Spatial Embedding Imposes Constraints on Neuronal Network Architectures

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Review

Spatial Embedding Imposes Constraints on Neuronal Network Architectures

Jennifer Stiso[1,2] and Danielle S. Bassett[1,3,4,5,*]

Recent progress towards understanding circuit function has capitalized on tools from network science to parsimoniously describe the spatiotemporal architecture of neural systems. Such tools often address systems topology divorced from its physical instantiation. Nevertheless, for embedded systems such as the brain, physical laws directly constrain the processes of network growth, development, and function. We review here the rules imposed by the space and volume of the brain on the development of neuronal networks, and show that these rules give rise to a specific set of complex topologies. These rules also affect the repertoire of neural dynamics that can emerge from the system, and thereby inform our understanding of network dysfunction in disease. We close by discussing new tools and models to delineate the effects of spatial embedding.

Highlights

The physical embedding of neural systems imposes constraints on the possible patterns of connections and the repertoire of functional motifs.

Prominent competing rules guiding the formation of brain networks include the minimization of wiring cost, and maximizing network efficiency and diversity. These rules lead to high local clustering with sparse long-distance connections.

Recent work suggests that intrinsic functional connectivity varies along dimensions that are tightly linked to the spatial embedding of the brain and to the topological properties that arise in the presence of spatial constraints. Similarly, these properties show widespread changes in various diseases.

There is a rich and growing repertoire of statistics, null models, and generative models to aid researchers in testing focused hypotheses about the role of physical embedding in neural systems.

Network Topology versus Geometry in Neural Systems

In contemporary neuroscience, increasing volumes of data are being used to answer the question of how heterogeneous and distributed interactions between neural units might give rise to complex behaviors. Such interactions form characteristic patterns across multiple spatial scales, spanning molecules and cells to brain regions and lobes [1]. An intuitive language in which to describe such interactions is network science, which elegantly represents interconnected systems as sets of **nodes** (see Glossary) linked by **edges**. Nodes often represent proteins, neurons, subcortical nuclei, or large cortical areas, and edges often represent either (i) structural links in the form of chemical bonds, synapses, or white matter tracts, or (ii) functional links in the form of statistical relations between nodal activity time series. Generally, the resultant network architecture can be fruitfully studied using tools from graph theory to obtain mechanistic insights pertinent to cognition [2], above and beyond those provided by studies of regional activation [3] (Box 1).

In particular, several fundamental questions in neuroscience are quintessentially network questions concerning the physical relationships between functional units. How does the physical structure of a circuit affect its function? How does coordinated activity at small spatial scales give rise to emergent phenomena at large spatial scales? How might alterations in neurodevelopmental processes lead to circuit malfunction in psychiatric disorders? How might pathology progressively spread through cortical and subcortical tissue, giving rise to the well-known clinical presentations of neurological disease? These questions collectively highlight the fact that the brain – and its multiple networks of interacting units – is physically embedded into a fixed 3D enclosure. The natural consequences of this embedding include diverse physical drivers of early connection formation and physical constraints on the resultant adult network architecture. Understanding the constitution and basal dynamics of the system therefore requires not only approaches to quantify and predict network **topology** but also tools, theories, and methods to quantify and predict network **geometry** and its role in both enabling and constraining system function.

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In this review we provide evidence to support the notion that consideration of the physical embedding of the brain will prove crucial for a holistic understanding of neural circuit function. We focus our comments on the utility of informing this consideration via emerging computational tools developed for the characterization of spatial networks. Perhaps as a historical artifact of its origins in mathematics, or its initial applications to abstract informational systems, network science often addresses the topology of systems in a way that is devoid of clear spatial characteristics [4]. However, in recent years, the field has steadily developed tools and intuitions for spatially embedded network systems [5]. In the light of these developments, we begin by

Box 1. Simple Network Statistics

In a network representation of the brain, units ranging from neurons or neuronal ensembles to nuclei and areas are represented as network nodes, and unit-to-unit interactions ranging from physical connections to statistical similarities in activity time series are represented as network edges. These connections can have independent topological and spatial distances (Figure IA). The architecture of the network can be quantitatively characterized using statistics from graph theory [105]. We mathematically define here some of the topological statistics mentioned elsewhere in this paper (Figure IB).

Degree and Strength

The degree of a node is the number of connections it has. In a binary graph encoded in the **adjacency matrix** A, where two regions i and j are connected if $A_{ij} = 1$, and not connected if $A_{ij} = 0$, then the degree $k_i = 1$ is defined as:

$$k_i = \sum_{i,j \in N} A_{ij}, \quad [\mathrm{I}]$$

where N is the set of all nodes. In a weighted graph, where A_{ij} is the strength of the connection between nodes i and j, then the strength s_i is defined as:

$$s_i = \sum_{i,j \in N} A_{ij}. \quad [\mathrm{II}]$$

Path Length and Network Efficiency

The term path length frequently refers to the average length of the shortest path in a network. The shortest path between any two nodes is given by the path requiring the fewest hops. The network efficiency is given by the inverse of the harmonic mean of the shortest path length. To be precise, we can write the path length of node i as:

$$L_i = \frac{1}{n} \sum_{i \in N} \frac{\sum_{i \in N, j \neq i} d_{i,j}}{n-1}, \quad [\mathrm{III}]$$

where $d_{i,j}$ is the shortest path length between two nodes and n is the number of nodes.

Clustering Coefficient

The clustering coefficient can be used to quantify the fraction of the neighbors of a node that are also neighbors with each other. Specifically, the clustering coefficient of node i is given by:

$$C_i = \frac{1}{n} \sum_{i \in N} \frac{2t_i}{k_i(k_i - 1)}, \quad [\mathrm{IV}]$$

where t_i is the number of triangles around node i [50]. The clustering coefficient of the network is the average clustering coefficient of all of its nodes.

Modularity

Although there are several modularity quality functions, the most common is

$$Q = \sum_{ij} [A_{ij} - \gamma P_{ij}] \delta(c_i c_j), \quad [\mathrm{V}]$$

where Q is the modularity quality index, P_{ij} is the expected number of connections between node i and node j under a specified null model, δ is the Kroenecker delta, and c_i indicates the community assignment of node i. The tuning parameter γ ranges from $(0, \infty)$ and can be used to tune the average community size.

Glossary

Adjacency matrix: an $N \times N$ matrix of a graph, where N is the number of nodes. Each element A_{ij} of the matrix gives the strength of the edge between nodes i and j.
Allometric scaling: in biology this term refers to the differential (compared to isometric scaling) growth of different aspects of physiology with respect to body size. We discuss here the allometric scaling of gray matter volume with respect to white matter volume, which is described with a power law.
Cycle: in applied algebraic topology, this refers to an empty space (or lack of edges) in a graph surrounded by all-to-all connected subgraphs of the same dimension. The dimension here refers to the number of nodes included in each all-to-all connected subgraph.
Edge: from the perspective of graph theory, an edge refers to a connection between nodes. From the perspective of neuroscience, an edge is a statistical dependency (functional) or estimated physical connection (structural) between nodes.
Geometry: in a network, the geometry reflects features of a graph in the context of physical space.
Hub: a central node in the network, typically having many connections.
Node: from the perspective of graph theory, the unit where edges connect in the graph. From the perspective of neuroscience, a node is a brain region, neuron, or protein whose interactions one wishes to understand.
Topology: the quantification of features of a graph in the context of space defined by the graph itself, without respect to any physical embedding.

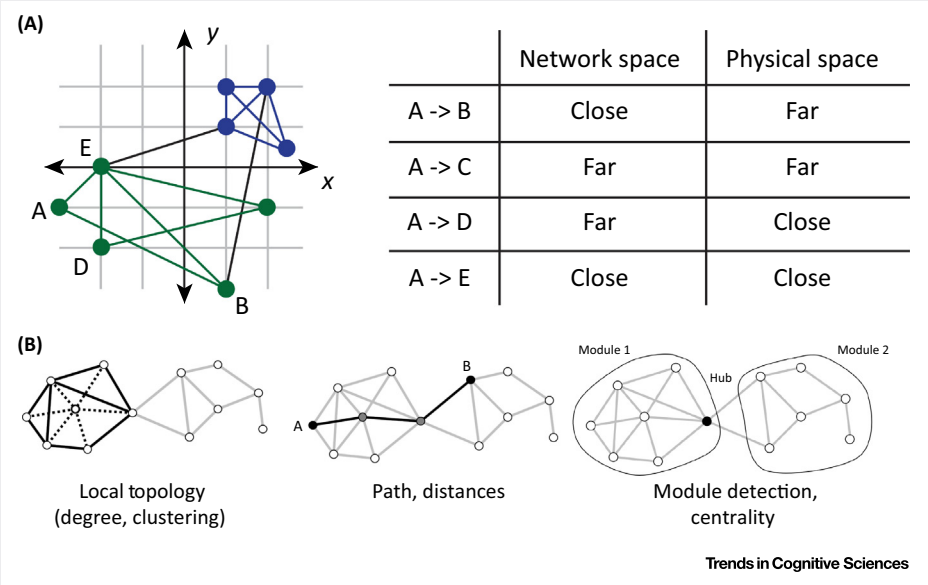

Figure I. Schematic of Network Measures. (A) An illustration of network space (topology) and physical space (geometry). The network is embedded into a physical space, indicated by the *x* and *y* axes. The topological and physical distances between the nodes are not necessarily related. (B) The network representation enables the calculation of local, mesoscale, and global features to describe the pattern of connections in topological space (as shown here) as well as the pattern of connections in physical space (as we describe in the main text). Adapted, with permission, from [1] and [87].

recounting observations from empirical studies addressing the question of how brain networks are embedded into physical space. Next, we discuss the relevance of this spatial embedding to an understanding of network function and dysfunction. We complement these empirical discussions with a more technical exposition on the relevant tools, methods, and statistical approaches to be considered when analyzing brain networks. Finally, we outline open questions regarding network architecture and circuit function, the answers to which will require a thorough appraisal of the role of physical space in brain network physiology.

Physical Constraints on Network Topology and Geometry

Diverse processes guide the formation of structural connections in neural systems [6,7]. Evidence from genetics suggests that neurons with similar functions, as operationalized by similar patterns of gene expression, tend to have more similar connection profiles than neurons with less similar functions [6,8,9], with the greatest similarity appearing at highly interconnected, metabolically demanding **hubs** [10]. Of course, it is important to note that some spatial similarity in expression profiles is expected because of the influence of spatial gradients of growth factors during development [6]. However, evidence suggests that interareal connectivity profiles in rodent brains are even more correlated with gene coexpression than would be expected simply based on such spatial relationships [8]. This heightened correlation could be partially explained by observations in mathematical modeling studies that neurons with similar inputs (and therefore potentially performing similar functions) tend to have more similar connection profiles than neurons with dissimilar inputs [11].

Nevertheless, although genetic coding and functional utility each play important roles, a key challenge lies in summarizing the various constraints on connection formation in a simple and

intuitive theory that can guide future predictions. One particularly acclaimed theory first outlined by Ramon y Cajal in 1899 [12] is that physical constraints on space, time, and material over development underlie connection formation. Metabolism related to neural architecture and function is costly, utilizing 20% of body energy, despite comprising only 2% of its volume [13]. Even the development of axons alone extorts a large material cost [6]. The existence of these pervasive costs motivated early work to postulate that wiring minimization is a fundamental driver of connection formation. Consistent with this hypothesis, axons in the brain seem to occupy a nearly optimal volume to minimize metabolic costs [14]. In addition, the neural architectures of multiple species [15,16] and at multiple scales [17] across different methods of data collection [18–20] are predominantly composed of wires extending over markedly short distances [6,21].

However, mounting evidence suggests that pressures for wiring minimization may compete against pressures for additional topological complexity [16] that could facilitate efficient communication [22–24]. Early evidence supporting the role of efficient communication came from the observation that one can fix the network architecture of interareal projections in the macaque cortex (and later human [22], mouse [9], and dendritic arbors [6,21]), and then rearrange the location of areas in space to obtain a configuration with significantly lower wiring cost [23]. Interestingly, for the connections whose length is decreased, most also tend to be those that shorten the characteristic path length – one of many ways to quantify how efficiently a network can support communication [23]. Notably, computational models that instantiate both constraints on wiring and efficient communication produce topologies more similar to the true topologies than do models that instantiate a constraint on wiring minimization alone [11,25]. Moreover, models that allow for changes in this tradeoff over developmental time-periods better fit observed connectome growth patterns than prior models, positing a mechanism of early connection to nearby sources, coupled with later expansion of older densely connected clusters to create topological diversity [26]. It is worth noting that other properties have been proposed as drivers in addition to communication efficiency, such as fine-scale chemical mechanisms of chemotaxis [27] and large-scale mechanisms driving functional diversity via long-distance connections [28]. Alternatives to the hypothesis that communication efficiency is a key driver include the preservation of hubs specifically [20].

It is precisely this balance between wiring minimization and communication efficiency that is thought to produce the complex network topologies observed in neural systems, as well as markedly precise spatial embedding [29,30]. A simple illustration of this precise embedding lies in the **allometric scaling** of white versus gray matter across species [31,32]. To better understand how this scaling relates to the topology of a single organism, it is useful to consider methods that can simultaneously (instead of independently) assess topology and geometry. One such method that has proved to be particularly useful in the study of neural systems from mice to humans is Rentian scaling, which assesses the efficiency of the spatial embedding of a network [22,33,34]. Originally developed in the context of computer circuits, Rentian scaling describes a power-law scaling relationship between the number of nodes in a volume and the number of connections crossing the boundary of the volume [6,22]. The existence of such a power law relationship with an exponent known as Rent's exponent is consistent with an efficient spatial embedding of a complex topology [35]. In addition, the Rent's exponent of connections in the human brain is proportional to the allometric scaling of gray and white matter volume across species, creating a putative link between the efficient embedding of a single system and the scaling of connectomes across evolution.

Reflections of Physical Constraints in Local, Mesoscale, and Global Network Topology

Across species, the brain consistently exhibits a set of topological features at local (single regions), meso (neural circuits), and global (entire connectome) scales that can be simply explained by a few spatial wiring rules [29,36,37]. At the local scale, multiple modalities have been used to demonstrate that a key conserved topological feature is the existence of hubs, or nodes of an unexpectedly high degree [38,39]. Such hubs emerge naturally in computational models in which the location of nodes are fixed in space, and edges between nodes are rewired to miminize average wiring length and to maximize topological efficiency by minimizing the average shortest path length (Box 1), although the number and degree of hubs varies systematically with the relative importance of the two constraints [21,25] (Figure 1). Importantly, when both constraints are balanced, networks contain several hubs of varying degrees, consistent with the topology observed in brain networks [25]. In brain networks, hubs tend to be linked by connections that are longer than expected [40,41], although their exact physical placement enables low wiring cost given the presence of hubs [42]. It is notable that such constraints can be implemented within the natural processes of development; for example, in adult *C. elegans*, hub neurons have been tracked back to the earliest born neurons in the

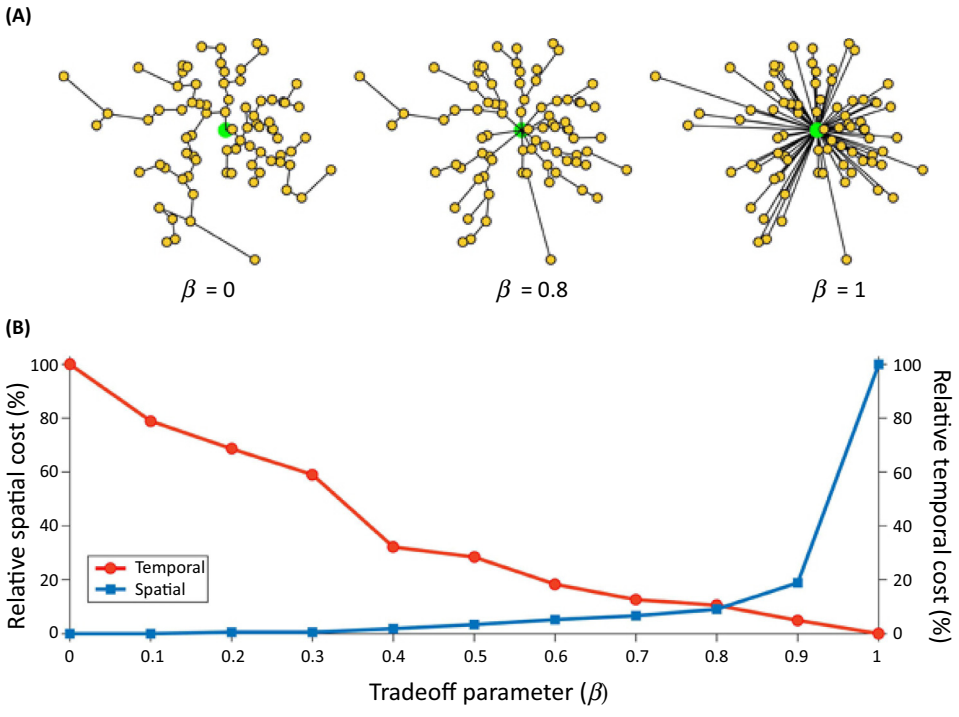

Figure 1. Effect of Wiring Minimization and Communication Efficiency on Network Topology. Networks were generated by modulating the balance between a constraint on wiring (referred to as a spatial cost) and a constraint on information routing efficiency (referred to as a temporal cost). The parameter β, which ranges between 0 and 1, tunes this balance by weighting spatial cost against temporal cost. When $\beta = 0$ only the spatial cost is considered, while when $\beta = 1$ only the temporal cost is considered. (A) Examples of networks at different values of β when only the spatial constraint exists (left), when only the temporal constraint exists (right), and when the two constraints are balanced (middle). Root nodes are shown in green and all other nodes are shown in yellow. (B) Spatial costs (blue) and temporal costs (red) vary as a function of β. Adapted, with permission, from [21].

embryo, which accumulate a large number of connections along the normative growth trajectory [30,43].

At the mesoscale, a key conserved topological feature is modularity, or the existence of internally dense and externally sparse communities of nodes [29,36,44]. The strength of modularity in a network is commonly quantified using a modularity quality index (Box 1). In computational models, this index obtained under pressures of wiring minimization and communication efficiency (quantified with path length) was more similar to that empirically measured in the connectomes of the macaque and *C. elegans* than to that obtained under either constraint separately [7,25]. Again it is notable that such constraints can be implemented within the natural processes of development; for example, in *Drosophila*, communities form when many neurons are born in a similar temporal window, and therefore typically share a common progenitor type, and thus a similar spatial location and genetic profile [30,45]. Genetically similar neurons being born in close proximity are likely to connect to one another, forming densely connected functional groups. Spaces between modules can form cavities or **cycles**, or intuitively holes in the network, that can be identified with emerging tools from applied algebraic topology (Box 2) [46]. The locations, prevalence, and weight structure of these cycles differ markedly between geometric and random networks [47,48], with patterns of functional connectivity among neurons exhibiting characteristics similar to those observed in spatially constrained geometric networks [49]. It will be interesting in the future to gain a deeper understanding of the relations between cycles and modules, and their emergence through the spatially constrained processes of development.

At the global scale, a key conserved topological feature is small-worldness, or the confluence of unexpectedly high clustering and short path length (Box 1) [50]. Such architecture is thought to be particularly conducive to a balance between local information processing within the clusters and global information transmission across the topologically long-distance connections [51]. Similar to the existence of hubs, modules, and cavities, small-world architecture in a network can naturally arise from spatial constraints on wiring [52]. Intuitively, clusters tend to form in

Box 2. Applied Algebraic Topology

Although graph theory is a powerful and accessible framework for analyzing complex networks, complementary information can be gained by using different mathematical formalisms. We describe here an alternative approach to studying structure in networks that relies on tools developed in the field of applied algebraic topology, specifically persistent homology [106]. Persistent homology can be used to study intrinsically mesoscale structures called cycles and cliques [107]. Cliques are all-to-all connected subsets of nodes in a network. The presence of many large cliques indicates many highly connected units are present in the network [108]. Cycles are looped patterns of cliques which may enclose a cavity, or topological void, within the network. Cliques and cavities by definition reside within a binary graph; however, one can expand a weighted network into a sequence of binary graphs via iterative thresholding [49,109]. Then, using persistent homology one can track the birth, persistence, and death of cavities along this sequence which gives a holistic insight into the global network (Figure IA).

In random graphs, the numbers of births and deaths across thresholds follow a characteristic pattern [48]. At high thresholds and low edge density, a few low-dimensional cavities exist, while at low thresholds and high edge density, more high-dimensional cavities exist (Figure IB) [48,110]. Interestingly, geometric graphs – which can be used to instantiate spatial constraints on the topology – show a markedly different distribution. There are many low-dimensional cavities, and fewer cavities with increasing dimension [47,48] (Figure IC). This general pattern has been recapitulated in functional networks constructed from firing of hippocampal neurons, indicating a geometric rather than a random nature to neuronal cofiring [49]. Furthermore, the persistent homology of human connectomes [46] and rat microcircuits [108] is distinct from that expected in a minimally wired null model. In humans, the presence of widespread subcortical connections leads to more cavities being born at high densities [46], while rat microcircuits display more high-dimensional cavities in general [108]. Further investigation into how wiring rules shape the topology of neural systems may shed light on how the spatial embedding of the brain shapes connectivity across scales and species.

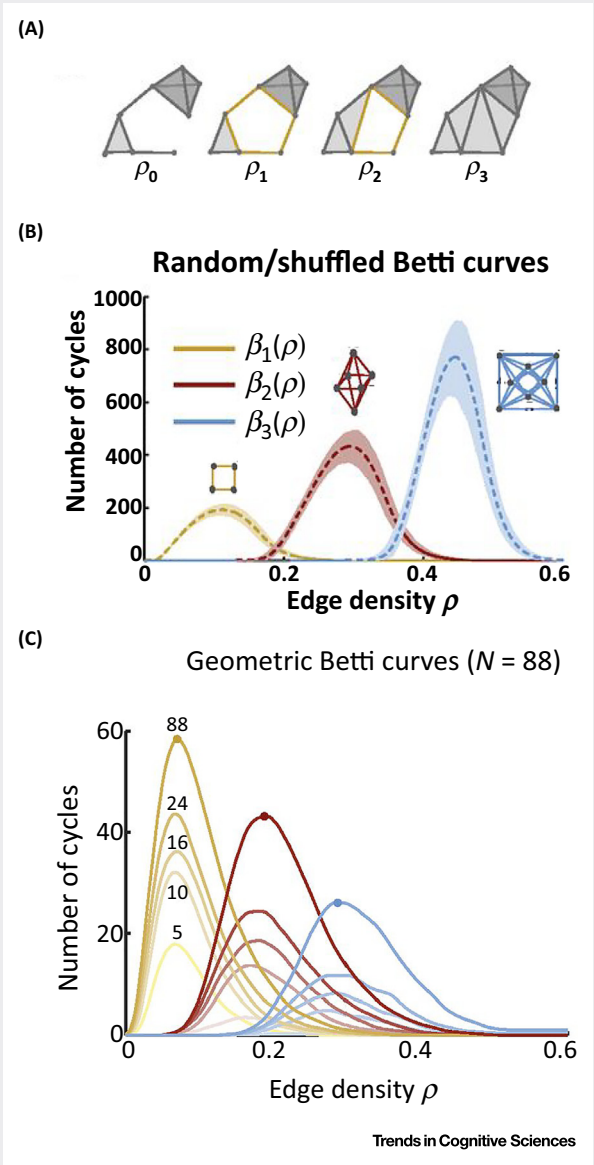

Figure I. Applied Algebraic Topology. (A) An illustration of thresholding a weighted network across different densities (ρ). At ρ_1 a cavity of dimension 1 is born (shown in yellow), which then dies at ρ_2. (B) The characteristic pattern of births and deaths (called Betti curves) for cycles of dimension 1 (yellow), dimension 2 (red), and dimension 3 (blue) from a random network. The cliques of each dimension are shown near each corresponding Betti curve for reference. (C) The same pattern, but for geometric networks. Different lines of the same color indicate different dimensions of embedding. Adapted, with permission, from [49].

spatially nearby regions to minimize wiring cost, while long-distance connections facilitating efficient communication tend to form only occasionally owing to their elevated wiring cost [53]. In concert with these empirical observations, computational models that account for wiring economy produce networks with small-world architectures reminiscent of those observed in real neural systems [54]. Collectively, these studies demonstrate the influence of parsimonious wiring rules on complex network topology. Future work could be directed to a better

understanding of the aspects of connectome topology that remain unexplained and thus may arise from more subtle rules [7].

Relevance of Network Geometry for Dynamics and Cognition

Pressures for wiring minimization and communication efficiency can exist alongside developmental processes that produce non-isotropically structured organs that result in patterning across multiple overlapping signaling gradients [27]. It is intuitively possible that such processes could also explain the observed differences in the network topologies of different sectors of the brain [55,56], which can impinge on the functions that those sectors are optimized to perform (Box 3). Indeed, prior work has noted the coexistence of complex structural topologies and spatial gradients of specific function [57], although it has been difficult to achieve a mechanistic understanding of exactly how the two relate to one another. One particularly promising recent line of investigation attempting to link the two mechanisms has proposed the existence of a set of primary spatial gradients that explains variance in large-scale connectivity [58,59] (Figure 2A). In both humans and macaques, the primary axis of variance is bounded on one end by the transmodal default-mode system, and on the other end by the unimodal sensory systems [59] (Figure 2B). Notably, this gradient is tightly linked to the geometry of the network, with the regions located at one end having maximal spatial distances from regions located at the other end [59]. In addition, the regions located at the peaks of the transmodal gradient have substantial overlap with structural hubs (whose putative role in the wiring economy has been discussed) in human connectomes [20,41,60]. Put simply, such evidence supports the notion that the cortex is fundamentally organized along a dimension of function from concrete to abstract, and that dimension manifests clearly in the spatial embedding of the network.

Box 3. Control Theory

Network control theory provides a potentially powerful approach for modeling neural dynamics [111]. Hailing from physics and engineering, network control theory characterizes a complex system as being composed of nodes interconnected by edges, and then specifies a model of network dynamics to determine how external input affects the time-varying activity of the nodes [112]. Most studies of network control in neural systems stipulate a linear, time-invariant model of dynamics:

$$\dot{x}(t) = \boldsymbol{A}x(t) + \boldsymbol{B}u(t), \quad [\mathrm{I}]$$

where x is some measure of brain state, A is a structural connectivity matrix, u is the input into the system (exogenous stimulation, or endogenous input from other brain regions), and B selects the control set, or regions to provide input to [113]. Assuming this model of dynamics, one can calculate the control energy required to reach specific brain states, which can be used as a state-dependent measure of the efficiency of control [114]. Control theory can also posit control metrics that quantify how efficiently a node would drive the brain to various states. Two commonly used metrics are average controllability and modal controllability [115]. When every node is included in the control set, average controllability is proportional to the average energy required to drive the node to any state [116]. Conversely, modal controllability is high in nodes where a small input will result in large perturbations to all eigenmodes of the system, and is interpreted to be high in nodes that can easily drive the brain to hard-to-reach states [117].

If these properties are important for helping the brain to transition between states, one would expect them not to be randomly distributed across the cortex but instead to be clustered into spatially constrained, functionally relevant systems. More specifically, one might expect functional systems that drive the brain to many accessible states, such as the default-mode system, to have high average controllability, while regions that drive the brain to hard-to-reach, cognitively demanding states (executive control areas) to have high modal controllability. Data from healthy human adults support these two hypotheses [117]. Moreover, both average and modal controllability increase across development and are correlated with cognitive performance generally [118]. The manner in which network control tracks individual differences reflects the fact that the capacity for a network to enact control is dependent upon its topology [119]. Further efforts will be necessary to distill exactly how spatial embedding and wiring constraints impinge on that control capacity, and how this relation is altered in psychiatric disorders [116].

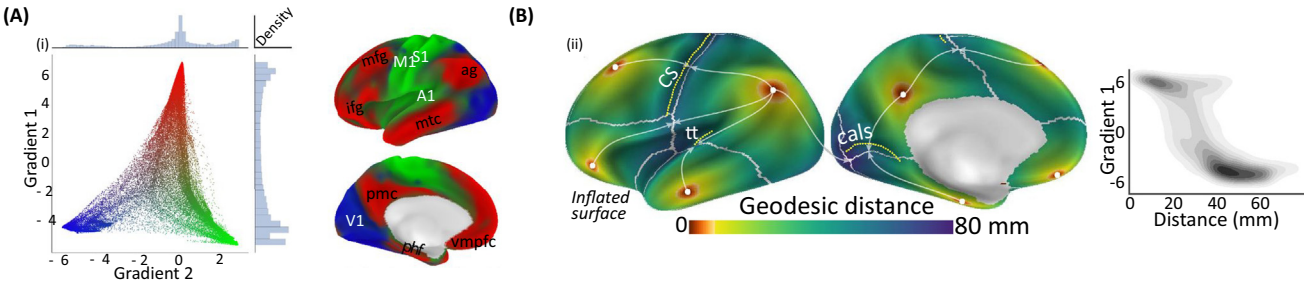

Figure 2. Spatial Distribution of Intrinsic Neural Activity. Principal gradients of functional connectivity calculated in the structural connections of both humans and macaques. The first two principal gradients explained ~40% of the observed variance. (A) (i) A scatterplot of the first two principal gradients, with transmodal regions shown in red, visual regions in blue, and sensorimotor regions in green. (ii) The same colors are used to show the distribution of points visualized on a cortical surface. The pattern suggests the existence of a macroscale gradient of connectivity that reflects the systematic integration of information across different sensory modalities. (B) (i) The minimum geodesic distance (mm) between each point on the cortical surface and the positive peaks of the first principal gradient. The peaks are shown as white circles. (ii) A scatterplot depicting the relationship between distance and location on the trans- to unimodal gradient. Put differently, transmodal regions with high values in the principal gradient are maximally distant from unimodal regions with low values in the principal gradient. Adapted, with permission, from [59].

The specific topology and spatial geometry of brain networks has important implications for the patterns of neural dynamics that one would expect to observe. Consider, for example, the patterns of intrinsic activity noted consistently across species, individuals, and imaging modalities in the default-mode system [61]. The consistent architecture of correlations between regional time-series in this system suggests a role for time-invariant structural features in organizing these dynamics. Consistent with this suggestion, functional connectivity in the default mode is more similar to its structural connectivity than other systems [62]. Recent work addressing the mechanisms of the stable intrinsic activity patterns in the default mode has posited the existence of so-called 'lag threads', or spatial progressions of whole-brain activity patterns at non-zero time-lags [63]. Notably, regions of the default mode participate in consistent lag thread motifs, where changes in the activity in one region reliably lead to changes in the activity of another region [61,63]. It has been postulated that these lag threads, both within and outside of the default mode, arise from infra-slow oscillations in membrane potential that travel between cortical layers [64], although further work parsing the relative role of passive propagation along structural pathways versus active neuromodulation in these patterns is needed.

In addition to characteristic dynamics of activity across the default mode, the brain also shows reliable wave-like cortical dynamics in both task and rest conditions that are important for neural computation [65–67]. Different aspects of these dynamics can be replicated by biophysical models of neuronal activity that account for the delay of activity propagation across axons, indicating that connection topology and the distance of connections might be important for their characteristic spread [68]. Using whole-brain human connectomes, these models can recreate metastable patterns of waves, sources, and sinks, where such patterns tend to emanate from hubs in the network more than from non-hubs [69]. Together, these results support the notion that features of the network topology created by the spatial embedding of the brain influence the reliable patterns of dynamics observed in the cortex.

Relevance of Network Geometry for Disease

The spatial architecture of brain networks not only impacts our understanding of dynamics and cognition but also our understanding of neurological disease and psychiatric disorders. Mounting evidence suggests that many diseases and disorders of mental health can be

thought of fruitfully as network disorders, where the anatomy and physiology of crossregional communication can go awry [70]. Intuitively, spatial anisotropies of developmental processes, or the spatial specificity of pathology, could also explain alterations in the spatial characteristics of brain networks [71]. Although there are many different neurological diseases with pathologies related to the spatial embedding of the brain (reviewed in [72]), we will limit our discussion in this review to epilepsy, a particularly common neurological disease, and to schizophrenia, a particularly devastating psychiatric disorder.

Despite a diverse pathophysiology but a renitent unifying biological manifestation, epilepsy is characterized by altered network dynamics in the form of seizures that display spatially consistent patterns. For example, an ictal period often begins with a marked spatial decorrelation followed by a period in which abnormally synchronized activity propagates in consistent spatial patterns [73,74]. In addition to broad patterns of spatial decorrelation, individual seizures also show stereotyped patterns of both spiral waves and traveling waves of activity [65,75,76]. *In silico* studies have demonstrated that a simple adaptive model of synaptically coupled and spatially embedded excitatory neurons can reproduce many basic features of these waveforms, including their speed and the size of the wavefront [75]. However, we have noted that traveling waves are not unique to epilepsy, and marked differences in wave propagation in healthy and epileptic cortical tissue suggest that the precise spatial progression is important, potentially supported by distinct underlying microstructures [77]. Finally, even interictal dynamics are altered in epilepsy, as manifested by marked decreases in average functional connectivity across the brain combined with local increases in functional connectivity and efficiency in default-mode areas [78,79]. These connectivity patterns have some utility in predicting seizure spread, but the guiding principles leading to these changes and how they relate to fine-scale patterns of activity remains unclear [80].

Although its pathophysiology is very distinct from that implicated in epilepsy, schizophrenia is also a condition marked by severe network disturbances that have broad ramifications for cognitive function [24,81]. Some of these network alterations appear to selectively affect connections of particular physical lengths, reflecting an alteration in the spatial embedding of the network [82]. Specifically, the evidence suggests a reduced hierarchical structure and increased connection distance in the anatomical connectivity of multimodal cortex in patients with schizophrenia compared to healthy controls, indicative of less efficient spatial wiring [81]. Moreover, in functional brain networks, patients display longer high-weight connections, decreased clustering, and increased topological efficiency in comparison to healthy controls [82]. The lack of strong, short-distance functional connections is in line with evidence from animal studies suggesting over-pruning of synapses in childhood-onset schizophrenia [82]. In addition, the location of hubs (with high metabolic cost) coincides tightly with gray matter loss in schizophrenia [42]. The intuitions gained here from a consideration of spatial network embedding offer important directions for future work linking non-invasive imaging phenotypes with invasive biomarkers of neural dysfunction in disease.

Statistics, Null Models, and Generative Models

In the previous sections we outlined developmental rules for efficient wiring, and we discussed the reflections of these rules in spatial patterns of healthy and diseased brain dynamics. Collectively, the studies reviewed motivate the broader use and further development of sophisticated and easily implementable tools for the analysis of the spatial embedding of a network [83]. We outline here the current state of the field in developing effective network statistics, network null models, and generative network models that account for spatial embedding.

Network Statistics

A simple way to examine network architecture in the context of spatial embedding is to incorporate the Euclidean distance of connections into local, mesoscale, and global statistics [82,84]. Arguably the simplest local statistics that remain spatially sensitive are the moments of the distribution of edge lengths in the network. One can also compute graph metrics that have been extended to consider space, such as physical network efficiency and physical edge betweenness [85]. Physical network efficiency uses the physically (rather than topologically) shortest path, then takes the inverse of the harmonic mean of this length, while physical edge betweenness provides the fraction of shortest physical paths between all node pairs that traverse a given edge [86]. One could also define a physical clustering coefficient in a similar manner. Finally, one can assess the system for Rentian scaling as described earlier, providing information on how efficiently the complex network topology has been embedded into the physical space [22,33,34]. In the context of neural systems, these spatially informed graph statistics can be used to account for the physical nature of information processing, propagation, and transmission.

Complementing local and global graph statistics is an assessment of the community structure of a network, a mesoscale property frequently assessed by considering the existence and strength of network modules [87]. From that community structure, one can determine the spatial embedding of communities, for example by assessing their laterality in bilaterally symmetric systems such as the brain [88,89]. One common way to assess community structure is to maximize a modularity quality function, which identifies assortative modules with dense within-module connectivity and sparse between-module connectivity [90] (methods to identify non-assortative communities are given in [91]). Statistically, this algorithm compares the strength of observed connections between two nodes in a community to that expected under a given a null model. The most commonly used null model in this context is the Newman–Girvan or configuration model, which preserves the strength distribution of the network [90]. However, this null model operationalizes a purely topological constraint – the strength distribution – and does not acknowledge any spatial constraints that may exist in the system. For this reason, many investigators across scientific domains have begun to develop alternative null models that account for physical constraints [92–94] on their system of interest.

In the context of brain networks, it is worth considering three distinct null models for modularity maximization that incorporate information about the physical space of the network embedding. First, one can directly incorporate the wiring minimization constraint observed in brain networks by defining a null model with a probability of connection between two nodes that decays exponentially with distance [92] (Figure 3A,B). Using this model, one can detect different and more spatially distributed modules than those obtained when one uses the configuration model [92] (Figure 3C–E). Second, one can employ gravity models [93], which account for the number of connections expected given a specific distance (typically a power law or inverse of distance) weighted by the relative importance of each location (typically a quantification of the population or size of a given location) [93,94]. Third, one can employ radiation models designed to capture the flow of information between regions, by weighting distance functions by the flux or flow of each location [94]. Of course, there exists no single correct null model for community detection that will suit every question in neuroscience. However, we propose that many studies could test tighter and more targeted hypotheses about community structure in brain networks by using a null model that accounts for the spatial nature of the brain.

Network Null Models

When considering a network representation of a neural system, one often computes a statistical quantity of interest and then compares this quantity to that expected in a random

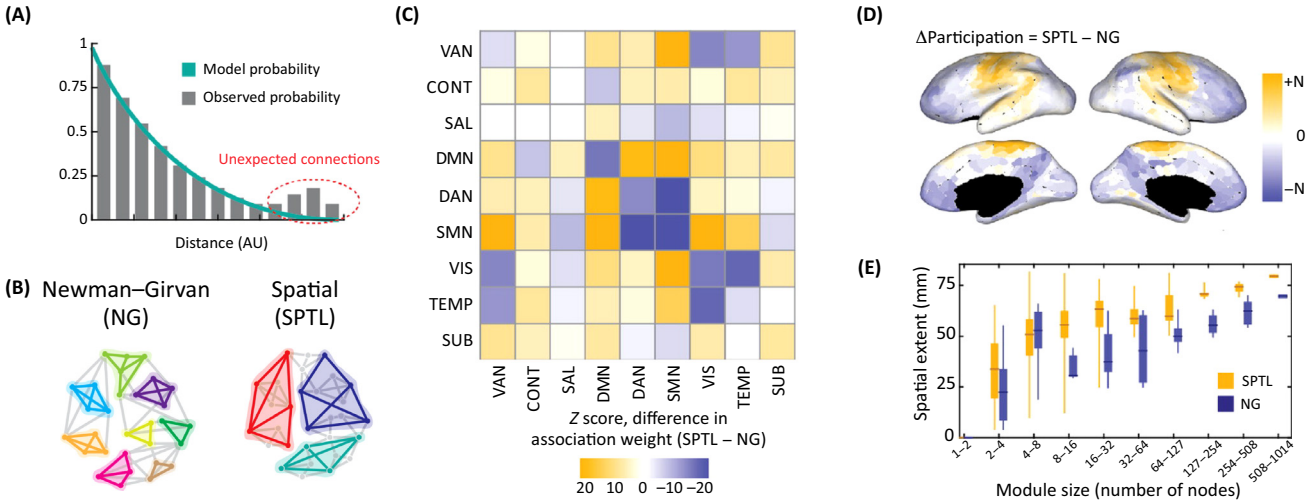

Figure 3. Community Structure Obtained with Spatially Embedded and Non-Embedded Null Models. (A) A schematic of a spatially informed null model. The model expects fewer long-distance connections than short-distance connections. (B) A schematic of the anticipated difference between the spatial (SPTL) null model and the Newman–Girvan (NG) null model; spatial communities will have longer-distance connections and not capture clustering of spatially nearby regions. (C) Differences in the association matrices between the two models. Positive (negative) numbers indicate when two nodes were more likely to be coassigned to the same module under the spatial (SPTL) model. (D) The difference in the participation coefficient between the spatial and NG models. The participation coefficient quantifies how diverse the connections of a node are across modules. (E) The difference in spatial spread of modules in both models; the spatially embedded model tends to produce modules that cover larger distances. Abbreviations: AU, arbitrary unit; CONT, control; DMN, default mode; DAN, dorsal attention; SAL, salience; SMN, somatomotor; SUB, subcortical; TEMP, temporal; VAN, ventral attention; VIS, visual. Adapted, with permission, from [92].

network null model. If the observed quantity is significantly greater or less than that expected, one concludes that the network under study shows meaningful architecture of potential relevance to the biology. Perhaps the most common random network null model is that which randomly permutes the locations of edges in the network while preserving the number of nodes, number of edges, and edge weight distribution. However, one may also be interested to determine whether observed statistics are different from what one would expect simply from the spatial embedding or wiring rules of the network [40,95,96]. To address these questions, one can rewire the observed network by conditionally swapping two links if the swap preserves the mean wiring length of the network [95]. By pairing this model with a reduced null model in which connections are only swapped if they reduce connection length, one can assess the role of long-distance connections in the network, which will be preserved in the spatial null but will not be preserved in the reduced null [95]. In addition to preserving the mean wiring length, one might also wish to preserve the full edge length distribution by, for example, (i) fitting a function to the relationship between the mean and variance of edge weights and their distances, (ii) removing the effect of that relationship from the data, (iii) randomly rewiring the network, and (iv) adding the effect back into the rewired network [40].

To complement insights obtained from edge-swapping algorithms, one can also construct null model networks by stipulating a wiring rule *a priori* while fixing the locations of nodes within the embedded system. In this vein, studies have fruitfully used null models based on minimum spanning tree and greedy triangulation methods [97,98]. A minimum spanning tree is a graph that connects all of the nodes in a network such that the sum of the total edge weights is minimal. To extend this notion to spatial networks, one can preserve the true geographic locations of all nodes in the empirical network and compute the minimum spanning tree on the matrix of Euclidean distances between all node pairs [86]. Representing the opposite extreme is

the greedy triangulation model, which is particularly relevant for the study of empirical networks that are planar (lying along a surface) as opposed to non-planar (lying within a volume). In the context of neural systems, planar or planar-like networks are observed in vasculature, and in thinned models of cortex that consider a single lamina [99]. To construct a greedy triangulation null model, one can preserve the true geographic locations of all nodes in the empirical network and iteratively connect pairs of nodes in ascending order of their distance while ensuring that no edges cross. After constructing such minimally and maximally wired null models, one can calculate relative measures of wiring length, physical efficiency, physical betweenness centrality, and community structure by normalizing the empirical values to those expected at the two extremes [86].

Generative Network Models

Generative network models can be used to test hypotheses about the rules guiding network growth, development, and evolution [100]. Often, an ensemble of generative models are constructed, and summary graph statistics from the empirical network are compared to the statistics of each of the generative models with the goal of inferring which wiring rule was most likely to have produced the observed architecture [11,101,102]. Evidence from such studies suggests that spatially embedded models tend to more accurately reproduce network measures of large-scale neural systems than models that do not account for space [101]. One particularly influential study considered 13 generative models that all incorporated a wiring probability that increased with distance [102]. Consistent with other work, the authors found that the model that only included the wiring minimization constraint was unable to recreate long-distance connections of individual connectomes in humans [7,11,102]. Successive generative models were then added that attempted to recreate some aspects of topology in addition to these geometric constraints [102]. The models that performed the best were those that preserved homophilic attraction such that connections preferentially formed between nodes that had similar connection profiles [102]. Generative models can also be used to determine the implicit geometric structure that would give rise to graphs with specific topological properties [103], and directly assess how the Euclidean space the network is embedded in relates to this geometry. Continued advancement of generative network models, and inclusion of additional biological features such as bilateral symmetry, is an exciting approach to test mechanistic predictions about how network topology forms in spatially embedded neural systems.

Concluding Remarks and Future Directions

The spatial embedding of the brain is an important driver of its connectivity, which in turn directly constrains neural function and by extension behavior. Emerging tools from network science can be used to assess this spatial architecture, thereby allowing investigators to test more specific hypotheses about brain network structure and dynamics. While we envisage that the use of these tools will significantly expand our understanding, it is also important to acknowledge their limitations. In particular, the majority of currently available network tools make the simplifying assumption that all of the relations of interests are strictly dyadic in nature, and exist between inherently separable components [104]. In truth, however, features that arise from spatial embedding can also manifest as continuous or overlapping maps and gradients [57], motivating the use of tools from applied algebraic topology that can account for non-dyadic interactions (Box 2). As the field moves forward, we envisage that existing and yet-to-be-developed tools for characterizing the spatial embedding of brain networks will prove crucial for our understanding of network processes underlying cognition, and of the alterations to those processes that accompany disease (see Outstanding Questions).

Outstanding Questions

How do spatially guided developmental processes constrain the formation of cycles in brain networks?

What are the aspects of connectome topology that remain unexplained by wiring minimization or communication efficiency, and thus may arise from more subtle rules?

How do the structural topologies that arise from physical growth rules support functional gradients?

What is the precise relationship between the invariant features of brain activity and the underlying anatomical structure?

How does the development of the connectome determine the spatial progression of activity through the cortex in health and disease?

To what extent can we link macroscale structural topology with small-scale developmental rules?

Can a deeper understanding of connectome development be used to help to identify new biomarkers for network diseases?

What additional rules can be incorporated into generative models of the brain to recapitulate its topology?

How can frontiers in network science help characterize non-dyadic relationships in the brain?

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