Unifying the essential concepts of biological networks: biological insights and philosophical foundations

Abstract

Over the last decades, network-based approaches have become highly popular in diverse fields of biology, including neuroscience, ecology, molecular biology and genetics. While these approaches continue to grow very rapidly, some of their conceptual and methodological aspects still require a programmatic foundation. This challenge particularly concerns the question of whether a generalized account of explanatory, organisational and descriptive levels of networks can be applied universally across biological sciences. To this end, this highly interdisciplinary theme issue focuses on the definition, motivation and application of key concepts in biological network science, such as explanatory power of distinctively network explanations, network levels, and network hierarchies.

1. The rise and promise of biological network science

Over the last two decades, network-based approaches for modelling and explaining complex biological systems have become ubiquitous in diverse fields of biology, for instance, in describing and analyzing the organization, function and stability of ecological communities, trophic webs, interactions of proteins and metabolites, brain circuits, gene regulation, or evolving organisms. This popularity is a result of the intrinsic interrelatedness of complex biological systems, the increasing availability of 'big data' and the need to process them, as well as the discovery of a few general features that appear to be common across biological networks, such as small-wordliness, scale-freeness, modularity and hierarchy. Studying these ubiquitous organizational features of networks across biological systems has yielded the promise of discovering universal fundamentals of (biological) network science, as well as the opportunity of developing tools and approaches that can be applied and exchanged across fields. This vast interest has been paralleled by extensive international funding efforts for promoting biological network research (e.g., Human Connectome Project[1], Genomics of Gene Regulation Project[2]).

While network-based research in biology continues to grow very rapidly, some of its most important conceptual and methodological aspects still require a programmatic foundation. This challenge particularly concerns the question of whether there exists a generalised account of explanatory, organisational and descriptive levels of networks that can be applied universally across biological sciences. Consequently, the central focus of this highly interdisciplinary theme issue is put on the definition, motivation and application of key concepts in biological network science, such as epistemic norms of distinctively network explanations, network levels, and network hierarchies. For instance, in fields as diverse as cell biology, ecology and genomics, the problem of levels arises in regard to capturing the spatial embedding of networks as well as the role of timescales in their evolution. In neuroscience, the problem of levels comes

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up with respect to the most appropriate ways of describing and interpreting hierarchies and scales, for instance, as gradients, sequences or nested modules.

An equally important and closely related foundational problem of network approaches is how to evaluate the features of good network explanations and how to establish the grades of their quality as a matter of a norm. This issue is best understood in terms of explanatory asymmetries[3]; for example, whether a system's dynamics explains the system's network features or *vice versa*. In brain networks, for instance, neural network topology and metabolic constraints shape neural dynamics – which in turn reshapes the network organization through activity-dependent plasticity. Likewise, in ecology, the topology of a trophic or mutualistic network constrains the ecological dynamics, but the network itself also evolves as a function of endogenous ecological features.

Given the diversity and pervasiveness of network approaches in biological sciences (Barabási, A. L. 2016; Barrat, A., Barthelemy, M., & Vespignani, A. 2008; Newman, M., Barabasi, A. L., & Watts, D. J. 2011; Seung, S. 2012; Sporns, O. 2012), as well as a number of recent publications that question the explanatory utility of some of the fundamental assumptions about the network organization of biological systems, such as that scale-free networks are pervasive in biological systems (Broido and Clauset 2018) or that the small-world description adequately captures the characteristic organization of brain networks (Hilgetag and Goulas 2016), this theme issue aims to provide a set of norms on the key network concepts such as levels, hierarchies and successful network explanations which can be universally applied across biological sciences.

Furthermore, the unique nature of the subject requires the inclusion of philosophical analyses to establish epistemic norms for well-defined concepts, and explanatory and modelling practices. Therefore, this theme issue includes contributions by four philosophers who provide epistemological analyses of the structure and epistemic norms of successful topological explanations (Kostić 2019), general norms of explanatory asymmetry based on a model's conditions of application (Jansson 2019), the heuristic and epistemic value of exploratory network models (Serban 2019), and analyses of network hierarchies and their integration into mechanistic theories of explanation (Bechtel 2019).

2. A perspective from philosophy

The contributions in this theme issue are organized thematically, starting with a philosophical analysis of what constitutes a successful distinctively topological explanation (Kostić 2019). Kostić (2019) provides a set of epistemic norms that govern a successful network/topological explanation, that is, the set of norms that helps to distinguish explanatory from merely predictive or descriptive network models. His theory of topological explanations provides three criteria for evaluating the success of any topological explanation, specifically (1) a criterion about what renders a topological explanation true of a particular system (facticity or veridicality criterion); (2) a criterion about explanatory power that governs two explanatory

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[3] A good explanation is asymmetric, i.e. if A explain B, then B should be explaining A, otherwise the explanation is either too permissive or circular.

modes of topological explanations (vertical and horizontal), and (3) a criterion about explanatory perspectivism (the pragmatic criterion), which determines the explanatory mode. Kostić then demonstrates how his theory accounts for explanatory asymmetries, which is one of the most fundamental issues in any theory of explanation. His solution to this problem stems directly from three criteria of his theory of topological explanations. He derives three bases of explanatory asymmetries in topological explanations: the counterfactual, property and perspectival, and illustrate how they work with the examples from cognitive neuroscience.

How networks relate to the general problem of explanatory directionality is the focus of Jansson's (2019) contribution. Jansson accepts from the outset the general counterfactual conception of explanation; that is, explanations as opposed to predictions or mere descriptions provide information about what the explanandum depends on, in the sense of what would have happened in non-actual circumstances given the dependence relation that it postulates. She argues that mathematical dependencies alone are not sufficient for understanding the grounds of explanatory directionality in non-causal explanations in general, and in network explanations in particular. Instead, she focuses on the conditions of application of these explanations. Jansson introduces a simplified modelling schema that illustrates four different types of dependencies. Each type of dependence according to her implies different kinds of conditions of application, which is captured by her notion of model aptness. The dependence relation by its very nature defines the 'depender' and the 'dependee', and in virtue of this definition, the conditions of application help to recover directionality in each particular case of explanation.

Bechtel (2019) approaches the issue of distinctively network or topological explanations from a general perspective and provides illustrations that networks are compatible with mechanisms. His reasoning is based on the analysis of ways in which bio-ontologies help to identify network modules and hierarchies. He challenges the view that network-based explanations are not mechanistic, but rather represent a new distinctively topological kind of explanations. As one of the reasons for thinking that networks are not mechanisms, he identifies the fact that large-scale network representations are flat (i.e. they are not organized into levels), whereas mechanisms are hierarchical, where parts constitute mechanisms and mechanisms constitute larger-scale mechanisms. He claims that it is misleading to think of networks as flat because networks are often organized hierarchically as well. A notable difference between networks and traditional mechanisms according to Bechtel is that, instead of representing how parts and operations perform or produce a mechanism of interest, the edges represent the connectivity data based on which the researchers construct a network or hierarchical relations.

This mechanistic and heuristic view of networks is further elaborated in the contribution by Serban (2019). She focuses on the exploratory function of network models, particularly on the role of network modularity in exploration and how it shapes the research heuristics, generates new concepts and methodologies and finally how it relates to explanations. Serban argues following Gelfart (2016) that exploratory models serve on the one hand a pragmatic and epistemic role by getting a research program off the ground, often by providing how-possibly explanations or proofs-of-principles or proofs-of-concepts. On the other hand, exploratory models serve a modal role by generating knowledge about what is causally or objectively possible. When applied specifically to network modularity, the exploratory function of network models is guided by the research questions such as what is represented in the model and what is not (the scale and the appropriate types of elements), which algorithms are used to analyze

the network properties as well as how the results of those analyses are cross-validated with the existing studies. To illustrate these points, she analyzes work on modularity in metabolic systems, specifically how early and influential network analyses done by Ravasz et al (2002) revealed that metabolic network have both scale-free topology as well as high clustering, which prompted Ravasz and colleagues to ask a far reaching question of whether metabolic systems are collections of functional modules or highly integrated systems.

3. A perspective from biology

Also relating to the heuristics of network modelling, Bzdok et al. (2019) offers a set of tools that can be used in assessing explanatoriness, exploratoriness and model aptness in network models. In the example of population neuroscience and the case of brain circuit alterations underlying autism spectrum disorder, Bzdok and colleagues advocate the analysis of brain networks, or connectomes, stringently as modelling approach. As the authors argue, a major challenge in population neuroscience and disease classification is not only to identify brain networks and their significance for brain function, but also to handle the substantial data sets that are currently extensively studied in large-scale research projects. These 'big data' approaches call for analytic strategies where the precision of (model) predictions can be quantified and the statistics about potential generalization can be derived. To that end, Bzdok et al. (2019) suggest analyzing brain connectomes using Bayesian strategies, which offer full probability estimates of network characteristics and afford to coherently handle uncertainty in model predictions. Hence, an analytical means is provided that goes beyond binary statements on existence versus non-existence of an effect while elegantly allowing to separate (epistemological) uncertainty and (biological) variability in a coherent manner. Such a framework also helps to reformulate model constraints in terms of hypothesis testing through model selection and provides a formative way to integrate (prior) knowledge in terms of prior distributions (cf. Tittgemeyer et al., 2018). Finally, the authors consider the explanatory power of brain network connections to furnish predictions about single individuals by appropriately handling all considered sources of variation in network approaches.

Normative aspects of clarifying the network concept of 'hierarchy' are discussed by Hilgetag and Goulas (2019). When investigating structure-function relationships in biological networks along spatiotemporal gradients or across a range of scales, it is necessary to consider hierarchical organization. In neuroscience, which is perhaps the prototypic field in which to ponder multi-scale spatial, temporal and topological structure (dimensions that are arising concurrently and in partial alignment, Betzel & Bassett, 2017), the notion of 'hierarchy' is frequently referred to in current concepts and indeed an integral aspect when it comes to the analysis or interpretation of brain networks (Meunier et al., 2010; Sporns, 2015). When considering hierarchies as a characteristic feature for brain networks, however, three questions arise: (1) How can hierarchy in brain connectivity be defined, (2) What is the evidence that the arrangement of brain networks follows hierarchical organization principles, and (3) Is it possible to introduce a hierarchical analysis scheme or algorithm that does not *a fortiori* call for a certain hierarchy definition?

To that end, Hilgetag & Goulas (2019) remind us that "concepts shape the interpretation of facts" and they question the precision and the functional implications of currently used

definitions of 'hierarchy' in brain networks: for instance, in the sense of a topological sorting of connections by their projection patterns, the sense of gradients of diverse structural or functional features, or an encapsulation of different scales of features.

A further step in establishing a universally applicable analysis of the concepts of network hierarchies and levels is distinguishing between levels in the actual organization of a system and in formulating explanations, which Bassett & Zurn (2019) approach by discussing how network structures support learnability.

Organisms constantly integrate information about their internal states with external environmental cues to adapt behavioral and autonomic responses to ensure their living. To make use of relational knowledge and to initiate adequate behavioral and physiological responses, the brain needs to be equipped with a network structure that has the capacity to represent, integrate and prioritize these internal and external signals.

In the context of rendering information integration and neural capacity efficient in this sense, Zorn & Bassett (2019) discuss the necessity of synchronicity in network architectures at two levels: the epistemic and computational (relating to a conceptual and neural level). By highlighting consequences from constraints on the learnability of relational knowledge, at one level, and physical constraints in neural systems, at another level, they argue for hierarchically modular networks to inform deeper explanations and mechanisms.

The work of Niquil et al. (2019) proposes a trinomial analysis of marine trophic webs that simultaneously captures network properties at three different levels. The authors distinguish between a global level of the entire network, the intermediate flow level and the individual node level. Their proposal is well suited for thinking about networks as nested hierarchies, because most of the available methods provide information about network properties at a single level, and require using multiple models in ensemble to obtain a unified and coherent understanding of an ecological network as a whole. Their approach is also particularly useful when applied to analyzing what they call "emergent properties" in ecological systems. To demonstrate the plausibility of their method, Niquil and colleagues applied this trinomial analysis to 16 food-web models to capture the dynamics of the bloom (rapid growth of the population of cyanobacteria in nutrient rich waters). Their analysis showed that sometimes there is "a strong agreement in the results from the 3 levels" (Niquil et al: pp 14), but also that sometimes there is a mismatch in the resulting network metrics across all three levels. This indicates that understanding why the results are aligned and why they are mismatched would not be possible without their trinomial analysis. This of course has further conceptual and epistemological advantages, because it allows to clearly distinguish and answer different types of explanation-seeking questions, which is yet another illustration of the explanatory perspectivism criterion in topological explanations (Kostić 2019: pp. 4).

The next two contributions provide heuristic tools and analyses for understanding network hierarchies and levels more generally, across biological fields and timescales.

Hierarchies and levels in biological (as well as artificial) networks are often reflections of complex systems. A necessary condition or, according to Solé & Valverde (2019), a common architectural trait, of complex systems is that of a network of higher-order organization demonstrated by non-identical elements connected by diverse interactions with no central control in which emergent complex behavior is exhibited. Especially in the context of biology, such an attribution of complexity to networks raises the questions regarding the evolution of

network complexity: Why is the network level relevant in seeking explanations for the origin of complexity? How do complex systems emerge, and how can the topological organization of these networks provide some insights into their evolutionary origins?

Solé and Valverde (2019) set out to elucidate this question by an alternative formulation of generative network models. In this perspective, and against arguments calling for selection-optimization, some networks reveal the generation of complex patterns resulting from reuse and can be modelled using duplication-rewiring rules lacking functionality. If such rules are responsible for network growth, they fundamentally constrain the structural outcome and shape network architecture as well as complexity.

Finally, Chavalarias (2019) treats the general issue of complexity in biological systems. Complex systems theory is concerned with the identification and characterization of common design elements that are observed across diverse natural, technological and social complex systems. Comprehension of complex systems in biology in particular is guided by the growing understanding that most organismal processes occur in the form of networks controlled by sensors, signals and effectors (Wolf et al., 2018). These networks reach hierarchical complexity that is unparalleled outside biology. Routes and patterns of the evolution of complexity in this context are poorly understood. To that end, Chavalarias proposes a general conceptual framework for the emergence of complexity. Under the assumption that life emerges from different levels of complexity and network theories provide a suitable formalisation or conceptual basis, he outlines theoretical consequences which reside in second-order cybernetics (Kaufmann 2019) to allow for new explanatory models for the phenomenon of life through network theory.

4. Outlook

The diversity and pervasiveness of network approaches in biological sciences on the one hand, and the lack of clear norms about the universal application of central network concepts across variety of biological sciences on the other, contribute to the methodological, conceptual and epistemic disunity in the highly specialized subfields of biology when it comes to this approach. In order to unify and systematize network approaches across biological sciences, this theme issue brings together scientists working in many diverse areas of biological sciences as well as philosophers working on foundational issues of network explanations and modelling, who together aim to develop universally applicable norms of network explanations (explanatory power and asymmetries, exploratory and heuristic function of network models) as well as systematize network concepts such as levels and hierarchies (levels and hierarchies in network organization and in network explanations).

We hope that this theme issue will be beneficial for the wide scientific community in both highly theoretical inquiries about the inner workings of science, its empirical and metaphysical commitments as well as in practical applications, such as designing policies for assessing the health of marine trophic webs, or guideless for applying the correct level of analyses or for choosing the most appropriate level of organization in diagnosing or treating certain neurological disorders or in enhancing cognition and learnability.

We also hope that interdisciplinary collaboration between philosophers and scientists in this theme issue will inspire and encourage the cross-disciplinary collaboration even beyond biological sciences such that it can serve as an example that various sciences are not separated by their particular specializations, and that a common set of foundational issues can only be solved by collaborative cross-disciplinary work.

5. **References**

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