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Review

Networks behind the morphology and structural design of living systems

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Abstract

Technological advances in imaging techniques and biometric data acquisition have enabled us to apply methods of network science to study the morphology and structural design of organelles, organs, and tissues, as well as the coordinated interactions among them that yield a healthy physiology at the level of whole organisms. We here review research dedicated to these advances, in particular focusing on networks between cells, the topology of multicellular structures, neural interactions, fluid transportation networks, and anatomical networks. The percolation of blood vessels, structural connectivity within the brain, the porous structure of bones, and relations between different anatomical parts of the human body are just some of the examples that we explore in detail. We argue and show that the models, methods, and algorithms developed in the realm of network science are ushering in a new era of network-based inquiry into the morphology and structural design of living systems in the broadest possible terms. We also emphasize that the need and applicability of this research is likely to increase significantly in the years to come due to the rapid progress made in the development of bioartificial substitutes and tissue engineering.

Keywords: Living systems; Network science; Structural design; Morphology; Spatial networks; Network physiology

1. Introduction

At the turn of the 21st century, we learned that seemingly very different networks have universal properties that pervade across social, biological, and technological systems. Watts and Strogatz [3] observed that electric power grids, food chains, brain networks, protein networks, transcriptional networks, and social networks are typically highly clus-

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tered with small characteristic path lengths. They have termed this the collective dynamics of 'small-world' networks and proposed a simple and intuitive model that reproduced these features with a minimal set of parameters. Further major breakthroughs include the growth and preferential attachment model that describes the universal scaling in degree distributions by Barabási and Albert [5], and the observation that many networks have groups of nodes that are much stronger connected to one another than to other nodes, which today is well-known as community structure [6].

These and many other seminal advances have ultimately given rise to network science [7–10], which has emerged as a key field of research that builds bridges between the social and natural sciences, and between research and technology and society in general. Indeed, several highly influential and cited reviews attest to this fact [11–20]. Nonetheless, some bridges are more difficult to build than others, and in particular in living systems the acquisition of accurate and reliable data has been the bottleneck towards greater discoveries.

Therefore, despite significant interest in studying the underlying organizing principles of various complex systems from the network perspective, a relatively small part of research was devoted exclusively to examining the structure, morphology, or the spatial arrangement of real-life systems with methods of network science [15,21,22]. Some exciting ideas emerged in geoscience-related fields [23,24], where spatial applications of the network theory have been used to describe sediment pathways [25,26], morphological partition and connectivity of river basins [27,28], landscape planning [29], cave passages [30], soil porous architecture [31,32], and rock fracture networks [33,34]. Interesting reports about structural connectivity analyses are also emerging in astronomy and have been used to describe large-scale topological structure of the Universe [35,36] and for the characterization of the internal structure of the superclusters of galaxies [37]. Notably, network analyses are increasingly used to represent the Earth's climatic patterns [38,39] and were proven useful for optimizing the spatial network structure of hydrometric stations [40]. Moreover, in material science, structural graph models were used to build up network representations of arrangements of particles and forces in granular materials [41–45], the structure of colloidal gels [46], and frictional contact forces in particle suspensions [47]. In the last years, these methodological principles are becoming popular in biomedical sciences as well. Technological advances in different imaging techniques have enabled us to precisely assess the morphology of various biological systems and network science approaches represent a viable route for their further quantification. Interactions between cells, interconnectivity of blood vessels, structural connectivity within the brain, the porous structure of bones, and relations between anatomical parts of the body can all be coped with the network formalism, as schematically presented in **Fig. 1**. In this manuscript, we provide an overview of how this framework can be used to describe structural organization rigorously and quantitatively in a variety of settings and develop a synthesis of structural network-based approaches in life sciences.

2. Network-based approaches to study intercellular interactions

Networks are a convenient abstraction tool for exploring how the relationships between individual components give rise to complex emergent properties, and in the last decade these ideas have been increasingly used to study cellular connectivity patterns. An appealing way to quantitatively analyze properties of intracellular interactions within organs is to consider them as networks. This approach can be applied to diverse biological systems. By mapping cellular associations, an important distinction is drawn between how cells are physically connected and how information is actually transferred between these cells. These have been termed structural and functional networks, respectively [48]. In functional multicellular networks, nodes represent individual cells and connections between them are established based on the temporal similarity of the measured cellular dynamics, as typically assessed by statistical similarity of time series (e.g., calcium signals) [49–53]. More directly related to the topic of this review are structural intercellular networks, which describe physical associations between cells and provide the mechanistic substrate for signal transfer through an organ. Moreover, patterns of cellular morphometric arrangement encode information about the forces generated by cells and play a vital role in both normal and pathological organ morphogenesis [48,54–56]. The extraction of cellular arrangements relies on imaging and subsequent computational analyses of the acquired data. In recent years, it has become apparent that the latter can benefit a lot if enriched by network science approaches, as both geometrical and network data provide a more detailed insight into the morphometric and organizational principles of different cellular assemblies.

Many of the topological analyzes of cellular networks focused on packed tissues (e.g., epithelia, skeletal muscle) as models to understand how cell organization determines the fate of an organ [48,57–59]. Epithelial morphogenesis, a dynamic process that occurs at multiple spatial scales is particularly well researched [60]. Early studies that

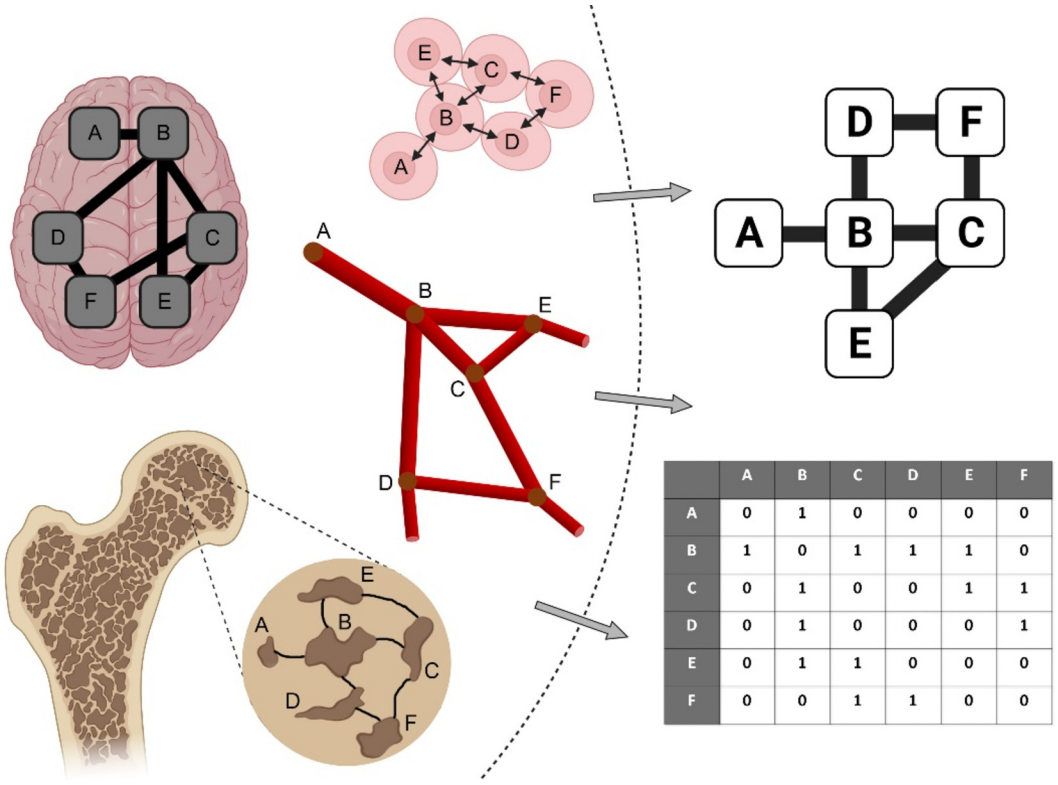

Fig. 1. Transforming the structural organization of various biological systems, such as multicellular contact patterns, structural brain connectivity, the porous structure of bones, and the interconnectivity of vessels into network language. Partly created with BioRender.com.

offered insights into epithelial organization used planar tissue networks and focused primarily on geometric features of individual cells such as cell topology and the number of contacts [56,57,61], and led to the formulation of empirical relationships such as Aboav-Weaire's law and Lewis's law [62,63]. However, a more comprehensive view of epithelial organization is obtained by considering the higher-order organization of cells, such as patterns in the network of interactions between cells. In this vein, Escudero et al. generated network representations of confocal images of epithelia based on cell-cell contacts, which allowed principles of complex networks theory to be used to study short- and long-range patterns in epithelial organization. They showed that the features of individual cells combined with the properties of the cellular network produce a defining signature (tessellated tissue) that distinguished epithelia from different organs, species, developmental stages, and genetic conditions. The network-based approach enables the characterization, quantification, and classification of normal and perturbed epithelia [60] and was later shown as a viable route to track the epithelial morphogenesis as well [1,48]. In **Fig. 2A** we present an example of how a cell interaction network is extracted from confocal images of the epithelial tissue. Such an abstraction eases a quantitative assessment of cell behavior with which one can elucidate the dynamics and biomechanical control of epithelial tissue morphogenesis. Moreover, the skeletal muscle, another example of packed tissue, has also been used as a model to understand the processes behind the regulation of cell organization [64]. Skeletal muscle consists of closely arranged fibers (type I and type II fibers arranged like polygons in a tessellation) separated by a fine layer of connective tissue, the endomysium. The relative distribution of fibers varies between different muscles, species, gender or even individuals and is important for muscle function, but little is known about how fiber arrangement is established and maintained. These issues have recently been successfully addressed by geometric and topological data analyses of skeletal muscle tissues with the aim to assess their organizational signatures [65]. Furthermore, a variety of pathogenic changes has been described in skeletal muscles of patients with various neuromuscular diseases, both neurogenic and myopathic disorders [66]. The identification of subtle topological changes of muscle cell organization in response to pathogenic conditions could improve diagnosis and therapeutic intervention prior to muscle degeneration [64]. With this in mind, Sáez et al. developed a new methodological framework that is based on network science approaches, so that the muscle

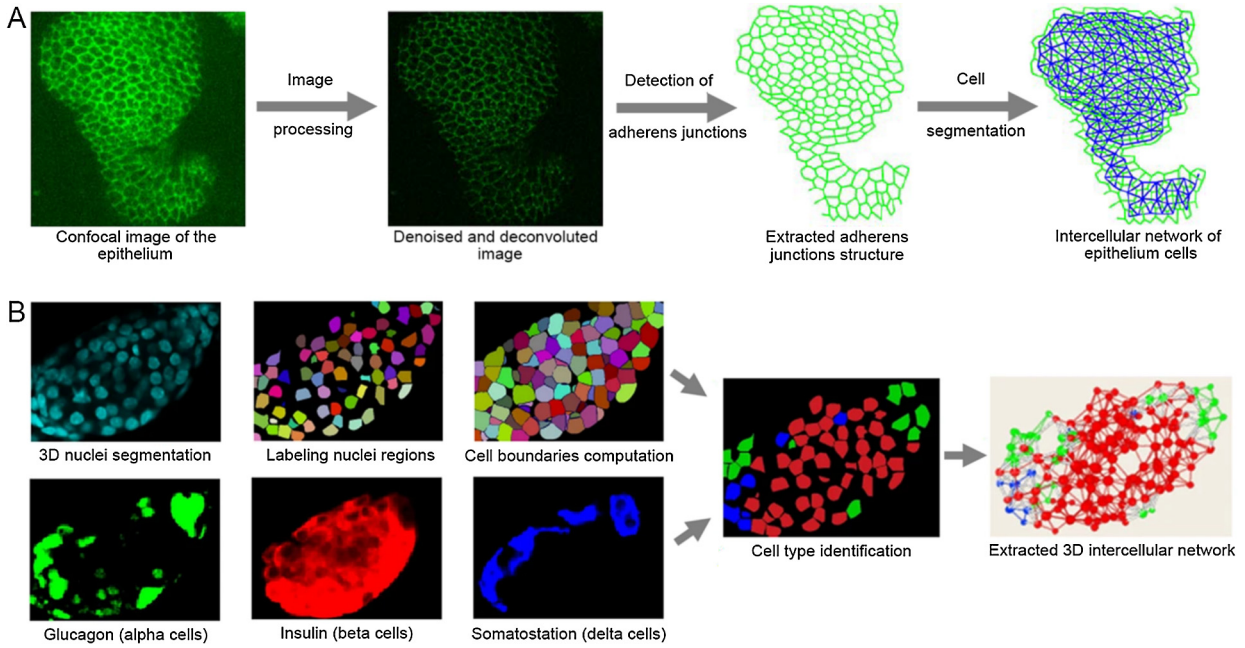

Fig. 2. Discretization and abstraction of intercellular interaction patterns into networks. A) Epithelial cell network. The acquired confocal images of epithelial tissue with labeled adherens junctions are processed and enhanced by deconvolution and noise reduction algorithms. After segmenting the cells, their structure is symbolically defined by a planar graph connecting the detected adherens junctions with edges (green). Then, the cells in the tissue are identified as faces of the adherens junctions graph and the cell network is constructed to describe the intercellular connectivity of the epithelial cells (blue). Reproduced from [1]. B) Pancreatic islet cells network. 3D confocal image stacks of islets of Langerhans and cell nuclei segmentation was used to extract the positions of individual cells. Combined immunofluorescence labeling of islets was used to identify three main types of endocrine cells: alpha-, beta- and delta-cells. This data along with the computed cell boundaries was used to construct the cell interaction network by establishing links between the cells whose zones were in contact. Reproduced from [4].

tissue image is regarded as a network in which fibers are nodes and fiber contacts are links. Their results have shown that segmentizing and building up networks form muscle biopsy images provides useful information and supports the diagnosis of muscular dystrophies and neurogenic atrophies [64].

Network analysis also provides a suitable framework to capture and quantify the unique cytoarchitecture that forms the basis for functional coupling between individual cells in the islets of Langerhans. The islets are multicellular structures that harbor insulin-secreting beta cells, glucagon-secreting alpha cells, and somatostatin-secreting delta cells, among other rarer cell types. The main function of islet cells, namely the maintenance of appropriate blood glucose levels, is achieved by coordinated action of different cell types in response to changes in circulating glucose levels [67]. Early work has addressed the problem of analyzing islet cytoarchitecture using large-scale imaging data obtained from pancreatic tissue sections. For example, Hoang et al. [68] and Kilimnik et al. [69] analyzed the spatial organization of alpha and beta cells based on manual recognition of the different islet cell types and calculated the direct cellular interactions based on a complex computation of distances and angles. Very recently, Félix- Martínez and Godínez-Fernández used network-derived metrics to describe the homo- and hetero-typic contacts within the islets even more precisely, with emphasis on structural differences between mouse and human islets [70,71]. Moreover, Striegel et al. focused on capturing and quantifying topological connectivity in the entire beta cell population in healthy and pathologically altered (i.e., type 2 diabetic) islets [72]. They utilized a network representation of the islets, in which nodes represent beta cells, and the connections signify intercellular connectivity. Using the standard network metrics allowed them to elucidate the principles of beta cell arrangement in islets as well as the distinguishment between control and diabetic islets [72]. Noteworthy, understanding the connectivity patterns between different islets cells and the configuration of the supporting regulatory signaling networks is an important step in understanding the structure of the paracrine signaling pathways that support islet function. In that respect, Nhu et al. developed an effective toolbox that contains all the necessary methods for nuclei segmentation, cell identification, and cell interaction analysis from volumetric microscopy images. They have used their framework to visualize the unique

architecture of islets and to gain new insights into the underlying complex communication networks, as demonstrated in **Fig. 2B** [4]. More recently, network-based approaches have also been used to elucidate structural basis for paracrine regulation of delta cells [73] and to study the architecture and endocrine cell interaction of the vascular network in unperturbed and transplanted human islets showing that the endogenous vascular network of islets is significantly altered after transplantation [74].

Network analysis has also been used to assess the pathological dysfunction of the endothelium, which occurs in the earliest stages of obesity. Endothelial cells appear to be highly heterogeneous and are organized as a communicating multicellular network that controls vascular function [75]. Wilson et al. [76] investigated the hypothesis that impaired endothelial heterogeneity and organization at the network level contribute to impaired vascular reactivity. In their study they studied the structural and functional components separately and it turned out that in obesity induces alterations solely in the functional network architecture. The altered organization of the network is associated with an impaired calcium signaling at the population level and deficient endothelial control of the vascular tone. Very recently, network-based approaches were proven useful also for performing structural analysis at the subcellular level. Specifically, Viana et al. [77] constructed mitochondrial networks from 3D from live-cell microscopic images of budding yeast cells. Their results revealed that mitochondria are highly interconnected networks that exhibit certain topological properties similar to other real-world spatial networks. The effectiveness and robustness of mitochondrial networks, a vital component of a normal biological function, was shown to be governed by fission and fusion dynamics. In sum, network approaches were recognized as an objective methodology to parametrize the complexity of mitochondria and could in principle be readily applied to other organelles as well [77–80].

3. Topological analyses of multicellular structures

While the importance of intercellular interactions is rather well understood, much less is known about how they regulate global properties of multicellular structures, which are much more than just the sum of the individual cells that make them up. The collective interactions between cells at the global level confer a higher-order functionality to the system through a structure-function relationship. Multicellular functionality thus arises from cellular associations and synergies and is not cell autonomous. Understanding the emergent properties of complex multicellular assemblies, and the structure-function relationship between cell organization and organ function remains a challenge. However, network-based analysis of global cellular topology possesses the potential to fill this gap by enabling the representation and quantification of organ-scale cellular interaction mapping [81–83]. Important in the context of multicellularity are also the forces generated by individual cells, which control many biological processes such as cell migration and division, but can also influence processes at the multicellular level. The forces generated are exerted by cells against the fibrous extracellular matrix are characterized by nonlinear elastic mechanics, allowing thereby the forces to propagate over long distances. Moreover, the extracellular matrix is composed of discrete fibers with a unique anisotropic and inhomogeneous architecture. These local heterogeneities result in non-trivial patterns of force transmission with propagation ranges, scaling, and local stiffness gradients that deviate from the average response of the network. Most importantly, it has been recently suggested that the use of network-based approaches could shed light on mechanical or even biochemical communication patterns between distant cells, a process that is relevant in various biological contexts where cells interact via a fibrous matrix, such as the restructuring of the reticular cell network during an immune response in lymph nodes, to assess the structure–function relationship and global cellular organization in the plant hypocotyl, or to characterize the actin cytoskeleton during morphogenesis [55].

Focusing on the latter, cells actively regulate the morphology of their actin cytoskeletal networks to control shape and mechanical forces during various multicellular processes. The actin cytoskeleton, a network of protein polymers, is not only responsible for the mechanical stability of cells but is also crucial for processes that require spatial and temporal variations in network structure, such as cell migration, cell division and intracellular transport. The cytoskeleton must therefore combine structural integrity and mechanical stability with the ability to reorganize and restructure the network rapidly and efficiently. Cells address this challenge by using actin-binding proteins to cross-link filamentous actin and construct complex dynamic networks. The molecular properties of the crosslinking proteins largely determine the structure, viscoelastic properties and dynamics of the resulting interconnected structures [84]. Although the molecular details of actin monomers and filaments and actin-associated proteins are well understood, quantifying actin-based transport in a larger cellular context remains a challenge. To address this problem, Breuer et al. [83] used network theory to provide a global, system-wide view of actin-based organelle transport. They developed a network-

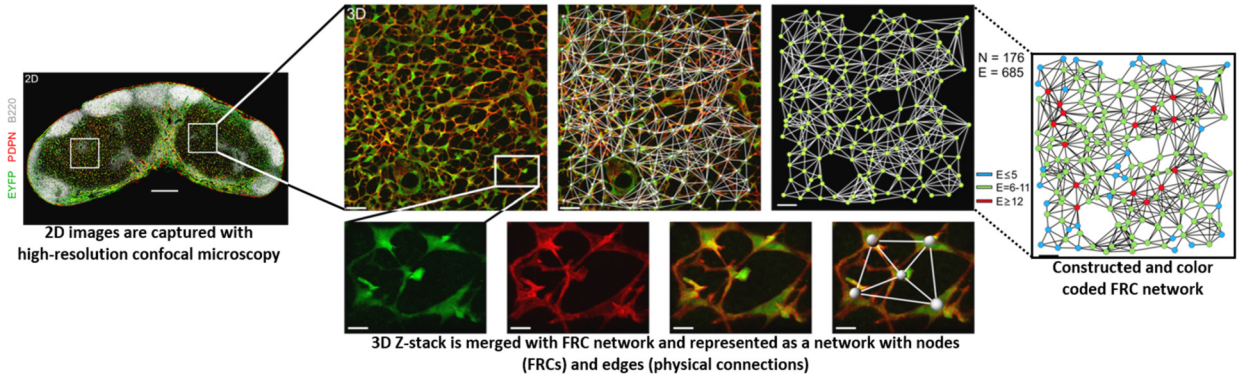

Fig. 3. Assessing the topology of the Fibroblastic Reticular Cell (FRC) network. First, high-resolution confocal microscopy is used to acquire images of a lymph node section stained with antibodies against the indicated markers. White rectangles on the 2D high-resolution image indicate representative T cell zones. The 3D reconstruction of the acquired z-stacks was applied to extract the FRC network. Nodes were identified as the enhanced yellow fluorescent protein (EYFP)-positive FRC centers of mass. The FRC network was then constructed by defining nodes as FRCs and edges as physical connections between adjacent cells. The presented FRC network sample contained 176 nodes and 685 edges and is color coded with highly connected nodes shown in red and low degree nodes in blue. Reproduced from [2].

based framework that accurately segmented the actin cytoskeleton, enabled analysis of the actin cytoskeletal transport system including its structure, design principles, dynamics, and control, and combined it with automated tracking of Golgi transport. They found that despite rapid reorganization, the actin cytoskeleton retains properties that support efficient transport in growing, partially and fully elongated hypocotyl cells over extended periods of time. They also showed that the properties of Golgi transport can be predicted from the properties of the system-wide organization of the actin cytoskeleton [83]. Along similar lines, Eliaz et al. [85] used network approaches to characterize the higher-level topologies of actomyosin networks and to study their dynamic reorganization through interactions with multivalent actin-binding proteins. By mapping the filamentous arrangements into networks, they acquired a detailed insight into the heterogeneous morphologies and higher-order topologies of actomyosin networks at a global level, which is an important step towards understanding how the actin-binding proteins manipulate the self-assembly of actin filaments into unique architectures that underlie the structural scaffold [85].

Another complex multicellular structure are lymph nodes, which can be considered as meeting points for circulating immune cells. Optimal communication between immune cells depends largely on the network of fibroblastic reticular cells (FRCs), which provide a specialized microenvironment for cellular interactions. FRCs produce a network of collagen fibers that form the cellular scaffold of lymph nodes and create distinct microenvironmental niches to provide key molecules that drive innate and adaptive immune responses and control immunoregulatory processes. While the role of FRCs in regulating immune responses has been extensively studied, the underlying principles of FRC network topology and their contribution to the overall functionality of lymph nodes is incompletely understood [86]. To address this issue, Novkovic et al. utilized a network theory-based systems approach to determine the topological properties and robustness of the lymph node FRC network. The procedure how the network structure was extracted from image sequences of tissue sections stained with fluorescent antibodies that bind to the reticular fibers and imaged with high-resolution confocal microscopy, is presented in **Fig. 3**. It turned out that the FRC network forms a lattice-like network with imprinted small-world topological features. Moreover, this complex structural organization was found to regenerate after a complete FRC ablation. This exceptional topological robustness of the FRC network represents an important example of how network connectivity facilitates tolerance to failure, a property common to other important biological and non-biological networks [2]. Recently, the same group used similar network approaches to additionally describe the micro-tubular conduit system generated by FRCs, which drains lymph fluid through a pipeline-like system to distribute small molecules and antigens. Interestingly, they found that the conduit system shows weaker small-worldness and lower resilience to perturbation compared to the FRC network [81].

Recent advances in whole organ 3D imaging at cellular resolution and computational image analysis have made it possible to extract organ-wide cellular interaction networks and annotate them by cell type. Such multidimensional topological phenotyping pipelines have recently proven successful for capturing both higher-level and local cellular interactions in the plant embryonic stem, i.e., hypocotyl [87]. This radially symmetric, multicellular assembly elongates

during early seedling development solely by cell expansion, so that cell topology is invariant throughout development. The hypocotyl also serves as a link between the above- and below-ground parts of the seedling during early growth, fulfilling both a transport and a structural function. Noteworthy, topological analyses have revealed the presence of coherent conduits of reduced path length through the epidermal atrichoblastic cell assemblies. Both robustness and plasticity of this higher-level feature of atrichoblast patterning was observed, irrespective of the genetic background [87]. Later, it has been argued that these approaches could be generalized to simultaneously capture different scales in plant systems. Specifically, with a multilayer network approach it would be possible to describe different scales ranging from the molecular, cellular, organ (multicellular), whole organism, and ecological levels, which would enable us to understand plants on an integrated and quantitative systems level [88].

In recent years, methods and measures derived from network theory have also been used to study the complex organization of the osteocyte network. Osteocytes, the most abundant cells in bone, are known to orchestrate bone remodeling by translating mechanical strains into biochemical signals, exchange minerals from bone surfaces and communicate among themselves and with other cells on bone surfaces [89,90]. They form a complex cellular structure within a bone porosity consisting of canaliculi and lacunae, that together comprise the osteocyte lacuno-canalicular network (OLCN). In 2013 Kerschnitzki et al. [91] visualized and topologically quantified the osteocyte network in mineralized bone sections with confocal laser scanning microscopy. They converted the osteocyte structure to a network consisting of nodes (a juncture of three or more canaliculi) and edges (canaliculi linking two nodes). They showed that osteocytes form dense and highly organized single scale networks with a high level of communication between cells. Later, only a few studies assessed the topological architecture and connectivity of the osteocyte canalicular network [91–93], mainly due to technical limitations, as a high spatial resolution along with a span over large enough volumes is required. In 2016 Mabilleau et al. [92] chose to stain osteocyte and their dendrite-like processes rather than the lacuno-canalicular system. They investigated the osteocyte network topology in a mouse model of high fat-induced type 2 diabetes. They evidenced modification of the osteocyte network topology in diabetic animals, for instance a higher number of hubs, an increased mean node degree, and a more pronounced scale-free character of the network as opposed to the single-scale characteristic observed in lean controls. Based on their previously work [91], Kollmannsberger et al. [94] demonstrated an improved strategy for image processing and analyzed the OLCN in two different bone types from mouse and sheep. They represented the OLCN as a weighted non-directed graph, where weights represent the length of the edges, and used different quantitative measures from the theory of complex networks, to investigate how efficient the network is organized with regard to intercellular transport and communication. Despite the differences at the tissue level (the regularly organized bone tissue from sheep is more efficiently organized than the irregular bone tissue from mice), the topological properties of the OCLN at the subcellular level, such as exponentially distributed edge lengths and a tree-like topology, are independent of bone type from different species. Moreover, the clustering along important paths linking distant regions of the network reveals the small-world like topology of the OLCN as a result of adaptation towards efficient organization.

Network science approaches were found suitable to be applied in the morphological interpretation of bone tissue as well. The harder outer layer of the bone, essential for mechanical support, is the cortical bone. The cortical bone comprises a highly intricate network of voids and canals, required to nourish the bone living cells and removing toxic substances from the bone interior [95]. During bone growth, the organization of the canals is continuously modified to enhance the mechanical strength of the bone structure [96,97]. Understanding the topology of the bone canals provides a good prediction of the canals organization and connectivity and plays a major role in the development of diseases (e.g., osteoporosis) [98,99]. By using image processing and analysis tools, the three-dimensional reconstruction of a bone can be obtained and represented in terms of a complex network [99–102]. Specifically, the cortical bone structure can be represented and studied in terms of geographical complex networks, where nodes represent the confluence of channels or branching points, while the edges correspond to the channels or trabeculae [98,99,101]. In geographical networks each node has a well-defined spatial position, which plays a role in shaping the connectivity structure. Topological measurements obtained from such networks can be used to characterize and analyze the canal system organization and the robustness. It has been shown that the distribution of the node degrees of the bone canal network obtained from a portion of a cat femur follows a truncated power law [101], which implies the existence of some highly connected nodes (hubs). Few years later Palhara-Viana et al. [102] extended these investigations with respect to modularity and resilience to attacks. The network, representing the canals structure of a cortical bone from the leg of a young chicken, was found to be highly modular, where each community exhibited specific topological properties which relate to special mechanical function of those regions. In addition, because the shortest path lengths between

pairs of nodes is relatively large, no small-world character was confirmed. Finally, the prevalence of nodes of degree 3 was identified in both the cat femur network [101] and chicken phalange network [102], suggesting a possible universal feature of bone canals system.

4. Network-based approaches to assess the structure of neural interactions

Nowadays, the brain is increasingly perceived as complex network of neural interactions, both at the microscopic and macroscopic level [103–105]. The recently emerging field of network neuroscience provides a holistic approach to the brain structure and function from an explicitly integrative perspective [105]. The mainstream in large-scale brain networks research are the so-called functional networks, which are generated from temporal activity patterns and reflect statistical dependence between brain region activities. The construction of such macro-networks can be based on various brain mapping techniques, such as functional MRI, EEG, and MEG, whereby two functional domains of the brain are considered as connected if their temporal correlation exceeds a given threshold. However, how the neuronal dynamics unfolds depends strongly on the architecture of anatomical connections between regions of the cerebral cortex [106,107]. Therefore, specific attention is devoted also to the brain's structural connectivity. Structural brain networks usually describe anatomical parcellation of the brain and links signify physical connections between different areas that are acquired from MRI or histological data [108,109]. **Fig. 4** illustrates how the brain's structural connectivity acquired with diffusion MRI serves as a basis for the construction of the structural brain network.

The structural brain network comprises anatomically distinct brain regions mathematically defined as nodes and the structural pathways connecting pairs of regions defined as links. The concept of the "connectome" is based on the idea of knowing the elements of the network and their interconnections [110]. Several properties of brain networks have already been identified. Some of these encompass a small-world character [109] and the presence of hub regions, which play pivotal roles in the coordination of information flow [106]. Furthermore, the modular and hierarchically modular organization of brain networks also became apparent. Chen et al. reported a modular architecture of the structural network in the human brain using cortical thickness measurements [111]. Namely, modularity implies that at different topological levels there will be further sub-modules. There are several general advantages to modular and hierarchically modular network organization, including greater robustness, adaptivity, and evolvability of network function [112]. Further research has shown that certain hub regions form a so-called "rich club", characterized by a tendency for high-degree nodes to be more densely connected among themselves than with nodes of a lower degree [113]. Important to note is also the spatial structure of the network. The brain is contained within a 3D volume, and the structural connections are metabolically driven to minimize total wiring distance. These notions can be captured by spatial network models that embed networks into 3D Euclidean space and penalize the formation of long-distance connections [114]. Furthermore, the anatomical network of the brain is dependent on several factors. For instance, intelligence has been linked to unique brain structural organization and results from more efficient information transfer [115]. Furthermore, age was shown to crucially affect the structural brain networks [116], as the brain undergoes structural changes during our lifetime. Significant changes are observed during adolescence, e.g., increase of the integrity of white matter bundles, as well as during aging, whereby the efficiency of the structural network of the brain increases in a nonlinear fashion [117]. The effect of aging on the modular organization of structural brain networks was investigated by Wu et al. [118], who studied structural brain networks in various differently aged individuals. Their findings showed a notable decrease in the connector ratio and the inter-module connections in subjects from the old age group. They concluded that the brain network develops into a more distributed organization from young to middle age with a subsequent bigger change and shift to a more localized organization in old age [118]. Additionally, there are also sex-related structural and functional differences between humans. Some of these include a higher raw cortical thickness and white matter complexity in female adults but higher raw volumes, raw surface areas, etc., in males [119]. Along these lines, Zhao et al. [120] studied sex-related differences in brain connectivity patterns and their findings reveal sex-specific characteristics in anatomical rich-club organization and structural-functional coupling, which might indicate network mechanism of sex-based differences in cognitive function.

In the last decade, brain connectivity concepts have become increasingly important also in terms of clinical applications. The progress in understanding the brain network organization has made it possible to assess network changes in neurological and psychiatric diseases, such as dementia, multiple sclerosis, schizophrenia, epilepsy, and many others [121,122]. In this vein, pathophysiological models of brain disorders are conceptualized as disruptions of neuronal connectivity. Recent studies of structural brain networks have shown that brain hubs are particularly vulnerable to

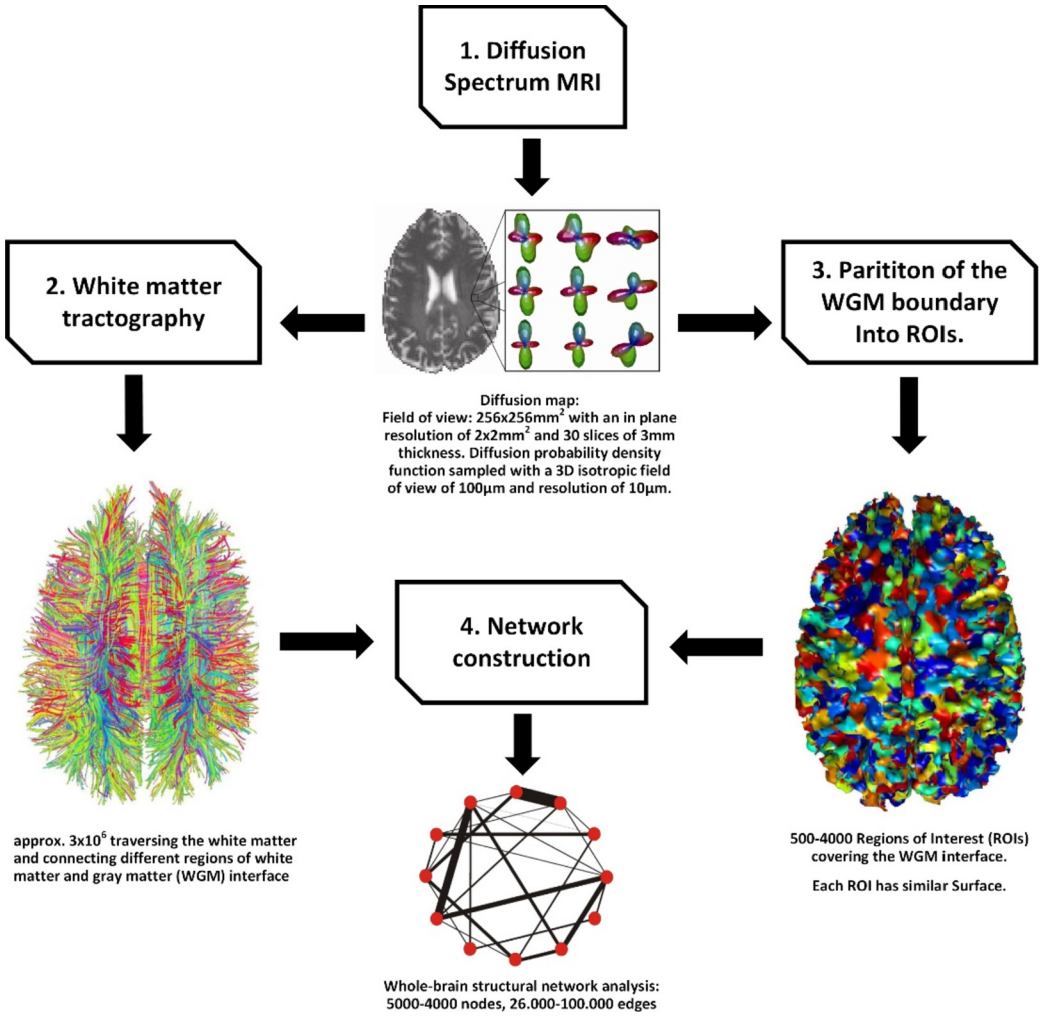

Fig. 4. The procedure of mapping the brain anatomical connectivity into a structural brain network. First, diffusion spectrum MRI was carried out (1), which provided local tissue characteristics, in particular by the orientation of axonal bundles existing in the brain. Based on the diffusion map, the paths laid by the white matter axonal bundles (2) and anatomical brain regions (3) were determined. Finally, the outputs from steps 2 and 3 were combined to construct the structural brain network, in which specific brain regions become nodes and the fibers were transformed into edges (4). The extracted network portrays the density of white matter connections between any two regions of gray matter. Reproduced from [109].

dysfunction, as they are characterized by high metabolic and blood flow rates as well as a high topological value that supports integrative processing. As such, they might represent a common pathway in neurological disorders [123]. In general, neurological diseases are associated with a decreased global efficiency and network integrity, but the network analysis possesses even further abilities explore how the connectivity patterns are changed in specific diseases and how the altered network structure relates to cognitive and behavioral impairments (for a systematic review see [124]). Therefore, brain imaging along with the ability to quantify the network structure holds great promise for future clinical use in the management of neurodegenerative disorders, even though there remain significant challenges before these approaches could be used in everyday practice.

In modern neuroscience, one of the central questions is how the brain structure affects the function and dynamics [125,126]. The efforts to address this longstanding issue often rely on tools from the realms of the network theory [127]. Recently, the multilayer network formalism has emerged as a promising approach to investigate simultaneously the structural and functional information. By this means, the brain network can be represented by two layers: one reflecting anatomical connectivity, and the other encoding functional relationships [128–130]. Several extracted network parameters, such as the multiplex motifs, were shown to be more informative than their single-layer coun-

terparts taken separately [131]. Moreover, the utilization of multimodal neuroimaging data encompassing structural and functional information was proven beneficial also in studying hierarchical community structure of brain networks [132]. However, to date, there are relatively few neuroscientific and clinically-oriented studies that incorporate the multilayer description of the intricate relation of structural and functional brain networks. Further studies that explore how this multimodal relationship correlates with clinical features, cognitive styles, treatment response and prognosis in various neuronal disorders are required.

Moving from macroscale to microscale, network approaches are nowadays widely used to capture neural interactions on the level of individual cells as well. The so-called science of micro-connectomics focuses on the analysis of small neuronal networks that are typically reconstructed at the level of individual synapses and gap junctions [133]. Till today, comprehensive topological analyses have only been performed in small invertebrate neural systems, such as the connectomes of *C. elegans* [134,135] and *Drosophila melanogaster* [136]. In essence, these small neuronal networks share many structural similarities with large scale connectivity patterns in animals of higher taxonomic level and humans, such as a heavy-tailed distribution, a hierarchical modular organization, small-world characteristics, and a rich-club structure [134,137,138]. These complex topological patterns may be associated with the existence of represent evolutionarily preserved network phenotypes for optimized neuronal computation, perhaps representing the outcome of an economical trade-off between biological costs and functionally adaptive value [133]. However, to what extent the connectomes of simple model organisms can be translated to the connectivity that is found in neuronal networks of higher animals, is not yet clear, even though the recent studies point toward a high degree of similarity. The problem is that assessing the whole-brain connectivity at the scale of individual synapses is technically extremely challenging [139]. With technological advances in imaging techniques, it has become possible to extract partial connectomes in samples of mammalian brains and quantify them with network-based approaches [140], but the micro-connectomics in the mammalian brain is still in its infancy [133].

Much more practically feasible is to study the structural organization and function of neuronal networks *in vitro*. Along the past decades, cultured neuronal networks have constituted a fundamental tool for scientists, as one of the benchmark models for the study of the central nervous system, including neuronal growth and network formation [141,142]. These networks make it possible to perform extremely specific and detailed experiments and provide a means to study basic concepts and questions (e.g., memory, connectivity etc.) [143]. However, the issue of why and how an assembly of isolated (cultured) neurons self-organizes to form a complex neural network is a fundamental problem [144]. Previous studies have revealed that utilizing tools from the network theory can be very beneficial to objectively extract the morphological characteristics of *in vitro* neuronal networks. Specifically, Shefi et al. studied the neuronal architectures of cultured neural networks and reported, that while *in vitro* cultured networks lack some specific features of *in vivo* neuronal networks, they retain many others. They develop organotopic synaptic connections and exhibit a rich variety of electrical properties similar to those observed *in vivo* [141]. The analysis of the networks in founded on the "neuron paradigm" to correctly identify the building blocks of the network (vertices – neurons, edges – synapses). The authors concluded that based on the clustering coefficient and the characteristic path lengths their networks fall into the category of small world networks. Furthermore, the growing process demonstrated the unique type of growth structure of the culture with concentrations of neuronal cell bodies interconnected by nerve tracts [141]. In a similar study Woiterski et al. [142] examined the formation of mouse retinal ganglion cell networks *in vitro* using time-lapse video microscopy and a time-resolved graph theoretical analysis. During the early development of retinal ganglion cell networks, they identified different stages which involved the reduction from a network with maximal complexity to an optimized network. At both stages, the networks displayed robust small-world properties [142]. Another article [145] describes a novel network-based segmentation algorithm which operates on large scale images acquired by phase-contrast microscopy, and therefore by a fully non-invasive technique (i.e., no addition of chemicals). The algorithm accurately identified the relevant network's units and reconstructed the wiring of network connectivity with an overall computational cost, which scales linearly with the image size. The authors were able to characterize the networks topology and morphology during the maturation process. Furthermore, they were able to pinpoint mechanisms that took place at different culturing stages [145]. Furthermore, in a recent article by Tlaie et al. [146] the authors explored the interplay between the topological relevance of a neuron and its dynamical traces in experimental cultured neuronal networks. By analyzing the network structure via optical microscopy techniques as well as additionally simulating a dynamic neuronal model, the authors tried to derive detailed connectivity, topological and structure-dynamics relationship properties of the cultured networks. Their results suggest that the morphology

of the evolving networks exhibits small-world properties as well as that it might be possible to infer the degree distribution of the network from node dynamical measurements [146].

Finally, "micro-connectomics" offers important insights into the wiring rules of neuronal network organization on a small scale and helps in understanding and modeling neuronal function[133]. Nevertheless, we must not forget that important properties are not always universally invariant with respect to the level of detail. These strongly depend on the specific level on which a network is observed [147]. Connectomics on different scales (micro, meso and macro) are all important, however microscale study results cannot address all properties of brain connectivity in large brains (e.g., humans). To map features of connectome topology across scales, from cells to whole-brain systems, will require future research in structural connectomics and inclusion of new physiological parameters (e.g., connectional microstructure, neurotransmitter receptors, plasticity, neuromodulatory effects) [148].

5. Biological fluid transportation networks

Many biological fluid transport networks, such as branching patterns of blood vessels, venation in plant leaves, fungal networks, and slime molds are optimized to redirect flow as dictated by the needs of the system [149–153]. There is immense interest in identifying how the branching network architecture, resource distribution, flow, and damage resilience affect biological function and how do these features relate to the allometric scaling theory [154–158]. In recent studies it has been shown that investigating these circulatory systems can benefit largely when assessed from a network-based perspective, not only through quantification and understanding of transport processes in hierarchical and loopy networks [159–164], but also through reconstruction of vascular architectures from imperfect data [165–167]. Whether transportation networks are assessed on the microscopic or the macroscopic scale, and irrespective of the imaging technique, the first step is the throughput automated image analysis, involving noise reductions, filtering, and thresholding, followed by morphological processing to achieve a firm skeletonization. Afterwards, describing the extracted vectorized structures as networks offers a new tissue anatomy description. This description does not only reveal structural clusters emerging as different regions of the tissue but can also be linked with virtual perfusion simulations to evaluate the function of the transportation network [168]. The methodology to construct networks and perform network-based analyses of recorded vasculatures is demonstrated in **Fig. 5**. The authors have utilized single plane illumination microscopy to obtain the entire 3D capillary structure of mouse brains [169]. The methodology enables a precise evaluation of geometric properties of individual vessels as well as the topological organization of the extracted vascular network.

Recent advances in high-resolution imaging techniques have evoked the interest to study the geometric and topological properties of micro-vascular networks. Due to extraordinarily high demands and vulnerability to discontinuities of energy substrate and oxygen delivery, particular attention is given to the structure and its relation to the hemodynamics of cerebrovascular systems [153,156,170]. Network-based analyses of the brain cerebral microvascular networks have revealed that the angioarchitectures are devoid of subnetworks of microvessels that are fully connected among themselves, but only connected to the main network with one or a few edges. This suggests that the level of microvessels importantly contributes to the control of the flow, but they do not provide sufficient collateral flow to perfuse tissue when a penetrating arteriole or venule is blocked [153]. Of course, one of the major motives for investigating the cerebrovascular network topology is the pathophysiology of ischemic stroke. Recent studies succeeded in performing blood flow simulations in realistic microvascular networks with the aim to better understand how local disruptions of cerebral blood flow impact the local and global perfusion. The study of Schmid et al. [171] has revealed that besides the baseline flow rate in the occluded capillary, the severity of a microstroke is strongly affected by the local vascular topology. In a similar vein, El-Bouri et al. [172] simulated how micro-emboli occluding vessels relate to the microvascular network structure and how they interfere with blood flow parameters. Moreover, Hahn et al. [169] have studied how glioblastoma multiforme alters the structural and functional properties of the cerebrovascular network. Their in-depth analyses have indicated that tumor growth alters the geometric properties of individual vessels only marginally, whereas the collective changes in the vascular network that could only be assessed with network approaches, such as a decomposition of large modular structures, are much more profound. Other examples incorporating explicitly network-based approaches to extract and study microarchitectures include the retinal vascular network [167,173,174], livers of rodents [175,176], mouse kidney [166], mouse capillary coronary network architecture [177], and mouse fat pads [168]. Finally, network science approaches were found beneficial also at the macro-anatomical level, where tools from the realms of the network theory have been used to investigate the topological characteristics and stability of

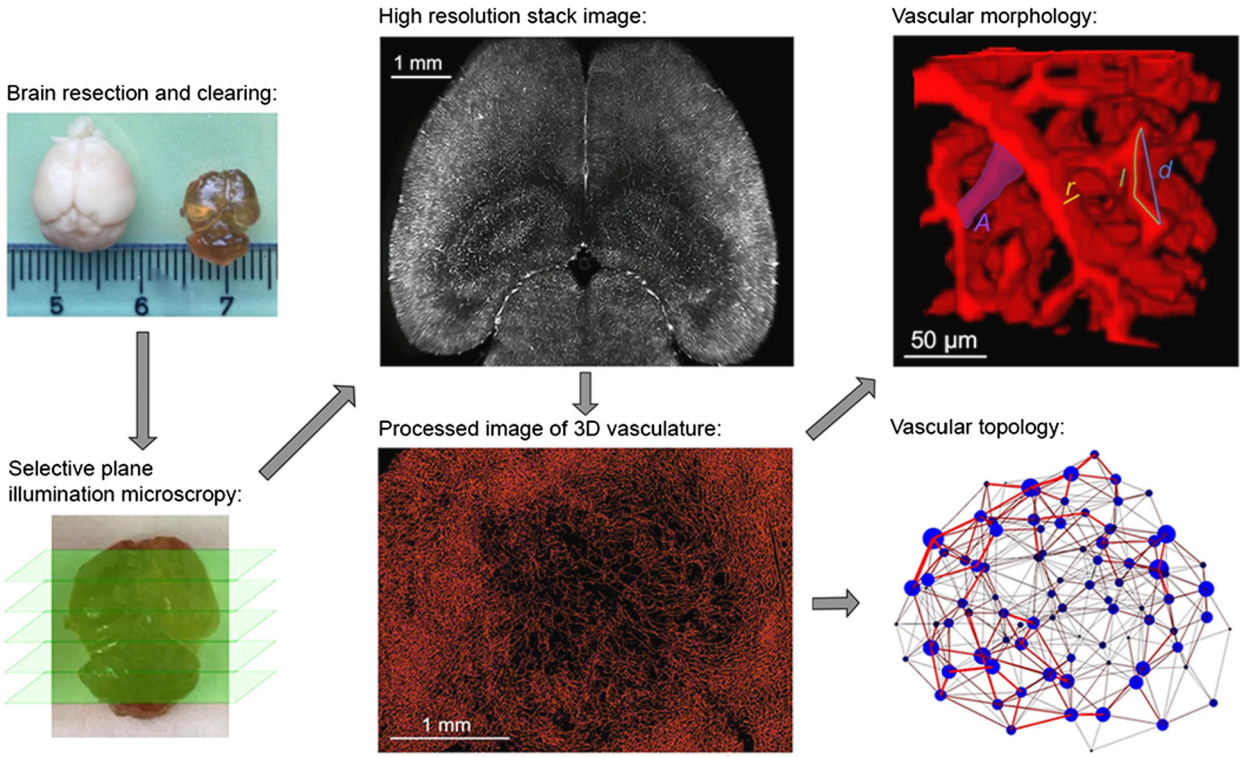

Fig. 5. Acquisition, processing and geometric quantifications of cerebrovascular networks of the mouse brain. After the brain resection and clearing, selective plane illumination microscopy was used to image the microvasculature in the entire brain by fluorescent excitement of the lectin marker. The acquired image stacks were processed and segmented to obtain the skeletonized version of the dataset and extract the topology of the vascular network and to assess the 3D vessel morphology. Reproduced from [169].

the pial vascular system in rodents [178], to identify collateral networks between branches of the posterior intercostal arteries [179], and to provide an objective framework for the evaluation cardiovascular tree derived from coronary angiography images [180].

Analogous to the branching patterns of blood vessels, the leaf venation networks are spatially embedded transport network as well and share a lot of functional principles with animal vasculatures, except they do not use active forcing to achieve circulation. The leaf vein networks are highly reticulate, featuring several orders of nested and hierarchically organized loops. The topology of this transport network is crucial for the function of the entire organ, as it delivers water, redistributes nutrients and, in addition, serves as structural mesh to provide mechanical support [163, 181]. This has stimulated interest into quantitative characterization of the topological properties related to reticulation [182,183]. Most importantly, in some recent studies it was reported that it can be very beneficial to use network-based approaches to describe the diverse leaf vascular patterns [184,185]. Furthermore, interconnected transport networks are also formed by mycelial fungi and plasmodial slime moulds. Unlike animal or plant vascular systems, the network formed by these organisms is not part of the organism, it is the organism. These networks develop as the organism forages for new resources and have not only to ensure the transport nutrients from sites of acquisition to the growing tips to sustain further exploration for resources, but also maintain the integrity in the face of predation from small grazing invertebrates [150]. Given the importance of network architecture in resource acquisition, transport efficiency, and resilience, it is important to develop quantitative measures that can help us to explore the interplay between the structural and functional organization of these organisms. Recent advances in contrast-independent pattern extraction algorithms and the incorporation of tools from the armamentarium of network theory have provided a promising framework to address these issues and offer novel perspectives and insights into the operation of fungal and Physarum networks [150,159,186–189]. These design principles nevertheless share many similarities with man-made networks and inspire the development of next-generation transportation and communication network optimization techniques [190–194].

6. Anatomical network analysis

Network theory offers a well-established framework to study systems in morphological sciences such as comparative anatomy or physical anthropology, specifically by building anatomical networks. Anatomical networks are abstract representations of an organism's topology, where interactions among anatomical parts form distinct connectivity patterns that give the system its characteristic structure and clarify the functional and developmental relationships between the anatomical parts, including growth [195–198].

The fundamental principles of comparative anatomy were laid down in the early 19th century with Geoffroy Saint-Hilaire's "principle of connections" [199]. He was the first who placed the criterion of structure before function and shape in the identification of morphological similarity among different anatomical parts. In the 20th century several conceptual frameworks for morphology based on connectivity have been proposed [200–203], although no methodological advances were effectively made until the 21st century, when Rasskin-Gutman introduced models based on the network theory to study the structural relationship among skeletal parts of archosaurs [197,198]. In the last decade, Esteve-Altava and co-workers have developed a new approach for the analysis of connectivity relations in morphological systems, the so-called anatomical network analysis [195,197,204]. According to this new quantitative tool, bone structures, such as the skull or limbs, can be precisely modeled as an undirected network, in which network nodes represent individual bones and connections between them, formed by joints, sutures or synchondroses. Other relationships between parts, such as composition, position, orientation, shape, and size, are not considered. As such, anatomical networks represent abstract representations of an organism's topology, focusing only on how constituent parts are interrelated or arranged in the body.

Using this framework, Esteve-Altava et al. have reassessed the evolutionary trend known as "Williston's Law" in the tetrapod, demonstrating that the loss and fusion of bones during evolution increases the morphological complexity of the skull [205–207]. Furthermore, they used anatomical network analysis to study the formation of bone articulations and the modular organization of the human skull [208–210]. They showed that the human skull is a small-world network divided into two connectivity modules, cranial and facial. The facial module shows a hierarchical organization composed of smaller sub-modules or blocks, whereas the cranial module has a regular organization of connections. Moreover, the network analyses of the human skull have been extended by merging skeletal, cartilaginous, and muscular anatomical parts of the head [211]. These units represent the nodes of the musculoskeletal network, whose connections represent the physical articulations, tendinous joints, and fibrous fusions of muscles onto bones and cartilages. The muscular network can also be treated separately from the skeletal network. **Fig. 6** shows an example of the skeletal and muscular anatomical networks. The skeletal network comprises 45 bones and cartilages articulated at 86 contact surfaces (sutures, synchondroses and synovial joints) and is divided into eight modules (**Fig. 6A**). The muscular network comprises 136 muscles sparsely connected at 78 contact points (fiber fusions and well-defined tendons) and divides into three major modules and 21 smaller blocks of 4 to 2 muscles each (**Fig. 6B**). Since neither muscles nor bones function as independent entities, the representation of the musculoskeletal system as a graph is very promising, as it eases the analysis of bone dependences in isolation from muscle dependences, which can further enrich our understanding of human head modularity. Notably, this approach has been applied first to individual parts of the body, including the head [211], upper and lower limbs [212]. Along similar lines, Murphy et al. [213] constructed a highly simplified whole-body musculoskeletal network using hypergraph approach by representing bones as nodes and muscles as hyperedges linking those nodes. Noteworthy, the utilization of anatomical network analysis was also proven successful to study the macroevolution of diverse anatomical parts among different extinct and extant tetrapod species, from mammals [214–217] to reptiles [218]. For instance, Esteve-Altava et al. [219] compared the anatomical organization of fins (extant lobe-finned fishes) and limbs (early tetrapods) using network models and reveal an evolutionary transition toward less integrated, more modular appendages.

Finally, of particular interest is how the human motor control is shaped by the coordination of muscle activity under the anatomical constraints imposed by the musculoskeletal system. To address this issue, Kerkman et al. [220] investigated the structure-function relationship of the human musculoskeletal system by analyzing the relation between the anatomical structure of the musculoskeletal system and the functional organization of distributed neural circuitry from which motor behaviors emerge. To this purpose they investigated the relation between anatomical networks defined by the physical inter-muscle connectivity and functional networks extracted from EMG-based intermuscular coherence assessed during postural tasks [221]. The multiplex network analysis has revealed a strong and frequency-specific relationship between anatomical connections in the musculoskeletal systems and correlated inputs to spinal motor

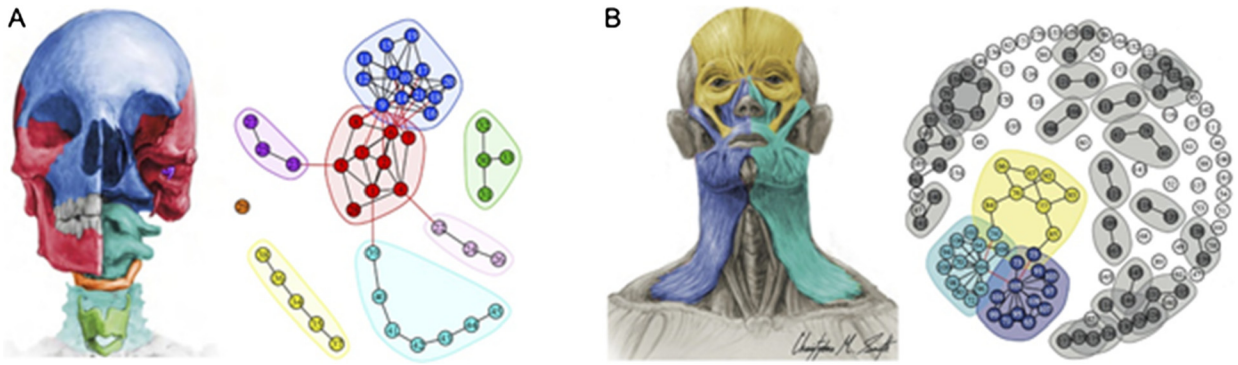

Fig. 6. Modules of the head skeleton and musculature determined by anatomical network analysis. The skeletal network (A) comprises 45 bones and cartilages articulated at 86 contact surfaces (sutures, synchondroses and synovial joints) and divides into eight modular: the cranial complex (red); the facial complex (blue); the thyroid complex (green); the thoracic complex (yellow); the cervical complex (cyan); the ossicles complexes (light and dark purple); hyoid one-bone module (orange). The muscular network (B) comprises 136 muscles sparsely connected at 78 contact points (fiber fusions and well-defined tendons) and divides into three major modules: the ocular/upper face complex (yellow); the orofacial complexes (light and dark blue); the 21 smaller blocks of inter-connected muscles (gray). In the absence of bones, several muscles are totally disconnected from the three major muscle modules (white). Reproduced from [211].

neurons and represents a nice example on how network physiology approaches can be used to examine structure–function relationships within the body.

7. Conclusion

Tools from the armamentarium of the complex network theory are nowadays recognized as a general and powerful theoretical framework for assessing real-world systems. Their wide applicability is to a significant extent a consequence of their natural suitability to represent and study the relations between individual components in virtually any discrete system. For these reasons, we are witnessing in the last two decades an explosion of multidisciplinary studies in which the complex network methods are applied to social sciences [222–228], linguistics [229–231], ecological systems [232–234], economics [235,236], and a wide range of engineered and technological systems [38,237–241]. With the recent advances in high-throughput imaging technologies these concepts have also become an indispensable tool in biomedical research at different scales and organizational levels [20,52,104,153,242,243]. Formally, the studies of interaction patterns within complex living systems can be categorized into examinations of the structural connectivity, e.g., network architecture, and functional connectivity, which refers to the underlying dynamical processes. In this vein, structural connectivity derives from the system's anatomy, whereas the functional connectivity is inferred from the system's dynamics which are represented by fluxes and transformations of energy, matter, or information between structural units [244]. It is known that the structure and function are closely intertwined – the structure always affects function, and the function very often affects the structure, although the timescales of the reciprocity and feedback of the later may differ [244,245]. Nevertheless, identifying the principal aspects of the network dynamics and how it derives from specific structural features remains one of the key challenges in complex systems research [11,194,246–249].

In the present contribution we focused exclusively on structural connectivity patterns in living systems. We described how the recent developments in the quantitative analysis of complex networks have been successfully translated to studies of the structure and morphological complexity of different biological systems. Branching patterns of blood vessels, anatomical connections in the musculoskeletal system or within the brain, and intercellular interactions can all be regarded as a spatial network in which location of nodes and edges in space can heavily affect both the structure of the network as well as the underlying organizational principles. Data abstraction into networks allows for the performance of topological analyses, which do not only ease the structural characterization of biological networks but also enables to highlight nodes with special properties that can be correlated with the biological importance of individual components. Using network-based approaches it is possible to identify which regions in the brain play a central role in supporting an integrated function, which bifurcations in the vascular network are vital for proper biological fluid transport, how bone growth co-dependency patterns affect the development and evolution of the skeleton,

and which cells within multicellular assemblies are crucial for communication between distant cells. We argue that network science and the models, methods and algorithms developed in this field will help to address these issues in further detail, ushering in a new era of network-based inquiry into the structure and its relation to function of various biological systems. We also believe that in the near future, the need for quantitative structural connectivity analyses will grow even further due to the rapid progress in tissue engineering and the development of bioartificial substitutes for organs and tissues.

Data accessibility

This article does not contain any additional data.

CRediT authorship contribution statement

All authors contributed to the design of the study and writing of the manuscript.

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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