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Hopf Bifurcation of Multiple Sclerosis Model with Time Delay and Saturation Function Reaction

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Abstract

In this paper, the stability and Hopf bifurcation of multiple sclerosis model with time delay and saturation function reaction are studied. At first, the stability condition of trivial equilibrium point is given, and the stability of non-negative equilibrium point is discussed. Then, the existence condition of Hopf bifurcation is given by choosing the added time delay τ as the bifurcation parameter. The direction of Hopf bifurcation and the stability of its periodic solution are analyzed by using canonical form theory and central manifold theorem. Finally, the conclusion is drawn by numerical analysis.

Keywords

MS Model, Saturation Functional Response Function, Time Delay, Equilibrium Points, Stability, Hopf Bifurcation

1. Introduction

Multiple Sclerosisis is a common demyelinating disease of the central nervous system. In the acute active stage, there are multiple inflammatory demyelinating spots in the white matter of the central nervous system, which are calcified due to the proliferation of glial fibers. It is characterized by multiple lesions, remission and recurrence, and is mainly found in the optic nerve, spinal cord and brain stem, mostly in young and middle age, with more women than men [1]-[4]. The ODE model of MS was first proposed by Broome and others in 2011 with biochemical theory [5]. In the same year, H.K. Alexander and L.M. Wahl proposed the model (1.1) [6]. In 2014, W.J. Zhang, L.M. Wahl and P. Yu considered another inhibition mechanism: active regulatory T cells can directly reduce the effector T cells of their own reactions, and introduce terminal differentiation regulatory T cells and ignore the secretion of IL-2 [7]. In 2021, W.J. Zhang and P. Yu made a correlation analysis of five-dimensional, four-dimensional and three-dimensional models [8].

$$\begin{cases} \dot{A} = f\tilde{v}G - (\sigma_1 R + b_1) A - \mu_A A, \\ \dot{R} = (\pi_1 E + \beta) A - \mu_R R, \\ \dot{E} = \lambda_E A - \mu_E E, \\ \dot{G} = \gamma E - \tilde{v}G - \mu_G G. \end{cases} \tag{1.1}$$

In the model (1.1), A represents mature professional antigen presenting cells (pAPCs); R represents active "natural" regulatory T cells (nTregs); E represents active (effector) conventional T cells; G represents the particular self-antigen of interest, that has been released from host cells (free antigen). According to the definition of parameters, all parameters except b_1, π_1 and β are positive numbers, and $f \in [0,1]$.

Active regulatory T cells will inhibit the maturation of professional antigen presenting cells, while mature professional antigen presenting cells will activate the maturation of regulatory T cells [9]. When the target cell density increases, the action rate of the two cells will gradually saturate. Based on the above discussion, it is assumed that the interaction between full-time antigen presenting cells and activity regulating T cells is nonlinear, and the saturated functional response function is added to obtain:

$$\begin{cases} \dot{A} = f\tilde{v}G - \left(\dfrac{a_1 \sigma_1 R}{1 + a_2 R} + b_1 \right) A - \mu_A A, \\ \dot{R} = (\pi_1 E + \beta) A - \mu_R R, \\ \dot{E} = \lambda_E A - \mu_E E, \\ \dot{G} = \gamma E - \tilde{v}G - \mu_G G, \end{cases} \tag{1.2}$$

where $\dfrac{a_1 \sigma_1 R}{1 + a_2 R}$ is the saturated functional response function, which is a commonly used Holling-2 function. It can reflect the limitation of nTregs processing ability, that is, when there are too many pAPCs, nTregs will be "busy" and unable to further improve their action rate.

For convenience, the model is dimensionless, and it is assumed that

$$u = cA, \quad v = dR, \quad w = eE, \quad x = yG, \quad T = qt.$$

Let's assume that the letters are different from the above and define dimensionless parameters

$$a = \frac{a_2 f \beta^2 \gamma \tilde{v}}{\pi_1 q^3}, \quad b = \frac{a_1 \sigma_1}{a_2 q}, \quad c = \frac{\mu_R}{q}, \quad m = \frac{\pi_1 \lambda_E}{a_2 \beta^2}, \quad n = \frac{\mu_E}{q}, \quad d = \frac{\tilde{v} + \mu_G}{q},$$

and still use t to represent T, the model can be reduced to:

$$\begin{cases} \dfrac{\mathrm{d}u}{\mathrm{d}t} = ax - \dfrac{buv}{1+v} - u, \\ \dfrac{\mathrm{d}v}{\mathrm{d}t} = uw + u - cv, \\ \dfrac{\mathrm{d}w}{\mathrm{d}t} = mu - nw, \\ \dfrac{\mathrm{d}x}{\mathrm{d}t} = w - dx. \end{cases} \tag{1.3}$$

H.K. Alexander and L.M. Wahl assume that T cells and target host cells are constant and unrestricted when proposing the model, and ignore all spatial effects and time delays. In fact, there is a delay of several days between the time when a conventional T cell meets a professional antigen presenting cell and the time when its fully differentiated offspring can perform its effector function [10]. For regulating T cells, the time length may be significant, which depends on the time course of immune response. A realistic method to simulate this effect is to introduce delay into the equation, so adding delay parameters can be obtained:

$$\begin{cases} \dfrac{\mathrm{d}u}{\mathrm{d}t} = ax - \dfrac{bu(t-\tau)v(t-\tau)}{1+v(t-\tau)} - u, \\ \dfrac{\mathrm{d}v}{\mathrm{d}t} = uw + u - cv, \\ \dfrac{\mathrm{d}w}{\mathrm{d}t} = mu - nw, \\ \dfrac{\mathrm{d}x}{\mathrm{d}t} = w - dx. \end{cases} \tag{1.4}$$

This is a four-dimensional MS model with time delay and saturation function. In this paper, the existence and stability of the equilibrium point of this model and the parameter conditions of Hopf bifurcation are studied, and the bifurcation direction and stability of the periodic solution of bifurcation are also studied.

2. Positive Invariance of Solution and Existence of Positive Equilibria

Lemma 2.1. If $(u(t), v(t), w(t), x(t))$ is a solution of model (1.4) with initial conditions $u(\theta) = \varphi_1(\theta)$, $v(\theta) = \varphi_2(\theta)$, $w(\theta) = \varphi_3(\theta)$, $x(\theta) = \varphi_4(\theta)$, where $\varphi_i(\theta) \in C^+ = \{\varphi(\theta) \in C[-\tau, 0], \varphi(\theta) > 0\}$, $i = 1,2,3,4$. Then for all $t \ge 0$, $u(t) \ge 0$, $v(t) \ge 0$, $w(t) \ge 0$, $x(t) \ge 0$.

Proof: When $t \in [0, \tau]$, by the first equation in (1.4), we have

$$u(t) = \mathrm{e}^{-t}\left\{\varphi_1(0) + \int_0^t \left[ax - bu(s-\tau)\frac{v(s-\tau)}{1+v(s-\tau)}\right]\mathrm{e}^s \mathrm{d}s\right\}.$$

Notice that $\varphi_1(0) > 0$, implies that $u(t) \ge 0$, $t \in [0, \tau]$.

Similarly, according to the last three equations of (1.4)

$$
\begin{aligned}
v(t) &= \mathrm{e}^{-ct}\left[\varphi_2(0)+\int_0^t (uw+u)\mathrm{e}^{cs}\mathrm{d}s\right],\\
w(t) &= \mathrm{e}^{-nt}\left[\varphi_3(0)+\int_0^t mu\mathrm{e}^{ns}\mathrm{d}s\right],\\
v(t) &= \mathrm{e}^{-dt}\left[\varphi_4(0)+\int_0^t w\mathrm{e}^{ds}\mathrm{d}s\right],
\end{aligned}
$$

and $\varphi_i(0)>0$, $i=2,3,4$, we also have $v(t)\ge 0$, $w(t)\ge 0$, $x(t)\ge 0$, $t\in[0,\tau]$. By the recursive method, we have $u(t)\ge 0$, $v(t)\ge 0$, $w(t)\ge 0$, $x(t)\ge 0$, for all $t\ge 0$. □

Obviously, models (1.3) and (1.4) have the same equilibria. Therefore, (1.4) has a trivial equilibrium point $E_0=(0,0,0,0)$. To solve the positive equilibrium $E^*=(u^*,v^*,w^*,x^*)$ of model (1.4), we first need to discuss Equation (2.1)

$$m(am-dn-bdn)u^2+n(am-dn-bdn)u+cn(am-dn)=0. \tag{2.1}$$

Suppose $\Delta>0$, the solution of Equation (2.1) $u_1=\dfrac{-b_0+\sqrt{b_0^2-4a_0c_0}}{2a_0}$ and $u_2=\dfrac{-b_0-\sqrt{b_0^2-4a_0c_0}}{2a_0}$, have the following three situations:

where

$$
\begin{aligned}
a_0 &= m(am-dn-bdn),\\
b_0 &= n(am-dn-bdn),\\
c_0 &= cn(am-dn),\\
\Delta &= b_0^2-4a_0c_0.
\end{aligned}
$$

1) If $a_0>0$, $b_0>0$, $c_0>0$, namely $am-dn-bdn>0$ holds, u_1 and u_2 are all negative roots.

2) If $a_0<0$, $b_0<0$, $c_0<0$, namely $am-dn<0$ holds, u_1 and u_2 are all negative roots.

3) If $a_0<0$, $b_0<0$, $c_0>0$, namely $dn<am<dn+bdn$ holds, u_1 is a negative root, u_2 is a positive root.

In the third case, the model (1.4) has a positive equilibrium point $E^*=\left(u^*,\dfrac{mu^{*2}+nu^*}{cn},\dfrac{mu^*}{n},\dfrac{mu^*}{dn}\right)$.

Theorem 2.1. Assuming that $am(n-4cm)>dn(n-4cm+bn)$ and $dn<am<dn+bdn$ hold, and any of the following conditions holds, model (4.1) has unique positive equilibrium solution E^*.

(H_1) If $n-4cm\le 0$ holds, $dn<am<dn+bdn$.

(H_2) If $0<n-4cm\le 1$ holds, $dn<am<dn+bdn$.

(H_3) If $n-4cm>1$ holds, $dn<am<dn+dn\left(1+\dfrac{b}{n-4cm}\right)$.

3. Stability Analysis of Equilibria and Existence of Hopf Bifurcation

Lemma 3.1. 1) If $am<dn$ holds, E_0 is locally asymptotically stable.

2) If $am > dn$ holds, E_0 is saddle point.

Proof: The Jacobian matrix of model (1.4) at E_0 is

$$J_{E_0} = \begin{pmatrix} -1 & 0 & 0 & a \\ 1 & -c & 0 & 0 \\ m & 0 & -n & 0 \\ 0 & 0 & 1 & -d \end{pmatrix}$$

The characteristic equation at E_0 is

$$(\lambda + c)\left[\lambda^3 + (1+d+n)\lambda^2 + (d+n+dn)\lambda + dn - am\right] = 0.$$

One of the eigenvalues is $\lambda_1 = -c < 0$, which only needs to be considered

$$\lambda^3 + (1+d+n)\lambda^2 + (d+n+dn)\lambda + dn - am = 0.$$

By Hurwitz criterion, if $am < dn$ holds, $\Delta_3 > 0$, E_0 is asymptotically stable; if $am > dn$ holds, $\Delta_3 < 0$, calculate the Jacobian determinant at E_0

$$det\left(J_{E^*}\right) = c(dn - am) < 0$$

Therefore, the equilibrium point E_0 is the saddle point. □

The Jacobian matrix of model (1.4) at E^* is

$$J_{E^*} = \begin{pmatrix} -\dfrac{bv^*}{1+v^*} - 1 & -\dfrac{bu^*}{\left(1+v^*\right)^2} & 0 & a \\ w^* + 1 & -c & u^* & 0 \\ m & 0 & -n & 0 \\ 0 & 0 & 1 & -d \end{pmatrix}$$

The characteristic equation at E^* is

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 + \left(b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4\right)\mathrm{e}^{-\lambda\tau} = 0, \tag{3.1}$$

where

$$a_1 = 1 + c + d + n$$

$$a_2 = c + d + n + cd + cn + dn$$

$$a_3 = cd + cn + dn + cdn - am$$

$$a_4 = cdn - acm$$

$$b_1 = \frac{am}{dn} - 1$$

$$b_2 = (c+d+n)\left(\frac{am}{dn} - 1\right) + \frac{bcv^*}{\left(1+v^*\right)^2}$$

$$b_3 = (cd + cn + dn)\left(\frac{am}{dn} - 1\right) + \frac{bmu^*}{\left(1+v^*\right)^2} + (d+n)\frac{bcv^*}{\left(1+v^*\right)^2}$$

$$b_4 = acm - cdn + \frac{bcdnv^*}{\left(1+v^*\right)^2} + \frac{bdmu^*}{\left(1+v^*\right)^2}$$

When $\tau = 0$, the equation becomes

$$\lambda^4+\left(a_1+b_1\right)\lambda^3+\left(a_2+b_2\right)\lambda^2+\left(a_3+b_3\right)\lambda+\left(a_4+b_4\right)=0. \tag{3.2}$$

If

$$ac>bu^*\left(c+d+n\right) \tag{3.3}$$

holds, by Hurwitz criterion, all roots of (3.2) have negative real parts, and E^* is asymptotically stable.

When $\tau>0$, $\mathrm{i}\omega$ is the root of (3.2) if and only if ω satisfies

$$\omega^4-\mathrm{i}a_1\omega^3-a_2\omega^2+\mathrm{i}a_3\omega+a_4+\left(-b_1\omega^3-b_2\omega^2+\mathrm{i}b_3\omega+b_4\right)\left(\cos\omega\tau-\mathrm{i}\sin\omega\tau\right)=0$$

Separating its real and imaginary parts gets

$$\begin{cases}\omega^4-a_2\omega^2+a_4=\left(b_1\omega^3-b_3\omega\right)\sin\omega\tau+\left(b_2\omega^2-b_4\right)\cos\omega\tau\\ -a_1\omega^3+a_3\omega=\left(b_1\omega^3-b_3\omega\right)\cos\omega\tau+\left(-b_2\omega^2+b_4\right)\sin\omega\tau\end{cases} \tag{3.4}$$

further,

$$\omega^8+s\omega^6+t\omega^4+p\omega^2+q=0 \tag{3.5}$$

where

$$\begin{aligned}&s=a_1^2-2a_2-b_1^2\\&t=a_2^2+2a_4-2a_1a_4+2b_1b_3-b_2^2\\&p=a_3^2-2a_2a_4+2b_2b_4-b_3^2\\&q=a_4^2-b_4^2\end{aligned}$$

Let $r=\omega^2$, then (3.5) can be written in the form

$$r^4+sr^3+tr^2+pr+q=0$$

Let

$$h\left(r\right)=r^4+sr^3+tr^2+pr+q, \tag{3.6}$$

Notice that

$$h'\left(r\right)=4r^3+3sr^2+2tr+p, \tag{3.7}$$

Definition:

$$P_0=\frac{8t-3s^2}{16},\ Q_0=\frac{s^3-4ts+8p}{32},\ D_0=\frac{Q_0^2}{4}+\frac{P_0^3}{27},\ \sigma=\frac{-1+\sqrt{3}i}{2}.$$

According to Cartan formula, the maximum real root of Equation (3.7) has the following conditions:

1) If $D_0>0$ holds

$$r_1^*=-\frac{s}{4}+\sqrt[3]{-\frac{Q_0}{2}+\sqrt{D_0}}+\sqrt[3]{-\frac{Q_0}{2}-\sqrt{D_0}};$$

2) If $D_0=0$ holds

$$r_2^*=\max\left\{-\frac{s}{4}-2\sqrt[3]{\frac{Q_0}{2}},-\frac{s}{4}+\sqrt[3]{\frac{Q_0}{2}}\right\};$$

3) If $D_0 < 0$ holds

$$r_3^* = \max\left\{-\frac{s}{4}+2\operatorname{Re}\{\xi\}, -\frac{s}{4}+2\operatorname{Re}\{\xi\sigma\}, -\frac{s}{4}+2\operatorname{Re}\{\xi\bar{\sigma}\}\right\},$$

where $\xi = \sqrt[3]{-\frac{Q_0}{2}+\sqrt{D_0}}$.

Lemma 3.1. The following conclusions hold for Equation (3.6)

1) If $q < 0$ holds, $\lim_{x\to\infty} h(r) = +\infty$, $h(0) = q < 0$, $h(r) = 0$ has at least one positive real root.

2) If $q \ge 0$ holds, then (3.6) has no positive real root when any of the following conditions holds

i) $D_0 > 0$, $r_1^* < 0$;

ii) $D_0 = 0$, $r_2^* < 0$;

iii) $D_0 < 0$, $r_3^* < 0$.

3) If $q \ge 0$ holds, then (3.6) has at least one positive real root when any of the following conditions holds

i) $D_0 > 0$, $r_1^* > 0$, $f(r_1^*) < 0$;

ii) $D_0 = 0$, $r_2^* > 0$, $f(r_2^*) < 0$;

iii) $D_0 < 0$, $r_3^* > 0$, $f(r_3^*) < 0$.

Suppose the third case in Lemma 3.1 holds, Equation (3.6) has positive root, without loss of generality, there are three positive roots, defined as r_1, r_2, r_3, r_4. Then (3.5) has three positive roots $\omega_1 = \sqrt{r_1}$, $\omega_2 = \sqrt{r_2}$, $\omega_3 = \sqrt{r_3}$, $\omega_4 = \sqrt{r_4}$.

By (3.4), there is

$$\cos\omega\tau = \frac{\left(b_2\omega^2-b_4\right)\left(-a_1\omega^3+a_3\omega\right)-\left(\omega^4-a_2\omega^2+a_4\right)\left(b_1\omega^3-b_3\omega\right)}{\left(b_1\omega^3-b_3\omega\right)^2+\left(b_2\omega^2-b_4\right)^2}$$

Let

$$\tau_k^{(j)} = \frac{1}{\omega_k}\left\{\arccos\frac{\left(b_2\omega^2-b_4\right)\left(-a_1\omega^3+a_3\omega\right)-\left(\omega^4-a_2\omega^2+a_4\right)\left(b_1\omega^3-b_3\omega\right)}{\left(b_1\omega^3-b_3\omega\right)^2+\left(b_2\omega^2-b_4\right)^2}+2j\pi\right\},$$

where $k = 1,2,3,4$, $j = 1,2,3,\cdots$, then $\pm i\omega_k$ is a pair of pure imaginary roots of the characteristic equation at E^*.

Define

$$\tau_0 = \tau_{k_0}^{(0)} = \min\tau_k^{(0)},\ \omega_0 = \omega_{k_0}.$$

Let $\lambda(\tau) = \alpha(\tau)+i\omega(\tau)$. From the previous discussion, we know that $\alpha(\tau_0) = 0$, remember $\omega(\tau_0) = \omega_0$. Substitute $\lambda(\tau)$ into the equation and derive τ.

$$\frac{\mathrm{d}\lambda}{\mathrm{d}\tau} = \frac{I}{J}$$

where

$$\begin{aligned} I &= \lambda \mathrm{e}^{-\lambda\tau}\left(b_1\lambda^3+b_2\lambda^2+b_3\lambda+b_4\right) \\ J &= 4\lambda^3+3a_1\lambda^2+2a_2\lambda+a_3+\mathrm{e}^{-\lambda\tau}\left(3b_1\lambda^2+2b_2\lambda+b_3\right) \\ &\quad -\mathrm{e}^{-\lambda\tau}\tau\left(b_1\lambda^3+b_2\lambda^2+b_3\lambda+b_4\right) \end{aligned}$$

Substitute τ_0 into $\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}$ and simplify

$$\left.\frac{\mathrm{d}\left(\operatorname{Re}\lambda(\tau)\right)}{\mathrm{d}\tau}\right|_{\tau=\tau_0}=\frac{LN+MQ}{N^2+Q^2}$$

where

$$L=\left(b_1\omega_0^4-b_3\omega_0^2\right)\cos\omega_0\tau_0+\left(-b_2\omega_0^3+b_4\omega_0\right)\sin\omega_0\tau_0$$

$$M=\left(-b_2\omega_0^3+b_4\omega_0\right)\cos\omega_0\tau_0+\left(-b_1\omega_0^4+b_3\omega_0^2\right)\sin\omega_0\tau_0$$

$$\begin{aligned}N=&\left[-3b_1\omega_0^2+b_3-\tau_0\left(-3b_2\omega_0^2+b_4\right)\right]\cos\omega_0\tau_0\\&+\left[b_1\omega_0+\tau_0\left(b_1\omega_0^3-b_3\omega_0\right)\right]\sin\omega_0\tau_0+a_3\end{aligned}$$

$$\begin{aligned}Q=&\left[b_1\omega_0+\tau_0\left(b_1\omega_0^3-b_3\omega_0\right)\right]\cos\omega_0\tau_0\\&+\left[3b_1\omega_0^2-b_3+\tau_0\left(-3b_2\omega_0^2+b_4\right)\right]\sin\omega_0\tau_0-4\omega_0^3-3a_1\omega_0^2+2a_1\omega_0.\end{aligned}$$

If $\frac{LN+MQ}{N^2+Q^2}\neq 0$ holds, the system appears Hopf bifurcation at τ_0.

Theorem 3.1 Suppose that (1) in Lemma 3.1 holds, τ_0 and ω_0 are defined above.

1) If $0\le\tau<\tau_0$, E^* is locally asymptotically stable.

2) If $\tau>\tau_0$, E^* is unstable.

3) If $\frac{LN+MQ}{N^2+Q^2}\neq 0$, then system (1.4) un-dergoes a Hopf bifurcation at E^* as τ passes through the τ_0.

4. Direction and Stability of Hopf Bifurcation

In the last section, the existence conditions of Hopf bifurcation have been determined. This section will calculate and determine the direction of Hopf bifurcation and the stability of periodic solution according to Poincaré-Andronov-Hopf theorem [11] [12].

Set $u=u_1(\tau t)-u^*$, $v=u_2(\tau t)-v^*$, $w=u_3(\tau t)-w^*$, $x=u_4(\tau t)-x^*$, $u(t)=\left(u_1(t),u_2(t),u_3(t),u_4(t)\right)^{\mathrm{T}}$, $\tau=\tau^*+\mu$, μ is the Hopf bifurcation value of the model, $\pm\mathrm{i}\omega_0$ is a pair of pure imaginary roots of the characteristic equation corresponding to E^*, the phase space is chosen as $C=C\left([-1,0],\mathbb{R}^4\right)$, modeled as the following functional differential equation

$$\dot{u}=L_\mu\left(u_t\right)+f\left(\mu,u_t\right). \tag{4.1}$$

Let $\phi=\left(\phi_1,\phi_2,\phi_3,\phi_4\right)^{\mathrm{T}}\in C\left([-1,0],\mathbb{R}^4\right)$. Define $L_\mu(\phi)=A_1\phi(0)+A_2\phi(-1)$, where

$$A_1=\left(\tau^*+\mu\right)\begin{pmatrix}-1 & 0 & 0 & a\\ w^*+1 & -c & u^* & 0\\ m & 0 & -n & 0\\ 0 & 0 & 1 & -d\end{pmatrix}$$

$$A_2=\left(\tau^*+\mu\right)\begin{pmatrix} -\frac{bv^*}{1+v^*} & -\frac{bu^*}{\left(1+v^*\right)^2} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$f\left(\mu,\phi\right)=\left(\tau^*+\mu\right)\begin{pmatrix} n_1\phi_2^2\left(-1\right)-n_2\phi_1\left(-1\right)\phi_2\left(-1\right) \\ \phi_1\left(0\right)\phi_3\left(0\right) \\ 0 \\ 0 \end{pmatrix},$$

where $n_1=\frac{bu^*}{\left(1+v^*\right)^3}$, $n_2=\frac{b}{\left(1+v^*\right)^2}$.

According to Riesz representation theorem, there exists a bounded variation function matrix $\eta\left(\theta,\mu\right)$, $\theta\in\left[-1,0\right]$, such that

$$L_\mu\left(\phi\right)=\int_{-1}^{0}\phi\left(\theta\right)\mathrm{d}\eta\left(\theta,\mu\right),\ \phi\in C.$$

Choose

$$\eta\left(\theta,\mu\right)=A_1\delta\left(\theta\right)-A_2\delta\left(\theta+1\right),$$

where

$$\delta\left(\theta\right)=\begin{cases}1, & \theta=0,\\ 0, & \theta\neq 0.\end{cases}$$

Define

$$A\left(\mu\right)\phi=\begin{cases}\frac{\mathrm{d}\phi\left(\theta\right)}{\mathrm{d}\theta}, & \theta\in\left[-1,0\right),\\ \int_{-1}^{0}\mathrm{d}\eta\left(\xi,\mu\right)\phi\left(\xi\right), & \theta=0;\end{cases}$$

$$R\left(\sigma\right)\phi=\begin{cases}0, & \theta\in\left[-1,0\right),\\ f\left(s,\phi\right), & \theta=0,\end{cases}$$

where $\phi\in C^1\left(\left[-1,0\right],\left(\mathbb{R}^4\right)^*\right)$, the system (4.1) can be expressed as

$$\dot{u}_t=A\left(\mu\right)u_t+R\left(\mu\right)u_t,\ u_t=u\left(t+\theta\right),\ \theta\in\left[-1,0\right].$$

In the following, the adjoint theory, centripetal flow theory and canonical form theory are used to discuss and define the formal adjoint operator of A for $\psi\in C^1\left(\left[-1,0\right],\mathbb{R}^4\right)$.

$$A^*\psi\left(s\right)=\begin{cases}-\frac{\mathrm{d}\psi\left(s\right)}{\mathrm{d}s}, & s\in\left(0,1\right],\\ \int_{-1}^{0}\mathrm{d}\eta^{\mathrm{T}}\left(t,0\right)\psi\left(-t\right), & s=0.\end{cases}$$

For ϕ and ψ define the bilinear inner product

$$\left\langle\psi,\phi\right\rangle=\bar{\psi}\left(0\right)\phi\left(0\right)-\int_{-1}^{0}\int_{0}^{\theta}\bar{\psi}\left(\xi-\theta\right)\mathrm{d}\eta\left(\theta\right)\phi\left(\xi\right)\mathrm{d}\xi. \tag{4.2}$$

It satisfies $\langle \psi, A\phi \rangle = \langle A^* \psi, \phi \rangle$, where $\eta(\theta) = \eta(\theta, 0)$, then A^* is the conjugate operator of $A(0)$, if $\pm \mathrm{i}\omega_0 \tau_0$ is eigenvalues of $A(0)$, they are also eigenvalues of A^*.

Lemma 4.1 Let $A(0)$ correspond to the feature root $\mathrm{i}\omega_0\tau_0$ and A^* correspond to the feature root $-\mathrm{i}\omega_0\tau_0$, and respectively the feature vectors are

$$q(\theta) = (1, C_1, C_2, C_3)^{\mathrm{T}} \mathrm{e}^{\mathrm{i}\omega_0\tau_0\theta}, \quad q^*(s) = M(1, C_4, C_5, C_6)^{\mathrm{T}} \mathrm{e}^{\mathrm{i}\omega_0\tau_0 s},$$

meanwhile $\langle q^*(s), q(\theta) \rangle = 1$, $\langle q^*(s), \overline{q}(\theta) \rangle = 0$, then

$$C_1 = \frac{1 + w^*}{c + \mathrm{i}\omega_0} + \frac{mu^*}{(c + \mathrm{i}\omega_0)(n + \mathrm{i}\omega_0)}$$

$$C_2 = \frac{m}{n + \mathrm{i}\omega_0}$$

$$C_3 = \frac{m}{(d + \mathrm{i}\omega_0)(n + \mathrm{i}\omega_0)}$$

$$C_4 = -\frac{bu^*}{(c + \mathrm{i}\omega_0)(1 + v^*)^2} \mathrm{e}^{-\mathrm{i}\omega_0\tau_0}$$

$$C_5 = -\frac{bu^{*2}}{n(c + \mathrm{i}\omega_0)(1 + v^*)^2} \mathrm{e}^{-\mathrm{i}\omega_0\tau_0} + \frac{a}{n(d + \mathrm{i}\omega_0)}$$

$$C_6 = \frac{a}{d + \mathrm{i}\omega_0}$$

$$\overline{M} = \frac{1}{1 + C_1\overline{C_4} + C_2\overline{C_5} + C_3\overline{C_6} - \tau_0 \mathrm{e}^{-\mathrm{i}\omega_0\tau_0} \left[\frac{bv^*}{1 + v^*} + \frac{bu^* C_1}{(1 + v^*)^2} \right]}$$

Proof: Let $q(\theta)$ be the eigenvector of $A(0)$ corresponding to $\mathrm{i}\omega_0\tau_0$,

$$A(0)q(\theta) = \frac{\mathrm{d}q(\theta)}{\mathrm{d}\theta} = \mathrm{i}\omega_0\tau_0 q(\theta), \quad \theta \in [-1, 0).$$

Calculated

$$q(\theta) = (1, C_1, C_2, C_3)^{\mathrm{T}} \mathrm{e}^{\mathrm{i}\omega_0\tau_0\theta}, \quad \theta \in [-1, 0).$$

Since

$$A(0)q(0) = \mathrm{i}\omega_0\tau_0 q(0) = \int_{-1}^{0} \mathrm{d}\eta(\xi)(1, C_1, C_2, C_3)^{\mathrm{T}} \mathrm{e}^{\mathrm{i}\omega_0\tau_0\xi}, \quad \theta = 0,$$

then

$$\mathrm{i}\omega_0\tau_0 (1, C_1, C_2, C_3)^{\mathrm{T}} = \tau_0 \left(A_1 + A_2 \mathrm{e}^{\mathrm{i}\omega_0\tau_0} \right) (1, C_1, C_2, C_3)^{\mathrm{T}}$$

The values of C_1, C_2, C_3 can be obtained.

Similarly, we can get C_4, C_5, C_6.

Now calculate the value of M, from (4.2) you can get

$$
\begin{aligned}
&\left\langle q^*(s), q(\theta)\right\rangle \\
&= \bar{q}^*(0)q(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \bar{q}^*(\xi-\theta)\,\mathrm{d}\eta(\theta)\,q(\xi)\,\mathrm{d}\xi \\
&= \bar{M}\Big[(1,C_4,C_5,C_6)(1,C_1,C_2,C_3)^{\mathrm{T}} \\
&\quad -\int_{-1}^{0}\int_{\xi=0}^{\theta}(1,\bar{C}_4,\bar{C}_5,\bar{C}_6)\,\mathrm{d}\eta(\theta)(1,C_1,C_2,C_3)^{\mathrm{T}}\,\mathrm{e}^{\mathrm{i}\omega_0\tau_0\xi}\,\mathrm{d}\xi\Big] \\
&= \bar{M}\left\{1 + C_1\overline{C_4} + C_2\overline{C_5} + C_3\overline{C_6} - \tau_0\mathrm{e}^{-\mathrm{i}\omega_0\tau_0}\left[\frac{bv^*}{1+v^*} + \frac{bu^*C_1}{\left(1+v^*\right)^2}\right]\right\}
\end{aligned}
$$

Notice that $\left\langle q^*(s), q(\theta)\right\rangle = 1$, then let

$$
\bar{M}^{-1} = 1 + C_1\overline{C_4} + C_2\overline{C_5} + C_3\overline{C_6} - \tau_0\mathrm{e}^{-\mathrm{i}\omega_0\tau_0}\left[\frac{bv^*}{1+v^*} + \frac{bu^*C_1}{\left(1+v^*\right)^2}\right],
$$

and because

$$
\begin{aligned}
-\mathrm{i}\omega_0\tau_0\left\langle q^*(s), q(\theta)\right\rangle &= \left\langle q^*(s), A\bar{q}(\theta)\right\rangle = \left\langle A^*q^*(s), \bar{q}(\theta)\right\rangle \\
&= \left\langle -\mathrm{i}\omega_0\tau_0 q^*(s), \bar{q}(\theta)\right\rangle = \mathrm{i}\omega_0\tau_0\left\langle q^*(s), q(\theta)\right\rangle,
\end{aligned}
$$

we have $\left\langle q^*(s), \bar{q}(\theta)\right\rangle = 0$. □

Let's calculate the coordinates of the central manifold C_0 when $\mu = 0$. Assuming that u_t is the solution of (4.1) when $\mu = 0$, define

$$
z(t) = \left\langle q^*(s), u_t\right\rangle,\ W(z,\bar{z},\theta) = u_t(\theta) - 2\,\mathrm{Re}\left\{z(t)q(\theta)\right\}. \tag{4.3}
$$

On the central manifold C_0

$$
W(t,\theta) = W\left(z(t),\bar{z}(t),\theta\right) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots,
$$

where z, $\bar{z}$ is the local coordinate of the central manifold C_0 on q^*, $\bar{q}^*$. If u_t is real, then W is also real. Only the real number solution is considered here, so when $\mu = 0$

$$
\dot{z}(t) = \left\langle q^*, \dot{u}_t\right\rangle = \left\langle q^*, A(\mu)u_t + R(\mu)u_t\right\rangle = \mathrm{i}\omega_0\tau_0 z + \bar{q}^*(0)f_0(z,\bar{z}), \tag{4.4}
$$

where

$$
f_0(z,\bar{z}) = f\left(0, W\left(z(t),\bar{z}(t),\theta\right)\right) + 2Re\left\{z(t)q(\theta)\right\}.
$$

Equation (4.4) can be written as

$$
\dot{z}(t) = \mathrm{i}\omega_0\tau_0 z(t) + g(z,\bar{z}),
$$

where

$$
g(z,\bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots, \tag{4.5}
$$

because

$$
g(z,\bar{z}) = \bar{q}^*(0)f_0(z,\bar{z}) = \tau_0\bar{M}\left(f_1 + \bar{C}_4 f_2 + \bar{C}_5 f_3 + \bar{C}_6 f_4\right), \tag{4.6}
$$

where

$$f_0 = \left(\tau^* + \mu\right)\begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{pmatrix} = \left(\tau^* + \mu\right)\begin{pmatrix} n_1 u_{2t}^2\left(-1\right) - n_2 u_{1t}\left(-1\right) u_{2t}\left(-1\right) \\ u_{1t}\left(0\right) u_{3t}\left(0\right) \\ 0 \\ 0 \end{pmatrix}.$$

Notice that $u\left(t,\theta\right) = W\left(t,\theta\right) + zq\left(\theta\right) + \overline{zq}\left(\theta\right)$, $q\left(\theta\right) = \left(1, C_1, C_2, C_3\right)^{\mathrm{T}} \mathrm{e}^{\mathrm{i}\omega_0\tau_0\theta}$, then

$$u_{1t}\left(0\right) = z + \overline{z} + W_{20}^{(1)}\left(0\right)\frac{z^2}{2} + W_{11}^{(1)}\left(0\right) z\overline{z} + W_{02}^{(1)}\left(0\right)\frac{\overline{z}^2}{2} + \cdots,$$

$$u_{3t}\left(0\right) = C_2 z + \overline{C_2}\overline{z} + W_{20}^{(3)}\left(0\right)\frac{z^2}{2} + W_{11}^{(3)}\left(0\right) z\overline{z} + W_{02}^{(3)}\left(0\right)\frac{\overline{z}^2}{2} + \cdots,$$

$$u_{1t}\left(-1\right) = \mathrm{e}^{-\mathrm{i}\omega_0\tau_0} z + \mathrm{e}^{\mathrm{i}\omega_0\tau_0}\overline{z} + W_{20}^{(1)}\left(-1\right)\frac{z^2}{2} + W_{11}^{(1)}\left(-1\right) z\overline{z} + W_{02}^{(1)}\left(-1\right)\frac{\overline{z}^2}{2} + \cdots,$$

$$u_{2t}\left(-1\right) = C_1\mathrm{e}^{-\mathrm{i}\omega_0\tau_0} z + \overline{C_1}\mathrm{e}^{\mathrm{i}\omega_0\tau_0}\overline{z} + W_{20}^{(2)}\left(-1\right)\frac{z^2}{2} + W_{11}^{(2)}\left(-1\right) z\overline{z} + W_{02}^{(2)}\left(-1\right)\frac{\overline{z}^2}{2} + \cdots.$$

Expand (4.5) and compare the coefficient with (4.4) to get

$$g_{20} = 2\overline{M}\tau_0\left(n_1 C_1^2 \mathrm{e}^{-2\mathrm{i}\omega_0\tau_0} - n_2 C_1 \mathrm{e}^{-2\mathrm{i}\omega_0\tau_0} + C_2\overline{C}_4\right),$$

$$g_{11} = \overline{M}\tau_0\left[2n_1 C_1\overline{C}_1 - n_2\left(C_1 + \overline{C}_1\right) + \left(C_2 + \overline{C}_2\right)\overline{C}_4\right],$$

$$g_{02} = 2\overline{M}\tau_0\left(n_1\overline{C}_1^2 \mathrm{e}^{2i\omega_0\tau_0} - n_2\overline{C}_1 \mathrm{e}^{2\mathrm{i}\omega_0\tau_0} + \overline{C}_2\overline{C}_4\right),$$

$$\begin{aligned} g_{21} = \overline{M}\tau_0\Big[& 2n_1\left(C_1 W_{11}^{(2)}\left(-1\right)\mathrm{e}^{-\mathrm{i}\omega_0\tau_0} + \overline{C}_1 W_{20}^{(2)}\left(-1\right)\mathrm{e}^{\mathrm{i}\omega_0\tau_0}\right) \\ & - n_2\left(2W_{11}^{(2)}\left(-1\right)\mathrm{e}^{-\mathrm{i}\omega_0\tau_0} + W_{20}^{(2)}\left(-1\right)\mathrm{e}^{\mathrm{i}\omega_0\tau_0} + \overline{C}_1 W_{20}^{(1)}\left(-1\right)\mathrm{e}^{-\mathrm{i}\omega_0\tau_0}\right) \\ & + \overline{C}_4\left(2W_{11}^{(3)}\left(0\right) + W_{20}^{(3)}\left(0\right) + \overline{C}_2 W_{20}^{(1)}\left(0\right) + 2C_2 W_{11}^{(1)}\left(0\right)\right)\Big]. \end{aligned}$$

To calculate the value of g_{21}, calculate W_{11} and W_{20} below, notice that

$$\dot{W} = \dot{u}_t - \dot{z} - \dot{\overline{z}}\overline{q}\left(\theta\right) = \begin{cases} AW - 2\operatorname{Re}\left\{\overline{q^*}\left(0\right) f_0\left(z,\overline{z}\right) q\left(\theta\right)\right\}, & \theta \in \left[-1,0\right), \\ AW - 2\operatorname{Re}\left\{\overline{q^*}\left(0\right) f_0\left(z,\overline{z}\right) q\left(\theta\right)\right\} + f_0\left(z,\overline{z}\right), & \theta = 0. \end{cases}$$

Then

$$\dot{W} = AW + H\left(z,\overline{z},\theta\right) \tag{4.7}$$

where

$$H\left(z,\overline{z},\theta\right) = H_{20}\left(\theta\right)\frac{z^2}{2} + H_{11}\left(\theta\right) z\overline{z} + H_{02}\left(\theta\right)\frac{\overline{z}^2}{2} + \cdots. \tag{4.8}$$

According to (4.7)

$$H\left(z,\overline{z},\theta\right) = -\overline{q}^*\left(0\right) f_0 q\left(\theta\right) - q^*\overline{f_0}\overline{q}\left(\theta\right) = -g\left(z,\overline{z}\right) q\left(\theta\right) - \overline{g}\left(z,\overline{z}\right)\overline{q}\left(\theta\right),\ \theta \in \left[0,1\right).$$

So

$$H_{20}\left(\theta\right) = -g_{20} q\left(\theta\right) - \overline{g}_{02}\overline{q}\left(\theta\right),\ H_{11}\left(\theta\right) = -g_{11} q\left(\theta\right) - \overline{g}_{11}\overline{q}\left(\theta\right).$$

On the central manifold C_0 near the origin, there is

$$\dot{W} = W_z \dot{z} + W_{\overline{z}} \overline{z}, \tag{4.9}$$

substitute $\dot{z}(t) = \mathrm{i}\omega_0 \tau_0 z(t) + g(z, \overline{z})$ into (4.9) to get

$$\begin{aligned} \dot{W} = {} & \mathrm{i}\omega\tau_0 W_{20} z^2 + W_{20}\left(g_{20}\frac{z^2}{2} + g_{11} z\overline{z} + g_{02}\frac{\overline{z}^2}{2} + g_{21}\frac{z^2\overline{z}}{2} + \cdots \right) \\ & - \mathrm{i}\omega\tau_0 W_{11} z\overline{z} + W_{11}\left(\overline{g}_{20}\frac{\overline{z}^2}{2} + g_{11} z\overline{z} + g_{02}\frac{\overline{z}^2}{2} + g_{21}\frac{\overline{z}^2 z}{2} + \cdots \right) \\ & + \mathrm{i}\omega\tau_0 W_{11} z^2 + W_{11}\left(g_{20}\frac{z^2}{2} + g_{11} z\overline{z} + g_{02}\frac{\overline{z}^2}{2} + g_{21}\frac{z^2\overline{z}}{2} + \cdots \right) \\ & - \mathrm{i}\omega\tau_0 W_{02} z^2 + W_{20}\left(\overline{g}_{02}\frac{\overline{z}^2}{2} + g_{11} z\overline{z} + g_{02}\frac{\overline{z}^2}{2} + g_{21}\frac{\overline{z}^2 z}{2} + \cdots \right) \end{aligned}$$

By comparing the coefficients of $\frac{z^2}{2}$ and $z\overline{z}$, we can get

$$(A - 2\mathrm{i}\omega_0\tau_0) W_{20}(\theta) = -H_{20}(\theta), \quad A W_{11}(\theta) = -H_{11}(\theta). \tag{4.10}$$

From the definition of A and (4.10)

$$\begin{aligned} W_{20}(\theta) &= +\frac{\mathrm{i}g_{20}}{\omega_0\tau_0} q(\theta) + \frac{\mathrm{i}\overline{g}_{02}}{3\omega_0\tau_0} \overline{q}(\theta) + E_1 e^{2\mathrm{i}\omega_0\tau_0\theta}, \\ W_{11}(\theta) &= -\frac{\mathrm{i}g_{11}}{\omega_0\tau_0} q(\theta) + \frac{\mathrm{i}\overline{g}_{11}}{\omega_0\tau_0} \overline{q}(\theta) + E_2, \end{aligned} \tag{4.11}$$

where

$$E_1 = \begin{pmatrix} E_1^{(1)} \\ E_1^{(2)} \\ E_1^{(3)} \\ E_1^{(4)} \end{pmatrix}, \quad E_2 \begin{pmatrix} E_2^{(1)} \\ E_2^{(2)} \\ E_2^{(3)} \\ E_2^{(4)} \end{pmatrix}.$$

Let $\theta = 0$ in $H(z, \overline{z}, \theta)$, and you can calculate E_1, E_2. In fact

$$\begin{aligned} H(z, \overline{z}, \theta) &= -2\,\mathrm{Re}\left\{ \overline{q}^*(0) f_0 q(\theta) \right\} + f_0, \\ H_{20}(0) &= -g_{20} q(0) - \overline{g}_{02} \overline{q}(0) + f_{zz}, \\ H_{11}(0) &= -g_{11} q(0) - \overline{g}_{11} \overline{q}(0) + f_{z\overline{z}}, \end{aligned}$$

where

$$f_0 = f_{zz}\frac{z^2}{2} + f_{z\overline{z}} z\overline{z} + f_{\overline{z}^2}(\theta)\frac{\overline{z}^2}{2} + \cdots.$$

Combined with the definition of A, we can get

$$\begin{aligned} A W_{20}(0) &= \int_{-1}^{0} \mathrm{d}\eta(\xi) W_{20}(\xi) = 2\mathrm{i}\omega_0\tau_0 W_{20}(0) + g_{20} q(0) + \overline{g}_{02} \overline{q}(0) - f_{zz}, \\ A W_{11}(0) &= \int_{-1}^{0} \mathrm{d}\eta(\xi) W_{11}(\xi) = g_{11} q(0) + \overline{g}_{11} \overline{q}(0) - f_{z\overline{z}}, \end{aligned} \tag{4.12}$$

where

$$f_{zz} = 2\tau_0 \begin{pmatrix} \left(n_1 C_1^2 - n_2 C_1\right) e^{-2i\omega_0\tau_0} \\ C_2 \\ 0 \\ 0 \end{pmatrix}, \quad f_{z\bar{z}} = \tau_0 \begin{pmatrix} 2n_1 C_1 \bar{C}_1 - n_2 \left(C_1 + \bar{C}_1\right) \\ C_2 + \bar{C}_2 \\ 0 \\ 0 \end{pmatrix}.$$

Substituting (4.11) into (4.12) shows that

$$\left(2i\omega_0\tau_0 I - A_1 - A_2 e^{-2i\omega_0\tau_0}\right) E_1 = f_{zz},$$
$$\left(A_1 + A_2\right) E_2 = -f_{z\bar{z}}.$$

Thus,

$$E_1 = \left(2i\omega_0\tau_0 I - A_1 - A_2 e^{-2i\omega_0\tau_0}\right)^{-1} f_{zz},$$
$$E_2 = -\left(A_1 + A_2\right)^{-1} f_{z\bar{z}}.$$

Then g_{21} can be determined, and the following values can be calculated:

$$C_1(0) = \frac{i}{2\omega_0\tau_0}\left(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2\right) + \frac{1}{2}g_{21},$$
$$\mu_2 = -\frac{\operatorname{Re} C_1(0)}{\operatorname{Re} \lambda'(\tau_0)},$$
$$\beta_2 = 2\operatorname{Re} C_1(0),$$
$$T_2 = -\frac{1}{\omega_0\tau_0}\left(\operatorname{Im} C_1(0) + \mu_2 \operatorname{Im} \lambda'(\tau_0)\right).$$

Theorem 4.1. For the model (1.4), there are

1) $\mu_2 > 0$ determines the direction of Hopf bifurcation, β_2 determines the stability of bifurcation periodic solutions. When $\mu_2 > 0$ (that is $\beta_2 < 0$), the Hopf bifurcation is supercritical and the bifurcated periodic solution is stable. When $\mu_2 < 0$ (that is $\beta_2 > 0$), the Hopf bifurcation is subcritical and the bifurcated periodic solution is unstable.

2) T_2 determines the period of the bifurcation periodic solution. When $T_2 > 0$, the period length is increasing. When $T_2 < 0$, the period length is decreasing.

5. Numerical Simulation

In this part, we select three groups of parameters to satisfy the corresponding conditions of the theorem, and numerical simulation of model (1.4).

5.1. Choose Parameters

$$a = 2.5,\ b = 2.4,\ c = 0.5,\ m = 1.6,\ n = 0.5,\ d = 10.005,$$

then $am - dn = -1.0025 < 0$. From lemma (3.1), the trivial equilibrium point E_0 of model (1.4) is globally asymptotically stable.

5.2. Choose Parameters

$$a = 3,\ b = 0.2,\ c = 0.5,\ m = 1.3,\ n = 0.46,\ d = 7.4,$$

then $am - dn = 0.496 > 0$. From lemma (3.1), the trivial equilibrium point E_0 of model (1.4) is saddle point, the system has a unique positive equilibrium $E^* = (0.5345, 2.6840, 1.5106, 0.2041)$.

When $\tau = 0$, $ac - bu^*(c + d + n) = 0.6062 > 0$, so E^* is asymptotically stable.

When $\tau \neq 0$, according to the formulas (3.3) - (3.6), we have $\tau_0 = 18.1599$.

By Theorem 3.1, with the increasing of τ, the system will produce a Hopf bifurcation, and the following conclusions are true.

1) When $\tau < \tau_0$, the equilibrium point E^* of MS model is gradually stable, as shown in Figure 1.

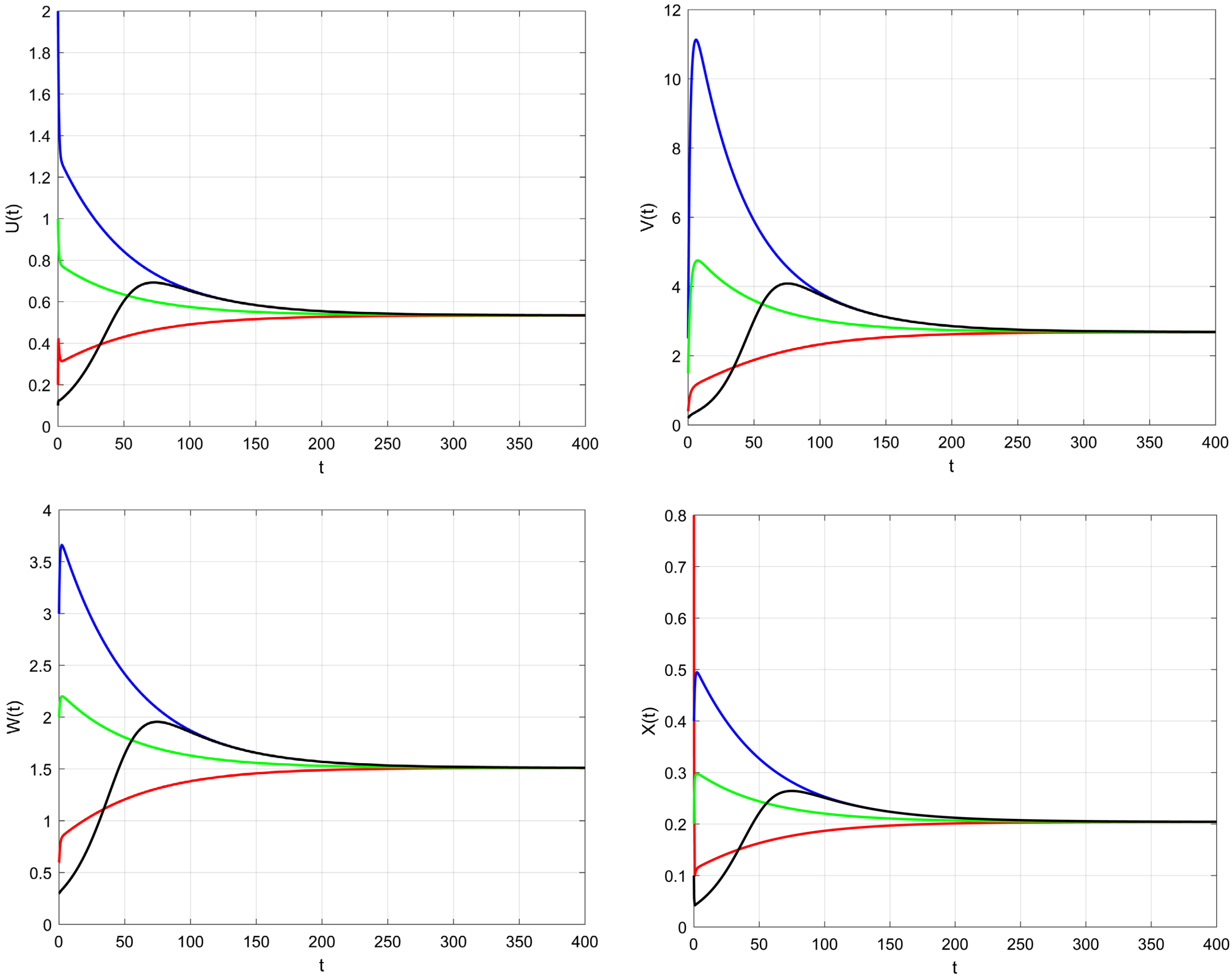

Figure 1. When $\tau = 0.05$, trajectory diagram of $u(x)$, $v(t)$, $w(t)$, $x(t)$.

2) When τ through τ_0, the system experiences Hopf bifurcation at the equilibrium point E^*.

3) When $\tau > \tau_0$, the periodic solution appears, as shown in Figure 2.

The following calculate the parameters that determine the properties of the Hopf bifurcation.

$$\lambda'(\tau_0) = -0.0015 - 0.0006\mathrm{i},\ C_1(0) = 0.7385 - 2.0133\mathrm{i},$$
$$\mu_2 = 485.0769 > 0,\ \beta_2 = 1.4770 > 0,\ T_2 = 1.7312 > 0.$$

According to the theorem 4.1, the Hopf bifurcation is supercritical, the bifurcation periodic solution is unstable, and the period of the bifurcation periodic solution increases gradually.

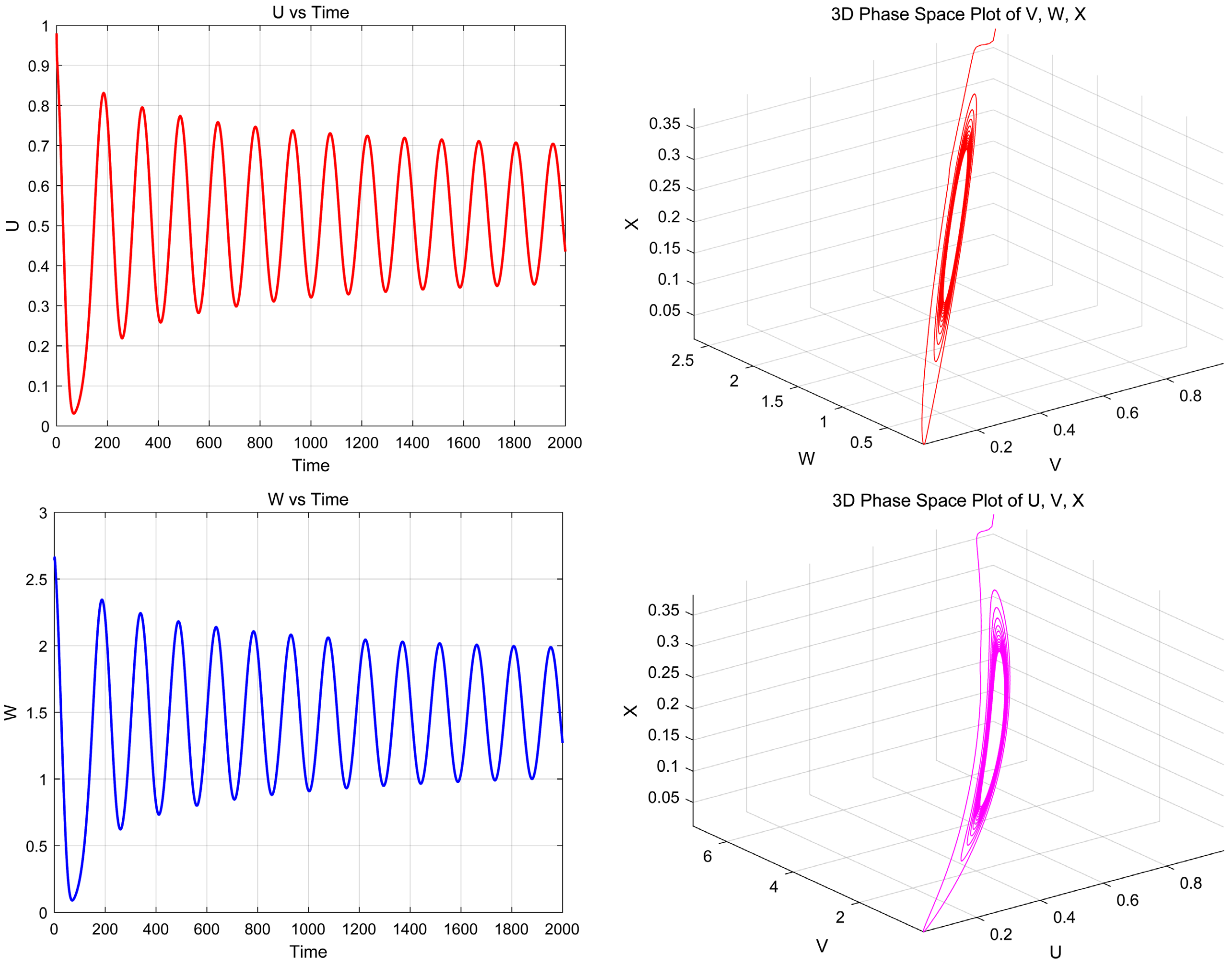

Figure 2. When $\tau = 19$, trajectory diagram of $u(x)$ and $v(t)$, $w(t)$, $x(t)$.

5.3. Choose Parameters

$$a = 2.5,\ b = 2.4,\ c = 0.5,\ m = 1.44,\ n = 0.5,\ d = 6.005,$$

this data is obtained by reducing the value of λ_E from the data in reference [6]. Then $am - dn = 0.5975 > 0$. From lemma (3.1), the trivial equilibrium point E_0 of model (1.4) is saddle point, the system has a unique positive equilibrium $E^* = (0.0405, 0.904, 0.1166, 0.0194)$.

When $\tau = 0$, $ac - bu^*(c + d + n) = 0.5693 > 0$, so E^* is asymptotically stable.

When $\tau \neq 0$, according to the formulas (3.3) - (3.6), we have $\tau_0 = 6.7272$.

By Theorem 3.1, with the increasing of τ, the system will produce a Hopf bifurcation, and the following conclusions are true.

1) When $\tau < \tau_0$, the equilibrium point E^* of MS model is gradually stable, as shown in **Figure 3**.

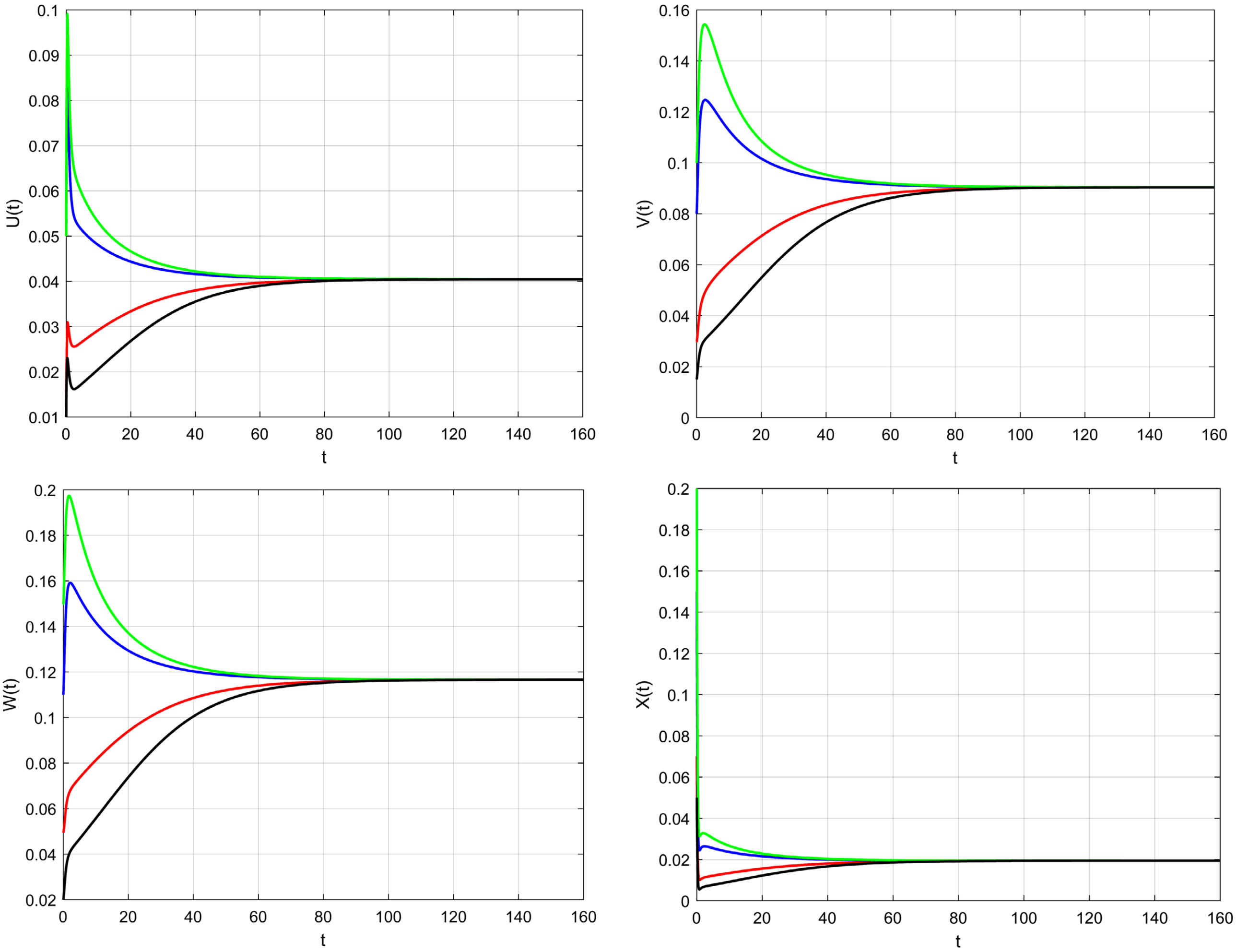

Figure 3. When $\tau = 0.02$, trajectory diagram of $u(x)$, $v(t)$, $w(t)$, $x(t)$.

2) When τ through τ_0, the system experiences Hopf bifurcation at the equilibrium point E^*.

3) When $\tau > \tau_0$, the periodic solution appears, as shown in **Figure 4**.

The following calculate the parameters that determine the properties of the Hopf bifurcation.

$$\lambda'(\tau_0) = 0.0163 - 0.0127\mathrm{i},\ C_1(0) = 13056.1510 + 33226.5965\mathrm{i},$$
$$\mu_2 = -801753.4938 < 0,\ \beta_2 = 26112.3021 > 0,\ T_2 = -23006.6211 < 0.$$

According to the theorem 4.1, the Hopf bifurcation is subcritical, the bifurcation periodic solution is unstable, and the period of the bifurcation periodic solution becomes smaller gradually.

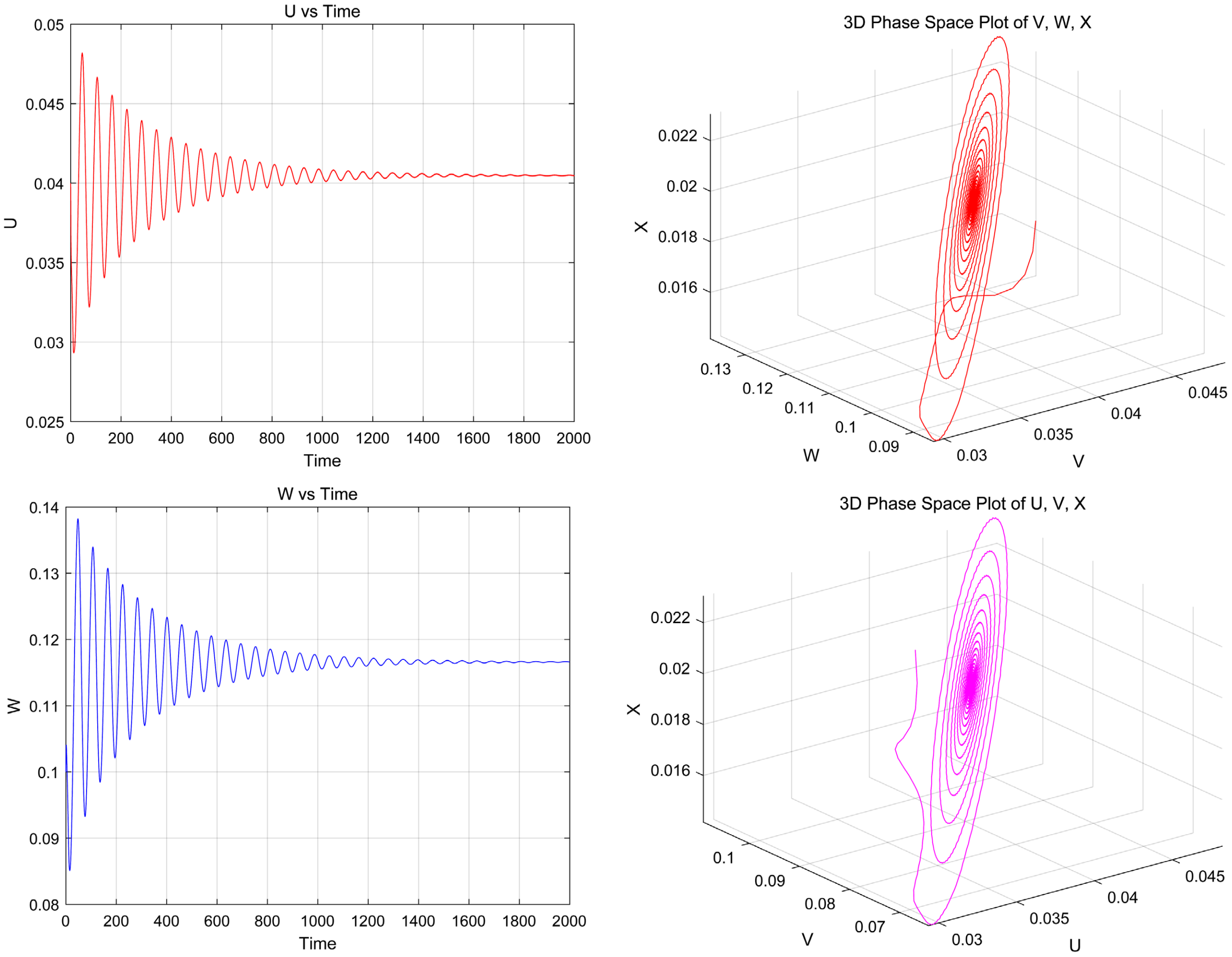

Figure 4. When $\tau = 10$, trajectory diagram of $u(x)$ and $v(t)$, $w(t)$, $x(t)$.

6. Conclusions

In this paper, we discuss the MS model with time delay and saturated functional response function. We first analyze the conditions for the existence and stability of equilibrium point. We study the existence and properties of hopf bifurcation with time delay parameters as bifurcation parameters. The added delay parameter will not affect the stability of trivial equilibrium point, but will affect the stability of nontrivial equilibrium point. When certain conditions are met, there will be a critical value of τ_0, which will make the system produce Hopf bifurcation when $\tau = \tau_0$, and the system will exhibit periodic oscillation when $\tau > \tau_0$.

The nontrivial equilibrium solution can be interpreted as an autoimmune state. Mathematically, this equilibrium seems to be a "static" state of the system, but in fact, the individuals that make up each population are constantly changing, so the population size remains unchanged. When pathological plaques appear in the body, the immune system will remove the diseased cells. When the immune system can inhibit the growth of the diseased cells, the immune system will be in a stable state, and the solution curve of the model will show that it oscillates first and then tends to be stable. When the immune system can not inhibit the growth of diseased cells, the immune system is unstable, and the model solution curve will fluctuate irregularly or periodically [13] [14]. Biologically, this means that new effects T cells will be constantly produced, attacking the target host cells and resulting in damage to the body. Therefore, appropriately reducing the concentration or function of effector T cells may alleviate the symptoms of multiple sclerosis. With the deepening of research, people will find better solutions.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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