Optimal Control of SIR-Model using Genetic Algorithm and Optimal Dosing Strategy against Bacteria

by

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Abstract

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This thesis explores the application of genetic algorithms to optimize control strategies in the SIR (Susceptible-Infected-Recovered) model. It aims to minimize infection rates and the associated costs by incorporating control strategies like vaccination and educational campaigns. The genetic algorithm is employed to identify optimal intervention strategies, effectively reducing the infected population and expediting recovery processes.

In addition, the research digs into dosing strategies for combating infections caused by susceptible and resistant bacteria. Although the genetic algorithm has not yet been applied in this thesis, the groundwork is laid for its future use to determine optimal dosing regimens. This aspect of the study aims to balance eradicating susceptible bacteria while containing resistant strains, ultimately improving treatment outcomes.

This research contributes valuable insights into managing infectious diseases and antibiotic resistance by providing a foundation for efficient and cost-effective intervention strategies.

Declaration of Authorship

I, Atiq ALI, declare that the dissertation, which I at this moment submit for the degree *Masters* at the Lahore University of Management Sciences, is my work and has not previously been submitted by me for a degree at this or any other tertiary institution.

Signed:

Date:

"Thanks to my solid academic trainers, Dr. Adnan Khan and Sir Sultan Sial, who have been available anytime and supported me during my graduate studies and research. "

Atiq Ali

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Chapter 1

Introduction

In recent years, the rapidly increasing challenge of infectious diseases and antibiotic resistance has underlined the urgent need for innovative and effective intervention strategies. The Susceptible-Infected-Recovered (SIR) model is a foundational tool in epidemiological modeling, providing critical insights into disease transmission and control dynamics. It is possible to improve the effectiveness of these models by integrating modern computational techniques such as genetic algorithms.

This thesis investigates the application of genetic algorithms to optimize control strategies within the SIR model framework. A genetic algorithm, inspired by natural selection and evolution principles, is a powerful optimization tool capable of dealing with complex solution spaces to identify optimal or near-optimal solutions. This research leverages these capabilities to identify effective intervention strategies that minimize infection rates and the associated costs. Genetic algorithms' theoretical foundations and efficacy have been well documented in the literature, with significant contributions such as those by Thede (2004)[11] providing a comprehensive introduction to their mechanics and applications.

In addition to optimizing control strategies for infectious diseases, this study also explores optimal dosing strategies for combating bacterial infections, mainly focusing on the dynamics between susceptible and resistant bacterial populations. The emergence of antibiotic-resistant bacteria poses a significant threat to global health, necessitating strategies to eradicate susceptible bacteria and manage resistant strains effectively. Khan and Imran (2018)[6] highlight the complexity of this challenge and propose various dosing strategies to combat both susceptible and resistant bacteria. Similarly, Ali et al. (2022) [2] emphasize the importance of effective antibiotic dosing in resistant strains, demonstrating the need for robust models to guide treatment protocols.

The objectives of this research are twofold: first, to develop and validate a genetic algorithm-based approach for optimizing the control of infectious diseases using the SIR model, and second, to explore optimal antibiotic dosing strategies to combat bacterial infections, focusing on balancing efficacy and resistance management. By addressing these objectives, this thesis aims to contribute valuable insights and

methodologies for managing infectious diseases and antibiotic resistance more efficiently and cost-effectively.

The SIR model, originally detailed by Smith and Moore (2004) [10], forms the basis of the epidemiological modeling in this study. The model's relevance and application have been further expanded by Bakare et al. (2014) [3], who conducted an optimal control analysis of a SIR epidemic model with constant recruitment. These foundational works provide the theoretical framework upon which this research builds.

Furthermore, the application of genetic algorithms in this context is supported by extensive literature. Lambora et al. (2019) [7] provide a comprehensive review of genetic algorithms, highlighting their versatility and effectiveness in solving complex optimization problems. Mathew (2012) [9] also offers valuable insights into the operational mechanisms and applications of genetic algorithms, reinforcing their suitability for the optimization tasks undertaken in this study.

In the subsequent chapters, we will delve into these approaches' theoretical foundations and practical applications by providing a comprehensive overview of the methodologies employed and the results obtained. Through this research, we aspire to advance the field of epidemiological modeling and contribute to the global effort in managing infectious diseases and antibiotic resistance.

Chapter 2

Preliminaries

2.1 Introduction to Genetic Algorithms (GAs)

Genetic algorithms (GAs) represent a class of optimization algorithms inspired by natural selection and evolution principles. Within the framework of GAs, a population of potential solutions to a given problem is evolved over successive generations to find an optimal or near-optimal solution. This population-based approach imitates the process of natural selection, where individuals with favorable characteristics are more likely to survive and produce offspring.

The key components of a genetic algorithm include:

1. **Population:** Let $P = \{x_1, x_2, x_3, \dots\}$ denote the population of N candidates solutions, where each x_i represents are potential solution to the optimization problem.
2. **Selection:** It is the process by which individuals from the population are chosen to become parents for the next generation. Selection methods typically favor individuals with higher fitness, $F(x_i$, which is determined by their performance in solving the problem.
3. **Crossover:** It's a genetic operation that combines the genetic material of two parent solutions to produce offspring solutions. Let x_i' represent the offspring solution created by the crossover between parent solutions x_i and x_j. This part introduces diversity into the population and promotes exploration of the solution.
4. **Mutation:** It's also a genetic operation that introduces random changes to individual solutions, promoting the exploration of new areas of the solution space. Mutation helps prevent premature convergence to sub-optimal solutions.

The population evolves towards better solutions through successive selection, crossover, and mutation generations. GAs are well-suited for optimization problems with large solution spaces, non-linearity, and multiple objectives. Their ability to efficiently explore and exploit the solution space makes them applicable to various domains, including engineering, finance, and biology. Genetic algorithms have been widely

applied in optimizing public health interventions. For instance, Ajantha Devi et al. (2022) [1] demonstrated a genetic algorithm-based vaccine optimization technique to control COVID-19, highlighting the versatility and effectiveness of this approach in managing epidemic outbreaks.

In this thesis, we use the power of genetic algorithms to optimize control strategies within the Susceptible-Infectious-Recovered (SIR) model, a cornerstone of epidemiological modeling. By integrating GAs into the optimization process, we aim to identify effective intervention strategies for managing infectious diseases and mitigating their spread. Optimal control strategies, as explored by Islam and Biswas [5], can significantly contribute to slowing down the progression of multiple antibiotic resistances within the human body.

The pseudocode of the genetic algorithm is given below.

Algorithm 1: Genetic Algorithm

```
Function GeneticAlgorithm()
    Step 1: Initialize parameters and the objective function;
        Generate an initial population of random values;
    Step 2: repeat for a specified number of generations;
        Step 2.1: Evaluate the fitness of each individual in the population;
        Step 2.2: Select parents based on their fitness using a selection method;
        Step 2.3: Create a new population by applying crossover and mutation;
            Step 2.3.1: For each pair of parents;
                Step 2.3.1.1: Perform crossover with a certain probability;
                Step 2.3.1.2: Apply mutation to the offspring with a certain
                  probability;
        Step 2.4: Ensure the new population remains within the defined bounds;
        Step 2.5: Replace the old population with the new population;
    Step 3: Find the best solution in the final population;
    Step 4: Output the best value of u and the minimum value of the objective
      function;
```

Example 1 *Solve the following Optimization Problem with initial condition as* $x(0) = 1$ *and* $y(0) = 0$.

$$ArgMin_u \quad J(u) = \int_0^1 \left[x(t) - y(t) + \frac{u^2}{2} \right] dt \tag{2.1}$$

Subject to,

$$\dot{x} = 2x + 4y + u \tag{2.2}$$
$$\dot{y} = x - y - u \tag{2.3}$$

We can find the exact solution to this optimization problem in the following way, From Eq. (2.3),

$$\begin{aligned} & x = \dot{y} + y + u \\ \implies & \dot{x} = 2(\dot{y} + y + u) + 4y + u \\ \implies & \dot{x} = 2\dot{y} + 6y + 3u \end{aligned} \tag{2.4}$$

After taking the derivative of Eq. (2.3) w.r.t t,

$$\begin{aligned} & \ddot{y} = \dot{x} - \dot{y} \\ \implies & \dot{x} = \ddot{y} + \dot{y} \end{aligned} \tag{2.5}$$

Substituting Eq. (2.4) in Eq. (2.5), we get,

$$\begin{aligned} & \ddot{y} + \dot{y} = 2\dot{y} + 6y + 3u \\ \implies & \ddot{y} - \dot{y} - 6y = 3u \end{aligned} \tag{2.6}$$

Now the homogeneous solution of Eq. (2.6) is as follows:

$$y(t) = c_1 e^{3t} + c_2 e^{-2t}$$

The non-homogeneous solution is as follows:

$$y(t) = -\frac{1}{2}u$$

Therefore, the general solution is,

$$y(t) = c_1 e^{3t} + c_2 e^{-2t} - \frac{1}{2}u$$

After applying the initial conditions, we get, $c_2 = \frac{1}{2}a - c_1$

$$\begin{aligned} \therefore \quad & y(t) = c_1 e^{3t} + \left(\frac{1}{2}u - c_1\right) e^{-2t} - \frac{1}{2}u \\ \implies & \dot{y} = 3c_1 e^{3t} - (u - 2c_1) e^{-2t} \end{aligned}$$

Now using Eq. (2.3),

$$\begin{aligned} x &= \dot{y} + y + u \\ x(t) &= 3c_1e^{3t} - (u - 2c_1)e^{-2t} + c_1e^{3t} + \frac{1}{2}(u - 2c_1)e^{-2t} - \frac{1}{2}u + u \\ x(t) &= 4c_1e^{3t} - \frac{1}{2}(u - 2c_1)e^{-2t} + \frac{1}{2}u \end{aligned}$$

After using the initial condition $x(0) = 1$, *we get* $c_1 = \frac{1}{5}$, *and the solution of the system of the differential equation is as follows:*

$$x(t) = \frac{4}{5}e^{3t} - \frac{1}{10}(5u - 2)e^{-2t} + \frac{1}{2}u \tag{2.7}$$

$$y(t) = \frac{1}{5}e^{3t} + \frac{1}{10}(5u - 2)e^{-2t} - \frac{1}{2}u \tag{2.8}$$

Now, let's compute the integral of the objective function:

$$\begin{aligned} J(u) &= \int_0^1 \left[x(t) - y(t) + \frac{u^2}{2}\right] dt \\ &= \int_0^1 \left[\frac{3}{5}e^{3t} - \frac{1}{5}(5u - 2)e^{-2t} + u + \frac{u^2}{2}\right] dt \\ &= \frac{1}{5}e^{3t} + \frac{1}{10}(5u - 2)e^{-2t} + ut + \frac{u^2}{2}t\Big|_0^1 \\ &= \frac{1}{5}e^3 + \frac{1}{10}(5u - 2)e^{-2} - \left(\frac{1}{5} + \frac{1}{10}(5u - 2)\right) + u + \frac{u^2}{2} \\ &= \frac{1}{5}e^3 + \frac{1}{2}e^{-2}u - \frac{1}{5}e^{-2} - \frac{1}{5} - \frac{1}{2}u + \frac{1}{5} + u + \frac{u^2}{2} \\ &= \frac{1}{5}e^3 - \frac{1}{5}e^{-2} + \frac{1}{2}(e^{-2} + 1)u + \frac{u^2}{2} \end{aligned}$$

Thus,

$$J(u) = \frac{1}{5}e^3 - \frac{1}{5}e^{-2} + \frac{1}{2}(e^{-2} + 1)u + \frac{u^2}{2} \tag{2.9}$$

In order to minimize $J(u)$,

$$\begin{aligned} J(u) &= \frac{1}{5}e^3 - \frac{1}{5}e^{-2} + \frac{1}{2}(e^{-2} + 1)u + \frac{u^2}{2} \\ J'(u) &= \frac{1}{2}(e^{-2} + 1) + u \\ J'(u) = 0 &\implies u = -\frac{1}{2}(e^{-2} + 1) \approx -0.568 \end{aligned}$$

Thus we get the value of u *that minimizes the function* $J(u)$ *satisfying the constraints.*

We were able to solve this problem due to the problem's simplicity, but this traditional method will not work out when we have a very complex optimization problem.

Genetic Algorithms are beneficial for solving very complex optimization problems. We solved the same problem using a genetic algorithm with a population size of 20, 100 generations, mutation rate 0.1, and crossover rate 0.7, and got the value of u as -0.527. This is very close to the exact value of u solved earlier.

2.2 Introduction to the SIR Model

The SIR model is a simple mathematical model used to understand the spread of infectious diseases within a population. It is named after the three compartments, and it divides the population into susceptible (S), infected (I), and recovered (R).

1. **Susceptible (S):** This group comprises individuals susceptible to infectious disease. They have not yet been infected and can potentially contract the disease if they encounter any infected individual.
2. **Infected (I):** This group consists of individuals currently infected with the disease and can transmit it to susceptible individuals. In the SIR model, once individuals become infected, they remain infectious for a certain period before recovering.
3. **Recovered (R):** This group includes individuals who have recovered from the infection and are now immune to it. In some variations of the model, this group may also include individuals who have been vaccinated against the disease.

The dynamics of the SIR model are governed by a set of differential equations that describe how the number of individuals in each compartment changes over time. These equations consider the disease's transmission rate, the infection's duration, and the recovery rate.

The basic equations of the SIR model are as follows:

$$\begin{aligned}\frac{dS}{dt} &= -\lambda SI \\ \frac{dI}{dt} &= \lambda SI - \gamma I \\ \frac{dR}{dt} &= \gamma I\end{aligned}$$

But in this paper, we will work on the modified version of SIR Model, which is described as follows:

$$\frac{dS}{dt} = A - \beta S - \lambda SI + \mu R$$
$$\frac{dI}{dt} = \lambda SI - (\alpha + \beta + \gamma)I$$
$$\frac{dR}{dt} = \gamma I - (\beta + \mu)R$$

In this model, S represents the proportion of the population that is susceptible to the disease, while I denotes the proportion currently infected, and R signifies those who have recovered. The total population size N is the sum of these three groups. Additionally, A indicates the rate of population growth, while α represents the disease-induced death rate, and β signifies the natural death rate. The recovery rate is denoted by γ, and λ represents the transmission rate of the disease. Furthermore, μ indicates the rate at which immunity diminishes over time. Finally, the expressions $\frac{dS}{dt}$, $\frac{dI}{dt}$, and $\frac{dR}{dt}$ depict the rates of change of susceptible, infected, and recovered individuals, respectively, over time.

The SIR model provides insights into the dynamics of infectious disease outbreaks, such as the peak of infections, the pandemic, the overall number of infections, and the effectiveness of intervention strategies like vaccination or social distancing. However, it is a simplified model and may not capture all aspects of real-world epidemics. Extensions and variations of the SIR model, such as the SEIR model, which includes an exposed compartment for individuals in the latent period of the disease, are often used to address specific scenarios and factors influencing disease spread.

2.3 Optimal Dosing Strategy against Bacteria

Antibiotics are crucial in manufacturing antibiotic medicines; they effectively combat bacterial infections and save countless lives. However, the emergence of antibiotic resistance poses a significant threat to global public health, highlighting the importance of optimizing dosing strategies to maximize efficacy while minimizing the development of resistance. Developing mathematical models can help us understand the dynamics of bacterial growth, antibiotic action, and the evolution of resistance, ultimately informing the design of optimal dosing regimens.

Consider the following model:

$$\frac{dS}{dt} = d_S(S_0 - S) - \frac{1}{\gamma} f(A)u,$$
$$\frac{dA}{dt} = d_A(A_0(t) - A) - p(A)u,$$
$$\frac{du}{dt} = f(A) - d_u - g(A, S)u,$$

where S represents the nutrient concentration, A the antibiotic concentration, and u the susceptible bacterial population. The parameters are defined as follows: S_0 is the initial nutrient concentration, $A_0(t)$ is the time-varying initial antibiotic concentration, d_S is the nutrient flow rate, d_A is the antibiotic dilution rate, d_u is the growth rate of the susceptible bacterial population, γ is the conversion rate of nutrients to bacteria, $p(A)$ is the uptake rate of bacteria, $f(A)$ is the nutrient-dependent growth rate of the bacteria, and $g(A, S)$ is the function describing the effect of antibiotic concentration on bacterial killing.

The first equation models the change in nutrient concentration over time. The first term, $d_S(S_0 - S)$, represents the influx or outflux of nutrients towards an equilibrium concentration S_0. The second term, $\frac{1}{\gamma} f(A)u$, represents the consumption of nutrients by the bacteria, where the rate of consumption depends on the bacterial growth rate $f(A)$ and the population u, scaled by the conversion rate γ.

The second equation models the change in antibiotic concentration over time. The first term, $d_A(A_0(t) - A)$, describes the dynamics of antibiotic concentration towards a time-varying level $A_0(t)$, accounting for dilution. The second term, $p(A)u$, represents the uptake or neutralization of antibiotics by the bacteria, with the uptake rate depending on the current antibiotic concentration A and bacterial population u.

The third equation models the change in the bacterial population over time. The first term, $f(A)$, represents the growth of the bacterial population, which depends on the antibiotic concentration A. The second term, d_u, represents the bacteria's natural death or dilution rate. The third term, $g(A, S)u$, describes the killing effect of the antibiotics on the bacterial population, which is influenced by both the antibiotic concentration A and the nutrient concentration S.

In this thesis, we will explore the antibiotic dosing strategy considering both susceptible and resistant bacteria, which is defined as follows:

$$
\begin{aligned}
\frac{dS}{dt} &= d_S(S_0 - S) - \frac{1}{\gamma}[f(S)u + f_0(S)u_0] \\
\frac{dA}{dt} &= d_A(A_0(t) - A) - p(A)[u + u_0] \\
\frac{du}{dt} &= [f(S) - d_u - g(S, A)]u + q f_0(S)u_0 - \mu u u_0 \\
\frac{du_0}{dt} &= [f_0(S)(1 - q) - d_u - g_0(S, A)]u_0 + \mu u u_0
\end{aligned}
$$

Where u_0 represents the resistance bacteria population, $f_0(S)$ represents the growth rate of the resistant bacteria, $g_0(S, A)$ is the function describing the effect of the antibiotic concentration on bacterial killing, q and $1 - q$ are probabilities for missegregation and conjugation, and μ is the rate of conversion of susceptible to resistant bacteria.

2.4 Motivation for Using Genetic Algorithms

Optimizing control strategies within the Susceptible-Infectious-Recovered (SIR) model represents a multifaceted challenge, engendering the need to balance complex dynamics, multiple objectives, and uncertainties inherent in epidemiological systems. The motivation behind applying genetic algorithms (GAs) as the optimization technique came from their unique capabilities and proven track record in addressing such challenges.

Firstly, genetic algorithms excel in handling the inherent complexity of the SIR model and its control optimization. Unlike traditional optimization methods, which may struggle with high-dimensional and nonlinear problems, GAs are well-suited for exploring large solution spaces and identifying near-optimal solutions even in complex dynamics.

Secondly, optimizing control strategies in the SIR model often involves optimizing multiple conflicting objectives, such as minimizing infection rates, maximizing recovery rates, and minimizing economic costs.

Furthermore, the flexibility and adaptability of genetic algorithms make them well-suited for tailoring the optimization process to the specific characteristics of the SIR model and control objectives. GAs can efficiently explore and exploit the solution space by adapting the population of candidate solutions over successive generations, effectively identifying optimal control strategies.

Chapter 3

Optimal Control of SIR Model

3.1 SIR Model

The SIR model is a simple mathematical model used to understand the spread of infectious diseases within a population. It is named after the three compartments, and it divides the population into susceptible (S), infected (I), and recovered (R).

1. **Susceptible (S):** This group comprises individuals susceptible to infectious disease. They have not yet been infected but can be infected if they encounter an infected individual.
2. **Infected (I):** This group consists of individuals currently infected with the disease and can transmit it to susceptible individuals. In the SIR model, once individuals become infected, they remain infectious for a certain period before recovering.
3. **Recovered (R):** This group includes individuals who have recovered from the infection and are now immune to it. In some variations of the Model, this group may also include individuals who have been vaccinated against the disease.

The dynamics of the SIR model are governed by a set of differential equations that describe how the number of individuals in each compartment changes over time. These equations consider the disease's transmission rate, the infection's duration, and the recovery rate.

The SIR model operates on the flow principle between these compartments based on specific parameters. The dynamics of the Model are governed by a set of ordinary differential equations (ODEs) that describe how the number of individuals in each compartment changes over time.

The SIR model provides insights into the dynamics of infectious disease outbreaks, such as the peak of infections, the overall number of infections, and the effectiveness of intervention strategies like vaccination, educational campaigns, quarantine, or social distancing. However, it is a simplified model and may not capture all aspects of real-world epidemics. Extensions and variations of the SIR model, such as the SEIR

model, which includes an exposed compartment for individuals in the latent period of the disease, are often used to address specific scenarios and factors influencing disease spread.

3.2 Mathematical Formulation

The basic set of equations for the SIR model are as follows:

$$\frac{dS}{dt} = -\lambda \cdot SI \tag{3.1}$$

$$\frac{dI}{dt} = \lambda \cdot SI - \gamma \cdot I \tag{3.2}$$

$$\frac{dR}{dt} = \gamma \cdot I \tag{3.3}$$

Where:

- S is the number of susceptible individuals,
- I is the number of infectious individuals,
- R is the number of recovered individuals,
- $N = S + I + R$ is the total population size,
- λ is the transmission rate (rate of infection),
- γ is the recovery rate (the rate at which infectious individuals recover from the population).

The formulation of the Model connects the rates at which individuals transition between these compartments: Susceptible (S), Infectious (I), and Recovered (R). At any given time, the rate of change in the number of susceptible individuals ($\frac{dS}{dt}$) is influenced by two primary factors. Firstly, the transmission from infectious individuals ($\lambda \cdot SI$) defines the rate at which susceptible individuals become infected upon contact with infectious ones. Secondly, the negative sign denotes the decrease in susceptible individuals over time as they fail to resist the infection.

Similarly, the rate of change in the number of infectious individuals ($\frac{dI}{dt}$) is governed by the interaction of new infections and recoveries. New infections ($\lambda \cdot SI$) occur as susceptible individuals become infected, while recoveries ($\gamma \cdot I$) signify the rate at which infectious individuals recover from the disease, where γ represents the recovery rate. The balance between these processes defines the net change in contagious individuals over time, shaping the epidemic's trajectory within the population.

Lastly, the rate of change in the number of recovered individuals ($\frac{dR}{dt}$) is solely dictated by the recovery rate (γ) and the current number of infectious individuals (I).

This term reflects how individuals move from the infectious category to the recovered as they recover from the disease.

However, in this thesis, we will work on the modified version of the SIR Model that considers the population growth rate, natural and disease-induced death rate, and loss of immunity rate. i.e.

$$\frac{dS}{dt} = AN - \beta S - \lambda SI + \mu R \tag{3.4}$$

$$\frac{dI}{dt} = \lambda SI - (\alpha + \beta + \gamma)I \tag{3.5}$$

$$\frac{dR}{dt} = \gamma I - (\beta + \mu)R \tag{3.6}$$

To control the spread of the disease, Bakare et al. (2014) [3] introduced the control variables $u_1(t)$ and $u_2(t)$ in this model. These are defined as the proportion of infected people treated by vaccination and the proportion of susceptible people cautioned by educational campaigns.

$$\frac{dS}{dt} = AN - \beta S - \lambda SI + \mu R - u_2(t)S \tag{3.7}$$

$$\frac{dI}{dt} = \lambda SI - (\alpha + \beta + \gamma)I - u_1(t)I \tag{3.8}$$

$$\frac{dR}{dt} = \gamma I - (\beta + \mu)R + u_1(t)I + u_2(t)S \tag{3.9}$$

Here, $u_1(t)$ represents the control variable associated with vaccination campaigns. It denotes the rate at which individuals are vaccinated against the infectious disease over time. In the equation for the rate of change of contagious individuals ($\frac{dI}{dt}$), the term $u_1(t)I(t)$ signifies the impact of vaccination on reducing the number of infectious individuals. As more individuals are vaccinated, the disease's effective transmission rate decreases, reducing the number of new infections.

In the equation for the rate of change of recovered individuals ($\frac{dR}{dt}$), the term $u_1(t)I(t)$ represents the individuals who recover from the disease due to vaccination. Vaccination increases the rate at which infectious individuals move to the recovered compartment.

Where $u_2(t)$ represents the control variable associated with educational campaigns that aim to change human behavior to reduce disease transmission. It denotes the effectiveness of educational interventions in promoting behaviors such as social distancing, hand hygiene, and mask-wearing. In the equation for the rate of change of susceptible individuals ($\frac{dS}{dt}$), the term $u_2(t)S(t)$ reflects the impact of educational campaigns on reducing the susceptibility of individuals to infection.

Similarly, in the equation for the rate of change of recovered individuals ($\frac{dR}{dt}$), the term $u_2(t)S(t)$ represents the individuals who become less susceptible to infection

due to educational campaigns. These control variables allow for a dynamic intervention strategy, where the rates of vaccination and effectiveness of educational campaigns can be adjusted over time to optimize disease control efforts and reduce the spread of infectious diseases within the population.

For convenience, we make the following substitution to count each compartment as a proportion of the total population. i.e.

$$\frac{S}{N} \to S; \quad \frac{I}{N} \to I; \quad \frac{R}{N} \to R; \quad \frac{SI}{N} \to SI$$

We get,

$$\begin{aligned}
\frac{d}{dt}\left(\frac{S}{N}\right) &= \frac{AN}{N} - \beta\frac{S}{N} - \lambda\frac{SI}{N} + \mu\frac{R}{N} - u_2(t)\frac{S}{N} \\
\frac{d}{dt}\left(\frac{I}{N}\right) &= \lambda\frac{SI}{N} - (\alpha+\beta+\gamma)\frac{I}{N} - u_1(t)\frac{I}{N} \\
\frac{d}{dt}\left(\frac{R}{N}\right) &= \gamma\frac{I}{N} - (\beta+\mu)\frac{R}{N} + u_1(t)\frac{I}{N} + u_2(t)\frac{S}{N}
\end{aligned}$$

Which implies,

$$\frac{dS}{dt} = A - \beta S - \lambda SI + \mu R - u_2 S \tag{3.10}$$

$$\frac{dI}{dt} = \lambda SI - (\alpha+\beta+\gamma)I - u_1 I \tag{3.11}$$

$$\frac{dR}{dt} = \gamma I - (\beta+\mu)R + u_1 I + u_2 S \tag{3.12}$$

Where:

- S is a proportion of the population that is susceptible,
- I is a proportion of the population that is infected,
- R is a proportion of the population that is recovered,
- N is the total population size ($N = S + I + R$),
- A is the incremental rate for the population growth,
- α is the disease-induced death rate,
- β is the natural death rate,
- γ is the recovery rate,
- λ is the transmission rate,

- μ is the rate of loss of immunity,
- $u_1(t)$ is the proportion of the population treated by vaccination to the population over time.
- $u_2(t)$ is the intensity of educational campaigns that raise awareness among the population over time.
- $\frac{dS}{dt}$, $\frac{dI}{dt}$, and $\frac{dR}{dt}$ represent the rates of change of susceptible, infected, and recovered individuals over time, respectively.

So far, we have the dynamics for the SIR Model. Still, we have to choose u_1 and u_2 so that the total proportion of susceptible and infected people, the cost of vaccination, and educational campaigns are minimized. For that, we have defined the objective function as follows:

$$J\left(u_1(t), u_2(t)\right) = \int_{t_0}^{t_f} S(t) + I(t) + A_1 \frac{u_1^2(t)}{2} + A_2 \frac{u_2^2(t)}{2}\, dt \tag{3.13}$$

subject to (3.10 - 3.12).

The proof of positivity, boundedness, and existence and uniqueness of the solution of this optimization was proved by Bakare et al. (2014) [3]. The proof of the positive invariance and boundedness of the solution is as follows:

Theorem 1 *Given $S(0) \geq 0, I(0) \geq 0, R(0) \geq 0$, the solutions $(S(t), I(t), R(t))$ of model (3.10 - 3.12) are positively invariant for all $t > 0$.*

Proof:

Let $Z = \sup\{t > 0 \mid S > 0, I > 0, R > 0\}$, from Eq. (3.10) we have,

$$\frac{dS}{dt} = A - \beta S - \lambda S I + \mu R - u_2 S$$

Or

$$\frac{dS}{dt} + (\beta + u_2 + \lambda I)\, S = A + \mu R \tag{3.14}$$

The integrating factor is,

$$e^{\int_0^t (\beta + u_2 + \lambda I(s))ds} \quad or \quad e^{(\beta+u_2)t + \lambda \int_0^t I(s)ds}$$

Multiplying the integration factor on both sides of Eq. (3.14).

$$e^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\left[\frac{dS}{dt}+(\beta+u_2+\lambda I)\,S\right]=e^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\,(A+\mu R)$$

$$e^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\frac{dS}{dt}+Se^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\,(\beta+u_2+\lambda I)=e^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\,(A+\mu R)$$

$$\frac{d}{dt}\left[Se^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\right]=e^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\,(A+\mu R)$$

Integrating both sides w.r.t t, we get,

$$\int_0^t\frac{d}{dt}\left[Se^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}\right]dt=\int_0^t\left[e^{(\beta+u_2)\xi+\lambda\int_0^\xi I(s)ds}\,(A+\mu R)\right]d\xi$$

$$S(t)e^{(\beta+u_2)t+\lambda\int_0^t I(s)ds}-S(0)=\int_0^t\left[e^{(\beta+u_2)\xi+\lambda\int_0^\xi I(s)ds}\,(A+\mu R)\right]d\xi$$

$$S(t)=S(0)e^{-\left[(\beta+u_2)t+\lambda\int_0^t I(s)ds\right]}+e^{-\left[(\beta+u_2)t+\lambda\int_0^t I(s)ds\right]}\int_0^t\left[e^{(\beta+u_2)\xi+\lambda\int_0^\xi I(s)ds}\,(A+\mu R)\right]d\xi \tag{3.15}$$

Since,

$S(0)\geq 0,\quad e^{-\left[(\beta+u_2)t+\lambda\int_0^t I(s)ds\right]}\geq 0,$ *and* $\int_0^t\left[e^{(\beta+u_2)\xi+\lambda\int_0^\xi I(s)ds}\,(A+\mu R)\right]d\xi\geq 0$

Then Eq. (3.15) implies $S(t)\geq 0$.

Similarly, to show $I(t)\geq 0$, *consider the Eq. (3.11).*

$$\begin{aligned}
\frac{dI}{dt}&=\lambda SI-(\alpha+\beta+\gamma)I-u_1I\\
\frac{1}{I}\frac{dI}{dt}&=\lambda S(t)-(\alpha+\beta+\gamma+u_1)\\
\int_0^t\frac{1}{I}dI&=\int_0^t\left[\lambda S(s)-(\alpha+\beta+\gamma+u_1)\right]ds\\
\ln(I(t))-\ln(I(0))&=\int_0^t\left[\lambda S(s)-(\alpha+\beta+\gamma+u_1)\right]ds\\
\ln(I(t))&=\ln(I(0))\int_0^t\left[\lambda S(s)-(\alpha+\beta+\gamma+u_1)\right]ds\\
I(t)&=I(0)e^{\int_0^t[\lambda S(s)-(\alpha+\beta+\gamma+u_1)]ds}
\end{aligned}$$

Since, $I(0)\geq 0$ *and* $e^{\int_0^t[\lambda S(s)-(\alpha+\beta+\gamma+u_1)]ds}\geq 0$, *which implies that* $I(t)\geq 0$.

In the same way, we can show $R(t)\geq 0$, *consider the Eq. (3.12);*

$$\frac{dR}{dt} = \gamma I - (\beta + \mu)R + u_1 I + u_2 S$$

Or,

$$\frac{dR}{dt} + (\beta + \mu)R = (\gamma + u_1)I + u_2 S \tag{3.16}$$

The integrating factor is,

$$e^{\int_0^t (\beta+\mu)dt} \quad or \quad e^{(\beta+\mu)t}$$

Multiplying the integrating factor on both sides of Eq. (3.16), we get,

$$\begin{aligned} e^{(\beta+\mu)t}\frac{dR}{dt} + (\beta+\mu)Re^{(\beta+\mu)t} &= (\gamma+u_1)Ie^{(\beta+\mu)t} + u_2 Se^{(\beta+\mu)t} \\ \frac{d}{dt}\left[R(t)e^{(\beta+\mu)t}\right] &= (\gamma+u_1)Ie^{(\beta+\mu)t} + u_2 Se^{(\beta+\mu)t} \\ \int_0^t \frac{d}{dt}\left[R(t)e^{(\beta+\mu)t}\right]dt &= \int_0^t \left[(\gamma+u_1)I(s)e^{(\beta+\mu)s} + u_2 S(s)e^{(\beta+\mu)s}\right]ds \end{aligned}$$

$$R(t) = R(0)e^{-(\beta+\mu)t} + e^{-(\beta+\mu)t}\int_0^t \left[(\gamma+u_1)I(s)e^{(\beta+\mu)s} + u_2 S(s)e^{(\beta+\mu)s}\right]ds \tag{3.17}$$

Since $R(0) \geq 0$, $e^{-(\beta+\mu)t} \geq 0$, $\int_0^t \left[(\gamma+u_1)I(s)e^{(\beta+\mu)s} + u_2 S(s)e^{(\beta+\mu)s}\right]ds \geq 0$ *which implies that* $R(t) \geq 0$.

Theorem 2 *All solutions* $(S(t), I(t), R(t))$ *of model (3.10 - 3.12) are Bounded.*
Proof:

Since the model (3.10 - 3.12) refers to the complete population, therefore,

$$N = S + I + R \implies \frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt}$$

We get,

$$\frac{dN}{dt} = A - \beta S - \lambda SI + \mu R - u_2 S + \lambda SI - (\alpha + \beta + \gamma)I - u_1 I + \gamma I - (\beta + \mu)R + u_1 I + u_2 S$$

$$\begin{aligned} &\implies \frac{dN}{dt} = A - \beta(S + I + R) - \alpha I \\ &\implies \frac{dN}{dt} = A - \beta N - \alpha I \\ &\implies \frac{dN}{dt} \geq A - \beta N \end{aligned}$$

Therefore,

$$\limsup_{t\to\infty} N(t) \leq \frac{A}{\beta}$$

Which implies,

$$S + I + R \leq \frac{A}{\beta}$$

But in Theorem 1 we proved that $S, I, R \geq 0$, which completes the proof that S, I and R are bounded.

Theorem 3 *Suppose the objective functional is*

$$\min_{u_1,u_2} \left\{ J(u_1, u_2) = \int_0^T \left(S(t) + I(t) + \frac{u_1^2}{2} + \frac{u_2^2}{2} \right) dt \right\}$$

where

$$0 \leq u_1(t) \leq 1 \text{ and } 0 \leq u_2(t) \leq 1 \text{ s.t } t \in [0, T]$$

subject to the dynamic constraints of system equations (3.10 - 3.12) with $S(0) = S_0$, $I(0) = I_0$ and $R(0) = R_0$, then there exists an optimal control

$$u^* = (u_1^*, u_2^*)$$

such that

$$\min_{(u_1,u_2)} J(u_1, u_2) = J(u_1^*, u_2^*)$$

subject to the control system (3.10 - 3.12) with the initial conditions.

Proof:
This is proved by Bakare et al. (2014) [3] using Pontryagin's Maximum Principle.

In the next section, we use an optimization technique, a genetic algorithm, to optimize our problem.

3.3 Optimization Methodology (Genetic Algorithm)

The Genetic Algorithm is an optimization method consisting of four fundamental steps. Firstly, it begins with an initialization phase, generating an initial population of potential solutions. Secondly, individuals in the population are selected based on their fitness values, which are evaluated using a predefined fitness function that quantifies how well they solve the optimization problem. Then, chosen individuals go through the crossover by exchanging genetic material to create offspring with characteristics inherited from their parents. Finally, mutation introduces random changes to the genetic material of some individuals, promoting genetic diversity in the population. Through iterations of selection, crossover, and mutation, the GA

evolves the population over generations, ultimately converging towards solutions that approximate the optimal solution to the given optimization problem.

$$\text{ArgMin}_{(u_1,u_2)} J\left(u_1(t), u_2(t)\right) = \int_{t_0}^{t_f} \left[S(t) + I(t) + \frac{u_1^2(t)}{2} + \frac{u_2^2(t)}{2} \right] dt$$

Constrainted to,

$$\begin{aligned}
\frac{dS}{dt} &= A - \beta S - \lambda SI + \mu R - u_2 S \\
\frac{dI}{dt} &= \lambda SI - (\alpha + \beta + \gamma) I - u_1 I \\
\frac{dR}{dt} &= \gamma I - (\beta + \mu) R + u_1 I + u_2 S
\end{aligned}$$

The values of the parameters are as follows:

TABLE 3.1: Description, Symbols, and Values of parameters

Description	**Symbols**	**Values**	**Reference**
Incremental rate for population growth	A	0.03	[3]
Disease-induced death rate	α	0.1	[12]
Natural death rate	β	0.02	[12]
Recovery rate	γ	0.005	[3]
Disease transmission rate	λ	0.75	[12]
Rate of loss of immunity	μ	0.00137	[3]

Population:
The Population in the Genetic Algorithm serves as a collection of potential solutions to the optimization problem. Each individual within the population represents a candidate solution, and a set of parameters characterizes it. In our optimization problem, the parameters correspond to the values of $u_1(t)$ and $u_2(t)$, which determine the vaccination and education campaign strategies, respectively; we have initialized with a population size of 50.

Selection:
Selection is a critical component of the Genetic Algorithm and involves choosing individuals from the population for reproduction based on their fitness values. Fitness represents the quality or effectiveness of each individual's solution to the optimization problem. In this implementation, we have calculated the fitness of each individual using the cost function, which, in our case, is,

$$J\left(u_1(t), u_2(t)\right) = \int_{t_0}^{t_f} S(t) + I(t) + \frac{u_1^2(t)}{2} + \frac{u_2^2(t)}{2}\, dt$$

It evaluates the performance of the vaccination and education campaign strategies. In our problem, we used tournament selection to choose individuals from the population for the next steps of the algorithm. Selection ensures that individuals with better fitness values have a higher probability of being selected for reproduction.

Crossover:
It is a genetic operator that combines the genetic material of two-parent individuals to produce offspring with characteristics inherited from both parents. Crossover enables the exploration of new regions of the search space by creating diverse combinations of solutions. In our problem, we have used blending crossover, where the parameters u_1 and u_2 of the parent individuals are blended based on a randomly generated blending factor. This blending factor determines the degree of influence of each parent on the offspring's parameters, allowing for controlled exploration of the search space.

Mutation:
The mutation is another genetic operator used in the Genetic Algorithm to introduce diversity into the population by randomly altering the parameters of some individuals. It serves as a mechanism for exploring new regions of the search space and preventing premature convergence to sub-optimal solutions. In our problem, we have applied Gaussian mutation, where small Gaussian-distributed random values perturb the individuals' parameters u_1 and u_2. The mutation rate controls the mutation probability for each parameter, determining the extent of parameter perturbation. Mutation ensures that the population continues to explore the search space and avoids getting stuck in local optima.

3.4 Results and Analysis

Now, let's look at the dynamics of the Model from current time $t_0 = 0$ to time $T = 40$ days. If we consider the initial susceptible population as 80% Infected as 20%, and Recovered as 0%, then we get the following;

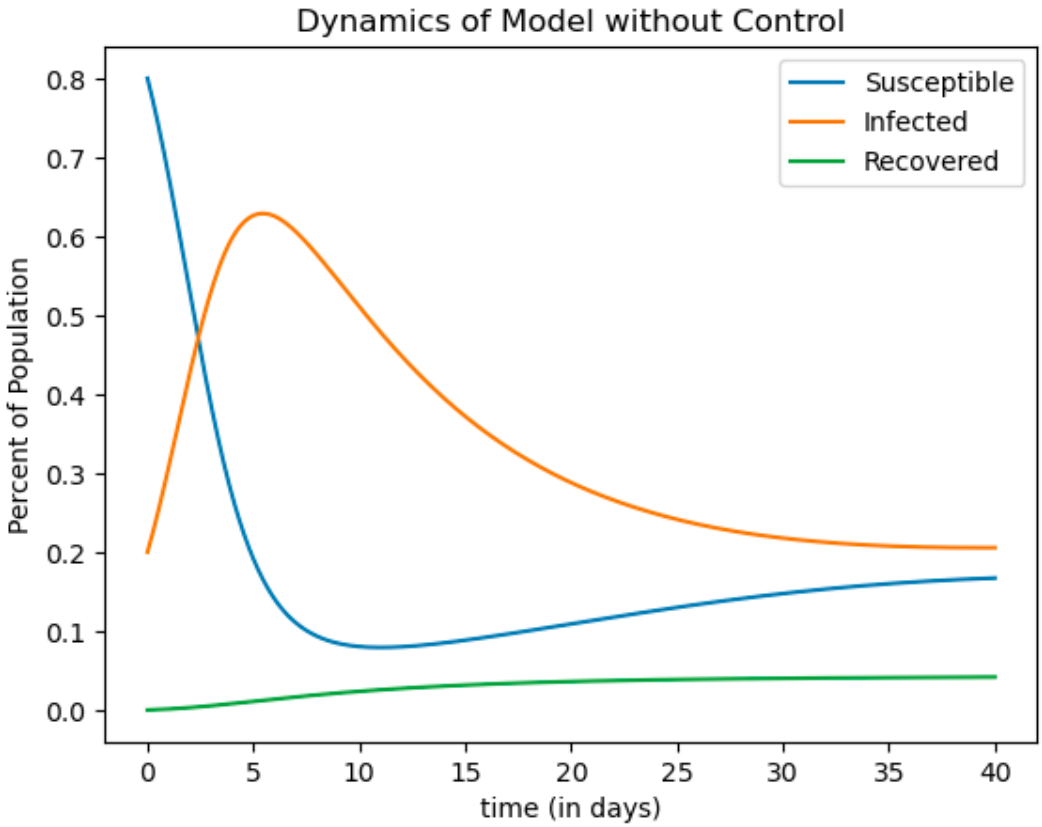


FIGURE 3.1: Model without any control

The graph illustrates a concerning trend: the entire population fails to resist the disease, with no signs of recovery. To mitigate this crisis, we must take action. We aim to increase the number of recovered individuals by implementing interventions represented by u_1 and u_2. However, to execute this strategy effectively, we require optimal values for u_1 and u_2 that control the disease's spread and minimize costs. To achieve this, we used a Genetic Algorithm, enabling us to find the most advantageous control parameters. Below are the optimal values we obtained from the genetic algorithm.

$$u_1 = 0.16390382, \quad \& \quad u_2 = 0.32812675$$

Now, if we want to control the spread by one vaccination, we have the following dynamics:

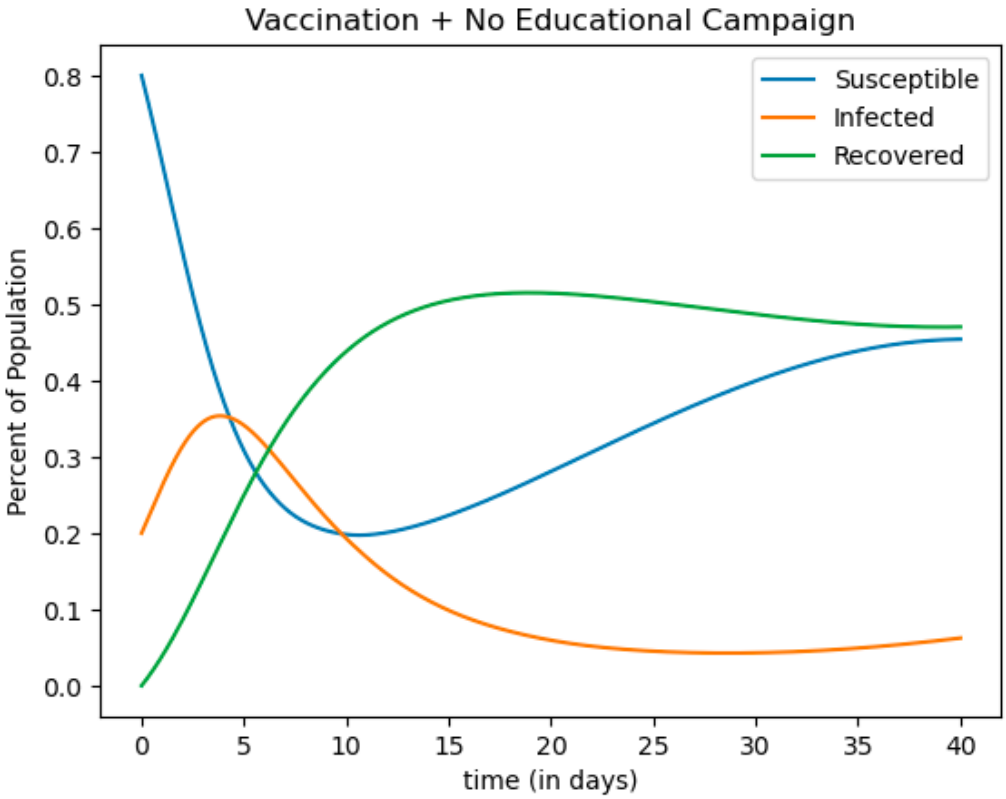


FIGURE 3.2: Model With Vaccination but without Educational Campaign

The current outcome is notably improved compared to the scenario without intervention. Initially, the number of recovered individuals is on the rise. However, after 15 days, a decline sets in, accompanied by a slight uptick in infections around the 30-day mark. This suggests that the current intervention is insufficient for long-term effectiveness. Thus, we must introduce another strategy. Now, let's consider implementing education campaigns instead of vaccination to curb the spread of the disease.

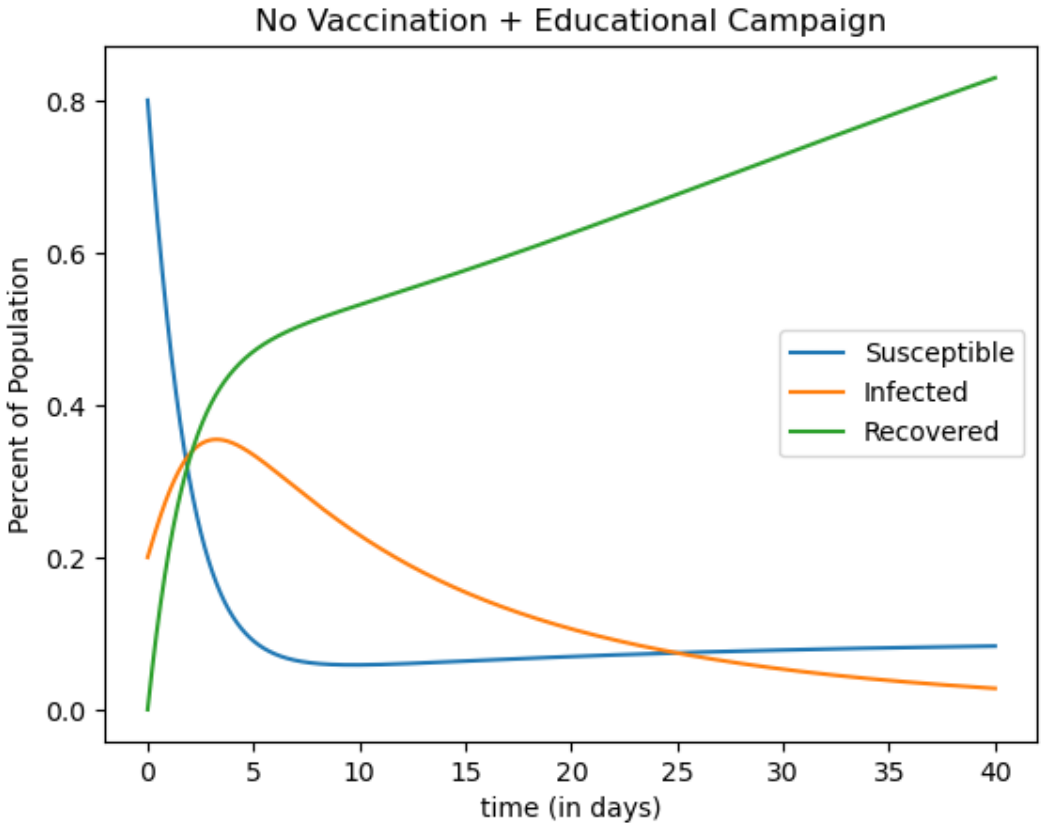


FIGURE 3.3: Model Without Vaccination but Educational Campaign

This revised strategy appears significantly more promising. However, upon closer examination of the diagram, we observe a gradual but persistent increase in the number of susceptible, currently standing at 7%. This upward trend could potentially rise in the future. Our ultimate objective is to minimize the number of susceptible, ideally approaching zero; if not, then at least there should not be even a slight increase while maximizing the number of recoveries.

Considering this, we hypothesize that implementing both strategies simultaneously may yield even more favorable outcomes. After implementing this combined approach, the dynamics of the graphs unfold as follows:

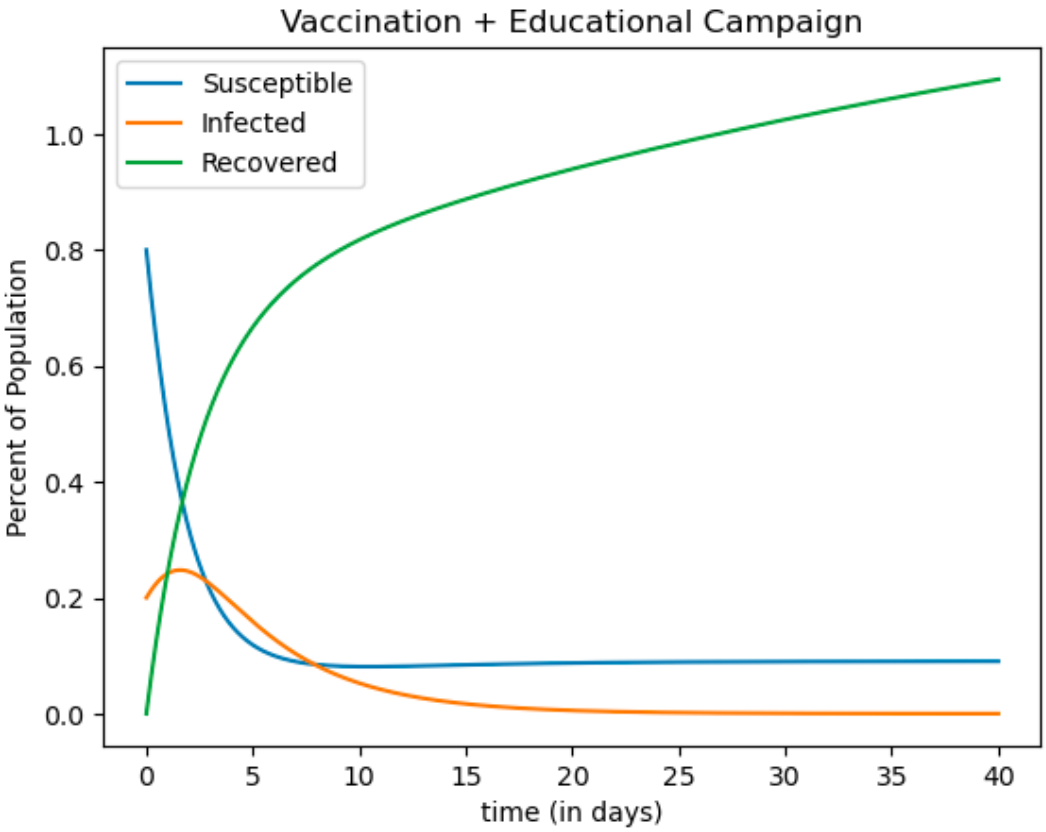


FIGURE 3.4: Model With Vaccination and Educational Campaign

The susceptible population remains at approximately 7%, displaying stability and no signs of further increase under the influence of both strategies. Conversely, the recovered population is steadily approaching its peak, reaching upwards of 90%, which seems the best strategy to control the spread of the disease.

Now let's have a look at the values of control variables, $u_1(t)$ and $u_2(t)$ that change from initial time t_0 to final time t_f.

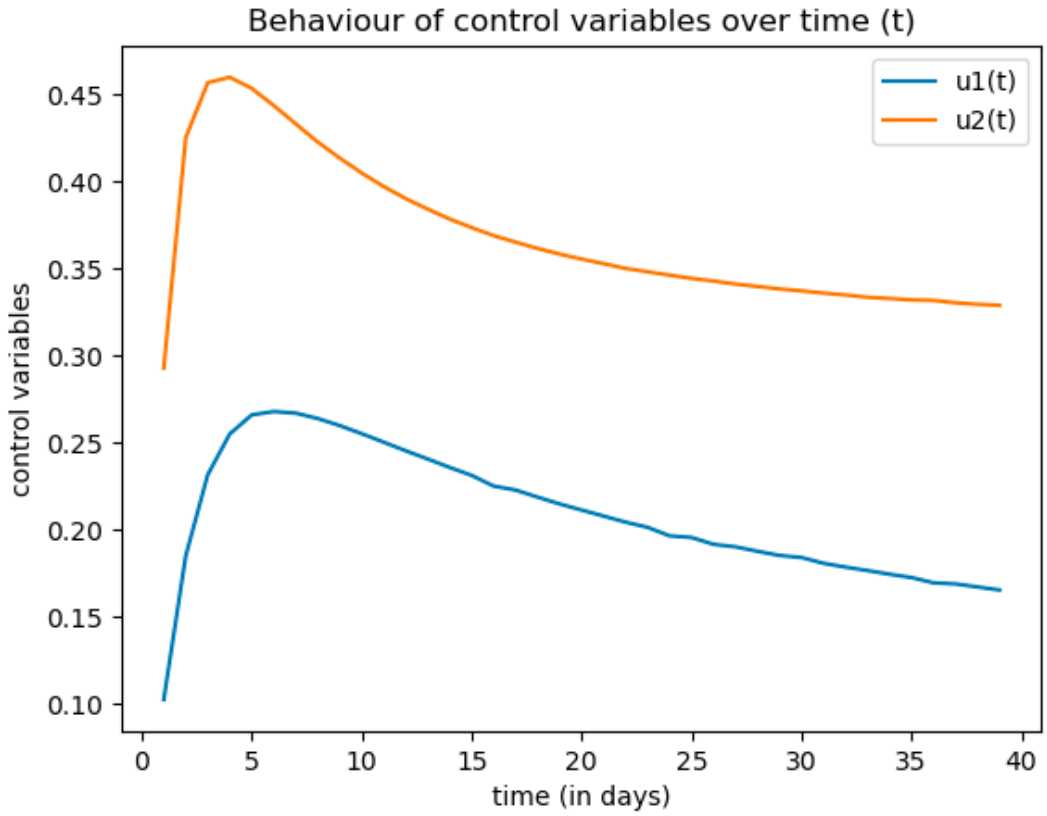


FIGURE 3.5: Control variable

The graph depicting the control variables shows that vaccination and education campaigns should peak around the 5th day. This observation aligns with the dynamics in the absence of control variables. As the infected population peaks around the 5th day, it logically necessitates heightened vaccination and educational campaigns to control the spread effectively.

Chapter 4

Optimal Dosing Strategy against Bacteria

4.1 Dosing Strategy against Bacteria

The growing challenge of antibiotic resistance necessitates innovative strategies to manage bacterial infections effectively. Optimization models for antibiotic use, such as the one developed by Massad et al. (2008) [8], can provide insights into the optimal allocation of antibiotics to minimize resistance while maximizing treatment efficacy. Understanding the dynamics of bacterial populations under the influence of antibiotics and nutrient availability is highly crucial for developing these strategies. Bifurcation analysis and global dynamics studies, like those conducted by Cen et al. (2017) [4], are crucial for understanding the behavior of antibiotic resistance within hospital settings and can inform the development of effective control strategies.

This chapter delves into an optimal dosing strategy using a sophisticated mathematical model based on the dynamics of susceptible and resistant bacterial populations, incorporating nutrient and antibiotic interactions.

We consider a model involving four differential equations that capture the interplay between nutrient concentration (S), antibiotic concentration (A), susceptible bacteria (u), and resistant bacteria (u^+). The model is structured as follows:

$$
\begin{aligned}
\frac{dS}{dt} &= d_S(S_0 - S) - \frac{1}{\gamma}[f(S)u + f_0(S)u_0] \\
\frac{dA}{dt} &= d_A(A_0(t) - A) - p(A)[u + u_0] \\
\frac{du}{dt} &= [f(S) - d_u - g(S,A)]u + qf_0(S)u_0 - \mu u u_0 \\
\frac{du_0}{dt} &= [f_0(S)(1-q) - d_u - g_0(S,A)]u_0 + \mu u u_0
\end{aligned}
$$

This chapter explores optimal dosing strategies that can effectively manage bacterial populations, minimizing the prevalence of resistant strains and eliminating susceptible bacteria. By leveraging the mathematical model, we seek to identify dosing regimens that balance antibiotic efficacy and resistance management, contributing to the broader goal of sustainable antibiotic use in clinical settings.

4.2 Mathematical Formulation

The basic model for dosing against bacteria captures the interactions between nutrients, antibiotics, and susceptible bacterial populations:

$$\begin{aligned}
\frac{dS}{dt} &= d_S(S_0 - S) - \frac{1}{\gamma} f(A)u, \\
\frac{dA}{dt} &= d_A(A_0(t) - A) - p(A)u, \\
\frac{du}{dt} &= f(A)u - d_u u - g(A,S)u,
\end{aligned}$$

where S represents the nutrient concentration, A the antibiotic concentration, and u the susceptible bacterial population.

S_0 is the initial nutrient concentration, and $A_0(t)$ is the time-varying initial antibiotic concentration. d_S is the nutrient flow rate, d_A is the antibiotic dilution rate, and d_u is the natural death or dilution rate of the bacteria. γ is the conversion rate of nutrients to bacteria, $p(A)$ is the uptake rate of antibiotics by the bacteria, $f(A)$ is the nutrient-dependent growth rate of the bacteria, and $g(A,S)$ is the function describing the effect of antibiotic concentration on bacterial killing.

To incorporate resistant bacterial populations, conjugation, and mis-segregation, the model is extended as follows:

$$\begin{aligned}
\frac{dS}{dt} &= d_S(S_0 - S) - \frac{1}{\gamma}[f(S)u + f_0(S)u_0], \\
\frac{dA}{dt} &= d_A(A_0(t) - A) - p(A)[u + u_0], \\
\frac{du}{dt} &= [f(S) - d_u - g(S,A)]u + q f_0(S)u_0 - \mu u u_0, \\
\frac{du_0}{dt} &= [f_0(S)(1-q) - d_u - g_0(S,A)]u_0 + \mu u u_0,
\end{aligned}$$

The first equation describes the variation in nutrient concentration (S). Nutrients flow into the system at a rate dS from a source with concentration S_0. These nutrients are consumed by both susceptible and resistant bacterial populations at different rates. The growth rates of bacteria are represented by functions $f(S)$ and $f_0(S)$, with

γ denoting the yield constant, which signifies the conversion of nutrients to bacteria. Nutrients also flow out of the system at rate dS.

The second equation delineates the dynamics of antibiotic concentration (A). Antibiotic enters the system at rate dA from a source with concentration $A_0(t) = A_m\delta(t)$, which varies over time due to the dosing strategy employed. Here A_m is the maximum Antibiotic that can be given at a time, and $\delta(t)$ is a fraction depending on time. Antibiotic concentration diminishes due to uptake by bacteria, which is assumed to occur uniformly for susceptible and resistant strains, as well as constant dilution.

Susceptible bacteria grow naturally at rate $f(S)$ while being flushed out at rate du and killed by the antibiotic at rate $g(S, A)$. The term $qf_0(S)u_0$ accounts for mis-segregation, where susceptible bacteria acquire resistance with probability q. The term $\mu u u_0$ represents the conversion of susceptible bacteria to resistant strains, modeled by mass action.

The last equation depicts the dynamics of resistant bacteria. The density of resistant bacteria increases due to the horizontal transmission of the resistance gene via conjugation. A proportion of resistant bacteria, denoted by $(1 - q)$, increase at rate $f_0(S)$, while the remaining fraction transitions back to the susceptible category due to mis-segregation. The entire resistant sub-population is eliminated at rate $g_0(S, A)$ by the antibiotic and is washed out at rate du.

We aim to minimize the number of susceptible and resistant bacteria using the minimum quantity of antibiotics. So, our optimization problem involves defining clear objectives and constraints tailored to the specific context of bacterial resistance evolution. We consider the following objective functions to be optimized:

$$J[\delta(t), u(t_f), u_+(t_f)] = Wu(t_f) + W_0u_0(t_f) + \frac{1}{2}\int_{t_0}^{t_f} W_A\delta(t)^2dt \tag{4.1}$$

Subject to the following differential equations representing the dynamics of bacterial resistance evolution within the chemostat:

$$\frac{dS}{dt} = d_S(S_0 - S) - \frac{1}{\gamma}[f(S)u + f_0(S)u_0] \tag{4.2}$$

$$\frac{dA}{dt} = d_A(A_0(t) - A) - p(A)[u + u_0] \tag{4.3}$$

$$\frac{du}{dt} = [f(S) - d_u - g(S, A)]u + qf_0(S)u_0 - \mu u u_0 \tag{4.4}$$

$$\frac{du_0}{dt} = [f_0(S)(1 - q) - d_u - g_0(S, A)]u_0 + \mu u u_0 \tag{4.5}$$

Where, the functions $f(S)$, $f_0(S)$, $p(A)$, $g(S, A)$, and $g_0(S, A)$ are defined as follows:

$$f(S) = \frac{mS}{a+S}$$

$$f_0(S) = \frac{m_0 S}{a+S}$$

$$p(A) = \frac{\nu A}{L_1 + A}$$

$$g(S,A) = \frac{kS}{a+S} \times \frac{A}{L+A}$$

$$g_0(S,A) = \frac{k_0 S}{a+S} \times \frac{A}{L+A}$$

Here, m, m_0, a, ν, k, k_0, L, and L_1 are constants governing the behavior of the model. Here, m_0 is constrained to be less than or equal to m, and k_0 is constrained to be less than k.

These functions capture the growth rates of susceptible and resistant bacteria ($f(S)$ and $f_0(S)$), the uptake rate of antibiotics ($p(A)$), and the rates of bacterial death due to antibiotics for both susceptible and resistant strains ($g(S,A)$ and $g_0(S,A)$). They are formulated to reflect the complex interactions between nutrient availability, antibiotic concentration, and bacterial population dynamics within the chemostat.

4.3 Optimization Methodology (Genetic Algorithm)

The Genetic Algorithm is an optimization method consisting of four fundamental steps. Firstly, it begins with an initialization phase, generating an initial population of potential solutions. Secondly, individuals in the population are selected based on their fitness values, which are evaluated using a predefined fitness function that quantifies how well they solve the optimization problem. Then, chosen individuals go through the crossover by exchanging genetic material to create offspring with characteristics inherited from their parents. Finally, mutation introduces random changes to the genetic material of some individuals, promoting genetic diversity in the population. Through iterations of selection, crossover, and mutation, the GA evolves the population over generations, ultimately converging towards solutions that approximate the optimal solution to the given optimization problem.

$$\text{ArgMin}_{(u,u_0)} J[\delta(t), u(t_f), u_0(t_f)] = Wu(t_f) + W_0 u_0(t_f) + \frac{1}{2}\int_{t_0}^{t_f} W_A \delta(t)^2 dt$$

Constrained to,

$$\frac{dS}{dt} = d_S(S_0 - S) - \frac{1}{\gamma}[f(S)u + f_0(S)u_0]$$
$$\frac{dA}{dt} = d_A(A_0(t) - A) - p(A)[u + u_0]$$
$$\frac{du}{dt} = [f(S) - d_u - g(S, A)]u + qf_0(S)u_0 - \mu u u_0$$
$$\frac{du_0}{dt} = [f_0(S)(1 - q) - d_u - g_0(S, A)]u_0 + \mu u u_0$$

The values of the parameters are as follows:

TABLE 4.1: Description, Symbols, and Values of parameters [6]

Description	**Symbols**	**Values**
Substrate Feed Concentration	S_0	0.2
Maximum Antibiotic Dosage Concentration	A_m	3
Substrate Dilution Rate	d_S	0.23
Antibiotic Dilution Rate	d_A	0.23
Bacteria Dilution Rate	d_u	0.23
Yield Constant	γ	0.8
Probability of Mis-segregation	q	0.1
Rate of plasmid transfer during Conjugation	μ	0.0000001
Maximum Growth Rate for Susceptible Bacteria	m	0.417
Maximum Growth Rate for Resistant Bacteria	m_0	0.416
Maximum Antibiotic Uptake	ν	0.345
Maximum Kill Rate for Susceptible Bacteria	k	0.96
Probability of Mis-segregation	q	0.1
Rate of plasmid transfer during Conjugation	μ	0.0000001
Maximum Growth Rate for Susceptible Bacteria	m	0.417
Maximum Growth Rate for Resistant Bacteria	m_0	0.416
Maximum Antibiotic Uptake	ν	0.345
Maximum Kill Rate for Susceptible Bacteria	k	0.96
Maximum Kill Rate for Resistant Bacteria	k_0	0.87
Half Saturation Constant for Bacteria Growth	a	0.1
Half Saturation Constant for Bacteria Kill	L	0.1
Half Saturation Constant for Antibiotic Uptake	L_1	0.1
Antibiotic Cost Sensitivity	W_A	0.001
Susceptible Bacteria Cost Sensitivity	W	1
Resistant Bacteria Cost Sensitivity	W_0	1
Period of Dosing Regimen	T	8

Population: The population consists of a set of individuals, each representing a potential solution to the optimization problem. Each individual is a list of floating-point numbers that denote a strategy for the antibiotic concentration over time. The initial population is generated using the 'toolbox.population' function, which creates a list of 100 individuals.

Selection: The selection process uses tournament selection ('toolbox.select'), where a set of individuals is randomly chosen, and the best (with the lowest fitness value) is selected for the next generation. This ensures that better solutions have a higher

chance of being passed on to the next generation.

Crossover: The two-point crossover method ('toolbox.mate') is used, which selects two crossover points within the parents' genomes and exchanges the segments between these points. The crossover probability is set to 0.7, meaning there is a 70% chance that two individuals will undergo crossover. Mutation introduces random changes to an individual's genetic makeup, promoting genetic diversity. Gaussian mutation ('toolbox.mutate') is used, where a small random value drawn from a Gaussian distribution is added to each gene in an individual with a certain probability. The mutation probability is set to 0.2, meaning there is a 20% chance that any given gene will be mutated.

Mutation: After running for 100 generations, the algorithm selects the best individual from the final population as the optimal strategy. The fitness function evaluates how well an individual's strategy minimizes the sum of the susceptible ('u') and resistant bacteria ('u_0') concentrations at the final time point, as well as the sum of the strategy values to discourage excessive antibiotic use. This is achieved by defining the antibiotic concentration function 'A_0' based on the individual's strategy, integrating the system of ODEs with this antibiotic strategy, and computing the fitness as the negative sum of 'u', 'u_0', and the strategy values.

4.4 Results and Analysis

The Dynamics of the spread of susceptible and resistant bacteria is as follows:

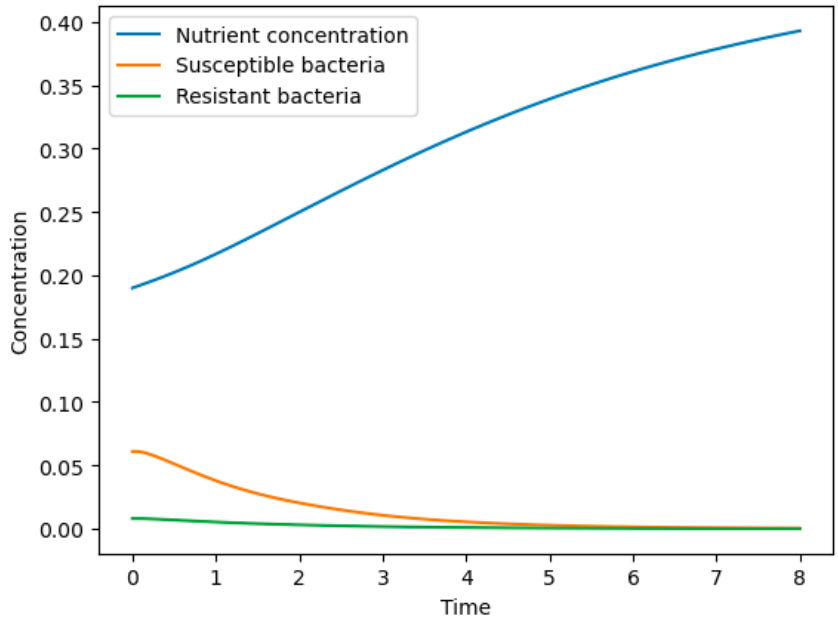
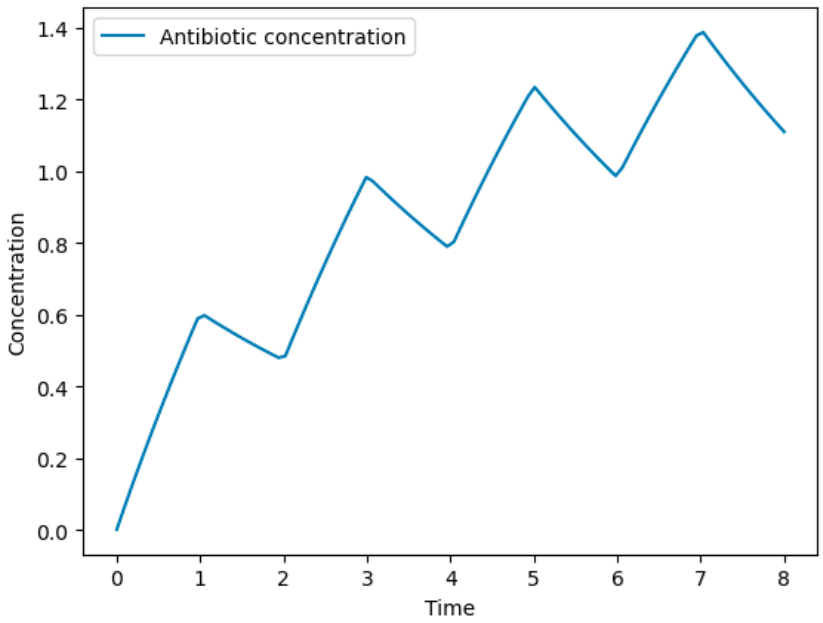


FIGURE 4.1: Control variable

The graph shows that the susceptible and resistant bacteria population starts at approximately 0.06 and 0.02, respectively. By the 8th hour, the populations of both types of bacteria have nearly declined to zero. Concurrently, the nutrient concentration increases steadily, reaching a value of 0.40 by the 8th hour.



The graph illustrates that on the first day, only 0.6 concentration of antibiotic should be used, and around 0.5 concentration on the next day, and so on till about 1.0 concentration on the 8th day when the susceptible and resistant bacterial population would eventually vanish.

Chapter 5

Conclusion

In this thesis, we have explored the optimal control of infectious diseases through the SIR model, extended by incorporating factors such as population growth, natural and disease-induced death rates, and loss of immunity. The modified SIR model, enhanced with control variables representing vaccination and educational campaigns, provides a robust framework for designing and implementing effective disease control strategies.

We introduced a comprehensive version of the SIR model that includes additional compartments and parameters to reflect real-world scenarios accurately. This model accounts for natural and disease-induced mortality, population growth, and immunity loss, making it a versatile tool for studying infectious disease dynamics. By integrating control variables for vaccination ($u_1(t)$) and educational campaigns ($u_2(t)$), we demonstrated how dynamic interventions can be optimized to minimize the spread of the disease. These variables allow us to adjust strategies in real-time, ensuring a responsive approach to disease management. The positivity and boundedness of the solutions were rigorously proven, ensuring the model's reliability and stability. The existence and uniqueness of the optimal control solution were established using Pontryagin's Maximum Principle, providing a solid theoretical foundation for the applied control strategies.

A genetic algorithm was used to solve the optimization problem. This method's iterative nature and ability to handle complex, non-linear problems made it suitable for finding the optimal control strategies that minimize the objective function, which includes the proportion of susceptible and infected individuals and the costs associated with vaccination and educational campaigns.

The results obtained from the modified SIR model with optimal control strategies highlight the effectiveness of combining vaccination and educational campaigns in reducing the overall impact of infectious diseases. The optimization methodology demonstrated that significantly reduced disease prevalence and associated costs could be achieved by dynamically adjusting the control measures over time.

5.1 Future work

- Reinforcement learning techniques can be another good approach to finding the optimal control of the disease model.
- Including additional compartments, such as an exposed (E) class or age-structured populations, could further enhance the model's applicability, and a genetic algorithm can provide a good result in this case.
- Exploring other optimization methods, such as machine learning algorithms or advanced control theory techniques, could provide more efficient and effective solutions.
- Applying the model to real-world data from past and ongoing epidemics could validate its practical utility and help refine the parameters and control strategies.

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