

Dynamical Phase Modulation and Oscillatory Detuning in Applied Neurostimulation

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Abstract

Neural architectures that are operative in higher order cognition, including consciousness, memory, and motor planning, undergo complex changes in global organization during neurological disease. Increasingly, neurostimulation is therapeutically used for restoring these functions, although the mechanisms of restoration are largely unknown. Extant studies reveal, on the other hand, that non-linear and dynamical principles govern global brain organization, seen in operational features such as persistence, stability, flexibility and non-localization that are likely to be evoked by neurostimulation. These dynamical features are instantiated in neural oscillations, a key mechanism regulating brain function and communication. Due to stochastic influences, oscillator synchronization and desynchronization exhibit limit cycle attractor dynamics, which are characterized by persistent phase modulation rather than fixed point, stationary phase locking. Phase modulation governs information exchange by temporally gating transfer and guiding the trajectory of information distribution. Activation of attractor forces by modest input drive induces dynamic, phase difference detuning that results in phase preference shifts, whereas strong input drive induces low stability phase relations that promote oscillator dissociation and new pair formation. These dynamical features of oscillator behavior are likely to facilitate information transfer to neural networks during neurostimulation of higher order functions.

Keywords: neurostimulation; phase modulation; limit cycle attractors; neural communication; information transfer; neural oscillations; weakly coupled oscillators

Introduction

Neural architectures that are operative in higher order cognition, like consciousness, memory, and motor planning, undergo complex changes in global organization during neurological disease. Metastability indices of the default mode network in Alzheimer's dementia, for example, are reduced in decoupled, desynchronized states, revealing that the disease significantly reduces the brain's ability to entrain regional dynamical activity [1]. In the case of epilepsy, seizures typically entail various sequelae, such as brief changes in perception and behavior [2], mild convulsions [3], and temporary loss of consciousness [4]. While the neurophysiological factors leading to these sequelae are currently unknown, it is known that epileptogenesis affects brain areas well beyond the initial seizure foci [5], implicating the involvement of large scale brain interactions. Consistent with these observations, functional connectivity is impaired in large scale brain networks extending both bilaterally and via subcortical structures [6,7].

Therapeutic interest in restoring these cognitive functions has in recent decades focused on neurostimulation, which can modulate neural activity by targeted electrical and/or magnetic stimuli [8]. Originally used chiefly for motor disorders neurostimulation is increasingly employed for a wide range of neural disorders, including epilepsy as well as psychiatric dysfunctions. For the most part, mechanisms evoked by neurostimulation are unknown. On the other hand neuroscientists have made great advances in understanding how brains are able to sustain function and to generate the wide variety and flexibility of behaviors displayed by humans and animals. Although a complete understanding of human cognition remains a distant objective, these studies show that neural operation is governed by non-linear dynamical principles, which feature functional distribution, persistence, stability, and flexibility, despite the presence of significant background noise [9,10]. Considerable evidence now suggests that these mechanisms emerge from functional elements that can be assembled and reassembled to sustain cognition [11], which appear to be the basis for higher order neural

architectures. Hence, the restoration of diseases such as epilepsy is likely to depend on the reassembly of these dynamical building blocks to their normal operative organization.

Extant studies suggest that among the chief mechanisms in which these dynamical elements are instantiated are brain oscillations, which exhibit attractor like features [12]. Oscillators, for instance, are naturally cyclical, hence they are repetitive and rhythmic. Moreover, they resist change when perturbed, a phenomenon that is especially evident during synchronization [13]. Significantly, oscillations have been shown to be involved in many aspects of brain function [14], like that of memory consolidation, and are likely to be the basis of information transfer in brain communication. Singer, notably, proposed in the 1990's the then novel thesis that information transfer entailed the combinatorial properties of brain oscillations [15]. Due to their ability to undergo synchronization and desynchronization with other oscillations, they are capable of participating in a virtually unlimited number of representations, a capability that overcame the theoretical constraints posed by the earlier Hubel and Wiesel model, with limited coding variety. Further developments have revealed that the temporal patterning of neuronal discharges by means of delay coupled oscillator networks enables the formation of select relations between distributed assemblies of neurons [16], which has suggested an even broader potential for representational options by the introduction of variations in temporal sequencing.

Significantly, disease states have been shown to modify oscillatory patterning. In the case of epilepsy, epileptogenesis frequently involves long distance oscillatory interactions that are posited to affect consciousness [17]. In related findings cross frequency coupling between epileptic electrical activity and slow brain oscillations - thought to mediate interareal coordination of brain activity - [18] has been observed.

While restoring normal function to altered disease states is likely to involve changes in the basic patterning of oscillatory elements, modifying this patterning has posed a difficult challenge due to the dynamic and complex environment in which these elements are embedded. For neurostimulation precise temporal and spatial resolution constitutes an ideal objective, with minimal interrogation of target oscillators. However, due to the dynamic nature of the oscillator field the effects of carefully circumscribed stimuli can be short-lived [19]. Critically, such impact is highly dependent on the state of the neural field. Because of the field's dynamic character, many perturbation paradigms have opted to use either a very strong pulse, essentially resetting and disrupting the activity of the target network, or to use a continuous or repetitive pulse in order to establish and maintain a desired effect. For example, one study [20] that entrained a local neuron population with a 40 Hz train of pulses showed that both the neural population response and animal behavior depended on the phase at which the stimulus arrived at the population. While these studies illustrate effects introduced by stimulation, a number of concerns become apparent with these regimes due to the dynamic nature of brain activity. Stimulation can, for instance suppress any ongoing local processing and so interfere and contaminate relevant neural signals. The introduction of stimuli, moreover, clearly affects the stability of oscillator associations, modulating information transfer in unexpected ways.

Indeed, modulating dysfunctional oscillatory states is likely to require accounting for their dynamical properties; this is to say that because these states are governed by dynamical principles, their manipulation will require interventional protocols that incorporate these principles during stimulation by modulating, for example, the stability of oscillator interactions during synchronization and desynchronization. Beyond the dynamic features

instantiated in these mechanisms it will also be necessary to account for how dynamical principles underpin functionally relevant activity. It is posited, for instance, that oscillatory synchronization functions to direct communication within the brain; hence, how dynamical principles govern the directing of information transfer will need to be accounted for in restoring the functional features of cognition. Accordingly, this paper will explore how modulatory input can influence the dynamical properties of oscillator interactions that govern information exchange and computational flexibility.

(2) Dynamical Activation States in Oscillatory Structures

Dynamical principles governing neural organization

Subject to persistent internal as well as sensory and motor activity, the brain is influenced by many sources that tend to change its physical state globally as well as regionally. This, coupled with the multifunctionality of most brain domains, means that as a general rule any given brain region is continually exposed to multiple perturbations. To preserve stability and sustain functional operation neural systems have evolved dynamical mechanisms that assist in resisting spurious input and maintaining organizational order. To conceptualize these mechanisms, changes in the state of a given region may be conceived in terms of a state variable that changes as a function of the perturbations experienced by that region. Defined in this way, and for the simple case of a constant stimulus with no other influences occurring within a region, a variable reflecting the system state will grow unabated. While such constancy is clearly unphysiological, a similar result is also obtained in cases involving variable and spontaneous perturbations, a condition endemic to the brain. In this latter case, the system state fluctuates in response to the ongoing noisy influences. With time, the output of the system will likewise continue to grow unchecked; in other words, as long as noise is experienced the value of the variable reflecting the system state will continue to grow and experience no negative change. Similarly, in all circumstances the rate of perturbations will also be positive. Relating this latter parameter to the state variable provides a measure of how much the system changes as a function of its prior history and so provides a measure of the influence of the system state on inputs that it receives.

Mathematically, such a relation can be expressed as:

$du/dt = u(t) = u(1)$ where the rate of change of the state, represented by du/dt is a function of the instantaneous value of the state variable [9]

In this expression the effect of perturbations is simply added to the prior value of the state variable and remains positive with spurious input. However, because uncontrolled inputs can have untoward effects on behavior and bodily regulation, such a condition is clearly incompatible with organized cognitive function; hence, capacities for maintaining stability and regulating the changes that do occur are required by the nervous system. The brain, particularly, must have mechanisms that both monitor the existing state of a domain and correct unwanted input affecting its function. That is, the capacity to correct for spurious input and restore the system to its original state must be defined in relation to the value of the system state.

Abstractly, this capacity may be described by relating the rate of change of the system to the deviation from a system resting value. Mechanisms enabling this capacity thereby return the system to an established set point when perturbed, and so oppose changes due to perturbations. Mathematically this may be written as:

$du(t)/dt = -(u(t) - b)$ (2) where b is also a function of the system state and negative.

In this expression the resetting force that returns a system response towards the system's resting level thus depends upon the current activation relative to the resting level b . This latter is oriented in the opposite direction so that when the activation is greater than the resting level, the rate of change is negative, and when lesser the rate of change is positive. In both cases the change is always directed to a point of stability.

While the description of these mechanisms is mathematically abstract, their dynamic features are very likely instantiated in physical mechanisms occurring during neural activity, since changes observed in neural state variables within the brain are known to be transient and to return to their resting state level after having been driven out of it by perturbations [21]. For the attractor like behavior described above, network outputs are not determined by the inputs alone, but are also affected by the network state, which in physiological circumstances is often measured by neuronal firing rates, on the premise that there is a consistent relationship between the evolution of a neuron's spike rate over time and that of some external feature of the environment, behavioral output, or brain process. This relationship is generally conceived in terms of a 'tuning', where maximal firing rates are related to certain optimal conditions and where lesser firing levels reflect feature dimensions located at a given spatial or non-spatial distance from this optimum. Hubel and Wiesel have shown, for example, that many neurons fire maximally in the visual cortex in response to particular directions of movement, and much less so apart from these directions. Input in the form of firing rates thus modifies the internal state of a network.

Due to the dependence of network output on its prior state, networks in which input is relayed directly forward to other networks, i.e., feed forward organizations, are unlikely to support such dynamic activity. Outputs affected by the system's prior state require instead a feedback organization that returns the output to the network, where further changes in output are determined by the network's current state. Significantly, most networks in the brain – some 95% - are known to employ negative feedback, a revelation of the importance of this type of organization to brain function [22].

Dynamic features of neural oscillators

One of several rhythmic elements in the brain, neural oscillators are distinguished by attractor like properties [22]. They are stable, resisting influences that tend to distort them, before returning to a preferred configuration. Additionally, they are capable of tracking stimuli that result in their occupation of new phase relations. Finally, they can undergo transitions from preferred oscillatory interactions to relations with alternative oscillator partners. Beside these properties, they are known to operate in many brain functions, where they are proposed to underlie mechanisms of information transfer [23]. The instantiation of dynamical properties in neural oscillators, therefore, appears to be a key mechanism by which dynamical principles become instantiated in brain function.

Oscillations have been known for decades, chiefly through observations of electroencephalogram (EEG) signals that are thought to reflect global electrical patterning. Recorded externally in the EEG, they appear as small

amplitude, rhythmic and intermittent signals that are poorly localized spatially. When recorded subdurally from the surface of the pia mater in the electrocortigram (ECoG), by contrast, a variety of brain rhythms can be detected across different behavioral states [24]. Locally, circuit oscillations can arise from the intrinsic oscillations of constituent neurons, or from the circuit connectivity, or from a combination of the two. In general, these network systems are composed of neural pools with fast positive feedback and slower negative feedback that functions to generate oscillations [12]. One way in which this may be conceived is in terms of an initial fast excitation that drives up neural firing, e.g., through positive feedback, until a slower inhibition is recruited to bring down population activity. As excitatory drive to interneurons wanes, the network begins to overcome inhibition and the next cycle begins again, leading to repetitive rhythmic behavior [25].

Unlike fixed point attractors, however, oscillating networks behave as limit cycles, which appear as closed loops in plots of state variables against time [26]. Mathematically, a limit cycle forms a closed trajectory in phase space having the property that at least one other trajectory approaches it asymptotically, either as time approaches infinity or as time approaches negative infinity. Since the limit cycle is determined by the system state over time, perturbations that modify the system state can either translate the cycle along the state axis, shifting the cycle to a new attractor state – that is, as a function of amplitude - or along the horizontal axis as a function of time along the limit cycle - that is, as a function of the limit cycle phase. The limit cycle trajectory therefore describes the eventual periodic behavior of the system, where small perturbations from this closed trajectory are induced by the system to return to it. Perturbations affecting the time axis are often regarded as independent of the position along the time cycle; that is, those of similar magnitude induce a phase shift of similar magnitude regardless of the position along the cycle where they are introduced. Conversely, perturbations of dissimilar magnitude induce correspondingly greater or lesser phase shifts. Very strong stimuli, on the other hand, shift the limit cycle vertically, resulting in new attractor states. Oscillators are particularly distinguished by their ability to combine with other oscillators through synchronization, and to dissociate and form new pairs through desynchronization. Dynamically, oscillator pairs can reduce to fixed point attractors, achieving maximal points of stability at complete phase alignment. In the noisy environment of the brain, however, oscillator pairs become themselves new limit cycle attractors that occupy new limit cycle trajectories.

(3) Information transfer is governed by dynamical properties

While neuronal ensembles giving rise to oscillations have evolved dynamical principles to ensure the stability of elementary functional units, communication between neurons and networks remains essential to higher order cognition and the generation of behavioral variety. Hence, brain function must also rely on dynamical principles for information capture, which is implicit in the interactions between these units. *By extension, it is likely that abnormal brain functioning can be traced to aberrations in communication that are influenced by these principles and which will therefore need to be overcome in neurostimulation regimes.*

Information capture in attractors

Dynamically, information capture may be conceptualized from the perspective of input to an attractor, which results in an alteration to the attractor state (although the precise form of neural information is debated, it is generally agreed that some form of activity modification must occur in sender receiver neural organizations) [27]. Under conditions of input, the stability of the attractor is a function of three parameters, the original state variable plus those of the resting level and the input to the system. For a constant input this may be described mathematically as:

$u'(t) = -u(t) + b + s$. (3) where s is the value of the input and the remaining parameters retain their prior designations.

When there is no input, that is, when $s = 0$, the state of the system is at rest and equal to the resting state value; hence also, since the system is at its most stable point, the rate of change of state is also equal to zero. However, with input – that is, when s has a positive or negative value – the overall value of the system state is changed from its initial resting level by the value of s . The value of the system state when the rate of change equals 0 is thus the sum of $b + s$; that is, the overall state of the system has adjusted to a new resting level, and the attractor is seen to track changes in input. As long as the value of the input remains the same, the attractor will remain at this level and further changes in input will modify the state value according to their magnitude. Typically, however, the input is variable, since the value of s is often some function of time.

$$u'(t) = -u(t) + b + s(t) \quad (4)$$

The ability of the attractor to track input changes means that in these circumstances the system state will reflect the value of the continuously changing variable.

Besides tracking input changes, attractors receiving sufficiently strong input can undergo transitions to new attractors; that is, they can display decisional behavior, shifting from one attractor to a second and vice versa. For the special case of self excitation of a network, for example, strong inputs induce a state of self excitation through recurrent connections, which tends to persist even when input levels are reduced [9]. Dynamically, this can be conceptualized as the induction of a second attractor state, which itself resists the changes incurred by reduced stimulus input. Moderate input stimuli, however, are insufficient to induce self excitation and the first attractor remains occupied; hence, the system state is capable of occupying two levels, depending on the magnitude of input received. The ability to transition between attractor events, thereby affords the computational possibility of performing decisions.

Information capture in oscillator attractors

In like manner, attractor like properties govern information capture in neural oscillators. However, as a limit cycle the dynamical properties instantiated in oscillators are described by time variable functions. Instead of a single resting state level, the resting state varies as some time dependent function. Since oscillators are periodic, this function is described in terms of a cycle,

where the state value is related to the proportion of time traversed through the cycle (usually given as a function of the sine of this value). Moderate inputs to such attractors modulate the resting level, therefore, as a function of oscillator phase; that is as a function of the temporal position within the cycle.

Because of the cyclical nature of the oscillator, the detection of a perturbation typically means that the phase change must be gauged with respect to another cyclical event [13,22]. Moreover, discharging the perturbation to downstream neurons requires that the receiving network be modulated in some fashion, generally attributed to spike timing dependent plasticity that modulates phase changes in another oscillator. Accordingly, information transfer is usually posited to involve oscillatory interactions, with the sending oscillator tending to modify the phase and spike generating period of the receiver. The prevailing thesis for information transfer via oscillatory interactions, the Communication through Coherence theory (CTC), posits that transfer occurs only when the phases of each oscillator become aligned [13, 28]. According to this thesis, the sensitivity of the receiver assembly to the conjunction of phases is maximal during full synchronization.

Premised on Huygens 17th century observation that pendulum clocks [29,30] adjust their rhythms with respect to each other, the tendency to synchronize – where the oscillators have a preferred phase-relation with respect to each other and that they adjust their phases as a function of their phase difference – implicates the presence of native forces in neural networks, which tend to adjust the phases between the two to achieve a point of maximum stability. A new attractor is therefore generated from the combination of two limit cycles; hence the process of combining oscillators is itself dynamical and exhibits attractor behavior. The phase adjustments observed during synchronization (and desynchronization) can be described by a phase response curve (PRC) [30, 31], which reflects the mutual forces that coupled oscillators exert on each other depending on their relative phases.

The PRC thus defines how much a given force exerted by one oscillator at a given phase will delay or advance another oscillator's phase, as a function of the latter's phase. Thus, the PRC also defines which phase-relations among oscillators occur preferentially, thereby representing attractor points in the phase-relations of the oscillators. For phase synchronization, the attractor point along the phase response curve occurs when the oscillators' phases are most aligned and the force between them is least. By extension the greatest force is experienced when phase differences are maximal. Phase response curves, accordingly, document the variation in stability experienced by the two oscillators as they move through a phase precession cycle in their progression toward phase alignment. In addition to native coupling forces that strengthen the bond between oscillator pair members, intrinsic frequency differences exert separation forces between pair members. Such 'detuning' forces can be attributed to an innate cyclical momentum possessed by each oscillator. Due to the innate resistance to frequency change, detuning opposes the coupling that occurs during synchronization.

Both detuning and coupling forces are incorporated in the Adler equation, which has been shown to provide a mathematical description of the chief forces affecting oscillator interactions [13].

$$d\Delta\theta(t)/dt = \Delta\omega(t) + K\sin\theta(t) + N_p \quad (5)$$

where $d\Delta\theta(t)/dt$ is the instantaneous rate of precession; $\Delta\omega(t)$ is the time evolution of the frequency difference of the oscillator pair members; $K\sin\theta(t)$ is the coupling variation as a function of time; and N_p is the phase variation due to network noise

For phase synchronization between oscillators with nearby frequencies, that is, for oscillators within a given ‘frequency band’, the Adler equation accounts for the cumulative tendency toward synchronization [13]. In the absence of other influences the process of synchronization can be described deterministically. Modulating the forces, and so influencing how information capture affects their pairing, however, are significant influences on synchronization that can be attributed to intrinsic noise as well as potentially additional factors. As will be argued below, the effect of these additional factors is to prevent full synchronization, calling into question the mechanistic basis of the Communication through Coherence thesis and suggesting alternative mechanisms that enable information capture in oscillator networks.

Full synchronization, termed phase-locking, can be regarded as the constancy of the instantaneous phase-relation between oscillators. This means that there is no phase precession and that the instantaneous phase of one oscillator always maintains a uniform relation with the instantaneous phase of the other (phase-locking has a value of 1. Its observation in some examples has served as the basis of the postulate that information transfer occurs only when oscillator phases are fully aligned. Neural synchronization in the gamma-range, for example, has been observed in subcortical [32,33] and cortical areas [34] and gamma rhythms emerge in the visual cortex during processing of visual stimuli [35,36].

Information capture in oscillators is unlikely to entail strict phase locking

The requirement by the CTC theory for information transfer to occur by phase locking however, means that the transfer of information requires a stationary relation between the two oscillators. Dynamically, this can be interpreted as the arrival of the two at a point of maximal stability in which detuning and coupling forces have achieved a balance. Yet this also implies that input drive is no longer modifying a second oscillator through the exertion of a ‘force’ since any effects on the second oscillator introduced by input drive have already been attained prior to phase alignment. The absence of such a force suggests, rather, that phase-locking is unlikely to be either completely synchronous or completely asynchronous in neural operation, a condition in which the member of oscillator pairs continually precess with respect to each other. This therefore implies that phase-locking can be, indeed is, typically both incomplete and of different magnitudes.

In fact, a number of physical factors contribute to prevent the perfectly phase-locked state, including factors like the extent of phase alignment in the population [13], frequency modulation due to the phase dependency of the coupling constant [37], intermittency of alignment [38], and oscillator disruption that may be occasioned by excessive coupling strength [39]. Neural oscillations, for instance, exhibit stochastic behavior, where neural signals go in and out of synchrony [13] with episodic desynchronization.

Noise, particularly, is intrinsic to neural activity, and can be expected to exacerbate the degradation of partial phase locking occurring between oscillators during detuning intervals (or neural networks approximated by oscillators) [19]. There is, for example, indirect evidence that for cortical gamma oscillations the frequency and amplitude evolution over time is noisy and complex [40] and changes as a function of cortical state [41]. Noise can, for instance, be due to the inherent instability among neurons generating the network oscillation, resulting in phase variation. Synchronization of ‘weakly coupled oscillators’ is therefore considered in a statistical sense where a predominant fraction of ‘micro’ oscillating circuits determine the behavior of the population oscillator; which is to say that the overall oscillatory distribution may be considered to have a certain phase variance range. Noise effects can be expected, moreover, to modulate coupling strength, shifting a proportion of the individual cycling circuits into a non-oscillatory range or other effects.

Accordingly, phase modulation is rarely completely arrested. This means that the attractor generated from the combination of two parent oscillators is rarely a fixed point, but asymptotically becomes itself a limit cycle attractor, with domains of greater and lesser stability. Physically, the influence of noise and other effects leads to a broad range of conditions of partial synchronization. In this regime, oscillators display frequency differences, meaning that they phase precess, yet still have preferred phase-relations that are reflected in non-uniform phase-relation distributions. Indeed, partial synchronization implies a preference for particular phase-relations despite undergoing continual phase precession. Accordingly, information capture appears as dynamical and occurs as the two oscillators merge their frequency differences through detuning [13]. Indeed, even in the hypothetical case of an absence of noise, it is unlikely (due to detuning) for synchronization to be perfect due to the interval required for detuning (detuning is not instantaneous), and imperfect synchronization can be expected to generate changes in phase relations and frequency among oscillators over time.

Preferred phase relations, wherein information is likely to occur, may be conceptualized by comparing theoretical behaviors among synchronous, asynchronous, and partially synchronous regimes [37], seen in Figure 1.

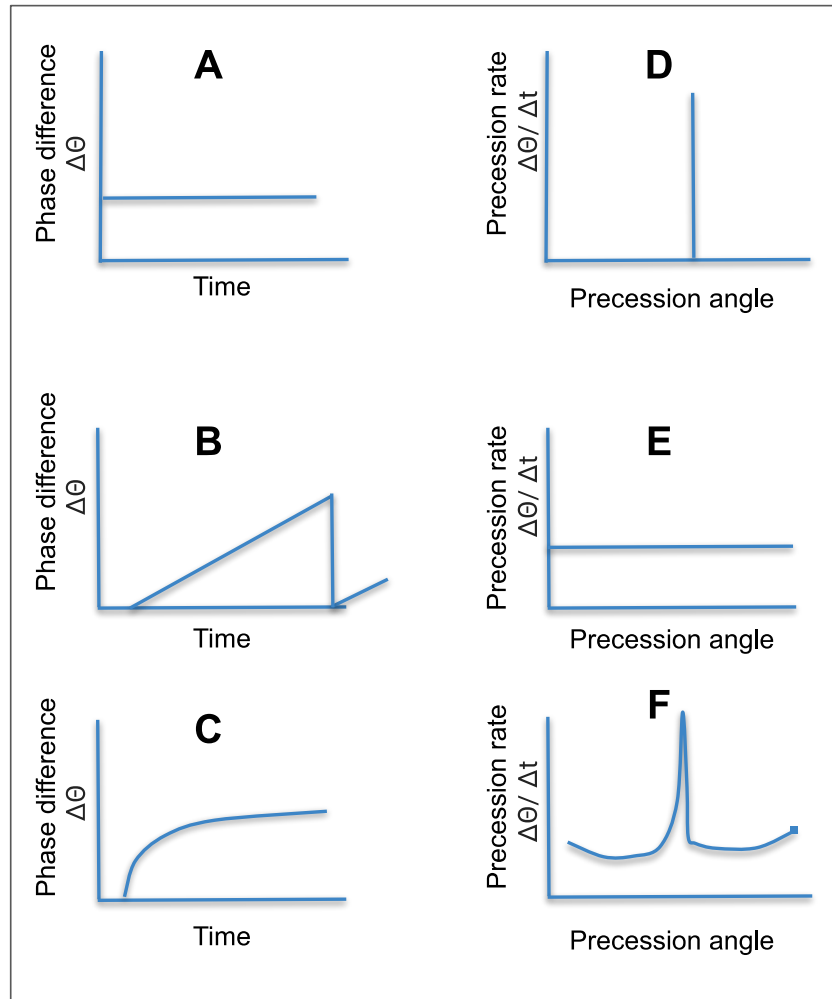


Figure 1. Phase precession modulation during oscillator synchronization. Synchrony between two oscillators is governed by two factors, the difference between the intrinsic oscillator frequencies and the coupling strength between them. The individual phase evolution for each of two oscillators A and B is mathematically described: $d\theta_A/dt = \omega_A(t)$ and $d\theta_B/dt = \omega_B(t)$; From TWCO theory, the evolution of the phase precession angle, θ_P , is: $d\theta_P/dt = (\omega_A(t) - \omega_B(t)) + K\sin(\theta_P(t)) + N_P$ (Adler equation). A,D. Rigid phase locking occurs when the rate of precession equals 0 and the phase difference angle is a constant value. B,E. The rate of precession is constant and oscillation precesses through all phase angles. C,F. With coupling the precession rate is variable and described by the sine of the phase precession angle. Slowing occurs when the phase difference angle is small, termed the phase overlap range, and speed increases when the phase difference is large. Ongoing frequency modulation dictates that information transfer occurs within a region of phase overlap rather than at a point of phase alignment [13].

In a complete or perfect phase-locking state, the phase-relation is constant (no phase precession) and the synchronized oscillators do not have a frequency mismatch. Here, perfect synchrony is observed in phase time plots as a constancy of phase difference over time and a rate of precession equal to zero. This is to say that under full phase locking, the intrinsic frequencies of both oscillators have aligned with respect to each other, so that their intrinsic frequencies are equal. This constancy of phase may be distinguished from the case where synchrony is absent; that is, where the phase locking equals 0 and the intrinsic frequencies of the two oscillators

do not vary with respect to each other; accordingly, the phase difference is described by a linear function and the rate of change of the phase difference between the two is constant. An intermediate phase locking value, on the other hand, means that the predictive value of a given oscillator is less than 1 (but more than 0) for correctly yielding the value of the other, and the oscillators can be expected to precess with respect with each other. Precession, here, will vary as a function of the phase angle difference. Coupling is strongest at the preferred phase angle, i.e., where the phase difference is minimal, and the rate of phase difference change is least. For

weakly coupled oscillators the instantaneous frequency change - the rate of phase change over time - remains above zero at the preferred phase angle and rises as the coupling approaches its minimum value where the phase angle difference is maximum. The introduction of coupling, therefore, functions to modulate the rate of phase precession, increasing it for greater phase differences, and slowing it when the phase difference is least.

The fact that the dominant state is characterized by incomplete phase-locking, and therefore phase precession, entails that oscillators in this state will traverse all possible phase-relations over time. [13]. It means further that depending on the instantaneous frequency difference between the oscillators and the coupling constant, the instantaneous phase-locking can vary between 0 and nearly 1at points throughout the precession cycle, as seen in Figure 1. Hence, the limit cycle attractor formed from their combination will also continually cycle through greater and lesser domains of stability as phase precession is modulated.

Accordingly, no periods of phase locking are likely to occur during oscillator pairing, a physical circumstance that is at odds with the Communication through Coherence thesis of information transfer. The stationary model proposed by the CTC, for example, which assumes that the underlying oscillatory dynamics are stable at a fixed phase-relation and shared frequency, is reflected in the frequent use of stationary methods for assessing synchronization, such as spectral coherence [13] that, accordingly, are purported to assess information transfer.

(4) Information transfer entails dynamical changes in oscillator stability

Consistent with ongoing changes in phase relations it has been observed that gamma oscillation frequency fluctuates strongly over time [42] and that different cortical locations can express different preferred frequencies at a single moment in time [43]. Synchronization is thus primarily a non-stationary process [44] because oscillators mutually adjust their rhythms through phase shifts (i.e. through changes in the instantaneous frequency).

Given that stationary periods of phase alignment are absent during oscillatory mergers, hence, this raises the important question of which mechanisms underlie information transfer and highlights the role of phase modulation as potentially key to mediating communication within and between neural networks. The dynamic influence of detuning, particularly, apparent in the instantaneous rate of phase change occurring during precession, is mechanistically more consilient with information transfer that occurs within a stochastic neural environment, which promotes ongoing and variable phase modulation. For example, it has been shown that the frequency preference of gamma oscillations shifts as a function of input drive, both in experimental studies [45] and in computational studies of gamma-generating networks [46]. Moreover, changes in the difference in input drive between two oscillators lead to corresponding differences in the frequency difference between the oscillators. Therefore, input drive regulates the frequency preference of a network; hence, it also induces oscillator detuning [13]. Cumulatively, these observations support the notion that frequency modulation is key to information exchange, especially within gamma oscillatory networks, where the function of inputs is to modulate

inter oscillator stability through adjustments in the internal phase relations of the oscillator pair members.

As noted, input drive has the effect of shifting oscillatory phase, with inputs of equal magnitude adjusting the phase equally regardless of the point along the cycle at which inputs are introduced [47]; hence, detuning forces experienced by oscillator pairs are proportioned to the magnitude of the input received. This observation is a strong indication that information transfer is related to the dynamic events occurring during oscillator pairing as the two partners synchronize their relative frequencies. Attractor forces evoked by detuning, accordingly, underlie the capture of input drive, possibly through phase preference shifts [13] or other, as yet, undetermined physical changes.

Limit cycle formation during oscillator pairing, in consequence, can be expected to exert multiple effects on information transfer, dictating how, when, what and where information is transferred. This means particularly: how, detuning mechanisms promote information transfer; when, limit cycle formation imposes temporal restrictions when information can be exchanged within the precession cycle; what, input drive is selected according to its magnitude and origin; and where, information is exchanged via new attractor associations.

Detuning mechanisms promote information transfer (How)

Input drive dictates that phase advances correspond to the magnitude of the captured stimuli, shifting the phase precession angle and the extent of detuning. Accordingly, detuning dynamics govern the processing of input, adjusting frequency preference output during synchronization mergers.

Limit cycle features determine when information transfer takes place (When)

Occurring preferentially during minimal phase difference means, in the first place, that information transfer is dictated by the properties of the phase precession cycle – that is, transfer does not take place continuously, but rather occurs during a restricted temporal domain within the precession cycle, gating the release of information to a preferred period within the phase overlap domain of the cycle.

Significantly, temporal gating appears to also function in cross frequency coupling, where it is posited to structure information transfer [23]. Gating in this latter instance is hypothesized to generate syntactical rules governing information decoding [23]. Such rules determine semantic content from a limited number of elements allowing for the formation of a multitude of combinations. In the case of neuronal communication it is hypothesized that the fundamental element of neuronal syntax is an assembly of neurons discharging together in a cycle. Rhythmic inhibitory volleys provide for alternating windows of suppressed and heightened excitability that structure information flow by transiently silencing principal cell output Its occurrence in narrower frequency bands as seen here suggests that information gating is a more generalizable mechanism that may be evoked across a hierarchy of syntactical organization. In both instances phase modulation is likely to govern gating processes, which is a result of the detuning that occurs during coupling.

Determining which and how much input drive is selected (What)

Input drive, as noted, has the effect of shifting oscillator phase and so modifying the precession angle, i.e., the phase difference angle, between the members of the oscillator pair. Because the phase shift is proportioned to the magnitude of the input drive and also to the magnitude of detuning – which is detected in frequency preferences dictated by detuning - this latter has the effect of quantitatively assessing input.

Consistent with this, it has been proposed [23] that for effective communication there is a requirement for limiting information content to useable packets [23]. This may be defined as the maximal quantity of information transferred per event, here determined by the period of the phase precession cycle. Hence, the cycle period dictates the upper limit for information content. From the point of view of the downstream (“reader” or “integrator”) target cells, the input drive per event represents the collective activity of upstream neurons, which must fall within the [48] time-integrating window, which are combined as a unitary event. Spikes of upstream neurons which fire outside the integration time window constitute elements of another event or different source [23]. The capture of input drive, accordingly, can vary from a minimum to a maximum value, the latter determined by the upper temporal bound of the precession cycle.

Limit cycle features enable computational variability via new oscillator associations (Where)

Due to stability variation along the precession cycle, large inputs timed to coincide with points of minimal stability – e.g., wide precession angles - can exceed the ability of the attractor pair to retain input, destabilizing their union and leading to new attractor combinations. With sufficient input synchronization forces will no longer sustain the limit cycle constructed by the oscillator pair and the lead oscillator will instead construct a new pair composed from the lead oscillator and its new partner. Indeed, the fact that phase modulation of the oscillator pair progresses through points of maximal and minimal stability is naturally structured to enable separation of the pair at points of minimum stability. By extension, regulation of separation is theoretically achievable through timing mechanisms that advance phase and modify position along a stability axis [20].

Consistent with this, the theory of weakly coupled oscillators (TWCO) proposes that coupling between oscillator members is only moderate and that input drive functions largely to adjust phase [49]. Dynamically, this means that the oscillator state varies primarily along the time axis, and that input drive that significantly shifts the vertical (amplitude) axis will generate new limit cycle attractors [9,13,37] Significantly, synchronization properties of V1 cortical gamma rhythms have been shown to be predicted by TWCO theory [13]. Information transfer, accordingly, is largely limited to moderate input drive dictated by phase modulation during oscillator to oscillator interactions, whereas new computational features for information processing are acquired with strong stimuli.

The effect of strong stimuli, therefore, is to shift the phase precession angle to the limit cycle boundary, a point of minimal stability, where stochastic input can elevate it out of its primary stability basin. Given sufficient input, a new limit cycle attractor is then formed with a unique trajectory and

corresponding stability and instability domains. The new limit cycle thus occupies a second attractor basin, minimizing the likelihood of return to the prior limit cycle in analogy with fixed point attractors. The effect of strong stimuli is thus to generate two attractor states with distinct stability boundaries. For oscillator limit cycle attractors, accordingly, stochastic inputs have the important function of breaching stability barriers when proximate to large precession angle, boundary conditions; that is, only in response to strong stimuli. Importantly, computational abilities conferred by oscillator recombination, that is, by transitioning between limit cycles, can be hierarchically extended, enabling high level information processing and representation.

Conclusion

Neurostimulation is enjoying a widespread renaissance as a therapeutic medium for neurological disease. Beginning with successful applications for treating Parkinson’s Disease neurostimulation has also proved therapeutic for tremors, dyskinesia, and dystonia. Its expanding repertoire now includes epilepsy and stroke and such degenerative diseases as Alzheimer’s dementia, as well as a growing list of psychiatric diseases [8]. Deep brain stimulation has shown promise, for instance, in treating obsessive compulsive disorder and Gilles de la Tourette syndrome and to have a salutary effect on major depressive syndrome.

Despite the promise of the therapy, on the other hand, its mechanisms of action remain for the most part unknown and their improved characterization is needed to advance the technology. Facilitating this characterization is a growing understanding of how non-linear dynamical principles govern neural activity, especially through the brain’s chief regulatory mechanisms, neural oscillations. Indeed, the organizational complexity and functional diversity of the human brain is unrivalled in the natural world, despite the presence of noise and other significant physical limitations that degrade signal processing, an operational order that can be traced to the instantiation of such principles. The understanding of how these principles influence oscillations can therefore be expected to advance neurostimulation protocols used for therapeutic applications.

The ability to regulate information transfer to brain activity, particularly, can be expected to modulate functional organization directly. This paper shows that neurostimulation can be expected to modulate functional organization through dynamical events affecting stability, which can be observed in phase modulation and oscillatory transitions, unlike currently proposed mechanisms of phase alignment which are inconsistent with oscillator dynamics.

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