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Research paper

Stability analysis in COVID-19 within-host model with immune response

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ABSTRACT

The 2019 coronavirus disease (COVID-19) is now a global pandemic. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative pathogen of COVID-19. Here, we study an in-host model that highlights the effector T cell response to SARS-CoV-2. The stability of a unique positive equilibrium point, with viral load \( V^* \), suggests that the virus may replicate fast enough to overcome T cell response and cause infection. This overcoming is the bifurcation point, near which the orders of magnitude for \( V^* \) can be sensitive to numerical changes in the parameter values. Our work offers a mathematical insight into how SARS-CoV-2 causes the disease.

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the official name given to the virus behind the 2019 coronavirus disease (COVID-19) [1]. This pathogen is now the cause of a global pandemic, which began late December 2019 in Wuhan, China [2–4]. As of October 25, 2020, World Health Organization and the European CDC estimates are at least 42 million confirmed cases and 1.1 million deaths. The health, economic, and social impacts of the coronavirus pandemic have urged worldwide action [5–7].

Several SIR type epidemiological mathematical models have been proposed to assist policy makers in order to infer disease-control interventions [8–10], as well as tools to track epidemic trajectories (e.g., [7]) have been widely developed. While potential vaccines and antiviral drugs are under investigation [2,11,12], epidemiological models have underlined the relevance of social distancing interventions as the main weapon so far to mitigate the epidemic.

Previous coronavirus outbreaks in Asia 2003 (SARS-CoV) and in Saudi Arabia 2012 (MERS-CoV) have uncovered similar aspects to SARS-CoV-2. For example, viral dynamics in patients with MERS-CoV [13] showed that viral levels peak during the second week with a median value of 7.21 (log10 copies/mL) in the severe patient group, and about 5.54 (log10 copies/mL) in the mild group. In patients with SARS, the virus peaked at 5.7 (log10 copies/mL) between 7 to 10 days after onset [14]. For COVID-19, the viral peak was approximately 8.85 (log10 copies/mL) before 5 days post symptoms onset (dpso) [15].

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COVID-19 patients with severe disease reported a mean viral load on admission 60 times higher than that of the mean of mild disease cases, implying that higher viral loads relate clinical outcomes [16]. Furthermore, viral load persisted for 12 days after onset [16].

T cell responses play a key aspect for the management of the current COVID-19 pandemic. Lymphocyte subsets and cytokine profiles in the peripheral blood in [17] showed that the severe COVID-19 patients compared to those in the mild cases had significant decrease in T cell levels, especially CD8+ T cells, as well as increases in IL-6, IL-10, IL-2 and IFN-γ levels. In fact, recent studies [18] have suggested that pre-existing T cells present in the general population impact susceptibility and pathogenesis of SARS-CoV-2 infection. Another critical aspect of the immune systems is the B cell responses. A prospective cohort with COVID-19 patients in [19] showed that IgM started on day 7 while that of IgG was on day 10 and day 49 after illness onset. IgM and IgG titers are significantly higher in severe patients than non-severe patients. Ultimately, a collection of studies found that COVID-19 disease involves a range of biological mechanisms, including cellular-membrane entry points, elevated pro-inflammatory levels, and activation of immune cells—see, e.g., [12,20,21] for a review.

Bringing together the pathogenesis and the immune responses to COVID-19 are still needed. Mathematical models may provide conceptual frameworks to study immune responses to SARS-CoV-2 dynamics. At the moment, there are too few modeling efforts at the within-host level of the COVID-19 disease. The study in [22] employed a target cell model to estimate infection parameter values based on chest radiograph scoring system [23,24]. However, this model assumed the immune response as an implicit constant value contributing to the death of infected host cells. The study in [25] provided different mechanistic models to represent SARS-CoV-2 dynamics in patients with COVID-19. Among the different mathematical models in [25], the model with the best fit to viral load data presented in [26] prioritizes self-limiting viral replication and effector T cell responses, which may peak between 5 to 10 days post onset of symptoms. The models in [22] and [25] progressed our knowledge in SARS-CoV-2 dynamics, however there were no further stability analysis. Because of the importance to advance our understanding of how the immune system responds to SARS-CoV-2 [27,28], we study the mathematical model in [25] with effector T cell responses.

Our paper is organized as follows. The model describing SARS-CoV-2 dynamics and its respective bifurcation analysis is presented in Section 2, which characterizes the stability of the virus-free equilibrium point. Subsection 2.2 establishes the stability of a unique positive equilibrium point. Sensitivity analysis of the within-host model is introduced in Section 3. Discussions are presented in Section 4, where we provide insight into the results supported by numerical examples.

2. Bifurcation analysis

The model proposed in [25] that focuses on effector T cell responses is given by

\[
\frac{dV}{dt} = pV(1 - \frac{V}{K}) - c_TVT - cV, 
\]

(1)

\[
\frac{dT}{dt} = s_T + rT G(V) - \delta_T T, 
\]

(2)

where T is the number of effector T cells, and V is the density of SARS-CoV-2 (log10 copies/mL). The underlying assumption in this model is that viral clearance is mainly driven by T cell responses, this observation is based on different viral infections [29]. Here, the viral replication rate is \( p \) (1/day), maximum carrying capacity is \( K \) (log10 copies/mL), and viral clearance rate is \( c \) (1/day). Without infection, effector T cells remain to the homeostatic level \( T_0 = s_T/\delta_T \) (initial number of T cells), where \( s_T \) (cells/day) and \( \delta_T \) (1/day) are the homeostatic generation rate and the half-life of T cells, respectively. The activation of T cells during infection is represented with the term \( rT G(V) \), where

\[
G(V) = \frac{V^m}{V^m + k_T^m} 
\]

(3)

and \( r \) (1/day) is the maximum activation rate. The term \( c_TVT \) reflects the elimination of the virus by T cells with rate \( c_T \) (per T cell per day). The activation function \( G \) satisfies

\[
G(0) \text{ and } G'(V) = \frac{dG}{dV} > 0 \text{ for all } V > 0. 
\]

(4)

Two values control the rate of increase of \( G \), namely the coefficient \( m \) (dimensionless) and the half-saturation constant \( k_T \) (log10 copies/mL). The units for \( m \) and \( k_T \) render \( G(V) \) a dimensionless quantity.

The modeling work in [25] assumed a log-sigmoidal form of T cell activation, i.e., with \( m = 2 \). To allow for generality of our results, we can assume any bounded function \( G \) that satisfies (4). Complementing our analysis are numerical results using different sets of parameter values in Table 1.

We emphasize that the model (1)-(2) is minimal in its formulation, based on available data and potential limitations in parameter estimation. This model prioritizes effector T cell responses to SARS-CoV-2 in the host, leaving out other immunological mechanisms to c. Note that this model has a big potential to evaluate therapeutic strategies, e.g., inhibiting viral replication or enhancing T cell reinforcements. For our analysis, we assume a positive constant value for each parameter.
2.1. Bifurcation parameter

We obtain the bifurcation parameter from the stability of the equilibrium point where $V = 0$. This equilibrium point is uniquely given by

$$ E_0 = (0, s_T/\delta_T) = (0, T_0). $$

To determine the stability, we compute the Jacobian matrix

$$ J(V, T) = \begin{bmatrix} p(1 - \frac{V}{K}) - \frac{pV}{rT} - c_T T - c & -c_T V \\ r G(V) - c_T \end{bmatrix}. $$

Theorem 1. Let

$$ \lambda = p - c - c_T T_0. $$

Then $E_0$ is locally asymptotically stable for $\lambda < 0$, is non-hyperbolic for $\lambda = 0$, and is unstable (more precisely, a saddle) for $\lambda > 0$. Furthermore, $E_0$ is a stable node if $\lambda < 0$ but $\lambda \neq -\delta_T$, and $E_0$ is a degenerate stable node when $\lambda = -\delta_T$.

Proof. Evaluating the Jacobian matrix at $E_0$, i.e., $J(E_0)$, we obtain two eigenvalues: $-\delta_T$ and $\lambda$. Thus, $E_0$ is locally asymptotically stable for $\lambda < 0$, non-hyperbolic for $\lambda = 0$, and unstable for $\lambda > 0$. Consider the trace and the determinant of $J(E_0)$, which are

$$ T = \lambda - \delta_T \quad \text{and} \quad D = -\lambda \delta_T, $$

respectively. In the unstable case where $\lambda > 0$, we have $D < 0$, hence $E_0$ is a saddle. If $\lambda < 0$, then

$$ T^2 - 4D = (\lambda^2 - 2\lambda \delta_T + \delta_T^2) + 4\lambda \delta_T $$$$ = (\lambda + \delta_T)^2 \geq 0 $$

and $T^2 = 4D$ if and only if $\lambda = -\delta_T$. Therefore, $E_0$ is a stable node if $\lambda < 0$ but $\lambda \neq -\delta_T$, and $E_0$ is a degenerate stable node when $\lambda = -\delta_T$. 

From now on, the eigenvalue $\lambda$ will serve as our bifurcation parameter. Under any choice of parameter values, the value of $\lambda$ is always bounded by

$$ \lambda_{\min} < \lambda < \lambda_{\max}, \lambda_{\min} = -c - c_T T_0. $$

2.2. Positive equilibrium

We turn our attention to finding an equilibrium point $E^* = (V^*, T^*)$, where $V^* > 0$. The coordinates of $E^*$ satisfy the following equations:

$$ p\left(1 - \frac{V^*}{K}\right) - c_T T^* - c = 0, \quad (9) $$

$$ s_T + r T^* G(V^*) - \delta_T T^* = 0. \quad (10) $$

Equation (10) necessitates $T^* > 0$. By applying (7) to express $p$ in terms of $\lambda$, we solve Eq. (9) for $T^*$ and obtain

$$ T^* = \frac{p[V_{\max}(\lambda) - V^*]}{c_T K}, V^* > 0. \quad (11) $$
where
\[ V_{\text{max}}(\lambda) = \frac{(p - c)K}{p} = \left( \frac{\lambda + cT_0}{\lambda + cT_0 + c} \right) K. \] (12)

**Lemma 1.** If \( V^* > 0 \), then the following properties hold:

(A) \( T^* > 0 \) if and only if \( V^* < V_{\text{max}}(\lambda) \).

(B) The quantities \( V_{\text{max}}(\lambda) \), \( p - c \), and \( \lambda + cT_0 \) have equal sign.

**Proof.** Property (A) is a consequence of Eq. (11). We establish property (B) by taking signs through Eq. (12), and noting from the definition of \( \lambda \) that \( p = \lambda + cT_0 + c > 0 \). \( \Box \)

To establish the existence and uniqueness of \( E^* \), we establish that \( V = V^* \) solves the equation \( G(V) = G_0(V) \) where
\[ G_0(V) = \frac{\delta_T}{r} \left[ 1 - \frac{cT_0 K}{pV_{\text{max}}(\lambda) - V} \right]. \] (13)

Then \( G_0 \) is a rational function of \( V \), where the graph of \( y = G_0(V) \) has the vertical asymptote \( V = V_{\text{max}}(\lambda) \) and the horizontal asymptote \( y = \delta_T/r \). Furthermore,
\[ \frac{dG_0}{dV} = \frac{-cT_0 K}{rp[V_{\text{max}}(\lambda) - V]^2} < 0. \] (14)

and hence \( G_0 \) strictly decreases on its natural domain. Thus, \( G_0 \) has the unique root \( \hat{V}(\lambda) = V_{\text{max}}(\lambda) - \frac{cT_0 K}{p} \).

By virtue of Eq. (7) and (12), we have \( \hat{V}(\lambda) = \lambda K/p \), and \( \hat{V}(\lambda) > 0 \) if and only if \( \lambda > 0 \).

**Lemma 2.** Assuming \( p > c \), we have \( G_0(0) > 0 \) if and only if \( \lambda > 0 \).

**Proof.** We compute \( G_0(0) \) as
\[ G_0(0) = \frac{\delta_T}{r} \left[ 1 - \frac{cT_0 K}{pV_{\text{max}}(\lambda)} \right] = \frac{\delta_T \lambda}{\lambda + cT_0} \] (16)

where Eq. (7) and (12) provide \( pV_{\text{max}}(\lambda) = (p - c)K = (\lambda + cT_0)K \). Since \( \lambda + cT_0 = p - c > 0 \), we take signs through Eq. (16) and conclude that \( G_0(0) > 0 \) if and only if \( \lambda > 0 \). \( \Box \)

**Lemma 3.** Assuming \( p > c \), the function \( H = G_0 - G \) admits a unique root on the open interval \((0, V_{\text{max}}(\lambda))\) if and only if \( \lambda > 0 \). This root is unique and lies in the open interval \((0, \hat{V}(\lambda))\).

**Proof.** Recall Eq. (4), where \( G(0) = 0 \) and \( G'(V) > 0 \). Since \( G'_0(V) < 0 \) by (14), we see that \( H'(V) < 0 \) and \( H \) strictly decreases. Therefore, \( H \) has a root on \((0, V_{\text{max}}(\lambda))\) if and only if \( H(0) = G_0(0) > 0 \), i.e., \( \lambda > 0 \) by **Lemma 2**.

It follows from Eq. (15) that \( 0 < \hat{V}(\lambda) < V_{\text{max}}(\lambda) \) if and only if \( \lambda > 0 \). Since \( \hat{V}(\lambda) \) is the root of \( G_0 \), i.e., \( G_0(\hat{V}(\lambda)) = 0 \), we obtain
\[ H(\hat{V}(\lambda)) = G_0(\hat{V}(\lambda)) - G(\hat{V}(\lambda)) < 0 < H(0). \]

Thus, \( H \) admits a root on the open interval \((0, \hat{V}(\lambda))\); the strict decreasing property of \( H \) guarantees the uniqueness of this root. Finally, \( H \) has no root in the open interval \((\hat{V}(\lambda), V_{\text{max}}(\lambda))\) where \( G_0 < 0 \) and \( H < 0 \). Therefore, \( H \) has a root in \((0, V_{\text{max}}(\lambda))\) if and only if \( \lambda > 0 \), and this root is a unique value in \((0, \hat{V}(\lambda))\). \( \Box \)

**Theorem 2.** Consider the positive equilibrium point \( E^* = (V^*, T^*) \). Then
\[ T^* = \frac{p[V_{\text{max}}(\lambda) - V^*]}{cTK}, \] (17)

and \( V = V^* \) is the unique solution of \( G(V) = G_0(V) \) in the open interval \((0, \hat{V}(\lambda))\). Moreover, \( E^* \) exists if and only if \( p > c \) and \( \lambda > 0 \).

**Proof.** Equation (17) restates (11). According to both properties of **Lemma 1**, we have \( T^* > 0 \) and equivalently \( 0 < V^* < V_{\text{max}}(\lambda) \) only when \( p > c \). Assuming that \( p > c \), Eq. (10) yields
\[ G(V^*) = \frac{\delta_T}{r} - \frac{\delta_T}{r} = \frac{\delta_T}{r} \left( 1 - \frac{\delta_T}{\delta_T r} \right), \] (18)

or \( H(V^*) = G_0(V^*) - G(V^*) = 0 \) by applying (17). Therefore, \( V^* \) is the unique root of \( H \) in the open interval \((0, V_{\text{max}}(\lambda))\). We conclude by **Lemma 3** that \( E^* \) exists with unique coordinates if and only if \( p > c \) and \( \lambda > 0 \). \( \Box \)
Assuming the explicit form (3) of G, we can transform the equation \( H(V) = 0 \) by way of scaling. Since \( G \) strictly increases for \( V > 0 \), we can express \( V \) in terms of \( \mu = G(V) \) in a one-to-one correspondence given by
\[
\mu = \frac{V}{V^m + k_0^m} \iff V = k_1 \left( \frac{\mu}{1 - \mu} \right)^{1/m} \tag{19}
\]
for \( V > 0 \) and equivalently \( 0 < \mu < 1 \). Then we express \( G_0(V) \) as a function of \( \mu \): from equation (13) we have
\[
G_0(V) = \frac{\delta_T}{V} \left[ \frac{R(\mu) - Q(\lambda)S(\mu, \lambda)}{R(\mu) - S(\mu, \lambda)} \right],
\]
where
\[
Q(\lambda) = \frac{\lambda}{\lambda + cT_0}, \quad R(\mu) = k_1 \mu^{1/m}, \quad S(\mu, \lambda) = V_{\text{max}}(\lambda)(1 - \mu)^{1/m}.
\]
Hence, we can solve for \( V \) in the equation
\[
G(V) = G_0(V), \quad 0 < V < \hat{V}(\lambda) = \frac{\lambda K}{\lambda + c + c_T T_0}, \tag{20}
\]
by finding a root for the function
\[
h(\mu) := \mu - \frac{\delta_T}{V} \left[ \frac{R(\mu) - Q(\lambda)S(\mu, \lambda)}{R(\mu) - S(\mu, \lambda)} \right], \quad 0 < \mu < G(\hat{V}(\lambda)) < 1, \tag{21}
\]
and then evaluating the corresponding \( V \) with Eq. (19). One may prefer (21) over (20) to avoid evaluation at significantly large values.

**Theorem 3.** Suppose that the positive equilibrium point \( E^* \) exists, i.e., \( p > c \) and \( \lambda > 0 \). Let \( T \) and \( D \) denote the trace and determinant of Jacobian matrix \( J(E^*) \). Then \( T < 0 \), \( D > 0 \), and all eigenvalues of \( J(E^*) \) have negative real part; therefore, \( E^* \) is locally asymptotically stable. Moreover, \( E^* \) is a stable node for \( \Delta := T^2 - 4D > 0 \), a degenerate stable node for \( \Delta = 0 \), or a stable spiral for \( \Delta < 0 \).

**Proof.** Assuming the existence of \( E^* \), we evaluate Eq. (6) at \( E^* \) to get
\[
J(E^*) = \begin{bmatrix}
\frac{p(1 - V^*)}{K} - \frac{p_v}{r} - cT^* - c & -cT^* \\
\frac{-p_v}{r} & \frac{rG(V^*)}{T^*} + \delta_T
\end{bmatrix}.
\]
This Jacobian matrix reduces to
\[
J(E^*) = \begin{bmatrix}
\frac{-p_v}{r} & -cT^* \\
\frac{-p_v}{r} & \frac{rG(V^*)}{T^*} + \delta_T
\end{bmatrix}
\]
by application of Eqs. (9) and (18). The trace \( T \) and the determinant \( D \) of \( J(E^*) \) is given by
\[
T = -\left( \frac{p_v}{K} + \frac{\delta_T}{T^*} \right) \quad \text{and} \quad D = \frac{p_vT^*}{KL} + c_T rV^* G(V^*).
\]
Since both \( V^* \) and \( T^* \) are positive, and \( G(V^*) > 0 \) by (4), we have \( T < 0 \) and \( D > 0 \). Therefore, the characteristic equation of the matrix \( J(E^*) \), namely
\[
x^2 - Tx + D = 0 \quad \text{(in x)}
\]
has all coefficients positive. Equivalently, all eigenvalues of \( J(E^*) \) have negative real part according to the Routh-Hurwitz criterion. Therefore, \( E^* \) is locally asymptotically stable. If \( \Delta > 0 \), then the eigenvalues of \( J(E^*) \) are real and distinct, which determines \( E^* \) as a stable node. The degenerate stable node case holds when \( \Delta = 0 \), from which the eigenvalues are real and equal. Finally, \( \Delta < 0 \) makes the eigenvalues become complex conjugates with negative real part (i.e., \( T \)), hence \( E^* \) becomes a stable spiral. \( \Box \)

**Remark.** The change in qualitative behavior of \( E^* \) depends on the value of \( \Delta \) in Theorem 3, which is
\[
\Delta = \left( \frac{p_v}{K} - \frac{\delta_T}{T^*} \right)^2 - 4 r c_T V^* G(V^*) T^*.
\tag{22}
\]
We draw two observations:

1. If \( V^* \approx 0 \) or \( V^* \approx V_{\text{max}}(\lambda) \), then \( V^* T^* \approx 0 \) by Eq. (17). Thus, Eq. (22) yields \( \Delta \approx \left( \frac{p_v}{K} - \frac{\delta_T}{T^*} \right)^2 \) and \( E^* \) becomes either a stable node or a degenerate stable node.

2. For values of \( V^* \) that are neither small nor sufficiently near \( V_{\text{max}}(\lambda) \), increasing \( G'(V^*) \) drives \( \Delta \) towards negative values and \( E^* \) towards the stable spiral regime.

Regardless of the value of \( V^* \), the proof in Theorem 3 asserts that the eigenvalues of the Jacobian matrix \( J(E^*) \) have negative real parts, hence they never cross the imaginary axis of the complex plane. This result prevents Hopf bifurcation with respect to \( \lambda \).
Fig. 1. Bifurcation diagram for the model (1)-(2). Solid and dashed lines depict stable and unstable equilibrium points, respectively. The bifurcation occurs at $\lambda = 0$ (square marker). To generate the diagram, all values in the parameter set Mean of Table 1 are used, except for $p$ that is obtained from $\lambda$ via Eq. (7).

Fig. 2. The trace and discriminant values associated with the equilibrium point $E^*$. The blue line represents the negative trace $T$ of the Jacobian matrix $J(E^*)$ and the red line represents the discriminant $\Delta = T^2 - 4D$ where $D$ is the determinant. Observe that $\Delta = 0$ at $\lambda \approx 0.0153$, and $T$ approaches zero as $\lambda$ increases. All parameters except $p$ take values from the set Mean of Table 1, while $p = \lambda + c + cT_0$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Numerical example

Theorems 1, 2, and 3 characterize the existence and local stability of the equilibrium points $E_0 = (0, T_0)$ and $E^* = (V^*, T^*)$. We now complement these mathematical results with numerical simulations. Here, all parameters except $p$ take the values in the set Mean of Table 1. Observe that $p$ has a one-to-one correspondence with $\lambda$, namely $p = \lambda + c + cT_0$ by Eq. (7). Based on the maximum value of $p$ and $cT$ in Table 1, we may impose the following restriction: $-2 \leq \lambda \leq 2$. With our chosen parameter values, we generate our bifurcation diagram in Fig. 1.

To expand on the remark made after Theorem 3 and explore the possibility of oscillations in the viral load, we consider the trace $T$ and the discriminant $\Delta$ associated with $E^*$, as depicted in Fig. 2; the determinant is given by $D = \frac{1}{4}(T^2 - \Delta)$. Again, we choose set Mean in Table 1 and let $p = \lambda + c + cT_0$.

Fig. 3 depicts changes in the viral load trajectory with different values of $\lambda$. When $\lambda$ increases and crosses the bifurcation value $\lambda = 0$, the viral load switches from being strictly decreasing to strictly increasing, corresponding to the exchange of stability between $E_0$ and $E^*$ (Fig. 1). The next bifurcation is at $\lambda \approx 0.0153$, where the discriminant switches signs from positive to negative, and $E^*$ switches from being a stable node to a stable spiral. Fig. 3 shows the corresponding effect: the viral load begins to experience oscillations that dissipate over time. Further increasing $\lambda$ reduces the magnitude of $T$ to zero, thereby increasing $D$ with $D \approx -\frac{1}{4}\Delta$. Moreover, the point $(T, D)$ approaches the positive $D$-axis, and $E^*$ becomes a stable spiral that comes qualitatively close to being a center. Hence, the oscillations become more pronounced with a larger initial amplitude and a slower rate of dissipation, as confirmed numerically with the yellow and orange lines in Fig. 3. Another way to look at the long-term behavior of the model solution is a phase plane. Fig. 4 displays the solution curve $(V(t), T(t))$ for one of the cases $\lambda = 1$ in Fig. 3. This phase plane numerically validates the global asymptotic stability of $E^*$; we may also get the same result for $E_0$ when $\lambda < 0$. The solution curve appears dense near $E^*$, which reflects the aforementioned oscillations with slow dissipation.
3. Sensitivity analysis

A sensitivity analysis of the model given by equations (1) and (2) is presented in this section. The aim is to compute the dynamical change of the model solution with respect to each parameter. Firstly, let us consider the general state equation of a nonlinear dynamical system:

$$\dot{x} = f(t, x, \eta),$$  \hfill (23)

where $f(t, x, \eta)$ is continuous in $(t, x, \eta)$ and has continuous first partial derivatives with respect to $x \in \mathbb{R}^N$ and $\eta \in \mathbb{R}^M$. for all $(t, x, \eta) \in [t_0, t_f] \times \mathbb{R}^N \times \mathbb{R}^M$; $N$ is the number of states and $M$ is the number of parameters. It is possible to know how the solution of Eq. (23) changes, with respect to parametric variation, that is:

$$x_\eta(t, \eta) = \frac{\partial x(t, \eta)}{\partial \eta},$$  \hfill (24)

by means of the solution of the so-called sensitivity function:

$$\dot{S}(t) = A(t, \eta_0)S(t) + B(t, \eta_0), \quad S(t_0) = 0,$$  \hfill (25)

where $S(t) = x_\eta(t, \eta_0) \in \mathbb{R}^{N \times M}$, $A(t, \eta_0) = \frac{\partial f(t, x, \eta_0)}{\partial x} \in \mathbb{R}^{N \times N}$, and $B(t, \eta_0) = \frac{\partial f(t, x, \eta_0)}{\partial \eta} \in \mathbb{R}^{N \times M}$.

3.1. Numerical implementation

The in-host COVID-19 mathematical model has two states ($N = 2$) defined as: $x_1 = V$ and $x_2 = T$, the initial conditions are: $x_1(0) = 0.31$ and $x_2(0) = 10^6$. Let us define the set of the nine model parameters ($M = 9$) as $\eta_0 =$
\[sensitivity\] is, initially the patient is evaluated, considering the first three matrices \(p, K, c, s, r, m, k, \delta_t\). The sensitivity function in Eq. (25) has \(N \times M\) states, corresponding to the entries of the matrix \(S(t) = \frac{\partial x(t, \eta)}{\partial \eta} \in \mathbb{R}^{N \times M}\).

\[
S = \begin{bmatrix}
\frac{\partial x_1}{\partial p} & \frac{\partial x_1}{\partial K} & \frac{\partial x_1}{\partial c} & \frac{\partial x_1}{\partial s} & \frac{\partial x_1}{\partial r} & \frac{\partial x_1}{\partial m} & \frac{\partial x_1}{\partial k} & \frac{\partial x_1}{\partial \delta_t} \\
\frac{\partial x_2}{\partial p} & \frac{\partial x_2}{\partial K} & \frac{\partial x_2}{\partial c} & \frac{\partial x_2}{\partial s} & \frac{\partial x_2}{\partial r} & \frac{\partial x_2}{\partial m} & \frac{\partial x_2}{\partial k} & \frac{\partial x_2}{\partial \delta_t} \\
\end{bmatrix}.
\]

The matrices \(A(t, \eta_0) \in \mathbb{R}^{2 \times 2}\) and \(B(t, \eta_0) \in \mathbb{R}^{2 \times 9}\) in Eq. (25) are computed:

\[
A(t, \eta_0) = \begin{bmatrix}
\frac{\partial f_1(t, x, \eta)}{\partial x_1} & \frac{\partial f_1(t, x, \eta)}{\partial x_2} \\
\frac{\partial f_2(t, x, \eta)}{\partial x_1} & \frac{\partial f_2(t, x, \eta)}{\partial x_2} \\
\end{bmatrix},
\]

and

\[
B(t, \eta_0) = \begin{bmatrix}
\frac{\partial f_1(t, x, \eta)}{\partial p} & \ldots & \frac{\partial f_1(t, x, \eta)}{\partial \delta_t} \\
\frac{\partial f_2(t, x, \eta)}{\partial p} & \ldots & \frac{\partial f_2(t, x, \eta)}{\partial \delta_t} \\
\end{bmatrix}.
\]

and evaluated considering the nominal parameters reported in [25], in the specific case of the fitted model with data for the patient \(A\). The sub index 0 stands for the nominal value of each parameter. Considering these last three matrices and initial conditions \(S(0) = 0\) the sensitivity function (25) is solved. The solution of the sensitivity function provides the time variation of the model solutions regarding each parameter. Figs. 5 and 6 show the solution of the sensitivity function, that is, the effect of parametric variation on solutions \(V(t)\) and \(T(t)\), respectively. Fig. 7 shows the magnitude of parametric sensitivity of \(V(t)\) (top), and \(T(t)\) (bottom), respectively.
Fig. 7. Maximum magnitudes of the sensitivity solutions for each parameter (V top, T bottom).

Fig. 8. Solution V(t) varying initial condition V(0) = V_0(1 ± Δ).

Variations of initial conditions and parameters

In this second set of results, a variation on initial conditions of V(t) and T(t) are considered. Using the nominal initial condition V_0 = 0.31 and T_0 = 10^6, both initial conditions are varied such that the following conditions are met:

\[ V(0) = V_0(1 ± Δ) \] (26)

\[ T(0) = T_0(1 ± Δ) \] (27)

such that Δ ∈ [0, 1].

Fig. 8 shows V(t) considering a set of ten different initial conditions met condition (26); meanwhile, Fig. 9 depicts T(t) considering a set of ten different initial conditions met condition (27). With regard to parametric variation, Figs. 10 and 11 show V(t) and T(t) for ten different values of c_T, that is c_T = c_{T0} ± 100%c_{T0}, where c_{T0} is the nominal value of the parameter. Figs. 12 and 13 show parametric variation of p, for V(t) and T(t), respectively. Figs. 14 and 15 show variation of V(t) and T(t) when parameter c is modified. Finally, Figs. 16 and 17 show variation of V(t) and T(t) regarding the parameter m.

4. Discussion

The central theme of this work is a mathematical analysis of the model (1)-(2), one of the few models to describe the in-host dynamics of the SARS-CoV-2 disease. Among all in-host models considered in [25], this model provided the best fit to the viral load data in [26]. Since the parameters of this model characterize the effector T cell response to the pathogen, our stability and bifurcation analysis may help to understand how the immune system clears the pathogen.

Our analysis reveals that the parameter grouping

\[ λ = p - c - c_T T_0 \]
can drive the dynamics of our model (1)-(2). The value of $\lambda$ allows comparison between ambient viral replication and clearance by T cells, represented by the per capita rates $p - c$ and $c_T T_0$, respectively. By fixing the virus half-life $c$ and the homeostatic T cell count $T_0$, we observe that $\lambda$ linearly increases with the viral replication rate $p$ and linearly decreases with the clearance rate $c_T$. Thus, a biological meaning for $\lambda$ is viral fitness. The parameter $\lambda$ is also related to the within-host basic reproduction number

$$ R = \frac{p - c}{c_T T_0}, $$
Furthermore, we parameter corresponding the fast (large load for locally paces for asymptotically result we may emphasize the more viral features of SARS-CoV-2 magnitude the initial replication − , 1 ≈ λ , and mild sensitive to changes in near the bifurcation at λ = 0, which may suggest that SARS-CoV-2 infection is more severe once the viral replication overcomes the effector T cell clearance. Indeed, V star increases by four orders of magnitude from the bifurcation point. We determine from Fig. 1 that V = 1 at λ ≈ 7 × 10−10, V star = 100 (detection threshold) at λ ≈ 3.785 × 10−7, and V = 10000 at λ ≈ 3.367 × 10−5. These values correspond to R − 1 ≈ 1.434 × 10−8, R − 1 ≈ 7.756 × 10−6, and R − 1 ≈ 0.069 due to c₇ = 4.88 × 10−8.

The local asymptotic stability of E star suggests that a more rapid viral replication (large λ) can elevate peak viral loads corresponding to a large V star, which may be associated with mild and severe clinical features [16]. Comparing the different parameter sets in Table 1, we find a diverse range of V star: the smallest value (V star ≈ 494) comes from set I, while the largest value (V star ≈ 1.72 × 10⁷) is from set F.

We should emphasize that the local asymptotic stability of E star only describes the behavior of solutions near E star. In Fig. 4, we demonstrated the global asymptotic stability of E star where a solution that does not begin near E star still approaches E star. Furthermore, the solution curves for large λ in Fig. 3 describe oscillations in the viral load as it approaches V star. Further analysis is needed to verify these numerical examples with a Lyapunov function.

for which λ = c₇T₀(R − 1). Hence, λ > 0 is equivalent to R > 1, which indicates an effective viral replication rate that outpaces T cell clearance.

Our main result is comparable to previous in-host infectious disease modeling [30]. In short, our model yields a unique locally asymptotically stable equilibrium point x*, which is V = 0 for λ < 0 (Theorem 1) and the positive viral load V = V star for λ > 0 (Theorems 2 and 3). This means that the viral load V(t) of a solution near x* approaches the corresponding viral load at x*.

Thus, our local stability result agrees with the classic notion of a sufficient T cell response to eliminate the virus (large c₇), which may be counteracted with a reduced pool of T cells (small T₀). Meanwhile, the virus needs to achieve a fast replication (large p) to overcome T cell clearing; this is corroborated by the parameter estimates in Table 1 where p > c. In contrast, a suppressed viral replication (p < c) is sufficient for halting the infection. Therefore, antivirals that can inhibit the replication of SARS-CoV-2 [31,32] can play a central aspect during COVID-19.

The bifurcation diagram in Fig. 1 shows an increase in the viral load V star whenever λ is positive and increasing. Notably, the initial marginal gain of V star is sensitive to changes in λ near the bifurcation at λ = 0, which suggests that SARS-CoV-2 infection is more severe once the viral replication overcomes the effector T cell clearance. Indeed, V star initially increases by four orders of magnitude from the bifurcation point. We determine from Fig. 1 that V star = 1 at λ ≈ 7 × 10−10, V star = 100 (detection threshold) at λ ≈ 3.785 × 10−7, and V star = 10000 at λ ≈ 3.367 × 10−5. These values correspond to R − 1 ≈ 1.434 × 10−8, R − 1 ≈ 7.756 × 10−6, and R − 1 ≈ 0.069 due to c₇ = 4.88 × 10−8.

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A more thorough bifurcation analysis requires $r$ and $k_T$ as additional bifurcation parameters, setting the stage for searching nontrivial dynamics. Both $r$ and $k_T$ do not affect viral replication and the effector T cell clearance characterized by $\lambda$. Instead, they are part of the T cell activation term $rT G(V)$. Moreover, the combined effects of varying $r$ and $k_T$ may influence the monotone and concave properties of $G - G_0$ by Eqs. (3) and (13), thereby influencing the marginal increase of $V^*$ with $\lambda$. For an initial exploration on this idea, we take the parameter setting from Fig. 18, and then setting $r = 0.19375$ (this number, denoted $\bar{r}$, was obtained by trial and error). Then we obtain a qualitatively different bifurcation diagram in Fig. 18, where the branch of the positive equilibrium point changes concavity. Here, $V^*$ initially experiences a slow increase with $\lambda$ before progressing to higher orders of magnitude. We might call this peculiar observation a delayed saturation of the viral load, which is broken for either some sufficiently large $|r - \bar{r}|$ or some new value of $k_T$.

The asymptotic stability of the positive equilibrium (Theorem 3) means that the virus is expected to reach persistent levels. However, long-term persistence of the virus is associated with chronic diseases like HIV. The 2019 coronavirus disease is acute, where viral peaks are expected to occur for limited time.

Hence, it is relevant to ask what parameters can make $V^* \approx 100$, implying a theoretical undetected level of the virus. To this end, we recall that $V^*$ is the root of $H = G_0 - G$ in the open interval $(0, \hat{V}(\lambda))$ (Lemma 3), where $\hat{V}(\lambda)$ is the positive root of $G_0$; see Eq. (15). Thus, the viral load $V^*$ is below the detection threshold when $\hat{V}(\lambda) = \lambda K / p \leq 100$. However, this condition only applies to very small $\lambda / p$ with $K = 10^9$.

Alternatively, we may consider the explicit form of $G$, Eq. (3) where $m = 2$, and the definition of $G_0$ in (13). Note that reducing $k_T$ allows $G(V)$ to saturate for small values of $V$, while the value of $G_0(V)$ is inversely proportional to $r$. Therefore, the combined effect of reduced T cell tolerance to the virus (small $k_T$) and a faster T cell activation (large $r$) could play a key role in reducing the viral load, with the goal of having $V^* \approx 100$ for all $\lambda > 0$ not exceeding a physiological bound.

The trace and determinant values associated with $E^*$ provide another perspective to viral load peaks. Assuming parameter values from the set Mean in Table 1 and computing $p$ from $\lambda$, we find that $E^*$ is already a stable spiral for $\lambda$ above a small positive value (0.0153), where the discriminant is negative (Fig. 2) and viral load oscillations begin to emerge. As...
the solution trajectories in Fig. 3 indicate, the viral load oscillations become more pronounced with slower dissipation as $\lambda$ continues to increase; this effect is due to the qualitative behavior of $E^*$ approaching the non-hyperbolic center in the trace-determinant plane. In particular, the viral load experiences a larger initial local maximum (peak) and a smaller succeeding local minimum.

From the observations above, we draw the following interpretations. SARS-CoV-2 peak may have a determinant effect once the pathogen overcomes $T$ cell responses (i.e. when $\lambda$ crosses some small positive threshold). However, it may be
necessary for the virus to replicate fast (large $\lambda$) to experience a significant initial viral peak followed by reduction to levels below detection. Speaking mainly on theoretical terms, if we allow SARS-CoV-2 infection to continue over weeks, then the virus may possible re-emergence at an intermediate stage. Studies that support the idea of reinfection or fluctuating viral loads may agree with the findings here.

On a more technical side, we remark that the generation of our bifurcation diagrams entailed computational challenges. The sensitivity of $V^*$ near $\lambda = 0$ required values of $\lambda$ to be concentrated around the bifurcation value. For values of $m > 1$, evaluation of $G(V) = V^m/(V^m + k^p)$ requires first evaluating $V^m$ with the risk of losing numerical accuracy for large $V$. This motivated us to derive the auxiliary function

$$h(\mu) = \mu - \frac{\delta_T}{r} \left[ R(\mu) - Q(\lambda)S(\mu, \lambda) \right]$$

in Eq. (21). The root $\mu^*$ of $h$ in the subset $(0, G(\lambda))$ of the open interval $(0, 1)$ corresponds bijectively with $V^*$, now given by

$$V^* = k_T \left( \frac{\mu^*}{1 - \mu^*} \right)^{1/m}.$$  

Conversely, the viral load $V^*$ at the positive equilibrium point determines the corresponding $T$ cell activation rate, $rG(V^*) = r\mu^*$. The model (1)–(2) focuses on the interaction between SARS-CoV-2 and effector cells, but other important factors may play key roles during infection. Regulatory components of the immune system may be important for considering how $T$ cells clear a limited portion of the pathogen [33]. Finally, we may employ a multiscale modeling framework to evaluate how the severity of in-host infection can determine effective between-host transmission [30].

**CRediT authorship contribution statement**

Alexis Erich S. Almocera: Bifurcation Analysis, Writing - original draft. Griselda Quiroz: Sensitivity analysis, Writing - original draft. Esteban A. Hernandez-Vargas: Conceptualization, Resources, Supervision, Writing - review & editing.

**Declaration of Competing Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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