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# Functional modelling of cortical macro-networks

*Theses of the doctoral dissertation*

Mihály Bányai

Advisor:

Dr. Fülöp Bacsó (Wigner RCP)

Consultant:

Dr. György Strausz (BME MIT)

Department of Measurement and Information Systems,  
Budapest University of Technology and Economics

2013

## About the dissertation

The topic of my dissertation is the study of cortical macro-networks using mathematical models. The basic computational unit of the nervous system is the neuron, and the collective electric activity of such units implements all functionality expressed during behaviours of organisms. The neurons form larger organisational and computational units in the cortex in a hierarchical manner, and the largest scale network of such organisations is that of cortical areas. These ensembles, consisting of millions of cells, can be differentiated on an anatomical basis, and one can often determine the functionalities that they take part in the implementation of. Such information can be collected by anatomical and histological methods, and also by functional imaging, such as fMRI measurements. The knowledge, gathered by such methods about the structure and function of the large-scale cortical network, can be related to human and animal behavioural forms using mathematical models.

My dissertation consists of two main parts. In the first half I investigate the interaction between large-scale cortical structure and function using graph theoretical methods, and in the second, the cortical implementation of behavioural function and its dysfunctions, using dynamic statistical models. I put an emphasis on the role of the prefrontal area, responsible for high-level cognitive functions, in both parts.

## Signal flow in directed networks

### Preliminaries to the study

The static component of the network of cortical areas is anatomical connectivity. The construction of a precise connectivity map requires histological investigations in addition to the imaging studies. Such a map was created of the macaque visuo-tactile cortex, of which probabilistic graph theoretical analysis was able

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to make predictions [13]. The investigation of this graph from a signal propagation point of view, with an approach related to the one described here, was also conducted [14]. The methods presented here are built upon multiple trends, as present in the literature, of structurally characterising networks.

Random graphs greatly contribute to the understanding of real-world networks by describing the formation mechanisms of networks by sampling statistical generative models. They reproduce statistical properties of the real networks, such as degree distribution [15].

The hierarchical organisational principle bears a great importance in the formation of biological and artificial networks. [10]. Characterising graphs and their vertices in this regard can add an important point of view to understanding function.

The graphical representation of a network consisting of vertices and edges provides limited information about the functional role of vertices, and it is unsuitable for comparison of network structure. In the literature, one can find such a representation that maps graphs with the same structure to the same figure [1], but there has been no such representation available so far that contains functional information in an intuitive way.

### Goals

My goal was to investigate what implications can be inferred from the structure of networks regarding the signal flow on them. I wanted to achieve this using a method that meets the following criteria:

1. Uses the information that can be gathered from the global structure of the graph to characterise individual edges.
2. Is able to determine the role played by a single vertex in the signal flow.
3. Enables the comparison of real-world and model networks and the definition of a classification more precise than available previously, also on small networks.

I intended to apply this method for testing an algorithm that generates a precise model of the cortical area network.

## Methods

On a directed graph,  $G(V, E)$ , I defined an edge-based measure that describes the role of the given edge in the global signal flow, using shortest paths. These paths constitute the structural skeleton of the graph, and they determine the interaction of the vertices primarily.

**Convergence degree.** Given all shortest paths passing through the edge connecting vertices  $i$  and  $j$ , let the set of vertices that these paths originate from denoted by  $In(i, j)$ , and the set of vertices they terminate on by  $Out(i, j)$ . Then the convergence degree (CD) of the edge is 1, and its overlap measure is 2.

$$CD(i, j) = \frac{|In(i, j)| - |Out(i, j)|}{|In(i, j) \cup Out(i, j)|} \quad (1)$$

$$Ovl(i, j) = \frac{|In(i, j) \cap Out(i, j)|}{|In(i, j) \cup Out(i, j)|} \quad (2)$$

A positive convergence degree means that the edge transmits information by the shortest paths passing through it from a larger set of nodes to a smaller one, and a negative vice versa. The overlap is always positive, and characterises the participation of the edge in the feedback, circular component of the signal flow. Instead of the global characterisation, one can give a local one too, by only considering the paths leading to neighbours of the two endpoint vertices of the edge. or the position taken between these two extremes can be controlled by imposing restrictions on the lengths of the shortest paths.

## Publications

### Publications that serve as the bases of the theses

1. **Bányai M.**, Négyessy L., Bazsó F.: Organisation of signal flow in directed networks. *J Stat Mech*, P06001, 2011.
2. Négyessy L., **Bányai M.**, Bazsó F.: What makes the prefrontal cortex so appealing in the era of brain imaging? A network analytical perspective. *Acta Biologica Hungarica*, **63**(S1):38–53, 2012.
3. **Bányai M.**, Nepusz T., Négyessy L., Bazsó F.: Convergence properties of some random networks. In: IEEE Proceedings of the 7th International Symposium on Intelligent Systems and Informatics, Subotica, Serbia, 2009, pp. 241–245.
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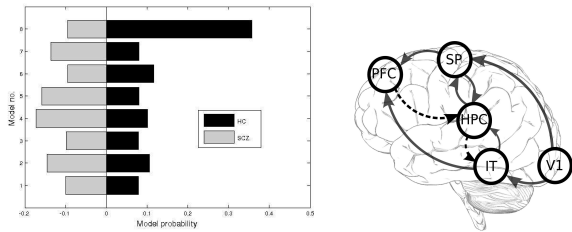


Figure 2: The result of Bayesian model comparison shows that the effect of the prefrontal cognitive control on the hippocampal areas is decreased in schizophrenia.

the formation of new hypotheses and testing them on data with a similar methodology. The results further the emergence of a diagnostic application, but are not sufficient for such themselves, as the use of the described alterations as biomarkers would require the integration of much more data and the implementation of meta-studies. For therapy and drug discovery applications, the results indicate a promising direction of development [4].

## Conclusion

Based on measurement data, I showed that during schizophrenia, the cognitive control exerted by higher-level cortical areas over temporal lobe areas is diminished, especially in the prefrontal-hippocampal connection. I supported this finding with Bayesian model selection and parameter estimation. I demonstrated that the results of the procedure are independent from the learning performance of the subjects, and reflect physiological alterations. I showed that the alteration of the intrinsic connections of prefrontal neural networks can also contribute to the dysfunction. The application of the results in diagnosis and therapy may be the subject of further research.

**Flow representation.** To be able to determine the roles vertices played in signal flow, I defined multiple vertex-based measures using CD.

$$\sigma_{in}^-(i) = \frac{1}{d_{in}(i)} \sum_{(j,i) \in E} \min(0, CD(j, i)) \quad (3)$$

$$\sigma_{out}^+(i) = \frac{1}{d_{out}(i)} \sum_{(i,j) \in E} \max(0, CD(i, j)) \quad (4)$$

$d_{in}$  and  $d_{out}$  mean the incoming and outgoing degrees of vertices. Quantities  $\sigma_{in}^+(i)$ ,  $\sigma_{out}^-(i)$ ,  $\sigma_{ovl}^+(i)$ ,  $\sigma_{ovl}^-(i)$  can be defined similarly. If we plot these numbers on a two-dimensional figure (using colours for overlap), we get a visual representation of the graph that is invariant on its automorphism group.

The role vertices play in signal flow can be described by the ratio of the measures above. If the sum CD on the incoming edges of a vertex is positive, then it behaves as a source of information in the network, in the opposite case, as a sink. These functions correspond to the positions assumed by the vertex in the quarter planes II and IV on the figure, to the extent of the distance from the origin. This property allows us to imply the role of the vertex in the hierarchy of the network: source vertices tend to assume a lower position than sinks do.

**Modified small world algorithm.** One can construct a precise model of the cortical area network in the aspect of information flow using a modified version of the small-world algorithm of Watts and Strogatz [18]. The algorithm consists of the following steps:

1. Choose the number of vertices of the graph ( $n$ ), and add  $n$  edges so they form a closed circle.

2. Determine the in-degree of each vertex ( $d_{in}$ ).
3. By normalising degrees, determine the probability that a vertex will become the target of a new edge.
4. If reciprocity or the clustering coefficient is to be controlled, distort the distribution accordingly.
5. By sampling the resulting distribution, determine the endpoints of the new edge, and add it to the graph.
6. If the desired number of edges is reached, the algorithm terminates, otherwise continue at step 2.

If there are several Hamiltonian circles in the network to be modelled, deletion of the edges in the original circle is unnecessary, as it only adds one Hamiltonian circle to the model graph.

## Results

**T 1/1.** *I showed that the convergence degree measure is suitable for investigating the structurally determined signal flow properties of directed networks, can be used to create more refined classification systems than traditional graph theoretical measures, and also to give a more precise definition of the signal processing roles of individual vertices and edges.*

**T 1/2.** *I devised a preferential rewiring graph generation algorithm that gives a better model of the cortical macro-network than previously defined random graph models in the sense of reproducing more structural properties.*

**T 1/3.** *I determined the role of the prefrontal area in cortical signal processing quantitatively using the convergence degree: the information flowing between cortical areas shows a strong convergence on the dorsolateral prefrontal cortex.*

Related publications for thesis points **T 1/1.**, **T 1/2.**, **T 1/3.**:

*from the task performance of the experimental subjects.*

**T 2/3.** *I showed, using a cellular network model of short term plasticity that the alteration of prefrontal synaptic dynamics, as observed in schizophrenia, drives the recall duration of working memory to a pathological regime.*

Related publications for thesis points **T 2/1.**, **T 2/2.**, **T 2/3.**:

- **Bányai M.**, Diwadkar V., Érdi P.: Model-based dynamical analysis of functional disconnection in schizophrenia. *NeuroImage*, **58**(3):870–877, 2011.
- **Bányai M.**, Diwadkar V., Érdi P.: Pathological Effects of Cortical Architecture on Working Memory in Schizophrenia. *Pharmacopsychiatry*, **43**(S1):592–597, 2010.

## Application of the results described in the theses

Results of model comparison are depicted in Figure 2. The difference between the functional subnetworks of schizophrenic and control subjects is expressed in a decrease of cognitive control exerted by higher-level areas over the behaviour of the temporal lobe and the hippocampal area, responsible for memory formation, in the patient group. This is consistent with the results of earlier models described in the literature, like the theory explaining auditory hallucinations by a cognitive deficit in agency determination [17].

The determination of the functional macro-network and the deficit model of the intrinsic connectivity of the prefrontal cortex both support the area interaction model of associative learning [3], in which the prefrontal cortex implements a switching mechanism between encoding and recall modes of memory.

As the mapping of the task-dependent, effective connectivity patterns between cortical areas is far from complete, the most important application of the results described in the theses is

by a variational method that only requires the values of the logarithm of the evidence distribution for the models. Approximations of these values are created during the parameter estimation, so this step is less computationally expensive [16].

I conducted the estimation of the probability distribution over the models for the patient and control groups separately, for two sets of models, one with varying combinations of connections in the control flow and one with varying effects of experimental inputs on those. To separate the variation caused by the differences in learning performance and the illness, I conducted the estimation of the model distribution separately for the subjects in the control group with learning performances no better than that of the subjects in the patient group.

**Synaptic modulation** To compare the normal and disordered functioning of the intrinsic dynamics in the PFC, I investigated the parameter dependence of the synaptic model described by 7 and 8. According to [9], calcium dynamics is altered in schizophrenia, which results in differences in short-term plasticity. To investigate possible causes of alterations in the working memory, I determined the effect of the change in parameters  $\tau_d$  and  $\tau_f$  on the recallable duration of memory patterns.

## Results

**T 2/1.** *I discovered using dynamic causal models that in patients with schizophrenia, the information flow between prefrontal and hippocampal areas during learning, responsible for cognitive control, is significantly damaged.*

**T 2/2.** *I showed that dynamic causal models are able to grasp the physiological differences caused by the illness independently*

- **Bányai M.**, Négyessy L., Bazsó F.: Organisation of signal flow in directed networks. *J Stat Mech*, P06001, 2011.
- Négyessy L., **Bányai M.**, Bazsó F.: What makes the prefrontal cortex so appealing in the era of brain imaging? A network analytical perspective. *Acta Biologica Hungarica*, **63**(S1):38–53, 2012.
- **Bányai M.**, Nepusz T., Négyessy L., Bazsó F.: Convergence properties of some random networks. In: IEEE Proceedings of the 7th International Symposium on Intelligent Systems and Informatics, Subotica, Serbia, 2009, pp. 241–245.

## Application of the results described in the theses

The application described in thesis 1/3. is illustrated in Figure 1. Furthermore, the method is applicable in the structural comparison of real-world networks. From these I conducted the analysis of the visuo-tactile cortical network of the macaque and an intracellular signal transmission protein network, showing a strong hierarchical structure in the latter. I evinced that, where known, the signal transmission roles of the vertices determined by convergence degree is consistent with biological function [11]. For the vertices with unknown function, the method provides a prediction.

A further application is the analysis of aggregated networks. These are large-scale representations of big networks, where we replace the more strongly connected sets of vertices by a single vertex. I analysed the aggregated version of the protein network mentioned above, the road network of a city and the procedure call graph of the kernel of an operating system. In the latter, I showed that control flow converges on low-level system calls. I showed the statistical connection between the sizes of clusters represented by the vertices and their convergence degree.

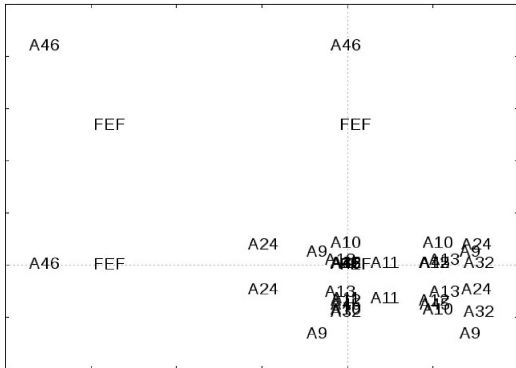


Figure 1: Depiction of prefrontal cortical areas in flow representation. From the position of the dorsolateral prefrontal cortex (Brodmann Area 46) assumed in quarter plane II, a role as an information sink can be implied.

By comparing the grouping of vertices based on signal flow properties and connectivity, I showed that these two kinds of clustering reveal different structural properties, and one can make implications about the regular or random nature of the organizational principle of the network based on their similarity.

## Conclusion

I defined the measure of convergence degree to investigate the effect of network structure on function. Using this I provided a more precise classification of real-world and model networks than available so far, and validated the algorithm that produces the random model of the cortical area network. Using convergence degree I determined that the prefrontal cortex is a target of the cortical information convergence. Further research may derive the structural constants of dynamical models defined on graphs, and their properties, from convergence degree.

The estimation of the posterior distribution is done by a numerical algorithm of the Expectation Maximisation (EM) type, that estimates the expectation and the covariance matrix of the posterior  $(\theta_y, C_{\theta|y})$  and the covariance matrix of the noise model  $(C_\epsilon)$  in an alternating fashion using an iterative gradient method [8]. The parameter values produced this way have been compared between the control and patient groups using a frequentist t-test and Bayesian model averaging as well.

**Model comparison.** The most consistent way of comparing model structures is when we can infer a complete probability distribution over the set of the  $k$  models. In the case of DCM-s this can be done by the definition of a hierarchical generative model, that describes the emergence of the measurement data of a whole group of  $n$  subjects in a probabilistic way. On the lower level of the model we use the distribution of the data series given a specific model structure, which is the marginal likelihood or evidence distribution of the DCM (11). For this we define the prior over different models as a multinomial distribution (12). Here parameters  $r$  mean the expectation of the data series of a given subject being generated by a given model. The expected value of these quantities over subjects gives the expected value of the posterior probability of models (13).

$$p(y_j | M) = \int p(y | \theta, M)p(\theta | M) d\theta \quad (11)$$

$$p(M | r) = \prod_{i=1}^k r_k^M \quad (12)$$

$$E(r_k) = E(p(M | y_1 \dots y_n)) \quad (13)$$

The parameters of the hierarchical model can be estimated



of memory processes. The selection of the voxels associated to these areas were made combining task-dependent activity and a probabilistic anatomical atlas.

**Definition of the model space.** The models to compare can contain different interaction networks of the five brain areas and different effects of the experimental conditions. For the definition I assumed the existence of two kinds of information flow in the cortex: a data flow from the sensory areas towards the higher-level areas and a control flow from high-level cognitive areas towards sensory systems. The model space represented different disconnections in the control flow and different deficiencies of the effects of experimental inputs, and also contained the model describing the fully connected flow. The inputs of the models were defined as the experimental conditions (presence of a visual input, encoding period, retrieval period, number of learning epochs so far).

**Parameter estimation.** The parameter sets of the models consist of the coupling matrices and hemodynamic parameters (9). These were fit to the data based on the Bayes rule (10) pairing each model ( $M$ ) with each measurement. The prior distribution of the parameters contained fixed zeros for connections not included in the given model and a zero-mean Gaussian distribution with a low variance ( $\mathcal{N}(0, C_p)$ ) for the rest. The likelihood is given by the model (5, 6) and a zero-mean Gaussian noise model ( $p(\epsilon) = \mathcal{N}(0, C_\epsilon)$ ), this way the posterior distribution also turns out to be Gaussian.

$$\theta = \{A, B, C, \theta_h\} \quad (9)$$

$$p(\theta | y, M) = \frac{p(y | \theta, M)p(\theta | M)}{p(y | M)} \quad (10)$$

## Model-based dynamical analysis of functional disconnection in schizophrenia

### Preliminaries to the study

The spatially detailed investigation of the functional networks of the whole cortex was made possible by fMRI technology. With this, a functional measurement about the whole brain can be conducted with the temporal resolution of 1-2 seconds and spatial resolution of 3 millimetres. From the voxel activations measured this way, the time series corresponding to certain cortical areas can be extracted utilising anatomical information and task-dependent activity. A drawback of the technology is that it measures neural activity in an indirect manner, as the sensor captures the relative concentration of deoxyhemoglobin in the space compartment corresponding to the voxels (BOLD signal). This is tightly coupled to neural activity, but the relationship is nonlinear, and its exact form is hard to determine. Functional subnetworks can be investigated by the estimation of connectivity between active regions.

Schizophrenia is a psychiatric disease affecting the lives of many, and its biological background is largely undiscovered. Experienced alterations of higher-order cognitive functions make it eligible to serve as a basis of a differential approach to the investigation of functional cortical subnetworks. A prevalent hypothesis attributes the symptoms of schizophrenia to the disconnection of such networks [5]. Additional to macro-network dysfunction, the intrinsic network dynamics of the prefrontal cortex is also altered during the disease [2],

**The experimental paradigm.** The experiment described by [3] investigates alterations of associative learning in schizophrenia patients using fMRI measurements. The 11 patients and 11 healthy controls had the task of memorising the position of simple objects on a grid. During the eight encoding and retrieval periods, 288 measurements were made of

the activity of the whole brain of each subject. The learning performance of patients was significantly lower than that of the controls, however, they were able to complete the task.

**Dynamic causal models.** Dynamic causal models (DCM) enable the complete statistical description of functional subnetworks [7].

$$\dot{x} = (A + \sum_{i=1}^N u_i B^i)x + Cu \quad (5)$$

$$y = \lambda(x, \theta_h) \quad (6)$$

The unobserved neural activity of the areas is described by a bilinear formula 5, where  $u$  denotes the time series representation of the conditions constituting the experimental paradigm.  $A$ ,  $B$  and  $C$  are coupling matrices that describe the interaction of areas, the direct effects of the inputs on the areas and the modulatory effects of inputs on intrinsic connections.

The  $\lambda$  nonlinear mapping describes the way the BOLD signal is emerging from the neural activity according to the Balloon model. Details of this are given in [6].

**Prefrontal synaptic model.** To investigate the intrinsic dynamics of the prefrontal cortex, one can define a synaptic model for integrate-and-fire neural networks [12].

$$\frac{dx}{dt} = \frac{1-x}{\tau_d} - ux\delta(t-t_{sp}) \quad (7)$$

$$\frac{du}{dt} = \frac{U-u}{\tau_f} - U(1-u)\delta(t-t_{sp}) \quad (8)$$

In formulae 7 and 8,  $x$  denotes the transmitter release probability, and  $u$  the amount of transmitter available on the presynaptic side. The ratio of time constants  $\tau_d$  and  $\tau_f$  determines the facilitatory or depressive nature of the synapses.

The model can give descriptions of the functional mechanism of working memory in multiple dynamical regimes [12].

## Goals

My goal was to define a model space based on fMRI measurements to investigate cortical subnetworks of associative learning that is suitable to reveal functional alterations related to schizophrenia using statistical parameter estimation and model comparison. My primary intention was to capture the role and alterations of control signals that are transmitted from the higher-level areas towards sensory areas. In addition, I wanted to investigate the possible effects of intrinsic structural alterations of the prefrontal cortex on learning and memory processes.

## Methods

The first step in the analysis of cortical subnetworks is the selection of the areas that participate in the implementation of the task. For the associative learning task the following five areas serve as vertices in the model network: primary visual cortex (V1), that receives sensory input due to the visual nature of the task, inferior temporal cortex (IT), responsible for object recognition and encoding in the ventral stream of the visual system, superior parietal cortex (SP), encoding location information in the dorsal stream, hippocampus (HPC), responsible for combining the partial information from the two streams and writing the pattern to the associative memory, and the dorsolateral prefrontal cortex (PFC), responsible for the cognitive control