Research Article

Global Dynamics of SARS-Cov-2 Virus-Cell Model Including Inflammatory Responses to Lung Cells

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Abstract

SARS-CoV-2 is the pathogen of COVID-19, which has caused a pandemic worldwide at the beginning of 2020. The clinical symptoms of SARS-CoV-2 infection are not identical, and the infected person can suffer from common cold to more severe diseases, such as pneumonia, which is an important cause of COVID-19 deaths. Virus dynamical behaviors of SARS-CoV-2 *in vivo* of infected persons determine their different clinical symptoms. In this paper, a new virus-cell model is proposed to study the dynamical behavior of SARS-CoV-2 including inflammatory responses, and then the global dynamics of this model are studied. By persistence theory and constructing Lyapunov functions, it shows that if $R_c < R_0 < 1$, the infection-free equilibrium of the model is globally asymptotically stable, which implies COVID-19 can heal itself *in vivo*. If $R_c < 1 < R_0$, the infected equilibrium without inflammatory is globally asymptotically stable, which implies SARS-CoV-2 would persistently exist *in vivo* without inflammatory response. If $1 < R_c < R_0$, the infected equilibrium with inflammatory is globally asymptotically stable, which implies SARSCoV-2 would persistently exist *in vivo* with inflammatory response. By the simulations, it shows that the activation of inflammatory cells would change the chest radiograph score of lung cells.

Keywords

SARS-CoV-2, COVID-19, Inflammatory response, Lyapunov function, Persistence theory

Introduction

The pathogen, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has infected more than 11,000,000 people worldwide and the coronavirus disease it causes, Corona Virus Disease 2019 (COVID-19), has caused more than 500,000 deaths as of June, 2020 [1]. For this pandemic, many 5 mathematical models have been proposed to study the transmission of COVID-19, especially for the estimation of its basic reproduction number R0 [2-4]. However, the virus-cell model is rarely mentioned about SARS-Cov-2, which is important in the study of virus dynamical behaviors *in vivo* of infected persons. And they determine the different clinical symptoms of SARS-CoV-2 infection from common cold to more severe diseases, such as pneumonia [5].

Nowak-Bangham's model was first studied in [6] to describe the virus-cell dynamics of Human Immunodeficiency Virus (HIV) *in vivo*. Its global stability was studied in [7,8]. In [9], the authors studied the global stability of a virus dynamics model with Beddington-DeAngelis term and immune response. For HIV, the virus-cell model has been considered to study the virus dynamics during infection-immunity processes. However, for SARS-Cov-2, the inflammation responses are more important, which would lead to pneumonia from common cold. The inflammation response is the body's defensive response to virus infection. When the body is infected, an inflammatory would respond to get rid of itself and restore health. Usually, the inflammation response is beneficial, but sometimes it can be harmful to attack the body's healthy tissues, such as lung cells. Uncontrolled inflammation due to infection can culminate in organ failure and death [10]. In view of this fact, we propose a new virus-cell model with inflammation responses, which reflects the inflammation process of SARxS-Cov-2. In the next section, we give the model description, and then we analyze the global stability of the model.

Formulation of the Model

In our model, $T(t)$ denotes the density of uninfected lung cells, $I(t)$ denotes that of infected lung cells, $C(t)$ denotes that of inflammatory cells and $V(t)$ denotes that of SARS-CoV-2. The healthy lung cells are assumed to reproduce with a constant rate Λ. The average lifetime of $T(t)$, $I(t)$, $C(t)$ and $V(t)$ are $1/d$, $1/\alpha$, $1/\gamma$ and $1/\mu$, respectively. Free SARS-CoV-2 is produced from infected lung cells at the rate ar and infects
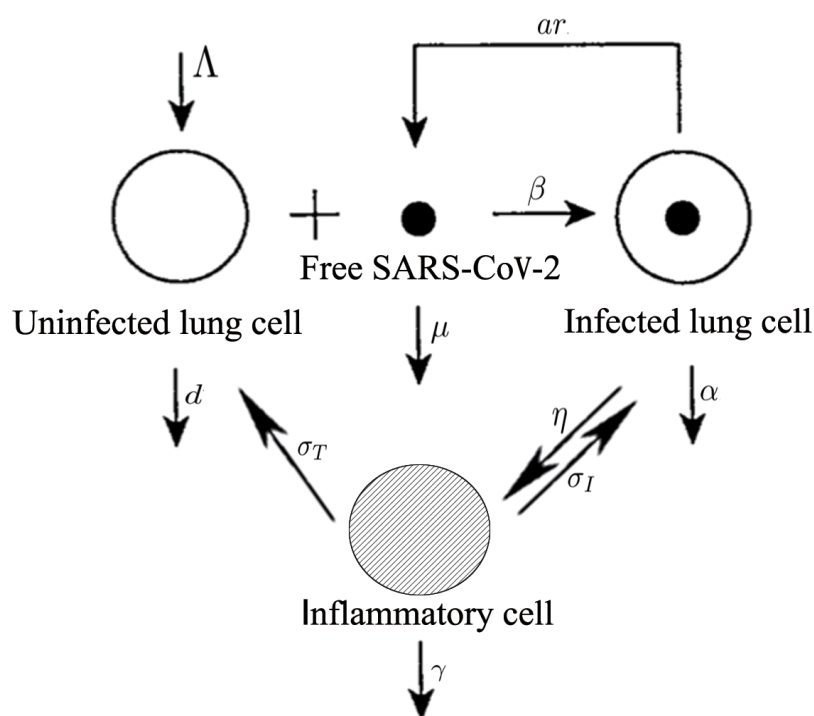
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Figure 1: A model for SARS-CoV-2 infection with inflammation responses *in vivo*.

the healthy lung cells at the rate β. Inflammatory cells are activated by the infected cells at the rate η. The advantage of inflammatory cells is to kill infected lung cells at the rate σ_I, but the disadvantage of them is to kill the healthy lung cells at the rate of σ_T. All the parameters are assumed positive.

According to Figure 1, the virus-cell dynamics model of SARS-CoV-2 is established as follows:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \Lambda - dT(t) - \beta V(t)T(t) - \sigma_T C(t)T(t), \\[2mm]
\dfrac{dI(t)}{dt} = \beta V(t)T(t) - \alpha I - \sigma_I C(t)I(t), \\[2mm]
\dfrac{dC(t)}{dt} = \eta C(t)I(t) - \gamma C(t), \\[2mm]
\dfrac{dV(t)}{dt} = arI(t) - \mu V(t).
\end{cases}
\tag{1}
$$

The system (1) has an infection-free equilibrium $E_0 = (T_0, 0, 0, 0) = (\frac{\Lambda}{d}, 0, 0, 0)$ corresponding to the maximal level of healthy lung cells. And if $R_0 = \dfrac{\Lambda \beta ar}{\mu \alpha d} > 1$, the system (1) has an infected equilibrium without inflammatory $E_1 = (\bar{T}, \bar{I}, 0, \bar{V}) = (\frac{\alpha \mu}{\beta ar}, \frac{d\mu}{\beta ar}(R_0 - 1), 0, \frac{d}{\beta}(R_0 - 1))$. By existence condition of positive equilibrium, we can get the basic reproductive number for system (1):

$$
R_c = \frac{\eta \Lambda \beta ar}{\eta \mu \alpha d + \beta ar \gamma \alpha}.
$$

If $R_c > 1$, there also exists an infected equilibrium with inflammatory $E^* = (T^*, I^*, C^*, V^*)$,

where $I^* = \dfrac{\gamma}{\eta}$, $V^* = \dfrac{ar\gamma}{\mu\eta}$, $T^* = \dfrac{\mu}{\beta ar}(\alpha + \sigma_I C^*)$, C^* is the unique positive root of

$$
\sigma_T \sigma_I C^2 + (\sigma_I d + \sigma_I \frac{\beta ar\gamma}{\mu\eta} \sigma_T \alpha)C - \frac{\Lambda \beta ar}{\mu} + d\alpha + \frac{\beta ar\gamma\alpha}{\mu\eta} = 0.
$$

Then we can obtain

$$
C^* = \frac{\sqrt{(\sigma_I d + \alpha \sigma_T \sigma_I \frac{\beta ar\gamma}{\mu\eta})^2 + 4\sigma_T\sigma_I(\frac{\Lambda\beta ar}{\mu} - d\alpha - \frac{\beta ar\gamma\alpha}{\mu\eta})} - (\sigma_I d + \alpha\sigma_T\sigma_I\frac{\beta ar\gamma}{\mu\eta})}{2\sigma_T\sigma_I}.
$$

Let $\omega(\phi)$ is the ω-limit set of ϕ. ϕ is a continuous semiflow on X_1, X_1 is a subset in metric space with metric d. $\phi : [0, \infty) \times X_1 \to X_1$ with $\phi_t \circ \phi_s = \phi_{t+s}$, $t, s \geq 0$; $\phi_0(x) = x$, $x \in X_1$. Let the solution of system (1) be $u(t) = u(t)(\phi) := (S(t), I(t), C(t), R(t))$. Thus, we can discuss the dynamics behavior of system (1) in the closed set $D = \{(T, I, C, V) \in R_+^4 : T \leq \frac{\Lambda}{d}\}$. And it is easy to see that D is positively invariant of system (1).

We define

$$
D_1 = \left\{(T, I, C, V) \middle| I = 0 \text{ or } V = 0, C = 0, 0 < T \leq \frac{\Lambda}{d}\right\},
$$

$$
\tilde{D}_2 = \left\{(T, I, C, V) \middle| I > 0, C > 0, V > 0, 0 < T \leq \frac{\Lambda}{d}\right\}, D_2 = D \setminus D_1.
$$

D_2 and $\tilde{D}_2$ are forward invariant.

Let

$$
\Omega^* = \bigcup_{y \in Y} \omega(Y), \omega(y) = \bigcap_{t \geq 0} \overline{\phi([0, \infty) \times y)}, Y = \{x = (T, I, C, V) \in D_1; \phi_t(x) \in D_1, \forall t > 0\}.
$$

Ω^* consists of equilibria E_0, E_1. These equilibria cannot be chained to each other in D_1. By analyzing the flow in neighborhood of each equilibrium, it is easy to see that Ω^* 40 is isolated in D and D_1 is a uniform strong repeller for $\tilde{D}_2$ [11,12]. If $u(t)$ stays close to E_0, we have three cases: if $I(0) = V(0) = 0$,

Chen and Yuan. Res Rev Infect Dis 2020, 3(2):81-86

Open Access | Page 82 |

then $I(t) = V(t) = 0$; if $I(0) > 0$ or $V(0) > 0$, $C(0) = 0$ then $I(t) > 0$, $V(t) > 0$ and $C(t) = 0$; if $I(0) > 0$ or $V(0) > 0$, $C(0) > 0$ then $I(t) > 0$, $V(t) > 0$ and $C(t) > 0$. Therefore, E_0 is isolated in D. Similarly, we can prove that E_1 is isolated in $\tilde{D}$.

Analysis of Stability

Theorem 1: If $R_c < R_0 < 1$, then E_0 is locally asymptotically stable; if $R_c < 1 < R_0$, then E_1 is locally asymptotically stable. If $1 < R_c < R_0$, then E_0 and E_1 is unstable, and E^* is locally asymptotically stable.

Proof: After calculation, it is shown that the Jacobian matrix of the vector field corresponding to system (1) is

$$J = \begin{pmatrix} -d - \beta V - \sigma_T C & 0 & -\sigma_T T & -\beta T \\ \beta V & -\alpha - \sigma_I C & -\sigma_I I & \beta T \\ 0 & \eta C & \eta I - \gamma & 0 \\ 0 & ar & 0 & -\mu \end{pmatrix}.$$

The characteristic equation associated with J at E_0 is given by

$$(\lambda + d)(\lambda + \gamma)(\lambda^2 + (\alpha + \mu)\lambda + \alpha\mu - \frac{\Lambda\beta ar}{d}) = 0. \tag{2}$$

If $R_c < R_0 < 1$, then all roots of equation (2) have negative real parts. Therefore, E_0 is locally asymptotically stable.

At E1, the associated characteristic equation is

$$(\lambda + \gamma - \eta\overline{I})(\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0) = 0, \tag{3}$$

where

$$A_2 = d + \beta\overline{V} + \alpha + \mu; A_1 = \alpha\mu - \beta\overline{T}ar + (\alpha + \mu)(d + \beta\overline{V}), A_0 = d\alpha\mu - d\beta\overline{T}ar + \beta\overline{V}\alpha\mu.$$

If $R_c < 1 < R_0$, then $\eta\overline{I} - \gamma < 0$. After calculation, it is shown that $A_2 > 0$, $A_0 > 0$, $A_1 > 0$ and $A_2A_1 - A_0 > 0$. Thus, the Routh-hurwitz criterion implies that all roots of equation (3) have negative real parts and then E_1 is locally asymptotically stable.

If $1 < R_c < R_0$, at least one of the roots of equations (2) or (3) has positive real part according to the calculation above, then E_0 and E_1 are unstable.

At E^*, the associated characteristic equation is

$$B_3 = \mu + \alpha + \sigma_T C^* + d + \beta V^* + \sigma_I C^*; \tag{4}$$

where

$$B_3 = \mu + \alpha + \sigma_T C^* + d + \beta V^* + \sigma_I C^*;$$

$$B_2 = (\mu + \alpha + \sigma_T C^*)(d + \beta V^* + \sigma_I C^*) + (\alpha\mu + \sigma_I\mu - \beta T^*ar + \sigma_I I^*\eta C^*);$$

$$B_1 = (d + \beta V^* + \sigma_I C^*)(\alpha\mu + \sigma_I\mu - \beta T^*ar + \sigma_I I^*\eta C^*) + \mu\sigma_I\eta I^*C^* + \beta T^*V^*(\sigma_T\eta C^* - \beta ar);$$

$$B_0 = (d + \beta V^* + \sigma_I C^*)\mu\sigma_I\eta I^*C^* + \beta\mu\sigma_T\eta T^*C^*V^*;$$

After calculation, it is shown that $B_3 > 0$, $B_2 > 0$, $B_1 > 0$, $B_0 > 0$, $B_3B_2 - B_1 > 0$ and $B_1B_2B_3 - B_0B_3^2 - B_1^2 > 0$. Thus, the Routh-hurwitz criterion implies that all roots of equation (4) have negative real parts and then E^* is locally asymptotically stable.

Theorem 2: If $R_c < R_0 < 1$, then E_0 is globally asymptotically stable in D; if $R_c < 1 < R_0$, then E_1 is locally asymptotically stable in D; if $1 < R_c < R_0$, then E^* is globally asymptotically stable in $\tilde{D}_2$.

Proof: According to Lyapunov function

$$L_1(T, I, C, V) = T_0(\frac{T}{T_0} - \ln\frac{T}{T_0}) + I + \frac{\alpha}{ar}V.$$

L_1 is continuous on the set D. The derivative of L_1 along the solution of model (1) is

$$\frac{dL_1}{dt} \leq \Lambda(2 - \frac{T}{T_0} - \frac{T_0}{T}) + \frac{\alpha\mu}{ar}(R_0 - 1)V.$$

It is obvious that $R_0 < 1$ ensures $\frac{dL_1}{dt} < 0$, for all $T, I, C, V > 0$.

Let $u(t) = (S(t), I(t), C(t), R(t))$ be the solution of system (1) with any $\Phi \in \omega(\phi) \subset D$. Then the invariance of $\omega(\phi)$ implies that $u(t) \in \omega(\phi)$ for $t \in R$. Since $u(t)$ is bounded and differentiable, if $R_0 < 1$, $\lim_{t\to\infty} T(t) = \frac{\Lambda}{d}, \lim_{t\to\infty} I(t) = 0, \lim_{t\to\infty} C(t) = 0$ and $\lim_{t\to\infty} V(t) = 0$. Therefore, we can obtain $\omega(\phi) = E_0$ and E_0 is globally attractive in D. From Theorem 1, we know that E_0 is locally asymptotically stable, then we get if $R_0 < 1$, E_0 is globally asymptotically stable in D.

For E_1, $R_c < 1 < R_0$ ensures the existence of it. Define Lyapunov function

$$L_2(T, I, C, V) = \overline{T}(\frac{T}{\overline{T}} - \ln\frac{T}{\overline{T}}) + \overline{I}(\frac{I}{\overline{I}} - \ln\frac{I}{\overline{I}}) + \frac{\alpha}{ar}\overline{V}(\frac{V}{\overline{V}} - \ln\frac{V}{\overline{V}}).$$

L_2 is continuous on the set D. The derivative of L_2 along the solution of model (1) is

$$\frac{dL_2}{dt} \leq d\overline{T}(2 - \frac{T}{\overline{T}} - \frac{\overline{T}}{T}) + \alpha\overline{I}(3 - \frac{\overline{T}}{T} - \frac{TV\overline{I}}{\overline{T}V I} - \frac{I\overline{V}}{\overline{I}V}) \leq 0.$$

Let $v(t) = (S(t), I(t), C(t), R(t))$ be the solution of system (1) with any $\Phi \in \omega(\phi) \subset D$. Since $(\overline{T}, \overline{I}, 0, \overline{V})$ ensures $\frac{dL}{dt} \ 0$, then the invariance of $\omega(\phi)$ implies

$$\lim_{t\to\infty} T(t) = \overline{T}, \lim_{t\to\infty} I(t) = \overline{I}, \lim_{t\to\infty} C(t) = 0 \text{ and } \lim_{t\to\infty} V(t) = \overline{V}.$$

Therefore, we can obtain $\omega(\phi) = E_1$ and E_1 is globally attractive in D. From Theorem 1, we know that E_1 is locally asymptotically stable, then we get if $R_c < 1 < R_0$, E_1 is globally asymptotically stable in D.

Next, we consider the stability of infected equilibrium with inflammation E^* by persistence theory. Since E_0, E_1 are isolated in D. Using Proposition 4.3 in [11], we can prove that D_1 is a uniform weak repeller for $\tilde{D}_2$; and using Theorem 4.5 in [11], we can prove that D_1 is a uniform strong repeller for $\tilde{D}_2$.

Then we get that there exists an $\in > 0$, such that

$$\lim \inf_{t\to\infty} \min\{I(t), C(t), V(t)\} > \in,$$

with $T(0) > 0$, $I(0) > 0$, $C(0) > 0$ and $V(0) > 0$ in $\tilde{D}_2$. Therefore, if $R_c < R_0 < 1$, E^* is the unique internal equilibrium of system (1). Since system (1) is persistent in $\tilde{D}_2$, E^* is locally asymptotically stable by Theorem 1, then

$$\lim_{t\to\infty} T(t) = T^*, \lim_{t\to\infty} I(t) = I^*, \lim_{t\to\infty} C(t) = C^* \text{ and } \lim_{t\to\infty} V(t) = V^*.$$

Therefore, if $R_c < R_0 < 1$, then E^* is globally asymptotically stable in $\tilde{D}_2$.

Chen and Yuan. Res Rev Infect Dis 2020, 3(2):81-86
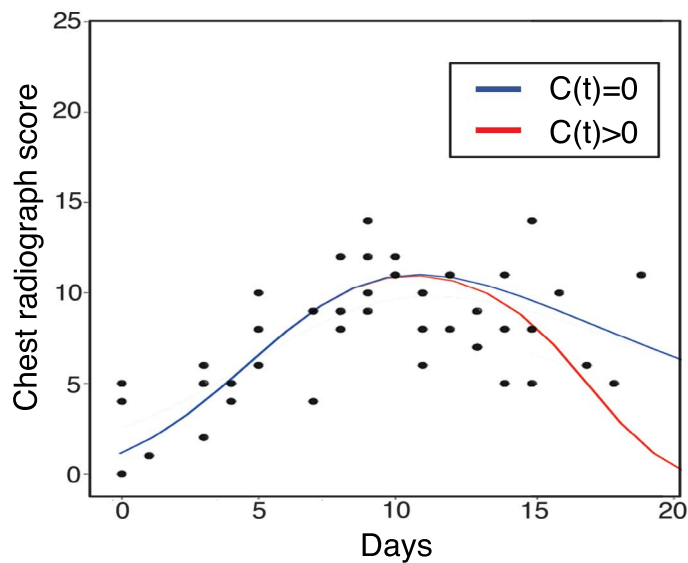
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Figure 2: The chest radiograph score data [14] and fitted result of SARS-CoV-2 virus cell model with inflammatory responses.

Table 1: Model parameters.

| Parameter	Description	Value	Source
Λ	Regeneration rate of uninfected lung cells	0.12	Est.
β	Infection rate of lung cells by virus	0.55	[13]
η	Activation rate of inflammatory cells by the infected cells	0.1	Est.
σ_I	Killing rate of infected lung cells by inflammatory cells	0.025	Est.
σ_T	Killing rate of uninfected lung cells by inflammatory cells	0.012	Est.
ar	Virus production rate per infected lung cells	0.24	[13]
1/d	Average lifetime of uninfected cells	1000	[13]
1/α	Average lifetime of infected cells	9	[13]
1μ	Average lifetime of SARS-CoV-2	0.187	[13]
1γ	Average lifetime of inflammatory cells	10	Est.
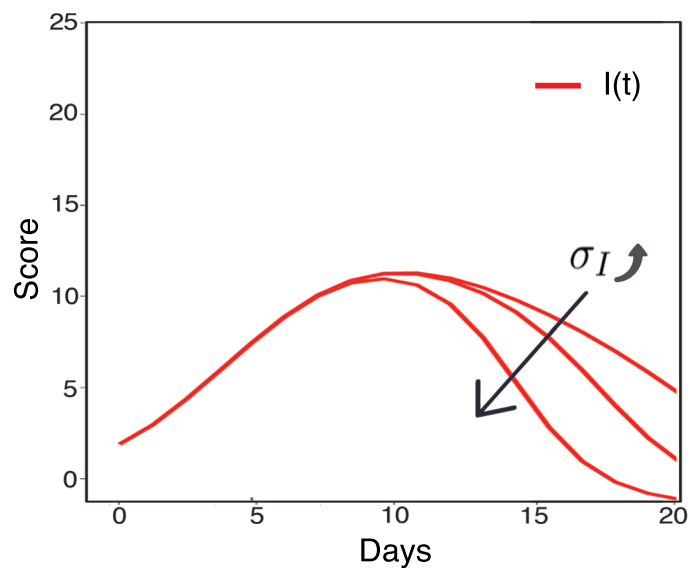
Figure 3: Effect of σ_I on the change of infected lung cells score.

Simulations

[13] has studied the virus-cell model of SARS-CoV-2 by the chest radiograph score data from serve patients (with high chest radiograph scores) [13,14]. Therefore, in this paper, we continue to consider the chest radiograph score as a way to reflect the infected lung cells by SARS-Cov-2, then we add the effect of inflammatory response by $C(t) > 0$. Figure 2 shows the fitted result of the model. The activation of inflammatory cells decrease the chest radiograph score more rapidly as the red line. It is the healthy response that the inflammatory cells becomes activated, clears the pathogen, and then begins a repair process and abates. The value of parameters is summarized in Table 1. Some of them were collected from [13], and others are estimated by MATLAB, using genetic algorithm. Figure 3 shows the effect of σ_I on the decrease of infected lung cells score, which is also proving of the advantage of in-flammatory cells.

However, since the inflammatory response is non-specific and is the first line of defense of the body against viral infec-tions, uncontrolled inflammatory response would kill more healthy infected lung cells, as shown in Figure 4. It would lead to the lung failure or even to death, which is the main cause of COVID-19 death. It is also worth noting that the activation of inflammatory cells never change the value of R_c by σ_I and σ_T. While, the value of average lifetime of inflammatory cells would change the value of R_c, as is shown in Figure 5, which implies the effect of inflammatory response on the decrease of virus infection rate *in vivo*. Figure 6 shows the sensitivity analysis of γ and η on R_c.
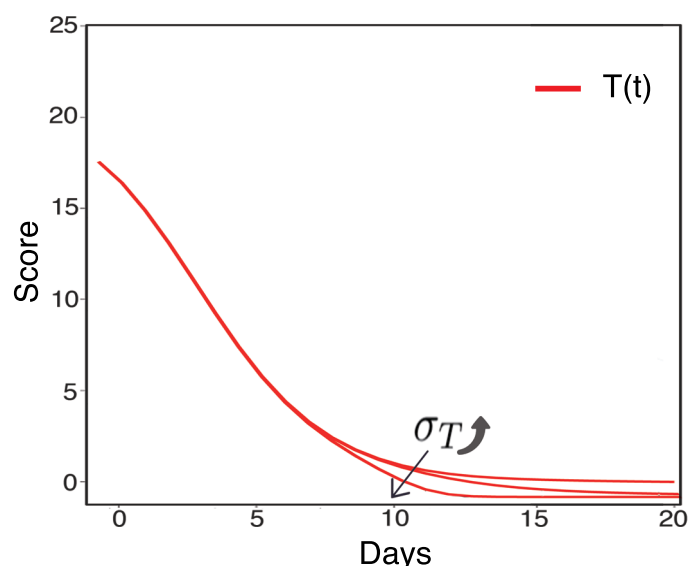
Discussion

Inflammation response is one of the reasons for fatal

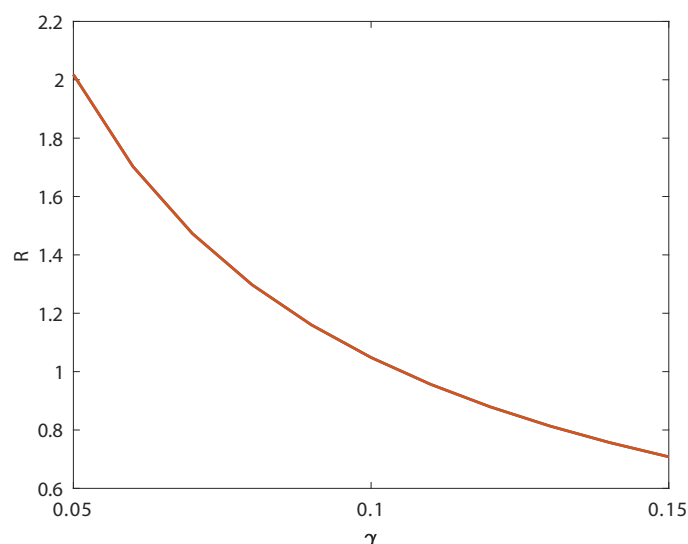**Figure 4:** Effect of σ_I on the change of uninfected lung cells score.
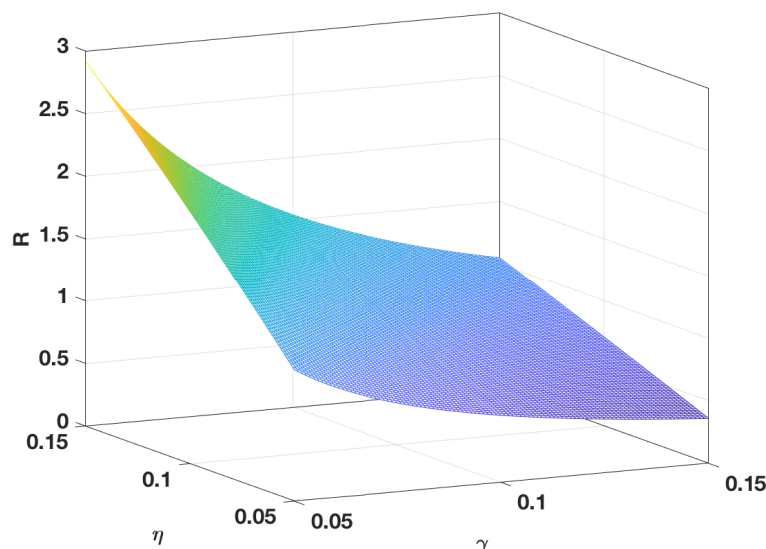

Figure 5: Sensitivity analysis of γ on R_C.

Figure 6: Sensitivity analysis of γ and η on R_C.

pneumonia caused by SARS-CoV-2. However, few studies on the mechanism of the inflammatory response during the SARS-CoV-2 infection processes *in vivo*. In this paper, a new virus-cell mathematical model is constructed to study the dynamical behavior of SARS-CoV-2 including inflammatory responses. Moreover, the rationality of this method is obtained through the simulations of the chest radiograph score.

Based on the stability conditions of model (1), we construct the basic reproductive number of the model, R_c. The R_c of SARS-CoV-2 with the inflammatory response is smaller than the original reproduction number R_0 without the inflammatory response. The addition of inflammatory responses changes the basic reproduction number R_0 to R_c. It shows that if $R_c < R_0 < 1$, the infection-free equilibrium of the model is globally asymptotically stable; if $R_c < 1 < R_0$, the infected equilibrium without inflammatory is globally asymptotically stable, if $1 < R_c < R_0$, the infected equilibrium with inflammatory is globally asymptotically stable.

$R_c < R_0$ implies that the inflammatory responses would decrease the rate of SARS-CoV-2 infection, which is beneficial to the body health. However, the infected equilibrium changes to two styles, infected equilibrium without inflammatory E_1 and infected equilibrium with inflammatory E^*. Different parameters, σ_I and σ_T, determine different E^*. If σ_T is so large that inflammatory cells attack healthy cells more strongly, with lower T^*, the clinical symptoms caused by pneumonia are more intense, which is an important cause of COVID-19 death. However, the activation of inflammatory cells are never changed the value of R_c by σ_I and σ_T, but changed by γ. It is an important result to give some help to understand the disease mechanism of SARS-CoV-2 *in vivo* and then give some advice to the diagnosis and treatment of COVID-19.

Acknowledgment

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