METHODS of DYNAMICAL BRAIN ACTIVITY ANALYSIS during COGNITIVE and VERBAL TASKS

I. TRANSMISSION of BRAIN ACTIVITY

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Understanding of cognitive and verbal functions requires analysis of dynamical interactions in brain. Information processing in brain is connected with a short time scale communication between brain structures, so the understanding of the dynamics of cognitive processes is beyond the reach of imaging methods such as fMRI or PET.

Electroencephalography:
- allows for recording brain processes in a short time scale
- is directly related to the activity of brain cells
- allows for establishing interrelations between brain structures
- gives spectral information
  - its spacial resolution is inferior to fMRI

From EEG recording, by application of proper estimator, it is possible to infer dynamical interactions between the brain structures.
Dynamical interactions study by functional connectivity estimation

- Methods of connectivity estimation
  - classical methods
  - methods based on Granger causality
  - nonlinear methods

- Multivariate autoregressive model and Directed Transfer Function – DTF

- Pitfalls inherent to the methods and how to avoid them

- Practical applications and estimation of dynamical brain activity propagation

- Estimation of ECoG transmission during verbal task
CORRELATION, COHERENCE

In case of **correlation** the direction of propagation for dominant frequency may be inferred from the delay obtained for the maximum of the function.

When multiple frequencies are present in the signal **coherence** is a better estimator:

\[ y_{xy}(f) = \frac{|S_{xy}(f)|^2}{S_x(f)S_y(f)}, \quad S_{xy}(f) = |S_{xy}(f)| \exp(i\Phi_{xy}(f)) \]

The delay in samples \( \Delta x \) can be computed from the formula: \( \Delta x = \frac{\Phi F_s}{fn} \), where \( f \) is the frequency for which the phase \( \Phi \) is calculated, \( F_s \) – sampling frequency. Since phase is dependent on frequency, so the delays may be found for particular frequencies. However we have to bear in mind that phase is determined modulo \( 2\pi \), therefore the result may be ambiguous.
The testable definition of causality was introduced by Granger (1969) in the field of economics. Granger defined causality in terms of predictability of time series:

If some series $X(t)$ contains information in past terms that helps in the prediction of series $Y(t)$, then $X(t)$ is said to cause $Y(t)$.

Granger causality principle is equivalent to

2-channel autoregressive model.

Granger causality was introduced for two channels, however as was pointed out by Granger* (1980) **test of causality is impossible unless the set of interacting channels is complete**. Granger causality may be extended to arbitrary number of channels in the framework of Multivariate Autoregressive Model (MVAR).

Directedness estimators defined in the framework of MVAR:

- Granger Causality Index, Geweke, 1982
- Directed Transfer Function (DTF), Kaminski & Blinowska, 1991
- Direct Directed Transfer Function dDTF
- Short-time Directed Transfer Function SDTF
- Partial Directed Coherence, Baccala & Sameshima, 2001

Multivariate autoregressive model (MVAR) fitted to the \( k \)-channel EEG process is expressed as:

\[
X(t) = \sum_{i=1}^{p} A(i)X(t-i) + E(t)
\]

Where: \( X \) - vector of \( k \) signals recorded in time: \( X(t) = (X_1(t), X_2(t), ..., X_k(t)) \), \( E(t) \) is the vector of white noise values, \( A(i) \) are the model coefficients and \( p \) is the model order.

Model order \( p \) may be found from Akaike (AIC) criterion:

\[
AIC(p) = 2\log(\det(V)) + \frac{2kp}{N}
\]

\( V \) – variance matrix, \( k \) – number of channels, \( N \) – number of data points
AR model generates signals which can hardly be distinguished from the experimental EEG

Experimental EEG

Simulated EEG

AR of order 3

AR of order 5

Impulse response function of MVAR is a sum of damped sinusoids, which is compatible with the character of EEG.
Assuming \( A(0) = -I \) (\( I \) - identity matrix), we can rewrite the autoregressive dependence in another form:

\[
E(t) = \sum_{j=0}^{p} A(j)X(t - j)
\]

Transforming the above equation to the frequency domain by application of \( Z \) transform we get:

\[
X(f) = A^{-1}(f)E(f) = H(f)E(f)
\]

The \( H(f) \) is called the transfer matrix of the system. \( f \) denotes frequency, \( z = e^{-2\pi imf\Delta t} \).
DTF – Directed Transfer Function

Directed Transfer Function introduced in 1991 by Kamiński and Blinowska * for arbitrary number of channels is based on the transfer function of the MVAR model.

The DTF function, describing transmission from channel $j$ to $i$ at frequency $f$ normalized in respect of inflows to destination channel $i$ is defined as:

$$\gamma_{ij}^2(f) = \frac{|H_{ij}(f)|^2}{\sum_{m=1}^{k} |H_{im}(f)|^2}$$

DTF: $\gamma_{ij}^2(f)$

DTF non normalized $\theta_{ij}^2(f) = |H_{ij}(f)|^2$ (Directly proportional to coupling)

DTF is robust in respect to random noise

EEG

+ noise

= signal in 1st chan.

$\Delta = 1$

$\Delta = 2$

EEG – experimental EEG from electrode P3, relaxed state

$\Delta$ – delay

noise – random noise from Gaussian distribution

noise amplitude/EEG amplitude = 3
In estimation of causality relations in multivariate systems there are several pitfalls

**Pitfall # 1**

Bivariate - multivariate

Bivariate coherence

Simulation

Result
By means of coherence it is not possible to determine reciprocal connections, which is easy by means of DTF* and in general by means of measures based on MVAR.

Bivariate Causality

Simulation

Result
Multivariate estimator (non-normalized DTF)
Surrogate data test

The "leak currents" indicating the accuracy of DTF are found from surrogate data – signals with disturbed phases. Surrogate data are obtained by transforming the data to the frequency domain, randomizing their phases and transforming back to the time domain.
Bivariate methods are misleading when the number of the interacting channels is greater than two.
Pitfall #2
Nonlinear - linear
**NONLINEAR METHODS**

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonlinear correlation – $h^2_{xy}$</td>
<td>piecewise approximation of the nonlinear regression curve</td>
<td>yes</td>
</tr>
<tr>
<td>Mutual Information</td>
<td>construction of histograms</td>
<td>no</td>
</tr>
<tr>
<td>Transfer Entropy</td>
<td>for estimation of probabilities</td>
<td>yes</td>
</tr>
<tr>
<td>Generalized Synchronization</td>
<td>reconstruction of phase space</td>
<td>possibly</td>
</tr>
<tr>
<td>Synchronization Likelihood</td>
<td>by embedding</td>
<td></td>
</tr>
<tr>
<td>Phase Synchronization</td>
<td>construction of phase histograms</td>
<td>no</td>
</tr>
</tbody>
</table>

Are EEG and LFP nonlinear? It has been shown by means of surrogate data test and linear/nonlinear forecasting that non-linearity of EEG and LFP is exception rather than a rule.

It has been also demonstrated that even for nonlinear signals linear measures are performing quite well.
Nonlinear methods:

- are very sensitive to noise
- rely to the large extent on reconstruction of phase space, hence need for long stationary data segments, which are hard to find
- are prone to systematic errors connected with the arbitrary choices (e.g. bin length in estimating probabilities, or lag of embedding procedure)
- are bivariate

Netoff et al. after application to non-linear signals measures of coupling: mutual information, phase correlation, continuity measure (generalised synchronisation) and linear correlation conclude:

“\textit{We have been as guilty as any of our colleagues in being fascinated by the theory and methods of nonlinear dynamics. Hence we have continually been surprised by robust capabilities of linear CC(correlation) to detect weak coupling in nonlinear systems, especially in the presence of noise}”

Connectivity in the beta band estimated by means of Synchronization Likelihood

Propagation obtained by means of DTF averaged for Alzheimer (AD), mild cognitive impairment (MCI) and normal (NOLD) groups.
Assuming that we have chosen estimators based on multivariate autoregressive approach we have to be conscious about pitfalls in MVAR.

They can be easily avoided.

Pitfall #3

Reference
WARNING!

The input data for the MVAR model should not be subjected to pre-processing, which introduces correlation between signals.

No bipolar, common average, source derivatio, Hjorth or Laplace transform may be used, since they disturb the correlation between channels.
DTF is insensitive in respect to volume conduction. It is based on phase differences between channels and volume conduction is practically zero phase propagation.

Therefore there is no need to use Laplace transform or project potentials on the cortex
Pitfall #4

Too small data length
MVAR is a parametric model – number of parameters should be much smaller than the number of data points, preferably of the order of magnitude

For MVAR:
no. coefficients/no data points = \(\frac{k^2p}{kN} = \frac{kp}{N} < 0.1\)

Where: \(k\) – no of channels, \(p\) – model order, \(N\) – no of data points in the window.

Data records cannot be constructed from non-contiguous segments

When multiple realizations are available the number of data points may be increased by ensemble averaging.
Practical applications:

Correspondence with known evidence

Confirmation of hypotheses
MVAR model was fitted to 21 channels of sleep EEG (10/20 system) simultaneously and DTF functions were determined.
Comparison of bivariate with multivariate estimators of propagation (alpha activity in wakefulness).
Normal group

stage 1

stage 2

stage 3+4

wakefulness

stage REM
Information processing in brain is effected in a short time scale. For its understanding the measurement window should be small, which is in contradiction with statistical requirements. For parametric model number of parameters should be smaller than number of data points.

For MVAR: 
\[
\frac{\text{no. coefficients}}{\text{no data points}} = \frac{k^2p}{kN} = kp/N
\]

Where: \( k \) – no of channels, \( p \) – model order, \( N \) – no of data points in the window.

When multiple realizations are available the number of data points may be increased by ensemble averaging.

This approach was used in design of:

**Short-time Directed Transfer Function**

When multiple realizations are available the model coefficients $a_i$ can be estimated by an ensemble averaging of correlation matrix:

$$
\hat{R}_{ij}(s) = \frac{1}{N_T} \sum_{r=1}^{N_T} \tilde{R}_{ij}^{(r)}(s) = \frac{1}{N_T} \sum_{r=1}^{N_T} \frac{1}{n-|s|} \sum_{t=1}^{n-|s|} X_i^{(r)}(t) X_j^{(r)}(t - s)
$$

Then MVAR model can be fitted to short data epochs and **Short-time Directed Transfer Function (SDTF)** can be determined.
Changes in amplitude during finger movement task

What are the changes of propagation?
Time course of the propagation of beta activity after movement

In motor task the short burst of propagation in gamma band from electrode C3 (primary motor cortex involved in finger movement). In case of movement imagination there are alternating flows from C3 and from Fz (supplementary motor area) – „cross talk“.

Continuous Attention Test (CAT)

The subject had to press the switch when the identical patterns occurred consecutively - situation “target”
First, in both conditions frontal structures show increased activity, then in case of non-target active inhibition is manifested by the transmission from rIFC (F8->C3), in the last phase for target the command of performing movement movement is connected with a burst from the right hand motor area (C3).

Prefrontal Cortex
Executive processes operating on the contents of working memory

Inferior frontal cortex
Inhibition in "go-no go" tasks

In non-target condition active inhibition from IFC or preSMA to hand area of motor cortex

In target condition in the final phase burst of activity from motor cortex (*gamma activity burst, beta rebound*)

Confirmation of hypotheses of active inhibition
Information Transfer During a Transitive Reasoning Task

Reasoning task

Memory task
Significant differences in propagation during reasoning task in comparison to memory task

We can relate the enhanced long-range transmission in the theta band obtained in our experiment to the fronto-parietal executive network, whereas short-range transfers from posterior sites in the gamma band could reflect the visuospatial sketchpad activity.

fMRI - reasoning tasks versus memory

Good correspondence between fMRI and DTF results – engagement of frontal and posterior structures. DTF additionally supplies spectral information and information about communication between structures.
General problem of connectivity: „small-world networks” and area-area connectivity.

Propagation during Reasoning task estimated by SDTF

We can observe two centers acting locally, exchanging information from time to time.

SDTF confirms hypothesis following from scaling rules – tightly coupled areas and less dense long-range connections.
local and distant connections
selection method

local = distance < 2
blue — local connections
red — distant connections
We have demonstrated the existence of a modular, well defined structure of brain networks during the performance of the working memory task. This observation is in line with the works considering the structure of the brain networks from the point of view of the efficiency of information transfer, white to gray matter ratios and saving the metabolic energy.

We have:
- tightly connected modules and more sparse long-distance connections exchanging information from time to time

Functional networks in brain are not random!
Auditory word repetition task. The subject responded to a series of auditory word stimuli by repeating them aloud.

Metod: SdDTF – Short time direct Directed Transfer Function. SdDTF is a modification of SDTF, in which cascade (indirect) flows are eliminated.
Recording: ECoG – subdural electrodes implanted in cortex of pre-surgical patient
SdDTF in high-gamma range (80-120 Hz)

3 stages of task performance:
1) Stimulus processing from stimulus onset (s) to stimulus offset (o) (750 ms)
2) response preparation from stimulus offset (o) to response onset (r) 750-1340 ms
3) response production, from (r) to the end of signal analysis 1349-2500 ms
Statistically significant changes of SdDTF from baseline (ECoG before stimulus).
The statistical testing methodology was based on „thin plate model” and comparison of the each window after stimulus with the window in the baseline)
Auditory perception (s) – (o) period

E9 – auditory association cortex
E3 – mouth/tongue area premotor/motor cortex

Flows between sites E1 and E2 (Brocas area) and E4 mouth/tongue motor cortex
Three stages of auditory word repetition task

a) Perception stage
b) Response preparation
3) Verbal response

a) Predominant increase in flow from auditory association cortex to mouth/tongue motor cortex (E9>E3), also flows via Wernicke’s area: E9>E11>E3

b) Flow increases between auditory association cortex and Broca’s area to mouth/tongue motor cortex (E2>E5), among sites in Wernicke’s area (E7>E11, E9>E11), and between Wernicke’s area and mouth/tongue motor cortex (E11>E5, E4>E11)

c) Flow increases from Broca’s area to tongue/mouth motor cortex (E2>E4, E1>E4), but also smaller flow increases from Wernicke’s area to mouth/tongue motor cortex (E7>E4, E11>E4) and from mouth/tongue motor cortex to Broca’s area (E4>E2 and E3>E2), perhaps reflecting the activation of feedback pathways while the patient speaks and hears his own spoken response.
Causal relations between spike trains and local field potentials

Rat hippocampal LFP were measured together with firing of 12 SUM (Supramammillary) neurons. Spikes were low-pass filtered (Butterwort filter) and 10% noise is added.

B. Kocsis, M. Kaminski *Dynamic changes in the direction of the theta rhythmic drive between supramammillary nucleus and the septohippocampal system;* Hippocampus **16**(6):531-540, 2006 (available online).

DTF can be used to evaluate causality between point processes e.g. spike trains.
During rest DTF showed predominant hippocampus-to-SUM direction of influence. In the episode of sensory stimulation the direction of drive from SUM to hippocampus was observed.

The study conducted by means of SDTF revealed dynamic relationship between SUM and septohippocampal theta oscillations in which the direction of the rhythmic drive changed depending on the origin and type of the rhythm.
DTF is:
• Robust in respect to noise
• Immune to volume conduction
• Supplies information about propagation in different frequency bands
• Evidence obtained by means of DTF is compatible with the knowledge gathered in the earlier studies based on invasive electrophysiological techniques or fMRI
• Provides an insight in the active brain and dynamic interactions between brain structures in cognitive tasks

Bivariate methods:
• Give misleading, disorganised patterns of connections
• Lead to unrealistic hypotheses about randomness of functional connectivity
MVAR - DTF software (MMULTAR) may be downloaded from:
http://eeg.pl/Software/mmultar_inst.zip

Practical Biomedical Signal Analysis Using MATLAB® assists readers in choosing the appropriate methods for solving concrete problems. It first describes in simple terms various methods of signal analysis. The next sections indicate which methods are the most appropriate for the given signal in a particular context. The authors cover both basic and advanced methods and use MATLAB® to discuss applications.

- Provides an introductory approach to biomedical signal analysis
- Discusses how and when to apply a wide range of methods
- Refers to MATLAB routines and Toolboxes
- Outlines the advantages and disadvantages of the methods in the context of applications

Contents

- **Introductory Concepts:** Linear time invariant systems, duality of time and frequency domain, uncertainty principle, hypothesis testing, surrogate data technique.
- **Single Channel Methods:** filters, hidden Markov model, Kalman filter, Stationary Signals: Fourier transform and parametric autoregressive model; Non-stationary Signals: time-frequency distributions, wavelet transform, matching pursuit, empirical mode decomposition;
- **Non-linear methods:** correlation dimension, entropy measures, DFA, Poincare and recurrence plots; Influence of noise.
- **Multiple Channel Methods:** multivariate autoregressive model, Granger causality, directed transfer function (DTF), partial directed coherence (PDC), principle component analysis (PCA), Independent component analysis (ICA), Influence of volume conduction and problems with bivariate methods for multivariate systems.
- **Application:**
  - brain electric and magnetic signals: EEG, MEG, IEG, ERP;
  - heart electric and magnetic signals: ECG, MCG, HRV, ECG, FMCG;
  - muscle signals: needle and surface electromyogram (EMG); electromyogram (EMG);
  - acoustic signals: phonocardiograms (PCG) and otocoustic emissions (OAE).

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