A Pivotal Restructuring of Modeling the Control of COVID-19 as Massive Vaccination is in Progress

by
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ABSTRACT

This paper presents a pivotal restructuring of modeling the control of COVID-19 even when massive vaccination is in progress. A new closed loop mathematical model to demonstrate how direct observations of the epidemiological compartments of population could be mapped to inputs, such that the social spread of the disease is asymptotically subdued. Mathematical details of the stabilization and robustness are included. A new engineered closed loop model is designed to control the spread of COVID-19 or its variants—that is, one input directly increases the time-rate of the compartment of population free of virus, F and the other input directly changes the time-rate of the susceptible compartment of population, S. Both inputs have collateral opposite influences on the time-rate of the infected compartment of population, I. The loop is closed around the new input-output model and designed so that the outputs reach the desired asymptotes. New surges of disease spread are not possible in appropriately designed stable closed loop models. However, extensive testing, contact tracing, and medical treatment of those found infected, must be maintained.

KEYWORDS: COVID-19, SARS-CoV-2, pandemic, social spread of disease, feedback control of corona virus, closed loop models, interventions for spread of corona virus, Batangas State University engineered closed loop model

1.0 Introduction and background

Starting with a very small outbreak of a coronavirus disease in Wuhan, China in December 2019, the World Health Organization (World Health Organization 2020a), on February 11, 2020, labeled the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the corresponding disease as Corona Virus Disease 2019 (COVID-19). By the same day, COVID-19 has grown to 43,103 confirmed cases world-wide, 42,708 in China, 395 in 24 other countries, 1,017 deaths in China, and one death for the rest of the world (World Health Organization 2020b). On March 11, 2020, WHO declared COVID-19 as a pandemic. By November 26, 2020, only 11 months since the outbreak in Wuhan, China, the pandemic has reached 59,816,510 confirmed cases and 1,410,378 deaths world-wide; 12,441,925 confirmed cases and 257,825 deaths in the United States; and 422,915 confirmed cases and 8,215 deaths in the Philippines (World Health Organization 2020c). There are other sources of data (Dong et al. 2020, C3ai DTI 2020a, C3ai DTI 2020b). As of December 1, 2020, there have been new surges of COVID-19 infection, for a variety of reasons, in many parts of the world, and the pandemic is still raging (Dong et al. 2020).

Several interventions have been employed to mitigate the exponential growth of COVID-19 such as quarantine or lockdown, wearing of masks, physical distancing, and frequent washing of hands. However, these interventions are unevenly practiced in some countries, and in many others, they are lifted soon after they "flatten the curve". Recently, several pharmaceutical companies have announced that vaccines will be available by the end of 2020. Initial availability would be limited to health care providers and other high-risk segments of the population. How should the vaccines be allocated? (Emmanuel et al. 2020). Allocations can be optimized (Sy et al. 2020). Each political jurisdiction will decide on prioritization and optimization. Some pharmaceutical companies have announced receiving Emergency Use Authorizations to have vaccines become available by the middle of 2021. These companies are still investigating the duration of efficacy of the vaccines. For the near term, there is a need to continue the interventions, or innovative ways to modify the interventions so they will become more effective, as we plan for vaccinating a large fraction of a population.
For some countries it will take several years to complete massive vaccinations. If the effectivity period for vaccines is about a year, massive vaccination will be needed for the foreseeable future with no end in sight. Current models in use today are still coping with large surges of disease spread and death. In this paper a shift in the structure of the control of coronoa virus is presented

2.0 Science models of disease spread

The first mathematical model to describe the spread of a disease was published in 1927 (Kermack and McKendrick 1927). The basic idea in the model is to divide the population into epidemiological compartments. In the Kermack and McKendrick model, the compartments of population N are: Susceptible (S), Infected (I), and Removed (R). The rates of change with respect to time of $S, I,$ and R, are modeled as functions of $S, I,$ and R, respectively. This model has been adopted for modeling the spread of COVID-19, with several layers of sub-societies, and each layer with more compartments beyond $S, I,$ and R, such as Exposed (E), Hospitalized (H), and further subdivision of I into Symptomatic and Asymptomatic (Chen et al. 2020). Others have further analyzed the Wuhan outbreak (Kucharski et al. 2020, Ndairou et al. 2020, Saad-Roy et al. 2020, Britton et al. 2020). SARS-CoV-2 is known to mutate, and mutation of viruses during propagation has been studied (Eletreby et al. 2019). There are updates available for the progression of COVID-19 (World Health Organization 2020c) including a science model with the updates (Dong et al. 2020). The effect of virus mutation, on therapeutics for COVID-19, has been studied also (Hou et al. 2020), and it appears that the mutation D614G propagates faster than the original SARS-CoV-2. They state that "current vaccine approaches directed against the WT (wild-type) spike should be effective against the D614G strains." (Hou et al. 2020).
In the only paradigm in use today, interventions are deployed to change the environment, resulting in changing direction of observations, and subsequent revised mathematical models. When the interventions are relaxed or removed altogether, subsequent observations will show that the disease spread will increase exponentially and the process repeats.
The main purpose of this paper is to provide a new engineered closed loop model for stabilizing systems such as a model for the social spread of disease. As in existing science models, the engineered closed loop model in this paper addresses the macro-scale level of modeling the spread of a disease, not necessarily COVID-19. The simplest science model is considered to modify into an engineered closed loop feedback system to focus on the advantages of closed loop models.

2.1 SIR science model

The starting point in the development of an engineered closed loop model with feedback of observation in Section 3 is the Kermack and McKendrick model (1927). Figure 1 shows a diagram of the Science Model. There are three differential equations but only two are independent because of the constraint $S + I + R = N$, where S = Susceptible, I = Infected, R = Removed and N = Population.

Normalizing the compartments of N, $s = \frac{S}{N}$, $i = \frac{I}{N}$, $r = \frac{R}{N}$, the constraint becomes $s + i + r = 1$. The rate of change with respect to time of s and the rate of change of r with respect to time are the postulated models

$$\frac{ds}{dt} = -\beta si \tag{1}$$

$$\frac{dr}{dt} = \gamma i \tag{2}$$

where β is the infectivity rate and γ is the recovery rate.

The rate of change of i with respect to time follows from the constraint,

$$\frac{ds}{dt} + \frac{di}{dt} + \frac{dr}{dt} = 0 \tag{3}$$

$$\frac{di}{dt} = \beta si - \gamma i \tag{4}$$

2.2 Modifying the SIR science model to the SIFD science model

The compartment R is divided into two sub-compartments, F and D, where F is the number of persons that are Free of Virus but possessing antibodies, and D is the number of persons that are Deceased. As in the SIR model, $S, I, F,$ and D, respectively, are normalized by dividing each by N, yielding

$$s + i + f + d = 1 \tag{5}$$

Figure 1 still represents the science model. The rate equations for $s, f,$ and d, respectively, are the proposed behavioral postulates as in (Kermack and McKendrick 1927)

$$\frac{ds}{dt} = -\beta si \tag{6}$$

$$\frac{df}{dt} = \gamma(1-\delta)i \tag{7}$$

$$\frac{dd}{dt} = \gamma\delta i \tag{8}$$

.

The rate equation for i is obtained from the constraint:

$$\frac{ds}{dt} + \frac{di}{dt} + \frac{df}{dt} + \frac{dd}{dt} = 0. \tag{9}$$

yielding Equation (4).

Observations are used to calibrate the parameters $\beta, \gamma,$ and δ. Analysis of the mathematical models leads to obtaining conditions that cause exponential growth, suggesting how instability can be avoided. A typical intervention in science models is to change the environment, such as modification in the use of (a) quarantine or lock down, (b) face masks, (c) physical distancing, and (d) contact tracing. These modifications in interventions can change the calibrated values of $\beta, \gamma,$ and δ so that stability can be achieved, after several cycles of modifications in the environment. It should be noted that the modifications in environment are carried out first and then the science model is constructed. However, experimental assessment of the effectiveness of the model is carried out after it is constructed.

3.0 Transition from science model to Batangas State University engineered closed loop model

There are two steps in the transition. The first step is to create inputs to the science model. The second step is to construct a mapping from the outputs to the inputs of the science model.

3.1 Creating the Batangas State University input-output model

The first step in the transition from a science model to an engineered model is to create inputs to the science model as indicated in Figure 2. There are intrinsic benefits to creating models with inputs and outputs (Tan et al. 2018). In this paper we create two inputs to the SIFD science model.

As in the science model without inputs, the rate equations, for $s, f,$ and d, are postulated. The rate equation for i is derived from the constraint in Equation (9) where the quantities z_1 and z_2 are inputs.

$$\frac{ds}{dt} = -\beta si + z_1 \tag{10}$$

$$\frac{di}{dt} = \beta si - \gamma i - z_1 - z_2 \tag{11}$$

$$\frac{df}{dt} = \gamma(1 - \delta)i + z_2 \tag{12}$$

and Equation (8).

The input z_1, when scaled up to z_1*N, is the number of persons per day that we plan to change the decrease in the susceptible rate S per day by. It has a simultaneous partial effect of opposite change in the infected I per day.

The input z_2 when scaled up to z_2*N is the additional increase in the number of persons per day that are free of virus and have antibodies in them, F per day. It has a simultaneous partial effect of reducing the infected I per day.

The Batangas State University input-output model is dynamic and nonlinear.

3.2 Closing the loop

Figure 3 shows the diagram of the closed loop system. The design of the two inputs of the Batangas State University input-output model in two-stages. The input z_1 is divided into two parts:

$$z_1 = z_{1N} + z_{1L} \tag{13}$$

The value of β in the science model is usually uncertain or variable but B_a is chosen to match a specific value, β^*. In the simulations, it is assumed that there are four different values of β: 0.05, 0.15, 0.20, and 0.25. Choosing $B_a = \beta^* = 0.15$ and $z_{1N} = B_a si$, the engineered model for $\beta = \beta^*$ becomes linear as indicated in Equations (8), (14), (15), (16)

$$\frac{ds}{dt} = z_{1L} \tag{14}$$

$$\frac{di}{dt} = -\gamma i - z_{1L} - z_2 \tag{15}$$

$$\frac{df}{dt} = \gamma(1-\delta)i + z_2. \tag{16}$$

The quantities s, i, f, and d are represented by $s = s_d + \Delta s, i = i_d + \Delta i, f = f_d + \Delta f$, and $d = d_d + \Delta d$. The quantities s_d, i_d, f_d, and d_d are desired constant asymptotes where i_d is always set equal to 0.

The first three linear differential equations can be written in matrix form as

$$\begin{bmatrix} \frac{d\Delta s}{dt} \\ \frac{d\Delta i}{dt} \\ \frac{d\Delta f}{dt} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -\gamma & 0 \\ 0 & \gamma(1-\delta) & 0 \end{bmatrix} \begin{bmatrix} \Delta s \\ \Delta i \\ \Delta f \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ -1 & -1 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} z_{1L} \\ z_2 \end{bmatrix} \tag{17}$$

$$A = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -\gamma & 0 \\ 0 & \gamma(1-\delta) & 0 \end{bmatrix} \tag{18}$$

$$B = \begin{bmatrix} 1 & 0 \\ -1 & -1 \\ 0 & 1 \end{bmatrix} \tag{19}$$

It can be readily verified that any value of the state is reachable and (A, B) is controllable (Åström and Murray 2020). Denoting the vector input by

$$\begin{bmatrix} z_{1L} \\ z_2 \end{bmatrix} = -K \begin{bmatrix} \Delta s \\ \Delta i \\ \Delta f \end{bmatrix} \tag{20}$$

where

$$K = \begin{bmatrix} k_1 & k_2 & k_3 \\ k_4 & k_5 & k_6 \end{bmatrix}. \tag{21}$$

The three eigenvalues of $A - BK$ can be specified arbitrarily. In particular, the eigenvalues can be set to be real and negative.

The three eigenvalues are chosen as $\lambda \approx -0, \lambda = -0.05, \lambda = -0.05$, the parameter $B_a = 0.15$ and the six coefficients in the matrix K as stated earlier. For simulation, the values for β are: 0.05, 0.15, 0.20, and 0.25.

The matrix, K, is calculated in MATLAB Control Toolbox using the command

K = place(A,B,p). (22)

Within a certain range of values of β, the final structure of the Batangas State University engineered nonlinear closed loop model equations are

$$\frac{d\Delta s}{dt} = -(\beta - B_a)(s_d\Delta i + \Delta s\Delta i) - k_1\Delta s - k_2\Delta i - k_3\Delta f \tag{23}$$

$$\frac{d\Delta i}{dt} = (\beta - B_a)(s_d\Delta i + \Delta s\Delta i) - \gamma\Delta i + k_1\Delta s + k_2\Delta i + k_3\Delta f + k_4\Delta s + k_5\Delta i + k_6\Delta f \tag{24}$$

$$\frac{d\Delta s}{dt} = -(\beta - B_a)(s_d\Delta i + \Delta s\Delta i) - k_1\Delta s - k_2\Delta i - k_3\Delta f$$
$$\frac{d\Delta f}{dt} = \gamma(1-\delta)\Delta i - k_4\Delta s - k_5\Delta i - k_6\Delta f \tag{25}$$

$$\frac{d\Delta d}{dt} = \gamma\delta\Delta i. \tag{26}$$

3.2.1 Setting the target asymptotic values and initial conditions

Using the Philippine population: 109,581,078 and data from the Philippine Department of Health, I_0 = 28,789, D_0 = 8,242, F_0 =387,266, as of November 26, 2020 (COVID 19 Update 2020) and the constraint: $s_0 + i_0 + f_0 + d_0 = 1$. Initial values: $s_0 = 0.9961$, $i_0 = 2.6272 \times 10^{-4}$, $f_0 = 0.0035$, $d_0 = 7.5214 \times 10^{-5}$. The initial values for $\Delta s, \Delta i, \Delta f,$ and Δd are $s_0 - s_d$, i_0, $f_0 - f_d, d_0 - d_d$, respectively.

Note that the constraint is given by $s_d + f_d + d_d = 1$. If vaccines are available, set f_d to be quite high, for example $f_d = 0.6$. Set $d_d > d_0$, $d_d = 6.32 \times 10^{-5}$. Thus, $s_d = 0.4 - 6.32 \times 10^{-5} = 0.3999368$.

3.3. Simulations

Figures 4, 5, 6, and 7 show plots of I, D, S, and F, at different scales. In Figures 4, 6, and 7, for plots of $S, F,$ and D, respectively, it is not possible to visually distinguish the curves for four different values of β, displaying not only stability, but also robustness as well. In Figure 5, the plot of the infected compartment of Philippine population, I, shows the four predictions for different values of β. Note that the scale of I is in thousands. The scale of the plot for D is also in thousands. Thus, D and I hardly affect S and F because $S + I + F + D = N$, where $S, F,$ and N are in the millions.

In Figure 8, notice that when $\beta = 0.25$, the maximum value of I is 2.3 million out of 108 million population compared with the corresponding maximum value of 5,400 using the closed loop model as shown in Figure 5. For the other values of β, the values of I in Figure 8 are still very much larger than the ones in Figure 5, using a closed loop model.

3.4 Stabilization and robustness properties of Batangas State University engineered closed loop model

The principal advantage of utilizing a closed loop model that includes a feedback mechanism for mapping the output to the input of the systems is the possibility of stabilization (Cruz 1971, Åström and Murray 2020, Åström and Kumar 2014). The Batangas State University engineered closed loop model is designed to be stable. Simulations show that the model remains stable for a range of values of β. Furthermore, the simulations show that the outputs are robust against

variations in the value of β (Cruz and Perkins 1964, Cruz et al. 1981a, Cruz et al. 1981b, Freudenberg et al. 1982).

4.0 Comparison of interventions in science models and engineered closed loop models

4.1 Science models

The prevailing method for the study of disease propagation, such as the spread of COVID-19 is through the construction of mathematical models. Typically, these models consist of sets of differential equations with parameters that are chosen so that computer simulations using the models would show results that closely approximate of real observations. If the observations indicate that the disease keeps growing, the model can be helpful in identifying what environmental conditions influence the growth. For example, the mathematical model could determine that some transmissivity parameters might have values that are too high, and interventions such as increased isolation of infected persons or increased use of face masks are warranted. With the interventions, as suggested by the model, new observations might indicate that growth has stopped or even reversed, and revised models would show that the new situations are stable. If the interventions are removed, there might be resurgence of growth in the spread of the disease. If the fixed intervention is not removed, it would be maintained at the latest level until a resurgence occurs for whatever reason. Note that the latest model is obtained after the latest change in the environment. However, experimental assessment of the effectiveness of the latest model is conducted after it is constructed.

4.2 Engineered closed loop models

The principal reason for using an engineered closed loop mathematical model, that adds a feedback mechanism of measured epidemiological compartments of population, to construct the inputs of the input-output model, is to provide a capability to stabilize the composite model (Åström and Murray 2020, Cruz 1971). Parameters of the input-output model are determined as in Section 4.1, using observations without feedback. However, experimental assessment of the effectiveness of the closed loop model cannot be accomplished until the processes of the closed loop model are in place. This is the same situation as in the science model because the effectiveness of the most recent science model can only be assessed after new observations are made and compared with the predicted outputs of the science model. Thus, policy makers need to allow that the interventions be modulated in accordance with the process of the closed loop model. As in the science model, new observations can be gathered to verify if the computer calculations of the closed loop model are reasonable approximations of new real observations. One major capability of using a closed loop model is that even if the input-output model is unstable, potentially, the entire system with feedback can be stable. When the closed loop model is designed to be stable, then the epidemiological compartments of population would tend to the designed asymptotic values, but the closed loop structure needs to be in place indefinitely. Testing will remain and if there is occasional infection, the infected persons will receive medical treatment, as appropriate, and contact tracing will be conducted. A second advantage of using a closed loop model is that it can be robust against variations in the parameters, such as the infectivity rate, β (Cruz and Perkins 1964, Cruz et al. 1981a, Cruz et al. 1981b, Freudenberg et al. 1982).

4.3 Other closed loop models

The only closed loop model in the literature was proposed by a team from the University of Montreal (Stewart et al. 2020). They used an input-output model proposed by the University of Notre Dame (Kantor 2020).

4.3.1 Notre Dame University input-output model

The University of Notre Dame model (Kantor 2020) added an input to the Kermack and McKendrick SIR Science Model (Kermack and McKendrick 1927). A control input u is introduced by multiplying β by *(1-u)* in the science model

$$\frac{ds}{dt} = -(1-u)\beta si \tag{27}$$

$$\frac{di}{dt} = (1-u)\beta si - \gamma i \tag{28}$$

together with Equation (2).

In Kantor (2020), simulations were performed for various fixed values of u, where $0 < u < 1$, to demonstrate mitigation of the propagation of COVID-19.

4.3.2 University of Montreal closed loop model

A University of Montreal team (Stewart et al. 2020) took the University of Notre Dame model and used the control input u to propose a closed loop function of the number of hospital beds available in a city. Several scenarios were discussed, including use of alternating fixed and output-dependent interventions. Their goal was to use feedback control to stabilize the system. However, the paper does not provide details of how the number of available hospital beds is related to the state variables of the model. No details are provided in the paper as to what the mathematical expression of the control u is, and no details are provided as to how their chosen u stabilizes the system.

4.3.3 Comparing the Notre Dame/Montreal model with the Batangas State University engineered closed loop model

The Notre Dame model introduced a multiplier $(1-u)$ wherever β appears. It has the conceptual effect of reducing the value of β, very similar to the science model of changing the environment to alter the value of β. In the Montreal closed loop model, their team proposed to use u of the Notre Dame model as a feedback function of the available hospital beds. The ultimate impact of this feedback function on stability would be quite complicated, without having a detailed analysis, not available in the literature. The Batangas State engineered closed loop model introduces the intervention at a broader level, without committing to reducing the value of β. The inputs z_1 and z_2 directly influence the rate of change of s, i, and f. Furthermore, the input z_2 implies utilizing vaccination, without increasing the infected compartment. This paper is the first to incorporate the effect of vaccination on input-output modeling of the spread of a disease. Furthermore, this paper is first to consider the use of a vaccine in a closed loop model incorporating a feedback mechanism to relate observations of epidemiological compartments of population, to the two modulated inputs or interventions.

5.0 Concluding remarks

The major contribution of this paper was the design of the Batangas State University engineered closed loop model that utilizes the outputs in tempering the inputs to control the spread of COVID-19. The model was demonstrated to be stable and robust against variations in the values of transmissivity, β. The Batangas State University engineered closed loop model

introduced an input (z_2) utilizing feedback, that led to a substantial increase in the number of epidemiological compartment of population that is Free of virus (F), without significant increase in the number of Infected (I). Even when the spread is reduced to almost zero, testing, contact tracing, and medical treatment of those tested positive, must continue as part of the closed loop process, to avoid new surges of infection, and further reduce mortality.

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Figure 1. Science model showing outputs or observations

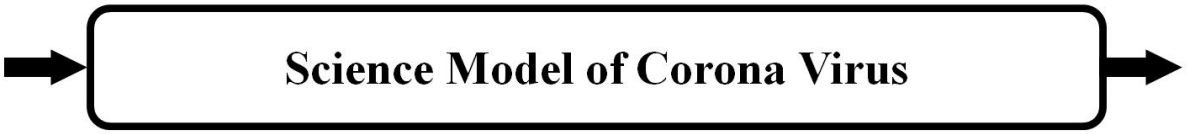

Figure 2. Creating an input-output model by adding inputs to the science model

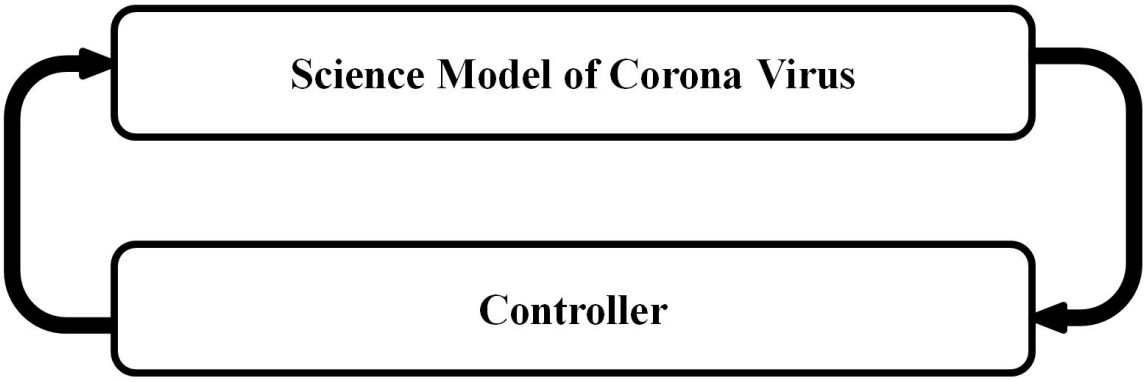

Figure 3. Mapping the outputs or observations to the inputs via a controller

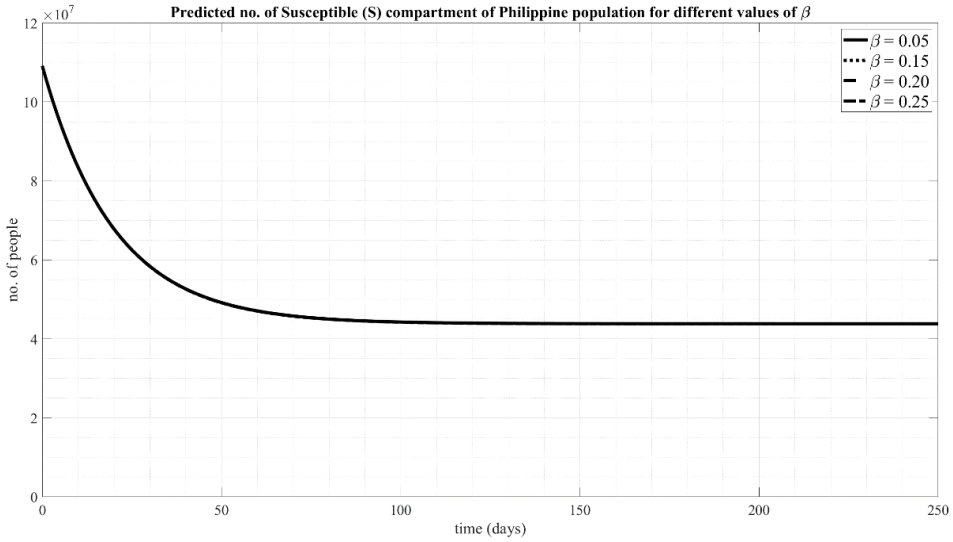

Figure 4. Predicted number of Susceptible (S) compartment of Philippine population for different values of β

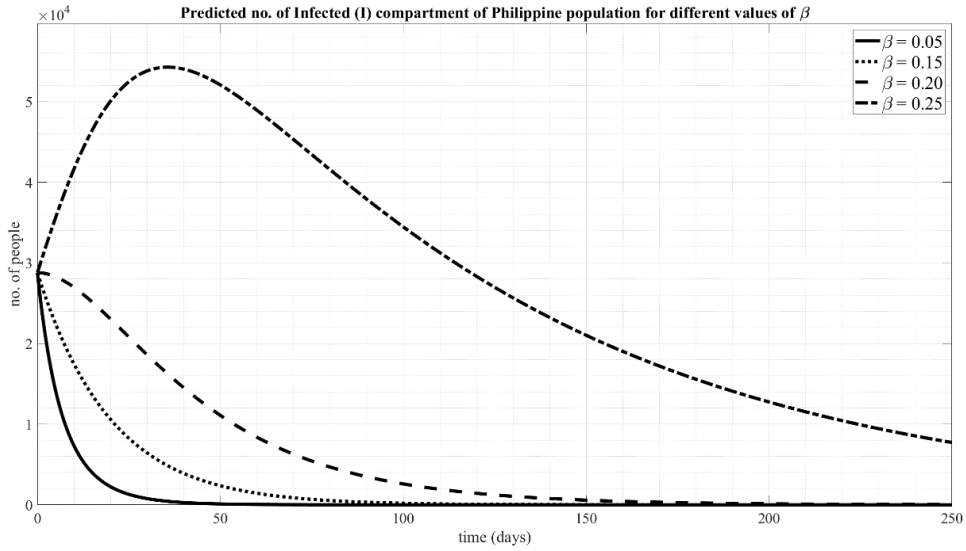

Figure 5. Predicted number of Infected (I) compartment of Philippine population for different values of β

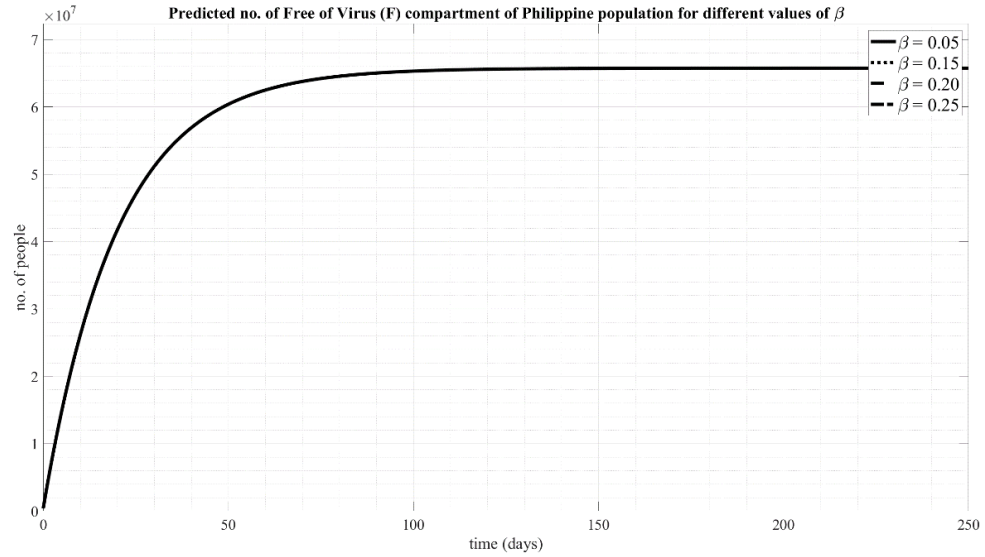

Figure 6. Predicted number of Free of Virus (F) compartment of Philippine population for different values of β

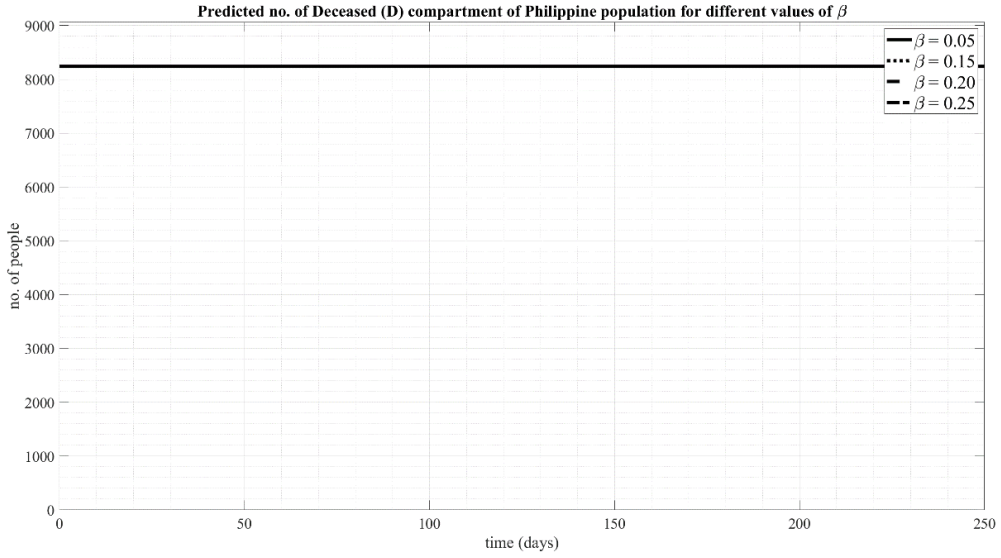

Figure 7. Predicted number of Deceased (D) compartment of Philippine population for different values of β

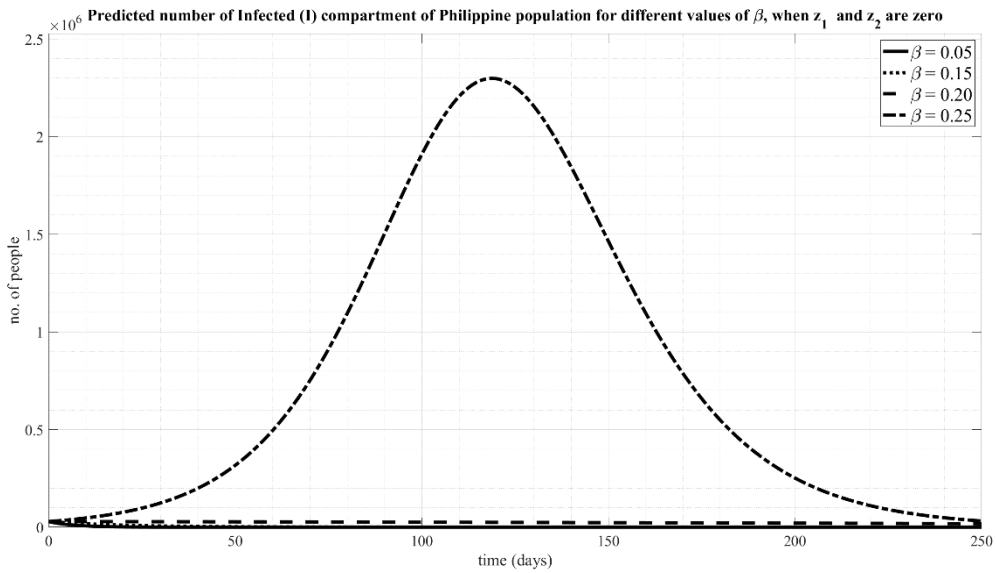

Figure 8. Predicted number of Infected (I) compartment of Philippine population for different values of β, when z_1 and z_2 are zero

Disclosure: There are no potential conflicts of interest.