

## EDITORIAL

## NETWORK PHYSIOLOGY: HISTORY, ROLE, AND SCOPE

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Network physiology is a contemporary concept that connects established systems physiology with modern interdisciplinary methodologies. This field examines the network-like interactions of physiological systems, utilizing computational and mathematical analyses of physiological signals to elucidate health and disease. Network physiology represents a significant shift in the study of human physiology. By emphasizing the interconnected nature of physiological systems, it surpasses traditional limitations and offers new understandings of health, disease, and human performance. The interdisciplinary nature and technological basis of this evolving field suggest substantial opportunities for future medical innovation and scientific discovery.

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The human body operates as an intricate system where various physiological systems synchronize to maintain balance. While individual systems like the cardiovascular, nervous, and endocrine systems have been extensively studied in isolation, the connections between them are equally crucial. Network physiology, a developing interdisciplinary area, offers a new perspective to examine these interactions, focusing on the network structure underlying physiological functions. By investigating the interplay among these systems, this field has the potential to revolutionize our understanding of health and disease.

Historically, physiology has often employed reductionism, a method that analyzes systems by dissecting them into individual components for separate study. Although this approach has yielded significant knowledge, it often neglected the interdependencies between systems. The origins of network physiology can be traced back to advancements in systems biology and computational physiology. In the 20<sup>th</sup> century, researchers began using computational models to simulate interactions between physiological components. The emergence of technological innovations such as big data analytics and machine learning enabled scientists to analyze physiological signals across multiple systems.

The ‘Human Physiome’ refers to a comprehensive framework or model that maps the interactions and interdependencies among various physiological systems in the human body. It aims to provide a holistic understanding of how different organ systems, such as the cardiovascular, nervous, respiratory, and endocrine systems, work together to maintain homeostasis and respond to changes in health and disease. By studying the human physiome, researchers can gain insights into the complex dynamics of these systems, identify patterns of dysfunction, and develop more effective diagnostic and therapeutic strategies.<sup>1</sup>

Network physiology gained formal recognition as a distinct field in the early 21<sup>st</sup> century, spurred by significant studies linking network theory to physiological phenomena.<sup>2</sup> Recent research has underscored the importance of network physiology in understanding complex physiological interactions, such as how different systems like the cardiovascular and respiratory systems synchronize to maintain homeostasis. Studies on heart rate variability highlighted how cardiac function depends not only on the heart itself but also on the central nervous system, respiratory dynamics, and endocrine responses. These findings emphasized the necessity of a network-based approach to physiology. Research has explored the application of adaptive networks in modelling physiological systems, demonstrating how dynamic interactions between subsystems contribute to emergent behaviours critical for physiological regulation, such as synchronization and phase transitions.<sup>3</sup> The practical applications of network physiology have also been a focus, with research on adaptive networks providing insights into how physiological systems reorganize in response to stress or disease states. This has implications for critical care, where real-time monitoring of network dynamics can inform interventions.<sup>2</sup> The integration of wearable biosensors and machine learning has become a significant area of focus, enabling continuous monitoring of physiological signals and offering new opportunities for personalized medicine and predictive modelling.

Network physiology is based on several core principles including network topology, interdisciplinarity, dynamical systems, and a health and disease framework. Network topology, the arrangement and interaction of nodes (physiological components) and edges (connections between them), is central to this discipline. Network physiology exemplifies interdisciplinary collaboration by integrating insights from physiology, computational biology, mathematics, and physics. Physiological systems are inherently

dynamic, and network physiology incorporates nonlinear dynamics to study how system states change over time. Similarly, by comparing healthy and diseased states, this field clarifies how disruptions in network interactions contribute to disease.

Network physiology offers significant insights into the mechanisms of health and disease. Unlike traditional methods that may focus on individual organs, this field examines interactions within and across systems. For example, by analyzing heart rate variability alongside respiratory and autonomic signals, researchers have identified network disruptions as early indicators of cardiovascular pathologies. In epilepsy, network analysis of brain regions has revealed pathways that propagate seizures. Similarly, studies in neurodegenerative diseases like Parkinson's have identified 'altered communication' between motor and autonomic systems. Beyond clinical settings, this field has applications in areas such as sports science, aging, and stress research.

The potential applications of network physiology are extensive. Integrating network analyses into clinical diagnostics could facilitate personalized treatment plans that account for system-wide interactions. Advances in wearable biosensors provide continuous physiological data streams, supporting real-time network analysis. Machine learning algorithms are well-suited to identify patterns in complex physiological networks, enhancing predictive modelling. Network physiology could also be applied to epidemiological studies, examining how population-level factors influence physiological networks.

Professor Plamen Ch. Ivanov (Boston University, US) formally introduced the field, explaining how health and disease could be redefined by focusing on the complex coordination and dynamic interactions of diverse physiological systems, networks,

and organs, rather than studying each in isolation. Professor Plamen Ch. Ivanov maintains a blog on network physiology on 'The Physiological Society UK' website. It introduces this emerging field and provides links to related webinars.<sup>4</sup>

'Frontiers in Network Physiology' is currently the only dedicated journal for network physiology with its first issue published in 2021. The journal's website introduces its scope as 'It focuses on the emerging field of network physiology, aiming to understand the dynamic interactions and integration of diverse physiological systems and sub-systems in health and disease.' The website also lists topics of interest and specifies that 'The journal encourages research focused on the development of novel biomedical device platforms for synchronized high-frequency recordings and the creation of the Human Physiome, a comprehensive dataset containing large-scale signals from multiple physiological systems.'<sup>5</sup>

Looking ahead, challenges such as standardizing methodologies, ensuring data privacy, and fostering interdisciplinary collaboration need to be addressed to fully realize the potential of this field.

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