

“NADIBA”

STARTPAGE

HUMAN RESOURCES AND MOBILITY (HRM)
ACTIVITY

MARIE CURIE ACTIONS

Marie Curie Intra-European Fellowships (EIF)

PART B Section 1

Non-linear analysis of dynamic interactions between brain areas

“NADIBA”

Non-linear Analysis of Dynamic Interactions between Brain Areas

NADIBA

B1.1 Scientific Quality of the project

Scientific/Technological quality, including any interdisciplinary and multidisciplinary aspects (specific concepts, in *italics*, are explained in the glossary at the end of this section)

The main research objective of NADIBA is to develop new methods to analyse the dynamics of interactions between activated brain areas using functional neuroimaging data. Specifically, NADIBA will improve understanding of the spatiotemporal dynamics of information processing by the brain and explore directed influences and interactions (*effective connectivity*) within and among specialised brain areas. Wider societal issues are strongly connected with the need for application of advanced analysis methods for clinical problems. Their application will directly result in an improvement of diagnostic (e.g., for *dyslexic subjects - dyslexia*) and rehabilitative as well as therapeutic measures for patients with brain dysfunctions (e.g. stroke patients). Such dysfunctions can result in changes in the dynamics of coordination and organization of the interactions between brain areas. Therefore, rehabilitation can thus be conceived as re-coordination and re-organization of the remaining parts of cerebral networks and their interactions. The activation of brain areas can be measured using neuroimaging techniques such as electroencephalogram (*EEG*), magnetoencephalography (*MEG*), and functional magnet resonance imaging (*fMRI*). *fMRI* data (*fMRI* image sequences; the time-course of a pixel is equivalent to a digitized signal) relies on the *BOLD* response. Particularly fine-scale understanding of brain processes can be achieved by combining *fMRI* with *EEG* imaging (either in sequence or simultaneously). This coupling combines the higher time resolution of the *EEG* with the higher spatial resolution of the *fMRI*.

But interactions between activated brain areas cannot be measured; interactions can only be quantified using appropriate analysis methods and modelling. Therefore, stimulated by this technological progress described above, the examination of interactions between brain regions is a rapidly growing focus of interdisciplinary and multidisciplinary neuroscience research. This endeavour can be greatly facilitated by the availability of a number of innovative analysis approaches, and so projects integrating mathematicians, physicists, engineers, physicians and psychologists are especially promising. Therefore, the availability of new analysis methods that can be applied in groundbreaking experimental and clinical neuroimaging studies currently determines progress in this field. Exactly this combination characterizes the NADIBA project and, therefore, its objectives are focused on methodological and application-related problems at the frontier of computational and clinical neurosciences. NADIBA’s two main objectives (levels) are derived from the following facts:

(1) There are three main requirements of a biologically plausible approach for analysis of interactions between brain regions: it must be multivariate, dynamic and nonlinear. Multivariate analysis is appropriate to describe mutual interactions of multiple signals because for the analysis of each signal, all other signals are involved. Multivariate time-variant approaches facilitate the quantification of transient interaction changes. Non-linear approaches are not restricted to processes generated by linear systems. The high degree of innovation of the NADIBA proposal results from the extending the state of the art of multivariate autoregressive models (*MVAR*). These extensions will result in new analysis approaches for dynamic interaction analysis based on time-variant, non-linear *MVAR* models. The methodological basis consists of the time-variant methods for interaction analysis, which were introduced worldwide for the first time by **IMSID**, the **host institute** (Institute of Medical Statistics, Computer Sciences and Documentation at University of Jena; publications e.g. in *Nature*, *IEEE Tr. BME*, *Signal Processing*, *J. Neuroscience Methods*).

SETAR model approaches are very suitable as a methodological basis for the dynamic interaction analysis of *EEG* and *fMRI* sequences provided by the underlying clinical and experimental studies. Consequently, the **methodological objective of NADIBA** is to develop multivariate, time-variant, non-linear methods for interaction analysis based on adaptive parameter estimation of multivariate self-exciting threshold autoregressive models (*MVSETAR*).

(2) The *EEG* data of the internationally highly ranked clinical study “Dyslexia: the possible benefit of multimodal integration of *fMRI* and *EEG* data” [6] can be used for the development of methods for interaction analysis based on *EEG* (event-related potentials, *ERP*, derived from the *EEG*). This interdisciplinary collaboration between IMSID and the Department of Child and Adolescent Psychiatry at University of Jena (joint project) showed the applicability of data fusion for dyslexia-specific data for the first time in the international scientific literature. This study used *fMRI*-constrained, distributed source models based on *ERP* data. Therefore, the use of these *ERP* data is connected with detailed knowledge about the generating source network. That is an enormous advantage because dynamic activation patterns were studied by the reconstruction of current source density in steps of 4×10^{-3} s. But the *fMRI* data of this study are unsuitable for the development of methods for time-variant interaction analysis because of their inadequate time resolution (4 s = 10 scans including 16 slices were acquired per stimulus block within 40 s). Therefore, NADIBA will make use of data from specially acquired *fast-fMRI* scans (1 slice) with a time resolution of 0.2 s for the development of methods for interaction analysis based on *fMRI* data. These data were acquired during a finger tapping experiment which was carried out at the Department of Medical Psychology, University Goettingen (Germany).

Both unique data sets are available for testing the new methods, guaranteeing the efficient feasibility of the project which is focused on methodological research. Additionally, the applicant is trained and experienced in the fields of time-variant signal processing (e.g. wavelet analysis) and in systems analysis. Additionally, the applicant has experiences with clinical applications. Therefore, a rapid professional integration into the IMSID research team and its collaborative network will be possible. Additionally, IMSID will profit from the incoming scientific competence of the applicant (Dr. G. Ungureanu of Romania) because her specific scientific profile complements the profile of methods of IMSID.

A strong interdisciplinary and multidisciplinary cooperation using the outstanding infrastructure of the University of Jena was necessary to enable the underlying clinical and experimental studies. Consequently, in the framework of NADIBA the Marie Curie applicant, Dr. Ungureanu, will benefit from this established, top-level research network, which is characterized by a high degree of local as well as national and international cooperation, integrating mathematicians, physicists, engineers, physicians and psychologists. The quality of the local interdisciplinary research in neuroscience and the corresponding cooperative infrastructure of the university are organized in an Interdisciplinary Centre for Clinical Research with a main topic of research “Clinically-oriented Neurosciences”. The methodical network consists of the “Brain Imaging Centre” (3Tesla MRI), a Core-Unit “MR Methodology”, the “Biomagnetic Centre”, and IMSID.

State-of the-art: Current approaches of interaction analysis are connected with the concepts of *functional* and *effective connectivity*. *Functional connectivity* is defined as the correlations between spatially remote neurophysiological events. Linear correlative interaction measures include cross-correlation and coherence spectrum and nonlinear approaches include mutual information and generalized synchronization (evaluated by [4]). *Effective connectivity* is defined as the influence one neuronal population has on another. Models of effective connectivity identify a suitable metric of influence among interconnected brain regions and generally require an anatomical model to specify which regions are connected. Regression-based approaches, such as Structural Equation Modelling, and Dynamic Causal Modelling are frequently used to make inferences about effective connectivity from *fMRI* data [11]. For both concepts the state-of-the-art methodology is available in the software package Statistical Parametric Mapping (SPM). SPM has been designed for the analysis of brain imaging data sequences and the associated theory was originally developed by Karl Friston (Wellcome Department of Imaging Neuroscience, University College London) for the routine analysis of functional neuroimaging data. Adequate *EEG/MEG* analysis methods are currently not incorporated SPM but are scheduled for a future release.

Multivariate autoregressive (*MVAR*) models are increasingly used tools for exploring causal interactions by combining modern causality theory with multivariate time-series analysis [14]. Several

authors have used the classical time-invariant *MVAR* approaches to derive directed measures of interaction by means of the non-symmetric parameters of the fitted multivariate autoregressive model. Based on the theory of linear stochastic processes, spectral related methods such as bivariate coherence are widely used. For high-dimensional data, spurious interaction between two components may appear because of the influence of a common source. For this reason it is important to differentiate between causal and non-causal or indirect interactions. Different methods have been developed that search for the interaction between two components, while excluding the influence of other components. Differentiation between direct and indirect influences in multivariate systems is enabled by graphical models applying partial coherence. Granger causality, as well as parametric approaches in the time and frequency domain for stationary and non-stationary systems, allow the detection of possible influences (e.g. [5]). Time-variant linear and non-linear *MVAR* modelling approaches to examine neuronal interactions were introduced for the first time by co-workers of the IMSID. These time-variant models are based on Kalman Filter, Least Mean Squares and Recursive Least Squares approaches [1, 2, 9, 10, 15].

Research methodology

The research methodology has been derived from methodological and application-related research objectives at the frontier of computational and clinical neurosciences. The working program is designed for project duration of one year and is divided into two levels: (L1) Development of methods and (L2) their application to data of the underlying studies.

(L1) Development of methods: Linear *MVAR* frequently fail to describe important properties of signals and this observation has led to the development of several non-linear alternatives. At present, research interest is focused on the investigation of four particular non-linear models: Bilinear models, threshold models, exponential autoregressive models and state dependent models. *SETAR* models are appropriate analysis tools for practical applications because a wide class of non-linear signals which includes the exponential and the bilinear models can be approximated by those threshold models. Additionally, compared with other non-linear models, *SETAR* models are more easily interpretable and tractable, and patterns which are characteristic of non-linear systems such as oscillations with amplitude-dependent frequencies, asymmetric limit cycles, jump resonances and synchronization phenomena can be generated by means of *SETAR* models. Therefore, *SETAR* model approaches are very suitable as a methodological basis for the interaction analysis of *EEG* and *fMRI* sequences provided by the underlying clinical and experimental studies. A *SETAR* model is given by a collection of autoregressive (*AR*) models and a corresponding number of thresholds which define a partition of the real axes. At each instant one *AR* model is chosen to be active, i.e. it is assumed to generate the corresponding observation. The active regime is determined by detecting the interval which covers the observation at a defined time point in the past.

The estimation of the model parameters can be performed in two steps: (1) Estimation of the structural parameters (model order, position of threshold, delay parameters) and (2) estimation of autoregressive parameters. A new method for the adaptive estimation of *AR* parameters of a *SETAR* was introduced for the first time by M. Arnold of IMSID [3]. This method has the advantage that it can also be efficiently applied in signals with nonstationary (time-varying) characteristics. This approach was extended to multivariate *SETAR* models (*MVSETAR*) [1], i.e. non-linear alternatives for time-variant *MVAR* models can be given.

The main methodological aim is to develop multivariate, time-variant, non-linear methods for interaction analysis, such as Directed Transfer Function (*DTF*) and Partial Directed Coherence (*PDC*), based on adaptive parameter estimation of *MVSETAR* models. Based on the regime dependent transfer matrices and *AR* parameters, state dependent *DTF* and *PDC* may be generalized.

The new approaches should be implemented by means of a suitable graphical user interface in Matlab® and tested by means of simulated data.

(L2) Application to data: In order to compare the language processing capacities between dyslexic and control subjects *ERP* data were derived from 17 dyslexic and 21 normal reading adolescents in two separate sessions using the same paradigm. Thirty-one electrodes were used for *EEG* recording

for each subject and situation and the *ERPs* were derived from *EEG* from a stimulus-triggered ensemble averaging (140 trials). Subjects had to decide (key press) whether two items that were visually presented at the same time were identical or not. These stimuli consisted of: (A) slash patterns as baseline condition, (B) letter strings, (C) high-frequent words, (D) reading pseudo words, and (E) rhyming of pseudo words. *EEG* and *ERP* data reflect each subject’s brain activity while engaged in these tasks. The developed methods will be applied to the *ERP* data to compute dynamic interaction profiles. The test statistics (differences between dyslexic and normal subjects) which will be required for the interpretation of the results will be provided by the IMSID research group “Statistics” (C. Hemmelmann) using multivariate and multiple statistical test strategies developed by this group [7, 8], which have been successfully applied in the field of language processing by the brain [12, 13]. Bootstrap methods and surrogate data will be used for statistical testing of difference between baseline condition (A) and test conditions (B-E).

Additionally, a finger tapping experiment was executed with 5 volunteers (visual instruction - red cue: motor resting; green cue: permission to self-paced finger tapping; 58 trials per subject; two situations active and resting condition). The methods developed will be applied to the *fast-fMRI* data of the study to compute dynamic interaction profiles. Bootstrap methods will be used for statistical testing (difference between resting and active situation).

Originality and innovative nature of the project

As shown above, the project objectives are focused on methodological and application-related problems at the frontier of computational and clinical neurosciences. The application level (L2) facilitates the immediate utilization of the new methods to neuroscience and clinical research (overall objectives). Correspondingly, the working programme (see section B2.3) is ambitious regarding both development of method and application.

Timeliness and relevance of the project

NADIBA is timely because it adapts time-variant non-linear methods to the newly available measurement technologies (*fast-fMRI*). Such methods are required to optimise application of the new technology and sets the next trends in applications in experimental and clinical neuroscience. As mentioned above the relevance of these methodological research activities results from different clinical problems. For example, dyslexia and stroke are accompanied with different deficits in language processing. The corresponding incidence rates illustrate the relevance of the project. 22 Mio dyslexic individuals, including 2.5 Mio dyslexic school children in the EC have a specific disorder in learning to read and spell. Since dyslexia occurs in all languages and presents a lifelong burden characterized by academic failure, poor school attendance, problems with social adjustments and unemployment (cited from: FP 6 - Life Sciences, Genomics and Biotechnology for Health; Project: Dyslexia genes and neurobiological pathways). Incidence rates for stroke from Europe and North America ranged from 130 and 830 per 100000 population; approximately 30% of all stroke patients suffer from language deficits). Therefore, the results of NADIBA have promise for leading directly into development of rehabilitative and therapeutic measures for stroke patients, as evidenced by the special issue “Effective Connectivity” (2004) of the journal *Neuroinformatics* and the special issue “Neuronal coordination in the brain: A signal processing perspective” (2005) of the journal *Signal Processing* (a journal of the European Association for Signal Processing). Additionally, the methodological approaches can be used in other research areas which deal with interaction analysis (e.g. machine diagnosis, seismology, analysis of biological interactions).

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GLOSSARY

dyslexia

Dyslexia is said to be a neurological disorder with biochemical and genetic markers. It is a disability in which a person's reading and/or writing ability is significantly lower than that which would be predicted by his or her general level of intelligence. Dyslexia is evident when accurate fluent word reading and or spelling develops incompletely or with great difficulty. This focuses on literacy learning at the 'word level' and implies that the problem is severe and persistent despite appropriate learning opportunity. Dyslexia is also associated with phonological difficulties, such as enunciation.

BOLD response

Blood oxygenation level dependent response. Haemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated. The magnetic resonance signal of blood is therefore different depending on the level of oxygenation. These differential signals can be detected using an appropriate MR pulse sequence as Blood Oxygenation Level Dependent contrast. Higher BOLD signal intensities arise from decreases in the concentration of deoxygenated haemoglobin since the blood magnetic susceptibility now more closely matches the tissue magnetic susceptibility. By collecting data in an MRI scanner with parameters sensitive to changes in magnetic susceptibility one can assess changes in BOLD contrast. These changes can be either positive or negative depending upon the relative changes in both cerebral blood flow and oxygen consumption. Increases in CBF that outstrip changes in oxygen consumption will lead to increased BOLD signal, conversely decreases in CBF that outstrip changes in oxygen consumption will cause decreased BOLD signal intensity. The precise relationship between neural signals and BOLD is under active research. In general, changes in BOLD signal are well correlated with changes in blood flow.

DTF

Directed transfer function. The directed transfer function method is a multi-channel analysis technique based on an MVAR modelling of the underlying processes. The DTF is defined by the so called Transfer Function computed on the basis of AR parameters. The DTF is a frequency-domain analysis technique to detect directions of interactions between components of multivariate signals. The DTF is a normalized quantity between 0 and 1.

EEG

Electroencephalogram. Electroencephalography is the neurophysiologic measurement of the electrical activity of the brain by recording from electrodes placed on the scalp, or in the special cases on the cortex. EEG has several strong sides as a tool of exploring the brain activity. The time resolution is very high. The EEG has a resolution down to sub-millisecond. The brain is thought to work through its electric activity. EEG is the only method to measure it directly. Other methods for exploring functions in the brain do rely on blood flow or metabolism which may be decoupled from the brain electric activity. Newer research typically combines EEG or MEG with MRI or PET to get high temporal and spatial resolution.

effective connectivity

Effective connectivity may be defined as the influence one neural system exerts over another, either at a synaptic or cortical level. Usually, effective connectivity is described by a connectivity matrix $C = (c_{ij})$. The matrix element c_{ij} represents the effective influence of a neural system j to a system i .

ERP

Event related potential. An event related potential is any stereotyped electrophysiological response to a stimulus. ERPs can be reliably measured using an EEG. As the EEG reflects thousands of simultaneously ongoing brain processes, the brain response to a certain stimulus or event of interest is usually not visible in the EEG. That is why, a magnitude of uniform stimuli is applied, and the responses are averaged synchronized according to points of stimulus times (trigger). Thus, the background activity is reduced and the ERP will be visible. ERPs are transient signal with pronounced waves, whose amplitudes and latencies are usually analyzed.

fast fMRI

Fast functional magnetic resonance imaging. The disadvantage of (f)MRI is the low time resolution. The sampling frequency is about 0.25 Hz. Scanning only one arbitrary positioned slice (instead of the whole brain volume), the sampling frequency may be increased to 5 Hz.

fMRI

Functional magnetic resonance imaging. Magnetic resonance imaging is a method of creating images of the inside of opaque organs in living organisms. It is primarily used to demonstrate pathological or other physiological alterations of living tissues and is a commonly used form of medical imaging. Medical MRI relies on the relaxation properties of excited hydrogen nuclei in water. When the object to be imaged is placed in a powerful, uniform magnetic field, the spins of the atomic nuclei with non-zero spin numbers within the tissue all align in one of two opposite directions: parallel to the magnetic field or antiparallel. fMRI describes the use of MRI to measure the haemodynamic response related to neural activity in the brain. The magnetic resonance signal of blood is depending on the level of oxygenation. These differential signals can be detected using an appropriate MR pulse sequence as Blood Oxygenation Level Dependent (BOLD) contrast. fMRI is one of the most recently developed forms of neuroimaging.

functional connectivity

Functional connectivity in neuroimaging is defined as the temporal correlations between remote neurophysiological events. Functional connectivity is a statement about observed correlations and does not provide any direct insight into how these correlations are mediated.

MEG

Magnetoencephalogram. Magnetoencephalography is the measurement of the magnetic fields produced by electrical activity in the brain. The combined magnetic fields from a region of about 50,000 active neurons can give rise to a net magnetic field that is measurable. Since current dipoles must have similar orientations to generate magnetic fields that reinforce each other, it is often the layer of pyramidal cells in the cortex, which are generally perpendicular to its surface, that give rise to measurable magnetic fields. Furthermore, it is often bundles of these neurons located in the sulci of the cortex with orientations parallel to the surface of the head that project measurable portions of their magnetic fields outside of the head. MEG promises good spatial resolution and extremely high temporal resolution; since MEG takes its measurements directly from the activity of the neurons themselves its temporal resolution is comparable with that of intracranial electrodes. MEG's strengths complement those of other brain activity measurement techniques such as electroencephalography, positron emission tomography, and functional magnetic resonance imaging whose strengths, in turn, complement MEG.

MVAR model

Multivariate autoregressive model. An autoregressive model of order p for an M -dimensional stationary process Y is determined by

$$Y(n) = \sum_{k=1}^p A_k \cdot Y(n-k) + \varepsilon(n),$$

where the $M \times M$ matrices A_k are weighting matrices for the past p process vectors, and with a zero mean Gaussian noise process ε . That is, the present of the process $Y(n)$ may be predicted by the last p process vectors except for the prediction error $\varepsilon(n)$. MVAR models are linear models.

MVSETAR model

Multivariate self exciting threshold autoregressive model. SETAR models are piecewise linear models. For an M -dimensional process Y , the state space \mathfrak{R}^M is decomposed in a finite number of pairwise disjunct subsets, which are called regimes. Within a regime, the process is described by an MVAR model. In addition to regimes, SETAR models exhibit a further structural parameter d . The delay d is used for the specification of the actual regime: It holds, the process Y is in a regime R at time n , if $Y(n-d) \in R$ is fulfilled. MVSETAR models are non-linear models.

PDC

Partial directed coherence. The PDC has been introduced to detect directed relationships between processes in multivariate dynamic systems. The underlying processes are modelled by MVAR processes. The PDC is a parametric approach in the frequency domain, since it is based on the Fourier transformation of the AR coefficient. The PDC accounts for the entire multivariate system and renders a differentiation between direct and indirect influences possible. The PDC is a normalized quantity between 0 and 1.