A DELAYED DYNAMICAL MODEL FOR COVID-19 THERAPY WITH DEFECTIVE INTERFERING PARTICLES AND ARTIFICIAL ANTIBODIES

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Abstract. In this paper, we use delay differential equations to propose a mathematical model for COVID-19 therapy with both defective interfering particles and artificial antibodies. For this model, the basic reproduction number $R_0$ is given and its threshold properties are discussed. When $R_0 < 1$, the disease-free equilibrium $E_0$ is globally asymptotically stable. When $R_0 > 1$, $E_0$ becomes unstable and the infectious equilibrium without defective interfering particles $E_1$ comes into existence. There exists a positive constant $R_1$ such that $E_1$ is globally asymptotically stable when $R_1 < 1 < R_0$. Further, when $R_1 > 1$, $E_1$ loses its stability and infectious equilibrium with defective interfering particles $E_2$ occurs. There exists a constant $R_2$ such that $E_2$ is asymptotically stable without time delay if $1 < R_1 < R_0 < R_2$ and it loses its stability via Hopf bifurcation as the time delay increases. Numerical simulation is also presented to demonstrate the applicability of the theoretical predictions.

1. Introduction. The global epidemic of coronavirus disease 2019 (COVID-19) is now a major global health threat [40]. COVID-19 is the result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is an enveloped positive-sense single-stranded RNA virus belongs to coronavirus (CoV) family. Typical symptoms of COVID-19 infection include dry cough, fever, fatigue, breathing difficulty, and bilateral lung infiltration in severe cases. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness [13] [38].

Respiratory droplet and contact transmission are the main transmission routes for person-to-person spread of SARS-CoV-2 [18]. The mainstay of clinical treatment consists of symptomatic management and oxygen therapy, with mechanical ventilation for patients with respiratory failure. Although several antiviral drugs, including the nucleotide analogue remdesivir, are being actively tested, none has been specifically approved for COVID-19. In addition to vaccine development and

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approaches that directly target the virus or block viral entry, treatments that address the immunopathology of the infection have become a major focus [5]. Defective interfering particles and artificial antibodies are proposed as potential therapies for COVID-19.

The therapy for COVID-19 uses defective interfering particles to prevent the replication of virus was proposed by researchers recently [41]. Defective interfering particles arise spontaneously by deletion mutations. The shortened genomes of the defective interfering particles cannot replicate unless they coinfect a cell with a normal virus. Upon coinfection, the DI genome replicates more quickly and outcompetes the normal virus. The coinfecting cell produces mostly defective interfering particles (DIPs) [12]. Several studies have associated defective interfering particles (DIPs) turn on the expression of IFNs and proinflammatory cytokines such as IL-1, TNF, and IL-6 [22] [31]. The strong interfering and immunostimulatory activities of defective interfering particles (DIPs) make them attractive candidates for antivirals [7] [23] [37]. In [41], Yao et al. have established a proof of principle that a synthetic defective interfering SARS-CoV-2 can replicate in cells infected with the virus and interfere with its replication. Influenza A virus (IAV) defective interfering particles (DIPs) were previously proposed for antiviral treatment against Influenza A infections [33] [37] [44]. In a recent study [27], Rand et al. conducted in vitro coinfection experiments with cell culture-derived DIPs and the IFN-sensitive SARS-CoV-2 in human lung cells. It showed that treatment with IAV DIPs leads to complete abrogation of SARS-CoV-2 replication. They proposed IAV DIPs as an effective antiviral agent for treatment of COVID-19, and potentially also for suppressing the replication of new variants of SARS-CoV-2.

Preclinical studies of neutralizing-antibody treatments for SARS-CoV-2 infection in several animal models have shown promising results, with marked reductions in viral loads in the upper and lower respiratory tracts [3]. The coronavirus binds to angiotensin-converting enzyme 2 (ACE2) through its S protein on the virion, and then the viral membrane fuses with the cell membrane. Subsequently, the RNA virus will replicate its genome inside the cell, and ultimately make new virions that will be secreted to infect other cells [19] [35]. The therapy was proposed to treat COVID-19 is the use of monoclonal antibodies that target the receptor binding domain of the SARS-CoV-2 S protein, thereby inhibiting engagement with the host cell entry receptor angiotensin-converting enzyme 2 (ACE2) [16] (see Figure 1). In [25], Pan et al. have isolated ten artificial antibodies from COVID-19 convalescent patients and their in vivo experiment of artificial antibodies using mice showed encouraging therapeutic and prophylactic efficacy against SARS-CoV-2. LY-CoV555 (also known as LY3819253), a potent antispikr neutralizing monoclonal antibody that binds with high affinity to the receptor-binding domain of SARS-CoV-2, was derived from convalescent plasma obtained from a patient with COVID-19. The antibody was developed by Eli Lilly after its discovery by researchers at AbCellera and at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases. In [6], Chen et al. examined the efficacy of LY-CoV555 in the treatment of mild or moderate COVID-19. In their interim analysis, the patients who received LY-CoV555 had fewer hospitalizations and a lower symptom, they proposed LY-CoV555 could become a useful treatment for emergency use in patients with recently diagnosed COVID-19.

Mathematical models can provide insights into the dynamics of viral load in vivo. In this paper, we consider to combine the above two potential treatments and we
propose a mathematical model to understand this approach of fighting a virus with DIPs and artificial antibodies.

A standard and classic in-host model in [26] for HIV infection can be described by the following differential equations:

\[
\begin{align*}
    x'(t) &= \lambda - dx - \beta xv, \\
    y'(t) &= \beta xv - ay, \\
    v'(t) &= ky - pv,
\end{align*}
\]

where \(x(t), y(t)\) and \(v(t)\) are the densities of uninfected target cells, infected target cells and the free virus, respectively, at time \(t\). The infection rate is \(\beta\). The healthy cell is assumed to be produced at a constant rate \(\lambda\). It is also assumed that once cells are infected, they may die at rate \(a\) either due to the action of the virus or the immune system, and in the mean time, they each produces virus particles at a rate \(k\) during their life which on average has length \(1/a\). \(p\) is the death rate of virus.

Many researchers also consider system (1) as a basic virus infection model for various other viruses, such as HBV [10], HCV [39]. In real situation, time is needed for the virus to contact a target cell and then the contacted cells to become actively affected [30] [34] [43] [45]. In [46], Zhu and Zou studied a HIV infection model with intracellular delay as follows

\[
\begin{align*}
    x'(t) &= \lambda - dx(t) - \beta x(t)v(t), \\
    y'(t) &= \beta x(t-\tau)v(t-\tau) - ay(t), \\
    v'(t) &= ky(t) - pv(t),
\end{align*}
\]

Several models have analysed the population dynamics of defective interfering particles. Bangham & Kirkwood [2] [15] and SzathmaHry [32] showed that fluctuating abundances of defective interfering particles and wild-type viruses often arise as a result of the predator-prey feedback dynamics between wild-type and defective interfering particles. Nelson and Perelson [24] developed a numerically realistic model of DIPs dynamics based on known parameters of HIV infection, they concluded that defective interfering particles (DIPs) are unlikely to survive or to influence HIV dynamics in peripheral blood, but may survive within infected lymphoid organs such as the lymph nodes and spleen. Frank proposed a reaction-diffusion model for the population dynamics of wild-type and defective interfering particles (DIPs), this model can predicts that the rate of cellular replacement strongly influences the role of defective interfering particles [8]. In [9], Frensing et al. proposed a model based on their experimental data demonstrate that DIPs rapidly accumulate...
during continuous virus propagation and, thus, represent a severe challenge for the productivity of the system.

In this paper, we proposed a delayed dynamical model for COVID-19 therapy with defective interfering particles and artificial antibodies. Let $T(t)$, $I(t)$, $V(t)$, $W(t)$ and $F(t)$ be the densities of susceptible host cells, infected cells, free virus, defective interfering particles and artificial antibodies, respectively, at time $t$. Susceptible host cells are produced at a constant rate $\lambda$, and die at a rate $d_1$. We assume that host cells infected by virus with a rate $\alpha$, and infected cells die at a rate $d_2$. The virus are removed from the plasma at a rate $d_3$ and the antibody as enhancement of viral clearance at a rate $\eta_2$. $\delta$ is the constant injection rate of artificial antibodies and $d_5$ is the death rate of antibody. For defective interfering particles, we have the following simple assumptions:

1. Defective interfering particles alone have no influence on healthy host cells (Defective interfering particles cant not replicate without normal virus).

2. When defective interfering particles attack infected cells $I$, defective interfering particles can replicate with the help of normal virus. Cells coinfected with normal virus and defective interfering particles produce only DIPs (this hypothesis is consistent with the previous results [2]). We assume defective interfering particle attacks infected cells at a rate $\eta_1$, and infected cells that attacked by defective interfering particles relasing defective interfering particles at a rate $k$.

3. Defective interfering particles (DIPs) turn on the expression proinflammatory cytokines to inhibit the replication of normal virus, we assume the inhibition function of the virus at a rate $\beta$. And so the virus production rate is given by $\gamma/(1 + \beta W)$. The death rate of defective interfering particle is $d_4$.

We assume that the probability density that a cell still remains infected for $\tau$ time units after being contacted by the virus obeys an exponentially decay function and we assume a constant death rate $a$ for infected but not yet virus-producing cells, the probability of surviving from time $t - \tau$ to $t$ is $e^{-a\tau}$, $\tau$ denotes the average time for a viral particle to go through the eclipse phase. The system describing these interactions is given by

$$
\begin{cases}
    T'(t) = \lambda - \alpha T(t)V(t) - d_1 T(t), \\
    I'(t) = \alpha e^{-\alpha \tau} T(t) V(t - \tau) - d_2 I(t) - \eta_1 W(t) I(t), \\
    V'(t) = \frac{\gamma I(t)}{1 + \beta W(t)} - d_3 V(t) - \eta_2 F(t) V(t), \\
    W'(t) = k\eta_1 W(t) I(t) - d_4 W(t), \\
    F'(t) = \delta - d_5 F(t).
\end{cases}
$$

The paper is structured as follows. In section 2, we will discuss the well-posedness of the solutions, equilibria and their stability. Also, in order to properly define biologically meaningful equilibria, the basic reproduction number $R_0$ will be defined. We analyze the stability of the three equilibria: disease-free equilibrium $E_0$, infectious equilibrium without defective interfering particles $E_1$, and infectious equilibrium with defective interfering particles $E_2$. It will be shown that $E_0$ is globally asymptotically stable for $0 < R_0 < 1$, $E_1$ is globally asymptotically stable for $R_1 < 1 < R_0$, where $R_1$ is a constant defined in terms of the system parameters. We also prove the existence of Hopf bifurcation at $E_2$ as time delay increases. A numerical example is present in Section 3 to demonstrate the theoretical predictions. Finally, conclusion and discussion are drawn in Section 4.
Figure 2. Pathogen viral particles $V$ infect normal cells $T$ producing infected cells $I$; $W$ can produce in infected cells; artificial antibodies $F$ bind to virus, infected cells are able to produce virus $V$ and defective interfering particles $W$.

2. Analytical results.

2.1. Positivity and boundedness of solutions. First, we assume that the initial conditions for the system (3) have the form

$$
T(\theta) = \phi_1(\theta), \quad I(\theta) = \phi_2(\theta), \quad V(\theta) = \phi_3(\theta),
$$

$$
W(\theta) = \phi_4(\theta), \quad F(\theta) = \phi_5(\theta), \quad \theta \in [-\tau, 0],
$$

(4)

where $\phi_i(\theta)(i = 1, 2, 3, 4, 5)$ are non-negative continuous functions on $\theta \in [-\tau, 0]$. From biological meaning, all variables in model (3) must be positive. Therefore, it is necessary to show that all solutions of the system (3) will be positive and bounded for all $t \geq 0$. We have the following result.

**Theorem 2.1.** All solutions of system (3) that satisfy the initial conditions (1) are positive for all $t \geq 0$.

**Proof.** For convenience, Let $X = C([-\tau, 0]; R^5)$ be the Banach space of continuous mapping from $[-\tau, 0]$ to $R^5$ equipped with the sup-norm. Let $X(t) = (T(t), I(t), V(t), W(t), F(t))^T$ and $X_t(\theta) = X(t + \theta)$ for $\theta \in [-\tau, 0]$. By the fundamental theory of FDEs [11], we know that there is a unique solution with the initial conditions (1). System (3) can be written as $X'(t) = F(X_t)$, where

$$
F(X_t) = \begin{bmatrix}
\lambda - \alpha T_t(0)V_t(0) - d_1 T_t(0) \\
\alpha e^{-\alpha \tau} T_t(-\tau) V_t(-\tau) - d_2 I_t(0) - \eta_1 W_t(0) I_t(0) \\
\gamma I_t(0) \\
\frac{\gamma I_t(0)}{1 + \beta W_t(0)} - d_3 V_t(0) - \eta_2 F_t(0) V_t(0) \\
k \eta_1 W_t(0) I_t(0) - d_4 W_t(0) \\
\delta - d_5 F_t(0)
\end{bmatrix}.
$$

(5)

It is easy to see that if any $\phi \in X$ satisfies $\phi \geq 0, \phi_i(0) = 0$ for some $i$, then $F_i(\phi) \geq 0$. Therefore, according to Theorem 2.1 (on page 81) in [29], we know that $X(t, \phi) \geq 0$ for all $t \geq 0$ in its maximal interval of existence if $\phi \geq 0$. $\square$

**Theorem 2.2.** All solutions of system (3) subject to initial conditions (1) are bounded for all $t \geq 0$. 

Proof. Let \( \Lambda(t) = e^{-\alpha\tau}T(t) + I(t + \tau) + \frac{d_2}{2\gamma}V(t + \tau) + \frac{1}{k}W(t + \tau) + F(t + \tau) \) and 
\[ \mu = \min \left\{ \frac{d_1}{2}, \frac{d_2}{2\gamma}, \frac{d_4}{k}, d_5 \right\}. \]
Therefore
\[ \frac{d\Lambda(t)}{dt} \leq e^{-\alpha\tau} \lambda + \delta - \mu \Lambda(t), \]
which implies that
\[ \Lambda(t) \leq \max \left\{ \Lambda(0), \frac{e^{-\alpha\tau} \lambda + \delta}{\mu} \right\}. \]
Since all solutions of system (3) subject to initial conditions are positive for all \( t \geq 0 \). This implies that \( \Lambda(t) \) is bounded, so are \( T(t), I(t), V(t), W(t), F(t) \).

2.2. Equilibria and basic reproduction number. It is clear that system (3) always has a unique disease-free equilibrium at \( E_0 = (\frac{\lambda}{\alpha\gamma}, 0, 0, 0, \frac{\delta}{d_5}) \). Following the next generation matrix method [36], the new infection and transition matrices are
\[ F = \begin{pmatrix} 0 & \frac{\alpha e^{-\alpha\tau}}{d_1} \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} d_2 & 0 \\ -\gamma & d_3 \end{pmatrix}. \] (6)
The basic reproduction number of system (3) is
\[ R_0 = \rho(FV^{-1}) = \frac{\lambda \alpha \gamma d_5 e^{-\alpha\tau}}{d_1 d_2 (d_3 d_5 + \delta)}. \] (7)
Solving the following equilibrium equations associated with (3)
\[ \begin{cases} \lambda - \alpha TV - d_1 T = 0, \\
\alpha e^{-\alpha\tau} TV - d_2 I - \eta_1 WI = 0, \\
\gamma I \left( 1 + \beta W \right) - d_3 V - \eta_2 FV = 0, \\
k_\eta WI - d_4 W = 0, \\
\delta - d_5 F = 0, \end{cases} \] (8)
we can get infectious equilibrium without defective interfering particles \( E_1 \) when 
\( W = 0 \), given as follows:
\[ E_1 = \left( \frac{d_2}{d_1 \alpha \gamma}, \frac{\lambda}{d_2} \left( 1 - \frac{1}{R_0} \right), \frac{d_1}{\alpha} (R_0 - 1), 0, \frac{\delta}{d_5} \right). \] (9)
Obviously, the infectious equilibrium without defective interfering particles \( E_1 \) exists
if and only if \( R_0 > 1 \).
We denote infectious equilibrium with defective interfering particles \( E_2 \) as \( (T_2, I_2, V_2, W_2, F_2) \) when \( W \neq 0 \). From (5), we obtain
\[ \begin{cases} T_2 = \frac{\lambda}{d_2 (d_5 + \delta)}, \\
I_2 = \frac{d_1}{d_4}, \\
V_2 = \frac{\gamma d_3 d_5}{k_\eta (1 + \beta W_2) (d_3 d_5 + \delta)}, \\
F_2 = \frac{\delta}{d_5}, \end{cases} \] (10)
and $W_2$ satisfies the following equation:

$$W_2^2 + BW_2 + C = 0,$$

where

$$B = \frac{1}{\beta} + \frac{d_2}{\eta_1} + \frac{d_4d_5\alpha\gamma}{k\eta_1d_1d_3d_5 + \delta},$$

$$C = \frac{d_2}{\beta\eta_1}(1 + \frac{d_4d_5\alpha\gamma}{k\eta_1d_1d_3d_5 + \delta} - \frac{\lambda\alpha\gamma d_5e^{-\alpha\tau}}{d_1d_2(d_3d_5 + \delta)}).$$

Since $B > 0$, quadratic equation (8) has a unique positive root if and only if $C < 0$. We denote $R_1$ as

$$R_1 = \frac{\lambda\alpha\gamma d_5k\eta_1e^{-\alpha\tau}}{d_2d_4d_5\alpha\gamma + k\eta_1d_2(d_3d_5 + \delta)}. \quad (12)$$

Note that

$$\frac{1}{R_1} = \frac{1}{R_0} + \frac{d_2d_4}{\lambda k\eta_1e^{-\alpha\tau}}. \quad (13)$$

Obviously, $C = \frac{d_2}{\beta\eta_1}[\frac{d_1d_4d_5\alpha\gamma}{d_1d_2(d_3d_5 + \delta)} + \alpha\gamma d_5](1 - R_1)$. When $R_1 > 1$, there exists infectious equilibrium with defective interfering particles $E_2$ of system (3). $R_1$ describes the condition for invasion of the defective interfering particles. If $R_1 > 1$, indicates that defective interfering particles can exist in the body, if $R_1 < 1$, the defective interfering particles will disappear in the body.

In order to analyze local stability of system (3) at an equilibrium $E_i(i = 0, 1, 2)$, we assume $E^* = (T^*, I^*, V^*, W^*, F^*)$ is an arbitrary equilibrium of system (3), the Jacobian matrix evaluated at $E^*$ leads us to the following characteristic equation

$$\begin{vmatrix} \xi + \alpha V^* + d_1 & 0 & \alpha T^* & 0 & 0 \\ -e^{-(a+\xi)}\alpha V^* & \xi + d_2 + \eta_1 W^* - e^{-(a+\xi)}\alpha T^* & -\eta_1 I^* & 0 & 0 \\ 0 & \frac{\gamma}{1 + \beta W^*} & \xi + d_3 + \eta_2 F^* & \beta\gamma I^* & \eta_2 V^* \\ 0 & 0 & -k\eta_1 W^* & \xi - k\eta_1 I^* + d_4 & 0 \\ 0 & 0 & 0 & \xi + d_5 & \xi + d_5 \end{vmatrix} = 0 \quad (14)$$

The roots of the characteristic equation determine the local stability of $E^*$.

2.3. Stability of the disease-free equilibrium $E_0$. First, for the local stability of $E_0$, we have the following theorem.

**Theorem 2.3.** When $R_0 < 1$, the disease-free equilibrium $E_0$ is locally asymptotically stable; when $R_0 > 1$, $E_0$ becomes unstable.

**Proof.** For the disease-free equilibrium $E_0$, some fundamental calculations give the corresponding characteristic equation

$$(\xi + d_1)(\xi + d_4)(\xi + d_5)[\xi^2 + b_1\xi + b_0(\tau)] = 0, \quad (15)$$

where

$$b_1 = d_2 + d_3 + \frac{\eta_2\delta}{d_5},$$

$$b_0(\tau) = d_2(d_3 + \frac{\eta_2\delta}{d_5}) - \frac{\lambda\alpha\gamma}{d_1}e^{-(a+\xi)\tau}.$$
The stability of $E_0$ by the sign of real part of roots of the Equation (12). Obviously, it suffices to only consider the following equation

$$D_0(\xi) = \xi^2 + (d_2 + d_3 + \frac{\eta_2 \delta}{d_5}) \xi + d_2(d_3 + \frac{\eta_2 \delta}{d_5}) - \frac{\lambda \alpha \gamma}{d_1} e^{-(\alpha + \xi)\tau}. \quad (16)$$

If $R_0 > 1$, it is easy to show for real $\xi$ that

$$D_0(0) = d_2(d_3 + \frac{\eta_2 \delta}{d_5})(1 - R_0) < 0, \quad \lim_{\xi \to +\infty} D_0(\xi) = +\infty.$$ 

Hence, $D_0(\xi) = 0$ has at least one positive real root. Therefore, if $R_0 > 1$, the disease-free equilibrium $E_0$ is unstable.

Now, consider $R_0 < 1$. When $\tau = 0$, equation (13) has the following form

$$D_0(\xi) = \xi^2 + (d_2 + d_3 + \frac{\eta_2 \delta}{d_5}) \xi + d_2(d_3 + \frac{\eta_2 \delta}{d_5}) - \frac{\lambda \alpha \gamma}{d_1}, \quad (17)$$

we know that the two roots of Equation (14) to have negative real part is equivalent to $d_2(d_3 + \frac{\eta_2 \delta}{d_5}) - \frac{\lambda \alpha \gamma}{d_1} > 0$, that is $R_0|_{\tau=0} < 1$. Therefore, all roots of (14) have negative real part when $R_0 < 1$.

When $\tau > 0$, Notice 0 is not a root of (13) because of $R_0 < 1$. Following the method in [28], we define $\xi = iw(w > 0)$ is a purely imaginary root of (13). Then we get

$$-w^2 + d_2(d_3 + \frac{\eta_2 \delta}{d_5}) = \frac{\lambda \alpha \gamma e^{-\sigma \tau}}{d_1} \cos(w \tau),$$

$$(d_2 + d_3 + \frac{\eta_2 \delta}{d_5})w = -\frac{\lambda \alpha \gamma e^{-\sigma \tau}}{d_1} \sin(w \tau). \quad (18)$$

Squaring and adding both equations of (15), it follows that

$$H_0(w^2) = w^4 + [(d_3 + \frac{\eta_2 \delta}{d_5})^2 + d_2^2]w^2 + 1 - R_0^2. \quad (19)$$

From $R_0 < 1$, we easily see that (16) has no positive roots. Therefore, all roots of (13) have negative real parts.

Further, for the global stability of disease-free equilibrium $E_0$. We have the following result.

**Theorem 2.4.** When $R_0 < 1$, the disease-free equilibrium $E_0$ is globally asymptotically stable.

**Proof.** We consturct the following Lyapunov function

$$L_0(t) = \frac{e^{-\sigma \tau}}{2} [T(t) - \frac{\lambda}{d_1}]^2 + \frac{\lambda}{d_1} I(t) + \frac{\lambda d_2}{d_1 \gamma} V(t) + \frac{\lambda}{kd_1} W(t) + \frac{1}{2} [F(t) - \frac{\delta}{d_5}]^2$$

$$+ \frac{\lambda \alpha e^{-\sigma \tau}}{d_1} \int_{t-\tau}^{t} T(s)V(s)ds. \quad (20)$$

Thus, we have
\[ L'_0(t) = e^{-\alpha t}[T(t) - \frac{\lambda}{d_1}[\lambda - \alpha T(t)V(t) - d_1 T(t)]
+ \frac{\lambda}{d_1}[\alpha e^{-\alpha t}T(t-\tau)V(t-\tau) - d_2 I(t) - \eta_1 W(t)I(t)]
+ \frac{\lambda d_2}{d_1}\gamma I(t) 1 + \beta W(t) - d_3 V(t) - \eta_2 F(t)V(t)]
+ \frac{\lambda}{k d_1}[k \eta_1 W(t)I(t) - d_4 W(t)]
+ (F(t) - \delta d_5)(\delta - d_5 F(t)) + \frac{\lambda e^{-\alpha t}}{d_1}[T(t)V(t) - T(t-\tau)V(t-\tau)]
= -e^{-\alpha t}[T(t) - \frac{\lambda}{d_1}2[\alpha V(t) + d_1] + \frac{\lambda d_2}{d_1}(\frac{1}{1 + \beta W(t)} - 1)I(t) - \frac{\lambda d_4}{k d_1}W(t)
- d_5[F(t) - \frac{\delta}{d_5}d_5 + \frac{\lambda d_2(d_3d_5)}{\gamma d_1 d_5}(R_0 - 1)V(t)]. \]

Note that \( T, I, V, W, F \) are positive. All terms of the right in (18) are nonpositive when \( R_0 < 1 \). \( L'_0 = 0 \) if and only if \( T = \lambda/d_1, F = \delta/d_5 \) and other variables are zero. By LaSalle’s invariance principle \[17\], we conclude that \( E_0 \) is indeed globally asymptotically stable.

### 2.4. Stability of the infectious equilibrium \( E_1 \)

When \( R_0 > 1 \), the disease-free equilibrium \( E_0 \) becomes unstable and bifurcates into the infectious equilibrium without defective interfering particles \( E_1 \). Thus, in order to study the stability of \( E_1 \), we assume \( R_0 > 1 \) in this section. We have the following result.

**Theorem 2.5.** When \( R_1 < 1 < R_0 \), the infectious equilibrium without defective interfering particles \( E_1 \) is locally asymptotically stable; when \( R_1 > 1 \), \( E_1 \) becomes unstable.

**Proof.** For convenience, we denote \( E_1 \) as \((T_1, I_1, V_1, W_1, F_1)\). From (11), the corresponding characteristic equation as follows
\[ \xi + d_5(\xi - k \eta_1 I_1 + d_4)[\xi^3 + b_{12}(\tau)\xi^2 + b_{11}(\tau)\xi + b_{10}(\tau) - (b_{21}(\tau)\xi + b_{20}(\tau))e^{-\xi \tau}] = 0, \]

where
\[ b_{12}(\tau) = d_1 R_0 + d_2 + d_3 + \frac{\eta_2 \delta}{d_5}, \]
\[ b_{11}(\tau) = d_1 d_2 R_0 + d_1(d_3 + \frac{\eta_2 \delta}{d_5})R_0 + d_2(d_3 + \frac{\eta_2 \delta}{d_5}), \]
\[ b_{10}(\tau) = d_1 d_2(d_3 + \frac{\eta_2 \delta}{d_5})R_0, \]
\[ b_{21}(\tau) = d_2(d_3 + \frac{\eta_2 \delta}{d_5})e^{-\alpha \tau}, \]
\[ b_{20}(\tau) = d_1 d_2(d_3 + \frac{\eta_2 \delta}{d_5})e^{-\alpha \tau}. \]

From (19),
\[ \xi_1 = -d_5 < 0, \]
\[ \xi_2 = \frac{k \eta_1 \lambda}{d_1}(1 - \frac{1}{R_1}). \]
It is obvious that $\xi_2 > 0$ and equation (19) has at least one positive real root if $R_1 > 1$. Therefore, $E_1$ becomes unstable when $R_1 > 1$.

Next, we consider $R_1 < 1 < R_0$. Note that $\xi_2 < 0$ when $R_1 < 1$. We consider the following equation
$$D_1(\xi) = \xi^3 + b_{12}(\tau)\xi^2 + b_{11}(\tau)\xi + b_{10}(\tau) - (b_{21}(\tau)\xi + b_{20}(\tau))e^{-\xi\tau} = 0, \quad (24)$$

It is easy to see that $\xi = 0$ is not a root of (21) if $R_0 > 1$. When $\tau = 0$, (21) has the following form
$$D_1(\xi) = \xi^3 + b_{12}(0)\xi^2 + (b_{11}(0) - b_{21}(0))\xi + b_{10}(0) - b_{20}(0). \quad (25)$$

Applying the Routh-Hurwitz criterion,
$$b_{12}(0) = d_1R_0 + d_2 + d_3 + \frac{\eta_2\delta}{d_5} > 0,$$
$$b_{11}(0) - b_{21}(0) = d_1d_2R_0 + d_1(d_3 + \frac{\eta_2\delta}{d_5})R_0 > 0,$$
$$b_{10}(0) - b_{20}(0) = d_1d_2(d_3 + \frac{\eta_2\delta}{d_5})(R_0 - 1) > 0,$$
$$b_{12}(0)(b_{11}(0) - b_{21}(0)) - b_{10}(0) + b_{20}(0) = (d_1R_0 + d_2 + d_3 + \frac{\eta_2\delta}{d_5})$$
$$\quad - d_1d_2(d_3 + \frac{\eta_2\delta}{d_5})(R_0 - 1) > 0.$$  

Therefore, any roots of (21) have negative real part when $\tau = 0$. Notice that $\xi = 0$ is not a root of (21). Next, we consider $\tau > 0$, $\xi = iw(w > 0)$ is the purely imaginary root of (21), and then obtain
$$-w^3 + b_{11}(\tau)w = b_{21}(\tau)w\cos(w\tau) - b_{20}(\tau)\sin(w\tau),$$
$$-b_{12}(\tau)w^2 + b_{10}(\tau) = b_{21}(\tau)w\sin(w\tau) + b_{20}(\tau)\cos(w\tau). \quad (27)$$

Squaring and adding both equations lead to
$$H_1(w^2) = w^6 + (b_{12}^2(\tau) - 2b_{11}(\tau))w^4 + (b_{11}^2(\tau) - 2b_{10}(\tau)b_{12}(\tau) - b_{21}(\tau)^2)w^2 + b_{10}(\tau)^2(\tau) - b_{20}(\tau)^2(\tau) = 0. \quad (28)$$

Note that
$$b_{12}^2(\tau) - 2b_{11}(\tau) = d_1^2R_0^2 + d_2^2 + (d_3 + \frac{\eta_2\delta}{d_5})^2 > 0,$$
$$b_{11}^2(\tau) - 2b_{10}(\tau)b_{12}(\tau) - b_{21}^2(\tau)$$
$$= (d_1d_2R_0)^2 + d_2^2(d_3 + \frac{\eta_2\delta}{d_5})^2R_0^2 + d_3^2(d_3 + \frac{\eta_2\delta}{d_5})^2(1 - e^{-\alpha\tau}) > 0,$$
$$b_{10}^2(\tau) - b_{20}^2(\tau) = (d_1d_2(d_3 + \frac{\eta_2\delta}{d_5}))^2(R_0^2 - e^{-\alpha\tau}) > 0,$$

note that all the coefficients of $H_1(w^2)$ is monotonically increasing for $0 < w^2 < \infty$ with $H_1(0) > 0$. Hence $E_1$ is locally asymptotically stable when $R_1 < 1 < R_0$. □

Also, $E_1$ is globally asymptotically stable.

**Theorem 2.6.** When $R_1 < 1 < R_0$, the infectious equilibrium without defective interfering particles $E_1$ is globally asymptotically stable.
Proof. We construct the following Lyapunov function
\[
L_1 = e^{-\sigma(T - T_1 \ln T)} + I - I_1 \ln I + \frac{d_2}{\gamma}(V - V_1 \ln V) + \frac{1}{k}W + \frac{d_2 \eta_2 V_1}{\delta \gamma}F \\
+ \int_{t-\tau}^{t} \left( \frac{T(s)V(s)}{T_1 V_1} - \ln \frac{T(s)V(s)}{T_1 V_1} \right) ds.
\]
(29)

Then
\[
L_1 = e^{-\sigma(1 - \frac{T_1}{T})T'} + (1 - \frac{I_1}{T})I' + \frac{d_2}{\gamma}(1 - \frac{V_1}{V})V' + \frac{1}{k}W' + \frac{d_2 \eta_2 V_1}{\delta \gamma}F'
\]
\[
+ \frac{T(t)V(t)}{T_1 V_1} - \frac{T(t - \tau)V(t - \tau)}{T_1 V_1} + \ln \frac{T(t - \tau)V(t - \tau)}{T_1 V_1}
\]
\[
\leq e^{-\sigma T_1} T_1 (2 - \frac{T_1}{T} - \frac{T_1}{T}) + e^{-\sigma \alpha T_1} V_1 [3 - \frac{T_1}{T} - \frac{IV_1}{IT_1 V_1} - \frac{I(T(t - \tau)V(t - \tau)}{IT_1 V_1}]
\]
\[
+ \ln \frac{T(t - \tau)V(t - \tau)}{T_1 V_1} + \frac{\lambda \eta_1 k_1}{d_1} (1 - \frac{1}{\lambda R_1}) W(t) - \frac{d_2 \eta_2}{\gamma} F(t) V(t) - \frac{d_3}{\gamma} V_1,
\]
(30)

according the following inequality ([14])
\[
n - \sum_{i=1}^{n} \frac{b_i}{a_i} + \ln \prod_{i=1}^{n} \frac{b_i}{a_i} \leq 0,
\]
(31)

we conclude that
\[
3 - \frac{T_1}{T} - \frac{IV_1}{IT_1 V_1} - \frac{I(T(t - \tau)V(t - \tau)}{IT_1 V_1} + \ln \frac{T(t - \tau)V(t - \tau)}{T_1 V_1} \leq 0.
\]
(32)

Thus, \( L_1' \leq 0 \) when \( R_1 < 1 \) and the equality holds if and only if \( (T, I, V, W, F) = E_1 \). By LaSalle’s invariance principle [17], we conclude that \( E_1 \) is globally asymptotically stable.

2.5. Stability of the infectious equilibrium \( E_2 \). From (5), we obtain the solution of defective interfering particles \( W \) satisfies the following equation
\[
W = \frac{d_2}{\eta_1} \frac{\lambda \alpha \gamma d_5 k_1 \eta_1 e^{-\sigma}}{d_2 d_4 d_5 \alpha \gamma + k_1 d_1 d_2 (d_3 d_5 + \delta)(1 + \beta w_0)} - 1.
\]
(33)

In this section, we denote \( R_1 \) and \( R_0 \) as
\[
R_1 = \frac{\lambda \alpha \gamma d_5 k_1 \eta_1 e^{-\sigma}}{d_2 d_4 d_5 \alpha \gamma + k_1 d_1 d_2 (d_3 d_5 + \delta)(1 + \beta w_0)},
\]
\[
R_0 = \frac{\lambda \alpha \gamma d_5 e^{-\sigma}}{d_1 d_2 (d_3 d_5 + \delta)(1 + \beta w_0)},
\]
where \( w_0 \) is the positive root of equation (8). \( E_2 \) has the following form
\[
E_2 = \frac{\lambda R_1}{d_1 R_0 \alpha} \frac{d_4}{k_1 \eta_1} \left( \frac{d_1}{R_1 - 1} \right), \frac{d_2}{\eta_1} \left( \frac{R_1}{R_1 - 1} \right), \frac{d_2}{d_5}.
\]

When \( R_1 > 1 \), the infectious equilibrium without defective interfering particles \( E_1 \) becomes unstable and there appears another infectious equilibrium with defective interfering particles \( E_2 \). We have the following result.

Theorem 2.7. There exists an \( R_2 \) such that when \( 1 < R_1 < R_0 < R_2, E_2 \) is asymptotically stable without delay.
Proof. For the infectious equilibrium with defective interfering particles $E_2$, the corresponding characteristic equation as follows

$$(\xi + d_5)[\xi^4 + m_3(\tau)\xi^3 + m_2(\tau)\xi^2 + m_1(\tau)\xi + m_0(\tau) - (n_2(\tau)\xi^2 + n_1(\tau)\xi + n_0(\tau))e^{-\xi\tau}] = 0,$$  

where

\begin{align*}
m_3(\tau) &= d_1 \frac{R_0}{R_1} + d_2 R_1 + d_3 + \frac{\eta_2 \delta}{d_5}, \\
m_2(\tau) &= d_1 d_2 R_0 + (d_1 \frac{R_0}{R_1} + d_2 R_1)(d_3 + \frac{\eta_2 \delta}{d_5}) + d_2 d_4 (R_1 - 1), \\
m_1(\tau) &= d_1 d_2 R_0 (d_3 + \frac{\eta_2 \delta}{d_5}) + d_2 d_4 (R_1 - 1)(d_1 \frac{R_0}{R_1} + d_3 + \frac{\eta_2 \delta}{d_5}), \\
m_0(\tau) &= d_2 d_4 (R_1 - 1) d_1 \frac{R_0}{R_1} (d_3 + \frac{\eta_2 \delta}{d_5}), \\
n_2(\tau) &= d_2 R_1 (d_3 + \frac{\eta_2 \delta}{d_5}) e^{-a\tau},
\end{align*}

\begin{align*}
n_1(\tau) &= d_1 d_2 R_1 (d_3 + \frac{\eta_2 \delta}{d_5}) e^{-a\tau} - \frac{k\beta d_1 d_2^2 (d_3 + \frac{\eta_2 \delta}{d_5})^2 (R_0 - R_1)(R_1 - 1)}{\alpha\gamma} e^{-a\tau}, \\
n_0(\tau) &= \frac{k\beta d_1 d_2^2 (d_3 + \frac{\eta_2 \delta}{d_5})^2 (R_0 - R_1)(R_1 - 1)}{\alpha\gamma} e^{-a\tau}.
\end{align*}

Note that $\xi_1 = -d_5 < 0$, we consider following equation

$$D_2(\xi) = \xi^4 + m_3(\tau)\xi^3 + m_2(\tau)\xi^2 + m_1(\tau)\xi + m_0(\tau) - (n_2(\tau)\xi^2 + n_1(\tau)\xi + n_0(\tau))e^{-\xi\tau}.$$  

When $\tau = 0$, (32) has the following form

$$D_2(\xi) = \xi^4 + m_3(0)\xi^3 + (m_2(0) - n_2(0))\xi^2 + (m_1(0) - n_1(0))\xi + m_0(0) - n_0(0).$$

We consider $0 < R_0 - R_1 < \epsilon$, using Routh-Hurwitz criterion [21], we obtain

\begin{align*}
\Delta_1 &= m_3(0) = d_1 \frac{R_0}{R_1} + d_2 R_1 + d_3 + \frac{\eta_2 \delta}{d_5} > 0, \\
\Delta_2 &= m_3(0)(m_2(0) - n_2(0)) - (m_1(0) - n_1(0)), \\
&= d_1 d_2 R_0 (d_1 \frac{R_0}{R_1} + d_2 R_1) + d_1 R_0 (d_3 + \frac{\eta_2 \delta}{d_5})(d_1 \frac{R_0}{R_1} + d_2 R_1 + d_3 + \frac{\eta_2 \delta}{d_5}) \\
&+ d_2^2 d_4 R_1 (R_1 - 1) + d_1 d_2 R_1 (d_3 + \frac{\eta_2 \delta}{d_5}) - \frac{k\beta d_1 d_2^2 (d_3 + \frac{\eta_2 \delta}{d_5})^2 (R_0 - R_1)(R_1 - 1)}{\alpha\gamma}, \\
\Delta_3 &= (m_1(0) - n_1(0))\Delta_2 - (m_0(0) - n_0(0))m_3(0)^2 \\
&= [d_1 d_2 (R_0 - R_1)(d_3 + \frac{\eta_2 \delta}{d_5}) + d_2 d_4 (R_1 - 1)(d_1 \frac{R_0}{R_1} + d_3 + \frac{\eta_2 \delta}{d_5})]$$
\end{align*}
We assert \( \Delta \) purely imaginary root of (32). We obtain that

\[
R^Ew\text{ without delay is asymptotically stable.}
\]

\[
2 - \tau - \Delta m^4 = (3\left(m + d - d^2 + d\tau\right)^2) > R_0(R_0 - R_1) - \frac{k\beta d_1 d_2(d + \frac{\eta \delta}{d_5})^2(R_1 - 1)(R_0 - R_1)}{\alpha \gamma}.
\]

\[
\Delta_4 = (m_0(0) - n_0(0))\Delta_3 = [d_2 d_4(R_1 - 1)d_1 R_0 R_1(d_3 + \frac{\eta \delta}{d_5}) - d_3 + \frac{\eta \delta}{d_5} - d_1 d_2 d_4(R_1 - 1) - \frac{k\beta d_1 d_2(d + \frac{\eta \delta}{d_5})^2(R_1 - 1)}{\alpha \gamma}.
\]

\[
\Delta_4 = (m_0(0) - n_0(0))\Delta_3 = [d_2 d_4(R_1 - 1)d_1 R_0 R_1(d_3 + \frac{\eta \delta}{d_5}) - d_3 + \frac{\eta \delta}{d_5} - d_1 d_2 d_4(R_1 - 1) - \frac{k\beta d_1 d_2(d + \frac{\eta \delta}{d_5})^2(R_1 - 1)}{\alpha \gamma}.
\]

\[
\Delta_4 = (m_0(0) - n_0(0))\Delta_3 = [d_2 d_4(R_1 - 1)d_1 R_0 R_1(d_3 + \frac{\eta \delta}{d_5}) - d_3 + \frac{\eta \delta}{d_5} - d_1 d_2 d_4(R_1 - 1) - \frac{k\beta d_1 d_2(d + \frac{\eta \delta}{d_5})^2(R_1 - 1)}{\alpha \gamma}.
\]

We assert \( \Delta_i > 0 \) for \( i = 1, 2, 3, 4 \) due to the arbitrary of \( \epsilon \). From above analysis, we conclude that there exists an \( R_2 \), when \( R_1 < R_0 < R_2 \), the infectious equilibrium \( E_2 \) without delay is asymptotically stable. \( \square \)

When \( \tau \neq 0 \), clearly, 0 is not the root of (32). Assuming \( \xi = iw(w > 0) \) is a purely imaginary root of (32). We obtain that

\[
w^4 - m_2(\tau)w^2 + m_0(\tau) = -n_2(\tau)w^2\cos(\omega \tau) + n_1(\tau)w\sin(\omega \tau) + n_0(\tau)\cos(\omega \tau),
\]

\[
- m_3(\tau)w^3 + m_1(\tau)w = n_2(\tau)w^2\sin(\omega \tau) + n_1(\tau)\cos(\omega \tau) - n_0(\tau)\sin(\omega \tau).
\]

(37)

Squaring and adding both equations of (34) lead to

\[
H_2(w^2) = w^8 + pw^6 + qw^4 + uw^2 + v,
\]

(38)

where

\[
p = m_3^2 - 2m_2,
\]

\[
q = m_2^2 + 2m_0 - 2m_1 m_3 - n_2^2,
\]

\[
u = m_1^2 - m_0 m_2 - n_1^2 - 2n_2 m_0,
\]

\[
v = m_0^2 - n_0^2.
\]
Let \( w^2 = s \), we have
\[
H_2(s) = s^4 + ps^3 + qs^2 + us + v. \tag{39}
\]
Thus,
\[
H'_2(s) = 4s^3 + 3ps^2 + 2qs + u. \tag{40}
\]
Set
\[
4s^3 + 3ps^2 + 2qs + u = 0. \tag{41}
\]
Let \( r = s + \frac{p}{4} \), we have
\[
r^3 + p_1 r + q_1 = 0, \tag{42}
\]
where \( p_1 = \frac{q}{2} - \frac{3}{16}p^2, q_1 = \frac{p^3}{32} - \frac{pq}{8} + \frac{u}{4} \). Define
\[
\Delta = \frac{q_1^2}{2} + \frac{p_1^3}{3}, \quad \zeta = \frac{-1 + i\sqrt{3}}{2},
\]
\[
r_1 = 3\sqrt{-\frac{q_1}{2} + \sqrt{\Delta}} + 3\sqrt{-\frac{q_1}{2} - \sqrt{\Delta}},
\]
\[
r_2 = 3\sqrt{-\frac{q_1}{2} + \sqrt{\Delta} \zeta} + 3\sqrt{-\frac{q_1}{2} - \sqrt{\Delta} \zeta^2},
\]
\[
r_3 = 3\sqrt{-\frac{q_1}{2} + \sqrt{\Delta} \zeta^2} + 3\sqrt{-\frac{q_1}{2} - \sqrt{\Delta} \zeta},
\]
\[
s_i = r_i - \frac{p}{4}, \quad i = 1, 2, 3.
\]
We cite the results in [20] about the existence of positive roots of the fourth-degree polynomial equation, namely, we have the following lemma.

**Lemma 2.8** ([20]).

1. If \( v < 0 \), then (35) has at least one positive root.
2. If \( v \geq 0 \) and \( \Delta \geq 0 \), then (35) has positive roots if and only if \( s_1 > 0 \) and \( H_2(s_1) < 0 \).
3. If \( v \geq 0 \) and \( \Delta < 0 \), then (35) has positive roots if and only if there exists at least one \( s^* \in \{s_1, s_2, s_3\} \) such that \( s^* > 0 \) and \( H_2(s^*) < 0 \).

Supposing one of the above three cases in Lemma 2.8 is satisfied, (36) has finite positive roots \( s_1, s_2, \ldots, s_k (k \leq 4) \). Therefore (35) has finite positive roots
\[
\tau_1 = \sqrt{s_1}, \quad \tau_2 = \sqrt{s_2}, \quad \ldots, \quad \tau_k = \sqrt{s_k}, \quad k \leq 4. \tag{43}
\]
For every fixed \( \tau_i \) (\( i \leq 4 \)), there has
\[
\tau_i^j = \frac{1}{\tau_i} (\arccos U_i + 2j\pi), \quad i = 1, 2, 3, \ldots, 4, \quad j = 0, 1, 2, \ldots, \tag{44}
\]
and
\[
U_i = \frac{(-m_3w_i^3 + m_1w_i)w_1^3 - (w_i^3 - m_2w_i^2 + m_0)(n_2w_i^2 - n_0)}{n_1^2w_i^4 + (n_2w_i^2 - n_0)^2}. \tag{45}
\]
Let
\[
\tau^* = \min \{\tau_i^0 | i = 1, 2, \ldots, k, k \leq 4\} = \frac{1}{w^*} \arccos U^*,
\]
\( w^* = \tau_i \) for some \( 1 \leq i \leq 4 \). Then (31) has a pair of purely imaginary roots \( \pm w_i \) when \( \tau = \tau^* \).

Differentiating both sides of Eq. (31) with respect to \( \tau \), we have
Lemma 2.9 ([20]).

\[
\frac{d}{d\tau}(Re\xi)^{-1}_{\tau=\tau'} = \frac{H'_2(w^2)}{n_1^2 w^2 + (n_2 w^2 - n_0)^2},
\]

(46)

Especially, supposing \( H'_2((w^*)^2) \neq 0 \), then

\[
\frac{d}{d\tau}(Re\xi)^{-1}_{\tau=\tau'} = \frac{H'_2((w^*)^2)}{n_1^2 (w^*)^2 + (n_2 (w^*)^2 - n_0)^2} > 0.
\]

(47)

Proof. From Eq.(32), we have

\[
e^{-\xi \tau} = \frac{\xi^4 + m_3(\tau)\xi^3 + m_2(\tau)\xi^2 + m_1(\tau)\xi + m_0(\tau)}{n_2(\tau)\xi^2 + n_1(\tau)\xi + n_0(\tau)}.
\]

(48)

Differentiating both sides of Eq.(32) with respect to \( \tau \) gives

\[
\left[ \frac{d\xi(\tau)}{d\tau} \right]^{-1} = 4\xi^3 + 3m_3(\tau)\xi^2 + 2m_2(\tau)\xi + m_1(\tau) - (2m_2(\tau)\xi + n_1)e^{-\xi \tau} + \tau e^{-\xi \tau} \frac{\Delta}{\xi} \Delta e^{-\xi \tau},
\]

where

\[
\Delta = n_2(\tau)\xi^2 + n_1(\tau)\xi + n_0(\tau).
\]

(49)

From Eq.(45) and Eq.(46), We have

\[
\frac{d}{d\tau}(Re\xi)^{-1}_{\tau=\tau'} = Re\left[ \frac{4\xi^3 + 3m_3(\tau)\xi^2 + 2m_2(\tau)\xi + m_1(\tau)}{\xi(\xi^4 + m_3(\tau)\xi^3 + m_2(\tau)\xi^2 + m_1(\tau)\xi + m_0(\tau))} \right]_{\xi=\text{Re}w_i}
\]

\[
- Re\left[ \frac{2n_2(\tau)\xi + n_1(\tau)}{n_2(\tau)\xi^2 + n_1(\tau)\xi + n_0(\tau)} \right]_{\xi=\text{Re}w_i}
\]

\[
= \frac{(w_i^4 - m_2(\tau)w_i^2 + m_0(\tau))(4w_i^4 + 2m_2(\tau)w_i)}{w_i(m_3(\tau)w_i^3 - m_1(\tau)w_i^2 + w_i^4 - m_2(\tau)w_i^2 + m_0(\tau))^2} + \frac{m_3(\tau)w_i^3 - m_1(\tau)w_i(m_1(\tau) - 3m_3(\tau)w_i)}{w_i(m_3(\tau)w_i^3 - m_1(\tau)w_i^2 + w_i^4 - m_2(\tau)w_i^2 + m_0(\tau))^2} - \frac{n_1(\tau)(m_2(\tau) - n_2(\tau)w_i^2)}{(n_0(\tau) - n_2(\tau)w_i^2)^2 + n_1^2w_i^2}.
\]

Simplify the above formula to get

\[
\frac{d}{d\tau}(Re\xi)^{-1}_{\tau=\tau'} = \frac{4w_i^6 + 3pw_i^4 + 2qw_i + u}{n_1^2 w_i^2 + (n_2 w_i^2 - n_0)^2} = \frac{H'_2(w^2)}{n_1^2 w_i^2 + (n_2 w_i^2 - n_0)^2},
\]

(50)

If \( \frac{d}{d\tau}(Re\xi)^{-1}_{\tau=\tau'} < 0 \), then (32) has a root with positive real part for \( \tau < \tau^* \) and close to \( \tau^* \), which contradicts Lemma 2.8. This completes the proof. \( \square \)

From lemma 2.9, we have the following result.

Theorem 2.10. When \( 1 < R_1 < \mathcal{R}_0 < R_2 \), there exists

\[
\tau^* = \min \{ \tau_i^0 | i = 1, 2, \ldots, k, k \leq 4 \}
\]

such that \( E_2 \) is asymptotically stable when \( \tau \in [0, \tau^*) \). Furthermore, if \( H'_2((w^*)^2) \neq 0 \) holds, and system (3) undergoes a Hopf bifurcation at \( E_2 \) when \( \tau = \tau^* \).
3. **Numerical results.** In this section, we use numerical examples and some simulations to demonstrate the theoretical results obtained in the previous sections. First, we assume the following parameters:

\[
\begin{align*}
\lambda &= 1, \alpha = \frac{1}{280}, d_1 = \frac{1}{180}, d_2 = 0.5, d_3 = d_4 = d_5 = 3, \\
\delta &= 90, \eta_1 = \frac{1}{260}, \eta_2 = \frac{1}{1600}, \beta = 0.008, k = 26, \gamma = 1.
\end{align*}
\]

Then the infectious equilibrium becomes

\[E_0 = (180, 0, 0, 30).\]

With the parameter values given in (48), it’s easy to see that \(0 < R_0 < 1\), \(E_0\) is globally asymptotically stable for these given parameter values. The simulation result is shown in Figure 3.1, indicating that all state variables, except for \(T\) and \(F\), converge to zero, and \(T\) converges to 180. It can be seen that the virus first increases and then monotonically decreases rapidly, while \(T\) and \(F\) always increases to equilibrium, the other variables monotonically decrease right from the beginning. They finally reach the infectious equilibrium \(E_0\).

![Figure 3.1](image1)

**Figure 3.** When \(R_0 < 1\), \(\tau = 1\), the disease-free equilibrium \(E_0\) is globally asymptotically stable.

Next, we consider the stability of \(E_1\) when \(R_1 < 1 < R_0\), we fixed

\[
\begin{align*}
\lambda &= 1, \alpha = \frac{1}{180}, d_1 = \frac{1}{180}, d_2 = 0.5, d_3 = d_4 = d_5 = 3, \\
\delta &= 90, \eta_1 = \frac{1}{160}, \eta_2 = \frac{1}{1600}, \beta = 0.008, k = 26, \gamma = 10.
\end{align*}
\]

With the parameter values given in (50), the infectious equilibrium without defective interfering particles \(E_1\) is globally asymptotically stable, as shown in Figure 3.2. We
choose $\tau = 0.8, 1, 1.5$, respectively. We found that the value of $\tau$ does not influence the stability of the infectious equilibrium $E_1$.

Now, we consider the stability of $E_2$ When $1 < R_1 < R_0$ and $0 < R_0 - R_1 < \epsilon$, we fix

$$\lambda = 1, \alpha = \frac{1}{180}, d_1 = \frac{1}{180}, d_2 = 0.5, d_3 = d_4 = d_5 = 3,$$
$$\delta = 90, \eta_1 = \frac{1}{160}, \eta_2 = \frac{1}{1600}, \beta = 0.008, k = 260, \gamma = 10.$$  \hspace{1cm} (54)

With the parameter values given in (50), the infectious equilibrium without defective interfering particles $E_1$ is globally asymptotically stable, as shown in Figure 3.3.

Finally, we consider possible Hopf bifurcation, we fixed

$$\lambda = 1, \alpha = \frac{1}{180}, d_1 = \frac{1}{180}, d_2 = 0.5, d_3 = d_4 = d_5 = 3,$$
$$\delta = 90, \eta_1 = \frac{1}{160}, \eta_2 = \frac{1}{1600}, \beta = 0.008, k = 2600, \gamma = 10.$$  \hspace{1cm} (55)

With the parameter values given in (52), the infectious equilibrium with defective interfering particles $E_2$ becomes unstable and a Hopf bifurcation occurs, leading to a family of periodic solutions. The simulation results shown in Figure 3.4. There is just one case where Hopf bifurcation occurs. There may be many other choices of the parameters that can occur Hopf bifurcation.
Figure 5. When $1 < R_1 < R_0$, $\tau = 1.6$, the infectious equilibrium with defective interfering particles $E_2$ is locally asymptotically stable.

Figure 6. When $1 < R_1 < R_0$, $\tau = 1.6$, the infectious equilibrium with defective interfering particles $E_2$ showing bifurcation to a stable limit cycle.
4. Conclusion and discussion. In this paper, we proposed a delay differential mathematical model for COVID-19 therapy with defective interfering particles and artificial antibodies. In section 2, we presented the positivity and boundedness of solutions for the system (3). The basic reproduction number $R_0$ was defined and three equilibria were given. We proved that $E_0$ is globally asymptotically stable when $R_0 < 1$ and the time delay does not destroy the globally asymptotical stability of $E_0$. $E_1$ is globally asymptotically stable when $R_1 < 1 < R_0$, and the time delay also does not destroy the globally asymptotically stable. For the stability of $E_2$, we proved that there exists an $R_2$, $E_2$ is locally asymptotically stability when $1 < R_1 < R_0 < R_2$. As the time delay increases, $E_2$ can undergo a Hopf bifurcation on proper conditions. The above descriptions reveal the role that each parameter plays in determining the global dynamics of the model and give some quantitative criteria in terms of the parameters for controlling the infection.

Artificial antibodies have great potential for the prevention and treatment of SARS-CoV-2 infection. When there are no defective interfering particles in vivo, there exists two equilibria: disease-free equilibrium $E_0$ and infectious equilibrium $E_1$. From (4), $R_0 = \frac{\lambda_0 \sigma d_2 e^{-e}}{d_1 d_3 (d_3 d_5 + \delta)}$, this implies that there exists a suitable value of $\delta$ makes $R_0 < 1$. Artificial antibodies do have a great impact on eliminating virus. In fact, a single injection of artificial antibodies is not helpful to eliminate the virus completely since artificial antibodies decay to zero throughout the body. We should consider multiple injections to ensure that artificial antibodies persist at a certain level in the body which may require more time and money. A concern for any antiviral therapeutic is the potential for acquiring drug resistance due to the rapid mutation of viral pathogens. Thus, the therapy only use artificial antibodies to against SARS-CoV-2 may not suffice.

Defective interfering particles (DIPs) could interfere with the virus by virtue of their faster replication in cells coinfected with the normal virus. From the basic reproduction number, defective interfering particles may have no impact on $R_0$. In this sense, introducing the defective interfering particles into the host does not help to eliminate the SARS-CoV-2 clearly. However, Comparing the infectious equilibrium without defective interfering particles $E_1 = (\frac{d_1}{\alpha \sigma}, \frac{d_2}{\alpha \gamma}, \frac{d_3}{\alpha \gamma} (R_0 - 1), 0, \frac{d}{\alpha \gamma})$ and infectious equilibrium with defective interfering particles $E_2 = (\frac{\lambda R_0}{d_1 \alpha \sigma}, \frac{d_1}{\alpha \gamma}, \frac{d_3}{\alpha \gamma} (\frac{R_0}{R_1} - 1), \frac{d_2}{\alpha \gamma} (R_1 - 1), \frac{d}{\alpha \gamma})$, it showed that defective interfering particles can reduce the viral load. When $R_0$ and $R_1$ are close enough, the viral load in vivo at a very low level. This results are consistent with a recent study [41]. In [41], Yao et al. have created a synthetic defective interfering version of SARS-CoV-2, reducing the viral load of infected cells by half in 24 hours. Defective interfering particles can replicate with the help of virus in vivo, avoid the trouble of multiple injections. Whether defective interfering particles can survive and reproduce in the body is a key factor in this therapy. We defined a quantity $R_1$ in our paper which determines the defective interfering particles can replicate in vivo or not. This quantity can be a certain of help for clinical research on the administration method of defective interfering particles.

Recent months have seen the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants [1] [4] [42], which could put more pressure on health-care systems and counter-measures such as vaccination programmes. In [41] and [25], they showed that artificial antibodies and defective interfering particles could be against SARS-CoV-2 variants. To better evaluate the effect of the
therapy, we need to extend the current model by incorporating more biological and epidemiological factors.

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