Uncovering Structural-Functional Coupling Alterations for Neurodegenerative Diseases

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Abstract. A confluence of neuroscience and clinical evidence suggests that the disruption of structural connectivity (SC) and functional connectivity (FC) in the brain is an early sign of neurodegenerative diseases years before any clinical signs of the disease progression. Since the changes in SC-FC coupling may provide a potential putative biomarker that detects subtle brain network dysfunction more sensitively than does a single modality, tremendous efforts have been made to understand the relationship between SC and FC from the perspective of connectivity, sub-networks, and network topology. However, the methodology design of current analytic methods lacks the in-depth neuroscience underpinning of to what extent the altered SC-FC coupling mechanisms underline the cognitive decline. To address this challenge, we put the spotlight on a neural oscillation model that characterizes the system behavior of a set of (functional) neural oscillators coupled via (structural) nerve fibers throughout the brain. On top of this, we present a physics-guided graph neural network to understand the synchronization mechanism of system dynamics that is capable of predicting self-organized functional fluctuations. By doing so, we generate a novel SC-FC coupling biomarker that allows us to recognize the early sign of neurodegeneration through the lens of an altered SC-FC relationship. We have evaluated the statistical power and clinical value of new SC-FC biomarker in the early diagnosis of Alzheimer's disease using the ADNI dataset. Compared to conventional SC-FC coupling methods, our physics-guided deep model not only yields higher prediction accuracy but also reveals the mechanistic role of SC-FC coupling alterations in disease progression.

Keywords: Brain structure-functional coupling · Imaging biomarkers · Neurodegenerative diseases

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1 Introduction

The human brain is a complex inter-wired system that emerges spontaneous functional fluctuations [2]. Like normal aging is characterized by brain structure and function changes contributing to cognitive decline, neuropathology events are also accompanied by network dysfunctions in both structural connectivity (SC) and functional connectivity (FC) [1,14]. Therefore, it is critical to understand the SC-FC relationship underlying the shift from healthy brain aging to the neurodegeneration diseases such as Alzheimer's disease (AD), which is imperative for the design and determination of effective interventions [6].

A growing body of research studies the statistical association between SC and FC from the perspectives of connectivity [9], sub-networks [8], and network topology [15]. For instance, SC-FC coupling at each brain region was constructed by calculating the Spearman-rank correlation between a row of the SC matrix and the corresponding row of the FC matrix in [9]. In the past decade, graph-theory-based analysis has been widely used in many connectome-based studies to capture topological differences between healthy and disease connectomes that reflect network segregation (such as clustering coefficients), integration (such as nodal centrality), and organization (such as rich-club structure) [18]. In this context, topological characteristics have been compared between SC and FC in [15], where SC was found to have a relatively stable and efficient structure to support FC that is more changeable and flexible.

However, current state-of-the-art SC-FC coupling methods lack integrated neuroscience insight at a system level. Specifically, many SC-FC coupling methods are mainly designed to find a statistical association between SC and FC topology patterns, lacking a principled system-level integration to characterize the coupling mechanism of how neural population communicates and emerges remarkable brain functions on top of the structural connectomes. To address this limitation, we present a new approach to elucidate the complex SC-FC relationship by characterizing the dynamical behaviors underlying a dissected mechanism. As shown in Fig. 1 (top), it might be challenging to directly link SC with FC. Alternatively, we sought to leverage the capital of well-studied biophysics models in neuroscience, acting as a stepping stone, to uncover the SC-FC coupling mechanisms, which allows us to generate novel SC-FC coupling biomarkers with great neuroscience insight (bottom).

In this regard, we conceptualize the human brain as a complex system. With that being said, spontaneous functional fluctuation is not random. Instead, there is a coherent system-level mechanism that supports oscillatory neural activities throughout the brain anatomy. Therefore, we assume that each brain region is associated with a neural population, which manifests frequency-specific spontaneous neural oscillations. Inspired by the success of Kuramoto model [12] in modeling coupled synchronization in complex systems, we conceptualize that these oscillatory neural units are physically coupled via nerve fibers (observed in diffusion-weighted MRI images). To that end, the coupled phase oscillation process on top of the SC topology is supposed to emerge the manifestation of self-organized fluctuation patterns as observed in the blood-oxygen-level-dependent

(BOLD) signal. Furthermore, we propose a novel graph neural network (GNN) to learn the dynamics of SC-FC coupling mechanism from a vast number of structural and functional human connectome data, which offers a new window to understand the evolving landscape of SC-FC relationships through the lens of phase oscillations.

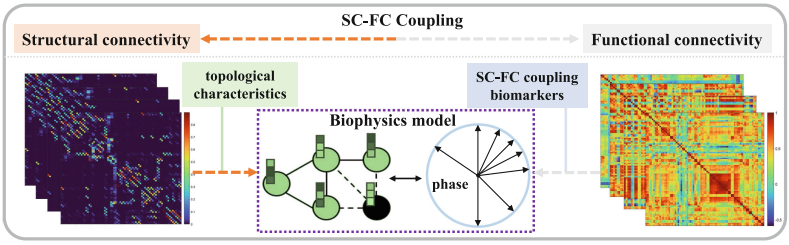

Fig. 1. Top: Conventional approaches mainly focus on the statistical association between SC and FC phenotypes. Bottom: We offer a new window to understand SC-FC coupling mechanisms through the lens of dynamics in a complex system that can be characterized using machine learning techniques.

In the neuroscience field, tremendous efforts have been made to elucidate the biological mechanism underlying the spatiotemporally organized low-frequency fluctuations in BOLD data during the resting state. In spite of the insightful mathematical formulation and physics principles, the tuning of model parameters heavily relies on neuroscience prior knowledge and thus affects the model replicability. On the flip side, machine learning is good at data fitting in a data-hungry manner, albeit through a "black-box" learning mechanism. Taking together, we have laid the foundation of our proposed deep model on the principle of the Kuramoto model, which allows us to characterize the SC-FC relationships with mathematical guarantees. Specifically, we first translate the Kuramoto model into a GNN architecture, where we jointly learn the neural oscillation process at each node (brain region) and allow the oscillation state (aka. graph embedding vector) to diffuse throughout the SC-constrained topological pathways. The driving force of our deep model is to dissect the non-linear mechanism of coupled synchronization which can replicate the self-organized patterns of slow functional fluctuations manifested in BOLD signals. Following the notion of complex system theory, we further propose to yield new SC-FC coupling biomarkers based on learned system dynamics. We have evaluated the statistical power and clinical value of our new biomarkers in recognizing the early sign of neurodegeneration using the ADNI dataset, where the promising result indicates great potential in other network neuroscience studies.

2 Method

Suppose the brain network of SC $\mathcal{G} = (\Xi, W)$ consists of N brain regions $\Xi = \{\xi_i | i = 1, ..., N\}$ and the region-to-region structural connectivities $W = [w_{ij}] \in$

$\mathcal{R}^{N\times N}$ measured from diffusion-weighted images. On the other hand, the mean time course of BOLD signal $x_i(t)(i = 1, ..., N, t = 1, ..., T)$ at each brain region forms a data matrix $X(t) = [x_i(t)]_{t=1}^{T} \in \mathcal{R}^{N\times T}$, which characterizes whole-brain functional fluctuations. In our work, we conceptualize that the human brain is a complex system where distinct brain regions are physically wired (coupled) via neuronal fibers. On top of this, the status of neural oscillation at each brain region is determined by an intrinsic state variable of brain rhythm $v_i(t)$. Multiple oscillators in the brain, each with their own frequency and phase, align their oscillations over time, which gives rise to the ubiquitous self-organized patterns of spontaneous functional fluctuations. To test this hypothesis, we present a deep model to reproduce the topology of traditional FC matrix $Q = [q_{ij}]_{i,j=1}^{N} \in \mathcal{R}^{N\times N}$, measured by Pearson's correlation [3], from the phase information of neural activities, where the synchronization of coupled oscillators is constrained by Kuramoto model [12].

2.1 Generalized Kuramoto Model for Coupled Neural Oscillations

The Kuramoto family of coupled oscillators is a fundamental example of a nonlinear oscillator that exhibits various qualitative behaviors observed in physical systems. Each individual oscillator in the Kuramoto family has an inherent natural frequency denoted as ω and is subject to global coupling mediated by a sinusoidal interaction function. The dynamics of each oscillator are governed by the following partial differential equation (PDE), as described in [4]:

$$\frac{d\theta_i}{dt} = \omega_i + \frac{1}{N}\sum_{j=1}^{N} K_{ij}\sin(\theta_i,\theta_j) \tag{1}$$

where θ_i denotes the phase of the oscillator i for the Kuramoto model, K_{ij} denotes the relative coupling strength from node i to node j, ω_i is the natural frequency associated with node i. The Kuramoto model is a well-established tool for studying complex systems, with its primary application being the analysis of coupled oscillators through pairwise phase interaction. The model enables each oscillator to adjust its phase velocity based on inputs from other oscillators via a pairwise phase interaction function denoted as K_{ij}. The Kuramoto model's versatility is due to its ability to generate interpretable models for various complex behaviors by modifying the network topology and coupling strength. However, capturing higher-order dynamics is challenging with the classic Kuramoto model due to its pre-defined dynamics ($K_{ij}\sin(\theta_i,\theta_j)$ in Eq. 1). To address this limitation, we propose a more general formulation to model a nonlinear dynamical system as:

$$\frac{dv_i}{dt} = f(v_i, \mathcal{H}(x_i)) + \sum_{j\neq i}^{N} w_{ij}c(v_i,v_j) \tag{2}$$

where the system dynamics is determined by the state variable of brain rhythm v_i on each node. Compared to Eq. 1, we estimate the natural frequency ω_i through

a non-linear function $f(\cdot)$, which depends on the current state variable v_i and the neural activity proxy x_i. Since the Hilbert transform ($\mathcal{H}(\cdot)$) has been widely used in functional neuroimaging research to extract the phase and amplitude information from BOLD signals [5,13], we further formulate the frequency function as $f(v_i, p_i)$, where $p_i = \mathcal{H}(x_i)$ represents the phase information of time course x_i by Hilbert transform.

Second, we introduce the coupling physics function $c(\cdot, \cdot)$ to characterize the nonlinear relationship between any two state variables v_i and v_j, where their coupling strength is measured by the structural connectivity w_{ij}. Following the spirit of the reaction-diffusion model in systems biology [11], the first and second terms in Eq. 2 act as the reaction process (predicting the intrinsic state variable v_i from the proxy signal x_i) and graph diffusion process (exchanging the state information throughout the SC network), respectively. Taking together, we present a deep Kuramoto model to reproduce FC network, where the functional fluctuations emerge from an evolving system of coupled neural oscillations.

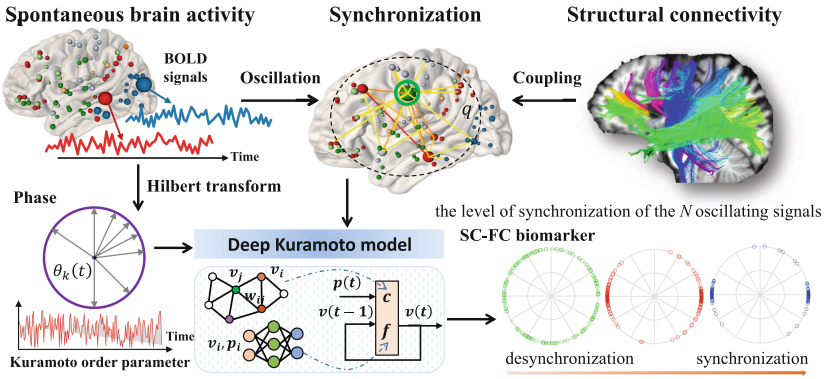

Fig. 2. The spatio-temporal learning framework of our proposed deep Kuramoto model. (Color figure online)

2.2 Deep Kuramoto Model for SC-FC Coupling Mechanism

The overview of our deep Kuramoto model is shown in Fig. 2. The input consists of (1) time-invariant coupling information from the SC matrix (top-right corner), (2) time-evolving phase information at each node $p_i(t)$ (top-left corner). As shown in the blue box, our physics-guided deep Kuramoto model is designed to capture the dynamics of neural oscillations in a *spatio-temporal learning* scenario. At each time point t, we deploy a fully-connected network (FCN) and a GNN to predict the first and second terms in Eq. 2, respectively, based on the current state v_i at each node ξ_i. Specifically, we deploy the FCN for the reaction process $f_\varphi(t) = \sigma\left(\beta_1 v(t) + \beta_2 p(t) + \mu\right)$, where $\sigma(\cdot)$ denotes the sigmoid

function. The parameters $\varphi = \{\beta_1, \beta_2, \mu\}$ are shared across nodes $\{v_i\}$. Meanwhile, we use a GNN to learn the hyper-parameters in the coupling function $c(\cdot)$ by $c_\vartheta(t) = \delta(WV\vartheta)$, δ is the $ReLu(\cdot)$ function and ϑ denotes the learnable parameter in the diffusion process.

The backbone of our deep Kuramoto model is a neuronal oscillation component where the evolution of state $v(t)$ is governed by the PDE in Eq. 2. Under the hood, we discretize the continuous process by recursively applying the following operations at the current time point T: (1) update current state by $v(T) = v(T-1) + \frac{dv}{dt}|_{T-1}$, where temporal change $\frac{dv}{dt}|_{T-1}$ is the combination of reaction (output of FCN) and diffusion (output of GNN) processes; (2) adjust the history of state variables $\{v_1, v_2, ..., v(T-1)\}$ such that Kuramoto model (with the latest parameters φ and ϑ) allows us to shoot the target state v_T by following the system dynamics $v(T) = v(0) + \int_0^T \frac{dv}{dt} dt$. To do so, we integrate the classic hybrid PDE solver [10] in our deep model.

The driving force of our deep Kuramoto model to minimize the discrepancy between the observed BOLD signal x_t and the reconstructed counterpart $\hat{x}_t = f^{-1}(v_t))$ which is supposed to emerge from the intrinsic neural oscillation process. In training our deep Kuramoto model, we use a variant of stochastic gradient descent (SGD), Adma, with a learning rate of 0.001, to optimize the network parameters. As well the detailed parameter setting is as follows: epoch = 500, dropout = 0.5, hidden dimension = 64.

2.3 Novel SC-FC Coupling Biomarkers

The valuable bi-product of our deep Kuramoto model of neural oscillation is a system-level explanation of how the neuro-system dynamics is associated with phenotypes such as clinical outcomes. In doing so, we introduce the Kuramoto order parameters ϕ_t to quantify the synchronization level at time t as $\phi_t = \frac{1}{N} real\{\sum_{i=1}^{N} e^{iv(t)}\}$, where $real(\cdot)$ denotes the real part of the complex number. In complex system area, ϕ is described as the synchronization level, aka. the metastability of the system [17], transiting from complete chaos ($\phi_t = 0$) and fully synchronization ($\phi_t = 1$).

Empirical SC-FC Coupling Biomarkers. As a proof-of-concept approach, we propose a novel SC-FC coupling biomarker $\mathbf{\Phi} = (\phi_{t_0}, \phi_{t_1}, ..., \phi_{t_T})$ (bottom right corner in Fig. 2) which records the evolution of system metastability underlying the neural activity. Since the neuroscience intuition of $\mathbf{\Phi}$ is in line with the functional dynamics, we expect the SC-FC biomarker $\mathbf{\Phi}$ to allow us to recognize subtle network dysfunction patterns between healthy and disease connectomes. To make the coupling biomarker invariant to the length of the time course, we further present a global summary of $\mathbf{\Phi}$ by counting the number of temporal transitions (called metastability transition count) between the minimal (less-synchronized) and maximum (less-chaotic) metastability statuses, called *SC-FC-META*.

SC-FC Coupling Network for Disease Diagnosis. To leverage the rich system-level heuristics from Kuramoto model, it is straightforward to integrate

a classification branch on top of $\mathbf{\Phi}$ which is trained to minimize the cross-entropy loss in classifying healthy and disease subjects. Thus, the tailored deep Kuramoto model for early diagnosis is called *SC-FC-Net*.

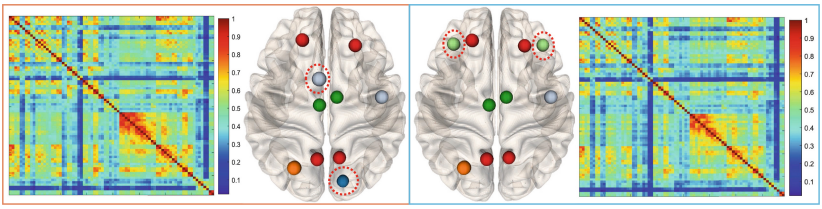

Fig. 3. Left: the conventional FC matrix. Right: the reproduced FC matrix. Middle: the detected hub nodes between conventional (left) and reproduced (right) FC matrices. The red circles denote the inconsistencies between the two FC matrices. (Color figure online)

3 Experiments

In this study, we evaluate the statistical power and clinical value of our learning-based SC-FC coupling biomarkers in separating Alzheimer's Disease (AD) from cognitively normal (CN) subjects using ADNI dataset [16]. The canonical Automated Anatomical Labeling (AAL) atlas [19] is used to parcellate the entire brain into 90 regions for each scan on which we construct 90×90 SC and mean BOLD signals at each brain region. There are in total of 250 subjects (73 AD vs. 177 CN). We examine the performance by *SC-FC-META* (empirical SC-FC coupling biomarker) and *SC-FC-Net* (physics-guided deep model) with comparison to graph convolutional network (GCN), recurrent neural network (RNN) and a PDE-based counterpart method (LTCNet) [10].

3.1 Validating the Neuroscience Insight of Deep Kuramoto Model

The main hypothesis is that spontaneous functional fluctuations arise from the phase oscillations of coupled neural populations. In this regard, we spotlight the topological difference between the conventional FC by Pearson's correlation on BOLD signal and the reproduced FC based on the state variable of brain rhythm $\{v_i(t)\}$. First, we display the population-average of conventional FC (Fig. 3 left) and our reproduced FC matrix (Fig. 3 right). Through visual inspection, the network topology between two FC matrices is very consistent, indicating the validity of applying our deep Kuromoto model in resting-state fMRI studies. Furthermore, we detect the hub nodes based on FC connectivity degree for each FC matrix [7] and evaluate the consensus of hub node detection results between conventional and reproduced FC matrices. As shown in the middle of Fig. 3, the majority of hub nodes have been found in both FC matrics, providing the quantitative evidence of model validity.

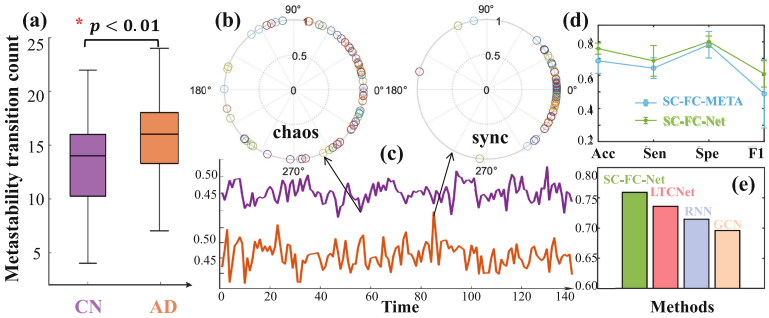

Fig. 4. (a) denotes the metastability transition count between CN and AD. (b) Snapshot of node phase visualizations at the chaos and synchronization stages. (c) Global dynamic (order parameter ϕ) in coupling parameter space. (d) The classification performance (AD vs. CN) on a shadow approach (SVM, blue) and our *SC-FC-Net* (green) by using our new learning-based SC-FC biomarker. Acc: accuracy, Sen: sensitivity, Sep, specificity, F1: F1-score. (e) The accuracies of diagnosing AD on four methods. (Color figure online)

3.2 Evaluation on Empirical Biomarker of *SC-FC-META*

First, the CN vs. AD group comparison on SC-FC coupling biomarker is shown in Fig. 4(a), where our novel SC-FC-META biomarker exhibits a significant difference at the level of $p < 0.01$. Second, we display two typical examples of less-synchronized status ($\phi_t \to 0$) and less-chaotic status ($\phi_t \to 1$) in Fig. 4(b), where we follow the convention of Kumamoto model to position all phases at time t along the circle. Thus, the synchronization level can be visually examined based on the (phase) point clustering pattern on the circle. Third, the time-evolving curve of metastability in CN (in purple) and AD (in brown) subjects are shown in Fig. 4(c), which provides a new insight into the pathophysiological mechanism of disease progression in the perspective of the system's stability level. Notably, there are much more transitions in AD than CN subjects, indicating that alterations in SC-FC coupling mechanism render AD subjects manifest reduced control over the synchronization from the coupled neural oscillations.

3.3 Evaluation on *SC-FC-Net* in Diagnosing AD

Herein, we first assess the accuracy of diagnosing AD using *SC-FC-META* and *SC-FC-Net*. The former method is a two-step approach where we first calculate the *SC-FC-META* biomarker for each subject and then train a SVM. While our *SC-FC-Net* is an end-to-end solution. The classification results are shown in Fig. 4(d), where the deep model *SC-FC-Net* (in green) achieves much more accurate classification results than the shallow model (in blue). Furthermore, we compare the classification result by *SC-FC-Net* with other deep models (trained on BOLD time course only) in Fig. 4(e). Our *SC-FC-Net* shows in average 2.3% improvement over the current state-of-the-art methods, indicating the potential of investigating SC-FC coupling mechanism in disease diagnosis.

4 Conclusion

We introduce a novel approach that combines physics and deep learning to investigate the neuroscience hypothesis that spontaneous functional fluctuations arise from a dynamic system of neural oscillations. Our successful deep model has led to the discovery of new biomarkers that capture the synchronization level of neural oscillations over time, enabling us to identify the coupling between SC and FC in the brain. We have utilized these new SC-FC coupling biomarkers to identify brains at risk of AD, and have obtained promising classification results. This approach holds great promise for other neuroimaging applications.

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