Chapter 1

Contemporary Delay Differential Equation Models and Analysis in Mathematical Biology

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In this chapter, we discuss the contemporary applications and analysis of delay differential equations in mathematical biology. We mainly review two important types of approaches for qualitative analysis of delay differential equation models. One is based on characteristic equations and the other is from the perspective of infinite dimensional dynamical systems. In order to bridge the gap between theoretical results and applications, we provide some examples illustrating how the two approaches are applied in analyzing delay differential equation models arising from mathematical ecology and epidemiology. We also present several other popular methods and concerns as well as prospective future research directions for delay differential equation modelling and analysis.

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1. Introduction

Delay differential equation (DDE) models have captured the interest and attention of mathematicians and biologists for at least two centuries and have been applied to sovling challenging problems in countless fields including ecology, epidemiology, immunology, microbiology, physiology, neuroscience, and environmental science [17]. The time delays in these models are often related to processes such as digestion [68], regeneration [57], the duration of certain life stages [66], the time between the infection of a cell and the release of new viruses [43], the incubation period of some diseases [64], and the duration of temporary immunity [45]. It is reasonable to assume that delays are distributed among the population by a continuous distribution function, with a positive variance representing the difference among individuals and a mean which can be approximated by a discrete delay. When a discrete delay is adopted, all individuals are assumed subject to the same delay and it can be regarded that delays are distributed by a δ-Dirac distribution [6]. The resulted DDEs with discrete delays usually render more tractability for qualitative analysis of the models. As mentioned in [1], there are three common ways to incorporate time delays in a mathematical model. Time delays are frequently introduced through several compartments [24, 43]. Time delays can occur as anticipated via aggregations in age-, size-, or stage-structured population models [4, 67]. Certainly, time delays may be included in models for a particular purpose [12, 53].

The presence of time delays together with the nonlinear terms in a model can dramatically affect the behavior of the solutions concerning the stability of steady states and the emergence and properties of oscillations which may not be observed if we simply use an ordinary differential equation (ODE) model as an approximation [16, 23, 44]. Large delays usually destablize a system [23] but exceptions may happen when some parameters are delay dependent (see, e.g., Section 2.3). In addition, Neubert and Klepac [39] showed that a dispersal delay (i.e., the travel time for interpatch migration) can stabilize the positive equilibrium of the predator-prey model, giving another exmaple different from the destablizing effects of delay

terms. With regard to oscillatory behaviors, DDE models could help reveal reasons behind some phenomena whereas ODEs may not be able to. For example, McCauley, Nelson and Nisbet [37] explained the empirical results on coexisting attractors in *Daphnia*-algal system by showing that a dynamic developmental delay in consumers together with the resource-dependent mortality can produce a new type of small-amplitude cycles which coexists with large-amplitude oscillations. Wang et al. [62] found that the maturation delay of predators almost completely determines the period of population cycles, and if the predator maturation delays are too large or too small, or the functional response takes the form of Holling type I , then population cycles do not appear, which seems to explain why some populations oscillate whereas others do not and why different species have different cyclic periods. Even if some ODE models can also generate cycles, they may not fit well with empirical data as DDEs do. Again in [62], Wang et al. found that the amplitude of the lemming-stoat cycles produced by the ODE model is much larger than observed whereas both the period and the amplitude coincide well with real data if the DDE model is used. DDE models can also reduce the number of variables and parameters in a model, leaving only those important ones of interest. This is particularly helpful when we have limited knowledge about some life stages that are not necessary to appear as a varible and may facilitate data fitting and parameter estimation. In medical science and epidemiology, time delay may serve as an important controllable parameter to evaluate treatment effectiveness, disease progression, or epidemic development. For instance, immunity duration is shown to be the most sensitive parameter for disease transmission in [45]. The effect of delayed diagnosis can also be investigated via a DDE model, which may be crucial in the control of tumor growth or a pandemic.

Incorporation of time delays makes DDEs more complex to analyze than ODEs. An ODE system of n equations has the n-dimensional Euclidean space $\mathbb{R}^n$ as its state space and the future state of an ODE system depends only on the state at present regardless of the past. In contrast, the state at a single time instant is not sufficient to determine the solution of a DDE system. The state space of DDEs is an infinite dimensional space of functions. In this chapter, we focus on retarded delay differential equations in which the time delays are only involved in the unknown variables but do not appear in the derivatives of the unknown variables. For the case when the derivatives of the unknown variables also involve delays (i.e., the so-called neutral delay differential equations), we refer readers to [16, 23]. We do not expand any detail of neutral DDEs here because they rarely

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have any direct application in biology. If r is the maximum delay in a system of DDEs, then the initial condition needs to be prescribed on the interval $[-r, 0]$ to determine the solution. Following the most well-developed theory and notations as those in [16, 23, 59], we denote $C \equiv C([-r, 0], \mathbb{R}^n)$ the Banach space of continuous functions mapping the interval $[-r, 0]$ into $\mathbb{R}^n$ with the topology of uniform convergence; i.e., for $\phi \in C$, the norm of ϕ is defined as $\|\phi\| = \sup_{-r \le \theta \le 0} |\phi(\theta)|$, where $|\cdot|$ is a norm in $\mathbb{R}^n$. For $x \in C([-r, \alpha], \mathbb{R}^n)$ and $t \in [0, \alpha]$ where $\alpha \ge 0$, we define $x_t \in C$ as $x_t(\theta) = x(t + \theta)$, $\theta \in [-r, 0]$. Assume that Ω is a subset of $\mathbb{R} \times C$ and $f : \Omega \to \mathbb{R}^n$ is a given function, then we have the following delay differential equations

$$x'(t) = f(t, x_t). \tag{1}$$

A function x is called a solution of system (1) on $[-r, \alpha)$ if $x \in C([-r, \alpha), \mathbb{R}^n)$, $(t, x_t) \in \Omega$ and x_t satisfies system (1) for $t \in [0, \alpha)$. For $\phi \in C$, we say $x(0, \phi)$ is a solution of (1) with initial value ϕ at 0 if there is an $\alpha > 0$ such that $x(0, \phi)$ is a solution of (1) on $[-r, \alpha)$ and $x_0(0, \phi) = \phi$. From $x(t, \phi)$ we can construct an element $x_t(\phi)$ in the state space C. See Figure 1 for the illustration of the state space of DDEs.
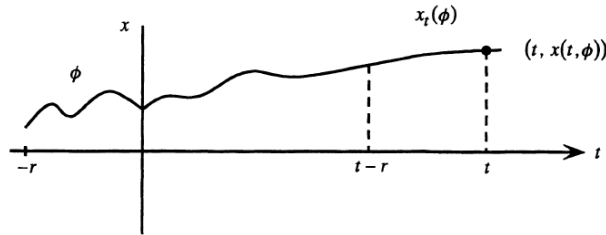

Fig. 1. $x_t(\phi)$ is obtained by translating the graph of $x(t, \phi)$ on the interval $[t - r, t]$ to the interval $[-r, 0]$. The figure was adopted from [59].

Now we consider the initial value problem (IVP)

$$\begin{aligned} x'(t) &= f(t, x_t), \quad t \ge \sigma, \\ x_\sigma &= \phi. \end{aligned} \tag{2}$$

The method of steps can be used to solve IVP (2) with discrete delays. However, in order to obtain existence, uniqueness and continuation results for more general cases such as distributed delay systems, we need to assume f to be continuous and satisfies the following Lipschitz condition:

(Lip) For all $a, b \in \mathbb{R}$ and $M > 0$, there is a $K > 0$ such that

$$|f(t, \phi) - f(t, \psi)| \le K\|\phi - \psi\|, \quad a \le t \le b, \ \|\phi\|, \|\psi\| \le M.$$

Theorem 1. *([58]) Suppose that f is continuous and satisfies the Lipschitz condition (Lip), $\sigma \in \mathbb{R}$, and $M > 0$. There exists $A > 0$, depending only on M such that if $\phi \in C$ satisfies $\|\phi\| \leq M$, then there exists a unique solution $x(t) = x(t, \phi)$ of system (2), defined on $[\sigma - r, \sigma + A]$. In addition, if K is the Lipschitz constant for f corresponding to $[\sigma, \sigma + A]$ and M, then*

$$\max_{\sigma - r \leq \eta \leq \sigma + A} |x(\eta, \phi) - x(\eta, \psi)| \leq \|\phi - \psi\| e^{KA}, \quad \|\phi\|, \|\psi\| \leq M. \qquad (3)$$

The assertion (3) indicates that the solution depends continuously on the initial data. Theorem 1 provides a local solution of the IVP (2) defined on $[\sigma - r, \sigma + A]$ for some $A > 0$, whereas in applications solutions are usually expected to be defined for all $t \geq \sigma$. If $x : I \to \mathbb{R}^n$ and $\hat{x} : J \to \mathbb{R}^n$ are two solutions of (2), where I, J are intervals of the form $[\sigma - r, \sigma + \alpha]$ or $[\sigma - r, \sigma + \alpha)$ with $0 < \alpha \leq \infty$, and if $I \subset J$, then we say that $\hat{x}$ is a continuation or an extension of x. A solution $x : I \to \mathbb{R}^n$ is noncontinuable if it has no extension to a larger interval. By a simple argument, we can obtain the existence of a unique noncontinuable solution of (2) and the maximal interval of existence must be right open. If the noncontinuable solution $x : [\sigma - r, \sigma + \alpha) \to \mathbb{R}^n$ of (2) satisfies $\alpha < \infty$, then it must "blow up" as $t \nearrow \sigma + \alpha$ [58].

Remark 1. ([58]) If f satisfies a global Lipschitz condition, that is, if K in (Lip) can be chosen independent of a, b and M, then the conclusions of Theorem 1 hold for all $A > 0$. In this case, the solution exists for all $t \geq \sigma$ and the inequality $\|x_t(\phi) - x_t(\psi)\| \leq \|\phi - \psi\| e^{K(t - \sigma)}$ holds for all $t \geq \sigma$.

The primary goal of this chapter is to review two popular ways of DDE model analysis: one is around the characteristic equation and the other is based on the theory of infinite dimensional dynamical systems. The characteristic equation method is used to analyze stability of autonomous DDEs by investigating the exitence of pure imaginary roots and crossing directions geometrically and algebraically. The abstract infinite dimensional dynamical systems approach can be applied to study global attractivity of steady states and uniform persistence of some specific systems, which seems more powerful as it can deal with both autonomous DDEs and some nonautonomous DDEs with multiple constant delays or periodic delays. Contemporary results about DDEs are too rich to include all in this single survey. We will focus on the two types of methods and give examples about how to apply them to analyze DDE models. Hopefully, our work can provide readers with sufficient materials from very basic introductory knowledge to hands-on research techniques and experience for analyzing

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DDE systems, especially for graduate students and applied mathematicians who are unfamiliar with DDEs.

This chapter is organized as follows. In Section 2, we introduce geometric and algebraic methods in analyzing four different characteristic equations derived from the stability analysis of four different classes of DDE models. In Section 3, we present the point of view of infinite dimensional dynamical systems in analyzing global attractivity and uniform persistence of DDE systems. We also provide most relevant and recent published works about the applications of the methods introduced in these two sections. In Section 4, we go through several other popular methods and point out concerns in DDE modelling and analysis. In Section 5, we discuss possible future research directions hoping to motivate more exciting works in DDE applications. We end the chapter with a brief discussion in Section 6.

2. Stability and bifurcation analysis via characteristic equation

Characteristic equations show great power in local stability and bifurcation analysis for autonomous DDEs. The characteristic equation derived from a DDE system is a transcendental equation instead of an algebraic equation, which makes the analysis of the characteristic roots more challenging than the ODE case.

2.1. *Characteristic equation and stability switching*

We consider a nonlinear autonomous special case of system (1) given by

$$x'(t) = f(x(t), x(t - \tau_1), x(t - \tau_2), \cdots, x(t - \tau_k)), \quad t \geq 0, \qquad (4)$$

where $\tau_1 > \tau_2 > \cdots > \tau_k > 0$. Suppose that system (4) has a unique solution maximally defined for all $t > 0$ satisfying the initial condition $x_0 = \phi \in C$, and it has a nontrivial equilibrium x^*.

Let $u(t) = x(t) - x^*$ and suppose that we get the following linearized system

$$u'(t) = Au(t) + \sum_{i=1}^{k} B_i u(t - \tau_i), \qquad (5)$$

where A and B_i $(i = 1, 2, \cdots, k)$ are matrices. Then the linear stability of x^* of system (4) is equivalent to that of the zero solution of system (5).

In order to investigate the stability of the zero solution of system (5), similar to the ODE case, we seek the solution $u(t) = e^{\lambda t} v,\ v \neq 0$. It is easy

to verify that $u(t) = e^{\lambda t}v$, $v \neq 0$, is a solution of (5) if and only if λ is a solution of the characteristic equation

$$\det[\lambda I - A - \sum_{i=1}^{k} e^{-\lambda \tau_i} B_i] = 0. \qquad (6)$$

According to the following theorem, whether the zero solution of system (5) is stable depends on whether all roots of the characteristic equation (6) have negative real parts.

Theorem 2 ([58]). *Suppose that* $\mathrm{Re}(\lambda) < \mu$ *for every characteristic root* λ. *Then there exists* $K > 0$ *such that*

$$|u(t, \phi)| \leq K e^{\mu t} \|\phi\|, \quad t \geq 0, \ \phi \in C, \qquad (7)$$

where $u(t, \phi)$ *is the solution of* (5) *satisfying* $u_0 = \phi$. *In particular,* $u = 0$ *is asymptotically stable for* (5) *if* $\mathrm{Re}(\lambda) < 0$ *for every characteristic root; it is unstable if there is a root satisfying* $\mathrm{Re}(\lambda) > 0$.

A favorable property about the characteristic equation is that $\det[\lambda I - A - \sum_{i=1}^{k} e^{-\lambda \tau_i} B_i]$ is an entire function, which implies that there are at most finitely many characteristic roots that have positive real part and each root has a finite order [58]. Note that $\det[\lambda I - A - \sum_{i=1}^{k} e^{-\lambda \tau_i} B_i]$ is a function of delays, and hence, the roots of the characteristic equation (6) are also functions of delays. Therefore, the variation in the lengths of delays may induce stability switches, i.e., the equilibrium changing from stable to unstable or vice versa. This is one of the most intriguing questions in DDE analysis. Indeed, in order to investigate the possibility of stability switches we only need to focus on the existence of pure imaginary roots of the characteristic equation since the sum of the multiplicities of characteristic roots in the open right half-plane can change only if a root appears on or crosses the imaginary axis (see, e.g., Theorem 1.4 in [23]). Another important observation is that complex characteristic roots always come in conjugate pairs (see, e.g., Proposition 4.2 in [58]). Therefore, we only need to seek pure imaginary root $i\omega$ with $\omega > 0$.

Next, we will introduce the geometric and algebraic methods presented in [1, 7, 23, 31] in analyzing characteristic equations derived from four different types of DDE models. In particular, for the DDE with one delay and delay independent parameters, we will present an alternative way to show the asymptotic locations of the characteristic roots, which is more detailed and descriptive than the historic proof given by Pontryagin [46]. In all these references, the authors made several assumptions which enable

us to focus on the existence of pure imaginary charateristic roots for certain values of the delays or out of technical requirements such as to guarantee the continuity and differentiability of some functions. We will not repeat those assumptions here but suppose they are automatically satisfied for each characteristic equation in the following subsections.

2.2. *DDEs with one delay and delay independent parameters*

For a DDE with one delay and delay independent parameters, the characteristic equation takes this form:

$$P_n(z) + Q_m(z)e^{-z\tau} = 0, \tag{8}$$

and we have the following result about stability switches:

Theorem 3. *([23]) Consider equation* (8), *where* $P(z)$ *and* $Q(z)$ *are analytic functions in* $\mathrm{Re}(z) > 0$ *and satisfy the following conditions:*

(i) $P(z)$ *and* $Q(z)$ *have no common imaginary root;*
(ii) $\overline{P(-iy)} = P(iy)$, $\overline{Q(-iy)} = Q(iy)$ *for real* y;
(iii) $P(0) + Q(0) \neq 0$;
(iv) $\limsup\{|Q(z)/P(z)| : |z| \to \infty, \mathrm{Re}(z) \geq 0\} < 1$;
(v) $F(y) \equiv |P(iy)|^2 - |Q(iy)|^2$ *for real* y *has at most a finite number of real zeros.*

Then the following statements are true:

(a) *If* $F(y) = 0$ *has no positive roots, then no stability switch may occur.*
(b) *If* $F(y) = 0$ *has at least one positive root and each of them is simple, then as* τ *increases, a finite number of stability switches may occur, and eventually the considered equation becomes unstable.*

Next, we will show that equation (8) has infinite zeros when

$$P_n(z) = \sum_{k=0}^{n} a_k z^k \text{ and } Q_m(z) = \sum_{k=0}^{m} b_k z^k$$

are polynomials in z with real coefficients and $m \leq n$. Furthermore, we will obtain the asymptotic behavior of the zeros with negative real parts.

Proposition 1. *For* $m \leq n$, *the generic transcendental equation* (8) *is asymptotically equivalent to* $e^{-z\tau} = az^k$ *for large* $|z|$, *where* $a = -\frac{a_n}{b_m}$, $k = n - m \geq 0$.

Lemma 1. *For $k = 0$, $e^{-z\tau} = a$ has infinite zeros with negative real parts.*

Proof. Let $z = \alpha + i\beta$, then $e^{-\alpha\tau}\cos(\beta\tau) = a$ and $e^{-\alpha\tau}\sin(\beta\tau) = 0$. We can get $\beta = l\pi/\tau$, $l \in \mathbb{Z}$ and $\alpha = -\frac{1}{\tau}\ln|a|$. The asymptotic equation $e^{-z\tau} = a$ has infinite zeros whose imaginary parts go to infinity as l increases and real parts are constant. $\qquad\square$

Lemma 2. *For $k > 0$ (a natural number), $e^{-z\tau} = az^k$ has infinite zeros with negative real parts.*

Proof. Let $z = \alpha + i\beta = A(\cos\theta + i\sin\theta)$, then

$$e^{-z\tau} = e^{-(\alpha+i\beta)\tau} = e^{-\alpha\tau}[\cos(\beta\tau) - i\sin(\beta\tau)],$$

$$az^k = a[A(\cos\theta + i\sin\theta)]^k = aA^k[\cos(k\theta) + i\sin(k\theta)].$$

Therefore,

$$e^{-\alpha\tau}\cos(\beta\tau) = aA^k\cos(k\theta), \tag{9}$$

$$-e^{-\alpha\tau}\sin(\beta\tau) = aA^k\sin(k\theta), \tag{10}$$

where $\alpha = A\cos\theta, \beta = A\sin\theta$.

$$(9)^2 + (10)^2: \quad e^{-2A\tau\cos\theta} = a^2 A^{2k}, \tag{11}$$

$$(10)/(9): \quad -\tan(A\tau\sin\theta) = \tan(k\theta). \tag{12}$$

From (12), we can get $l\pi - A\tau\sin\theta = k\theta$, and hence, $A = \frac{l\pi - k\theta}{\tau\sin\theta}$, where l can be any integer. Since $A > 0$, we need the restriction $l > k\theta/\pi$ if $\theta \in (2q\pi, (2q+1)\pi)$; $l < k\theta/\pi$ if $\theta \in ((2q-1)\pi, 2q\pi)$, where q can be any integer.

Substitute $A = \frac{l\pi - k\theta}{\tau\sin\theta}$ into (11), we have $e^{-2(l\pi - k\theta)\cot\theta} = a^2\left(\frac{l\pi - k\theta}{\tau\sin\theta}\right)^{2k}$.

Let $H(\theta) = e^{-2(l\pi - k\theta)\cot\theta} - a^2\left(\frac{l\pi - k\theta}{\tau\sin\theta}\right)^{2k}$, remember only the integer l is a changeable parameter, others are fixed. Later, we want to investigate whether there exists some integer l such that the function $H(\theta)$ has a zero.

Since $\cot\theta$ and $1/\sin\theta$ are continuous on $[\pi/2, \pi)$, so is $H(\theta)$.

Letting $\theta = \pi/2$, we have $e^{-2(l\pi - k\theta)\cot\theta} = 1$ and $a^2\left(\frac{l\pi - k\theta}{\tau\sin\theta}\right)^{2k} > 1$ if $l > \frac{\tau}{\pi\sqrt[k]{|a|}} + \frac{k}{2}$, then $H(\theta) < 0$. Letting $\theta \to \pi^-$, we get $e^{-2(l\pi - k\theta)\cot\theta} \to \infty$ and $a^2\left(\frac{l\pi - k\theta}{\tau\sin\theta}\right)^{2k} \to \infty$ if $l > k$, and

$$\lim_{\theta \to \pi^-} \frac{e^{-2(l\pi - k\theta)\cot\theta}}{a^2\left(\frac{l\pi - k\theta}{\tau\sin\theta}\right)^{2k}} = \infty$$

by L'Hôpital's rule, and hence, $H(\theta) \to \infty$. For $\theta \in [\pi/2, \pi)$, choose the integer $l > \max\left\{\frac{\tau}{\pi\sqrt[k]{|a|}} + \frac{k}{2}, k\right\}$, then there exists some $\theta_0 \in (\pi/2, \pi)$

such that $H(\theta_0) = 0$ by the Intermediate Value Theorem. Note that $l > \max\left\{\frac{\tau}{\pi\sqrt[k]{|a|}} + \frac{k}{2}, k\right\}$ also guarantees $A > 0$ for $\theta \in [\pi/2, \pi)$.

For $\theta \in [\pi/2, \pi)$, choose different l's satisfying the condition (l can be any integer greater than $\max\left\{\frac{\tau}{\pi\sqrt[k]{|a|}} + \frac{k}{2}, k\right\}$), then there are different pairs of (A, θ), because of the relationship $A = \frac{l\pi - k\theta}{\tau\sin\theta}$. Therefore there are infinite zeros with negative real parts of $e^{-z\tau} = az^k (k > 0)$. $\square$

Remark 2. Suppose $\lambda = Ae^{i\theta}$ with $\theta \in (\pi/2, \pi)$ is a zero of $e^{-z\tau} = az^k$, then θ and A should be dependent on l, i.e., $\theta(l)$ and $A(l)$. Since $\theta(l) \in (\pi/2, \pi)$, $\sin(\theta) \in (0, 1)$, then $A(l) = \frac{l\pi - k\theta(l)}{\tau\sin\theta(l)} \geq \frac{l\pi - k\pi}{\tau} \to \infty$ as $l \to \infty$.

Theorem 4. *Suppose $\lambda = Ae^{i\theta} = A(l)e^{i\theta(l)}$ with $\theta(l) \in (\pi/2, \pi)$ is a zero of $e^{-z\tau} = az^k (k > 0)$, then we have the following results:*

> *(i) $\theta(l) \to \pi/2$ as $l \to \infty$.*
> *(ii) $A(l) \to \infty$ as $l \to \infty$.*
> *(iii) The real part $A(l)\cos\theta(l) \to -\infty$ in the shape of the function $-\ln l$ as $l \to \infty$.*
> *(iv) The imaginary part $A(l)\sin\theta(l) \to \infty$ linearly as $l \to \infty$.*

Proof. Let $\theta(l) = \pi/2 + \delta(l)$, where $\delta(l) \in (0, \pi/2)$ and θ satisfies

$$H(\theta) = e^{-2(l\pi - k\theta)\cot\theta} - a^2\left(\frac{l\pi - k\theta}{\tau\sin\theta}\right)^{2k} = 0$$

$\Leftrightarrow$

$$e^{2(l\pi - k(\pi/2+\delta))\tan\delta} - a^2\left(\frac{l\pi - k(\pi/2+\delta)}{\tau\cos\delta}\right)^{2k} = 0$$

$\Leftrightarrow$

$$I(l) \triangleq \frac{a^2\left(\frac{l\pi - k(\pi/2+\delta)}{\tau\cos\delta}\right)^{2k}}{e^{2(l\pi - k(\pi/2+\delta))\tan\delta}} = 1.$$

Suppose $\delta(l) \nrightarrow 0$ and $\delta(l) \nrightarrow \pi/2$ as $l \to \infty$, then $\lim_{l\to\infty} I(l) = 0 \neq 1$, contradiction.

Suppose $\delta(l) \to \pi/2$ as $l \to \infty$, then

$$\lim_{l\to\infty} I(l) = \lim_{l\to\infty} \frac{a^2\left(\frac{l\pi - k\pi}{\tau\cos\delta}\right)^{2k}}{e^{2(l\pi - k\pi)/\cos\delta}} = \lim_{l\to\infty} \frac{a^2(J(l)/\tau)^{2k}}{e^{2J(l)}},$$

where $J(l) = (l\pi - k\pi)/\cos\delta(l)$.

Since $\delta(l) \to \pi/2$ as $l \to \infty$, then $\cos \delta(l) \to 0$ as $l \to \infty$, then $J(l) \to \infty$ as $l \to \infty$. Therefore,

$$\lim_{l \to \infty} I(l) = \lim_{J \to \infty} \frac{a^2 (J/\tau)^{2k}}{e^{2J}} = 0 \neq 1,$$

contradiction.

Consequently, $\delta(l) \to 0$ as $l \to \infty$, i.e., $\theta(l) \to \pi/2$. (i) is shown.

(ii) has been shown in Remark 2.

The real part of the zero is $A(l) \cos \theta(l) = \frac{l\pi - k\theta(l)}{\tau \sin \theta(l)} \cos \theta(l) = \frac{1}{\tau}(l\pi - k\theta(l)) \cot \theta(l) \triangleq -\frac{\chi}{\tau}$. Applying $\ln$ on both sides of $e^{-2(l\pi - k\theta) \cot \theta} = a^2 \left(\frac{l\pi - k\theta}{\tau \sin \theta} \right)^{2k}$ we get

$$2\chi = \ln \left(a^2 \left(\frac{l\pi - k\theta}{\tau \sin \theta} \right)^{2k} \right) \Leftrightarrow \chi = \ln |a| + k \ln \left(\frac{l\pi - k\theta}{\tau \sin \theta} \right).$$

Since $\theta \to \pi/2$ as $l \to \infty$, then $\chi(l) \to \infty$ behaves as $\ln |a| + k \ln \left(\frac{l\pi - k\pi/2}{\tau} \right)$, which is in the shape of the function $\ln l$. Therefore $A(l) \cos \theta(l) \to -\infty$ behaves as $-\ln |a|/\tau - \frac{k}{\tau} \ln \left(\frac{l\pi - k\pi/2}{\tau} \right)$, which is in the shape of the function $-\ln l$. (iii) holds.

The imaginary part $A(l) \sin \theta(l) = \frac{l\pi - k\theta(l)}{\tau} \to \infty$ is obvious, since $\theta(l) \to \pi/2$. And it behaves like $\frac{l\pi - k\pi/2}{\tau}$, which is a line, i.e., the imaginary part increases linearly. (iv) holds. $\square$

Define

$$f(z) = 1 - az^k e^{z\tau},$$

$$h(z) = az^k e^{z\tau} + \frac{P_n(z)}{Q_m(z)} e^{z\tau},$$

$$g(z) = 1 + \frac{P_n(z)}{Q_m(z)} e^{z\tau}.$$

For $z \neq 0$ (in fact, large amplitude implies this), $P_n(z) + Q_m(z) e^{-z\tau} = 0$ is equivalent to $g(z) = 0$, and $e^{-z\tau} = az^k$ is equivalent to $f(z) = 0$.

Lemma 3. *If $\lambda(l)$ is a zero of $f(z)$, then for $0 < r < \min\{\hat{r}, \frac{\pi}{2\tau}\}$, some $\hat{r} > 0$, independent of l, $\lambda(l)$ is the unique zero of $f(z)$ in the closed ball $\overline{B}_r(\lambda(l))$ for any large l.*

Proof. The difference of imaginary parts of two successive zeros of $f(z)$ is $A(l+1) \sin \theta(l+1) - A(l) \sin \theta(l) = \frac{(l+1)\pi - k\theta(l+1)}{\tau} - \frac{l\pi - k\theta(l)}{\tau} \to \frac{\pi}{\tau}$ as $l \to \infty$, since $\theta(l) \to \pi/2$ as $l \to \infty$, i.e., $\theta(l)$ converges. Therefore, $A(l +$

1) $\sin\theta(l+1) - A(l)\sin\theta(l) \geq \frac{\pi}{2\tau}$ for $l \geq \hat{l}$, some large $\hat{l} > 0$. Choose $\hat{r} > 0$ such that $\lambda(l)$ is the unique zero of $f(z)$ in the closed ball $\overline{B}_{\hat{r}}(\lambda(l))$ for $\max\left\{\frac{\tau}{\pi\sqrt[k]{|a|}} + \frac{k}{2}, k\right\} < l < \hat{l}$, finite number of l's. Consequently, choose $0 < r < \min\{\hat{r}, \frac{\pi}{2\tau}\}$, independent of l, then $\lambda(l)$ is the unique zero of $f(z)$ in the closed ball $\overline{B}_r(\lambda(l))$ for any $l > \max\left\{\frac{\tau}{\pi\sqrt[k]{|a|}} + \frac{k}{2}, k\right\}$, since $\text{Im}(\lambda(l+1) - \lambda(l)) \leq |\lambda(l+1) - \lambda(l)|$. For $k = 0$, $\text{Im}(\lambda(l+1)) - \text{Im}(\lambda(l)) \equiv \pi/\tau$, thus the result also holds for this special case. $\qquad\square$

Lemma 4. *Let* $\lambda = \lambda(l)$ *be a zero of* $f(z)$, *then* $|f(z)| \geq \eta/2$, $\forall z \in \partial B_r(\lambda(l))$, *for large* l, *where* $\eta = \min\{|1 - e^{\tau r e^{i\omega}}| : \omega \in [0, 2\pi]\} > 0$ *(independent of* l*).*

Proof. $1 - a\lambda^k e^{\lambda\tau} = 0 \Leftrightarrow e^{\lambda\tau} = \frac{1}{a\lambda^k}$, and $z \in \partial B_r(\lambda)$ can be expressed as $\lambda + re^{i\omega}$ with $\omega \in [0, 2\pi]$. Then $f(z) = f(\lambda + re^{i\omega}) = 1 - a(\lambda + re^{i\omega})^k e^{(\lambda + re^{i\omega})\tau} = 1 - a(\lambda^k + k\lambda^{k-1}re^{i\omega} + O(\lambda^{k-2}))e^{\lambda\tau}e^{\tau r e^{i\omega}} = 1 - a(\lambda^k + k\lambda^{k-1}re^{i\omega} + O(\lambda^{k-2}))\frac{1}{a\lambda^k}e^{\tau r e^{i\omega}} = 1 - e^{\tau r e^{i\omega}} - \left(\frac{kre^{i\omega}}{\lambda} + O(\frac{1}{\lambda^2})\right)e^{\tau r e^{i\omega}}$, then $|f(z)| = |f(\lambda + re^{i\omega})| = \left|1 - e^{\tau r e^{i\omega}} - \left(\frac{kre^{i\omega}}{\lambda} + O(\frac{1}{\lambda^2})\right)e^{\tau r e^{i\omega}}\right| \geq |1 - e^{\tau r e^{i\omega}}| - \left|\left(\frac{kre^{i\omega}}{\lambda} + O(\frac{1}{\lambda^2})\right)e^{\tau r e^{i\omega}}\right| \geq |1 - e^{\tau r e^{i\omega}}| - \left(\frac{kr}{|\lambda|} + O\left(\frac{1}{|\lambda|^2}\right)\right)e^{\tau r}$.

Claim: $|1 - e^{\tau r e^{i\omega}}| > 0$ for any $\omega \in [0, 2\pi]$, for any $r \in \left(0, \min\left\{\hat{r}, \frac{\pi}{2\tau}\right\}\right)$.

Proof of the claim: Suppose not, then $|1 - e^{\tau r e^{i\omega}}| = 0 \Leftrightarrow 1 - e^{\tau r e^{i\omega}} = 0 \Leftrightarrow 1 = e^{\tau r e^{i\omega}} \Leftrightarrow 1 = e^{\tau r \cos\omega}(\cos(\tau r \sin\omega) + i\sin(\tau r \sin\omega)) \Rightarrow \sin(\tau r \sin\omega) = 0$, i.e., $\cos(\tau r \sin\omega) = \pm 1$, but $e^{\tau r \cos\omega} > 0$, thus $\cos(\tau r \sin\omega) = 1$, i.e., $\tau r \sin\omega = 2p\pi$ $(\star)$, p is an integer. On the other hand, from $1 = e^{\tau r \cos\omega}$, we can get $\cos\omega = 0 \Rightarrow \sin\omega = \pm 1$, then $(\star)$ becomes $\pm\pi r = 2p\pi(*)$. Since p is an integer, all the values of r such that $(*)$ holds are discrete. Actually, 0 and $2\pi/\tau$ are two successive values of r satisfying $(*)$, then for $0 < r < \min\{\hat{r}, \frac{\pi}{2\tau}\} < \frac{2\pi}{\tau}$, $(*)$ never holds for any integer p. Thus the claim holds.

Choose $\eta = \min\{|1 - e^{\tau r e^{i\omega}}| : \omega \in [0, 2\pi]\} > 0$, which is independent of l, here the minimum is reachable, because $[0, 2\pi]$ is a compact set. Since $\left(\frac{kr}{|\lambda|} + O(\frac{1}{|\lambda|^2})\right)e^{\tau r} \to 0$ as $|\lambda| \to \infty$, or equivalently $l \to \infty$, then $|f(z)| = |f(\lambda + re^{i\omega})| \geq |1 - e^{\tau r e^{i\omega}}| - \left(\frac{kr}{|\lambda|} + O(\frac{1}{|\lambda|^2})\right)e^{\tau r} \geq \eta/2$, $\forall z \in \partial B_r(\lambda(l))$ (or $\forall \omega \in [0, 2\pi]$), for large l.

For the case $k = 0$, $|f(\lambda + re^{i\omega})| = |1 - e^{\tau r e^{i\omega}}|$, then the same $\eta > 0$ works for this special case. $\qquad\square$

Lemma 5. *Let $\lambda = \lambda(l)$ be a zero of $f(z)$, then $|h(z)| \to 0$, $\forall z \in \partial B_r(\lambda(l))$, as $l \to \infty$.*

Proof. Recall $a = -\frac{a_n}{b_m}$, $k = n - m \geq 0$. We have $h(z) = az^k e^{z\tau} + \frac{P_n(z)}{Q_m(z)} e^{z\tau} = \frac{(ab_{m-1}+a_{n-1})z^{n-1}+O(z^{n-2})}{Q_m(z)} e^{z\tau}$. For $z = \lambda + re^{i\omega}$, we have $h(\lambda + re^{i\omega}) = \frac{(ab_{m-1}+a_{n-1})\lambda^{m-1}+O(\lambda^{m-2})}{-a_n\lambda^m+O(\lambda^{m-1})} e^{\tau re^{i\omega}}$. Then $|h(\lambda + re^{i\omega})| \leq \left| \frac{(ab_{m-1}+a_{n-1})\lambda^{m-1}+O(\lambda^{m-2})}{-a_n\lambda^m+O(\lambda^{m-1})} \right| e^{\tau r}$.

Claim: $\left| \frac{(ab_{m-1}+a_{n-1})\lambda^{m-1}+O(\lambda^{m-2})}{-a_n\lambda^m+O(\lambda^{m-1})} \right| \to 0$ as $l \to \infty$.

Proof of the claim:

For the case $k > 0$, $\alpha = \text{Re}(\lambda) \to -\infty$ and $\beta = \text{Im}(\lambda) \to \infty$ as $l \to \infty$. If we write $\lambda = \alpha + i\beta$, then $\left| \frac{(ab_{m-1}+a_{n-1})\lambda^{m-1}+O(\lambda^{m-2})}{-a_n\lambda^m+O(\lambda^{m-1})} \right| = \frac{|(ab_{m-1}+a_{n-1})(\alpha+i\beta)^{m-1}+O((\alpha+i\beta)^{m-2})|}{|-a_n(\alpha+i\beta)^m+O((\alpha+i\beta)^{m-1})|}$. Expanding the parenthesis of $\alpha+i\beta$, it is easy to see $\left| \frac{(ab_{m-1}+a_{n-1})\lambda^{m-1}+O(\lambda^{m-2})}{-a_n\lambda^m+O(\lambda^{m-1})} \right| \to 0$ as $|\alpha|, |\beta| \to \infty$. For the case $k = 0$, the claim keeps the same, because the powers of λ are independent of k. $\alpha \equiv -\frac{1}{\tau} \ln |a|$, and $\beta \to \infty$ as $l \to \infty$, thus the claim still holds in this case.

Therefore, $|h(\lambda + re^{i\omega})| \to 0$ as $l \to \infty$. $\qquad\square$

Theorem 5. *There are infinite zeros with negative real parts of the generic transcendental function $P_n(z) + Q_m(z)e^{-z\tau}$ for the degree $m \leq n$. Furthermore, their real parts go to $-\infty$ asymptotically almost in the shape of $-\ln l$ and imaginary parts go to ∞ asymptotically almost linearly for $m < n$. Their real parts are almost constant and imaginary parts go to ∞ asymptotically almost linearly for $m = n$.*

Proof. Consider the case $m < n$ (or $k > 0$) first. Let $\lambda(l)$ be a zero of $f(z)$ with negative real part for each l. Choose $r \in (0, \min\{\hat{r}, \frac{\pi}{2\tau}\})$ small enough such that: for any $z(l) \in \partial B_r(\lambda(l))$, $\text{Re}(z(l)) \to -\infty$ almost in the same way as $\text{Re}(\lambda(l))$, as $l \to \infty$; i.e., $\text{Re}(z(l)) \to -\infty$ asymptotically almost in the shape of $-\ln l$. Similarly, $\text{Im}(z(l)) \to \infty$ asymptotically almost linearly.

By Lemma 4, there exists an $\eta = \eta(r)$, independent of l such that $|f(z)| \geq \eta/2$, $\forall z \in \partial B_r(\lambda(l))$, for large l. By Lemma 5, for $\epsilon \in (0, \eta/2)$, $|h(z)| < \epsilon$, $\forall z \in \partial B_r(\lambda(l))$, for large l. Choose $l > \max\left\{ \frac{\tau}{\pi \sqrt[k]{|a|}} + \frac{k}{2}, k \right\}$ large enough such that all the properties above hold. Then $|h(z)| < \epsilon < \eta/2 \leq |f(z)|$ for all $z \in \partial B_r(\lambda(l))$, for large l. By the *Rouché's* Theorem, $g(z) = f(z) + h(z)$ also has a zero in $B_r(\lambda(l))$ as $f(z)$ does, for suitable large

l. If the result holds for an l, then it holds for $l+1, l+2, \cdots$. Thus, there are infinite zeros of $g(z)$, i.e., there are infinite zeros of $P_n(z) + Q_m(z)e^{-z\tau}$.

By the choice of r at the beginning of this proof, all the zeros of $g(z)$ have negative real parts for large l, i.e., there are infinite zeros with negative real parts of $P_n(z) + Q_m(z)e^{-z\tau}$. Again by the choice of r, their real parts go to $-\infty$ asymptotically almost in the shape of $-\ln l$ and imaginary parts go to ∞ asymptotically almost linearly.

For the case $m = n$ (or $k = 0$), because Lemmas 3, 4 and 5 hold for this special case as we can see from the proofs of them, the *Rouché*'s Theorem can be applied and the property of negative real parts always hold if we choose $r \in (0, \min\{\hat{r}, \frac{\pi}{2\tau}\})$. Therefore, there are infinite zeros with negative real parts of $P_n(z) + Q_m(z)e^{-z\tau}$ when $m = n$. Similarly, after choosing small $r \in (0, \min\{\hat{r}, \frac{\pi}{2\tau}\})$, their real parts are almost constant and imaginary parts go to ∞ asymptotically almost linearly according to the proof of Lemma 1. $\qquad\square$

Corollary 1. *There are infinite zeros with negative real parts of the generic transcendental function $P_n(z) + \sum_{j=1}^{J} Q_{m_j}(z)e^{-z\tau_j}$ for the degree $m_J \leq m_{J-1} \leq \cdots \leq m_2 \leq m_1 \leq n$ and $\tau_j > 0$. Furthermore, their real parts go to $-\infty$ asymptotically almost in the shape of $-\ln l$ and imaginary parts go to ∞ asymptotically almost linearly except $m_J = m_{J-1} = \cdots = m_2 = m_1 = n$. Their real parts are almost constant and imaginary parts go to ∞ asymptotically almost linearly for $m_J = m_{J-1} = \cdots = m_2 = m_1 = n$.*

Proof. Consider $J = 2$ first, $P_n(z) + Q_{m_1}(z)e^{-z\tau_1} + Q_{m_2}(z)e^{-z\tau_2} = 0 \Leftrightarrow \frac{P_n(z)}{Q_{m_2}(z)} + \frac{Q_{m_1}(z)}{Q_{m_2}(z)}e^{-z\tau_1} + e^{-z\tau_2} = 0$, which is asymptotically equivalent to $az^{n-m_2} + bz^{m_1-m_2}e^{-z\tau_1} + e^{-z\tau_2} = 0$. For $az^{n-m_2} + bz^{m_1-m_2}e^{-z\tau_1} = 0$, we have the results from Theorem 5, that there are infinite zeros with negative real parts of this equation and they behave asymptotically almost like $\frac{a}{b}z^{n-m_1} + e^{-z\tau_1} = 0$. Similarly, we can get there are infinite zeros with negative real parts of $az^{n-m_2} + bz^{m_1-m_2}e^{-z\tau_1} + e^{-z\tau_2} = 0$ and they behave asymptotically almost like $az^{n-m_2} + bz^{m_1-m_2}e^{-z\tau_1} = 0$, and so like $\frac{a}{b}z^{n-m_1} + e^{-z\tau_1} = 0$. Therefore, there are infinite zeros with negative real parts of $P_n(z) + Q_{m_1}(z)e^{-z\tau_1} + Q_{m_2}(z)e^{-z\tau_2} = 0$ and they behave asymptotically almost like $\frac{a}{b}z^{n-m_1} + e^{-z\tau_1} = 0$.

For any natural number J, the mathematical induction allows us to generate the corollary step by step starting from dividing by $Q_{m_J}(z)$.

When two numbers of the set $\{n, m_1, m_2, \cdots, m_J\}$ are different, then obviously real parts of zeros go to $-\infty$ asymptotically almost in the shape of

$-\ln l$. When all of $n, m_1, m_2, \cdots, m_J$ are identical, then real parts of zeros are almost constant. Imaginary parts for both cases go to ∞ asymptotically almost linearly. $\qquad\square$

2.3. *DDEs with one delay and delay dependent parameters*

When we develop mathematical models to study population dynamics, due to the existence of distinct life stages, it is often necessary to incorporate time delays to derive the through-stage survival rate for some specific stage [5, 11]. To this end, we focus on the equation describing how the population in the corresponding stage decays:

$$\frac{dy(t)}{dt} = -\mu y(t),$$

where $y(t)$ is the population size of that specific stage at time t and μ is the constant death rate. Suppose that the inital population size is $y(t_0)$ and the duration of the stage is τ, then the through-stage survival rate is

$$\frac{y(t_0 + \tau)}{y(t_0)} = e^{-\mu\tau}, \tag{13}$$

which is a function of the delay τ. Then it is easy to conceive that these delay differential equation models will inevitably involve some delay dependent parameters through the delay dependent survival rate.

Beretta and Kuang [7] proposed practical guidelines that combine analytical work with graphical information to study some models with delay dependent parameters. To apply their results, we only need to carry out routine computations according to their analytical criteria and plot graphs of some explicit functions which can be easily obtained by using some software such as MATLAB or Maple.

The characteristic equation associated with a DDE with one delay and delay dependent parameters considered in [7] takes the following form:

$$D(\lambda, \tau) := P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0, \tag{14}$$

where

$$P(\lambda, \tau) = \sum_{k=0}^{n} p_k(\tau)\lambda^k \text{ and } Q(\lambda, \tau) = \sum_{k=0}^{m} q_k(\tau)\lambda^k$$

are polynomials in λ whose coefficients are continuous and differentiable functions of τ.

We write $P(\lambda, \tau) = P_R(\lambda, \tau) + iP_I(\lambda, \tau)$ and $Q(\lambda, \tau) = Q_R(\lambda, \tau) + iQ_I(\lambda, \tau)$, where P_R, P_I, Q_R, Q_I are real functions. If equation (14) admits

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a pair of conjugate pure imaginary roots $\pm i\omega$ $(\omega > 0)$, then ω must satisfies the following equation:

$$F(\omega, \tau) := |P(i\omega, \tau)|^2 - |Q(i\omega, \tau)|^2 = 0. \tag{15}$$

As we mentioned before, as τ varies, the roots of equation (14) will vary accordingly. Thus, it is reasonable to regard ω as a function of τ, that is, $\omega = \omega(\tau)$. Assume that $I \subseteq \mathbb{R}_{+0}$ is the set where $\omega(\tau)$ is a positive root of (15), that is, for all $\tau \in I$, $\omega(\tau)$ satisfies that $F(\omega(\tau), \tau) = 0$. It follows that $\omega(\tau)$ must satisfy the following equations:

$$\begin{cases} \sin \omega(\tau) = \frac{-P_R(i\omega(\tau),\tau)Q_I(i\omega(\tau),\tau)+P_I(i\omega(\tau),\tau)Q_R(i\omega(\tau),\tau)}{|Q(i\omega(\tau),\tau)|^2}, \\ \cos \omega(\tau) = \frac{-P_R(i\omega(\tau),\tau)Q_R(i\omega(\tau),\tau)+P_I(i\omega(\tau),\tau)Q_I(i\omega(\tau),\tau)}{|Q(i\omega(\tau),\tau)|^2}. \end{cases} \tag{16}$$

Furthermore, for any $\tau \in I$, we can define the angle $\theta(\tau) \in [0, 2\pi]$ as the solution of (16), that is,

$$\begin{cases} \sin \theta(\tau) = \frac{-P_R(i\omega(\tau),\tau)Q_I(i\omega(\tau),\tau)+P_I(i\omega(\tau),\tau)Q_R(i\omega(\tau),\tau)}{|Q(i\omega(\tau),\tau)|^2}, \\ \cos \theta(\tau) = \frac{-P_R(i\omega(\tau),\tau)Q_R(i\omega(\tau),\tau)+P_I(i\omega(\tau),\tau)Q_I(i\omega(\tau),\tau)}{|Q(i\omega(\tau),\tau)|^2}. \end{cases} \tag{17}$$

and introduce the functions $S_n : I \to \mathbb{R}$ as

$$S_n(\tau) := \tau - \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}, \quad \tau \in I, \ n \in \mathbb{N}_0. \tag{18}$$

The following theorem summarizes the main result of [7]:

Theorem 6 ([7]). *Assume that $\omega(\tau)$ is a positive real root of (15) defined for $\tau \in I, I \subseteq \mathbb{R}_{+0}$, and at some $\tau^* \in I$,*

$$S_n(\tau^*) = 0 \quad \text{for some } n \in \mathbb{N}_0. \tag{19}$$

Then a pair of simple conjugate pure imaginary roots $\lambda_+(\tau^*) = i\omega(\tau^*)$, $\lambda_-(\tau^*) = -i\omega(\tau^*)$ of (14) exists at $\tau = \tau^*$ which crosses the imaginary axis from left to right if $\delta(\tau^*) > 0$ and crosses the imaginary axis from right to left if $\delta(\tau^*) < 0$, where

$$\delta(\tau^*) = \text{sgn}\left\{ \frac{d\,\text{Re}\,\lambda}{d\tau} \bigg|_{\lambda=i\omega(\tau^*)} \right\} = \text{sgn}\{F_\omega'(\omega(\tau^*), \tau^*)\} \,\text{sgn}\left\{ \frac{dS_n(\tau)}{d\tau} \bigg|_{\tau=\tau^*} \right\}. \tag{20}$$

From (17), we can solve for $\theta(\tau)$ in terms of $\omega(\tau)$ and τ. From (15), we can solve for $\omega(\tau)$ in terms of τ. Then we can substitute the expressions of $\omega(\tau)$ and $\theta(\tau)$, both in terms of τ, into (18) to numerically solve for τ^* such that $S_n(\tau^*) = 0$ for some $n \in \mathbb{N}_0$. After that we can determine whether the

stability switch is towards stable or unstable according to whether $\delta(\tau^*)$ is negative or positive. The function $S_n(\tau)$ often has only two zeros for some $n \in \mathbb{N}_0$ and the stability normally changes from stable to unstable to stable, which is different from the case with only delay independent parameters where large delays usually distablize stability (see, e.g., [23]). When multiple S_n's have zeros, the stability switches become more complicated, staggering between stable and unstable. Some user friendly geometric and analytic criteria for stability switches related to first order and second order characteristic equations are provided in [7], which can be helpful for obtaining insightful analytical statements and conducting simulations.

We provide below an example about the application of the method introduced in [7]. Li and Shu [28] formulated the following model to investigate the dynamics of immune response to HTLV-1 infections.

$$
\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - d_1 x(t) - \beta x(t)y(t), \\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= \beta x(t)y(t) - d_2 y(t) - \gamma y(t)z(t), \\
\frac{\mathrm{d}z(t)}{\mathrm{d}t} &= \mu y(t-\tau)z(t-\tau) - d_3 z(t).
\end{aligned}
\tag{21}
$$

Here $x(t)$, $y(t)$, $z(t)$ are the number of uninfected CD4$^+$ target T cells, the number of infected CD4$^+$ target T cells, and the number of HTLV-1 specific CTLs, at time t, respectively. The delay τ represents the period of a chain events from antigenic activation to proliferation of CTLs. Following the procedure in [7], they assume that the characteristic equation associated with the linearization of system (21) at the positive equilibrium $P_2 = \left(\frac{\lambda\mu}{d_1\mu+\beta d_3}, \frac{d_3}{\mu}, \frac{\lambda\beta\mu-d_1 d_2\mu-\beta d_2 d_3}{(d_1\mu+\beta d_3)\gamma}\right)$ has a pair of pure imaginary roots $\xi = \pm i\omega(\omega > 0)$. Then ω is a positive root of the polynomial

$$
F(\omega) := \omega^6 + (a_2^2 - b_2^2 - 2a_1)\omega^4 + (a_1^2 - 2a_0 a_1 - b_1^2 + 2b_0 b_2)\omega^2 + (a_0^2 - b_0^2),
$$

where a_i and b_i, $i = 0, 1, 2$, are given in terms of the parameters of system (21), and there exists a sequence of bifurcation values τ_n such that $\pm i\omega$ ($\omega > 0$) are the pure imaginary roots of the characteristic equation. Then a direct visualization of stability switching is given by

$$
\mathrm{sgn}\left\{\left.\frac{\mathrm{d}\mathrm{Re}\xi}{\mathrm{d}\tau}\right|_{\xi=i\omega, \tau=\tau_n}\right\} = \mathrm{sgn}\{G'(\omega^2)\},
$$

where $G(u) = F(\sqrt{u})$ and $G(u)$ can have one, two, or three positive roots. Li and Shu [28] investigated the case when $G(u)$ has two positive roots and they showed that stability switches can happen for the positive equilibrium

P_2 and multiple stable periodic solutions can coexist when there are two sequences of Hopf bifurcation points. Li, Lin and Wang [26] extended the results of [28] by investigating the case when $G(u)$ has three positive roots (see Figure 2(a)) corresponding to three sequences of Hopf bifurcation points $\{\tau_n^{(j)}\}_{n=0}^{\infty}$, $j = 1, 2, 3$. They found that, in addition to the two families of bounded global Hopf bifurcation branches, there is a third family of unbounded Hopf branches along which period-doubling secondary bifurcations may occur (see Figure 2(b) for the three families of global Hopf branches and Figure 2(f) for the period doubling effect). They also showed that multiple stable periodic solutions can coexist under some parameter values (see Figures 2(c) and 2(d)).

2.4. *DDEs with two delays and delay independent parameters*

The parameters of some DDE models may be all independent of delays. For example, if the mortality rate δ for a specific life stage of a biological species is extremely small, then the probability for the population to survive that stage $e^{-\delta\tau}$ is approximately equal to 1. If we replace $e^{-\delta\tau}$ by 1, then the parameter is delay independent. Lin and Wang [31] exploited an algebraic method, which is different from those in [1, 7], to derive the criteria for stability switching and crossing directions for DDEs with two discrete delays and delay independent parameters. The characteristic equation that Lin and Wang considered in [31] is as follows:

$$D(\lambda, \tau_1, \tau_2) := P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0. \tag{22}$$

where τ_1 and τ_2 are the two delays in $\mathbb{R}_+$, and

$$P_l(\lambda) = \sum_{k=0}^{n_l} p_{lk}\lambda^k, \quad l = 0, 1, 2, 3$$

are polynomials with real coefficients.

The key idea is to separate the two delays τ_1 and τ_2:

$$D(i\omega, \tau_1, \tau_2) = (P_0(i\omega) + P_1(i\omega)e^{-i\omega\tau_1}) + (P_2(i\omega) + P_3(i\omega)e^{-i\omega\tau_1})e^{-i\omega\tau_2}. \tag{23}$$

Since $|e^{-i\omega\tau_2}| = 1$, we can obtain an equation involving only τ_1:

$$|P_0 + P_1 e^{-i\omega\tau_1}| = |P_2 + P_3 e^{-i\omega\tau_1}|, \tag{24}$$

which is equivalent to

$$|P_0|^2 + |P_1|^2 - |P_2|^2 - |P_3|^2 = 2A_1(\omega)\cos(\omega\tau_1) - 2B_1(\omega)\sin(\omega\tau_1), \tag{25}$$

where

$$A_1(\omega) = \operatorname{Re}(P_2\overline{P}_3) - \operatorname{Re}(P_0\overline{P}_1),$$
$$B_1(\omega) = \operatorname{Im}(P_2\overline{P}_3) - \operatorname{Im}(P_0\overline{P}_1).$$

If there is some ω such that $A_1(\omega)^2 + B_1(\omega)^2 = 0$, then all $\tau_1 \in \mathbb{R}_+$ are solutions of (24).

If $A_1(\omega)^2 + B_1(\omega)^2 > 0$, then there exists a continuous function $\phi_1(\omega)$ such that

$$A_1(\omega) = \sqrt{A_1(\omega)^2 + B_1(\omega)^2}\cos(\phi_1(\omega)),$$
$$B_1(\omega) = \sqrt{A_1(\omega)^2 + B_1(\omega)^2}\sin(\phi_1(\omega)).$$

Then, (25) becomes

$$|P_0|^2 + |P_1|^2 - |P_2|^2 - |P_3|^2 = 2\sqrt{A_1(\omega)^2 + B_1(\omega)^2}\cos(\phi_1(\omega) + \omega\tau_1). \quad (26)$$

Let

$$\cos(\psi_1(\omega)) = \frac{|P_0|^2 + |P_1|^2 - |P_2|^2 - |P_3|^2}{2\sqrt{A_1(\omega)^2 + B_1(\omega)^2}}, \ \ \psi_1 \in [0, \pi].$$

From this, we can solve for τ_1:

$$\tau_{1,n_1}^{\pm}(\omega) = \frac{\pm\psi_1(\omega) - \phi_1(\omega) + 2n_1\pi}{\omega}, \ n_1 \in \mathbb{Z}.$$

Note that τ_1 and τ_2 are in similar positions in (22). Therefore, we can use a similar argument to derive τ_2:

$$\tau_{2,n_2}^{\pm}(\omega) = \frac{\pm\psi_2(\omega) - \phi_2(\omega) + 2n_2\pi}{\omega}, \ n_2 \in \mathbb{Z},$$

where

$$\cos(\psi_2(\omega)) = \frac{|P_0|^2 - |P_1|^2 + |P_2|^2 - |P_3|^2}{2\sqrt{A_2^2 + B_2^2}}, \ \ \psi_2 \in [0, \pi],$$
$$A_2(\omega) = \sqrt{A_2(\omega)^2 + B_2(\omega)^2}\cos(\phi_2(\omega)),$$
$$B_2(\omega) = \sqrt{A_2(\omega)^2 + B_2(\omega)^2}\sin(\phi_2(\omega)),$$
$$A_2(\omega) = \operatorname{Re}(P_1\overline{P}_3) - \operatorname{Re}(P_0\overline{P}_2),$$
$$B_2(\omega) = \operatorname{Im}(P_1\overline{P}_3) - \operatorname{Im}(P_0\overline{P}_2).$$

Let Ω be the set of all $\omega \in \mathbb{R}_+$ satisfying (26). Lemma 3.2 of [31] shows that Ω consists of a finite number of intervals of finite length:

$$\Omega = \bigcup_{k=1}^{N} \Omega_k, \quad \Omega_k = [a_k, b_k].$$

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Here, $0 \leq a_1 < b_1 \leq a_2 < b_2 \leq \cdots \leq a_N < b_N < +\infty$ and $\Omega_1 = (0, b_1]$ if $a_1 = 0$. For any Ω_k, let $\phi_i(\omega)$ be the smallest continuous branch such that there exists an $\omega_i \in \Omega_k$ satisfying $\phi_i(\omega_i) > 0$. Then n_i has a lower bound $L_{i,k}, i = 1, 2$. The crossing curves are

$$\mathcal{T} = \bigcup_{\substack{k=1,2,\ldots,N \\ n_1 \geq L_{1,k} \\ n_2 \geq L_{2,k}}} \mathcal{T}_{n_1,n_2}^{\pm k} \bigcap \mathbb{R}_+^2, \tag{27}$$

where $\mathcal{T}_{n_1,n_2}^{\pm k} = \left\{ (\tau_{1,n_1}^{\pm}(\omega), \tau_{2,n_2}^{\mp}(\omega)) : \omega \in \Omega_k \right\}$. Note that when $\tau_1 = \tau_{1,n_1}^+(\omega)$, we have $\tau_2 = \tau_{2,n_2}^-(\omega)$, and when $\tau_1 = \tau_{1,n_1}^-(\omega)$, we have $\tau_2 = \tau_{2,n_2}^+(\omega)$, which can be verified by tedious computation.

Let $F(\omega) := (|P_0|^2 + |P_1|^2 - |P_2|^2 - |P_3|^2)^2 - 4(A_1^2 + B_1^2), \omega \geq 0$. Since $F(a_k) = F(b_k) = 0$, we have

$$\cos(\psi_i(a_k)) = \delta_i^a, \quad \cos(\psi_i(b_k)) = \delta_i^b,$$

where $\delta_i^a, \delta_i^b = \pm 1, \ i = 1, 2$. In application, we can calculate the values of δ_i^a and $\delta_i^b, \ i = 1, 2$, to judge the shape of the crossing curve $\mathcal{T}$ according to the following theorem:

Theorem 7 ([31]). $\mathcal{T}$ *defined in* (27) *is the set of all stability switching curves on the (τ_1, τ_2)-plane for* (22). *Furthermore, if $(\delta_1^a, \delta_2^a) = (\delta_1^b, \delta_2^b)$, then $\mathcal{T}_{n_1,n_2}^{+k}$ and $\mathcal{T}_{n_1+\delta_1^a,n_2-\delta_2^a}^{-k}$ form a loop on $\mathbb{R}^2$, and $\mathcal{T}$ is a set of closed continuous curves (Class I); while if $(\delta_1^a, \delta_2^a) \neq (\delta_1^b, \delta_2^b)$, $\mathcal{T}$ is a set of continuous curves with their two end points either on the axises or extending to infinity on the $\mathbb{R}_+^2$ region (Class II).*

By using the similar method in determining the crossing direction as in [14], Lin and Wang obtained the following result regarding the crossing direction for DDEs with two delays and delay independent parameters:

Theorem 8 ([31]). *The region on the left of $\mathcal{T}_{n_1,n_2}^{+k}(\mathcal{T}_{n_1,n_2}^{-k})$ has two more (less) characteristic roots with positive real parts.*

An example about plotting the crossing curves and determining the crossing directions for a Lotka-Volterra predator-prey model with two delays and delay independent parameters is given at the end of [31].

2.5. *DDEs with two delays and delay dependent parameters*

For models with two delays and delay dependent parameters, in order to investigate stability switches, we also need to consider the possibility of

characteristic roots crossing imaginary axis as the delays vary, which is similar to the case with one delay. However, for a model with one delay, the critical value τ^* at which pure imaginary roots occur is a point on the real line. In contrast, for a model with two delays τ and τ_1, the points $(\hat{\tau}, \hat{\tau}_1)$ at which pure imaginary roots appear constitute the crossing curves on the τ-τ_1 plane, and directional derivatives are needed to determine the crossing directions.

Recently, An et al. [1] presented a practical geometric method to study the stability switching properties of the following characteristic equation which may result from the stability analysis of some models involving two discrete delays and parameters depending on only one of the delays.

$$D(\lambda, \tau, \tau_1) := P_0(\lambda, \tau) + P_1(\lambda, \tau)e^{-\lambda\tau} + P_2(\lambda, \tau)e^{-\lambda\tau_1} = 0. \qquad (28)$$

Here $\tau \in I \subseteq \mathbb{R}_+$ and $\tau_1 \in \mathbb{R}_+$ are the two delays, and

$$P_l(\lambda, \tau) = \sum_{k=0}^{n_l} p_{lk}(\tau)\lambda^k, \quad l = 0, 1, 2$$

are polynomials in λ whose coefficients are bounded functions $p_{lk} : I \to \mathbb{R}$ of class C^1.

The goal is to find the crossing curves on which (28) has purely imaginary roots and to determine the crossing directions. As the length of any one side of a triangle must not exceed the sum of the lengths of the other two sides, if $\lambda = i\omega$ is a zero of (28) for some $(\tau, \tau_1) \in I \times \mathbb{R}_+$, then (ω, τ) satisfies

$$\begin{aligned}
|a_1(\omega, \tau)| + |a_2(\omega, \tau)| &\geq 1, \\
|a_1(\omega, \tau)| - |a_2(\omega, \tau)| &\leq 1, \\
|a_2(\omega, \tau)| - |a_1(\omega, \tau)| &\leq 1,
\end{aligned} \qquad (29)$$

where $a_l(\omega, \tau) = P_l(i\omega, \tau)/P_0(i\omega, \tau)$, $l = 1, 2$.

The steps for determining the crossing curves are summarized as follows:

Step 1. Determine the feasible region Ω for (ω, τ), based on (29). The admissible range of ω for each connected region of Ω are denoted by $I_k, k = 1, 2, \cdots, N$.

Step 2. Define the functions $S_n^{\pm} : \Omega \to \mathbb{R}$ by

$$S_n^{\pm}(\omega, \tau) = \tau - \frac{1}{\omega}[\arg(a_1(\omega, \tau)) + (2n-1)\pi \pm \theta_1(\omega, \tau)], \quad n \in \mathbb{Z}. \quad (30)$$

For each $\omega \in I_k$, there are τ-intervals $I_\omega^k := [\tau_\omega^{k,l}, \tau_\omega^{k,r}] \subseteq I$ on which inequalities (29) hold. For each fixed $\omega \in I_k$, identify the zeros of the $S_n^{\pm}$ in I_ω^k, and let ω take all the feasible values. Then, we get the curve $\mathcal{C} := \{(\omega, \hat{\tau}^{i\pm}(\omega)) : \omega \in I_k, S_n^{\pm}(\omega, \hat{\tau}^{i\pm}(\omega)) = 0\}$ on Ω.

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Step 3. For each $\hat{\tau}^{i\pm}(\omega)$, set up the corresponding values of τ_1:

$$\hat{\tau}_{1,i}^{j\pm}(\omega) = \frac{1}{\omega}[\arg(a_2(\omega, \hat{\tau}^{i\pm})) + (2j^{\pm} + 1)\pi \mp \theta_2(\omega, \hat{\tau}^{i\pm})], \qquad (31)$$

for $j = j_0^{\pm}, j_0^{\pm}+1, \cdots$, where $j_0^{\pm}$ are the smallest integers such that $\hat{\tau}_{1,i}^{j\pm}(\omega) > 0$, to obtain the crossing curve $\mathcal{T} = \{(\hat{\tau}^{i\pm}(\omega), \hat{\tau}_{1,i}^{j\pm}(\omega)) \in I_\omega^k \times \mathbb{R}_+ | \omega \in I_k\}$. The points on the crossing curve will determine the values of τ and τ_1 for which (28) has a pair of purely imaginary roots $\pm i\omega$.

Step 4. Calculate the crossing directions of the crossing curve according to the following Theorem 9. As in [14], we call the direction of the crossing curve $\mathcal{T}$ corresponding to increasing ω the positive direction, and the region on the right-hand (left-hand) side when we move along the positive direction of $\mathcal{T}$ the region on the right (left).

Theorem 9 ([1]). *The characteristic equation* (28) *admits a pair of conjugate roots* $\pm i\omega^*$, *for* $(\tau, \tau_1) = (\tau^*, \tau_1^*) \in \mathcal{T}$. *If* $\frac{\partial D}{\partial \lambda}(i\omega^*, \tau^*, \tau_1^*) \neq 0$, *then* (28) *has a pair of conjugate complex roots* $\lambda^{\pm}(\tau, \tau_1) = \alpha(\tau, \tau_1) \pm i\omega(\tau, \tau_1)$ *in some neighborhood of* (τ^*, τ_1^*), *such that* $\alpha(\tau^*, \tau_1^*) = 0$ *and* $\omega(\tau^*, \tau_1^*) = \omega^*$. *Furthermore,* $\lambda^{\pm}(\tau, \tau_1)$ *cross the imaginary axis from left to right, as* (τ, τ_1) *passes through the crossing curve to the region on the right (left) whenever* $\delta(\tau^*, \tau_1^*) > 0$ $(\delta(\tau^*, \tau_1^*) < 0)$, *where*

$$\delta(\tau^*, \tau_1^*) = -\text{Re}\left\{\left[P_{0\tau}^* e^{i\omega^* \tau_1^*} + (P_{1\tau}^* - i\omega^* P_1^*)e^{i\omega^*(\tau_1^* - \tau^*)} + P_{2\tau}^*\right]\overline{P_2^*}\right\}$$

with $P_l^* = P_l(i\omega^*, \tau^*)$ *and* $P_{l\tau}^* = \frac{\partial P_l}{\partial \tau}(i\omega^*, \tau^*)$, $l = 0, 1, 2$.

The most critical step above is to determine the curve $\mathcal{C}$ on the feasible region Ω. The curve $\mathcal{C}$ is the set of all zeros of the function $S_n^{\pm}(\omega, \tau)$. Due to the complexity of $S_n^{\pm}(\omega, \tau)$, we need to numerically solve for these zeros. Once the curve $\mathcal{C}$ is obtained, we can immediately deduce the shape of the crossing curves $\mathcal{T}$ by Propositions 3.12 and 3.13 in [1]. The four possible types of crossing curves include open-ended, closed, truncated, and spiral-like ones (see Appendix of [1] for examples about various types of crossing curves).

An example for the characteristic equation (28) with $P_0(\lambda, \tau) = \lambda + 1$, $P_1(\lambda, \tau) = 5e^{-\tau} - 0.5$, and $P_2(\lambda, \tau) = 2$ is discussed in [1] to provide visual illustrations for the analytical result. Figure 3 shows the curve $\mathcal{C}$ and the crossing curves $\mathcal{T}$ as well as the crossing directions.

When an increasing number of discrete delays are involved in a model, it would become more difficult to determine stability since the dimension of the stability switching surface increases. In addition, the characteristic equations could become more complex even for some models with two

delays and delay dependent parameters. For example, for the following characteristic equation

$$P_0(\lambda, \tau) + P_1(\lambda, \tau)e^{-\lambda\tau} + P_2(\lambda, \tau)e^{-\lambda\tau_1} + P_3(\lambda, \tau)e^{-\lambda(\tau+\tau_1)} = 0, \quad (32)$$

the four terms on the left hand side will produce a quadrilateral. In this case, although the method in [1] applies, much more complicated analysis may be needed.

The results of [1] include the results shown by [14] for the characteristic equations with two delays and delay independent parameters derived from single species population delay model but do not cover the results presented by [31] for the characteristic equation corresponding to multiple species models with two delays and delay independent parameters. According to the methods in [1, 7, 31], we can follow the routine procedures to analyze the possibility of stability switches of equilibria for DDEs with one or two delays. The characteristic equation also plays an important role in Hopf bifurcation analysis for establishing the existence of periodic solutions as the primary condition for Hopf bifurcation theorem is related to characteristic roots (see Theorem 6.1 in [58] and examples about Hopf bifurcations of DDEs in [26, 27, 45] and the references therein).

3. Global attractivity and uniform persistence via infinite dimensional dynamical systems

Many biological processes, such as predation, reproduction, migration, biodegradation and disease transmission are influenced by seasonal factors such as temperature, humidity, the availability of resources, etc. Therefore, it is reasonable to incorporate seasonality in some DDE models. In that case, we will have periodic delay differential equations, that is, DDEs with some parameters being periodic functions. An effective method to study such periodic DDEs is via the dynamical systems approach. The essential idea is that the existence and stability of periodic solutions of a periodic DDE system is equivalent to those of the fixed points of its associated Poincaré map. The uniform persistence of the periodic semiflow generated by a periodic DDEs also reduces to that of its associated Poincaré map. These abstract theories are so powerful that they also work for DDEs with periodic delays or multiple delays. In addition, the theories are not restricted to periodic DDEs but also apply to periodic ODEs and periodic PDEs. Of course, they also apply to autonomous systems since autonomous systems can be regarded as periodic systems with any fixed positive real

number being the period. However, for nonperiodic nonautonomous systems (e.g., almost periodic DDEs), we can not define a discrete or continuous dynamical system on the state space, and the skew-product semiflow approach is needed (see [49, 52, 77]). Next, we will first introduce the definition of Poincaré map associated with a given periodic DDE system, and then present the theory of threshold dynamics regarding glabal attractivity for monotone systems and the theory of uniform persistence. The definitions and theorems in this section are adopted from [77].

Now we assume that system (1) is a periodic system with period $\omega > 0$ and for any given $\phi \in C$, the solution $x(t, \phi)$ satisfying $x_0 = \phi$ is unique and exits globally on $[0, \infty)$. We define a family of mappings $T(t) : C \to C$, $t \geq 0$, by $T(t)\phi = x_t(\phi)$, $\forall \phi \in C$. Then $T(t)$ satiesfies the following properties:

(1) $T(0) = I$, where I is the identity map on C;
(2) $T(t + \omega) = T(t) \circ T(\omega)$, $\forall t \geq 0$;
(3) $T(t)\phi$ is continuous in $(t, \phi) \in [0, \infty) \times C$.

$T(t)$ is called the periodic semiflow generated by the periodic DDE system (1), and $S := T(\omega)$ is its associated Poincaré map. Since $S^n\phi = x_{n\omega}(\phi)$, $\forall n \geq 1$, $\phi \in C$, then the study of the dynamics of system (1) can be reduced to that of the discrete dynamical system $\{S^n\}$ on C.

3.1. *Global attractivity: threshold dynamics*

Let E be an ordered Banach space with positive cone P such that $\text{int}(P) \neq \emptyset$. For $x, y \in E$ we write $x \geq y$ if $x - y \in P$, $x > y$ if $x - y \in P \setminus \{0\}$, and $x \gg y$ if $x - y \in \text{int}(P)$. If $a < b$, we define $[a, b] := \{x \in E : a \leq x \leq b\}$.

Definition 1 ([77]). Let U be a subset of E, and $f : U \to U$ a continuous map. The map f is said to be monotone if $x \geq y$ implies that $f(x) \geq f(y)$; strictly monotone if $x > y$ implies that $f(x) > f(y)$; strongly monotone if $x > y$ implies that $f(x) \gg f(y)$.

A subset K of E is said to be order convex if $[u, v]_E \subset K$ whenever $u, v \in E$ satisfy $u < v$. Now we assume that $U \subseteq P$ is a nonempty, closed, and order convex set.

Definition 2. ([77]) A continuous map $f : U \to U$ is said to be subhomogeneous if $f(\lambda x) \geq \lambda f(x)$ for any $x \in U$ and $\lambda \in [0, 1]$; strictly subhomogeneous if $f(\lambda x) > \lambda f(x)$ for any $x \in U$ with $x \gg 0$ and $\lambda \in (0, 1)$;

strongly subhomogeneous if $f(\lambda x) \gg \lambda f(x)$ for any $x \in U$ with $x \gg 0$ and $\lambda \in (0, 1)$.

The following theorem establishes threshold dynamics regarding the existence and global attractivity of a strongly positive fixed point for two types of maps: either monotone and strongly subhomogeneous, or strongly monotone and strictly subhomogeneous.

Theorem 10 ([77]). *Let either $V = [0, b]_E$ with $b \gg 0$ or $V = P$. Assume that*

(1) $f : V \to V$ satisfies either of the following two conditions

   (C1) $f : U \to U$ is monotone and strongly subhomogeneous;
   (C2) $f : U \to U$ is strongly monotone and strictly subhomogeneous;

(2) $f : V \to V$ is asymptotically smooth, and every positive orbit of f in V is bounded;
(3) $f(0) = 0$, and $Df(0)$ is compact and strongly positive.

Then there exist threshold dynamics:

(a) If $r(Df(0)) \leq 1$, then every positive orbit in V converges to 0;
(b) If $r(Df(0)) > 1$, then there exists a unique fixed point $u^* \gg 0$ in V such that every positive orbit in $V \setminus \{0\}$ converges to u^*.

In applications, the fixed point may correspond to an equilibrium or a periodic solution, and the threshold parameter $r(Df(0))$ is usually the basic reproduction number $\mathcal{R}_0$. The theory of $\mathcal{R}_0$ for periodic DDEs has been developed by Zhao [76], and $\mathcal{R}_0$ can be estimated numerically according to Theorem 2.2 in [76] and Lemma 2.5 in [30]. Wu et al. [72] proposed another approach for numerical calculation of $\mathcal{R}_0$. The algorithm introduced by Posny and Wang [47] can also be modified to calculate $\mathcal{R}_0$ for periodic DDEs.

What is usually used in company with Theorem 10 is the theory of internally chain transitive set which helps lift the threshold dynamics of a subsystem to the entire system. This is particularly useful as most models are not monotone, and hence, we can not directly apply Theorem 10 to the original model. However, if we can find a subsystem or limiting subsystem satisfying the conditions of Theorem 10, then we can first obtain the threshold dynamics for the subsystem by Theorem 10 and then raise the result for the subsystem to the entire model system by using the theory of chain transitive sets presented as follows.

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Let (X, d) be a complete metric space with metric d, and $f : X \to X$ be a continuous map.

Definition 3. ([77]) A nonempty invariant set $A \subset X$ for f is said to be internally chain transitive if for any $a, b \in A$ and any $\epsilon > 0$, there is a finite sequence $x_1 = a, x_2, \ldots, x_{m-1}, x_m = b$ in A such that $d(f(x_i), x_{i+1}) < \epsilon$, $i = 1, \ldots, m - 1$. The sequence $\{x_1, \ldots, x_m\}$ is called an ϵ-chain in A connecting a and b.

Lemma 6. *([77]) Let $f : X \to X$ be a continuous map. Then the omega (alpha) limit set of any precompact positive (negative) orbit is internally chain transitive.*

Theorem 11. *([77]) Let A be an attractor and C a compact internally chain transitive set for $f : X \to X$. If $C \cap W^s(A) \neq \emptyset$, then $C \subset A$.*

Theorem 12. *([77]) Assume that each fixed point of f is an isolated invariant set, that there is no cyclic chain of fixed points, and that every precompact orbit converges to some fixed point of f. Then any compact internally chain transitive set is a fixed point of f.*

Note that, in Definition 3, every point x_i on the chain must locate inside the set A in order to make A an "internally" chain transitive set. If for some $a \in A$, $b \in A$, or $\epsilon > 0$, we can not find such a chain that totally lies inside A, then A is not an internally chain transitive set. Lemma 6 gives a very useful example for internally chain transitive sets. Theorem 11 is often used to deduce the omega limit set of a map. For example, if the attractor A consists of a single fixed point which is globally asymptotically stable, then according to Lemma 6 and Theorem 11, the omega limit set contains only that fixed point. If there are multiple fixed points that satisfy the conditions of Theorem 12, then the omega limit set is a set of a sinlge fixed point. In that case, we may try to prove by contradiction to obtain the unique possible omega limit set by excluding those impossble ones.

In recent years, periodic delays have attained an increasing attention in modeling species activities or disease transmission dynamics especially in the scenario of climate change as delays may vary seasonally. For example, the duration for malaria parasite development in mosquitoes are strongly affected by temperature, and hence, a periodic incubation delay is more reasonable than a constant one [65]. By using the methods in [40, 41], Wang and Zhao [65] formulated a seasonal malaria transmission model with a periodic delay $\tau(t)$ and proved the threshold result of global dynamics of

the model by using the theory of monotone and subhomogeneous systems and the theory of chain transitive sets, which gives a good example for the application of the theories introduced in this section. The model is given by the following system of DDEs:

$$
\begin{aligned}
\frac{dI_h(t)}{dt} =& \frac{c\beta(t)l(H - I_h(t))}{pI_h(t) + l(H - I_h(t))} I_m(t) - (d_h + \rho)I_h(t), \\
\frac{dS_m(t)}{dt} =& \mu(t) - B(t, I_h(t), S_m(t)) - d_m(t)S_m(t), \\
\frac{dE_m(t)}{dt} =& B(t, I_h(t), S_m(t)) - d_m(t)E_m(t) \\
& - (1 - \tau'(t))B(t - \tau(t), I_h(t - \tau(t)), S_m(t - \tau(t)))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi}, \\
\frac{dI_m(t)}{dt} =& (1 - \tau'(t))B(t - \tau(t), I_h(t - \tau(t)), S_m(t - \tau(t)))e^{-\int_{t-\tau(t)}^{t} d_m(\xi)d\xi} \\
& - d_m(t)I_m(t),
\end{aligned}
$$

$$(33)$$

where the variables $I_h(t)$, $S_m(t)$, $E_m(t)$ and $I_m(t)$ are the number of infectious humans, susceptible, exposed and infectious adult female mosquitoes at time t, respectively. The delay $\tau(t)$ represents the length of the extrinsic incubation period (i.e., the development duration for malaria parasites in mosquitoes). All constant parameters are positive, and the mosquito-related parameters $\mu(t)$, $\beta(t)$, $d_m(t)$, $\tau(t)$ are positive, continuous, ω-periodic for some $\omega > 0$ to reflect seasonality.

Comparing with the malaria model which has a constant delay in [64], one can see that a DDE model with periodic delays can not be obtained by simply replacing the constant delay τ with a periodic delay $\tau(t)$. Instead, we need to carry out analytical derivations and the term $(1 - \tau'(t))$ will occur in the end. A model with periodic delay can also be derived by using the technique of integration along characteristics (see, e.g., [36]). For the scalar DDE model with time-dependent delay, Brunner and Maset [9] proposed a method to construct a time-transformation function $t = h(s)$ such that $x(t)$ is the solution of an initial value problem with the scalar DDE $x'(t) = f(t, x(t), x(t - \tau(t)))$, where $\tau(t)$ is a time-dependent delay, and $y = x \circ h$ is a solution of the initial value problem with the DDE $y'(s) = h'(s)f(h(s), y(s), y(s - \tau^*))$, where τ^* is a constant delay. However, the existence and stability analysis of a periodic solution remains challenging. Nah and Wu [38] discussed the time transformation for the special case when $\tau(t)$ is a periodic function and derived the conditions for the existence of a periodic solution of the scalar DDE model with a periodic delay. For more interesting models with multiple periodic time delays or

nested periodic time delays (i.e., one delay being nested in another one), we refer readers to [20, 32, 67].

3.2. *Uniform persistence*

Uniform persistence characterizes the long-term existence or survival of some species or diseases. Abstractly, it is the concept that a closed subset of the state space repels the dynamics on its complementary set, and it provides a uniform estimate for the omega limit set, which sometimes is critical for obtaining a more detailed result about global dynamics [77].

Let $f : X \to X$ be a continuous map and $X_0 \subset X$ an open set. Define $\partial X_0 := X \setminus X_0$ and $M_\partial := \{x \in \partial X_0 : f^n(x) \in \partial X_0, n \geq 0\}$. Then we have the following definition for the abstract uniform persistence.

Definition 4. ([77]) A function $f : X \to X$ is said to be uniformly persistent with respect to $(X_0, \partial X_0)$ if there exists $\eta > 0$ such that $\liminf\limits_{n \to \infty} d(f^n(x), \partial X_0) \geq \eta$ for all $x \in X_0$.

As the word "uniform" indicates, all initial states in X_0 share the same η. For a given system, η only depends on X_0. Different X_0 may lead to different uniform persistence. It is also worth mentioning that ∂X_0 needs not to be the boundary of X_0. For an ODE system, it is enough to show $\liminf\limits_{n \to \infty} d(f^n(x), \partial X_0) \geq \eta$ for all $x \in X_0$ in order to obtain biologically the prolonged survival of species or continued existence of diseases, and the criteria for proving this are given in Theorem 1.3.1 in [77]. However, this is not the case for a DDE system. For example, suppose that for system (1) we have $X = C([-\tau, 0], \mathbb{R}_+)$ and set $X_0 = X \setminus \{0\}$, $\partial X_0 = \{0\}$, and the solutions are nonnegative, then for any $\varphi \in X_0$, $\liminf\limits_{t \to \infty} d(T(t)\varphi, \partial X_0) \geq \eta$ implies that

$$
\begin{aligned}
\eta &\leq \liminf_{t \to \infty} \|T(t)\varphi - 0\| \\
&= \liminf_{t \to \infty} \|x_t(\varphi)\| \\
&= \liminf_{t \to \infty} \max_{-\tau \leq \theta \leq 0} x(t + \theta, \varphi) \\
&= \liminf_{t \to \infty} \max_{t - \tau \leq s \leq t} x(s, \varphi).
\end{aligned}
\tag{34}
$$

However, what we need to obtain in application is $\liminf\limits_{t \to \infty} x(t, \varphi) \geq \delta$ for some $\delta > 0$. In other words, as the state space for a DDE system is infinite dimensional, the distance function $d(x, \partial X_0)$ induced by the maximum norm only gives rise to an abstract repelling property of ∂X_0, which can not

express the realistic biological meaning of uniform persistence for a biological system. Therefore, we need to extend the abstract uniform persistence to a more general case to derive the practical uniform persistence. See the following Definitions 5 and 6.

Definition 5. ([77])*A lower semicontinuous function $p : X \to \mathbb{R}_+$ is called a generalized distance function for $f : X \to X$ if for every $x \in (X_0 \cap p^{-1}(0)) \cup p^{-1}(0, \infty)$, we have $p(f^n(x)) > 0$, $\forall n \geq 1$.*

Definition 6. ([77]) *Let p be a generalized distance function for a continuous map $f : X \to X$. Then f is said to be uniformly persistent with respect to $(X_0, \partial X_0, p)$ if there exists $\eta > 0$ such that $\liminf_{n \to \infty} p(f^n(x)) \geq \eta$ for all $x \in X_0$.*

Suppose $X = C([-\tau, 0], \mathbb{R}^m)$ for a given DDE model, then a typical way to define the generalized function p is to let $p(\varphi) = \min_{1 \leq i \leq m}\{\varphi_i(0)\}$ for any given $\varphi = (\varphi_1, \cdots, \varphi_m) \in X$. In this way, $p(T(t)\varphi) = \min_{1 \leq i \leq m}\{x_i(t, \varphi)\}$. The following theorem provides the method to prove the practical uniform persistence.

Theorem 13. *([77]) Let p be a generalized distance function for continuous map $f : X \to X$. Assume that*

(P1) *f has a global attractor A;*
(P2) *There exists a finite sequence $M = \{M_1, \ldots, M_k\}$ of disjoint, compact, and isolated invariant sets in ∂X_0 with the following properties:*

    (a) *$\cup_{x \in M_\partial}\omega(x) \subset \cup_{i=1}^k M_i$;*
    (b) *no subset of M forms a cycle in ∂X_0;*
    (c) *M_i is isolated in X;*
    (d) *$W^s(M_i) \cap p^{-1}(0, \infty) = \emptyset$ for each $1 \leq i \leq k$.*

Then there exists $\delta > 0$ such that for any compact chain transitive set L with $L \nsubseteq M_i$ for all $1 \leq i \leq k$, we have $\min_{x \in L} p(x) > \delta$.

Before ending this section, we provide two examples about the application of the uniform persistence theory: one is about an epidemiological model for Lyme disease and the other is about an ecological model for seasonal predator-prey dynamics such as daphnia-algea interaction. Note that for epidemiological models we need to prove the existence of a uniform positive lower bound for disease-related variables only whereas for ecological models we need to find such a lower bound for all variables. However,

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sometimes it is challenging to do so. An effective way to solve this issue is to prove one or several of the variables bounded below with a positive bound first and then find the common lower bound for all variables.

The following Lyme disease model is developed by Wang and Zhao [66] and it involves three different life stages of tick population: larvae (L), nymphs (N: susceptible; n: infectious), adults (A: susceptible; a: infectious), and two host populations: mice (M: susceptible; m: infectious) and deer (H).

$$
\begin{aligned}
\frac{dM}{dt} &= (M+m)B_M(M+m) - \mu_M M - \alpha_2(t)\beta Mn, \\
\frac{dm}{dt} &= \alpha_2(t)\beta Mn - \mu_M m, \\
\frac{dL}{dt} &= T_b B_T(t, T_b) - \mu_L L - \alpha_1(t)L(M+m), \\
\frac{dN}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}K_N(t-\tau_l) - [\gamma + \alpha_2(t)(M+m) + \mu_N]N, \\
\frac{dn}{dt} &= e^{-(\mu_L+\mu_M)\tau_l}K_n(t-\tau_l) - [\gamma + \alpha_2(t)(M+m) + \mu_N]n, \\
\frac{dA}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}K_A(t-\tau_n) - (\mu_A + \xi H)A, \\
\frac{da}{dt} &= e^{-(\mu_N+\mu_M)\tau_n}K_a(t-\tau_n) - (\mu_A + \xi H)a, \\
\frac{dH}{dt} &= r_h - \mu_h H,
\end{aligned}
\tag{35}
$$

where

$$
\begin{aligned}
K_N(t) &= \alpha_1(t)[M(t) + (1-\beta_T)m(t)]L(t), \\
K_n(t) &= \alpha_1(t)\beta_T m(t)L(t), \\
K_A(t) &= \alpha_2(t)[M(t) + (1-\beta_T)m(t)]N(t), \\
K_a(t) &= \alpha_2(t)[(M(t)+m(t))n(t) + \beta_T m(t)N(t)].
\end{aligned}
$$

The model has three discrete delays $\tau_l(\approx 3 \text{ days})$, $\tau_n(\approx 5 \text{ days})$, and $\tau_a(\approx 10 \text{ days})$ representing the feeding durations of tick larvae on mice, tick nymphs on mice, and adult ticks on deer, respectively. The parameter r_h is the birth rate of deer, and μ_M, μ_L, μ_N, μ_A, μ_h are the mortality rates per mouse, per tick larva, per tick nymph, per adult tick, and per deer, respectively. β is a mouse's susceptibility to infection when bitten by an infectious tick nymph, and β_T is a tick's susceptibility to infection when feeding on an infected mouse. The individual biting rates of tick larvae and nymphs on mice are given by $\alpha_1(t)$ and $\alpha_2(t)$, respectively. The per

capita birth rate of ticks is $B_T(t, T_b) = r(t)\exp(-c(t)T_b)$, where $r(t)$ is the maximal birth rate of ticks, $c(t)$ is the strength of density dependence for adult ticks, and $T_b = e^{-(\mu_A + \mu_h)\tau_a}\xi[A(t-\tau_a)+a(t-\tau_a)]H(t-\tau_a)$ representing the density of egg-laying adults where ξ is the individual biting rate of adult ticks on deer. The model incorporated seasonality by assuming that $\alpha_1(t)$, $\alpha_2(t)$, $r(t)$ and $c(t)$ are positive continuous periodic functions with the same period. It is easy to see that the maximum delays that occur in the variables $M(t)$, $m(t)$, $L(t)$, $N(t)$, $n(t)$, $A(t)$, $a(t)$ and $H(t)$ are τ_n, τ_n, τ_l, τ_n, τ_n, τ_a, τ_a and τ_a, respectively. Hence, X is set as

$$X = C([-\tau_n, 0], \mathbb{R}_+^2) \times C([-\tau_l, 0], \mathbb{R}_+) \times C([-\tau_n, 0], \mathbb{R}_+^2) \times C([-\tau_a, 0], \mathbb{R}_+^3),$$

Since it only requires to show that there exists a uniform postive lower bound for all the variables related to infections, that is, m, n, and a, X_0 is set to be

$$X_0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6, \phi_7, \phi_8) \in X : \phi_i(0) > 0, i = 2, 5, 7\}.$$

By using the theory of uniform persistence for periodic semiflows, it is shown that under certain conditions, if the basic reproduction ratio is greater than 1, then the model system admits a positive ω-periodic solution and there exists a real number $\eta > 0$ such that any solution $(M(t,\varphi), m(t,\varphi), L(t,\varphi), N(t,\varphi), n(t,\varphi), A(t,\varphi), a(t,\varphi), H(t,\varphi))$ with $\varphi \in X_0$ satisfies $\liminf\limits_{t\to\infty}(m(t,\varphi), n(t,\varphi), a(t,\varphi)) \geq (\eta, \eta, \eta)$.

Wang, Wang and Li [63] studied the uniform persistence of the following periodic delayed predator-prey model

$$\frac{dB(t)}{dt} = r(t)B(t)\left(1 - \frac{B(t)}{K(t)}\right) - \gamma(t)\frac{B(t)}{K_1(t) + B(t)}P(t),$$
$$\frac{dP(t)}{dt} = \beta\gamma(t-\tau)e^{-\int_{t-\tau}^{t}\delta_j(s)ds}\frac{B(t-\tau)}{K_1(t-\tau) + B(t-\tau)}P(t-\tau) - \delta(t)P(t),$$

$$(36)$$

where $B(t)$ and $P(t)$ are the densities of prey and predator populations at time t, respectively. The prey population is assumed to grow according to the logistic law with the maximum per capita prey growth rate $r(t)$ and the carrying capacity $K(t)$. The functional response is of Holling type II, with the per capita predation rate $\gamma(t)$ and the half-saturation predation constant $K_1(t)$. The parameter β is the conversion rate of prey biomass to predator biomass. The predator maturation duration is τ, and the death rates for matured and immatured predators are $\delta(t)$ and $\delta_j(t)$, respectively. The parameters $r(t), K(t), \gamma(t), K_1(t), \delta(t)$ and $\delta_j(t)$ are positive, continuous and ω-periodic functions reflecting the effect of seasonality. The

probability that predators survive the maturation period is given by the exponential term $e^{-\int_{t-\tau}^{t} \delta_j(s)ds}$. Note that this form is different from the one given by (13) since the death rate of immatured predators here is not a constant. In order to prove uniform persistence, we set $X = C([-\tau, 0], \mathbb{R}_+^2)$. Instead of setting $X_0 = \{\phi = (\phi_1, \phi_2) \in X : \phi_1(0) > 0, \phi_2(0) > 0\}$, we let $X_0 = \{\phi = (\phi_1, \phi_2) \in X : \phi_2(0) > 0\}$. By using the theory of uniform persistence, we first show that system (36) is uniformly persistent with respect to the variable $P(t)$ when the basic reproduction number is greater than 1, that is, there exists $\bar{\eta} > 0$ such that $\liminf\limits_{t\to\infty} P(t, \varphi) \geq \bar{\eta}$ for all $\varphi \in X_0$. Then by making use of $\liminf\limits_{t\to\infty} P(t, \varphi) \geq \bar{\eta}$, we prove by contradiction that for any $\phi \in X_0$, $B(t_0, \phi) > 0$ for some t_0, and hence, $B(t, \phi) > 0$ all $t \geq t_0$. Consequently, by the invariance of the compact global attractor of the map $Q : X_0 \to X_0$, we obtain that there exists $\eta > 0$ such that $\liminf\limits_{t\to\infty} \min\{B(t, \phi), P(t, \phi)\} \geq \eta$ for all $\phi \in X_0$.

4. Other methods and concerns

In this section, we introduce several other important analytical methods and numerical tools as well as some concerns and cautions for DDE modeling and analysis.

4.1. *Other methods for DDE model analysis*

Liapunov functionals and LaSalle invariance principle provide another way to study global stability of equilibria for DDEs, which may help bypass the difficulty for investigating the characteristic equations. However, it is more challenging to find an appropriate Liapunov functional for DDEs than to establish a Liapunov function for ODEs. An effective rule is to (i) view DDEs as ODEs by setting delays to be zero and replacing x_t by $x(t)$ and find a Lyapunov function for the obtained ODEs; (ii) regard the Liapunov function as a Liapunov functional, find its derivative along the solutions of the DDEs, and add proper additional terms [23].

In almost all cases, distributed delays are more realistic than discrete delays but they bring more difficulties for analysis and it may be difficult to estimate the kernel from data as well [58]. However, when the kernel takes some special forms, we can reduce a DDE model with distributed delay into an ODE system by using the linear chain trick (see examples in [58]). Here we provide an example showing that the linear chain trick also applies to delayed partial differential equation models which will be

converted into PDEs. Shi et al. [56] proposed the following model to study
the spatiotemporal dynamics of animal species who move based on their
memory:

$$
\begin{aligned}
\frac{\partial u(x,t)}{\partial t} &= d_1 \Delta u(x,t) + d_2 \mathrm{div}(u(x,t)\nabla v(x,t)) + f(u(x,t)), && x \in \Omega, t > 0, \\
\frac{\partial u(x,t)}{\partial n} &= 0, && x \in \partial\Omega, t > 0,
\end{aligned}
\tag{37}
$$

with initial condition $u(x,t) = \eta(x,t)$ for $x \in \Omega$, $-\infty < t \leq 0$. Here
$u(x,t)$ is the population density at location x and time t, and $f(u(x,t))$
is the reaction term. The parameters d_1 and d_2 are the diffusion rate and
memory-based movement rate, respectively. The function $v(x,t)$ is defined
by

$$
v(x,t) = \int_{-\infty}^{t} \int_{\Omega} G(x,y,t-s)g(t-s)u(y,s)\mathrm{d}y\mathrm{d}s,
\tag{38}
$$

where $G(x,y,t)$ is the spatial weighting function measuring the familarity
of animals at location y with the information at location x and the depen-
dence of accumulated information in their mind on space, and it is set to
be the Green's function of the diffusion equation with homogeneous Neu-
mann boundary condition in [56]. The kernel $g(t)$ is the temporal weighing
function describing the process of knowledge gaining and memory waning
over time.

For the weak kernel case, that is, when $g(t) = \frac{1}{\tau}e^{-\frac{t}{\tau}}$, system (37) with v
given by (38) is equivalent to the following system of two reaction-diffusion
equations:

$$
\begin{aligned}
\frac{\partial u(x,t)}{\partial t} &= d_1 \Delta u(x,t) + d_2 \mathrm{div}(u(x,t)\nabla v(x,t)) + f(u(x,t)), && x \in \Omega, t > 0, \\
\frac{\partial v(x,t)}{\partial t} &= d_1 \Delta v(x,t) + \frac{1}{\tau}(u(x,t) - v(x,t)), && x \in \Omega, t > 0, \\
\frac{\partial u(x,t)}{\partial n} &= \frac{\partial v(x,t)}{\partial n} = 0, && x \in \partial\Omega, t > 0.
\end{aligned}
\tag{39}
$$

For the strong kernel case, that is, when $g(t) = \frac{t}{\tau^2}e^{-\frac{t}{\tau}}$, system (37)
with v given by (38) is equivalent to the following system of three reaction-
diffusion equations:

$$\frac{\partial u(x,t)}{\partial t} = d_1 \Delta u(x,t) + d_2 \mathrm{div}(u(x,t)\nabla v(x,t)) + f(u(x,t)), \quad x \in \Omega, t > 0,$$

$$\frac{\partial v(x,t)}{\partial t} = d_1 \Delta v(x,t) + \frac{1}{\tau}(w(x,t) - v(x,t)), \quad\quad\quad x \in \Omega, t > 0,$$

$$\frac{\partial w(x,t)}{\partial t} = d_1 \Delta w(x,t) + \frac{1}{\tau}(u(x,t) - w(x,t)), \quad\quad\quad x \in \Omega, t > 0,$$

$$\frac{\partial u(x,t)}{\partial n} = \frac{\partial v(x,t)}{\partial n} = \frac{\partial w(x,t)}{\partial n} = 0, \quad\quad\quad x \in \partial\Omega, t > 0.$$

$$(40)$$

As for numerical simulations of long-term dynamics of DDEs, MATLAB provides some very useful functions such as dde23 for constant delays and ddesd for time-dependent or state-dependent delays. DDE-BIFTOOL is a powerful software for computation and stability analysis of steady state solutions, their fold and Hopf bifurcations and periodic solutions of differential equations with several fixed discrete delays. However, we should use DDE-BIFTOOL with caution as it is mentioned in [27] that when S_n given by (18) has intersections with the τ-axis for some n, the Hopf branch may not extend correctly and the periodic solutions on the branch given by DDE-BIFTOOL may not be really preiodic solutions for the model, which can be checked by the Floquet multipliers or dde23 in MATLAB. For some Hopf branches, DDE-BIFTOOL even can not find periodic solutons around the Hopf bifurcation point, whose existence has been proven theoretically. Besides, XPPAUT is also a useful software that allows stability analysis of steady states of differential equations with several discrete delays.

4.2. *Caution and concerns*

It is always mysterious why the period of a solution can be different from the period of periodic forcing parameters. Even for an autonomous system, periodic solutions can occur. In [62], predator maturation delay can induce periodic solution and functional response can determine the amplitude. In [26], periodic solutions with different periods can coexist and period-doubling effect occurs. If a model satisfies the conditions of those theorems related to monotone and subhomogeneous systems, then we will obtain periodic solutions with the same period as the system. For example, a unique positive periodic solution is globally attractive when $R_0 > 1$ for a strongly monotone and strictly subhomogeneous system or subsystem. It is no doubt that such theorems of infinite dimensional dynamical systems

are powerful in exploring periodic solutions, however, such a theorem only applies to a specific type of monotone systems. Many realistic models are not monotone or do not have monotone subsystems. Then these theories will not work. By using the theory of uniform persistence, we can only prove the existence of some periodic solution but not uniqueness so it is possible that other solutions with a different period exist.

If a variable represents an amount of something (e.g., population, density or concentration, etc.), then it is natural to expect this variable to be nonnegative. Therefore, it is necessary and important to show the positivity of solutions of mathematical models including DDE models, that is, nonnegative initial functions lead to nonnegative solutions. Some researchers develop DDE models without checking this basic property and believe that the positivity of a model with small delays is similar to that of the corresponding ODE model. However, this can be wrong in many cases and it may take some efforts to prove the positivity for a DDE model such as establishing some addtional restrictions on the initial functions. For some DDE models positivity can be obviously observed by using the following Theorem 14 which is about the positive invariance of the cone $C_+ = \{\phi \in C : \phi(\theta) \geq 0, -r \leq \theta \leq 0\}$. Here we consider system (1) again, where $f : \mathbb{R} \times D \to \mathbb{R}^n$ is continuous and $D \subset C$ is open. We also assume that f is Lipschitz in x_t on each compact subset of $\mathbb{R} \times D$ so that initial value problems associated with (1) have unique solutions.

Theorem 14. *([59]) Assume that whenever $\phi \in D$ satisfies $\phi \geq 0$, $\phi_i(0) = 0$ for some i and $t \in \mathbb{R}$, then $f_i(t, \phi) \geq 0$. If $\phi \in D$ satisfies $\phi \geq 0$ and $t_0 \in \mathbb{R}$, then $x(t, t_0, \phi) \geq 0$ for all $t \geq t_0$ in its maximal interval of existence.*

This theorem can also be extended to study the positive invariance of some order intervals (see [59]). Note that when the conditions of Theorem 14 are not satisfied, we may need to find other conditions in order to guarantee the nonnegativity of solutions. For example, Bodnar [8] investigated the positivity of solutions for the following delayed logistic model

$$x'(t) = ax(t - \tau)\left(1 - \frac{x(t - \tau)}{K}\right), \qquad \text{for } t > 0,$$
$$x(t) = \phi(t), \qquad \text{for } t \in [-\tau, 0], \tag{41}$$

where a is the growth rate, K is the environment capacity, and τ is the population growth delay. Bodnar [8] showed that the solutions of this model can become negative in a finite interval of time. In addition, if $a\tau < \max\left\{x \in \mathbb{R} : -\frac{1}{16}x^3 - \frac{1}{4}x^2 + 1 = 0\right\}$ and the initial function ϕ satisfies $0 \leq \phi(t) \leq 1$ for $t \in [-1, 0]$, then the solution is nonnegative. From

this example, we can also see that the positivity of solutions of an ODE model may not be preserved if a time delay is incorpoerated since positivity obviously holds for the model $x'(t) = ax(t)(1 - \frac{x(t)}{K})$.

For ODEs with a continuous vector field, the solution exists to both the right and left of the initial time, that is, the solution through a point (σ, x_0) is defined on an interval $[\sigma - a, \sigma + a]$, $a > 0$. However, there will not exist a backward continuation of the solution for DDEs with a typical initial function. Theorem 5.1 of [18] gives sufficient conditions for the existence of backward solutions under some quite special initial data, which is very techniqal. For more examples and detailed discussions about backward continuation, we refer readers to [18, 58]. Since DDEs generally can't be solved backward in time, there is no well-developed theory of competitive DDE systems [59].

Models with three or more delays are rare and are difficult to analyze using the characteristic equation. The abstract dynamical systems approach may be used to deal with systems with multiple delays. When we use the theory of monotone dynamical systems to study models with multiple delays, we need to be careful with the choice of the state space if we need to establish strong monotonicity. In such cases, different components of the system usually require initial data specified on different intervals according to the delay value occured in each variable. Suppose r_i is the maximum delay that occurs in the i-th variable of a DDE system with n variables, then in order to build sufficient conditions for the system to generate eventually strongly monotone semiflows, typically we need to set the space as $C_r = \Pi_{i=1}^{n} C([-r_i, 0], \mathbb{R})$ instead of $C([-r, 0], \mathbb{R}^n)$ where $r = \max_{1 \leq i \leq n}\{r_i\}$. To illustrate this idea, Smith [59] discussed the following example:

$$
\begin{aligned}
x_1'(t) &= -x_1(t) + x_2(t - 1/2), \\
x_2'(t) &= x_1(t - 1) - x_2(t).
\end{aligned}
\tag{42}
$$

If the initial function $\phi = (\phi_1, \phi_2) \in C([-1, 0], \mathbb{R}^2)$ satisfies $\phi_1 = 0$ and $\phi_2(\theta) > 0$ for $\theta \in (-1, -2/3)$ and $\phi_2(\theta) = 0$ elsewhere in $[-1, 0]$, then by the method of steps of length $1/2$, we can obtain $x(t) = 0$ for all $t \geq -2/3$. Thus, $\phi > 0$ yet we don't have $x_t(\phi) \gg x_t(0) = 0$ for large t. This problem can be solved if we choose the state space to be $X = C([-1, 0], \mathbb{R}) \times C([-1/2, 0], \mathbb{R})$. Then whenever $\phi > 0$ we have $x_t(\phi) \gg 0$ for $t > 5/2$. Another example can be found in [66] where there are three delays $\tau_l < \tau_n < \tau_a$ in the Lyme disease model and we set $X = C([-\tau_n, 0], \mathbb{R}_+^2) \times C([-\tau_l, 0], \mathbb{R}_+) \times C([-\tau_n, 0], \mathbb{R}_+^2) \times C([-\tau_a, \mathbb{R}_+^3])$ instead of $C([-\tau_a, 0], \mathbb{R}_+^8)$ when we use the comparison principle and uniform persistence theory to

prove the threshold dynamics.

5. Future developments about DDE modelling and analysis

In this section, we introduce promising future developments about DDE modelling and analysis regarding the incorporation of time delay in nonsmooth models, the interaction of time delay and spatial movement, the influence of stochasticity on time-delay systems, and the application of D-DEs in data analysis.

5.1. *Nonsmooth DDE models*

Nonsmooth models have become ever more popular as they allow an intuitive description of markedly change, convert unsolvable problems into piecewise-solvable ones, and give an ideal expression of switching [21]. Incorporation of time delays in nonsmooth models may provide novel insights beyond the results of nonsmooth ODE models or classical delay-induced oscillations in smooth models. For example, stoichiomotric producer-grazer ODE models, which involve the nonsmooth minimum terms induced by Liebig's law, indicate that the grazers go extinct in low light intensities due to a shortage of food or in extremely high light intensities as a result of poor-quality food and they can survive in a broad range of intermediate light intensities [29, 35, 73]. Zhang, Niu and Wang [74] proposed a stoichiometric producer-grazer model with producers' digestion delay and they found that a large digestion delay can lead to grazer extinction under an intermediate light intensity.

Despite exciting applications of nonsmooth systems, it is difficult to solve or analyze them as the theorems about stability, attraction, bifurcation, and chaos of differentiable dynamical systems are inapplicable [21]. By phase plane fragmentation and parameter space partition, complete analyses for local and global stability of all equilibria and existence of limit cycles have been achieved in [29, 73] for stoichiometric producer-grazer ODE models. However, it is extremely challenging to obtain the non-negativity and boundedness of solutions when time delays are incorporated because the phase space becomes infinite dimensional. Novel mathematical approaches are also needed to give a complete analysis of possible bifurcations near the equilibrium on the critical curve for nonsmooth stoichiometric DDE models and to analyze other nonsmooth dynamical systems [74].

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5.2. *Delayed partial differential equations*

Delayed partial differential equations (DPDEs) emerge when we incorporate delays in PDE models or include diffusion or advection terms in DDE models. DPDEs have attracted increasing attention in both ecological and epidemiological modellings in recent years (see, e.g., [3, 25, 42, 70, 75]). If the delay in a DPDE model appears in the reaction term, then usually it has the same biological meaning as the one in a DDE model, such as maturation delay. The delay in a DPDE model can also be related to diffusion or advection, such as dispersal delay, i.e., the duration for animals to move from one patch to another. Future DPDE models could give rise to new spatio-temporal patterns or other complex dynamical behaviors which need to be explained analytically and biologically .

In recent two years, there also emerges an innovative area for DPDE application, that is, memory-based animal movement. Hao Wang has lead several pioneering works on this topic by developing and analyzing DPDE models (see, e.g., [2, 54–56, 60, 61, 71]). Different from the traditional cases such as a model with a maturation delay, a memory delay depicts the scenario in which spatial locations and attribute features memorized by a species at some past time determine their present movement tendency instead of life stage evolution, etc. Possible future modeling works for memory-based animal movement have been suggested in a recent review paper by Salmaniw et al. [50].

5.3. *Stochastic delay differential equations*

In addition to time delay, random and uncontrolled fluctuations (i.e., noise) are also ubiquitous and important factors affecting the dynamics of biological systems. For example, stochastic environmental or human perturbations could influence the growth rates and even the persistence and extinction of animal species [33, 69]. The tumor-immune interaction also involves both time delay and noise. The activation of immune response to tumors needs recruitment of immune cells from marrow bones and further training, which is a time-delayed process. Meanwhile, cancer usually mutates fast and there is much uncertainty in the proliferating rate of cancer cells [15]. In order to incorporate both time delay and stochasticity, we should develop stochastic delay differential equation (SDDE) models. To model some sudden pertubations such as earthquakes, hurricanes and epidemics we need to formulate SDDEs with jumps [69]. Although there are some interesting works on mathematical modellings with both time delay and

noise (see, e.g., [13, 19, 48, 69]), the application of stochastic DDEs is not as popular as deterministic DDEs. It is worth considering stochasticity more often when we develop delay models to explore biological problems in future.

The interest in exploring the influence of noise on SDDEs has motivated a lot of numerical studies, but there are few quantitative analytical results describing the dynamics [22]. An increasingly popular approach to studying SDDEs is multiscale analysis, which allows a separation of deterministic and stochastic effects. For example, in order to investigate the effect of small noise, Kłosek and Kuske [22] applied multiscale analysis to a linear SDDE with additive noise and multiplicative noise and a logistic S-DDE with additive noise by looking for solutions described by deterministic oscillations on the fast scale with stochastic amplitudes on the slow scale. They derived approximate stochastic envelope equations for deterministic oscillations near critical delays, providing an efficient analysis of the long time dynamics of the stochastic process with delay and identifying critical scalings for sustained oscillations due to the presence of noise. Note that if the noise dominates the dynamics either on the fast scale or on the slow scale, then multiscale analysis is impossible. Future SDDE models may induce new challenging mathematical problems and hence may promote the development of the theory for SDDEs.

5.4. *Data-driven DDE models*

The junction of big data and machine learning is driving a renaissance in modern dynamical systems, with fundamental models and analytical derivations yielding to data-driven approaches [10]. Data-driven problems can also involve time delays, and in this case DDE models should be employed. The challenges include revealing dynamics from data and exploring data-driven representations which make nonlinear DDEs susceptible to linear analysis. With the fast progress of data-driven techniques, more DDE models can be applied in critical data-driven problems such as predicting and controlling serious epidemics or pandemics (e.g., COVID-19 [34]), suggesting the treatment for cancer, explaining observed population dynamics (e.g., the four-to-five year lemming cycle on Greenland [51]), and understanding cognition and memory from neuron recordings [10].

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6. Discussion

In this chapter, we reviewed two important ways for analyzing DDE models: the characteristic equation method and the dynamical systems approach. For the characteristic equation method, we introduced the detailed procedures for the study of stability switches for four popular different types of DDEs arising from ecological and immunological modelling. The completion of these procedures need the combination of algebraic and geometric analyses as well as numerical computations via computers. For the dynamical systems approach, we presented the theories of monotone and subhomogeneous systems, chain transitive set, and uniform persistence. In application, these three theories in the field of infinite dimensional dynamical systems are usually used jointly in order to obtain the final result regarding threshold dynamics of global attractivity or uniform persistence, and they are particularly powerful in dealing with periodic model systems incorporating multiple delays or periodic delays. We also briefly summarized another two useful analytical methods including the construction of Lyapunov functionals and the linear chain trick for distributed delay models as well as several numerical tools for DDE simulations. Furthermore, we mentioned the cautions and concerns for DDE modelling and analysis. At last, we discussed some extensions about the applications of DDEs.

Almost all former original research papers or review articles in the field of DDE modelling and analysis focus on only at most one of the two main methods introduced in this chapter. Here we put the characteristic equation method and the infinite dimensional dynamical systems method together, hoping to give a clear comparision of their advantages so that people who are not experts in DDE modelling and analysis can be aware of which method to use for their research. Hopefully, our interpretations together with the multiple examples introduced in this chapter can make those abstract theories easy to understand and help beginners gain hands-on experience in applying DDEs to solving real-world problems.

In mathematical biology, fairly complicated and scientifically more interesting delay models, which are quite different from those examples we have presented in the above sections, can be developed and calibrated with laboratory or field experiments. We would like to end this chapter by the following delayed integro-differential equation model proposed by McCauley, Nelson and Nisbet [37] which gives a reasonable explanation for

the observed coexisting attractors in *Daphnia*-algal systems.

$$
\frac{\mathrm{d}F(t)}{\mathrm{d}t} = \underbrace{qF(t)\left(1 - \frac{F(t)}{k}\right)}_{logistic\ resource\ growth} - \underbrace{I_J\frac{F(t)}{F(t)+f_h}J(t)}_{ingestion\ by\ juveniles} - \underbrace{I_A\frac{F(t)}{F(t)+f_h}A(t)}_{ingestion\ by\ adults},
$$

$$
\frac{\mathrm{d}J(t)}{\mathrm{d}t} = \underbrace{\frac{\chi I_A \sigma_A}{\gamma}\frac{F(t)}{F(t)+f_h}A(t)}_{birth} - \underbrace{\frac{\chi I_A \sigma_A}{\gamma}\frac{F(t)}{F(t)+f_h}A(t-\tau(t))S(t)}_{maturation}
$$

$$
\underbrace{-\frac{\mu_J}{I_J\sigma_J}\frac{F(t)+f_h}{F(t)}J(t)}_{juvenile\ mortality},
$$

$$
\frac{\mathrm{d}A(t)}{\mathrm{d}t} = \underbrace{\frac{\chi I_A \sigma_A}{\gamma}\frac{F(t)}{F(t)+f_h}A(t-\tau(t))S(t)}_{maturation} - \underbrace{\frac{\mu_A}{I_A\sigma_A}\frac{F(t)+f_h}{F(t)}A(t)}_{adult\ mortality},
$$

$$
\frac{w}{\sigma_J I_J} = \underbrace{\int_{t-\tau(t)}^{t}\frac{F(\xi)}{F(\xi)+f_h}\mathrm{d}\xi}_{juvenile\ development},
$$

$$
S(t) = \underbrace{\exp\left(-\frac{\mu_J}{I_J\sigma_J}\int_{t-\tau(t)}^{t}\frac{F(\xi)+f_h}{F(\xi)}\mathrm{d}\xi\right)}_{juvenile\ survival}.
$$

$$(43)$$

The variables $F(t)$, $J(t)$ and $A(t)$ represent the densities of resource, juveniles and adults at time t, respectively. The resource has a logistic growth rate in which q is the maximum per-capita growth rate and k is the resource carrying capacity. The ingestion rates take the form of Holling-type II with f_h being the half saturation constant, I_J and I_A the maximum juvenile and adult ingestion rates, respectively. χ is the proportion of utilized carbon allocated to reproduction. γ is the carbon required to produce one new offspring. σ_J and σ_A are the proportions of ingested carbon that are utilized by juveniles and adults, respectively. w is the mass gain required to complete juvenile development. μ_J and μ_A are juvenile and adult mortality scalars, respectively. Both the juvenile and adult mortalities depend on resource density. The time delay depends on system states and need to be calculated via an integral constraint. Due to the enormous number of parameter combinations and the necessity of considering initial conditions, it is challenging to carry out bifurcation analysis with this class of model. They reduced the number of parameters by nondimensionalization,

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changed the problem into DDEs with a constant delay by a transformation in the time variable, and estimated the survival integral in terms of solutions to an ODE system. Tested by bioassay experiments, their model predictions indicate that the resource-dependent juvenile developmental duration (i.e., the delay) and the resource-dependent mortality combine to produce small-amplitude cycles, which may contribute to the coexistence of small- and large-amplitude cycles in other coupled consumer-resource systems as well.

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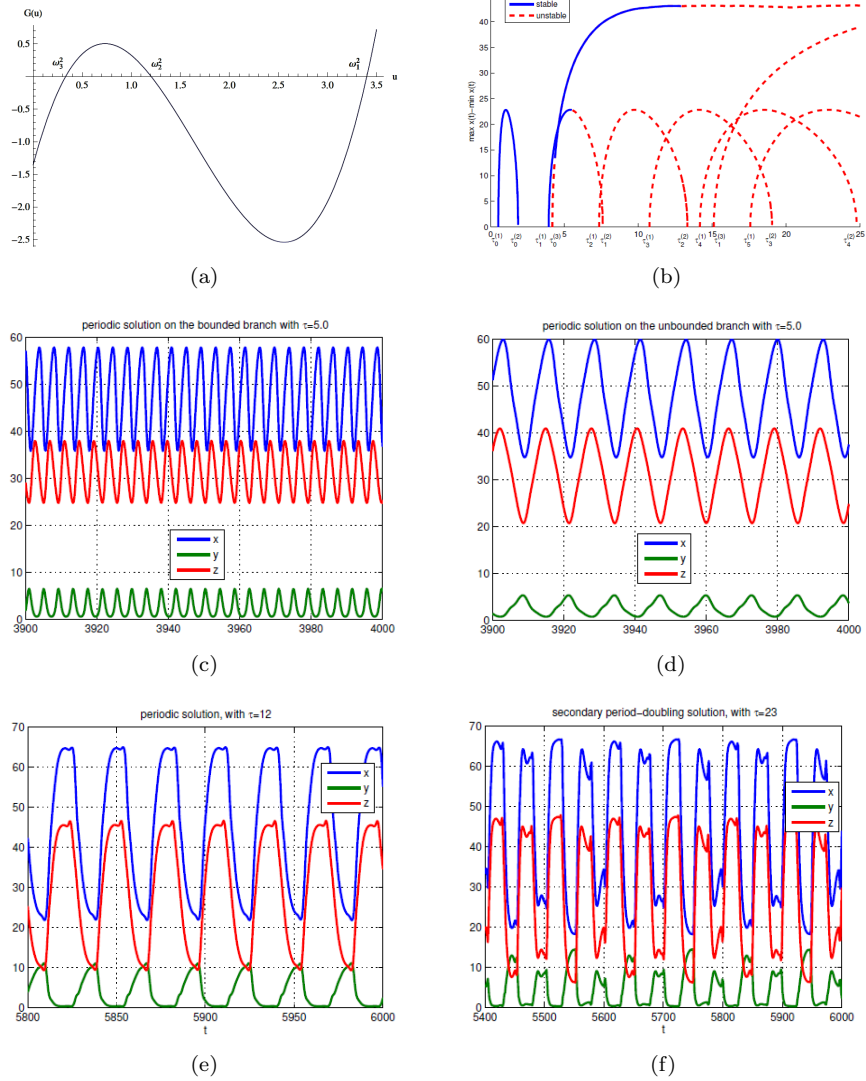
Fig. 2.   (a) Graph of $G(u)$ with three positive roots; (b) Bifurcation diagram for stability switch at P_2 and Hopf branches. Solid lines represent stable branches, and dashed lines represent unstable branches; (c)&(d) Coexistence of two stable periodic solutions under the same parameter values when $\tau = 5$; (e) Periodic solution along the unbounded Hopf branch when $\tau = 12$; (f) Secondary period-doubling solution along the unbounded Hopf branch when $\tau = 23$. Graphs were adapted from [26].
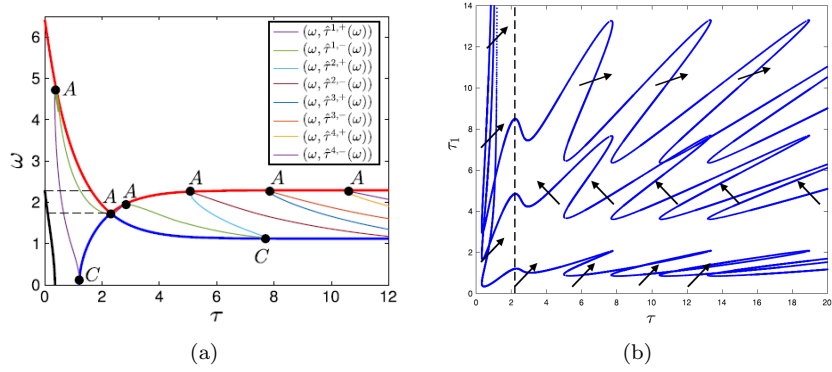
Fig. 3.   (a) The curve $\mathcal{C}$; (b) The crossing curves (open-ended and spiral-like, separated by the black dashed line) and crossing directions. Graphs were adapted from [1].