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


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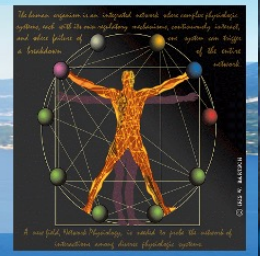
BOSTON UNIVERSITY

HARVARD MEDICAL SCHOOL

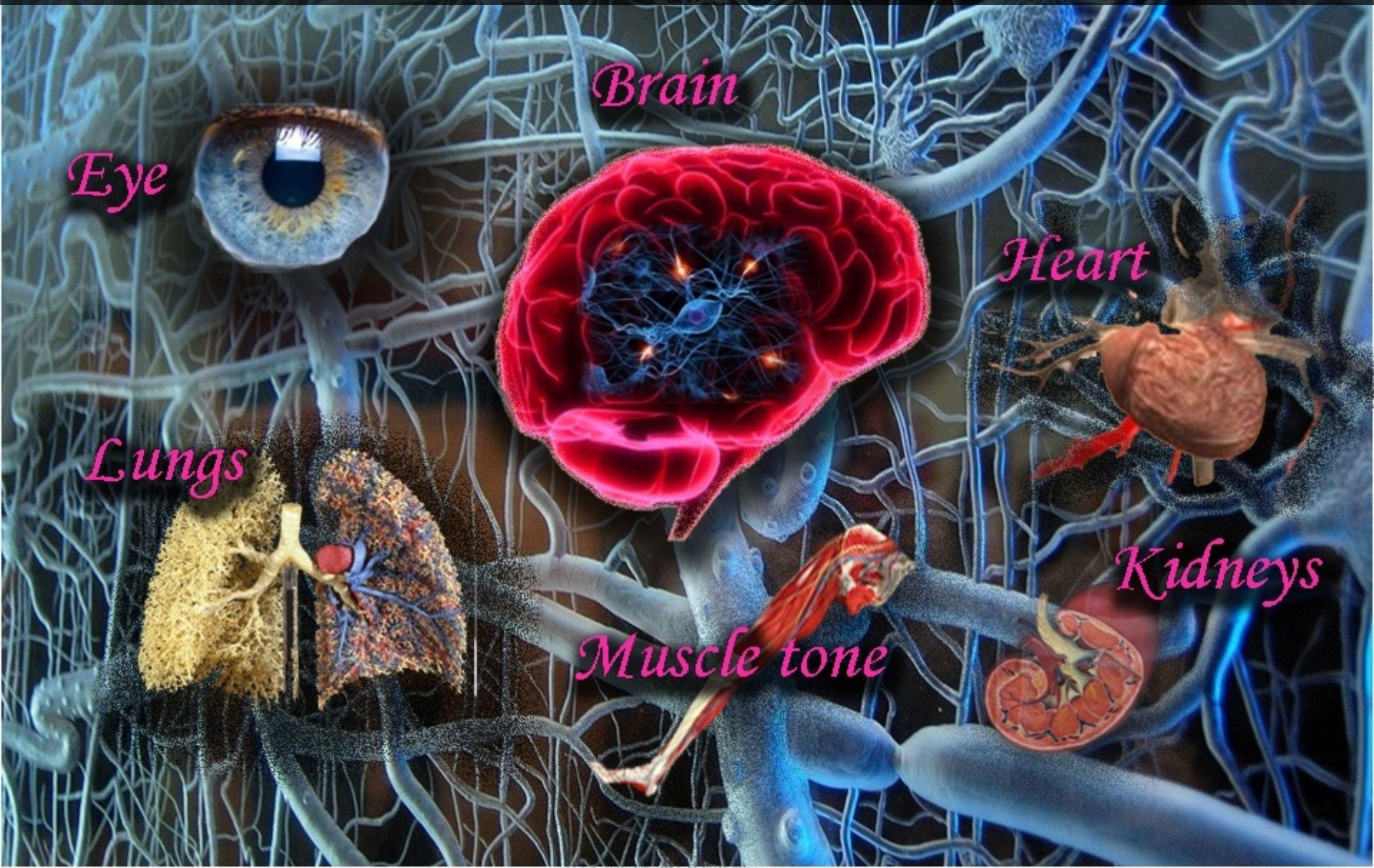
LAKE COMO SCHOOL OF ADVANCED STUDIES

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

Lake Como School of Advanced Studies, 24 - 29 July 2022

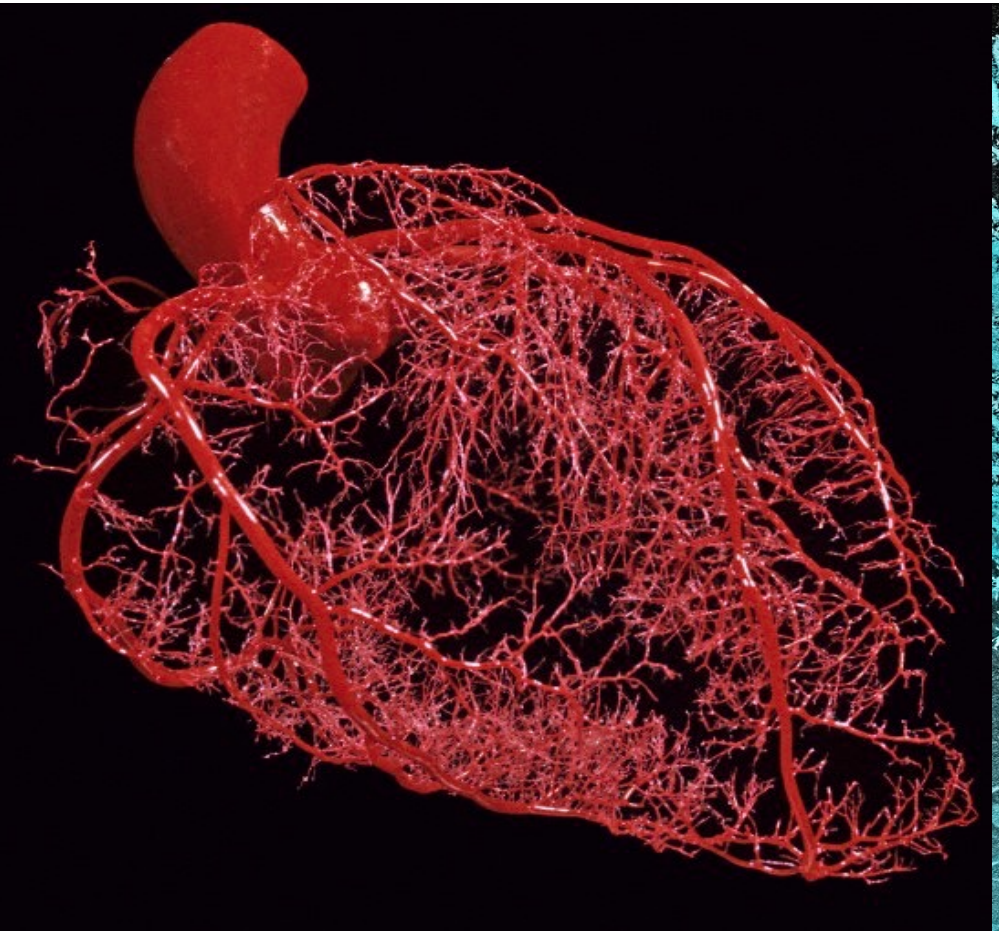


# Human Organism
## comprises diverse multi-component physiological systems

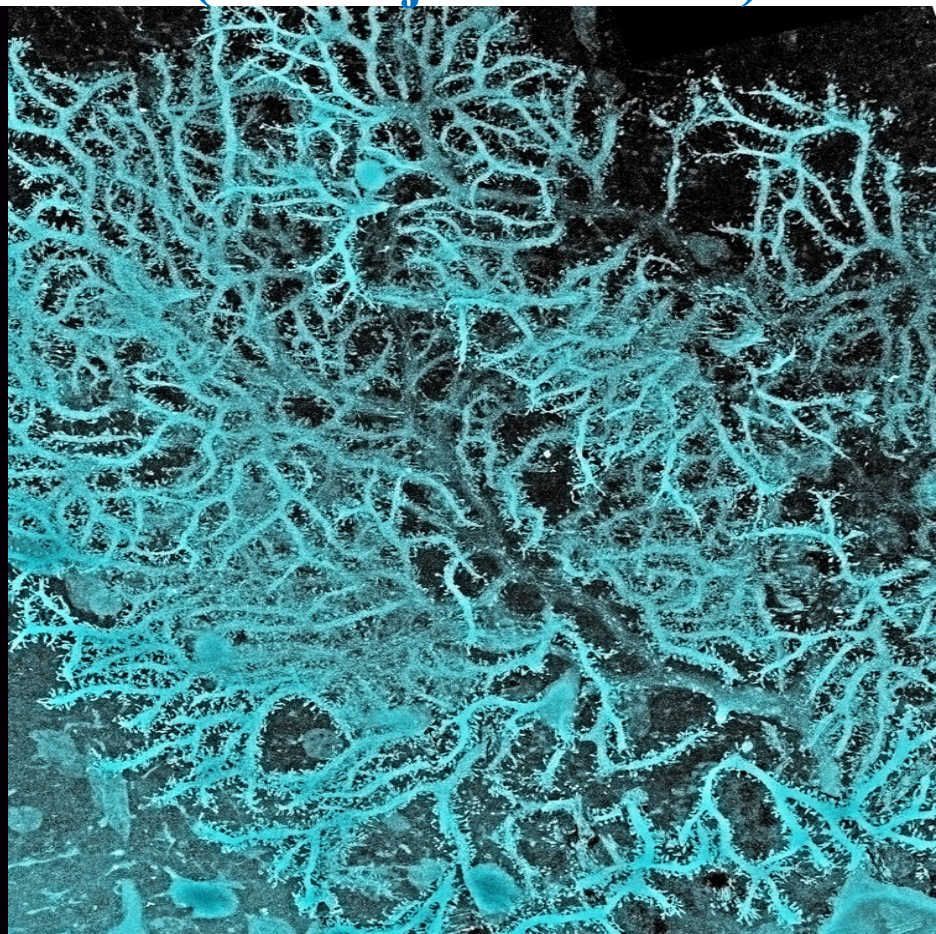


# Human Organism
## comprises diverse multi-component physiological systems

**Heart:** Vascular network

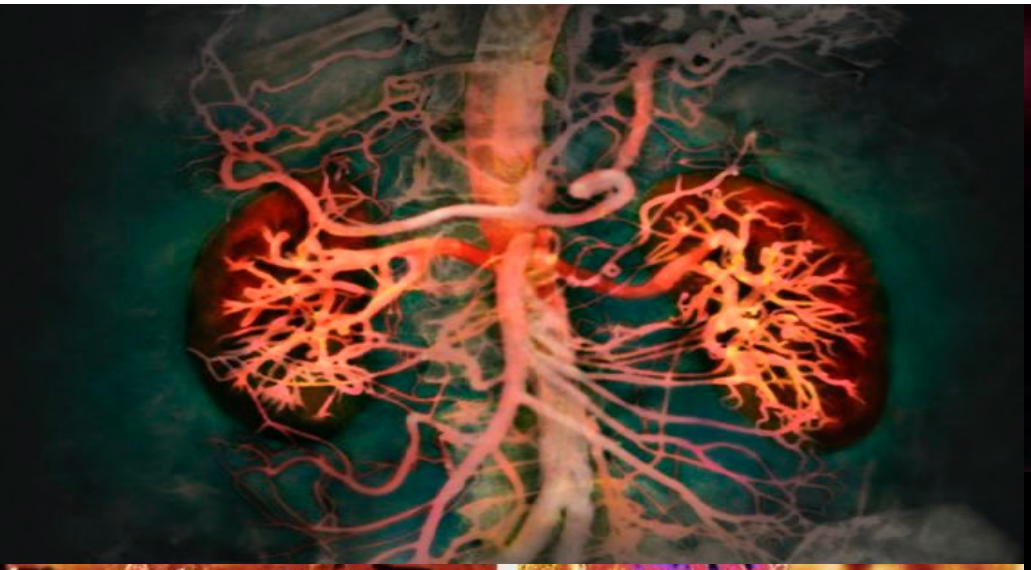


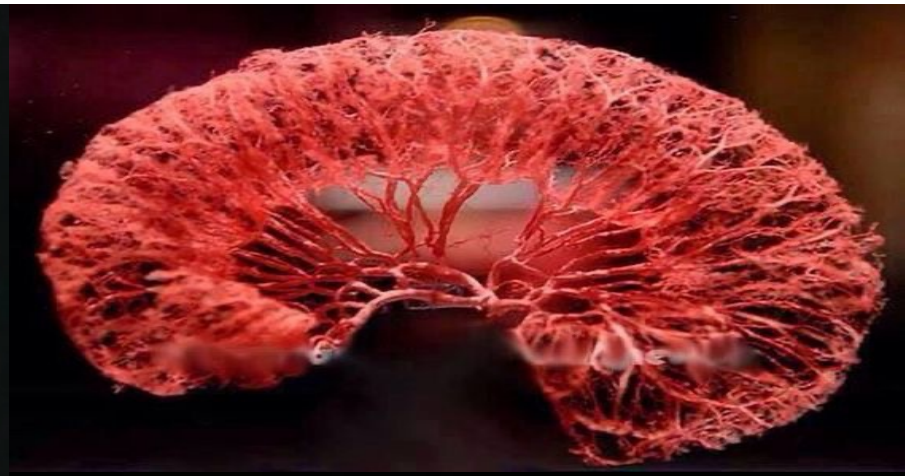
Conducting network
(Purkinje dendrites)

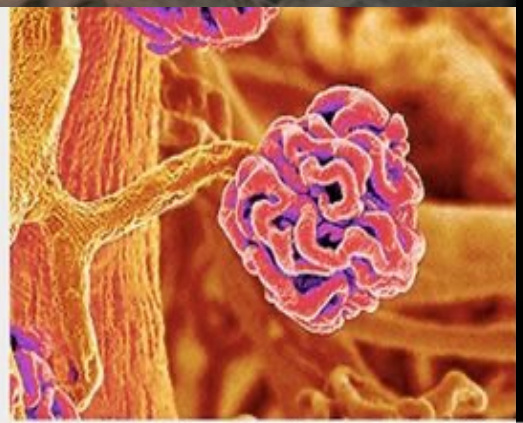


# Human Organism
## comprises diverse multi-component physiological systems

**Kidney:** Vascular network in decreasing scale

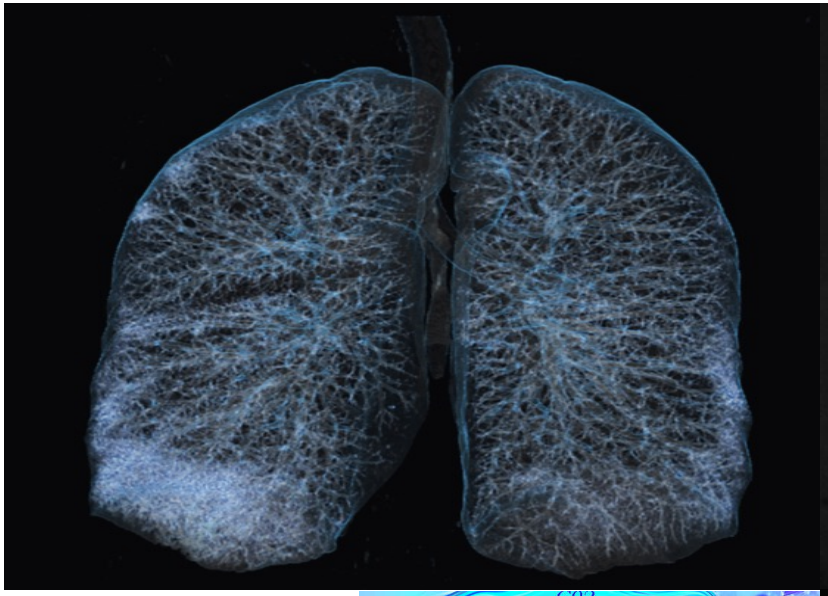


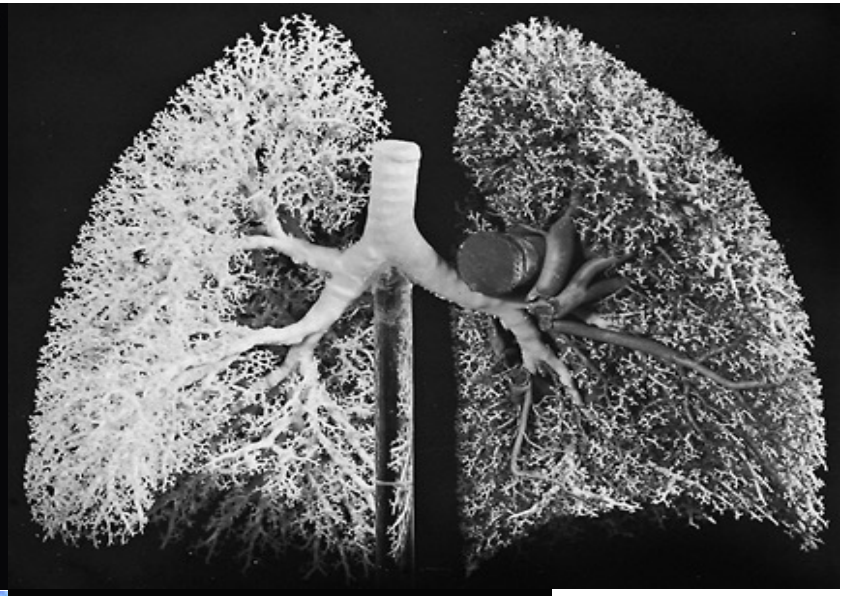


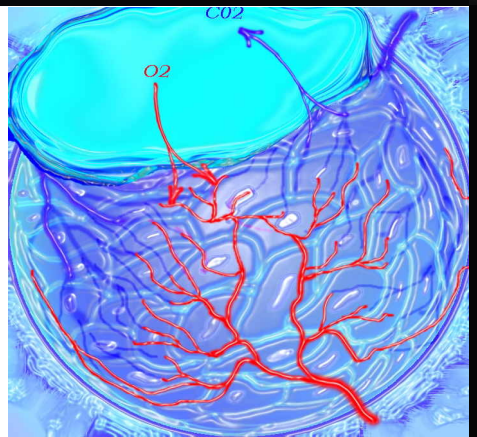


# Human Organism
## comprises diverse multi-component physiological systems

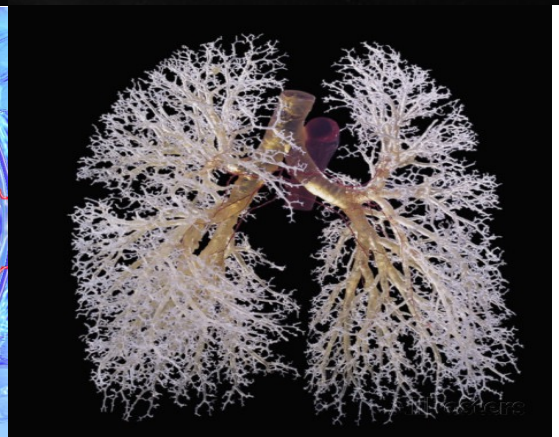
**Lungs:** High resolution image | Airways | Arteries and veins







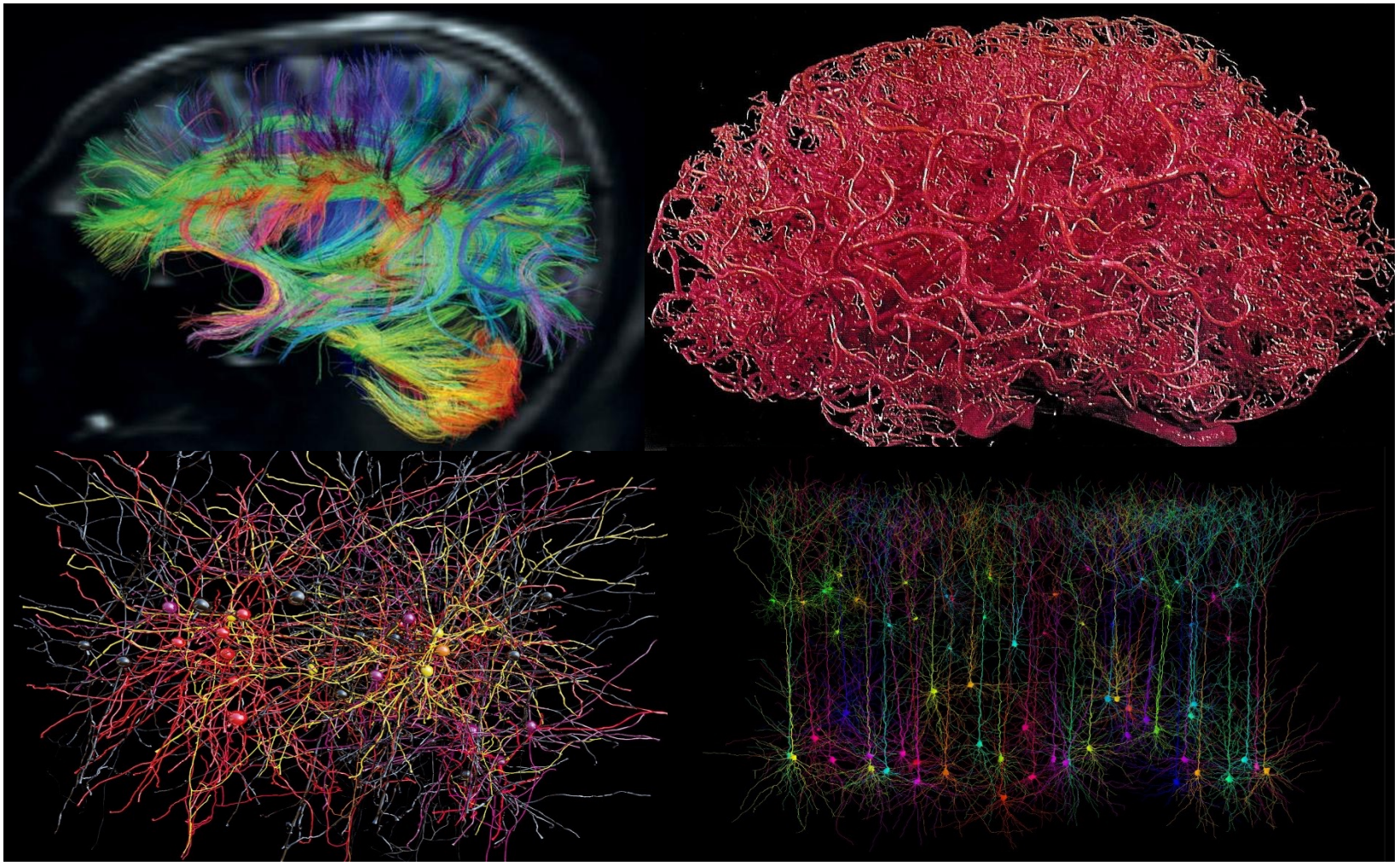

Single alveolus vascular network



Bronchial tree

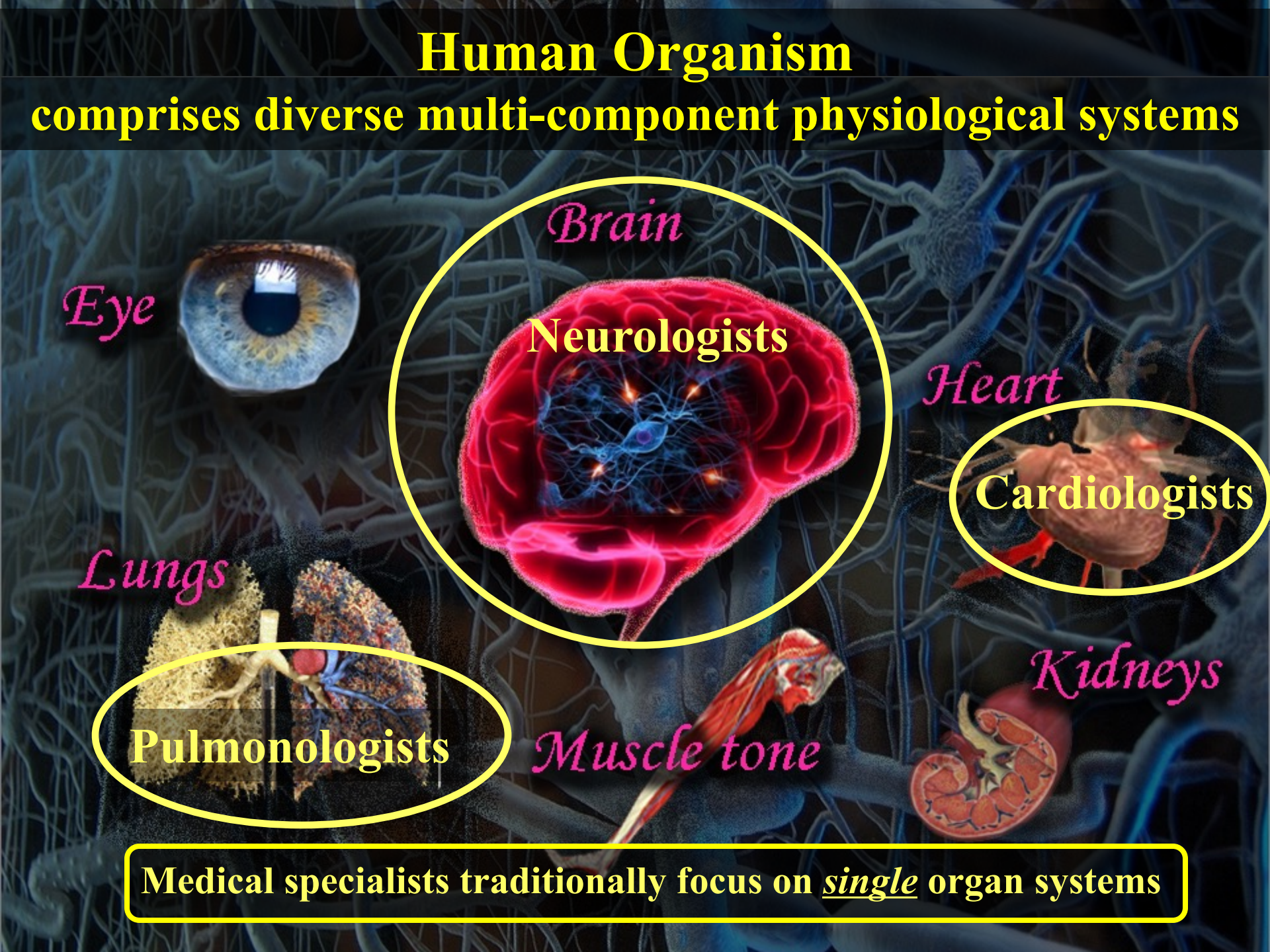
# Human Organism
## comprises diverse multi-component physiological systems

**Brain:** Neuronal and vascular network



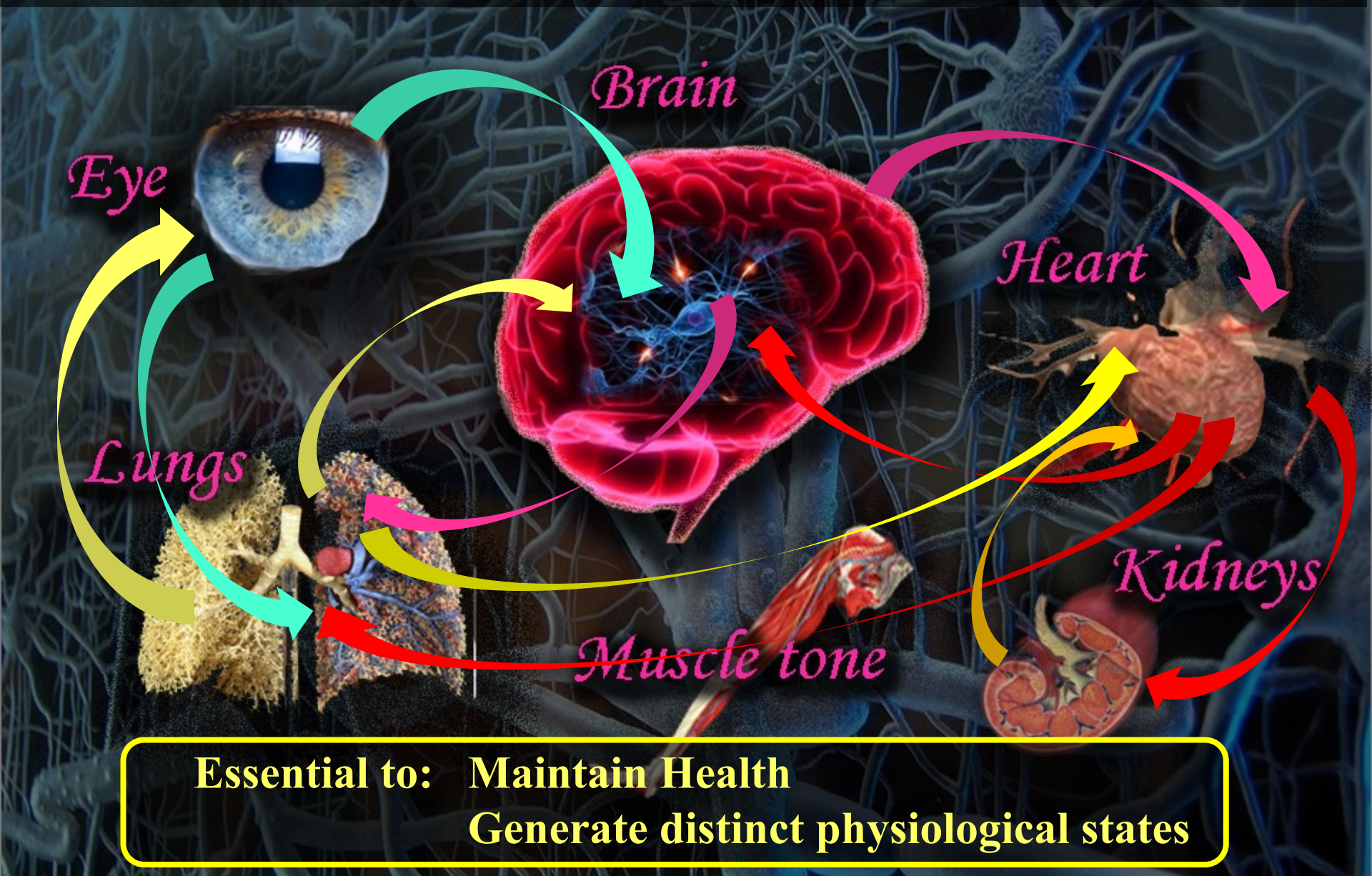
# Human Organism

## comprises diverse multi-component physiological systems



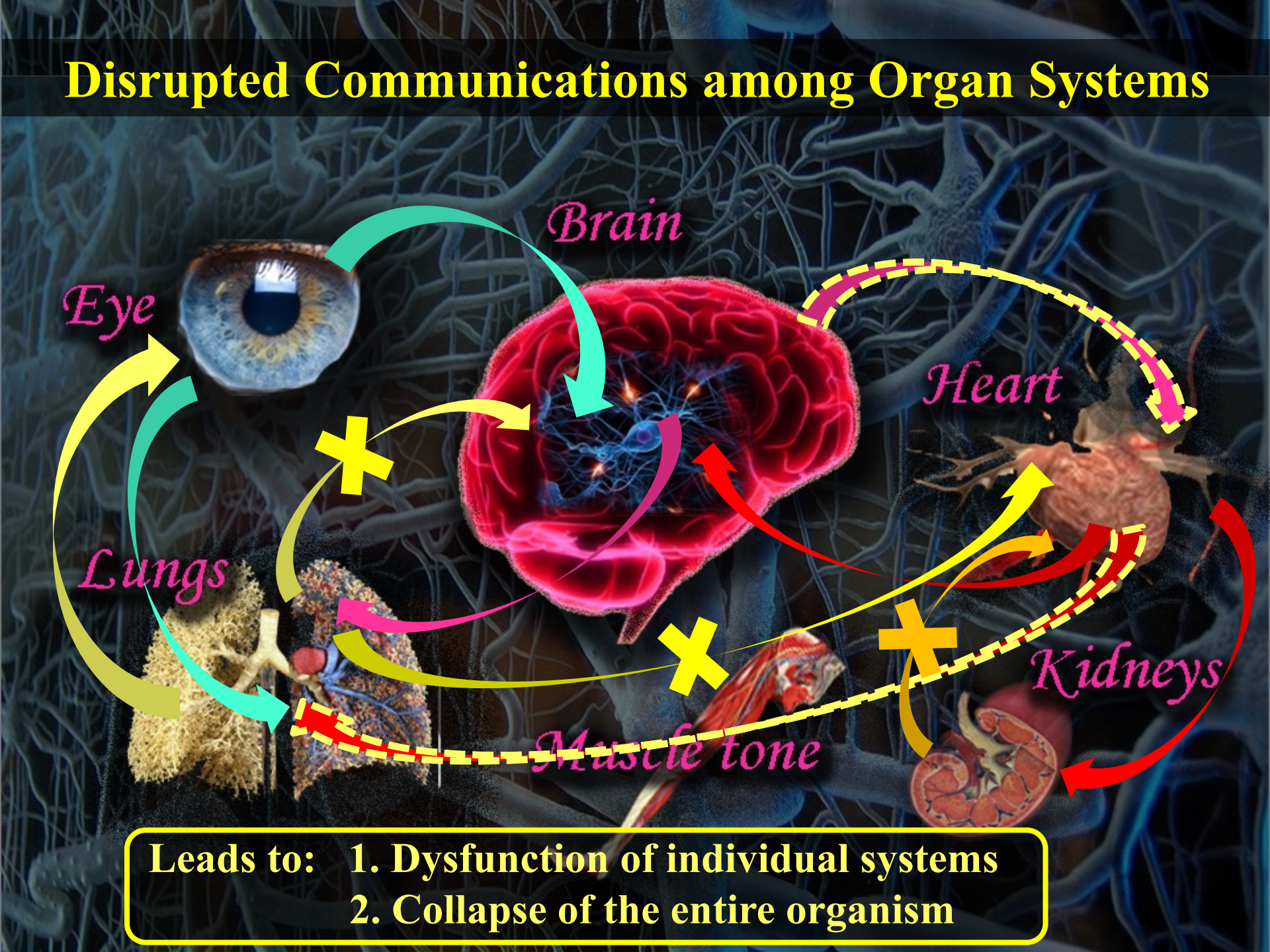

**Medical specialists traditionally focus on *single* organ systems**

# 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 !**

↓

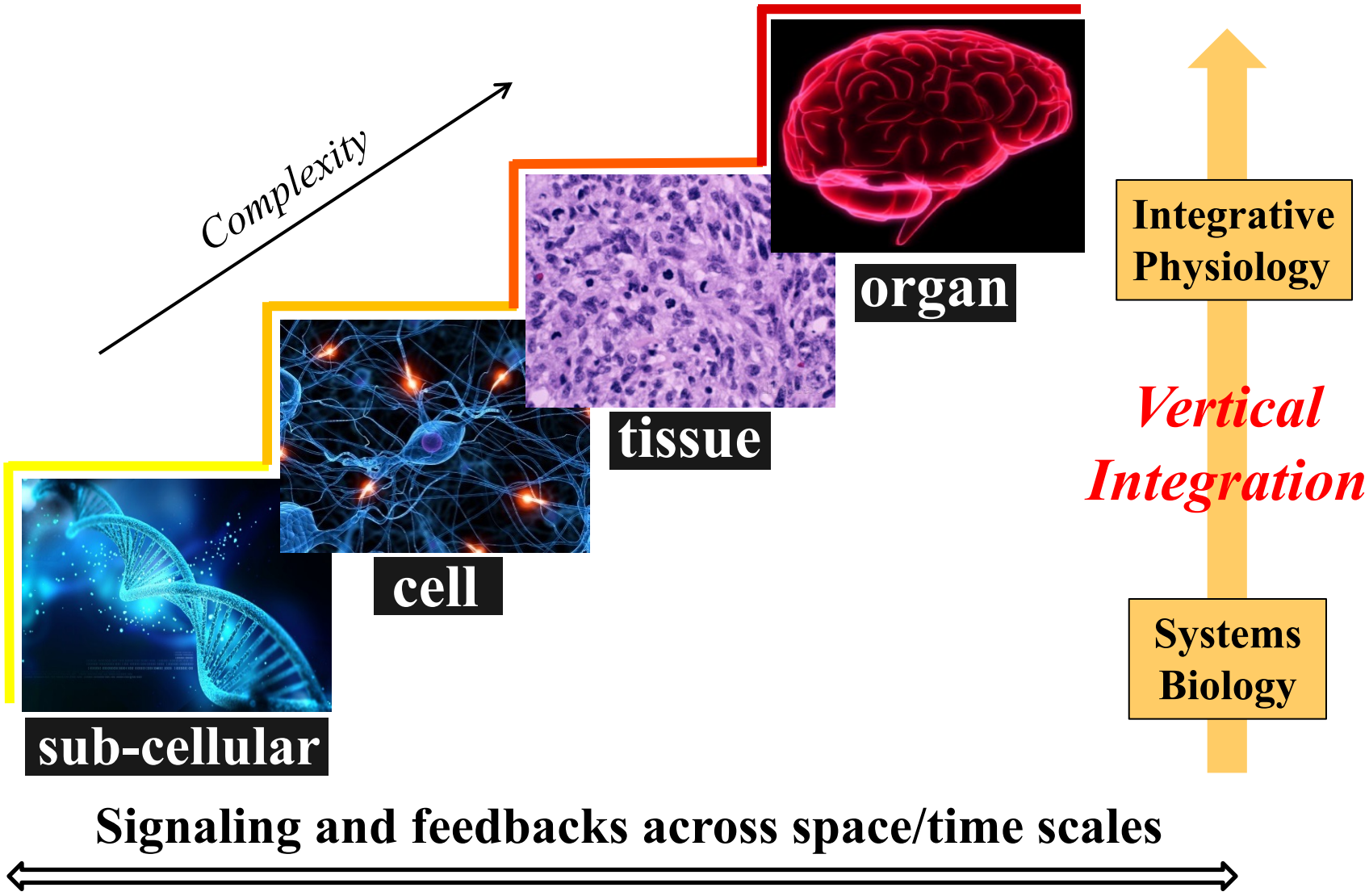
**Broad *clinical implications*: Coma, Multiple Organ Failure**

**Yet, despite the importance to:**

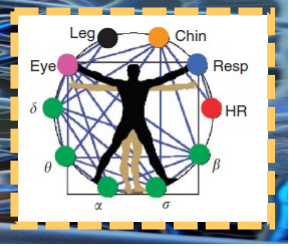
- **understanding basic physiologic functions**
- **clinical relevance**

**? 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

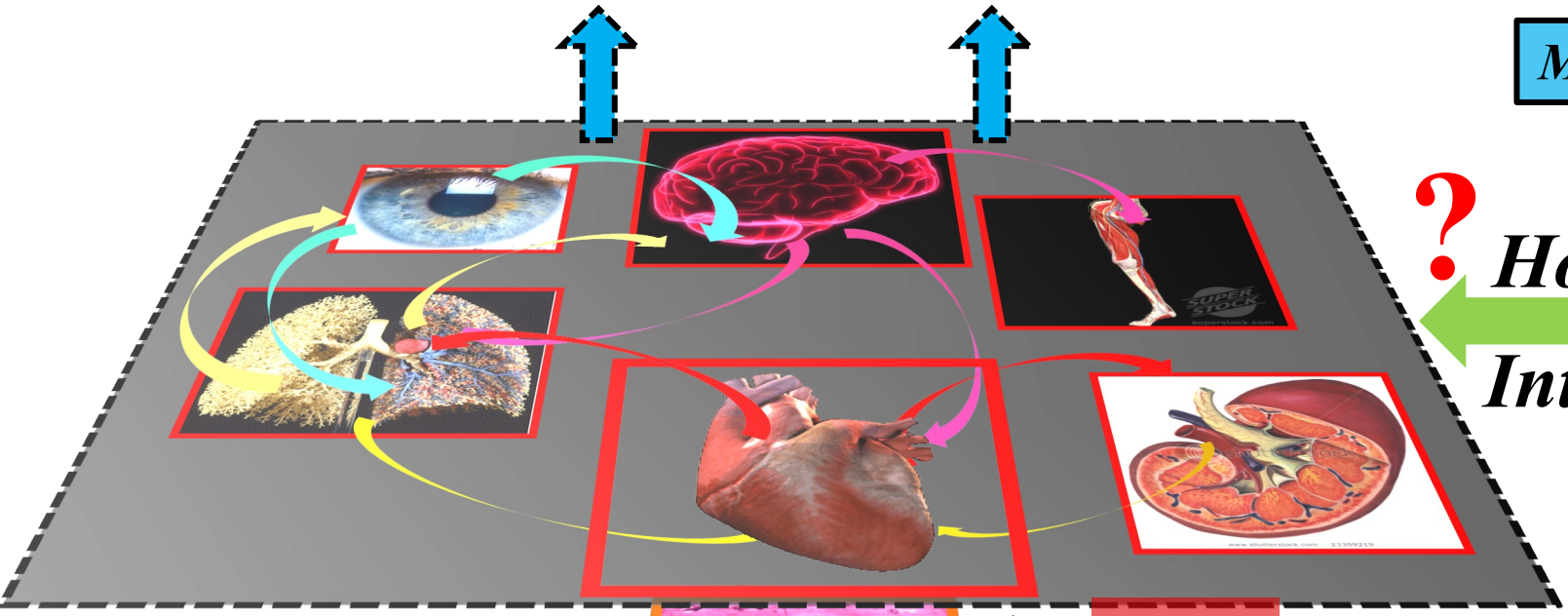


# Our Research Focus: Horizontal Integration




**Epidemiology / Population Health**

***Macroscopic***

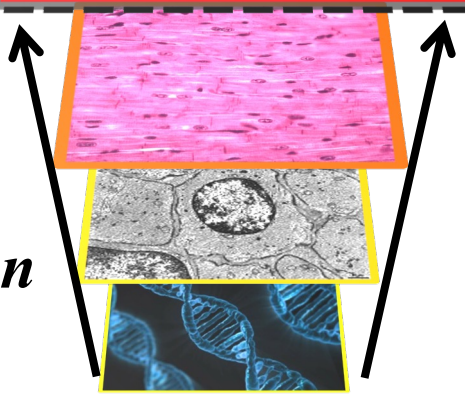


? ***Horizontal Integration***

**Integrative Physiology**

**Systems Biology**

***Vertical Integration***



**organs**

**tissue**

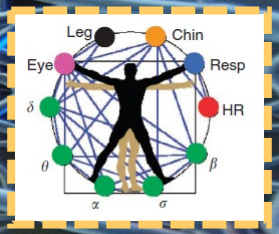
**cell**

**sub-cellular**

***Mesoscopic***

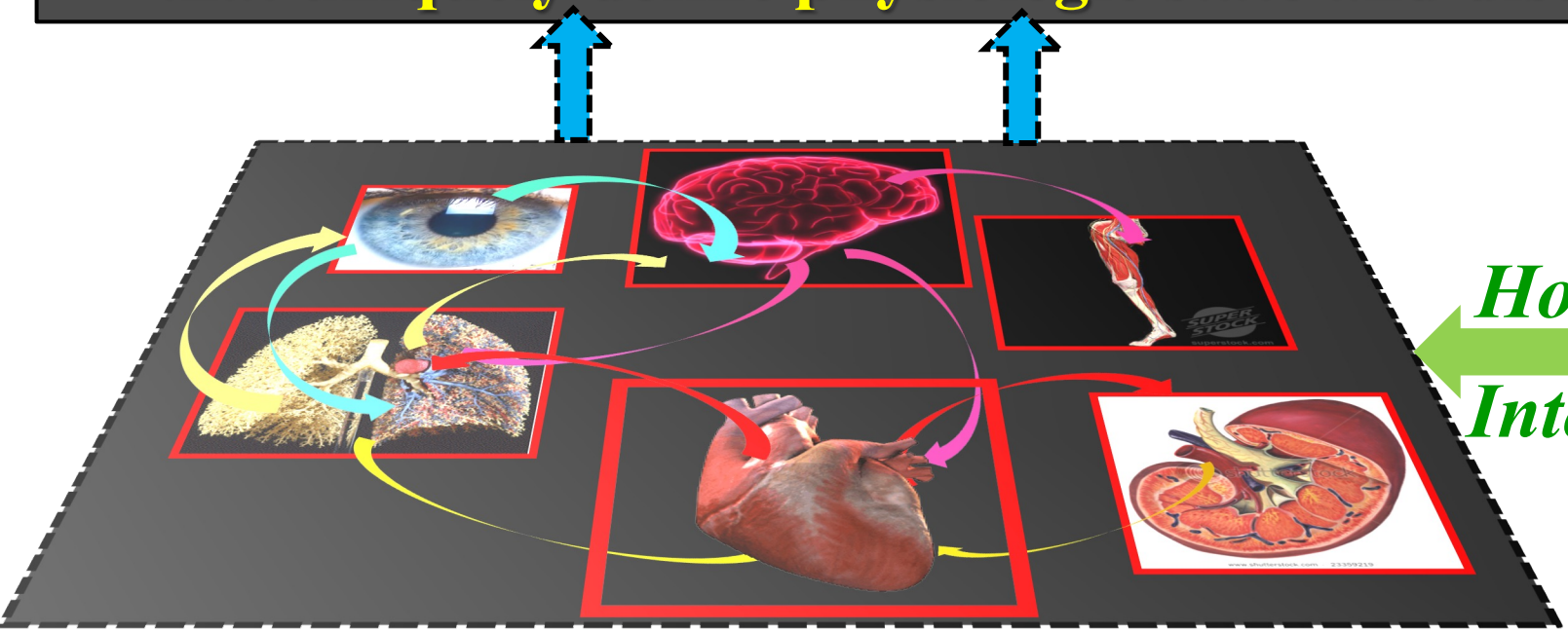
***Microscopic***

**Medicine defines health and disease through the state of individual organ systems.**




**Fundamental Question:**

**Are there "*blueprint reference*" network maps that uniquely define physiologic state and disease ?**

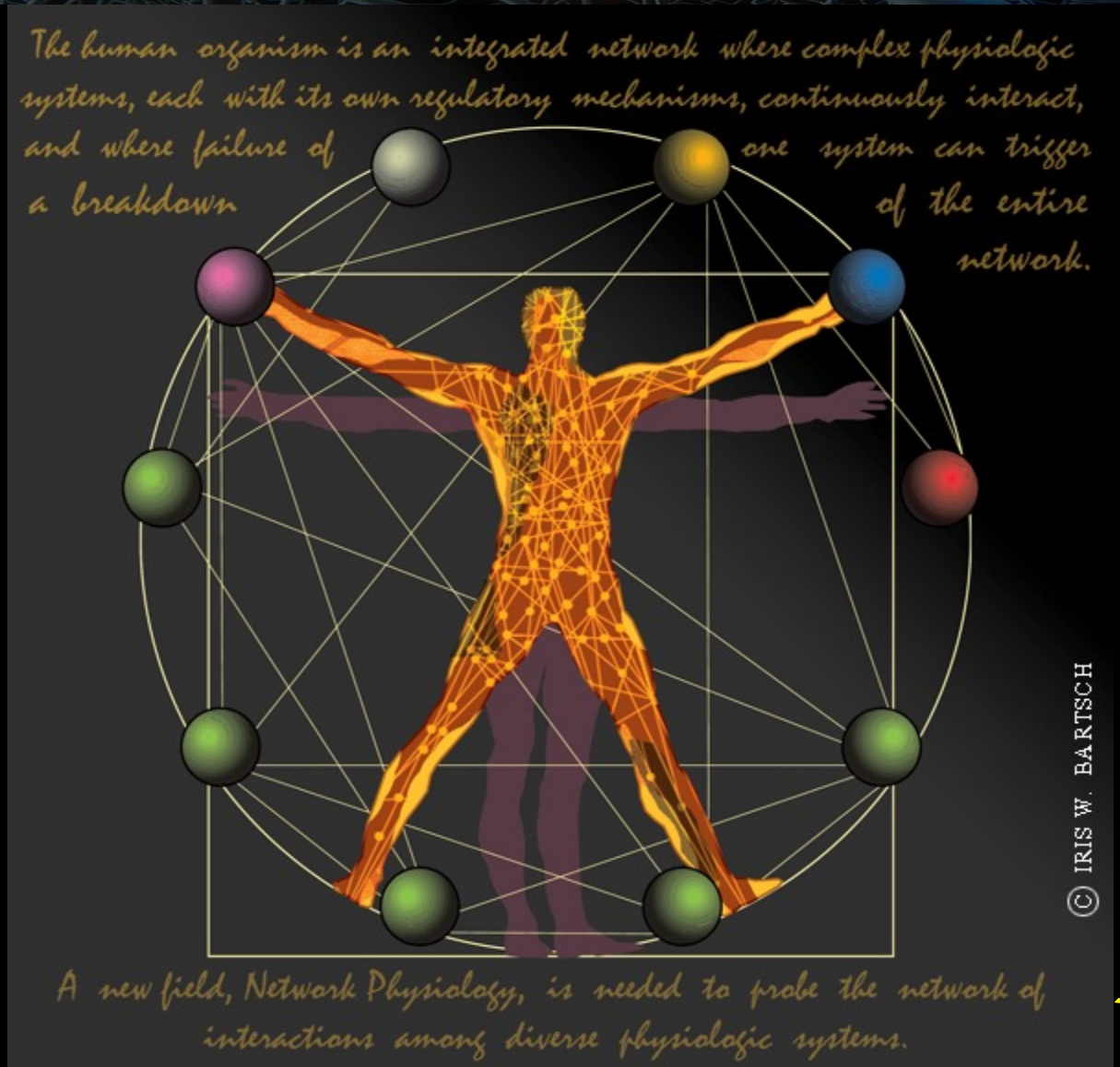


***Horizontal Integration***

**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.*

Level 1: Individual Systems

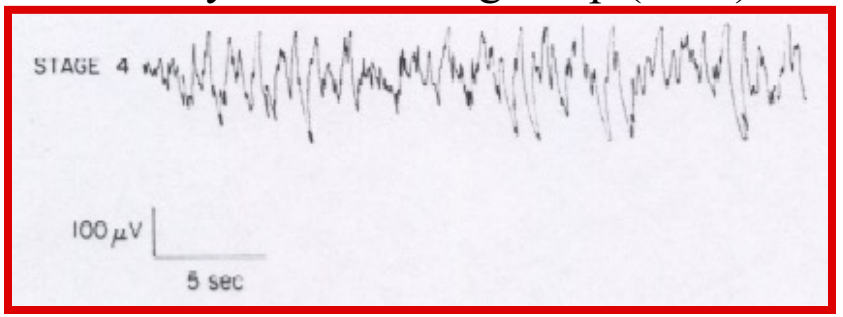
# Complex Variability in Physiologic Dynamics across spatio-temporal scales and levels of integration

**Is Physiologic Variability simply Noise?**

Complexity

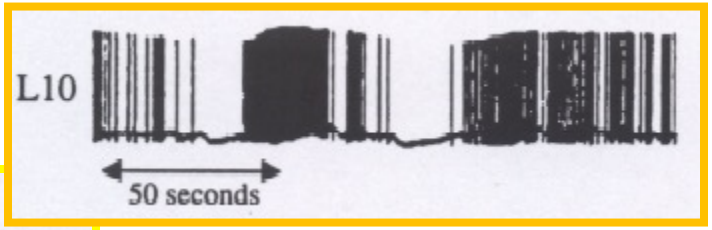
**organs**

Brain dynamics during sleep (EEG)



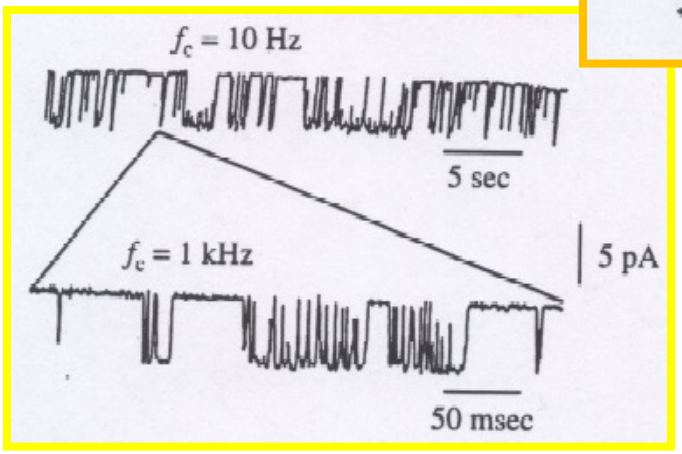

**cell**

Single neuron activity




**sub-cellular**

Ion channel kinetics




**New Concept: Fluctuations are *not* noise !**

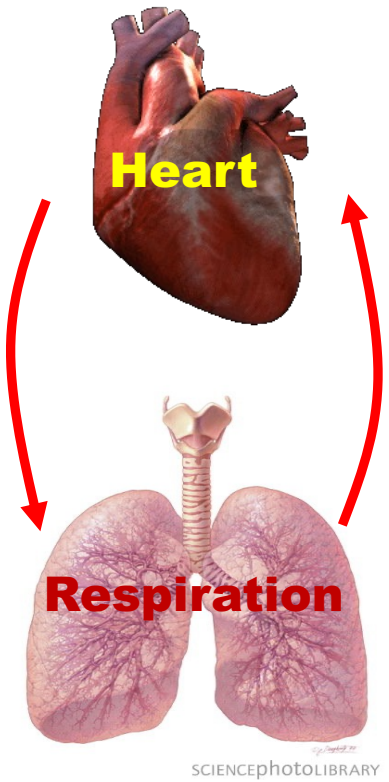
**Instead:** **Fluctuations contain hidden dynamical patterns related to underlying mechanisms**

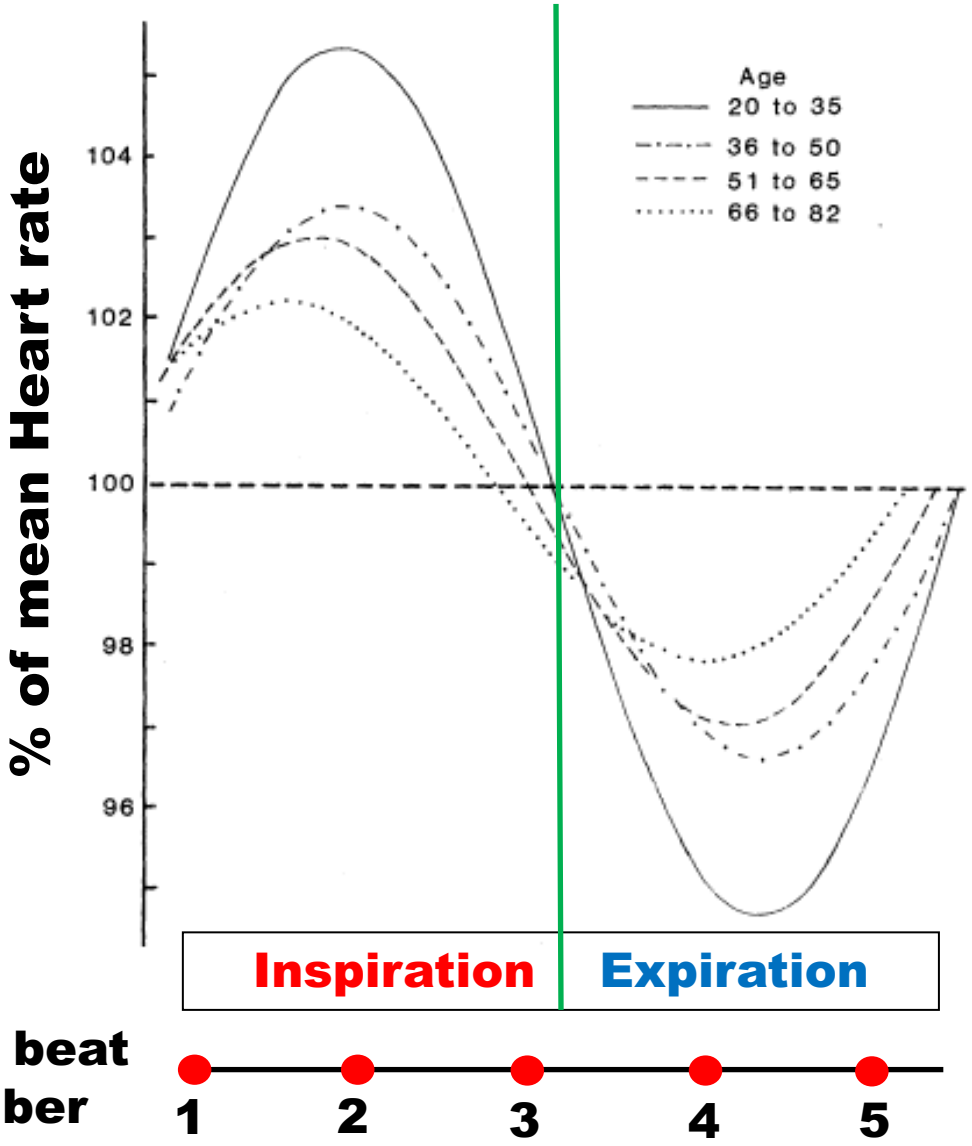
Level 2:
Pair-wise Coupling

# Cardio-respiratory Interaction
# Respiratory Sinus Arrhythmia (RSA)

**Inspiration → Heart rate ↑**

**Expiration → Heart rate ↓**

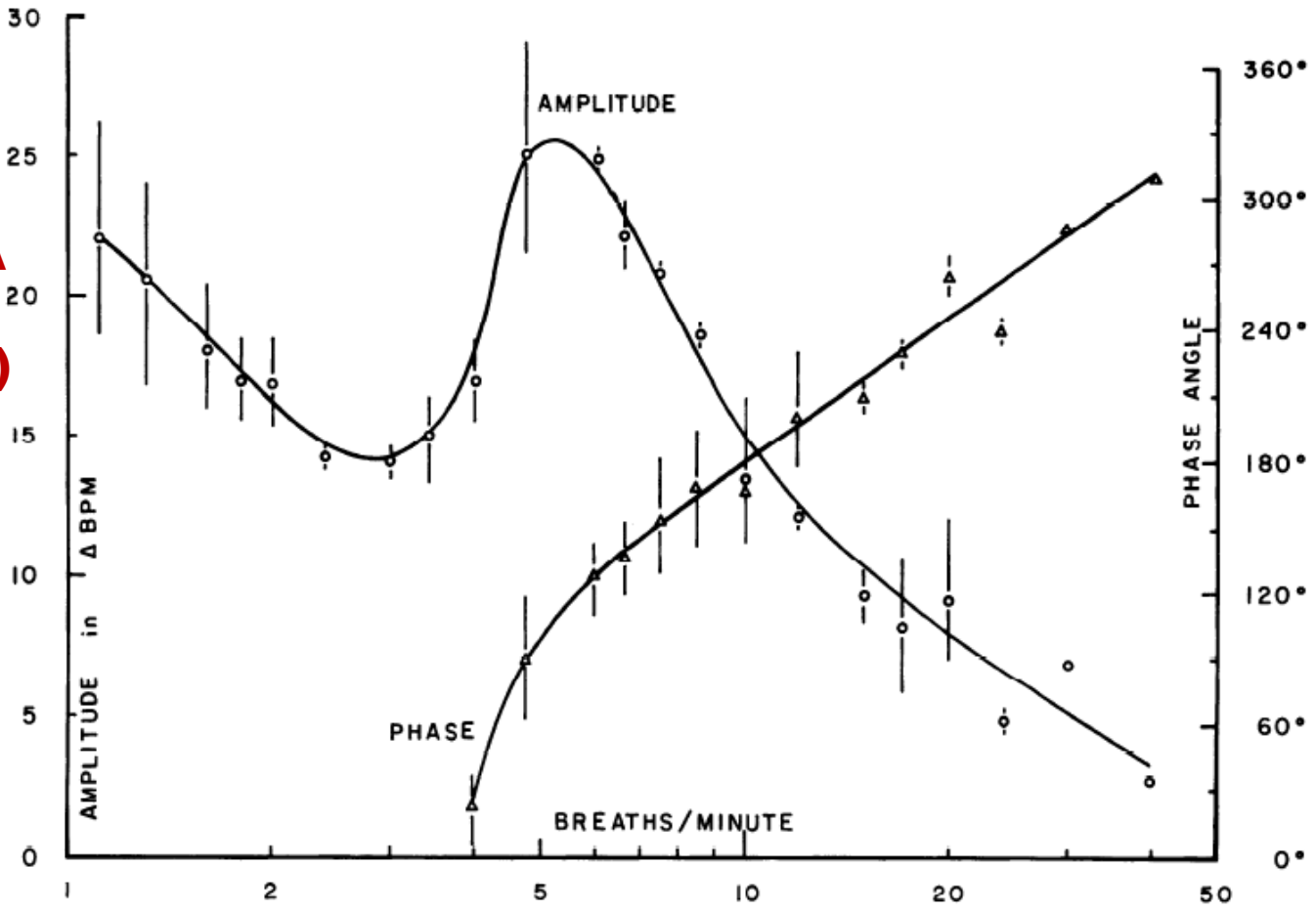


Level 2:
Pair-wise Coupling

# Cardio-respiratory Interaction
# Respiratory Sinus Arrhythmia (RSA)

**Strength of RSA (deviation from mean beats/min)**

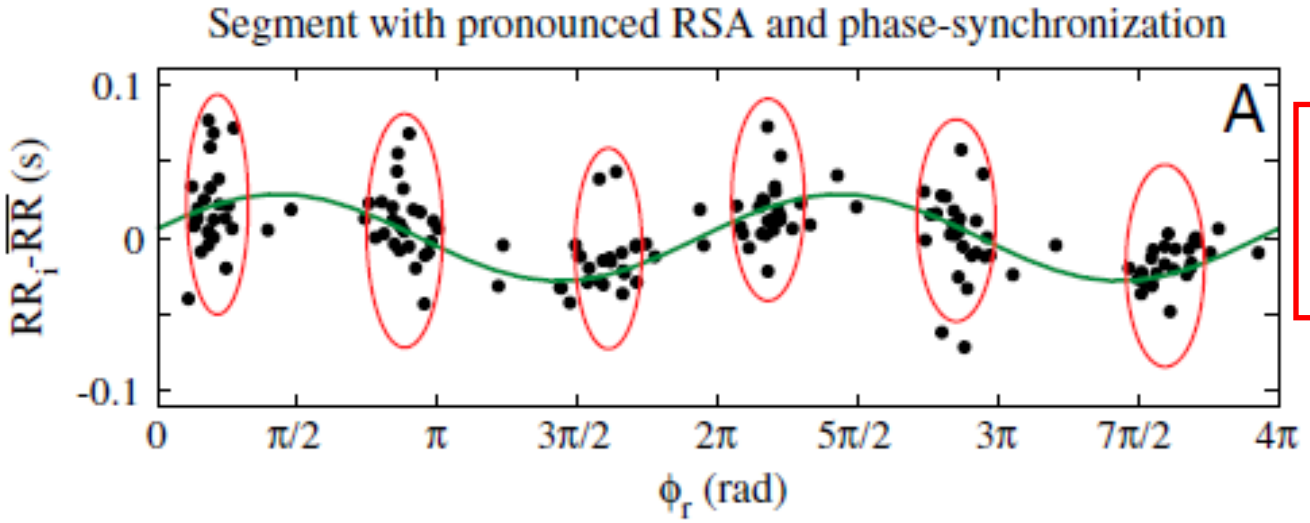



**Breathing Rate (breaths per min)**

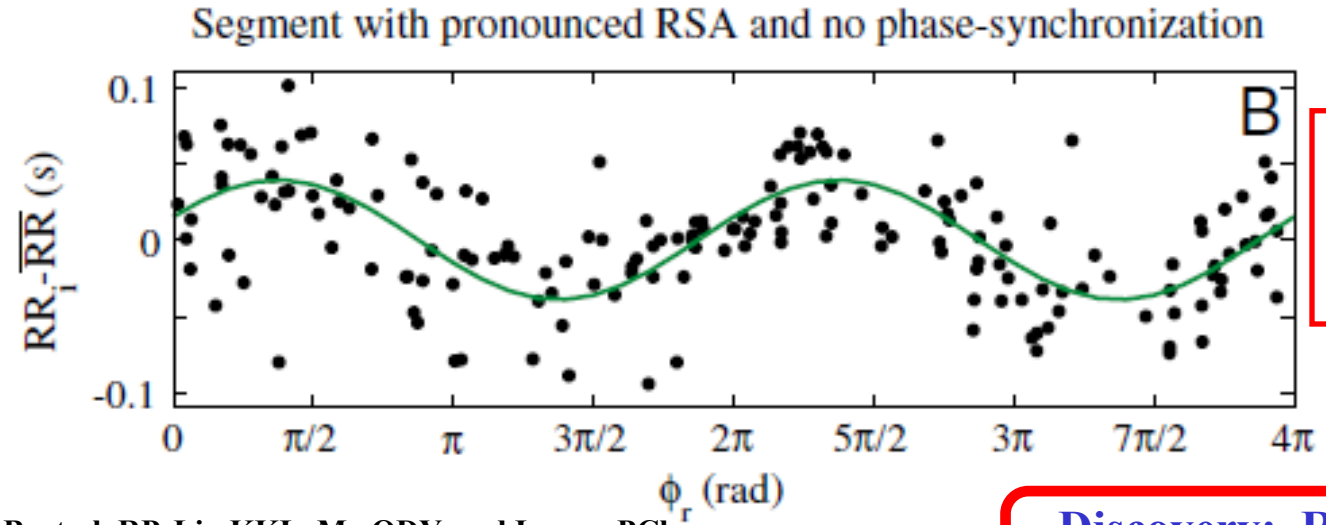
Angelone & Coulter, *J Appl Physiol* **19**, 479 (1964)

Level 2:
Pair-wise Coupling

# Coexisting forms of physiologic coupling
## Cardio-Respiratory interaction




**RSA & 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**

# 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

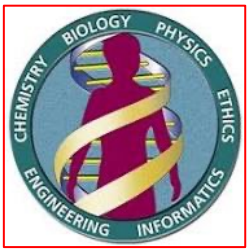
led to

***Data-Driven Discoveries***

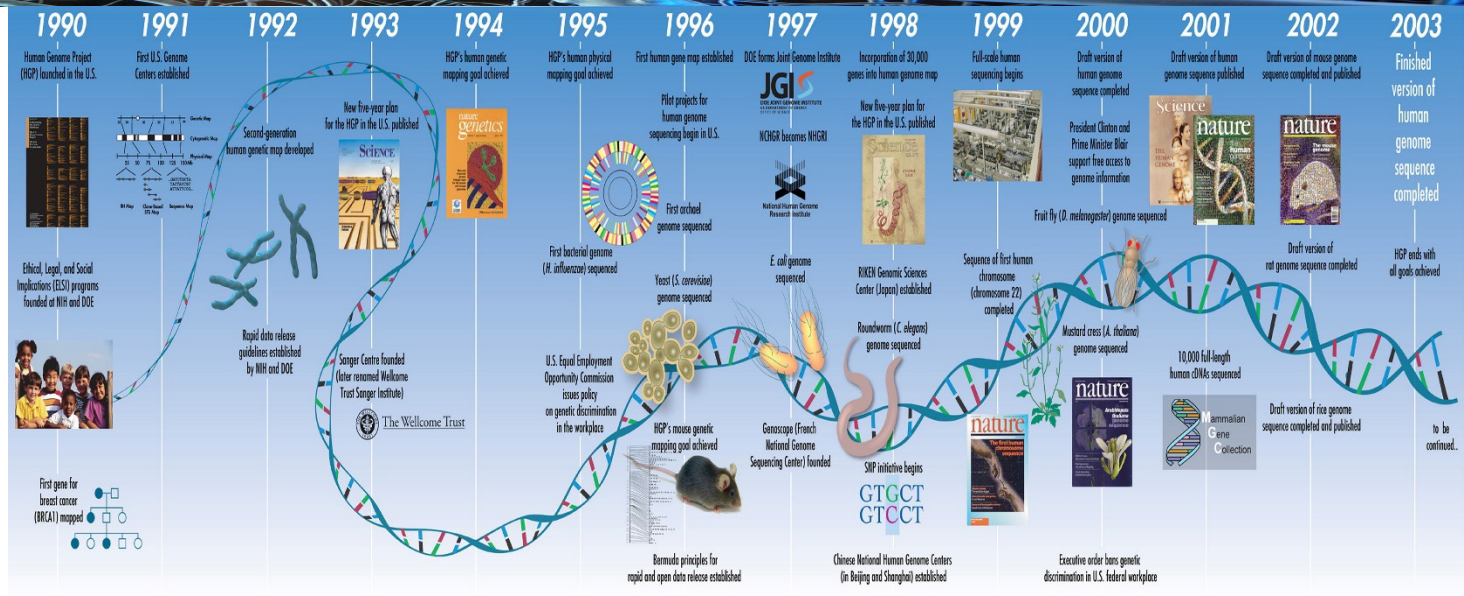
- Medicine
- Physiology
- Stat. Physics
- Applied Math
- Computer Sci.

# Big Data

# Systems Biology: mapping the Human Genome

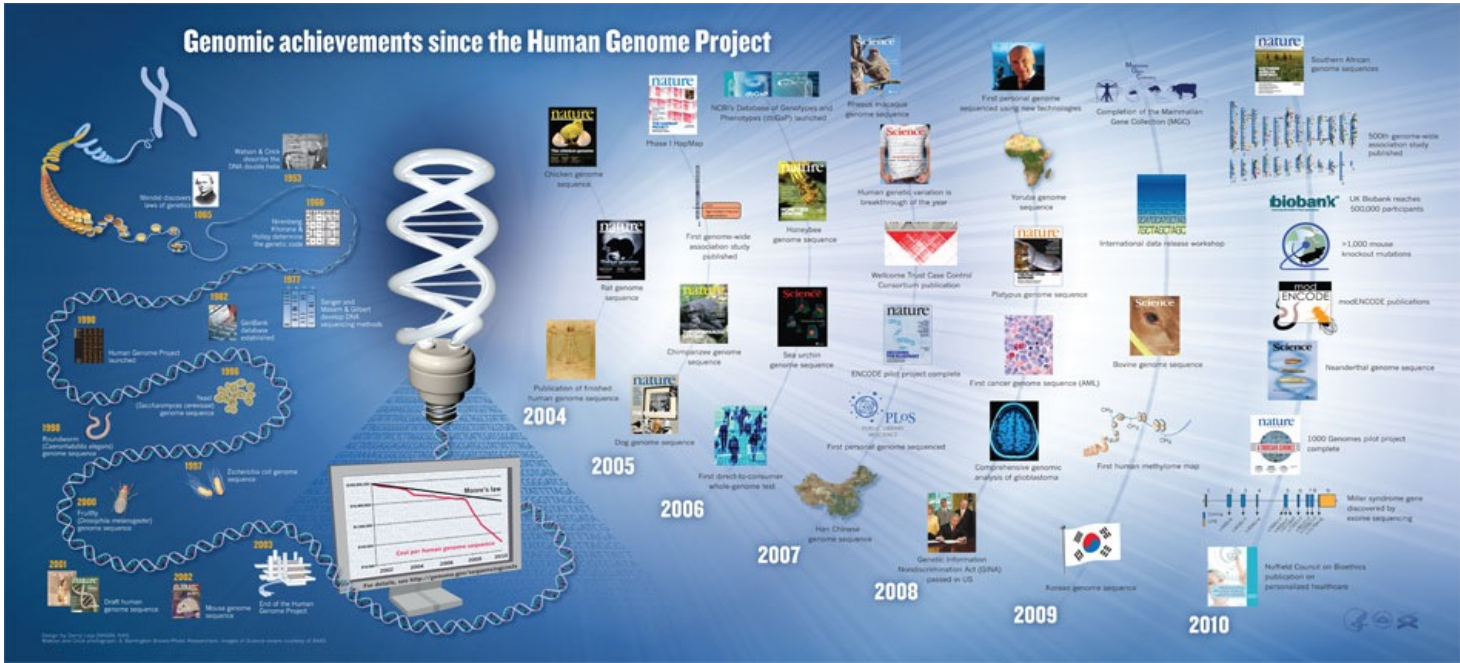



**Before**
***Human Genome Project***




**3 Billion**
**DNA base pairs**

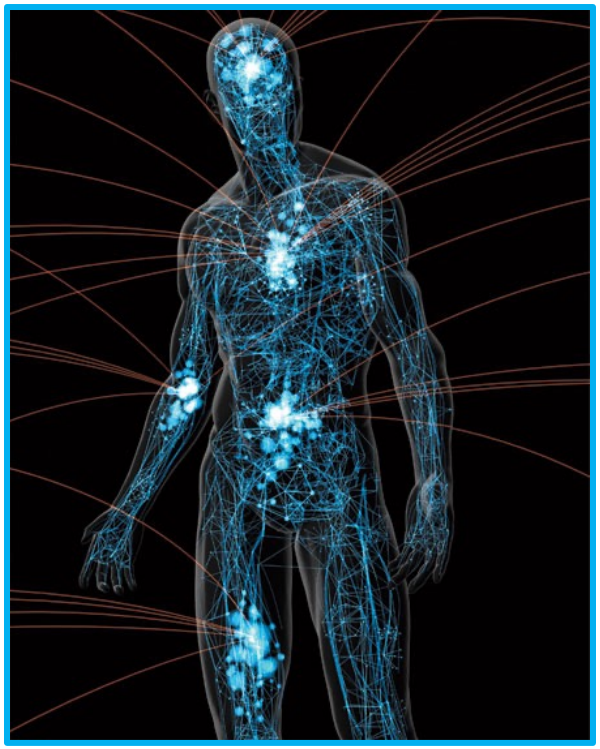
**After**
***Human Genome Project***



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

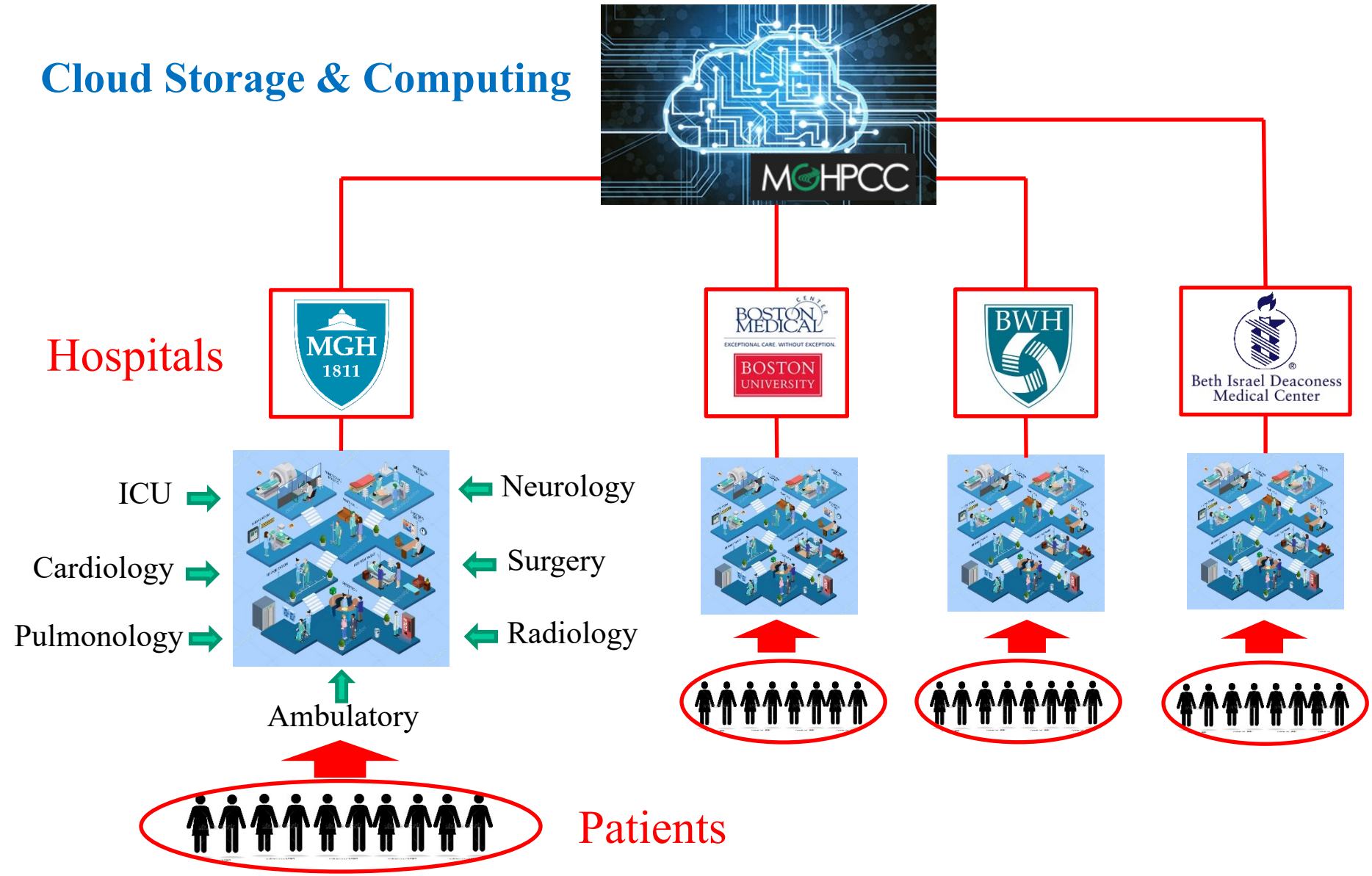
**High frequency recordings ($10^2$-$10^3$Hz)**
**Number of data points per person:**
**(just for 100 parameters)**

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

Big Data

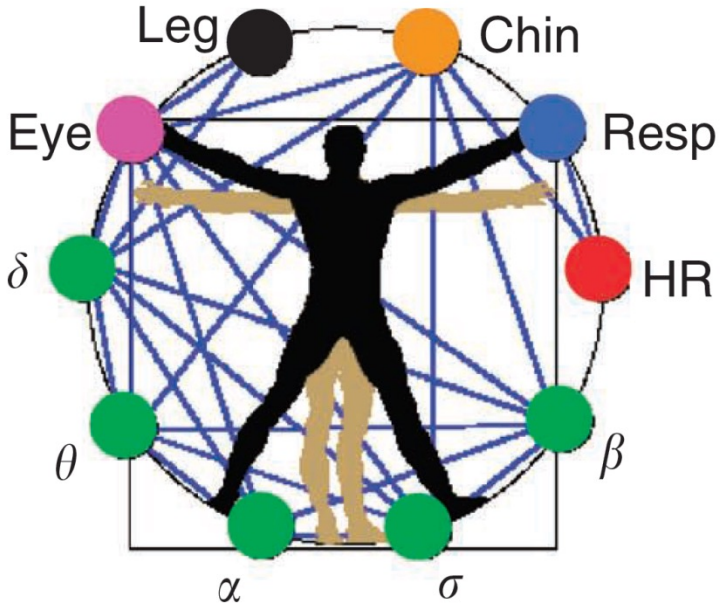
# Network Physiology

## Novel principles of integrating physiological data & metadata



Level 3: Networked Interactions

# Horizontal Integration of physiological interactions




**Physiological interactions**

## Physiologic recordings

Full-night polysomnographic data from healthy young subjects:

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

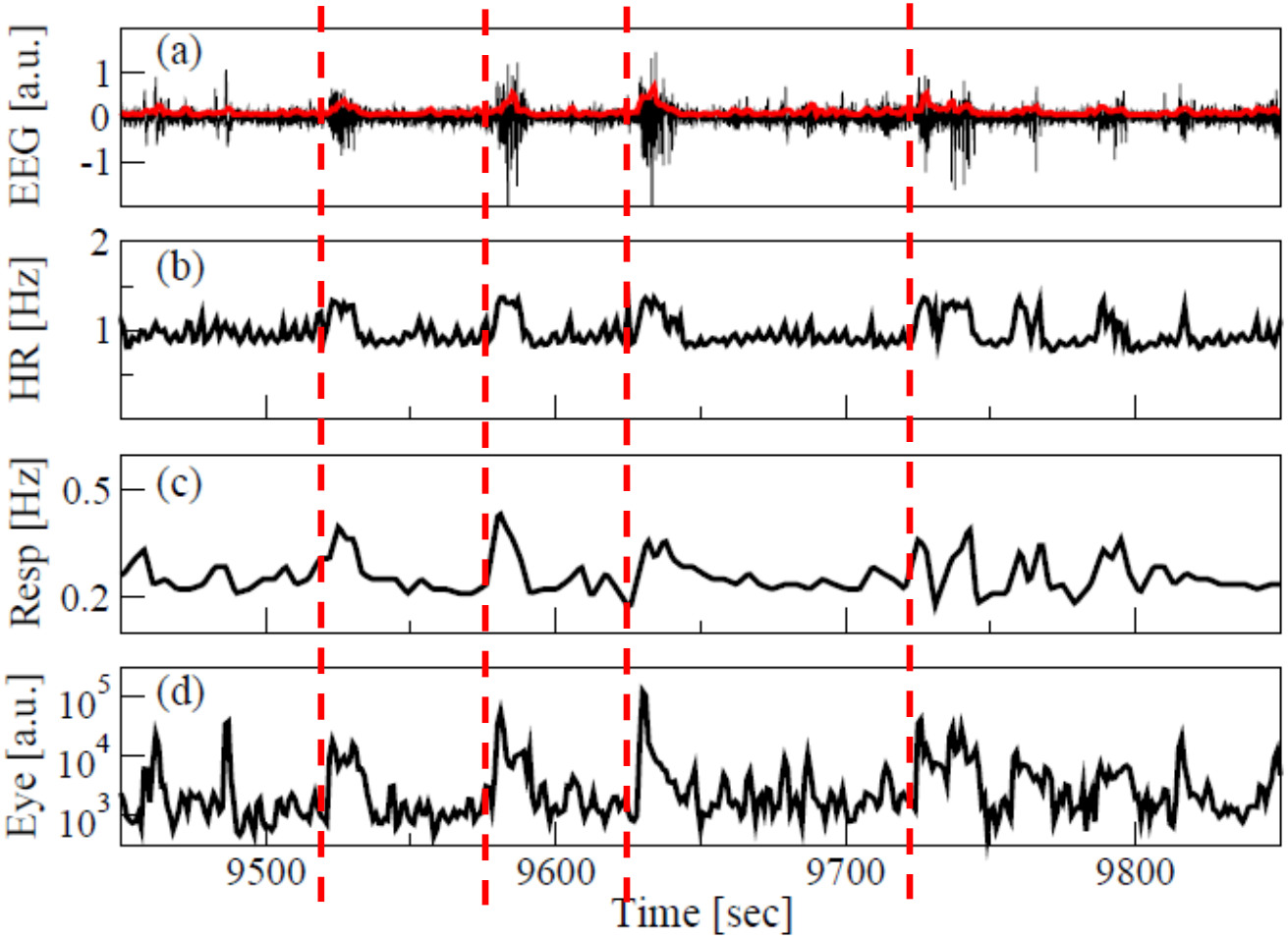
## Physiologic states

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

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

Data-Driven Observation

# Coordinated activity across diverse systems




**EEG-σ band: sleep spindles**

**Heart rate**

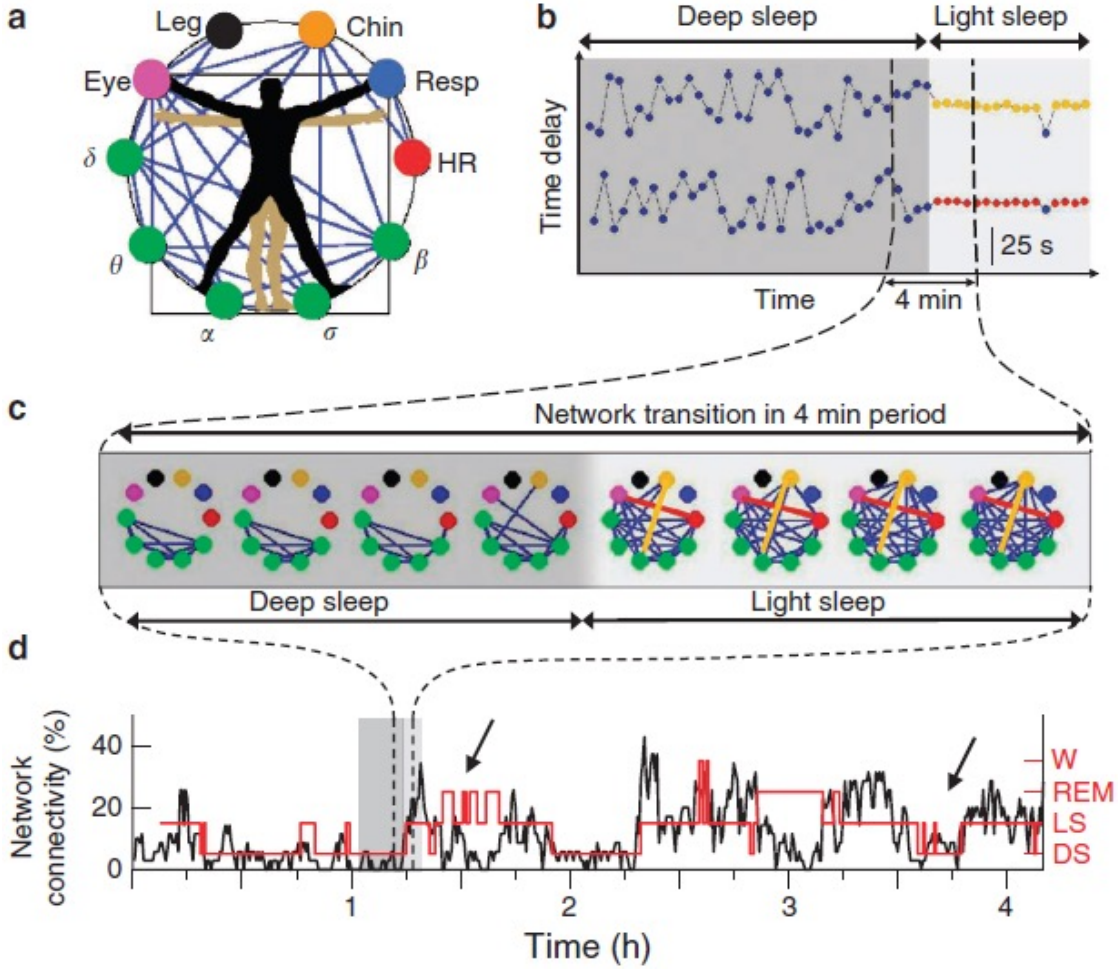
**Respiratory rate**

**Eye movements**

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

Data-Driven Discovery

# Transitions in the network of physiological interactions




← α – Chin interaction

← HR – Eye interaction

α – Chin link

HR – Eye link

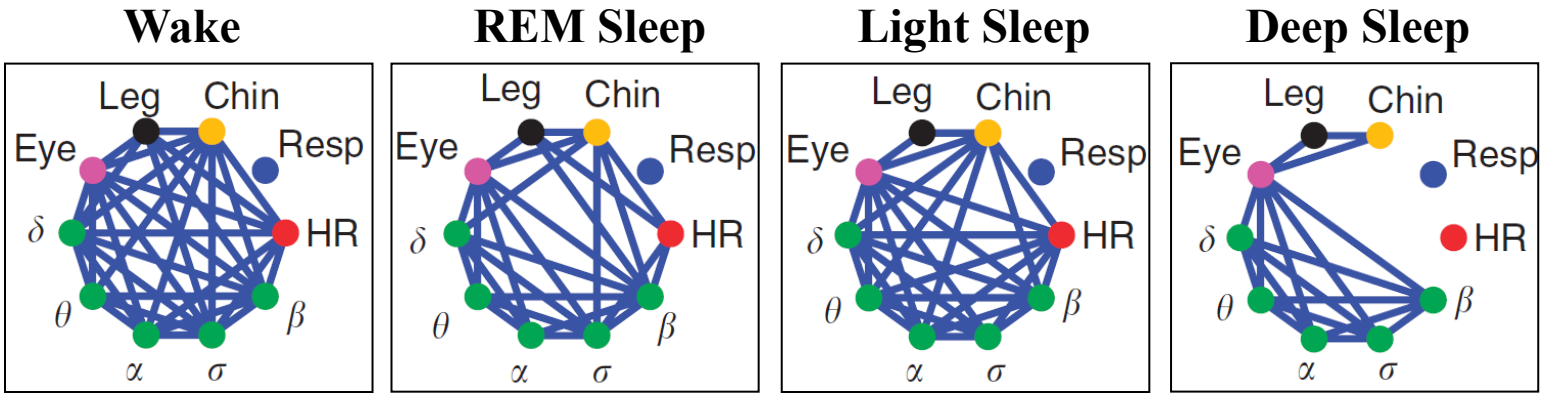
**Dynamical Evolution**

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

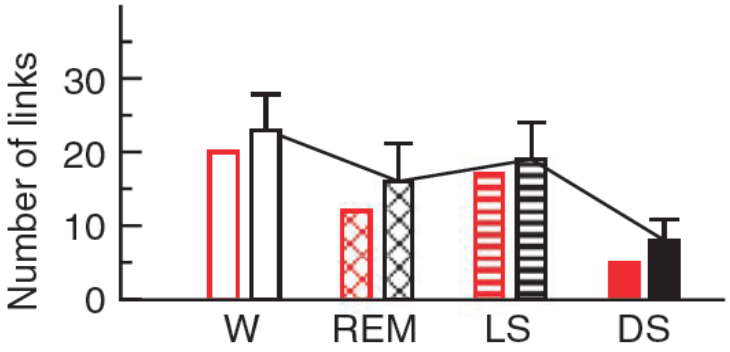
→ Fast reorganization of network connectivity with transitions across physiologic states

Data-Driven Discovery

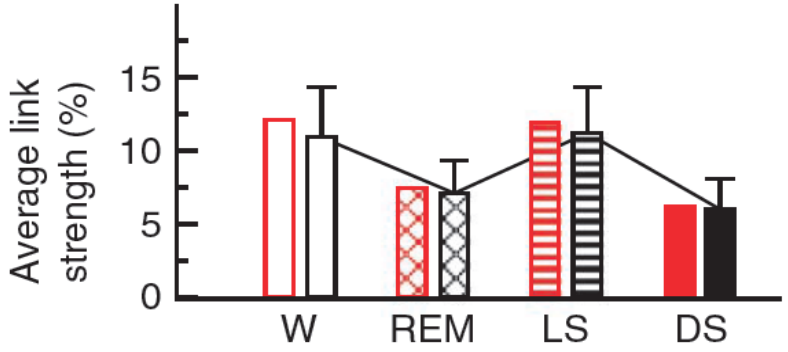
# Network Topology & Physiologic Function
## connectivity across sleep stages




**Network connectivity**




**Network link strength**



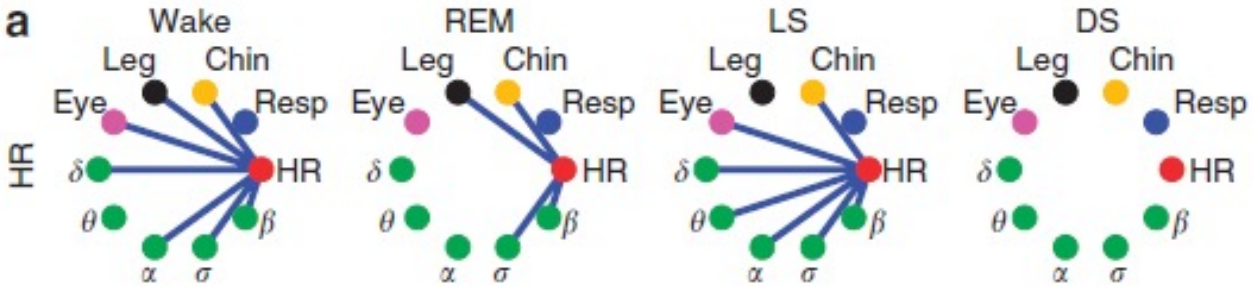

Bashan et al. *Nature Communications*, 3:702 (2012)

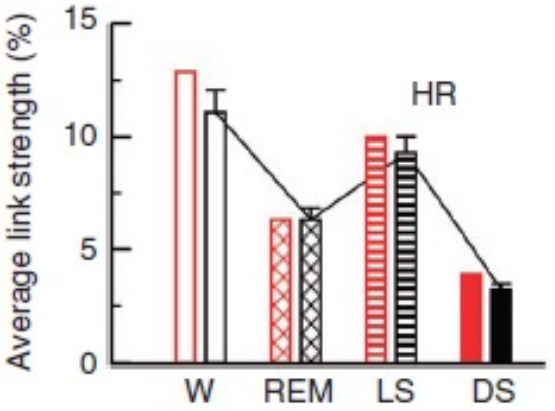
→ Network topology changes with physiologic states

Level 3: Networked Interactions

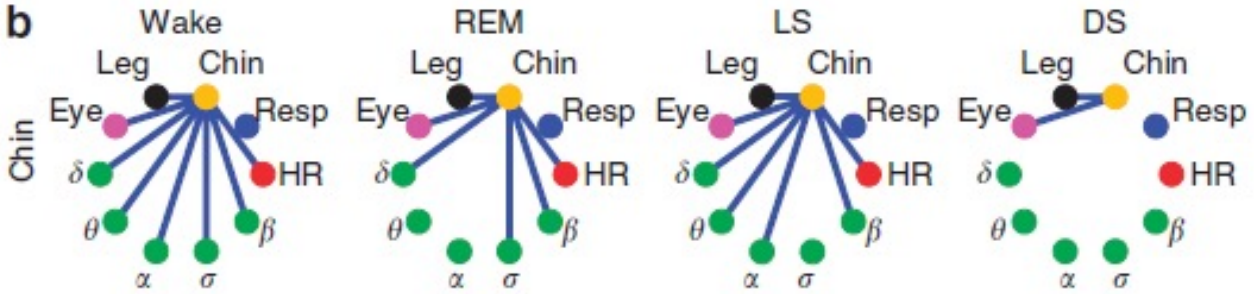
# Transitions in connectivity and link strength of individual network nodes across sleep stages

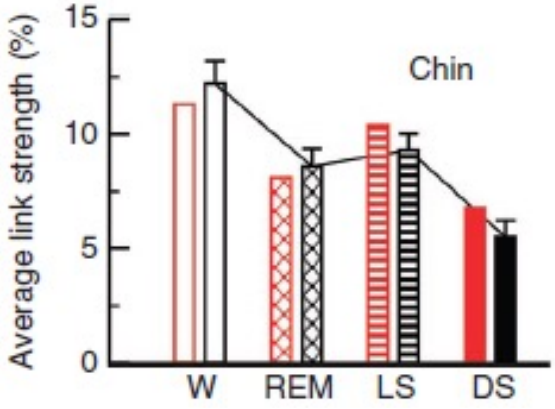
**Heart**




**Chin**




Robust sleep-stage stratification pattern in:

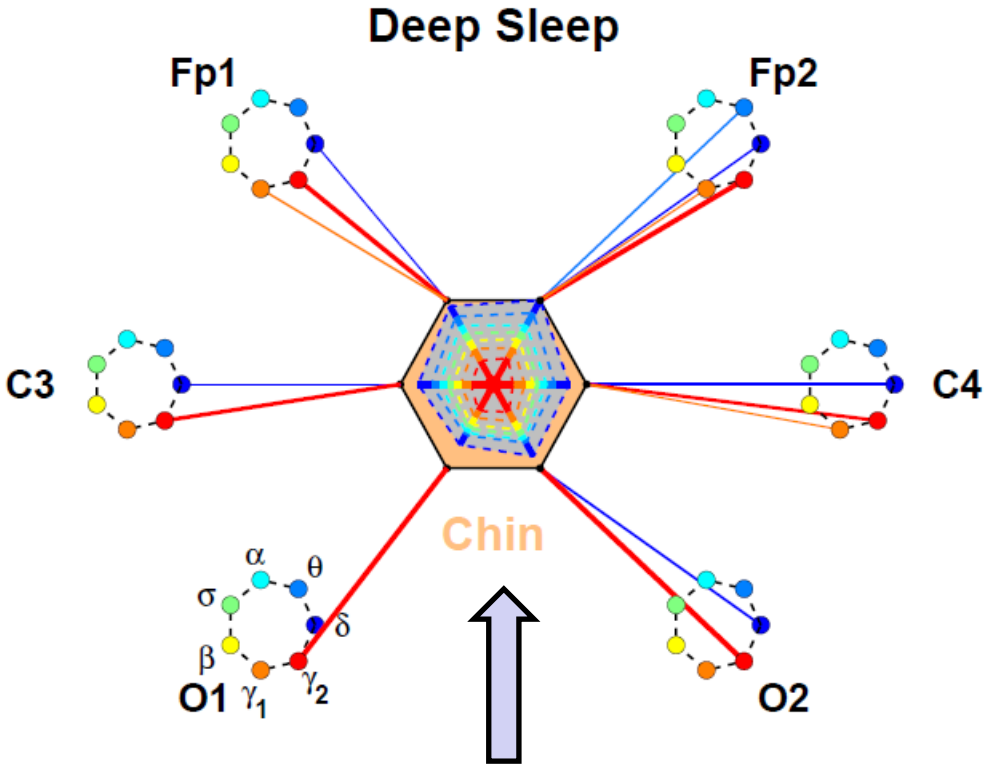
a) Individual node connectivity

b) Average link strength of individual nodes

Level 3: Networked Interactions

# 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**

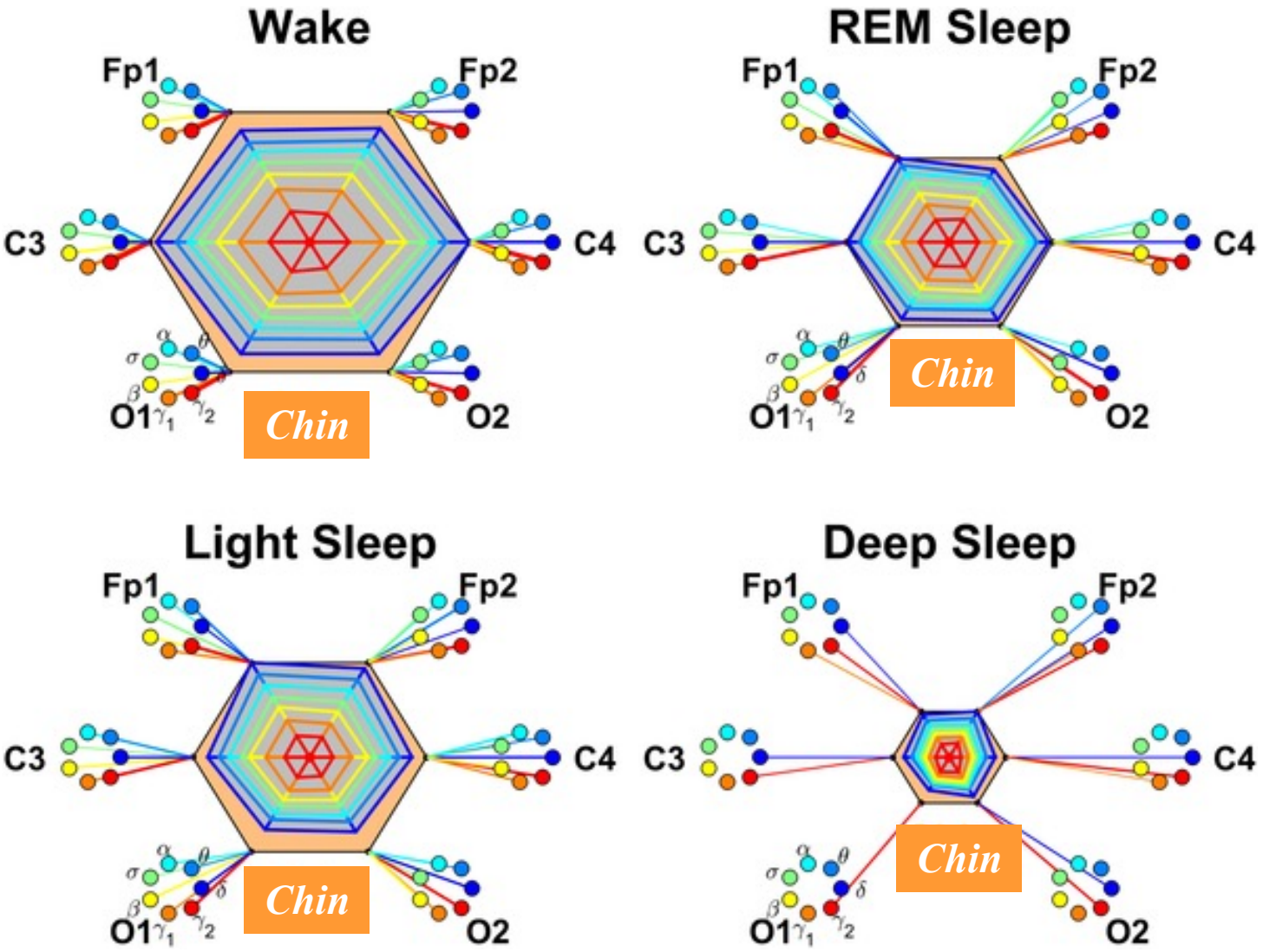
**Colors:**
**Frequency bands in the EEG signals**

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


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

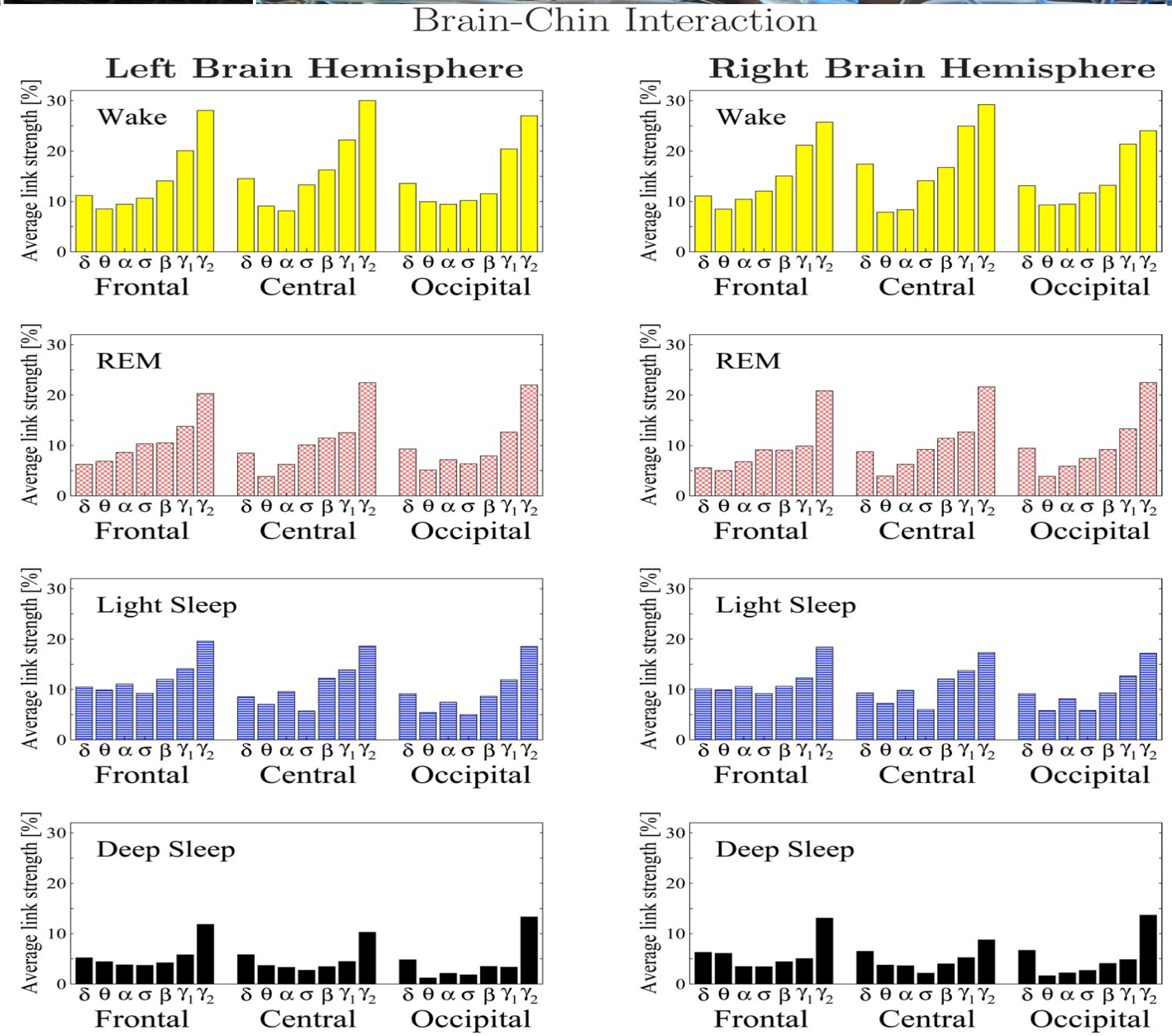
Level 3: Networked Interactions

# Visualization: different physiologic states



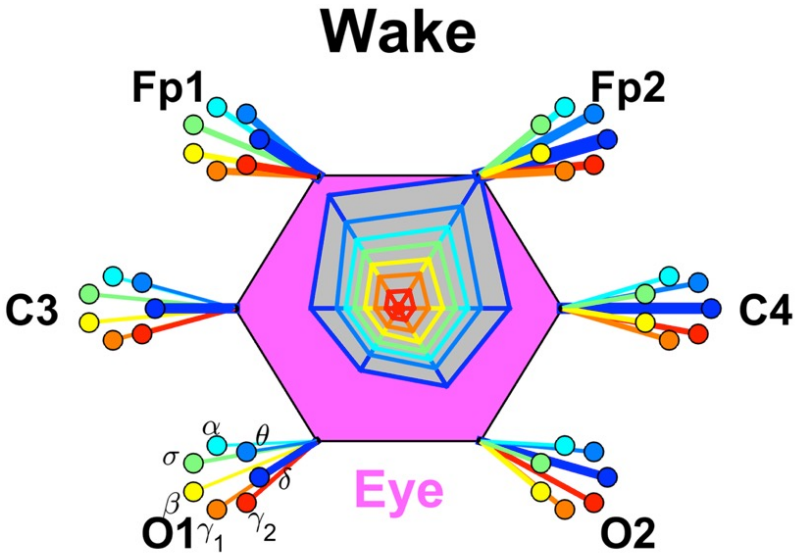

**Bartsch RP, Liu KKL, Bashan A, and Ivanov PCh**.
*Nework Physiology: how organ systems dynamically interact.* **PLOS ONE, 2015; 10(11): e0142143**

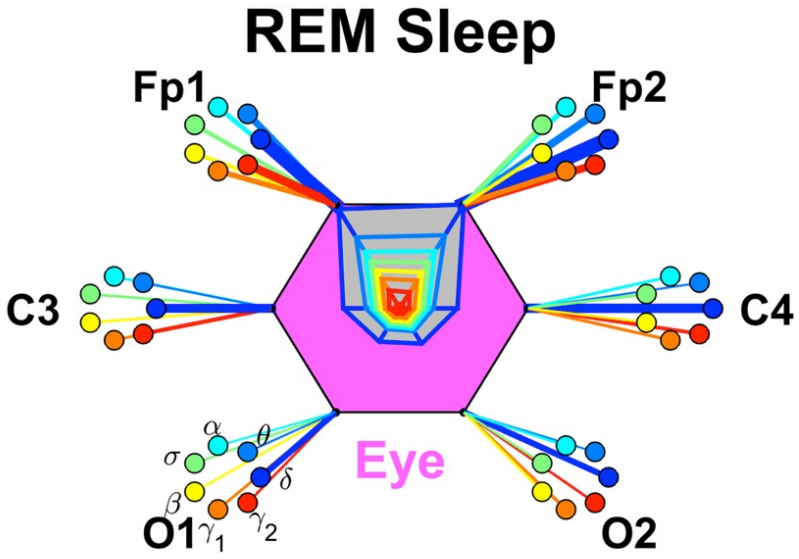
# Brain-organ interactions

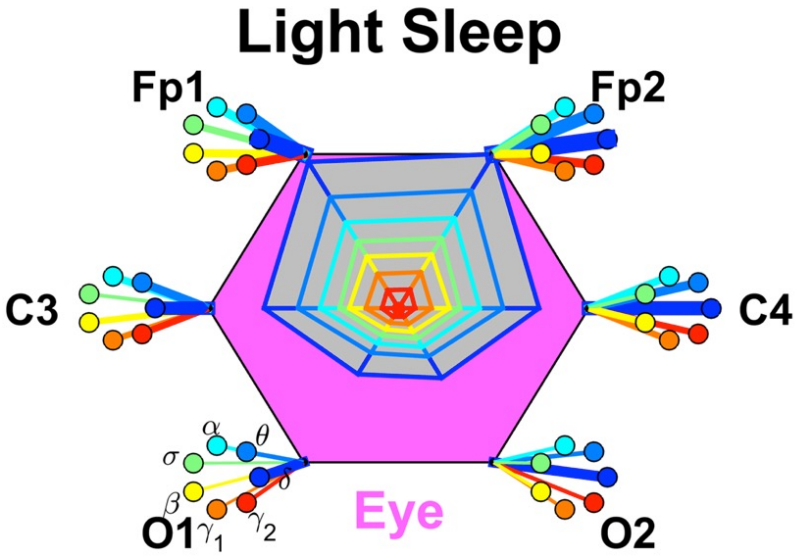


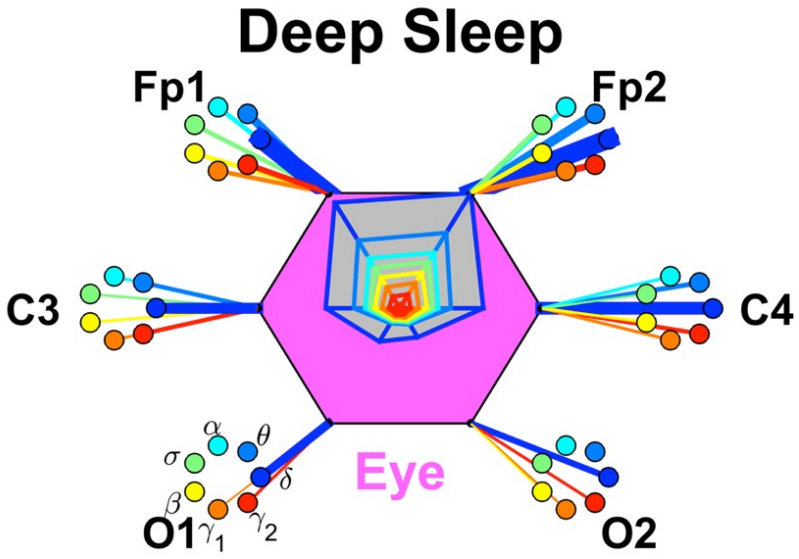

mediated by different frequency bands

# Visualization: different physiologic states



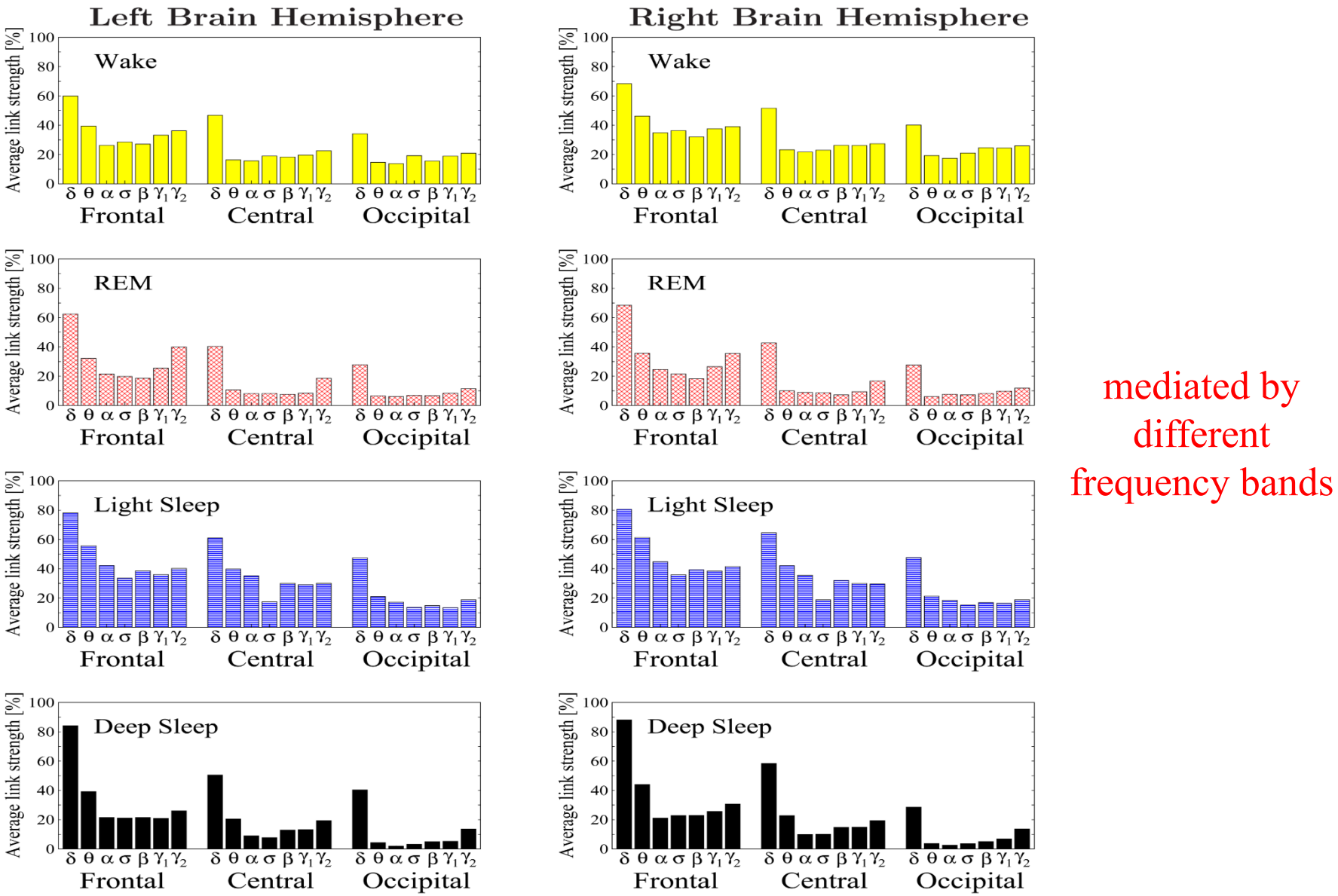



Level 3: Networked Interactions

# Brain-organ interactions

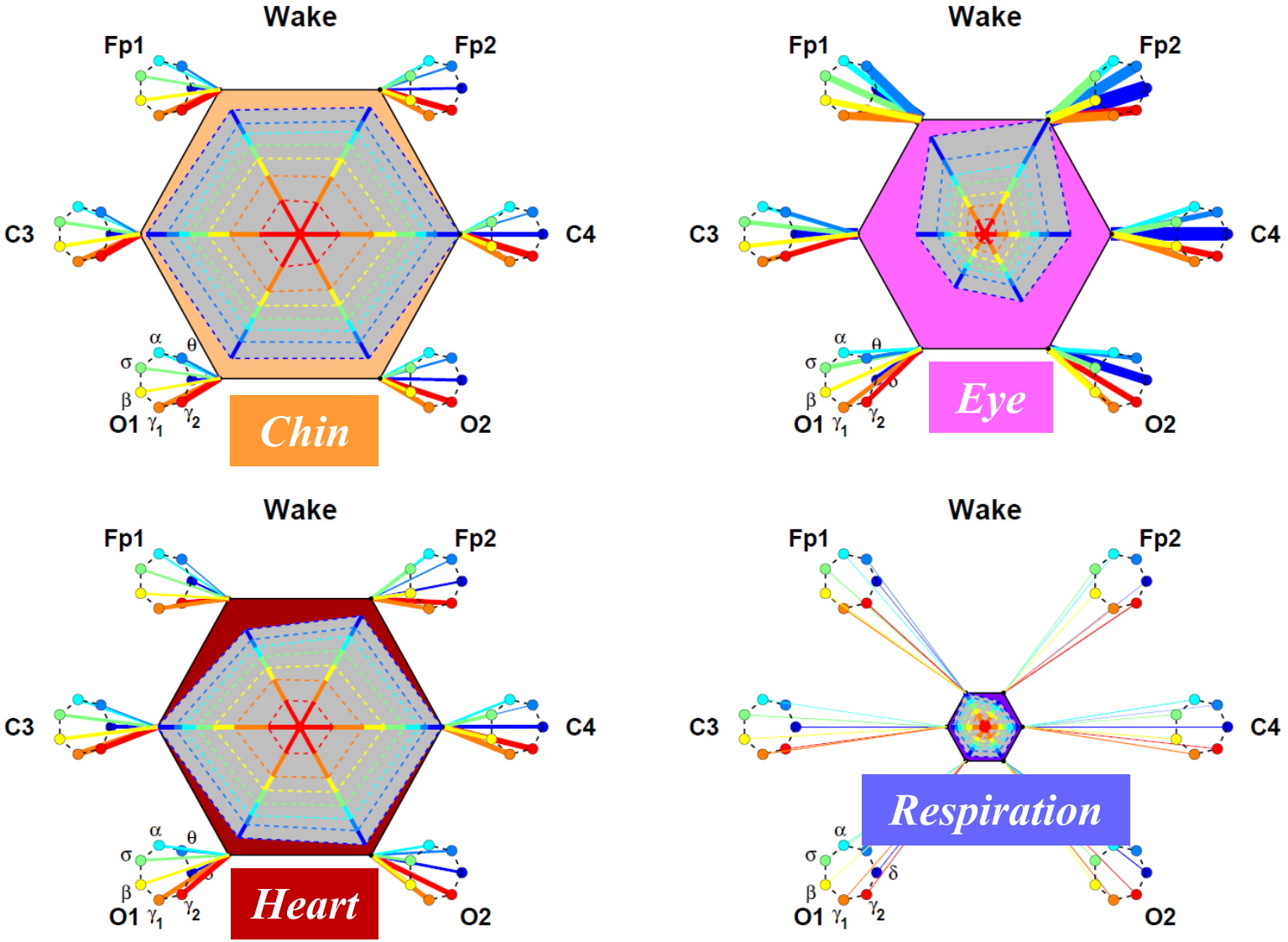
## Brain-Eye Interaction




mediated by different frequency bands

Level 3: Networked Interactions

# Maps for different organ systems




**Bartsch RP, Liu KKL, Bashan A, and Ivanov PCh.**
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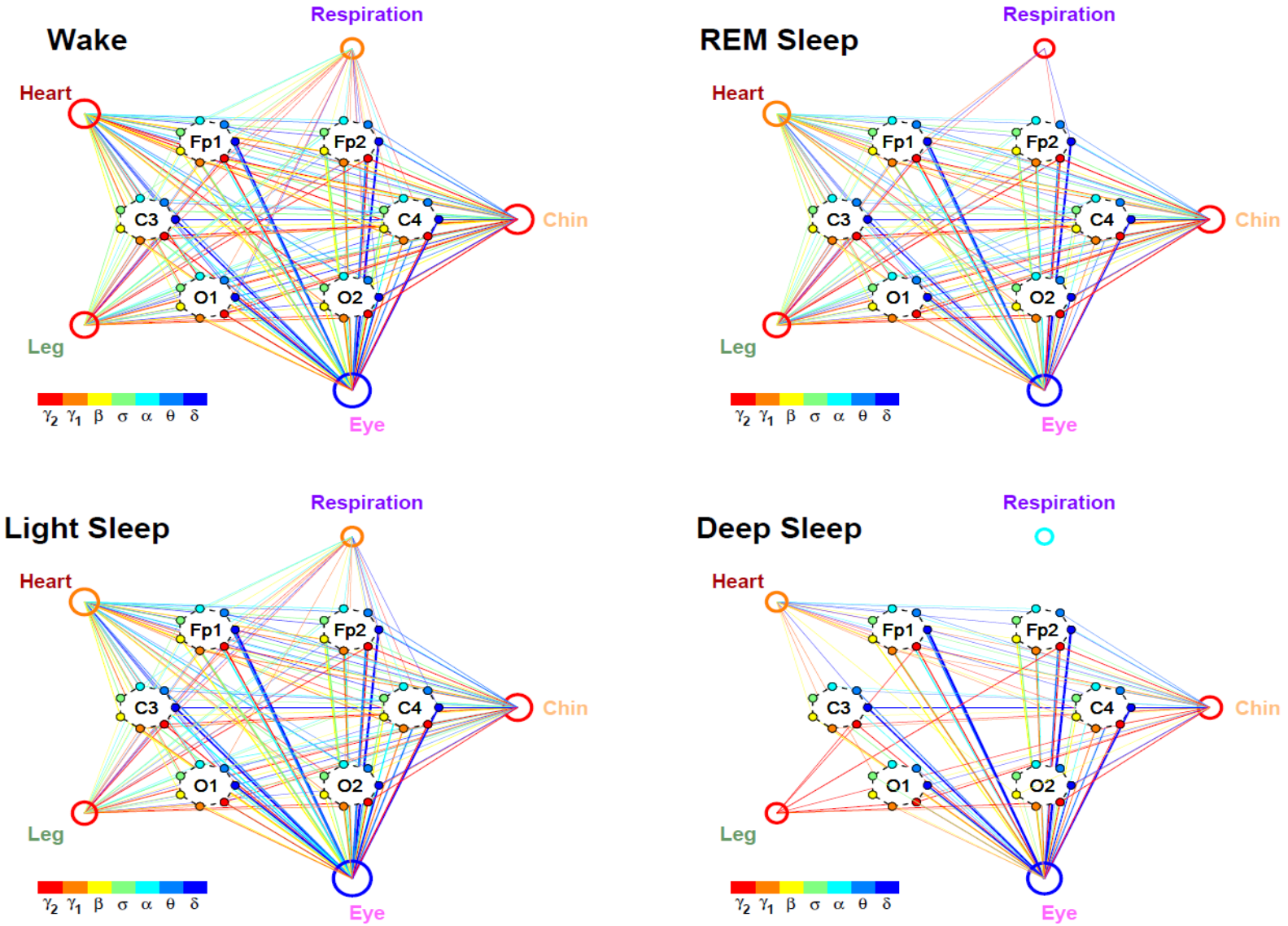
Level 3: Networked Interactions

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

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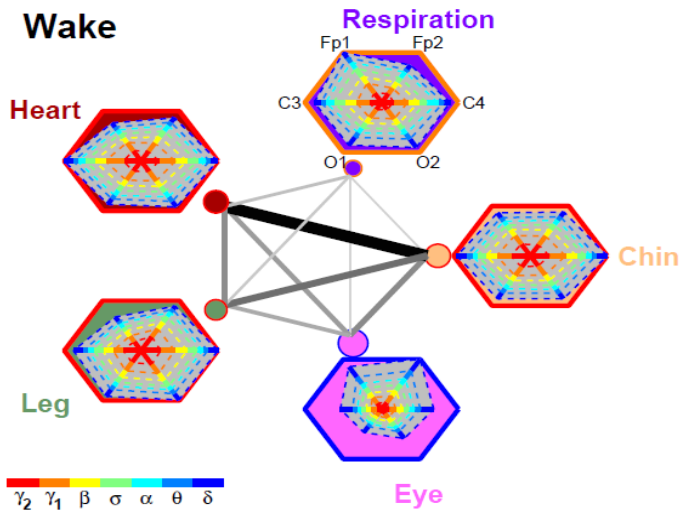
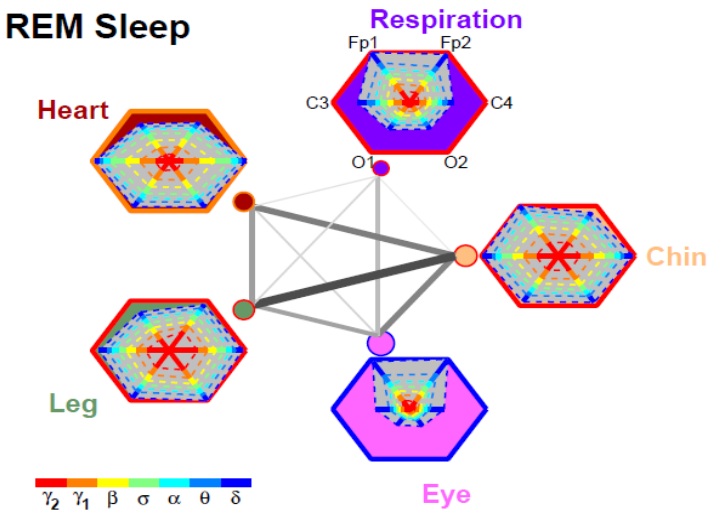
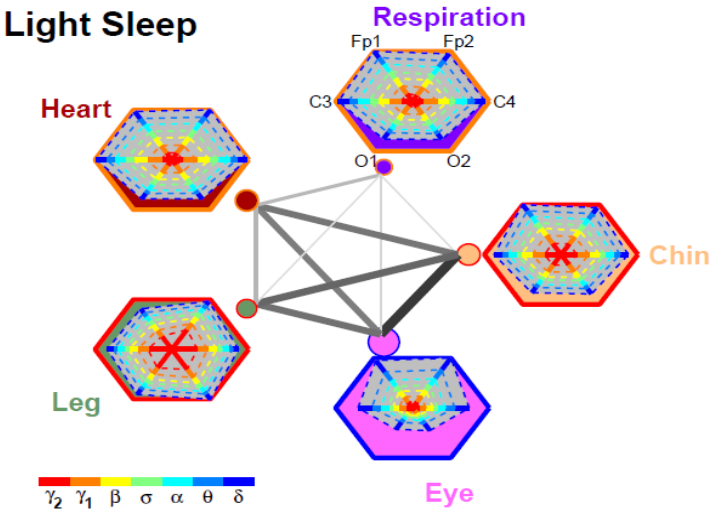
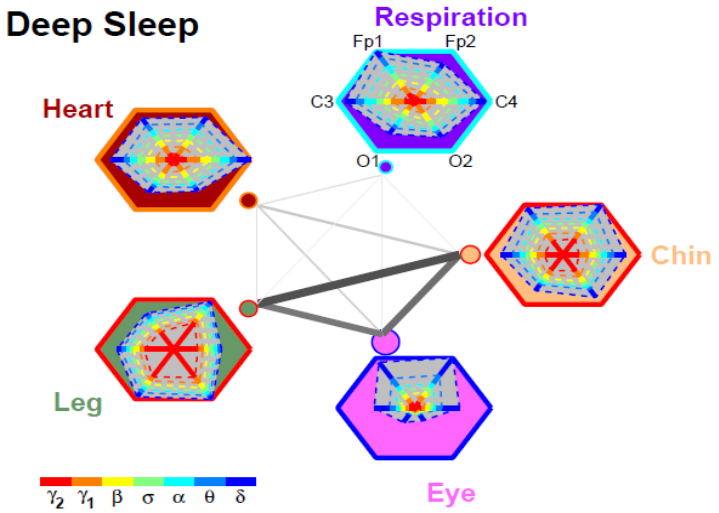
Level 3: Networked Interactions

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

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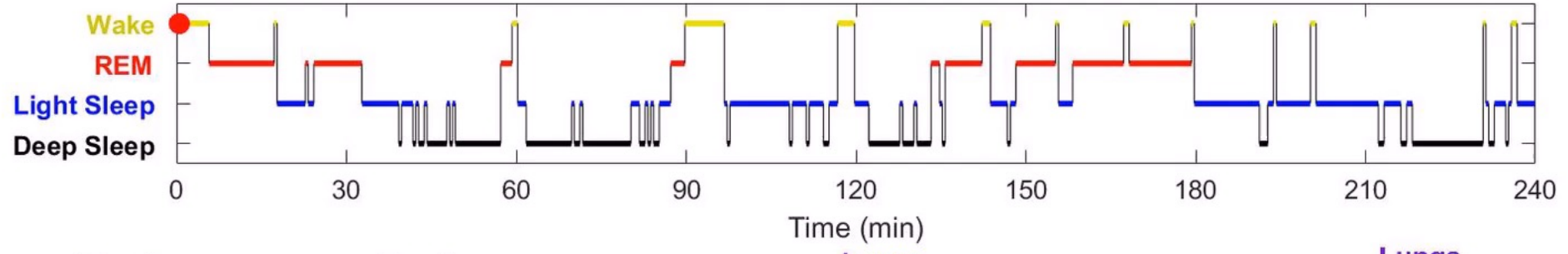
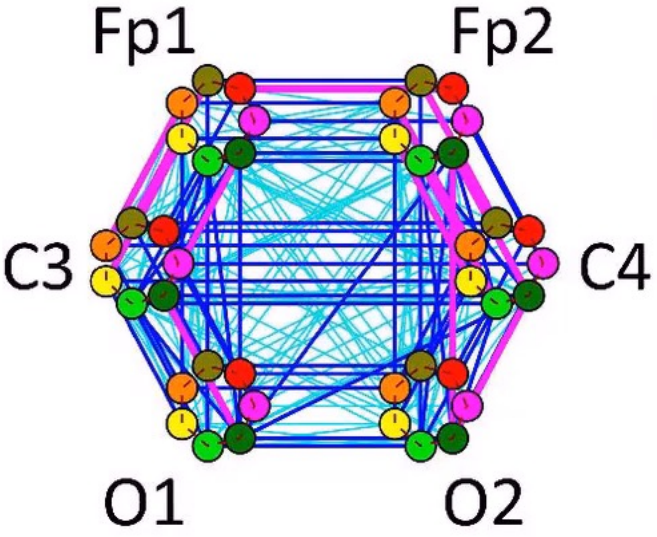
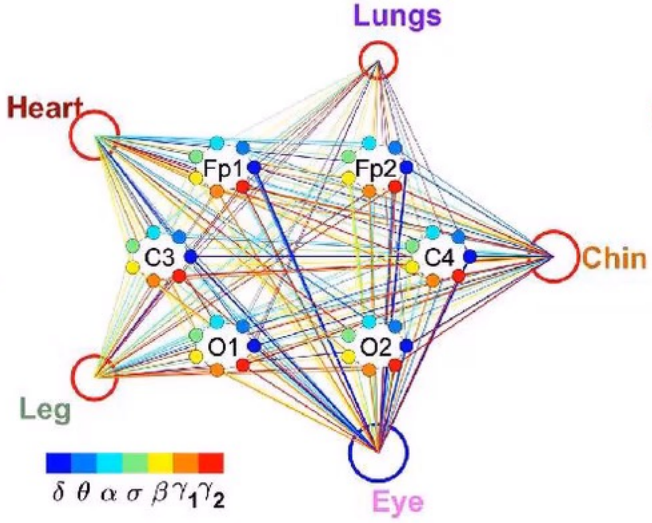
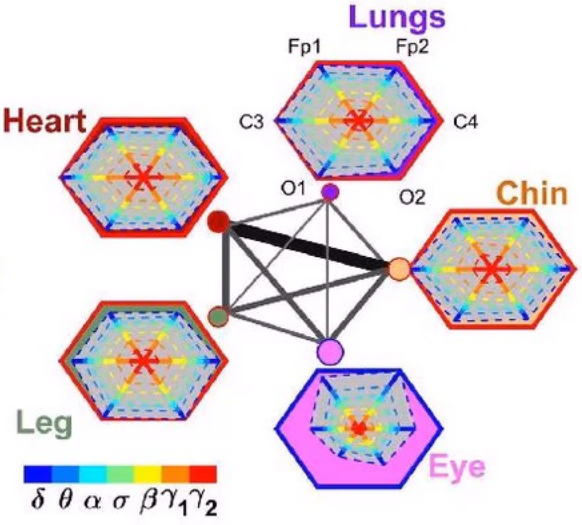
Level 3: Networked Interactions

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

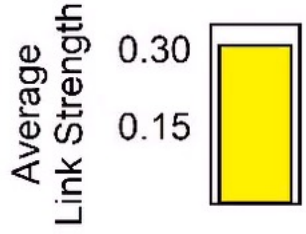


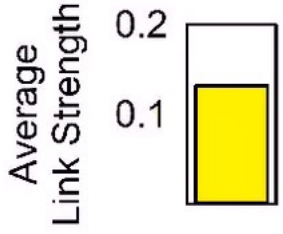



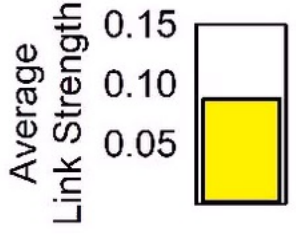

**Brain-Brain**




**Brain-Organ**

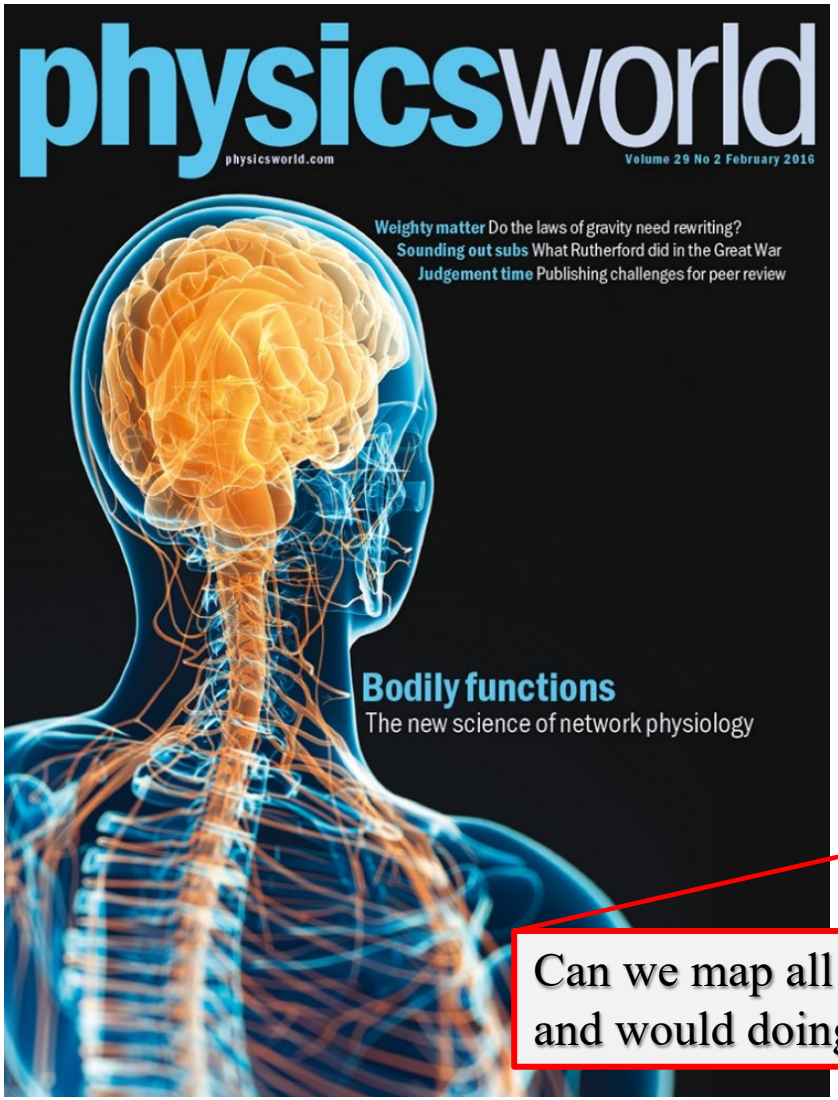


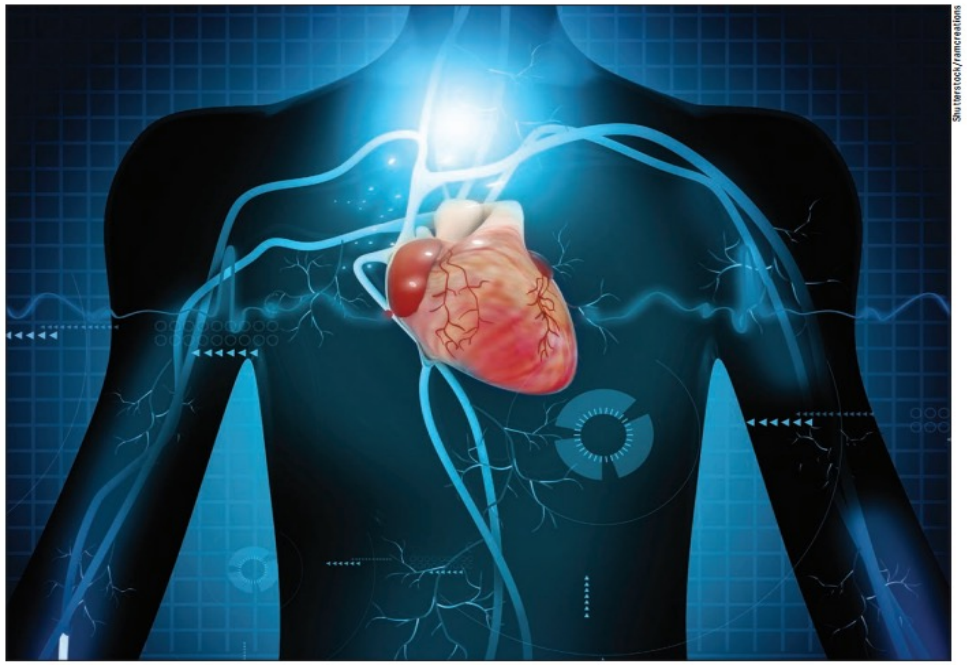

**Organ-Organ**



# 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.

least the beginnings of an answer. Having developed

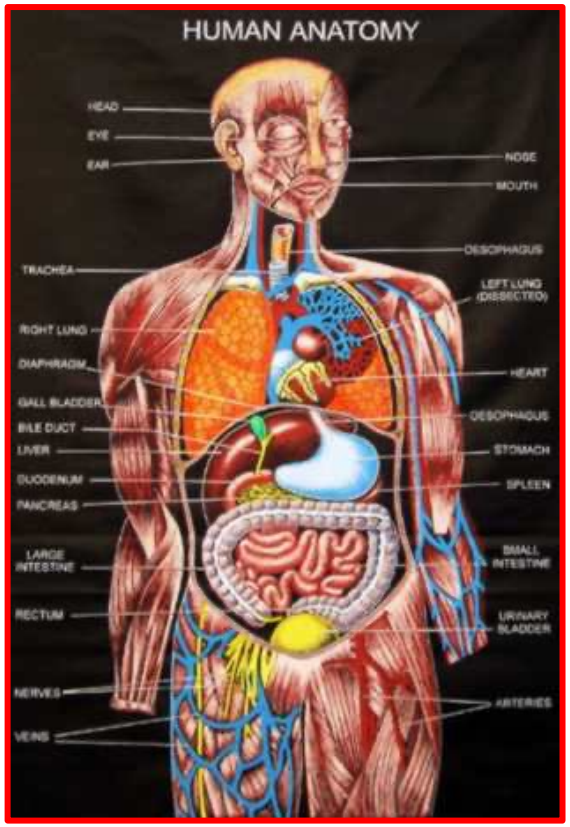
sciences until now," he says.

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

Vision

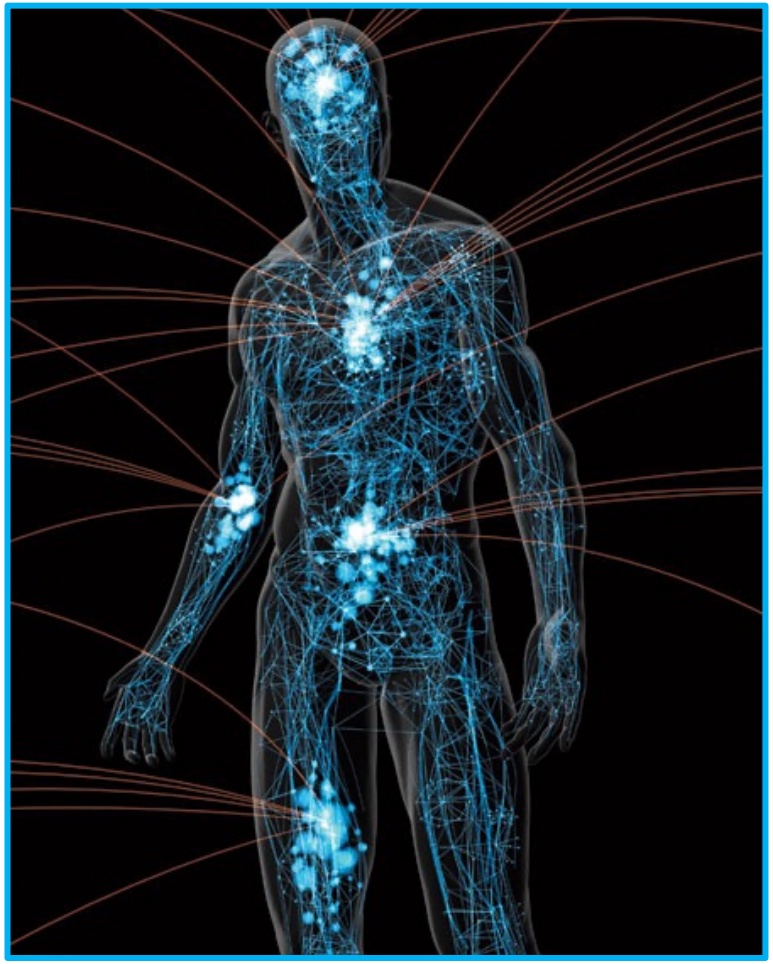
# Physiology and Medicine

*Atlas of Human Anatomy*




**need**

*Atlas of Dynamic Interactions of Organ Systems*



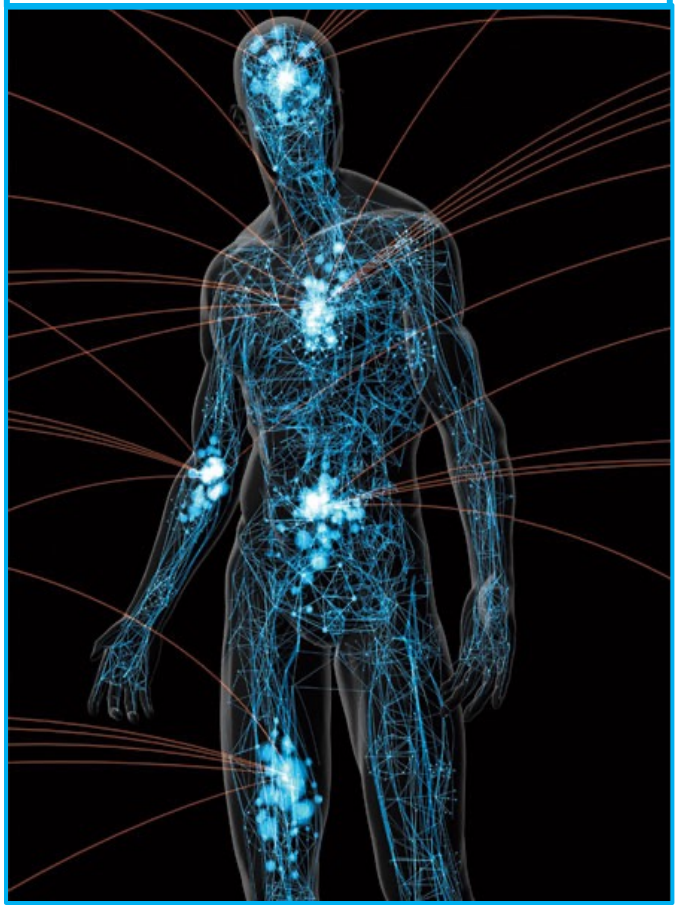
→ Revolutionize our knowledge and understanding of the fundamental mechanisms that regulate and coordinate organ-to-organ interactions

Vision

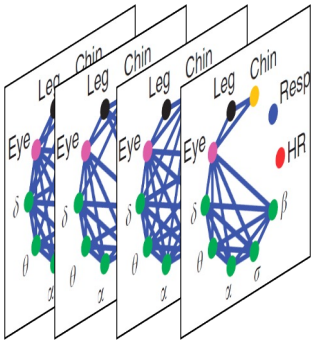
# Physiology and Medicine

## Such Atlas would contain:

***Atlas of Dynamic Interactions of Organ Systems***

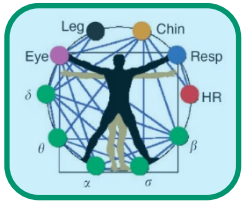


### Catalog of reference maps representing dynamical organ interactions under:

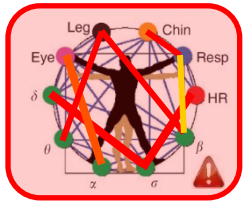



- healthy conditions
- age groups
- different physiologic states (rest/exercise, sleep/wake, sleep stages, circadian phases)
- pathological conditions (multiple organ failure, coma, heart failure, sleep apnea …)

### 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

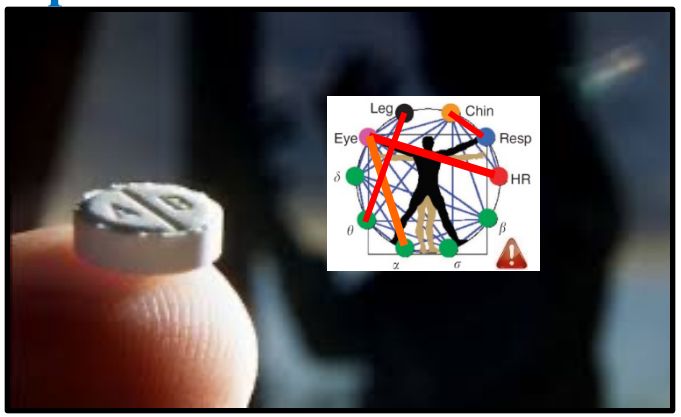
## Novel biomarkers


## New kind of Physicians


## Personalized health monitoring


## Next generation ICU monitoring devices and alert system

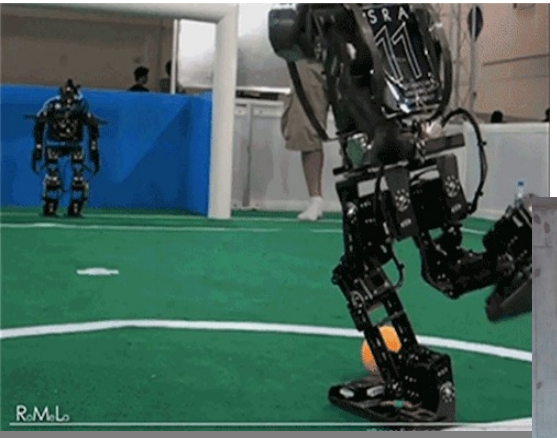

## Comprehensive assessment of drugs

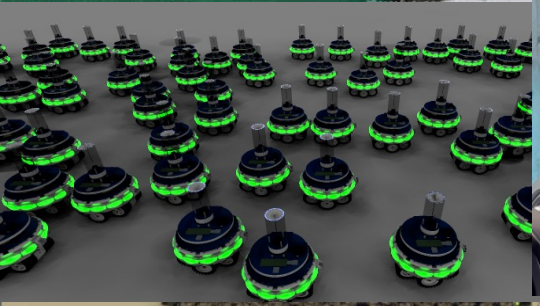


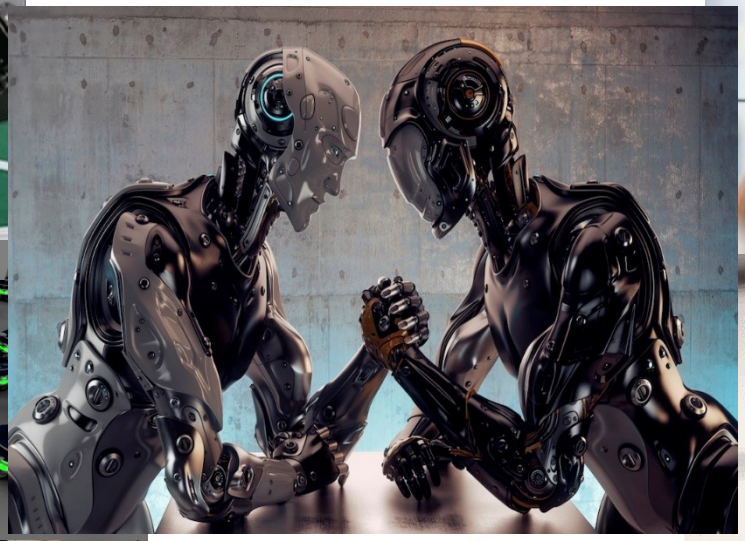
Vision & Impact

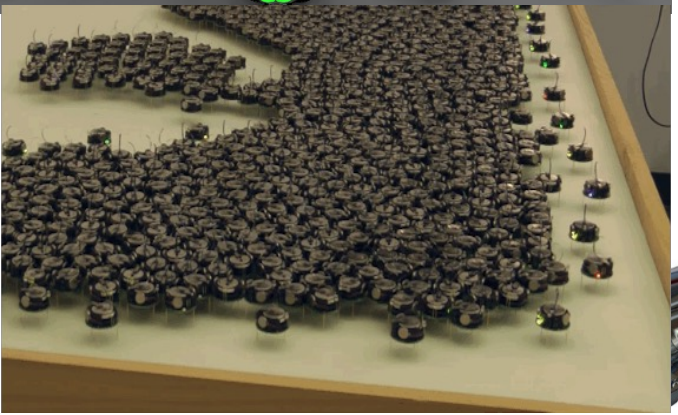
# Technology and AI: Robots and Cyborgs

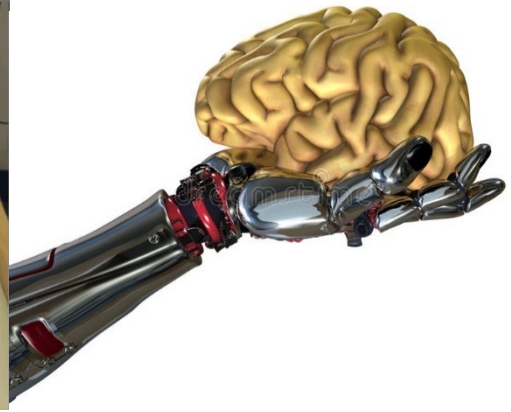
## Improve AI & robots, swarms of decentralized multirobot systems



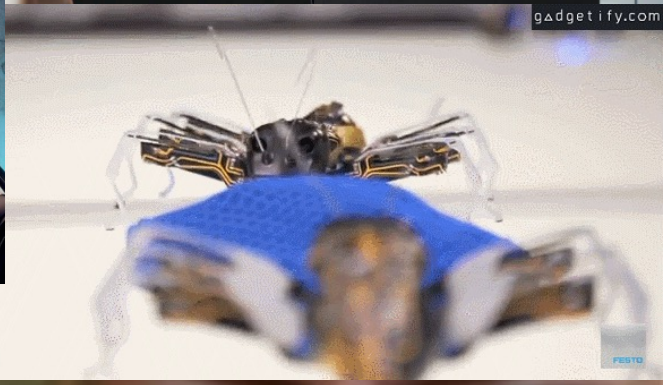








## Cyborgs: merge physiology & technology




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

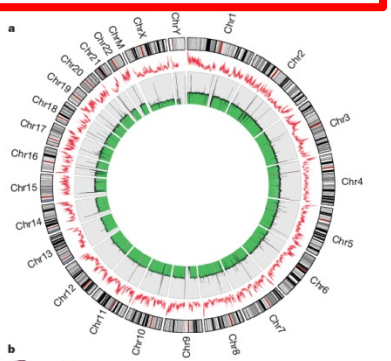
***(Now)***

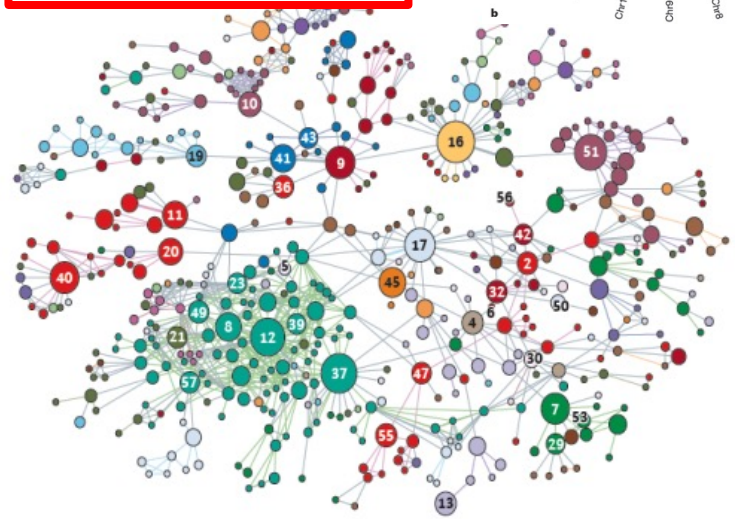
"Super Big Data"

↕

Personalized genetics

***(Future)***

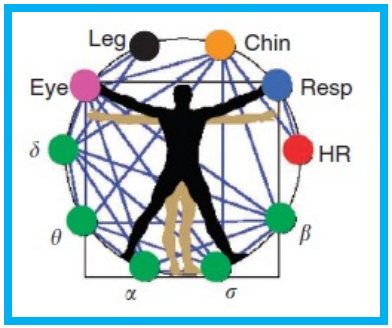




# Impact

# New Kind of Big Data: the Human Physiolome

## *Network Physiology*




*New methods*

Physiologic network topology

↕

Physiologic function

preliminary limited data

***(2012)***

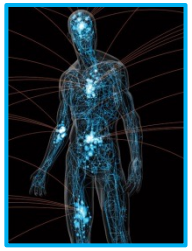
*New Kind Big Data*

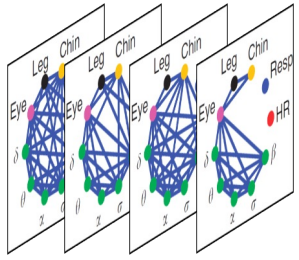
***Atlas of Dynamic Interactions of Organ Systems***

↕

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

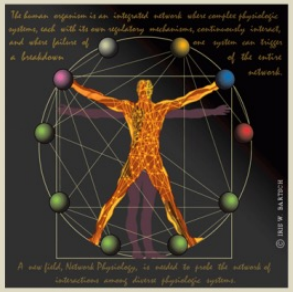
***(Future)***

*Our Group:*

**http://physics.bu.edu/labnetworkphysiology**

W.M. KECK FOUNDATION

# Keck Laboratory for Network Physiology



*Openings:*

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

*Support:*

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


W.M. KECK FOUNDATION

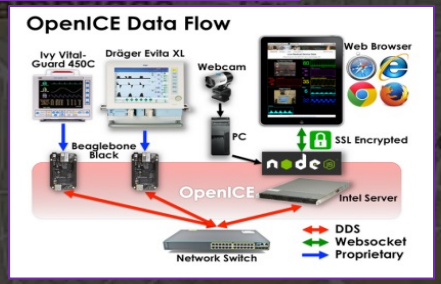
Collaboration

# Ongoing Program: Interdisciplinary Collaboration

W.M. KECK FOUNDATION

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

MD PnP™
Getting connected for patient safety™




MGH 1811

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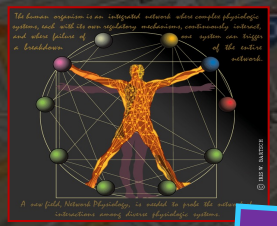
BOSTON UNIVERSITY

BOSTON MEDICAL CENTER

BU Physics



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