Mathematical Foundations for Measurement of Communication Efficiency in the Human Brain

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Abstract In this paper we provide a detailed mathematical (graph-theoretical) foundation for our newly developed metric for measurement of efficiency of communication in human brain. The metric is based on the assumption that the structural connectome paths facilitate the functional connectome. Our metric demonstrates that majority of the functional connections in the human brain can be explained by indirect functional paths. This further indicates that information transport in the human brain is a complex process, where multiple regions can participate as intermediary communication nodes.

1 Introduction

The human brain is a complex and dynamic network comprised of structurally connected and functionally interactive elements. These elements are critical for the brain to seamlessly manifest cognition and behaviour and can be measured with

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magnetic resonance imaging (MRI). Functional connectivity (FC) can be viewed as which brain regions utilise oxygenated blood at the same time while performing a specific function. Structural connectivity (SC) can be viewed as how physically connected brain regions are. Current methodologies are yet to mathematically elucidate how and where SC relates to FC within a suitable framework.

A recently introduced model [11] explains how the information is communicated in the brain to facilitate the synchronous activity in distant brain regions. That model relies on mathematical concepts and ideas introduced in [9]. The purpose of this paper is to elaborate on these ideas to provide a full explanation of the mathematical tools that we developed to underpin this model.

Classically, both the physical structure and the functional activity of the brain are represented in the form of graphs in a multilayer network. Each layer is a graph with the same set of nodes, one layer has structural edges and the other functional edges.

Most of the existing research approaches in the application of graph theory to neuroscience adapt existing techniques from other application fields, particularly social networks analysis. These early investigations have yielded interesting insights on how the brain is organised [3, 4]. It was suggested the human brain has small world properties [12], is modularised into distinct areas that perform specific roles [10] and maintains cost-efficient transmission of information [5, 8, 2].

Recent developments consider the structural layer as a transportation or communication network [1]. This makes sense as the general agreement is that communication occurs through neurons (and neuronal populations) from which complex brain functions arise [1]. To extend this idea, we ask: "how does structural connectivity permit the synchronicity of brain regions?" In [11] we proposed that functional synchronicity of brain regions must be facilitated by communication across structural paths.

In this paper, we provide a detailed description of the graph-theoretical machinery we utilised for analysis of SC-FC interaction. The paper is organised as follows. In Section 2 we present the mathematical method and equations for SC-FC interaction analysis. In Section 3 we apply the developed method to the human structural and functional connectome data provided by Human Connectome Project (HCP, `http://www.humanconnectome.org/`). Section 4 provides a brief summary and interpretation for our findings.

2 Mathematical method and equations

The structural and functional brain connectomes, after processing, are represented by two real-valued matrices. The elements of these matrices correspond to either the number of streamlines (in the case of structural connectome) or the synchronicity (in the case of functional connectome) between any two regions of the human brain. The matrices are both symmetric, have the same order, but not the same elements. Each node in the connectome is represented by the same row (or column) index in both matrices. These matrices represent undirected weighted graphs. After applying an appropriate (arbitrary) threshold θ to the matrix values, the matrices are converted into binary adjacency matrices with the element values of 0 and 1 if the original elements were less or equal, or greater than θ, respectively. The adjacency matrices represent undirected unweighted graphs.

We will denote by $A^{[s]}$ and $A^{[f]}$, and $w^{[s]}$ and $w^{[f]}$ the (binary) adjacency matrices for the structural and the functional connectome, and the edge weight matrices for the structural and the functional connectome, respectively. The set of nodes in the connectome is denoted by V, and for a given node in the connectome (that is, a vertex in the graphs), we denote by $d^{[s]}$ or $d^{[f]}$ its degree in the structural or functional layer respectively.

The matrix E represents a matrix whose elements are all 1, of appropriate order, and $\circ$ is the Hadamard (or element-wise) product of matrices.

In the following we present the mathematical formulations for the measures developed in [11].

2.1 Node-clustering (nodewise measure)

First, we define the matrix of direct SC-FC connections as

$$N = \frac{A^{[f]} \circ A^{[s]}}{2} \tag{1}$$

We start by recalling coefficients proposed in [6]. The number of triangles is given by

$$T(k) = \frac{\left(A^{[s]}(A^{[f]} \circ (E - A^{[s]}))A^{[s]}\right)_{kk}}{2}, \tag{2}$$

where the numerator is the number of structural tuples centred on node k closed by an FC edge ($A^{[f]}$), divided by 2 in order to control for the undirected layer. The term $E - A^{[s]}$ limits the FC edges to only those that are not present in the SC layer ($A^{[s]}$). In order to count a three cycle (i.e. triangle), we take only the element kk from the resulting matrix.

Again, we restrict induced paths to where a FC edge $A^{[f]}$ exists without a possible SC edge (i, j) reflected by $(E - A^{[s]})$.

2.2 Weighted edgewise equation

The *weight* of a path ikj is calculated as the minimum weight across its structural edges: $\min(w^{[s]}_{ik}, w^{[s]}_{kj})$. Given two vertices i and j, we propose to consider the path with the largest of the minimum of these path weights (i.e., $\max_{k \in V} \min(w^{[s]}_{ik}, w^{[s]}_{kj})$)

as the one most likely to facilitate communication between the brain regions i and j.

The weight of the maximum throughput triangle and the total throughput of the weighted triangles are then given by:

$$WT_{ij}^{\max} = A_{ij}^{[f]}(1 - A_{ij}^{[s]}) \max_{k \in V} \left(\min(w_{ik}^{[s]}, w_{kj}^{[s]}) \right), \tag{3}$$

$$WT_{ij}^{total} = A_{ij}^{[f]}(1 - A_{ij}^{[s]}) \sum_{k \in V} \left(\min(w_{ik}^{[s]}, w_{kj}^{[s]}) \right). \tag{4}$$

Any triangle containing a functional edge (i, j) and structural edges (i,k) and (k, j) has a structural edge of minimum weight. In line with our analogy of the structural layer being akin to a transportation network, this minimum weight provides the maximum possible throughput from i to j through k on the structural layer. We consider each vertex k in our set of nodes V, i.e. $k \in V$, as a possible intermediary node. Among all possible two-paths, the maximum throughput on paths from i to j considering intermediary nodes k is given by $\max_{k \in V} \left(\min(w_{ik}^{[s]}, w_{kj}^{[s]}) \right)$, while the total throughput is given by $\sum_{k \in V} \left(\min(w_{ik}^{[s]}, w_{kj}^{[s]}) \right)$. Finally, we are only interested in tuples that form a functional edge (i, j) which we count using $A_{ij}^{[f]}$, and excluding cases where there is also a structural edge (i, j) which are removed using the $(1 - A_{ij}^{[s]})$ term.

Note 1. If no intermediary node between vertex i and vertex j exists, then $\min(w_{ik}^{[s]}, w_{kj}^{[s]}) = 0$ for any $k \in V$, therefore $WT_{ij}^{\max} = 0$ and $WT_{ij}^{total} = 0$ (see Fig. 1).

Note 2. The values of $WT_{ij}^{\max}$ and WT_{ij}^{total} are small if every ikj path has low throughput. The value WT_{ij}^{total} is also small if there are few nodes structurally adjacent to both i and j. The values of $WT_{ij}^{\max}$ and WT_{ij}^{total} are large if some ikj path has large throughput (see Fig. 2). For the value WT_{ij}^{total} to be large, there also can be many nodes structurally adjacent to both i and j.

In order to count weighted subgraphs, we first define the summed minimum weight of subgraphs. For a given functional edge (i, j), the summed minimum weight of subgraphs that can be obtained using a structural neighbour k_1 incident to node i and a structural neighbour k_2 incident to node j, is given as follows:

$$S_{ij} = A_{ij}^{[f]}(1 - A_{ij}^{[s]}) \sum_{k_1, k_2 \in V} \min(w_{ik_1}^{s}, w_{k_2 j}^{s}). \tag{5}$$

The quantity S_{ij} can be thought of the total throughput that can be transmitted through both i and j (not necessarily on the same path).

A triangle exists if $k_1 = k_2$. The weighted proportion of subgraphs that are triangles is given by

$$S_{ij}^{prop} = \frac{A_{ij}^{[f]}(1-A_{ij}^{[s]})\sum_{k\in V}\min(w_{ik}^{[s]}, w_{kj}^{[s]})}{A_{ij}^{[f]}(1-A_{ij}^{[s]})\sum_{k_1,k_2\in V}\min(w_{ik_1}^{[s]}, w_{k_2j}^{[s]})} = \frac{WT_{ij}^{total}}{S_{ij}} \quad (6)$$

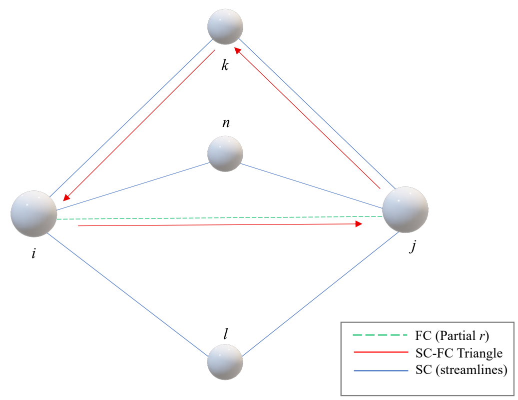

Figure 1: Unweighted triangles cannot consider structural connectivity edge weights that close functionally connected nodes i and j.

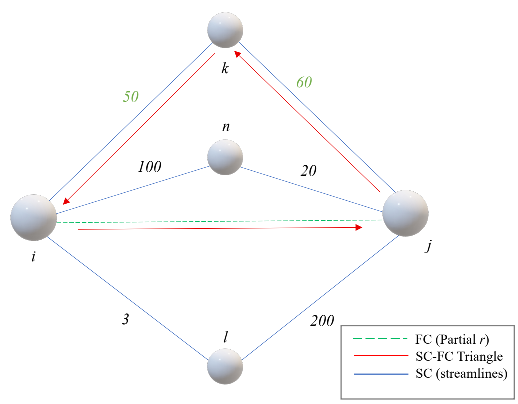

Figure 2: Our method weights structural tuples with the largest *minimum* edge weight facilitating communication between nodes i and j (the edge ik with weight 50).

Generally, if $S_{ij} = 0$, there are no subgraphs of this type, so we set $S_{ij}^{prop} = 0$. In our particular application, since the connectomes form connected graphs (there is no region in the brain that is disconnected from the rest of the brain), $S_{ij} \neq 0$.

Note 3. It is clear that $0 \leq S_{ij}^{prop} \leq 1$. $S_{ij}^{prop} = 0$, if there are no weighted triangles (regardless of whether there are any weighted subgraphs). $S_{ij}^{prop} = 1$, if every weighted subgraph is a triangle.

We now look at the the proportion of weighted induced subgraphs that are triangles.

In a similar way, we can define the ratio of the maximum throughput triangle to the induced subgraph with the highest weight on the function edge (i, j). We set

$$P_{ij} = A_{ij}^{[f]}(1 - A_{ij}^{[s]}) \max_{k_1,k_2 \in V} \min(w_{ik_1}^{[s]}, w_{k_2 j}^{[s]}).$$

The ratio is then defined to be

$$I_{ij}^{prop} = \frac{WT_{ij}^{\max}}{P_{ij}}. \tag{7}$$

P_{ij} can be thought as the maximum throughput that can be "sent" or "received" by both i and j. When $I_{ij}^{prop} = 1$, this means that this maximum throughput is achieved through an existing 2-path between i and j.

As before, we set $I_{ij}^{prop} = 0$ if $P_{ij} = 0$. In our experiments this does not happen.

2.3 Functional edge clustering (edgewise measure)

The *local clustering coefficient* is defined in [6] as:

$$C_k = \frac{\left(A^{[s]}(A^{[f]} \circ (E - A^{[s]}))A^{[s]}\right)_{kk}}{d_k^{[s]}(d_k^{[s]} - 1)(1 - c^{[s]}(k))}. \tag{8}$$

The local clustering coefficient C_k measures the proportion of structural tuples that are closed by an FC edge, out of the total number of structural tuples.

The functional connections between nodes that are not structurally connected are calculated with $A^{[f]} \circ (E - A^{[s]})$. Then the number of such connections where both vertices are adjacent to a node k is given by the numerator.

The number of two-paths centered around node k is given by $d_k^{[s]}(d_k^{[s]} - 1)$. We exclude those that are part of a triangle, using $(1 - c^{[s]}(k))$ where $c^{[s]}(k)$ is the directed clustering coefficient (the number of triangles containing the vertex k) as defined in [7].

While in [6] the main focus is given on a given structural node, here we propose a new measure that focuses on understanding how the synchronicity between two functional nodes is facilitated using structural information.

We start by definition the following quantity:

$$T_{ij} = ((A^{[s]})^2 \circ A^{[f]} \circ (E - A^{[s]}))_{ij}. \tag{9}$$

Here T_{ij} is the number of triangles (i, j, k) in the multiplex, satisfying the conditions:

1. The nodes i and j are functionally (counted by $A^{[f]}$) but not *directly* structurally connected (counted by $(E - A^{[s]})$). That is, we aim to "explain" the functional link between these nodes by looking for possible communication channels in the structural layer.
2. We then count the number of vertices k which are structurally connected to both i and j, indicating that there is a functional route between i and j through k. In other words, we count the number of 2-paths from i to j (counted by $(A^{[s]})^2$). See Figure 1.

To calculate coefficients (proportions) we consider the possibility that a longer structural path may facilitate communication between the functionally connected vertices i and j. An upper bound for the count of such paths is given by

$$(d_i^{[s]} - T_{ij})(d_j^{[s]} - T_{ij})A_{ij}^{[f]}(1 - A_{ij}^{[s]}),$$

that is, the number of neighbours of i that are not adjacent to j multiplied by the number of neighbours of j that are not adjacent to i.

The proportion of structural two-paths that facilitate a functional connection ij is therefore given by:

$$J_{ij}^{prop} = \frac{T_{ij}}{T_{ij} + (d_i^{[s]} - T_{ij})(d_j^{[s]} - T_{ij})A_{ij}^{[f]}(1 - A_{ij}^{[s]})}. \tag{10}$$

Alternatively, we can consider *all* potential structural paths between i and j, regardless of whether the edges could be part of a shorter structural 2-path:

$$R_{ij}^{prop} = \frac{T_{ij}}{d_i^{[s]} d_j^{[s]} A_{ij}^{[f]} (E - A_{ij}^{[s]})}. \tag{11}$$

The proportion of subgraph triangles R_{ij}^{prop} can be calculated by dividing T_{ij} by the total number of possible *triplets* (i.e. a subgraph that contains one neighbour incident to each edge end of a functional edge) reflected by counting all the neighbours of i and j. Again, we restrict this to where a FC edge $A^{[f]}$ exists without a possible SC edge (i, j) reflected by $(E - A^{[s]})$.

3 Application to the brain connectomes

We applied the measures described above (see [11] for details) to the publicly available brain connectome data obtained from Human Connectome Project (HCP, `http://www.humanconnectome.org/`). 484 subjects were included in the dataset. The data are available at three different resolutions, namely 68×68, 114×114 and 219×219 parcels, corresponding to the graph nodes in our analysis. We also generated 484 Watts-Strogatz random graphs of the densities equal to the densities of the structural connectome graphs. Then, we applied the calculation we proposed in the section above to true SC-FC pairs and the simulated connectomes where the structural connectome was replaced by its corresponding Watts-Strogatz random graph. The results of the calculations for 219×219 resolution are shown in Figures 3 and 4. Both figures show that there are nearly 4 times more functional connections, which are facilitated by indirect 2-paths.

The true connectomes had a mean of 1240.61 functional connections (standard deviation 84.66) explained by 1-paths and 4467.39 functional connections (standard deviation 353.68) explained by 2-paths. The Watts-Strogatz simulated connectomes have a mean of 1091.9 functional connections (standard deviation 77.4) explained by 1-paths, and 3393.49 functional connections (standard deviation 402.7) explained by 2-paths.

We also note that the distributions produced by synthetic Watts-Strogatz connectomes are much more symmetric with the real FC-SC connectomes skewed to the higher numbers of the FC edges explained by the given number of paths in the structural connectome.

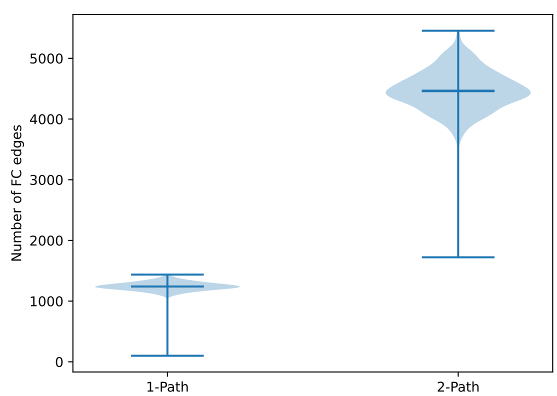

Figure 3: A box plot showing the number of FC edges that are closed by 1- and 2-path lengths for all 484 subjects at 219×219 resolution.

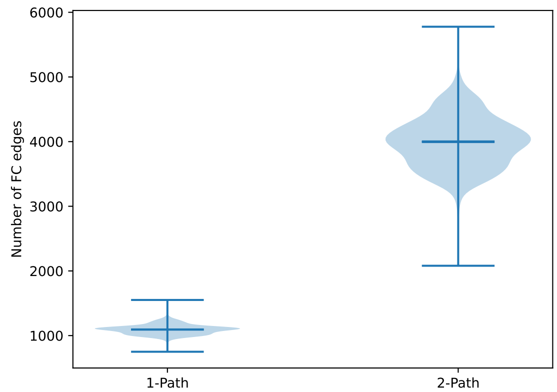

Figure 4: A box plot showing the number of FC edges that are closed by 1- and 2-path lengths in 484 219-node Watts-Strogatz graphs of the same density as the human connectomes considered in this study.

4 Conclusions

In this short paper, we describe a new graph-theoretic method for analysis of the relationship between structural and functional connectomes of the human brain.

The method is based on counting the paths of various lengths in the structural connectome, which are able to provide a physical communication links, which are described by the functional connectome.

We applied our method for the analysis of real human brain and synthetic (Watts-Strogatz) structural connectomes and real functional connectomes. As is evident from the comparison between the true connectomes and the randomly generated structural paths with true functional paths, there are more functional connections in the real brain, which may be facilitated by indirect multiple-node connections in the structural connectome.

We also demonstrate that, according to our introduced measure, Watts-Strogatz graphs exhibit somewhat different statistical properties in comparison to the real brain connectomes.

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