, an intracellular delay $\tau > 0$, and spatially heterogeneous parameters.

Let $\Omega \subset \mathbb{R}^n$ be a bounded connected domain with smooth boundary. The connectedness of Ω ensures that the spatial habitat forms a single continuous region, preventing the

decoupling of the infection dynamics into isolated subsystems and allowing the nonlocal dispersal and viral propagation to act throughout the entire domain. The model tracks three compartments densities at time $t \geq 0$ and position $x \in \bar{\Omega}$: target cells $T(t, x)$, infected cells $I(t, x)$, and free virus particles $V(t, x)$, governed by:

$$\begin{cases} \frac{\partial T}{\partial t} = a_1(x) - b_1(x) T(t, x) - \beta(x) T(t, x) V(t, x), \end{cases} \quad (3.1)$$

$$\begin{cases} \frac{\partial I}{\partial t} = -b_2(x) I(t, x) + \beta(x) T(t - \tau, x) V(t - \tau, x) e^{-s\tau}, \end{cases} \quad (3.2)$$

$$\begin{cases} \frac{\partial V}{\partial t} = d \int_{\Omega} J(x - y) V(t, y) dy - d V(t, x) - b_3(x) V(t, x) + a_2(x) I(t, x), \end{cases} \quad (3.3)$$

for $(t, x) \in \mathbb{R}_+ \times \bar{\Omega}$, where $d > 0$ is the viral diffusion coefficient. The initial condition is given by non-negative continuous functions $(\varphi_T, \varphi_I, \varphi_V)$ on $[-\tau, 0] \times \bar{\Omega}$. All parameters $a_1, a_2, b_1, b_2, b_3, \beta$ are strictly positive and uniformly continuous on $\bar{\Omega}$.

Biological interpretation. Target cells are produced at rate $a_1(x)$ and removed at rate $b_1(x)T$. Infection occurs upon contact with free virus at rate $\beta(x)TV$, but newly infected cells do not immediately produce virus: a latency period of duration τ elapses before they become productive, captured by the delayed term $\beta(x)T(t - \tau)V(t - \tau)e^{-s\tau}$ in (3.2), where $e^{-s\tau}$ is the probability of surviving the latency period. Infected cells are removed at rate $b_2(x)I$ and produce virus at rate $a_2(x)I$. Free virus is degraded at rate $b_3(x)V$ and spreads nonlocally through the operator $d \int_{\Omega} J(x - y)V(t, y) dy - dV(t, x)$ in (3.3), where J is the dispersal kernel introduced in (2.3).

3.2 Global Well-Posedness and Positivity

Let us consider the following function spaces

$$X = C([-\tau, 0] \times \bar{\Omega}, \mathbb{R}), \quad Y = X^3 \quad (3.4)$$

with the norm

$$\|\varphi\|_X = \sup_{x \in \bar{\Omega}} |\varphi(x)|, \quad \varphi \in X \quad (3.5)$$

and

$$\|(\varphi_1, \varphi_2, \varphi_3)\|_Y = \sqrt{|\varphi_1|^2 + |\varphi_2|^2 + |\varphi_3|^2}, \quad (\varphi_1, \varphi_2, \varphi_3) \in Y. \quad (3.6)$$

with positive cones $X_+ = C([-\tau, 0] \times \bar{\Omega}, \mathbb{R}_+)$ and $Y_+ = X_+^3$.

We set $u(t) = (T(t, \cdot), I(t, \cdot), V(t, \cdot))$, the system is reformulated as the abstract Cauchy problem:

$$\frac{du(t)}{dt} = A[u](t) + F[u](t), \quad u(t) \in Y_+, \quad (3.7)$$

where:

$$Au = \begin{pmatrix} -b_1(x) T \\ -b_2(x) I \\ d \int_{\Omega} J(x-y) V(y) dy - (d + b_3(x)) V \end{pmatrix}, \quad Fu = \begin{pmatrix} a_1(x) - \beta(x) TV \\ \beta(x) T(t - \tau, x) V(t - \tau, x) e^{-s\tau} \\ a_2(x) I \end{pmatrix}. \quad (3.8)$$

3.2.1 The Operator A Generates a Positive C_0 -Semigroup

Proposition 3.2.1

The operator A generates a uniformly continuous and strictly contractive semigroup $\{e^{At}\}_{t \geq 0}$ on Y . Furthermore, $e^{At}Y_+ \subset Y_+$ for all $t \geq 0$.

Proof. We decompose $A = A_0 + \tilde{A}$, where:

$$A_0 u = \begin{pmatrix} -b_1(x) T \\ -b_2(x) I \\ -(d + b_3(x)) V \end{pmatrix}, \quad \tilde{A} u = \begin{pmatrix} 0 \\ 0 \\ d \int_{\Omega} J(x-y) V(y) dy \end{pmatrix}. \quad (3.9)$$

We prove this proposition by verifying two main conditions.

Condition 1 — A_0 generates a uniformly continuous semigroup.

We first prove that A_0 generates a uniformly continuous semigroup on Y . Since A_0 is a diagonal operator, the abstract equation $\frac{du}{dt} = A_0 u$ decouples into three independent scalar Cauchy problems:

$$\frac{dT}{dt} = -b_1(x) T, \quad \frac{dI}{dt} = -b_2(x) I, \quad \frac{dV}{dt} = -(d + b_3(x)) V.$$

Each is a linear scalar ODE with constant-in-time coefficients, solved explicitly by:

$$T(t) = e^{-b_1(x)t} T(0), \quad I(t) = e^{-b_2(x)t} I(0), \quad V(t) = e^{-(d+b_3(x))t} V(0).$$

The semigroup generated by A_0 is therefore given explicitly by:

$$e^{A_0 t} u = \begin{pmatrix} e^{-b_1(x)t} T \\ e^{-b_2(x)t} I \\ e^{-(d+b_3(x))t} V \end{pmatrix}, \quad t \geq 0. \quad (3.10)$$

We verify that this defines a uniformly continuous semigroup in five steps.

Step 1 — Identity at $t = 0$. Evaluating (3.10) at $t = 0$:

$$e^{A_0 \cdot 0} u = \begin{pmatrix} e^0 T \\ e^0 I \\ e^0 V \end{pmatrix} = \begin{pmatrix} T \\ I \\ V \end{pmatrix} = u.$$

Hence $e^{A_0 \cdot 0} = \text{Id}_Y$.

Step 2 — Semigroup property. For any $t, s \geq 0$ and each component $i = 1, 2, 3$:

$$(e^{A_0 t} e^{A_0 s} u)_i = e^{-b_i(x)t} \cdot e^{-b_i(x)s} \cdot u_i = e^{-b_i(x)(t+s)} \cdot u_i = (e^{A_0(t+s)} u)_i,$$

using the identity $e^a e^b = e^{a+b}$. Hence $e^{A_0(t+s)} = e^{A_0 t} \circ e^{A_0 s}$.

Step 3 — Strong continuity at $t = 0$.

We must show that $\|e^{A_0 t} u - u\|_Y \rightarrow 0$ as $t \rightarrow 0^+$, for all $u \in Y$.

We begin by computing the difference $e^{A_0 t} u - u$ explicitly. For the target-cell component:

$$[e^{A_0 t} u - u]_T(x) = e^{-b_1(x)t} T(x) - T(x) = (e^{-b_1(x)t} - 1) T(x).$$

The same holds for I and V , replacing b_1 by b_2 and $d + b_3$ respectively. Taking the norm on Y :

$$\|e^{A_0 t} u - u\|_Y = \sup_{x \in \Omega} |e^{-b_i(x)t} - 1| \cdot |u_i(x)| \leq \sup_{x \in \Omega} |e^{-b_i(x)t} - 1| \cdot \|u\|_Y.$$

We now bound the factor $\sup_{x \in \Omega} |e^{-b_i(x)t} - 1|$. Since $\Omega \subset \mathbb{R}^n$ is a bounded domain with smooth boundary, its closure $\bar{\Omega}$ is closed and bounded in $\mathbb{R}^n$, hence compact by the Heine–Borel theorem (1.14.1). Consequently, as $b_i \in C(\bar{\Omega})$ and $\bar{\Omega}$ is compact, each b_i attains its supremum:

$$b_i^+ = \sup_{x \in \bar{\Omega}} b_i(x) < +\infty.$$

For any $x \in \bar{\Omega}$ and $t > 0$, applying the elementary inequality $|e^{-r} - 1| \leq r$, valid for all $r \geq 0$, with $r = b_i(x)t$:

$$|e^{-b_i(x)t} - 1| \leq b_i(x)t \leq b_i^+ t.$$

This bound is uniform in x , so taking the supremum over $\bar{\Omega}$ is valid. Setting $b^+ = \max\{b_1^+, b_2^+, d + b_3^+\}$, we obtain:

$$\sup_{x \in \Omega} |e^{-b_i(x)t} - 1| \leq b^+ t.$$

Substituting back:

$$\|e^{A_0 t} u - u\|_Y \leq b^+ t \|u\|_Y \xrightarrow{t \rightarrow 0^+} 0.$$

Step 4 — Uniform continuity. For $t, s \geq 0$, factorising

$$e^{-b_i(x)t} - e^{-b_i(x)s} = e^{-b_i(x)s} (e^{-b_i(x)(t-s)} - 1) \text{ and using } e^{-b_i(x)s} \leq 1:$$

$$\|e^{A_0 t} - e^{A_0 s}\|_{\mathcal{L}(Y)} \leq b^+ |t - s| \xrightarrow{|t-s| \rightarrow 0} 0.$$

Step 5 — Strict contractivity. Since $b_i(x) \geq b_i^- = \inf_{x \in \bar{\Omega}} b_i(x) > 0$, define $b^- = \min\{b_1^-, b_2^-, d + b_3^-\} > 0$. Then:

$$\|e^{A_0 t}\|_{\mathcal{L}(Y)} \leq e^{-b^- t} < 1 \quad \forall t > 0.$$

This completes the proof that A_0 generates a uniformly continuous and strictly contractive semigroup on Y .

Condition 2 — $\tilde{A}$ is bounded on Y .

We now prove that $\tilde{A}$ is a bounded linear operator on Y .

Step 1 — Identify the non-trivial component. By (3.2.1), only the third component of $\tilde{A}$ is non-zero:

$$[\tilde{A}u]_3(x) = d \int_{\Omega} J(x-y) V(y) dy.$$

Therefore $\|\tilde{A}u\|_Y = \|[\tilde{A}u]_3\|_X$.

Step 2 — Apply the triangle inequality. For any $x \in \bar{\Omega}$:

$$|[\tilde{A}u]_3(x)| \leq d \int_{\Omega} J(x-y) |V(y)| dy,$$

since $J \geq 0$ by Assumption (2.3).

Step 3 — Extract the supremum norm. Using $|V(y)| \leq \|V\|_X$ for all $y \in \Omega$:

$$d \int_{\Omega} J(x-y) |V(y)| dy \leq d \|V\|_X \int_{\Omega} J(x-y) dy.$$

Step 4 — Bound the integral of J . By Assumption (2.3), $\int_{\mathbb{R}^n} J(z) dz = 1$, so:

$$\int_{\Omega} J(x-y) dy \leq \|J\|_{L^1(\mathbb{R}^n)} = 1,$$

independently of x .

Step 5 — Conclude boundedness. Combining the above, for every $x \in \bar{\Omega}$:

$$|[\tilde{A}u]_3(x)| \leq d \|V\|_X \leq d \|u\|_Y.$$

Taking the supremum over x gives $\|\tilde{A}u\|_Y \leq d \|u\|_Y$. Hence $\tilde{A}$ is bounded with $\|\tilde{A}\|_{\mathcal{L}(Y)} \leq$

$d < \infty$.

Since A_0 generates a C_0 -semigroup on Y (3.2.1) and $\tilde{A}$ is bounded on Y (3.2.1), Corollary VI.1.11 of Engel and Nagel [6] guarantees that $A = A_0 + \tilde{A}$ generates a C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on Y .

Positivity preservation follows from a standard perturbation argument. The diagonal semigroup $e^{A_0 t}$ preserves Y_+ , since each multiplier $e^{-b_i(x)t}$ is strictly positive for all $t \geq 0$ and $x \in \bar{\Omega}$. The perturbation $\tilde{A}$ is likewise positive, as the kernel $J(x-y) \geq 0$ ensures that $\tilde{A}$ maps Y_+ into Y_+ . Since both $e^{A_0 t}$ and $\tilde{A}$ are positive, an application of Theorem 1.2 in Pazy [24] to the perturbed generator $A = A_0 + \tilde{A}$ guarantees $e^{At}Y_+ \subset Y_+$ for all $t \geq 0$. $\square$

This completes the proof of Proposition (3.2.1).

Proposition 3.2.2

The nonlinear operator $F : Y \rightarrow Y$ is locally Lipschitz continuous on Y .

Proof. We prove this proposition by verifying two main conditions.

Condition 1 — F is Fréchet differentiable on Y .

We first compute the Fréchet derivative of F at any point

$\psi = (\psi_T, \psi_I, \psi_V)^T \in Y$, and then verify that the remainder is $o(\|u - \psi\|_Y)$.

Computing the derivative. The nonlinear terms in F are products of the form $\beta(x)TV$. Applying the product rule $d(\beta TV) = \beta V dT + \beta T dV$, the Fréchet derivative at ψ , applied to a direction $\varphi = (\varphi_T, \varphi_I, \varphi_V)^T \in Y$, is:

$$F'[\psi](\varphi)(x) = \begin{pmatrix} -\beta(x) \psi_V(x) \varphi_T(x) - \beta(x) \psi_T(x) \varphi_V(x) \\ \beta(x) \psi_V(t - \tau, x) \varphi_T(t - \tau, x) e^{-s\tau} \\ + \beta(x) \psi_T(t - \tau, x) \varphi_V(t - \tau, x) e^{-s\tau} \\ a_2(x) \varphi_I(x) \end{pmatrix}. \quad (3.11)$$

Note that the **third** component $a_2(x)I$ is already linear in I , so its Fréchet derivative is simply $a_2(x)\varphi_I$, and the associated **remainder is zero**.

We now verify the **Fréchet differentiability** condition in **five steps**, focusing on the first component, which contains the essential nonlinearity.

Step 1 — Expand the difference $[F(u) - F(\psi)]_T$.

For any $u = (T, I, V)^T \in Y$, the first component satisfies:

$$[F(u)]_T - [F(\psi)]_T = (a_1(x) - \beta(x)TV) - (a_1(x) - \beta(x)\psi_T\psi_V) = -\beta(x)(TV - \psi_T\psi_V).$$

Step 2 — Separate the linear part from the remainder.

We add and subtract $\beta(x)\psi_TV$ inside the bracket to isolate the linear part:

$$TV - \psi_T\psi_V = TV - \psi_TV + \psi_TV - \psi_T\psi_V = (T - \psi_T)V + \psi_T(V - \psi_V).$$

We then write $V = \psi_V + (V - \psi_V)$ in the first term:

$$\begin{aligned} (T - \psi_T)V &= (T - \psi_T)[\psi_V + (V - \psi_V)] \\ &= (T - \psi_T)\psi_V + (T - \psi_T)(V - \psi_V). \end{aligned}$$

Substituting back:

$$TV - \psi_T\psi_V = \underbrace{(T - \psi_T)\psi_V + \psi_T(V - \psi_V)}_{\text{linear part}} + \underbrace{(T - \psi_T)(V - \psi_V)}_{\text{remainder}}.$$

Therefore:

$$[F(u)]_T - [F(\psi)]_T = \underbrace{-\beta(x)[\psi_V(T - \psi_T) + \psi_T(V - \psi_V)]}_{=[F'[\psi](u-\psi)]_T} - \underbrace{\beta(x)(T - \psi_T)(V - \psi_V)}_{=: R_T}.$$

Step 3 — Bound the remainder R_T .

For any fixed $x \in \bar{\Omega}$:

$$|R_T(x)| = |\beta(x)(T(x) - \psi_T(x))(V(x) - \psi_V(x))| \leq \beta^+ |T(x) - \psi_T(x)| |V(x) - \psi_V(x)|,$$

where $\beta^+ = \sup_{x \in \bar{\Omega}} \beta(x) < \infty$ by compactness of $\bar{\Omega}$.

Using $|T(x) - \psi_T(x)| \leq \|T - \psi_T\|_X$ and $|V(x) - \psi_V(x)| \leq \|V - \psi_V\|_X$:

$$|R_T(x)| \leq \beta^+ \|T - \psi_T\|_X \|V - \psi_V\|_X \leq \beta^+ \|u - \psi\|_Y^2.$$

Taking the supremum over $x \in \bar{\Omega}$:

$$\|R_T\|_X \leq \beta^+ \|u - \psi\|_Y^2.$$

Step 4 — Bound the remainder R_I for the second component.

The remainder for the second component is:

$$R_I(x) = -\beta(x)(T(t - \tau, x) - \psi_T(t - \tau, x))(V(t - \tau, x) - \psi_V(t - \tau, x))e^{-s\tau}.$$

Taking the absolute value and using $\beta(x) \leq \beta^+$:

$$|R_I(x)| \leq \beta^+ |T(t - \tau, x) - \psi_T(t - \tau, x)| |V(t - \tau, x) - \psi_V(t - \tau, x)| e^{-s\tau}.$$

Using $|T(t - \tau, x) - \psi_T(t - \tau, x)| \leq \|T - \psi_T\|_X$ and $|V(t - \tau, x) - \psi_V(t - \tau, x)| \leq \|V - \psi_V\|_X$:

$$|R_I(x)| \leq \beta^+ \|T - \psi_T\|_X \|V - \psi_V\|_X e^{-s\tau}.$$

Since $e^{-s\tau} \leq 1$ and $\|T - \psi_T\|_X \|V - \psi_V\|_X \leq \|u - \psi\|_Y^2$:

$$|R_I(x)| \leq \beta^+ \|u - \psi\|_Y^2.$$

Taking the supremum over $x \in \bar{\Omega}$:

$$\|R_I\|_X \leq \beta^+ \|u - \psi\|_Y^2.$$

Step 5 — Verify the Fréchet condition.

Combining Steps 3 and 4, and using $R_V = 0$ for the third component:

$$\frac{\|F(u) - F(\psi) - F'[\psi](u - \psi)\|_Y}{\|u - \psi\|_Y} \leq \frac{\|R_T\|_X + \|R_I\|_X}{\|u - \psi\|_Y} \leq \frac{2\beta^+ \|u - \psi\|_Y^2}{\|u - \psi\|_Y} = 2\beta^+ \|u - \psi\|_Y.$$

Therefore:

$$\frac{\|F(u) - F(\psi) - F'[\psi](u - \psi)\|_Y}{\|u - \psi\|_Y} \xrightarrow{\|u - \psi\|_Y \rightarrow 0} 0.$$

This is exactly the definition of Fréchet differentiability (1.11.1).

This completes the proof that F is Fréchet differentiable at every $\psi \in Y$.

Condition 2 — The map $\psi \mapsto F'[\psi]$ is continuous in operator norm.

We must show that:

$$\|F'[\psi] - F'[\tilde{\psi}]\|_{\mathcal{L}(Y)} \xrightarrow{\|\psi - \tilde{\psi}\|_Y \rightarrow 0} 0.$$

We proceed in **four steps**:

Step 1 — Compute $[F'[\psi] - F'[\tilde{\psi}]](\varphi)$ for the first component.

From (3.11), for the target-cell component:

$$\begin{aligned} [F'[\psi](\varphi) - F'[\tilde{\psi}](\varphi)]_T(x) &= -\beta(x) \psi_V(x) \varphi_T(x) - \beta(x) \psi_T(x) \varphi_V(x) \\ &\quad + \beta(x) \tilde{\psi}_V(x) \varphi_T(x) + \beta(x) \tilde{\psi}_T(x) \varphi_V(x) \\ &= -\beta(x) (\psi_V - \tilde{\psi}_V) \varphi_T - \beta(x) (\psi_T - \tilde{\psi}_T) \varphi_V. \end{aligned}$$

Step 2 — Bound the first component.

For any $\varphi \in Y$ with $\|\varphi\|_Y \leq 1$, applying the triangle inequality and using $\beta(x) \leq \beta^+$:

$$\begin{aligned} |[F'[\psi](\varphi) - F'[\tilde{\psi}](\varphi)]_T(x)| &\leq \beta^+ |\psi_V(x) - \tilde{\psi}_V(x)| |\varphi_T(x)| + \beta^+ |\psi_T(x) - \tilde{\psi}_T(x)| |\varphi_V(x)| \\ &\leq \beta^+ \|\psi_V - \tilde{\psi}_V\|_X \cdot 1 + \beta^+ \|\psi_T - \tilde{\psi}_T\|_X \cdot 1 \\ &\leq 2\beta^+ \|\psi - \tilde{\psi}\|_Y. \end{aligned}$$

Step 3 — Bound the second component.

By the identical argument applied to the infected-cell component (with $t - \tau$ in place of t and the factor $e^{-s\tau} \leq 1$):

$$|[F'[\psi](\varphi) - F'[\tilde{\psi}](\varphi)]_I(x)| \leq 2\beta^+ \|\psi - \tilde{\psi}\|_Y.$$

Step 4 — Third component and conclusion.

The third component satisfies $[F'[\psi](\varphi)]_V = a_2(x)\varphi_I$, which does not depend on ψ . Therefore:

$$[F'[\psi](\varphi) - F'[\tilde{\psi}](\varphi)]_V = 0.$$

Combining all three components and taking the supremum over $x \in \bar{\Omega}$ and over all $\|\varphi\|_Y \leq 1$:

$$\|F'[\psi] - F'[\tilde{\psi}]\|_{\mathcal{L}(Y)} \leq 4\beta^+ \|\psi - \tilde{\psi}\|_Y \xrightarrow{\|\psi - \tilde{\psi}\|_Y \rightarrow 0} 0.$$

This completes the proof that the map $\psi \mapsto F'[\psi]$ is continuous in operator norm. Hence F is continuously Fréchet differentiable on Y .

Final Step — Conclusion: F is locally Lipschitz.

Since F is continuously Fréchet differentiable on Y (Conditions 1 and 2), we apply the **Mean Value Inequality**: for any bounded set $B \subset Y$ and any $u, v \in B$:

$$\|F(u) - F(v)\|_Y \leq \sup_{\psi \in B} \|F'[\psi]\|_{\mathcal{L}(Y)} \cdot \|u - v\|_Y.$$

We bound $\|F'[\psi]\|_{\mathcal{L}(Y)}$ on B . For any $\varphi \in Y$ with $\|\varphi\|_Y \leq 1$, using (3.11) and $\beta(x) \leq \beta^+$:

$$\begin{aligned} \|F'[\psi](\varphi)\|_Y &\leq \beta^+ \|\psi_V\|_X \cdot \|\varphi_T\|_X + \beta^+ \|\psi_T\|_X \cdot \|\varphi_V\|_X + \beta^+ \|\psi_V\|_X \cdot \|\varphi_T\|_X \\ &\quad + \beta^+ \|\psi_T\|_X \cdot \|\varphi_V\|_X + \|a_2\|_\infty \|\varphi_I\|_X \\ &\leq 4\beta^+ \|\psi\|_Y + \|a_2\|_\infty. \end{aligned}$$

Since B is bounded, $\sup_{\psi \in B} \|\psi\|_Y < \infty$, and we define the Lipschitz constant:

$$L_B = 4\beta^+ \sup_{\psi \in B} \|\psi\|_Y + \|a_2\|_\infty < \infty.$$

Therefore, for all $u, v \in B$:

$$\|F(u) - F(v)\|_Y \leq L_B \|u - v\|_Y.$$

Since L_B is finite for every bounded set $B \subset Y$, the operator F is **locally Lipschitz** on Y . $\square$

Proposition 3.2.3

Let $u_0 = (\varphi_T, \varphi_I, \varphi_V) \in Y$. There exists $T_0 > 0$ such that system (3.1) has a unique solution:

$$u(\cdot, u_0) \in C([0, T_0), Y) \cap C^1((0, T_0), Y),$$

satisfying either $T_0 = +\infty$, or $\limsup_{t \rightarrow T_0^-} \|u(t, u_0)\|_Y = +\infty$. Moreover, if $u_0 \in Y_+$, then $u(t, u_0) \in Y_+$ for all $t \in (0, T_0)$.

Proof. We prove this proposition in **two parts**:

Part 1 — Existence and uniqueness.

Since A generates a C_0 -semigroup $\{e^{At}\}_{t \geq 0}$ on Y (Proposition 3.2.1) and F is locally Lipschitz on Y (Proposition 3.2.2), system (3.1) is equivalent to the following integral equation, known as the variation of constants formula:

$$u(t) = e^{At}u_0 + \int_0^t e^{A(t-\sigma)} F(u(\sigma)) d\sigma. \quad (3.12)$$

Derivation of (3.12). Multiply the abstract equation $\frac{du}{dt} - Au = F(u)$ by the integrating factor e^{-At} :

$$e^{-At} \frac{du}{dt} - e^{-At} Au = e^{-At} F(u).$$

The left-hand side is the derivative of $e^{-At}u(t)$:

$$\frac{d}{dt} [e^{-At}u(t)] = e^{-At} F(u(t)).$$

Integrating from 0 to t :

$$e^{-At}u(t) - u(0) = \int_0^t e^{-A\sigma} F(u(\sigma)) d\sigma.$$

Multiplying both sides by e^{At} and using $u(0) = u_0$ gives (3.12).

Existence and uniqueness via Banach Fixed Point Theorem. Define the map

$\Phi : C([0, T_0], Y) \rightarrow C([0, T_0], Y)$ by:

$$\Phi(u)(t) = e^{At}u_0 + \int_0^t e^{A(t-\sigma)} F(u(\sigma)) d\sigma.$$

We show that Φ is a contraction for T_0 small enough. For any $u, v \in C([0, T_0], Y)$:

$$\begin{aligned} \|\Phi(u)(t) - \Phi(v)(t)\|_Y &= \left\| \int_0^t e^{A(t-\sigma)} [F(u(\sigma)) - F(v(\sigma))] d\sigma \right\|_Y \\ &\leq \int_0^t \|e^{A(t-\sigma)}\|_{\mathcal{L}(Y)} \|F(u(\sigma)) - F(v(\sigma))\|_Y d\sigma. \end{aligned}$$

Since $\{e^{At}\}$ is contractive, $\|e^{A(t-\sigma)}\|_{\mathcal{L}(Y)} \leq e^{-b^-(t-\sigma)} \leq 1$. Since F is locally Lipschitz with constant L_B on a bounded set $B \supset \{u(t) : t \in [0, T_0]\}$:

$$\|\Phi(u)(t) - \Phi(v)(t)\|_Y \leq L_B \int_0^t \|u(\sigma) - v(\sigma)\|_Y d\sigma \leq L_B T_0 \sup_{\sigma \in [0, T_0]} \|u(\sigma) - v(\sigma)\|_Y.$$

Choosing $T_0 > 0$ small enough so that $L_B T_0 < 1$, the map Φ is a contraction on $C([0, T_0], Y)$. By applying the **Banach Fixed Point Theorem** (or the fixed point theorem), we find that Φ has a unique fixed point of (3.1).

The condition “either $T_0 = +\infty$ or $\limsup_{t \rightarrow T_0^-} \|u\|_Y = +\infty$ ” follows from the classical theory of abstract evolution equations, see Proposition 4.16 of Webb [31].

Part 2 — Positivity of the solution.

Assume $u_0 \in Y_+$, i.e. $\varphi_T, \varphi_I, \varphi_V \geq 0$ on $[-\tau, 0] \times \bar{\Omega}$. We prove $T(t, x) > 0$, $I(t, x) \geq 0$, $V(t, x) \geq 0$ for all $t \in (0, T_0)$ and $x \in \bar{\Omega}$.

Positivity of $T(t, x)$.

We argue by contradiction. Suppose there exist $\tilde{t} \in (0, T_0)$ and $x_0 \in \Omega$ such that:

$$T(\tilde{t}, x_0) = 0.$$

Since $T(0, x_0) = \varphi_T(0, x_0) \geq 0$ and T is continuous, we may define the first hitting time:

$$\hat{t} = \inf \{ t \in (0, T_0) : T(t, x_0) = 0 \}.$$

By continuity, $T(\hat{t}, x_0) = 0$. Since $T(t, x_0) > 0$ for all $t \in (0, \hat{t})$, the function $t \mapsto T(t, x_0)$ is non-increasing at $\hat{t}$, so:

$$\frac{\partial T}{\partial t}(\hat{t}, x_0) \leq 0. \quad (3.13)$$

On the other hand, substituting $T(\hat{t}, x_0) = 0$ into the first equation of (3.1):

$$\frac{\partial T}{\partial t}(\hat{t}, x_0) = a_1(x_0) - b_1(x_0) \underbrace{T(\hat{t}, x_0)}_{=0} - \beta(x_0) \underbrace{T(\hat{t}, x_0)}_{=0} V(\hat{t}, x_0) = a_1(x_0) > 0, \quad (3.14)$$

since $a_1(x_0) > 0$ strictly by assumption (2.3). Statements (3.13) and (3.14) are contradictory. Therefore:

$$T(t, x) > 0 \quad \forall t \in (0, T_0), x \in \bar{\Omega}.$$

Positivity of $I(t, x)$.

The second equation of (3.1) can be rewritten as a linear first-order ODE in I with a non-negative source term:

$$\frac{\partial I}{\partial t} + b_2(x) I = \beta(x) T(t - \tau, x) V(t - \tau, x) e^{-s\tau} \geq 0,$$

since $\beta(x) > 0$, $T \geq 0$ (proved above), $V \geq 0$ (from the initial condition for $t \leq 0$), and $e^{-s\tau} > 0$. Applying the variation of constants formula to this scalar ODE:

$$I(t, x) = \underbrace{e^{-b_2(x)t} I(0, x)}_{\geq 0} + \underbrace{\int_0^t e^{-b_2(x)(t-\sigma)} \beta(x) T(\sigma - \tau, x) V(\sigma - \tau, x) e^{-s\tau} d\sigma}_{\geq 0}.$$

Both terms are non-negative:

- $e^{-b_2(x)t} > 0$ always, and $I(0, x) \geq 0$ since $u_0 \in Y_+$,
- $e^{-b_2(x)(t-\sigma)} > 0$, $\beta(x) > 0$, $T(\sigma - \tau) \geq 0$, $V(\sigma - \tau) \geq 0$, $e^{-s\tau} > 0$.

Therefore:

$$I(t, x) \geq 0 \quad \forall t \in (0, T_0), x \in \bar{\Omega}.$$

Positivity of $V(t, x)$.

The third equation of (3.1) takes the form:

$$\frac{\partial V}{\partial t} = A_3 V + a_2(x) I(t, x),$$

where $A_3 \varphi = d \int_{\Omega} J(x - y) \varphi(y) dy - (d + b_3(x)) \varphi$ generates the positive semigroup $Q_3(t) = e^{A_3 t}$ established in Proposition (3.2.1). Applying the variation of constants formula:

$$V(t, x) = \underbrace{Q_3(t) \varphi_V(\theta, x)}_{\geq 0} + \underbrace{\int_0^t Q_3(t - \sigma) a_2(x) I(\sigma, x) d\sigma}_{\geq 0}.$$

Both terms are non-negative:

- $Q_3(t)$ is a positive semigroup and $\varphi_V(\theta, x) \geq 0$ since $u_0 \in Y_+$,
- $Q_3(t - \sigma)$ positive, $a_2(x) > 0$ by assumption, and $I(\sigma, x) \geq 0$ from above.

Therefore:

$$V(t, x) \geq 0 \quad \forall t \in (0, T_0), x \in \bar{\Omega}.$$

Combining Part 1 and Part 2, there exists a unique local solution $u(\cdot, u_0)$ of system (3.1), and $u(t, u_0) \in Y_+$ for all $t \in (0, T_0)$ whenever $u_0 \in Y_+$.

This completes the proof of Proposition (3.2.3). $\square$

Theorem 3.2.1

Let $u(t, u_0)$ be the unique solution of system (3.1) with $u_0 \in Y_+$. Then:

- (i) $u(t, u_0) : [0, +\infty) \rightarrow Y_+$ is the unique global solution, i.e. $T_0 = +\infty$,
- (ii) the semiflow $\{\Sigma(t)\}_{t \geq 0}$ defined by $\Sigma(t)(u_0) = u(t, u_0)$ is bounded dissipative.

Proof. By Proposition (3.2.3), either $T_0 = +\infty$ or $\|u(t)\|_Y \rightarrow +\infty$ as $t \rightarrow T_0^-$. To prove $T_0 = +\infty$, it suffices to show that $\|u(t)\|_Y$ remains uniformly bounded on $[0, T_0)$.

We establish this in **three steps**.

Step 1 — Uniform bound on T and I .

To bound T and I simultaneously, we introduce the auxiliary function:

$$z(t, x) = T(t, x) + I(t + \tau, x).$$

The idea behind this choice is the following: differentiating z with respect to t generates both $\frac{\partial T}{\partial t}$ and $\frac{\partial I(t+\tau)}{\partial t}$, whose infection terms $\pm \beta(x)TV$ appear with opposite signs and cancel up to the factor $(e^{-s\tau} - 1)$, which is non-positive. This allows us to eliminate the nonlinear term entirely.

Differential inequality for z .

Differentiating and substituting the equations of (3.1):

$$\begin{aligned} \frac{\partial z}{\partial t} &= \frac{\partial T}{\partial t} + \frac{\partial I(t + \tau, x)}{\partial t} \\ &= [a_1(x) - b_1(x)T - \beta(x)TV] + [-b_2(x)I(t + \tau) + \beta(x)T(t, x)V(t, x)e^{-s\tau}] \\ &= a_1(x) - b_1(x)T - b_2(x)I(t + \tau) + \beta(x)TV \underbrace{(e^{-s\tau} - 1)}_{\leq 0}. \end{aligned}$$

Since $s, \tau \geq 0$, we have $e^{-s\tau} \leq 1$, so the last term is non-positive. Discarding it:

$$\frac{\partial z}{\partial t} \leq a_1(x) - b_1(x)T - b_2(x)I(t + \tau).$$

Setting $b(x) = \min\{b_1(x), b_2(x)\} > 0$:

$$\frac{\partial z}{\partial t} \leq a_1(x) - b(x) [T + I(t + \tau)] = a_1(x) - b(x) z(t, x).$$

Solve the differential inequality.

Applying the variation of constants formula to the scalar inequality

$$\frac{\partial z}{\partial t} \leq a_1(x) - b(x)z:$$

$$z(t, x) \leq z(0, x) e^{-b(x)t} + \frac{a_1(x)}{b(x)} (1 - e^{-b(x)t}).$$

Since $e^{-b(x)t} \leq 1$ and $(1 - e^{-b(x)t}) \leq 1$ for all $t \geq 0$:

$$z(t, x) \leq z(0, x) + \frac{a_1(x)}{b(x)} =: D_1(x) < +\infty.$$

Since $T(t, x) \leq z(t, x)$, we conclude:

$$T(t, x) \leq D_1(x) \quad \forall t \in [0, T_0], x \in \bar{\Omega}.$$

Deduce the bound on $I(t, x)$.

From the bound $z(t, x) \leq D_1(x)$ and the non-negativity of both terms in

$z(t, x) = T(t, x) + I(t + \tau, x)$, we have:

$$0 \leq T(t, x) \leq D_1(x) \quad \text{and} \quad 0 \leq I(t + \tau, x) \leq D_1(x) \quad \forall t \in [0, T_0], x \in \bar{\Omega}.$$

The bound on I is expressed at time $t + \tau$, not at time t . To obtain a bound at time t , we perform the change of variable $s = t + \tau$, so that $t = s - \tau$. For all $s \geq \tau$:

$$I(s, x) = I((s - \tau) + \tau, x) \leq D_1(x).$$

It remains to handle the interval $s \in [0, \tau]$. On this interval, $I(s, x)$ is determined by the initial condition $\varphi_I \in Y_+$, which is continuous on the compact set $[-\tau, 0] \times \bar{\Omega}$. Therefore:

$$I(s, x) \leq \|\varphi_I\|_X < +\infty \quad \forall s \in [0, \tau], x \in \bar{\Omega}.$$

Combining both cases, define:

$$\tilde{D}_1(x) = \max\{D_1(x), \|\varphi_I\|_X\} < +\infty.$$

Then:

$$I(t, x) \leq \tilde{D}_1(x) \quad \forall t \in [0, T_0), \quad x \in \bar{\Omega}.$$

Next, we denote D_1 instead of $\tilde{D}_1$ for notational simplicity, keeping in mind that this constant accounts for both the asymptotic bound and the initial data on $[0, \tau]$.

Step 2 — Uniform bound on $\int_{\Omega} V \, dx$.

Before bounding $V(t, x)$ pointwise, we first control its spatial average. Integrating the third equation of (3.1) over Ω :

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} V(t, x) \, dx &= d \int_{\Omega} \int_{\Omega} J(x - y) V(t, y) \, dy \, dx - d \int_{\Omega} V \, dx \\ &\quad - \int_{\Omega} b_3(x) V \, dx + \int_{\Omega} a_2(x) I \, dx. \end{aligned}$$

Simplify the diffusion terms using Fubini's theorem.

Applying Fubini's theorem to exchange the order of integration in the double integral:

$$\int_{\Omega} \int_{\Omega} J(x - y) V(t, y) \, dy \, dx = \int_{\Omega} V(t, y) \left(\int_{\Omega} J(x - y) \, dx \right) \, dy.$$

By Assumption (2.3), $\int_{\mathbb{R}^n} J(x - y) \, dx = 1$ and $J \geq 0$, so:

$$\int_{\Omega} J(x - y) \, dx \leq \int_{\mathbb{R}^n} J(x - y) \, dx = 1 \quad \forall y \in \Omega.$$

Therefore:

$$d \int_{\Omega} \int_{\Omega} J(x - y) V(t, y) \, dy \, dx \leq d \int_{\Omega} V(t, y) \, dy.$$

The diffusion terms satisfy:

$$d \int_{\Omega} \int_{\Omega} J(x - y) V \, dy \, dx - d \int_{\Omega} V \, dx \leq 0.$$

Differential inequality for $\int_{\Omega} V \, dx$.

Using $b_3(x) \geq b_3^- = \inf_{x \in \Omega} b_3(x) > 0$ and the bound $I(t, x) \leq D_1(x)$ from Step (3.2.1):

$$\frac{d}{dt} \int_{\Omega} V \, dx \leq -b_3^- \int_{\Omega} V \, dx + \int_{\Omega} a_2(x) D_1(x) \, dx =: -b_3^- \int_{\Omega} V \, dx + C_1,$$

where $C_1 = \int_{\Omega} a_2(x) D_1(x) \, dx < +\infty$.

Apply the comparison principle.

Denote $P(t) = \int_{\Omega} V(t, x) dx$. Let $W(t)$ be the solution of:

$$\frac{dW}{dt} = -b_3^- W + C_1, \quad W(0) = P(0).$$

Since $\frac{dP}{dt} \leq -b_3^- P + C_1 = \frac{dW}{dt}$ and $P(0) = W(0)$, the comparison principle gives:

$$P(t) \leq W(t) \quad \forall t \geq 0.$$

Multiplying $\frac{dW}{dt} + b_3^- W = C_1$ by the integrating factor $e^{b_3^- t}$:

$$\frac{d}{dt} [e^{b_3^- t} W(t)] = C_1 e^{b_3^- t}.$$

Integrating from 0 to t :

$$e^{b_3^- t} W(t) - W(0) = \frac{C_1}{b_3^-} (e^{b_3^- t} - 1).$$

Multiplying by $e^{-b_3^- t}$:

$$W(t) = W(0) e^{-b_3^- t} + \frac{C_1}{b_3^-} (1 - e^{-b_3^- t}).$$

Since $e^{-b_3^- t} \leq 1$ and $(1 - e^{-b_3^- t}) \leq 1$:

$$W(t) \leq W(0) + \frac{C_1}{b_3^-} = \int_{\Omega} \varphi_V(0, x) dx + \frac{C_1}{b_3^-} =: D_2 < +\infty.$$

Therefore:

$$\int_{\Omega} V(t, x) dx \leq D_2 \quad \forall t \in [0, T_0).$$

Step 3 — Pointwise bound on $V(t, x)$.

The integral bound $\int_{\Omega} V dx \leq D_2$ does not directly give a pointwise bound, since the total mass could in principle be concentrated near a single point. We return to the pointwise equation for V and use D_2 to control the right-hand side.

Bound the convolution term.

For any fixed $x \in \bar{\Omega}$, since $J(x - y) \leq \sup_{\Omega \times \Omega} J$:

$$d \int_{\Omega} J(x - y) V(t, y) dy \leq d \cdot \sup_{\Omega \times \Omega} J \cdot \int_{\Omega} V(t, y) dy \leq d \cdot (\sup J) \cdot D_2.$$

This bound is uniform in x .

Bound the source term.

Using the bound from Step (3.2.1) and $a_2^+ = \sup_{x \in \bar{\Omega}} a_2(x) < \infty$,

$$D_1^+ = \sup_{x \in \bar{\Omega}} D_1(x) < \infty:$$

$$a_2(x) I(t, x) \leq a_2^+ \cdot D_1^+.$$

Define C_2 and write the scalar inequality.

Setting:

$$C_2 = d \cdot (\sup J) \cdot D_2 + a_2^+ \cdot D_1^+ < +\infty,$$

the pointwise equation for V satisfies the scalar differential inequality for each fixed $x \in \bar{\Omega}$:

$$\frac{\partial V(t, x)}{\partial t} \leq C_2 - (d + b_3^-) V(t, x).$$

Apply the comparison principle.

For each fixed x , let $W_x(t)$ satisfy:

$$\frac{dW_x}{dt} = C_2 - (d + b_3^-) W_x, \quad W_x(0) = \varphi_V(0, x).$$

By the comparison principle, $V(t, x) \leq W_x(t)$. Solving explicitly:

$$W_x(t) = \varphi_V(0, x) e^{-(d+b_3^-)t} + \frac{C_2}{d + b_3^-} (1 - e^{-(d+b_3^-)t}).$$

Since $e^{-(d+b_3^-)t} \leq 1$ and $(1 - e^{-(d+b_3^-)t}) \leq 1$:

$$V(t, x) \leq W_x(t) \leq \varphi_V(0, x) + \frac{C_2}{d + b_3^-}.$$

Taking the supremum over $x \in \bar{\Omega}$:

$$\|V(t, \cdot)\|_X \leq \|\varphi_V\|_X + \frac{C_2}{d + b_3^-} < +\infty \quad \forall t \in [0, T_0).$$

Step 4 — Global existence: $T_0 = +\infty$.

We now combine the bounds established in Steps 1–3 to show that $\|u(t)\|_Y$ is uniformly bounded on $[0, T_0)$.

From Step 1, we have for all $t \in [0, T_0)$ and $x \in \bar{\Omega}$:

$$\|T(t, \cdot)\|_X \leq D_1^+ := \sup_{x \in \bar{\Omega}} D_1(x) < +\infty, \quad \|I(t, \cdot)\|_X \leq \tilde{D}_1^+ < +\infty.$$

From Step 3, we have for all $t \in [0, T_0)$:

$$\|V(t, \cdot)\|_X \leq \|\varphi_V\|_X + \frac{C_2}{d + b_3^-} =: D_3 < +\infty.$$

Therefore, the norm of $u(t)$ in Y satisfies:

$$\begin{aligned}\|u(t)\|_Y &= \sqrt{\|T(t, \cdot)\|_X^2 + \|I(t, \cdot)\|_X^2 + \|V(t, \cdot)\|_X^2} \\ &\leq \sqrt{(D_1^+)^2 + (\tilde{D}_1^+)^2 + D_3^2} \\ &\leq \sqrt{2(D_1^+)^2 + D_3^2},\end{aligned}$$

for all $t \in [0, T_0)$. Since $\|u(t)\|_Y$ is bounded and cannot blow up, Proposition 3.2.3 forces:

$$T_0 = +\infty.$$

The unique global solution $u(t, u_0) : [0, +\infty) \rightarrow Y_+$ therefore exists.

The semiflow $\{\Sigma(t)\}_{t \geq 0} : \mathbb{R}_+ \times Y_+ \rightarrow Y_+$ generated by system (3.1) is defined by

$$\Sigma(t, u_0) = (T(t, \cdot, u_0), I(t, \cdot, u_0), V(t, \cdot, u_0)), \quad t \geq 0, \quad u_0 \in Y_+.$$

The semiflow $\{\Sigma(t)\}_{t \geq 0}$ is global.

Define the bounded set

$$\mathcal{S} = \left\{ u \in Y_+ : T(\cdot, x) \leq \frac{a_1(x)}{b_1(x)}, \quad 0 < T(\cdot, x) + I(\cdot, x) \leq M(x), \quad \int_{\Omega} V(\cdot, x) dx \leq \frac{1}{b_3^-} \int_{\Omega} a_2(x) M(x) dx, \quad x \in \bar{\Omega} \right\},$$

where $b_3^- = \min_{x \in \bar{\Omega}} b_3(x)$ and $M(x) = a_1(x) / \min\{b_1(x), b_2(x)\}$ for $x \in \bar{\Omega}$. By the estimates in Steps 1–3, the set $\mathcal{S}$ is positively invariant for system (3.1).

Step 5 — Bounded dissipativity.

The uniform bounds established in Steps 1–3 show that every solution eventually enters and remains in the bounded positively invariant set $\mathcal{S}$. Moreover, $\mathcal{S}$ absorbs every bounded subset of Y_+ . Consequently, the semiflow $\{\Sigma(t)\}_{t \geq 0}$ is **bounded dissipative**.

This completes the proof of Theorem (3.2.1). □

3.3 Asymptotic Smoothness and Compactness of the Semiflow

While Section (3.2) guarantees boundedness, the infinite-dimensional space Y requires compactness for the Lyapunov analysis in the next section. We prove that $\{\Sigma(t)\}_{t \geq 0}$ is asymptotically smooth via κ -condensing (1.13.3), decomposing $\Sigma(t) = \tilde{A}(t) + \tilde{F}(t)$ with $\tilde{A}(t)$ exponentially decaying and $\tilde{F}(t)$ compact.

Theorem 3.3.1: Compact Global Attractor [17]

The semiflow $\{\Sigma(t)\}_{t \geq 0}$ associated with system (3.1) is asymptotically smooth. Furthermore, $\{\Sigma(t)\}_{t \geq 0}$ has a compact global attractor in Y_+ .

Proof. For any initial condition $u_0(\theta, \cdot) = (\varphi_T(\theta, \cdot), \varphi_I(\theta, \cdot), \varphi_V(\theta, \cdot)) \in Y_+$, the semiflow associated with system (3.1) is defined by:

$$\Sigma(t, u_0) = (T(t, \cdot, u_0), I(t, \cdot, u_0), V(t, \cdot, u_0)), \quad u_0 \in Y_+, \quad t \geq 0.$$

Step 1 — Variation of constants formula for V .

Obviously, $V(t, \cdot, u_0)$ satisfies the following problem:

$$\begin{cases} \frac{\partial V(t, x)}{\partial t} = d \int_{\Omega} J(x - y) V(t, y, u_0) dy - dV(t, x, u_0) - b_3(x)V(t, x, u_0) + a_2(x)I(t, x, u_0), \\ V(0, x) = \varphi_V(\theta, x), \end{cases}$$

for $t \geq 0$ and $x \in \bar{\Omega}$. Applying the variation of constants formula to this linear inhomogeneous equation gives:

$$V(t, \cdot, u_0) = Q_3(t)\varphi_V + a_2(x) \int_0^t Q_3(t - \sigma) I(\sigma, \cdot, u_0) d\sigma, \quad (3.15)$$

where $Q_3(t) = e^{A_3 t}$ is the uniformly continuous semigroup generated by:

$$A_3\varphi(x) = d \int_{\Omega} J(x - y)\varphi(y) dy - (d + b_3(x))\varphi(x).$$

Step 2 — Principal eigenvalue of A_3 and exponential decay.

Following [35, Lemma 2.1], the operator A_3 possesses a principal eigenvalue of the form:

$$\mu_0 = - \inf_{\varphi \in L^2(\Omega), \|\varphi\|_{L^2} = 1} \left\{ \frac{d}{2} \int_{\Omega} \int_{\Omega} J(x - y)[\varphi(y) - \varphi(x)] dy dx + \int_{\Omega} (d + b_3(x))\varphi^2(x) dx \right\}.$$

Since $J \geq 0$ by Assumption (2.3) and $d + b_3(x) \geq d + b_3^- > 0$, both terms inside the infimum are non-negative. The second term satisfies:

$$\int_{\Omega} (d + b_3(x))\varphi^2(x) dx \geq (d + b_3^-)\|\varphi\|_{L^2}^2 = d + b_3^- > 0.$$

Therefore the infimum is strictly positive, which gives:

$$\mu_0 = -(d + b_3^-) < 0.$$

Consequently, there exists $\omega > 0$ sufficiently small such that $\mu_0 < -\omega < 0$, and the semigroup satisfies:

$$\|Q_3(t)\|_{\mathcal{L}(X)} \leq e^{-\omega t} \quad \forall t \geq 0. \quad (3.16)$$

Step 3 — Decomposition of the semiflow.

Using formula (3.15), we decompose the semiflow into two parts:

$$\Sigma(t, u_0) = \tilde{A}(t, u_0) + \tilde{F}(t, u_0),$$

where:

$$\tilde{A}(t, u_0) = (0, \quad 0, \quad Q_3(t)\varphi_V),$$

$$\tilde{F}(t, u_0) = \left(T(t, \cdot, u_0), \quad I(t, \cdot, u_0), \quad a_2(x) \int_0^t Q_3(t - \sigma) I(\sigma, \cdot, u_0) d\sigma \right), \quad u_0 \in Y_+, \quad t \geq 0.$$

By construction, $\Sigma(t, u_0) = \tilde{A}(t, u_0) + \tilde{F}(t, u_0)$, and formula (3.15) confirms the correctness of this decomposition.

Step 4 — The operator $\tilde{F}$ is compact: $\kappa(\tilde{F}(t, B)) = 0$.

Let $B \subset Y_+$ be any bounded set. We show that for each fixed $t \geq 0$, the set $\tilde{F}(t, B)$ is relatively compact in Y_+ .

Compactness of the T -component.

From Theorem (3.2.1), there exists $D_1^+ < \infty$ such that $|T(t, x, u_0)| \leq D_1^+$ for all $t \geq 0$, $x \in \bar{\Omega}$, and $u_0 \in B$. Hence the family $\{T(t, \cdot, u_0) : u_0 \in B\}$ is **uniformly bounded**.

To establish **equicontinuity in time**, we differentiate the first equation of system (3.1):

$$\left| \frac{\partial T}{\partial t}(t, x, u_0) \right| = |a_1(x) - b_1(x)T(t, x, u_0) - \beta(x)T(t, x, u_0)V(t, x, u_0)| \leq M,$$

where $M > 0$ is a finite constant that does not depend on t , x , or $u_0 \in B$. This uniform bound holds because a_1, b_1, β are continuous on the compact domain $\bar{\Omega}$, and T, V are uniformly bounded by Theorem 3.2.1.

Applying the **Mean Value Inequality** (1.14.1) to $t \mapsto T(t, x, u_0)$ for any $t_1, t_2 \in [0, t]$:

$$|T(t_1, x, u_0) - T(t_2, x, u_0)| \leq M |t_1 - t_2| \quad \forall x \in \bar{\Omega}, \quad u_0 \in B.$$

Since M is independent of x and $u_0 \in B$, for any $\varepsilon > 0$, choosing $\delta = \varepsilon/M$ gives:

$$|t_1 - t_2| < \delta \implies |T(t_1, x, u_0) - T(t_2, x, u_0)| < \varepsilon \quad \forall x \in \bar{\Omega}, \quad u_0 \in B.$$

The same δ works for all x and all $u_0 \in B$. Therefore the family $\{T(\cdot, x, u_0) : u_0 \in B\}$ is **uniformly equicontinuous in t** .

By the **Arzelà-Ascoli Theorem** (1.14.2), combined with uniform boundedness and

uniform equicontinuity, the family $\{T(t, \cdot, u_0) : u_0 \in B\}$ is relatively compact in X . Therefore:

$$\kappa(\{T(t, \cdot, u_0) : u_0 \in B\}) = 0.$$

Compactness of the I -component.

By the identical argument applied to:

$$\left| \frac{\partial I}{\partial t}(t, x, u_0) \right| = |-b_2(x)I + \beta(x)T(t - \tau)V(t - \tau)e^{-s\tau}| \leq M',$$

where $M' > 0$ is again independent of t , x , and $u_0 \in B$ (using $T, V \leq D_1^+, D_3$ from Theorem (3.2.1) and $e^{-s\tau} \leq 1$). The Mean Value Theorem then gives equicontinuity in t , and Arzelà-Ascoli (1.14.2) gives:

$$\kappa(\{I(t, \cdot, u_0) : u_0 \in B\}) = 0.$$

Compactness of the third component.

The third component of $\tilde{F}$ is: $a_2(x) \int_0^t Q_3(t - \sigma)I(\sigma, \cdot, u_0) d\sigma$.

Since the family $\{I(\sigma, \cdot, u_0) : u_0 \in B\}$ is relatively compact in X for each $\sigma \in [0, t]$, and since $Q_3(t - \sigma)$ is a bounded operator and $a_2(x)$ is bounded and continuous on $\bar{\Omega}$, the integral inherits this compactness. Therefore:

$$\kappa\left(\left\{a_2(x) \int_0^t Q_3(t - \sigma)I(\sigma, \cdot, u_0) d\sigma : u_0 \in B\right\}\right) = 0.$$

It follows from the compactness of $T(t, \cdot, u_0)$ and $I(t, \cdot, u_0)$ ($i = 1, 2$) and the positivity of $Q_3(t)$ that the operator $\tilde{F}$ is compact. Hence, for any bounded set $B \subset Y_+$ and $t \geq 0$:

$$\kappa(\tilde{F}(t, B)) = 0. \tag{3.17}$$

Step 5 — The operator $\tilde{A}$ contracts κ exponentially.

For any $u_0 \in Y_+$, using the definition of $\tilde{A}$ and the decay estimate (3.16):

$$\|\tilde{A}(t, u_0)\|_Y = \|Q_3(t)\varphi_V\|_X \leq \|e^{A_3 t}\varphi_V\|_X \leq e^{-\omega t}\|\varphi_V\|_X \leq e^{-\omega t}\|u_0\|_Y.$$

Taking the operator norm:

$$\|\tilde{A}(t)\|_{\mathcal{L}(Y)} \leq e^{-\omega t}, \quad t > 0. \tag{3.18}$$

For any bounded set $B \subset Y_+$:

$$\kappa(\tilde{A}(t, B)) \leq \|\tilde{A}(t)\|_{\mathcal{L}(Y)} \cdot \kappa(B) \leq e^{-\omega t} \kappa(B).$$

Step 6 — Key estimate and κ -condensing property.

Combining Steps 4 and 5 with the subadditivity of κ (1.13.3):

$$\kappa(\Sigma(t, B)) \leq \kappa(\tilde{A}(t, B)) + \kappa(\tilde{F}(t, B)) \leq \|\tilde{A}(t)\| \kappa(B) + 0 \leq e^{-\omega t}, \quad t > 0.$$

Thus the semiflow $\{\Sigma(t)\}_{t \geq 0} : \mathbb{R}_+ \times Y_+ \rightarrow Y_+$ is a κ -contraction of order $e^{-\omega t}$ on Y_+ .

Since $\{\Sigma(t)\}_{t \geq 0}$ is κ -condensing, Lemma (1.13.1) gives that $\{\Sigma(t)\}_{t \geq 0}$ is **asymptotically smooth**.

Theorem (3.2.1) implies that $\{\Sigma(t)\}_{t \geq 0}$ is point dissipative on Y_+ and the positive orbits of bounded subsets of Y_+ are bounded. [19, Theorem 2.6] and the asymptotic smoothness of $\{\Sigma(t)\}_{t \geq 0}$ ensure that $\{\Sigma(t)\}_{t \geq 0}$ has a **compact global attractor** in Y_+ . The proof is completed. $\square$

3.4 Global Stability of the Infection-Free Steady State

In this section, we establish the global asymptotic stability of the infection-free steady state

$$P_0 = (T^0(x), 0, 0), \quad T^0(x) = \frac{a_1(x)}{b_1(x)}, \quad x \in \bar{\Omega},$$

under the threshold condition $\mathcal{R}_0 \leq 1$. The analysis relies on the compact global attractor established in Section (3.3), which provides the compactness framework required for the application of the LaSalle invariance principle.

The proof proceeds in two steps. We first establish the threshold relationship between the principal eigenvalue λ_0 and $\mathcal{R}_0$ (Theorem 3.4.1), and then prove global asymptotic stability through the construction of an explicit Lyapunov functional whose integral kernel is the positive eigenfunction φ_0 of the linearised problem around P_0 .

3.4.1 The Eigenvalue problem and the basic reproduction number

Consider the eigenvalue problem linearised around the infection-free steady state $P_0 = (T^0(x), 0, 0)$:

$$d \int_{\Omega} J(x-y) \varphi(y) dy - d\varphi(x) + \left(\frac{\beta(x)a_2(x)T^0(x)}{b_2(x)} e^{-s\tau} - b_3(x) \right) \varphi(x) = \lambda \varphi(x), \quad x \in \bar{\Omega}. \quad (3.19)$$

This can be rewritten as $(A_3 + \mathcal{F}_3)\varphi = \lambda\varphi$, where $\mathcal{F}_3[\varphi](x) = \frac{\beta(x)a_2(x)T^0(x)}{b_2(x)} e^{-s\tau} \varphi(x)$.

Following [35, Lemma 2.1], problem (3.19) possesses a principal eigenvalue:

$$\lambda_0 = - \inf_{\varphi \in L^2(\Omega), \|\varphi\|_{L^2} = 1} \left\{ \frac{d}{2} \int_{\Omega} \int_{\Omega} J(x-y) [\varphi(y) - \varphi(x)] dy dx - \int_{\Omega} \left(\frac{\beta(x)a_2(x)T^0(x)}{b_2(x)} e^{-s\tau} - b_3(x) \right) \varphi^2(x) dx \right\}, \quad (3.20)$$

associated with a strictly positive eigenfunction $\varphi_0(x) > 0$ on $\bar{\Omega}$.

The next generation operator $\mathcal{R} : X \rightarrow X$ is defined by:

$$\mathcal{R}[\psi](x) = \frac{\beta(x)a_2(x)T^0(x)e^{-s\tau}}{b_2(x)} \int_0^{+\infty} Q_3(t)\psi(x) dt = \mathcal{F}_3(-A_3)^{-1}[\psi](x), \quad (3.21)$$

where $(-A_3)^{-1}$ is well-defined since $\mu_0 = s(A_3) < 0$. The basic reproduction number is then:

$$\mathcal{R}_0 = r(\mathcal{R}), \quad (3.22)$$

where $r(\cdot)$ denotes the spectral radius.

Theorem 3.4.1: [17, Theorem 2.3]

The principal eigenvalue λ_0 has the same sign as $\mathcal{R}_0 - 1$ and $s(A)$.

Proof. Problem (3.19) is equivalent to the operator eigenvalue equation:

$$(A_3 + \mathcal{F}_3)\varphi(x) = \lambda\varphi(x), \quad x \in \bar{\Omega}.$$

Its principal eigenvalue satisfies $\lambda_0 = s(A_3 + \mathcal{F}_3)$, where $s(\cdot) = \sup\{\operatorname{Re} \mu : \mu \in \sigma(\cdot)\}$ denotes the spectral bound, following [1, Lemma 2.2].

The arguments of [33, Proposition 2.4] show that the operator A_3 is resolvent-positive and satisfies $s(A_3) < 0$. Applying [28, Theorem 3.5] to the decomposition $A_3 + \mathcal{F}_3$, we conclude that $s(A_3 + \mathcal{F}_3)$ has the same sign as $r(\mathcal{F}_3(-A_3)^{-1}) - 1 = r(\mathcal{R}) - 1 = \mathcal{R}_0 - 1$.

Therefore λ_0 has the same sign as $\mathcal{R}_0 - 1$, and the proof is completed. $\square$

Remark 3.4.1. The same approach in [32, 28] demonstrates that $\mathcal{R}_0 - 1$ and $s(A_3)$ have the same sign.

Theorem 3.4.2: Global asymptotic stability [17, Theorem 4.1]

If $\mathcal{R}_0 \leq 1$, then the infection-free steady state P_0 is globally asymptotically stable in $\mathcal{S}$.

Proof. We construct a Lyapunov functional that is non-negative along every solution in $\mathcal{S}$, vanishes only at P_0 , and has non-positive time derivative when $\mathcal{R}_0 \leq 1$.

Step 1 — Construction of the Lyapunov functional.

Let $\varphi_0(x) > 0$ be the strictly positive eigenfunction of problem (3.19) associated with λ_0 . Define the function $g : (0, +\infty) \rightarrow \mathbb{R}_+$ by:

$$g(z) = z - 1 - \ln z \geq 0 \quad \forall z > c > 0,$$

with $g(z) = 0$ if and only if $z = 1$. Define:

$$U(t) = \int_{\Omega} \varphi_0(x) \left[T^0(x) g\left(\frac{T(t, x)}{T^0(x)}\right) + e^{s\tau} I(t, x) + \frac{e^{s\tau} b_2(x)}{a_2(x)} V(t, x) + \beta(x) \int_{-\tau}^0 T(t+\theta, x) V(t+\theta, x) d\theta \right] dx.$$

Step 2 — Non-negativity and zeros.

Since $g \geq 0$ and all remaining terms are non-negative (Proposition 3.2.3), $U(t) \geq 0$ for all $t \geq 0$. Moreover:

$$U(t) = 0 \iff T(t, x) = T^0(x), \quad I(t, x) \equiv 0, \quad V(t, x) \equiv 0 \iff u(t, \cdot) = P_0.$$

Step 3 — Computing $\frac{dU}{dt}$.

Differentiating along solutions of system (3.1) and substituting the equations for $\partial_t T$, $\partial_t I$, $\partial_t V$:

$$\begin{aligned} \frac{dU}{dt} &= \int_{\Omega} \varphi_0(x) \left(1 - \frac{T^0}{T} \right) \left(a_1(x) - b_1(x)T - \beta(x)TV \right) dx \\ &\quad + \int_{\Omega} \varphi_0(x) e^{s\tau} \left(-b_2(x)I + \beta(x)T(t-\tau)V(t-\tau)e^{-s\tau} \right) dx \\ &\quad + \int_{\Omega} \varphi_0(x) \frac{e^{s\tau} b_2(x)}{a_2(x)} \left(d \int_{\Omega} J(x-y)V(t, y) dy - dV - b_3(x)V + a_2(x)I \right) dx \\ &\quad + \int_{\Omega} \varphi_0(x) \beta(x) \left(TV - T(t-\tau)V(t-\tau) \right) dx. \end{aligned}$$

Using $a_1(x) = b_1(x)T^0(x)$ and cancelling the terms $\pm\beta(x)TV$ and $\pm b_2(x)I$ that appear with opposite signs across the four lines:

$$\frac{dU}{dt} = \int_{\Omega} \varphi_0(x) b_1(x) T^0(x) \left(2 - \frac{T^0(x)}{T} - \frac{T}{T^0(x)} \right) dx \quad (3.23)$$

$$+ \int_{\Omega} \varphi_0(x) \beta(x) T^0(x) V dx \quad (3.24)$$

$$+ \frac{e^{s\tau} b_2(x)}{a_2(x)} \int_{\Omega} \varphi_0(x) \left[d \int_{\Omega} J(x-y)V(t, y) dy - dV - b_3(x)V \right] dx. \quad (3.25)$$

Step 4 — Simplifying the nonlocal diffusion term.

We apply Fubini's theorem and the symmetry $J(x-y) = J(y-x)$ (Assumption 2.3) to the convolution in (3.25):

$$\int_{\Omega} \varphi_0(x) d \int_{\Omega} J(x-y)V(t, y) dy dx = \int_{\Omega} V(t, x) d \int_{\Omega} J(x-y)\varphi_0(y) dy dx.$$

From the eigenfunction equation (3.19):

$$d \int_{\Omega} J(x-y) \varphi_0(y) dy - d \varphi_0(x) = \lambda_0 \varphi_0(x) - \left(\frac{\beta(x) a_2(x) T^0(x)}{b_2(x)} e^{-s\tau} - b_3(x) \right) \varphi_0(x).$$

Substituting into (3.25):

$$(3.25) = \frac{e^{s\tau} b_2(x)}{a_2(x)} \lambda_0 \int_{\Omega} \varphi_0(x) V(t, x) dx - \int_{\Omega} \varphi_0(x) \beta(x) T^0(x) V dx.$$

The last term cancels (3.24) exactly. Equation (3.23) + (3.24) + (3.25) therefore reduces to:

$$\frac{dU}{dt} = \underbrace{\int_{\Omega} \varphi_0(x) b_1(x) T^0(x) \left(2 - \frac{T^0(x)}{T} - \frac{T}{T^0(x)} \right) dx}_{=: \mathcal{I}_1 \leq 0} + \underbrace{\frac{e^{s\tau} b_2(x)}{a_2(x)} \lambda_0 \int_{\Omega} \varphi_0(x) V(t, x) dx}_{=: \mathcal{I}_2}. \quad (3.26)$$

Step 5 — Sign of $\frac{dU}{dt}$ when $\mathcal{R}_0 \leq 1$.

Sign of $\mathcal{I}_1$: For any $T > 0$ and $T^0 > 0$, a direct computation gives:

$$T^0(x) \left(2 - \frac{T^0(x)}{T} - \frac{T}{T^0(x)} \right) = - \frac{(T(t, x) - T^0(x))^2}{T(t, x)} \leq 0.$$

Since $\varphi_0 > 0$ and $b_1 > 0$:

$$\mathcal{I}_1 \leq 0, \quad \text{with equality if and only if } T(t, x) = T^0(x).$$

Sign of $\mathcal{I}_2$: If $\mathcal{R}_0 \leq 1$, then $\lambda_0 \leq 0$ by Theorem 3.4.1. Since $\varphi_0 > 0$ and $V \geq 0$:

$$\mathcal{I}_2 \leq 0, \quad \text{with equality if and only if } \lambda_0 = 0 \text{ or } V(t, x) \equiv 0.$$

Therefore, from (3.26):

$$\frac{dU}{dt} \leq 0 \quad \forall t \geq 0.$$

Step 6 — Largest invariant set.

Define $\mathcal{M} = \{u \in \mathcal{S} : \frac{dU}{dt} = 0\}$. On $\mathcal{M}$, necessarily $T = T^0$ and $V \equiv 0$. Substituting into the I-equation of system (3.1):

$$\frac{\partial I}{\partial t} = -b_2(x) I(t, x) + \beta(x) T^0(x) \underbrace{V(t - \tau, x)}_{=0} e^{-s\tau} = -b_2(x) I(t, x),$$

which gives $I(t, x) \rightarrow 0$ exponentially as $t \rightarrow +\infty$. Therefore the largest positively invariant subset of $\mathcal{M}$ is $\{P_0\}$.

Since the semiflow $\{\Sigma(t)\}_{t \geq 0}$ has a compact global attractor in Y_+ (Theorem 3.3.1),

and since $\frac{dU}{dt} \leq 0$ on $\mathcal{S}$ with the largest invariant subset of $\mathcal{M}$ being $\{P_0\}$, the global asymptotic stability of the steady state P_0 follows from LaSalle's Invariance Principle (Theorem 1.12.1). The proof is finished.

□

Conclusion

This work has presented a mathematical study of within-host viral infection dynamics, progressing from classical models to a spatially heterogeneous framework combining nonlocal diffusion, intracellular delay, and position-dependent parameters.

Chapter 2 examined two foundational models. The ODE model of Nowak *et al.* established the classical within-host framework and provided an explicit formula for $\mathcal{R}_0$ via the next-generation matrix method. Wang *et al.* incorporated Fickian diffusion for the virus compartment, introducing spatial structure into the model.

Chapter 3 is devoted to the analysis of the spatially heterogeneous viral infection model with intracellular delay and nonlocal diffusion proposed by Liu *et al.* This model incorporates nonlocal diffusion of free virions through a probability kernel J , allowing virions to interact across distant spatial locations, which local diffusion cannot capture, together with intracellular delay $\tau > 0$ and spatially heterogeneous parameters. Three main results were established. Global well-posedness and positivity of solutions were proved via semigroup theory and the Banach fixed point theorem. Asymptotic smoothness of the semiflow and the existence of a compact global attractor were obtained through a κ -contraction argument based on the Kuratowski measure of noncompactness. Finally, the global asymptotic stability of the infection-free steady state P_0 when $\mathcal{R}_0 \leq 1$ was established via an explicit Lyapunov functional whose kernel is the strictly positive eigenfunction φ_0 of the linearised problem around P_0 .

These results confirm that $\mathcal{R}_0$ governs a sharp biological threshold: when $\mathcal{R}_0 \leq 1$, the infection dies out regardless of initial conditions and spatial heterogeneity. As perspectives, the incorporation of an immune response or a nonlinear incidence rate represent natural extensions that would further enrich the present framework.

Bibliography

- [1] P. W. Bates and G. Zhao, Existence, uniqueness and stability of the stationary solution to a nonlocal evolution equation arising in population dispersal, *J. Math. Anal. Appl.*, vol. 332, no. 1, pp. 428–440, 2007.
- [2] H. Cartan, *Differential Calculus*, Hermann, Paris, 1971.
- [3] E. A. Coddington and N. Levinson, *Theory of Ordinary Differential Equations*, McGraw-Hill, New York, 1955.
- [4] J. Dieudonne, *Elements d'analyse: Tome I: Fondements de l'analyse moderne*, 3rd ed., Gauthier-Villars, Paris, 1979.
- [5] P. van den Driessche and J. Watmough, "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission," *Mathematical Biosciences*, vol. 180, pp. 29–48, 2002.
- [6] K.-J. Engel and R. Nagel, *One-Parameter Semigroups for Linear Evolution Equations*, Graduate Texts in Mathematics, Springer, New York, 2000.
- [7] N. Fenichel, "Geometric singular perturbation theory for ordinary differential equations," *Journal of Differential Equations*, vol. 31, pp. 53–98, 1979.
- [8] D. M. Grobman, "Homeomorphisms of systems of differential equations," *Doklady Akademii Nauk SSSR*, vol. 128, pp. 880–881, 1959.
- [9] J. K. Hale, *Asymptotic Behavior of Dissipative Systems*, American Mathematical Society, Providence, RI, 1988.
- [10] P. Hartman, "A lemma in the theory of structural stability of differential equations," *Proceedings of the American Mathematical Society*, vol. 11, no. 4, pp. 610–620, 1960.
- [11] P. Hartman, *Ordinary Differential Equations*, 2nd ed., SIAM, Philadelphia, 2002.

- [12] R. A. Horn and C. R. Johnson, *Matrix Analysis*, 2nd ed., Cambridge University Press, 2013.
- [13] H. K. Khalil, *Nonlinear Systems*, 3rd ed., Prentice Hall, Upper Saddle River, NJ, 2002.
- [14] E. Kreyszig, *Introductory Functional Analysis with Applications*, Wiley, New York, 1978.
- [15] T. Kuniya and J. Wang (2017). Lyapunov functions and global stability for a spatially diffusive SIR epidemic model. *Applicable Analysis*, 96(11), 1935–1960.
- [16] J. P. LaSalle, Some Extensions of Liapunov's Second Method, *IRE Trans. Circuit Theory* **7** (1960), no. 4, 520–527.
- [17] L. Liu, R. Xu, and Z. Jin, "Global dynamics of spatial heterogeneous viral infection model with intracellular delay and nonlocal diffusion," *Applied Mathematical Modelling*, vol. 82, pp. 150–167, 2020.
- [18] A. M. Lyapunov, *The General Problem of the Stability of Motion*, Taylor & Francis, London, 1992 (original work published 1892).
- [19] P. Magal and X.-Q. Zhao, Global attractors and steady states for uniformly persistent dynamical systems, *SIAM J. Math. Anal.* **37** (2005), no. 1, 251–275.
- [20] J. R. Munkres, *Topology*, 2nd ed., Prentice Hall, Upper Saddle River, NJ, 2000.
- [21] D. Murray, *Mathematical Biology*, Springer, Berlin, 1993.
- [22] J. D. Murray, *Mathematical Biology I: An Introduction*, 3rd ed., Springer, New York, 2002.
- [23] M. A. Nowak, S. Bonhoeffer, A. M. Hill, R. Boehme, H. C. Thomas, and H. McDade, "Viral dynamics in hepatitis B virus infection," *Proceedings of the National Academy of Sciences*, vol. 93, no. 9, pp. 4398–4402, 1996.
- [24] A. Pazy (1983). *Semigroups of Linear Operators and Applications to Partial Differential Equations*. Springer, New York.
- [25] L. Perko, *Differential Equations and Dynamical Systems*, 3rd ed., Springer, New York, 2001.
- [26] W. Rudin, *Principles of Mathematical Analysis*, 3rd ed., McGraw-Hill, New York, 1976.

- [27] H. L. Smith and H. R. Thieme, *Dynamical Systems and Population Persistence*, American Mathematical Society, Providence, RI, 2011.
- [28] H. R. Thieme, Spectral bound and reproduction number for infinite-dimensional population structure and time heterogeneity, *SIAM J. Appl. Math.*, vol. 70, no. 1, pp. 188–211, 2009.
- [29] K. Wang and W. Wang, "Propagation of HBV with spatial dependence," *Mathematical Biosciences*, vol. 210, no. 1, pp. 78–95, 2007.
- [30] K. Wang, W. Wang, and X. Liu, "Global dynamics of a spatial heterogeneous viral infection model with intracellular delay and nonlocal diffusion," *Nonlinear Analysis: Real World Applications*, vol. 40, pp. 1–24, 2018.
- [31] G. Webb (1985). *Theory of Nonlinear Age-Dependent Population Dynamics*. CRC Press.
- [32] Y. Wu and X. Zou, Dynamics and profiles of a diffusive host–pathogen system with distinct dispersal rates, *J. Differential Equations*, vol. 264, pp. 4989–5024, 2018.
- [33] Y. Yang and W.-T. Li, Dynamics of a nonlocal dispersal SIS epidemic model with Neumann boundary conditions, *J. Differential Equations*, vol. 263, pp. 5963–5994, 2017.
- [34] X.-Q. Zhao, *Dynamical Systems in Population Biology*, Springer-Verlag, New York, 2003.
- [35] G. Zhao and S. Ruan, Spatial and temporal dynamics of a nonlocal viral infection model, *SIAM J. Appl. Math.* **78** (2018), no. 4, 1954–1980.