Graph theory to explore resting state brain functional connectivity

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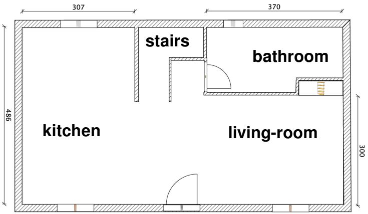
Sixièmes rencontres de Statistique Avignon-Marseille

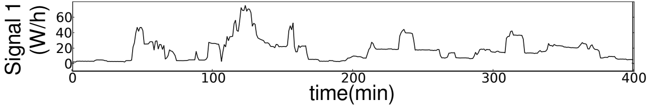
Multivariate time series structured in a network

A simple example: recording electric consumption

A simple sensor recording the overall electrivity consumption



Observed univariate time series

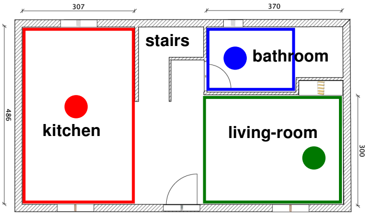


$$X(k)$$
$$1 \leq k \leq N$$

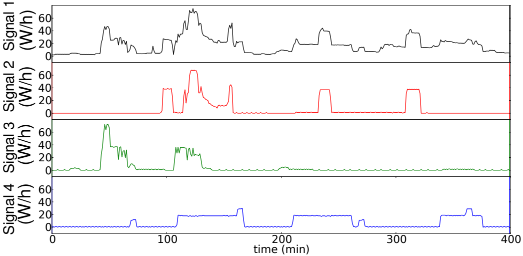
[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

Multivariate time series structured in a network

Multiple sensors in different places of the house



Observed multivariate time series



$X_1(k)$

$X_2(k)$

$X_3(k)$

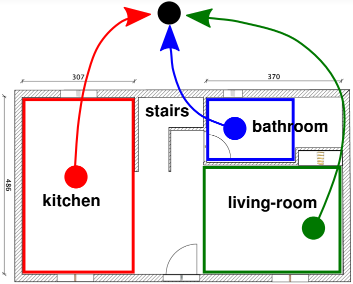
$X_4(k)$

$1 \leq k \leq N$

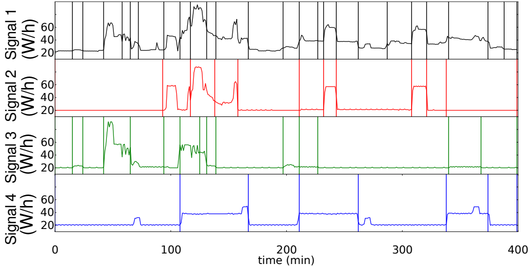
[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

Multivariate time series structured in a network

Multiple sensors in different places of the house with possible links



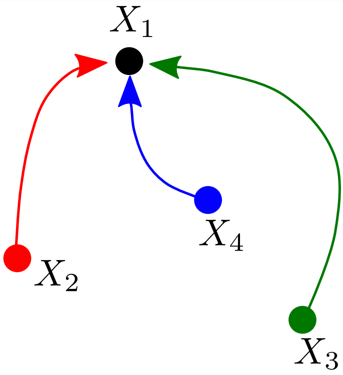
Observed multivariate time series with multiple change point detection



$$\begin{pmatrix} X_1(k) \\ X_2(k) \\ X_3(k) \\ X_4(k) \end{pmatrix} = \mathbf{X}(k)$$
$$1 \leq k \leq N$$

[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

Multivariate time series structured in a network



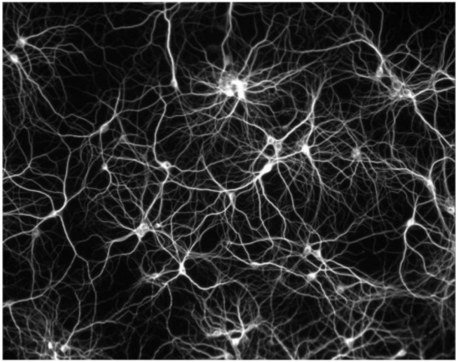
Definition of the network (or graph):

- nodes: X_1, X_2, X_3 and X_4
- edges: X_2-> X_1, X_3-> X_1, X_4-> X_1
- adjacency matrix:

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

[**Harlé** *et al.* IEEE Trans. Sig. Proc. 2016]

The brain as a network



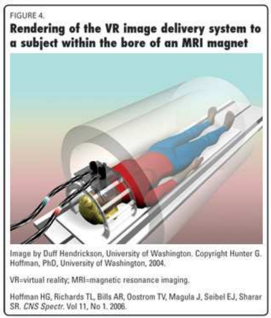
- 10^{11} neurons
- Connected via axons and dendrites (10^{14} connections)
- Transmission of nerve signals (segregated and distributed information)

Functional Magnetic Resonance Imaging – fMRI:

[Ogawa 1990, Kwong 1991]

Measure of the haemodynamic response related to neural activity in the brain.

BOLD(Blood-oxygen-level dependent)= MRI contrast of blood deoxyhemoglobin



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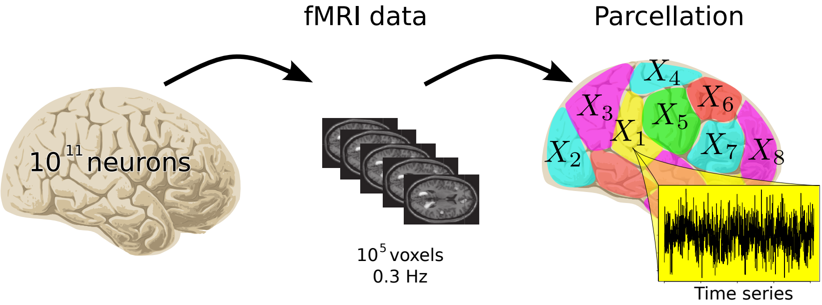
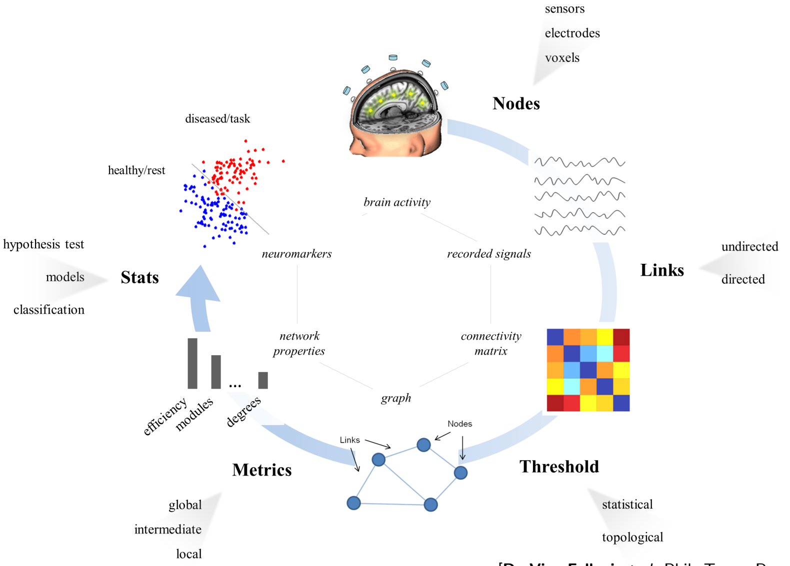
IRMaGe, GIN, UGA

Exploring the brain using networks analysis

Hundreds of time series corresponding to brain regions



Exploring the brain using networks analysis

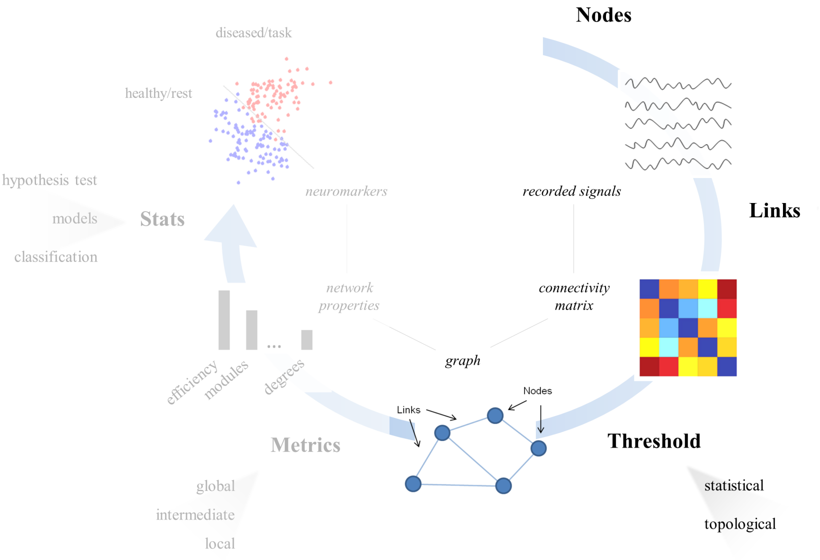


[**De Vico Fallani** *et al.* Phil. Trans. Roy. B 2014]

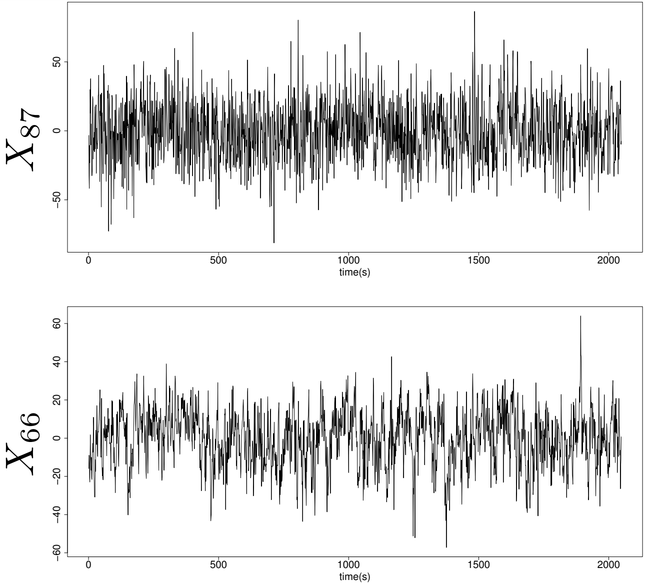
Outline of the talk

- Part I: Wavelets, Correlation, fractal connectivity
- Part II: Graphs construction, comparison; Applications on coma patients

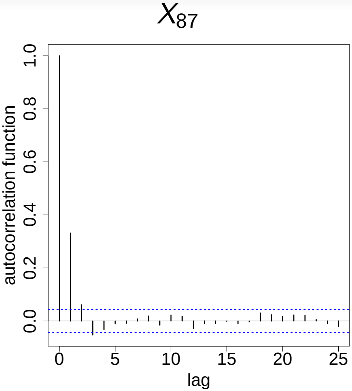
Part I: Inference of networks

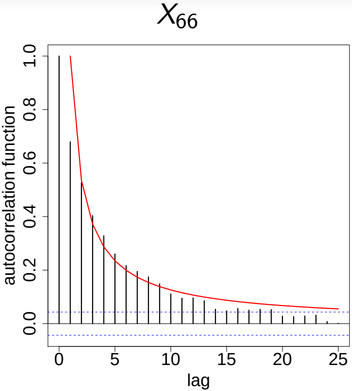


Long memory property of the brain time series



Long memory property of the brain time series





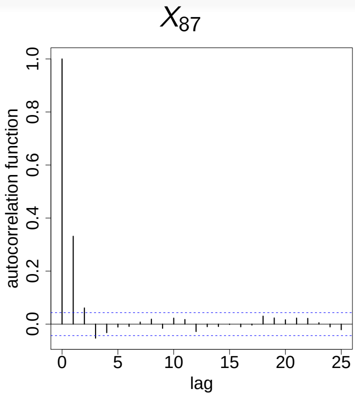
autocorrelations not summable

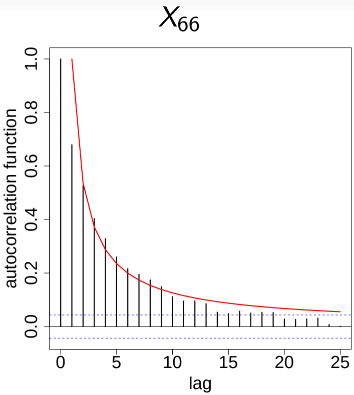
$$\rho(\lambda) = Corr(X(t+\lambda), X(t)) \sim \lambda^{2d-1}$$

Note: For an *ARMA process*,

$$|\rho(\lambda)| \leqslant b|a|^{\lambda}, \qquad 0 < b < \infty, \qquad 0 < a < 1$$

Long memory property of the brain time series





autocorrelations not summable

A simple example, $X(1), \ldots, X(N)$, random variables,

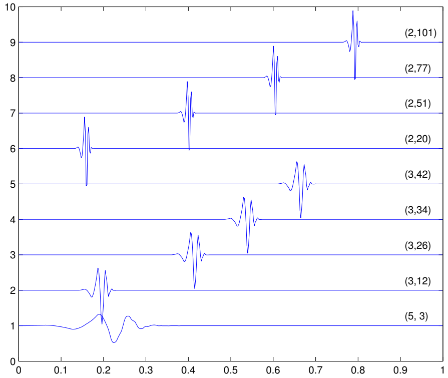
$$\widehat{X} := N^{-1} \sum_{i=1}^{N} X(i), \qquad \mathbb{V}(\widehat{X}) = \frac{\sigma^2}{N^2} \sum_{i,j=1}^{N} Corr(X(i), X(j))$$

Let (ϕ, ψ) define a father and a mother wavelets

For any scale $j \geqslant 0$ and location $k \in \mathbb{Z}$ we consider the wavelet coefficient of the signals $X_\ell(\cdot)$, for $\ell = 1, \ldots, p$,

$$W_{j,k}(\ell) \approx \int X_\ell(t)\psi_{j,k}(t)dt$$

An example of ψ, Daubechies 8



Wavelets and long memory time series

Under specific hyptothesis on the wavelet basis,

- Wavelets are acting as a differentiation process,

$$W_{j,k}(\ell) = (\downarrow^j [\tilde{h}_{j,\cdot} \star \Delta^M X_\ell])_k,$$

where

- Δ is the finite difference operator, $\Delta X(k) = X(k) - X(k-1)$
- $\tilde{h}_{j,\cdot}$ are the adequate trigonometric polynom coefficient,
- $\downarrow^j$ is the downsampling operator.

[**Achard and Gannaz** J. Time Series Analysis 2015]
[**Moulines** *et al.* 2007]

Wavelets and long memory time series

Under specific hyptothesis on the wavelet basis,

- Wavelets are acting as a differentiation process,

$$W_{j,k}(\ell) = (\downarrow^j [\tilde{h}_{j,\cdot} \star \Delta^M X_\ell])_k,$$

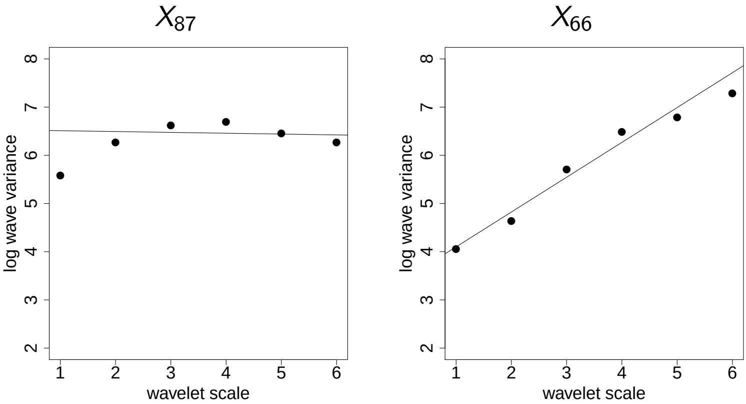
- $\{W_{j,k}(\ell)\}_{k\in\mathbb{Z}}$ and bivariate process $\{W_{j,k}(\ell), W_{j,k'}(m)\}_{k\in\mathbb{Z}}$ are covariance-stationary and with short dependence.

$$\mathrm{Cov}(W_{j,k}(\ell), W_{j,k'}(m)) = \int_{-\pi}^{\pi} D_{0;0}^{(j)}(\lambda; (\ell, m))\mathrm{e}^{i\lambda(k-k')} d\lambda.$$

where $D_{0;0}^{(j)}(\lambda; (\ell, m))$ is the joint spectral density of $\{W_{j,k}(\ell), W_{j,k}(m)\}_{k\in\mathbb{Z}}$

[**Achard and Gannaz** J. Time Series Analysis 2015]
[**Moulines** *et al.* 2007]

Wavelet scalogram



$$\sigma^2(j) = \mathbb{V}(W_{j,k}) \sim 2^{2dj}$$

[**Flandrin** 1992]
[**Abry and Veitch** 1998]
[**Moulines** *et al.* 2007]

Wavelets and correlation

$\mathbf{X} = \{\mathbf{X}(k), k \in \mathbb{Z}\}$ long memory process, $1 \leqslant \ell, m \leqslant p$,

Wavelet variance	Wavelet covariance
$\sigma_\ell^2(j) = \mathbb{V}(W_{j,k}(\ell))$	$\theta_{\ell,m}(j) = \mathrm{Cov}(W_{j,k}(\ell), W_{j,k}(m))$
$\widehat{\sigma}^2(j) := \frac{1}{n_j} \sum_{k=0}^{n_j} W_{j,k}^2$	$\widehat{\theta}_{\ell,m}(j) := \frac{1}{n_j} \sum_{k=0}^{n_j} (W_{j,k}(\ell) W_{j,k}(m))$

[**Percival** *et al.* 2000]
[**Whitcher** *et al.* 2000]

Wavelet correlation

$$\rho_{\ell,m}(j) = \frac{\theta_{\ell,m}(j)}{\sigma_\ell(j)\sigma_m(j)}$$

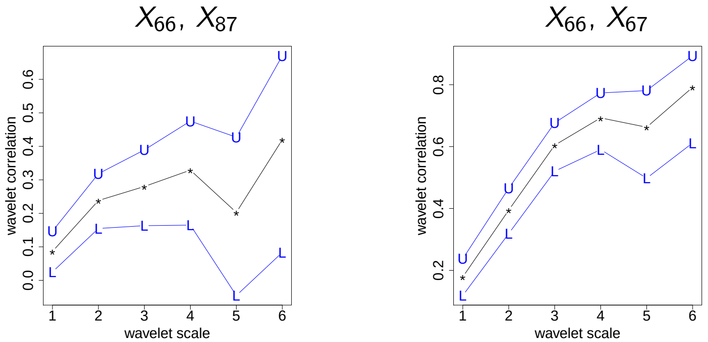
Wavelets and correlation

Proposition

$\mathbf{X} = \{\mathbf{X}(k), k \in \mathbb{Z}\}$ *long memory process,* $\widehat{\rho}_{\ell,m}(j) := \widehat{\theta}_{\ell,m}/(\widehat{\sigma}_\ell(j)\widehat{\sigma}_m(j))$

$$\sqrt{(n_j - 3)}(z(\widehat{\rho_{\ell,m}}(j)) - z(\rho_{\ell,m}(j))) \xrightarrow{\mathcal{L}} \mathcal{N}(0,1)$$

where z in the Fisher transform.



[**Achard** *et al.* J. Neurosci. 2006] [**Whitcher** *et al.* 2000]

Construction of the adjacency matrices

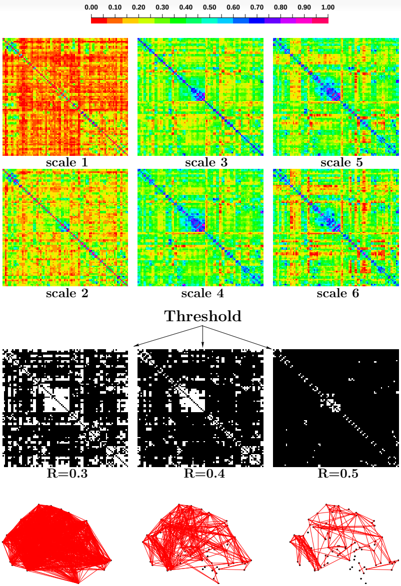
→ pair-wise inter-regional correlations

- Wavelets MODWT
- Connectivity = Correlation

→ adjacency matrix
Threshold ?

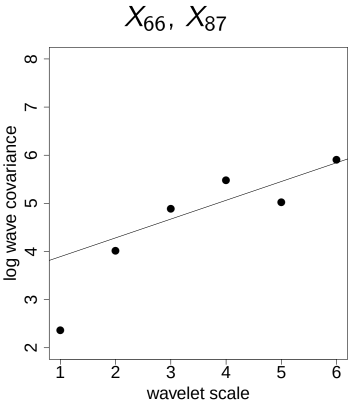
→ Undirected graphs : small-world properties

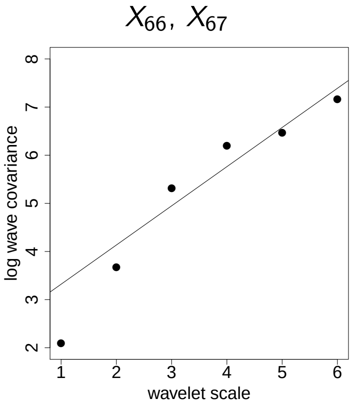
[**Achard** *et al.* J. Neurosci. 2006]



Wavelets and correlation

$\mathbf{X} = \{\mathbf{X}(k), k \in \mathbb{Z}\}$ long memory process, $1 \leqslant \ell, m \leqslant p$,





$$\theta_{\ell,m}(j) \sim 2^{j(d_\ell + d_m)}$$

[**Achard** *et al.* J. Neurosci. 2006]
[**Achard** *et al.* PRE 2008]

Multivariate long memory model

Definition ($M(d)$ process)

$\mathbf{X}$ long memory with memory parameters $\mathbf{d} = (d_1, d_2, \ldots, d_p)$

$$\mathbf{Z} = \mathrm{diag}(\Delta^{D_\ell}, \ell = 1, \ldots, p)\mathbf{X}$$

$\mathbf{D} > \mathbf{d} - 1/2$, $\mathbf{Z}$ is covariance-stationary with a spectral density matrix given by for all (ℓ, m),

$$f_{\ell,m}^{(D_\ell, D_m)}(\lambda) = \frac{1}{2\pi}\Omega_{\ell,m}(1 - e^{-i\lambda})^{-d_\ell{}^s}(1 - e^{i\lambda})^{-d_m{}^s} f_{\ell,m}^S(\lambda), \quad \lambda \in [-\pi, \pi],$$

- $d_m^S = d_m - D_m$ for all m
- $f_{\ell,m}^S(\cdot)$ correspond to the short memory behaviour
- $\Omega_{\ell,m}$ is the coupling between X_ℓ and X_m

[**Achard and Gannaz** J. Time Series Analysis 2015]
[**Moulines** *et al.* 2007]

Multivariate long memory model

The generalized spectral density of a long memory process $\mathbf{X}$ is:

$$\mathbf{f}(\lambda) = \boldsymbol{\Omega} \circ (\mathrm{diag}((1 - e^{-i\lambda})^{-\mathbf{d}})\mathbf{f}^S(\lambda)\mathrm{diag}((1 - e^{+i\lambda})^{-\mathbf{d}}))$$

- $\boldsymbol{\Omega}$ long-run covariance matrix, corresponding to the fractal connectivity
- $\mathbf{d}$ vector of long-range dependences of each series
- $\mathbf{f}^S(\cdot)$ short-range behaviour
  $\forall \lambda \in (-\pi, \pi)$, $\|\mathbf{f}^S(\lambda) - 1\|_\infty \leqslant L|\lambda|^\beta$
  with $L > 0$ and $0 < \beta \leqslant 2$.

Remark: If $\boldsymbol{\Omega}$ is the identity matrix, the model is equivalent to univariate $M(d)$

[**Achard and Gannaz** J. Time Series Analysis 2015]
[**Moulines** *et al.* 2007]

Example of multivariate long memory process

Example: bivariate ARFIMA(0,d,0), with $\Omega = \begin{pmatrix} 1 & \omega \\ \omega & 1 \end{pmatrix}$

$$\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \rightsquigarrow \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \Omega\right)$$

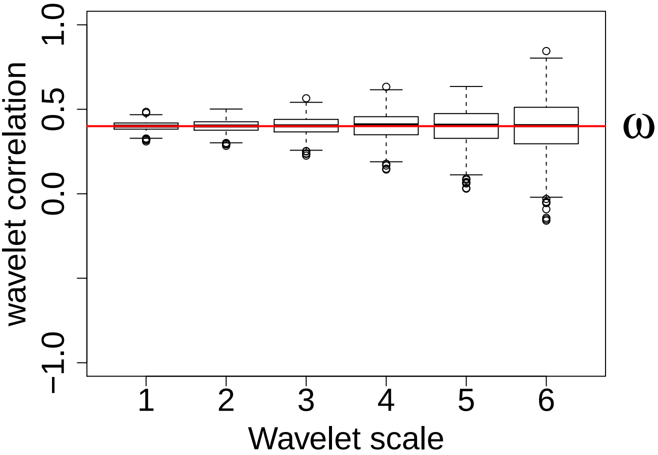
$$\begin{aligned} (1-\mathbb{L})^{-d_1} u_1 &= X_1 \\ (1-\mathbb{L})^{-d_2} u_2 &= X_2 \end{aligned}$$

with $\mathbb{L}$ lag-operator. For all integer D,
$(1-\mathbb{L})^D X(t) = (1-\mathbb{L})^{D-1}(X(t) - X(t-1))$.
For fractionnal coefficient δ,

$$(1-\mathbb{L})^\delta = \sum_{k=0}^{\infty} \frac{\Gamma(\delta+1)}{\Gamma(k+1)\Gamma(\delta-k+1)}(-1)^k \mathbb{L}^k$$

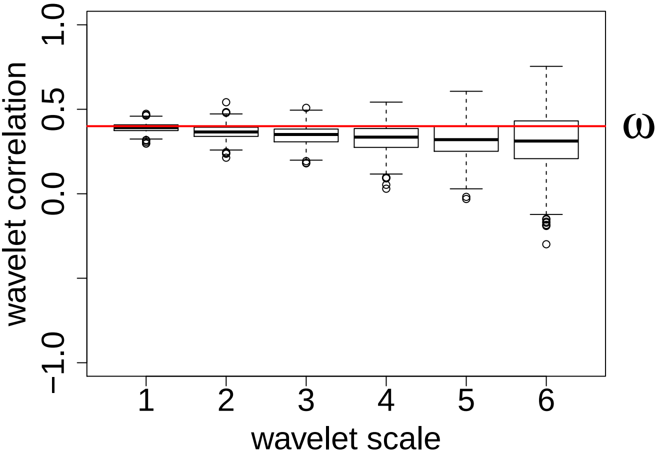
Long-memory effects on empirical correlation

Boxplots of $Corr\{W_{j,k}(1), W_{j,k}(2)\}$ for $d_1 = 0.2$ and $d_2 = 0.2$.



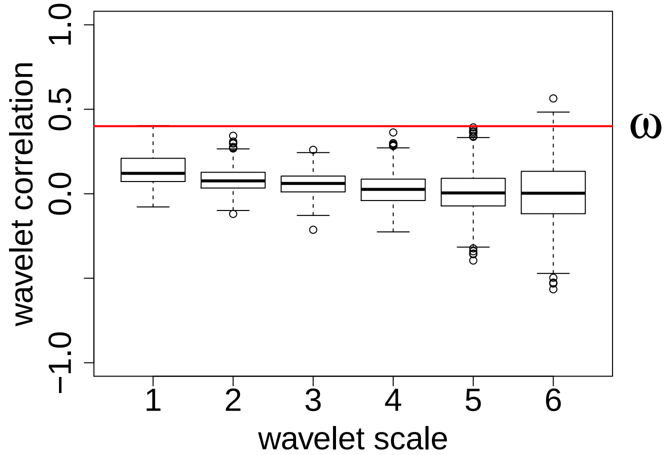
Long-memory effects on empirical correlation

Boxplots of $Corr\{W_{j,k}(1), W_{j,k}(2)\}$ for $d_1 = 0.2$ and $d_2 = 0.6$.



Long-memory effects on empirical correlation

Boxplots of $Corr\{W_{j,k}(1), W_{j,k}(2)\}$ for $d_1 = 0.2$ and $d_2 = 1.2$.



Mathematical formulation

- Suppose we observe $\mathbf{X}(1), \ldots, \mathbf{X}(N)$, with $N = 2^J$.
- For any $j \geqslant 0$, $k \in \mathbb{Z}$ we define $W_{j,k}(\ell)$ the wavelet coefficient of the series X_ℓ evaluated with the observations $X_\ell(1), \ldots, X_\ell(N)$.
- The covariance of the wavelet coefficients at resolution j, $\theta_{\ell,m}(j) = Cov(W_{j,k}(\ell), W_{j,k}(m))$ does not depend on k.

$\hookrightarrow$ What is the behaviour of $Cov(W_{j,k}(\ell), W_{j,k}(m))$?

$\hookrightarrow$ Can we estimate the fractal covariance $\mathbf{\Omega}$ with $\theta_{\ell,m}(\cdot)$?

Mathematical formulation

Generalization to multivariate long memory processes.

Proposition

Under some hypothesis

$$\left|\theta_{\ell,m}(j) - \Omega_{\ell,m}\cos(\pi(d_\ell - d_m)/2)K(d_\ell + d_m)2^{j(d_\ell+d_m)}\right| \leqslant C\,L\,2^{j(d_\ell+d_m-\beta)}$$

$\hookrightarrow$ Presence of a phase-shift, due to the difference between the long-memory parameters.

$\hookrightarrow$ Problem of identifiability when $d_\ell - d_m = 1$.

[**Achard and Gannaz** J. Time Series Analysis 2015]
[**Moulines** *et al.* 2007]

Wavelet Whittle estimation

Wavelet Whittle approximation of the negative log-likelihood

$$\mathcal{L}(\mathbf{G}, \mathbf{d}) = \frac{1}{n} \sum_{j=j_0}^{j_1} \left[n_j \log \det \left(\mathbf{\Sigma}_j(\mathbf{d}) \right) + \sum_k \mathbf{W}_{j,k}^T \mathbf{\Sigma}_j(\mathbf{d})^{-1} \mathbf{W}_{j,k} \right],$$

$\mathbf{\Sigma}_j(\mathbf{d})_{\ell,m} = 2^{j(d_\ell + d_m)} \mathbf{G}_{\ell,m}(\mathbf{d})$.

The minimum for fixed **d** is attained for

$$\hat{G}_{\ell,m}(\mathbf{d}) = \frac{1}{n} \sum_{j=j_0}^{j_1} \frac{\sum_{k \in \mathbb{Z}} W_{j,k}(\ell) W_{j,k}(m)}{2^{j(d_\ell + d_m)}},$$

empirical version of $\frac{1}{n} \sum_{j=j_0}^{j_1} n_j \frac{\theta_{\ell,m}(j)}{2^{j(d_\ell + d_m)}}$.

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$\boldsymbol{\Sigma}_j(\mathbf{d})_{\ell,m} = 2^{j(d_\ell+d_m)} \mathbf{G}_{\ell,m}(\mathbf{d})$.

We define two estimators for long memory parameters and fractal connectivity

Definition

$$\begin{aligned} \hat{\mathbf{d}} &= \underset{\mathbf{d}}{argmin}\, \mathcal{L}(\hat{\mathbf{G}}(\mathbf{d}), \mathbf{d}) \\ \hat{\Omega}_{\ell,m} &= \hat{G}_{\ell,m}(\hat{\mathbf{d}}) \,/\, \left(K(\hat{d}_\ell + \hat{d}_m) cos(\pi(\hat{d}_\ell - \hat{d}_m)/2) \right) \end{aligned}$$

Asymptotic results

Theorem

Under certain condition, if j_0 and j_1 are chosen such that $\log(N)^2(2^{-j_0\beta} + N^{-1/2}2^{j_0/2}) \to 0$ and $j_0 < j_1 \leqslant j_N$ then

$$\hat{\mathbf{d}} - \mathbf{d}^0 = O_{\mathbb{P}}(2^{-j_0\beta} + N^{-1/2}2^{j_0/2}),$$

$$\begin{aligned} \forall(\ell, m) \in \{1, \dots, p\}^2, \\ \hat{G}_{\ell,m}(\hat{\mathbf{d}}) - G_{\ell,m}(\mathbf{d}^0) &= O_{\mathbb{P}}(\log(N)(2^{-j_0\beta} + N^{-1/2}2^{j_0/2})), \\ \hat{\Omega}_{\ell,m} - \Omega_{\ell,m} &= O_{\mathbb{P}}(\log(N)(2^{-j_0\beta} + N^{-1/2}2^{j_0/2})). \end{aligned}$$

[**Achard and Gannaz** J. Time Series Analysis 2015]

Application on real data

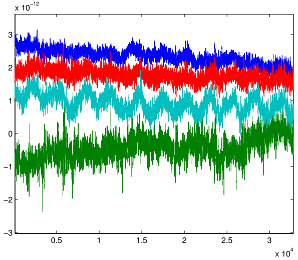
Achard, Bassett, Meyer-Lindenberg, Bullmore (2008)

MEG data acquired from a healthy 43 year old woman studied during rest with eyes open at the National Institute of Mental Health Bethesda, MD using a 274-channel CTF MEG system VSM MedTech, Coquitlam, BC, Canada operating at 600 Hz.

Examples of 4 arbitrary signals.

We consider $N = 2^{15}$ time points for each of the 274 time series.

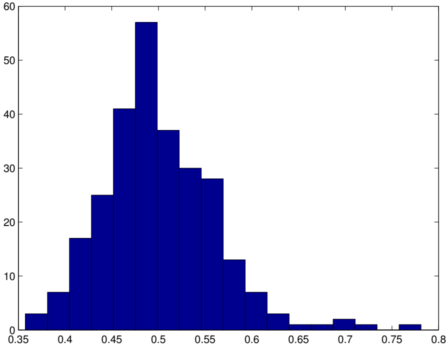
Fourier does not work.



[**Achard** *et al.* PRE 2008]

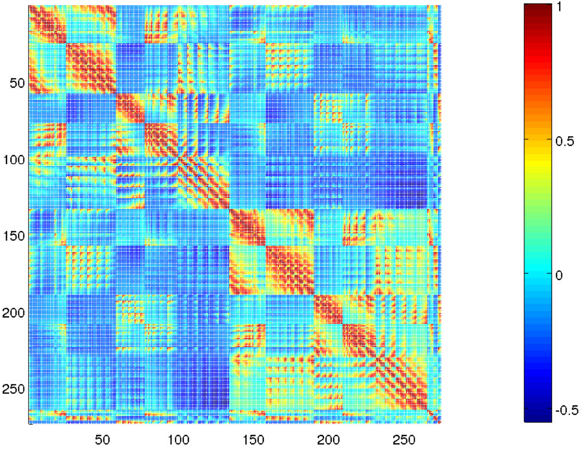
Application on real data

Histogram of the estimated long memory parameters d.



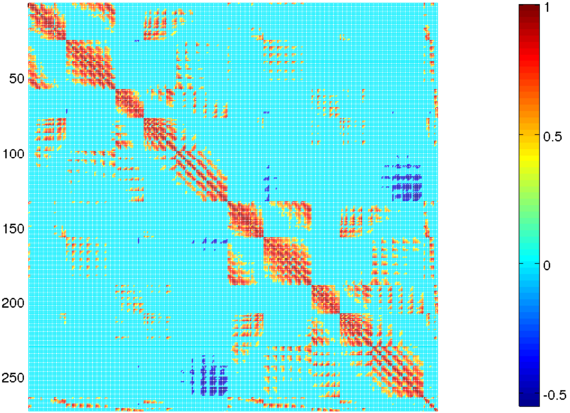
Application on real data

Estimated correlation matrix.

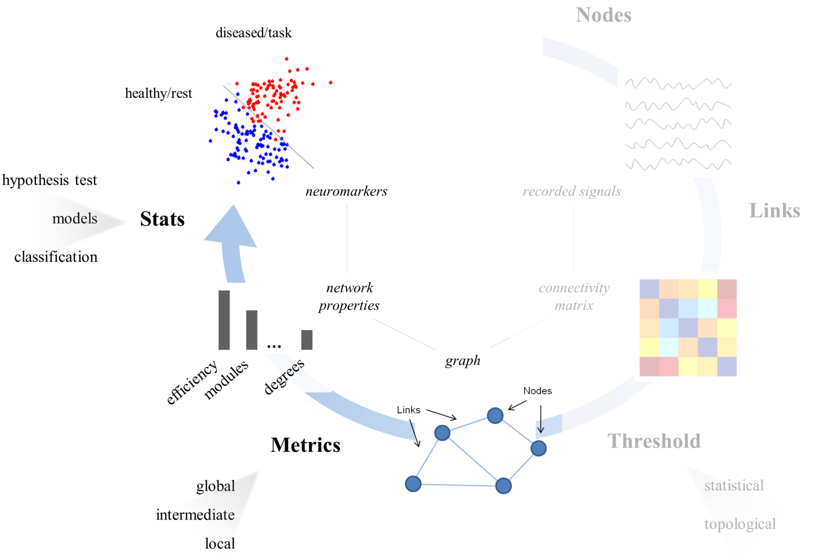


Application on real data

Estimated correlation matrix with a threshold at 0.4.



Part II: Comparison of networks



Construction of the adjacency matrices

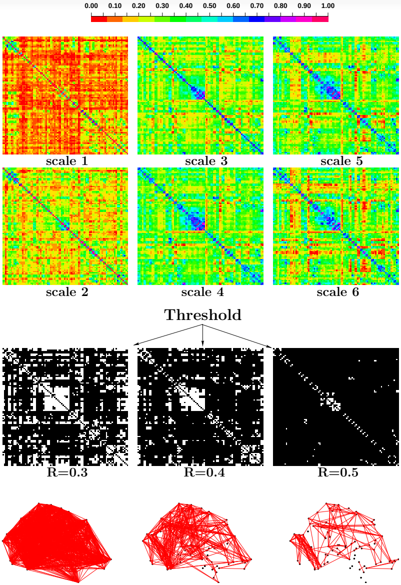
→ pair-wise inter-regional correlations

- Wavelets MODWT
- Connectivity = Correlation

→ adjacency matrix Threshold ?

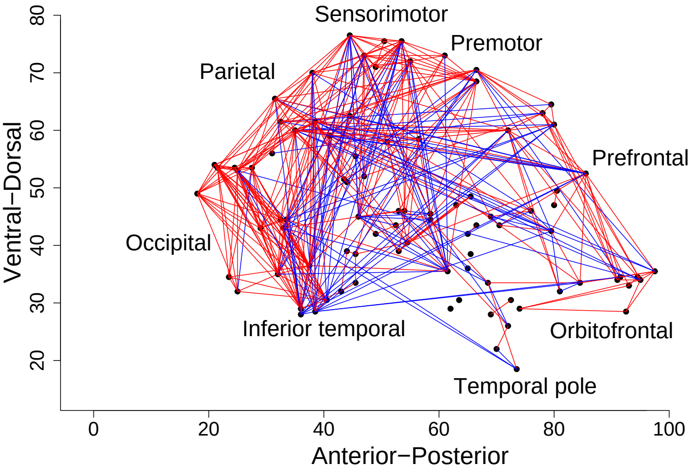
→ Undirected graphs : small-world properties

[**Achard** *et al.* J. Neurosci. 2006]



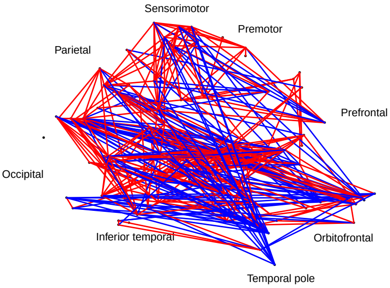
Individual graphs: representation of networks for a given threshold

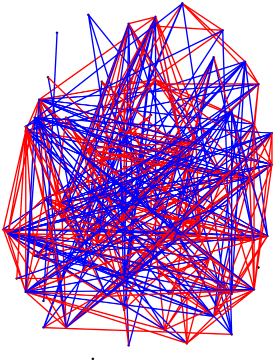
90 regions in the brain – 40 minutes scanning – 400 mostly connected pairs



An example with fMRI data

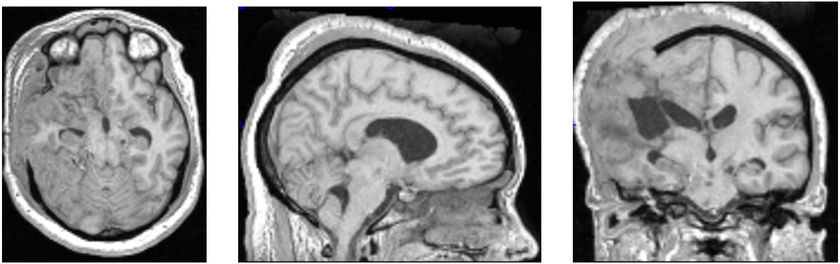
90 regions in the brain – 5 minutes scanning – 400 mostly connected pairs

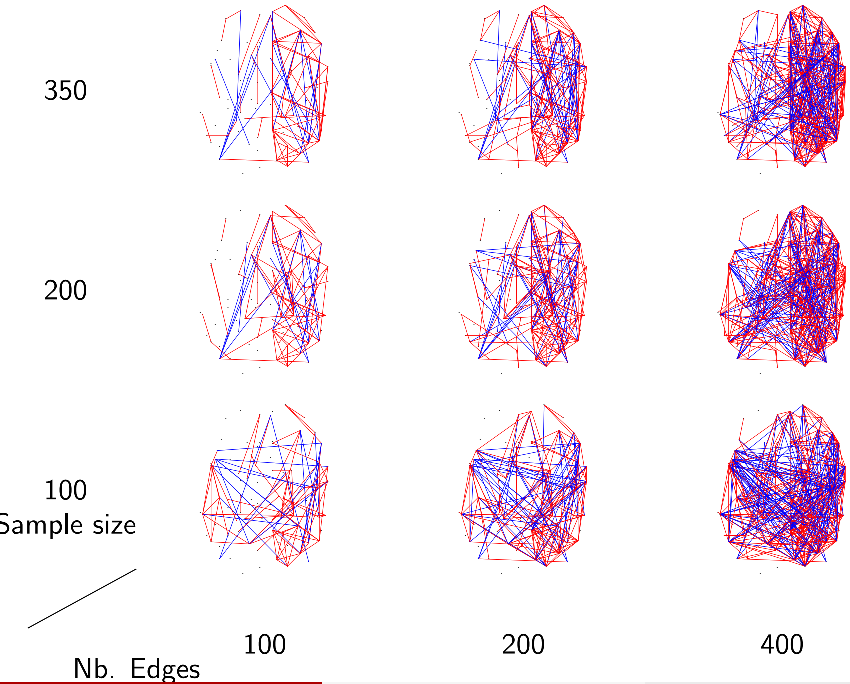




An example with fMRI data

An example using a patient with craniectomy on the left part of the brain.




350
200
100
Sample size
100
200
400
Nb. Edges

Construction of the adjacency matrices

Hypothesis tests: for all i, j, $1 \leqslant i, j \leqslant p$, $\quad i \neq j$

$$\mathcal{H}_0 : \rho_{i,j} = 0 \qquad \mathcal{H}_1 : \rho_{i,j} \neq 0$$

Problems :

- Multiple hypotheses tests : 4005 tests
  $\rightarrow$ Need to compare graphs with same number of edges
  $\rightarrow$ Maximise interesting properties
- The tests are dependent, classical approaches are not working

[**Achard** *et al.* J. Neurosci. 2006]
[**Hero** *et al.* 2013]
[**Drton** *et al.* 2004]

Multiple hypotheses tests

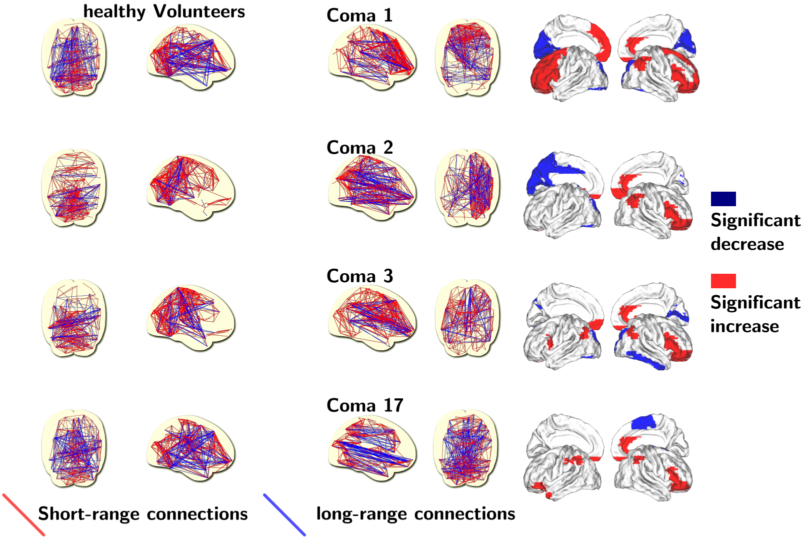
Number of errors committed when testing 4005 null hypothesis
n_0 = number of true null hypotheses

	Not rejected	Rejected	Total
True null hypotheses	$\mathbf{U}$	$\mathbf{V}$	n_0
Non-true null hypotheses	$\mathbf{T}$	$\mathbf{S}$	$4005 - n_0$
	$4005 - \mathbf{W}$	$\mathbf{W}$	4005

- $PCER = E(\mathbf{V}/4005) < \alpha$ if each tests control at level α.
  $\rightarrow$ do not take into account the multiple test.
- $FWER = P(\mathbf{V} \geqslant 1) < \alpha$ if each tests control at level $\alpha/4005$.
  $\rightarrow$ Problem when the number of hypotheses is large, too conservative.
- $FDR = P(\mathbf{W} > 0)E(\mathbf{V}/\mathbf{W}|\mathbf{W} > 0)$, i.e. control of the proportion of rejected null hypotheses which are erronously rejected.
  $\rightarrow$ less stringent, and a gain in power.

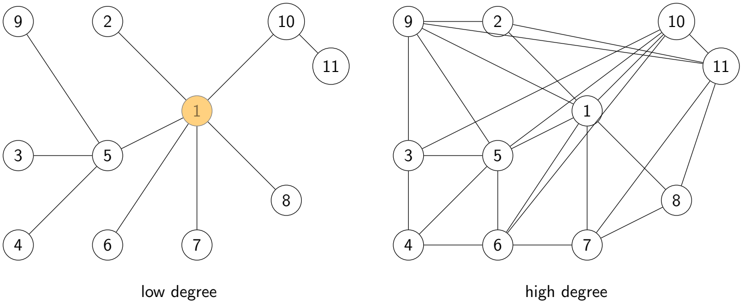
Marine Roux PhD

Brain connectivity of coma patients



[**Achard** *et al.* PNAS 2012]

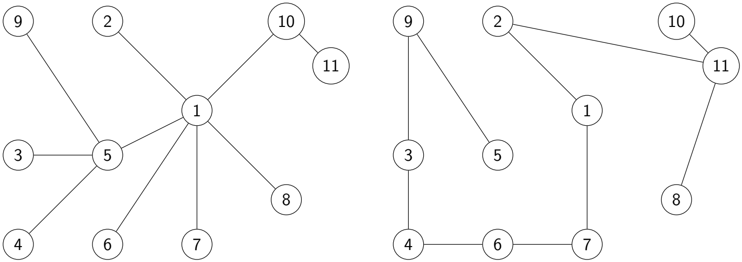
Graph features: degree



Degree = number of connections that node makes to other nodes.
$G = [G_{ij}]_{1 \leqslant i,j \leqslant N}$ is the adjacency matrix $1 \leqslant i, j \leqslant N$, $\quad G_{ij} = 0$ or 1.

$$D_i = \sum_{j \in G} G_{ij}.$$

Graph features: global efficiency



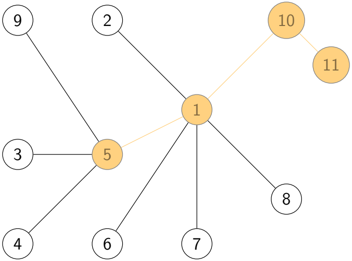
Eglob close to 1　　　　Eglob close to 0

Efficiency = inverse of the harmonic mean of the minimum path length L_{ij} between a node i and all the other nodes j in the graphs.

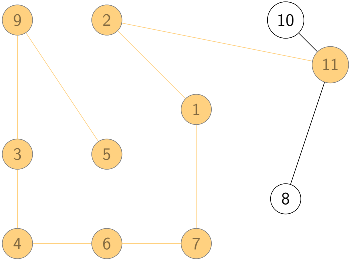
$$Eglob_i = \frac{1}{N-1} \sum_{j \in G} \frac{1}{L_{ij}}$$

[**Latora** *et al.* 2002]

Graph features: global efficiency



Eglob close to 1



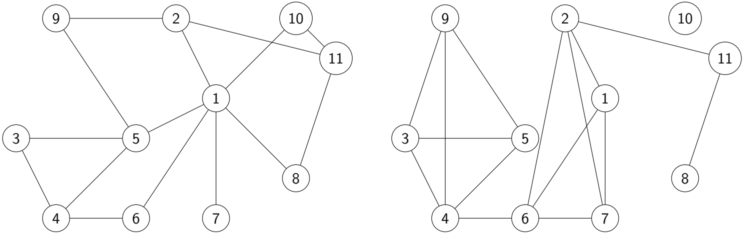
Eglob close to 0

Efficiency = inverse of the harmonic mean of the minimum path length L_{ij} between a node i and all the other nodes j in the graphs.

$$Eglob_i = \frac{1}{N-1} \sum_{j \in G} \frac{1}{L_{ij}}$$

[**Latora** *et al.* 2002]

Graph features: clustering



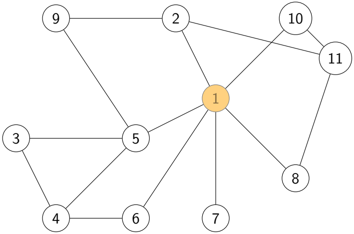
Clust close to 0 Clust close to 1

Clustering, also called "local efficiency" = measure of information transfer in the immediate neighbourhood of each node.

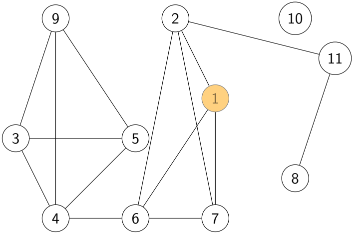
$$Clust_i = \frac{1}{N_{G_i}(N_{G_i}-1)} \sum_{j,k \in G_i} \frac{1}{L_{jk}},$$

[**Latora** *et al.* 2002]

Graph features: clustering



Clust close to 0



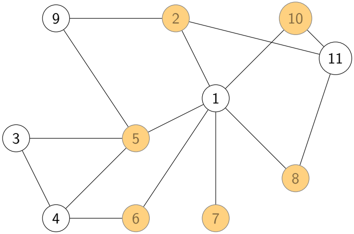
Clust close to 1

Clustering, also called "local efficiency" = measure of information transfer in the immediate neighbourhood of each node.

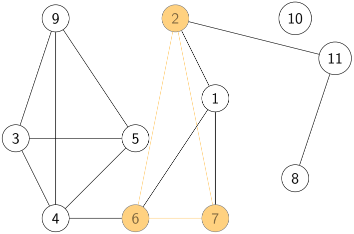
$$Clust_i = \frac{1}{N_{G_i}(N_{G_i} - 1)} \sum_{j,k \in G_i} \frac{1}{L_{jk}},$$

[**Latora** *et al.* 2002]

Graph features: clustering



Clust close to 0



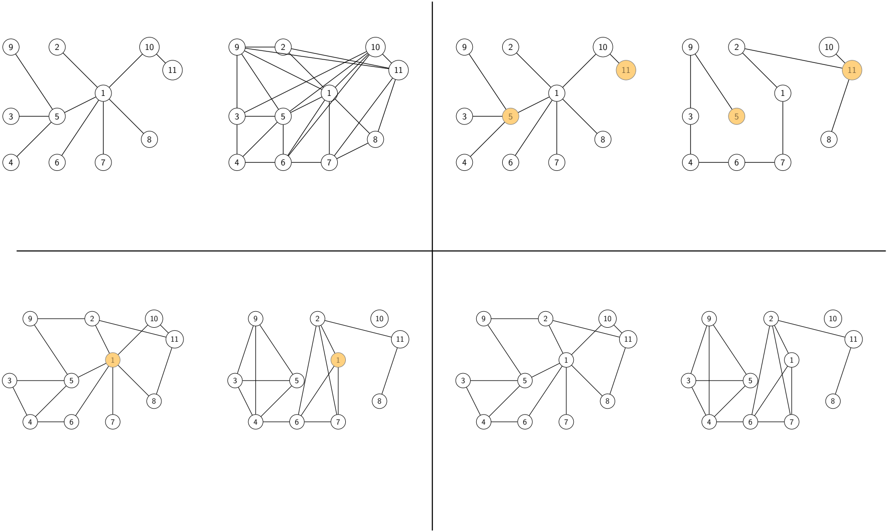
Clust close to 1

Clustering, also called "local efficiency" = measure of information transfer in the immediate neighbourhood of each node.

$$Clust_i = \frac{1}{N_{G_i}(N_{G_i}-1)} \sum_{j,k \in G_i} \frac{1}{L_{jk}},$$

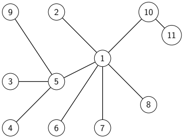
[**Latora** *et al.* 2002]

Interpretation of graph metrics

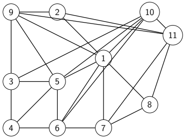


Interpretation of graph metrics

Cost

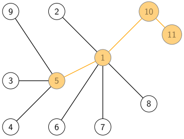


Low Cost

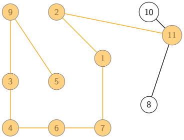


High Cost

Efficiency

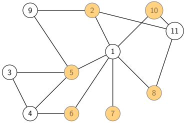


High Eglob

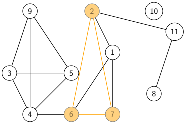


Low Eglob

Clustering

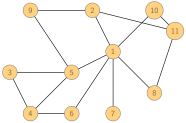


Low Clust

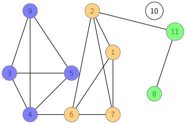


High Clust

Modularity



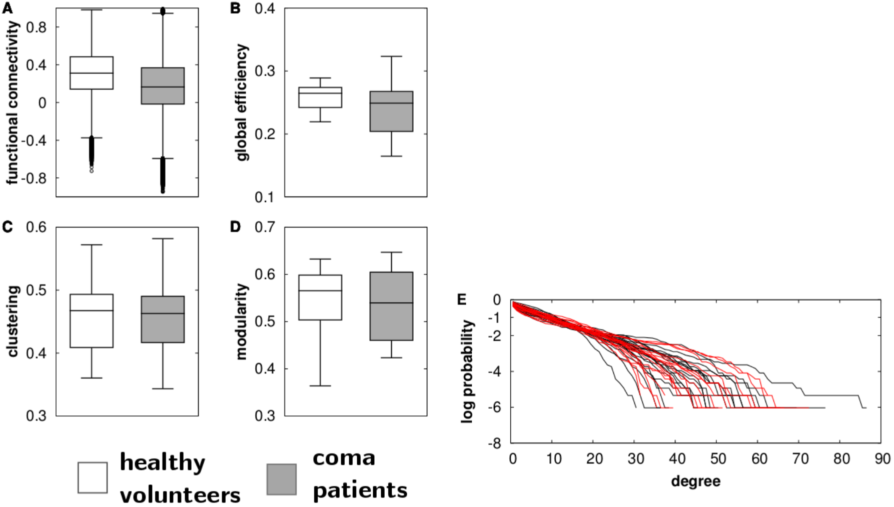
Low Modularity



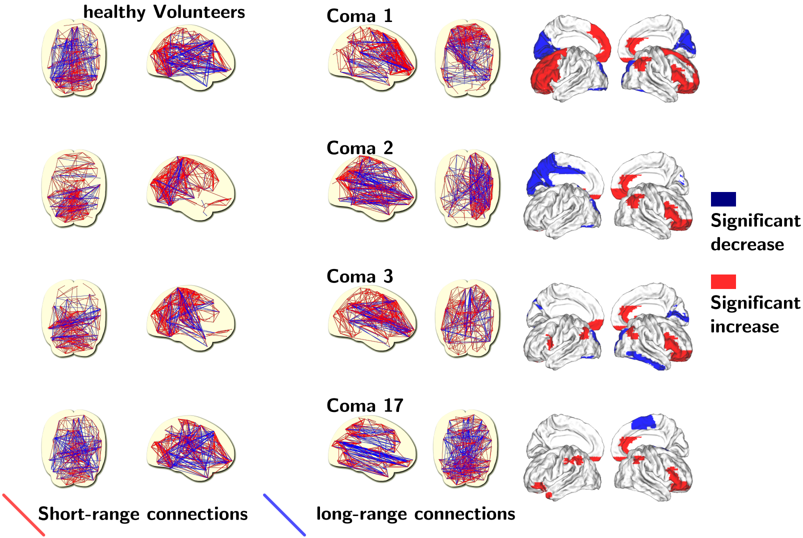
High Modularity

Results: global connectivity and network topology

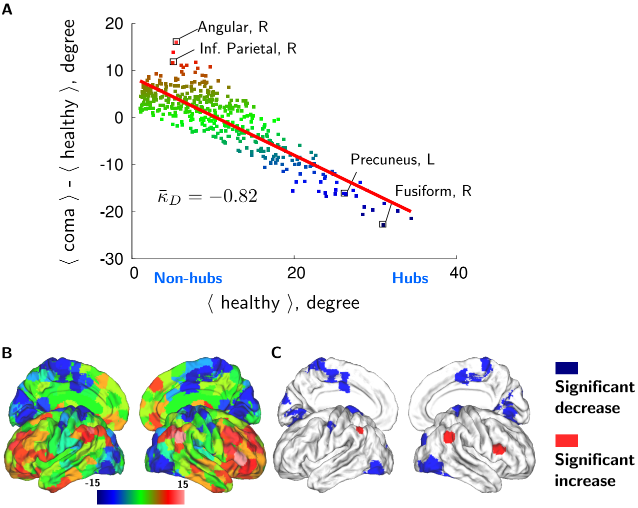
No significant difference on global measure of functional connectivity



Examples of connectivity graphs



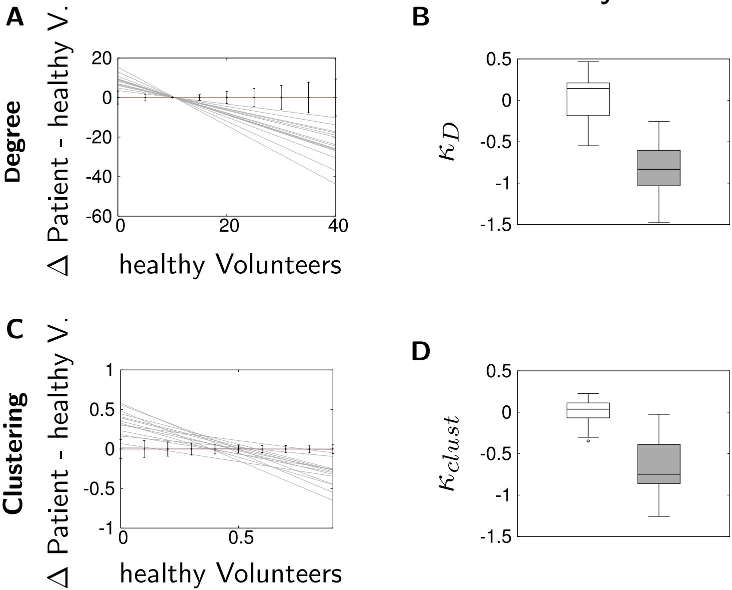
Results: nodal connectivity



⟨ coma ⟩ - ⟨ healthy ⟩, degree

Results: hub disruption index

One index to discriminate the coma and healthy volunteers



Manifold learning of patients

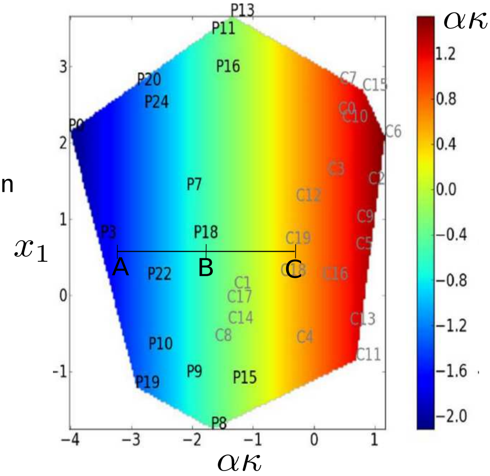
P* : DOC

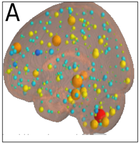
C* : healthy

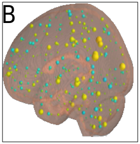
dimension reduction
ISOMAP

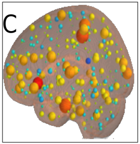
Evolution of global efficiency

Distance between networks







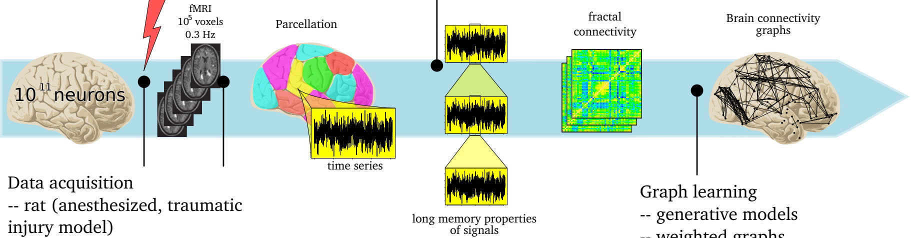


[**Renard** *et al.*, in preparation]

Conclusion and future work

Noise and distortion:
-- physiological noise
-- hemodynamic response

Statistics of BOLD signal
-- multivariate long memory model
-- robustness



Data acquisition
-- rat (anesthesized, traumatic injury model)
-- human (traumatic brain injury)

Graph learning
-- generative models
-- weighted graphs
-- model selection

Thanks to my collaborators