Sensitivity Analysis of COVID-19 Transmission Dynamics

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Abstract: Corona Virus Disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The virus is spread between people during close contact via small droplets produced by coughing, sneezing, talking etc. In the present work, the transmission dynamics of the COVID- 19 is studied using SEIHR epidemic compartmental model. Basic reproduction number is computed with the help of the method of Next Generation Matrix. Stability of equilibrium points of the model is discussed. Sensitivity analysis of the model is performed to determine the relative importance of the model parameters. Simulations are made to illustrate the mathematical results graphically.

Keywords: COVID-19, Compartmental Model, Stability, Sensitivity Analysis, Basic Reproduction Number.

I. INTRODUCTION

The infectious disease COVID-19 can affect human of almost all ages worldwide. The disease was first identified in December 2019 in Wuhan city, which is the capital of China's Hubei province. On 24 April 2020, more than 2.71 million conform cases have been reported in 110 countries and territories. More than 191,228 deaths and more than 745,092 people have recovered [1]. Wuhan is the most seriously affected city in China. When the infection started in Wuhan, the available medical resources of the health system for diagnosing and treating the infected cases were not sufficient, because of that number of infections kept on increasing rapidly. Some hospitals began to receive confirmed cases and started to provide adequate hospital beds to infected individuals for diagnosis and treatment. Because of sufficient medical resources, the number of infectious population started decreasing in Wuhan. Therefore, the medical resources can be considered as one of the main reasons for controlling the transmission of COVID-19 (during the period of Jan. 23rd to Mar. 6th, 2020) [2].

Mathematical compartmental models help to understand transmission dynamics of infectious disease from various angles ([3], [4], [5], [6], [7], [8]). These models have been effective tools to understand and propose control measures of the infectious diseases. A number of mathematical models are developed to observe and analyze the rapid spread of infectious disease in order to control and minimize the transmission of them through quarantine and other measures. Wang et al. built a time-dependent model of COVID-19 to study the effect of medical resources on transmission of COVID-19 in Wuhan [2]. Y. Li et al. established the time series models based on different mathematical formulas according to the variation law of the original data of Wuhan city [5].

While modeling infectious diseases, it is very important to determine the model parameter which is the most sensitive in the transmission of the disease. So, sensitivity analysis is important in mathematical studies. By the study of sensitivity analysis, Chitnis et al. determined important parameters in the spread of malaria [8]. Also, Phaijoo and Gurung discussed sensitivity of model parameters in the transmission

of dengue disease [9]. In the present work, we study the transmission dynamics of COVID - 19 following the work of Wang et al. [2]and perform sensitivity analysis to identify the most sensitive parameter in the model of COVID-19.

II. MATHEMATICAL MODEL OF COVID-19

For the formulation of the model, total population at time t is denoted by $N(t)$, it is subdivided into seven classes: Susceptible: $S(t)$, Pre-stage Exposed: $E_1(t)$, Post-stage Exposed: $E_2(t)$ Infected with mild symptoms: $I_1(t)$, Infected with serious symptoms: $I_2(t)$, Hospitalized: $H(t)$ and Recovered: $R(t)$. So, $N(t) = S(t) + E_1(t) + E_2(t) + I_1(t) + I_2(t) + H(t) + R(t)$. It is assumed that hospitalized individual is isolated and cannot contact with susceptible individual. Infectious individuals include $E_2(t)$, $I_1(t)$ and $I_2(t)$. Incubation period of COVID-19 is as long as 2 to 14 days [5]. In the pre-stage exposed: $E_1(t)$, people are infected but not infectious. But in post-stage exposed: $E_2(t)$, people are infectious, so they can infect to others. Transmission of the disease COVID-19 is described in the flow diagram fig.1.

The birth rate and natural death rate are denoted by μ. Susceptible individuals $S(t)$ can be infected with COVID-19 by effective contact with infectious individuals. We consider that c represents the mean number of infectious individuals contacting with $S(t)$; β is the transmission probability and θ $(0 < \theta < 1)$ accounts for reduction in transmissibility of $E_2(t)$ compare to $I_2(t)$. Assume that q is the proportion of $E_2(t)$ to keep in the quarantine and $p = 1 - q$ represents the un-quarantined proportion of post-stage exposed individuals. So, p is infectious. Assume that θ_1 $(0 < \theta_1 < 1)$ accounts for reduction in transmissibility of $I_1(t)$ compare to $I_2(t)$. Due to opening the hospital, ε represents the exponential decay of contact rate of infected individuals to susceptible individuals [2]. Let ε_1 denotes the minimum proportion of contact rate of infected individuals to susceptible individuals under the measure of opening the hospital.

In the present model, the susceptible individuals get infected of COVID -19 when they come in contact with the infectious individuals $E_2(t)$, $I_1(t)$ and $I_2(t)$ at the rates $\frac{c\beta\theta pE_2}{N}$, $\frac{c\beta\theta_1\varepsilon_1 I_1}{N}$ and $\frac{c\beta\varepsilon_1 I_2}{N}$ respectively. So, the susceptible individuals move to the class $E_1(t)$ at the rate of α, where

$$\alpha = \frac{c\beta\theta pE_2}{N} + \frac{c\beta\theta_1\varepsilon_1 I_1}{N} + \frac{c\beta\varepsilon_1 I_2}{N}$$

Infected individuals $I_1(t)$) and $I_2(t)$can be admitted to hospital at the rate of η_1 and η_2 respectively.

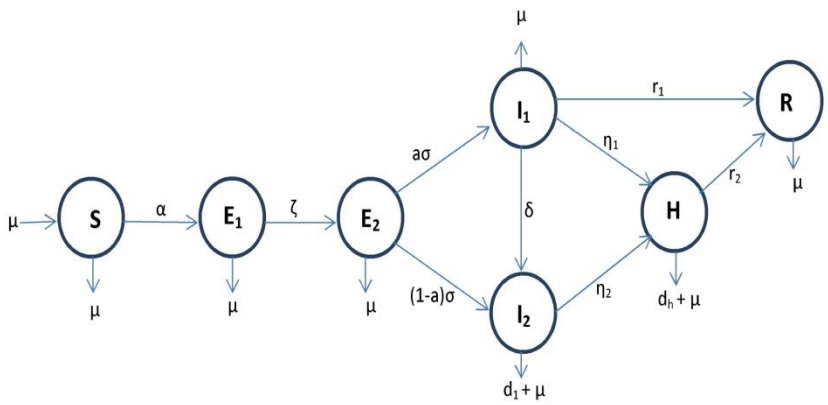

Figure 1: Flow Diagram of Transmission of COVID-19

The mathematical model of the transmission of COVID-19 [2] described by the fig.1 is as follows:

$$\frac{ds}{dt} = \mu N - c\theta\beta pE_2\frac{S}{N} - c\theta_1\beta\epsilon_1 I_1\frac{S}{N} - c\beta\epsilon_1 I_2\frac{S}{N} - \mu S$$
$$\frac{dE_1}{dt} = c\theta\beta pE_2\frac{S}{N} + c\theta_1\beta\epsilon_1 I_1\frac{S}{N} + c\beta\epsilon_1 I_2\frac{S}{N} - (\xi + \mu)E_1$$
$$\frac{dE_2}{dt} = \xi E_1 - (\sigma + \mu)E_2$$
$$\frac{dI_1}{dt} = a\sigma E_2 - (\delta + \eta_1 + \gamma_1 + \mu)I_1 \quad (2.1)$$
$$\frac{dI_2}{dt} = (1-a)\sigma E_2 + \delta I_1 - (\eta_2 + d_1 + \mu)I_2$$
$$\frac{dH}{dt} = \eta_{1I_1} + \eta_2 I_2 - (\gamma_h + d_h + \mu)H$$
$$\frac{dR}{dt} = \gamma_1 I_1 + \gamma_h H - \mu R$$

Model parameters are described in the following table (1)

Table 1: Parameter Description Table [13]

Parameters	Description	Value	Dimension
c	Contact rate	13.8	per day
β	Transmission probability	0.036	Dimensionless
$1/\xi$	Pre-stage exposed period	1.52	per day
$1/\sigma$	Post- stage exposed period	6,67	per day
δ	Transition rate from I_1 toI_2	0.2	per day
a	Proportion to E_2 enteringI_1	0.8	Dimensionless
η_1	Average hospitalization rate ofI_1	0.31	per day
η_2	Average hospitalization rate of I_2	0.7	per day
θ_1	Infection reduction fraction ofI_1	0.87	Dimensionless
θ	Infection reduction fraction ofI_2	0.72	Dimensionless
γ_1	Recovery rate of I_1	1/12.5	per day
γ_h	Recovery rate of H	0.05	per day
d_1	Disease induced death rate ofI_2	0.055	per day
d_h	Disease induced death rate of$H$	0.049	per day
ε_1	Proportion of contact rate	0.1	Dimensionless

A. Positivity, Existence and Uniqueness of Solution

Theorem 1. The solutions of the system (2.1) are nonnegative for all t > 0.

Proof: Suppose $M = \{(S, E_1, E_2, I_1, I_2, H, R) \in \mathbb{R}^7 : 0 \leq S, E_1, E_2, I_1, I_2, H, R\}$
To prove M is positively invariant, we observe the behaviors of the state variables in M.

a) At the boundary, $S = 0$, we have, $\frac{ds}{dt} = \mu N > 0$

Thus the solution cannot cross the boundary $S = 0$.

b) At the boundary, $E_1 = 0$, we have

$$\frac{dE_1}{dt} = c\theta\beta pE_2\frac{S}{N} + c\theta_1\beta\epsilon_1 I_1\frac{S}{N} + c\beta\epsilon_1 I_2\frac{S}{N}$$

If $E_1 = 0, S > 0, E_2 > 0, I_1 > 0, I_2 > 0$, then $\frac{dE_1}{dt} > 0$

If $E_1 = 0, S > 0, E_2 > 0, I_1 > 0, I_2 = 0$, then $\frac{dE_1}{dt} > 0$

If $E_1 = 0,\ S > 0,\ E_2 > 0,\ I_1 = 0,\ I_2 > 0$, then $\frac{dE_1}{dt} > 0$

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If $E_1 = 0,\ S = 0,\ E_2 > 0,\ I_1 > 0,\ I_2 > 0$, then $\frac{dE_1}{dt} > 0$

In each case $\frac{dE_1}{dt} \geq 0$, so the solution cannot cross the boundary $E_1 = 0$.

c) At the boundary, $E_2 = 0$, we have $\frac{dE_1}{dt} = \xi E_2$.

If $E_2 = 0,\ E_1 > 0$ then $\frac{dE_2}{dt} > 0$. Thus the solution cannot cross the boundary $E_2 = 0$.

d) At the boundary, $I_1 = 0$, we have $\frac{dI_1}{dt} = a\alpha E_2$.

If $I_1 = 0,\ E_2 > 0$ then $\frac{dI_1}{dt} > 0$. Thus the solution cannot cross the boundary $I_1 = 0$

e) At the boundary, $I_2 = 0$, we have $\frac{dI_2}{dt} = (1-a)\alpha E_2 + \delta I_1$.

If $I_2 = 0,\ E_2 > 0,\ I_1 > 0$, then $\frac{dI_2}{dt} > 0$.

If $I_2 = 0,\ E_2 > 0,\ I_1 = 0$, then $\frac{dI_2}{dt} > 0$.

If $I_2 = 0,\ E_2 = 0,\ I_1 > 0$, then $\frac{dI_2}{dt} > 0$.

Thus the solution cannot cross the boundary $I_2 = 0$

f) At the boundary,$H = 0$, we have $\frac{dH}{dt} = \eta_{1I_1} + \eta_2 I_2$.

If $H = 0,\ I_1 > 0,\ I_2 > 0$, then $\frac{dH}{dt} > 0$.

If $H = 0,\ I_1 > 0,\ I_2 = 0$, then $\frac{dH}{dt} > 0$.

If $H = 0, I_1 = 0,\ I_2 > 0$, then $\frac{dH}{dt} > 0$.

Thus the solution cannot cross the boundary $H = 0$.

g) At the boundary, $R = 0$, we have $\frac{dR}{dt} = \gamma_1 I_1 + \gamma_h H$.

If $R = 0,\ I_1 > 0,\ H > 0$, then $\frac{dR}{dt} > 0$.

If $R = 0,\ I_1 > 0,\ H = 0$, then $\frac{dR}{dt} > 0$.

If $R = 0,\ I_1 = 0,\ H > 0$, then $\frac{dR}{dt} > 0$.

Thus the solution cannot cross the boundary $R = 0$.

Therefore, the solution of the system (2.1) cannot exit M by crossing the boundary of any of the state variables.

Assume that the system of equation (2.1) has the following initial conditions

$S > 0,\ E_1 \geq 0,\ E_2 \geq 0\ I_1 > 0,\ I_2 > 0, H \geq 0,\ R \geq 0$ (2.2)

Theorem 2. Consider the system of equations (2.1) with nonnegative initial conditions (2.2). Solutions to the system of equations (2.1) with initial conditions (2.2) exist and are unique for all $t \geq 0$.

Proof: Let$x(t) = (S,\ E_1,\ E_2,\ I_1,\ I_2,\ H,\ R) \in \mathbb{R}^7$. Then the system (2.1) can be written in the form $\frac{dx}{dt} = g(x)$. Let g_i denote the components of the vector field$g$ for $i = 1, 2, 3, 4, 5, 6, 7$, we have,

$$g_1 = \mu N - c\theta\beta p E_2 \frac{S}{N} - c\theta_1\beta\epsilon_1 I_1 \frac{S}{N} - c\beta\epsilon_1 I_2 \frac{S}{N} - \mu S$$

$$g_2 = c\theta\beta p E_2 \frac{S}{N} + c\theta_1\beta\epsilon_1 I_1 \frac{S}{N} + c\beta\epsilon_1 I_2 \frac{S}{N} - (\xi + \mu)E_1$$

$g_3 = \xi E_1 - (\sigma + \mu)E_2$

$g_4 = a\sigma E_2 - (\delta + \eta_1 + \gamma_1 + \mu)I_1$

$g_5 = (1-a)\sigma E_2 + \delta I_1 - (\eta_2 + d_1 + \mu)I_2$

$g_6 = \eta_{1I_1} + \eta_2 I_2 - (\gamma_h + d_h + \mu)$

$g_7 = \gamma_1 I_1 + \gamma_h H - \mu R$

The vector field g consists of the algebraic polynomials of state variables. Thus $g_i \epsilon\ \mathbb{R}^7$ are continuous autonomous functions and partial derivatives $\frac{\partial g_i}{\partial S}, \frac{\partial g_i}{\partial E_1}, \frac{\partial g_i}{\partial E_2}, \frac{\partial g_i}{\partial I_1}, \frac{\partial g_i}{\partial I_2}, \frac{\partial g_i}{\partial H}, \frac{\partial g_i}{\partial R}$ exist and are continuous. Hence by Existence and Uniqueness Theorem, a unique solution of the system $\frac{dx}{dt} = g(x)$ exists for any initial condition $x(0) \epsilon\ \mathbb{R}^7$[10].

B. *Equilibrium Points and Basic Reproduction Number*

The system of equations (2.1) has two equilibrium points; the disease free equilibrium point $\boldsymbol{P_0} = \left(\frac{\boldsymbol{S}}{\boldsymbol{N}}, \boldsymbol{0}, \boldsymbol{0}, \boldsymbol{0}, \boldsymbol{0}, \boldsymbol{0}, \boldsymbol{0}\right)$ and endemic equilibrium point $\boldsymbol{P_1} = (\boldsymbol{S}^*, \boldsymbol{E_1}^*, \boldsymbol{E_2}^*, \boldsymbol{I_1}^*, \boldsymbol{I_2}^*, \boldsymbol{H}^*, \boldsymbol{R}^*)$. Further, basic reproduction number is defined as the average number of secondary infections caused by single infectious individual during his/her entire infectious life time [11], [12]. The number is denoted by $\boldsymbol{R_0}$. Assume that $\boldsymbol{F}$ is the matrix of transmission terms and $\boldsymbol{V}$ is the matrix of transition terms of the system (2.1). R_0 is defined as the spectral radius of the matrix $\boldsymbol{FV^{-1}}$ i.e., $\boldsymbol{\rho}\ (\boldsymbol{FV^{-1}})$ and is obtained by using the Next Generation Matrix Method [6], [11], [12]. For the model (2.1);

$$F = \begin{bmatrix} 0 & \frac{c\beta\theta p E_2}{N} & \frac{c\beta\theta_1\varepsilon_1 I_1}{N} & \frac{c\beta\varepsilon_1 I_2}{N} \\ \xi & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \qquad V = \begin{bmatrix} -u & 0 & 0 & 0 \\ \xi & -w & 0 & 0 \\ 0 & a\sigma & -v & 0 \\ 0 & (1-a)\sigma & \delta & -q \end{bmatrix},$$

Where $u = \mu + \xi,\ v = \delta + \eta_1 + \gamma_1 + \mu,\ w = \sigma + \mu,\ q = \eta_2 + d_1 + \mu$
Thus the basic reproduction number at the disease free equilibrium point P_0 is

$$R_0 = \sqrt{\frac{\beta c\xi\left(p\theta vq + \varepsilon_1\sigma(\gamma_1 - a\gamma_1 + \delta + \eta_1 + \mu + a(\theta_1 q - \eta_1 - \mu))\right)}{uvqw}}$$

The disease free equilibrium point always exists in the absence of infection of the disease that is $R_0 < 1$ and endemic equilibrium point always exists when $R_0 > 1$.

C. *Stability Analysis*

Theorem 3. (Local Stability of Disease free equilibrium) Disease free equilibrium point of the system of equations (2.1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.
Proof: About the disease free equilibrium point, the Jacobian matrix for the system of equations (2.1) has the block matrix

$$J = \begin{bmatrix} M_1 & M_2 \\ 0 & F - V \end{bmatrix}$$

If all the eigenvalues of the Jacobian matrix Jhave negative real parts, then the disease free equilibrium is asymptotically stable [12]. Since J is upper triangular matrix, eigenvalues of J are those of M_1 and $F - V$. The eigenvalue of matrix M_1 is $-\mu < 0$ and $-q < 0$. Now stability of the disease free equilibrium depends on the eigenvalues of $F - V$ where F is non-negative and V is non-singular M matrix [13]. Again, all the eigenvalues of $F - V$ have negative real parts if and only if $\rho(F\,V^{-1}) < 1$ [12]. Here, $R_0 = \rho(F\,V^{-1})$, therefore the disease free equilibrium is locally asymptotically stable if $R0 < 1$.

If $\rho(F\,V^{-1} > 1$ then $s(F - V) > 1$ [12]. That means, if $R_0 = \rho(F\,V^{-1}) > 1$, spectral abscissa of the matrix $F - V$ is positive. It shows that, at least one eigenvalue of $F - V$ has positive real part and so, the disease free equilibrium point is unstable. Hence, the disease free equilibrium is unstable if $R_0 > 1$.

Theorem 4. The system of equations (2.1) has an endemic equilibrium point $P_1 = (S^*, E_1{}^*, E_2{}^*, I_1{}^*, I_2{}^*, H^*, R^*)$which exists only if $R_0 > 1$.

Proof: In the deterministic model (2.1) of COVID-19, if the basic reproduction number R_0increases through unity, the stability of disease free equilibrium changes from stable to unstable. The disease free equilibrium point P_0 is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. So, at P_0 the system attains a bifurcation at $R_0 = 1$, which is called the backward bifurcation. At $R_0 = 1$, we have

$$\beta c\xi\left(p\theta vq + \varepsilon_1\sigma\left(\gamma_1 - a\gamma_1 + \delta + \eta_1 + \mu + a(\theta_1 q - \eta_1 - \mu)\right)\right) \qquad (3.1)$$

On substituting the values of the model parameters from table 1 in (3.1), we get $\beta = 0.0193$. Thus the equilibrium point P_0 is asymptotically stable if $\beta < 0.0193$ and P_0 is unstable if $\beta > 0.0193$. The study of the stability of the model (2.1) shows that P_1 is unstable when P_0 is asymptotically stable for $\beta < 0.0193$ and it is stable when $\beta > 0.0193$. Therefore, $\beta = 0.0193$ is the bifurcation value (refer figure 2 and 3).

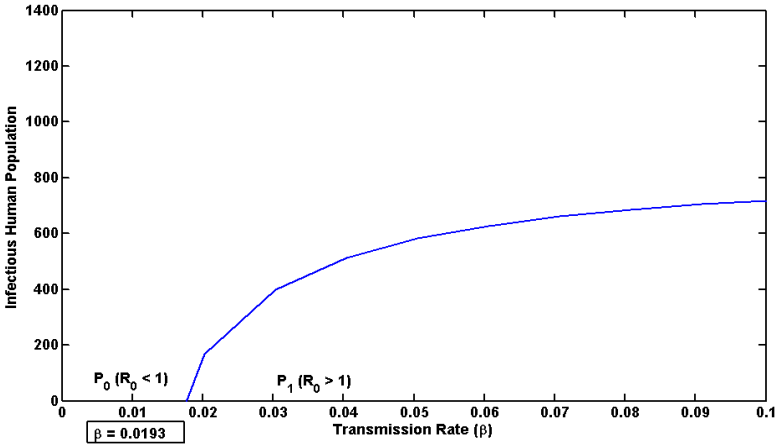

Figure 2: Bifurcation Diagram of COVID-19.

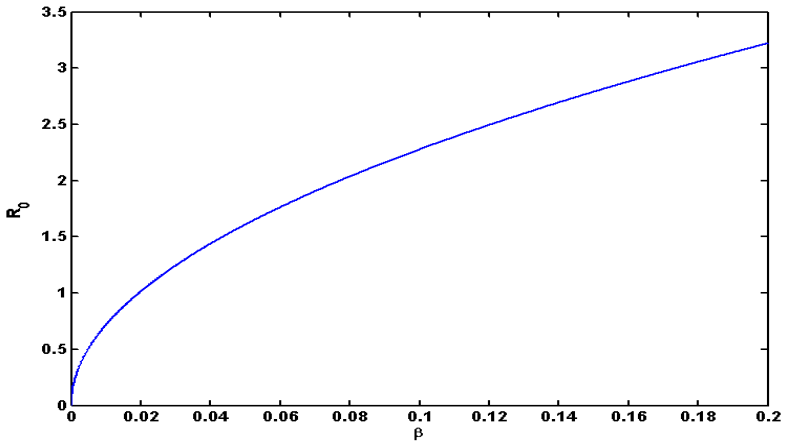

Figure 3: Change of basic reproduction number with respect to β.

D. Sensitivity Analysis

For sensitivity analysis we use the normalized sensitivity index [8], [9]. The normalized sensitivity index of variable R_0 that depends on parameter α is defined as

$$\gamma_{\alpha}^{R_0} = \frac{\partial R_0}{\partial \alpha} \times \frac{\alpha}{R_0}$$

We take $\alpha = \mu, c, \xi, \beta, \delta, \eta_1, \eta_2, \theta, \theta_1, \gamma_1, d_1, \varepsilon_1$

We evaluate the sensitivity indices at the baseline parameter values using definition as given in the table 1. The positive value of the sensitivity indices describes that prevalence of the disease increases with increases in parameter value. Here $\gamma_{\beta}^{R_0} = 0.5$ means increasing (or decreasing) the transmission probability by 10%, increases (or decreases) R_0 by 5%. The negative value of the sensitivity indices describes that prevalence of the disease decreases with increases in parameter value.

Here $\gamma_{\eta_1}^{R_0}$ =-0.0.006 means increasing (or decreasing) the value of $\eta_1$by 10%, decreases (or increases) R_0 by 0.06%. Table 2 shows that contact rate and probability of transmission rate is most positive sensitive parameters to the basic reproduction number among other parameters.

Table 2: Sensitivity Analysis of Model Parameters

S N	Parameters	Baseline Values	Sensitivity Indices
1	μ	0.000039	-0.00030
2	c	13.5	0.5
3	ξ	1/1.52	0.00029
4	β	0.036	0.5
5	δ	0.2	0.0099
6	η_1	0.31	-0.0059
7	η_2	0.7	0.0094
8	θ_1	0.87	0.0157
9	θ	0.72	0.4853
10	γ_1	1/12.5	-0.0015
11	d_1	0.055	0.00073
12	ε_1	0.1	-0.0015

III. NUMERICAL RESULT AND DISCUSSION

Simulation of the results is carried out to observe the effect of the parameters of the model on the transmission dynamics and spread of COVID-19. For the simulation, numerical values are used from table 2. Fig. 4 describes the population dynamics of exposed, infectious, hospitalized and recovered individuals in the transmission dynamics of COVID-19. With the decreasing population size of exposed individuals, the infectious population size increases. After the hospitals begin to confirm the COVID-19 cases and provide the supportive medical resources, the infectious population size starts decreasing because the infectious individuals move to the hospitals. The hospitalized population size increases initially due to the hospitalization of infectious individuals, the population decreases later due to the death and recovery from the disease (refer figure 4).

Figures 5 to 8 are showing the simulated analysis for the sensitivity of the model parameters in the system (2.1). These figures describe the dynamics of infectious population with different values of model parameters. The infectious population increases with increasing the value of the parameters c, β, ξ, δ, since these parameters have positive sensitivity indices (table 2).

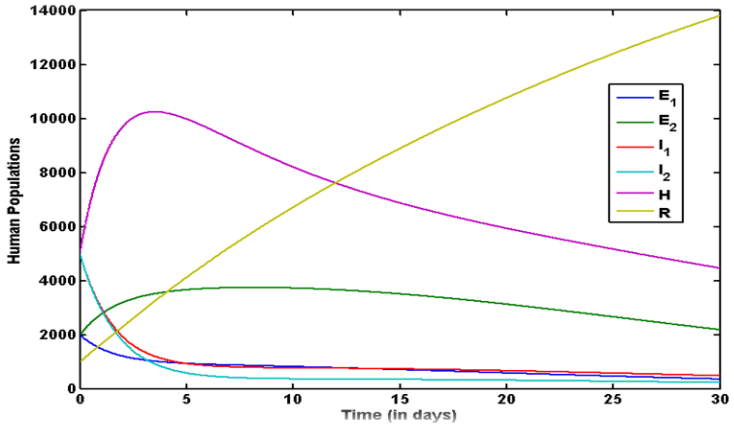

Figure 4: Human population of six states.

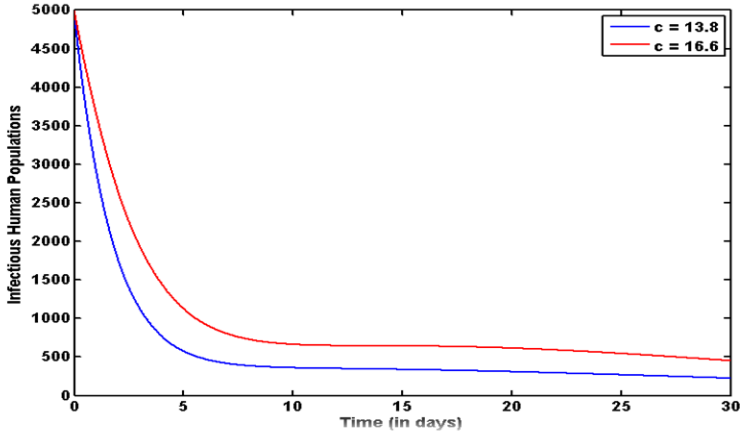

Figure 5: Effect of different value of contact rate on I_1.

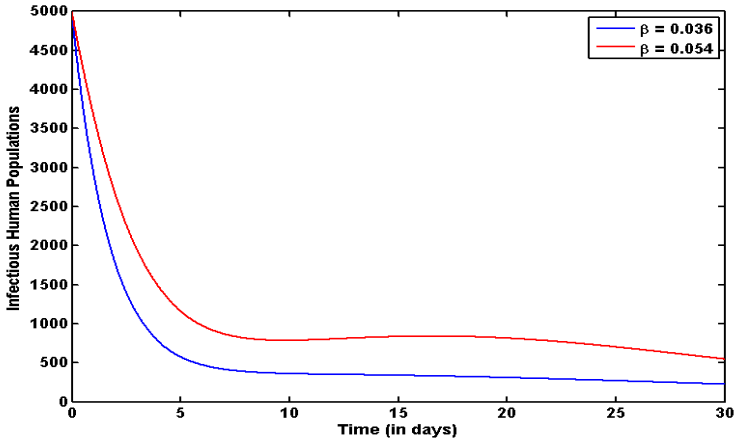

Figure 6: Effect of different value of β on I_1.

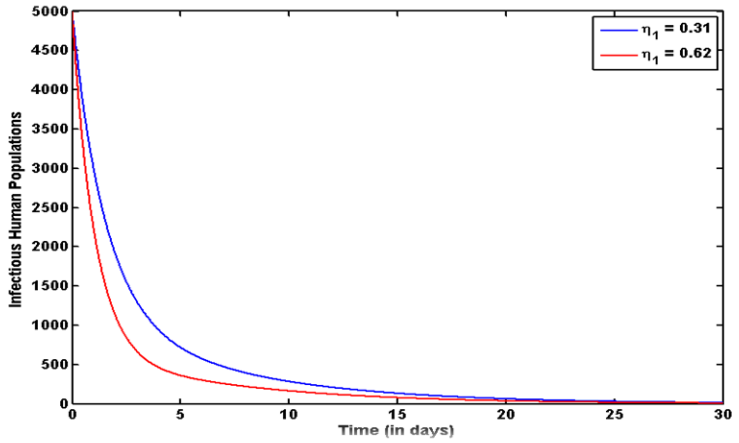

Figure 7: Effect of different value of η_1 on I_1.

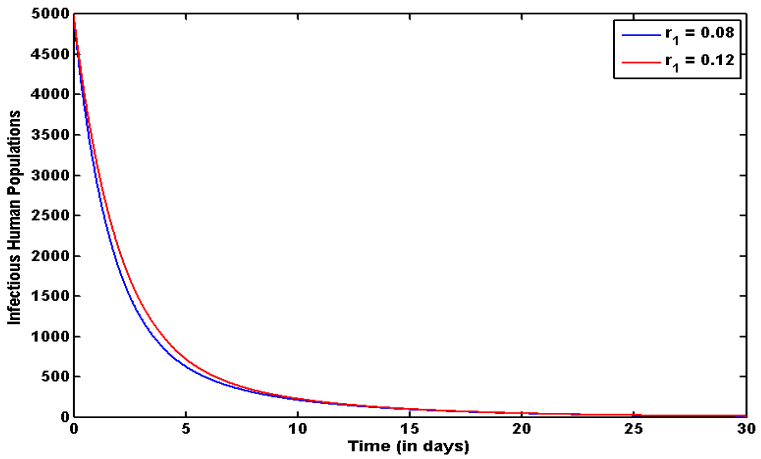

Figure 8: Effect of different value of γ_1 on I_1.

Since the parameters η_1, γ_1 have negative sensitivity indices, these parameters contribute to decrease the infectious population. Thus, the parameters with positive sensitivity index increase the infectious population and the parameters with negative sensitivity index decrease the infectious population. From table 2, c and β are the most positive parameters; and η_1 is the most negative sensitive parameter. So,

when c and β increase, the transmission of disease increases and when η_1 increases, the transmission of the disease decreases. Therefore, we can reduce the infection of the disease by controlling the contact rate and transmission rate of the disease.

IV. CONCLUSION

COVID-19 is currently significant issue in the world. In the present work, we have discussed the SEIHR model of COVID-19 taking pre-stage and post stage exposed classes; mild and serious infectious classes. We observed the system (2.1) has bifurcation near the disease free equilibrium point at the transmission rate β = 0.0193. We performed the sensitivity analysis to determine the sensitive model parameter in the transmission of COVID-19. We observed that contact rate c, transmission rate β and hospitalization rate η_1 most important sensitive model parameters. Increasing the contact rate and transmission rate of disease increases the infectious population and increasing the hospitalization rate of infected people, decrease the infectious population. Thus, we can decrease the prevalence of COVID-19 by increasing the hospitalization rate of infected people and decreasing the direct contact between the susceptible and infected individual. Therefore, our study suggests that to reduce the contact rate 'Lock Down' the city and minimize the transmission of disease, quarantine of infected individual are most important works for control the infectious disease COVID-19.

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