

Network Physiology: Mapping interactions between complex physiological systems

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and

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Brigham and Women's Hospital & Harvard Medical School

**BOSTON
UNIVERSITY**



**HARVARD
MEDICAL SCHOOL**



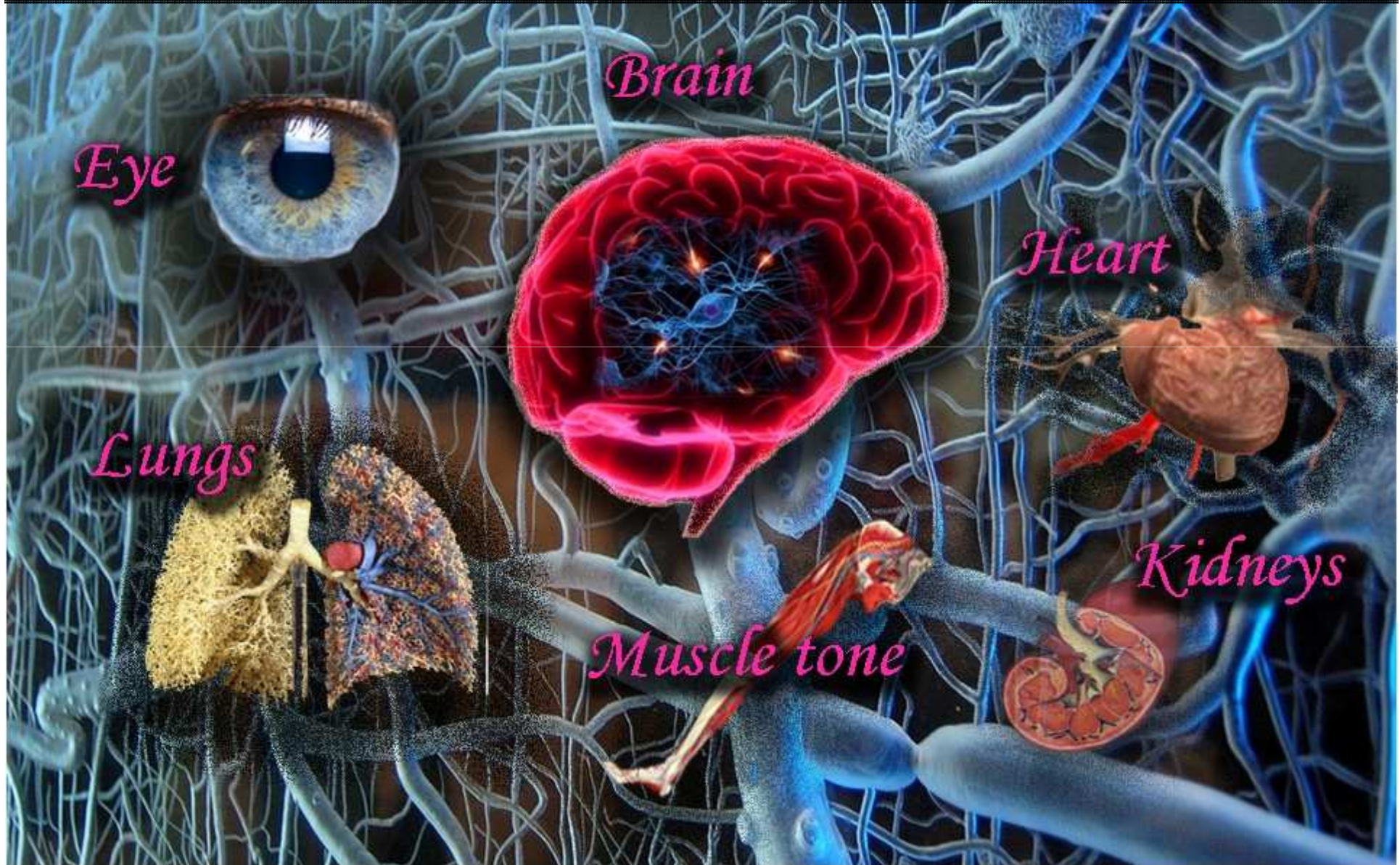
**UNIVERSIDAD
DE MÁLAGA**

Departamento de Física Aplicada II

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04 April 2016

Human Organism comprises diverse multi-component physiological systems



Human Organism comprises diverse multi-component physiological systems

Eye



Brain



Neurologists

Heart



Cardiologists

Lungs



Pulmonologists

Muscle tone



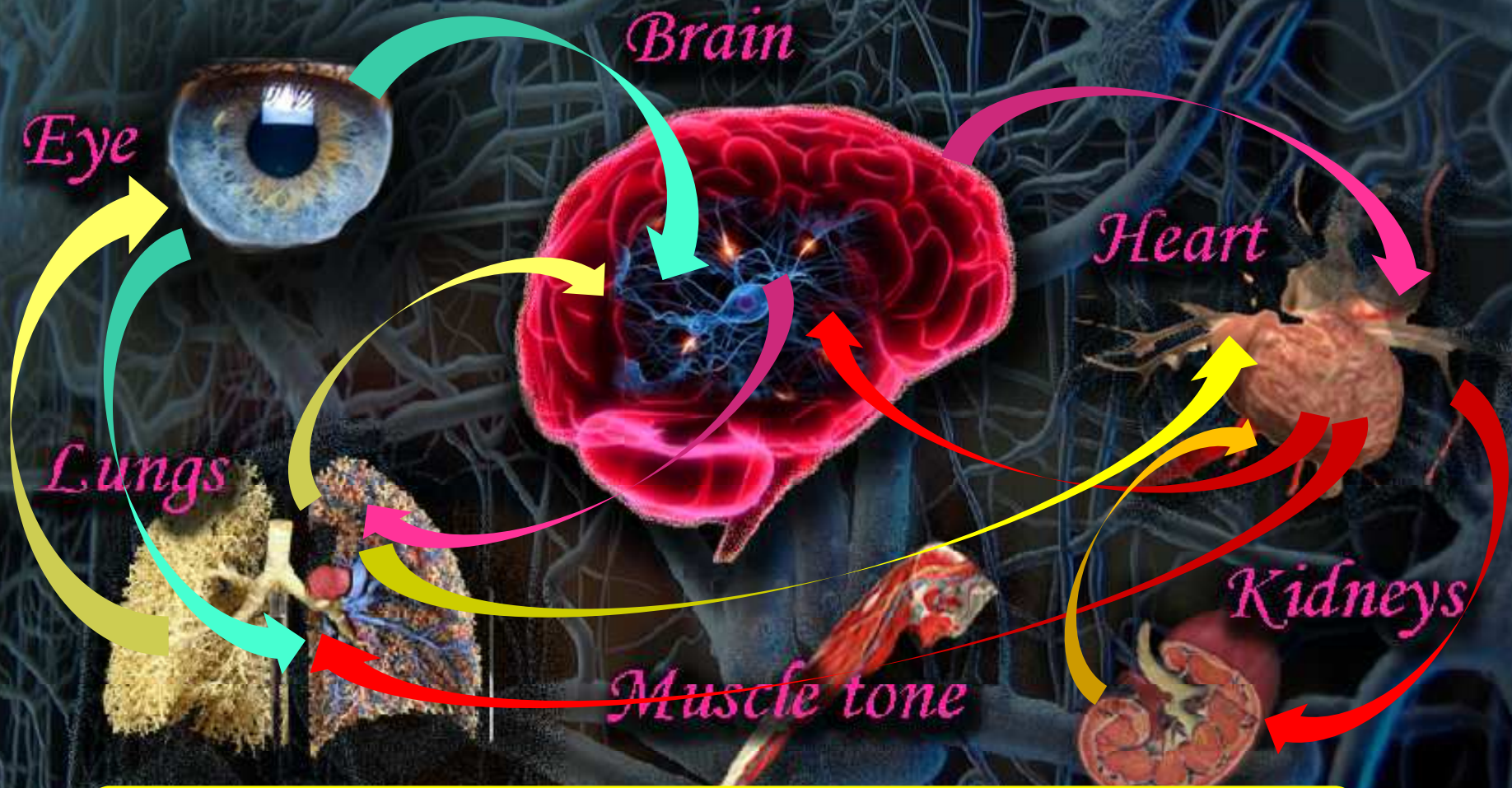
Kidneys



Medical specialists traditionally focus on single organ systems

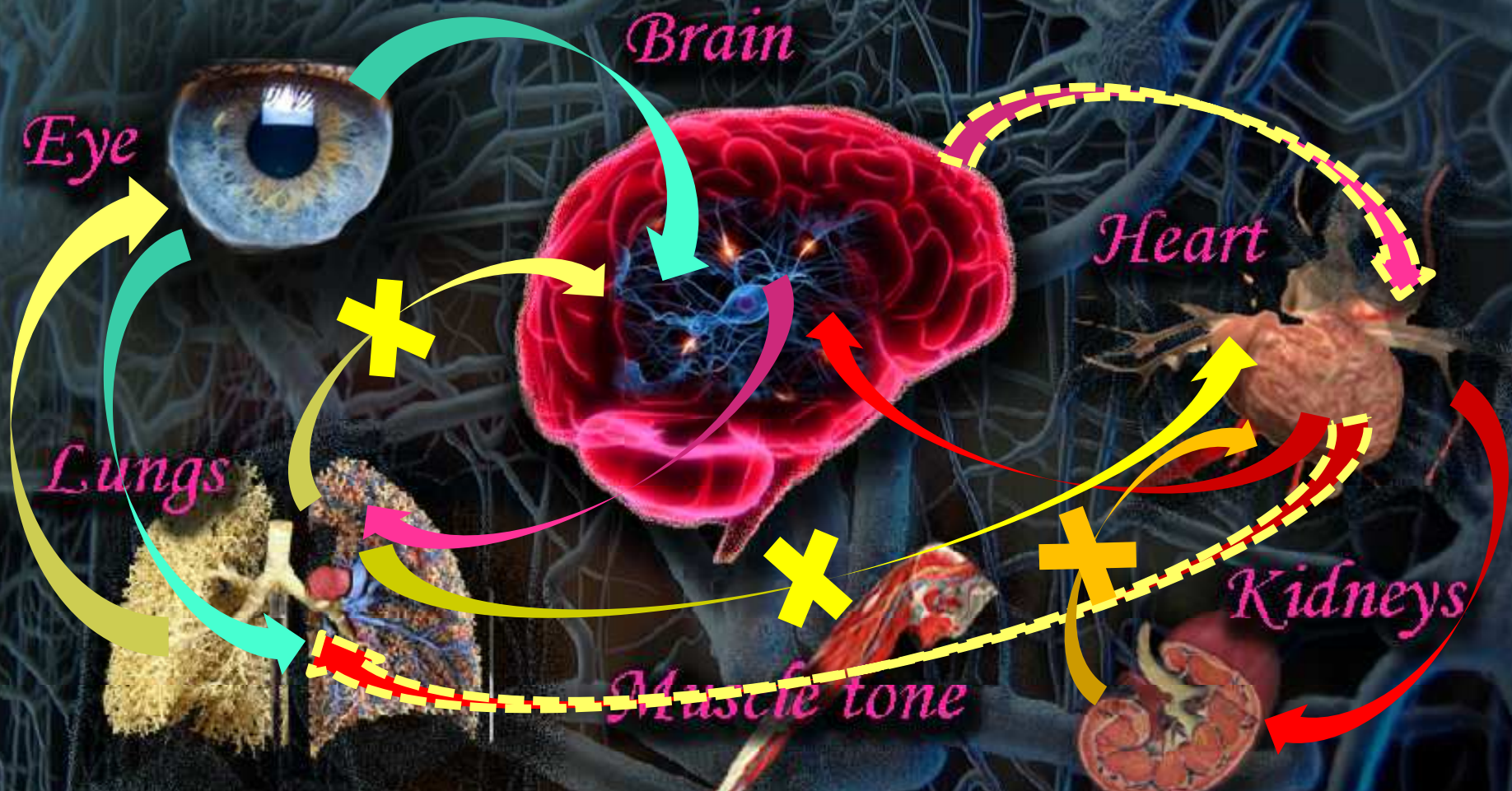
Human Organism – Integrated Network

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

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



Even structurally intact and functioning individual systems
→ **Not** sufficient for Health !



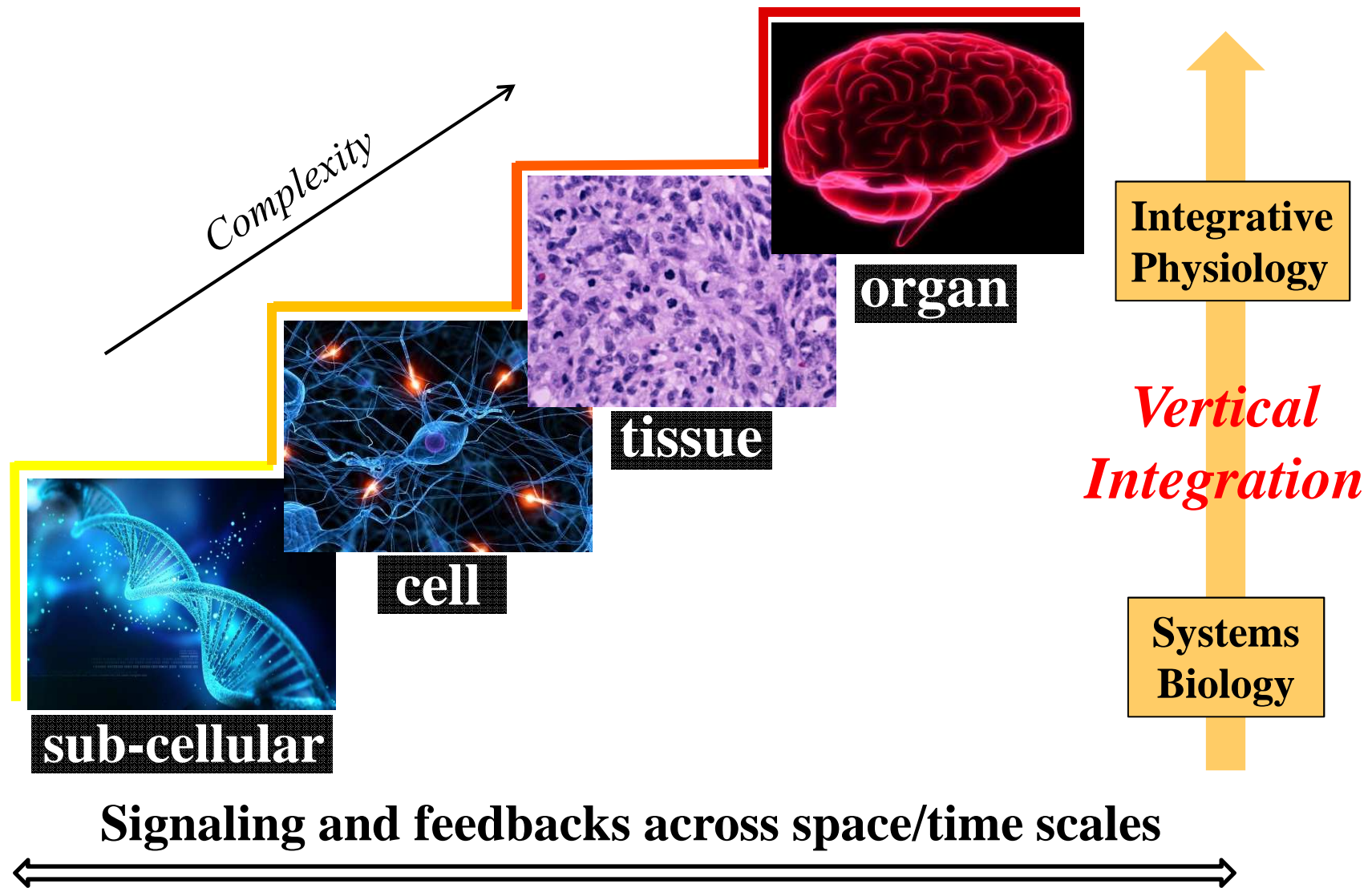
Broad *clinical implications*: Coma, Multiple Organ Failure

Yet, despite the importance to:

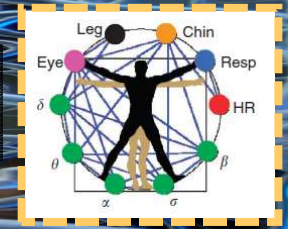
- understanding basic physiologic functions
- clinical relevance

• **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



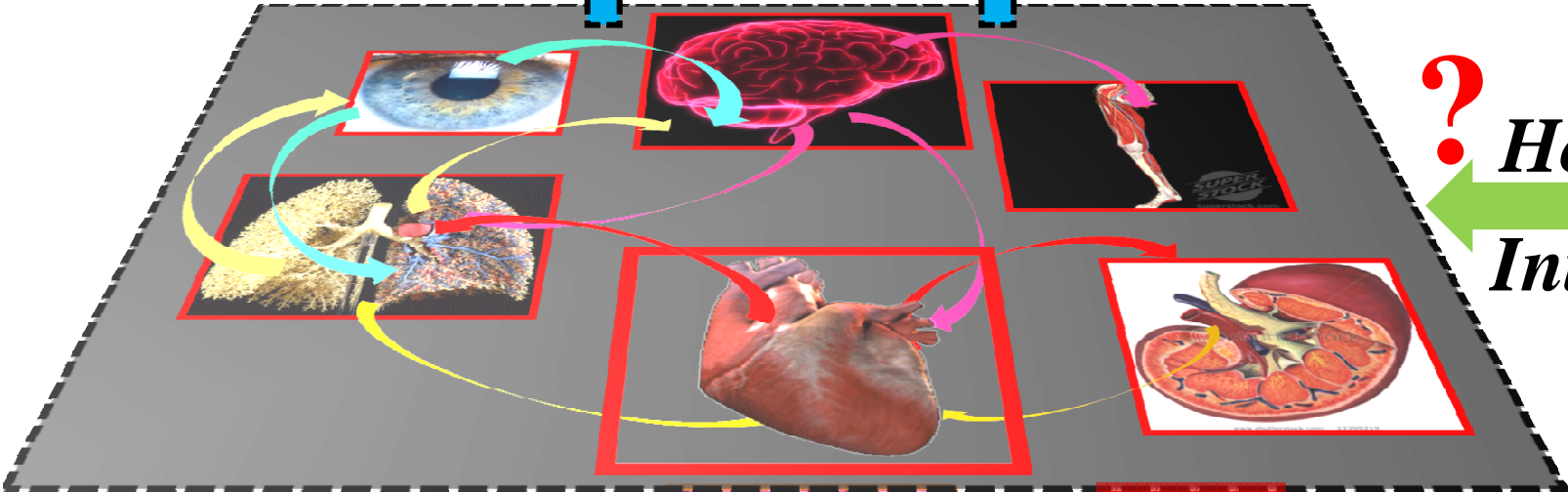
Our Research Focus: Horizontal Integration



Epidemiology / Population Health

Macroscopic

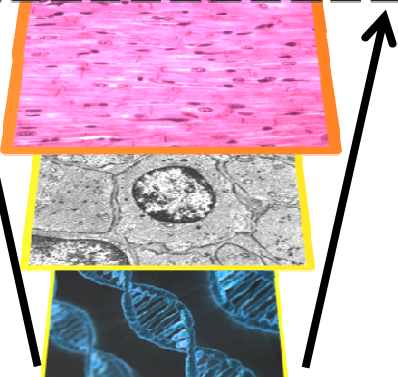
? *Horizontal Integration*



Integrative Physiology

Systems Biology

Vertical Integration



organs

tissue

cell

sub-cellular

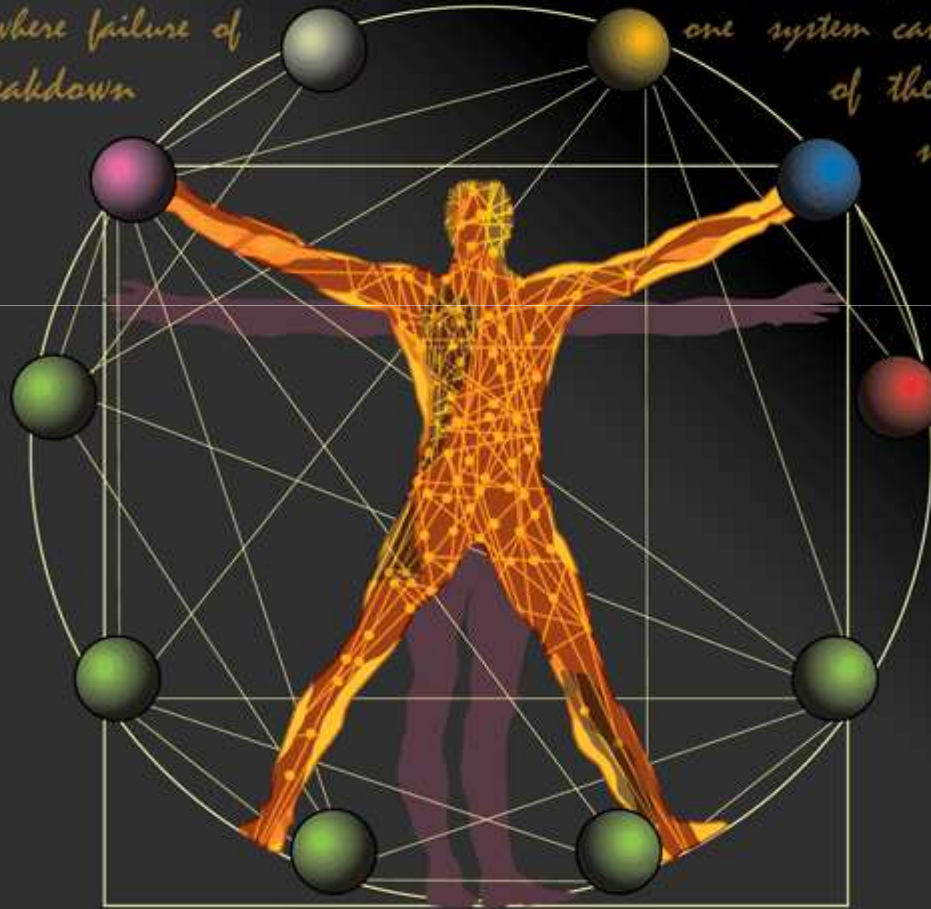
Mesosopic

Microscopic

Our Research Program

New Research Direction: Shifting the focus from single organ systems to the network of organ interactions

The human organism is an integrated network where complex physiologic systems, each with its own regulatory mechanisms, continuously interact, and where failure of one system can trigger a breakdown of the entire network.



A new field, Network Physiology, is needed to probe the network of interactions among diverse physiologic systems.

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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



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.

The human organism is an integrated network where complex physiological systems, each with its own regulatory mechanisms, continuously interact and whose failure is a breakdown of the critical network.

A new field, Network Physiology, is needed to guide the network of interactions among diverse physiological systems.

Science News Cover Story, 2012

When Networks Network

Once studied solo, systems display surprising behavior when they interact

By Elizabeth Quill

Half a dozen times each night, your slumbering body performs a remarkable feat of coordination. During the deepest stages of sleep, the body's support systems run on their own timetable. Your cells have along in your brain, their chemical general- ingers sense that sleep is the right time to go. Yet, the brain and torso with overlapping critical and uncoordinated activities. This neural conversation has little to do with your heart, which pumps blood to its own rhythm through the body's arteries and veins. Our theories why life is the result and down the way. It is a complex, multi-scale system that makes the lights flash and glow. It's a network. A network of neurons, organs, cells, of airways and lungs, of heart and vessels, of muscles and bones, of the body's every part.

Every couple of hours, though, in an effort to "re-wire" the network, the brain sends a signal. Suddenly, there's synchrony. All the electrical activity of sleep deep starts to connect with its surroundings. Each network - from the group of cells in the brain to the muscles and bones - starts to "talk" to each other. The result is a new kind of network. A network that is more than the sum of its parts.

— just the larger truth.

This change, marking the transition from sleep to light sleep, has only recently been understood in detail. Thanks to a new look at when and how the body's neural networks link up to form an interconnected network.

“As I go from one state to another, I immediately see the links between the physiological systems change,” says Plamen Ch Ivanov, a biophysicist at Boston University. “It’s quite surprising.”

And it’s not just in Boston. Similar changes happen all the time in every day life. Problems of all sorts constantly occur. How do you get your car started, allowing connections to help you drive. How do you get your computer to work, allowing connections to help you work. How do you get your social circle, your network of friends to flourish, your phone, books, power grids and online - and connect online.

A rich area of research has been devoted to understanding how it works - whether in healthy organs, people, computers or countries - and how it fails. An advance in the late 1990s to a focus on network science, and sophisticated analyses of how networks function and sometimes fail, have recently led to a new look at the human body. It's not enough to know isolated networks, work, and how they interact. Today, the field is not network science, but the science of networks.

“When we think about a single work in isolation, we see a small piece of the context,” says Plamen Ch Ivanov, a biophysicist and engineer at Boston University. “We’re going to make predictions that match that system.”

Their single-network concept, networks of networks, are everywhere. In walking up the stairs, in going to work and seeing your car, in connecting networks. When you're in a meeting, a meeting, a meeting, you're having the effects of each perform well in normal times, but also come with connection. In a landmark study, researchers at Boston University and elsewhere have developed methods for analyzing the way networks of networks can suddenly break down, allowing the load along with the good might lead to a sort of “flow of” an emerging, integrated system that not only performs well in normal times, but also comes with connection. In a landmark study, researchers at Boston University and elsewhere have developed methods for analyzing the way networks of networks can suddenly break down, allowing the load along with the good might lead to a sort of “flow of” an emerging, integrated system that not only performs well in normal times, but also comes with connection.

Hunting Evolution | Discovering DNA in Fall | Secrets of Science

Science News
MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC • SEPTEMBER 21, 2012

Linking Up
Perils and promises of connecting networks

Star Factory
Survival of Tattlers
Climo-Saving Centers

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

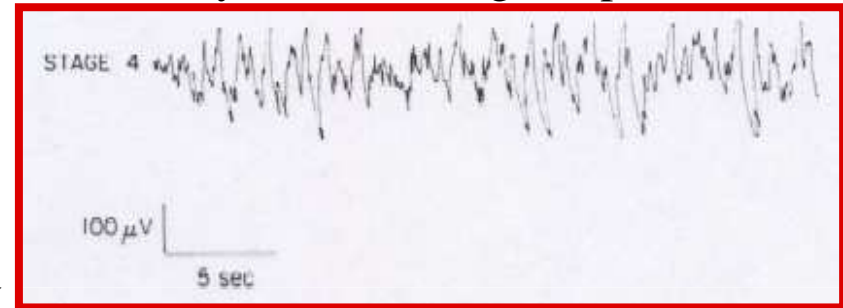
Complex Variability in Physiologic Dynamics across spatio-temporal scales and levels of integration

Is Physiologic
Variability
simply Noise?

Complexity

organs

Brain dynamics during sleep (EEG)



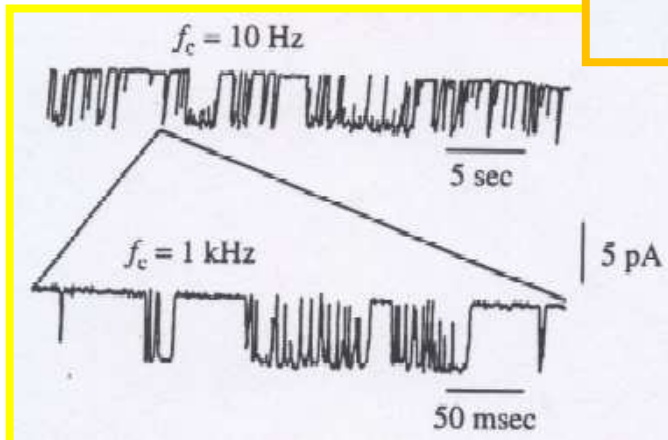
cell

Single neuron activity



sub-cellular

Ion channel kinetics



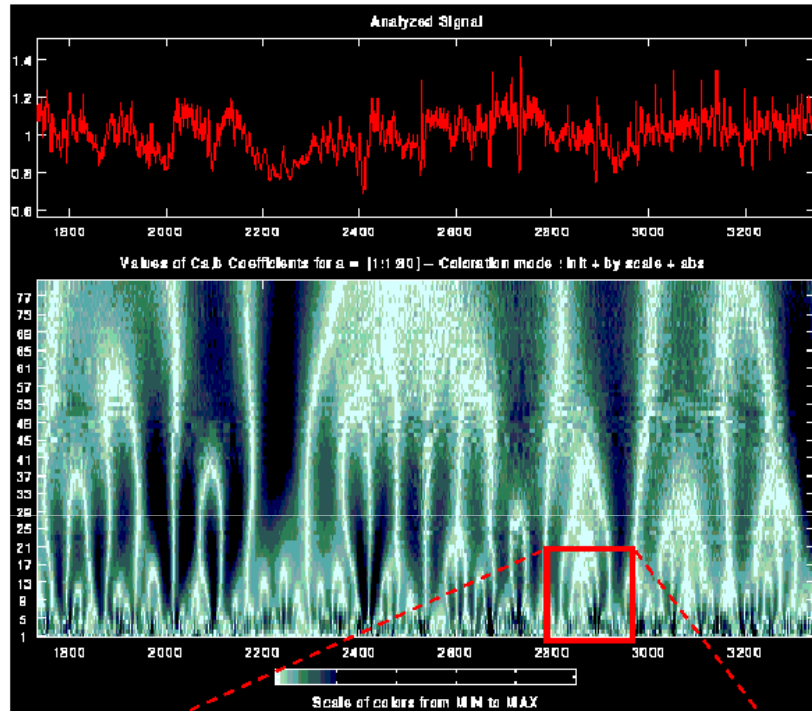
New Concept: Fluctuations are *not* noise !

Instead:

Fluctuations contain hidden
dynamical patterns related to
underlying mechanisms

Self-similar cascades

Heart rate data

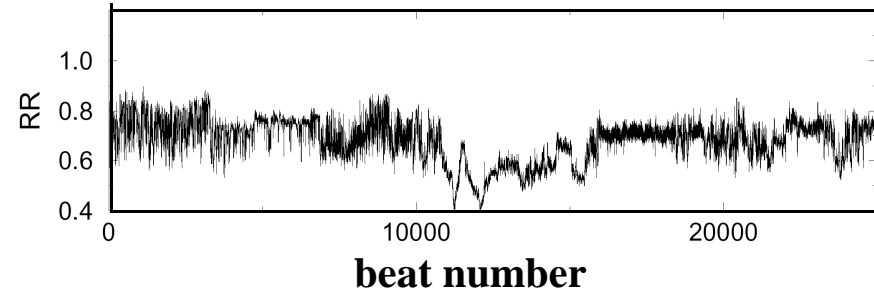
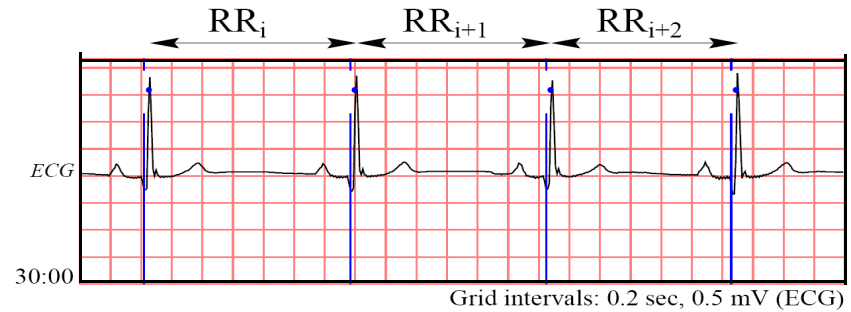


Scale of Analysis

New Methodology

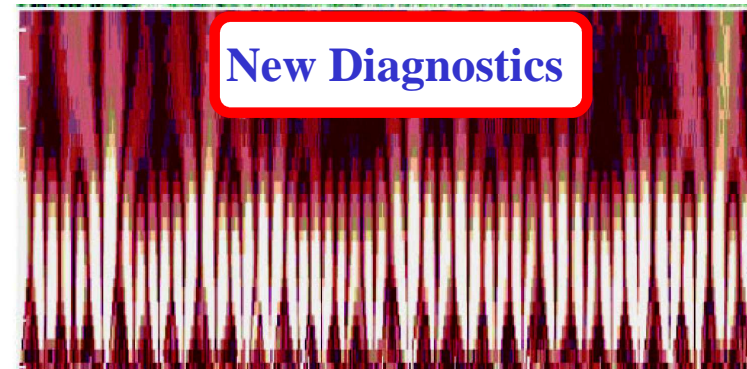


Time



Sleep apnea

New Diagnostics

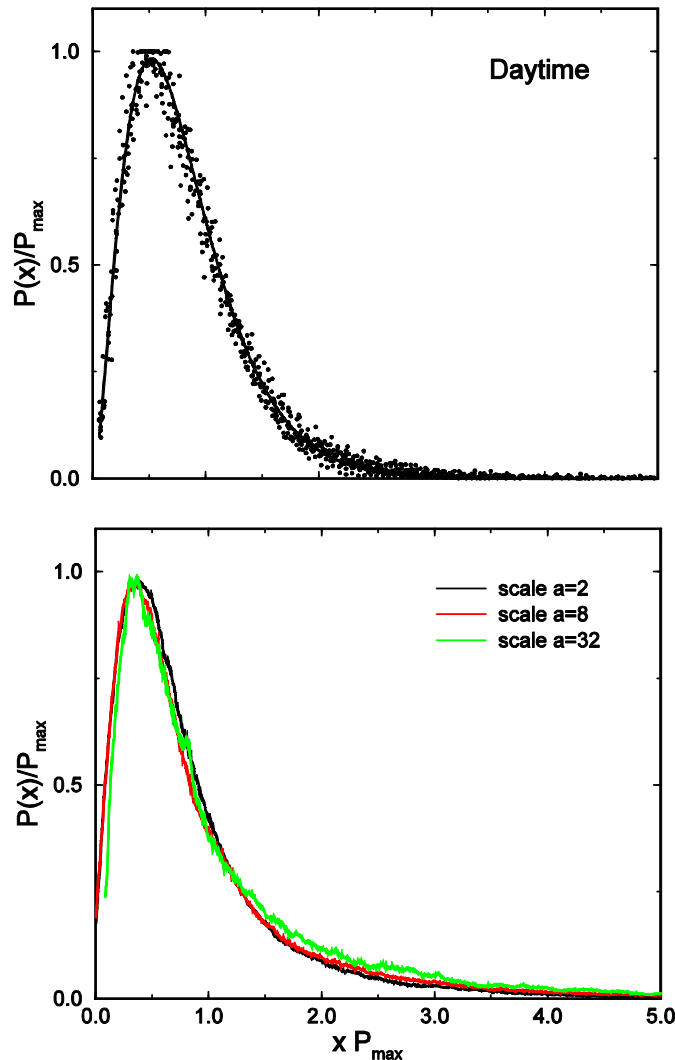


P.Ch. Ivanov *et al.* *Nature* **383**:323 (1996).
P.Ch. Ivanov *et al.* *Chaos* **11**: 641 (2001).
P.Ch. Ivanov *et al.* *Wavelets in Physics*,
(Cambridge Univ. Press, 1998).

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

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

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

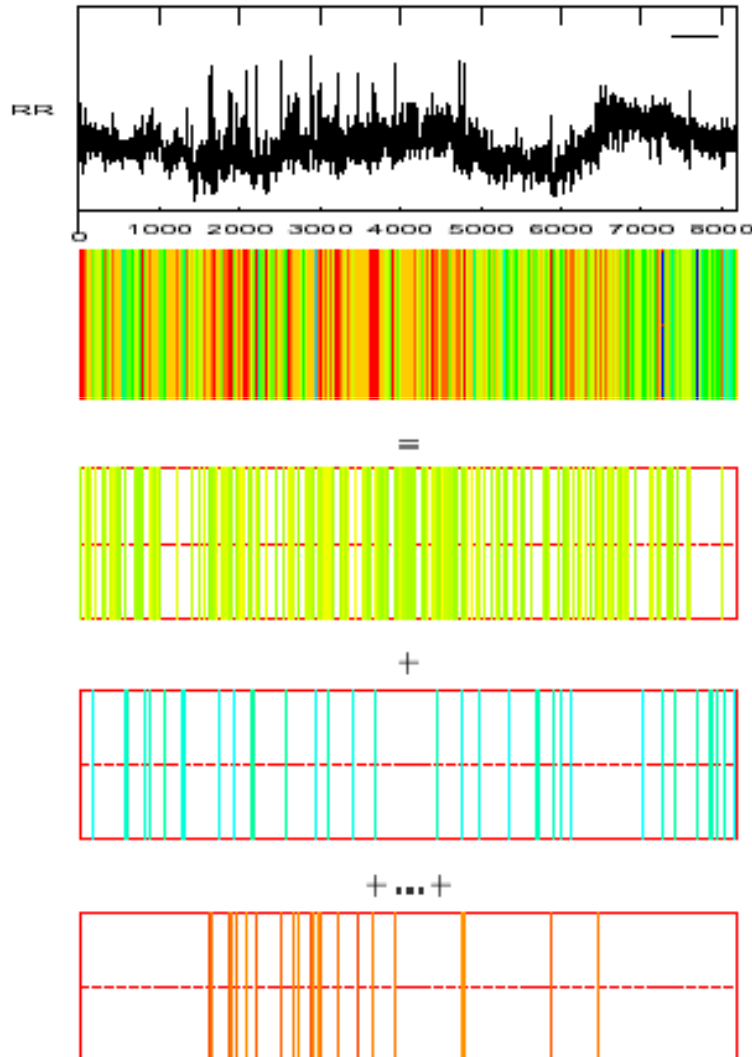


Scale-invariance

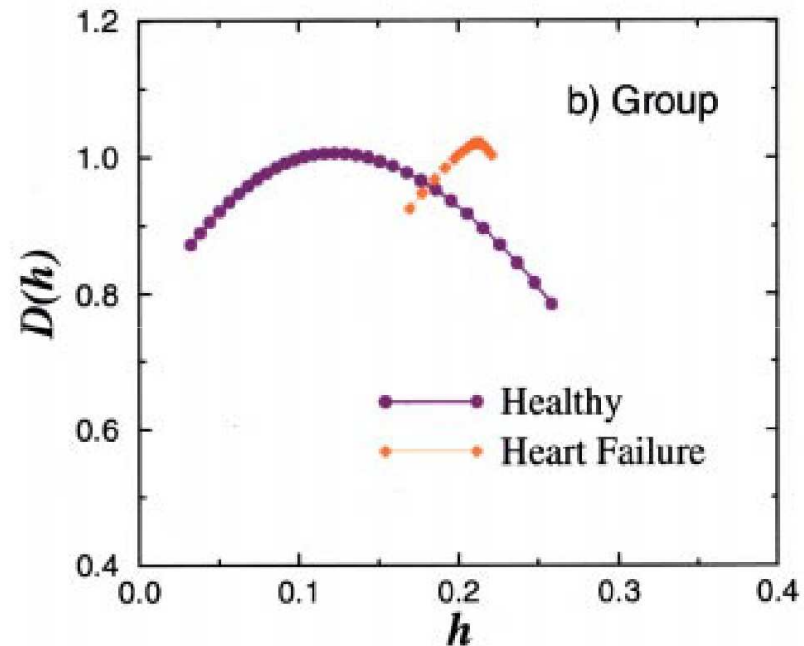
“data collapse” over a range of time scales

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

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

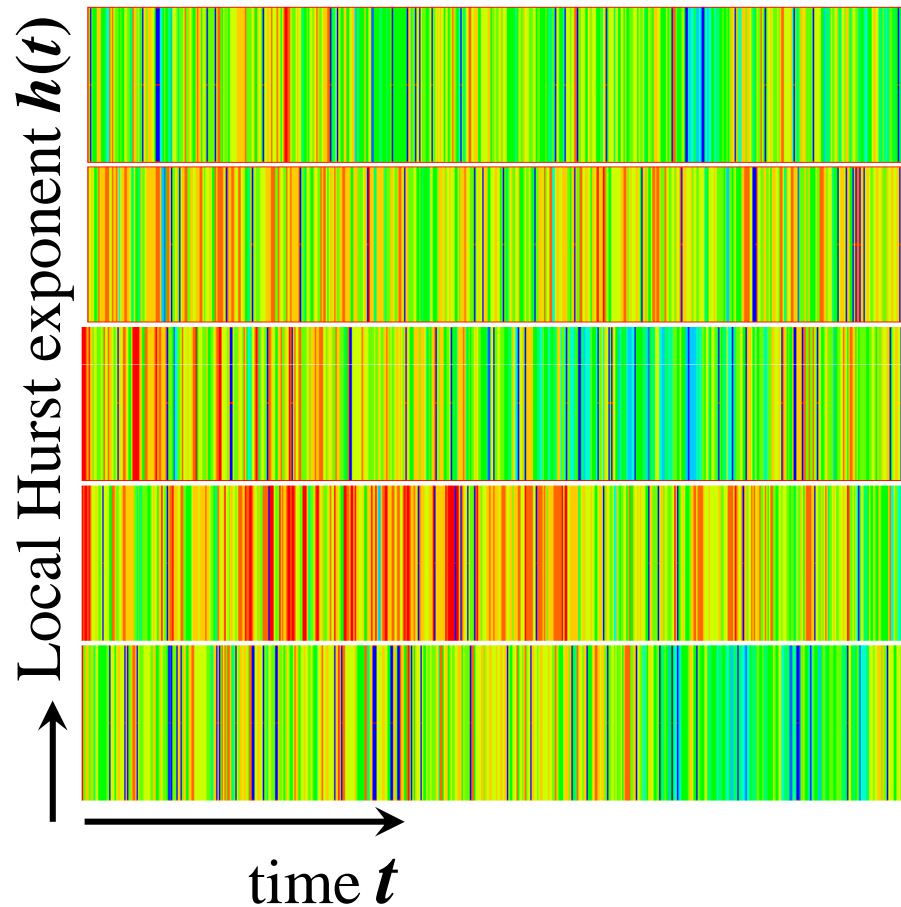
P. Ch. Ivanov et al., NATURE 399: 461 (1999)

New Technology



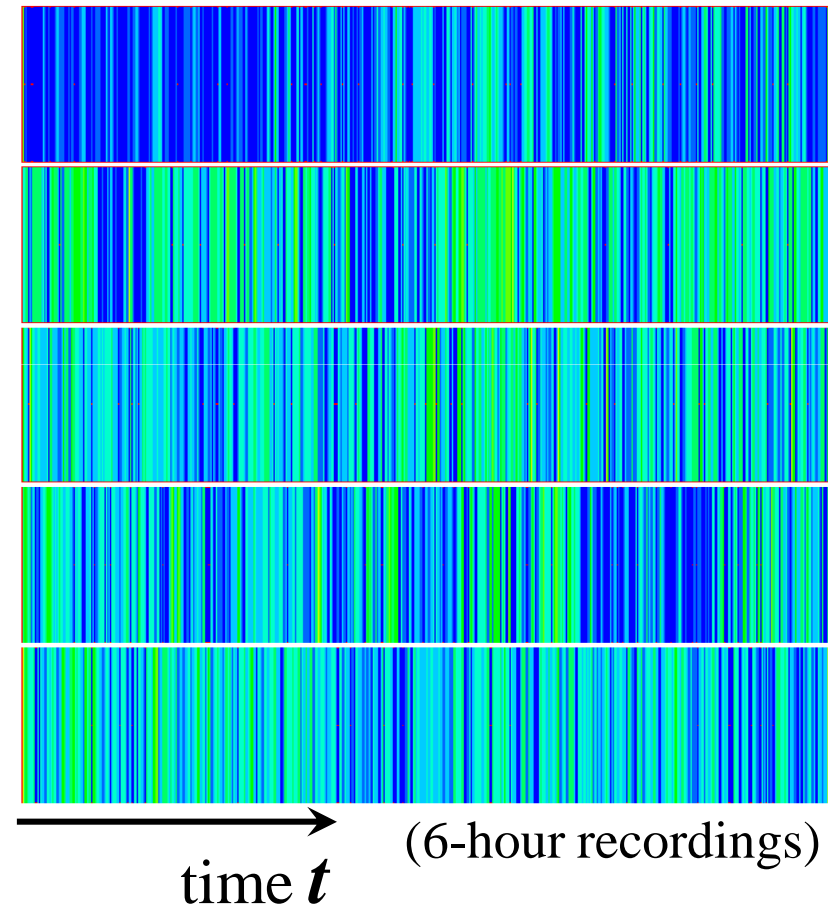
New Diagnostics

5 healthy subjects



Multicolor ↔ **Multifractal**

5 heart failure subjects



Monocolor ↔ **Monofractal**

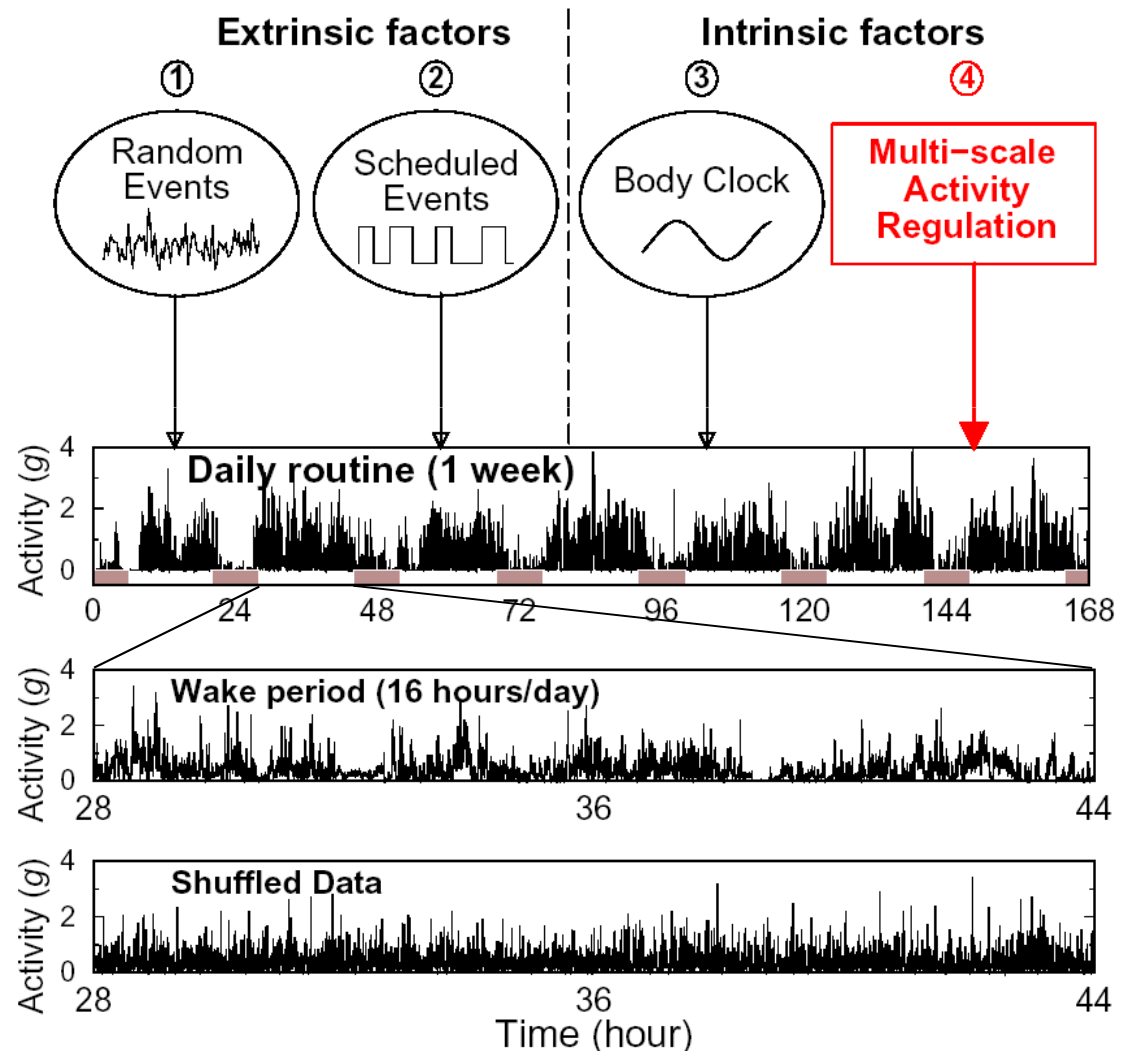
Motor Activity: Wrist motion fluctuations

Motivation:

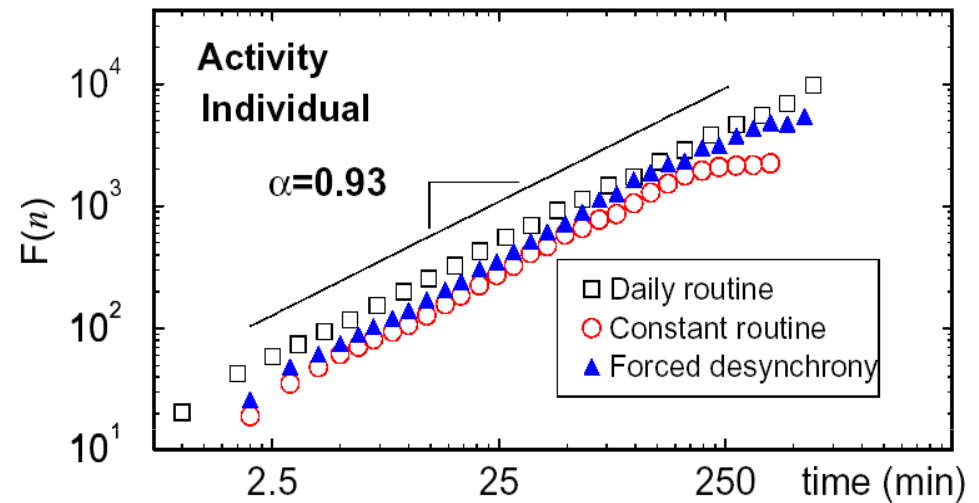
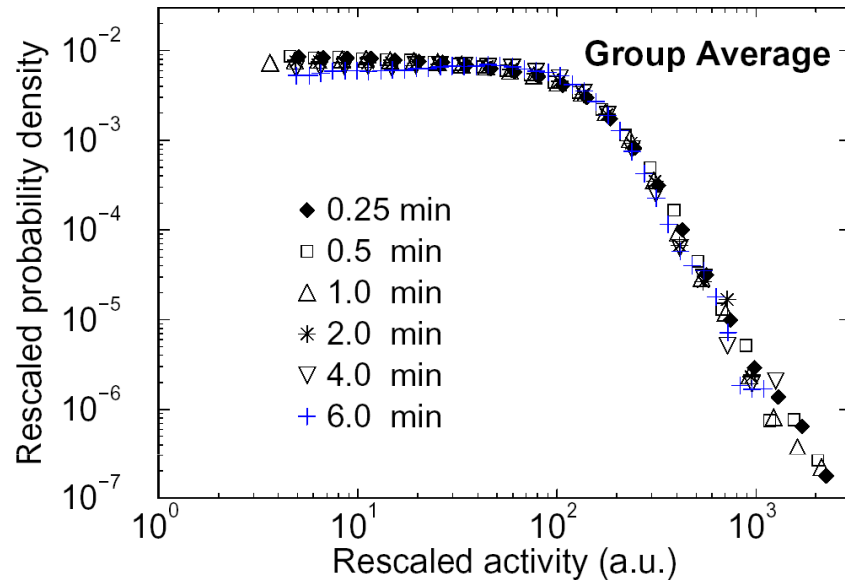
Test hypothesis that there are *intrinsic stable patterns* in human motor activity.



*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

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).

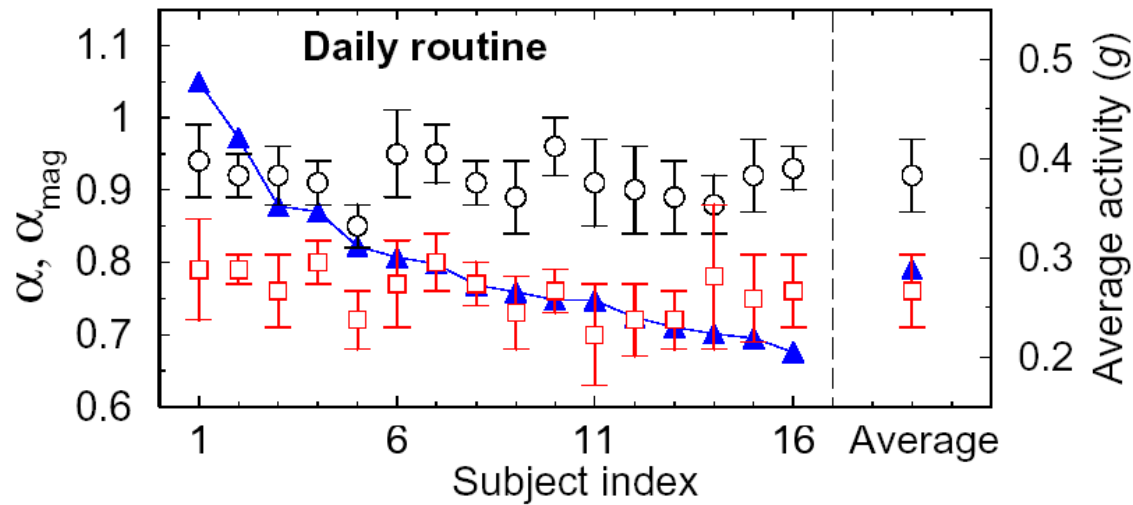


Smart
wristband

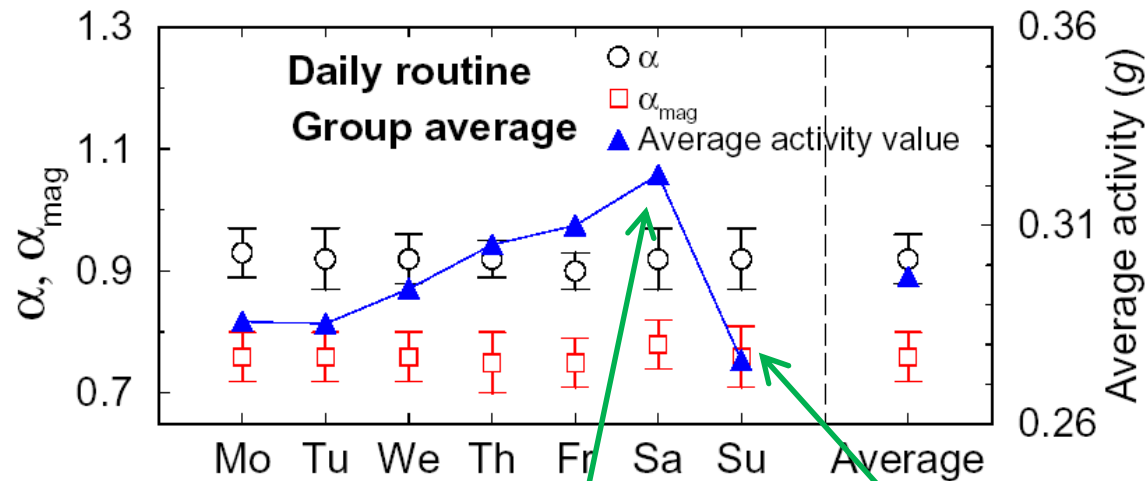
**Level 1:
Individual Systems**

**Locomotor system dynamics:
wrist motion fluctuations**

Scaling exponents independent of activity level



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



Party time!

Day of rest!

Scaling exponents --- remarkably consistent for:

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

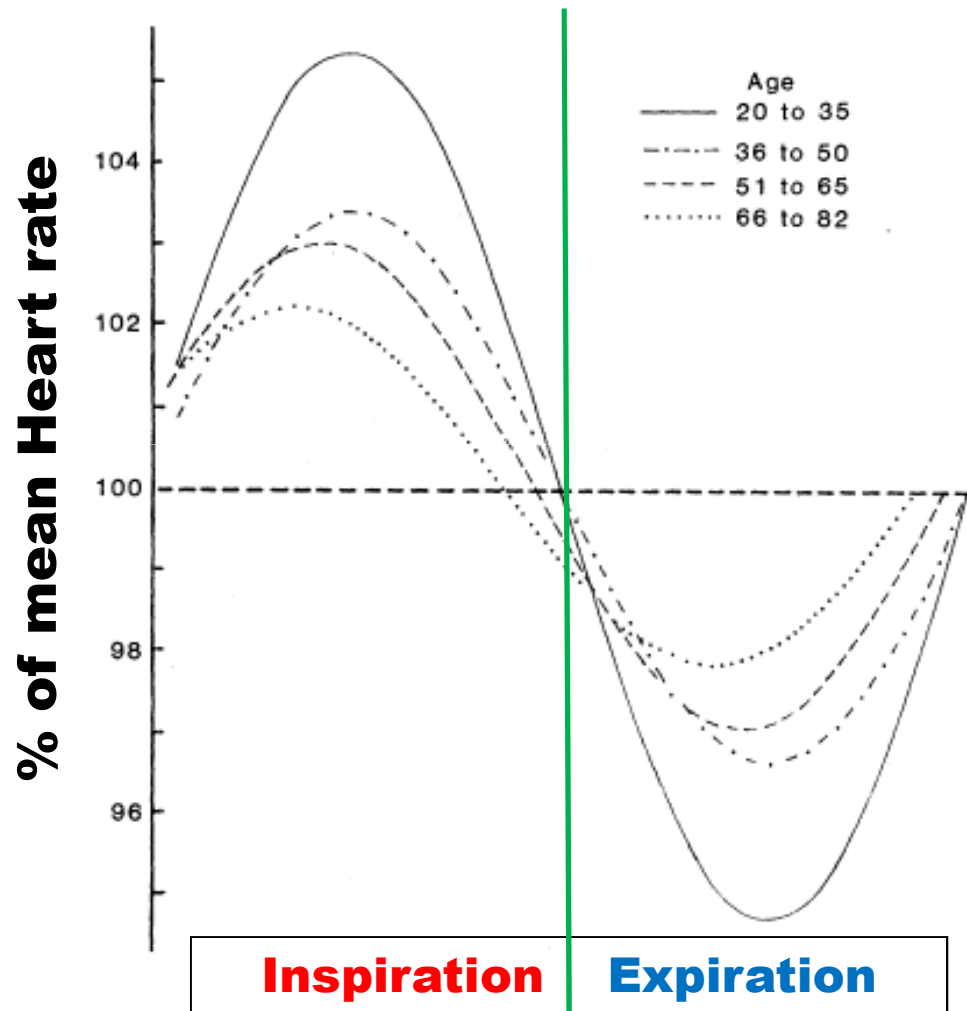
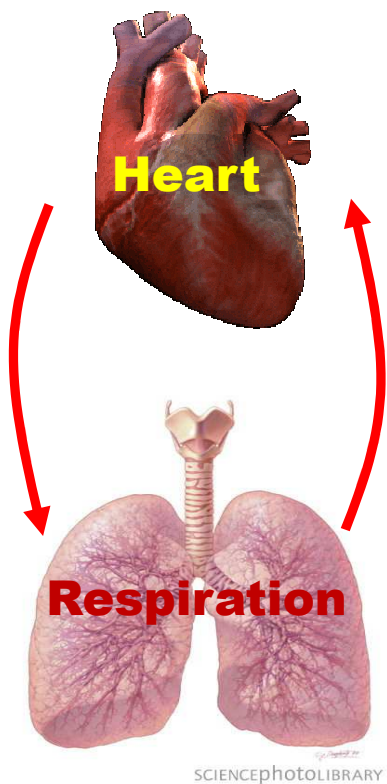
Level 2:
Pair-wise Coupling

Cardio-respiratory Interaction

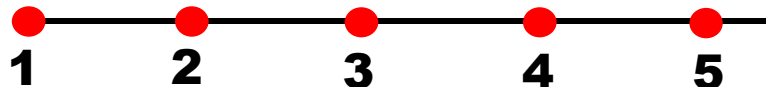
Respiratory Sinus Arrhythmia (RSA)

Inspiration → Heart rate ↑

Expiration → Heart rate ↓



Heart beat
number



Level 2:
Pair-wise Coupling

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:

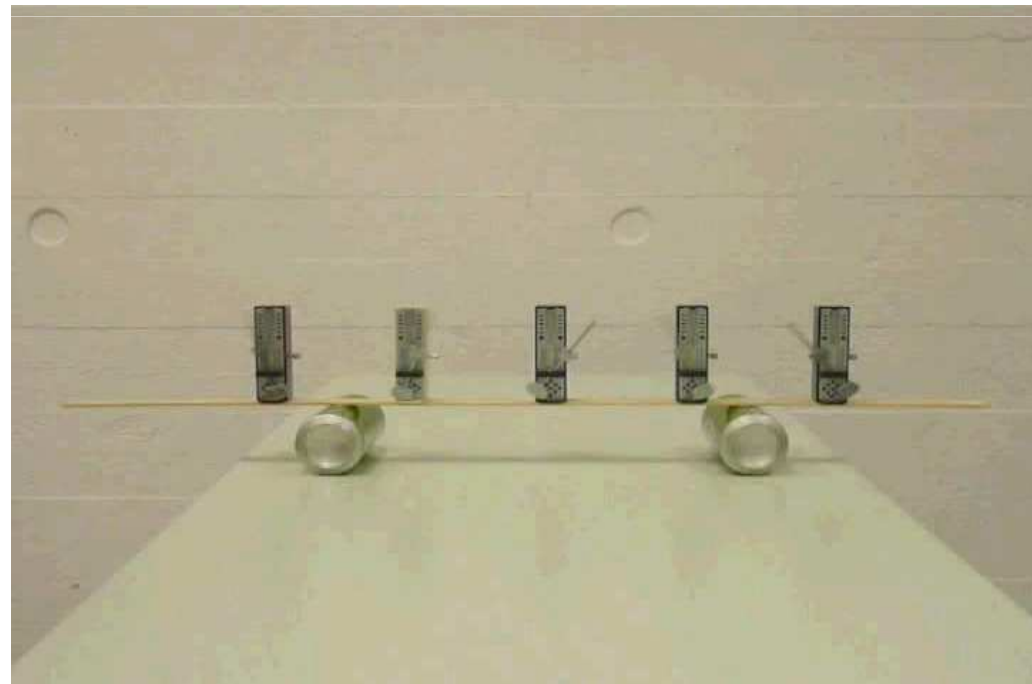
**different frequencies,
different phases**

→ No synchronization

End:

**same frequencies, same phase
difference (“phase locked”)**

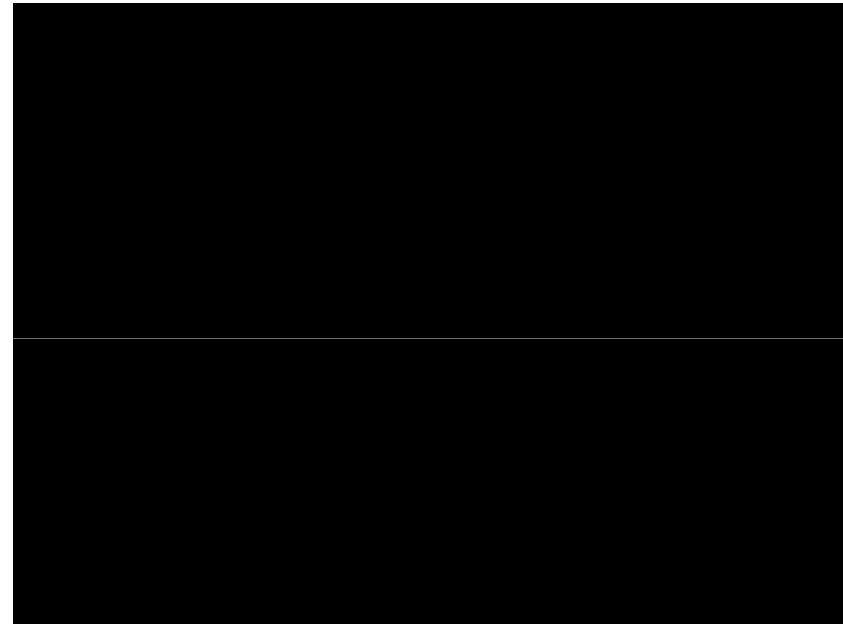
→ Synchronization



Level 2:
Pair-wise Coupling

Cardio-respiratory Interaction Phase Synchronization

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

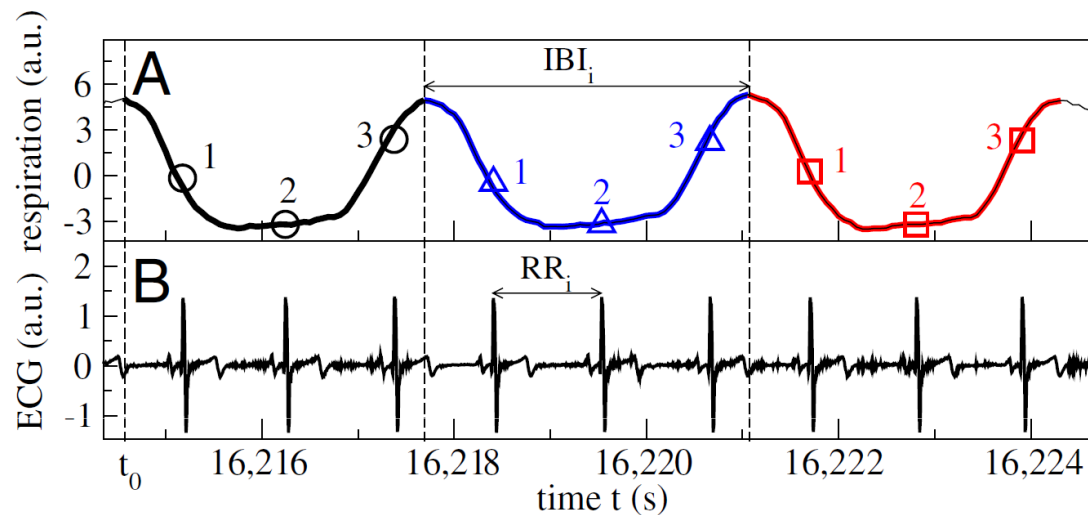
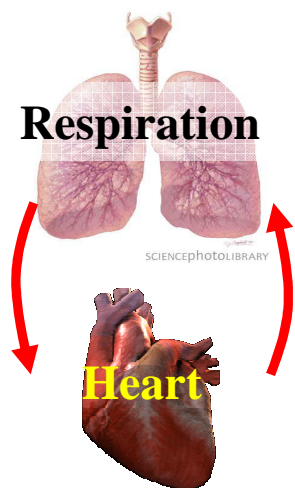


Millenium bridge reopened in February 2002:

- 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

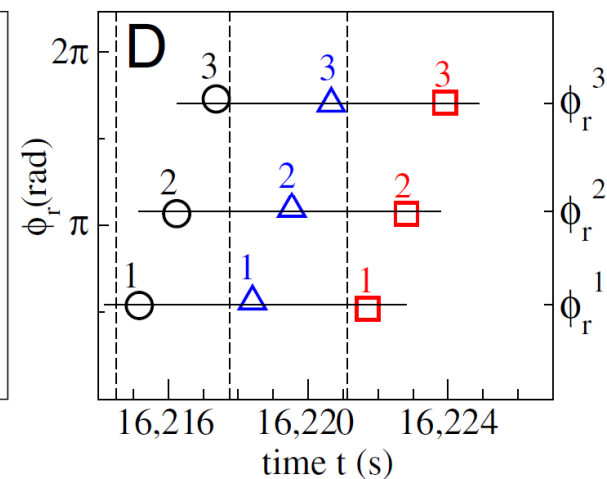
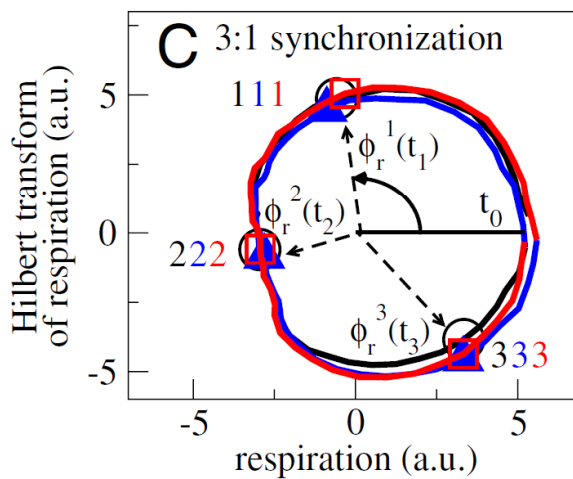
Cardio-respiratory Interaction Phase Synchronization



Phases collapse



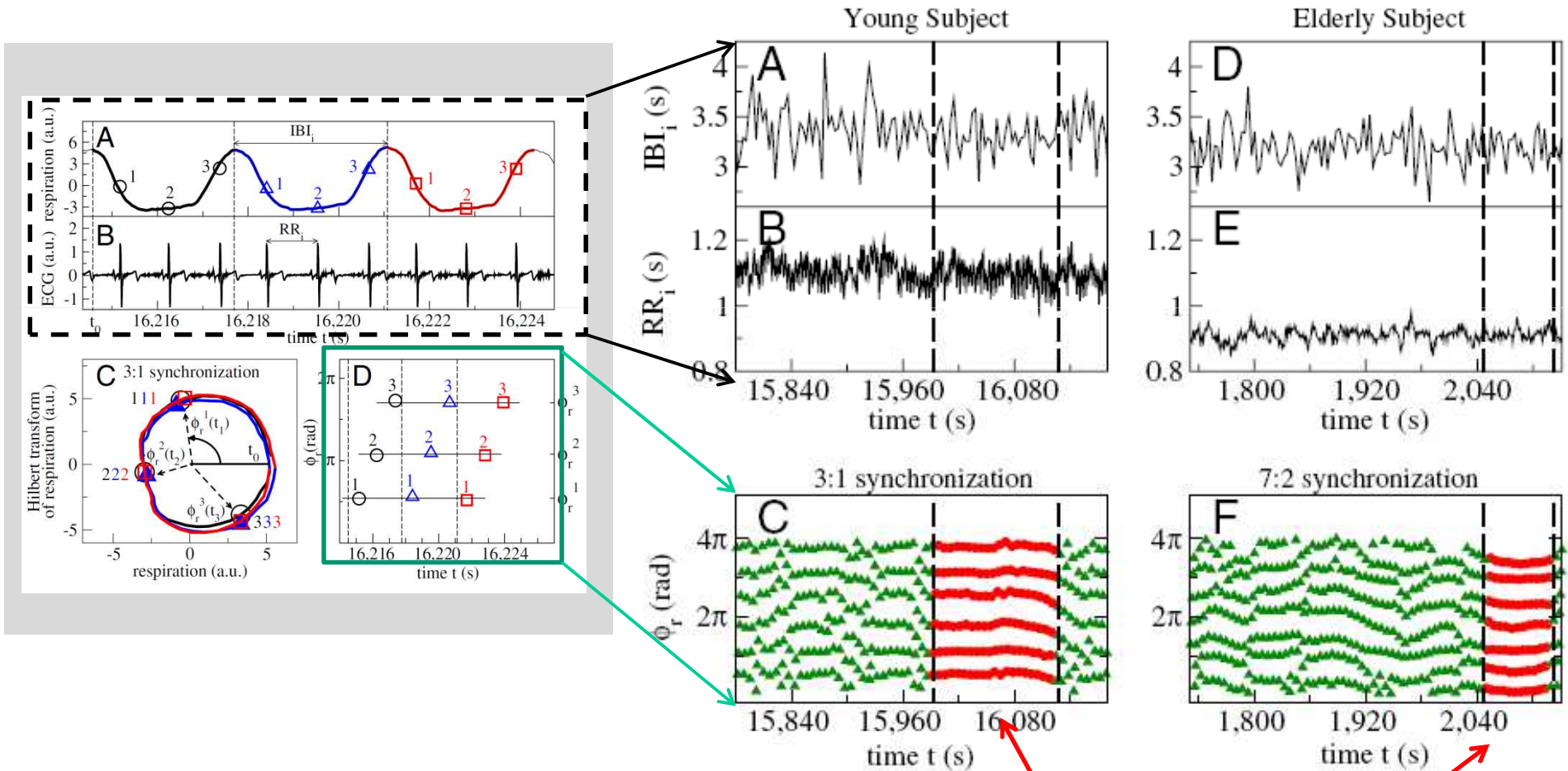
Phase synchronization



Level 2:
Pair-wise
Coupling

Cardio-respiratory Interaction

Phase Synchronization despite continuous fluctuations

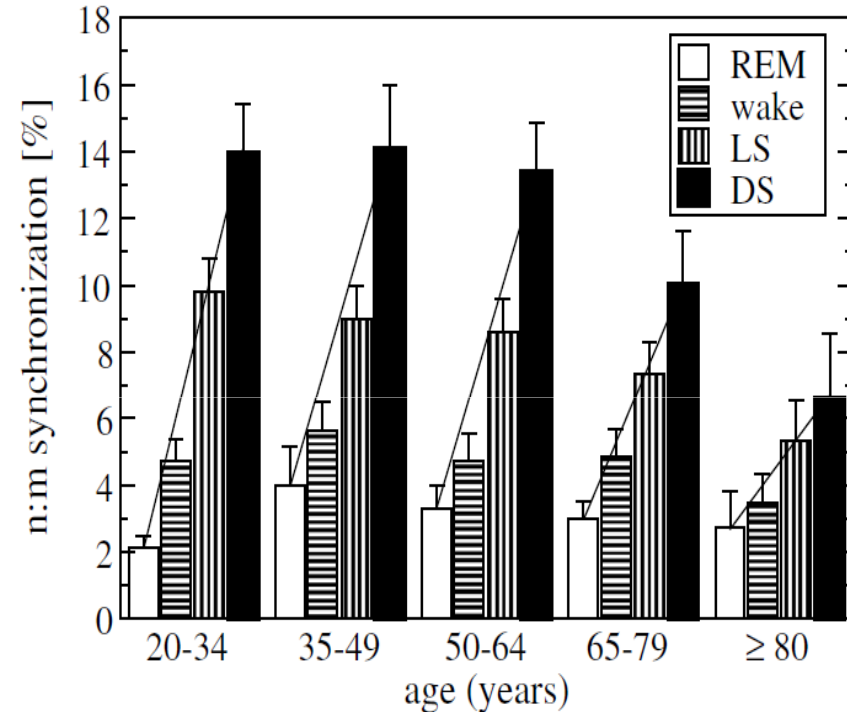
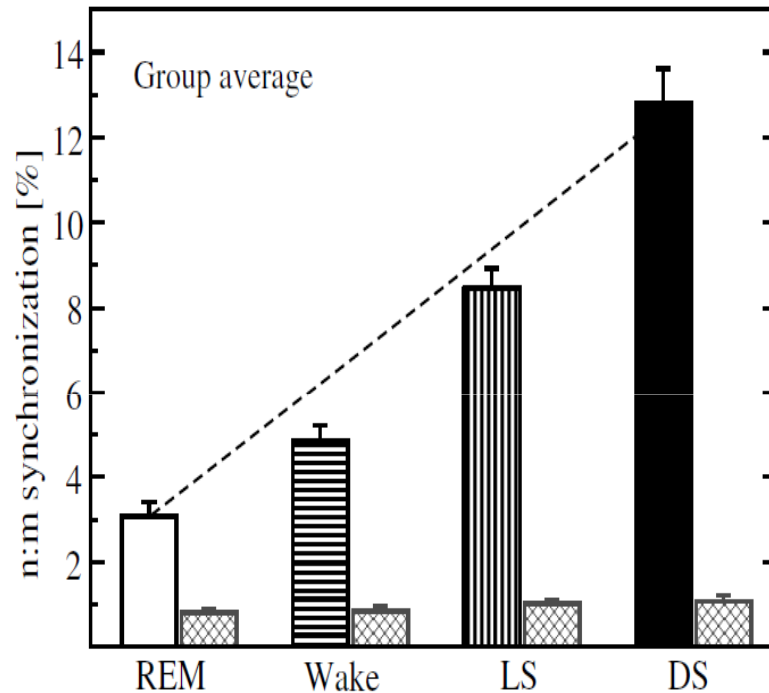


Segments of Synchronization

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

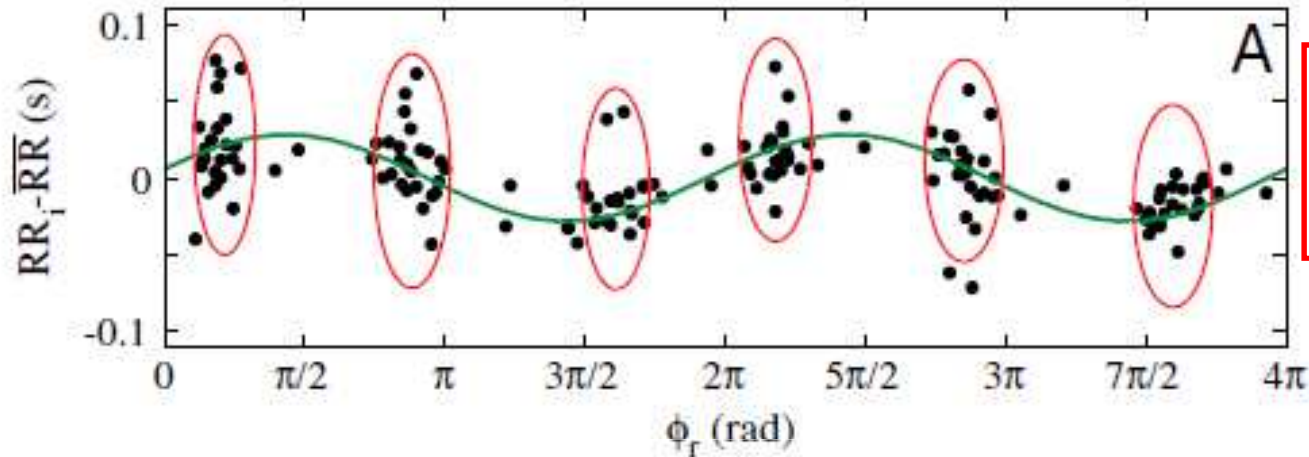


Discovery:
Phase transitions in cardio-respiratory coupling

Level 2:
Pair-wise Coupling

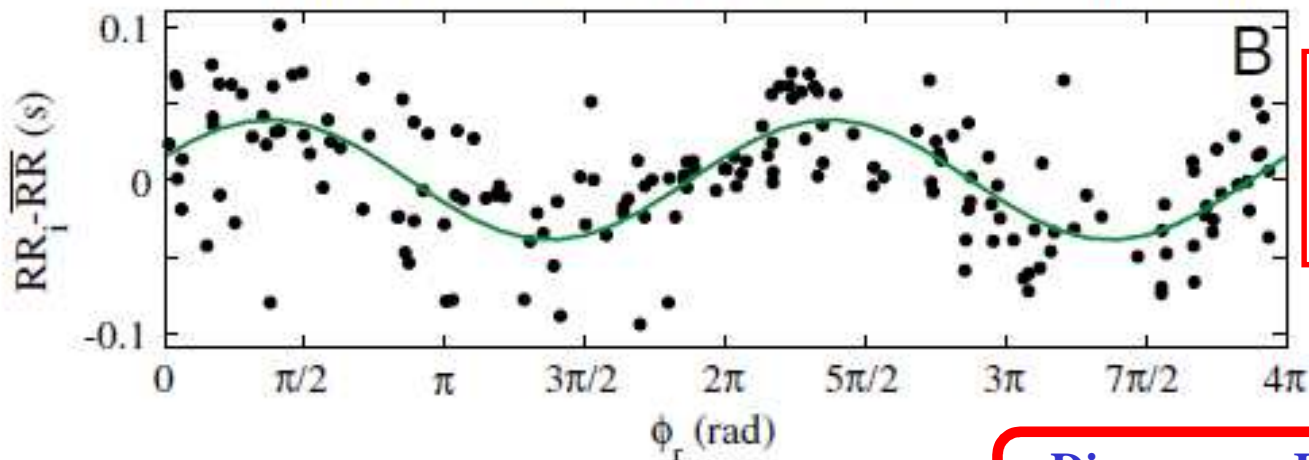
Coexisting forms of physiologic coupling Cardio-Respiratory interaction

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:

Physiology: cardiac, respiration, gait, sleep, brain

Medicine: novel diagnostic measures

Physical Sciences: oil recovery, climate, seismology, astronomy

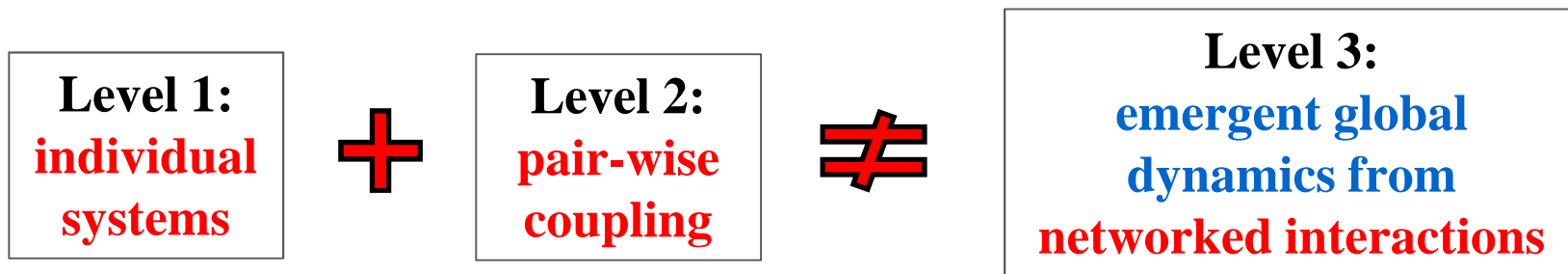
Economics: stock markets, company growth, commodities ...

Impact

**Level 3:
Networked
Interactions**

Challenges in understanding emergent network behaviors

Levels of Complexity:



Level 3:

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

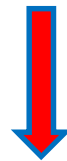
Currently: No available technology and theoretical framework

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:

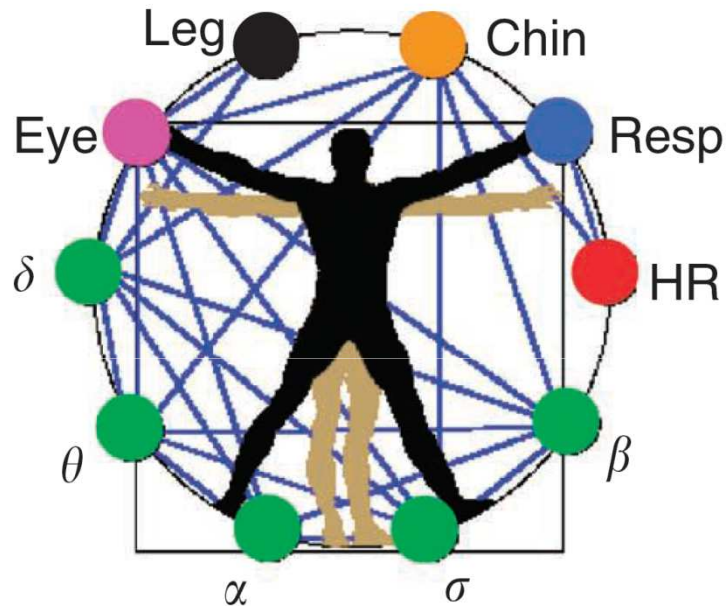
Introduced new concept – *Time Delay Stability (TDS)*
Developed a novel method



Infer/quantify interactions
among *diverse* dynamical systems

**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

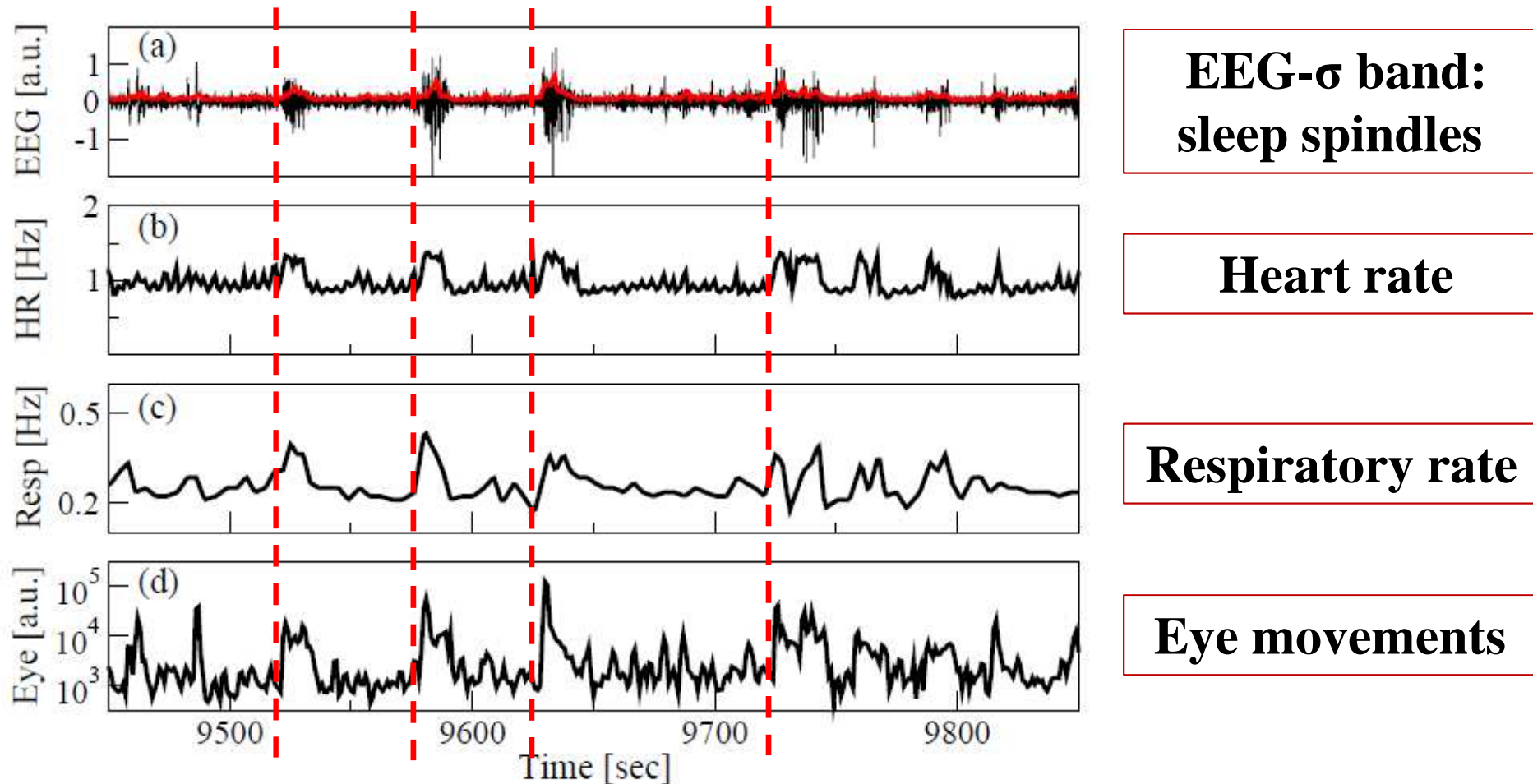
Physiologic states

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

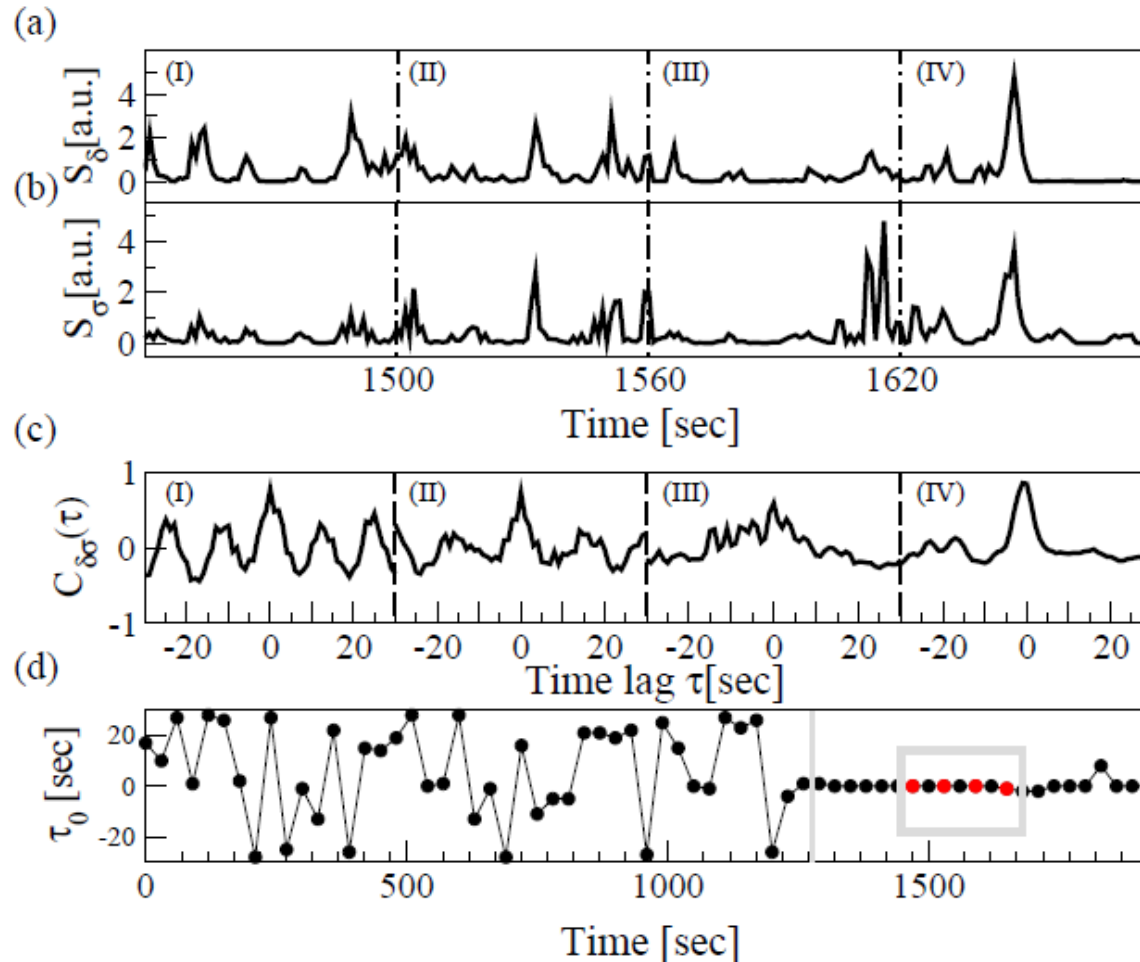
**Data-
Driven
Observation**

Coordinated activity across diverse systems



→ 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

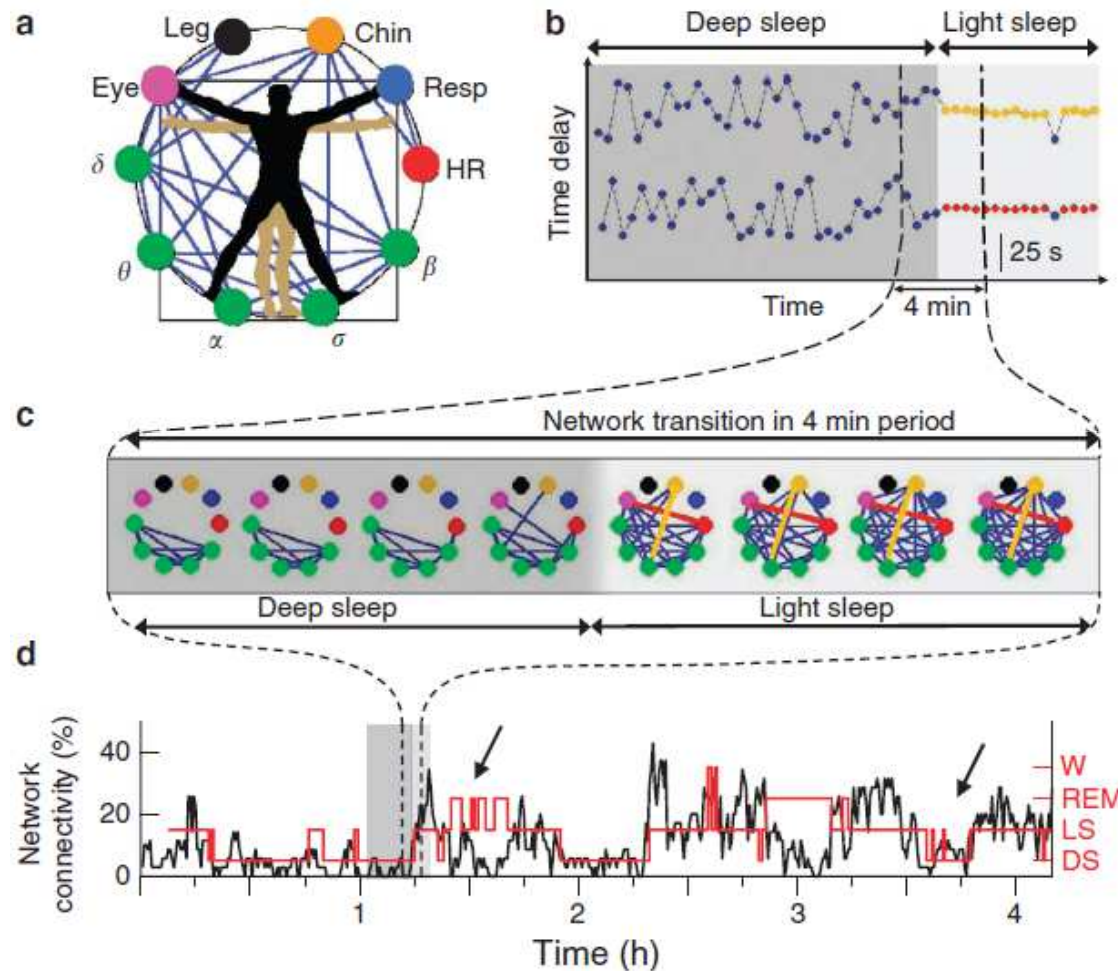
normalized spectral
power of EEG- σ band

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

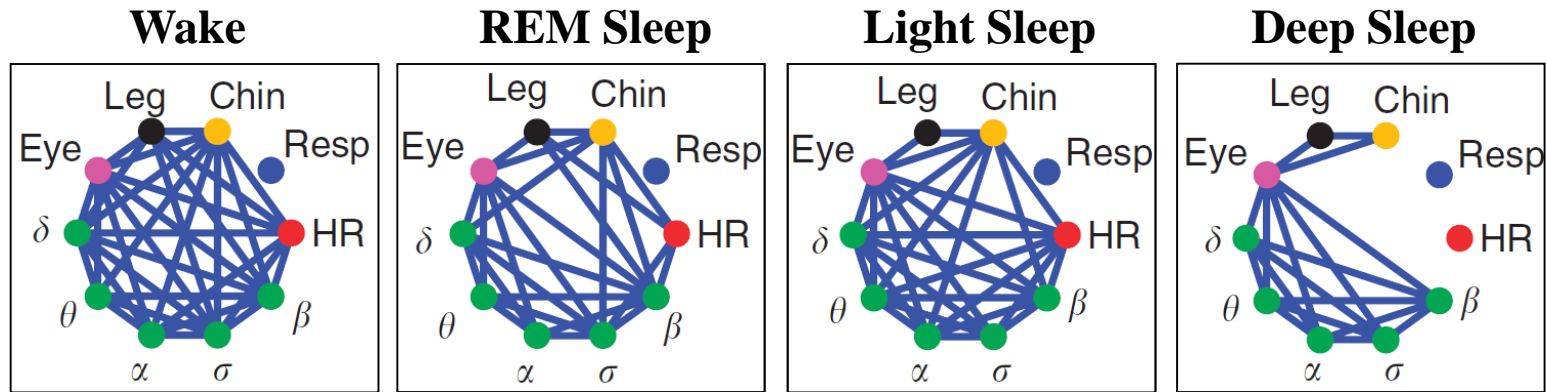
α - Chin link

HR - Eye link

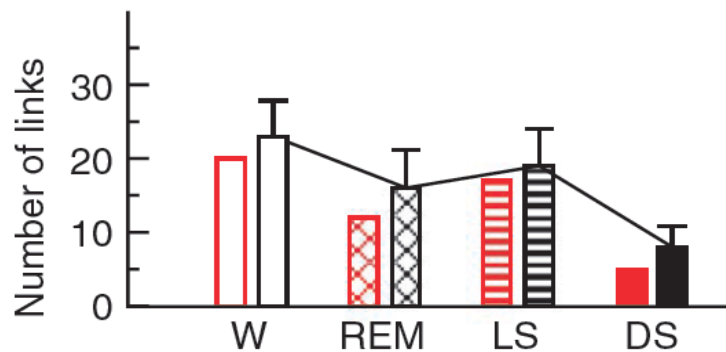
Dynamical Evolution

→ Fast reorganization of network connectivity with transitions across physiologic states

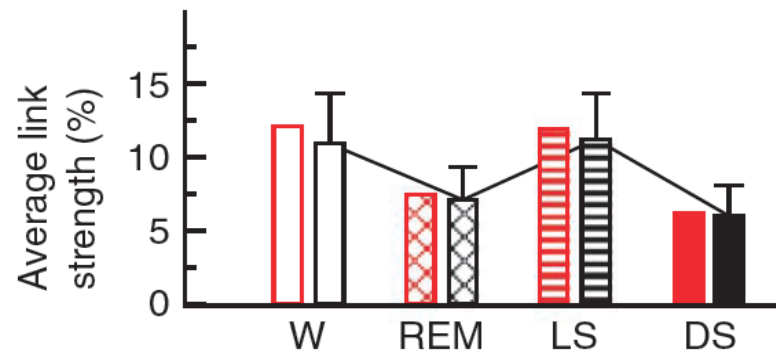
Network Topology & Physiologic Function connectivity across sleep stages



Network connectivity



Network link strength

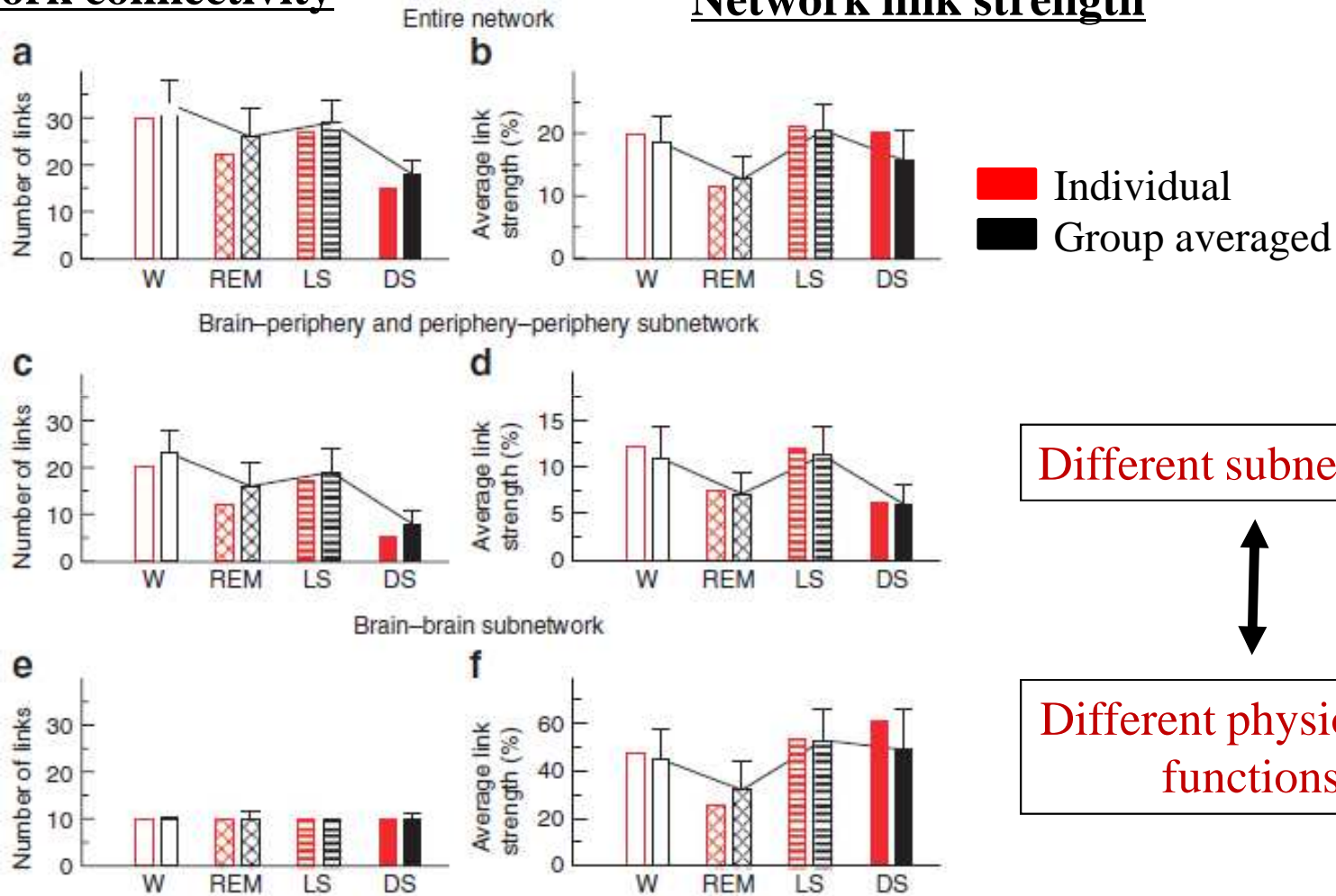


→ Network topology changes with physiologic states

Network of networks across sleep stages

Network connectivity

Network link strength



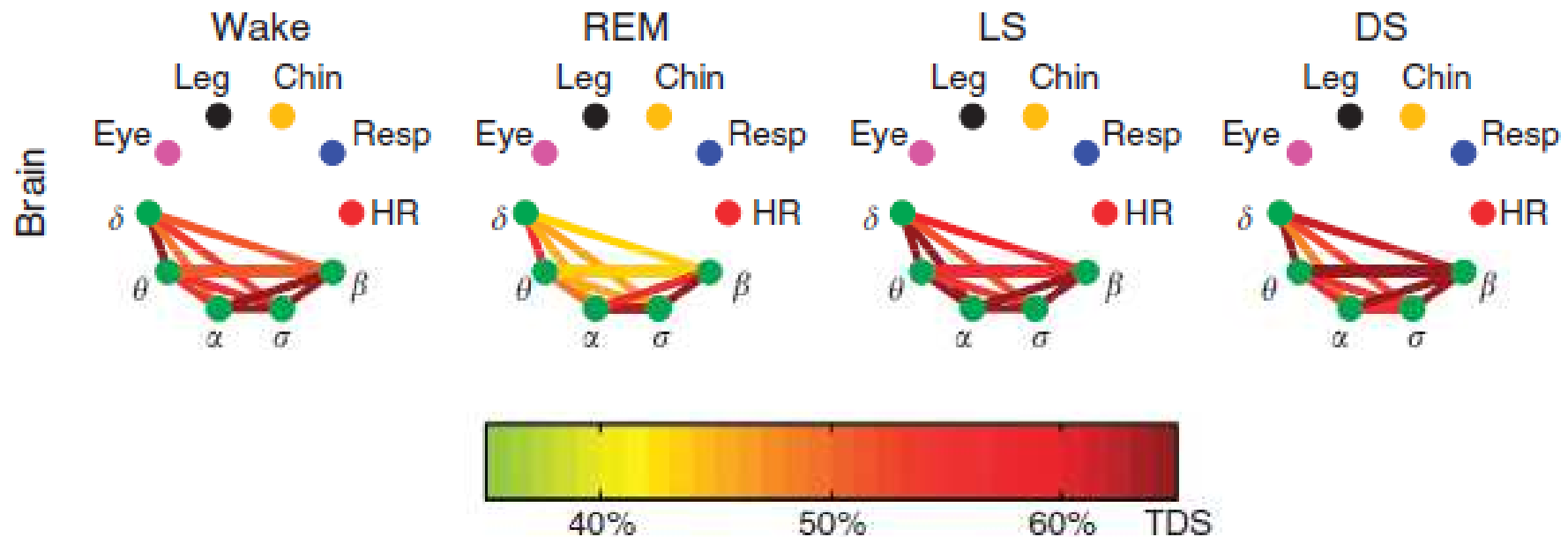
Different subnetworks



Different physiologic functions

→ Robust sleep-stage stratification pattern

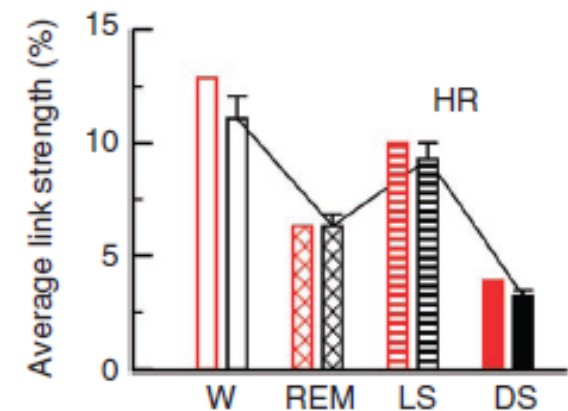
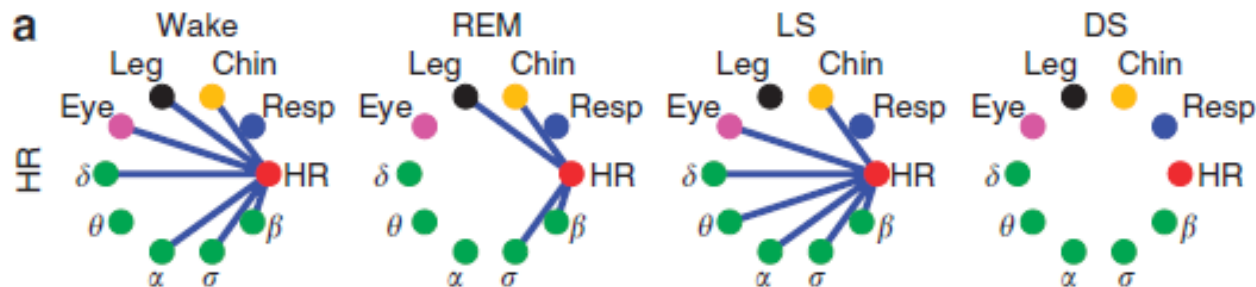
Network connectivity and link strength of the brain–brain sub-network for different sleep stages



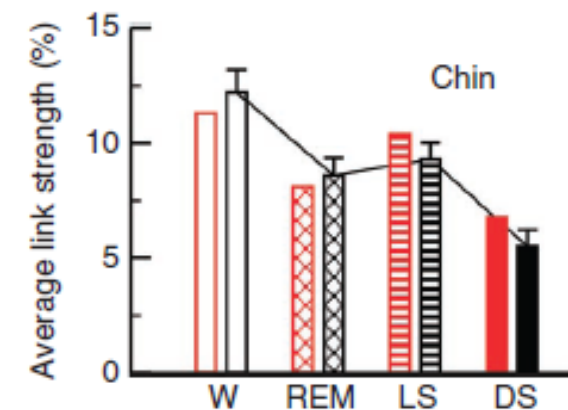
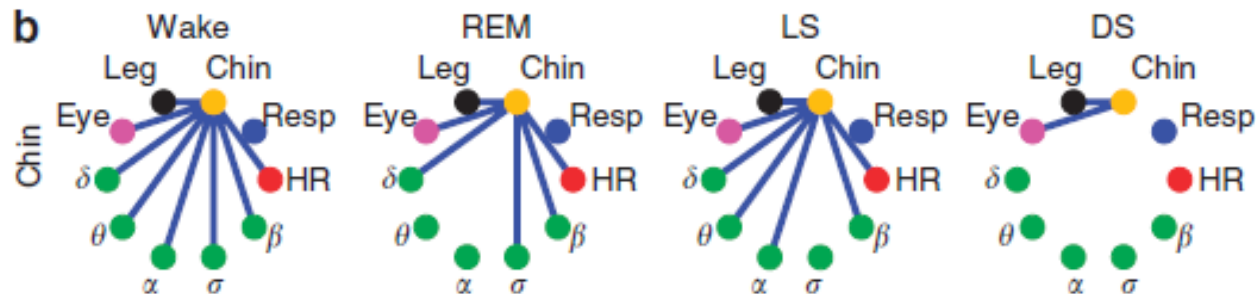
Topology of brain-brain sub-network → no change
Strength of network links → significant change

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

Heart



Chin

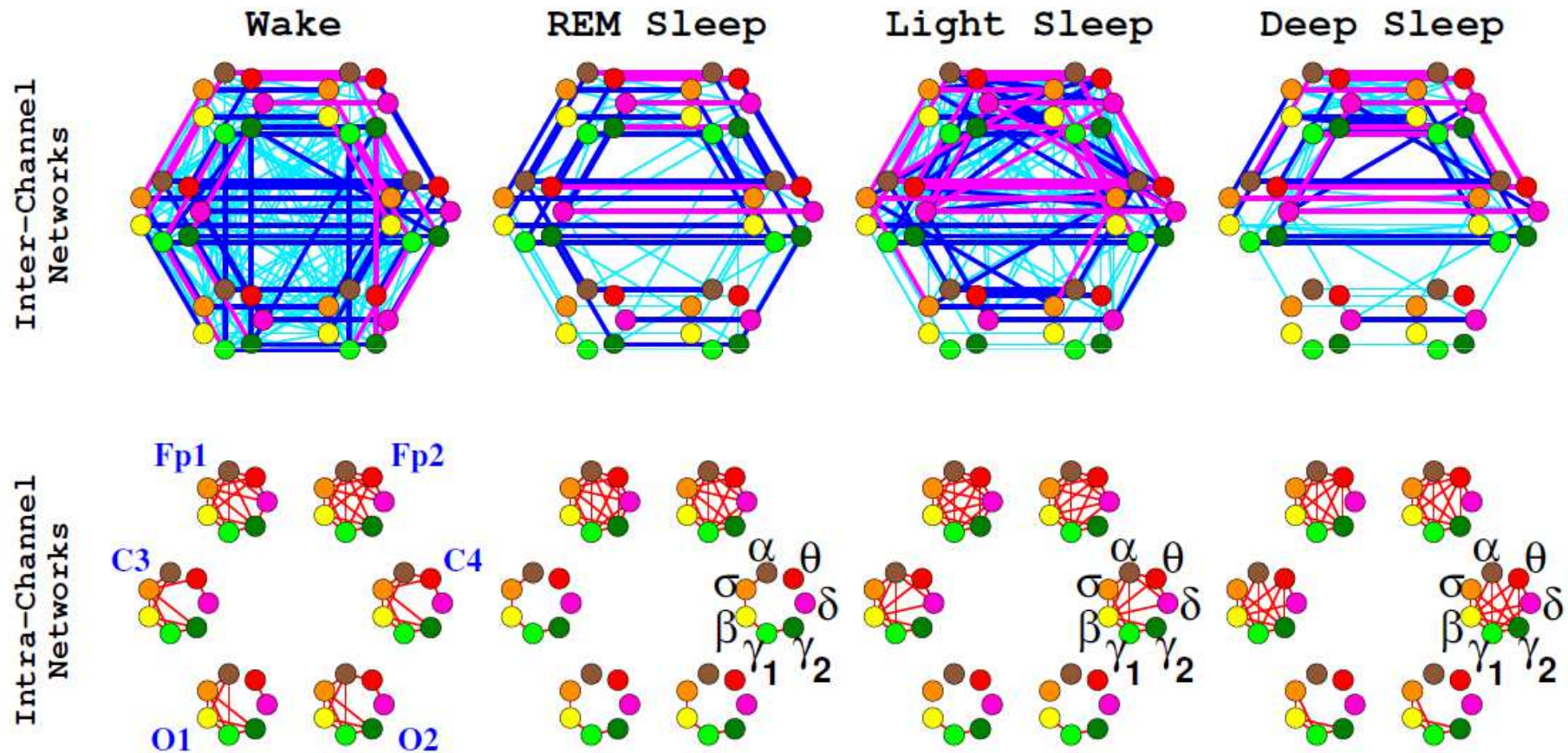


Robust sleep-stage stratification pattern in:

- Individual node connectivity
- Average link strength of individual nodes

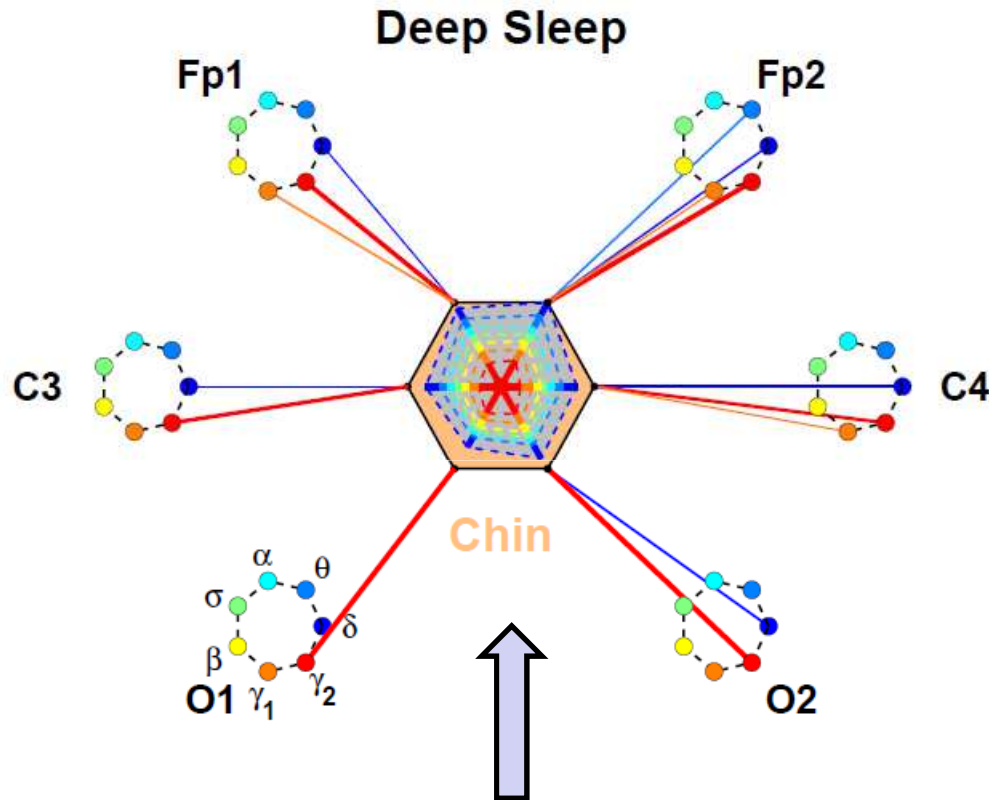
Network Physiology

Networks of brain activity across sleep stages



Phase transition in link strength and network topology

Maps of physiologic interactions



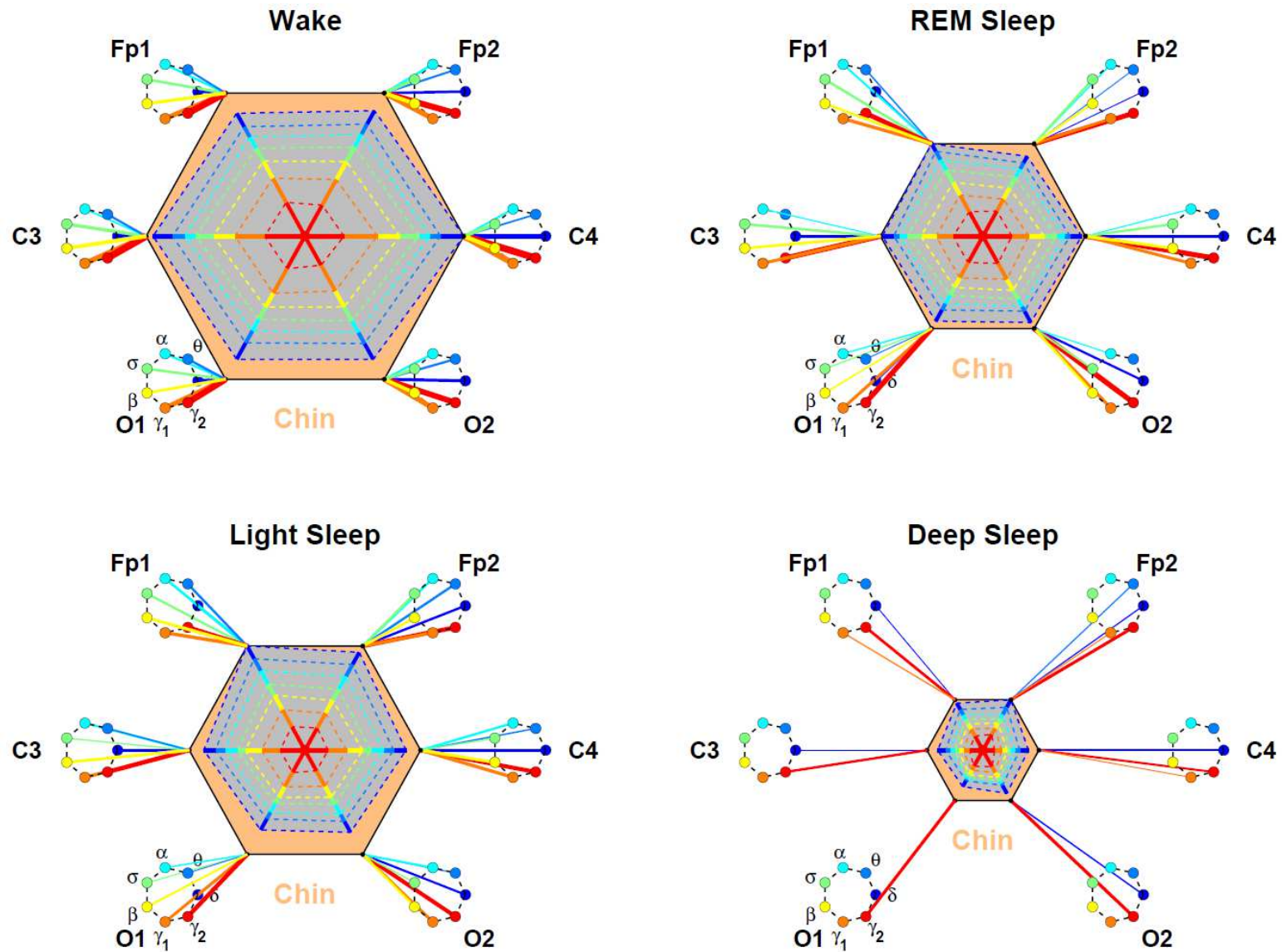
*Radar Chart in the Hexagon:
Brain Control on the target organ*

Location of the nodes:
Brain EEG Channels

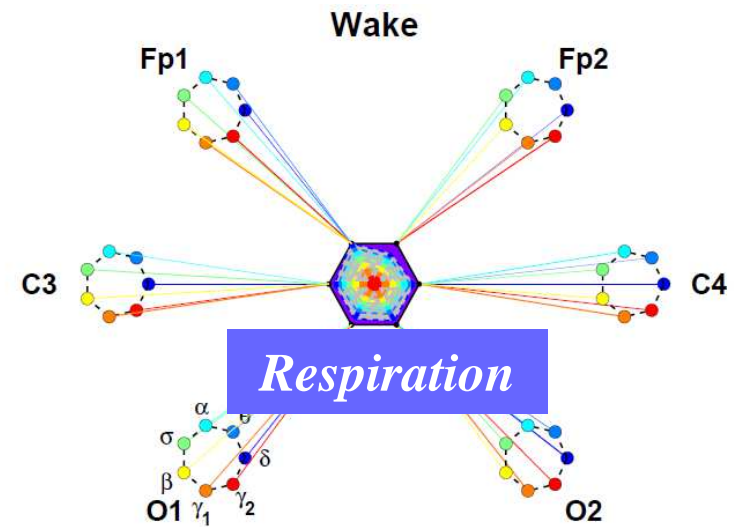
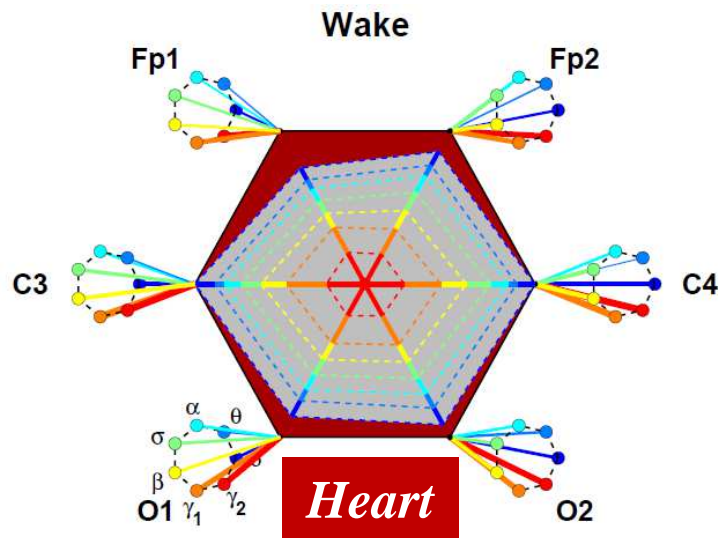
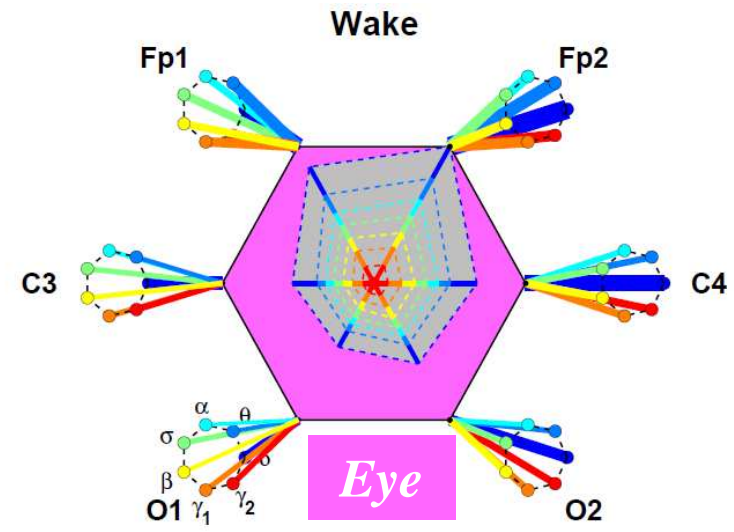
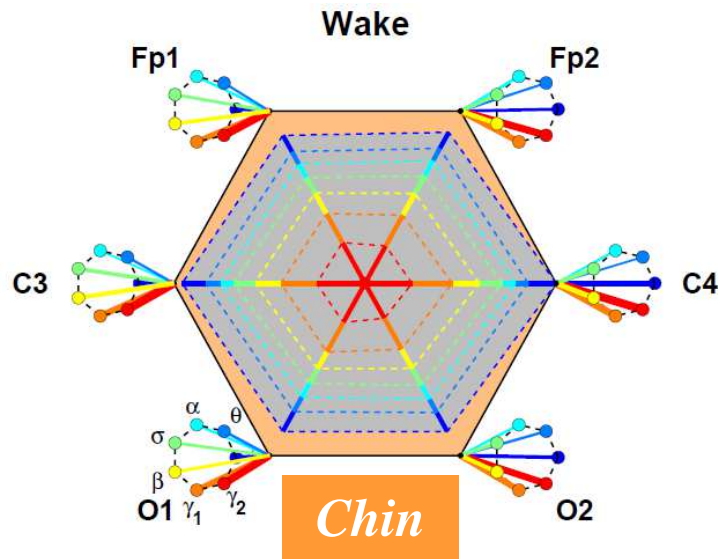
Colors:
Frequency bands in the EEG
signals

Width of the links:
Coupling strength between the
systems

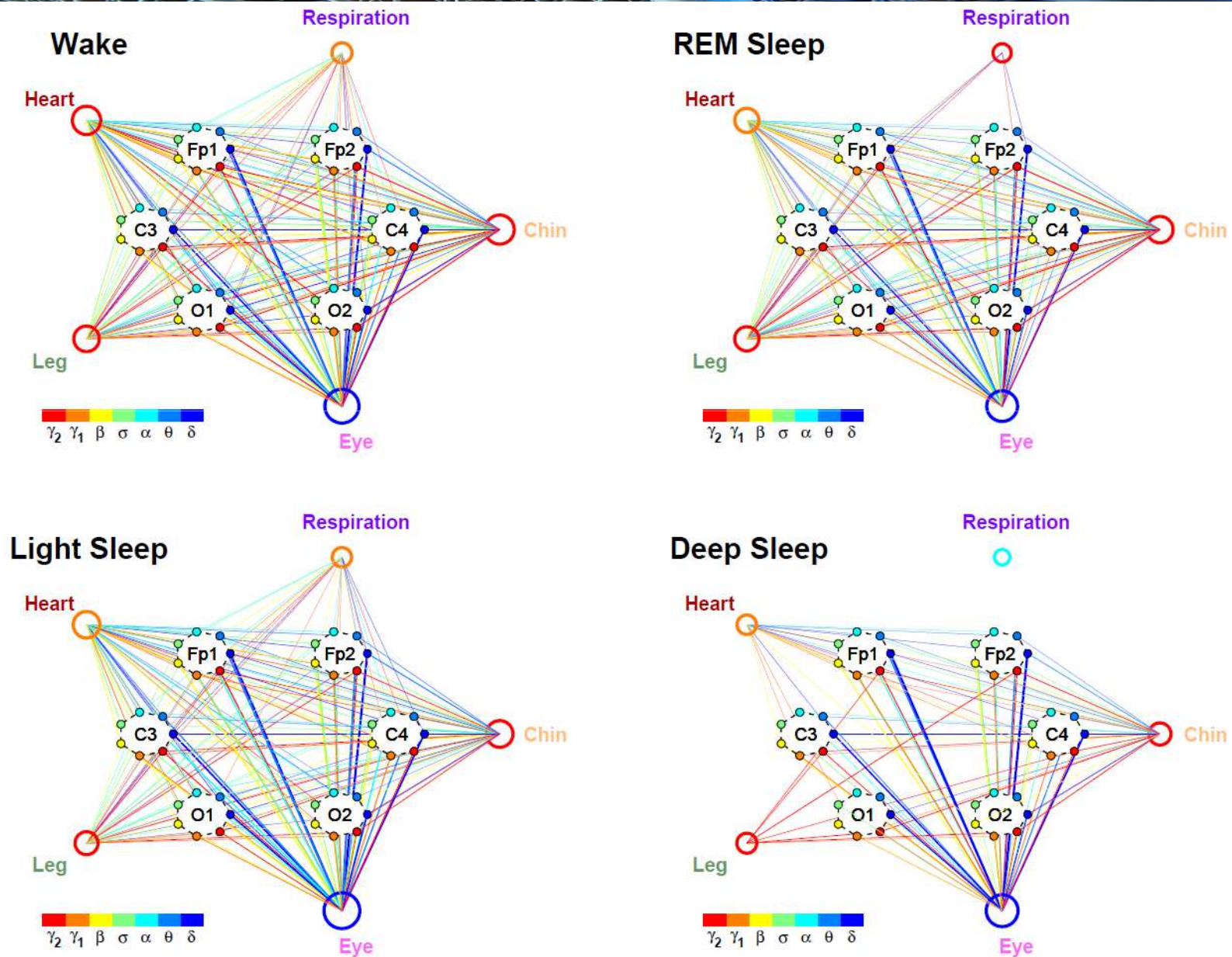
Visualization: different physiologic states



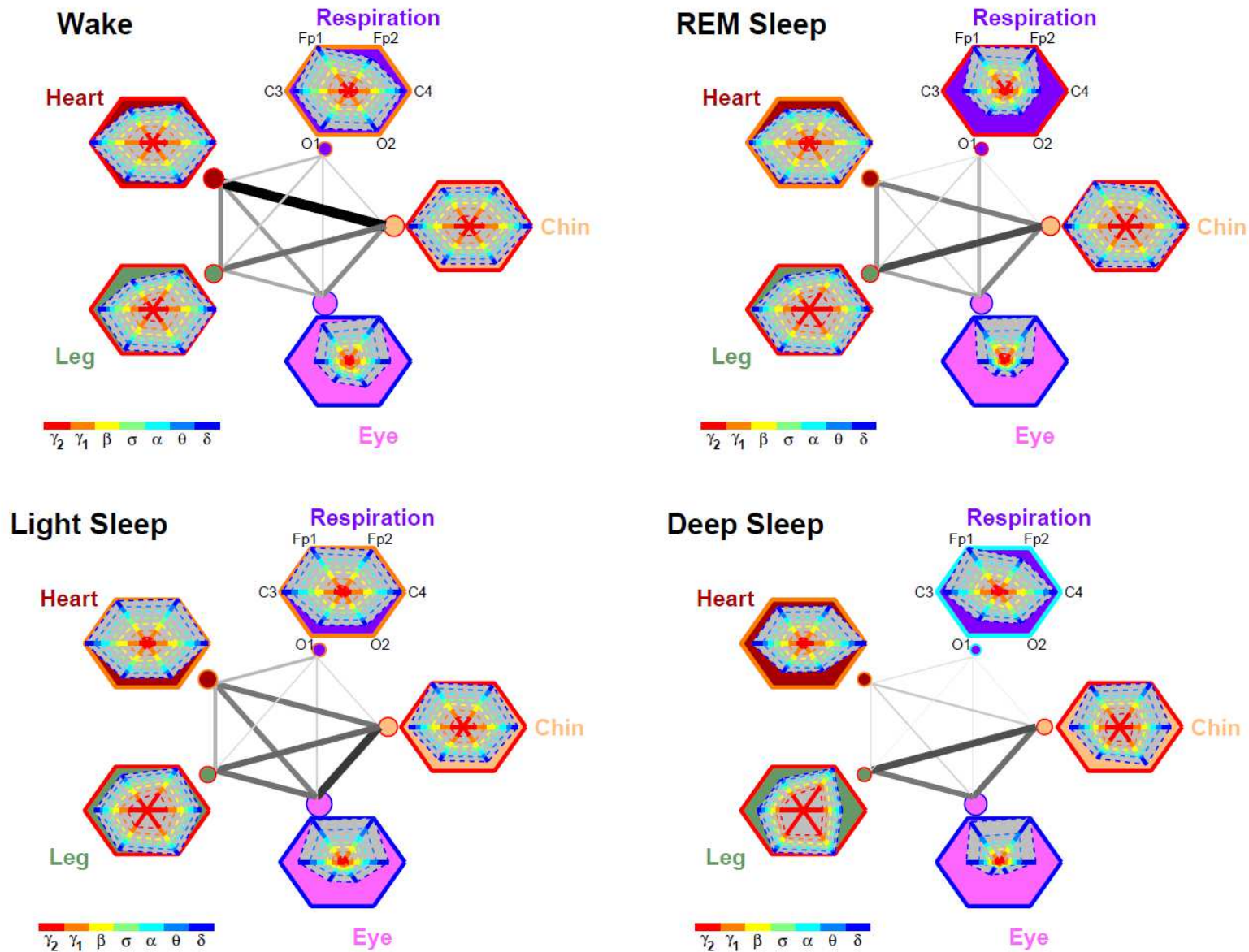
Maps for different organ systems



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

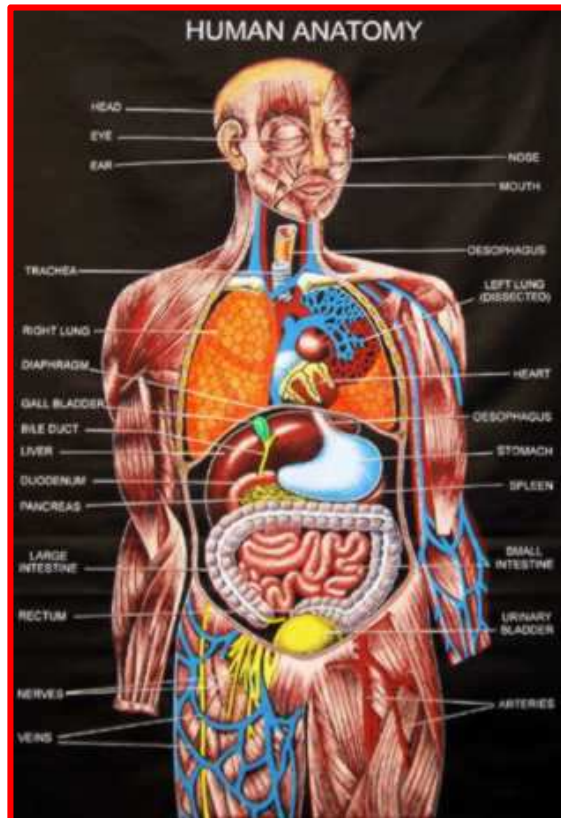


Vision

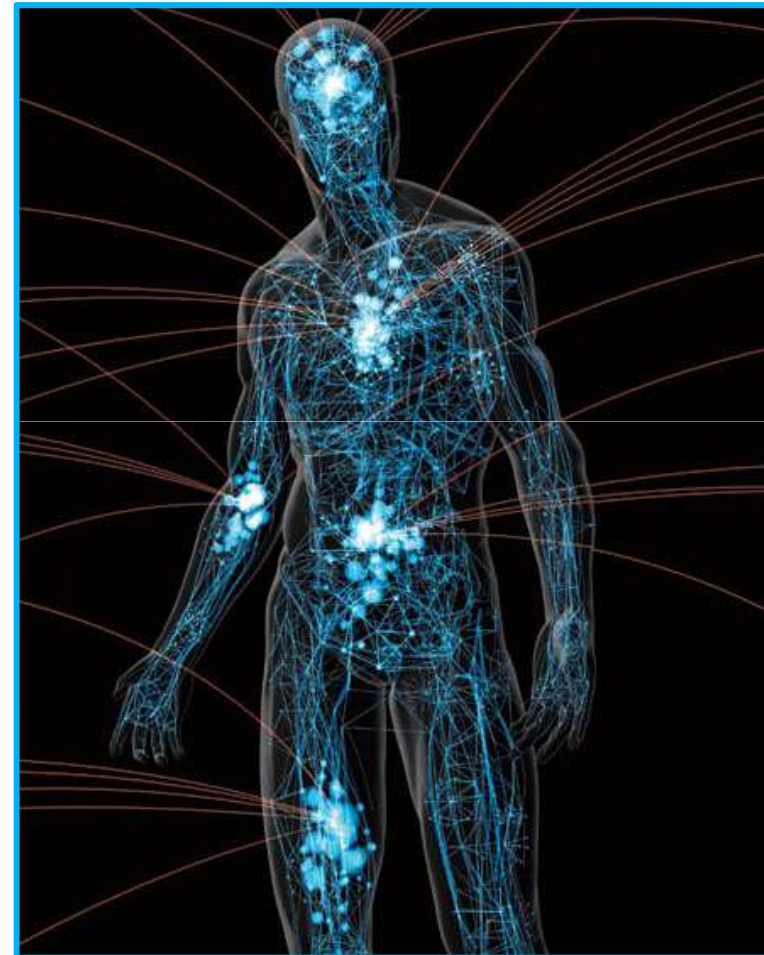
Physiology and Medicine

Atlas of Dynamic Interactions of Organ Systems

Atlas of Human Anatomy



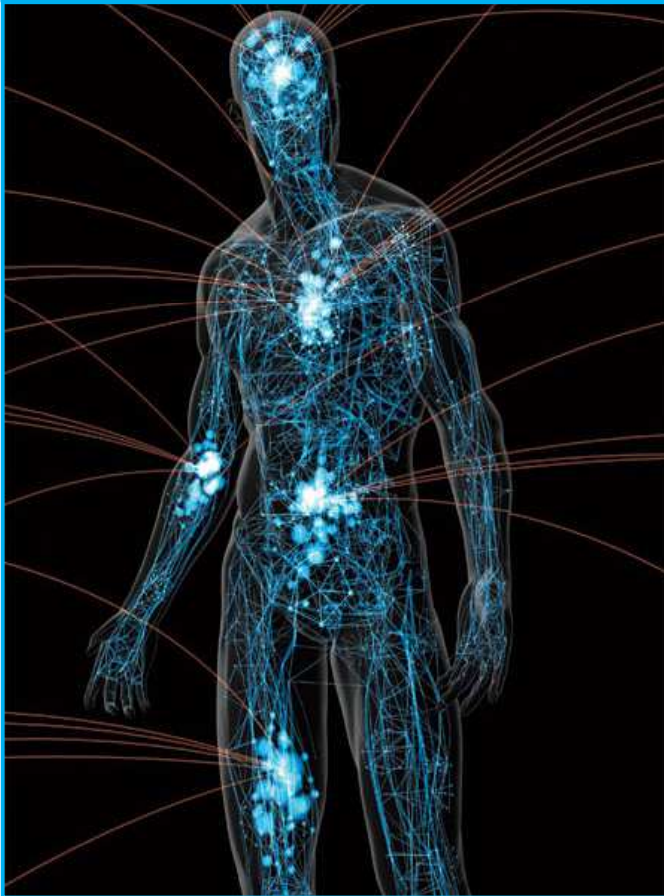
need
→



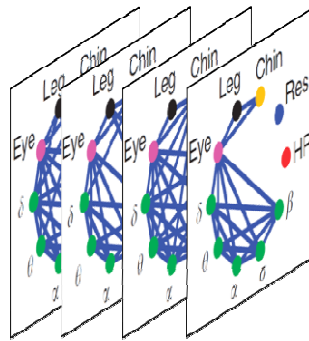
→ Revolutionize our knowledge and understanding of the fundamental mechanisms that regulate and coordinate organ-to-organ interactions

Such Atlas would contain:

Atlas of Dynamic Interactions of Organ Systems

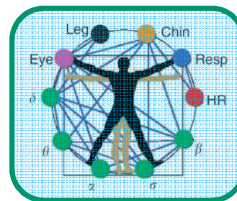


Catalog of reference maps representing dynamical organ interactions under:

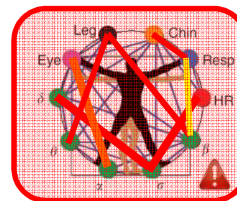


- healthy conditions
- age groups
- different physiologic states (rest/exercise, sleep/wake, sleep stages, circadian phases)
- pathological conditions (multiple organ failure, coma, heart failure, sleep apnea ...)

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

Vision
&
Impact

Physiology and Medicine

Novel biomarkers



New kind of Physicians



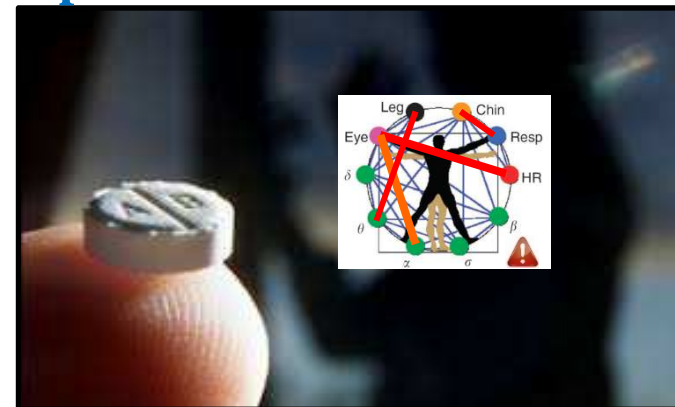
Personalized health monitoring



Next generation ICU monitoring devices and alert system



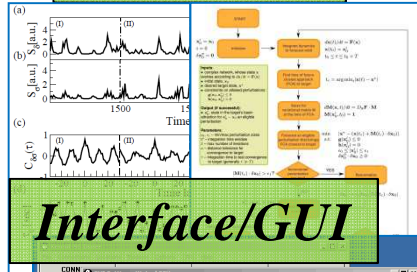
Comprehensive assessment of drugs



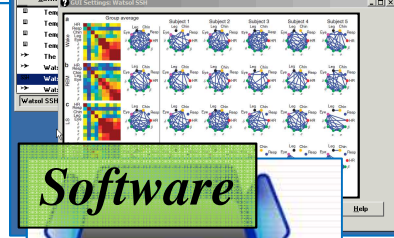
Impact

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

Algorithms



Interface/GUI



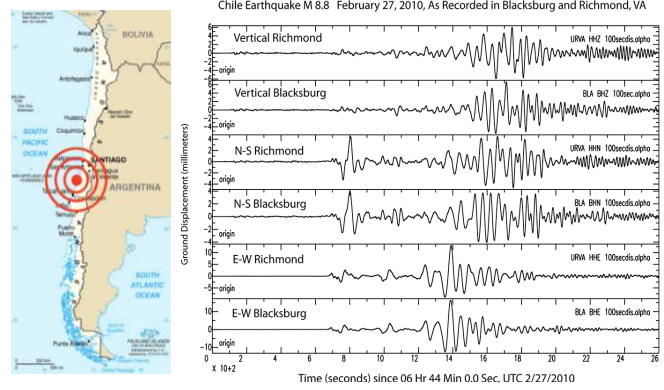
Software



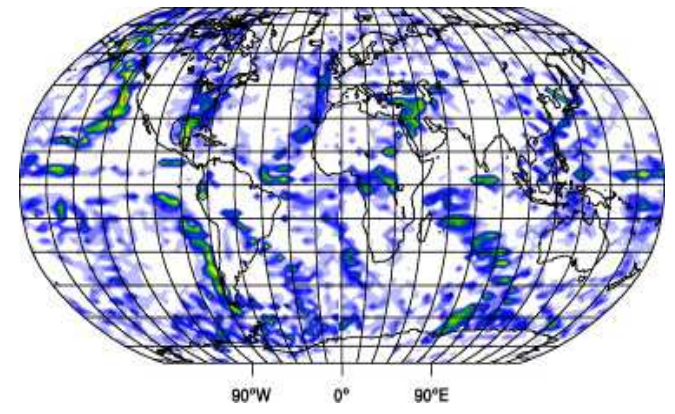
Toolbox



Geosciences



Climate

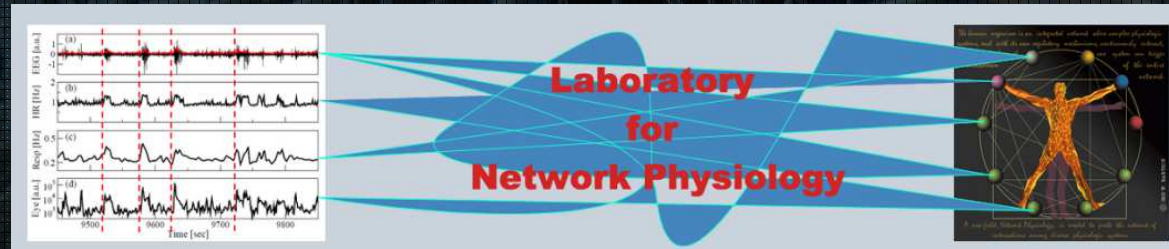


Economics/Finance



Plant Science





Our Group:

<http://physics.bu.edu/labnetworkphysiology>

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- **US–Israel Binational Science Foundation Grant**
- **Office of Naval Research (ONR Grant 000141010078)**

