DIANA CONSTANZA GARCÍA RINCÓN

**Performance of partial directed coherence
subject to volume conduction effects**

São Paulo

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Orientator: Prof. Luiz Antonio Baccalá.

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Este trabalho é dedicado aos meus pais Carlos e Constanza que sempre acreditaram em mim e tem sido fonte de inspiração.

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*"No se fracasa en un día."
(Carlos García, mi padre)*

Resumo

A forte relação que processamento cognitivo e comportamento coerente tem com redes neurocognitivas justifica o enorme interesse atual em modelamento de conectividade cortical. Este fato tem justificado o desenvolvimento de estimadores de conectividade desde a clássica coerência bivariada até a noção multivariada de *coerência parcial direcionada* (PDC) que exhibe informação a cerca de dependências temporais que permitem expor relações de causa e efeito. O presente trabalho examina o desempenho da PDC no contexto de EEG de escalpo cujo valor em pesquisa sob os efeitos de *condução de volume* (VC) tem sido objeto de uma quantidade substancial de questionamentos na medida em que obscurece a observação da dinâmica das fontes corticais. Por meio de considerações analíticas e simulações, mostramos que é possível mitigar os erros de estimação devidos à VC através da escolha judiciosa da configuração de eletrodos e da referência de terra. Esta observação permite resolver o conflito acerca da adequabilidade da inferência cortical baseada em EEG de escalpo.

Palavras-chave: conectividade funcional. EEG. modelo autoregressivo vetorial. coerência parcial direcionada. condução de volume.

Abstract

The strong relationship between cognitive processing and coherent behaviour and neurocognitive networks justifies the current huge interest in cortical functional connectivity modeling. This has fostered the development of connectivity estimators from the classical bivariate coherence concept to the notion of multivariate partial directed coherence (PDC) which provides information about temporal dependencies exposing cause and effect relationships. This work examines PDC performance for scalp EEG data whose research value has been subject to much debate in the light of the presence of volume conduction (VC) effects that often obscure the actual nature of cortical source dynamics. Through analytical considerations and simulations we show that even though (VC) can hinder accurate connectivity estimation, one can mitigate its effects by a judicious choice of scalp electrode configuration/ground reference. This observation allows settling the connectivity estimation adequacy debate in the presence of PDC.

Keywords: functional connectivity. EEG. vector autoregressive model. partial directed coherence. volume conduction.

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List of abbreviations and acronyms

EEG	Electroencephalography
ECoG	Electrocorticography
iEEG	intracranial EEG
AR	Autoregressive
VAR	Vector Autoregressive
GC	Granger Causality
DC	Directed Coherence
DTF	Directed Transfer Function
PDC	Partial Directed Coherence
gPDC	Generalized Partial Directed Coherence
iPDC	Information Partial Directed Coherence
iCoh	Imaginary Coherence
VC	Volume Conduction
SNR	Signal to Noise Ratio
BEM	Boundary Element Method
FEM	Finite Element Method
CSF	Cerebrospinal fluid
PCA	Principal Component Analysis
ICA	Independent Component Analysis

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1 Introduction

Recent times have witnessed the development of many noninvasive methods for brain data analysis. Foremost among them are techniques for processing electroencephalographic (EEG) signals as they allow probing cortical activity information in a simple and economical way within the temporal resolution required for dealing with cognitive processes and allied neurocognitive networks.

Large-scale brain networks are interactions between distributed specialized brain regions (BRESSLER; TOGNOLI, 2006; BRESSLER; MENON, 2010). The interdependencies between distant but functionally related neural populations is usually referred as *connectivity*, that provides clues to the sequential temporal activity of neural processes in brain networks (SAUSENG; KLIMESCH, 2008), it can be studied through the mechanism of EEG phase synchronization (HORWITZ, 2003; FINGELKURTS; FINGELKURTS; KAHKONEN, 2005).

Some tools have been developed to estimate functional connectivity through phase synchronization whereas some other ones like *Partial directed coherence* (PDC) target the identification of interdependencies between neural populations in the frequency domain (BACCALÁ; SAMESHIMA, 2001) by exposing the existing links and their directional influence in what is an improvement over previous efforts that estimate functional connectivity most notably using classical coherence. PDC, like other estimators, is based on *Granger causality*, which uses the *vector autoregressive* model to detect the presence of causality.

PDC is quite general in its applicability and is by no means restricted to the analysis of neural signals. However, in the context of EEG the measurements taken from the scalp, one must take into account *volume conduction* (VC) effects on top of correlations among neocortical sources. Volume conduction takes place because tissues between the source at the cortex and the recording electrode at the scalp respond electrically and lead to the appearance of impressed currents (SANEI; CHAMBERS, 2013) of instantaneous propagation (KURGANSKY, 2013).

The main reason for the present study is a controversy whereby the presence of VC can mask the actual underlying cortical connectivity. Some researchers (GINTER et al., 2001; KAMIŃSKI et al., 2001; BRZEZICKA et al., 2011; BLINOWSKA, 2011; KAMINSKI; BLINOWSKA, 2014) argue that the instantaneous nature of VC should have no bearing on VAR estimation based estimators, whereas others (KURGANSKY, 2013; GÓMEZ-HERRERO, 2010; KURGANSKY, 2010; SILFVERHUTH et al., 2012; HAUFE et al., 2013; CHO et al., 2015) claim the exact opposite.

Here, our aim is to settle this matter by gauging VC's implications on PDC mediated connectivity estimation. Initially through an analytical approach by considering volume conduction first as a general source mixing phenomenon, and then modelling it through an ideal head model, finally we illustrate our theoretical results through numerical experiments.

Before proceeding, we briefly recap the problem by contrasting the different conflicting views on the matter and their key argument.

1.1 General considerations

EEG signals at the scalp surface provide a distorted view of the original cortical activity. The spatial distribution of the active regions of the cortex, together with the geometry and the electrical properties of the head determine the distribution of the currents throughout the scalp surface. Consequently, cortical electrical activity spreads across the scalp and reflects an unknown linear combination of cortical sources plus additive noise both biological and instrumental in nature (BAILLET; MOSHER; LEAHY, 2001; STINSTRÄ; PETERS, 1998). Though this is well known, VC influence on cortical connectivity estimation is still under debate. According to one view, connectivity estimators based on Granger causality, such as PDC, are immune to volume conduction and therefore that is no need for elaborate preprocessing techniques. By contrast, another view claims that cortical connectivity estimated with PDC is highly sensitive to VC. Thus, some methods to eliminate or decrease volume conduction effects have been developed that include elaborate preprocessing steps (GROETSCH; GROETSCH, 1993; HANSEN, 1998; VOGEL, 2002; GRECH et al., 2008; GÓMEZ-HERRERO, 2010).

Next, we summarize the different opposing views about this subject and the evidence behind them.

View A: PDC is immune to VC

By definition, connectivity estimators based on Granger causality detect a link only when a nonzero phase difference is present. However, VC only affects instantaneous interactions, producing no phase difference between recording electrodes. Thus, as some argue, these estimators should be immune to VC artifacts and they should not lead to the detection of spurious links (BLINOWSKA, 2011; KAMINSKI; BLINOWSKA, 2014). Therefore, no preprocessing to compensate for the impact of VC on connectivity estimation should be necessary. The only preprocessing that leaves connectivity unchanged are: (1) mean subtraction, (2) variance normalization and (3) digital filtering if it bears no altering of signal phases. In fact, according to (BLINOWSKA, 2011; KAMINSKI; BLINOWSKA, 2014) common average reference subtraction must be avoided.

Support for this view comes from the topographical agreement of *directed transfer function* (DTF), a technique related to PDC, and results of its application to physiological experiments. This evidence stems from studies that estimate connectivity using EEG data without preprocessing and correctly confirm interpretations derived from independent physiological and anatomical perspectives (GINTER et al., 2001; BRZEZICKA et al., 2011; KAMIŃSKI et al., 2001). Figure 1 shows the estimated DTF connectivity during stage 2 sleep over the 7 to 15 Hz frequency range. The paths of causal influence from anterior areas are consistent with prefrontal cortex anatomic projection pathways.

Figure 1 – Patterns of causal influences during stage 2 sleep. The gray scale represents the degree of connection estimated.

Source: (KAMIŃSKI et al., 2001).

The first known effort to investigate noise as a VC effect on PDC was made by Astolfi et al. in (ASTOLFI et al., 2005) and (ASTOLFI et al., 2007). Using EEG data from a channel and a predefined VAR process, they calculated a VAR process at the scalp. Then, using an inverse problem technique, they estimated cortical source activities and their connectivity via PDC. The analyzed parameters were SNR level and signal duration. They concluded PDC estimator has a moderate error (below 7%) with an SNR of 3 or more for a duration of at least 75 s using reconstructed sources. Another work in this same direction, but using a more complicated VAR process and considering decimation, was made in (SILFVERHUTH et al., 2012).

The effect of synchronous noise from instantaneous interactions in using PDC is studied in (BACCALÁ et al., 2013); they applied a rigorous statistical test to a VAR process with synchronized common noise in one case and with correlated noise in another. Both interference signals influence the instantaneous interactions between the EEG channels much as VC effects do, by modifying PDC magnitude, yet, without preventing successful connectivity inference.

View B: PDC is affected by VC

The linear combination of sources at the scalp was considered first in (KURGANSKY, 2010). Using EEG data recording from distant electrodes $F7$ and $O1$, they introduced artificial linear combinations of varying magnitudes between the two signals. Then, they calculated PDC for the original data and for the latter, showing an increase in the estimated connectivity when there is an increase in the projection coefficient. Their results are shown in Figure 2. However, they did not use any statistical threshold to infer connectivity presence. Moreover, they completely ignored the nature of the possible linear combinations given the electrical properties and dimension of the head, nor did they take into account the spatial configuration of sources and sensors.

Figure 2 – Simulation of source linear mixing influence on the PDC, $\pi_{F7 \leftarrow O1}(f)$ (solid line) and $\pi_{O1 \leftarrow F7}(f)$ (dashed line). Increasing mixing factor $g(0, 0.2, 0.4, 0.6)$. The frequency (in Hz) is plotted along the horizontal axis.

Source: (KURGANSKY, 2010).

The ability of PDC to measure connectivity from EEG data was tested using a boundary element method (BEM) model of the head by (HAUFE et al., 2013) who imposed a bivariate process to simulate two cortical sources with information flow from the left ($C3$) to the right ($C4$). Subsequently, they used a realistic head model to obtain scalp EEG signals, whose connectivity estimation was carried out using 2, 19 and 59 EEG channels. Finally, three different statistical tests were applied for connectivity inference at the scalp (see Figure 3). The authors suggest that volume conduction severely affects connectivity analyses, depending on the connectivity estimator and the statistical test. So, they proposed a procedure to reduce its influence. To our knowledge, this is the most

comprehensive work so far. Some variables to characterize the phenomenon such as the distance between electrodes, common synchronized noise and the multisource scenario were not considered. Moreover, the statistical test (using PDC) to decide if there is connectivity or not, was not employed.

Figure 3 – Comparison of effective connectivity between simulated EEG sensor measurements as estimated by Granger causality (GC), PDC and phase-slope index (PSI) using permutation testing (PERMUT), time inversion testing (TIME INV) and antisymmetrization testing (ANTISYMM). Granger-causal measures are calculated using bivariate MVAR modeling (GC/PDC 2), as well as multivariate modeling of either 19 or 59 channels (GC/PDC 19/59), respectively. red and yellow colors stand for information outflow and blue and cyan stand for information inflow.

Source ([HAUFE et al., 2013](#)).

1.2 Problem Statement

PDC performance under VC remains unknown, even though it is widely used by researchers (THAKOR; TONG, 2004; MONTIEL et al., 2005; ASTOLFI et al., 2008; VAROTTO et al., 2012a; VAROTTO et al., 2012b; KIMISKIDIS et al., 2013). There have been some efforts aimed at understanding VC effects on PDC connectivity detection. Yet, a great deal is still needed to clearly understand the implications of VC on connectivity detection by scalp EEG.

1.3 Main objective

Our attention is focused on PDC estimation and its performance to detect true cortical connectivity while taking into account possible impairing VC effects. VC implications on connectivity estimation are still under debate so there is a pressing need for evidence to clearly settle the matter. This therefore is the overall objective of this work.

Some previous studies have examined this issue through simulation obtaining divergent results as we mentioned in section 1.2. Moreover, no analytical work about this issue has been made to our knowledge. Given the absence of explicit theoretical analysis of the VC effect on the estimation of PDC, we propose to use an analytical volume conduction model of the human head to explain its consequences.

Specific objectives

- Finding the impact of VC on PDC analytically, if the VC effects are considered as a generic linear combination of signals and additive noise.
- Characterizing the nature of source mixing in terms of an analytical volume conductor model of the head.
- Determining the impact of PDC under VC, considering the head model.
- Proposing the best scenarios where VC impact can be minimized without having to resort to using inverse solutions.

1.4 Text organization

In this regard, the rest of this work is divided into three main parts. Part I is dedicated to a theoretical revision of fundamental concepts. Part II corresponds to our theoretical findings, which are illustrated through the numerical experiments presented in Part III of the document. The last chapter sums up both conclusions and further work.

Part I

Theory revision

2 Connectivity in Brain Networks

Large-scale brain networks connect neural populations distributed throughout the brain. Each neural population is distinguished from its neighbours by its unique local organizational structure allied to its local activity pattern. Each neural population can thus be identified as a node in a network that acts interdependently, but in connection with other network nodes. As result, cognitive functions and coherent behaviour emerge from conversions of information through time-dependent dynamical interactions between brain areas operating over large scales (BRESSLER; MENON, 2010). Therefore the key to understand these networks is not so much the individual activity of each brain area (WERNICKE, 1970) but the dynamic nature of the links between them — their connectivity (BOLLOBÁS; KOZMA; MIKLÓS, 2010).

Cortical connectivity can be analyzed from two different perspectives: (a) anatomical connectivity and (b) functional connectivity. The first one refers to anatomical links between regions. The second one is related to the perceived interaction between different regions of the cortex even when it takes place at distant locations. Our objective is functional connectivity, referred hereinafter simply as *connectivity*.

Phase synchronization over multiple frequency bands is the most studied mechanism involved in connectivity. The synchronization of the activities of different brain areas is performed by specific *rhythms*, based on the oscillatory bioelectrical activity of neuronal networks (VARELA et al., 2001), (SAUSENG; KLIMESCH, 2008). This synchronization of oscillatory activity has been assumed as essential for supporting multisensory perception and cognitive activity (SENKOWSKI et al., 2008). The phase synchronization phenomenon is found in human EEG across many brain areas and frequencies. The same frequency synchrony bands are found in different individuals during the same behaviour (VARELA et al., 2001). Therefore, the study of cortical functional connectivity at each specific frequency bandwidth has become one of the most important problems of electroencephalography (KURGANSKY, 2013).

3 Connectivity Estimators

Methods for quantitative estimation of connectivity have evolved during the last decades to measure both, the direction and the strength of the information flow between cortical areas (ASTOLFI; BABILONI, 2008). The conventional measure of connectivity is the classical *coherence* function (BENDAT; PIERSOL, 1966), expressing the degree of synchrony between a pair of EEG channels. However, coherence does not allow adequate assessment of causality or signal flow directionality. Over the last few years, new estimators based on Granger Causality (GRANGER, 1969) emerged to describe the direction of the information flow. For the bivariate case, *directed coherence* (DC) (KAMITAKE; HARASHIMA; MIYAKAWA, 1984) was introduced to describe mutual synchronicity and directionality between a pair of cortical areas (WANG; TAKIGAWA, 1992), (BACCALÁ; SAMESHIMA, 1998). However, neither coherence nor DC can distinguish between direct and indirect interactions. In the latter case, a third cortical area may be mediating the information flow between the perceived activity in the measured nodes.

The generalization of the notion of DC to the multivariate case, where more than just two cortical areas are interconnected in a neurocognitive network is a more realistic and useful perspective. To examine the multivariate case, *multivariate autoregressive model* (MVAR) (*vector autoregressive model* (VAR)) have been introduced. Using the natural interpretation of VAR models as filters, *Directed Transfer Function* (DTF) (KAMINSKI; BLINOWSKA, 1991) was introduced, exposing both direct and indirect flows of the propagating signals. In order to exclusively expose direct flows between channels, *Partial Directed Coherence* was proposed in (BACCALÁ; SAMESHIMA, 2001). PDC singles out only the direct flows between channels. The authors of DTF and PDC have made some variations of the estimators to turn them into more reliable connectivity measures (BLINOWSKA, 2011; FLORIN et al., 2011; BACCALÁ; SAMESHIMA, 2001; KURGANSKY, 2013).

This chapter contains a brief review of the evolution of the connectivity estimators from coherence to partial directed coherence. Also, we explain the VAR model as representation of the temporal dependencies between cortical regions to develop the Granger causality concept and all its allied estimators.

3.1 Coherence

Coherence is a statistical measure of synchrony between two time series in the frequency domain. The frequency fluctuations among two stationary series $x[n]$ and $y[n]$,

are related to their cross-covariance function defined as:

$$\sigma_{xy}(\tau) = \varepsilon(x[n + \tau] - \mu_x)(y[n] - \mu_y) \quad (3.1)$$

So,

$$\sigma_{yx}(\tau) = \sigma_{xy}(-\tau) \quad (3.2)$$

Without loss of generality, let $\mu_x = \mu_y = 0$. In that case, (3.2) reduces to cross-correlation function $r_{xy}(\tau)$ between x and y . In analogy with the *Wiener-Khintchine* theorem (WIENER, 1930; KHINTCHINE, 1934), the cross-correlation function in frequency domain is the cross-spectrum as

$$\begin{aligned} S_{xy}(f) &= \lim_{T \rightarrow \infty} \frac{1}{T} \varepsilon\{X_T(f)Y_T^*(f)\} = \sum_{\tau=-\infty}^{\infty} r_{xy}(\tau)e^{-j2\pi f\tau} \\ &= |S_{xy}(f)|e^{j\phi_{xy}(f)} \end{aligned} \quad (3.3)$$

This implies the relationship,

$$S_{yx}(f) = \overline{S_{xy}(f)} \quad (3.4)$$

Therefore, the *coherence function* can be defined, as the normalization of the cross-spectrum by the power spectrum of each time series.

$$C_{xy}(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)} \quad (3.5)$$

At any frequency, it satisfies:

$$0 \leq C_{xy}(f) \leq 1 \quad (3.6)$$

cause of the nature of the Cauchy-Schwarz inequality,

$$|S_{xy}(f)|^2 \leq S_{xx}(f)S_{yy}(f) \quad (3.7)$$

Since the phase of the cross-spectrum is the phase difference between the two time series (NUNEZ; SRINIVASAN, 2006) (also known as *relative phase*), it follows that coherence provides a normalized measure of phase synchronization.

Note the similarity between (3.5) and the conventional squared correlation coefficient, which takes the form

$$\rho_{xy}^2 = \frac{\sigma_{xy}^2}{\sigma_x^2 \sigma_y^2} \quad (3.8)$$

Where σ_x^2 and σ_y^2 are the variances of each time series. This analogy helps to interpret the coherence as an estimator that increases with amplitude covariance at each particular frequency. Due to such frequency-dependence, coherence is a very useful measure if one is interested in the synchronization over certain frequency ranges.

Finally, consider a more general form that applies to m multiple time series $\mathbf{x}_i(n) = \{x_1(n), x_2(n), \dots, x_m(n)\}$. In that case we have a cross-spectral density matrix $\mathbf{S}(f)$

$$\mathbf{S}(f) = \begin{bmatrix} S_{11}(f) & S_{12}(f) & \cdots & S_{1m}(f) \\ S_{21}(f) & S_{22}(f) & \cdots & S_{2m}(f) \\ \vdots & \vdots & \ddots & \vdots \\ S_{m1}(f) & S_{m2}(f) & \cdots & S_{mm}(f) \end{bmatrix} \quad (3.9)$$

By extension, the coherence is defined for each pair of time series and is given by (BENDAT; PIERSOL, 1966)

$$C_{ij}(f) = \frac{|S_{ij}(f)|^2}{S_{ii}(f)S_{jj}(f)} \quad (3.10)$$

3.2 Granger Causality (GC)

In contrast to coherence, *Granger causality* lacks the symmetry evident in equation (3.5). The symmetry of coherence, where $C_{xy}(f) = C_{yx}(f)$ makes it impossible to distinguish the direction of information flow. Granger Causality involves temporal concepts of cause and effect, allowing one to point out the direction of information flow; in particular, the autoregressive model is very useful as a representation of the temporal dependencies, used to develop the Granger causality concept.

The representation of interdependencies among time series by the autoregressive model (AR) is widely accepted and used (PARDEY; ROBERTS; TARASSENKO, 1996). This characterisation of EEG data offers a signal representation using just a few parameters, facilitating physiological interpretation (FRANASZCZUK; BLINOWSKA, 1985). However, it is not always appropriate, EEG time series must satisfy stationarity and linearity, properties of autoregressive processes. Thus, evoked potentials that include transient time-dependencies and non-linearities are not immediately characterizable by AR processes (WRIGHT; KYDD; SERGEJEV, 1990). In this sense, we represent linear causality relationships among EEG time series, not the entire dynamics of each of them.

3.2.1 Autoregressive model

An autoregressive model of order p , $\text{AR}(p)$ can be interpreted as a filter whose output depends linearly on its own past values and on some innovation noise uncorrelated to such output. An $\text{AR}(p)$ model is described as

$$x[n] = \sum_{k=1}^p a[k]x[n-k] + w[n] \quad (3.11)$$

Where $w[n]$ corresponds to an innovation noise that works as input to the AR filter. So, time series $x[n]$ at time index $n=1,2,\dots,N$ is represented as a weighted sum of the samples

at previous time indices, where p is the maximum lag known as the order of the AR(p) process. The linear combination is weighted according to the AR coefficients $a[k]$.

Given a linear and stationary temporal series, it is possible to model it as an autoregressive process using a numerical method such as the Levinson recursion, Burg algorithm, MLE method, least squares among others (MARPLE, 1987). All those algorithms numerically solve the Yule-Walker equations given by

$$\begin{bmatrix} r_{xx}[0] & r_{xx}^*[1] & \cdots & r_{xx}^*[p] \\ r_{xx}[1] & r_{xx}[0] & \cdots & r_{xx}^*[p-1] \\ \vdots & \vdots & \ddots & \vdots \\ r_{xx}[p] & r_{xx}[p-1] & \cdots & r_{xx}[0] \end{bmatrix} \begin{bmatrix} 1 \\ a[1] \\ \vdots \\ a[p] \end{bmatrix} = \begin{bmatrix} \sigma^2 \\ 0 \\ \vdots \\ 0 \end{bmatrix} \quad (3.12)$$

Where the matrix is the Hermitian Toeplitz autocorrelation matrix of $x[n]$ and σ^2 is the innovation noise variance.

3.2.2 Multivariate autoregressive model

Consider the vector $\mathbf{x}[n]$ composed of m time series or channels $x_i[n]$ indexed at $1 \leq n \leq N$.

$$\mathbf{x}[n] = \begin{bmatrix} x_1[n] \\ \vdots \\ x_m[n] \end{bmatrix} \quad (3.13)$$

Making an extension of the AR model to the multivariate or multichannel version with m channels, the VAR model is described as,

$$\mathbf{x}[n] = \sum_{k=1}^p \mathbf{A}[k] \mathbf{x}[n-k] + \mathbf{w}[n] \quad (3.14)$$

Where the VAR coefficient matrices, $\mathbf{A}[k]$ ($m \times m$) describe the linear combination between the past samples of the m channels until the maximum lag p , the model order.

Factorization of the vector $\mathbf{x}[n]$ can be made in order to express the autoregressive model as a block vector inner product

$$\begin{aligned} \mathbf{I}_m \mathbf{x}[n] - \sum_{k=1}^p \mathbf{A}[k] \mathbf{x}[n-k] &= \mathbf{w}[n] \\ \begin{bmatrix} \mathbf{I}_m & -\mathbf{A}[1] & \cdots & -\mathbf{A}[p] \end{bmatrix} \begin{bmatrix} \mathbf{x}[n] \\ \vdots \\ \mathbf{x}[n-p] \end{bmatrix} &= \begin{bmatrix} \mathbf{w}[n] \\ \vdots \\ \mathbf{w}[n-p] \end{bmatrix} \\ \mathbf{a}_p \mathbf{x}_p[n] &= \mathbf{w}_p[n] \end{aligned} \quad (3.15)$$

where

$$\mathbf{a}_p = \begin{bmatrix} \mathbf{I}_m & -\mathbf{A}[1] & \cdots & -\mathbf{A}[p] \end{bmatrix} \quad (3.16)$$

Postmultiplying (3.15) by $\underline{\mathbf{x}}_p^H[n]$ and taking the expectation,

$$\varepsilon \{ \underline{\mathbf{a}}_p \underline{\mathbf{x}}_p[n] \underline{\mathbf{x}}_p^H[n] \} = \underline{\mathbf{a}}_p \varepsilon \{ \underline{\mathbf{x}}_p[n] \underline{\mathbf{x}}_p^H[n] \} = \varepsilon \{ \underline{\mathbf{w}}_p[n] \underline{\mathbf{x}}_p^H[n] \} \quad (3.17)$$

So, the *Hermitian block – Toeplitz* matrix $\underline{\mathbf{R}}_p$ is defined as,

$$\begin{aligned} \underline{\mathbf{R}}_p &= \varepsilon \{ \underline{\mathbf{x}}_p[n] \underline{\mathbf{x}}_p^H[n] \} \\ &= \begin{bmatrix} \varepsilon \{ \mathbf{x}[n] \mathbf{x}^H[n] \} & \cdots & \varepsilon \{ \mathbf{x}[n] \mathbf{x}^H[n-p] \} \\ \vdots & \ddots & \vdots \\ \varepsilon \{ \mathbf{x}[n-p] \mathbf{x}^H[n] \} & \cdots & \varepsilon \{ \mathbf{x}[n-p] \mathbf{x}^H[n-p] \} \end{bmatrix} \\ &= \begin{bmatrix} \mathbf{R}_{xx}[0] & \mathbf{R}_{xx}[1] & \cdots & \mathbf{R}_{xx}[p] \\ \mathbf{R}_{xx}[-1] & \mathbf{R}_{xx}[0] & \cdots & \mathbf{R}_{xx}[p-1] \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{R}_{xx}[-p] & \mathbf{R}_{xx}[-p+1] & \cdots & \mathbf{R}_{xx}[0] \end{bmatrix} \end{aligned} \quad (3.18)$$

and,

$$\begin{aligned} \varepsilon \{ \underline{\mathbf{w}}_p[n] \underline{\mathbf{x}}_p^H[n] \} &= \varepsilon \left\{ \mathbf{w}[n] \left(\mathbf{w}^H[n] + \sum_{k=1}^p \mathbf{x}^H[n-k] \mathbf{A}_p^H[k] \right) \right\} \\ &= \begin{bmatrix} \mathbf{P}_p & \mathbf{0} & \cdots & \mathbf{0} \end{bmatrix} \end{aligned} \quad (3.19)$$

Where all-zero matrices are $m \times m$ and the matrix $\mathbf{P}_p = \varepsilon \{ \underline{\mathbf{w}}[n] \underline{\mathbf{w}}^H[n] \}$ is the covariance matrix of the m innovation noises in equation (3.15), which are uncorrelated with past values. Therefore, replacing these results in equation (3.17), it is defined the multichannel version of the Yule-Walker equations.

$$\underline{\mathbf{a}}_p \underline{\mathbf{R}}_p = \begin{bmatrix} \mathbf{P}_p & \mathbf{0} & \cdots & \mathbf{0} \end{bmatrix} \quad (3.20)$$

It is possible to solve equation (3.20) with numerical methods, such as Levinson algorithm, Viera-Morf method, Nuttall-Strand method, among others (MARPLE, 1987; LÜTKEPOHL, 2007).

Based on the concept of autoregressive model and particularly on the bivariate one, Granger introduced a few concepts related to causality, where the VAR coefficients play a significant role (GRANGER, 1969). The fundamental idea of Granger causality is that a cause cannot come after the effect. Thus, if the variance of the signal y estimation is reduced by the inclusion of x in the prediction, then x G-causes y .

VAR modelling is suitable for Granger causality analyses because it uses information from the channels interacting in the process and thus permits analysis of the presence of direct causal influence between channels. Suppose that the system composed of channels x and y can be modelled as a bivariate VAR process. In that case, the influence of x on y can be determined analysing the sequence of VAR coefficients $a_{yx}[k]$ for all possible k lags. If the coefficients $a_{yx}[k]$ are jointly significantly different from zero, there is direct influence from channel x to channel y and therefore, x G-causes y .

3.3 Directed Coherence (DC)

Based on the temporal relation of the signals, DC is defined in the frequency domain to describe the correlation between pairs of signals considering the direction of information flow. Thus, DC provides an estimator characterizing both directional and spectral properties of the signals involving a multivariate system. In fact, DC solves the issue of cause and effect between time series in the Granger causality sense and involves the inference of the presence of feedback loops between time series (KAMITAKE; HARASHIMA; MIYAKAWA, 1984; WANG; TAKIGAWA, 1992; BACCALA et al., 1998; BACCALÁ; SAMESHIMA, 1998).

The definition of directed coherence (SAITO; HARASHIMA, 1981) is based on VAR models and spectral factorization (WANG; TAKIGAWA, 1992; BACCALA et al., 1998; BACCALÁ; SAMESHIMA, 1998). For the case of stationary signals, their joint second order statistics is sufficiently described by their power spectral density and cross-power spectra contained in the cross-spectral density matrix $\mathbf{S}(f)$, which can be written in the unique form

$$\mathbf{S}(f) = \mathbf{H}(f) \Sigma_{\mathbf{w}} \mathbf{H}^H(f) \quad (3.21)$$

where $\Sigma_{\mathbf{w}}$ is the noise covariance matrix and $\mathbf{H}(f)$ is the transfer function matrix of the system.

The asymmetry of $\mathbf{H}(f)$ means that the information flow from x_i to x_j is different from that in the opposite direction. This suggests that the direction of information flow is implicitly included in the transfer function matrix, whose elements are a kind of measure of direction flow, i.e. the causal interactions. However, in order to be able to compare results from different time series, a normalization is performed. This normalization is similar to that employed for classical coherence, giving properties similar to it and resulting in the definition of DC from x_j to x_i as

$$DC_{i \leftarrow j}(f) = \frac{\sigma_{jj} H_{ij}(f)}{\sqrt{\sum_{r=1}^M \sigma_{jj}^2 |H_{rj}|^2}} = \frac{\sigma_{jj} H_{ij}(f)}{\sqrt{S_{ii}(f)}} \quad (3.22)$$

where $H_{ij}(f)$ is the directed transfer function from x_j to x_i , $S_{ii}(f)$ is the power spectral density of x_i , σ_{jj} is the variance of $w_j[n]$. Thus, $DC_{i \leftarrow j}(f)$ represents the fraction of the power of x_i that is due to the past of x_j (BACCALA et al., 1998).

This basic model holds under the assumption that the signals can be modelled as a M-channel VAR process (eq. (3.14)) with noise vector $\mathbf{w}[n]$. In the frequency domain, the VAR model can be expressed as

$$\begin{aligned} \mathbf{X}(f) &= \sum_{k=1}^p \mathbf{A}[k] \mathbf{X}(f) \exp(-j2\pi f k) + \mathbf{W}(f) \\ \left[\mathbf{I} - \sum_{k=1}^p \mathbf{A}[k] \exp(-j2\pi f k) \right] \mathbf{X}(f) &= \mathbf{W}(f) \end{aligned} \quad (3.23)$$

where $\mathbf{W}(f)$ is the cross-spectral density matrix of $\mathbf{w}[n]$.

Consequently, the transfer function matrix is

$$\mathbf{H}(f) = [\mathbf{I} - \sum_{k=1}^p \mathbf{A}[k] \exp(-j2\pi f k)]^{-1} \quad (3.24)$$

So, the DC is fully described for a multivariate autoregressive model.

3.4 Directed Transfer Function (DTF)

As we mentioned above, the transfer function matrix contains the causal interaction between the channels in the frequency domain. Thus, the element $H_{ij}(f)$ describes the connection between x_j influencing x_i . Considering this, Kaminski and Blinowska proposed the DTF estimator in (KAMINSKI; BLINOWSKA, 1991), defined as

$$DTF_{i \leftarrow j}(f) = \frac{|H_{ij}(f)|^2}{\sum_{r=1}^M |H_{ir}(f)|^2} \quad (3.25)$$

which redefines DC to a different normalization. However, this estimator provides both, direct as indirect links, misleading in the identification of intermediating structures in a network.

3.5 Partial Directed Coherence (PDC)

To offer a representation for Granger causality descriptors in the frequency domain, Baccalá and Sameshima proposed the PDC concept in (BACCALÁ; SAMESHIMA, 2001) as

$$PDC_{i \leftarrow j}(f) = \pi_{ij}(f) = \frac{\bar{A}_{ij}(f)}{\sqrt{\sum_{r=1}^M |\bar{A}_{rj}(f)|^2}} = \frac{\bar{A}_{ij}(f)}{\sqrt{\bar{\mathbf{a}}_j^H(f) \bar{\mathbf{a}}_j(f)}} \quad (3.26)$$

where $\bar{A}_{ij}(f)$ is an element of the matrix $\bar{\mathbf{A}}(f) = [\bar{\mathbf{a}}_1 \cdots \bar{\mathbf{a}}_p]$ defined as (see Eq. 3.23)

$$\bar{\mathbf{A}}(f) = \mathbf{I} - \sum_{k=1}^p \mathbf{A}[k] \exp(-j2\pi f k) \quad (3.27)$$

Observe that the elements of the matrix $\bar{\mathbf{A}}(f)$ in Eq. 3.23 are connected with the Fourier transforms of the time series of matrix elements of the VAR coefficient matrices. Furthermore, the element $\bar{A}_{ij}(f)$ shows the frequency filtering of $X_j(f)$ before it becomes part of $X_i(f)$. Directed influence of $x_j[n]$ on $x_i[n]$ can be measured by $|\bar{A}_{ij}|$, nevertheless it needs to be normalized as the others estimators. Thus, $\pi_{ij}(f)$ is normalized with respect to the cumulative influence of channel $x_j[n]$ on all channels, including channels $x_i[n]$ and $x_j[n]$. Summarizing, PDC reflects the Granger causality's fundamental idea in the frequency domain.

In comparison with DTF and DC, PDC does not need the inversion of a matrix, making its implementation easy. Besides, if $\pi_{ij}(f)$ is significantly different from zero, there is a direct influence from x_j to x_i . Thus, PDC provides the direct links only and therefore, allows to identify every single link in a network.

3.5.1 Generalized PDC (gPDC) and information PDC (iPDC)

More general expressions for PDC were formulated later: generalized PDC (gPDC) and information PDC (iPDC) proposed in (BACCALÁ; SAMESHIMA; TAKAHASHI, 2007) and (TAKAHASHI; BACCALÁ; SAMESHIMA, 2010) respectively.

$$gPDC_{i \leftarrow j}(f) = g\pi_{ij}(f) = \frac{\frac{1}{\sigma_i} \bar{A}_{ij}(f)}{\sqrt{\sum_{r=1}^M \frac{1}{\sigma_r} |\bar{A}_{rj}(f)|^2}} \quad (3.28)$$

$$iPDC_{i \leftarrow j}(f) = i\pi_{ij}(f) = \frac{\frac{1}{\sigma_i} \bar{A}_{ij}(f)}{\sqrt{\bar{\mathbf{a}}_j \Sigma_w^{-1} \bar{\mathbf{a}}_j^H}} \quad (3.29)$$

The difference between the three forms of PDC is in the scaling, gPDC and iPDC do a standarization of the time series. Additionally, iPDC deals with interaction effect size in the presence of instantaneous causality which is reflected in the the noise covariance matrix $\mathbf{P}_p$ cross-terms.

3.5.2 Asymptotic theory for PDC: iPDC

The test is based on determining the null hypothesis threshold taking into account PDC asymptotic behaviour. This also allows finding the asymptotic confidence intervals for $|\pi_{ij}(f)|^2$ when H_0 does not hold because for a stable stationary Gaussian VAR(p) process, the maximum likelihood estimator $|\hat{\pi}_{ij}(f)|^2$ is consistent and asymptotically normal if $|\pi_{ij}(f)|^2 \neq 0$ (BACCALÁ; SAMESHIMA; TAKAHASHI, 2007).

Conversely, if the null hypothesis ($|\pi_{ij}(f)|^2 = 0$) is true, the resulting distribution for $|\pi_{ij}(f)|^2$ is that of a linear combination of at most two properly weighted χ_1^2 random variables with frequency-dependent weights (BACCALÁ et al., 2013). These are available through the AsympPDC package (SAMESHIMA; BACCALÁ, 2011).

$$H_0 : |\pi_{ij}(f)|^2 = 0 \quad (3.30)$$

$$H_1 : |\pi_{ij}(f)|^2 \neq 0 \quad (3.31)$$

4 The Effect of Volume Conduction

Volume conduction makes scalp EEG signals look rather different at distinct locations on the scalp when compared to electrocorticographic (ECoG) and/or intracranial EEG (iEEG) over the same spatial scale (NUNEZ; SRINIVASAN, 2006). The transmission of electric and magnetic fields through a volume conductor (the head's biological tissues) produces degrading effects according to the conducting properties and the geometry of the tissues between the source and its recording site (PICTON, 1988).

Two qualitative VC characteristics are well known. First, signal propagation through the tissues is independent of frequency in the band of the EEG waves (NUNEZ, 1981). Second, cortical source activity measured at the scalp is a low-pass spatially filtered version of the sources (space averaged) caused by the separation between cortex and scalp, and the relatively low and high conductivities of the skull and *cerebrospinal fluid* (CSF) respectively (COOPER et al., 1965; NUNEZ, 1981; SRINIVASAN et al., 1996).

The frequency independence mentioned above is derived from the electrical properties of the tissues at the appropriate spatial scale. To define the spatial scale of interest, consider that scalp EEG measurements are influenced by a tissue mass containing 10^8 to 10^9 neurons plus the fluid in between (NUNEZ; SRINIVASAN, 2006). At this macroscopic scale and at the characteristic low brain frequencies, the medium is linear in both its conductivity and its dielectric properties (FERREE; ERIKSEN; TUCKER, 2000; GONÇALVES et al., 2003; GABRIEL; PEYMAN; GRANT, 2009). Such linearity leads to an independence of tissue resistivities on frequency.

To illustrate the spatial filtering of the cortical activity, Srinivasan et al. developed a mathematical model of the VC transfer function, concluding that source signals are low-pass spatially filtered due to the high brain to skull conductivity ratio (SRINIVASAN et al., 1996). This produces highly smoothed potentials at the scalp, which are observable in the unprocessed EEG. This smoothness can be interpreted as due to a combination of the cortical sources at each location of the scalp surface. So, a cortical source can be recorded by several scalp electrodes, because they can not exclusively obtain the electrical activity corresponding to its exact location projected on the cortex.

In the light of the above, one must acknowledge that VC produces instantaneous effects at the scalp leading to linear combinations between source activities (BAILLET; MOSHER; LEAHY, 2001; STINSTRAS; PETERS, 1998). Therefore, VC provides a spatial weighting function relating cortical sources $\mathbf{s}[n]$ and the scalp surface potentials $\mathbf{x}[n]$, where the i channel is represented by (NUNEZ; CUTILLO, 1995; BAILLET; MOSHER;

LEAHY, 2001; BACCALÁ; SAMESHIMA, 2015; KURGANSKY, 2010)

$$x_i[n] = \sum_{j=1}^K \Omega_{ij} s_j[n] + u_i[n] \quad (4.1)$$

Additional artifacts are further represented by $u_i[n]$, they are of biological and measurement origin. Furthermore, $u_i[n]$ could be composed of independent noise but also, may come from synchronized common noise sources that add instantaneous interactions to the recording data at the scalp. Thus, the vector representation for M EEG channels results

$$\begin{bmatrix} x_1[n] \\ \vdots \\ x_M[n] \end{bmatrix} = \mathbf{\Omega} \begin{bmatrix} s_1[n] \\ \vdots \\ s_K[n] \end{bmatrix} + \begin{bmatrix} u_1[n] \\ \vdots \\ u_M[n] \end{bmatrix} \quad (4.2)$$

$$\mathbf{x}[n] = \mathbf{\Omega} \mathbf{s}[n] + \mathbf{u}[n] \quad (4.3)$$

where $\mathbf{\Omega}$ represents the weighting function that depends on the location of the sources at the cortex, the location of the electrodes at the scalp and on the electrical properties of the brain and its coverings. The elements of the $\mathbf{\Omega}$ matrix are real valued because VC does not alter the phases of the signals generated at the cortex. In this sense, if one wishes to represent connections on the $\mathbf{s}[n]$ space, knowledge of $\mathbf{\Omega}$ matrix must be available.

Part II

Theoretical results

5 Theoretical proceeding

The term *volume conduction* refers to the fact that recorded EEG signals reflect not only the activity of the bioelectrical cortical source located just under each electrode, but also a linear combination of all other sources. The scalp potential appears as result of the current flow from the cortex, through the tissues of the head towards the scalp surface. After such propagation, each channel records a mixture of signals generated by several sources. Thus, calculations using EEG signals may wrongly reflect the true functional interaction between cortical regions, since the same source may be present at different channels.

To understand the theoretical approach consider the block diagram in Figure 4, where the connectivity at source and sensor spaces is characterized by its corresponding PDC. The proposal is to find explicit expressions for the PDC at the scalp as function of the situation at the cortex in order to make a comparison between both connectivities, especially the differences from the original connectivity at the cortex.

Figure 4 – Block diagram of the theoretical procedure.

Source: authorship

Sources and sensors are related by the Ω matrix, which represents the linear mixture of sources at the scalp. It can be considered as a generic mixture, where the analysis is focused in the structure of the matrices. Furthermore, that matrix can be characterized according with an analytical model of the head, allowing to analysis the VC impact on the connectivity in an EEG context. Both analysis consider different types of references to obtain the time-series at the scalp:

- Reference at infinity
- Reference at the head surface
- Instantaneous average as reference
- Local references

5.1 Volume conduction as source mixing

We are interested in PDC mediated connectivity detection. In chapter 6, we analyse the implications of source mixing on the autoregressive model estimated at the scalp as required for PDC computations by comparing it with the original VAR model at the cortex and its original connectivity. Here we consider very general expressions without specific regard of the volume conduction model of the head.

As already mentioned, autoregressive processes are used to express causality information between sources. Suppose that there are N_s active sources $\mathbf{s}[n]$, related in a Granger-causality sense by the following vector autoregressive process

$$\mathbf{s}[n] = \sum_{h=1}^p \mathbf{A}[h] \mathbf{s}[n-h] + \mathbf{w}[n] \quad (5.1)$$

where $\mathbf{A}[h]$ is the coefficient matrix for lag h . The vector $\mathbf{w}[n]$ is white zero mean gaussian innovation noise.

Now, let N_e be the number of electrodes that record $\mathbf{x}[n]$ signals, which in turn are associated with the source activity by

$$\mathbf{x}[n] = \mathbf{\Omega} \mathbf{s}[n] \quad (5.2)$$

$$\begin{aligned} &= \mathbf{\Omega} \left(\sum_{h=1}^p \mathbf{A}[h] \mathbf{s}[n-h] + \mathbf{w}[n] \right) \\ &= \sum_{h=1}^p \mathbf{\Omega} \mathbf{A}[h] \mathbf{s}[n-h] + \mathbf{\Omega} \mathbf{w}[n] \end{aligned} \quad (5.3)$$

The *leadfield matrix* (CUFFIN; COHEN, 1979), $\mathbf{\Omega}$ describes the linear combination of the sources and depends on the relevant geometry, tissue electrical properties, as well as on source and sensor spatial distributions. Each element Ω_{ed} describes the contribution of the d -th source to the signal recorded by the e -th electrode. For convenience and without loss of generality, we choose the diagonal element Ω_{ee} to represent the biggest contribution to $x_e[n]$ (see Figure 5). For analytical simplicity we refer to source $s_e[n]$ as the one associated to electrode $x_e[n]$.

Figure 5 – Elements of the leadfield matrix distinguishing associated sources from non-associated sources. The intensity of the influence of a source on a sensor is represented by the gray intensity.

Source: authorship

It is important to have in mind that $\mathbf{\Omega}$ components are real numbers since head tissue impedances are only of resistive character at macroscopic scales in the EEG frequency range (WOLPAW; WOLPAW, 2012; NUNEZ; CUTILLO, 1995).

Thus, (5.3) represents an input-output model from sources to electrodes. Sensor level connectivity analysis has relied on applying GC/PDC estimation directly to $\mathbf{x}[n]$ data. To do so, VAR modelling is applied to it so that the actual result of modelling produces:

$$\mathbf{x}[n] = \sum_{h=1}^p \mathbf{B}[h] \mathbf{x}[n-h] + \mathbf{v}[n] \quad (5.4)$$

The crucial point that needs to be addressed is to which extent some of the original structure of the $\mathbf{A}[h]$ matrices describing source causality is preserved in $\mathbf{B}[h]$ which describes electrode causality. To investigate this, additional hypotheses are necessary. Those considered in this work are listed as follows according to (a) the presence and level of extra additive noise and (b) the relative number of sources (N_s) and electrodes (N_e):

1. $N_s = N_e$ see Sec. 6.1.
2. $N_s > N_e$ see Sec. 6.2.
3. $N_s < N_e$ see Sec. 6.3.

Each one of these alternatives is considered in the following sections where hypotheses regarding relative source magnitude effects are used to derive approximate results.

Additive noise

In the presence of significant additive noise, the actually measured signal is given by:

$$\tilde{\mathbf{x}}[n] = \mathbf{\Omega} \mathbf{s}[n] + \mathbf{q}[n] \quad (5.5)$$

As a matter of fact the latter scenario can only be described appropriately via *state space* models (SZEDERKÉNYI; LAKNER; GERZSON, 2006). One effect of not explicitly considering the presence of additive noise is the introduction of modelling bias, which is difficult to analytically predict. This observation prompts us to forego such analysis and restrict our theoretical considerations only to the case of zero added noise.

5.2 Volume conduction as analytical head model

In chapter 7, we characterize the source mixing according to an analytical VC head model. First it is necessary to obtain the scalp generated by a point cortical source, that allows us to analytically express the leadfield matrix in order to analyse the source mixing impact on the scalp.

6 Volume conduction as source mixing

To illustrate our results, we use an example where each source is independent, and thus without mutual connectivity. This scenario is very convenient for our analyses because all the connectivity detected at the sensor space would be exclusively produced by the effects of volume conduction. The following equations describe our VAR(3) process imposed at the source space:

$$\begin{aligned} s_1[n] &= 0.677s_1[n-1] + 0.175s_1[n-2] + 0.297s_1[n-3] \\ s_2[n] &= 0.75s_2[n-1] - 0.125s_2[n-2] \\ s_3[n] &= 0.6s_3[n-1] - 0.7s_3[n-2] + 0.04s_3[n-3] \end{aligned} \quad (6.1)$$

In this case, all the VAR coefficient matrices $\mathbf{A}[h]$ are diagonal, reflecting the absence of inter-sources causality. Furthermore, Figure 6 shows the $|gPDC|^2$ value and the connectivity inference using the statistical test proposed in (BACCALÁ; SAMESHIMA; TAKAHASHI, 2007), where the lack of connectivity in the system is evident.

Figure 6 – PDC detection at source space. The (i, j) subplot represents the link $s_j[n] \rightarrow s_i[n]$. Diagonal subplots contain the normalized spectra of the sources. The green lines are no connectivity detected and red lines are connectivity detected. The figure shows only one repetition of the simulation.

Source: authorship

All the simulations in this chapter are repeated 500 times, followed by the calculation of the mean $|gPDC|$ value (see Figure 7a), as well as the percentage of connectivity detection using the statistical test (as in 7b). As one can see, the mean gPDC value is about 1 for the influence of each source on itself, where the percentage of detected connectivity reaches 100%. All the absent links are correctly identified with close to zero percentage of connectivity detected.

Figure 7 – Imposed connectivity at the source space across 500 repetitions. The (i, j) subplot represents the link $s_j[n] \rightarrow s_i[n]$. Left: gPDC mean value; Right: Percentage of detected connectivity at the source space.

Source: authorship

6.1 Case: $N_e = N_s$

Let $K = N_e = N_s$ refer to this identical number of channels and sources, resulting in a square leadfield matrix $\mathbf{\Omega}$ that characterizes this case. In the absence or neglectable additive noise, it is relatively easy to theoretically deduce the form of the $\mathbf{B}[h]$ matrices. The real cortical regions are represented by equivalent point sources located near the recording electrodes as in (MAKEIG et al., 2004) for the sake of simplified interpretation. Additionally, if it is nonsingular, the lagged samples of $\mathbf{s}[n]$ can be expressed as

$$\mathbf{s}[n-h] = \mathbf{\Omega}^{-1} \mathbf{x}[n-h], \quad \forall h = 1, 2, \dots, p$$

Thus, the VAR process at the scalp, (5.2) can be written as

$$\begin{aligned} \mathbf{x}[n] &= \sum_{h=1}^p \mathbf{\Omega} \mathbf{A}[h] \mathbf{\Omega}^{-1} \mathbf{x}[n-h] + \mathbf{\Omega} \mathbf{w}[n], \\ \mathbf{x}[n] &= \sum_{h=1}^p \mathbf{B}[h] \mathbf{x}[n-h] + \mathbf{v}[n] \end{aligned} \tag{6.2}$$

where the original innovations noise covariance matrix is modified to $\mathbf{v}[n] = \mathbf{\Omega} \mathbf{w}[n]$, which covariance matrix is

$$\begin{aligned} \mathbf{\Sigma}_{\mathbf{v}} &= \varepsilon \left\{ (\mathbf{\Omega} \mathbf{w}[n]) (\mathbf{\Omega} \mathbf{w}[n])^H \right\} \\ &= \varepsilon \left\{ \mathbf{\Omega} \mathbf{w}[n] \mathbf{w}^H[n] \mathbf{\Omega}^T \right\}, \\ &= \mathbf{\Omega} \mathbf{\Sigma}_{\mathbf{w}} \mathbf{\Omega}^T \end{aligned} \tag{6.3}$$

In other words, even if $\mathbf{\Sigma}_{\mathbf{w}}$ is diagonal, one cannot expect $\mathbf{\Sigma}_{\mathbf{v}}$ in general to be so as well.

Furthermore, from (6.2) is easy to see that the observed Granger causality structure at the scalp becomes represented by

$$\mathbf{B}[h] = \mathbf{\Omega} \mathbf{A}[h] \mathbf{\Omega}^{-1} \tag{6.4}$$

For further reference we employ the frequency domain in our considerations as employed by PDC. Thus in absence of additive noise the required system description is afforded by

$$\begin{aligned}
 \bar{\mathbf{B}}(f) &= \mathbf{I} - \sum_{h=1}^p \mathbf{B}[h] \exp^{-i2\pi fh} \\
 &= \mathbf{I} - \mathbf{\Omega} \sum_{h=1}^p \mathbf{A}[h] \exp^{-i2\pi fh} \mathbf{\Omega}^{-1} \\
 &= \mathbf{\Omega} [\mathbf{I} - \mathbf{A}(f)] \mathbf{\Omega}^{-1} \\
 &= \mathbf{\Omega} \bar{\mathbf{A}}(f) \mathbf{\Omega}^{-1}
 \end{aligned} \tag{6.5}$$

which describes connectivity at the electrode level after the mixing VC effects. By comparison of (6.4) with (6.5), note that the relationship among matrices of sensors and sources is exactly the same in both frequency and time domains.

At this point, it might be worth digressing somewhat about the effect of $\mathbf{\Omega}$ on the inferred models. The central point regards conditions that leave the structure of $\bar{\mathbf{A}}(f)$ unchanged when gauged from the point of view of measuring $\bar{\mathbf{B}}(f)$ through direct modeling. In full generality if $\bar{\mathbf{A}}(f)$ and $\mathbf{\Omega}$ commute, i.e. if

$$\mathbf{\Omega} \bar{\mathbf{A}}(f) = \bar{\mathbf{A}}(f) \mathbf{\Omega} \tag{6.6}$$

then

$$\bar{\mathbf{A}}(f) = \bar{\mathbf{B}}(f) \tag{6.7}$$

so that connectivity is not just structurally preserved but also completely so. In practice (6.6) is never satisfied with probability 1. This demands the consideration of some approximate cases presented next. To do so we need the following

Lemma 1. *The coefficients of $\bar{\mathbf{B}}(f) = \mathbf{\Omega} \bar{\mathbf{A}}(f) \mathbf{\Omega}^{-1}$ are given by:*

$$\bar{b}_{ij}(f) = \frac{1}{\det(\mathbf{\Omega})} \underline{\Omega}_i \sum_{k=1}^K \bar{\mathbf{a}}_k c_{jk} \tag{6.8}$$

where

$$\begin{aligned}
 \bar{\mathbf{A}}(f) &= [\bar{\mathbf{a}}_1 \quad \bar{\mathbf{a}}_2 \quad \cdots \quad \bar{\mathbf{a}}_K] & \bar{\mathbf{a}}_j &= \begin{bmatrix} \bar{a}_{1j} \\ \bar{a}_{2j} \\ \vdots \\ \bar{a}_{Kj} \end{bmatrix} \\
 \mathbf{\Omega} &= \begin{bmatrix} \underline{\Omega}_1 \\ \underline{\Omega}_2 \\ \vdots \\ \underline{\Omega}_K \end{bmatrix} & \underline{\Omega}_i &= [\Omega_{i1} \quad \Omega_{i2} \quad \cdots \quad \Omega_{iK}]
 \end{aligned}$$

and where c_{jk} stand for the elements of the cofactor matrix of $\mathbf{\Omega}$.

Proof

The VAR coefficient matrix at the scalp can be written as

$$\begin{aligned}
 \bar{\mathbf{B}} &= \mathbf{\Omega} \bar{\mathbf{A}}(f) \mathbf{\Omega}^{-1} \\
 &= \begin{bmatrix} \underline{\Omega_1} \\ \underline{\Omega_2} \\ \vdots \\ \underline{\Omega_K} \end{bmatrix} \begin{bmatrix} \mathbf{a_1} & \mathbf{a_2} & \cdots & \mathbf{a_K} \end{bmatrix} \frac{1}{\det(\mathbf{\Omega})} \mathbf{C}^T \\
 &= \frac{1}{\det(\mathbf{\Omega})} \begin{bmatrix} \underline{\Omega_1} \mathbf{a_1} & \underline{\Omega_1} \mathbf{a_2} & \cdots & \underline{\Omega_1} \mathbf{a_K} \\ \underline{\Omega_2} \mathbf{a_1} & \underline{\Omega_2} \mathbf{a_2} & \cdots & \underline{\Omega_2} \mathbf{a_K} \\ \vdots & & \ddots & \vdots \\ \underline{\Omega_K} \mathbf{a_1} & \underline{\Omega_K} \mathbf{a_2} & \cdots & \underline{\Omega_K} \mathbf{a_K} \end{bmatrix} \begin{bmatrix} c_{11} & c_{21} & \cdots & c_{K1} \\ c_{12} & c_{22} & \cdots & c_{K2} \\ \vdots & & \ddots & \vdots \\ c_{1K} & c_{2K} & \cdots & c_{KK} \end{bmatrix}
 \end{aligned}$$

Now, we can express the elements of $\bar{\mathbf{B}}(f)$:

$$\begin{aligned}
 b_{ij}(f) &= \frac{1}{\det(\mathbf{\Omega})} \begin{bmatrix} \underline{\Omega_i} \mathbf{a_1} & \underline{\Omega_i} \mathbf{a_2} & \cdots & \underline{\Omega_i} \mathbf{a_K} \end{bmatrix} \begin{bmatrix} c_{j1} \\ c_{j2} \\ \vdots \\ c_{jK} \end{bmatrix} \\
 &= \frac{1}{\det(\mathbf{\Omega})} \sum_{k=1}^K \underline{\Omega_i} \mathbf{a_k} c_{jk} \\
 &= \frac{1}{\det(\mathbf{\Omega})} \underline{\Omega_i} \sum_{k=1}^K \mathbf{a_k} c_{jk}
 \end{aligned}$$

■

6.1.1 Triangular leadfield matrix

A weak sufficient condition for structure preservation is represented by lower square triangular matrices, which form a group with respect to matrix multiplication (CARRELL, 2005). As a recap, lower triangular matrices are composed of zeros above the main diagonal. The weakness of this result stems from the improbability that $\bar{\mathbf{A}}(f)$ and $\mathbf{\Omega}$ be both strictly lower triangular in practice. Note that, upper triangular matrices also form a matrix multiplication group so that similar results apply.

A distinction is essential to the triangular matrix considerations: it guarantees that those initially zero coefficients above the main diagonal remain so, but it does not exclude the modification of some entries in other positions, changing its value to zero or from zero. An example suffices to show this.

Consider a *cascade connection* which is characterized by a source s_1 that influences s_2 directly which in turn does it for s_3 and so on. Structurally this is easily represented by

a lower triangular matrix $\bar{\mathbf{A}}(f)$:

$$\bar{\mathbf{A}}(f) = \begin{bmatrix} \alpha & 0 & 0 \\ \alpha & \alpha & 0 \\ 0 & \alpha & \alpha \end{bmatrix} \quad (6.9)$$

where α represents nonzero values. Even if $\mathbf{\Omega}$ is lower triangular, it is impossible to guarantee whether b_{31} will remain zero. Observe that the cascade structure represented by (6.9) depends on the numbering of source structures. Naturally all the group property ensures is that $\bar{b}_{ij}(f) = 0$ for $j > i$, which can generate some artificial links as shown in Figure 8.

Figure 8 – Diagram of a triangular leadfield matrix leading propagation from source to sensor space for three independent sources. Dashed lines are the theoretical spurious connectivity at the sensor space.

Source: authorship

Furthermore, connectivity estimation can be impacted using a triangular leadfield matrix, even with a diagonal $\bar{\mathbf{A}}(f)$. Consider that the temporal dependencies at the source space are described by the VAR(3) process of equation (6.1), which has a diagonal $\bar{\mathbf{A}}(f)$. Then, impose a lower triangular leadfield matrix with random values ($N(0, 1)$) under the main diagonal, generating a unique leadfield matrix for every repetition. The resulting scenario at the sensor space after all the repetitions is shown in Figure 9, where the impact of source mixing is evident. The gPDC value for all the links remains close to zero, although the percentage of connectivity detected shows a spurious cascade connection at the sensor level.

6.1.2 Diagonal leadfield matrix

A special case arises when $\mathbf{\Omega}$ is both lower and upper triangular, producing no structural changes. This is summed up in

Lemma 2. For a diagonal $\mathbf{\Omega}$, the coefficients of $\bar{\mathbf{B}}(f) = \mathbf{\Omega} \bar{\mathbf{A}}(f) \mathbf{\Omega}^{-1}$ are given by:

$$\bar{b}_{ij}(f) = \frac{\Omega_{ii}}{\Omega_{jj}} \bar{a}_{ij}(f) \quad (6.10)$$

Figure 9 – Conectivity at the sensor space with no causality between sources and lower triangular leadfield matrix. Left: gPDC value; Right: Percentage of detected connectivity.

Source: authorship

Proof

The i -th row of a diagonal leadfield matrix is given by

$$\underline{\Omega}_i = \begin{bmatrix} 0 & \dots & \Omega_{ii} & \dots & 0 \end{bmatrix} \quad (6.11)$$

and the cofactors of Ω result

$$c_{ij} = \begin{cases} 0 & \text{for } i \neq j \\ \frac{|\Omega|}{\Omega_{ii}} & \text{for } i = j \end{cases} \quad (6.12)$$

Thus,

$$\begin{aligned} \bar{b}_{ij}(f) &= \frac{1}{|\Omega|} \begin{bmatrix} 0 & \dots & \Omega_{ii} & \dots & 0 \end{bmatrix} \sum_{k=1}^K \bar{\mathbf{a}}_{\mathbf{k}} c_{jk} \\ &= \frac{1}{|\Omega|} \Omega_{ii} \sum_{k=1}^K \bar{a}_{ik} c_{jk} \\ &= \frac{1}{|\Omega|} \Omega_{ii} \bar{a}_{ij} c_{jj} \\ &= \frac{\Omega_{ii}}{\Omega_{jj}} \bar{a}_{ij} \end{aligned}$$

■

In other words, in this case volume conduction manifests itself just as a relative gain with no structural impact on the original $\bar{\mathbf{A}}(f)$. This desirable scenario mirrors cases when every electrode records activity from just one single source, as shown in Figure 10.

Figure 10 – Diagram of a diagonal leadfield matrix leading propagation from source to sensor space for three independent sources.

Source: authorship

The latter is illustrated through our example with no connectivity at source space using a diagonal leadfield matrix, where the non-zero values has a normal distribution, $N(0, 1)$. So, for every repetition, there is a different leadfield matrix. Both results, gPDC value and percentage of detected connectivity provide correct information about the connectivity at the source space, see Figure 11.

Figure 11 – Conectivity at the sensor space with no causality between sources and diagonal leadfield matrix. Left: gPDC value; Right: Percentage of detected connectivity.

Source: authorship

6.1.3 Almost diagonal leadfield matrix

Let us study the case where all the influences from non-associated sources have the maximum value ε , which is much lower than the influence coming from the associated source for every electrode, $\varepsilon \ll \Omega_{ii}$. So, we can state the following

Lemma 3. Given $\varepsilon \ll \Omega_{kk}$ and a leadfield matrix Ω of the form:

$$\Omega = \begin{bmatrix} \Omega_{11} & & \varepsilon \\ & \ddots & \\ \varepsilon & & \Omega_{KK} \end{bmatrix} \quad (6.13)$$

The elements of $\bar{\mathbf{B}}(f) = \mathbf{\Omega} \bar{\mathbf{A}}(f) \mathbf{\Omega}^{-1}$ can be approximated by

$$\bar{b}_{ij}(f) \approx \frac{\Omega_{ii}}{\Omega_{jj}} \bar{a}_{ij}(f) + \varepsilon \left[\frac{\Omega_{ii}}{\Omega_{jj}} \sum_{\substack{k=1 \\ k \neq j \\ k \neq i}}^K \frac{\bar{a}_{ik}(f)}{\Omega_{kk}} + \frac{1}{\Omega_{jj}} \left(\bar{a}_{ii}(f) + \sum_{\substack{m=1 \\ m \neq i}}^K \bar{a}_{mj}(f) \right) \right] + \mathcal{O}(\varepsilon^2) \quad (6.14)$$

■

The detailed proof of the previous lemma is available in appendix D.

Observe that the coefficient $\bar{b}_{ij}(f)$ is mostly influenced by its analogous at the source space ($\bar{a}_{ij}(f)$), while the influence coming from the rest of terms is reduced by ε . Thus, although the impact of volume conduction was greatly reduced, the terms multiplied by ε could affect $\bar{b}_{ij}(f)$.

The nature of the links represented by the coefficients at the source space in (6.14) can be classified as:

1. $\bar{a}_{ij}(f)$: Link emanating from $s_j[n]$ and arriving to $s_i[n]$.
2. $\sum_{\substack{k=1 \\ k \neq j \\ k \neq i}}^K \bar{a}_{ik}$: Links arriving $s_i[n]$.
3. $\sum_{\substack{m=1 \\ m \neq i}}^K \bar{a}_{mj}$: Links emanating from $s_j[n]$.
4. $\bar{a}_{ii}$ and $\bar{a}_{jj}$: Influence of $s_i[n]$ on itself and $s_j[n]$ on itself.

It is important to note that the coefficients at the source space that could produce spurious connectivity are related with the two specific sources involved in the actual link of interest.

The results of our numerical example are shown in Figure 12 for an almost diagonal leadfield matrix, where ε ranges from 0 to 0.99 and all the diagonal elements are equal to one.

gPDC can identify the actual link independently of the ε value. Conversely, the percentage of detection increases as the ε value increases. For low values of ε , the error in connectivity inference is low for all the links.

Figure 12 – Conectivity at the sensor space with no causality between sources and almost diagonal leadfield matrix with $\varepsilon = [0, 0.99]$. Left: mean value of the estimated $|gPDC|$ (gray scale $[0, 1]$); Right: Percentage of detected connectivity (gray scale $[0, 100\%]$).

Source: authorship

6.1.4 Activity from a non-associated source

Now, consider a diagonal Ω except for the Ω_{cd} element, which accounts for what sensor $x_c[n]$ picks up from the source $s_d[n]$ in addition to the effect of its own associated source, $s_c[n]$, i.e. formally:

$$\Omega = \begin{bmatrix} \Omega_{11} & & 0 \\ & \ddots & \\ 0 & \Omega_{cd} & \ddots \\ & & & \Omega_{KK} \end{bmatrix} \quad (6.15)$$

Its cofactor matrix is given by

$$\mathbf{C} = \begin{bmatrix} c_{11} & & 0 \\ & \ddots & \\ 0 & c_{dc} & \ddots \\ & & & c_{KK} \end{bmatrix} \quad (6.16)$$

where

$$c_{dc} = \prod_{\substack{k \neq c \\ k \neq d}}^n \Omega_{kk} \neq 0 \quad c_{kk} = \prod_{i \neq k} \Omega_{ii} \neq 0$$

Therefore, from (6.8), the only link affected by the non diagonal element is the one with the same indices ($\bar{b}_{cd}(f) \neq 0$).

$$\bar{b}_{ij}(f) = \frac{1}{|\Omega|} \begin{cases} \Omega_{ii} \bar{a}_{ij} c_{jj} & \text{if } i \neq c \text{ and } j \neq d \\ \Omega_{cc} (\bar{a}_{cd} c_{dd} + \bar{a}_{cc} c_{dc}) + \Omega_{cd} (\bar{a}_{dd} c_{dd} + \bar{a}_{dc} c_{dc}) & \text{if } i = c \text{ and } j = d \end{cases} \quad (6.17)$$

Thus non-zero coefficients can be produced even when there is no connectivity from $s_d \rightarrow s_c$ ($\bar{a}_{cd}(f) = 0$). The fact that $\Omega_{cd} \neq 0$ alters the value of $\bar{b}_{cd}(f)$ and leads to spurious link detection from $x_d[n]$ to $x_c[n]$ while all other links remain unaltered in (6.17).

Figure 13 – Propagation diagram from source to sensor space leaded by a leadfield matrix diagonal except for Ω_{31} . Dashed line is the theoretical spurious connectivity expected at the sensor space.

Source: authorship

Thus, under the asymmetric structure represented by (6.15), apparent artificial unidirectional connectivity at the sensor space could be observed if one electrode records activity from its own associated source and from another (non-associated) source, as Figure 13 shows. In that case, the additional source produces an apparent influence that manifests itself as connectivity and thus implies incorrect inference of directional influence.

In our numerical example for this case, the leadfield matrix is set as the identity except for the entry Ω_{13} , which varies from zero to one.

Figure 14 – Connectivity at the sensor space with no causality between sources and diagonal leadfield matrix except for $\Omega_{13} = [0, 1]$. Left: mean value of the estimated $|gPDC|$ (gray scale $[0, 1]$); Right: Percentage of detected connectivity (gray scale $[0, 100\%]$).

Source: authorship

The percentage of connectivity detected (14) was affected by the non-zero value, creating a false connection in its place. This happens even though gPDC average values remain correct.

6.1.5 Bipolar Recording

Thus far we have assumed that the potentials represented by $x_i(n)$ are measured with reference to a point at infinity, something that does not happen in practice. To circumvent this limitation one often resorts to bipolar recording of some kind, i.e. by dealing with the difference between the $x_i(n)$ potential and some other quantity. Among the possibilities one may

1. Employ a common reference electrode, usually represented by the mastoid or auricular electrodes, for which the absence of an immediately related cortical source is a plausible assumption (Sec. 6.1.5.1).
2. Employ the average potential among electrodes as a reference (Sec. 6.1.5.2).
3. Employ a local differential electrode setting (Sec. 6.1.5.3)

Each one of these scenarios poses a slightly different set of consequences for sensor level based connectivity inference as we examine next.

6.1.5.1 Common reference electrode

For definiteness, let the reference electrode measurements with respect to infinity be denoted $x_r(n)$ whose potential is given by a suitable combination of sources:

$$x_r[n] = \Omega_{r1}s_1[n] + \cdots + \Omega_{rK}s_K[n] \quad (6.18)$$

Then the actual i -th measurement referenced to $x_r[n]$ becomes

$$x_i^r[n] = x_i[n] - x_r[n] = (\Omega_{i1} - \Omega_{r1})s_1[n] + \cdots + (\Omega_{iK} - \Omega_{rK})s_K[n] \quad (6.19)$$

which is equivalent to a leadfield matrix with rows $\underline{\Gamma}_i = \underline{\Omega}_i - \underline{\Omega}_r$.

To facilitate correct connectivity detection, a diagonal $\mathbf{\Gamma}$ would be desirable. That requires that the influence coming from a source must be the same for both, its non-associated recording electrodes and for the reference electrode. Then, the ideal common reference signal is

$$x_r[n] = \varepsilon \sum_{k=1}^K s_k[n] \quad (6.20)$$

where $\varepsilon \ll \Omega_{kk}$ for $k = 1, 2, \dots, K$.

Interestingly when sensors are sufficiently apart (see section 7.3.2), this can actually happen since source influence at the scalp is essentially constant (NUNEZ; SRINIVASAN, 2006) sufficiently far away from the source.

6.1.5.2 Average reference

Another commonly suggested EEG measurement setup (DIEN, 1998) is represented by using the average between electrodes as a reference under the excuse that this might offer protection against ground noise. Mathematically this is the equivalent of defining

$$x_r[n] = \frac{1}{K} \sum_{e=1}^K x_e[n] \quad (6.21)$$

In matrix form, the referenced channels are given by

$$\begin{bmatrix} x_1^r \\ \vdots \\ x_K^r \end{bmatrix} = \mathcal{A} \begin{bmatrix} x_1 \\ \vdots \\ x_K \end{bmatrix} \quad (6.22)$$

where the averaging matrix

$$\mathcal{A} = \begin{bmatrix} 1 - 1/K & -1/K & \cdots & -1/K \\ -1/K & 1 - 1/K & \ddots & -1/K \\ \vdots & \vdots & \ddots & \vdots \\ -1/K & -1/K & \cdots & 1 - 1/K \end{bmatrix} \quad (6.23)$$

can be easily shown singular. Moreover, if $\mathbf{\Omega}$ is diagonal, the resulting effective leadfield matrix would not be. This therefore would effectively not only imply the loss of one channel due to an implicit linear combination but would also scramble eventual source data.

6.1.5.3 Local reference

To analyse the case, recall first the $x_i[n]$ referenced to infinity:

$$x_i[n] = \Omega_{ii}s_i[n] + \sum_{\substack{d=1 \\ d \neq i}}^K \Omega_{id}s_d[n] \quad (6.24)$$

where the only term that is desirable is the first one, containing the activity from the source associated to the i -th electrode. The undesired terms correspond to recorded activity from non-associated sources, recalling section 6.1.4.

In this case, the ideal local reference helps on the elimination of the influence coming from non-associated sources, as on the amplification of the local activity which comes from the associated source. Thus, the ideal local reference $x_r[n]$ subtracted from $x_i[n]$ is

$$x_r[n] = -G \Omega_{ii}s_i[n] + \sum_{\substack{k=1 \\ k \neq i}}^K \Omega_{ik}s_k[n] \quad (6.25)$$

which records the same signal as $x_i[n]$ from all its non-associated sources. Besides, it records the associated source, whose influence has opposite sign of the recording electrode has.

Our proposal is to take advantage of apriori information to select the appropriate local reference. Since any non-associated source cause an artificial link coming from that source, we try to eliminate the influence of every source causing the detection of links arriving to the recording electrode of interest. The idea is to perform a first connectivity inference with a common reference. Then, given a recording electrode i -th and the links arriving to it, we pick all the channels that feed such links. Those channels can be over non-associated sources to $x_i[n]$, and as result, producing spurious links.

That information allows us to find the optimal local reference that records a mixture of the main channels influencing the connectivity inference. It depends on the head geometry and the spatial configuration of source-sensor spaces. The possibility of finding local references is given in 7.3.4.

6.2 Case: $N_e < N_s$

In this situation $\mathbf{\Omega}$ is rectangular and column rank defective since there are too few electrodes to represent the existing sources independently. However, this system can be assume as a one with same number of sources and electrodes, where the associated source of each channel is a combination of the most influential sources on that channel, ignoring the detailed causality of every single source. That is only possible when the more influential sources to each channel are unique for every channel on the system.

6.3 Case: $N_e > N_s$

When we have more electrodes than cortical dipoles, the resulting leadfield matrix is rectangular, so it is an ill-posed problem. Consequently, the expressions for the VAR process at the scalp are different from those presented in section 6.1.

As we already demonstrate, the full connectivity information is contained in the sensors when there is the same number of them than the number of sources. However, in most cases there are more sensors than sources, which are at unknown locations. Therefore, we recommend to use a method to reduce the dimensionality to find the sensors most closely associated to every single source.

A widely used statistical method with no need of inverse solutions is the linear method known as *principal component analysis* (PCA). Its main purpose is dimensionality reduction by discriminating the original sensor signals based on the covariance between the potential variations at the electrode sites. The resulting components are orthogonal oriented in directions of largest variance in the data (DEMŠAR et al., 2013).

PCA has been proved effective to extract spatial patterns underlying the scalp EEG (KOLES; LAZAR; ZHOU, 1990; GÓMEZ-HERRERO et al., 2008; REYNOLDS;

RICHARDS, 2009). However, the temporal information is change in the component weights since each component is a linear combination of the original EEG signals (RICHARDS, 2004). The latter occurs because the identification on components is done to assuming that they are orthogonal, which is not necessarily true. Similarly, the *independent component analysis* (ICA) computes components assuming them as non-gaussian and independent, which are in direct opposition to the PDC assumptions. Furthermore, those demixing methods ignore information about the conductive properties of the tissues and the spatial distributions of sources and sensors. Consequently, its source signal reconstruction is not convenient for connectivity identification.

Thus, we recommend PCA or ICA to compute the topographical map from the scalp EEG. Then, take the main channel that composes each of the main components as the EEG channels associated to every source. So the ill-posed problem is reduced to a well-posed problem, and it can be handle as in section 6.1. Note that we just recommend PCA or ICA to select the appropriate EEG channels, with no recommendation regarding computed components.

6.4 Discussion

In this chapter we analysed the VC effect as a general linear combination of sources. For convenience we focused on the case when the numbers of electrodes and sources is the same.

One of the biggest findings of this chapter is that $\bar{\mathbf{B}}(f)$ is related to $\bar{\mathbf{A}}(f)$ exactly in the same way as $\mathbf{B}[h]$ is related to $\mathbf{A}[h]$. Thus, the results of this chapter hold for PDC as well as for VAR process and therefore for any Granger-causality based estimator.

A very useful analytical result is the explicit expression for the PDC coefficient under the source mixing effect. This allows finding the specific impact of source mixing on PDC estimation and the best possible scenarios to avoid the implications. That expression shows that a non-null PDC value at the source space is generally estimated at the sensor space also as non-null. Thus, the detection of existing links is almost guaranteed.

The fundamental issue in connectivity detection at the sensor level is the structure of both matrices, $\bar{\mathbf{A}}(f)$ and $\mathbf{\Omega}$. Which completely avoid the source mixing effect, so $\bar{\mathbf{A}}(f) = \bar{\mathbf{B}}(f)$ if they commute. Consequently PDC estimation and connectivity inference are exactly the same as in the source space. However, is essentially very improbable calling for the study of alternative scenarios.

Another ideal case occurs when the leadfield matrix is diagonal, since the only impact of source mixing is an attenuation of every source signal. In that case, the temporal and frequency dependencies remain as at the source level. This is desirable because it

leads to no change in the connectivity structure.

By studying a more general structure of the leadfield matrix, we examine the almost diagonal structure, where each electrode mostly records information from a single source, while the contribution from other sources remains at a very low value. This scenario provides a PDC estimation close to that of a diagonal leadfield matrix, but with a little error. Besides being similar to the ideal case, it is a more realistic scenario than the one with diagonal leadfield matrices, for the reason that even ignoring the model of the head, there are infinite mathematically possible leadfield matrix with almost diagonal structure.

Therefore we focus on the transformation of non-diagonal leadfield matrices into diagonal without strong assumptions beyond those already mentioned. Hence, we regard the effect of real references rather than one located at infinity as an approach to achieving the mentioned transformation of the leadfield matrix, and therefore an improvement on the information of each new referenced signal. Specifically, we analyse three kinds of references, a common sensor, the instantaneous average of all sensor signals and a particular reference for every sensor or local reference.

The common reference scenario implies a huge improvement, since its use allows to transform the almost diagonal leadfield ideal referenced matrix into a diagonal one. The latter is possible if all the little influences coming from non-associated sources arrive in the same proportion at every sensor, including the reference sensor. The possibility of that scenario depends of course, on the volume conduction model of the head and it is beyond the scope of this chapter.

Conversely, the instantaneous average of the sensor signals as reference seems to obstruct the transformation of the leadfield matrix into diagonal. Particularly in the case where the number of sensors and sources is the same, because such reference reduces the dimensionality of the sensor space. Moreover, because of the nature of the average, it needs to contain complete information of the sensor space. Therefore, some further considerations are necessary to use this reference in the scenario with more sensors than sources.

Finally, the local reference takes advantage of its specificity, allowing the correction of a very common scenario in EEG, the incidence of a bigger than expected contribution from non-associated sources. That undesirable situation seems to be overcome by subtracting the appropriate reference for every sensor. The selection of the optimal references depends on a priori information offered by a preliminary step of connectivity inference using a common reference. Hence, the connectivity overdetected is overcome based on the knowledge of the detected links and under the light of the theoretical result which claims that a $\Omega_{cd} \neq 0$ lead to $\bar{b}_{cd}(f) \neq 0$, producing spurious detected links at the sensor space.

In summary, we have described the main impact of volume conduction on PDC estimation from an analytical point of view. Furthermore, we also demonstrated that

under the correct situations it is possible to overcome source mixing without the use of an inverse volume conduction head model.

Besides exposing the theoretical results, we provided an illustrative example of every analysed scenario to corroborate the findings. Interestingly, in all cases PDC mean values seem more insensitive to the source mixing than the statistical test. Thus, this could indicate that other tests could be developed to exploit the PDC value stability, as claimed in ([HAUFE et al., 2013](#)).

7 VC as analytical head model

As discussed so far, the linear combination of cortical sources can affect connectivity inference at the scalp. The leadfield matrix determines the specific source mixing. In turn, that matrix depends on the electrical properties and spatial distributions of sources and sensors contained in a head model. Thus, this chapter considers VC described by an analytical head model. The organization of the chapter is as follows:

- Section 7.1 is a brief review of an analytical volume conduction model of the head, providing an expression for the scalp potential caused by dipole sources.
- In section 7.2 we use a spherical head model to determine the specific way in which such combination operates, representing it through the leadfield matrix.
- In section 7.3 there is an analysis of the impact of VC on PDC performance. Then we propose some spatial configurations of sensors to reduce volume conduction impact on the connectivity detection considering in view of the head model.

7.1 Volume conduction model of the head

The model shown here was developed by (NUNEZ; SRINIVASAN, 2006), and was chosen because it includes the *cerebro spinal fluid* (CSF) layer and because it was very useful in previous works, such as (SRINIVASAN et al., 1996) where it was used to show the spatial filtering effect of volume conduction. Later, (SRINIVASAN; NUNEZ; SILBERSTEIN, 1998) used it to demonstrate the artificial coherence due to VC at close distances between EEG electrodes.

Here we consider a head model composed of four concentric spherical shells assumed to be homogeneous and isotropic. These four shells represent brain, CSF, skull and scalp, as shown in Figure 15. Each tissue is characterized by its electrical conductivity and radius, whose selection is presented in appendix A; the chosen values are shown in table 1. The detailed revision of the model is presented in the appendix B.

Figure 15 – Schematic of the 4-sphere head model.

Source: authorship.

Table 1 – Radius and conductivity values of each tissue in the head model.

i	Tissue	Radius (cm)	Conductivity (S/m)
1	Brain	7.68	0.295
2	CSF	7.86	1.59
3	Skull	8.49	0.0287
4	Scalp	9.12	0.43
5	Air	> 9.12	0

Source: authorship.

7.1.1 Scalp Potential

The scalp potential at $\mathbf{r} = (r_4, \theta, \phi)$, which satisfies the appropriate boundary conditions, generated by a dipole located at $\mathbf{r}_0 = (r_0, \theta_0, \phi_0)$ is given by

$$G_{\text{scalp}}(\theta, \phi, \theta_0, \phi_0) = \frac{1}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} \frac{4\pi}{2l+1} H_l \sum_{m=-l}^l Y_{lm}(\theta, \phi) \cdot Y'_{lm}(\theta_0, \phi_0) \quad (\text{B.46 revisited})$$

$$= \frac{1}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} H_l P_l(\cos \chi) \quad (\text{B.47 revisited})$$

where $Y_{lm}(\theta, \phi)$ is the spherical harmonic function of degree l and order m and $Y'_{lm}(\theta, \phi)$ is its complex conjugate. H_l is the coefficient related to the degree l , it has all the information about the propagation through the specific tissues with the established dimensions and conductivities. $P_l(\cos(\chi))$ is the Legendre polynomial of l degree. The angle χ is formed by the separation between sensor and dipole as Figure 16 shows it. Equation (B.46) also

Figure 16 – Scheme with locations of source: $\mathbf{r}_0 = (r_0, \theta_0, \phi_0)$; sensor: $\mathbf{r} = (r, \theta, \phi)$ and the χ angle between them.

Source: authorship

corresponds to the Green's function for the Poisson's equation of the scalp surface potential (ARFKEN, 2013; SRINIVASAN et al., 1996).

Generalizing for any brain source distribution, the scalp potential may be expressed as an integral over all brain volume tissue:

$$\Phi(\mathbf{r}, t) = \iiint_{\text{Brain}} \mathbf{G}(\mathbf{r}, \mathbf{r}_0) \cdot \mathbf{P}(\mathbf{r}_0, t) dV(\mathbf{r}_0) \quad (7.1)$$

where $\mathbf{P}(\mathbf{r}_0, t)$ is the source field in time domain. All the geometric and conductive properties of the head volume conductor are included in $\mathbf{G}(\mathbf{r}, \mathbf{r}_0)$.

The choice of point sources allows us to discretize the source space in voxels. Thus, the source field (WOLPAW; WOLPAW, 2012) can be expressed as

$$\mathbf{P}(\mathbf{r}, t) = P_0 s(t) \delta(\mathbf{r} - \mathbf{r}_0) \hat{\mathbf{a}}_0 \quad (7.2)$$

where the amplitude of the dipole moment per unit volume is $P_0 = 1.5 \mu A / mm^2$, according with the dimensions and currents of the sources selected in appendix C. The time dependency is reflected in $s(t)$. The position of a dipole within the entire cortex is $\mathbf{r}_0 = (r_0, \theta_0, \phi_0)$ and $\hat{\mathbf{a}}_0$ is the unit vector normal to the local cortical surface. So, (7.1) may then expressed as the weighted sum over active point sources. Applying the specific source field $\mathbf{P}(\mathbf{r}, t)$ of M active sources at the cortex, the scalp potential results in

$$\Phi(\mathbf{r}, t) = P_0 \sum_{m=1}^M s_m(t) G_{\text{scalp}}(\mathbf{r}, \mathbf{r}_m) \quad (7.3)$$

Given that the k -electrode is at $\mathbf{r}_k = (r_k, \theta_k, \phi_k)$, the potential recorded by it is a weighted sum of the influence of every cortical source. In this particular case with spherical symmetry, the influence of the m th cortical dipole on the k th electrode depends on the angular distance between them, χ_{km} . Thus, the potential recorded by the k th electrode is

$$\Phi(\mathbf{r}_k, \mathbf{r}_m, t) = P_0 s_m(t) G_{\text{scalp}}(\mathbf{r}_k, \mathbf{r}_m) \quad (7.4)$$

$$= \frac{P_0}{4\pi\sigma_1 r_0^2} s_m(t) \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{km}) \quad (7.5)$$

7.1.2 Parameters dependency

Locating the dipole at different depths (r_0) results in the scalp potential shown in Figure 17a. Since the magnitude of the potential decays rapidly with the dipole depth, just the most superficial cortical dipoles are considered from here on. Of course, deeper sources produce lower scalp potentials, so we choose to use superficial dipole sources ($r_0 = 7.58 \text{ cm}$) that generate the greatest EEG magnitudes. The maximum value reached at the scalp is $0.9 \mu V$, of course, multiple synchronous dipoles produce much larger potentials due to superposition (NUNEZ; SRINIVASAN, 2006).

Figure 17 – Scalp potential at a location separated by χ_{ed} degrees from the dipole source. (a) Scalp potential produced by a radial dipole at 5 different depths r_0 . (b) Scalp potential for 4 representative scalp to skull conductivity ratios according to age.

Source: authorship.

The poorly conducting skull combined with the highly conducting CSF and moderately conducting scalp are known to affect EEG measurements. Furthermore, it is known that skull conductivity decreases with age, changing the impact of VC. Specifically, scalp to skull conductivity ratio of 5 represents children, the ratio of 8 represents adolescents, the ratio of 15 represents most adults, and lastly the ratio of 30 represents cadavers (WENDEL et al., 2010). In Figure 17b the scalp potential is presented for the mentioned cases, indicating that EEG measurements produce better recordings in terms of volume conduction effects on younger subjects. Children scalp potential decreases rapidly, providing more accurate measurements, and therefore improving EEG spatial resolution.

7.2 Leadfield matrix

Recalling the expressions developed in appendix B, if at the cortex there are N_d dipoles, the scalp potential recorded by the e -th electrode can be written as

$$\Phi(\gamma_e, t) = P_0 \sum_{d=1}^{N_d} s_d(t) G_{\text{scalp}}(\gamma_e, \gamma_d) \quad (7.3 \text{ revisited})$$

$$= P_0 \begin{bmatrix} G_{\text{scalp}}(\gamma_e, \gamma_1) & \cdots & G_{\text{scalp}}(\gamma_e, \gamma_{N_d}) \end{bmatrix} \mathbf{s}(t) \quad (7.6)$$

where $\mathbf{s}(t)$ is a vector of size $N_d \times 1$. For convenience, we use the compact notation $\gamma = (\theta, \phi)$ for the angular location of electrodes (γ_e) and sources (γ_d).

Generalizing for N_e electrodes we can write in vectorial form:

$$\frac{\Phi(t)}{P_0} = \begin{pmatrix} G_{\text{scalp}}(\gamma_1, \gamma_1) & G_{\text{scalp}}(\gamma_1, \gamma_2) & \cdots & G_{\text{scalp}}(\gamma_1, \gamma_{N_d}) \\ G_{\text{scalp}}(\gamma_2, \gamma_1) & G_{\text{scalp}}(\gamma_2, \gamma_2) & \cdots & \vdots \\ \vdots & \cdots & \ddots & \vdots \\ G_{\text{scalp}}(\gamma_{N_e}, \gamma_1) & \cdots & \cdots & G_{\text{scalp}}(\gamma_{N_e}, \gamma_{N_d}) \end{pmatrix} \mathbf{s}(t) \quad (7.7)$$

where

$$\Phi(t) = \begin{bmatrix} \Phi(\mathbf{r}_1, t) \\ \vdots \\ \Phi(\mathbf{r}_{N_e}, t) \end{bmatrix} \quad (7.8)$$

is the column vector composed by the scalp potential recorded by N_e electrodes. The matrix in (7.7) corresponds to the leadfield matrix $\mathbf{\Omega}$. It leads the linear combination at the scalp according with the volume conductor model of the head and allows us to analyse PDC performance under VC effects via explicit analytical expressions.

The dependency with the spatial distributions at source and sensor spaces is evident by expanding the Green's function:

$$\frac{\Phi(t)}{\Phi_0} = \begin{pmatrix} \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{11}) & \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{12}) & \cdots & \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{1N_d}) \\ \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{21}) & \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{22}) & \vdots & \vdots \\ \vdots & \cdots & \ddots & \vdots \\ \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{N_e 1}) & \cdots & \cdots & \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{N_e N_d}) \end{pmatrix} \mathbf{s}(t) \quad (7.9)$$

As mentioned above, the diagonal entries correspond to the largest influence of a source to an electrode, so they are called to be associated. The non-diagonal entries Ω_{ed} represent the contribution of the source $s_d(t)$ to the potential recorded by the e -th electrode.

Besides of the clasification according to the intensity of the sources influence, the leadfield matrix entries depend on two different angular distances. The diagonal entries depend on the distances between each electrode and its associated dipole (χ_{ee}), while the

non-diagonal entries depends on the separation between the electrode and each of their non-associated dipoles (χ_{ed}) as it is shown in Figure 18. The latter distance can be related to the electrode distance, since by definition every electrode is very close to its associated source.

Figure 18 – Angular distances considered in the leadfield matrix. χ_{ee} is the distance between an electrode and its associated dipole source. χ_{ed} is the distance between an electrode and a non-associated dipole, it can be interpreted as electrode distance.

Source: authorship.

Figure 19 shows the normalized Green's function as the influence of a dipole over an electrode depending on the angular distance between them. The maximum influence is achieved when the source is just under the electrode. As they moving away one another, source influence decays until 5% of the maximum, which occurs at 41.61 degrees of distance. For larger distances, the influence stays low, under 5% of the maximum value.

Figure 19 – Normalized Green's function with a 5% of error around zero.

Source: authorship.

We consider EEG discrete time signals recorded at a sample frequency $f_s = 1/T$. Accordingly, the cortical signals are assumed discrete also, represented as $\mathbf{s}(nT) = \mathbf{s}[n]$, where the brackets indicate that it is a discrete-time variable and $n = 0, 1, 2, \dots, N$. In concordance with the notation for the time-series at the scalp, the discrete-time scalp potential is hereinafter referred to as $\mathbf{x}[n]$. Thus, equation (7.9) becomes

$$\mathbf{x}[n] = \mathbf{\Omega} \mathbf{s}[n] \quad (7.10)$$

7.3 VC impact on PDC depending on the recording type

Now we use the leadfield matrix to analytically solve the forward problem and obtain the scalp potential at the electrode sites. On this basis, we analyse the PDC estimation subject to VC as the head model. The VC impact is studied for four reference types: the reference at infinity, the average signal as reference, a common reference placed on the head surface and a local reference for each recording electrode.

7.3.1 Reference at infinity

Source and sensor spaces with same number of elements is the scenario most deeply studied in this work. Under this situation, it is possible overcome the volume conduction if the leadfield matrix is diagonal. Thus, we focus on the condition for the non-diagonal entries:

$$\sum_{l=1}^{\infty} H_l P_l(\cos \chi_{ed}) = 0, \quad \forall e \neq d \quad (7.11)$$

The normalized value of the contribution of a source to a non-associated electrode is the same as in Figure 19. That potential is zero only at a particular distance, 55 degrees. Thus, a diagonal leadfield is a remote possibility. Instead, we can think of the best possible scenario, which consists of an almost diagonal leadfield matrix, where the ε value is up to 5% of the maximum possible influence, making the approximation $\varepsilon^2 \approx 0$ reasonable (already made in Section 6.1.3). Therefore, a separation distance of at least 42 degrees must be maintained between every electrode and all its non-associated sources.

Assuming that source locations are known, we can place each electrode at its optimum position, exactly over its corresponding sources (see Figure 19). The leadfield matrix becomes

$$\Omega = \begin{pmatrix} \sum_{l=1}^{\infty} H_l & \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{12}) & \cdots & \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{1K}) \\ \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{21}) & \sum_{l=1}^{\infty} H_l & \vdots & \vdots \\ \vdots & \cdots & \ddots & \vdots \\ \sum_{l=1}^{\infty} H_l P_l(\cos \chi_{K1}) & \cdots & \cdots & \sum_{l=1}^{\infty} H_l \end{pmatrix} \quad (7.12)$$

which is symmetric because the angular positions of electrodes and their associated dipoles are the same. In order to obtain an almost diagonal matrix, the electrodes must stay over every sources and keep a minimum distance of 42 degrees as mentioned in 7.2.

In Figure 20a there is a proposed spatial distribution of electrodes, where the leadfield matrix has the desired almost diagonal structure. For the most basic scenario of two electrodes: one is located at the top or vertex of the head, and the second one located anywhere inside the shaded area, where the angle between them are bigger than 45 degrees.

Figure 20 – Left: Proposed spatial distribution for electrodes above sources. Superior view. Right: Imaginary reference planes.

Source: authorship (left). (GEVINS; LE, 1998) (right).

Thus, the electrode distance is big enough to get the minimum influence possible from the non-associated dipole.

More generally, an ideal spatial distribution of sensors and sources is also shown in Figure 20a where all the electrodes have a minimum distance of 41 degrees between them. Note that the distance between adjacent electrodes is almost over the threshold, thus numerical experiments are crucial to determine the validity of that electrode spatial distribution, and the minimum electrode distance.

The proposed spatial distribution in Figure 20a of sensors is very close to the widely used 10-20 international EEG standard (JASPER, 1958), shown in Figure 21. Observe that according with the standard, it is reasonable to assume a distance of 180 degrees between the electrodes *Fpz* and *Oz*, and between *T3* and *T4* (See Figure 20b) (GEVINS; LE, 1998; PARK et al., 2010; TOWLE et al., 1993). Therefore it is possible to recognize analogous positions between our proposal and the EEG standard. Also it is important to highlight that the 10-20 EEG standard provides scalp locations which correlate well with the expected cortical areas without calling for neuroimaging procedures (HOMAN; HERMAN; PURDY, 1987; HERWIG; SATRAPI; SCHÖNFELDT-LECUONA, 2003; JURCAK; TSUZUKI; DAN, 2007).

If the exact location of the sources are not longer known, the diagonal entries of the leadfield matrix ceases to be constant, since they depend on the angle between each electrode and its associated source, χ_{ee} (see Figure 18). To obtain an almost diagonal leadfield matrix that minimizes the volume conduction, we need to satisfy the condition (7.11), so that each electrode must be at least 42 degrees apart from any non associated source. Because of the uncertainty of the location of the sources, the electrodes must be enough apart to guarantee that leadfield matrix is almost diagonal.

Figure 21 – 10-20 EEG standard. AC-PC line passes through the center of the fitted sphere.

Source: adapted from (FOLDVARY-SCHAEFER; GRIGG-DAMBERGER, 2012).

On the basis of the above, we propose the spatial electrode distribution of Figure 22, keeping more free space between sensors. In our proposal, there is a distance-radius of 41 degrees around every electrode, keeping that space for associated sources. All the sources under a shaded circle mostly influences the electrode at the center of that circle, so they are considered as associated sources. Thus, each of the cortical sources is associated only with one electrode. The uncertainty about the location of the sources greatly reduces

Figure 22 – Proposal of spatial distribution for electrodes when there is source location uncertainty. Top view.

Source: Own authorship.

the maximum number of electrodes from 19 to 6.

A more detailed analysis reveals that the associated electrode must be closer than 20 degrees to its associated source in order to minimize the influence from non-associated sources. Figure 23 shows the non-diagonal to diagonal leadfield elements ratio, where one can see that an electrode has a spurious influence of at least 20% coming from a non-associated source if it is located further than 20 degrees (3.18 cm) from its associated source.

Figure 23 – Leadfield elements ratio. Ideal reference. The black line is at $\chi_{ed} = 45^\circ$, analogous case to 10-20 standard

Source: authorship.

In the light of the above discussion, one must be cautious about the location of the electrodes. Topographic maps and other resources can be useful in the approximate source location to place the electrodes efficiently. Furthermore, the associated area of a radius-distance of 3.18 cm is a convenient size to study neurocognitive networks.

7.3.2 Common reference electrode

According to the previous chapter, if the spatial distribution of the electrodes allows obtaining an almost diagonal leadfield matrix (as in (6.13)), then the ideal common reference we are looking for is given by

$$x_r[n] = \varepsilon_r \sum_{k=1}^K s_k[n] + \Omega_{rr} w_r[n] \quad (7.13)$$

where the attenuation coming from all the active sources is exactly the same at the reference electrode. Since all the leadfield matrix elements have the same behaviour as in Figure 19, we can see that its value is almost constant in the shaded area, specially when the distance between the electrode and the source is bigger than 100 degrees. That gives us an idea of the ideal location for the common reference, the farthest possible place, the bottom of the head. This implies that all the sources are farther away so that the distance between each of them and the reference is at least 90 degrees, i.e. $\varepsilon_r = -5\%$ for all the sources.

This is illustrated in Figure 24, where we subtract the bottom reference from the normalized scalp potential. The potential becomes stable and closer to zero for distances greater than 80 degrees, but it reaches 5% of the maximum at 47 degrees. Thus, the subtraction of a common reference can give us the requested diagonal leadfield matrix that completely avoid the source mixing produced by volume conduction.

Figure 24 – Effect of a common reference located at the bottom of the head with known source locations. Normalized scalp potential due to a dipole source referenced at infinity and at the bottom of the head.

Source: authorship.

Generalizing for the case where the exact location of the sources is unknown, we have to analyse the implications of non-zero distance between the electrode and its associated source to guarantee that its influence is much larger than that coming from the other sources.

Figure 25 shows the leadfield elements ratio Γ_{ed}/Γ_{ee} by using a reference at the bottom of the head. To overcome the possible interference from a non-associated source, the non-diagonal to diagonal leadfield elements ratio must be close to zero. It is evident that a common reference at the bottom of the head helps to improve the leadfield matrix structure towards a diagonal one. Particularly for spatial distributions where the electrodes are separated by more than 60 degrees and each of them is at closer distances than 10 degrees from its associated source. For larger shifts between electrodes and their associated sources (χ_{ee}), the necessary electrode separation (χ_{ed}) becomes larger. Generalizing, the influence from a non-associated source is diminished for distances larger than 90 degrees. Thus, a reference electrode that records part of the source information is helpful to overcome some effects of volume conduction on connectivity detection.

Figure 25 – Leadfield elements ratio using a common reference located at the bottom of the head. The black line is at $\chi_{ed} = 45^\circ$, analogous case to 10-20 standard.

Source: authorship.

This theoretical result agrees with several previous works. In (NUNEZ et al., 1997) the bottom of the head as reference was suggested to estimate correlation and coherency. They claimed that the analogous real electrode is linked digitally mastoids or earlobes reference. This serves to cancel some of the volume conduction effect at large distances, since they are not genuinely electrically inactive (HAGEMANN; NAUMANN; THAYER, 2001).

7.3.3 Average reference

Using the instantaneous average as reference implies a dimensional reduction, as explained in Sec. 6.1.5.2. Thus, its use can transform a well-posed problem into an ill-posed one. Additional regularization methods could be required.

Furthermore, according to (JUNGHÖFER et al., 1999), average reference use requires sufficient electrode density and an even distribution of the electrodes at the sensor space, since the idea of the average reference is to remove the background common to all the scalp. Otherwise, if the electrodes are concentrated in one region of the scalp, then the average is biased toward that region. Moreover, the specific implications of applying average reference on connectivity inference via PDC are unknown.

7.3.4 Local reference

As in Sec. 6.1.5.3, this scenario includes a local reference for each recording electrode. Every single local reference may subtract the specific non-associated sources that mostly influence the recording electrode from that electrode.

The separation between a recording electrode and its corresponding reference is a new parameter to consider in this case. Thus, assuming that each electrode is over its associated source, our analyse is reduced to only two distances, between each electrode and its non-associated sources (associated to electrode distance) and between each electrode and its local reference. Figure 26 shows the conventions to measure those angular distances. For purposes of clarification, there are drawn two possible places for the local reference of

Figure 26 – Angular distances: Separation between two dashed lines is the angle between an electrode and a non-associated source (χ_{ed}) or electrode distance; Areas in orange and blue are the angles between the local reference and its recording electrode (χ_{er}) when the angle is positive and negative respectively.

Source: authorship.

the red recording electrode. The distance between the local reference and its recording electrode (χ_{er} angle) is positive when the reference is moving away from the non-associated source, otherwise it is negative.

The optimum distances must guarantee that the influence from the non-associated source is much lower than the one coming from the associated source. Figure 27 shows the ratio of the non-associated to associated elements of the leadfield matrix that results after the subtraction of the reference. That ratio must be very close to zero to obtain an almost diagonal or even diagonal leadfield matrix $\mathbf{\Gamma}$, resulting after the local reference subtraction.

As expected, the influence coming from a non-associated source becomes lower as it gets away from the recording electrode. If that distance is larger than 45 degrees, Γ_{ed}/Γ_{ee} ratio is at most 0.05. In those cases, the local reference can be positioned at any distance away from the non-associated source ($\chi_{er} > 0$). However, it is also possible to locate the reference moving closer to non-associated source ($\chi_{er} < 0$), keeping a minimum distance of 30 degrees from that source.

Now let us analyse the particular case of $\chi_{ed} = 45^\circ$, which corresponds to adjacent electrodes in the standard 10-20 of EEG (black line in the Figure). In that case, if the

Figure 27 – Local reference effect with known source locations. The black line is at $\chi_{ed} = 45^\circ$, analogous case to 10-20 standard.

Source: authorship

reference is moving away from the non-associated source and if it keeps a minimum distance of 10 degrees from the recording electrode, the Γ_{ed}/Γ_{ee} ratio is almost constant with a mean value of 0.044. Conversely, if the reference is closer to the non-associated source and if it keeps a maximum distance of 10 degrees to its recording electrode, the Γ_{ed}/Γ_{ee} ratio becomes less than 0.09. For a distance of 20 degrees between the reference and its recording electrode, the ratio increases up to 0.18.

In conclusion, the best position choice for the local references is away from the non-associated sources ($\chi_{er} > 0$) to diminish its influence. However, that is not always possible, since that locations may be outside the sensor space. Therefore, there are also optimum positions of local references at $\chi_{er} < 0$. Both cases allow a system with an almost diagonal leadfield matrix, where the non-associated sources that most affect the connectivity inference are reduced. In particular, for the case analogous to the EEG standard electrode positions, it is possible to greatly reduce the impact from non-associated sources locating the recording electrodes at a distance of 45 degrees (as in the 10-20 standard). Additionally, the local references can be placed at 11.25 degrees from its respective recording electrode. In this way, it is possible to use the EEG international standard 10-05, which tries to keep a constant distance between electrodes equal to a quarter of the same distance in the 10-20 EE standard (OOSTENVELD; PRAAMSTRA, 2001; JURCAK; TSUZUKI; DAN, 2007). Thus, in accord with our analysis the local reference can be located at 11.25 degrees from its recording electrode.

7.4 Discussion

In this chapter we considered volume conduction effects as specified by an analytical spherical head model. That model provides us the Green's function, allowing the computation of the leadfield matrix. In this fashion we characterized source mixing as depending on tissues conductivity, on thickness and radius of each of the concentric spheres, on source depth and on spatial distributions of sources and sensors. All the model parameters were chosen in conformity to widely used values, while the spatial distribution of sources and sensors are the main concern of the chapter.

Source and sensor spatial distributions were described by the angular distances between those elements. They were used to identify the best spatial configurations to reduce the source mixing effect considering different type of references, they are: reference at infinity, a common reference on the head, the instantaneous average as reference and a local reference for each recording electrode. The optimum position of the references were also examined.

Considering the reference at infinity, the scalp potential is maximum exactly over the cortical source and it decreases as the field point moves away from the source, until it reaches a stable value close to zero. Therefore, the influence from a distant source is not zero. Consequently, the best possible scenario is to obtain an almost diagonal leadfield matrix. With the electrodes exact over each of the sources, we proposed a spatial distribution where the distance between adjacent electrodes is 45 degrees to minimize VC. This is analogous to the widely used 10-20 EEG standard, which was designed to obtain evenly distributed electrodes in meaningful measurement sites. Furthermore, we analyse the implications of a non-zero angular distance between electrode and its associated source. In that case, we estimate that a maximum distance of 20 degrees (equivalent to 3.18 cm) minimizes the influence from non-associated sources. For distances less than 10 degrees, the behaviour is very similar to the one when each electrode is exactly over its source.

If the reference is located on the head, instead of at infinity we determined the bottom of the head as the ideal location of that common reference. At the bottom of the head, all sources influence in the same exact proportion, therefore that point contains a common background of the scalp potential, its subtraction helps to differentiate more the electrode signals. Thus, it suppose an improvement with respect to the "ideal" reference at infinity. In fact, the non-diagonal elements corresponding to distant source-electrode pairs become zero, so it is possible to obtain the desired diagonal leadfield matrix. That can occur if each electrode is at more than 90 degrees from all its non-associated sources. When the electrodes are not exactly above the associated electrodes ($\chi_{ee} \neq 0$), the leadfield matrix is more likely to be almost diagonal. The latter is possible if the minimum distance between electrodes is 45 for $\chi_{ee} < 10^\circ$ and it increases for larger distances between associated electrode-source.

By comparison, the reference at infinity provides an almost diagonal leadfield matrix, which can be diagonal over a very narrow range of distances, whereas using a common reference at the bottom can result in a diagonal leadfield matrix for a broad range of electrode distances. However, the reference at infinity behaves in the same way as described for electrodes shifted from its associated sources, the largest possible shift is 15 degrees. Conversely, using a reference at the bottom of the head, the same behaviour remains only for shifts lower than 10 degrees.

Another possible common reference is the instantaneous average signal. The use of this reference type implies risks of polar effect given by an odd spatial distribution of the electrodes (JUNGHÖFER et al., 1999). Moreover, we know that it implies a dimensionality reduction that may be helpful in a scenario with more electrodes than sources, which is a very common one.

Finally, we consider the possibility of correcting an almost diagonal leadfield matrix from the previous cases and transform it into a diagonal one using an adequate local reference for every recording electrode. Once, connectivity inference is performed using a common reference, it is possible to identify the non-associated sources that most influence on every single electrode. Thus, we use the local reference to reduce or even diminish such influences, trying to isolate the local influence of the associated source. We analyse the case with an electrode distribution given by 10-20 EEG standard, where the optimum local references can be placed at 11.25 degrees from the recording electrode. At least theoretically, this recording type provides the best PDC performance.

Part III

Numerical Experiments

8 Methodology

In this chapter we illustrate our theoretical developments by comparing the connectivity inference via PDC at both source and sensor spaces through numerical experiments. The following summarises the simulation methodology.

From a known ground truth at the source space we compare with the allied results at the sensor space. The main steps for each repetition of the experiment are presented in Figure 28.

Figure 28 – Block diagram of the methodology for the simulations.

Source: Own authorship.

8.1 Source space

First we characterize the imposed source space, in particular its temporal dependencies and connectivity inference.

8.1.1 VAR process generation

Let us start imposing the causality structure on the source space represented in the VAR coefficient matrix, $\mathbf{A}[h]$. So, the first step is to generate the time-series of the sources, $\mathbf{s}[n]$. The VAR process generation is done by passing the independent innovation noise with normal distribution $N(0, 1)$ through the VAR filter with the imposed dynamics.

In all the simulated scenarios we impose the following VAR(p) process ([BACCALÁ; SAMESHIMA, 2001](#)):

$$\begin{aligned}
 s_1[n] &= 0.95\sqrt{2}s_1[n-1] - 0.9025s_1[n-2] + w_1[n] \\
 s_2[n] &= 0.5s_1[n-2] + w_2[n] \\
 s_3[n] &= 0.5s_1[n-2] - 0.4s_1[n-3] + w_3 \\
 s_4[n] &= -0.5s_1[n-2] + 0.25\sqrt{2}s_4[n-1] + 0.25\sqrt{2}s_5[n-1] + w_4[n] \\
 s_5[n] &= -0.25\sqrt{2}s_4[n-1] + 0.25\sqrt{2}s_5[n-1] + w_5[n] \\
 s_6[n] &= 0.5s_5[n-3] + w_6[n]
 \end{aligned} \tag{8.1}$$

For every generated source 1000 observation points are used after a burn-in period of 100 to ensure stationarity. Figure 29 shows the diagram of the source network VAR process in (8.1).

Figure 29 – Diagram depicting the mutual influences on each series due to the past states of the other series, corresponding to the multivariate autoregressive model given by equation (8.1).

Source: authorship.

8.1.2 VAR model estimation

The VAR model of the source signals is estimated using the Nutall-Strand algorithm; the model order is obtained via Akaike's information criterion ([MARPLE, 1987](#)). This step provides us the estimated VAR coefficient matrix at the cortex, $\hat{\mathbf{A}}[h]$.

8.1.3 PDC estimation and connectivity inference

PDC has a rigorous statistical test to infer the connectivity considering the asymptotic behaviour of PDC (BACCALÁ et al., 2013). Therefore, this step involves computing the generalized PDC value (equation (3.28)), as well as the inference of connectivity at the cortex calculated at a significance level of 1%. Figure 30 displays a single trial example. For gPDC values above threshold, the figure also shows the allied confidence intervals.

Figure 30 – gPDC value and connectivity inference at the cortex for one repetition. The non-diagonal (i, j) subplot represents the link $s_j[n] \rightarrow s_i[n]$, while the diagonal subplots contain the normalized spectra of the sources. The green and red lines are no connectivity detected and connectivity detected respectively at a significance level of 1%.

Source: authorship.

Note that all the source connectivities are in accord with the imposed model. Besides, signals have an oscillation around at the normalized frequency 0.125, therefore that is the frequency of interest.

8.1.4 PDC performance measurements

After 500 repetitions, PDC performance is computed as follows:

8.1.4.1 Generalized PDC mean value:

The average value over the 500 repetitions is computed and displayed as in Figure 31, where it is close to zero values for absent links, as expected.

8.1.4.2 Percentage of detected connectivity

This value represents the number of times in which connectivity was detected for every pair of sources/electrodes in a particular direction as a proportion of the 500 trials. This quantity measures the robustness of the connectivity inference for every link in a particular direction. This result for model (8.1) is shown in Figure 31, and Confirms the single trial behaviour of Figure 30.

Figure 31 – PDC performance at the source space. Left: gPDC value; Right: Percentage of detected connectivity.

Source: authorship

8.2 Sensor space

The results of PDC performance at the scalp should desirably be as close as possible to that of the cortex. So, we use the analytical head model to calculate the forward solution as explained next.

8.2.1 Forward solution

In order to find the scalp potential at the electrode positions, we set first the spatial configuration of both source and sensor spaces. That means that we locate dipoles and sensors at particular configurations over the cortex and scalp, respectively.

The proposed scenarios can be clasified depending on the certainty about the locations and size of the sources. Thus, the electrodes are located exactly over its source or not. Additionally, a superposition of dipoles is used to simulate cortical regions rather than dipole sources.

8.2.1.1 Angular distances and leadfield matrix calculation

Once the spatial configuration at source and sensor space are determined, it is possible to calculate the specific leadfield matrix for each case. The latter is established from the Green's function for the angular distances between every electrode and every single dipole.

8.2.1.2 Scalp potential calculation

The forward model gives the time-series at the scalp using the linear combinations given by

$$\mathbf{x}[n] = \mathbf{\Omega} \mathbf{s}[n]$$

8.2.1.3 Bipolar derivation and Additive noise

We simulate every spatial configuration using different references, at infinity, at the bottom of the head, the average of all electrode signals and local reference. Moreover, for the average reference case we add some additive noise at different SNR in order to regularize the problem.

Finally, the VAR model is estimated at the scalp in order to compute the PDC value and establish its connectivity inference performance at the scalp.

8.2.2 Software and code

All the data processing are performed off-line using MATLAB ([MATLAB, 2015](#)). In particular, we use the following packages and functions:

- The Main program to set the options of every spatial configuration. It integrates all the functions and packages. It is available in the Annex [A](#).
- The VAR process at the cortex are generated using the functions *VARCoefficients* and *AR_dynam*. They are available in Annex [B](#).
- The estimation of the VAR model and PDC value, as well as the connectivity inference are computed using the open-source *AsympPDC* package ([SAMESHIMA; BACCALÁ, 2011](#)):

<http://www.lcs.poli.usp.br/~baccala/pdc/>

- The Green function of the forward head model is described by the function *Head_Model*, while the distance from every electrode to every dipole is calculated in *DistanceEleDip*. Both functions are in Annex [C](#).

- The leadfield matrix and the theoretical VAR coefficient matrix at the scalp are calculated by the function *VC_Coeff*. The scal time-series is computed by the function *linearCombOmega*. Both functions are available in Annex D.
- The bipolar derivations, as well as the additive noise are implemented using the functions *Bipolar* and *AddNoise*, both available in Annex E.
- The Monte Carlo simulation and PDC performance measurements were performed using the functions *VC_MONTE_CARLO* and *Monte_Carlo_Mine* available in Annex F.

8.3 Conventions

8.3.1 Coordinate systems:

The cartesian coordinates used throughout all the simulations are shown in Figure 32. They are defined by the location of four standard electrodes, which stay at the edge of the sensor space. Additionally, spherical coordinates are used due to the shape of the head model. See the detail in Figure 32.

Figure 32 – Used coordinates for the spatial distributions.

Source: Adapted from (GEVINS; LE, 1998).

8.3.2 Views of the head:

To show each of the considered spatial configurations, a figure is presented with the specific locations of sources and electrodes in spherical schemes. Those schemes represent the head from the right lateral, superior and posterior views. In Figure 33 is it shown the equivalent with a more realistic shape.

Figure 33 – Views of the head used in all the schemes that describe specific spatial configurations.

Source: authorship.

8.3.3 Sources and sensors:

Each electrode and its associated electrode have the same color. When, there is several possible positions for dipoles or electrodes, they are represented with a palette of similar colors recognizable for their path or common region. Additionally, the electrodes are identified with the a number corresponding to the dynamics of its associated source in (8.1).

8.3.4 Angular distances:

In some spatial configurations, it is considered that sensors and electrodes follow a well specified path. In that cases, the results are shown as function af the angular distance between two adjacent electrodes.

8.3.5 Normalized frequency:

The frequency domain in all of the figures is adimensional, since it is a normalized frequency ranges from 0 to 0.5. The frequency of interest is 0.125, where the oscillation occurs as it is shown in Figure 30.

8.3.6 Percentage of detected connectivity and mean PDC value:

Both results are presented as a plot matrix composed of all links in the system. The Percentage ranges between 0 and 100, while the PDC value rangens between 0 and 1. Both are represented as scale of colors or simply as a curve. All the results are shown for the entire frequency domain or at the frequency of interest for some cases.

Each of the links in the graphical representation contains the involving electrodes, as well as the direction of the information flow. For instance, the link from $x_j[n]$ to $x_i[n]$ correspond in the figures to the subplot in the i th row and j th column.

9 Results

The simulated spatial configurations can be clasified in four general cases according to the knowledge about the exact location of the sources and their size:

- Known dipole source locations [9.1.1](#)
- Unknown dipole source locations [9.1.2](#)
- Large cortical areas [9.1.3](#)
- Small cortical areas [9.1.4](#)

Four recording types are considered in each spatial configuration. Specifically they are: a reference at the infinity, a reference at the bottom of the head, instantaneous average as reference and a local reference for each recording electrode. The location and number of references is the main difference between those types.

9.1 Critical scenarios

All the spatial configurations reported in this chapter have adjacent distances over the critical value which guarantees good PDC performance (see Figures [23](#), [25](#) and [27](#)). Those scenarios allows us to see PDC performance at the electrode distance threshold, as well as at larger distances (for non adjacent electrodes).

9.1.1 Known dipole source locations

Our first proposed spatial configuration contains six sources and sensors, where its ϕ angle is always separated by 60 degrees, while the θ angle increases from $\theta = 30^\circ$ to $\theta = 90^\circ$. Thus, the distance between two adjacent electrodes is 30 degrees close to the head and 60 degrees at the the edge of the sensor space. An illustration of this scenario is presented in Figure [34](#).

The angular distance in the result figures corresponds to the separation between adjacent electrodes. For instance, consider the separation between electrodes 1 and 2 or between 2 and 4, in both cases that distance increases from 30 degrees to 60 degrees. Starting close to the top of the head and ending at the edge of the sensor space.

Figure 34 – Scheme of spatial configuration with known exact dipole positions. The distance between adjacent electrodes increases from 30 to 60 degrees.

Source: authorship

9.1.1.1 Reference at infinity

PDC performance for the spatial configuration of Figure 34 with reference at the infinity is shown in Figure 35. When looking for the optimum scenario for all the six

Figure 35 – Connectivity at the sensor space for the spatial configuration of Figure 34 with reference at infinity. Distance measured between two adjacent electrodes. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

electrodes, none can be found, since for every position on the considered path, there is at least one overdetected connection. Additionally, note that the link from $x_1[n]$ to $x_6[n]$ does not exist in the source space, however it is detected for all the possible positions of this scenario. Moreover, the links leaving $x_4[n]$, $x_5[n]$ and $x_6[n]$ arriving to $x_1[n]$ are wrongly detected when the electrodes are more separated. Apart from that, the rest of overdetected links disappear as the distance between electrodes becomes larger, confirming the theoretical results in section 7.3.1. Furthermore, misdetection is negligible, since all the existing links are detected in 100% of the repetitions, which confirms our theoretical

results in section 6.1.

Figure 36 – Percentage of detected connectivity at the frequency of interest (0.125) for the spatial configuration of Figure 35 with reference at the bottom of the head. Distance measured between two adjacent electrodes. $\alpha = 1\%$

Source: authorship

Figure 36 shows the percentage of detected connectivity at the frequency of interest (0.125). Looking at all the links arriving $x_1[n]$ it is possible to identify that the level of wrong detection is low for a narrow band of distances between electrodes. Particularly, the links between closer electrodes ($x_2[n] \rightarrow x_1[n]$ and $x_3[n] \rightarrow x_1[n]$) are more likely to be correctly identified as the distance between them approximates 55 degrees (see Sec. 7.3.1). However, when those electrodes are at the ideal separation, the level of connectivity increases for links between farther electrodes (like $x_3[n] \rightarrow x_1[n]$, $x_4[n] \rightarrow x_1[n]$ and $x_5[n] \rightarrow x_1[n]$), since they are at larger separations than the ideal one, at 55 degrees. Additionally note that the absent link $x_1[n] \rightarrow x_6[n]$ involving the aparted electrodes is highly detected for all the considered locations in this scenario, with a maximum percentage of detection of 86% for the largest separation between electrodes.

9.1.1.2 Reference at the bottom of the head

PDC performance for the spatial configuration of Figure 34 with a common reference at the bottom of the head is shown in Figure 37.

The PDC value in Figures 35 and 37 is almost identical to the one at the source space, with very low values for the absent links. So, it is possible to intuitively relate the cortical connectivity and the PDC value by using either, a reference at infinity or at the bottom of the head.

This scenario has an uniform behaviour for all the absent links, since the spurious detected connectivity decreases as the electrodes move apart. Very good PDC performance is achieved at electrode distance greater than 54 degrees, where all the links are detected correctly (see Sec. 7.3.2). The bottom reference improves the results for the entire sensor

Figure 37 – Connectivity at the sensor space for the spatial configuration of Figure 34 and reference at the bottom of the head. Distance measured between two adjacent electrodes. Left: gPDC mean value; Right: Percentage of detected connectivity.

Source: authorship

Figure 38 – Percentage of detected connectivity at the frequency of interest (0,125) for the spatial configuration of Figure 35 with reference at the bottom of the head. Distance measured between two adjacent electrodes. $\alpha = 1\%$

Source: authorship

space, although some links from close electrodes as $x_2 \rightarrow x_1[n]$ and $x_3[n] \rightarrow x_1[n]$ are overdetected over a broader distance band in comparison with the reference at infinity. This confirms our theoretical results. Conversely, misdetection is negligible, since all the existing links are detected in almost 100% of the repetitions.

Figure 38 shows the percentage of detected connectivity at the frequency of interest (0.125). In all cases, that value decreases for absent links as the distance between electrodes increases. At 54 degrees of distance between adjacent electrodes, the percentage of connectivity does not exceed 8% for all the absent links. This happens because, the leadfield matrix is closer to be diagonal as the distance between electrodes is larger than 54 degrees.

9.1.1.3 Average as reference

As the average reference implies a dimensionality reduction, the problem becomes ill-posed. To overcome that we add some uncorrelated additive noise. This helps to differentiate the sensor signals.

Additionally, we take this opportunity to show the additive noise effects by simulation.

Additive Noise Assume a spatial configuration with six symmetrically distributed electrodes, all with $\theta = 45^\circ$ as shown in Figure 39.

Figure 39 – Scheme of spatial configuration with exact known dipole positions, the distance between two adjacent electrodes is 41.4 degrees. The reference is at infinity.

Source: authorship

PDC performance for this spatial configuration with reference at the infinity and uncorrelated additive noise with SNR from 1 to 3 is shown in Figure 40.

Figure 40 – Connectivity at the sensor space for the spatial configuration of Figure 39 with SNR from 1 to 3. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

The presence of additive noise does not alter the detection of the existing links. Instead, it helps to mitigate the overdetetection caused by source mixing. That improvement only occurs for SNR lower than 1.5. Even under these circumstances, overdetetection is not completely overcome at any link.

Figure 41 shows the percentage of detected connectivity at the frequency of interest (0.125). All values remain at almost constant values with the maximum value of 61% of

Figure 41 – Percentage of detected connectivity at the frequency of interest (0.125) for the spatial configuration of Figure 40 with SNR from 1 to 3 and reference at infinity. $\alpha = 1\%$

Source: authorship

connectivity detection on link $x_1[n] \rightarrow x_6[n]$.

Average reference: For the simulation of the average as reference, we use additive noise with SNR of 10, to guarantee that the effect of the noise is only the regularization of the problem. PDC performance for the spatial configuration of Figure 34 with the instantaneous average signal as reference is shown in Figure 42.

PDC mean values are not intuitively related to the connectivity inference, since all of them are close to zero.

The connectivity inference only overdetects two absent links, which are fixed for electrode distances larger than 41,4 degrees. Furthermore, the detection of the existing links is not always close to 100%, the link $x_1[n] \rightarrow x_2[n]$ has a percentage of detected connectivity of 5% at high frequencies when the electrodes are at 30 degrees apart from their closest neighbour.

Figure 43 shows the percentage of detected connectivity at the frequency of interest (0,125). PDC performance is good, with a maximum overdetetection of 12% of the link from $x_1[n]$ to $x_6[n]$, which have a separation of 50 degrees or more.

Figure 42 – Connectivity at the sensor space with the spatial configuration of Figure 34 and average as reference. Distance measured between two adjacent electrodes. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

Figure 43 – Percentage of detected connectivity at the frequency of interest (0.125) for the spatial configuration of Figure 40 with average as reference. $\alpha = 1\%$

Source: authorship

9.1.1.4 Local reference

The simulation of using local references is performed with the spatial distribution of Figure 44. It is composed of six symmetrically distributed electrodes around the z axis and with a common theta angle, $\theta = 45^\circ$. The reference electrodes are located at 11,25 degrees of its recording electrode. The distance between a local reference and the most influential non-associated source is larger than the distance between the recording electrode and that undesirable source. PDC performance for this scenario is shown in Figure 45.

All the existing connections are correctly detected in 100% of the repetitions. At the frequency of interest (0.125), 3% or less is the level of detection for the absent links. Moreover, for higher frequencies, the percentage of detection rises on two absent links, reaching a maximum of 12% in $x_2[n] \rightarrow x_1[n]$. Furthermore, the PDC value is very similar

Figure 44 – Scheme of spatial configuration with known exact dipole locations. Distance between adjacent recording electrode of 41.4 degrees. Local reference at 11.25 degrees from its recording electrode.

Source: authorship

Figure 45 – Connectivity at the sensor space for the spatial configuration of Figure 44 using local references. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

to its analogous at the source space, as in the cases using a reference at the bottom of the head or at infinity.

This is the best PDC performance reached for this spatial configuration in comparison with all the other references for this exact spatial configuration, where the distance between two adjacent electrodes is 41,4 degrees in analogy to the 10-20 EEG standard.

9.1.2 Unknown dipole source locations

This scenario is composed by six sources and its associated electrodes. Each source can be placed within a radius-distance of 20 degrees around its associated electrode; 500 repetitions were performed for each of 100 random source locations. Figure 46 shows all the considered positions. This spatial configuration is the closest version of the proposal in Figure 22. The minimum distance between adjacent electrodes is of 60 degrees (like between x_1 and x_3) as it is shown in Figure 46.

Figure 46 – Scheme of spatial configuration with unknown exact dipole locations. Minimum distance of 60 degrees between adjacent electrodes. Each dipole is located in a radius-distance of maximum 20 degrees from its associated electrode.

Source: authorship

9.1.2.1 Reference at infinity

The PDC performance for the spatial configuration of Figure 46 with reference at the infinity is shown in Figure 47.

In this scenario, several absent links are overdected, specially those arriving $x_1[n]$ are wrongly detected with a maximum of 55% of detected connectivity. That value corresponds to the link $x_6[n] \rightarrow x_1[n]$, whose electrodes are further from each other. Additionally, note the strong presence of the absent link $x_1[n] \rightarrow x_6[n]$ with 56% of connectivity detected. Apart from that, all the existing links are detected in almost 100% of the repetitions.

At the frequency of interest (0.125), PDC performance exhibits a maximum overdedection of 22% for the links arriving to $x_1[n]$ and of 51% for the link from $x_1[n]$ to $x_6[n]$.

Furthermore, the PDC value stays close to zero for the absent links, allowing to relate it with the connectivity at the source space.

Figure 47 – Connectivity at the sensor space with the spatial configuration of Figure 46 and reference at infinity. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

9.1.2.2 Reference at the bottom of the head

The PDC performance for the spatial configuration of Figure 46 with reference at the bottom of the head is shown in Figure 48.

Figure 48 – Connectivity at the sensor space with the spatial configuration of Figure 46 and reference at the bottom of the head. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

Only the absent link from $x_3[n]$ to $x_1[n]$ is overdetected, with 19% of maximum detected connectivity at a frequency of 0.36, while at the frequency of interest that link is detected in 4% of the repetitions. Furthermore, all the existing links are detected in almost 100% of the repetitions in the entire frequency domain.

The PDC value looks very similar to the one at the sources space, with close to zero values in the absent links.

9.1.2.3 Average as reference

The PDC performance for the spatial configuration of Figure 46 using the instantaneous average signal as reference is shown in Figure 49.

Figure 49 – Connectivity at the sensor space with the spatial configuration of Figure 50 and average as reference. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

Spurious connectivity is detected in all the links arriving to $x_1[n]$ with 54% or less detected connectivity. The link from $x_1[n]$ to $x_6[n]$ is also falsely detected with a percentage of detected connectivity of 52%. The rest of the links are correctly detected. Furthermore, the PDC value is close to zero in every single link making impossible a direct association with the connectivity at the source space.

At the frequency of interest (0.125), the percentage of detected connectivity in absent links does not exceed 11% for all the links, except for $x_1[n] \rightarrow x_6[n]$, where that value is 48%.

9.1.2.4 Local reference

PDC performance for the spatial configuration of Figure 50 with local reference for every electrode is shown in Figure 51. The local references are at 22.5 degrees from their associated electrodes.

In this case, the local reference helps to completely fix the source mixing issue, since the maximum overdetection does not exceed 4% over the entire frequency domain and 3% at the frequency of interest. Moreover, all the existing links are detected in almost 100% of the repetitions, except at frequencies lower than 0.05.

Furthermore, PDC values look very similar to those at the source space, reflecting the true connectivity.

Figure 50 – Scheme of spatial configuration with unknown dipole locations. Dipoles located in a radius-distance of maximum 20 degrees from its associated electrode. Minimum distance of 60 degrees between adjacent recording electrodes. Local reference at 22.5 degrees from its recording electrode.

Source: authorship

Figure 51 – Connectivity at the sensor space with the spatial configuration of Figure 50. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

9.1.3 Large cortical areas

Now, consider that each active source is composed of 100 dipole sources at a maximum distance of 20 degrees from its associated electrode. The scheme of the spatial distributions of sources and electrodes is the same as shown in Figure 46.

The behaviour of this scenario with active cortical regions is very similar to that already considered for dipole sources shifted from its associated electrode (Section 9.1.2). PDC performance in this case is a little better in the overdetection problem present in both scenarios. The use of a reference at the bottom of the head helps to improve the overdetection present in the link $x_3[n] \rightarrow x_1[n]$, whose detected connectivity falls from 22% to 11%. For the rest of references, the detection percentages decrease in just 1% or 2% in comparison with the previous case involving source dipoles rather than cortical areas.

9.1.4 Small cortical areas

Now, consider the configuration shown in Figure 52, where the sources are cortical regions with a radius of 10 degrees around their associated electrodes. Six electrodes are symmetrically distributed around the z axis and at the same theta angle, $\theta = 45^\circ$ in analogy with the 10-20 EEG standard. The separation between adjacent electrodes is 41.4 degrees.

Figure 52 – Scheme of spatial configuration: cortical regions with a radius of 10 degrees. Separation between adjacent electrodes of 41.4 degrees.

Source: authorship

9.1.4.1 Reference at infinity

PDC performance for the spatial configuration of Figure 52 with reference at the infinity is shown in Figure 53.

Figure 53 – Connectivity at the sensor space with the spatial configuration of Figure 52 and reference at infinity. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

PDC values look very similar to those at the source space. About the detected connectivity, some links are overdetected, reaching a detection level of 31% on the link $x_1[n] \rightarrow x_6[n]$. Other overdetected absent links do not exceed 22% of detected connectivity in the entire frequency domain. The majority of links are correctly detected, including all the existing links. At the frequency of interest, all the absent links have a detection connectivity level inferior to 19% ($x_1[n] \rightarrow x_6[n]$).

Comparing with the same spatial configuration considering dipole sources rather than areas (see Figure 35), PDC performance is better for cortical areas. Specially, in the absent problematic link involving distant electrodes ($x_1[n] \rightarrow x_6[n]$).

9.1.4.2 Reference at the bottom of the head

PDC performance for the spatial configuration of Figure 52 with reference at the bottom of the head is shown in Figure 54.

Figure 54 – Connectivity at the sensor space with the spatial configuration of Figure 52 and reference at the bottom of the head. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

All the links are correctly detected with two exceptions. The absent links arriving $x_1[n]$ from its two closest electrodes are overdetected in up to 83% of the repetitions. However, this value is considerably lower for frequencies close to the frequency of interest (0.125).

In comparison with its analogous spatial distribution, but considering single dipole sources (compare to Figure 38), there is an improvement when considering the absent links.

Apart from that, PDC values look very similar to those at the source space.

9.1.4.3 Average as reference

PDC performance for the spatial configuration of Figure 52 using the instantaneous average as reference is shown in Figure 55.

Figure 55 – Connectivity at the sensor space with the spatial configuration of Figure 52 and average as reference. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

As in all the previous cases using the instantaneous average as reference, PDC values do not reflect the actual connectivity at the source space.

On the other hand, the connectivity detected is correct in almost all the links with some exceptions. The absent links arriving $x_1[n]$ are overdetected in 18.4% or less of the repetitions. Besides, the absent link $x_1[n] \rightarrow x_6[n]$ is detected in 29% of the repetitions.

At the frequency of interest (0.125), there is an overdetection of 21% on the link $x_1[n] \rightarrow x_6[n]$, while for the rest of the absent links, this value falls to less than 3%.

9.1.4.4 Local reference

PDC performance for the spatial configuration of Figure 56 using local references is shown in Figure 57. The scenario is composed of six symmetrically distributed recording electrodes and at the same theta angle, $\theta = 45^\circ$. The local references are located at 11.25 degrees from its recording electrode. Additionally, the cortical regions have a radius of 10 degrees around their associated electrodes.

In this scenario there are four overdetected absent links with a percentage of detection inferior to 19%. The rest of the absent links are detected in less than 6% of the repetitions.

At the frequency of interest (0.125), the maximum overdetection occurs in the link $x_6[n] \rightarrow x_4[n]$ detected in 16% of the repetitions. The rest of the absent links are detected

Figure 56 – Scheme of spatial configuration using local references: cortical regions with a radius of 10 degrees. Distance between adjacent electrodes is 41,4 degrees. Local reference at 11,25 degrees from its recording electrode.

Source: authorship

Figure 57 – Connectivity at the sensor space with the spatial configuration of Figure 52 using local references. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

in less than 8% of the repetitions.

9.2 Optimum scenario

The following is a simulation of a slightly different scenario where the adjacent electrode distance is within the optimum values. A new configuration using local references is shown in Figure 58. It is a correction that follows from found theory about local references (see Sec. 7.3.4) combined with unknown exact source locations with reference at infinity (see Sec. 7.3.1). The latest was applied to assumed cortical areas rather than dipole sources.

In this new scenario the electrodes are symmetrically distributed around the z axis, but now they are a common theta angle of $56^\circ.25$ rather than 45° . Thus, the distance

Figure 58 – Scheme of spatial configuration using local references: cortical regions with a radius of 8 degrees. Distance between adjacent electrodes is 56.25 degrees. Local reference at 11.25 degrees from its recording electrode.

Source: authorship

between adjacent electrodes is 46.6 degrees. The underlying cortical areas occupy a radius of 8 degrees around their associated electrodes. The local references are placed at 11.25 degrees from each recording electrode in the direction of the largest influence coming from a non-associated source.

PDC performance for the spatial configuration of Figure 58 using the instantaneous average as reference is shown in Figure 59.

Figure 59 – Connectivity at the sensor space with the spatial configuration of Figure 52 using local references. Left: gPDC value; Right: Percentage of detected connectivity. $\alpha = 1\%$

Source: authorship

Under this scenario, the maximum overdetection is of 6% in the link from $x_6[n]$ to $x_4[n]$. Moreover, the percentage of detected connectivity for all the links is very close to the actual ones at the source space over the entire frequency domain. The obtained results for this scenario are reported as the last scenario in Table 2.

9.3 Discussion

At this point it is worth confronting our theoretical results with the numerical experiments. For the sake of simplicity we restrict our considerations to the $f = 0.125$ frequency where most signal power resides even though the numerical results were shown for other frequencies as well with somewhat distinct performance.

To facilitate the analysis, our numerical results have been summarized in Table 2 as a function of the used reference and scenario. Most importantly the table records the extreme cases of best and worst PDC performance in (wrongly) spotting absent links in each case.

Table column entries are as follows: **Reference** column records the type of electrical reference: (a) at *infinity*, (b) at the *bottom* of the head, (c) with respect to an *average* of electrode values and (d) using *local* references. The **Source Size** column (which describes source geometry: as a) *point* source, or (b) as stemming from a *small* cortical area as opposed to a (c) *large* area. Note that exact point source locations may be taken as either known or unknown. The column **% Detected** singles out some connections contained in column **Links** and the percentage of times they are detected and the relative electrode **Distance** values are in degrees. Column (**% good**) grades how good the results are percentagewise for the spatial configuration in Figure 34. The last column indicates the range of electrode distance where the connectivity detection of all the absent links is inferior to 10% for each spatial configuration.

A common feature of the table is that all configurations possess electrode separation ranges of good PDC performance, regardless of whether one is using point sources whose position is known or unknown or even localized source distributions (large and small).

For a reference at infinity, the electrode distance range associated with mostly correct connectivity inference lies between 42 and 60 degrees. If all the electrodes are separated within the latter parameters, the connectivity detection (error) level is lower than 10% and almost reaches the prescribed 1% significance statistical test level used in our detections. Moreover, the worst results correspond to links involving electrodes separated by more than 60 degrees where false detections reach an 86% level. Similar observations hold for the other scenarios as well.

The best single common reference scenario is associated with the the head bottom reference electrode. In this configuration correct absent link detection is below 5% as long as electrode separation is above 54 degrees. In this scenario the range of viable low error electrode separations makes it a convenient option.

The table also shows that the best performance when local bipolar references are used. Even under the least favourable conditions, wrong connectivity detection is below 20%. Wrong connectivity detection falls below 6% for electrode separations above 42

Table 2 – Summary of numerical results.

Reference	Source size	Known	% Detected	Distance	Links	% good	Opt. distance
infinity	point	yes	0	50°- 120°	6 $\leftarrow$ 2	88	42°-60°
			86	60°- 180°	6 $\leftarrow$ 1		
		no	1	60°	5 $\leftarrow$ 3	76	
			47	180°	6 $\leftarrow$ 1		
	large area		1	60°	5 $\leftarrow$ 3	76	
			51	180°	6 $\leftarrow$ 1		
	small area		1	41°,4	5 $\leftarrow$ 6	96	
			19	90°	6 $\leftarrow$ 1		
bottom	point	yes	0	50°- 120°	1 $\leftarrow$ 4	100	>54°
			100	30°- 42°	1 $\leftarrow$ 3		
		no	0,5	90°	1 $\leftarrow$ 5	100	
			3	60°	1 $\leftarrow$ 3		
	large area		0,8	90°	1 $\leftarrow$ 5	100	
			4	60°	1 $\leftarrow$ 3		
	small area		1	90°	2 $\leftarrow$ 6	92	
			14	41°,4	1 $\leftarrow$ 2		
average	point	yes	0	30°- 60°	5 $\leftarrow$ 3	100	30°-50°
			12	50°- 60°	6 $\leftarrow$ 1		
		no	1	60°	5 $\leftarrow$ 3	96	
			43	180°	6 $\leftarrow$ 1		
	large area		1	60°	5 $\leftarrow$ 3	96	
			43	180°	6 $\leftarrow$ 1		
	small area		0,8	41°,4	5 $\leftarrow$ 6	96	
			21	90°	6 $\leftarrow$ 1		
local	point	yes	0	90°	3 $\leftarrow$ 4	96	>41°,4
			3	41°,4	1 $\leftarrow$ 2		
		no	0,8	60°	4 $\leftarrow$ 2	100	
			1,4	60°	1 $\leftarrow$ 3		
	large area		0,8	60°	4 $\leftarrow$ 2	100	
			1,4	60°	1 $\leftarrow$ 3		
	small area		0,8	90°	2 $\leftarrow$ 6	96	
			16	60°	4 $\leftarrow$ 6		
			0,8	101°,25	1 $\leftarrow$ 6	100	
			5,4	46°,6	4 $\leftarrow$ 6		

Source: authorship.

degrees. In this scenario, the largest electrode separation range is achieved leading to correct detection levels as high as 94%.

To summarize, two reference systems stand out as the best ones: (a) the bottom head ground (the equivalent of using the mastoids) as long as electrode separations are above 60 degrees and (b) the use of local references as long as they are chosen along the direction of the most influential non-associated source, something that could be subject to prior empirical determination using a reference ground at infinity.

One common aspect of all simulations is that PDC performs very well for actually existing links. Detection in this case is somewhat lower when a signal average is used as a

reference which constitutes an added reason to avoid this option.

Another regularity is the virtual equivalence between single sources and distributed localized sources. This is a convenient observation since single source results may therefore be used in predicting estimation behaviour for more general source distributions. In particular, dipoles distributed over small cortical regions behave in a way that is similar to that of dipole sources exactly under their associated electrodes. Therefore, our analysis for dipole sources at known exact locations applies to cortical regions spread over a radius inferior to 10 degrees under the electrode.

10 Conclusions and Future Work

This work was motivated by trying to address an existing controversy regarding the conflicting claims as to whether Volume conduction is deleterious for scalp EEG based neural connectivity estimation.

Time and space constraints have limited the present research to reporting a single detailed dynamics calling for its extension to more general settings. Another possible criticism is that the simulations employed a multi-layer spherical source propagation model which by itself has some limitations in so far as leading to more general conclusions which need to be examined under more realistic cortical models.

Despite this some general conclusions can be drawn:

1. Volume conduction can be potentially harmful in falsifying connectivity results based on scalp measurements. This happens depending on the form of the leadfield matrix $\mathbf{\Omega}$. The effect becomes more severe as $\mathbf{\Omega}$ is perturbed away from a diagonal shape.
2. The claim that PDC's sole reliance on phase delay for connectivity estimation robustness does not hold. Wise ground reference configuration choice and electrode placement geometry are the actual critical factors.
3. It is possible to arrange scalp electrodes so as to minimize the effect of VC even if the underlying source distribution is not precisely known.
4. A key factor in mitigating VC is the use of an appropriate electrode reference system, where a properly disposed local bipolar arrangement outperforms other popular ground reference configurations. This preference is associated with an apparent robustness with respect to electrode distribution.
5. There is room for investigating alternative connectivity detection criteria under VC.

Together these observations explain why researchers do report conflicting observations when trying to infer connectivity using sensor space measurements. Yet these observations reveal that some measure of reliable connectivity estimation is in principle attainable as long as an adequate electrode/reference configuration setup is adopted.

References

- ADELOYE, A.; KATTAN, K. R.; SILVERMAN, F. N. Thickness of the normal skull in the american blacks and whites. *American Journal of Physical Anthropology*, Wiley, v. 43, n. 1, p. 23–30, 1975.
- ARFKEN, G. B. *Mathematical methods for physicists*. [S.l.]: Academic press, 2013.
- ASTOLFI, L.; BABILONI, F. *Estimation of cortical connectivity in humans*. [S.l.]: Morgan & Claypool publishers, 2008.
- ASTOLFI, L. et al. Assessing cortical functional connectivity by linear inverse estimation and directed transfer function: simulations and application to real data. *Clinical neurophysiology*, Elsevier, v. 116, n. 4, p. 920–932, 2005.
- ASTOLFI, L. et al. Comparison of different cortical connectivity estimators for high-resolution eeg recordings. *Human brain mapping*, Wiley Online Library, v. 28, n. 2, p. 143–157, 2007.
- ASTOLFI, L. et al. Neural basis for brain responses to tv commercials: a high-resolution eeg study. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, IEEE, v. 16, n. 6, p. 522–531, 2008.
- AYLWARD, E. H. et al. Effects of age on brain volume and head circumference in autism. *Neurology*, AAN Enterprises, v. 59, n. 2, p. 175–183, 2002.
- BABILONI, F. et al. A high resolution eeg method based on the correction of the surface laplacian estimate for the subject's variable scalp thickness. *Electroencephalography and clinical neurophysiology*, Elsevier, v. 103, n. 4, p. 486–492, 1997.
- BACCALÁ, L. et al. Unified asymptotic theory for all partial directed coherence forms. *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, The Royal Society, v. 371, n. 1997, p. 20120158, 2013.
- BACCALA, L. et al. Studying the interaction between brain structures via directed coherence and granger causality. *Applied Signal Processing*, n. 5, 1998.
- BACCALÁ, L. A.; SAMESHIMA, K. Directed coherence: a tool for exploring functional interactions among brain structures. *Methods for neural ensemble recordings*, p. 179–192, 1998.
- BACCALÁ, L. A.; SAMESHIMA, K. Partial directed coherence: a new concept in neural structure determination. *Biological cybernetics*, Springer, v. 84, n. 6, p. 463–474, 2001.
- BACCALÁ, L. A.; SAMESHIMA, K. On neural connectivity estimation problems. *Milan*, 2015.
- BACCALÁ, L. A.; SAMESHIMA, K.; TAKAHASHI, D. Generalized partial directed coherence. In: IEEE. INTERNATIONAL CONFERENCE ON DIGITAL SIGNAL PROCESSING, 15. *Conference...* [S.l.], 2007. p. 163–166.

- BAILLET, S.; MOSHER, J. C.; LEAHY, R. M. Electromagnetic brain mapping. *Signal Processing Magazine, IEEE*, v. 18, n. 6, p. 14–30, 2001.
- BAUMANN, S. B. et al. The electrical conductivity of human cerebrospinal fluid at body temperature. *IEEE Transactions on Biomedical Engineering*, IEEE, v. 44, n. 3, p. 220–223, 1997.
- BENDAT, J. S.; PIERSON, A. G. Measurement and analysis of random data. Wiley, 1966.
- BLINOWSKA, K. J. Review of the methods of determination of directed connectivity from multichannel data. *Medical & biological engineering & computing*, Springer, v. 49, n. 5, p. 521–529, 2011.
- BOAS, M. L. *Mathematical methods in the physical sciences*. New York: Wiley, 1966. v. 2.
- BOLLOBÁS, B.; KOZMA, R.; MIKLÓS, D. *Handbook of large-scale random networks*. [S.l.]: Springer Science & Business Media, 2010. v. 18.
- BRESSLER, S. L.; MENON, V. Large-scale brain networks in cognition: emerging methods and principles. *Trends in cognitive sciences*, Elsevier, v. 14, n. 6, p. 277–290, 2010.
- BRESSLER, S. L.; TOGNOLI, E. Operational principles of neurocognitive networks. *International Journal of Psychophysiology*, Elsevier, v. 60, n. 2, p. 139–148, 2006.
- BRZEZICKA, A. et al. Information transfer during a transitive reasoning task. *Brain topography*, Springer, v. 24, n. 1, p. 1–8, 2011.
- BUDAK, B. M.; SAMARSKII, A. A.; TIKHONOV, A. N. *A Collection of Problems on Mathematical Physics: International Series of Monographs in Pure and Applied Mathematics*. [S.l.]: Elsevier, 2013. v. 52.
- BUSHBY, K. et al. Centiles for adult head circumference. *Archives of disease in childhood*, BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health, v. 67, n. 10, p. 1286–1287, 1992.
- CARRELL, J. B. Fundamentals of linear algebra. *University of British Columbia*, Jul, 2005.
- CASANOVA, M. F.; OPRIS, I. *Recent Advances on the Modular Organization of the Cortex*. [S.l.]: Springer, 2015.
- CHO, J.-H. et al. Influence of the head model on eeg and meg source connectivity analyses. *NeuroImage*, Elsevier, v. 110, p. 60–77, 2015.
- CLERC, M. et al. In vivo conductivity estimation with symmetric boundary elements. *International Journal of Bioelectromagnetism*, v. 7, p. 307–310, 2005.
- COOPER, R. et al. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalography and clinical neurophysiology*, Elsevier, v. 18, n. 3, p. 217–228, 1965.
- COSGROVE, K. P.; MAZURE, C. M.; STALEY, J. K. Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biological psychiatry*, Elsevier, v. 62, n. 8, p. 847–855, 2007.

- CUFFIN, B. N.; COHEN, D. Comparison of the magnetoencephalogram and electroencephalogram. *Electroencephalography and clinical neurophysiology*, Elsevier, v. 47, n. 2, p. 132–146, 1979.
- DEMŠAR, U. et al. Principal component analysis on spatial data: an overview. *Annals of the Association of American Geographers*, Taylor & Francis, v. 103, n. 1, p. 106–128, 2013.
- DIEN, J. Issues in the application of the average reference: Review, critiques, and recommendations. *Behavior Research Methods, Instruments, & Computers*, Springer, v. 30, n. 1, p. 34–43, 1998.
- FAVOROV, O. V.; WHITSEL, B. L.; TOMMERDAHL, M. Discrete, place-defined macrocolumns in somatosensory cortex: lessons for modular organization of the cerebral cortex. In: *Casanova, M. F. ; Opris, L. Recent Advances on the Modular Organization of the Cortex*. Netherlands: Springer, 2015. p. 143–155.
- FERREE, T. C.; ERIKSEN, K. J.; TUCKER, D. M. Regional head tissue conductivity estimation for improved eeg analysis. *IEEE Transactions on Biomedical Engineering*, IEEE, v. 47, n. 12, p. 1584–1592, 2000.
- FINGELKURTS, A. A.; FINGELKURTS, A. A.; KAHKONEN, S. Functional connectivity in the brain: is it an elusive concept? *Neuroscience & Biobehavioral Reviews*, Elsevier, v. 28, n. 8, p. 827–836, 2005.
- FLORIN, E. et al. Reliability of multivariate causality measures for neural data. *Journal of neuroscience methods*, Elsevier, v. 198, n. 2, p. 344–358, 2011.
- FOLDVARY-SCHAEFER, N.; GRIGG-DAMBERGER, M. M. Identifying interictal and ictal epileptic activity in polysomnograms. *Sleep Medicine Clinics*, Elsevier, v. 7, n. 1, p. 39–58, 2012.
- FRANASZCZUK, P.; BLINOWSKA, K. Linear model of brain electrical activity. eeg as a superposition of damped oscillatory modes. *Biological cybernetics*, Springer, v. 53, n. 1, p. 19–25, 1985.
- GABRIEL, C.; PEYMAN, A.; GRANT, E. Electrical conductivity of tissue at frequencies below 1 mhz. *Physics in medicine and biology*, IOP Publishing, v. 54, n. 16, p. 4863, 2009.
- GEODESICS, N. C. E. Conductivity analysis for high-resolution eeg. 2008.
- GESELOWITZ, D. B. On bioelectric potentials in an inhomogeneous volume conductor. *Biophysical journal*, The Biophysical Society, v. 7, n. 1, p. 1, 1967.
- GEVINS, A. S.; LE, J. *Spatial measurement of EEG electrodes*. [S.l.]: Google Patents, 1998. US Patent 5,817,029.
- GINTER, J. et al. Phase and amplitude analysis in time frequency space application to voluntary finger movement. *Journal of neuroscience methods*, Elsevier, v. 110, n. 1, p. 113–124, 2001.
- GÓMEZ-HERRERO, G. Brain connectivity analysis with eeg. *Tampereen teknillinen yliopisto. Julkaisu-Tampere University of Technology. Publication; 877*, 2010.

- GÓMEZ-HERRERO, G. et al. Measuring directional coupling between eeg sources. *Neuroimage*, Elsevier, v. 43, n. 3, p. 497–508, 2008.
- GONÇALVES, S. I. et al. In vivo measurement of the brain and skull resistivities using an eit-based method and realistic models for the head. *IEEE Transactions on Biomedical Engineering*, IEEE, v. 50, n. 6, p. 754–767, 2003.
- GRANGER, C. W. Investigating causal relations by econometric models and cross-spectral methods. *Econometrica: Journal of the Econometric Society*, JSTOR, p. 424–438, 1969.
- GRECH, R. et al. Review on solving the inverse problem in eeg source analysis. *Journal of neuroengineering and rehabilitation*, BioMed Central, v. 5, n. 1, p. 1, 2008.
- GROETSCH, C. W.; GROETSCH, C. *Inverse problems in the mathematical sciences*. [S.l.]: Springer, 1993. v. 52.
- GUTIÉRREZ, D.; NEHORAI, A.; MURAVCHIK, C. H. Estimating brain conductivities and dipole source signals with eeg arrays. *IEEE transactions on biomedical engineering*, IEEE, v. 51, n. 12, p. 2113–2122, 2004.
- HAEUSSINGER, F. B. et al. Simulation of near-infrared light absorption considering individual head and prefrontal cortex anatomy: implications for optical neuroimaging. *PLoS One*, Public Library of Science, v. 6, n. 10, p. e26377, 2011.
- HAGEMANN, D.; NAUMANN, E.; THAYER, J. F. The quest for the eeg reference revisited: a glance from brain asymmetry research. *Psychophysiology*, v. 38, n. 5, p. 847–857, 2001.
- HANSEN, P. C. *Rank-deficient and discrete ill-posed problems: numerical aspects of linear inversion*. [S.l.]: Siam, 1998. v. 4.
- HAUFE, S. et al. A critical assessment of connectivity measures for eeg data: a simulation study. *NeuroImage*, Elsevier, v. 64, p. 120–133, 2013.
- HERWIG, U.; SATRAPI, P.; SCHÖNFELDT-LECUONA, C. Using the international 10–20 eeg system for positioning of transcranial magnetic stimulation. *Brain topography*, Springer, v. 16, n. 2, p. 95–99, 2003.
- HNIZDO, V. On the laplacian of $1/r$. *European Journal of Physics*, IOP Publishing, v. 21, n. 1, p. L1, 2000.
- HOMAN, R. W.; HERMAN, J.; PURDY, P. Cerebral location of international 10–20 system electrode placement. *Electroencephalography and clinical neurophysiology*, Elsevier, v. 66, n. 4, p. 376–382, 1987.
- HORI, H. et al. The thickness of human scalp: normal and bald. *Journal of Investigative Dermatology*, Elsevier, v. 58, n. 6, p. 396–399, 1972.
- HORWITZ, B. The elusive concept of brain connectivity. *Neuroimage*, Elsevier, v. 19, n. 2, p. 466–470, 2003.
- JACKSON, J. D. *Classical electrodynamics*. [S.l.]: Wiley, 1999.
- JASPER, H. H. The ten twenty electrode system of the international federation. *Electroencephalography and clinical neurophysiology*, v. 10, p. 371–375, 1958.

- JUNGHÖFER, M. et al. The polar average reference effect: a bias in estimating the head surface integral in eeg recording. *Clinical Neurophysiology*, Elsevier, v. 110, n. 6, p. 1149–1155, 1999.
- JURCAK, V.; TSUZUKI, D.; DAN, I. 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. *Neuroimage*, Elsevier, v. 34, n. 4, p. 1600–1611, 2007.
- KAMINSKI, M.; BLINOWSKA, K. A new method of the description of the information flow in the brain structures. *Biological cybernetics*, Springer, v. 65, n. 3, p. 203–210, 1991.
- KAMINSKI, M.; BLINOWSKA, K. J. Directed transfer function is not influenced by volume conduction?inexpedient pre-processing should be avoided. *Frontiers in computational neuroscience*, Frontiers Media SA, v. 8, 2014.
- KAMIŃSKI, M. et al. Evaluating causal relations in neural systems: Granger causality, directed transfer function and statistical assessment of significance. *Biological cybernetics*, Springer, v. 85, n. 2, p. 145–157, 2001.
- KAMITAKE, T.; HARASHIMA, H.; MIYAKAWA, H. A time-series analysis method based on the directed transinformation. *Electronics and Communications in Japan (Part I: Communications)*, Wiley Online Library, v. 67, n. 6, p. 1–9, 1984.
- KHINTCHINE, A. Korrelationstheorie der stationären stochastischen prozesse. *Mathematische Annalen*, Springer, v. 109, n. 1, p. 604–615, 1934.
- KIKINIS, R. et al. Routine quantitative analysis of brain and cerebrospinal fluid spaces with mr imaging. *Journal of Magnetic Resonance Imaging*, Wiley Online Library, v. 2, n. 6, p. 619–629, 1992.
- KIMISKIDIS, V. K. et al. Transcranial magnetic stimulation (tms) modulates epileptiform discharges in patients with frontal lobe epilepsy: a preliminary eeg-tms study. *International journal of neural systems*, World Scientific, v. 23, n. 01, p. 1250035, 2013.
- KOLES, Z. J.; LAZAR, M. S.; ZHOU, S. Z. Spatial patterns underlying population differences in the background eeg. *Brain topography*, Springer, v. 2, n. 4, p. 275–284, 1990.
- KURGANSKY, A. Some methodological issues of studying cortico-cortical functional connectivity with vector autoregressive model of multichannel eeg. *Zh. Vyssh. Nervn. Deyat. im. I.P. Pavlova*, 2010.
- KURGANSKY, A. Quantitative measures of cortical functional connectivity: A state-of-the-art brief survey. *Human Physiology*, Springer, v. 39, n. 4, p. 432–440, 2013.
- LAI, Y. et al. Estimation of in vivo human brain-to-skull conductivity ratio from simultaneous extra-and intra-cranial electrical potential recordings. *Clinical neurophysiology*, Elsevier, v. 116, n. 2, p. 456–465, 2005.
- LATIKKA, J.; KUURNE, T.; ESKOLA, H. Conductivity of living intracranial tissues. *Physics in medicine and biology*, IOP Publishing, v. 46, n. 6, p. 1611, 2001.
- LAW, S. K. Thickness and resistivity variations over the upper surface of the human skull. *Brain topography*, Springer, v. 6, n. 2, p. 99–109, 1993.

- LÜTKEPOHL, H. *New introduction to multiple time series analysis*. [S.l.]: Springer Science & Business Media, 2007.
- LYNNERUP, N. Cranial thickness in relation to age, sex and general body build in a danish forensic sample. *Forensic science international*, Elsevier, v. 117, n. 1, p. 45–51, 2001.
- MAKEIG, S. et al. Electroencephalographic brain dynamics following manually responded visual targets. *PLoS biology*, v. 2, p. 747–762, 2004.
- MARPLE, S. L. Digital spectral analysis: with applications. *Englewood Cliffs, NJ, Prentice-Hall.*, 1987.
- MATLAB. *version 8.5.0 (R2015a)*. Natick, Massachusetts: The MathWorks Inc., 2015.
- MONTIEL, T. et al. Differential effects of the substrate inhibitor l-trans-pyrrolidine-2, 4-dicarboxylate (pdc) and the non-substrate inhibitor dl-threo- β -benzyloxyaspartate (dl-tboa) of glutamate transporters on neuronal damage and extracellular amino acid levels in rat brain in vivo. *Neuroscience*, Elsevier, v. 133, n. 3, p. 667–678, 2005.
- MOON, P.; SPENCER, D. E. *Field theory handbook: including coordinate systems, differential equations and their solutions*. [S.l.]: Springer, 2012.
- MOREIRA-GONZALEZ, A.; PAPAY, F. E.; ZINS, J. E. Calvarial thickness and its relation to cranial bone harvest. *Plastic and reconstructive surgery*, LWW, v. 117, n. 6, p. 1964–1971, 2006.
- NUNEZ, P. L. A study of origins of the time dependencies of scalp eeg: I-theoretical basis. *Biomedical Engineering, IEEE Transactions on*, IEEE, n. 3, p. 271–280, 1981.
- NUNEZ, P. L.; CUTILLO, B. A. *Neocortical dynamics and human EEG rhythms*. [S.l.]: Oxford University Press, USA, 1995.
- NUNEZ, P. L.; SRINIVASAN, R. *Electric fields of the brain: the neurophysics of EEG*. [S.l.]: Oxford university press, 2006.
- NUNEZ, P. L. et al. Eeg coherency: I: statistics, reference electrode, volume conduction, laplacians, cortical imaging, and interpretation at multiple scales. *Electroencephalography and clinical neurophysiology*, Elsevier, v. 103, n. 5, p. 499–515, 1997.
- OOSTENDORP, T. F.; DELBEKE, J.; STEGEMAN, D. F. The conductivity of the human skull: results of in vivo and in vitro measurements. *IEEE transactions on biomedical engineering*, IEEE, v. 47, n. 11, p. 1487–1492, 2000.
- OOSTENVELD, R.; PRAAMSTRA, P. The five percent electrode system for high-resolution eeg and erp measurements. *Clinical neurophysiology*, Elsevier, v. 112, n. 4, p. 713–719, 2001.
- PARDEY, J.; ROBERTS, S.; TARASSENKO, L. A review of parametric modelling techniques for eeg analysis. *Medical engineering & physics*, Elsevier, v. 18, n. 1, p. 2–11, 1996.
- PARK, J. S. et al. A proposal of new reference system for the standard axial, sagittal, coronal planes of brain based on the serially-sectioned images. *Journal of Korean medical science*, v. 25, n. 1, p. 135–141, 2010.

- PICTON, T. *Handbook of electroencephalography and clinical neurophysiology: human event-related potentials*. [S.l.]: Elsevier, Amsterdam, The Netherlands, 1988.
- REYNOLDS, G. D.; RICHARDS, J. E. Cortical source localization of infant cognition. *Developmental neuropsychology*, Taylor & Francis, v. 34, n. 3, p. 312–329, 2009.
- RICHARDS, J. E. Recovering dipole sources from scalp-recorded event-related-potentials using component analysis: principal component analysis and independent component analysis. *International Journal of Psychophysiology*, Elsevier, v. 54, n. 3, p. 201–220, 2004.
- SAITO, Y.; HARASHIMA, H. Tracking of information within multichannel {EEG} record causal analysis in {EEG}. *Yamaguchi N, Fujisawa K (eds) Recent advances in {EEG} and {EMG} data processing*. Elsevier, Elsevier, p. 133–146, 1981.
- SAMESHIMA, K.; BACCALÁ, L. A. *AsympPDC Package v. 2b User Guide*. [S.l.], 2011.
- SANEI, S.; CHAMBERS, J. A. *EEG signal processing*. New York: John Wiley & Sons, 2013.
- SAUSENG, P.; KLIMESCH, W. What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience & Biobehavioral Reviews*, Elsevier, v. 32, n. 5, p. 1001–1013, 2008.
- SCAHILL, R. I. et al. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Archives of neurology*, American Medical Association, v. 60, n. 7, p. 989–994, 2003.
- SCHWAN, H. P.; KAY, C. F. Capacitive properties of body tissues. *Circulation Research*, Am Heart Assoc, v. 5, n. 4, p. 439–443, 1957.
- SENKOWSKI, D. et al. Crossmodal binding through neural coherence: implications for multisensory processing. *Trends in neurosciences*, Elsevier, v. 31, n. 8, p. 401–409, 2008.
- SILFVERHUTH, M. J. et al. Experimental comparison of connectivity measures with simulated eeg signals. *Medical & biological engineering & computing*, Springer, v. 50, n. 7, p. 683–688, 2012.
- SRINIVASAN, R. Anatomical constraints on source models for high-resolution eeg and meg derived from mri. *Technology in cancer research & treatment*, NIH Public Access, v. 5, n. 4, p. 389, 2006.
- SRINIVASAN, R.; NUNEZ, P. L.; SILBERSTEIN, R. B. Spatial filtering and neocortical dynamics: estimates of eeg coherence. *Biomedical Engineering, IEEE Transactions on*, IEEE, v. 45, n. 7, p. 814–826, 1998.
- SRINIVASAN, R. et al. Spatial sampling and filtering of eeg with spline laplacians to estimate cortical potentials. *Brain topography*, Springer, v. 8, n. 4, p. 355–366, 1996.
- STINSTRA, J.; PETERS, M. The volume conductor may act as a temporal filter on the ecg and eeg. *Medical and Biological Engineering and Computing*, Springer, v. 36, n. 6, p. 711–716, 1998.
- STRATTON, J. A. *Electromagnetic theory*. New York: John Wiley & Sons, 2007.

- SZEDERKÉNYI, G.; LAKNER, R.; GERZSON, M. *Intelligent control systems: an introduction with examples*. [S.l.]: Springer Science & Business Media, 2006. v. 60.
- TAKAHASHI, D. Y.; BACCALÁ, L. A.; SAMESHIMA, K. Information theoretic interpretation of frequency domain connectivity measures. *Biological cybernetics*, Springer, v. 103, n. 6, p. 463–469, 2010.
- THAKOR, N. V.; TONG, S. Advances in quantitative electroencephalogram analysis methods. *Annu. Rev. Biomed. Eng.*, Annual Reviews, v. 6, p. 453–495, 2004.
- TOSAKA, M. et al. Superficial subarachnoid cerebrospinal fluid space expansion after surgical drainage of chronic subdural hematoma. *Acta neurochirurgica*, Springer, v. 157, n. 7, p. 1205–1214, 2015.
- TOWLE, V. L. et al. The spatial location of eeg electrodes: locating the best-fitting sphere relative to cortical anatomy. *Electroencephalography and clinical neurophysiology*, Elsevier, v. 86, n. 1, p. 1–6, 1993.
- VARELA, F. et al. The brainweb: phase synchronization and large-scale integration. *Nature reviews neuroscience*, v. 2, n. 4, p. 229–239, 2001.
- VAROTTO, G. et al. Epileptogenic networks of type ii focal cortical dysplasia: a stereo-eeg study. *Neuroimage*, Elsevier, v. 61, n. 3, p. 591–598, 2012.
- VAROTTO, G. et al. Enhanced frontocentral eeg connectivity in photosensitive generalized epilepsies: a partial directed coherence study. *Epilepsia*, Wiley Online Library, v. 53, n. 2, p. 359–367, 2012.
- VARSAVSKY, A.; MAREELS, I.; COOK, M. *Epileptic seizures and the EEG: measurement, models, detection and prediction*. [S.l.]: CRC Press, 2016.
- VOGEL, C. R. *Computational methods for inverse problems*. [S.l.]: Siam, 2002. v. 23.
- WANG, G.; TAKIGAWA, M. Directed coherence as a measure of interhemispheric correlation of eeg. *International journal of psychophysiology*, Elsevier, v. 13, n. 2, p. 119–128, 1992.
- WENDEL, K.; MALMIVUO, J. Correlation between live and post mortem skull conductivity measurements. In: IEEE. *Engineering in Medicine and Biology Society, 2006. EMBS'06. 28th Annual International Conference of the IEEE*. [S.l.], 2006. p. 4285–4288.
- WENDEL, K. et al. The influence of csf on eeg sensitivity distributions of multilayered head models. *IEEE Transactions on Biomedical Engineering*, IEEE, v. 55, n. 4, p. 1454–1456, 2008.
- WENDEL, K. et al. The influence of age and skull conductivity on surface and subdermal bipolar eeg leads. *Computational intelligence and neuroscience*, Hindawi Publishing Corp., v. 2010, p. 9, 2010.
- WERNICKE, C. The aphasic symptom-complex: a psychological study on an anatomical basis. *Archives of Neurology*, American Medical Association, v. 22, n. 3, p. 280–282, 1970.
- WIENER, N. Extrapolation, interpolation and smoothing of stationary time series john wiley & sons inc. and technology press, mtt. *Acta Math.*, Stockk., v. 55, p. 117, 1930.

WOLPAW, J.; WOLPAW, E. W. *Brain-computer interfaces: principles and practice*. [S.l.]: OUP USA, 2012.

WRIGHT, J.; KYDD, R.; SERGEJEV, A. Autoregression models of eeg. *Biological cybernetics*, Springer, v. 62, n. 3, p. 201–210, 1990.

ZHANG, Y.; DRONGELEN, W. V.; HE, B. Estimation of in vivo brain-to-skull conductivity ratio in humans. *Applied physics letters*, v. 89, n. 22, 2006.

APPENDIX A – Head tissue electrical properties

Parameter choices

As we mentioned, we need the radius and conductivity of every shell to characterize each of the considered tissues of the head model.

Radius and thickness

Scalp:

Since the scalp is the outermost tissue of the head, its radius is also the radius head, a common used measure in the latter case is the head circumference. Measurements for subjects with ages range between 17 and 83, with average age of 40 were made in (BUSHBY et al., 1992), obtaining a mean value of $54.5 \pm 3 \text{ cm}$ for women and $57 \pm 3 \text{ cm}$ for men. Similar results was found later in (AYLWARD et al., 2002), where they found an average head circumference of $57.33 \pm 0.36 \text{ cm}$, equivalent to a radius of $r_4 = 9.12 \pm 0.06 \text{ cm}$ for subjects older than 18 years old and $55.89 \pm 2.25 \text{ cm}$ with a radius of $r_4 = 8.89 \pm 0.36$ for subjects of any age group.

Additionally, scalp thickness obtained by extraction from dead and living subjects, founding a mean value of 5.4 mm (HORI et al., 1972). Then, measurements from magnetic resonance images in (BABILONI et al., 1997) result in $6.3 \pm 2.4 \text{ mm}$ with a great variability across subjects and regions of the head. The local scalp thickness was significantly higher in the temporal than in the parietal-occipital and frontal areas.

Skull:

From lateral radiographs of the head, it was measured an average skull thickness of $6.95 \pm 1.7 \text{ mm}$ from subjects with age between 30 to 50 years old, which is the most stationary period of life (ADELOYE; KATTAN; SILVERMAN, 1975). Later, it was found a mean thickness of $5.2 \pm 0.8 \text{ mm}$ from an adult human skull (LAW, 1993) and $6.32 \pm 0.07 \text{ mm}$ (MOREIRA-GONZALEZ; PAPAY; ZINS, 2006) from 281 skulls. Alternatively, from autopsia the mean measured value was $6.29 \pm 1.4 \text{ cm}$ (LYNNERUP, 2001).

CSF:

The cerebrospinal fluid compartment depends on the dimensions of its surrounding tissues because is a liquid. However, we can look for the normal volume value of this fluid, which is $104.48 \pm 29.21 \text{ cm}^3$ for subarachnoid CSF and $121.4 \pm 34 \text{ cm}^3$ in total (KIKINIS et al., 1992). Since the CSF sorrounds the brain entirely, we estimate the thickness of the subarachnoid space as a spherical shell with the known volume surrounding an inner concentric sphere corresponding to the brain, with its measured volume. Such a calculated value most lie under 3 mm as it was found in (TOSAKA et al., 2015).

$$V_{brain} + V_{CSF} = \frac{4\pi}{3} r_{CSF}^3 \quad (\text{A.1})$$

So,

$$Thickness_{CSF} = r_{CSF} - r_{brain} \quad (\text{A.2})$$

where the brain radius r_{brain} and CSF radius r_{CSF} are used provisionally to calculate the corticocranial space or CSF thickness.

Brain:

The brain dimensions, are measure generally in terms of its volume. In (AYLWARD et al., 2002), they performed volumetric MRI and segmentated brain from CSF and extra cerebral tissue, including the cerebellum and brainstem, founding that the brain volume found was $1269.54 \pm 114.99 \text{ cm}^3$. Later, in (SCAHILL et al., 2003) Rachael et.al found a brain volume of $1275 \pm 0.7 \text{ cm}^3$ for healthy subjects in an age group from 20 to 40 years old, where there is no significant association between age and hippocampal volume. More recently the measurements converge to 1130 cm^3 for females and 1260 cm^3 for males (COSGROVE; MAZURE; STALEY, 2007). As we mentioned above, this parameter is used to calculate the thickness of the subarachnoid space and therefore, the brain radius, particularly we used the most recent value for men, 1260 cm^3 .

Summary

All the radius, thickness and proportions are registered in Table 3. Note that the scale proportions between the radius agree with the values used in (LAI et al., 2005; FERREE; ERIKSEN; TUCKER, 2000) for a 4-spheres head model, 1:0.93:0.86:0.84.

Conductivity

We look for the electrical conductivity of each tissue to be considered in the head model or the ratio between them, which is an usual reported value.

Table 3 – External radius and thickness chosen to use in the spherical model.

Tissue	Radius (cm)	Thickness (cm)	proportion
Scalp	9.12	0.63	1
Skull	8.49	0.63	0.9309
CSF	7.86	0.18	0.8618
Brain	7.68	~	0.8421

Source: Own authorship.

Brain:

In general, the conductivity brain reported in different studies converge to similar values. In living tissue, was measured a brain conductivity of $0.285 S/m$ (LATIKKA; KUURNE; ESKOLA, 2001), concording with a previous report of $0.26 S/m$ in (FERREE; ERIKSEN; TUCKER, 2000). More recent values for conductivity are a little higher, as the case of (GONÇALVES et al., 2003; GUTIÉRREZ; NEHORAI; MURAVCHIK, 2004; WENDEL; MALMIVUO, 2006; GEODESICS, 2008; GABRIEL; PEYMAN; GRANT, 2009), with an average value of $0.295 \pm 0.04 S/m$ which is chosen to the spherical model and is very close to all the values reported in several studies.

CSF:

The electrical conductivity of the human cerebrospinal fluid at body temperature is $\sigma_{CSF} = 1.79 S/m$ (BAUMANN et al., 1997), such a value was validated in (FERREE; ERIKSEN; TUCKER, 2000) minimizing the error for a 4-sphere head model. Posteriorly, it was measured in living patients, obtaining an average of $1.25 S/m$ (LATIKKA; KUURNE; ESKOLA, 2001). Then, in 2009, the value was obtained from living pigs, to be $1.59 \pm 1.18 S/m$ (GABRIEL; PEYMAN; GRANT, 2009). This last value validated a previous measurement of the CSF conductivity in (GEODESICS, 2008).

Skull:

Both measurements, in vivo and in vitro, revealed a skull conductivity of about $0.015 S/m$ and a brain to skull conductivity ratio of 15, considering same conductivity for scalp and brain (OOSTENDORP; DELBEKE; STEGEMAN, 2000). Similar skull conductivity was found in (FERREE; ERIKSEN; TUCKER, 2000), with a value of $0.018 S/m$. In 2003, a brain to skull conductivity ratio of 42 ± 27 with brain conductivity of $0.33 \pm 7.7 S/m$ were reported in (GONÇALVES et al., 2003). Another study measured the brain to skull conductivity ratio in 5 living subjects through cortical imaging technique and simultaneous intra and extra cranial potential recordings with a subdural excitation. Using head models with three and four shells, the optimal values reported for the best inverse

solution are 25.7 ± 7 and 22.6 ± 7 respectively, they considered that the conductivities of the scalp and brain are equal (LAI et al., 2005) and the CSF conductivity as the triple of them. Similar results were reported in (GUTIÉRREZ; NEHORAI; MURAVCHIK, 2004), with brain to skull conductivity ratios of 25.38 and 25.10 for two subjects. Two years later, in (WENDEL; MALMIVUO, 2006), the live skull conductivity measurement was $0.053 S/m$ much higher than any other reported, they claim that the brain to skull conductivity ratio ranges from 5 to 10, which is much lower than all previous measurements. In the same year, a value of $\sigma_{brain}/\sigma_{skull} = 18.7 \pm 2.1 S/m$ obtained from experiments in vivo was reported in (ZHANG; DRONGELEN; HE, 2006). Posteriorly, a brain to skull conductivity ratio of 15 was showed in (GEODESICS, 2008), where a noninvasive technique was used to measure conductivity in two living subjects, and optimizing the conductivity for a realistically shaped high-resolution finite difference head model. More recently in (WENDEL et al., 2010), a scalp to skull conductivity ratio of 15 was reported for most adults. This last result was chosen to be used in the head model, since it is the more recent and it was calibrated for a head model.

Scalp:

The scalp conductivity values found have no convergence, with a range from $0.33 S/m$ (GONÇALVES et al., 2003), $0.5 S/m$ (GEODESICS, 2008) to $0.88 S/m$ (CLERC et al., 2005). However, the scalp to brain conductivity ratio from (FERREE; ERIKSEN; TUCKER, 2000; LAI et al., 2005; GEODESICS, 2008) converges to 1.44, providing a value close to $0.43 S/m$ used in (WENDEL et al., 2010).

Summary

See the table 4 with the chosen conductivities for the parameters of the head model.

Table 4 – Mean of conductivities reported and chosen value. In S/m

Tissue	Conductivity [S/m]	Ratio
Brain	0.295	1/1.46
CSF	1.59	~
Skull	0.0287	1/15
Scalp	0.43	1

Source: Own authorship.

APPENDIX B – Volume conduction model of the head

The goal of this section is to make a revision of a forward solution to the scalp potential generated by a cortical source, which was developed by (NUNEZ; SRINIVASAN, 2006). The head model is an idealization of the head, it is sphere shaped composed by four concentric shells, where each one is an isotropic homogeneous medium that represents a head tissue: brain, CSF (cerebrospinal fluid), skull and scalp. The inclusion of CSF is an improvement over the classic 3-sphere model. It is important because of the high CSF conductivity which implies a low resistance path to the current with respect to the skull layer (CHO et al., 2015; WENDEL et al., 2008; NUNEZ; SRINIVASAN, 2006). The current source is considered as a dipole along the z axis, at $(r_0, 0, 0)$ (where $r_0 < r_1$) to take advantage of the azimuthal symmetry, where the scalp potential only depends on the theta angle.

Assumptions

Considering the macroscopic scale and the low frequencies of ion oscillations in the tissues, capacitive effects are negligible. Thus the fields are uncoupled and quasistatic, the electric field can be expressed as the gradient of the potential

$$\mathbf{E} = -\nabla\Phi \quad (\text{B.1})$$

According with experimental results, the tissues of interest are linear in their conductive properties. Therefore, the Ohm's law for linear conductors (See equation (B.2)) is a good approximation to describe the current density in regions beyond the site of an action potential.

$$\mathbf{J}_{ohm} = \sigma\mathbf{E} \quad (\text{B.2})$$

Additionally, negligible tissue capacitance (SCHWAN; KAY, 1957) implies that equation of charge conservation becomes

$$\nabla \cdot \mathbf{J} = 0 \quad (\text{B.3})$$

The active regions can be included through the representation of sources by a distribution of an impressed current density or equivalently, a current dipole moment per unit volume, $\mathbf{J}_s$ (GESELOWITZ, 1967), modifying equation (B.2) in active regions to:

$$\mathbf{J} = \sigma\mathbf{E} + \mathbf{J}_s \quad (\text{B.4})$$

Figure 60 – Homogeneous medium with active regions containing charges and therefore, current sources $s(\mathbf{r}, t)$.

Source: Original.

Combined, the above equations lead to (B.5) that relates current sources to the potential distribution in the volume conductor

$$\begin{aligned}\nabla \cdot \mathbf{J} &= \nabla \cdot \sigma \mathbf{E} + \nabla \cdot \mathbf{J}_s \\ 0 &= -\nabla \cdot \sigma \nabla \Phi + \nabla \cdot \mathbf{J}_s \\ 0 &= -\sigma \nabla^2 \Phi - s(\mathbf{r}, t)\end{aligned}\tag{B.5}$$

where the volume source current is defined by

$$s(\mathbf{r}, t) = -\nabla \cdot \mathbf{J}_s(\mathbf{r}, t)\tag{B.6}$$

Equation (B.5) can be divided into two cases depending on the region within the homogeneous medium: *Laplace's equation* for passive regions where there are no current sources

$$\sigma \nabla^2 \Phi = 0\tag{B.7}$$

and *Poisson's equation* for active regions with current sources $s(\mathbf{r}, t)$,

$$\sigma \nabla^2 \Phi = s(\mathbf{r}, t)\tag{B.8}$$

This holds for the brain, the innermost sphere containing neurons that convert chemical energy to electric energy, which behave as electric current dipoles. Thus, the brain is the active region where there are electrical charges concentrated in certain subvolumes, as indicated in Figure 60.

Unique solutions to both differential equations are specified by satisfying the boundary conditions on all surfaces.

Solution to Laplace's equation in spherical coordinates

The potential at any point where there is no current source is described by the Laplace's equation. Because of the spherical shape of the head model, spherical coordinates (r, θ, ϕ) are convenient as indicated in the Figure 61, where the Laplace's equation is given

Figure 61 – Spherical coordinates (r, θ, ϕ) as commonly used in physics: radial distance r , polar angle θ , and azimuthal angle ϕ .

Source: Original.

by

$$\nabla^2 \Phi(\mathbf{r}) = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \Phi}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \Phi}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \left(\frac{\partial^2 \Phi}{\partial \phi^2} \right) = 0 \quad (\text{B.9})$$

The general solution to the Laplace's equation in spherical coordinates is (MOON; SPENCER, 2012)

$$\Phi_L(r, \theta) = \sum_{l=0}^{\infty} \left[A_l \left(\frac{r}{a} \right)^l + \frac{B_l}{r^{l+1}} \right] P_l(\cos \theta) \quad (\text{B.10})$$

where $P_l(\cos \theta)$ is the Legendre polynomial of l th degree, the theta angle corresponds to the position of the field point. The values of the coefficients A_l and B_l are determined applying the appropriate boundary conditions at each surface. If the medium is inside a sphere ($r = b$), B_l must be zero to ensure a finite potential at $r = 0$, resulting

$$\Phi_L(r, \theta) = \sum_{l=0}^{\infty} A_l \left(\frac{r}{b} \right)^l P_l(\cos \theta) \quad (\text{B.11})$$

Alternatively, if the medium is outside a sphere ($r = a$), $A_l = 0$

$$\Phi_L(r, \theta) = \sum_{l=0}^{\infty} B_l \left(\frac{a}{r} \right)^{l+1} P_l(\cos \theta) \quad (\text{B.12})$$

Therefore, the potential in a spherical shell bounded by $r = a$ and $r = b$ ($a \leq r \leq b$) is defined by

$$\Phi_i(r, \theta) = \sum_{l=0}^{\infty} \left[A_l \left(\frac{r}{b} \right)^l + B_l \left(\frac{a}{r} \right)^{l+1} \right] P_l(\cos \theta) \quad a \leq r \leq b \quad (\text{B.13})$$

Solution to Poisson's equation

The Poisson's equation corresponds to mediums with charges, so we start to compute the potential in a field point generated by a dipole in an homogeneous medium.

Potential in an infinite homogeneous medium

The potential at $\mathbf{r}$ generated by a distributed current of density $\mathbf{J}_s$ within an homogeneous volume having conductivity σ is (STRATTON, 2007)

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \int_V \frac{\nabla \mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dv' \quad (\text{B.14})$$

To prove that the potential in equation (B.14) is solution to the Poisson's equation, let apply the laplacian operator with respect to $\mathbf{r}$

$$\begin{aligned} \nabla^2 \Phi(\mathbf{r}) &= \frac{1}{4\pi\sigma} \int_V \nabla \mathbf{J}_s(\mathbf{r}') \nabla^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dv' \\ &= \frac{1}{4\pi\sigma} \int_V \nabla \mathbf{J}_s(\mathbf{r}') 4\pi \delta(\mathbf{r} - \mathbf{r}') dv' \\ &= \frac{\nabla \mathbf{J}_s(\mathbf{r})}{\sigma} \\ &= \frac{s(\mathbf{r}, t)}{\sigma} \end{aligned} \quad (\text{B.15})$$

which use the singular nature of the laplacian of the inverse of $(1/R)$ (HNIZDO, 2000) to complete our check on equation (B.14) as a solution of Poisson's equation, (B).

We are interested in the scenario where the source is concentrated at a dipole over the z axis, which impresses a current of magnitude I , with a pole separation of $2d$ and centered at $\mathbf{r}_0 = (r_0, \theta_0 = 0, \phi_0 = 0, 2\pi)$. So, the potential generated by such current source is solution to the Poisson's equation

$$\nabla^2 \Phi = \frac{I}{\sigma} [\delta(\mathbf{r} - \mathbf{r}_0 - \mathbf{d}) - \delta(\mathbf{r} - \mathbf{r}_0 + \mathbf{d})] \quad (\text{B.16})$$

According to equation (B.14), the potential at $\mathbf{r}$ is

$$\Phi(\mathbf{r}) = \frac{I}{4\pi\sigma} \left(\frac{1}{|\mathbf{r} - \mathbf{r}_0 - \mathbf{d}|} - \frac{1}{|\mathbf{r} - \mathbf{r}_0 + \mathbf{d}|} \right) \quad (\text{B.17})$$

As the head model is spherical, we are looking for a more convenient expression in the appropriate coordinates.

Let us express the distance R (see Figure 62) from each source, $\mathbf{r}_0 = (r_0 \pm d, \theta_0 = 0, \phi)$ to the field point, $\mathbf{r} = (r, \theta, \phi)$ as

$$\begin{aligned} |\mathbf{r} - (\mathbf{r}_0 \pm \mathbf{d})| &= \sqrt{[\mathbf{r} - (\mathbf{r}_0 \pm \mathbf{d})] \cdot [\mathbf{r} - (\mathbf{r}_0 \pm \mathbf{d})]} \\ &= \sqrt{r^2 + (r_0 \pm d)^2 - 2r(r_0 \pm d) \cos \theta} \\ &= r \sqrt{1 + [(r_0 \pm d)/r]^2 - 2[(r_0 \pm d)/r] \cos \theta} \end{aligned} \quad (\text{B.18})$$

Figure 62 – Source and field point vectors with respect to the origin O. Consider $d \ll r_0$ in the figure.

Source: Original.

set $h = (r_0 \pm d)/r$ and $x = \cos \theta$

$$|\mathbf{r} - (\mathbf{r}_0 \pm \mathbf{d})| = r\sqrt{1 - 2hx + h^2} \quad (\text{B.19})$$

so, the inverse of such distance, which appears in equation (B.18) becomes

$$\frac{1}{|\mathbf{r} - (\mathbf{r}_0 \pm \mathbf{d})|} = \frac{1}{r\sqrt{1 - 2hx + h^2}} \quad (\text{B.20})$$

Now, set $y = 2hx - h^2$ and making the power expansion of the expression (B.20) in Taylor series evaluating at $y = 0$:

$$\begin{aligned} \frac{1}{\sqrt{1 - 2hx + h^2}} &= \frac{1}{\sqrt{1 - y}} \\ &= f(y) \\ &= f(0) + f'(0)y + \frac{f''(0)}{2!}y^2 + \frac{f'''(0)}{3!}y^3 + \dots \\ &= 1 + \frac{y}{2} + \frac{3y^2}{8} + \frac{5y^3}{16} + \frac{35y^4}{128} + \dots \end{aligned} \quad (\text{B.21})$$

for values of $|h| < 1$ the series converges, that is satisfied because our interest is the potential at locations farther to the center of the head than the source ($r > r_0 \Leftrightarrow h = r_0/r < 1$).

Replacing again $y = 2hx - h^2$ in equation (B.21), expanding and factoring

$$\begin{aligned} \frac{1}{\sqrt{1 - 2hx + h^2}} &= 1 + hx + h^2 \left(\frac{3x^2}{2} - \frac{1}{2} \right) + h^3 \left(\frac{5x^3}{2} - \frac{3x}{2} \right) + \dots \\ &= 1 + hx + \frac{h^2}{2} (3x^2 - 1) + \frac{h^3}{2} (5x^3 - 3x) + \frac{h^4}{8} (35x^4 - 30x^2 + 3) + \dots \end{aligned} \quad (\text{B.22})$$

Note that the coefficient of h^l corresponds to the Legendre Polynomial of order l (BOAS, 1966), therefore the series expansion can be expressed as

$$\frac{1}{\sqrt{1 - 2hx + h^2}} = P_0(x) + P_1(x)h + P_2(x)h^2 + P_3(x)h^3 \dots = \sum_{l=0}^{\infty} P_l(x)h^l \quad (\text{B.23})$$

Replacing the previous result in equation (B.17) results

$$\begin{aligned}\Phi(\mathbf{r}) &= \frac{Ir}{4\pi\sigma} \sum_{l=0}^{\infty} \left(\frac{r_0+d}{r}\right)^l P_l(\cos\theta) - r \sum_{l=0}^{\infty} \left(\frac{r_0-d}{r}\right)^l P_l(\cos\theta) \\ &= \frac{I}{4\pi\sigma} \sum_{l=0}^{\infty} \left[\frac{(r_0+d)^l - (r_0-d)^l}{r^{l+1}} \right] P_l(\cos\theta) \quad r > r_0\end{aligned}\quad (\text{B.24})$$

Now, the factor containing the dipole distance is expressable as a binomial series

$$\begin{aligned}(r_0+d)^l &= \sum_{k=0}^l \binom{l}{k} r_0^{l-k} d^k \\ &= r_0^l + l r_0^{l-1} d + l(l-1) r_0^{l-2} d^2 + l(l-1)(l-2) r_0^{l-3} d^3 \dots \\ &= r_0^l \left(1 + l \left(\frac{d}{r_0}\right) + l(l-1) \left(\frac{d}{r_0}\right)^2 + l(l-1)(l-2) \left(\frac{d}{r_0}\right)^3 \dots \right)\end{aligned}\quad (\text{B.25})$$

Since $d \ll r_0$ is assumed, the dominant term in the expansion will be to first order of d/r_0 . Then,

$$\begin{aligned}r_0+d)^l - (r_0-d)^l &= r_0^l \left(1 + \frac{dl}{r_0} \right) - r_0^l \left(1 - \frac{dl}{r_0} \right) \\ &= r_0^l \frac{2dl}{r_0} \\ &= 2dl \frac{r_0^l}{r_0^2}\end{aligned}$$

Substituting in equation (B.24) it is found the potential in an homogeneous medium due to a dipole source at r_0 in spherical coordinates

$$\Phi_P(\mathbf{r}) \cong \frac{Id_0}{4\pi\sigma r_0^2} \sum_{l=1}^{\infty} \left(\frac{r_0}{r}\right)^{l+1} l P_l(\cos\theta) \quad r > r_0 \quad (\text{B.26})$$

where $d_0 = 2d$. Equation (B.26) is the *particular solution* of the Poisson's equation (B.16).

Uniqueness solution of Poisson's equation

The potential in equation (B.14) obeys Poisson's equation at each point within the volume V, when the surface boundaries are at infinity. If the medium is finite, the integration needs to exclude sources outside the volume V. This makes it clear that the particular solution, (B.14) is neither unique nor complete and it has no information about the position and shape of the volume medium. Such information helps to prescribed conditions at the boundary of the volume, provided by the solution of the Laplace's equation (homogeneous solution of (B)). The superposition principle allows to express the complete solution of the Poisson's equation as

$$\Phi(r, \theta, \phi) = \Phi_p + \Phi_h \quad (\text{B.27})$$

where Φ_P and Φ_H are the particular and homogeneous solution of the Poisson's equation in a volume V .

The innermost sphere is the only one containing sources in the head model. Therefore, the potential must obey the Poisson's equation for $(r_0 < r < r_1)$. It is required a finite solution at every point, since the origin is within the innermost sphere, $B_l(1) = 0$ to satisfy the former condition. Additionally, all the series expansion must converge, resulting in an homogenous solution:

$$\Phi_H(\mathbf{r}) = \sum_{l=1}^{\infty} \left[A_l(1) \left(\frac{r}{r_1} \right)^l \right] P_l(\cos \theta) \quad r_0 < r \leq r_1 \quad (\text{B.28})$$

and the complete solution for the sphere associated with the brain with conductivity σ_1 is

$$\Phi_1(r, \theta, \phi) = \sum_{l=0}^{\infty} \left[\frac{Id_0}{4\pi\sigma_1 r_0^2} l \left(\frac{r_0}{r} \right)^{l+1} + A_l(1) \left(\frac{r}{r_1} \right)^l \right] P_l(\cos \theta) \quad (\text{B.29})$$

to completely specified the potential, the $A_l(1)$ coefficients are calculated to satisfy boundary conditions as it is explained in the following section.

Piecewise uniform medium and boundary conditions

So far, the medium was assumed uniform, allowing the use of simple expressions that are valid only for uniform homogeneous media. Next, we consider inhomogeneities by approximating the volume conductor by a collection of regions, each one of which is homogeneous, resistive, and isotropic, where the current density is linearly related to the electric field intensity. The boundary conditions relate the different mediums, completing the specification of the electric field throughout the model.

The behaviour of an electrostatic field can be described by the continuity equation

$$\sigma \nabla \cdot \mathbf{E} = 0 \quad (\text{B.30})$$

and, because of equation (B.1), the electric field is irrotational:

$$\nabla \times \mathbf{E} = 0 \quad (\text{B.31})$$

From equation (B.30), we know that on the boundary, where the conductivity changes abruptly, the condition is

$$\mathbf{n} \cdot (\sigma_i \mathbf{E}_i - \sigma_{i+1} \mathbf{E}_{i+1}) = 0 \quad (\text{B.32})$$

and the continuity condition followed from (B.31) becomes

$$\mathbf{n} \times (\mathbf{E}_i - \mathbf{E}_{i+1}) = 0 \quad (\text{B.33})$$

Figure 63 – Surface separating two adjacent homogeneous subregions i and $i + 1$.

Source: Original.

The latter conditions represent the continuity of radial current density and of tangential potential respectively (BUDAK; SAMARSKII; TIKHONOV, 2013)

$$\Phi_i = \Phi_{i+1} \quad \text{Tangential potential continuity} \quad (\text{B.34a})$$

$$\sigma_i \frac{\partial \Phi_i}{\partial r} = \sigma_{i+1} \frac{\partial \Phi_{i+1}}{\partial r} \quad \text{Normal current continuity} \quad (\text{B.34b})$$

To obtain the unknown coefficients $A(i)$ and $B(i)$ one must constrain the problem by determining boundary conditions. At each interface between two layers i and $i + 1$ (see Figure 63), one must satisfy the continuity conditions mentioned above. The tangential potential continuity at the interface $r = r_i$ separating two bounded mediums without sources is expressed as

$$A_l(i+1) \left(\frac{r_i}{r_{i+1}} \right)^l + B_l(i+1) = A_l(i) + B_l(i) \left(\frac{r_{i-1}}{r_i} \right)^{l+1} \quad (\text{B.35})$$

and the normal current density continuity results in

$$A_l(i+1) \frac{l}{r_{i+1}} \left(\frac{r_i}{r_{i+1}} \right)^{l-1} - B_l(i+1) \frac{l+1}{r_i} = \frac{\sigma_i}{\sigma_{i+1}} \left[A_l(i) \frac{l}{r_i} - B_l(i) \frac{l+1}{r_{i-1}} \left(\frac{r_{i-1}}{r} \right)^{l+1} \right] \quad (\text{B.36})$$

The surrounding medium of the scalp (outermost shell) is the air, which is a perfect dielectric with conductivity zero, therefore no current density is fluxing out of the head and consequently:

$$\sigma_4 \frac{\partial \Phi_4}{\partial r} = 0 \quad (\text{B.37})$$

at the outer surface of the scalp.

Model coefficients

Solving the continuity equations, starting from the last one (equation (B.37)), we can establish the following quantities:

$$r_{ij} = \frac{r_i}{r_j} \quad \sigma_{ij} = \frac{\sigma_i}{\sigma_j}$$

$$\begin{aligned}
M_l &= \frac{l}{l+1} r_{43}^{l+1} \\
N_l &= \frac{r_{34}^l - \frac{l+1}{l} M_l}{r_{34}^l + M_l} \\
V_l &= \frac{\sigma_{34} - N_l}{r_{23}^{l+1} \left(\frac{l+1}{l} \sigma_{34} + N_l \right)} \\
R_l &= \frac{r_{23}^l - \frac{l+1}{l} V_l}{r_{23}^l + V_l} \\
Y_l &= \frac{\sigma_{23} - R_l}{r_{12}^{l+1} \left(\frac{l+1}{l} \sigma_{23} + R_l \right)} \\
Z_l &= \frac{r_{12}^l - \frac{l+1}{l} Y_l}{r_{12}^l + Y_l}
\end{aligned}$$

So, the coefficients result:

$$B_l(4) = A_l(4) M_l \quad (\text{B.38})$$

$$A_l(4) = \frac{A_l(3) + B_l(3) r_{23}^{l+1}}{r_{34}^l + M_l} \quad (\text{B.39})$$

$$B_l(3) = A_l(3) V_l$$

$$A_l(3) = \frac{A_l(2) + B_l(2) r_{12}^{l+1}}{r_{23}^l + V_l}$$

$$B_l(2) = A_l(2) Y_l$$

$$A_l(2) = \frac{A_l(1) + \Phi_0 r_{01}^{l+1}}{r_{12}^l + Y_l}$$

$$A_l(1) = \Phi_0 r_{01}^{l+1} \frac{Z_l + \sigma_{12} \frac{l+1}{l}}{\sigma_{12} - Z_l}$$

where

$$\Phi_0 = \frac{I d_0}{4\pi\sigma_1 r_0^2} l \quad (\text{B.40})$$

which is the potential produced by a dipole in an infinite medium of conductivity σ_1 at distance r_0 .

After some manipulations we find that the quantity Φ_0 can be factorized because it is a factor for all of the coefficients $A_l(i)$ and $B_l(i)$. So, for $A_l(1)$ and $A_l(2)$ take $\Phi_0 = 1$ and take out the real value of that quantity in the following way:

$$\Phi_i(r, \theta) = \frac{I d_0}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} \left[A_l \left(\frac{r}{r_i} \right)^l + B_l \left(\frac{r_{i-1}}{r} \right)^{l+1} \right] l P_l(\cos \theta) \quad r_{i-1} < r < r_i \quad (\text{B.41})$$

Note that the sum starts from the term $l = 1$ according with the current conservation in the case of a dipole source. Now we have a new expression for each of the spherical shells with the amplitude of the dipole source explicitly expressed.

Scalp potential

The potential at the surface of the scalp, at $r = r_4$ produced by a radial dipole at the cortex is given by

$$\begin{aligned}\Phi_{scalp}(\theta, \phi) &= \Phi_4(r_4, \theta, \phi) \\ &= \frac{Id_0}{4\pi\sigma r_0^2} \sum_{l=1}^{\infty} [A_l(4) + B_l(4)r_{34}^{l+1}] l P_l(\cos \theta)\end{aligned}\quad (\text{B.42})$$

For convenience, let us make $H_l = [A_l(4) + B_l(4)r_{34}^{l+1}] l$. Thus, the scap potential can be expressed simply as

$$\Phi_{scalp}(\theta, \phi) = \frac{Id_0}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} H_l P_l(\cos \theta) \quad (\text{B.43})$$

The solution given in equation (B) considers a radial dipole on the z axis exclusively. The generalization of such a result has to consider a radial dipole at any angle (θ_0, ϕ_0) in the cortex. The *addition theorem* (ARFKEN, 2013) for spherical harmonics provides an useful tool because of the association among Legendre polynomials and spherical harmonics, it establishes that

$$P_l(\cos \chi) = \frac{4\pi}{2l+1} \sum_{m=-l}^l Y_{lm}(\theta, \phi) Y'_{lm}(\theta', \phi') \quad (\text{B.44})$$

where χ describes the angle between two unit vectors oriented to θ, ϕ and θ', ϕ' . $Y_{lm}(\theta, \phi)$ is the spherical harmonic function of degree l and order m and $Y'_{lm}(\theta, \phi)$ is its complex conjugate. Spherical harmonics form a complete set of orthogonal functions on the sphere and therefore are the basis to the expansion of a general function on the surface of a sphere. Inserting this result (equation (B.44)) back into equation (B) yields

$$\Phi_{scalp}(\theta, \phi, \theta_0, \phi_0) = \frac{Id_0}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} \frac{4\pi}{2l+1} H_l l \sum_{m=-l}^l Y_{lm}(\theta, \phi) \cdot Y'_{lm}(\theta_0, \phi_0) \quad (\text{B.45})$$

and for a unit moment dipole

$$G_{scalp}(\theta, \phi, \theta_0, \phi_0) = \frac{1}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} \frac{4\pi}{2l+1} H_l \sum_{m=-l}^l Y_{lm}(\theta, \phi) \cdot Y'_{lm}(\theta_0, \phi_0) \quad (\text{B.46})$$

The solution given by equation (B.46) corresponds to Green's function for Poisson's equation (B.26) for the scalp surface potential (ARFKEN, 2013; SRINIVASAN et al., 1996). That is, the scalp potential, which satisfies the appropriate boundary conditions, generated by a unit point source located at (r_0, θ_0, ϕ_0) , in our case such a source is a dipole.

Note that because of the addition theorem, we can also express the Green's function as:

$$G_{scalp}(\theta, \phi, \theta_0, \phi_0) = \frac{1}{4\pi\sigma_1 r_0^2} \sum_{l=1}^{\infty} H_l P_l \cos \chi \quad (\text{B.47})$$

where χ is the angle between the field point or sensor location and the dipole.

APPENDIX C – Dipole sources

Our analyses is about macroscale, so it is important to take into account the cross-scale transformation from action potentials produce by single neurons to current generated by entire cortical regions. To manage the cross-scale issue, let think about the analysis from electromagnetic theory. In particular the two formulations of the Maxwell's equations, which can be for microscale or macroscale scenarios. As we mentioned, the microscale version takes into account the position and intensity of every single charge inside the medium. For macroscopic aggregates of matter, that kind of information is totally unknown, even in a small volume of cortex is impossible to stablish the exact position of all charges generated in a biochemical process, so the solution of the equations is impossible. Conversely, the macroscale Maxwell equations describe large-scale behaviour without considering these single charge scale details (JACKSON, 1999). Similarly, for the purpose of quantifying the dynamics of 10^{10} cortical neurons, it is employed intermediate scale sources, known as *mesoscopic sources* which consist of sufficiently large number of neurons so as to exhibit certain average properties which are independent of its exact inner circuitry.

Cortical organisation is such that the analysis of the electrical activity generated differs significantly depending on the scale of interest. At subregional scale, cortical morphology is characterized by its columnar functional organisation consisting of *macro-columns*, with a diameter of $500 - 800 \mu m$ and approximately $1 mm^3$ of tissue volume that produce *meso-scopic* fields. The tangential connections between macrocolumns are organized on the principle of functional relatedness and not simple physical proximity (FAVOROV; WHITSEL; TOMMERDAHL, 2015). Smaller still are the *minicolumns* which are attributable to be radial cords of neuronal cells about $30 - 50 \mu m$ in diameter that produce *micro-scopic* fields (See Figure 64) (VARSAVSKY; MAREELS; COOK, 2016; CASANOVA; OPRIS, 2015). The vast majority (about 85%) of cell axons are aligned normal to the local cortical surface ().

Each unified source formed of an arrangement of smaller sources is defined by its electric dipole moment per unit volume

$$\mathbf{P}(\mathbf{r}, t) = \frac{1}{W} \iiint_W \mathbf{w} s(\mathbf{r}, \mathbf{w}, t) dW(\mathbf{w}) \quad (\text{C.1})$$

where W represents a small volume of tissue, where $s(\mathbf{r}, \mathbf{w}, t)$ is the local volume source current inside a tissue volume with vector location $\mathbf{r}$, and $\mathbf{w}$ is the location vector of sources within $dW(\mathbf{w})$ (NUNEZ; SRINIVASAN, 2006). The vector $\mathbf{r}$ locates the unified sources, where the vector $\mathbf{w}$ locates the microscopic current sources, as in Figure 65. W tissue volumes must satisfy two conditions (JACKSON, 1999; WOLPAW; WOLPAW,

Figure 64 – Visual representation of different scales found in the cortex.

Source: (VARSAVSKY; MAREELS; COOK, 2016).

Figure 65 – Visual representation of a W volume tissue. The mixing of sources and sinks ($s(\mathbf{r}, \mathbf{w}, t)$) results in a dipole moment per unit volume $\mathbf{P}(\mathbf{r}, t)$.

Source: Original.

2012):

1. Electroneutrality at EEG frequencies: current consists of movement of positive and negative ions in opposite directions, but the total charge in the tissue volume is essentially zero. Thus, the scale of W should be large enough to contain many microsources, so the mixing of microsources and microsinks will be approximately balanced.
2. The size of the tissue volume W should be sufficiently small compared to the recording distance, ensuring that quadrupole and higher terms contributions to be negligible.

Therefore, we consider a mesosource generated by a macrocolumn to be $\mathbf{P}(\mathbf{r}, t)$, with 1mm^2 of cross section area and 3 mm of length, oriented radially and with a current per unit volume of $1\mu\text{A}/\text{mm}^3$ (SRINIVASAN, 2006; VARSAVSKY; MAREELS; COOK, 2016), where the source length is assumed to be the average tick of the cortex, since nearly all EEG signals are generated by cortical sources. That mesosource choice seems adequate because the macrocolumn scale is large enough to not distinguish the source mixing caused by approximately 10^9 distributed *inhibitory* and *excitatory* synapses producing current in opposite directions. Additionally, the length of the mesosource is much less than the cortex-scalp distance, which is in average of $14.5 \pm 1.4\text{mm}$ (HAEUSSINGER et al., 2011).

APPENDIX D – Almost diagonal leadfield matrix

Lemma 4. *Given a leadfield matrix $\mathbf{\Omega}$ of the form:*

$$\mathbf{\Omega} = \begin{bmatrix} \Omega_{11} & & \varepsilon \\ & \ddots & \\ \varepsilon & & \Omega_{KK} \end{bmatrix} \quad (6.13 \text{ revisited})$$

The elements of $\mathbf{B} = \mathbf{\Omega A \Omega}^{-1}$ can be approximated by

$$b_{ij} \approx \frac{\Omega_{ii}}{\det(\mathbf{\Omega})} \varepsilon \left(a_{ii} g_{ji} + \sum_{\substack{k=1 \\ k \neq i \\ k \neq j}}^K a_{ik} g_{jk} \right) + \frac{\Omega_{ii}}{\Omega_{jj}} a_{ij} \quad (D.1)$$

where g_{jk} is a polynomial of ε with order $K - 1$ and without independent term (order zero).

Proof

Given an almost diagonal lead field matrix (eq. (6.13)), with cofactors C_{ijk} . Its determinant can be expressed as

$$\det(\mathbf{\Omega}) = \Omega_{KK} C_{KKK} + \varepsilon \sum_{m=1}^{K-1} C_{Km_K}$$

where the subscript K represents the size of the matrix from which C_{ijk} is cofactor.

Note that the (i, i) submatrix of $\mathbf{\Omega}$ is almost diagonal, preserving the form of equation (6.13). Therefore, we can express the diagonal cofactors with the same form of $\det(\mathbf{\Omega})$ in terms of cofactors from smaller matrices

$$\begin{aligned} \det(\mathbf{\Omega}) &= \Omega_{KK} \left(\Omega_{K-1,K-1} C_{K-1,K-1,K-1} + \varepsilon \sum_{m=1}^{K-2} C_{K-1,m_{K-1}} \right) + \varepsilon \sum_{m=1}^{K-1} C_{Km_K} \\ &= \Omega_{KK} \Omega_{K-1,K-1} C_{K-1,K-1,K-1} + \varepsilon \left(\Omega_{KK} \sum_{m=1}^{K-2} C_{K-1,m_{K-1}} + \sum_{m=1}^{K-1} C_{Km_K} \right) \end{aligned}$$

Extending all the diagonal cofactors iteratively, we get to

$$\det(\mathbf{\Omega}) = \prod_{k=1}^K \Omega_{kk} + \varepsilon F_K \quad (D.2)$$

where F_K represents all the terms associated to non-diagonal cofactors. Note that the first term of the determinant corresponds to the determinant of a diagonal matrix, while the rest of terms are reduced by the ε factor.

Using the expressions for the determinant of $\mathbf{\Omega}$, we can find the diagonal cofactor C_{KK_K} , which has an analogous form

$$C_{KK_K} = \prod_{k=1}^{K-1} \Omega_{kk} + \varepsilon F_{K-1} \quad (\text{D.3})$$

and similarly for any diagonal cofactor

$$C_{ii_K} = \prod_{\substack{k=1 \\ k \neq i}}^K \Omega_{kk} + \varepsilon F_{ii_{K-1}} \quad (\text{D.4})$$

Conversely, in order to calculate the non-diagonal cofactors, observe that the (K, m) submatrix used to calculate C_{Km_K} has a column and a row with all its entries equal to ε : the last column $(K-1)$ and the m -th row. Therefore, the cofactor results

$$C_{Km_K} = \varepsilon \left(C_{m, K-1_{K-1}} + \sum_{\substack{q=1 \\ q \neq m}}^{K-1} C_{q, K-1_{K-1}} \right)$$

where the first term is the cofactor of an almost diagonal submatrix of size $K-1$, so it has the same form of the determinant of $\mathbf{\Omega}$. Moreover, the rest of cofactors have the same form of C_{Km_K} for smaller matrices. Extending the last expression, C_{Km_K} can be expressed as function of cofactors of smaller submatrices.

$$\begin{aligned} C_{Km_K} &= \varepsilon \left(\prod_{\substack{k=1 \\ k \neq m}}^{K-1} \Omega_{kk} + \varepsilon F_{m, K-1_{K-1}} + \sum_{\substack{q=1 \\ q \neq m}}^{K-1} C_{q, K-1_{K-1}} \right) \\ &= \varepsilon \left[\prod_{\substack{k=1 \\ k \neq m}}^{K-1} \Omega_{kk} + \varepsilon F_{m, K-1_{K-1}} + \varepsilon \sum_{\substack{q=1 \\ q \neq m}}^{K-1} \left(\prod_{\substack{k=1 \\ k \neq q-1}}^{K-2} \Omega_{kk} + \varepsilon F_{m, K-1_{K-1}} + \sum_{\substack{q=1 \\ q \neq m}}^{K-1} C_{q, K-1_{K-1}} \right) \right] \end{aligned}$$

making $\varepsilon^2 \approx 0$

$$C_{Km_K} \approx \varepsilon \prod_{\substack{k=1 \\ k \neq m}}^{K-1} \Omega_{kk}$$

This result stands for any non-diagonal cofactor of the $\mathbf{\Omega}$ matrix. So,

$$C_{ij_K} \approx (-1)^{i+j} \varepsilon \prod_{\substack{k=1 \\ k \neq i \\ k \neq j}}^K \Omega_{kk} \quad (\text{D.5})$$

Using the expression for $\det(\mathbf{\Omega})$ of equation (D.2) and for non-diagonal cofactors of $\mathbf{\Omega}$, we can find the unknown terms of the diagonal cofactor (see equation (D.3))

$$\begin{aligned} C_{KKK} &= \Omega_{K-1,K-1} C_{K-1,K-1K-1} + \varepsilon \sum_{m=1}^{K-2} C_{K-1,mK-1} \\ &= \prod_{k=K-2}^{K-1} \Omega_{kk} C_{K-2,K-2K-2} + \varepsilon \Omega_{K-1,K-1} \sum_{l=1}^{K-3} C_{K-2,lK-2} + \varepsilon^2 \sum_{m=1}^{K-2} \prod_{\substack{m=1 \\ m \neq m}}^{K-2} \Omega_{mm} \end{aligned}$$

Continuing with the last procedure to expand the cofactor and approximating $\varepsilon^2 \approx 0$

$$C_{KKK} \approx \prod_{k=1}^{K-1} \Omega_{kk}$$

and similarly for any diagonal cofactor

$$C_{iiK} = \prod_{\substack{k=1 \\ k \neq i}}^K \Omega_{kk} \quad (\text{D.6})$$

In summary, the cofactors result

$$C_{ijK} \approx \begin{cases} P_i & \text{for } i = j \\ \varepsilon P_{ij} & \text{for } i \neq j \end{cases} \quad (\text{D.7})$$

where we use the following notation

$$P_{ij} = \prod_{\substack{k=1 \\ k \neq i \\ k \neq j}}^K \Omega_{kk} \quad (\text{D.8})$$

By analogy with the diagonal cofactor, the determinant of the lead field matrix can be expressed as

$$\det(\mathbf{\Omega}) \approx \prod_{k=1}^K \Omega_{kk} = P \quad (\text{D.9})$$

Finally, using the equation (6.8), the autoregressive coefficients at the scalp are given by

$$b_{ij} = \frac{1}{\det(\mathbf{\Omega})} \begin{bmatrix} \varepsilon & \cdots & \Omega_{ii} & \varepsilon & \cdots \end{bmatrix} \sum_{k=1}^K \mathbf{a}_k C_{jkK} \quad (\text{D.10})$$

expanding the sum:

$$\begin{aligned} \sum_{k=1}^K \mathbf{a}_k C_{jkK} &= \mathbf{a}_j C_{jjK} + \sum_{\substack{k=1 \\ k \neq j}}^K \mathbf{a}_k C_{jkK} \\ &\approx \mathbf{a}_j P_j + \varepsilon \sum_{\substack{k=1 \\ k \neq j}}^K \mathbf{a}_k (-1)^{j+k} P_{jk} \end{aligned}$$

Now, replace the last result in equation (D.10)

$$\begin{aligned}
b_{ij} &\approx \frac{1}{P} \begin{bmatrix} \varepsilon & \cdots & \Omega_{ii} & \varepsilon & \cdots \end{bmatrix} \left(\mathbf{a}_j P_j + \varepsilon \sum_{\substack{k=1 \\ k \neq j}}^K \mathbf{a}_k P_{jk} \right) \\
&\approx \frac{1}{P} \left\{ \Omega_{ii} \left(a_{ij} P_j + \varepsilon \sum_{\substack{k=1 \\ k \neq j}}^K a_{ik} P_{jk} \right) + \varepsilon P_j \sum_{\substack{m=1 \\ m \neq i}}^K a_{mj} \right\} \\
&\approx \frac{\Omega_{ii}}{\Omega_{jj}} a_{ij} + \varepsilon \left(\frac{\Omega_{ii}}{\Omega_{jj}} \sum_{\substack{k=1 \\ k \neq j}}^K \frac{a_{ik}}{\Omega_{kk}} + \frac{1}{\Omega_{jj}} \sum_{\substack{m=1 \\ m \neq i}}^K a_{mj} \right) \\
&\approx \frac{\Omega_{ii}}{\Omega_{jj}} a_{ij} + \varepsilon \left[\frac{\Omega_{ii}}{\Omega_{jj}} \sum_{\substack{k=1 \\ k \neq j \\ k \neq i}}^K \frac{a_{ik}}{\Omega_{kk}} + \frac{1}{\Omega_{jj}} \left(a_{ii} + \sum_{\substack{m=1 \\ m \neq i}}^K a_{mj} \right) \right]
\end{aligned}$$

Note that the prove does not provide the sign of the non-diagonal cofactors. However that is not a problem because we just need the magnitudes of the biggest terms.

Annex

ANNEX A – Main programm

```

1 %% MAIN PROGRAM %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
2 %% Software Packages
3 addpath (genpath(' ./Funcoes_Pacotes'))
4
5 rng('default')
6
7 %% ***** SETTINGS *****
8
9 %% Time Series Generation at cortex
10 version = 'Area_BuscaRef'; % Version of the simulation
11 % Cortical regions, Local references
12 fs = 128; % Sample frequency
13 Nx = 1e3; % Number of samples
14 waste = 0.1; % Percentage to remove at the begining
15 rep = 500; % Number of repetitions of the simulation
16 Ndipoles = 6;
17
18 %% Set lead field matrix
19 Nchannels = 6;
20 known = 0; % Dipole positions: known or unknown
21 area = 1; % 0 —> Point sources; 1 —> Area sources
22 bipolar = 1; % 0 —> Unipolar; 1 —> Bipolar
23 local = 1; % 0 —> Common ref; 1 —> Local ref
24 ref = [7 7 7 7 7 7]; % Reference electrode for every electrode; 0
    —> average ref
25 SNR = inf;
26 Npos = 100; % Npos scenarios of spatial distributions
27 Leadfield = 'head';
28 % 'diagonal' —> Diagonal leadfield matrix.
29 % 'triangular' —> Triangular leadfield matrix.
30 % 'onlyCD' —> Diagonal leadfield matrix, except for element G(c,d).
31 % 'almost' —> Almost diagonal leadfield matrix.
32 % 'head' —> Leadfield matrix given by head model.
33
34 N = 60; % Maximum harmonics degree for head model
35
36 if strcmp(Leadfield, 'head') % VC as Head Model
37     if area == 0 && known == 1 % Dipoles with known locations
38         Ntrials = 30; % Number of positions for dipole-electrode
            paths
39         Thetad = [45, 45; ... % Extrem theta angles of dipole1
40                 45, 45; ...
41                 45, 45; ...

```

```

42         45, 45; ...
43         45, 45; ...
44         45, 45]*pi/180; % Extrem theta angles of dipole6
45
46     Phid = [pi/6, pi/6; ... % Extrem phi angles of dipole1
47            -pi/6, -pi/6; ...
48            pi/2, pi/2; ...
49            -pi/2, -pi/2; ...
50            5*pi/6, 5*pi/6; ...
51            -5*pi/6, -5*pi/6]; % Extrem phi angles of dipole6
52     else % Dipoles are uniformly distributed across a determined area
53         Ntrials = Npos;
54         CAP_Th = pi/4; % Solid angle of the spherical cap
55
56     Th = [90, 90;... % Theta angle of cap1 center
57          90, 90;...
58          45, 45;...
59          45, 45;...
60          90, 90;...
61          90, 90]*pi/180;
62
63     Ph = [pi/4, pi/4;...
64          -pi/4, -pi/4;...
65          pi/2, pi/2;...
66          -pi/2, -pi/2;...
67          3*pi/4, 3*pi/4;...
68          -3*pi/4, -3*pi/4]; % Phi angle of cap6 center
69
70     [Thetad, Phid] = SphCAP(Ndipoles, Npos, 7.9, CAP_Th, Th, Ph);
71     end
72
73     if bipolar ==1 && local == 1
74         detectd{1} = [2 3 4 5 6];
75         detectd{2} = [1 4];
76         detectd{3} = [1];
77         detectd{4} = [1 5];
78         detectd{5} = [4];
79         detectd{6} = [1 5];
80         [Thetae, Phie, ref] = LocalPos(Thetae, Phie, detectd, mov);
81     end
82     [Nchannels, ~] = size(Thetae);
83
84     PlotScheme(version, Ntrials, Ndipoles, Thetad, Phid, Nchannels, Thetae,
85               Phie, bipolar, ref, known);
86
87 %% MONTE CARLO SIMULATION with Causality Analysis

```

```

88 metric = 'info';
89 alpha = 0.01;
90 nFreqs = fs;
91
92 %% ERROR ACCOUNT
93 f_lim = [0 fs/2]/fs; % Freq. band of interest [Hz]
94 d_link = [1 2]; % d_lim is given for the pair d_link=[i j]; i —> electrode
    & j —> dipole
95
96 %% %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% START PROCESSING
    %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
97 % *****
98 %%
99 [xName, yName, xPath, yPath] = NameData(rep, Nx, version); % File names and
    paths
100 %% Cortex *****
101 %
102 % time-series generation
103 [A, links, fp] = VARCoefficients(Ndipoles);
104 x = AR_dynam( A, Nx, waste, rep ); % Series Generation at the cortex
105
106 %% Forward solution
    *****
107 if strcmp(Leadfield, 'diagonal') || strcmp(Leadfield, 'triangular')
108     Npos = 1;
109     d_link = [1 1];
110 elseif strcmp(Leadfield, 'onlyCD') || strcmp(Leadfield, 'almost')
111     d_link = [1 1];
112 end
113
114 if strcmp(Leadfield, 'head')
115     [Hn, K0] = Head_Model(N);
116     distance = DistanceEleDip(Npos, Ndipoles, Thetad, Phid, Nchannels,
        Thetae, Phie, known);
117     [G, B] = VC_Coeff(A, distance, Hn, N);
118     distance = distance*180/pi; % Distance in degrees
119     if known == 0,
120         distance = nan(Nchannels, Ndipoles, Npos);
121         distance(d_link(1), d_link(2), :) = 1:Npos;
122     end
123 elseif strcmp(Leadfield, 'diagonal') || strcmp(Leadfield, 'triangular')
124     [G, distance] = VC_comb(Leadfield, Ndipoles, Nchannels, rep);
125 else
126     [G, distance] = VC_comb(Leadfield, Ndipoles, Nchannels, Npos);
127 end
128
129 if length(SNR) > 1,

```

```

130     d_lim = [SNR(1), SNR(end)];
131     distance = nan(Nchannels, Ndipoles, length(SNR));
132     distance(d_link(1), d_link(2), :) = SNR;
133 else
134     d_lim = [distance(d_link(1), d_link(2), 1), distance(d_link(1), d_link
(2), end)]; % Chosen distance band
135 end
136
137 % Scalp time-series computation *****
138 fprintf('Calculation of scalp potential \n');
139 y = linearCombOmega(x, G); % Series Generation at the scalp
140 clear x
141
142 if area == 1
143     y = sum(y, 4);
144     d_lim = [1 1];
145 end
146
147 if bipolar ==1, [y, Nchannels] = Bipolar(y, ref);end
148 if SNR < Inf, y = AddNoise(SNR, y); end
149
150 % MonteCarlo
151 [c_Scalp, MonteName, MontePath] = VC_MONTE_CARLO(y, yName, nFreqs, alpha,
metric);
152 clear y
153 fprintf('Saving results\n');
154 save(MontePath, '-v7.3')

1 function [xName, yName, xPath, yPath] = NameData(rep, Nx, version)
2 %% Named Data
3 xName = ['Cortex' '_rep_' num2str(rep) '_Nx_' num2str(Nx) '.mat'];
4 yName = ['Scalp' version '_rep_' num2str(rep) '_Nx_' num2str(Nx) '.mat'];
5
6 PWD = '.';
7 xPath = fullfile(PWD, 'Results', xName);
8 yPath = fullfile(PWD, 'Results', yName);
9 end

```


ANNEX B – VAR process generation

```

1 function [A, links , fp] = VARCoefficients(Ndipoles)
2 if Ndipoles == 3
3     error('Only VAR(p) process with Ndipoles bigger than four.')
4 elseif Ndipoles >= 5
5     fp = 0.13;
6     links = [2,1 ; 3,1 ; 4,1 ; 4,5 ; 5,4];
7     A{1,1} = zeros(Ndipoles);
8     A{1,1}(1:5, 1:5) = [0.95*1.41 0 0 0 0; ...
9                         0 0 0 0 0; ...
10                        0 0 0 0 0; ...
11                        0 0 0 0.25*1.41 0.25*1.41; ...
12                        0 0 0 -0.25*1.41 0.25*1.41];
13     A{2,1} = zeros(Ndipoles);
14     A{2,1}(1,1) = -0.9025;
15     A{2,1}(2,1) = 0.5;
16     A{2,1}(4,1) = -0.5;
17     A{3,1} = zeros(Ndipoles);
18     A{3,1}(3,1) = -0.4;
19 %     A{1,1}(4,5) = 0;
20 if Ndipoles > 5
21 %     A{3,1}(6,6) = -0.9025;
22     A{3,1}(6,5) = 0.5;
23     A{2,1}(3,1) = 0.5;
24 end
25 end
26
27 end

```

```

1 function [ x ] = AR_dynam( A, Nx, waste, rep, innovation )
2 %% Dynamic of the dipoles
3 % generate the dynamic of the dipoles according to the inputs:
4
5 % A{p,1}(Ndipoles, Ndipoles) —> VAR coefficients
6 % Nx —> Duration of the signal in amount of samples
7 % waste —> Percentage to remove at the begining to remove transient.
8
9 rng default;
10
11 if ~exist('waste','var'), waste = 0.1; end
12
13 [p, ~] = size(A);
14 [Ndipoles, ~] = size(A{p});
15
16 L = round(Nx/(1-waste)); % 10^L maximo comprimento do sinal
17 w = randn(L, Ndipoles, rep); % Generate white noise
18 if nargin == 5 % Innovation noise provided
19     w(L-Nx+1:L, :, :) = innovation;
20 end
21 x = zeros(L, Ndipoles, rep);
22
23 x(1:p+1, :, 1:rep) = w(1:p+1, :, 1:rep);
24
25 for i = 1:rep
26     for n = p+1:L,
27         x0 = x(:, :, i)';
28         for q = 1:p
29             x0(:, n) = x0(:, n) + A{q}*x0(:, n-q); %0.5*x(t-q, 1) + 0.3*x(t
-2,1) + 0.4*x(t-p,3) + w(t, :, i);
30         end
31         x(n, :, i) = x0(:, n)'+w(n, :, i);
32     end
33 end
34
35 % **** Cut transient data ****
36 x(1:round(waste*L), :, :) = [];
37
38 end

```

ANNEX C – VC model of head: Green function

```

1 function [Hn, K0] = Head_Model(N)
2 % 4-sphere head model
3 % N —> Maximum order of the Legendre polynomials
4
5 % Chosen Parameters
6 % Radius [cm]
7 rz = 7.58; % Dipole
8 r1 = 7.68; % Brain
9 r2 = 7.86; % CSF
10 r3 = 8.49; % Skull
11 r4 = 9.12; % Scalp
12
13 % Conductivity [S/m]
14 s1 = 0.295;
15 s2 = 1.59;
16 s3 = 0.0287;
17 s4 = 0.43;
18
19 % radius ratios
20 rz1 = rz/r1;
21 r12 = r1/r2;
22 r23 = r2/r3;
23 r34 = r3/r4;
24 r43 = r4/r3;
25
26 %conductivity ratios
27 s12 = s1/s2;
28 s23 = s2/s3;
29 s34 = s3/s4;
30
31 D = 200; % 1/D is the Theta resolution for the cosine of the Legendre
    Polynomials
32 Th = pi; % Maximum Theta
33 Theta = linspace(0,Th,D);
34
35 % Initialize parameters
36 Mn = nan(1,N);
37 Nn = nan(1,N);
38 Qn = nan(1,N);
39 Rn = nan(1,N);

```

```

40 Sn = nan(1,N);
41 Tn = nan(1,N);
42
43 A1 = nan(1,N);
44
45 A2 = nan(1,N);
46 B2 = nan(1,N);
47
48 A3 = nan(1,N);
49 B3 = nan(1,N);
50
51 A4 = nan(1,N);
52 B4 = nan(1,N);
53
54 Hn = nan(1, N);
55 Pn = nan(D,N);
56 % Diag = zeros(1, N); % Diagonal entries of Lead Field Matrix
57 % NonDiag = zeros(D, N+1); % Non-diagonal entries of the lead field
    matrix
58 % NonDiag_n = zeros(D,N);
59
60
61 Po = 1.5e-6; % Po = 1.5 uA/mm^2
62 K0 = Po/(4*pi*0.33e-3*(rz*10)^2);
63
64 for n = 1:N
65 Mn(n) = r43^(n+1)*n/(n+1);
66 Nn(n) = (r34^n-Mn(n)*(n+1)/n)/(r34^n+Mn(n));
67 Qn(n) = (s34-Nn(n))/(r23^(n+1)*(Nn(n)+s34*(n+1)/n));
68 Rn(n) = (r23^n-Qn(n)*(n+1)/n)/(r23^n+Qn(n));
69 Sn(n) = (s23-Rn(n))/(r12^(n+1)*(Rn(n)+s23*(n+1)/n));
70 Tn(n) = (r12^n-Sn(n)*(n+1)/n)/(r12^n+Sn(n));
71 K = K0*n;
72 % Model Coefficients
73 A1(n) = K*rz1^(n+1)*(Tn(n)+s12*(n+1)/n)/(s12-Tn(n));
74 A2(n) = (A1(n)+K*rz1^(n+1))/(r12^n+Sn(n));
75 B2(n) = A2(n)*Sn(n);
76 A3(n) = (A2(n)+B2(n)*r12^(n+1))/(r23^n+Qn(n));
77 B3(n) = A3(n)*Qn(n);
78 A4(n) = (A3(n)+B3(n)*r23^(n+1))/(r34^n+Mn(n));
79 B4(n) = A4(n)*Mn(n);
80 Hn(n) = A4(n) + B4(n)*r34^(n+1);
81
82 % Legendre Polynomials
83 P = legendre(n, cos(Theta));
84 Pn(:,n) = P(1,:)';
85

```

```

86 % Lead field matrix elements vs. Sphere Harm degree
87 % Diag(n) = sum(Hn(1:n));
88 % NonDiag(:, n+1) = NonDiag(:, n) + Hn(n)*Pn(:, n);
89
90 % NonDiag_n(:,n) = Hn(n)*Pn(:,n);
91 end
92
93 end

```

```

1 function [distance] = DistanceEleDip(Npos, Ndipoles, Thetad, Phid,
    Nchannels, Thetae, Phie, known)
2 %% Calculate electrode-dipole distance
3 if size(Thetae) ~= size(Phie), error('Theta and Phi must have same
    dimensions'); end
4 if size(Thetae, 1) ~= Nchannels, error('Number of dipoles and Theta/Phi
    rows must be the same'); end
5 if size(Thetae, 2) ~= 2, error('Each dipole has to have its extreme angular
    positions'); end
6
7 if known == 1
8     if size(Thetad) ~= size(Phid), error('Theta and Phi must have same
        dimensions'); end
9     if size(Thetad, 1) ~= Ndipoles, error('Number of dipoles and Theta/Phi
        rows must be the same'); end
10    if size(Thetad, 2) ~= 2, error('Each dipole has to have its extreme
        angular positions'); end
11
12    Thd = nan(Ndipoles, Npos);
13    Phd = nan(Ndipoles, Npos);
14    for d = 1:Ndipoles
15        Thd(d, 1:Npos) = linspace(Thetad(d,1), Thetad(d,2), Npos);
16        Phd(d, 1:Npos) = linspace(Phid(d,1), Phid(d,2), Npos);
17    end
18 elseif known == 0
19     Thd = Thetad;
20     Phd = Phid;
21 end
22
23 The = nan(Nchannels, Npos);
24 Phe = nan(Nchannels, Npos);
25
26 for e = 1:Nchannels
27     The(e, 1:Npos) = linspace(Thetae(e,1), Thetae(e,2), Npos);
28     Phe(e, 1:Npos) = linspace(Phie(e,1), Phie(e,2), Npos);

```

```

29 end
30
31 distance = nan(Nchannels, Ndipoles, Npos);
32 for e = 1:Nchannels
33     for d = 1:Ndipoles
34         signo = sign( sign(Phe(e,:) - Phd(d,:)) + sign(The(e,:) - Thd(d,:)) +
35             sign( sign(Phe(e,:) - Phd(d,:)) .* sign(The(e,:) - Thd(d,:)) ) );
36         distance(e, d, :) = signo.*acos( cos(The(e,:)).*cos(Thd(d,:)) + sin
37             (The(e,:)).*sin(Thd(d,:)).*cos( Phe(e,:) - Phd(d,:) ) );
38     end
39 end
40
41 %{
42 for e=1:Nchannels
43     for d = 1:Ndipoles
44         [distance, I] = sort(distance(e,d,:));
45         Thd(d, :) = Thd(d,I);
46         Phd(d, :) = Phd(d,I);
47     end
48 end
49 %}
50 end

```

ANNEX D – Lead field matrix

```

1 function [G, epsilon] = VC_comb(Leadfield, Ndipoles, Nchannels, Npos)
2 % Leadfield matrix with imposed structure
3 epsilon = linspace(0, 0.2, Npos);
4
5 switch (Leadfield)
6     case 'diagonal'
7         epsilon = 1;
8         for r=1:Npos
9             G{1}(:, :, r) = diag( diag(randn(Nchannels, Ndipoles)) );
10        end
11     case 'triangular'
12         epsilon = 1;
13         for r=1:Npos
14             G{1}(:, :, r) = tril(randn(Nchannels, Ndipoles));
15        end
16     case 'onlyCD'
17         G = cell(1, Npos);
18         epsilon = 10*epsilon;
19         for r=1:Npos
20             G{r} = eye(Nchannels, Ndipoles);
21             G{r}(1,3) = epsilon(r);
22        end
23     case 'almost'
24         G = cell(1, Npos);
25         for r=1:Npos
26             G{r} = epsilon(r)*ones(Nchannels, Ndipoles);
27             G{r} = G{r} - diag(diag(G{r}));
28             G{r} = G{r} + eye(Nchannels, Ndipoles);
29        end
30 end
31
32 if length(epsilon) ~= 1
33     ep = nan(Nchannels, Ndipoles, Npos);
34     ep(1,1,:) = epsilon;
35     epsilon = ep;
36 end

```

```

1 function [ G, B ] = VC_Coeff(A, distance , Hn, N)
2 %% VOLUME CONDUCTION IN PDC ESTIMATION
3 % INPUTS:
4 % A{p,1}(Ndipoles , Ndipoles) —> VAR Matrix coefficients
5 % p —> Model order
6 % Ndipoles —. Amount of dipoles
7 % Nchannels —> Amount of channels
8 % distance(Nchannels , Ndipoles , Npos); —> Angular dist. dipole-electrode
9 % Npos —> Amount of samples in the distance axis
10
11 % OUTPUTS
12 % G{1, Npos} —> Lead Field matrix for Npos spatial distributions of
    sources & sensors
13 % B{p, Npos} —> VAR scalp coeff. for p lags and Npos spatial dist.
14
15 [p, ~] = size(A);
16 [Nchannels , Ndipoles , Npos] = size(distance);
17 distance = abs(distance);
18
19 %% Lead field matrix and VAR coefficients at the scalp
20 G = cell(1, Npos);
21 iG = cell(1, Npos);
22 B = cell(p, Npos);
23
24 for d = 1:Npos
25     for i = 1:Nchannels
26         for j = 1:Ndipoles
27             %Pn = legendreP(1:N, cos(distance(i, j, d))); % Legendre
    Polynomials degrees 1 to N
28             %G{d}(i,j) = Hn*Pn';
29             %
30             % Aqui inicia una parte por version anterior a 2015R
31             Pn = nan(N,1);
32             Coeff = 0;
33             for n = 1:N;
34                 P = legendre(n, cos(distance(i,j,d))); % Legendre
    Polynomials
35                 Pn(n) = P(1);
36                 Coeff = Coeff + Hn(n)*Pn(n);
37             end
38
39             G{d}(i,j) = Coeff;
40             %}
41         end
42     end
43
44     iG{d} = pinv(G{d}); % pseudoinverse

```

```

45
46     for k = 1:p
47         B{k,d} = G{d}*A{k}*iG{d};    % VAR coefficients at the scalp
48     end
49 end
50
51 end

```

```

1 function y = linearCombOmega(x, G)
2 %% Input
3 % x(Nx, Ndipoles, rep) —> Time series at the cortex
4 % G{1, Npos}(Nchannels, Ndipoles) —> Lead Field Matrix
5
6 [Nx, ~, rep] = size(x);
7 [~, Npos] = size(G);
8 [Nchannels, ~, repG] = size(G{1});
9
10 %y = cell(Npos,1);
11 y = nan(Nx, Nchannels, rep, Npos);
12
13 for pos = 1:Npos
14     for r = 1:rep
15         %y{pos}(:, :, r) = (G{pos}*x(:, :, r))';
16         if repG > 1
17             y(:, :, r, pos) = (G{pos}(:, :, r)*x(:, :, r))';
18         else
19             y(:, :, r, pos) = (G{pos}*x(:, :, r))';
20         end
21     end
22 end
23
24 end

```


ANNEX E – Bipolar recording and Additive Noise

```

1 %% Bipolar recording
2 function [y, Nchannels] = Bipolar(y, ref)
3 % Bipolar difference
4 [ ~, Nchannels, rep, Npos ] = size(y);
5 if ref == 0 % Average reference
6     for pos = 1:Npos
7         for r = 1:rep
8             Xav = mean( y(:, :, rep, Npos), 2 );
9         end
10        Xav = repmat(Xav, [1, Nchannels]);
11        y(:, :, r, pos) = y(:, :, r, pos) - Xav;
12    end
13 else % Common and local reference
14     for i = 1:Nchannels
15         if ref(i) ~= i
16             y(:, i, :, :) = y(:, i, :, :) - y(:, ref(i), :, :);
17         end
18     end
19     y(:, ref, :, :) = [];
20     [~, Nchannels, ~, ~] = size(y);
21 end
22 end

1 %% ADDITIVE NOISE
2
3 function y = AddNoise(SNR, y)
4 fprintf( '\n Adding noise. \n' );
5 rng( 'shuffle' )
6 [Nx, Nchannels, rep, Npos] = size(y);
7 ruido = randn(Nx, Nchannels, rep, Npos);
8 if length(SNR)==1
9     for t = 1:Npos
10        for r = 1:rep
11            for c = 1:Nchannels
12                y(:, c, r, t) = y(:, c, r, t) + ruido(:, c, r, t)*var(y(:, c, r, t))/
13                SNR;
14            end
15        end
16    end
17 end

```

```

14         end
15     end
16 else
17     if Npos > 1
18         error('Several positions and several SNR values at the same time')
19     else
20         z = nan(Nx, Nchannels, rep, length(SNR));
21         for vol = 1:length(SNR)
22             for r = 1:rep
23                 for c = 1:Nchannels
24                     z(:,c,r,vol) = y(:,c,r,1) + ruido(:,c,r,1)*var(y(:,c,r
,1))/SNR(vol);
25                 end
26             end
27         end
28         y = z;
29     end
30 end
31 end

```

ANNEX F – MonteCarlo simulation with causality analysis

```

1 function [c_Scalp, MonteName, MontePath] = VC_MONTE_CARLO(y, yName, nFreqs,
    alpha, metric)
2 [~, Nchannels, ~, Npos] = size(y); % Scalp time series
3
4 PDC = nan(Npos, Nchannels, Nchannels, nFreqs);
5 stdPDC = nan(Npos, Nchannels, Nchannels, nFreqs);
6 SS = nan(Npos, Nchannels, Nchannels, nFreqs);
7 COH = nan(Npos, Nchannels, Nchannels, nFreqs);
8 M = nan(Npos, Nchannels, Nchannels);
9 DETC = nan(Npos, Nchannels, Nchannels, nFreqs);
10
11
12 fprintf('MonteCarlo simulation. \n')
13 for t = 1:Npos
14     fprintf('Actual position: %d of %d \n', t, Npos);
15     [ PDC(t, :, :, :), stdPDC(t, :, :, :), SS(t, :, :, :), COH(t, :, :, :), M(t, :, :), DETC(
        t, :, :, :) ] = Monte_Carlo_Mine( y(:, :, :, t), nFreqs, alpha, metric );
16
17 end
18
19 c_Scalp.FP = DETC;
20 clear DETC
21 c_Scalp.M = M;
22 clear M
23 c_Scalp.pdc = PDC;
24 clear PDC
25 c_Scalp.stdPDC = stdPDC;
26 clear stdPDC
27 c_Scalp.SS = SS;
28 clear SS
29 c_Scalp.coh = COH;
30 clear COH
31
32 yName = strrep(yName, '.mat', '');
33 MonteName = [yName '__Npos_' num2str(Npos) '.mat'];
34 MontePath = fullfile('./Results/MonteCarlo', MonteName);
35 end

```

```

1 function [ PDC, stdPDC, SS, COH, M, DETC ] = Monte_Carlo_Mine( x, nFreqs,
    alpha, metric)
2
3 [NX, NChan, rep] = size(x);
4
5 format compact
6
7 var_opts      = struct( 'maxIP', 10, 'criterion', 2, 'alg', 1, 'kernel
    ', 'm', 'kernel_params', [ 1, 1, 1 ] );
8 gct_opts      = struct( 'gct_signif', alpha, 'igct_signif', alpha );
9 caus_analysis_opts = struct( 'caus_analysis_type', 'pdc', 'nFreqs', nFreqs,
    'alpha', alpha, 'metric', metric, 'type1', 'Linear', 'type2', 'Pearson'
    );
10 flgPrintResults = 0;
11 reverseStr = '';
12 for r = 1 : rep
13     [c( r, : )] = caus_analysis( x( :, :, r ), var_opts, gct_opts,
        caus_analysis_opts, flgPrintResults );
14     if mod( r, 50 ) == 0
15         msg = sprintf( [ '
            _____\n', ...
                'Obtaining PDC values for:\n', ...
                'N = ', num2str( NX ), ' points', ...
                '\ntrial = %d\n'], r );
16         fprintf( [ reverseStr, msg ] );
17         reverseStr = repmat( sprintf( '\b' ), 1, length( msg ) );
18     end
19 end
20
21 M = zeros( NChan, NChan );
22 DETC = zeros( NChan, NChan, nFreqs );
23 PDC = zeros( NChan, NChan, nFreqs );
24 stdPDC = zeros( NChan, NChan, nFreqs );
25 SS = zeros( NChan, NChan, nFreqs );
26 COH = zeros( NChan, NChan, nFreqs );
27
28 reverseStr = '';
29 for i = 1 : NChan
30     for j = 1 : NChan
31         for r = 1 : rep
32             if j == i
33                 M( i, j ) = NaN;
34             else
35                 if any( squeeze( c( r, : ).pdc_th( i, j, : ) ) )
36                     M( i, j ) = M( i, j ) + 1;
37                 end
38             end
39         end
40     end
41 end

```

```

42         fI = find(~isnan(c(r,:).pdc_th(i,j,:)));
43         DETC(i,j,fI) = DETC(i,j,fI)+1;
44     end
45     PDC(i,j,:) = mean(abs(c(r,:).pdc(i,j,:)));
46     stdPDC(i,j,:) = std(abs(c(r,:).pdc(i,j,:)));
47     SS(i,j,:) = mean(abs(c(r,:).SS(i,j,:)));
48     COH(i,j,:) = mean(abs(c(r,:).coh(i,j,:)));
49     end
50     if mod( r, 50 ) == 0
51         msg = sprintf( [ '
52             'Obtaining contingency table for:\n', ...
53             'N = ', num2str( NX ), ' points', ...
54             '\ntrial = %d\n'], r );
55         fprintf( [ reverseStr, msg ] );
56         reverseStr = repmat( sprintf( '\b' ), 1, length( msg ) );
57     end
58 end
59 DETC = DETC / rep * 100;
60 M = M / rep * 100;
61 end

```