

Computational Models of Typical and Atypical Brain Network Development

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ABSTRACT

Over the last decade, the organization of brain networks at both micro- and macroscales has become a key focus of neuroscientific inquiry. This has revealed fundamental features of brain network organization—small-worldness, modularity, heavy-tailed degree distributions—and has highlighted how these structural features support brain function. However, the driving forces that shape brain networks over the course of development have begun to be explored only recently. Here, we review recent efforts to gain insights into the mechanisms of brain development through generative modeling of both macroscale human brain networks and microscale cellular connectomes in *Caenorhabditis elegans* and other organisms. We show how these mathematical models can begin to shed light on the biological processes that drive and constrain the development of brain networks. Finally, we show how generative network models can translate genetic and environmental differences into variability in developmental trajectories, leading to diverse cognitive and mental health outcomes in children and young people.

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Over the course of a typical pregnancy, the fetal brain grows at an average rate of 250,000 neurons per minute, eventually forming 100 billion neurons, interconnected by hundreds of trillions of synapses (1). Many of these connections are local, but neuronal populations also organize to form white matter fiber bundles, which allow them to connect across large anatomical distances. This white matter growth and maturation can be detected noninvasively using diffusion-weighted magnetic resonance imaging (2), and while major white matter tracts are apparent already in utero, the large-scale connectivity of the human brain is further refined during the first 2 decades of life (3–5).

This protracted developmental period and the sheer number and complexity of processes involved raise two fundamental questions for developmental neuroscience: First, how can the resulting brains be so similar—reliably wired to perform the myriad tasks supporting human cognition? Second, how can the resulting brains be so different—allowing genetic and environmental forces to influence brain architecture and lead to neurodiverse outcomes?

One strategy that may help us begin to address these questions is to consider the brain as a complex network whose nodes represent large-scale anatomical brain regions and whose links represent white matter connections derived from neuroimaging data. Such a network perspective allows us to characterize the organization or architecture of connections between various regions of the brain. Crucially, it also allows us to ask about the mechanisms or driving forces that may shape brain networks into the architectures we observe. In particular, we can seek to identify basic wiring rules based on biological and physical constraints, which determine the probability for any pair of brain regions

to become connected at every point in developmental time (5). Such a network-based, connection-centric view of brain development is likely to be informative for two convergent reasons.

First, we already know that many aspects of cognition in both health and disease depend critically on the large-scale network of interactions between spatially separated populations of neurons (6–10). It is reasonable therefore to ask whether the emergence of cognitive functions during childhood and adolescence is driven by network-level changes that can be captured by simple wiring rules.

Second, networks are ubiquitous across many other domains, from social and transportation networks to protein interactions, as well as the internet. In neuroscience, networks have been used to understand large-scale brain organization (how macroscopic brain regions connect to one another), as well as the microcircuitry of neuronal connections. Strikingly, the application of network science to this broad spectrum of real-world systems has revealed that many of them share key organizational features—from the existence of modules and hub nodes to so-called small-world properties (11). This implies that many insights gleaned from one specific organism will be generalizable and that there is much to be gained by drawing on insights from other disciplines to accelerate progress in developmental neuroscience (12).

In this article, we will review the growing literature on computational modeling of driving forces shaping brain networks into their characteristic topologies at microscopic and especially macroscopic scales. In particular, we will present a rich body of research on generative network models and how they may be built on to understand typical and atypical trajectories of brain development in children and young people.

GENERATIVE NETWORK MODELS

In the context of network science, a generative model is a set of rules that can be used to generate a network with a required set of characteristics (13). The simplest network model is the Erdős-Rényi model, where the wiring rule is simply that each node connects to every other node with a fixed probability p (14). The resulting networks are called random networks because their connections display no structure apart from a characteristic network density that is tuned by the parameter p .

Real-world networks, on the other hand, tend to display some obvious structure, and in the last 2 decades a series of seminal articles have been published that first highlight the ubiquity and functional importance of a particular network feature and then propose simple wiring rules that may give rise to it. For example, Barabasi and Albert (15) observed that many real-world networks have a heavy-tailed degree distribution, where most nodes have just a few connections, but certain so-called hub nodes have a very high degree of connectivity. This deviates sharply from the degree distribution expected for an Erdős-Rényi network, so the authors proposed a new generative model based on the idea of preferential attachment: Each new node added to the network will preferentially attach to preexisting nodes with high degree, therefore increasing their connectivity even further and generating a number of highly connected hub nodes in the final network (15). Preferential attachment has intuitive interpretations in many real-world contexts. For example, in social networks, new individuals joining a community may preferentially link to individuals who are already well connected, reflecting their popularity or various leadership roles they fulfill.

Around the same time, Watts and Strogatz (16) observed that many complex networks exhibit the small-world property of simultaneously having high clustering (where the immediate neighbors of any given node are likely to also be interconnected) and high efficiency [where it only takes a few steps, on average, to traverse the network; see (17)]. Small-world architectures emerge naturally, for example, in situations where nodes tend to form densely connected communities but occasionally form connections between communities also, as is the case in social networks. The authors highlighted that this type of organization is not only ubiquitous—from social networks to the *Caenorhabditis elegans* neural network—but is also of functional relevance, conferring “enhanced signal-propagation speed, computational power, and synchronizability” (16) to the network. Interestingly, Watts and Strogatz (16) also showed that small-worldness emerges easily when starting from a locally connected lattice network and randomly rewiring a small fraction of connections.

Since these seminal articles were published, a number of other models have been proposed to capture individual network properties, such as modularity (18) or the preponderance of short-range connections in spatially embedded networks (19–23). Taken together, this body of work has prepared the ground for more applied uses of generative network models, which seek to quantitatively fit a range of network features observed in a real-world network. In such applied settings, the process for designing generative models can be summarized in the following 5-step recipe (13):

1. Make a list of stylized facts observed in the data.
2. Propose a plausible but parsimonious mechanism that could lead to the emergence of the stylized facts identified in step 1.
3. Fit the parameters of the model and compare with other models.
4. Validate the model on independent data.
5. Think of what the model does not capture, then return to step 1, with this new observation acting as an additional stylized fact.

While these steps are easy to state, in practice both the validity and the utility of a network model will depend on the investigator’s ingenuity in selecting appropriate stylized facts and in proposing a mechanism that strikes an appropriate balance between parsimony and plausibility. In particular, when choosing stylized facts, investigators look for empirical observations (facts) that are stylized in that they capture the broad features (but not necessarily the fine details) of the network. These stylized facts ought to be statistically robust (24), functionally relevant (16), and surprising when compared with appropriate null models (25).

Similar to many other real-world networks, brain networks at both macro- and microscales have hub nodes and a heavy-tailed degree distribution, exhibit high modularity, and are small-world networks with high clustering and high efficiency (11). In addition, the brain is also a spatial network, and as such the distribution of connection lengths is heavily skewed toward short connections (21,26). The challenge then is to capture all these properties simultaneously with relatively simple, parsimonious, and biologically plausible models containing just one or two factors and therefore just one or two free parameters.

ECONOMIC WIRING PRINCIPLES IN HUMAN BRAIN NETWORKS

Ever since Cajal’s work in the 19th century (27), it has been acknowledged that nervous systems are wired in an economical way that does not waste material or energy on unnecessarily long connections. It therefore seems natural to start with a model implementing this simple spatial constraint first. Indeed a number of such models were put forward (19–23,28). For example, in 2004, Kaiser and Hilgetag (28) proposed a generative model where the probability of connecting a new node i to a preexisting node j decreases exponentially with the distance d_{ij} between the 2 nodes:

$$P_{ij} = \beta e^{-\alpha d_{ij}}$$

As the authors pointed out, the distance penalty in this model is not only motivated from an evolutionary perspective but could also easily be implemented biologically, for example through gradients of guidance molecules, which decay exponentially with distance (28). Despite its simplicity, the model is able to capture not only the predominance of short-range connections, but also the high clustering observed empirically in brain networks.

While the model generates networks that are significantly more brainlike than random Erdős-Rényi networks, it is also quite clear that the drive to minimize wiring cost is not the only

constraint relevant in shaping brain networks. Kaiser and Hilgetag (29) also published an elegant study a couple of years later explicitly showing that both the known wiring diagram of the nematode *C. elegans* and the macaque connectome obtained from tract-tracing studies featured more long-range connections than expected if the networks had been optimized purely to preserve wiring. Subsequent articles (30,31) described that both these networks could be rewired to minimize connection cost, but that this would come at the expense of reducing network efficiency—increasing the number of steps it would take to traverse the network. Building on the insights of Watts and Strogatz (16) regarding the key role of a network’s efficiency in its function, several studies showed that the efficiency of human brain networks also correlates with IQ across the population, such that individuals with a higher IQ have, on average, a brain with higher network efficiency (32,33) [but see also (34), which fails to find such a link between functional network efficiency and IQ]. Taken together, these and other studies suggest that brain development may be operating under competing constraints of reducing energy expenditure (by limiting long-range connections) but increasing information processing (for which some long-range connections are beneficial) [see (26) and references therein].

Building on this idea of economic trade-offs in brain wiring, Vértés *et al.* (35) proposed a family of generative models explicitly embodying an economic trade-off between the cost $D_{i,j}$ and value $K_{i,j}$ of forming each connection. As the network grows, the probability of connecting 2 nodes i and j at each time step takes the form:

$$P_{i,j} \propto D_{i,j} K_{i,j}$$

where $D_{i,j}$ represents the cost of the putative connection and is some decreasing function of the distance between nodes i and j and where $K_{i,j}$ represents the value of this connection in terms of network function.

A straightforward extension of the preferential attachment model by Barabasi and Albert (15) suggests for example that the value term $K_{i,j}$ might correspond to the product of the 2 nodes’ degree. However, by fitting these models to large-scale

brain networks, Vértés *et al.* (35) showed that the best-fitting model for the probability of nodes i and j connecting to each other at each time step is:

$$P_{i,j} \propto d_{i,j}^{-\eta} k_{i,j}^{\gamma}$$

where $d_{i,j}$ is the distance between nodes i and j , and $k_{i,j}$ is the number of common neighbors between nodes i and j (Figure 1A). Intuitively, the first term in the model is a distance penalty based on the cost of maintaining long-range connections, and the second term is a bias toward clustering or linking similar regions with a large overlap in their existing connections (35). This second factor $k_{i,j}$ can also be called a homophily factor by analogy to social networks, where 2 people with many friends in common are likely to also become friends, even if they live relatively farther apart. This factor therefore tends to promote the formation of hubs and to connect hubs even if they are far apart.

The model has 2 parameters η and γ , which calibrate the relative importance of the cost and value factors. Fitting parameters η and γ to brain networks derived from neuroimaging data allows the model to simultaneously reproduce the empirically observed degree distribution and distance distribution of connections in human brain networks, as well as their level of clustering, modularity, and efficiency (Figure 1B). Interestingly, the same model also proved to have wide applicability across different modalities, scales, and species. While the model was initially developed in the context of functional brain networks derived from resting-state functional magnetic resonance imaging data, it is arguably more natural to develop generative network models for anatomical brain networks based on diffusion tensor imaging data (36). In 2016, Betzel *et al.* (37) showed that the same model also provides an excellent fit to anatomical brain networks and is outperformed only by a closely related model that includes a normalized version of the homophily term, called matching index. Recent work also found that the same models, trading off connectivity cost versus homophily, provide a good fit to anatomical brain networks in the mouse (38) and even to the formation of functional networks in *in vitro* cortical cultures (39).

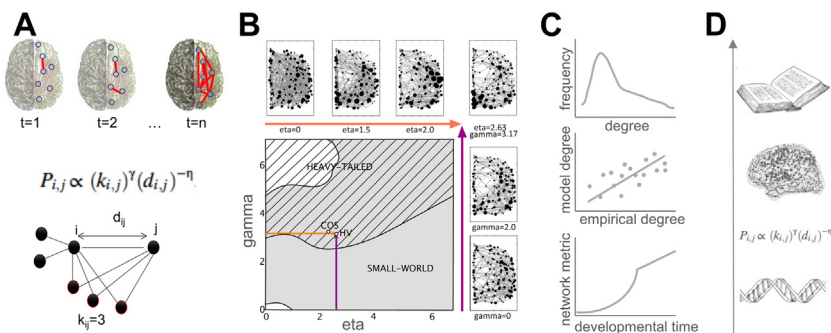


Figure 1. (A) Schematic of the generative network model proposed by Vértés *et al.* (35). Edges are added at successive time steps t (top). The probability of adding a given edge connecting nodes i and j is given by $P_{i,j}$, which is a function of the distance $d_{i,j}$ between the nodes and a function of the number $k_{i,j}$ of neighbors i and j already shared in common (bottom). (B) Phase diagram of the model shown in panel (A). Orange and purple arrows show sections through phase space, varying only η or γ , respectively, while the other parameter is held at its optimal value estimated in healthy volunteers (HV). Schematics of the networks obtained at various points along these sections are also shown. Increasing parameter η results in fewer long-range connections, while increasing parameter γ results in the emergence of hub nodes. The optimal parameters are slightly detuned when fitting the model to brain networks for people with childhood-onset schizophrenia (COS). (C) Schematic representation of 3 families of stylized facts. (Top) The model seeks to capture aspects of the topology of the empirical adult network, such as the degree distribution. (Middle) The model seeks to capture aspects of the topography of the empirical adult network, such as the location of hubs. This can be quantified by correlating the modeled and empirical degree across nodes. (Bottom) The model seeks to capture aspects of network growth, such as how a given network metric varies over developmental time. (D) Generative models can offer a mechanistic link from genetic and environmental factors to altered wiring rules, to varying brain network organization, and to behavioral differences.

As described in step 5 of our recipe, a key part of generative network modeling is to keep designing increasingly accurate models. One approach is to apply the recipe iteratively, identifying features of the empirical network that are not well captured by the best current models and considering these as additional stylized facts for the next iteration. A second, more hypothesis-driven approach is to include additional domain-specific factors, which we expect might improve model fit or explain more complex features of the network. In the next section, we will explore both of these approaches in the context of cellular scale connectomes in *C. elegans* before translating the resulting insights back to human brain network modeling.

LESSONS FROM MODELING CELLULAR-SCALE BRAIN NETWORKS

A striking result in network neuroscience is that the same organizational principles (e.g., modules, hubs, small-world networks) seem to apply across scales and species, from large-scale human brain networks all the way down to the cellular scale of the nematode *C. elegans* (12). It is natural therefore to ask whether the same wiring rules also underpin these diverse networks. *C. elegans* offers a unique opportunity to explore this question, as it is to date the only organism for which a full wiring diagram exists (40,41). In addition, we have access to the birth time of each individual neuron (node) in the network so that we can move from generative network models (which seek to replicate stylized facts about the final, adult network) to growth models (which seek to capture growth curves for specific properties). For example, in 2013, Nicosia *et al.* (42) showed that the growth of the *C. elegans* neural network undergoes a transition from an accelerated to a constant increase in the number of links (synaptic connections) as a function of the number of nodes (neurons) and that this transition happens at the time of hatching. They also found that a trade-off model of the form $P_{i,j} \propto D_{i,j} K_{i,j}$ was again able to provide a close fit to a range of stylized facts (Figure 1C), including 1) aspects of the final network topology, such as distribution of nodal degree, local efficiency, and connection distance; 2) aspects of the final network topography, such as anatomical location of high-degree nodes and connection densities within and between anatomically defined ganglia; and 3) the characteristic shape of the growth curve, switching from accelerated to constant increase in connections as new neurons are born after hatching.

Unsurprisingly, accurately modeling these increasingly sophisticated stylized facts was made possible only by including additional domain knowledge into the model. A first crucial step was to account for the fact that the connection distance between any pair of neurons will be shorter at earlier stages of development, as the worm grows in length. Therefore, $d_{i,j}$ was estimated as the Euclidean distance between neurons i and j at the time of birth of the neurons, as extrapolated based on the worm's elongation during development. This dynamic assessment of connection cost was crucial, especially to matching the shape of the growth curve.

A second novel aspect of this model is that the best-fitting value term $K_{i,j}$ is not a homophily term in this case, but rather a simpler preferential attachment term, such that a newborn neuron j is more likely to connect to an existing node i if it has

higher degree k_i , as defined by the eventual degree of each node in the adult network. From a biological perspective, new neurons might know about the final degree of other neurons if this was genetically predetermined and signaled in some way. This idea is supported by the finding across scales and species that high-degree hub nodes display a shared transcriptomic signature [(43) and references therein]. Such an implicit genomic patterning is likely what allows the model to match the topography of the neural network (i.e., the anatomical location of its eventual hubs and other features).

Recently, a series of articles have asked how these considerations of anatomical growth and genetic patterning translate to human brain networks. While early work on generative models attempted only to match topological characteristics (global clustering, global efficiency, modularity, and degree distribution), more recent work has asked whether the same models also provide good fits for topography (44–46). This can be evaluated by correlating nodal properties (such as degree) between the empirical and synthetic networks to assess, for example, whether high-degree hubs of the synthetic network are located in the correct anatomical regions. Interestingly, these articles reach opposite conclusions, with Arnatkevičiūtė *et al.* (45) reporting no correlation whatsoever, while Akarca *et al.* (44) report moderate correlations both for node degree and for other network properties. Although this is an area of active research, we speculate that the discrepancy may relate to technical differences in parcellation or tractography methods as well as differences in how best-fitting model parameters are estimated and/or in how the network growth is initialized, based on a seed of initial connections (44).

Interestingly, in keeping with the insights from *C. elegans*, Arnatkevičiūtė *et al.* (45) show that moderate fits to network topography can also be recovered by incorporating genetic constraints, effectively replacing the spatial distance penalty in the model by a penalty for connecting regions with dissimilar transcriptomic profiles. Similar results were also obtained by Oldham *et al.* (46), who show that this genetic constraint alone can match or even outperform trade-off models (although based on a different formulation from the trade-off models previously studied). One intriguing possibility is that the genetic patterning of brain regions already includes both a spatial constraint and topographic information, effectively providing a biological implementation of the proposed trade-off between cost and value. This genomic hypothesis is also consistent with recent work showing that the process of cell division sets up a spatial patterning of gene expression profiles across the brain and that this map can be used to efficiently encode axonal routes (47). It is worth noting that preferential connection of regions with similar transcriptomic profiles also aligns with the observation that regions with similar cytoarchitecture (potentially indexed by transcriptomic similarity) tend to preferentially connect (48–50).

Separately, Oldham *et al.* (46) also evaluated the importance of anatomical growth in human brain networks by modeling how the pairwise distance between brain regions increases over developmental time. As with *C. elegans*, they showed that this dynamic treatment of spatial constraints substantially improved model fit across a range of trade-off models taking distance into account. As relevant data become available, it will be interesting to implement a dynamic version of genetic

constraints, taking into account transcriptomic differentiation of brain regions over developmental time. Indeed, it is likely that time-related constraints, similar to spatial ones, might also be genetically encoded.

It is worth noting that, separate from generative modeling, there is a large body of work on computational modeling of brain development (51–58) that explicitly considers biophysical properties and processes such as neurogenesis (51,52), neurite growth (53), or cell division (47). These are not the focus of the current review, but we refer the reader, for example, to recent work comparing detailed mechanistic simulations to generative modeling (57). As with the genomic encoding of spatial constraints described above, it is likely that some of the features used in generative models (such as homophily) can be derived from more biologically detailed ontogenetic simulations (58).

MODELING INDIVIDUAL VARIABILITY IN HUMAN BRAIN NETWORKS

So far we have seen that computational models with just 2 parameters have surprising explanatory power for how the complexity of brain wiring may reliably emerge. However, for these models to become useful accounts of developmental processes in the brain, they will need also to allow for individual variability, and, crucially, they will need to link this variability to genetic and environmental factors.

Vértes *et al.* (35) provided a first indication that this may be possible by showing that many of the abnormal properties of brain functional networks in people with schizophrenia could be captured by the original model $P_{i,j} \propto d_{i,j}^{-\eta} k_{i,j}^{\gamma}$ with only a small detuning of model parameters η and γ (Figure 1B). Subsequently, in the context of anatomical brain networks, Zhang *et al.* (59) showed, that best-fitting parameters η and γ varied between individuals in a way that correlates with polygenic risk for schizophrenia. Most recently, working with *ex vivo* neuroimaging of mouse connectomes, Carozza *et al.* (38) also showed that early life adversity (in the form of a maternal separation paradigm) can influence best-fitting η and γ parameters and thereby shift the constraints that govern the formation of the structural connectome at the level of the individual. Separately, Akarca *et al.* (44) showed that subtle individual variations in best-fitting η and γ parameters were also associated with a range of cognitive scores in a large cohort of children with increased neurodevelopmental risk of poor cognitive outcomes (Figure 2).

Taken together, these studies suggest that both genetic and environmental risk factors can influence the brain's wiring rules

by calibrating the trade-off between connectivity cost and homophily. For example, a slightly lower eta value in some individuals will lead to reduced distance penalty during network growth, such that relatively more long-distance connections are allowed to develop. In turn, the resulting topological differences in the developing brain networks can lead to a diversity of cognitive and behavioral outcomes (Figure 1D).

OUTLOOK AND FUTURE DIRECTIONS

Generative network modeling is uniquely placed to offer a mechanistic explanation for how genetic and environmental factors shape developing brain networks and predispose certain children and young people to mental health and cognitive disorders. Future work in this area will likely focus on exploring in more detail the impact of genetic and other factors on wiring rules. At the same time, models will seek to capture increasingly complex features of brain networks, including features from algebraic topology (60,61) and multiplex representations of brain networks (62). As described above, this work will depend crucially on understanding the methodological factors—from parcellation to model fitting—that influence model performance.

It will also be important to move toward a growth modeling framework and seek to capture the developmental trajectory of brain network organization, as opposed to just the final state. This will likely require adapting our models in at least 3 ways. First, we will need to include time-resolved aspects of brain anatomy [as suggested by (42,46)]. Second, we will need to adapt models to account not only for the creation of binary edges between brain regions but also for the tuning of connection weights that occurs through synaptic pruning and plasticity. Third, we will likely need to allow for some connections to get weaker rather than stronger over time, as pruning is well known to be a key component of early brain development (4). Finally, it is also possible that the parameters or even wiring rules themselves cannot be considered constant over developmental time (37), which would add yet another layer of complexity. Ultimately, as we develop these increasingly sophisticated models of both typical and atypical brain development, these may suggest early interventions to steer network growth away from undesirable states.

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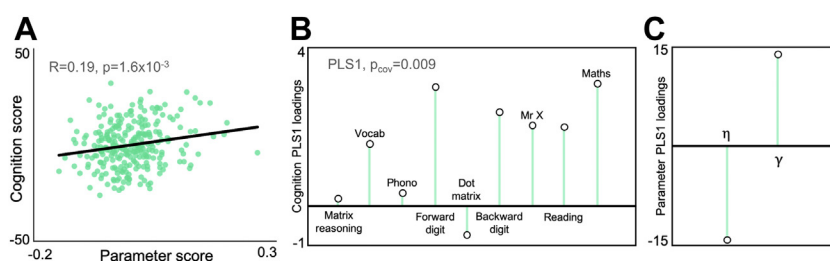


Figure 2. Association between wiring parameters (η and γ) and cognitive outcomes in the CALM (Centre for Attention Learning and Memory) cohort of children ($N = 270$). **(A)** Using a partial least squares regression, Akarca *et al.* (44) identified a linear combination of various markers of cognitive performance in childhood (cognition score), which correlated significantly with a linear combination of the wiring parameters (parameter score) ($r = 0.191$, $p = 1.63 \times 10^{-3}$). **(B)** The loadings or contributions of the 9 individual cognitive tests onto the final parameter score. Large-magnitude wiring parameters (e.g., large negative η values and large positive γ values) are shown to be associated with increased cognitive scores.

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ARTICLE INFORMATION

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