The within-host viral kinetics of SARS-CoV-2

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Abstract

In this work, we use a within-host viral dynamic model to describe the SARS-CoV-2 kinetics in host. Chest radiograph score data are used to estimate the parameters of that model. Our result shows that the basic reproductive number of SARS-CoV-2 in host growth is around 3.79. Using the same method we also estimate the basic reproductive number of MERS virus is 8.16 which is higher than SARS-CoV-2. The PRCC method is used to analyze the sensitivities of model parameters and the drug effects on virus growth are also implemented to analyze the model.

Keywords: SARS-CoV-2; MERS; differential equation model; basic reproductive number.

1 Introduction

At the end of 2019, a new type of coronavirus, SARS-CoV-2, began to threaten the people in China, especially in Hubei province. As of March.3, 2020, 80302 individuals have been confirmed to be infected by this virus in China, including 2946 deaths. To mitigate the spread of the virus, the Chinese Government has progressively implemented metropolitan-wide quarantine in Wuhan and several nearby cities from Jan 23–24, 2020 [18]. The virus has also spread to several other countries, such as the Republic of Korea, Japan, Italy, and USA. Around the world, many new deaths are reported every day.

Chest CT is used to assess the severity of lung involvement in COVID-19 [14], which is the name of that new coronavirus caused disease [17]. Before Feb.13, the new cases in China were confirmed by nucleic acid testing. After that day, the diagnostic criterion has been improved, composed of not only the

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nucleic acid testing but also the CT test. The destructed pulmonary parenchyma and the resulting inflammation can be reflected from the chest radiograph [13]. Chest radiograph score method is a useful way to quantify the destruction of pulmonary parenchyma and in this study, our data set is based on this.

Several works are [7,18] nowcasting and forecasting the number of confirmed cases of COVID-19. Meanwhile, some works [6,15] overview the characteristics, exposure history, and illness timelines of confirmed cases. All of these works focus on population dynamics of COVID-19, while, the works about the viral dynamics in host are rare. In this work, we use the within-host viral dynamic model [1,11] to describe the SARS-CoV-2 kinetics in host and the parameters of that model are estimated via the chest radiograph score. Moreover, using the CT score data of MERS that shown in Oh et. al [13], the paramters of MERS virus are also estimated as a comparision group. All of the results are shown in the third section.

2 Method

We use the following ordinary differential equation model to simulate the coronavirus within-lung growth:

$$\begin{cases} \dfrac{dE_p(t)}{dt} = d_E\Big(E_p(0) - E_p(t)\Big) - \beta E_p(t)v(t), \\ \dfrac{dE_p^*(t)}{dt} = \beta E_p(t)v(t) - d_{E^*}E_p^*(t), \\ \dfrac{dv(t)}{dt} = \pi_v E_p^*(t) - d_v v(t), \end{cases} \tag{1}$$

where $E_p(t)$, $E_p^*(t)$ and $v(t)$ are the number of uninfected pulmonary epithelial cells, infected pulmonary epithelial cells and the virus. β is the infection rate of virus, π_v is the virus production rate, $E_p(0)$ is the initial value of uninfected epithelial cells, and the term $d_E E_p(0)$ assumes a constant regeneration of uninfected epithelial cells. d_E, d_{E^*} and d_v are the death rate of uninfected pulmonary epithelial cells, infected pulmonary epithelial cells and the virus, respectively. The death rate of $E_p(t)$ is the natural clearance rate of pulmonary epithelial cells, while, d_{E^*} and d_v are the combination of the natural clearance rate and elimination by the immunity system. This model was also used to describe the within-lung infection process of flu virus [5,11].

By the definition of generation matrix of basic reproduction number R_0 [3], the R_0 of model (1) can be written as,

$$R_0 = \frac{\beta \pi_v E_p(0)}{d_{E^*} d_v}. \tag{2}$$

This number is an important value to measure whether the epidemic or species could die out or not [16]. In this study, the sensitivity analysis result of R_0 is shown in the next section.

In this study, the chest radiograph score data from serve patients (with high chest radiograph scores) are collected from the work of Pan et. al [14] and Oh et. al [13] Our estimation is based on these two data sets. We consider the chest radiograph score as a way to reflect the infected pulmonary epithelial cells [13, 14], which is also the target attacked by the immune cell [12]. Thus by the Poisson distribution, the likelihood that used to extimate parameters can be written as,

$$L = \sum_i \left(D_i \log \left(E_p^*(t_i) \right) - E_p^*(t_i) - \log \Gamma(D_i + 1) \right), \tag{3}$$

where D_i is the smoothed chest radiograph score of the serve patient at time t_i, $E_p^*(t_i)$ is the solution of $E_p^*(t)$ at time t_i, and $\log \Gamma(x)$ is log-gamma function, respectively. The prior distributions of the parameters of model (1) are based on the previous works [5, 10].

3 Results

Table 1: Model parameters

Parameter	Description (units)	Mean value of COVID-19 (std)	Mean value of MERS (std)	Source
$E_p(0)$	The initial value of uninfected epithelial cells (score)	$25 - E_{p^*}(0)$	$25 - E_{p^*}(0)$	[13, 14]
$E_{p^*}(0)$	The initial value of infected epithelial cells (score)	2.59 (0.61)	0.89 (0.28)	MCMC
$v(0)$	The initial value of virus(score)	0.061 (0.0503)	0.0075 (0.0099)	MCMC
π_v	Virus production rate per infected epithelial cells (day^{-1})	0.24 (0.22)	0.15 (0.16)	MCMC
β	Infection rate of epithelial cells by virus ($\text{day}^{-1}\text{score}^{-1}$)	0.55 (0.55)	1.28 (1.37)	MCMC
d_E	Death rate of epithelial cells (day^{-1})	10^{-3}	10^{-3}	[5]
d_{E^*}	Death rate of infected epithelial cells (day^{-1})	0.11 (0.01)	0.056 (0.0053)	MCMC
d_v	Death rate of virus (day^{-1})	5.36 (6.42)	4.64 (0.89)	MCMC
R_0	Basic reproduction number	3.79 (0.54)	8.16 (1.13)	MCMC

Figure.1 shows the fitted result of our model and Table.1 summarizes the estimation results of the parameters and R_0 of our model (1). We estimate that the death rate of these two virus are 5.36 (COVID-19) and 4.64 (MERS) per day,

which is larger than the clearance rate of the virus on the outside surface [4]. This result shows the immune system can clear the virus directly. The estimation result also shows that the R_0 of SARS-CoV-2 in serve patients is around the mean value 3.79 which is lower than that of MERS virus (8.16). These results illustrate that the immune system can not clear the virus effectively at the beginning time of symptom onset. By these estimated parameters of COVID-19, the solutions of model (1) are illustrated in Figure .2.

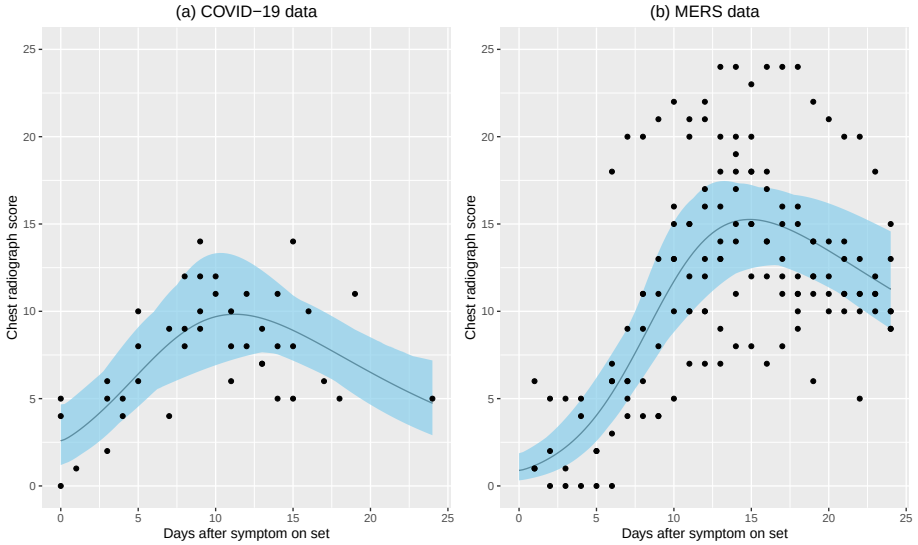

Figure 1: The chest radiograph score data and fitted result of (a) COVID-19, and (b) MERS. The dark line is the mean value of fitted result, while, the 95% confidence interval is shown in blue. The black points are the chest radiograph score data.

The partial rank correlation coefficient (PRCC) method [9] is used to do the sensitivity analysis of R_0. The result (Figure .3) shows that the parameters $E_p(0)$, β, π_v, d_{E^*}, and d_v have almost the same level of influence on R_0. Parameters d_{E^*}, and d_v have negative correlations with R_0, while $E_p(0)$, β, π_v have positive correlations. The positive correlation of $E_p(0)$ with R_0 may give a explanation on why the babys, who have small amount of pulmonary epithelial cells, are not likely to get infected and have lower mortality ([15] Table 1).

Drug therapy is also a topic discussed widely on viral dynamics [1]. For the coronavirus there are some drugs that may have a positive influence on decreasing the virus load [8]. In this study, we assume that the drug can drop the infection rate β to 0.1β, and the simulated results are shown in Figure .4. These results show that the earlier to give an effective drug to a serve patient, the better to relieve symptoms.

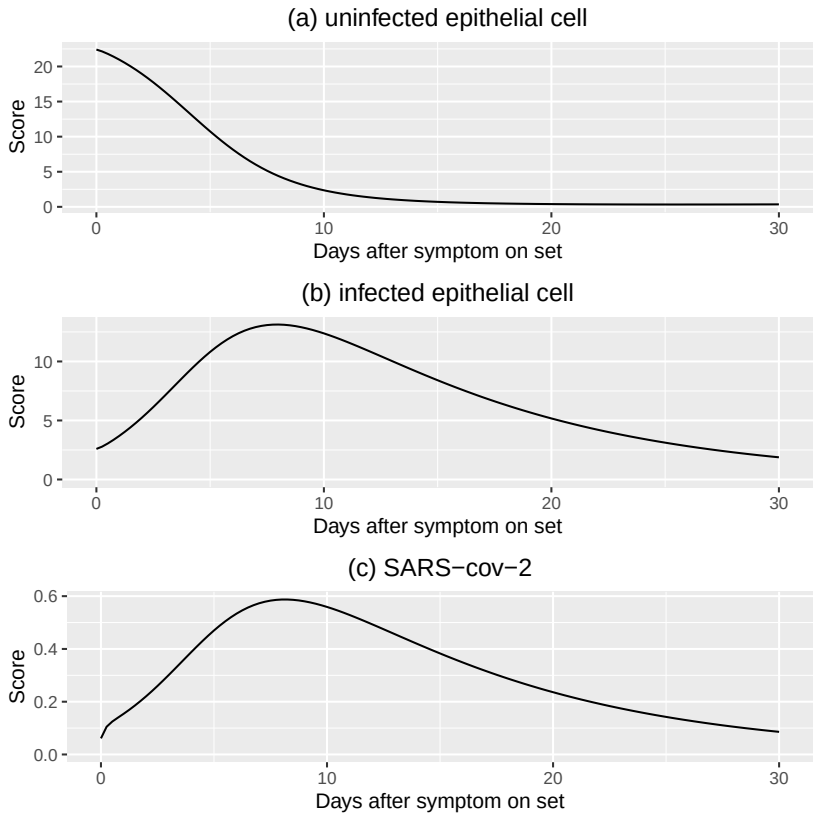

Figure 2: The solutions of model (1) with the parameters of COVID-19 that shown in Table.1.

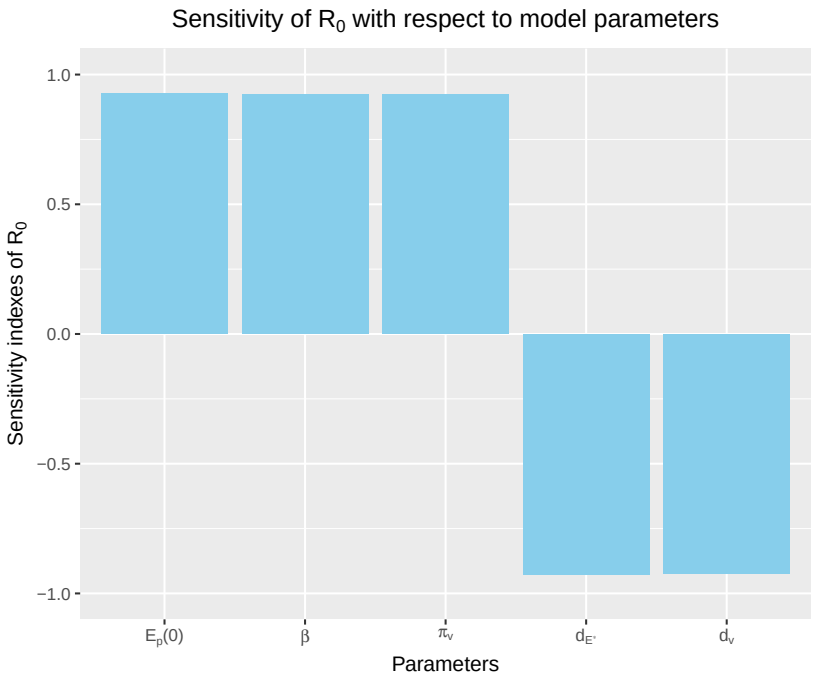

Figure 3: Sensitivity of R_0 with respect to $E_p(0)$, β, π_v, d_{E^*}, and d_v. The samples of parameters are taken from the uniform distribution $U(0.8p, 1.2p)$, where p is used to illustrate the mean value of parameters of COVID-19 that shown in Table.1.

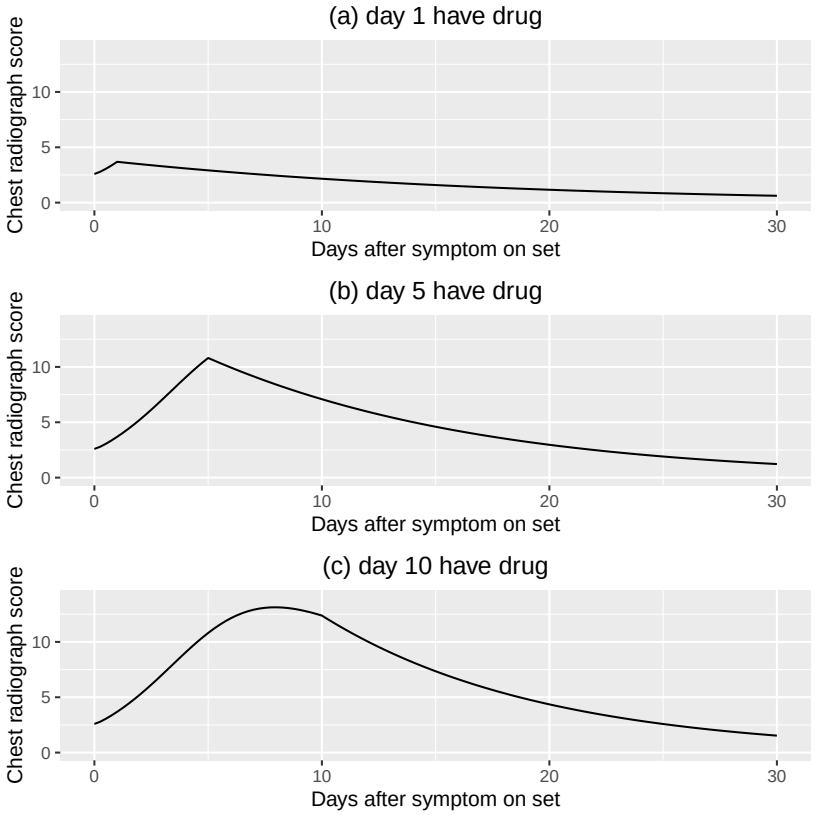

Figure 4: The simulated result of chest radiograph score of patients with COVID-19 and the beginning time of having drug is (a) the first day, (b) the fifth day, and (c) the tenth day after symptom onset. In this simulation, the drug effect is assumed to decrease the infection rate β to 0.1β.

4 Discussion

Based on the chest radiograph data, we estimate the parameters and basic reproductive number of the model (1). The R_0 of SARS-CoV-2 in host growth is 3.79, which is higher than HCV (2.3, [2]), but lower than the flu virus (23, [10]). Comparing the estimated parameters of SARS-CoV-2 with MERS coronavirus, the MERS have a higher virulence to infect the pulmonary epithelial cells (larger R_0) and with a small initial value of infected cell. These may esplain why the MERS have a higher mortality and smaller incubation period [6, 13]. By the PRCC method, the sensitivity analysis is also done on the R_0, and the positive correlation of $E_p(0)$ with R_0 may give a possible reason why the baby patients are less likely to die of this virus. We also analyze the drug therapy and its effect on the virus growth, and the result illustrates that early medication is effective for treatment.

The methods we used in this study are following the previous works by Miao et. al [10,11]. This is the first time for this methodology to be used in the COVID-19 and our work shows some new results of the within-host properties of this virus. All of the source codes are available at the GitHub (`https://github.com/ChentongLi/SARS-CoV-2_viral_kinetic`). Anyone could use these codes to estimate and forecast the chest radiograph score of the patients.

The major limitation of this study is that the chest radiograph score is not the real data of the infected pulmonary epithelial cells but just an approximation. Moreover, we assume that the immunne effect on viruses and infected epithelial cells are constant values. This is because the data of antibody and effective CD8 cells of that virus are rarely known. If we could get more accurate data, the results will be much better.

We believe this study could give some help to the diagnosis and treatment of the COVID-19. For other disease that infect the lung, this method we believe also could be used to do analysis.

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