RESEARCH

Investigating the effects of immunization tactics on essential variables of S-I-R outbreak model

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ABSTRACT

In our current study, we focus on analyzing an infectious disease model. By employing nonlinear optimization and optimal control techniques, we are able to identify strategies that are more effective in controlling transmission and predicting the global spread of infectious diseases. The integration of epidemiology, mathematical modeling, and computational tools allows us to develop and validate theories for disease prevention and management. This research utilizes numerical methods to visualize the solutions to key control problems, such as assessing the impact of vaccination on these models. Additionally, a global sensitivity analysis using the LHS Monte Carlo approach, specifically the Partial Rank Correlation Coefficient (P.C.), has been conducted to investigate the crucial parameters in the model equations. Ultimately, this study aims to enhance our understanding of the spread of infectious diseases and contribute to the development of innovative concepts in disease control.

Key words: *SIR model; Travelling wave; Vaccine effect; Numerical solution*

INTRODUCTION

The Mathematical modeling involves the conversion of biological systems into a theoretical and mathematical framework, utilizing biological parameters.

Mathematical modeling

Mathematical modeling involves the conversion of biological systems into a theoretical and mathematical framework, utilizing biological parameters. This is followed by the use of computer code to solve the model system computationally, which enables the prediction of the future of infectious diseases. In order to comprehend the epidemiology of infectious diseases, it is crucial to have information on the behavior of each individual, as it plays a significant role [1,2].

The SIR Model

The SIR model is a widely used mathematical technique for modeling infectious diseases. With the emergence and rapid spread of new pandemic diseases, there has been a need for the development of new methods of study. Mathematical modeling has become a popular field in epidemiology, attracting scientists from various disciplines. Numerous academic models have been developed to describe the transmission of communicable diseases, involving the assignment of population compartments with labels such as S, I, or R. These compartments describe the mechanisms of infectious diseases and their stage of infection, and are useful in analyzing the impact of public health interventions on disease spread. The SIR model specifically studies the population of susceptible, infectious, and recovered or removed individuals over time. The sizes of these compartments are time-varying functions that can be determined through the use of model parameters and initial conditions. During a plague, governments often issue various control measures to mitigate or contain the spread of the disease. These external interventions can have an instantaneous effect on both the transmission and recovery rates, making it necessary to generalize the SIR model to accommodate unique stages of mitigation rules, such as social distancing, transportation restrictions, mandatory mask-wearing, and city lockdowns, as seen in recent COVID-19 outbreaks.

In this research, we focus on studying the S-I-R model, which is a basic epidemiological model composed of Susceptible, Infected, and Recovered individuals. By analyzing these models, we aim to gain insights into the dynamics of simple epidemic diseases. Additionally, we propose equivalent optimal control problems for these epidemic models and solve them numerically using the backward-forward sweep method with the fourth order Runge-Kutta method. Finally, we perform a global sensitivity analysis using the Latin Hypercube Sampling Monte Carlo method and the Partial Rank Correlation Coefficient (PRCC) to identify the key parameters that have the most significant impact on the spread or control of infectious diseases [3].

RELATED STUDIES

William Ogilvy Kermack and Anderson gray McKendrick did introduced the well-known SIR model for the first time in 1927. They considered a fixed populace length and divided it into three distinctive homogeneous groups of people: the susceptible, the infectious, and the recovered, excluding natural births and deaths, and deaths through epidemic disease. Balram Dubey and his co-authors have investigated the global dynamics of SIR model wherein the occurrence rate is being considered as Beddington-DeAngelis kind and the remedy rate as Holling kind. They revealed that the disease-free equilibrium is locally

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asymptotically stable while reproduction number is much less than one [2], and his coauthors did analyzed the compartmental SIR models for disease transmission. They calculated the simple reproduction number and the final size of the epidemic. They additionally studied the models with a couple of compartments and treatment of infective.

Mathematical SIR version of COVID-19 in the form of differential equations was obtained by [4], and showed that protection, exposure, and death rates affect people with the elapse of time.

Comparison between the vaccinated percentages for herd immunity for SIR epidemiology model against the current percentage of vaccinated individuals was discussed by [2], while [3], presented a SIR model with a constant vaccination technique. He showed that the vaccine has full efficacy, so that the vaccinated peoples will not be re-infected. Later, [5] and his coauthors constructed the SIR model that includes vaccination, immunity loss, and relapse.

The utilization of optimal control theory has emerged as a novel approach in modeling dynamic SIR systems of infection. This approach involves a set of differential equations that describe the trajectories of a control variable, aiming to minimize the cost function. In the 1950s, Bellman and Pontryagin introduced a method that significantly reduced the computational burden associated with solving dynamic systems by employing the principle of optimality [5]. Optimal Control (OC) theory, within the context of a dynamic system, entails defining a manipulation problem and determining the state trajectories over a specific time period in order to minimize an overall performance index [6]. The challenge of determining the control variable can be transformed into an extension of the calculus of variations [5]. One notable application of the calculus of variations was Hamilton's principle, also known as the principle of Least action. Lev S. Pontryagin, along with his colleagues V. G. Boltyanskii, R. V. Gamkrelidz, and E. F. Misshchenko, extended the calculus of variations to optimal control theory by introducing the Pontryagin maximum principle [2]. This principle establishes suitable conditions for optimization problems that involve differential equations as constraints. OC can be applied to problems where the calculus of variations is not applicable, including those that involve constraints on function derivatives. As the number of variables and system parameters increases, analytical solutions for optimal control problems become infeasible, necessitating the use of numerical methods.

Optimal control methods

In OC, the modeling of a dynamic system typically involves the utilization of a set of ordinary differential equations. These equations are based on the specifications of conditions at the endpoints of the domain. Depending on how these conditions are specified, the differential equations can be classified as either Initial Value Problems (IVP) or Boundary Value Problems (BVP). In an initial value problem, all the conditions are specified at the initial point. On the other hand, a boundary value problem requires the conditions to be specified at both the initial and final points.

To solve initial value problems, there are various numerical techniques available, including Euler, Runge-Kutta, and adaptive techniques. For boundary value problems, shooting techniques can be employed.

Among these techniques, the Euler method is a commonly used single-step method for solving this system. It involves discretization of the differential equation.

$x = f(x(t), t)$.

A convenient estimation can be derived from this situation: The accuracy and complexity of the calculation are inversely related and are greatly influenced by the selected value for h. As h decreases, the calculation becomes more time-consuming but also more precise. This approach encounters challenges when applied to higher order systems, making it arduous to achieve an effective Euler approximation. Consequently, it becomes necessary to employ more precise and intricate methods, such as the Runge-Kutta method.

The Runge-Kutta method is a numerical technique used to solve differential equations. It is a multiple-step method, meaning that the solution at a given time is obtained from previous values. In this method, the solution at time t_{k+1} is obtained using the values t_{j-k}, t_k, and j: where j represents the number of steps.

To approximate a differential equation of the form

$x = f(x(t), t)$,

the second order Runge-Kutta method can be used. This method provides an approximation x_{n+1} of $x(t)$ at the point t_{n+1}. It is worth noting that both the second and fourth order Runge-Kutta methods have errors of order h^3 and h^5, respectively.

Runge-Kutta method is a multiple-step method. In this technique, we obtain the solution at time t_{k+1} from the values t_{j-k}, t_k and j is the number of steps. To approximate a differential equation of the form

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we can use the second order Runge-Kutta method For the second and fourth order Runge-Kutta method, the approximation x_{n+1} of $x(t)$ at the point t_{n+1} has an error of order h_3 and h_5.

In this research, we study the most basic epidemiological models S-I-R model (composed by Susceptible-Infected-Recovered). For these models, we develop some analytical results that are useful in understanding of simple epidemic diseases. We continue this study by proposing the equivalent optimal control problems of the mentioned epidemic models and we numerically solve them using the back-ward-forward sweep method with fourth order Runge-Kutta. Finally, we perform global sensitivity analysis by LHS Monte Carlo method using PRCC to identify the key parameters that contribute most significantly to the spread or control of the infectious diseases.

DESCRIPTION OF THE SIR EPIDEMIC MODEL

The SIR model is a mathematical framework used to analyze the dynamics of infectious diseases within a population over time. It focuses on three main groups: Susceptible individuals (S), those who are currently Infected (I), and individuals who have either Recovered or died (R). The primary goal of this model is to predict the number of individuals in each group at any given time during the course of an epidemic.

This model is particularly effective for infectious diseases that are transmitted from person to person and where recovery provides long-lasting immunity, such as measles, mumps, and rubella. It has proven to be reasonably accurate in predicting the spread and impact of these types of diseases.

In recent times, the rapid spread of pandemic diseases has led to increased interest in mathematical modeling within the field of epidemiology. Many scientists from various disciplines have been drawn to this area of research. Numerous mathematical models have been developed to describe the transmission of communicable diseases, and among these models, the classical Kermack-McKendrick SIR epidemic model has gained prominence.

The Kermack-McKendrick model builds on the concept of compartments, where individuals are categorized into different groups based on their disease status. The model assumes that the total population remains constant throughout the epidemic and that the rate of increase in the number of infected individuals is directly proportional to the contact between susceptible and infected individuals. Additionally, the model assumes a constant removal rate, which includes both recovery and death. By incorporating these assumptions, the classical S-I-R model takes shape and provides a valuable tool for understanding and predicting the dynamics of infectious diseases within a population, its described as:

$$\frac{dS}{dt} = -\beta IS + \delta R$$

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

$$\frac{dR}{dt} = \gamma I - \delta R \quad (1)$$

Where,

β = rate of infection,
γ = rate of recovery
δ = rate of immunity loss.

If $\delta = 0$, we assume a model without immunity loss. In the first equation of system (1), susceptible decreases according to the number of contacts between infective *I* and susceptible *S*.

Since there is decreasing the rate of change of susceptible over time, then from the first equation we get $-\beta\ IS$. The rate of change of infective *I* increases by *IS* and decreases by $\gamma\ I$. The term βIS has been added to the second equation of system (1) which is due to the increasing the contact between S and *I*. The negativity of γI is showing decreasing the rate of change in infective *I* by moving to the next stage which is recovered or died. The term γI has been added *t* in the third equation which means that the rate of changing the recovered *R* is increasing by this factor (Fig. 1).

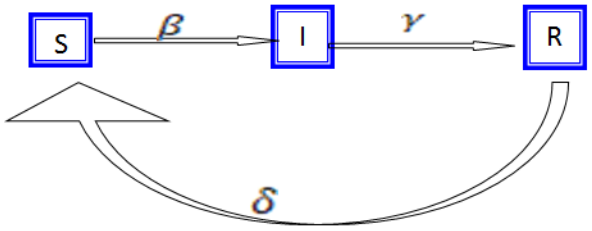

Figure 1) *The SIR schematic model for system (2.1),*
S = Susceptible Compartment, I = Infective Compartment, R = Removed Compartment

Interpretation of the SIR model

We explore if the disease will spread, and is the max number of infective Imax and how many people catch the disease. We consider the general S-I-R model derived from equations 1.

$$\frac{dS}{dt} = -\beta IS$$

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

$$\frac{dR}{dt} = \gamma I \quad (2)$$

At the start of outbreak we have $S = S_0$, $I = I_0$ and $R = 0$. Total population size remains constant during epidemic; therefore, the rate of change of S + I + R must be zero:

$$\frac{d}{dt}(S + I + R) = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0, S + I + R = S_0 + I_0 \quad (3)$$

To find out if the disease will spread, we need to check that

$$\frac{dI}{dt} = I(\beta S - \gamma) < 0, \quad S \leq S_0$$

Therefore if

$$S_0 > \frac{\gamma}{\beta} = \frac{1}{q}$$

Then the disease will spread, hence $\frac{1}{q}$ is the constant ration which is the fraction of population that comes to contact with individual during the period of infectious. However, if the reproductive number or the ratio number $R_0 = \frac{\beta S_0}{\gamma} > 1,$ we have epidemic. This ratio represents the number of secondary infection in the population caused by initial primary infection.

For maximum number of infective or I_{max}, use

$$\frac{Ds}{dt} \text{ and } \frac{Di}{dt} \left[\frac{Ds}{dt} = -Bis + \Delta r\right] \text{ and } \left[\frac{dI}{dt} = \beta IS - \gamma I.\right],$$

this gives

$$\frac{dI}{dS} = \frac{\beta IS - \gamma I.}{-\beta IS} = -1 + \frac{\gamma}{\beta S} = -1 + \frac{1}{qS}$$

Assuming,

$$I + S - \frac{1}{q}\ln S = I_0 + S_0 - \frac{1}{q}\ln S_0 \quad (4)$$

Then,

$$I_{max} = I_0 + S_0 - \frac{1}{q}(1 + \ln(qS_0))$$

Here, I_{max} represents the maximum number of people who have the disease at a given time. When q (contact parameter) is large, it means that the number of people get infected is equally large eg. for COVID-19, the value for q (contact parameter) is high since disease easily transmitted.

To reduce the reproduction rate, one can reduce the number of susceptible, S_0. Here is where intervention measures such as vaccination becomes useful. Vaccination can go further than being used for just individuals, but it can be beneficial in large scale communities by preserving the effective reproduction rate below the level which would allow an epidemic to spread. However, an epidemic can start and spread very quickly if the reproduction rate rises beyond the critical value for an epidemic.

To find out how many people catch the disease, based on the first assumption, the total population is constant and to end the disease,

the number of infected need to go down to zero (end of out-break): hence

$S+I+R=S_0+I_0$, and R (end) = − S (end) + $I_0 + S_0$,

Here, S (end) is unknown. From (2.4), we have S (end) $-\frac{1}{q}$ ln (S (end)) = $I_0 + S_0 - \frac{1}{q}\ln S_0$

The graph of S (end) is decreasing and shows at small value of S (end) and larger q, we have larger value for R (end).

Limitation of SIR model

The SIR model is a straightforward method for calculating disease spread, but it may oversimplify complex disease processes. For instance, it does not account for the latent period between exposure and infection, which is crucial in the context of COVID-19. The SEIR model, which includes an "E" category for exposed but not yet contagious individuals, addresses this issue. However, further modifications to the model are necessary to capture the time-dependent effects of community mitigation strategies. Additionally, the SIR model assumes homogeneous mixing of the population, which is not representative of real-world social structures. Furthermore, the model assumes a closed population with no migration, births, or deaths from other causes, which may not be accurate in many scenarios.

OC PROBLEM FOR S-I-R MODEL

In this section, we introduce an Optimal Control (OC) problem aimed at investigating the dynamics of the S-I-R model. The OC problem utilizes a vaccination process (u) as a means to regulate the spread of the disease. We denote x_1 as the susceptible population, x_2 as the infected population proportion and x_3 as the proportion of the population that has either recovered or deceased. The definition of the optimal control problem is as follows:

$$\min_{u} \; J[x(t),u(t)] = \int_{t_0}^{t_f}[x_2 + e^2]\,dt. \tag{5}$$

$$\text{s.t } \frac{dx_1}{dt} = -\beta x_1 x_2 + \delta x_3 - u x_1 \tag{6}$$

$$\frac{dx_2}{dt} = \beta x_1 x_2 - \gamma x_2 . \tag{7}$$

$$\frac{dx_3}{dt} = \gamma x_2 - \delta x_3. \tag{8}$$

$$x(t_0) = [x_1(0),\ x_2(t),\ x_3(0)]. \tag{9}$$

With x (t) = (x_1 (t) , x_2 (t) , x_3 (t))
and λ (t) =(λ_1 (t), λ_2 (t),λ_3(t)),

with the initial conditions x_1

$x_1(0) = 6 \times 10^7$, $\dot{x_2}(0) = 10^7$, $x_3(0) = 10$,

and the parameter

$\beta = 5\times10^{-9}$, $\gamma = 0.12$, $\delta = 1/60$.

We consider the problem (4.1) and constraints (4.2)-(4.4). With x (t) = (x_1 (t), x_2 (t), x_3 (t)) and and λ (t) = (λ_1 (t), λ_2 (t) , λ_3 (t)).
The Hamiltonian of this problem can be written as
H(t , x (t) , u (t) , λ (t)) = $Ax_2 + u^2 + \lambda_1(-\beta x_1 x_2 + \delta x_3 - u x_1) +$

$\lambda_2(\beta x_1 x_2 - \gamma x_2) + \lambda_3(\gamma x_2 - \delta x_3)$

A =weight parameter describing the comparative importance of the two terms in the functional. Using the PMP the optimal control problem can be studied with the state variables

$$\dot{x}_1 = -\beta x_1 x_2 + \delta x_3 - u x_1.$$

$$\dot{x}_2 = \beta x_1 x_2 - \gamma x_2.$$

$$\dot{x}_3 = \gamma x_2 - \delta x_3.$$

And the adjoint variables are:

$$\dot{\lambda}_1 = \lambda_1(u + \beta x_2) + \lambda_2 \beta x_2$$

$$\dot{\lambda}_2 = -A + \lambda_1 \beta x_1 - \lambda_2(\beta x_1 - \gamma) - \lambda_3 \gamma$$

$$\dot{\lambda}_3 = \lambda_3\delta - \lambda_1\delta$$

with transversality conditions $\lambda(t_f)=0$. The figure below demonstrates the optimal curves for the states variables and optimal control corresponding to S-I-R model (Fig.2).

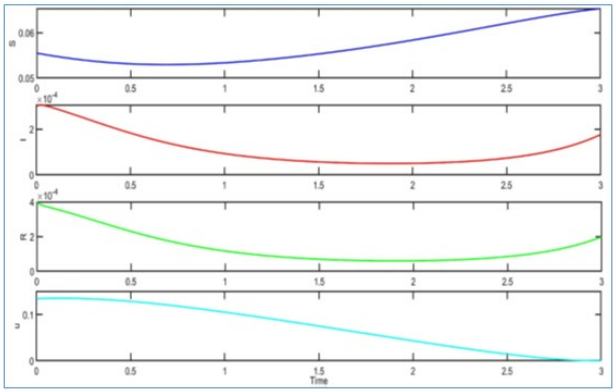

Figure 2) *Solutions of optimal control problem for S-E-I-R model (2.1). u: =Vaccination related variable, S: =Susceptible Population, I: =Infective Population, R: =Removed Population*

SENSITIVITY ANALYSIS

Global sensitivity analysis is a powerful tool that enables the evaluation of the relative effects of each input parameter and the interactions between them on the model output. By determining the variation of input parameters within a certain range, we can identify which parameters and interactions have the most influential impact on the overall behavior of a model. This is particularly important for highly nonlinear models like SIR-type models, which require sensitivity analysis to quantify the sensitivity of a single parameter and its interaction with others. Through sensitivity analysis, we can optimize the model by accurately estimating the influential parameters and initial values of the state variables, and provide policymakers with useful information to control the influential parameter. There are several types of global sensitivity analyses, including weighted average of local sensitivity analysis, partial rank correlation coefficient, multi-parametric sensitivity analysis, Fourier Amplitude Sensitivity Analysis (FAST), and Sobol's method, which can be used for systems pharmacology models. The Latin Hypercube Sampling (LHS) method is frequently used for global sensitivity analysis, and there are also other methods for calculating main effect and total effect sensitivity indices, with the method of Sobol being one of the most important. The Latin Hypercube Sampling (LHS) method is a technique used for sampling that requires fewer samples compared to simple random sampling in order to achieve the same level of accuracy. In the LHS method, the

random parameter distributions are divided into N equal probability intervals, where N represents the sample size. It is recommended to choose N to be at least k+1, where k is the number of parameters being varied. In cases where the variation interval for a particular parameter is very large, the sampling can be performed on a logarithmic scale.

In the LHS method, sampling is conducted independently for each parameter by randomly selecting values from each Probability Density Function (PDF). It is possible to sample each interval once for each parameter without replacement. The LHS matrix is constructed with N rows, representing the number of simulations or sample size, and k columns, representing the number of varied parameters. Consequently, N model solutions can be simulated by utilizing each combination of parameter values, which correspond to each row of the LHS matrix.

Partial Rank Correlation Coefficient (PRCC) results for S-I-R model
The S-I-R model underwent a parameter sensitivity analysis through the LHS Monte Carlo method using PRCC with uniform distributions for the 95% confidence intervals. The purpose of this analysis was to determine the biological parameters that have the most significant impact on the model system. The global sensitivity results, including p-values for the S, I, and R compartments, are presented in figure 3.

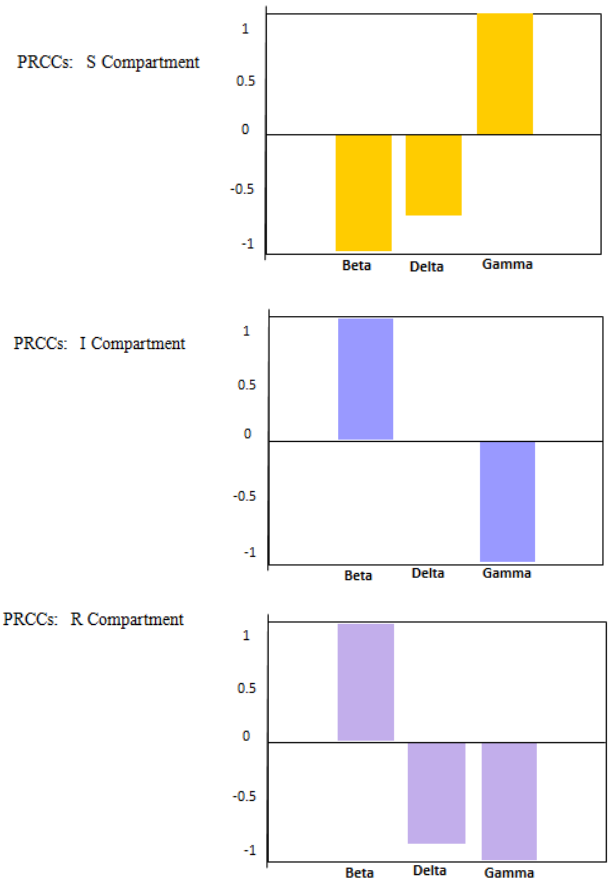

Figure 2) *Global uncertainty and sensitivity analysis of calculated different parameters for S-I-R model*

CONCLUSIONS

The spread of infectious diseases can occur through human-to-human, human-to-animal, or animal-to-animal transmission. Mathematical modeling of infectious disease spread has been extensively studied, particularly in light of the COVID-19 pandemic. To develop an effective infectious disease dynamic model, a system of ordinary differential equations is necessary to cover the spread process, spread law, and spread trend of infectious diseases.

This paper focused on the S-I-R model and presented analytical results that can be useful in studying simple epidemics. The evolution of compartmental models over time, specifically Susceptible-Infected-Recovered, was displayed for various parameter values. Optimal control was also considered, but due to the complexity of the presented optimal control problems, numerical solutions were used to obtain optimal curves for the state variables and optimal control for each control problem separately.

Uncertainty analysis and sensitivity analysis were applied to epidemiological models to investigate the uncertainty in system output generated from uncertainty in parameter inputs. The key parameters in the spread of infectious diseases were determined using a sampling-based method (Partial Rank Correlation Coefficient-PRCC). LHS/PRCC method with uniform distributions for the 95 percent confidence intervals on the model Equation (1) and Equation (2) were applied. The study found that some parameters positively and some negatively affected the spread of disease. Major among them is vaccination.

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