



Brain synchronizability, a false friend

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A B S T R A C T

Synchronization plays a fundamental role in healthy cognitive and motor function. However, how synchronization depends on the interplay between local dynamics, coupling and topology and how prone to synchronization a network is, given its topological organization, are still poorly understood issues. To investigate the synchronizability of both anatomical and functional brain networks various studies resorted to the Master Stability Function (MSF) formalism, an elegant tool which allows analysing the stability of synchronous states in a dynamical system consisting of many coupled oscillators. Here, we argue that brain dynamics does not fulfil the formal criteria under which synchronizability is usually quantified and, perhaps more importantly, this measure refers to a global dynamical condition that never holds in the brain (not even in the most pathological conditions), and therefore no neurophysiological conclusions should be drawn based on it. We discuss the meaning of synchronizability and its applicability to neuroscience and propose alternative ways to quantify brain networks synchronization.

1. Introduction

Consider a network in which each node is a dynamical system, e.g. an oscillator, and the links are couplings between these nodes. Can these oscillators synchronize with each other creating a coherent state and, if so, under what circumstances is this state stable? Given a particular dynamical system and coupling scheme, the *Master Stability Function* (MSF) formalism (Pecora and Carroll, 1998; Boccaletti et al., 2006; Arenas et al., 2008) allows relating the stability of the fully synchronized state to the spectral properties of the underlying matrix of connections, and assessing which network structures can maintain complete synchronization of the whole network.

At the macroscopic scales of typical non-invasive neuroimaging techniques, brain activity can be thought of as the collective dynamics of a set of coupled dynamical units. Synchronization among these units has been suggested to be a basic mechanism of healthy brain functioning (Varela et al., 2001). Thus, at first glance, the problem above may seem to apply to brain activity, justifying the use of the MSF formalism to quantify brain network synchronizability. However, all formalisms are created to address very specific questions and come with their own set of formal and theoretical assumptions, the compliance with which ultimately decides whether they can be used in a given context.

In the remainder, we argue that some essential characteristics of the brain render the MSF framework difficult to apply to neuroscience, review some misunderstandings about the synchronizability construct, and propose alternative ways to understand synchronization in brain networks.

2. Brain synchronizability

The use of synchronizability, initially designed to study theoretical models, rapidly extended to the analysis of real datasets and, in the context of neuroscience, to quantify the ability of *anatomical* (Chavez et al., 2011; Zhao et al., 2011; Ton et al., 2014; Phillips et al., 2015; Tang et al., 2017) and *functional* (de Haan et al., 2012; Bassett et al., 2006; Reijneveld et al., 2007; Stam and Reijneveld, 2007; Schindler et al., 2008; Deuker et al., 2009; van Wijk et al., 2010; Jalili and Knyazeva, 2011; van Dellen et al., 2012; Tahaei et al., 2012; Bialonski and Lehnertz, 2013; Lehnertz et al., 2014; Niso et al., 2015; Khambhati et al., 2016) brain networks to synchronize. For example, Tang and co-workers (Tang et al., 2017) investigated how the human brain's anatomical organization evolves from childhood to adulthood by measuring changes in the synchronizability parameter, and proposed that during the course of development human brain anatomy evolves towards an organization that limits synchronizability (Tang et al., 2017). The authors suggested that as the brain evolves towards its mature state, it reduces its ability to synchronize, and that this reduction would help increase brain controllability. Furthermore, a few studies focused on the effects of different pathologies on brain synchronizability, such as epilepsy (Schindler et al., 2008; van Dellen et al., 2012; Tahaei et al., 2012; Bialonski and Lehnertz, 2013; Lehnertz et al., 2014; Niso et al., 2015; Khambhati et al., 2016), Alzheimer's disease (Phillips et al., 2015; de Haan et al., 2012), or schizophrenia (Jalili and Knyazeva, 2011), showing statistically significant changes in the synchronizability parameter in association with these

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<https://doi.org/10.1016/j.neuroimage.2019.04.029>

Received 20 September 2018; Received in revised form 28 March 2019; Accepted 8 April 2019

Available online 12 April 2019

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diseases. Interestingly, epilepsy was associated with an increased synchronizability during interictal activity (Lehnertz et al., 2014), while it decreased during ictal activity (Schindler et al., 2008). Functional networks synchronizability has been reported to decrease the electroencephalographic (EEG) activity of schizophrenic patients (Jalili and Knyazeva, 2011). Studies using magnetoencephalography (MEG) showed that synchronizability values depend on the frequency band considered when constructing functional networks (Bassett et al., 2006).

While changes in synchronizability clearly exist, is this particular metric measuring what it is supposed to measure?

3. The master stability function formalism

The meaning and scope of the synchronizability construct should be understood in the MSF theoretical context it is predicated upon.

Given a group of N diffusively coupled dynamical systems whose dynamics in isolation follows $\dot{\mathbf{x}} = \mathbf{F}_i(\mathbf{x}_i)$, the evolution of the whole system is given by the equation:

$$\dot{\mathbf{x}}_i(t) = \mathbf{F}(\mathbf{x}_i(t)) - \sigma \sum_{j=1}^N a_{ij} [\mathbf{H}(\mathbf{x}_j) - \mathbf{H}(\mathbf{x}_i)], i = 1, \dots, N \quad (1)$$

where \mathbf{x}_i is the m -dimensional state vector of the i th oscillator, σ the coupling strength, $\mathbf{H}(\mathbf{x})$ a vectorial output function and a_{ij} the elements of the adjacency matrix \mathbf{A} , with $a_{ij} = 1$ if system (i.e., node) i and j are connected and zero otherwise. Since oscillators are coupled in a diffusive way, i.e., with a linear coupling proportional to the difference between their state variables, we can introduce into equation (Pecora and Carroll, 1998) the Laplacian matrix defined as $\mathbf{L} = \mathbf{D} - \mathbf{A}$, where \mathbf{D} is a diagonal matrix whose elements l_{ij} are the degree (i.e., the number of neighbours) of each node (Boccaletti et al., 2006). Equation (Pecora and Carroll, 1998) then reads

$$\dot{\mathbf{x}}_i(t) = \mathbf{F}(\mathbf{x}_i(t)) - \sigma \sum_{j=1}^N l_{ij} \mathbf{H}(\mathbf{x}_j), i = 1, \dots, N \quad (2)$$

and the coupling term is basically dependent on the coupling strength σ and the elements of the Laplacian matrix l_{ij} ¹. Here we consider the Laplacian matrix to be symmetric (which ensures that its eigenvalues are real), as it simplifies the definition of the MSF and, in turn, it is the most common situation in the neuroscience literature using the MSF methodology. For identical systems with the same coupling function $\mathbf{H}(\mathbf{x})$, the synchronized state is a solution of $\dot{\mathbf{x}}_s = \mathbf{F}(\mathbf{x}_s)$, with $\mathbf{x}_1 = \mathbf{x}_2 = \dots = \mathbf{x}_N = \mathbf{x}_s$. Next, a linear stability analysis around the synchronization manifold can be carried out. This involves checking whether the Lyapunov exponents corresponding to phase space directions transverse to the synchronization manifold are all negative. To do so, a deviation $\delta \mathbf{x}_i(t) = \mathbf{x}_i(t) - \mathbf{x}_s(t)$ from the synchronous state \mathbf{x}_s is introduced and the linear stability of the whole system evaluated, obtaining an m -dimensional variational equation, m being the number of variables of the dynamical system \mathbf{x} (Pecora and Carroll, 1998; Boccaletti et al., 2006; Arenas et al., 2008):

$$\dot{\xi} = [J\mathbf{F}(\mathbf{x}_s) - \nu J\mathbf{H}(\mathbf{x}_s)]\xi, \quad (3)$$

where J is the Jacobian operator and the independent variable ν is defined as $\nu_i = \sigma \lambda_i$, λ_i being the non-zero eigenvalues of the Laplacian matrix. Finally, the stability of the synchronization manifold can be obtained by studying the parametrical behaviour of the maximum Lyapunov $\lambda_{\max}(\nu)$ as function of ν . $\Psi(\nu) = \lambda_{\max}(\nu)$ with $\nu \in [0, \infty)$ is referred to as the *master stability function* (Pecora and Carroll, 1998; Boccaletti et al.,

2006). Importantly, the MSF as a pure function of ν is independent of the network of connections between the dynamical systems. However, considering a specific network of connections determines particular values of ν_i , which can be related to the MSF, ultimately determining the conditions for the stability of the synchronization manifold of that specific network. Overall, the MSF tells how (i) the dynamical system, through \mathbf{F} and (ii) the network topology, through the second term on the right side of equation (Boccaletti et al., 2006) concur in determining the stability of the synchronization manifold. Note that, the term *synchronizability* refers to the stability of the *global synchronization* state.

The synchronization manifold is stable when all ν_i s associated with the non-zero eigenvalues of the Laplacian matrix lie in a region in which the MSF is negative. However, different dynamical systems with different coupling functions lead to qualitatively different MSFs (see Fig. 1a for details), which can be classified as (Boccaletti et al., 2006): class I (always

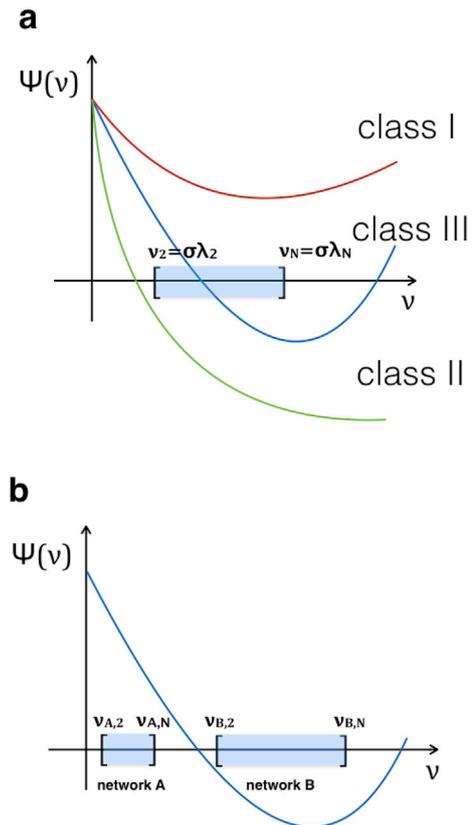


Fig. 1. Master Stability Function $\Psi(\nu)$ as a function of the parameter ν . ν is related to the $(N-1)$ non-zero eigenvalues λ_i of the network Laplacian matrix as $\nu_i = \sigma \lambda_i$ where σ is the coupling strength. The synchronization manifold is stable when all ν_i lie in a region where the MSF is negative. MSFs can be classified as (Boccaletti et al., 2006): class I (always positive), class II (always negative above a threshold ν_2) and class III (negative only within a specific region $[\nu_2, \nu_N]$). Note that, when the MSF has several minima and maxima, the stability region may not be unique (Huang et al., 2009); these MSF classes are not depicted in the figure. (a) Qualitative example of ν_i of a network that would synchronize class I and II dynamical systems, but not class III (assuming that $\lambda_N/\lambda_2 > \nu_N/\nu_2$). The interval $[\nu_2, \nu_N]$ contains the eigenvalues of the Laplacian matrix corresponding to a given network. Note that in this particular example only for the class II system are values of the MSF corresponding to the set of ν_i all negative, indicating that the synchronization manifold is locally stable. (b) Counter-example showing that defining synchronizability parameter as the inverse of the dispersion of the eigenvalues can be misleading: network A has lower dispersion (i.e., higher synchronizability) but lies in the region of the MSF where the synchronization manifold is unstable, while network B, has higher dispersion (and lower synchronizability) but can synchronize. In this qualitative example, we consider the Laplacian matrix to be symmetric.

¹ An adaptation to weighted networks can easily be obtained by including the weights of the connections in \mathbf{A} and replacing the node degree by the node strength (i.e., the sum of the weights of node's links).

positive), class II (always negative above a threshold) and class III (negative only within a specific region). Interestingly, in the context of brain networks, synchronizability is commonly evaluated as if the brain were a class III system, although no proof of it exists. Thus, the lower the ratio r between the largest and smallest (non-zero) eigenvalues (i.e. $r = \lambda_N/\lambda_2$), the more packed the eigenvalues of the Laplacian are and the highest the ability to fall within a window where the MSFs is always negative. In that sense, brain networks' synchronizability is sometimes (Tang et al., 2017) quantified by the dispersion of the eigenvalues of the Laplacian matrix L ².

3.1. Synchronizability: some common misconceptions

The meaning of synchronizability and the questions it allows addressing are a matter of frequent confusion and numerous misconceptions.

An important issue is whether synchronizability can be measured when ignoring the characteristics of the dynamics. Stability under perturbations exists when all eigenvalues of the combinatorial Laplacian matrix $\{\lambda_i\}$ fall within the region of stability due to the fact that the coupling is strong enough to guarantee that the MSF enters the region but weak enough to guarantee that it does not leave this region from the other side. Thus, the value of the coupling strength σ is crucial to determine ν_i once the values of λ_i are obtained from the network structure. Synchronizability is ultimately determined by the sign of the MSF evaluated at points that are indeed given by the spectrum of the Laplacian matrix and an overall coupling strength. The functional form of the MSF crucially depends on the dynamics of the coupled oscillators and the function that couples its state variables to those of other oscillators (Nishikawa and Motter, 2010; Huang et al., 2009). Depending on the shape of the MSF, dynamical systems may never synchronize, always synchronize above a certain coupling strength or synchronize only for coupling strength values within a certain range (Boccaletti et al., 2006; Huang et al., 2009). While the MSF for various families of dynamical systems is typically convex for generic oscillator systems, its exact shape depends not only on the dynamical systems but also on the kind of coupling between them. Thus, quantifying the synchronizability of anatomical brain networks using a parameter based on the eigenvalues of the Laplacian matrix alone, without information about the underlying dynamical oscillators and their coupling function and strength cannot ensure that the whole system falls within MSF's stability region. In other words, it is not the network structure *per se* that is synchronizable, but the particular combination of dynamical systems, coupling strength and network structure formed by the connections between these systems. While the eigenvalues of the Laplacian matrix likely contain potentially valuable information of some sort (Phillips et al., 2015; de Haan et al., 2012), eigenvalue dispersion of the anatomical network alone without at least some information on node dynamics cannot determine the system class one is dealing with, and conclusions on its MSF are no more than guesses (see Fig. 1a). Furthermore, the stability region may not be unique (Huang et al., 2009), and the MSF classes may not be limited to the three depicted in Fig. 1a, further complicating the interpretation of MSF theory's r .

Two related important questions are: what are high or low synchronizability values telling us? When can synchronizability values be compared? The bare comparison of synchronizability values across dynamical systems and the characterization of a given topology as being more or less synchronizable than another are potentially problematic: insofar as different dynamical systems haven't necessarily got similar

² The dispersion of the eigenvalues of the Laplacian matrix is given the following expression: $1/s^2 = \sigma^2(N-1)/\sum_{i=1}^{N-1} |\lambda_i - \bar{\lambda}|^2$ with $\bar{\lambda} = (1/N-1)\sum_{i=1}^{N-1} \lambda_i$, σ being the coupling strength of the N nodes in the anatomical network and λ_i the i -th eigenvalue of the Laplacian matrix.

MSFs, the synchronizability parameter of a brain network cannot be compared with others as long as its MSF is unknown.

Perhaps at the root of most other ones, a major problematic issue relates to the frequent confusion between *synchronizability* and *synchronization*. The synchronizability parameter does not tell if the system is synchronized or not: a system can be highly synchronizable without being synchronized, and synchronized with a low synchronizability parameter (see Fig. 1b).

Finally, it is worth stressing that the synchronizability construct only applies to anatomical networks. This is because the MSF formalism relies on a *structural property*, i.e. the connectivity pattern between dynamical units, which should be complemented by the coupling strength. However, the construction of functional networks relies on the reported coordination between brain regions, i.e. a *dynamical property*. Therefore, functional networks are not the cause of a certain level of synchronizability, but their consequence.

3.2. Why synchronizability should not be used (in neuroscience)

Even discounting the technical issues discussed above, fundamental reasons make the MSF-based synchronizability inapplicable to neuroscience.

Crucially, in its original formulation (Pecora and Carroll, 1998), the MSF applies to diffusively-coupled *identical* dynamical systems, i.e. all interacting units of the network should have the same variables and internal parameters. However, irrespective of the scale at which it is observed, the brain is dynamically highly heterogeneous, ruling out an application of the MSF. While the MSF formalism can be generalized to heterogeneous systems, this comes at the price of rather restrictive conditions hampering its application to brain data (Nishikawa and Motter, 2010; Sun et al., 2009; Zhang and Motter, 2018). No less importantly, the condition of diffusivity, is also grossly violated in the brain.

Perhaps the most fundamental obstacle to the use of the MSF in brain sciences is represented by two issues related to the definition of synchronization. First, while various kinds of synchronization, including phase (Varela et al., 2001), generalized (Stam and van Dijk, 2002), and relay synchronization (Vicente et al., 2008) have been reported for brain dynamics, and may even coexist (Malagarriga et al., 2017), synchronizability refers to a specific synchronization mode, *complete* synchronization. Complete synchronization requires that all dynamical units have *exactly* the same phase and amplitude once the synchronization manifold is reached, a state that has never been reported in the brain (not even in its most pathological conditions). Second, physics and neuroscience understand synchronization in fundamentally different ways: in the former, synchronization refers to a global and stable state, while in the latter to a local and transient one. While local complete synchronization may be a relevant mechanism or a reasonable modelling representation of functionally segregated regions or circuits, its dynamics is necessarily transient. Brain dynamics has in general a complex phase space geometry, and possibly no *stricto sensu* attractor at all (Rabinovich et al., 2008; Tognoli and Kelso, 2014), a scenario that cannot be dealt with using the MSF in its current form.

4. Towards neurophysiologically plausible alternatives to synchronizability

Several technical systems, e.g. power grids, wireless communication systems, require stable synchronization of their units (Kinzel et al., 2010; Tyrrell et al., 2010; Rohden et al., 2012, 2014; Motter et al., 2013). Synchronizability represents, to good approximation, a construct that can be used to model and regulate their dynamics and function. However, synchronizability refers to a type of synchronization that the brain does not, certainly should not, and possibly cannot achieve in a stable way. In addition to being incompatible with the dynamical and functional heterogeneity of normal brain functioning, a completely synchronized state represents a considerable loss of complexity, and would likely be

associated with an unphysiological energetic cost (Torrealdea et al., 2009; Moujahid et al., 2011).

Before figuring out possible alternatives to the MSF-based synchronizability, one should perhaps address the following question: why is the MSF framework used although it is so evidently at odds with neurophysiological stylized facts? What makes the MSF a convenient tool? While a unique coupling function for all network nodes and some hypotheses on the coupling matrix are convenient mathematical conditions which ensure the existence of an invariant set representing the complete synchronization manifold and considerably simplify the analysis of its stability, using steady state dynamics and complete synchronization dispenses with defining spatial topography and temporal scales of the target process.

To figure out possible alternatives to the MSF-based synchronizability construct one needs to understand both the role played by synchronization within this conceptual framework and the objective pursued by the studies using it and the problems that they aim to address. On the one hand, while in neuroscience synchronization typically refers to *transient* bivariate coupling between two neuronal ensembles, the synchronization referred to by synchronizability is in fact better thought of as a (*steady-state*) process on a network. On the other hand, from a teleological viewpoint, resorting to the MSF formalisms can be understood in terms of the need to address the relationship between structure (or, more precisely, the topology defined on it) and dynamics in complex systems (Arenas et al., 2008; Skardal et al., 2014; Menck et al., 2013; Ponten et al., 2010). Furthermore, this relationship must be understood at all meaningful spatial scales of the brain (Kelso et al., 2013). Given an observed dynamics and topological organization, a construct teleologically equivalent to synchronizability may possibly be framed in terms of a networked system's propensity to enter a *functionally desirable* state or regime, as in (Wang and Slotine, 2005). But what dynamical states or regimes may represent a valuable target, the distance from which may be used as a neurophysiologically meaningful benchmark?

The true difficulty in finding alternatives to the MSF-based synchronizability is that one loses the uniqueness and task-invariance of the complete synchronization state and needs to cope with brain dynamics' spatial heterogeneity and temporal multiscale nature, and brain function's translational invariance. To define a valid equivalent of synchronizability will likely require three key ingredients: neurophysiologically plausible and functionally meaningful order parameters describing collective brain activity; mechanisms through which they may emerge; and, no less importantly, those through which they may wane. On the one hand, this should for instance involve considering networks of heterogeneous oscillators and plausible synchronization processes, compatible with metastable dynamics (Tognoli and Kelso, 2014; Deco et al., 2017; Roberts et al., 2019). On the other hand, the mechanisms through which neural assemblies interact and their role in human brain function at various scales of brain anatomy and dynamics should be better understood at both functional/computational and algorithmic/dynamical levels. These mechanisms are likely context-specific, and various ones may even coexist (Malagarriga et al., 2017). As a consequence, the definition of a dynamical target may vary as a function of the putative role of synchrony *lato sensu* in the target activity. On the one hand, dynamical references may be associated with different dynamical regimes, e.g. cluster synchronization, in which patterns or sets of synchronized elements emerge, chimera-like states, i.e. spatiotemporal patterns with coexisting coherence and incoherence, or partial synchronization, where only some parts of the network synchronize, while others do not (Zhou and Kurths, 2006; Abrams et al., 2008; Bi et al., 2016). Importantly, these dynamical regimes would induce spatial scales. On the other hand, rather than statistically stationary states, what is needed is an analysis of their dynamics, stability, bifurcations, and symmetries (Abrams et al., 2008; Pecora et al., 2014). Importantly, a reference regime should also replicate the temporal scales of some (task-specific or task-independent) reference brain activity. The construct may for instance contain predictive information on the properties of and on the conditions under which these

clusters form and dissolve. Defining meaningful dynamical target processes and some sort of distance from them to given observed ones, understanding whether and the extent to which these may emerge from interactions between local dynamics and network topology are all highly non-trivial but fundamental questions, finding answers to which will likely keep the neuroscience community busy for some time to come.

5. Concluding remarks

We have argued that not only is the synchronizability construct an inadequate tool to quantify brain networks' ability to synchronize, but the problem itself to which it is supposed to provide an answer appears to be ill-posed when studying brain dynamics. More generally, the brain differs in many essential ways from the systems (e.g. the electrical power-grid or the Internet) most network theory constructs were originally designed to account for. Neuroscience, a field where network theory has only relatively recently come to the foreground (Bullmore and Sporns, 2009), has so far mainly borrowed its tools and concepts without inspiring fresh theory, and this has exposed it to the risks inherent in such an application: over-, under- and misuse of existing tools (Papo et al., 2014, 2016). The brain's unique properties can help promoting a fundamental reformulation of network neuroscience for benefit of both neuroscience and graph theory.

Acknowledgements

D.P. acknowledges financial support from the program *Accueil de Talents* of the Métropole Européenne de Lille and from the Labex (laboratory of excellence) DISTALZ (Development of Innovative Strategies for a Transdisciplinary approach to Alzheimer's disease). J.M.B. is funded by MINECO (project FIS2017-84151-P).

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