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CORONAVIRUS DISEASE (COVID-19) MATHEMATICAL MODELING FOR SENSITIVITY ANALYSIS AND FUTURE BEHAVIOR PREDICTION

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Abstract. Numerous descriptive studies of the clinical data for coronavirus illness (COVID-19) are currently available. Computational simulations and mathematical modeling are useful tools that support international efforts to estimate important transmission characteristics. Dynamical analysis and computational techniques are frequently needed for the model equations, which are crucial for managing the illness. This paper first examines a few coronavirus models that can answer significant queries regarding international health care and make significant recommendations. Next, we use a system of differential equations to simulate the illness. We develop earlier models for the coronavirus and add sensitivity analysis and some important computer simulations. As a result, three distinct methods are used to calculate the local sensitivities for each model state with regard to the model parameters: non-normalizations, half normalizations, and complete normalizations. Sensitivity study results indicate that nearly every model parameter may play a part in the virus's propagation among vulnerable, exposed, and quarantined individuals. More precisely, person-to-person communication rates, confined exposure rates, and transfer rates of exposed persons all play a significant part in the disease's propagation. Healthcare systems should focus more on intervention measures, and individuals should self-quarantine in order to effectively minimize the disease, according to one potential approach.

Keywords and phrases*:* Coronavirus disease (COVID-19), mathematical modeling, sensitivity analysis, differential equations, computational simulations.

INTRODUCTION

The enormous worldwide health impact of the new coronavirus (COVID-19) has made understanding and forecasting it crucial. Up until March 20, 2020, there were over 210,000 instances of coronavirus illness, including about 9,000 fatalities, in more than 168 countries and territories worldwide [18]. Given the rising global incidence of coronavirus illness, it is critical to understand its dynamics as soon as feasible. Although a number of mathematical, computational, clinical, and examination studies have recently been proposed for illness modeling, prediction, therapy, and control, there is still opportunity for improvement. Modeling new coronavirus diseases has grown crucial in recent years, and a number of mathematical

Several computational studies have been suggested for the forecasting of disease dynamics. Due to their large quantity and lack of formal review evaluation and acceptance by reputable journals, we do not review related preprint papers here. Muhammad and Abdon [5] suggested using fractional derivatives to minimize infections. When bats and unidentified hosts leave the virus there, they believe that the seafood market is the primary source of infection. They created a fractional model, reduced the model to the seafood market, and then used data from January 2020 to parameterize the model. The study's basic reproduction data was 2.4829. To investigate the disease's spread, Sha et al. created a discrete-time stochastic epidemic model with binomial distributions [4]. Fitting to freshly released data from the People's Republic of China's National Health Commission is used to estimate model parameters. According to their modeling, the nation's verified instances of the illness will peak around the

end of February 2020. A deterministic compartmental model was developed by Tang et al. in [15] based on the clinical course of the illness, the individuals' epidemiological status, and management strategies. According to their calculations, the control reproduction number might reach 6.47. A sensitivity analysis indicates that treatments like isolation and quarantine can lower it. Another study presented in [10] used COVID-19 case data from Wuhan and a stochastic transmission model. They employed sequential Monte Carlo simulation to determine the transmission rate over time, modeling transmission as a geometric random walk process. According to their estimations, the spread of the disease most likely ended in Wuhan in late January 2020, but cases that go from Wuhan to other countries could potentially cause epidemics. In order to determine the fundamental reproduction number and evaluate the transmissibility of SARS-CoV-2, Chen et al. created a simple model known as the Reservoir–People (RP) transmission network and used the next generation matrix approach [3]. Their results showed that 3.58 subsequent infections were anticipated. Based on recent technological advancements for the identification and confirmation of additional infected cases, Tang et al. revised their earlier assessment of the novel coronavirus's transmission risk [16]. They recalculated the daily reproduction number based on a time-dependent dynamic model of contact and diagnosis rate; at the end of January 2020, they found that the effective daily reproduction ratio had already dropped below 1. The effectiveness of quarantine procedures is another mathematical model for this new pathogen. After the incubation period, it is assumed that every infected person is isolated. Disease progression is effectively influenced by the fundamental reproduction number R0 [17]. Many modeling techniques have been proposed thus far for the prediction of novel coronavirus diseases, but much remains to be improved. The results could be improved by defining models as mass action laws with reaction rate constants and figuring out how sensitive each model state is to model parameters. Various local sensitivity analyses for non-normalizations, half normalizations, and complete normalizations in computational simulations for COVID-19 are a subject that has not received enough attention. Sensitivity analysis must be more thoroughly and properly considered in a complex modeling instance such as novel coronavirus dynamics. Sensitivity analysis was employed in a small number of relevant studies [12, 15], but only in a few specific variables and situations. The paper's simplicity of the identification of the essential model parameters is another innovation. This makes the model easier to use for biologists who are not as familiar with mathematical modeling and also makes it easier to enhance the model for further development.

1. Mathematical modeling for coronavirus disease

The transmission of infectious diseases can be described using a variety of models. The "Susceptible–Exposed–Infectious–Recovered" model is the most well-defined model in this subject. This is sometimes referred to as the SEIR model [11]. The clinical process, epidemiological individuals, and therapeutic measures form the basis of the model's core concept. As a result, the SEIR model for infectious diseases has been studied in conjunction with intervention compartments including therapy, isolation (hospitalization), and quarantine. We build upon the earlier coronavirus disease (COVID-19) model presented in [15, 16], the model diagram, and the individual component interactions shown in Figure 1. For the confirmed examples in China, the model's initial populations and interaction parameters are acquired.

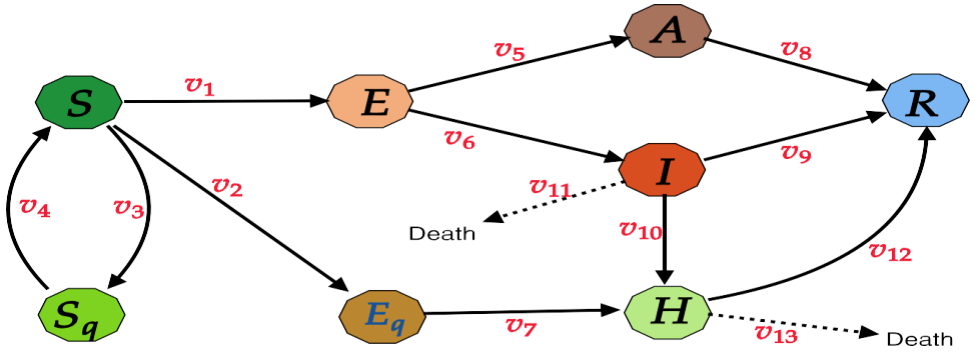


Figure 1. The model interaction individuals for the coronavirus disease (COVID-19) with reaction rates.

The model reactions with their rates are shown below:

$$\begin{array}{cccc} S \xrightarrow{v1} E, & S \xrightarrow{v2} E_q, & S \xrightarrow{v3} S_q. & S_q \xrightarrow{v4} S, \\ E \xrightarrow{v5} A, & E \xrightarrow{v6} I, & E_q \xrightarrow{v7} H, & A \xrightarrow{v8} R, \end{array} \tag{2.1}$$

$I \xrightarrow{\nu_{13}} R$, $I \longrightarrow H$, $I \longrightarrow$ null, $H \longrightarrow R$, $H \longrightarrow$ null.

The model populations (variables) with their biological descriptions are given in Table 1. Furthermore, the model constant interactions (parameters) with their definitions are described in Table 2.

TABLE 1. The model variables for coronavirus disease (COVID-19) with their biological meaning.

No.	Variables	Biological Descriptions
1	S	Susceptible Individuals
2	E	Exposed Individuals
3	I	Symptomatic Infected Individuals
4	A	Pre-symptomatic Individuals
5	S_q	Quarantined Susceptible Individuals
6	E_q	Quarantined Exposed Individuals
7	H	Quarantined Infected (Hospitalized) Individuals
8	R	Recovered Individuals

TABLE 2. The model reaction constants (parameters) and initial individual populations for COVID-19 epidemic outbreak with their biological definitions, all data are confirmed cases in China presented in [15].

Symbols	Biological definitions	Estimated values
$S(0)$	Initial susceptible individuals	11.081×10^6
$E(0)$	Initial exposed individuals	105.1
$I(0)$	Initial symptomatic infected individuals	27.679
$A(0)$	Initial pre-symptomatic infected individuals	53.839
$S_q(0)$	Initial quarantined susceptible individuals	739
$E_q(0)$	Initial quarantined exposed individuals	1.1642
$H(0)$	Initial quarantined hospitalized individuals	1
$R(0)$	Initial recovered individuals	2
k_1	Contact rate	14.781
k_2	Probability of transmission per contact	2.1011×10^{-8}
k_3	Quarantined rate of exposed individuals	1.8887×10^{-7}
k_4	Transition rate of exposed individuals to the infected class	$\frac{1}{7}$
k_5	The multiple of the transmissibility of A to I	0.3
k_6	Rate at which the quarantined uninfected contacts were released into the wider community	$\frac{1}{14}$
k_7	Probability of having symptoms among infected individuals	0.86834
k_8	Transition rate of symptomatic infected individuals to the quarantined infected class	0.13266
k_9	Transition rate of quarantined exposed individuals to the quarantined infected class	0.1259
k_{10}	Recovery rate of symptomatic infected individuals	0.33029
k_{11}	Recovery rate of asymptomatic infected individuals	0.13978
k_{12}	Recovery rate of quarantined infected individuals	0.11624
k_{13}	Disease-induced death rate	1.7826×10^{-5}

TABLE 3. The reaction rates for the model diagram with their definitions.

Reaction number	Definition of reaction rsates
r_1	$v_1 = k_1k_2(1-k_3)S(I+k_5A)$
r_2	$v_2 = k_1k_2k_3S(I+k_5A)$
r_3	$v_3 = k_1k_3(1-k_2)S(I+k_5A)$
r_4	$v_4 = k_6S_q$
r_5	$v_5 = k_5(1-k_7)E$
r_6	$v_6 = k_4k_7E$
r_7	$v_7 = k_9E_q$
r_8	$v_8 = k_{11}A$
r_9	$v_9 = k_{10}I$
$r10$	$v10 = k8I$
$r11$	$v11 = k13I$
$r12$	$v12 = k12H$
$r13$	$v13 = k13H$

Using equations (2.5)–(2.7), the model dynamics are described by the following system of non-linear ordinary differential equations

$$\begin{aligned}
&\frac{dS}{dt} = v_4 - (v_1 + v_2 + v_3), \quad \frac{dE}{dt} = v_1 - (v_5 + v_6),\\
&\frac{dI}{dt} = v_6 - (v_9 + v_{10} + v_{11}), \quad \frac{dA}{dt} = v_5 - v_8,\\
&\frac{dS_q}{dt} = v_3 - v_4 \quad \frac{dE_q}{dt} = v_2 - v_7,\\
&\frac{dH}{dt} = v_7 + v_{10} - (v_{12} + v_{13}), \quad \frac{dR}{dt} = v_8 + v_9 + v_{12}.
\end{aligned} \tag{2.2}$$

The model reaction rates $\{v_i,\ i = 1, 2, \ldots, 13\}$ are defined in Table 3.

The model initial populations are expressed in the following equation

$$\begin{aligned}
&S(0) = S_0 \geq 0,\ E(0) = E_0 \geq 0,\ I(0) = I_0 \geq 0,\ A(0) = A_0 \geq 0,\\
&S_q(0) = S_q^0 \geq 0,\quad E_q(0) = E_q^0 \geq 0,\quad H(0) = H_0 \geq 0,\quad R(0) = R_0 \geq 0.
\end{aligned} \tag{2.3}$$

In addition, the contacts between susceptible and infected people lead to a "decrease" in the number of susceptible because all model parameters are positive, see Table 2. We assume k_2 1 and k_3 1. These conditions provide " $-SI$" terms in model (2.2).

1.1. Sensitivity analysis

It is necessary for more understanding the biological system dynamics modelled with mass action law to do sensitivity analysis. So, the output of the mathematical model will be investigated easier. Here, we present the basics of our calculations. We consider n reversible reactions which are given below

$$\sum_{j=1}^{m} a_{ij}x_j^{k+1} = \sum_{j=1}^{m} b_{ij}x_j^{k}, \quad i = 1, 2, \ldots, n, \tag{2.4}$$

$$\mathrm{d}t \quad {}^{i\ i} \qquad i \in J \subset \mathrm{R} \tag{2.6}$$

where $\pi_{ij} = b_{ij} - a_{ij}$, for $i = 1, 2, ..., n$ and $j = 1, 2, .., m$. Equation (2.6) can be written as follows:

$$\frac{\mathrm{d}x_j}{\mathrm{d}t} = h_j(x, k), \tag{2.7}$$

where $x \in \mathrm{R}^m$ and $k \in \mathrm{R}^n$. The more details and descriptions about chemical reactions and their differential equations with some applications in system biology can be found in [6]. An assumption is that the model input is a vector of parameters, and the model output is a vector of model states(variables). Local sensitivity is the change in model variables x_j, $j = 1, 2, .., m$ with respect to the model parameters k_p, $p = 1, 2, ..., n$. Basically, the model equation of sensitivity for each variable with respect to the parameters is given

$$s_{jp} = \frac{\partial x_j}{\partial k_p} = \lim_{\Delta k_p \to 0} \frac{x_j(k_p + \Delta k_p) - x_j(k_p)}{\Delta k_p}. \tag{2.8}$$

Finite difference approximation can be used to calculate equation (2.8) as follows:

$$s_{jp} = \frac{\partial x_j}{\partial k_p} \approx \frac{x_j(k_p + \Delta k_p) - x_j(k_p)}{\Delta k_p}. \tag{2.9}$$

Generally, direct sensitivity analysis has been used to calculate sensitivity equation that differential equations are solved for sensitivity coefficients.

$$\frac{\partial s_{jp}}{\partial t} = \frac{\partial}{\partial t}\frac{\partial x_j}{\partial k_p} = \frac{\partial}{\partial k_p}\frac{\partial x_j}{\partial t} = \frac{\partial}{\partial k_p} h_j(x(t), k). \tag{2.10}$$

Equation (2.10) can be further driven by the chain rule of differentiation. Finally, the local sensitivity equation takes the Jacobian matrix as follows

$$\dot{\mathrm{S}} = \mathrm{H}_{kp} + \mathbf{J}.\mathrm{S}, \ p = 1, 2, ..., n, \tag{2.11}$$

where the matrices S, H_{kp} and $\mathbf{J}$ are defined by

$$\mathrm{S} = \begin{bmatrix} \frac{\partial x_1}{\partial k_p} \\ \frac{\partial x_2}{\partial k_p} \\ \vdots \\ \frac{\partial x_m}{\partial k_p} \end{bmatrix}, \quad \mathrm{H}_{kp} = \begin{bmatrix} \frac{\partial h_1}{\partial k_p} \\ \frac{\partial h_2}{\partial k_p} \\ \vdots \\ \frac{\partial h_m}{\partial k_p} \end{bmatrix}, \quad \mathbf{J} = \begin{bmatrix} \frac{\partial h_1}{\partial x_1} & \frac{\partial h_1}{\partial x_2} & \cdots & \frac{\partial h_1}{\partial x_m} \\ \frac{\partial h_2}{\partial x_1} & \frac{\partial h_2}{\partial x_2} & \cdots & \frac{\partial h_2}{\partial x_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial h_m}{\partial x_1} & \frac{\partial h_m}{\partial x_2} & \cdots & \frac{\partial h_m}{\partial x_m} \end{bmatrix}.$$

The initial conditions of system (2.11) are determined by the input parameter k_p and the initial conditions of the output variables x_j. Readers can see further details and improvements of sensitivity analysis with its applications on systems biology in [1, 2, 6–9, 13, 14, 19]. The local sensitivity values given in equation (2.11) can be computed using *SimBiology* Toolbox in MATLAB with three different techniques: non normalizations, half normalizations and full normalizations. Accordingly, in a complicated modeling case like new coronavirus dynamics, it is necessary to pay attention to sensitivity analysis more accurately and widely. Thus, we analyze the coronavirus equations given in system (2.2) and calculating all local sensitivities for the model states with respect to model parameters.

2. Computational results

The complex models of the spread of infectious diseases sometimes can not be well understood only by biological tools. This is why computational simulations and mathematical modeling is used, specially in helping health care programs. Studying these models theoretically helps biologists to predict future model dynamics and identify critical model parameters. The values of parameters and initial populations in this study are obtained

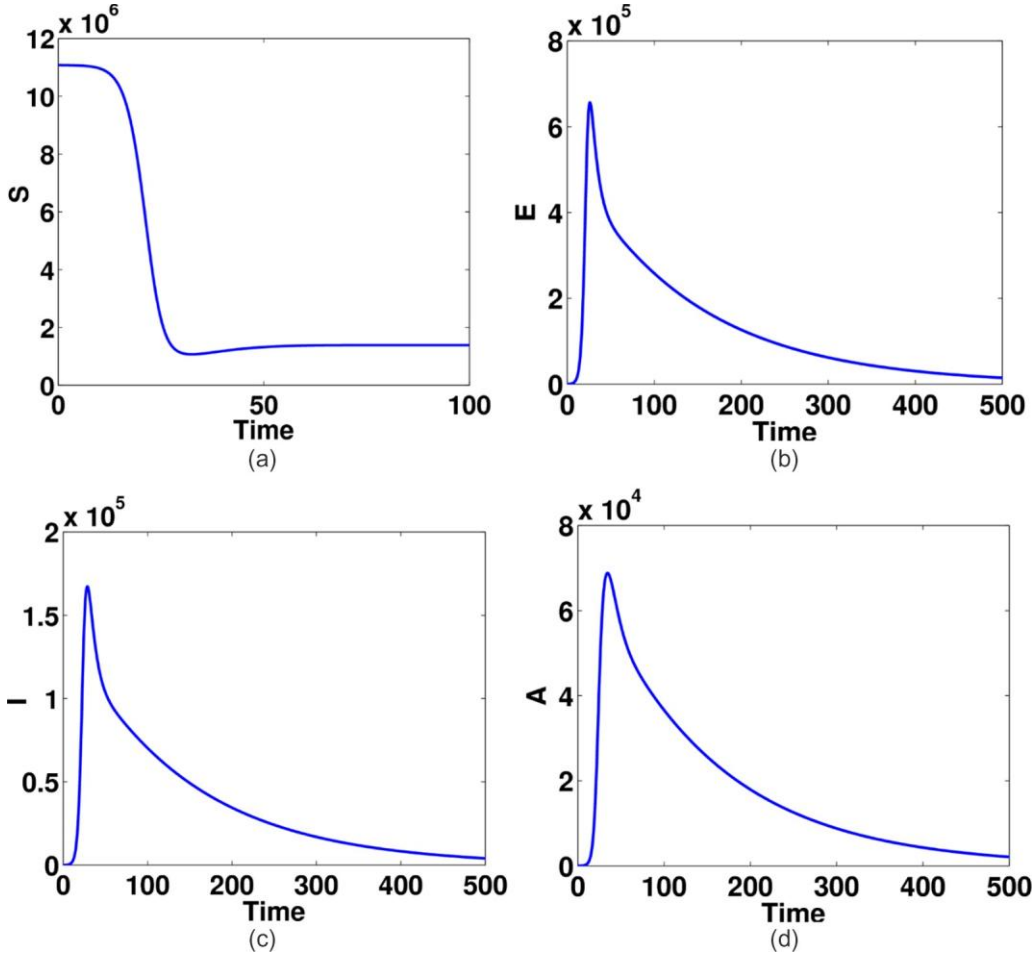


FIGURE 2. Computational simulations for the model states given in system (2.2) of the COVID- 19 using MATLAB, vertical lines represent model populations and horizontal lines show time in days, there are model dynamics of (a) susceptible individuals, (b) exposed individuals (c) symptomatic infected individuals, (d) pre-symptomatic infected individuals.

from the National Health Commission of the Republic of China's WHO situation report, which was published in [15]. Using SBedit for MATLAB, we compute the numerical approximate solutions of the model equations (2.2) for

various parameters and initial populations; see Figures 2 and 3. This leads to the conclusion that population model states have a distinct model dynamic. For model parameters and initial populations taken from the WHO situation report provided in [15], numerical simulations are calculated on two-dimensional planes. The study's findings offer a significant advancement in forecasting model dynamics for future development initiatives, treatments, and health care plans.

Utilizing the concept of local sensitivity analysis given in equation (2.11) is another promising step for additional research and model development. The local sensitivity of each model state in relation to model constants is determined using the SimBiology Toolbox for MATLAB. As shown in Figures 4-6, we calculate the model sensitivities using three distinct methods: non-normalizations, half normalizations, and complete normalizations. It's interesting to note that the results give us more insight into the model and help us determine the crucial model parameters. For the novel coronavirus model, for instance, it appears that the set {k2, k5, k6, k7, k8, k10, k13} is the most important collection of model parameters, whereas the set {k1, k9, k11, k12} is the least important set; see Figure 4. Figure 5 demonstrates that

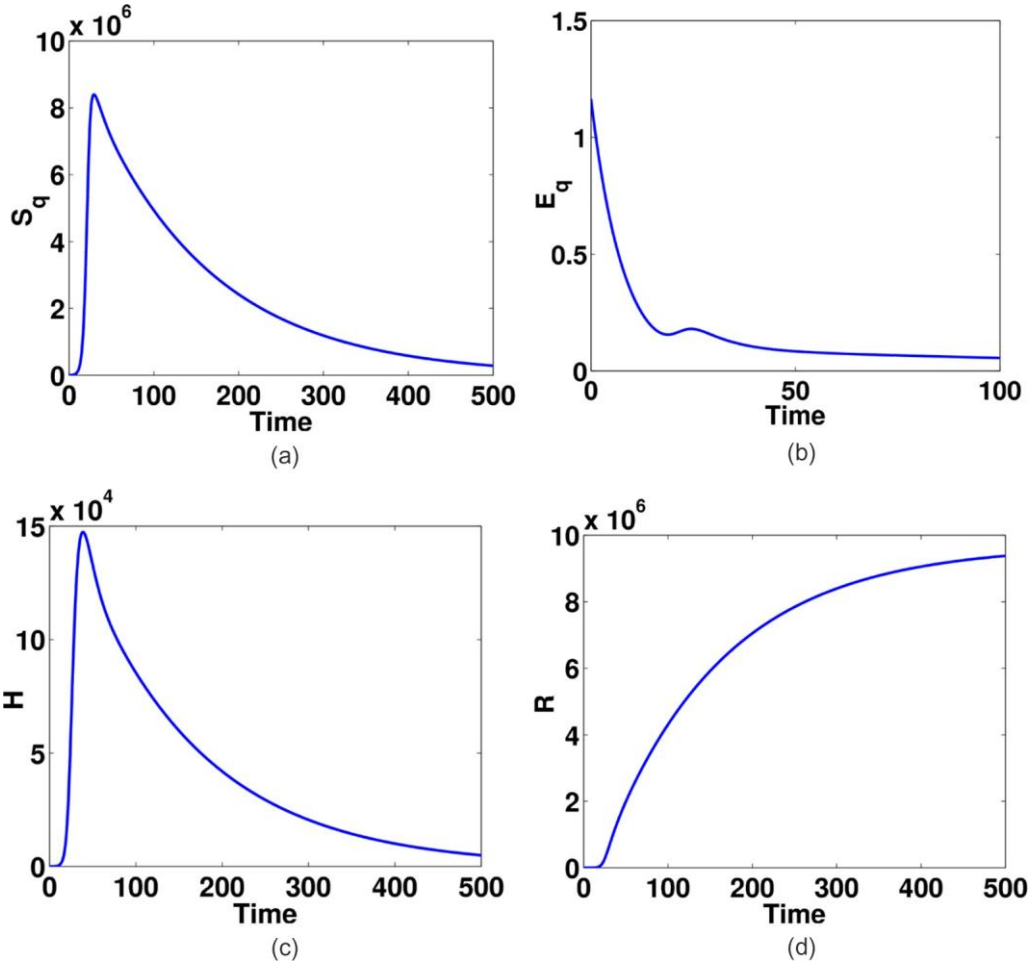


FIGURE 3. Computational simulations for the model states given in system (2.2) of the COVID- 19 using MATLAB, vertical lines represent model populations and horizontal lines show time in days, there are model dynamics of (a) quarantined susceptible individuals, (b) quarantined exposed individuals (c) quarantined hospitalized individuals, (d) recovered individuals.

parameters k_1, k_6, k_9 and k_{12} are mainly the less critical model parameters while the other model parameters are generally sensitive to the model. Figure 6 provides us that the set of parameters $\{k_6, k_9, k_{12}, k_{13}\}$ is the less sensitive model parameters, whereas the rest of the model parameters become sensitive for the model variables. As a result, identifying critical model parameters in this study based on computational simulations is an effective way to further study the model practically and theoretically and give some suggestions for future improvements of the novel coronavirus vaccination programs, interventions and controlling the spread of disease.

3. Discussions

In order to lessen the impact of the novel coronavirus on communities, efforts are concentrated globally and several healthcare solutions have been explored. It is evident that this virus poses a risk to public health and spreads quickly among people. According to the study's findings, health care systems should focus more on a set of sensitive characteristics than on less sensitive ones. This aims to lower the number of people who have contracted the illness and stop the new coronavirus from spreading more broadly on the

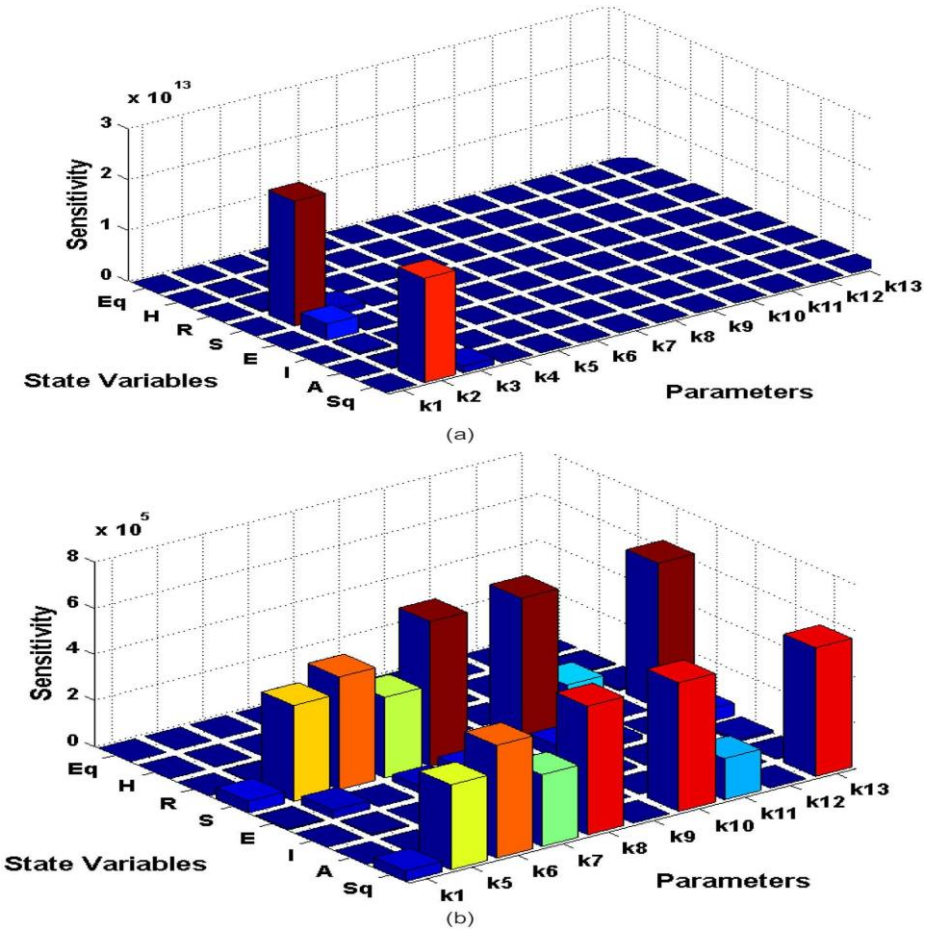


FIGURE 4. Local sensitivity analysis with **non-normalizations** in computational simulations for the coronavirus disease (COVID-19) using MATLAB, in this technique the parameters k_2, k_3 and k_4 are very sensitive compared to the other parameters thus two figures are computed, (a) the sensitivity of all variables with respect to all parameters, (b) the sensitivity of all variables with respect to all parameters except k_2, k_3 and k_4.

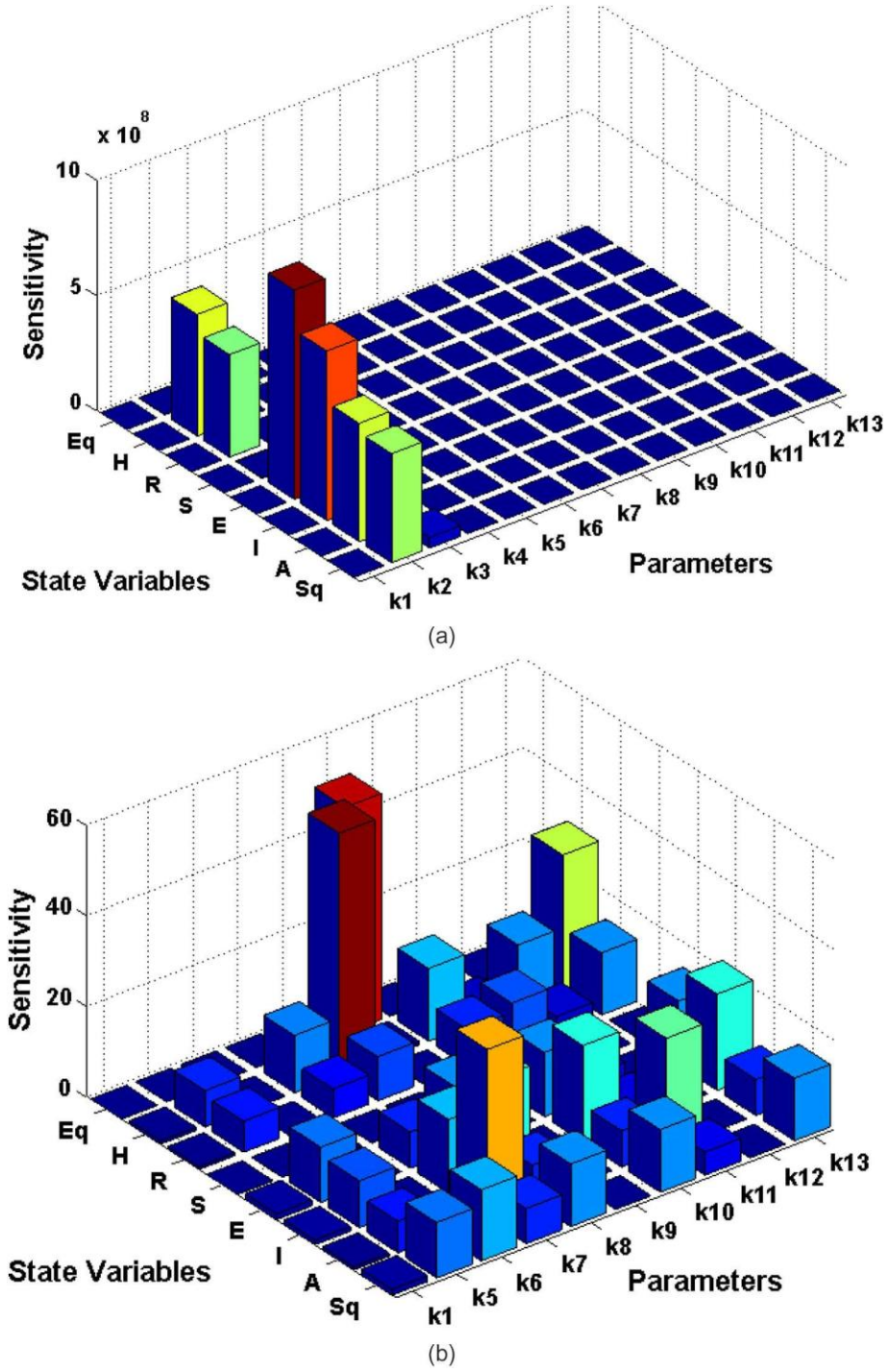


FIGURE 5. Local sensitivity analysis with **half normalizations** in computational simulations for the coronavirus disease (COVID-19) using MATLAB, in this technique the parameters k_2, k_3 and k_4 are very sensitive compared to the other parameters thus two figures are computed, (a) the sensitivity of all variables with respect to all parameters, (b) the sensitivity of all variables with respect to all parameters except k_2, k_3 and k_4.

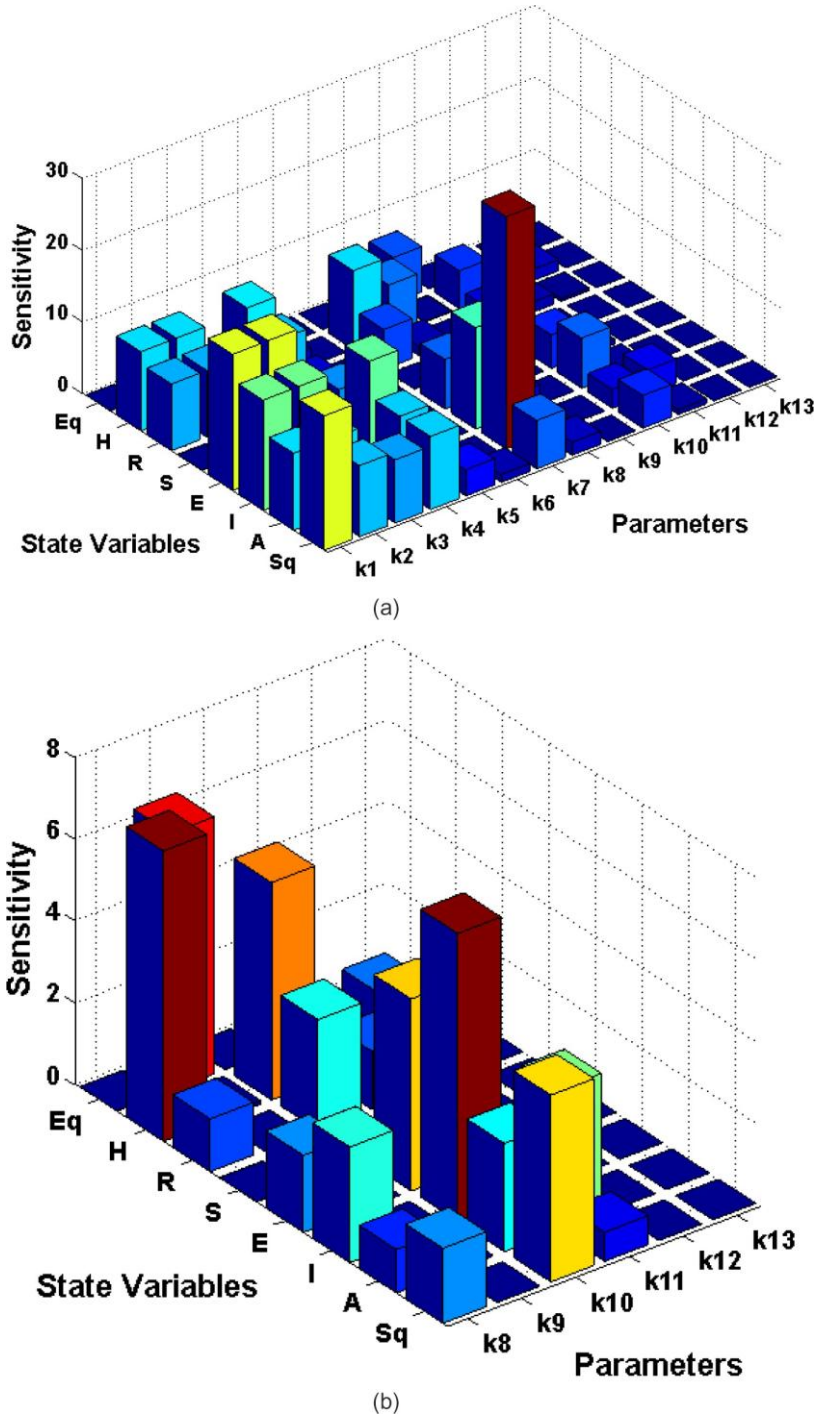


FIGURE 6. Local sensitivity analysis with **full normalizations** in computational simulations for the coronavirus disease (COVID-19) using MATLAB, in this technique the set of param- eters $\{k_1, k_2, k_3, k_4, k_5, k_6, k_7\}$ are very sensitive compared to the other parameters thus two figures are computed, (a) the sensitivity of all variables with respect to all parameters, (b) the sensitivity of all variables with respect to the set of parameters $\{k_8, k_9, k_{10}, k_{11}, k_{12}, k_{13}\}$.

community. It may help community interventions that can mitigate the impact of coronavirus disease. Computational results here provide some important suggestions to healthcare responsibilities as the most important response strategy to delay the spread of disease.

Interestingly, calculating sensitivity analysis based on non-normalization technique shows some important points. Firstly, susceptible (S), exposed (E) and quarantined susceptible (S_q) individuals are very sensitive to k_2 (transmission per contact); see Figure 4a. Another interesting result is that almost all model parameters may have an affective role on spreading this virus among susceptible and quarantined susceptible people; see Figure 4b. This gives us how public health partners pay more attention priority on interventions for these two groups. According to local sensitivity analysis with half normalizations in computational simulations, a set of individuals E, I, A, S_q, H, R are very sensitive to the parameter k_2; see Figure 5a. This is again contact between person–to–person has a great role in spreading this disease. The other factors may have also role to infect people in different levels, this is clearly occurred in our computational simulation given in Figure 5b. Specially, transition rate of symptomatic infected individuals to the quarantined infected class, impacts on the hospital capacity. Accordingly, computational results based on local sensitivity for full normalizations show that most of the reaction rate constants have a great role on model variable sensitivities, this clearly shown in Figure 6. More interestingly, it can be concluded that the most effective factors on spreading coronavirus are person–to–person communicate rate, quarantined exposed rate and transition rate of exposed individuals to the infected individuals. Our computational results confirms that healthcare responsible organizations in the worldwide should more pay attention to stay people at home and reduce the communication and contacts.

Similar to the findings of Figure 5b, Figure 6b demonstrates that H, the number of hospitalized patients, is very sensitive to k_8 (transition rate of symptomatic infected individuals to the quarantined infected class). Moreover, it can be concluded from the Figure 6a that the more the quarantined rate of exposed individuals controlled, the less the susceptible individuals, such as old persons, need to be quarantined. Accordingly, it can be seen that the quarantined exposed individuals E_q are more sensitive to k_9 (transition rate of quarantined exposed individuals to the quarantined infected class), see Figures 5b and 6b. It can be suggested that their movements should be limited outside of their home or current places. In the quarantine places, anyone there should separate themselves from others by staying in a specific space and using a different equipment, bathroom and kitchen.

4. Conclusions

It is challenging to research and determine crucial model parameters for the infectious disease models. Some mathematical techniques are required to describe the model dynamics for such systems. Sensitivity analysis and computational simulations, however, will aid in future model dynamics research and prediction. The coronavirus disease (COVID-19) model is complex, and in order to improve interventions and healthcare programs, various mathematical tools are needed. In this work, we examined several earlier studies on this illness and proposed mathematical models for future investigations and advancements. A few computational simulations are used to discuss the dynamics of model states.

To determine each model state's sensitivity to model parameters, we used the concept of local sensitivity. To determine the model sensitivities, three methods are examined: non-normalizations, half-normalizations, and full normalizations. These give us a significant advancement in identifying the essential components of the model. International attempts to lower the number of people affected with the disease and stop the spread of new conronaviruses across the population may benefit from computational results. According to our findings, for instance, the person-to-person communication rate, the quarantined exposed rate, and the transfer rate of exposed individuals to the infected individuals are the most effective determinants on the transmission of coronavirus.

Additionally, in light of the possible shortage of hospital capacity and its significant impact on national governments' ability to provide healthcare responsibly worldwide. Planning a specific course of action, such as quarantining the vulnerable people as soon as possible, appears to be essential to avoiding the hospital bed crisis. In order to better control this disease, the medical community should focus more on the quarantine areas. To stop the virus from spreading by touching shared surfaces, it is strongly advised that anyone in the quarantine areas be kept apart from the others and should only use their own bedroom, toilet, and equipment. It's interesting to note that the processes suggested here can be expanded upon and used in a variety of coronavirus models for various situations worldwide. Future model enhancements, interventions, and immunization campaigns will benefit from it.

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