Initiation and Building the Foundation of a New Interdisciplinary Field Network Physiology

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Focus on the emerging new fields of network physiology and network medicine

Plamen Ch Ivanov^{1,2,3,6}, Kang K L Liu^{1,4} D and Ronny P Bartsch⁵

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Focus on Network Physiology and Network Medicine



References * Citations *

Article information

Abstract

Despite the vast progress and achievements in systems biology and integrative physiology in the last decades, there is still a significant gap in understanding the mechanisms through which (i) genomic, proteomic and metabolic factors and signaling pathways impact vertical processes across cells, tissues and organs leading to the expression of different disease phenotypes and influence the functional and clinical associations between diseases, and (ii) how diverse physiological systems and organs coordinate their functions over a broad range of space and time scales and horizontally integrate to generate distinct physiologic states at the organism level. Two emerging fields, network medicine and network physiology, aim to address these fundamental questions. Novel concepts and approaches derived from recent advances in network theory, coupled dynamical systems, statistical and computational physics show promise to provide new insights into the complexity of physiological structure and function in health and disease, bridging the genetic and sub-cellular level with intercellular interactions and communications among integrated organ systems and sub-systems. These advances form first building blocks in the methodological formalism and theoretical framework necessary to address fundamental problems and challenges in physiology and medicine. This 'focus on' issue contains 26 articles representing state-of-the-art contributions covering diverse systems from the sub-cellular to the organism level where physicists have key role in laying the foundations of these new fields.

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- 1. Introduction
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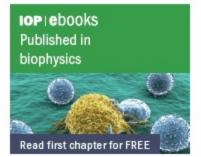
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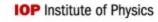
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Focus on Network Physiology and Network Medicine

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

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Focus on the emerging new fields of network physiology and network medicine

Plamen Ch Ivanov et al 2016 New J. Phys. 18 100201

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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.
- Information flow on network topology.
- Cascades of failure across systems.
- Networks of physiological networks.

The articles listed below complete the full collection.

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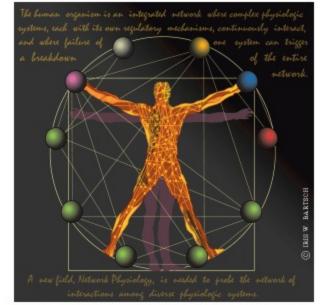


Figure. The human organism is an integrated network where complex physiologic systems, each with their own regulatory mechanisms, continuously interact, and where the failure of one system can trigger a breakdown of the entire network. A new field, network physiology, is needed to probe the network of interactions among diverse physiological systems. (Image copyright: Iris W Bartisch.)

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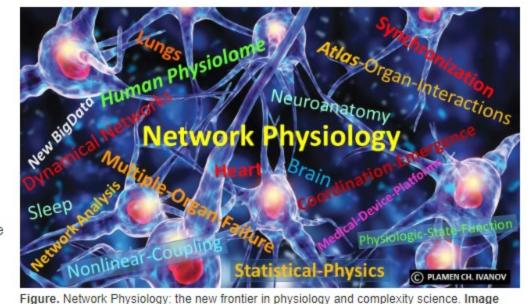
The new field of Network Physiology: redefining health and disease through networks of physiological interactions

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

Books

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, e.g. wake and sleep, consciousness and unconsciousness. Disrupting organ communications can lead to dysfunction of individual systems or to collapse of the entire organism, as observed under clinical conditions



credit: Plamen Ch. Ivanov

such as sepsis, coma and multiple organ failure. Yet, despite the importance to basic physiology and clinical practice we do not know the principles and mechanisms through which diverse physiological systems and organs dynamically interact over a range of space and time scales and integrate to generate a variety of behaviors and distinct physiologic states at the organism level.

The emerging new interdisciplinary field of Network Physiology aims to address this fundamental question. In addition to defining health and disease through structural, dynamical and regulatory changes in individual physiological systems, the new conceptual framework of Network Physiology focuses on the coordination and network interactions among diverse organ systems and subsystems as a hallmark of physiologic state and function.

A fundamental problem encountered in physical, biological and physiological systems is to quantify and understand phenomena where global behavior across systems emerges out of networked interactions among dynamically-changing entities with coupling forms that are function of time. Currently, there are no adequate analytic tools and theoretical framework to probe physiologic interactions among diverse systems.

The objective of this focus collection is to (i) provide a forum for developing new methodologies and theoretical framework to address problems and challenges in Network Physiology; (ii) to initiate the development of new databases of continuous and synchronous recordings of multiple physiological parameters; and (iii) to promote data-driven discoveries of the basic physiologic laws and control mechanisms that underlay physiologic interactions during various physiological states and under pathological conditions.

We aim to bring together basic physiologists, medical specialists and clinical practitioners with researchers from the fields of biomedical engineering, signal processing, nonlinear dynamics and statistical physics.

Of particular interest will be new approaches to identify and quantify forms of physiologic coupling as well as developing new and littleexplored areas of network science of relevance to integrated physiological systems, including the following:

- Studies on structural and dynamical aspects of physiological systems that transcend space and time scales.
- Functional forms of physiologic coupling, time variation and effects of pair-wise interactions on the dynamics and control of individual systems.
- Networks comprised of diverse physiological systems and associations between physiologic network structure and physiologic
- Evolution of pair-wise coupling and network topology with transitions across physiologic states; basic principles of hierarchical network reorganization.
- The role of time-dependent network interactions for emergent transitions in network topology and function.
- Manipulation, control and global dynamics of networks in response to clinical treatment.
- Information flow on network topology in relation to cellular and neuronal assemblies and autonomic control of organ systems.
- Networks of physiological networks transcending interactions of sub-systems to interactions among organs.
- Cascades of failure across systems as encountered in ICU critical care.

Papers

Resting-state functional connectivity analysis of the mouse brain using intrinsic optical signal imaging of cerebral blood volume dynamics

Yuto Yoshida et al 2018 Physiol. Meas. 39 054003







Disentangling respiratory sinus arrhythmia in heart rate variability records

Çağdaş Topçu et al 2018 Physiol. Meas. 39 054002

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Weighty matter Do the laws of gravity need rewriting?
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Bodily functions

The new science of network physiology



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 ity. Studying these fluctuations, he says, could give 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 as possible. Just think how both your heartbeat and your breathing speed up if you receive a shock – or how, in a starker example, the failure of one organ can lead to a cascade of failures in other organs, sometimes resulting in death.

But just how are our organs connected? Plamen Ivanov – a physicist at Boston University and Harvard Medical School in the US – thinks he may have at least the beginnings of an answer. Having developed and expanded upon the types of analyses found in the statistical physics of complex networks, Ivanov and is now known, first began in the mid-1990s, when he others believe that the fluctuating outputs of organs, commonly considered "noise" by today's physiologists, are in fact evidence of an underlying connectiv-

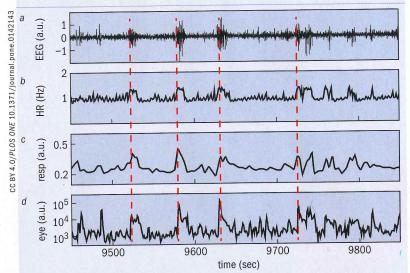
us an entirely new window into the workings of the human body – and help us prevent things going wrong.

Ivanov has grand ambitions. He wants to draw on statistical physics to build a human atlas, or "human physiolome" - a comprehensive map of all the interactions between organs in the human body. Like the Human Genome Project, which over 13 years uncovered the genetic blueprint of humans, Ivanov believes a human physiolome will revolutionize the analytic approaches of clinical practice. "It will pose new questions that have not been posed by the natural sciences until now," he says.

Ivanov's work on "network physiology", as the field began investigating the fluctuations in heart rates of both healthy human subjects and those suffering from sleep apnoea, when breathing during sleep Jon Cartwright is a freelance journalist based in Bristol, UK, http://jcartwright. co.uk

Physics World February 2016

1 Co-ordinated activity from diverse organ systems



Segments of synchronously recorded physiological signals including (a) brain EEG signal, (b) heart rate, (c) respiratory rate and (d) eye movement recording. Co-ordinated bursting activities with a certain time delay are consistently observed across the output signals of organ systems. Red dashed lines highlight a train of four significant bursts. These bursts transcend all systems and indicate networked communications among the systems.

becomes irregular. Everyone's heart rate fluctuates, so if you measure someone's heart rate to be an average of, say, 60 beats per minute, the time between neighbouring pulses could be at a rate of more like 50 or 70 beats per minute.

Ivanov found that, for people with sleep apnoea, these fluctuations were random, whereas for healthy subjects the distribution of fluctuations could be described by a single function over a wide range of timescales (1996 *Nature* **383** 323). In other words, there appeared to be an underlying temporal structure to the heart-rate fluctuations in healthy people, in the sense that the time between any two pulses is in some way related to the time between another two pulses – seconds, minutes or even hours in the past. "It turns out that these fluctuations are not noise," says Ivanov. "They are very structured."

Working with colleagues at Boston and other institutions, Ivanov made some further interesting observations about scaling functions and power laws, which also describe temporal structure. He found that unique power laws could describe unique physiological states - not just being awake or being asleep, but different stages of sleep, including light sleep, deep sleep and rapid-eye-movement (REM) sleep. Intriguingly, an "asleep" power law could persist if a person was actually awake at an unusual time, for instance if he or she had travelled to a different time zone. Even more curious was that the researchers found a similarity between the diminished heart-rate fluctuations in the "half awake" physiological states of early morning and diminished fluctuations in those suffering from heart problems. The result, which goes against the popular idea that poorly hearts ought to exhibit more irregularities, could point to an underlying mechanism to explain why most heart attacks happen in the morning (2007 IEEE Eng. Med. Biol. Mag. 26 33).

The human physiolome

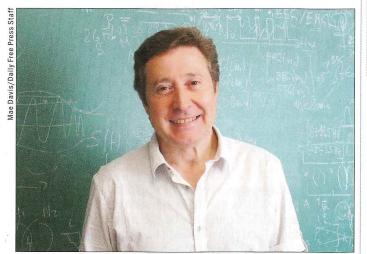
The application of statistical physics to physiology does not end with heart-rate analysis. Ivanov and colleagues have also found power laws to describe fluctuations in breathing, fluctuations in the movement of a person's hands and fluctuations in a person's gait. But the power laws appeared to extend beyond individual limbs and organs. Even in his mid-1990s work on heart-rate fluctuations, Ivanov knew that the cardiovascular and respiratory systems must be in some way "talking" to each other - after all, there was a heart-rate power law for healthy subjects, but not for those with a respiratory disorder, sleep apnoea. Indeed, in 2000 Ivanov and colleagues showed that sleep apnoea could be diagnosed not from respiratory recordings - the traditional method, which requires hospitalization - but from inexpensive, home-monitored heart-rate recordings (2000 Comput. Cardiol. 27 753). The group recently uncovered several further, independent couplings between the cardiovascular and respiratory systems, which undergo dramatic transitions from one sleep stage to another (2012 PNAS 109 10181).

Could this type of communication be continuously mapped somehow, not just between the cardio-vascular and respiratory systems, but among all the body's organs? Certainly, recent decades have seen a dramatic upsurge in the application of statistical-physics techniques to complex networks. By analysing widely available information such as Internet traffic and mobile-phone data, physicists have found new insights into underlying sociological behaviour. But whereas mobile phones and IP addresses are all similar types of node, each type of human organ is very different. Worse, the links between organs are continuously changing, and operate on a vast hierarchy of timescales.

In 2012 Ivanov and an interdisciplinary team of scientists made some headway by coming up with a concept called time-delay stability. This concept relies on measuring the time between fluctuations in the output signals of one physiological system, such as cardiovascular, and the emergence of corresponding modulations in another, such as the respiratory. According to the researchers, the longer the period during which this delay is constant – for example, the constant period during which a fluctuation in heart rate is followed by a fluctuation in breathing a few seconds later – the stronger the coupling between the two systems.

To test the time-delay stability concept, Ivanov and colleagues analysed existing sleep data taken from 36 healthy volunteers. The data consisted of heart rates, breathing and brain activity, as well as eye, leg and chin movements. The researchers found that all of these physiological systems appeared to be poorly coupled during deep sleep, but more connected when a subject transitioned into REM sleep. The links became stronger in the light-sleep phase, and stronger still when the subjects finally awoke. Based on these promising findings, it was these researchers who proposed the creation of the field of network physiology (2012 *Nature Comms* 3 702).

In November 2015 Ivanov and colleagues finished



Mind over body Plamen Ivanov created the field of network physiology.

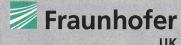
a more in-depth analysis of the data, and found that each organ has its own network of interactions with different areas of the brain, and with other organs (*PLOS ONE* 10.1371/journal.pone.0142143). Interestingly, there appear to be rules governing the reorganization of brain-organ and organ-organ interactions when a subject undergoes a transition to a different sleep stage; despite the uniqueness of the networks for each organ, these reorganization rules appeared to be the same for each of them (figure 1).

"Remarkably, these networked communications are so flexible that they can change and adjust within seconds [during] a transition from one physiological state to another – something we had not expected," says Ivanov. "This shows an amazing flexibility and responsiveness in the way organ systems optimize and coordinate to generate different physiological functions during different physiological states."

For Ivanov, this work could mark the beginnings of a human physiolome. And indeed he now has support: in July 2015, he was awarded a \$1m (£660000) grant by the W M Keck Foundation to develop network physiology. But he insists the path ahead will not be easy. "These are only the first steps in this new field," he says. "Network physiology poses many new questions and challenges for which we do not yet have the necessary analytic [instrumentation] and theoretical framework."

Even so, he continues, the challenges will be worth it to generate a new type of "big data". The human physiolome will contain "streams of continuously recorded, high frequency, synchronized physiological signals under different physiological states and clinical conditions, [which] will change the way medicine operates today and will integrate more and more data-driven analytic approaches in clinical practice", he says. "In the future, this new big data will have a similar impact on science, medical practice and health care as the Human Genome Project has today."

• New Journal of Physics, from IOP Publishing – which also publishes Physics World – recently released a collection of articles in its "Focus on Network Physiology and Network Medicine", http://ow.ly/WdA0L



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First International Summer Institute on Network Physiology (ISINP)



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

website: isinp.lakecomoschool.org

The focus of this summer institute is to integrate empirical and theoretical knowledge across disciplines with the aim to understand in different contexts ~ from extensive data analyses and modeling approaches to clinical practice ~ how diverse physiological systems and subsystems dynamically interact to produce health and disease. This will be an interactive event with lectures ranging from physics, applied mathematics and biomedical engineering to neuroscience, physiology and clinical medicine, covering a range of physiologic systems from the cellular to the organ level, and will discuss the challenges, current frontiers and future developments in the emerging field of

Network Physiology. The institute will address a diverse audience of graduate students, postdocs, research scientists and faculty across a broad range of disciplines and fields, and will provide opportunities for the researchers to exchange new ideas and viewpoints, forge new collaborations and train the next generation of young scientists.

Invited Speakers



Ronny P. Bartsch Physics Department, Bar-Ilan University, Israel



Stefano Boccaletti Institute for Complex Systems Florence, Italy



Eberhard Bodenschatz
Max Plank Institute for
Dynamics and Self-Organization
Goettingen, Germany



Timothy G. Buchman Critical Care Centers Emory University , USA



Edward T. Bullmore Behavioural and Clinical Neuroscience Institute, Cambridge University, UK



Luca Faes
Bruno Kessler Foundation
and BIOtech Center,
University of Trento, Italy



Klaus Lehnertz
Department of Epileptology
Bonn University, Germany



Kang K L Liu
Department of Physics
Brandeis University, USA



Hagen Malberg
Institute for Biomedical
Engineering, Dresden University
of Technology, Germany



J. Randall Moorman
Center for Advanced Medical
Analytics University of Virginia



Louis M. Pecora Naval Research Laboratory Washington, DC, USA



Thomas Penzel Sleep Center, Charité Hospital Berlin, Germany



Arkady S. Pikovsky
Departmant of Physics and Astronomy
University of Potsdam, Gremany



Michael G. Rosenblum

Departmant of Physics and Astronomy
University of Potsdam, Gremany



Antonio Scala
CNR Institute for Complex Systems
University of Roma "La Sapienza"
Italy



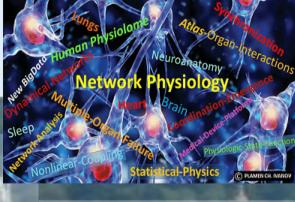
Ruedi Stoop Institute for Neuroinformatics ETH Zürich, Switzerland



Sebastiano Stramaglia Department of Applied Physics University of Bari, Italy



Béla Suki Department Biomedical Engineering Boston University, USA



Institute Organizer and Director



Plamen Ch. Ivanov
Director, Keck Laboratory
for Network Physiology
Boston University, USA

Contacts & Location



Villa del Grumello
Via per Cernobbio, 11
22100 Como, Italy.
Ms. Mariagiovanna Falasconi
tel. +39 031 579813
fax +39 031 573395
Email: info@lakecomoschool.org
www.lakecomoschool.org







Physiological Measurement











Plamen Ch. Ivanov recieves Pythagoras Prize

posted Feb 27, 2015, 10:04 AM by Network Physiology [updated Dec 1, 2017, 1:46 PM]

Professor Plamen Ch. Ivanov, a native of Sofia, Bulgaria, has received the prestigious Pitagor (Pythagoras) Prize.

The Pitagor Prize is the highest award in Bulgaria for scientific achievements. The award is given annually by the Bulgarian government to honor scientists in the fields of natural sciences, medicine and technology.

The 2014 Pitagor Prize was given in recognition of Dr. Ivanov's seminal contributions to interdisciplinary science at the interface of physics physiology and medicine, for uncovering basic laws of dynamical interactions among physiological systems, and for pioneering a new field, Network Physiology.

The 2014 Pitagor science awards ceremony was hosted by the Ministry of Education and Science of Bulgaria, and was attended by government officials and representatives of the Bulgarian Academy of Sciences, leading universities and institutions.



Prof. Plamen Ch. Ivanov (center) is accompanied by the Deputy Prime Minister of Bulgaria, Dr. Daniela Bobeva (left) and the Minister of Education and Science, Prof. Anelia Klisarova (right).