Input data optimization tool for analysis of effective brain connectivity in fMRI

MARTIN LAMOŠ, TOMÁŠ SLAVÍČEK, JIŘÍ JAN
Department of Biomedical Engineering
Brno University of Technology
Kolejní 2906/4, 612 00 Brno
CZECH REPUBLIC
lamos@feec.vutbr.cz http://www.dbme.feec.vutbr.cz

Abstract: Functional magnetic resonance imaging utilizing the blood oxygenation level dependent effect as an indicator of local activity is a very useful technique to identify active brain regions. Currently, there is a growing interest in studying the connectivity between different brain regions. This contribution describes one of the methods used to investigate effective connectivity and its inconveniences, which may occur during group data processing. The developed software tool is presented as a possible solution and its benefits are proved on real fMRI experiment.

Key-Words: fMRI, dynamic causal modelling, connectivity, SPM, group analysis, MATLAB.

1 Introduction

Brain activity mapping using functional magnetic resonance imaging (fMRI) is an indirect technique, where blood supply changes in particular brain centers are detected by measuring BOLD (Blood Oxygenation Level Dependent) signal. Apart from the exploratory analysis itself that implies the mapping of active brain areas based on the design of the experiment, there is a growing interest to analyse functional organisation in the brain [1].

Functional organisation of brain areas is given by functional integration and functional specialisation principles. Cortical areas belonging to some aspect of perceptual or motoric processing are defined with help of functional specialisation. However, one brain area only does not have to perform some specific function in the brain. Many more cortical regions can be involved in this process. The connection between participating regions is realised by functional integration using connectivity. The revelation of integrations themselves is possible for example by the explanation of an effect which has one brain area to another or by finding temporal correlations of activities across different brain regions. The connectivity mentioned above can be one of three different types: anatomical, functional and effective.

Anatomical connectivity is a slightly specific in comparison with other two types, because it seeks real connections between neurons or neuronal populations. Functional connectivity expresses a statistical dependency (correlation, covariation, etc.) between neurophysiological events, which are significantly spatially distant from each other. Unfortunately, functional connectivity methods are unable to describe causes of statistical dependencies, because there could be more than one possible reason of causal link between two events, such as physiological or movement related noise [2]. The evaluation of functional connectivity can be realised by techniques like a multidimensional scaling (MDS), correlation of temporal courses, multivariate analysis of covariance (MANCOVA), principal component analysis (PCA) and independent component analysis (ICA).

Effective connectivity clearly refers to effect of one neural system to another. Methods are very dependent on models of interactions, from which are derived the quality and the reliability of achieved inferences. Main approaches for identification of the effective connectivity are psychophysiological interactions, structural equations modelling, multidimensional autoregressive models, Granger causality and dynamic causal modelling (DCM) [3]. None of these methods is exploratory technique, thus it is always necessary to determine a hypothesis, which will define areas for analysis, their connections, system inputs and possible modulations of connections.

There is a possibility to consider the effective connectivity approaches as a more novel evolutionary step of functional connectivity (from the last decade methods development point of view).
More space is dedicated to effective connectivity in next parts of this paper due to the idea.

Considering statistical character of data processing in fMRI, group data are usually used for getting relevant results from analysis and making more accurate subsequent inferences. However, the most frequently used software tool for general fMRI analysis, SPM8 toolbox (Functional Imaging Laboratory, Wellcome department of Imaging Neuroscience, Institute of Neurology at University College London, UK), has no exploratory tool for working with group data.

This paper focuses on group analysis problem regarding the DCM method. In the next chapter there is a description of DCM as one of the effective connectivity technique. Thereafter, the software tool developed in this study is presented. Last chapters describe usage the tool on real measured data and summarize obtained results.

### 2 Dynamic Causal Modelling

The DCM method enables to make inferences about neural effects based on real measured fMRI data. The main idea is to estimate model parameters of neuronal system whose outputs correspond accurately to observed (measured) BOLD response [3]. The model also takes into account nonlinear and dynamic character of measured BOLD response. The time course of modelled BOLD signal is created by conversion of modelled neuronal dynamics into hemodynamic response using convolution with HRF (Hemodynamic Response Function). Thereafter, the model structure and state equations are defined on the basis of used modality (fMRI in this case).

The state model of DCM consists of two different levels [3]. The first one is not possible to observe directly using fMRI, it represents simple model of neuronal dynamics in the system of \( k \) connected brain areas. Every component of the system \( i \) represents one state variable \( z_i \) and system dynamics is described by a change of neural state vector in time. However, neural state variables do not correspond to any neurophysiological measurement directly, together they constitute the description of neuronal population in given areas. This hidden level of DCM simulates how the neural dynamics is driven by external stimulation. Excitations from stimulation are described by external inputs \( u \), which are connected to the model two different ways. One of them is a response to direct effect at given areas, second one affects the strength of connection between regions. The time development of neural state vector \( z = [z_1, z_2, ..., z_j]^T \) is given by [3]

\[
\dot{z} = F(z, u, \theta),
\]

where \( F \) stands for nonlinear function describing neurophysiological activity \( z \) in \( k \) brain areas, \( u \) are system inputs (mentioned above) and \( \theta \) corresponds to others model parameters, which are time invariant in contrast to \( z \) and \( u \). The function \( F \) has a bilinear form and parameters of neural state equation \( \theta = A, B_1, ..., B_m \). \( C \) can be presented as a partial derivation of \( F \) [3]

\[
\dot{z} = Az + \sum_{j=1}^{m} u_j B_j z + Cu
\]

\[
A = \frac{\partial F}{\partial z},
\]

\[
B_j = \frac{\partial^2 F}{\partial z \partial u_j} = \frac{\partial}{\partial u_j} \cdot \frac{\partial F}{\partial z} \quad (3)
\]

\[
C = \frac{\partial F}{\partial u}
\]

Parameter matrices \( A, B_1, B_2, ..., B_m \), \( C \) express three parts, which made the core of modelled neural dynamics [3]:

1. Intrinsic effective connectivity between cortex regions is independent on the task stimulation and mediated by anatomical connections (matrix \( A \)).
2. Modulation of effective connectivity, which is dependent on the stimulation (matrices \( B_1, ..., B_m \)).
3. Direct inputs into the system, which are driving the activity of neuronal population in the specific area (matrix \( C \)).

The main difference between effects caused by modulatory and driving inputs (matrices \( B \) and \( C \) ) is in the manner they influence the neuronal system. Driving input induces direct synaptic responses in target area, while modulatory input changes synaptic responses in target area based on influences of other brain areas.

The second level of state DCM model is hemodynamic model, which describes conversion of neuronal activity into BOLD response [4]. DCM combines neural dynamics model with biophysiological plausible and experimentally verified hemodynamic model, which is based on balloon model. The model is individually defined for each ROI (region of interest) and considers following physiological processes. Changes in neural activity in the region cause vasodilatation, which leads to increased blood flow and results in local changes of blood volume and haemoglobin concentration. This means that a BOLD signal can be predicted as a nonlinear function of blood volume and concentration of deoxyhemoglobin [4].
Fig. 1: Graphical user interface of developed software tool

The DCM models are estimated using EM (Expectation Maximization) algorithm, which iteratively finds parameters in the way of maximal model plausibility and thus decreases error between observed (measured) data and model [3].

3 Developed software tool

During this study software tool for patients and brain regions selection for connectivity analysis using DCM has been developed. The tool serves as advanced results explorer and enables user to show both individual and group-level activation maps, examine detailed statistics of all persons in the study and set ROI (region of interest) coordinates for DCM analysis.

Main purpose of this software tool is to ensure minimal activations (statistical values) in all selected ROIs among all persons in the study. This is very important from two reasons, the first is to maintain required SNR (Signal to Noise Ratio) and data consistency for DCM analysis. Using lenient threshold level leads to low SNR in extracted data. The second reason is that if there is no detected activation in target location for signal extraction, the SPM software automatically shifts the source zone for extraction to the nearest above-threshold (active) region. The distance between intended and selected regions can be significant, thus it is not certain that the extracted signal comes from target area, where user want to analyse connectivity.

Using presented software tool, neuroscientists can check if selected threshold level is applicable among all persons and ROIs, alternatively they can find potentially problematic coordinates or more suitable threshold level for signal extraction. In extreme cases, such as data corruption, this software tool can help identify inappropriate persons (results) for further analysis.

Since fMRI analyses were performed in SPM8 software, which runs in the MATLAB environment, the developed software tool also uses MATLAB.

Graphical user interface is divided into two main sections, see Fig. 1. On the left side, there is a panel dedicated to show group activation map, cursor position indicated in voxels and mm (in standardized MNI – Montreal Neurological Institute space) and other user-adjustable settings. Right panel is multifunctional and provides functions related to activation maps of individuals and ROI coordinates management. Moreover, user can display group variability map and so called “minimal statistics map”, which represents minimal statistical values among all subjects for each voxel. Visualization method of activation maps is similar to SPM, fully interactive and intuitive. There are 3 types of thresholding including FWE correction.

After specifying ROI coordinates, user can display summary statistics of all subjects in a...
summarizing table. This helps to make decisions about specified dataset before extracting signals for DCM analysis. Software also supports automated loading of files and data export for further usage.

4 Experiment
Data from specific experiment called oddball were used to demonstrate problems of group DCM analysis in SPM8 software and to show benefits obtained by using developed tool to optimize dataset prior to performing DCM analysis. The visual oddball task [5] involved three types of stimuli, which were presented to the subject in a random fashion. Stimuli were represented by yellow colored capital letters on black background, X for targets (15% of all cases), O for frequent (70%) and other letters as distractors (15%). Subjects were instructed to press a button when target appeared and not to respond to any other types of stimuli. The experiment was performed on 10 subjects (3 females and 7 males at average age of 25 years).

Fig.2: Activations (red areas; saturation corresponds to the significance of the thresholded T value) obtained after group analysis. Significance level p<0.05 FDR (False Discovery Rate).

Measurements were made in 1.5T Siemens Symphony MRI scanner. Gradient echo sequences with TR of 1660ms were used to acquire T2-weighted functional images at resolution of 64×64×15 voxels. Field of view was set to 250×250mm with slice thickness of 6mm. The experiment was divided into 4 sessions, each of 256 scans and 84 stimuli. Anatomical high resolution T1-weighted images were acquired with matrix size of 256×256×160 voxels.

Obtained data were preprocessed in SPM8 toolbox. Movement correction was made by spatial registration of functional scans to the first one. Anatomical and functional images were coregistered and then spatially normalized to MNI (Montreal Neurological Institute) space. Next step was smoothing with 8mm kernel of Gaussian filter in order to comply with normal distribution prerequisite and to increase SNR [6].

<table>
<thead>
<tr>
<th>Table 1: Target brain locations for DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain area</td>
</tr>
<tr>
<td>MiddleFrontalGyrus (MFG)</td>
</tr>
<tr>
<td>InferiorParietalLobule (IPL)</td>
</tr>
<tr>
<td>InferiorFrontalGyrus (IFG)</td>
</tr>
</tbody>
</table>

After preprocessing, the functional data were analysed using general linear model (GLM) to obtain individual activation maps. Those results served as input to group analysis realised by one sample t-test (Fig. 2). Target brain locations for DCM analysis were specified by neurologists based on group activation maps. Selected coordinates for signal extraction are summarised in Table 1. Obtained signals represent first eigenvector from time course of voxels located in sphere with center at selected location and radius of 8mm.
Fig. 3: Model variants of connections for DCM

Table 2: DCM analysis summary (orange label means non-provable results, blue label indicates falsely plausible model selection)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Bayesian model selection</th>
<th>Active voxels in MFG, IPL, IFG</th>
<th>Max. shift of area [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability of model 1</td>
<td>Probability of model 2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.95</td>
<td>35, 15, 22</td>
</tr>
<tr>
<td>2</td>
<td>0.06</td>
<td>0.94</td>
<td>14, 13, 24</td>
</tr>
<tr>
<td>3</td>
<td>0.45</td>
<td>0.55</td>
<td>32, 27, 28</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
<td>0.50</td>
<td>4, 2, 4</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>0.75</td>
<td>36, 28, 10</td>
</tr>
<tr>
<td>6</td>
<td>0.08</td>
<td>0.92</td>
<td>29, 34, 35</td>
</tr>
<tr>
<td>7</td>
<td>0.04</td>
<td>0.96</td>
<td>28, 5, 38</td>
</tr>
<tr>
<td>8</td>
<td>0.08</td>
<td>0.92</td>
<td>34, 52, 25</td>
</tr>
<tr>
<td>9</td>
<td>0.01</td>
<td>0.99</td>
<td>37, 1, 23</td>
</tr>
<tr>
<td>10</td>
<td>0.01</td>
<td>0.99</td>
<td>25, 14, 44</td>
</tr>
</tbody>
</table>

Two model variants of connections between specified locations were designed (Fig. 3). The first one represented reciprocal connection among all areas, while the second model disallowed mutual influence between IFG and MFG. The driving input was set in both cases to IPL, no modulation inputs were selected due to the design of experiment. The last step was Bayesian model selection in order to compare both models.

5 Results
Acquired results (Table 2) are in conformity with assumptions that specific model 2 (Fig. 3 bottom) is more plausible than universal model 1 (Fig. 3 top) for majority of tested subjects. However, some subjects (number 3, 4 and 5) show no significant difference between models. There could be many reasons for this. It can be proved, that mentioned subjects don’t have active voxels in at least one of the target areas. In that case, extraction zone is automatically shifted and signals no longer come
from intended area. This leads to low significance of estimated models for most situations, because signals used in DCM originate from brain areas not involved in the experiment. Unfortunately, results may be falsely plausible (like subject 9 in this study) in some cases, which may confuse neuroscientists evaluating the data.

Software tool presented in this paper is designed to help user optimize input dataset prior the DCM analysis. It was able to identify both low levels of activations and insufficient quantity of active voxels in target areas of subjects 3, 4 and 9 in the study (Fig. 4). This perfectly corresponds with problematic results of DCM analysis of those subjects as mentioned above.

![Summary table showing activation values in ROIs for all subjects](image)

**Fig.4: Summary table showing activation values in ROIs for all subjects (checkbox indicates significant activation)**

### 6 Conclusion

In this paper common problems of group DCM analysis using SPM8 software were discussed. In particular, inconveniences related to proper coordinates selection and suitable choice of the threshold level for signal extraction. A novel software tool, which can help to overcome mentioned complications, was introduced. Its benefits have been demonstrated on real dataset from fMRI experiment which involved DCM analysis. One of the main contribution which brings the developed tool into the group data processing is the way of user friendly data visualisation. The presented software seems to be a suitable supplementary tool for work with group data in SPM8 toolbox.

### 7 Acknowledgements

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### References:


