Optimal entrainment of neural oscillator ensembles

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Abstract
In this paper, we derive the minimum-energy periodic control that entrains an ensemble of structurally similar neural oscillators to a desired frequency. The state-space representation of a nominal oscillator is reduced to a phase model by computing its limit cycle and phase response curve, from which the optimal control is derived by using formal averaging and the calculus of variations. We focus on the case of a 1:1 entrainment ratio and suggest a simple numerical method for approximating the optimal controls. The method is applied to asymptotically control the spiking frequency of neural oscillators modeled using the Hodgkin–Huxley equations. Simulations are used to illustrate the optimality of entrainment controls derived using phase models when applied to the original state-space system, which is crucial for using phase models in control synthesis for practical applications. This work addresses a fundamental problem in the field of neural dynamics and provides a theoretical contribution to the optimal frequency control of uncertain oscillating systems.

(Some figures may appear in colour only in the online journal)

1. Introduction

The synchronization of oscillating systems is an important and extensively studied scientific concept with numerous engineering applications [1]. Examples include the oscillation of neurons [2], sleep cycles and other pacemakers in biology [3–5], semiconductor lasers in physics [6], and vibrating systems in mechanical engineering [7]. Among many well-studied synchronization phenomena, the asymptotic synchronization of an oscillator to a periodic control signal, called entrainment, is of fundamental scientific and engineering importance [8, 9].

The entrainment, and hence frequency control, of an oscillating system can be examined by considering its phase response curve (PRC) [10, 11], which quantifies the shift in asymptotic phase due to an infinitesimal perturbation in the state. The classic phase coordinate transformation [12] for studying nonlinear oscillators was used together with formal averaging [13] to develop a model of synchronization in coupled chemical oscillations [14]. Since then, phase models have become indispensable in physics, chemistry and biology for studying oscillating systems where the full state-space model is complicated or even unknown, but where the phase can be estimated from partial state observations, and the PRC can be approximated experimentally [15]. They have been successfully applied to investigate many synchronization phenomena [16], focusing on synchronization emerging in networks of interacting oscillators and on the response of large collections of oscillators to periodic external stimuli [17, 18]. Such models have long been of interest to neuroscientists [19, 20], for whom the intrinsic occurrence and extrinsic imposition of entrainment in networked oscillators is of particular interest [21, 22]. Several studies have been motivated by the prospect of using dynamical systems theory to improve the effectiveness of deep brain stimulation (DBS) as a clinical therapy for epilepsy and Parkinson’s disease [23–25]. Concurrently, others have concentrated on the use of phase models in order to attain desired design objectives for electrochemical [26, 27] and neural [28, 29] systems, including recent work that approaches the use of phase models in neuroscience from a control theoretic perspective [30, 31]. The control of neural spiking using minimum energy inputs with constrained amplitude and charge balancing has also recently been examined [32, 33]. These studies have demonstrated...
that phase-model reduction provides a practical approach to synthesizing near-optimal controls that achieve design goals for oscillating neural systems.

Much of the work on the control of neural oscillators is based on the assumption that each neuron behaves according to pre-defined underlying dynamics, such as the Hodgkin–Huxley equations [34], which constitute a widely studied model of action potential propagation in a squid giant axon. However, in practical applications of neural control and engineering, the systems in question are collections of biological neurons that exhibit variation in parameters that characterize the system dynamics, specifically the frequency of oscillation and sensitivity to external stimuli. Although such a system consists of a finite collection of subsystems, it contains so many unobservable elements, each with parameter uncertainty, that its collective dynamics are most practically modeled by indexing the subsystems by a parameter varying on a continuum. The control of such neural systems therefore lies within an emerging and challenging area in mathematical control theory called ensemble control, which encompasses a class of problems involving the guidance of an uncountably infinite collection of structurally identical dynamical systems with parameter variation by applying a common open-loop control [35]. In the context of phase model reduction, the appropriate indexing parameter for such a collection of oscillating systems is the natural frequency. Therefore, a practical approach to the optimal design of inputs that entrain a collection of neurons is to first consider a family of phase models with a common nominal PRC and natural frequency varying over a specified interval. Optimal waveforms that entrain a collection of phase oscillators with the greatest range of frequencies by weak periodic forcing have been characterized for certain oscillating chemical systems [36], and this approach has been extended to a method for the optimal entrainment of oscillating systems with an arbitrary PRC [37].

In this paper, we develop a method for engineering weak, periodic signals that entrain ensembles of structurally similar uncoupled oscillators with variation in system parameters to a desired target frequency without the use of state feedback. In addition, we present an efficient numerical method for approximating optimal waveforms by minimizing over a compact interval a polynomial whose coefficients depend on the PRC of the entrained oscillator. A related computation is performed to approximate the region in the energy–frequency plane, called Arnold tongues [15], in which the entrainment of an oscillator with a given PRC by a particular waveform occurs. Previous studies have examined the use of averaging to derive Arnold tongues for sinusoidal forcing of phase oscillators [38, 39]. We use such graphs to characterize the performance of optimal controls derived using the PRC for the entrainment of the original oscillator in state space, which is the ultimate purpose of using phase-model-based control. This important validation, which is largely lacking in the literature, is performed using the Hodgkin–Huxley equations as an example. The results of this work can also be viewed as a method for constructing a control to optimally shape the Arnold tongue for an entrainment task involving an ensemble of neurons.

In the following section, we discuss the phase coordinate transformation for a nonlinear oscillator and the available numerical methods for computing the PRC. In section 3, we describe how averaging theory is used to study the asymptotic behavior of an oscillating system and use the calculus of variations to derive the minimum energy entrainment control for a single oscillator with an arbitrary PRC. In section 4, we formulate and solve the problem of minimum energy entrainment of oscillator ensembles, for which the optimal controls can be synthesized by using an efficient procedure involving Fourier series and Chebyshev polynomials detailed in appendix A. Throughout the paper, important concepts are illustrated graphically by providing examples using the Hodgkin–Huxley model, which is described in appendix C, and its corresponding PRC. We provide computed Arnold tongues in addition to those derived using our theory, which verify that the optimal inputs derived here are a significant improvement on commonly used entrainment waveforms. In section 5, we describe several computational results that provide further justification for our approach. Finally, in section 6, we discuss our conclusions and future extensions of this work.

2. Phase models

The phase coordinate transformation is a well-studied model reduction technique that is useful for studying oscillating systems characterized by complex nonlinear dynamics and can also be used for system identification when the dynamics are unknown. Consider a full state-space model of an oscillating system, described by a smooth ordinary differential equation system

\[ \dot{x} = f(x, u), \quad x(0) = x_0, \]  

(1)

where \( x(t) \in \mathbb{R}^n \) is the state and \( u(t) \in \mathbb{R} \) is a control. Furthermore, we require that (1) has an attractive, non-constant limit cycle \( \gamma(t) = \gamma(t + T) \), satisfying \( \dot{\gamma} = f(\gamma, 0) \), on the periodic orbit \( \Gamma = \{ \gamma \in \mathbb{R}^n : \gamma = \gamma(t) \text{ for } 0 \leq t < T \} \subset \mathbb{R}^n \). In order to study the behavior of this system, we reduce it to a scalar equation

\[ \dot{\psi} = \omega + Z(\psi)u, \]  

(2)

which is called a phase model, where \( Z \) is the PRC and \( \psi(t) \) is the phase associated with the isochron on which \( x(t) \) is located. The isochron is the manifold in \( \mathbb{R}^n \) on which all points have asymptotic phase \( \psi(t) \) [40]. The conditions for validity and accuracy of this model have been determined [41], and the reduction is accomplished through the well-studied process of phase coordinate transformation [42], which is based on Floquet theory [43, 44]. The model is assumed valid for inputs \( u(t) \) such that the solution \( x(t, x_0, u) \) to (1) remains within a neighborhood \( U \) of \( \Gamma \).

To compute the PRC, the period \( T = 2\pi/\omega \) and the limit cycle \( \gamma(t) \) must be approximated to a high degree of accuracy. This can be done using a method for determining the steady-state response of nonlinear oscillators [45] based on perturbation theory [46] and gradient optimization [47]. The PRC can then be computed by integrating the adjoint of
the linearization of (1) [20], or by using a more efficient and numerically stable spectral method developed more recently [48]. A software package called XPPAUT [49] is commonly used by researchers to compute the PRC. The PRC of the Hodgkin–Huxley system with nominal parameters, obtained using a technique derived from the method of Malkin [12], is displayed in figure 1.

3. Entrainment of oscillators

Suppose that one desires to entrain the system (2) to a new frequency $\Omega$ using a periodic control $u(t) = v(\Omega t)$, where $v$ is $2\pi$-periodic. We have adopted the weak forcing assumption, i.e. $v = \varepsilon v_1$, where $v_1$ has unit energy and $\varepsilon \ll 1$, so that given this control the state of the original system (1) is guaranteed to remain in a neighborhood $U$ of $\Gamma$ in which the phase model (2) remains valid [41]. Now define a slow phase variable by $\phi(t) = \psi(t) - \Omega t$, and call the difference $\Delta \omega = \omega - \Omega$ between the natural and the forcing frequencies the frequency detuning. The dynamic equation for the slow phase is

$$\dot{\phi} = \psi - \Omega = \Delta \omega + Z(\Omega t + \phi)v(\Omega t),$$

(3)

where $\phi$ is the phase drift. In order to study the asymptotic behavior of (3) it is necessary to eliminate the explicit dependence on time on the right-hand side, which can be accomplished by using formal averaging [14]. Given a periodic forcing with frequency $\Omega = 2\pi/T$, we denote the forcing phase $\theta = \Omega t$. If $P$ is the set of $2\pi$-periodic functions on $\mathbb{R}$, we can define an averaging operator $\langle \cdot \rangle : P \to \mathbb{R}$ by

$$\langle x \rangle = \frac{1}{2\pi} \int_0^{2\pi} x(\theta) d\theta.$$

(4)

The weak ergodic theorem for measure-preserving dynamical systems on the torus [13] implies that for any periodic function $v$, the interaction function $\Lambda_v(\phi) = \langle Z(\theta + \phi)v(\theta) \rangle$

$$= \frac{1}{2\pi} \int_0^{2\pi} Z(\theta + \phi)v(\theta) d\theta$$

$$= \lim_{T \to \infty} \frac{1}{T} \int_0^T Z(\Omega t + \phi)v(\Omega t) dt$$

(5)

exists as a smooth, $2\pi$-periodic function in $P$. By the formal averaging theorem [2],

$$\dot{\psi} = \Delta \omega + \Lambda_v(\phi) + O(\varepsilon^2)$$

(6)

approximates (3) in the sense that there exists a change of variables $\varphi = \phi + \varepsilon h(\psi, \phi)$ that maps solutions of (3) to those of (6). A detailed derivation is provided in appendix B. Therefore, the weak forcing assumption $v = \varepsilon v_1$ with $\varepsilon \ll 1$ allows us to approximate the phase drift equation by

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

(7)

The averaged equation (7) is independent of time and can be used to study the asymptotic behavior of the system (2) under periodic forcing. We say that the system is entrained by a control $u = v(\Omega t)$ when the phase drift equation (7) satisfies $\varphi = 0$. This will eventually occur if there exists a phase $\varphi^*$ satisfying $\Delta \omega + \Lambda_v(\varphi^*) = 0$. The range of frequencies to which the Hodgkin–Huxley system can be entrained by several waveforms is illustrated in figure 2. Because $\Lambda_v(\varphi)$ is not identically zero, when the system is entrained, there exists at least one phase $\varphi^* \in [0, 2\pi]$ that is an attractive fixed point of (7). In practical applications, it is desirable to achieve entrainment with a control of minimum energy. By defining the phases $\varphi_- = \arg \min_\varphi \Lambda_v(\varphi)$ and $\varphi_+ = \arg \max_\varphi \Lambda_v(\varphi)$, we can formulate the minimum energy entrainment of an oscillator as a variational optimization problem. The objective function to be minimized is the energy $\langle v^2 \rangle$, and entrainment can be achieved when $\omega + \Lambda_v(\varphi_+) \geq \Omega$ if $\Omega > \omega$ and $\omega + \Lambda_v(\varphi_-) \leq \Omega$ if $\Omega < \omega$. This inequality is active for the optimal waveform and hence can be expressed as the equality constraint

$$\Delta \omega + \Lambda_v(\varphi_+) = 0, \quad \text{if}\quad \Omega > \omega,$$

$$\Delta \omega + \Lambda_v(\varphi_-) = 0, \quad \text{if}\quad \Omega < \omega.$$  

(8)

Figure 1. Hodgkin–Huxley PRC: the natural period and frequency of oscillation are $T \approx 14.638$ ms and $\omega \approx 68.315$ Hz, respectively.

Figure 2. Interaction functions $\Lambda_v(\varphi)$ as defined in (5) of the Hodgkin–Huxley PRC for sinusoidal ($v_1$) and square-wave ($v_2$) inputs of RMS energy $P_{\text{RMS}} = 0.2$, and with the optimal waveform $v_+$ for increasing frequency ($\times$) of energy $P_{\text{RMS}} = 0.1301$. The waveform $v_-$ is shown in section 3 to be a re-scaling of the PRC. Here, $\Lambda_v$ is scaled by dividing by the natural frequency $\omega$, in order to show the range of target frequencies $\Omega$ to which $v$ and $v_\pm$ can entrain the system, as indicated by $A$ and $B$, respectively. Equation (7) has a fixed point for values of $\Omega$ up to 2.6% greater than $\omega$ for each control, but the optimal control requires 35% less than the RMS energy. The argument of $\Lambda_v$ is $\varphi$, i.e. the averaged phase drift of the oscillator.
the objective using a multiplier $\lambda$, resulting in the cost
\[
\mathcal{J}[v] = (v^2) - \lambda(\Delta \omega + \Lambda_v(\varphi_+))
\]
\[
= (v^2) - \lambda\left(\Delta \omega + \frac{1}{2\pi} \int_{0}^{2\pi} Z(\theta + \varphi_+)v(\theta)\,d\theta\right)
\]
\[
= \frac{1}{2\pi} \int_{0}^{2\pi} \left[v(\theta)(v(\theta) - \lambda Z(\theta + \varphi_+)) - \lambda \Delta \omega\right]d\theta. \tag{9}
\]
Applying the Euler–Lagrange equation, we obtain the necessary condition for an optimal solution, which yields a candidate function
\[
v(\theta) = \frac{\lambda}{2}Z(\theta + \varphi_+), \tag{10}
\]
which we substitute into constraint (8) and solve for the multiplier, $\lambda = -2\Delta \omega/(Z^2)$. Consequently, the minimum energy controls are
\[
v_+(\theta) = -\frac{\Delta \omega}{(Z^2)}Z(\theta + \varphi_+), \quad \text{if } \Omega > \omega,
\]
\[
v_-(\theta) = -\frac{\Delta \omega}{(Z^2)}Z(\theta + \varphi_-), \quad \text{if } \Omega < \omega. \tag{11}
\]
In practice, we omit the phase ambiguity $\varphi_+$ or $\varphi_-$ in solution (11) because entrainment is asymptotic. The minimum energy input that entrains (2) to a frequency $\Omega$ in the neighborhood of its natural frequency $\omega$ is given by (11) where $\theta = \Omega t$.

In addition to deriving the optimal control, we are interested in viewing the Arnold tongue, which is a plot of the minimum root mean square (RMS) energy $P_\epsilon(\Omega) = \sqrt{\langle v^2 \rangle}$ required for the entrainment of the system by a control $v$ to a given target frequency $\Omega$. This is accomplished by substituting into (8) the expression $v(\theta) = P_\epsilon(\Omega)v_1(\theta)$, where $v_1$ is a unit energy normalization of $v$. The RMS energy is used because the boundary of the entrainment region is approximately linear and yields a clear visualization \cite{38, 39}. This results in
\[
\Delta \omega + \Lambda_v(\varphi_+)P_\epsilon(\Omega) = 0, \quad \text{if } \Omega > \omega,
\]
\[
\Delta \omega + \Lambda_v(\varphi_-)P_\epsilon(\Omega) = 0, \quad \text{if } \Omega < \omega, \tag{12}
\]
which in turn yields the Arnold tongue boundary estimate given by
\[
P_\epsilon(\Omega) = \begin{cases} 
-\Delta \omega/\Lambda_v(\varphi_+), & \text{if } \Omega > \omega, \\
-\Delta \omega/\Lambda_v(\varphi_-), & \text{if } \Omega < \omega. \end{cases} \tag{13}
\]
The boundaries of the theoretical Arnold tongues for the controls $v_+$ and $v_-$, as well as computed values of the RMS forcing energy required to enthrain the Hodgkin–Huxley system using these controls, are shown in figure 3.

In this section, we have shown that the minimum energy periodic control $u(t) = v(\theta)$ that entrains a single oscillator with the natural frequency $\omega$ to a target frequency $\Omega$ is a re-scaling of the PRC, where $\theta = \Omega t$ is the forcing phase. Observe that this control will entrain oscillators with natural frequencies between $\omega$ and $\Omega$ to the target $\Omega$ as well. In the following section, we derive the minimum energy periodic control that entrains each member of a family of oscillators, all of which share the same PRC but which can have a natural frequency taking any value in a specified interval, to a single target frequency $\Omega$.

4. Entrainment of an ensemble of oscillators

Recall that in practice biological neurons exhibit variation in parameters that characterize the system dynamics, which must be taken into account when designing optimal entrainment controls for neuron ensembles. We approach this issue by modeling the ensemble as a collection of phase models where each PRC is that of a nominal neuron, and the frequencies are distributed in an appropriate interval. A justification of this approach and a sensitivity analysis is provided in section 5.

Specifically, we consider a collection of systems $\dot{x} = f(x, u, p)$, where $x \in \mathbb{R}^n$ is the state, $u \in \mathbb{R}$ is a scalar control and $p \in D \subset \mathbb{R}^d$ is a vector of constant parameters varying on a hypercube $D$ containing a nominal parameter vector $\alpha$. These systems can be reduced to a scalar phase model $\dot{\theta} = \omega(p) + Z(\theta, p)u$, where the natural frequencies and PRCs depend on the parameter vector $p$. In order to design a control that entrains the ensemble for all $p \in D$, we approximate the ensemble by $[\dot{\theta} = \omega(p) + Z(\theta, \alpha)u : p \in D]$, where $Z(\theta, \alpha)$ is the nominal PRC.

We develop the required theory by extending the approach in section 3 to derive a single minimum energy periodic control signal $v(\Omega t)$ that guarantees entrainment for each system in the ensemble of oscillators
\[
\mathcal{F} = \{ \dot{\psi} = \omega + Z(\psi)u : \omega \in (\omega_-, \omega_+) \} \tag{14}
\]
to a frequency $\Omega$. We call the range of frequencies that are entrained by the control $v$ the locking range $\mathcal{R}[v] = [\omega_-, \omega_+]$. 

Figure 3. Arnold tongues for optimal waveforms for the frequency increase ($v_+$) and decrease ($v_-$) of the Hodgkin–Huxley oscillator. Theoretical boundaries predicted by phase reduction theory are shown as lines, and values computed using (a) the Hodgkin–Huxley PRC and (b) the Hodgkin–Huxley equations are shown as points. These values are computed using a line search over the RMS forcing energy, and (a) closely approximates (b).
this condition, which depends on the ensemble parameters $\omega$ by the control optimization problem.

For target frequencies $\Omega$ near $\omega_2$, $v_*$ can entrain $F$ using 35% less energy. We require $\Delta \omega_2 < \Delta \omega_1$ and $\Delta \omega_1 > \Delta \omega_2$ to guarantee the entrainment of the ensemble. The Arnold tongues for the sine and square waves are identical.

and when $(\omega_1, \omega_2) \subset R[v_*]$, we say that the ensemble $F$ is entrained. This requirement results in the constraints

$$\Delta \omega_+ \triangleq \omega_+ - \Omega = -\Lambda_v(\varphi_-) \geq \omega_2 - \Omega \triangleq \Delta \omega_2, \quad \Delta \omega_- \triangleq \omega_+ - \Omega = -\Lambda_v(\varphi_+) \leq \omega_1 - \Omega \triangleq \Delta \omega_1. \tag{15}$$

Note that $\Omega \in [\omega_-, \omega_+]$ always holds, because an oscillator with the natural frequency $\Omega$ is always entrained when forced with the same frequency. The relationship between the interaction function $\Lambda_v$, the locking range $R[v]$ and the frequency dispersion $(\omega_1, \omega_2)$ of the family $F$ is illustrated in figure 4. The objective of minimizing control energy $\langle v^2 \rangle$ given the constraints (15) gives rise to the optimization problem

$$\min_{k \in \mathcal{P}} J[k] = \langle v^2 \rangle, \quad k \in \mathcal{P},$$

s.t. $\Delta \omega_2 + \Lambda_v(\varphi_-) \leq 0, \quad -\Delta \omega_1 - \Lambda_v(\varphi_+) \leq 0. \tag{16}$

If $\omega_2 < \Omega$ (resp. $\omega_1 > \Omega$), then problem (16) is solved by the control $v_*$, where $\Delta \omega = \Delta \omega_1$ (resp. $\Delta \omega = \Delta \omega_2$) in (11); however, these are not the only instances where that solution is optimal. See, for instance, case (B) in figure 5(a). Understanding the Arnold tongue that characterizes the entrainment of the ensemble $F$ by a control $v$ will clarify the condition when (11) is optimal. We derive this condition, which depends on the ensemble parameters $\omega_1$ and $\omega_2$ as well as the target frequency $\Omega$, and then consider the case in which another class of optimal solutions is superior. These two cases are illustrated in figure 5(b).

**Figure 4.** The negative of the interaction function $(-\Lambda_v)$ of the Hodgkin–Huxley PRC (a) with a square-wave (□) input $v_{\text{sq}}$ of RMS energy $P = 0.2$ and (b) with the optimal waveform $v_*$ for increasing frequency $(\times)$ of energy $P = 0.1301$. The control $v_3$ achieves a locking range $R[v_3] = [\omega - 0.0112, \omega + 0.0112]$ that is symmetric about the natural frequency $\omega$, while the control $v_4$ achieves a non-symmetric locking range $R[v_4] = [\omega - 0.0041, \omega + 0.0112]$. For target frequencies $\Omega$ near $\omega_2$, $v_*$ can entrain $F$ using 35% less energy. We require $\Delta \omega_2 < \Delta \omega_1$ and $\Delta \omega_1 > \Delta \omega_2$ to guarantee the entrainment of the ensemble. The Arnold tongues for the sine and square waves are identical.

**Figure 5.** (a) Arnold tongues of Hodgkin–Huxley neuron ensembles for several controls, where the target $\Omega$ is the nominal natural frequency. Note that the boundaries for sinusoidal- and square-wave forcing coincide. The span of each horizontal bar represents the range of natural frequencies of a family $F$ of oscillators with the Hodgkin–Huxley PRC. The vertical location of each bar represents the minimum RMS energy required to entrain $F$ by the indicated waveform. The control $v_3$ is optimal for ensemble (A), and $v_*$ is optimal for ensemble (B). The waveform $v_*$, which is optimal for entraining the family (C) to $\Omega = \frac{1}{2}(\omega_1 + \omega_2)$, achieves entrainment with the RMS energy 0.26, which is 21% lower than the RMS energy 0.33 required to do so with a sine or square wave (D), whose Arnold tongues coincide. (b) The appropriate optimal waveform depends on the location of $\Omega$ with respect to $(\omega_1, \omega_2)$. If $\Omega$ is in the case I region, then $v_3$ (resp. $v_*$) is optimal. Otherwise, we use $v_*$, which depends on $\omega_1, \omega_2$ and $\Omega$. Recall also the assumption $Q \ast < 0$.

**Case I: A re-scaled PRC is optimal for the entrainment of the ensemble.** To derive the conditions when (11) is optimal, we focus on the use of $v_3$ to entrain $F$ to a frequency $\Omega \in (\omega_1, \omega_2)$ when $\Delta \omega_1 = \Delta \omega_2 > -\Delta \omega_1$, noting that the case where $\Delta \omega_2 < -\Delta \omega_1 = -\Delta \omega_2$ and $v_*$ is used is symmetric. Because $\omega_2$ is the natural frequency in the ensemble farthest from $\Omega$, we use $\Delta \omega = \Delta \omega_2$. Then, the first constraint in (16) is active, yielding $-\Delta \omega_2 = \Lambda_v(\varphi_-) = \Omega - \omega_1$, so that $\omega_+ = \omega_2$ is the upper bound on the locking range $R[k]$, as desired. It remains to determine $\Lambda_v(\varphi_+) = \Omega - \omega_1$, from which we obtain the lower bound $\omega_-$ on $R[k]$. Let us denote $\Delta \varphi = \varphi_+ - \varphi_-$ and define

$$Q(\Delta \varphi) = \langle Z(\theta + \Delta \varphi)Z(\theta) \rangle. \tag{17}$$

We can define an inner product $(\cdot, \cdot) : \mathcal{P} \times \mathcal{P} \to \mathbb{R}$ by $(f, g) = \langle fg \rangle$, so that the Cauchy–Schwartz inequality

$$|\langle g, f \rangle| \leq \langle g, g \rangle^{1/2} \langle f, f \rangle^{1/2}. \tag{18}$$

...
yields \( |Q(\Delta \phi)| \leq \langle Z^2 \rangle = Q(0) \). Furthermore, the periodicity of \( Z \) results in \( Q(\Delta \phi) = (Z(\theta + \Delta \phi)Z(\theta)) = (Z(\theta)Z(\theta - \Delta \phi)) = Q(-\Delta \phi) \). Combining (5), (11) and (17), we can write

\[
\Lambda_+ (\phi) = (Z(\theta + \phi) v_-(\theta)) = -\frac{\Delta \omega_2}{\langle Z^2 \rangle} Q(\phi - \phi_-),
\]

resulting in

\[
\Delta \omega_+ = \Lambda_+(\phi-) = -\Delta \omega_2, \tag{19}
\]
as expected. Observe that \( \Lambda_+(\phi) \) is maximized when \( Q(\phi - \phi_-) \) is minimized, and hence, to find \( \Lambda_+(\phi_+) \), it suffices to find the minimum value \( Q_+ \) of \( Q(\Delta \phi) \). Assume for now that \( Q_+ < 0 \), which is true for the Hodgkin–Huxley PRC and typical for type II neurons. The practical considerations for finding \( Q_+ \) are discussed in appendix A. It follows that

\[
\Lambda_+(\phi+) = -\frac{\Delta \omega_2}{\langle Z^2 \rangle} Q_+ \tag{20}
\]
and the lower bound of \( R[k] \) is \( \omega_- = \Omega - \Lambda_+(\phi_+) \). If \( \omega_- < \omega_1 \), then \( (\omega_1, \omega_2) \subset R[k] \), and hence, the control \( v_- \) in (11), with \( \Delta \omega = \omega_2 - \Omega \), is the minimum energy solution to problem (16) and entrains \( F \) to the frequency \( \Omega \).

Now let us define \( v(\theta) = P_{\omega_-}(\omega) v(\theta) \), where \( \bar{v} \) is the unit energy normalization of a control \( v \). Substituting this expression into (15), we can obtain the minimum RMS energy \( P_{\omega_-}(\omega) \) required to entrain the member of \( F \) with a natural frequency \( \omega \) to \( \Omega \) using the control \( v_- \). Because \( \Lambda_+(\phi) = \Lambda_{\bar{v}}(\phi)P_{\omega_-}(\omega) \), this yields

\[
\begin{align*}
\Delta \omega_+ + \Lambda_{\bar{v}}(\phi_-)P_{\omega_-}(\omega) & = 0, & \omega > \Omega, \\
\Delta \omega_- + \Lambda_{\bar{v}}(\phi_+)P_{\omega_-}(\omega) & = 0, & \omega < \Omega.
\end{align*}
\]
\[
\tag{21}
\]
Because \( \bar{v} = Z/\sqrt{\langle Z^2 \rangle} \), it follows that \( \Lambda_{\bar{v}}(\phi)(\sqrt{Z^2}) = Q(\phi - \phi_-) \), and substituting this into (21) and solving for \( P_{\omega_-}(\omega) \) yields

\[
P_{\omega_-}(\omega) = \begin{cases} 
\frac{1}{\sqrt{\langle Z^2 \rangle}} (\omega - \Omega), & \text{if } \Omega < \omega, \\
\frac{\sqrt{\langle Z^2 \rangle}}{\omega - \Omega}, & \text{if } \Omega > \omega.
\end{cases}
\tag{22}
\]

The boundaries of the Arnold tongues for \( v_- \) and \( v_+ \) in (11) are shown in figure 5(a), and examples of oscillator ensembles for which they are optimal are indicated. The optimal entrainment problem is fully characterized by the PRC \( Z \) and frequency range \((\omega_1, \omega_2) \), as well as the target frequency \( \Omega \). To determine whether the problem is optimally solved by (11), we derive the decision criterion by combining the definition \( \Lambda_+(\phi_+) = -\Delta \omega_- \) with (20) and (19) to obtain

\[
\Delta \omega_- \Lambda_+ = \frac{Q_+}{\langle Z^2 \rangle} \tag{23}
\]
This determines the boundary of the range of \( \Omega \) in relation to \((\omega_1, \omega_2) \) when \( v_- \) is optimal, and the derivation of the optimal range when \( v_+ \) is optimal is symmetric. Therefore, if

\[
\frac{\Delta \omega_1}{\Delta \omega_2} \geq \frac{Q_+}{\langle Z^2 \rangle} \quad \text{or} \quad \frac{\Delta \omega_2}{\Delta \omega_1} \geq \frac{Q_+}{\langle Z^2 \rangle}, \tag{24}
\]
then the minimum energy solution to problem (16) that entrains each member of \( F \) is

\[
v(\theta) = \begin{cases} 
\frac{-\Delta \omega_1}{\langle Z^2 \rangle} Z(\theta + \phi_+), & \text{if } \Delta \omega_2 < -\Delta \omega_1, \\
\frac{-\Delta \omega_2}{\langle Z^2 \rangle} Z(\theta + \phi_-), & \text{if } -\Delta \omega_1 < \Delta \omega_2.
\end{cases}
\tag{25}
\]

In practice, we omit the phase ambiguity \( \phi_- \) or \( \phi_+ \) in solution (25). Condition (24) is illustrated as case I in figure 5(b). When (24) does not hold, solution (25) is not optimal for problem (16), as in example (C) in figure 5(a), which motivates the derivation of the optimal solution (37).

Case II: A difference of shifted PRCs is optimal for the entrainment of the ensemble. To solve (16) when (25) is not optimal, as in (D) in figure 5(a), we adjoin the constraints in (16) to the minimum energy objective function using multipliers \( \mu_- \) and \( \mu_+ \), giving rise to the cost functional

\[
\mathcal{J}[v] = \langle v^2 \rangle - \mu_-(\Delta \omega_+ + \Lambda_+(\phi_-)) - \mu_+(\Delta \omega_- + \Lambda_+(\phi_+)) = \langle v^2 \rangle - \mu_-(\Delta \omega_+ + (Z(\theta + \phi_-) v(\theta))) - \mu_+(\Delta \omega_- + (Z(\theta + \phi_+) v(\theta)))
\]

\[
= \frac{1}{2\pi} \int_0^{2\pi} \left( v(\theta) [v(\theta) - \mu_- Z(\theta + \phi_-) v(\theta)] + \mu_+ Z(\theta + \phi_+) v(\theta) - \mu_+ \Delta \omega_+ \right) d\theta.
\tag{26}
\]

Solving the Euler–Lagrange equation yields

\[
v(\theta) = -\frac{1}{2} [\mu_+[Z(\theta + \phi_+) - \mu_- Z(\theta + \phi_-)]],
\tag{27}
\]
which we substitute back into problem (16) to obtain

\[
\langle v^2 \rangle = \frac{1}{4} (\mu_+ Z(\theta + \phi_+) + \mu_- Z(\theta + \phi_-))^2
\]

\[
= \frac{1}{4} (\mu_+^2 Z^2 + \mu_-^2 Z^2 - \mu_+ \mu_- Z(\theta + \phi_-)) + \frac{1}{2} \mu_+ Z^2
\]

\[
= \frac{1}{4} (\mu_+^2 + \mu_-^2) Z^2 - \frac{1}{2} \mu_+ \mu_- Q(\Delta \phi), \tag{28}
\]

\[
\Lambda_+(\phi_-) = (Z(\theta + \phi_-) v(\theta)) = -\frac{1}{2} \mu_+ Z^2 + \frac{1}{2} \mu_- Q(\Delta \phi), \tag{29}
\]

\[
\Lambda_+(\phi_+) = (Z(\theta + \phi_+) v(\theta)) = \frac{1}{2} \mu_+ Z^2 - \frac{1}{2} \mu_- Q(\Delta \phi). \tag{30}
\]

Substituting (28)–(30) into problem (16) simplifies the functional optimization problem to a nonlinear programming problem in the variables \( \mu_- \), \( \mu_+ \), and \( Q(\Delta \phi) \), namely

\[
\min \mathcal{J}[\mu_-, \mu_+, Q(\Delta \phi)] = \frac{1}{4} (\mu_+ Z(\theta + \phi_-) - \mu_- Z(\theta + \phi_-))^2 - \frac{1}{2} \mu_+ \mu_- Q(\Delta \phi)
\]

s.t. \( \Delta \omega_+ + \frac{1}{2} \mu_+ Z(-\Delta \omega_+) \leq 0, \)

\[
-\Delta \omega_+ + \frac{1}{2} \mu_+ Z(-\Delta \omega_-) \leq 0,
\tag{31}
\]

When one of the constraints is not active, either \( \mu_- = 0 \) (resp. \( \mu_- = 0 \)), and problem (26) is reduced to problem (9) with \( \lambda = \mu_- \) (resp. \( \lambda = -\mu_+ \)). This occurs when condition (24) holds, and solution (25) is optimal. In the case that condition (24) does not hold, it follows that both constraints in problem (31) are active. The multipliers can be solved for, yielding

\[
\mu_+ = \frac{2(\Delta \omega_1 Z^2 - \Delta \omega_2 Q(\Delta \phi))}{(Z^2 - Q(\Delta \phi))(Z^2 + Q(\Delta \phi))},
\tag{32}
\]

\[
\mu_- = \frac{2(\Delta \omega_1 Q(\Delta \phi) - \Delta \omega_2 Z^2)}{(Z^2 - Q(\Delta \phi))(Z^2 + Q(\Delta \phi))}.
\]
For these multipliers, the objective in problem (31) is reduced to a function of \( Q = Q(\Delta \varphi) \) given by
\[
\mathcal{J}[Q] = \frac{(\Delta \omega_1 (Z^2) - \Delta \omega_2 Q)^2 + (\Delta \omega_1 Q - \Delta \omega_2 (Z^2))^2}{(\langle Z^2 \rangle - Q_0)^2(Z^2 + Q_0)^2} \quad \text{(33)} 
\]
\[
- \frac{2(\Delta \omega_1 (Z^2) - \Delta \omega_2 Q)(\Delta \omega_1 Q - \Delta \omega_2 (Z^2))}{(\langle Z^2 \rangle - Q_0)^2(Z^2 + Q_0)^2}. 
\]

Differentiating the cost (33) with respect to \( Q \) results in
\[
\frac{d\mathcal{J}[Q]}{dQ} = -2 \frac{\Delta \omega_1 \Delta \omega_2 Q^2 - (\Delta \omega_1^2 + \Delta \omega_2^2)(Z^2) Q + \Delta \omega_1 \Delta \omega_2 (Z^2)^2}{(\langle Z^2 \rangle - Q_0)^2(Z^2 + Q_0)^2}. 
\]

Because condition (24) does not hold, it follows that \( Q > \Delta \omega_1 (Z^2)/\Delta \omega_2 \), and hence, (34) is positive for all admissible values of \( Q(\Delta \varphi) \), so that the cost (33) increases when \( Q(\Delta \varphi) \) does. Therefore, the objective (33) is minimized when \( Q(\Delta \varphi) \) is, which occurs when \( Q(\Delta \varphi) = Q_*= Q(\Delta \varphi_*) \). Therefore, the problem (31) is solved when \( \Delta \varphi = \Delta \varphi_* \), and the multipliers are as in (32). Therefore, when
\[
\frac{\langle Z^2 \rangle}{Q_*} \leq \Delta \omega_1 \Delta \omega_2 \leq \frac{Q_*}{\langle Z^2 \rangle}, 
\]
case II is in effect, and the minimum energy solution to problem (16) that entrains \( \mathcal{F} \) is
\[
v(\theta) = \frac{(\Delta \omega_1 Q_* - \Delta \omega_1 (Z^2))}{(\langle Z^2 \rangle - Q_*)(\langle Z^2 \rangle + Q_*)} Z(\theta + \varphi_*) 
+ \frac{(\Delta \omega_1 Q_* - \Delta \omega_2 (Z^2))}{(\langle Z^2 \rangle - Q_*)(\langle Z^2 \rangle + Q_*)} Z(\theta + \varphi_-). 
\]

The locking range is exactly \( R[k] = [\omega_1, \omega_2] \), satisfying the entrainment constraints (15). In practice, we omit the phase ambiguity in the solution by using the equivalent control
\[
v_*(\theta) = \frac{(\Delta \omega_1 Q_* - \Delta \omega_1 (Z^2))}{(\langle Z^2 \rangle - Q_*)(\langle Z^2 \rangle + Q_*)} Z(\theta + \varphi_*) 
+ \frac{(\Delta \omega_1 Q_* - \Delta \omega_2 (Z^2))}{(\langle Z^2 \rangle - Q_*)(\langle Z^2 \rangle + Q_*)} Z(\theta), 
\]

with the energy
\[
E_*^2 = \frac{(\Delta \omega_1^2 + \Delta \omega_2^2)(Z^2) - 2 \Delta \omega_1 \Delta \omega_2 Q_*}{(\langle Z^2 \rangle - Q_*)(\langle Z^2 \rangle + Q_*)}. 
\]

The Arnold tongue for entrainment using \( v_* \) can be generated by applying the approach used for \( v_- \) in (21). The advantage of the appropriate optimal control over a sinusoidal or square-wave forcing input is illustrated in figures 5 and 6(a). In the special case where \( \Omega = \frac{1}{2}(\omega_1 + \omega_2) \), solution (37) reduces exactly to the control \( v_* \) that maximizes the locking range \( R[k] \) for a fixed control energy, which is achieved when \( \Delta \omega_1 = \Delta \omega_- \) [36, 37]. The theoretical contribution presented here provides a clarification of the symmetry properties of that particular case. The Arnold tongues that characterize entrainment properties of an ensemble \( \mathcal{F} \) are computed and plotted for several controls in figure 6(a), which clearly demonstrates that \( v_* \) can entrain an ensemble \( \mathcal{F} \) using a lower RMS energy than that required by a sinusoidal waveform.

5. Sensitivity analysis and discussion

In this section, we provide the results of several numerical simulations that further justify our approach to the entrainment of neural ensembles. In particular, we examine the effect of parameter variation on the PRC and optimal entrainment control for an ensemble of neurons. We also provide a visualization of the uncertainty in the entrainment properties of a neuron ensemble that arises due to such parameter variation. This is done by computing an Arnold tongue distribution, in which the minimum RMS energy required for the entrainment of the ensemble to a given target frequency \( \Omega \) is a random variable with a probability density on the positive real line, instead of a single value, for each \( \omega \in (\omega_1, \omega_2) \). We demonstrate that the optimal entrainment waveform is minimally sensitive to variation in underlying system parameters, that it is always superior to a generic waveform such as a sinusoid or square pulse train and that its amplitude can be appropriately chosen to entrain the neuron with the most problematic parameter set in the ensemble.

The following sensitivity analysis can be performed to examine the effect of parameter variation on the PRC of an
oscillator. Suppose that \( p = (p_1, \ldots, p_d) \) are the parameters that characterize the system dynamics \( \dot{x} = f(x, u, p) \), with the nominal values \( \alpha = (\alpha_1, \ldots, \alpha_d) \). The phase reduction then depends on \( p \) and has the form \( \dot{\theta} = \omega(p) + Z(\theta, p)u \). We compute the PRC \( Z(\cdot, p) \) at each corner of a hypercube \( D = \prod_{i=1}^{d} \left[ \beta_i, \gamma_i \right] \), where \((\beta_i, \gamma_i)\) is a small confidence interval for \( \alpha_i \). The corner points of \( D \) are examined in particular to analyze the aggregate effect of uncertainty in all parameters. If the \( 2^d \) curves so obtained are similar to the nominal PRC, then the optimal controls derived using the latter will be near optimal for the entrainment of an uncertain ensemble. Such a robustness property is important in practical neural entrainment applications, because biological oscillators exhibit significant variation from any nominal model. Our analysis of the sensitivity of the Hodgkin–Huxley PRC to parameter variation appears in figure 7, in which we have used \((\beta_i, \gamma_i) = (0.98\alpha_i, 1.02\alpha_i)\) for the \( d = 7 \) parameter values in the model. For each of the corner points of \( D \), we plot in figure 7(b) the PRC, normalized to unit energy, and find that it does not vary significantly from the nominal curve. This supports our assertion that the optimal entrainment waveform is minimally sensitive to variation in underlying system parameters. Note that the energy of the PRC can take different values for the same value of \( \omega \), depending on the original system parameters, and approximately follows an exponential trend, as shown in figure 7(c).

Although minor variations in Hodgkin–Huxley neuron model parameter values do not significantly affect the shape of the PRC, they do have a significant effect on the amplitude and, hence, the entrainment properties of a neuron ensemble forced by a fixed waveform \( v \). The resulting uncertainty is visualized as an Arnold tongue distribution, which is the probability distribution of the minimum RMS control energy required to entrain an ensemble of oscillators, with the parameter set distributed on a given probability space \( D \), as a function of natural frequency \( \omega \). In practice, we estimate this empirically for a hypercube \( D \) with an uniform probability measure by uniformly randomly generating samples \( p_k \in D \) of the parameter for \( k = 1, \ldots, N \), for which we compute the natural frequency \( \omega_k \) of the perturbed Hodgkin–Huxley model and the minimum RMS control energy \( P_k(v) \) required to entrain the \( k \)th model using \( v \). This results in \( N \) samples that are plotted on the energy–frequency plane, as shown in figure 8(a), which displays the empirical Arnold tongue distribution, using \( N = 500 \) samples, for a sinusoidal control waveform and for the optimal waveform \( v^\ast \) that maximizes the range of entrainment. From visual inspection, one concludes that the optimal waveform entrains the perturbed model using lower energy than the sinusoid in the majority of cases. More distinctly, figure 8(b) displays the ratio between the minimum RMS energy levels required to entrain each parameter set \( p_k \) using the optimal control and a sinusoid, as a function of the natural frequency \( \omega_k \). The ratio is not only below unity in most cases, with an average of 0.78, but there is also a clear trend line at 0.8 in the frequency range \( 0.95 < \omega < 0.99 \), with a much lower ratio for natural frequencies near the target \( \Omega \). This result strongly supports the assertion that the optimal ensemble entrainment waveform derived using our method is superior to traditional waveforms, such as the sinusoid, not only for phase-reduced models, but also for the underlying non-reduced dynamical system model.

In practice, given a confidence region hypercube \( D \) for the parameter set \( P \) of a neuron ensemble, the PRC can be computed at each corner point of \( D \) and can be used to approximate the corresponding Arnold tongue when the perturbed system is entrained by the optimal waveform \( v^\ast \) for the nominal parameter set. In order to assure the robust entrainment of the entire ensemble, the RMS energy of \( v^\ast \) should be chosen such that it entrains the oscillator with the worst case parameter set, whose theoretical Arnold tongue is indicated by the top dashed line in figure 9. The nominal oscillator is entrained with an RMS energy 24% lower than the worst-case scenario. This difference is very near the average of 22% less than the RMS energy that the optimal waveform requires to entrain an oscillator with parameter uncertainty. It follows that simply by using the waveform \( v^\ast \) instead of
Figure 8. (a) Arnold tongue distributions for an ensemble of Hodgkin–Huxley neurons with uniform random parameter variation on \((\beta, \gamma) = (0.98 \alpha, 1.02 \alpha)\), where \((\alpha_1, \ldots, \alpha_5)\) are the nominal values for the parameters \(V_m, V_C, \xi, \eta, \gamma, \alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \) and \(c\). The target \(\Omega\) is the nominal natural frequency. There are \(N = 500\) randomly perturbed parameter sets used to generate empirical distributions (points) for entrainment with a sinusoid \(v_s(\cdot)\) and the optimal waveform for entrainment to \(\Omega = \frac{1}{2}(\omega_1 + \omega_2)\) with \(v_s(\cdot)\). Solid lines denote theoretical Arnold tongue boundaries. (b) The ratio \(\eta = P_\eta(v_s)/P_\eta(v_c)\) plotted as a function of \(\omega/\Omega\), i.e. the natural frequency of the neuron with the parameter set \(P_\eta\) (re-scaled by the target frequency). The optimal waveform requires an average of 22% less than the RMS energy for entrainment than a sinusoid.

Figure 9. Theoretical Arnold tongues for entrainment of Hodgkin–Huxley neurons with parameter sets at the corner points of \(D\) with \((\beta, \gamma) = (0.98 \alpha, 1.02 \alpha)\), where the target \(\Omega\) is the nominal natural frequency are bounded by the best- and worst-case scenarios (dashed lines).

a square wave or sinusoid, one can significantly enhance the likelihood that the entrainment of an ensemble will be robust to such parameter variation.

6. Conclusions

We have developed a method for the minimum energy entrainment of oscillator ensembles to a desired frequency using weak periodic forcing. Our approach is based on phase model reduction and formal averaging theory. We also derive an approximation of the entrainment region in the energy–frequency space for an oscillator ensemble. The entrainment of phase-reduced Hodgkin–Huxley neurons is considered as an example problem, and Arnold tongues are computed to evaluate the effectiveness of our controls. The results closely match the theoretical bounds when the weak forcing requirement is fulfilled. The optimal waveforms produce a similar result when applied to the original model, which suggests that optimal entrainment controls derived using a phase model are optimal for the original system, provided the oscillator remains within a neighborhood of its limit cycle. We have justified our approach of considering an ensemble with common PRC and varying frequency by a sensitivity analysis of the PRC and optimal waveform to variation in model parameters. The results of our simulations suggest that stimuli based on inherent dynamical properties of neural oscillators can result in significant improvement in energy efficiency and performance over traditional pulses both in theory and in practical neural engineering applications. This work provides a basis for evaluating the effectiveness of phase-reduction techniques for the control of oscillating systems with parameter uncertainty. In the future, we will extend the theory of optimal entrainment of oscillator ensembles to the case of \(n : m\) entrainment, where \(m\) cycles of the oscillator occur for every \(n\) control cycles. We will also derive controls that most rapidly entrain an ensemble of oscillators with an uncertain initial state. The approach described here is of direct interest to researchers in neuroscience, chemistry and vibration control in engineered systems.

Appendix A. Numerical issues

Because the PRC \(Z(\theta)\) and forcing waveform \(v(\theta)\) are both \(2\pi\)-periodic, we represent them using Fourier series:

\[
Z(\theta) = \frac{1}{2} a_0 + \sum_{n=1}^{\infty} a_n \cos(n\theta) + \sum_{n=1}^{\infty} b_n \sin(n\theta),
\]

\[
v(\theta) = \frac{1}{2} c_0 + \sum_{n=1}^{\infty} c_n \cos(n\theta) + \sum_{n=1}^{\infty} d_n \sin(n\theta).\]

Using trigonometric angle sum identities and the orthogonality of the Fourier basis, we can express the interaction function \(\Lambda_v\) as equation

\[
\Lambda_v(\varphi) = \langle Z(\theta + \varphi)v(\theta) \rangle = \frac{a_0 c_0}{4} + \frac{1}{2} \sum_{n=1}^{\infty} [a_n c_n + b_n d_n] \cos(n\varphi) + \frac{1}{2} \sum_{n=1}^{\infty} [b_n c_n - a_n d_n] \sin(n\varphi).
\]

\[\text{(A.3)}\]
In addition, for any \( \varphi_1, \varphi_2 \in [0, 2\pi) \), periodicity of \( Z \) and \( \nu \) ensures that \( (Z(\theta + \varphi_1) \nu(\theta + \varphi_2)) = (Z(\theta + \varphi_1 - \varphi_2) \nu(\theta)) \).

Let \( y = \cos(\varphi) \), so that we can write

\[
\Lambda_n(\varphi) = \ell_n(y) = \frac{\delta_{\Pi, \Pi}}{4} + \frac{1}{2} \sum_{n=1}^{\infty} [a_n c_n + b_n d_n] T_n(y) + \frac{1}{2} \sum_{n=1}^{\infty} [b_n c_n - a_n d_n] \sqrt{1 - y^2} u_n(y),
\]

where \( T_n \) is the \( n \)th Chebyshev polynomial of the first kind, and \( U_n \) is the \( n \)th Chebyshev polynomial of the second kind. If \( y_* \) is a minimizer of \( \ell_n(y) \) over \( y \in [-1, 1] \), then \( \varphi_* = \arccos(y_*) \) is a minimizer of \( \Lambda_n(\varphi) \) over \( \varphi \in [-\pi, \pi] \). Recall that \( Q(\Delta \varphi) = (Z(\theta + \Delta \varphi) Z(\theta)) \) satisfies \( Q(\Delta \varphi) = Q(-\Delta \varphi) \), so that

\[
Q(\Delta \varphi) = \frac{a_0^2}{4} + \frac{1}{2} \sum_{n=1}^{\infty} [a_n^2 + b_n^2] \cos(n \Delta \varphi).
\]

To find \( Q_0 \) and \( \Delta \varphi \), it is sufficient to minimize a truncation of the series in (A.5) in the most numerically expedient way, whether explicitly as \( Q(\Delta \varphi) = \Lambda_n(\Delta \varphi) \) as in (A.3) or by using the change of variables \( y = \cos(\Delta \varphi) \) and minimizing \( \ell_n(y) \) as in (A.4), in which case the objective polynomial is with the compact domain \([-1, 1] \subseteq \mathbb{R} \).

**Appendix B. Averaging theory**

Given a periodic input \( \nu(\Omega t) \) with period \( T \) and frequency \( \Omega = 2\pi / T \), denote the forcing phase \( \Theta = \Omega t \), so that \( d\Theta = \Omega \, dt \). Kuramoto [14] bases his theory on the idea that if the forcing is ‘weak’, then the phase difference \( \psi(t) = \Theta(t) - \Omega t \) is ‘slow’, so \( \phi(t) \) is nearly constant over a single period \([0, T]\).

We substitute \( \Theta = \Omega t \) and write

\[
\phi = \Delta \omega + Z(\phi + \Omega \Theta) k(\Theta) \approx \Delta \omega + \frac{1}{T} \int_{\Theta}^{\Theta + T} Z(\phi + \Theta) k(\Theta) d\Theta.
\]

Let \( \mathcal{S} = \{ \Theta : \mathbb{R} \rightarrow \mathbb{R} : f(\Theta) = f(\Theta + 2\pi) \} \) be the set of \( 2\pi \)-periodic functions on \( \mathbb{R} \). If we define an averaging operator \( \langle \cdot \rangle : \mathcal{S} \rightarrow \mathbb{R} \) by \( \langle x \rangle = \frac{1}{2\pi} \int_{0}^{2\pi} x(\Theta) d\Theta \) and define the interaction function \( \Lambda_n(\phi) = \langle Z(\phi + \Theta) \nu(\Theta) \rangle \), then the phase drift dynamics become \( \dot{\Theta} = \Delta \omega + \Lambda_n(\phi) \).

This approach can be justified more rigorously as follows. Let \( \zeta = \phi - \Delta \omega t \), and so

\[
\dot{\zeta} = \phi - \Delta \omega t = Z(\phi + \Theta) k(\Theta) = \varepsilon Z(\zeta + \Delta \omega t + \Theta) k(\Theta) = \varepsilon Z(\zeta + (\Delta \omega / \Omega + 1) \Theta) k(\Theta) =: \varepsilon g(\zeta, \omega t).
\]

We now state the following theorem, which is a modification of theorem 9.4 in [2].

**Theorem (Formal averaging).** Consider a dynamical system \( \dot{\zeta} = \varepsilon g(\zeta, \omega t) \), where \( g \) is \( 2\pi \)-periodic in both \( \zeta \) and \( \omega t \). Suppose the average of \( g \) given by

\[
\overline{g}(\varphi) = \lim_{T \to \infty} \frac{1}{T} \int_{0}^{T} g(\varphi, \Omega \Theta) d\Theta = \frac{1}{2\pi} \int_{0}^{2\pi} g(\varphi, \Theta) d\Theta = \langle g(\varphi, \Theta) \rangle
\]

exists as a smooth function for \( \varphi \in \mathbb{R} \). Then, \( \dot{\varphi} = \varepsilon \overline{g}(\varphi) + \Theta(\varphi) \epsilon(\varphi) \) approximates \( \zeta = \varepsilon g(\zeta, \omega t) \), in the sense that there is a change of variables \( \zeta = \varphi + \epsilon h(\omega t, \varphi) \), where

\[
h(\varphi, \Theta) = \frac{1}{\Omega} \int_{0}^{\Theta} [g(\varphi, \sigma) - \overline{g}(\varphi)] d\sigma
\]

that maps solutions of \( \dot{\zeta} = \varepsilon g(\zeta, \omega t) \) to those of \( \dot{\varphi} = \varepsilon \overline{g}(\varphi) + \Theta(\varphi) \epsilon(\varphi) \).

**Proof.** We first note that \( \overline{g}(\varphi) = \langle g(\varphi, \Theta) \rangle = g(\varphi, \Theta) \), is a result of the weak ergodic theorem for measure-preserving dynamical systems on the torus [13]. Substitute \( \zeta = \varphi + \epsilon h(\omega t, \varphi) \) into \( \dot{\varphi} = \varepsilon \overline{g}(\varphi) + \Theta(\varphi) \epsilon(\varphi) \), and so

\[
\dot{\zeta} = \left(1 + \epsilon \frac{\partial}{\partial \varphi} h(\omega t, \varphi) \right) \dot{\varphi} + \epsilon \frac{\partial}{\partial \varphi} h(\omega t, \varphi) = \varepsilon g(\varphi, \Theta) + \Theta(\varphi) \epsilon(\varphi).
\]

Because \( \left(1 + \epsilon \frac{\partial}{\partial \varphi} h(\omega t, \varphi) \right)^{-1} = 1 - \epsilon \frac{\partial}{\partial \varphi} h(\omega t, \varphi) + \Theta(\varphi) \epsilon(\varphi) \), then

\[
\dot{\zeta} = \varepsilon g(\varphi, \Theta) - \varepsilon \frac{\partial}{\partial \varphi} h(\omega t, \varphi) + \Theta(\varphi) \epsilon(\varphi) = \varepsilon g(\varphi, \Theta) - \varepsilon [g(\varphi, \Theta) - \overline{g}(\varphi)] + \Theta(\varphi) \epsilon(\varphi) = \varepsilon g(\varphi, \Theta) + \Theta(\varphi) \epsilon(\varphi).
\]

When \( \epsilon \ll 1 \), the solution to \( \dot{\varphi} = \varepsilon \overline{g}(\varphi) \) approximates the solution to \( \dot{\zeta} = \varepsilon g(\zeta, \omega t) \) up to order \( \Theta(\varphi) \epsilon(\varphi) \). □

The averaged phase drift equations therefore satisfy

\[
\dot{\phi} = \dot{\zeta} + \Delta \omega = \Delta \omega + \varepsilon \overline{g}(\zeta, \omega t) = \Delta \omega + \varepsilon (g(\zeta, \omega t) + \Theta(\varphi) \epsilon(\varphi)) = \Delta \omega + \langle Z(\phi + \Theta) \nu(\Theta) \rangle + \Theta(\varphi) \epsilon(\varphi). \]

With the ‘weak’ forcing assumption \( \epsilon \ll 1 \), we can approximate the averaged phase drift dynamics by \( \dot{\phi} = \Delta \omega + \Lambda_n(\phi) \).

**Appendix C. The Hodgkin–Huxley model**

The Hodgkin–Huxley model describes the propagation of action potentials in neurons, specifically the squid giant axon, and is used as a canonical example of neural oscillator dynamics. The equations are

\[
eV = I_0 + I(t) - \overline{g}_K h(V - V_{Nax}) m^3 - \overline{g}_K (V - V_K)m^4 - \overline{g}_L (V - V_L),
\]

\[
m = a_m(V)(1 - m) - b_m(V)m,
\]

\[
h = a_h(V)(1 - h) - b_h(V)h,
\]

\[
n = a_n(V)(1 - n) - b_n(V)n,
\]

\[
a_m(V) = 0.1(V + 40)/(1 - \exp(-V + 40)/10),
\]

\[
b_m(V) = 4 \exp(-V + 65)/18,
\]

\[
a_h(V) = 0.07 \exp(-V + 65)/20,
\]

\[
b_h(V) = 1/(1 + \exp(-V + 35)/10),
\]

\[
a_n(V) = 0.01(V + 55)/(1 - \exp(-V + 55)/10),
\]

\[
b_n(V) = 0.125 \exp(-V + 65)/80.
\]

The variable \( V \) is the voltage across the axon membrane; \( m, h \) and \( n \) are the ion gating variables; \( I_0 \) is a baseline current that induces the oscillation; and \( I(t) \) is the control input. The unit
of $V$ is millivolt and the unit of time is millisecond. Nominal parameters are $V_{Na} = 50 \text{mV}$, $V_{K} = -77 \text{mV}$, $V_{L} = -54.4 \text{mV}$, $\bar{g}_{Na} = 120 \text{ mS cm}^{-2}$, $\bar{g}_{K} = 36 \text{ mS cm}^{-2}$, $\bar{g}_{L} = 0.3 \text{ mS cm}^{-2}$, $I_{inj} = 10 \mu \text{A cm}^{-2}$ and $c = 1 \mu \text{F cm}^{-2}$, for which the period of oscillation is $T = 14.6384 \pm 10^{-5} \text{ ms}$.

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