



## Generative models of the human connectome



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### ABSTRACT

The human connectome represents a network map of the brain's wiring diagram and the pattern into which its connections are organized is thought to play an important role in cognitive function. The generative rules that shape the topology of the human connectome remain incompletely understood. Earlier work in model organisms has suggested that wiring rules based on geometric relationships (distance) can account for many but likely not all topological features. Here we systematically explore a family of generative models of the human connectome that yield synthetic networks designed according to different wiring rules combining geometric and a broad range of topological factors. We find that a combination of geometric constraints with a homophilic attachment mechanism can create synthetic networks that closely match many topological characteristics of individual human connectomes, including features that were not included in the optimization of the generative model itself. We use these models to investigate a lifespan dataset and show that, with age, the model parameters undergo progressive changes, suggesting a rebalancing of the generative factors underlying the connectome across the lifespan.

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### Introduction

The human connectome represents a network map of the brain in which regions and inter-regional connections are rendered into the nodes and edges of a graph. In this format, the connectome can be analyzed using tools from network science and graph theory (Bullmore and Sporns, 2009; Sporns, 2014). Network analyses of the connectome have revealed a host of attributes that are likely essential for healthy brain function, including hierarchical and multi-scale modules (Bassett et al., 2010; Betzel et al., 2013), highly connected, highly central hubs (Hagmann et al., 2008; van den Heuvel and Sporns, 2013), and a rich club of mutually connected, high-degree regions (van den Heuvel and Sporns, 2011). Additionally, the connectome's topology (the pattern in which its connections are configured) is thought to play an important role in shaping task-evoked and spontaneous brain activity (Hermundstad et al., 2013; Goñi et al., 2014; Mišić et al., 2015).

The connectome is an example of a physical network whose nodes and edges are embedded in Euclidean space (Barthélemy, 2011). Consequently, the formation of connections carries a material and metabolic cost that increases with connection length (Bullmore and Sporns, 2012). To remain within the limits of viability, the human connectome maintains disproportionately many short-range (i.e. low cost) connections. Despite the importance of conserving connection cost, previous work in model organisms has shown that wiring minimization alone cannot account for all the connectome's topological features (Kaiser and Hilgetag, 2006; Costa et al., 2007a). Rather, connectome networks strike a balance wherein the formation of costly features like hubs and rich clubs trades off with a drive to reduce the total cost of wiring.

The conditions that allow this tradeoff to emerge are the central topic of this paper, and one that we explore using generative models applied to human connectome data obtained from individual participants. In the context of complex networks, generative modeling refers to a set of approaches for creating synthetic networks with properties similar to those of real-world networks. One example among many (Watts and Strogatz, 1998; Kumar et al., 2000; Solé et al., 2002; Vázquez et al., 2003; Dall and Christensen, 2002; Middendorf et al., 2005) is the

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preferential attachment model (Barabási and Albert, 1999), which generates synthetic networks with heavy-tailed degree distributions similar to those observed in many real-world socio-technical networks.

In this report we build upon and expand the tradition of generative models for brain networks by fitting many different generative models to single-subject human connectome data and comparing models in terms of their overall performance. The models we investigate combine two distinct mechanisms for network growth: 1) geometric wiring rules which influence connection formation by favoring either shorter or longer connections and 2) non-geometric rules that ignore the distance between two regions and, instead, form connections on the basis of some shared topological relationship. Some of the models we consider implement rules that mimic well-established growth mechanisms like geometric random graphs, preferential attachment, degree assortativity, and homophilic attraction. In all cases, our aim is to discover wiring rules that produce synthetic networks with properties similar to those of observed connectomes.

To this end, we tuned our models' parameters to generate realistic synthetic networks. We found that the best-fitting model was one that penalized the formation of longer connections while increasing the likelihood of forming connections between brain regions with similar connectivity profiles (homophily). We cross-validated this result, comparing synthetic and observed connectomes along measures other than those used in the optimization process and using three different datasets. Finally, we fit the optimal generative model to data from a lifespan study (with ages ranging from 7 to 85 years) and found that the penalty on long-distance connections weakened monotonically with age. Older subjects' connectomes were fit poorly compared to those of younger individuals, a result driven primarily by an inability to match edge length and clustering coefficient distributions. This suggests that the human connectome undergoes a characteristic reorganization across the lifespan.

## Methods

### Data acquisition and processing

A total of  $N = 40$  healthy participants underwent an MRI session on a 3-T Siemens Trio scanner with a 32-channel head-coil. The magnetization-prepared rapid gradient-echo (MPRAGE) sequence was 1 mm in-plane resolution and 1.2 mm slice thickness. The DSI sequence included 128 diffusion-weighted volumes plus one reference  $b_0$  volume, maximum  $b$ -value of  $8000 \text{ s} \cdot \text{mm}^{-2}$  and  $2.2 \times 2.2 \times 3.0 \text{ mm}$  voxel size. The echo planar imaging (EPI) sequence was 3.3 mm in-plane resolution and 0.3 mm slice thickness with TR of 1920 ms. DSI and MPRAGE data were processed using the Connectome Mapping Toolkit (Daducci et al., 2012). Segmentation of gray and white matter was based on MPRAGE volumes. The cerebral cortex was parcellated into  $n = 219$  ROIs (Cammoun et al., 2012), of which we retained the 108 comprising the right hemisphere. We enforced an average connectome density of  $\rho \approx 10\%$ , resulting in a streamline threshold of 27 streamlines (i.e. a minimum of 27 streamlines must have connected two regions for us to consider the presence of an anatomical connection). These same data have been analyzed elsewhere (Avena-Koenigsberger et al., 2014; Goñi et al., 2014; Betzel et al., 2013).

### Generative algorithm

In this report we construct synthetic networks using a generative model. The algorithm for producing synthetic networks is simple. Starting with a sparse seed network (62 bi-directional edges that were common across all 40 participants), edges were added one at a time over a series of steps until  $M$  total connections were placed (where  $M = 576 \pm 57$  connections across subjects). At each step we allow for the possibility that any pair of unconnected nodes,  $u$  and  $v$ , will be connected. Connections are formed probabilistically, where the relative

probability of connection formation is given by:

$$P(u, v) = E(u, v)^\eta \times K(u, v)^\gamma. \quad (1)$$

In this expression  $E(u, v)$  denotes the Euclidean distance between brain regions  $u$  and  $v$ . The exponent  $\eta$  controls the characteristic connection length. When  $\eta < 0$ , short-range connections are favored, while  $\eta > 0$  increases the probability of forming longer connections. The other term,  $K(u, v)$ , represents an arbitrary non-geometric relationship between nodes  $u$  and  $v$  and the value of  $\gamma$  scales its relative importance. The precise definition of  $K(u, v)$  is flexible and can be varied to realize different wiring rules. For instance, setting  $K(u, v) = k_u k_v$  and  $\gamma > 0$  implements a variant of preferential attachment, wherein higher degree nodes are more likely to become connected. Alternative definitions can be used to implement rules such as degree assortativity (e.g.  $K(u, v) = |k_u - k_v|$ , where nodes with similar/dissimilar numbers of connections preferentially connect to one another) or homophily (e.g.  $K(u, v) = \sum_w a_{uw} a_{vw}$  where connections form between nodes with more or fewer common neighbors). In Table 1 we show a complete list of all non-geometric wiring rules. We limit our analysis to generative models whose wiring rules include only two components, though we could accommodate more components, in principle. We impose this limit in an effort to focus on highly simple, idealized models of network growth.

To prevent cases where  $P(u, v)$  is undefined (e.g. if  $K(u, v) = 0$  and  $\gamma < 0$  then  $P(u, v) = \infty$ , we add  $\epsilon = 10^{-6}$  to each  $K(u, v)$  before raising it to the power,  $\gamma$ ). Over the course of the generative process new edges are added to the synthetic network which necessarily changes the value of  $K(u, v)$ . Accordingly, at each step we update  $K(u, v)$  and the corresponding changes to  $P(u, v)$ . If, at any step, the edge  $\{u, v\}$  is added to the synthetic network, then  $P(u, v) = 0$  for all subsequent steps. See Fig. S14 for an illustration of the model using a toy network model.

In our model we use Euclidean distance as a proxy for the cost of the connection between brain regions  $u$  and  $v$ . It is worth noting that there are alternative measures for quantifying the cost or spatial relatedness of node pairs, including measures derived from the network's spatial embedding (Friedman et al., 2015). Another candidate measure of, perhaps, greater neurobiological interest is fiber length, which measures the actual curved trajectories of white-matter tracts rather than the straight-line (Euclidean) distance between brain region centroids. While Euclidean distance and fiber length are correlated with one another, there are many instances where the fiber length of a connection is much longer than what would be expected given Euclidean distance. A more detailed discussion of this topic can be found in the Appendix (Figs. S10 and S11).

### Evaluating synthetic network fitness

To assess the fitness of a synthetic network we calculated its energy, which measures how dissimilar a synthetic network is to the observed connectome. Intuitively, if the two networks have many properties in common, then the synthetic network's energy is small. Specifically, a synthetic network's energy was defined as:

$$E = \max(KS_k, KS_c, KS_b, KS_e) \quad (2)$$

where the arguments are Kolmogorov–Smirnov statistics which quantify the discrepancy between the synthetic and observed connectomes in terms of their degree ( $k$ ), clustering ( $c$ ), betweenness centrality ( $b$ ), and edge length ( $e$ ) distributions. Here, edge length refers to the Euclidean distance between the centroids of two connected brain regions. By taking the maximum of the four statistics we consider a synthetic network to be only as fit as its greatest discrepancy.

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