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Global Stability of Latency Equilibria on Mathematical Model for Human Inflammatory Response to Coronavirus Infection

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Abstract. Latent phase of Coronavirus infection is a period of time in which an infected person is noninfectious and asymptomatic, so that it does not have a high risk of transmission. We construct a mathematical model that describes human inflammatory response system, i.e. interaction between pro-inflammatory and anti-inflammatory cytokine during Coronavirus infection to identify the sufficient condition for global stability of latency equilibria of the model, so that the latency period of an infected person can be maintained and transmission of Coronavirus can be prevented. The model is a three-dimensional differential equation system that has an equilibria that represents the latent phase of Coronavirus infection. The latency equilibria is globally asymptotically stable if the maximum concentration of Coronavirus is less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus. Fulfillment of the sufficient condition to create a globally asymptotically stable latency equilibria results in Coronavirus infection on the infected person will remain in latent phase, so that Coronavirus transmission can be suppressed.

INTRODUCTION

Covid-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus [1]. Covid-19 was first reported in Wuhan, Hubei Province, China [2], [3]. Since 2020, Covid-19 has become global pandemic as announced by WHO [4]. By 27 July 2021, there are 194 million Covid-19 positive cases and more than 4 million death cases [5].

Reproduction of Coronavirus takes place in a bat as its natural host [6], [7]. Coronavirus can be transmitted from animal to human or between humans [8], [9]. Close contact, droplets, and objects contaminated with the virus can become a means of the virus transmission [10]. Latent phase of Coronavirus infection is a period of time when an infected person is asymptomatic and noninfectious [11]. It is a period before an infected person can transmit the infection to another person [11].

Coronavirus infection in human body is responded by an inflammatory response system which contains interaction between pro-inflammatory and anti-inflammatory cytokine [7], [12], [13]. Pro-inflammatory cytokine is induced to respond the existence of Coronavirus and it induces anti-inflammatory cytokine as its reductor in order to maintain it from being overexpression [14].

Mathematical models of human inflammatory response to Coronavirus infection have been constructed in [12]

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and [13]. The model in [13] only concerns on characterizing the dynamics between pro-inflammatory cytokine and anti- inflammatory cytokine in common condition while the model in [12] also concerns on characterizing the dynamics of the two cytokines, but especially in cytokine storm condition [15], [16]. Coronavirus has not been included as a variable in these two models, so that we still do not know the dynamics of Coronavirus in human body, especially during the latent phase. In this research, we construct a new mathematical model which includes Coronavirus as a new variable, so that we can characterize the sufficient condition related to Coronavirus concentration to maintain the infection in the latent phase and does not progress to the infectious phase. Furthermore, the transmission of Coronavirus can be suppressed.

MATHEMATICAL MODEL

Covid-19 is caused by Coronavirus that exists in the human body. In this paper, we focus on latent phase of Coronavirus infection. In contrast to active viral infection characterized by continuous viral replication, latent viral infection is inactive or dormant, not chronic, persistent, and static [17], i.e. the virus reaches a certain concentration, does not replicate anymore [18], and lasts until the host cell dies [17]. Based on this fact, we decide to form the change of Coronavirus concentration in the body into logistic model which is appropriate to describe the latent Coronavirus infection phenomenon, because it has an interpretation to denote the static concentration of Coronavirus in latent viral infection, i.e. carrying capacity that represents the maximum concentration of Coronavirus in latent infection.

The presence of Coronavirus in the human body is responded by inflammatory response which consists of pro-inflammatory cytokine and anti-inflammatory cytokine interaction [7], [12], [13]. Pro-inflammatory cytokine is produced to respond Coronavirus infection [14], [12], [13] while anti-inflammatory cytokine is induced by the pro-inflammatory cytokine to keep it from being overproduction [14] by reducing its concentration [7], [12], [13], because the overproduction of pro-inflammatory cytokine causes cytokine storm [19], i.e. inflammation on blood vessels which can lead to death. Pro-inflammatory and anti-inflammatory cytokine also undergo a natural degradation [7], [12], [13].

Based on the interaction between Coronavirus, pro-inflammatory cytokine, and anti-inflammatory cytokine in the inflammatory response system due to the Coronavirus infection, we define some variables and parameters. The variable definition is listed in Table 1.

TABLE 1. Model variables.

Variable	Interpretation	Initial Value	Unit
V	Coronavirus concentration	Estimation	$pg/mL.noc^{a}$
P	Pro-inflammatory cytokine concentration	Estimation	$pg/mL.noc^{a}$
A	Anti-inflammatory cytokine concentration	Estimation	$pg/mL.noc^{a}$
t	Time	Estimation	$hour$

[a] noc is number of cells

All of the variables are non-negative, because V, P, A represent concentration and t denotes time. The parameter definition are listed in Table 2.

TABLE 2. Model parameters.

Parameter	Interpretation	Value	Unit	Reference
κ	Coronavirus replication rate	0.343 ± 0.178 or 0.81	$\frac{pg}{mL.hour.noc^{a}}$	Assumption
σ	Induction rate of pro-inflammatory cytokine due to Coronavirus infection	0.009 ± 0.004 or 0.81	$\frac{pg}{mL.hour.noc^{a}}$	Assumption
ω	Induction rate of anti-inflammatory cytokine due to its interaction with pro-inflammatory cytokine	0.009 ± 0.004 or 0.81	$\frac{pg}{mL.hour.noc^{a}}$	[20]
μ	Ratio of Coronavirus replication rate to the maximum concentration of Coronavirus	0.751 ± 0.198	$\frac{pg}{mL.noc^{a}}$	Assumption
φ	Degradation rate of pro-inflammatory cytokine due to its interaction with anti-inflammatory cytokine	0.343 ± 0.178	$\frac{pg}{mL.hour.noc^{a}}$	[20]
ϑ	Natural degradation rate of pro-inflammatory cytokine	0.751 ± 0.198	$hour^{-1}$	[20]

ε	Natural degradation rate of anti-inflammatory cytokine	0.87 ± 0.281	$hour^{-1}$	[20]

[a] noc is number of cells

All of the parameters are positive, because they represent the interaction rate between the cytokines and Coronavirus.

Interactions between Coronavirus, pro-inflammatory cytokine, and anti-inflammatory cytokine in the inflammatory response system due to the Coronavirus infection are illustrated in compartment diagram presented in Figure 1.

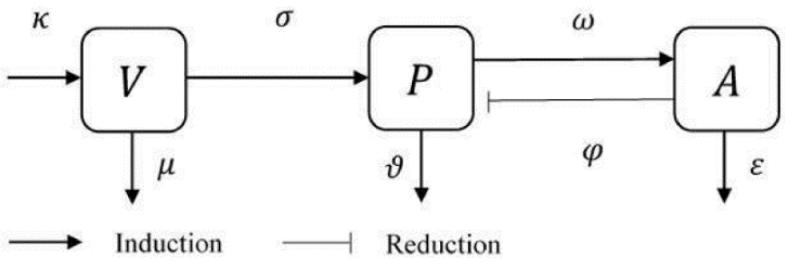


FIGURE 1. Compartment diagram of the interaction between Coronavirus, pro-inflammatory cytokine, and anti-inflammatory cytokine in the inflammatory response system due to Coronavirus infection.

By referring to the compartment diagram in Figure 1, we construct the mathematical model as a non-linear ordinary differential equation system with three-dimensional variable and seven-dimensional parameter as follows.

$$\frac{dV}{dt} = V(\kappa - \mu V) \tag{1}$$

$$\frac{dP}{dt} = \sigma VP - \varphi PA - \vartheta P \tag{2}$$

$$\frac{dA}{dt} = \omega PA - \varepsilon A \tag{3}$$

Equation (1) represents the rate of change in Coronavirus concentration with respect to time. The first term denotes Coronavirus replication and death which is denoted by a logistic form with κ as the Coronavirus replication rate and μ is the ratio of Coronavirus replication rate to the maximum concentration of Coronavirus. It follows logistic form, because the latent viral infection is persistent and static [17], so that Coronavirus does not replicate anymore [18] and lasts until the host cell dies [17]. This phenomenon fits the logistic model that has a maximum limit interpretation expressed by the carrying capacity which represents the static concentration of Coronavirus in latent viral infection.

Equation (2) represents the rate of change in pro-inflammatory cytokine with respect to time. The first term is the induction of pro-inflammatory cytokine concentration caused by Coronavirus infection with σ as the rate. The second term is the reduction of pro-inflammatory cytokine concentration caused by the interaction between pro-inflammatory cytokine and anti-inflammatory cytokine with ϕ as the rate. The third term is the reduction of pro-inflammatory cytokine concentration caused by its natural degradation with ϑ as the rate.

Equation (3) represents the rate of change of anti-inflammatory concentration with respect to time. The first term is the induction of anti-inflammatory cytokine concentration caused by the interaction between pro-inflammatory cytokine and anti-inflammatory cytokine with ω as the rate. The second term is the reduction of anti-inflammatory cytokine concentration caused by its natural degradation with v as the rate.

POSITIVITY AND BOUNDEDNESS

Positivity and boundedness of the model solution should be guaranteed in order to get the biological interpretations of the solution. Furthermore, the interpretations make the model more realistic.

Positivity of the model solution states that the solution will be positive for every time which is appropriate for expression of concentration described by the model variables.

Theorem 1. The set $\Omega = \left\{(V, P, A) \in \mathbb{R}^3_+ \cup \{0\} : V \leq \frac{\kappa}{\mu}\right\}$ is a positive invariant set with $V(0), P(0), A(0) \geq 0$ as the initial condition for the model and for all $t \in [0, \tau]$.

Proof: According to Equation (1), we obtain $\frac{dV}{dt} = V(\kappa - \mu V) \geq -\mu V^2$. Based on this inequality, we get $V(t) \geq \frac{1}{\mu t} \geq 0$. According to Equation (3), we obtain $\frac{dA}{dt} = \omega PA - \varepsilon A \geq -\varepsilon A$. Based on this inequality, we get $A(t) \geq e^{-\varepsilon t} \geq 0$. According to Equation (2), we obtain $\frac{dP}{dt} = \sigma VP - \varphi PA - \vartheta P \geq -\varphi PA - \vartheta P = -(\varphi A + \vartheta)P$. Based on this inequality, we get $P(t) \geq e^{-(\varphi \int A(t)dt + \vartheta)t} \geq 0$. We obtain $V(t), P(t), A(t) \geq 0$ and they are $\in \Omega$ for $t \in [0, \tau]$.

In Theorem 1, we obtain that the model solution will be bounded, so that the solution is not blow up to unlimited expression. It is appropriate with the fact that a concentration of a substance in the body has a maximum limit.

Theorem 2. The solution of the model $V(t), P(t), A(t)$ with $V(0), P(0), A(0) \geq 0$ as the initial condition for the model is bounded for all $t \in [0, \tau]$.

Proof: Solution of Equation (1) is $V(t) = \frac{V(0)\frac{\kappa}{\mu}}{\left(\frac{\kappa}{\mu} - V(0)\right)e^{-\kappa t} + V(0)}$, so that $\lim_{t \to \infty} \sup V(t) \leq \frac{\kappa}{\mu} = M_1$. Therefore, $V(t)$ is bounded. By adding Equation (2) and Equation (3), we get

$$\begin{aligned} \frac{dP}{dt} + \frac{dA}{dt} &= \sigma VP - \vartheta P - \varepsilon A \\ &\leq \frac{\sigma\kappa}{\mu} P - \vartheta P - \varepsilon A \\ &= -\left(\vartheta - \frac{\sigma\kappa}{\mu}\right) P - \varepsilon A \\ &\leq -\eta(P + A), \end{aligned}$$

with $\eta = \min\left\{\left(\vartheta - \frac{\sigma\kappa}{\mu}\right), \varepsilon\right\}$. Hence, we obtain $\left(P(t) + A(t)\right) \leq e^{-\eta t} = M_2$. Therefore, $P(t)$ and $A(t)$ are bounded.

LATENCY EQUILIBRIA

Latency equilibria is important to identify the noninfectious and asymptomatic condition in Coronavirus infection. The latency equilibria was investigated by solving $\frac{dV}{dt} = \frac{dP}{dt} = \frac{dA}{dt} = 0$ [13]. In the calculation, we want to generate the latent phase of Coronavirus infection through equilibria interpretation represented by two conditions. The first condition states that Coronavirus reaches its maximum concentration in latent phase $\left(V = \frac{\kappa}{\mu}\right)$, because latent viral infection is persistent and static [17], so that Coronavirus does not replicate anymore [18] and lasts until the host cell dies [17]. The second condition states that pro-inflammatory and anti-inflammatory cytokine are not produced $(P = A = 0)$ in Coronavirus latent infection, because the virus is inactive or dormant in latent viral infection [17], so that the infection does not cause inflammation.

Theorem 3. The latency equilibria is $E_l = \left(\frac{\kappa}{\mu}, 0, 0\right)$ which exist for all conditions.

Proof: By setting $\frac{dV}{dt} = \frac{dP}{dt} = \frac{dA}{dt} = 0$, we obtain

$$V(\kappa - \mu V) = 0 \quad (4)$$

$$\sigma VP - \varphi PA - \vartheta P = 0 \quad (5)$$

$$\omega PA - \varepsilon A = 0 \quad (6)$$

Based on Equation (6), we obtain $A = 0$ or $P = \frac{\varepsilon}{\omega}$. We choose $A = 0$, because virus is inactive or dormant in latent viral infection [17], so that the infection does not cause inflammation, i.e. anti-inflammatory cytokine are not produced in Coronavirus latent infection. We substitute $A = 0$ to Equation (5), so that we get $P = 0$ or $V = \frac{\vartheta}{\sigma}$. We choose $P = 0$, because virus is inactive or dormant in latent viral infection [17], so that the infection does not cause inflammation, i.e. pro-inflammatory cytokine are not produced $(P = A = 0)$ in Coronavirus latent infection. According to Equation (4), we obtain $V = 0$ or $V = \frac{\kappa}{\mu}$. We choose $V = \frac{\kappa}{\mu}$, because latent viral infection is persistent and static [17], so that Coronavirus does not replicate anymore [18] and lasts until the host cell dies [17], i.e. it reaches its maximum concentration in latent phase. Based on the calculation, we obtain an equilibria

$$E_l = \left(\frac{\kappa}{\mu}, 0,0\right)$$

E_l exists for all conditions, because the parameters values are positive including κ and μ. Since E_l satisfies the to conditions for latent viral infection stated in the beginning of this section, this equilibria is called latency equilibria which describes the condition of Coronavirus infection that remains in the latent phase, so that the infection is asymptomatic and noninfectious.

STABILITY ANALYSIS

Dynamics of Coronavirus, pro-inflammatory, and anti-inflammatory cytokine relative to E_l are characterized through its local and global stability analysis.

Local Stability

Local stability analysis describes the dynamic of the solution when the initial condition is around the latency equilibria. This analysis is carried out by linearization method.

Theorem 4. If $\frac{\kappa}{\mu} > \frac{\vartheta}{\sigma}$, then E_l is saddle. If $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$, then E_l is locally asymptotically stable.

Proof: The Jacobian matrix of the system at E_l is

$$J\left(\frac{\kappa}{\mu}, 0,0\right) = \begin{pmatrix} -\kappa & 0 & 0 \\ 0 & \frac{\sigma\kappa}{\mu} - \vartheta & 0 \\ 0 & 0 & -\varepsilon \end{pmatrix} \tag{7}$$

Based on the Jacobian matrix in Equation (7), the Jacobian matrix at the infection equilibria E_l is. Let λ is the eigen value of the Jacobian matrix in Equation (7) and I is an 3×3 identity matrix. We obtain a characteristic equation $\left|\lambda I - J\left(\frac{\kappa}{\mu}, 0,0\right)\right| = 0$ which is equivalent to

$$(\lambda + \kappa)\left[\lambda - \left(\frac{\sigma\kappa}{\mu} - \vartheta\right)\right](\lambda + \varepsilon) = 0 \tag{8}$$

Based on Equation (8), we get the eigen value of Jacobian matrix in Equation (7) are $\lambda_1 = -\kappa < 0$, $\lambda_2 = \frac{\sigma\kappa}{\mu} - \vartheta$, and $\lambda_3 = -\varepsilon < 0$. According to this result, if $\frac{\sigma\kappa}{\mu} - \vartheta > 0$ which is equivalent to $\frac{\kappa}{\mu} > \frac{\vartheta}{\sigma}$, then the equilibria E_l is saddle. If $\frac{\sigma\kappa}{\mu} - \vartheta < 0$ which is equivalent to $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$, then the equilibria E_l is asymptotically stable.

Global Stability

Global stability analysis for the latency equilibria describes the characteristic that should be fulfilled in order to make Coronavirus infection in latent phase for a long time and any initial condition.

Theorem 5. E_l is globally asymptotically stable if $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$.

Proof: By defining $L = P + A$, we obtain

$$\begin{aligned} \frac{dL}{dt} &= \sigma VP - \vartheta P - \varepsilon A \\ &\leq \frac{\sigma\kappa}{\mu} P - \vartheta P - \varepsilon A \\ &\leq \left(\frac{\sigma\kappa}{\mu} - \vartheta\right) P - \varepsilon A \\ &\leq 0 \end{aligned}$$

Beside that, $\frac{dL}{dt} = 0$ if and only if $P = 0$ and $A = 0$. It shows that the largest invariant set in $\left\{(V, P, A) \in \Omega, \frac{dL}{dt} = 0\right\}$ is E_l. According to LaSalle-Lyapunov Theorem [21], E_l is globally asymptotically stable.

NUMERICAL SIMULATION

In local case, the dynamics are simulated when the maximum concentration of Coronavirus is greater than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus and when the maximum concentration of Coronavirus is less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus. These simulations are created to illustrate the difference between the saddle and asymptotically stable dynamics around the latency equilibria if the sufficient condition is fulfilled. In global case, the dynamics are simulated when the maximum concentration of Coronavirus is less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus. This simulation is created to illustrate the globally asymptotically stable dynamics towards the latency equilibria for any initial conditions if the sufficient condition is fulfilled.

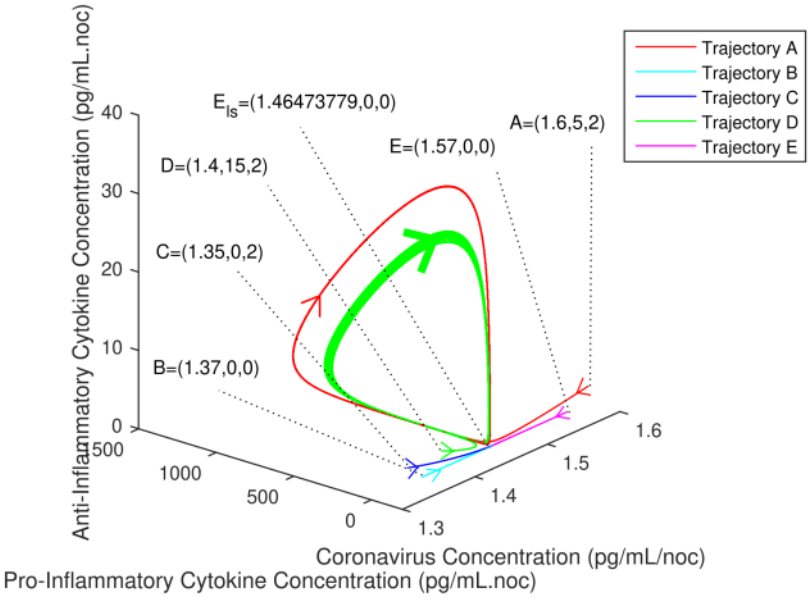
Local Dynamics

Dynamics of the system solution are obtained by setting the parameter values, so that they fulfill the sufficient condition to generate two different local dynamic of the latency equilibria, i.e. the saddle dynamic which requires $\frac{\kappa}{\mu} > \frac{\vartheta}{\sigma}$ and locally asymptotically stable dynamic which requires $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$. The parameter values are listed in Table 3.

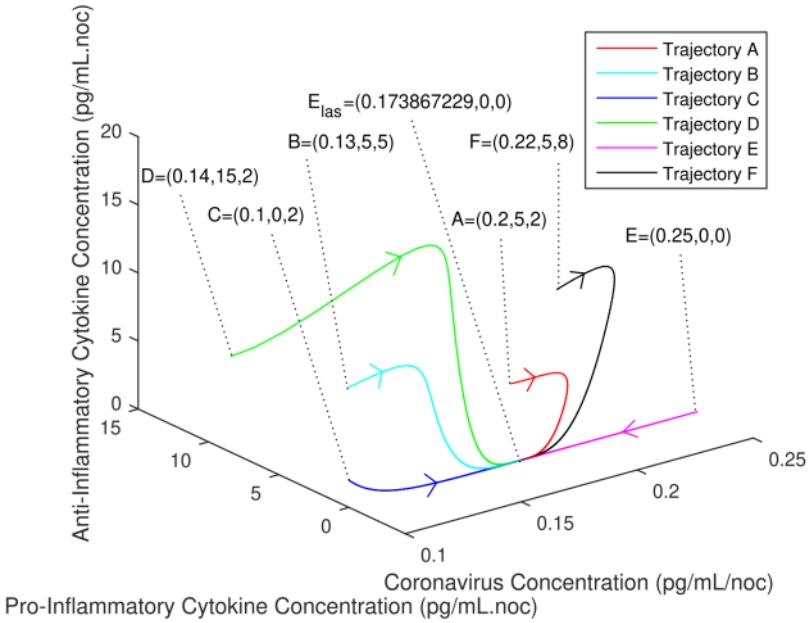
TABLE 3. Parameter values for the simulation of the latency equilibria local stability dynamic.

Parameter	Saddle Dynamic Case Value	Locally Aymptotically Stable Dynamic Case Value
κ	0.81	0.165
σ	0.81	0.005
ω	0.005	0.81
μ	0.553	0.949
φ	0.165	0.521
ϑ	0.553	0.949
ε	1.151	0.589

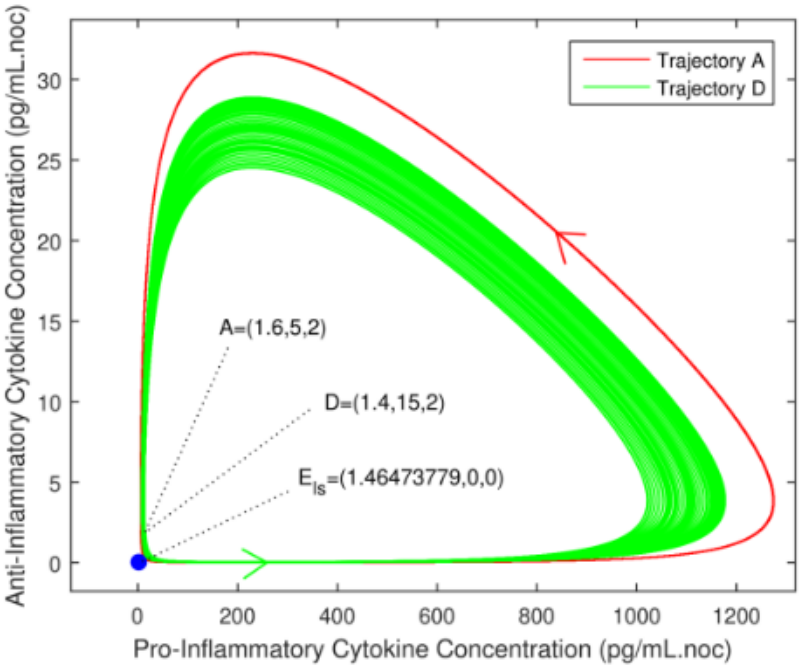
Based on the parameter values in Table 3, we obtain the latency equilibria in saddle dynamic case is $E_{ls} = (0.727, 1.189, 0)$ and in locally asymptotically stable dynamic case is $E_{las} = (0.727, 1.189, 0)$. The simulation is presented in Figure 2.



(a)



(b)



(c)

FIGURE 2. Saddle dynamic of the system solution around El_S (a), locally asymptotically stable dynamic of the system solution around El_{as} (b), and periodic solution in saddle dynamic of the system solution around El_S (c).

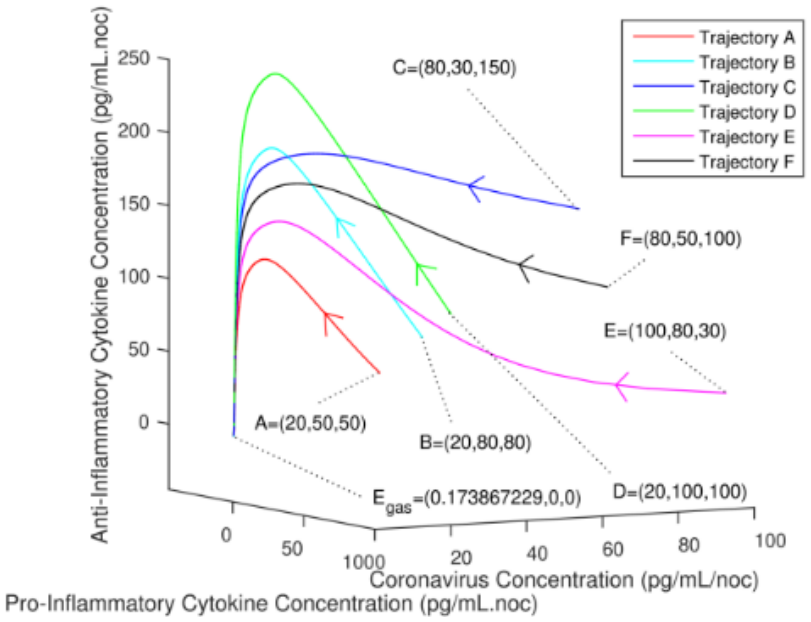
Simulation in Figure 2 (a) illustrates the saddle dynamic around the latency equilibria when $\frac{\kappa}{\mu} > \frac{\vartheta}{\sigma}$, i.e. the maximum concentration of Coronavirus is less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus. It generates two manifold, i.e. stable manifold and unstable manifold. The stable manifold converge to the latency equilibria while the unstable manifold move out from the latency equilibria and form some periodic solutions. This saddle dynamic represents two possibilities on the dynamics of Coronavirus, pro-inflammatory cytokine, and anti-inflammatory

cytokine concentration around the latency equilibria. The first one is converge to the latency equilibria which implies the maintenance of latent phase in Coronavirus infection for a long time when the initial condition is around the latency equilibria, so that Coronavirus transmission can be suppressed. The second one is move out from the latency equilibria and form a periodic solution which implies Coronavirus still infects, so that the inflammation always occurs. The inflammation is responded by the reciprocal interaction between pro-inflammatory cytokine and anti-inflammatory cytokine forming a cycle. A clearer illustration of the cycle can be seen in Figure 2 (c).

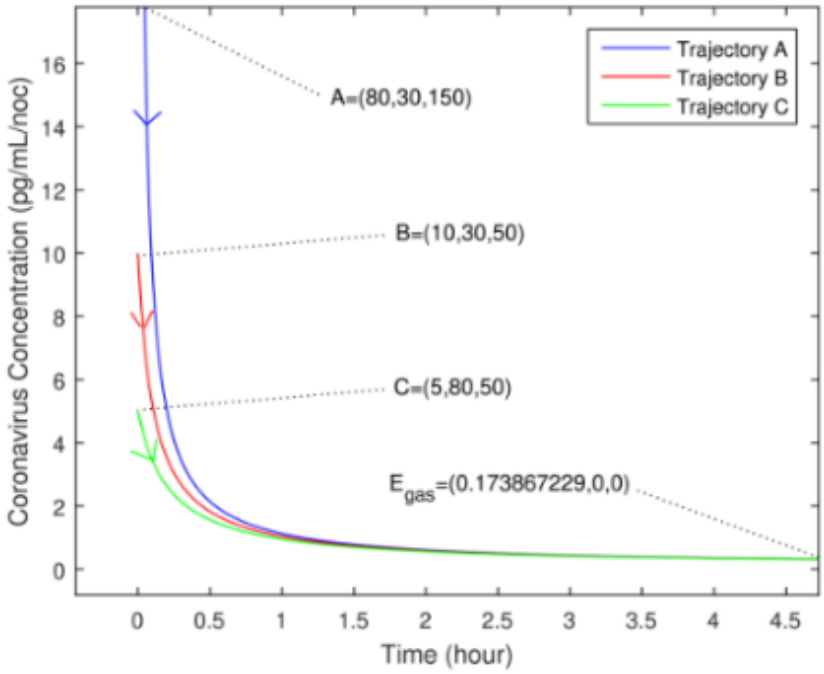
Simulation in Figure 2 (b) illustrates the locally asymptotically stable dynamic around the latency equilibria when $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$. The dynamic of Coronavirus, pro-inflammatory cytokine, and anti-inflammatory cytokine concentration around the latency equilibria converge to the latency equilibria when the maximum concentration of Coronavirus is less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro- inflammatory cytokine concentration caused by Coronavirus. It represents the maintenance of the latent phase in Coronavirus infection for a long time when the initial condition is around the latency equilibria. In this condition, Coronavirus transmission can be suppressed, but only for initial conditions that around the latency equilibria.

Global Dynamics

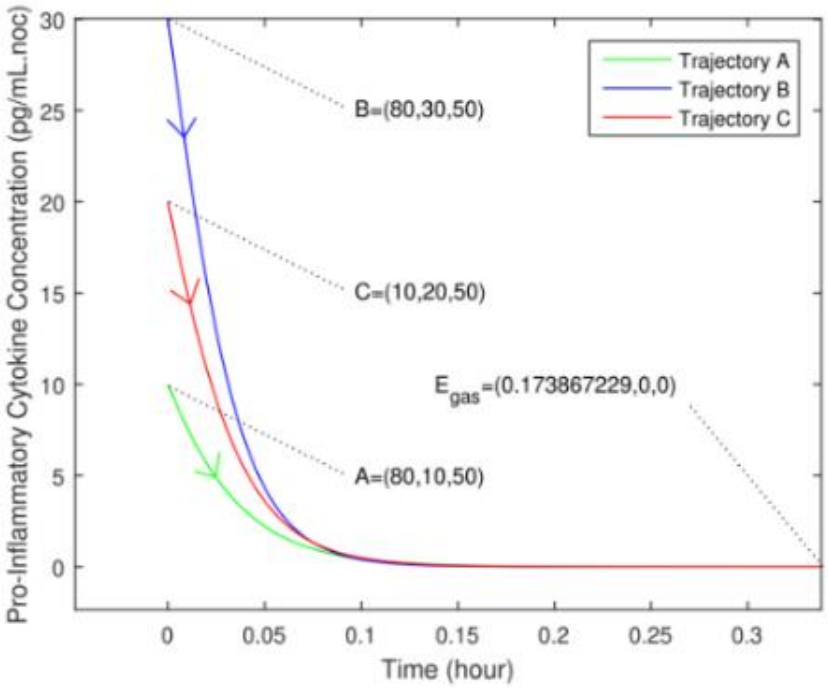
Dynamic of the system solution is obtained by setting the parameter values, so that they fulfill the sufficient condition to generate the globally asymptotically stable dynamic of the latency equilibria, i.e. $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$. We set the parameter values to be the same as the parameter value in the local dynamic simulation, because they have the same sufficient condition. We obtain the latency equilibria in globally asymptotically stable dynamic case is $E_{gas} = (0.727,1.189,0)$. The simulation is presented in Figure 3.



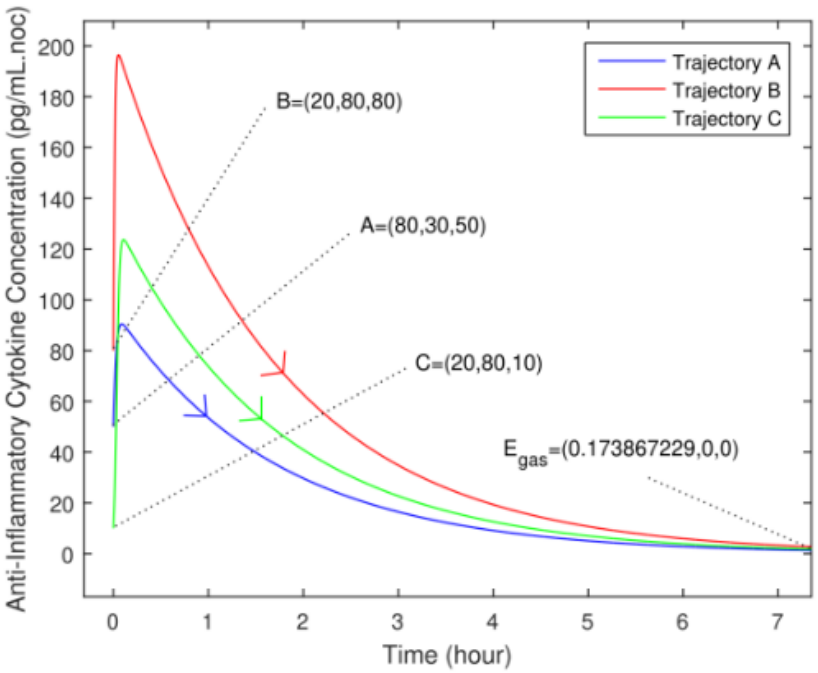
(a)


Trajectory A
Trajectory B
Trajectory C
A=(80,30,150)
B=(10,30,50)
C=(5,80,50)
E_gas=(0.173867229,0,0)
Coronavirus Concentration (pg/mL/noc)
Time (hour)
0
2
4
6
8
10
12
14
16
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5

(b)


Trajectory A
Trajectory B
Trajectory C
B=(80,30,50)
C=(10,20,50)
E_gas=(0.173867229,0,0)
A=(80,10,50)
Pro-Inflammatory Cytokine Concentration (pg/mL.noc)
Time (hour)
0
5
10
15
20
25
30
0
0.05
0.1
0.15
0.2
0.25
0.3

(c)



(d)

FIGURE 3. Globally asymptotically stable dynamic of E_{gas} (a), Coronavirus concentration dynamic with respect to time relative to E_{gas} (b), pro-inflammatory cytokine concentration dynamic with respect to time relative to E_{gas} (c), and anti-inflammatory cytokine concentration dynamic with respect to time relative to E_{gas} (d).

Simulations in Figure 3 illustrate the globally asymptotically stable dynamic of the latency equilibria. They represent the dynamics of Coronavirus, pro-inflammatory cytokine, and anti-inflammatory cytokine concentration that converge to the latency equilibria for a long time and any initial condition if the sufficient condition, i.e. $\frac{\kappa}{\mu} < \frac{\vartheta}{\sigma}$ is fulfilled. It means that the latent phase of Coronavirus infection can be maintained for a long time and any initial condition if the maximum concentration of Coronavirus is less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus, so that the transmission of Coronavirus can be suppressed.

CONCLUSION

Latency equilibria represents a condition when Coronavirus infection remains in latent phase, so that an infected person is noninfectious and asymptomatic. The maximum concentration of Coronavirus should be less than the ratio between the natural degradation of pro-inflammatory cytokine and the increasing rate of pro-inflammatory cytokine concentration caused by Coronavirus in order to maintain the latent condition of Coronavirus infection in an infected person for any initial condition, so that the transmission of Coronavirus can be suppressed.

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