brain connectivity in the source space
the impact of regularization and of finite data length

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introduction

credits - 1

the 'methods for image and data analysis (MIDA)' group:

- solar physics and space weather
- biomedicine
- neuroscience
- inverse problems, machine learning, pattern recognition

people:

- staff: mp (UNIGE and CNR), anna maria massone (UNIGE and CNR), alberto sorrentino (UNIGE and CNR), federico benvenuto (UNIGE), cristina campi (UNIPD)
- 2 contractors
- 4 post-docs
- 3 PhD students

credits - 2

thanks to the (past and present) 'neuro' side of the MIDA group:

- alberto sorrentino
- sara sommariva
- elisabetta vallarino
- cristina campi
- annalisa pascarella
- federica sciacchitano
- gianvittorio luria

thanks to (past and present) collaborators:

- lauri parkkonen (aalto university)
- lino nobili (ospedale niguarda)
- BESA GmbH
- the MEG core team at IRCCS besta
- thomas serre (brown university)
- maureen clerc (INRIA)
- livio narici (roma 3)
- ITAB

our perspective

our perspective

neuroscience: reconstruction, in time and space and from indirect measurements, of the neural activity of human brain

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math: solution of dynamical, ill-posed inverse problems

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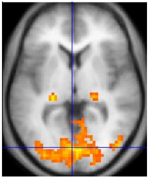
applications:

- clinical data
- validation of devices
- **visual system**
- **connectivity**

functional brain imaging

from indirect to direct information:



- connected to blood
- low time resolution
- image analysis 'by comparison'

functional brain imaging

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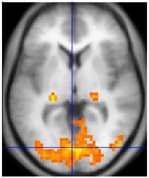

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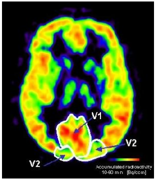
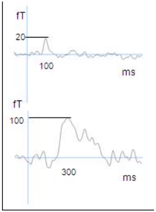


- connected to (glucose) metabolism
- low time resolution
- inverse methods

functional brain imaging

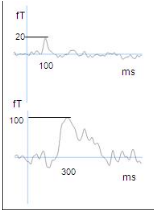
from indirect to indirect information (continued):



- connected to electromagnetic field
- high time resolution
- inverse methods

functional brain imaging

from indirect to indirect information (continued):



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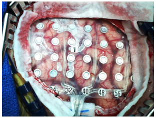

- connected to electric currents
- (very) invasive

our perspective (continued)

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math: solution of dynamical, ill-posed inverse problems

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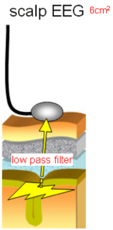
experimental data: neurophysiology (EEG, MEG, ECoG, SEEG)

models of data formation

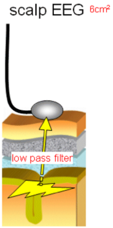
experimental data

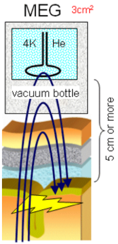
experimental data



- source space: cortex
- data space: scalar field (μV) on the whole scalp

experimental data





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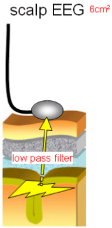

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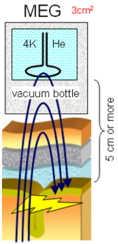

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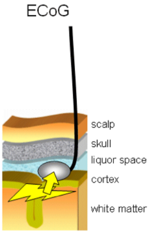
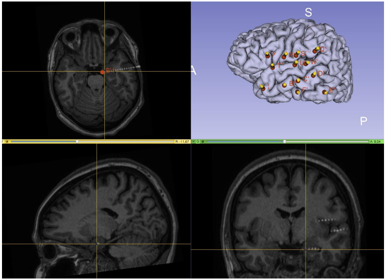


- source space: cortex
- data space: scalar field (μV) on a limited part of the cortex

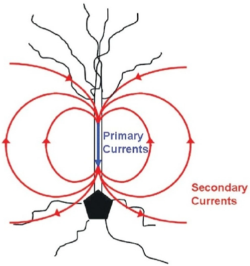
experimental data

stereo EEG (SEEG)



- source space: cortex
- data space: many cortical points along a line

maxwell



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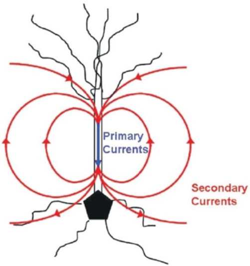
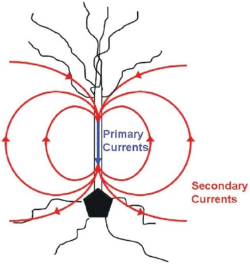


$$j = j_p + j_s$$

maxwell



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$$j_s = \sigma e$$

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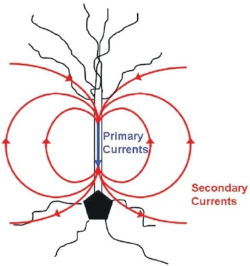

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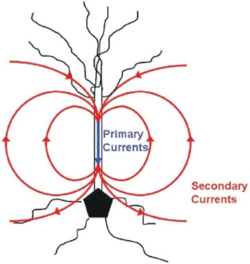

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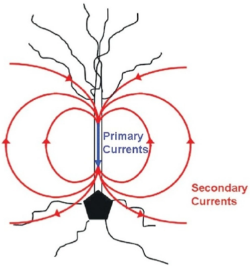

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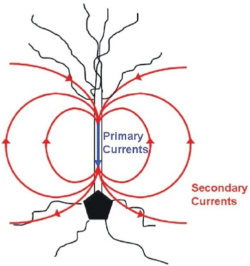
$$\frac{\partial e}{\partial t} = 0, \frac{\partial b}{\partial t} = 0 \Rightarrow b(r,t) = \frac{\mu_0}{4\pi} \int_\Omega j(r',t) \times \frac{r - r'}{|r - r'|^3} dr'$$

maxwell



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biot-savart: $b(r,t) = \frac{\mu_0}{4\pi} \int_\Omega [j_p(r',t) - \sigma(r')\nabla v(r',t)] \times \frac{r - r'}{|r - r'|^3} dr'$

lead-field matrix

neurophysiology forward problem: compute the lead-field matrix Λ mapping input primary point sources $j_p(t)$ onto output (either scalar or vector) data

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- MEG:

$$b(t) = \Lambda j_p(t)$$

- EEG, ECoG, SEEG:

$$V(t) = \Lambda j_p(t)$$

numerical methods (FEM, BEM, FDTD) needed

(pursiainen, sorrentino, campi and piana, *inverse problems*, 2011)

source modeling

inverse problem: ill-posedness

neurophysiology inverse problem: compute j_p **given measurements of** $b(t)$ **or** $V(t)$

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example: the MEG case

Theorem 1:: *the null space of the Biot-Savart operator* $BS : [C(V)]^3 \to [C(\partial V)]^3$ *contains the linear subspace*

$$M = \{j = \triangle m \ , \ m \in [C_0^2(V)]^3\}$$

(Kress, Kuhn, Potthast, *Inverse Problems*, 2002)

Theorem 2:: *the Biot-Savart operator* $BS : [L^2(V)]^3 \to [L^2(\partial V)]^3$ *is compact*

(Cantarella, De Turck, Gluck, *J. Math. Phys.*, 2001)

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in general: the lead-field matrix Λ is ill-conditioned and therefore the inverse problem

$$b_t(V_t) = \Lambda j_t$$

is numerically unstable

source models

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distributed sources and linear imaging methods:

- the neural current is a continuous vector field
- the inverse problem is linear
- imaging methods produce estimates of the current strength at each point in the brain

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focal sources and non-linear parameter identification methods:

- $j^p(r) = \sum_{i=1}^{\nu} q^i \delta(r - r_q^i)$
- a whole active area is represented by a single current dipole
- the parameters to estimate via non-linear optimization are ν, q_i, r_q^i

inversion methods

imaging methods (tikhonov regularization):

$$\hat{j}_t = \arg\min_{j_t} \left(\|\Lambda \cdot j_t - b_t\|_{\Sigma}^2 + \alpha \|j_t\|_{L^\beta(\Omega)}^\beta \right)$$

- α: regularization parameter tuning the trade-off between stability and fitting
- $\beta = 2$: sLORETA, eLORETA, beamformers, MNE (hämäläinen and ilmoniemi, *med. biol. eng. comput.*, 1994)
- $\beta = 1$: sparsity enhancement (uutela et al, *neuroimage*, 1999)

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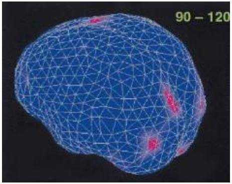
parametric methods (bayesian approaches):

$$\pi(j_p|b) = \pi(b|j_p)\pi(j_p)$$

- temporal evolution possibly encoded in the kolmogorov equation (sorrentino et al, *human brain mapp.*, 2009)
- dynamic filtering of static dipoles (sorrentino et al, *ann. appl. stat.*, 2013)
- semi-linear formulations (campi et al, *inverse problems*, 2008; sommariva et al, *inverse problems*, 2014)

inversion methods: examples



(uutela, hämäläinen, somersalo, *neuroimage*, 1999)

(sorrentino et al, *human brain mapp.*, 2009)

applications: visual system

response to noisy visual stimulation

objective: to study brain responses to variations in SNR of cognitive visual stimuli

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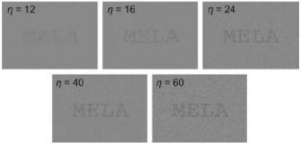
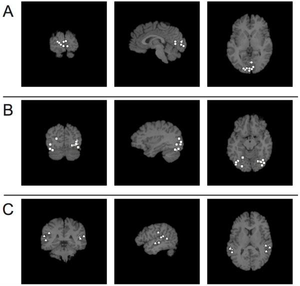
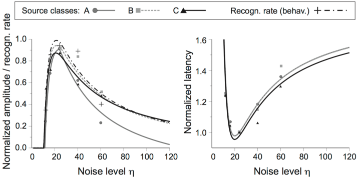


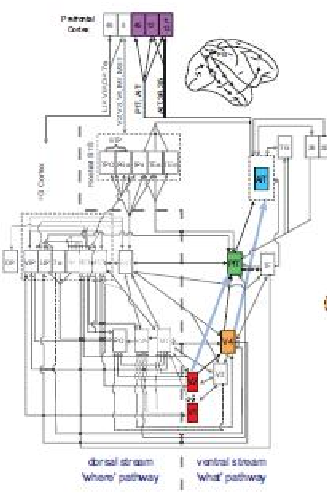




(sorrentino, parkkonen, piana, massone, narici, sannita, *clin. neurophys.*, 2006)

a visual model

a theory of object recognition (serre, oliva, poggio, PNAS, 2007):



- feedforward computation in the ventral stream
- animals vs non-animals categorization tasks
- learning algorithms predict the level and the pattern of performance achieved by humans

an ECoG experiment

experimental paradigm and grid:

an ECoG experiment

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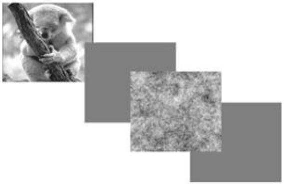
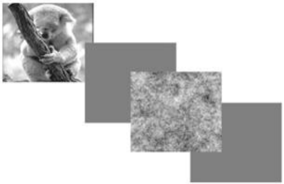
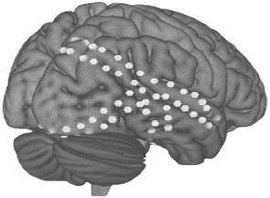


- 320 trials
- stimulus: 34 ms
- blank: 34 ms
- noisy image: 34 ms

an ECoG experiment

experimental paradigm and grid:





- 320 trials
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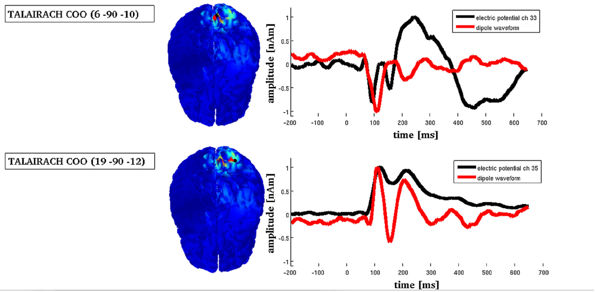
- 3 strips
- parietal-occipital lobe
- 64 electrodes

results: validation

(pascarella, todaro, clerc, serre, piana, *journal of neuroscience methods*, 2016)



results: neuroscience

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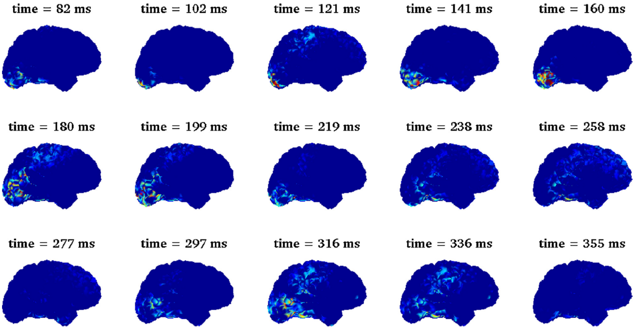
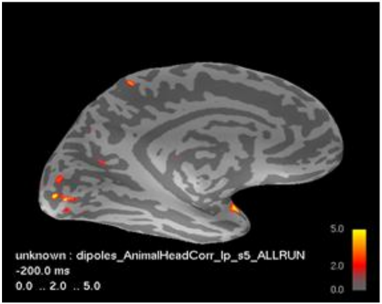


results: neuroscience

First results:



- dipoles for all latencies superimposed
- peaks at 130 ms (V1), 180 ms (V2), 220 ms (IT)
- some later activity in V1 (feedback???)

applications: connectivity

connectivity: definitions

structural connectivity:

- identification and assessment of white matter fiber tracts within the brain
- modalities: diffusion tensor imaging

functional connectivity:

- analysis of the temporal correlation between active cortical areas
- modalities: EEG, MEG
- effective connectivity = functional connectivity + causality

functional connectivity: the pipeline

EEG/MEG time series

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EEG/MEG time series

$\downarrow$

data inversion $\rightarrow$ neural current time series

functional connectivity: the pipeline

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dimension reduction + PCA $\rightarrow$ active region (AR) time series

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EEG/MEG time series

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↓

computation of a connectivity measure between each pair of AR time series

functional connectivity: the pipeline

EEG/MEG time series

$\downarrow$

data inversion $\rightarrow$ neural current time series

$\downarrow$

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$\downarrow$

computation of a connectivity measure between each pair of AR time series

$\downarrow$

statistical test for connectivity significance

connectivity measures: ingredients

1. each i-th AR is represented by a time series $x_i(t)$, $t = 1, \ldots, T$

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3. covariance: if $\mathbf{x}(t) = (x_1(t), \ldots, x_N(t))$ is the set of all AR time series and $\mathbf{X}(t)$ is the corresponding N-th dimensional stochastic process, then

$$\Gamma_{ij}^{\mathbf{X}}(k) := \mathbb{E}(X_i(t)X_j(t-k)) \quad k \in \mathbb{N}$$

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4. cross power spectrum: if

$$\hat{X}_i(f, T) := \sum_{t=0}^{T} X_i(t)e^{-itf}$$

then

$$S_{ij}^{\mathbf{X}}(f) := \sum_{k=-\infty}^{+\infty} \Gamma_{ij}^{\mathbf{X}}(k)e^{-ikf} = \lim_{T\to\infty} \frac{1}{T+1} \mathbb{E}[\hat{X}_i(f, T)\hat{X}_j^*(f, T)]$$

connectivity measures: imaginary part of coherency

$$IC_{ij}^{\mathbf{x}}(f) := \frac{\text{Im}\left(S_{ij}^{\mathbf{x}}(f)\right)}{\sqrt{S_{ii}^{\mathbf{x}}(f) S_{jj}^{\mathbf{x}}(f)}}$$

theorem (nolte et al, *clinical neurophys.*, 2004; chella et al, *neuroimage*, 2014): the imaginary part of coherency is zero if the sources are independent

connectivity measures: partial directed coherence

(baccalà and sameshima, *biological cybernetics*, 2001)

$\mathbf{X}(t)$ is fitted by means of a multivariate autoregressive process:

$$\mathbf{X}(t) = \sum_{k=1}^{p} A(k)\mathbf{X}(t-k) + \epsilon(t)$$

- p model order
- $A(k) \in M_N(\mathbb{R})$ coefficient matrix
- $\{\epsilon(t)\}_{t=-\infty}^{+\infty}$ white noise process

$$PDC_{ij}^{\mathbf{X}}(f) := \frac{|\overline{A}_{ji}(f)|}{\sqrt{\sum_{n=1}^{N} |\overline{A}_{ni}(f)|^2}}$$

where $\overline{A}_{ji}(f) = \delta_{ji} - \sum_{k=1}^{p} A_{ji}(k)e^{-ikf}$

connectivity measures: granger causality

definition (granger, *econometrica*, 1969): $X_i(t)$ is said to granger-cause $X_j(t)$ if the future of $X_j(t)$ can be better predicted by exploiting the information contained in the past of $X_i(t)$ rather than exploiting the information contained in the past of $X_j(t)$

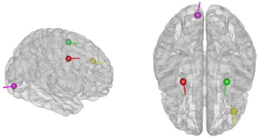
spectral formulation (geweke, *j. am. stat. ass.*, 1982): after fitting $\mathbf{X}(t)$ with a multivariate autoregressive process, compute

$$fGC_{ij}(f) = \ln\left(\frac{|S^{\mathbf{X}}_{jj}(f)|}{|S^{\mathbf{X}}_{jj}(f) - H_{ji}(f)(\Sigma_{ii} - \Sigma_{ij}\Sigma_{jj}^{-1}\Sigma_{ji})H^{*}_{ji}(f)|}\right) ,$$

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

an experiment with synthetic data: data simulation

(sommariva et al, *brain topography*, 2017)



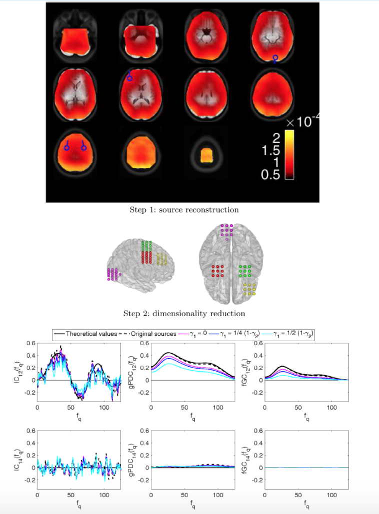
$$\mathbf{x}(t_p) = (x_1(t_p), x_2(t_p), x_3(t_p), x_4(t_p))^T \quad p = 1, \ldots, P$$

$$\mathbf{x}(t_p) = \sum_{k=1}^{K} A(k)\mathbf{x}(t_{p-k}) + \epsilon(t_p)$$

$$A(k) = \begin{pmatrix} A_{11}(k) & 0 & 0 & 0 \\ A_{12}(k) & A_{22}(k) & 0 & 0 \\ A_{13}(k) & 0 & A_{33}(k) & 0 \\ 0 & 0 & 0 & A_{44}(k) \end{pmatrix}$$

$$\mathbf{y}(t_p) = \Lambda\mathbf{x}(t_p) + \mathbf{n}(t_p)$$

an experiment with synthetic data: computation of connectivity (sommariva et al, *brain topography*, 2017)



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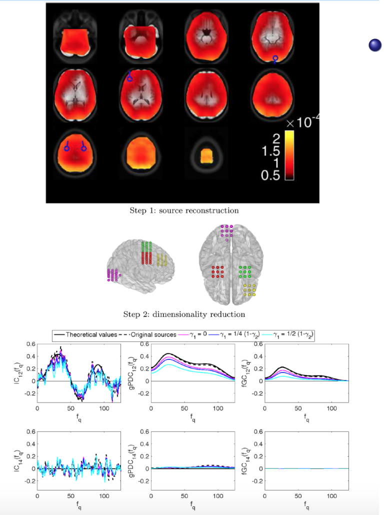
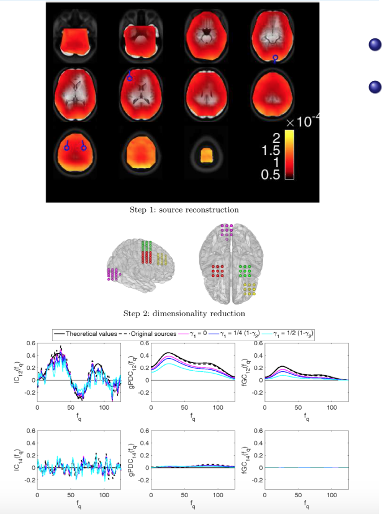


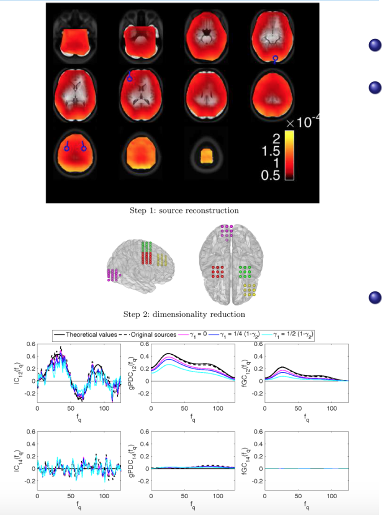
- source reconstruction: eLORETA

an experiment with synthetic data: computation of connectivity (sommariva et al, *brain topography*, 2017)



- source reconstruction: eLORETA
- dimensionality reduction:
  - sum of activity in the reconstructed AR voxels
  - application of PCA to project the activity in each AR onto the direction of maximum power

an experiment with synthetic data: computation of connectivity (sommariva et al, *brain topography*, 2017)



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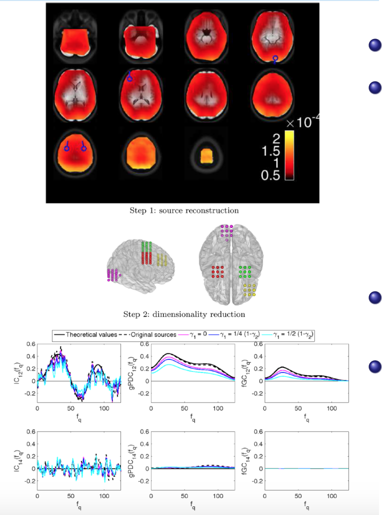

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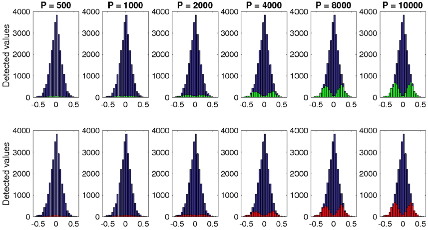
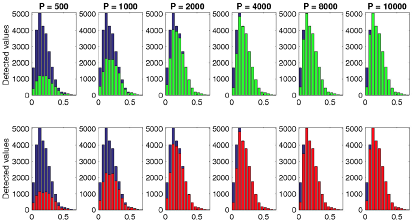
- dimensionality reduction:
  - sum of activity in the reconstructed AR voxels
  - application of PCA to project the activity in each AR onto the direction of maximum power
- computation of three connectivity measures (IC, PDC, granger causality)
- statistical test for thresholding: null hypothesis via two surrogate data approaches (phase-randomized surrogate data; autoregressive surrogate data)

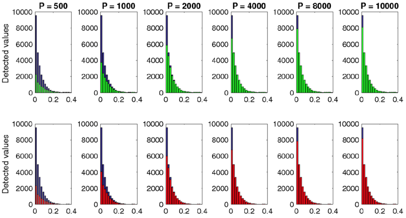
impact of finite data length: histograms

(sommariva et al, *brain topography*, 2017)



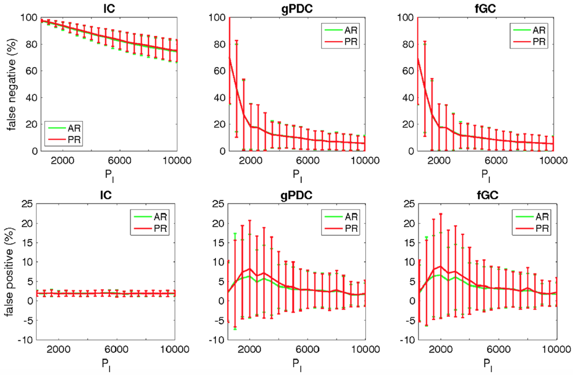
Imaginary part of Coherency





impact of finite data length: false negatives and positives

(sommariva et al, *brain topography*, 2017)



discussion of results

(sommariva et al, *brain topography*, 2017)

- IC more conservative: statistical tests passed at large theoretical values; more false negatives
- model-based measures work fine when data are accurately fitted
- PDC and granger causality probably better for longer data lengths
- robustness with respect to noise for all three connectivity measures

open issue: the impact of regularization on connectivity

two technical questions?

- what is the impact of the inversion method on the computed connectivity measure?
- for connectivity measures based on cross power spectrum, what is the impact of regularization on the estimation of the cross power spectrum?

estimation of the power spectrum

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work in progress (vallarino et al, *inverse problems*, in preparation):

- analytical result for white noise processes and tikhonov method
- the difference in the estimate depends on both the frequency complexity and the signal-to-noise-ratio

to-do list

we are currently trying to answer to the following questions?

- to what quantitative extent is estimating connectivity in the cortical space more accurate than estimating connectivity in the sensors' space?
- are parametric methods better than imaging methods for computing connectivity measures in the cortical space?
- is it possible to study the connectivity problem as a one-step inverse problem from the data time series to the cross-power spectrum?
- is it possible to identify significant connectivity between cortical areas activated by visual recognition?
- are we able to exploit this possible connectivity effects for applications in deep learning?