POLITECNICO DI TORINO

Corso di Laurea Magistrale in Ingegneria Matematica

Tesi

Epidemic modelling of dengue fever transmission dynamics

Relatori
prof. Alessandro Rizzo
prof. Lorenzo Zino

Candidato
Alessandro Casu

firma dei relatori

. . . . . .
. . . . . .

firma del candidato

. . . . . .

Anno Accademico 2023-2024

Ringraziamenti

Ringrazio in primo luogo il professor Alessandro Rizzo per avermi dato fiducia sin da subito, e per la positività che mi ha trasmesso riguardo alla bontà del nostro lavoro. Un grandissimo e caloroso ringraziamento va al professor Lorenzo Zino, con cui ho avuto il piacere di collaborare sin dall'inizio di questa tesi, e che mi ha guidato attraverso tutte le sue fasi, con gentilezza e disponibilità.

Questa tesi mette la parola fine ad un lungo percorso, caratterizzato da dedizione e fatica, ma soprattutto dalle persone che mi sono state vicine, che mai dimenticherò, e che qui di seguito ringrazio.

Non ringrazierò solo persone, ma anche un luogo: il Collegio Einaudi, che è stato per tutti questi anni la mia casa. Ogni anno tra quelle mura ha luogo un'esperienza umana di valore inestimabile, di cui sarò per sempre grato e di cui custodirò sempre i ricordi. Un grazie speciale a Emma, Martina S., Vito, Stefano, Massimiliano, Fred, Paolo P., Andrea E., Andrea L., Cosma, Chiara, Gianluca, Giuliana, Lorenzo G., Luca, Matteo A., Mirko, Sebi, Pio, Gabriele A., Luigi e Paolo M. per un'infinità di momenti, risate, esperienze e follie avuti insieme in quel di San Paolo. Un altro grazie speciale a Lorenzo I., Martina B., Daniele, Annalú, Franco e Jacopo per quest'ultimo anno passato insieme in quel della Mole, a suon di sessioni di palestra, calcetto e risate. Un grazie particolare a Marco, Rossella, Alessandro e Francesco per la nostra forte amicizia, che non conosce distanze, e su cui so bene di poter contare in futuro.

Un grazie a Pierantonio, compagno di viaggio dall'inizio alla fine nell'avventura in Corea, che mi ha dato una mano a superare alcuni dei tantissimi culture shock. Grazie anche a Matteo C. e Andrea B. per essere stati grandi compagni di squadra nell'ultima sfida che il Politecnico aveva in serbo per me. Grazie anche a Mihaela, Giacomo S., Gabriele F. e Mack per un'infinità di risate in questi anni. Grazie anche agli amici di giù: Chiara, Noemi, Ester, Riccardo, Bruno, Esmeralda e il Pintusone, che, pur avendo avuto poche occasioni per incontrci in questi anni, sono rimasti gli stessi, facendomi sempre sentire a casa.

Un enorme grazie va al buon vecchio Valerio, con cui commento la politica da quando sedevamo ai banchi delle elementari, e che continueremo a fare per il resto della nostra vita, probabilmente. Un enorme grazie anche a Carlo, per la sua lealtà, e per essere stato una solida spalla nei momenti più difficili. Un enorme e doveroso grazie a Luca e Sara, per la loro generosità e per la cura che ripongono nella nostra amicizia, che conserverò per sempre. Grazie anche a mio fratello, Luca, per la sua generosità e per riuscire a farmi ridere anche nei momenti di sconforto.

Infine, un immenso grazie alle due persone senza le quali niente di tutto ciò si sarebbe mai realizzato: mia mamma e mio babbo. Grazie, in particolare, a babbo per avermi trasmesso molti interessi, determinazione, e l'importanza di pensare sempre due volte. Grazie a mamma per avermi sempre sostenuto, trasmesso tranquillità, e per i sacrifici a cui si è sempre sottoposta per rendermi felice. Dedico a voi due questa tesi, che chiude un capitolo estremamente prezioso della mia vita. Ma sappiate che ora ne inizia uno nuovo, e io ho ancora bisogno di voi:)

Alessandro

Summary

Dengue fever, caused by the dengue virus and transmitted by *Aedes* mosquitoes, presents a significant public health challenge, especially in tropical regions. We investigate its transmission dynamics using various epidemiological mathematical models, focusing on both host (humans) and vector (*Aedes* mosquitoes) populations. In order to highlight the importance of the climatic region for the disease spread, we analyze both models within a single area (compartmental) and a model with a tropical and non-tropical area (network). The initial compartmental population model employs the Susceptible-Infected-Susceptible (SIS) framework for both the host and the mosquito population, accounting for contagion and recovery rates. Further compartmental population models incorporate vector population dynamics using an open Susceptible-Infected (SI) framework, including birth and death rates while excluding recovery rates, to reflect mosquitoes' shorter lifespan. Control measures, such as vector control and health policies, are also integrated into these models as additional terms in the differential equations. The network model explores the impact of imported cases and international travel on disease dynamics, highlighting how interconnected regions can influence and enhance disease transmission. The network model is then tested through simulations with parameter values from the literature and some assumptions. What-if scenarios such as the potential survival of *Aedes aegypti* in non-tropical regions due to climate change are explored to predict future trends and outbreak risks. By identifying epidemic thresholds, analyzing effectiveness of controls and simulating various scenarios with the choice of parameters, this thesis offers insights into effective strategies for controlling dengue transmission and preventing outbreaks, contributing to the broader field of epidemiology.

Contents

List of Tables

List of Figures

Chapter 1

Introduction

Dengue fever, a mosquito-borne tropical disease caused by the dengue virus [3], is transmitted to humans through bites from infected female *Aedes* mosquitoes. It poses a significant public health challenge, with over one-third of the global population at risk. The disease is caused by four related but distinct viruses, DENV-1 to DENV-4, and can lead to a range of clinical manifestations. These vary from asymptomatic or mild symptoms, such as fever, headaches, and joint and muscle pains, to severe and potentially fatal hemorrhagic conditions. Estimates suggest that over 390 million dengue infections occur annually, with 96 million showing symptomatic severity.

Primary dengue infections are often asymptomatic, but a secondary infection with a different serotype is the primary risk factor for severe disease. Infection with one serotype confers lifelong immunity to that specific virus but only temporary protection against other serotypes. Once this cross-protection diminishes, a secondary infection with a different serotype increases the risk of severe disease through Antibody-Dependent Enhancement (ADE). ADE occurs when antibodies from the first infection recognize the new serotype but instead of neutralizing it, they facilitate its entry into target cells, increasing viral load and disease severity.

There is no specific treatment for dengue. Uncomplicated cases require only supportive care, while severe cases necessitate hospitalization. Due to the complexities of dengue, vaccine development aims to create a tetravalent vaccine that provides long-term protection against all four serotypes. A safe, effective, and affordable tetravalent vaccine would significantly aid in controlling the disease and reducing transmission and mortality rates.

While several candidate tetravalent vaccines are in development, with two having completed phase 3 clinical trials, an effective and safe one is not yet available.

Therefore, vector control is still the primary strategy for preventing dengue transmission, and epidemic models happen to be crucial for guiding decisions, since they offer insights into the complex epidemiological dynamics of dengue. [4]

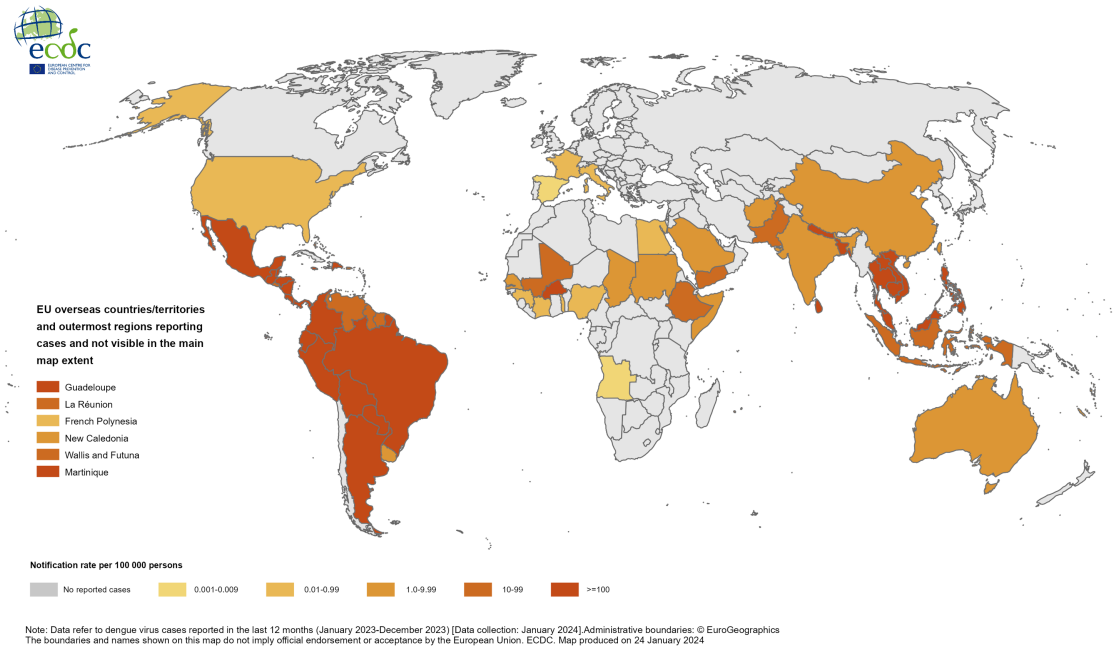


Figure 1.1: Dengue cases from January to December 2023 [1]

Increasing temperatures and rainfall are extending the range of mosquitoes carrying the dengue virus, leading to a significant rise in cases. Over 4.5 million dengue cases have been reported in 80 countries in 2023, with projections indicating that by 2080, an additional 2 billion people could be at risk. These outbreaks have been particularly severe, with a World Health Organization official calling them a "canary in the coal mine of the climate crisis".

Reported dengue cases have surged from around 500,000 in 2000 to 5.2 million in 2019. Improved diagnostics and reporting partly explain this increase, but factors such as population growth, urbanization, travel, and climate change also play significant roles. *Aedes* mosquitoes thrive in warmer temperatures, leading to higher transmission rates and expansion into new areas.

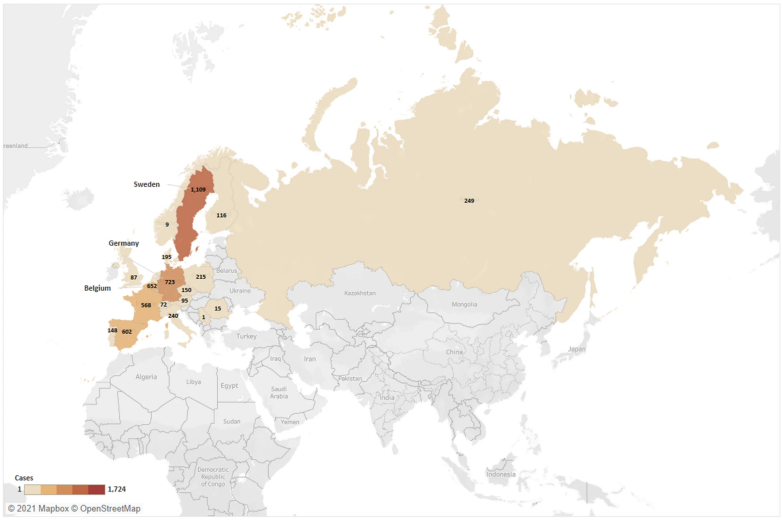
As global temperatures rise, new areas will become hospitable for these mosquitoes. Scientists predict an expansion of the transmission belt northwards and upwards, with more months suitable for transmission and increased opportunities for the disease to spread. Moreover, cases can be reported in both endemic and non-endemic countries due to the importation of viremic travelers, facilitated by international travel. In Europe, three countries reported sporadic autochthonous cases between January 1 and December 5, 2023. Italy recorded the highest number with 82 cases, followed by France with 43 cases, and Spain with 3 cases. [5][6]

Travelers to tropical regions can contract the infection through bites from *Aedes aegypti* mosquitoes, which are primarily responsible for spreading dengue fever in these areas. In non-tropical regions, transmission mainly occurs via *Aedes albopictus*, a secondary vector with a broader range of hosts, including birds, cats, dogs, and other mammals.

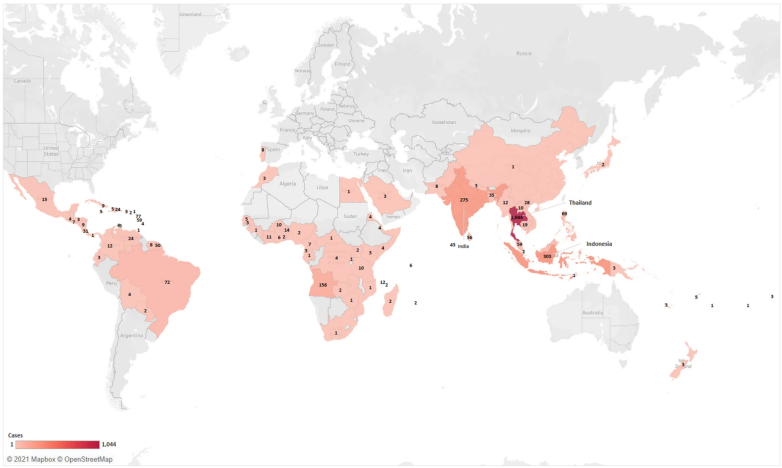
The rapid speed of travel by planes and trains enables viremic travelers to move from disease-endemic regions to non-endemic ones. This movement, coupled with the increasing presence of competent vectors in non-endemic regions due to global warming and globalization, allows viremic travelers to potentially transmit the virus to local susceptible populations. However, the diagnosis of dengue is often delayed due to its mild and undifferentiated symptoms, hindering timely treatment and actions to prevent transmission. This situation can lead to an imported index case causing autochthonous transmission, potentially spiraling into an outbreak.

Endemicity is further facilitated by factors such as conducive breeding sites in crowded urban communities, lack of vector control, climate change, and vector adaptation. Given the emerging global impact of imported dengue, understanding the trend of dengue importation and its geographical sources is crucial. This knowledge can inform policy, risk assessment, and intervention strategies to prevent and delay dengue outbreaks. [7]

This thesis aims to present a series of dengue-specific epidemiological compartmental models, organized by increasing complexity. Initially, the objective is to accurately simulate the contagion dynamics, wherein the spread of infection in a host population is interdependent with that in a vector population, and vice versa. Subsequently, the focus shifts to studying the dynamics resulting from imported dengue cases, an issue of growing concern for health authorities in Europe and other regions where dengue is not endemic. As is common in mathematical epidemiological studies, this research focuses on identifying the necessary conditions to achieve a disease-free equilibrium in the models, thereby determining the epidemic thresholds when possible. Additionally, some models incorporate spread controls that can be interpreted as vector control measures or health policies aimed at counteracting or promoting behaviors in host populations. The last among the developed models, which is the one over a network, is also tested through simulations using parameter choices derived from studies that attempted to estimate them, along with other assumptions. Among the simulations, we include what-if scenarios such as the potential survival of *Aedes aegypti* in non-tropical regions due to climate change to predict future trends and outbreak risks.



(a) European countries reporting imported cases of dengue over the years [7]



(b) Sources of imported dengue into Europe over the years [7]

Figure 1.2

Chapter 2

Background theory

To begin, let us introduce the fundamental concepts of graph theory, compartmental epidemic models and dynamical systems' stability theory, including characterization of monotonicity, as these will form the foundation of the models we will develop.

2.1 Basic elements of graph theory

Graphs are mathematical objects consisting of *nodes* (also known as vertices) connected by *links* (also known as edges).

If a graph comprises n nodes, they collectively form a set of positive integer indices $\mathcal{V} = \{1, \ldots, n\}$. Nodes are connected through a set of directed links $\mathcal{E} \subseteq \mathcal{V} \times \mathcal{V}$, such that $(i, j) \subseteq \mathcal{E}$.

For any pair of nodes $i, j \in \mathcal{V}$, we define the *connection strength* $a_{ij} \geq 0$, which indicates the degree of connection from node i to node j, such that $a_{ij} > 0 \iff (i, j) \in \mathcal{E}$. These connection strengths are organized into a (*weighted*) *adjacency matrix* $A \in \mathbb{R}_{\geq 0}^{n \times n}$. The triple $\mathcal{G} = (\mathcal{V}, \mathcal{E}, A)$ defines the *graph*.

A network is considered *undirected* if its corresponding adjacency matrix is symmetric, i.e., $A = A^\top$; otherwise, it is labeled as *directed*. A network is *connected* (*strongly connected* for directed networks) if its adjacency matrix A is irreducible, meaning that for any pair of nodes i and j, there exists a sequence of nodes $v_1 = i, v_2, \ldots, v_k = j$ such that $(v_l, v_{l+1}) \in \mathcal{E}$ for $l = 1, \ldots, k-1$. A network is *unweighted* if the adjacency matrix of the corresponding graph A has binary entries, where all non-zero entries (representing links) are equal to 1.

Given a node $i \in \mathcal{V}$, k_i denotes its (weighted) *degree*, defined as $k_i = \sum_{j \in \mathcal{V}} a_{ij}$.

In an unweighted network, the degree k_i equals the number of nodes that node i is connected to, known as its *neighbors*.

A dynamic network is characterized by a time-varying graph $\mathcal{G}(t) = (\mathcal{V}, \mathcal{E}(t), A(t))$,

where t may be a discrete or continuous index. The n nodes in the node set $\mathcal{V} = 1, \ldots, n$ remain unchanged over time and are interconnected through a time-varying set of links $\mathcal{E}(t)$. The matrix $A(t) \in \mathbb{R}_{\geq 0}^{n \times n}$ represents the time-varying (weighted) adjacency matrix, indicating the strengths of connections between nodes at time t. [8]

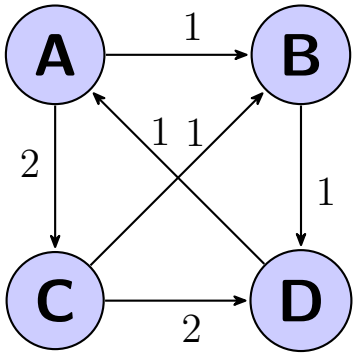


Figure 2.1: A directed and weighted graph with nodes A, B, C, and D. Some edges have a weight of 1 and others have a weight of 2.

2.2 Basic elements of compartmental models in epidemiology

2.2.1 Standard SI model

The simplest model of an infectious disease, known as the SI model, classifies individuals as either susceptible (S) or infective (I). In this model, susceptible individuals can become infective through contact with infective individuals. We assume that the population is well-mixed, meaning every person has an equal probability of coming into contact with any other person. Note that this is a significant approximation.

To derive the governing differential equation for the SI model, we analyze the number of individuals who become infective over a small time interval Δt. Let $\beta \Delta t$ represent the probability that a random infective individual infects a random susceptible individual during this interval. With S susceptible individuals and I infective individuals, the expected number of new infections in the population during time Δt is given by $\beta \Delta t S I$. Therefore,

$$I(t + \Delta t) = I(t) + \beta \Delta t S(t) I(t)$$

Taking the limit as $\Delta t \to 0$, we obtain the differential equation:

$$\frac{dI}{dt} = \beta SI$$

Assuming a constant population size N and neglecting births and deaths, we have $S + I = N$. This allows us to eliminate S and rewrite the equation as:

$$\frac{dI}{dt} = \beta NI\left(1 - \frac{I}{N}\right)$$

This equation is recognized as a logistic equation, with a growth rate of βN and a carrying capacity of N. As $t \to \infty$, $I \to N$, meaning the entire population will eventually become infective. [9]

2.2.2 SI model with vital dynamics

To incorporate vital dynamics into an SI model, let ω and μ represent the birth and death rates, respectively. To maintain a constant population size, one should assume $\omega = \mu$. The ordinary differential equations (ODEs) for the model then become:

$$\begin{cases} \frac{dS}{dt} = \omega - \beta SI - \mu S \\ \frac{dI}{dt} = \beta SI - \mu I \end{cases}$$

The terms ω and μS in the equation for $\frac{dS}{dt}$ account for the births and deaths among the susceptible individuals, while βSI represents the infection process. Similarly, in the equation for $\frac{dI}{dt}$, βSI represents the new infections, and μI accounts for the deaths among the infective individuals.

To find the steady-state solution, we set $\frac{dS}{dt} = 0$ and $\frac{dI}{dt} = 0$:

$$\begin{cases} 0 = \omega - \beta SI - \mu S \\ 0 = \beta SI - \mu I \end{cases}$$

From the second equation:

$$S = \frac{\mu}{\beta}$$

As mentioned, when $\omega = \mu$, it implies that the population remains constant, so $S + I = N$. Therefore:

$$I = N - S = N - \frac{\mu}{\beta}$$

Thus, the final number of infected individuals is related to both the vital dynamics and the infection rate β. The parameter β can be determined by analyzing the steady-state condition, as shown in the equations above. [10]

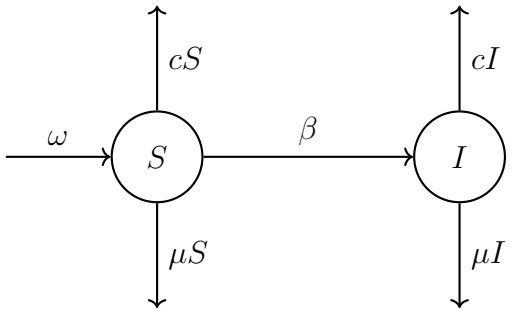


Figure 2.2: In an SI model with vital dynamics, susceptible individuals (S) transition to infective individuals (I) with rate β. The birth rate (ω) contributes to the susceptible population, while the death rate (μ) reduces both the susceptible and infective populations. Additionally, when dealing with a population of vectors that spread a disease, control terms with weight c may be included to model interventions.

2.2.3 SIS model

The standard SI model may be extended to the SIS model, where an infective can recover and become susceptible again. We assume that the probability that an infective recovers during time Δt is given by $\gamma \Delta t$. Then the total number of infective people that recover during time Δt is given by $I\gamma\Delta t$, and

$$I(t + \Delta t) = I(t) + \beta \Delta t S(t) I(t) - \gamma \Delta t I(t)$$

or as $\Delta t \to 0$,

$$\frac{dI}{dt} = \beta SI - \gamma I$$

Using $S + I = N$, we eliminate S to obtain

$$\frac{dI}{dt} = (\beta N - \gamma) I \left(1 - \frac{I}{N - \gamma/\beta}\right)$$

which is again a logistic equation, but now with growth rate $\beta N - \gamma$ and carrying capacity $N - \gamma/\beta$. In the SIS model, an epidemic will occur if $\beta N > \gamma$. And if an epidemic does occur, then the disease becomes endemic with the number of infectives at equilibrium given by $I_* = N - \gamma/\beta$, and the number of susceptibles given by $S_* = \gamma/\beta$.

In general, an important metric for whether or not an epidemic will occur is called the basic reproductive ratio or number. The basic reproductive ratio is defined as the average number of people that one infected individual will transmit the infection to in a fully susceptible population. To compute the basic reproductive

ratio, define $l(t)$ to be the probability that an individual initially infected at $t = 0$ is still infective at time t. Since the probability of being infective at time $t + \Delta t$ is equal to the probability of being infective at time t multiplied by the probability of not recovering during time Δt, we have

$$l(t + \Delta t) = l(t)(1 - \gamma \Delta t)$$

or as $\Delta t \to 0$,

$$\frac{dl}{dt} = -\gamma l$$

With initial condition $l(0) = 1$,

$$l(t) = e^{-\gamma t}$$

Now, the expected number of secondary infections produced by a single primary infective over the time period $(t, t + \Delta t)$ is given by the probability that the primary infective is still infectious at time t multiplied by the expected number of secondary infections produced by a single infective during time Δt; that is, $l(t)S(t)\beta\Delta t$. Here, the definition of the basic reproductive ratio assumes that the entire population is susceptible so that $S(t) = N$. Therefore, the expected number of secondary infectives produced by a single primary infective in a completely susceptible population is

$$\int_0^\infty \beta l(t) N \, dt = \beta N \int_0^\infty e^{-\gamma t} \, dt = \frac{\beta N}{\gamma}$$

The basic reproductive ratio, written as

$$\mathcal{R}_0 = \frac{\beta N}{\gamma}$$

We can see that in the SIS model an epidemic will occur if $\mathcal{R}_0 > 1$. In other words, an epidemic can occur if, on average, one infected individual in a fully susceptible population infects more than one other individual.

In the SIS model, after an epidemic occurs the population reaches an equilibrium between susceptible and infective individuals. The effective basic reproductive ratio of this steady-state population can be defined as $\beta S_*/\gamma$, and with $S_* = \gamma/\beta$ this ratio is equal to 1. Clearly, for a population to be in equilibrium, an infective individual must infect on average one other individual before he or she recovers. [9]

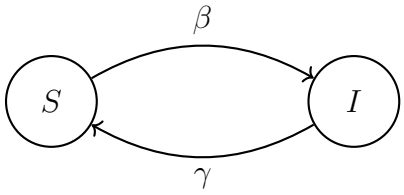


Figure 2.3: In a simple SIS model, S transitions to I with parameter β, and I transitions back to S with parameter γ.

2.3 Stability in dynamical systems

Let χ be a locally compact metric space. A dynamical system (also known as a flow map) with state space χ is a continuous function

$$\phi : \mathbb{R} \times \chi \to \chi$$

such that:

1. $\phi(0, x) = x$ for every $x \in \chi$;
2. $\phi(t, \phi(s, x)) = \phi(t + s, x)$ for every $t, s \in \mathbb{R}$ and $x \in \chi$.

For a dynamical system $\phi : \mathbb{R} \times \chi \to \chi$ and $x \in \chi$:

- The **orbit** through x is the set $\gamma(x) = \{\phi(t, x) : t \in \mathbb{R}\}$.
- The **positive orbit** through x is the set $\gamma^+(x) = \{\phi(t, x) : t \geq 0\}$.
- x is an **equilibrium** if $\phi(t, x) = x$ for all $t \in \mathbb{R}$, i.e., if $\gamma(x) = \{x\}$.
- x is a **periodic point** if x is not an equilibrium and there exists $T > 0$ such that $\phi(T, x) = x$. The smallest such T is the **period**.
- A **cycle** is the orbit of a periodic point.

For a dynamical system $\phi(t, x)$, a set $\mathcal{M} \subseteq \chi$ is:

- **Invariant** if $x \in \mathcal{M} \implies \gamma(x) \subseteq \mathcal{M}$.
- **Positively invariant** if $x \in \mathcal{M} \implies \gamma^+(x) \subseteq \mathcal{M}$.

For a point $x \in \chi$:

- The **positive limit set** is $\Lambda^+(x) = \{y \in \chi : \exists \text{ sequence } t_k \to +\infty \text{ s.t. } \phi(t_k, x) \to y\}$.

- The **prolonged orbit** is $D^+(x) = \{y \in \chi : \exists\, y_k \to y,\, x_k \to x,\, t_k \geq 0 \,\text{s.t.}\, \phi(t_k, x_k) = y_k\}$.
- The **prolonged limit set** is $J^+(x) = \{y \in \chi : \exists\, y_k \to y,\, x_k \to x,\, t_k \to +\infty \,\text{s.t.}\, \phi(t_k, x_k) = y_k\}$.

Theorem 2.3.1 (Poincaré-Bendixson)**.** *Let $\chi = \mathbb{R}^2$ and let x be a point such that the trajectory $\gamma^+(x)$ is bounded. Then the following alternatives hold:*

- *The set $\Lambda^+(x)$ consists of an equilibrium point.*
- *The set $\Lambda^+(x)$ consists of a cycle.*
- *The set $\Lambda^+(x)$ consists of the support of a closed curve, on which at least one equilibrium point lies, and which can be represented as the union (finite or infinite) of equilibrium points and open trajectories.*

Corollary 2.3.2. *If $x \in \mathbb{R}^2$ is such that $\overline{\gamma^+(x)} \subseteq C$ where $C \subseteq \mathbb{R}^2$ is bounded and contains no equilibrium points, then there exists a cycle in C.*

Corollary 2.3.3. *If $C \subseteq \mathbb{R}^2$ is the interior region of a cycle, then C contains at least one equilibrium point.*

Definition 2.3.1. *Given a dynamical system $\phi(t, x)$, a compact $\mathcal{M} \subseteq \chi$ and a set $B(\mathcal{M}, \delta) = \bigcup_{x \in \mathcal{M}} B(x, \delta)$ where $B(x, \delta)$ is a sphere of centre x and radius δ:*

- *The system is **Lagrange stable** if $\gamma^+(x)$ is bounded for every $x \in \chi$.*
- *$\mathcal{M}$ is (**Lyapunov**) **stable** if for every $\epsilon > 0$ there exists $\delta > 0$ such that*

$$x \in B(\mathcal{M}, \delta) \implies \gamma^+(x) \subseteq B(\mathcal{M}, \epsilon).$$

Definition 2.3.2. *Given a point $x \in \chi$ and a set $\mathcal{M} \subseteq \chi$*

- *x is **attracted** by $\mathcal{M}$ if $\lim_{t \to +\infty} dist(\phi(t, x), \mathcal{M}) = 0$.*
- *x is **uniformly attracted** by $\mathcal{M}$ if for every $\epsilon > 0$, there exist $\delta > 0$ and $T > 0$ such that $dist(x, y) < \delta \implies dist(\phi(t, y), \mathcal{M}) < \epsilon$ for all $t \geq T$.*
- *$\mathcal{A}(\mathcal{M}) = \{x \in \chi \mid x \text{ is attracted by } \mathcal{M}\}$ is the **basin of attraction** of $\mathcal{M}$.*
- *$\mathcal{A}_u(\mathcal{M}) = \{x \in \chi \mid x \text{ is uniformly attracted by } \mathcal{M}\}$ is the **basin of uniform attraction** of $\mathcal{M}$.*

Note that the distance between the point $\phi(t, x)$ and the set $\mathcal{M}$ is defined as $dist(\phi(t, x), \mathcal{M}) = \inf_{y \in \mathcal{M}} \|\phi(t, x) - y\|$.

Definition 2.3.3. *Given a compact $\mathcal{M} \subseteq \chi$*

- *$\mathcal{M}$ is an **attractor** if there exists $\eta > 0$ such that $B(\mathcal{M}, \eta) \subseteq \mathcal{A}(\mathcal{M})$.*
- *A cycle that is an attractor is called a **limit cycle**.*

Theorem 2.3.4. *If $\mathcal{M}$ is compact and stable, then $\mathcal{A}(\mathcal{M}) = \mathcal{A}_u(\mathcal{M})$.*

Definition 2.3.4. *A compact set $\mathcal{M} \subseteq \chi$ is **asymptotically stable** if it is a stable attractor. In this case, $\mathcal{A}(\mathcal{M}) = \mathcal{A}_u(\mathcal{M})$ is the region of asymptotic stability.*

Theorem 2.3.5. *If $\mathcal{M} \subseteq \chi$ is compact, positively invariant, and a uniform attractor, then $\mathcal{M}$ is stable.*

Definition 2.3.5. *The motion associated with a point x is:*

- ***Stable** if for every $\epsilon > 0$ there exists $\delta > 0$ such that $dist(x, y) < \delta \implies dist(\phi(x, t), \phi(y, t)) < \epsilon$ for all $t \geq 0$.*
- ***(Locally) asymptotically stable** if it is stable and there exists $\delta_0 > 0$ such that $dist(x, y) < \delta_0 \implies \lim_{t \to +\infty} dist(\phi(x, t), \phi(y, t)) = 0$.*

Definition 2.3.6 (Global stability)**.** *A compact set $\mathcal{M}$ is **globally asymptotically stable** if $\mathcal{A}(\mathcal{M}) = \chi$.*

Finite-dimensional continuous-time dynamical systems associated with autonomous ordinary differential equations (ODEs) can be written in the form

$$\dot{x} = f(x)$$

where $x \in \mathbb{R}^n$ is the state vector and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a vector field of class $\mathcal{C}^r$ $(r \geq 1)$.

Theorem 2.3.6 (Stability via first-order approximation)**.** *Given a system in the form*

$$\dot{x} = Ax + \tilde{f}(x), \quad x \in \mathbb{R}^n$$

where $\tilde{f}$ is a function such that $\lim_{\|x\| \to 0} \frac{\|\tilde{f}(x)\|}{\|x\|} = 0$. If all the eigenvalues of A have negative real parts, then the origin is a (locally) asymptotically stable equilibrium for the system. If A has one or more eigenvalues with positive real parts, the origin is unstable for the system.

[11][2]

Note that any nonlinear system $\dot{x} = f(x)$, with $f \in C^1$ and $f(\mathbf{0}) = \mathbf{0}$, can be rewritten as $\dot{x} = f(x) = Ax + \tilde{f}(x)$, where $A = J_f(\mathbf{0})$ is the Jacobian matrix evaluated at $\mathbf{0}$, and $\|\tilde{f}(x)\| = O(\|x\|^2)$ as $x \to \mathbf{0}$.

Moreover, by employing a change of variables, we are able to linearize around any equilibrium. Let y be such that $y = x - x^*$, where x^* is an equilibrium point for $\dot{x} = f(x)$. Then the system can be rewritten in terms of y as:

$$\dot{y} = g(y), \quad \text{where} \quad g(y) = f(y + x^*).$$

Note that $g(\mathbf{0}) = f(x^*) = \mathbf{0}$. The Jacobian matrix J_g of $g(y)$ at $y = \mathbf{0}$ is given by:

$$J_g = \left.\frac{\partial g}{\partial y}\right|_{y=\mathbf{0}}.$$

Since $g(y) = f(y + x^*)$, it follows that:

$$J_g = \left.\frac{\partial f}{\partial x}\right|_{x=x^*}.$$

Thus, J_g is the Jacobian matrix of $f(x)$ evaluated at the equilibrium point x^*.

If all eigenvalues of the Jacobian matrix J_g have negative real parts, the equilibrium point x^* is asymptotically stable. If at least one eigenvalue of J_g has a positive real part, the equilibrium point x^* is unstable. If all eigenvalues of J_g have non-positive real parts (with at least one eigenvalue having a real part equal to zero), further analysis is required. In this case, linearization may be inconclusive, and other methods, such as Lyapunov's direct method, may be necessary to determine stability.

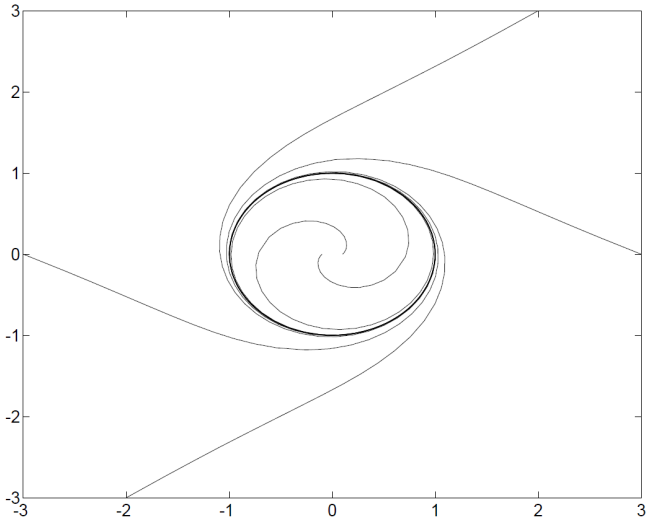


Figure 2.4: System with a single equilibrium point and a single cycle [2]

2.4 Monotone dynamical systems

In this section, we provide an introduction to monotone dynamical systems, i.e., dynamical systems that preserve a partial order in the state space. A partial order on a set χ is a binary relation $\leq$ that is reflexive (i.e., $x \leq x$ for every $x \in \chi$), antisymmetric (i.e., if $x \leq y$ and $y \leq x$ then $x = y$), and transitive (i.e., if $x \leq y$ and $y \leq z$ then $x \leq z$). Note that the term "partial" indicates that not every pair of elements in χ needs to be comparable. When every two elements in χ are comparable, the order is called "total".

Definition 2.4.1. *Let χ be a state space equipped with a partial order $\leq$. A dynamical system $\phi : \mathbb{R} \times \chi \to \chi$ is **monotone** if*

$$x \leq y \implies \phi(t, x) \leq \phi(t, y), \quad \forall t \geq 0.$$

Definition 2.4.1 states that a monotone system is such that, if two initial conditions are ordered, the same same order is kept by the trajectories at any time $t \geq 0$.

While the theory can be developed in a very general setting, we shall now focus on dynamical systems associated to differential equations on $\mathbb{R}^n$. We shall use the following notational convention for vectors x, y in $\mathbb{R}^n$: inequalities are meant to hold true entry-wise: so, e.g., $x \leq y$ means that $x_i \leq y_i$ for every $i = 1, \ldots, n$.Clearly, the relation $\leq$ induces a partial ordering on $\mathbb{R}^n$. In the following, we are going to focus on the case where the dynamical system is associated to an autonomous differential equation

$$\dot{x} = f(x)$$

where $f : \chi \to \mathbb{R}^n$ is a $\mathcal{C}^1$ vector field (though Lipschitz-continuity would suffice), and $\chi \subseteq \mathbb{R}^n$ is a nonempty closed invariant set. In this case, the monotonicity property can be given a simple characterization as illustrated in the following. First, it is easily seen that every single-dimensional dynamical system is monotone, as stated below.

Proposition 2.4.1. *Every dynamical system $\phi : \mathbb{R} \times \chi \to \chi$ with state space $\chi \subseteq \mathbb{R}$ is monotone.*

We first focus on the class of linear dynamical systems and provide necessary and sufficient conditions for their monotonicity. To this end, we introduce the following definitions.

Definition 2.4.2. *A dynamical system with state space $\mathbb{R}^n$ is positive if it leaves the nonnegative orthant $\mathbb{R}^n_+$ invariant.*

Definition 2.4.3. *A matrix $A \in \mathbb{R}^{n\times n}$ is referred to as **Metzler** if its off-diagonal entries are nonnegative, i.e.,*

$$A_{ij} \geq 0 \quad \forall i \neq j.$$

Proposition 2.4.2. *Consider a linear dynamical system $\dot{x} = Ax$ on $\mathbb{R}^n$. The following statements are equivalent:*

1. *The system is monotone.*
2. *The system is positive.*
3. *The matrix A is Metzler.*

We now move on to the case of multi-dimensional non-linear systems.

Lemma 2.4.3. *A dynamical system $\dot{x} = f(x)$ with closed state space χ and Lipschitz-continuous vector field $f : \chi \to \mathbb{R}^n$ is monotone if and only if*

$$f_i(x) \leq f_i(y),$$

for every x and y in χ and $1 \leq i \leq n$ such that

$$x \leq y, \quad x_i = y_i$$

Theorem 2.4.4. *A dynamical system $\dot{x} = f(x)$ with closed state space $\chi \subseteq \mathbb{R}^n$ and Lipschitz-continuous vector field $f : \chi \to \mathbb{R}^n$ is monotone if and only if the Jacobian matrix $J_f(x)$ is a Metzler matrix for almost every x in χ.*

[12]

2.5 Deterministic network SIS model

We now consider the deterministic network SIS epidemic model. Let n be the number of populations interacting according to a nonnegative interaction matrix $W \in \mathbb{R}^{n\times n}_{\geq 0}$, where W_{ij} represents the rate at which members of population i meet members of population j. Let $x_i(t)$ and $y_i(t)$ be the fractions of susceptible and infected individuals in population i ($i = 1, \ldots, n$), respectively. Let $\beta > 0$ and $\gamma > 0$ be the contagion and recovery rates. The evolution of the epidemic is then given by:

$$\dot{x}_i = \beta x_i \sum_{j=1}^{n} W_{ij} y_j - \gamma y_i \qquad \dot{y}_i = \beta x_i \sum_{j=1}^{n} W_{ij} y_j - \gamma y_i$$

for $i = 1, \ldots, n$. As in the scalar case, we notice that $\dot{x}_i + \dot{y}_i = 0$, allowing us to eliminate the variables x_i and rewrite the deterministic network SIS epidemic model in terms of the fractions of infected individuals in the different populations:

$$\dot{y}_i = \beta(1 - y_i) \sum_{j=1}^{n} W_{ij} y_j - \gamma y_i, \quad i = 1, \ldots, n.$$

We have the following result:

Lemma 2.5.1. *Consider the deterministic network SIS model with an irreducible interaction matrix W, transmission rate $\beta > 0$, and recovery rate $\gamma > 0$. Then:*

(i) Every equilibrium point $y^* \neq \mathbf{0}$ is such that $y^* > \mathbf{0}$.

(ii) There exists at most one positive equilibrium point $y^* > \mathbf{0}$.

Theorem 2.5.2. *Consider the deterministic network SIS model with an irreducible interaction matrix W, transmission rate $\beta > 0$, and recovery rate $\gamma > 0$. Let λ_W be the dominant eigenvalue of W (i.e. $|\lambda_W| = \max\{|\lambda_1|, |\lambda_2|, \ldots, |\lambda_n|\}$). Then:*

- *If $\beta\lambda_W \leq \gamma$, then $\mathbf{0}$ is a globally asymptotic equilibrium point for the system in $[0,1]^n$.*
- *If $\beta\lambda_W > \gamma$, then $\mathbf{0}$ is an unstable equilibrium point, and there exists an endemic equilibrium point y^* in $(0,1]^n$ that is locally asymptotically stable and attracts the whole $[0,1]^n \setminus \{\mathbf{0}\}$.*

[12]

Chapter 3

Compartmental models

We are interested in studying dengue spread dynamics to determine the most effective methods for halting transmission and achieving a disease-free status. Dengue is prevalent in tropical regions, and cases that are "imported" (where individuals travel to other countries, contract dengue, and return infected) pose significant concerns for European authorities. In mathematical modelling, dengue is peculiar because its spread requires the coexistence of both a host population (humans) and a vector population (mosquitoes) in the same area since transmission occurs only when a vector bites a host. Therefore, it is necessary to include at least one host population and one vector population when formalizing the model. In the compartmental models, we assume that the human and mosquito populations coexist within the same region and do not have any external interactions.

3.1 Modeling dengue dynamics with the SIS Framework

The initial model we consider represents the scenario of one host population and one vector population using the SIS (Susceptible-Infected-Susceptible) framework.

To this purpose let us define the following quantities and parameters:

- $s_1(t) \in [0,1]$: The fraction of susceptible hosts in the host population.
- $x_1(t) \in [0,1]$: The fraction of infected hosts in the host population.
- $s_2(t) \in [0,1]$: The fraction of susceptible vectors in the vector population.
- $x_2(t) \in [0,1]$: The fraction of infected vectors in the vector population.
- $\beta_1 > 0$: The contagion rate from hosts to vectors.

- $\gamma_1 > 0$: The recovery rate of hosts.
- $\beta_2 > 0$: The contagion rate from vectors to hosts.
- $\gamma_2 > 0$: The recovery rate of vectors.

The health states of the populations are described by the two-dimensional state variables $[s_1(t), x_1(t)]^\top$ and $[s_2(t), x_2(t)]^\top$, which evolve according to the following systems of ordinary differential equations (ODEs):

$$\begin{cases} \dot{s_1}(t) = -\beta_2 x_2(t) s_1(t) + \gamma_1 x_1(t) \\ \dot{x_1}(t) = \beta_2 x_2(t) s_1(t) - \gamma_1 x_1(t) \end{cases} \qquad \begin{cases} \dot{s_2}(t) = -\beta_1 x_1(t) s_2(t) + \gamma_2 x_2(t) \\ \dot{x_2}(t) = \beta_1 x_1(t) s_2(t) - \gamma_2 x_2(t) \end{cases} .$$

Since the total mass in both populations is preserved (i.e. $\dot{s_i} + \dot{x_i} = 0$, $i = 1,2$), the two systems consist of linearly dependent equations. Consequently, they can be reduced to a single nonlinear ODE for each population, from which it is straightforward to observe that the domain $[0,1]^2$ is positively invariant. Therefore, after coupling the two equations, we obtain the following system:

$$\begin{cases} \dot{x_1}(t) = -\gamma_1 x_1(t) + \beta_2 (1 - x_1(t)) x_2(t) \\ \dot{x_2}(t) = -\gamma_2 x_2(t) + \beta_1 (1 - x_2(t)) x_1(t) \end{cases} . \tag{3.1}$$

Let us observe that if we were to consider the specific case $\beta_1 = \beta_2 = \beta$ and $\gamma_1 = \gamma_2 = \gamma$, we could use the results from 2.5.2: the interaction matrix is

$$W = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix},$$

and with $\lambda_W = 1$, we have that if $\beta \leq \gamma$, then $\mathbf{0}$ is a globally asymptotically stable equilibrium point for the system in $[0,1]^2$. Otherwise, $\mathbf{0}$ is an unstable equilibrium point, and there exists an endemic equilibrium point x^* in $(0,1]^2$ that is locally asymptotically stable and attracts the whole $[0,1]^2 \setminus \mathbf{0}$. In this case, the expression of the endemic equilibrium is $x_1^* = x_2^* = \frac{\beta^2 - \gamma^2}{\beta(\beta+\gamma)}$. The division between the two behaviors the system can exhibit in the specific case can also be discerned using the epidemic threshold. This is achieved by determining whether the ratio β/γ is less than or equal to 1 or greater than 1.

In general ($\beta_1 \neq \beta_2$ and $\gamma_1 \neq \gamma_2$), the equilibria are $\mathbf{0}$ and (x_1^*, x_2^*), with

$$\begin{cases} x_1^* = \frac{\beta_1\beta_2 - \gamma_1\gamma_2}{\beta_1(\gamma_1 + \beta_2)} \\ x_2^* = \frac{\beta_1\beta_2 - \gamma_1\gamma_2}{\beta_2(\gamma_2 + \beta_1)} \end{cases} .$$

Using 2.3.6, we can determine the conditions under which the disease-free equilibrium is locally asymptotically stable.

Let us call

$$f(x_1, x_2) = \begin{bmatrix} \dot{x_1} \\ \dot{x_2} \end{bmatrix},$$

then we can calculate the Jacobian matrix of $f(x_1, x_2)$, which is

$$J_f(x_1, x_2) = \begin{bmatrix} -\gamma_1 - \beta_2 x_2 & \beta_2 - \beta_2 x_1 \\ \beta_1 - \beta_1 x_2 & -\gamma_2 - \beta_1 x_1 \end{bmatrix}.$$

Remark 1. *Consider the dynamical system 3.1. There are no limit cycles in the system because it is positive monotone, given that the Jacobian matrix $J_f(x)$ is Metzler.*

Theorem 3.1.1. *Consider the dynamical system 3.1. The epidemic threshold is determined by the ratio $\frac{\beta_1\beta_2}{\gamma_1\gamma_2}$, and the following statements hold:*

- *If $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} < 1$, the disease-free equilibrium $(x_1^o, x_2^o) = (0, 0)$ is globally asymptotically stable.*
- *If $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} > 1$, the disease-free equilibrium $(x_1^o, x_2^o) = (0, 0)$ is unstable, and there exists a unique endemic equilibrium (x_1^*, x_2^*) that is globally asymptotically stable.*

Proof. The Jacobian matrix at the disease-free equilibrium $(0, 0)$ is:

$$J_f(0{,}0) = \begin{bmatrix} -\gamma_1 & \beta_2 \\ \beta_1 & -\gamma_2 \end{bmatrix}$$

The eigenvalues of $J_f(0{,}0)$ are the solutions to the characteristic equation:

$$\det(J_f(0{,}0) - \lambda I) = \begin{vmatrix} -\gamma_1 - \lambda & \beta_2 \\ \beta_1 & -\gamma_2 - \lambda \end{vmatrix} = 0$$

Hence, we find the following:

$$\lambda_{1,2} = \frac{-(\gamma_1 + \gamma_2) \pm \sqrt{(\gamma_1 + \gamma_2)^2 - 4(\gamma_1\gamma_2 - \beta_1\beta_2)}}{2}$$

The disease-free equilibrium $(0, 0)$ is locally asymptotically stable if both eigenvalues have negative real parts. This occurs if and only if $\gamma_1\gamma_2 > \beta_1\beta_2$, i.e.,

$\frac{\beta_1\beta_2}{\gamma_1\gamma_2} < 1$. Moreover, the other equilibrium (x_1^*, x_2^*) exists in $\chi = [0,1]^2$ if and only if $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} > 1$.

To determine the stability of (x_1^*, x_2^*), we linearize the system around (x_1^*, x_2^*) and analyze the Jacobian matrix evaluated at (x_1^*, x_2^*):

$$J_f(x_1^*, x_2^*) = \begin{bmatrix} -\frac{\beta_1(\gamma_1+\beta_2)}{\beta_1+\gamma_2} & \frac{\gamma_1(\beta_1\beta_2+\beta_2\gamma_2)}{\beta_1(\gamma_1+\beta_2)} \\ \frac{\gamma_2(\beta_1\beta_2+\beta_1\gamma_1)}{\beta_2(\gamma_2+\beta_1)} & -\frac{\beta_2(\gamma_2+\beta_1)}{\beta_2+\gamma_1} \end{bmatrix}$$

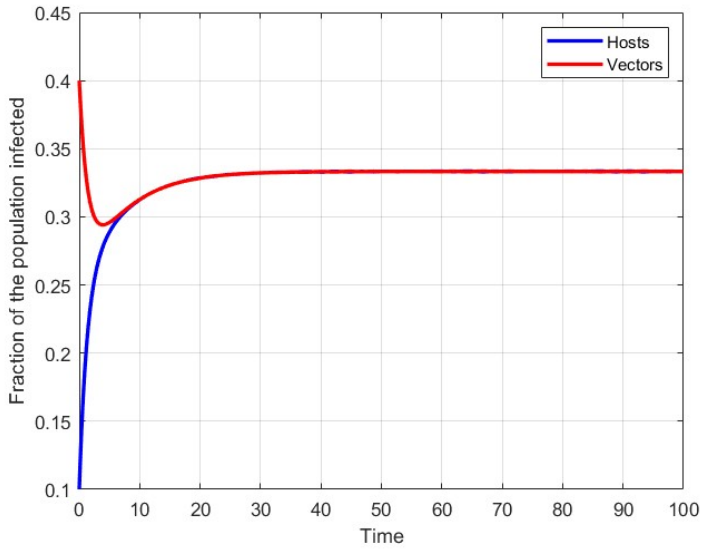
The eigenvalues of this matrix have negative real parts if and only if $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} > 1$, ensuring that (x_1^*, x_2^*) is globally asymptotically stable (note that here $\mathbf{0}$ is a singularity and it does not undermine global stability).

Thus, if $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} < 1$, the disease-free equilibrium $(0, 0)$ is globally asymptotically stable. If $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} > 1$, the disease-free equilibrium is unstable, and there exists a unique globally asymptotically stable endemic equilibrium (x_1^*, x_2^*). Hence, the epidemic threshold of this model is determined by $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} = 1$. □

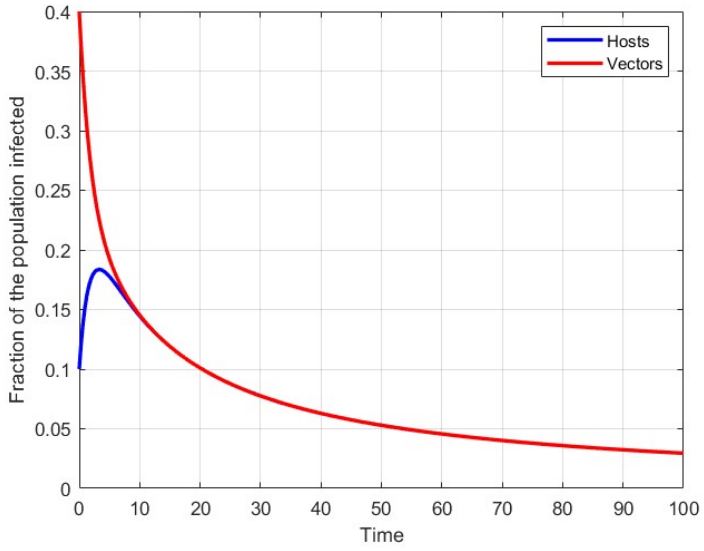
In 3.1 and 3.2, we simulate the model's behaviors for the specific case $\beta_1 = \beta_2 = \beta$ and $\gamma_1 = \gamma_2 = \gamma$ and the general case.

In the specific case simulation, we simulate both $\beta/\gamma = 1.5$ (i.e., above the epidemic threshold), and $\beta/\gamma = 1$ (i.e., below the epidemic threshold). Below the epidemic threshold, both trajectories converge to the disease-free equilibrium; above the epidemic threshold, they both converge to the endemic equilibrium $x_i^* = \frac{1}{3}$, $i = 1,2$.

In the general case simulation, we simulate both $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} > 1$ (i.e., above the epidemic threshold) and $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} = 1$ (i.e., at the epidemic threshold). At the epidemic threshold, both trajectories converge to the disease-free equilibrium; above the epidemic threshold, they converge to population-specific endemic equilibria.

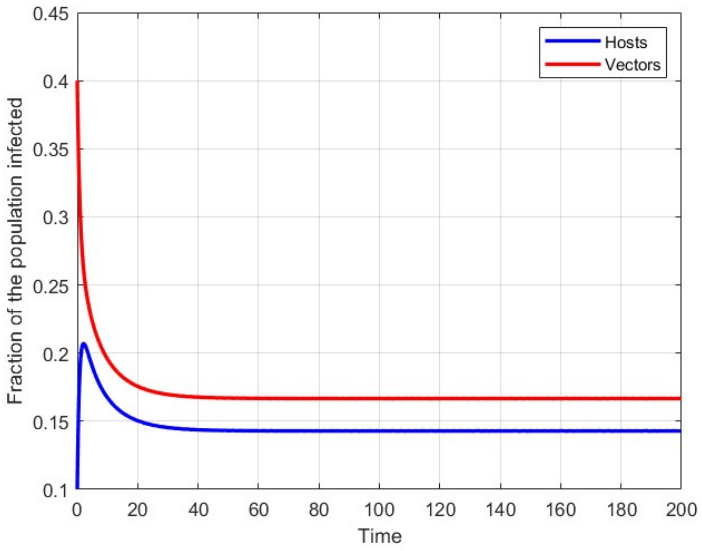


(a)

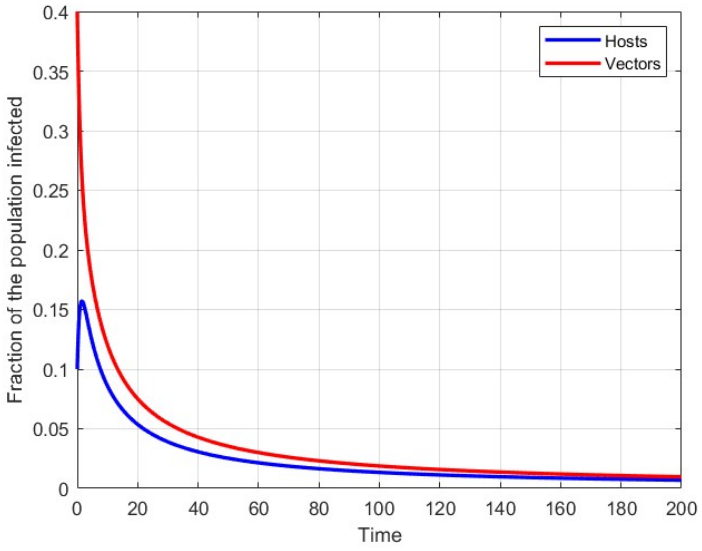


(b)

Figure 3.1: Two trajectories with same initial conditions $x_1(0) = 0.1$ and $x_2(0) = 0.4$ of the two populations SIS model 3.1 with $\beta_1 = \beta_2 = \beta$ and $\gamma_1 = \gamma_2 = \gamma$: (a) $\beta/\gamma = 1.5$ (i.e., above the epidemic threshold); (b) $\beta/\gamma = 1$ (i.e., below the epidemic threshold). Below the epidemic threshold, both trajectories converge to the disease free equilibrium; above the epidemic threshold, they both converge to the endemic equilibrium $x_i^* = \frac{1}{3}$, $i = 1,2$.



(a)



(b)

Figure 3.2: Two trajectories with same initial conditions $x_1(0) = 0.1$ and $x_2(0) = 0.4$ of the general two populations SIS model 3.1: (a) $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} > 1$ (i.e., above the epidemic threshold); (b) $\frac{\beta_1\beta_2}{\gamma_1\gamma_2} = 1$ (i.e., at the epidemic threshold). At the epidemic threshold, both trajectories converge to the disease free equilibrium; above the epidemic threshold, they converge to population-specific endemic equilibria.

3.2 Modeling the vector population dynamics with a SI

When formalizing a dengue spread dynamics model, it is appropriate to consider the significant gap between the lifespan of hosts and vectors. The lifespan of female mosquitoes is estimated to be less than two months. Therefore, it is suitable to omit the recovery dynamics of mosquitoes from dengue disease while incorporating birth and death rates for the vector population.

In this model, we use an open SI framework to model the vector population dynamics. For this purpose, we need to redefine the quantities related to the vector population. We can no longer use fractions of susceptible and infected vectors, as the set $[0,1]^3$ is not positively invariant. Hence, we define S_2 and X_2 as the number of susceptible and infected vectors, respectively, which sum to a total vector population that varies with time.

However, we keep an SIS framework to model the dynamics in the host population. Therefore, we can still use the quantities $s_1(t)$ and $x_1(t)$ such that $s_1(t) + x_1(t) = 1$. Let us define $\omega > 0$ and $\mu > 0$ as the vector recruitment and death rates, respectively. While we start with four ODEs, we find again that the equations for $\dot{s_1}$ and $\dot{x_1}$ are linearly dependent, allowing us to reduce the system to three equations.

The model is described by the following system of ODEs:

$$\begin{cases} \dot{x_1}(t) = -\gamma_1 x_1(t) + \beta_2(1 - x_1(t))X_2(t) \\ \dot{S_2}(t) = \omega - \mu S_2(t) - \beta_1 x_1(t) S_2(t) \\ \dot{X_2}(t) = \beta_1 x_1(t) S_2(t) - \mu X_2(t) \end{cases}, \tag{3.2}$$

which is characterized by equilibria

$$\begin{cases} x_1^o = 0 \\ S_2^o = \frac{\omega}{\mu} \\ X_2^o = 0 \end{cases} \quad \begin{cases} x_1^* = \frac{\omega\beta_1\beta_2 - \mu^2\gamma_1}{\omega\beta_1\beta_2 + \mu\gamma_1\beta_1} \\ S_2^* = \frac{\gamma_1\mu + \beta_2\omega}{\beta_2(\beta_1 + \mu)} \\ X_2^* = \frac{\omega\beta_1\beta_2 - \mu^2\gamma_1}{\mu\beta_1\beta_2 + \mu^2\beta_2} \end{cases}.$$

The Jacobian of the system is

$$J_f(x_1, S_2, X_2) = \begin{bmatrix} -\gamma_1 - \beta_2 X_2 & 0 & \beta_2(1 - x_1) \\ -\beta_1 S_2 & -\mu - \beta_1 x_1 & 0 \\ \beta_1 S_2 & \beta_1 x_1 & -\mu \end{bmatrix}.$$

Theorem 3.2.1. *Consider the dynamical system 3.2. The epidemic threshold for this model is determined by the condition:*

$$\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} = 1.$$

If $\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} < 1$*, the disease-free equilibrium* $\left(0, \frac{\omega}{\mu}, 0\right)$ *is locally asymptotically stable. If* $\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} > 1$*, the disease-free equilibrium is unstable and the endemic equilibrium* (x_1^*, S_2^*, X_2^*) *is locally asymptotically stable.*

Proof. Consider the Jacobian of the system at the disease-free equilibrium $\left(0, \frac{\omega}{\mu}, 0\right)$:

$$J_f\left(0, \frac{\omega}{\mu}, 0\right) = \begin{bmatrix} -\gamma_1 & 0 & \beta_2 \\ -\frac{\beta_1\omega}{\mu} & -\mu & 0 \\ \frac{\beta_1\omega}{\mu} & 0 & -\mu \end{bmatrix}.$$

The eigenvalues are given by:

$$\begin{cases} \lambda_1 = -\mu \\ \lambda_{2,3} = \frac{1}{2\mu}\left(-\gamma_1\mu - \mu^2 \pm \sqrt{\mu}\sqrt{\gamma_1^2\mu - 2\gamma_1\mu^2 + \mu^3 + 4\beta_1\beta_2\omega}\right) \end{cases}.$$

To ensure that $\left(0, \frac{\omega}{\mu}, 0\right)$ is locally asymptotically stable, all eigenvalues must have negative real parts. This is true if and only if:

$$\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} < 1.$$

Whereas

$$J_f\left(x_1^*, S_2^*, X_2^*\right) = J_f\left(\frac{\omega\beta_1\beta_2 - \mu^2\gamma_1}{\omega\beta_1\beta_2 + \mu\gamma_1\beta_1}, \frac{\gamma_1\mu + \beta_2\omega}{\beta_2(\beta_1 + \mu)}, \frac{\omega\beta_1\beta_2 - \mu^2\gamma_1}{\mu\beta_1\beta_2 + \mu^2\beta_2}\right) =$$

$$\begin{bmatrix} -\frac{\gamma_1\mu\beta_1 + \omega\beta_1\beta_2}{\mu(\mu+\beta_1)} & 0 & \frac{\mu\gamma_1\beta_1\beta_2 + \mu^2\gamma_1\beta_2}{\omega\beta_1\beta_2 + \mu\gamma_1\beta_1} \\ -\frac{\beta_1\gamma_1\mu + \beta_1\beta_2\omega}{\beta_2(\beta_1+\mu)} & -\mu - \frac{\omega\beta_1\beta_2 - \mu^2\gamma_1}{\omega\beta_2 + \mu\gamma_1} & 0 \\ \frac{\beta_1\gamma_1\mu + \beta_1\beta_2\omega}{\beta_2(\beta_1+\mu)} & \frac{\omega\beta_1\beta_2 - \mu^2\gamma_1}{\omega\beta_2 + \mu\gamma_1} & -\mu \end{bmatrix},$$

whose eigenvalues are

$$
\begin{aligned}
\lambda_1 &= -\mu \\
\lambda_{2,3} &= \frac{1}{2\beta_1\beta_2\mu(\beta_1+\mu)(\gamma_1\mu+\beta_2\omega)}\times \\
&\Bigg(-\beta_1^2\beta_2\gamma_1^2\mu^2 - \beta_1^3\beta_2^2\mu\omega - 2\beta_1^2\beta_2^2\gamma_1\mu\omega - 2\beta_1^2\beta_2^2\mu^2\omega - \beta_1\beta_2^2\mu^3\omega - \beta_1^2\beta_2^3\omega^2 \\
&+ \Big(\beta_1^2\beta_2\gamma_1^2\mu^2 + \beta_1^3\beta_2^2\mu\omega + 2\beta_1^2\beta_2^2\gamma_1\mu\omega + 2\beta_1^2\beta_2^2\mu^2\omega + \beta_1\beta_2^2\mu^3\omega + \beta_1^2\beta_2^3\omega^2\Big)^2. \\
&- 4\Big(-\beta_1^4\beta_2^2\gamma_1^3\mu^5 - 2\beta_1^3\beta_2^2\gamma_1^3\mu^6 - \beta_1^2\beta_2^2\gamma_1^3\mu^7 + \beta_1^5\beta_2^3\gamma_1^2\mu^3\omega \\
&- 3\beta_1^3\beta_2^3\gamma_1^2\mu^5\omega - 2\beta_1^2\beta_2^3\gamma_1^2\mu^6\omega + 2\beta_1^5\beta_2^4\gamma_1\mu^2\omega^2 + 3\beta_1^4\beta_2^4\gamma_1\mu^3\omega^2 \\
&- \beta_1^2\beta_2^4\gamma_1\mu^5\omega^2 + \beta_1^5\beta_2^5\mu\omega^3 + 2\beta_1^4\beta_2^5\mu^2\omega^3 + \beta_1^3\beta_2^5\mu^3\omega^3\Big)\Bigg)^{\frac{1}{2}}
\end{aligned}
$$

These eigenvalues are all with negative real part when the following condition holds:

$$
\begin{aligned}
&\Big(\beta_1\gamma_1^2\mu^2 + \beta_2\mu(\beta_1^2+\mu^2+2\beta_1(\gamma_1+\mu))\omega + \beta_1\beta_2^2\omega^2\Big)^2 > \\
&+ \gamma_1^3\mu^4(8\beta_1\mu^2 + 4\mu^3 + \beta_1^2(\gamma_1+4\mu)) \\
&+ 2\beta_2\gamma_1^2\mu^3(-\beta_1^3 + 7\beta_1\mu^2 + 4\mu^3 + 2\beta_1^2(\gamma_1+\mu))\omega \\
&+ \beta_2^2\mu^2(\beta_1^4 + 4\beta_1^3(-\gamma_1+\mu) + 4\beta_1\mu^2(\gamma_1+\mu) \\
&+ \mu^3(4\gamma_1+\mu) + \beta_1^2(6\gamma_1^2 - 4\gamma_1\mu + 6\mu^2))\omega^2 \\
&- 2\beta_1\beta_2^3\mu(\beta_1^2+\mu^2+2\beta_1(-\gamma_1+\mu))\omega^3 + \beta_1^2\beta_2^4\omega^4,
\end{aligned}
$$

which simplifies to the expression

$$\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} > 1.$$

When this condition holds, the equilibrium $\left(0, \frac{\omega}{\mu}, 0\right)$ is unstable, while the endemic equilibrium (x_1^*, S_2^*, X_2^*) is locally asymptotically stable.

Therefore, the epidemic threshold for this model is determined by the condition:

$$\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} = 1.$$

□

In 3.3 we perform time simulations of this model with the conditions $(\omega, \mu, \beta_1, \beta_2, \gamma_1) =$ (1,0.1,0.2,0.2,0.3) (indicating the system is above the epidemic threshold since $\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} = 13.33$) and with $(\omega, \mu, \beta_1, \beta_2, \gamma_1) =$ (1,0.2,0.2,0.2,1) (indicating the system is at the epidemic threshold since $\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} = 1$). Above the epidemic threshold, the disease becomes endemic among both populations, whereas at the epidemic threshold, the number of susceptible vectors and the fraction of susceptible hosts both converge to $\mathbf{0}$.

Note that in the simulation the ratio is well above the epidemic threshold. Interestingly, for values of the ratio close to 1 but greater, the human population reaches a disease-free equilibrium, while the mosquito population does not.

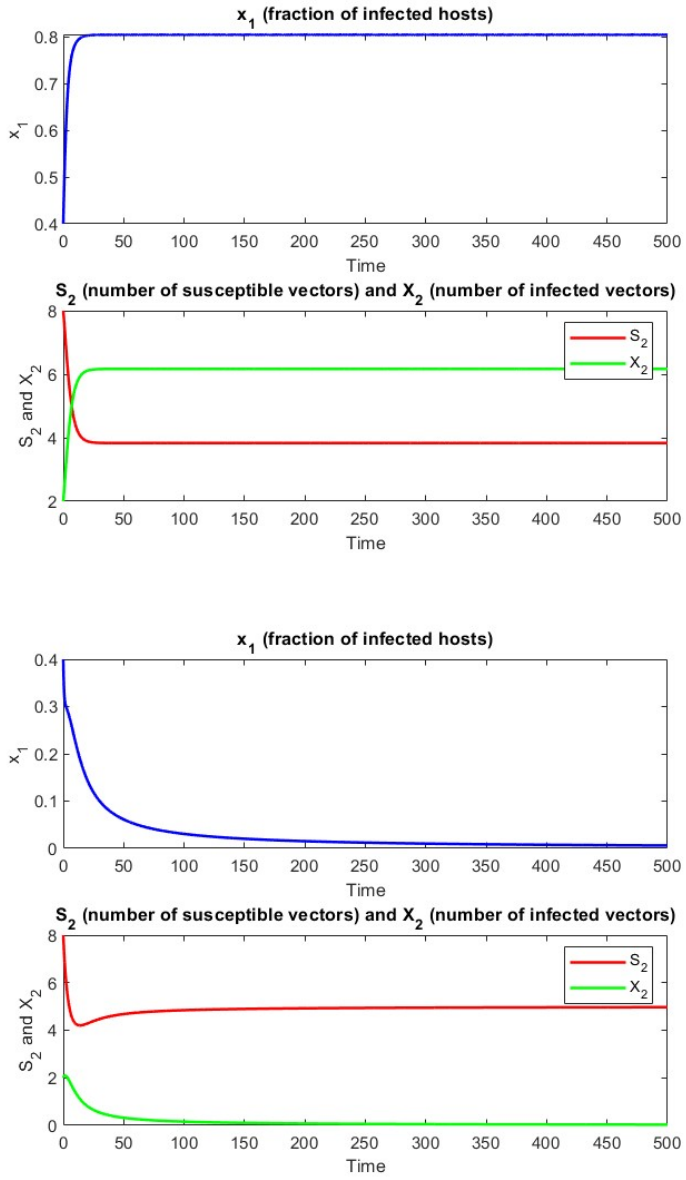


Figure 3.3: Two trajectories with initial conditions $x_1(0) = 0.4$, $S_2(0) = 8$ and $X_2(0) = 2$ for the model with vector dynamics as SI and host dynamics as SIS 3.2: (a) with $(\omega, \mu, \beta_1, \beta_2, \gamma_1) = (1,0.1,0.2,0.2,0.3)$ (i.e., above the epidemic threshold since $\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} = 13.33$); (b) with $(\omega, \mu, \beta_1, \beta_2, \gamma_1) = (1,0.2,0.2,0.2,1)$ (i.e., at the epidemic threshold since $\frac{\beta_1\beta_2\omega}{\gamma_1\mu^2} = 1$). Above the epidemic threshold, the disease becomes endemic among both populations; at the epidemic threshold, the number of susceptible vectors and the fraction of susceptible hosts both converge to $\mathbf{0}$.

Chapter 4

Epidemic control over the SI-SIS compartmental model

4.1 Adding a vector control term

We now try adding a linear vector control term u_1. This term shall be interpreted as vector killing, which affects both susceptible and infected vectors. We first consider the linear vector control terms $u_{11} = -c_1 S_2(t)$ and $u_{12} = -c_1 X_2(t)$.

Therefore, we obtain the following system of ODEs:

$$\begin{cases} \dot{x_1}(t) = -\gamma_1 x_1(t) + \beta_2(1 - x_1(t))X_2(t) \\ \dot{S}_2(t) = \omega - \mu S_2(t) - \beta_1 x_1(t) S_2(t) - c_1 S_2(t) \\ \dot{X}_2(t) = \beta_1 x_1(t) S_2(t) - \mu X_2(t) - c_1 X_2(t) \end{cases} . \tag{4.1}$$

The system is characterized by the following equilibria:

$$\begin{aligned} x_1^{*(1)} &= 0 \\ S_2^{*(1)} &= \frac{\omega}{\mu + c_1} \\ X_2^{*(1)} &= 0 \end{aligned}$$

and

$$
\begin{aligned}
x_1^{*(2)} &= \frac{-c_1^2\gamma_1 - 2c_1\gamma_1\mu - \gamma_1\mu^2 + \beta_1\beta_2\omega}{\beta_1(c_1\gamma_1 + \gamma_1\mu + \beta_2\omega)} \\
S_2^{*(2)} &= \frac{c_1\gamma_1 + \gamma_1\mu + \beta_2\omega}{\beta_2(c_1 + \beta_1 + \mu)} \\
X_2^{*(2)} &= \frac{-c_1^2\gamma_1 - 2c_1\gamma_1\mu - \gamma_1\mu^2 + \beta_1\beta_2\omega}{\beta_2(c_1 + \mu)(c_1 + \beta_1 + \mu)}
\end{aligned}
$$

The Jacobian of the system is

$$
J_f(x_1, S_2, X_2) = \begin{bmatrix} -\gamma_1 - \beta_2 X_2 & 0 & \beta_2(1 - x_1) \\ -\beta_1 S_2 & -\mu - c_1 - \beta_1 x_1 & 0 \\ \beta_1 S_2 & \beta_1 x_1 & -\mu - c_1 \end{bmatrix}.
$$

Theorem 4.1.1. *Consider the dynamical system (4.1). The epidemic threshold for this model is determined by the condition:*

$$
\frac{\beta_1\beta_2\omega}{\gamma_1(\mu + c_1)^2} = 1.
$$

If $\frac{\beta_1\beta_2\omega}{\gamma_1(\mu+c_1)^2} < 1$*, the disease-free equilibrium* $\left(0, \frac{\omega}{\mu+c_1}, 0\right)$ *is the sole equilibrium and it is locally asymptotically stable. If* $\frac{\beta_1\beta_2\omega}{\gamma_1(\mu+c_1)^2} > 1$*, the disease-free equilibrium is unstable and the endemic equilibrium* $\left(x_1^{*(2)}, S_2^{*(2)}, X_2^{*(2)}\right)$ *is locally asymptotically stable.*

Proof. Consider the Jacobian of the system at the disease-free equilibrium $\left(0, \frac{\omega}{\mu+c_1}, 0\right)$:

$$
J_f\left(0, \frac{\omega}{\mu + c_1}, 0\right) = \begin{bmatrix} -\gamma_1 & 0 & \beta_2 \\ -\frac{\beta_1\omega}{\mu+c_1} & -\mu - c_1 & 0 \\ \frac{\beta_1\omega}{\mu+c_1} & 0 & -\mu - c_1 \end{bmatrix}.
$$

To ensure that $\left(0, \frac{\omega}{\mu+c_1}, 0\right)$ is locally asymptotically stable, all eigenvalues must have negative real parts. This is true if and only if:

$$
\frac{\beta_1\beta_2\omega}{\gamma_1(\mu + c_1)^2} < 1.
$$

When this condition is satisfied, $\left(0, \frac{\omega}{\mu+c_1}, 0\right)$ is the sole equilibrium, and thus, it is locally asymptotically stable.

Whereas

$$J_f\left(x_1^{*(2)}, S_2^{*(2)}, X_2^{*(2)}\right) =$$

$$\begin{bmatrix} -\frac{\gamma_1(\mu+c_1)+\beta_2\omega}{\mu+c_1} & 0 & \frac{\beta_2(\beta_1\beta_2\omega-c_1^2\gamma_1-2c_1\gamma_1\mu-\gamma_1\mu^2)}{\beta_1(\mu+c_1)(\mu+c_1+\beta_1)} \\ -\frac{\beta_1\omega}{\beta_2(c_1+\beta_1+\mu)} & -(\mu+c_1)-\frac{\omega\beta_1\beta_2-\mu^2\gamma_1}{\mu\beta_1\beta_2+\mu^2\beta_2} & 0 \\ \frac{\beta_1\omega}{\beta_2(c_1+\beta_1+\mu)} & \frac{\omega\beta_1\beta_2-\mu^2\gamma_1}{\omega\beta_2+\mu\gamma_1} & -(\mu+c_1) \end{bmatrix},$$

whose eigenvalues are all with negative real part when the following condition holds:

$$\frac{\beta_1\beta_2\omega}{\gamma_1(\mu+c_1)^2} > 1.$$

When this condition holds, the equilibrium $\left(0, \frac{\omega}{\mu+c_1}, 0\right)$ is unstable, while the endemic equilibrium $\left(x_1^{*(2)}, S_2^{*(2)}, X_2^{*(2)}\right)$ is locally asymptotically stable.

Therefore, the epidemic threshold for this model is determined by the condition:

$$\frac{\beta_1\beta_2\omega}{\gamma_1(\mu+c_1)^2} = 1.$$

□

As we work with increasingly complex models, it is clear that the Jacobian associated with the system often ceases to be Metzler. Consequently, we cannot readily conclude that the system lacks limit cycles. Instead, we must employ other analytical or numerical methods to investigate this. A common approach to detect limit cycles is by simulating the system's state space orbits. In Figure 4.1, we simulate several orbits for the 4.1 model. Although their behavior appears to suggest absence of limit cycles, proving it may be challenging.

4.2 Adding a control term for hosts

Let us now consider an extension of the previous model that incorporates an additional term: a control factor representing self-protective behavior by the hosts. This behavior reduces the infection rate between host and vector populations, and it can be implemented in various ways, such as wearing long sleeves to reduce the chance of being bitten, using body gel, limiting the time windows are left open, or exercising caution when encountering mosquitoes.

The system of ODEs is the following:

$$\begin{cases} \dot{x_1}(t) = -\gamma_1 x_1(t) + (\beta_2 - c_2)(1 - x_1(t))X_2(t) \\ \dot{S}_2(t) = \omega - (\mu + c_1)S_2(t) - \beta_1 x_1(t)S_2(t) \\ \dot{X}_2(t) = \beta_1 x_1(t)S_2(t) - (\mu + c_1)X_2(t) \end{cases} . \tag{4.2}$$

Equilibria of this system are two, and the endemic equilibrium is characterized by a very long and complex expression.

The disease-free equilibrium is $(0, \frac{\omega}{\mu+c_1}, 0)$.

The Jacobian is:

$$J_f(x_1, S_2, X_2) = \begin{bmatrix} -\gamma_1 - (\beta_2 - c_2)X_2 & 0 & (\beta_2 - c_2)(1 - x_1) \\ -\beta_1 S_2 & -(\mu + c_1) - \beta_1 x_1 & 0 \\ \beta_1 S_2 & \beta_1 x_1 & -(\mu + c_1) \end{bmatrix}.$$

$J_f(0, \frac{\omega}{\mu+c_1}, 0)$ has eigenvalues

$$\begin{cases} \lambda_1 = -\mu - c_1 \\ \lambda_{2,3} = \frac{1}{2(c_1+\mu)} \times \Big(-c_1^2 - c_1\gamma_1 - 2c_1\mu - \gamma_1\mu - \mu^2 \mp (c_1 + \mu)^{\frac{1}{2}}(c_1^3 - 2c_1^2\gamma_1 + c_1\gamma_1^2 + 3c_1^2\mu - \\ 4c_1\gamma_1\mu + \gamma_1^2\mu + 3c_1\mu^2 - 2\gamma_1\mu^2 + \mu^3 - 4c_2\beta_1\omega + 4\beta_1\beta_2\omega)^{\frac{1}{2}}\Big) \end{cases} .$$

Therefore, $(0, \frac{\omega}{\mu+c_1}, 0)$ is locally asymptotically stable iff

$$g(c_1, c_2) = \beta_1\beta_2\omega - c_1^2\gamma_1 - 2c_1\gamma_1\mu - \gamma_1\mu^2 - c_2\beta_1\omega < 0.$$

When introducing controls, it is important to consider the associated costs. Costs can be economic or can represent the level of restrictions that a government wants to minimize for the well-being of the population. In order to achieve the controls' minimization, it is useful to formalize an optimization problem for a cost or budget function where we ensure to stay under the epidemic threshold. This approach aims to determine the minimal controls required to achieve the disease-free equilibrium.

We are interested in implementing this problem and will employ a linear cost function to do so:

$$C(c_1, c_2) = ac_1 + bc_2,$$

where $a > 0$ and $b > 0$ are arbitrary weights.
Hence, the optimization problem is

$$\begin{aligned} \text{minimize} \quad & C(c_1, c_2) \\ \text{subject to} \quad & g(c_1, c_2) \leq 0, \\ & -c_1 \leq 0, \\ & -c_2 \leq 0, \\ & c_2 - \beta_2 \leq 0. \end{aligned}$$

Proving that the minimum of the problem is found for values which are at the border of $g(c_1, c_2)$ (i.e. $g(c_1, c_2) = 0$) is simple: since $a > 0$ and $b > 0$, the value of $C(c_1, c_2)$ will increase with c_1 and/or c_2. Let us assume, for contradiction, that there exist a point (c_1', c_2') such that $g(c_1', c_2') < 0$ and such that $C(c_1', c_2')$ is the minimum. But we find that by reducing slightly the value of either c_1' or c_2' or both, while still maintaining the constraint, the value of $C(c_1', c_2')$ decreases: hence $C(c_1', c_2')$ does not uphold the definition of minimum.

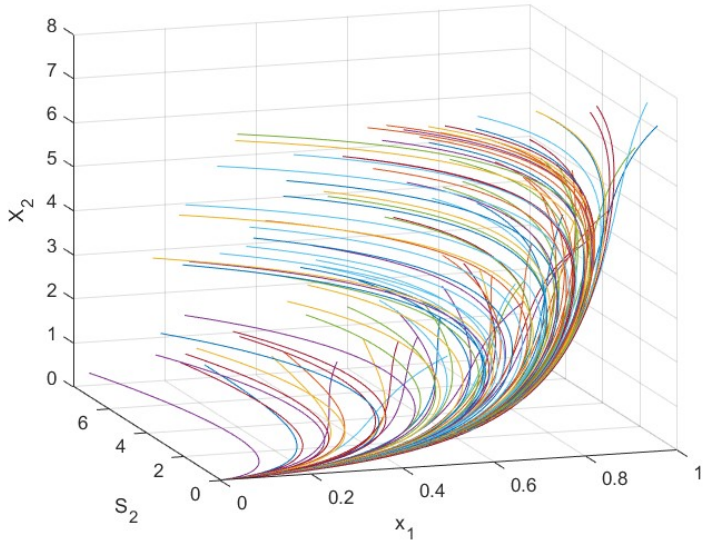
The optimal value of the problem is the following:

$$p^* = \begin{cases} b\frac{\beta_1\beta_2\omega - \gamma_1\mu^2}{\beta_1\omega} & \text{if } (a > \frac{2b\gamma_1\mu}{\beta_1\omega} \wedge \frac{\gamma_1\mu^2}{\beta_1\omega} < \beta_2 \leq \frac{b^2\gamma_1^2\mu^2 - 2ab\beta_1\gamma_1\mu\omega + a^2\beta_1^2\omega^2}{b^2\beta_1\gamma_1\omega}) \\ -a\mu + a\sqrt{\frac{\beta_1\beta_2\omega}{\gamma_1}} & \text{if } (a > \frac{2b\gamma_1\mu}{\beta_1\omega} \wedge \beta_2 > \frac{b^2\gamma_1^2\mu^2 - 2ab\beta_1\gamma_1\mu\omega + a^2\beta_1^2\omega^2}{b^2\beta_1\gamma_1\omega}) \\ & \vee (a \leq \frac{2b\gamma_1\mu}{\beta_1\omega} \wedge \beta_2 > \frac{\gamma_1\mu^2}{\beta_1\omega}) \\ 0 & \text{if } \beta_2 \leq \frac{\gamma_1\mu^2}{\beta_1\omega} \\ +\infty & \text{otherwise} \end{cases}$$

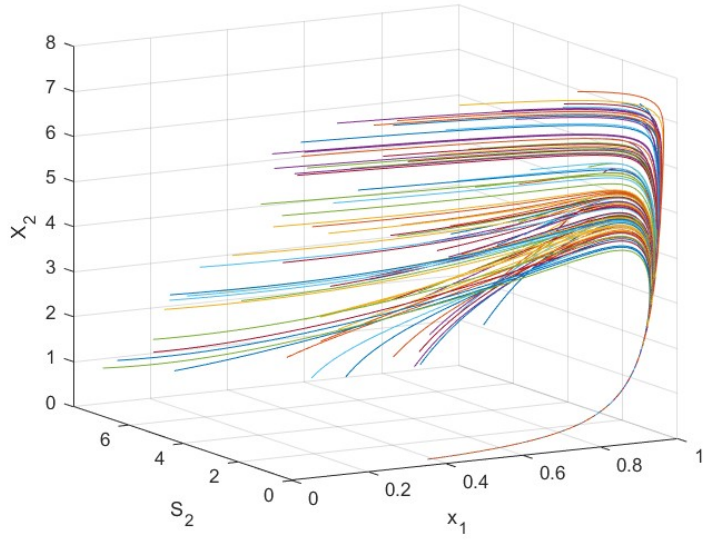
So, among the possible optimal values obtainable when the problem is feasible, we are dealing with the following values of c_1^* and c_2^*: $(0, \frac{\beta_1\beta_2\omega - \gamma_1\mu^2}{\beta_1\omega})$, $(\sqrt{\frac{\beta_1\beta_2\omega}{\gamma_1}} - \mu, 0)$, and (0,0).

As expected, when the problem is feasible, p^* is null when no controls are needed to achieve the disease-free equilibrium. The other two possible values of p^* indeed lie on the curve defined by $g(c_1, c_2) = 0$. Interestingly, with a linear budget function like $C(c_1, c_2)$, the optimal values are achieved using either one control or the other, but not a combination of both.

In Figure 4.2, we simulate state space orbits for the model described in 4.2. The simulations did not reveal the presence of limit cycles.

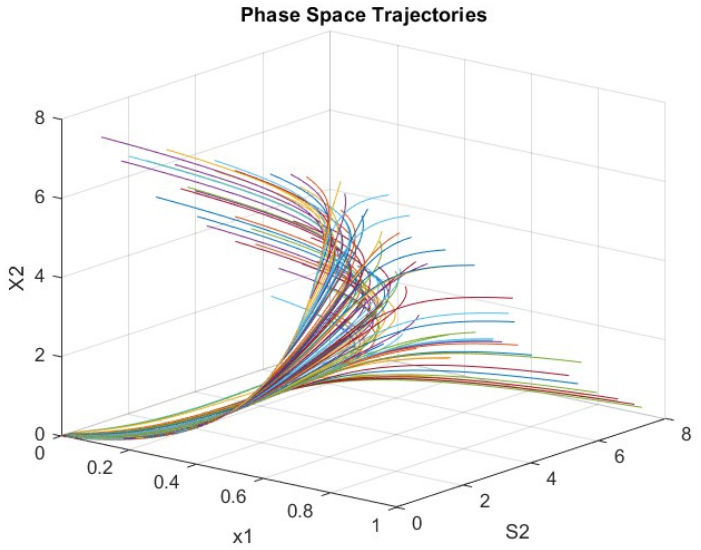


(a) State space orbits with $(\omega, \mu, \beta_1, \beta_2, \gamma_1, c_1) = (0.04, 0.2, 0.2, 0.9, 0.9, 0.8)$ and a population of $N = 8$ vectors for the model with a vector control term 4.1

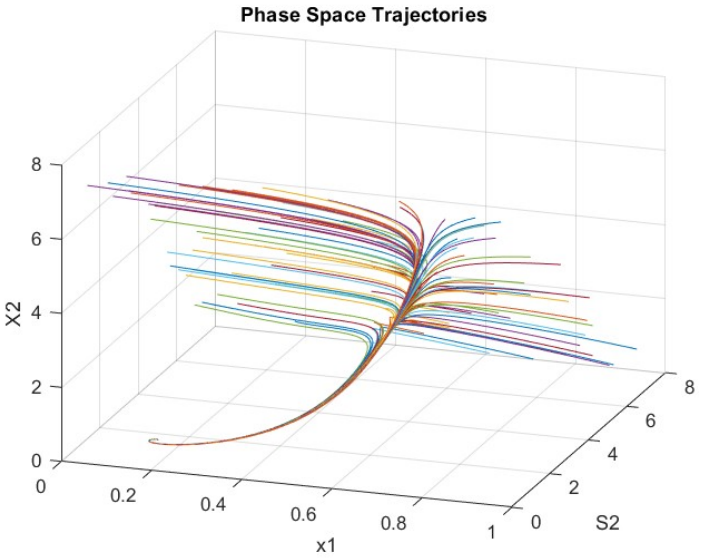


(b) State space orbits with $(\omega, \mu, \beta_1, \beta_2, \gamma_1, c_1) = (0.04, 0.2, 0.2, 0.9, 0.9, 0)$ and a population of $N = 8$ vectors for the model with a vector control term 4.1; note that when $c_1 = 0$ equations are equivalent to the ones of 3.2.

Figure 4.1



(a) State space orbits with $(\omega, \mu, \beta_1, \beta_2, \gamma_1, c_1, c_2) = (0.04, 0.2, 0.2, 0.9, 0.9, 0.8, 0.2)$ and a population of $N = 8$ vectors for the model with two control terms 4.2.



(b) State space orbits with $(\omega, \mu, \beta_1, \beta_2, \gamma_1, c_1, c_2) = (0.4, 0.2, 0.9, 0.9, 0.9, 0.4, 0.4)$ and a population of $N = 8$ vectors for the model with two control terms 4.2.

Figure 4.2

Chapter 5

Network model and simulations

Dengue disease is becoming an increasing concern for authorities in southern Europe due to climate change enhancing the chances of *Aedes aegypti* specimens surviving the winter and becoming endemic. However, the primary concern at present is imported cases: when people from areas where *Aedes aegypti* is non-endemic travel to countries where it is endemic, they may contract the disease and bring it back to their home country. Even if *Aedes aegypti* is not present in their area, *Aedes albopictus* may be, and, as stated in the introduction, the latter is also capable of transmitting the infection. Therefore, imported cases can enhance the spread of the infection in areas where *Aedes aegypti* is non-endemic.

We are interested in investigating this dynamic and find it necessary to separate the populations of hosts and vectors in tropical and non-tropical areas into different nodes. Therefore, we use equations for a model with a total of four populations: one for hosts and one for vectors in the non-tropical area, and analogous populations for the tropical area. For simplicity, we will model the population dynamics of both hosts and vectors using the SIS framework. Thus, we will be dealing with four populations: two of hosts and two of vectors, each belonging to either a tropical node or a non-tropical one.

5.1 A geographical network consisting of two nodes

Given this framework, it is helpful to modify the notation to write equations in a more compact way. We will use the index 1 for the non-tropical region and 2 for the tropical region. Additionally, since we are using the SIS model, the equations

for susceptible and infected individuals will be linearly dependent. Therefore, we can reduce the system from eight equations to four, keeping only the equations for the fractions of infected hosts or vectors. We will denote the fractions of infected hosts with x and the fractions of infected vectors with y. Hence, we obtain the following system of ODEs:

$$\begin{cases} \dot{x}_1(t) = \beta_{y_1} y_1(t)(1 - x_1(t)) - \gamma_{x_1} x_1(t) + \beta_{y_2 x_1} y_2(t)(1 - x_1(t)) \\ \dot{y}_1(t) = \beta_{x_1} x_1(t)(1 - y_1(t)) - \gamma_{y_1} y_1(t) + \beta_{x_2 y_1} x_2(t)(1 - y_1(t)) \\ \dot{x}_2(t) = \beta_{y_2} y_2(t)(1 - x_2(t)) - \gamma_{x_2} x_2(t) + \beta_{y_1 x_2} y_1(t)(1 - x_2(t)) \\ \dot{y}_2(t) = \beta_{x_2} x_2(t)(1 - y_2(t)) - \gamma_{y_2} y_2(t) + \beta_{x_1 y_2} x_1(t)(1 - y_2(t)) \end{cases} . \tag{5.1}$$

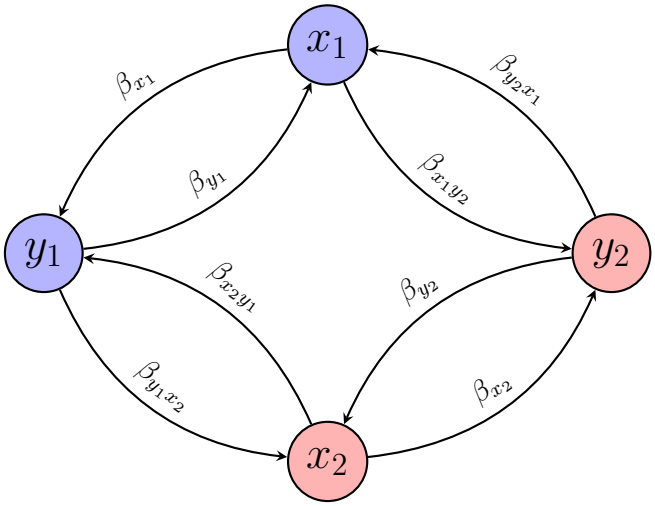


Figure 5.1: Two nodes model's graph 5.1

As we got back to a SIS framework for all populations, the disease-free equilibrium is again $\mathbf{0}$.

The Jacobian of the system is:

$$J_f(x_1, y_1, x_2, y_2) = \begin{bmatrix} A & B \\ C & D \end{bmatrix}$$

where

$$A = \begin{bmatrix} -\gamma_{x_1} - \beta_{y_1} y_1 - \beta_{y_2 x_1} y_2 & \beta_{y_1}(1 - x_1) \\ \beta_{x_1}(1 - y_1) & -\gamma_{y_1} - \beta_{x_1} x_1 - \beta_{x_2 y_1} x_2 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & \beta_{y_2 x_1}(1 - x_1) \\ \beta_{x_2 y_1}(1 - y_1) & 0 \end{bmatrix},$$

$$C = \begin{bmatrix} 0 & \beta_{y_1x_2}(1-x_2) \\ \beta_{x_1y_2}(1-y_2) & 0 \end{bmatrix}, \quad D = \begin{bmatrix} -\gamma_{x_2} - \beta_{y_1x_2}y_1 - \beta_{y_2}y_2 & \beta_{y_2}(1-x_2) \\ \beta_{x_2}(1-y_2) & -\gamma_{y_2} - \beta_{x_1y_2}x_1 - \beta_{x_2}x_2 \end{bmatrix}.$$

Remark 2. *The Jacobian $J_f(x_1, y_1, x_2, y_2)$ is a Metzler matrix. Consequently, the system described in 5.1 is monotone, which implies that the system does not exhibit limit cycles.*

While it is straightforward to identify the disease-free equilibrium of the system as $\mathbf{0}$, determining the other possible equilibria, both analytically and computationally, is challenging. Therefore, we will limit our analysis to the stability of the disease-free equilibrium. To proceed, let us calculate the Jacobian matrix at the disease-free equilibrium:

$$J_f(0,0,0,0) = \begin{bmatrix} -\gamma_{x_1} & \beta_{y_1} & 0 & \beta_{y_2x_1} \\ \beta_{x_1} & -\gamma_{y_1} & \beta_{x_2y_1} & 0 \\ 0 & \beta_{y_1x_2} & -\gamma_{x_2} & \beta_{y_2} \\ \beta_{x_1y_2} & 0 & \beta_{x_2} & -\gamma_{y_2} \end{bmatrix}.$$

The expressions for the eigenvalues of $J_f(0,0,0,0)$ are quite complex and difficult to handle. However, to provide an expression for the condition under which $\mathbf{0}$ is asymptotically stable, let us consider the specific case:

$$\begin{cases} \beta_{x_1} = \beta_{x_2} = \beta_x \\ \beta_{y_1} = \beta_{y_2} = \beta_y \\ \gamma_{x_1} = \gamma_{x_2} = \gamma_x \\ \gamma_{y_1} = \gamma_{y_2} = \gamma_y \end{cases}.$$

These equalities describe a scenario where transmission rates within areas and recovery rates are equal, while cross-area transmission rates may differ. This scenario is significant because, due primarily to climate change, *Aedes aegypti* may become endemic in temperate areas, leading to at least a partial convergence of these rates in the future.

When this applies, expressions of the eigenvalues are the following:

$$\begin{aligned} \lambda_{1,2} = \frac{1}{2}(&-\gamma_x - \gamma_y \pm (4\beta_x\beta_y + 2\beta_{x_2y_1}\beta_{y_1x_2} + 2\beta_{x_1y_2}\beta_{y_2x_1} + 2\sqrt{4\beta_{x_1y_2}\beta_{x_2y_1}\beta_y^2} \\ &+ 4\beta_x\beta_{x_2y_1}\beta_y\beta_{y_1x_2} + \beta_{x_2y_1}^2\beta_{y_1x_2}^2 + 4\beta_x\beta_{x_1y_2}\beta_y\beta_{y_2x_1} + 4\beta_x^2\beta_{y_1x_2}\beta_{y_2x_1} \\ &- 2\beta_{x_1y_2}\beta_{x_2y_1}\beta_{y_1x_2}\beta_{y_2x_1} + \beta_{x_1y_2}^2\beta_{y_2x_1}^2)^{\frac{1}{2}} + \gamma_x^2 - 2\gamma_x\gamma_y + \gamma_y^2) \end{aligned}$$

$$\lambda_{3,4} = \frac{1}{2}(-\gamma_x - \gamma_y \pm ((\gamma_x + \gamma_y)^2 - 2(-2\beta_x\beta_y - \beta_{x_2y_1}\beta_{y_1x_2} - \beta_{x_1y_2}\beta_{y_2x_1} + (4\beta_{x_1y_2}\beta_{x_2y_1}\beta_y^2 + 4\beta_x\beta_{x_2y_1}\beta_y\beta_{y_1x_2} + \beta_{x_2y_1}^2\beta_{y_1x_2}^2 + 4\beta_x\beta_{x_1y_2}\beta_y\beta_{y_2x_1} + 4\beta_x^2\beta_{y_1x_2}\beta_{y_2x_1} - 2\beta_{x_1y_2}\beta_{x_2y_1}\beta_{y_1x_2}\beta_{y_2x_1} + \beta_{x_1y_2}^2\beta_{y_2x_1}^2)^{\frac{1}{2}} + 2\gamma_x\gamma_y))^{\frac{1}{2}}).$$

The equilibrium is locally asymptotically stable if all the eigenvalues have negative real part, which implies the following:

$$4\beta_x\beta_y + 2\beta_{x_2y_1}\beta_{y_1x_2} + 2\beta_{x_1y_2}\beta_{y_2x_1} + 2\Big(\beta_{x_1y_2}^2\beta_{y_2x_1}^2 + \beta_{y_1x_2}(4\beta_x\beta_{x_2y_1}\beta_y + \beta_{x_2y_1}^2\beta_{y_1x_2} + 4\beta_x^2\beta_{y_2x_1}) + \beta_{x_1y_2}(4\beta_{x_2y_1}\beta_y^2 + 4\beta_x\beta_y\beta_{y_2x_1} - 2\beta_{x_2y_1}\beta_{y_1x_2}\beta_{y_2x_1})\Big)^{\frac{1}{2}} < 4\gamma_x\gamma_y$$

Therefore, we have identified the condition necessary to achieve an asymptotically stable disease-free equilibrium for this specific case.

While our analysis is confined to the geographical network model using the simpler SIS framework, it may be worthwhile to incorporate the SI model with vital dynamics. This would allow us to account for the significant differences in lifespan between vectors and hosts.

In Figure 5.2, we simulate a three-dimensional projection of the four-dimensional state space for several tens of orbits. As expected, the orbits exhibit monotone behavior, given that the Jacobian of the system is a Metzler matrix.

5.2 Simulation with parameters' values taken from literature

Once epidemiological models are constructed, the only way to determine their potential usefulness in real-world scenarios is by researching and finding the most accurate estimates for their parameters. This allows for the evaluation of whether these models can reliably predict the dynamics of the epidemic they are designed to simulate.

We start with a simulation of the network model to illustrate an ordinary disease spread scenario.

We select some parameters based on findings from the literature on dengue epidemic modeling. However, because we chose to model the dynamics of two populations using an SIS framework, some parameters have no equivalents in the

comprehensive set of articles we analyzed. Most articles model both host and vector populations using an SI framework with vital dynamics.

In our framework, we do not need to search information on birth and death rates, as we have assumed they are similar. Consequently, this dynamic, where populations consist of individuals or hosts that do not change over time, is indeed similar to those in an SI framework.

However, we must address other parameters that do not appear in SI models and thus need to be assumed. For instance, we have to make an assumption about the recovery rate of the vectors. In SI frameworks, this is not defined due to the short lifespan of mosquitoes; it is reasonable to assume that mosquitoes, once they contract the virus, will die while still infected.

The chosen values for the parameters of model 5.1 are in the following table, where y is the abbreviation for year:

Parameters	**Values**	**Sources**
β_{x_1}	$\frac{9}{8}\beta_{y_1}$	[13], with assumptions[1]
β_{x_2}	$\frac{9}{8}\beta_{y_2}$	[13]
β_{y_1}	9.97×10^{-4} weeks^{-1}	From [14], rescaled[2]
β_{y_2}	$2\gamma_{x_2}$	[15]
γ_{x_1}	γ_{x_2}	[14], with assumptions[3]
γ_{x_2}	9.97×10^{-1} weeks^{-1}	[14]
γ_{y_1}	$2\gamma_{y_2}$	From [15], doubled[4]
γ_{y_2}	4.9×10^{-1} weeks^{-1}	[15], with assumptions[5]
$\beta_{y_2x_1}$	9.97×10^{-3} weeks^{-1}	From [14], rescaled
$\beta_{x_2y_1}$	9.97×10^{-4} weeks^{-1}	From [14], rescaled
$\beta_{y_1x_2}$	9.97×10^{-6} weeks^{-1}	From [14], rescaled
$\beta_{x_1y_2}$	9.97×10^{-5} weeks^{-1}	From [14], rescaled

Table 5.1

In Figure 5.3, we represent the network model graph again with the parameter choices reported in Table 5.1. Meanwhile, in Figure 5.4, we present the associated time simulation. This choice of parameters leads to an equilibrium state where the disease is highly endemic in the tropical area in both the vector and host populations, while it has reached zero or near-zero levels of contagion in the non-tropical area. These results describe well enough the ordinary disease spread scenario that the world is experiencing nowadays, where dengue is still not endemic and manageable in temperate countries, while characterized by concerning levels of spread in tropical countries. However, as previously stated, this state of the spread may well change, primarily due to climate change.

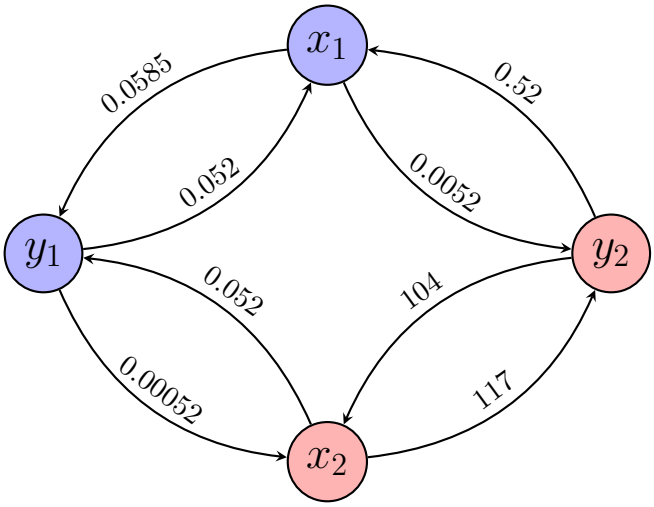
[1]Most of the studies which lead to parameters' estimation have been conducted for areas where dengue is endemic: however we are assuming that the ratios between the contagion rates β_{x_i} and β_{y_i} are the same both in the tropical area ($i = 2$) and in the non-tropical one ($i = 1$).

[2]It is reasonable to assume that $\beta_{y_2x_1} > \beta_{y_1}$ because imported cases are more prevalent than endemic ones in temperate areas like Europe.

[3]While in tropical areas one may expect to find vectors that transmit higher viral loads than in non-tropical ones, we are assuming that the hosts' recovery rate is the same in both areas.

[4]Nowadays, a population of *Aedes aegypti* (the mosquito with the highest dengue viral load) can only survive for a few months in a temperate climate. Moreover, temperate areas are characterized by smaller vector populations, resulting in a consequently smaller number of infected vectors.

[5]In the extensive set of articles we reviewed to choose the parameter values, there is no vector recovery rate since a SIS framework for the vector population has never been adopted. Hence, we use the vector death rate value as a substitute.



$\gamma_{x_1} = 52$
$\gamma_{y_1} = 51.1$
$\gamma_{x_2} = 52$
$\gamma_{y_2} = 25.55$

Figure 5.3: Network model's graph with parameters' values: each parameter is measured in years $^{-1}$; edges' weights are contagion rates (β).

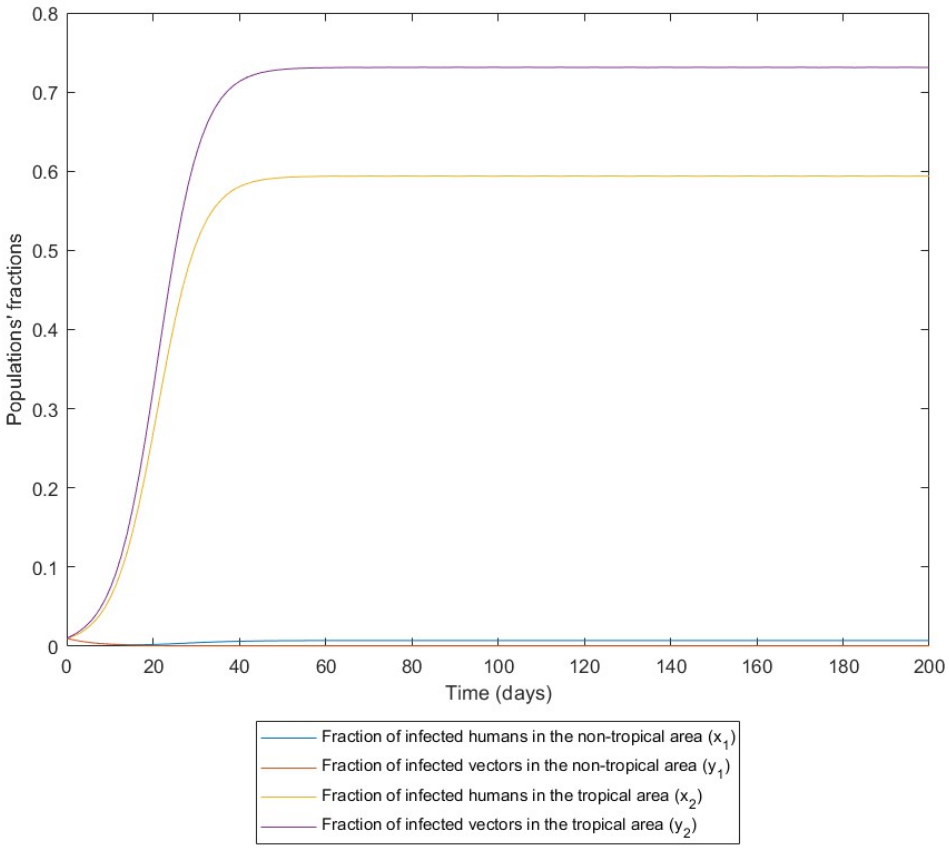


Figure 5.4: Time simulation for parameters' values reported in 5.1 and with $(x_1(0), y_1(0), x_2(0), y_2(0)) = (0.01, 0.01, 0.01, 0.01)$.

5.3 What-if scenario: *Aedes aegypti* is able to survive in areas generally considered non-tropical

Let us now consider a what-if scenario: as previously mentioned, climate change is a major concern in dengue epidemiology due to the potential for *Aedes aegypti* (which, along with *Aedes albopictus*, can transmit the virus to humans) to become an endemic species in regions such as southern Europe. The stable presence of *Aedes aegypti* in new areas is likely to lead to an increase in contagion, significantly raising the risk of an outbreak.

We aim to investigate this scenario using the network model. If we imagine that in a few years, a population of *Aedes aegypti* is present year-round in a non-tropical area, this situation would result in a significantly lower recovery rate for the non-tropical vector population γ_{y_1} and an increase in the contagion rate β_{y_1}. Specifically, let us consider the case where β_{y_1} changes from 0.052 y^{-1} to 52 y^{-1} and γ_{y_2} changes from 51.1 y^{-1} to 25.55 y^{-1}. We summarize these changes in the following table, where we highlight the parameters which have changed with respect to the ordinary scenario simulation:

Parameters	**Values**	**Sources**
β_{x_1}	$\frac{9}{8}\beta_{y_1}$	[13], with assumptions
β_{x_2}	$\frac{9}{8}\beta_{y_2}$	[13]
β_{y_1}	$\frac{1}{2}\beta_{y_2}$	Assumed
β_{y_2}	$2\gamma_{x_2}$	[15]
γ_{x_1}	γ_{x_2}	[14], with assumptions
γ_{x_2}	9.97×10^{-1} weeks^{-1}	[14]
γ_{y_1}	γ_{y_2}	Assumed
γ_{y_2}	4.9×10^{-1} weeks^{-1}	[15], with assumptions
$\beta_{y_2x_1}$	9.97×10^{-3} weeks^{-1}	From [14], rescaled
$\beta_{x_2y_1}$	9.97×10^{-4} weeks^{-1}	From [14], rescaled
$\beta_{y_1x_2}$	9.97×10^{-6} weeks^{-1}	From [14], rescaled
$\beta_{x_1y_2}$	9.97×10^{-5} weeks^{-1}	From [14], rescaled

Table 5.2

In Figure 5.5, we present the time simulation corresponding to this choice of parameters. We observe an equilibrium state where dengue is endemic in both the tropical and the non-tropical areas, while still maintaining a greater percentage of infected in both the host and vector populations in the tropical area.

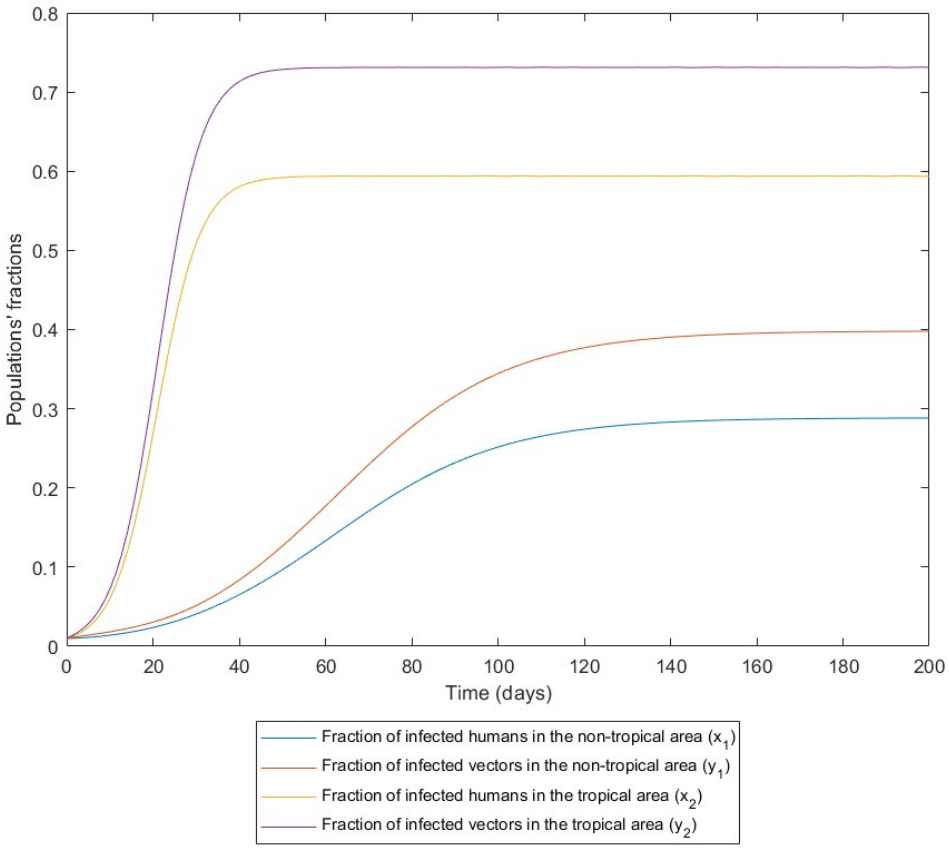


Figure 5.5: Time simulation for parameters' values reported in 5.2 and with $(x_1(0), y_1(0), x_2(0), y_2(0)) = (0.01, 0.01, 0.01, 0.01)$.

5.4 What-if scenario: event that leads to increased movement of people between areas

Let us now consider another what-if scenario: imagine an event leading to increased movement of people between countries, particularly from tropical to temperate regions (for instance, the Paris Summer Olympics 2024). This increase in host movement may influence various contagion rates defined in the network model, potentially raising the risk of an outbreak. Specifically, during a significant international event in a non-tropical country, we might expect a large influx of people from around the globe, including those from tropical regions where dengue is prevalent. While this scenario could impact many parameters in the network model, we focus on the case where only one parameter changes: $\beta_{x_2y_1}$, which increases from 0.052 y^{-1} to 5.2 y^{-1}.

Parameters	**Values**	**Sources**
β_{x_1}	$\frac{9}{8}\beta_{y_1}$	[13], with assumptions
β_{x_2}	$\frac{9}{8}\beta_{y_2}$	[13]
β_{y_1}	9.97×10^{-4} weeks^{-1}	From [14], rescaled
β_{y_2}	$2\gamma_{x_2}$	[15]
γ_{x_1}	γ_{x_2}	[14], with assumptions
γ_{x_2}	9.97×10^{-1} weeks^{-1}	[14]
γ_{y_1}	$2\gamma_{y_2}$	From [14], rescaled
γ_{y_2}	4.9×10^{-1} weeks^{-1}	[15], with assumptions
$\beta_{y_2x_1}$	9.97×10^{-3} weeks^{-1}	From [14], rescaled
$\beta_{x_2y_1}$	9.97×10^{-2} weeks^{-1}	From [14], rescaled
$\beta_{y_1x_2}$	9.97×10^{-6} weeks^{-1}	From [14], rescaled
$\beta_{x_1y_2}$	9.97×10^{-5} weeks^{-1}	From [14], rescaled

Table 5.3

In 5.6, we simulate this scenario and observe an increase in the percentage of infections among both vectors and hosts in the non-tropical area, compared to the ordinary scenario. This simulation illustrates a plausible situation due to the extensive spread of international travel. Although the infection spread among hosts in the non-tropical area remains low, the results suggest that competent health authorities should consider implementing control or precautionary measures.

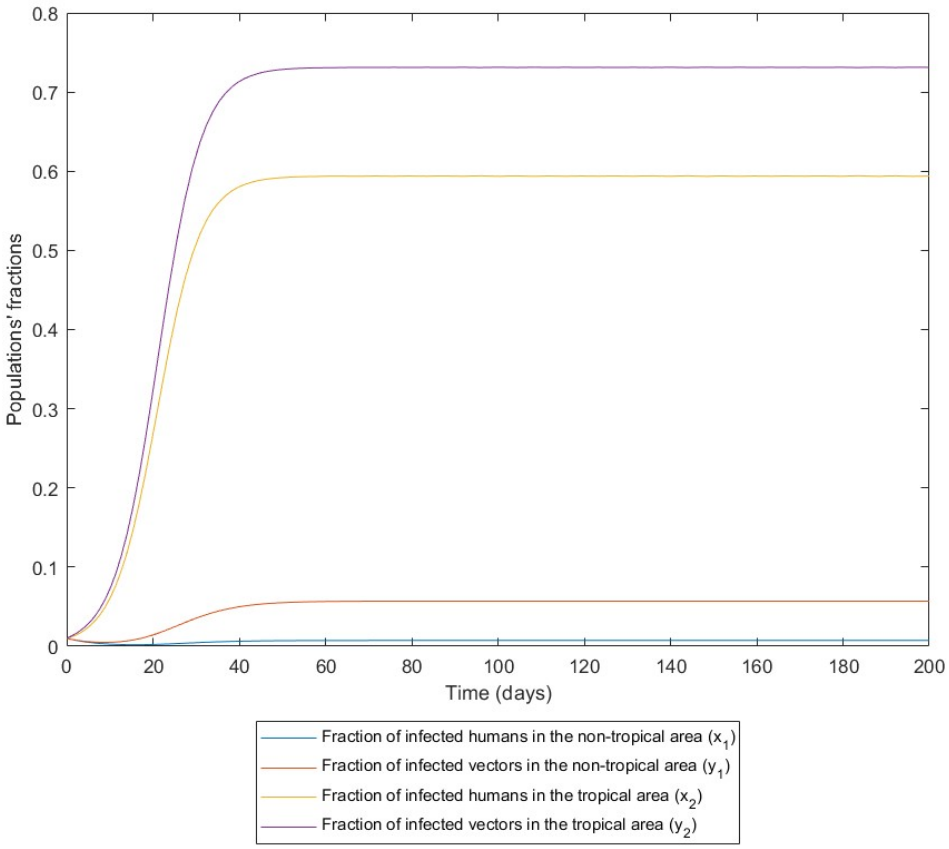
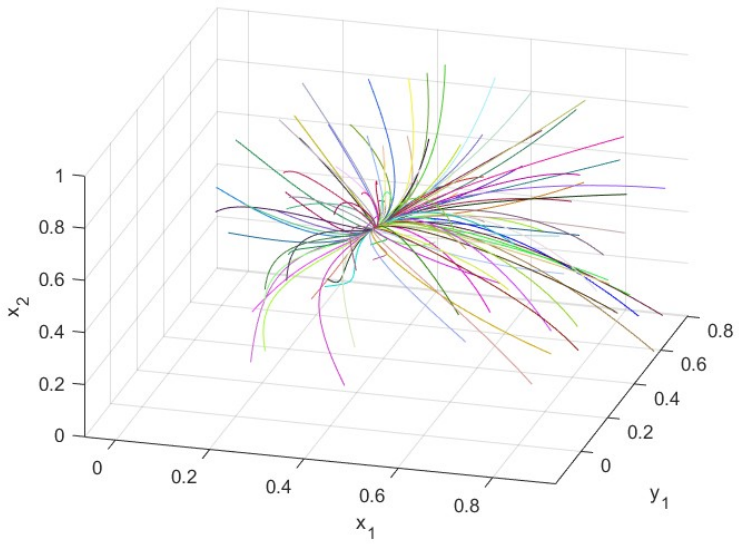
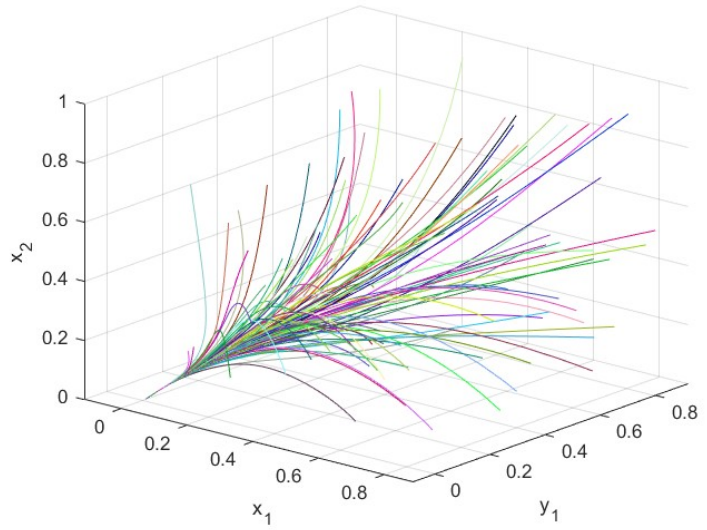


Figure 5.6: Time simulation for parameters' values reported in 5.3 and with $(x_1(0), y_1(0), x_2(0), y_2(0)) = (0.01, 0.01, 0.01, 0.01)$.



(a) State Space Trajectories with $(\beta_{x_1}, \beta_{x_2}, \beta_{y_1}, \beta_{y_2}, \gamma_{x_1}, \gamma_{x_2}, \gamma_{y_1}, \gamma_{y_2}, \beta_{y_2x_1}, \beta_{x_2y_1}, \beta_{y_1x_2}, \beta_{x_1y_2}) = (0.5, 0.5, 0.5, 0.5, 0.4, 0.4, 0.5, 0.5, 0.01, 0.5, 0.3, 0.3)$ for the two nodes model 5.1



(b) State Space Trajectories with $(\beta_{x_1}, \beta_{x_2}, \beta_{y_1}, \beta_{y_2}, \gamma_{x_1}, \gamma_{x_2}, \gamma_{y_1}, \gamma_{y_2}, \beta_{y_2x_1}, \beta_{x_2y_1}, \beta_{y_1x_2}, \beta_{x_1y_2}) = (0.5, 0.5, 0.5, 0.5, 0.7, 0.7, 0.5, 0.5, 0.01, 0.1, 0.1, 0.1)$ for the two nodes model 5.1

Figure 5.2

Chapter 6

Conclusions

This thesis explored the interesting transmission dynamics of dengue fever using various mathematical epidemiological models. By focusing on both human hosts and mosquito vectors, we examined several frameworks categorizable as compartmental models and a complex network model that accounts for geographical and environmental variations.

The basic compartmental SIS model highlighted the interdependent spread of dengue between host and vector populations. We demonstrated that the disease-free equilibrium is achievable under specific conditions where the basic reproduction number is less than one. Extending this model by incorporating birth and death rates for mosquitoes provided a more realistic representation of dengue dynamics and allowed for the evaluation of vector control measures.

The inclusion of vector control terms showed how targeted interventions, such as mosquito reduction strategies, can significantly impact the disease dynamics. The modified model demonstrated that effective vector control can shift the epidemic threshold, reducing the likelihood of outbreaks even in high-risk areas.

The network model, which differentiates between tropical and non-tropical regions, provided insights into the impact of environmental factors and human mobility on disease spread. Simulations showed how climate change could enable *Aedes* mosquitoes to spread the disease in previously inhospitable regions, posing new public health challenges. This model also emphasized the role of international travel in spreading dengue, highlighting the need for coordinated global surveillance and intervention efforts.

Overall, this thesis contributes to the field of epidemiology by showing the utility of mathematical models in understanding and controlling dengue fever. The results suggest the need for integrated vector management, robust health policies, and international cooperation to mitigate the spread of dengue. Future research could enhance these models by integrating vital dynamics into the network framework, expanding the geographical network to include multiple nodes representing the

world's dengue hotspots linked to specific temperate regions, and incorporating more intricate epidemiological dynamics of dengue. This could involve accounting for varying states of immunity, such as partial or total immunity due to dengue antibody-dependent enhancement mechanism.

Bibliography

[1] European Centre for Disease Prevention and Control. Dengue cases january-december 2023, 2024. https://www.ecdc.europa.eu/en/publications-data/dengue-cases-january-december-2023.

[2] Andrea Bacciotti. Analisi della stabilità.

[3] Wikipedia. Dengue. Available at https://en.wikipedia.org/wiki/Dengue_fever.

[4] Maíra Aguiar, Vizda Anam, Konstantin B. Blyuss, et al. Mathematical models for dengue fever epidemiology: A 10-year systematic review. *Physics of Life Reviews*, 40:65–92, 2022. https://www.sciencedirect.com/science/article/pii/S1571064522000045?via%3Dihub.

[5] Vaishnavi Chandrashekhar. As temperatures rise, dengue fever spreads and cases rise. *Yale Environment 360*, November 2023. https://e360.yale.edu/features/dengue-fever-climate-change#:~:text=With%20temperatures%20and%20rainfall%20increasing,risk%20of%20infection%20by%202080.

[6] AboutPharma. Cresce la diffusione della dengue: Italia prima in europa per casi autoctoni nel 2023, 2023.

[7] X. W. S. Gwee, P. E. Y. Chua, and J. Pang. Global dengue importation: a systematic review. *BMC Infectious Diseases*, 21(1):1078, Oct 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8524397/.

[8] Lorenzo Zino and Ming Cao. Analysis, prediction, and control of epidemics: A survey from scalar to dynamic network models. *IEEE Circuits and Systems Magazine*, 21:4–23, 2021. https://ieeexplore.ieee.org/document/9614087.

[9] Jeffrey R. Chasnov. *Mathematical Biology*. Createspace Independent Publishing Platform, 2018. https://math.libretexts.org/Bookshelves/Applied_Mathematics/Mathematical_Biology_(Chasnov).

[10] Institute for Disease Modeling. *SI and SIS models*, 2023. https://docs.idmod.org/projects/emod-generic/en/2.20_a/model-si.html.

[11] Giacomo Como. Lecture slides for the course 'Sistemi nonlineari per l'ingegneria', 2023.

[12] Giacomo Como. Lecture notes on monotone and contractive dynamical systems with applications. 2023.

[13] José Lourenço and Mario Recker. Viral and epidemiological determinants of the invasion dynamics of novel dengue genotypes. *PLoS Neglected Tropical Diseases*, 4(11):e894, 2010. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0000894.

[14] Maíra Aguiar and Nico Stollenwerk. Mathematical models of dengue fever epidemiology: multi-strain dynamics, immunological aspects associated to disease severity and vaccines. *Communication in Biomathematical Sciences*, 1:1, 12 2017. https://journals.itb.ac.id/index.php/cbms/article/view/5767.

[15] J. K. Ghosh, U. Ghosh, and S. Sarkar. Qualitative analysis and optimal control of a two-strain dengue model with its co-infections. *International Journal of Applied and Computational Mathematics*, 6(1):161, 2020. https://doi.org/10.1007/s40819-020-00905-3.