Brain Connectivity Variable Resolution Electromagnetic Tomographic Analysis (bcVARETA): next generation Electrophysiological Source Imaging (ESI) toolbox

Arioksy Areces-Gonzalez (1,2), Deirel Paz-Linares (1,3), Eduardo Gonzalez-Moreira (1,4), Jorge Bosch-Bayard (1,5), Pedro A. Valdes-Sosa (1,3)\*

(1) Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China. (2) School of Informatics, University of Pinar del Río “Hermanos Saiz Montes de Oca”, Pinar del Rio, Cuba. (3) Neuroinformatics Department, Cuban Center for Neurosciences, Havana, Cuba. (4) Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA. (5) McGill Centre for Integrative Neurosciences MCIN, Ludmer Centre for Mental Health, Montreal Neurological Institute, McGill University, Montreal, Canada.

\* Correspondence:

Pedro A. Valdes-Sosa

pedro.valdes@neuroinformatics-collaboratory.org

Keywords:

Electrophysiological Source Imaging (ESI), Magneto-electroencephalogram (MEEG), Inverse Problem (IP), Variable Resolution Electromagnetic Tomographic Analysis (VARETA), Low Resolution Electromagnetic Tomographic Analysis (LORETA), Approximated Bayesian Computations (ABC)

**Summary**

Electrophysiological Source Imaging (ESI) reconstructs functional brain or body images defined by a current source fields that cause their remote observations as an electromagnetic field recorded by sensors. Due to a linear electromagnetic forward model, ESI resolution is ideal and promises a high-end appliance elucidating the intricate mechanisms that govern brain function in time or frequency domains. However, an electromagnetic forward model, the spatial convolution yield by solutions to the Poisson equation in head media, renders ESI an inverse problem under high dimensionality and degeneracy: due to the huge amount of latent source variables compared to very limited data variables from few sensor point recordings. Moreover, specifying the functional brain connectivity images as the target for ESI target leads to dimensionality and degeneracy which is essential at describing brain mechanisms,

a few data (sensor point recordings) inverse problem solutions for the corresponding of electromagnetism.

ESI achieving a a group of imaging methods with the aim of uncovering the mechanisms underpinnning brain function with appropiate temporal and spectral resolution. and time : Brain Connectivity Variable Resolution Electromagnetic Tomographic Analysis (BC-VARETA). BC-VARETA is meant to be the distribute our recent advances developed methods on the third generation of nonlinear methods for MEEG Time Series analysis. Into the state of the art of MEEG analysis, the methodology underlying our tool (BC-VARETA) brings out several assets. First: Constitutes a truly Bayesian Identification approach of Linear Dynamical Systems in the Frequency Domain, grounded in more consistent models (third generation) for the joint nonlinear estimation of MEEG Sources Activity and Connectivity. Second: Achieves Super-Resolution, through the iterative solution of a Sparse Hermitian Sources Graphical Model that underlies the Connectivity Target Function. Third: Tackles efficiently in High Dimensional and Complex set up the estimation of connectivity, those constituting technical issues that challenge current MEEG source analysis methods. Fourth: Incorporates priors at the connectivity level by penalizing the groups of variables, corresponding to the Gray Matter anatomical segmentation, and including a probability mask of the anatomically plausible connections, given by synaptic transmission in the short-range (spatially invariant empirical Kernel of the connections strength decay with distance) and long-range (White Matter tracks connectivity strength from Diffusion Tensor Imaging). Along with the implementation of our method, we include in this toolbox a benchmark for the validation of MEEG source analysis methods, that would serve for the evaluation of sophisticated methodologies (third generation). It incorporates two elements. First: A realistic simulation framework, for the generation of MEEG synthetic data, given an underlying source connectivity structure. Second: Sensitive quality measures that allow for a reliable evaluation of the source activity and connectivity reconstruction performance, based on the Spatial Dispersion and Earth Movers’ Distance, in both source and connectivity space.

Introduction

Currently there is a consent in the neuroscience community that neural communication patterns between brain regions (brain networks) play a crucial role in brain function at behavior and cognition levels (Avena-Koenigsberger, 2018). In the neuroscience field, brain networks topology builds on dense synaptic connections, between individual neurons at the microscale, which are modeled at the mesoscale as nodes with certain connection patterns: directed or undirected (Salvador, et al., 2005, Estrada, 2012). This has been evidenced by the progress of invasive or noninvasive brain imaging techniques up until now.

Histological studies in the past uncovered several aspects of brain networks organization at the mesoscale (Brodmann, 1909; Hässler, 1967; Passingham, 1973; Allman, 1988; Collins et al., 2005; Zilles et al., 1979, 2004; Bailey and Bonin, 1950; Economo and Koskinas, 1925; Jones, 1962). First: The brain cortex possesses a columnar organization with seven layers (granular or agranular) of morphologically and functionally different neuron types (pyramidal, spiny and smooth). Second: The synaptic connections follow a layer specific organization. Spiny striate cells in granular layers act as receptors of excitatory impulses from pyramidal neurons in the infra-agranular layers or inhibitory also from pyramidal neurons in supra-agranular layers. This takes effect in inter-layer communication patterns of three types: intracolumnar (directed connections) and intercolumnar in both short range (lateral undirected connections) and long range (forward or backward directed connections).

The analysis of Blood Oxygenation Dependent (BOLD) signal registered by Functional Magnetic Resonance Imaging (fMRI), can reflect the neural correlates (responses and connectivity) of brain function during task or resting state. Also based on MRI, the Diffusion Weighted Imaging (DWI) allows to extract the probabilistic maps of the long-range connectivity due to white matter tracks. These constitute at most, what is available to investigate the connectivity noninvasively, with spatial resolution that can reach the columnar level, providing reliable correlates of spatially distributed neural activity. Unfortunately, these techniques do not reflect directly the neural dynamics or synaptic transmission. The BOLD signal is a consequence of a slow (spans over seconds) metabolic/hemodynamic cascade which is activated by synaptic activity, thus it does not reach the milliseconds time-scale of faster brain rhythms. DWI provides structural probabilistic maps of the plausible connections, based on the diffusion of water across White Matter tracks, but cannot reveal precisely the pathways that take effect in neural communication.

Non-invasive electrophysiological recordings, such as magneto/electroencephalography (MEEG), bring an ideal scenario to cover the gap of other slower and indirect imaging methods, e.g. the previously cited fMRI. Its direct link to local field potentials (associated to synaptic events) and high temporal resolution (milliseconds) allows the tracking of the neural processes underlying human perception and cognition (Schomer and Lopes da Silva 2011, Hämäläinen, et al., 1993). This is explained given the local field potential of synchronized neural activity within neural masses (generators), which creates a noninvasively observable Primary Current Density (PCD). An accurate estimation of the PCD given these signals would thus provide a representation of the neural dynamic, therefore the MEEG based connectivity analysis constitutes a strong approach to study brain functional networks in Resting State (RS) or Event Related Potential (ERP) (Schoffelen and Gross, 2009; Smit, et al., 2008).

Unfortunately, the analysis of MEEG sources activity (PCD reconstruction) constitutes a severely ill-posed problem, i.e. the MEEG Inverse Problem (MEEG-IP). The reasons for this are two: First, the small amount of data (hundreds of scalp recording points) compared to the large amount of Gray Matter generators (thousands) to be estimated. Second, smearing of the sources activity when projected from the generators space to the scalp sensors via the Lead Field, this has been pinpointed “Volume Conduction Effect”. Due to the latter the number of sensors that would carry relevant information about source activity is limited, rendering the former situation a theoretical (not practical) shortcoming (Hassan and Wendling, 2018). It is affirmed that the only solution to this problem would be developing MEEG source analysis methods which might be flexible enough to incorporate priors on the spatio-temporal patterns source activity, or what would be better: jointly on source activity and connectivity.

Up to now, the MEEG source analysis models can be classified into the Bayesian formalism as three main generations, accounting for how these models make use of prior information about connectivity (covariances or precisions). First Generation: Uses a fixed covariance structure while solving the source activity estimation by a linear formula, e.g. Minimum Norm (MN) (Hämäläinen and Ilmoniemi, 1994) and LORETA (Pascual-Marqui et al., 1994). Second Generation: Regards embedded priors on the source activity and a diagonal covariance (variances) structure, while the estimation is tackled by nonlinearly dependent formulas of both source activity and connectivity, e.g. Exact LORETA (eLORETA) (Pascual-Marqui, 2002), Multiple Penalized Least Squares (MPLS) (Vega-Hernández et al., 2008) and Structured Sparse Bayesian Learning (SSBL) (Paz-Linares et al., 2017). Third Generation: It does as the second generation but with a full covariance structure, e.g. Variable Resolution Tomographic Analysis (VARETA) (Valdes-Sosa, 1996, Bosch-Bayard, et al., 2001) and Restricted Likelihood Maximization (ReLM) (Patterson and Thompson, 1971, Harville, 1977; Friston et al., 2007; Wipf et al., 2009; Belardinelli et al., 2012; Wu et al., 2016).

Nevertheless, ESI methods have been developed mainly to estimate activation and not connectivity. Indistinctively, these have been implemented as a first stage before connectivity postprocessing (second step) or statistical analysis of the Sources’ time series (Sakkalis, 2011, Bastos and Schoffelen, 2016), such as Granger Causality (Granger, 1969), Dynamical Causal Models (DCM) (Penny, 2004), frequency domain connectivity measures like Coherence (Coh) (Tucker, et al. 1986; Srinivasan, et al., 2007; Guillon, et al., 2017), Partial Coherence (PCoh) (Lopes da Silva, et al., 1980), Directed Coherence (DC) and Partial Directed Coherence (PDC) (Baccalá and Sameshima, 2001), population statistical analysis of the results for source activity and connectivity features extraction (Hipp et al., 2012; Babiloni et al., 2005; Brookes, 2001).

The use of first and second generation MEEG methods is quite generalized into the state of the art, meanwhile, using third generation methods seems limited only to theoretical studies. From this, a severe methodological error stands out: the use of the “two steps” approach towards connectivity analysis, which renders the estimation unprecise due the ill-conditioning of the MEEG-IP. This conceptual problem relies on the idea that the simultaneously estimation of activation and connectivity has been unappreciated. This is something totally deliberated given the state-space nature of the MEEG model (Galka, et al., 2004, Valdes-Sosa, 2004), and its subsequent interpretation as Gaussian Graphical Models.

This work serves as continuation to theoretical developments of a model meant to revendicate the third generation of MEEG source analysis methods: Brain Connectivity Variable Resolution Tomographic Analysis (BC-VARETA) (Paz-Linares&Gonzalez-Moreira et al., 2018a; Paz-Linares&Gonzalez-Moreira et al., 2018b). This was strongly motivated by the idea on the unification of a well stablished third generation method VARETA (Valdes-Sosa, 1996, Bosch-Bayard, et al., 2001) and the theory of high dimension covariance of precision matrices (Maurya, 2016, McGillivray, 2016, Ledoit and Wolf 2015, Cai, et al., 2016, Adegoke, et al., 2018).

Objectives

In this paper, we present a third generation opensource toolbox based on BC-VARETA model (BC-VARETA 1.0), for super-resolution and high dimensional MEEG connectivity analysis. This will be possible due to the implementation of an efficient algorithm for the Group LASSO (structured sparsity) model directly on the source precision matrix. It allows for incorporating in the estimation procedure information about brain anatomical areas or prior probability maps of the connectivity in the short and long range. This approach is meant for the analysis stationary time series in the frequency domain, through the estimation of an underlaying Hermitian Embedded Gaussian Graphical Models (HEGGM), that arises from the Bayesian representation of Linear State Space Models (LSSM). We built a validation Benchmark based on in simulations, which incorporates inverse crime evaluation, noise from biological and instrumentation origin, realistic sources set up and quality measures of both source activity and connectivity reconstruction. This Benchmark sets the conditions for further evaluation of third generation MEEG methods. Finally, we present a study devoted demonstrate the efficacy of our source analysis tool in both synthetic and real examples.

The technical route of BC-VARETA 1.0 consists in the following steps:

Lead Field computation by the extraction od head model from the individual subject T1 MRI.

Definition of anatomical regions on the individual subject cortical surface.

Extraction data samples by the Discrete Fourier Transform (DFT) of the sensors time series in multiple windows.

Initial screening of sources by the second generation method SSBL, which allows to reduce the source space dimensionality.

Precision matrix estimation by BC-VARETA method.

Computation of the Partial Coherence as measure of the Neural generators Functional Connectivity.

Preparing WorkSpace