

# The New Field of Network Physiology: Mapping the Human Physiolome

**Plamen Ch. Ivanov**

**Physics Department, Boston University**

**and**

**Division of Sleep Medicine**

**Brigham and Women's Hospital & Harvard Medical School**

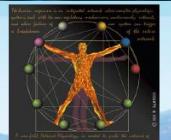


HARVARD  
MEDICAL SCHOOL



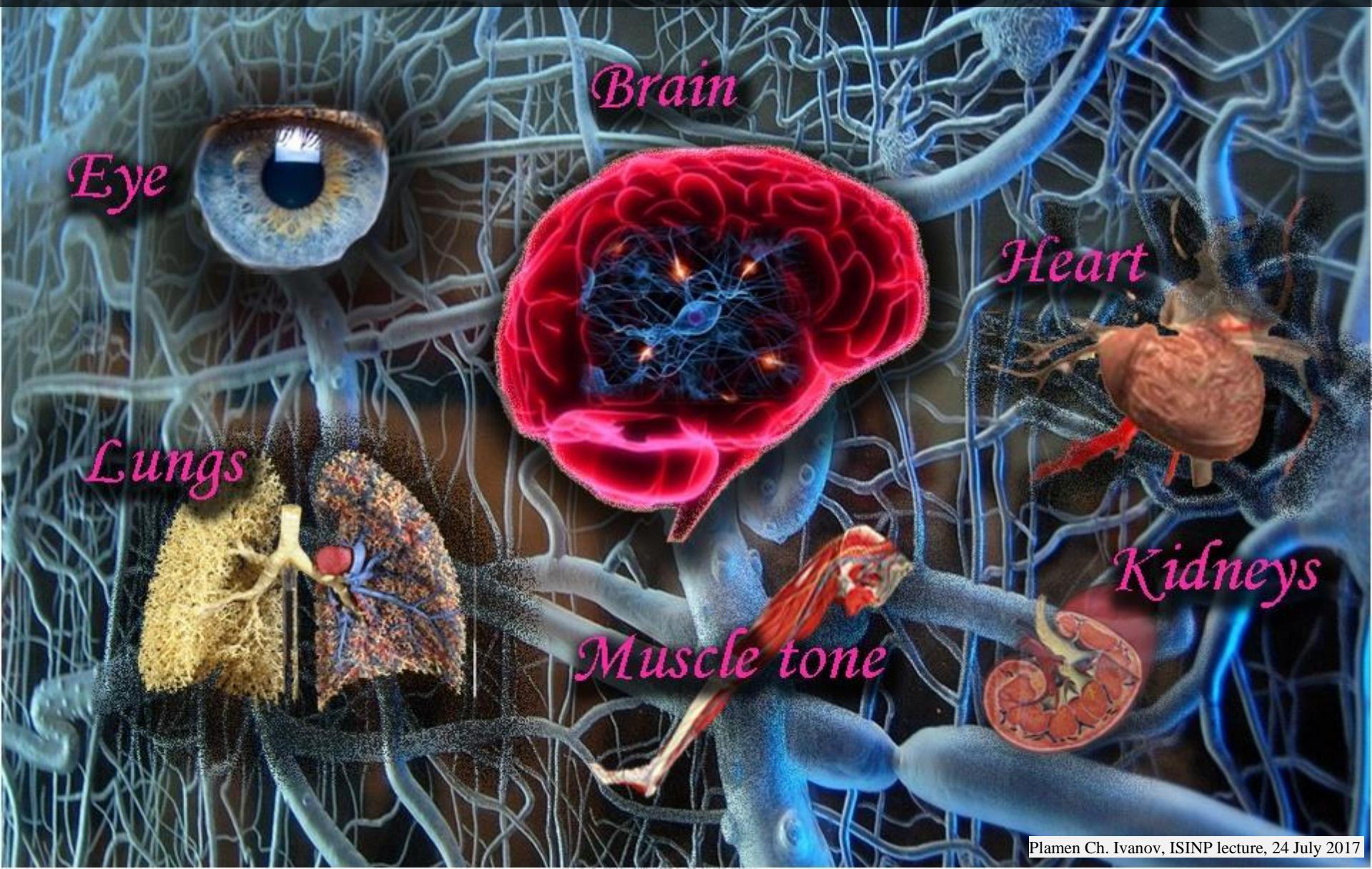
**First International Summer Institute  
on Network Physiology (ISINP)**

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



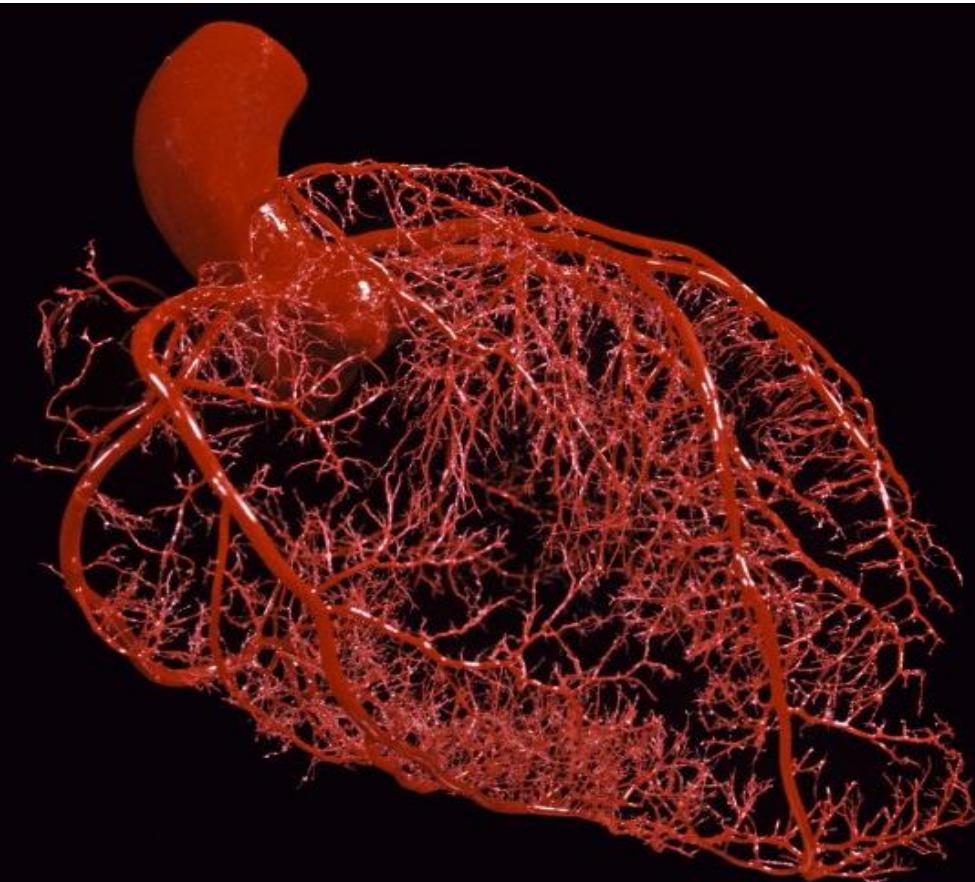
# Human Organism

## comprises diverse multi-component physiological systems

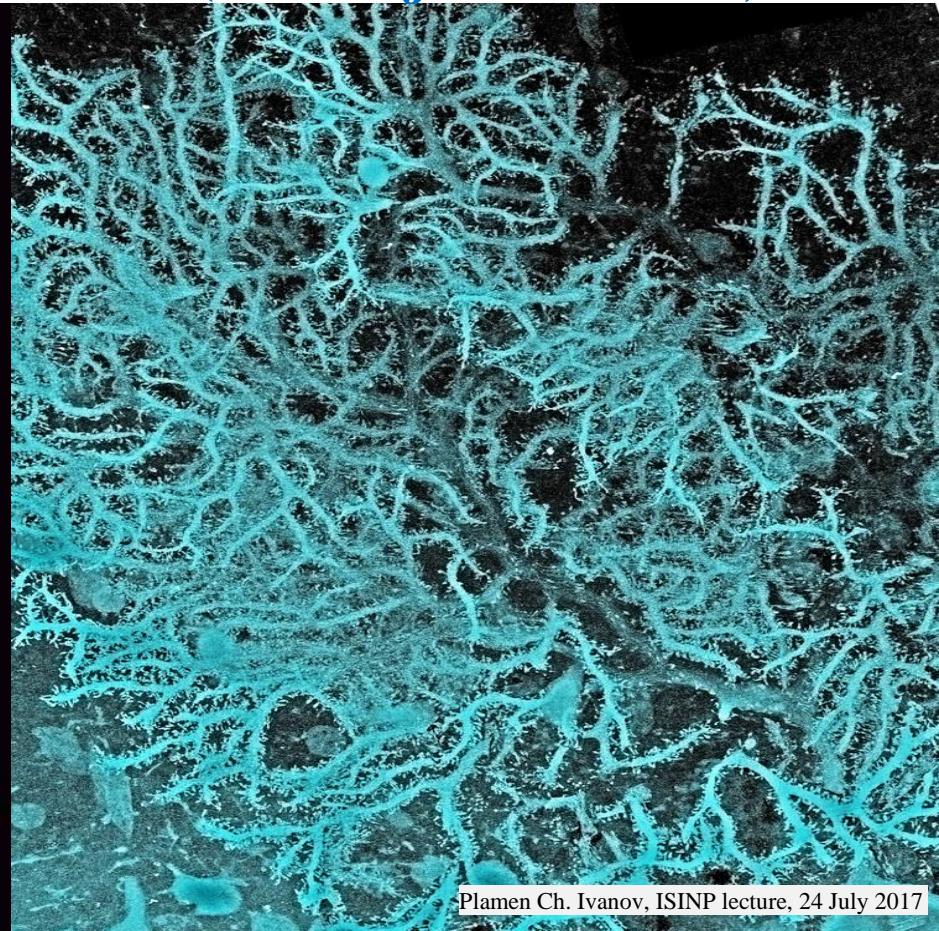


# Human Organism comprises diverse multi-component physiological systems

Heart: Vascular network

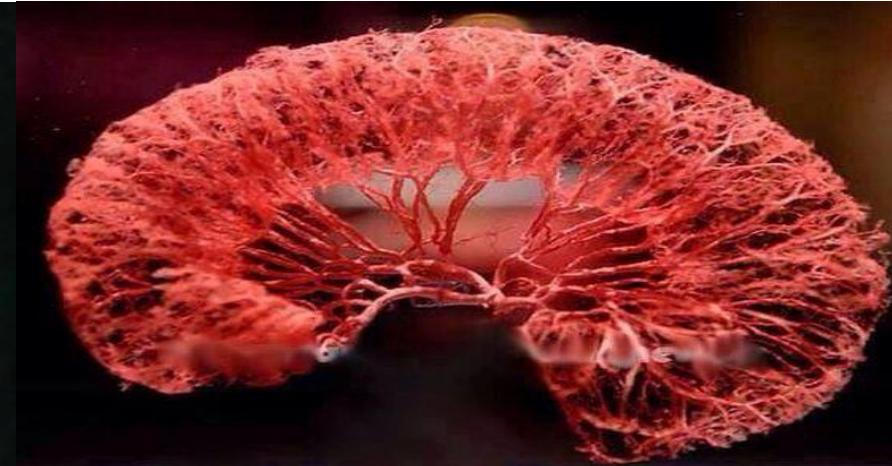
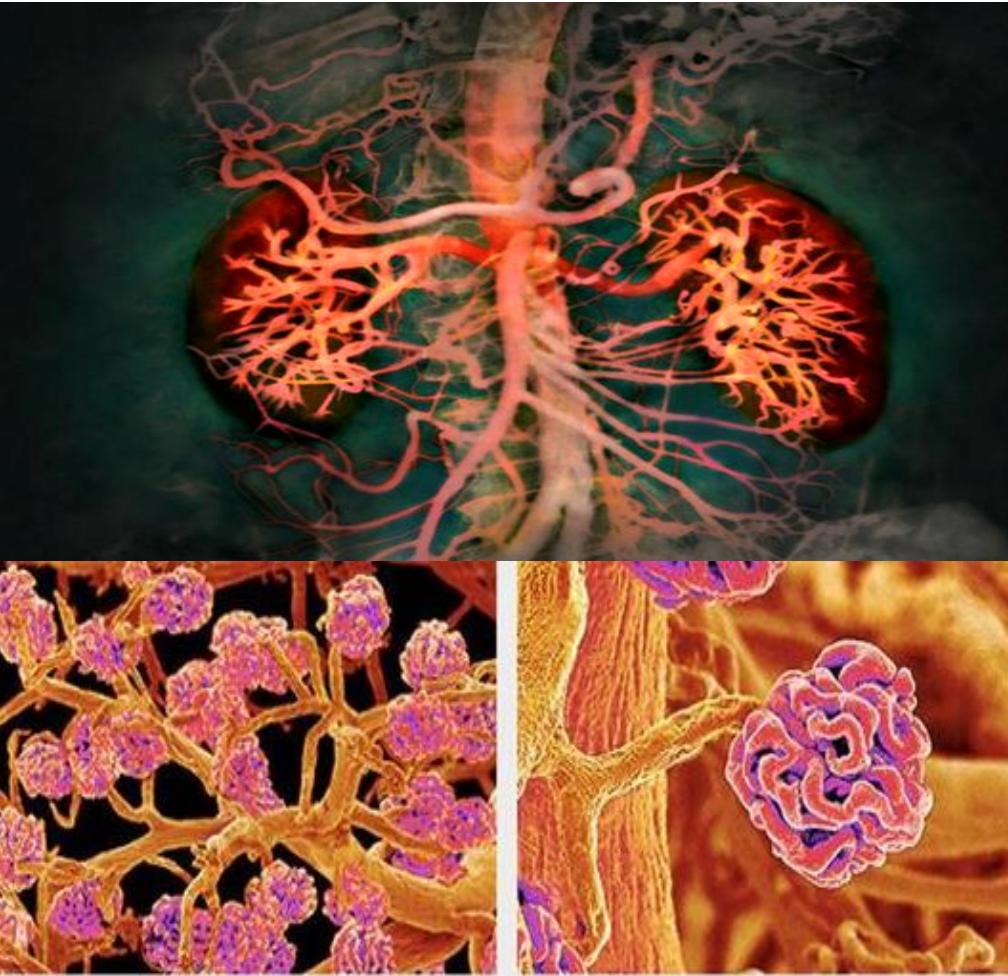


Conducting network  
(Purkinje dendrites)



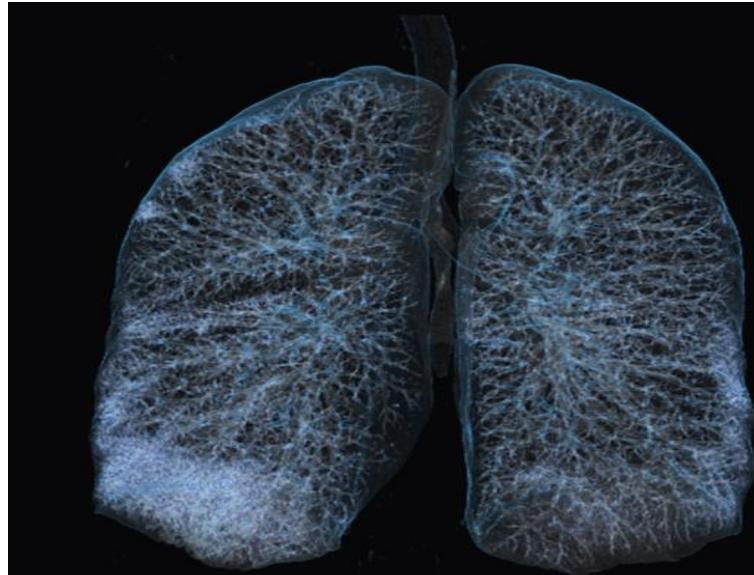
# Human Organism comprises diverse multi-component physiological systems

Kidney:      Vascular network in decreasing scale

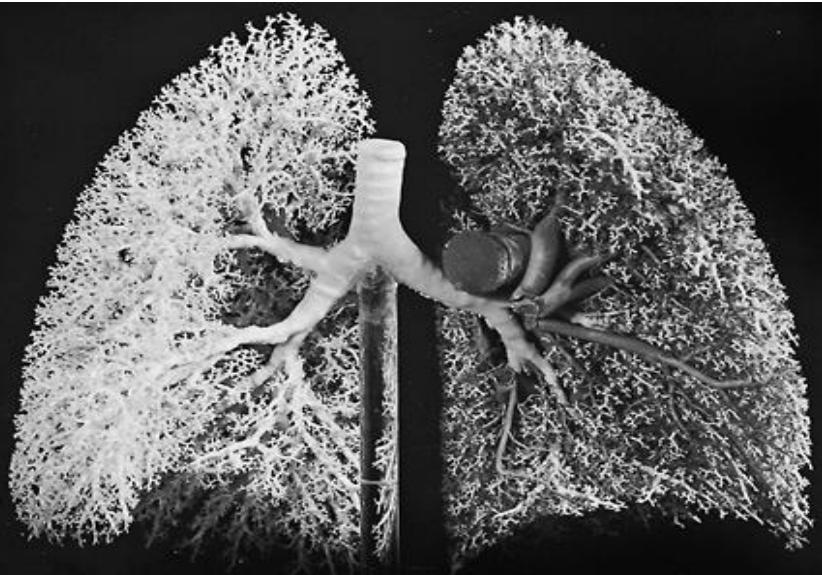


# Human Organism comprises diverse multi-component physiological systems

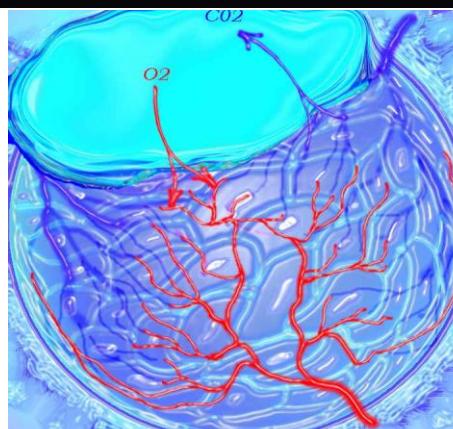
Lungs: High resolution image



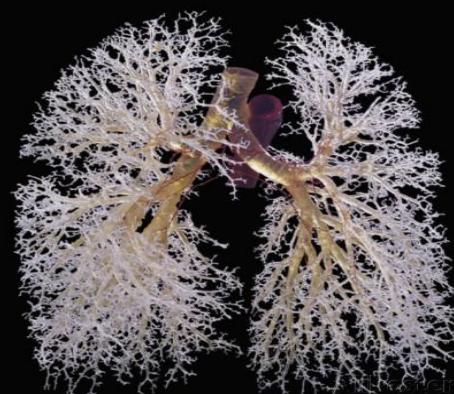
Airways



Arteries and veins



Single alveolus  
vascular network

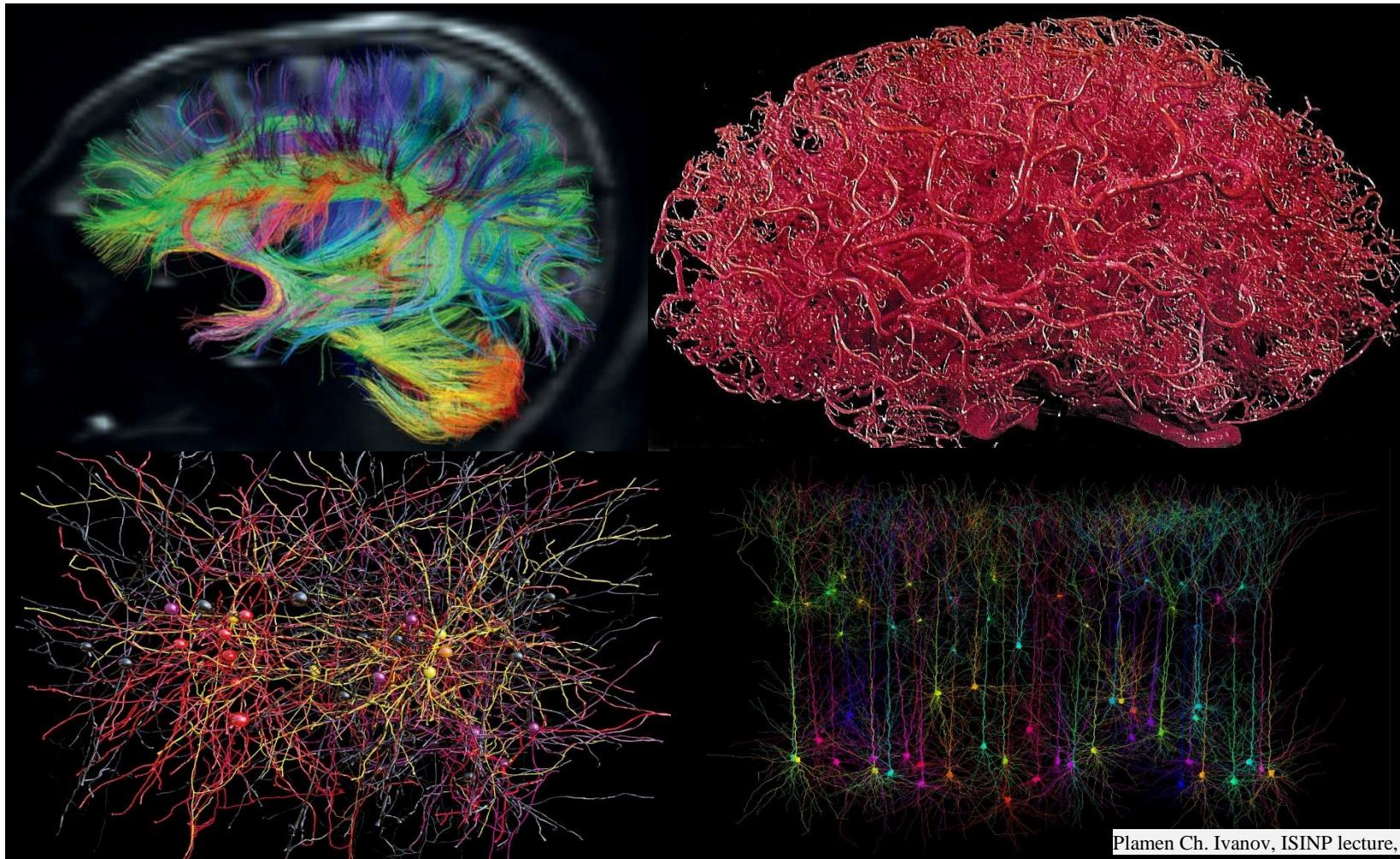


Bronchial tree

# Human Organism comprises diverse multi-component physiological systems

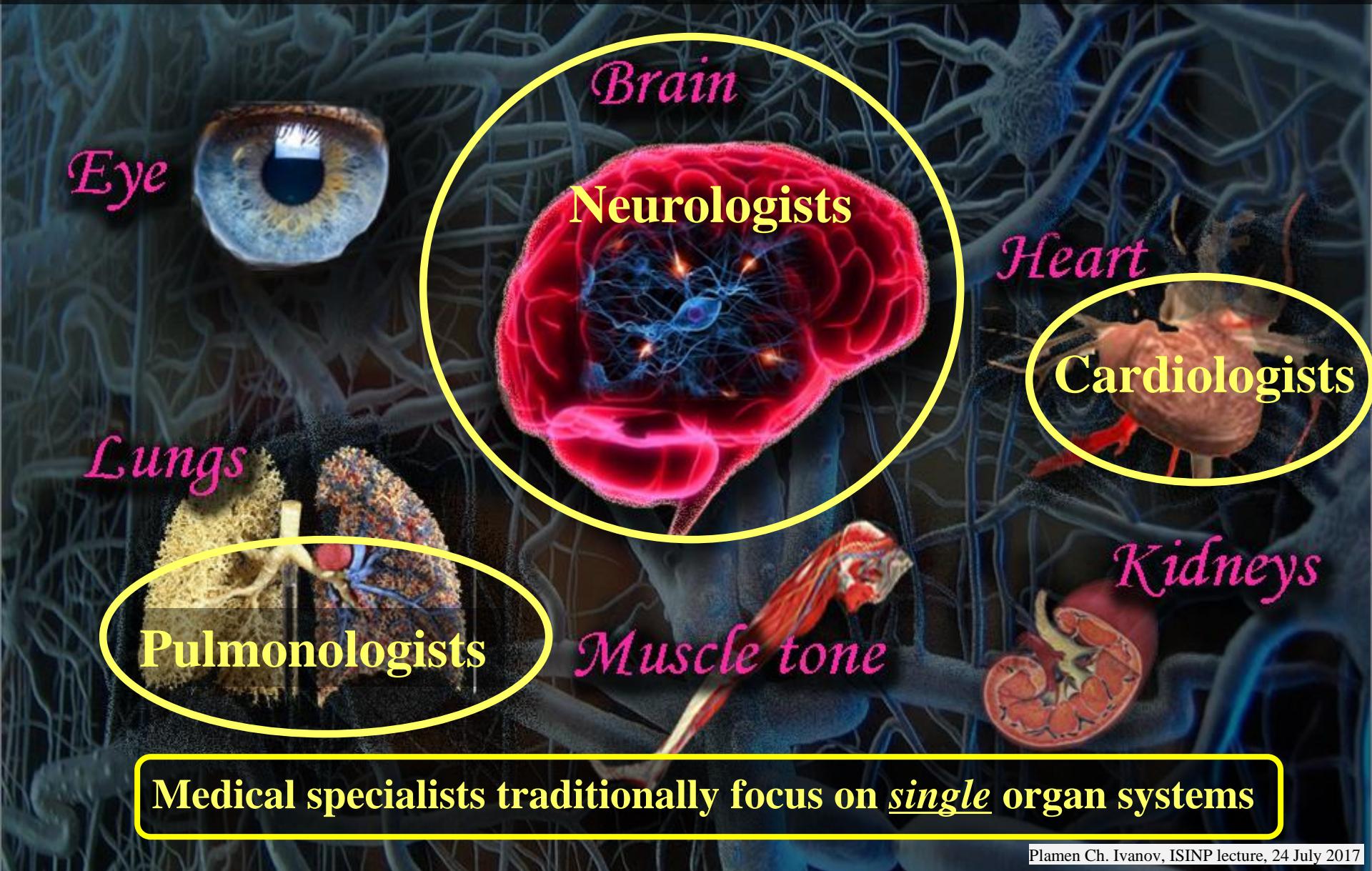
Brain:

Neuronal and vascular network



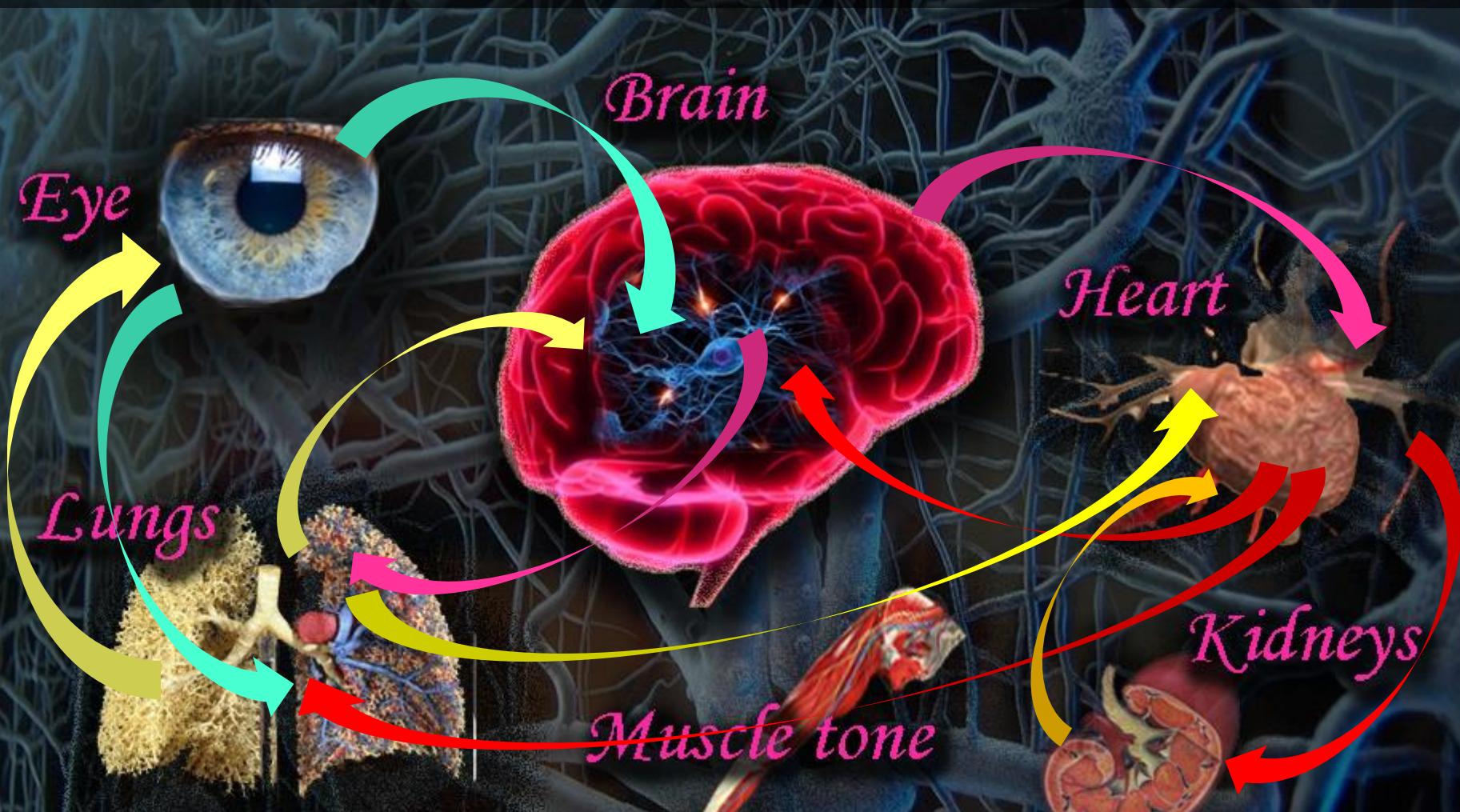
# Human Organism

## comprises diverse multi-component physiological systems



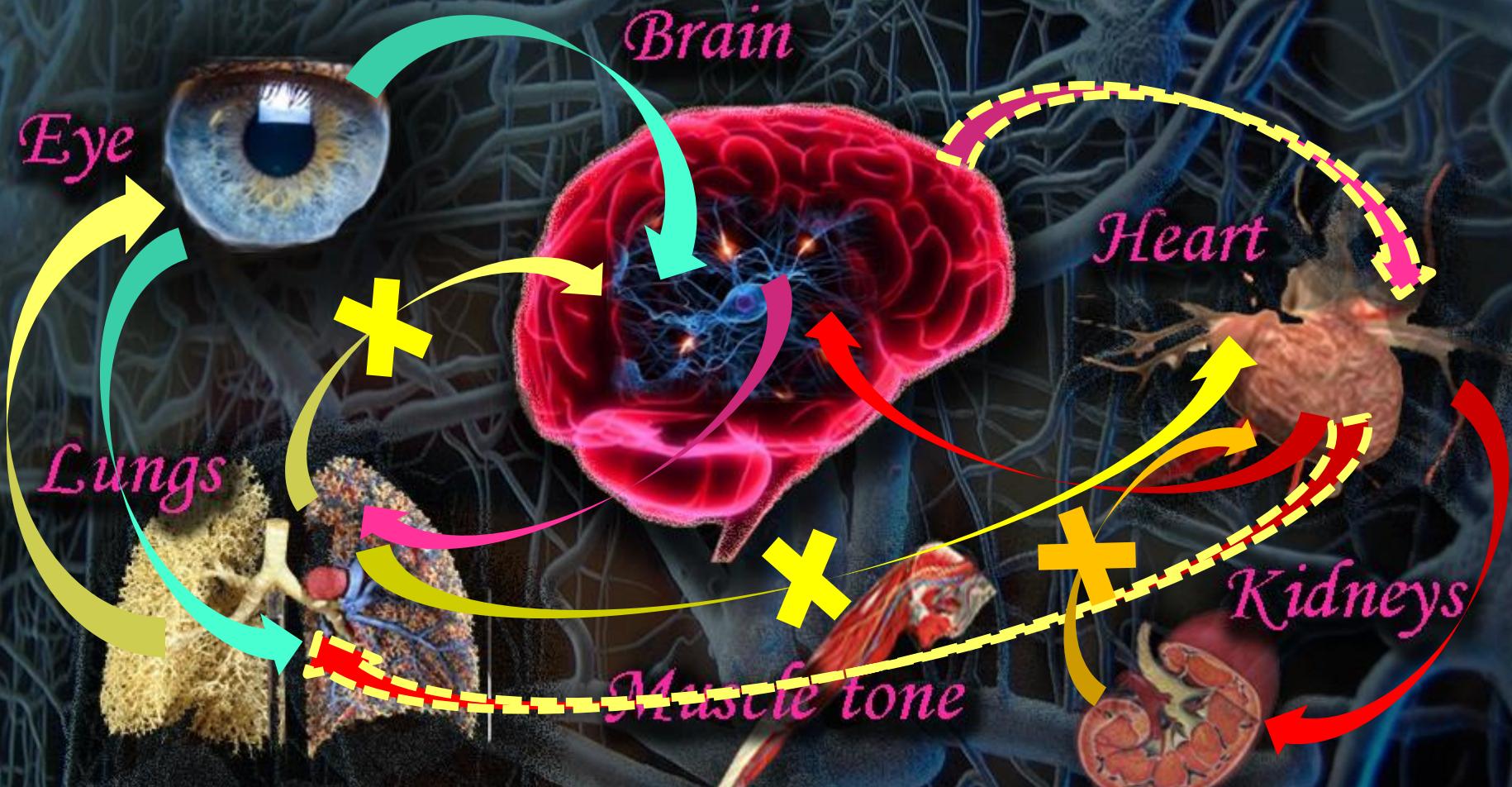
# Human Organism – Integrated Network

## 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 !



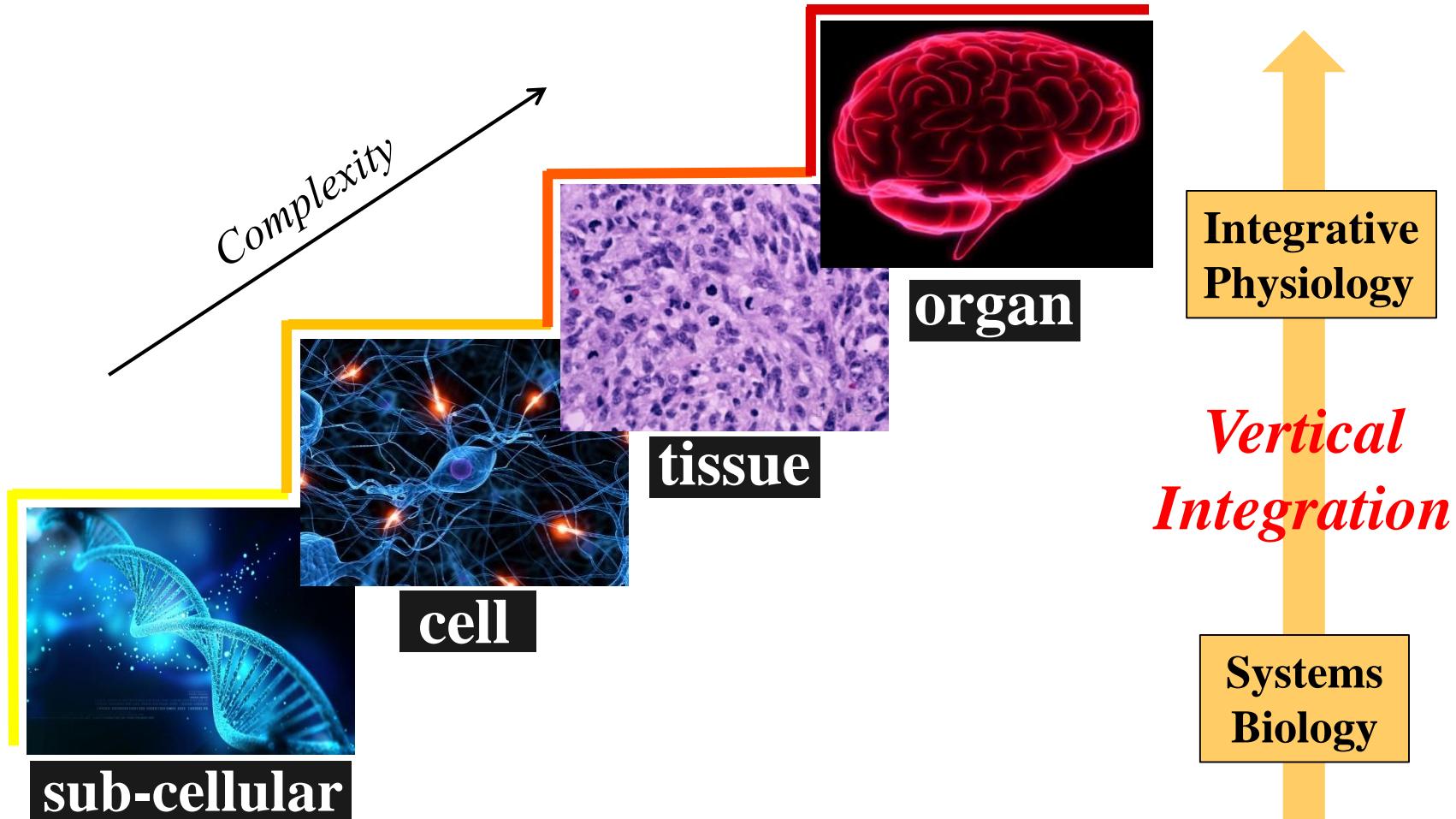
Broad *clinical implications*: Coma, Multiple Organ Failure

Yet, despite the importance to:

- understanding basic physiologic functions
- clinical relevance

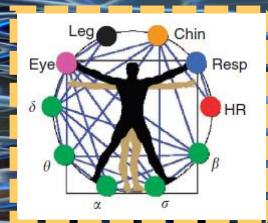
? we do not know how organ systems dynamically interact  
as a network to coordinate and optimize their functions

# Current Research Focus of Systems Biology and Integrative Physiology

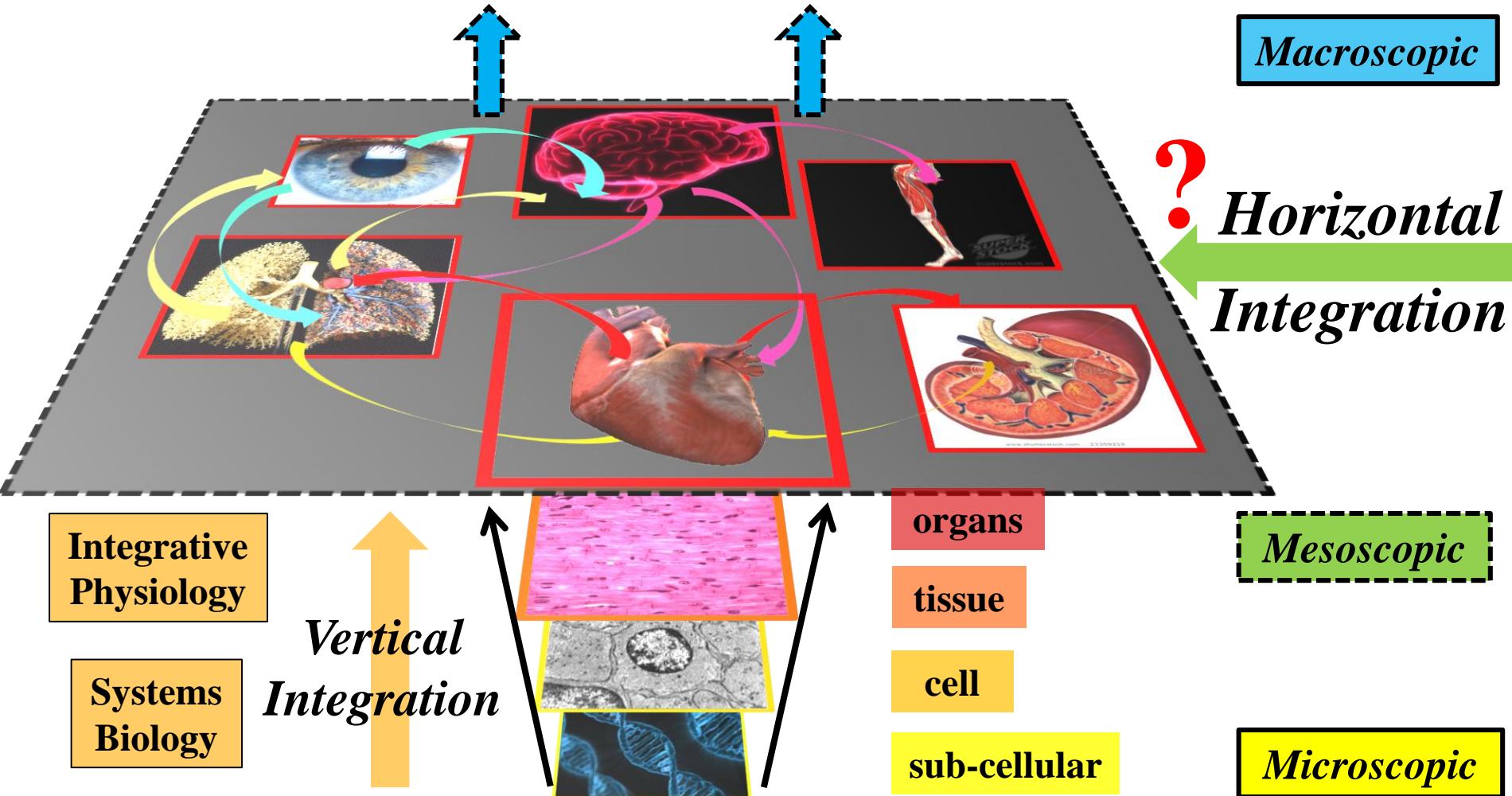


Signaling and feedbacks across space/time scales

# Our Research Focus: Horizontal Integration



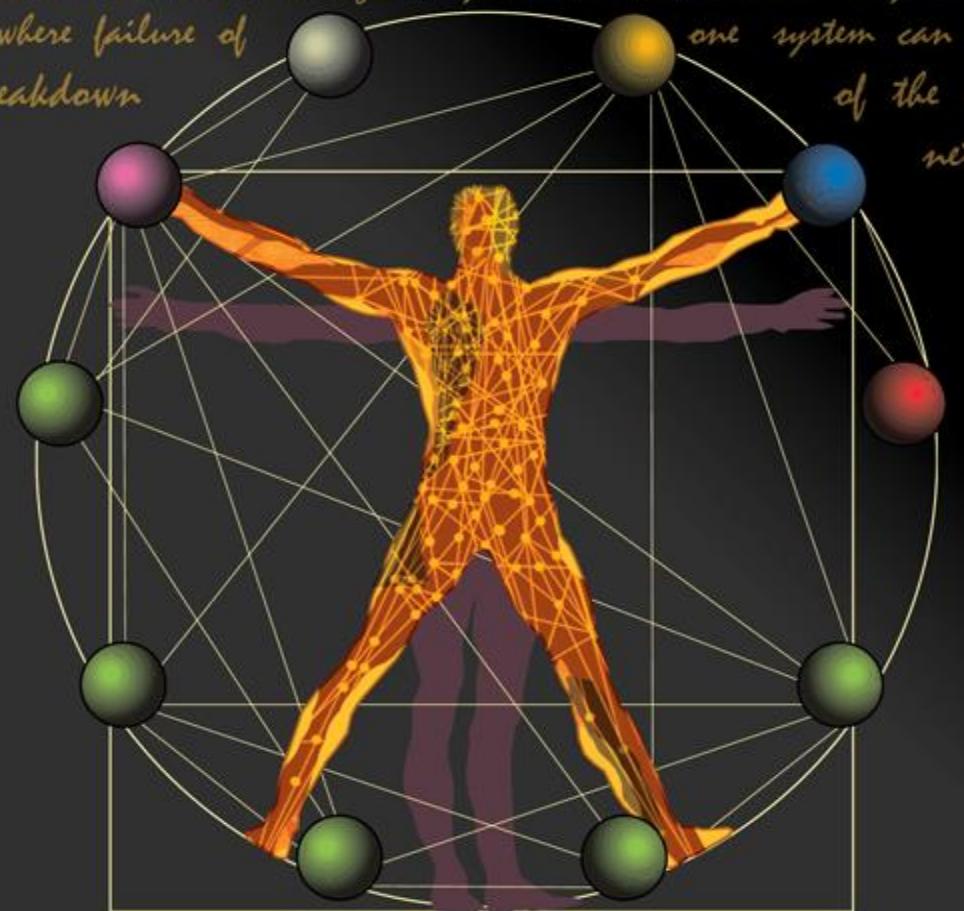
## Epidemiology / Population Health



# 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:



*Nature Communications* vol. 3:702 (2012)

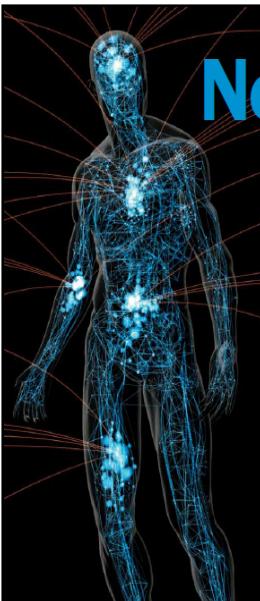
**"Network Physiology reveals relations between network topology and physiological function"**

**Generated Broad Interests in the Community**

1<sup>st</sup> Symposium on Network Physiology and Medicine, Oct. 2012



Science News Cover Story, 2012



The illustration shows a human figure with internal organs and systems represented by glowing blue and white nodes connected by lines, forming a complex network.

**When Networks Network**

Once studied solo, systems display surprising behavior when they interact

By Elizabeth Quill

Half a dozen times each night, your staggering body performs a remarkable feat of coordination. During the deepest stages of sleep, the body's activity slows to near its own怠息. Nerve cells hum along in your brain, their rhythmic general activity creating a series of smaller stages. Yet, like waves and trains with overlapping routes but unpermeating schedules, the body's systems have little to say to your heart, which pumps blood to its own rhythm through the body's arteries and veins. But as you move from the depths and down the wispiness in seemingly random splits and spurs, And music fluctuations that make you want to dance, you enter the a vacuum. Networks of muscles, fibrin cells, once-and-langs, of heart and veins, all stop. You're still, except every couple of hours, though. In as little as 30 seconds, the barriers break down and the body begins to move. As the displaced activity of deep sleep starts to connect with its surrounding networks, the body's systems begin to talk to one another. And the heart joins the team. This is what happens when you wake from a night's sleep; it may recently have been understood in detail – thanks to a new look at when and how the body's myriad networks link up to form an interconnected whole.

**ScienceNews**

Linking Up  
Perils and promises of connecting networks

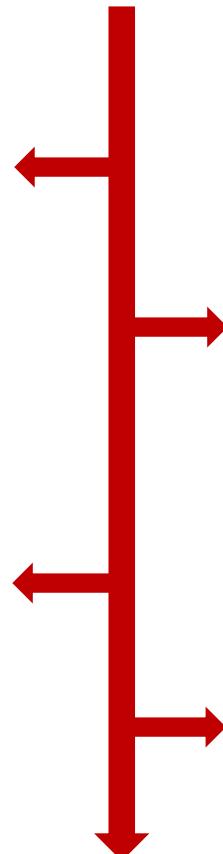
Star Factory  
Natural Tinkers  
Crisis-Solving Careers

Hunting ExoEarths | Dethroning DNA in Full | Secrets of Seismos

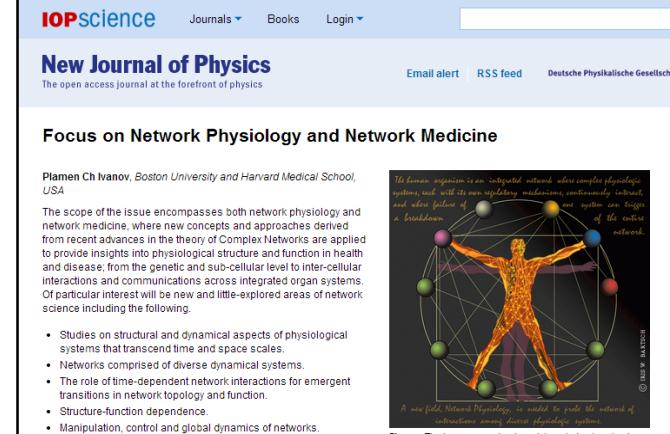
Volume 30 Number 10 • September 22, 2012

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September 22, 2012 | SCIENCE NEWS | 19



Special Issue, 2014



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**New Journal of Physics**  
The open access journal at the forefront of physics

Email alert RSS feed Deutsche Physikalische Gesellschaft

**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 physiologic systems exist with their own regulatory mechanisms, continuously interacting with other facets of the organism, and systems of the external world.

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



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**Physiological Measurement**

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

**Scope**

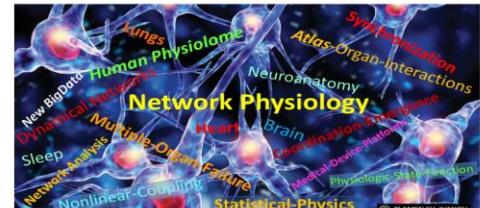
The human organism is an integrated network, where physiological systems and organs, each with its own regulatory mechanism, continuously interact to coordinate their functions. Physiological interactions are essential to produce distinct physiologic states,

**Special Issue, 2016**

The new field of Network Physiology: redefining health and disease through networks of physiological interactions

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

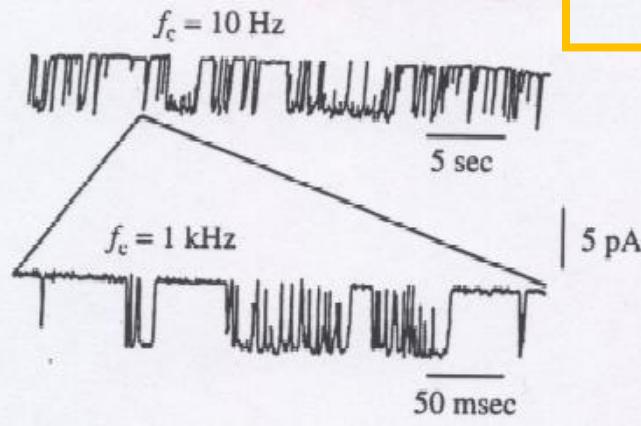
**Network Physiology**



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

Is Physiologic  
Variability  
simply Noise?

sub-cellular  
Ion channel kinetics



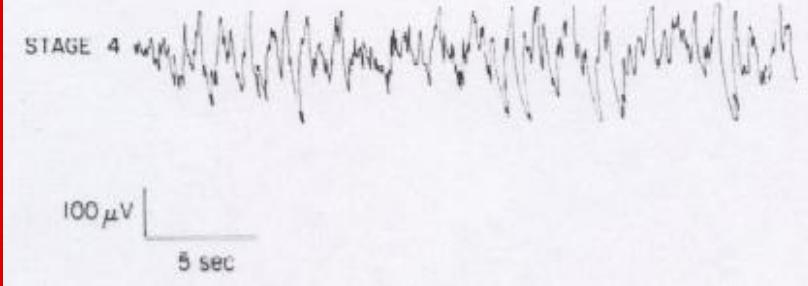
Complexity

Single neuron activity

cell

organs

Brain dynamics during sleep (EEG)



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

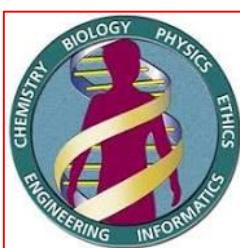
Stat. Physics

Applied Math

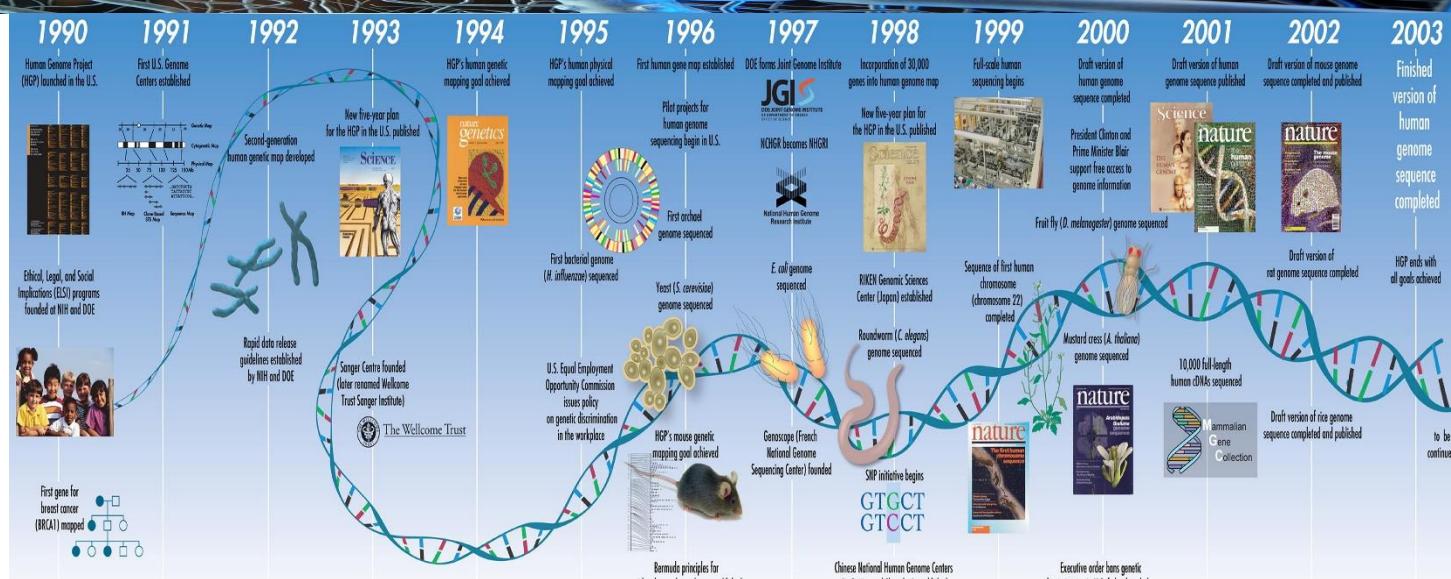
Computer Sci.

# Big Data

# Systems Biology: mapping the Human Genome

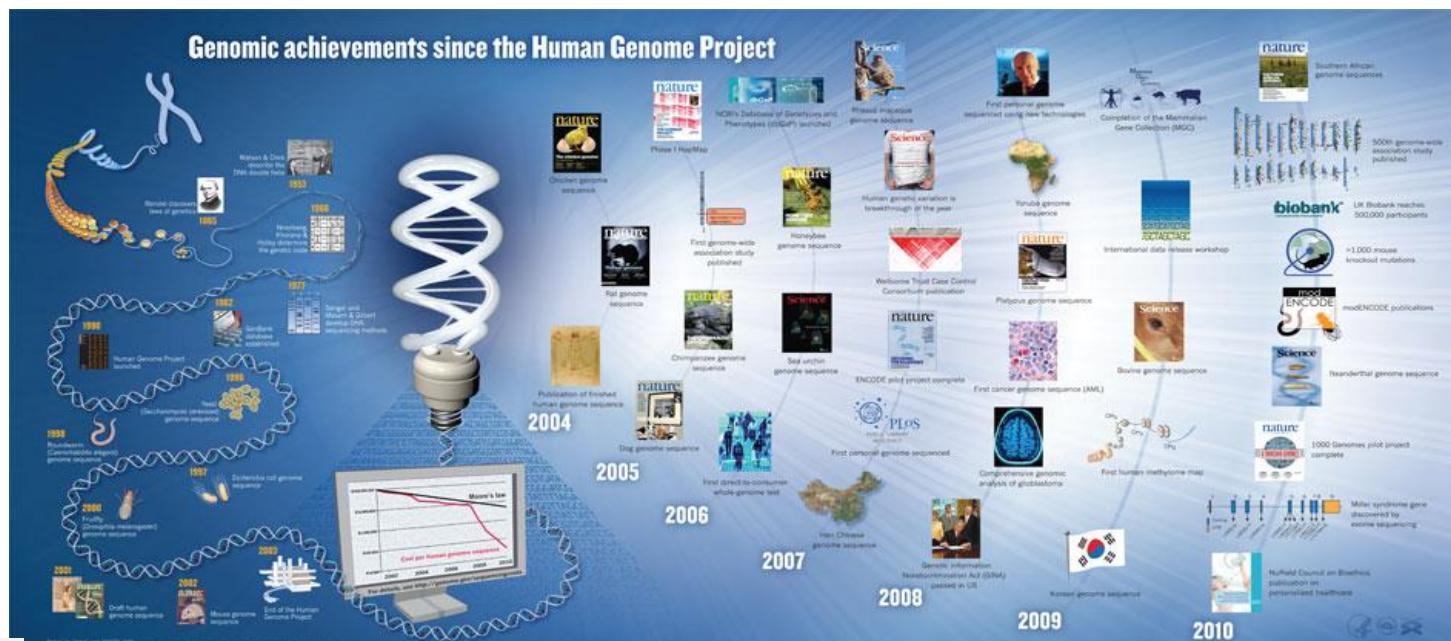


## Before Human Genome Project

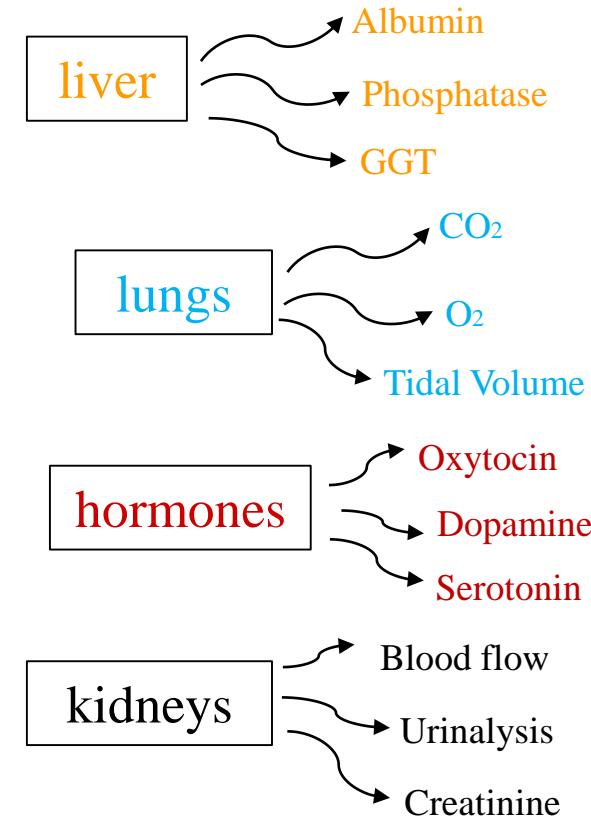
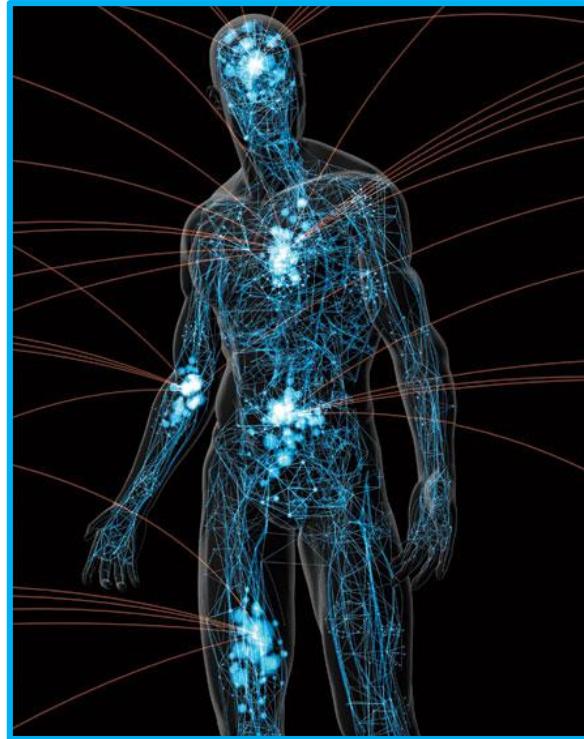
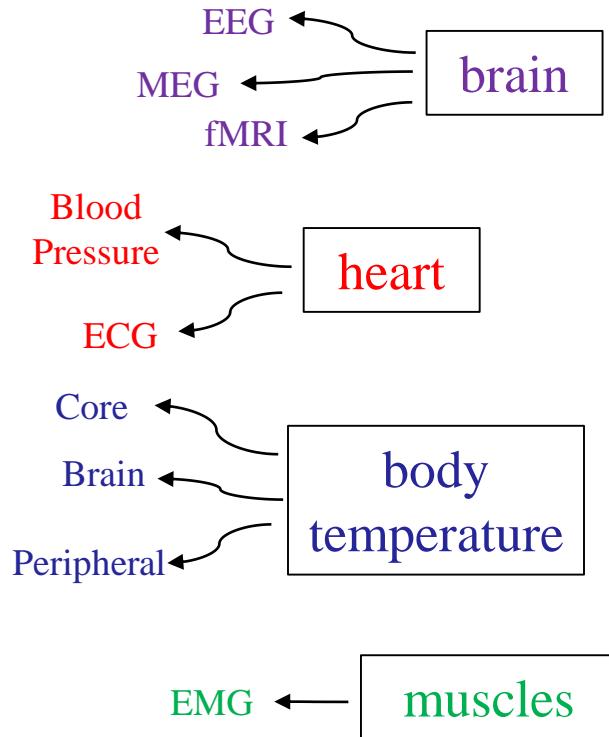


3 Billion  
DNA base pairs

## After Human Genome Project



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



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

1 Day	1 Year	Life Time
$\sim 10^{10}$	$\sim 10^{12}$	$\sim 10^{14}$

### Cloud Storage & Computing



### Hospitals



ICU →



← Neurology

Cardiology →

← Surgery

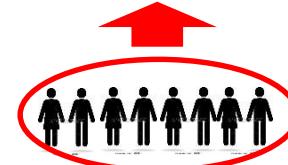
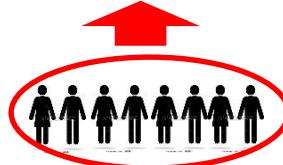
Pulmonology →

← Radiology

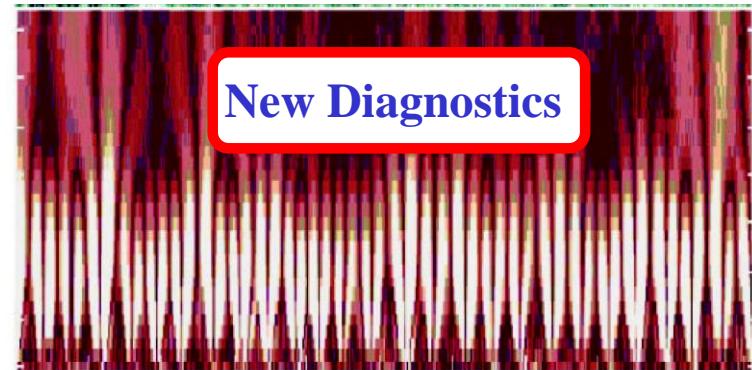
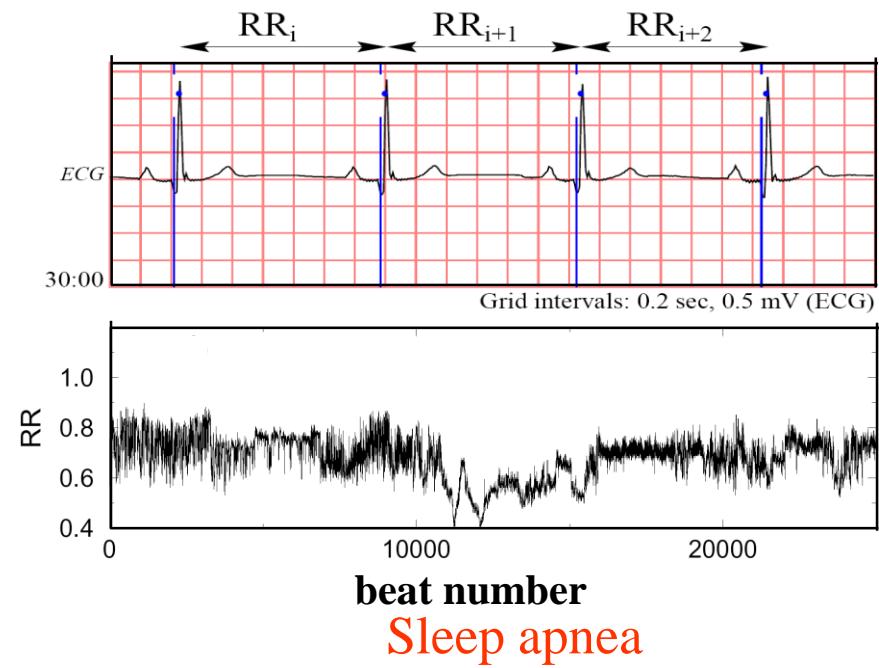
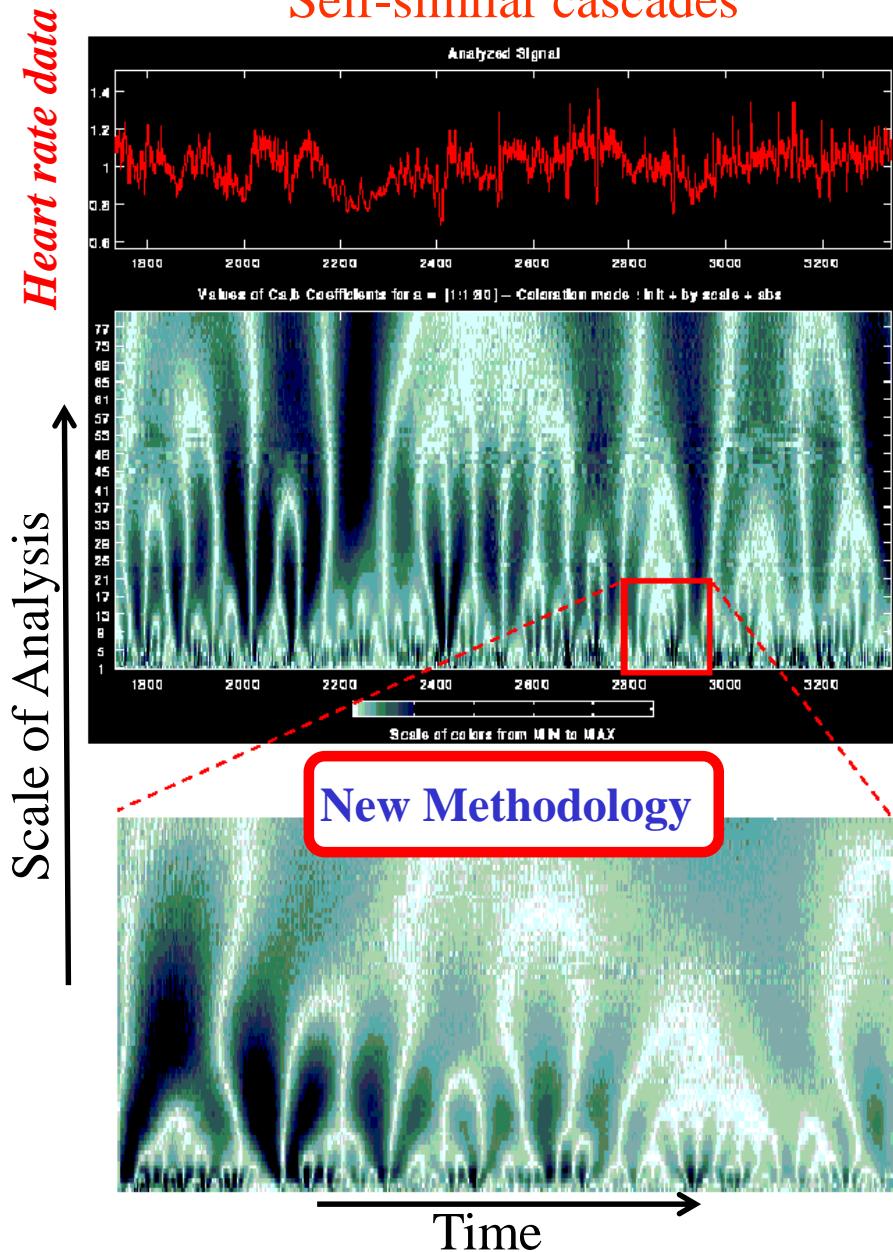
Ambulatory



Patients



## Self-similar cascades

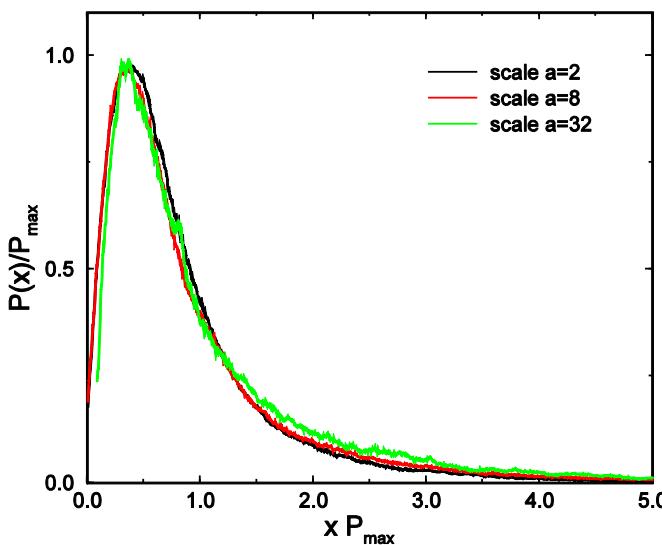
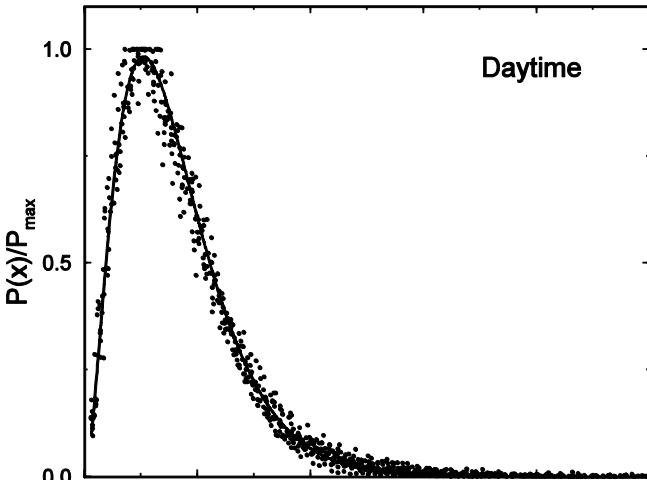


P.Ch. Ivanov *et al.* *Wavelets in Physics*,  
(Cambridge Univ. Press, 1998).

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

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

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

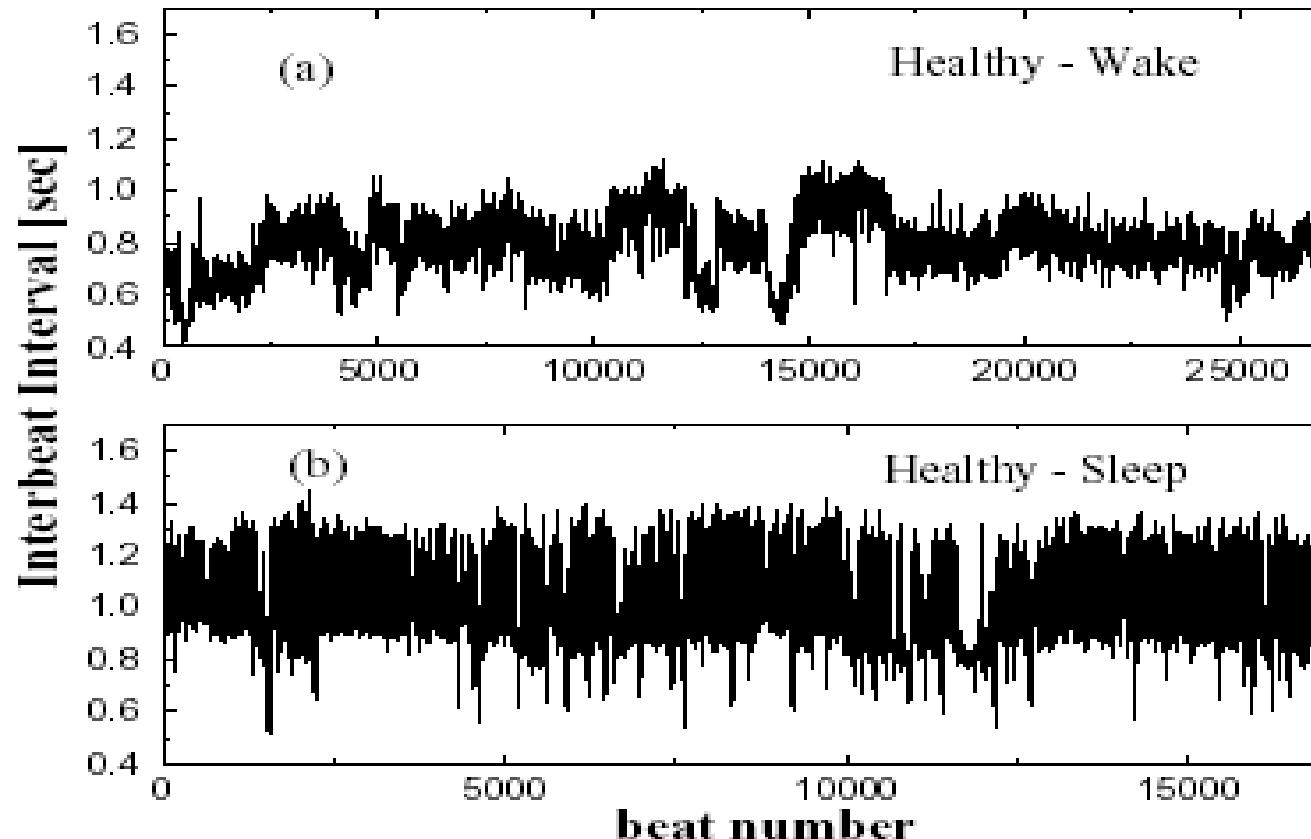


Scale-invariance

“data collapse” over a range of time scales

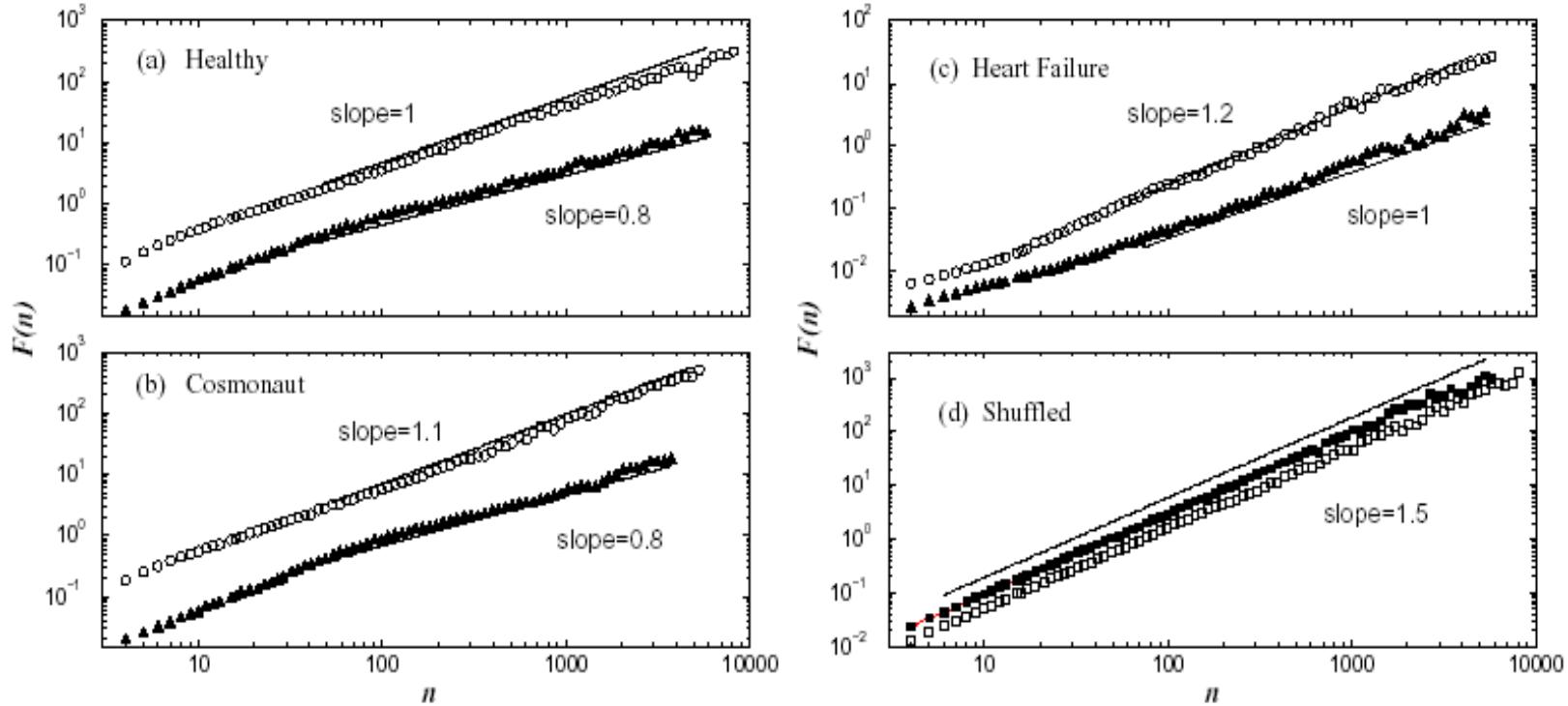
P.Ch. Ivanov *et al.* *Nature* **383**:323 (1996).

## Heartbeat fluctuations during sleep and wake



Average RR<sub>Sleep</sub> > Average RR<sub>Wake</sub>  
SD<sub>Sleep</sub> > SD<sub>Wake</sub>

## Scaling difference in heartbeat dynamics during sleep and wake



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

$\alpha_{\text{Sleep}} \approx 0.8$

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

$\alpha_{\text{Sleep}} \approx 1$

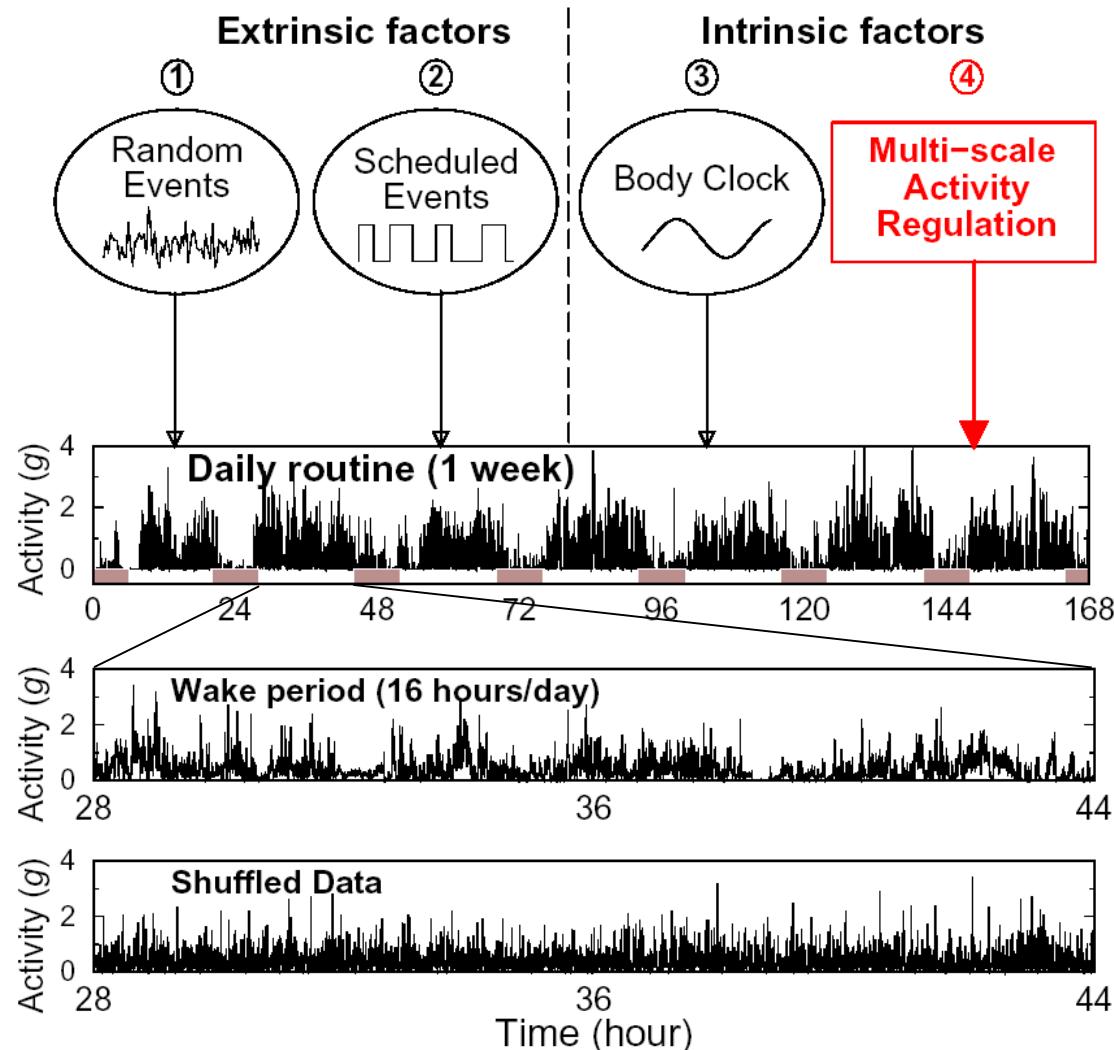
## Motor Activity: Wrist motion fluctuations

### Motivation:

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

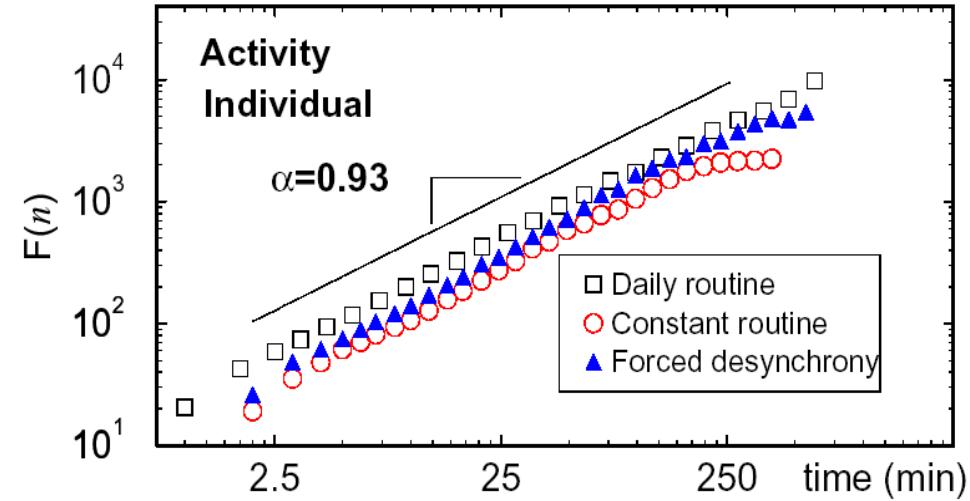
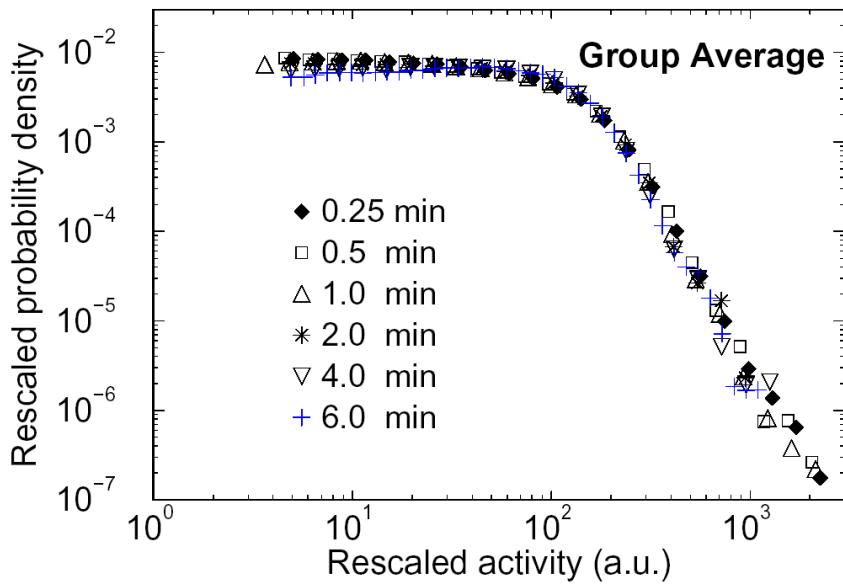


*Magnitudes of  
wrist acceleration*



# 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

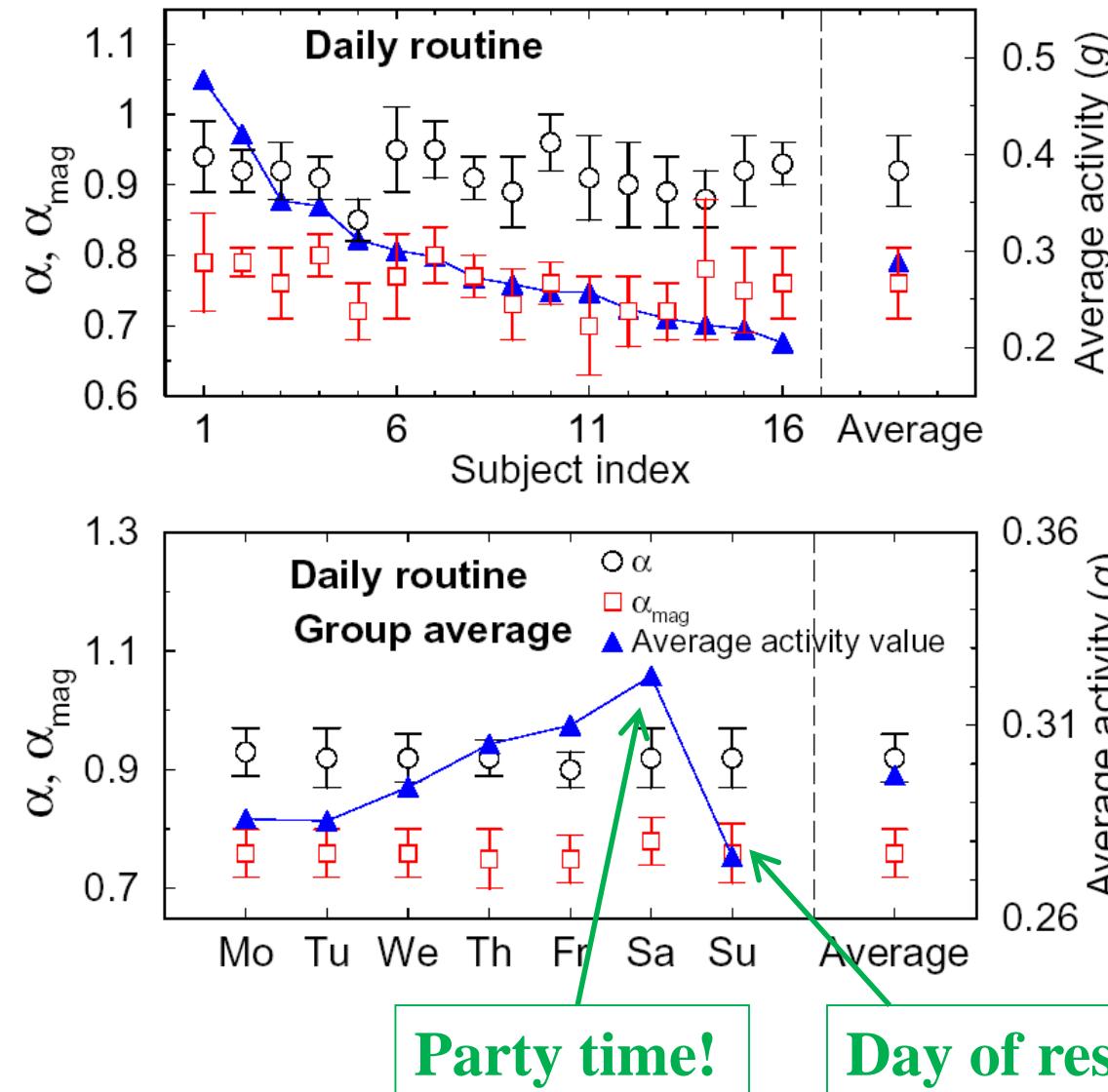
- K. Hu et al. *Physica A* 337: 307 (2004).  
 P. Ch. Ivanov et al., *PNAS* 104: 20702 (2007).  
 K. Hu et al., *Neuroscience* 149: 508 (2007).



Smart  
wristband

# Locomotor system dynamics: wrist motion fluctuations

## Scaling exponents independent of activity level



Protocol	$\alpha$	$\alpha_{mag}$
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

Scaling exponents ---  
remarkably consistent for:  

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

# 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**

# 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

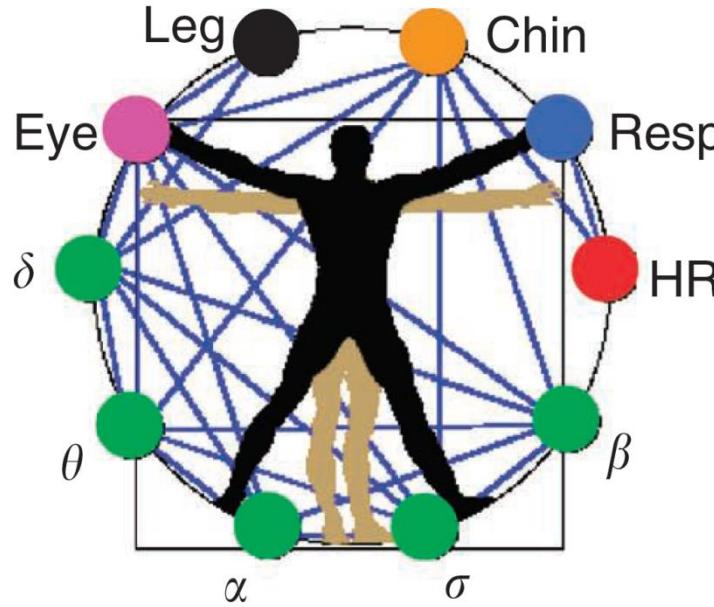
We made *first* inroads:

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



Infer/quantify interactions  
among diverse dynamical systems

# Horizontal Integration of physiological interactions



## Physiological interactions

- Network of dynamical interactions; study the evolution of multiple physiologic interactions across different physiologic states

## Physiologic recordings

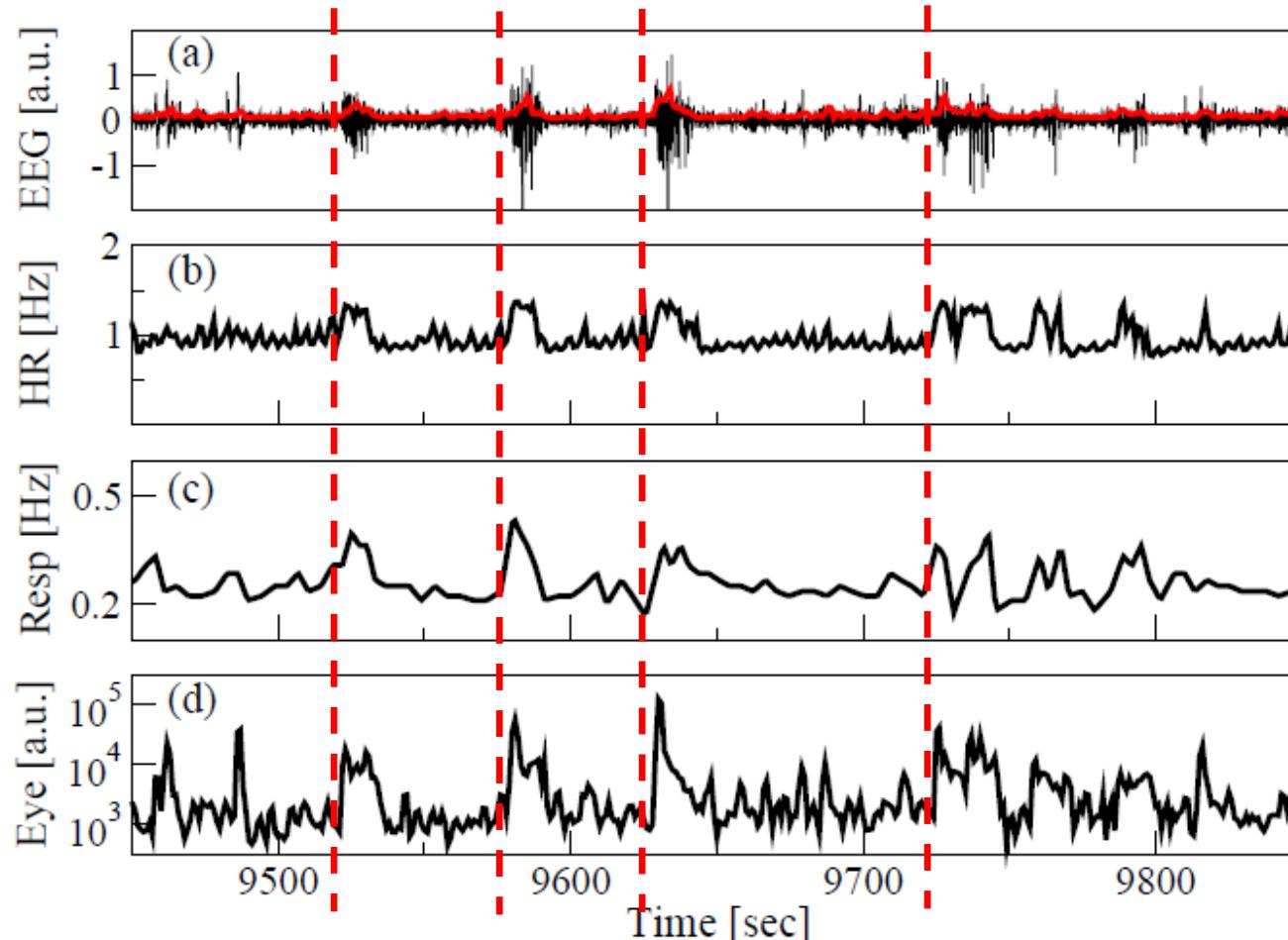
Full-night polysomnographic data from healthy young subjects:

- 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)

# Coordinated activity across diverse systems



**EEG- $\sigma$  band:  
sleep spindles**

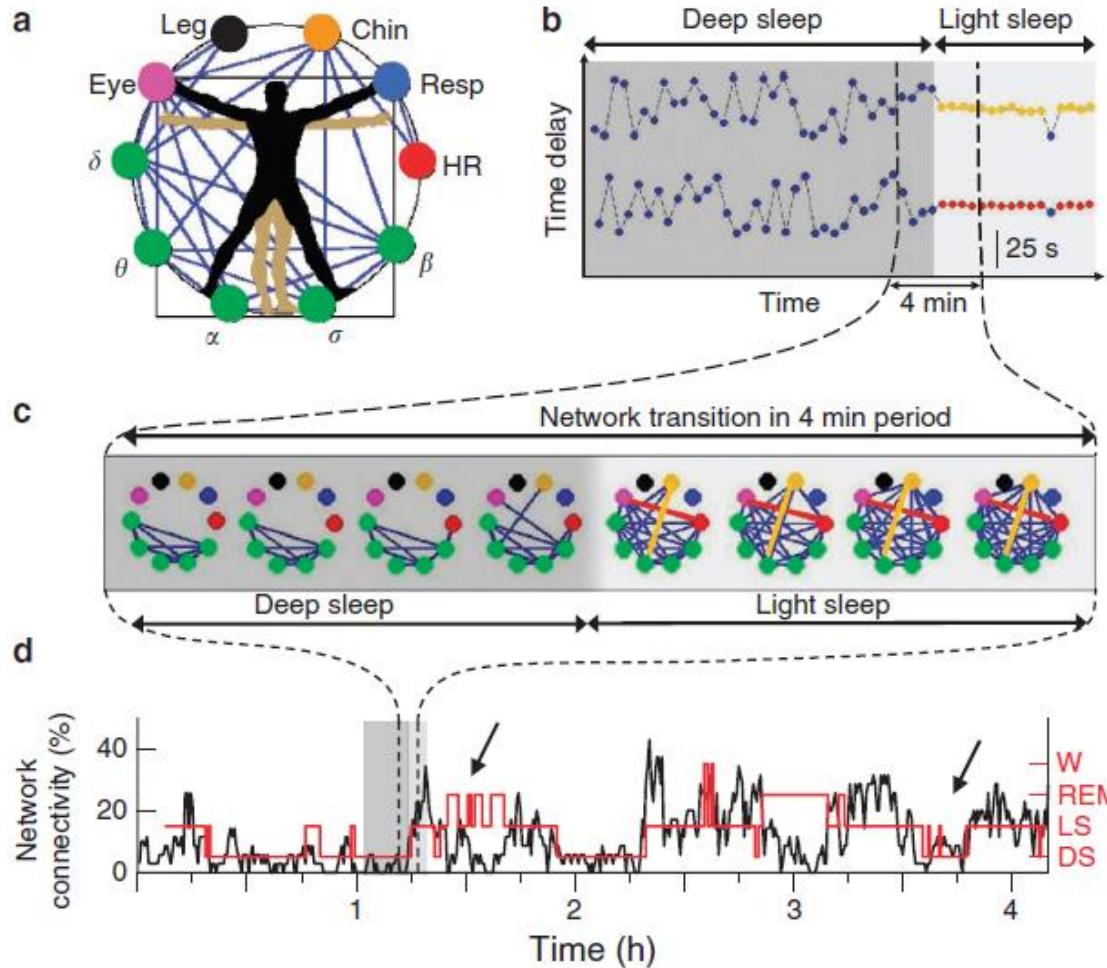
**Heart rate**

**Respiratory rate**

**Eye movements**

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

# Transitions in the network of physiological interactions



←  $\alpha - \text{Chin}$  interaction  
←  $\text{HR} - \text{Eye}$  interaction

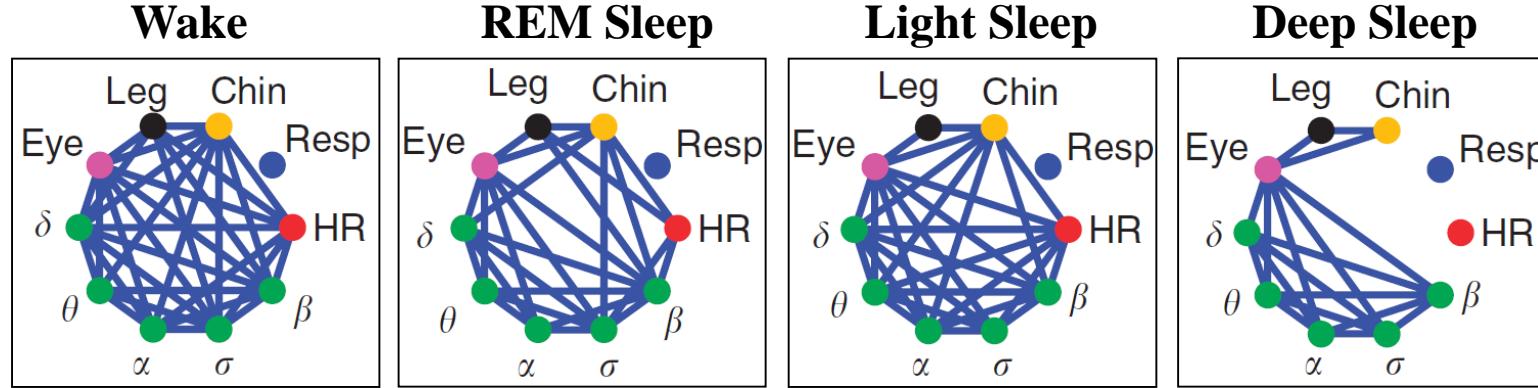
$\alpha - \text{Chin}$  link  
 $\text{HR} - \text{Eye}$  link

## Dynamical Evolution

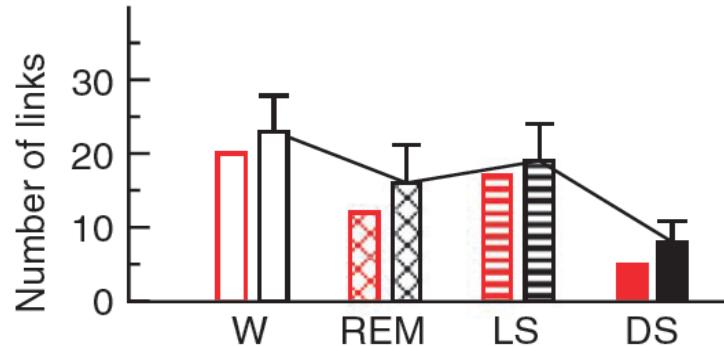
Bashan et al. *Nature Communications*,  
3:702 (2012)

→ Fast reorganization of network connectivity with transitions across physiologic states

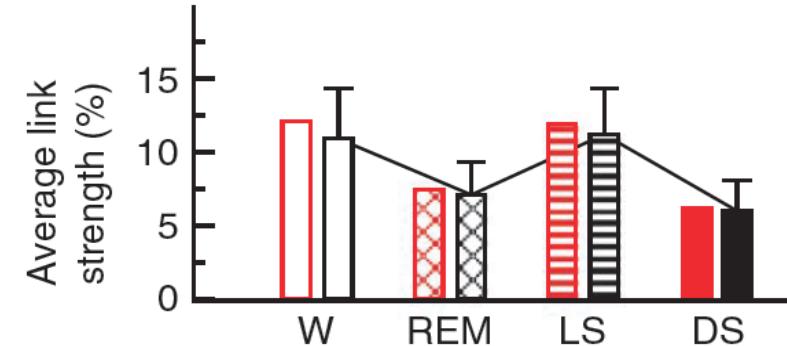
# Network Topology & Physiologic Function connectivity across sleep stages



Network connectivity



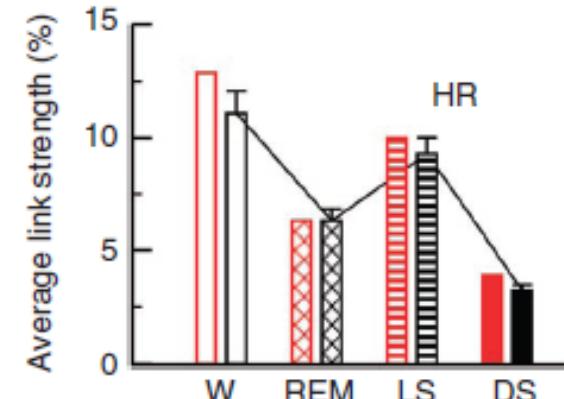
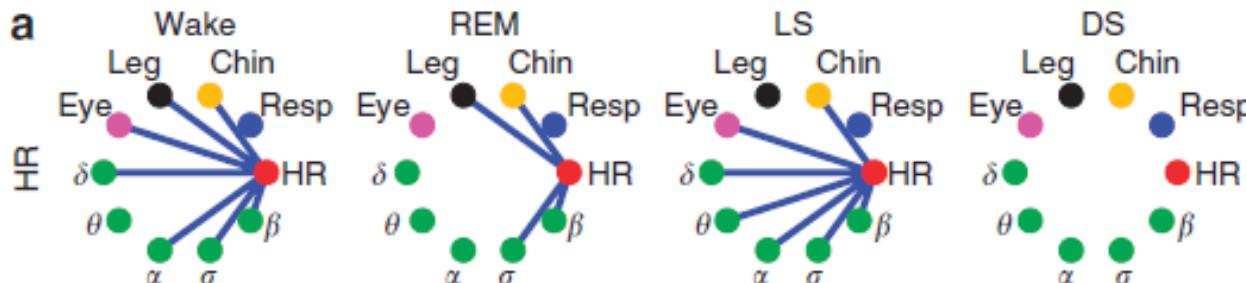
Network link strength



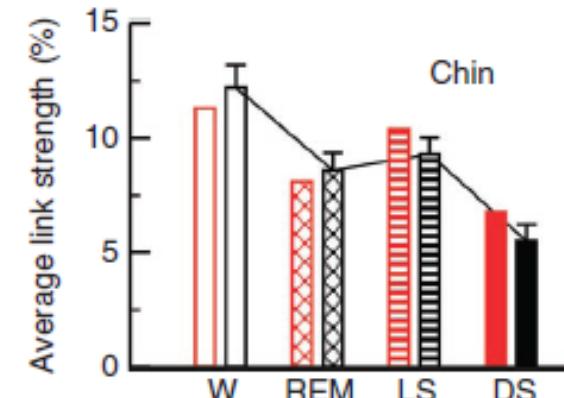
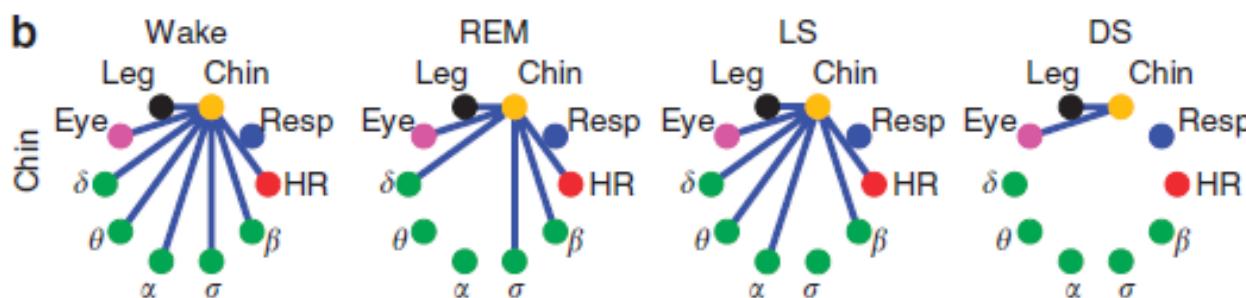
→ Network topology changes with physiologic states

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

## Heart



## Chin

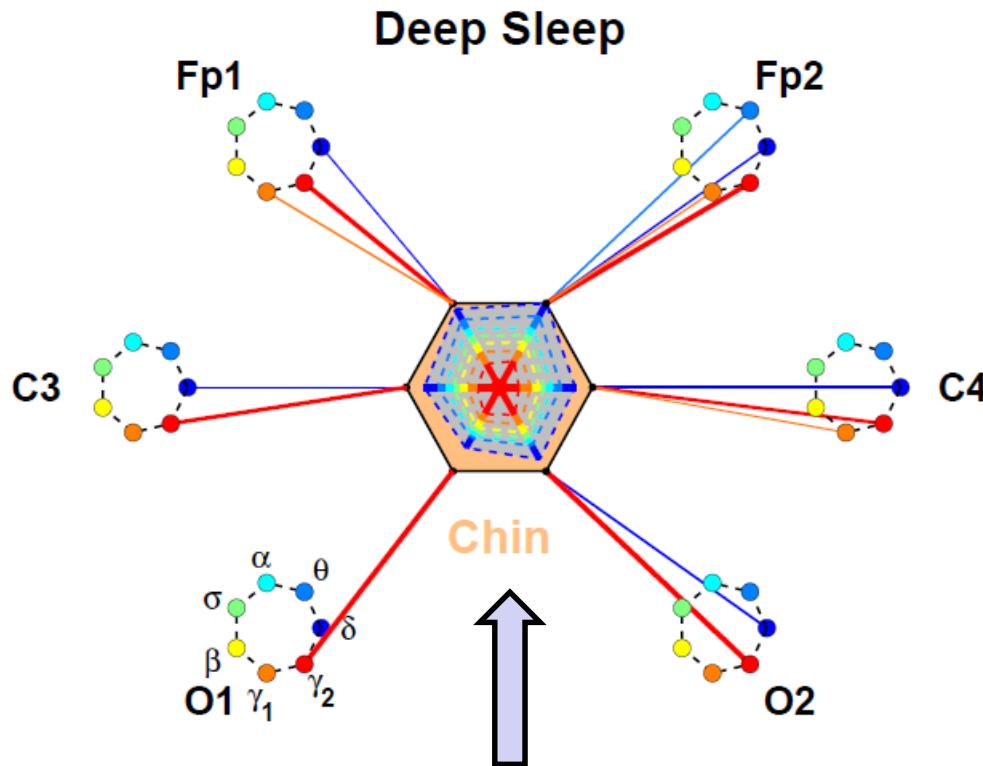


Robust sleep-stage stratification pattern in:

- Individual node connectivity
- Average link strength of individual nodes

# Maps of physiologic interactions

**Key question:** How brain communications modulate organ dynamics?



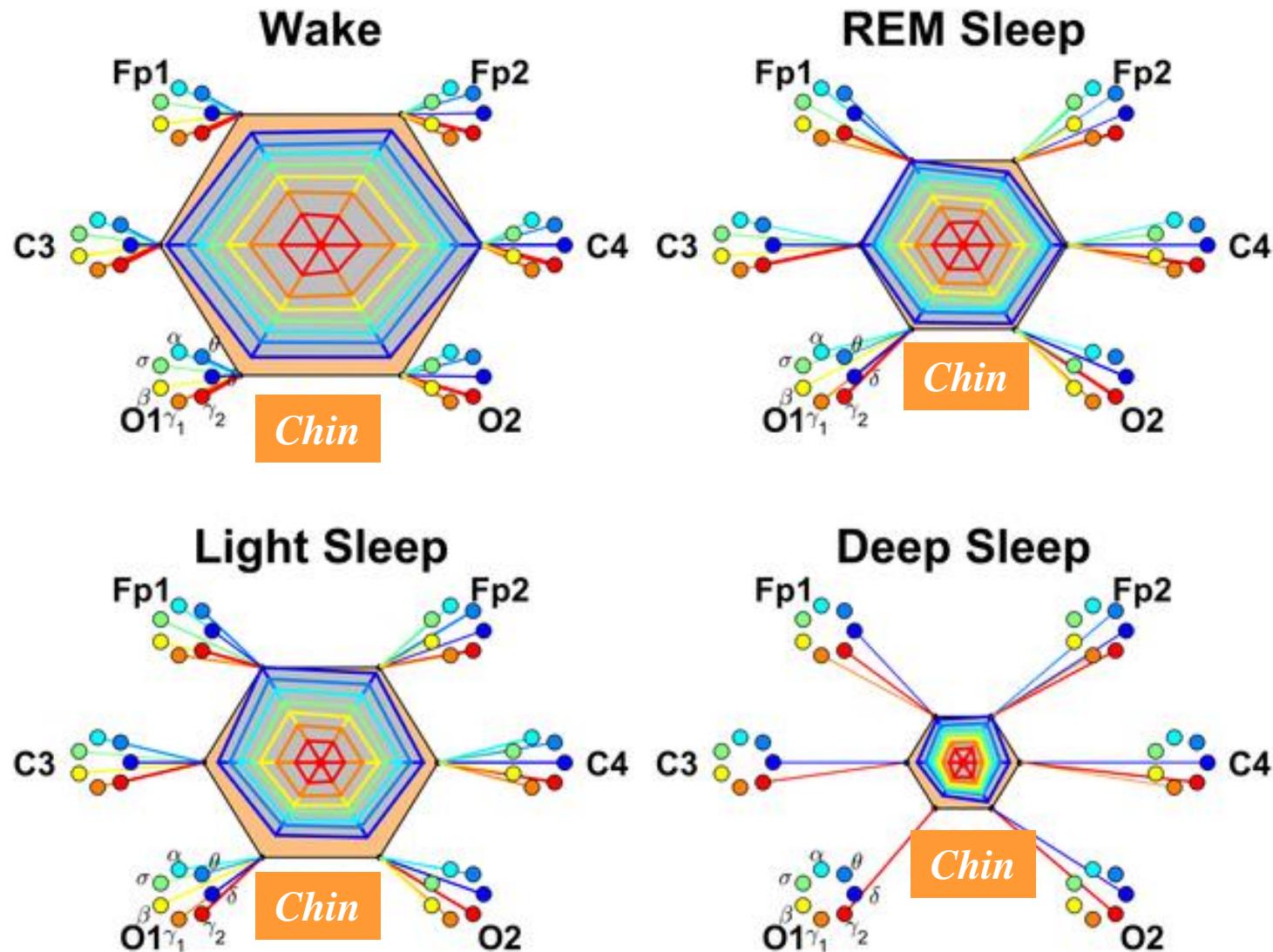
**Radar Chart in the Hexagon:  
Brain Control on the target organ**

**Location of the nodes:  
Brain EEG Channels**

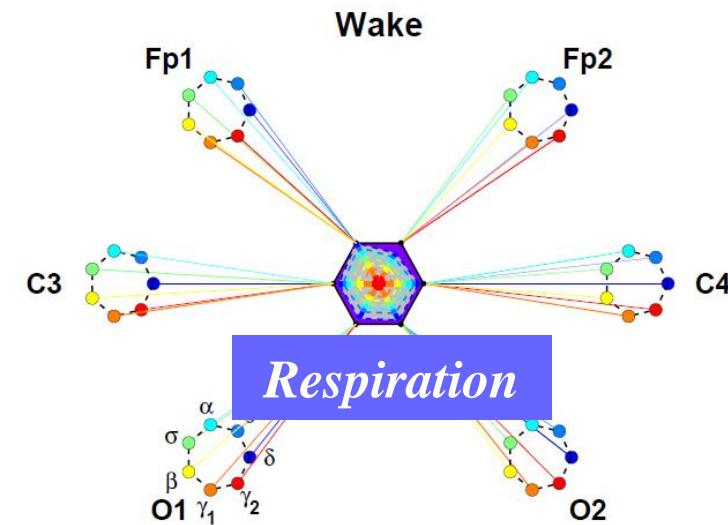
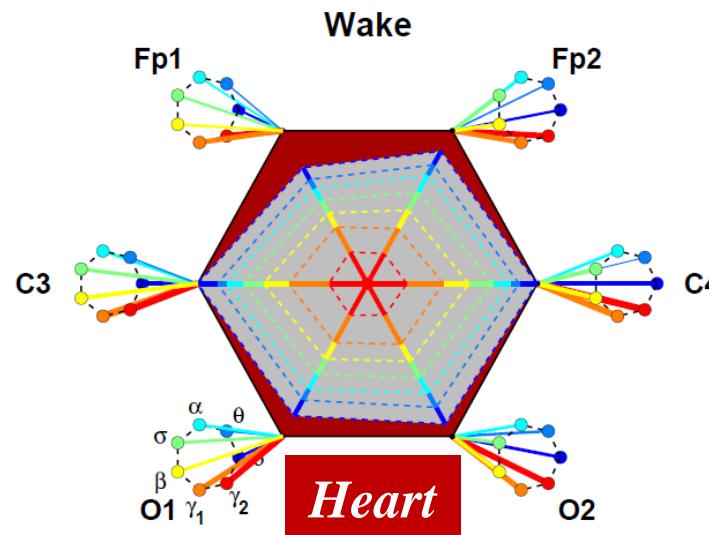
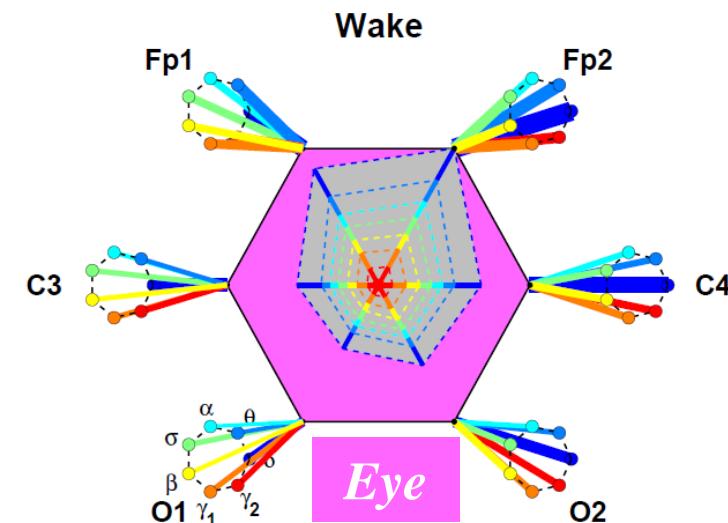
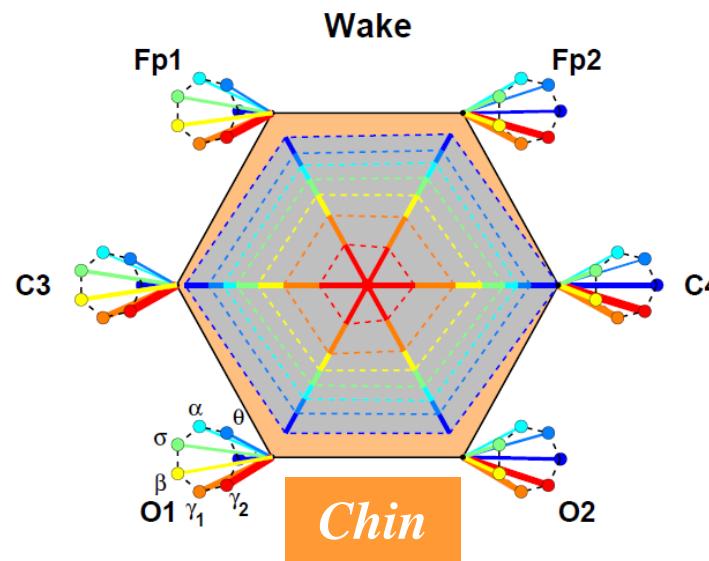
**Colors:  
Frequency bands in the EEG  
signals**

**Width of the links:  
Coupling strength between the  
systems**

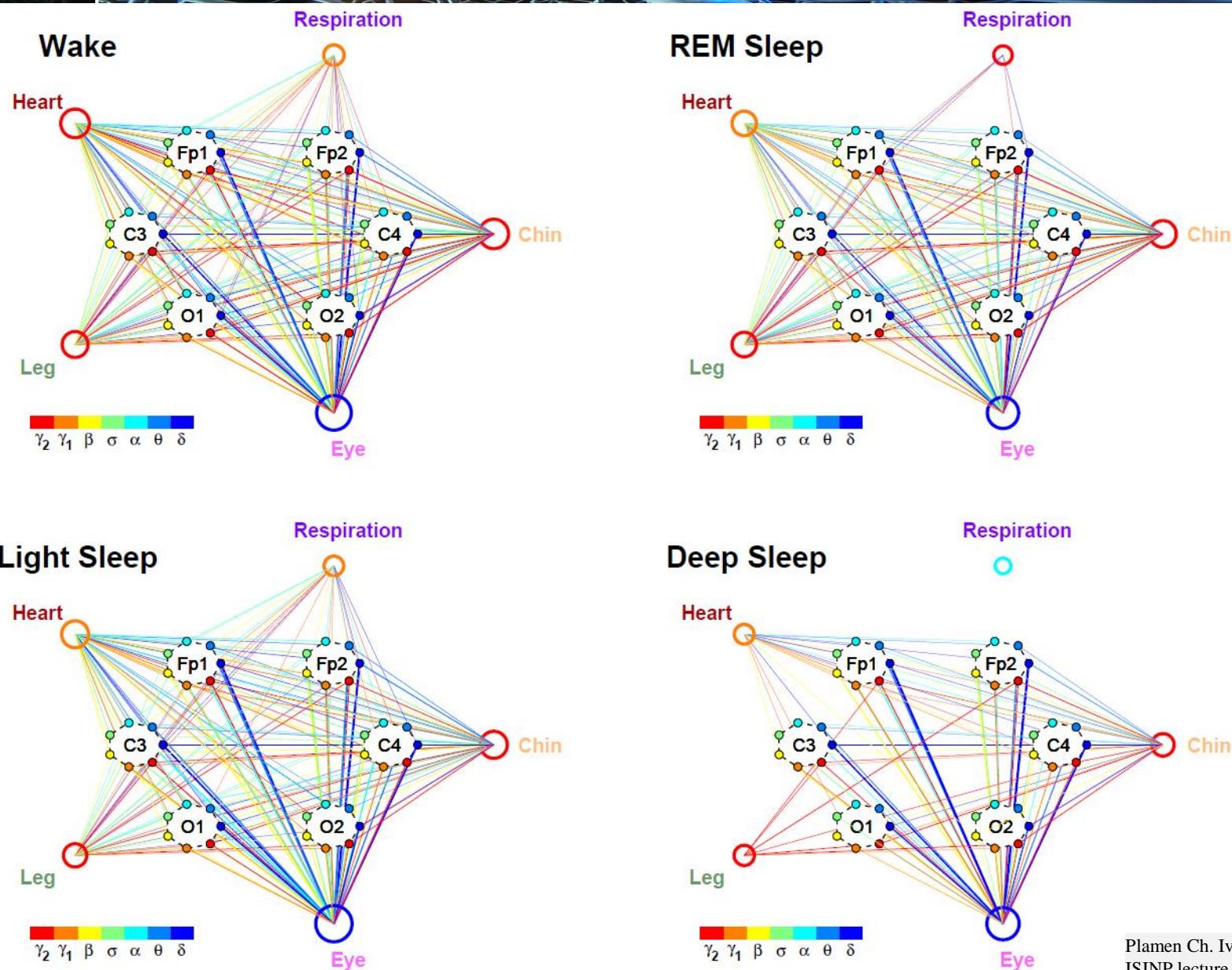
# Visualization: different physiologic states



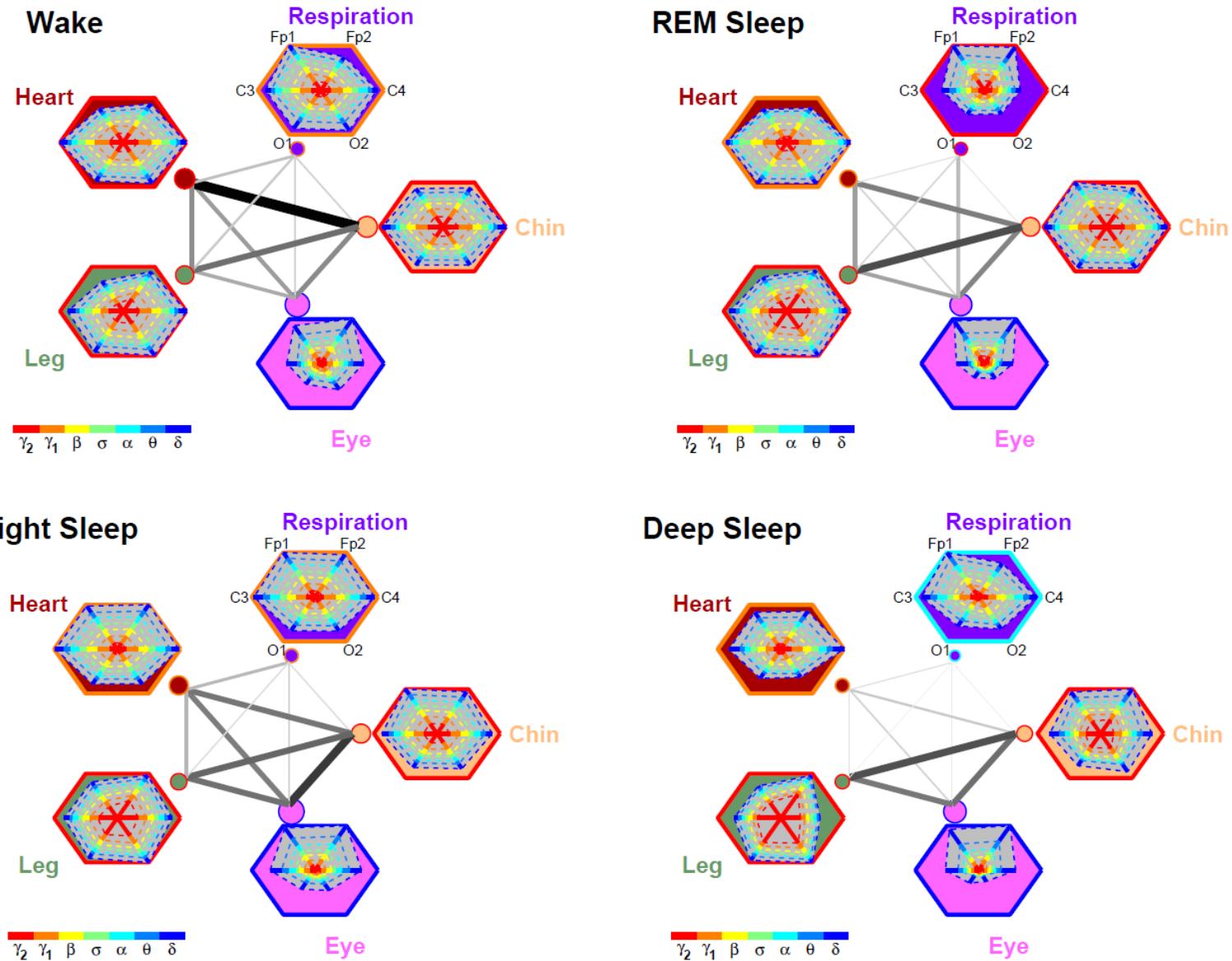
# Maps for different organ systems



# 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

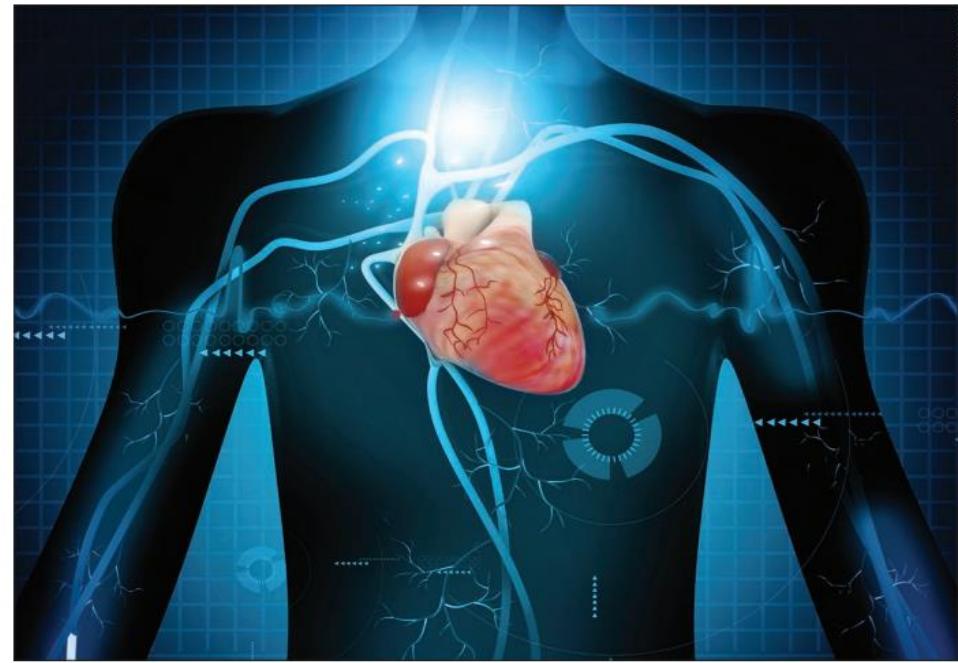
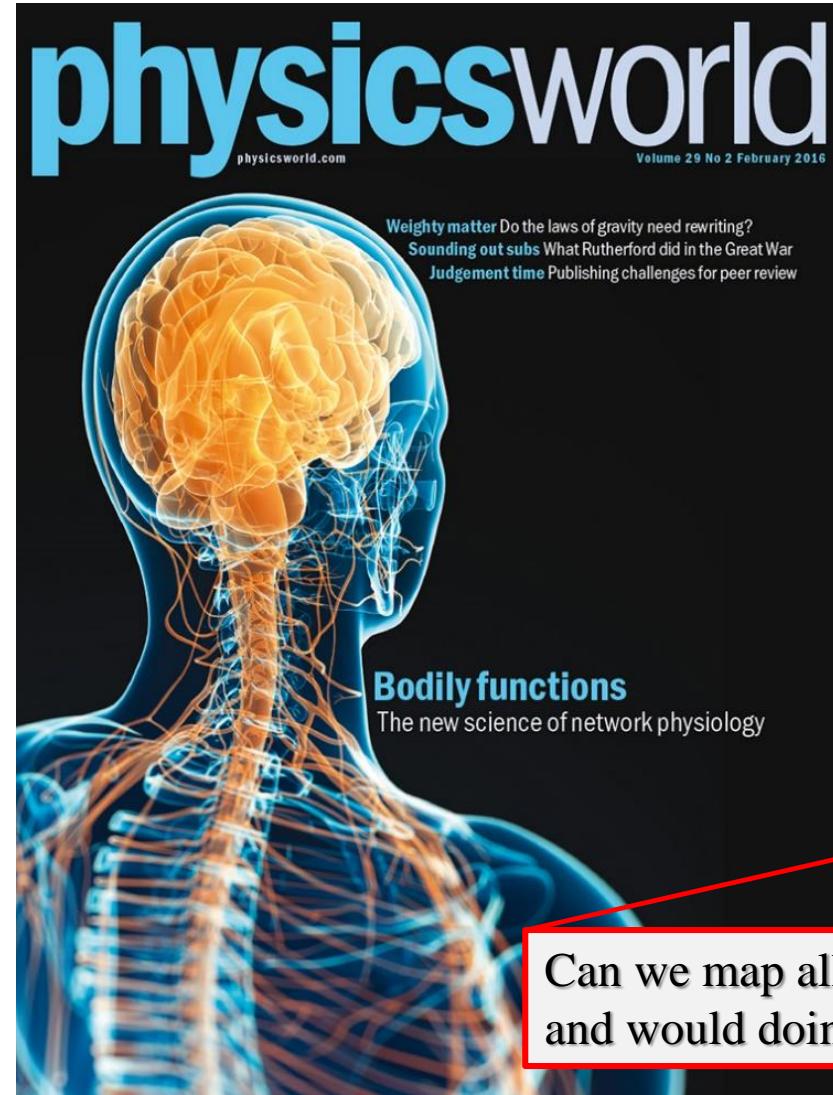


# Network Physiology

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

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

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

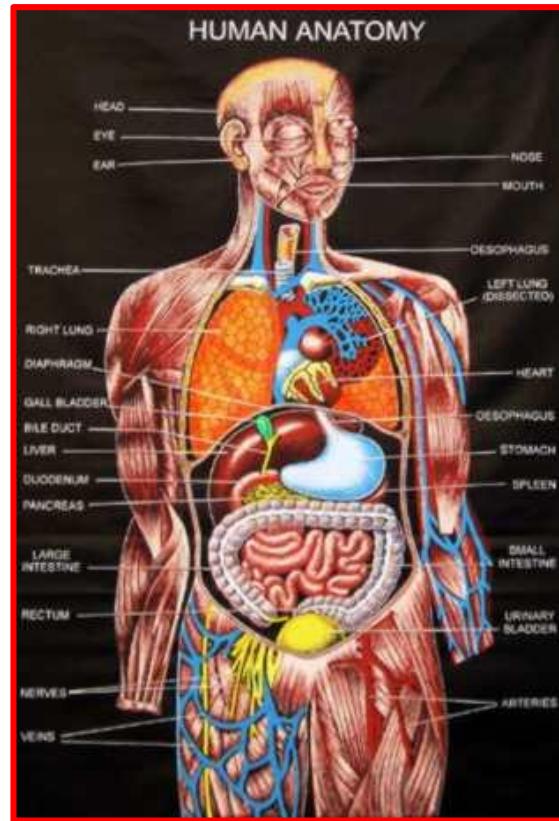
Can we map all the information being circulated in the human body, and would doing so be any use?

least the beginnings of an answer. Having developed sciences until now," he says.

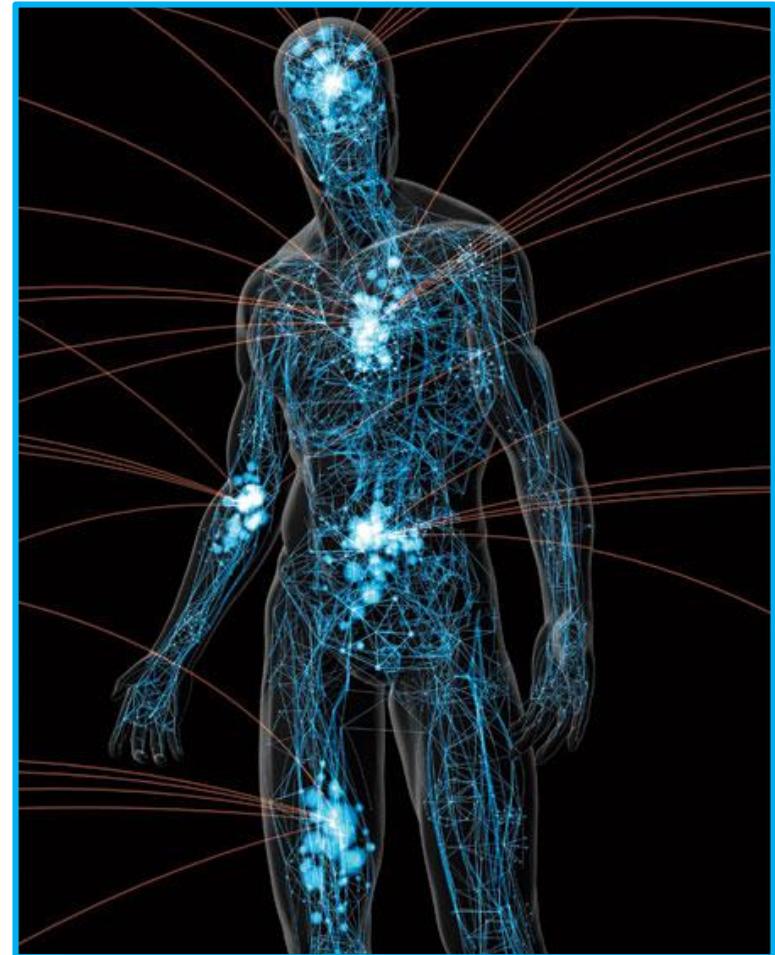
Plamen Ch. Ivanov, ISINP lecture, 24 July 2017

*Atlas of Dynamic Interactions  
of Organ Systems*

*Atlas of Human Anatomy*



need  
→

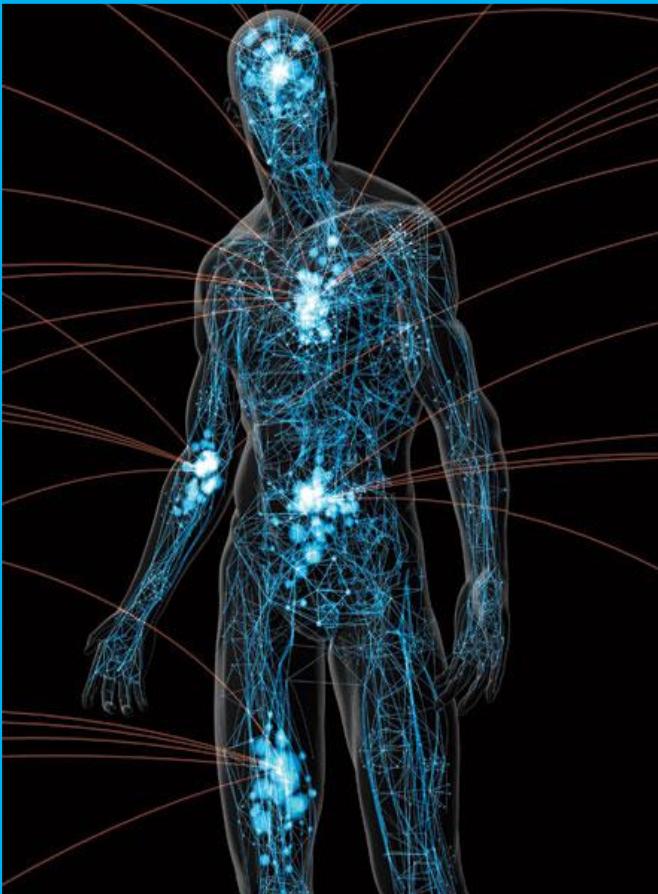


- Revolutionize our knowledge and understanding of the fundamental mechanisms that regulate and coordinate organ-to-organ interactions

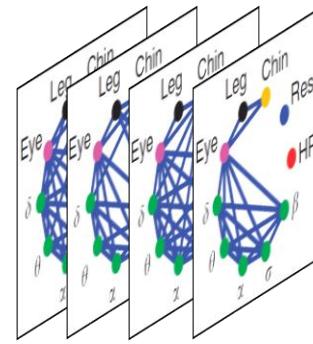
# Physiology and Medicine

Such Atlas would contain:

## *Atlas of Dynamic Interactions of Organ Systems*

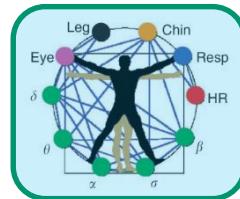


Catalog of reference maps representing dynamical organ interactions under:

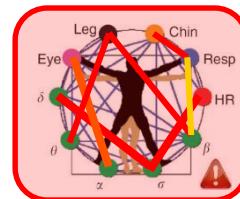


- healthy conditions
- age groups
- different physiologic states (rest/exercise, sleep/wake, sleep stages, circadian phases)
- pathological conditions (multiple organ failure, coma, heart failure, sleep apnea ...)

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

# Physiology and Medicine

## Novel biomarkers



## New kind of Physicians



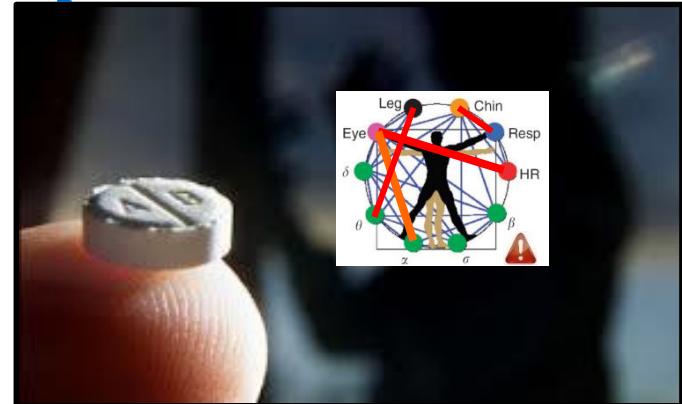
## Personalized health monitoring



## Next generation ICU monitoring devices and alert system

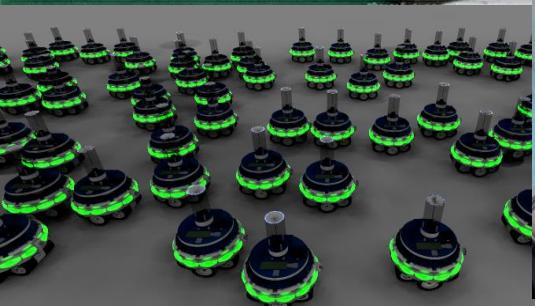


## Comprehensive assessment of drugs

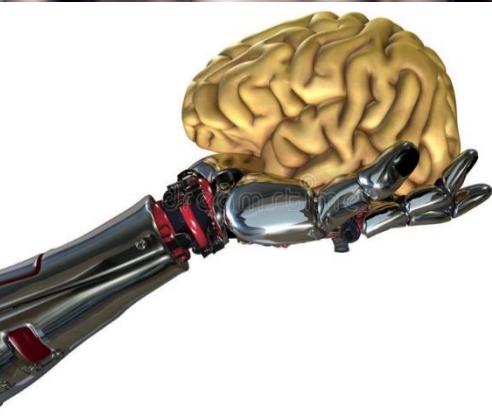
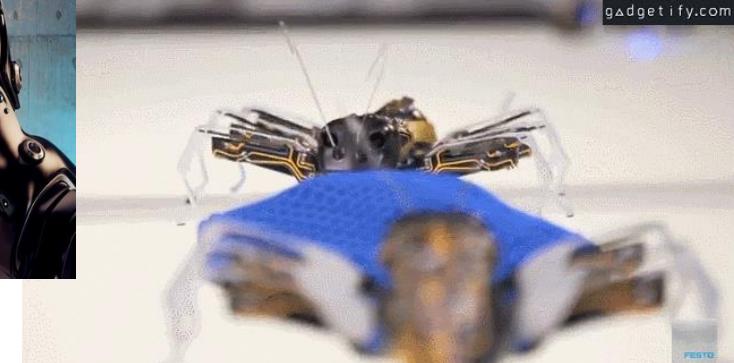


# Technology and AI: Robots and Cyborgs

Improve AI & robots, swarms  
of decentralized multirobot systems



Cyborgs: merge physiology & technology



## Human Genome



Motivated  
Big Data

Genetic mutation  
Disease  
limited sequences  
(1950's – 1980's)



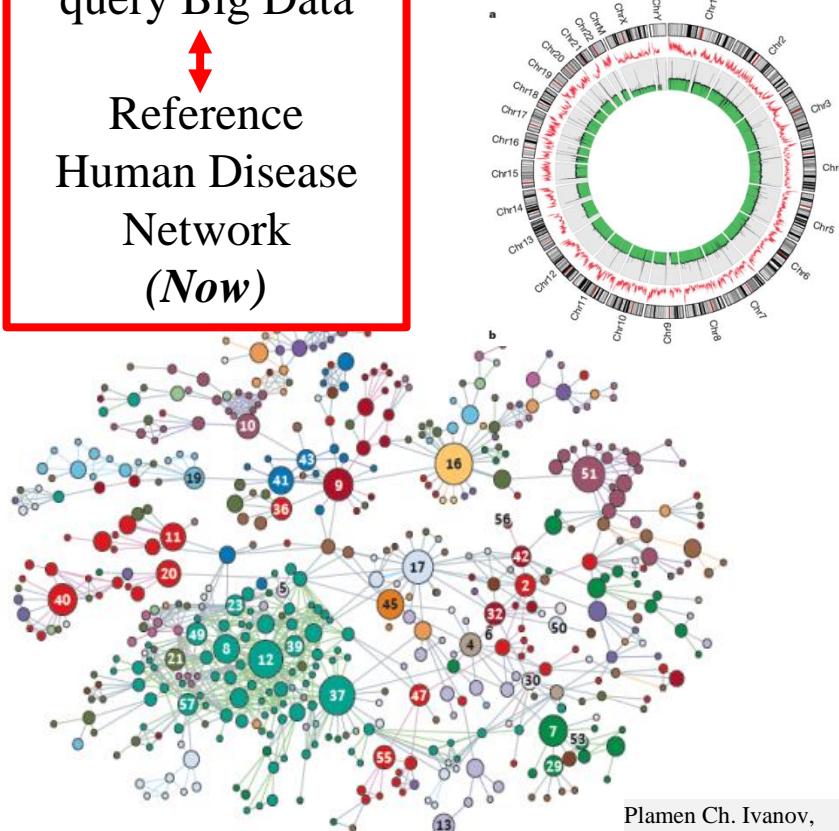
Human Genome Project  
Reference genome  
Complete sequencing  
Limited individuals  
**(1990 – 2003)**

Required  
New Methods

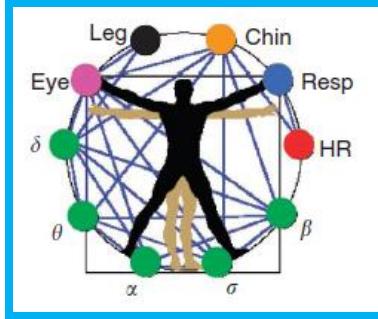
New methods to query Big Data  
Reference Human Disease Network  
**(Now)**

Next  
Big Data

“Super Big Data”  
Personalized genetics  
**(Future)**



## Network Physiology

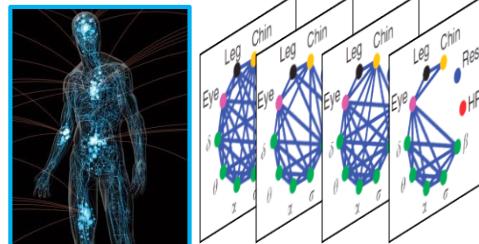


New methods

Physiologic network topology  
↓  
Physiologic function  
preliminary limited data  
**(2012)**

*Atlas of Dynamic Interactions of Organ Systems*

Blueprint Base Reference of Physiologic Maps  
**(2015 – 2020)**



New Kind Big Data

Next Big Data

**“Physiolome”**

First Big Data on continuous parallel recordings of organ systems

Reference Catalog of Physiologic Maps on Conditions, Diseases, Drugs

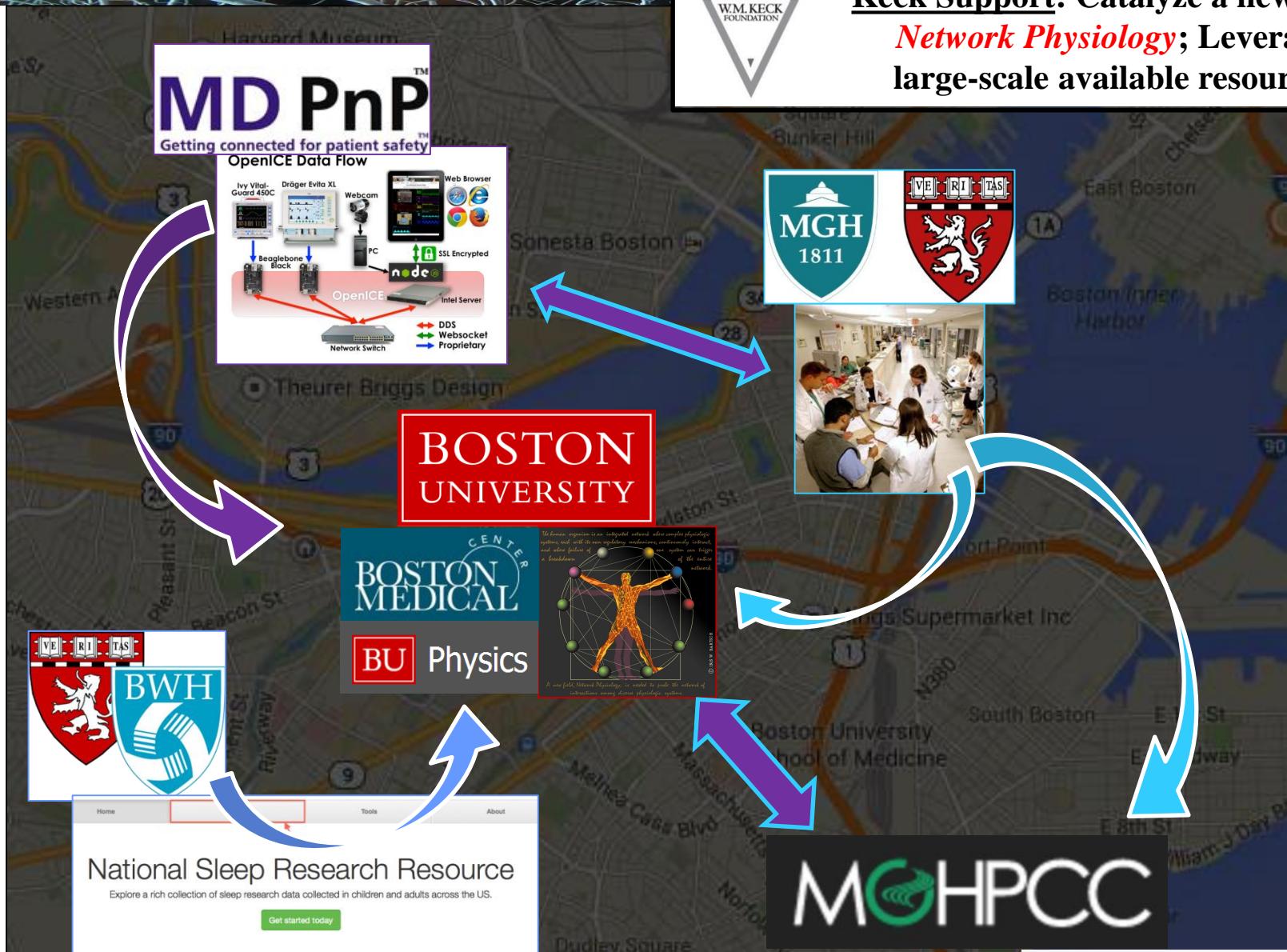
Clinical practice  
ICU monitoring devices  
**(Future)**

“Super Big Data”  
↑  
Daily personalized monitoring and health assessment based on Network Physiology  
**(Future)**



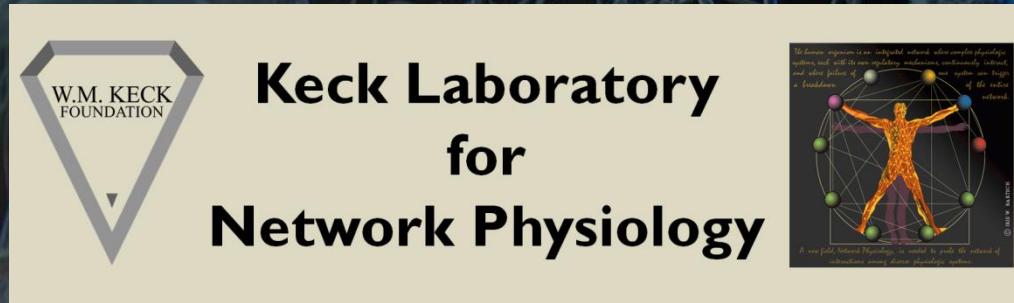
# Collaboration

# Ongoing Program: Interdisciplinary Collaboration



# Our Group:

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



## Group members:

Kang Liu, Ronny Bartsch,  
Qianli Ma, Chuanhua Bian,  
Gustavo Zampier, Aijing Lin,  
Xiaolin Huang, Aylin Cimenser  
Xiyun Zhang, Wanting Xiong  
Fabrizio Lombardi, Chengyu Huo,  
Jilin Wang

## Support:

- *Atlas of Dynamic Interactions among Organ Systems*

## *Openings:*

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



## *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)

## *Support:*

- W. M. Keck Foundation
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- European Community project DAPHNet/FP6 IST
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