



Adjoint Method Provides Phase Response Functions for Delay-Induced Oscillations

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Limit-cycle oscillations induced by time delay are widely observed in various systems, but a systematic phase-reduction theory for them has yet to be developed. Here we present a practical theoretical framework to calculate the phase response function $Z(\theta)$, a fundamental quantity for the theory, of delay-induced limit cycles with infinite-dimensional phase space. We show that $Z(\theta)$ can be obtained as a zero eigenfunction of the adjoint equation associated with an appropriate bilinear form for the delay differential equations. We confirm the validity of the proposed framework for two biological oscillators and demonstrate that the derived phase equation predicts intriguing multimodal locking behavior.

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Delay differential equations (DDEs) are an increasingly important tool in various areas of science and engineering including nonlinear optics, traffic flow, climate systems, and biological regulations [1–6]. For example, cortical neurons have delays in transmission of electrical spikes [7,8] and gene-protein interactions have several sources of delay such as the transcription of proteins from mRNA [9–15], both of which lead to rhythmic activities. Often single biological oscillators are coupled together through mutual interaction to generate synchronous rhythms, which plays important functional roles, e.g., neural information processing and somite segmentation [12,16]. Various DDEs [5,7–15] have been proposed as models of such biological rhythms, which typically exhibit limit-cycle oscillations.

For limit-cycle oscillators described by ordinary differential equations, a standard mathematical method to address the issue of synchrony is to reduce the oscillators perturbed by mutual interaction to simple phase models. Each oscillator is described by a scalar equation

$$\frac{d}{dt}\theta(t) = \omega + Z(\theta)p(t), \quad (1)$$

where θ is the phase of the oscillator, ω is the natural frequency, and $p(t)$ represents perturbations. The function $Z(\theta)$, which is the focus of this study, quantifies the linear response of the oscillator's phase to the applied perturbations, which we call the phase response function (also called the phase sensitivity function [17] or the infinitesimal phase resetting curve [18]). It quantitatively captures essential dynamics of the oscillator and is a fundamental quantity for the phase-reduction theory. Based on the fact that $Z(\theta)$ is actually an eigenfunction of an adjoint linear operator derived from the full system of equations, a convenient semianalytical method, called the adjoint

method, that provides numerically accurate $Z(\theta)$ has been widely used [18,19].

The reduction to the phase model is valid as long as the mutual interaction between the oscillators is sufficiently weak. By plugging the mutual interaction term into $p(t)$ and averaging Eq. (1), we can obtain a simple phase model in the general form [18,20,21],

$$\frac{d}{dt}\theta_j = \omega_j + \sum_k \Gamma_{jk}(\theta_k - \theta_j), \quad (j = 1, 2, \dots), \quad (2)$$

where θ_j is the phase of the j th oscillator, ω_j denotes its natural frequency, and Γ_{jk} is the phase coupling function representing the effective interaction between oscillators j and k . Γ_{jk} is a periodic function calculated by convolving the mutual interaction term $p(t)$ with $Z(t)$.

The above phase-reduction theory has been widely used to study synchronization properties of various types of coupled oscillators [18,20,21]. However, somewhat surprisingly, the phase-reduction theory for delay-induced oscillations has not been formally developed. In particular, a practical theoretical framework to calculate $Z(\theta)$ has been missing for delay-induced limit cycles. Thus, direct numerical simulations have been mainly used to investigate the synchronization of DDEs [12–14]. One possible reason for this would be the infinite-dimensional nature of DDEs. Limit cycles of DDEs reside in infinite-dimensional phase space and the standard adjoint method for ordinary low-dimensional limit cycles [18] cannot be applied directly. Note that delays in the oscillator's intrinsic dynamics are essentially different from delays in the coupling between oscillators; the latter can be investigated by a simple extension of the conventional phase-reduction theory [1,22,23].

In this study, we develop an adjoint method to compute $Z(\theta)$ for limit cycles exhibited by DDEs. A key factor is the introduction of a mathematically appropriate dual product (bilinear form) for DDEs [24–26], which enables us to properly define the phase θ and calculate $Z(\theta)$ for limit cycles in infinite-dimensional phase space. As examples, we consider biological oscillations in cortico-thalamic and gene-regulatory models, and demonstrate that the method nicely works through comparisons to direct perturbation methods, analytical computations near the bifurcation point, and numerical computations of weakly coupled systems. Moreover, based on the obtained $Z(\theta)$, we reveal that the coupled system can exhibit intriguing multimodal phase-locking behavior, in which the number of stable phase differences increases with the time delay.

Our aim is to derive a phase equation (1) from a DDE of the form

$$\frac{d}{dt}X(t) = F(X(t), X(t - \tau)) \quad (3)$$

by properly calculating $Z(\theta)$, where $X(t) \in \mathbb{R}^N$ is a column vector of N real components and τ is a nonnegative constant delay. We assume that this DDE has a linearly stable limit cycle whose period is T . As formulated by Hale [25] and Campbell [27], a DDE is considered a functional differential equation by introducing a function-space representation of $X(t)$, $X^{(t)}(\sigma) \equiv X(t + \sigma)(-\tau \leq \sigma \leq 0)$, where $X^{(t)} \in C_0$ and $C_0 = C([-\tau, 0] \rightarrow \mathbb{R}^N)$ is a space of continuous functions that map the interval $[-\tau, 0]$ into \mathbb{R}^N . Namely, the DDE is considered an infinite-dimensional dynamical system whose phase space is the function space C_0 . From Eq. (3), the dynamics of $X^{(t)}(\sigma)$ can be described as

$$\begin{aligned} \frac{d}{dt}X^{(t)}(\sigma) &= \frac{d}{d\sigma}X^{(t)}(\sigma) \quad (-\tau \leq \sigma < 0), \\ \frac{d}{dt}X^{(t)}(\sigma) &= F(X^{(t)}(0), X^{(t)}(-\tau)) \quad (\sigma = 0). \end{aligned} \quad (4)$$

We denote the limit-cycle orbit as $X_0(t)$ and a small deviation from it as $Y(t)$, i.e., $X(t) = X_0(t) + Y(t)$. The linearized equation for $Y(t)$ can then be written as

$$-\frac{d}{dt}Y(t) + F_1(t)Y(t) + F_2(t)Y(t - \tau) = 0, \quad (5)$$

where $F_j(t) = \partial_{x_j}F(x_1, x_2)$ ($j = 1, 2$) is evaluated at $(x_1, x_2) = (X_0(t), X_0(t - \tau))$. Although the coefficients $F_1(t)$ and $F_2(t)$ of $Y(t)$ are time-dependent periodic functions, this linearized equation is still a DDE. We denote a linear operator \hat{L} as

$$\begin{aligned} (\hat{L}Y^{(t)})(\sigma) &= -\frac{d}{dt}Y^{(t)}(\sigma) + \frac{d}{d\sigma}Y^{(t)}(\sigma) \quad (-\tau \leq \sigma < 0), \\ (\hat{L}Y^{(t)})(\sigma) &= -\frac{d}{dt}Y^{(t)}(\sigma) + F_1(t)Y^{(t)}(0) \\ &\quad + F_2(t)Y^{(t)}(-\tau) \quad (\sigma = 0), \end{aligned} \quad (6)$$

by introducing a function $Y^{(t)} \in C_0$ as $Y^{(t)}(\sigma) = Y(t + \sigma)(-\tau \leq \sigma \leq 0)$.

Following Halanay [24], Hale [25], and Simmendinger [26], an adjoint equation to Eq. (5) can be introduced as

$$\frac{d}{dt}Y^*(t) + Y^*(t)F_1(t) + Y^*(t + \tau)F_2(t + \tau) = 0, \quad (7)$$

where $Y^*(t) \in \mathbb{R}^{N^*}$ is a row vector of N real components. Introducing again a functional representation $Y^{(t)*}(s) \equiv Y^*(t + s)(0 \leq s \leq \tau)$, where $Y^{(t)*} \in C_0^*$ and $C_0^* = C([0, \tau] \rightarrow \mathbb{R}^{N^*})$ is now a space dual to C_0 consisting of functions that map the interval $[0, \tau]$ into \mathbb{R}^{N^*} . Then, an adjoint operator \hat{L}^* of \hat{L} is derived as

$$\begin{aligned} (\hat{L}^*Y^{(t)*})(s) &= \frac{d}{dt}Y^{(t)*}(s) - \frac{d}{ds}Y^{(t)*}(s) \quad (0 < s \leq \tau), \\ (\hat{L}^*Y^{(t)*})(s) &= \frac{d}{dt}Y^{(t)*}(s) + Y^{(t)*}(0)F_1(t) \\ &\quad + Y^{(t)*}(\tau)F_2(t + \tau) \quad (s = 0). \end{aligned} \quad (8)$$

The above adjoint equation and the adjoint linear operator are associated with a bilinear form that is appropriately defined for DDEs [26],

$$\langle \psi, \phi; t \rangle \equiv \psi(0)\phi(0) + \int_{-\tau}^0 \psi(\xi + \tau)F_2(t + \xi + \tau)\phi(\xi)d\xi, \quad (9)$$

where $\phi \in C_0$ and $\psi \in C_0^*$. It is easy to show that $dX_0^{(t)}/dt$ is a zero eigenfunction of the linear operator \hat{L} by differentiating Eq. (6) with respect to t . Now, let $y_0^{(t)*}$ denote the zero eigenfunction of the adjoint operator \hat{L}^* and $p^{(t)}(\sigma) = pU(\sigma)\delta(t - t_a)$ an infinitesimal perturbation applied to the oscillator at time $t = t_a$, where p is a tiny constant, U is a unit step (Heaviside) function, and δ is a Dirac delta function. The function U indicates that only the $X_0^{(t_a)}(0)$ component of the whole oscillator state $X_0^{(t_a)} \in C_0$ is perturbed. Namely, only the present component of the oscillator state can be modified and its past components cannot be changed. Then, similar to the case of ordinary differential equations [18,20], projection of the perturbation onto the phase component can be represented using the bilinear product as $\langle y_0^{(t)*}, p^{(t)}; t \rangle$. This quantity is equal to $y_0^{(t_a)*}(0)p^{(t_a)}(0)$, because $p^{(t)}(\sigma) = 0$ when $-\tau \leq \sigma < 0$. Therefore, $y_0^{(t_a)*}(0) = y_0^*(t_a)$ should be identical to $Z(\theta = \omega t_a)$ after appropriate normalization.

In actual calculations, the limit-cycle solution $X_0(t)$ is obtained numerically. Using the numerical solution $X_0(t)$, we can integrate Eq. (7) backwards in time from arbitrary initial conditions to obtain $y_0^*(t)$, because functional components other than $y_0^*(t)$ have positive eigenvalues and therefore eventually vanish (in reverse time) due to the linear stability of $X_0(t)$ (by virtue of the Floquet theorem [26]). We further normalize the amplitude of $y_0^*(t) = y_0^{(t)*}(0)$ as

$$\left\langle y_0^{(t)*}, \frac{d}{dt}X_0^{(t)}; t \right\rangle = \omega = \frac{2\pi}{T}. \quad (10)$$

The phase response function is then given by $Z(\theta) = y_0^*(t = \theta/\omega) = y_0^{*(t=\theta/\omega)^*}(0)$. This procedure gives an adjoint method for delay-induced limit cycles described by DDEs and is the main result of this study. If we take the limit of $F_2 \rightarrow 0$ or $\tau \rightarrow 0$, the proposed adjoint method for DDEs becomes identical to the conventional adjoint method for ordinary differential equations. Therefore, the above method is actually a natural extension of the adjoint method to delay-induced oscillations.

We now evaluate Z of several types of DDEs by the adjoint method proposed above and demonstrate that the results agree well with those obtained by a direct perturbation method or by analytical calculations near the bifurcation point. To check the validity of the adjoint method, we calculate $Z(\theta)$ by directly applying weak impulsive perturbations to the DDE exhibiting limit-cycle oscillations. Namely, we kick the orbit $X(t)$ out of the limit cycle, wait for the orbit to come back to the limit cycle, and measure the asymptotic phase difference caused by the kick. It is notable that the actual time course of the orbit $X(t)$ typically exhibits several “kickbacks” of period τ before finally coming back to the limit cycle due to the delay. We thus need to run the numerical simulation long enough, so that the whole time course of X from $X(t - \tau)$ to $X(t)$ returns sufficiently close to the limit cycle in calculating the asymptotic phase difference.

A crucial difference between the adjoint method and the direct perturbation method should be emphasized here. The adjoint method is semianalytic in the sense that it directly solves a linear equation for Z itself, whereas the direct perturbation method is semiexperimental and relies on direct simulations of the perturbed system. The latter method is vulnerable to incorrect estimations of the phase response, because strong perturbations induce nonlinearity in the phase response and weak perturbations result in tiny phase responses that are difficult to measure accurately. Therefore, the adjoint method has a great advantage in computing Z for given mathematical models.

As the first example, we consider a second-order differential equation with a linear delay term and a cubic nonlinearity,

$$\frac{d^2x(t)}{dt^2} = \gamma \frac{dx(t)}{dt} + \alpha x(t) + \beta x(t - \tau) + \epsilon x(t)^3. \quad (11)$$

This is a simplified cortico-thalamic model for electroencephalogram rhythms [7,8]. We take the parameters as $\beta = -0.4$, $\gamma = -2.0$, $\epsilon = -10.0$, $\tau = 8.0$, and vary α as a control parameter. At $\alpha = -0.051$, this model undergoes a Hopf bifurcation and yields a small amplitude limit cycle in the vicinity of this bifurcation point. We here take $\alpha = -0.039$, which gives small amplitude oscillation. Then, the center-manifold reduction is applicable to Eq. (11) and the phase response function can be analytically obtained as $Z(\phi) \approx \sqrt{-3\epsilon/4\mu} 2 \cos\phi / \{-\gamma[1 - \Omega\tau \cot(\Omega\tau)]\}$, where $\Omega = 0.20$ is the Hopf frequency and $\mu = 0.012$ is a scaled bifurcation parameter (see Ref. [8] for details).

Since Eq. (11) is a second-order differential equation, we denote the dynamical variables as $X(t) = (x(t), dx(t)/dt)^T$ and the limit-cycle solution as $X_0(t) = (x_0(t), dx_0(t)/dt)^T$. Then, the functions $F_1(t)$ and $F_2(t)$, which are required for the adjoint Eq. (7) as well as for the bilinear form Eq. (9), are given as

$$F_1(t) = \begin{bmatrix} 0 & 1 \\ \alpha + 3\epsilon x_0(t)^2 & \gamma \end{bmatrix}, \quad F_2(t) = \begin{bmatrix} 0 & 0 \\ \beta & 0 \end{bmatrix}, \quad (12)$$

respectively. Because $F_2(t)$ is constant, the bilinear form does not depend on time in this case. We compare the phase response functions obtained by the adjoint method and by the direct perturbation method with the analytical results in Fig. 1 [28]. We can confirm that both the adjoint method and the direct perturbation method give phase response functions that agree well with the theoretical curve.

One characteristic feature of the DDEs is that even a very simple equation can exhibit complex dynamics when the parameter is far from the bifurcation point. The phase reduction can still be applicable to such cases as long as the coupling is weak, in contrast to the center-manifold reduction that is valid only near the bifurcation point [8]. We here calculate $Z(\theta)$ for such cases and use it to predict the behavior of coupled oscillators. To see the system behavior distant from the bifurcation point, we simulate Eq. (11) at $(\alpha, \beta) = (-0.1, -5.0)$ with τ being varied as the control parameter. When τ is small, the origin is linearly stable. As τ is increased, the origin loses its stability and the system starts to exhibit complex orbits. The time course of $x(t)$ and the orbit projected on the $(x, dx/dt)$ plane are plotted for $\tau = 2.5$ [Figs. 2(a) and 2(b)] and for $\tau = 8$ [Figs. 2(c) and 2(d)]. The orbit is more complex for larger

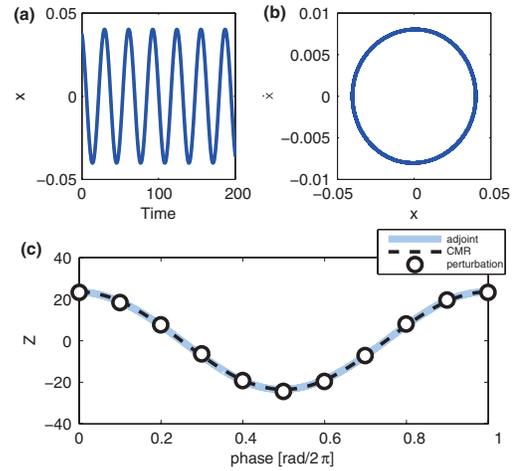


FIG. 1 (color). (a) Limit-cycle oscillations and (b) the attractor projected onto the $(x, dx/dt)$ plane of the delay-induced limit cycle exhibited by Eq. (11). (c) $Z(\theta)$ with respect to perturbations applied to the dx/dt component. Black broken line indicates the analytical result obtained by the center-manifold reduction (CMR). Blue curve and brown circles are the results of the adjoint method and the direct perturbation method, respectively.

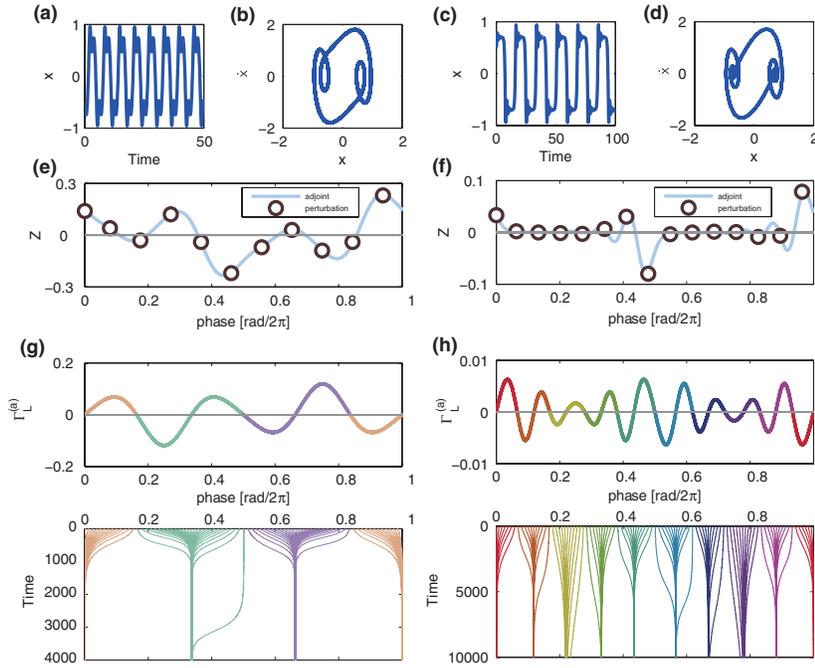


FIG. 2 (color). (a)–(d) Time course of $x(t)$ and projection of the orbit on the $(x, dx/dt)$ plane for $\tau = 2.5$ [(a) and (b)] and $\tau = 8$ [(c) and (d)]. (e),(f) $Z(\theta)$ obtained by the adjoint method (solid line) and the direct perturbation method (brown circles). [$\tau = 2.5$ (e) and $\tau = 8$ (f)]. (g),(h) $\Gamma_L^{(a)}(\phi)$ and multimodal phase locking of two coupled identical oscillators. [$\tau = 2.5$ (g) and $\tau = 8$ (h)]. As τ becomes large, the two oscillators tend to synchronize at more various phase differences. Each color indicates the predicted basin that converges to the same stationary phase difference predicted by the adjoint method (upper panels), which is confirmed by the numerical simulations (lower panels).

time delay ($\tau = 8$). $Z(\theta)$ obtained by the adjoint method and by the direct perturbation method are plotted and compared in Figs. 2(e) and 2(f). The adjoint method provides appropriate $Z(\theta)$ even when the parameters are far from the bifurcation points.

We now consider two symmetrically coupled oscillators and introduce a linear coupling $L(\dot{x}_2 - \dot{x}_1)$ [or $L(x_1 - x_2)$] to the variables $x_1(t)$ [or $x_2(t)$] with coupling intensity $L = 0.02$. The phase difference between the two oscillators $\phi(t) = \theta_1(t) - \theta_2(t)$ then obeys $\dot{\phi}(t) = \Gamma_L^{(a)}(\phi)$, where $\Gamma_L^{(a)}(\phi) = \Gamma_L(\phi) - \Gamma_L(-\phi)$ is given by the antisymmetric component of the phase coupling function $\Gamma_L(\theta) = \frac{1}{T} \int_0^T Z(t + \theta/\omega) L(\dot{x}_2(t) - \dot{x}_1(t)) dt$. Figures 2(g) and 2(h) display $\Gamma_L^{(a)}(\phi)$ and the transient dynamics of the phase difference for varying initial phase differences [$\tau = 2.5$ for (g) and $\tau = 8.0$ for (h)]. It can be seen that initial phase differences between two oscillators, which are uniformly distributed initially, eventually converge to fixed phase differences predicted from the function $\Gamma_L^{(a)}(\phi)$ [29]. The number of phase-locking points increases with τ , reflecting the increasing complexity of the limit-cycle orbit and $Z(\theta)$. Thus, we can theoretically predict interesting phase-locking characteristics of the coupled delay-induced limit-cycle oscillations using $Z(\theta)$ obtained by the adjoint method.

Next, we investigate a more complex model of gene regulation in which nonlinear delayed feedback plays an essential role,

$$\frac{dx(t)}{dt} = k_1 S \frac{(K_d)^p}{(K_d)^p + x(t-\tau)^p} - k_2 E_T \frac{x(t)}{K_m + x(t)}. \quad (13)$$

We choose the parameters $k_1 = 1.0$, $k_2 = 1.0$, $S = 2.0$, $K_d = 1.0$, $E_T = 1.0$, $K_m = 0.1$, $p = 2.0$ and vary the time delay τ as a control parameter [15,28]. We restrict ourselves to the situation where $x(t)$ is positive. As τ becomes larger,

the fixed point at $x(t) = 1.09$ [30] loses stability and a limit-cycle solution arises as shown in Figs. 3(a) and 3(b) for $\tau = 5$. In this case, F_1 and F_2 are given by

$$F_1(t) = -k_2 E_T \frac{K_m}{[K_m + x_0(t)]^2}, \quad (14)$$

$$F_2(t) = -k_1 S \frac{p(K_d)^p x_0(t-\tau)^{p-1}}{[(K_d)^p + x_0(t-\tau)^p]^2},$$

and therefore the bilinear form Eq. (9) is time dependent.

We numerically solve the adjoint problem and compare the results with the direct perturbation method. As shown in Fig. 3(c), both results are in good agreement. As a further verification, we calculate $\langle y_0^{(t)*}, dX_0^{(t)}/dt; t \rangle$ over an interval of $0 \leq t < T$. This quantity gives the projection of the velocity $dX_0^{(t)}/dt$ of the limit cycle, which resides in the infinite-dimensional function space C_0 , onto the direction along the limit-cycle orbit. It gives a scalar $d\theta/dt$, which should be equal to the constant frequency ω . Figure 3(d) shows $\langle y_0^{(t)*}, dX_0^{(t)}/dt; t \rangle$ and compares it with $y_0^{(t)*}(0)[dX_0^{(t)}(0)/dt]$, i.e., a product with only the first term of the bilinear form Eq. (9), which we might naively expect as the projection onto the limit-cycle solution. We can see that the proper combination $\langle y_0^{(t)*}, dX_0^{(t)}/dt; t \rangle$ (green line) is actually kept constant, namely, the phase advances constantly at a rate $\omega = 0.365$. In contrast, the quantity $y_0^{(t)*}(0)[dX_0^{(t)}(0)/dt]$ (red curve) greatly fluctuates and does not give the correct natural frequency ω . Only when this quantity is added to the second term of the bilinear form Eq. (9) (blue curve), is the correct ω is obtained. This result also confirms the validity of the adjoint method based on the bilinear form Eq. (9).

In summary, we developed an adjoint method that gives the phase response function of limit-cycle oscillations

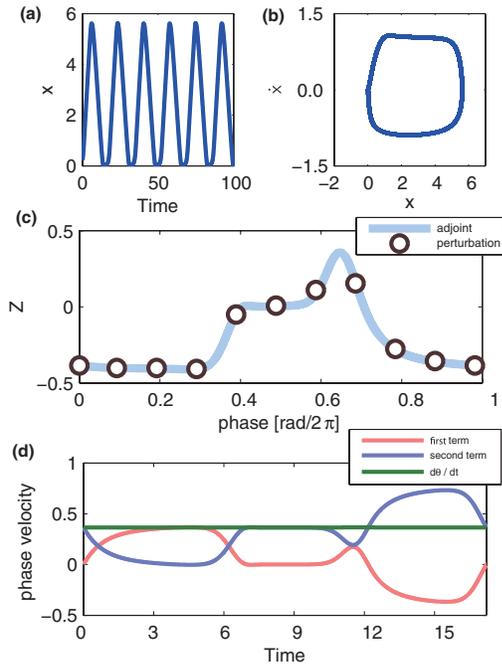


FIG. 3 (color). (a) Time course of $x(t)$. (b) Projection of the orbit on the $(x, dx/dt)$ plane. (c) $Z(\theta)$ obtained by the adjoint method (solid line) and the direct perturbation method (brown circles). (d) Projection of the velocity dx/dt onto the phase component by the bilinear product $\langle y_0^{(t)*}, dX_0^{(t)}/dt; t \rangle = d\theta/dt$. The red curve and the blue curve show the first term and the second term of the bilinear form Eq. (9), respectively. The green curve shows the whole bilinear product.

exhibited by DDEs. We confirmed the validity of the method by comparing the results with those obtained by direct perturbation methods as well as by analytical computations near the bifurcation point. As examples, we considered biological oscillations in cortico-thalamic and gene-regulatory models, and demonstrated that the method works nicely for these systems. Moreover, we revealed that intriguing multimodal phase-locking states can occur, in which the number of the stable phase shifts increases with the time delay in the cortico-thalamic model.

Our present study provides a practical theoretical framework to systematically analyze synchronization of weakly coupled delay-induced limit-cycle oscillators, which would serve as a powerful tool in investigating synchronization of brain activities and entrainment of circadian rhythms to daylight. More detailed investigations on networks of such biological oscillators with stochastic fluctuations and their biological relevance will be discussed elsewhere. Delay differential equations are used to describe diverse phenomena in science and engineering, and therefore the adjoint method developed in this study should have a wide applicability.

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- [28] The origin of the phase θ is defined as $x = 0$ with positive dx/dt for the cortico-thalamic model and as the maximum value of x for the gene regulation model.
- [29] The phase difference ϕ is stable when ϕ satisfies $\Gamma_L^{(a)}(\phi) = 0$ and $d\Gamma_L^{(a)}(\phi)/d\phi > 0$. The theory predicts that there are three different values of the stable phase shift for $\tau = 2.5$ and nine for $\tau = 8$.
- [30] This stable point is given by a positive solution of $x^3 - x = 0.2$.