Signal processing in Network Physiology: quantifying network dynamics of organ interactions

1st Plamen Ch. Ivanov*
Keck Laboratory for Network Physiology, Department of Physics, Boston University, Boston, USA
Email: plamen@buphy.bu.edu

2nd Jilin W. J. L. Wang
Keck Laboratory for Network Physiology, Department of Physics, Boston University, Boston, USA
Email: near@bu.edu

3rd Xiyun Zhang
Keck Laboratory for Network Physiology, Department of Physics, Boston University, Boston, USA
Department of Physics, Jinan University, Guangzhou, China
Email: xiyunzhang@jnu.edu.cn

***Abstract*—A fundamental problem in new field of Network Physiology is how organ systems in the human body dynamically interact to coordinate and synchronize their functions, and integrate as a network to generate distinct states and behaviours at the organism level. Physiological systems exhibit complex dynamics, operate at different time scales, and are regulated by multi-component mechanisms, which poses challenges to studying physiologic coupling and network interactions. We present a method based on the concept of time delay stability to probe transient physiologic network interactions in a group of healthy subjects during sleep. We investigate the multi-layer network structure and dynamics of interactions among (i) physiologically relevant brain rhythms within and across cortical locations, (ii) brain rhythms and key peripheral organ systems, and (iii) organ systems with each other. We demonstrate that each physiologic state (sleep stage) is characterized by a specific network structure and link strength distribution, and that the entire physiological network undergoes hierarchical reorganization across layers with transition from one stage to another. Our findings are consistent across subjects, and indicate a robust association of network structure and dynamics with physiologic state and function. The presented approach provides a new framework to explore physiologic states through networks of organ interactions.**

***Index Terms*—Network Physiology, time series analysis, time delay stability, coupling, dynamic networks, brain rhythms, sleep**

I. Introduction

The human organism comprises various physiological systems, each with its own structural organization and dynamic complexity, leading to transient, fluctuating and nonlinear signals. States and functions at the organism level are traditionally defined by the dynamics of individual organ systems, and their modulation in response to internal and external perturbations. However, coordinated network interactions among systems are essential to generate distinct physiologic states and to maintain health. These interactions occur through different coupling forms [1], [2], stochastic and nonlinear feedbacks across spatio-temporal scales and at multiple levels of integration to optimize and coordinate organ functions. Currently there is no established theoretical framework, computational and analytic formalism to probe interactions between diverse systems in the human organism. Here we present a new methodology adequate to identify and quantify coupling of systems with different temporal characteristics and signal outputs. We apply Network Physiology approach [3]–[5] and the novel concept of time delay stability [6], and we demonstrate their utility to study transient synchronous bursts in systems dynamics as a fundamental form of physiologic network communications. We investigate new aspects of network interactions among brain rhythms across and within cortical locations, and their relation to neural plasticity in response to changes in autonomic regulation underlying different physiologic states. Further, we uncover dynamical features of brain-organ and organ-organ networks as a new signature of physiologic control, and establish association of network structure and dynamics with physiologic state and function. The presented methodology is an initial step in developing novel signal processing and computational tools, and reported findings establish building blocks of an atlas of dynamical interactions among key organ systems in the human body.

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II. Method

Data We analyze output signals from key physiological systems synchronously and continuously recorded during nighttime sleep from 52 healthy young subjects (26 female, 26 male, ages 20-34 years; average duration 7.9h; participants provided written informed consent; research protocol 3380X

approved by the Institutional Review Boards of Boston University; data collection conducted according to the principles expressed in the Declaration of Helsinki; sleep stages scored in 30s epochs by certified technicians; EU SIESTA databases). Signals include EEG (channels Fp1, Fp2, C3, C4, O1 and O2), ECG, respiratory waves, EOG, EMG from chin and leg. From the raw signals we extract: spectral power in windows of 2s with 1s overlap for all physiologically relevant cortical rhythms (EEG frequency bands): δ (0.5-3.5Hz), θ (4-7.5Hz), α (8-11.5Hz), σ (12-15.5Hz), β (16-19.5Hz), γ_1 (20-33.5 Hz), γ_2 (34-99.5 Hz); variance of EOG and EMG in 2s windows with 1s overlap; heartbeat RR intervals and interbreath intervals are re-sampled to 1Hz after which values are inverted to obtain heart rate and respiratory rate. Thus, all time series have the same time resolution of 1s before the analysis.

Time Delay Stability (TDS) Method Physiological systems exhibit complex time-varying dynamics characterized by coherent bursts in activation across systems in response to modulation in physiologic state and condition (Fig.1 Top left). We develop a new approach to (i) quantify pair-wise coupling and network interactions among diverse systems with bursting dynamics, and (ii) track the evolution of networks of organ interactions across states and conditions. We introduce a novel concept, Time Delay Stability (TDS), and a TDS method (Fig.1) to study the time delay with which bursts of activity in a given system are consistently followed by corresponding bursts in the signal output of other systems. Within this framework, periods of TDS, i.e., constant time delay between bursts in the activation of two systems, indicate coupling.

To probe the interaction between two physiologic systems X and Y, we consider their output signals $\{x\}$ and $\{y\}$, each of length N. We divide signals $\{x\}$ and $\{y\}$ into N_L overlapping segments of equal length L=60s. We chose an overlap of $L/2$=30s which corresponds to the time resolution of the conventional sleep-stage scoring epochs, and thus $N_L = [2N/L]$. Prior to analysis, each segment is normalized separately to zero mean and unit standard deviation to remove constant trends and to assure that the estimated coupling between signals is not affected by their relative amplitudes.

Next, we calculate the cross-correlation function,

$$C^{\nu}_{xy}(\tau) = \frac{1}{L}\sum_{i=1}^{L} x^{\nu}_{i+(\nu-1)\frac{L}{2}}\ y^{\nu}_{i+(\nu-1)\frac{L}{2}+\tau}, \qquad (1)$$

within each segment $\nu = 1, \ldots, (N_L - 1)$ by applying periodic boundary conditions. For each segment ν we define the time delay τ_0^{ν} corresponding to the maximum in the absolute value of $C^{\nu}_{xy}(\tau)$ in this segment:

$$\tau_0^{\nu} = \tau\big|_{|C^{\nu}_{xy}(\tau)|\geq|C^{\nu}_{xy}(\tau')|\quad\forall\tau'}. \qquad (2)$$

Time periods of stable interrelation between two signals are represented by segments of approximately constant τ_0 in the newly defined series of time delays, $\{\tau_0^{\nu}\}_{\nu=1,\ldots,N_L-1}$. In contrast, absence of stable coupling between the signals corresponds to large fluctuations in τ_0 (Fig.1 Top right).

Third, we identify two systems as linked if their corresponding signals exhibit a time delay that does not change by more than $\pm$1s for several consecutive segments ν. We track the values of τ_0 along the series $\{\tau_0^{\nu}\}$: when for at least four out of five consecutive segments ν (corresponding to a window of 5×30s) the time delay remains in the interval $[\tau_0 - 1, \tau_0 + 1]$ these segments are labeled as stable. This procedure is repeated for a sliding window with a step size one along the entire series $\{\tau_0^{\nu}\}$. The TDS value is finally calculated as the fraction (%TDS) of stable points in the time series $\{\tau_0^{\nu}\}$. Thus, longer

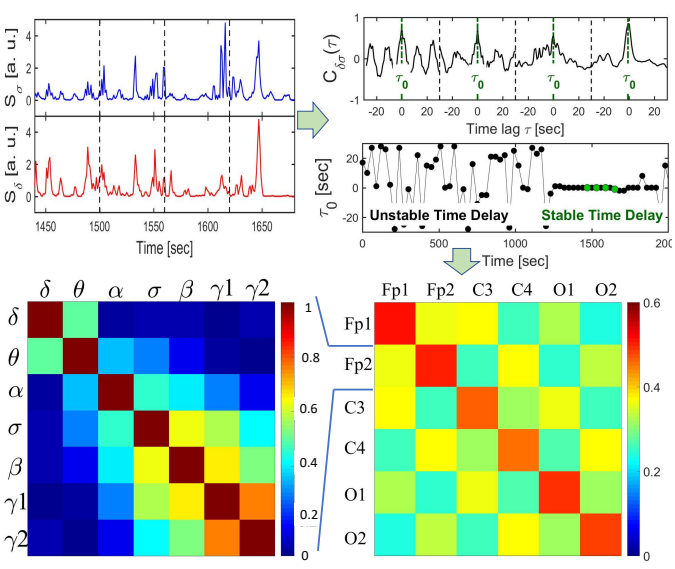

Fig. 1: **Degree of coupling between brain rhythms quantified by Time Delay Stability (TDS).** Schematic presentation of the TDS method. (Top left) Segments of time series representing EEG spectral power $S(\sigma)$ and $S(\delta)$ of the σ and δ cortical rhythms shown for consecutive 60s windows (vertical dashed lines). (Top right) Coordinated synchronous bursts in $S(\sigma)$ and $S(\delta)$ lead to pronounced cross-correlation $C_{\delta\sigma}$ with dominant peak within each time window located at time lag τ_0, representing the time delay between the two signals. Time delay τ_0 between $S(\sigma)$ and $S(\delta)$ is plotted for consecutive 60s windows with step of 30s (green dots mark τ_0 for the windows shown in the $C_{\delta\sigma}$ plot). Note the transition at $\sim$ 1200s from a segment with strongly fluctuating τ_0 to a stable time delay regime with $\tau_0 \approx$ constant. Such regime of time delay stability (TDS) indicates the onset of physiological coupling. The fraction of time (%) in the EEG recording when TDS is observed quantifies the degree of coupling strength (%TDS). (Bottom left) TDS matrix representing the degree of coupling between different brain rhythms (δ, θ, α, σ, β, γ_1, and γ_2) derived from two cortical locations (Fp1 and Fp2 EEG channels). Matrix elements represent the coupling strength, measured as %TDS, for each pair of brain rhythms. (Bottom right) TDS matrix representing the average coupling of all brain rhythms across each pair of EEG channels (Fp1, Fp2, C3, C4, O1, O2). Matrix elements show cortical rhythms interactions for one representative healthy young subject during Wake. Color code indicates the average coupling strength.

periods of TDS between the output signals of two systems reflect more stable interaction and stronger coupling between these systems, and the links strength in physiologic networks is determined by the percentage of time when TDS is observed: higher %TDS corresponds to stronger links.

We have tested several different values for the window size L, i.e., L = 30, 60, 120, and 180s with non-overlapping windows as well as window overlaps L/2 and L/4. The overall TDS results were not significantly different for the different combinations of L and overlap, however, there was a tendency to noisier τ_0 vs t signals for shorter windows and less overlap (Fig.1 Top left). On the other hand larger windows reduce the time resolution of the TDS.

The TDS method is general, and can be applied to diverse systems with bursting dynamics. It is more reliable in identifying physiological coupling compared with traditional cross-correlation, cross-coherence, and classical Granger causality approaches, which are not suitable for heterogeneous non-stationary signals with time varying coupling, and are affected by the degree of auto-correlations and irregular bursts embedded in these signals [3], [7].

Averaging procedure for estimating links strength and links number in physiological networks We introduce a procedure to quantify the group average strength of a particular network link for a physiological state (sleep stage). A standard averaging procedure, where the strength of a network link during a given sleep stage is first calculated for one subject and is then averaged for all subjects, would give equal weight for all subjects in the group average. However, we note that the total duration of each sleep stage (sum of all episodes of a given stage) during night-time sleep varies from subject to subject. Thus, we perform a weighted averaging procedure where the contribution of each subject in the group average link strength for a given sleep stage is weighted proportionally to the total duration of this sleep stage during the night.

Specifically, links in our network analysis are obtained by quantifying TDS for each pair of physiological systems after calculating the weighted average for all subjects during a given physiological state (sleep stage): %TDS$= (\Sigma_i s_i/\Sigma_i S_i) \times 100$ where S_i indicates the total duration of a given sleep stage for subject i, and s_i is the total duration of TDS within S_i for the considered pair of physiological signals.

Artifacts related to specific behaviors of individual subjects (excessive movement, respiratory perturbations, etc.) or to the quality of recording of specific channels (due to loose lead contact) may lead to outliers in the estimate of some links strength in the network for a given subject. Further, links that are outliers in the physiological network of one subject may not be outliers in the network of another subject (same artifacts may not repeat for different subjects). To address this problem, for each pair of physiological signals (specific network link) we obtain the distribution and standard deviation of %TDS values (link strength) derived from all subjects in the group. Subjects for whom the considered network link has %TDS value above the group average + 2 st.dev. are then removed, and a weighted average for the link is obtained based on the remaining subjects in the group, thus removing outliers in the calculation of the group-averaged link strength. This procedure is repeated for each link in the network. Considering all network links for all subjects in our database during a given physiologic state, this procedure led to $< 3\%$ of links removed as outliers in the calculation of the reported group average results for the different physiological networks.

A network link between two systems is defined when their interaction is characterized by TDS value above a significance threshold determined by a surrogate analysis test. For the surrogate test we calculate the average %TDS + 2 st.dev. from 200 realizations of pairs of output signals, where each signal is randomly taken from different subjects, and thus, physiological coupling should not be presented. Based on this surrogate test we obtain a 95% confidence level threshold of %TDS=2.5% for networks link strength, indicating that links with %TDS$>$2.5% are physiologically relevant.

III. Results

We focus on physiological systems network dynamics during sleep because sleep stages are well-defined physiological states with specific neuroautonomic regulation, and external influences due to physical activity or sensory inputs are reduced. The structure of our database, comprising of multi-channel synchronously recorded signals from different organ systems, allows to investigate the dynamics of interactions among organ systems and their network organization during different physiological states (sleep stages). Utilizing the TDS method, specially tailored to probe interactions among diverse systems with different dynamics, we aim to quantify coupling between organ systems and their network characteristics. This is essential to understand how physiologic regulation underlying a given state influences the dynamics of organ network communications, and how integration of organ systems as a network leads to emergent behaviours and physiological functions at the organism level [8].

Networks of brain rhythms interactions across cortical locations We first investigate the network of interactions among different brain rhythms. Sleep stages are traditionally defined by the presence of dominant brain rhythms in cortical EEG dynamics. However, little is known whether and how brain rhythms across cortical locations interact as a network to generate sleep stages [9]. We consider seven distinct cortical rhythms from six cortical areas (EEG channels) that are traditionally used in sleep-stage scoring. Our TDS analysis shows pronounced coupling for all pairs of rhythms, well above the significance threshold Th=2.5%TDS, indicating physiologically relevant network interactions. Further, we find that the complex network of brain rhythms interactions across locations changes with transition from one sleep stage to another. A clear sleep-stage stratification is observed when we coarse-grain the network by averaging the coupling strength over all pairs of rhythms for each two cortical areas – globally the network is characterized by much stronger coupling among brain rhythms during Wake and LS compared to REM and DS, as demonstrated by the coarse-grained TDS matrix in Fig.2.

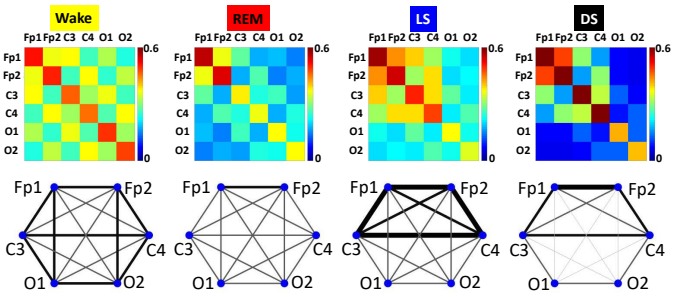

Fig. 2: **Dynamic networks of brain rhythms interactions across cortical locations and transitions with physiological states.** (Top) Time Delay Stability (TDS) matrices representing the average strength of coupling among all cortical rhythms (EEG frequency bands) across EEG channels, obtained from continuous overnight recordings for different sleep stages and averaged for a group of healthy subjects. Color code for matrix elements marks the coupling strength (%TDS). Transitions across sleep stages lead to changes in the average coupling strength of brain rhythm interactions across cortical locations and associated reorganization in TDS matrix structure characterized by stronger interactions during Wake and LS (warmer colors) compared to REM and DS (colder colors). (Bottom) Network representation of the group average TDS matrices for different sleep stages. Network nodes indicate cortical areas: Frontal (Fp1 and Fp2), Central (C3 and C4) and Occipital (O1 and O2). Each network link represents the coupling strength averaged over all pairs of rhythms from two different cortical areas, where wider and darker links indicate stronger coupling. Links are separated in four modules (with %TDS <12%; 12%-30%; 30%-38%; >38%). Dramatic reorganization in network structure is observed with transition from one sleep stage to another, with more homogeneous links (coupling strength) distribution during Wake and REM, heterogeneous and modularized links during LS and DS. Reorganization in network links heterogeneity is paralleled by a pronounced sleep-stage stratification pattern – average network links strength is significantly different comparing all four sleep stages (one-way ANOVA rank test $p \leq 0.001$), and pairwise comparisons of Wake vs REM and LS vs DS both show significant difference (Mann-Whitney test $p \leq 0.001$).

Moreover, there is a pronounced reorganization in network topology with transition across physiologic states, where each sleep state is characterized by specific modules of cortical locations with strong or weak interactions (Fig.2).

Network interactions among brain rhythms within cortical areas We next investigate the network of brain rhythms interactions within each of the six cortical locations separately. We find that higher frequency brain rhythms exhibit stronger coupling (i.e. more synchronous bursting activity) – a behaviour which is consistently observed for all six cortical locations and sleep stages, as shown by the TDS matrices in Fig.3. With transition from one sleep stage to another, there is a significant reorganization in both links strength and topology

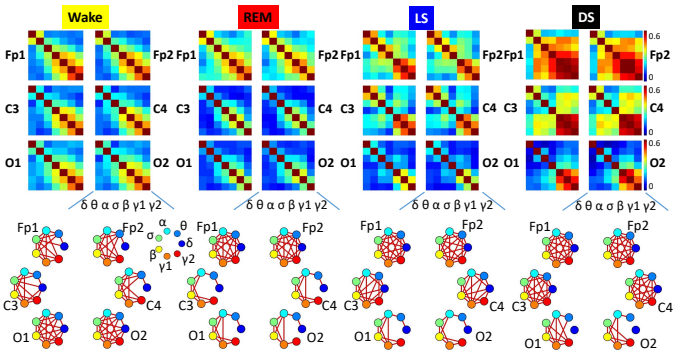

Fig. 3: **Plasticity in network interactions among brain rhythms at specific cortical locations as function of physiologic state.** (Top) Time Delay Stability (TDS) matrices quantify interactions for specific pairs of cortical rhythms (EEG frequency bands δ, θ, α, σ, β, γ_1, and γ_2) within six cortical areas (EEG channels: Frontal Fp1 and Fp2, Central C3 and C4, Occipital O1 and O2). Color code of matrix elements marks the coupling strength for each pair of brain rhythms averaged over a group of healthy subjects. Changes in TDS matrix structure for different brain areas and sleep stages indicates plasticity of brain rhythms interactions as function of physiologic state. (Bottom) Network presentation of the TDS matrices at six cortical locations for different sleep stages. Network nodes in color mark cortical rhythms derived from a given EEG channel representing a cortical location. Network links (in red) represent the strength of interaction for each pair of brain rhythms at a given EEG channel location (only links with $\%\text{TDS} \geq 25\%$ are shown). Network connectivity significantly changes at cortical locations during a given sleep stage, as well as with transition across stages (one-way ANOVA tests $p \leq 0.001$), indicating a complex reorganization and plasticity in brain rhythm interactions necessary to facilitate physiologic functions associated with distinct physiologic states.

for all local networks of brain rhythms interactions: while Wake is characterized by similar network link strength and topology for all six cortical areas, local networks of brain rhythms interactions during REM, LS and DS exhibit different structure with higher connectivity and link strength in the two Frontal areas compared to the Central and Occipital areas.

Dynamics of brain-organs interactions Brain dynamics play an important role in the neuroautonomic regulation of organ systems. However, it remains unknown how brain rhythms simultaneously coordinate the function of different organs. We analyze the coupling of all seven brain rhythms from all six cortical locations with five key organ systems. We find that subnetworks of brain rhythms interacting with distinct organ systems exhibit different average links strength, indicating a more synchronous activity and stronger coupling of brain rhythms with the dynamics of some organ systems compared to others, as shown by different size of network nodes in Fig.4. Further, we find that while all brain rhythms play certain role in the network of brain-organs interactions, a particular rhythm

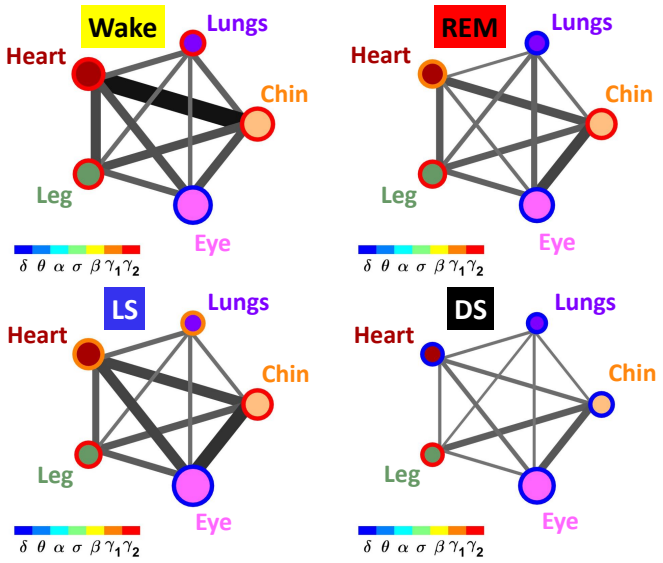

Fig. 4: **Dynamic networks of organ interactions across sleep stages.** Interactions among organ systems are represented by weighted undirected graphs, where network links between organ systems reflect the strength of dynamic coupling measured as %TDS and averaged for a group of healthy subjects. Darker and thicker links correspond to stronger interaction with higher %TDS. Network nodes represent key organ systems. The size of each organ node is proportional to the strength of the overall interaction of the organ with all brain rhythms at six cortical EEG channel locations (see Fig. 3). Color bars represent physiologically relevant cortical rhythms (EEG frequency bands). The circumference color of each organ node corresponds to the cortical rhythm exhibiting dominant coupling with the organ system when averaged over all cortical locations. Significant reorganization in network topology (links strength) for different sleep stages (all stages comparison one-way ANOVA rank test $p \leq 0.001$, and pairwise comparisons of Wake vs REM and LS vs DS with Mann-Whitney test $p \leq 0.003$) indicates an association between organs network interactions and physiologic function.

serves as the main mediator of network communications for a given organ system. Thus, a very structured dynamic network of brain-organs interaction emerges, where different brain rhythms are involved as main mediators of the function of different organ systems during a given physiological state (marked by different node circumference color in Fig.4). With transition from one sleep stage to another, a different brain rhythm may take the role as the main mediator in network interaction with a given organ system – e.g., brain-heart network interactions are mediated by γ_2 rhythms during Wake, γ_1 and β rhythms during REM and LS, and δ rhythms during DS, reflecting previously unrecognized aspects in the autonomic regulation of organ systems (Fig.4) [10].

Networks of organ interactions Finally, we apply our TDS analysis to probe interactions among organ systems. We find that pairs of organ systems are characterized by different coupling and correspondingly by different group average network links strength. As in the cases of brain-brain and brain-organs interactions, our analyses show that each sleep stage is characterized by a specific network topology of organ interactions (Fig.4).

The reported here findings for the group average network characteristics (topology and link strength) are consistent with results obtained for individual subjects in our database, indicating a robust association of organ network interactions with physiologic state and function.

IV. Summary

We show that the concept of time delay stability and the TDS method we developed can be successfully employed to quantify the coupling and network interactions of systems with complex time-varying and diverse dynamics. Utilizing continuous recording during sleep from healthy young subjects, we demonstrate that each sleep stage is uniquely characterized by a network of physiologic interactions across scales in the human organism – from coupling among brain rhythms within and across cortical locations to networks of organ interactions. We find that with transition from one state to another, physiologic network structure undergoes a consistent reorganization that occurs across scales. The presented Network Physiology approach and empirical findings provide new insights in the mechanisms of autonomic regulation underlying physiologic states, and can help our understanding of how behaviours and functions emerge at the organism level out of integrated network interaction among diverse systems.

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