Network Physiology: Mapping interactions between complex physiological systems

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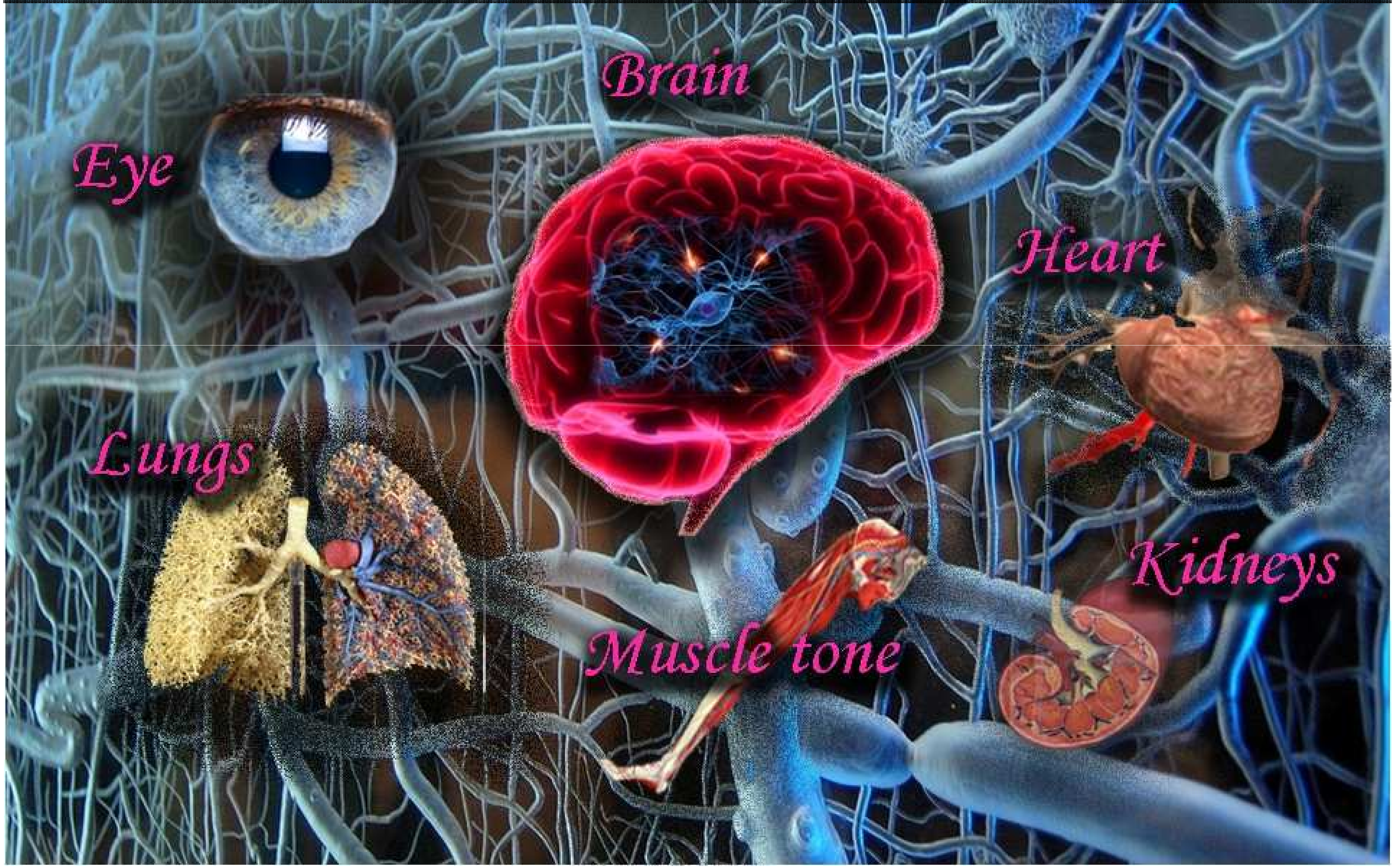
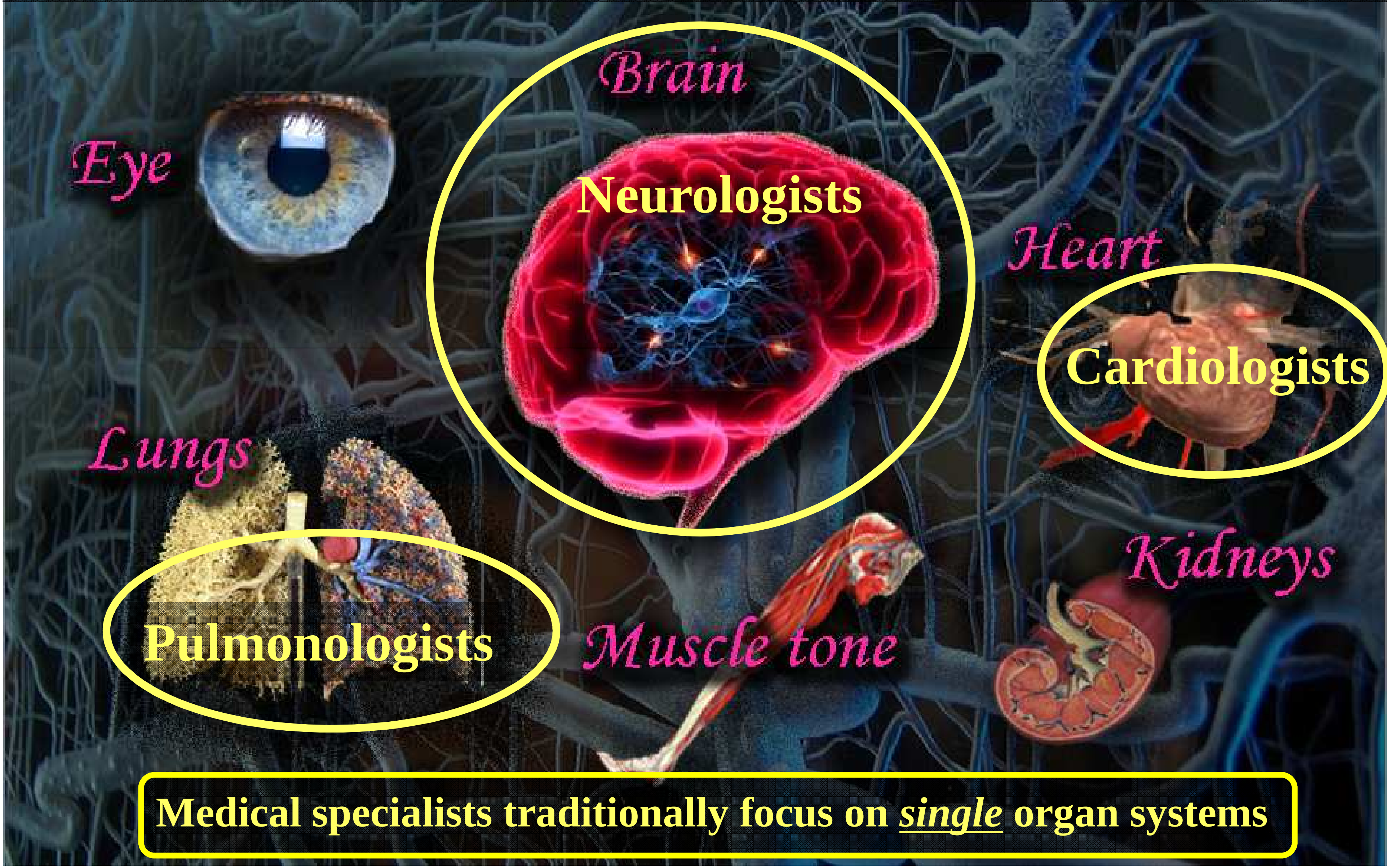
04 April 2016

Human Organism comprises diverse multi-component physiological systems

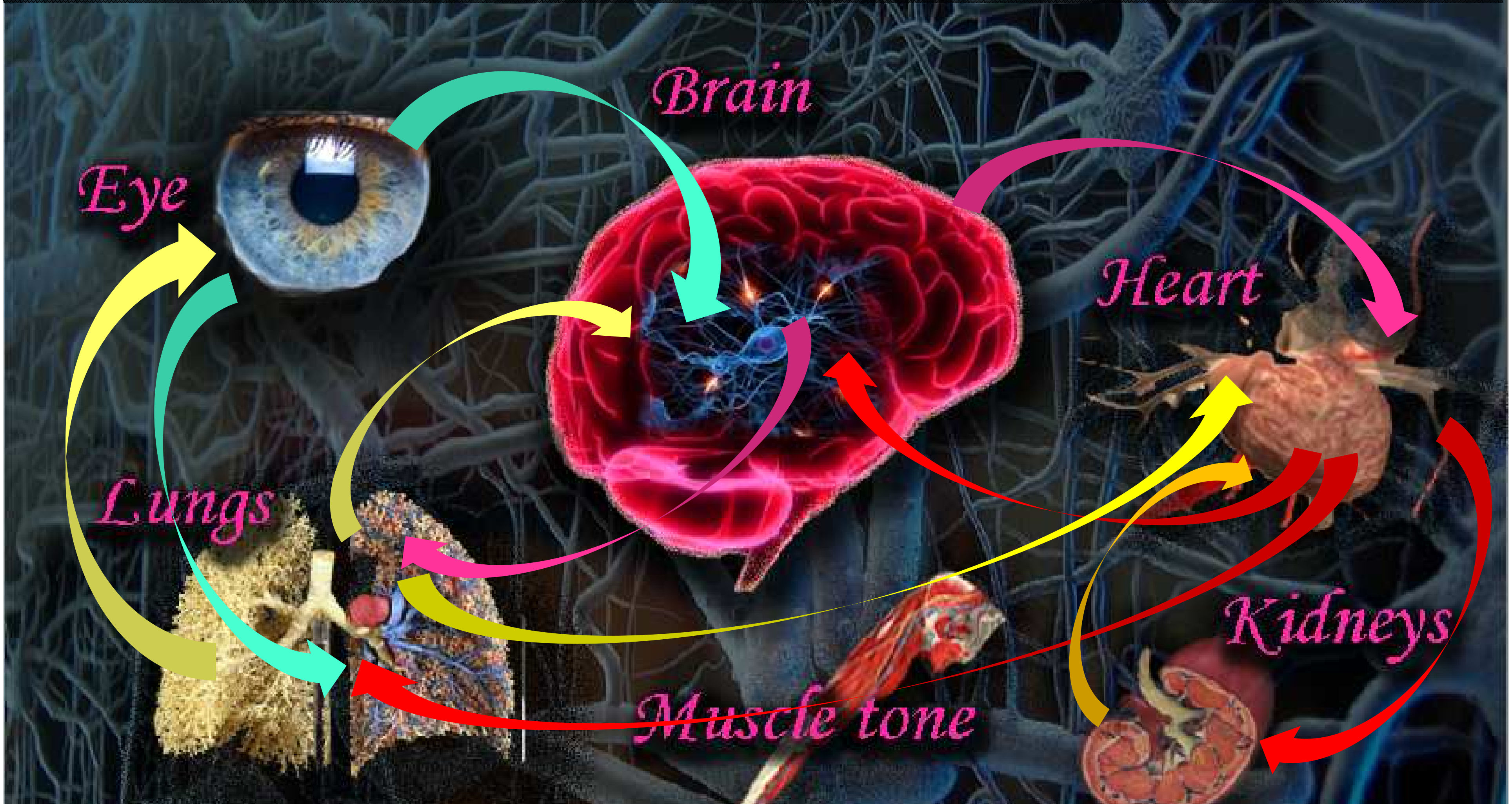


Human Organism comprises diverse multi-component physiological systems



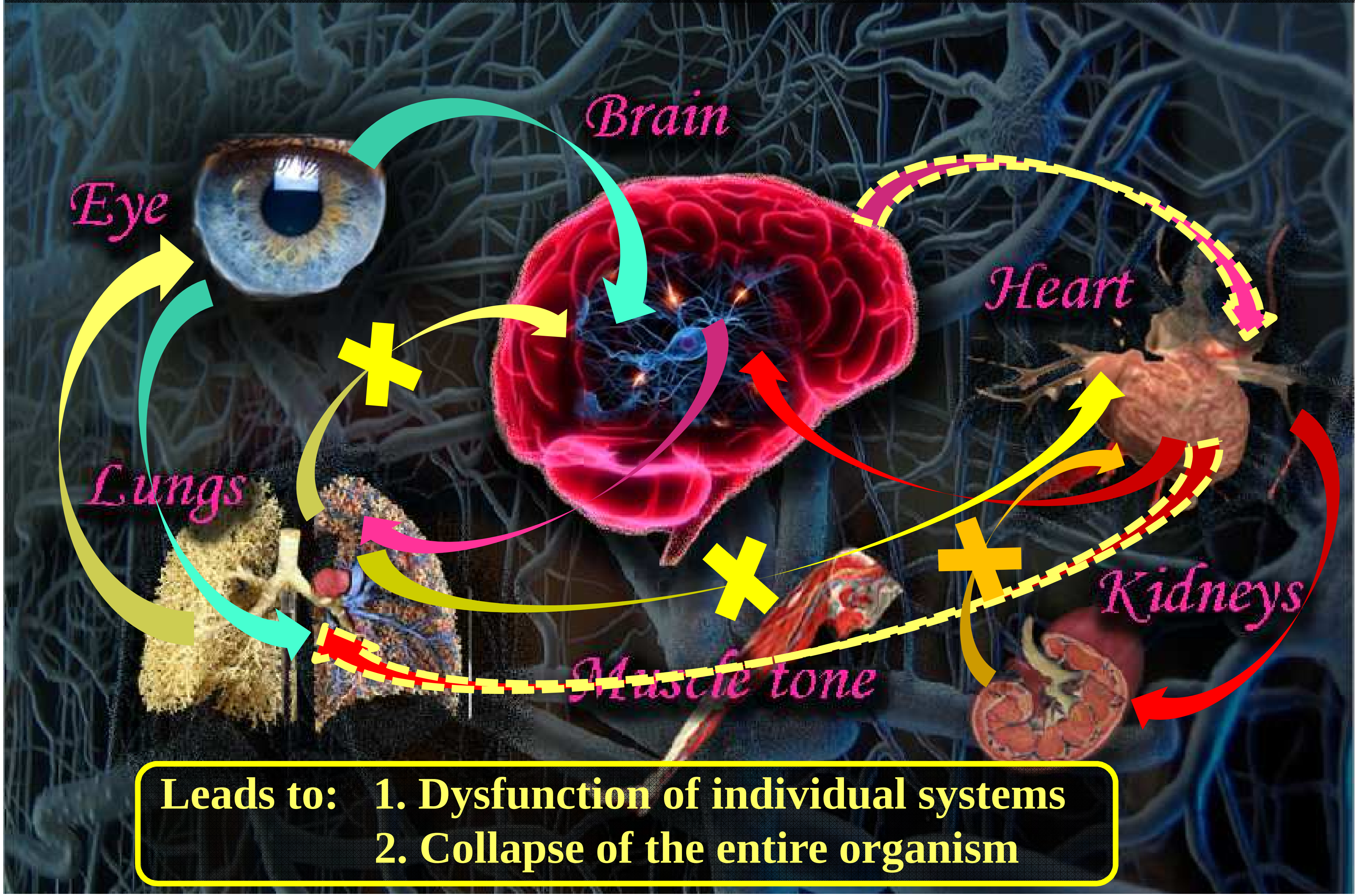
Medical specialists traditionally focus on _single_ organ systems

Human Organism – Integrated Network
Coordinated Interactions of Organ Systems



Essential to: **Maintain Health**
Generate distinct physiological states

Disrupted Communications among Organ Systems



Human Organism – Integrated Network of interconnected and interacting organ systems

Failure of one system may trigger a *<u>cascade of failures</u>* leading to a breakdown of the entire organism

Even structurally intact and functioning individual systems

→ Not sufficient for Health !

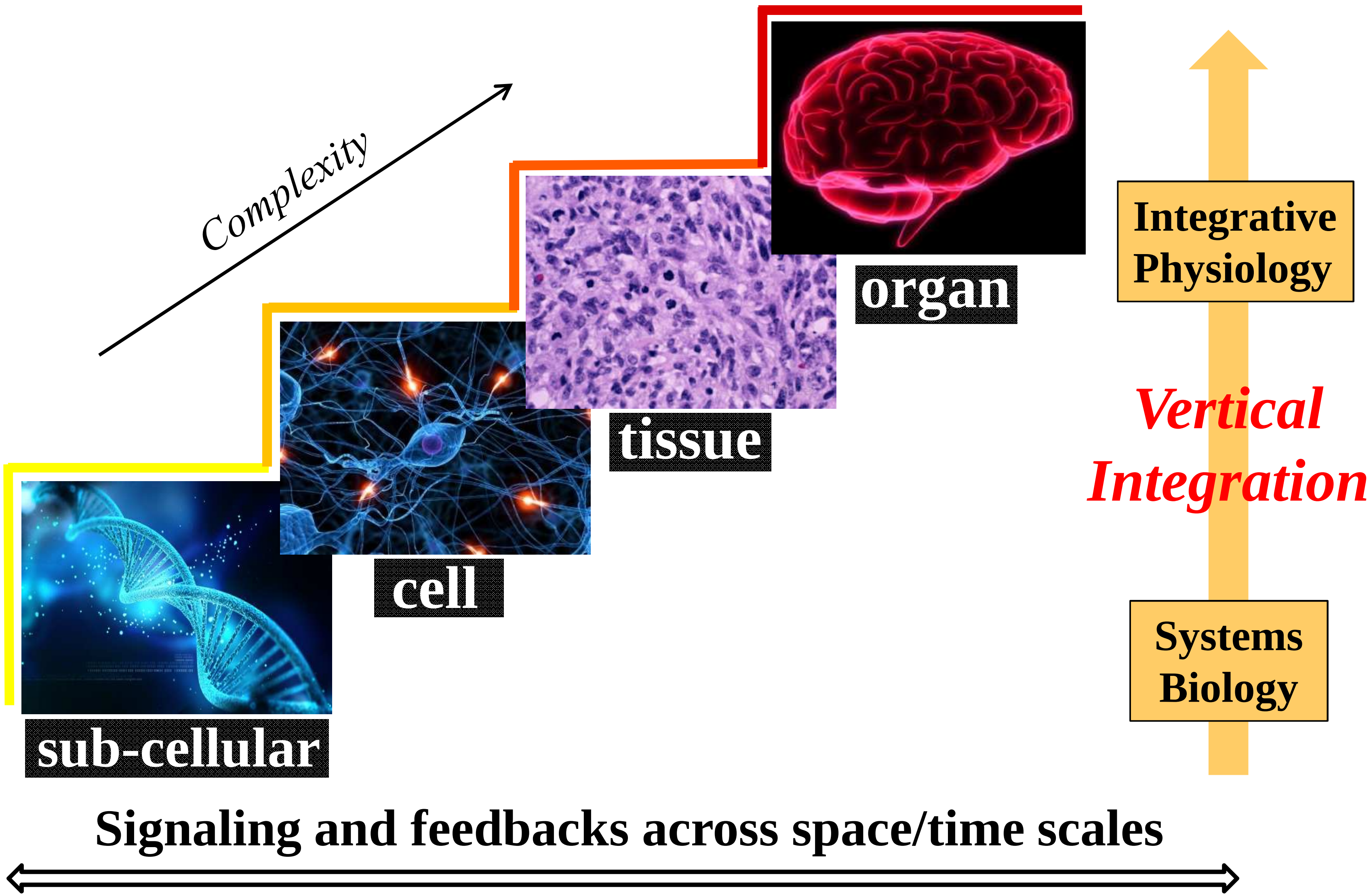
Broad *<u>clinical implications</u>*: Coma, Multiple Organ Failure

Yet, despite the importance to:

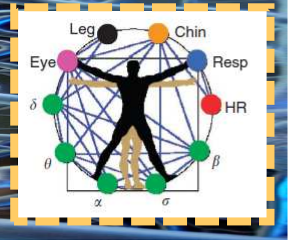
- **understanding basic physiologic functions**
- **clinical relevance**

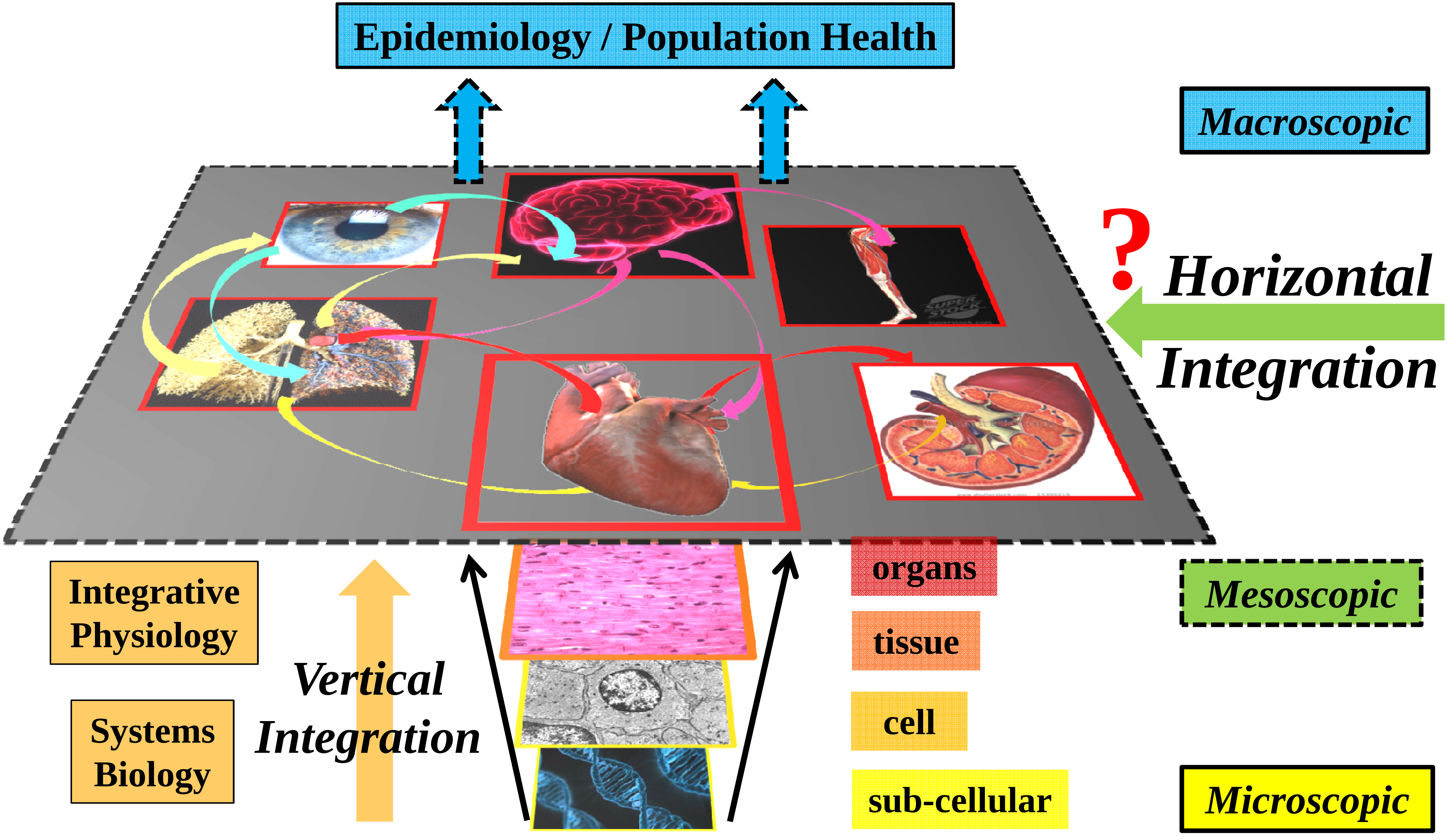
? we <u>do not know</u> how organ systems dynamically interact as a network to coordinate and optimize their functions

Current Research Focus of Systems Biology and Integrative Physiology



Our Research Focus: Horizontal Integration

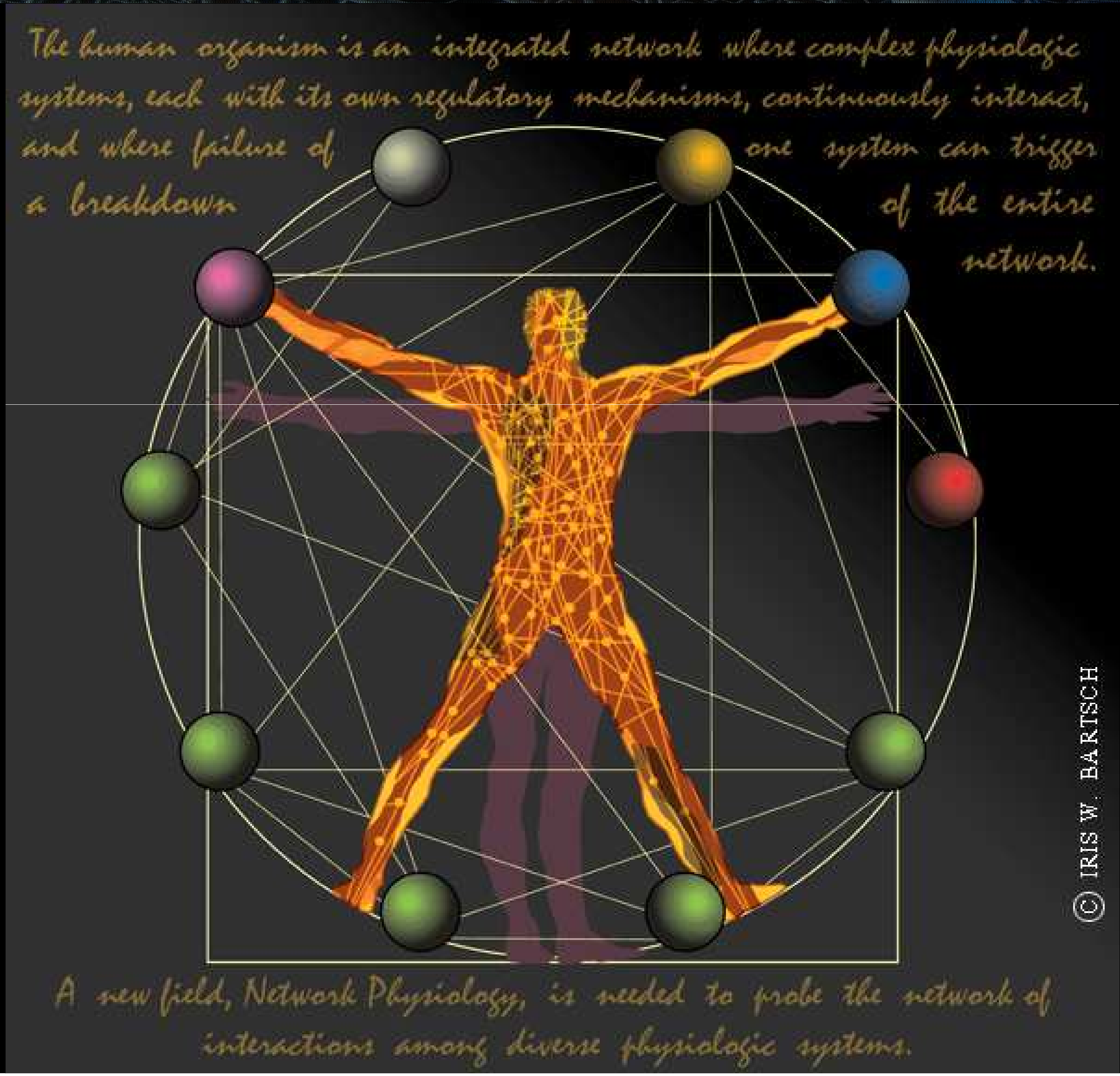




Our Research Program

New Research Direction:

Shifting the focus from single organ systems to the network of organ interactions



A new field

Network Physiology

needed to probe interactions among diverse physiologic systems.

New Field of Research: Network Physiology

First Work: BOSTON UNIVERSITY

Nature Communications vol. 3:702 (2012)

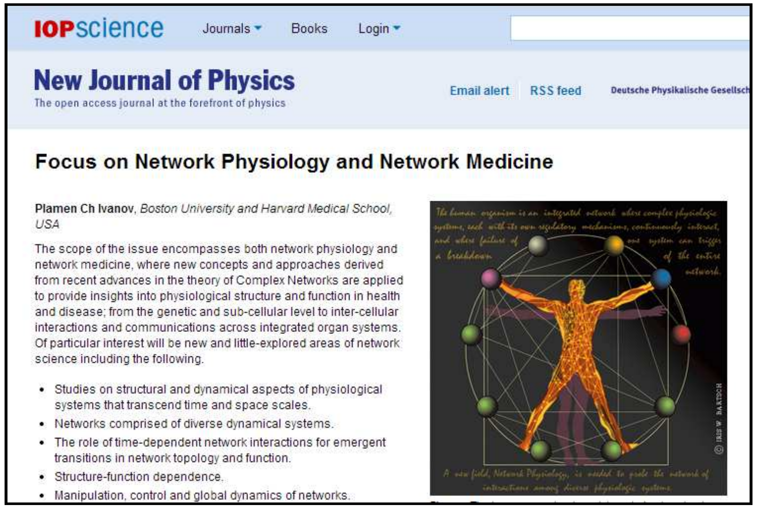
"Network Physiology reveals relations between network topology and physiological function"

Generated Broad Interests in the Community

1st Symposium on Network Physiology and Medicine, Oct. 2012

HARVARD CATALYST | THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Special Issue, 2014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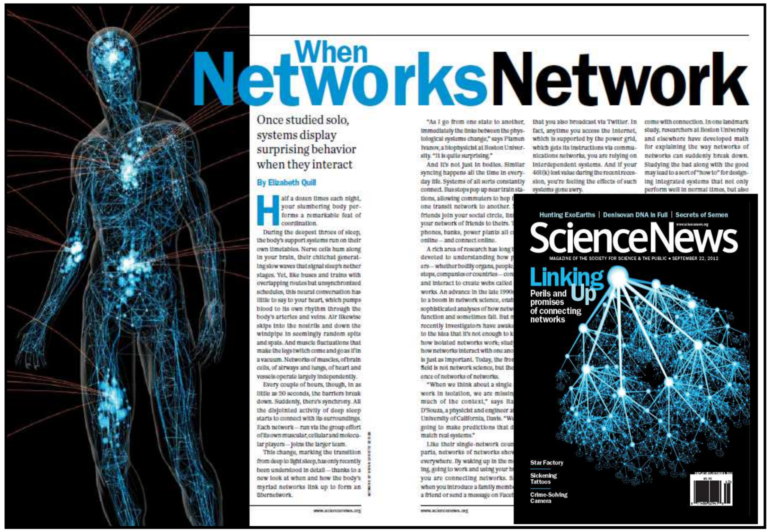
Focus on Network Physiology and Network Medicine

Plamen Ch Ivanov, *Boston University and Harvard Medical School, USA*

The scope of the issue encompasses both network physiology and network medicine, where new concepts and approaches derived from recent advances in the theory of Complex Networks are applied to provide insights into physiological structure and function in health and disease; from the genetic and sub-cellular level to inter-cellular interactions and communications across integrated organ systems. Of particular interest will be new and little-explored areas of network science including the following.

- Studies on structural and dynamical aspects of physiological systems that transcend time and space scales.
- Networks comprised of diverse dynamical systems.
- The role of time-dependent network interactions for emergent transitions in network topology and function.
- Structure-function dependence.
- Manipulation, control and global dynamics of networks.

Science News Cover Story, 2012



Challenges:

How to identify and quantify interactions among diverse systems?

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

led to

Data-Driven Discoveries

Physiology | Stat. Physics | Applied Math

Level 1:
Individual
Systems

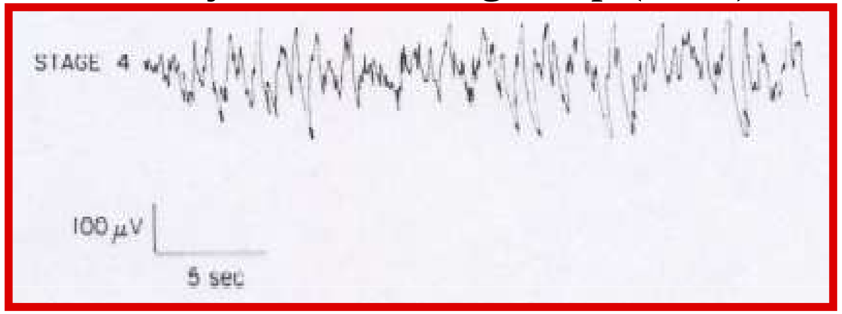
Complex Variability in Physiologic Dynamics across spatio-temporal scales and levels of integration

Is Physiologic Variability simply Noise?

Complexity

organs

Brain dynamics during sleep (EEG)

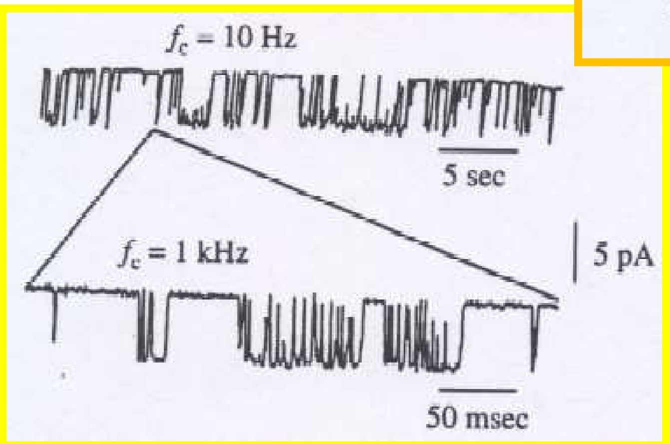


cell

Single neuron activity

sub-cellular

Ion channel kinetics



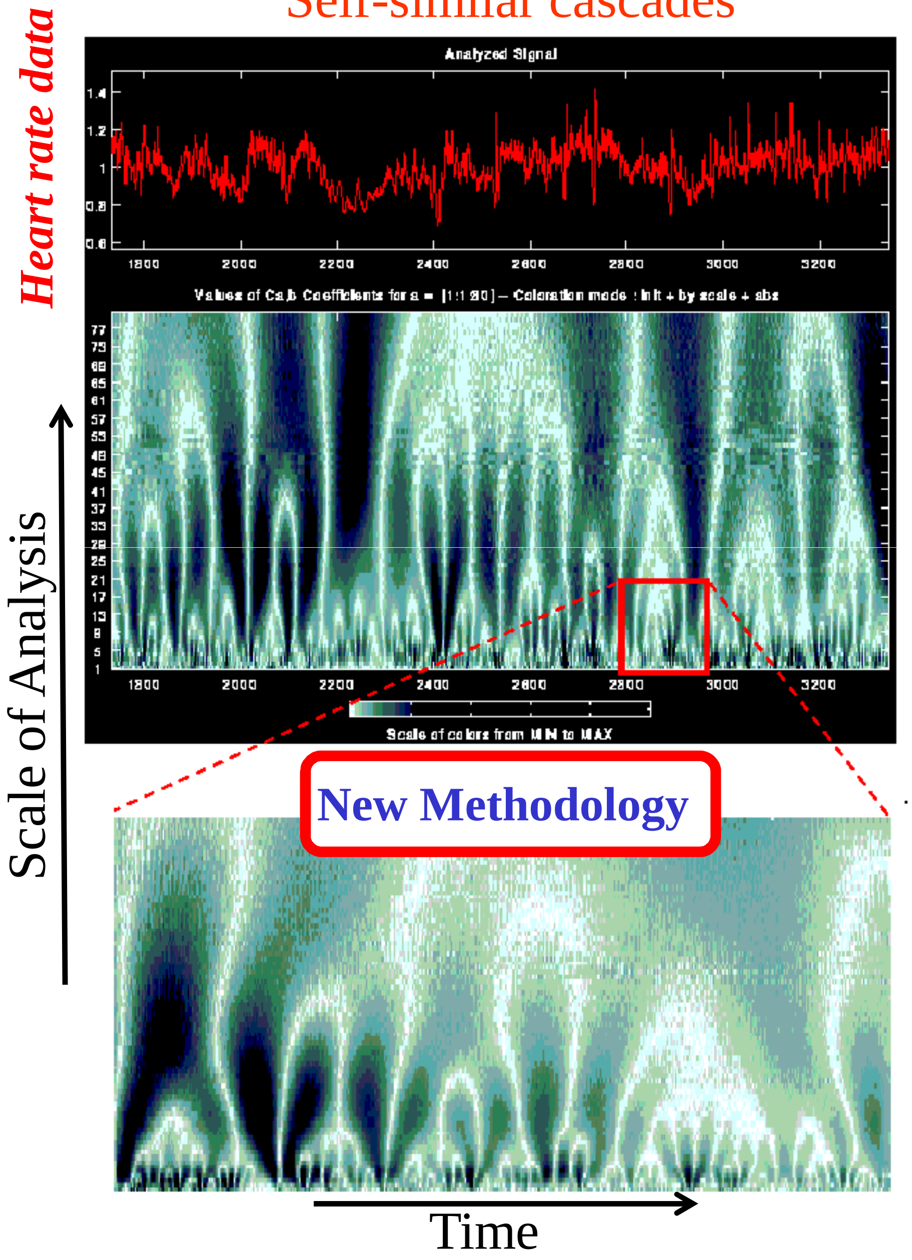
<u>New Concept:</u> Fluctuations are *<u>not</u>* noise !

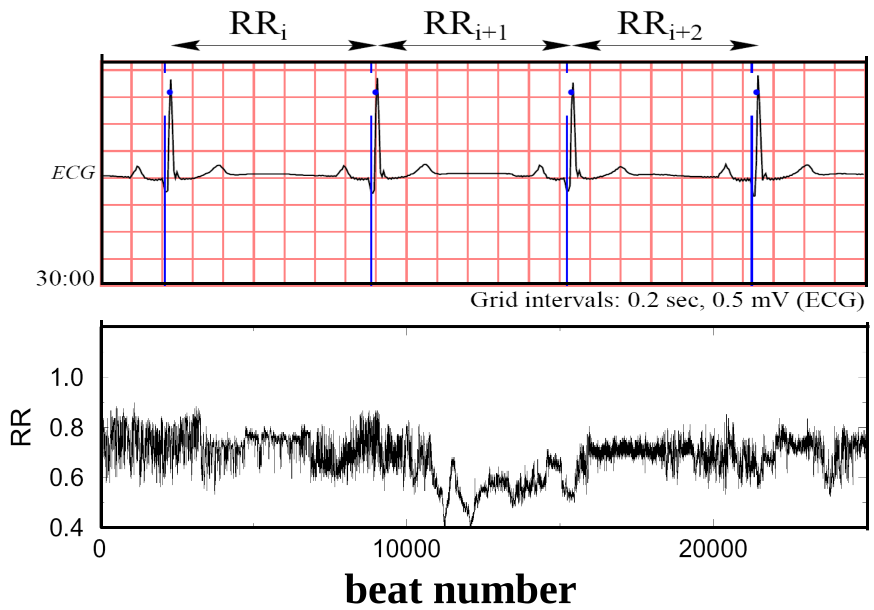
Instead: **Fluctuations contain hidden dynamical patterns related to underlying mechanisms**

Level 1:
Individual Systems

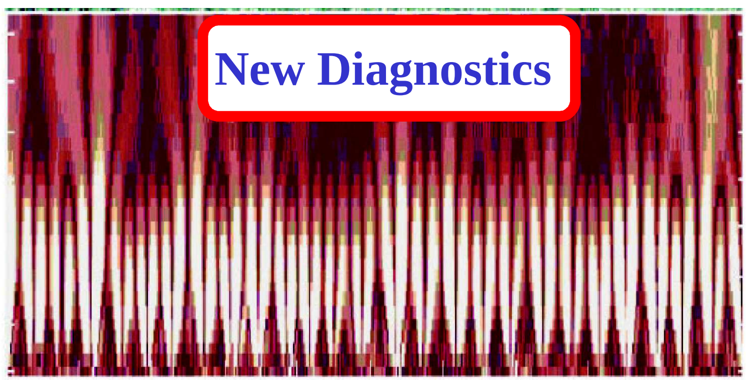
Scale-invariance in heartbeat fluctuations

Self-similar cascades





Sleep apnea



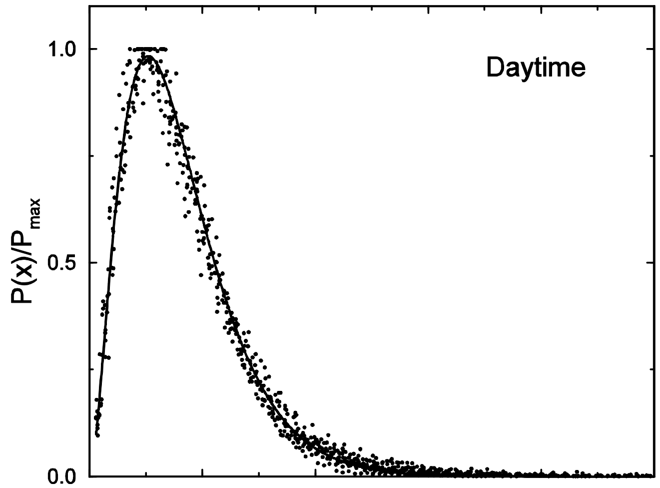
P.Ch. Ivanov *et al.* *Nature* **383**:323 (1996).
P.Ch. Ivanov *et al.* *Chaos* **11**: 641 (2001).
P.Ch. Ivanov *et al.* *Wavelets in Physics*,
(Cambridge Univ. Press, 1998).

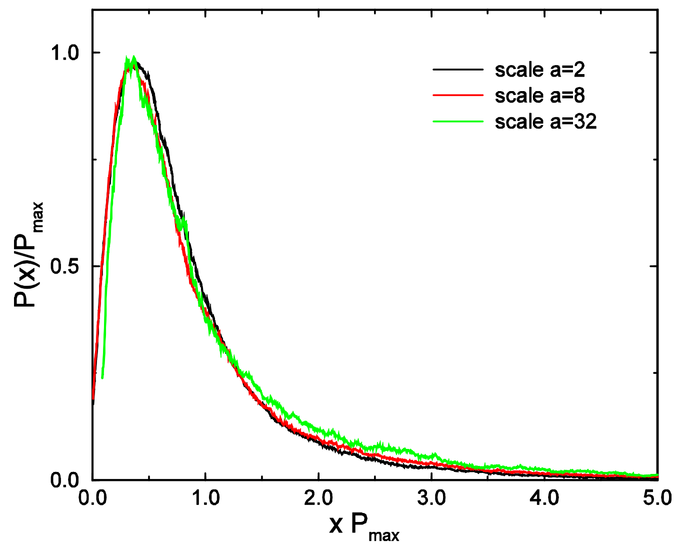
Scale-invariance in heartbeat fluctuations

New Method:

Cumulative variation amplitude analysis (CVAA)

Data → Wavelet Transform → Hilbert Transform → Amplitude distribution





Universal behavior across subjects

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

Gamma distribution

Generalized homogeneous function

$$P(\lambda^{\alpha}x,\lambda^{\beta}b)=\lambda P(x,b)$$

$$(\alpha=-1 \quad \beta=1)$$

Scale-invariance

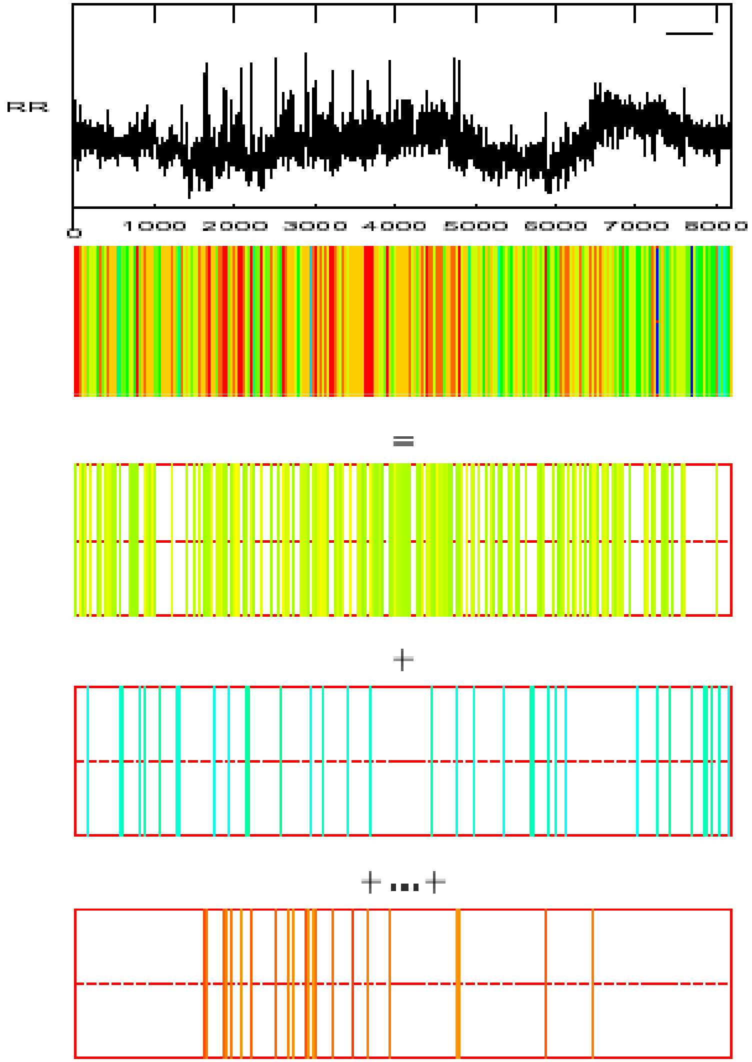
"data collapse" over a range of time scales

P.Ch. Ivanov *et al.* *Nature* **383**:323 (1996).

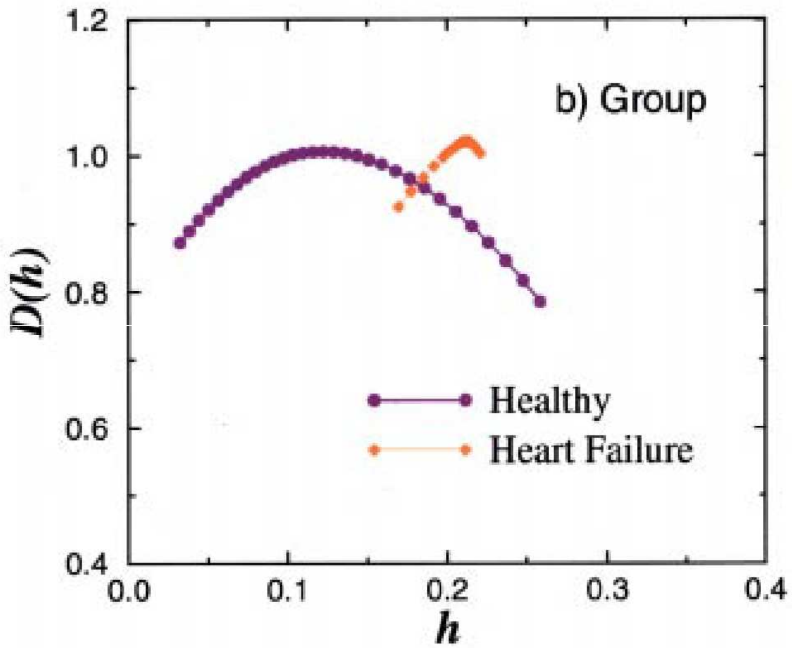
Level 1:
Individual Systems

Multifractal organization in heartbeat fluctuations

New Technology:



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



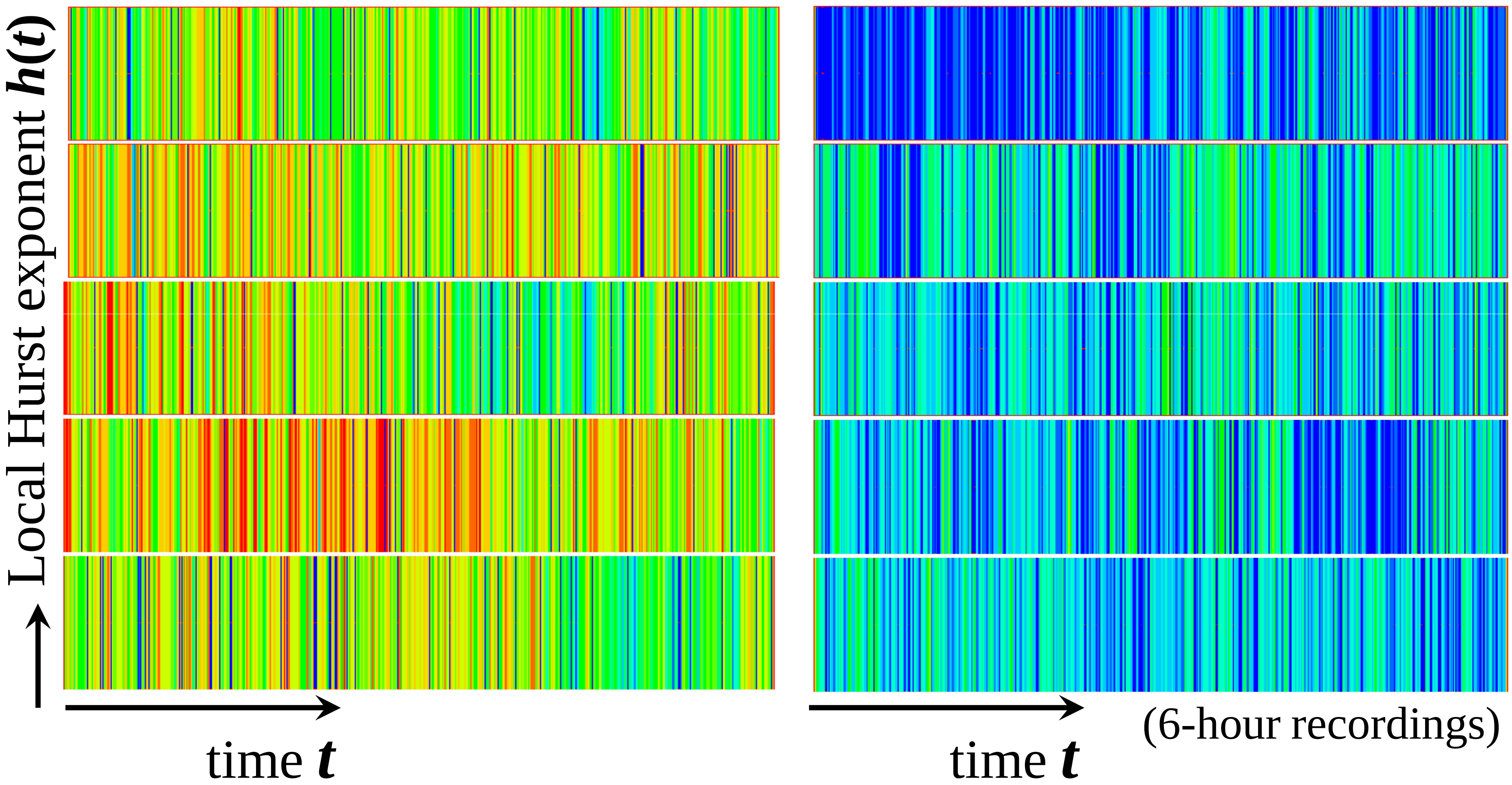
Discovery: ***Fractals within Fractals***
Multiple fractal sets with different fractal dimension – turbulence-like behavior

*P. Ch. Ivanov et al., NATURE **399**: 461 (1999)*

Multifractal organization in heartbeat fluctuations

New Technology → **New Diagnostics**

5 healthy subjects | 5 heart failure subjects



Multicolor ↔ Multifractal | **Monocolor ↔ Monofractal**

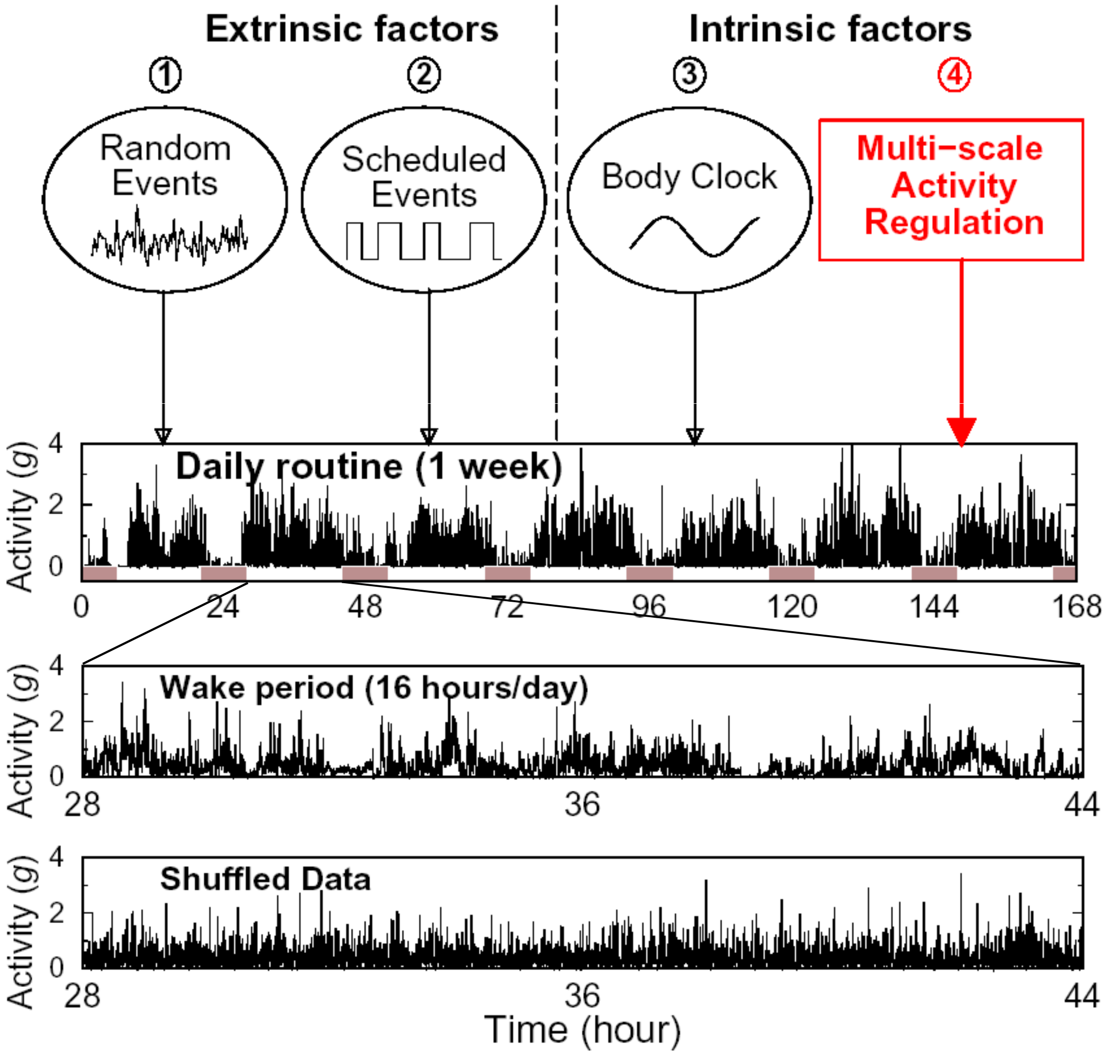
P.Ch. Ivanov *et al.* *Chaos* **11**: 641 (2001).

Motor Activity: Wrist motion fluctuations

Motivation:

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

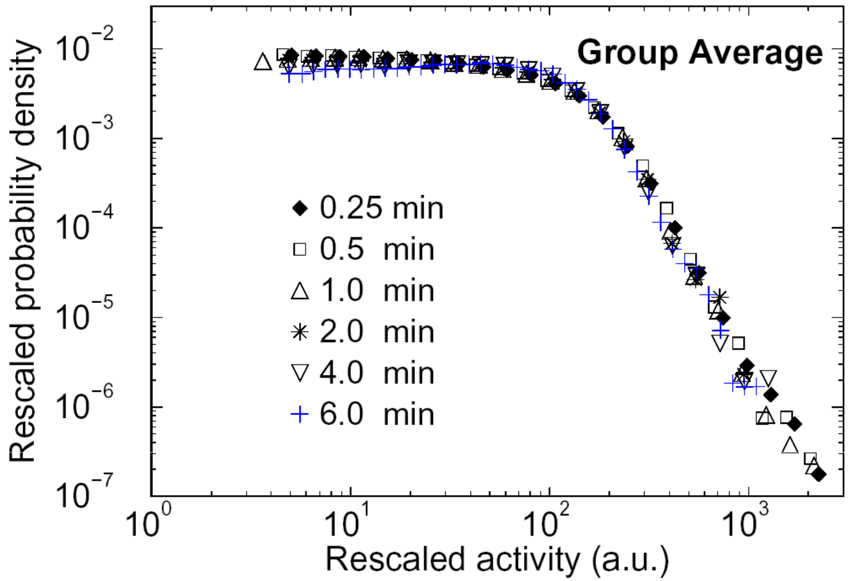
Magnitudes of wrist acceleration

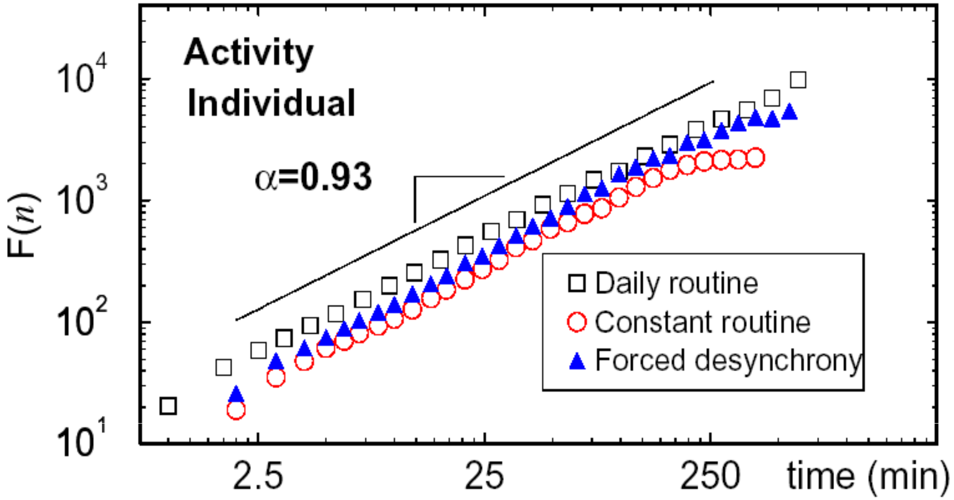


Level 1:
Individual Systems

Locomotor system dynamics

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

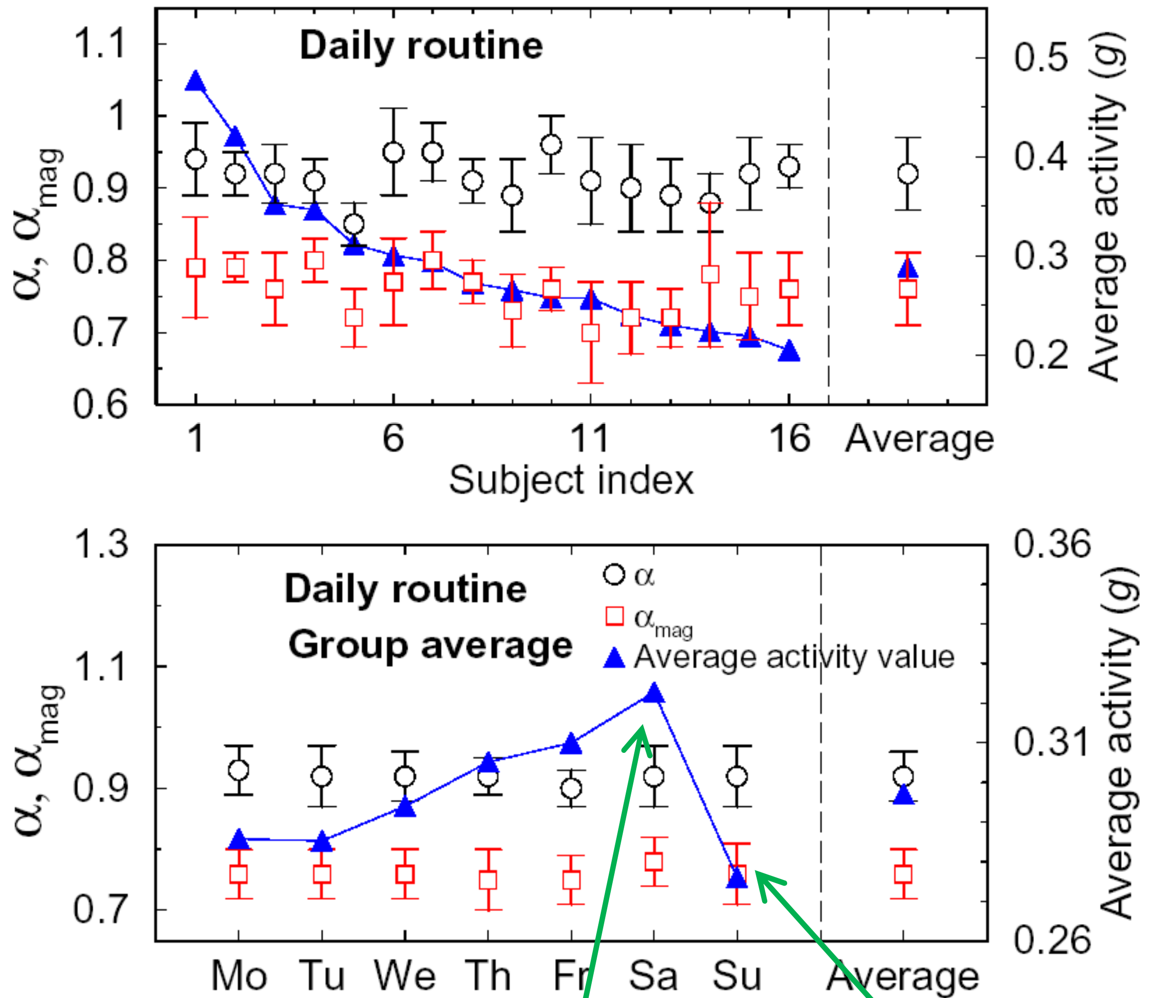
K. Hu et al. ***Physica A*** 337: 307 (2004).
P. Ch. Ivanov et al., ***PNAS*** 104: 20702 (2007) .
K. Hu et al., ***Neuroscience*** 149: 508 (2007).

Smart wristband

Level 1:
Individual Systems

Locomotor system dynamics: wrist motion fluctuations

Scaling exponents independent of activity level



Protocol	α	α_{mag}
Daily routine	0.92 $\pm$ 0.05	0.78 $\pm$ 0.06
Constant routine	0.88 $\pm$ 0.05	0.82 $\pm$ 0.05
Forced desynchrony	0.92 $\pm$ 0.03	0.80 $\pm$0.04

Scaling exponents --- remarkably consistent for:

- all subjects
- all protocols
- all days of the week.

Party time!

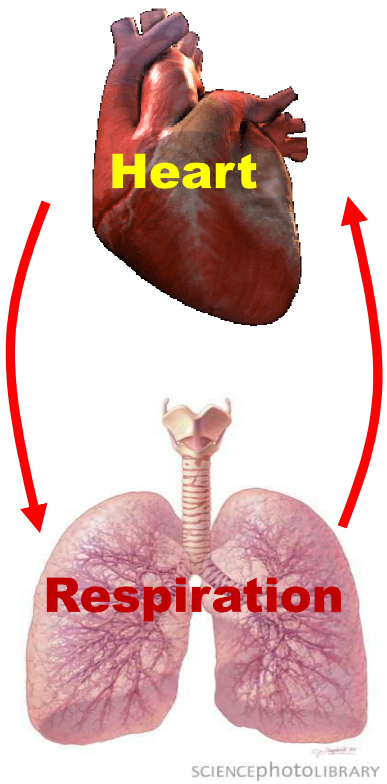
Day of rest!

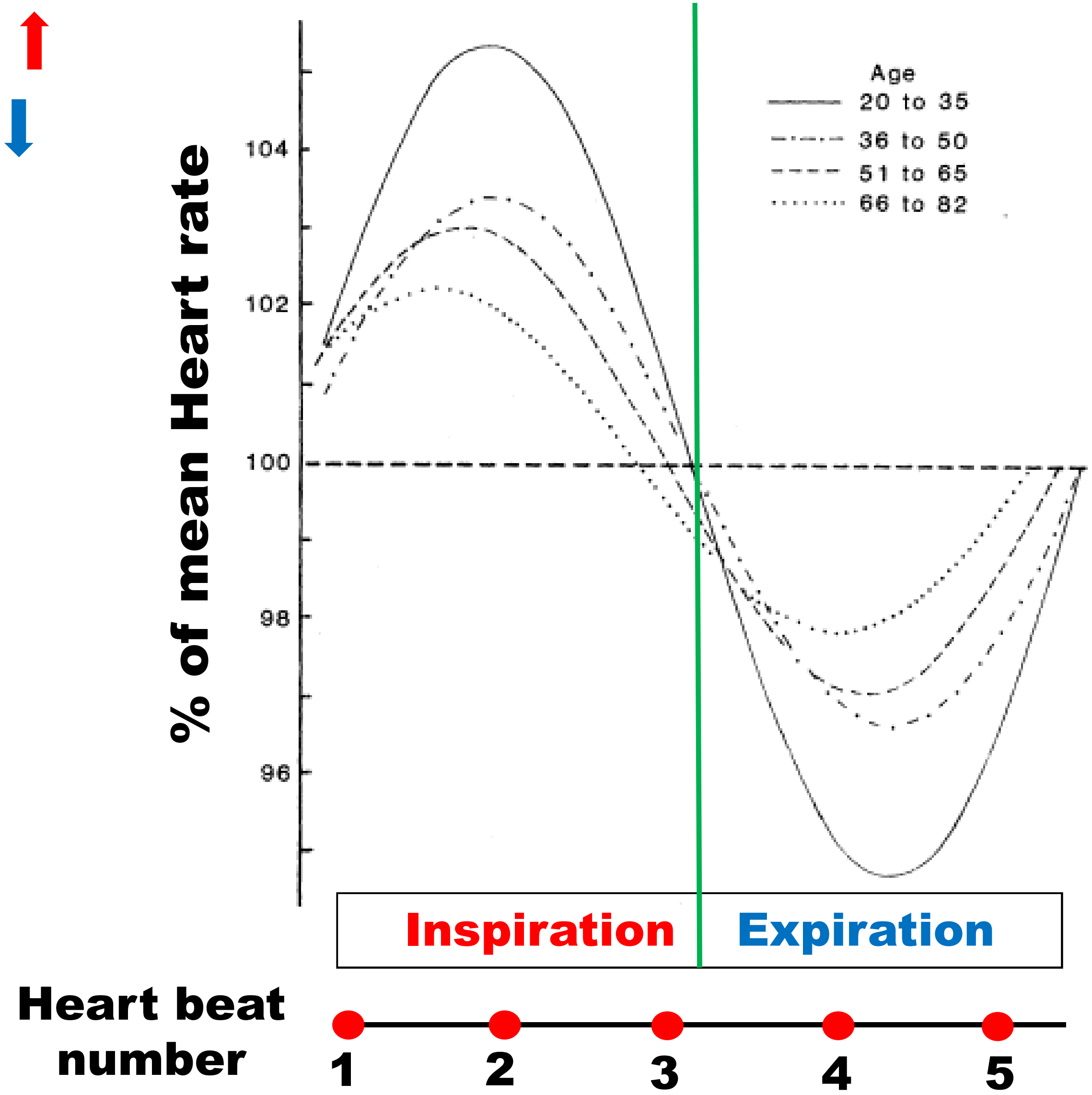
Level 2:
Pair-wise Coupling

Cardio-respiratory Interaction
Respiratory Sinus Arrhythmia (RSA)

Inspiration → Heart rate ↑

Expiration → Heart rate ↓





Cardio-respiratory Interaction
Phase Synchronization

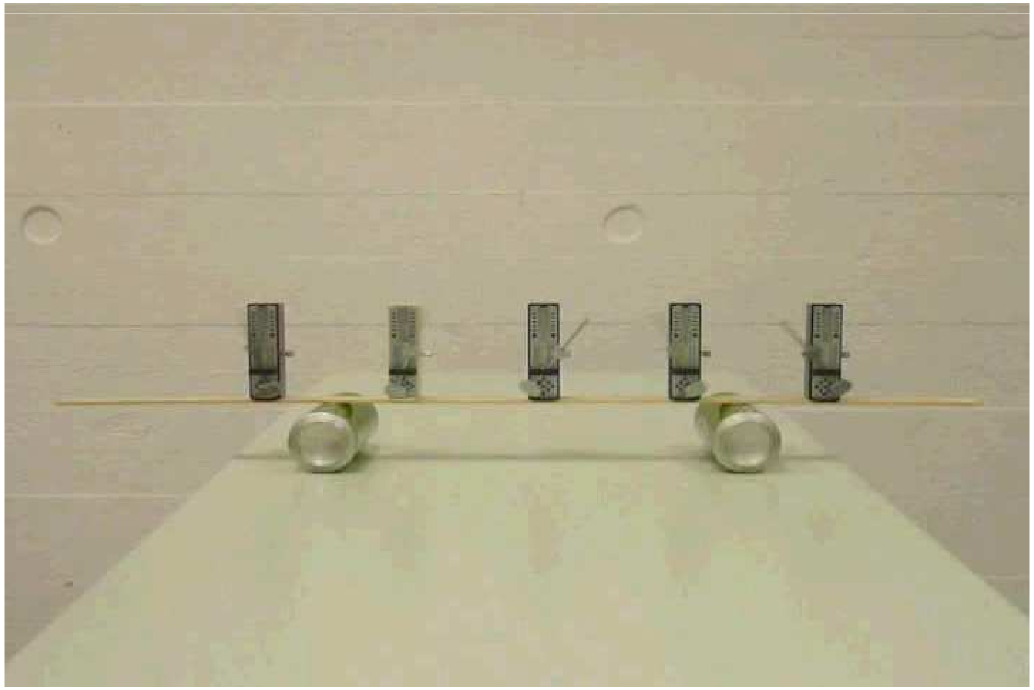
"Synchronization is an adjustment of rhythms of self-sustained oscillators due to their weak interaction."

Pikovsky, Rosenblum, Kurths. Synchronization: a universal concept in nonlinear sciences (Cambridge University Press 2001)

Coupled Metronomes

Start:
different frequencies,
different phases
→ No synchronization

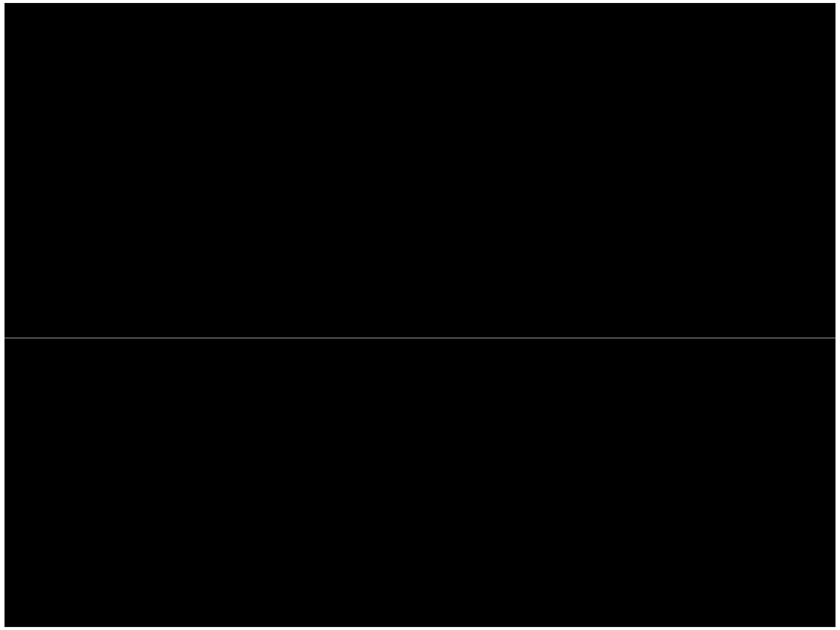
End:
same frequencies, same phase difference ("phase locked")
→ Synchronization



Level 2:
Pair-wise Coupling

Cardio-respiratory Interaction
Phase Synchronization

- **London: Millennium (“Wobbly”) bridge opening day June 10, 2000**

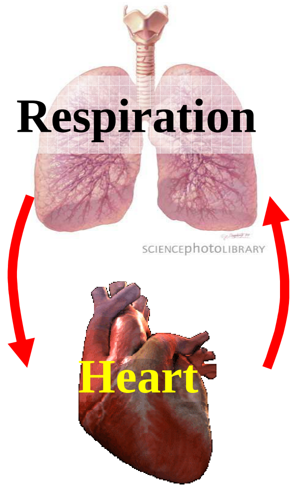


Millenium bridge reopened in February 2002:

- after 5 Million £ spent on bridge modifications
- research based on work by S. Strogatz et al. Nature 438, 43 (2005)

Level 2:
Pair-wise Coupling

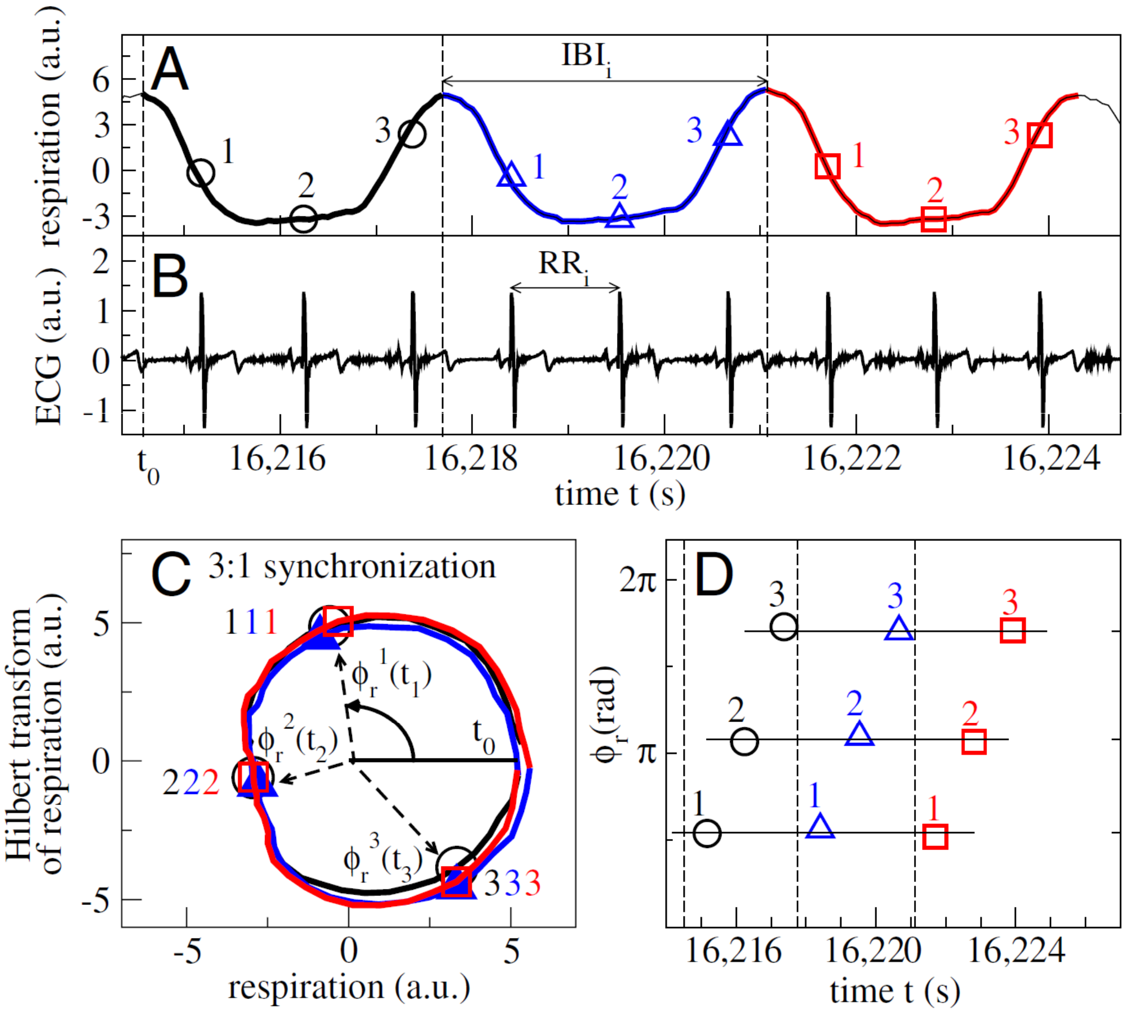
Cardio-respiratory Interaction Phase Synchronization



Phases collapse

⇕

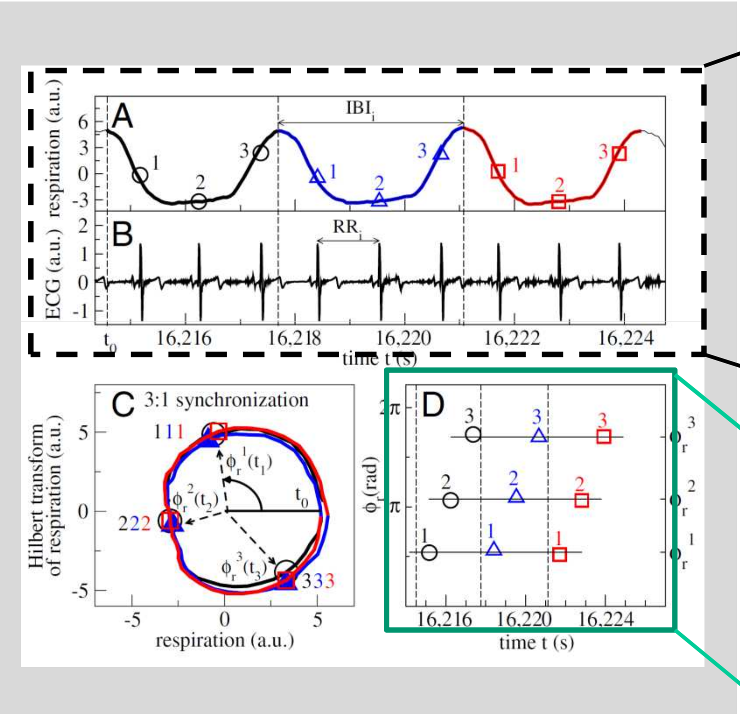
Phase synchronization

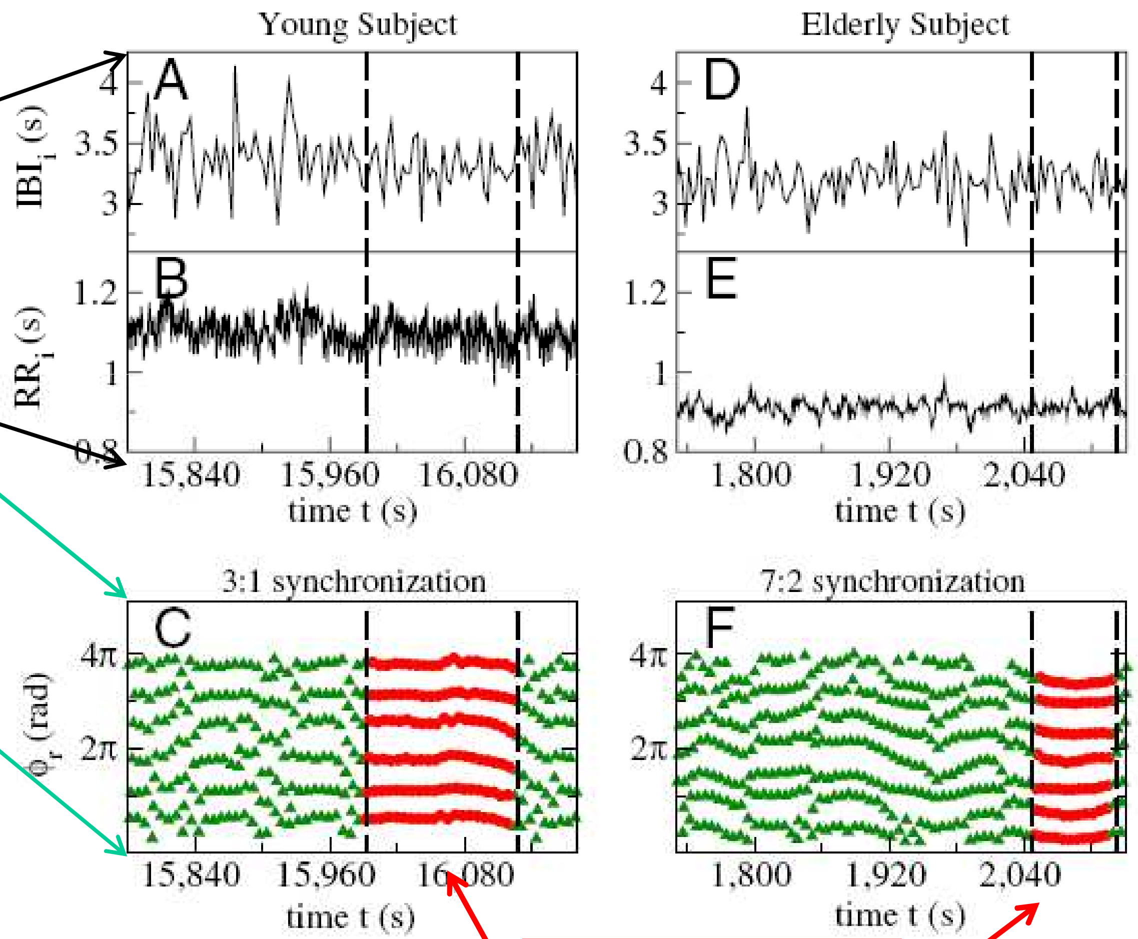


Level 2: Pair-wise Coupling

Cardio-respiratory Interaction

Phase Synchronization despite continuous fluctuations



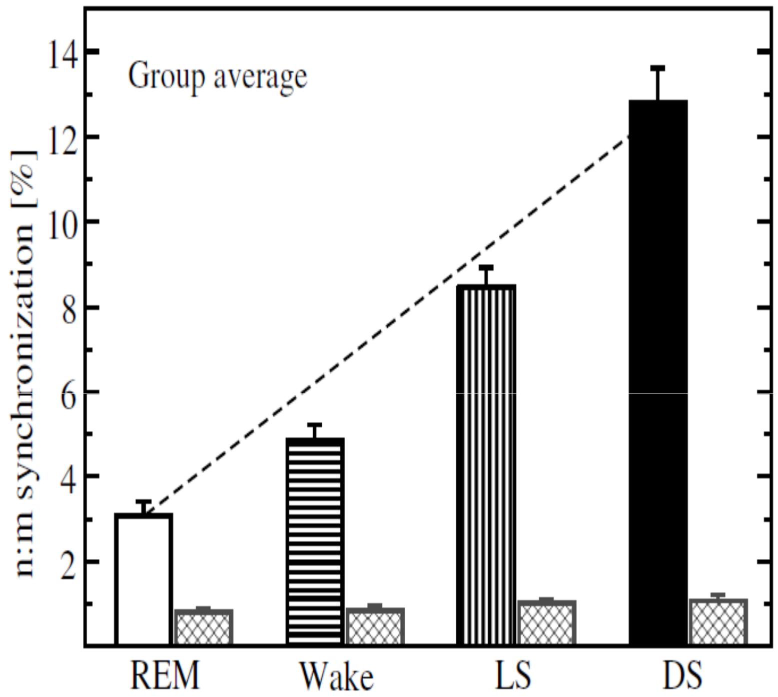


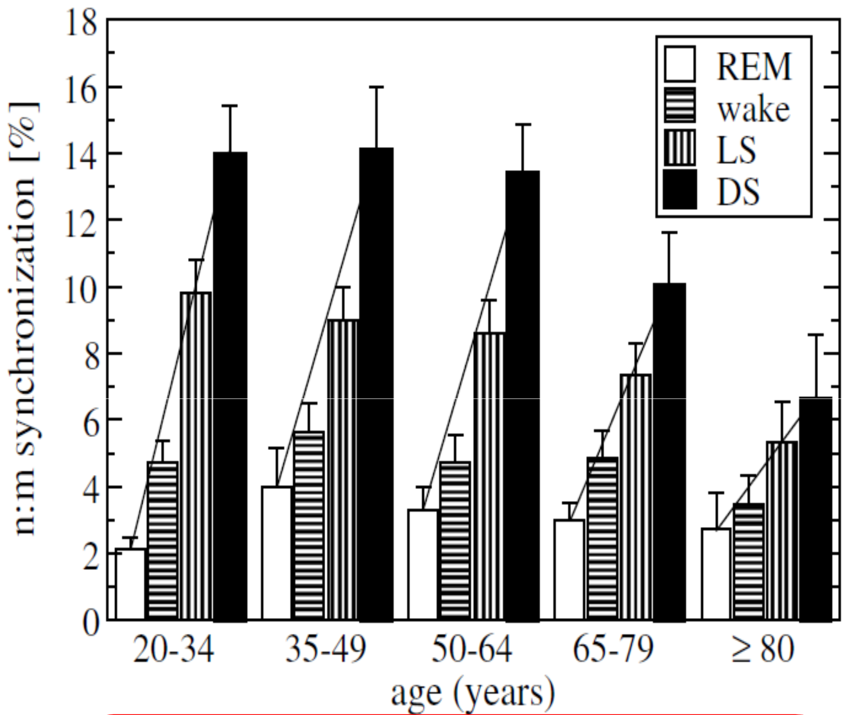
Segments of Synchronization

Level 2:
Pair-wise Coupling

Cardio-respiratory Interaction
Phase Synchronization

Pronounced stratification of synchronization is stable for all age groups





400% increase in synchronization from REM to deep sleep

Discovery:
Phase transitions in cardio-respiratory coupling

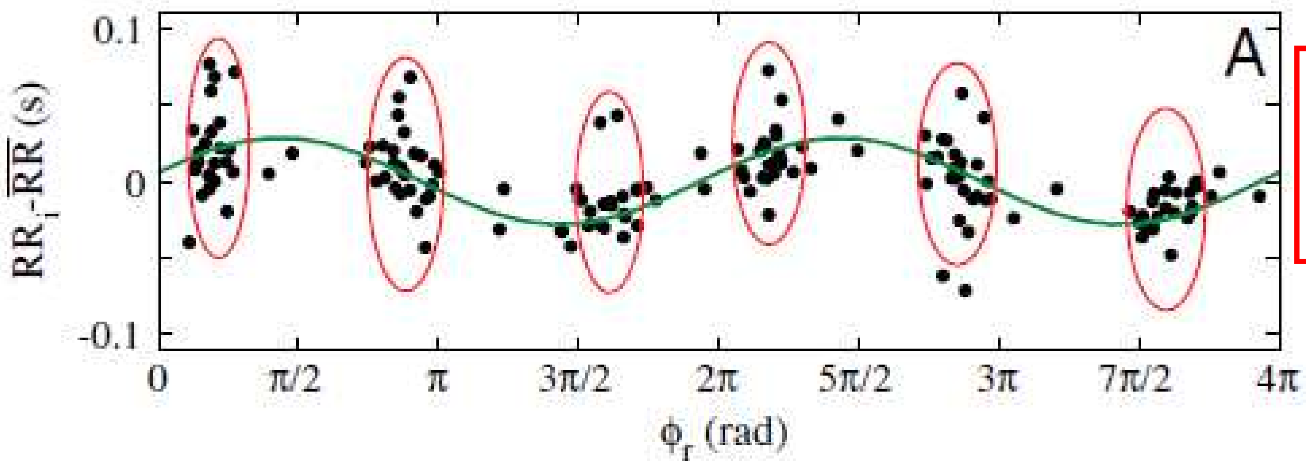
RP Bartsch, AY Schumann, JW Kantelhardt, T Penzel, PCh Ivanov
“Phase transitions in physiologic coupling”, *PNAS* **vol. 109**, p. 10181 (2012)

Level 2:
Pair-wise Coupling

Coexisting forms of physiologic coupling

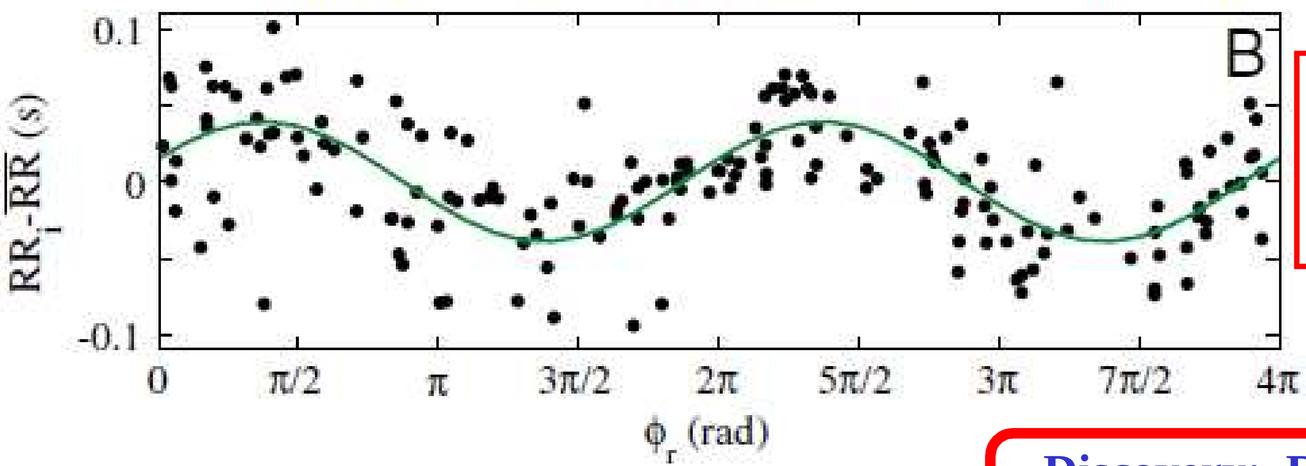
Cardio-Respiratory interaction

Segment with pronounced RSA and phase-synchronization



RSA & Synchronization

Segment with pronounced RSA and no phase-synchronization



RSA w/o Synchronization

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

Track Record

Impact of our prior work and developed technologies

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
- Wavelet-transform Modulus Maxima Analysis (WTMM) – ***PRL*** 98, ***Nature*** 99
- 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:

Impact

Physiology: cardiac, respiration, gait, sleep, brain

Medicine: novel diagnostic measures

Physical Sciences: oil recovery, climate, seismology, astronomy

Economics: stock markets, company growth, commodities …

Challenges in understanding emergent network behaviors

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

Level 3: Networked Interactions

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

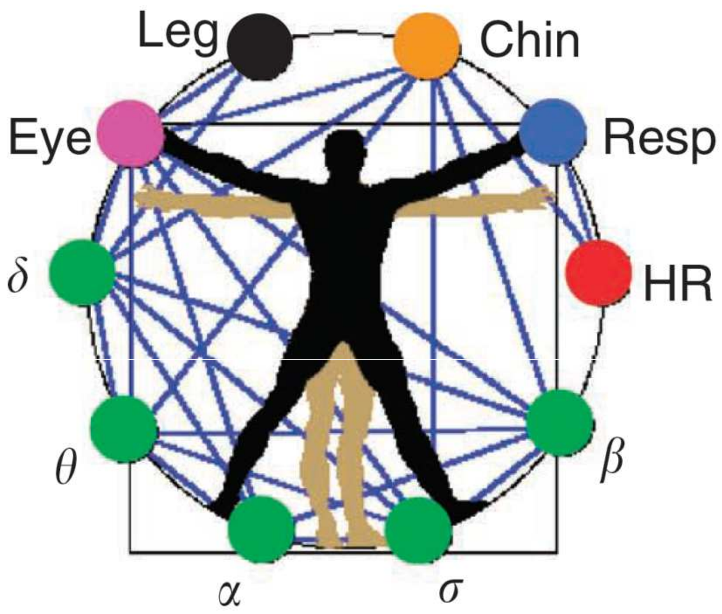
We made *first* inroads:

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

Infer/quantify interactions
among *diverse* dynamical systems

Level 3:
Networked
Interactions

Horizontal Integration of physiological interactions



Physiological interactions

Physiologic recordings

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

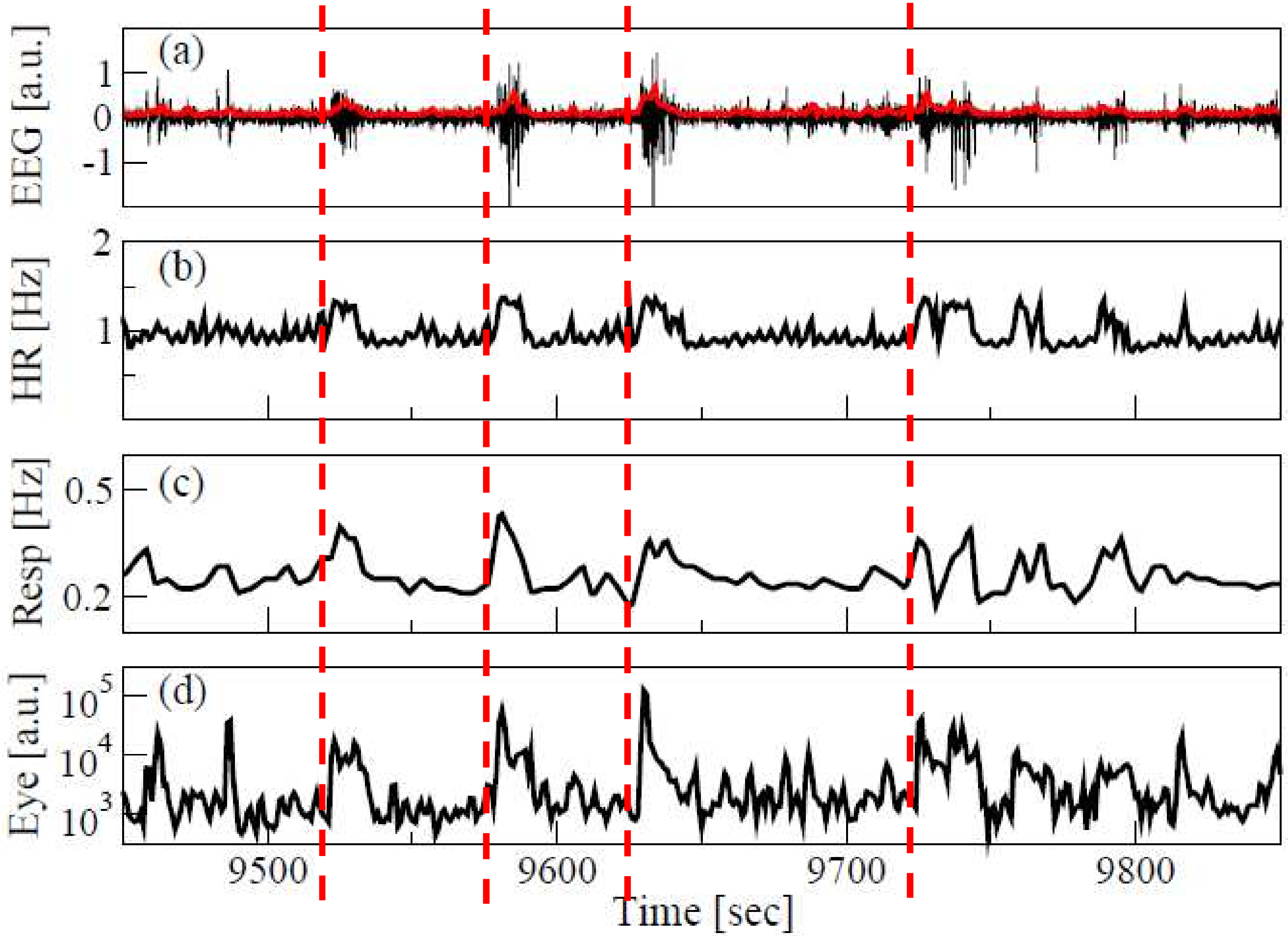
Physiologic states

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

Data-
Driven
Observation

Coordinated activity across diverse systems



EEG-σ band: sleep spindles

Heart rate

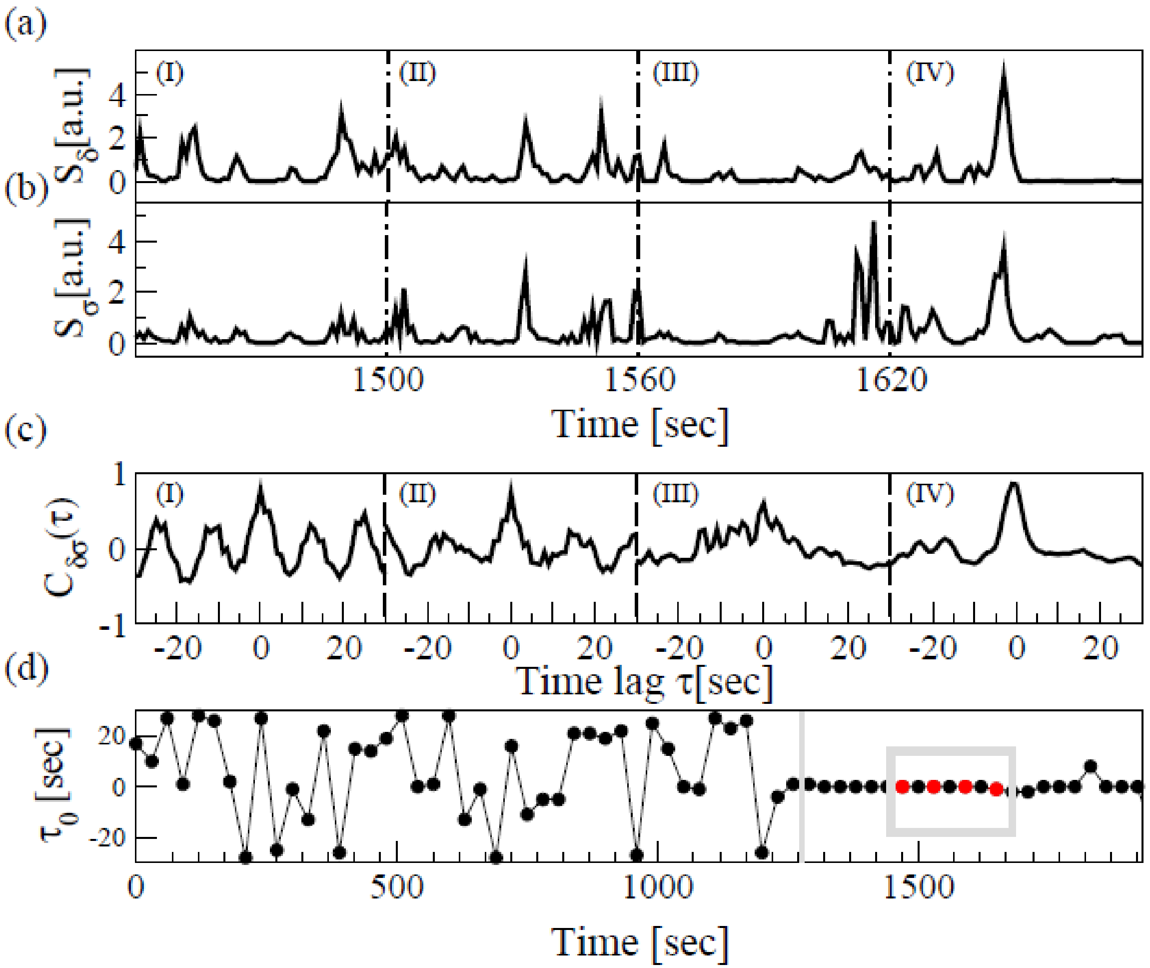
Respiratory rate

Eye movements

→ Bursts in the dynamics of one system are coordinated with bursts in other systems with stable time delay

Data-Driven Concept

Quantifying interactions between diverse systems: concept of Time Delay Stability



normalized spectral power of EEG-δ band

normalized spectral power of EEG-σ band

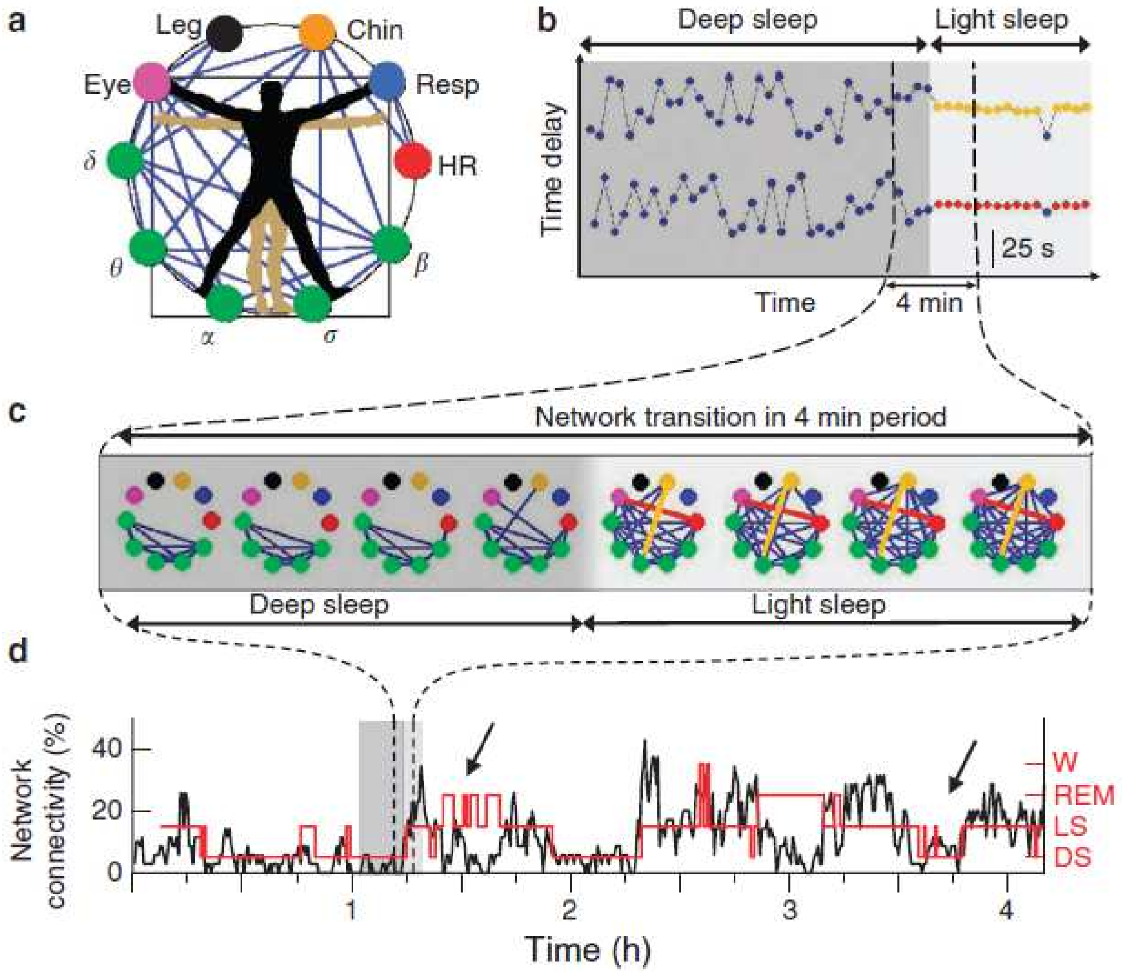
Cross-correlation function vs. time lag in 30 sec windows

Time delay vs. real time

→ Time periods of constant time delay indicate stable interaction represented by network links

Data-Driven Discovery

Transitions in the network of physiological interactions



α – Chin interaction

HR – Eye interaction

α – Chin link

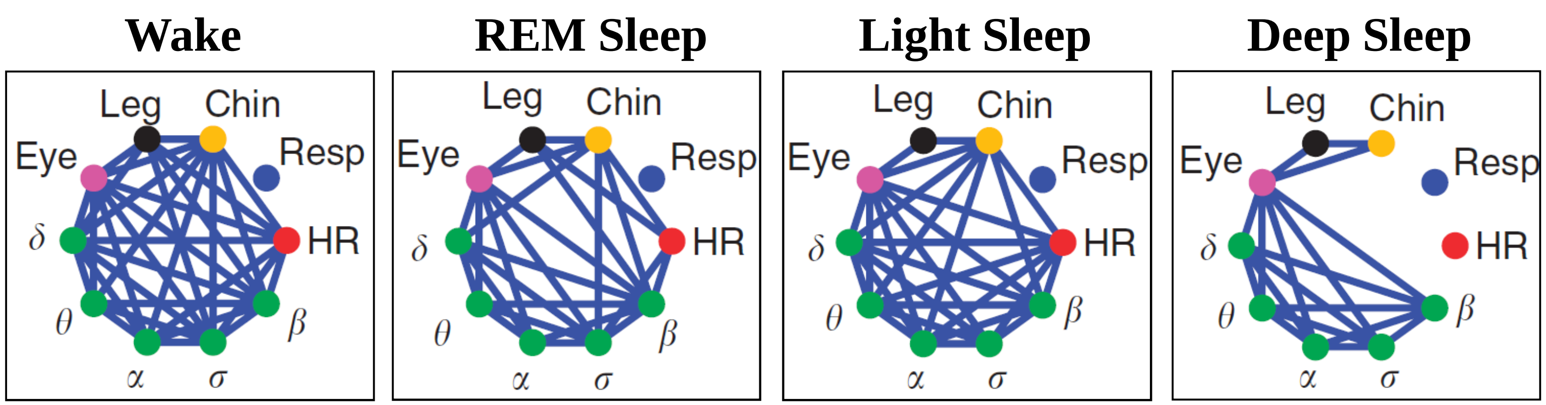
HR – Eye link

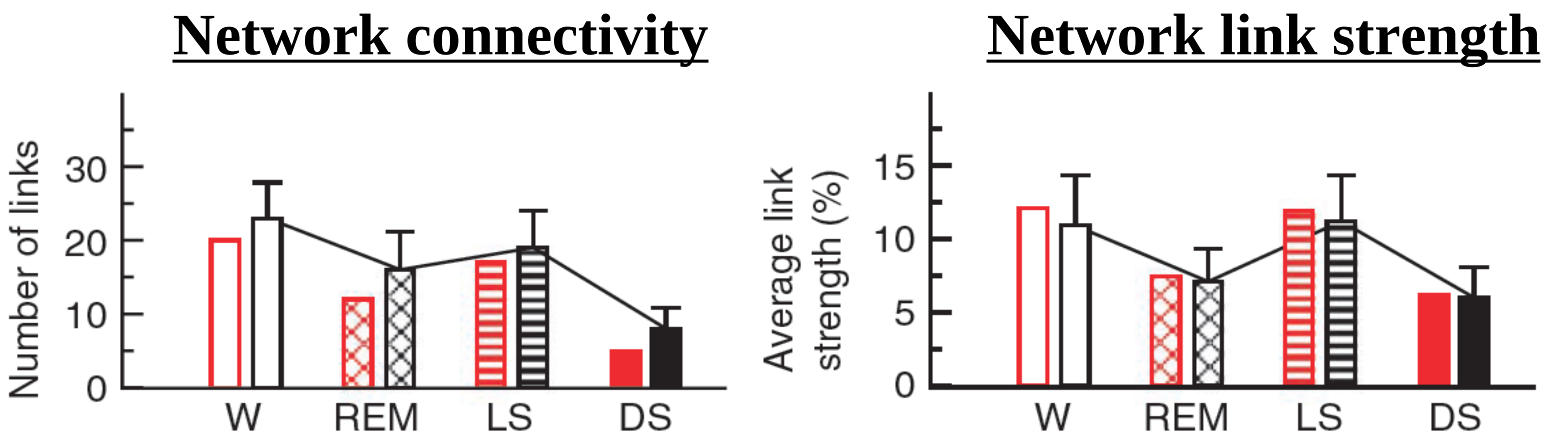
Dynamical Evolution

→ Fast reorganization of network connectivity with transitions across physiologic states

Data-Driven Discovery

Network Topology & Physiologic Function connectivity across sleep stages

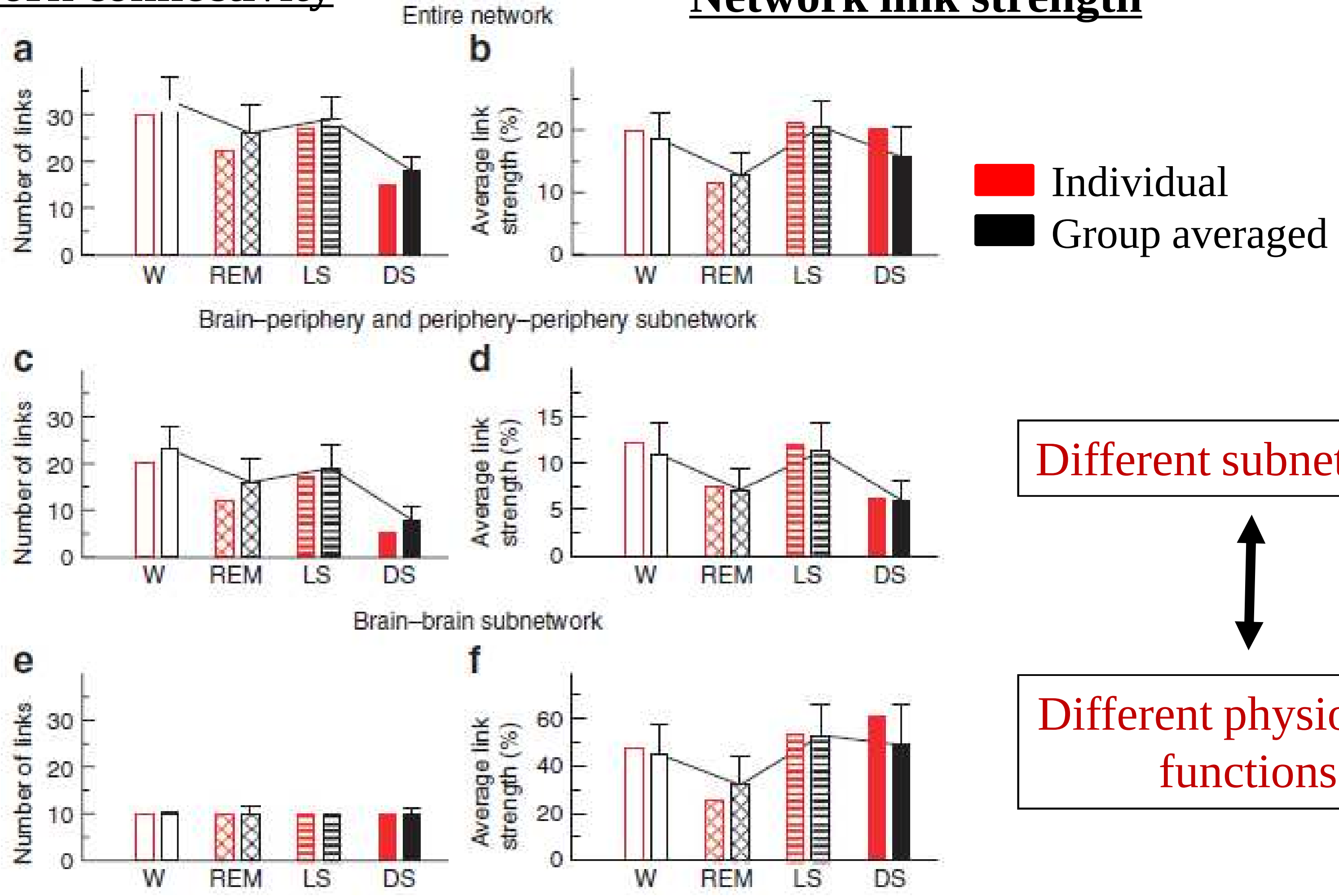




→ Network topology changes with physiologic states

Network of networks across sleep stages

Network connectivity | **Network link strength**

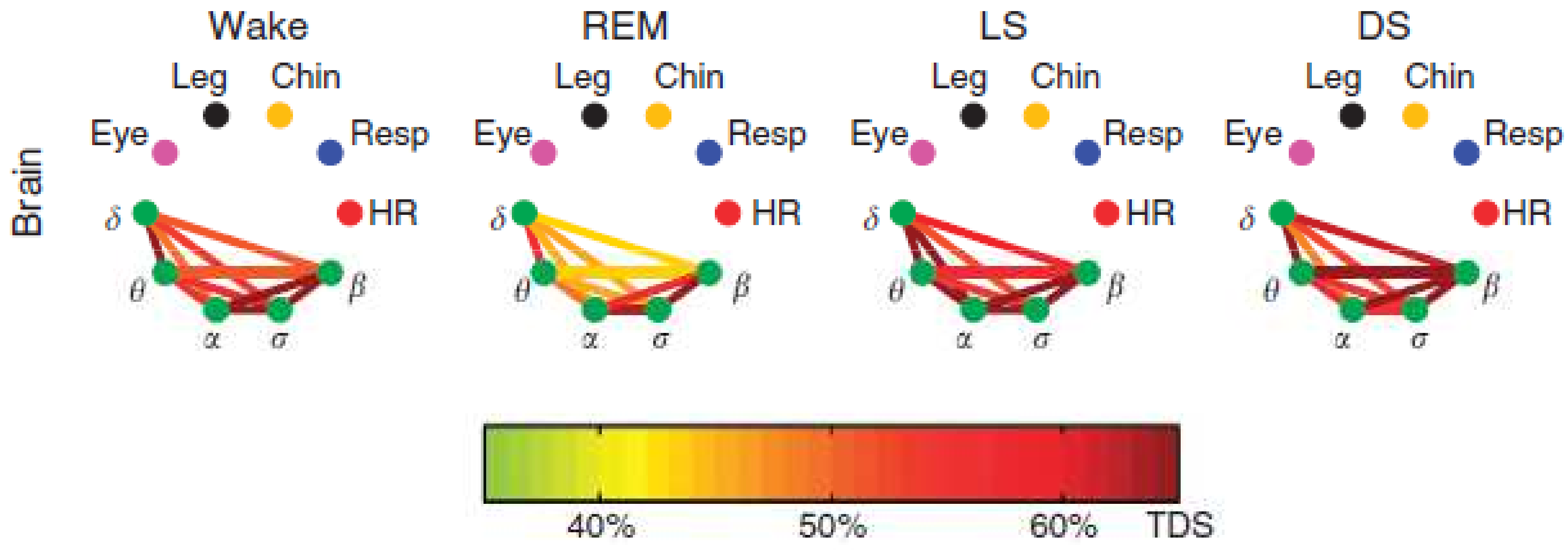


Different subnetworks

Different physiologic functions

→ Robust sleep-stage stratification pattern

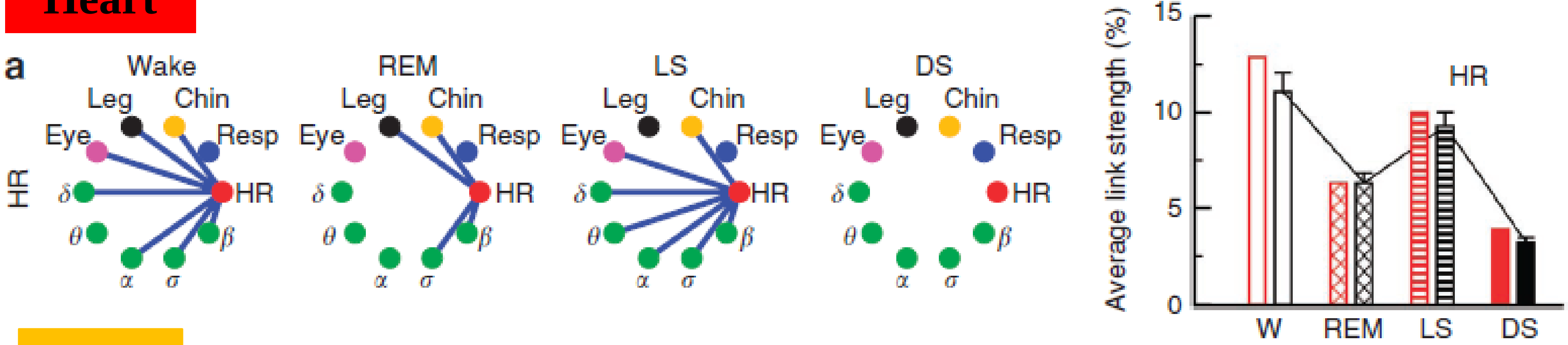
Network connectivity and link strength of the brain–brain sub-network for different sleep stages



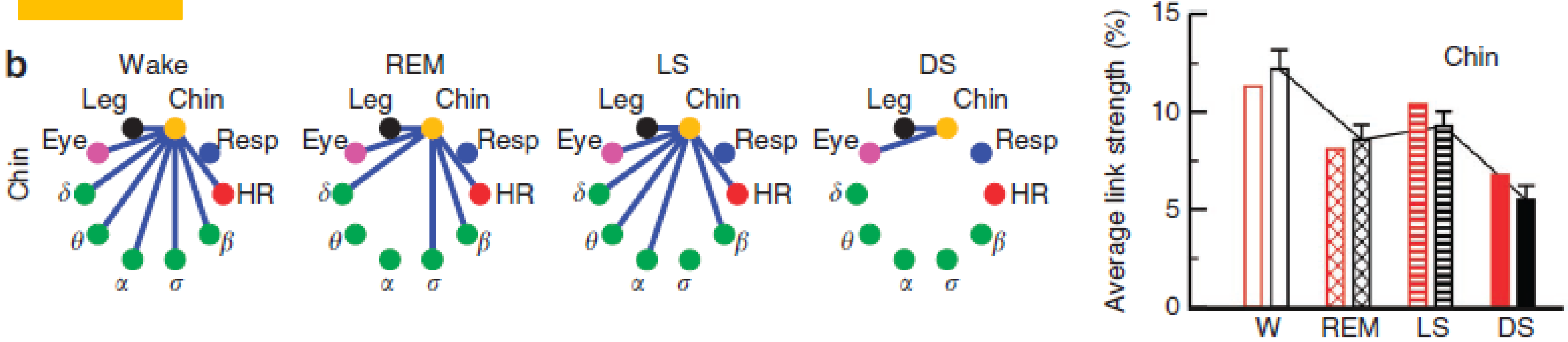
Topology of brain-brain sub-network → no change
Strength of network links → significant change

Transitions in connectivity and link strength of individual network nodes across sleep stages

Heart



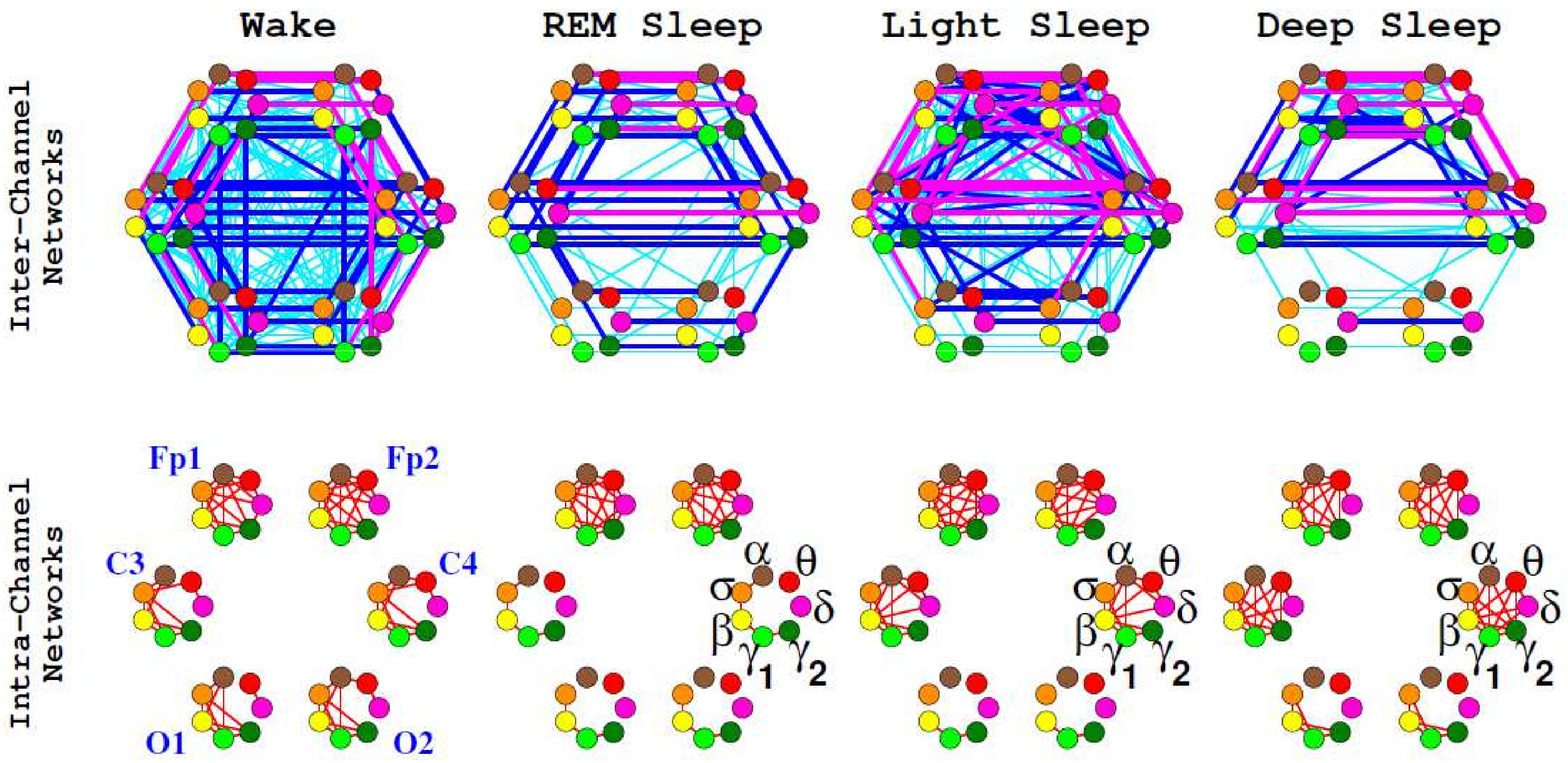
Chin



Robust sleep-stage stratification pattern in:

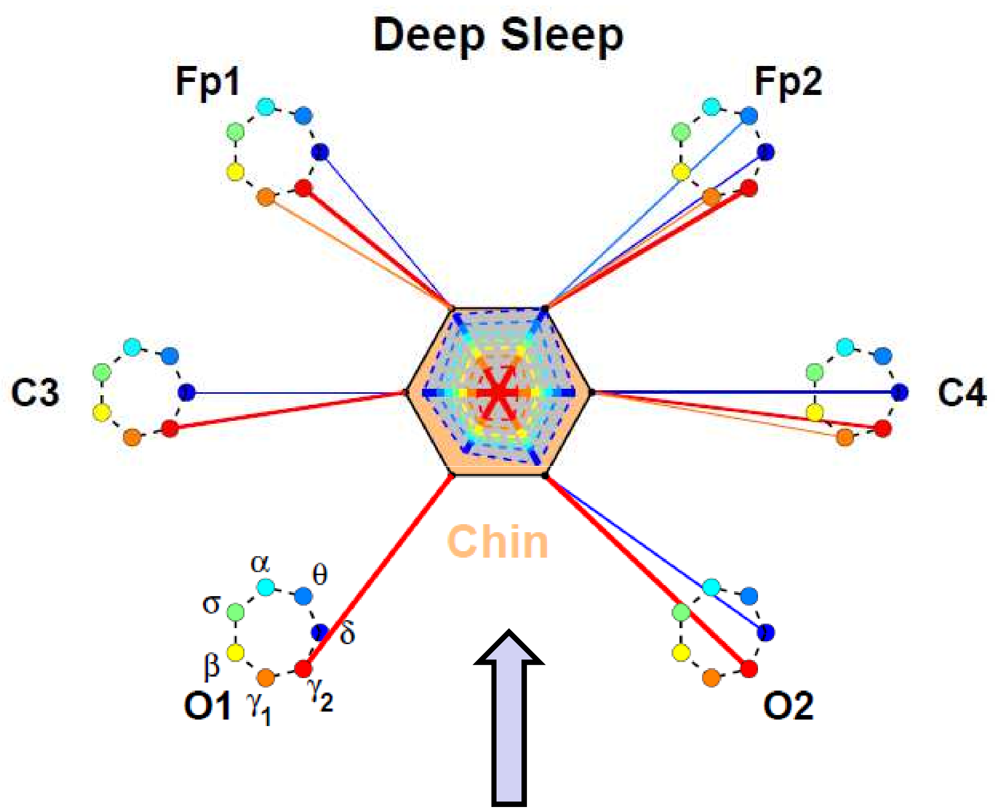
a) Individual node connectivity
b) Average link strength of individual nodes

Network Physiology
Networks of brain activity across sleep stages



Phase transition in link strength and network topology

Maps of physiologic interactions



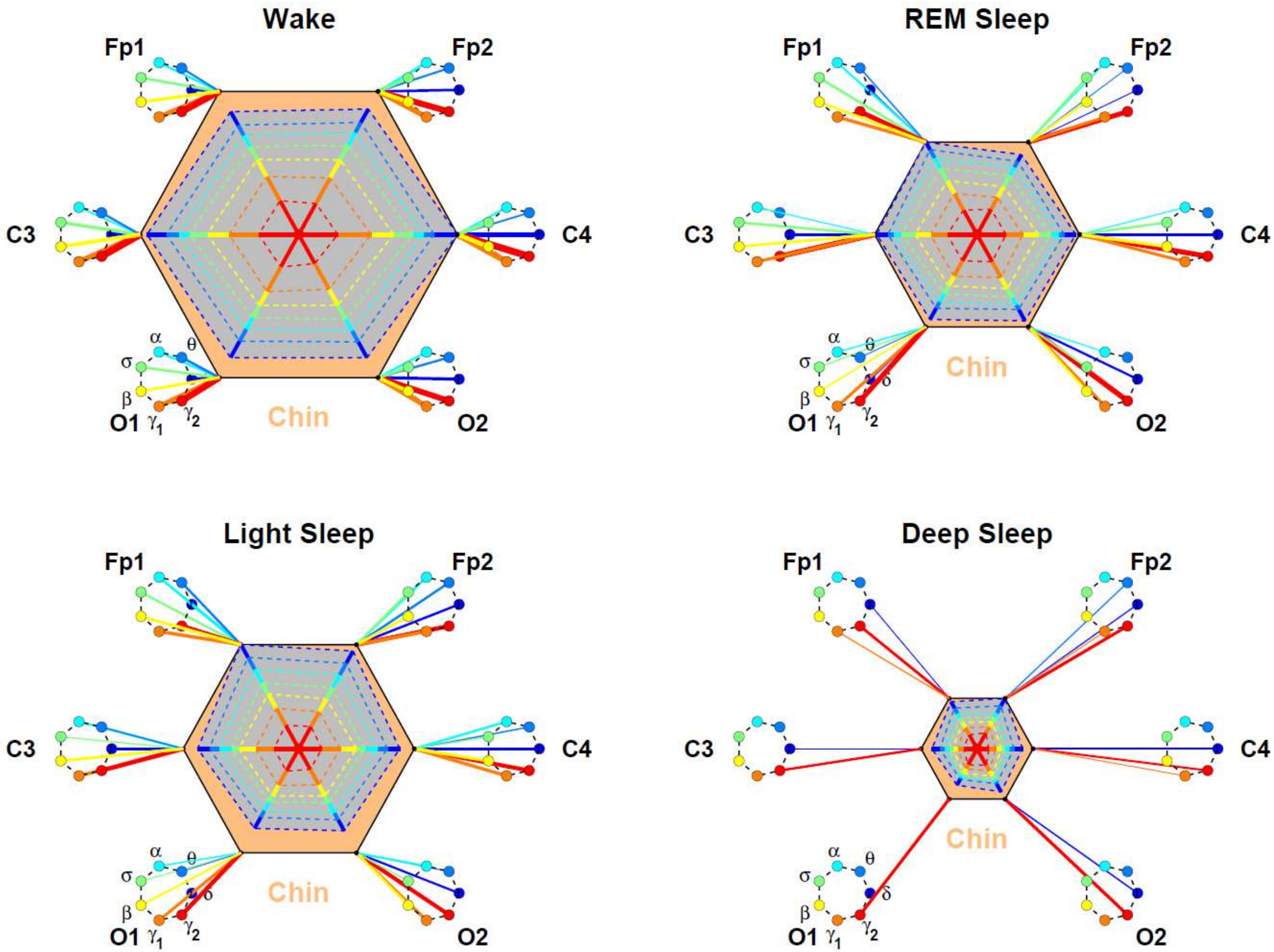
Location of the nodes:
Brain EEG Channels

Colors:
Frequency bands in the EEG signals

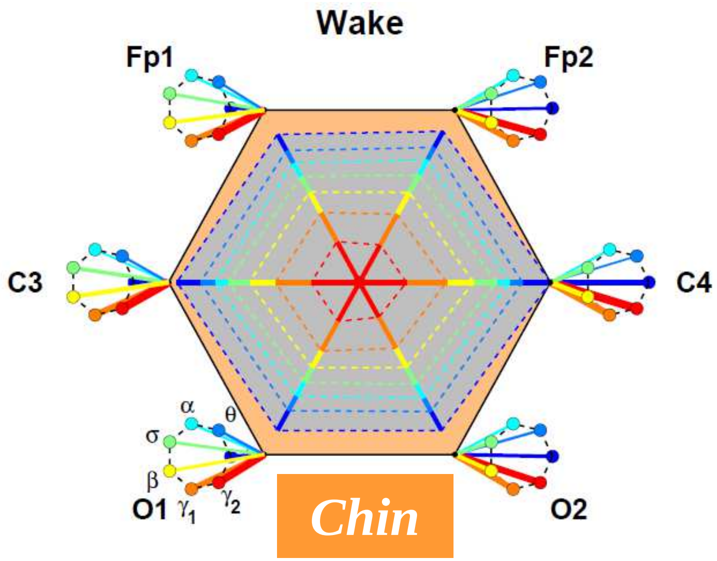
Width of the links:
Coupling strength between the systems

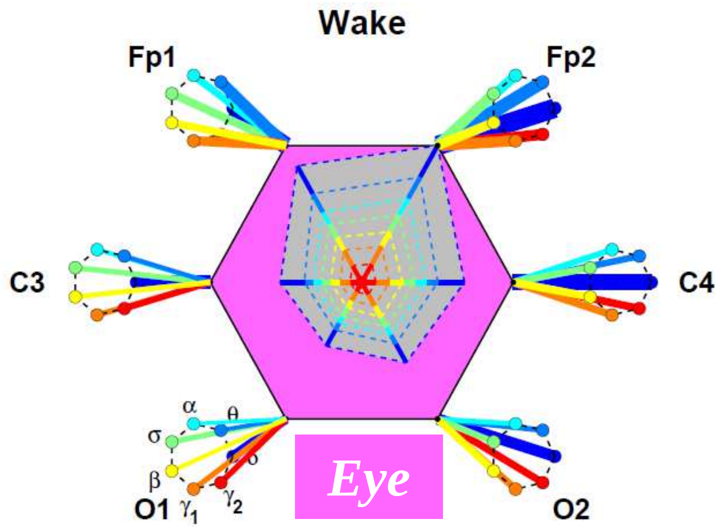
Radar Chart in the Hexagon:
Brain Control on the target organ

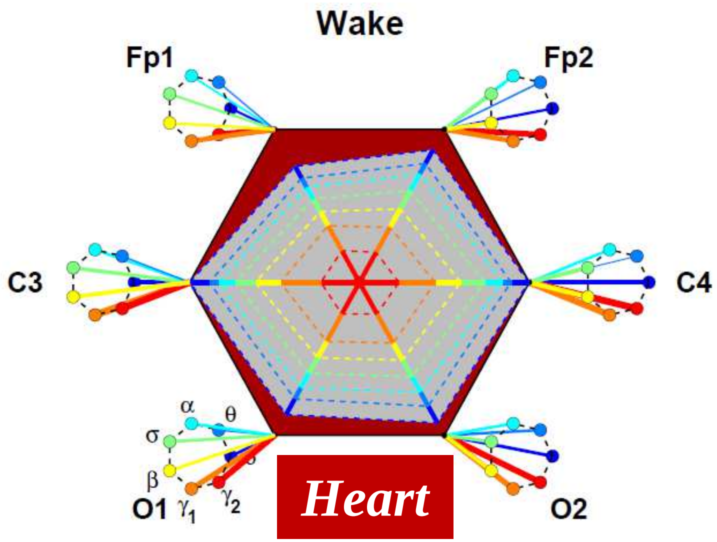
Visualization: different physiologic states

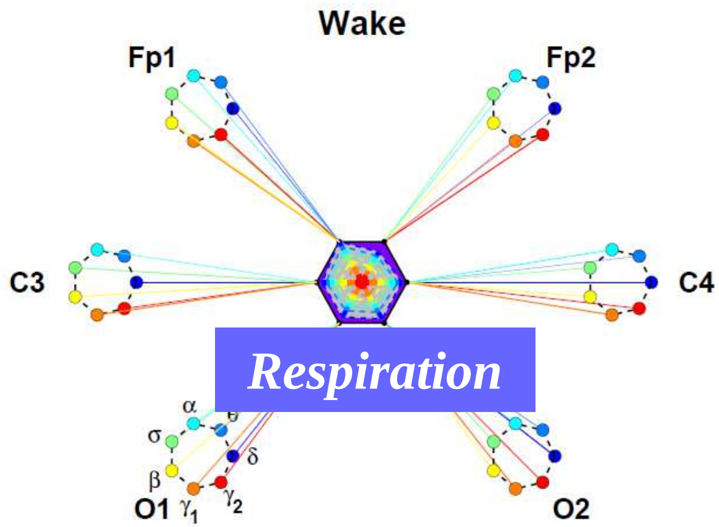


Maps for different organ systems

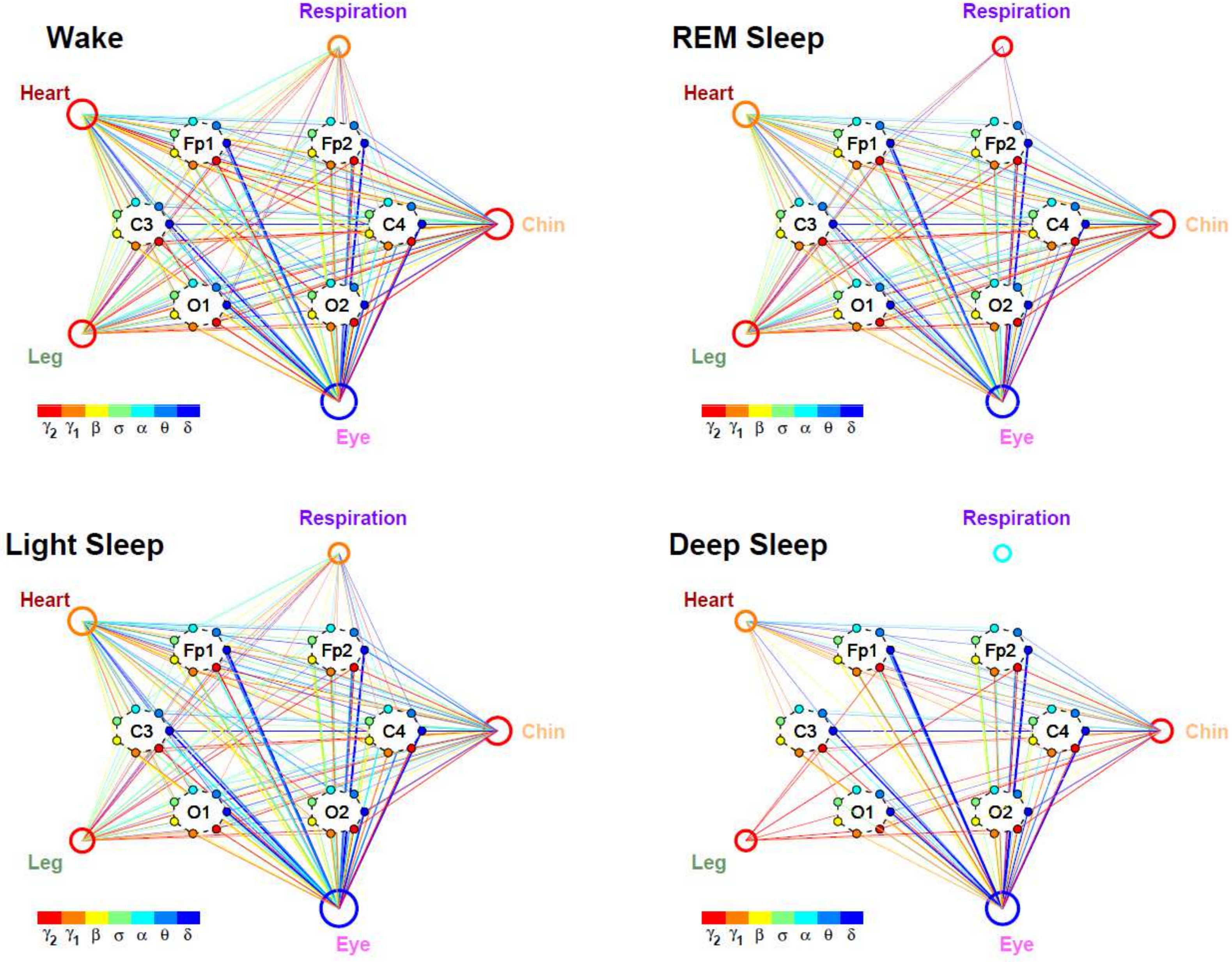




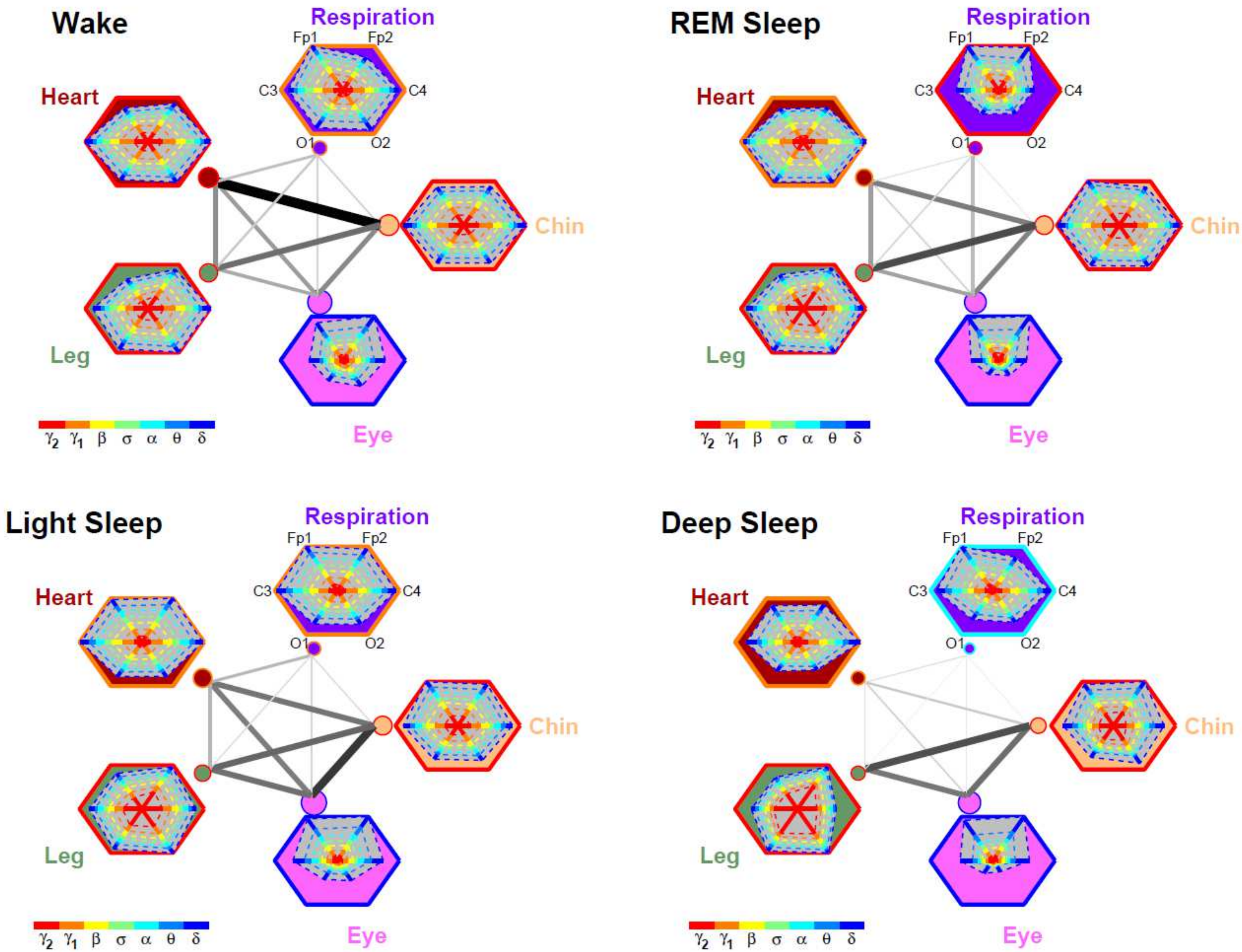




Network Physiology: Networks of brain activity and other physiologic systems across sleep stages



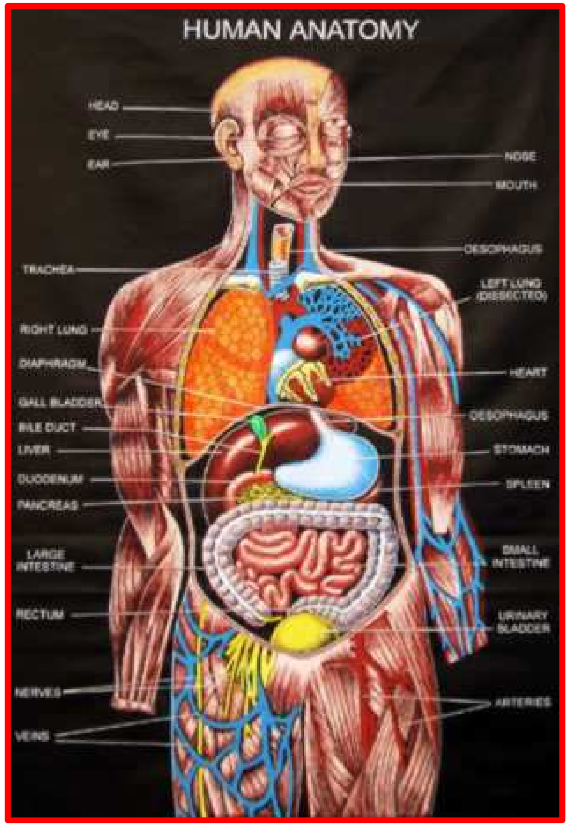
Network Physiology: Networks of brain activity and other physiologic systems across sleep stages



Vision

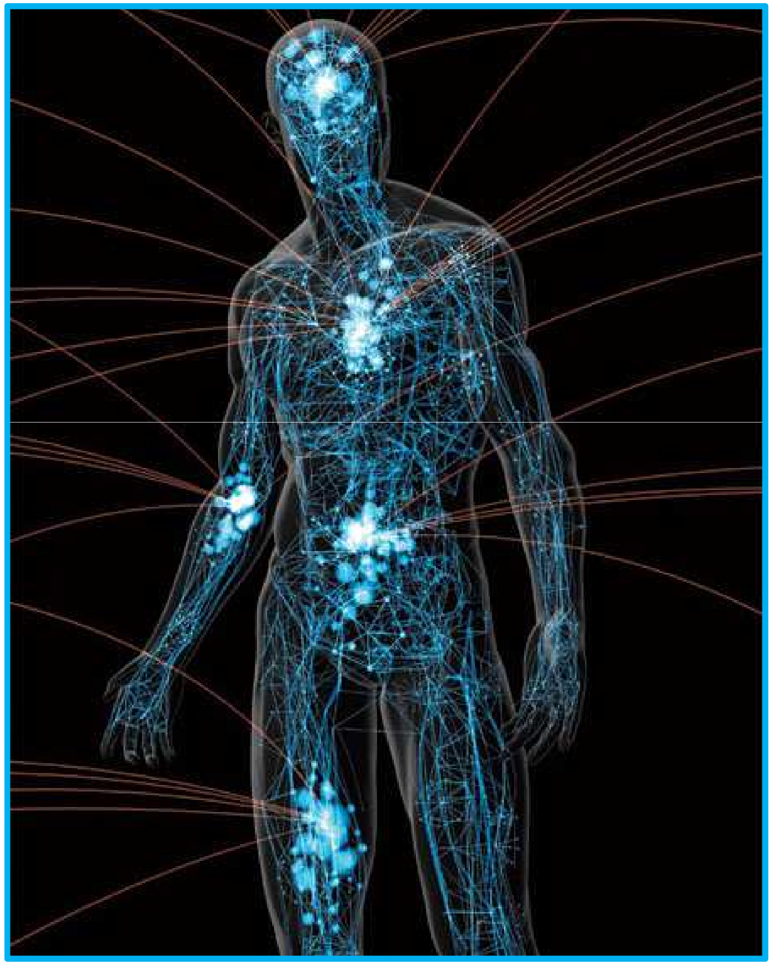
Physiology and Medicine

Atlas of Human Anatomy



need →

Atlas of Dynamic Interactions of Organ Systems



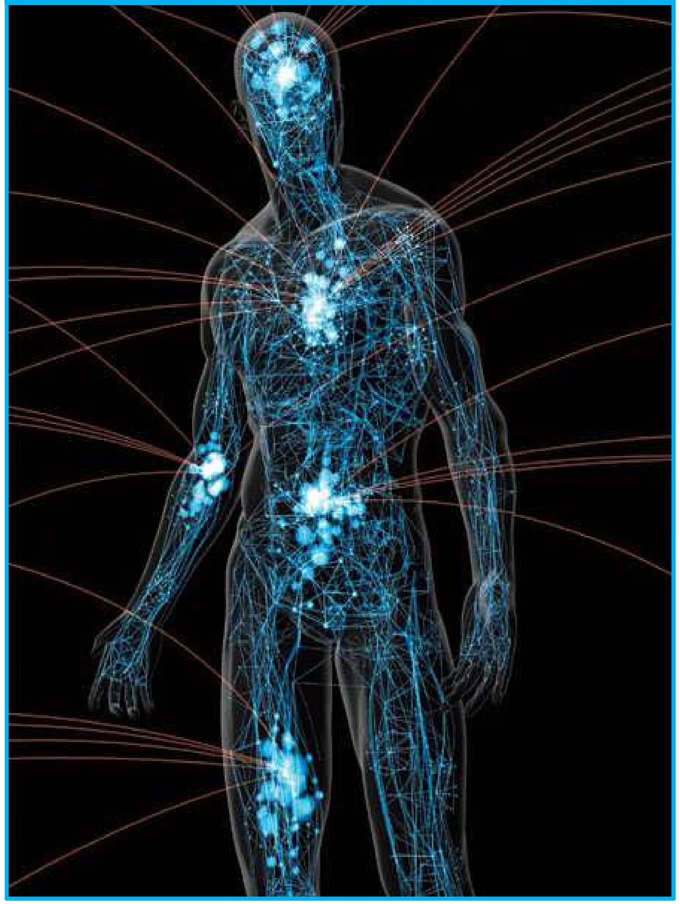
→ Revolutionize our knowledge and understanding of the fundamental mechanisms that regulate and coordinate organ-to-organ interactions

Vision

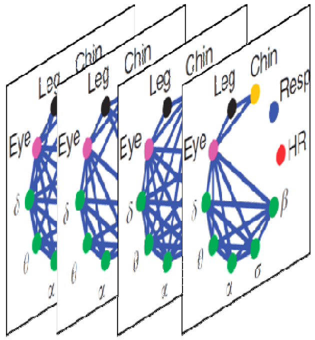
Physiology and Medicine

Such Atlas would contain:

Atlas of Dynamic Interactions of Organ Systems

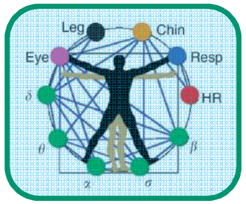


Catalog of reference maps representing dynamical organ interactions under:

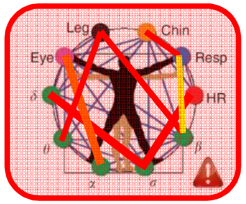


- **healthy conditions**
- **age groups**
- **different physiologic states (rest/exercise, sleep/wake, sleep stages, circadian phases)**
- **pathological conditions (multiple organ failure, coma, heart failure, sleep apnea …)**

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**

Vision & Impact

Physiology and Medicine

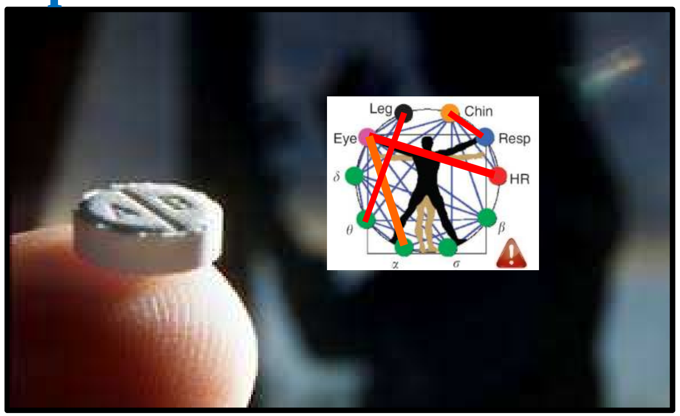
Novel biomarkers

New kind of Physicians

Personalized health monitoring

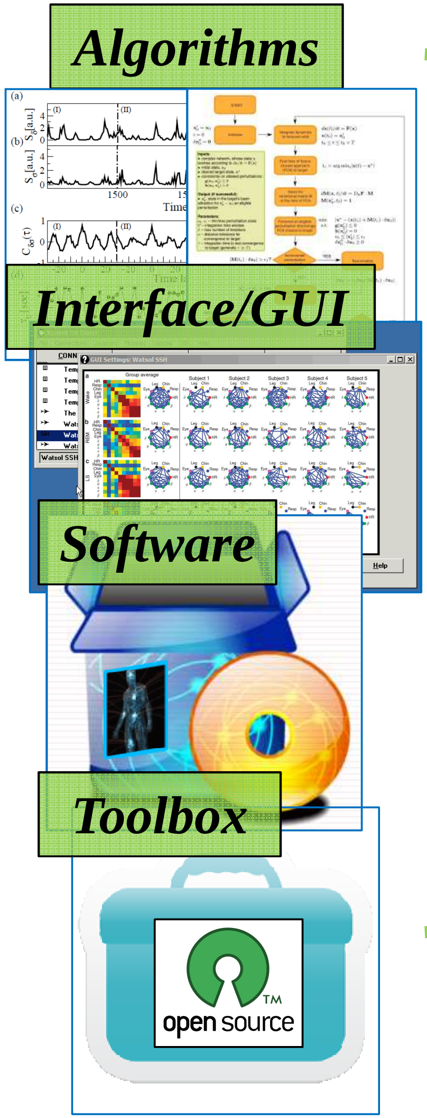
Next generation ICU monitoring devices and alert system

Comprehensive assessment of drugs

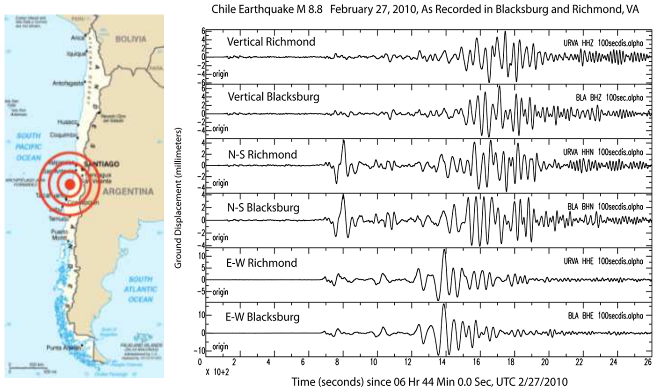


Impact

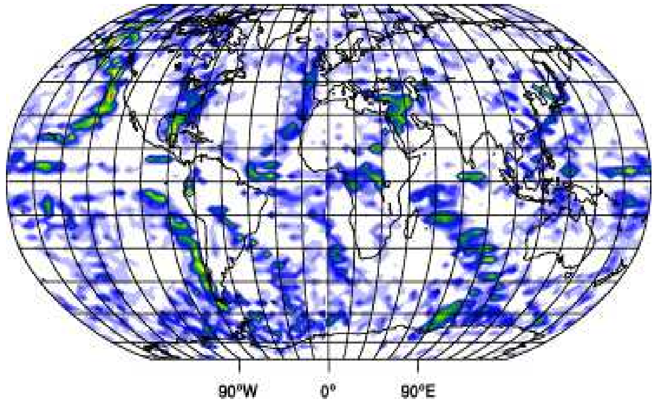
Application of the proposed novel methods and theoretical framework to other fields



Geosciences

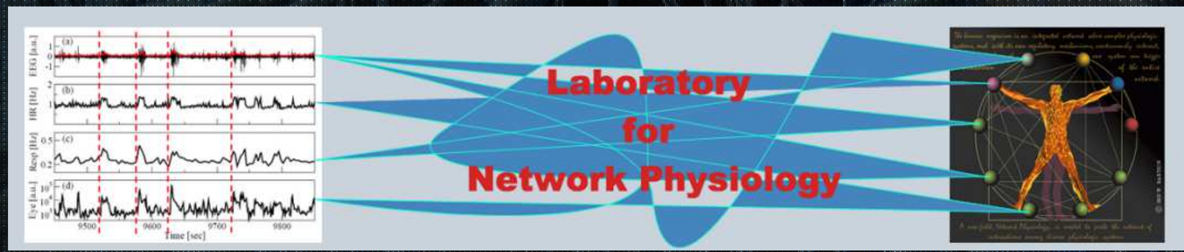


Climate



Economics/Finance

Plant Science



Our Group:

http://physics.bu.edu/labnetworkphysiology

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