The New Field of Network Physiology: Mapping the Human Physiolome

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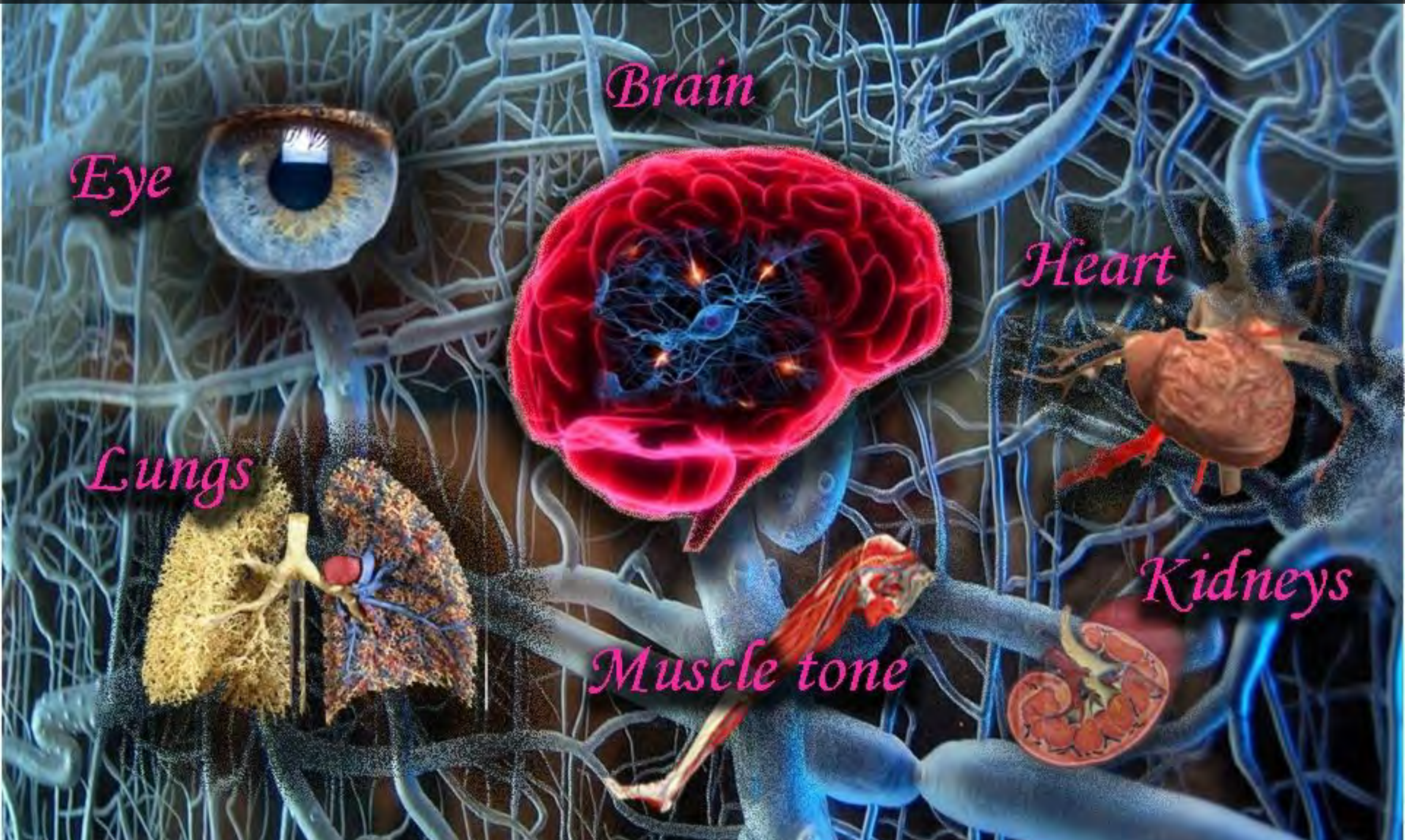
BOSTON UNIVERSITY

HARVARD MEDICAL SCHOOL

First International Summer Institute on Network Physiology (ISINP)

Lake Como School of Advanced Studies, 24 July - 29 July 2017

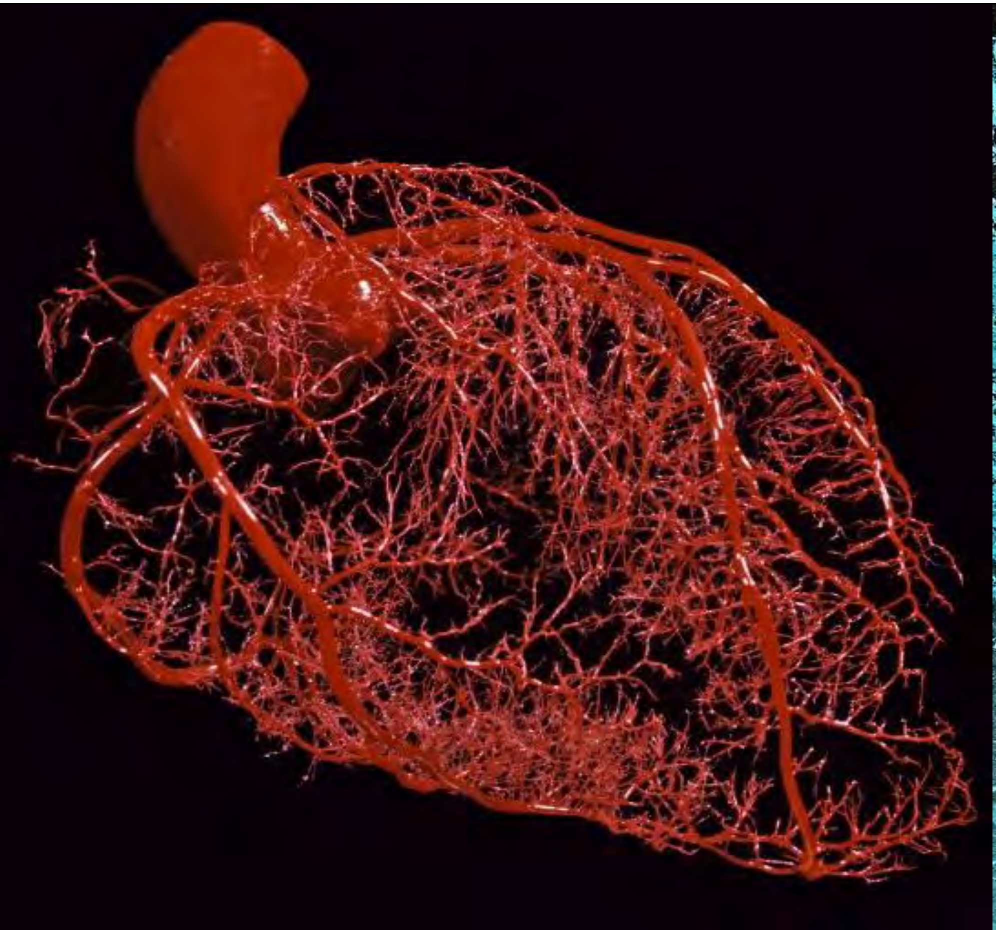
Human Organism
comprises diverse multi-component physiological systems

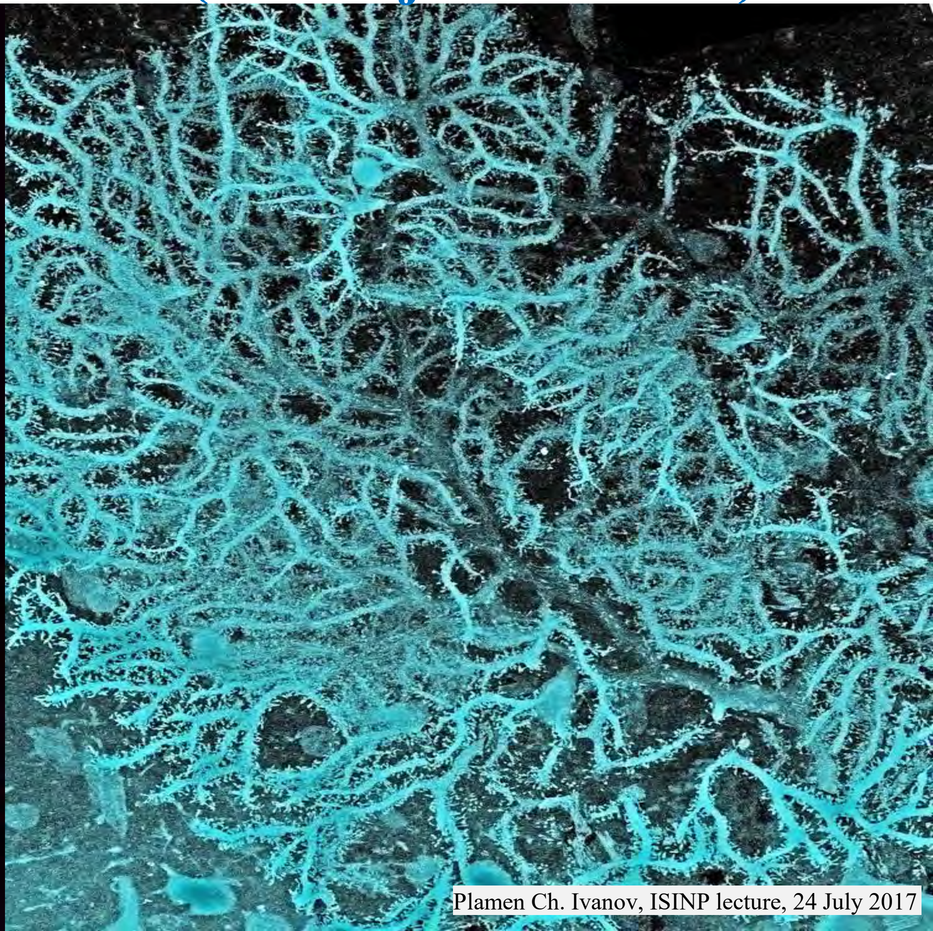


Human Organism
comprises diverse multi-component physiological systems

Heart: Vascular network

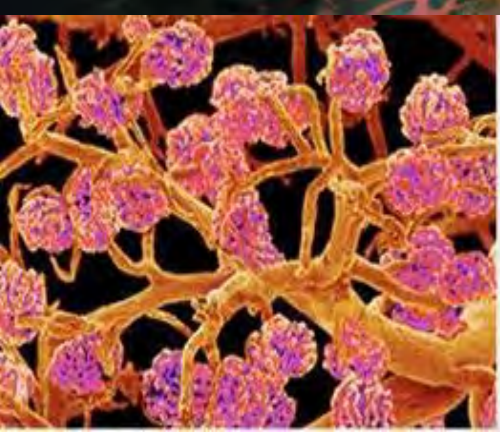
Conducting network (Purkinje dendrites)

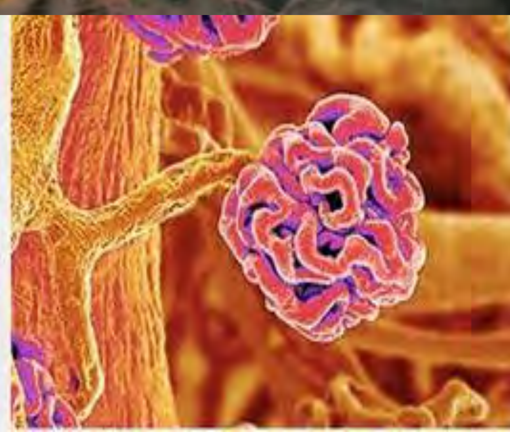




Human Organism
comprises diverse multi-component physiological systems

Kidney: **Vascular network in decreasing scale**





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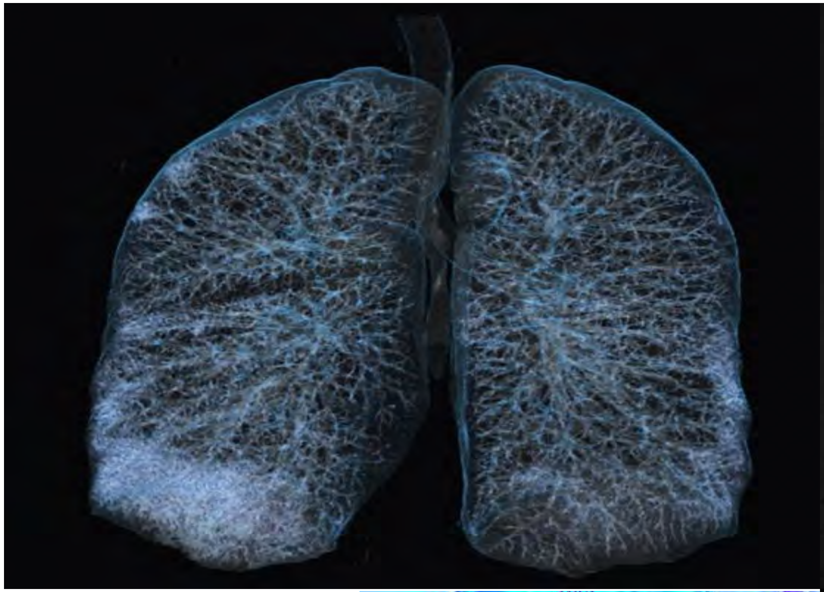
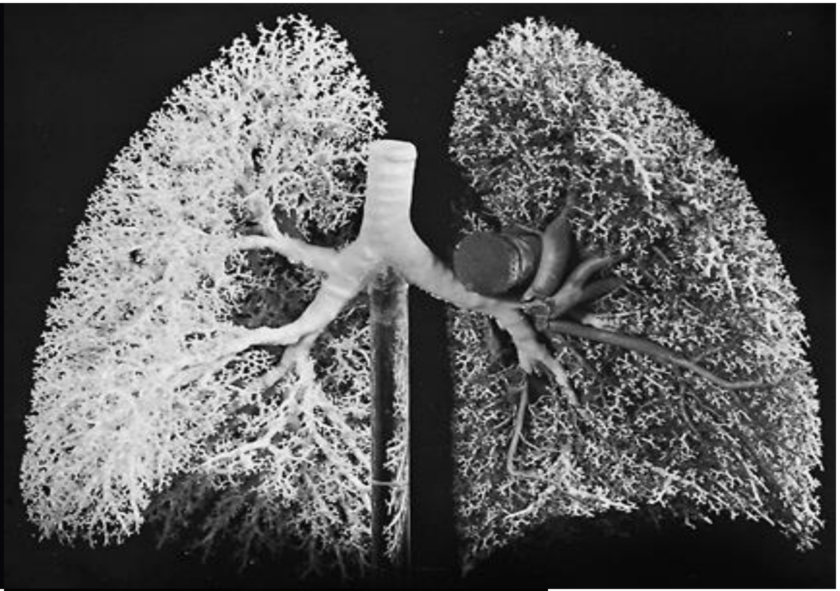
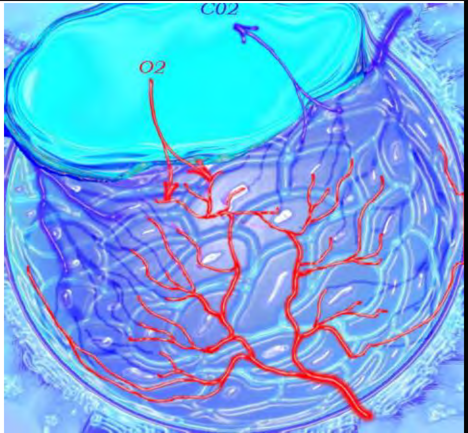
Human Organism
comprises diverse multi-component physiological systems

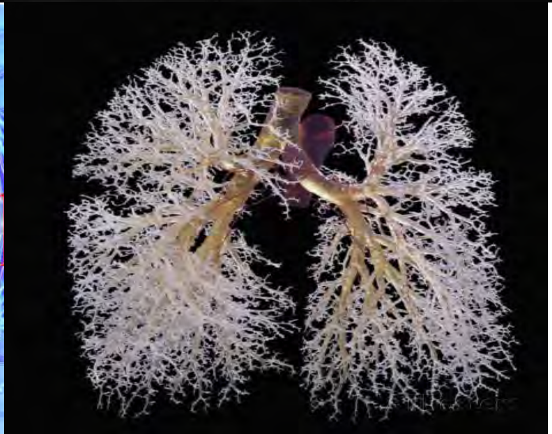
Lungs: High resolution image — Airways — Arteries and veins





Single alveolus vascular network





Bronchial tree

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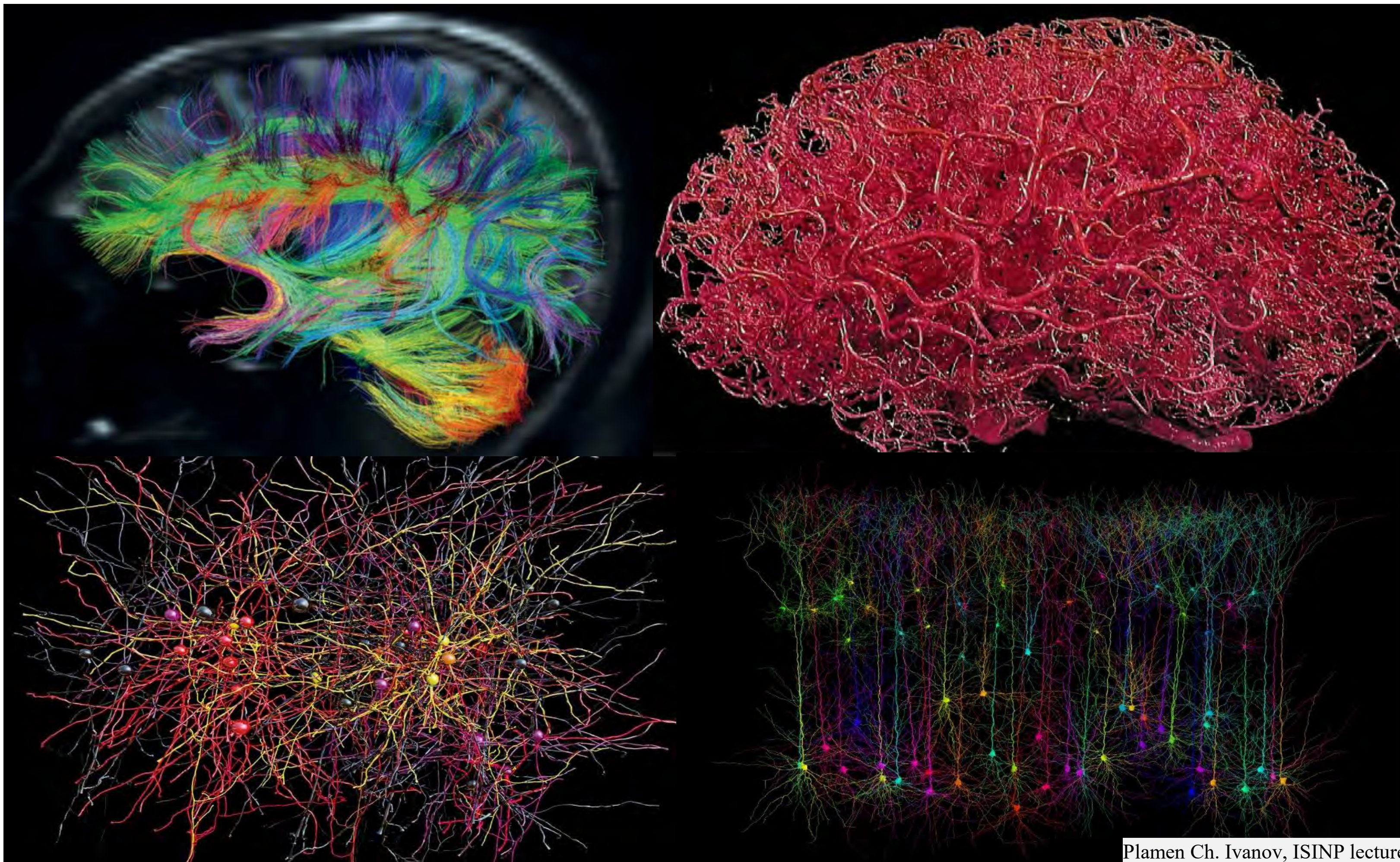
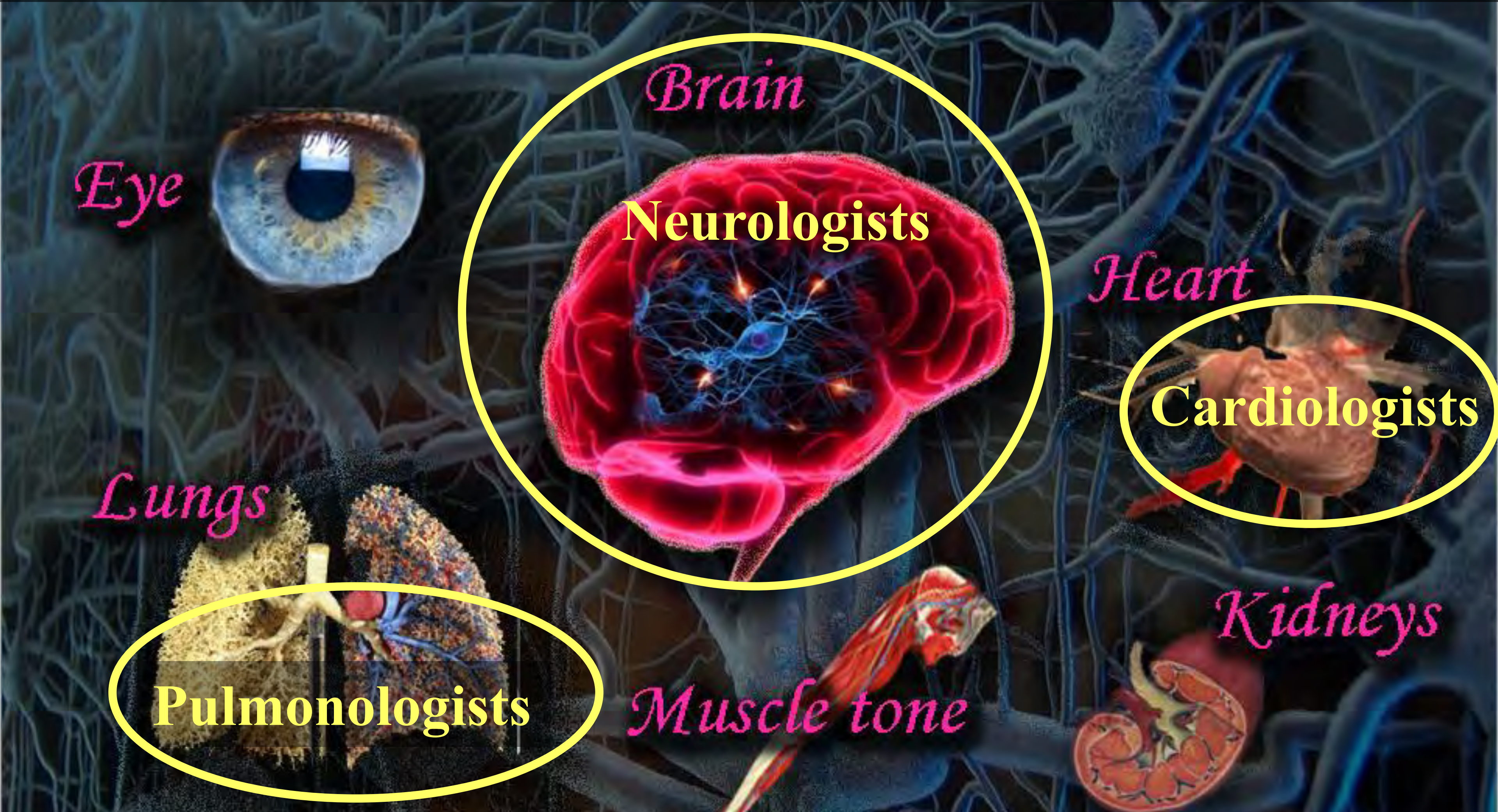
Human Organism
comprises diverse multi-component physiological systems

Brain: Neuronal and vascular network



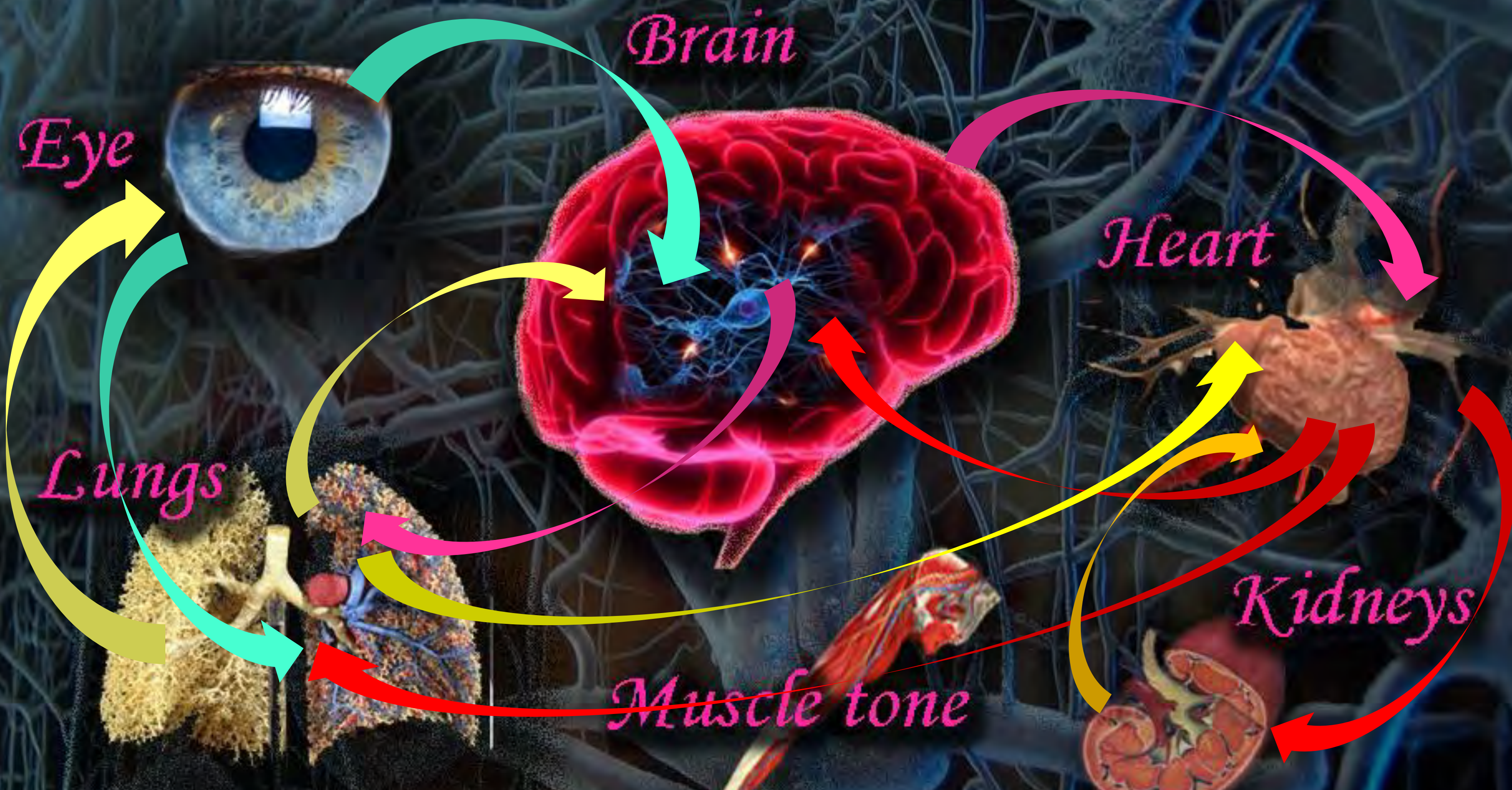
Human Organism

comprises diverse multi-component physiological systems



Medical specialists traditionally focus on <u>*single*</u> organ systems

Human Organism – Integrated Network
Coordinated Interactions of Organ Systems



Essential to: Maintain Health
Generate distinct physiological states

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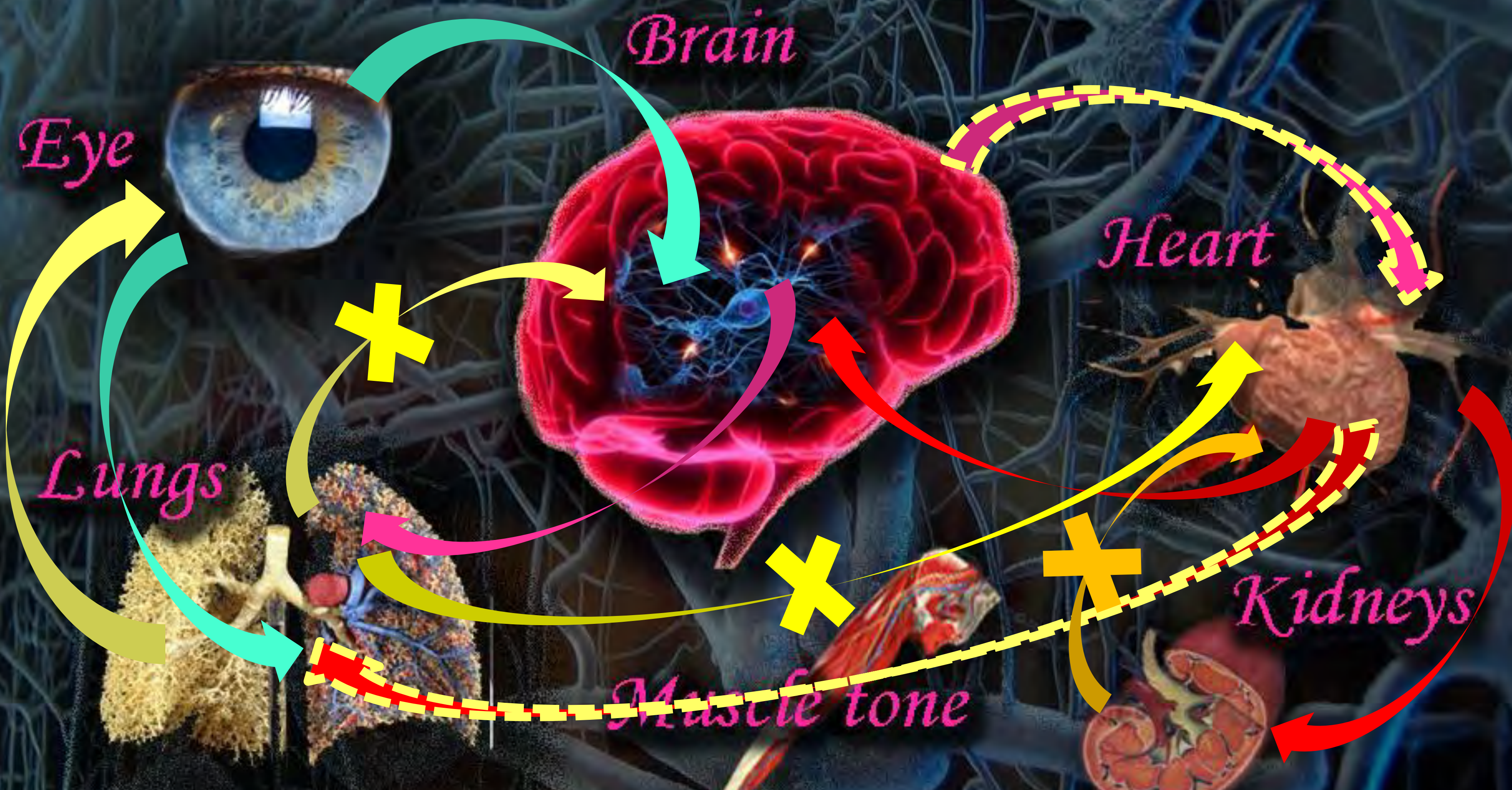
ISINP lecture,
24 July 2017

Disrupted Communications among Organ Systems



Leads to: 1. Dysfunction of individual systems
2. Collapse of the entire organism

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ISINP lecture,
24 July 2017

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 **!**

⬇

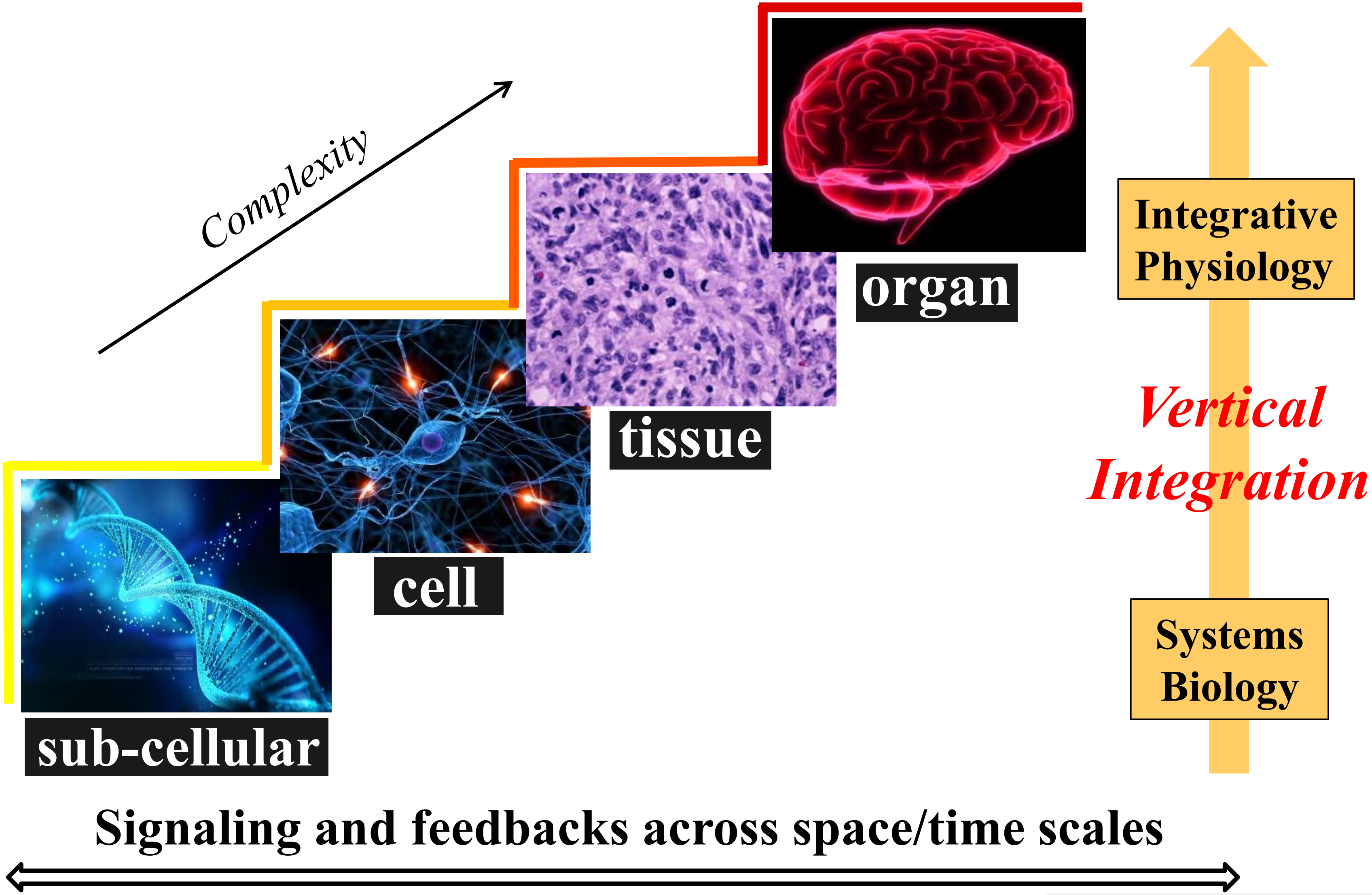
Broad *clinical implications*: Coma, Multiple Organ Failure

Yet, despite the importance to:

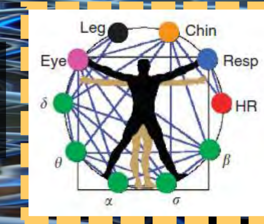
- **understanding basic physiologic functions**
- **clinical relevance**

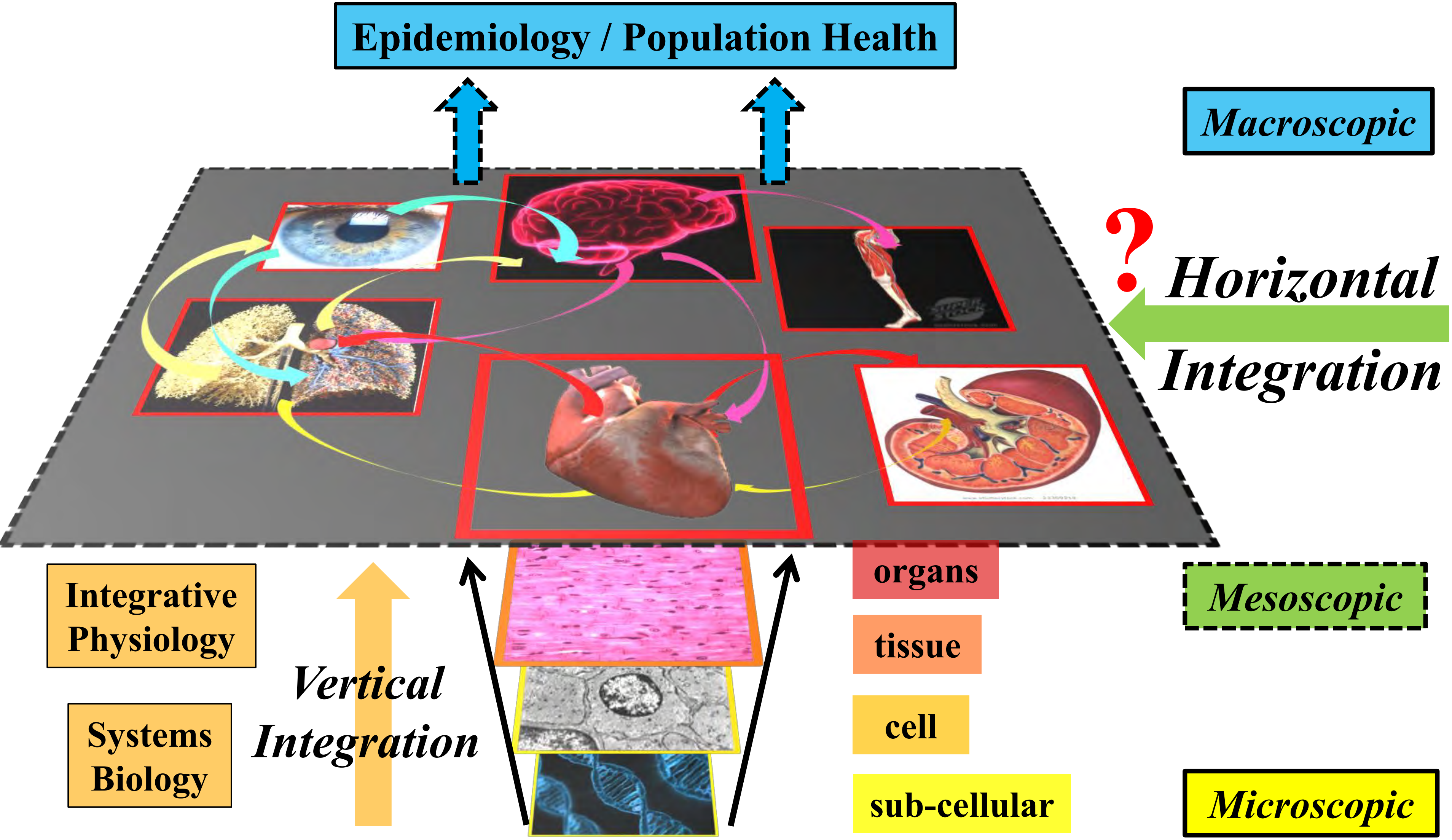
? **we do not know how organ systems dynamically interact as a network to coordinate and optimize their functions**

Current Research Focus of Systems Biology and Integrative Physiology



Our Research Focus: Horizontal Integration

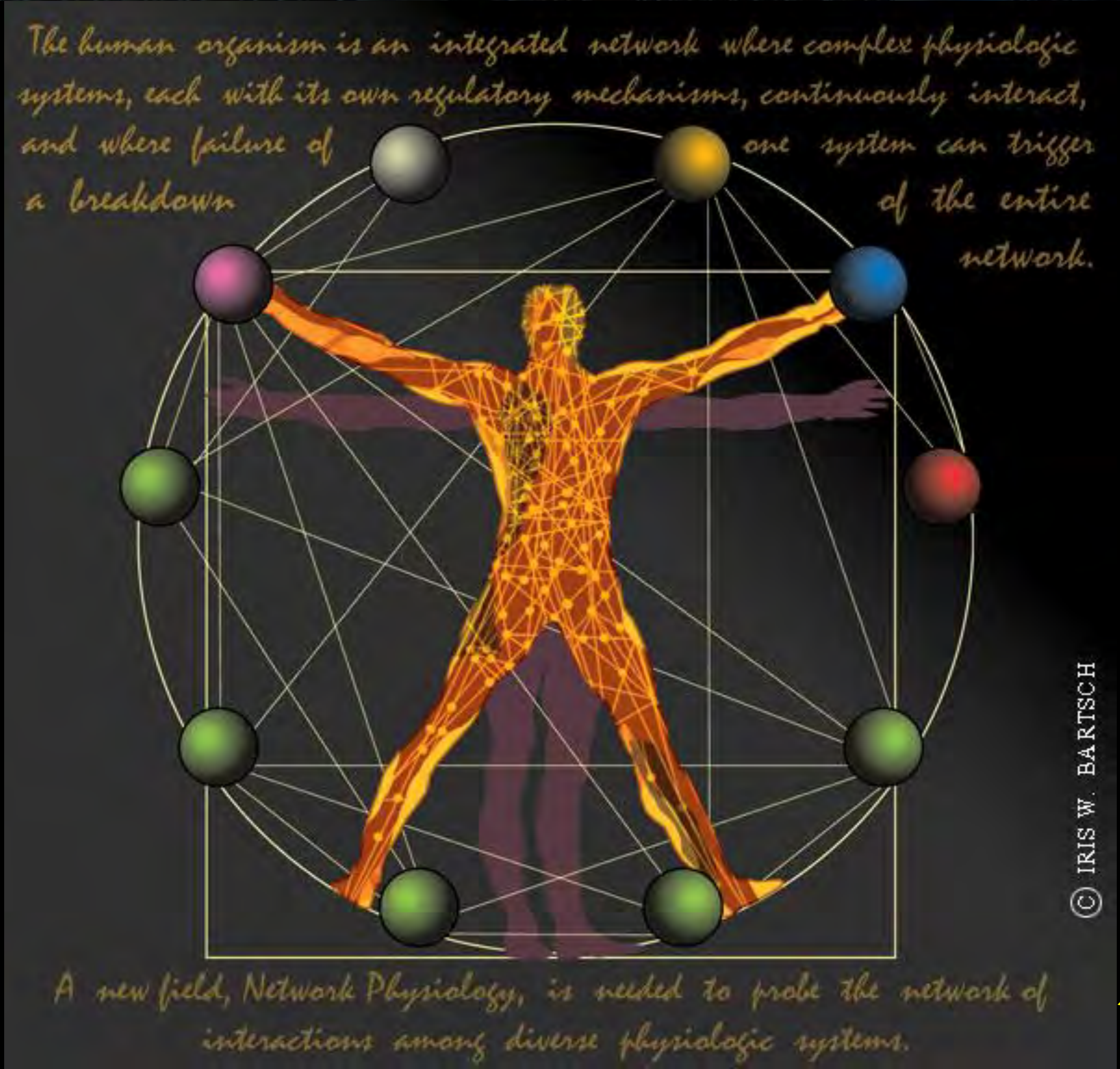




Our Research Program

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"

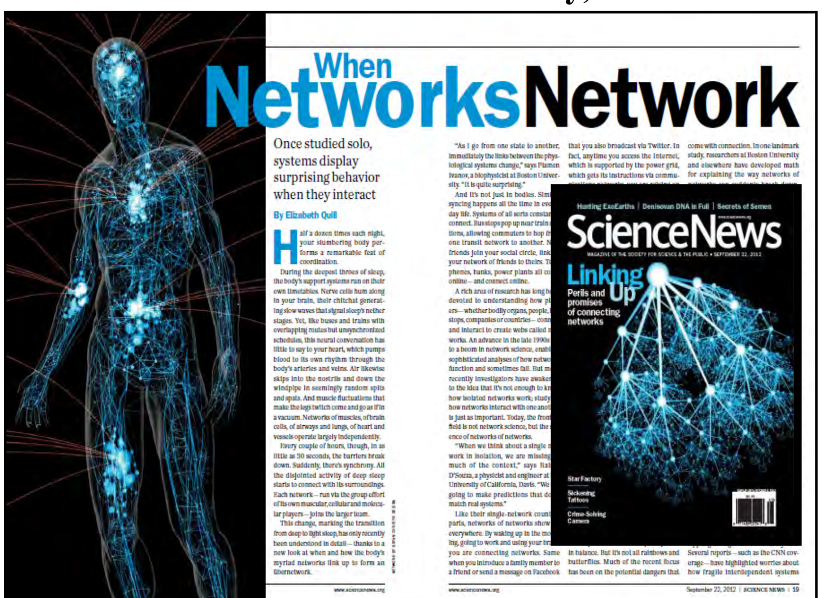
nature COMMUNICATIONS

Generated Broad Interests in the Community

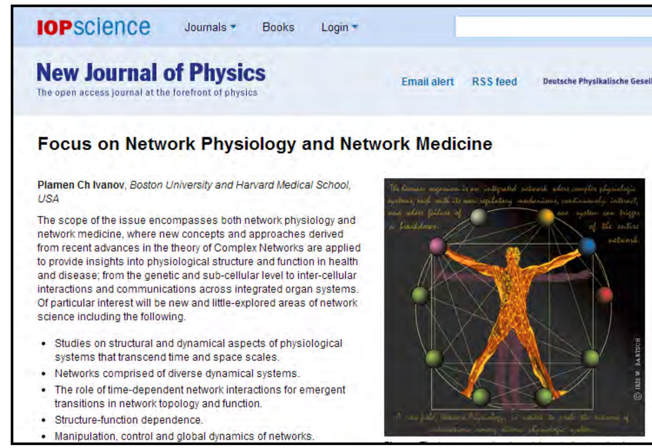
1st Symposium on Network Physiology and Medicine, Oct. 2012

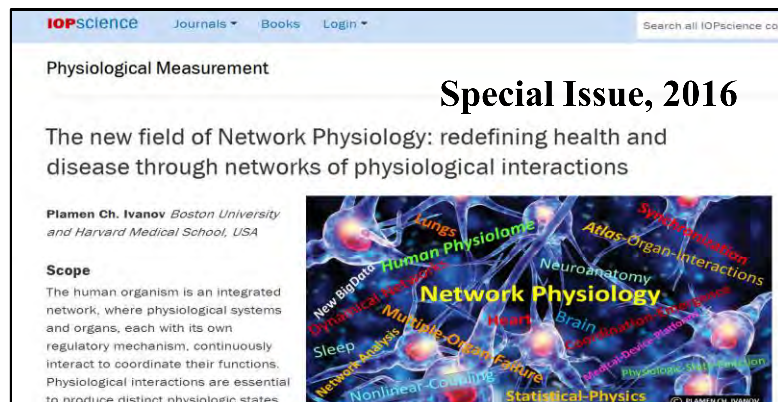
HARVARD CATALYST | THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Science News Cover Story, 2012



Special Issue, 2014





Level 1: Individual Systems

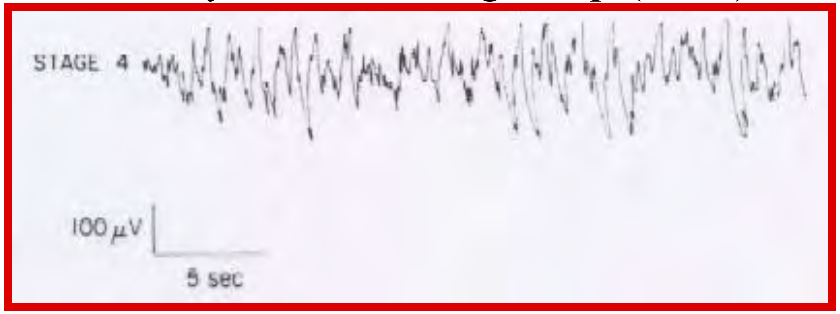
Complex Variability in Physiologic Dynamics across spatio-temporal scales and levels of integration

Is Physiologic Variability simply Noise?

Complexity

organs

Brain dynamics during sleep (EEG)

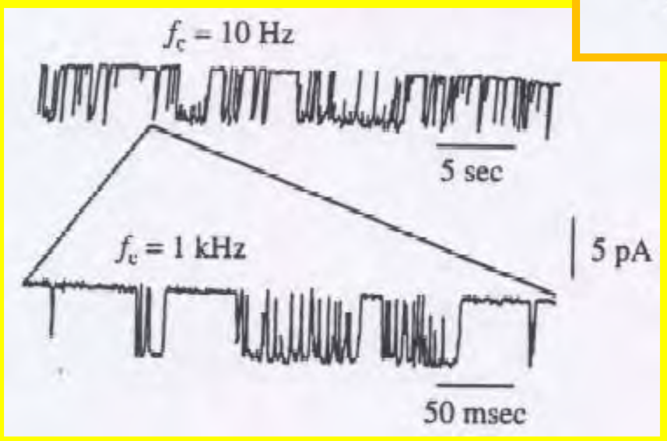


cell

Single neuron activity

sub-cellular

Ion channel kinetics



New Concept: Fluctuations are *not* noise !

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

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

Level 3: complex global behaviors out of interactions among diverse systems

To address these Challenges:

- introduce new concepts
- innovate interdisciplinary approaches
- develop new methods and technology
- analyze continuous physiologic recordings

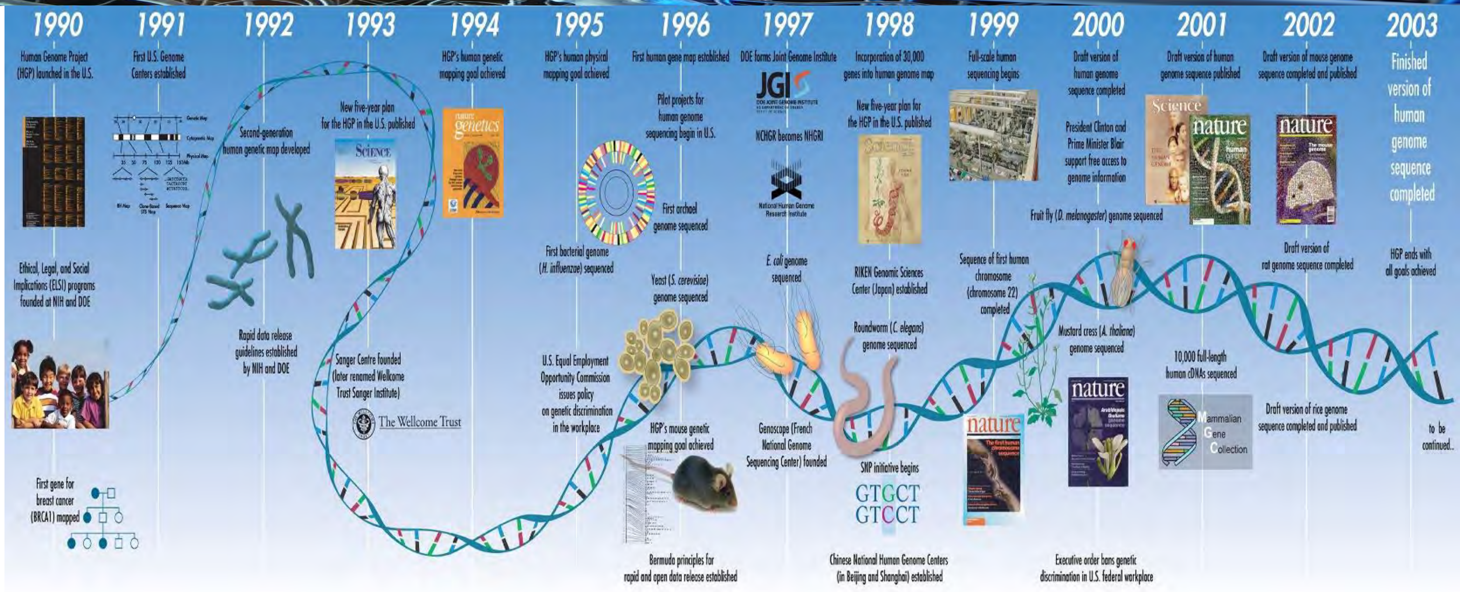
led to

Data-Driven Discoveries

- Physiology
- Stat. Physics
- Applied Math
- Computer Sci.

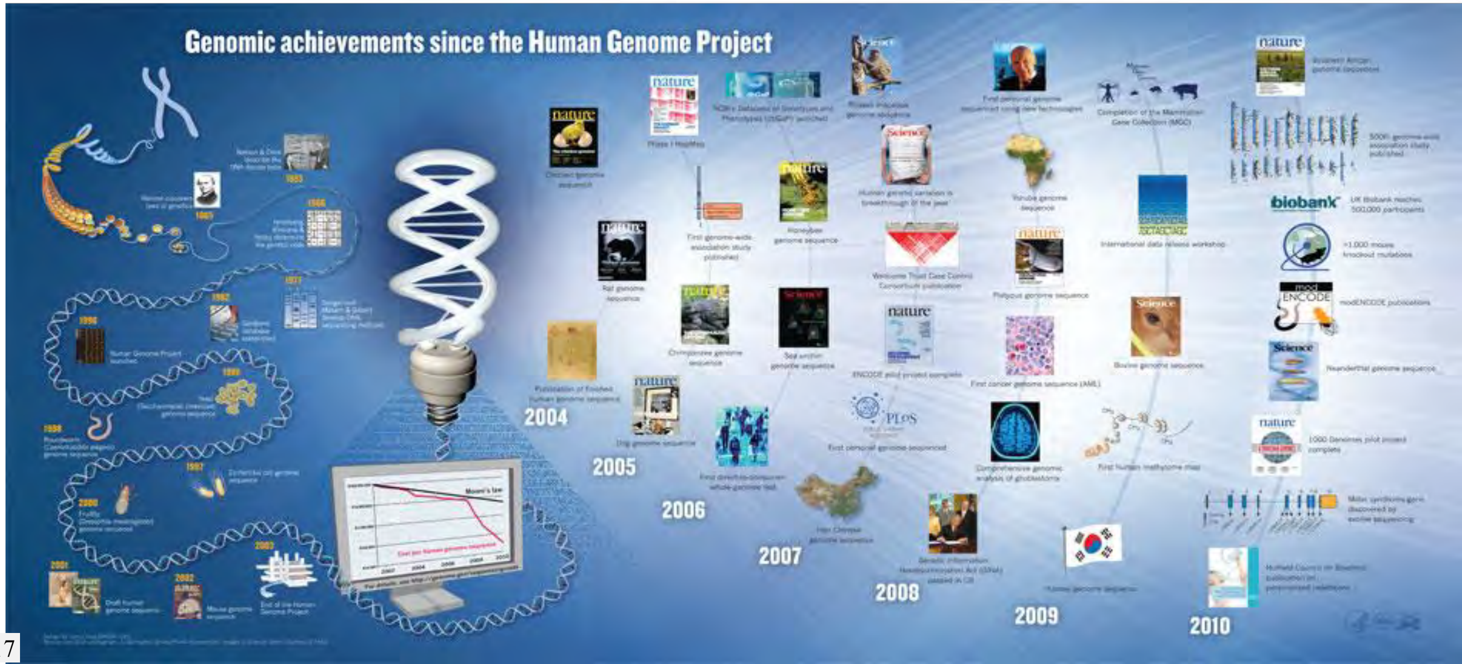
Big Data

Systems Biology: mapping the Human Genome



Before
Human Genome Project

3 Billion
DNA base pairs



After
Human Genome Project

Big Data

Network Physiology

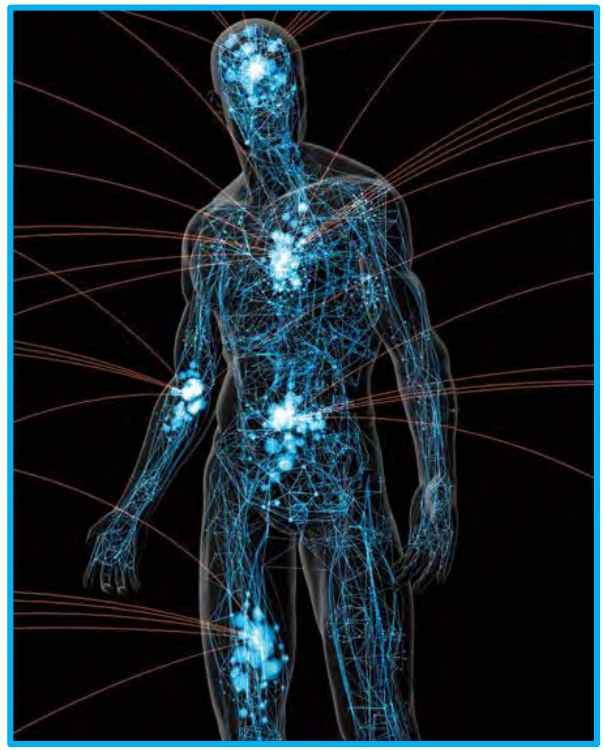
Human body produces gigantic amount of Data & Information
Continuous streams of waveforms and physiologic parameters

brain → EEG, MEG, fMRI

heart → Blood Pressure, ECG

body temperature → Core, Brain, Peripheral

muscles → EMG



liver → Albumin, Phosphatase, GGT

lungs → CO_2, O_2, Tidal Volume

hormones → Oxytocin, Dopamine, Serotonin

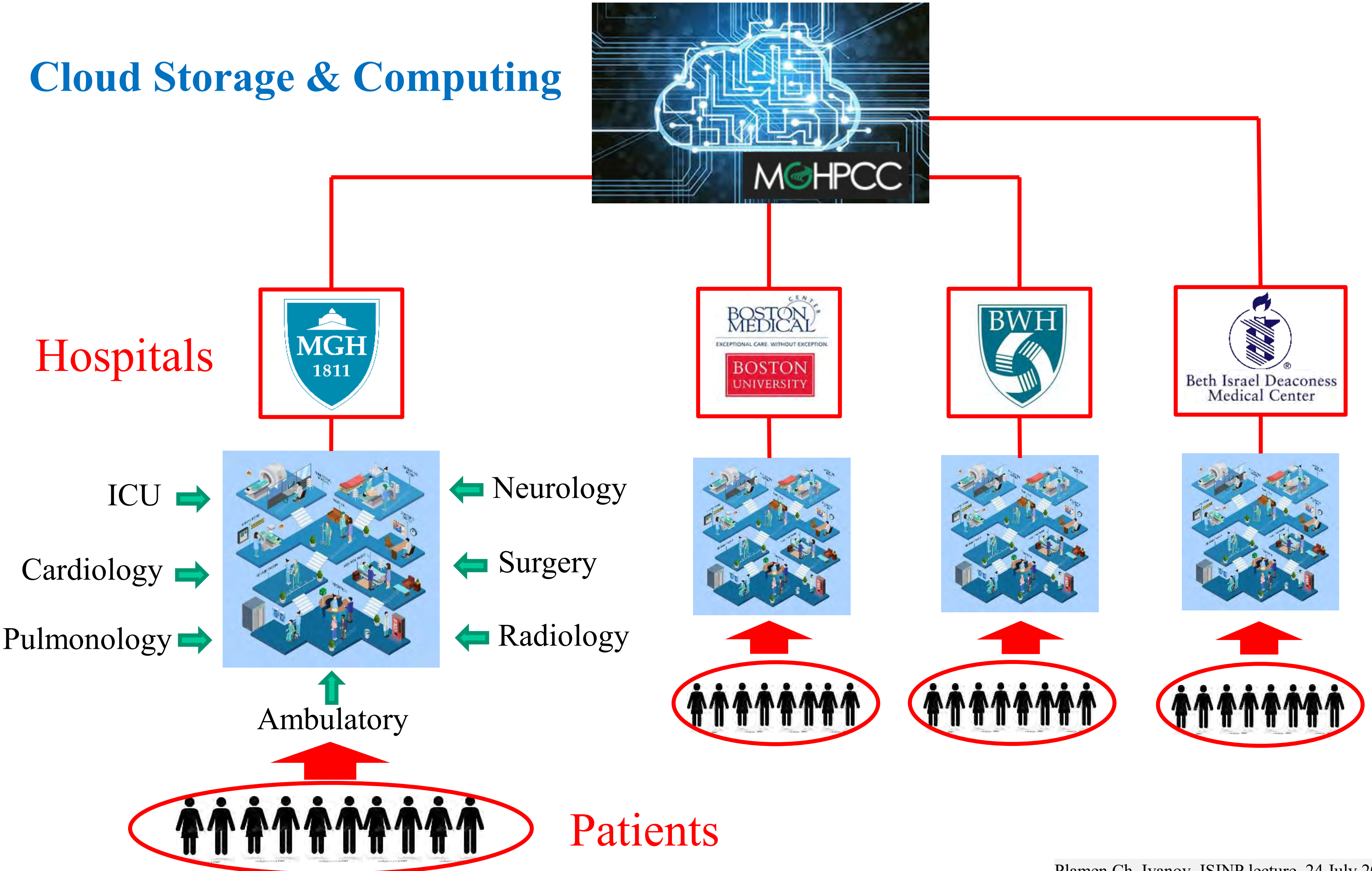
kidneys → Blood flow, Urinalysis, Creatinine

High frequency recordings (10^2-10^3Hz)
Number of data points per person:
(just for 100 parameters)

1 Day	1 Year	Life Time
~10^{10}	~10^{12}	~10^{14}

Network Physiology

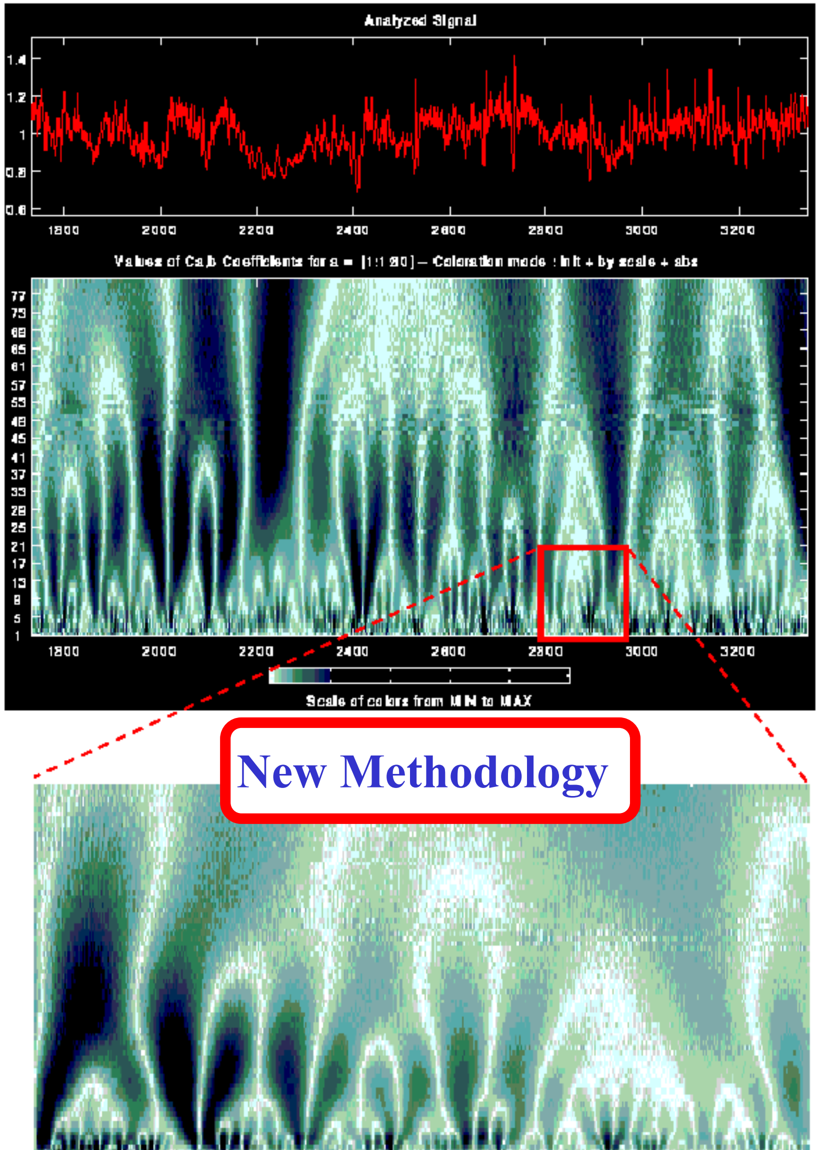
Novel principles of integrating physiological data & metadata



Scale-invariance in heartbeat fluctuations

Self-similar cascades

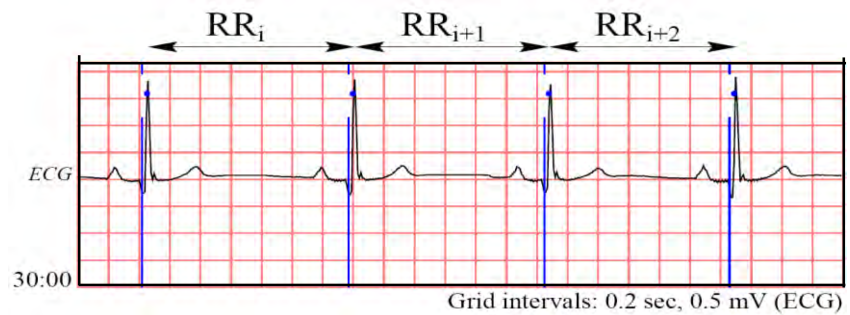
Heart rate data

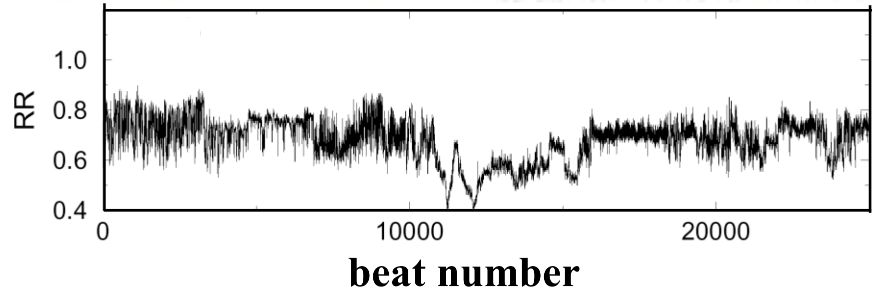


Scale of Analysis

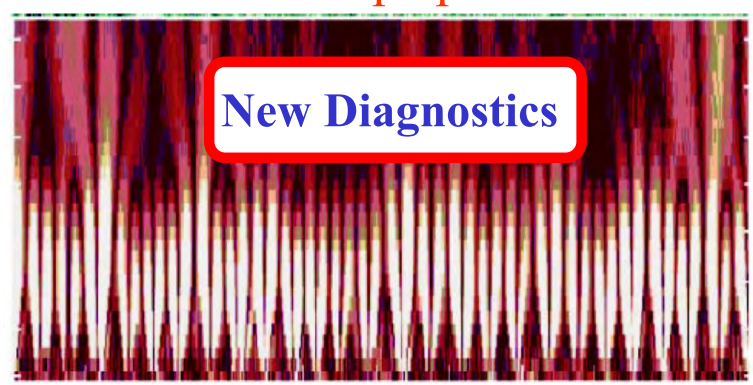
New Methodology

Time





Sleep apnea



New Diagnostics

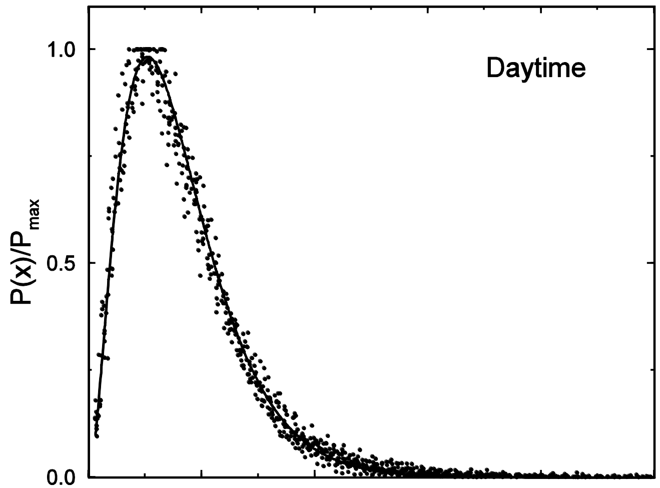
P.Ch. Ivanov *et al. Wavelets in Physics,* (Cambridge Univ. Press, 1998).

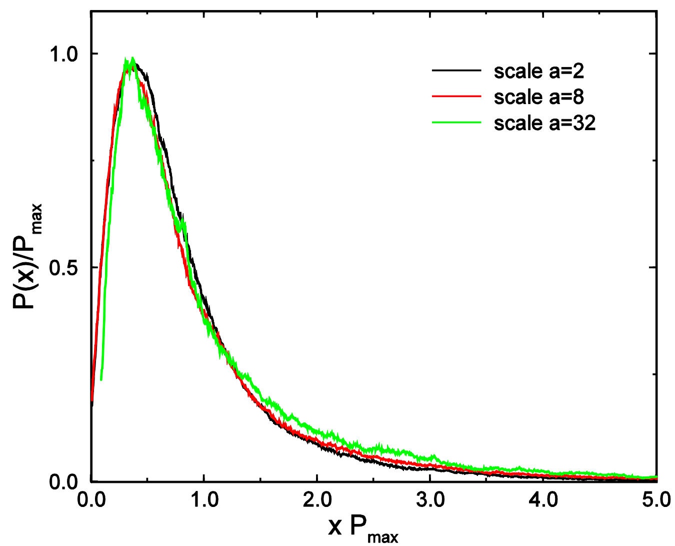
Scale-invariance in heartbeat fluctuations

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

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

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

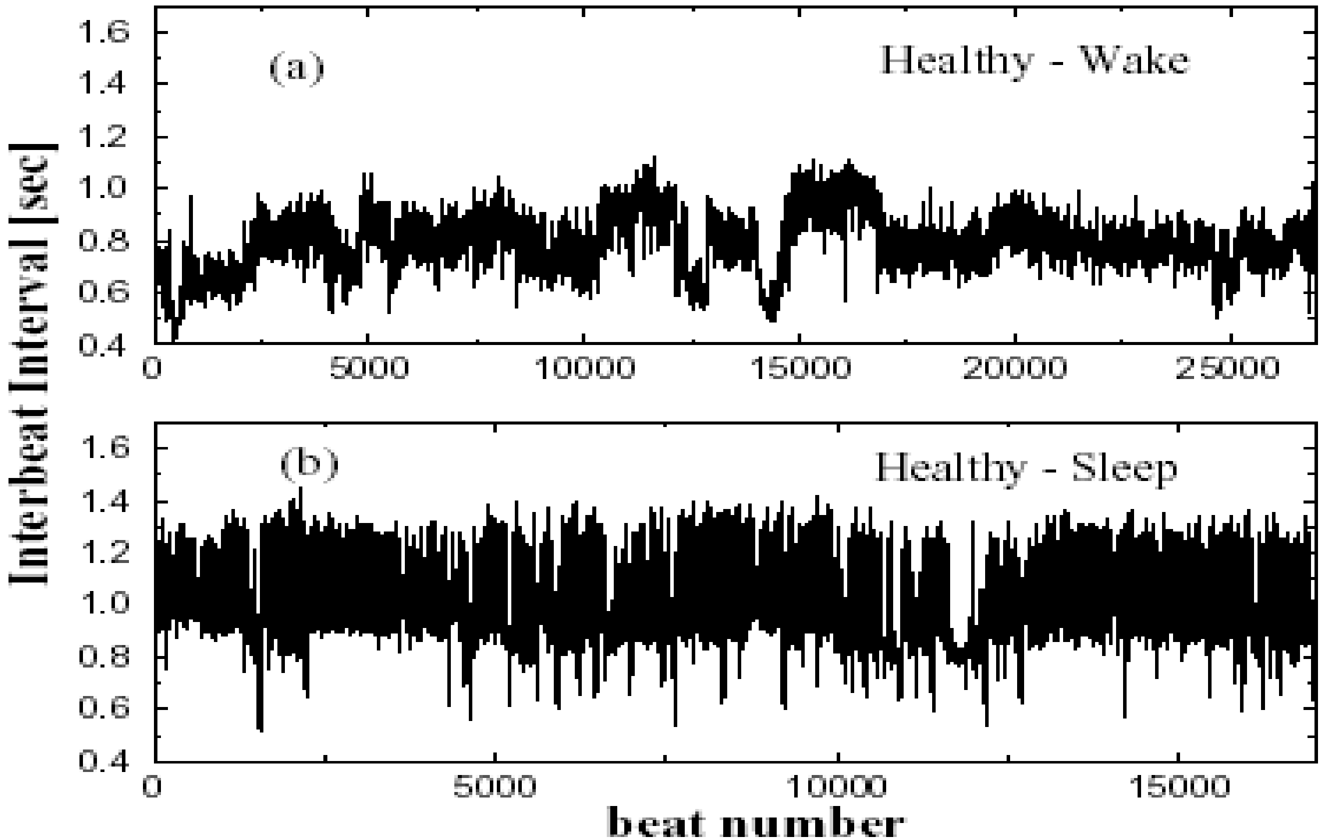
Scale-invariance

"data collapse" over a range of time scales

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

Scale-invariance in heartbeat fluctuations

Heartbeat fluctuations during sleep and wake

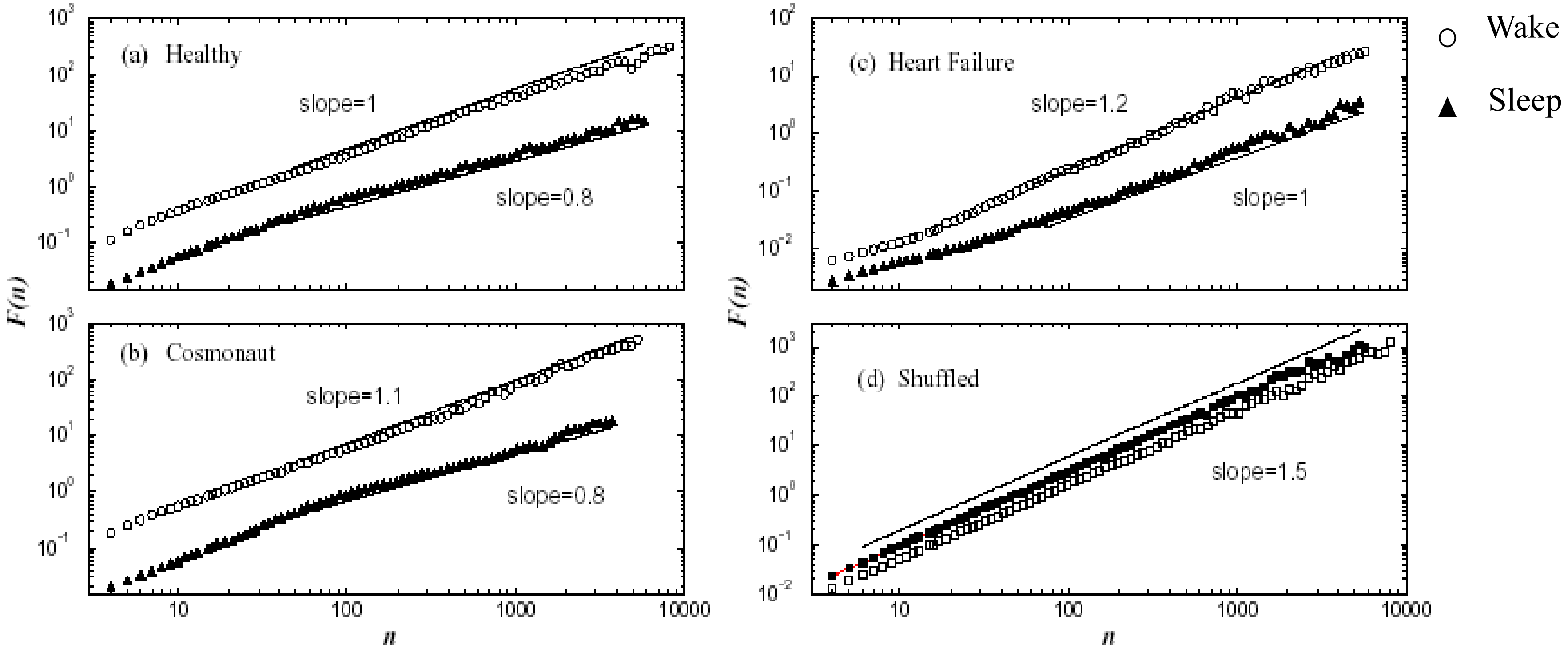


Average RR_{Sleep} > Average RR_{Wake}

SD_{Sleep} > SD_{Wake}

Scale-invariance in heartbeat fluctuations

Scaling difference in heartbeat dynamics during sleep and wake



Healthy: $\alpha_{Wake} \approx 1$

$\alpha_{Sleep} \approx 0.8$

Heart failure: $\alpha_{Wake} \approx 1.2$

$\alpha_{Sleep} \approx 1$

P.Ch. Ivanov *et al. Europhys. Lett.* **48**: 594 (1999).

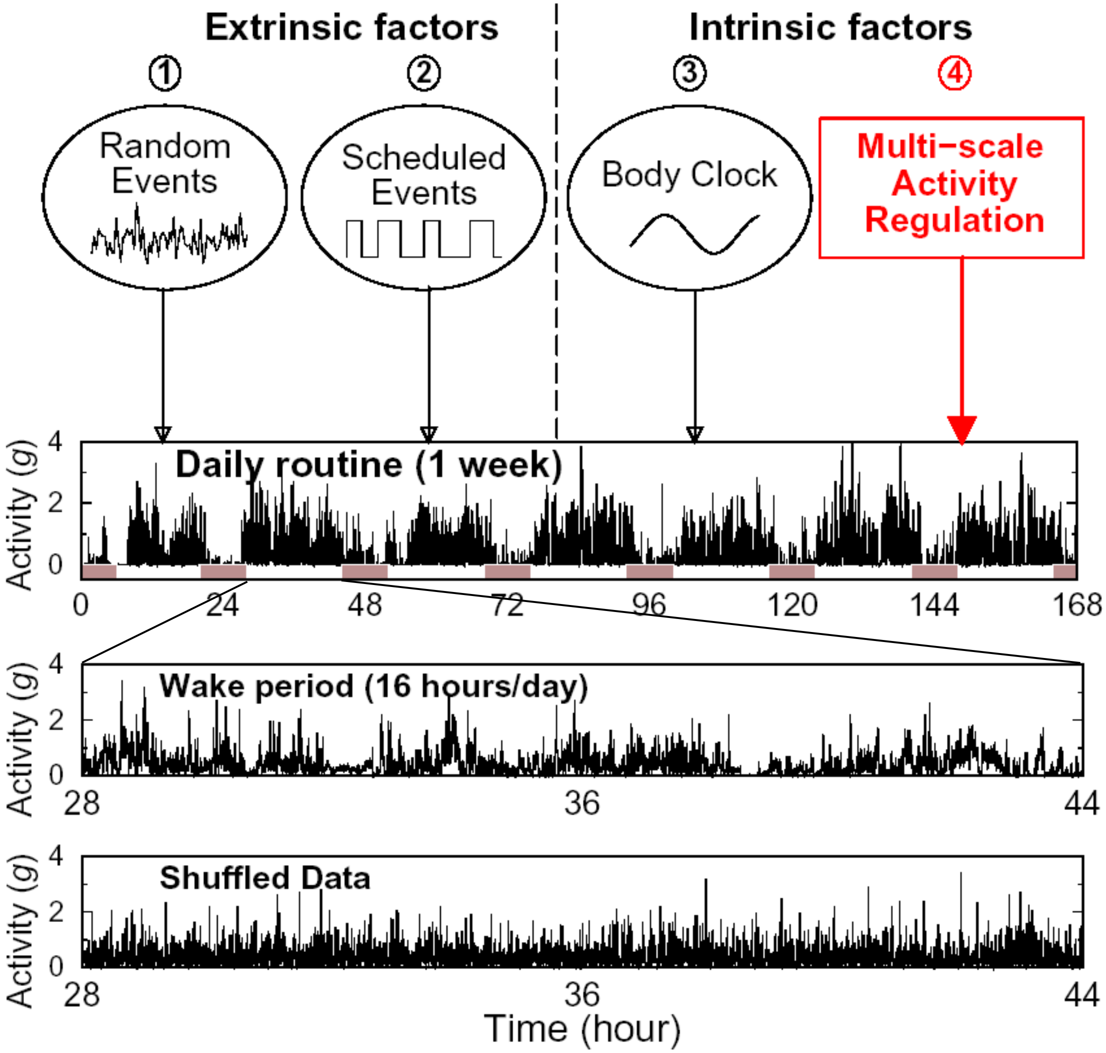
Locomotor system dynamics

Motor Activity: Wrist motion fluctuations

Motivation:

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

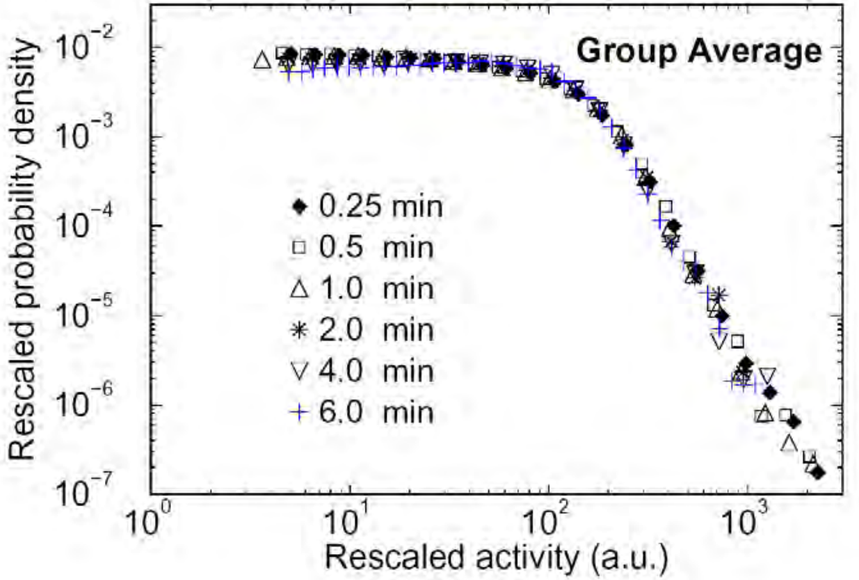
Magnitudes of wrist acceleration

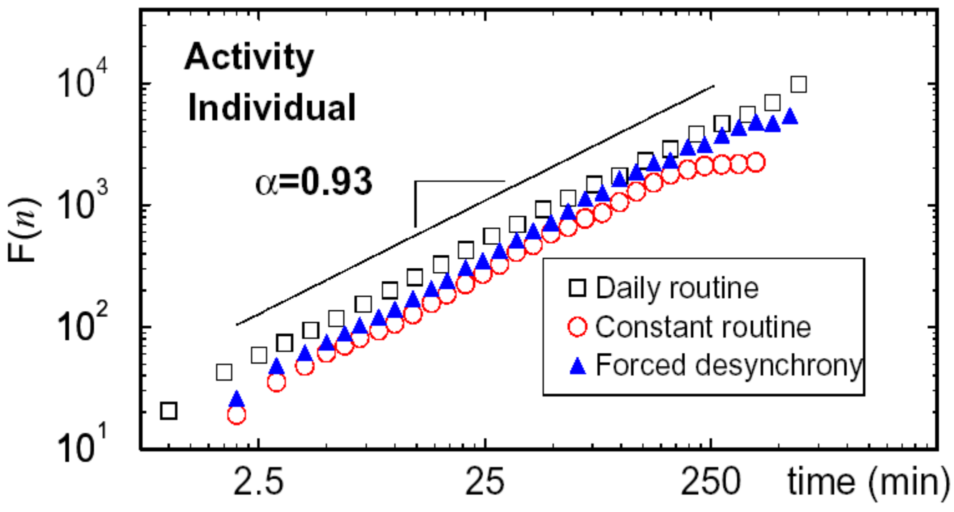


Level 1: Individual Systems

Locomotor system dynamics

Motor Activity: Wrist motion fluctuations





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

- Long-range correlations
→ long-term memory

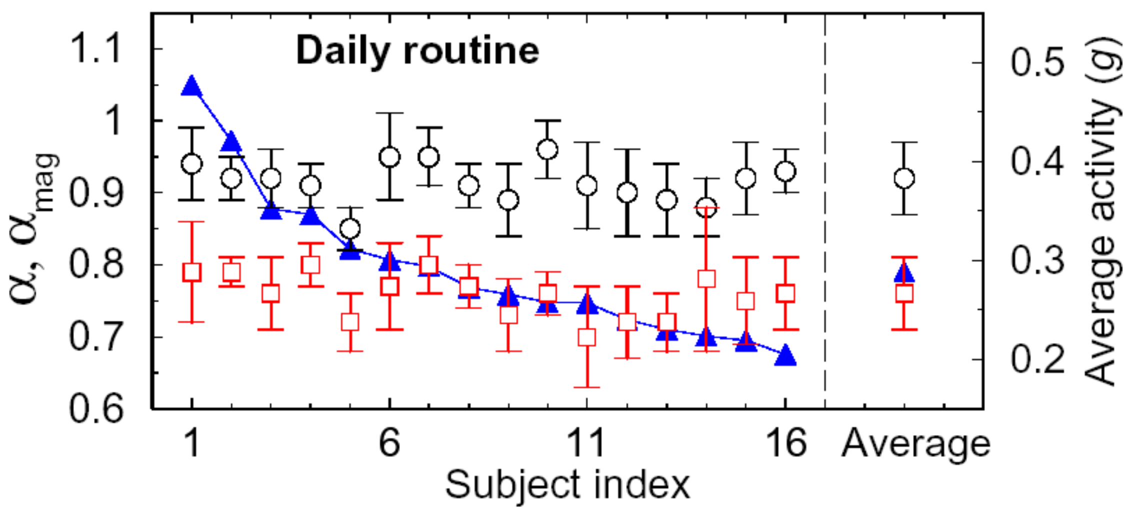
Discovery: **Universal scale-invariant organization in human activity fluctuations**

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).

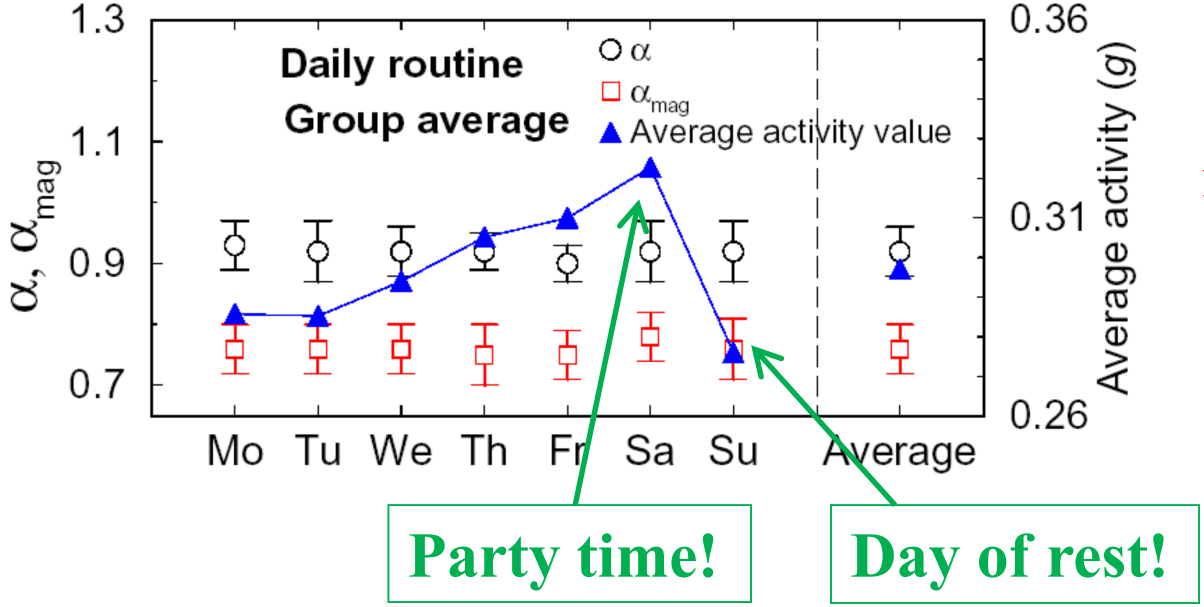
Smart wristband

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.

Level 3: Networked Interactions

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:

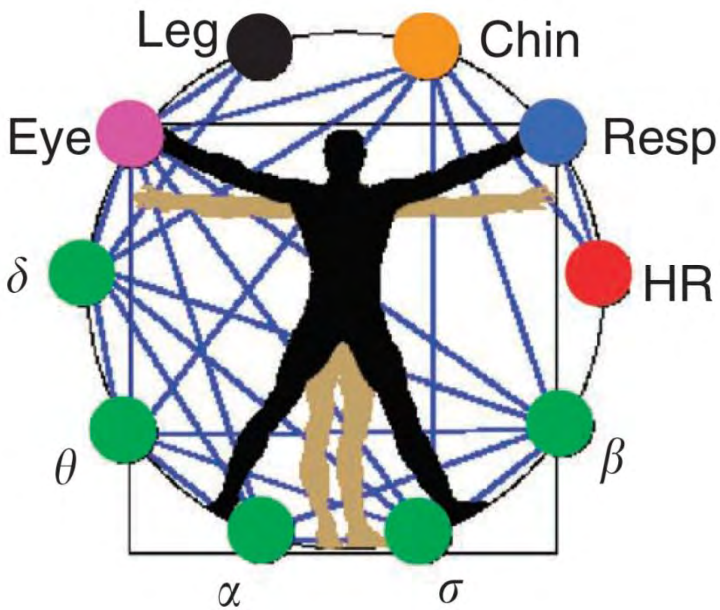
Introduced new concept – *Time Delay Stability* (TDS)
Developed a novel method

↓

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:

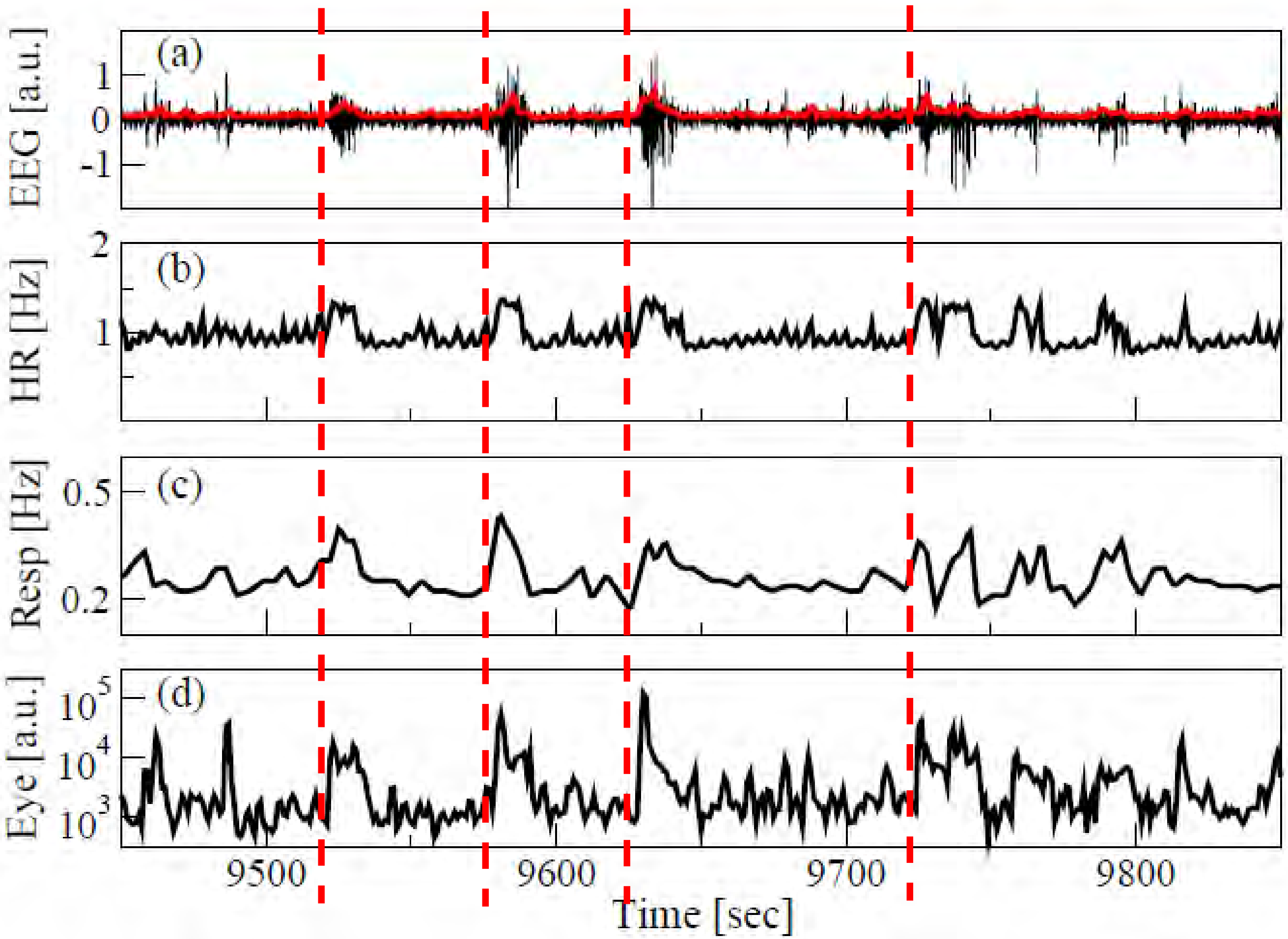
- Brain activity - EEG
- Eye movement - EOG
- Muscle tone - EMG
- Respiration
- Heart dynamics - ECG

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

Coordinated activity across diverse systems



EEG-σ band: sleep spindles

Heart rate

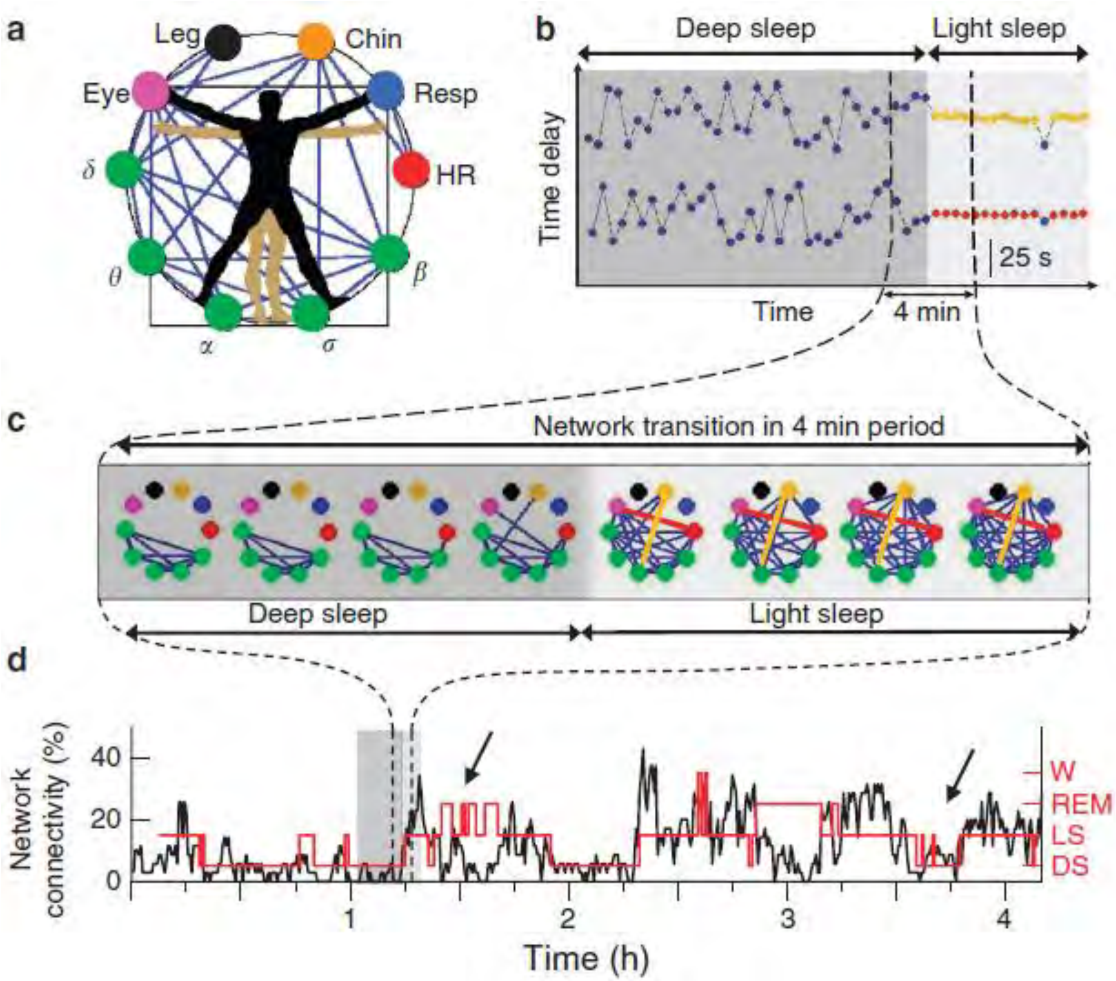
Respiratory rate

Eye movements

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

Data-Driven Discovery

Transitions in the network of physiological interactions



α – Chin interaction

HR – Eye interaction

α – Chin link

HR – Eye link

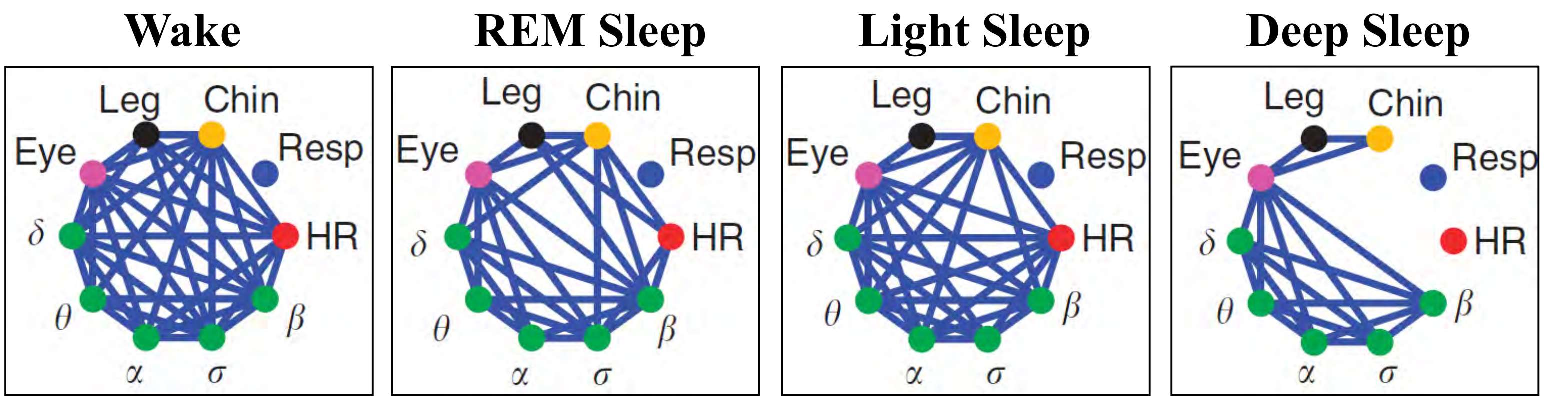
Dynamical Evolution

Bashan et al. *Nature Communications*, 3:702 (2012)

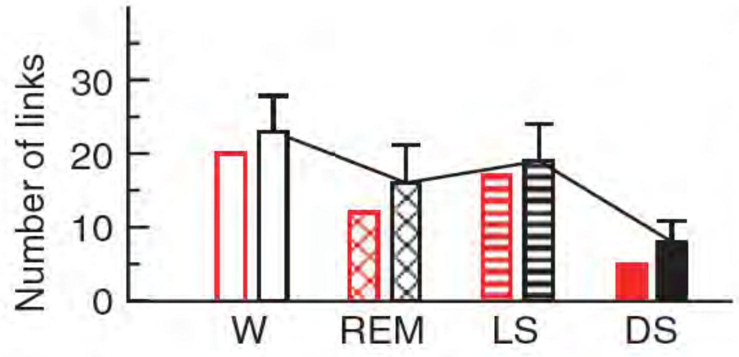
→ Fast reorganization of network connectivity with transitions across physiologic states

Data-Driven Discovery

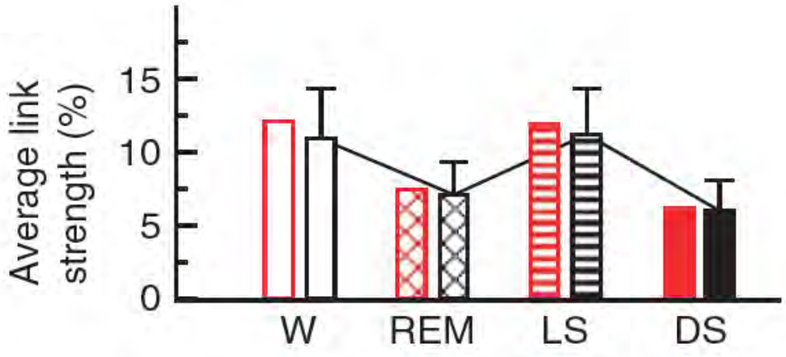
Network Topology & Physiologic Function connectivity across sleep stages



Network connectivity



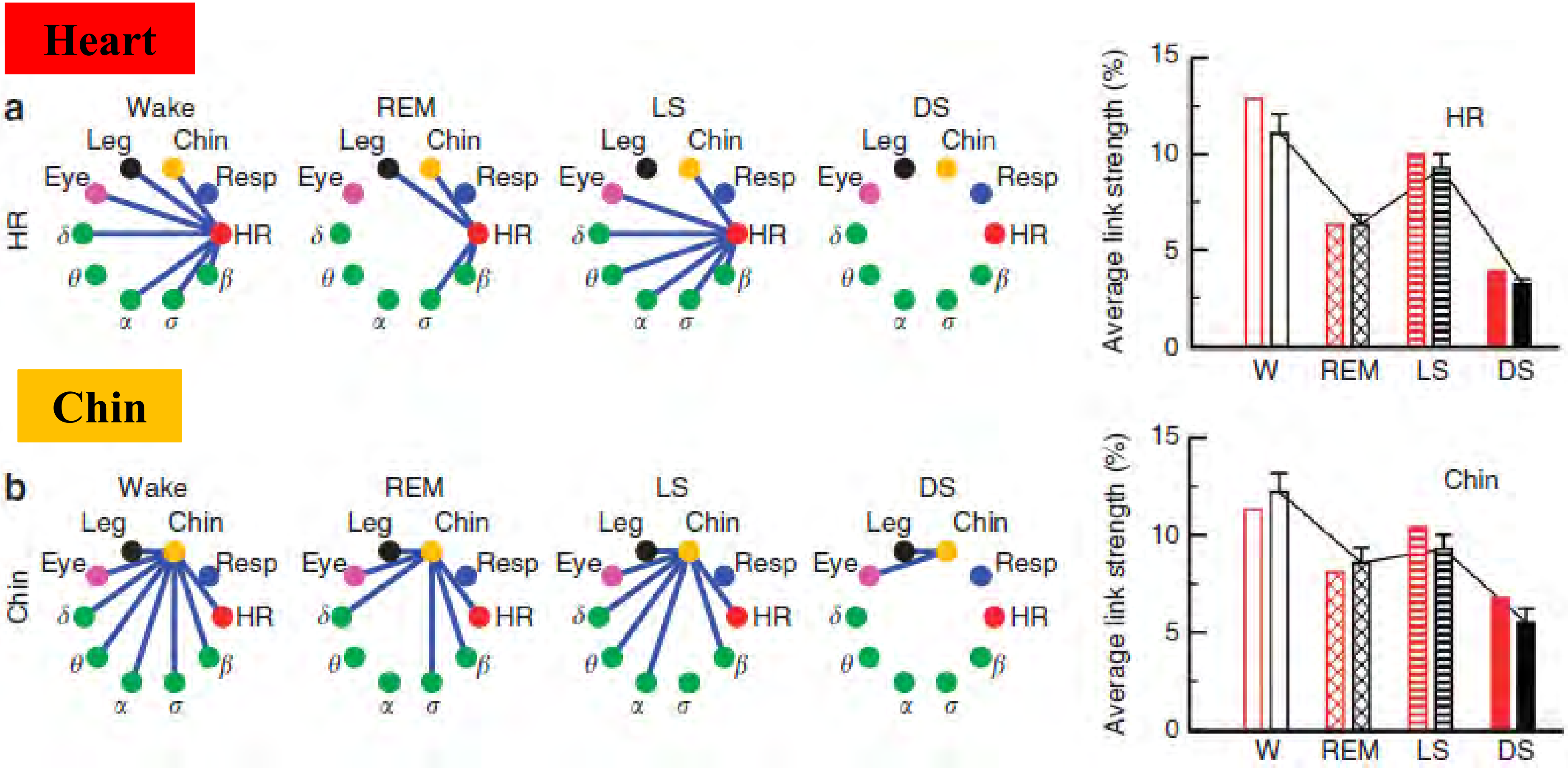
Network link strength



→ Network topology changes with physiologic states

Level 3: Networked Interactions

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



Robust sleep-stage stratification pattern in:

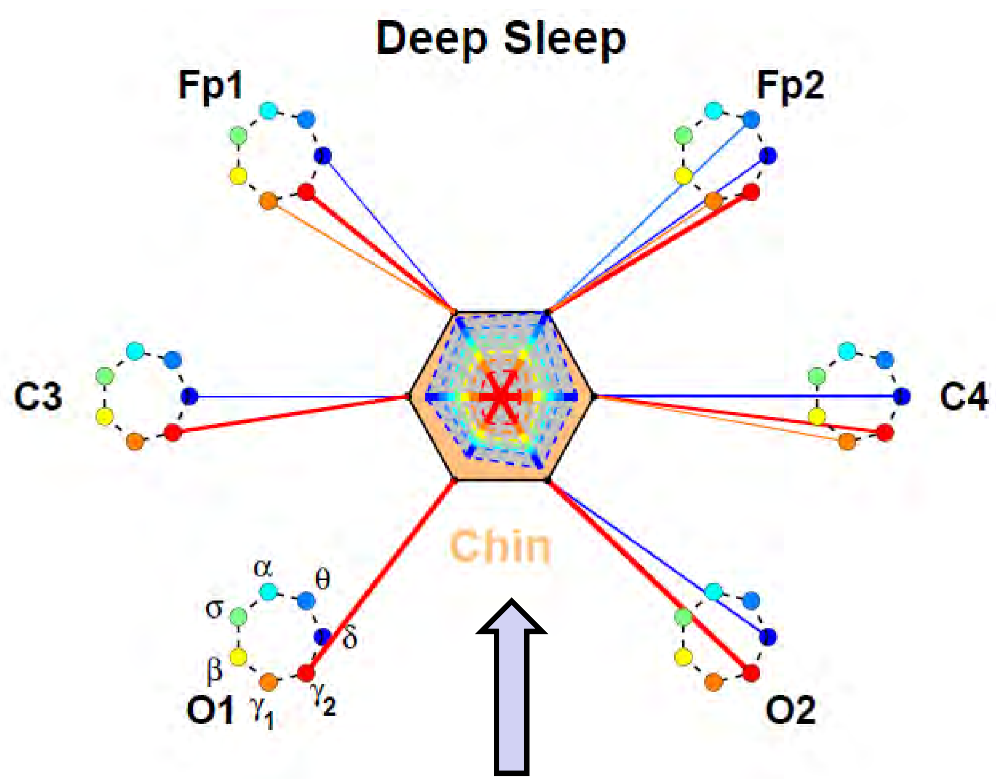
a) Individual node connectivity

b) Average link strength of individual nodes

Level 3: Networked Interactions

Maps of physiologic interactions

Key question: How brain communications modulate organ dynamics?



Location of the nodes:
Brain EEG Channels

Colors:
Frequency bands in the EEG signals

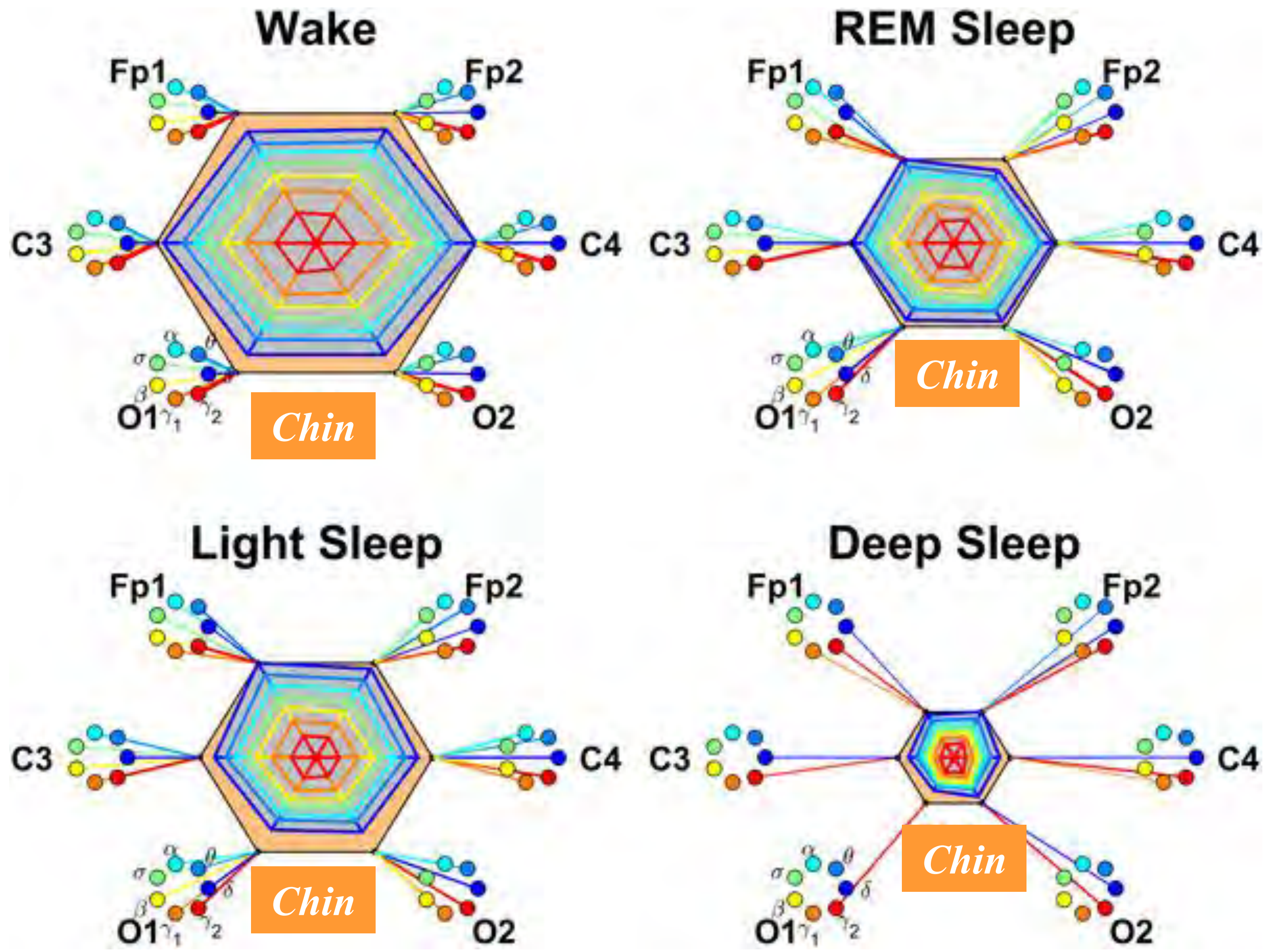
Width of the links:
Coupling strength between the systems

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

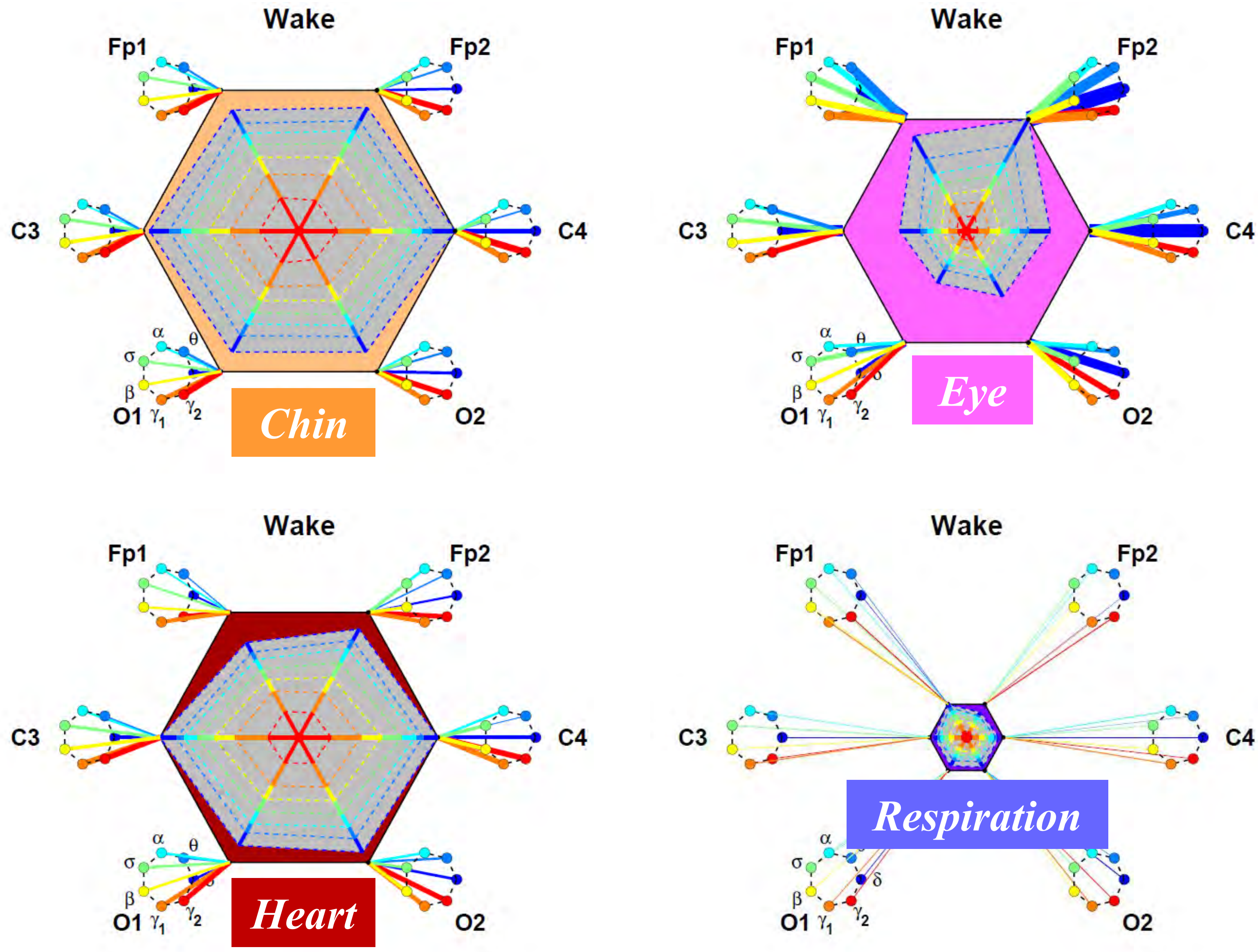
Bartsch RP, Liu KKL, Bashan A, and Ivanov PCh.
Nework Physiology: how organ systems dynamically interact. **PLOS ONE, 2015; 10(11): e0142143**

Level 3: Networked Interactions

Visualization: different physiologic states

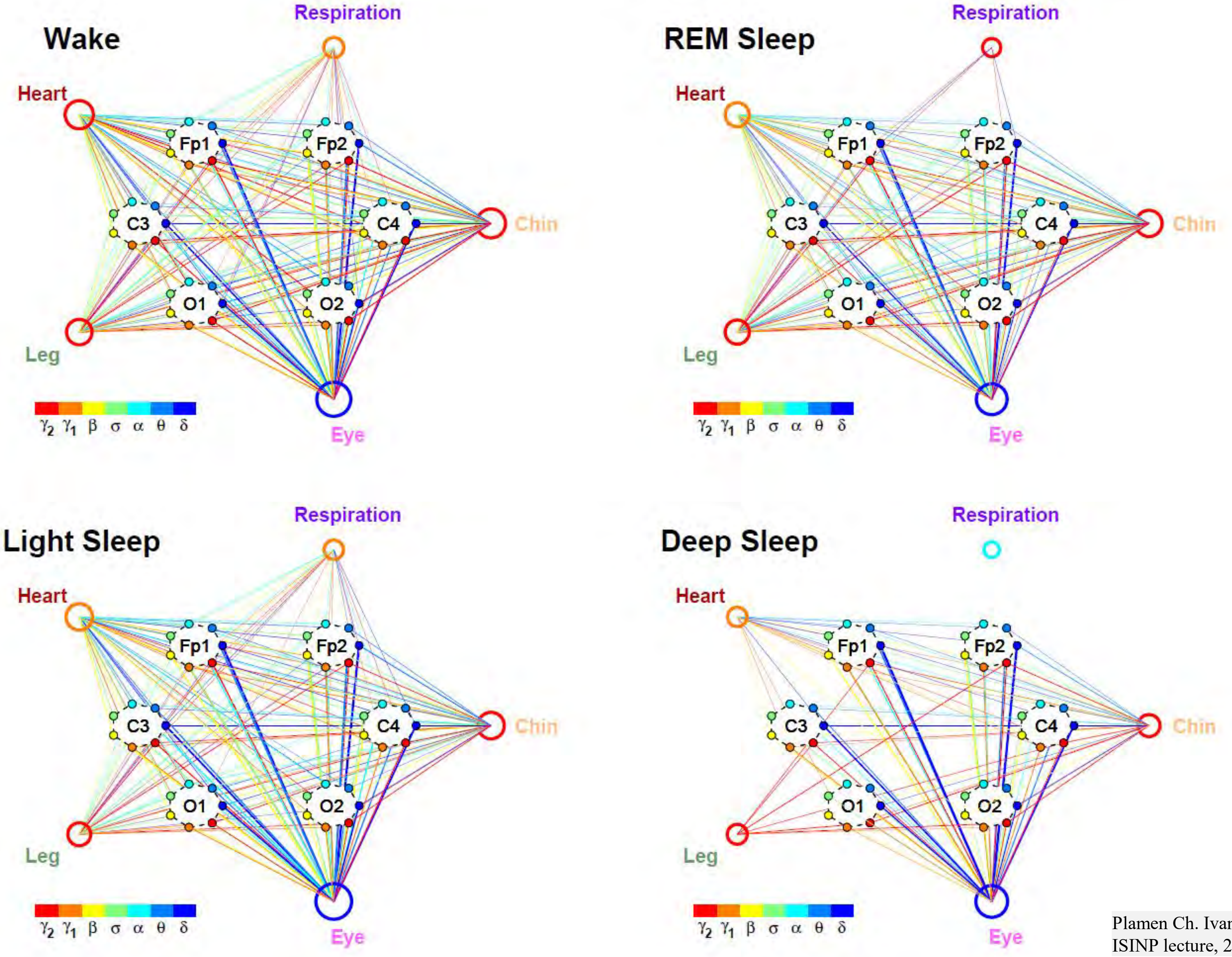


Maps for different organ systems



Level 3: Networked Interactions

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



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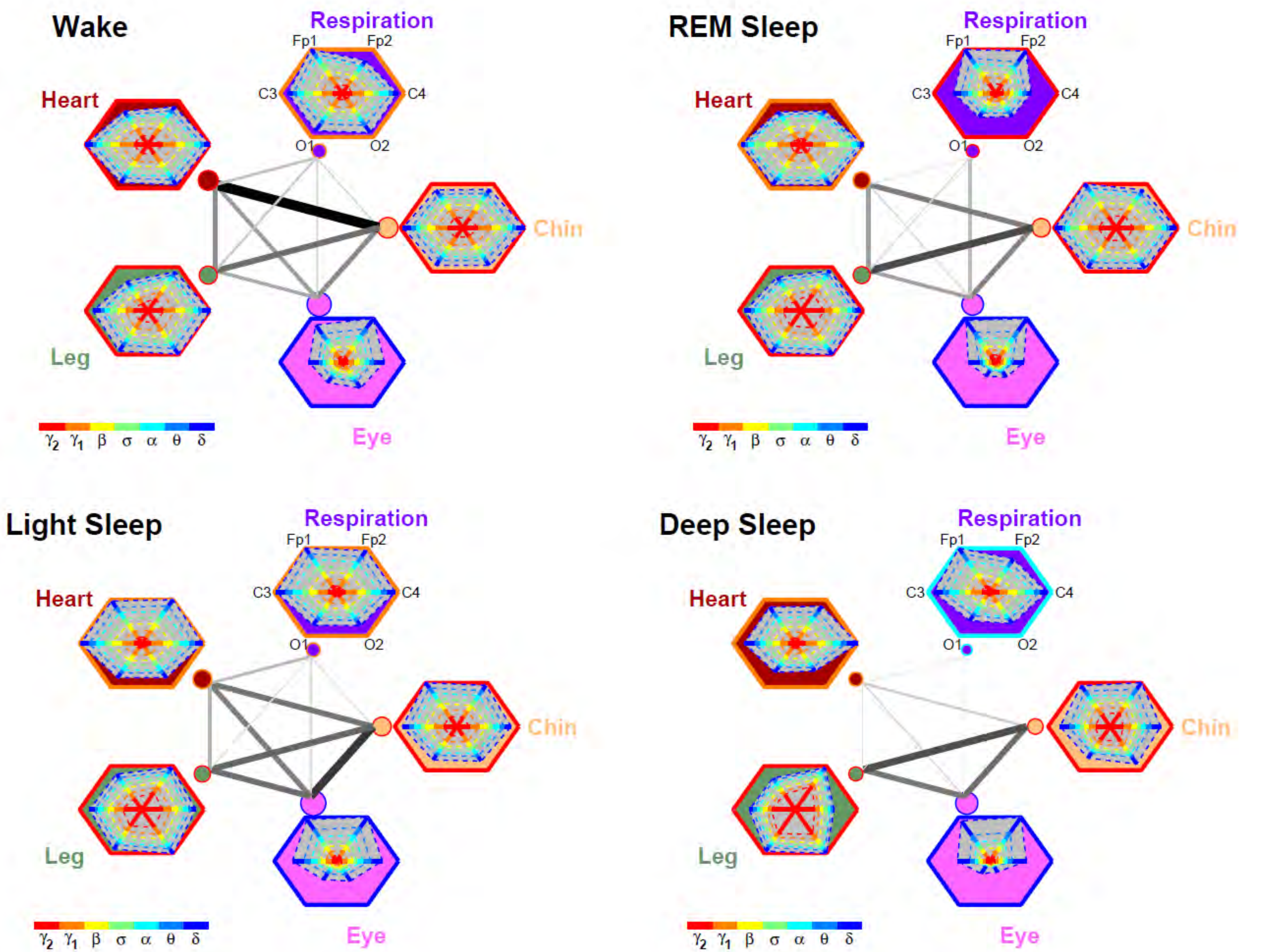
ISINP lecture, 24 July 2017

Level 3: Networked Interactions

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



Network Physiology

IOP Institute of Physics ? → Medicine/Clinical Practice

Revealing the network within

Can we map all the information being circulated in the human body, and would doing so be any use? **Jon Cartwright** explores the emerging interdisciplinary field of "network physiology"

It might seem obvious to say that everything in the human body is connected. Without a doubt, your various organs – heart, liver, lungs – work together to keep you alive, and functioning as close to normally ... least the beginnings of an answer. Having developed

ity. Studying these fluctuations, he says, could give us an entirely new window into the workings of the human body – and help us prevent things going wrong. Ivanov has grand ambitions. He wants to draw on ... sciences until now," he says.

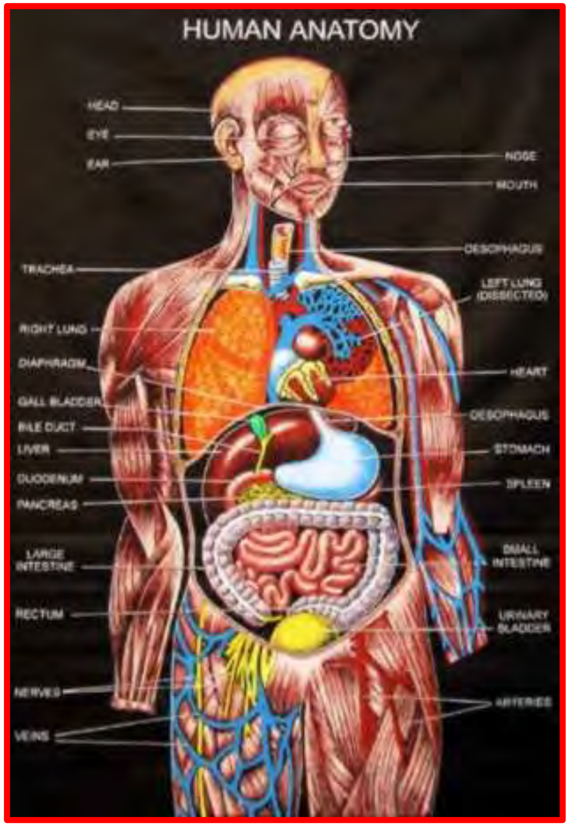
Jon Cartwright is a freelance journalist based in Bristol, UK, http://jcartwright.

Can we map all the information being circulated in the human body, and would doing so be any use?

Vision

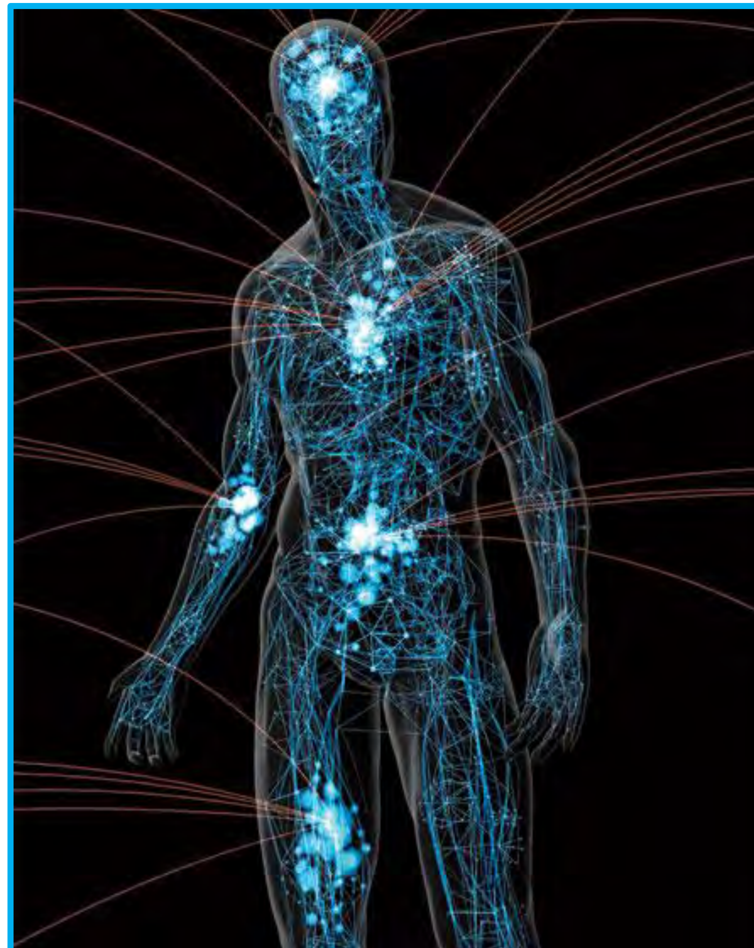
Physiology and Medicine

Atlas of Human Anatomy



need →

Atlas of Dynamic Interactions of Organ Systems



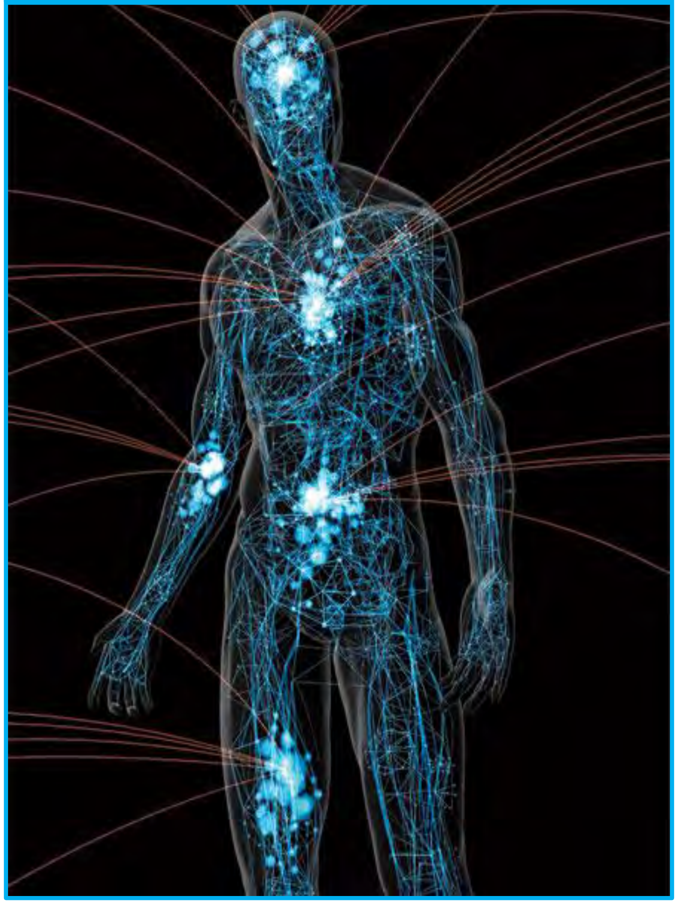
→ Revolutionize our knowledge and understanding of the fundamental mechanisms that regulate and coordinate organ-to-organ interactions

Vision

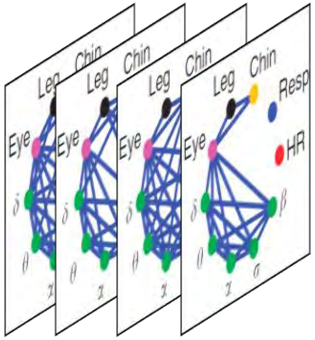
Physiology and Medicine

Such Atlas would contain:

Atlas of Dynamic Interactions of Organ Systems

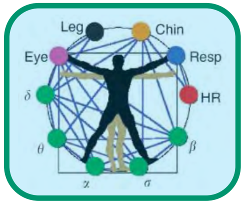


Catalog of reference maps representing dynamical organ interactions under:

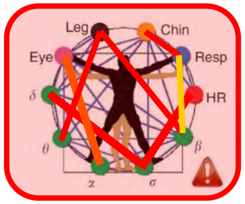


- **healthy conditions**
- **age groups**
- **different physiologic states (rest/exercise, sleep/wake, sleep stages, circadian phases)**
- **pathological conditions (multiple organ failure, coma, heart failure, sleep apnea …)**

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**

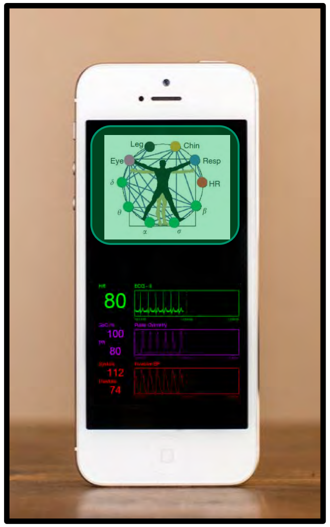
Vision & Impact

Physiology and Medicine

Novel biomarkers

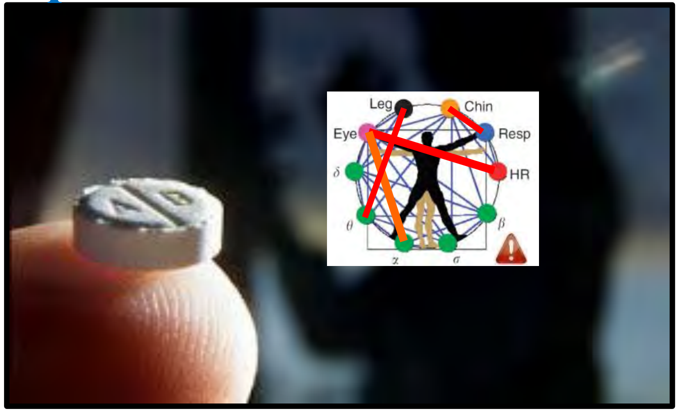
New kind of Physicians

Personalized health monitoring



Next generation ICU monitoring devices and alert system

Comprehensive assessment of drugs

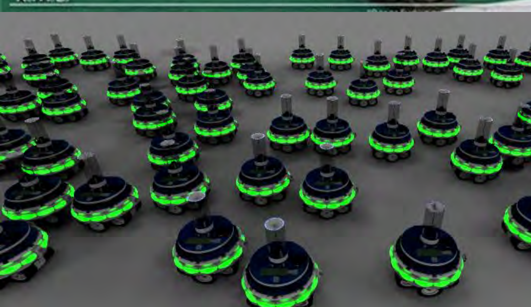


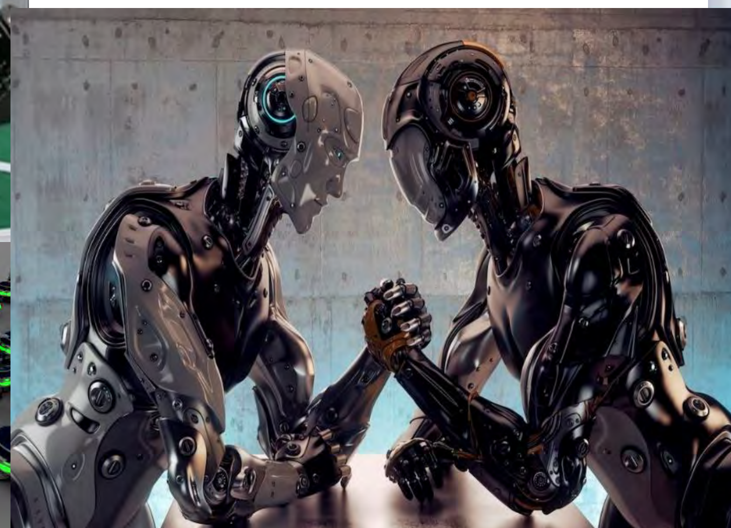
Vision
&
Impact

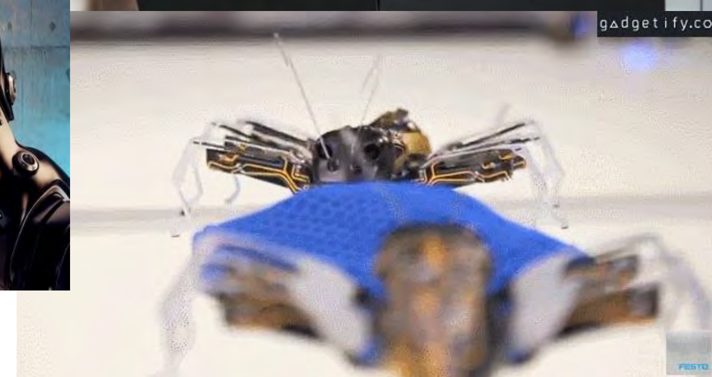
Technology and AI: Robots and Cyborgs

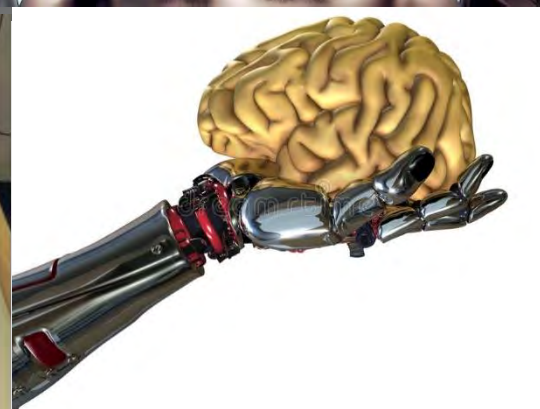
Improve AI & robots, swarms of decentralized multirobot systems

Cyborgs: merge physiology & technology









Impact

Big Data

Human Genome

Motivated Big Data →

Genetic mutation
↕
Disease

limited sequences
(1950's – 1980's)

Required New Methods →

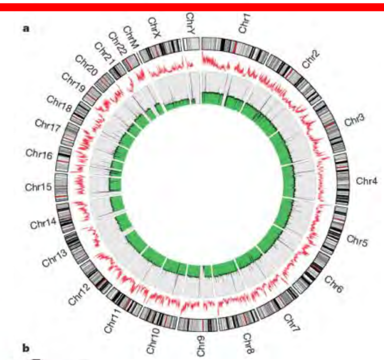
Human Genome Project
↕
Reference genome

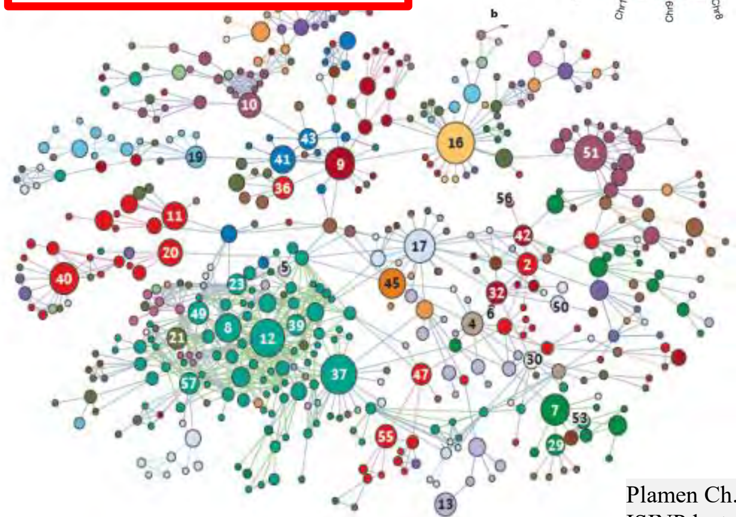
Complete sequencing
Limited individuals
(1990 – 2003)

Next Big Data →

New methods to query Big Data
↕
Reference Human Disease Network
(Now)

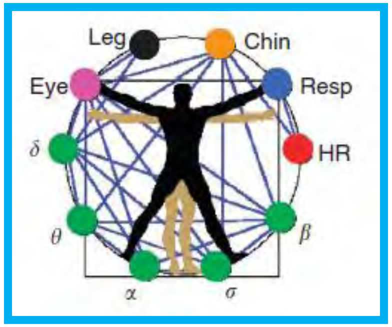
"Super Big Data"
↕
Personalized genetics
(Future)





Impact New Kind of Big Data: the Human Physiolome

Network Physiology



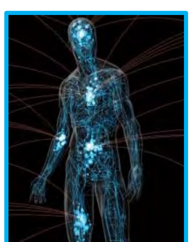
New methods

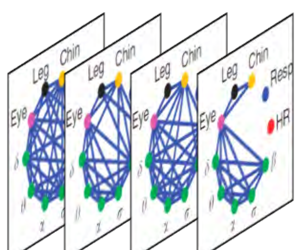
Physiologic network topology
↕
Physiologic function

preliminary limited data
(2012)

New Kind Big Data

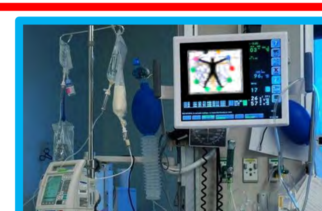
Atlas of Dynamic Interactions of Organ Systems
↕
Blueprint Base Reference of Physiologic Maps
(2015 – 2020)



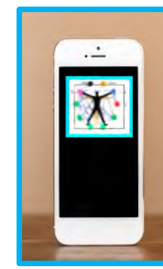


Next Big Data

"Physiolome"
First Big Data on continuous parallel recordings of organ systems
↕
Reference Catalog of Physiologic Maps on Conditions, Diseases, Drugs
↕
Clinical practice
ICU monitoring devices
(Future)



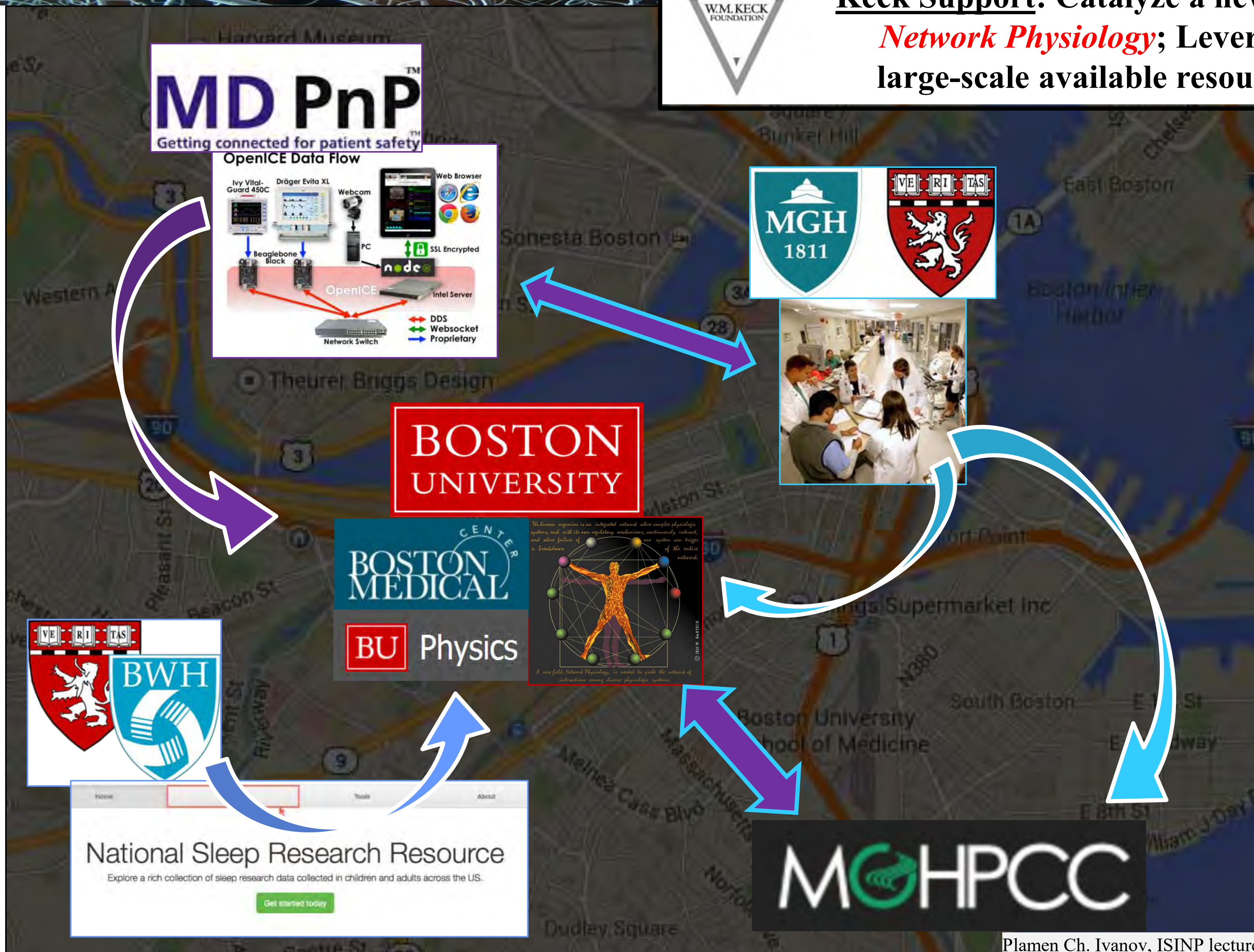
"Super Big Data"
↕
Daily personalized monitoring and health assessment based on Network Physiology
(Future)



Collaboration

Ongoing Program: Interdisciplinary Collaboration

Keck Support: Catalyze a new field, *Network Physiology*; Leverage large-scale available resources

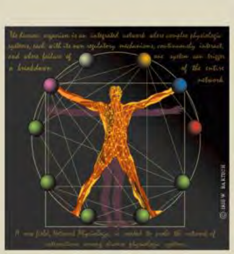


Our Group:

http://physics.bu.edu/labnetworkphysiology

W.M. KECK FOUNDATION

Keck Laboratory for Network Physiology



Group members:

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Xiaolin Huang, Aylin Cimenser
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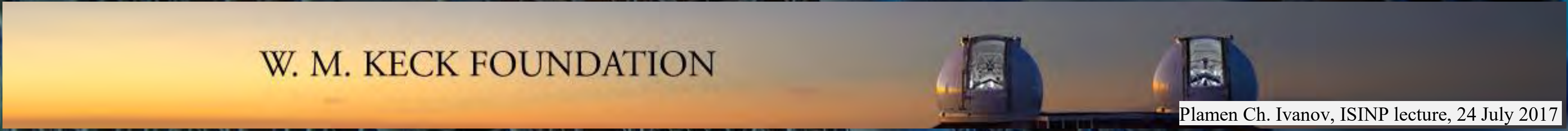
Fabrizio Lombardi, Chengyu Huo,
Jilin Wang

Openings:

- **Research Scientists**
- **Visiting Researchers**

Support:

- ***Atlas of Dynamic Interactions among Organ Systems***



Publications:

- Network Physiology reveals relations between network topology and physiological function. *Nature Communications* vol. 3:702 (2012)
- Phase transitions in physiologic coupling. *PNAS* vol. 109, p. 10181 (2012)
- Three independent forms of cardio-respiratory coupling: transitions across sleep stages. *Computing in Cardiology* vol. 41:781-784 (2014)
- Network Physiology: Mapping Interactions Between Networks of Physiologic Networks. In "*Networks of Networks: the last Frontier of Complexity*", Springer 5394; pp. 203-222 (2014)
- Network Physiology: How Organ Systems Dynamically Interact *Plos One* vol. 10(11): e0142143 (2015)

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