Optimal Waveform for Fast Entrainment of Weakly Forced Nonlinear Oscillators

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For many biological and engineered systems, a central function or design goal is to abbreviate the time required to synchronize a rhythmic process to an external forcing signal. We present a theory for deriving the input that effectively minimizes the average transient time required to entrain a phase model, which enables a practical technique for constructing fast entrainment waveforms for general nonlinear oscillators. This result is verified in numerical simulations using the Hodgkin-Huxley neuron model, and in experiments on an oscillatory electrochemical system.

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The entrainment process is fundamental to numerous scientific and engineering applications in which oscillating systems are asymptotically synchronized to an external periodic signal [1,2]. The ability to optimize entrainment has important implications for achieving rapid cardiac resynchronization [3] and quick adjustment from jet lag [4], maximizing the growth rate of plants [5], and implementing phase-locked loop circuits and injection-locked microintegrated oscillators [6]. When the weak perturbation approximation is made, a rescaling of the phase response curve (PRC) was shown to be the minimum energy signal for spiking or entraining oscillators at a given period [7–9], and a weighted sum of appropriately shifted PRCs maximizes the range of frequency detunings for which entrainment occurs [10,11]. An alternative essential objective is to minimize the time to entrainment at a given forcing signal energy, in order to establish a fixed phase relationship between the system and forcing signal as soon as possible after the forcing is applied [12]. This notion of fast entrainment can also be used to minimize the time required to reestablish entrainment after interruptions caused by disturbances [13].

In this Letter, we use phase model reduction to derive an asymptotically optimal waveform that maximizes the average rate of entrainment for general weakly forced nonlinear oscillators. The rate of entrainment is characterized by the coefficient of exponential decay in the phase difference between the system and forcing signal. We present a theory by which the entrainment time scale is minimized for a specified forcing energy, where the optimal waveform is a sum of the PRC and its derivative with weights that depend on the difference between the natural and forcing frequencies. These findings can be applied to weakly nonlinear oscillators just past the Hopf bifurcation, as well as strongly nonlinear relaxation oscillators. We confirm our results with numerical simulations using the Hodgkin-Huxley (HH) neuron model, as well as in experiments on an oscillatory chemical system arising through the electrodissolution of nickel in sulfuric acid.

Phase coordinate transformation is a model reduction technique that is useful for examining nonlinear oscillating systems [14,15], and can also be used for system identification when the dynamics are complex or unknown [2]. Such models have been studied extensively, with a particular focus on neural [14,16] and electrochemical [17–19] systems. Consider a full state-space model described by a smooth ordinary differential equation system $\dot{x} = f(x, u)$, $x(0) = x_0$, where $x(t) \in \mathbb{R}^n$ is the state and $u(t) \in \mathbb{R}$ is a control, with an attractive, nonconstant limit cycle $\gamma(t) = \gamma(t + T)$ that satisfies $\dot{\gamma} = f(\gamma, 0)$ on the periodic orbit $\Gamma = \{y \in \mathbb{R}^n\colon y = \gamma(t) \text{ for } 0 \le t < T\} \subset \mathbb{R}^n$. This system is reduced to a scalar phase equation

$$\dot{\psi} = \omega + Z(\psi)u, \tag{1}$$

where ω is the natural frequency of oscillation, Z is a smooth PRC, and $\psi(t)$ is the asymptotic phase [20]. The model is valid for inputs u such that the state-space system remains within a neighborhood U of Γ [21], and the PRC can be computed numerically [14,22,23].

The primary objective in entrainment design is to lock the system to an input with the desired frequency Ω using a control $u(t) = v(\Omega t)$ where v is 2π periodic. We make the weak perturbation approximation, i.e., $v = \varepsilon v_1$ where v_1 has unit energy and $\varepsilon \ll 1$, so that given this control the actual state of the system is guaranteed to remain in U, and the phase model (1) remains valid. We define a slow phase variable $\phi(t) = \psi(t) - \Omega t$ that satisfies the dynamic equation $\dot{\phi} = \dot{\psi} - \Omega = \Delta\omega + Z(\Omega t + \phi)v(\Omega t)$, where $\Delta\omega = \omega - \Omega$ denotes the detuning between the natural and forcing frequencies. To study the asymptotic behavior of the slow phase, we eliminate the explicit dependence on time on the right-hand side by using formal averaging [17]. Given a periodic forcing with frequency Ω, we denote the forcing phase $\theta = \Omega t$. We also define an averaging operator $\langle\cdot\rangle\colon \mathcal{P} \to \mathbb{R}$ on the set of 2π-periodic functions by

$\langle x \rangle = 1/(2\pi) \int_0^{2\pi} x(\theta) d\theta$. The weak ergodic theorem for measure-preserving dynamical systems on the torus [24] implies that for any periodic function v, the interaction function

$$\begin{aligned}\Lambda_v(\phi) &= \langle Z(\theta + \phi) v(\theta) \rangle \\ &= \frac{1}{2\pi} \int_0^{2\pi} Z(\theta + \phi) v(\theta) d\theta \\ &= \lim_{T\to\infty} \frac{1}{T} \int_0^T Z(\Omega t + \phi) v(\Omega t) dt \end{aligned} \tag{2}$$

is a smooth function in $\mathcal{P}$. Using the weak perturbation approximation and the formal averaging theorem [25], the time-averaged slow phase dynamics are, up to $\mathcal{O}(\varepsilon^2)$,

$$\dot{\varphi} = \Delta\omega + \Lambda_v(\varphi). \tag{3}$$

Equation (3) is used to study the asymptotic behavior of (1) under periodic forcing. We say that the system is entrained by a control $u = v(\Omega t)$ when (3) satisfies $\dot{\varphi} = 0$, which eventually occurs if there exists a phase φ_* satisfying $\Delta\omega + \Lambda_v(\varphi_*) = 0$. For nonzero control waveform v and nonzero PRC Z, the function $\Lambda_v(\varphi)$ is not identically zero, so when the system is entrained there exists at least one $\varphi_* \in [0, 2\pi)$ that is an attractive fixed point of (3). We have shown that the minimum energy periodic waveform that entrains a single oscillator with natural frequency ω to a target frequency Ω is a rescaling of the PRC, given by $v(\theta) = -\Delta\omega Z(\theta)/\langle Z^2 \rangle$ [9,11].

Our goal here is to entrain the system (1) to a target frequency Ω as quickly as possible by using a periodic control v of fixed power $P = \langle v^2 \rangle$. Ideally, the interaction function would be of a piecewise-constant form, so that the averaged slow phase φ converges to a fixed point φ_* at a uniform rate from any initial value. However, the discontinuity as $\varphi \to \varphi_*$ would result in a singularity in the control v, making it infeasible in practice. An alternative is to maximize $|\dot{\varphi}_*|$, the rate of convergence of the averaged slow phase in the neighborhood of its attractive fixed point φ_*. The calculus of variations can then be used to obtain a smooth optimal candidate solution that also performs well in practice. When the system (3) is entrained by a control v, there exists an attractive fixed point φ_* satisfying $\Lambda_v(\varphi_*) + \Delta\omega = 0$ and $\Lambda_v'(\varphi_*) < 0$, where $'$ is the differentiation operator. In order to maximize the rate of entrainment in a neighborhood of φ_* using a control of power P, the value of $|\dot{\varphi}|$ should be maximized for values of φ near φ_*, which occurs when $-\Lambda_v'(\varphi_*)$ is large. This results in the following problem formulation for fast entrainment:

$$\max_{v\in\mathcal{P}} \mathcal{J}[v] = -\Lambda_v'(\varphi_*) \tag{4}$$

$$\text{s.t.} \quad \langle v^2 \rangle = P \tag{5}$$

$$\Lambda_v(\varphi_*) + \Delta\omega = 0. \tag{6}$$

The constraints can be adjoined to the objective using multipliers λ and μ to yield the formulation

$$\begin{aligned}\mathcal{J}[v] &= -\Lambda_v'(\varphi_*) + \lambda(\langle v^2 \rangle - P) + \mu(\Lambda_v(\varphi_*) + \Delta\omega) \\ &= -\langle Z'(\theta + \varphi_*) v(\theta) \rangle + \lambda(\langle v^2 \rangle - P) \\ &\quad + \mu(\langle Z(\theta + \varphi_*) v(\theta) \rangle + \Delta\omega) \\ &= \frac{1}{2\pi} \int_0^{2\pi} (v(\theta)[\mu Z(\theta + \varphi_*) - Z'(\theta + \varphi_*) + \lambda v(\theta)] \\ &\quad - \lambda P + \mu \Delta\omega) d\theta. \end{aligned} \tag{7}$$

The associated Euler-Lagrange equation is

$$\mu Z(\theta + \varphi_*) - Z'(\theta + \varphi_*) + 2\lambda v(\theta) = 0, \tag{8}$$

and solving for v yields the candidate solution

$$v(\theta) = \frac{1}{2\lambda} [Z'(\theta + \varphi_*) - \mu Z(\theta + \varphi_*)]. \tag{9}$$

The multipliers λ and μ can be found by substituting (9) into the constraints (5) and (6). This yields the equations

$$\frac{1}{4\lambda^2} [\langle (Z')^2 \rangle - 2\mu \langle Z'Z \rangle + \mu^2 \langle Z^2 \rangle] = P, \tag{10}$$

$$\frac{1}{2\lambda} [\langle Z'Z \rangle - \mu \langle Z^2 \rangle] = -\Delta\omega. \tag{11}$$

Because Z is 2π periodic, one can show, e.g., using Fourier series, that $\langle Z'Z \rangle = 0$, so that (11) easily yields $\mu = 2\Delta\omega\lambda/\langle Z^2 \rangle$. Substituting this result into (10) leads to a quadratic equation (10) for λ. Now, by substituting (9) into $\Lambda'(\varphi_*) = \langle Z(\theta + \varphi_*) v(\theta) \rangle$ we obtain $\Lambda'(\varphi_*) = \langle (Z')^2 \rangle / (2\lambda)$, so we choose $\lambda < 0$ when solving (10) for λ in order to maximize the objective in (4). Thus the optimal waveform and multiplier simplify to

$$v(\theta) = \frac{Z'(\theta)}{2\lambda} - \frac{\Delta\omega Z(\theta)}{\langle Z^2 \rangle}, \qquad \lambda = -\frac{1}{2} \sqrt{\frac{\langle (Z')^2 \rangle}{P - \frac{(\Delta\omega)^2}{\langle Z^2 \rangle}}}, \tag{12}$$

where we disregard the phase shift φ_*, because the entrainment process is asymptotic. For zero frequency detuning, the optimal waveform is a rescaling of the derivative Z' of the PRC. As $|\Delta\omega|$ increases, v continuously transforms towards Z, which is the minimum energy waveform for frequency control [9]. This transition reflects the conceptual tradeoff between the fast entrainment objective (4) and frequency control constraint (6), which can be satisfied only when $P > (\Delta\omega)^2/\langle Z^2 \rangle$.

Consider a system with a sinusoidal PRC, given by $Z(\theta) = a \sin(\theta)$. Using angle sum identities and the fact that in this case $\langle (Z')^2 \rangle = \langle Z^2 \rangle$, one can show that v is of form $v(\theta) = P \sin(\theta)$. Indeed, for the case of a sinusoidal PRC, a sinusoidal input optimizes the minimum energy [9] and rapid phase-locking objectives simultaneously. However, the utility of our approach is most evident for oscillating systems with complex dynamics, in particular those that exhibit relaxation, and hence higher harmonics

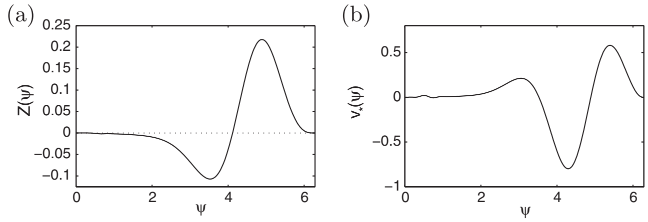

FIG. 1. (a) PRC of the HH model; (b) Optimal fast entrainment waveform v for HH system at $\Omega = \omega$ and $P = 0.1$ mW.

in the PRC. As an example, consider the HH system [26], which is a fundamental model used in the study of neural dynamics [11]. When the baseline current I_b injected into the axon is sufficiently high, the voltage V spikes repeatedly. Our goal is to modulate the additional injected current $I(t)$ to entrain the spiking frequency to a desired target Ω in as short a time as possible. We first reduce the HH system to a phase model as in (1) where $u = I(t)$, where $\omega \approx 0.429$ rad/sec, and the PRC Z is given in Fig. 1(a). After selecting the control power P and the target frequency Ω, we use (12) to compute the optimal waveform v, which is shown in Fig. 1(b). Numerically, we use the Fourier series coefficients of Z to evaluate expressions derived from the PRC, such as Z', $\langle Z^2 \rangle$, and so on. In this computational example, we focus on initial convergence rates for fast entrainment, which can be quantified by the rate k at which the phase difference between successive interspike intervals converges exponentially to zero, according to $\Delta\varphi_n = e^{-kn}$, as shown in Fig. 2. The optimal

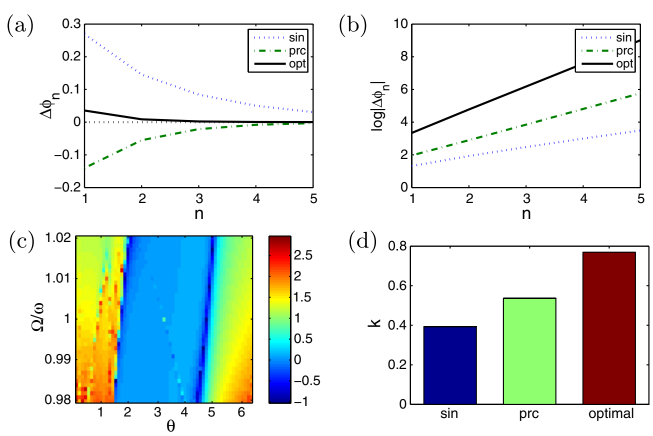

FIG. 2 (color online). Simulations with the HH model: (a) Convergence of phase difference $\Delta\varphi_n$ between interspike intervals; (b) Exponential fit for k when $\Omega = 1.01\omega$ and $P = 0.5$. The k values are 0.5415, 0.9510, and 1.4139 for sine, PRC, and optimal waveforms, respectively. (c) Initial convergence rates k (in color) for 5 cycles with $\Omega \in [0.98\omega, 1.02\omega]$ and $\theta(0) \in [0, 2\pi]$ when using the optimal waveform. (d) Average initial k on $(\Omega, \theta(0)) \in [0.98\omega, 1.02\omega] \times [0, 2\pi]$ for sine, PRC, and optimal waveforms is 0.3933, 0.5365, and 0.7691, respectively. Initial divergence takes place in 7.69%, 12.73%, and 6.04% of initial conditions for sine, PRC, and optimal waveforms, respectively.

waveform (12) achieves a significantly greater average rate k for all values of Ω and initial states on Γ.

The experimental utility of the phase model technique for fast entrainment is demonstrated by manipulating an oscillatory chemical process [27]. A standard three-electrode setup was used with a 1 mm diameter nickel working, a $Hg/Hg_2SO_4/(sat)K_2SO_4$ reference, and a Pt coated Ti rod counterelectrode immersed in 3 mol/L sulfuric acid solution at 10 °C. The nickel working electrode was polarized with a potentiostat (Gamry Instruments, Reference 600) at a circuit potential $V = V_0 + AF(\theta)$, where A and F are the forcing amplitude and waveform, respectively, and V_0 is the base potential. Each forcing waveform F has power $P = 0.5$. The current, proportional to the dissolution rate, was measured by the potentiostat at a rate of 200 Hz. When 1 kΩ resistance was attached to the nickel wire, nonlinear current oscillations with a period of 2.11 s were obtained at $V_0 = 1.15$ V as shown in the inset of Fig. 3. In each instance of the experiment, the PRC, such as the example in Fig. 3(a), was obtained using the pulse perturbation method [10,28]. The phase of the oscillation was obtained using the linear interpolation technique [2] by setting the phase of the nth current peak to $2\pi n$. The transformation of the PRC as the circuit potential increases has been previously analyzed in detail [28].

Using (12), an optimal fast entrainment waveform was constructed for equal forcing and natural frequencies, $\Omega = \omega$, in order to remove the effect of the frequency control constraint (6). When the optimal waveform with amplitude of $A = 12.5$ mV was applied to entrain the free-running chemical oscillator, the phase difference between the current oscillations and the forcing signal, shown in Fig. 4(a), monotonically decreased until a final phase difference of $\phi_f = 5.51$ rad was attained after 30 sec.

The behavior of the phase difference $\Delta\phi(t) = \phi(t) - \phi_f$ after 20 sec can be closely described by an exponential decay $\ln[\Delta\phi(t)/\Delta\phi(0)] = -kt$, which is shown in Fig. 4(b), with a rate of entrainment $k = 0.243$ s^{-1} for

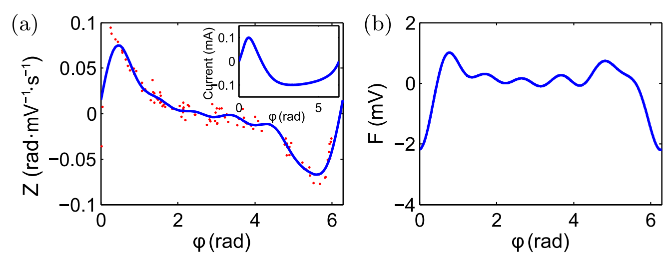

FIG. 3 (color online). Electrodissolution experiments: (a) PRC and current waveform (inset) of the electrochemical oscillations. The PRC is measured by stimulating the system using a sequence of pulses ($A = 200$ mV magnitude and $\tau = 0.05$ s pulse width) and measuring the corresponding phase shift (Φ) as a function of the phase; $Z = \Phi/(A\tau)$ rad/mV/s measurements (dots) and Fourier fit with five harmonics (curve). (b) Optimal waveform using (12) with $\Omega = \omega$, $P = 0.5$, and the PRC in (a).

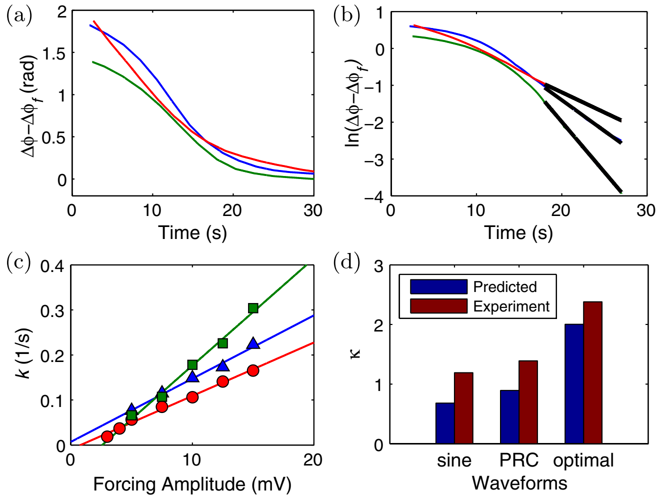

FIG. 4 (color online). Electrodissolution experiments: (a) Phase difference $\Delta\phi(t)$ for sine (dashed), PRC (thin), and optimal (thick) forcing at $A = 12.5$ mV. (b) Semilog plot of $\Delta\phi(t)$ from (a). For $t > 20$ sec after forcing is applied, $\Delta\phi(t)$ decays exponentially to zero. Rates of entrainment (slope of the linear fits): $k(\sin) = 0.1093\,\mathrm{s}^{-1}$, $k(Z) = 0.167\ \mathrm{s}^{-1}$, $k(\text{optimal}) = 0.243\ \mathrm{s}^{-1}$. (c) Rate of entrainment as a function of forcing amplitude for sin (○), PRC (△), and optimal (□) forcing. The slopes κ in $\mathrm{s}^{-1}\,\mathrm{mV}^{-1}$ of the fitted lines characterize the performance of the waveforms for fast entrainment. (d) Normalized entrainment rates predicted from PRC estimates [left: $\kappa(\sin) = 0.68$, $\kappa(\text{PRC}) = 0.89$, $\kappa(\text{optimal}) = 2.00$] and measured experimentally [right: $\kappa(\sin) = 1.19$, $\kappa(\text{PRC}) = 1.39$, $\kappa(\text{optimal}) = 2.38$] are highest for the optimal waveform.

the optimal waveform. This rate was found to be lower for other waveforms such as sine and the PRC Z itself, as shown in Figs. 4(a) and 4(b). To compensate for measurement errors and data processing inaccuracies, we measured the rate k at 7 amplitudes A between 2.5 and 15 mV. The slopes κ of the k vs A plots in Fig. 4(c) correspond to $-\Lambda_v'(\varphi_*)$ for normalized PRC and v, and are compared, along with values predicted using the estimated PRC for each experiment, in Fig. 4(d). The optimal waveform performs significantly better.

The proposed technique for constructing optimal fast entrainment waveforms can be applied to any nonlinear oscillator, and requires no knowledge about its initial state. Entrainment is achieved over the minimum number of cycles possible for a given control energy such that phase model approximation and averaging remain valid. The conditions required for such approximations to be appropriate for entrainment have been explored in previous work [11,21]. When the initial slow phase of the system is far from a stable fixed point, several cycles may be required for convergence to the phase-locked state to be realized, and this occurs least on average for the optimal waveform. In contrast to previous studies on the control of oscillators using phase models [7–10,20,21], the derivative of the phase response curve (PRC) plays an important role in addition to the PRC itself. The methodology is promising for fast reestablishment of entrainment in oscillators that intermittently break phase locking due to environmental or internal effects, such as biological systems with fluctuations in chemical reaction rates due to the small number of molecules in a cell [29]. Finally, observe that our methodology is suitable for weak phase resetting, while strong resetting requires control approaches that do not depend on averaging but involve substantial changes to the state of the oscillator.

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