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Reply to comment

Uncovering the secrets of nature's design
Reply to comments on "Networks behind the morphology and structural design of living systems"

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We want to thank all the experts for their insightful and very interesting comments that have been provided in response to our review "Networks behind the morphology and structural design of living systems" [1]. We are delighted by the positive opinions expressed in these comments, which contribute to the broader scientific community's understanding of the field, as well as the identification of outstanding methodological issues and challenges for future research.

In this reply, we would like to highlight that the methods of network science have long proven their value in relevantly addressing various issues across many scientific disciplines, including of course, the field of biomedicine. The theoretical and computational tools developed by physicists, mathematicians, and computer scientists are reaching a new level of maturity that not only promotes the development of biomedical applications, but also has the potential to establish methodological concepts for the computer-assisted diagnosis and treatment of diseases in the near future. However, interdisciplinary research in these areas still faces some challenges, mainly referring to how bio-imaging and analysis pipelines can be integrated under unified frameworks and dealing with incomplete data.

In their comment Chen&Fu [2] have emphasized that network theory has evolved to the point where it can provide a next-generation understanding of biological systems, particularly from the integrative multiscale and multilayer perspective. This approach is critical to addressing the complexity of studying hierarchical systems (e.g., brain structure and functional interactions). Also, incorporating mathematical frameworks like evolutionary game theory could improve our understanding of how biological networks emerge and interact. One promising way to increase the applicability of network methods in this area is to combine physiological models that represent the dynamics and functions of individual components at different scales. We also recognize the significance of ontological networks and knowl-

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edge graphs for conveying domain-specific knowledge. Indeed, merging multiscale information with multimodal metadata will accelerate progress in research on living systems, extending beyond neuroscience. Recent developments in single-cell RNA sequencing and spatial transcriptomics allow for a more detailed multilayer approach to exploring protein-protein interactions and identifying cell types. Furthermore, innovative network-based analytics that considers multiscale and multilayer representations are required to answer open questions about early cancer detection and metastasis using circulating tumour DNA and imaging techniques. We also agree that the field must address the challenges of enormous amounts of data and the demand for automated, transparent, and reproducible analysis workflows. In addition, the vulnerability of automated imaging analysis to perturbations such as the mentioned one-pixel attack highlights the need for comprehensive evaluation and validation of computer-assisted pathology diagnostic methods before clinical use. Only in this manner the potential of network-based approaches to solve public health challenges and promote biomedical innovations can fully be realized.

We are also grateful for the constructive comment made by Volpert [3], who presented additional aspects of structural networks that play a crucial role in understanding the morphology and functioning of animal and plant organisms. We strongly agree with his idea that structural networks are characterized by their optimization (e.g., respiratory system), mutual interaction and coordination (e.g., respiration, blood circulation, other systems), as well as time synchronization (e.g., brain connectome and cognitive activity). We want to build upon these examples and draw the readers' attention to the premise of the constructal law of design and evolution in nature [4,5]. This theory states that the occurrence of design and pattern in nature is based on a law of physics [4]. It is a thermodynamic principle according to which flow systems (any flow configuration), such as watersheds and vascular networks, evolve to gain more global performance over time [6]. This law helps to understand systems' universality and composition, be it animate (e.g., lungs) as well as inanimate (e.g., river basins, deltas). These systems, for example, display the same flow architecture, the dendrite. As Bejan A. [7] stated, design is flow. Focusing on the lungs and the vasculature system, the constructal theory states that the similarities in the structure of these networks are explained by the fact that their construction responds to the same type of constraints that lead to the overall optimization. For example, a non-optimized vascular network would be very costly in terms of energy, as can be deduced from Murray and Poiseuille's laws. The constraints seemingly shape the network dynamically. Nevertheless, in the case of biological networks such as vascular and bronchial networks, this same system of constraints, although it explains the functioning of these networks, is not the efficient cause of their existence. The constructal theory can explain the structure of this network, but it does not explain the existence of lungs. Its value lies in the fact that it provides an idealized physicomathematical model of living systems that is embedded in a more general mechanistic explanatory framework [6].

In his comment, Blinder [8] agrees with our conclusions that the tools from the armamentarium of the complex network theory are a powerful approach to assess biological systems, either extracted from morphological or from functional relationships. Describing diverse discrete systems within this unified conceptual framework eases the identification of universal and hidden patterns, which is one of the most beautiful aspects of complexity science. The author, on the other hand, warns us to stay grounded despite all the effort and progress. In the last two and a half decades, we have witnessed tremendous growth in these studies, but often network metrics are not always consistently used. We agree with these findings and welcome the author's appeal for caution in interpreting network analyses, as well as the need to be aware of limitations. We must bear in mind that a single metric cannot fully capture the complexity of the biological system being studied at a level of detail sufficient for uncovering the underlying mechanism(s) governing biological processes. As an example, Blinder highlights neural networks, where a simple network description is not sufficient to adequately describe the organizational principles of this complex system. Namely, there are different types of connections (e.g., inhibitory or excitatory), they vary in synaptic strength, and they change with time. For these reasons, an increasing number of researchers in this field are turning to the formalism of multilayer networks, that has indeed been recognized as the "next-generation" tool to cope with such inevitable challenges, that go well beyond neuroscience and biological systems research [9–12].

Along similar lines, Xia and Wang [13] highlighted in their comment higher-order interactions, which can capture more complex structural patterns in networks than traditional pairwise network models. With the so-called higher-order networks, interactions can be represented by hypergraphs and simplicial complexes [14–16]. The complex representations of nodes and their interactions involve the use of information theory to infer high-order statistical correlation in complex biological systems. The methodology has already been applied to describe interactions among different brain regions [17] or to time series data [18]. We fully agree with the ideas expressed by Xia and Wang and believe that these emerging concepts will affect the evolution of network science, including the field of biomedical

research. As a matter of fact, in recent studies, the conception of higher-order interaction has been linked with the field of network medicine [19,20]. In principle, network medicine provides a framework for organizing diverse multiomics data using the principles of network theory. It enables us to understand the concepts of disease as a complex interplay of genetic, metabolic, proteomic, and environmental factors. Taking into account the complex high-order interactions between multiple genes, proteins, and other molecules, represents a promising and largely untapped potential for identifying key biological pathways and targets for drug development.

Furthermore, Rodrigues [21] has excellently pointed out that in network science, we need to distinguish between studies that focus on i) examining network architectures, ii) simulating dynamic processes on networks, and iii) various applications of network analysis. However, we must be aware that all of these areas are intertwined. Therefore, we agree with the comment that our review only tells a part of the story and that in future studies more emphasis should be given to the interrelation of the structure and dynamics. The current research in this area is principally devoted to the construction of functional networks from time series, but we must be aware that many correlation-based methods can lead to spurious connections and a biased network structure. Therefore, it would be worthwhile to pay more attention to how to infer causal relations between the elements, allowing us to better understand the information flow and how it relates to the structure. It is worth noting that computational frameworks to assess such issues are increasingly being developed [22]. Furthermore, in his comment, Rodrigues [21] also made a good point by emphasizing that when mapping biological structures, missing data is a rule, not an exception. We strongly agree with this statement. Whenever we deal with advanced microscopic techniques that capture various biological structures, such as vasculatures or multicellular structures, the data is always incomplete. These are also the reasons why more and more researchers are paying attention to various computational techniques of reconstruction and evaluation of results [23,24]. We believe that in the future, together with the progress we are witnessing in the field of machine learning, we will acquire new methodological tools that will allow for objective analysis and comparison of results from different laboratories around the world.

Overall, the contributors share our view that network science is one of the key tools for understanding the structural as well as functional principles of various biomedical systems. However, there are still limitations and open issues in both the theoretical aspects of network science and the acquisition and integration of data from different sources and levels of biological organization. As a young and rapidly evolving field, these challenges should be seen as opportunities for researchers to critically evaluate current research and develop new methods. Ultimately, this will lead to more integrated perspectives on the functioning of biological systems and the design of bioartificial substitutes for organs, making network science a major driving force for progress in human medicine.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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