Multipulse phase resetting curves

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In this paper, we introduce and study systematically, in terms of phase response curves, the effect of dual-pulse excitation on the dynamics of an autonomous oscillator. Specifically, we test the deviations from linear summation of phase advances resulting from two small perturbations. We analytically derive a correction term, which generally appears for oscillators whose intrinsic dimensionality is >1. The nonlinear correction term is found to be proportional to the square of the perturbation. We demonstrate this effect in the Stuart-Landau model and in various higher dimensional neuronal models. This deviation from the superposition principle needs to be taken into account in studies of networks of pulse-coupled oscillators. Further, this deviation could be used in the verification of oscillator models via a dual-pulse excitation.

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I. INTRODUCTION

The weakly connected oscillator theory is often used to show conditions under which oscillators are synchronized [1]. In this theory, small perturbations to an oscillator do not influence the amplitude but have a significant effect on its phase. This allows for a drastic reduction in the description of the oscillator: instead of operating with the original, possibly high-dimensional set of equations, only one phase variable is used for each oscillator. In the case of weakly coupled oscillators, phase description is sufficient to find the conditions under which oscillators get synchronized, provided the phase reduction is accurate enough. One of the assumptions used in this approach is the principle of superposition, which states that the effect of several small perturbations on the period of the oscillation can be considered independently and then summed.

In this paper, we examine the phase dynamics beyond the superposition principle. More precisely, we consider the effect of two relatively small perturbations on the phase for various types of oscillators. Our main tool in the description of the phase dynamics is the phase response curve (PRC; $\delta\varphi$), which is widely used in both theoretical and experimental studies, especially in the field of neuroscience [1–5]. The PRC measures the shift of the phase of the oscillator due to an external pulse as a function of the phase at which the pulse is applied. In other terms, the PRC measures the local change in the period of the oscillator due to a pulse perturbation at various time points within the period. The oscillation can either advance or delay based on the sign of the PRC. To determine the PRC, one often performs an experiment just according to the definition of the PRC; this can be accomplished for individual biological neurons [6] and for complex oscillating systems like those responsible for circadian rhythms in the brain [7,8] (see Refs. [9–11] for other biophysical examples). Furthermore, the PRC concept can be applied not only to individual oscillators, but also to collective modes [12,13].

The shape of the PRC curve is shown to be critical for the synchronization properties of the oscillator networks [14]. However, in the synchronization problem, an oscillator is subject not just to one external pulse, but to a series of pulses from the external force or another oscillator (or several other oscillators if more than two oscillators are coupled). Thus, in order to apply the PRC concept in such situations, one has to know how the oscillator responds to a series of pulses. If the superposition principle holds, then the sum of two small perturbations will independently influence the period of the oscillator according to the PRCs for single inputs and, thus, can be linearly added to predict the overall phase shift. However, if the perturbations are not small, one generally expects deviation from this simple superposition. In this paper we systematically consider the effect of two pulses on the oscillator's phase and characterize the deviations from the pure superposition as nonlinear effects. We illustrate these effects also for several realistic models of neuron dynamics.

II. PHASE DYNAMICS AND DEFINITION OF MULTIPULSE PRC

A. Pure phase dynamics

We start with the simplest case, where the oscillator is described by just one variable, the phase φ (to be assumed 2π periodic), which grows uniformly in time:

$$\dot{\varphi} = \omega. \tag{1}$$

Suppose that the action of a forcing pulse with strength ε is described by the standard PRC $\varepsilon S(\varphi,\varepsilon)$ [here the dependence of S on ε accounts for nonlinear terms, so that $S(\varphi,0)$ is the linear PRC]. Consider now the action of two pulses, at times t_0 and $t_0+\tau$, having strengths ε_0 and ε_1, respectively. Just after the first pulse

$$\varphi_+(t_0) = \varphi(t_0) + \varepsilon_0 S(\varphi(t_0),\varepsilon_0).$$

Just prior to the second pulse the phase is

$$\varphi(t_0+\tau) = \varphi_+(t_0) + \omega\tau = \varphi(t_0) + \omega\tau + \varepsilon_0 S(\varphi(t_0),\varepsilon_0),$$

and after the second pulse

$$\varphi_+(t_0+\tau) = \varphi(t_0) + \omega\tau + \varepsilon_0 S(\varphi(t_0),\varepsilon_0) + \varepsilon_1 S(\varphi(t_0)+\omega\tau+\varepsilon_0 S(\varphi(t_0),\varepsilon_0),\varepsilon_1).$$

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Thus, the overall effect of two pulses,

$$\Delta\varphi = \varepsilon_0 S(\varphi(t_0),\varepsilon_0) + \varepsilon_1 S(\varphi(t_0)+\omega\tau+\varepsilon_0 S(\varphi(t_0),\varepsilon_0),\varepsilon_1), \quad (2)$$

can be simply calculated via the superposition of two single-pulse PRC functions, $\varepsilon S(\varphi,\varepsilon)$. In the linear approximation, where $\varepsilon S(\varphi,\varepsilon) \approx \varepsilon S(\varphi,0)$, one obtains just the sum:

$$\Delta\varphi \approx \varepsilon_0 S(\varphi(t_0),0) + \varepsilon_1 S(\varphi(t_0)+\omega\tau,0).$$

B. General consideration

Now we consider a general situation where periodic oscillations are described by a limit cycle $\mathbf{x}_0(t)$ in an N-dimensional phase space. The crucial notion simplifying the consideration is that of isochrons [15], which are submanifolds of codimension 1 foliating the phase space and having the same phase as the corresponding points in the limit cycle. This allows one to represent the phase space as $(\mathbf{a},\varphi)$, where $\mathbf{a}$ is an $(N-1)$-dimensional "amplitude," and the phase obeys the same equation, (1). Without loss of generality, to simplify notations, we can assume that in the limit cycle the amplitude vanishes, $\mathbf{a}=0$.

In terms of the phase and the amplitude, a pulse that kicks the system resets state $(\mathbf{a},\varphi)$ as

$$\varphi \to \varphi + \varepsilon\Phi(\mathbf{a},\varphi,\varepsilon), \quad \mathbf{a} \to \mathbf{a} + \varepsilon\mathbf{A}(\mathbf{a},\varphi,\varepsilon),$$

where, again, $\Phi(\mathbf{a},\varphi,0)$ and $\mathbf{A}(\mathbf{a},\varphi,0)$ correspond to a linear approximation. The usual PRC is defined for the initial state on the limit cycle ($\mathbf{a}=0$), so $S(\varphi,\varepsilon)=\Phi(0,\varphi,\varepsilon)$. We now apply as above, two pulses, at times t_0 and $t_0+\tau$, assuming that the system is initially in the limit cycle. Then after the first pulse

$$\varphi_+(t_0) = \varphi(t_0) + \varepsilon_0 S(\varphi(t_0),\varepsilon_0), \quad \mathbf{a}_+(t_0) = \varepsilon_0\mathbf{A}(0,\varphi(t_0),\varepsilon_0).$$

Just prior to the second pulse

$$\varphi(t_0+\tau) = \varphi_+(t_0) + \omega\tau = \varphi(t_0) + \omega\tau + \varepsilon_0 S(\varphi(t_0),\varepsilon_0),$$
$$\mathbf{a}(t_0+\tau) = \mathcal{L}^\tau(t_0)\mathbf{a}_+(t_0) = \mathcal{L}^\tau(t_0)\varepsilon_0\mathbf{A}(0,\varphi(t_0),\varepsilon_0),$$

where $\mathcal{L}^\tau$ is the operator describing the evolution of the amplitudes. After the second pulse the new phase is

$$\varphi_+(t_0+\tau) = \varphi(t_0+\tau) + \varepsilon_1\Phi(\mathbf{a}(t_0+\tau),\varphi(t_0+\tau),\varepsilon_1)$$

and the overall phase shift due to two pulses (two-pulse PRC) is

$$\delta\varphi = \varepsilon_0 S(\varphi(t_0),\varepsilon_0) + \varepsilon_1\Phi(\mathbf{a}(t_0+\tau),\varphi(t_0+\tau),\varepsilon_1). \quad (3)$$

Comparing this with expression (2) we see that now the effect is not a superposition of two PRCs but contains the amplitude-dependent phase reset function Φ. The difference between expression (2) and expression (3) gives the nontrivial effect of multiple pulses on the phase of the oscillator as the nonlinear correction term Δ:

$$\begin{aligned}\Delta &= \delta\varphi - \Delta\varphi = \varepsilon_1\Phi(\mathcal{L}^\tau(t_0)\varepsilon_0\mathbf{A}(0,\varphi(t_0),\varepsilon_0),\varphi(t_0) \\ &\quad + \omega\tau + \varepsilon_0 S(\varphi(t_0),\varepsilon_0),\varepsilon_1) \\ &\quad - \varepsilon_1 S(\varphi(t_0)+\omega\tau+\varepsilon_0 S(\varphi(t_0),\varepsilon_0),\varepsilon_1) \\ &= \varepsilon_1\Phi(\mathcal{L}^\tau(t_0)\varepsilon_0\mathbf{A}(0,\varphi(t_0),\varepsilon_0),\varphi(t_0)+\omega\tau \\ &\quad + \varepsilon_0 S(\varphi(t_0),\varepsilon_0),\varepsilon_1) - \varepsilon_1\Phi(0,\varphi(t_0)+\omega\tau \\ &\quad + \varepsilon_0 S(\varphi(t_0),\varepsilon_0),\varepsilon_1). \end{aligned} \quad (4)$$

From this expression one can see that the result essentially depends on the action of the amplitude evolution operator $\mathcal{L}^\tau$: if $\mathcal{L}^\tau(t_0)\mathbf{A} \approx 0$, correction (4) vanishes. Thus, the nontrivial effect of the two-pulse excitation of an oscillator depends crucially on the relation between the interpulse time interval τ and the relaxation time of the amplitude t_a (characteristic time scale of the amplitude evolution operator $\mathcal{L}$); it is most pronounced if $\tau \lesssim t_a$. If the amplitude is multidimensional, t_a is the time of the slowest decay.

In the leading order in the powers of $\varepsilon_0,\varepsilon_1$, we can represent the nonlinear correction as

$$\Delta \approx \varepsilon_1\varepsilon_0\mathcal{L}_l^\tau(t_0)\mathbf{A}(0,\varphi(t_0),0)\frac{\partial}{\partial\mathbf{a}}\Phi(\mathbf{a},\varphi(t_0)+\omega\tau + \varepsilon_0 S(\varphi(t_0),0),0)|_{\mathbf{a}=0}, \quad (5)$$

where $\mathcal{L}_l$ is the linearized evolution operator for the amplitudes, which describes their relaxation to $0 \sim \exp[-t/t_a]$.

This can be generalized to n pulses with amplitudes $(\varepsilon_0,\ldots,\varepsilon_{n-1},\varepsilon_n)$ and different time shifts between them $(\tau_0,\ldots,\tau_{n-1})$. Then the leading terms will be quadratic ones $(\sim\varepsilon_0\varepsilon_1,\varepsilon_0\varepsilon_2,\varepsilon_1\varepsilon_2,\ldots)$, while also higher order corrections (e.g., $\sim\varepsilon_0\varepsilon_1\varepsilon_2$) will appear. Most important are the nonlinear terms including neighboring pulses, because, as argued above, the effect decreases with the time interval between the pulses. Another straightforward generalization is the case where two pulses are different and are described by functions Φ_0, $\mathbf{A}_0$, Φ_1, $\mathbf{A}_1$.

C. Example: A Stuart-Landau oscillator

The Stuart-Landau oscillator is a two-dimensional model described in polar coordinates as

$$\dot{R} = \mu R(1-R^2), \quad \dot{\theta} = 1+\alpha-\alpha R^2.$$

Here the frequency of the limit cycle, which is a circle with radius $R=1$, is normalized to 1, parameter α describes nonisochronicity of oscillations, and μ is the relaxation rate of the amplitude. The phase φ defined in the whole plane (except for the origin) is

$$\varphi = \theta - \frac{\alpha}{\mu}\ln R.$$

Evolution of the variables R and θ can be explicitly solved as

$$\begin{pmatrix} R(t) \\ \theta(t) \end{pmatrix} = U^{t-t_0}\begin{pmatrix} R(t_0) \\ \theta(t_0) \end{pmatrix} = \begin{pmatrix} \left[1+\frac{1-R(t_0)^2}{R(t_0)^2}e^{-2\mu(t-t_0)}\right]^{-1/2} \\ \theta(t_0)+t-t_0-\frac{\alpha}{2\mu}\ln(R(t_0)^2+(1-R(t_0)^2)e^{-2\mu(t-t_0)}) \end{pmatrix},$$

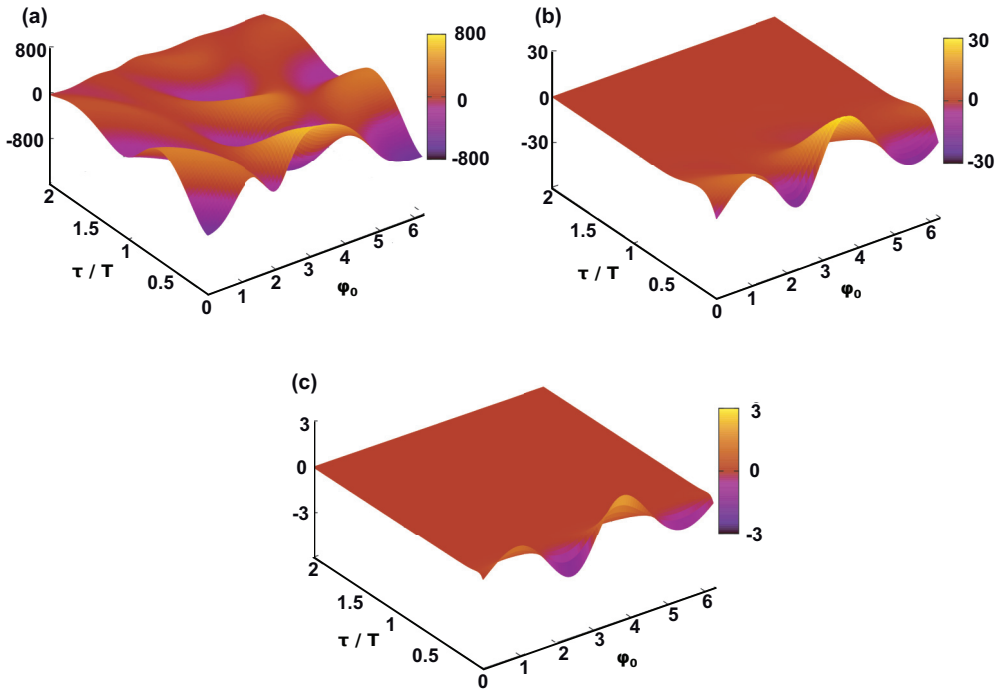

FIG. 1. (Color online) The normalized nonlinear effect of two-pulse action on the Stuart-Landau oscillator $\Delta \cdot \varepsilon^{-2}$ vs the phase φ_0 and the time shift between pulses τ (normalized by the cycle period), for $\varepsilon = 0.1$, $\alpha = 3$, and three values of μ [$\mu = 0.1$ (a), $\mu = 0.5$ (b), and $\mu = 2$ (c)]. For large μ the effect is pronounced for very small time intervals between two pulses only.

which defines the operator $\mathcal{L}$. We assume that the pulse is acting in direction x, i.e., at the pulse

$$R\cos\theta \to R\cos\theta + \epsilon, \quad R\sin\theta \to R\sin\theta.$$

This fully describes the system, and one can find expressions for the PRCs $\Delta\varphi$ and $\delta\varphi$ (see Appendix A). Using these formulas, we calculated the nonlinear correction term Δ and a plot of this is depicted in Fig. 1. Here we take $\varepsilon_0 = \varepsilon_1 = 0.1$ and present results for different values of μ. As expected, the most pronounced effect is for small μ.

For this equation it is possible to obtain the leading term in order $\sim\varepsilon_0\varepsilon_1$ in the expansion of the nonlinear correction term

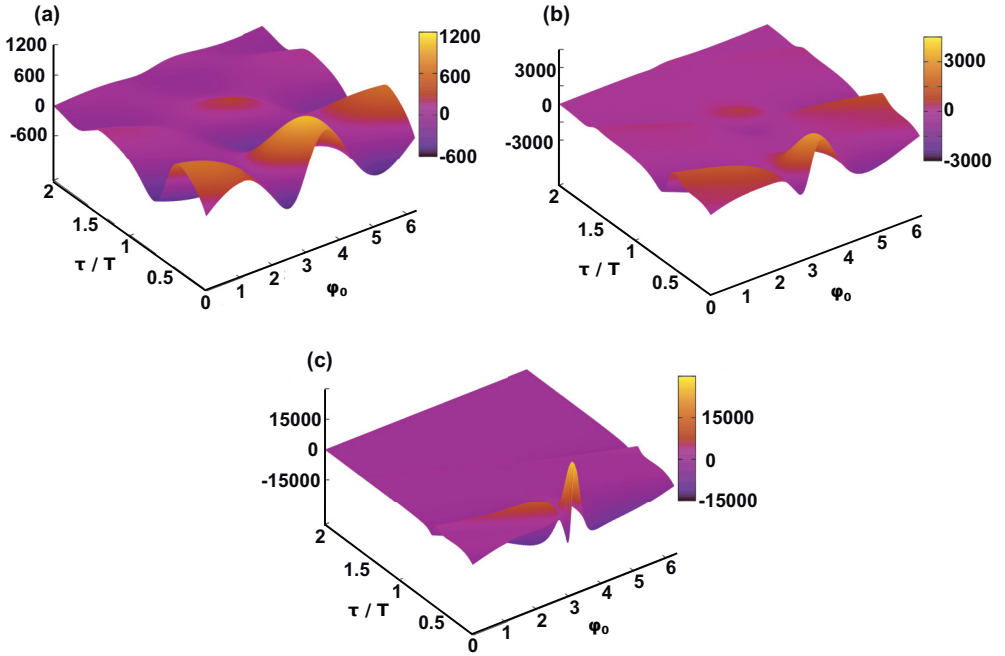

FIG. 2. (Color online) Same as Fig. 1, but for the modified Stuart-Landau oscillator, Eq. (7). Parameter values: (a) $\alpha = 3$, $\mu = 0.1$, $\varepsilon = 0.01$, $b = 0.3$; (b) $\alpha = 3$, $\mu = 0.1$, $\varepsilon = 0.01$, $b = 0.7$; (c) $\alpha = 3$, $\mu = 0.1$, $\varepsilon = 0.001$, $b = 0.95$.

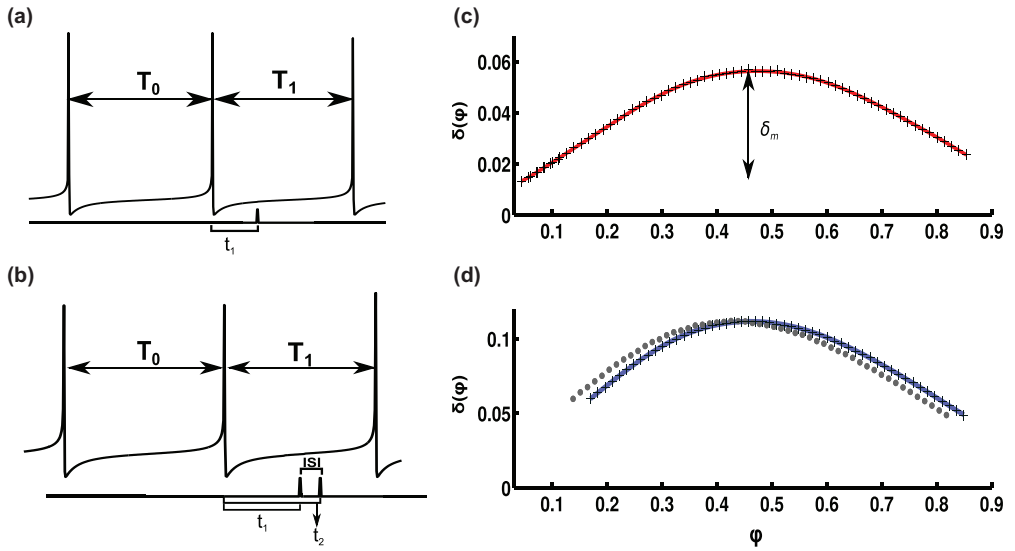

FIG. 3. (Color online) Illustration of how the PRC is computed for a quadratic integrate-fire neuron. (a) Single pulse; (b) double pulse. T_0 is the original period when no input occurred; T_1 is the period when there was an input at time t_1 with input phase $\varphi_1 = t_1/T_0$. (c) PRC $\delta\varphi = (T_0 - T_1)/T_0$ for single input (black crosses) along with its fit [solid (red) line; $\bar{\delta}_1(\varphi_1)$]. In (c) and (d) the x axis depicts the input phase φ. (d) PRC for two inputs with ISI = 10 ms. Filled (gray) circles indicate the change in period vs the first input; PRC with respect to the second input is plotted as black crosses. The prediction from the superposition principle is plotted as the solid (blue) line $[\bar{\delta}_1(\varphi_1) + \bar{\delta}_1(\varphi_2)]$.

in pulse strengths analytically (see Appendix A):

$$\Delta \approx \varepsilon_0\varepsilon_1\left(1 + \frac{\alpha^2}{\mu^2}\right)e^{-2\mu\tau}\cos\varphi_0\sin(\varphi_0 + \tau). \quad (6)$$

This expression fits numerics very closely for $\varepsilon \lesssim 0.01$.

D. Example: A modified Stuart-Landau oscillator

Our second example is a modification of the Stuart-Landau oscillator proposed in [16]:

$$\dot{R} = \mu R(1 - R^2), \quad \dot{\theta} = 1 - br\cos\theta + \alpha - \alpha R^2. \quad (7)$$

Here large values of parameter b produce highly nonuniform growth of angle variable θ, so that the relation between φ and θ is strongly nonlinear. As a result, the isochrons crowd in the region around $\theta \approx 0$, where the evolution of θ is slow. Also, the nonlinear correction term becomes very large in this region, as illustrated in Fig. 2.

III. NEURON MODELS

The PRC is commonly used to describe neuron models. In this context, the PRC can characterize the properties of neurons, especially their synchronizability. In many systems a neuron receives inputs from many other neurons, therefore,

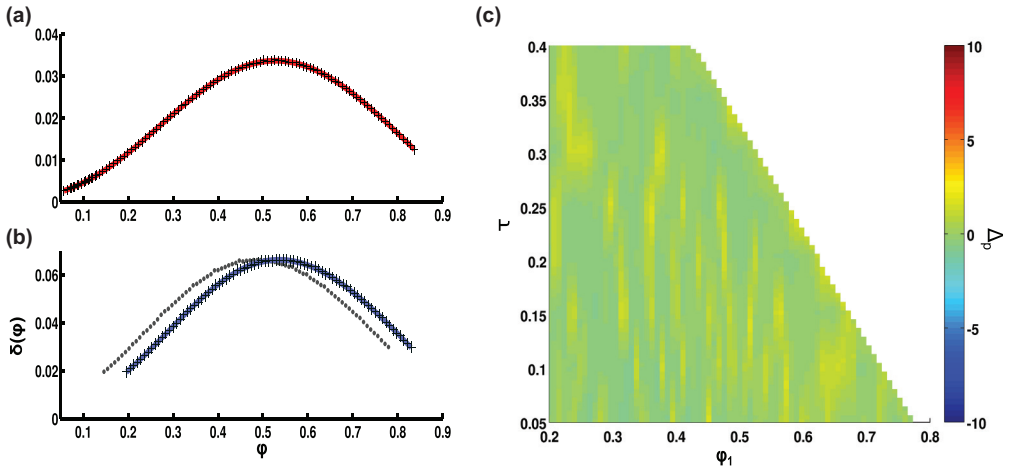

FIG. 4. (Color online) Wang-Buzsáki model. (a) PRC for single input along with its fit [solid (red) line], $\delta(\varphi) = (T_0 - T_1)/T_0$. (b) PRC for two inputs with ISI = 10 ms. Filled (gray) circles indicate the PRC with respect to the first input, and the PRC with respect to the second input is plotted as black cross. The prediction from the superposition principle is plotted as the solid (blue) line. (c) Deviation from linear superposition (Δ_p) for different τ's or ISIs and φ_1, which is the input phase of the first input.

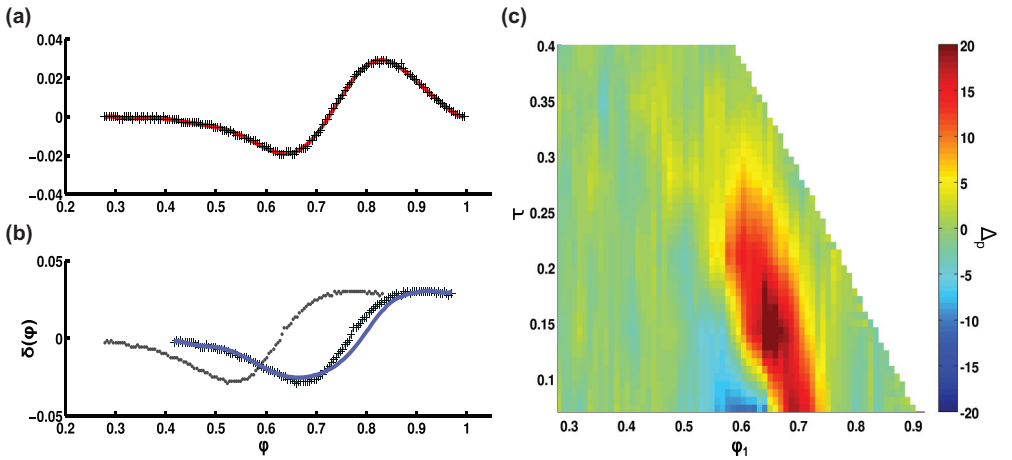

FIG. 5. (Color online) Original Hodgkin-Huxley model. Caption same as for Fig. 4.

it is critical to understand how multiple pulses affect the PRC response of neurons. Below we test four neuron models for the dual-pulse effect. Although generally the theory presented in Sec. II B is applicable to spiking neurons as well, practically one does not follow the continuous phase of the oscillations but focuses on the spiking events (these events are readily available in experiments too). Therefore, for spiking neurons, the PRC and the nonlinear correction term have to be measured in terms of the spike times as opposed to phase shifts at arbitrary points as done in the previous section. It is convenient to normalize the correction term by the peak-to-trough value of the PRC for single input as shown below. We first illustrate these definitions in Fig. 3, using the quadratic integrate-and-fire model [17]. [Note that traditionally in this context the phase t/T_0 and the PRC $\delta\varphi = (T_1 - T_0)/T_0$ are normalized by 1, and not by 2π.] This one-dimensional model corresponds to the pure phase dynamics in Sec. II A, so it does not demonstrate nonlinear effects of deviations from the superposition.

In general, the models of neurons are classified based on their PRC curves as types I and II. The type I PRC has only phase advance in response to perturbation, while type II PRC includes both phase delay and advance [4]. We further consider both type I and type II neuron models in this study. We tested the Wang-Buzsáki model (type I; based on [18]), the original Hodgkin-Huxley model (type II; based on [19]), and a modified Hodgkin-Huxley model (type I; based on [20]). The equations for all the models are given in Appendix B. All of these models are three-dimensional, which is required for any deviation from linear superposition.

To characterize the deviation from the superposition of two input pulses, we use the quantity

$$\Delta_p = (\delta_2(\varphi_2) - \bar{\delta}_1(\varphi_1) - \bar{\delta}_1(\varphi_2))\frac{100}{\delta_m}, \tag{8}$$

where $\delta_2(\varphi_2)$ is the measured PRC for the second pulse, $\bar{\delta}_1(\varphi_1)$ and $\bar{\delta}_1(\varphi_2)$ are the expected PRCs of single pulses, and δ_m is the amplitude of the single-pulse PRC (this normalization provides a better visualization of the deviation from the superposition of single-pulse PRCs). We present the results for the three neuron models in Figs. 4–6, where the main dependence of Δ_p on the first input phase and on the interspike interval (ISI) between two applied pulses τ is depicted in Fig. 4(c) by color coding.

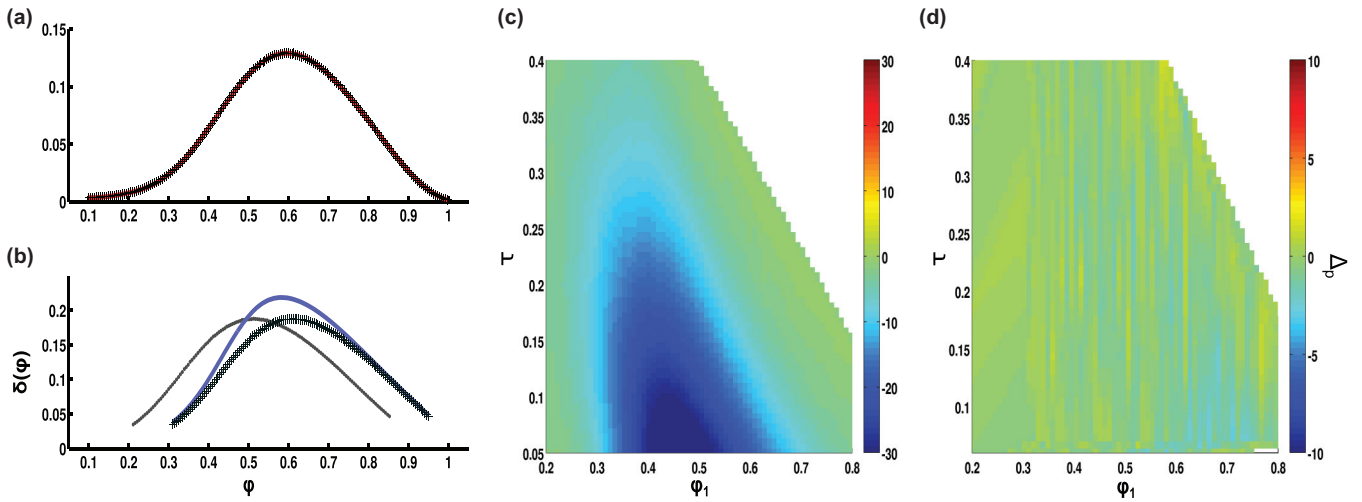

FIG. 6. (Color online) Modified Hodgkin-Huxley model. (a–c) Caption same as for Fig. 4. (c, d) $\rho = 1.0$. Error for modified Hodgin-Huxley model with slower evolution, $\rho = 0.5$ (see Appendix B for definition of ρ).

We observed that some neuron models show pronounced nonlinear effects, as the two-pulse response deviates from the expected PRC based on the superposition principle, while for other models the linear superposition was able to predict the PRC for two pulses accurately. The Wang-Buzsáki model (Fig. 4) appears to be of the latter type, while both the original Hodgkin-Huxley system (Fig. 5) and its modified version (Fig. 6) show nonlinear effects in the two-pulse PRC. The Wang-Buzsáki and modified Hodgkin-Huxley model had type I PRCs, and the original Hodgkin-Huxley model had a type II PRC, suggesting that there is no relationship between the type of PRC and the origin of this deviation. Further, the bifurcation type for spiking from the resting state also did not determine the existence of error, since the Wang-Buzsáki model and the modified Hodgkin-Huxley model possess a saddle-node bifurcation, while the original Hodgkin-Huxley model demonstrates an Andronov-Hopf bifurcation.

There were two main findings from the analytical results in Sec. II that can be qualitatively compared with the neuronal models presented in this section. The first result was that the nonlinear correction term was proportional to the square of the perturbation, (6). We tested this in the modified Hodgkin-Huxley model and observed similar qualitative results (Fig. 7). Second, the square of the decay time constant of the amplitude term in the oscillator due to perturbation was inversely proportional to the nonlinear correction term, (4). Thus, a faster relaxation dynamics of the neuron leads to a lower error. We observed this in the modified neuron model when the parameter ρ was reduced to 0.5; the time constant of the h variable increased, promoting membrane hyperpolarization. The membrane hyperpolarization then reduced the membrane time constant through closing voltage-gated channels, i.e., faster relaxation dynamics, which led to a shorter ISI and a smaller error. Thus, the main features of general limit cycle oscillators, and in particular of the Stuart-Landau oscillator, can be qualitatively extended to some of the neuron models.

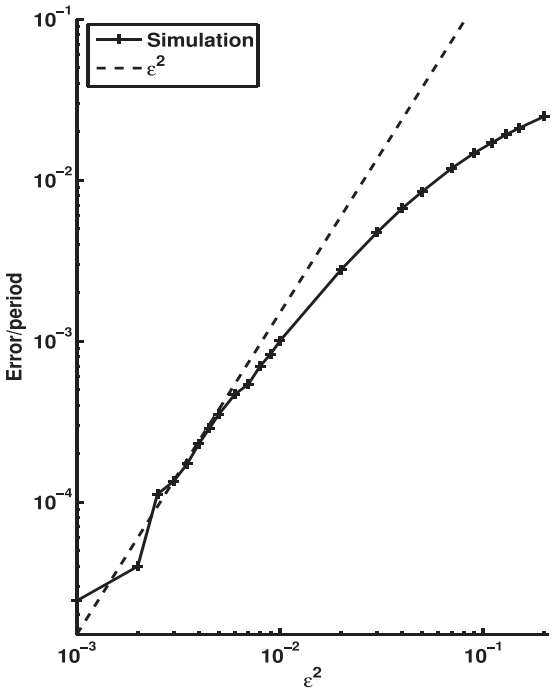

FIG. 7. Relationship between ϵ^2 and Δ/period. The division by period was used for comparison with the Landau-Stewart oscillator simulations and does not change the relationship between ϵ^2 and Δ, since the period was the same for all ϵ^2.

IV. CONCLUSION

In this paper we have developed a theory of the response of an autonomous oscillator to two-pulse perturbation. We found that the action of two pulses generally deviates from the superposition of two one-pulse responses, and this nonlinear effect, which is proportional to the product of the perturbations' amplitudes, significantly depends on the relation of the interval between the pulses and the relaxation time of the oscillator. In the case of fast relaxation or a large time interval between the pulses, the nonlinear effect vanishes. We have demonstrated this property for several models: the standard Stuart-Landau oscillator, the modified version for this oscillator with a highly nonuniform motion over the cycle, and three neuron models, including the classical Hodgkin-Huxley system.

We stress here that in our study, the term "nonlinearity" of the PRC has been used in two contexts. For a one-pulse PRC, nonlinearity means that the phase response cannot be represented as an amplitude of the pulse multiplied by a function of the phase; in particular, the form of the curve may depend on the pulse amplitude. For two pulses, we use the term nonlinearity to describe a deviation from the superposition principle; this effect in the leading order is proportional to the product of the pulses' amplitudes. We have shown that nonlinearity of the single-pulse PRC does not necessarily lead to nonlinearity for a two-pulse excitation: the purely phase model in Sec. II A is a good illustration of this. Both nonlinear effects may distort a simple picture of the neuron's dynamics under external forcing. In particular, in [17] it was suggested that a relatively weak noisy current to the neuron can be applied to obtain the PRC, by solving the equation that relates the infinitesimal (linear) PRC to the external voltage through optimization methods. However, this method does not account for the nonlinear correction which we showed in this study. In some neurons, we showed that the nonlinear effect can have a significant effect on the multipulse PRC compared to the single-pulse PRC, and thus the continuous perturbation method may produce erroneous results. Thus, further studies are required to validate the method proposed in [17].

We see two main application fields for our approach. First, it can be used for diagnostics of oscillators. While the usual PRC allows characterization of the sensitivity of the phase to an external action, the nonlinear terms in the two-pulse response allow characterization of relaxation processes. In particular, one-pulse PRCs of the Wang-Buzsáki model and of the modified Hodgkin-Huxley model are very similar [cf. Figs. 4(a) and 6(a)], but their two-pulse PRCs are completely different; this may be useful for designing models to fit experimental data. Two-pulse PRCs can be estimated from experimental data and this information can be used to design optimally a model that provides the best description of the data. The second field of application is the incorporation of these effects into the synchronization theory of pulse

coupled oscillators. Indeed, in a network an oscillator usually experiences inputs from many other units, and in the absence of synchrony the time intervals between the incoming pulses can be rather small. In this case the nonlinear "interference" of the actions is mostly pronounced and may contribute significantly to the synchronization properties. In particular, we expect that incorporating the effects of two-pulse PRCs into the methods used in predicting synchronizability (which are currently based solely on PRCs developed in Ref. [14]) would increase the accuracy of such approaches.

ACKNOWLEDGMENTS

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APPENDIX A: PRC FOR THE STUART-LANDAU OSCILLATOR

We briefly outline the majors steps in obtaining the approximate nonlinear correction term for the Stuart-Landau oscillator using an expansion in ε. Several intermediate steps are not shown to make the presentation brief. Section II C provides the phase equation and the evolution operator for the Stuart-Landau oscillator.

At $t = 0$, let $R = 1, \theta = \theta_0$. After the ε_0 pulse at $t = 0$, $\tilde{R} = \sqrt{(\cos\theta_0 + \epsilon_0)^2 + \sin^2\theta_0)}$ and $\tilde{\theta}_0 = \arctan(\sin\theta_0/(\cos\theta_0 + \epsilon_0))$, which, upon expansion, gives $\tilde{R} = 1 + \epsilon_0\cos\theta_0 + \epsilon_0^2(\frac{\sin^2\theta_0}{2}) + O(\varepsilon^3)$ and $\tilde{\theta}_0 = \theta_0 - \epsilon_0\sin\theta_0 + \epsilon_0^2\sin\theta_0\cos\theta_0 + O(\varepsilon^3)$. From here we ignore all $O(\varepsilon^3)$, cubic, and higher order terms.

The phase shift due to the ε_0 pulse is

$$\Delta\varphi_0 = \tilde{\theta}_0 - \theta_0 - \frac{\alpha}{\mu}\ln\tilde{R} = \arctan(\sin\theta_0/(\cos\theta_0 + \epsilon_0)) - \theta_0 - \frac{\alpha}{\mu}\ln\sqrt{(\cos\theta_0 + \epsilon_0)^2 + \sin^2\theta_0)},$$

$$\begin{aligned}\Delta\varphi_0 &= \arctan\frac{-\epsilon_0\sin\theta_0}{1 + \epsilon_0\cos\theta_0} - \frac{\alpha}{\mu}\ln\sqrt{(\cos\theta_0 + \epsilon_0)^2 + \sin^2\theta_0)} \\ &\approx -\epsilon_0\left(\sin\theta_0 + \frac{\alpha}{\mu}\cos\theta_0\right) + \frac{1}{2}\epsilon_0^2\left(\sin 2\theta_0 + \frac{\alpha}{\mu}\cos 2\theta_0\right).\end{aligned}$$

At time τ

$$\begin{pmatrix} R(\tau) \\ \theta(\tau) \end{pmatrix} = U^\tau \begin{pmatrix} \tilde{R} \\ \tilde{\theta}_0 \end{pmatrix},$$

$$\begin{aligned}\theta(\tau) &= \tilde{\theta}_0 + \tau - \frac{\alpha}{2\mu}\ln(\tilde{R}^2 + (1 - \tilde{R}^2)\exp(-2\mu\tau)) \\ &\approx \tau + \theta_0 - \epsilon_0\sin\theta_0 + \epsilon_0^2\sin\theta_0\cos\theta_0 - \frac{\alpha}{2\mu}\ln\left(\left(1 + 2\epsilon_0\cos\theta_0 + \epsilon_0^2\right) + \left(-2\epsilon_0\cos\theta_0 - \epsilon_0^2\right)e^{-2\mu\tau}\right) \\ &\approx \tau + \theta_0 - \epsilon_0\left[\sin\theta_0 + \frac{\alpha}{\mu}\cos(1 - e^{-2\mu\tau})\right] + \epsilon_0^2\left[\sin\theta_0\cos\theta_0 - \frac{\alpha}{2\mu}(1 - e^{-2\mu\tau} - 2\cos^2\theta_0(1 - e^{-2\mu\tau})^2)\right] \\ &\equiv \tau + \theta_0 - \epsilon_0 E + \epsilon_0^2 F,\end{aligned}$$

$$R(\tau) = \left[\frac{\tilde{R}^2}{\tilde{R}^2 + (1 - \tilde{R}^2)e^{-2\mu\tau}}\right]^{1/2} \approx \left[\frac{1 + 2\epsilon_0\cos\theta_0 + \epsilon_0^2}{1 + 2\epsilon_0\cos\theta_0 + \epsilon_0^2 + \left(-2\epsilon_0\cos\theta_0 - \epsilon_0^2\right)e^{-2\mu\tau}}\right]^{1/2},$$

$$\begin{aligned}R(\tau)^2 &\approx \frac{1 + 2\epsilon_0\cos\theta_0 + \epsilon_0^2}{1 + 2\epsilon_0\cos\theta_0(1 - e^{-2\mu\tau}) + \epsilon_0^2(1 - e^{-2\mu\tau})} \\ &\approx 1 + 2\epsilon_0\cos\theta_0 e^{-2\mu\tau} - 4\epsilon_0^2\cos^2\theta_0(1 - e^{-2\mu\tau}) + \epsilon_0^2 e^{-2\mu\tau} + 4\epsilon_0^2\cos^2\theta_0(1 - e^{-2\mu\tau})^2 \\ &\approx 1 + 2\epsilon_0\cos\theta_0 e^{-2\mu\tau} + \epsilon_0^2[-4\cos^2\theta_0(1 - e^{-2\mu\tau})e^{-2\mu\tau} + e^{-2\mu\tau}] \\ &\equiv 1 + \epsilon_0 C + \epsilon_0^2 D.\end{aligned}$$

After the second pulse (ε_1) at time τ, $\hat{R}(\tau) = \sqrt{(R(\tau)\cos\theta(\tau) + \epsilon_1)^2 + (R(\tau)\sin\theta(\tau))^2}$ and $\hat{\theta}(\tau) = \arctan(R(\tau)\sin\theta(\tau)/(R(\tau)\cos\theta(\tau) + \epsilon_1))$. So the final phase shift is $\Delta\varphi_{0,1} = \hat{\theta}(\tau) - \theta_0 - \tau - \frac{\alpha}{2\mu}\ln\hat{R}^2(\tau)$, which needs to be compared to prediction from linear superposition, which is given as $\Delta\varphi_0 + \Delta\varphi_1$. We first expand $\cos\theta(\tau)$, $\hat{R}(\tau)$, and $\hat{\theta}(\tau)$, since they are used in the comparison as

$$\cos\theta(\tau) = \cos\left(\tau + \theta_0 - \epsilon_0 E + \epsilon_0^2 F\right) \approx \cos(\tau + \theta_0) - \epsilon_0 E\sin(\tau + \theta_0) + \epsilon_0^2\left(-\frac{1}{2}E^2\cos(\tau + \theta_0) - F\sin(\tau + \theta_0)\right),$$

$$\hat{R}^2(\tau) = R^2(\tau) + 2R(\tau)\epsilon_1\cos\theta(\tau) + \epsilon_1^2 \approx 1 + \varepsilon_0 C + \varepsilon_0^2 D + 2\varepsilon_1\left(1 + \frac{1}{2}\varepsilon_0 C\right)(\cos(\theta_0 + \tau) + \varepsilon_0 E\sin(\tau + \theta_0)) + \epsilon_1^2,$$

$$\hat{\theta}(\tau) = \arctan(R(\tau)\sin\theta(\tau)/(R(\tau)\cos\theta(\tau)+\varepsilon_1)) \approx \theta(\tau) - \frac{\varepsilon_1}{R(\tau)}\sin\theta(\tau) + \frac{\varepsilon^2}{R^2(\tau)}\sin\theta(\tau)\cos\theta(\tau)$$
$$\approx \tau + \theta_0 + \epsilon_0 E - \varepsilon_1\sin(\tau+\theta_0) + \epsilon_0^2 F + \varepsilon_0\varepsilon_1\left[-\cos(\theta_0+\tau)E + \frac{1}{2}\sin(\theta_0+\tau)C\right] + \varepsilon_1^2\sin(\theta_0+\tau)\cos(\theta_0+\tau),$$

$$\Delta\varphi_0 + \Delta\varphi_1 = \Delta\varphi_0 + \arctan\left(\frac{\sin(\theta_0+\Delta\varphi_0+\tau)}{(\cos(\theta_0+\Delta\varphi_0+\tau)+\epsilon_1)}\right) - (\theta_0+\Delta\varphi_0+\tau)$$
$$- \frac{\alpha}{2\mu}\ln(\cos(\theta_0+\Delta\varphi_0+\tau)+\epsilon_1)^2 + \sin^2(\theta_0+\Delta\varphi_0+\tau)$$
$$\approx \Delta\varphi_0 + \arctan\frac{-\epsilon_1\sin(\theta_0+\Delta\varphi_0+\tau)}{1+\epsilon_1\cos(\theta_0+\Delta\varphi_0+\tau)} - \frac{\alpha}{\mu}\ln\left(1+2\varepsilon_1\cos(\theta_0+\Delta\varphi_0+\tau)+\varepsilon_1^2\right)$$
$$\approx -\epsilon_0\left(\sin\theta_0 + \frac{\alpha}{\mu}\cos\theta_0\right) + \frac{1}{2}\epsilon_0^2\left(\sin 2\theta_0 + \frac{\alpha}{\mu}\cos 2\theta_0\right) + \varepsilon_1\left[\sin(\theta_0+\Delta\varphi_0+\tau) + \frac{\alpha}{\mu}\cos(\theta_0+\Delta\varphi_0+\tau)\right]$$
$$+ \frac{1}{2}\varepsilon_1^2\left[\sin 2(\theta_0+\Delta\varphi_0+\tau) + \frac{\alpha}{\mu}\cos 2(\theta_0+\Delta\varphi_0+\tau)\right],$$

$$\Delta\varphi_{0,1} = \hat{\theta}(\tau) - \theta_0 - \tau - \frac{\alpha}{2\mu}\ln\hat{R}^2(\tau)$$
$$= \epsilon_0 E - \varepsilon_1\sin(\tau+\theta_0) + \epsilon_0^2 F + \varepsilon_0\varepsilon_1\left[-\cos(\theta_0+\tau)E + \frac{1}{2}\sin(\theta_0+\tau)C\right] + \varepsilon_1^2\sin(\theta_0+\tau)\cos(\theta_0+\tau)$$
$$- \frac{\alpha}{2\mu}\ln\left[1+\varepsilon_0 C + \varepsilon_0^2 D + 2\varepsilon_1\left(1+\frac{1}{2}\varepsilon_0 C\right)(\cos(\theta_0+\tau) + \varepsilon_0 E\sin(\tau+\theta_0)) + \epsilon_1^2\right].$$

Finally, the difference between the prediction from superposition and the actual phase reset (after substitutions) is given as

$$\Delta\varphi_{0,1} - (\Delta\varphi_0 + \Delta\varphi_1)$$
$$= \epsilon_0\left[\sin\theta_0 + \frac{\alpha}{\mu}\cos(1-e^{-2\mu\tau})\right] - \varepsilon_1\sin(\tau+\theta_0) + \epsilon_0^2\left[\sin\theta_0\cos\theta_0 - \frac{\alpha}{2\mu}(1-e^{-2\mu\tau} - 2\cos^2\theta_0(1-e^{-2\mu\tau})^2)\right]$$
$$+ \varepsilon_0\varepsilon_1\left[-\cos(\theta_0+\tau)\left[\sin\theta_0 + \frac{\alpha}{\mu}\cos(1-e^{-2\mu\tau})\right] + \frac{1}{2}\sin(\theta_0+\tau)2\cos\theta_0 e^{-2\mu\tau}\right] + \varepsilon_1^2\sin(\theta_0+\tau)\cos(\theta_0+\tau)$$
$$- \frac{\alpha}{2\mu}\ln\left[1+\varepsilon_0 2\cos\theta_0 e^{-2\mu\tau} + \varepsilon_0^2[-4\cos^2\theta_0(1-e^{-2\mu\tau})e^{-2\mu\tau} + e^{-2\mu\tau}]\right.$$
$$\left. + 2\varepsilon_1\left(1+\frac{1}{2}\varepsilon_0 2\cos\theta_0 e^{-2\mu\tau}\right)(\cos(\theta_0+\tau) + \varepsilon_0\left[\sin\theta_0 + \frac{\alpha}{\mu}\cos(1-e^{-2\mu\tau})\right]\sin(\tau+\theta_0)) + \epsilon_1^2\right]$$
$$- \left[-\epsilon_0\left(\sin\theta_0 + \frac{\alpha}{\mu}\cos\theta_0\right) + \frac{1}{2}\epsilon_0^2\left(\sin 2\theta_0 + \frac{\alpha}{\mu}\cos 2\theta_0\right) + \varepsilon_1\left[\sin(\theta_0+\Delta\varphi_0+\tau)\right.\right.$$
$$\left.\left. + \frac{\alpha}{\mu}\cos(\theta_0+\Delta\varphi_0+\tau)\right] + \frac{1}{2}\varepsilon_1^2\left[\sin 2(\theta_0+\Delta\varphi_0+\tau) + \frac{\alpha}{\mu}\cos 2(\theta_0+\Delta\varphi_0+\tau)\right]\right],$$

which, upon several steps of algebraic reductions and ignoring cubic or higher ε terms, gives

$$\Delta\varphi_{0,1} - (\Delta\varphi_0 + \Delta\varphi_1) \approx \varepsilon_0\varepsilon_1\left(1+\frac{\alpha^2}{\mu^2}\right)e^{-2\mu\tau}\cos\varphi_0\sin(\varphi_0+\tau).$$

APPENDIX B: NEURON MODELS

In these models I_{stim} is the external input.

Wang-Buzáki model [18]:

$$\begin{aligned}
&\dot{v} = -0.1(v+65) - 9n^4(v+90) - 35m_\infty^3 h(v-55) - I_{\text{stim}}; \quad \dot{h} = (h_\infty - h)/h_\tau, \quad \dot{n} = (n_\infty - n)/n_\tau,\\
&m_\infty = \alpha_m/(\alpha_m+\beta_m); \quad \alpha_m = -(v+35)/(10(e^{-(v+35)/10}-1)), \quad \beta_m = 4e^{-(v+60)/18};\\
&h_\infty = \alpha_h/(\alpha_h+\beta_h), \quad h_\tau = 1/(5(\alpha_h+\beta_h)), \quad \alpha_h = 0.07e^{-(v+58)/20}, \quad \beta_h = 1/(e^{-(v+28)/10}+1);\\
&n_\infty = \alpha_n/(\alpha_n+\beta_n), \quad n_\tau = 1/(5(\alpha_n+\beta_n)); \quad \alpha_n = -0.01(v+34)/(e^{-(v+34)/10}-1), \quad \beta_n = 0.125e^{-(v+44)/80}.
\end{aligned} \tag{B1}$$

Hodgkin-Huxley model [19]:

$$\begin{aligned}
\dot{v} &= -0.5(v+65) - 36n^4(v+77) - 120m_\infty^3 h(v-50) - I_{\text{stim}}; \quad \dot{h} = (h_\infty - h)/h_\tau, \quad \dot{n} = (n_\infty - n)/n_\tau, \\
m_\infty &= \alpha_m/(\alpha_m+\beta_m); \quad \alpha_m = -0.1(v+40)/(e^{-(v+40)/10}-1), \quad \beta_m = 4e^{-(v+65)/18}; \\
h_\infty &= \alpha_h/(\alpha_h+\beta_h), \quad h_\tau = 1/(\alpha_h+\beta_h), \quad \alpha_h = 0.07e^{-(v+65)/20}, \quad \beta_h = 1/(e^{-(v+35)/10}+1); \\
n_\infty &= \alpha_n/(\alpha_n+\beta_h), \quad n_\tau = 1/(\alpha_n+\beta_n); \quad \alpha_n = -0.01(v+55)/(e^{-(v+55)/10}-1), \quad \beta_n = 0.125e^{-(v+65)/80}.
\end{aligned} \tag{B2}$$

Modified Hodgkin-Huxley model [20]:

$$\begin{aligned}
\dot{v} &= (-0.0317(v+77.8) - 30.032m_\infty^3 h(v-49.8) - 5.315n(v+100.4) - I_{\text{stim}})/0.75; \\
\dot{h} &= -\rho(h-h_\infty)/h_\tau, \quad \dot{n} = -\delta(n-n_\infty)/n_\tau, \quad m_\infty = \alpha_m/(\alpha_m+\beta_m); \\
\alpha_m &= 0.182(v+25)/(1-e^{-(v+25)/9}), \quad \beta_m = 0.124(-v-25)/(1-e^{-(-v-25)/9}); \\
h_\infty &= \alpha_h/(\alpha_h+\beta_h), \quad h_\tau = 1/(2.953(\alpha_h+\beta_h)); \\
h_\infty &= 1/(1+e^{(v+55)/6.2}); \quad \alpha_h = 0.024(v+40)/(1-e^{-(v+40)/5}), \quad \beta_h = 0.0091(-v-65))/(1-e^{-(-v-65)/5}); \\
n_\infty &= \alpha_n/(\alpha_n+\beta_n), \quad n_\tau = 1/(2.953(\alpha_n+\beta_n)); \quad \alpha_n = 0.02*(v-25)/(1-e^{-(v-25)/9}), \\
\beta_n &= -0.002*(v-25)/(1-e^{(v-25)/9}).
\end{aligned} \tag{B3}$$

Here, ρ is the factor which was reduced to 0.5 in Fig. 6.

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