SAPIENZA
UNIVERSITÀ DI ROMA

FONDAZIONE SANTA LUCIA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
Ospedale di rilievo nazionale e di alta specializzazione per la riabilitazione neuromotoria

Basis of the estimation of connectivity: general principles and measures of causality

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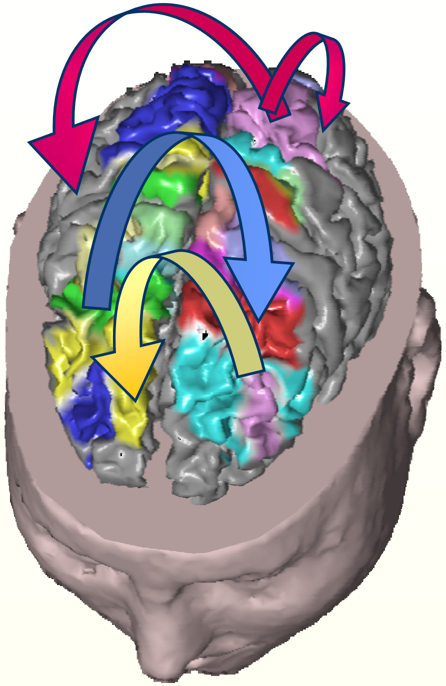
Beyond the brain mapping: the study of cortical connectivity



- Functional neuroimaging brain maps reveal where the cortical activations appear during the execution of a task
- The central question is how the areas involved in a task cooperate one to each other
- How to define the information flow between the cortical activities?

Connectivity: Different definitions

Different definitions of connectivity

- Anatomical Connectivity = the existence of anatomical links allowing the information flow from a cerebral district to another one.
- Effective Connectivity = the simplest brain circuit that would produce the same temporal relationship as observed experimentally between cortical sites
- Functional Connectivity = the existence of temporal correlation between the activity recorded in different cerebral sites

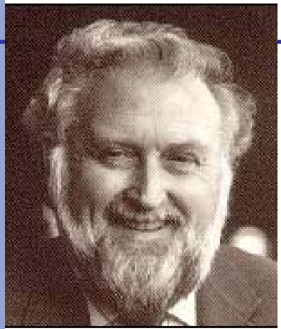
To estimate connectivity we need an operative mathematical definition

Definition of causality in the statistical sense

Norbert Wiener (1956). First definition of causality in a statistical framework:

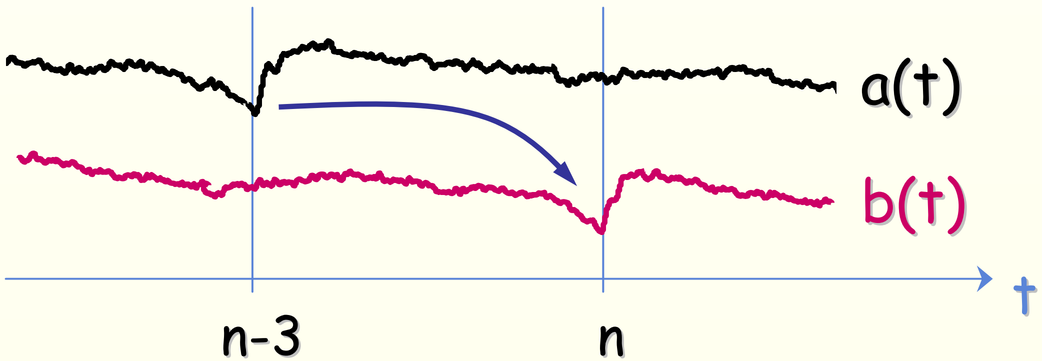
Given two simultaneously measured signals, if one can predict the first signal better by incorporating the past information from the second signal than using only information from the first one, then the second signal can be called causal to the first one (Wiener, 1956).

Granger Causality



Economist Clive Granger (Nobel Laureate in 2003),
1969: Mathematical formulation of Wiener's definition

Given two time series a(t) and b(t), a(t) is said to Granger-cause b(t) if the insertion of a(t)'s past into an autoregressive modelization of b(t) significantly improves prediction of b(n), that is, if it reduces the prediction error.

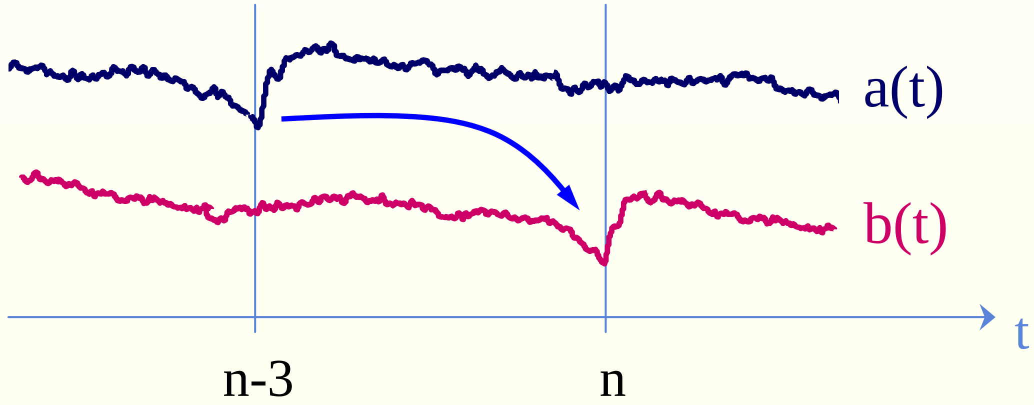


Granger causality and AR

By means of a Bivariate Autoregressive Modeling of a(t) and b(t): a(t) is said to Granger-cause b(t) if by inserting a(t)'s past samples in the autoregressive modelization of b(t) this can reduce the prediction error:

a(t) → b(t) : b can be modelized as

$$b(n) = B_1 b(n-1)+\ldots+B_N b(n-N)+A_1 a(n-1)+A_2 a(n-2)+\ldots+A_M a(n-M)+n(t)$$



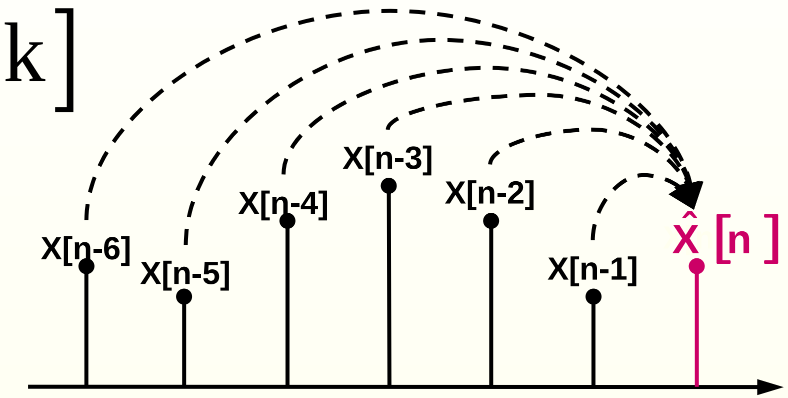
It can be a(t) → b(t) without necessarily being b(t) → a(t)

-> DIRECTIONALITY

Autoregressive linear prediction

- An autoregressive (AR) filter can be used as a linear predictor

$$\hat{x}[n] = -\sum_{k=1}^{p} a[n]\, x[n-k]$$



- The prediction error is:

$$e[n] = x[n] - \hat{x}[n]$$

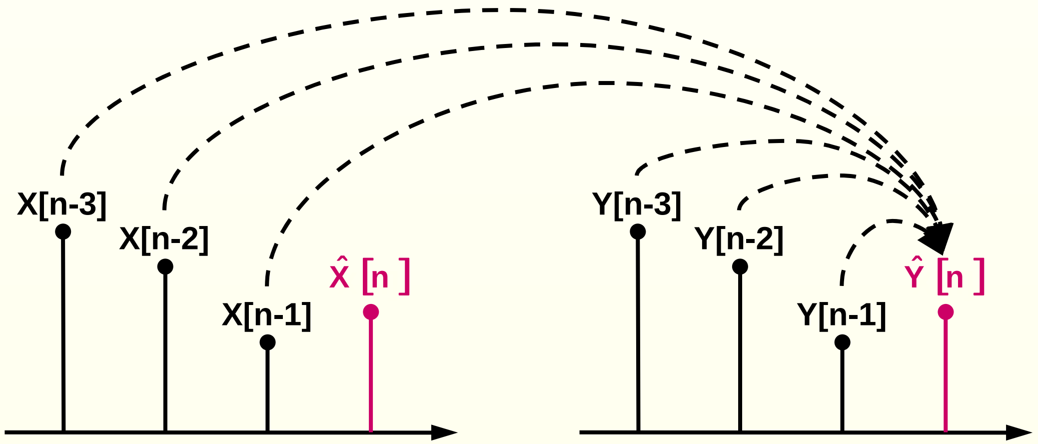
- We must determine the coefficients a[k], by minimizing the power of the error e[n]

Bivariate autoregressive modeling

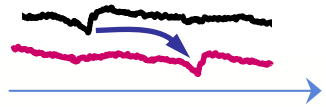
- The autoregressive prediction of y is made by including information about the past samples of another signal x:

$$x[n] = \sum_{k=1}^{p} a_{xy}[k]x[n-k] + \sum_{k=1}^{p} b_{xy}[k]y[n-k] + e_{xy}[n]$$

$$y[n] = \sum_{k=1}^{p} a_{yk}[k]x[n-k] + \sum_{k=1}^{p} b_{yx}[k]y[n-k] + e_{yx}[n]$$



Granger Causality Test



- By comparing univariate and bivariate AR:

$$x[n] = \sum_{k=1}^{p} a_x[k]x[n-k] + e_x[n]$$

$$y[n] = \sum_{k=1}^{p} a_y[k]y[n-k] + e_y[n]$$

$a_x[k]$ and $a_y[k]$ are the model parameters,

p is the model order

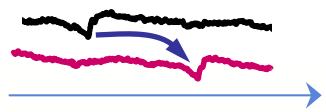
e_x and e_y are the uncertainties or the residual noises associated with the model. Here, the prediction error depends only on the past values of the own signal.

$$x[n] = \sum_{k=1}^{p} a_{xy}[k]x[n-k] + \sum_{k=1}^{p} b_{xy}[k]y[n-k] + e_{xy}[n]$$

$$y[n] = \sum_{k=1}^{p} a_{yk}[k]x[n-k] + \sum_{k=1}^{p} b_{yx}[k]y[n-k] + e_{yx}[n]$$

Here, the prediction error for each individual signal depends on the past values of both signals.

Granger Causality Test



The prediction performances for both models can be assessed by the variances of the prediction errors:

$$V_{x|x} = \mathrm{var}(e_x) \qquad V_{y|y} = \mathrm{var}(e_y)$$

For univariate models

$$V_{x|x,y} = var(e_{xy}) \qquad V_{y|y,x} = var(e_{yx})$$

For bivariate models

where var(.) indicates variance operator, X|X_ and X|X_,Y_ indicate predicting X by its past values alone and by past values of X and Y, respectively. If $V_{X|X,Y}<V_{X|X}$ then Y causes X in the sense of Granger causality. A measure of Granger Causality from y to x can the be expressed as:

$$\boxed{G_{y \to x} = \ln\left(\frac{V_{x|x}}{V_{x|x,y}}\right)}$$

If the past of Y does not improve the prediction of X, then $V_{x|x,y} \approx V_{x|x} \Rightarrow G \approx 0$

Any improvement in prediction of X by the inclusion of Y: $V_{x|x,y} \downarrow \quad \Rightarrow G \uparrow$

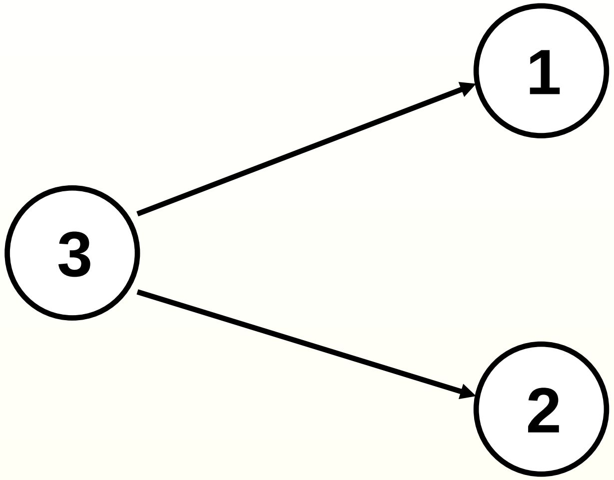
Advantages and limitations of Granger Causality Test

- Advantages:
  - DIRECTIONALITY $G_{y \to x} \neq G_{x \to y}$
  - Statistical definition

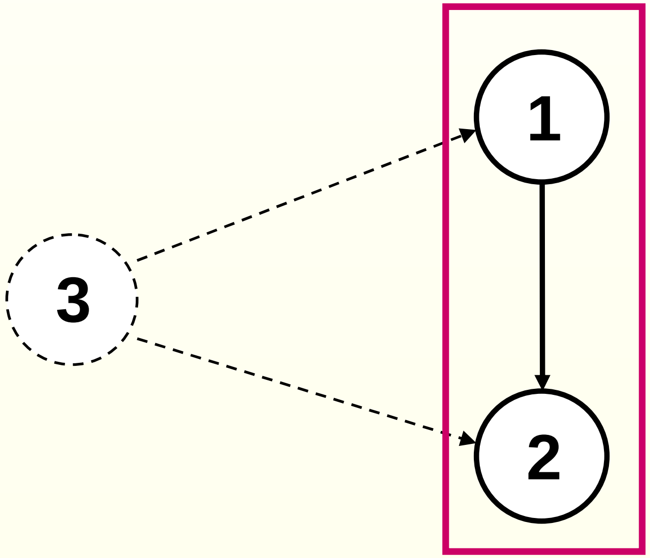
- Limitations:
  - Defined in the time domain (in the time window we used to identify the model) provided that the signals are stationary in that window
  - <u>True causality can only be assessed if the set of two time series contains all possible relevant information and sources of activities for the problem</u> (Granger, 1980).

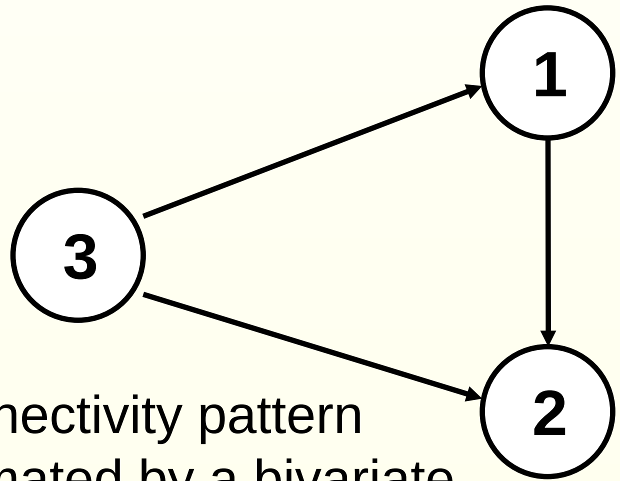
Limitations of the bivariate methods

If the sources of activities for the problem are more than 2:



Bivariate modelization of signals 1 and 2 does not recognize that the correlation between the two signals is due to a common effect of 3 (which is not included in the model)

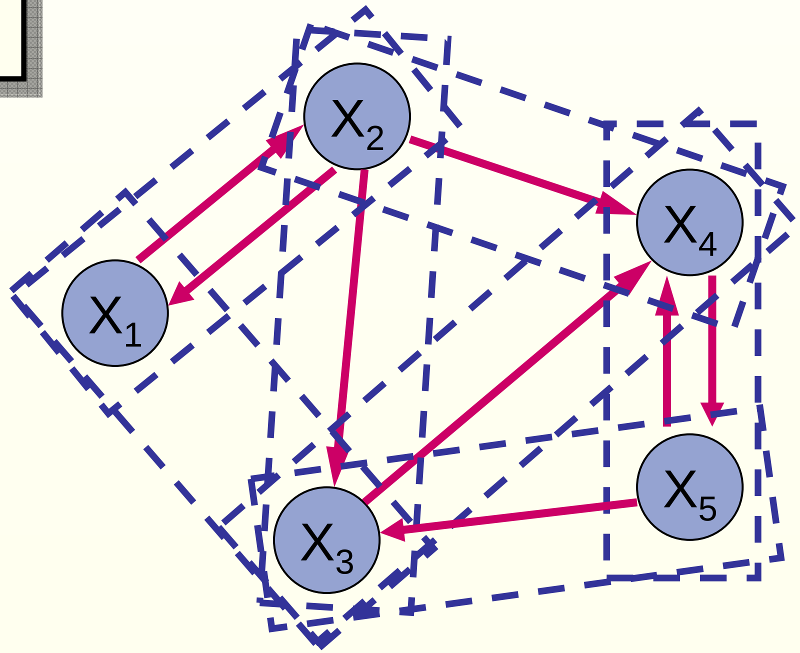




Connectivity pattern estimated by a bivariate method

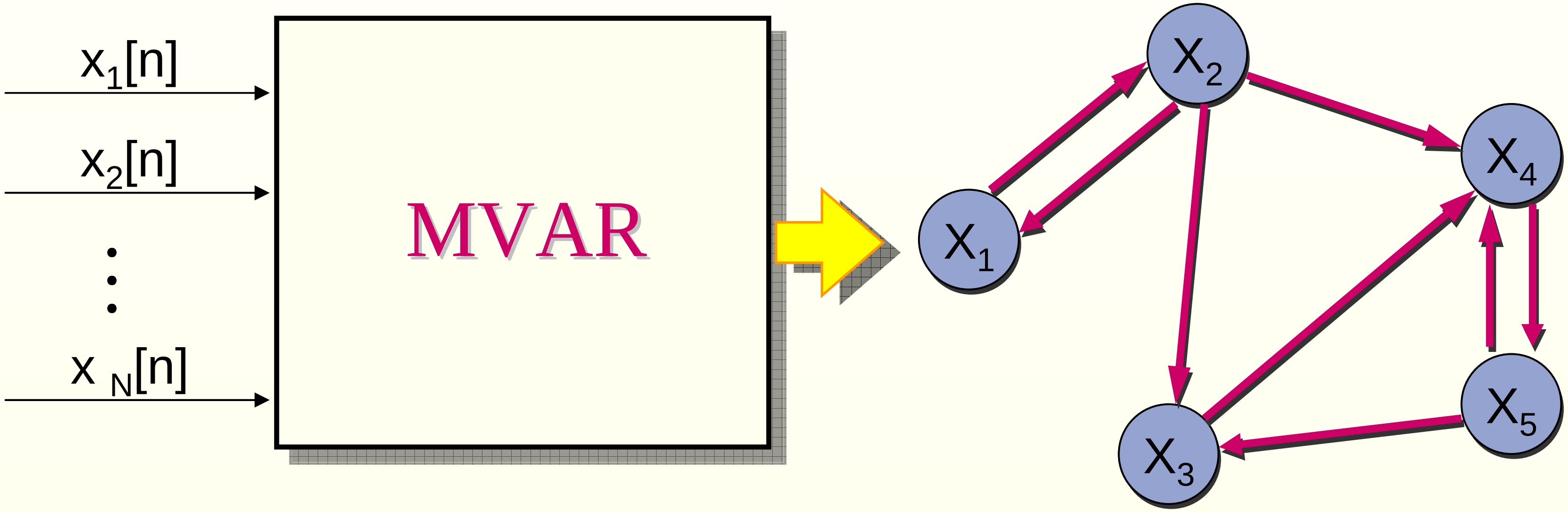
Bivariate methods for multiple signals

BIVARIATE METHODS: a model for each couple of signals in a set



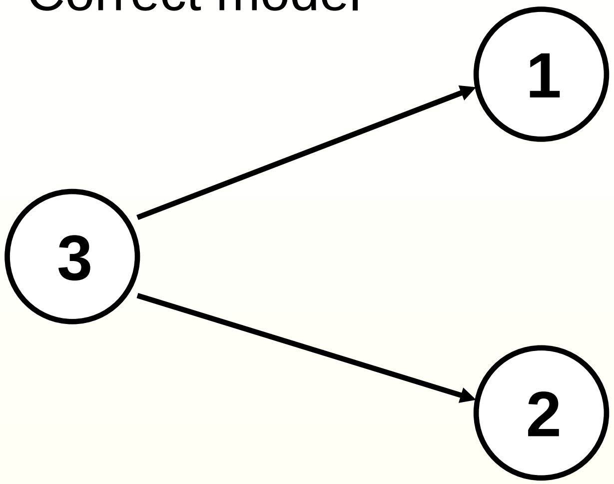
Multivariate methods

MLTIVARIATE METHODS: The connectivity pattern is obtained by a unique model estimated on the entire set of data and takes into account all their interactons



Multivariate methods

Correct model



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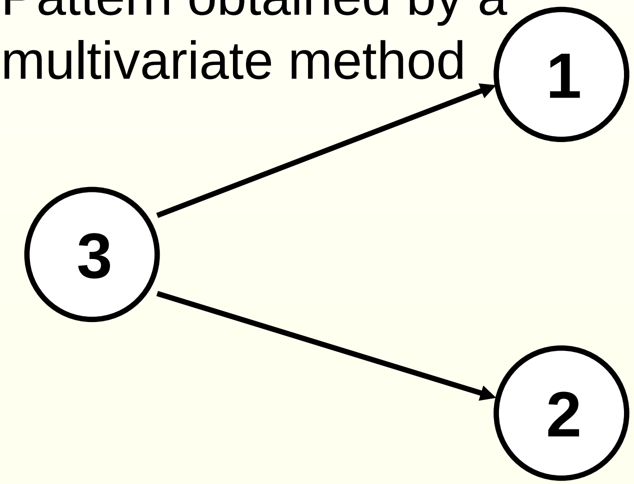
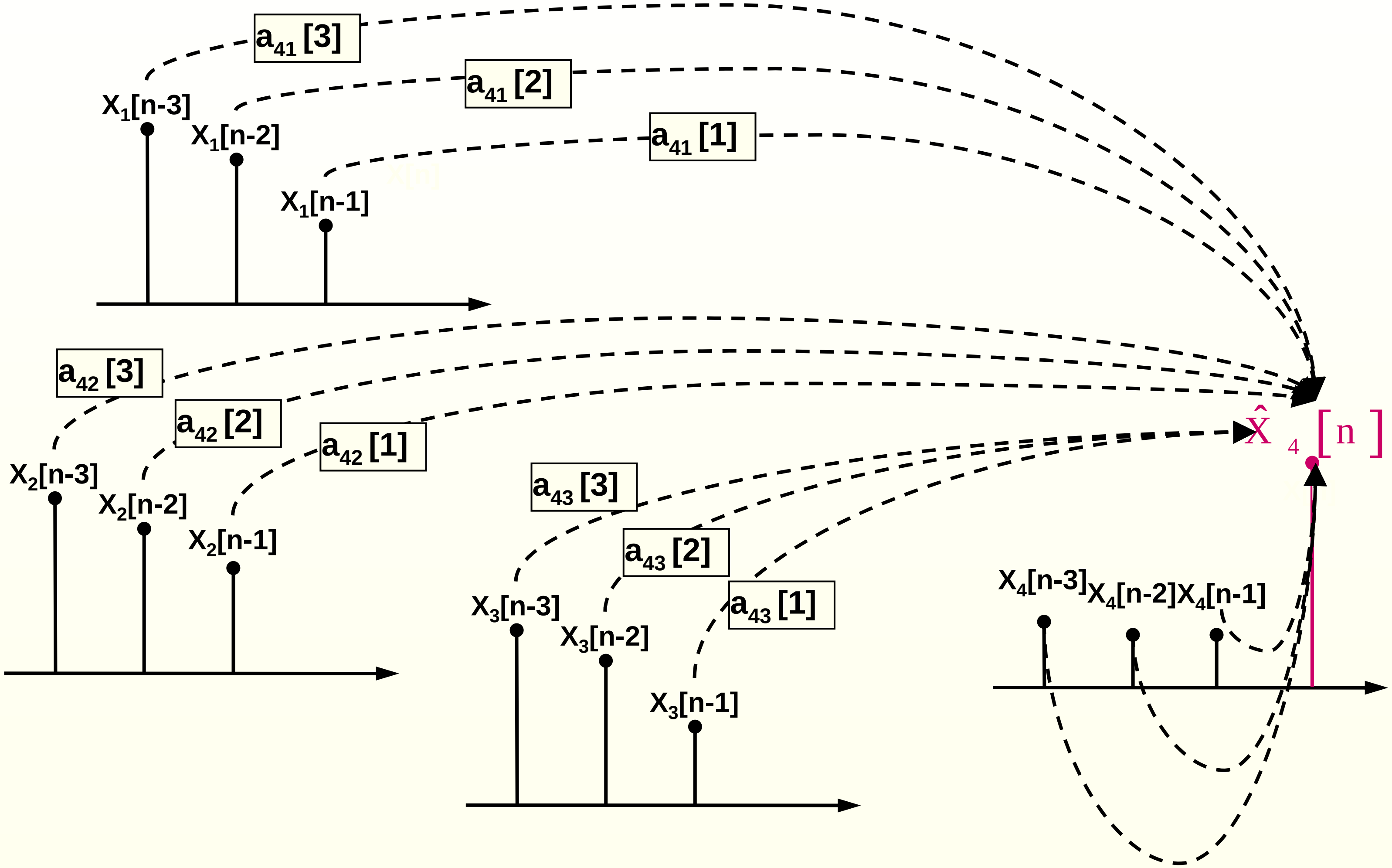
Pattern obtained by a multivariate method



Multivariate methods, by building a unique model based on all the signals, use all the information at disposal and thus allow a better comprehension of the relationship between the signals

Multivariate Autoregressive Models (MVAR)



Multivariate Autoregressive Models (MVAR)

- Given a set of N signals: $\bar{X} = \begin{bmatrix} x_1[1] & x_2[1] & \cdots & x_N[1] \end{bmatrix}^T$
- A Multivariate Autoregressive Model of order p is:

$$
\begin{aligned}
x_1[n] &= -\sum_{k=1}^{p} a_{11}[k]x_1[n-k] - \sum_{k=1}^{p} a_{12}[k]x_2[n-k] - \cdots - \sum_{k=1}^{p} a_{1N}[k]x_N[n-k] + e_1[n] \\
x_2[n] &= -\sum_{k=1}^{p} a_{21}[k]x_1[n-k] - \sum_{k=1}^{p} a_{22}[k]x_2[n-k] - \cdots - \sum_{k=1}^{p} a_{2N}[k]x_N[n-k] + e_2[n] \\
&\vdots \\
x_N[n] &= -\sum_{k=1}^{p} a_{N1}[k]x_1[n-k] - \sum_{k=1}^{p} a_{N2}[k]x_2[n-k] - \cdots - \sum_{k=1}^{p} a_{NN}[k]x_N[n-k] + e_N[n]
\end{aligned}
$$

Multivariate Autoregressive Models (MVAR)

- The model parameters are N·N·p:

$$\bar{a}[1]=\begin{bmatrix} a_{11}[1] & \cdots & a_{1N}[1] \\ \vdots & \ddots & \vdots \\ a_{N1}[1] & \cdots & a_{NN}[1] \end{bmatrix} \quad \bar{a}[2]=\begin{bmatrix} a_{11}[2] & \cdots & a_{1N}[2] \\ \vdots & \ddots & \vdots \\ a_{N1}[2] & \cdots & a_{NN}[2] \end{bmatrix} \quad \cdots \quad \bar{a}[p]=\begin{bmatrix} a_{11}[p] & \cdots & a_{1N}[p] \\ \vdots & \ddots & \vdots \\ a_{N1}[p] & \cdots & a_{NN}[p] \end{bmatrix}$$

- And the N variances of the residuals:

$$S_E=\begin{bmatrix} \sigma_1 \\ \sigma_2 \\ \vdots \\ \sigma_N \end{bmatrix}$$

Total number of parameters to be estimated:N·N·p+N=N(N·p+1)

MVAR in the frequency domain

$$\sum_{k=0}^{p} A(k)X(t-k) = E(t)$$

$$\overline{A}(f)\overline{X}(f) = \overline{E}(f)$$

Where: $A_{ij}(f) = \sum_{k=0}^{p} a_{ij}[k] e^{-j2\pi fTk}$

$$\overline{A}(f) = \begin{bmatrix} A_{11}(f) & \cdots & A_{1N}(f) \\ \vdots & \ddots & \vdots \\ A_{N1}(f) & \cdots & A_{NN}(f) \end{bmatrix}$$

$$\overline{X}(f) = \begin{bmatrix} X_1(f) \\ \vdots \\ X_N(f) \end{bmatrix} \qquad \overline{E}(f) = \begin{bmatrix} E_1(f) \\ \vdots \\ E_N(f) \end{bmatrix}$$

MVAR in the frequency domain

- We can write the previous equation as follows

$$\overline{X}(f) = \overline{A}^{-1}(f)\overline{E}(f) = \overline{H}(f)\overline{E}(f)$$

where H(f) is the TRANSFER MATRIX of the MVAR filter:

$$\overline{H}(f) = \overline{A}^{-1}(f) = \begin{bmatrix} H_{11}(f) & \cdots & H_{1N}(f) \\ \vdots & \ddots & \vdots \\ H_{N1}(f) & \cdots & H_{NN}(f) \end{bmatrix}$$

Directed Transfer Function (DTF)

- *DIRECTED TRANSFER FUNCTION (DTF)* from j to i is defined on the basis of matrix H (Kaminski and Blinowska, 1991, 2001):

$$\boxed{\theta_{ij}(f) = \left|H_{ij}(f)\right|^2}$$

- Normalized DTF:

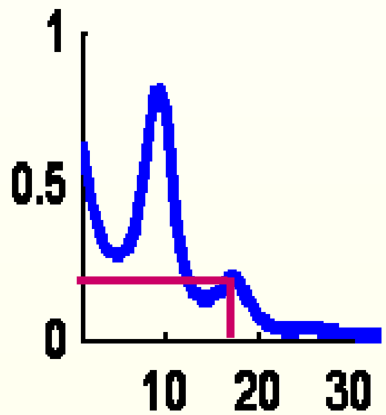
$$\boxed{\theta_{ij}(f) = \frac{\left|H_{ij}(f)\right|^2}{\sum_{m=1}^{N}\left|H_{im}(f)\right|^2}}$$

With: $\sum_{n=1}^{N}\theta_{in}(f) = 1$

Directed Transfer Function (DTF)

- Since $H_{ij}(f) \neq H_{ji}(f)$, we have: $\boxed{\theta_{ij}(f) \neq \theta_{ji}(f)}$

The value of DTF_{ij} at a certain frequency f_0 represents the existence of a causality link directed from j to i



Partial Directed Coherence (PDC)

- *PARTIAL DIRECTED COHERENCE (PDC)* from j to i is defined on the basis of matrix A (Baccalà and Sameshima, 2001):

$$\boxed{\pi_{ij}(f) = \left|A_{ij}(f)\right|^2}$$

- Different normalization of PDC are provided, for instance (Astolfi et al, 2007):

$$\boxed{\pi_{ij}(f) = \frac{\left|A_{ij}(f)\right|^2}{\sum_{m=1}^{N}\left|A_{im}(f)\right|^2}}$$

Where: $\sum_{n=1}^{N} \pi_{in}(f) = 1$

Partial Directed Coherence (PDC)

- Also for PDC, since $A_{ij}(f) \neq A_{ji}(f)$

$$\boxed{\pi_{ij}(f) \neq \pi_{ji}(f)}$$

The value of PDC_{ij} at a certain frequency f_0 represents the existence of a causality link directed from j to i

Partial Directed Coherence (PDC) & Directed Transfer Function (DTF)

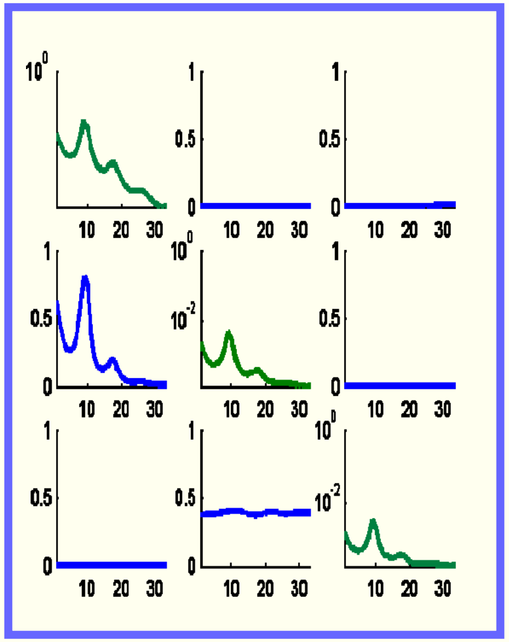
$$\sum_{k=0}^{p} A(k)X(t-k) = E(t) \quad \Rightarrow \quad A(f)X(f)=E(f)$$

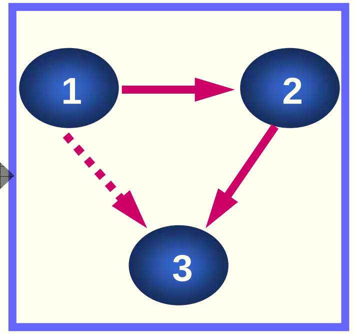
$$X(f)=H(f)E(f)$$

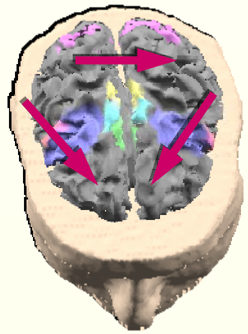
$$PDC_{ij}(f) = \frac{\left|A_{ij}\right|^2}{\sum_{m=1}^{L}\left|A_{mi}(f)\right|^2}$$

$$DTF_{ij}(f) = \frac{\left|H_{ij}\right|^2}{\sum_{m=1}^{L}\left|H_{mi}(f)\right|^2}$$

PDC_{ij} and DTF_{ij} estimate the influence of the region j toward the region i







Differences between DTF and PDC

- Similar results
- Due to their mathematical formulation, and to matrix inversion:
  - DTF describes the sum of all influences directed from i to j (direct and indirect)
  - PDC describes only direct influences
  - If no direct influence is present, DTF can still have a significant value, while PDC does not.
  - Depending on the kind of information we are interested in, we can decide which one we need to use.

Simulation study

Objectives:

To perform a comparative study of the different spectral estimators of the connectivity, based on some specific questions:

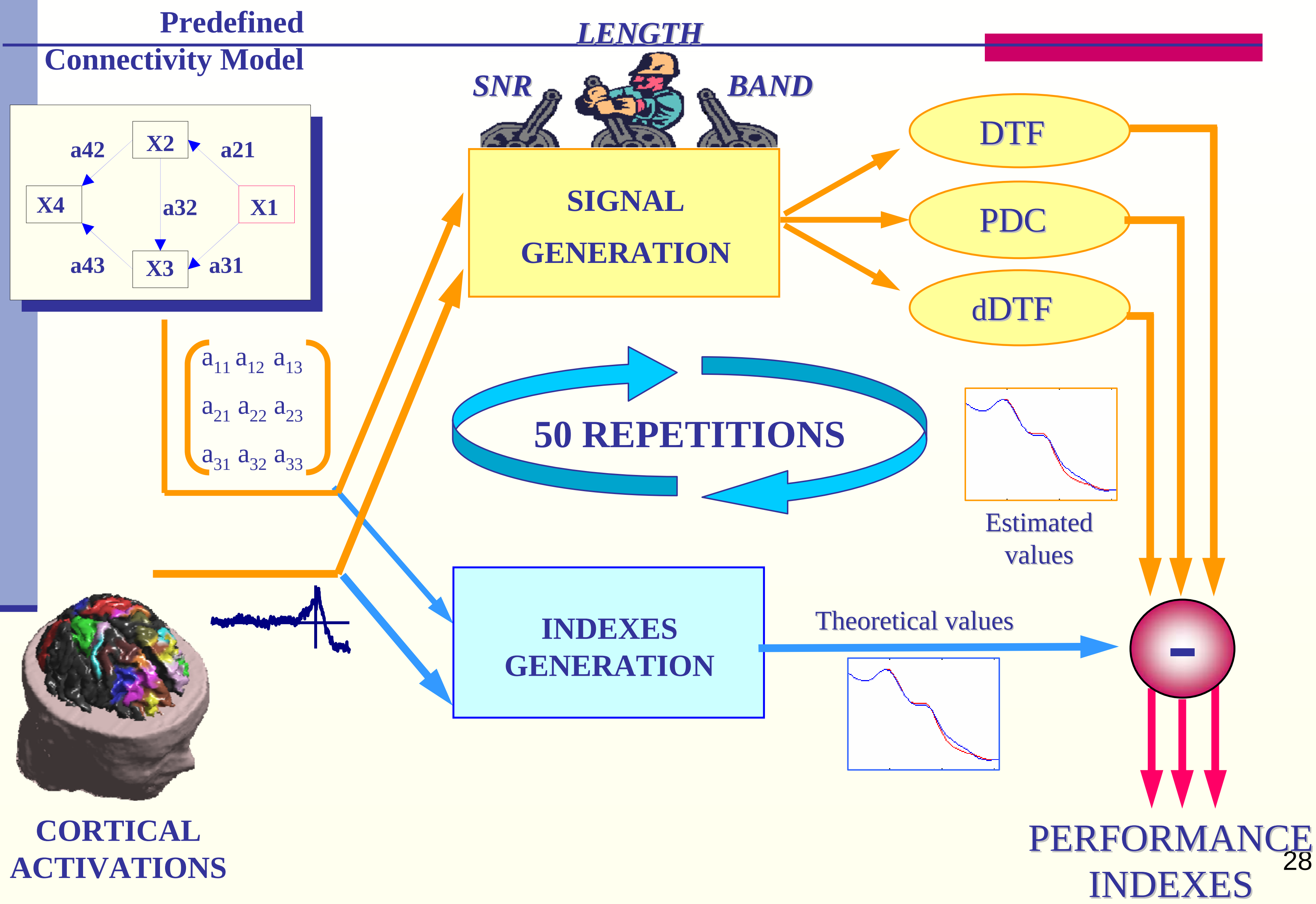
1) How do DTF, PDC, and dDTF perform in the discrimination of direct or indirect causality patterns?

2) How are the estimators influenced by different factors affecting the EEG recordings, like the signal to noise ratio and the amount of data available?

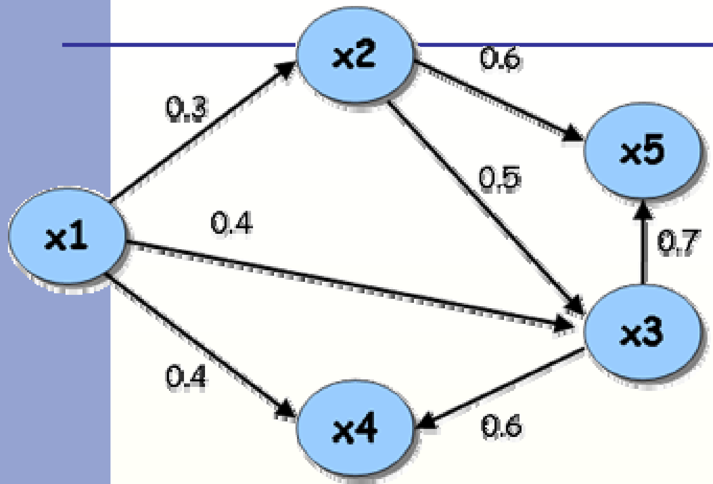
3) What is the most effective method for estimating a connectivity model under the conditions usually encountered in standard EEG recordings?

Astolfi et al, 2007

Simulation Setup



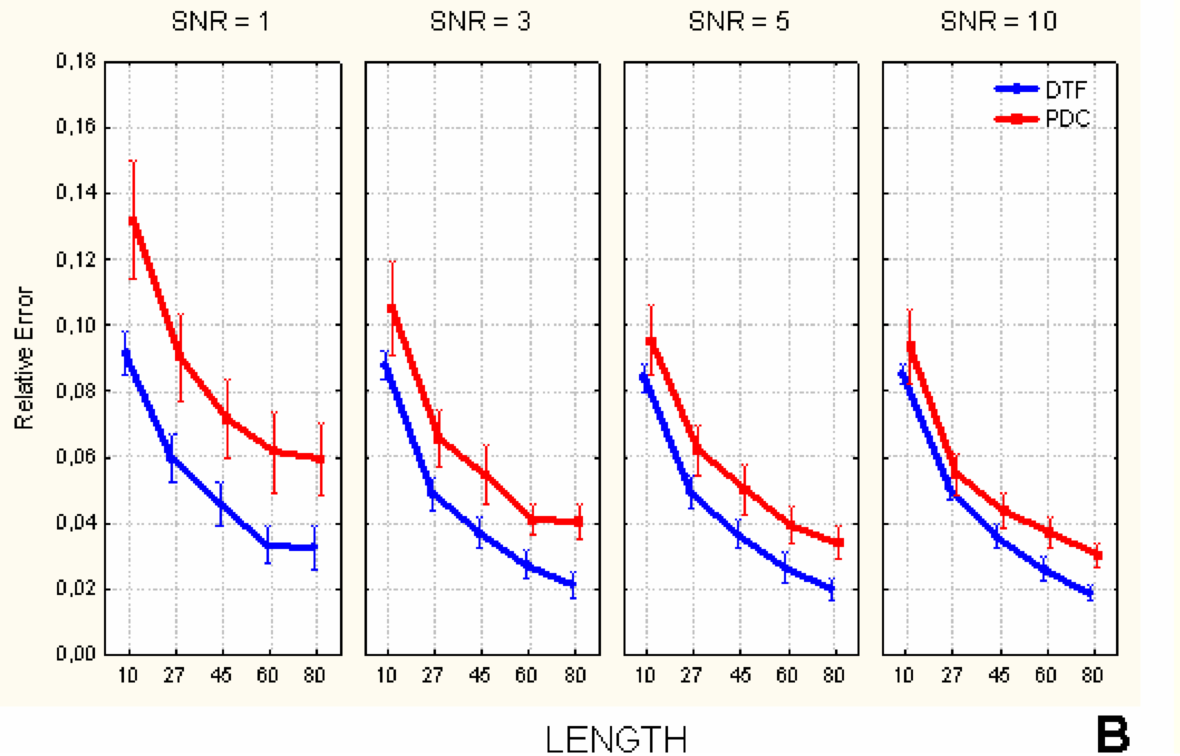
Simulation Results



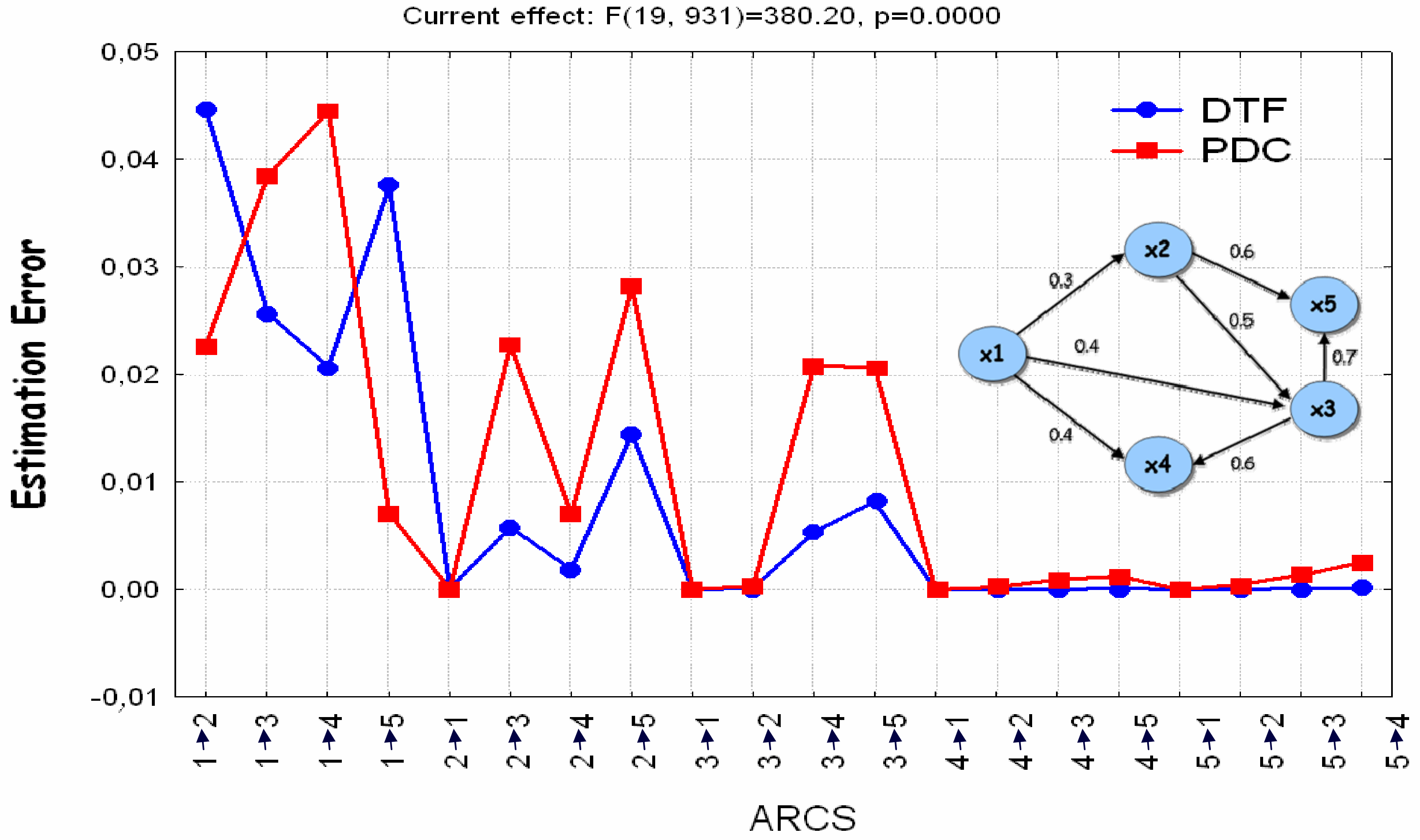
5 ROIs connectivity model

Analysis of Variance: influence of the different levels of the SNR and LENGTH on the estimation for DTF and PDC.

95% confidence interval of the mean errors computed across the simulations.

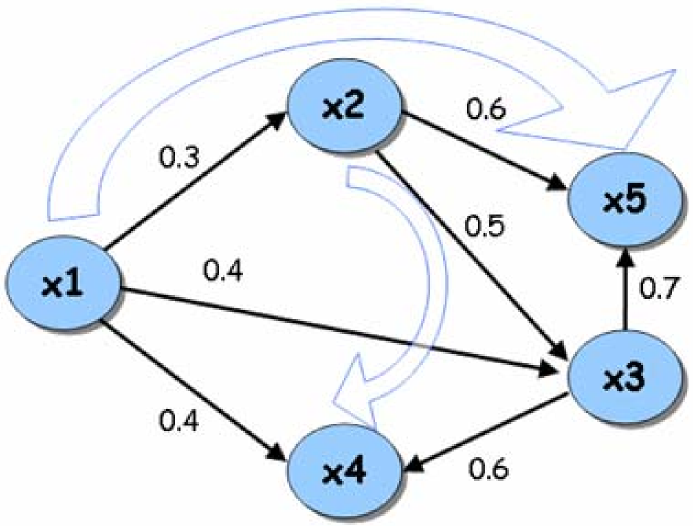


Simulation Results



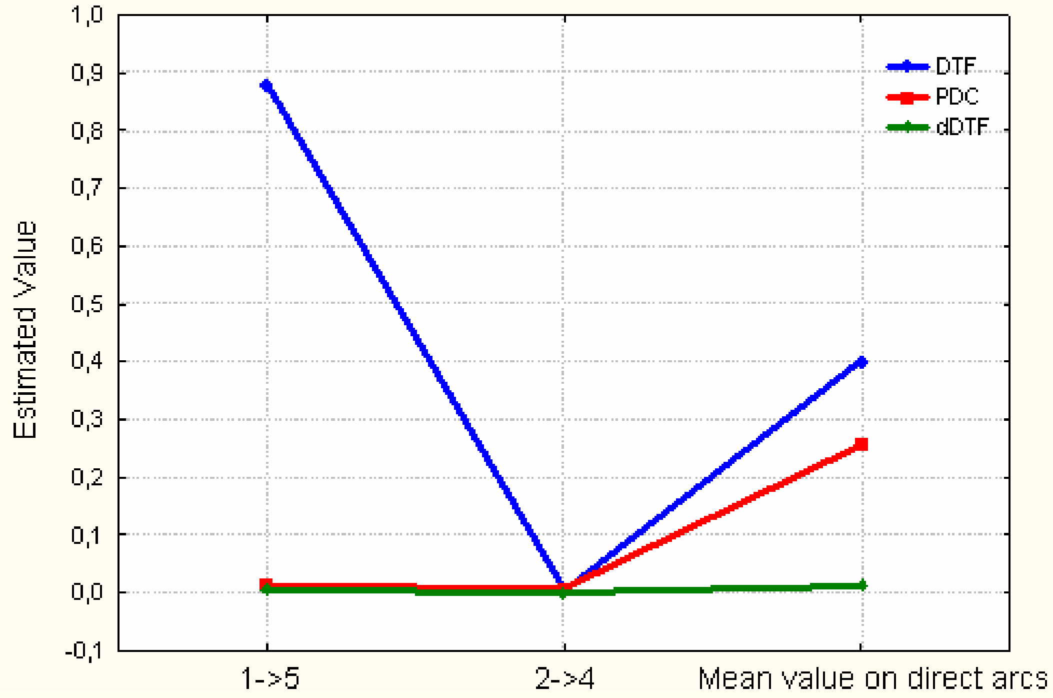
Error on single arcs for DTF and PDC.

Simulation Results



Indirect connectivity paths

Values estimated by DTF, PDC and dDTF on the indirect arcs 1->5 and 2->4, and average value on the direct arcs.

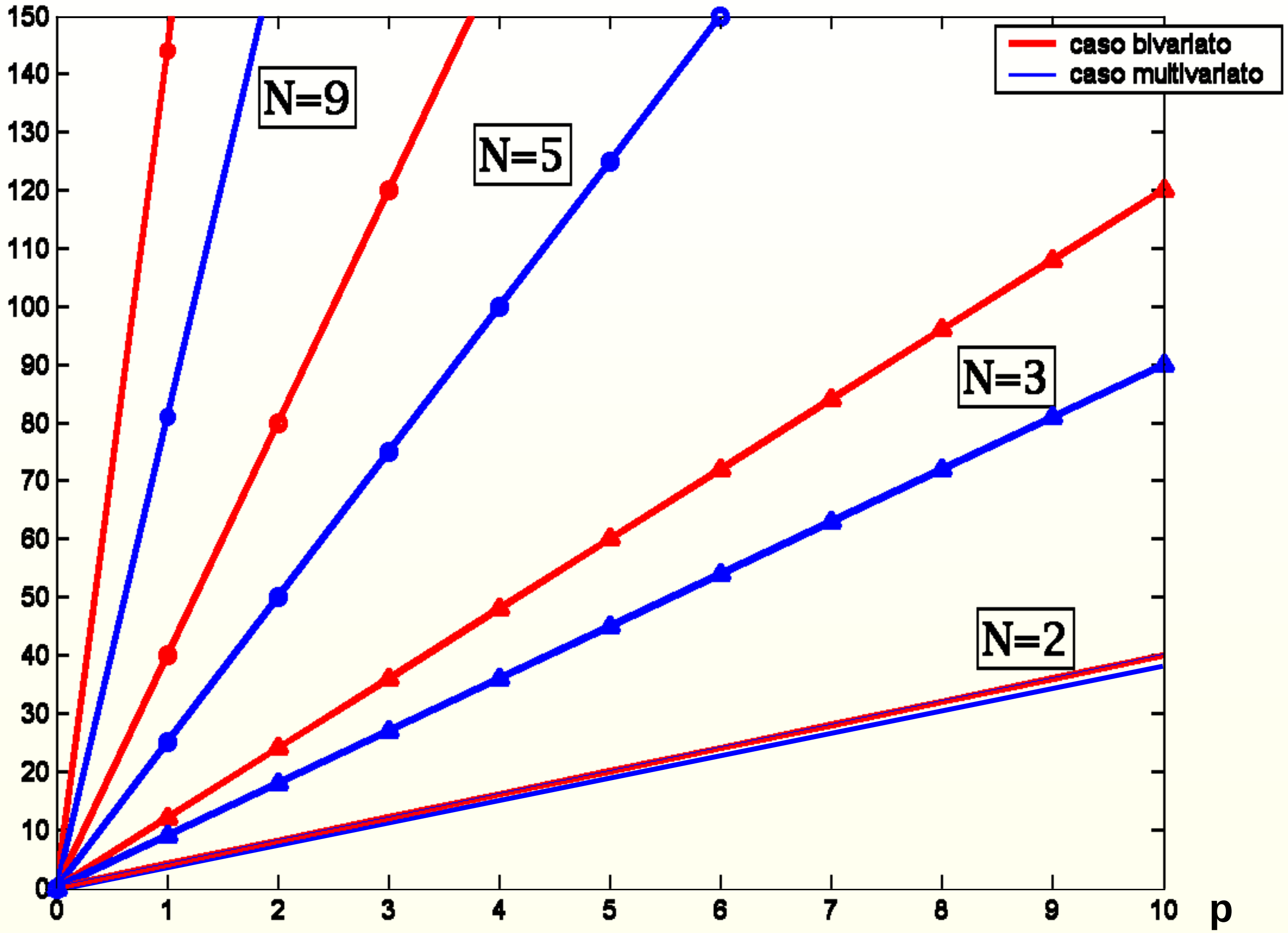


Computational cost

- Bivariate case:
  - N signals
  - Order p
  - N(N-1)/2 models,
  - 4p parameters for each model: $\boxed{2(N^2-N)p}$
- Multivariate case:
  - N signals
  - order p $\boxed{N^2p}$

Computational cost

N° parameters



Bivariate and multivariate: when and which

- Bivariate methods:
  - Limitations:
    - Higher computational cost
    - Less precision
  - Advantages:
    - No limit to the number of signals
    - To be used when short data segments are available

Bivariate and multivariate: when and which

- Multivariate methods:
  - Limitations:
    - Limitation in the number of channels/signal that can be modelized
  - Advantages:
    - Better estimation performances
    - Allows for inserting all data sources in the model

Time-varying connectivity estimation

Why a time-varying measure of cortical connectivity?

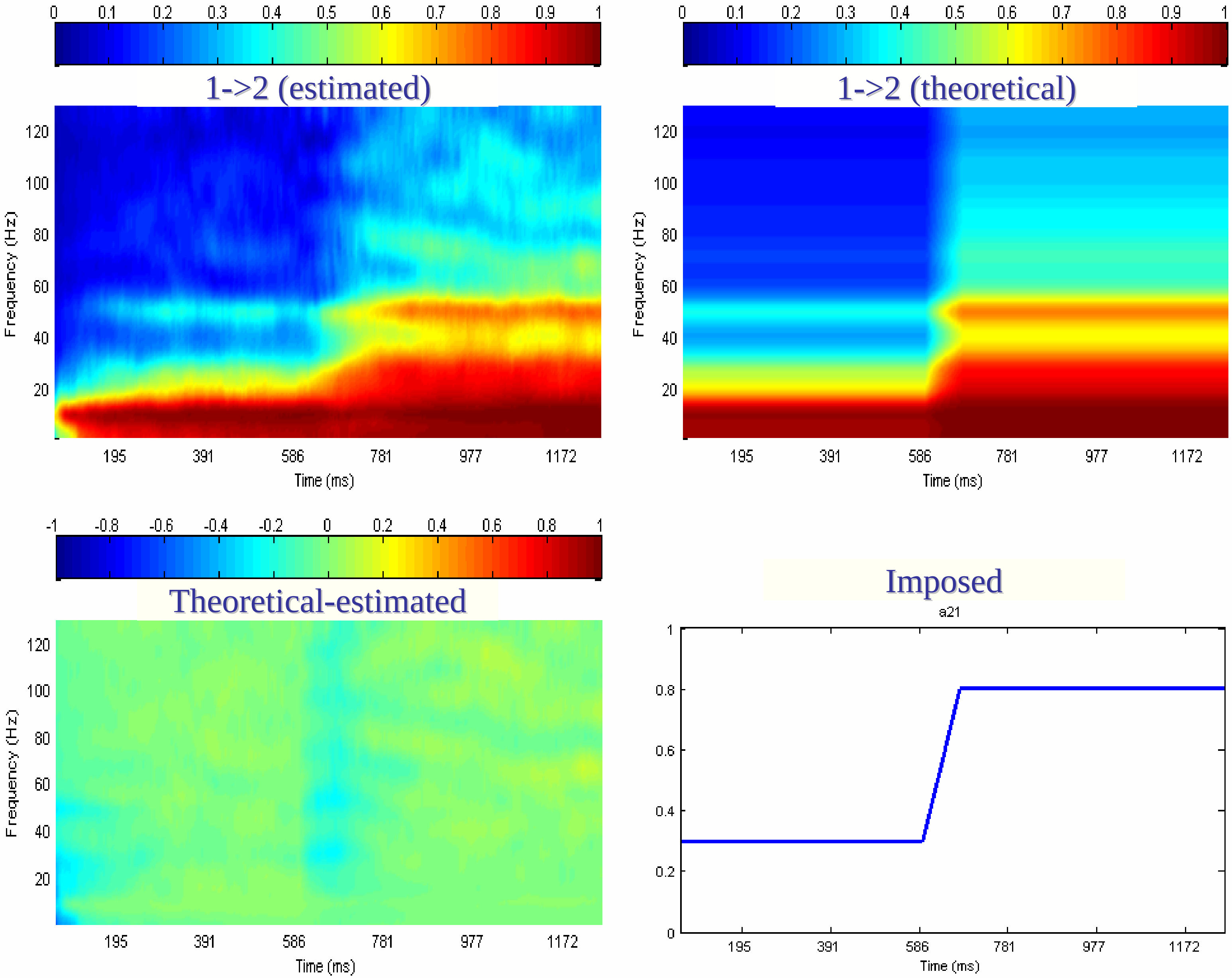
MVAR based methods for the connectivity estimation are able to describe direction and strength of the interactions between cortical areas, but their classical estimation requires the stationarity of the signals in the time interval under examination

- Transient pathways of information transfer remains hidden
- It's not possible to follow the rapidly changing brain connectivity

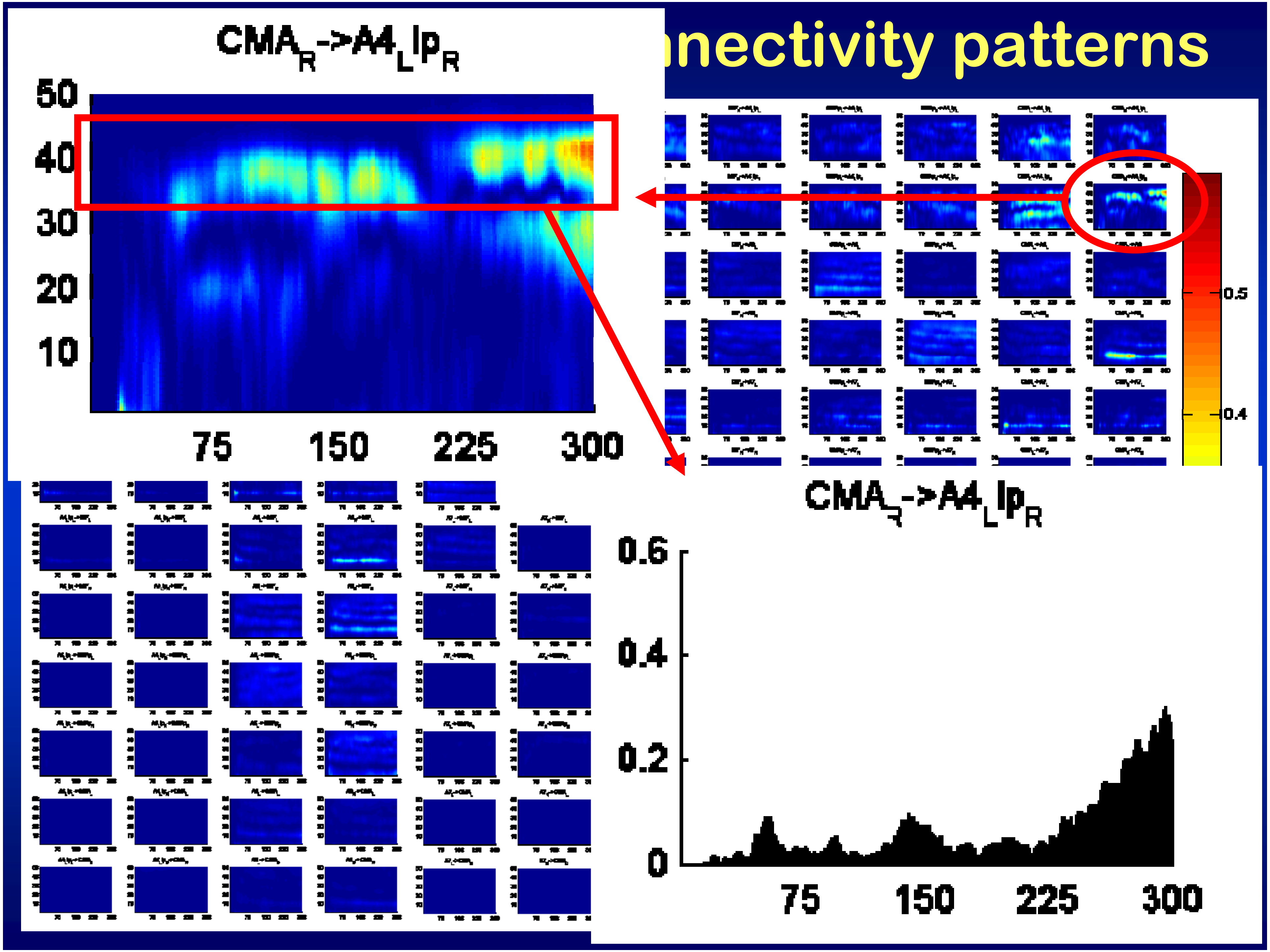
TIME-VARYING ESTIMATORS based on an MVAR model with time-dependent parameters (adaptive fit, Recursive Least Squares with Forgetting Factor, Hesse et al, 2003)

RESULT: Time-frequency distributions of Granger causality

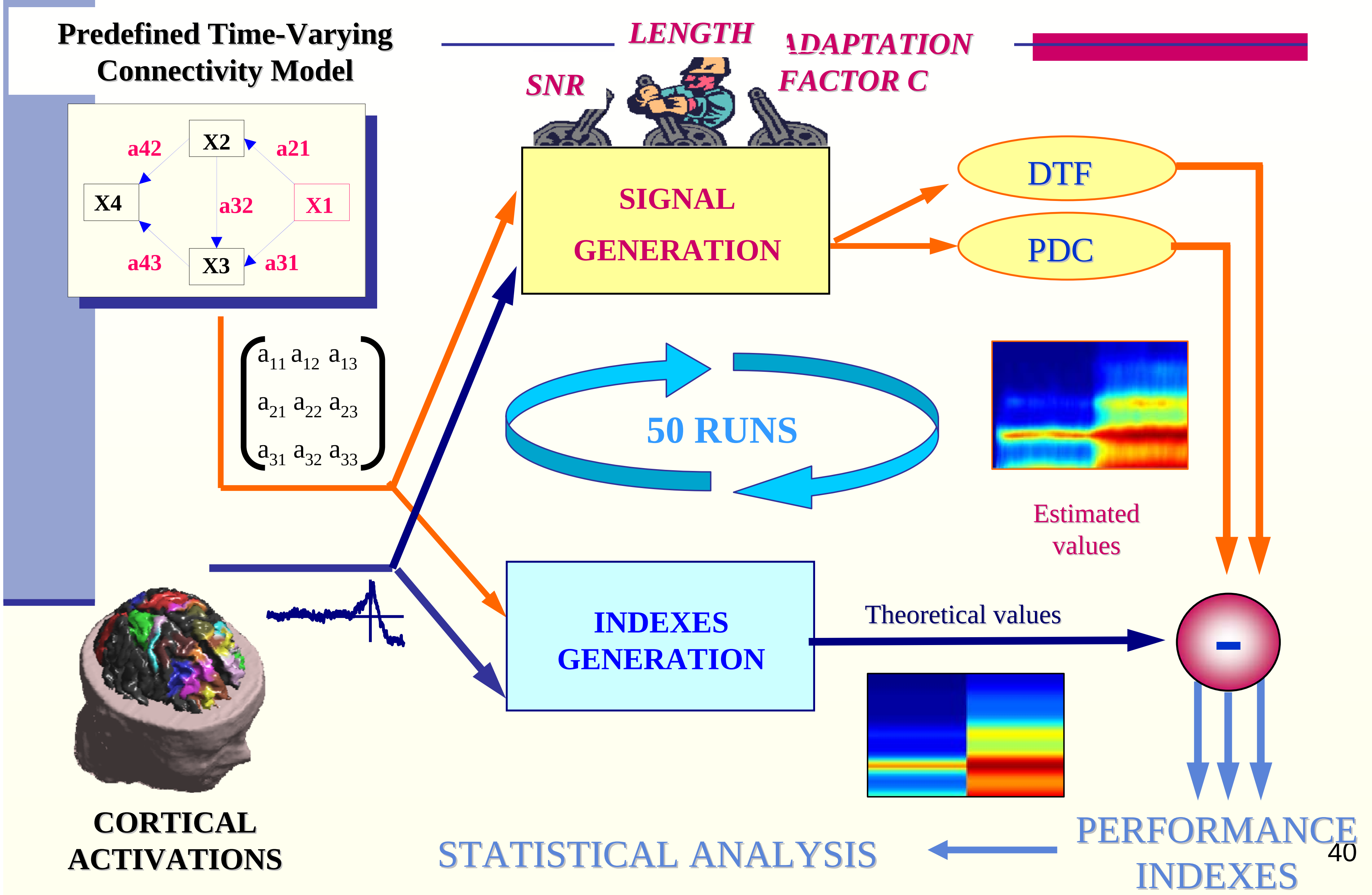
Time-varying connectivity between ROIs (simulation)



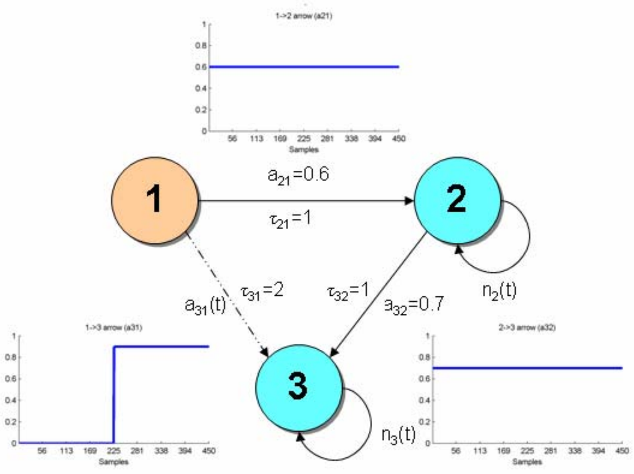
nectivity patterns



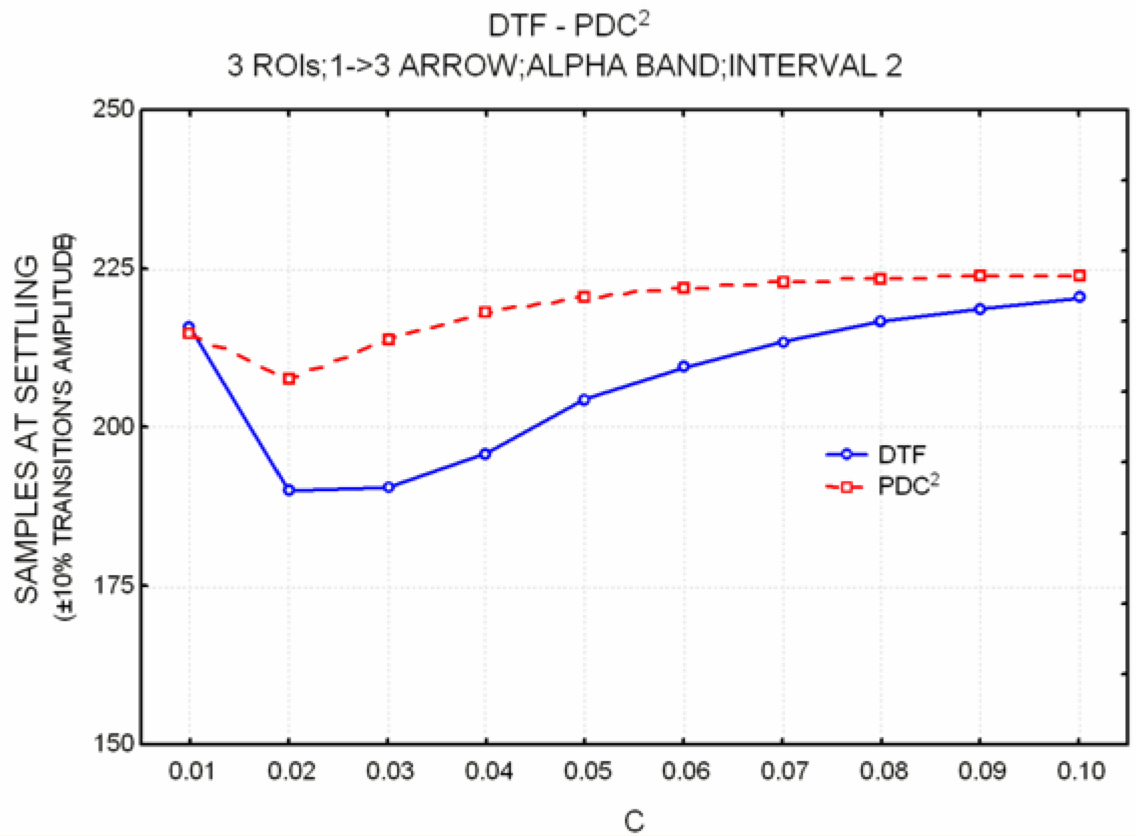
Simulation Setup



Simulation results



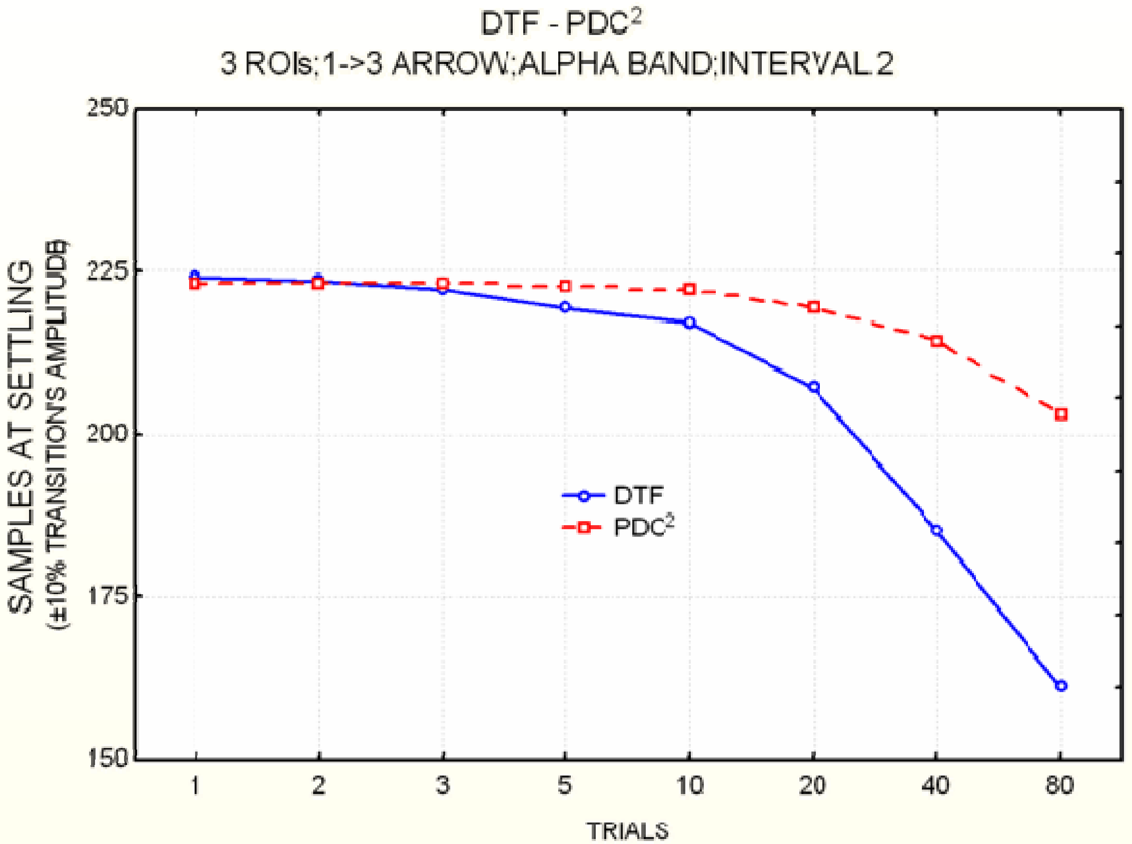
Time-varying model imposed on simulated signals (3 cortical areas)



Analysis of Variance: influence of the different choices of the factors C on the adaptation speed of time-varying DTF and PDC.

ANOVA performed on the Time at settling (10% of the transition amplitude)

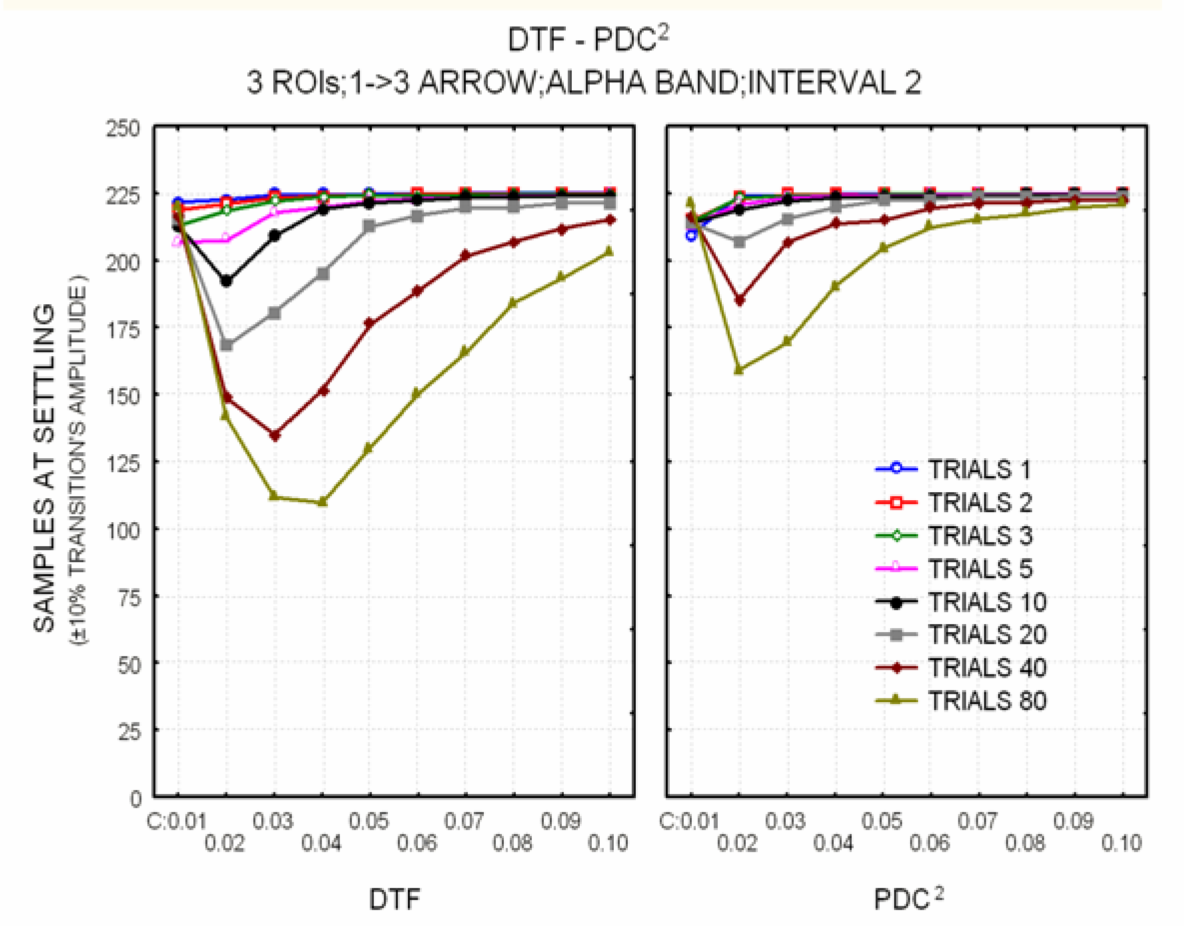
Simulation results



Analysis of Variance: influence of the number of trials on the adaptation speed of time-varying DTF and PDC.

ANOVA performed on the Time at settling (10% of the transition amplitude)

Simulation results



Analysis of Variance: two-way effect of adaptation factor C and number of trials on the adaptation speed of time-varying DTF and PDC.

ANOVA performed on the Time at settling (10% of the transition amplitude)

Applications: will be shown tomorrow (during the hands-on part of the course)

Non-linear Methods

- Mutual Information:
  - based on information theory
  - tells us how much extra information one gets from one signal X by knowing the outcomes of a second one Y
  - quantifies the statistical dependencies between the two variables X and Y, with no assumption about the form of their respective densities and implicitly their generating processes
  - Is asymmetric index → no direction
- Phase synchronisation
  - the phases of two coupled nonlinear (noisy or chaotic) oscillators may synchronize even if their amplitudes remain uncorrelated
  - It's based on the quantification of the phase locking
- Event Synchronisation
  - useful in case of point-like events, like the firing of a neuron or the appearance of epileptic spikes in an EEG recording

Non-linear Vs Linear approaches

- Nonlinear methods entail very high computational demands in comparison to the linear ones, and may not be robust to nonstationariness.
- Reliable estimations of the MI often requires a large amount of data, a constraint that is sometimes in conflict with the requisite of stationarity in the case of experimental data.
- Nonlinear approaches should be regarded as a complement of the linear approach that allows getting a more comprehensive picture of the analyzed data. The information provided by multivariate nonlinear analysis does not necessarily coincide with that of the linear methods. Both approaches may assess different parts of the interdependence between the signals. Additionally, from the methodological point of view, linear methods sometimes present better properties that their nonlinear counterparts, such as robustness against noise.

Linear and non-linear approaches

- “In consequence, a rigorous approach to the study of any neurophysiological data set should not be biased towards nonlinear methods. Quite on the contrary, the linear approach should be the initial choice, and it is indeed a healthy practice to try first the traditional approaches before going to the more complicated ones. Only if we have good reasons to think that there is any nonlinear structure either in the data themselves or in the interdependence between them should the nonlinear approach be adopted. And even in this case, the best strategy would consist in using both linear and nonlinear methods alike to be sure that we have gathered all the information available from the signals.” (Pereda et al, 2005)

- REFERENCES:

  - Pereda, Quian Quiroga and Bhattacharya, 2005
  - David, Cosmelli and Friston, Neuroimage, 2004.

Questions?

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REFERENCES

- Time-varying connectivity:
  - L. Astolfi, F. Cincotti, D. Mattia, F. De Vico Fallani, A. Tocci, A. Colosimo, S._Salinari, M. G. Marciani, W. Hesse, H. Witte, M.Ursino, M.Zavaglia and F. Babiloni, Tracking the time-varying cortical connectivity patterns by adaptive multivariate estimators, IEEE Trans on Biomedical Engng., 2008 Mar;55(3):902-13
- Multivariate connectivity methods:
  - L. Astolfi, F. Cincotti, D.Mattia, M.G. Marciani, L. Baccala, F. de Vico Fallani, S. Salinari, M. Ursino, M. Zavaglia, L. Ding, J.C. Edgar, G.A. Miller , B. He and F. Babiloni. Comparison of different cortical connectivity estimators for high-resolution EEG recordings. Hum Brain Mapp. 2007 Feb;28(2):143-57
  - L. Astolfi, F. Cincotti, D.Mattia, M.G. Marciani, L. Baccalà, F. de Vico Fallani, S. Salinari, M. Ursino, M. Zavaglia, and F. Babiloni. Assessing Cortical Functional Connectivity By Partial Directed Coherence: Simulations And Application To Real Data. IEEE Trans Biomed Eng. 2006 Sep;53(9):1802-12.
  - Baccalà L.A., Sameshima K, Partial Directed Coherence: a new concept in neural structure determination. Biol Cybern, 84: 463-474, 2001.
  - Kaminski M, Blinowska K. A new method of the description of the information flow in the brain structures. Biol. Cybern. 1991;65: 203-210.
- Non-linear methods:
  - Evaluation of different measures of functional connectivity using a neural mass model, Olivier David, Diego Cosmelli and Karl J. Friston, NeuroImage 21 (2004) 659–673