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Focus on the emerging new fields of Network Physiology and Network Medicine

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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 inter-cellular 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.

1. Introduction

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

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function of time. In the context of systems biology, human physiologyand medicine, recent advances in complex networks theory [1, 2] have stimulated and facilitated the development of new fields of research.

Studies initiated by physicists have utilized graph theory and network approaches to cellular interactions to build genetic, protein-protein interaction, metabolic and regulatory networks with the aim to understand the associations between genomic and proteomic factors and disease phenotypes [3–7]. This has led to the emergence of network medicine as a new interdisciplinary field of active research [8–11].

Following the reductionist approach, systems biology has traditionally focused on identifying key elements inside the cell and on establishing their role in cellular function. Recent research in systems biology has been facilitated also by integrative network approaches where graph theory is utilized to obtain knowledge graphs, connecting biological observations of relationships among cell elements, with the aim to uncover complex intra-cellular signaling pathways and to treat available genomic, proteomic and metabolic information in a generalized systematic way. Thus, fundamental questions related to how genomic and proteomic factors relate to the suppression or expression of particular disease phenotypes have triggered a shift in paradigm leading to the emerging new field of network medicine. Further, this new field has developed novel concepts and methods to establish and predict associations between clusters of different disease phenotypes and shared genes [6, 7, 12]. The network medicine framework made it also possible to define and predict the role of genes and proteins in the expression of a particular disease based on the neighborhood of genes in the network (network motifs and modules), allowing to identify potential new genes that may play role in disease phenotype expression [5, 12–15]. This new perspective led to identification of disease genes based on correlations between their location in the interactome and their network topology.

Establishing functional relationships between the signature of specific genes in the network environment and their potential role in the mechanisms underlying disease phenotype expression is a fundamental breakthrough due to network medicine, as currently only about 10% of all genes have known disease association [16]. The integrative framework of network medicine has helped to further extend genetic and phenotypic networks derived for intra-cellular interactions to account for tissue and organ specificity in gene connectivity and disease association, and to establish principles of gene interactions across cells and tissues [17–20]. More recent developments in network medicine have added another level of integration through layered multiplex networks that combine genetic networks with a wide range of co-morbidity factors to understand their role in modifying the action of disease-causing genes [17] and the likelihood of disease phenotype expression in the presence of other diseases and risk factors [21, 22].

Investigations of intra- and inter-cellular signaling pathways and how alterations in these pathways lead to cascades of failure across protein and metabolic interaction networks opened the way to build the human disease network [23] – a fundamental discovery resulting from network medicine that reveals interrelations and clustering among distinct diseases

based on information derived from networks of genomic, proteomic and metabolic interactions [11, 24].

Analytic tools from complex networks theory offer new avenues to systematically explore how cellular components exert their functions through network interactions across cells, tissues and organs in order to elucidate the molecular mechanisms underlying particular diseases and associations between diseases. In turn, the developments and discoveries in network medicine have initiated new directions of research in complex networks, posing new fundamental questions to network theory — for example, the role of individual nodes in network controllability — that require novel mathematical formalism and theoretical framework. Because of the inherent cross-fertilization from biology and medicine to statistical physics and network science, network medicine has emerged as a separate, self-sustained interdisciplinary field.

Advances in network medicine have laid the foundation of the human disease network by connecting microscopic cellular level genomic, proteomic and metabolic networks with human epidemiology at the macroscopic organism level. While systems biology and integrative physiology have focused on the vertical integration from the sub-cellular and cellular level to tissues and organs [25], there is a wide gap of knowledge in the direction of horizontal integration at the level of organ-to-organ interactions. A new field, network physiology, has emerged to fill this gap and to address the fundamental question of how physiological systems coordinate, synchronize and integrate their dynamics to optimize functions and to maintain health. Physiologic interactions occur at multiple levels and spatio-temporal scales to generate distinct physiologic states, e.g., wake and sleep, light and deep sleep, consciousness and unconsciousness. Thus, investigations in network physiology have focused on (i) structural and functional connectivity of physiologic networks underlying individual organ systems and their sub-systems [26–29], and (ii) how global behavior at the organism level, i.e., different physiologic states and functions, arise out of networked interactions among organ systems to generate health or disease [30, 31]. Disrupting organ communications and their dynamical coordination can lead to dysfunction of individual systems or to collapse of the entire organism, e.g., coma, multiple organ failure [32, 33]. Thus, in addition to the traditional approach in physiology that defines 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 as a hallmark of physiologic state and function.

Novel computational tools and analytic formalism developed in the field of network physiology have added new rich dimensions to our understanding of physiologic states and functions. The network physiology perspective has redefined physiologic states from point of view of dynamic networks of organ interactions. This has helped establishing first associations of distinct physiologic states and conditions with network topology and with the temporal characteristics of organ interactions (network links) even when network topology remains unchanged [30, 31]. It was discovered that brain-organ interactions have preferred channels of communication (frequency bands) that are specific for each organ [34] and recent efforts in the community by physicists and physiologists that focused on networks of

brain-heart interactions identified new aspects of coupling and feedback mechanisms [35]. By developing the theoretical framework necessary to uncover basic principles of (i) integration among diverse physiologic systems that leads to complex physiologic functions at the organism level, and (ii) hierarchical reorganization of physiological networks and their evolution across states and conditions, investigations in the field of network physiology provide the building blocks of a first atlas of dynamic organ interactions.

Although the interdisciplinary research in both network physiology and network medicine takes advantage of the rapid development in complex networks theory, it is important to note the different focus, philosophy and theoretical problems in these new fields. In general, links in network medicine focus on characterizing statistical correlation and dependency, and research is focused on the global consequences of network topology and structure for identifying the specific role of genomic and proteomic factors in expression of disease phenotypes [11]. In contrast, in network physiology, links represent dynamical coordination between diverse systems and subsystems with transient characteristics, and a fundamental question is how physiologic states and functions emerge out of the collective dynamics of integrated physiological systems [34, 36]. Moreover, markedly different global behaviors can emerge from the same network topology due to minor temporal changes in the functional form of physiologic interactions. This poses new challenges to further develop generalized methodology adequate to quantify complex dynamics of networks where nodes are not identical but represent diverse dynamical systems with diverse forms of coupling which continuously change in time. Because of the new type of problems, the specificity of related challenges and the necessity of new theoretical framework and interdisciplinary efforts, network physiology has developed into a new field of research.

Network physiology and network medicine are not simply an application of established concepts and approaches in complex networks theory to existing fields of biomedical research. Their scope extends far beyond applying knowledge from one field (physics and applied mathematics) to solve problems in another (systems biology, physiology and medicine), and require new computational and analytical approaches to extract information from complex data, to infer transient interactions between dynamically changing systems, and to quantify global behavior at the organism level generated by networks of interactions that are function of time. In fact, in recent years, e have already witnessed the broad impact of introducing novel concepts and methods derived from modern statistical physics and network theory to biology and medicine, shifting the paradigm from reductionism to a new integrative framework essential to address fundamentally new problems in systems biology, neuroscience, physiology, clinical medicine [37] and even drug discovery [38]. A central focus of research within this integrative framework is the interplay between structural connectivity and functional dependency, a key problem in neuroscience and brain research [27, 29]. As a result, new physical models have been motivated and proposed to investigate the dynamical consequences of networks [39–44], which in turn trigger more theoretical questions for statistical physicists. These synergetic effects certainly establish network medicine and network physiology as new fields in the landscape of contemporary biomedical esearch. Understanding the relationship, conceptual difference, the broad horizon and impact of network physiology and network medicine is important to facilitate an active

and productive dialog among physicists, biologists, physiologists, neuroscientists and clinicians, which is the central focus of this special issue.

In recent years, physicists have made significant contributions in both fields of research that led to discoveries with potential for broad clinical applications. This focus issue is a collection of interdisciplinary contributions highlighting new developments at the interface between physics, physiology and medicine, including: novel applications of complex networks theory to ask new questions in systems biology; human disease networks; new physics of synchronization phenomena in networks of oscillators; new insights in neural networks and brain structural and functional connectivity; innovative methods to probe physiological time series from individual systems and the impact of individual systems on the dynamics of the entire physiologic network; dynamical networks of organ systems and functional forms of coupling; and clinical applications derived from networks of physiologic interactions.

2. Network Medicine

2.1. New perspectives on systems biology

In contrast to the traditional reductionist approach in systems biology, where focus of investigation is to identify and quantify the role of single molecules, individual genes and separate cellular components, recent advances in complex networks theory allow for a more holistic approach through studies of networks of interacting cellular components across multiple levels, from single molecules, genes and proteins to signaling pathways and functional modules across cells and tissues.

Investigating the chromatin interaction network, Boulos et al. [45] took advantage of a graphical theoretical approach to uncover “master” replication initiation zones organized at the N/U-domain borders that play key role in the 3D organization of the human DNA. Utilizing a thermodynamic out-of-equilibrium variational principle approach to cellular metabolic networks, De Martino et al. [46] identify intracellular flux patterns from extracellular metabolic interactions and the role of non-equilibrium steady states for the function of metabolic networks. Lin et al. [47] develop a Boolean network framework to investigate the dynamics and function of the p53 regulatory network and the role of this network in tumor suppression, identifying two-phase dynamics in response to DNA damage and oncogene activation. Elucidating the signaling network for a two-cell system, Jolly et al. [48] provide first insights on the operating principles and communication mechanisms that govern evolutionary processes of cell development and tumor progression. Extending two dimensional elastic springs network models of lung tissue, Oliveira et al. [49] investigate the formation and growth of isolated regions of collagen deposition in the lung cell network that increase lung tissue stiffness and lead to the progression of pulmonary fibrosis. With a new focus on the mesoscale, Klimm et al. [50] propose a framework based on a set of graph descriptors to characterize the position that each individual node takes within the modular and hierarchical architecture of complex networks to assess the influence of individual nodes to the global dynamics of the network.

2.2. Towards the human disease network

Network studies in systems biology have initially focused on deriving information from single molecular networks, protein interaction networks, metabolic and regulatory networks. Advances in network theory within the framework of network medicine make it possible to gain new insights into the properties of biological networks more generally. Since cellular signaling processes can spread the effect of a specific genetic abnormality along the network of links by altering the activity of other gene products that carry no defects, disease phenotype is rarely a consequence of an abnormality of a single gene product but reflects a broad range of biological processes that interact in a complex network. Relying on new emerging tools from network and graph theory, recent investigations in network medicine aim to quantify the complex interdependencies among cellular components that lead to functional and causal relationships among distinct disease phenotypes. To address the question of how various human genes associate with different diseases, studies have focused on quantifying network characteristics that distinguish disease genes from others, on detecting correlations between gene network location and local network topology, and on identifying disease modules based on network clustering of disease genes.

Investigating cell regulatory pathways related to hypoxia genes that are responsible for increasing oxygen supply and optimizing cellular metabolism under limited oxygen supply, Wang et al. [51] employ the network medicine framework to identify modules of hypoxia and cardiovascular disease genes within the human protein interactome. The work leads to new insights on the relationship between hypoxia and cardiovascular diseases and to improved prediction of novel genes that may be associated with cardiovascular disease. Another line of investigations focuses on co-controllability of networks, identifying the minimal set of driver nodes that control an entire network and quantifying mutual control characteristics of multiple networks as encountered in the human interactome. A study by Sun [52] considers a drug-disease-gene network that consist of gene-gene, disease-disease and drug-drug networks to investigate co-controllability among these networks, and to uncover underlying mechanisms of the drug-disease-gene network with applications to disease treatment and drug design.

These works are great examples of the utility of the network medicine framework where a number of questions about signaling pathways, metabolic interactions, regulatory networks and cell/tissue communications can be formulated and investigated in a systematic and integrative way. Moving forward from a single network to interdependent networks (multiplex) while shifting the focus from quantifying structural properties to exploring basic principles of controllability of these networks opens new questions in systems biology that will lead to new theoretical developments in complex networks.

3. Network Physiology

3.1. Unique challenges

A different kind of network problems arise when considering the complex dynamics and network interactions among integrated physiological organ systems and sub-systems, which is a focus of investigations in the field of network physiology. Physiological systems under

neural regulation exhibit non-stationary, intermittent, scale-invariant and nonlinear behaviors. Their output dynamics transiently change in time with different physiologic states and under pathologic conditions, in response to changes in the underlying control mechanisms. This complexity is further compounded by various coupling and feedback interactions among different systems, the nature of which is not understood. Quantifying these physiologic interactions is a major challenge as (i) the structural and neural control networks that underlie each physiologic organ system include many individual components, connected through nonlinear interactions that lead to high degree of complexity; and (ii) each integrated physiological system exhibits multiple simultaneous interactions and forms of coupling with other systems, thus forming a network of distinct physiologic networks.

Recent research efforts have focused on temporal networks [53], where traditional graph approaches to static network topology are extended to time-dependent structures, and are employed to investigate new phenomena related to changes in fundamental properties of networks, including the loss of transitivity and the emergence of time ordering of links [53]. However, the inherent complexity of physiological systems and the problems that arise from network physiology are beyond the scope of the current-state-of-the-art in temporal networks. Specifically, current approaches to temporal networks do not account for the complex dynamics of individual physiological systems (network nodes) and for the heterogeneity of physiological networks comprised of diverse systems where coupling forms (individual network links) vary in time. Moreover, the formalism employed in temporal networks requires a well-defined time-scale, which is not adequate for physiologic networks where scale-invariant dynamics and temporal feedbacks over a broad range of time scales are well-known hallmarks of integrated physiological systems. Currently, there is no established analytic instrumentarium and theoretical framework suitable to probe networks comprised of diverse systems with different output dynamics, operating on different time scales, and to quantify dynamic networks of organ interactions from continuous streams of noisy and transient signals.

3.2. New physics in network physiology

To develop adequate tools for network physiology and to probe how physiologic states and functions emerge out of coordinated networked interactions among physiological systems and sub-systems, recent efforts focus on understanding global network behavior and function where network nodes are dynamical in nature and links strength changes in time. Theoretical investigations on networks of nonlinear oscillators provide new insights on emergent synchronization and de-synchronization phenomena, the role of individual node output dynamics on the global behavior of the network, emergence of network sub-clusters with different dynamical behaviors, and effects of noise and perturbations on the state of global network dynamics. In that context, Rothkegel and Lehnertz [54] investigate small-world networks of pulse-coupled integrate-and-fire oscillators to generate global network dynamics characterized by irregular behaviors, and by the formation of separate coexisting and self-organized subnetworks with coordinated patterns of alternating synchronization and de-synchronization, as observed in brain neuronal populations and in organ systems interactions. Combing a theoretical model based on Granger causality with electrophysiology data from epileptic brain and gene expression time series, Stramaglia et al.

[55] investigate the effects of synergy and redundancy in the inference of information flow that characterize interactions in dynamical networks of physiological systems. Traxl et al. [56] study the effects of noise and global coupling strength on the synchronization patterns in dynamical networks of coupled oscillators with different topologies, and report a general scaling law for the synchronizability of such networks. Adopting the complexity matching principle to coupled networks, Mafahim et al. [57] investigate critical behavior in networks where nodes are presented by integrate-and-fire models, and highlight the role of inhibitory links in controlling global network dynamics. Employing a dynamical Bayesian inference approach, Stankovski et al. [58] develop a method suitable to detect and reconstruct effective connectivity of oscillator networks with time-evolving coupling in the presence of noise. Incorporating network dynamics of the decision-making model with a subornation process, West et al. [59] demonstrate the utility of fractional calculus in describing the dynamics of individual elements in complex networks.

3.3. New approaches and insights to neuroscience

Within the conceptual framework of network physiology, the traditional research paradigms of neural networks and maps that focus on structural and functional brain connectivity are now extended to the dynamical interplay between global network topology and emergent network dynamics to better understand physiologic states and functions as emergent phenomena of integration across space and time scales, from a single neuron to the brain system level. By investigating the structure of neural graphs derived from the brain and the neural systems of different species, Muller et al. [60] discover that instead of being characterized by maximally small-world topology, neural graphs derived from real systems reside at the borderline regime of small-worldness, close to random graph topology. In the context of spike activity of neural networks, Huang et al. [61] uncover that spike-timing dependent plasticity facilitates sequence learning, and investigate the key relationship between training and retrieval speed in neural networks. Introducing stochastic delay to a class of Wilson-Cowan models, Goychuk and Goychuk [62] investigate critical avalanche dynamics emerging from a balanced feed-forwarded network of excitatory and inhibitory neurons. Such theoretical approaches provide new mechanistic insights to critical avalanches and self-organized criticality type behavior recently reported in sleep dynamics [63–66] as well as for in-vitro neuronal groups [67–69]. Employing a network model of three different neuronal populations, Mosqueiro et al. [70] demonstrate how integrated sleep-wake dynamics and brain communications can be controlled by orthogonal (e.g. excitatory vs. inhibitory) mechanisms of neural transmission, while at the same time reproducing the distinct firing rates of the different neuronal populations. The work opens a new direction to investigate the origin of distinct brain rhythms, and the role of specialized neuronal populations in sleep regulation.

3.4. New data science methodology to probe physiologic interactions

Establishing various forms of dynamical coupling and the mechanisms underlying interactions between pairs of organ systems and their respective structural and regulatory networks is an essential building block in network physiology to investigate how coordinated communications among multiple organ systems integrated as a network lead to distinct physiologic states and conditions. Utilizing phase-dynamics reconstruction analysis

on triplets of network nodes, Kralemann et al. [71] propose a novel approach to detect and quantify directional connectivity in dynamical networks of nonlinear oscillators from multivariate time series data. To probe the network of interaction between the brain and the heart, Faes et al. [72] propose an information dynamics framework and entropy-based measures to investigate flows of information between these two systems compared to the information stored by each system separately, in order to explore changes in neural regulation across different sleep stages. Time-variant coherence analysis is applied by Piper et al. [73] to explore the dynamics of the central autonomic network that controls the cardiovascular and cardiorespiratory systems and their interactions with the brain in epileptic patients to quantify the role of epileptic neural networks on sympathetic cardiac control. Advanced signal and image-processing methods to quantify various aspects of brain-heart network interactions within the framework of Network Physiology have been further extended [35] following this focus issue on network medicine and network physiology. Another important question in this line of research is how temporal dynamics of individual network components contribute to global network behavior at the system level. Investigating bursts of activity in networks of neurons, Ferrari et al. [74] propose a novel approach to determine whether bursting dynamics arise from inherent node properties or emerge as a consequence of integrated network interactions.

4. New Clinical Applications

The studies discussed above present first steps in adapting and developing data analysis methods and models necessary to address fundamental questions in network physiology and medicine. These pioneering works open new possibilities for broad clinical applications. The network medicine framework is extended to multiplex networks by Chmiel et al. [75] to build a co-morbidity network of human diseases, and to track the dramatic structural changes this network undergoes across the life time of patients, associated with formation of new disease clusters and hubs within the co-morbidity network. Scala et al. [76] demonstrate the utility of the novel physiologic network approach to dentistry, and how it can facilitate and improve current diagnostic and dental surgical procedures by deriving network information from interacting co-dependent skeletal and dentoalveolar components. Identifying influential nodes in a wound healing-related network of biological processes using mean first-passage time, Arodz and Bonchev [77] show that the network medicine paradigm can be useful to explore the cell signaling pathways and protein networks involved in the healing of skin wounds. Another clinical application of network physiology is a novel “fingerprinting” method, developed by Fernandes et al. [78], that combined with whole-brain anatomical parcellation provides a detailed quantitative assessment of deep brain stimulation with implications for Parkinson’s disease and other neurological disorders.

5. Summary and outlook

The interdisciplinary works contributed to this focus issue by leading experts highlight new exciting developments in the emerging fields of network medicine and network physiology. Applications of analytical tools derived from established network theory enable new discoveries in network medicine in relation to the human genome, proteome and metabolome to construct disease networks and track the evolution of co-morbidity

associations with aging. In network physiology, novel theoretical works combining nonlinear dynamical systems with distinct forms of time-varying interactions under different network topologies uncover new physics that mimics (i) the complex dynamics observed in many individual organ systems, as well as (ii) emerging global behaviors and integrated functions at the organism level. Both fields show great promise in addressing new challenges arising from rapidly accumulating data and increasing complexity. It is also important to note current limitations, when one explores uncharted territory through the perspectives of these new fields. On one hand, despite many recent advances in network medicine, as presented also in this focus issue, the progress towards a reliable network-based approach to disease is still limited by the incompleteness of the available data on protein-protein interactions, metabolic networks and information of biological regulatory pathways that are heavily relying on large scale biomedical experiments [11]. Meanwhile, as network medicine moves towards the dynamic interactome [79], it would certainly require new advances in temporal and adaptive networks to probe temporal variations in network topology and function. On the other hand, network physiology is still at an early stage (network building phase), where broad-scale empirical investigations are needed to establish a general framework to identify and define dynamical links among physiological systems, and to construct the specific physiological networks that dictate particular integrative functions. Since physiological systems communicate via complex mechanisms manifested through various functional forms of coupling, there is an urgent need to integrate distinct forms of pair-wise physiologic interactions into a general framework. Overcoming these limitations is challenging but also highly rewarding — uncovering fundamental principles of hierarchical organization, coordination and evolution in networks of physiologic interactions across different levels of integration (from sub-cellular to organism level) will in turn stimulate the development of new data-science methodology to probe complex physiologic dynamics with broad impact on both basic biomedical research and clinical practice.

In summary, the unique challenges, interdisciplinary nature and the complexity involved in these new areas demand physicists with multi-disciplinary background, able to identify unique, specific and physiologically relevant problems, and to introduce adequate computational and analytic formalism. Equipped with the ability to propose minimal models and general mechanisms to generate a variety of emergent macroscopic phenomena from microscopic interactions, physicists have an essential role to play in laying the ground work and building the theoretical framework of network physiology and network medicine.

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