Analyzing the Topology of Brain Networks and Modeling Axonal Sprouting Post-Stroke

Amrita Mahesh*. Srivarshini Ganesan**

**BS18B002*

***BE18B020*

Abstract: Axonal sprouting is a process that involves the reinnervation of previously denervated muscle fibers by fine processes from intact axons. Large-scale, widespread axonal sprouting observed after a stroke is known to be an emergent property of brain networks. Brain networks provide information about the connections between anatomical brain regions through fiber tracts. These networks are also known to show properties of small-world networks and high robustness against node failures and targeted attacks. Here, we analyze five different neuron connectivity networks to understand their properties and robustness. These networks show small-world properties and are highly robust to both random failures and targeted attacks on 'hub' nodes. We then model the process of axonal sprouting in the post-stroke cortex, specifically in the macaque cerebral cortex network, to understand how the properties of the networks change after rewiring in the form of sprouting has taken place. We see that artificially inducing lesions affect many network properties. We simulate three different types of axonal sprouting to 'repair' this network. We see that large-scale, unbounded axonal sprouting can potentially aid in recovering some properties of the network. However, the small-world property of the cortical network, which is hypothesized to be crucial in its functioning as an integrator of information, is not recovered by this repair process. Our model of axonal sprouting points to a potential reason why strokes in the brain can be so devastating despite having this extensive repair mechanism.

Keywords: Stroke, Connectivity, Small-world, Network, Cortex, Sprouting

1. INTRODUCTION

One of the most remarkable properties of all biological systems is that they demonstrate emergent behavior at every level of complexity. Whether it is a group of biomolecules functioning together as a cell, a group of cells working together as a tissue, a group of tissues functioning as an organ, or a group of organs operating as a unique organism; at each stage, it is the emergent properties that allow them to sustain life. The brain is a fascinating organ that exhibits the ability to learn, remember, combine all the sensory information and provide the proper response. Even complex properties of the brain, like consciousness, have been shown to be an emergent property(Feinberg and Mallatt, 2020).

These emergent properties are not observed in the individual neurons that make up the brain and, therefore, must arise from the topology of the brain network. Thus, understanding the connectivity between the different anatomical brain regions becomes essential to deciphering emergence(Marconi et al., 2012). Brain networks usually have a small-world topology. Studies have shown that small-world networks have the maximum statistical complexity(Tan and Cheong, 2017), and therefore, the complex brain networks having a small-world architecture is not accidental and, in fact, play a crucial role in its proper functioning.

Small-world architecture enables networks to have both independent specialized modules and integrated information processing, both of which are essential for a brain network(Bassett and Bullmore, 2006). Small-world networks are also robust to perturbations like random node failures or targeted attacks. Following Ramón y Cajal's law of conservation of space, cytoplasm, and conduction time, small world networks allow complex connectivity with minimum wire length(Bullmore and Sporns, 2009).

The importance of the topology in normal brain functioning has been further highlighted by studies on brain networks in Alzheimer's disease, where a loss of the small-world characteristics has been observed(Sanz-Arigita et al., 2010). In another study, a model for Epilepsy was developed by modulating the small-world attributes of a network(Netoff, 2004). In light of these observations, we analyze five brain networks to understand their topology. We also subject these networks to random node failures and targeted attacks to probe their robustness.

Axonal sprouting is another essential property of the brain that involves the reinnervation of previously denervated muscle fibers by fine processes from intact axons(Tam and Gordon, 2009). Axonal sprouting has been observed in various mammals, including mice, primates, and humans. The mechanisms that enable sprouting have been explored in some detail at the molecular level as well as the cellular level. There

are three major kinds of sprouting observed in the brain; reactive, reparative, and unbounded axonal sprouting(Carmichael et al., 2017).

Reactive sprouting is observed around the region of the stroke and is a local response to tissue injury. It is involved in limited recovery after stroke, and this axonal sprouting can be observed even if glial growth inhibitor signaling is increased. Reparative axonal sprouting, on the other hand, occurs over a long distance and tends to connect functionally related areas of the brain. Unbounded axonal sprouting involves increased axonal sprouting that is widespread, aberrant, and involves connections between parts of the brain which may not be functionally related (Carmichael et al. 2017).

1.1 Objectives

The objective of this study is to understand the topology and properties of neuronal networks and analyze their robustness to random and targeted attacks. We also aim to model different types of axonal sprouting as observed in the post-stroke cortex.

We simulate stroke by artificially creating a lesion in the rhesus macaque cortical network and model the three types of axonal sprouting(Alstott et al., 2009). We analyze the changes in network properties when the network is attacked and subsequently 'repaired' by the simulated axonal sprouting.

2. METHODS

2.1 Network Data

The brain networks were obtained from the Network Repository.(Amunts et al., 2013; Rossi and Ahmed, 2015) These were analyzed as undirected networks. Duplicate edges were removed in all the networks. The nodes in these networks represent anatomical regions of the cortex, and the edges represent the fiber tracts connecting these regions. This connectome information was originally obtained using a tracer.

2.2 Network Parameters and Topology

The distribution of the degree and clustering coefficient was plotted using Python. The small world characteristic 'ω' was calculated as defined by Telesford et al. (Telesford et al., 2011)

$$\omega = \frac{L_r}{L} - \frac{c}{c_L}$$

Here,

- L_r is the mean average shortest path length of a large number of Erdos-Renyi networks having the same number of nodes and same average connectivity of the original network
- L is the average shortest path length of the original network
- C is the average clustering coefficient of the network
- C_L is the average clustering coefficient of a regular lattice with the same number of nodes and edges as the original network

2.3 Random and Targeted attacks

Random node failures were modeled by removing nodes and their associated edges at random and checking for the formation of more than one connected component. Targeted attacks were made based on three different measures; degree centrality, betweenness centrality, and closeness centrality. For each of the centrality measures, the node with the highest centrality was successively removed from the network, and the resulting number of connected components and the characteristic path length of the perturbed network were analyzed. A robust network should not disintegrate into multiple components, and the characteristic path length should not increase exponentially upon node removal.

2.4 Visualization

The graph networks were visualized using Gephi software (Bastian et al., 2009) and the nodes were spatially arranged using the Force Atlas Layout.

2.5 Modeling Axonal Sprouting

Axonal sprouting was modeled using the connectome data of the rhesus macaque cerebral cortex. An artificial 'lesion' was introduced into the network to simulate the loss of connectivity brought about by ischemic stroke.

Lesions were formed by removing a selected 'hub' node and then removing a subset of its neighbors as well as its second neighbors (neighbors of neighbors) in order to mimic the large-scale loss of connectivity observed in a stroke. The nodes chosen to generate the lesion were kept constant. The lesion is simulated by removing half of the neighbors of the initial 'core point' from which the stroke originates. In order to model the propagation of loss of connectivity through the network, 25% of the edges from the neighbors of the core point were also removed. The small and large lesions respectively were created by choosing different core points - the large lesion was simulated by removing node 29 with a degree of 87, and the small lesion was simulated by removing node 24 with a degree of 20 (median).

Reactive axonal sprouting was modeled by randomly sampling half of the nodes affected by the lesion and then randomly generating an edge between the affected node and another node that is within a distance that is less than the average calculated path length. Reparative axonal sprouting was modeled by sampling 50% of all the nodes in the network and randomly generating an edge between the sampled node and another node in the network which is at a distance greater than the calculated average path length. This was done to capture the local/short-range and widespread/long-range nature of reactive and reparative axonal sprouting, respectively.

Unbounded axonal sprouting was modeled such that it did not depend on node distance as it is much more widespread than the other two types of sprouting. In this case, all nodes in the network were randomly connected to another node in the network, given that they did not have an already existing edge between them.

3. RESULTS AND DISCUSSION

3.1 The chosen networks demonstrate small-word characteristics

The number of nodes, number of edges, average degree, and small-world parameters of all the five networks are listed in Table 1a and Table 1b.

Table 1a. Summary of the number of nodes and edges of the five brain networks

Network	Number of nodes	Number of edges
Cat brain	65	730
Macaque-cortex1	91	1401
Macaque-brain2	91	528
Macaque-interareal	93	2262
Macaque-brain1	242	3054

Table 2b. Average degree, characteristic path length, average clustering coefficient and small-world parameter for all the five brain networks

Network	Average degree	Charac-teristic path length	Average Clustering coefficient	Small world parameter ω
Cat brain	22	1.699	0.661	0.072
Mac-cortex1	30	1.658	0.743	-0.005
Mac-brain2	12	1.868	0.86	-0.123
Mac-interareal	48	1.471	0.849	0.152
Mac-brain1	25	2.217	0.45	0.272

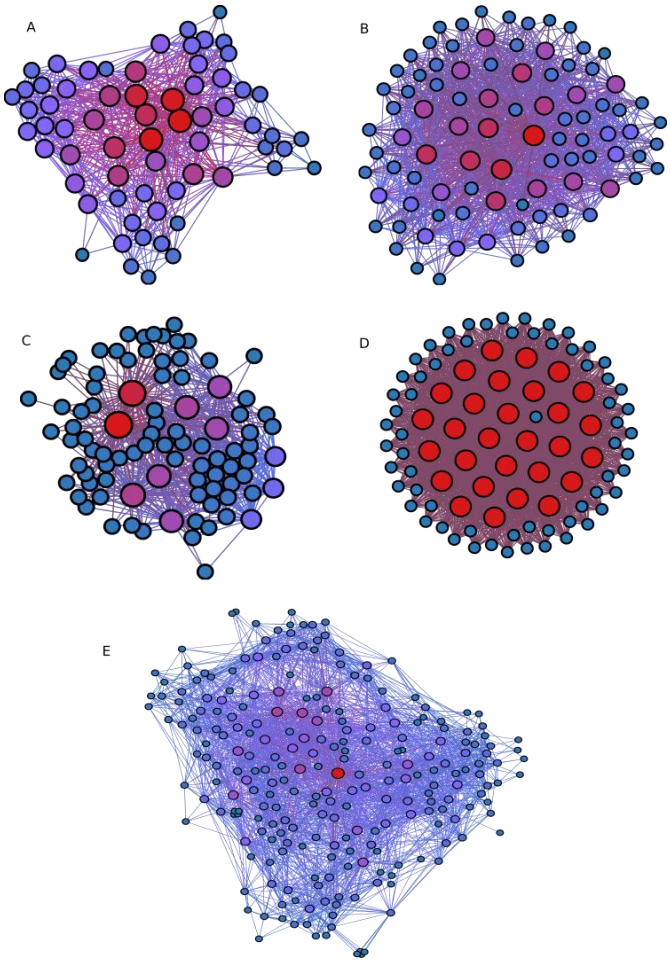

Figure 1: All the networks were visualized in gephi using Force Atlas Layout. The size and the color intensity of each node are proportional to its degree. A) Cat brain, B) Macaque cortex 1, C) Macaque brain 2, D) Macaque interareal, E) Macaque brain 1

The network visualizations are shown in Figure 1. The cat brain network, Macaque-cortex 1, and the Macaque-brain 2 networks have a few nodes with very high degrees (red-colored nodes) and a huge number of nodes with a low degree, which is characteristic of a small-world network. Their power-law degree distributions also reflect this (refer to Figure 2).

The macaque-interareal network is an interesting network where every red node is connected to every other red node and all blue nodes, while each blue node is only connected to all the red nodes. Therefore, the degree of every red node is 92, and the degree of every blue node is 29. Since there are only two unique types of nodes in this network, this network has been excluded from further analysis.

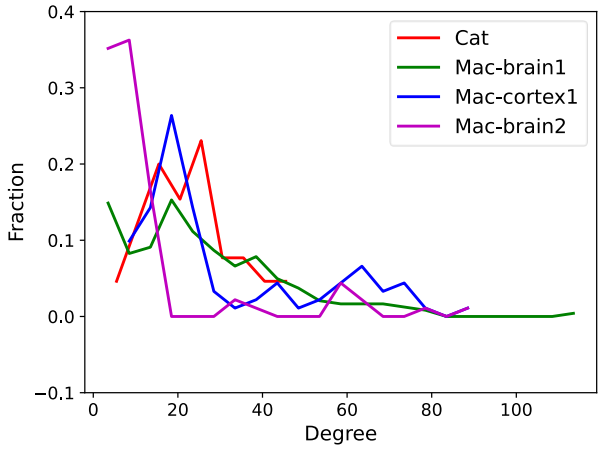

Figure 2: The degree distribution of the networks. The Macaque-cortex1, Macaque-brain2, and Macaque-brain1 networks have a power-law distribution, characteristic of small-world networks.

The Macaque-brain 1 network has a power law degree distribution, but it does not have high clustering (refer Figure 3). Therefore, they were not as robust to targeted attacks as other networks.

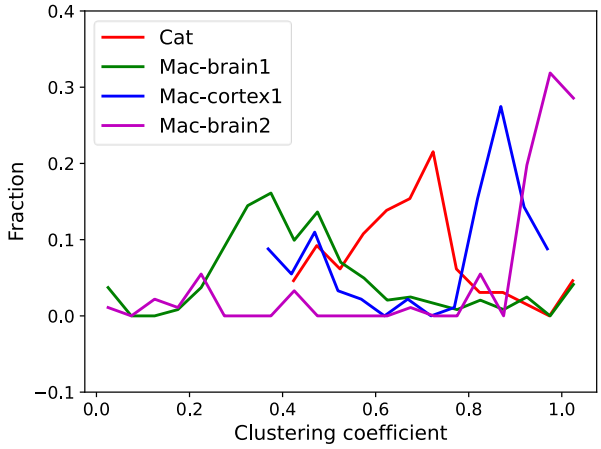

Figure 3: The clustering coefficient distribution of the networks. The Macaque-cortex1 and Macaque-brain2 networks have high clustering, characteristic of small-world networks.

3.2 Macaque-cortex1 and Cat-brain networks are robust to targeted attacks

In Figure 4, we see that the Macaque-cortex-1 and Cat-brain networks are robust to targeted attacks as the networks only disintegrate after a large number of hub nodes have been removed. In both these networks, the average shortest path lengths increase gradually upon removal of hub nodes (refer Figure 5). Therefore, these networks are highly robust to targeted attacks.

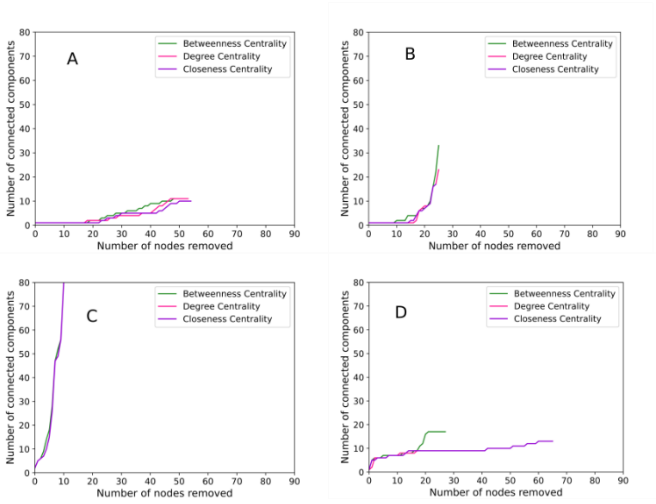

Figure 4:). A) Cat brain, B) Macaque cortex 1, C) Macaque brain 2, D) Macaque brain 1

The number of connected components present when nodes are removed successively based on the highest betweenness centrality (green curves), degree centrality (magenta curves), and closeness centrality (violet curves. The trend was similar for all three centrality measures except in the Macaque-brain-1 network where the removal of nodes with higher betweenness centrality disrupts the network more rapidly compared to the removal of nodes with a high degree or closeness centrality. Macaque-brain-1 and Macaque-brain-2 networks are not very robust to targeted attacks compared to the other two networks.

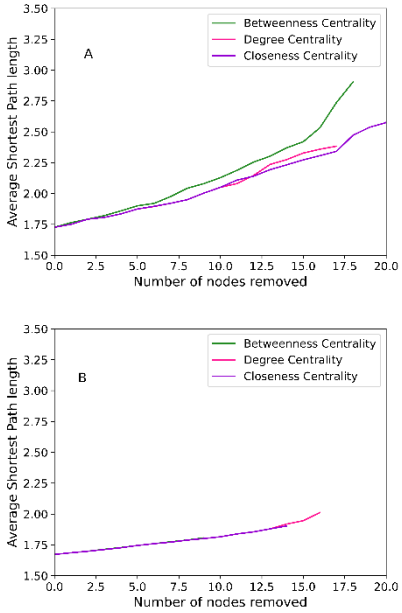

Figure 5: A) Cat brain, B) Macaque cortex 1

The average shortest path length of the network when nodes are removed successively based on the highest betweenness centrality (green curves), degree centrality (magenta curves), and closeness centrality (violet curves). The trend was similar for all three centrality measures. Beyond a certain number of node removals, when the network begins to disintegrate, the average shortest path length of the network cannot be defined anymore. Hence, we have considered only node removals till when the network hasn't disintegrated. Since the Macaque-brain1 and Macaque-brain2 disintegrate instantly upon hub node removal, this analysis could not be done for these networks.

Since the Macaque-cortex1 network has the smallest omega (small-world parameter), a power-law degree distribution, high clustering, and robustness to targeted attacks, we chose this network for modeling axonal sprouting.

3.3 The networks are robust to random attacks

We simulated the effect of random node removals on all the five networks. These networks are highly robust to random attacks (refer to Table 2). The low percentage of nodes in the case of the macaque brain 1 may have been due to the relatively larger number of nodes and edges in the network. Hence, removing even 20% of the nodes was enough to disintegrate the network and create more than one connected component. We see that the rhesus macaque interareal network is the most robust against random node failure.

Table 2. Percentage of nodes that need to be removed (randomly) to disintegrate the network

Network	Percentage of nodes removed
Cat brain	73.09
Macaque-cortex1	84.53
Macaque-brain2	43.39
Macaque-interareal	97.87
Macaque-brain1	20.98

3.4 Simulated lesions lead to a large decrease in small-worldness

The properties of the networks on which lesions were simulated are tabulated in Table 3. Due to the random nature of edge removal, the number of edges removed has not been reported. As expected, the larger lesion causes a larger change in network properties, including average degree, characteristic path length, and omega. In both the small and large lesions, the average degree decreases, the characteristic path length increases and the omega of the network is increased.

Table 3. Average degree, characteristic path length, and small-world parameter for the original network and the networks with small and large lesion

Network	Avg. degree	Char. path length	Omega
Original network	30	1.658	-0.005
Large lesion	23	1.745	0.210
Small lesion	27	1.699	0.171

The change in network properties is expected due to the loss of connectivity observed in strokes. We also see that the large lesion has a bigger impact on network connectivity. These results have been observed in experimental studies where the small-worldness of cortical connectivity networks decreases after stroke(Caliandro et al., 2017).

3.5 Sprouting changes the network properties

The different types of sprouting combined with both small and large lesions give rise to different network properties, summarized in Table 4.

Table 4. Average degree, characteristic path length, and small-world parameter for the networks post reactive, reparative and unbounded sprouting.

Lesion type	Sprouting type	Avg. degree	Char. path length	Omega
Small	Reactive	27	1.694	0.115
Large	Reactive	24	1.733	0.190
Small	Reparative	28	1.687	0.166
Large	Reparative	24	1.738	0.238
Small	Unbounded	29	1.674	0.165
Large	Unbounded	25	1.724	0.254

In both large and small lesions, reactive and reparative sprouting do not cause a large change in average degree from the lesioned network. The network does not appear to recover its original average degree value of 30, except in the case of unbounded sprouting in a network with small lesion, where the average degree goes up to 29.

The value of the characteristic path length follows a similar pattern, where the characteristic path length is at its minimum value when the lesion is small and unbounded axonal sprouting takes place. The small-worldness of the network shows a decreasing trend in the case of large lesions as we move from reactive to reparative and then unbounded sprouting. This is expected as this network has been largely rewired. For the small lesion, the small-worldness is similar for both reparative and unbounded axonal sprouting. The network does not recover its small-world property even after the process of sprouting. It has been hypothesized that the small-world nature of the cortex is crucial to its functioning in integrating various sources of information in the brain - this information is particularly relevant in the observed case as we see that this property cannot be recovered even after extensive axonal sprouting.

4. CONCLUSION

Network topologies are simple yet effective parameters to understand the functioning of the network. They can be used to distinguish networks in normal vs disease conditions. These parameters can be used to build realistic models of the disease condition, which can then help us understand and treat these diseases in a better way.

We observe that even though axonal sprouting occurs in stroke affected brain networks, the small-world properties are not restored and this may explain why stroke is so devastating.

4. LIMITATIONS

In the networks we obtained from the Network Repository, we did not have the information about what anatomical region each node represents. Therefore, we could not correlate hub nodes with their importance in actual brain functioning. We were also not able to target specific anatomical areas while modeling stroke. The lesions were chosen at random for comparison of results, while actual strokes may take place at any location within the brain.

Additionally, the cortical connectivity network has been estimated using anatomy, and this connectivity may not be applicable at the axonal level where sprouting actually occurs. Additionally, estimation of various parameters used to model axonal sprouting is challenging as most studies involve the molecular mechanisms involved in sprouting, and there is very less information available about the specific effect that these types of sprouting have on connectivity.

In this study, we used networks with a relatively small number of nodes. These analyses can be extended to large networks in order to estimate these parameters more accurately.

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Appendix

All the python codes, figures, and data files have been attached in this Drive folder:

Amrita Srivarshini Supplementary files