Graph Theoretical Analysis of the Brain. An Overview.

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Introduction

The brain is a highly interconnected network; more precisely it has a complicated structural and functional connectivity among its basic constituents, i.e. neurons, synapses and brain regions.

The human brain is a complex network whose operations depend on how its neurons are linked to each other. When attempting to understand the workings of a complex network, it needs to known how its elements are connected, and how these elements and connections cooperate to generate network functions. The human *connectome* describes the complete set of all neural connections of the human brain.

It is remarkable how substantively different systems share key characteristics that can be identified by specific parameters such as: connectivity, centrality, clustering, modularity (just to mention a few). We are going to describe them in the following sections.

Actually a central goal in Neuroscience is to get an accurate mapping of the human connectome, which describes the complete set of all neural connections of the human brain. In other

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words it defines the network map of the anatomical connections in the human brain (but the concept can be expanded to the animal brain).

But if we aim to focus our interest on brain connectivity, we should introduce besides the connectome, other important concepts such as the *parcellation* and *neural connectivity*. The parcellation is the subdivision of the brain into areas or regions (these areas as we shall see later may be classified as structural or functional). The neural connectivity can be organized in three different typologies that may be correlated: structural, functional and effective connectivity. The structural connectivity may be imaged as the anatomical description of all physical projections between the different cerebral areas as well as neurons; when we talk about projections we mean both the anatomical projections and directed anatomical pathways, and synaptic connections among different neurons. The functional connectivity is strictly related to the activation of different cerebral areas not necessarily anatomically close, it is defined as the statistical dependence between the time series of two network nodes (e.g. brain regions or neurons) [13]. Generally structural and functional connectivity are different and do not coincide apart the resting state network, defined as the set of brain regions showing coherent functional connectivity during task free spontaneous activity. Finally the effective connectivity, which is a special case of functional connectivity and it is defined as the causal interactions between distinct nodes of the cerebral network, i.e. units within a nervous system (for more details we refer the readership to [23]).

Concerning the organization of the cerebral network, Graph analysis enabled important discoveries: the *small-world* and the *scale-free organization*.

The small world organization is a network that has well defined characteristics: high level of clustering or more precisely higher than the one proper of regular networks and an average shortest path length equal to the one observed in random networks. The scale free organization may be viewed as a network whose degree distribution follows a power law function. All these neural architectures will be treated in the following.

There is strong agreement [26] that nervous systems in animals and humans, from the neuronal level up to macroscopic levels, are characterized by a combination of high clustering (a measure of local connectedness) and short path length (indicative of global integration). All these characteristics are proper of small-world networks. In addition, brain networks have a broad degree distribution that is approximately scale-free, with a preponderance of highly connected hub areas that together constitute a “rich club” [23], [24]. This broad degree distribution implies that different nodes of brain networks differ widely from one another in terms of their centrality and connectedness. This fact is really important since subsets of highly connected nodes play a fundamental role in information transmission inside the brain. The role is so important that these subsets of highly connected nodes are referred to as “rich club” [28]. In addition anomalies in rich club organization can be interpreted as an index of the onset or presence of neurological diseases like schizophrenia [31].

The small world architecture well represents the human brain network because this architecture provides a balance between the segregation and integration of parallel information transmission, so in this sense it has been interpreted as an optimal kind of architecture. Specifically, networks with a small-world organization may constitute an optimal solution to all the networks that must be balanced the conflicting constraints of reducing wiring costs and facilitating infor-

mation flow [3], [10].

Generally, hubs and more specifically rich-club components, handle most of the information traffic in brain networks [30]. This should emphasize how important is their detection in a graph theoretical analysis of human connectome. As a practical example, understanding particular neural architectures, as well as hubs and rich-club formation, could be a marker of the onset of neurological diseases (we refer the reader to these interesting papers: [4], [31]). There is an increasing number of papers concerning the application of Graph Theory to the study of brain modeling. In particular, [9], [25] are really a good example of how Graph Theory can give a great help in the study of the human connectome.

This paper is structured into four sections:

1. In section 1 we show the most important concepts, topological and physical metrics used in Graph Theory when applied to Neuroscience.
2. In section 2 the meaning of structural, functional and effective connectivity, as well as the strong and weak points of their analysis, is proposed.
3. Section 3 outlines possible ways of modeling the brain network.
4. In Section 4 conclusions are described.

1. Modeling the connectome by means of Neurobiological Graph

As already mentioned there is an intricate relationship between the structural and functional connectivity of the cerebral cortex [21]. In fact anatomical connections among cortical areas determine their functional connectivity. Conversely, the functional connectivity can shape anatomical connectivity by means of plastic changes that can occur in the brain during development, evolution and traumatic events.

In this section we give some useful notions proper of Graph Theory and largely employed in Neuroscience. With the purpose to be more effective, we split our analysis into four categories: general mathematical concepts (graph, nodes, and edges), topological and physical metrics (path length, efficiency, motifs and modularity, clustering coefficient and centrality, cost, and efficiency), models (small-world and scale-free organization) and finally the matrices of particular interest in neuro graphical analysis.

1.1. General notion on Graphs

A graph is a mathematical representation of a network. It is usually indicated with $G = (V, E)$, where V is the set of *vertices* (also referred to as nodes) and E is the set of *edges*. Any edge consists of a pair of vertices, and can be distinguished according to four different categories: directed, undirected, binary and weighted edges.

An edge is *directed* when its starting vertex and its ending vertex are specified, otherwise it is said to be *undirected*. Whenever it is possible to associate a number (for example a probability) to an edge then this number is called the *weight* of the edge, on the contrary if no weight is associated to an edge then the edge is *binary*.

It is helpful to remark that a node can be associated to a cerebral region or, just to give an experimental example, to the point of the scalp where an electrode is placed during an EEG experiment or to a voxel in a fMRI experiment.

When making research on brain dynamics, and in particular on functional connectivity (cf. subsection 2.2), it is fundamental representing the linear interactions between brain regions. These interactions are based on the *covariance matrix* of the experimental data (obtained for example from an fMRI[1] experiment). This is a typical case of multivariate data analysis. The first step in analyzing multivariate data is computing the mean vector and the *variance-covariance* matrix. The mean vector consists of the means of each variable. The covariance matrix entries equal the variances[2] of the variables along the main diagonal and the covariances between each pair of variables otherwise. Hence, since Graph Theory is largely based on matrix calculation, it is of great help in achieving this goal.

A *subgraph* of a graph is a subset of its vertices together with all the edges connecting members of the subset. In other words, a subgraph of a graph is some smaller portion of that graph.

1.2. Topological and Physical metrics

Recent studies have suggested that human structural and functional brain connection networks can be constructed using multimodal neuroimaging data and that their topological organization can be characterized quantitatively using various graph theory metrics [8], [19].

1.2.1. Path length, average path length, shortest path length

A *path* is a trail in which all vertices (except perhaps the first and last ones) are distinct.

In a binary graph, the path length of a path between nodes i and j is defined as the number $l_{i,j}$ of edges. The shortest path length is the distance between nodes i and i. The *shortest path length* is the distance between nodes i and j.

The *average path length*, l, also known as *characteristic path length*, is the average among the shortest path lengths, averaged over all pairs of nodes. This provides a measure of the extent of overall communication efficiency of a network. The average path length can be short, for example in the case of random and/or complex networks, or long, in the case of regular lattices. In case the network has nodal pairs without connecting paths the *harmonic mean* is exploited, namely, the reciprocal of the average of the reciprocals [17].

[1] fMRI is the acronym of functional Magnetic Resonance Imaging. fMRI measures the hemodynamic signals, which are only indirectly related to neural activity. This technique allows the reconstruction of spatially localized signals with millimetric resolution. In particular the measures are based on the contrast between the magnetic susceptibility of oxygenated hemoglobin and deoxygenated hemoglobin in each volume element (called voxel).

[2] Given two vectors X and Y, representing two variables (e.g. two sets of measures), the variance of X is defined as $s^2 = \sum_{i=1}^{N} \frac{(X_i - \bar{X})^2}{N-1}$, where $\bar{X}$ is the mean of the X. The formula for computing the covariance of the variables X and Y is $COV(X, Y) = \sum_{i=1}^{N} \frac{(X_i - \bar{X})(Y_i - \bar{Y})}{N-1}$, with $\bar{X}$ and $\bar{Y}$ denoting the means of X and Y, respectively.

1.2.2. Motifs and modules

Motifs are the "basic structures" [20] that repeats in a graph. Said differently, motifs are connected subgraphs whose periodical displacement can generate the whole network that, consequently, can be represented by composing the basic structures, for instance triangles pr more complex subgraphs, exactly like in a jigsaw puzzle.

We think that the study of motifs in neurobiological analysis will play an important role. This fact is supported by the observation that complex brains have developed a highly efficient network architecture whose structural connectivity 2.1 is capable of generating a large repertoire of functional states, which are dependent by functional connectivity 2.2. Hence, a first interesting step in cerebral brain network analysis is to detect possible characteristic network building blocks (called *structural* and *functional motifs*) in neuroanatomical data sets. A second step is to identify, if possible, a set of structural motifs that occur in significantly increased numbers. Hopefully, this set should be as small as possible in order that it is mathematically relevant.

Sporn and Kotter [20] suggested the hypothesis that brain networks maximize both the number and the diversity of *functional motifs*, while the repertoire of *structural motifs* remains small. Using functional motif number as a cost function in an optimization algorithm, they obtained network topologies that resemble real brain networks across a broad spectrum of measures, including the attributes proper of small-world organization 1.3.1. These results are consistent with the hypothesis that highly evolved neural architectures are organized to maximize functional repertoires and to support highly efficient integration of information.

The *modules* [18] are subgraphs consisting of sets of vertices that are more strongly connected to each other than to the rest of the network. Identifying modules inside a graph is really important, since they play an important role in local information transfer. More modules can or cannot communicate by means of connections (edges) so they influence different functional aspects of the network, and are responsible of the normal and abnormal activity through the network.

It was shown [18] that modularity can be expressed in terms of the eigenvectors of a characteristic matrix for the network, called modularity matrix. This process leads to a spectral algorithm for community detection that provides results of high quality in short running times.

In case of it is also possible to define modules within modules, in this case the network is said to have a *hierarchical modularity*.

1.2.3. Clustering Coefficient and centrality

The *clustering coefficient* of a vertex is a local concept. It refers to a single vertex and is defined as the probability that the neighbors of this vertex (all other vertices to which it is connected by an edge) are also connected to each other. Since the clustering coefficient of a vertex is a probability, it assumes real values ranging between 0 and 1.

The clustering coefficient is considered to be a measure of the local connectivity or "cliqueness" of a graph (for more detail about "cliqueness" we refer the readership to [6]).

At a global level it is necessary to deal with the *average clustering coefficient* C. It refers to the whole network, and it is defined as the average of the clustering coefficients of all individual vertices.

We remark that the clustering coefficient, motifs and modules are descriptions of network structure at increasingly larger scales.

High clustering is associated with robustness of a network that is resilience against random network damages. If a given vertex shows a high-degree *centrality*, i.e. if it maintains numerous connections with other nodes in the graph, then the vertex is called "hub" [22]. In other words a hub is a node that occupies a central position inside the network.

There are several metrics/measures to identify centrality, but none of them is unquestionable to select a hub. Here are a few:
The *node degree*, k, is the number of edge attached to a single node. Highly connected nodes have large node degree. The node degree distribution represents the probability of a given node degree over all node degrees in the network.

It is evident that the clustering coefficient of a vertex is strictly linked to the degree of that vertex. The question is to determine the likelihood that a vertex has a degree k, which, statistically speaking is a Bayesian distribution $P(V, E|k)$. The degree is a global measure of a graph. While for a random graph the corresponding degree distribution is a Binomial, many complex networks show other degree distributions.

Concerning the degree distribution, there are two interesting opposite examples: regular and random graphs.

A *regular* graph is a graph where each vertex has the same number of neighbors; i.e. every vertex has the same degree.

Conversely, a *random* graph is obtained when, starting with a set of N isolated nodes, successive edges between them are added at random. Alternatively, every edge occurs independently with probability p, and the distribution of degrees k follows a binomial distribution [17], namely:

$$P(k) = \binom{N}{k} p^k (1-p)^{N-k}. \tag{1}$$

Notably, if N is large then the distribution is Poissonian. In this case, if we denote by z, the average number of edges to which each of the N nodes is connected, the Poissonian distribution takes the form:

$$P(k) \simeq \frac{z^k \exp(-z)}{k!}, \tag{2}$$

where $k!$ is the factorial of the degree k.

We remark that, from a neurobiological point of view, these distributions laws do not involve a dynamical approach, i.e. the variable time is not taken into account; rather the approach is

quantitative and discrete (for instance, the sample could be a set of subjects).

Regular and random graphs are very important to define the small-world model.

Closeness centrality and centrality. *Closeness centrality* is based on the length of the average shortest path between a node and all nodes in the graph. It can be identified as the inverse of the sum of all length paths joining to arbitrary nodes:

$$C_c(i) = \frac{1}{\sum_{j=1}^{n} l_{i,j}}. \tag{3}$$

The *Normalized Closeness Centrality* is also employed, namely:

$$C_c^{'}(i) = \frac{C_c(i)}{N-1}, \tag{4}$$

where N is the total number of nodes of the graph (or of a sub-graph).

Betweenness centrality. The basic intuition on which *betweenness centrality* rests is that a node is central, if it is between many pairs of other nodes (see also [2]).

More formally, betweenness centrality B_C counts the fraction of shortest paths going through a given node with respect to the total number of shortest paths from the starting node to the ending one [7]. In a mathematical way, said i an arbitrary node belonging to a graph G, B_C of the node i is given by:

$$B_C(i) = \sum_{j \neq k \neq i \in G} \frac{\sigma_{j,k}(i)}{\sigma_{j,k}}, \tag{5}$$

where $\sigma_{j,k}(i)$ is the number of geodesic[3] paths connecting node j and k with the constrain to pass through node i and $\sigma_{j,k}$ is the number of geodesic path between the node j and k.

1.2.4. Cost

The simplest estimator of the physical *cost of a network* is the connection density, which is the actual number of edges in the graph as a proportion of the total number of possible edges. The cost is threshold-dependent [16], [1], the threshold plays a fundamental role in determining the adjacency matrix (see subsection 1.4). Thus, it is possible to represent various measures of network organization within each group as a function of cost and to compare topological and anatomical properties of the graphs between groups while ensuring that the number of edges is the same for each group over the range of considered thresholds [5].

1.2.5. Efficiency

In Graph Theory the efficiency of a network is a measure of how efficiently it exchanges information [16]. There are two kinds of efficiency: global and local.

[3]For any two vertices j and k in a graph G, the distance between j and k is defined to be the length of the shortest path between j and k. generally it is denoted $d(j,k)$.

Global efficiency. The *global efficiency* is related to global topological metrics, in particular it is defined as the inverse of the average shortest path length.

$$E_{glob} = \frac{1}{N(N-1)} \sum_{i,j \in N, i \neq j} \frac{1}{d_{i,j}}. \tag{6}$$

This means that random and complex networks have high global efficiency of parallel information transfer. On the contrary the efficiency is low for regular lattices.

It is useful to note that a shorter distance means higher routing efficiency because information is exchanged via fewer steps.

Local efficiency. Differently from the global efficiency, the *local efficiency* is related to segregation. This means that it regards sub-graphs rather than graphs.

The Local efficiency is the mean of the efficiencies of all subgraphs G_i of neighbors of each of the vertices of the graph. In particular, the local efficiency of a vertex is the inverse of the average shortest path connecting all neighbors of that vertex.

The average local efficiency E_{loc} is given by:

$$E_{loc} = \frac{1}{N} \sum_{i \in N} E\left(G_i\right), \tag{7}$$

where $E(G_i)$ is the efficiency of $i - th$ subgraph G_i of neighbors of each of the vertices of the graph.

1.3. Models

Basically there are two relevant models in neuro-graphical theoretical analysis, namely small-world and scale-free networks.

These models are especially important in the study of functional connectivity. For example, an interesting survey on small-world and scale-free organization in the special case of resting-state functional connectivity in the human brain was led by van den Heuvel et al. [27].

1.3.1. Small-world

The small-world was firstly introduced by Watts and Strogatz [33]. It is an important model to characterize the organization principles that govern a remarkable variety of complex networks, such as social, economic, and biological. In details, the small-world is a network with specific characteristics: high local clustering (high clustering coefficient C compared to the clustering of a comparable random graph C_R), and low minimum path length between any pair of nodes (short characteristic path length $\bar{l}$, i.e. comparable with the one of a random network $\bar{l}_R$).
If we introduce a scalar σ, defined as: $\sigma = \frac{\frac{C}{C_R}}{\frac{\bar{l}}{\bar{l}_R}}$, then the small-world is characterized by having $\sigma > 1$.

In short, small-world is a topological organization mostly structured with a few random connections.

It is worthy to note that the Watts and Strogatz model fails to explain other important properties of natural networks such as modularity and broad degree distributions with hub like nodes. As an improvement was necessary, Barabási and Albert the scale-free model that, in the writers' opinion, should be viewed as integration of the small-world network.

Several scientists such as Bullmore [8], Sporns [23], Stam [26] agree about the nervous systems in animals and humans, from the neuronal level up to macroscopic levels, is characterized by a small-world architecture.

It is important clarify a point regarding small world organization: in subsection 1.2.1 we talked about the average shortest path length, but what about the longer paths (we mean path longer compared to the average path length)? Are they important? The answer is yes, despite the fact they demand a high cost (in terms of energy). It is assumed that a small number of long-distance shortcuts exist among locally connected nodes. A first approach states that these shortcuts are randomly placed within the network's architecture but there are other conjectures, in hub modeling, that suggest that these shortcuts aggregate hub nodes [29], so improving the global efficiency.

1.3.2. Scale-free organization

Most networks in the real world, however, have very different degree distributions. Most are highly right-skewed, meaning that a large majority of nodes have low degree, if compared with the degrees of a small number of hubs.

Some networks, notably the brain, the World Wide Web, and some social networks are found to have degree distributions that approximately follow a power law: $P(k) \sim k^{\gamma}$, where k is the degree and γ is a scaling constant. This power law distribution reflects the presence of large number of highly connected nodes or hubs. Such networks are called scale-free networks and have attracted particular attention for their structural and dynamical properties.

Basically, the scale-free model, as suggested by the name, is a model of a growing network. In this model an initial number of vertices, each of which has a particular degree k, is fixed. Then as a second step a new vertex is added, and it is connected to existing vertices with a probability that depends upon the degree of that node. This procedure is repeated, and each step is a iteration: at any iteration a new vertex, with a connection probability function of its degree, is added. So, the more the nodes have a high degree the more likely to receive more connections, increasing their degree even further. This is known in literature as preferential attachment. The most interesting feature of the model is the shape of its degree distribution.

Scale-free networks explain pretty well the presence of hubs in networks, and suggest how a hub may form. However, even scale-free model has weak points/limitations: this model is able to explain very well neither clustering nor modules.

Scale-free networks are very resistant to random errors, but quite sensitive to targeted attacks, this could be shown by using the efficiency [11].

In Neurobiology these models are very important. For example, van den Heuvel et al. [27] led a voxel-based study giving information about a possible scale-free organization of functional connectivity in the human brain.

Graph characteristics from these connectivity networks were computed. They found that the clustering-coefficient of these networks turned out to be much higher than the clustering-coefficient of comparable random graphs, together with a short average path length, indicating a small-world organization. Furthermore, the connectivity distribution of the number of inter-voxel connections followed a power-law scaling with an exponent close to 2, suggesting a scale-free network topology.
This points out a kind of combination between small-world and scale-free organization of the functionally connected human brain. The result is interpreted as evidence for a highly efficient organization of the functionally connected brain, where voxels are mostly connected with their direct neighbors. This implies that clustered sub-networks can be highlighted, which are held together by a small number of strongly connected hub-voxels that ensure a deep level of overall connectivity.

1.4. Most important matrices in Neuroscientific Graph Theory

In order to studying structural and functional brain networks, it is fundamental to handle with important matrices and follow a sequence of steps to create them.

First, it needs to define the network nodes.
Second, generate an *association* matrix (also known as connection matrix), i.e. a matrix to establish the interrelationships between nodes to determine all possible pairwise associations between them.
Third, fix strategies for thresholding association matrices, generally the threshold is represented by a cost to get a graph.
Four, produce an *adjacency* binary matrix A, where an entry a_{ij} is 1 or 0 depending, respectively, if, according to the selected threshold, there is an edge between the corresponding nodes i and j or there is not. For undirected graph adjacency matrix is symmetrical.

2. Graph Theory applied to Neuroscience: Analyzing a connectome

In the last section we introduced the main concepts and tools concerning Graph Theory. One question could arise in reader's mind: why Graph Theory is so important in Neuroscience? The answer is that research in this field is centered around questions of how to relate brain functioning to parameters characterizing brain connectivity both in healthy people and in patient affected by neuropathologies. Graph Theory is a perfect candidate in succeeding this challenge, just think about that there are studies claiming that certain brain abnormalities and disorders, like schizophrenia and autism, may be a result of an altered connectivity between brain regions [10]. This altered connectivity could be traduced in changing in topological and physical metrics.

Analyzing the connectome, and its related issues, demands to know three categories of connectivity: structural, functional and effective [23].

Up to now we have detailed information at the cellular level, but there is still much to do at mesoscopic and macroscopic level. In particular we aim to understand how different brain areas are interconnected not only structurally, i.e. anatomically, but also at the functional level, meaning with this term the activity of various brain areas statistically correlated as a result of a stimulus.

The main characteristics of structural, functional and effective connectivity are going to be shown in the following. Then some points of attention in using graphical analysis are pointed out.

2.1. Structural connectivity

Structural connectivity, also called, *anatomical connectivity* pertains to the anatomical connection between brain areas. It forms the connectome [21] through synaptic contacts between neighboring neurons or fiber tracks connecting neuronal ensembles in spatially distant brain regions. These cerebral pathways, i.e. the whole set of such fiber tracks, are called *white matter*. On short time scales (sec, min), anatomical connections are quite persistent and stable, while for longer time spans substantial plasticity may be observed [15].

At present the relationship between anatomical connectivity and functional (and effective) connectivity is not fully understood. However, studies have been undertaken to bridge the gap between these types of connectivity analysis. These efforts have been made possible mainly thanks to the employ of new techniques such as diffusion tensor imaging (DTI) which allow tracking fibers constituting the structural connectivity and form the neuronal basis for functional correlations.

2.2. Functional connectivity

Friston [13] defined the *functional connectivity* as the temporal dependency of neuronal activation patterns of anatomically separated brain regions.

Basically, functional connectivity refers to statistical dependencies between distinct and (even) distant regions (in an Euclidean sense) of information processing neuronal populations. Hence, it is a statistical concept which relies on statistical measures, such as correlation, covariance, spectral coherence, or phase locking. In this regard it is worthy to recall that statistical dependencies are highly time dependent, and fluctuate on multiple time scales ranging form milliseconds to seconds.

We would like to emphasize that functional connectivity (as well as effective connectivity) cannot be derived from direct measures but, rather, it can be inferred from statistical measures and analysis.

Modeling the functional networks is one of the most interesting topics of research in cerebral network analysis [32].

2.3. Effective connectivity

In addition to functional connectivity Friston [13] also defined the *effective connectivity*, which is a special kind of functional connectivity. In detail, effective connectivity describes the influence that one neuronal system or a brain region exerts upon another.

This clearly results in reflecting causal interactions between activated brain areas. In this case direction plays an important role; in fact direction gives information on which regions influence others. From an experimental point of view statistical causality can be inferred from network perturbations or time series analysis. Techniques based on network perturbations generally need

structural information as input, while TSA-based techniques, like Granger causality, may be considered model-free [15].

Both functional and effective connectivity refer to abstract concepts with no immediate connection to anatomical connectivity which physically mediates such correlations.

2.4. Some points of attention in studying connectome by means of Graph Theory

When applying Graph Theory to the study of brain connectivity some points of attention should be considered in the analysis.

2.4.1. Nodes position

One problem with Graph Theory analysis is that network mapping is heavily influenced by a priori choice of brain regions and connectivity (i.e. position of nodes and edges). Hence, the choice of the brain atlas during data elaboration is critical.

As a consequence it is useful to consider all the characteristics that a macroscopic map should ideally possess. Actually there are no specific macroscopic criteria for delineating the brain into anatomically, functionally and biologically meaningful valid nodes. Basically, up to date, the choice of node positions is empirical. Moreover we should consider that this constraint is also a consequence of the limited spatial and temporal resolution of current (imaging) measure technologies.

There are different ways to define nodes in studying the connectomics by means of imaging techniques. Fornito et al. [12] show, in an effective way, strong and weak points of these different approaches. In short, they selected four different categories to define nodes in imaging connectomic[4] (for more details we refer the reader to the above cited paper).

1. Anatomical
In this case Node definition is based on a priori anatomical information, i.e. an anatomical brain atlas (such as Montreal Neurological Institute and Talairach-Tournoux Atlas).
Its strong points are: rapid and intuitive parcellation; low computational burden; high reliability.
Its weak points are: low resolution; likely low validity; large variations in node size.

2. Random
This way consists in randomly parceling the brain into discrete nodes of similar size, and at varying resolutions.
Its strong points are: minimizes node size variations; multi-resolution (i.e. an analysis connected with the study of wavelets).
Its weak points are: unclear validity/reliability.

3. Functional
Here the node definition rests on a priori functional information, such as coordinates of peak

[4]Connectomics is the production and study of connectomes, i.e. comprehensive maps of connections within an organism's nervous system, typically its brain. The ultimate goal of connectomics is to map the human brain. For example, this can be done by means of imaging survey techniques; in this case we talk of imaging connectomics.

activations or meta-analytic results.
Its strong points are: strong validity, given research hypotheses; good reliability; equal node sizes.
Its weak points are: definitions are data-specific; difficult to apply to diffusion data; may miss some regions; definitions based on activation criteria may be unrelated to connectivity.

4. Voxel-based
In this last case each image voxel represents a distinct node.
Its strong points are: data-driven [5]; good reliability; high resolution.
Its weak points are: unclear validity; computationally intensive; risk of spurious short-range connectivity due to partial volume/smoothing effects [6].

In the light of what written it is clear that there is a gap between the "ideal" map of connectome and what represents the best practice within the constraints of available neuroimaging techniques [12].

2.4.2. Resolution

Another problem that may arise is that the brain regions of interest are somewhat constrained by the size of the voxels. Hence, for example in experiments involving fMRI, which uses voxels that are few millimeters cubed, the brain regions will have to be defined on a larger scale. Two of the statistical methods that are commonly applied to network analysis can work on the single voxel space scale, but graph theory methods are extremely sensitive to the way nodes are defined with.

The resolution is really a focal point. The reader could think that the best resolution is at the level of the neuron, but there is no evidence that this would be the optimal choice to understand the brain structure and function. It should be taken into account that brain connectivity and brain dynamics are organized across multiple spatio-temporal scales (see for example [14]). Hence, there is not an optimal choice of the scale and this is an additional difficulty in fixing the position of nodes. For example fMRI data have spatial resolution of *millimeters* or *centimeters* and a temporal resolution in the order of *milliseconds* (in the best case) or *minutes* (in the worst case) and this is a critical point to consider when deciding to fix nodes.

3. Possible ways to generate Complex Brain Network models

There are several toolboxes which are devoted to compute graph metrics and indices from connectivity matrices. The following toolboxes can be downloaded for free:

- Gephi. Gephi is an interactive visualization and exploration platform for all kinds of networks and complex systems, dynamic and hierarchical graphs. Runs on Windows, Linux and Mac OS X. Gephi is open-source. `http://gephi.github.io/`

[5] Data driven means that progress in an activity is compelled by data, rather than by intuition or personal experience.
[6] The partial volume effect can be defined as the loss of apparent activity in small objects or regions because of the limited resolution of the imaging system. Spatial smoothing means that data points are averaged with their neighbors.

- Cytoscape. Cytoscape is an open source software platform for complex network analysis and visualization. Its features for data integration, analysis, and visualization and apps are based on *Java*^{TM} technology. `http://www.cytoscape.org/`
- The Brain Connectivity Toolbox (BCT). This toolbox has been implemented by Sporns, Rubinov and others and contains several topological metrics under the form of Matlab code. `https://sites.google.com/site/bctnet/`
- The Matlab Tool for Network Analysis package. It is a toolbox from the Massachusetts Institute of Technology. It consists of a Matlab Tools for Network Analysis, it is not strictly conceived for complex brain analysis but it is useful. `http://strategic.mit.edu/downloads.php?page=matlab_networks`
- igraph. igraph is a network analysis package. It is open source and free. igraph can be programmed in GNU R, Python and C/C++. `http://igraph.org/redirect.html`

4. Conclusions

In summary, Graph Theory gives us a powerful tool and language to study, analyze and treat with networks. Its most interesting advantage is that it allows us to define exactly the networks and to quantify network properties at all different levels.

The real challenges focus on modern network theory. Though many steps forward have been done, just think about small-word and scale-free models, most have to be done. In fact, as already mentioned in this paper, none of them solves all problems. There is an urgent need of models that explain how cerebral networks can emerge, and the most representative topological and physical metrics, such as high clustering, short paths, modules and hubs can arise by means of the optimization of a number of realistic assumptions.
In addition, such models should explain, as better as possible, the nature of dynamical processes taking place on the networks, as well as the one-to-one (or circular) causality between network topology and network dynamics.

Future research will most likely involve integrative models of brain structural and functional connectivity with multimodal neuroimaging data, exploring whether graph-based brain network analysis could yield reliable biomarkers for disease diagnosis and treatment [12].

These are the challenges of modern network theory, which still demands to come up with models that combine mathematical formalism and elegance with solid explanatory efficiency.

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