Mathematical modeling of viral infection dynamics and immune response in SARS-CoV-2: A computational framework for testing drug efficacy

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Abstract—SARS-CoV-2 has emerged to cause the outbreak of COVID-19, which has expanded into a worldwide human pandemic. Although detailed experimental data on animal experiments would provide insight into drug efficacy, the scientists involved in these experiments would be exposed to severe risks. In this context, we propose a computational framework for studying infection dynamics that can be used to capture the growth rate of viral replication and lung epithelial cell in presence of SARS-CoV-2. Specifically, we formulate the model consisting of a system of non-linear ODEs that can be used for visualizing the infection dynamics in a cell population considering the role of T cells and Macrophages. The major contribution of the proposed simulation method is to utilize the infection progression model in testing the efficacy of the drugs having various mechanisms and analyzing the effect of time of drug administration on virus clearance.

Clinical Relevance—The proposed computational framework incorporates viral infection dynamics and role of immune response in Covid-19 that can be used to test the impact of drug efficacy and time of drug administration on infection mitigation.

I. INTRODUCTION

In December 2019, a serious outbreak occurred in China due to coronavirus, which is named as the novel COVID-19. The novel COVID-19, which caused this infection belongs to the family of SARS, a Severe Acute Respiratory Syndrome (SARS-CoV) [1]. The SARS-CoV-2 exponentially expanded across the globe into a human pandemic. Patients with severe infection suffer from acute respiratory distress, resulting in multiple organ failures and fatality.

Coronaviruses are enveloped positive-stranded RNA viruses, and generally infect the epithelial cells in the respiratory and gastrointestinal tract. COVID-19 is a highly contagious disease indicating the need for widespread vaccination. In the absence of any effective drug with an unknown epidemiological life cycle, mathematical models are crucial for studying various pathophysiological processes and immunological responses of real-world problems. By using mathematical models for these processes, information on drug efficacy can be obtained [2], [3].

In this context, we plan to build a computational framework for visualizing SARS-CoV-2 infection dynamics in presence of immune response and analyzing the effect of drug efficacy on virus clearance (Figure 1). To achieve this, an ODE model was developed which was validated from the experimental data collected on growth of SARS-CoV-2 from throat swab samples [4]. Additionally, the model includes the response of adaptive and innate immune system, which was validated using bronchoalveolar lavage fluid (BALF) sample obtained from patients with moderate and severe COVID-19 infections [5].

The existing mathematical models for viral infection are mostly target-cell limited models that have been developed to understand the mechanism of viral infection inside the host cells [2], [3], [6]. These model variables generally include: uninfected target cells, which in the case of SARS-CoV-2 infection is the lung epithelial cells, infected target cells, which are capable of producing virus particles and the virus particle itself. None of the previous models incorporate the dynamics of T cells and macrophages in regulation of the infection progression.

In order to identify the contribution of T cells and Macrophages, firstly, we formulate and compare two models where model 1 (EIVT mode) considers E, representing uninfected epithelial cells, I representing infected epithelial cells, V representing virus and T representing T cells. Whereas model 2 (EIVTM model) consists of a fifth entity M, representing the macrophages along with the variables considered in EIVT model. Secondly, parameter estimation was performed using sequential quadratic programming

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algorithm using real patient data. Finally, the model framework was used to test the impact of drugs having mechanisms targeting infection rate, viral production and viral clearance. The infection mitigation by addition of drug at different time post-infection was investigated. The major novelty of the current work is the development of a computational framework incorporating viral infection progression and role of immune response in Covid-19 with an aim of testing the effect of drugs having various mechanisms and efficiencies on infection mitigation.

II. MATERIALS AND METHODS

A. Mathematical models

In this work, we construct a set of mathematical models to understand the dynamics of SARS-CoV-2 infection by introducing the effect of innate and adaptive immune system in response to SARS-CoV-2 infection, in the target cell limited model. First, we combined the target cell limited model [6] along with the minimalistic model for virus and T cell [3] interaction to obtain a model structure. The structure considering only adaptive immune response consists of four variables: uninfected epithelial cells (Epitheliali), infected epithelial cells (Epitheliali), virus and T cells (Tcell), dynamics for which is shown below (EIYTV model):

\[
\frac{d[\text{Epitheliali}]}{dt} = -\beta[\text{Epitheliali}][\text{Virus}] \quad (1)
\]

\[
\frac{d[\text{Virus}]}{dt} = \beta[\text{Epitheliali}][\text{Virus}] - \delta[\text{Epitheliali}] \quad (2)
\]

\[
\frac{d[\text{Tcell}]}{dt} = p[\text{Epitheliali}] \left[1 - \frac{\text{Virus}}{K}\right] - cT[\text{Virus}][\text{Tcell}] - e[\text{Virus}] \quad (3)
\]

\[
\frac{d[\text{Virus}]}{dt} = sT + r[\text{Tcell}] \frac{(\text{Virus})^m}{k^m + (\text{Virus})^m} - \mu_T[\text{Tcell}] \quad (4)
\]

Here, the rate of virus infection into the uninfected epithelial is represented by \( \beta \). The rate at which the uninfected cells get infected represents the rate of formation of infected cells. The infected cells are eliminated with a rate \( \delta \). The virus growth is represented using a logistic growth function, where \( p \) represents the rate of virus production from the infected cells and \( K \) is the maximum carrying capacity of the virus or the maximum viral load specific for any individual. \( c_T \) represents the virus clearance rate due to presence of T cells. The natural death of the virus is modelled using a log linear function while the T cell is modelled as in Esteban et al. [3].

Secondly, to identify the role of innate immune system on the virus dynamics, a new ODE for the macrophage has been introduced to the previous set (EIYTV model) as:

\[
\frac{d[\text{Macrophage}]}{dt} = s_M + \frac{k_M[\text{Tcell}]}{k_M + \text{Tcell}} - \mu_M[\text{Macrophage}] \quad (5)
\]

Here, macrophage homoeostasis is modelled as \( s_M \) and activation rate of macrophages is represented as a function of T cells. It is because the cytokines released by T cell stimulate the macrophages [7] which in turn engulf the virus particle. Due to the presence of macrophages, the virus dynamics then changes to:

\[
\frac{d[\text{Virus}]}{dt} = p[\text{Epitheliali}] \left[1 - \frac{\text{Virus}}{K}\right] - [\text{Virus}](c_T[\text{Tcell}] + c_M[\text{Macrophage}]) - e[\text{Virus}] \quad (6)
\]

Here, an additional term has been added to represent the virus clearance rate (\( c_M \)) due to presence of Macrophages. The model was further tuned to obtain the severe and moderate virus infection cases by varying the parameters corresponding to virus infection (\( \beta \)), death rate of infected cells (\( \delta \)), maximum carrying capacity of virus (\( K \)) and kill rate due to T cells (\( c_T \)).

The parameters were selected based on a parameter estimation strategy to match the viral kinetics in the Covid-19 patients reported in Wolfel et al. [4]. The clinical data presented in Wolfel et al. [4] was used for the model validation. The data consists of the time course of viral load collected from nine patients from a single hospital in Munich, Germany (Jan 2020). The viral load data is reported in copies/ml per whole swab. To further validate the model, BALF sample data reported in Liao et al. [5], was used. BALF is a useful medical procedure used for diagnosing the lung pathologies. The data on immune cells was obtained from BALF of moderate and severe Covid-19 patients from Shenzhen Third people Hospital in China (Jan –Feb 2020).

B. Parameter Estimation

A set of coupled ordinary differential equations initial value problems (ODE-IVPs) was solved using fourth-order Runge-Kutta scheme using MATLAB ODE solver ODE45. Minimization of the root mean square error (RMSE) between the experimental and simulated data was performed for estimating kinetic parameters using the sequential quadratic programming algorithm in the MATLAB optimizer fmincon. To achieve this, a non-linear programming (NLP) problem with the RMSE function as the objective function (as described in Eq. 7), where N is the number of sample points (clinical data) available, Exp_i and Sim_i signify the i_th experimental and simulated data point obtained from the model, respectively. The rate constants were set as the decision variables. The parameter set giving the lowest RMSE was finally chosen.

\[
\text{RMSE} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\text{Exp}_i - \text{Sim}_i)^2} \quad (7)
\]

C. Parametric Sensitivity analysis and Simulation of antiviral drug efficacy

In order to assess the parameters which significantly affect the progression of viral infection in case of SARS-CoV-2 infection, a parametric sensitivity analysis was performed. Figure 2 shows the percent variation in viral dynamics obtained when parameters were varied in \( \pm 20\% \) range of their base values one at a time.

The analysis shows that viral growth is highly sensitive to the parameters representing infection rate and production rate in the initial growth phase. Also, viral growth is highly sensitive to the clearance/death rate in the later time points. These three parameters were then chosen as antiviral drug targets. To study the effect of antiviral drug the model was extended by multiplying the potential drug target parameters (\( \beta, p \) and \( c \)) one at a time with a factor (1-\( \epsilon \)) where \( 0<\epsilon<1 \), which determined the drug efficiency (a value of 1 implies 100% drug efficacy). The simulations were performed for varying drug efficacy (\( \epsilon \)) and also the time of drug introduction. A ratio of time-averaged virus concentration was calculated as follows:
\[ \lambda = \frac{\langle V(t)_{T>0} \rangle}{\langle V(t)_{T=0} \rangle} \]  

(8) 

Where, the time averaged viral load is given by:

\[ \langle V(t)_{T} \rangle = \frac{1}{\Delta t} \int_{T}^{T+\Delta t} dt V(t) \]

In Eq. 8, numerator is the time averaged viral load with drug administration \((\varepsilon > 0)\), and the denominator is the time averaged viral load without drug administration \((\varepsilon = 0)\), till 10th day from the starting of drug.

\( T \) refers to the time (in days) post infection, when drug is administered \((T < t < T+\Delta t)\), where \(\Delta t = 10\).

### III. RESULTS

Two models (EIVT and EIVTM) were compared with respect to the virus growth profile. Figure 3a shows the time profiles of uninfected cells, infected cells and virus when only adaptive (T cell) immunity is considered (EIVT model) and Figure 3b shows the similar time profile when both adaptive (T cell) and innate (Macrophages) immunity is considered (EIVTM model). To study the effect of presence of Macrophages all other parameters with respect to other variables have been kept same in both the cases. The results show that the severity of viral infection decreases when both immune system act in clearing the viral infection.

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**Figure 2. Parametric sensitivity analysis showing percentage variation in virus count with respect to time for (a) +20% variation in parameters (b) -20% variation in parameters**

**Figure 3. Time course of uninfected epithelial cells, infected epithelial cells and virus when (a) only T cell dynamics is incorporated (EIVT model) (b) both T cell and macrophage dynamics is incorporated (EIVTM model).**

**Figure 4. Comparison of time course of virus profile for clinical and simulated data obtained from EIVT and EIVTM model for (a) Patient A data and (b) Patient B data.**

The comparison between the experimental and simulated data from the two models are presented in Figure 4. Since there is a variability in responses within the patients, we performed parameter estimation for multiple patients. For two representative patients’ data, we found that RMSE obtained for patient A (Figure 4a) from EIVT model was four times higher than that obtained from EIVTM model. Whereas, RMSE obtained for patient B (Figure 4b) from EIVT model was two times higher than that obtained from EIVTM model. Thus, in both the cases EIVTM model provided a better fit as compared to EIVT model.

Next we validated our model using the patient data on ratio of macrophage to T cell obtained from the BALF sample analysis corresponding to healthy case, mild infection case and severe infection case [5]. Figure 5 shows the comparison of the ratio of Macrophage to T cell from experiment and simulation. The result shows that the model is capable of emulating the experimental data for mild and severe cases, where healthy case is considered as model initial condition.

In order to show a proof of concept that the model can be used for assessment of drug efficacy in clearing the viral infection, the model simulations were performed by varying drug efficiency and time of drug administration (Figure 6). Figures 6a, 6b and 6c show viral growth profiles obtained by varying drug efficiency starting from 0 to 100% for the parameters \(\beta, p, c\). The results show that a complete virus removal can be achieved if a 100% effective drug for blocking either infection rate or virus production rate is administered.

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**Figure 5. Comparison of ratio of Macrophage to T cell as obtained from the BALF sample analysis of healthy, mild and severe patients with the ratio of Macrophage to T cell obtained from the EIVTM model at peak virus infection.**
Specifically, this model was used for testing the effect of drug administration time post infection. Figures 6d, 6e and 6f show three cases: drug administration from 4th, 8th and 12th day post infection, respectively with varying drug efficiency for the parameters $\beta$, $p$ and $c$. The result shows that even if virus clearance is obtained using a 100% effective drug (drug 3), administered from 4 days after infection, only upto 60% virus removal can be achieved (Figure 6f). In contrast, 100% infection removal can be achieved by administering drugs targeting the infection rate (drug 1) or virus production rate (drug 2) in the early infection phase (Figure 6d and 6e). If administered at the very late phase (12th day), it is possible to achieve upto 80% virus removal, if the drug is targeting the infection rate. However, drugs targeting production rate and virus clearance rate could not clear the infection by more than 20% if introduced in the later infection phase. Hence, the results show that an early administration of antivirals is crucial for viral clearance [8].

IV. DISCUSSION

Herein, we propose a mathematical model to study the dynamics of viral infection and effect of drug administration in novel SARS-CoV-2 in the presence of adaptive and innate immune cells. The model was tested and parameter estimation was performed for two real patient’s data [4]. The study shows that viral growth decreases when both T cells and Macrophages act together to counter the infection rather than only T cells. The results also show that drug targeting the infection rate parameter is most effective in blocking the viral infection. The other limitation of proposed framework is that it could not capture the fluctuation in viral count of the patients which could be due to varying levels of cytokines. In this context, we plan to extend this model to account for the effects of interleukins and further validate it with other clinical data collected from different patients. We also plan to upgrade the model so that various drugs including dexamethasone, tocilizumab, irbesartan that are under clinical trial can be tested using the proposed framework. Specifically, depending on the patient to patient variability in existing infection levels, the time required for viral eradication can be estimated.

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