# **Optimizing Brain Networks Topologies Using Multi-objective Evolutionary Computation**

Roberto Santana · Concha Bielza · Pedro Larrañaga

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Abstract The analysis of brain network topological features has served to better understand these networks and reveal particular characteristics of their functional behavior. The distribution of brain network motifs is particularly useful for detecting and describing differences between brain networks and random and computationally optimized artificial networks. In this paper we use a multi-objective evolutionary optimization approach to generate optimized artificial networks that have a number of topological features resembling brain networks. The Pareto set approximation of the optimized networks is used to extract network descriptors that are compared to brain and random network descriptors. To analyze the networks, the clustering coefficient, the average path length, the modularity and the betweenness centrality are computed. We argue that the topological complexity of a brain network can be estimated using the number of evaluations needed by an optimization algorithm to output artificial networks of similar complexity. For the analyzed network examples, our results indicate that while original brain networks have a reduced structural motif number and a high functional motif number, they are not optimal with respect to these two topological features. We also investigate the correlation between the structural and functional motif numbers, the average path length and the clustering coefficient in random, optimized and brain networks.

R. Santana (⊠) · C. Bielza · P. Larrañaga Universidad Politécnica de Madrid, Campus de Montegacedo sn. 28660, Boadilla del Monte, Madrid, Spain e-mail: roberto.santana@upm.es

C. Bielza e-mail: mcbielza@fi.upm.es

P. Larrañaga e-mail: pedro.larranaga@fi.upm.es **Keywords** Brain networks · Evolutionary algorithm · Network motifs · Multi-objective optimization · Network optimization

# Introduction

In complex brains, neurons form highly sophisticated networks underlying flexible and specialized behavior. The analysis of neural connectivity in nematodes (Cherniak 1994) and of sensory areas in the cerebral cortex of different mammals (Cherniak 2004) has served to understand the characteristic features of these network topologies. As is the case of other complex networks (Dorogovtsev et al. 2008), brain networks may have a small-world network structure (Watts and Strogatz 1998), i. e. they may be characterized by high degree of clustering with short path lengths linking the nodes, at the level of anatomical as well as functional connectivity small-world properties (Reijneveld et al. 2007).

In this paper we investigate the topological characteristics of optimized artificial networks that resemble brain networks. Network descriptors are used to compare natural, random and artificial networks. We expect this type of analysis to provide clues for identifying organizational principles in brain networks. There are a variety of topological measures that have been applied to the study of brain cortical networks. They include structural measures such as the node degree, clustering coefficient and motifs (Costa and Sporns 2005; Costa et al. 2007a, b, c; Rodrigues and Costa 2009) and dynamic measures that depend on the particular characteristics of a given dynamic process that is being executed in the network (Costa et al. 2007a, b, c; Rodrigues and Fontoura Costa 2009; Wang et al. 2008). Structural measures of brain networks can provide a very rich landscape of structural and functional brain organization. Local network characteristics (e.g. node degree) serve to characterize and differentiate between their particular roles of the regions in the brain's structural organization. Global network measures (e.g. modularity) provide a different perspective of the cortical network organization, revealing, for example, how different regions jointly interact.

The paper focuses on the process of generating artificial networks by optimizing the number of network motifs they contain. Motifs (Milo et al. 2002) are small network building blocks that are defined by their size and interconnection patterns. Some researchers (Sporns and Kötter 2004) have stated that it could be possible to gain insight into the rules governing the structure of complex networks by investigating their composition from motifs. The distribution of motifs has been investigated for biological and artificial networks (Bullmore and Sporns 2009; Kashtan and Alon 2005; Milo et al. 2002; Sporns and Kötter 2004). Although the work presented in this paper focuses on the use of motifs for the optimization process, we also analyze other global topological network measures: the clustering coefficient, the average path length, the modularity and the betweenness centrality.

In Sporns and Kötter (2004), motifs are used to study information processing in brain networks. In these networks, structural motifs are identified as a set of brain areas and pathways that can potentially engage in different patterns of interactions. Authors introduce functional motifs to refer to specific combinations of nodes and connections (contained in the structural motifs) that may be recruited or activated in the course of neural information processing. By rewiring random networks and imposing a cost function that maximizes the functional motif number, network topologies are generated that resemble real brain networks across different attributes such as node degree.

Structural optimization problems in artificial brain networks can be defined as problems that imply the identification of a network topology that satisfies a number of constraints (generally determined by characteristics of the original brain network) and is optimal (or non-dominated) with respect to a measure (or set of measures) defined in the space of networks.

Our work is built from the results achieved in Sporns and Kötter (2004). We intend to determine how brain networks are related to artificial networks that share some of the original brain network attributes. A novelty of our approach is that we address the creation of the artificial network as a multi-objective optimization problem in which different objectives are simultaneously optimized. As a result, we obtain a set of non-dominated solutions that expands the scope of the analysis of the relationships between natural and artificial brain networks. In particular, it is possible to locate natural networks within an "optimality map" defined by two or more objectives. This optimality map is estimated by an approximation to the Pareto front of non-dominated solutions. By applying different dissimilarity measures in this map, we can get a fuller perspective of the brain network specificity with respect to similar optimized artificial brain networks (Kashtan and Alon 2005; Milo et al. 2002; Sporns and Kötter 2004).

The optimization algorithm itself is also used as a framework for studying the brain network topology. We address questions such as how likely is to obtain an artificial network with a similar or higher degree of optimality than the original brain network? How much computational effort, measured as the number of evaluations needed by the algorithm, will take to achieve these results? What type of problem information can be used to diminish the computational cost of the algorithm? We argue that optimization methods can be employed to compare different brain networks by contrasting the complexity of the respective optimization processes conducted to output networks similar to each original brain network. This is an interesting result since, although it is possible to estimate how a graph topology departs from randomness, it is more difficult to find measures to compare the global topological complexities of two given graphs.

The paper is organized as follows. In Section Brain Networks and Motifs brain networks and graphical motifs are introduced and the main problem addressed in the paper is defined. Section Multi-objective Optimization covers the use of evolutionary algorithms for multi-objective optimization. Our proposal on the use of evolution of artificial brain networks is explained in Section Evolutionary Algorithms for Multi-objective Optimization of Brain Networks. Related work is discussed in Section Related Work. The experimental framework and the numerical results of the experiments are presented in Section Experiments. Finally, the conclusions of our paper and trends for future research are set out in Section Conclusions.

#### **Brain Networks and Motifs**

It was observed some time ago (Edelman and Mountcastle 1978) that there are possibly regularities in the local wiring patterns of most of neurons and that neurons appear to be clustered in terms of connections with distant brain regions. These observations led to simplifications that enabled an approximation of the large-scale organization of the primate cerebral cortex based on the examination of the gross connections between cortical areas (Young 1993). In

general, brain activity can be modeled as a dynamic process acting on a network; each vertex of the structure represents an elementary component, such as brain areas, groups of neurons or individual cells (De Lucia et al. 2005) and edges or arcs between vertices represent some sort of interaction between the elementary components. We call to such a representation of a brain structure or function a *brain network*.

The brain network topology is a key element for understanding the behavior of the represented process. Therefore, several works have addressed the analysis of the topological characteristics of these networks. Additionally, *artificial brain networks* that resemble brain networks (in terms of predefined topological features) have also been employed to investigate the specific brain network characteristics.

# Structural and Functional Motifs

A (*structural*) motif (Milo et al. 2002; Sporns and Kötter 2004) is a connected graph or network consisting of M vertices and a set of edges (for directed graphs, maximally  $M^2-M$ ; with connectedness ensured, minimally M-1) forming a subgraph of a larger network. For each M, there is a limited set of distinct motif classes.

A *functional motif* of a given structural motif consists of the original *M* vertices of the structural motif, but contains only a subset of its edges. A *connected motif* is a structural motif that forms a strongly connected graph. In a connected motif, all the constituent vertices can be reached from all other constituent vertices.

A motif frequency spectrum records the number of distinct motifs in each structural motif lass. The motif number is the total number of distinct occurrences of any motif of size *M*. The motif diversity is the number of classes that are represented within the network by at least one example.

The *motif fingerprint* of a vertex is the number of distinct structural motifs of size *M* in which the vertex participates. *Motif participation number* is the number of instances of a given motif class in which a particular vertex participates.

Figure 1 shows all structural motifs for motif class M=3. Motifs *a*, *b*, and *c* are functional motifs of the structural motif *e*. Motif *g* is a connected motif. Figure 2 shows an example of a directed network. The motif frequency spectrum of this network is (1,5,1,0,1,0,0,0,0,0,0,0,0), where motifs are ordered as in Fig. 1. The network motif number is 8 and the motif diversity is 4 (only motifs of type *a*, *b*, *c* and *e* are represented in the graph). The motif fingerprint of vertex 1 is 3 since it participates in motifs (3,2,1), (5,6,1) and (2,1,6). The motif participates in motifs (5,6,1), (4,5,6) and (5,6,2), which are all of type *b*.

To investigate the networks, we employ four network measures widely used in the literature. The *clustering* 



Fig. 1 All structural motifs for motif class M=3

*coefficient* of a node is defined as the fraction of the existing number of links over the total possible number of neighbor-neighbor links (Watts and Strogatz 1998). The clustering coefficient of a network (denoted c) is computed as the average of the clustering coefficient for all network nodes.

Let a path be a sequence of linked nodes that never visit a single node more than once. The *path length* between two vertices is the number of vertices in the shortest path between them (Watts and Strogatz 1998). The average path length (L) is the average of the path lengths between the connected nodes of a network.

Given an organization of a network in modules, its *modularity* is the fraction of arcs within modules minus the expected fraction of such arcs. To compute an optimal decomposition of the network in modules we use the Newman's spectral optimization method, generalized to directed networks (Leicht and Newman 2008). The *betweenness centrality* (Costa et al. 2007a, b, c) of vertex *u* is computed as  $B_u = \sum_{ij} \frac{\sigma(iuj)}{\sigma(ij)}$  where  $\sigma(iuj)$  is the number of shortest paths between vertices *i* and *j* that pass through



Fig. 2 Directed network

vertex u and  $\sigma(ij)$  is the total number of shortest paths between i and j.

#### Brain Network Motifs

Sporns and Kötter (2004) study brain networks information processing by analyzing their motif distribution. Characteristic functional and structural motifs are detected in neuroanatomical data sets. Some functional motifs are identified as very frequent in significantly increased numbers (Sporns and Kötter 2004). The authors hypothesize that "brain networks maximize both the number and diversity of functional motifs, while the repertoire of structural motifs remains small".

To further investigate this hypothesis, artificial brain networks were created. The procedure was carried out by rewiring random networks and imposing a cost function that maximizes the functional motif number. This singleobjective optimization process is done using an evolutionary algorithm that evolves artificial network topologies. Sporns and Kötter reported that by maximizing the functional motif number a significant decline in the number of structural motifs is achieved. They also tried to maximize the structural motif number, but the obtained networks were very different to real brain networks in terms of different structural attributes.

Here, we study the hypothesis advanced by Sporns and Koetter replacing single- by multi-objective optimization. The idea is to simultaneously maximize the functional motif number and minimize the structural motif number. These are the two objectives of the optimization problem.

The so-called Pareto set of solutions (see next section for formal definitions on Pareto-optimality) is employed to analyze the structural relationship of the original brain networks with the optimized artificial networks. This set is also useful for giving measures of the relationship between the two objectives involved in the optimization process and other topological network descriptors.

# **Multi-objective Optimization**

# Pareto Dominance

We consider a maximization problem with k objective functions  $f_i(x) \to \mathbb{R}, i \in \{1, ..., k\}$ , where the vector function f maps each solution  $\mathbf{x} \in \mathcal{X} \subset \mathcal{R}^n$  to an objective vector  $f(x) = (f_1(\mathbf{x}), ..., f_k(\mathbf{x})) \in \mathcal{R}^k$ . It is also assumed that the underlying dominance structure is given by the Pareto dominance relation "y dominates  $\mathbf{x}$ " that is defined as  $\forall \mathbf{x}, \mathbf{y} \in \mathcal{X}, \mathbf{x} \leq_{\mathcal{F}} \mathbf{y} \Leftrightarrow f_i(\mathbf{x}) \leq f_i(\mathbf{y}) \forall i$ , where  $\mathcal{F} = \{f_1, ..., f_k\}$ . The Pareto (optimal) set is given as  $\{\mathbf{x} \in \mathcal{X} \mid \exists \mathbf{y} \in \mathcal{X} \setminus \{\mathbf{x}\} : \mathbf{x} \leq_{\mathcal{F}} \mathbf{y}\}$ . Conflicting and Harmonious Objectives

A key issue in multi-objective optimization problems is to determine how objectives are related. This information is useful for gaining a better understanding of the problem. There have been several attempts (Brockhoff and Zitzler 2006; Deb 2001; Purshouse and Fleming 2003) to define the types of relationships that exist between different sets of objectives in a multi-objective problem.

Considering relationships between pairs of criteria (Purshouse and Fleming 2003) in a *conflicting* relationship, performance in one criterion improves as performance in the other is seen to deteriorate. If the relationship is *harmonious*, improvement in one criterion is rewarded with simultaneous improvement in the other. The criteria may be *independent* of each other, where a change to one criterion does not affect the other.

Conflicting, harmonious and independent objectives can be detected by analyzing the correlations between the objectives in a given set of solutions (Deb and Saxena 2005; López et al. 2008). This measure can support a priori unknown knowledge about the problem, particularly in situations involving many objectives where it is difficult to empirically determine how they are related. This type of information can be used to simplify the problem.

Notice that the relationship between the objectives may change in particular areas of the search space. We could, for instance, set a threshold on the different objectives and then investigate the correlations between the objectives from samples of this constrained subspace. In our case, we will use the correlations to quantify the relationships between different objectives in randomly sampled solutions and in solutions from a Pareto set approximation.

# **Evolutionary Algorithms for Multi-objective Optimization of Brain Networks**

In this section we introduce the evolutionary optimization approach used in this paper to evolve networks. First, the problem representation and the objectives of the optimization problem are presented. Then, two variants of the evolutionary algorithm are introduced.

Problem Representation and Problem Objectives

Given a brain network represented using a directed network, we will consider artificial brain networks with the same number of vertices and arcs. This topological constraint, used in previous approaches (Sporns and Kötter 2004), guarantees a minimum topological similarity between the real and artificial networks. In addition, this step preserves the local node statistics, while removing the effects of global topology.

Each directed network G = (V, E) will be represented by a matrix where each entry  $e_{i,j}=1$  means that there is an arc from vertex  $V_i$  to  $V_j$  and  $V = \{V_1,...,V_k\}$  is the set of vertices. Self connections are not allowed and therefore the maximum number of arcs in the network is  $n = k^2 - k$ . We associate each possible arc with a variable and represent a solution as a binary vector  $\mathbf{x} = (x_1,...,x_n)$  where  $x_i=1$  means that the corresponding arc is included in the network and 0 otherwise.

We will focus on the optimization of two objectives: 1) maximization of the sum of functional motifs participation  $f_1(\mathbf{x})$  and 2) minimization of the sum of the structural motifs participation  $f'_2(\mathbf{x})$ . For practical reasons the second objective is transformed into the opposite function  $f_2(\mathbf{x}) = -f'_2(\mathbf{x})$ . Notice, that this choice of the objectives indirectly addresses the maximization of the functional motif number and the minimization of the structural motif number.

# Evolutionary Algorithm

Evolutionary algorithms (EAs) (Goldberg 1989; Holland 1975) are population-based global optimization methods that can deal with non-differentiable, discontinuous and multimodal functions. These algorithms have been successfully applied to different problems in neuroscience (Defoin-Platel et al. 2009; Gerken et al. 2006; Pettinen et al. 2006). EAs have proved to be particularly suitable to address multi-objective optimization functions when the variation operators they employ are appropriately modified to account for the existence of more than one objective.

In this paper we present two variants of an EA to evolve optimal artificial brain networks for the case of the biobjective problem described in the previous section. The first variant is an adaptation of the EA introduced in Sporns and Kötter (2004) to evolve brain networks by optimizing a single-objective problem. The rationale behind this choice is twofold. On the one hand, the rewiring operator used by the EA presented in Sporns and Kötter (2004) guarantees that the generated solutions will satisfy the constraints related to the indegree and outdegree of the vertices. On the other hand, the algorithm can be easily adapted to deal with the bi-objective case by modifying the selection step.

Pareto-ranking selection is the selection method of choice. It orders individuals according to the Pareto front to which they belong. Individuals in the first front (non-dominated solutions) come first, followed by individuals that are only dominated by those in the first front and so on. Within each front, solutions are ordered according to the average rank of their objective or fitness functions. After the entire population has been ordered, a percentage T of the population is selected by truncation selection.

Algorithm 1 shows the EA pseudocode. Since the topological constraints are enforced in step 1, the algorithm starts with a set of feasible solutions. Rewiring is applied by replacing two randomly selected arcs  $e_{i,j}$  and  $e_{k,l}$  by arcs  $e_{i,j}$  and  $e_{k,j}$ . In this way, the indegree and outdegree of the vertices involved are not modified.

Notice that the algorithm does not use any information about objective functions in the application of the variation operator (the rewiring). Since rewiring is blind to the effect that it will have on the objective values of the modified solutions, we can expect its application to produce both better and worse solutions. For the same reason however, it guarantees that no bias related to the objectives that are being optimized is introduced to generate new solutions.

1	Generate an initial population $D_0$ of $M$ networks that satisfy the topological constraints
2	$\mathrm{t} \leftarrow 1$
3	do {
4	Evaluate all the objectives for solutions in $D_{t-1}$
5	$D_{t-1}^{Se} \leftarrow \text{Select } N \text{ individuals from } D_{t-1} \text{ using Pareto-ranking selection}$
6	Randomly sample $M - N$ individuals from $D_{t-1}$ (the selected parents)
$\gamma$	Rewire the sampled networks by exchanging $2$ arcs between $4$ vertices
8	Form population $D_t$ by joining the $M - N$ generated solutions and $D_{t-1}^{Se}$
g	$\mathrm{t} \leftarrow \mathrm{t} + 1$
10	} until Stop criterion is met

Algorithm 1: Evolutionary algorithm

Algorithm 1 is appropriate for comparing how difficult is to evolve a brain network for an optimization algorithm guided only by selection. However it can be too inefficient in terms of the number of evaluations needed to output optimal solutions of more complex problems. Therefore, we propose a variant of Algorithm 1 in which a local search optimization procedure is inserted before step 4. The local optimization method, which is described in Algorithm 2, works by selecting sub-networks of a candidate network and applying a guided variation operator. Instead of randomly rewiring any two arcs, selected arcs are only exchanged if the objective values for the selected subnetwork improves after rewiring. The idea is that local improvements in the objective values may lead to an improvement in the objective values computed for the whole network. On the other hand, by constraining the computation of functions to the subnetworks, the cost of the evaluation step is reduced. Algorithm 2 uses the size of the subnetwork r and the maximal number of trials (*maxtrials*) as input parameters for obtaining a subnetwork that improves the candidate subnetwork.

Since the operators applied by both algorithms do not modify the indegree and outdegree, all generated networks have the same topological characteristics of the original brain network throughout the evolution. Therefore, the Pareto set is searched in the space of feasible solutions. The stop criterion used is a maximum number of generations. The choice for the parameters used by the algorithm is explained in Section Experiments.

# Algorithm 2: Local optimization method

1	$l \leftarrow 1$
2	do {
3	Select a random subset of $r$ network nodes (subnetwork ${\cal G}_l)$ from the given network ${\cal G}$
4	Select two arcs in $G_l$ that can be swapped without altering the indegree and out-degree of the involved nodes
5	Create a candidate subnetwork $G'_l$ by swapping the selected arcs
6	Compute objective values for subnetworks $G_l$ and $G'_l$
$\tilde{\gamma}$	If $G'_l$ is better than $G_l$ for the two objective values, replace $G_l$ by $G'_l$ in G
8	} <b>until</b> Network G has been modified or $l = maxtrials$

To estimate the computational effort required by the algorithms, we use the number of evaluations conducted during the evolution. For the simple variant of the EA, the number of evaluations is computed as  $e = M + (g - 1) \cdot (M - N)$ , where g is the number of generations and M the population size. For the EA using local optimization method (EA-Local), we compute the number of (local) evaluations required by the local optimization method each time it is called. This is  $e_{local} = \frac{r \cdot etrials}{n}$ , where etrials is the number of steps needed by the optimization step.  $E_{local}$  is the sum of all such evaluations, and the number of evaluations needed by this EA variant is estimated as  $e = M + (g - 1) \cdot (M - N) + E_{local}$ .

#### **Related Work**

In addition to the work presented in Sporns and Kötter (2004), which has been already discussed in previous sections, there are a number of papers related to our work.

Recently, the combination of more than one objective has been proposed as a better alternative for neuronal model parameter optimization (Druckmann et al. 2007a, b). The idea is to use several error functions jointly in order to compare the experimental voltage traces and the model response on the basis of individual features of interest. Although these papers highlight the importance of applying multi-objective optimization in neuroscience, the application domain as well as the goal of the multi-objective approach are different to ours.

Another way to obtain optimized network structures (in terms of modularity) is by optimizing dynamic functions. Kashtan and Alon (2005) have produced evidence that switching between related goals (represented by different but related objective functions) as part of an evolutionary optimization approach can result in the emergence of modular network structures and network motifs. Changing environments represented by dynamic objective functions could be used to some extent to obtain robust solutions with respect to different objectives. However, as the number of objectives is increased, and particularly if they are conflicting, it is not clear how these approaches could support a good covering of the solution space, which is inherent to good Pareto set approximations.

#### Experiments

The objectives of the experiments are threefold. First, in Sections Relationships Between Objectives and Comparison Between the Original and Random Generated Networks, we investigate the relationship between the functional motif number and the structural motif number objectives associated with different network topological characteristics for randomly generated artificial brain networks. We intend to determine whether the relationship between the objectives is conflicting or harmonious and if there are important differences between the original and the randomly generated brain networks.

In a second step, in Section Behavior of the Evolutionary Algorithm, we evaluate the capacity of the evolutionary algorithm to find a set of artificial brain networks that simultaneously optimize the two different objectives and compute the computational effort required to optimize the networks.

Finally, in Section Comparison Between the Original and Optimized Networks, the Pareto set approximation is used to investigate to what extent the original brain networks maximize the number of functional motifs while keeping the value of the structural motifs low, which is the hypothesis advanced in Sporns and Kötter (2004). The Pareto set approximation is also employed to find topological differences between the optimized and the original brain networks.

#### **Experimental Framework**

We use a set of four matrices representing brain networks and previously employed in Sporns and Kötter (2004).<sup>1</sup> Some of the original matrices were modified to remove areas with few known connections or areas that are not part of the cerebral cortex. See Sporns and Kötter (2004) for details on how they were modified.

A connection matrix of the macaque visual cortex is based on Felleman and Van Essen (1991). The modified matrix (*fve30*) has n=30 and |E| = 311. Another version (*fve32*) of the connection matrix of the macaque visual cortex has n=32 and |E| = 315. A large-scale corticocortical connectivity matrix of the visual and sensorimotor areas (*macaque47*) has n=47 and |E| = 505. It has been previously applied in experiments conducted in Honey et al. (2007). The connection matrix of the macaque cortex is based on Young (1993). The modified matrix (*macaque71*) has n=71 and |E| = 746.

# Characteristics of the Implementation

The EAs were implemented using MATEDA-2.0 software (Santana et al. 2010), a modular implementation of estimation of distribution algorithms programmed in Matlab that can be used to implement genetic and other classes of evolutionary algorithms. The computation of the number of structural and functional motifs was implemented using the brain connectivity toolbox (Sporns 2002).

The simple EA was used for problems *fve30* and *fve32*. The EA with additional local optimization step (EA-Local) was applied to problems *macaque47* and *macaque71*. This decision was motivated by the fact that the simple EA was unable to output solutions better than the *macaque47* and *macaque71* brain networks. The EAs use a population size of 500 individuals, and the maximal number of generations for each problem were 200 for *fve30* and *fve32*, 500 for *macaque47*, and 1000 for *macaque71*. The truncation parameter was T=0.5. There were 20 executions for each problem. The characteristics of the selected networks are described in Table 1.

# Numerical Results

We use the artificial networks generated to investigate the three issues stated at the beginning of Section Experiments.

#### **Relationships Between Objectives**

We start by forming a set of randomly generated networks. This set comprises all the initial populations of artificial brain networks generated by the EA. It includes 10,000 networks.

The randomly generated solutions are investigated by computing the correlations between the two objectives considered in the optimization process. The goal is to determine whether the structural and functional motif numbers are conflicting or harmonious objectives. Totally harmonious objectives would mean that singleobjective optimization is enough to generate a good set of solutions.

We also analyze correlations with and between the clustering coefficient and the average path length since they serve to define different classes of networks, particularly small-world networks. The goal is to find out whether the multi-objective optimization of structural and functional motifs has an effect on other

 Table 1 Some network measures of the brain networks used in the experiments

Network	п	E	mean $(V_i)$	С	L
fve30	30	311	10.3667	0.5510	1.7256
fve32	32	315	9.8438	0.5746	1.7698
macaque47	47	505	10.7447	0.5805	2.0500
macaque71	71	746	10.5070	0.4710	2.3252

*n* Number of vertices. |E| Number of edges. *mean*( $V_i$ ) Average degree. *c* Clustering coefficient. *L* Average path length

<sup>&</sup>lt;sup>1</sup> The data sets in Matlab format can be retrieved from http://www.indiana.edu/~cortex/CCNL.html

topological characteristics of the optimized networks. Thus, as a first step, we compute the correlations in randomly generated brain networks.

Table 2 shows the correlations between the different objectives for randomly generated artificial brain networks for the *fve30*, *fve32*, *macaque47* and *macaque71* networks.  $m_s$  and  $m_f$  respectively represent the structural and functional motif number. c is the clustering coefficient and L the average path length.

A first conclusion from the table is that the number of structural motifs has a strong negative correlation to the number of functional motifs. The correlations between  $m_s$  and  $m_f$  are similar for all the problems. Since a decrease in the number of structural motifs determines a likely increase in the number of functional motifs, our two objectives are very harmonious. However, a lower number of structural motifs does not always determine a higher number of functional motifs, i.e. the objectives are not totally harmonious, and we cannot optimize both of them by optimizing only one. Care must be taken about extrapolating the results of the correlation between the objectives to non-random population samples. For example, it may be difficult to improve both objectives simultaneously in a population of highly optimized solutions.

Regarding the other correlations, they are generally weak. Particularly interesting is the correlation between c and L, which is negative in all cases, though very low.

# Comparison Between the Original and Random Generated Networks

In this section, the original and random brain networks are compared in terms of different local and global topological descriptors. Local topological measures such as the number of structural and functional motifs provide a perspective for the understanding of the network properties. However, to better characterize cortical networks, it is also important to study them in terms of their global topological measures. This type of study may reveal other larger scale properties important for understanding brain structural and functional organization.

In the first step, structural and functional motifs are used to compare the original brain network to the set of randomly generated networks. Figure 3 shows the structural motif number against the functional motif number for all randomly sampled networks (dots) in the initial populations. The same measures are shown for each original brain network (triangle) located in the upper left corner. It is clear from Fig. 3 that each original brain network notably outperforms its respective set of randomly generated networks in terms of both objectives. This fact confirms that brain networks significantly depart from random networks in terms of the structural and functional motif numbers. The brain networks shown in Fig. 3 have a lower

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Table 2

	fve30				fve32				macaqu	e47			macaqu	e71		
	sm	тf	с	Т	sm	fm	С	Г	SW	fm	с	Г	Stu	fm	С	Т
sm	1.00	-0.88	-0.08	0.10	1.00	-0.88	-0.16	0.11	1.00	-0.91	-0.20	0.12	1.00	-0.95	-0.23	0.06
fu		1.00	0.17	-0.17		1.00	0.24	-0.14		1.00	0.26	-0.16		1.00	0.27	-0.10
С			1.00	-0.14			1.00	-0.21			1.00	-0.26			1.00	-0.20
Г				1.00				1.00				1.00				1.00
m <sub>s</sub> St	ructural mo	tif number. 1	m <sub>f</sub> Functions	al motif num	ber. c Clus	tering coeffi	cient. L Ave	rage path ler	ıgth							





structural motif number and a higher functional motif number than the random networks. This calls for a need to optimize the random networks.

In the next step some global topological measures are computed for the original and randomly sampled networks. Figure 4 shows the average path length against the clustering coefficient for randomly sampled networks (dots) and for the original networks (triangle). This figure also includes the measures computed for the optimized networks (stars) but this information will be analyzed in Section Comparison Between the Original and Optimized Networks.

Although the shapes of the clouds of points represented in Fig. 4 vary, we find that the original networks have higher average path lengths in all cases. The clustering coefficients are also higher than for the random networks. These results reveal that although some topological characteristics, e.g. indegree and outdegree values, are forced to be the same, random and real networks remain topologically very different.

In addition to the average path length and the clustering coefficient, we have computed the modularity and the betweeness connectivity of the networks. Figure 5 shows the modularity against the betweenness centrality for randomly sampled networks (dots) and the original networks (triangle). This figure also includes the measures computed for the optimized networks (stars) but this information will be analyzed in Section Comparison Between the Original and Optimized Networks. Similarly to the previously analyzed global measures, the modularity and the betweenness centrality of the original network are very different to these measures computed for the 10,000 random networks. The original network has higher modularity and betweeness centrality values than random networks.

The results presented in this section serve to illustrate that cortical networks depart from similar random networks both in terms of local and global network topological characteristics. These results will also serve to highlight the effect that multi-objective optimization has in the search for artificial brain networks.

#### Behavior of the Evolutionary Algorithm

The evolutionary algorithm plays a fundamental role in outputting the optimized networks. It has to guarantee that the initial random solutions from which the algorithm starts are progressively replaced by networks with better objective values. To evaluate the capacity of the EA to generate good quality solutions, we compute the non-dominated set of solutions from all the solutions sampled in every execution. Then, a final set of all the absolute non**Fig. 4** Average path length against clustering coefficient for randomly sampled networks (*dots*), the optimized networks (*stars*) and the original network (*triangle*)



dominated solutions is computed from the sets of all the executions.

Figure 6 shows the structural motif number against the functional motif number for non-dominated solutions learned in each run of the EA (blue dots), and absolute non-dominated solutions (stars). For comparison purposes, the objective values of the original networks are also plotted in the graphs (triangle). Since some of the triangles representing the original network measures are difficult to locate, dashed lines highlight their coordinates.

Clearly the evolutionary search leads to a remarkable improvement in the artificial networks. The objective values for the original networks, which were much better than for the random networks (see Fig. 3) are not as different as the objective values corresponding to the Pareto front approximations.

To determine the suitability of the EAs for finding networks better than the original brain networks, we scrutinize each run of the EAs, extracting statistics to evaluate algorithm performance. We also estimate the computational effort by computing the average number of evaluations needed to reach objective values equal to or better than those of the brain networks. The information is shown in Table 3.

Looking at Table 3, we see that the difficulty the EAs have in achieving both objectives is not the same. In all cases, the EAs need fewer function evaluations to find

solutions that have a better number of functional motifs than the corresponding brain network (columns  $e_1, e_2$ ,  $e_{\{1,2\}}$ ). This does not necessarily mean, though it does suggest, that the brain networks analyzed are more optimized in terms of the number of functional motifs than in terms of structural motifs. Table 3 also provides information about the difference the four brain problems have in terms of complexity. Network fve32 is the easiest for the EA to solve. For this network the algorithm achieves a high success rate with a relatively small number of function evaluations. Notably, the corresponding brain network has more nodes and links than network fve30. This means that fewer number of nodes does not necessarily imply less complexity and an easier optimization problem. Finally, by analyzing the average number of generations and evaluations (other columns) needed to optimize the two objectives individually and simultaneously, we find that, on average, it takes longer for the EAs to find solutions that optimize the two objectives simultaneously. Optimizing one of the objectives separately, even the hardest one, is no guarantee that both objectives will be optimized in the solution achieved.

# Comparison Between the Original and Optimized Networks

Figure 6 reveals that although considerably better than random solutions, original brain networks by no means





Fig. 6 Structural motif number against functional motif number for non-dominated solutions learned in each run of the EA (*blue dots*), and absolute nondominated solutions (*stars*) and original brain networks (*triangle*)

Table 2 Different measures of also

Table 5 Diffe	cient measures of	aigoriui	in perion	liance						
Network	Alg.	$S_1$	$S_2$	$S_{\{1,2\}}$	$g_1$	$g_2$	$g_{\{1,2\}}$	$e_1$	<i>e</i> <sub>2</sub>	$e_{\{1,2\}}$
fve30	EA	13	20	12	186.61	148.05	187.92	93308	74025	93958
fve32	EA	20	20	19	182.20	147.20	182.37	91100	73600	91184
macaque47	EA-Local	20	20	20	191.95	161.45	193.55	123860	96002	125390
macaque71	EA-Local	15	18	14	876.13	748.50	871.79	7167500	5780900	7114300

 $S_1$  (respectively  $S_2$ ) is the number of executions at which at least one solution has been found whose first objective value, the structural motif number, (respectively the second objective value, the functional motif number) is better than the first objective value (respectively the second) of the original brain network.  $S_{\{1,2\}}$  is the number of executions at which at least one solution has been found that is better than the original brain network for the two objective values simultaneously.  $g_1$ ,  $g_2$  and  $g_{\{1,2\}}$  are respectively the average number of generations needed to reach the solutions computed from successful runs used to calculate  $S_1$ ,  $S_2$  and  $S_{\{1,2\}}$ .  $e_1$ ,  $e_2$  and  $e_{\{1,2\}}$  show similar information but for the number of evaluations made by the algorithms

minimize structural or maximize functional complexity at the same time. Also taking the multi-objective perspective, we can determine which of the two objectives the original networks are closer to optimize. Figure 6 shows that while the structural motif number of the original network is lower than for most of the non-dominated solutions, the functional motif number is also lower, i.e. optimized artificial networks have a higher functional motif number with the same or even a smaller structural motif number.

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We further investigate this issue by computing the average motif frequency spectrum for evolved artificial brain networks and compare it to the original network motif frequency spectrum. Figures 7, 8, 9 and 10 show the structural and functional motif spectra computed for the four problems. The motif spectra shown for the optimized brain networks have been computed as the average motif spectrum of all the networks in the Pareto set approximation of each EA run.

Clearly the motif spectra for the original and optimized networks are very similar in all the charts for all problems. In some cases the differences between the motif spectra are almost indistinguishable. Also, the motif spectrum of the original network is similar to the average of the optimized network. The differences between the motif spectrum of the



Fig. 7 Motif spectra for network *fve30*. a) Original network (structural). b) Optimized network (structural). c) Original network (functional). d) Optimized network (functional) Fig. 8 Motif spectra for network fve32. a) Original network (structural). b) Optimized network (structural). c) Original network (functional). d) Optimized network (functional)

500

300

250

200

3500

3000

2500

1500

1000

500



original network with respect to the motif spectrum of individual optimized solutions are more remarkable (data not shown). Additionally, notice that the increased occurrence of structural motif 9 for motifs of size M=3 agrees with previous analysis of natural and single-objective optimized artificial brain networks (Sporns and Kötter 2004).

To have a wider perspective of the difference between the original and evolved networks, the same global topological measures presented in Section Comparison Between the Original and Random Generated Networks were computed for the evolved networks. Results for the average path length and the clustering coefficients are shown in Fig. 4. Results for the modularity and the betweenness centrality are shown in Fig. 5.

There are two main relevant observations that can be made from the analysis of these figures. The first is that for some global measures, evolved networks never reach the values of the original networks. This is the case, for example, for the average path length and the modularity. Evolved networks have always lower average path length and modularity than the original networks. This fact is not very surprising since, the optimization algorithm is not conceived to optimize these measures.

The second relevant fact is that, for all the global topological measures considered, the optimized networks are closer to the original networks than the random networks. This fact seems to indicate that by optimizing the number of structural and functional motifs, other global topological measures are also optimized. In fact, in some cases it can be appreciated that the original networks are not optimal in terms of the global topological measure considered. For example it can be seen in Fig. 5, that betweenness centrality values of some optimized networks are above those of the original fve network.

As in the analysis conducted for the randomly generated solutions, we computed, from the set containing the Pareto approximations of all the runs, the correlations between the two objectives considered in the optimization process. Their correlation with the clustering coefficient and the average path length of the networks was also computed. We also analyze correlations with and between the clustering coefficient and the average path length for these solutions.

Table 4 shows the correlations between the different objectives for the optimized artificial brain networks for all the networks. Correlations are quite unlike from the data shown in Table 2. The sign of the correlation between structural and functional motif number has changed for networks fve30 and fve32, and the correlation for the other two networks is closer to 0 (see also Fig. 6).

Fig. 9 Motif spectra for network *macaque47*. a) Original network (structural). b) Optimized network (structural). c) Original network (functional). d) Optimized network (functional)



It is difficult to find a common pattern for all the problems and correlation appears to depend on the particular class of problem and the Pareto set approximation that has been found. These results corroborate the fact that, in the space of optimized solutions, both the topological characteristics of the networks and number of related characteristics that serve to describe the networks, e.g. c and L, change.

# Conclusions

We identify two main, closely related but different contributions in the paper. The first, which we consider to be a methodological contribution, is the application of a multiobjective optimization approach to evolve the networks. This optimization algorithm is able to find highly optimized artificial networks that are usually better than the original brain networks. Although the choice of the network measures to be optimized, i.e. the number of structural and functional motifs, is important, it is not essential for the application of the methodology that we propose to evolve the networks. The rationale of using multi-objective optimization remains valid if other measures are used. By outputting a Pareto set approximations, we can investigate the trade-off between the different objectives involved, revealing the sometimes complex relationships between them. Also the specific scheme used for evolutionary optimization is applicable if other network measures are considered as objectives. The only changes required if other measures are used instead of the number of structural and functional motifs will be the local search procedure. Note that, in general, attaining optimality for one of the objectives does not necessarily mean that the other objectives will be optimal. This is the case only if there are redundant objectives.

The second contribution is related to the questions originally posed in Sporns and Kötter (2004). One of our findings is the somewhat expected evidence that the original networks are not optimal in terms of their number of structural and functional motifs. Since the original cortical networks we use represent only an approximation of the true cortex connectivity, probably with missing connections, they are unlikely to optimize the network measures used as objectives. However, we have also shown that this is not the only information that can be extracted from the Pareto fronts of the optimized networks. They are also informative in terms of the relationships between the objectives. For instance, their analysis reveals that it is generally easier for optimized networks to optimize the number of functional motifs than the number of structural motifs. We have presented evidence that the optimization process itself, and not only the results of the multievolutionary search, can be useful. In particular, we have Fig. 10 Motif spectra for network *macaque71*. a) Original network (structural). b) Optimized network (structural). c) Original network (functional). d) Optimized network (functional)



shown that the computational effort measured in terms of the number of evaluations can be used to compare the complexity of different structural brain problems. Additionally, the number of evaluations can be employed to compare how difficult it is to achieve the different objectives.

By combining the use of local and global measures to analyze brain connectivity, we have also extended previous work presented in Sporns and Kötter (2004). The analysis of the local topological measures does not capture all the complexity of cortical networks. In particular, there is no guarantee that large-scale topological properties will be captured if we focus only on local topological network measures. It is noteworthy that brain organization relies on both local and global connectivity. On the other hand, our results indicate that, by relying exclusively on the multiobjective optimization of local network measures, it is possible to obtain artificial networks that are closer to the original networks in terms of the analyzed global topological measures. They are, at least to some extent, optimized with respect to these global network measures. Furthermore, our results show that, in some cases, the optimized networks are also better than the original network in terms of global network measures.

Finally, we have investigated the correlation between the structural and functional motif numbers, the average path length and the clustering coefficient in random, optimized and natural brain networks. We initially expected the analysis of the correlations between network measures to provide additional insight into the relationships between them. This was the case for the measures used for the optimization whose correlation values mapped to very harmonious objectives. However, we have found that, at least for the case of the computed networks, there is not a strong correlation between the average path length, the clustering coefficient and the other measures.

# Future Work

In our analysis, no important differences were found between the distribution of motifs for the original and optimized brain networks. However, so far only motifs of size M=3 have been considered. It is not clear if differences could exist for higher values of M. Furthermore, we have not investigated how the topology of optimal artificial networks could change with M. Generally, the identification of topological descriptors that, on one hand, serve to accurately describe the specificities of the natural brain networks, and on the other hand, could be used to obtain artificial brain networks following an optimization approach, is an open question.

A straightforward extension of our work is to consider more than two objectives to describe the network topology. It has to be taken into account, though, that evolutionary

	fve30				fve32				macaqu	e47			macaque	71		
	sm	fm	С	Γ	sm	fut	с	Г	sm	fu	С	Г	sm	тf	С	Т
21	1.00	0.36	-0.02	-0.02	1.00	0.28	-0.05	-0.05	1.00	-0.22	-0.15	-0.10	1.00	-0.52	-0.48	-0.34
ıf		1.00	0.05	0.06		1.00	0.51	0.07		1.00	0.15	0.23		1.00	0.52	0.13
			1.00	0.00			1.00	0.25			1.00	-0.16			1.00	0.44
				1.00				1.00				1.00				1.00

algorithm performance falls when there are too many objectives, and more sophisticated strategies should be used to deal with these cases (Deb and Saxena 2005).

One point that hinders the application of EAs is their scalability. The use of adjacency matrices to represent candidate solutions is very costly in memory terms; it grows quadratically with the number of variables. This is particularly evident when population-based optimization algorithms like EAs are employed. Therefore, more research is required to conceive alternative problem representations. The application of other representations such as generative network models (Leskovec et al. 2010) should be investigated.

Finally, another open research trend is the design of more accurate EAs that are able to detect and model structural regularities from the set of selected solutions. One alternative is to use estimation of distribution algorithms (EDAs) (Larrañaga and Lozano 2002; Muhlenbein and Paaß 1996) for network evolution. EDAs are a class of EAs that employs probabilistic models instead of genetic operators to generate the new solutions. EDAs can more efficiently deal with problems with interacting variables than classical genetic algorithms and other EAs. However, traditional EDAs experience difficulties when representing variable interactions in constrained problems (Santana et al. 2009). In the evolution of artificial brain networks it has to be guaranteed that the generated solutions are feasible (i.e. the topological constraints are satisfied). Conceiving probabilistic models able to respect topological relationships between the graph nodes and amenable for use in EDA sampling is another open research trend.

# **Information Sharing Statement**

The brain networks data sets used in this paper are in Matlab format and can be retrieved from http://www.indiana.edu/ ~cortex/CCNL.html. MATEDA-2.0 is downloadable from http://www.sc.ehu.es/ccwbayes/members/simrsantana/software/ matlab/MATEDA.html. The brain connectivity toolbox (Sporns 2002) is available at http://sites.google.com/a/brainconnectivity-toolbox.net/bct/metrics.

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## References

Brockhoff, D., & Zitzler, E. (2006). Dimensionality reduction in multiobjective optimization: The minimum objective subset problem. In K.-H. Waldmann, & U. M. Stocker (Eds.), *Operations Research*, Proceedings 2006. Selected Papers of the Annual International Conference of the German Operations Research Society (GOR), Jointly Organized with the Austrian Society of Operations Research ({"O}GOR) and the Swiss Society of Operations Research (SVOR) (pp. 423–429). Karlsruhe, Germany, September 6–8, 2006.

- Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience*, 10, 1–13.
- Cherniak, C. (1994). Component placement optimization in the brain. *The Journal of Neuroscience, 14*, 2418–2427.
- Cherniak, C. (2004). Global optimization of cerebral cortex layout. Proceedings of the National Academy of Sciences (PNAS), 101 (4), 1081–1086.
- Costa, L. F., & Sporns, O. (2005). Hierarchical features of large-scale cortical connectivity. *The European Physical Journal B*, 48(4), 567–573.
- Costa, L. F., Sporns, O., Antiqueira, L., Nunes, M. G. V., Oliveira, M., & Oliveira Jr, O. N. (2007). Correlations between structure and random walk dynamics in directed complex networks. *Applied Physics Letters*, *91*(054107). doi:10.1063/1.2766683.
- Costa, L. F., Kaiser, M., & Hilgetag, C. C. (2007). Predicting the connectivity of primate cortical networks from topological and spatial node properties. *BMC Systems Biology*, 1(1), 16.
- Costa, L. F., Rodrigues, F. A., Travieso, G., & Boas, P. R. V. (2007). Characterization of complex networks: a survey of measurements. *Advances in Physics*, 56(1), 167–242.
- Deb, K. (2001). Multi-objective optimization using evolutionary algorithms. Chichester: Wiley.
- Deb, K., & Saxena, D. K. (2005). On finding Pareto-optimal solutions through dimensionality reduction for certain large-dimensional multi-objective optimization problems. KanGAL Report 2005011, Kanpur Genetic Algorithms Laboratory (KanGAL). Indian Institute of Technology Kanpur.
- Defoin-Platel, M., Schliebs, S., & Kasabov, N. (2009). Quantuminspired evolutionary algorithm: a multimodel EDA. *IEEE Transactions on Evolutionary Computation*, 13(6), 1218–1232.
- De Lucia, M., Bottaccio, M., Montuori, M., & Pietronero, L. (2005). Topological approach to neural complexity. *Physical Review E. Statistical, Nonlinear, and Soft Matter Physics*, 71, 016114.
- Dorogovtsev, S. N., Goltsev, A. V., & Mendes, J. F. F. (2008). Critical phenomena in complex networks. *Reviews of Modern Physics*, 80 (4), 1275–1335.
- Druckmann, S., Banitt, Y., Gidon, A., Schuermann, F., Markram, H., & Segev, I. (2007). A novel multiple objective optimization framework for constraining conductance-based neuron models by experimental data. *Frontiers in Neuroinformatics*, 1(1), 7–18.
- Druckmann, S., Berger, T. K., Hill, S., Schuermann, F., Markram, H., & Segev, I. (2007). Evaluating automated parameter constraining procedures of neuron models by experimental and surrogate data. *Biological Cybernetics*, 99, 371–379.
- Edelman, G. M., & Mountcastle, V. B. (1978). The mindful brain. Cambridge: MIT Press.
- Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex*, 1, 1–47.
- Gerken, W. C., Purvis, L. K., & Butera, R. J. (2006). Genetic algorithm for optimization and specification of a neuron model. *Neurocomputing*, 69, 1039–1042.
- Goldberg, D. E. (1989). Genetic algorithms in search, optimization, and machine learning. Reading: Addison-Wesley.
- Holland, J. H. (1975). Adaptation in natural and artificial systems: An introductory analysis with applications to biology, control, and artificial intelligence. Ann Arbor: University of Michigan Press.
- Honey, C. J., Kötter, R., Breakspear, M., & Sporns, O. (2007). Network structure of cerebral cortex shapes functional connec-

tivity on multiple time scales. Proceedings of the National Academy of Sciences (PNAS), 104, 10240–10245.

- Kashtan, N., & Alon, U. (2005). Spontaneous evolution of modularity and network motifs. *Proceedings of the National Academy of Sciences (PNAS), 102*(39), 13773–13778.
- Larrañaga, P., & Lozano, J. A. (Eds.). (2002). Estimation of distribution algorithms. A new tool for evolutionary computation. Boston/Dordrecht/London: Kluwer Academic Publishers.
- Leicht, E. A., & Newman, M. E. J. (2008). Community structure in directed networks. *Physical Review Letters*, 100, 118703.
- Leskovec, J., Chakrabarti, D., Kleinberg, J., Faloutsos, C., & Gharamani, Z. (2010). Kronecker graphs: an approach to modeling networks. *The Journal of Machine Learning Research*, 11, 985–1042.
- López, A., Coello, C. A., & Chakraborty, D. (2008). Objective reduction using a feature selection technique. In M. Keijzer (Ed.), *Proceedings* of the 10th Annual Conference on Genetic and Evolutionary Computation GECCO-2008 (pp. 673–680). New York: ACM.
- Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., & Alon, U. (2002). Network motifs: simple building blocks of complex networks. *Science*, 298, 824–827.
- Muhlenbein, H., & Paaß, G. (1996). From recombination of genes to the estimation of distributions I. Binary parameters. In H.-M. Voigt, W. Ebeling, I. Rechenberg, & H.-P. Schwefel (Eds.), *Parallel problem* solving from nature - PPSN IV, vol. 1141 of lectures notes in computer science (pp. 178–187). Berlin: Springer.
- Pettinen, A., Yli-Harja, O., & Linne, M. L. (2006). Comparison of automated parameter estimation methods for neuronal signaling networks. *Neurocomputing*, 69, 1371–1374.
- Purshouse, R. C., & Fleming, P. J. (2003). Conflict, harmony and independence: Relationships in evolutionary multicriterion optimisation. In C. M. Fonseca, P. J. Fleming, E. Zitzler, K. Deb, & L. Thiele (Eds.), Evolutionary multi-criterion optimization: Second International Conference, EMO 2003, vol. 2632 of lecture notes in computer science (pp. 16–30). Berlin-Heidelberg: Springer.
- Reijneveld, J. C., Ponten, S. C., Berendse, H. W., & Stam, C. J. (2007). The application of graph theoretical analysis to complex networks in the brain. *Clinical Neurophysiology*, *118*(11), 2317–2331.
- Rodrigues, F. A., & Costa, L. F. (2009). A structure-dynamic approach to cortical organization: number of paths and accessibility. *Journal of Neuroscience Methods*, 183(1), 57–62.
- Rodrigues, F. A., & Fontoura Costa, L. (2009). Signal propagation in cortical networks: a digital signal processing approach. *Frontiers* in Neuroinformatics, 3(24), 1–13.
- Santana, R., Larrañaga, P., & Lozano, J. A. (2009). Research topics on discrete estimation of distribution algorithms. *Memetic Computing*, 1(1), 35–54.
- Santana, R., Bielza, C., Larrañaga, P., Lozano, J. A., Echegoyen, C., Mendiburu, A., et al. (2010). MATEDA: estimation of distribution algorithms in MATLAB. *Journal of Statistical Software*, 35(7), 1–30.
- Sporns, O. (2002). Neuroscience databases. A practical guide, chapter graph theory methods for the analysis of neural connectivity patterns (pp. 171–186). Boston/Dordrecht/London: Kluwer Academic Publisher.
- Sporns, O., & Kötter, R. (2004). Motifs in brain networks. PLoS Biology, 2(11), e369.
- Wang, S. P., Pei, W. J., & He, Z. Y. (2008). Random walks on the neural network of c. elegans. In *Proceedings of the 2008 International Conference on Neural Networks and Signal Processing* (pp. 142–145).
- Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of smallworld networks. *Nature*, 393(6684), 440–442.
- Young, M. P. (1993). The organization of neural systems in the primate cerebral cortex. *Proceedings of Biological Science*, 252 (1333), 13–18.