NEUROSCIENCE and CONNECTIVITY ESTIMATION

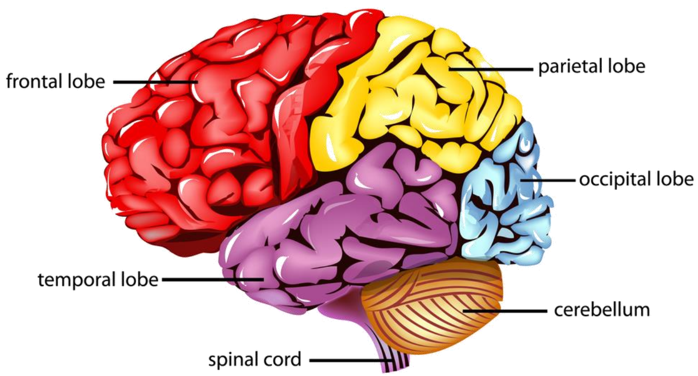
Bioinformatics

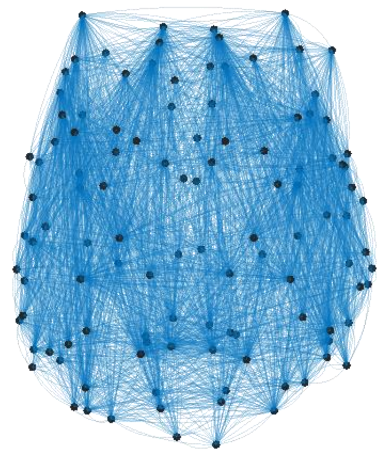
ay 2018-2019

Manuela Petti

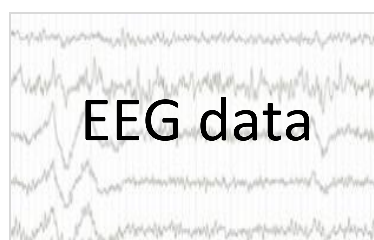
21/11/2018 - 28/11/2018

Neuroscience





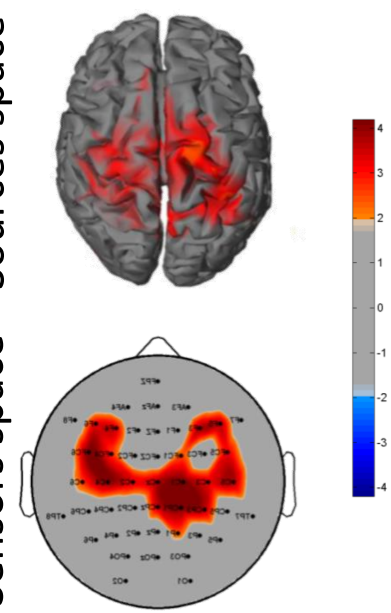
Complex system



Spectral analysis

Sources space

Sensors space



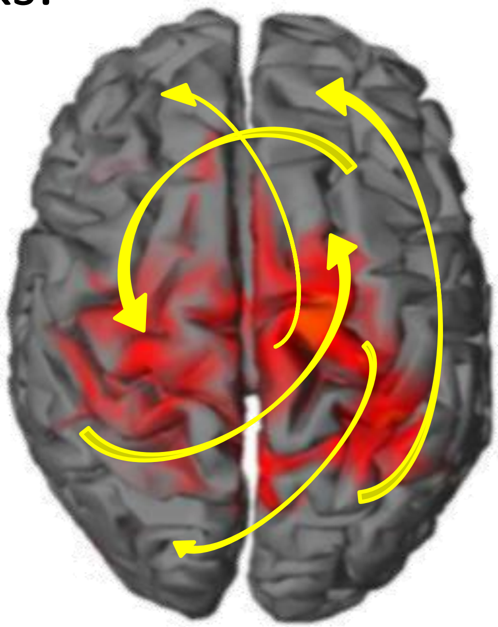
Beyond the brain mapping: the study of brain connectivity

- Functional neuroimaging brain maps reveal where the cortical activations appear for example during the execution of a task

- The next step is to understand how the cerebral areas involved in a task cooperate for its execution

- Understanding communications in brain networks:
  - More interesting than regional activations
  - May indicate some abnormal situations

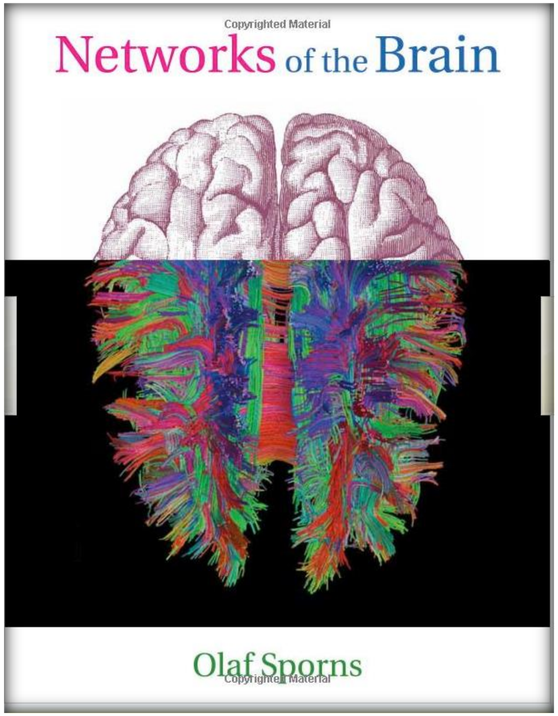
- Different definitions of the information flow between the cortical activities



Brain as a complex network

Network theory is a branch of mathematics concerned with the analysis of the structure of graphs, the mathematical abstraction of networks

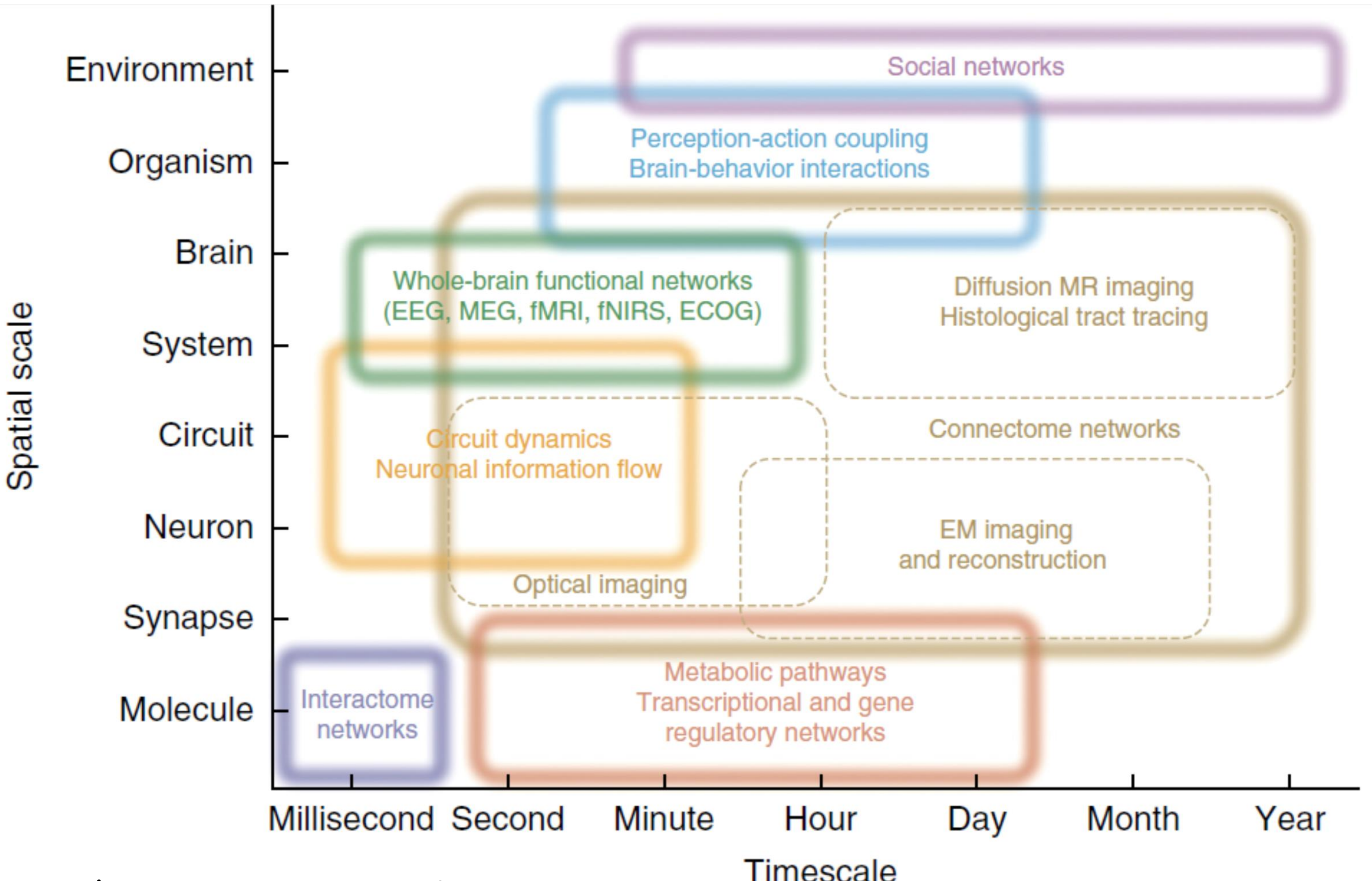
Network theory allows:
- the topological analysis
- the understanding of the emergence (complex behavior spontaneously emerges out of simple interactions), functioning and evolution of networks
- the dynamical processes occurring on networks



Application of network theory to neuroscience
→ Complex system vision of the brain

Network Neuroscience

Network science can be applied to the patterns obtained by studying the brain anatomy and activity at different spatial and temporal scales



Bassett and Sporns, Net Neurosci, 2017

Network Neuroscience

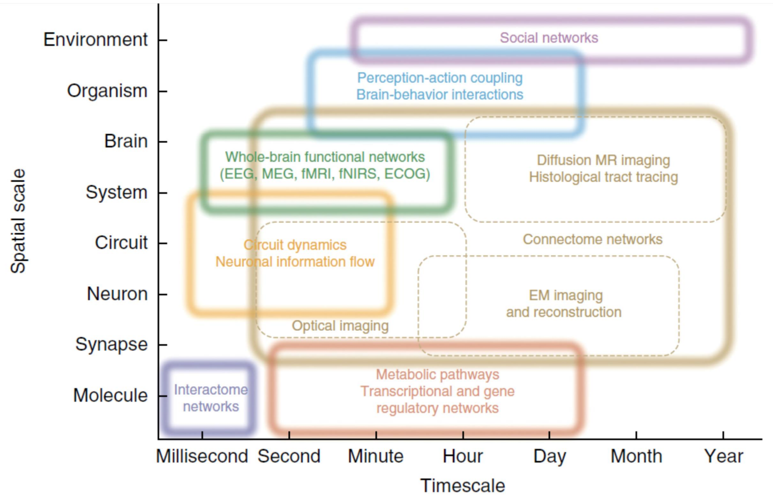
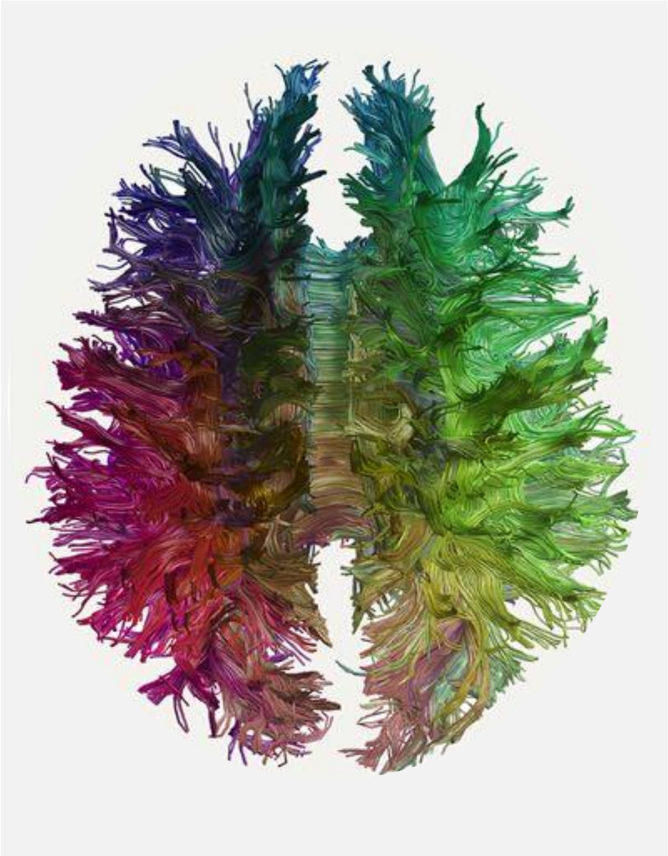


Figure 1 Networks on multiple spatial and temporal scales. Network neuroscience encompasses the study of very different networks encountered across many spatial and temporal scales. Starting from the smallest elements, network neuroscience seeks to bridge information encoded in the relationships between genes and biomolecules to the information shared between neurons. It seeks to build a mechanistic understanding of how neuron-level processes give rise to the structure and function of large-scale circuits, brain systems and whole-brain structure and function. However, network neuroscience does not stop at the brain, but instead asks how these patterns of interconnectivity in the CNS drive and interact with patterns of behavior: how perception and action are mutually linked and how brain-environment interactions influence cognition. Finally, network neuroscience asks how all of these levels of inquiry help us to understand the interactions between social beings that give rise to ecologies, economies and cultures. Rather than reducing systems to a list of parts defined at a particular scale, network neuroscience embraces the complexity of the interactions between the parts and acknowledges the dependence of phenomena across scales. Box dimensions give outer bounds of the spatial and temporal scales at which relational data are measured and interactions unfold, and over which networks exhibit characteristic variations and dynamic changes. Inspired by an iconic image of neuroscience recording methods, last updated in ref. 1. ECOG, intracranial electrocorticography; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; MEG, magnetoencephalography.

Bassett and Sporns, Net Neurosci, 2017

Network Neuroscience

- **Anatomical Connectivity**: the existence of anatomical links allowing the information flow from a cerebral district to another one →
  - Nodes: neurons or cortical areas
  - Edges: axons or fiber tracts



Network Neuroscience

- **Functional Connectivity**: the existence of temporal *relation* between the activity recorded in different cerebral sites

The concept of functional brain connectivity is crucial to understand how communication between cortical regions is organized: brain areas interacting with a functional connection are not necessarily connected by a direct physical link; on the other hand, an anatomical link does not necessarily imply that a functional connection has established at any time point

Definition of Connectivity

Brain functional connectivity can be estimated from a wide range of biomedical signals and with different neuroimaging techniques

- functional magnetic resonance imaging (fMRI)
- electroencephalography (EEG)
- magnetoencephalography (MEG)
- positron emission tomography (PET)

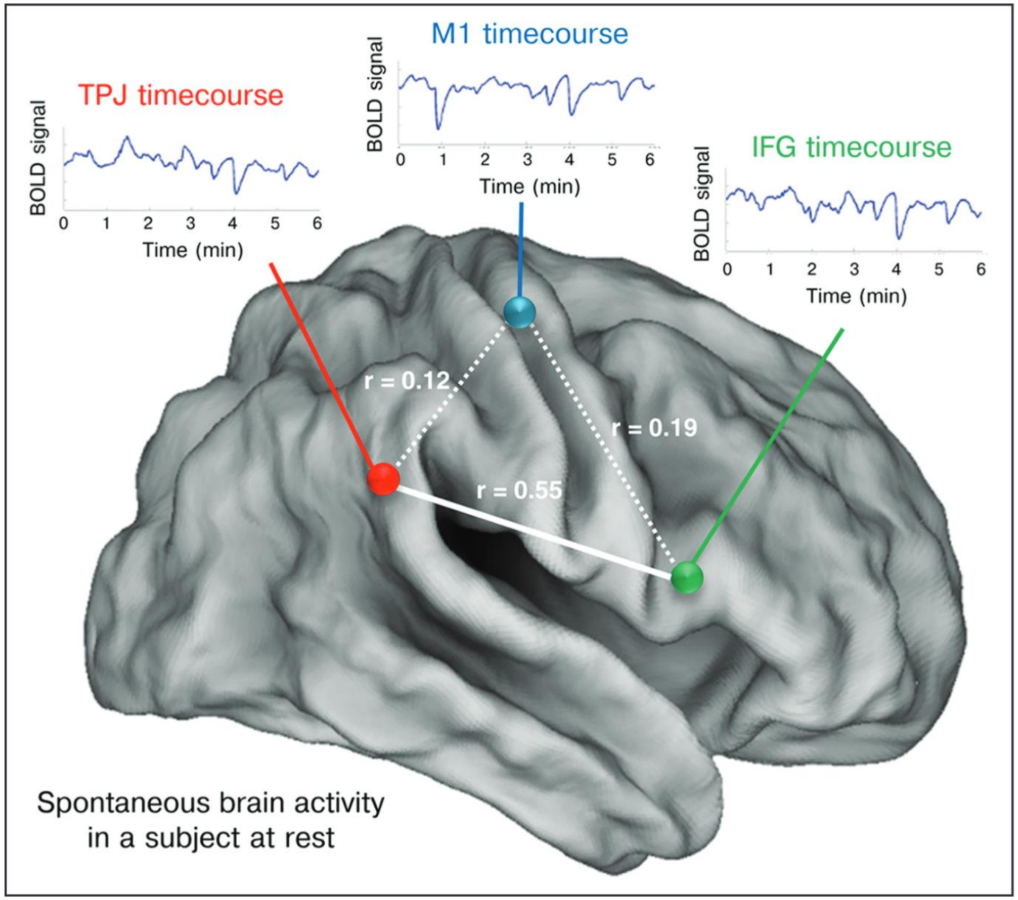
Functional Brain Connectivity:
Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a specific magnetic resonance imaging procedure to measure brain activity by detecting associated changes in blood flow

Brain activity is measured through low frequency blood oxygenation level dependent (BOLD) signal in the brain

fMRI technique is characterized by high spatial resolution, but by poor time resolution.

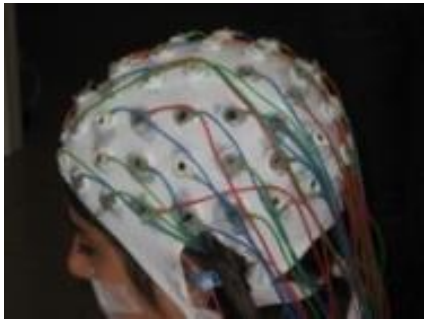
Functional Brain Connectivity:
Functional magnetic resonance imaging

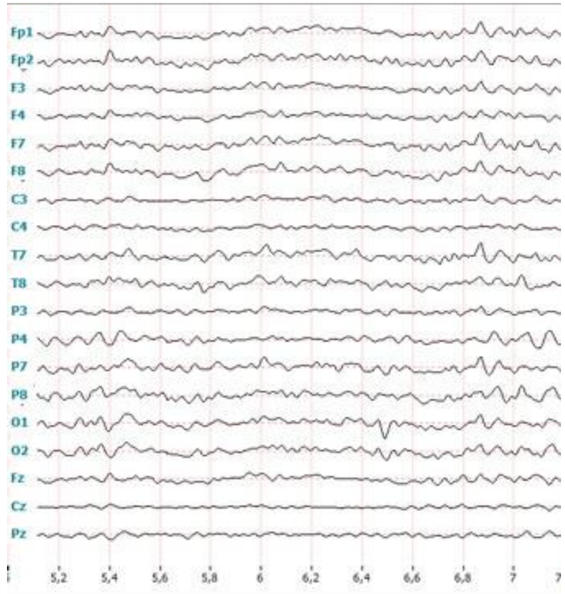


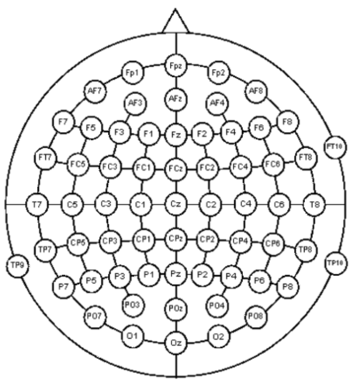
Gillebert and Mantini, The Neuroscientist, 2012

Figure 1. Basic principles of functional connectivity measured from resting state fMRI data. Low-frequency spontaneous fluctuations in the blood oxygen level–dependent (BOLD) signal are compared between multiple brain regions, and selective correlations are used to map the organization of brain systems (networks). Similarities in the BOLD time courses are assessed by temporal correlation, which may be significant (continuous white line) or not significant (dashed white line). In the example provided here, BOLD time course are extracted from areas right IFG, right M1, and right TPJ of a single subject. Spontaneous fluctuations between right IFG and right TPJ are significantly correlated (functionally connected); conversely, M1 shows no significant correlations with the other two areas. IFG = inferior frontal gyrus; M1 = primary motor cortex; TPJ = temporoparietal junction.

Functional Brain Connectivity:
EEG signals







EEG Main Advantages

- high temporal resolution on the order of milliseconds
- EEG setups are portable and thus usable in realistic situations
- EEG can be used in subjects who are incapable of making a motor response

From **EEG signals** recorded on the scalp, different kind of analysis can be performed

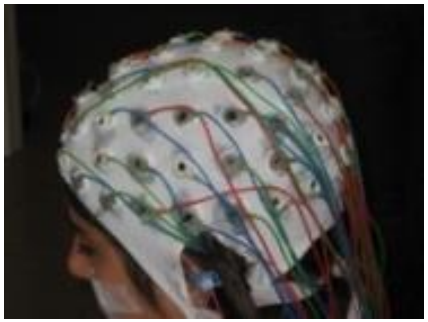
- Brain activity
- Brain connectivity

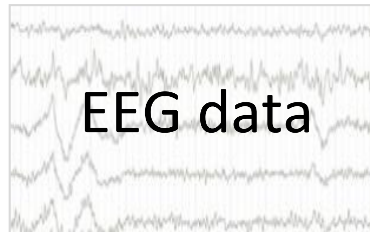
ACCURACY

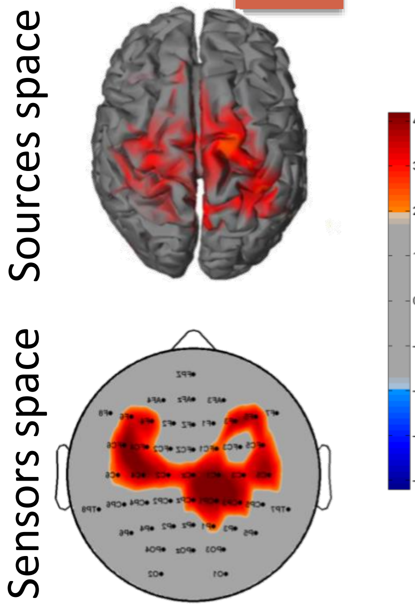
High Density recording

(HD EEG: 61, 128, 256 channels)

Non-invasive estimation of the cortical activity







Statistical comparison

- **task** vs **baseline**
- **between groups:** group1 vs group2
- **within group:** condition1 vs condition2

From **EEG signals** recorded on the scalp, functional connectivity can be estimated using methods based on **Granger causality**: they are defined both **in time** as well as **in frequency** domain and allow to reconstruct the **direction of information flows**

Autoregressive Model

In statistics and signal processing, an **autoregressive model** (AR) is a type of random process that is usually used to model and predict various types of natural phenomena

In an AR model, the signal x[n] is represented in terms of its prior samples as follows:

$$x[n] = e[n] - a_1 x[n-1] - a_2 x[n-2] - \cdots - a_p x[n-p]$$

where

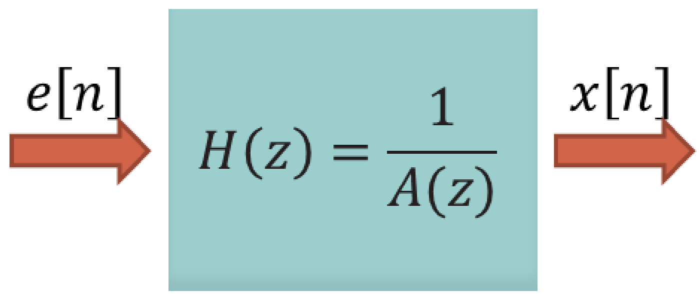
- $e[n]$ is assumed to be zero mean white Gaussian noise with a variance of σ^2
- p: order of the AR model
- $x[n-i]$: signal sample *i* time periods prior to the current sample at *n*
- a_i : coefficients or parameters of the AR model

Estimation of model coefficients → Yule Walker equations

Autoregressive Model

$$x[n] = e[n] - a_1 x[n-1] - a_2 x[n-2] - \cdots - a_p x[n-p]$$

AR model as a system model in which the biosignal $x[n]$ is assumed to be the output of a linear time-invariant system that is driven by a white noise input $e(n)$



Transfer Function

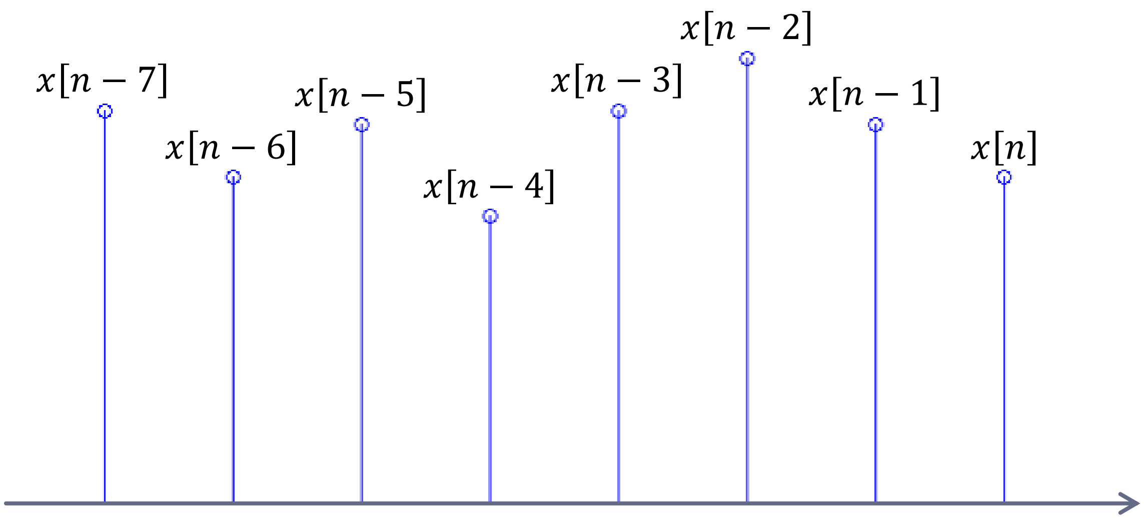
a_i determine the locations of the poles of the system model

$$\frac{X(z)}{E(z)} = \frac{1}{1 - \sum_{k=1}^{p} a_k z^{-k}} = \frac{1}{A(z)}$$

Autoregressive linear prediction

AR model as an attempt to predict the current signal sample based on *p* past values of the signal weighted by constant coefficients

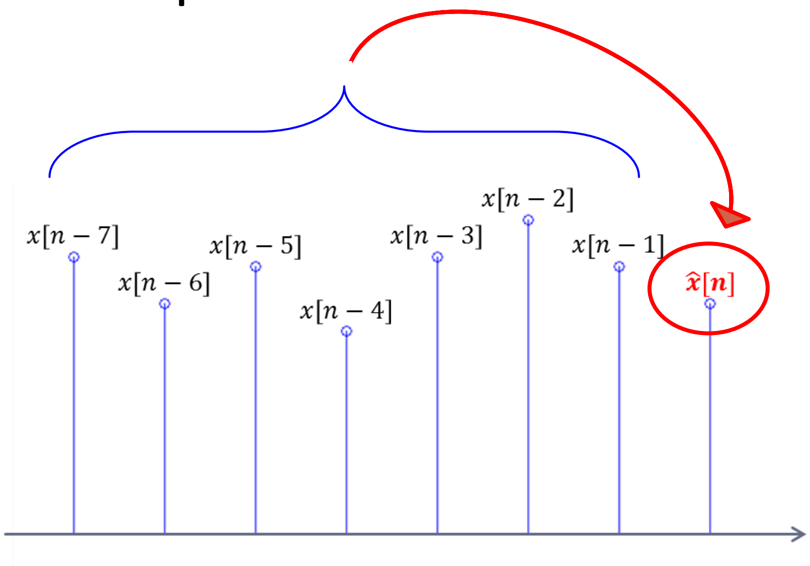
$$x[n] = e[n] - a_1 x[n-1] - a_2 x[n-2] - \cdots - a_p x[n-p]$$



Autoregressive linear prediction

We estimate the best model by trying to minimize the mean squared error between the signal sample predicted by the model and the actual measured signal sample

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



The prediction error is

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

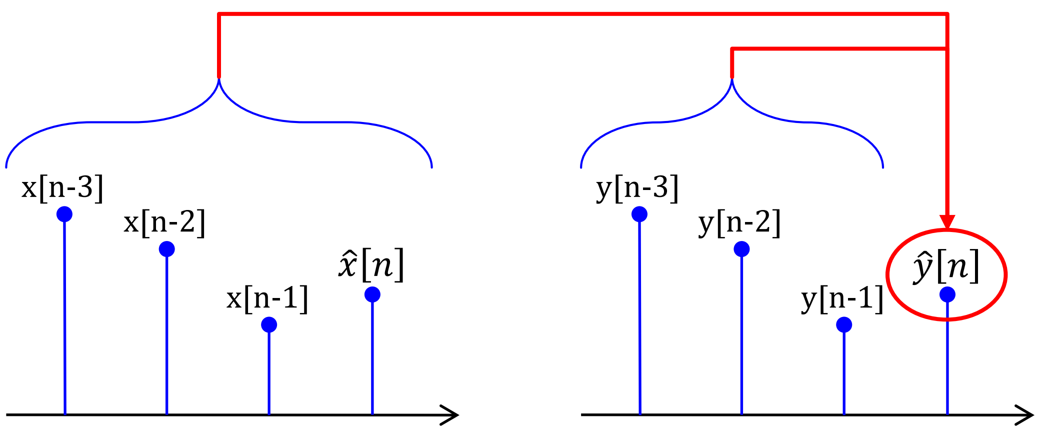
We must determine the coefficients a[k], by minimizing the power of the error e[n]

Bivariate Autoregressive Modeling

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

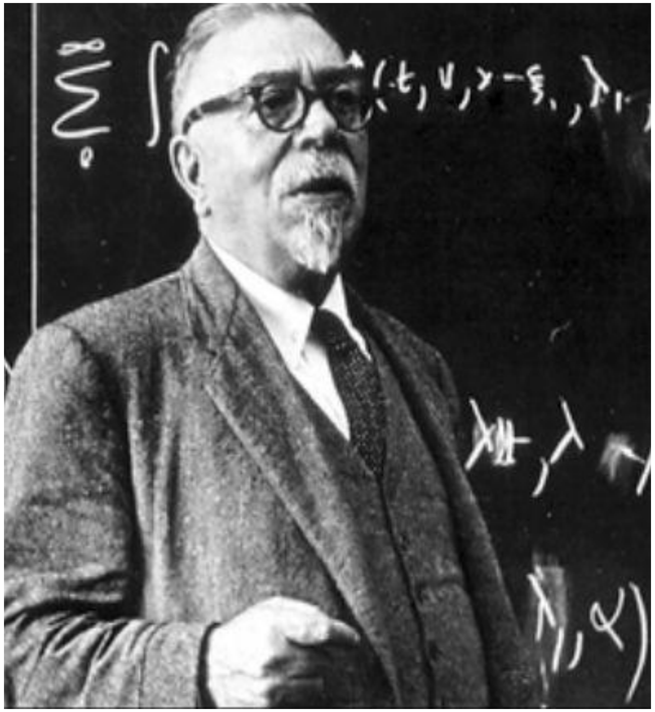
$$\hat{x}[n] = \sum_{k=1}^{p} a_{xy}[k]x[n-k] + \sum_{k=1}^{p} b_{xy}[k]y[n-k] + e_{xy}[n]$$

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



Definition of causality

Norbert Wiener



First definition of causality in a statistical framework:

We can determine a causal influence of one time series on another, if the predication of one time series can be improved by incorporating the knowledge of the second one

Norbert Wiener
The Theory of Prediction, 1956

Granger Causality

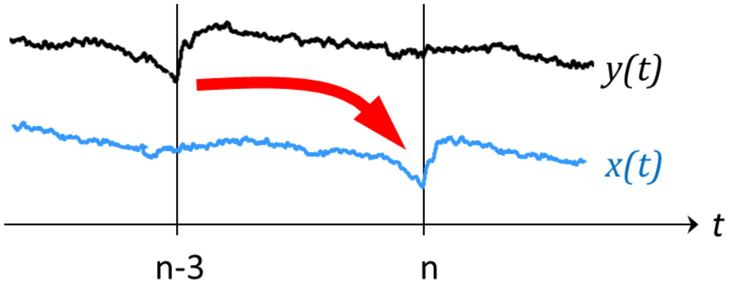
Clive Granger

An observed time series *y[n]* is said to **Granger-cause** another series *x[n]* if the knowledge of *y[n]*'s past **significantly improves the autoregressive prediction** of *x[n]*:

$$x[n] = B_1 x[n-1] + \ldots + B_N x[n-N] + e_X[n]$$

$$x[n] = B_1 x[n-1] + \ldots + B_N x[n-N] + A_1 y[n-1] + A_2 y[n-2] + \ldots + A_m y[n-M] + e_{X,Y}[n]$$

$$e_{x,y}[n] < e_x[n]$$

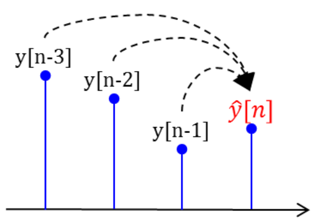


Clive Granger, 1969

Granger Causality Test

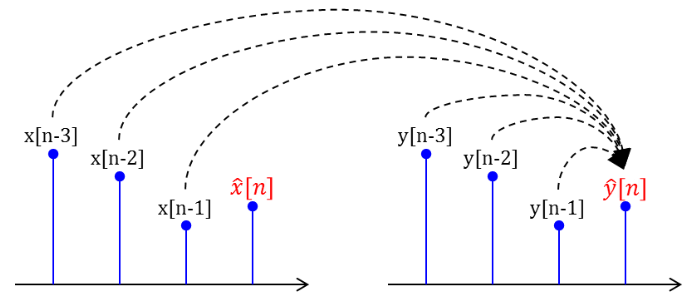
The prediction performances for both models can be assessed by the variances of the prediction errors:

For univariate models



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

For bivariate models



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

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.

Granger Causality Test

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 $V_{X|X,Y} < V_{X|X}$ then *y* Granger-causes *x*

If the past of *y* does not improve the prediction of X:

$$V_{x|x,y} \approx V_{x|x} \Rightarrow G \approx 0$$

If there is an improvement in prediction of X by the inclusion of Y:

$$V_{x|x,y} \downarrow \;\; \Rightarrow G \uparrow$$

Advantages and limitations of Granger Causality Test

- Pros
  - directionality
  - Statistical definition

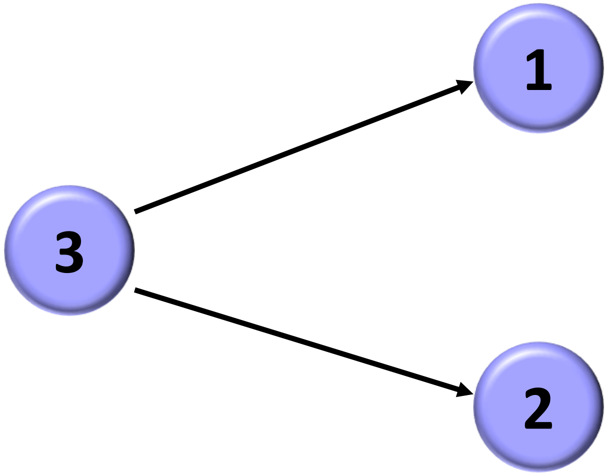
$$G_{y \to x} \neq G_{x \to y}$$

- Cons

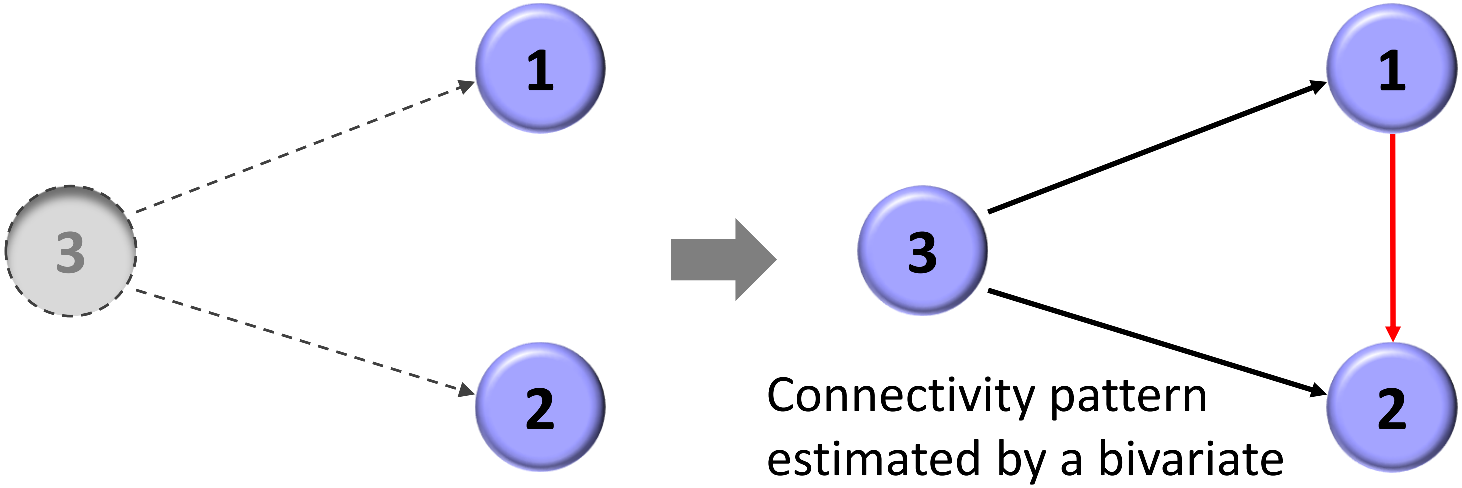
  True causality can only be assessed if the set of two time series contains all possible relevant information and sources of activities for the problem (Granger, 1980)

Limitation of bivariate methods

The sources of activities are more than 2:



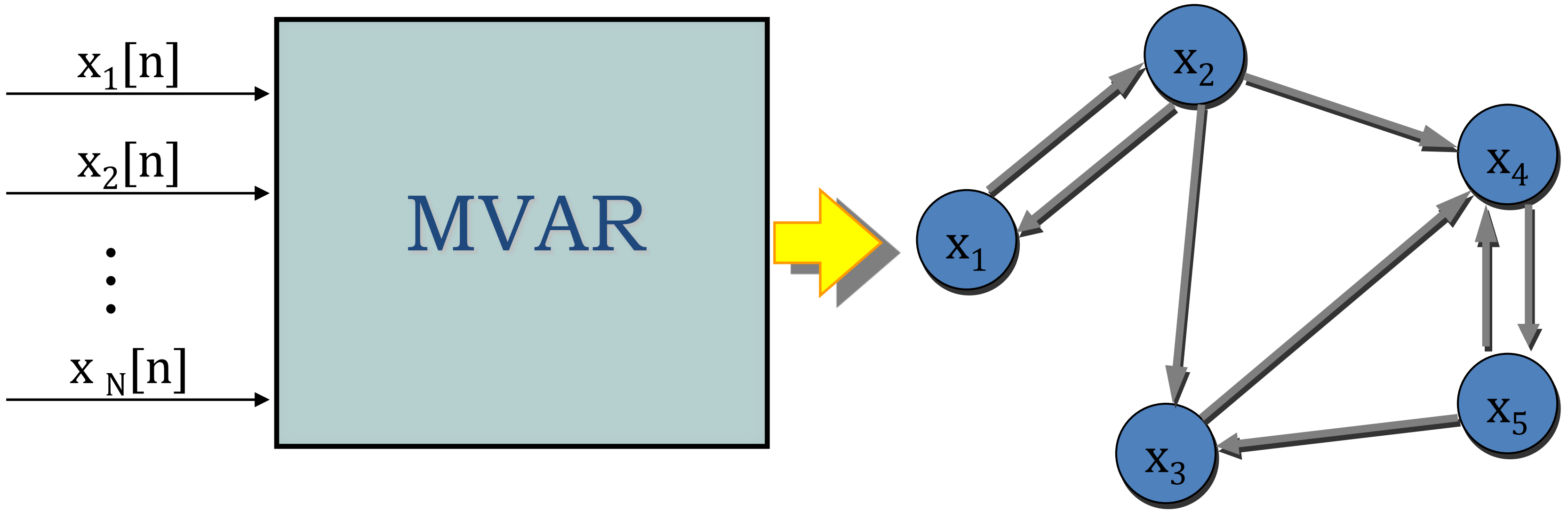
Bivariate modelization of signals 1 and 2 does not recognize that the link between the two signals is due to a common effect of 3 (which is not included in the model)



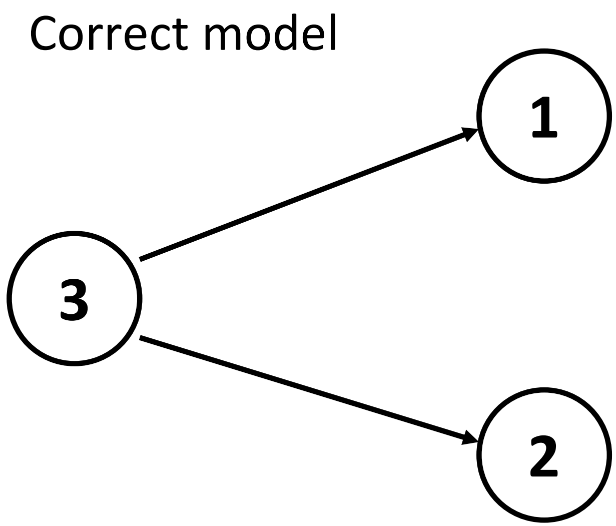
Connectivity pattern estimated by a bivariate method

Multivariate methods

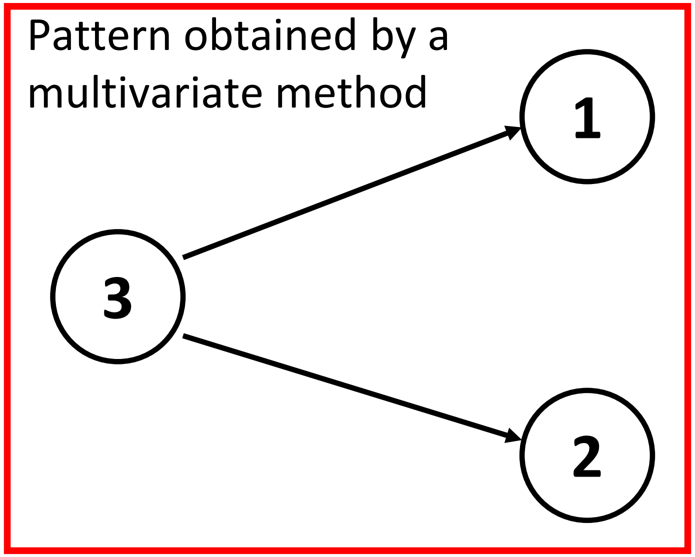
MULTIVARIATE METHODS: the connectivity pattern is obtained by a unique model estimated on the entire set of data and takes into account all their interactions



Multivariate methods



=



A unique model based on all the signals

MVAR methods use all the available information at the same time allowing a better comprehension of the relationship between the signals

conditional Granger Causality (cGC)

conditional Granger Causality (cGC) measures the influence of one time series on another time series in the presence of a third

Giving 2 time series x and z, the joint autoregressive representation for x and z by using the knowledge of their past measurement can be expressed as:

$$\begin{cases} x[n] = \sum_{i=1}^{N} a_{1i} x[n-i] + \sum_{i=1}^{M} c_{1i} z[n-i] + \varepsilon_1[n] \\ z[n] = \sum_{i=1}^{M} b_{1i} z[n-i] + \sum_{i=1}^{N} d_{1i} x[n-i] + \varepsilon_2[n] \end{cases}$$

conditional Granger Causality (cGC)

Incorporating the knowledge of third time series, the vector autoregressive mode can be represented involving three time series **x[n]** , **y[n]** and **z[n]** can be represented as

$$\begin{cases} x[n] = \sum_{i=1}^{N} a_{2i} x[n-i] + \sum_{i=1}^{K} b_{2i} y[n-i] + \sum_{i=1}^{M} c_{2i} z[n-i] + \varepsilon_3[n] \\ y[n] = \sum_{i=1}^{N} d_{2i} x[n-i] + \sum_{i=1}^{K} e_{2i} y[n-i] + \sum_{i=1}^{M} f_{2i} z[n-i] + \varepsilon_4[n] \\ z[n] = \sum_{i=1}^{N} g_{2i} x[n-i] + \sum_{i=1}^{K} h_{2i} y[n-i] + \sum_{i=1}^{M} k_{2i} z[n-i] + \varepsilon_5[n] \end{cases}$$

conditional Granger Causality (cGC)

The conditional Granger Causality form **y** to **x** conditional on **z** can be defined as:

$$G_{y\rightarrow x|z} = ln\left(\frac{|var(\varepsilon_1)|}{|var(\varepsilon_3)|}\right)$$

When the causal influence from **y** to **x** is entirely mediated by **z**, the coefficient b_{2i} is uniformly zero, and the two autoregressive models for two time series and three time series will be exactly the same → var($\boldsymbol{\varepsilon}_1$) = var($\boldsymbol{\varepsilon}_3$).

$G_{\mathbf{y\rightarrow x|z}}$ = 0 → **y** cannot further improve the prediction of **x** including past measurements of **y** conditional on **z**.
var($\boldsymbol{\varepsilon}_1$) > var($\boldsymbol{\varepsilon}_3$) anf $G_{\mathbf{y\rightarrow x|z}}$ → there is still a direct influence from **y** to **x** conditional on the past measurements of **z**

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:

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

MVAR models

$$x_1[n] = -\sum_{k=1}^{p} a_{11}[k] x_1[n-k] - \sum_{k=1}^{p} a_{12}[k] x_2[n-k] - \cdots - \sum_{k=1}^{p} a_{1N}[k] x_N[n-k] + e_1[n]$$

$$x_2[n] = -\sum_{k=1}^{p} a_{21}[k] x_1[n-k] - \sum_{k=1}^{p} a_{22}[k] x_2[n-k] - \cdots - \sum_{k=1}^{p} a_{2N}[k] x_N[n-k] + e_2[n]$$

$$\vdots$$

$$x_N[n] = -\sum_{k=1}^{p} a_{N1}[k] x_1[n-k] - \sum_{k=1}^{p} a_{N2}[k] x_2[n-k] - \cdots - \sum_{k=1}^{p} a_{NN}[k] x_N[n-k] + e_N[n]$$

- Model parameters to be estimated: *N x N x p*

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

MVAR in the frequency domain

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

$$\sum_{k=0}^{p} A[k]X[n-k] = E[n]$$

FREQUENCY DOMAIN

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

$$\boxed{\begin{aligned} X(f) &= A^{-1}(f)E(f) = \\ &= H(f)E(f) \end{aligned}}$$

MVAR models

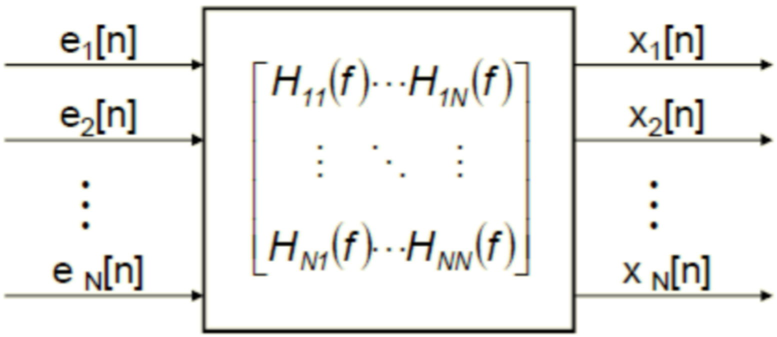
TIME DOMAIN

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

FREQUENCY DOMAIN

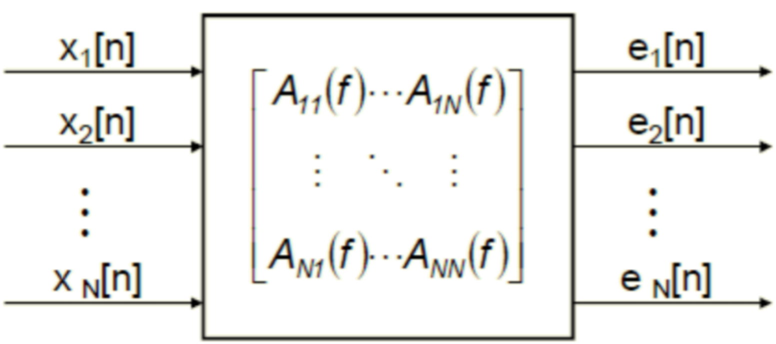
$$\boxed{A(f)X(f) = E(f)}$$

$$\boxed{\begin{aligned} X(f) &= A^{-1}(f)E(f) = \\ &= H(f)E(f) \end{aligned}}$$



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

output of a linear time-invariant system that is driven by a white noise input e[n]



$$A(f)X(f) = E(f)$$

linear predictor

Spectral Estimators based on MVAR

TIME DOMAIN

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

FREQUENCY DOMAIN

$$A(f)X(f) = E(f)$$

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

PARTIAL DIRECTED COHERENCE (**PDC**)

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

Baccalà and Sameshima, 2001

DIRECTED TRANSFER FUNCTION (**DTF**)

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

Kaminski and Blinowska, 1991

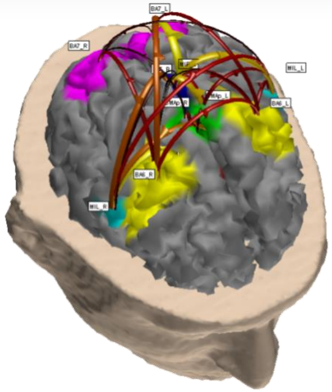
Higher performances when the aim is to accurately reconstruct the exact pattern of interactions between signals and distinguish the direct influence from those mediated by other signals

It measures the overall effect of one signal on another, considering both direct and indirect paths

Connectivity estimation in neuroscience

The description of communication between cortical activations during specific tasks, or even at rest, can provide important insights into the neural mechanisms at the basis of cognitive functions, their modifications resulting from different pathological conditions and their reorganization due to a specific treatment or to spontaneous recovery (cortical plasticity)

Brain as a complex network

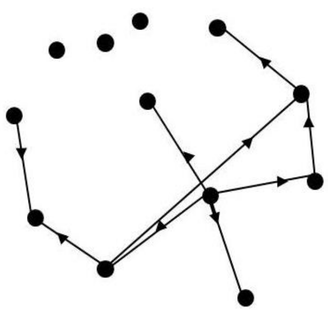


Brain connectivity

Information flows between different brain regions

Need to:

- **understand** the network organization
- **quantify** brain connectivity properties
- **look for markers** based on connectivity

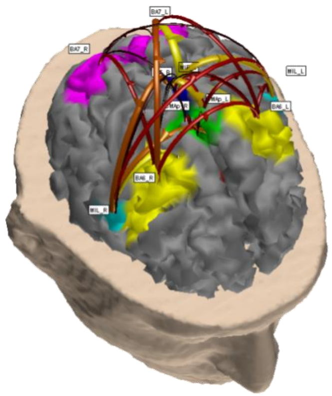


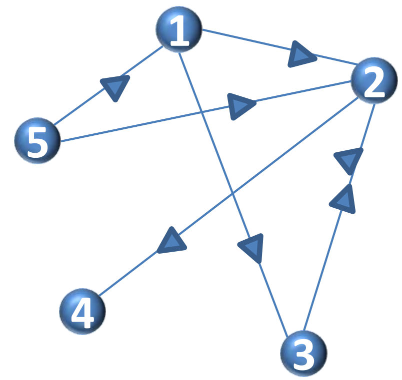
Graph theory

a **graph** is a mathematical object consisting of a set of **nodes** (brain areas) linked by means of **edges** (anatomical/functional connections)

Graph indices

Graph theory in Neuroscience





$$A=\begin{bmatrix} 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \end{bmatrix}$$

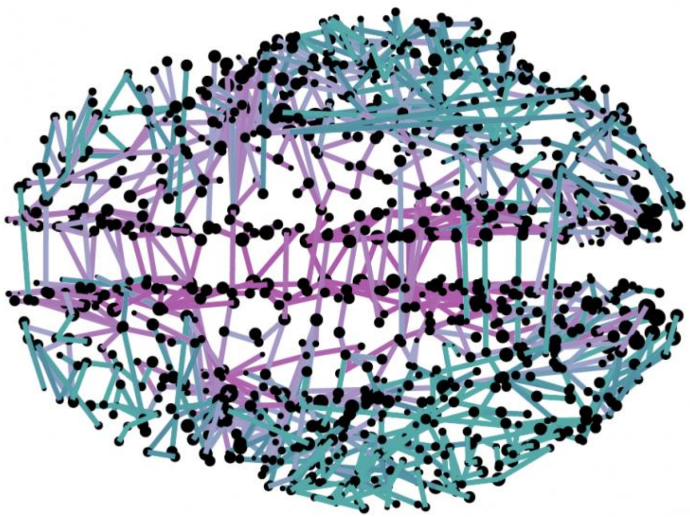
- Measures of integration
- Measures of segregation
- Measure of centrality

- Modularity and divisibility

- Motifs analysis

- Community detection

Graph theory in Neuroscience



Microscopic	Mesoscopic	Macroscopic
Degree (in-out)	*Motifs*	*Average Path length*
Betweenness centrality	*Modularity*	*Clustering coefficient*
Closeness centrality		*Global efficiency*
eigenvector centrality		*Local efficiency*