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Global sensitivity analysis of COVID-19 mathematical model

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Abstract In this paper, we applied the Sobol’s method on an already existing mathematical model of coronavirus disease 2019 (covid-19). The objectives of this research work are to study the individual effects of involved parameters as well as combine (mutual) effects of parameters on output variables of covid-19 model. The study is also useful to identify the ranking of key model parameters and factors fixing. The ultimate goal is to identify the controlling parameters, which eventually will help decision makers to explore various policy options to control the covid-19 pandemic. For this purpose, first we present the model with its basic properties that are positivity and existence of solution. Then use the Sobol’s method to discuss the individual effects of involved parameters as well as combine (mutual) effects of parameters on output variables of covid-19 model. Finally, we present the results, discussions and concluding remarks about key model parameters and identifying the controlling parameters, which eventually will help decision makers to explore various policy options to control the covid-19 pandemic.

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1. Introduction
Mathematical models are useful to understand the behavior of an infection when it enters a community and investigate under which conditions it will be wiped out or continued. Currently covid-19 is of great concern to researches, governments and all peoples because of the high rate of the infection spread and the significant number of deaths occurred. In December 2019, coronavirus was first reported in Wuhan, China is an infectious disease caused by a newly discovered coronavirus. The virus that causes covid-19 is mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. Coronavirus confirmed cases reached nearly four million in 187 countries and approximately more than 295,000 people have lost their lives due to this pandemic several researchers did a lot of effort for modeling of this disease see [1–9]. In this paper, we applied sensitivity analysis on an already existing model of covid-19 [1] to study the impact of model parameters and their interaction effects on outputs variables [10–18]. The study is useful for policy makers to make
policies to reduce the cases of covid-19 pandemic by controlling the key model parameters. Sensitivity analysis is mainly divided into two parts; local and global sensitivity analysis. In local sensitivity analysis (LSA), the effect of a single parameter is studied on output variables [10,11,14]. While, in global sensitivity analysis (GSA), the impact of parameters feasible regions and their interactions effects on output variables are studied [10,12,15,16]. In this work, we applied sensitivity analysis (Sobol’s method) on input parameters, from here known as input quantities of interest (QoI) to study their impact on output variables or output quantities of interest (QoI) [15].

The paper is organized as: In Section 2, the formulation of covid-19 model is presented along with the basic properties that are positivity of the model and existence of the solution. Also a brief explanation of sensitivity analysis is present in this section. A working algorithm is also given to compute the sensitivity indices using the method of Sobol. In Section 3, computational setup is defined before computing the sensitivity indices. The important results are discussed in Section 4. Finally, the main conclusions are drawn in Section 5. In order to solve covid-19 model, Matlab (Copyright 1984–2012 The MathWorks, Inc., Version R2012a) built-in solver ode45 was used.

2. Mathematical model of covid-19

Let \( N(t) \) be the population size at time, \( t \) which further decomposed into four subclasses: (i) susceptible population \((S(t))\), (ii) exposed individuals \((E(t))\), infected population from corona \((I(t))\), recovered population from disease which are alive \((R(t))\) and death bodies due to corona \((D(t))\). The resulting nonlinear, coupled, first order system of ordinary differential equations (ODEs) describing the covid-19 pandemic is [1],

\[
S(t) = \Lambda - \sigma SE - \gamma R,
\]

\[
E(t) = -(K + \phi)E + \sigma SE + \gamma I,
\]

\[
I(t) = -\beta I + KE
\]

\[
R(t) = -\gamma R + \phi E + \beta I,
\]

\[
D(t) = \mu I.
\]

Here, \( \Lambda \) denotes the migrated population into the considered community, \( \gamma \) shows the contact rate between \( S(t) \) and \( E(t) \). Similarly \( \sigma \) shows the contact rate between \( S(t) \) and \( I(t) \). \( \mu \) represents death rate due to corona of the infected population, \( \beta \) is the recovery rate, which recovered from disease and alive, \( \phi \) is the exposed population that directly goes to recovered class and \( K \) is the rate at which exposed population joined the infected class.

2.1. Basic properties

**Theorem 2.1 (Positivity).** Let \((S(0), E(0), I(0), R(0))\) be any initial data belonging to \( \mathbb{R}^4_+ \) and \((S(t), E(t), I(t), R(t))\) be the solution corresponding to the initial data. Then, the set \( \mathbb{R}^4_+ \) is a positively invariant set of the model (1).

**Proof.** First, set \( \dot{\lambda}_1 = \sigma E \) and \( \dot{\lambda}_2 = \sigma I \), then first equation of (1) implies that

\[
\frac{dS}{dt} = \Lambda - \lambda_1 S - \lambda_2 S + \gamma R,
\]

or

\[
\frac{dS}{dt} \geq \Lambda - \lambda_1 S - \lambda_2 S.
\]

Assume the solution of the system (1) exists in a certain interval \( J \subseteq [0, +\infty) \), then for all \( t \in J \), the above equation can be solved as,

\[
\frac{dS}{dt} + (\lambda_1 + \lambda_2) S \geq \Lambda
\]

implies that

\[
S(t) e^{\int_{(\lambda_1 + \lambda_2)}(\lambda_1 + \lambda_2) dt} \geq S(0) + \int_0^t \lambda_1 S e^{\int_{(\lambda_1 + \lambda_2)} (\lambda_1 + \lambda_2) dw} dv,
\]

\[
S(t) \geq S(0) e^{-\int_{(\lambda_1 + \lambda_2)} (\lambda_1 + \lambda_2) dt} + e^{-\int_{(\lambda_1 + \lambda_2)} (\lambda_1 + \lambda_2) dt} \int_0^t \lambda_1 S e^{\int_{(\lambda_1 + \lambda_2)} (\lambda_1 + \lambda_2) dw} dv > 0.
\]

Hence, \( S(t) \) is positive for all values of \( t \) in the considered interval. As second equation of the system (1) implies that

\[
\frac{dE}{dt} = -(K + \phi)E + \sigma SE + \gamma SI \geq -(K + \phi)E,
\]

or

\[
\frac{dE}{dt} \geq -(K + \phi)E,
\]

can be written as

\[
\frac{dE}{E} \geq -(K + \phi)dt, \ (E \neq 0).
\]

By integrating, we get

\[
\ln E \geq -(K + \phi) t + C,
\]

\[
E \geq e^{-(K + \phi) t + C},
\]

\[
E \geq C_i e^{-(K + \phi) t},
\]

at \( t = 0 \),

\[
E \geq E(0) e^{-(K + \phi) 0} \geq 0.
\]

Hence, \( E(t) \) is positive for all values of \( t \). Similarly for rest of the classes it is proved that \( I(t) \) and \( R(t) \) are positive for all values of \( t \). The proof is complete.

2.2. Existence and uniqueness of the solution

The general form of the first order ODE is:

\[
\dot{y} = g(t, y), \ y(t_0) = y_0.
\]

Use the following theorem for establishing the existence and uniqueness of solution for proposed model.

**Theorem 2.2.** [Uniqueness of Solution] Suppose the domain \( D \):

\[
|t - t_0| \leq a, \ |y - y_0| \leq b, \ y = (y_1, y_2, \ldots, y_n), \ y_0 = (y_0, y_0, \ldots, y_0),
\]

and suppose that \( h(t, y) \) satisfies the Lipschitz condition:
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\[ |H(t, y_1) - H(t, y_2)| \leq k|y_1 - y_2|, \quad (4) \]

and whenever the pairs \((t, y_1) \in D\) and \((t, y_2) \in D\), where \(k\) is used to represent a positive constant. Then, there exist a constant \(\delta > 0\) such that there exists a unique (exactly one) continuous vector solution \(y(t)\) of the system \((2)\) in the interval \([t - \delta, t] \subseteq \delta\). It is important to note that condition \((2.10)\) is satisfied by requirement that:

\[
\frac{\partial H_i}{\partial y_j}, \quad i, j = 1, 2, \ldots, n, \quad (5)
\]

be continuous and bounded in the domain \(D\).

**Lemma 2.1.** If \(H(t, y)\) has continuous partial derivative \(\frac{\partial H_i}{\partial y_j}\) on a bounded closed convex domain \(\mathfrak{H}\) (i.e., convex set of real numbers), where \(\mathfrak{H}\) is used to denote real numbers, then it satisfies a Lipschitz condition in \(\mathfrak{H}\). Our interest is in the domain:

\[ 1 \leq E \leq \mathfrak{H}, \quad (6) \]

So, we look for a bounded solution of the form

\[ 0 < \mathfrak{H} < \infty, \quad (7) \]

**Theorem 2.3.** Let \(D\) denotes the domain defined in \((3)\) such that \((4)\) and \((5)\) hold. Then there exists a solution of model \((1)\), which is bounded in the domain \(D\).

**Proof.** Let

\[ H_1 = \lambda - \varepsilon S - x_5 I + \gamma R, \quad (8) \]

\[ H_2 = -(K + \phi)E + \varepsilon S + x_5 I, \quad (9) \]

\[ H_3 = -(\beta + \mu)I + KE, \quad (10) \]

\[ H_4 = -\gamma R + E + \beta I. \quad (11) \]

Now we want to present that \(\frac{\partial H_i}{\partial y_j}, j = 1, 2, 3, 4\) are continuous and bounded. For this purpose, we performed the following partial derivatives. For class \(S\), from Eq. \((8)\):

\[
\frac{\partial H_i}{\partial S} = -\varepsilon S, \quad |\frac{\partial H_i}{\partial S}| < \infty, \\
\frac{\partial H_i}{\partial S} = |\varepsilon S| < \infty, \\
\frac{\partial H_i}{\partial S} = -\varepsilon S, \quad |\frac{\partial H_i}{\partial S}| < \infty, \\
\frac{\partial H_i}{\partial S} = |\varepsilon S| < \infty,
\]

and

\[ \frac{\partial H_i}{\partial E} = \gamma, \quad |\frac{\partial H_i}{\partial E}| < \infty. \]

For class \(E\), from Eq. \((9)\):

\[
\frac{\partial H_i}{\partial E} = \varepsilon E, \quad |\frac{\partial H_i}{\partial E}| < \infty, \\
\frac{\partial H_i}{\partial E} = |\varepsilon E| < \infty, \\
\frac{\partial H_i}{\partial E} = -(K + \phi) + \varepsilon S, \quad |\frac{\partial H_i}{\partial E}| < \infty,
\]

\[ \frac{\partial H_i}{\partial E} = |-(K + \phi) + \varepsilon S| < \infty, \]

\[ \frac{\partial H_i}{\partial E} = \varepsilon S, \quad |\frac{\partial H_i}{\partial E}| < \infty, \\
\frac{\partial H_i}{\partial E} = |\varepsilon S| < \infty, \\
\frac{\partial H_i}{\partial E} = -(K + \phi) + \varepsilon S, \quad |\frac{\partial H_i}{\partial E}| < \infty, \\
\frac{\partial H_i}{\partial E} = |-(K + \phi) + \varepsilon S| < \infty, \]

\[ \frac{\partial H_i}{\partial E} = \gamma, \quad |\frac{\partial H_i}{\partial E}| < \infty. \]

Hence, it is proved that all the partial derivatives are continuous and bounded, so, by **Theorem (2.2)**, we conclude that there exist a unique solution of system \((1)\) in the region \(D\). \( \square \)

### 2.3. Global sensitivity analysis

Sensitivity analysis studies the impact of input factors (parameters, in-output boundary conditions, etc) on output variables. As described before, two types of analysis are used for sensitivity analysis; (i) local sensitivity analysis (LSA) and (ii) global sensitivity analysis (GSA). In LSA, the impact of a small parameter perturbation on outputs is studied at a time, while other parameters remain fixed at their nominal values. On the other hand, GSA studies the impact of individual model parameters (within feasible regions) as well as interaction/combine effects of all parameters on output variables. In this paper, a variance-based Sobol’s method is applied on a mathematical model of covid-19 to study the impact of model parameters and their interaction effects on output variables. Here, we just present the working algorithm (algorithm-I) used to compute the main and total sensitivity indices. For more details regarding LSA/GSA methods, their basic theme, limita-
Algorithm 1. (To compute Sobol’s main $(S_i)$ and total sensitivity indices $(S_{iT})$)

1. Input QoI := model parameters i.e. $A, \mu, x_e, x_i, \gamma, K, \phi$ and $\beta$.

Output QoI := $S(t), E(t), I(t), R(t)$ and $D(t)$.

2. Generate two random numbers matrices $A$ and $B$ of order $N \times L$ using Latin hypercube sampling LHS. Where, $N$ and $L$ are the total count of model simulations and uncertain parameters respectively.

3. for $i = 1 : N$, compute solution for matrices $A$ and $B$ and save the model runs as $Y_A$ and $Y_B$. end of $i$ loop.

4. for $j = 1 : L$, define matrix $C_j$, which is matrix A except the $j^{th}$ column of matrix $B$. Compute and save the model runs for each $C_j$ as $Y_{C_j}$.

5. for $p = 1 : T_s$, where $(T_s := output time series = 5)$ for $t = 1 : t_n$, where $(t_n := 21$ days, with $100$ sample/time points) compute the time dependent main $(S_{main})$ and total sensitivity indices $(S_{total})$ of each parameter at each time-point of output variables $(S(t), E(t), I(t), R(t), D(t))$, using the estimator offered by Jansen [19,20].

6. The time dependent main sensitivity index can be calculated as:

\[
S_{main} = 1 - \frac{1}{SN_{total}} \sum_{n=1}^{N} \left( Y_A^{(n)} - Y_{C_j}^{(n)} \right)^2,
\]

where,

\[
V_{main} = \frac{1}{N} \sum_{n=1}^{N} \left( Y_A^{(n)} \right)^2 - E_{main}^2 \text{ and}
\]

\[
E_{main} = \left( \frac{1}{N} \sum_{n=1}^{N} Y_B^{(n)} \right)^2.
\]

The time dependent total sensitivity index can be computed as:

\[
S_{total} = \frac{1}{SN_{total}} \sum_{n=1}^{N} \left( Y_A^{(n)} - Y_{C_j}^{(n)} \right)^2,
\]

where,

\[
V_{total} = \frac{1}{N} \sum_{n=1}^{N} \left( Y_A^{(n)} \right)^2 - E_{total}^2 \text{ and}
\]

\[
E_{total} = \left( \frac{1}{N} \sum_{n=1}^{N} Y_B^{(n)} \right)^2.
\]

The total variance $(V_{(j)})$ and the expectation $(E_{(j)})$ are also calculated at each time-point of output QoI with respect to each input QoI. end of $j$ loop.

6. for $s = 1 : L$, compute main effect, $S_i$ and total effect, $S_{iT}$ of each input QoI on output QoI. end of $s$ loop.

3. Computational setup for GSA

In sensitivity analysis, the impact of input QoI are studied on output QoI, so identification of input and output QoI is important. Within this work, model parameters i.e. $A, \mu, x_e, x_i, \gamma, K, \phi, \beta$ are considered as input QoI, whereas $S(t), E(t), I(t), R(t)$ and $D(t)$ are taken as output QoI. Each model parameter is randomized within ±10% of its nominal value using Latin hypercube sampling (LHS) and their impact in term of main $(S_i)$ and total sensitivity indices $(S_{iT})$ are studied.

Where, $S_i$ means individual (main) effect of $i^{th}$ model parameter on output QoI and $S_{iT}$ is the sum of main effect of $i^{th}$ parameter and its interaction effects with other parameters on output QoI. Moreover, if $\sum_{j=1}^{L} S_i = 1$, then the model is called additive and in that case we don’t have interaction effects of parameters. In case if there exist parameters interaction effects then $\sum_{i=1}^{L} S_i < 1$. Where, parameter interaction

---

**Fig. 1** Covid-19 model simulations with nominal parameter values, $A = 0, \mu = 0.12, x_e = 0.3, x_i = 0.4, \gamma = 0.23, K = 0.3, \phi = 0.25, \beta = 0.45$ with initial conditions are $S(0) = 100, E(0) = 10, I(0) = 3, R(0) = 0, D(0) = 0$ [1].
effects can be identified using the expression $|\sum_{i=1}^{L}(S_i - S_{T_i})|$. In this study, ranking of key model parameters and factor fixing are done by using $S_i$ and $S_{T_i}$ respectively. Further, model equations are solved using Matlab built-in solver $\texttt{ode45}$, which took 0.014 s to compute the single model solution, see Fig. 1. Covid-19 pandemic was studied for 21 days, consist of 100 equally spaced time points. Initially, the model was run for $N = [1000; 2000; 3000; 5000; 10000]$ and the results of last simulations i.e. $N = 10000$ are shown in the coming section. The total time to calculate the main ($S_i$) and total sensitivity indices ($S_{T_i}$), was 52 min, see Table 1 for complete computational costs. For model simulations, a laptop was used (Intel (R) core (TM) i3-7020U CPU @ 2.30 GHz, 2.30 GHz and 4 GB of RAM).

## 4. Results and discussion

The results of this research work are explained in two parts, (i) propagation and visualization of parametric uncertainty and (ii) global sensitivity analysis.

### Table 1 Individual and total costs while computing the main and total sensitivity indices of Sobol’s method with different model runs.

| N    | Input QoI                           | Output QoI                          | Computational cost |
|------|-------------------------------------|-------------------------------------|--------------------|
| 1000 | $[A, \mu, \sigma, \gamma, K, \phi, \beta]$ | $[S(t), E(t), I(t), R(t), D(t)]$   | 148 s              |
| 2000 | $\text{\ldots}$                    | $\text{\ldots}$                    | 300 s              |
| 3000 | $\text{\ldots}$                    | $\text{\ldots}$                    | 467 s              |
| 5000 | $\text{\ldots}$                    | $\text{\ldots}$                    | 770 s              |
| 10000| $\text{\ldots}$                    | $\text{\ldots}$                    | 1400 s             |
|      |                                     |                                     | total time $= 3085$ s $= 52$ min |

Fig. 2 Visualization of the uncertainty in output QoI with $N = 10000$ different parameter sets obtained using Latin hypercube sampling.
4.1. Propagation and visualization of uncertainty

In this section, propagation and visualization of the uncertainty are discussed. Uncertainty in model parameters are generated using Latin hypercube sampling (LHS) \[10,15\], where each parameter is randomized \(\pm 10\%\) from its nominal value. Using \textit{ode45}, the parametric uncertainty is propagated through the model by considering different parameter sets, like \(N = \{1000; 2000; 3000; 5000; 10000\}\). Here, \(N\) is total number of model runs or different parameter sets used to compute the model simulations. The results of \(N = 10000\) are shown in Fig. 2 and center lines (red) show the mean values of \(N = 10000\) simulations at 100 sample points. Results shown that at the beginning, the uncertainty in the output QoI is negligible, however when the time increased from 2 days then the uncertainty also increased in \(E(t), I(t), R(t),\) and \(D(t)\). Visualization of parametric uncertainty is helpful to study the overall changes in the output QoI w.r.t. variations in input QoI. Unfortunately by using such techniques, we can not find which parameters contribute most/least on output uncertainty. In order to quantify the impact of model parameters and their interaction effects on output QoI, global sensitivity analysis is used.

4.2. Global sensitivity analysis (GSA)

In GSA (Sobol’s method), the model output uncertainty is decomposed and then assigned to its input parameters. Using the algorithm of Sobol’s method, we got two sensitivity indices (i) \(S_i\) and (ii) \(S_{T_i}\). The results of both sensitivity indices are shown in Fig. 3. Generally, main effects are used for ranking of key parameters and total effects are used for factor fixing.
4.2.2. Controlling parameters in covid-19 model

As mentioned earlier, the ultimate goal of this work is to identify the controlling parameters of covid-19 model, which eventually help decision makers to explore various policy options to control the covid-19 pandemic. Model parameters which contribute most on output uncertainty are consider as controlling parameters. For example, the parameter $\beta$ (see Fig. 3, (top)) is the controlling parameter for both $E(t)$ and $I(t)$ classes. So, on the basis of this result, the decision makers could adopt such policies which control $E(t)$ and $I(t)$ classes of covid-19 by controlling the model parameter $\beta$.

5. Conclusion

In this paper, we presented the positivity and existence and uniqueness of the solution for the existing proposed model of covid-19 and successfully applied global sensitivity analysis method (Sobol’s method). The Sobol’s method was used to determine the main effects, interaction effects, ranking of key/controlling parameters and factor fixing. Key results of sensitivity analysis are summarized as:

1. The impact of 10% variations of $\mu$ has larger effect on $D(t)(45\%)$, while low sensitivity is observed for other output QoI.
2. Main effects of $x_e$ and $x_i$ are negligible on almost all output QoI. But interaction effects of both parameters are significant.
3. The parameter $\gamma$ shows strong sensitivity only for $R(t)(82\%)$.
4. The contributions of $K$ on output uncertainty of $S(t)$, $E(t)$, $I(t)$ and $D(t)$ are 10%, 58%, 18% and 17% respectively.
5. The parameter $\phi$ showed major contributions in output uncertainty for both $E(t)$ (40%) and $I(t)$ (20%).
6. The parameter $\beta$ is most influential for both $I(t)$ (58%) and $D(t)$ (29%).
7. Strong interaction effects of parameters $\mu (17\%), x_e (68\%), x_i (59\%), K (24\%), \phi (63\%)$, and $\beta (48\%)$ are observed only for $S(t)$, see Figs. 3, (bottom) and 4.

4.2.1. Ranking and factor fixing

Ranking of key parameters is another important aspect of Sobol’ method. Each row in Fig. 3, (top) shows the ranking of key model parameters for specific output QoI. For example, the ranking of key model parameters for $E(t)$ (second row) is $K(58\%)$ which is most important parameter followed by $\phi(40\%)$. On the other hand, total or interaction effects are important only for $S(t)$. In general, we can fix $\Lambda$ on its nominal value in complete covid-19 model, while for a specific model output the factor fixing is different.
7. Strong interaction effects of parameters $\mu(17\%), \alpha(68\%), \gamma(59\%), K(24\%), \phi(63\%),$ and $\beta(48\%)$ are observed only for $S(t)$.
8. In general, $\alpha$ can be fixed on its nominal value.
9. Parameters which contribute most on output uncertainty are considered as controlling parameters.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article cited there in.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors Contribution

Authors are equally contributed in preparing this manuscript.

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