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Analytical Bounds on the Critical Coupling Strength in a Population of Heterogeneous Biological Oscillators

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***Abstract*— Synchronization of nonlinear oscillators is a ubiquitous phenomenon in the biological sciences; however, existing analytical techniques are ill-equipped to handle the large amount of heterogeneity present in realistic populations of biological oscillators. Using phase reduction, we derive upper and lower bounds on the critical coupling strength required to achieve frequency synchronization in a population with both arbitrarily distributed natural frequencies and phase response properties. Numerical simulations reveal that these bounds are reasonably tight in a network of oscillatory neurons as might be relevant to diseases characterized by pathological neural synchronization such as epilepsy or Parkinson's disease. Furthermore, we show how the upper bounds can be altered by including the influence of a periodic external perturbation.**

I. INTRODUCTION

Synchronization of networked oscillators is a fascinating phenomenon with abundant examples in the biological sciences. For instance, excessive neural synchronization is thought to contribute to the motor symptoms including tremor and rigidity associated with Parkinson's disease [24], [5], [19], loss of synchronization is thought to contribute to both hearing loss [23] and the development of diabetes [18], and synchronization of populations of neurons in the suprachiasmatic nucleus is responsible for the mammalian circadian clock [2]. Networks of phase oscillators are commonly represented mathematically by the following equation

$$\dot{\theta}_i = \omega_i - \frac{K}{N}\sum_{j=1}^{N}\Gamma_i(\theta_i - \theta_j), \qquad i = 1,\dots,N. \tag{1}$$

Here, $\theta_i \in [0, 2\pi)$ is the phase of oscillator i, Γ_i represents a phase difference coupling function for oscillator i, K is a positive constant giving the strength of the coupling, and N is the number of oscillators. The network (1) is coupled in an all-to-all fashion, so that all oscillators can influence each other. Mathematical analysis of the Kuramoto [14] and other related models [1] provides a starting point to study synchronization in such networks, but existing analytical techniques often cannot account for the large amount of heterogeneity and relatively general coupling functions that are common in most realistic biological networks.

One can characterize the tendency of a network to synchronize by finding its critical coupling strength, K_c, the point at which the network transitions from an incohesive to a highly synchronized state. Different notions of synchronization can be defined when discussing critical coupling. In this manuscript, we will be interested in frequency synchronization and phase cohesion. A solution to (1) is said to be *frequency synchronized* at time t^* if $\dot{\theta}_i(t) = \dot{\theta}_j(t)$ for all i and j and for all times $t \geq t^*$. The system can achieve *exponential frequency synchronization* if all $\dot{\theta}_i$ exponentially converge to a common frequency ω^* as t approaches infinity. *Phase cohesion* is a more general notion of synchronization that is achieved at time t^* if there exists a length $\gamma \in [0, \pi)$ such that for all i and $t \geq t^*$, an arc of length γ can be found that contains $\theta_i(t)$.

When the number of oscillators is small, a network can be analyzed in great detail (e.g. [16]) making it possible to analytically determine critical coupling values. As the number of oscillators grows, assumptions such as restricting Γ_i to be sinusoidal [6], [11] or restricting coupling functions and natural frequencies to be identical [3], [7] can make a problem more analytically tractable so that bounds on the critical coupling strength can be determined. In this work, we derive separate necessary conditions and sufficient conditions for phase cohesion and frequency synchronization of (1). These conditions do not require explicit knowledge of the properties of any individual oscillator, but rather assume that their properties fall within some expected range. These conditions can be used to infer upper and lower bounds on K_c.

The remainder of this paper is organized as follows. Section II gives a derivation of our main result in the context of a biologically relevant population of oscillators. Section III provides numerical results comparing determined critical coupling values to upper and lower bounds for a network of periodically firing neurons, and Section IV gives concluding remarks.

II. A SUFFICIENT CONDITION TO ACHIEVE PHASE COHESION AND FREQUENCY SYNCHRONIZATION

While equation (1) provides a useful framework to analyze a network of oscillators, biological oscillators usually do not exhibit explicit phase difference coupling. However, with the appropriate mathematical transformations these systems can be analyzed in this context. To this end, consider a weakly forced population of oscillators, each with a stable limit cycle

$$\dot{\mathbf{x}}_i = F(\mathbf{x}_i) + \varepsilon G_i(t), \quad \mathbf{x}_i \in \mathbb{R}^M, \quad i = 1,\dots,N, \tag{2}$$

where $\mathbf{x}_i$ is a state vector and $G_i \in \mathbb{R}^M$ represents an external perturbation, and $0 < \varepsilon \ll 1$. For simplicity, we will take $G_i(t) = [u_i(t), 0, \dots, 0]^T$ so that perturbations are only given to a single state variable, but note that the analysis to follow can be amended to include perturbations to multiple variables in a straightforward manner.

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In the limit that external perturbations are small, (2) is well approximated in phase reduced form [28], [10]

$$\dot{\theta}_i = \omega_i + \varepsilon Z_i(\theta_i) u_i(t), \quad i = 1, \ldots, N, \tag{3}$$

where, θ_i, ω_i and N are defined identically to (1), and $Z_i(\theta_i)$ is the phase response curve of oscillator i which describes the phase change associated with a δ-function perturbation, and $u_i(t)$ is a general external perturbation to oscillator i. In phase reduced coordinates, the phase θ_i gives an oscillator's location in phase space with respect to its limit cycle $\boldsymbol{\zeta}_i$. In the analysis to follow, we will assume that when perturbations u_i are of order ε, each oscillator will remain order ε close to $\boldsymbol{\zeta}_i$. This implies that to leading order ε there is a one-to-one correspondence between the phase and the system's state variables, i.e. $\mathbf{x}_i(\theta_i) = \boldsymbol{\zeta}_i(\theta_i) + \mathscr{O}(\varepsilon)$. The formulation (3) allows the population to have both significantly different phase response curves and natural frequencies.

Unless stated otherwise, the derivations to follow will assume $u_i(t)$ results from all-to-all inter-oscillator coupling so that $u_i(t) = (K/N)\sum_{j=1}^{N} c(\mathbf{x}_i, \mathbf{x}_j) = (K/N)\sum_{j=1}^{N} f(\theta_i, \theta_j) + \mathscr{O}(\varepsilon)$. Here, $K > 0$, c is a function of the states of each oscillator, and f can be determined by evaluating c on a given oscillator's limit cycle. With these definitions, (3) can be rewritten to leading order ε,

$$\dot{\theta}_i = \omega_i - \varepsilon Z_i(\theta_i)\left(\frac{K}{N}\sum_{j=1}^{N} f(\theta_i, \theta_j)\right). \tag{4}$$

Note that $f(\theta)$ is a 2π periodic function in both θ_i and θ_j. An equation of the form (4) is general enough to describe, for instance, chemical synaptic coupling [7], or voltage difference coupling [12] in a network of neurons. For the remainder of the analysis, we will assume that $Z_i(\theta)$ and $f(\theta_i, \theta_j)$ are both bounded functions. To allow for heterogeneity in (4), we will take $\omega_i = \omega_o + \Delta\omega_i \in [\omega_o - \Delta\omega, \omega_o + \Delta\omega]$ with $\Delta\omega \geq 0$ and $Z_i(\theta) \in [Z_{\min}(\theta), Z_{\max}(\theta)]$ where $Z_{\min}(\theta)$ and $Z_{\max}(\theta)$ respectively represent the maximum and minimum values that any Z_i can take.

To begin, we first let $\phi_j = \theta_j - \omega_o t$ so that (4) becomes

$$\dot{\phi}_i = \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N} Z_i(\phi_i + \omega_o t) f(\phi_i + \omega_o t, \phi_j + \omega_o t). \tag{5}$$

Additionally, we define $\varphi_{i,j} = \phi_i - \phi_j$ and write

$$\dot{\phi}_i = \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N} Z_i(\varphi_{i,j} + \phi_j + \omega_o t) f(\varphi_{i,j} + \phi_j + \omega_o t, \phi_j + \omega_o t). \tag{6}$$

Noting that (6) is T-periodic, with $T = 2\pi/\omega_o$, its dynamics can be approximated using averaging theory, [21], [8]

$$\begin{aligned}\dot{\vartheta}_i &= \frac{1}{T}\int_0^T \Big[\Delta\omega_i \\ &\quad - \frac{\varepsilon K}{N}\sum_{j=1}^{N} Z_i(\varphi_{i,j} + \phi_j + \omega_o t) f(\varphi_{i,j} + \phi_j + \omega_o t, \phi_j + \omega_o t)\Big] dt \\ &= \Delta\omega_i - \frac{\varepsilon K}{TN}\int_0^T \left[\sum_{j=1}^{N} Z_i(\varphi_{i,j} + \omega_o t) f(\varphi_{i,j} + \omega_o t, \omega_o t)\right] dt.\end{aligned} \tag{7}$$

Note that in the last line of (7), ϕ_j can be neglected because it is common to all terms in the T-periodic integrand. Next, we will let $Z_i(\theta) = \overline{Z}(\theta) + \Delta Z_i(\theta)$ where

$$\begin{aligned}\overline{Z}(\theta) &= (Z_{\max}(\theta) + Z_{\min}(\theta))/2, \\ \Delta Z_i(\theta) &= Z_i(\theta) - \overline{Z}(\theta).\end{aligned} \tag{8}$$

We then rewrite (7) as follows:

$$\begin{aligned}\dot{\vartheta}_i &= \Delta\omega_i - \frac{\varepsilon K}{TN}\int_0^T \Bigg[\sum_{j=1}^{N}\left(\overline{Z}(\varphi_{i,j} + \omega_o t) + \Delta Z_i(\varphi_{i,j} + \omega_o t)\right) \\ &\qquad \times f(\varphi_{i,j} + \omega_o t, \omega_o t)\Bigg] dt \\ &= \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N}\underbrace{\frac{1}{T}\int_0^T \left[\left(\overline{Z}(\varphi_{i,j} + \omega_o t) f(\varphi_{i,j} + \omega_o t, \omega_o t)\right)\right] dt}_{\Gamma_i^{\text{common}}(\varphi_{i,j})} \\ &\quad + \frac{\varepsilon K}{N}\sum_{j=1}^{N}\underbrace{\frac{1}{T}\int_0^T \left[\Delta Z_i(\varphi_{i,j} + \omega_o t) f(\varphi_{i,j} + \omega_o t, \omega_o t)\right] dt}_{\Gamma_i^{\text{individual}}(\varphi_{i,j})} \\ &= \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N}\left(\Gamma_i^{\text{common}}(\varphi_{i,j}) + \Gamma_i^{\text{individual}}(\varphi_{i,j})\right) \\ &= \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N}\Gamma_i(\varphi_{i,j}).\end{aligned} \tag{9}$$

Here, Γ_i^{common} represents a phase difference coupling common to each oscillator, $\Gamma_i^{\text{individual}}$ is a phase difference determined by the particular value of $Z_i(\theta_i)$, and Γ_i represents the total phase difference coupling for oscillator i. We note that if the terms in the right hand side of (9) are small enough ϑ_i will be a good approximation of ϕ_i [21], [8]. We are now in a position to state and prove the following theorem:

Theorem 2.1: Sufficient Conditions for Phase Cohesion and Frequency Synchronization

For some some $\gamma \in (0, \pi)$ consider the following conditions:

(1) For all i and j, $\min_{a \in [0,\gamma]}[\Gamma_i(a) - \Gamma_j(a - \gamma)] \geq 2\Delta\omega/(\varepsilon K)$

(2) For all i, there exists $\delta_i > 0$ such that when $-\gamma \leq \varphi \leq \gamma$, $\frac{d}{d\varphi}\Gamma_i(\varphi) > \delta_i$

If **(1)** is satisfied, then:

(i) if $\max_{i,j}|\vartheta_i(t_0) - \vartheta_j(t_0)| \leq \gamma$ for some t_0, it follows that, $|\vartheta_i(t) - \vartheta_j(t)| \leq \gamma$ for all $t > t_0$.

If **(1)** and **(2)** are satisfied, then:

(ii) if $\max_{i,j}|\vartheta_i(t_0) - \vartheta_j(t_0)| \leq \gamma$, for some $t = t_0$, the network (7) is exponentially frequency synchronized.

We note that Theorem 2.1 is only valid for the averaged system equations (7). However if the inter-oscillator coupling is small enough, then ϑ_i is well approximated by θ_i. If additionally the averaged equations (7) achieve stable frequency synchronization, then the unaveraged equations (4) will have an associated stable periodic orbit when the coupling is small enough, as discussed in [21] and [8].

Proof:

(1 $\implies$ (i)) Suppose $\max_{i,j}|\vartheta_i(t_0) - \vartheta_j(t_0)| = \gamma$. Consider a subset of any two oscillators from the larger population ϑ_m and ϑ_n such that $\vartheta_m(t_0)-\vartheta_n(t_0)=\gamma$. Using (9) we may write

$$\dot{\vartheta}_m-\dot{\vartheta}_n=\Delta\omega_m-\Delta\omega_n-\frac{\varepsilon K}{N}\sum_{j=1}^{N}\left(\Gamma_m(\varphi_{m,j})-\Gamma_n(\varphi_{n,j})\right). \tag{10}$$

For all j, we know that $\gamma=\varphi_{m,j}(t_0)-\varphi_{n,j}(t_0)$. Using condition 1, we can provide an upper bound for (10)

$$\begin{aligned}\dot{\vartheta}_m-\dot{\vartheta}_n&=\Delta\omega_m-\Delta\omega_n-\frac{\varepsilon K}{N}\sum_{j=1}^{N}\left(\Gamma_m(\varphi_{m,j})-\Gamma_n(\varphi_{m,j}-\gamma)\right)\\&\leq 2\Delta\omega-\frac{\varepsilon K}{N}\sum_{j=1}^{N}(2\Delta\omega/\varepsilon K)=0. \qquad (11)\end{aligned}$$

Equation (11) implies that the phase difference of any two oscillators cannot grow larger than γ, therefore, the maximum phase difference between any two oscillators is upper bounded by γ for $t>t_0$ which implies statement (i).

(1) and **(2)** $\implies$ **(ii)** Suppose $\max\limits_{i,j}|\vartheta_i(t_0)-\vartheta_j(t_0)|=\gamma$. From (i) we know that the maximum phase difference between any two oscillators will be upper bounded by γ for all future time. Noting that we can write $\varphi_{i,j}=\vartheta_i-\vartheta_j$, we take the time derivative of (9)

$$\frac{d}{dt}\dot{\vartheta}_i=-\sum_{j=1}^{N}a_{i,j}(t)(\dot{\vartheta}_i-\dot{\vartheta}_j), \tag{12}$$

where $a_{i,j}(t)=\frac{\varepsilon K}{N}\frac{d}{d\varphi}\Gamma_i(\varphi)|_{\vartheta_i(t)-\vartheta_j(t)}$. We can rewrite (12) as a linear time-varying consensus algorithm

$$\frac{d}{dt}\dot{\vartheta}=L(t)\dot{\vartheta}, \tag{13}$$

where $\vartheta=[\vartheta_1,\vartheta_2,\ldots,\vartheta_N]^T$, and L is a matrix with diagonal terms $L_{i,i}(t)=-\sum_{j\neq i}^{N}a_{i,j}(t)$, and off-diagonal terms $L_{i,j}(t)=a_{i,j}(t)$. Notice that the row sums of L are always equal to zero. We know that the off-diagonal terms $a_{i,j}(t)>\frac{\varepsilon K}{N}\delta_i>0$, are bounded, and continuous functions of time. Furthermore, at each time instant, the matrix is fully populated so that, in the graph theoretical sense [4], any node is reachable from any other node. We invoke Theorem 1 from [17] to conclude that all components $\frac{d}{dt}\dot{\vartheta}_i$ must exponentially approach the same value (i.e. they achieve consensus). Suppose now that $\lim_{t\to\infty}\frac{d}{dt}\dot{\vartheta}\neq 0$, where 0 is an appropriately sized vector of zeros. Then when the population achieves consensus, for all i, $\dot{\vartheta}_i$ is unbounded in time. We know, however, from (9) that this is not possible, since Γ_i is a bounded function so that $\dot{\vartheta}_i$ cannot be arbitrarily large. Therefore, when the population achieves consensus, $\frac{d}{dt}\dot{\vartheta}=0$. Thus, for each i, $\dot{\vartheta}_i$ will approach a constant. Suppose that there exist some i and j such that $\lim_{t\to\infty}\dot{\vartheta}_i=\omega_i^*$ and $\lim_{t\to\infty}\dot{\vartheta}_j=\omega_j^*$ with $\omega_i^*\neq\omega_j^*$. If this is the case, then at some time τ, $|\vartheta_i(\tau)-\vartheta_j(\tau)|=\pi$, which contradicts (i), thereby implying statement (ii). ■

A. A Practical Upper Bound for the Critical Coupling Strength

If the phase response curve of each oscillator is explicitly known, Theorem 2.1 could be applied in a straightforward way, computing each $\Gamma_i(\varphi)$ individually. However, when N is large, this could be a very time consuming process. Furthermore, as is often the case with biological systems [25], the phase response curves may not be known *a priori*, and measuring them may not be possible. In these cases, we provide a strategy to determine an upper bound for the critical coupling strength without the need to determine any individual phase response curves.

For a general system, from equation (9), $\Gamma_i(\varphi_{i,j})$ can be written as the sum of two terms

$$\Gamma_i(\varphi_{i,j})=\Gamma_i^{\text{common}}(\varphi_{i,j})+\Gamma_i^{\text{individual}}(\varphi_{i,j}). \tag{14}$$

The contribution Γ_i^{common} is the same among all oscillators, but $\Gamma_i^{R,\text{individual}}$ depends on the specific phase response curve of oscillator i. Recalling the definition given in equation (8), for any oscillator, $|\Delta Z_i(\theta)|\leq(Z_{\max}(\theta)-Z_{\min}(\theta))/2\equiv Z_d(\theta)$, giving the bound

$$\begin{aligned}-\frac{1}{T}\int_0^T&\Big[\big|Z_d(\varphi_{i,j}+\omega_o t)f(\varphi_{i,j}+\omega_o t,\omega_o t)\big|\Big]dt\\&\leq\Gamma_i^{\text{individual}}(\varphi_{i,j})\\&\quad\leq\frac{1}{T}\int_0^T\Big[\big|Z_d(\varphi_{i,j}+\omega_o t)f(\varphi_{i,j}+\omega_o t,\omega_o t)\big|\Big]dt.\end{aligned} \tag{15}$$

Equation (15) can be used to calculate upper and lower bounds on $\Gamma_{\max}(\varphi)=\max\limits_i(\Gamma_i(\varphi))$ and $\Gamma_{\min}(\varphi)=\min\limits_i(\Gamma_i(\varphi))$, the maximum and minimum possible coupling functions, respectively, for any oscillator in the population. Keeping in mind condition 1 from Theorem 2.1, one can verify the following upper bound on K_c, the critical coupling strength for phase cohesion in the network:

$$\varepsilon K_c\leq\frac{2\Delta\omega}{\beta},\quad\beta=\max_{\gamma\in(0,\pi)}\left[\min_{a\in[0,\gamma]}[\Gamma_{\min}(a)-\Gamma_{\max}(a-\gamma)]\right]. \tag{16}$$

The upper bound (16) may appear onerous at first glance, but is straightforward to calculate after $\Gamma_{\min}$ and $\Gamma_{\max}$ have been determined.

If we also require a guarantee of frequency synchronization, from condition 2 from Theorem 2.1, the derivatives of the phase difference coupling must always be positive and bounded away from zero. Similar to the strategy used above, we can take the derivative of (14) to yield

$$\begin{aligned}\frac{d}{d\varphi}\Gamma_i(\varphi)=\frac{1}{T}\int_0^T&\Bigg[\left(\overline{Z}(\varphi+\omega_o t)f(\varphi+\omega_o t,\omega_o t)\right)'\\&+\Delta Z_i'(\varphi+\omega_o t)f(\varphi+\omega_o t,\omega_o t)\\&+\Delta Z_i(\varphi+\omega_o t)f'(\varphi+\omega_o t,\omega_o t)\Bigg]dt\\\geq\frac{1}{T}\int_0^T&\Bigg[\left(\overline{Z}(\varphi+\omega_o t)f(\varphi+\omega_o t,\omega_o t)\right)'\\&+\min\Big(\Delta Z_i'(\varphi+\omega_o t)f(\varphi+\omega_o t,\omega_o t)\\&+\Delta Z_i(\varphi+\omega_o t)f'(\varphi+\omega_o t,\omega_o t)\Big)\Bigg]dt\end{aligned} \tag{17}$$

where $' \equiv d/d\varphi$. If we wish to guarantee that condition 2 from Theorem 2.1, holds, we can restrict γ to include only values for which $\frac{d}{d\varphi}\Gamma_i(\varphi)$ is guaranteed to be positive and bounded away from zero for $|\varphi| \leq \gamma$ for any oscillator in the population.

B. A Lower Bound for the Critical Coupling Strength

Here, we adapt a strategy employed to lower bound the critical coupling for Kuramoto oscillators [11]. Suppose the population of oscillators is in a frequency synchronized state. Consider any two oscillators within this population. From (9), we can write

$$\dot{\vartheta}_m - \dot{\vartheta}_m = 0 = (\Delta\omega_m - \Delta\omega_n) - \frac{\varepsilon K}{N}\sum_{j=1}^{N}(\Gamma_m(\varphi_{m,j}) - \Gamma_n(\varphi_{n,j})). \tag{18}$$

Because (18) holds for any choice of oscillator, we can write

$$\varepsilon K_c \geq \frac{2\Delta\omega}{\max\limits_{\varphi}\left(\Gamma_{\max}(\varphi)\right) - \min\limits_{\varphi}\left(\Gamma_{\min}(\varphi)\right)}. \tag{19}$$

Here, we can use the bounds (15) to determine the maximum and maximum that the functions in the denominator can attain, thereby lower bounding the critical coupling strength. We note that (19) is also valid for phase cohesion, because if the distance between oscillators is constrained to be less than $\gamma \geq 0$, there must be some time at which $\dot{\vartheta}_m - \dot{\vartheta}_m = 0$ (or becomes arbitrarily close to zero), otherwise the phase differences between oscillators would be unbounded.

C. Promoting Synchronization with Additional External Forcing

When inter-oscillator coupling is not sufficient to synchronize the population, an additional external perturbation common to all oscillators may be used to promote synchronization. Consider the network of oscillators (4) with the addition of a periodic common external forcing $\varepsilon u_{\text{ext}}(\theta_{\text{ext}})$ where $\theta_{\text{ext}} \in [0, 2\pi)$ is the external stimulus phase which evolves according to $\theta_{\text{ext}}(t) = \theta_{\text{ext}}(0) + \omega_o t$;

$$\dot{\theta}_i = \omega_o + \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N} Z_i(\theta_i) f(\theta_i, \theta_j) + \varepsilon\eta Z(\theta_i) u_{\text{ext}}(\theta_{\text{ext}}). \tag{20}$$

Here, $\eta > 0$ determines the magnitude of external forcing. Letting $\phi_j = \theta_j - \omega_o t$ and $\phi_{\text{ext}} = \theta_{\text{ext}} - \omega_o t$, we may rewrite (20) as

$$\begin{aligned}\dot{\phi}_i &= \Delta\omega_i \\ &\quad - \frac{\varepsilon K}{N}\sum_{j=1}^{N} Z_i(\phi_i + \omega_o t) f(\phi_i + \omega_o t, \phi_j + \omega_o t) \\ &\quad + \varepsilon\eta Z_i(\phi_i + \omega_o t) u_{\text{ext}}(\theta_{\text{ext}} + \omega_o t).\end{aligned} \tag{21}$$

Because (21) is T-periodic, where $T = 2\pi/\omega_o$, in an analogous strategy used in the reduction of (5) from Section II, we define $\varphi_{i,j} = \phi_i - \phi_j$ and $\varphi_{i,\text{ext}} = \phi_i - \theta_{\text{ext}}$. When the terms in the right hand side of (21) are small, using averaging [21], [8] it can be approximated by

$$\begin{aligned}\dot{\vartheta}_i &= \Delta\omega_i \\ &\quad - \frac{\varepsilon K}{N}\int_0^T \frac{1}{T}\left[\sum_{j=1}^{N} Z_i(\varphi_{i,j} + \phi_j + \omega_o t)\right. \\ &\qquad\qquad \left. \times f(\varphi_{i,j} + \phi_j + \omega_o t, \phi_j + \omega_o t)\right] dt \\ &\quad + \varepsilon\eta \underbrace{\int_0^T \left[\frac{1}{T} Z_i(\varphi_{i,\text{ext}} + \theta_{\text{ext}} + \omega_o t) u_{\text{ext}}(\theta_{\text{ext}} + \omega_o t)\right] dt}_{S_i(\varphi_{i,\text{ext}})} \\ &= \Delta\omega_i - \frac{\varepsilon K}{N}\sum_{j=1}^{N}\Gamma_i(\varphi_{i,j}) + \varepsilon\eta S_i(\varphi_{i,\text{ext}}).\end{aligned} \tag{22}$$

Note that in (22), the term θ_{ext} can be neglected in the T-periodic integrand. Recall that Γ_i was defined in equation (9). As in (14), we may write $S_i(\varphi_{i,\text{ext}})$ as the sum of contributions from the part of the PRC common to all oscillators and the part of the PRC unique to each oscillator

$$\begin{aligned}S_i^{\text{common}}(\varphi_{i,\text{ext}}) &= \frac{1}{T}\int_0^T \left[\overline{Z}(\varphi_{i,\text{ext}} + \omega_o t) u_{\text{ext}}(\omega_o t)\right] dt \\ S_i^{\text{individual}}(\varphi_{i,\text{ext}}) &= \frac{1}{T}\int_0^T \left[\Delta Z_i(\varphi_{i,\text{ext}} + \omega_o t) u_{\text{ext}}(\omega_o t)\right] dt.\end{aligned} \tag{23}$$

With these definitions, we can determine the following bound

$$\begin{aligned}&-\frac{1}{T}\int_0^T \left[\left|Z_d(\varphi_{i,\text{ext}} + \omega_o t) u_{\text{ext}}(\omega_o t)\right|\right] dt + S_i^{\text{common}}(\varphi_{i,\text{ext}}) \\ &\quad \leq S_i(\varphi_{i,\text{ext}}) \\ &\quad \leq \frac{1}{T}\int_0^T \left[\left|Z_d(\varphi_{i,\text{ext}} + \omega_o t) u_{\text{ext}}(\omega_o t)\right|\right] + S_i^{\text{common}}(\varphi_{i,\text{ext}}).\end{aligned} \tag{24}$$

We define the upper and lower bounds on (24) to be $S_{\max}$ and $S_{\min}$, respectively. Suppose, in the spirit of Theorem 2.1, for some $\gamma \in (0, \pi)$ we want to know if the population of oscillators will be phase cohesive with an associated arc length of γ. To this end, suppose that at some time t_0, for all i and j, $|\vartheta_i(t_0) - \vartheta_j(t_0)| \leq \gamma$. Then, by examining any two oscillators for which $\vartheta_m(t_0) - \vartheta_n(t_0) = \gamma$, using (22) we may write

$$\begin{aligned}\dot{\vartheta}_m - \dot{\vartheta}_n = (\Delta\omega_m - \Delta\omega_n) - &\left[\frac{\varepsilon K}{N}\sum_{j=1}^{N}(\Gamma_m(\varphi_{m,j}) - \Gamma_n(\varphi_{n,j}))\right. \\ &\left. + \varepsilon\eta\left(S_n(\varphi_{n,\text{ext}}) - S_m(\varphi_{m,\text{ext}})\right)\right].\end{aligned} \tag{25}$$

We know that $\varphi_{m,j}(t_0) - \varphi_{n,j}(t_0) = \varphi_{m,\text{ext}}(t_0) - \varphi_{n,\text{ext}}(t_0) = \gamma$. Suppose that $\vartheta_m(t_0) \geq \theta_{\text{ext}}(t_0) \geq \vartheta_n(t_0)$. Then, for all i, $|\varphi_{i,\text{ext}}(t_0)| \leq \gamma$. Let

$$\begin{aligned}\mu = \max_{\gamma\in(0,\pi)} &\left[\varepsilon K \min_{a\in[0,\gamma]}\Big(\Gamma_{\min}(a) - \Gamma_{\max}(a - \gamma)\Big)\right. \\ &\left. + \varepsilon\eta \min_{a\in[0,\gamma]}\Big(S_{\min}(a - \gamma) - S_{\max}(a)\Big)\right].\end{aligned} \tag{26}$$

Using (25), if $\mu \geq \max_{i,j}(\Delta\omega_i - \Delta\omega_j)$, then, for some value of γ, $\dot{\vartheta}_m - \dot{\vartheta}_n \leq 0$, implying that the network is phase cohesive.

When η from equation (26) is zero (i.e. the external forcing is zero), μ is identical to β from equation (16). If the internal coupling between oscillators is not strong enough to guarantee phase cohesiveness, then an external periodic stimulus may be used to provide an additional synchronizing influence. According to this result, the external stimulus must be close in period to the natural period of each oscillator, and the stimulus phase must be between the phases of the largest and smallest oscillators. In this work, we do not give a specific procedure for finding stimuli to promote synchronization, but in a related problem, [26] found that useful stimuli could be designed by providing a negative (resp. positive) external perturbation when the of the derivative of the PRC $(dZ/d\theta)$ is positive (resp. negative) and large in magnitude relative to the allowable spread in the PRCs $(Z_d(\theta))$.

III. NUMERICAL CRITICAL COUPLING RESULTS IN A POPULATION OF NEURAL OSCILLATORS

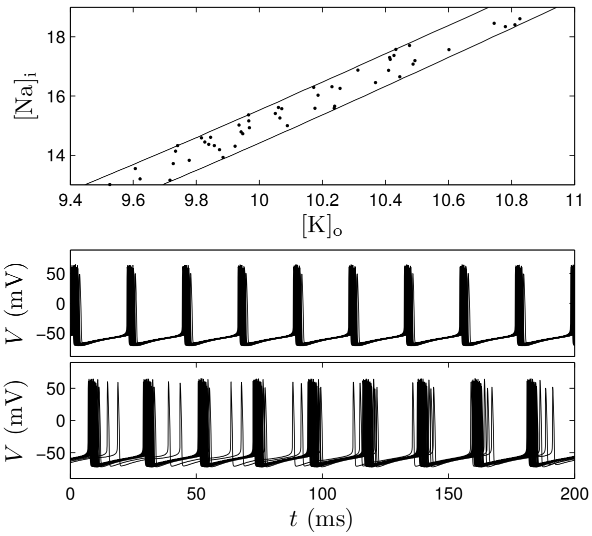

Fig. 1. The top panel shows an example of 50 randomly chosen ion concentrations for (27) from a region shown between solid lines. Voltage traces for an example network of $N = 50$ neurons from (27) after initial transients have died out. In the middle panel $K = 0.019 > K_c$. In the bottom panel, $K = 0.015 < K_c$.

We consider a six-dimensional conductance-based model for a neural network with intracellular and extracellular ion concentration dynamics [13]. For convenience of notation, the explicit order ε dependence on the coupling strength is dropped in the following example. The synaptically coupled transmembrane voltage dynamics are given by

$$\begin{aligned} C\dot{V}_j =& f_V(V_j, n_j, h_j, [\mathrm{K}]_{\mathrm{o_j}}, [\mathrm{Na}]_{\mathrm{i_j}}, [\mathrm{Ca}]_{\mathrm{i_j}}) \\ &+ \frac{K}{N}\sum_{k=1}^{N}(V_j - V_G)s_k(t-\tau), \qquad j = 1,\dots,N \qquad (27) \end{aligned}$$

Here, K is the maximal conductance, N is the total number of neurons, $V_G = 60\mathrm{mV}$ so that the synapses are inhibitory, $\tau = 2\mathrm{ms}$ is a constant time delay, and s_k is the synaptic variable of neuron j which evolves according to (c.f. [7])

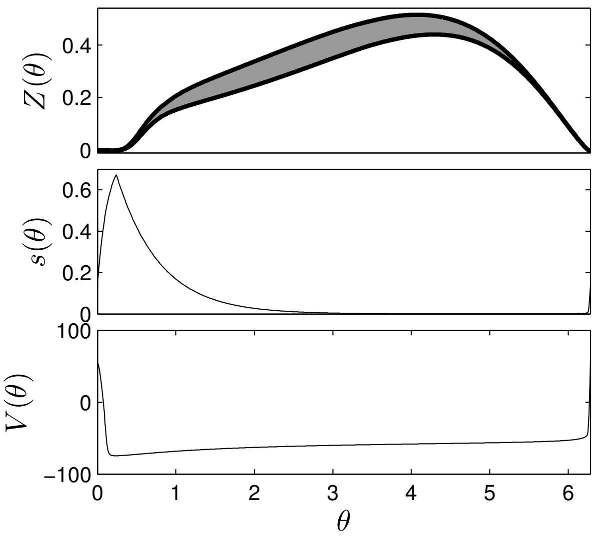

Fig. 2. This choice of ion concentrations from Figure 1 produces PRCs for neurons which lie within the shaded region in the top panel. The middle and bottom panels give approximate values of the synaptic variable s and transmembrane voltage variable V as a function of θ for each neuron.

$$\dot{s}_j = \alpha(1 - s_j)(1/(1 + \exp(-(V_j - V_T)/\sigma_T))) - \beta_2 s_j, \quad (28)$$

where $\alpha = 2$, $V_T = -37$, $\sigma_T = 2$, and $\beta_2 = 0.6$. For a full description of all functions and parameters from (27), we refer the reader to [13], and unless otherwise stated, parameter values and dynamics are identical to those in [13]. Throughout the trials, the intracellular sodium ($[\mathrm{Na}]_\mathrm{i}$) and extracellular potassium ($[\mathrm{K}]_\mathrm{o}$) concentrations are taken to be constant, and uniformly randomly sampled from the region in the top panel of Figure 1. For this choice of ion concentrations, the resulting natural periods of oscillation are between 20 and 21 milliseconds, and the resulting PRCs always lie within the grey band shown in the top panel of Figure 2. In an example network of $N = 50$ neurons shown in the middle and bottom panels of Figure 1, we find that for $K \approx 0.017$ neurons fire periodically in a phase cohesive manner. In the absence of coupling, the dynamic equations describing each neuron asymptotically approach a limit cycle, for which we assume that in the limit of small coupling, s_i and V_i are well approximated as functions of θ_i, shown in the middle and bottom panels of Figure 2, respectively. When we make this assumption, we can rewrite (27) in the same form as (4) and straightforwardly apply our bounding methodology from Section II. Equation (15) is used to calculate $\Gamma_{\max}$ and $\Gamma_{\min}$, shown in the top panel of Figure 3. These bounds are then used to calculate upper and lower bounds on the critical coupling strength required for phase cohesion using (16) and (19), respectively, shown as dashed lines in the bottom panel of Figure 3. Over multiple trials, we simulate (27) with different values of N for different realizations of randomly chosen ionic concentrations. For each trial, we slowly and incrementally lower the coupling strength, K, and take K_c to be value of K just before the neurons are no longer phase cohesive. Bars in the bottom panel of Figure 3 represent the maximum and minimum values of K_c over 80 trials, with the average value of K_c shown with an 'x'. The upper bound and lower bound on K_c is about 1.5 times larger and 3.5 times smaller, respectively, than the average numerically determined value of K_c.

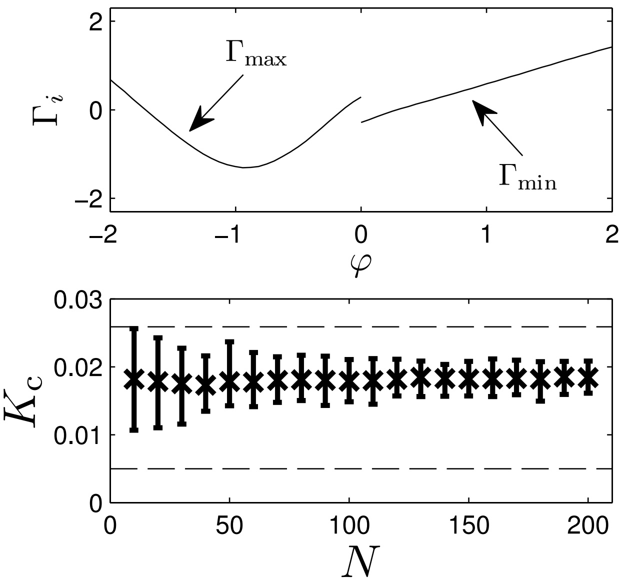

Fig. 3. The top panel shows $\Gamma_{\min}$ and $\Gamma_{\max}$ to calculate upper and lower bounds in (16) and (19). The bottom panel gives the maximum and minimum critical coupling values over 80 samples of neurons randomly chosen from a uniforn distribution for each choice of N. The average value of K_c is represented with an 'x' and the bars represent the maximum and minimum values of K_c.

IV. CONCLUSION

We have derived a necessary and a sufficient condition for frequency synchronization and phase cohesion in an all-to-all network of biologically realistic oscillators with arbitrarily distributed natural frequencies and phase response curves. These conditions can be used to determine upper and lower bounds for critical coupling for synchronization for a population of phase oscillators with both arbitrarily distributed natural frequencies and phase response curves. In a network of neural oscillators, we find that these bounds are reasonably tight. Furthermore, when the differences in natural frequencies between oscillators and the coupling strength is sufficiently small, this bounding procedure can be adapted to capture the influence of an external perturbation common to all oscillators. We note that contraction theory [15], [22] cannot be straightforwardly applied to the problem of finding the critical coupling strength in the network (4) because the uncertainty in network parameters may not be known *a priori*.

Further investigation into this bounding procedure could be useful when applied to biological problems where synchronization plays an important role. For instance, various authors have investigated external perturbations to inhibit pathological entrainment in neural networks that may have relevance to Parkinson's disease [9], [20], [27]. Using bounding methodologies similar to those in this manuscript, one could investigate how different pharmacological agents could modify network parameters which increase either upper or lower bounds on the critical coupling strength.

The methodology presented in this manuscript is not without limitations. Current results are derived assuming all-to-all coupling between oscillators, which represents an oversimplification of most biological networks. Future work will adapt these consensus results to be used with more general coupling topologies. Also, because biological networks rarely take the form (1) (i.e. coupled through phase differences), both phase reduction [28], [10] and dynamical averaging [21], [8] must be used to manipulate the governing equations to take the form used in this work. As with all methodologies that rely on these reduction strategies, current theoretical results are valid in the limit that the coupling between oscillators is weak, and derived bounds may break down as the interaction between oscillators becomes stronger. Even if this is the case, however, analysis in the limit of weak coupling generally provides qualitative information about how a network behaves as coupling becomes stronger. Furthermore, analytical bounds on the critical coupling strength are derived for (4) which is an order ε approximation for the phase reduction of (3) and future work will be devoted to understanding how the neglected $\mathcal{O}(\varepsilon^2)$ terms influence frequency synchronization and phase cohesion in the network.

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