A Grid Framework for Non-Linear Brain fMRI Analysis

Rodolfo ANDRADE[a,1], Ilídio OLIVEIRA[a,b], José Maria FERNANDES[a,b], João Paulo Silva CUNHA[a,b]

[a] *IEETA – Universidade de Aveiro, Portugal*

[b] *Dep. of Electronics, Telecommunications and Informatics, Universidade de Aveiro, Portugal*

Abstract. Functional magnetic resonance imaging (fMRI) is an imaging technique that can be used to characterize brain physiological activity, usually presented as 3D volumes in function of time. In the context of our previous work in nonlinear association studies in electroencephalogram (EEG) time series, we were able to identify clinical relevant features useful in clinical diagnosis. The use of a similar approach in fMRI, now adapted for 3D time series, is both appealing and new. Such time series analysis imposes challenging requirements regarding computational power and medical image management. In this paper we propose a grid architecture framework to support the typical analysis protocol of association analysis applied to fMRI. The system, implemented using the gLite middleware, provides the necessary support to manage brain images and run non-linear fMRI analysis methods.

Keywords. Non-linear fMRI analysis methods; brain function; medical imaging; Grid computing.

Introduction

fMRI is a relatively new MRI based technique that allows monitoring of the brain activation patterns by measuring the magnetic variation induced by changes in the blood flow associated to brain neural activity. The neural activity produces an hemodynamic response —an increase in blood flow, with a delay of about two seconds— richer in oxyhemoglobin to compensate the increase in oxygen consumption. This change in oxyhemoglobin is called the Blood Oxygen Level Dependent response or BOLD effect [1]. When BOLD activations and deactivations are time related with specific events, they can be correlated to the event's metabolic response in the brain [2]. This is a valuable tool for studies ranging from brain diseases (e.g. Alzheimer [3], Parkinson [4]) to study normal brain function in aging [5].

One major problem of this technique is that BOLD changes are small, in the order of 3-5% from the background MRI imaging signal [6]. A methodological problem with fMRI analysis is that there is no unique model for the hemodynamic response function (HRF) [7]. This may compromise the fMRI interpretation since it depends on the HRF activation model used.

[1] Corresponding author: Rodolfo Andrade, IEETA – Universidade de Aveiro; E-mail: randrade@ieee.org.

The traditional approach to analyze fMRI series is based on statistical parametric mapping (SPM) [8]. In SPM it is assumed that through structured paradigms with clearly distinguishable states (usually activation/no activation paradigms related with the studied brain function) it is possible to infer related brain areas to BOLD changes in fMRI through general linear models (GLM) [9]. This is done by finding fMRI voxels which are statistically and linearly correlated with the paradigm activation model in time. One example among several, is given by Powell et al. [10] in which SPM is used to infer memory related brain areas.

The major drawback of SPM is that it assumes and uses unproven response models and linear assumptions in the analysis, in which no model clearly relates studied tasks and BOLD response in the brain [7]. This is worsen by the fact that BOLD response has nonlinear contributions that should be also taken into account [11]. For these reason, SPM fMRI analysis is dependent on several factors to obtain statically significant results [12] and demands expertise to extract relevant information from the analysis results [13]. In this context, non-linear models, parametric and non-parametric, are attractive approaches that deserve attention.

Following our previous work in nonlinear association studies in electroencephalogram (EEG) time series [14-16], where we were able to identify clinical relevant features useful in clinical diagnosis, the use of a similar approach in fMRI, now adapted for 3D time series, is both appealing and a novelty.

Such computer-based analysis imposes high-requirements with respect to medical image management (raw data and results) and processing times, as detailed in the next sections.

In this paper we propose a grid architecture framework to support the typical analysis protocol of association applied to fMRI. The system, implemented using the gLite middleware, provides the necessary support to manage brain images and run non-linear fMRI analysis methods.

1. Background on fMRI Time Series Association Analysis

The basic procedure for association analysis between time series consists in determining the association level of two time series using an association measure. In case of this association measure being non-linear we are performing a non-linear association analysis. The extension to 3D fMRI time series analysis is straight forward by performing a voxel time series pair-wise association analysis. The drawback is that, when considering 3D volumes in time, the number of pairs to analyze increases, increasing both the computational complexity of the overall process and the management of the results.

To illustrate this fact, consider a sequence of 5 minutes of fMRI with a volume acquisition of 16 64x64 slices acquired from top to bottom of the head at each 3 seconds where the final result consists of 200 volumes of 64x64x16 voxels. Performing association analysis as described would imply:

- (64x64x16)x(64x64x16) volumes, in the worst case, where the association is not symmetric (e.g. using the h^2 association measure [14]) and for each voxel a volume is generated containing the association coefficient with all other voxels.
- The overall computational complexity would be at least supra linear (several association measures have supra linear complexity).

- In addition, considering time delay analysis would increase any of the previously referred issues.

2. The BImageG Grid Framework

2.1. Overall System Architecture

Grid infrastructures are being successfully used in medical image processing to handle the demanding requirements of large images storage and communication, and to enable complex analysis workflows [17-19]. They provide the ability to seamless aggregate distributed computational power, extensive storage resources and high-bandwidth networking. In addition, Grids also ensure a proper level of security, both at identity (digital certificates) and access (Virtual Organizations management) levels. Building upon the state of the art Grid middleware, we propose a Grid enabled framework to provide the computational power and data access needed to run non-linear analysis applied to fMRI (Figure 1).

The association analysis of fMRI can be applied to different parts of the 3D volume independently. This enables a natural parallelization of the association analysis protocol. In a grid environment, the analysis of each volume partition can map to the creation of one job.

Users harness from the computing resources pool using a web portal. In this portal, the user (typically a biomedical engineering researcher) is able to select the intended fMRI analysis protocol, though currently only the non-linear time series association is implemented.

The portal delegates the user requests in the BImageG application layer, which provides the necessary services to generate grid job workflows (according to the fMRI research protocol chosen by the user), suitable to the grid environment, allowing a

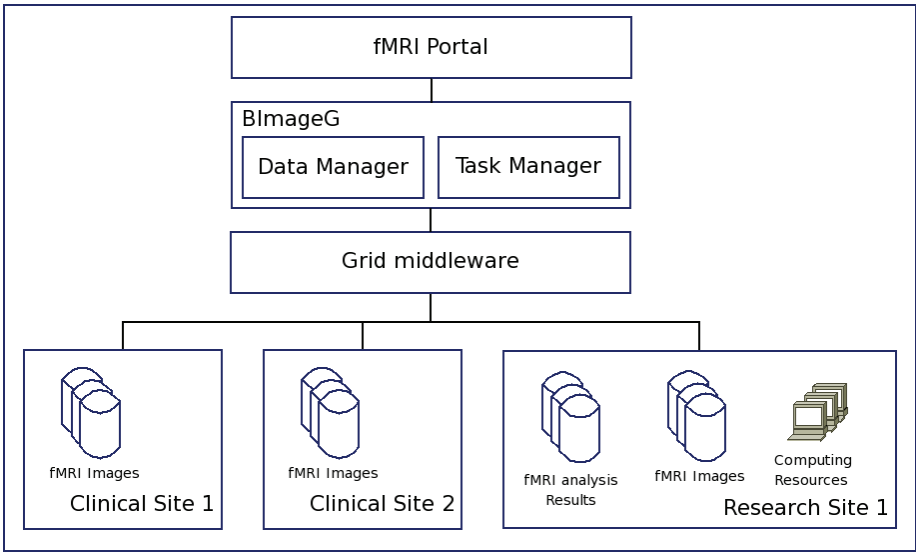

Figure 1. fMRI analysis framework, building on top of Grid services.

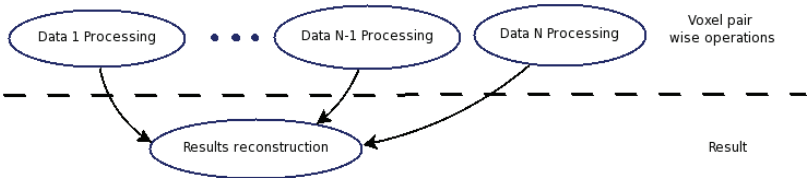

Figure 2. Grid job workflow of an fMRI association analysis method.

efficient use of the resources available (Figure 2). In our system, BImageG stands for brain imaging grid services.

The BImageG layer also provides grid-aware data management services for fMRI, such as volume or time-series extraction and normalization. Data management is being deployed at a single research site but, in the future, BImageG will be used to securely access fMRI repositories from several sites. Besides integrating the "source" fMRI image repositories, the system will rely on additional repositories, distributed among different sites, to store fMRI analysis results and temporary data that can be generated in the course of analysis workflows.

2.2. Supporting Research Workflows on BImageG

The BImageG holds the two main system components: the Task manager and the Data manager.

The Task Manager generates the jobs that will run in the grid and then implements the specific job workflow, submitting each job at its due time. This involves the jobs state continuous monitoring and a correct management of the data generated during the job workflow. In the association analysis procedure we divide the data and then apply the process (e.g.: a voxel pair wise association) to each segment of data. Each one of these tasks is a job that will be run in the grid. The partition of data and generation of jobs takes into account the availability of computing resources in the grid (Figure 2).

The research workflow is often pre-defined. Nevertheless, we provide a flexible

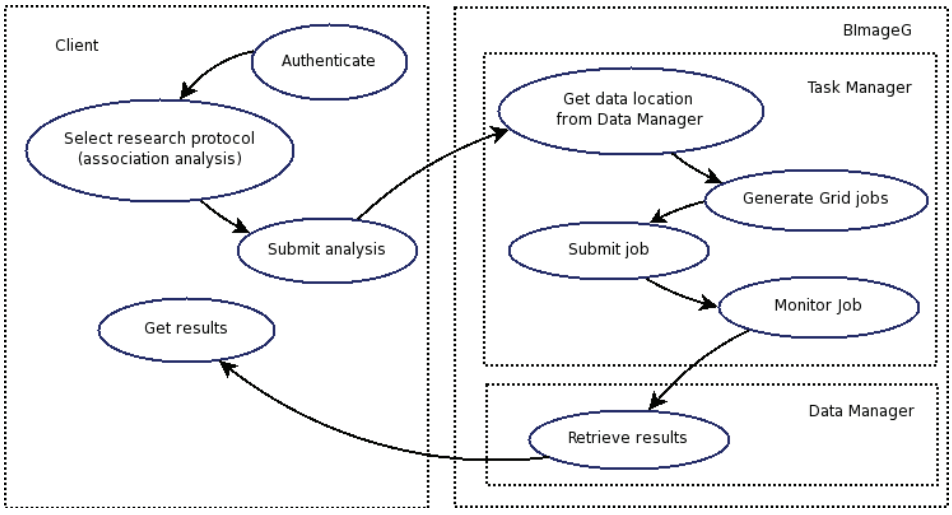

Figure 3. Typical workflow when running an fMRI association analysis.

approach for researchers to create and submit their own custom research workflows. To accomplish this, the fMRI portal allows the user to select a research problem specification, by importing a XML file which describes the intended job workflow. Later, the task manager can interpret the XML specification and generate the Grid job workflow that will be run on the target execution environment. When the job workflow is complete, the results are retrieved and made available to the user (Figure 3).

The Data Manager will be responsible for the fMRI specific data operations, such as normalization, fMRI 3D volumes data extraction, data conversion and retrieval.

BImageG is currently built on top of gLite[2] middleware, using the Java APIs available for data and job management, running on the pan-European EGEE pre-production Grid infrastructure.

gLite is continuously evolving and integrating new services; in the biomedical area, a Medical Data Manager that provides anonymization and security necessary to work with medical data and the integration with DICOM servers is under development [20]. This could be a major development to our objectives since image repositories in clinical sites are usually available through DICOM servers.

3. Preliminary Results

We have implemented the services necessary to test the protocol of association analysis over gLite middleware. In this pilot experiment, we use a fMRI sequence of an epileptic patient to calculate voxel pair wise operations in a fMRI. The sequence is composed of 3D volumes of 16 64x64 slices acquired from top to bottom of head at each 3 sec, for 5 minutes.

The use of the framework is illustrated for a specific brain area (Figure 4), represented by a particular voxel (a). The result of the association analysis in relation to a specific voxel (b) is a volume. Here we present two axial views where is possible to visualize clearly spatial areas that present positive correlation (warm colors) and negative correlation (blue tones). These correlations can be related used to find time dependences between a specific brain area and other brain regions. The next step is assessing the value of these findings within clinical models, supported in fMRI acquisition protocol design.

Input **Results**

a) a specific brain area as a voxel b) Correlation generated by BImageG.

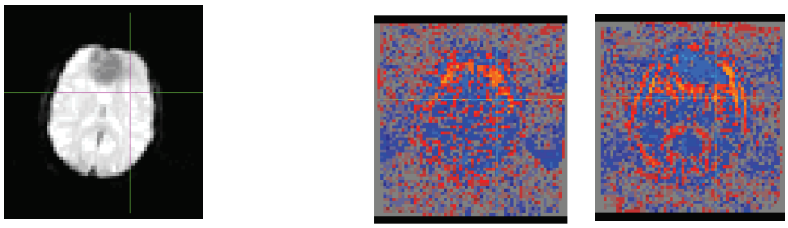

Figure 4. fMRI analysis results: the correlation between brain areas, represented as association maps (b), and specific brain areas, represented in the example by a localized voxel (a), can be used to infer time dependencies between different brain areas. These dependencies can be later interpreted within clinical models. In (b) warm colors represent positive correlations while blue tones negative.

[2] http://glite.web.cern.ch/glite/

4. Discussion and Conclusions

Other projects have been successfully using the Grid to analyze fMRI data. The Virtual Laboratory for e-Science [21] project is working in a infrastructure to facilitate the management and analysis of fMRI data and is using the LCG-2 grid middleware. Other preeminent example is the north-American Biomedical Informatics Research Network (BIRN) [22] which deploys a specific testbed on fMRI, the FBIRN, working on the development of methods to analyze multi-site fMRI data.

We implemented a framework to support the association analysis and illustrated its use over a fMRI sequence. While this target has been achieved, other issues are under development, such as the summarizing and analysis of the results. Both issues have efficiency implications at grid level: the summarizing of results may imply further computational processing to provide friendly human readable results.

For that reason the current framework was centered in the support to the association calculations and not on post processing, although it is able to handle – not in the most efficient way – with the overwhelming size of result volumes.

The infrastructure created was able to run the fMRI association analysis using gLite middleware. Further studies must be accomplished to evaluate the most efficient way of generating the grid job workflows in order to minimize the grid middleware overhead. One possible way of increasing the efficiency of this infrastructure would be to transfer services provided by the data manager in the BImageG to the repositories' sites (move computation to data). This would decrease the transfer time of data over the grid.

References

[1] S. Ogawa, T. M. Lee, A. R. Kay, and D. W. Tank, "Brain magnetic resonance imaging with contrast dependent on blood oxygenation," *Proc. Natl. Acad. Sci. USA,* vol. 87, pp. 9868-9872, 1990.

[2] K. Uludag, D. J. Dubowitz, E. J. Yoder, K. Restom, T. T. Liu, and R. B. Buxton, "Coupling of cerebral blood flow and oxygen consumption during physiological activation and deactivation measured with fMRI," *Neuroimage,* vol. 23, pp. 148-55., 2004.

[3] S. A. Rombouts, R. Goekoop, C. J. Stam, F. Barkhof, and P. Scheltens, "Delayed rather than decreased BOLD response as a marker for early Alzheimer's disease," *Neuroimage,* vol. 26, pp. 1078-85, Jul 15 2005.

[4] A. O. Ceballos-Baumann, "Functional imaging in Parkinson's disease: activation studies with PET, fMRI and SPECT," *J Neurol,* vol. 250 Suppl 1, pp. I15-23, Feb 2003.

[5] M. D'Esposito, L. Y. Deouell, and A. Gazzaley, "Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging," *Nat Rev Neurosci,* vol. 4, pp. 863-72, Nov 2003.

[6] R. Turner and T. Jones, "Techniques for imaging neuroscience," *Br Med Bull.,* vol. 65, pp. 3-20., 2003.

[7] D. A. Handwerker, J. M. Ollinger, and M. D'Esposito, "Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses," *Neuroimage,* vol. 21, pp. 1639-51., 2004.

[8] K. J. Friston, P. Fletcher, O. Josephs, A. Holmes, M. D. Rugg, and R. Turner, "Event-related fMRI: characterizing differential responses," *Neuroimage,* vol. 7, pp. 30-40., 1998.

[9] P. McCullagh and J. A. Nelder *Generalized Linear Models*. London: Chapman and Hall, 1989.

[10] H. W. Powell, M. J. Koepp, M. P. Richardson, M. R. Symms, P. J. Thompson, and J. S. Duncan, "The application of functional MRI of memory in temporal lobe epilepsy: a clinical review," *Epilepsia,* vol. 45, pp. 855-63., 2004.

[11] K. L. Miller, W. M. Luh, T. T. Liu, A. Martinez, T. Obata, E. C. Wong, L. R. Frank, and R. B. Buxton, "Nonlinear temporal dynamics of the cerebral blood flow response," *Hum Brain Mapp,* vol. 13, pp. 1-12, May 2001.

[12] G. K. Aguirre, J. A. Detre, E. Zarahn, and D. C. Alsop, "Experimental design and the relative sensitivity of BOLD and perfusion fMRI," *Neuroimage,* vol. 15, pp. 488-500., 2002.

[13] S. J. Kiebel and K. J. Friston, "Statistical parametric mapping for event-related potentials (II): a hierarchical temporal model," *Neuroimage.,* vol. 22, pp. 503-20., 2004.
[14] J. P. Cunha and P. G. de Oliveira, "A new and fast nonlinear method for association analysis of biosignals," *IEEE Trans Biomed Eng,* vol. 47, pp. 757-63, Jun 2000.
[15] J. P. S. Cunha, P. Guedes de Oliveira, J. Ramalheira , J. Lopes, and A. Martins da Silva, "Is Background EEG Analysis Relevant on Predicting Epilepsy Evolution?," in *8th European Congress of Clinical Neurophysiology*, Munich, Germany, 1996.
[16] A. Martins da Silva and J. P. S. Cunha, "Scalp EEG Recordings: Inter Ictal / Ictal Location and Spreading of epileptiform events," *Acta Neurol Scand,* vol. suppl 152, pp. 17-19, 1994.
[17] V. Breton, K. Dean, T. Solomonides, I. Blanquer, V. Hernandez, E. Medico, N. Maglaveras, S. Benkner, G. Lonsdale, S. Lloyd, K. Hassan, R. McClatchey, S. Miguet, J. Montagnat, X. Pennec, W. De Neve, C. De Wagter, G. Heeren, L. Maigne, K. Nozaki, M. Taillet, H. Bilofsky, R. Ziegler, M. Hoffman, C. Jones, M. Cannataro, P. Veltri, G. Aloisio, S. Fiore, M. Mirto, I. Chouvarda, V. Koutkias, A. Malousi, V. Lopez, I. Oliveira, J. P. Sanchez, F. Martin-Sanchez, G. De Moor, B. Claerhout, and J. A. Herveg, "The Healthgrid White Paper," *Studies in health technology and informatics,* vol. 112, pp. 249-321, 2005.
[18] J. Montagnat, F. Bellet, H. Benoit-Cattin, V. Breton, L. Brunie, H. Duque, Y. Legré, I. E. Magnin, L. Maigne, S. Miguet, J. M. Pierson, L. Seitz, and T. Tweed, "Medical Images Simulation, Storage, and Processing on the European DataGrid Testbed," *Journal of Grid Computing,* vol. 2, p. 387, 2004.
[19] S. R. Amendolia, J. Galvez, D. Manset, W. Hassan, F. Estrella, C. Del Frate, M. Odeh, T. Hauer, and R. McClatchey, "Deployment of a grid-based medical imaging application," *Stud Health Technol Inform,* vol. 112, pp. 59-69, 2005.
[20] J. Montagnat, D. Jouvenot, C. Pera, A. Frohner, P. Kunszt, B. Koblitz, N. Santos, and C. Loomis, "Bridging clinical information systems and grid middleware: a Medical Data Manager," *Studies in health technology and informatics,* vol. 120, pp. 14-24, 2006.
[21] S. D. Olabarriaga, R. G. Belleman, J. G. Snel, and A. J. Nederveen, "Towards a virtual laboratory for FMRI data management and analysis," *Stud Health Technol Inform,* vol. 120, pp. 43-54, 2006.
[22] J. S. Grethe, C. Baru, A. Gupta, M. James, B. Ludaescher, M. E. Martone, P. M. Papadopoulos, S. T. Peltier, A. Rajasekar, S. Santini, I. N. Zaslavsky, and M. H. Ellisman, "Biomedical informatics research network: building a national collaboratory to hasten the derivation of new understanding and treatment of disease," *Studies in health technology and informatics,* vol. 112, pp. 100-109, 2005.