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GLOBAL ATTRACTIVITY OF A CIRCADIAN PACEMAKER MODEL IN A PERIODIC ENVIRONMENT

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Abstract. In this paper, we propose a delay differential equation with continuous periodic parameters to model the circadian pacemaker in a periodic environment. First, we show the existence of a positive periodic solution by using the theory of coincidence degree. Then we establish the global attractivity of the periodic solution under two sufficient conditions. These conditions are easily verifiable and are independent of each other. Some numerical simulations are also performed to demonstrate the main results.

1. **Introduction.** Circadian rhythms are generated by biological clocks that seem to be ubiquitous in nature, ranging from periodic biochemical reactions in molecular organisms to complex structures in the mammalian brain. Several mathematical and physical models have been proposed over the years in order to explain different features of circadian systems in general (see, for example, [1, 2, 4, 5, 9, 10, 13, 14, 15, 22, 23, 24, 26] and the references therein).

Most of the aforementioned models are deterministic and continuous and are built with coupled oscillators. It is difficult to completely understand the dynamics of these models since too many parameters are involved. Lema *et al* [14] recently proposed a simple model of circadian pacemaker described by the following delay differential equation,

$$\frac{\mathrm{d}E(t)}{\mathrm{d}t} = -K_d E(t) + \frac{K_e}{1 + [E(t-\delta)/K_i]^n}\,, \tag{1}$$

where E represents the level of the mature clock protein, K_e is the expression rate constant, δ represents a time delay, K_i is the inhibition rate constant, n is the Hill coefficient and K_d is the degradation rate constant. For a more general delayed model based on a molecular mechanism, we refer to Scheper *et al* [20, 21].

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Lema *et al* analyzed model (1) numerically only. Based on a bifurcation analysis, it is shown that there is a periodic solution when δ is greater than a threshold value. They claimed that the periodic solution is stable and therefore their model is realistic and reasonable. However, this is only partially true. In fact, after translating the equilibrium to the origin, we can see that model (1) is of delayed monotone with a negative feedback. This type of differential equations have been studied by Krisztin in detail [11]. It follows from [11] that the limit cycle attracts all nontrivial solutions only when the delay is restricted in certain interval.

It has been observed that light, temperature and certain chemicals can affect many circadian rhythms (see, for example, the references in [14]). To study the effects of environment and the photoperiodic (*i.e.*, parametric) entrainment, Lema *et al* separately perturbed K_e, K_d, or added to K_e the positive half of a sinusoidal function of time. One purpose of this paper is to give a rigorous analysis for their simultaneous effects. More precisely, we consider

$$\frac{\mathrm{d}E(t)}{\mathrm{d}t} = -K_d(t)E(t) + \frac{K_e(t)}{1 + \left[\frac{E(t-\tau(t))}{K_i(t)}\right]^n}\,, \tag{2}$$

where we assume that

(H) $K_d \in C(\mathbb{R},\mathbb{R})$, K_e, $\tau \in C(\mathbb{R},[0,\infty))$, and $K_i(t) \in C(\mathbb{R},(0,\infty))$ are ω-periodic with $\omega > 0$ and $n \geq 1$.

Note that (2) models a circadian pacemaker in a periodic environment. As seen in (H), the degradation rate K_d is not assumed to be non-negative since the environment fluctuates randomly and a negative K_d may take account for the enhancement of the clock protein. There are also some discrete models reflecting the consequences of periodic environment. As an example, we refer to Webb [25] for the interesting periodical cicada problem.

For convenience we introduce the notation for a continuous ω-periodic function f:

$$f^* = \max_{0\leq t\leq\omega} f(t)\,, \quad f_* = \min_{0\leq t\leq\omega} f(t)\,, \quad \text{and} \quad \overline{f} = \frac{1}{\omega}\int_0^\omega f(t)\,\mathrm{d}t\,.$$

In the view of the background of (2), we choose $C = C([-\tau^*,0],[0,\infty))$ and define $\|\phi\| = \max_{-\tau^*\leq\theta\leq 0} |\phi(\theta)|$ for $\phi \in C$. Then for $\phi \in C$ and $t_0 \in \mathbb{R}$, it is easy to see that equation (2) has a unique solution $E : [-\tau^* + t_0, \infty) \to [0,\infty)$ with the initial value ϕ, that is, $E_{t_0} = \phi$, where as usual, $E_t \in C$ is defined by $E_t(\theta) = E(t+\theta)$ for $\theta \in [-\tau^*, 0]$.

As pointed out by Freedman and Wu [6] and Kuang [12], it would be of interest to study the existence of periodic solutions for systems with periodic delay. In the literature, for non-autonomous periodic systems, it is often assumed that the delays are integer-multiples of the period (see [18, 19, 27]). This assumption reduces the existence of a periodic solution for the delayed case to that of a non-delayed case. However, in our model (2), we do not make this assumption. To establish the existence of a periodic solution to (2), we shall rely on the powerful and effective method of coincidence degree. This method always gives us natural and easily verifiable conditions (see, for example, [3, 16, 17]).

Unlike [14], we shall show that (2) always has an ω-periodic solution and the existence is independent of the magnitude of delay. Moreover, this periodic solution is globally asymptotically stable under two independent sufficient conditions. This indicates that the circadian rhythm is an intrinsic characteristic.

The organization of this paper is as follows. In Section 2, we show that (2) has a positive ω-periodic solution under the natural assumption that both $\overline{K_d}$ and $\overline{K_e}$ are positive. Then, in Section 3, we establish two easily verifiable sufficient conditions which guarantee the global attractivity of the positive ω-periodic solution obtained in Section 2. One of the criteria is delay-independent while the other is delay-dependent. Moreover, these two sufficient conditions are shown to be independent of each other by examples in Section 4. Some numerical simulations are also performed to demonstrate our results in Section 4.

2. **Existence of a positive periodic solution.** For the convenience of the readers, we shall cite the continuation theorem. In order to do this, we begin with some concepts.

Let X and Z be normed vector spaces. Let $L : \operatorname{Dom} L \subset X \to Z$ be a linear mapping and $N : X \to Z$ be a continuous mapping. The mapping L is said to be a Fredholm mapping of index zero if $\dim \operatorname{Ker} L = \operatorname{codim} \operatorname{Im} L < \infty$ and $\operatorname{Im} L$ is closed in Z. If L is a Fredholm mapping of index zero, then there exist continuous projectors $P : X \to X$ and $Q : Z \to Z$ such that $\operatorname{Im} P = \operatorname{Ker} L$ and $\operatorname{Im} L = \operatorname{Ker} Q = \operatorname{Im}(I-Q)$. It follows that $L|\operatorname{Dom} L \cap \operatorname{Ker} P : (I-P)X \to \operatorname{Im} L$ is invertible and its inverse is denoted by K_P. If Ω is a bounded open subset of X, the mapping N is called L-compact on $\overline{\Omega}$ if $(QN)(\overline{\Omega})$ is bounded and $K_P(I-Q)N : \overline{\Omega} \to X$ is compact. Because $\operatorname{Im} Q$ is isomorphic to $\operatorname{Ker} L$, there exists an isomorphism $J : \operatorname{Im} Q \to \operatorname{Ker} L$.

Theorem 2.1 (Continuation Theorem, [7]). *Let L be a Fredholm mapping of index zero and let N be L-compact on $\overline{\Omega}$. Suppose*

(a): *for each $\lambda \in (0,1)$, every solution x of $Lx = \lambda Nx$ is such that $x \notin \partial\Omega$;*
(b): *$QNx \neq 0$ for each $x \in \partial\Omega \cap \operatorname{Ker} L$ and*

$$\deg\{JQN, \Omega \cap \operatorname{Ker} L, 0\} \neq 0 .$$

Then the equation $Lx = Nx$ has at least one solution lying in $\operatorname{Dom} L \cap \overline{\Omega}$.

Now, we are ready to prove the following main result of this section.

Theorem 2.2. *In addition to (H), we assume that both $\overline{K_d}$ and $\overline{K_e}$ are positive. Then (2) has at least one positive ω-periodic solution.*

Proof. Since we are concerning with positive solutions of (2), we make the change of variable,

$$E(t) = \exp(x(t)) . \tag{3}$$

Then (2) can be rewritten as

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -K_d(t) + \frac{K_e(t)\exp(-x(t))}{1 + \left[\frac{\exp(x(t-\tau(t)))}{K_i(t)}\right]^n} . \tag{4}$$

Take

$$X = Z = \{x \in C(\mathbb{R},\mathbb{R}) : x(t+\omega) = x(t) \text{ for } t \in \mathbb{R}\}$$

and define

$$\|x\|_\omega = \max_{t\in[0,\omega]} |x(t)| , \quad x \in X \text{ or } Z .$$

Equipped with the above norm $\|\cdot\|_\omega$, both X and Z are Banach spaces. For any $x \in X$, because of periodicity, one can easily check that $\Delta(x,t) := -K_d(t) + \frac{K_e(t)\exp(-x(t))}{1+\left[\frac{\exp(x(t-\tau(t)))}{K_i(t)}\right]^n} \in C(\mathbb{R},\mathbb{R})$ is ω-periodic. Let

$$
\begin{aligned}
L:&\quad \operatorname{Dom} L = \{x \in X : x \in C^1(\mathbb{R},\mathbb{R})\} \ni x \mapsto \tfrac{\mathrm{d}x(t)}{\mathrm{d}t} \in Z\,,\\
P:&\quad X \ni x \mapsto \tfrac{1}{\omega}\textstyle\int_0^\omega x(t)\,\mathrm{d}t \in X\,,\\
Q:&\quad Z \ni z \mapsto \tfrac{1}{\omega}\textstyle\int_0^\omega z(t)\,\mathrm{d}t \in Z\,,\\
N:&\quad X \ni x \mapsto \Delta(x,t) \in Z\,.
\end{aligned}
$$

Here, for any $k \in \mathbb{R}$, we also identify it as the constant function in X or Z with the constant value k. It is easy to see that

$$
\begin{aligned}
&\operatorname{Ker} L = \mathbb{R}\,,\\
&\operatorname{Im} L = \{z \in Z : \textstyle\int_0^\omega z(t)\,\mathrm{d}t = 0\} \text{ and it is closed in } Z,\\
&\dim \operatorname{Ker} L = \operatorname{codim} \operatorname{Im} L = 1 < \infty
\end{aligned}
$$

and P, Q are continuous projectors such that

$$
\operatorname{Im} P = \operatorname{Ker} L\,, \quad \operatorname{Im} L = \operatorname{Ker} Q = \operatorname{Im}(I-Q)\,.
$$

It follows that L is a Fredholm mapping of index zero. Furthermore, the generalized inverse (to L) $K_P : \operatorname{Im} L \to \operatorname{Ker} P \cap \operatorname{Dom} L$ is given by

$$
(K_P(z))(t) = \int_0^t z(s)\,\mathrm{d}s - \frac{1}{\omega}\int_0^\omega \int_0^u z(s)\,\mathrm{d}s\mathrm{d}u\,.
$$

Thus,

$$
\begin{aligned}
((QN)x)(t) &= \frac{1}{\omega}\int_0^\omega \Delta(x,s)\,\mathrm{d}s\,,\\
((K_P(I-Q)N)x)(t) &= \int_0^\omega \Delta(x,s)\,\mathrm{d}s - \frac{1}{\omega}\int_0^\omega\int_0^u \Delta(x,s)\,\mathrm{d}s\mathrm{d}u\\
&\quad - \left(\frac{t}{\omega} - \frac{1}{2}\right)\int_0^\omega \Delta(x,s)\,\mathrm{d}s\,.
\end{aligned}
$$

Clearly, QN and $K_P(I-Q)N$ are continuous. For any bounded open subset $\Omega \subset X$, $(QN)(\overline{\Omega})$ is obviously bounded. Moreover, applying the Arzela-Ascoli Theorem, one can easily show that $\overline{(K_P(I-Q)N)(\overline{\Omega})}$ is compact. Therefore, N is L-compact on $\overline{\Omega}$ with any bounded open subset $\Omega \subset X$.

To apply Theorem 2.1, we need to find an appropriate open bounded subset in X. Consider the operator equation $Lx = \lambda Nx$, $\lambda \in (0,1)$, that is,

$$
\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda\Delta(x,t)\,, \quad \lambda \in (0,1)\,. \tag{5}
$$

Let $x(t) \in X$ be a solution of (5) for some $\lambda \in (0,1)$. Then $\int_0^\omega \frac{\mathrm{d}x(t)}{\mathrm{d}t}\,\mathrm{d}t = 0$. It follows that

$$
\int_0^\omega K_d(t)\,\mathrm{d}t = \int_0^\omega \frac{K_e(t)\exp(-x(t))}{1+\left[\frac{\exp(x(t-\tau(t)))}{K_i(t)}\right]^n}\,\mathrm{d}t\,. \tag{6}
$$

Thus,

$$\begin{aligned}
\int_0^\omega \left|\frac{\mathrm{d}x}{\mathrm{d}t}\right| \mathrm{d}t &= \lambda \int_0^\omega \left| K_d(t) + \frac{K_e(t)\exp(-x(t))}{1+\left[\frac{\exp(x(t-\tau(t)))}{K_i(t)}\right]^n}\right| \mathrm{d}t \\
&< \int_0^\omega \left[|K_d(t)| + \frac{K_e(t)\exp(-x(t))}{1+\left[\frac{\exp(x(t-\tau(t)))}{K_i(t)}\right]^n}\right] \mathrm{d}t \\
&= \int_0^\omega (|K_d(t)| + K_d(t))\,\mathrm{d}t \\
&= (\overline{|K_d|} + \overline{K_d})\omega\,,
\end{aligned}$$

that is,

$$\int_0^\omega \left|\frac{\mathrm{d}x}{\mathrm{d}t}\right| \mathrm{d}t < (\overline{|K_d|} + \overline{K_d})\omega := \alpha\,. \tag{7}$$

Since $x \in X$, there exist ξ, $\eta \in [0,\omega]$ such that

$$x(\xi) = \min_{t\in[0,\omega]} x(t) \quad \text{and} \quad x(\eta) = \max_{t\in[0,\omega]} x(t)\,. \tag{8}$$

From (6) and (8), we get

$$\overline{K_d}\omega \le \int_0^\omega K_e(t)\exp(-x(\xi))\,\mathrm{d}t = \overline{K_e}\omega\exp(-x(\xi))$$

and hence

$$x(\xi) \le \ln\overline{K_e} - \ln\overline{K_d}\,.$$

This, combined with (7), gives us

$$x(t) \le x(\xi) + \int_0^\omega \left|\frac{\mathrm{d}x(t)}{\mathrm{d}t}\right| \mathrm{d}t < \ln\overline{K_e} - \ln\overline{K_d} + \alpha := H_2\,. \tag{9}$$

On the other hand, it follows from (6), (8) and (9) that

$$\overline{K_d}\omega \ge \exp(-x(\eta)) \int_0^\omega \frac{K_e(t)}{1+\left[\frac{\exp(H_2)}{K_i(t)}\right]^n} \mathrm{d}t = \beta\omega\exp(-x(\eta))\,,$$

where $\beta = \overline{\left(\frac{K_e}{1+\left[\frac{\exp(H_2)}{K_i}\right]^n}\right)}$. So

$$x(\eta) \ge \ln\beta - \ln\overline{K_d}\,.$$

This, combined with (7), gives us

$$x(t) \ge x(\eta) - \int_0^\omega \left|\frac{\mathrm{d}x}{\mathrm{d}t}\right| \mathrm{d}t > \ln\beta - \ln\overline{K_d} - \alpha := H_1\,. \tag{10}$$

It follows from (9) and (10) that

$$\|x\|_\omega < \max\{|H_1|, |H_2|\} := H\,.$$

Obviously, H is independent of λ.

Now, let's consider $(QN)(x)$ with $x \in \mathbb{R}$. Note that

$$(QN)(x) = -\overline{K_d}\omega + \int_0^\omega \frac{K_e(t)\exp(-x)}{1+\left[\frac{\exp(x)}{K_i(t)}\right]^n} \mathrm{d}t\,.$$

If $(QN)(x) = 0$, then one can easily see that $H_1 < x < H_2$.

Take $\Omega = \{x \in X : \|x\|_\omega < H\}$. It is clear that Ω satisfies the condition (a) in Theorem 2.1. When $x \in \partial\Omega \cap \operatorname{Ker} L = \partial\Omega \cap \mathbb{R}$, $x = \pm H$. From the argument in the previous paragraph, we see that $(QN)(x) \neq 0$. An easy computation gives

$$\deg\{JQN, \Omega \cap \operatorname{Ker} L, 0\} = -1 \neq 0\,,$$

here we take J to be the identity map. By now, we have shown that Ω satisfies all the assumptions of Theorem 2.1. Hence, $Lx = Nx$ has at least one solution $\tilde{x} \in \operatorname{Dom} L \cap \overline{\Omega}$. Set $\tilde{E}(t) = \exp(\tilde{x}(t))$. Then $\tilde{E}$ is a positive ω-periodic solution of (2). This completes the proof. □

3. **Stability of the periodic solution.** In this section, we give two sufficient conditions which guarantee the stability of the periodic solution obtained in Theorem 2.2. One is delay-independent while the other is delay-dependent. Before stating them, we introduce a function

$$B(n) = \begin{cases} \frac{n^2-1}{4n}\left(\frac{n+1}{n-1}\right)^{\frac{1}{n}}, & \text{if } n > 1, \\ 1\,, & \text{if } n = 1. \end{cases}$$

Note that $\lim_{n\to 1^+} B(n) = B(1)$. Then a simple calculus computation gives us

$$\frac{nx^{n-1}}{K^n\left(1+\left(\frac{x}{K}\right)^n\right)^2} \leq \frac{B(n)}{K} \quad \text{for } x \geq 0, \tag{11}$$

where K is a positive constant.

THEOREM 3.1. *In addition to the assumptions of Theorem 2.2, we further assume that either $K_{d*} > B(n)\left(\frac{K_e}{K_i}\right)^*$ or $\overline{K_d} > B(n)\overline{\left(\frac{K_e}{K_i}\right)}\exp(K_d^*\tau^*)$. Then the ω-periodic solution $\tilde{E}(t)$ obtained in Theorem 2.2 is globally and exponentially stable, that is, if $E(t)$ is any positive solution of (2) then there exist positive constants M and γ such that*

$$\|(E-\tilde{E})_t\| \leq Me^{-\gamma(t-t_0)}\|(E-\tilde{E})_{t_0}\|\,, \quad t \geq t_0\,. \tag{12}$$

Proof. Since both E and $\tilde{E}$ are solutions of (2), we have

$$\begin{aligned} &\frac{\mathrm{d}}{\mathrm{d}t}[E(t)-\tilde{E}(t)] \\ = \;& -K_d(t)(E(t)-\tilde{E}(t)) + K_e(t)\left[\frac{1}{1+\left(\frac{E(t-\tau(t))}{K_i(t)}\right)^n} - \frac{1}{1+\left(\frac{\tilde{E}(t-\tau(t))}{K_i(t)}\right)^n}\right] \\ = \;& -K_d(t)(E(t)-\tilde{E}(t)) \\ & - K_e(t)\frac{n(\zeta(t))^{n-1}}{(K_i(t))^n\left(1+\left(\frac{\zeta(t)}{K_i(t)}\right)^n\right)^2}(E(t-\tau(t))-\tilde{E}(t-\tau(t)))\,, \end{aligned}$$

where $\zeta(t)$ is a number between $E(t-\tau(t))$ and $\tilde{E}(t-\tau(t))$. Using the upper right derivative and (11), we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\left|E(t)-\tilde{E}(t)\right| \leq -K_d(t)|E(t)-\tilde{E}(t)| + B(n)\frac{K_e(t)}{K_i(t)}\|(E-\tilde{E})_t\|\,. \tag{13}$$

If $K_{d*} > B(n)\left(\frac{K_e}{K_i}\right)^*$, then it follows from (13) that

$$\frac{\mathrm{d}}{\mathrm{d}t}\left|E(t)-\tilde{E}(t)\right| \le -K_{d*}|E(t)-\tilde{E}(t)| + B(n)\left(\frac{K_e}{K_i}\right)^* \|(E-\tilde{E})_t\|\,.$$

By Lemma 5.1 in Gopalsamy and Sariyasa [8], there exists a positive constant γ such that

$$|E(t)-\tilde{E}(t)| \le e^{-\gamma(t-t_0)}\|(E-\tilde{E})_{t_0}\|\,,\quad t\ge t_0\,.$$

So (12) follows immediately.

Now, we assume that $\overline{K_d} > B(n)\overline{\left(\frac{K_e}{K_i}\right)}\exp(K_d^*\tau^*)$. It follows from (13) that

$$\frac{\mathrm{d}}{\mathrm{d}t}e^{\int_{t_0}^t K_d(s)\,\mathrm{d}s}|E(t)-\tilde{E}(t)| \le B(n)\frac{K_e(t)}{K_i(t)}\|(E-\tilde{E})_t\|e^{\int_{t_0}^t K_d(s)\,\mathrm{d}s}\,,\quad t\ge t_0\,.$$

Then, for $t \ge t_0$,

$$\begin{aligned} & e^{\int_{t_0}^t K_d(s)\,\mathrm{d}s}|E(t)-\tilde{E}(t)| \\ \le\ & |E(t_0)-\tilde{E}(t_0)| + \textstyle\int_{t_0}^t B(n)e^{\int_{t_0}^u K_d(s)\,\mathrm{d}s}\frac{K_e(u)}{K_i(u)}\|(E-\tilde{E})_u\|\,\mathrm{d}u \\ \le\ & \|(E-\tilde{E})_{t_0}\| + \textstyle\int_{t_0}^t B(n)e^{\int_{t_0}^u K_d(s)\,\mathrm{d}s}\frac{K_e(u)}{K_i(u)}\|(E-\tilde{E})_u\|\,\mathrm{d}u\,. \end{aligned}$$

Thus, for $t\ge t_0$ and $\theta\in[-\min\{\tau^*, t-t_0\}, 0]$, we have

$$\begin{aligned} & e^{\int_{t_0}^t K_d(s)\,\mathrm{d}s - K_d^*\tau^*}|E(t+\theta)-\tilde{E}(t+\theta)| \\ \le\ & e^{\int_{t_0}^{t+\theta} K_d(s)\,\mathrm{d}s}|E(t+\theta)-\tilde{E}(t+\theta)| \\ \le\ & \|(E-\tilde{E})_{t_0}\| + \textstyle\int_{t_0}^{t+\theta} B(n)e^{\int_{t_0}^u K_d(s)\,\mathrm{d}s}\frac{K_e(u)}{K_i(u)}\|(E-\tilde{E})_u\|\,\mathrm{d}u \\ \le\ & \|(E-\tilde{E})_{t_0}\| + \textstyle\int_{t_0}^{t} B(n)e^{\int_{t_0}^u K_d(s)\,\mathrm{d}s}\frac{K_e(u)}{K_i(u)}\|(E-\tilde{E})_u\|\,\mathrm{d}u \end{aligned}$$

or

$$\begin{aligned} & |E(t+\theta)-\tilde{E}(t+\theta)| \\ \le\ & e^{-\int_{t_0}^t K_d(s)\,\mathrm{d}s + K_d^*\tau^*}\|(E-\tilde{E})_{t_0}\| \\ & + \int_{t_0}^t B(n)e^{-\int_u^t K_d(s)\,\mathrm{d}s + K_d^*\tau^*}\frac{K_e(u)}{K_i(u)}\|(E-\tilde{E})_u\|\,\mathrm{d}u\,. \end{aligned}$$

So, for $t\ge t_0$,

$$\begin{aligned} \|(E-\tilde{E})_t\| \le\ & e^{-\int_{t_0}^t K_d(s)\,\mathrm{d}s + K_d^*\tau^*}\|(E-\tilde{E})_{t_0}\| \\ & + \int_{t_0}^t B(n)e^{-\int_u^t K_d(s)\,\mathrm{d}s + K_d^*\tau^*}\frac{K_e(u)}{K_i(u)}\|(E-\tilde{E})_u\|\,\mathrm{d}u \end{aligned}$$

or

$$\begin{aligned} & e^{\int_{t_0}^t K_d(s)\,\mathrm{d}s}\|(E-\tilde{E})_t\| \\ \le\ & e^{K_d^*\tau^*}\|(E-\tilde{E})_{t_0}\| \\ & + \int_{t_0}^t B(n)e^{K_d^*\tau^*}\frac{K_e(u)}{K_i(u)}e^{\int_{t_0}^u K_d(s)\,\mathrm{d}s}\|(E-\tilde{E})_u\|\,\mathrm{d}u\,. \end{aligned}$$

By Gronwall's inequality, we have

$$e^{\int_{t_0}^t K_d(s)\,\mathrm{d}s}\|(E-\tilde{E})_t\| \le e^{K_d^*\tau^* + \int_{t_0}^t B(n)\frac{K_e(u)}{K_i(u)}\exp(K_d^*\tau^*)\,\mathrm{d}u}\|(E-\tilde{E})_{t_0}\|\,,\quad t\ge t_0\,.$$

Then, for $t \geq t_0$,

$$\begin{aligned}
& \|(E-\tilde{E})_t\| \\
\leq\ & e^{K_d^*\tau^*}\|(E-\tilde{E})_{t_0}\|e^{\int_{t_0}^{t}[-K_d(s)+B(n)\frac{K_e(s)}{K_i(s)}]\exp(K_d^*\tau^*)\,\mathrm{d}s} \\
=\ & e^{K_d^*\tau^*}\|(E-\tilde{E})_{t_0}\|e^{(\int_{t_0}^{t_0+\lfloor\frac{t-t_0}{\omega}\rfloor\omega}+\int_{t_0+\lfloor\frac{t-t_0}{\omega}\rfloor\omega}^{t})[-K_d(s)+B(n)\frac{K_e(s)}{K_i(s)}\exp(K_d^*\tau^*)]\,\mathrm{d}s} \\
\leq\ & e^{K_d^*\tau^*-\left(K_{d*}-B(n)\left(\frac{K_e}{K_i}\right)^*\exp(K_d^*\tau^*)\right)\omega} \\
& \times e^{[-\overline{K_d}+B(n)\overline{\left(\frac{K_e}{K_i}\right)}\exp(K_d^*\tau^*)]\omega\lfloor\frac{t-t_0}{\omega}\rfloor}\|(E-\tilde{E})_{t_0}\| \\
\leq\ & Me^{-\gamma(t-t_0)}\|(E-\tilde{E})_{t_0}\|,
\end{aligned}$$

where

$$\begin{aligned}
M &= \exp\left(K_d^*\tau^*+\omega\left(\overline{K_d}-K_{d*}+B(n)\exp(K_d^*\tau^*)\left(\left(\frac{K_e}{K_i}-\overline{\left(\frac{K_e}{K_i}\right)}\right)^*\right)\right)\right) \\
\gamma &= \overline{K_d}-B(n)\overline{\left(\frac{K_e}{K_i}\right)}\exp(K_d^*\tau^*).
\end{aligned}$$

That is, (12) holds. This completes the proof. □

4. **Numerical simulations.** In this section, we give some numerical simulations to demonstrate our results. For simplicity, we take $n = 1$ and $K_i \equiv 1$, that is, we consider

$$\frac{\mathrm{d}E(t)}{dt} = -K_d(t)E(t) + \frac{K_e(t)}{1+E(t-\tau(t))}. \tag{14}$$

Observe that equation (14) is equivalent to the following integral equation,

$$E(t) = E(t_0)e^{-\int_{t_0}^{t}K_d(s)\,\mathrm{d}s} + \int_{t_0}^{t}\frac{K_e(s)}{1+E(s-\tau(s))}e^{-\int_s^t K_d(u)\,\mathrm{d}u}\,\mathrm{d}s.$$

It follows that we can approximate the value of $E(t_0 + h)$ (h is our step size for simulation) by

$$E(t_0+h) = E(t_0)e^{-hK_d(t_0)} + \frac{K_e(t_0)}{1+E(t_0-\tau(t_0))}h.$$

Now we consider the following two examples.

Example 4.1. Assume $K_d(t) = 4 + \sin(\pi t)$, $K_e(t) = 1 + \cos(\pi t)$, and

$$\tau(t) = \begin{cases} 1.1-(t-\lfloor t\rfloor), & t \in \cup_{k=0,1,2,\dots}[2k, 2k+1), \\ 0.1+(t-\lfloor t\rfloor), & t \in \cup_{k=0,1,2,\dots}[2k+1, 2(k+1)). \end{cases}$$

Then $K_{d*} = 3 > 2 = B(1)K_e^*$ and all other conditions of Theorem 3.1 are satisfied. Thus, by the first criterion of Theorem 3.1, (14) admits a 2-periodic solution, which is globally exponentially stable. Some numerical simulations are given in Figure 1. Note that $B(1)\overline{K_e}\exp(K_d^*\tau^*) = \exp(5.5) > 4 = \overline{K_d}$, that is, the second criterion of Theorem 3.1 fails.

Example 4.2. Assume $K_d(t) = 4 + \sin(\pi t)$, $K_e(t) = 1 + 3\cos(\pi t)$, and

$$\tau(t) = \begin{cases} 0.2-0.1(t-\lfloor t\rfloor), & t \in \cup_{k=0,1,2,\dots}[2k, 2k+1), \\ 0.1+0.1(t-\lfloor t\rfloor), & t \in \cup_{k=0,1,2,\dots}[2k+1, 2(k+1)). \end{cases}$$

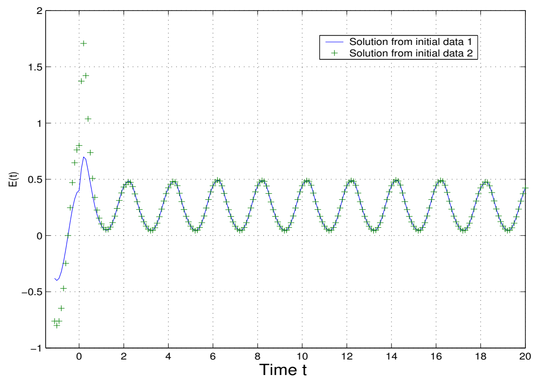

FIGURE 1. Numerical simulations for Example 4.1. Here we choose the step size $h = 0.1$ and the two sets of initial data are: (1) $E(s) = 0.4\cos(\pi s)$ and (2) $E(s) = 0.8\cos(\pi s)$ for $s \in [-1.1, 0]$.

Then $\underline{K_{d*}} = 3 < 4 = B(1)K_e^*$. The first criterion in Theorem 3.1 fails. However, $\overline{K_d} = 4 > e = B(1)e^{K_d^* \tau^*}\overline{K_e}$. Therefore, by the second criterion of Theorem 3.1, we know that (14) admits a 2-periodic solution which is globally attractive and some corresponding numerical simulations are given in Figure 2.

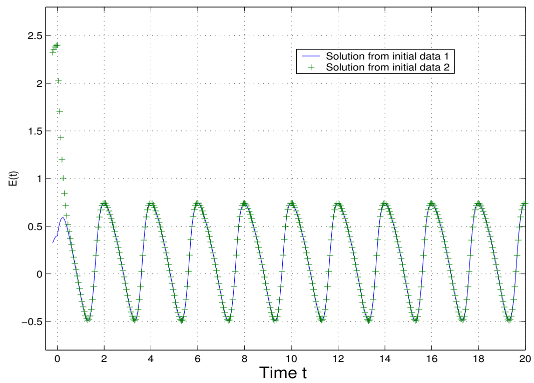

FIGURE 2. Numerical simulations for Example 4.2. Here we choose the step size $h = 0.05$ and the two sets of initial data are: (1) $E(s) = 0.4\cos(\pi s)$ and (2) $E(s) = 2 + \cos(\pi s)$ for $s \in [-0.2, 0]$.

Let us conclude this section with some remarks.

REMARK 4.1. *It follows from the above two examples that the two criteria in Theorem 3.1 are independent of each other.*

REMARK 4.2. *If, in Example 4.2, we replace* $\tau(t)$ *by*

$$\tau(t) = \begin{cases} 13 - (t - \lfloor t \rfloor), & t \in \cup_{k=0,1,2,\ldots}[2k, 2k+1), \\ 12 + (t - \lfloor t \rfloor), & t \in \cup_{k=0,1,2,\ldots}[2k+1, 2(k+1)), \end{cases} \tag{15}$$

then $\tau^* = 13$*. It is easy to check that Theorem 3.1 is not applicable. Some numerical simulations are given in Figure 3, which indicate that the periodic solution to (14)*

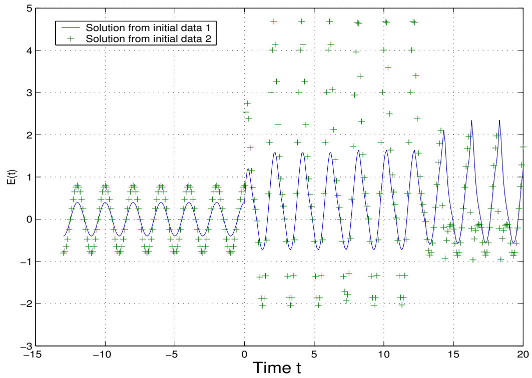

FIGURE 3. Numerical simulations for (14) with τ given by (15) and the same K_d and K_e as in Example 4.2. Here we choose our step size $h = 0.1$ and the two sets of initial data are: (1) $E(s) = 0.4\cos(\pi s)$ and (2) $E(s) = 0.8\cos(\pi s)$ for $s \in [-13, 0]$.

may not be globally stable.

REMARK 4.3. *Note that in the above examples, the variable delays $\tau(t)$ take special forms. For a general periodic variable delay, since there exists an integer m such that $t - \tau(t) \in [t_m, t_m + h)$, we can use $E(t_m)$ to approximate $E(t - \tau(t))$. Using this approach if the variable delay in Example 4.1 is changed to $\tau(t) = 1 + \cos(\pi t)$, we have the numerical simulations shown in Figure 4.*

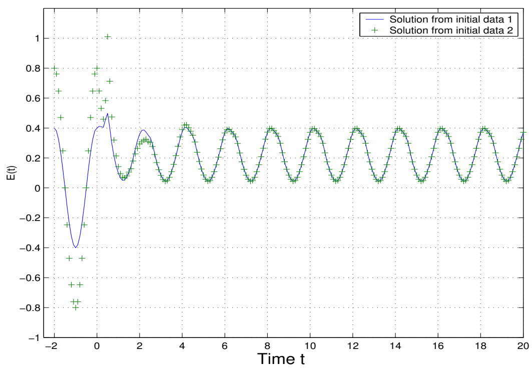

FIGURE 4. Numerical simulations for (14) with $\tau(t) = 1 + \cos(\pi t)$ and the same K_d and K_e as in Example 4.1. Here we choose the step size $h = 0.1$ and the two sets of initial data are: (1) $E(s) = 0.4\cos(\pi s)$ and (2) $E(s) = 0.8\cos(\pi s)$ for $s \in [-2, 0]$.

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