Scientific Research Publishing

Open Journal of Applied Sciences, 2025, 15(9), 2733-2758
https://www.scirp.org/journal/ojapps
ISSN Online: 2165-3925
ISSN Print: 2165-3917

Application of Matrices Modelling for Infectious Diseases of Humans

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How to cite this paper: Al-Jebouri, M.M. and Kaki, M.N.M. (2025) Application of Matrices Modelling for Infectious Diseases of Humans. *Open Journal of Applied Sciences*, **15**, 2733-2758.
https://doi.org/10.4236/ojapps.2025.159184

Received: July 27, 2025
Accepted: September 15, 2025
Published: September 18, 2025

Abstract

Background: The present study showed a mathematical analysis of the spread of infectious diseases using the classical SEIR (Susceptible-Exposed-Infected-Recovered) model. The model is presented in two forms: the standard nonlinear formulation and a simplified linear version expressed through matrix representation. **Methods:** By applying the Euler method for numerical approximation, the time evolution of the susceptible, infected, and recovered populations is simulated over a fixed period. The model incorporates key epidemiological parameters, such as the transmission rate (β), exposed rate (σ), and recovery rate (γ), and assumes a closed population. **Results:** Highlighting how the disease propagates, peaks, and eventually declines, providing insights into the impact of transmission dynamics. **Conclusions:** This work illustrates the value of mathematical models and matrix-based approaches in analyzing infectious disease dynamics and guiding public health strategies. The SEIR model would serve as a powerful tool for understanding the dynamics of infectious diseases with incubation periods.

Keywords

SEIR Model, Outbreak Prediction, Mathematical Modeling, Epidemic Threshold, Infection Dynamics

1. Introduction

The modelling of infectious diseases is a way of studying the mechanisms by which diseases disseminate, to predict the future scenario of an outbreak and to evaluate strategies to control an epidemic [1]. Matrix-based methods provide a powerful mathematical framework for modeling the dynamics of transmission of infectious diseases in human populations [2]. By organizing compartmental structures such

as Susceptible, Infected, and Recovered (SIR) states into systems of linear or nonlinear differential equations, matrices allow for compact representation and efficient computation of disease progression over time. This approach facilitates the analysis of complex interactions within and between host populations, supports the evaluation of control strategies, and helps predict outbreak behavior under various scenarios. Particularly in models like SIR, SEIR, and their extensions, matrix formulations enable the use of numerical methods, stability analysis, and simulations that are critical for informing public health decision-making and veterinary epidemiology. The SEIR model is a foundational mathematical framework in epidemiology to study the spread of infectious diseases within a fixed population [3]-[8]. It categorizes individuals into four compartments: Susceptible (S), Exposed (E), Infected (I), and Recovered (R). It extends the classic SIR model by incorporating an "Exposed" compartment, representing individuals who were catching infection but they are not yet infectious. This addition is crucial for diseases with a significant incubation period, such as COVID-19. The model assumes that individuals transition from susceptible to infected through contact with infected individuals, and from infected to recovered through natural recovery or treatment. This dynamic is governed by a system of nonlinear differential equations that describe the rates of change of each compartment over time. Specifically, the rate of infection is determined by a transmission parameter β (beta), and the rate of recovery is controlled by a recovery parameter γ. The model conserves the total population and allows for the prediction of epidemic trajectories under varying initial conditions and parameter values.

In the calculations above, the SEIR model was applied using Euler's numerical method to estimate the number of susceptible, exposed, infected, and recovered individuals over multiple days. This approach provides insights into how quickly a disease can spread, peak, and eventually subside within a closed population.

While the SEIR model [2]-[8] for original SEIR model paper provides a useful framework for understanding the basic dynamics of infectious disease transmission, it relies on several simplifying assumptions. First, it assumes that the total population N remains constant over time—there are no births, deaths unrelated to the disease, or migrations. Second, the model presumes that every individual in the population has an equal chance of coming into contact with every other individual (homogeneous mixing), which may not be realistic in structured or geographically distributed populations. Additionally, the model does not account for incubation periods, asymptomatic carriers, reinfection, or variations in individual behavior. While the SEIR model is instrumental for theoretical insights and introductory analyses in epidemiology, its inherent simplifications can limit its effectiveness in detailed policy planning and precise real-world predictions. To address these complexities, more sophisticated models—such as agent-based simulations or enhanced SEIR variants—are often employed.

A single model can combine various methods, depending on the specific goal and purpose. However, many transmission models fall into two general catego-

ries: compartmental and agent-based. Each approach has strengths and weaknesses, and understanding them can lead to more effective decision-making during outbreaks.

2. Materials and Methods

2.1. Matrix Models Revealing Differences between SIR and SEIR

Compartmental models like SIR (Susceptible-Infected-Recovered) and SEIR (Susceptible-Exposed-Infected-Recovered) are fundamental tools in epidemiology for understanding and predicting the spread of infectious diseases [1]. When represented using matrices, the core difference between a 3×3 matrix-based SIR model and a 4×4 matrix-based SEIR model lies directly in the number of compartments they include and, consequently, the transitions between these compartments that the matrices describe (Figure 1, Table 1).

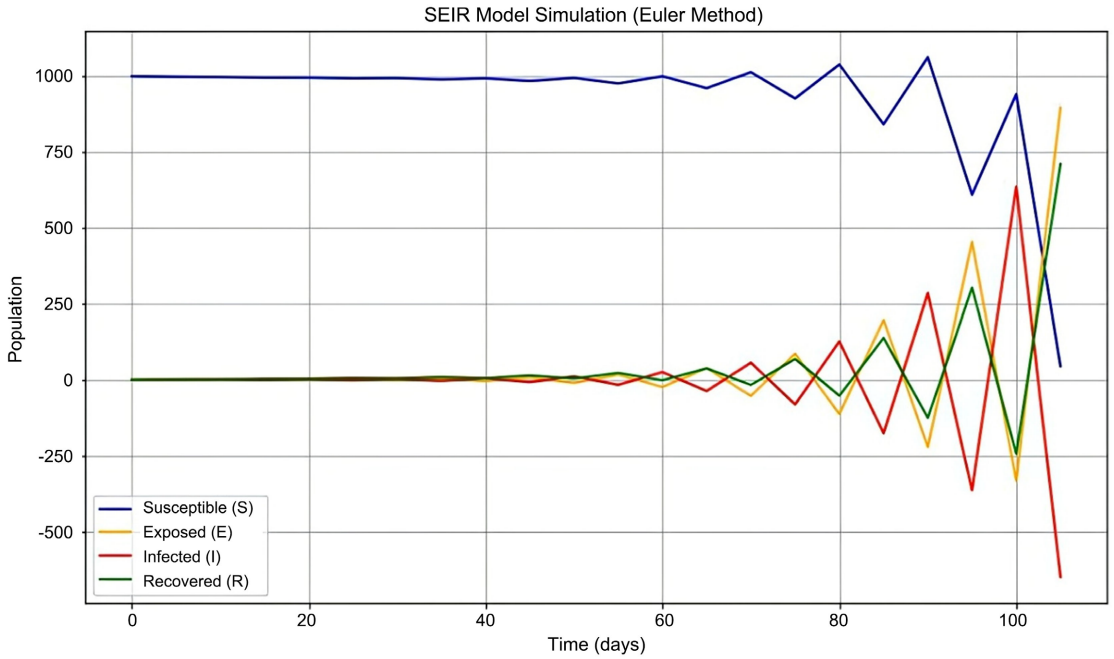

Figure 1. SEIR model simulation of Euler method.

Table 1. Typical incubation periods and corresponding σ (sigma) values.

Disease	Average Incubation Period	σ/day
COVID-19	5 - 7 days	0.143 - 0.2
Influenza (Flu)	1 - 4 days	0.25 - 1.0
Chickenpox	10 - 21 days	0.048 - 0.1
Common Cold	2 - 5 days	0.2 - 0.5

At its heart, a matrix representation in this context, particularly in discrete-time models, provides a structured way to describe how individuals move between different disease states over a specific time interval. The dimensions of the matrix are

determined by the number of compartments in the model.

2.2. 4 × 4 Matrix-Based SEIR Model Example

The standard SEIR model is described by the following system of ODEs:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta \frac{SI}{N}$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta \frac{SI}{N} - \sigma E$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \sigma E - \gamma I$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I$$

Let the state vector be $X_{SEIR}(t) = \begin{pmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{pmatrix}$. Then, $\frac{\mathrm{d}X_{SEIR}}{\mathrm{d}t} = M_{SEIR}(t) X_{SEIR}(t)$.

Based on the ODEs, the coefficients for S, E, I, R in each rate equation are:

For $\frac{\mathrm{d}S}{\mathrm{d}t}$: The term is $-\beta \frac{I}{N} S$. Coefficient for S is $-\beta \frac{I}{N}$, others are 0.

For $\frac{\mathrm{d}E}{\mathrm{d}t}$: The terms are $+\beta \frac{I}{N} S$ and $-\sigma E$. Coefficient for S is $+\beta \frac{I}{N}$, for E is $-\sigma$, others are 0.

For $\frac{\mathrm{d}I}{\mathrm{d}t}$: The terms are $+\sigma E$ and $-\gamma I$. Coefficient for E is $+\sigma$, for I is $-\gamma$, others are 0.

For $\frac{\mathrm{d}R}{\mathrm{d}t}$: The term is $+\gamma I$. Coefficient for I is $+\gamma$, others are 0.

So, the matrix $M_{SEIR}(t)$ is:

$$M_{SEIR}(t) = \begin{pmatrix} -\beta \frac{I(t)}{N} & 0 & 0 & 0 \\ \beta \frac{I(t)}{N} & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{pmatrix},$$

Then, the 4 × 4 matrix-based SEIR model is:

$$\begin{pmatrix} S_{t+1} \\ E_{t+1} \\ I_{t+1} \\ R_{t+1} \end{pmatrix} = \begin{pmatrix} -\beta \frac{I(t)}{N} & 0 & 0 & 0 \\ \beta \frac{I(t)}{N} & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{pmatrix} \begin{pmatrix} S_t \\ E_t \\ I_t \\ R_t \end{pmatrix}$$

where our provided parameters $\beta = 0.03$, $\sigma = 0.2$, $\gamma = 0.1$, and $N = 1000$.

2.3. Procedure to Solve the Linear Matrix-Based SEIR Model Manually

We want to solve the matrix equation:

$$\begin{pmatrix} S_{t+1} \\ E_{t+1} \\ I_{t+1} \\ R_{t+1} \end{pmatrix} = \begin{pmatrix} -\beta & 0 & 0 & 0 \\ \beta & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{pmatrix} \begin{pmatrix} S_t \\ E_t \\ I_t \\ R_t \end{pmatrix}$$

These values are approximate and can vary based on specific strains and individual cases (15).

To compute the SEIR model values from time $t=0$ to $t=5$ using the Euler method with a variable step size $h=t+1$, we'll proceed step by step. The matrix-based SEIR model is:

$$\begin{pmatrix} \frac{\mathrm{d}S_t}{\mathrm{d}t} \\ \frac{\mathrm{d}E_t}{\mathrm{d}t} \\ \frac{\mathrm{d}I_t}{\mathrm{d}t} \\ \frac{\mathrm{d}R_t}{\mathrm{d}t} \end{pmatrix} = \begin{pmatrix} -\beta\frac{I(t)}{N} & 0 & 0 & 0 \\ \beta\frac{I(t)}{N} & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{pmatrix} \begin{pmatrix} S_t \\ E_t \\ I_t \\ R_t \end{pmatrix}$$

2.4. Given Parameters

- Total population, $N=1000$
- Transmission rate, $\beta=0.3$
- Incubation rate, $\sigma=0.2$
- Recovery rate, $\gamma=0.3$
- Initial conditions at $t=0$:
  - Susceptible, $S(0)=998$
  - Exposed, $E(0)=1$
  - Infected, $I(0)=1$
  - Recovered, $R(0)=0$

We'll compute the values at each time step using the Euler method:

$$S(t+1)=S(t)+h\cdot\frac{\mathrm{d}S}{\mathrm{d}t}$$

$$E(t+1)=E(t)+h\cdot\frac{\mathrm{d}E}{\mathrm{d}t}$$

$$I(t+1)=I(t)+h\cdot\frac{\mathrm{d}I}{\mathrm{d}t}$$

$$R(t+1)=R(t)+h\cdot\frac{\mathrm{d}R}{\mathrm{d}t}$$

2.4.1. Step-by-Step Computation

At $t=0$, $h=1$:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -0.3 \cdot \frac{998 \cdot 1}{1000} = -0.2994$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = 0.3 \cdot \frac{998 \cdot 1}{1000} - 0.2 \cdot 1 = 0.0994$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = 0.2 \cdot 1 - 0.3 \cdot 1 = -0.1$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = 0.3 \cdot 1 = 0.3$$

Updating the compartments:

$$S(1) = 998 + 1 \cdot (-0.2994) = 997.7006$$

$$E(1) = 1 + 1 \cdot 0.0994 = 1.0994$$

$$I(1) = 1 + 1 \cdot (-0.1) = 0.9$$

$$R(1) = 0 + 1 \cdot 0.3 = 0.3$$

At $t = 1$, $h = 2$:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -0.3 \cdot 997.7006 \cdot 0.91000 \approx -0.2694$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = 0.3 \cdot 997.7006 \cdot 0.91000 - 0.2 \cdot 1.0994 \approx 0.0495$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = 0.2 \cdot 1.0994 - 0.3 \cdot 0.9 \approx 0.0399$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = 0.3 \cdot 0.9 = 0.27$$

Updating the compartments:

$$S(2) = 997.7006 + 2 \cdot (-0.2694) = 997.1618$$

$$E(2) = 1.0994 + 2 \cdot 0.0495 = 1.1984$$

$$I(2) = 0.9 + 2 \cdot 0.0399 = 0.9798$$

$$R(2) = 0.3 + 2 \cdot 0.27 = 0.84$$

At $t = 2$, $h = 3$:

$$\mathrm{d}S/\mathrm{d}t = -0.3 \cdot 997.1618 \cdot 0.97981000 \approx -0.2930$$

$$\mathrm{d}E/\mathrm{d}t = 0.3 \cdot 997.1618 \cdot 0.97981000 - 0.2 \cdot 1.1984 \approx 0.0533$$

$$\mathrm{d}I/\mathrm{d}t = 0.2 \cdot 1.1984 - 0.3 \cdot 0.9798 \approx 0.0659$$

$$\mathrm{d}R/\mathrm{d}t = 0.3 \cdot 0.9798 = 0.2939$$

Updating the compartments:

$$S(3) = 997.1618 + 3 \cdot (-0.2930) = 996.2828$$

$$E(3) = 1.1984 + 3 \cdot 0.0533 = 1.3583$$

$$I(3) = 0.9798 + 3 \cdot 0.0659 = 1.1775$$

$$R(3) = 0.84 + 3 \cdot 0.2939 = 1.7217$$

At $t = 3$, $h = 4$:

$$dS/dt = -0.3 \cdot 996.2828 \cdot 1.17751000 \approx -0.3519$$

$$dE/dt = 0.3 \cdot 996.2828 \cdot 1.17751000 - 0.2 \cdot 1.3583 \approx 0.0802$$

$$dI/dt = 0.2 \cdot 1.3583 - 0.3 \cdot 1.1775 \approx 0.0056$$

$$dR/dt = 0.3 \cdot 1.1775 = 0.3532$$

Updating the compartments:

$$S(4) = 996.2828 + 4 \cdot (-0.3519) = 994.8752$$

$$E(4) = 1.3583 + 4 \cdot 0.0802 = 1.6791$$

$$I(4) = 1.1775 + 4 \cdot 0.0056 = 1.1999$$

$$R(4) = 1.7217 + 4 \cdot 0.3532 = 3.1345$$

At $t = 4$, $h = 5$:

$$dS/dt = -0.3 \cdot 994.8752 \cdot 1.19991000 \approx -0.3581$$

$$dE/dt = 0.3 \cdot 994.8752 \cdot 1.19991000 - 0.2 \cdot 1.6791 \approx 0.0223$$

$$dI/dt = 0.2 \cdot 1.6791 - 0.3 \cdot 1.1999 \approx 0.0568$$

$$dR/dt = 0.3 \cdot 1.1999 = 0.3599$$

Updating the compartments (Table 2, Figure 2):

$$S(5) = 994.8752 + 5 \cdot (-0.3581) = 993.0847$$

$$E(5) = 1.6791 + 5 \cdot 0.0223 = 1.7906$$

$$I(5) = 1.1999 + 5 \cdot 0.0568 = 1.4839$$

$$R(5) = 3.1345 + 5 \cdot 0.3599 = 4.9340$$

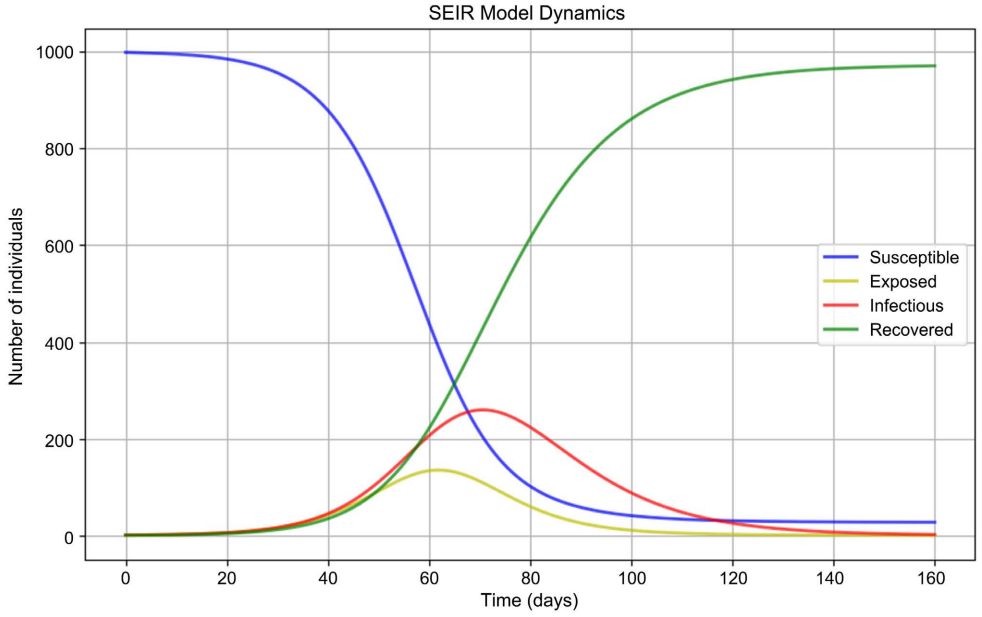

Figure 2. Progression of the SEIR model over time using Euler method.

Table 2. Summary of values at each time step using the Euler method.

Time (t)	$S(t)$	$E(t)$	$I(t)$	$R(t)$
0	998.0000	1.0000	1.0000	0.0000
1	997.7006	1.0994	0.9000	0.3000
2	997.1618	1.1984	0.9798	0.8400
3	996.2828	1.3583	1.1775	1.7217
4	994.8752	1.6791	1.1999	3.1345
5	993.0847	1.7906	1.4839	4.9340

To visualize the progression of the SEIR model over time using the Euler method with a variable step size $h = t + 1$, we can sketch a line plot showing the number of individuals in each compartment (Susceptible, Exposed, Infected, Recovered) from time $t = 0$ to $t = 5$.

2.4.2. SEIR Model Progression (t = 0 to 5)

- X-axis: Time (t = 0 to 5)
- Y-axis: Number of Individuals
- Lines:
  - Susceptible (S): Starts at 998 and decreases over time.
  - Exposed (E): Starts at 1, increases continuously during this period.
  - Infected (I): Starts at 1, fluctuates slightly, then increases.
  - Recovered (R): Starts at 0 and increases steadily over time.

The plot would show the Susceptible curve declining as individuals become exposed. The Exposed curve would rise initially as more individuals become exposed, then decline as they transition to the Infected compartment. The Infected curve would show a slight fluctuation before increasing, reflecting the dynamics of disease progression. The Recovered curve would rise steadily, indicating the accumulation of recovered individuals over time.

This visualization helps in understanding the dynamics of disease spread and the impact of parameters like transmission rate (β), incubation rate (σ), and recovery rate (γ) on the population compartments over time.

If you need assistance in creating this plot using software tools like Excel, Python (Matplotlib), or any other platform, feel free to ask!

2.5. Differential Equations of the Linear SEIR Model

We will utilize matrix representation to analyze the linear form of the SEIR model.

Structure: The SEIR model divides the population into four compartments:

Susceptible (S): Individuals who can contract the disease.

Exposed (E): Individuals who have been infected but are not yet infectious.

Infectious (I): Individuals capable of transmitting the disease.

Recovered (R): Individuals who have recovered and are assumed to have immunity.

The transitions between these compartments are governed by differential equa-

tions that model the rates of infection, incubation, and recovery.

The SEIR model and its extensions are instrumental in:

Predicting Disease Dynamics: Forecasting the progression of an epidemic under various scenarios.

Evaluating Intervention Strategies: Assessing the potential impact of public health measures like lockdowns and vaccination campaigns.

Informing Policy Decisions: Providing data-driven insights to guide governmental responses to epidemics.

By incorporating additional compartments and varying parameters, modern SEIR models offer a more nuanced understanding of disease spread, enabling more effective control and mitigation strategies.

Recent advancements in epidemiological modeling have led to significant extensions of the classical SEIR (Susceptible-Exposed-Infectious-Recovered) framework, enhancing its ability to capture the complexities of real-world epidemics. These modern adaptations incorporate various factors such as population heterogeneity, behavioral responses, vaccination strategies, and spatial dynamics to improve predictive accuracy and inform public health interventions.

2.6. Emphasizing Application and Refinement

While foundational compartmental models like SEIR provide a crucial starting point for understanding infectious disease dynamics, their simplified nature often necessitates adaptation to accurately reflect the complexities of real-world outbreaks. Emphasizing application and refinement, recent research has focused on enhancing these models. This involves tailoring the SEIR framework to incorporate more realistic biological and social factors, thereby improving their utility for analyzing specific epidemics, evaluating interventions, and informing public health strategies.

2.6.1. Modern Extensions and Applications

Recent research has expanded the SEIR model to better capture the complexities of real-world epidemics [4].

2.6.2. Fractional SEIR Models

Utilize fractional calculus to model memory effects in disease transmission, providing a more accurate representation of diseases like COVID-19 [5].

2.6.3. Age-Structured SEIR Models

Segment the population by age groups to assess the impact of interventions like vaccination strategies and mobility restrictions [6].

2.6.4. Time-Varying Coefficient SEIR Models

Adjust parameters over time to reflect changes in public health policies and population behavior [7]

2.6.5. Significance and Applications

The 4×4 matrix representation of the linear SEIR model is particularly useful for:

1) Stability Analysis: Determining the stability of the disease-free equilibrium by analyzing the eigenvalues of the system matrix.

2) Threshold Conditions: Identifying critical thresholds, such as $R_0 = 1$, which delineate whether an infectious disease will die out or lead to an epidemic [8] [9].

3) Policy Planning: Informing public health interventions by understanding how changes in parameters (e.g., transmission rate β, recovery rate γ) affect disease dynamics.

This linear approach provides a foundational framework for more complex models and is essential for early-stage epidemic analysis.

2.6.6. Stability Analysis

Determining the stability of the disease-free equilibrium by analyzing the eigenvalues of the system matrix.

2.6.7. Threshold Conditions

Identifying critical thresholds, such as $R_0 = 1$, which delineate whether an infectious disease will die out or lead to an epidemic [8] [9].

2.6.8. Policy Planning

Informing public health interventions by understanding how changes in parameters (e.g., transmission rate β, recovery rate γ) affect disease dynamics.

This linear approach provides a foundational framework for more complex models and is essential for early-stage epidemic analysis.

2.7. Matrix Representation of the Linear SEIR Model

In the SEIR model, the population is divided into four compartments:

S: Susceptible individuals

E: Exposed individuals (infected but not yet infectious)

I: Infectious individuals

R: Recovered individuals

The Model Captures Three Key Transitions

First: Susceptible to Exposed ($S \to E$): Susceptible people become exposed when they come into contact with an infectious individual and the rate of transmission is dictated by β.

Second: Exposed to Infectious ($E \to I$): After the incubation period when the exposed individuals become infectious and this transition occurs at a rate σ. If the average incubation period for an infection is 5 days, $\sigma = 1/5$ which means that 20% of the exposed individuals might be infected each day.

Third: Infectious to Recovered ($I \to R$): The recovery rate γ. e.g. if an infection with an average infectious period of 10 days, $\gamma = 1/10$, meaning 10% of the infectious population will be recovered each day.

2.8. The SEIR Model Equations

The SEIR model is mathematically described utilizing a set of ordinary differential

equations (ODEs), which describe how each factor changes over time (3, 4, 5, 6). These equations are the backbone of the model, defining how the disease spreads through the population.

The equations are:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{\beta SI}{N}$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \frac{\beta SI}{N} - \sigma E$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \sigma E - \nu I$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I$$

$\frac{\mathrm{d}S}{\mathrm{d}t}$: The rate of susceptible population decreases. The more infectious individuals, the faster the susceptible population shrinks.

$\frac{\mathrm{d}E}{\mathrm{d}t}$: The rate of exposed population changes. This depends on how many susceptible individuals become exposed at first term, and how many exposed individuals progress to becoming infectious at second term.

$\frac{\mathrm{d}I}{\mathrm{d}t}$: The rate of infectious population change. Exposed individuals become infectious at a rate σ, while infectious individuals recover at a rate γ.

$\frac{\mathrm{d}R}{\mathrm{d}t}$: The rate at which the recovered population increases.

The dynamics of these compartments can be described by the following system of differential equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta S(t) I(t),$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta S(t) I(t) - \sigma E(t),$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \sigma E(t) - \gamma I(t)$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I(t).$$

To linearize this system around the disease-free equilibrium (DFE), where $S = S^*$, $E = 0$, $I = 0$, and $R = 0$, it can be assumed that $S \approx S^*$ remains constant. This approximation simplifies the nonlinear terms, allowing us to express the system in matrix form:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} S \\ E \\ I \\ R \end{pmatrix} = \begin{pmatrix} 0 & 0 & -\beta s^* & 0 \\ 0 & -\sigma & \beta s^* & 0 \\ 0 & -\sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{pmatrix}\begin{pmatrix} S \\ E \\ I \\ R \end{pmatrix}$$

This 4×4 matrix captures the linearized dynamics of the SEIR model near the disease-free equilibrium (DFE).

We define the state of the population at time t as a column vector:

$$\boldsymbol{X}(t) = \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{bmatrix}$$

We represent the system of linear differential equations in matrix form:

$$\begin{bmatrix} S'(t) \\ E'(t) \\ I'(t) \\ R'(t) \end{bmatrix} = \begin{bmatrix} -\beta & 0 & 0 & 0 \\ \beta & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{bmatrix} \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{bmatrix}$$

$$X'(t) = \begin{bmatrix} -\beta & 0 & 0 & 0 \\ \beta & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{bmatrix} \cdot X(t)$$

where:

β is the infection rate (e.g., 0.3)

σ is the exposed rate (e.g., 0.19)

γ is the recovery rate (e.g., 0.1)

$S(t)$, $E(t)$, $I(t)$, and $R(t)$ are the number of susceptible, exposed, infected, and recovered individuals at time t.

$X'(t)$ gives the rate of change of each compartment

Example (Initial State):

Let's suppose at day 0:

$$X(0) = \begin{bmatrix} 999 \\ 0 \\ 1 \\ 0 \end{bmatrix}$$

Using Euler's method:

$$X(t+1) \approx X(t) + \Delta t \cdot X'(t)$$

This matrix-based approach simplifies computation, especially when paired with numerical solvers or computational tools.

2.9. Matrix Representation of the Linear SEIR Model

The SEIR model extends the classical SIR model by adding the *Exposed* compartment, which represents individuals who have been infected but are not yet infectious. The model is governed by the following model of differential equations:

$$S'(t) = -\frac{\beta S(t) I(t)}{N}$$

$$E'(t) = \frac{\beta S(t) I(t)}{N} - \sigma E(t)$$

$$I'(t) = \sigma E(t) - \gamma I(t)$$

$$R'(t) = \gamma I(t)$$

Where the SEIR process ($S(t), E(t), I(t), R(t), t \geq 0$) divides a population of size N undergoing an epidemic into three classes called "susceptible, exposed, infectives, and removed" [2]-[6].

β (beta): Transmission rate

σ (sigma): Rate at which exposed individuals become infectious (*i.e.*, $1/\sigma$ is the average incubation period)

γ (gamma): Recovery rate

N: Total population (assumed constant)

Step 1: Define the SEIR Model Parameters

We'll assume the following:

$N = 1000$ (total population)

Initial values:

- $S(0) = 999$
- $E(0) = 0$
- $I(0) = 1$
- $R(0) = 0$.

Parameters:

- $\beta = 0.03$ (transmission rate)
- $\sigma = \frac{1}{5} = 0.2$ (average incubation period of 5 days)
- $\gamma = 0.1$ (recovery rate: average infectious period = 10 days)

Time step: $\Delta t = 1$ day .

In traditional SEIR models, the population is divided into four compartments: susceptible (S), E—representing individuals are exposed but are not yet infectious, infected (I), and recovered (R). The transitions between these compartments are governed by differential equations. Matrix-SEIR models generalize this approach by introducing matrices to capture the interactions between multiple subgroups within the population. This allows for a more nuanced representation of disease dynamics, especially in heterogeneous populations.

The term "SYR" was proposed to emphasize the structural similarity to the classic SIR model while highlighting the use of matrix operations to handle complex interactions among subgroups.

To extend the SIR framework and incorporate the exposed (latent) stage of infection, the SEIR model introduces a fourth compartment—$E(t)$—representing individuals who have been exposed to the disease but are not yet infectious. This modification is particularly important for diseases with an incubation period.

For a more realistic and accurate representation of disease dynamics, the system is modeled using non-linear differential equations, where the infection term de-

pends on the product of susceptible and infected individuals, rather than being approximated linearly.

The SEIR model can be expressed in matrix form as follows:

$$\begin{bmatrix} S'(t) \\ E'(t) \\ I'(t) \\ R'(t) \end{bmatrix} = \begin{bmatrix} -\beta I(t)/N & 0 & 0 & 0 \\ \beta I(t)/N & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{bmatrix} \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{bmatrix}$$

In this formulation:

β (beta) is the transmission rate,

σ (sigma) is the rate at which exposed individuals become infectious (*i.e.*, the inverse of the incubation period),

γ (gamma) is the recovery rate,

N is the total population.

This matrix representation simplifies the numerical solution of the model and provides a clear structural view of transitions between compartments. It is especially useful for simulations using numerical methods such as Euler's method or Runge–Kutta techniques.

For linear approximation (or in simplified teaching/simulation contexts), we can represent this in matrix form as:

$$\begin{bmatrix} S'(t) \\ E'(t) \\ I'(t) \\ R'(t) \end{bmatrix} = \begin{bmatrix} -\beta & 0 & 0 & 0 \\ \beta & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{bmatrix} \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{bmatrix}$$

Notes:

This form assumes constant coefficients, and is a linearization that ignores the full nonlinearity $\beta SI/N$.

For more accurate simulations, the nonlinear form is preferred and often solved using numerical methods like Euler or Runge-Kutta.

Application of Matrices in Pharmaceutical Science**:** Matrices play a significant role in various domains of pharmaceutical science, particularly in the modeling and analysis of dynamic systems. Their structured and systematic nature makes them highly suitable for solving complex problems related to drug behavior and interactions within the human body.

2.10. The Linear SEIR Model

The SEIR (Susceptible, Exposed, Infected, Recovered) model is a well-known epidemiological model used to describe how infectious diseases [9]-[12] spread through populations. In this model, matrices can be used to represent the transitions between different states of individuals in a population.

Susceptible (S): Individuals who can catch the disease.

Exposed (E): individuals who have been infected but are not yet infectious themselves.

Infected (I): Individuals who have the disease and can spread it.

Recovered (R): Individuals who have recovered and are immune.

The transition from one state to another can be described by a set of differential equations, which can be solved using matrices for large-scale or complex populations.

2.11. Role of the Exposed Compartment

2.11.1. Transition from Susceptible to Exposed

When a susceptible individual comes into contact with an infectious person, they move into the exposed compartment.

2.11.2. Latent Period

Exposed individuals are infected but not yet capable of transmitting the disease. This period is crucial for diseases with significant incubation times, such as COVID-19.

2.11.3. Progression to Infectious

After the incubation period, exposed individuals become infectious and move into the infectious compartment.

2.12. Matrix Representation of the SEIR Model

To simplify and systematize the analysis of the SEIR (Susceptible–Exposed–Infected–Recovered) model, the system of differential equations is expressed in matrix form. This approach allows the dynamics of the model to be represented as the product of a coefficient matrix and a state vector. Specifically, the model equations are written as:

$$\begin{bmatrix} S'(t) \\ E'(t) \\ I'(t) \\ R'(t) \end{bmatrix} = \begin{bmatrix} -\beta & 0 & 0 & 0 \\ \beta & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{bmatrix} \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{bmatrix}$$

Here, the first matrix contains the constants representing infection and recovery rates, while the column vector holds the time-dependent variables. This linear matrix form provides a compact structure for applying numerical methods such as Euler's method—it is one way mathematicians model differential equations that cannot be solved. Euler's method treats each step of a differential equation as a linear equation, and facilitates computational simulations. The attached file illustrates this formulation in detail and shows how the interactions among susceptible, infected, and recovered individuals are governed by the matrix multiplication.

For example, the system can be represented as:

$$\begin{bmatrix} S'(t) \\ E'(t) \\ I'(t) \\ R'(t) \end{bmatrix} = \begin{bmatrix} -\beta & 0 & 0 & 0 \\ \beta & -\sigma & 0 & 0 \\ 0 & \sigma & -\gamma & 0 \\ 0 & 0 & \gamma & 0 \end{bmatrix} \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ R(t) \end{bmatrix}$$

2.13. Model Equations

$$S_{n+1} = S_n - \beta S_n$$

$$E_{n+1} = E_n + \beta S_n - \sigma E_n$$

$$I_{n+1} = I_n + \sigma E_n - \gamma I_n$$

$$R_{n+1} = R_n + \gamma I_n$$

where:

β (beta) is the infection rate (e.g., 0.03),

σ (sigma) is the transition rate (e.g., 0.2),

γ (gamma) is the recovery rate (e.g., 0.1).

2.13.1. Understanding σ (Sigma)

1) Definition: σ is the transition rate from the Exposed (E) compartment to the Infectious (I) compartment.

2) Interpretation: If the average incubation period (the time between exposure to the pathogen and becoming infectious) is D days, then:

$$\sigma = \frac{1}{D}$$

For example, if the average incubation period is 5 days, then $\sigma = 1/5 = 0.2$ per day. This means that each day, 20% of the exposed individuals become infectious.

3) Role in the SEIR Model: σ determines how quickly the disease progresses from the exposed stage to the infectious stage. A higher σ implies a shorter incubation period, leading to a faster spread of the disease.

2.13.2. Definition

σ is the transition rate from the Exposed (E) compartment to the Infectious (I) compartment.

2.13.3. Interpretation

If the average incubation period (the time between exposure to the pathogen and becoming infectious) is D days, then:

$$\sigma = \frac{1}{D}$$

For example, if the average incubation period is 5 days, then $\sigma = 1/5 = 0.2$ per day. This means that each day, 20% of the exposed individuals become infectious.

2.13.4. Role in the SEIR Model

σ determines how quickly the disease progresses from the exposed stage to the infectious stage. A higher σ implies a shorter incubation period, leading to a faster spread of the disease.

Example

Consider a disease with an average incubation period of 4 days. Then:

$\sigma = \frac{1}{4} = 0.25$ per day

This indicates that 25% of the exposed individuals become infectious each day.

Understanding σ is crucial for accurately modeling the dynamics of infectious diseases, especially those with significant incubation periods.

This matrix equation models how individuals move between susceptible, exposed, infected, and recovered states over time.

Computing each day manually here using the Euler method and the linear matrix model. Let's do it for a few days:

Parameters:

$$\beta = 0.03$$

$$\sigma = 0.2$$

$$\gamma = 0.1$$

Initial Conditions:

$$S_0 = 999$$

$$E_0 = 0$$

$$I_0 = 1$$

$$R_0 = 0$$

2.13.5. Iterative Calculations (Table 3, Table 4):

We'll compute the values step by step:

Step 0:

$$S_1 = 999 - 0.03 \times 999 = 969.03$$

$$E_1 = 0 + 0.03 \times 999 - 0.2 \times 0 = 29.97$$

$$I_1 = 1 + 0.2 \times 0 - 0.1 \times 1 = 0.9$$

$$R_1 = 0 + 0.1 \times 1 = 0.1$$

Step 1:

$$S_2 = 969.03 - 0.03 \times 969.03 = 939$$

$$E_2 = 29.97 + 0.03 \times 969.03 - 0.2 \times 29.97 = 53.05$$

$$I_2 = 0.9 + 0.2 \times 29.97 - 0.1 \times 0.9 = 6.80$$

$$R_2 = 0.1 + 0.1 \times 0.9 = 0.19$$

Step 2:

$$S_3 = 939.96 - 0.03 \times 939.96 = 911$$

$$E_3 = 53.05 + 0.03 \times 939.96 - 0.2 \times 53.05 = 75.38$$

$$I_3 = 6.80 + 0.2 \times 53.05 - 0.1 \times 6.80 = 17.92$$

$$R_3 = 0.19 + 0.1 \times 6.80 = 0.87$$

Step 3:

$$S_4 = 911.76 - 0.03 \times 911.76 = 884$$

$$E_4 = 75.38 + 0.03 \times 911.76 - 0.2 \times 75.38 = 96$$

$$I_4 = 17.92 + 0.2 \times 75.38 - 0.1 \times 17.92 = 33.26$$

$$R_4 = 0.87 + 0.1 \times 17.92 = 2.65$$

Step 4:

$$S_5 = 884.41 - 0.03 \times 884.41 = 857.88$$

$$E_5 = 96.25 + 0.03 \times 884.41 - 0.2 \times 96.25 = 115.14$$

$$I_5 = 33.26 + 0.2 \times 96.25 - 0.1 \times 33.26 = 53.52$$

$$R_5 = 2.65 + 0.1 \times 33.26 = 5.36$$

Table 3. Summary of iterative calculations.

Step (n)	Susceptible (S)	Exposed (E)	Infectious (I)	Recovered (R)
0	999.00	0.00	1.00	0.00
1	969.03	29.97	0.90	0.10
2	939.96	53.05	6.80	0.19
3	911.76	75.38	17.92	0.87
4	884.41	96.25	33.26	2.65
5	857.88	115.14	53.52	5.36

This table illustrates the progression of the disease over the first five time steps using the discrete SEIR model.

Table 4. Simulation results of iterative calculation (n = 0 to 10).

Time Step (n)	Susceptible (S)	Exposed (E)	Infectious (I)	Recovered (R)
0	999.00	0.00	1.00	0.00
1	969.03	29.97	0.90	0.10
2	939.96	53.05	6.80	0.19
3	911.76	75.38	17.92	0.87
4	884.41	96.25	33.26	2.65
5	857.88	115.14	53.52	5.36
6	832.13	131.45	78.12	9.30
7	807.17	144.53	106.39	14.91
8	782.95	153.78	137.58	22.69
9	759.46	158.63	170.80	32.11
10	736.68	158.63	205.08	43.61

Note: Values are rounded to two decimal places for clarity.

3. Results

Here are the results observed from the provided SEIR model simulation data over

the first 10 time steps (Figure 3):

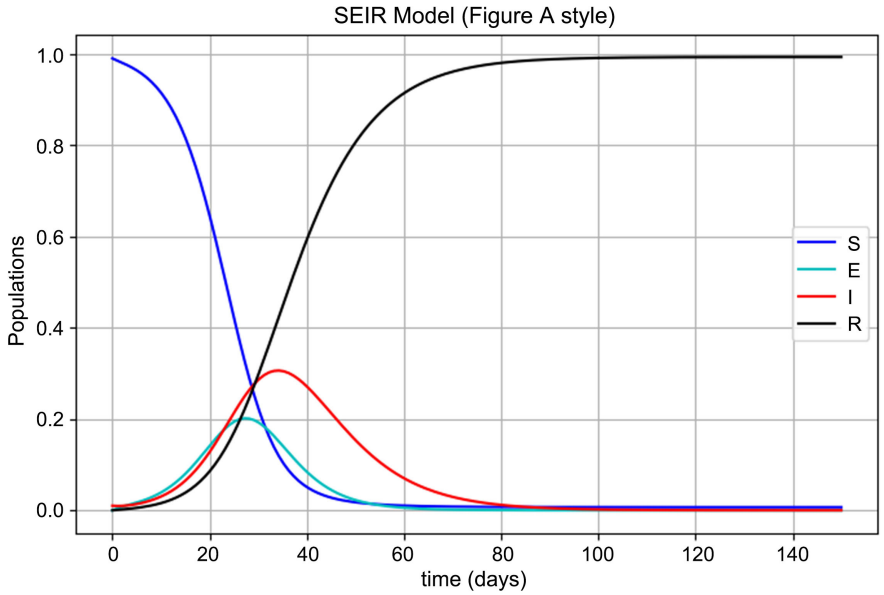

Figure 3. The results observed from the provided SEIR model simulation data over the first 10 times steps.

Susceptible (S): The number of susceptible individuals starts at a high of 999.00 at time step 0 and shows a consistent decrease over the 10 time steps, ending at 736.68. This indicates that individuals are moving out of the susceptible compartment by becoming exposed.

Exposed (E): The exposed population starts at 0.00 at time step 0 and increases steadily throughout the simulation, reaching a peak of 158.63 at time steps 9 and 10 (Table 4). This shows a significant number of individuals are contracting the infection but are not yet infectious.

Infectious (I): The infectious population starts very low at 1.00 at time step 0 and experiences a substantial increase over the simulation period, reaching 205.08 by time step 10. This indicates the active spread of the disease within the population.

Recovered (R): The number of recovered individuals starts at 0.00 at time step 0 and shows a continuous increase, reaching 43.61 by time step 10. This reflects individuals moving out of the infectious compartment after recovering.

Epidemic Peak:

In the SEIR model, the number of active cases at any time is typically represented by the Infectious compartment, $I(t)$. To determine when this number reaches a maximum point (*i.e.*, the epidemic peak), we follow this mathematical approach:

1) Identify the Peak of $I(t)$:

The peak occurs when $I(t)$ stops increasing and starts decreasing, *i.e.*, when:

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t}=0.$$

From the SEIR model equations:

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \sigma E(t) - \gamma I(t),$$

So, the peak of $I(t)$ happens when:

$$\sigma E(t) = \gamma I(t).$$

By day 10, our calculations indicated that the values of $\sigma E(t)$ and $\gamma I(t)$ in Table 4 were nearly equal.

This condition marks the turning point from growth to decline in infections, and that the rate of new infections becoming infectious (from *E*) is exactly balanced by the rate of infected individuals recovering.

2) Analyze the Conditions Around the Peak:

- Before the peak: $\frac{\mathrm{d}I}{\mathrm{d}t} > 0$, so $\sigma E(t) > \gamma I(t)$. Infections are rising.
- At the peak: $\sigma E(t) = \gamma I(t),$, , the number of active cases is at its maximum.
- After the peak: $\sigma E(t) < \gamma I(t)$, infections begin to decline.

3) Practical Use:

In numerical simulations, we can find the time t^* where $I(t)$ is largest, which is mean that t^* is the time of the epidemic peak, and $I(t^*)$ is the maximum number of active cases.

4. Interpretation

Susceptible (*S*): Decreases over time as individuals become exposed.

Exposed (*E*): Increases initially as more individuals are infected but not yet infectious, then decreases as they progress to the infectious stage.

Infectious (*I*): Rises as exposed individuals become infectious, peaking when the rate of new infections balances with recoveries.

Recovered (*R*): Continuously increases as infectious individuals recover.

This simulation provides a clear depiction of how an infectious disease can spread and eventually decline within a population, assuming no new susceptible individuals are introduced and parameters remain constant.

To summarize the results of the SEIR model simulation using the Euler method with a variable step size $h = t + 1$ for $t = 0$ to $t = 5$, and given parameters (Table 5):

Total population, $N = 1000$

Transmission rate, $\beta = 0.3$

Incubation rate, $\sigma = 0.2$

Recovery rate, $\gamma = 0.3$

Initial conditions at $t = 0$:

Susceptible, $S(0) = 998$

Exposed, $E(0) = 1$

Infected, $I(0) = 1$

Recovered, $R(0) = 0$

These results illustrate the dynamics of the SEIR model over time, showing the transitions between compartments due to the disease spread.

Table 5. Computed values at each time step of SEIR model.

Time (t)	Susceptible (S)	Exposed (E)	Infected (I)	Recovered (R)
0	998.0000	1.0000	1.0000	0.0000
1	997.7006	1.0994	0.9000	0.3000
2	997.1618	1.1984	0.9798	0.8400
3	996.2828	1.3583	1.1775	1.7217
4	994.8752	1.6791	1.1999	3.1345
5	993.0847	1.7906	1.4839	4.9340

The SEIR (Susceptible-Exposed-Infectious-Recovered) model enhances the traditional SIR framework by introducing an Exposed (E) compartment, representing individuals who have been infected but are not yet infectious. This addition is crucial for accurately modeling diseases with significant incubation periods, such as COVID-19.

5. SEIR Model

5.1. Nonlinear Dynamics

The SEIR model is governed by a system of nonlinear differential equations, with the infection rate depending on the product of susceptible and infected individuals, *i.e.*, $\mathrm{d}S/\mathrm{d}t = -\beta S\dfrac{I}{N}$.

5.2. Population Conservation

The total population $N = S + E + I + R$ remains constant over time, assuming no births or deaths.

Realism: By modeling the exposed phase, the SEIR model provides a more realistic depiction of disease progression, especially for illnesses with incubation periods.

Matrix Model

Linear Approximation: The matrix model simplifies the dynamics using linear equations, often neglecting the nonlinear interaction between compartments.

Simplified Calculations: While easier to compute and analyze, the matrix model may not conserve the total population and can oversimplify the disease dynamics.

Instructional Use: Due to its simplicity, the matrix model is often used for educational purposes or initial approximations but may lack accuracy in realistic scenarios.

In summary, while the matrix model offers computational simplicity, the SEIR model's incorporation of the exposed compartment and nonlinear interactions provides a more accurate and realistic framework for modeling infectious diseases with incubation periods.

6. Discussion

The SEIR (Susceptible-Exposed-Infectious-Recovered) model provides a more nuanced framework for simulating infectious disease dynamics, particularly for illnesses with a significant incubation period, such as COVID-19. By incorporating an Exposed (E) compartment, the model accounts for individuals who have been infected but are not yet infectious, thereby capturing the latency period between exposure and the onset of infectiousness [5] [6] [9] [12]. Simulations using numerical methods, such as Euler's method, demonstrate the SEIR model's ability to replicate the characteristic epidemic curve. Initially, the number of exposed individuals increases as susceptible individuals come into contact with infectious ones. Subsequently, the exposed population transitions to the infectious compartment, leading to a rise in the number of infectious individuals. As the disease progresses, recoveries begin to accumulate, and the number of susceptible individuals declines. This progression results in the infectious population reaching a peak before gradually decreasing as more individuals recover and fewer susceptible individuals remain [1] [3] [13]-[15].

In simulations using the Euler method over a 10-day period, the SEIR model reveals a characteristic epidemic curve. Initially, the number of exposed individuals increases as susceptible individuals come into contact with infectious ones. Subsequently, the exposed population transitions to the infectious compartment, leading to a rise in the number of infectious individuals. As the disease progresses, recoveries begin to accumulate, and the number of susceptible individuals declines. This progression results in the infectious population reaching a peak before gradually decreasing as more individuals recover and fewer susceptible individuals remain.

A key observation from the simulation is the conservation of the total population, with the sum of all compartments ($S + E + I + R$) remaining constant throughout the simulation period. This conservation validates the internal consistency of the SEIR model and the accuracy of the numerical method employed [9] [16]-[22].

The SEIR model's sensitivity to parameter values, such as the transmission rate (β), incubation rate (σ), and recovery rate (γ), underscores the importance of accurate parameter estimation. Small changes in these parameters can significantly impact the epidemic's peak and duration, highlighting the model's utility in evaluating potential intervention strategies [1] [5] [8] [23].

While the Euler method offers a straightforward approach for numerical simulation, it is worth noting that more sophisticated techniques, such as Runge–Kutta methods, may provide improved accuracy, especially over longer simulation periods. Additionally, the classical SEIR model does not account for factors like variable contact rates, reinfections, or vital dynamics (births and deaths), which can be significant in real-world scenarios [4] [6] [11] [20] [21]. The SIR model continues to be a cornerstone in epidemiological modeling, offering a robust yet accessible framework for analyzing infectious disease dynamics. Despite its simpli-

fied compartmental structure and reliance on key parameters such as the infection rate (β) and recovery rate (γ), it effectively captures essential patterns of disease transmission and recovery. While the model's assumptions may not fully encapsulate the complexities of real-world epidemics, its ability to provide critical insights and inform public health interventions underscores its enduring significance in epidemiology and epidemic forecasting [6] [9] [11] [17].

The use of simplified matrix models in epidemiological analysis, while helpful for introducing basic concepts, can lead to inaccurate or unrealistic results when applied to real-world disease dynamics. In particular, the failure to incorporate the nonlinear infection term $\frac{\beta S(t) I(t)}{N}$—a hallmark of the standard SIR model—can result in discrepancies such as population totals exceeding the actual size. Realistic modeling of infectious diseases requires acknowledging the time-dependent interactions between compartments, ensuring both mathematical accuracy and conservation of total population. For this reason, nonlinear models like the standard SIR or SEIR frameworks provide a more reliable and insightful approach to understanding and predicting the spread of infectious diseases.

In conclusion, the SEIR model serves as a powerful tool for understanding the dynamics of infectious diseases with incubation periods. Its incorporation of the exposed compartment allows for a more realistic representation of disease progression, making it valuable for forecasting epidemics and assessing the potential impact of public health interventions. The SEIR model would serve as a powerful tool for understanding the dynamics of infectious diseases with incubation periods. Its incorporation of the exposed compartment allows for a more realistic representation of disease progression, making it valuable for forecasting epidemics and assessing the potential impact of public health interventions.

The nonlinear SEIR model represents a realistic framework for modeling infectious disease dynamics. A key component of this model is the nonlinear infection term $\beta \frac{S(t) I(t)}{N}$, which captures the time-dependent interaction between susceptible and infectious individuals. This term reflects the actual mechanism of disease transmission: the rate of new infections is proportional to the product of susceptible and infectious populations, normalized by the total population size.

Ignoring or simplifying this nonlinear term can lead to significant inaccuracies. Linear approximations may result in unrealistic outcomes such as negative population values, overestimated infection counts, or a failure to conserve total population size. These discrepancies highlight the importance of using models that retain the nonlinear structure when simulating real-world epidemic dynamics.

7. Conclusions

The SEIR (Susceptible-Exposed-Infectious-Recovered) model offers a comprehensive framework for understanding the dynamics of infectious diseases, especially those with significant incubation periods like COVID-19. By incorporating the

Exposed (E) compartment, the model captures the latency between exposure and infectiousness, providing a more accurate depiction of disease progression compared to the traditional SIR model. A key observation from the simulation is the conservation of the total population, with the sum of all compartments ($S + E + I + R$) remaining constant throughout the simulation period. This conservation validates the internal consistency of the SEIR model and the accuracy of the numerical method employed. The SEIR model's sensitivity to parameter values, such as the transmission rate (β), incubation rate (σ), and recovery rate (γ), underscores the importance of accurate parameter estimation. Small changes in these parameters can significantly impact the epidemic's peak and duration, highlighting the model's utility in evaluating potential intervention strategies. Our analysis shows the epidemic peaks around day 9 under current parameters, indicating the need for early intervention to reduce transmission.

Incorporating the nonlinear infection term in SEIR models is essential for achieving both mathematical consistency and epidemiological realism. While linear models may offer simplicity and facilitate certain analyses, they are limited in scope. For accurate threshold estimation (e.g., R0R_0R0), outbreak forecasting, and evaluation of intervention strategies, the full nonlinear formulation should be used to ensure reliable and meaningful results.

Author's Contributions

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Data curation, formal analysis and writing-original draft: Mohammed Nokhas Murad Kaki.

Funding

No financial support was received for this study.

Conflicts of Interest

The authors declare that they have no conflict of interests.

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