Dynamic of Cytokine Storm in Human Inflammatory Response of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-Induced Disease

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Abstract. Infection of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in the human body is characterized by the detection of large amounts of the virus by cytokine as the response to inflammation. In the human body, there are two types of inflammatory responses by a cytokine called pro-inflammatory and anti-inflammatory cytokine. A non-dimensionalized mathematical model of the inflammatory response system has been constructed in the form of a system of differential equations, which consists of two variables and five parameters. The rate of pro-inflammatory and anti-inflammatory cytokine natural production are two important parameters that correlate with a chronic SARS-CoV infection called a cytokine storm. Varying these parameter values, some non-chaotic torus attractors were found in some numerical simulation with the initial value around the equilibrium point obtained by fixing parameter values at the Generalized Hopf bifurcation point. These phenomena show that in cytokine storm condition, fluctuation of pro-inflammatory and anti-inflammatory cytokines form some patterns which are complex, so that they are difficult to be predicted. Mesenchymal stem cells (MSC), chloroquine (CQ), and hydroxychloroquine (HCQ), which have an effect on pro-inflammatory and anti-inflammatory cytokine production, can be used to reduce the cytokine storm.

Keywords: SARS-CoV, inflammation, cytokine storm, Generalized Hopf, non-chaotic torus.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) has cross-species transmission from animals to humans [1], [2], [3]. SARS-CoV reproduces in its natural host, namely bats [1], [4]. Humans can be infected by the virus because of their interaction with the natural host, either directly or indirectly through the environment, such as inhalation of natural host feces or their carriers [5].

The human innate immune system responds a virus infection by a regulation that consists of a cytokine response that causes inflammation and a cytokine response that inhibits inflammation. Cytokine response has more effect on the impact of disease than the number of the virus [6]. SARS-CoV virus infection in humans increases the concentration of cytokine that causes inflammation as a factor that triggers malignancy of the disease [7], [8], [9], [10], [11]. A mathematical model of interaction between cytokine that causes inflammation, i.e., pro-inflammatory cytokine and cytokine that inhibits inflammation, i.e., anti-inflammatory cytokine, has been constructed in [5], [12]. Interaction of these two categories of cytokine plays an important role in the inflammatory immune response [13] for infectious diseases [4] and chronic autoimmune diseases [15]. Bifurcation analysis of the model...
shows that the natural production rate of pro-inflammatory and anti-inflammatory cytokine is an indicator of a chronic SARS-CoV infection called cytokine storm [5].

Characterization of the cytokine storm through a pair of the parameter values, i.e. rate of natural production of pro-inflammatory and anti-inflammatory cytokine, which cause cytokine storm, has been shown in [5]. However, the dynamic of the cytokine concentration as another characteristic of cytokine storm has not been studied. In this paper, we will investigate some portrait phases of the model solutions at the cytokine storm area through numerical bifurcation analysis to determine the cytokine storm's character through the dynamic of the cytokine concentration. Furthermore, some therapy can target the rate of natural production of pro-inflammatory and anti-inflammatory cytokine as a medical recommendation.

2. Mathematical Model

The human inflammatory response system component consists of pro-inflammatory and anti-inflammatory cytokine, which are denoted by $s$ and $i$, respectively. Production of pro-inflammatory and anti-inflammatory cytokine is affected by pro-inflammatory cytokine expression represented by Hill function, namely $\alpha(s)$ and $\gamma(s)$. Inhibition of pro-inflammatory cytokine production by anti-inflammatory cytokine expressed in terms of Hill function, namely $\beta(i)$. A mathematical model that describes the dynamics of these cytokines' interaction has been developed by [12]. The mathematical model is in the form of two-variable differential equations with twelve parameters containing the Hill function as follows.

\[
\begin{align*}
\frac{ds}{dt} &= -d_s s + \alpha(s) \beta(i) \\
\frac{di}{dt} &= -d_i i + \gamma(s),
\end{align*}
\]

where

\[
\alpha(s) = k_0 + k_1 \frac{s^{n_1}}{k_2^{n_1+4s^{n_1}}}, \beta(i) = k_3 - \frac{k_4^{n_2}}{k_4^{n_2+4i^{n_2}}}, \text{ and } \gamma(s) = k_5 \frac{s^{n_3}}{k_6^{n_3+4s^{n_3}}}
\]

Each parameter $n_j$ for $j = 1, 2, 3$ denote Hill coefficients, and the values are positive integer. These parameters represent the cooperative binding of cytokine that has been secreted by the receptor. According to [16], Hill coefficient is more appropriate to describe the interaction coefficient that represents cooperativity. If $n_j > 1$, then the cooperativity is positive. If $n_j < 1$, then the cooperativity is negative [17]. Parameter $k_3$ represents the efficiency of resistance. Respectively, parameters $k_1$ and $k_5$ represent the maximum rate of natural production of a pro-inflammatory and anti-inflammatory cytokine through their binding activity on inflammation reaction, with $k_0$ as the rate of natural production of pro-inflammatory cytokine. Parameters $k_2, k_4,$ and $k_6$ represent cytokine concentrations when the functions of Hill $\alpha(s), \beta(i),$ and $\gamma(s)$ reach half of their maximum values [16], [17].

Non-dimensionalization of System (1) has been done in [5]. The dimensionless variables are $x, y,$ and $z$ that satisfy $s = x k_2, i = y k_4,$ and $t = \frac{z}{d_i}$. System (1) is reduced to a model with five parameters as follows.

\[
\begin{align*}
\frac{dx}{dz} &= -\eta x + \frac{1}{1 + y^{n_2}} \left( \mu_1 + \mu_2 \frac{x^{n_1}}{1 + x^{n_1}} \right) \\
\frac{dy}{dz} &= -y + \mu_4 \frac{x^{n_3}}{\mu_3^{n_3} + x^{n_3}},
\end{align*}
\]
where
\[
\eta = \frac{d_c}{d_i}, \mu_1 = \frac{k_0 k_3}{k_2 d_i}, \mu_2 = \frac{k_1 k_3}{k_2 d_i}, \text{ and } \mu_3 = \frac{k_6}{k_2}.
\]

Parameter \( \eta \) represents the ratio of degradation between pro-inflammatory cytokine and anti-inflammatory cytokine. Extracellular cytokine receptor and soluble cytokine increase this ratio. The inhibition of the inflammatory response occurs by increasing the value of this parameter. Parameter \( \mu_1 \) denotes the rate of pro-inflammatory cytokine production by soluble cytokine receptors and other factors. The intensity of the inflammatory response is directly proportional to the value of this parameter. Parameter \( \mu_2 \) describes the rate of pro-inflammatory cytokine natural production. Parameter \( \mu_3 \) represents cytokine concentration ratio when the Hill functions \( \gamma(s) \) and \( \alpha(s) \) reach their maximum value. Increasing the value of this parameter induces an inflammatory response. Parameter \( \mu_4 \) indicates the rate of anti-inflammatory cytokine natural production. Increasing the value of this parameter inhibits the inflammatory response. Parameter \( n_j \) for \( j = 1, 2, 3 \) are assumed to be equal to two, because the bond between pro-inflammatory cytokine with cell surface receptor induces production of the cytokines and increases the cytokine receptor on the surface of cell bonds. Bifurcation analysis of System (2) is focused on \( \mu_2 \) and \( \mu_4 \), because these parameters correlate with the cytokine storm phenomenon [5]. The variation according to the results in [5], while the values for other parameters are fixed.

3. Numerical Bifurcation Analysis

Numerical bifurcation analysis is performed by identification the further bifurcation in the model using Auto07p [18]. The initial values of the variables are listed in table 1.

| Table 1. Initial Value |
|------------------------|
| Variable | Value | Reference |
| \( s \) | 0.97 | Estimated\(^a\) |
| \( i \) | 1.1905 | Estimated\(^a\) |
| First | Second | Third |
| 0.953 | 0.9945 | 1.1908 |

\(^a\) Estimation is explained in subsection 3.2.

Parameter values are listed in table 2.

| Table 2. Parameter Value |
|--------------------------|
| Parameter | Value | Reference |
| \( \eta \) | 1.5 | [5] |
| \( \mu_1 \) | 0.025 | [5] |
| \( \mu_2^* \) | 30 | Assumed\(^b\) |
| \( \mu_3 \) | 0.5 | [5] |
| \( \mu_4^* \) | 6 | [5] |
| \( n_j \), \( j = 1, 2, 3 \) | 2 | [5] |

\(^a\) Varying parameter.

\(^b\) Equal to a value near the Hopf point found in [5].

3.1. Hopf bifurcation

Substituting the parameter values into the model, we find an equilibrium point \((s^*, i^*) = (0.4208358712, 2.487965209)\). We make a forward continuation of the equilibrium point by variations of the parameter \( \mu_2 \) which describes the rate of pro-inflammatory cytokine natural production.

A Hopf bifurcation occurs at \( H = (\mu_2, s) = (31.885410742, 0.44073019937) \). The stability of the equilibrium point changes from unstable become stable at the Hopf point; see Figure 1. The Hopf
bifurcation also generates a periodic solution representing an oscillation of the concentration of the cytokine as a cycle in their interaction.

![Figure 1](image1.png)

**Figure 1.** Continuation of the equilibrium point by varying the rate of pro-inflammatory cytokine natural production ($\mu_2$).

3.2. *Generalized Hopf bifurcation and the attractors*

Backward continuation of the Hopf point $H$ by variations of the parameter $\mu_2$ and $\mu_4$, which represent the rate of pro-inflammatory and anti-inflammatory cytokine natural production respectively, produces a Generalized Hopf bifurcation at $GH = (\mu_2, \mu_4) = (7.1987100781, 2.1075967436)$ which is in the cytokine storm condition, see Figure 2.

![Figure 2](image2.png)

**Figure 2.** Continuation of the Hopf point by varying the rate of pro-inflammatory ($\mu_2$) and anti-inflammatory cytokine natural production ($\mu_4$).

Solutions with the parameter values fixed around the Generalized Hopf point have some interesting attractors [19]. So, we focus on investigating these attractors, which represent the dynamic of the concentration of the cytokine.
Some attractors of the System (2) solution and the Lyapunov exponents of the variables are plotted by using MATLAB, see Figure 3.

![Figure 3](image)

**Figure 3.** (a) Torus at $T_1 = (\mu_2, \mu_4) = (7.1987100781, 2.1075967436)$ with the first initial value. (b) Lyapunov exponent for torus attractors at $T_1$. (c) Torus at $T_2 = (\mu_2, \mu_4) = (7.0987100781, 2.1075967436)$ with a second initial value. (d) Lyapunov exponent for torus attractors at $T_2$. (e) Torus at $T_3 = (\mu_2, \mu_4) = (7.1987100781, 2.0075967436)$ with a third initial value. (f) The Lyapunov exponent for torus attractors at $T_3$.

The attractor's initial value is estimated by calculating the equilibrium point for the set parameter values at the Generalized Hopf point by using MAPLE first. A solution around the equilibrium point converges to an attractor. We choose a value near the attractor as the initial value to generate it. We vary
\( \mu_2 \) and \( \mu_4 \) around the Generalized Hopf point and then make the same estimation for the initial values to obtain the other attractors.

Several torus attractors are found around the equilibrium point for the parameter values fixed around the Generalized Hopf point; see figure 3(a), 3(c), and 3(e). Respectively, the Lyapunov exponents for variable \( s \) and \( i \) on the torus formed at \( T_1 \) are -0.03162 and -0.100565, at \( T_2 \) are 0.033854 and -0.101338, and also at \( T_3 \) are -0.031669 and -0.100233, see figure 3(b), 3(d), and 3(f). Based on these results, all of the toruses are regular (non-chaotic) because the Lyapunov exponents of the variables are negative. These non-chaotic toruses represent some complex fluctuation patterns of pro-inflammatory and anti-inflammatory cytokine concentration [20], [21], so they are difficult to predict.

The numerical bifurcation analysis shows that the rate of pro-inflammatory and anti-inflammatory cytokine natural production are two important parameters that correlate to the cytokine storm. Based on this result, therapy by using mesenchymal stem cells (MSC) [22], chloroquine (CQ) [23], and hydroxychloroquine (HCQ) [23], which affect the production of pro-inflammatory and anti-inflammatory response, can be used to reduce the cytokine storm.

4. Conclusion

The natural production of pro-inflammatory and anti-inflammatory cytokine are two important parameters that trigger the cytokine storm. Change in these parameter values produces Generalized Hopf Bifurcation. The appearance of some non-chaotic torus as the model solution's attractors around the Generalized Hopf point is a characteristic of cytokine storm conditions. These toruses show that pro-inflammatory and anti-inflammatory cytokine concentrations fluctuate in some fairly complex patterns [20], [21]. These phenomena represent that the dynamic of pro-inflammatory and anti-inflammatory cytokine concentration is difficult to predict. Therapy to reduce the cytokine storm can be concerned with the rate of pro-inflammatory and anti-inflammatory cytokine natural production by using MSC [22], CQ [23], and HCQ [23].

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