

# Normalized Connectomes Show Increased Synchronizability with Age through Their Second Largest Eigenvalue\*

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**Abstract.** The synchronization of different brain regions is widely observed under both normal and pathological conditions, such as epilepsy. However, the relationship between the dynamics of these brain regions, the connectivity between them, and the ability to synchronize remains an open question. We investigate the problem of inter-region synchronization in networks of Wilson–Cowan/neural field equations with homeostatic plasticity, each of which acts as a model for an isolated brain region. We consider arbitrary connection profiles with only one constraint: the rows of the connection matrices are all identically normalized. We found that these systems often synchronize to the solution obtained from a single, self-coupled neural region. We analyze the stability of this solution through a straightforward modification of the master stability function (MSF) approach and found that synchronized solutions lose stability for connectivity matrices when the second largest positive eigenvalue is sufficiently large for values of the global coupling parameter that are not too large. This result was numerically confirmed for ring systems and lattices and was also robust to small amounts of heterogeneity in the homeostatic set points in each node. Finally, we tested this result on connectomes obtained from 196 subjects over a broad age range (4–85 years) from the Human Connectome Project. We found that the second largest eigenvalue tended to decrease with age, indicating an increase in synchronizability that may be related to the increased prevalence of epilepsy with advancing age.

**Key words.** synchronizability, dynamical systems theory, network neuroscience, connectomes, master stability functions

**AMS subject classifications.** 37N25, 92B20, 92B25

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**1. Introduction.** Neuroscience has gained the ability to noninvasively map the structural and functional connectivity of the brain in a diverse group of subjects with the emergence of large-scale connectomics initiatives (Van Essen et al., 2013; Behrens and Sporns, 2012). This capability has created a cornucopia of neuroimaging data in the form of connection matrices or connectomes. These connectomes determine how brain regions are coupled either structurally via white matter tracts, or functionally through correlations. However, a natural problem emerges with this glut of data: How do we use it?

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The initial approach in analyzing these connectomes originates from graph theory, with the nodes of the network corresponding to the vertices of a mathematical graph and the elements of the connection matrix determining the edges of the graph (Bondy and Murty, 1976). The connectomes are then analyzed for graph-based statistics, such as connectivity, mean in/out degrees, average shortest path length, average motif strengths and frequencies, or community structures, to name a few (Romme et al., 2017). Typically, these statistics are average properties of the connections between individual nodes or small populations of nodes over the entire graph, although some may be more global in nature. These graph-based statistics have proven useful for summarizing and elucidating the differences between connectomes of healthy individuals and those of subjects with pathological conditions (Van den Heuvel et al., 2016).

However, the dynamics of a large network are not solely determined by graph-based statistics. Indeed, dynamical systems theory tells us that the eigenvalues of the connection matrix are often the critical determining factor of the stability of any particular solution (Schaub et al., 2015). This statement was clarified further in (Pecora and Carroll, 1998) through the derivation of the so-called master stability function (MSF). The MSF determines under what conditions a dynamical system synchronizes and only depends on the eigenvalues of a connection matrix rather than any explicit graph-based measure.

Given the power of the MSF approach, computational neuroscience has recently started analyzing connectome eigenvalues rather than graph-based statistics (Tang et al., 2017). This is typically done by taking the raw structural connectome and computing the Laplacian matrix. This is a critical step required to apply standard MSF analysis. Owing to its construction, the Laplacian effectively assumes that neurons have diffusive coupling, where strong within-region connections exactly balance connections between regions, resulting in no net-coupling between the nodes when they synchronize (Tang et al., 2017; Nishikawa and Motter, 2010). Unfortunately, the evidence for diffusive coupling is scant, which has led to well-warranted caution on the applicability of this assumption and the MSF to neuroscience in (Papo and Buldú, 2019).

Here, we address this criticism of the MSF approach by considering an alternate coupling assumption for diffusion tensor imaging (DTI)-derived structural connectomes. Rather than assuming diffusive connectivity, we instead assume that each neural region has the same level of incoming activity. Biologically, this could be achieved by the growth or pruning of dendritic spines at synapses, which would adjust the synaptic weights (Segal and Andersen, 2000; Bonhoeffer and Yuste, 2002). In our theoretical work, we achieve this through a normalization process, where the incoming weights for each node are divided by the total weight sum for that node. We tested our approach on a network of Wilson–Cowan nodes with intranode inhibitory homeostatic plasticity (Hellyer et al., 2016; Nicola et al., 2018; Vogels et al., 2011) and various synthetic connectivity matrices. Unlike previous work in (Tang et al., 2017; Nishikawa and Motter, 2010), we also derive explicitly the MSF for these networks based on this dynamical model, which thereby allows us to determine the explicit region of stability/instability and derive a stability criterion for the eigenvalues of the normalized connectivity matrices. We find that the magnitude of the second largest eigenvalue (SLE) of the normalized connectivity matrix is the critical determining factor for the stability of the synchronized state, while the largest eigenvalue is identical for all connectomes due to normalization. Finally, we ap-

plied this approach to DTI-derived structural connectome data from the Human Connectome Project for  $n = 196$  subjects over a broad age range (4–85 years). We find that the SLE of these normalized connectomes decreases with age. Extrapolating from our analysis, we find that this implies increasing synchronizability with age. This partially mirrors the epidemiology of epilepsy, where prevalence increases with advancing age (Beghi and Giussani, 2018; Leppik et al., 2006), indicating a potential diagnostic use of the eigenvalues of the DTI-derived structural connectomes.

**2. Model description.** In order to apply the MSF approach, an explicit model of the dynamics of the nodes and coupling between nodes is necessary. Here, we consider a modification of the Wilson–Cowan system (Wilson and Cowan, 1972) first developed in (Hellyer et al., 2016; Nicola et al., 2018). This system is described by three dynamical variables,

$$(1) \quad \tau_1 \frac{dE_k}{dt} = -E_k + \phi \left( \sum_{j=1}^N W_{kj}^{EE} E_j - W_k^{EI} I_k \right),$$

$$(2) \quad \frac{dI_k}{dt} = -I_k + \phi(W^{IE} E_k),$$

$$(3) \quad \tau_2 \frac{dW_k^{EI}}{dt} = I_k(E_k - p), \quad k = 1, 2, \dots, N,$$

where  $E_k$  is the activity of the excitatory population of neurons within the  $k$ th node, and  $I_k$  is the activity of the inhibitory population in the  $k$ th node (see Figure 1A). The synaptic weights  $W^{\alpha\beta}$  denote connections between neurons in population  $\beta = E, I$  to neurons in population  $\alpha = E, I$ , where  $E$  and  $I$  denote the excitatory and inhibitory populations, respectively. The weights  $W_{kj}^{EE}$  represent excitatory connections between populations in different nodes. All other connections are intranodal. The weight  $W_k^{EI}$  is the homeostatically adjusted inhibitory weight. The population activities are variables that are confined to the interval  $(0, 1)$ . They loosely correspond to the proportion of neurons active in node  $k$  and are thus “neural-field” or “mean-field” approximations to a large population of neurons. These are regularly used in computational neuroscience to investigate diverse network level phenomena (Kilpatrick and Ermentrout, 2013; Ermentrout, 1998; Folias and Ermentrout, 2012; Coombes, 2010; Breakspear, 2017; Bressloff, 2019; Pinto et al., 1996; Park and Ermentrout, 2018). The inhibitory homeostatic weight  $W_k^{EI}$  drives the excitatory population activity  $E_k$  towards the homeostatic set-point  $p$ .

All synaptic weights satisfy the requirement that

$$W_{kj}^{EE} > 0, \quad W^{IE} > 0, \quad W_k^{EI} > 0,$$

where the excitatory/inhibitory character of the weight is carried by the signs in (1)–(3).

The sigmoidal transfer function  $\phi(x)$  satisfies the following properties:

$$0 < \phi(x) < 1, \quad x \in \mathbb{R}, \quad \phi'(x) > 0, \quad x \in \mathbb{R}, \quad \lim_{x \rightarrow -\infty} \phi(x) = 0, \quad \lim_{x \rightarrow \infty} \phi(x) = 1.$$

In numerical simulations, we will primarily consider the logistic transfer function

$$\phi(x) = \frac{1}{1 + \exp(-ax)}.$$

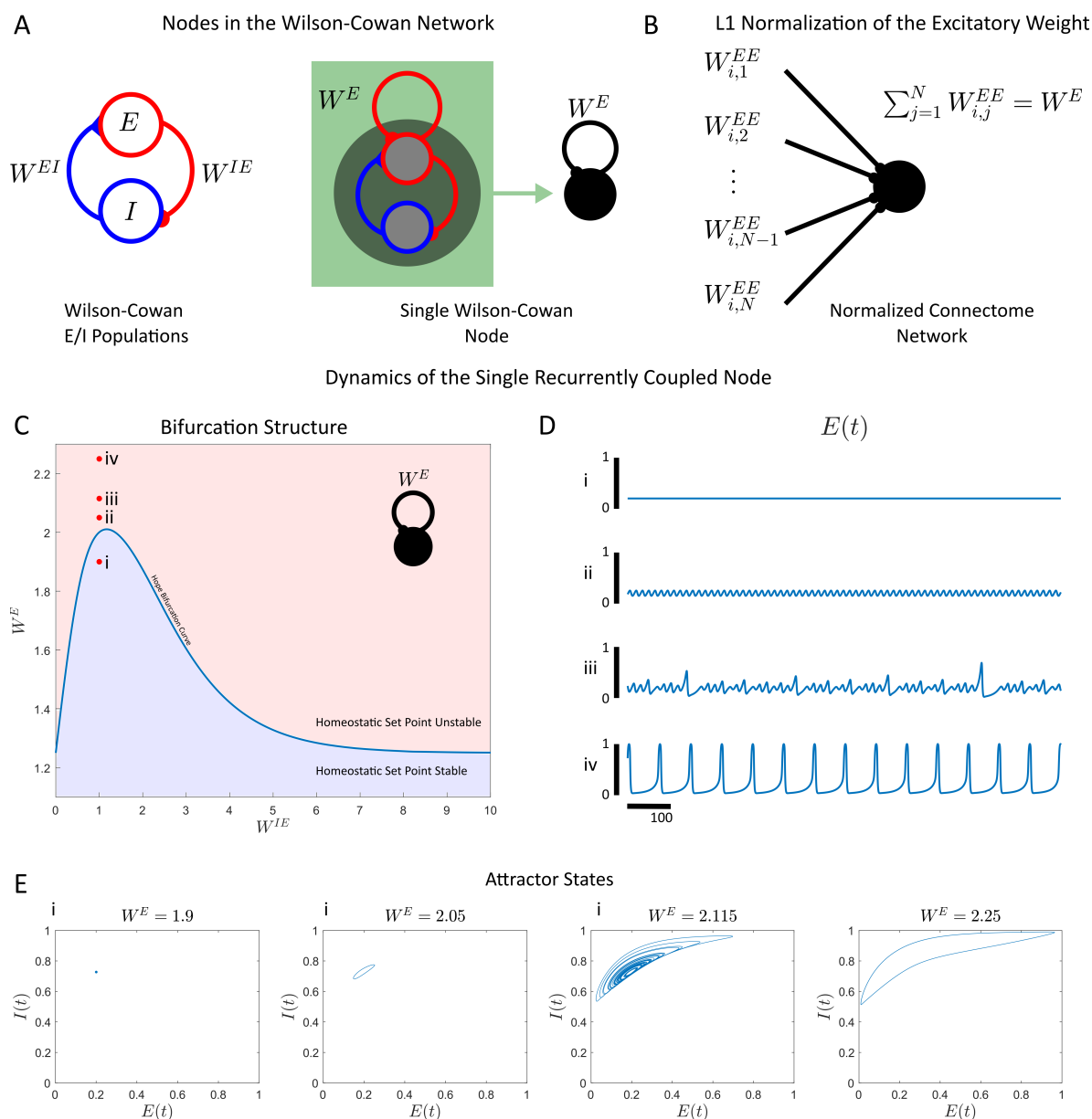


**Figure 1.**  $L_1$  normalization and dynamics of the single recurrently coupled node. Large-scale synchronization to the single self-coupled node dynamics. (A) A single node of the Wilson-Cowan system (left) with homeostatic plasticity consists of an excitatory population ( $E$ ), an inhibitory population ( $I$ ), and weights  $W^{EI}$ ,  $W^{IE}$  coupling these two populations together. The weight  $W^{EI}$  is dynamic and serves to maintain a homeostatic set point in  $E$ . Nodes are connected together via the excitatory populations with weights  $W^{EE}$  (middle). An important driver of network behavior is the single recurrently coupled node (right). (B) The normalization condition applied in larger networks,  $\sum_{j=1}^N W_{i,j}^{EE} = W^E$ , is an  $L_1$  normalization condition on each vector of input weights. (C) The local bifurcation diagram of the single recurrently coupled node; a Hopf bifurcation curve (blue) delineates the region where the homeostatic set point is stable (blue) and unstable (red). (D) Dynamics of the excitatory population for different values of  $W^E$ :  $W^E = 1.9$  (i),  $W^E = 2.05$  (ii),  $W^E = 2.115$  (iii),  $W^E = 2.25$  (iv). (E) Projections of the steady state attractors into the  $(E, I)$  plane. Details of parameter values and numerical methods can be found in Appendices A and B.

To prevent individual nodes from saturating due to excessively high inputs, or becoming quiescent due to insufficient input, we assume that the input weights of each neural region are normalized (Figure 1B). Mathematically, this assumption becomes the following:

$$(4) \quad \sum_{j=1}^N W_{ij}^{EE} = W^E, \quad i = 1, 2, \dots, N, \quad (\text{constant row sum for all nodes})$$

$$(5) \quad W_{ij}^{EE} \geq 0, \quad i, j = 1, 2, \dots, N.$$

The two conditions (4) and (5) immediately imply that the weight matrix  $\mathbf{W}^{EE}$  has identical  $L_1$  normalized row-sums. Recall that the  $L_1$  norm of a vector  $x \in \mathbb{R}^n$  is defined as  $\|x\|_1 = \sum_{i=1}^n |x_i|$ . Further, (4) also implies that the largest eigenvalue of  $\mathbf{W}^{EE}$  is  $W^E$  by the Perron–Frobenius theorem. Before we proceed further we note that it is convenient to write the coupling matrix  $\mathbf{W}^{EE}$  as follows:

$$(6) \quad \mathbf{W}^{EE} = W^E \mathcal{L}^{EE}, \quad \sum_{j=1}^N \mathcal{L}_{kj}^{EE} = 1, \quad k = 1, 2, \dots, N.$$

Before we proceed with the analysis of the main system in (1)–(3), we will first look at a general system below to show how the MSF analysis is commonly applied to neural systems via diffusive coupling.

**2.1. Comparison with diffusive coupling.** The system of equations (1)–(3) when coupled with (4) and (5) is a departure from the commonly used diffusive coupling assumption, which has been recently criticized as being unsupported by biological evidence (Papo and Buldú, 2019). In this section, we briefly outline the key differences between these two coupling profiles in a generalized form. First, a system of oscillators governed by the dynamics  $\dot{\mathbf{x}} = F(\mathbf{x})$  is diffusively coupled if the model has the form

$$(7) \quad \dot{\mathbf{x}}_i = F(\mathbf{x}_i) - \sum_{j=1}^N W_{ij} (G(\mathbf{x}_j) - G(\mathbf{x}_i)),$$

where  $\mathbf{W}$  is any possible connectivity matrix and  $G$  is any coupling function. This is a convenient assumption, as it lets one perform the MSF analysis by rearranging terms and considering the Laplacian matrix

$$(8) \quad \dot{\mathbf{x}}_i = F(\mathbf{x}_i) - \sum_{j=1}^N L_{ij} G(\mathbf{x}_j),$$

where  $L_{ij} = W_{ij}$  if  $i \neq j$  and  $L_{ij} = -\sum_{j=1}^N W_{ij}$  if  $i = j$ . In the diffusively coupled case, synchronized solutions of the full network, i.e.,  $\mathbf{x}_i(t) = \mathbf{x}(t)$ ,  $i = 1, \dots, N$ , correspond to solutions of the isolated nodes  $\mathbf{x}' = F(\mathbf{x})$ . Note that the contribution of the coupling vanishes at synchronization.

If we consider the same node dynamics ( $\mathbf{x}' = F(\mathbf{x})$ ) and coupling function  $G(\mathbf{x})$ , the model with the normalized coupling assumption becomes

$$(9) \quad \dot{\mathbf{x}}_i = F(\mathbf{x}_i) - \sum_{j=1}^N W_{ij} G(\mathbf{x}_j), \quad \sum_{j=1}^N W_{ij} = W \quad \forall i.$$

With normalized coupling, synchronized solutions of the network correspond to solutions of the single, self-coupled node,

$$\mathbf{x}' = F(\mathbf{x}) - WG(\mathbf{x}).$$

Here, the coupling is strong at synchronization, and the solution that an oscillator synchronizes to is not necessarily a solution displayed by any isolated node. Crucially, the MSF approach can still be used to analyze synchronization phenomena in the normalized coupling case, as shown, for example, in (Choe et al., 2010; Heiligenthal et al., 2011). The key point here is that applying MSF analysis to study synchronization phenomena is not explicitly reliant on assuming that the system is diffusively coupled. One can consider the more biologically plausible assumption of normalized coupling. In neural systems, the biological basis for the normalized coupling assumption is that if the nodes are receiving too much excitatory input, their activities could easily diverge, while nodes that receive insufficient inputs would hardly be active at all. Thus, networks should adjust the synaptic weights to prevent either too much or too little activity for healthy functioning (Segal and Andersen, 2000; Bonhoeffer and Yuste, 2002).

### 3. Analysis.

**3.1. Local analysis of equilibria.** Before we consider the synchrony of solutions, we must first investigate when nonequilibrium solutions to (1)–(3) actually exist. For any connectome, the stable equilibrium point determined by the homeostatic set point destabilizes for a sufficiently large  $W^E$ , as was first derived in our earlier work (see (Nicola et al., 2018)). We summarize the main results of this study here for brevity and ease of reference:

1. All nodes share the common equilibrium point  $E_k = p, I_k = \phi(W^{IE}p), W_k^{EI} = \frac{W^E p - \phi^{-1}(p)}{\phi(W^{IE}p)}$ ,  $k = 1, 2, \dots, N$ . This is the only equilibrium point of the  $N$  node system. For convenience, we will refer to this equilibrium point as  $\mathbf{z}$ .
2. The characteristic polynomial for the system (1)–(3) always decomposes into a product of  $N$  cubic polynomials, where each cubic polynomial is of the same general form but with coefficients that depend on the eigenvalues  $r_1, r_2, \dots, r_N$  of  $\mathcal{L}^{EE}$  as in the following:

$$C(\lambda) = \prod_{i=1}^N \left( Q(\lambda) - W^E \frac{r_i \lambda (\lambda + 1) \phi'(\phi^{-1}(p))}{\tau_1} \right),$$

$$Q(\lambda) = \lambda^3 + \lambda^2 \left( \frac{1}{\tau_1} + 1 \right) + \lambda \left( \frac{1}{\tau_1} + \frac{\bar{W}^{EI} \phi'(\phi^{-1}(p)) \phi'(W^{IE}p) W^{IE}}{\tau_1} + \frac{\bar{I}^2 \phi'(\phi^{-1}(p))}{\tau_1 \tau_2} \right) + \frac{\bar{I}^2 \phi'(\phi^{-1}(p))}{\tau_1 \tau_2}.$$

3. The cubic polynomial associated with the maximum eigenvalue of  $\mathcal{L}^{EE}$ , 1, induces a Hopf bifurcation of the equilibrium point. While the general form for the bifurcation curve is complicated, it is typically of the form

$$(10) \quad W^{EE} = g(W^{IE}),$$

where  $g(x)$  is a nonmonotonic, unimodal function (Figure 1C; see (Nicola et al., 2018) for the exact functional form).

Result 1 follows directly from the form of (1)–(3), while results 2 and 3 are derived in (Nicola et al., 2018).

This Hopf bifurcation coincides with the bifurcation curve of the single recurrently coupled node. In fact, all invariant sets (equilibria, limit cycles, etc.) for the single recurrently coupled node exist for any  $L_1$  normalized connectome. For the single recurrently coupled node, these invariant sets are stable and transition from low amplitude oscillations to chaos, mixed-mode chaos, and mixed-mode oscillations (Figure 1C–E) for progressively larger  $W^E$  (Nicola et al., 2018).

As we will see from the MSF analysis below, networks with  $L_1$  normalized connectomes can synchronize to these states depending on the eigenvalue spectrum of the  $L_1$  normalized weight matrix and, in particular, the magnitude of the SLE of the normalized connectome.

**3.2. Master stability function analysis.** To investigate this system more generally than in (Nicola et al., 2018) and study the stability of synchronized solutions, we conducted large-scale simulations of a variety of connectome types (see Figure 2). First, as in (Nicola et al., 2018), we found that networks of homeostatically coupled Wilson–Cowan nodes readily synchronized to attractor states of the single recurrently coupled node system with a self coupling strength of  $W^E$  (Figure 2A–D),

$$(11) \quad \tau_1 \frac{dE}{dt} = -E + \phi(W^E E - W^{EI} I),$$

$$(12) \quad \frac{dI}{dt} = -I + \phi(W^{IE} E),$$

$$(13) \quad \tau_2 \frac{dW^{EI}}{dt} = I(E - p).$$

We refer to the nonequilibrium point attractor solutions to (11)–(13) as  $(E_s(t), I_s(t), W_s^{EI}(t))$ . This result was consistent across a variety of common coupling types, such as small ring networks, lattices, and small-world networks. However, some connectomes could display non-synchronized solutions for a given value of  $W^E$ , such as larger rings ( $N > 9$ ), weak coupling networks, and larger lattices (see Figure 2E). Thus, some connectomes have the capability of destabilizing the synchronized solution arising from the single recurrently coupled node.

To investigate the loss of stability as a function of the underlying weight matrices, we slightly modified the traditional MSF approach (see Figure 3A). First, we consider perturbations of the synchronized solution

$$(14) \quad \epsilon_k = E_k - E_s, \quad i_k = I_k - I_s, \quad \omega_k = W_k^{EI} - W_s^{EI}.$$

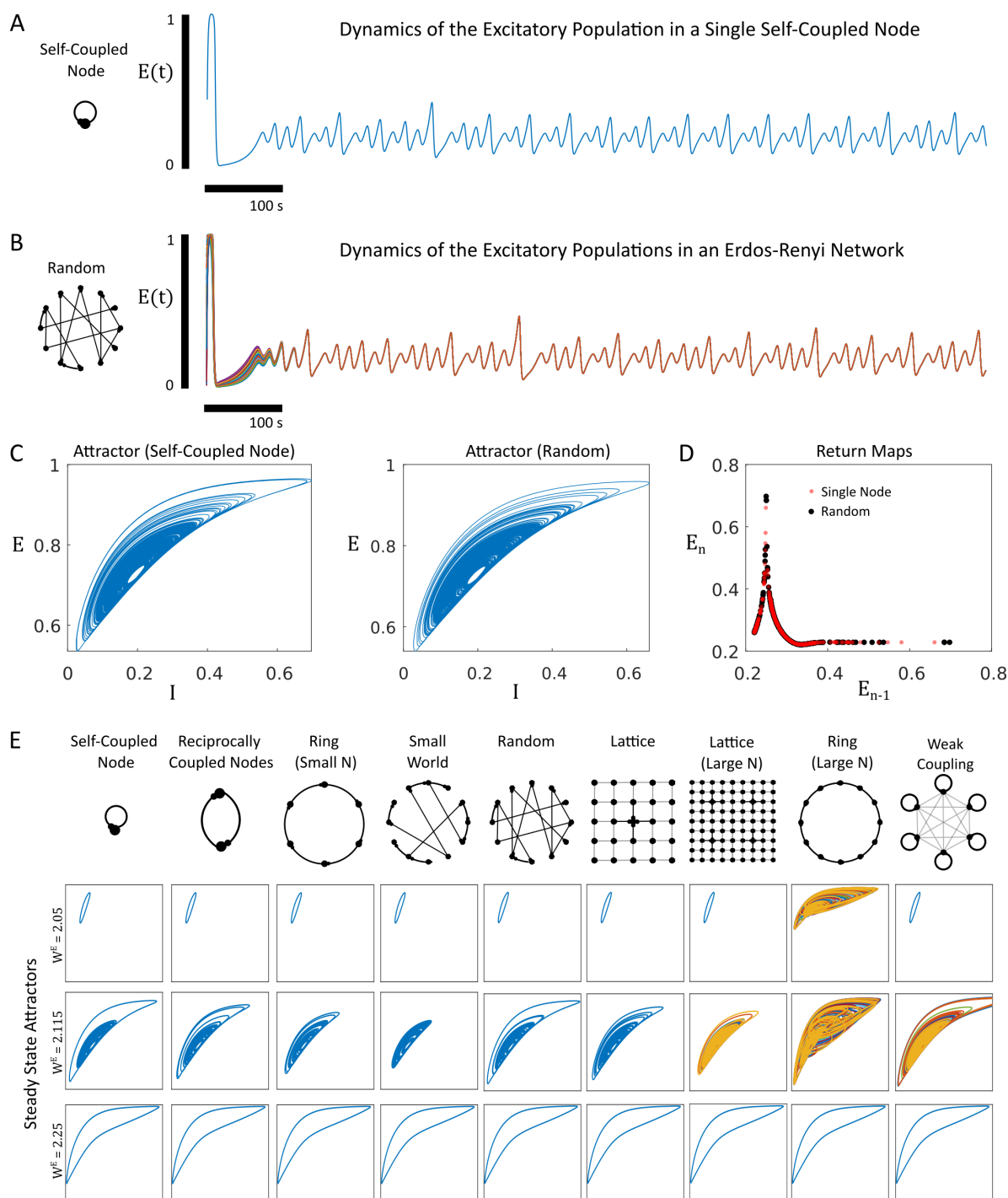


**Figure 2.** Large-scale synchronization to the single self-coupled node dynamics. (A) The activity for the excitatory population  $E(t)$  for a single recurrently coupled node for  $W^E = 2.115$  in the chaotic dynamics regime considered by (Nicola et al., 2018). (B) An Erdős-Rényi coupled network with  $N = 100$  nodes, with an  $L_1$  normalized connectome with an identical  $W^E$  as in (A). The nodes all synchronize onto a chaotic attractor. (C) The steady state attractors for the single-node system in (A) and the 100-node Erdős-Rényi system in (B). (D) The return maps for the excitatory populations of both networks, where the  $(n-1)$ th peak of  $E(t)$  is plotted against the  $n$ th peak. As the return maps broadly overlap, the two attractors are identical. (E) Steady state attractors for a single self-coupled node at  $W^E = 2.05$ ,  $W^E = 2.115$ , and  $W^E = 2.25$ ; two nodes with reciprocal coupling; a ring consisting of  $N = 7$  nodes; A Watts-Strogatz small-world network with  $N = 200$  nodes; a random network with  $N = 100$  nodes; a  $10 \times 10$  lattice network; a  $20 \times 20$  lattice network; a ring with  $N = 10$  nodes; and a system with  $N = 50$  nodes that have strong self-coupling but random weak-coupling to other nodes. Some systems display robust synchronization phenomena across states, while other systems desynchronize. Details of parameter values and numerical methods can be found in Appendices A and B.

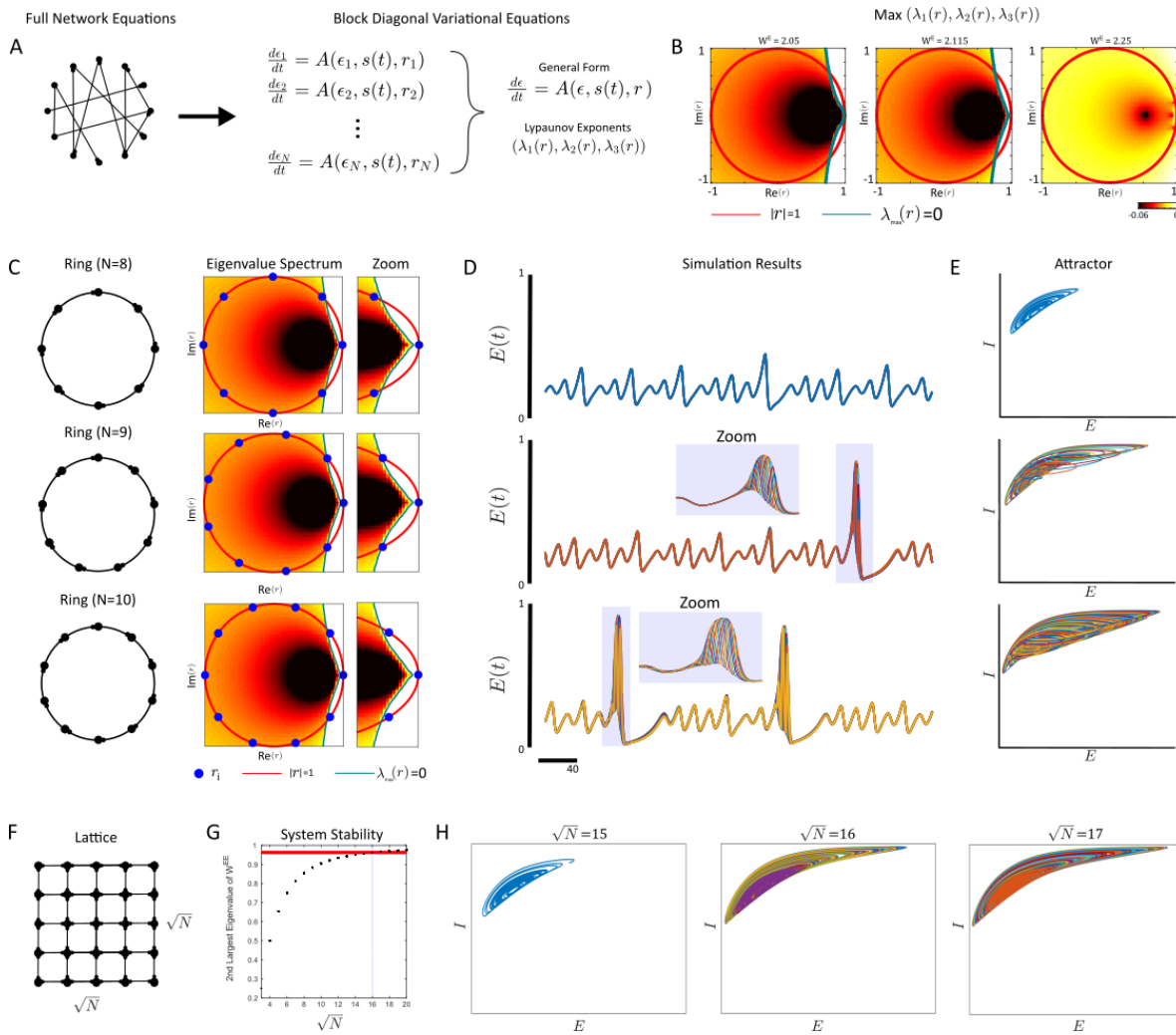


**Figure 3.** MSF analysis for  $L_1$  normalized connectomes. (A) To derive the MSF for the synchronized solution (SS) to any connectome, the original dynamical system is first linearized and diagonalized into a general form involving the independent perturbations to the dynamics  $\epsilon$ , and the eigenvalues of the matrix  $W^{EE}$ . The MSF can be numerically approximated for any weight matrix by resolving the Lyapunov exponents for the general block over a mesh in  $r$ . The largest positive eigenvalue yields the MSF. (B) The numerically derived MSFs for the Wilson-Cowan system (1)–(3) for the values  $W^E = 2.05$  (limit cycle SS), 2.115 (chaotic attractor SS), and 2.25 (relaxation oscillator SS). (C) The MSF for  $W^E = 2.115$  applied to rings of increasing size. (D) The dynamics of the simulated network. Note that the nonfully synchronized attractors for  $N = 9, 10$  display periods of synchronization along with periods of desynchronization. (E) Steady state attractors projected onto the  $(E, I)$  plan for the  $N$  node ring network. (F) Lattices of size  $\sqrt{N} \times \sqrt{N}$  with nearest neighbor coupling. (G) The MSF analysis for  $W^E = 2.115$  predicts the onset of instability to the synchronous solution at  $\sqrt{N} = 16$ . (H) Network attractor states for  $\sqrt{N} = 15, 16, 17$ .

These generate the following variational equations:

$$\begin{aligned} \epsilon'_k &= E'_k - E'_s = \frac{1}{\tau_1} \left( -\epsilon_k + \phi'(W^E E_s - W_s^{EI} I_s) \left( \sum_{j=1}^N W_{kj}^{EE} \epsilon_j - W_s^I i_k - \omega_k I_s \right) + H.O.T. \right), \\ i'_k &= I'_k - I'_s = -i_k + \phi'(W^{IE} E_s) W^{IE} \epsilon_k + H.O.T., \\ \omega'_k &= (W_k^{EI})' - (W_s^{EI})' = \frac{1}{\tau_2} (i_k (E_s - p) + I_s \epsilon_k) + H.O.T., \end{aligned}$$

where *H.O.T.* denotes higher order terms. Dropping the H.O.T. and considering the linearization in matrix form yields

$$(15) \quad \tau_1 \epsilon' = -\epsilon + \phi'(W^E E_s - W_s^{EI} I_s) \cdot (W^{EE} \epsilon - W_s^{EI} \cdot i - I_s \cdot \omega),$$

$$(16) \quad i' = -i + \phi'(W^{IE} E_s) W^{IE} \epsilon,$$

$$(17) \quad \tau_2 \omega' = (E_s - p) \cdot i + I_s \cdot \epsilon.$$

As in the traditional MSF approach, we consider the case where the matrix  $W^{EE}$  is diagonalizable:

$$(18) \quad W^{EE} = P D P^{-1}, \quad \eta_\epsilon = P^{-1} \epsilon, \quad \eta_i = P^{-1} i, \quad \eta_\omega = P^{-1} \omega.$$

Then we have

$$(19) \quad \tau_1 \eta'_\epsilon = P^{-1} (-P \eta_\epsilon + \phi'(W^E E_s - W_s^{EI} I_s) (P D \eta_\epsilon - W_s^{EI} \cdot P \eta_i - I_s \cdot P \eta_\omega)),$$

$$(20) \quad \tau_1 \eta'_\epsilon = -\eta_\epsilon + \phi'(W^E E_s - W_s^{EI} I_s) \cdot (D \eta_\epsilon - W_s^{EI} \cdot \eta_i - I_s \cdot \eta_\omega),$$

$$(21) \quad \eta'_i = -\eta_i + \phi'(W^{IE} E_s) W^{IE} \cdot \eta_\epsilon,$$

$$(22) \quad \tau_2 \eta'_\omega = (E_s - p) \cdot \eta_i + I_s \cdot \eta_\epsilon.$$

Simplifying yields the following  $N$  independent, 3-dimensional systems:

$$(23) \quad \tau_1 \eta'_\epsilon = -\eta_\epsilon + \phi'(W^E E_s - W_s^{EI} I_s) (\hat{r}_k \eta_\epsilon - W_s^{EI} \eta_i - I_s \eta_\omega),$$

$$(24) \quad \eta'_i = -\eta_i + \phi'(W^{IE} E_s) W^{IE} \eta_\epsilon,$$

$$(25) \quad \tau_2 \eta'_\omega = (E_s - p) \eta_i + I_s \eta_\epsilon,$$

where  $\hat{r}_k, k = 1, \dots, N$ , are the eigenvalues of  $W^{EE}$ . The important point here is that given an attractor state for fixed  $W^E$ ,  $(E_s(t), I_s(t), W_s^I(t))$ , we can assess the stability for any weight matrix  $W^{EE}$  by analyzing the stability of the equilibrium point, 0, of the decoupled blocks in (23)–(25) above. These blocks only differ in their dependence on the eigenvalue  $\hat{r}_k$  of  $W^{EE}$ . In fact, for fixed  $W^E$  we need only do the analysis for  $\hat{r}_k$  such that  $|\hat{r}_k| \leq W^E$  for all  $k$ , as required by the  $L_1$  normalization constraint on  $W^{EE}$ .

Note that for all subsequent simulations and plots, we will consider  $r_k = \frac{\hat{r}_k}{W^E}$ , which corresponds to an eigenvalue of the normalized matrix  $\mathcal{L}^{EE}$ , which has a maximal eigenvalue of 1.

While (23)–(25) may not seem particularly useful at first glance, they reduce the analysis of the stability of the synchronized state for any connectome to a simple numerical algorithm (Pecora and Carroll, 1998) by decoupling the computation of  $3N$  eigenvalue problems into  $N$ , separate, 3-dimensional systems. One exploits this by treating (23)–(25) as a general form and using them (in conjunction with (11)–(13)) to compute the Lyapunov exponents over a mesh in the  $(\text{Re}(r), \text{Imag}(r))$  space (see Figure 3B). Then, the eigenvalues can be computed for any connectome  $W^{EE} = W^E \mathcal{L}^{EE}$  and the corresponding Lyapunov exponents of the synchronized solution immediately determined simply by a look-up operation on the precomputed mesh (see Figure 3B).

We applied this procedure and found that for values of  $W^E$  near the Hopf bifurcation of the single recurrently coupled node, the maximum Lyapunov exponent is positive for sufficiently large eigenvalue magnitudes,  $|r|$ . However, for a suitably large  $W^E$ , the synchronized solution is stable for all  $|r|$  as all Lyapunov exponents are nonpositive for  $|r| < 1$ .

To test this result, we considered two diagonalizable connectomes, the ring and lattice solutions, and determined when the synchronized state loses stability as a function of the network size,  $N$ . Our MSF analysis shows that the eigenvalues of the ring cross into the positive Lyapunov exponent region for  $N = 9$  (see Figure 3C). Indeed, we find that simulations of rings for  $N = 8, 9, 10$  show that the synchronized solution is stable for  $N = 8$  and unstable for larger  $N$ . However, the attractor state for  $N > 8$  node ring systems has periods of synchrony interspersed with bursts of asynchrony (see Figure 3D,E). For lattice-based connectomes, we find that for an  $\sqrt{N} \times \sqrt{N}$  lattice, the MSF analysis predicts the instability of the synchronized solution initiating at  $\sqrt{N} = 16$  (see Figure 3G), which was also confirmed by our numerical simulations (see Figure 3H).

Thus, for the Wilson–Cowan system considered here, the stability of the synchronized solution is largely determined by the SLE of the connectome. The larger the magnitude of the SLE, the greater the potential for desynchronization, while the smaller the magnitude of the SLE, the greater the stability of the synchronous solution.

**4. Network simulations with heterogeneous nodes.** While MSF analysis can determine when synchronized solutions lose stability, it is limited by the assumption that all nodes are homogeneous, which is another valid criticism in (Papo and Buldú, 2019). However, recent analysis of alternate diffusively coupled neural systems has indicated that as long as the heterogeneity is suitably small, MSF analysis is still a reasonable predictor of synchronization (Pereira et al., 2014).

To investigate whether the stability of the synchronized solution was robust to heterogeneity in the nodes for our system, we simulated the ring networks with varying levels of heterogeneity (see Figure 4). In particular, we considered the case where the homeostatic set-point  $p$  for the different nodes was chosen from a uniform distribution over small intervals around the default value of  $p = 0.2$ :

$$(26) \quad \tau_2 \frac{dW_k^{EI}}{dt} = I_k(E_k - p_k), \quad p_k \in U[0.2 - \epsilon, 0.2 + \epsilon].$$

The plastic weight  $W^{EI}$  now tries to drive the excitatory nodes to their distinct set-points:  $E_k \rightarrow p_k$  (see Figure 4A).

To quantify the magnitude of synchrony, we computed the Kuramoto order parameter

$$(27) \quad R(t) = \frac{1}{N} \sum_{k=1}^N e^{i\phi_k(t)} = |R(t)|e^{i\psi(t)},$$

where  $\phi_k$  is the phase of the  $k$ th node, as measured by  $E_k(t)$ . See Appendix B for details on how this was implemented. Fully synchronized states correspond to  $|R(t)| = 1$ , while states with a uniform (or uniformly clustered) phase distribution over the unit circle correspond to  $|R(t)| = 0$  (see Figure 4B).

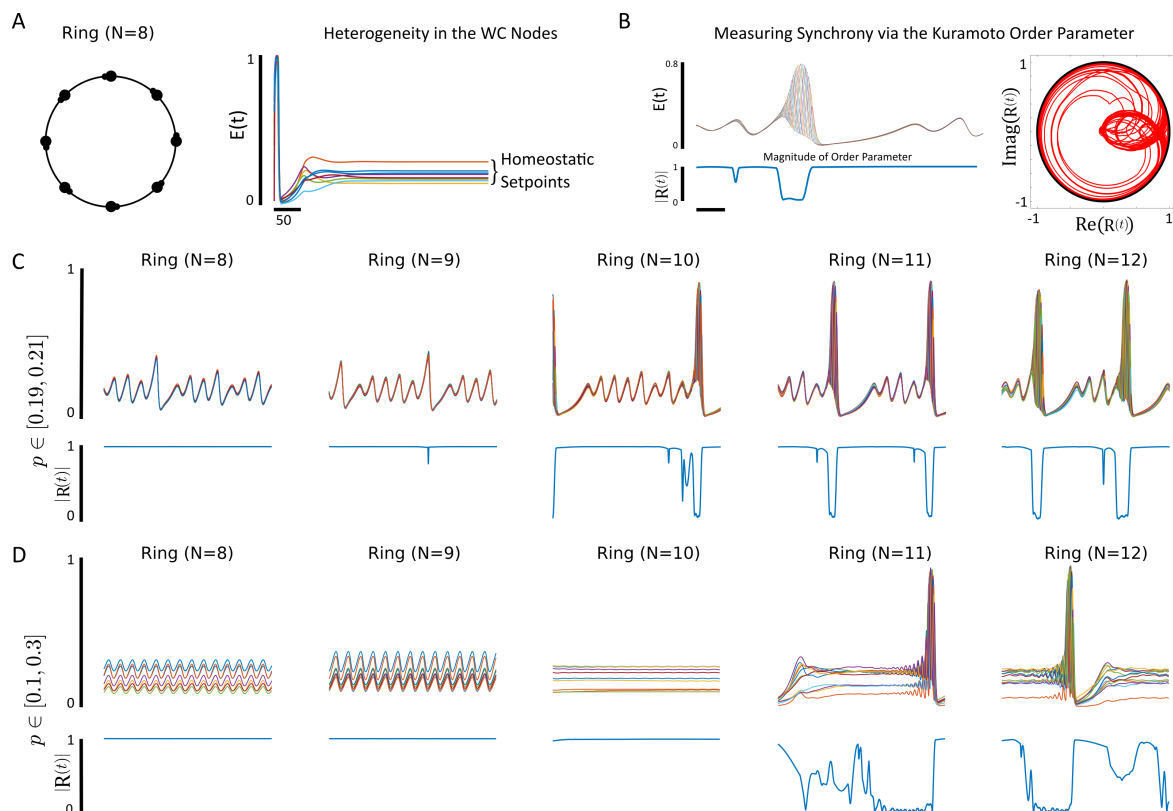


**Figure 4.** Synchronization persists for small amounts of system heterogeneity. (A) A ring network identical to that in Figures 2 and 3 but with different homeostatic set points for each single node, and  $W^E = 2.115$ . (B) To quantify partial synchrony in heterogeneous systems, we employed the Kuramoto order parameter  $R(t)$ . Perfectly synchronized systems have an  $|R(t)| = 1$ , while asynchronously distributed systems have  $|R(t)| = 0$ . (C) Simulated networks (top) of  $N = 8 - 12$  rings with heterogeneity in their homeostatic set points ( $p$  randomly distributed with a uniform distribution in  $[0.19, 0.21]$ ). The magnitude of the Kuramoto order parameter is plotted in blue (bottom). (D) Identical to (C), but with  $p$  uniformly distributed in  $[0, 1, 0.3]$ .

For small amounts of heterogeneity ( $\epsilon = 10^{-2}$ ), the stability of the synchronized solution is largely similar to the homogeneous case (see Figure 4C), with the destabilization of synchrony at a ring size of  $N = 9$ . However, larger amounts of heterogeneity between nodes ( $\epsilon = 10^{-1}$ ) can completely destroy the synchronized attractor state, including restoring the stability of the equilibrium point (see Figure 4D). Thus, the numerical simulations indicate that the synchronized solution in a mildly heterogeneous system may retain the stability characteristics of the homogeneous system, as in the network considered by (Pereira et al., 2014).

**5. Synchronization of networks with biological connectomes.** The analysis of the model above indicates that the SLE of an  $L_1$  normalized connectome determines the stability of the synchronized solution and hence can be used as a synchrony metric. Larger values lead to instability (low synchronizability), while smaller values indicate greater stability of synchronized solutions (high synchronizability). This is markedly different from stability criteria invoked for models with the diffusive coupling assumption, where the spread of the eigenvalues of the

Laplacian is often used as the determinant of stability (Tang et al., 2017; Nishikawa and Motter, 2010). In particular, (Tang et al., 2017; Nishikawa and Motter, 2010) use the synchrony metric

$$\begin{aligned}\frac{1}{\sigma^2} &= \frac{d^2(N-1)}{\sum_{i=1}^{N-1}(\lambda_i - \bar{\lambda})^2}, \\ \bar{\lambda} &= \sum_{i=1}^{N-1} \lambda_i, \\ d &= \frac{1}{N} \sum_i \sum_{j \neq i} L_{ij},\end{aligned}$$

where  $L$  is the Laplacian of the DTI structural connectivity matrix and  $\lambda_i$  are the eigenvalues of  $L$ . Note that as the row-sum of the Laplacian is identically 0, only the nonzero eigenvalues (hence the  $N - 1$  terms in the sums) are used to compute this metric. Here, high values of  $1/\sigma^2$  are considered to correspond to high synchronizability and low values to low synchronizability. Note that the eigenvalues of the Laplacian and an  $L_1$  normalized matrix need not coincide (see Appendix C for a simple counterexample), and thus they generate different metrics for synchronizability that need not be related. Further, the metric  $\frac{1}{\sigma^2}$  is only valid as a synchronization metric under an alternate set of modeling assumptions rather than those considered here. In particular, the MSF must have an isolated island of stability, which is referred to as “class-III” stability (Papo and Buldú, 2019; Boccaletti et al., 2006).

Given the lack of correspondence between these synchronization criteria, we investigated whether or not the SLE differs across real connectomes (Figure 5). Thus, we utilized publicly available data sets from the UCLA Multimodal Connectivity Database (NKI RS sample), <http://umcd.humanconnectomeproject.org/>, consisting of DTI connectomes from 196 subjects ranging from 4 to 85 years of age (Brown et al., 2012). These connectomes consist of 188 nodes corresponding to different brain regions (Figure 5A). For the purpose of comparison, we considered both the  $L_1$  normalization and the Laplacian transformation of the raw connectomes (Figure 5B).

After normalization, we found that the SLE of the connectomes exhibited a linear decrease with age (Figure 5C,D) as measured by a Pearson correlation coefficient ( $\rho = -0.28$ ,  $p = 6.54 \cdot 10^{-5}$ ). This decreasing strength in the SLE indicates a broad increase in the synchronizability associated with old age. We found that this was also present in the synchronizability metric of the Laplacian,  $\sigma^2$ , albeit with a weaker correlation ( $\rho = 0.21$ ,  $p = 2.6 \cdot 10^{-3}$ ).

Our analysis has shown that the SLE is a potential predictor for synchronizability. However, it is inherently global and does not implicate any particular node in the network as contributing towards synchronizability. To investigate the impacts of individual nodes further, we applied a node-deletion protocol. Nodes were individually deleted for each of the 196 connectomes; then the resulting weights were renormalized and the SLE was recomputed and compared to the SLE without node deletion (Figure 5F–I). We found that across the subjects, many nodes consistently increased/decreased the SLE for the resultant matrix (Figure 5G,H), with the most impactful nodes increasing or decreasing the SLE by no more than 1%–2%. We found that overall, the deletions were slightly more likely to result in SLE increases (56.46% of deletions) rather than decreases (43.54% of deletions), which was statistically significant (Wilcoxon signed-rank test,  $n = 36847$ ,  $p \ll 10^{-4}$ ).

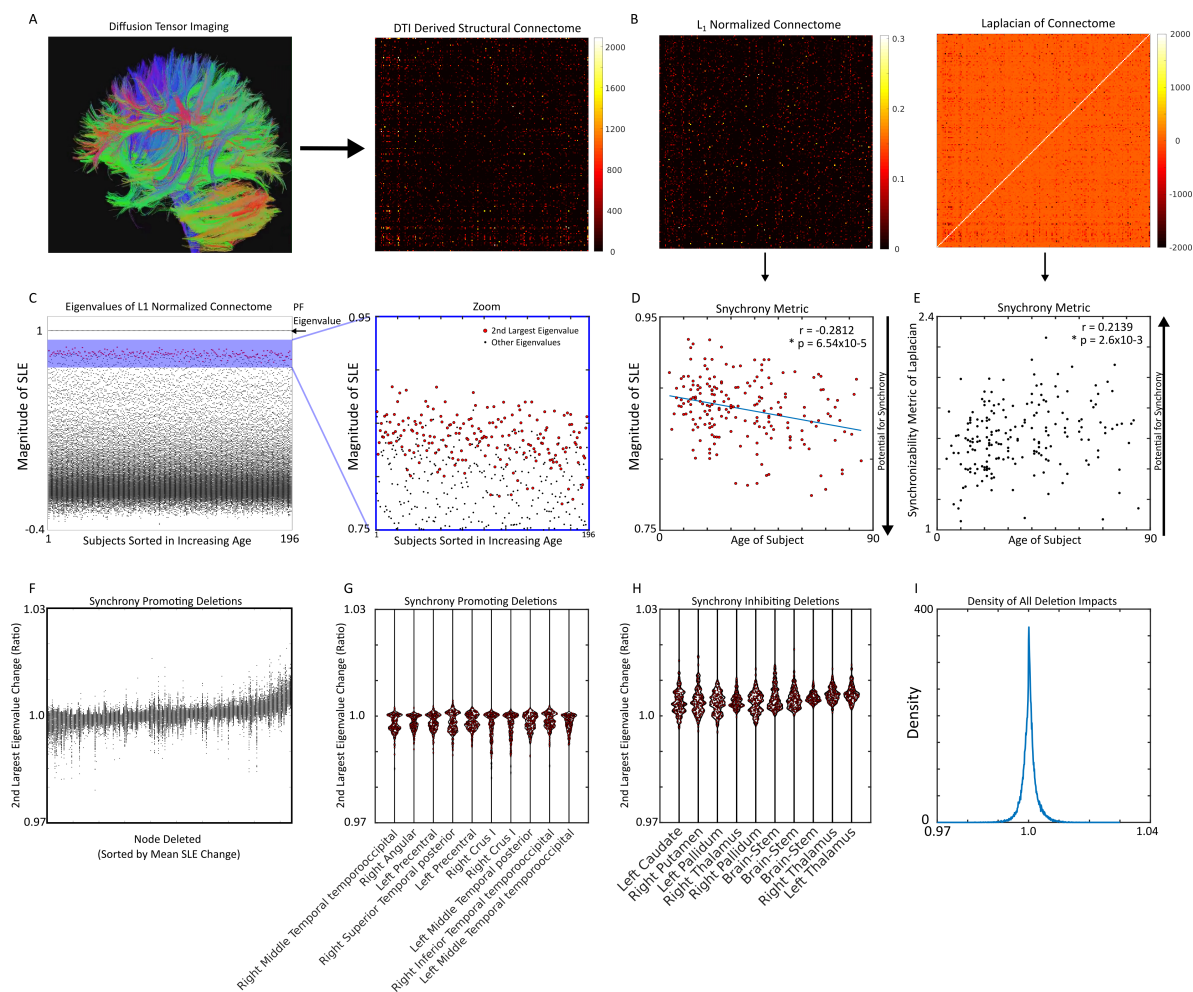


**Figure 5.** The SLE of  $L_1$  normalized connectomes decreases with age. (A) Diffusion tensor imaging (DTI) is used to create a connectivity matrix detailing the white-matter tracts connecting different regions of the brain. (B) The raw DTI connectivity matrix can be transformed into matrices which allows us to apply MSF analysis: with either the  $L_1$  normalized connectome (normalized coupling) or the Laplacian (diffusive coupling). (C) The eigenvalues of  $L_1$  normalized connectivity matrix. The dominant eigenvalue is always the Perron–Frobenius eigenvalue ( $r_{max} = 1$ ). The SLE is highlighted (red) (zoom, right). (D) The SLE decays with age  $r = -0.2812$ ,  $p = 6.54 \times 10^{-5}$ . (E) The synchronizability metric for the Laplacian (see description in the text). (F) Nodes are sequentially deleted while the SLE of the renormalized connectome is recomputed and compared to the full weight matrix. (G) The top 10 synchrony promoting deletions, as measured by smallest relative change of the SLE. (H) The top 10 synchrony inhibiting deletions, as measured by the largest relative change of the SLE. (I) The distribution of all deletions. The far left image in (A) is attributed to jgmarcelino from Newcastle upon Tyne, UK, Attribution 2.0 Generic (CC BY 2.0), <https://creativecommons.org/licenses/by/2.0>, and is available via Wikimedia Commons, <https://commons.wikimedia.org/wiki/File:Connectome.jpg>.

**6. Discussion.** With the glut of neuroimaging data, a natural question emerges as to how to best make use of structural connectomes. We considered a dynamical systems model in the form of a network of Wilson–Cowan nodes with intranode inhibitory homeostatic plasticity, with the coupling between nodes determined by arbitrary  $L_1$  normalized connectomes. We considered a variety of connection matrix types, both synthetic (rings, weak coupling, lattices, etc.) and experimentally obtained from DTI data. Through modification of the MSF approach, we found that networks with a sufficiently large SLE could destabilize the synchronized state. This result persisted when we considered small amounts of heterogeneity in the homeostatic set points of the individual nodes, but it perished for a sufficiently large distribution of heterogeneity. Finally, we tested the SLE of real connectomes from the NKI Rockland data set, <http://umcd.humanconnectomeproject.org/>, and found a decrease in the SLE of the normalized connectomes with age, indicating an increase in the network synchronizability.

Our results on real connectomes indicate a general increase in synchronizability with age. This, at face value, seems to contradict the decrease in synchronizability recently reported by (Tang et al., 2017). However, there is one critical difference between the data sets we consider: the age of the subjects. In (Tang et al., 2017), the authors considered subjects in the 8–22 age group and found a general decrease in synchronizability with age in 882 developing subjects. Our result, on the other hand, consists of 196 subjects over a much broader age range (7–85), and we find an increase rather than a decrease in synchronizability with advancing age. One possible explanation is that both results are valid. In developing children, there is a general decrease in synchronizability which reaches a plateau. However, as adults enter into advanced age, synchronizability begins to increase again due to white-matter degeneration. Thus, these combined results would seem to indicate that for a sufficiently large sample covering a broad age range, synchronizability is a unimodal function with a minimum at adulthood. This hypothesis is supported by the epidemiology of epilepsy. The prevalence of epilepsy with age is a u-shaped curve with increased synchronizability in children and the elderly (Beghi and Giussani, 2018; Leppik et al., 2006).

The normalized coupling we consider here has been applied in other, nondiffusive coupled based studies. For example, (Coombes et al., 2018) consider normalized coupling in nonsmooth Wilson–Cowan type systems. By means of a piecewise continuous approximation to the sigmoid function, the authors directly compute the Floquet multipliers for limit cycle solutions and even analyze synchrony to limit cycle solutions directly. Here, we consider identical coupling in a smooth Wilson–Cowan system with homeostatic plasticity and analyze synchrony in general (e.g., chaotic synchronization) with the MSF approach. The normalized coupling assumption is also more commonly used in delay-coupled networks (Choe et al., 2010; Heiligenthal et al., 2011; Huddy and Sun, 2016), for example, to investigate so-called amplitude death in synchronized systems (Huddy and Sun, 2016), transitions between different types of chaos as a function of coupling strength (Heiligenthal et al., 2011), and the control of synchronous states (Choe et al., 2010) in constant-row-sum, delay-coupled oscillator systems. We remark here that this previous literature demonstrates that (1) normalized coupling can be considered as an alternate assumption to diffusive coupling, and (2) the MSF approach is readily extendable to normalized coupling. Our work directly applies these two principles to study synchronization in neuronal networks in a model-driven way.

Recently, the applicability of MSF analysis to brain synchronizability has been criticized

(Papo and Buldú, 2019). Two of the major criticisms levied at MSF analysis in (Papo and Buldú, 2019) are (1) the functional form of the MSF is dependent on the dynamics of the system, and thus considering the eigenvalues alone can lead to erroneous results; (2) the homogeneity and diffusive coupling assumption in the MSF approach make it difficult to apply; and (3) there is a lack of a dynamical model when applying synchronizability metrics. All of the criticisms raised by (Papo and Buldú, 2019) are valid and important to investigate. Here, we find that considering a Wilson–Cowan system with homeostatically regulated inhibitory plasticity yielded one of two behaviors: stability of the synchronized state regardless of the eigenvalues of the normalized matrix, or instability of the synchronized solution for weight matrices with a sufficiently large SLE. Unlike prior work (Tang et al., 2017), we considered the normalized coupling case, yielding alternate MSF profiles and biologically plausible modeling for the neural regions. Further, we did find that the MSF analysis was somewhat permissive of heterogeneity in the nodes. While the criticisms in (Papo and Buldú, 2019) are valid, the analyses conducted here yield diagnostic measures in the form of eigenvalue functions that may be worth examining in real subjects for comparison across subjects.

**Appendix A. Network subtype parameters.** For all networks considered, the parameters used are as in Table 1.

**Table 1**

*Table of parameters for simulations, unless otherwise specified by a figure caption.*

|                     |                          |
|---------------------|--------------------------|
| $\tau_1$            | 2                        |
| $\tau_2$            | 5                        |
| $a$                 | 5                        |
| $p$                 | 0.2                      |
| $N$ (ring)          | 7 (small), 10 (large)    |
| $N$ (Erdős–Rényi)   | 100                      |
| $N$ (small world)   | 200                      |
| $N$ (lattice)       | 100 (small), 400 (large) |
| $N$ (weak coupling) | 50                       |

**A.1. Ring networks.** Rings were generated by having each node connected to the next with a weight of  $W^E$ :

$$W_{i+1,i}^{EE} = W^E, \quad i = 1, 2, \dots, N-1, \quad W_{1,N}^{EE} = W^E.$$

**A.2. Small-world networks.** Small-world networks are generated using the algorithm of (Watts and Strogatz, 1998). A bidirectional ring network is created where each neuron is connected to its  $k$  previous and next nearest neighbors with the weight  $\frac{W^E}{2k}$ . Then, a parameter  $0 \leq \beta \leq 1$  is used to set the probability of random rewiring where node  $(i, j)$  is randomly permuted with  $(i, k)$  for each  $i = 1, 2, \dots, N$ , and  $i < j < i + k/2$ . The values  $\beta = 0.7$  and  $k = 20$  were taken in all simulations.

**A.3. Random networks.** Random networks were generated by first creating a random weight matrix  $Q_{ij}^{EE} = q_{ij}$ , where  $q_{ij}$  was a uniform random variable on  $[0, 1]$ , and then normalizing rows in  $Q^{EE}$  with  $W^{EE}$ .

**A.4. Lattice networks.** Lattices are generated by setting the nodes on a  $\sqrt{N} \times \sqrt{N}$  square lattice. Node  $(i, j)$  receives input weights of strength  $\frac{W^E}{4}$  from nodes  $(i+1, j)$ ,  $(i-1, j)$ ,  $(i, j+1)$ , and  $(i, j-1)$ . Finally, periodic boundary conditions are applied at the edges  $i = N, 1$  and  $j = N, 1$ .

**A.5. Weak coupling networks.** Weak coupling networks are generated by first creating a random matrix,

$$(28) \quad Q_{ij}^{EE} = \delta_{ij} + \lambda \cdot q_{ij},$$

where  $q_{ij}$  is a uniformly distributed random number, and  $\delta_{ij}$  is the Kronecker delta. Then,  $W^{EE}$  is given by normalizing  $Q^{EE}$  with  $W^E$ :

$$W^{EE}(i, j) = W^E \cdot \frac{Q^{EE}(i, j)}{\sum_{j=1}^N Q^{EE}(i, j)}.$$

The parameter  $\lambda$  controls how weak the non-self-coupling components of the weight matrix were and was set to  $\lambda = 10^{-3}$ .

**Appendix B. Numerical methods.** All simulations were conducted in MATLAB2019a, with the ODE45 numerical integration subfunction used for all simulations. The tolerance parameter values (RelTol and AbsTol) were increased to  $10^{-14}$  to ensure accurate integration from the default  $10^{-6}$  values.

**B.1. Numerically computing Lyapunov exponents.** The Lyapunov exponents were numerically computed by the algorithm described in (Wolf et al., 1985). The code can be found online through the modelDB link.

**B.2. Numerically computing the Kuramoto order parameter.** The Kuramoto order parameter is computed directly by first using the findpeaks function in MATLAB2019a to detect the peaks of the chaotic or periodic solutions. These peaks are taken to have a phase of  $2\pi$  at time  $t^*$ , the location of the peak ( $\phi_k(t^*) = 2\pi$ ) with the phase value reset to 0 in the next time step  $t^* + \Delta t$ . The phase is linearly interpolated for all other time points between  $[0, 2\pi]$ . While this is a crude approximation to the actual phase, we found that other numerical methods (e.g., the Hilbert transform) were yielding poor estimates to the phase due to the mixed-mode nature of the periodic or chaotic solutions.

**Code availability statement.** The code can be found on modelDB (McDougal et al., 2017) under accession number 266577 (<https://senselab.med.yale.edu/modeldb/enterCode?model=266577>).

**Appendix C. Lack of correspondence between eigenvalues of different matrix transforms.** While the raw DTI matrix eigenvalues are fixed, one potentially reasonable assumption is that the eigenvalues of the  $L_1$  normalized connectome and the Laplacian are somehow related. Here, we will show that this is not necessarily the case. In particular, consider the  $2 \times 2$  symmetric matrix

$$D = \begin{pmatrix} w_1 & w_2 \\ w_2 & w_3 \end{pmatrix}, \quad L(D) = \begin{pmatrix} w_2 & -w_2 \\ -w_2 & w_2 \end{pmatrix}, \quad N(D) = \begin{pmatrix} \frac{w_1}{w_1+w_2} & \frac{w_2}{w_1+w_2} \\ \frac{w_2}{w_2+w_3} & \frac{w_3}{w_2+w_3} \end{pmatrix},$$

which yields as eigenvalues

$$\lambda(L(D)) = \{0, 2w_2\}, \quad \lambda(N(D)) = \left\{1, \frac{w_3w_1 - w_2^2}{(w_1 + w_2)(w_3 + w_2)}\right\}.$$

Thus, the eigenvalues of the Laplacian are entirely determined (for this case) by the off diagonal elements, while the eigenvalues of the normalized matrix are a rational function dependent on all matrix elements.

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