Network Physiology: Mapping interactions between complex physiological systems

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Human Organism comprises diverse multi-component physiological systems
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Medical specialists traditionally focus on single organ systems.
Human Organism – Integrated Network
Coordinated Interactions of Organ Systems

Essential to: Maintain Health
Generate distinct physiological states
Disrupted Communications among Organ Systems

Leads to: 1. Dysfunction of individual systems
2. Collapse of the entire organism
**Human Organism – Integrated Network of interconnected and interacting organ systems**

<table>
<thead>
<tr>
<th>Failure of one system may trigger a <em>cascade of failures</em> leading to a breakdown of the entire organism</th>
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<tbody>
<tr>
<td>Even structurally intact and functioning individual systems → <strong>Not</strong> sufficient for Health！</td>
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<tr>
<td>Broad <em>clinical implications</em>: Coma, Multiple Organ Failure</td>
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*Yet, despite the importance to:*
  *understanding basic physiologic functions*
  *clinical relevance*

*we do not know how organ systems dynamically interact as a network to coordinate and optimize their functions*
Current Research Focus of Systems Biology and Integrative Physiology

Vertically integrating sub-cellular, tissue, cell, and organ levels

Signaling and feedbacks across space/time scales

Integrative Physiology

Systems Biology

Vertical Integration
Our Research Focus: Horizontal Integration

Epidemiology / Population Health

Macroscopic

Horizontal Integration

Mesoscopic

Microscopic

Integrative Physiology

System Biology

Vertical Integration

organs
tissue
cell
sub-cellular
New Research Direction:
Shifting the focus from single organ systems
to the network of organ interactions

Our Research Program

A new field
Network Physiology

needed to probe interactions among diverse physiologic systems.
1st Symposium on Network Physiology and Medicine, Oct. 2012

“Network Physiology reveals relations between network topology and physiological function”

Generated Broad Interests in the Community

Special Issue, 2014

Science News Cover Story, 2012
Levels of Complexity:

Level 1: noisy/non-stationary output signals of individual organ systems

Level 2: transient, nonlinear and coexisting forms of pair-wise coupling

To address these Challenges:

- we introduced new concepts
- innovated interdisciplinary approaches
- developed new methods and technology
- analyzed continuous physiologic recordings

Data-Driven Discoveries

led to

- Physiology
- Stat. Physics
- Applied Math
Complex Variability in Physiologic Dynamics across spatio-temporal scales and levels of integration

Is Physiologic Variability simply Noise?

Level 1: Individual Systems

- organs
  Brain dynamics during sleep (EEG)

- cell
  Single neuron activity

- sub-cellular
  Ion channel kinetics

New Concept: Fluctuations are not noise!

Instead: Fluctuations contain hidden dynamical patterns related to underlying mechanisms
Heart rate data

Self-similar cascades

Level 1: Individual Systems

Scale-invariance in heartbeat fluctuations

Heart rate data

Scale of Analysis

Beat number

Sleep apnea

New Methodology

New Diagnostics

Universal behavior across subjects

\[ P(x, b) = \frac{b^{\nu+1}}{\Gamma(\nu + 1)} \cdot x^\nu \cdot e^{-bx} \]

Gamma distribution

Generalized homogeneous function

\[ P(\lambda^\alpha x, \lambda^\beta b) = \lambda P(x, b) \]

\[ (\alpha = -1, \beta = 1) \]

Scale-invariance

“data collapse” over a range of time scales

Multifractal organization in heartbeat fluctuations

New Technology:

To quantify non-stationarity in local Hurst exponents of complex signals

Discovery: Fractals within Fractals
Multiple fractal sets with different fractal dimension – turbulence-like behavior

P. Ch. Ivanov et al., NATURE 399: 461 (1999)
5 healthy subjects

Local Hurst exponent $h(t)$

$5$ heart failure subjects

Multicolor $\leftrightarrow$ Multifractal

Monocolor $\leftrightarrow$ Monofractal

(time $t$)

(6-hour recordings)

Motor Activity: Wrist motion fluctuations

**Motivation:**
Test hypothesis that there are *intrinsic stable patterns* in human motor activity.

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**Magnitudes of wrist acceleration**
Motor Activity: Wrist motion fluctuations

- Stable distribution over time scales
  → scale invariance in wrist acceleration

- Long-range correlations
  → long-term memory

**Discovery:** Universal scale-invariant organization in human activity fluctuations

**Level 1: Individual Systems**

**Locomotor system dynamics:**

**wrist motion fluctuations**

Scaling exponents independent of activity level

<table>
<thead>
<tr>
<th>Protocol</th>
<th>$\alpha$</th>
<th>$\alpha_{mag}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily routine</td>
<td>0.92</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>± 0.05</td>
<td>± 0.06</td>
</tr>
<tr>
<td>Constant routine</td>
<td>0.88</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>± 0.05</td>
<td>± 0.05</td>
</tr>
<tr>
<td>Forced desynchrony</td>
<td>0.92</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>± 0.03</td>
<td>± 0.04</td>
</tr>
</tbody>
</table>

- Party time!
- Day of rest!

Scaling exponents --- remarkably consistent for:
- all subjects
- all protocols
- all days of the week.
Cardio-respiratory Interaction
Respiratory Sinus Arrhythmia (RSA)

Inspiration $\rightarrow$ Heart rate $\uparrow$
Expiration $\rightarrow$ Heart rate $\downarrow$

Heart beat number

% of mean Heart rate

Heart beat number

Inspiration
Expiration

Age
- 20 to 35
- 36 to 50
- 51 to 65
- 66 to 82

Heart rate changes with age.
“Synchronization is an adjustment of rhythms of *self-sustained* oscillators due to their weak interaction.”


**Start:**
- different frequencies,
- different phases
  → No synchronization

**End:**
- same frequencies, same phase difference (“phase locked”)
  → Synchronization
• London: Millennium ("Wobbly") bridge opening day June 10, 2000

Millenium bridge reopened in February 2002:
- after 5 Million £ spent on bridge modifications
- research based on work by S. Strogatz et al. Nature 438, 43 (2005)
Cardio-respiratory Interaction
Phase Synchronization

Level 2: Pair-wise Coupling

Phases collapse

Heart
Respiration

C 3:1 synchronization

2π

φ_r

φ_r

1

2

3

1

2

3

IBI_i

ECG (a.u.) respiration (a.u.)

time t (s)

0

6

0

16.216

16.218

16.220

16.222

16.224

t_0

0

5

respiration (a.u.)

-5

-2π

-5

16.216

16.220

16.224
Level 2: Pair-wise Coupling

Cardio-respiratory Interaction
Phase Synchronization despite continuous fluctuations

Segments of Synchronization
Pronounced stratification of synchronization is stable for all age groups.

**Cardio-respiratory Interaction**

**Phase Synchronization**

**Level 2: Pair-wise Coupling**

**Discovery:**
Phase transitions in cardio-respiratory coupling

400% increase in synchronization from REM to deep sleep

RP Bartsch, AY Schumann, JW Kantelhardt, T Penzel, PCh Ivanov
Coexisting forms of physiologic coupling
Cardio-Respiratory interaction

Level 2: Pair-wise Coupling

Bartsch RP, Liu KKL, Ma QDY, and Ivanov PCh.
Three independent forms of cardio-respiratory coupling: transitions across sleep stages. Computing in Cardiology, 2014; 41:781-784

Discovery: RSA and Synchronization
Two coexisting forms of coupling
Our track record in addressing levels of complexity:

**Level 1: noisy/non-stationary output signals of individual systems**

Methods:
- Cumulative Variation Amplitude Analysis (CVAA) – *Nature* 96, *Chaos* 01
- Magnitude and Sign Scaling Analysis (MSA) – *PRL* 01, *PRE* 02, *PRE* 09
- Detrended Fluctuation Analysis (DFA) – *PRE* 01, 02, 05, 06, 10; *PNAS* 04, 07
- Data Segmentation Algorithm (DSA) – *PRL* 01, *Nature* 02, *EJPB* 12

**Level 2: transient, nonlinear and coexisting forms of pair-wise coupling**

Methods:
- Detrended Cross-Correlation Analysis (DCCA) – *EJPB* 07, *EJPB* 09
- Phase Synchrogram Algorithm (PSA) – *PRE* 06, *PRL* 07, *PNAS* 09, *PNAS* 12
- Instantaneous Phase Increments Cross-Correlation (IPIC) – *PRE* 06

**Applications:**
- **Physiology:** cardiac, respiration, gait, sleep, brain
- **Medicine:** novel diagnostic measures
- **Physical Sciences:** oil recovery, climate, seismology, astronomy
- **Economics:** stock markets, company growth, commodities …
Levels of Complexity:

Level 1: individual systems
Level 2: pair-wise coupling
Level 3: emergent global dynamics from networked interactions

Level 3: - global dynamics are not simply the sum of individual behaviors
- minor changes in the interactions lead to significant global effects

Currently: No available technology and theoretical framework
Challenges in understanding health as emergent behavior of physiologic interactions

1. Systems of oscillatory, stochastic or mixed type
2. Systems with non-stationary and non-linear output signals
3. Systems acting on different scales from msec to hours
4. Systems coupled with multiple coexisting forms of interaction

We made first inroads:

Introduced new concept – Time Delay Stability (TDS)
Developed a novel method

Infer/quantify interactions among diverse dynamical systems
Physiologic recordings

Full-night polysomnographic data from healthy young subjects:
- Brain activity - EEG
- Eye movement - EOG
- Muscle tone - EMG
- Respiration
- Heart dynamics - ECG

Physiologic states

Sleep stages: wake, REM sleep, light sleep (LS), deep sleep (DS)

→ Network of dynamical interactions; study the evolution of multiple physiologic interactions across different physiologic states
Quantifying interactions between diverse systems: concept of Time Delay Stability

EEG-σ band: sleep spindles
Heart rate
Respiratory rate
Eye movements

→ Bursts in the dynamics of one system are coordinated with bursts in other systems with stable time delay
Quantifying interactions between diverse systems: concept of Time Delay Stability

- Normalized spectral power of EEG-δ band
- Normalized spectral power of EEG-σ band
- Cross-correlation function vs. time lag in 30 sec windows
- Time delay vs. real time

→ Time periods of constant time delay indicate stable interaction represented by network links
Transitions in the network of physiological interactions

α – Chin interaction
HR – Eye interaction
α – Chin link
HR – Eye link

Dynamical Evolution

→ Fast reorganization of network connectivity with transitions across physiologic states
Network Topology & Physiologic Function
connectivity across sleep stages

Wake
REM Sleep
Light Sleep
Deep Sleep

Network connectivity

Network link strength

→ Network topology changes with physiologic states
Network connectivity

Network link strength

Different subnetworks

Different physiologic functions

→ Robust sleep-stage stratification pattern
Network connectivity and link strength of the brain–brain sub-network for different sleep stages

Topology of brain-brain sub-network $\rightarrow$ no change
Strength of network links $\rightarrow$ significant change
Transitions in connectivity and link strength of individual network nodes across sleep stages.

Robust sleep-stage stratification pattern in:

a) Individual node connectivity
b) Average link strength of individual nodes
Network Physiology
Networks of brain activity across sleep stages

Phase transition in link strength and network topology
Maps of physiologic interactions

Location of the nodes: Brain EEG Channels

Colors: Frequency bands in the EEG signals

Width of the links: Coupling strength between the systems

Radar Chart in the Hexagon: Brain Control on the target organ

Deep Sleep

Fp1

Fp2

C3

C4

Chin

O1 γ₁ γ₂

O2

σ α θ β
Visualization: different physiologic states

Wake

REM Sleep

Light Sleep

Deep Sleep
Maps for different organ systems

- Chin
- Eye
- Heart
- Respiration
Network Physiology: Networks of brain activity and other physiologic systems across sleep stages

Wake

REM Sleep

Light Sleep

Deep Sleep
Network Physiology: Networks of brain activity and other physiologic systems across sleep stages
Revolutionize our knowledge and understanding of the fundamental mechanisms that regulate and coordinate organ-to-organ interactions.
Such Atlas would contain:

**Atlas of Dynamic Interactions of Organ Systems**

Catalog of reference maps representing dynamical organ interactions under:

- healthy conditions
- age groups
- different physiologic states (rest/exercise, sleep/wake, sleep stages, circadian phases)
- pathological conditions (multiple organ failure, coma, heart failure, sleep apnea ...)

Quantitative assessment of variability in coupling strength for each map at a given state or condition

- Boundaries of coupling variability for normal conditions
- Establishing a **critical zone** for disease development as a function of age and physiologic state
Physiology and Medicine

Novel biomarkers

New kind of Physicians

Personalized health monitoring

Next generation ICU monitoring devices and alert system

Comprehensive assessment of drugs
Application of the proposed novel methods and theoretical framework to other fields

- Geosciences
- Climate
- Algorithms
- Interface/GUI
- Plant Science
- Economics/Finance
- Software
- Toolbox
Our Group:
http://physics.bu.edu/labnetworkphysiology

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