Maximizing relaxation time in oscillator networks with implications for neurostimulation

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***Abstract*— High frequency deep brain stimulation (HF-DBS) is a pervasive clinical neurostimulation paradigm in which rapid ($>$ 100Hz) pulses of electrical current are invasively delivered to the brain. Here, we use dynamical systems analysis to provide hypotheses regarding the frequency-specificity of the therapeutic effects of HF-DBS. Using phase oscillator-based models, we study the relaxation time of a synchronized network following impulsive stimulation. In particular, by approximating a standard DBS pulse by a finite-energy (Dirac) delta function, we show the existence of a minimum bound on the frequency of stimulation necessary to keep the network in a desynchronized regime. If, as evidence suggests, pathological synchronization is central to the pathology in DBS-responsive disorders, then the analysis gives conceptual insight into why lower frequency and/or randomized stimulation therapy is less effective, and provides a way to study alternative design strategies.**

I. Introduction

High frequency deep brain stimulation (HF-DBS) is among the most established and widely-used forms of therapeutic neurostimulation, particularly in the treatment of Parkinson's Disease (PD). In HF-DBS, rectangular charge-balanced electrical pulses (see Fig. 1) are delivered at frequencies in excess of 100Hz via an invasively implanted electrode. Significant research effort has been directed toward understanding the therapeutic mechanisms of HF-DBS (see, e.g., [1], [2], and the references therein). In the context of PD in particular, recent hypotheses point to a putative desynchronization of neuronal activity [3], [2] as being central to the efficacy of the treatment. Such a mechanism is supported by evidence that oscillatory synchrony is tightly associated with the neuropathology of PD [4], [5].

A persistent question in the clinical implementation of HF-DBS relates to the selection of the so-called stimulation parameters (pulse-width, frequency, etc.), which affect the treatment efficacy and vary between patients. Computational models have been used as a means to study these parameters in biophysically detailed settings [2], [6], [7]. We note, furthermore, several empirical observations concerning frequency-sensitivity of the therapeutic effect. First, it has been shown in DBS studies that low frequency stimulation ($<$ 100 Hz) is therapeutically less effective in treating symptoms [3], [8]. Similarly, when the stimulation pulse is delivered according to a Poisson process, efficacy worsens, even if the mean rate is commensurate with conventional HF-DBS [9]. In this paper, we present a dynamical hypothesis concerning this frequency-sensitivity through the use of dynamical systems analysis of underactuated, networked oscillator models.

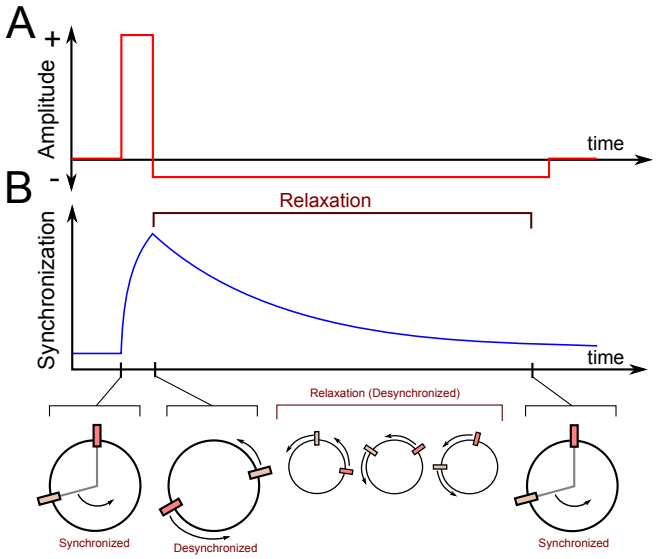

Fig. 1. (A) A standard charge-balanced pulse design used in high frequency deep brain stimulation (HF DBS) where a short duration large amplitude cathodic part is followed by a long duration small amplitude anodic part. (B) Dynamical response of coupled oscillators to a common input in the form of (A). The impulsive action of the cathodic part in (A) drives the state of the oscillators to a 'desynchronized state'. During the relatively mild action of the anodic part, the oscillators relax from the 'desynchronized state' to the 'synchronized state'.

Specifically, under the aforementioned assumption that (de-)synchronization is central to the therapeutic effect of HD-DBS, we consider the actions of a rectangular pulse acting as a common input to a network of phase oscillators of the Kuramoto-form, where each oscillator models a highly-reduced set of dynamics for a neuron, parameterized to produce global network synchronization [10], [11]. The pulse in Fig. 1 (A) can, in the dynamical sense, be understood as creating two epochs: (i) a brief, temporally punctate forcing epoch in which the phases of oscillators are driven apart (Fig. 1 (B)); and (ii) a longer epoch in which the network is relatively unforced and phases relax to the dynamical fixed points of the network, i.e., a synchronized state (Fig. 1 (B)). The key idea is that, in order to avoid excessive synchronization, this relaxation epoch must be sufficiently brief. By approximating the cathodic part of the pulse as a Dirac-delta function, we establish an upper-bound for

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the relaxation time, which amounts to a lower-bound of the frequency at which de-synchronization is maintained. Thus, we provide a way of conceptually understanding the degradation in therapeutic efficacy of low frequency and randomized patterns of stimulation from the perspective of dynamical systems.

The rest of the paper is organized as follows: In Section II, we describe the oscillator network model and define metrics of synchronization. In Section III, we compute the relaxation time. Then, in Section IV, we establish a bound on the frequency of stimulation by maximizing relaxation time between consecutive pulses. The paper ends with Discussion and Conclusions.

II. Preliminaries

A. Oscillator Network Model

We consider a population of interacting neuronal oscillators, modeled with the standard Kuramoto formalism as follows:

$$\frac{\mathrm{d}\theta_{\mathrm{i}}(\mathrm{t})}{\mathrm{dt}} = \omega_i - \frac{K}{N}\sum_{j=1}^{N}\sin(\theta_i(t)-\theta_j(t)) + \alpha_i u(t) \qquad (1)$$

Here $\theta_i(t) \in [0, 2\pi]$ for $i = 1, 2, \cdots, N$ represents the phase of the i^{th} oscillator at time t; N is the total number of oscillators; ω_i is the natural frequency of oscillation of the i^{th} oscillator; K is the global coupling gain parameter. The parameter α_i for $i = 1, 2, \cdots, N$ determines the effect of the common external input $u(t)$ (i.e., the stimulation input) on the i^{th} oscillator.

We define $\phi_i(t) = \theta_i(t) - \theta_N(t)$ as the phase difference between i^{th} and the N^{th} oscillator at time t. Clearly, $\phi_i(t) \in [-\pi, \pi]$ for $i = 1, 2, \cdots, N-1$ and $t \geq 0$ is periodic with a period of 2π. Rewriting Eq. 1 in terms of $\phi_i(t)$ for $i = 1, 2, \cdots, N-1$ with $\omega_{i,N} \equiv \omega_i - \omega_N$ and $\alpha_{i,N} \equiv \alpha_i - \alpha_N$, we obtain

$$\begin{aligned}\frac{\mathrm{d}\phi_{\mathrm{i}}(\mathrm{t})}{\mathrm{dt}} = \omega_{i,N} - \frac{K}{N}\sum_{j=1}^{N}(\sin(\phi_i(t)-\phi_j(t)) + \sin(\phi_j(t))) \\ + \alpha_{i,N}u(t)\end{aligned} \qquad (2)$$

The model (1) is a highly reduced dynamical representation of interacting neurons, where each neuron is assumed to be intrinsically oscillating. It is a frequently used model for tractable analysis of synchronization and other properties of neuronal networks [11].

Remark 1: The system (1) is an *underactuated* system, i.e., the input $u(t)$ is common to all oscillators in the system and no individual oscillator is addressed with its own independent input. Underactuation is a property of many neurostimulation technologies [12].

B. Definitions and Assumptions

Definition 1: The oscillator network defined by Eq. 1 is said to be:

1) *Frequency synchronized* if $|\frac{\mathrm{d}\phi_{\mathrm{i}}(\mathrm{t})}{\mathrm{dt}}| = 0$ for all $i = 1, 2, \cdots, N-1$ and for all $t \in \mathbb{R}$ where $\mathbb{R}$ is the real one dimensional space.
2) *Asymptotically frequency synchronized* if $\lim_{t\to\infty}|\frac{\mathrm{d}\phi_{\mathrm{i}}(\mathrm{t})}{\mathrm{dt}}| = 0$ for all $i = 1, 2, \cdots, N-1$.
3) *Desynchronized* at time t if $|\frac{\mathrm{d}\phi_{\mathrm{i}}(\mathrm{t})}{\mathrm{dt}}| > 0$ for at least one $i \in \{1, 2, \cdots, N-1\}$.

Assumption 1: The global coupling gain parameter K in Eq. 1 is greater than the critical coupling gain parameter K_c [13] such that the system (1), with $u(t) = 0$, exhibits a stable synchronized state (fixed point).

Definition 2: We define $B_\varepsilon(\phi_0) = \{\phi \in [-\pi, \pi]^{N-1} : ||\phi - \phi_0|| \leq \varepsilon\} \backslash \{\phi_0\}$ as an arbitrary small $\varepsilon(> 0)$ ball centered around $\phi_0 \in [-\pi, \pi]^{N-1}$. Here $\phi = \{\phi_1, \phi_2, \cdots, \phi_{N-1}\}^T$.

Definition 3 (Relaxation Time): Let the system (2) have an initial condition $\phi(0) = \phi_0$ that lies within the region of attraction of the stable fixed point, denoted ϕ^s_{eq}, of Eq. 2. We define the *relaxation time*, T, as

$$T = \inf\{t \geq 0 : \phi(t) \in B_\varepsilon(\phi^s_{eq}), \phi(0) = \phi_0\}, \qquad (3)$$

i.e., the time it takes for $\phi(t)$ to enter $B_\varepsilon(\phi^s_{eq})$.

III. Maximum Relaxation Time

We now proceed to characterize an upper bound on the relaxation time.

A. Two Oscillator Systems

We consider the system (2) with $N = 2$. By writing $\phi_1(t) \equiv \phi(t)$, we obtain

$$\frac{\mathrm{d}\phi(\mathrm{t})}{\mathrm{dt}} = \omega_{1,2} - K\sin(\phi(t)) + \alpha_{1,2}u(t) \qquad (4)$$

We analyze the system (4) with $u(t) = 0$ for $t \geq 0$, where, without loss of generality, we assume that $\omega_{1,2} > 0$. As stated in Assumption 1, we also assume that $K > K_c = \omega_{1,2}$, such that the system exhibits the stable and unstable fixed points, $\phi^s_{eq} = \sin^{-1}\frac{\omega_{1,2}}{K}$ and $\phi^u_{eq} = \pi - \phi^s_{eq}$, respectively. In this case, the space $R_s = [-\pi, \pi]\backslash\{\pi - \phi^s_{eq}\}$ is the region of attraction of ϕ^s_{eq}.

We consider a ball $B_\varepsilon(\phi^s_{eq})$ (see Definition 2) around ϕ^s_{eq}. Clearly, any trajectory starting outside $B_\varepsilon(\phi^s_{eq})$, but within R_s will reach $B_\varepsilon(\phi^s_{eq})$ in finite time. The following result characterizes the maximum relaxation time in the system (4) with $u(t) = 0$, $t \geq 0$.

Lemma 1: The relaxation time is maximum for the system (4) with $u(t) = 0$, $t \geq 0$ if $\phi(0) \in B_\varepsilon(\phi^u_{eq})$.

Proof: Note, first, that the system (4), with $u(t) = 0$, $K > \omega_{1,2}$, is bounded and no periodic orbit exists. Now, let $\phi(0) \in B_\varepsilon(\phi^s_{eq})$ and consider the evolution of the system in negative time. It follows that, as $t \to -\infty$, $\phi(t)$ approaches ϕ^u_{eq}, i.e., in negative time, the trajectory approaches the unstable fixed point asymptotically. Thus, for $\phi(0) \in B_\varepsilon(\phi^u_{eq})$ the relaxation time (3) increases as ε decreases, and the result follows. ∎

The meaning of the result is rather intuitive. The longest relaxation time, i.e., the time it takes for the system (4) to synchronize, occurs when the initial states lie near the unstable fixed point (excluding the degenerate case when $\phi(0) = \phi^u_{eq}$ and (3) not defined).

B. Three Oscillator System

Now, let us consider the system (4) with $N = 3$:

$$\frac{\mathrm{d}\phi_1(\mathrm{t})}{\mathrm{dt}} = \omega_{1,3} - \frac{K}{3}(\sin(\phi_1(t) - \phi_2(t)) + 2\sin(\phi_1(t)) + \sin(\phi_2(t))) + \alpha_{1,3}u(t) \tag{5a}$$

$$\frac{\mathrm{d}\phi_2(\mathrm{t})}{\mathrm{dt}} = \omega_{2,3} - \frac{K}{3}(\sin(\phi_2(t) - \phi_1(t)) + 2\sin(\phi_2(t)) + \sin(\phi_1(t))) + \alpha_{2,3}u(t) \tag{5b}$$

We first analyze the system (5) for $\omega_{1,3} = \omega_{2,3} = 0$ and $u(t) = 0$ for all $t \geq 0$. Under these conditions, the system (5) possesses one stable fixed point $\phi^s_{eq} = (0,0)$, two unstable fixed points $\phi^{u^+}_{eq} = (2\pi/3, -2\pi/3)$ and $\phi^{u^-}_{eq} = (-2\pi/3, 2\pi/3)$ and eight saddle fixed points $(\pm pi, \pm pi), (\pm pi, \mp pi), (\pm pi, 0), (0, \pm pi)$, for all $K > 0$. Moreover, the space $[-\pi, \pi]^2$, excluding the unstable fixed points, the saddle fixed points and the stable manifolds of the saddle fixed points, is the region of attraction of ϕ^s_{eq}.

Consider the ball $B_\varepsilon(\phi^s_{eq})$ around the stable fixed point. Clearly, any trajectory starting outside $B_\varepsilon(\phi^s_{eq})$, but within the region of attraction of ϕ^s_{eq} will reach $B_\varepsilon(\phi^s_{eq})$ in finite time. A result analogous to Lemma 1 now follows.

Lemma 2: The relaxation time is maximum for the system (5) with $u(t) = 0$, $t \geq 0$ and $\omega_{1,3} = \omega_{2,3} = 0$ if $\phi(0) \in B_\varepsilon(\phi^{u^+}_{eq}) \cup B_\varepsilon(\phi^{u^-}_{eq})$ except the stable manifolds of the saddle fixed points.

The proof of Lemma 2 is identical to the proof of Lemma 1, except that there are two unstable equilibrium points in this case. We note that, while the above specification was made for analytical purposes, the conclusion of Lemma 2 remains unchanged when $\omega_{1,3} \neq \omega_{2,3}$.

C. $N > 3$ Oscillator Systems

In higher dimensions ($N > 3$), the analytical development made above is more challenging. Nevertheless, the results are, fundamentally, generalizable. Specifically, we can state:

Lemma 3: Under Assumption 1, the relaxation time (3) of the system (2) is maximized when the initial condition lies within $B_\varepsilon(\phi^u_{eq})$, where ϕ^u_{eq} is any unstable fixed point.[1]

Under the hypothesis that desynchronization is the therapeutic mechanism of HF DBS, the conclusion of Lemma 3 provides a minimum bound on the frequency of HF DBS. We examine this further in the next section.

IV. Minimum Frequency of Stimulation

In the context of the model, the temporally punctate cathodic pulse in Fig. 1 (A) will serve to impulsively distribute the phase of neurons quasi-randomly in the state space of the system. The subsequent, longer, anodic part provides minimal input and, as described in the introduction, the system effectively relaxes, with a relaxation time in the sense of (3). With this observation, for simplicity, we approximate a single pulse of the classical HF DBS by a finite intensity impulse (Dirac-Delta) function, $\delta(t)$, and define the input $u(t)$ in (1) as $u(t) = h\delta(t - t_j)$. Here, t_j is the time at which an impulse is delivered. Then, the system (2) can be rewritten as

$$\frac{\mathrm{d}\phi_i(\mathrm{t})}{\mathrm{dt}} = \omega_{i,N} - \frac{K}{N}\sum_{j=1}^{N}(\sin(\phi_i(t) - \phi_j(t)) + \sin(\phi_j(t))) \tag{6}$$

with $\phi_i(t_j) = \phi_i(t_j^-) + \alpha_{i,N}h$. Here, $\phi_i(t_j^-)$ is the phase difference between the i^{th} and the N^{th} oscillator at the time just before the arrival of the impulse at $t = t_j$.

A. Two oscillator system

We return to the system (6) with $N = 2$. Without loss of generality, we assume that $\alpha_{1,2} > 0$ and $\omega_{1,2} > 0$. We define $R = B_\varepsilon(\phi^s_{eq}) \times \{\phi^s_{eq}, \phi^u_{eq}\} \backslash \{\phi^s_{eq} - \varepsilon, \phi^s_{eq} + \varepsilon\}$ as the pathological (synchronized) regime of the system, where $\phi^s_{eq} = \sin^{-1}\frac{\omega_{1,2}}{K}$ and $\phi^u_{eq} = \pi - \phi^s_{eq}$ are, again, the stable and the unstable fixed points of the system (6), respectively. That is, if $\phi_1(t) \in R$ at time t, the system is synchronized.

Now, suppose that $\phi_1(0) = \phi^s_{eq} + \varepsilon$, such that the system is initially close to synchronized. Furthermore, suppose that the intensity of the impulse is bounded such that $h \in (0, h_{max})$ where $h_{max} = \frac{\pi - 2\phi^s_{eq} - \varepsilon}{\alpha_{1,2}}$, such that a single impulse produces, at most, one oscillation. Then, in order to keep the system desynchronized, an impulse $u(t) = h\delta(t - t_1)$ must be applied to the system at $t = t_1 = 0$. From (6), this impulse results in $\phi_1(0^+) = \phi^s_{eq} + \varepsilon + \alpha_{1,2}h$. With this, we compute the time T it takes the system to return to $\phi_1(T) = \phi^s_{eq} + \varepsilon$ (on the boundary of $B_\varepsilon(\phi^s_{eq})$), i.e., the relaxation time. Solving the system (6) with $\phi_1(0) = \phi^s_{eq} + \varepsilon + \alpha_{1,2}h$ and $\phi_1(T) = \phi^s_{eq} + \varepsilon$ results in

$$T = t_1 + f(\phi_1(T)) - f(\phi_1(0)) \tag{7}$$

where

$$f(x) = \frac{1}{\sqrt{K^2 - \omega_{1,2}}}\log\left[\frac{\omega_{1,2}\tan\frac{x}{2} - K - \sqrt{K^2 - \omega_{1,2}}}{\omega_{1,2}\tan\frac{x}{2} + K - \sqrt{K^2 - \omega_{1,2}}}\right].$$

Clearly, T is the maximum time (or $1/T$ is the minimum frequency) at which the next impulse input $u(t) = h\delta(t - t_2)$ must be applied to the system in order to prevent the system from synchronizing. If $t_2 > T$ then the system will enter R and reside there for the duration $t_2 - T$, as shown in Fig. 2. In this sense, the period T corresponds to the minimum frequency of stimulation required to keep the two oscillator system desynchronized.

1) Low Frequency Stimulation: It is clear from Fig. 2 that if the frequency, f, of a periodic pulse based stimulation is less than $\frac{1}{T}$, the oscillators will synchronize between consecutive pulses. That is, low frequency stimulations will fail in keeping the two oscillator system entirely desynchronized, i.e., in the non-pathological regime.

2) Randomized Patterns of Stimulation: Suppose that stimulation is delivered using randomly timed impulses of constant intensity (h), with a mean frequency of $\geq \frac{1}{T}$. Clearly, the probability of having two consecutive impulse inputs with a time difference greater than T is greater than zero and the

[1] To be technically complete, this assumes that ϕ^u_{eq} exists and $B_\varepsilon(\phi^u_{eq})$ is within the region of attraction of the stable fixed point of the system.

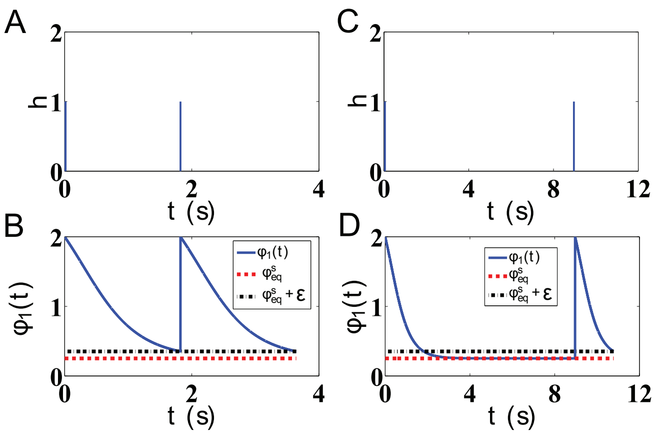

Fig. 2. Minimum frequency of constant-intensity, impulsive stimulation necessary to keep a two oscillator system in the desynchronized (non-pathological) regime: (A) Impulsive input with frequency sufficient to keep the oscillators in the desynchronized (non-pathological) regime defined by $\phi_1(t) \in [\phi^s_{eq} + \varepsilon, 2]$. (B) System trajectory (i.e., $\phi_1(t)$) of two globally coupled Kuramoto oscillators in response to input in (A). The trajectory never enters the synchronized regime, noting that the phase difference $\phi_1(t) = \phi^s_{eq}$ (shown by partially broken line (red)) is the stable fixed point of the oscillators. (C) Impulsive input as in (A), but with slower frequency. (D) System trajectory corresponding to input in (C), where we see that the system enters the sychronized regime between consecutive impulses.

system will enter R for nontrivial durations of time. Thus, random patterns of stimulation will fail in keeping the two oscillator system desynchronized.

B. $N > 2$ Oscillators Case

For the system consisting of more than two oscillators, it is difficult to derive closed-form expressions analogous to (7). However, the conclusions of the above analysis for two oscillators remain applicable for such systems. In particular,

Hypothesis 1: Assuming desynchronization is involved in the therapeutic mechanism of HF DBS, the neuronal activity associated with the pathology resynchronizes during the relaxation time between two consecutive pulses. Thus, resynchronization is prevalent during low frequency and random stimulation patterns, which makes these strategies less therapeutically effective.

Remark 2: Obviously, the actual dynamics of a neuronal network are immeasurably more complex than the model (2). Nevertheless, we suggest that the dynamical insight suggested here is physiologically meaningful. Specifically, we posit that the mechanisms of phase quasi-randomization via a cathodic pulse, followed by relativey-unforced (anodic) relaxation, will occur under the assumption that the network in question exhibits (pathological) synchronization.

V. Conclusions

In this paper, we have studied the inter-pulse relaxation time of a system of globally coupled Kuramoto oscillators with impulsive stimulation as a common forcing input. Such a system is a low-dimensional model for a network of synchronized neurons actuated through pulsatile neurostimulation. We have shown that the relaxation time is maximum when the initial states of the oscillators lie in an arbitrarily small neighborhood of an unstable fixed point of the system. Based on this characterization, we then showed the existence of a minimum bound on the frequency of stimulation required to keep the oscillators desynchronized, i.e., in a non-pathological regime. In particular, we hypothesize that the neuronal populations associated with DBS-responsive disorders remain excessively synchronized (i.e., pathological) for low and random stimulation patterns, due to the interpulse interval being longer than the relaxation time. By altering the shape of the DBS pulse, it may, in principle, be possible to steer the state of the system to precisely control the relaxation time [14], [15]. Issues of design for underactuated and uncertain neuronal populations in this context may be considered in future work.

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