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Research article

The role of time delays in P53 gene regulatory network stimulated by growth factor

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Abstract: In this paper, a delayed mathematical model for the P53-Mdm2 network is developed. The P53-Mdm2 network we study is triggered by growth factor instead of DNA damage and the amount of DNA damage is regarded as zero. We study the influences of time delays, growth factor and other important chemical reaction rates on the dynamic behaviors in the system. It is shown that the time delay is a critical factor and its length determines the period, amplitude and stability of the P53 oscillation. Furthermore, as for some important chemical reaction rates, we also obtain some interesting results through numerical simulation. Especially, S (growth factor), k_3 (rate constant for $Mdm2_p$ dephosphorylation), k_{10} (basal expression of PTEN) and k_{14} (Rate constant for PTEN-induced Akt dephosphorylation) could undermine the dynamic behavior of the system in different degree. These findings are expected to understand the mechanisms of action of several carcinogenic and tumor suppressor factors in humans under normal conditions.

Keywords: growth factor; P53-Mdm2 network; time delays; Hopf bifurcation; oscillation

1. Introduction

Numerous studies have shown that P53 plays a key role in determining cell survival and death. More than 50 percent of cancer patients are detected with mutations in the P53 gene [1]. High levels of the mutant p53 protein were found in mouse tumors as early as 1983 [2]. In subsequent studies, abnormal expression of P53 protein was also found in a variety of human tumors [3, 4, 5]. In normal human cells, P53 is generally kept at a low level due to the downregulation of Mdm2 (murine double minute2) [6], which also helps cells avoid premature aging and apoptosis [7]. In general, with cells stimulated by hypoxia, DNA damage and impair of telomere function, P53 is rapidly produced and activated [8]. As a transcription factor, P53 prevents (or at least alleviates) damage caused by mutations, thereby regulating the expression of genes involved in various cellular functions, including cell cycle arrest,

DNA damage repair, and apoptosis [9]. Previous investigation has proved that the specific function of P53 closely related to its level. When a weak stimulus is felt, P53 rapidly rises to a moderate level, thereby making cell cycle arrest and avoiding the inheritance of abnormal DNA replication to the next generation. Until the damage was eliminated, the expression level of P53 returned to the normal level [10, 11, 12]. Moreover, a large damage can cause the level of P53 rises to a higher state in order to induce apoptosis [13, 14]. As we all know, P53 promotes transcription of its target gene Mdm2 (a P53-specific E3 ubiquitin ligase), which contributes to the degradation of P53 in return [15, 16]. In fact, many cancer treatment programs are related to the network that is based on the P53-Mdm2 negative feedback loop [17, 18]. Clinically, when the P53 protein is mutated, for example, mutations in the P53 protein make cells resistant to chemotherapy drugs [19, 20]. However, when the P53 mutant protein is knocked out or interfered with, chemotherapy-induced apoptosis can be restored [21, 22].

In recent years, many scholars dedicated to investigate the P53-Mdm2 feedback network. In 2000, the researchers theoretically modeled the P53 damped oscillations and also found that the negative feedback of P53-Mdm2 with time delay can led to the occurrence of P53 oscillation [23]. In 2005, Ma and his collaborators explored the mechanism of P53 pulse generation in theory at the IBM Watson Research Center in the United States [24]. In 2007, the Tysons team constructed a theoretical model of the P53 network response to DNA damage and explored the dynamics of P53 pulse-determining cell fate whose view is that the number of P53 pulses determining cell fate [25]. The more perfect result is that for mild lesions, a small amount of P53 pulses cause cell cycle arrest, and cells can return to normal after repair is completed. Whereas for severe damage, persistent P53 pulses kill the irreparable cell by activating downstream apoptosis program [25]. In 2009, Zhang et al. constructed a more comprehensive P53 network model and concluded that the fate of cells is closely related to the P53 pulse [26]. In 2011, the study of Zhang et al. shows that a sequential predominance of distinct feedback loops may elicit multiple-phase dynamical behaviors [27]. Only the research of Tingzhe Sun et al. shows that the kinetics of P53 under non-stressed conditions is triggered by an excitatory mechanism, and cells can only respond fully in the face of severe damage[28]. Although a large number of studies have been done, most of them were based on stress (DNAdamage, radiation, hypoxia, etc.). However, researches on non-stress situations are rarely involved. Moreover, as for these systems, the transcription, translation and integration into the polymer are usually seen as instant. In fact, the impact of the time delay of transcription and translation on the system in real biological processes is not negligible [29], especially multiple simultaneous time delays occur at the same time. Admittedly, there are several mathematical models of p53 that include time delays [7, 28, 30, 31], which just illustrated that the objective existence of time delay is recognized. These studies have perfectly studied the dynamic mechanism of the p53 pulse from different aspects. But without exception, they did not specially focus on the role of time delay on the system. For example, Purvis et al. proposed a delayed computational model and identified a sequence of precisely timed drug additions that alter p53 pulses to instead produce a sustained p53 response that suggested that the drug is efficient and can directly influencing cellular fate decisions[7]. Even though there are three delays including Nutlin-3 activity delay, p53-induced expression of Mdm2 and Wip1 (Wild type p53-induced phosphatase 1) delays, the effect of time delay on the dynamic process is not received attention. Zhang et al. established a complex model without time delay to study the signal threshold to elicit cell death and the time delay between signal and response [30]. It should be noticed that the time delay there refers to the time required from the onset of external signal to the apoptosis triggered by the system. A mathematical model with two time delays that respectively represent the time consumed on the transcription of Mdm2 and wip1 activated by p53 is proposed by Sun et al. The model described the negative feedback loop Wip1 - ATM (mutated in the disease ataxia telangiectasia) \rightarrow P53 \rightarrow Wip1 except to the core negative feedback loop formed by P53 and Mdm2 to study the excitability of p53 pulses and the effect of Wip on the p53 pulses [28]. Chong et al. developed a delayed mathematical model that incorporated the molecular interactions in the core regulation of p53 and the apoptosis initiation module involving Puma, Bcl2 and Bax and demonstrated how molecular interactions and stress signaling of the p53 network dictate cell fate decisions [31]. Although there are 10 time delays, their dynamic effects on the p53 pulse are also lacked. Here, we consider the following facts. P53 is regulated by ARF (ADP-ribosylation factor), which exerts an anti-cancer role by combining with Mdm2 (or $Mdm2_p$), and is considered to be the main regulator of P53, so it is well known to promote the activation and stability of P53 [32]. Previous studies have shown that Growth factors in serum not only induce the transcriptional activation of Mdm2 [33], but the activation of Akt (protein kinase B) which phosphorylates Mdm2 promoting $Mdm2_p$ nuclear accumulation [34]. P53 trans-activates PTEN (gene of phosphate and tension homology deleted on chromsome ten), a tumor suppressor that dampens Akt activation by dephosphorylating PIP3 [34, 35]. Especially, this paper places emphasis on the effect of positive feedback loop P53 \rightarrow PTEN –I Akt \rightarrow Mdm2 –I P53 and two time delays that respectively represent the p53-induced expression of Mdm2 and PTEN delays on the dynamic of the system. On the above interaction facts among biological molecules, we focus on the dynamics of P53 under non-stressed conditions based on the model which was given by Xinyu Tian, Bo Huang, Xiao-Peng Zhang et al. in 2017 [36].

The novelty of this paper is that most studies have considered the dynamic behavior of P53 under stress, while our study considered the non-stress state and studied the delay in detail. First of all, the effects of time delay on the P53 oscillation is analyzed in two different cases including there are one time delay and two time delays co-exist by using Hopf bifurcation theory. Previous studies have well demonstrated that negative feedback loop with time delay can produce oscillations and the network which includes coupled positive and negative feedback loops can also generate oscillations when negative feedback plays the main role[37, 38]. It is quite important that we find the relative length of the double time delays is likely to control the dynamic properties of the system in the coupled positive and negative feedback loops. In addition, we consider the influences of several important chemical reaction rates that relating to P53 directly or indirectly.

This paper is organized as follows. In Section 2, we introduced the materials and method. In Section 3, we give numerical simulation results of the influences of time delays and key parameters on the P53 oscillation behaviors. Discussion is made in Section 4. Conclusion is drawn in Section 5. The theoretical derivations about the properties of Hopf bifurcations are presented in Supplementary.

2. Materials and method

As can be seen from Figure 1. Growth factors promote Mdm2 accumulation and Akt activation, while active Akt can promote the transfer of Mdm2 into the nucleus and phosphorylate Mdm2. The phosphorylated Mdm2 can be denoted by $Mdm2_p$, which has a more pronounced ability to degrade P53[34]. $Mdm2_p$ can be further phosphorylate to $Mdm2_{pp}$. The latter ability of $Mdm2_{pp}$ to degrade P53 is very weak[39]. The increase of the total amount of Mdm2 in the nucleus indirectly leads to a decrease in the level of P53. In verse, P53 promotes the transcription and translation of Mdm2. Thus,

a negative feedback loop of P53-Mdm2 is formed. On the other hand, PTEN can inhibit the activity of Akt and convert it to inactive Akt_0 to reduce the conversion of Mdm2 to $Mdm2_p$ and thus indirectly promote the accumulation of P53. P53 can also promotes PTEN transcription. So the interations construct a positive feedback loop P53-PTEN-ATK-Mdm2. ARF binds to two forms of Mdm2 and inhibits the degradation of P53. Among these regulation process, it should be noticed that from DNA to protein, all transcription, transport and translation take time [40, 41, 42], which is ignored by the previous theoretical study [36]. We considered that both Mdm2 and PTEN could be upregulated by a means of a transcription activation from P53[15, 43, 44]. Based on the related literatures mentioned above, we developed a delayed ODEs system to model the P53-PTEN-Akt-Mdm2 network, which is shown as (2.1).

Next, we mainly imply the stability and bifurcation theory to analyze the dynamic behavior of system (2.1). First, by selecting time delays as the bifurcation parameters and analyzing the distribution of the roots of the corresponding characteristic equation in detail, we mainly investigate the stability of positive equilibrium and the existence of Hopf bifurcation. Further, their direction and properties of the oscillatory dynamic are also researched by using normative theory and central manifold method. Moreover, the dynamic influences of four important parameters, namely S (concentration of serum), k_3 (Rate constant for Mdm_{2p} dephosphorylation), k_{10} (Basal expression rate of PTEN) and k_{14} (Rate constant for PTEN-induced Akt dephosphorylation) on the P53-PTEN-Akt-Mdm2 network are discussed. In addition, some numerical simulations are executed by using the software Mathematica 11 to verify the theoretical predictions. Finally, the discussion and conclusion are drawn.



Figure 1. Schematic diagram of the P53-PTEN-Akt-Mdm2 network. The solid arrows indicate degradation and transformation, and the dashed arrows indicate transcription and promotion. The line with bar end indicates inhibition. See tex for the detail relationships.

 $k_{-a}(t) \mathbf{v}(t)$

Table 1. State variable description of the system (2.1).					
Variable Symbol	Description	Reference			
x	The concentration of MDM2, which is evenly distributed in the nucleus and cytosol	[36]			
у	The concentration of phosphorylated MDM2, which is mainly distributed in the nucleus	[36]			
z	The concentration of MDM2-ARF complex	[36]			
и	The concentration of MDM2p-ARF complex	[36]			
v	The concentration of P53 in the nucleus	[36]			
р	The concentration of PTEN, which is a P53 target and inhibits Akt activation by dephosphorylating PIP3	[36]			
q	The concentration of active Akt	[36]			

Table 1 State variable description of the system (2, 1)

$$\begin{aligned} \frac{dx}{dt} &= \frac{k_1[S]}{K_1 + [S]} + \frac{k_2[v(t - \tau_1)]^{n_1}}{K_2^{n_1} + [v(t - \tau_1)]^{n_1}} + D_1 z(t) + \frac{k_3 y(t)}{K_3 + y(t)} - k_4 a x(t) - \frac{k_5 q(t) x(t)}{K_4 + x(t)} - d_1 x(t), \\ \frac{dy}{dt} &= D_2 u(t) + \frac{k_5 q(t) x(t)}{K_4 + x} - k_6 a y(t) - \frac{k_3 y(t)}{K_3 + y(t)} - d_2 y(t), \\ \frac{dz}{dt} &= k_4 a x(t) - D_1 z(t) - d_3 z(t), \\ \frac{du}{dt} &= k_6 a y(t) - D_2 u(t) - d_4 u(t), \\ \frac{dv}{dt} &= k_7 - \frac{k_8 x(t) v(t)}{K_5 + v(t)} - \frac{k_9 y(t) v(t)}{K_6 + v(t)} - d_5 v(t), \\ \frac{dp}{dt} &= k_{10} + \frac{k_{11} [v(t - \tau_2)]^{n_2}}{K_7^{n_2} + [v(t - \tau_2)]^{n_2}} - d_6 p(t), \\ \frac{dq}{dt} &= \frac{k_{12} [S]}{K_8 + [S]} \frac{A - q(t)}{K_9 + A - q(t)} - \frac{k_{13} q(t)}{K_{10} + q(t)} - \frac{k_{14} p(t) q(t)}{K_{11} + q(t)}. \end{aligned}$$

where τ_1 and τ_2 respectively represent transcriptional delays of Mdm2 and PTEN triggered by P53, and the meaning of all the variables are given in Table 1 and related parameters are given in Table 2.

3. Results

In this section, we will focus on the effects of two time delays including τ_1 and τ_2 and four important parameters related to P53 including S, k_3 , k_{10} , k_{14} on the system oscillations. All the numerical simulations are performed via Mathematical 11.

3.1. Effects of time delay τ_1 on the system

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For the legibility of the text, we only give short explanation for the theoretical results and the expatiatory and tedious theoretical derivations and results are put in the Supplementary Section. Then numerical simulations of time delay τ_1 on the system (2.1) are given when $\tau_2 = 0$.

3.1.1. Theoretical analysis about Hopf bifurcation and its properties

There is a positive equilibrium solution $E^* = (x^*, y^*, z^*, u^*, v^*, p^*, q^*)$ by setting the right-hand side of the equation equal to zero in (2.1). Then we can get the linearized equation near the equilibrium as

Table 2. List of the meanings and values of parameters in the system (2.1).

Parameter	Description	value	Reference
S	serum concentration; it is proportional to the concentration of GFs; GFs induce mitogenic signals	0.035	[36]
а	Free ARF protein($P14^{ARF}$)	0.03	[36]
k_1	Rate constant of MDM2 expression induced by serum(is proportional to the concentration of GFs)	0.15µM/h	[24, 45]
k_2	Rate cconstant of P53-mediated expression of Mdm2	$0.9\mu M/h$	[24]
k_3	Rate constant for $Mdm2_p$ dephosphorylation	$12\mu M/h$	[36]
k_4	Rate constant for Mdm2/ARF ossociation	43(µMh)	[36]
k_5	Rate constant Mdm2 phosphorylation mediated by Akt	56/h	[36]
k_6	Rate constant for $Mdm2_p/ARF$ ossociation	10/(µMh)	[36]
k_7	Basal rate constant of P53 expression	8μ/h	[25, 44]
k_8	Rate constant for Mdm2p-mediated P53 degradation	5/h	[36]
k_9	Rate constant for Mdm2p-mediated P53 degradation	18/h	[36]
k_{10}	Basal expression rate of PTEN	$0.05 \mu M/h$	[36]
k_{11}	Rate constant of P53-dependent synthesis of PTEN	$0.7 \mu M/h$	[36]
k_{12}	Rate constant for Akt phosphorylation induced by growth factors	12.9µM/h	[36]
k_{13}	Rate constant for Akt dephosphorylation	$9.4 \mu M/h$	[46, 47]
k_{14}	Rate constant for PTEN Cinduced Akt dephosphorylation ;refering to the dephosphorylation of PIP3 by PTEN	30/h	[36]
K_1	Michaelis constant for Mdm2 expression triggered by growth factors	0.0045	[36]
K_2	Hill constant for P53-induced expression of Mdm2	$0.5 \mu M$	[36]
K_3	Michaelis constant for $Mdm2_p$ dephosphorylation	$0.081 \mu M$	[36]
K_4	Michaelis constant for Akt-mediated phosphorylation of Mdm2	$0.5 \mu M$	[36]
K_5	Michaelis constant for Mdm2-mediated P53 degradation	$0.5 \mu M$	[36]
K_6	Michaelis constant for $Mdm2_p$ -mediated P53 degradation	$0.1 \mu M$	[36]
K_7	Hill constant for P53-induced expression of PTEN greater than that of Mdm2	$1 \mu M$	[36]
K_8	Michaelis constant for Akt activation triggered by growth factor	0.0147	[36]
K_9	Threshold of the total enzyme amount for Akt activation	0.35µM	[36]
K_{10}	Michaelis constant for Akt dephosphorylation	$0.2 \mu M$	[36]
K_{11}	Michaelis constant for PTEN-induced Akt dephosphorylation	$0.6 \mu M$	[36]
D_1	Rate constant for Mdm2-ARF disassociation	6/h	[36]
D_2	Rate constant for $Mdm2_p$ -ARF disassociation	24/h	[36]
d_1	Half-life of Mdm2 is about 90 min	0.5/h	[36]
d_2	Degradation rate of $Mdm2_p$	0.1/h	[36]
d_3	Degradation rate of Mdm2-ARF complex	0.6/h	[36]
d_4	Degradation rate of $Mdm2_p$ -ARF complex	0.6/h	[36]
d_5	Half-life of P53 is about 5-20 min	3.6/h	[36]
d_6	Degradation rate of PTEN	0.5/h	[36]
А	total amount of Akt, which is much more than active Akt and is considered a constant	2.5	[36]
n_1	Hill coefficient of P53-dependent expression of Mdm2	4	[36]
n_2	Hill coefficient of P53-dependent synthesis of PTEN	3	[36]
$ au_1$	Time delay of P53 transcription for Mdm2	30–75min	estimate
$ au_2$	Time delay of P53 transcription for PTEN	10-15min	estimate

follows

$$\begin{cases} \frac{dx}{dt} = c_1 x(t) + c_2 y(t) + c_3 z(t) + c_4 e^{-\lambda \tau_1} v(t) + c_5 q(t), \\ \frac{dy}{dt} = c_6 x(t) + c_7 y(t) + c_8 u(t) + c_9 q(t), \\ \frac{dz}{dt} = c_{10} x(t) - c_{11} z(t), \\ \frac{du}{dt} = c_{12} y(t) + c_{13} u(t), \\ \frac{dv}{dt} = c_{12} y(t) + c_{13} u(t), \\ \frac{dv}{dt} = c_{14} x(t) + c_{15} y(t) + c_{16} v(t), \\ \frac{dp}{dt} = c_{17} v(t) + c_{18} p(t), \\ \frac{dq}{dt} = c_{19} p(t) + c_{20} q(t), \end{cases}$$
(3.1)

where $c_i(i = 1, ..., 20)$ are decided by the parameters in system (2.1) and the positive equilibrium solution $E^* = (x^*, y^*, z^*, u^*, v^*, p^*, q^*)$ and the actual formulas are given in the Supplementary Section.

Furthermore, the characteristic equation of the system (3.1) is given as

$$m_{1} + m_{3}\lambda + m_{5}\lambda^{2} + m_{7}\lambda^{3} + m_{9}\lambda^{4} + m_{11}\lambda^{5} + m_{13}\lambda^{6} - \lambda^{7} + e^{-\lambda\tau_{1}}\left(m_{2} + m_{4}\lambda + m_{6}\lambda^{2} + m_{8}\lambda^{3} + m_{10}\lambda^{4} + m_{12}\lambda^{5} + m_{14}\lambda^{6}\right) = 0.$$
(3.2)

where $m_i(i = 1, ..., 14)$ are depended on the parameters $c_i(i = 1, ..., 20)$ and the actual formulas can be found in the Supplementary Section.

Suppose $\pm i\omega(\omega > 0)$ is a pair of pure virtual roots of the characteristic equation (3.2), then ω satisfies the following condition

$$m_{1} + im_{3}w - m_{5}w^{2} - im_{7}w^{3} + m_{9}w^{4} + im_{11}w^{5} - m_{13}w^{6} + iw^{7} + (m_{2} + im_{4}w) - m_{6}w^{2} - im_{8}w^{3} + m_{10}w^{4} + im_{12}w^{5} - m_{14}w^{6})(\cos w\tau_{1} - i\sin w\tau_{1}) = 0.$$
(3.3)

Through a large amount of calculation which is displayed in the Supplementary Section, it is found that there exists unique positive root w_0 of equation (3.3). Moreover,

$$\tau_1^{(j)} = \frac{1}{w_0} \arccos \frac{E}{F} + \frac{2\pi j}{w_0}, j = 0, 1, 2, 3, \cdots$$
 (3.4)

Define $\tau_1^0 = \min \left\{ \tau_1^{(j)} > 0 \right\}_{j=0}^{+\infty}$. Thus, when $\tau = \tau_1^0$ equation (3.2) has a pair of pure imaginary roots $\pm iw_0$.

Furthermore, it is verified that the condition

$$\operatorname{sgn}\left\{\frac{d\operatorname{Re}(\lambda(\tau_1))}{d\tau_1}\Big|_{\tau_1=\tau_1^0}\right\} = \operatorname{sgn}\left\{\operatorname{Re}\left[\frac{d\lambda(\tau_1)}{d\tau_1}\right]^{-1}\Big|_{\tau_1=\tau_1^0}\right\} > 0$$
(3.5)

is holds.

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It indicates that the root of characteristic equation(3.2) changes though negative to positive that corresponds to the positive equilibrium of system (2.1) is changed from stability to instability as the time delay τ_1 increases and crosses the threshold τ_1^0 . What is more, Hopf bifurcation of the positive equilibrium solution occurs at the threshold $\tau_1 = \tau_1^0$. Concretely, the system is asymptotically stable when $\tau_1 \in [0, \tau_1^0)$, while it is unstable when $\tau_1 > \tau_1^0$. Thus, τ_1^0 is a vital critical value and represents the length of time delay need for the system arising oscillation behavior.

In addition, according to the normal form of functional differential equation, the following four index to depict the properties of the above Hopf bifurcation are obtained.

$$\begin{cases} C_{1}(0) = \frac{i}{2w_{0}\tau_{1}^{0}} \left(g_{11}g_{20} - 2|g_{11}|^{2} - \frac{|g_{02}|^{2}}{3} \right) + \frac{g_{21}}{2}, \\ \mu_{2} = -\frac{\operatorname{Re}\left\{C_{1}(0)\right\}}{\operatorname{Re}\left\{\lambda'\left(\tau_{1}^{0}\right)\right\}}, \\ T_{2} = -\frac{\operatorname{Im}\left\{C_{1}(0)\right\} + \mu_{2}\operatorname{Im}\left\{\lambda'\left(\tau_{1}^{0}\right)\right\}}{w_{0}\tau_{1}^{0}}, \\ \beta_{2} = 2\operatorname{Re}\left\{C_{1}(0)\right\}. \end{cases}$$
(3.6)

Among them, μ_2 determines the direction of Hopf bifurcation. If $\mu_2 > 0$, then the Hopf bifurcation is supercritical and the bifurcating periodic solutions exist for $\tau > \tau_1^0$, and while it is subcritical when $\mu_2 < 0$ and the bifurcating periodic solutions exist for $\tau < \tau_1^0$. The stability of the bifurcating periodic solutions is depended on β_2 . Especially, the bifurcating periodic solutions in the center manifold are stable when $\beta_2 < 0$, while they are unstable if $\beta_2 > 0$. The period of the bifurcating periodic solutions is determined by T_2 . If $T_2 > 0$, the period increases. When $T_2 < 0$, the period decreases.

3.1.2. Numerical simulation on the oscillation derived from Hopf bifurcation

In this section, we will perform numerical simulation to study the affect of time delay τ_1 on the system (2.1). On the one hand, it will further verify the correctness of the above theoretical derivation. On the other hand, it will give a more intuitively understand on the importance of time delay τ_1 . Except for the special parameter changes, all others are taken from Table 2. It is easy to calculated that there is a approximate positive equilibrium $E^*(0.56548, 0.37000, 0.11052, 0.00451, 0.39694, 0.18240, 0.33258)$. The critical value of τ_1 is calculated as $\tau_1^0 = 0.70454767059$ by the formula (3.4). The four important indexes are also calculated as follows according to the formulas (3.6).

$$\begin{cases} C_1(0) = -36.9894 - 42.7627i, \\ \mu_2 = 30.4674, \\ T_2 = 81.8789, \\ \beta_2 = -73.9788. \end{cases}$$
(3.7)

In order to vividly show the affect of τ_1 , we used different values to obtain a series of images of Mdm2+ $Mdm2_p$, P53, PTEN and Akt concentrations over time as shown in Figure 2. We can see that the system is stable when $\tau_1 = 0$. But as its increases, the system begins to change from stable to progressively stable. When τ_1 reaches the value $\tau_1^0 \approx 0.70455$, the system experiences Hopf bifurcation and changes from asymptotic stability to sustained oscillation, which is consistence with the above

theoretical conclusion. As τ_1 continues to increase, the system still keeps oscillating continuously. At the same time, the magnitude and period of the oscillation of the system become larger. As identified by the above calculated values $\mu_2 > 0$, $T_2 > 0$ and $\beta_2 > 0$, which suggested that the Hopf bifurcation is subcritical and the period and amplitude of the oscillations increases as τ_1 increases. Therefore, the behavior of the system can be indirectly controlled by regulating the time delay τ_1 . Moreover, we plot their images by setting discrete time delays $\tau_1 = 0.75$, $\tau_1 = 0.8$, $\tau_1 = 0.85$, $\tau_1 = 0.95$, $\tau_1 = 1.05$ separately as shown in Figure 3. From Figure 3(a) and (b) we can see that both of the magnitude and period of P53 and $Mdm2_{tot}$ increases as time delay τ_1 gradually varies from small to big. Figure 3(c) and (d) respectively shows that magnitude and period of PTEN and Akt are also added as time delay τ_1 increases. Interestingly, the oscillation valleys of PTEN nearly remain unchanged. But for the the Akt, its oscillation peaks almost stayed the same. For more visual observation, the change in the period and amplitude are drawn in Figure 4, which illustrated that both of the period and amplitude of four molecule including P53, $Mdm2_{tot}$, PTEN and Akt are increased as the time delay τ_1 increases. The increase degrees of the period for the four molecules are almost the same as shown in Figure 4(a), which is coordinate to the experiments. However, the increase degrees of the amplitude for the four molecules are different as shown in Figure 4(b), which is $Mdm2_{tot}$, P53, PTEN and Akt in the order from small to large and the biological meanings are mysterious.



Figure 2. Influences of time delay on the dynamic properties of P53 and related important components. The system parameters still take the values in Table 2 and Table 3. As shown in Figure A to C, when the delay of τ_1 is small, the system is stable and the level of P53 is almost constant. From C to F, it can be seen that when the hysteresis increases, the system becomes unstable and P53 oscillates, and the amplitude and period increase with the time delay. The numerical simulation consistent with the theoretical result that when $0 < \tau_1 < \tau_1^0 \approx 0.70455$, the positive equilibrium E^* is asymptotically stable, it is unstable for $\tau_1 > \tau_1^0 \approx 0.70455$.



Figure 3. The concentration changes of four molecules including $Mdm2_{tot}$, P53, Akt and PTEN when the time delay τ_1 takes 0.75, 0.8, 0.85, 0.95, 1.05. (a) The P53 concentration changes as time delay τ_1 increases. (b) The $Mdm2_{tot}$ concentration changes as time delay τ_1 increases. (c) The PTEN concentration changes as time delay τ_1 increases. (d) The Akt concentration changes as time delay τ_1 increases.



Figure 4. The changing trends of the period and amplitude of P53, $Mdm2_{tot}$, PTEN and Akt with respect to time delay τ_1 . (a) The period changing trends of the four molecules. (b) The amplitude changing trends of the four molecules.

3.2. Effects of τ_1 and τ_2 on the system

In the Supplementary, we have only proved the existence of Hopf bifurcation when τ_1 varies. According to the above subsection, we identified that system (2.1) undergoes a supercritical Hopf bifurcation at the positive equilibrium E^* when $\tau_1 = \tau_1^0$. However, we do not consider the time delay τ_2 of P53-promoting transcription of PTEN for the convenience of the study. In fact, the time delay does exist. Therefore, it is necessary to study the co-regulation of τ_1 and τ_2 . In this subsection, we take τ_1 to satisfy the oscillation condition and then make the τ_2 varies. By comparing Figure 5 (b) and (c), (a) and (e), (d) and (f), we get that the system oscillation is enhanced by τ_1 , which is agree with the above analysis. Intestinally, if we comparing Figure 5 (a) and (b), (c) and (d), (e) and (f), the inverse phenomenon occurs, which is he system oscillation is suppressed by τ_2 . Therefore, the relative sizes between τ_1 and τ_2 determines the degree of oscillation. To our knowledge, transcription and splicing of intron sequences increase the time required for the extension and splicing of genes to mature RNA [40, 48, 49]. Thus, an effective way to vary the time delay is changing the number of introns within the gene. Takashima et al. previously showed that deletion of all three introns within the Hes7 gene reduces the time delay by 19 min and completely abolishes oscillatory expression [50]. Based on conclusion that each consecutive intron splicing in mammalian cells required about 0.4 to 7.5 minutes [51, 52], the number of introns within the genes of Mdm2 and PTEN can be calculated in order to achieve the desired length of time delay τ_1 and τ_2 , which requires specific experimental verification. Time delays τ_1 and τ_2 can flexibly regulate the oscillation dynamics of P53. Experiments have shown that P53 oscillation dynamics is closely related to many diseases including cancer [9, 25, 26, 27]. In particular, P53 oscillation can promote the cells to repair damage. And if the damage is too severe to repair, it can also promote the cell trigger the programmed cell death. In this way, the cells can avoid the wrong genetic information from being inherited to the next generation of cells. Therefore, the above research results provide a method for regulating P53 oscillation dynamics through time delays, which may provide a new insight for the treatment of cancer and other diseases.



Figure 5. Influences of double time delays on dynamic properties of four molecules including $Mdm2_{tot}$, P53, Akt and PTEN. (a) The concentration changes of the four molecules when $\tau_1 = 0.75$, $\tau_2 = 0$. (b) The concentration changes of the four molecules when $\tau_1 = 0.75$, $\tau_2 = 0.1$. (c) The concentration changes of the four molecules when $\tau_1 = 0.85$, $\tau_2 = 0.1$. (d) The concentration changes of the four molecules when $\tau_1 = 0.85$, $\tau_2 = 0.2$. (e) The concentration changes of the four molecules when $\tau_1 = 0.95$, $\tau_2 = 0.2$. (f) The concentration changes of the four molecules when $\tau_1 = 0.95$, $\tau_2 = 0.2$.

3.3. Dependence of dynamics on the important chemical reaction rates related to P53

In this subsection, in order to more comprehensive understand the P53 oscillation dynamic, a Sobol sensitivity analysis is performed to examine the influence of each parameter k_i (i = 1, 2, ..., 14) on the P53 gene regulatory network using the ODE sensitivity package in R software. The evolution processes of the parameter sensitivity indices including the first order and total Sobol' indices for the P53 gene regulatory system (2.1) are shown in Figure 6. The first order Sobol' indices measures the pure interaction influence of the variables, while the total sensitivity index measures the influence of the variables including all interactions of any order and it reflects the individual influence of all factors plus every interaction effect [53]. Using the total Sobol' indices for the concentration of MDM2 denoted by x, a clear order of series parameters have been established: k_3 has the largest total effect, followed by S, k_7 , k_{11} , k_5 , k_8 , k_2 , k_{12} , k_{14} , k_{10} and so on. In addition, considering the influence of some parameters that have important biological significance and can cause the essential changes in the system, this subsection will focus on the four parameters S, k_3 , k_{10} , and k_{14} to elaborate the cooperative effects among them and two time delays on the system dynamics. In concretely, growth factor S in serum not only induce the transcriptional activation of Mdm2, but the activation of Akt which, phosphorylates Mdm2, promoting its nuclear accumulation and further enhance inhibition to P53 [36]. Both of Mdm2 and $Mdm2_p$ have the ability to induce the P53 degradation. k_3 represents the rate constant for $Mdm2_p$ dephosphorylation. $Mdm2_p$ has the stronger degradation ability on P53 than Mdm2 [24, 54]. In other words, the greater k_3 , the greater dephosphorylation rate of $Mdm2_p$, this will convert $Mdm2_p$ into Mdm2 and increase P53 indirectly. Thus, S and k_3 can indirectly affect the kinetics of P53. k_{10} is the basal expression rate of PTEN and k_{14} refers to the rate constant for PTEN induced Akt dephosphorylation. Both of them reflect the strength of the positive feedback loop P53 \rightarrow PTEN –I Akt \rightarrow Mdm2 – P53 including P53 and PTEN. The larger the k_{10} , the more PTEN is produced, which in turn promotes the positive feedback loop of P53 leading to an increase in P53. The larger the k_{14} , the less Akt is phosphorylated, the more P53 produced due to the weak repression of P53 from Mdm2. Obviously, both of the values k_{10} and k_{14} are important to the system dynamic behavior.



Figure 6. Evolution processes of parameter sensitivity for state variable x. (a) The first order Sobol' indices. (b) The total Sobol' indices.

Now, we will discuss the the cooperative effects of S, k_3 , k_{10} and k_{14} with the time delays respectively, and the simulation results are obtained in Figure 7, 8, 9, and 10. Here, we set the time delay $\tau_1 = 0.8$ and only with τ_2 varies. Especially, we consider three values τ_2 , which is 0, 0.1, and 0.15 in turn. On the one hand, if we horizontally observe the Figure 7, it is obviously that the parameter S can induce and block the oscillation of the four molecules in all three sets of the time delays. The oscillation range occurs at a neighborhood of $S \approx 0.035$. On the other hand, if we vertically observe the Figure 7, it can be find that the time delay τ_2 has the inhibitory role on the system oscillation in all three sets of the time delays, which is in accordance with the above results. S represents the Serum concentration that promotes the concentration of Mdm2 so that S indirectly against the accumulation of P53 concentration. Too much or too little serum concentration will not cause the produce of system oscillation, only moderate serum concentration will induce it. For the parameter k_3 , k_{10} and k_{14} , we can get the same result with S. First, observing the Figures 8, 9, and 10 horizontally, we will find that regardless which value set of the time delays, the three parameters k_3 , k_{10} and k_{14} can induce the oscillation of the four molecules or make it disappear. Then, looking at the Figures 8, 9, and 10 vertically, it can also be found that no matter which value of the parameters k_3 , k_{10} and k_{14} takes, the time delay τ_2 has a suppressive effect on system oscillation. In particular, the parameter range of the system oscillation is $k_3 \approx 11.2$, $k_{10} \approx 0.04$ and $k_{14} \approx 24$ in sequence when other parameters keep fixed. In summary, under the influence of time delays, the system has strong sensitivity to four parameters and is also strictly controlled by the them. The k_3 , k_{10} and k_{14} are all indirectly enhance the P53 concentration. Similarly with S, neither too large nor too small parameters can cause system oscillations, and only appropriately large parameters can do it.

In order to obtain a more visual perspective on the cooperative effect of two time delays and four important parameters, bifurcation diagrams of P53 with respect to four important parameters under different cases of time delay are given in Figure 11. The existence of Hopf bifurcation indicates that the system oscillation occurs. It can be seen that there are three common characters among the Figures 11(a), (b), (c) and (d). One of them is that the Hopf bifurcation occurs only when $\tau_1 = 0.8$, $\tau_2 = 0$, while under other two cases including $\tau_1 = 0, \tau_2 = 0$ and $\tau_1 = 0.8, \tau_2 = 0.1$ the bifurcation phenomenon can not be observed. This led us to conclude that time delay τ_1 has the opposite effect on the P53 oscillation production than τ_2 . Concretely, τ_1 can prompt the P53 oscillation occur, whereas τ_1 tends to hold back the oscillation. From a biological point of view, P53 oscillation means that the cell choices to repair the damage in response to stresses. The second common character is that bistability occurs only when $\tau_1 = 0.8$, $\tau_2 = 0$, while under other two cases including $\tau_1 = 0$, $\tau_2 = 0$ and $\tau_1 = 0.8$, $\tau_2 = 0.1$ the bistability phenomenon can not be found. The bistability of P53 is an important feature, which corresponding to the switch of cell fate decision. More specifically, the low steady-state means that the cell stays on a normal cell cycle state, while the high steady-state means that the cell triggers appoptosis when upon extra stimulations. Both of the DNA damage repair and appoptosis are the preventive measures of cells to avoid disease or cancers [8, 9, 10, 11, 12, 13, 14]. Therefore, τ_1 provides two ways to prevent the occurrence of diseases. The third common character is that time delays τ_1 and τ_2 is helpful to accumulate or silent the activity of P53 as can be seen by comparing the pink and blue lines, which suggested that the time delays τ_1 and τ_2 have the ability to flexibly control the state of P53. On the other hand, there are also two main differences among the Figures 11(a), (b), (c) and (d). The first one is the parameter s has the opposite role than other three parameters. As s increases, the P53 concentration is declined. But as k_3 , k_{10} and k_{14} increases, the P53 concentration is raised. The second one is that the switch in the Figure 11(c) is irreversible, while others are reversible because the parameter k_{10} can not be negative. This indicates that the apoptosis triggered by the cooperation of k_{10} and τ_1 is irredeemable death. The above analysis again shows that p53 oscillation is regulated by two time delays and four important parameters. The specific conclusion is a prediction, which needs further verification by subsequent biological experiments.



Figure 7. The effects of parameter s on the dynamical behaviors of four molecules, including $Mdm2_{tot}$, P53, Akt and PTEN, under different conditions of time delay τ_2 . The upper panel (a), (b), (c) and (d) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0$, but the value of S takes 0.032, 0.035, 0.038, 0.042 in turn. The middle panel (e), (f), (g) and (h) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.1$, but the value of S takes 0.03, 0.041, 0.045 in turn. The lower panel (i), (j), (k) and (l) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.15$, but the value of s takes 0.03, 0.035, 0.041, 0.045 in turn.



Figure 8. The effects of parameter k_3 on the dynamical behaviors of four molecules, including $Mdm2_{tot}$, P53, Akt and PTEN, under different conditions of time delay τ_2 . The upper panel (a), (b), (c) and (d) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0$, but the value of k_3 takes 10.5, 11.2, 12, 12.6 in turn. The middle panel (e), (f), (g) and (h) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.1$, but the value of k_3 takes 10.5, 11.2, 12, 12.6 in turn. The lower panel (i), (j), (k) and (l) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.15$, but the value of k_3 takes 10.5, 11.2, 12, 12.6 in turn.



Figure 9. The effects of parameter k_{10} on the dynamical behaviors of four molecules, including $Mdm2_{tot}$, P53, Akt and PTEN, under different conditions of time delay τ_2 . The upper panel (a), (b), (c) and (d) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0$, but the value of k_{10} takes 0.03, 0.04, 0.05, 0.06 in turn. The middle panel (e), (f), (g) and (h) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.1$, but the value of k_{10} takes 0.03, 0.06 in turn. The lower panel (i), (j), (k) and (l) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.15$, but the value of k_{10} takes 0.03, 0.04, 0.05, 0.06 in turn.



Figure 10. The effects of parameter k_{14} on the dynamical behaviors of four molecules, including $Mdm2_{tot}$, P53, Akt and PTEN, under different conditions of time delay τ_2 . The upper panel (a), (b), (b) and (d) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0$, but the value of k_{14} takes 24, 27, 30, 33 in turn. The middle panel (e), (f), (g) and (h) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.1$, but the value of k_{14} takes 24, 27, 30, 33 in turn. The lower panel (i), (j), (k) and (l) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.1$, but the value of k_{14} takes 24, 27, 30, 33 in turn. The lower panel (i), (j), (k) and (l) shown the concentration changes of four molecules $\tau_1 = 0.8$ and $\tau_2 = 0.15$, but the value of k_{14} takes 24, 27, 30, 33 in turn.



Figure 11. Bifurcation diagrams of the P53 visas four important parameters under three cases including (1) $\tau_1 = 0, \tau_2 = 0$; (2) $\tau_1 = 0.8, \tau_2 = 0$; (3) $\tau_1 = 0, \tau_2 = 0.1$. (a) Bifurcation diagram of the P53 visas parameter *s*. (b) Bifurcation diagram of the P53 visas parameter k_{10} . (d) Bifurcation diagram of the P53 visas parameter k_{14} . The black line represents the unstable equilibrium point. All other lines including red, blue, pink lines denote the stable equilibrium point. The symbol HB signify the Hopf bifurcation point.

4. Discussion

In this paper, we studied a mathematical model of the core regulatory network of cell fate decision that responds to growth factor instead of DNA damage. It contains seven major components and two key time delays. In our model, the dynamics of the P53-PTEN-Akt-Mdm2 network is studied using Hopf bifurcation theory and numerical simulation. The results help us understand how normal cells respond to growth factor stimuli, thereby preventing the occurrence and development of disease. Here, we just studied the effect of time delay on the P53-PTEN-Akt-Mdm2 network, whereas the downstream networks including survival and apoptosis module have not been considered. Beyond that, It has been reported that aberrant expression of miRNAs and a global decrease of their levels are often observed in multiple types of human cancer cells. In addition, the P53 pathway are often crosstalk with E2F and NF-kB signalling pathway. Therefore, more extensively network should be further investigated for

comprehensive understand the potential mechanism of P53 related network in the future.

5. Conclusion

In this paper, we proposed a delayed mathematical model to describe the P53-PTEN-Akt-Mdm2 network and mainly focused on Hopf bifurcation and oscillation behavior of the system. Firstly, we analyse the role of time delays in the system and find that the time delay could cause Hopf bifurcation. In order to facilitate the research, we let $\tau_2 = 0$ and the threshold value $\tau_1^0 \approx 0.70455$ for generating the Hopf bifurcation is obtained by calculation. Then, we obtain that the period and amplitude increase theoretically and numerically with the rising of τ_1 . Besides, for the first step of numerical simulation, we verify the existence of Hopf bifurcation consistent with theoretical derivation. Next, we take τ_2 into account that τ_1 and τ_2 and infer that τ_1 and τ_2 can cause oscillation and suppressed oscillation respectively. More important is that we found that the relative size of τ_2 and τ_2 controls the pulse shape of P53. The dynamic properties of the whole system could be subverted for their minor change. Furthermore, we study the influences of four important parameters, namely S(concentration of serum), k_3 (Rate constant for $Mdm2_p$ dephosphorylation), k_{10} (Basal expression rate of PTEN) and k_{14} (Rate constant for PTEN-induced Akt dephosphorylation) in the system. The results indicate that we obtained is the stability and the amplitude of the periodic solution could also be destroyed by their minor changes. We mainly focus on the dynamic properties of P53 and its related components under non-stress conditions, therefore this research might be helpful to further understand the mechanism of P53 and its related components under the normal circumstances and provide a new perspective for preventing cancer.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supplementary

1. The existence of Hopf bifurcations

For the convenience of presentation, we set x, y, z, u, v, p and q to represent Mdm2, Mdm2_p, MA, M_pA , P53, PTEN and Akt respectively. And parameters of the model are replaced by the form in Table 1, our system will be converted to

$$\begin{aligned} \left(\frac{dx}{dt} = \frac{k_1[S]}{K_1 + [S]} + \frac{k_2[v(t - \tau_1)]^{n_1}}{K_2^{n_1} + [v(t - \tau_1)]^{n_1}} + D_1 z(t) + \frac{k_3 y(t)}{K_3 + y(t)} - k_4 a x(t) - \frac{k_5 q(t) x(t)}{K_4 + x(t)} - d_1 x(t), \\ \frac{dy}{dt} = D_2 u(t) + \frac{k_5 q(t) x(t)}{K_4 + x} - k_6 a y(t) - \frac{k_3 y(t)}{K_3 + y(t)} - d_2 y(t), \\ \frac{dz}{dt} = k_4 a x(t) - D_1 z(t) - d_3 z(t), \\ \frac{du}{dt} = k_6 a y(t) - D_2 u(t) - d_4 u(t), \\ \frac{dv}{dt} = k_7 - \frac{k_8 x(t) v(t)}{K_5 + v(t)} - \frac{k_9 y(t) v(t)}{K_6 + v(t)} - d_5 v(t), \\ \frac{dp}{dt} = k_{10} + \frac{k_{11} [v(t - \tau_2)]^{n_2}}{K_7^{n_2} + [v(t - \tau_2)]^{n_2}} - d_6 p(t), \\ \frac{dq}{dt} = \frac{k_{12}[S]}{K_8 + [S]} \frac{A - q(t)}{K_9 + A - q(t)} - \frac{k_{13} q(t)}{K_{10} + q(t)} - \frac{k_{14} p(t) q(t)}{K_{11} + q(t)}. \end{aligned}$$
(5.1)

Obviously, it is easy to get a positive equilibrium solution by setting the right-hand side of the equation equal to zero in (6.1), which is quite consistent with the actual biological background and significance. For the convenience of research, we set $\tau_2 = 0$ and $E^* = (x^*, y^*, z^*, u^*, v^*, p^*, q^*)$ as a positive balance point of the system(6.1), and then we can get the linearization equation near the equilibrium as follows

$$\begin{cases} \dot{x}(t) = c_1 x(t) + c_2 y(t) + c_3 z(t) + c_4 e^{-\lambda} v(t) + c_5 q(t), \\ \dot{y}(t) = c_6 x(t) + c_7 y(t) + c_8 u(t) + c_9 q(t), \\ \dot{z}(t) = c_{10} x(t) - c_{11} z(t), \\ \dot{u}(t) = c_{12} y(t) + c_{13} u(t), \\ \dot{v}(t) = c_{14} x(t) + c_{15} y(t) + c_{16} v(t), \\ \dot{p}(t) = c_{17} v(t) + c_{18} p(t), \\ \dot{q}(t) = c_{19} p(t) + c_{20} q(t). \end{cases}$$
(5.2)

where

$$\begin{aligned} c_1 &= \frac{-K_5 K_4 q^*}{(K_4 + x^*)^2} - ak_4 - d_1, \ c_2 &= \frac{K_3 k_3}{(K_3 + y^*)^2}, \ c_3 &= D_1, \ c_4 &= \frac{4K_2^4 k_2 (v^*)^3}{(K_4^4 + (v^*)^4)^2} \\ c_5 &= \frac{-k_5 x^*}{K_4 + x^*}, \ c_6 &= \frac{K_4 k_5 q^*}{(K_4 + x^*)^2}, \ c_7 &= \frac{-K_3 k_3}{(k_3 + y^*)^2} - ak_6 - d_2, \ c_8 &= D_2, \\ c_9 &= \frac{k_5 x^*}{K_4 + x^*}, \ c_{10} &= ak_4, \ c_{11} &= -D_1 - d_3, \ c_{12} &= ak_6, \ c_{13} &= -D_2 - d_4, \\ c_{14} &= \frac{-k_8 v^*}{K_5 + v^*}, \ c_{15} &= \frac{-k_9 v^*}{K_6 + v^*}, \ c_{16} &= \frac{-K_5 k_8 x^*}{(K_5 + v^*)^2} - \frac{K_6 k_9 y^*}{(K_6 + v^*)^2} - d_5 \\ c_{17} &= \frac{3K_7^3 k_{11} (v^*)^2}{(K_7^3 + (v^*)^3)^2}, \ c_{18} &= -d_6, \ c_{19} &= \frac{-k_{14} q^*}{(K_{11} + q^*)}, \end{aligned}$$

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$$c_{20} = \frac{-k_{12}SK_9}{(K_8 + S)(K_9 + A - q^*)^2} - \frac{K_{10}k_{13}}{(K_{10} + q^*)^2} - \frac{K_{11}k_{14}p^*}{(K_{11} + q^*)^2}.$$

Furthermore, we can get the characteristic equations of equations (6.2)

$$m_{1} + m_{3}\lambda + m_{5}\lambda^{2} + m_{7}\lambda^{3} + m_{9}\lambda^{4} + m_{11}\lambda^{5} + m_{13}\lambda^{6} - \lambda^{7} + e^{-\lambda\tau_{1}}\left(m_{2} + m_{4}\lambda + m_{6}\lambda^{2} + m_{8}\lambda^{3} + m_{10}\lambda^{4} + m_{12}\lambda^{5} + m_{14}\lambda^{6}\right) = 0.$$
(5.3)

where

 $m_1 = c_5 c_8 c_{11} c_{12} c_{14} c_{17} c_{19} - c_5 c_7 c_{11} c_{13} c_{14} c_{17} c_{19} + c_2 c_9 c_{11} c_{13} c_{14} c_{17} c_{19} + c_3 c_9 c_{10} c_{13} c_{15} c_{17} c_{19}$ $+ c_5 c_6 c_{11} c_{13} c_{15} c_{17} c_{19} - c_1 c_9 c_{11} c_{13} c_{15} c_{17} c_{19} + c_3 c_8 c_{10} c_{12} c_{16} c_{18} c_{20} - c_1 c_8 c_{11} c_{12} c_{16} c_{18} c_{20}$ $-c_3c_7c_{10}c_{13}c_{16}c_{18}c_{20} - c_2c_6c_{11}c_{13}c_{16}c_{18}c_{20} + c_1c_7c_{11}c_{13}c_{16}c_{18}c_{20},$ $m_2 = c_4 c_8 c_{11} c_{12} c_{14} c_{18} c_{20} - c_4 c_7 c_{11} c_{13} c_{14} c_{18} c_{20} + c_4 c_6 c_{11} c_{13} c_{15} c_{18} c_{20}$ $m_3 = -c_3c_8c_{10}c_{12}c_{16}c_{18} + c_1c_8c_{11}c_{12}c_{16}c_{18} + c_3c_7c_{10}c_{13}c_{16}c_{18} + c_2c_6c_{11}c_{13}c_{16}c_{18}$ $-c_1c_7c_{11}c_{13}c_{16}c_{18} - c_3c_8c_{10}c_{12}c_{20}c_{18} + c_1c_8c_{11}c_{12}c_{20}c_{18} + c_3c_7c_{10}c_{13}c_{20}c_{18}$ $+ c_2 c_6 c_{11} c_{13} c_{20} c_{18} - c_1 c_7 c_{11} c_{13} c_{20} c_{18} + c_3 c_7 c_{10} c_{16} c_{20} c_{18} + c_2 c_6 c_{11} c_{16} c_{20} c_{18}$ $-c_1c_7c_{11}c_{16}c_{20}c_{18} + c_1c_8c_{12}c_{16}c_{20}c_{18} + c_8c_{11}c_{12}c_{16}c_{20}c_{18} + c_2c_6c_{13}c_{16}c_{20}c_{18}$ $-c_1c_7c_{13}c_{16}c_{20}c_{18} + c_3c_{10}c_{13}c_{16}c_{20}c_{18} - c_1c_{11}c_{13}c_{16}c_{20}c_{18} - c_7c_{11}c_{13}c_{16}c_{20}c_{18}$ $+ c_5 c_7 c_{11} c_{14} c_{17} c_{19} - c_2 c_9 c_{11} c_{14} c_{17} c_{19} - c_5 c_8 c_{12} c_{14} c_{17} c_{19} + c_5 c_7 c_{13} c_{14} c_{17} c_{19}$ $-c_2c_9c_{13}c_{14}c_{17}c_{19} + c_5c_{11}c_{13}c_{14}c_{17}c_{19} - c_3c_9c_{10}c_{15}c_{17}c_{19} - c_5c_6c_{11}c_{15}c_{17}c_{19}$ $+ c_1 c_9 c_{11} c_{15} c_{17} c_{19} - c_5 c_6 c_{13} c_{15} c_{17} c_{19} + c_1 c_9 c_{13} c_{15} c_{17} c_{19} + c_9 c_{11} c_{13} c_{15} c_{17} c_{19}$ $-c_3c_8c_{10}c_{12}c_{16}c_{20} + c_1c_8c_{11}c_{12}c_{16}c_{20} + c_3c_7c_{10}c_{13}c_{16}c_{20} + c_2c_6c_{11}c_{13}c_{16}c_{20}$ $-c_1c_7c_{11}c_{13}c_{16}c_{20},$ $m_4 = -c_4 c_8 c_{11} c_{12} c_{14} c_{18} + c_4 c_7 c_{11} c_{13} c_{14} c_{18} - c_4 c_6 c_{11} c_{13} c_{15} c_{18} + c_4 c_7 c_{11} c_{14} c_{20} c_{18}$ $-c_4c_8c_{12}c_{14}c_{20}c_{18} + c_4c_7c_{13}c_{14}c_{20}c_{18} + c_4c_{11}c_{13}c_{14}c_{20}c_{18} - c_4c_6c_{11}c_{15}c_{20}c_{18}$ $-c_4c_6c_{13}c_{15}c_{20}c_{18} - c_4c_8c_{11}c_{12}c_{14}c_{20} + c_4c_7c_{11}c_{13}c_{14}c_{20} - c_4c_6c_{11}c_{13}c_{15}c_{20},$ $m_5 = c_3 c_8 c_{10} c_{12} c_{16} - c_1 c_8 c_{11} c_{12} c_{16} - c_3 c_7 c_{10} c_{13} c_{16} - c_2 c_6 c_{11} c_{13} c_{16}$ $+ c_1 c_7 c_{11} c_{13} c_{16} - c_3 c_7 c_{10} c_{18} c_{16} - c_2 c_6 c_{11} c_{18} c_{16} + c_1 c_7 c_{11} c_{18} c_{16}$ $-c_1c_8c_{12}c_{18}c_{16} - c_8c_{11}c_{12}c_{18}c_{16} - c_2c_6c_{13}c_{18}c_{16} + c_1c_7c_{13}c_{18}c_{16}$ $-c_3c_{10}c_{13}c_{18}c_{16} + c_1c_{11}c_{13}c_{18}c_{16} + c_7c_{11}c_{13}c_{18}c_{16} + c_{11}c_{13}c_{18}c_{16}$ $-c_3c_7c_{10}c_{20}c_{16} - c_2c_6c_{11}c_{20}c_{16} + c_1c_7c_{11}c_{20}c_{16} - c_1c_8c_{12}c_{20}c_{16}$ $-c_8c_{11}c_{12}c_{20}c_{16} - c_2c_6c_{13}c_{20}c_{16} + c_1c_7c_{13}c_{20}c_{16} - c_3c_{10}c_{13}c_{20}c_{16}$ $+ c_1 c_{11} c_{13} c_{20} c_{16} + c_7 c_{11} c_{13} c_{20} c_{16} - c_2 c_6 c_{18} c_{20} c_{16} + c_1 c_7 c_{18} c_{20} c_{16}$ $-c_3c_{10}c_{18}c_{20}c_{16} + c_1c_{11}c_{18}c_{20}c_{16} + c_7c_{11}c_{18}c_{20}c_{16} - c_8c_{12}c_{18}c_{20}c_{16}$ $+ c_1 c_{13} c_{18} c_{20} c_{16} + c_7 c_{13} c_{18} c_{20} c_{16} + c_3 c_8 c_{10} c_{12} c_{18} - c_1 c_8 c_{11} c_{12} c_{18}$ $-c_3c_7c_{10}c_{13}c_{18} - c_2c_6c_{11}c_{13}c_{18} + c_1c_7c_{11}c_{13}c_{18} - c_5c_7c_{14}c_{17}c_{19}$ $+ c_2 c_9 c_{14} c_{17} c_{19} - c_5 c_{11} c_{14} c_{17} c_{19} - c_5 c_{13} c_{14} c_{17} c_{19} + c_5 c_6 c_{15} c_{17} c_{19}$

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 $\begin{aligned} &-c_1c_9c_{15}c_{17}c_{19} - c_9c_{11}c_{15}c_{17}c_{19} - c_9c_{13}c_{15}c_{17}c_{19} + c_3c_8c_{10}c_{12}c_{20} \\ &-c_1c_8c_{11}c_{12}c_{20} - c_3c_7c_{10}c_{13}c_{20} - c_2c_6c_{11}c_{13}c_{20} + c_1c_7c_{11}c_{13}c_{20} \\ &-c_3c_7c_{10}c_{18}c_{20} - c_2c_6c_{11}c_{18}c_{20} + c_1c_7c_{11}c_{18}c_{20} - c_1c_8c_{12}c_{18}c_{20} \\ &-c_8c_{11}c_{12}c_{18}c_{20} - c_2c_6c_{13}c_{18}c_{20} + c_1c_7c_{13}c_{18}c_{20} - c_3c_{10}c_{13}c_{18}c_{20} \\ &+c_1c_{11}c_{13}c_{18}c_{20} + c_7c_{11}c_{13}c_{18}c_{20}, \\ m_6 &= c_4c_8c_{11}c_{12}c_{14} - c_4c_7c_{11}c_{13}c_{18}c_{14} - c_4c_7c_{11}c_{20}c_{14} + c_4c_8c_{12}c_{20}c_{14} \\ &-c_4c_7c_{13}c_{18}c_{14} - c_4c_{11}c_{13}c_{18}c_{14} - c_4c_7c_{11}c_{20}c_{14} + c_4c_8c_{12}c_{20}c_{14} \end{aligned}$

- $-c_4c_7c_{13}c_{20}c_{14} c_4c_{11}c_{13}c_{20}c_{14} c_4c_7c_{18}c_{20}c_{14} c_4c_{11}c_{18}c_{20}c_{14}$
- $-c_4c_{13}c_{18}c_{20}c_{14} + c_4c_6c_{11}c_{13}c_{15} + c_4c_6c_{11}c_{15}c_{18} + c_4c_6c_{13}c_{15}c_{18}$
- $+ c_4 c_6 c_{11} c_{15} c_{20} + c_4 c_6 c_{13} c_{15} c_{20} + c_4 c_6 c_{15} c_{18} c_{20},$

 $m_7 = -c_3 c_8 c_{10} c_{12} + c_1 c_8 c_{11} c_{12} + c_1 c_8 c_{16} c_{12} + c_8 c_{11} c_{16} c_{12}$ $+ c_1 c_8 c_{18} c_{12} + c_8 c_{11} c_{18} c_{12} + c_8 c_{16} c_{18} c_{12} + c_1 c_8 c_{20} c_{12}$ $+ c_8 c_{11} c_{20} c_{12} + c_8 c_{16} c_{20} c_{12} + c_8 c_{18} c_{20} c_{12} + c_3 c_7 c_{10} c_{13}$ $+ c_2 c_6 c_{11} c_{13} - c_1 c_7 c_{11} c_{13} + c_3 c_7 c_{10} c_{16} + c_2 c_6 c_{11} c_{16}$ $-c_1c_7c_{11}c_{16} + c_2c_6c_{13}c_{16} - c_1c_7c_{13}c_{16} + c_3c_{10}c_{13}c_{16}$ $-c_1c_{11}c_{13}c_{16} - c_7c_{11}c_{13}c_{16} + c_3c_7c_{10}c_{18} + c_2c_6c_{11}c_{18}$ $-c_1c_7c_{11}c_{18} + c_2c_6c_{13}c_{18} - c_1c_7c_{13}c_{18} + c_3c_{10}c_{13}c_{18}$ $-c_1c_{11}c_{13}c_{18} - c_7c_{11}c_{13}c_{18} + c_2c_6c_{16}c_{18} - c_1c_7c_{16}c_{18}$ $+ c_3 c_{10} c_{16} c_{18} - c_1 c_{11} c_{16} c_{18} - c_7 c_{11} c_{16} c_{18} - c_1 c_{13} c_{16} c_{18}$ $-c_7c_{13}c_{16}c_{18} - c_{11}c_{13}c_{16}c_{18} + c_5c_{14}c_{17}c_{19} + c_9c_{15}c_{17}c_{19}$ $+ c_3 c_7 c_{10} c_{20} + c_2 c_6 c_{11} c_{20} - c_1 c_7 c_{11} c_{20} + c_2 c_6 c_{13} c_{20}$ $-c_1c_7c_{13}c_{20} + c_3c_{10}c_{13}c_{20} - c_1c_{11}c_{13}c_{20} - c_7c_{11}c_{13}c_{20}$ $+ c_2 c_6 c_{16} c_{20} - c_1 c_7 c_{16} c_{20} + c_3 c_{10} c_{16} c_{20} - c_1 c_{11} c_{16} c_{20}$ $-c_7c_{11}c_{16}c_{20} - c_1c_{13}c_{16}c_{20} - c_7c_{13}c_{16}c_{20} - c_{11}c_{13}c_{16}c_{20}$ $+ c_2 c_6 c_{18} c_{20} - c_1 c_7 c_{18} c_{20} + c_3 c_{10} c_{18} c_{20} - c_1 c_{11} c_{18} c_{20}$ $-c_7c_{11}c_{18}c_{20} - c_1c_{13}c_{18}c_{20} - c_7c_{13}c_{18}c_{20} - c_{11}c_{13}c_{18}c_{20}$ $-c_1c_{16}c_{18}c_{20}-c_7c_{16}c_{18}c_{20}-c_{11}c_{16}c_{18}c_{20}-c_{13}c_{16}c_{18}c_{20},$ $m_8 = c_4 c_7 c_{11} c_{14} - c_4 c_8 c_{12} c_{14} + c_4 c_7 c_{13} c_{14} + c_4 c_{11} c_{13} c_{14}$ $+ c_4 c_7 c_{18} c_{14} + c_4 c_{11} c_{18} c_{14} + c_4 c_{13} c_{18} c_{14} + c_4 c_7 c_{20} c_{14}$ $+ c_4 c_{11} c_{20} c_{14} + c_4 c_{13} c_{20} c_{14} + c_4 c_{18} c_{20} c_{14} - c_4 c_6 c_{11} c_{15}$ $-c_4c_6c_{13}c_{15}-c_4c_6c_{15}c_{18}-c_4c_6c_{15}c_{20},$ $m_9 = -c_3c_7c_{10} - c_3c_{13}c_{10} - c_3c_{16}c_{10} - c_3c_{18}c_{10} - c_3c_{20}c_{10}$ $-c_2c_6c_{11} + c_1c_7c_{11} - c_1c_8c_{12} - c_8c_{11}c_{12} - c_2c_6c_{13}$ $+ c_1 c_7 c_{13} + c_1 c_{11} c_{13} + c_7 c_{11} c_{13} - c_2 c_6 c_{16} + c_1 c_7 c_{16}$ $+ c_1 c_{11} c_{16} + c_7 c_{11} c_{16} - c_8 c_{12} c_{16} + c_1 c_{13} c_{16} + c_7 c_{13} c_{16}$

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$$\begin{aligned} + c_{11}c_{13}c_{16} - c_{2}c_{6}c_{18} + c_{1}c_{7}c_{18} + c_{1}c_{11}c_{18} + c_{7}c_{11}c_{18} \\ - c_{8}c_{12}c_{18} + c_{1}c_{13}c_{18} + c_{7}c_{13}c_{18} + c_{11}c_{13}c_{18} + c_{1}c_{16}c_{18} \\ + c_{7}c_{16}c_{18} + c_{11}c_{16}c_{18} + c_{13}c_{16}c_{18} - c_{2}c_{6}c_{20} + c_{1}c_{7}c_{20} \\ + c_{1}c_{11}c_{20} + c_{7}c_{11}c_{20} - c_{8}c_{12}c_{20} + c_{1}c_{13}c_{20} + c_{7}c_{13}c_{20} \\ + c_{11}c_{13}c_{20} + c_{1}c_{16}c_{20} + c_{7}c_{16}c_{20} + c_{11}c_{16}c_{20} + c_{13}c_{16}c_{20} \\ + c_{11}c_{18}c_{20} + c_{7}c_{18}c_{20} + c_{11}c_{18}c_{20} + c_{13}c_{18}c_{20} + c_{16}c_{18}c_{20}, \\ m_{10} &= -c_{4}c_{7}c_{14} - c_{4}c_{11}c_{14} - c_{4}c_{13}c_{14} - c_{4}c_{18}c_{14} - c_{4}c_{20}c_{14} + c_{4}c_{6}c_{15}, \\ m_{11} &= c_{2}c_{6} - c_{1}c_{7} + c_{3}c_{10} - c_{1}c_{11} - c_{7}c_{11} + c_{8}c_{12} - c_{1}c_{13} - c_{7}c_{13} - c_{11}c_{13} \\ - c_{16}c_{18} - c_{1}c_{20} - c_{7}c_{20} - c_{11}c_{20} - c_{13}c_{20} - c_{16}c_{20} - c_{18}c_{20}, \\ m_{12} &= c_{4}c_{14}, \\ m_{13} &= c_{1} + c_{7} + c_{11} + c_{13} + c_{16} + c_{18} + c_{20}, \\ m_{14} &= 0. \end{aligned}$$

In order to theoretically analyze the sufficient conditions for generating oscillations, we assume that iw(w > 0) is a root of equation (6.3). Then, bring *iw* into equation (6.3) to get:

$$m_{1} + im_{3}w - m_{5}w^{2} - im_{7}w^{3} + m_{9}w^{4} + im_{11}w^{5} - m_{13}w^{6} + iw^{7} + (m_{2} + im_{4}w) - m_{6}w^{2} - im_{8}w^{3} + m_{1}0w^{4} + im_{12}w^{5} - m_{14}w^{6})(\cos w\tau_{1} - i\sin w\tau_{1}) = 0.$$
(5.4)

Separating the real part and the imaginary part we can get

$$\begin{cases} m_1 - m_5 w^2 + m_9 w^4 - m_{13} w^6 = -(m_2 - m_6 w^2 + m_{10} w^4 - m_{14} w^6) \cos w \tau_1 \\ -(m_4 w - m_8 w^3 + m_{12} w^5) \sin w \tau_1, \\ m_3 w - m_7 w^3 + m_{11} w^5 + w^7 = -(m_4 w - m_8 w^3 + m_{12} w^5) \cos w \tau_1 \\ -(-m_2 + m_6 w^2 - m_{10} w^4 + m_{14} w^6) \sin w \tau_1. \end{cases}$$
(5.5)

Then there will be

$$\begin{cases} \cos w\tau_{1} = \frac{E}{F} \\ \sin w\tau_{1} = \frac{M+N}{F}, \\ F = (-m_{4}w + m_{8}w^{3} - m_{12}w^{5})^{2} - (m_{2} - m_{6}w^{2} + m_{10}w^{4} - m_{14}w^{6}) \times \\ (-m_{2} + m_{6}w^{2} - m_{10}w^{4} + m_{14}w^{6}) \\ E = (-m_{1} + m_{5}w^{2} - m^{9}w^{4} + m_{13}w^{6})(m_{2} - m_{6}w^{2} + m_{10}w^{4} - m_{14}w^{6}) \\ + (-m_{4}w + m_{8}w^{3} - m_{12}w^{5})(m_{3}w - m_{7}w^{3} + m_{11}w^{5} + w^{7}) \\ M = (m_{2}m_{3} - m_{1}m_{4})w + (m_{4}m_{5} - m_{3}m_{6} - m_{2}m_{7} + m_{1}m_{8})w^{3} \\ + (-m_{1}m_{12} + m_{11}m_{2} + m_{10}m_{3} + m_{6}m_{7} - m_{5}m_{8} - m_{4}m_{9})w^{5} \\ N = (m_{2} - m_{14}m_{3} + m_{13}m_{4} + m_{12}m_{5} - m_{11}m_{6} - m_{10}m_{7} + m_{8}m_{9})w^{7} \\ + (m_{10}m_{11} - m_{6} + m_{14}m_{7} - m_{13}m_{8} - m_{12}m_{9})w^{9} \\ + (m_{10} + m_{12}m_{13} - m_{11}m_{14})w^{11} - m_{14}w^{13} \end{cases}$$

$$(5.6)$$

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The above equations are squared and then the equations of the equal sign are added separately. Then, there will be

$$w^{14} + w^{12}(2m_{11} + m_{13}^2) + w^{10}(-2m_7 + m_{11}^2 + m_{12}^2 - 2m_9m_{13}) + w^8(2m_3 + m_9^2 - m_{10}^2) - 2m_7m_{11} - 2m_8m_{12} + 2m_5m_{13}) + w^6(m_7^2 + m_8^2 - 2m_5m_9 + 2m_6m_{10} + 2m_3m_{11} + 2m_4m_{12} - 2m_1m_{13}) + w^4(m_5^2 - m_6^2 - 2m_3m_7 - 2m_4m_8 + 2m_1m_9 - 2m_2m_{10}) + w^2(m_3^2) + m_4^2 - 2m_1m_5 + 2m_2m_6) + m_1^2 - m_2^2 = 0.$$
(5.7)

Moreover, it is easy to verify that

$$\begin{split} & 2m_{11} + m_{13}^2 > 0, \ -2m_7 + m_{11}^2 + m_{12}^2 - 2m_9m_{13} > 0, \\ & 2m_{13} + m_{10}^2 - m_{10}^2 - 2m_7m_{11} \\ & -2m_8m_{12} + 2m_5m_{13} > 0, \\ & m_7^2 + m_8^2 - 2m_5m_9 + 2m_6m_{10} + 2m_3m_{11} + 2m_4m_{12} \\ & -2m_1m_{13} > 0, \\ & m_5^2 - m_6^2 - 2m_3m_7 - 2m_4m_8 + 2m_1m_9 - 2m_2m_{10} > 0 \\ & m_3^2 + m_4^2 - 2m_1m_5 + 2m_2m_6 > 0, \\ & m_1^2 - m_2^2 < 0. \end{split}$$

Therefore, equation (6.7) exists unique positive root w_0 . From (6.6) we can get

$$\tau_1^{(j)} = \frac{1}{w_0} \arccos \frac{E}{F} + \frac{2\pi j}{w_0}$$

where $j=0,1,2,3\cdots$. And we define $\tau_1^0 = \min \{\tau_1^{(j)} > 0\}_{j=0}^{+\infty}$. Thus, when $\tau = \tau_1^0$ equation (6.3) has a pair of pure imaginary roots $\pm iw_0$. Next we will prove that the root of equation (6.3) has a strict negative real part at $\tau_1 \in [0, \tau_1^0)$, and there are at least two roots containing positive real parts when $\tau_1 \in (\tau_1^0, \tau_1^m)$, where *m* is the minimum positive integer satisfying for $\tau_1^0 < \tau_1^m$.

Lemma 6.1 [55] For the exponential polynomial $P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2} \cdots e^{-\lambda\tau_m})$ in the process of $(\tau_1, \tau_2, \cdots, \tau_m)$ changes, only when $P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2} \cdots e^{-\lambda\tau_m})$ has a zero point on the imaginary axis, or when it has a zero point through the imaginary axis, the sum of the zeros in the half-open plane is likely to change. Where

$$P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2} \cdots e^{-\lambda\tau_m}) = \lambda^n + p_1^{(0)}\lambda^{n-1} + \cdots + p_{n-1}^{(0)}\lambda + p_n^{(0)} + (p_1^{(1)}\lambda^{n-1} + \cdots + p_{n-1}^{(1)}\lambda + p_n^{(1)})e^{-\lambda\tau_1} + \cdots + (p_1^{(m)}\lambda^{n-1} + \cdots + p_{n-1}^{(m)}\lambda + p_n^{(m)})e^{-\lambda\tau_m}.$$
(5.8)

It can be seen from the lemma that it is only necessary to prove that the root of the equation (6.3) has a strict negative real part at $\tau_1 = 0$. And then as $\tau_1 = \tau_1^0$, a pair of pure imaginary roots $\pm iw_0$ are derived, therefore, for the second half of our results we only need to prove the following formula: $\frac{d\text{Re}(\lambda(\tau_1))}{d\tau_1}\Big|_{\tau_1=\tau_1^0} > 0$. The left and right ends of the second equation of equation (6.5) are derived for A respectively, we can get

$$m_{3} - 3m_{7}w_{0}^{2} + 5m_{11}w_{0}^{4} + 7w_{0}^{6} + (2m_{5}w_{0} - 4m_{9}w_{0}^{3} + 6m_{13}w_{0}^{5})i + (\cos w_{0}\tau_{1}^{0} - i\sin w_{0}\tau_{1}^{0})[(m_{2} - m_{6}w_{0}^{2} + m_{10}w_{0}^{4} - m_{14}w_{0}^{6} + (m_{4} - m_{8}w_{0}^{3} + m_{12}w_{0}^{5})i)(-iw_{0}/\lambda'(\tau_{1}^{0}) - \tau_{1}^{0}) + m_{4} - 3m_{8}w_{0}^{2} + 5m_{12}w_{0}^{4} + (2m_{6}w_{0} - 4m_{10}w_{0}^{3} + 6m_{14}w_{0}^{5})i] = 0.$$
(5.9)

Let $A = m_3 - 3m_7w_0^2 + 5m_{11}w_0^4 + 7w_0^6$, $B = 2m_5w_0 - 4m_9w_0^3 + 6m_{13}w_0^5$,

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$$\begin{split} \mathbf{C} &= \cos w_0 \tau_1^0 - \mathbf{i} \sin w_0 \tau_1^0, \ D &= m_2 - m_6 w_0^2 + m_{10} w_0^4 - m_{14} w_0^6, \\ E &= m_4 - m_8 w_0^3 + m_{12} w_0^5, \ F &= m_4 - 3m_8 w_0^2 + 5m_{12} w_0^4, \\ G &= 2m_6 w_0 - 4m_{10} w_0^3 + 6m_{14} w_0^5. \\ \text{Furthermore,} \left[\frac{d\lambda(\tau_1)}{d\tau_1} \right]^{-1} \Big|_{\tau_1 = \tau_1^0} &= \frac{\mathbf{i}}{w_0} \left[\frac{-(A+B) - C(F+G)}{C(D+E)} + \tau_1^0 \right]. \\ \text{Then by calculating we can get} \\ \text{sgn} \left\{ \frac{d\text{Re}(\lambda(\tau_1))}{d\tau_1} \Big|_{\tau_1 = \tau_1^0} \right\} &= \text{sgn} \left\{ \text{Re} \left[\frac{d\lambda(\tau_1)}{d\tau_1} \right]^{-1} \Big|_{\tau_1 = \tau_1^0} \right\} > 0. \end{split}$$

Therefore, we prove that the root of characteristic equation(6.5) crosses the virtual axis from left to right as $\lambda(\tau_1^0) = \pm iw_0$. Obviously, Hopf bifurcation of the positive equilibrium solution occurs at $\tau_1 = \tau_1^0$. Besides, the system is progressively stable when $\tau_1 \in [0, \tau_1^0)$ while, if $\tau_1 > \tau_1^0$ it is unstable. So for our system, τ_1^0 is a vital quantity, it could predict the oscillation of P53 or not.

2. Properties of Hopf bifurcations

In the previous section, we have obtained that the system (6.2) undergoes a Hopf bifurcation or Turing-Hopf bifurcation at the positive constant $(x^*, y^*, z^*, u^*, v^*, p^*, q^*)$ when $\tau_1 = \tau_1^0$. In this section, we will study the properties of Hopf bifurcation and the stability of bifurcated periodic solutions by using the normal form theory and central manifold theory due to Hassard, Kazarinoff and Wan[56]. Throughout this section, we always assume that system (2.1) undergoes Hopf bifurcation when $\tau_1 = \tau_1^0$ at the positive equilibrium $(x^*, y^*, z^*, u^*, v^*, p^*, q^*)$, and the corresponding purely imaginary roots of the characteristic equation are $\pm iw_0$. Subsequently, we let $\bar{x} = x(t) - x^*, \bar{y} = y(t) - x^*, \bar{z} = z(t) - z^*, \bar{u} = u(t) - u^*, \bar{v} = v(t) - v^*, \bar{p} = p(t) - p^*, \bar{q} = q(t) - q^*$. And we still denote $\bar{x}, \bar{y}, \bar{z}, \bar{u}, \bar{v}, \bar{p}, \bar{q}$ as x, y, z, u, v, pandq. Moreover, let $\tau_1 = \tau_1^0 + \gamma$ normalizing the time delay τ_1 by the time-scaling $t \to t/\tau_1$, and the system (2) transform to

$$\begin{pmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \\ \dot{u} \\ \dot{v} \\ \dot{p} \\ \dot{q} \end{pmatrix} = (\tau_1^0 + \gamma) \begin{pmatrix} c_1 & c_2 & c_3 & 0 & c_4 e^{-\lambda} & 0 & c_5 \\ c_6 & c_7 & 0 & c_8 & 0 & 0 & c_9 \\ c_{10} & 0 & c_{11} & 0 & 0 & 0 & 0 \\ 0 & c_{12} & 0 & c_{13} & 0 & 0 & 0 \\ c_{14} & c_{15} & 0 & 0 & c_{16} & 0 & 0 \\ 0 & 0 & 0 & 0 & c_{17} & c_{18} & 0 \\ 0 & 0 & 0 & 0 & 0 & c_{19} & c_{20} \end{pmatrix} \begin{pmatrix} x \\ y \\ z \\ u \\ v \\ p \\ q \end{pmatrix} +$$

$$(\tau_{1}^{0} + \gamma) \begin{pmatrix} \sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{11}^{(i)}(v^{*})v(t-1)^{i} + f_{12}^{(i)}(y^{*})y^{i} + f_{13}^{(i)}(x^{*})q^{*}x^{i} + if_{13}^{(i-1)}(x^{*})qx^{i-1} \right] \\ \sum_{i=2}^{\infty} \frac{1}{i!} \left[-f_{13}^{(i)}(x^{*})q^{*}x^{i} - if_{13}^{(i-1)}(x^{*})qx^{i-1} + f_{12}^{(i)}(y^{*})y^{i} \right] \\ 0 \\ 0 \\ \sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{51}^{(i)}(v^{*})x^{*}v^{i} + if_{51}^{(i-1)}(v^{*})xv^{i-1} + f_{52}^{(i)}(v^{*})y^{*}v^{i} + if_{52}^{(i-1)}(v^{*})yv^{i-1} \right] \\ \sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{71}^{(i)}(q^{*})q^{i} + f_{72}^{(i)}(q^{*})q^{i} + f_{73}^{(i)}(q^{*})q^{*}q^{i} + if_{73}^{(i-1)}(q^{*})pq^{i-1} \right] \end{pmatrix}$$

where c_1, c_2, \cdots, c_{20} is consistent with the previously defined, and

$$\begin{split} f_{11}^{(2)}(v) &= \frac{32k_2v^{10}}{\left(K_2^4 + v^4\right)^3} - \frac{44k_2v^6}{\left(K_2^4 + v^4\right)^2} + \frac{12k_2v^2}{K_2^4 + v^4}, \\ f_{11}^{(3)}(v) &= -\frac{384k_2v^{13}}{\left(K_2^4 + v^4\right)^4} + \frac{672k_2v^9}{\left(K_2^4 + v^4\right)^3} - \frac{312k_2v^5}{\left(K_2^4 + v^4\right)^2} + \frac{24k_2v}{K_2^4 + v^4} \\ f_{12}^{(2)}(v) &= \frac{2k_3y}{\left(K_3 + y\right)^3} - \frac{2k_3}{\left(K_3 + y\right)^2}, \\ f_{12}^{(3)}(v) &= -\frac{6k_3y}{\left(K_4 + x\right)^2} + \frac{6k_3}{\left(K_4 + x\right)^2}, \\ f_{13}^{(1)}(x) &= \frac{k_5x}{\left(K_4 + x\right)^2} - \frac{k_5}{K_4 + x}, \\ f_{13}^{(2)}(x) &= -\frac{2k_5x}{\left(K_4 + x\right)^3} + \frac{2k_5}{\left(K_4 + x\right)^3}, \\ f_{13}^{(3)}(x) &= \frac{6k_5x}{\left(K_4 + x\right)^4} - \frac{6k_5}{\left(K_4 + x\right)^3}, \\ f_{51}^{(1)}(v) &= \frac{k_8v}{\left(K_5 + v\right)^2} - \frac{k_8}{K_5 + v}, \\ f_{51}^{(2)}(v) &= -\frac{2k_8v}{\left(K_5 + v\right)^3} + \frac{2k_8}{\left(K_5 + v\right)^2}, \\ f_{51}^{(3)}(v) &= \frac{6k_8v}{\left(K_5 + v\right)^4} - \frac{6k_8}{\left(K_5 + v\right)^3}, \end{split}$$

$$\begin{split} f_{52}^{(1)}(v) &= \frac{k_9 v}{(K_6 + v)^2} - \frac{k_9}{K_6 + v}, f_{52}^{(2)}(v) = -\frac{2k_9 v}{(K_6 + v)^3} + \frac{2k_9}{(K_6 + v)^2}, \\ f_{52}^{(3)}(v) &= \frac{6k_9 v}{(K_6 + v)^4} - \frac{6k_9}{(K_6 + v)^3}, f_{61}^{(2)}(v) = \frac{18k_{11}v^7}{(K_7^3 + v^3)^3} - \frac{24k_{11}v^4}{(K_7^3 + v^3)^2} + \frac{6k_{11}v}{K_7^3 + v^3}, \\ f_{61}^{(3)}(v) &= -\frac{162k_{11}v^9}{(K_7^3 + v^3)^4} + \frac{270k_{11}v^6}{(K_7^3 + v^3)^3} - \frac{114k_{11}v^3}{(K_7^3 + v^3)^2} + \frac{6k_{11}}{K_7^3 + v^3}, \\ f_{71}^{(2)}(q) &= \frac{2k_{12}(A - q)S}{(A + K_9 - q)^3(K_8 + S)} - \frac{2k_{12}S}{(A + K_9 - q)^2(K_8 + S)}, \\ f_{71}^{(3)}(q) &= \frac{6k_{12}(A - q)S}{(A + K_9 - q)^4(K_8 + S)} - \frac{6k_{12}S}{(A + K_9 - q)^3(K_8 + S)}, \\ f_{72}^{(2)}(q) &= -\frac{2k_{13}q}{(K_{10} + q)^3} + \frac{2k_{13}}{(K_{10} + q)^2}, \\ f_{72}^{(3)}(q) &= \frac{6k_{13}q}{(K_{10} + q)^4} - \frac{6k_{13}}{(K_{10} + q)^3}, \end{split}$$

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$$\begin{split} f_{73}^{(1)}(q) &= \frac{k_{14}q}{(K_{11}+q)^2} - \frac{k_{14}}{K_{11}+q}, \\ f_{73}^{(2)}(q) &= -\frac{2k_{14}q}{(K_{11}+q)^3} + \frac{2k_{14}}{(K_{11}+q)^2}, \\ f_{73}^{(3)}(q) &= \frac{6k_{14}q}{(K_{11}+q)^4} - \frac{6k_{14}}{(K_{11}+q)^3}. \end{split}$$

Let

$$U = (u_1(t), u_2(t), u_3(t), u_4(t), u_5(t), u_6(t), u_7(t))^T$$

= $(x(t), y(t), z(t), u(t), v(t), p(t), q(t))^T$

And define $C = C([-1, 0], \mathbb{R}^7)$, then (6.2) becomes to

$$\dot{U} = L_{\gamma}(U_t) + f(\gamma, U_t) \tag{5.10}$$

where $L_{\gamma}: C \to R^7, f: R \times C \to R^7$ whose specific form is as follows

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where $\phi = (\phi_1(t), \phi_2(t), \phi_3(t), \phi_4(t), \phi_5(t) \phi_6(t), \phi_7(t))^T \in C$. According to the Riesz representation theorem there exists a 7 × 7 matrix function $\eta(\theta, \gamma)$, which is bounded variogram on $\theta \in [-1, 0]$ such that $L_{\gamma}\phi = \int_{-1}^{0} d\eta(\theta, \gamma) \phi(\theta)$ for $\phi \in C([-1, 0], R^7)$.

In fact, we can choose

where $\delta(\theta)$ is Dirac delta function . And we define

$$\Lambda_{\gamma}\phi = \begin{cases} \frac{d\phi(\theta)}{d\theta}, \theta \in [-1,0), \\ \int_{-1}^{0} d\eta(\theta,\gamma)\phi(\theta), \theta = 0, \end{cases} \text{ and } R_{\gamma}\phi = \begin{cases} 0, \theta \in [-1,0), \\ f(\gamma,\phi), \theta = 0. \end{cases}$$
(5.14)

Obviously, we can transform (6.10) to the following form

$$\dot{U} = \Lambda_{\gamma} U_t + R_{\gamma} U_t \tag{5.15}$$

where $U_t(\theta) = U(t + \theta)$. For $\psi \in C^1([-1, 0], (R^7)^*)$, we define

$$\Lambda_{\gamma}^{*}\psi(s) = \begin{cases} \frac{-d\psi(s)}{ds}, \theta \in (0, -1], \\ \int_{-1}^{0} d\eta^{T}(t, \gamma)\psi(-t), s = 0, \end{cases}$$
(5.16)

and

$$\langle \psi(s), \phi(\theta) \rangle = \bar{\psi}(s) \phi(0) - \int_{-1}^{0} \int_{\xi=0}^{\theta} \bar{\psi}(\xi-\theta) d\eta(\theta) \phi(\xi) d\xi, \qquad (5.17)$$

which is a bilinear inner product. Obviously, Λ_0 and Λ_0^* are adjoint operators for each other. In addition, $\pm iw_0\tau_1^0$ are the eigenvalues of Λ_0 . Therefore, they are also eigenvalues of Λ_0^* . We let $q(\theta)$ be the eigenvector of Λ_0 corresponding to $iw_0\tau_1^0$ and $q^*(s)$ be the eigenvector of Λ_0^* corresponding to $-iw_0\tau_1^0$, which meet the following conditions

$$q(\theta) = e^{iw_0\tau_1^0\theta}(1, v_1, v_2, v_3, v_4, v_5, v_6)^T,$$

$$q^*(s) = Ge^{iw_0\tau_1^0s}(1, v_1^*, v_2^*, v_3^*, v_4^*, v_5^*, v_6^*).$$
(5.18)

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From $\Lambda_0 q(0) = iw_0 \tau_1^0 q(0)$ and $\Lambda_0^* q^*(0) = -iw_0 \tau_1^0 q^*(0)$, it is easy to deduce

$$\begin{aligned} v_1 &= -\frac{v_{11}}{v_{12}} \\ v_{11} &= (-c_{14}c_{17}c_{19}c_9 + c_6 (c_{16} - iw_0) (c_{18} - iw_0) (c_{20} - iw_0)) (c_{13} - iw_0) \\ v_{12} &= (-c_{15}c_{17}c_{19}c_9 + (c_{16} - iw_0) (c_{18} - iw_0) (c_{20} - iw_0) (c_7 - iw_0)) (c_{13} - iw_0) \\ -c_{12}c_8 (c_{16} - iw_0) (c_{18} - iw_0) (c_{20} - iw_0) \end{aligned}$$

$$v_{2} = -\frac{v_{21}}{v_{22}}$$

$$v_{21} = c_{10}$$

$$v_{22} = c_{11} - iw_{0}$$

$$\begin{split} v_3 &= -\frac{v_{31}}{v_{32}} \\ v_{31} &= c_{12} \left(c_9 c_{14} c_{17} c_{19} - c_6 c_{16} c_{18} c_{20} \right) + c_{12} (i c_6 c_{16} c_{18} + i c_6 c_{16} c_{20} \\ &+ i c_6 c_{18} c_{20} \right) w_0 + c_{12} \left(c_6 c_{16} + c_6 c_{18} + c_6 c_{20} \right) w_0^2 - i c_6 c_{12} w_0^3 \\ v_{32} &= -c_9 c_{13} c_{15} c_{17} c_{19} - c_8 c_{12} c_{16} c_{18} c_{20} + c_7 c_{13} c_{16} c_{18} c_{20} + \\ (i c_8 c_{12} c_{16} c_{18} - i c_7 c_{13} c_{16} c_{18} + i c_9 c_{15} c_{17} c_{19} + i c_8 c_{12} c_{16} c_{20} - \\ i c_7 c_{13} c_{16} c_{20} + i c_8 c_{12} c_{16} c_{20} - i c_7 c_{13} c_{16} c_{18} c_{20} - i c_7 c_{13} c_{16} c_{18} c_{20} - \\ i c_{13} c_{16} c_{18} c_{20} \right) w_0 + \left(c_8 c_{12} c_{16} - c_7 c_{13} c_{16} + c_8 c_{12} c_{18} - c_7 c_{13} c_{16} c_{20} - \\ - c_7 c_{16} c_{18} - c_{13} c_{16} c_{18} + c_8 c_{12} c_{20} - c_7 c_{13} c_{20} - c_7 c_{16} c_{20} - \\ - c_7 c_{16} c_{20} - c_{13} c_{18} c_{20} - c_{16} c_{18} c_{20} \right) w_0^2 + \left(-i c_8 c_{12} + i c_7 c_{13} + i c_7 c_{16} \right) \\ + i c_{13} c_{16} + i c_7 c_{18} + i c_{13} c_{18} + i c_{16} c_{18} + i c_7 c_{20} + i c_{13} c_{20} + i c_{16} c_{20} + \\ i c_{18} c_{20} \right) w_0^3 + \left(c_7 + c_{13} + c_{16} + c_{18} + c_{20} \right) w_0^4 - i w_0^5 \end{split}$$

 $\begin{aligned} v_4 &= -\frac{v_{41}}{v_{42}} \\ v_{41} &= w_0^4 c_{14} - c_8 c_{12} c_{14} c_{18} c_{20} + c_7 c_{13} c_{14} c_{18} c_{20} - c_6 c_{13} c_{15} c_{18} c_{20} + \\ w_0^2 (c_8 c_{12} c_{14} - c_7 c_{13} c_{14} + c_6 c_{13} c_{15} - c_7 c_{14} c_{18} - c_{13} c_{14} c_{18} + c_6 c_{15} c_{18} \\ -c_7 c_{14} c_{20} - c_{13} c_{14} c_{20} + c_6 c_{15} c_{20} - c_{14} c_{18} c_{20}) + w_0^3 (c_7 c_{14} + c_{13} c_{14} \\ -c_6 c_{15} + c_{14} c_{18} + c_{14} c_{20}) \mathbf{i} + w_0 (c_8 c_{12} c_{14} c_{18} - c_7 c_{13} c_{14} c_{18} + \\ c_6 c_{13} c_{15} c_{18} + c_8 c_{12} c_{14} c_{20} - c_7 c_{13} c_{14} c_{20} + c_6 c_{13} c_{15} c_{20} - c_7 c_{14} c_{18} c_{20} \\ -c_{13} c_{14} c_{18} c_{20} + c_6 c_{15} c_{18} c_{20}) \mathbf{i} \\ v_{42} &= -\mathbf{i} w_0^5 - c_9 c_{13} c_{15} c_{17} c_{19} - c_8 c_{12} c_{16} c_{18} c_{20} + c_7 c_{13} c_{16} c_{18} c_{20} + \\ w_0^4 (c_7 + c_{13} + c_{16} + c_{18} + c_{20}) + w_0^3 (- c_8 c_{12} + c_7 c_{13} + c_7 c_{16} + \\ c_{13} c_{16} + c_7 c_{18} + c_{13} c_{18} + c_{16} c_{18} + c_7 c_{20} + c_{13} c_{20} + c_{16} c_{20} + c_{18} c_{20}) \mathbf{i} \\ + w_0^2 (c_8 c_{12} c_{16} - c_7 c_{13} c_{16} + c_8 c_{12} c_{18} - c_7 c_{13} c_{16} c_{18} - c_{7} c_{16} c_{18} - c_{13} c_{16} c_{18} \\ + c_8 c_{12} c_{20} - c_7 c_{13} c_{20} - c_7 c_{13} c_{16} c_{18} + c_9 c_{15} c_{17} c_{19} + c_8 c_{12} c_{16} c_{20} \\ -c_{16} c_{18} c_{20}) + w_0 (c_8 c_{12} c_{16} c_{18} - c_7 c_{13} c_{16} c_{18} + c_9 c_{15} c_{17} c_{19} + c_8 c_{12} c_{16} c_{20} \\ -c_7 c_{13} c_{16} c_{20} + c_8 c_{12} c_{18} c_{20} - c_7 c_{13} c_{16} c_{18} + c_9 c_{15} c_{17} c_{19} + c_8 c_{12} c_{16} c_{20} \\ -c_7 c_{13} c_{16} c_{20} + c_8 c_{12} c_{18} c_{20} - c_7 c_{13} c_{16} c_{18} c_{20} - c_{13} c_{16} c_{18} c_{20} - c_{13} c_{16} c_{18} c_{20} \\ -c_7 c_{13} c_{16} c_{20} + c_8 c_{12} c_{18} c_{20} - c_7 c_{13} c_{16} c_{18} c_{20} - c_7 c_{13} c_{16} c_{18} c_{20} - c_{13} c_{16} c_{18} c_{20} - c_{13} c_{16} c_{18} c_{20} \\ -c_7 c_{13} c_{16} c_{20} + c_8 c_{12} c_{18} c_{20} - c_7 c_{13} c_{16} c_{18} c_{20} - c_7$

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 $v_5 = -\frac{v_{51}}{v_{61}}$ $v_51 = -w_0^3 c_{14} c_{17} + (-c_6 c_{15} c_{17} c_{20} + c_7 c_{13} c_{14} c_{17} - c_6 c_{13} c_{15} c_{17}$ $+c_{13}c_{14}c_{17}c_{20} - c_8c_{12}c_{14}c_{17})w_0 - c_{14}c_{17}c_{20} + iw_0^2(c_6c_{15}c_{17} - c_{14}c_{17}c_{20})w_0 - c_{14}c_{17}c_{20})w_0 + iw_0^2(c_6c_{15}c_{17} - c_{14}c_{17}c_{20})w_0 - c_{14}c_{17}c_{20})w_0 + iw_0^2(c_6c_{15}c_{17} - c_{14}c_{17}c_{17})w_0 + iw_0^2(c_6c_{17}c_{17}c_{17})w_0 + iw_0^2(c_6c_{17}c_{17}c_{17})w_0 + iw_0^2(c_6c_{17}c_{17}c_{17})w_0 + iw_0^2(c_6c_{17}c_{17}c_{17})w_0 + iw_0^2(c_6c_{17}c_{17}c_{17})w_0 + iw_0^2(c_6c_{17}c_{17}c_{17})w_0 + iw_0^2($ $c_{13}c_{14}c_{17} - c_{14}c_{17}c_{20} - c_{7}c_{14}c_{17}) + i(c_{7}c_{13}c_{14}c_{17}c_{20} - c_{8}c_{12}c_{14}c_{17}c_{20})$ $-c_6c_{13}c_{15}c_{17}c_{20}$ $v52 = -w_0^5 + w_0^3(c_7c_{13} + c_7c_{16} - c_8c_{12} + c_7c_{18} + c_7c_{20} + c_{13}c_{20} + c_{13}c_{20}$ $c_{16}c_{20} + c_{13}c_{16} + c_{13}c_{18} + c_{16}c_{18} + c_{18}c_{20}) + w_0(c_8c_{12}c_{16}c_{18} - c_7c_{13}c_{16}c_{18})$ $+c_9c_{15}c_{17}c_{19} + c_8c_{12}c_{16}c_{20} - c_7c_{13}c_{16}c_{20} + c_8c_{12}c_{18}c_{20} - c_7c_{13}c_{18}c_{20}$ $-c_7c_{16}c_{18}c_{20}) - iw_0^4(c_7 + c_{13} + c_{16} + c_{18} + c_{20}) + iw_0^2(c_7c_{13}c_{16} - c_{16}c_{18}c_{20}) + iw_0^2(c_7c_{13}c_{16}c_{18}c_{20}) + iw_0^2(c_7c_{13}c_{16}c_{18}c_{20}) + iw_0^2(c_7c_{13}c_{16}c_{18}c_{20}) + iw_0^2(c_7c_{13}c_{16}c_{18}c_{20}) + iw_0^2(c_7c_{13}c_{16}c_{18}c_{20}) + iw_0^2(c_7c_{13}c_{16}c_{20}c_{20}c_{20}c_{20}) + iw_0^2(c_7c_{13}c_{20$ $c_{8}c_{12}c_{16} - c_{8}c_{12}c_{18} + c_{7}c_{13}c_{18} + c_{7}c_{16}c_{18} + c_{13}c_{16}c_{18} + c_{7}c_{16}c_{20}$ $+c_{13}c_{16}c_{20} + c_{7}c_{18}c_{20} + c_{13}c_{18}c_{20} + c_{16}c_{18}c_{20} - c_{8}c_{12}c_{20} + c_{7}c_{13}c_{20})$ $+i(c_8c_{12}c_{16}c_{18}c_{20} - c_{13}c_{16}c_{18}c_{20} - c_7c_{13}c_{16}c_{18}c_{20} + c_9c_{13}c_{15}c_{17}c_{19})$ $v61 = w_0(c_6c_{15}c_{17}c_{19} - c_7c_{14}c_{17}c_{19} - c_{13}c_{14}c_{17}c_{19}) + i(w_0^2c_{14}c_{17}c_{19})$ $+c_8c_{12}c_{14}c_{17}c_{19} - c_7c_{13}c_{14}c_{17}c_{19} + c_6c_{13}c_{15}c_{17}c_{19})$ $v62 = -w_0^5 + w_0^3(c_{13}c_{16} - c_8c_{12} + c_7c_{13} + c_7c_{16} + c_7c_{18} + c_{13}c_{18} + c_{13}c_{1$ $c_{16}c_{18} + c_7c_{20} + c_{13}c_{20} + c_{16}c_{20} + c_{18}c_{20}) + w_0(c_8c_{12}c_{16}c_{18} - c_7c_{13}c_{16}c_{18})$ $+c_8c_{12}c_{16}c_{20} + c_9c_{15}c_{17}c_{19} + c_8c_{12}c_{18}c_{20} - c_7c_{13}c_{16}c_{20} - c_7c_{13}c_{18}c_{20}$

 $-c_7c_{16}c_{18}c_{20} - c_{13}c_{16}c_{18}c_{20}) - iw_0^4(c_7 + c_{13} + c_{16} + c_{18} + c_{20})$

 $+iw_0^2(c_7c_{13}c_{16} - c_8c_{12}c_{16} - c_8c_{12}c_{18} + c_7c_{13}c_{18} + c_7c_{16}c_{18} + c_{13}c_{16}c_{18} - c_8c_{12}c_{20} + c_7c_{13}c_{20} + c_7c_{16}c_{20} + c_{13}c_{16}c_{20} + c_7c_{18}c_{20} + c_{13}c_{18}c_{20} + c_{16}c_{18}c_{20} + i(c_8c_{12}c_{16}c_{18}c_{20} - c_7c_{13}c_{16}c_{18}c_{20} + c_9c_{13}c_{15}c_{17}c_{19})$

 $\begin{aligned} v_1^* &= -\frac{V11}{V12} \\ V11 &= (c_{13} + iw_0) \left(-c_5 c_{15} c_{17} c_{19} - (c_{18} + iw_0) (c_{20} + iw_0) \left(c_4 c_{15} e^{i\tau_1^0 w_0} - c_2 (c_{16} + iw_0) \right) \right) \\ V12 &= (-c_9 c_{15} c_{17} c_{19} + (c_7 + iw_0) (c_{16} + iw_0) (c_{18} + iw_0) (c_{20} + iw_0)) (c_{13} + iw_0) \\ -c_8 c_{12} (c_{16} + iw_0) (c_{18} + iw_0) (c_{20} + iw_0) \end{aligned}$

$$v_2^* = -\frac{c_3}{c_{11} + iw_0}$$

$$\begin{split} v_3^* &= -\frac{V31}{V32} \\ V31 &= c_8(ic_4c_{15}w_0^2e^{i\tau_1^0w_0} + c_4c_{15}c_{18}w_0e^{i\tau_1^0w_0} + c_4c_{15}c_{20}w_0e^{i\tau_1^0w_0} - ic_4c_{15}c_{18}c_{20}e^{i\tau_1^0w_0} + c_2w_0^3 \\ -ic_2c_{16}w_0^2 - ic_2c_{18}w_0^2 - ic_2c_{20}w_0^2 - c_2c_{16}c_{18}w_0 - c_2c_{16}c_{20}w_0 - c_2c_{18}c_{20}w_0 - ic_5c_{15}c_{17}c_{19} \\ +ic_2c_{16}c_{18}c_{20}) \\ V32 &= -ic_7w_0^4 - ic_{13}w_0^4 - ic_{16}w_0^4 - ic_{18}w_0^4 - ic_{20}w_0^4 + c_8c_{12}w_0^3 - c_7c_{13}w_0^3 - c_{7}c_{16}w_0^3 - c_{13}c_{16}w_0^3 \\ -c_7c_{18}w_0^3 - c_{13}c_{18}w_0^3 - c_{16}c_{18}w_0^3 - c_{7}c_{20}w_0^3 - c_{13}c_{20}w_0^3 - c_{16}c_{20}w_0^3 - c_{18}c_{20}w_0^3 - ic_8c_{12}c_{16}w_0^2 \\ +ic_7c_{13}c_{16}w_0^2 - ic_8c_{12}c_{18}w_0^2 + ic_7c_{13}c_{18}w_0^2 + ic_7c_{16}c_{18}w_0^2 + ic_{13}c_{16}c_{18}w_0^2 - ic_8c_{12}c_{20}w_0^2 \\ +ic_7c_{13}c_{20}w_0^2 + ic_7c_{16}c_{20}w_0^2 + ic_{13}c_{16}c_{20}w_0^2 + ic_{13}c_{16}c_{20}w_0^2 + ic_{13}c_{16}c_{20}w_0^2 \\ -c_8c_{12}c_{16}c_{18}w_0 + c_7c_{13}c_{16}c_{18}w_0 - c_{9}c_{15}c_{17}c_{19}w_0 - c_8c_{12}c_{16}c_{20}w_0 + c_{7}c_{13}c_{16}c_{20}w_0 - c_8c_{12}c_{16}c_{18}c_{20}w - c_8c_{12}c_{16}c_{18}c_{20}w_0 + c_{7}c_{13}c_{16}c_{20}w_0 + c_{13}c_{16}c_{18}c_{20}w_0 + ic_{9}c_{13}c_{15}c_{17}c_{19} + ic_{8}c_{12}c_{16}c_{18}c_{20} \\ -ic_7c_{13}c_{16}c_{18}c_{20} + w_0^5 \end{split}$$

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$$\begin{split} & V41 = ic_4 w_0^4 e^{ir_1^0 w_0} + c_4 c_7 w_0^3 e^{ir_1^0 w_0} + c_4 c_{13} w_0^3 e^{ir_1^0 w_0} + c_4 c_{18} w_0^3 e^{ir_1^0 w_0} + c_4 c_{20} w_0^3 e^{ir_1^0 w_0} \\ & + ic_4 c_8 c_{12} w_0^2 e^{ir_1^0 w_0} - ic_4 c_7 c_{13} w_0^2 e^{ir_1^0 w_0} - ic_4 c_7 c_{18} w_0^2 e^{ir_1^0 w_0} - ic_4 c_{13} c_{18} w_0 e^{ir_1^0 w_0} \\ & - ic_4 c_7 c_{20} w_0^2 e^{ir_1^0 w_0} + c_4 c_8 c_{12} c_{20} w_0 e^{ir_1^0 w_0} - c_4 c_7 c_{13} c_{20} w_0 e^{ir_1^0 w_0} \\ & - c_4 c_7 c_{13} c_{18} w_0 e^{ir_1^0 w_0} + c_4 c_8 c_{12} c_{20} w_0 e^{ir_1^0 w_0} - c_4 c_7 c_{13} c_{20} w_0 e^{ir_1^0 w_0} - c_4 c_7 c_{13} c_{20} w_0 e^{ir_1^0 w_0} \\ & - c_4 c_7 c_{13} c_{18} c_{20} w_0 e^{ir_1^0 w_0} - ic_4 c_8 c_{12} c_{18} c_{20} e^{ir_1^0 w_0} + ic_4 c_7 c_{13} c_{18} c_{20} e^{ir_1^0 w_0} - ic_5 c_1 c_{19} w_0^2 \\ & - c_4 c_{13} c_{18} c_{20} w_0 e^{ir_1^0 w_0} - ic_4 c_8 c_{12} c_{18} c_{20} e^{ir_1^0 w_0} + ic_4 c_7 c_{13} c_{18} c_{20} e^{ir_1^0 w_0} - ic_5 c_1 c_{17} c_{19} w_0^2 \\ & - c_5 c_7 c_{17} c_{19} w_0 + c_2 c_{9} c_{17} c_{19} w_0 - c_5 c_{13} c_{17} c_{19} w_0 - ic_5 c_8 c_{12} c_{17} c_{19} + ic_5 c_7 c_{13} c_{17} c_{19} \\ & - ic_2 c_9 c_{13} c_{17} c_{19}, \\ V42 &= ic_7 w_0^4 + ic_{13} w_0^4 + ic_{16} w_0^4 + ic_{18} w_0^4 + ic_{20} w_0^4 - c_8 c_{12} w_0^3 + c_7 c_{13} w_0^3 + c_7 c_{16} w_0^3 + c_{13} c_{16} w_0^3 \\ & + c_7 c_{18} w_0^3 + c_{13} c_{18} w_0^3 + c_{16} c_{18} w_0^3 + c_7 c_{20} w_0^3 + c_{16} c_{20} w_0^3 + c_{16} c_{20} w_0^3 + c_{16} c_{20} w_0^2 \\ & - ic_7 c_{13} c_{16} w_0^2 + ic_8 c_{12} c_{18} w_0^3 - ic_7 c_{13} c_{16} c_{20} w_0^2 - ic_{13} c_{16} c_{18} w_0^2 + ic_8 c_{12} c_{20} w_0^2 \\ & - ic_7 c_{13} c_{20} w_0^2 - ic_7 c_{13} c_{16} c_{20} w_0^2 - ic_7 c_{16} c_{18} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0^2 \\ & - ic_7 c_{13} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 - c_7 c_{16} c_{18} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 \\ & - ic_7 c_{13} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 \\ & - ic_7 c_{13} c_{16} c_{18} w_0 - c_7 c_{13} c_{16} c_{20$$

 $v_5^* = -\frac{V51}{V52}$

$$\begin{split} V51 &= c_4 c_9 c_{15} c_{19} w_0 e^{i\tau_1^0 w_0} - ic_4 c_9 c_{13} c_{15} c_{19} e^{i\tau_1^0 w_0} - c_5 c_{19} w_0^3 + ic_5 c_7 c_{19} w_0^2 - ic_2 c_9 c_{19} w_0^2 \\ &+ ic_5 c_{13} c_{19} w_0^2 + ic_5 c_{16} c_{19} w_0^2 - c_5 c_8 c_{12} c_{19} w_0 + c_5 c_7 c_{13} c_{19} w_0 - c_2 c_9 c_{13} c_{19} w_0 + c_5 c_7 c_{16} c_{19} w_0 \\ &- c_2 c_9 c_{16} c_{19} w_0 + c_5 c_{13} c_{16} c_{19} w_0 + ic_5 c_8 c_{12} c_{16} c_{19} - ic_5 c_7 c_{13} c_{16} c_{19} + ic_2 c_9 c_{13} c_{16} c_{19} \\ &V52 &= ic_7 w_0^4 + ic_{13} w_0^4 + ic_{16} w_0^4 + ic_{18} w_0^4 + ic_{20} w_0^4 - c_8 c_{12} w_0^3 + c_7 c_{13} w_0^3 + c_7 c_{16} w_0^3 \\ &+ c_{13} c_{16} w_0^3 + c_7 c_{18} w_0^3 + c_{13} c_{18} w_0^3 + c_{16} c_{18} w_0^3 + c_7 c_{20} w_0^3 + c_{13} c_{20} w_0^3 + c_{16} c_{20} w_0^3 \\ &+ c_{13} c_{16} c_{18} w_0^2 + ic_8 c_{12} c_{16} w_0^2 - ic_7 c_{13} c_{16} w_0^2 + ic_8 c_{12} c_{18} w_0^2 - ic_7 c_{13} c_{16} c_{20} w_0^2 \\ &- ic_{13} c_{16} c_{18} w_0^2 + ic_8 c_{12} c_{20} w_0^2 - ic_7 c_{13} c_{20} w_0^2 - ic_7 c_{13} c_{16} c_{20} w_0^2 - ic_7 c_{18} c_{20} w_0^2 \\ &- ic_{13} c_{16} c_{18} w_0^2 + ic_8 c_{12} c_{20} w_0^2 + c_8 c_{12} c_{16} c_{18} w_0 - c_7 c_{13} c_{16} c_{20} w_0^2 - ic_7 c_{13} c_{16} c_{20} w_0^2 \\ &- c_{13} c_{16} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 + c_8 c_{12} c_{18} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 \\ &+ c_8 c_{12} c_{16} c_{20} w_0 - c_7 c_{13} c_{16} c_{20} w_0 + c_8 c_{12} c_{18} c_{20} w_0 - c_7 c_{13} c_{16} c_{18} c_{20} w_0 \\ &- c_{13} c_{16} c_{18} c_{20} w_0 - ic_9 c_{13} c_{15} c_{17} c_{19} - ic_8 c_{12} c_{16} c_{18} c_{20} + ic_7 c_{13} c_{16} c_{18} c_{20} - w_0^5, \end{split}$$

$v_6^* = -\frac{V61}{V62}$

$$\begin{split} &V61 = -c_4c_9c_{15}w_0^2e^{ir_1^0w_0} + ic_4c_9c_{13}c_{15}w_0e^{ir_1^0w_0} + ic_4c_9c_{15}c_{18}w_0e^{ir_1^0w_0} + c_4c_9c_{13}c_{15}c_{18}e^{ir_1^0w_0} \\ &+c_5w_0^4 - ic_5c_7w_0^3 + ic_2c_9w_0^3 - ic_5c_{13}w_0^3 - ic_5c_{16}w_0^3 - ic_5c_{18}w_0^3 + c_5c_8c_{12}w_0^2 - c_5c_7c_{13}w_0^2 \\ &+c_2c_9c_{13}w_0^2 - c_5c_7c_{16}w_0^2 + c_2c_9c_{16}w_0^2 - c_5c_{13}c_{16}w_0^2 - c_5c_{7}c_{18}w_0^2 + c_2c_9c_{18}w_0^2 - c_5c_{13}c_{18}w_0^2 \\ &-c_5c_{16}c_{18}w_0^2 - ic_5c_8c_{12}c_{16}w_0 + ic_5c_{7}c_{13}c_{16}w_0 - ic_2c_9c_{13}c_{16}w_0 - ic_5c_8c_{12}c_{16}c_{18} \\ &-ic_2c_9c_{13}c_{18}w_0 + ic_5c_{7}c_{16}c_{18}w_0 - ic_2c_9c_{16}c_{18}w_0 + ic_5c_{13}c_{16}c_{18}w_0 - c_5c_8c_{12}c_{16}c_{18} + c_5c_{7}c_{13}c_{16}c_{18} \\ &-c_2c_9c_{13}c_{16}c_{18}, \\ V62 &= c_7w_0^4 + c_{13}w_0^4 + c_{16}w_0^4 + c_{18}w_0^4 + c_{20}w_0^4 + ic_8c_{12}w_0^3 - ic_{7}c_{13}w_0^3 - ic_{7}c_{16}w_0^3 - ic_{13}c_{16}w_0^3 \\ &-ic_7c_{18}w_0^3 - ic_{13}c_{18}w_0^3 - ic_{16}c_{18}w_0^3 - ic_{7}c_{20}w_0^3 - ic_{13}c_{20}w_0^3 - ic_{16}c_{20}w_0^3 - ic_{18}c_{20}w_0^3 + c_8c_{12}c_{16}w_0^2 \\ &-c_{7}c_{13}c_{16}w_0^2 + c_8c_{12}c_{18}w_0^2 - c_{7}c_{13}c_{18}c_{20}w_0^2 - c_{13}c_{16}c_{18}w_0^2 - c_{13}c_{16}c_{18}w_0 \\ &+ic_{7}c_{13}c_{16}c_{18}w_0 - ic_{9}c_{15}c_{17}c_{19}w_0 - ic_{8}c_{12}c_{16}c_{20}w_0 + ic_{7}c_{13}c_{16}c_{20}w_0 - ic_{8}c_{12}c_{16}c_{18}c_{20}w_0 \\ &+ic_{7}c_{13}c_{16}c_{18}c_{20}w + ic_{7}c_{13}c_{16}c_{18}c_{20}w_0 - ic_{8}c_{12}c_{16}c_{18}c_{20}w_0 \\ &+ic_{7}c_{13}c_{16}c_{18}c_{20}w + ic_{7}c_{13}c_{16}c_{18}c_{20}w_0 + ic_{13}c_{16}c_{18}c_{20}w_0 - ic_{8}c_{12}c_{16}c_{18}c_{20}w_0 \\ &+ic_{7}c_{13}c_{16}c_{18}c_{20}w + ic_{7}c_{13}c_{16}c_{18}c_{20}w_0 \\ &+ic_{7}c_{13}c_{16}c_$$

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From

 $\frac{1}{(1+\bar{v}_1v_1^*+\bar{v}_2v_2^*+\bar{v}_3v_3^*+\bar{v}_4v_4^*+\bar{v}_5v_5^*+\bar{v}_6v_6^*)+\tau_1^0e^{iv_0\tau_1^0}c_4v_4}}$ The above \bar{v}_1 and \bar{v}_1^* represent the conjugate plural of v_1 and v_1^* respectively and the other analogy. Next we will compute the coordinate to describe the center manifold C_0 at $\gamma = 0$ using the way of Hassard et al[56].

We let U_t be the solution of (6.15) at at $\gamma = 0$ and define

$$z(t) = \langle q^*, x_t \rangle$$

$$W(t, \theta) = U_t(\theta) - 2\operatorname{Re}\left\{z(t) q(\theta)\right\}.$$
(5.19)

On the center manifold C_0 , we can regard $W(t, \theta)$ as

$$W(z,\bar{z},\theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots$$
(5.20)

In fact, z(t) and $\bar{z}(t)$ are local coordinates for center manifold C_0 in the direction of q^* and \bar{q}^* . It is easy to know that $W(t, \theta)$ is real only when $U_t(\theta)$ is real. We just consider it is a real solution of (6.10), and then

$$\begin{aligned} \dot{z}(t) &= \left\langle q^*, \dot{U}_t \right\rangle \\ &= \left\langle q^*, \Lambda_0 U_t + R_0 U_t \right\rangle \\ &= \left\langle \Lambda_0^* q^*, U_t \right\rangle + \left\langle q^*, f(0, U_t) \right\rangle \\ &= i w_0 \tau_1^0 z + \bar{q}^* \left(0 \right) f(0, W(z, \bar{z}, \theta) + 2Re\left\{ z\left(t \right) q\left(\theta \right) \right\} \right) \\ &= i w_0 \tau_1^0 z + \bar{q}^* \left(0 \right) f_0, \end{aligned}$$
(5.21)

$$f_0 = f(0, W(z, \bar{z}, \theta) + 2Re\{z(t) q(\theta)\})$$
(5.22)

$$\dot{z}(t) = iw_0 \tau_1^0 z + g(z, \bar{z}),$$
(5.23)

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where

$$g(z,\bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots$$
 (5.24)

The following formula can be obtained from equations (6.19) and (6.20).

$$U_{t} = W(t,\theta) + 2Re \{z(t) q(\theta)\}$$

= $W_{20}(\theta) \frac{z^{2}}{2} + W_{11}(\theta) z\bar{z} + W_{02}(\theta) \frac{\bar{z}^{2}}{2} + zq + \bar{z}\bar{q} \cdots$
= $W_{20}(\theta) \frac{z^{2}}{2} + W_{11}(\theta) z\bar{z} + W_{02}(\theta) \frac{\bar{z}^{2}}{2} + e^{iw_{0}\tau_{1}^{0}\theta}(1, v_{1}, v_{2}, v_{3}, v_{4}, v_{5}, v_{6})^{T}z$
+ $e^{-iw_{0}\tau_{1}^{0}\theta}(1, \bar{v}_{1}, \bar{v}_{2}, \bar{v}_{3}, \bar{v}_{4}, \bar{v}_{5}, \bar{v}_{6})^{T}\bar{z} + \cdots$ (5.25)

Combined with (6.12), (6.22), (6.25), we have

$$\begin{split} g(z,\bar{z}) &= \bar{q}^{*}\left(0\right) f_{0} \\ &= \bar{q}^{*}\left(0\right) f\left(0, U_{l}\right) \\ &= \bar{G}\tau_{1}^{0}\left(1, \bar{v}_{1}^{*}, \bar{v}_{2}^{*}, \bar{v}_{3}^{*}, \bar{v}_{4}^{*}, \bar{v}_{5}^{*}, \bar{v}_{6}^{*}\right) \times \\ \left(\begin{array}{c} \sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{11}^{(i)}(v^{*})\phi_{5}(-1)^{i} + f_{12}^{(i)}(y^{*})\phi_{2}^{i}(0) + \right. \\ &f_{13}^{(i)}(x^{*})q^{*}\phi_{1}^{i}(0) + if_{13}^{(i-1)}(x^{*})\phi_{7}(0)\phi_{1}^{i-1}(0) \right] \\ \sum_{i=2}^{\infty} \frac{1}{i!} \left[-f_{13}^{(i)}(x^{*})q^{*}\phi_{1}^{i}(0) - if_{13}^{(i-1)}(x^{*})\phi_{7}(0)\phi_{1}^{i-1}(0) + f_{12}^{(i)}(y^{*})\phi_{2}^{i}(0) \right] \\ &0 \\ 0 \\ \sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{51}^{(i)}(v^{*})x^{*}\phi_{5}^{i}(0) + if_{51}^{(i-1)}(v^{*})\phi_{1}(0)\phi_{5}^{i-1}(0) \right] \\ &\sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{61}^{(i)}(v^{*})y^{*}\phi_{5}^{i}(0) + if_{52}^{(i-1)}(v^{*})\phi_{2}(0)\phi_{5}^{i-1}(0) \right] \\ &\sum_{i=2}^{\infty} \frac{1}{i!} \left[f_{71}^{(i)}(q^{*})\phi_{7}^{i}(0) + f_{72}^{(i)}(q^{*})\phi_{7}^{i}(0) + f_{73}^{(i)}(q^{*})p^{*}\phi_{7}^{i}(0) + if_{73}^{(i-1)}(q^{*})\phi_{6}(0)\phi_{7}^{i-1}(0) \right] \end{split}$$

Comparing the coefficients with equation (6.24), we obtain

$$g_{20} = \bar{G}\tau_{1}^{0} \left[f_{13}^{(2)}(x^{*})q^{*} + f_{12}^{(2)}(y^{*})v_{1}^{2} - f_{13}^{(2)}(x^{*})q^{*}\bar{v}_{1}^{*} - f_{12}^{(2)}(y^{*})v_{1}^{2}\bar{v}_{1}^{*} \right. \\ \left. + e^{-2i\tau_{1}^{0}w_{0}}f_{11}^{(2)}(v^{*})v_{4}^{2} + 2f_{51}^{(1)}(v^{*})v_{4}\bar{v}_{4}^{*} + 2f_{52}^{(1)}(v^{*})v_{1}v_{4}\bar{v}_{4}^{*} + f_{61}^{(2)}(v^{*})v_{4}^{2}\bar{v}_{5}^{*} \\ \left. + 2f_{13}^{(1)}(x^{*})v_{6} - 2f_{13}^{(1)}(x^{*})\bar{v}_{1}^{*}v_{6} + 2f_{73}^{(1)}(q^{*})v_{5}v_{6}\bar{v}_{6}^{*} + f_{71}^{(2)}(q^{*})v_{6}^{2}\bar{v}_{6}^{*} + \\ \left. f_{72}^{(2)}(q^{*})v_{6}^{2}\bar{v}_{6}^{*} + f_{73}^{(2)}(q^{*})p^{*}v_{6}^{2}\bar{v}_{6}^{*} + f_{51}^{(2)}(v^{*})v_{4}^{2}\bar{v}_{4}^{*}x^{*} + f_{52}^{(2)}(v^{*})v_{4}^{2}\bar{v}_{4}^{*}y^{*} \right]$$

$$g_{11} = \bar{G}\tau_1^0 [f_{13}^{(2)}(x^*)q^* + f_{12}^{(2)}(y^*)v_1\bar{v}_1^* - f_{13}^{(2)}(x^*)q^*\bar{v}_1^* - f_{12}^{(2)}(y^*)v_1\bar{v}_1\bar{v}_1^*$$

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$$+ f_{11}^{(2)}(v^{*})v_{4}\bar{v}_{4} + f_{51}^{(1)}(v^{*})v_{4}\bar{v}_{4}^{*} + f_{52}^{(1)}(v^{*})\bar{v}_{1}v_{4}\bar{v}_{4}^{*} + f_{51}^{(1)}(v^{*})\bar{v}_{4}\bar{v}_{4}^{*} + f_{51}^{(1)}(v^{*})\bar{v}_{4}\bar{v}_{4}^{*} + f_{52}^{(1)}(v^{*})v_{1}\bar{v}_{4}\bar{v}_{4}^{*} + f_{51}^{(2)}(v^{*})v_{1}\bar{v}_{4}\bar{v}_{4}^{*} + f_{51}^{(2)}(v^{*})v_{1}\bar{v}_{4}\bar{v}_{4}^{*} + f_{51}^{(2)}(v^{*})v_{4}\bar{v}_{4}\bar{v}_{5}^{*} + f_{13}^{(1)}(x^{*})v_{6} - f_{13}^{(1)}(x^{*})\bar{v}_{1}v_{6} + f_{13}^{(1)}(x^{*})\bar{v}_{6} - f_{13}^{(1)}(x^{*})\bar{v}_{1}\bar{v}_{6} + f_{73}^{(1)}(q^{*})\bar{v}_{5}v_{6}\bar{v}_{6}^{*} + f_{71}^{(2)}(q^{*})v_{6}\bar{v}_{6}\bar{v}_{6}^{*} + f_{71}^{(2)}(q^{*})v_{5}\bar{v}_{6}\bar{v}_{6}^{*} + f_{71}^{(2)}(q^{*})v_{6}\bar{v}_{6}\bar{v}_{6}^{*} + f_{72}^{(2)}(q^{*})v_{4}\bar{v}_{4}\bar{v}_{4}x^{*} + f_{52}^{(2)}(v^{*})v_{4}\bar{v}_{4}\bar{v}_{4}\bar{v}_{4}x^{*} + f_{52}^{(2)}(v^{*})v_{4}\bar{v}_{4}\bar{v}_{4}\bar{v}_{4}x^{*} + f_{52}^{(2)}(v^{*})\bar{v}_{1}\bar{v}_{4}\bar{v}_{5}\bar{v}_{5}\bar{v}_{5}\bar{v}_{6$$

$$\begin{split} g_{21} &= \bar{G}\tau_{1}^{0} \Big[f_{13}^{(3)}(x^{*})q^{*} + f_{12}^{(3)}(y^{*})v_{1}^{2}\bar{v}_{1} - f_{13}^{(3)}(x^{*})\bar{v}_{1}^{*}q^{*} - f_{12}^{(3)}(y^{*})v_{1}^{2}\bar{v}_{1}\bar{v}_{1} \\ &+ e^{-ir_{1}^{0}w_{0}}f_{11}^{(3)}(v^{*})v_{4}^{2}\bar{v}_{4} + f_{51}^{(2)}(v^{*})v_{4}^{2}\bar{v}_{4}^{*} + f_{52}^{(2)}(v^{*})\bar{v}_{1}v_{4}^{2}\bar{v}_{4}^{*} + 2f_{51}^{(2)}(v^{*})v_{4}\bar{v}_{4}\bar{v}_{4}^{*} \\ &+ 2f_{52}^{(2)}(v^{*})v_{1}v_{4}\bar{v}_{4}\bar{v}_{4}^{*} + f_{61}^{(3)}(v^{*})v_{4}^{2}\bar{v}_{4}\bar{v}_{5}^{*} + 2f_{13}^{(2)}(x^{*})v_{6} - 2f_{12}^{(2)}(x^{*})\bar{v}_{6}\bar{v}_{6}^{*} \\ &f_{13}^{(2)}(x^{*})\bar{v}_{6} - f_{13}^{(2)}(x^{*})\bar{v}_{6}\bar{v}_{7}^{*} + f_{73}^{(2)}(q^{*})\bar{v}_{5}v_{6}^{*}\bar{v}_{6}^{*} + 2f_{73}^{(2)}(q^{*})v_{5}v_{6}\bar{v}_{6}^{*} + \\ &f_{13}^{(3)}(q^{*})v_{6}^{2}\bar{v}_{6}\bar{v}_{6}^{*} + f_{73}^{(3)}(q^{*})v_{6}^{2}\bar{v}_{6}\bar{v}_{6}^{*} + 2f_{13}^{(2)}(x^{*})q^{*}w_{11}^{1}(0) \\ &- 2f_{13}^{(2)}(x^{*})q^{*}\bar{v}_{1}^{*}w_{11}^{1}(0) + 2f_{12}^{(1)}(v^{*})v_{4}\bar{v}_{4}w_{11}^{1}(0) + 2f_{13}^{(1)}(x^{*})v_{6}w_{11}^{*}(0) + \\ &2f_{13}^{(1)}(x^{*})v_{6}\bar{v}_{1}^{*}w_{11}^{*}(0) + 2f_{12}^{(2)}(y^{*})v_{1}w_{1}^{*}w_{11}^{*}(0) + 2f_{52}^{(1)}(v^{*})v_{1}\bar{v}_{4}^{*}w_{11}^{*}(0) + \\ &2f_{61}^{(2)}(v^{*})v_{4}\bar{v}_{4}^{*}w_{11}^{*}(0) + 2f_{13}^{(1)}(v^{*})\bar{v}_{4}^{*}w_{11}^{*}(0) + 2f_{52}^{(1)}(v^{*})v_{1}\bar{v}_{4}^{*}w_{11}^{*}(0) + \\ &2f_{13}^{(2)}(x^{*})q^{*}w_{11}^{*}(0) - 2f_{13}^{(1)}(x^{*})\bar{v}_{1}^{*}w_{11}^{*}(0) + 2f_{73}^{(2)}(q^{*})v_{5}\bar{v}_{6}^{*}w_{11}^{*}(0) + \\ &2f_{13}^{(2)}(x^{*})q^{*}w_{11}^{*}(0) - 2f_{13}^{(2)}(x^{*})q^{*}\bar{v}_{1}^{*}w_{11}^{*}(0) + 2f_{73}^{(2)}(q^{*})p^{*}v_{6}\bar{v}_{6}^{*}w_{11}^{*}(0) + \\ &2f_{12}^{(2)}(q^{*})v_{6}\bar{v}_{6}^{*}w_{11}^{*}(0) - 2f_{13}^{(2)}(x^{*})q^{*}\bar{v}_{1}^{*}w_{10}^{*}(0) + f_{51}^{(1)}(v^{*})\bar{v}_{4}\bar{v}_{4}^{*}w_{20}^{*}(0) + \\ &f_{13}^{(2)}(x^{*})q^{*}w_{10}^{*}w_{10}^{*}(0) - f_{13}^{(2)}(x^{*})q^{*}\bar{v}_{1}^{*}w_{11}^{*}(0) + 2f_{73}^{(2)}(q^{*})p^{*}v_{6}\bar{v}_{6}^{*}w_{11}^{*}(0) + \\ &f_{13}^{(2)}(x^{*})\bar{v}_{1}\bar{v}_{1}w_{20}^{*}(0) - f_{13}^{(2)}(x^{*})\bar{v}$$

Since $W_{20}(\theta)$ and $W_{11}(\theta)$ are unknown in g_{21} , we will continue to solve for $W_{20}(\theta)$ and $W_{11}(\theta)$.

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From (6.15) and (6.21) we have

$$\begin{split} \dot{W} &= \dot{U}_{t} - \dot{z}(t) q(\theta) - \dot{\bar{z}}\bar{q}(\theta) \\ &= \Lambda_{0}U_{t} + R_{0}U_{t} - \left[iw_{0}\tau_{1}^{0}z(t) + \bar{q}^{*}(0) f_{0}(z,\bar{z})\right]q(\theta) \\ &- \left[-iw_{0}\tau_{1}^{0}z(t) + q^{*}(0) \bar{f}_{0}(z,\bar{z})\right]\bar{q}(\theta) \\ &= \begin{cases} \Lambda_{0}W - 2\Re\left(\bar{q}^{*}(0) f_{0}(z,\bar{z})\right), \theta \in [-1,0) \\ \Lambda_{0}W - 2\Re\left(\bar{q}^{*}(0) f_{0}(z,\bar{z})\right) + f_{0}, \theta = 0 \\ &= \Lambda_{0}W + H(z,\bar{z},\theta) \end{split}$$
(5.27)

where

$$H(z,\bar{z},\theta) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots$$
 (5.28)

Differentiating formula (6.20) for *t* we can have

$$\begin{split} \dot{W} &= W_{z}\dot{z} + W_{\bar{z}}\dot{z} \\ &= (W_{20}(\theta) z + W_{11}(\theta) \bar{z} \cdots) \left(iw_{0} \tau_{1}^{0} z + g(z, \bar{z}) \right) \\ &+ (W_{11}(\theta) z + W_{02}(\theta) \bar{z} \cdots) \left(-iw_{0} \tau_{1}^{0} \bar{z} + \bar{g}(z, \bar{z}) \right). \end{split}$$
(5.29)

Bring (6.27) into (6.29), we obtain

$$\begin{split} \dot{W} &= \Lambda_0 \left(W_{20} \left(\theta \right) \frac{z^2}{2} + W_{11} \left(\theta \right) z \bar{z} + W_{02} \left(\theta \right) \frac{\bar{z}^2}{2} + \cdots \right) \\ &+ H_{20} \left(\theta \right) \frac{z^2}{2} + H_{11} \left(\theta \right) z \bar{z} + H_{02} \left(\theta \right) \frac{\bar{z}^2}{2} + \cdots \\ &= \left(\Lambda_0 W_{20} \left(\theta \right) + H_{20} \left(\theta \right) \right) \frac{z^2}{2} + \left(\Lambda_0 W_{11} \left(\theta \right) + H_{11} \left(\theta \right) \right) z \bar{z} \\ &+ \left(\Lambda_0 W_{02} \left(\theta \right) + H_{02} \left(\theta \right) \right) \frac{\bar{z}^2}{2} + \cdots . \end{split}$$
(5.30)

Compare the coefficients of z^2 and $z\overline{z}$ in (6.29) and (6.30) to obtain the following equation

$$\left(\Lambda_0 - 2iw_0\tau_1^0 I\right) W_{20}(\theta) = -H_{20}(\theta), \qquad (5.31)$$

and

$$\Lambda_0 W_{11}\left(\theta\right) = -H_{11}\left(\theta\right),\tag{5.32}$$

where I is unit matrix or unit transformation. From (6.27) we can get

$$H(z, \bar{z}, \theta) = -\bar{q}^{*}(0) f_{0}q(\theta) - q^{*}(0) \bar{f}_{0}\bar{q}(\theta)$$

$$= -g(z, \bar{z}) q(\theta) - \bar{g}(z, \bar{z}) \bar{q}(\theta)$$

$$= -\left(g_{20}\frac{z^{2}}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^{2}}{2} + \cdots\right)q(\theta)$$

$$-\left(\bar{g}_{20}\frac{\bar{z}^{2}}{2} + \bar{g}_{11}z\bar{z} + \bar{g}_{02}\frac{z^{2}}{2} + \cdots\right)\bar{q}(\theta)$$

(5.33)

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for $\theta \in [-1, 0)$. Comparing the corresponding coefficients of (6.28), (6.33) we can get the following equation

$$H_{20}(\theta) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta)$$
(5.34)

$$H_{11}(\theta) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta).$$
(5.35)

From (6.31) we can obtain

$$\Lambda_0 W_{20}(\theta) = 2iw_0 \tau_1^0 W_{20}(\theta) - H_{20}(\theta).$$
(5.36)

According the definition of Λ_0 and $q(\theta)$ and combining (6.34), then

$$\dot{W}_{20}(\theta) = 2iw_0\tau_1^0 W_{20}(\theta) + g_{20}q(0) e^{iw_0\tau_1^0\theta} + \bar{g}_{02}\bar{q}(0) e^{-iw_0\tau_1^0\theta}$$
(5.37)

$$W_{20}(\theta) = \frac{ig_{20}}{w_0\tau_1^0}q(0)e^{iw_0\tau_1^0\theta} + \frac{i\bar{g}_{02}}{3w_0\tau_1^0}\bar{q}(0)e^{-iw_0\tau_1^0\theta} + N_1e^{2iw_0\tau_1^0\theta}$$
(5.38)

where $N_2 = \left(N_2^{(1)}, N_2^{(2)}, N_2^{(3)}, N_2^{(4)}, N_2^{(5)}, N_2^{(6)}, N_2^{(7)}\right)^T$ is also a constant vector. Next we just need to calculate N_1 and N_2 . From (6.31), (6.32) and the define of Λ_0 the following equations can be exported.

$$\int_{-1}^{0} d\eta \left(\theta\right) W_{20}\left(\theta\right) = 2iw_0 \tau_1^0 W_{20}\left(0\right) - H_{20}\left(0\right)$$
(5.39)

$$\int_{-1}^{0} d\eta \left(\theta\right) W_{11}\left(\theta\right) = -H_{11}\left(0\right)$$
(5.40)

where $\eta(\theta) = \eta(0, \theta)$. From (6.27) we have

$$H_{20}(0) = -g_{20}q(0) - \bar{g}_{02}\bar{q}(0)$$

$$+ \tau_{1}^{0} \begin{pmatrix} f_{13}^{(2)}(x^{*}) q^{*} + f_{12}^{(2)}(y^{*}) v_{1}^{2} + e^{-2iw_{0}\tau_{1}^{0}} f_{11}^{(2)}(v^{*}) v_{4}^{2} + 2f_{13}^{(1)}(x^{*}) v_{6} \\ -f_{13}^{(2)}(x^{*}) q^{*} - f_{12}^{(2)}(y^{*}) v_{1}^{2} - 2f_{13}^{(1)}(x^{*}) v_{6} \\ 0 \\ 0 \\ 2f_{51}^{(1)}(v^{*}) v_{4} + 2f_{52}^{(1)}(v^{*}) v_{1}v_{4} + f_{51}^{(2)}(v^{*}) v_{4}^{2}x^{*} + f_{52}^{(2)}(v^{*}) v_{4}^{2}y^{*} \\ f_{61}^{(2)}(v^{*}) v_{4}^{2} \\ 2f_{73}^{(1)}(q^{*}) v_{5}v_{6} + f_{71}^{(2)}(q^{*}) v_{6}^{2} + f_{72}^{(2)}(q^{*}) v_{6}^{2} + f_{73}^{(2)}(q^{*}) p^{*}v_{6}^{2} \end{pmatrix}$$
(5.41)

$$\begin{split} H_{11}(0) &= -g_{11}q(0) - \bar{g}_{11}\bar{q}(0) \\ & + f_{13}^{(2)}(x^{*})q^{*} + f_{12}^{(2)}(y^{*})v_{1}\bar{v}_{1} + f_{11}^{(2)}(v^{*})v_{4}\bar{v}_{4} + f_{13}^{(1)}(x^{*})v_{6} + f_{13}^{(1)}(x^{*})\bar{v}_{6} \\ & -f_{13}^{(2)}(x^{*})q^{*} - f_{12}^{(2)}(y^{*})v_{1}\bar{v}_{1} - f_{13}^{(1)}(x^{*})v_{6} - f_{13}^{(1)}(x^{*})\bar{v}_{6} \\ & 0 \\ & 0 \\ & f_{11}^{(1)}(v^{*})v_{4} + f_{52}^{(1)}(v^{*})\bar{v}_{1}v_{4} + f_{51}^{(1)}(v^{*})\bar{v}_{4} + f_{52}^{(1)}(v^{*})v_{1}\bar{v}_{4} + f_{51}^{(2)}(v^{*})v_{1}\bar{v}_{4} + f_{52}^{(2)}(v^{*})v_{4}\bar{v}_{4}x^{*} + f_{52}^{(2)}(v^{*})v_{4}\bar{v}_{4}y^{*} \\ & f_{61}^{(1)}(v^{*})v_{4}\bar{v}_{4} \\ & f_{73}^{(1)}(q^{*})\bar{v}_{5}v_{6} + f_{73}^{(1)}(q^{*})v_{5}\bar{v}_{6} + f_{71}^{(2)}(q^{*})v_{6}\bar{v}_{6} + f_{72}^{(2)}(q^{*})v_{6}\bar{v}_{6} + f_{73}^{(2)}(q^{*})p^{*}v_{6}\bar{v}_{6} \end{split}$$
(5.42)

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Substituting (6.38) and (6.41) into (6.39), we obtain

$$\int_{-1}^{0} d\eta \left(\theta\right) \left(\frac{\mathrm{i}g_{20}}{w_{0}\tau_{1}^{0}}q\left(0\right)e^{\mathrm{i}w_{0}\tau_{1}^{0}\theta} + \frac{\mathrm{i}\bar{g}_{02}}{3w_{0}\tau_{1}^{0}}\bar{q}\left(0\right)e^{-\mathrm{i}w_{0}\tau_{1}^{0}\theta} + N_{1}e^{2\mathrm{i}w_{0}\tau_{1}^{0}\theta}\right)$$

$$= 2\mathrm{i}w_{0}\tau_{1}^{0}\left(\frac{\mathrm{i}g_{20}}{w_{0}\tau_{1}^{0}}q\left(0\right) + \frac{\mathrm{i}\bar{g}_{02}}{3w_{0}\tau_{1}^{0}}\bar{q}\left(0\right) + N_{1}\right) - H_{20}\left(0\right).$$
(5.43)

And then since $iw_0\tau_1^0$ is the eigenvalues of Λ_0 , which corresponding eigenvector q(0). Furthermore, From (6.43) to

$$\begin{pmatrix} 2iw_0\tau_1^0 I - \int_{-1}^0 e^{2iw_0\tau_1^0\theta} d\eta(\theta) \end{pmatrix} N_1$$

$$= \tau_1^0 \begin{pmatrix} f_{13}^{(2)}(x^*) q^* + f_{12}^{(2)}(y^*) v_1^2 + e^{-2iw_0\tau_1^0} f_{11}^{(2)}(v^*) v_4^2 + 2f_{13}^{(1)}(x^*) v_6 \\ -f_{13}^{(2)}(x^*) q^* - f_{12}^{(2)}(y^*) v_1^2 - 2f_{13}^{(1)}(x^*) v_6 \\ 0 \\ 0 \\ 2f_{51}^{(1)}(v^*) v_4 + 2f_{52}^{(1)}(v^*) v_1 v_4 + f_{51}^{(2)}(v^*) v_4^2 x^* + f_{52}^{(2)}(v^*) v_4^2 y^* \\ f_{61}^{(2)}(v^*) v_4^2 \\ 2f_{73}^{(1)}(q^*) v_5 v_6 + f_{71}^{(2)}(q^*) v_6^2 + f_{72}^{(2)}(q^*) v_6^2 + f_{73}^{(2)}(q^*) p^* v_6^2 \end{pmatrix}$$

$$(5.44)$$

Similarly, we can get

$$\int_{-1}^{0} d\eta (\theta) N_{2}$$

$$= -\tau_{1}^{0} \begin{pmatrix} f_{13}^{(2)} (x^{*}) q^{*} + f_{12}^{(2)} (y^{*}) v_{1} \bar{v}_{1} + f_{11}^{(2)} (v^{*}) v_{4} \bar{v}_{4} + f_{13} 1 v_{6} z Z + f_{13}^{(1)} (x^{*}) \bar{v}_{6} \\ -f_{13}^{(2)} (x^{*}) q^{*} - f_{12}^{(2)} (y^{*}) v_{1} \bar{v}_{1} - f_{13}^{(1)} (x^{*}) v_{6} - f_{13}^{(1)} (x^{*}) \bar{v}_{6} \\ 0 \\ 0 \\ f_{51}^{(1)} (v^{*}) v_{4} + f_{52}^{(1)} (v^{*}) \bar{v}_{1} v_{4} + f_{51}^{(1)} (v^{*}) \bar{v}_{4} + f_{52}^{(1)} (v^{*}) v_{1} \bar{v}_{4} + f_{52}^{(2)} (v^{*}) v_{4} \bar{v}_{4} x^{*} + f_{52}^{(2)} (v^{*}) v_{4} \bar{v}_{4} y^{*} \\ f_{61}^{(2)} (v^{*}) v_{4} \bar{v}_{4} \\ f_{73}^{(1)} (q^{*}) \bar{v}_{5} v_{6} + f_{73}^{(1)} (q^{*}) v_{5} \bar{v}_{6} + f_{71}^{(2)} (q^{*}) v_{6} \bar{v}_{6} + f_{72}^{(2)} (q^{*}) v_{6} \bar{v}_{6} + f_{73}^{(2)} (q^{*}) p^{*} v_{6} \bar{v}_{6} \\ \end{cases}$$

$$(5.45)$$

Finally, according to the definition of $\eta(\theta)$, we can solve N_1 , N_2 and g_{21} . Besides we can also get the following values

$$\begin{split} C_{1}(0) &= \frac{i}{2w_{0}\tau_{1}^{0}} \left(g_{11}g_{20} - 2|g_{11}|^{2} - \frac{|g_{02}|^{2}}{3} \right) + \frac{g_{21}}{2}, \\ \mu_{2} &= -\frac{\text{Re}\{C_{1}(0)\}}{\text{Re}\{\lambda'(\tau_{1}^{0})\}}, \\ T_{2} &= -\frac{Im\{C_{1}(0)\} + \mu_{2}Im\{\lambda'(\tau_{1}^{0})\}}{w_{0}\tau_{1}^{0}}, \\ \beta_{2} &= 2\text{Re}\left\{ C_{1}(0) \right\}. \end{split}$$

From the above discussion we can get the following results:

(1) The direction of Hopf bifurcation is determined by μ_2 : if $\mu_2 > 0$ (resp. $\mu_2 < 0$), then the Hopf bifurcation is supercritical (resp. subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_1^0$

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(resp. $\tau < \tau_1^0$);

(2) The stability of the bifurcating periodic solutions is depended on β_2 , the bifurcating periodic solutions in the center manifold are stable (resp. unstable) for $\beta_2 < 0$ (resp. $\beta_2 > 0$);

(3) The period of the bifurcating periodic solutions is determined by T_2 : the period increases if $T_2 > 0$ (resp. decreases $T_2 < 0$).



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