

Development of Differential Connectivity Graph for Characterization of Brain Regions Involved in Epilepsy

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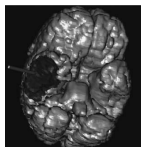
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Introduction

Context

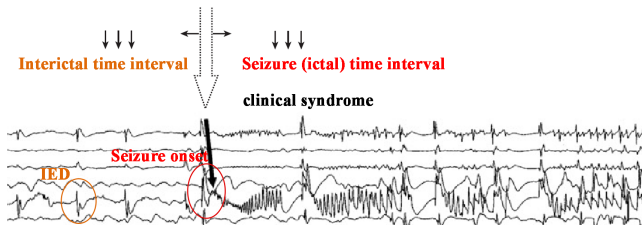


[Lüders & Bingaman, 2008]

- Life of epileptic patients is not easy.
- Over 30% of epileptic patients do not have seizure control with drugs.
- Drug-resistant epileptic patients are the candidates for surgery [Lüders & Bingaman, 2008].
- Currently 400 patients undergo resective surgery yearly in France [Devaux et al., 2008].

Epilepsy

- Seizures are associated with increase of transient electrical activity
- Interictal epileptiform discharges (IEDs): waves or complexes distinguished from background activity [Chatrian et al., 1974].

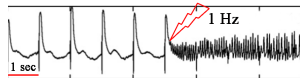


[David et al., 2008]

- Seizure onset zone (SOZ): the region of the first electrophysiological changes is detected at seizure onset.
- IED region: the site responsible for IEDs generation.

How does the surgeon determine the regions to be removed?

- Different clinical knowledge: like EEG, fMRI, studying clinical syndromes (semiology), etc
- SOZ detection: visual inspection of EEG
 - during spontaneous seizures
 - electrically stimulated seizures
- Epileptologist dependent and time consuming
- Number of seizures are very limited: not enough for statistically reliable results.
- Are SOZs congruent with leading IED regions?



[David et al., 2008]

[Alarcon, 1996, Alarcon et al., 1997, Hufnagel et al., 2000, Le Van Quyen et al., 1998, Ortega et al., 2008a, Lai et al., 2007, Ortega et al., 2008b, Wilke et al., 2009, Bourien et al., 2005, Monto et al., 2007, Wendling et al., 2009].

Objectives

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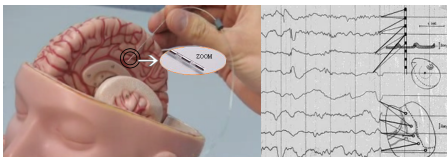
- The estimation of leading IED regions through a reliable and repeatable method
- Comparison between IED regions and SOZ

How to reach this objective

- Scalp EEG: noninvasive, high temporal and poor spatial resolution.
- fMRI: noninvasive, high spatial, poor temporal resolution, not suitable for motor seizure [Rosenow & Lüders, 2001].
- Solutions to enhance poor spatial resolution of scalp EEG:
 - Inverse models
 - Implanted intracerebral depth electrodes: intracerebral EEG (iEEG).
 - high temporal and spatial resolution
 - invasive
 - limited to the covered area



<http://www.medgadget.com>



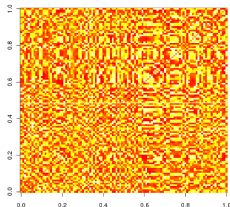
<http://www.diximedical.net>

[Lüders & Bingaman, 2008]

How to identify regions related to IEDs?

Why connectivity graph?

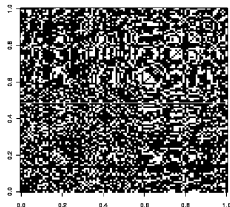
- The similarity (coupling) between signal pairs increases during IED time interval [Towle et al., 1998, Wendling et al., 2005, Ortega et al., 2008b].
- We study the couplings between signal pairs.
- Useful mathematical tools to study the couplings can be coupling matrices or graphs.
- For 100 channels: 100×100 coupling matrix.



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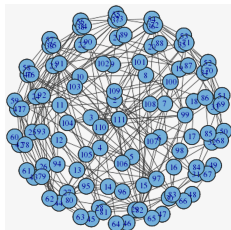
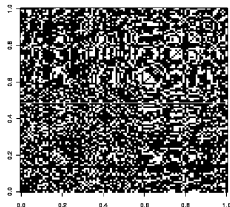
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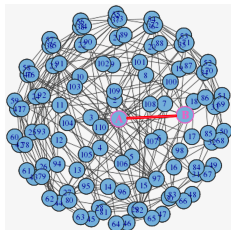
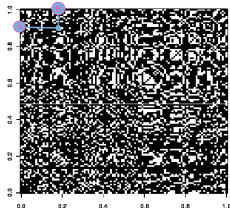
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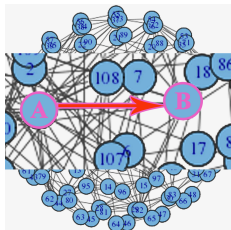
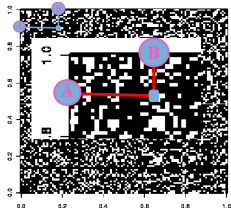
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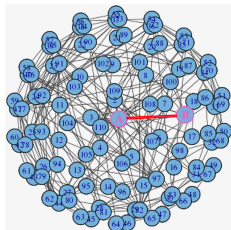
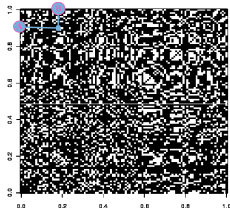
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- We study the couplings between signal pairs.
- Useful mathematical tools to study the couplings can be coupling matrices or graphs.
- The coupling matrix and graph include the information.



Previous IED related graphs

Previous studies

- Previous graphs of studying IED events are complex.
- We look for simpler graph.
- We use both IED and non-IED time intervals.
- One can calculate two separate graphs for IED and non-IED and compare them.
- Single reliable graph including discriminated connections.

Outline

- 1 Directed differential connectivity graph (dDCG)
 - Basic idea of DCG
 - DCG calculation
 - Characterization of dDCG
 - Multiple graph analysis
- 2 Experimental results
 - dDCG
 - Leading IED regions
- 3 Conclusion and Perspectives

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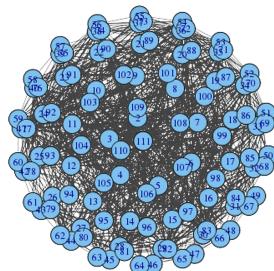
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Problem statement

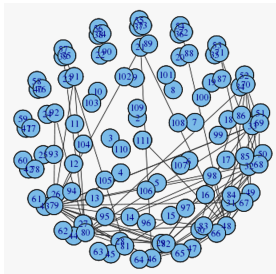
Problems of available connectivity graphs for the estimation of IED regions.



classic IED related graph

- Using only IED time intervals.
- Include non-interested connections.
- Complicated (high-density electrode array iEEG) \implies difficult interpretation

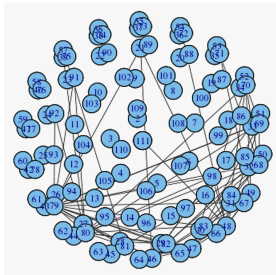
Differential connectivity graph (DCG)



DCG

- Differential is related to “making the difference”.
- One may consider of making the difference between two separated IED and non-IED graphs.

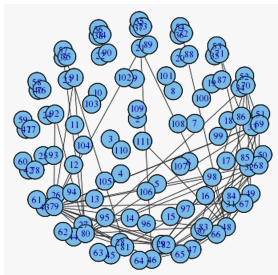
Differential connectivity graph (DCG)



DCG

- **DCG identifies the discriminated connections between two brain states (*IED* and *non-IED*).**
- DCG uses both *IED* and *non-IED* periods.
- Preserve the significantly changing connections by comparing their couplings.
- the effect of common events is decreased.

Differential connectivity graph (DCG)



DCG

- **DCG identifies the discriminated connections between two brain states (*IED* and *non-IED*).**
- DCG needs to select *IED* and *non-IED* time intervals from the same recordings.
- Sufficient number of *IED* and *non-IED* periods
- Statistically reliable

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DCG

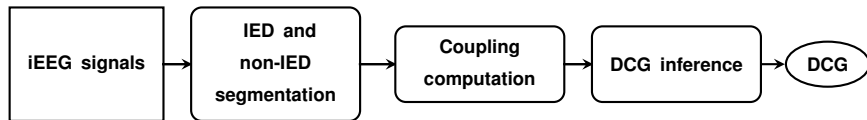
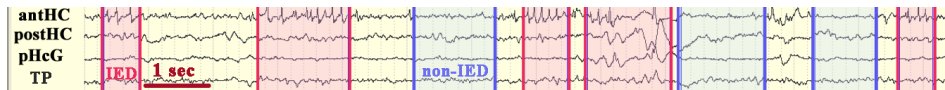


Diagram of DCG calculation.

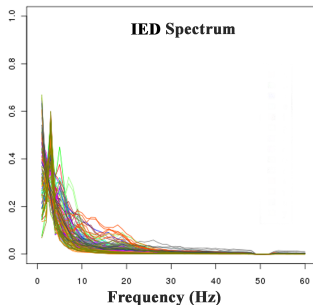
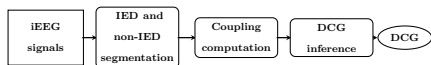
IED and non-IED time intervals

iEEG recordings of a typical patient for about 14 seconds.



- Onsets and offsets of IED and non-IED time intervals.

Different frequency bands



- Lower frequencies have higher contribution.
- Wavelet transforms:
 - narrower bands for lower frequencies.
 - well adapted for the analysis of non-stationary EEG signals

[Clark et al., 1995, Senhadji & Wendling, 2002, Adeli et al., 2003, Indiradevi et al., 2008, Conlon et al., 2009].

Coupling computation

- Wavelet cross-correlation [Whitcher et al., 2000, Achard et al., 2006, Ali, 2009]

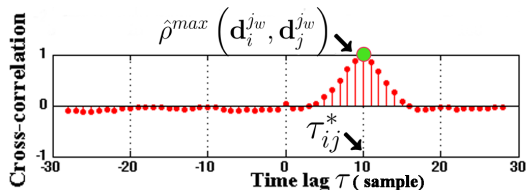
$$\hat{\rho}(\mathbf{d}_i^{jw}, \mathbf{d}_j^{jw}, \tau) = \frac{\widehat{\text{cov}}(\mathbf{d}_i^{jw}[k], \mathbf{d}_j^{jw}[k - \tau])}{\sqrt{\widehat{\text{var}}(\mathbf{d}_i^{jw}[k])\widehat{\text{var}}(\mathbf{d}_j^{jw}[k - \tau])}}$$

- The maximum MODWT cross-correlation (MMCC) is our formal coupling measure, MODWT: the maximal overlap discrete wavelet transform

[Percival, 1995, Whitcher et al., 2000].

$$\tau_{ij}^* = \arg \max_{\tau} (|\hat{\rho}(\mathbf{d}_i^{jw}, \mathbf{d}_j^{jw}, \tau)|)$$

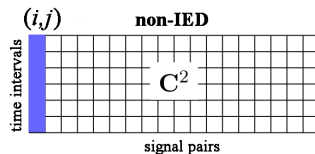
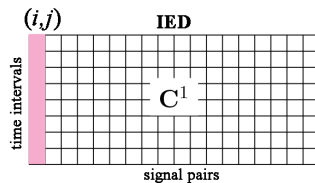
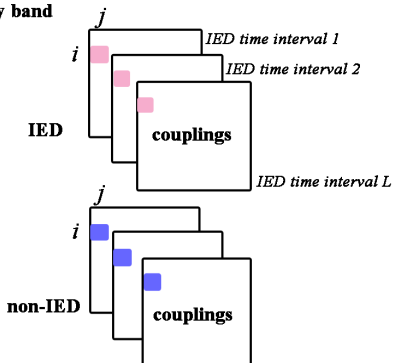
$$\hat{\rho}^{\max}(\mathbf{d}_i^{jw}, \mathbf{d}_j^{jw}) = \hat{\rho}(\mathbf{d}_i^{jw}, \mathbf{d}_j^{jw}, \tau_{ij}^*)$$



DCG construction

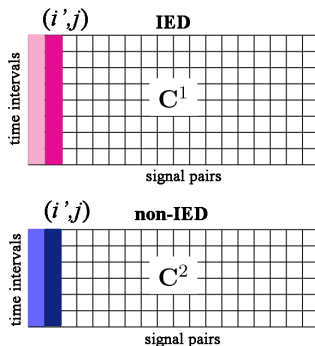
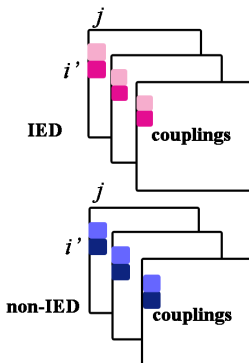
- Main idea of DCG: if the couplings between signal pair (i, j) change significantly \Rightarrow connection between nodes i and j .
- Statistically reliable.
- We use permutation method.

For each frequency band

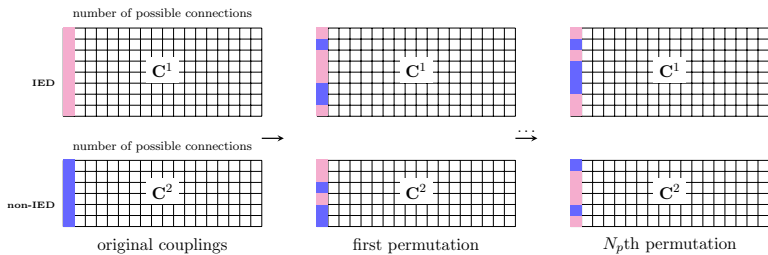


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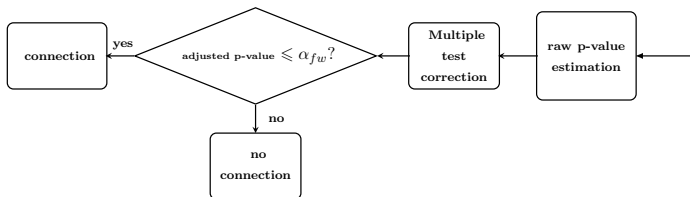
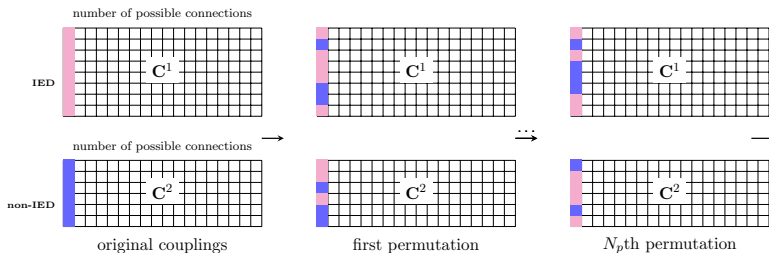
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Permutation



Permutation



Summary

- DCG is a new method for computation of graphs [Amini et al., 2010b].
- DCG focuses on connections whose couplings change significantly between two states.
 - in this work, IED/non-IED
 - generalized to other applications
- Main properties of DCG:
 - Couplings are calculated in different frequency bands using wavelet
 - J frequency bands: J DCGs
 - DCG is statistically reliable, large number of IED and non-IED time intervals and permutation

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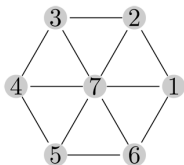
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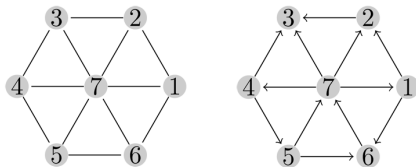
3 Conclusion and Perspectives

Relevance of the nodes of directed DCG (dDCG)



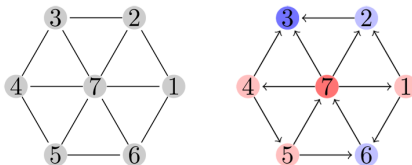
- dDCG: set of brain regions involved in IED events.
- **Definition:**
 - **Source:** the amount of emitting information $>$ the amount of receiving information
 - **Sink:** the amount of emitting information $<$ the amount of receiving information

Relevance of the nodes of directed DCG (dDCG)



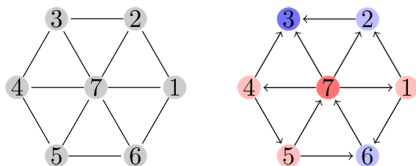
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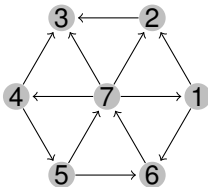
Relevance of the nodes of directed DCG (dDCG)



- dDCG: set of brain regions involved in IED events.
- **Definition:**
 - **Source:** the amount of emitting information $>$ the amount of receiving information
 - **Sink:** the amount of emitting information $<$ the amount of receiving information
- assumption: this information is related to IED events
- source nodes are leading IED regions
- We aim to define the source nodes of directed DCG

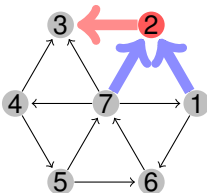
Can we use classic graph measures for source identification?

- Total degree (TD) = sum of outgoing edges - sum of ingoing edges
- the information carried by each edge is unknown.



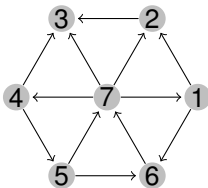
Can we use classic graph measures for source identification?

- Total degree (TD) = sum of outgoing edges - sum of ingoing edges
- node 2: $TD(2) = 1 - 2 = -1$
- the information carried by each edge is unknown.



Global efficiency (GE)

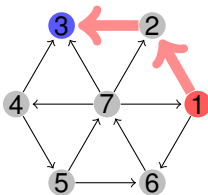
- **Definition:** How efficient a node communicates with the rest of graph.
- **Measuring GE ?**



$$L_G = \begin{pmatrix} 3 & 1 & 2 & 3 & 4 & 1 & 2 \\ \infty & \infty & 1 & \infty & \infty & \infty & \infty \\ \infty & \infty & \infty & \infty & \infty & \infty & \infty \\ 3 & 3 & 1 & 3 & 1 & 2 & 2 \\ 2 & 2 & 2 & 2 & 3 & 1 & 1 \\ 2 & 2 & 2 & 2 & 3 & 3 & 1 \\ 1 & 1 & 1 & 1 & 2 & 2 & 3 \end{pmatrix}$$

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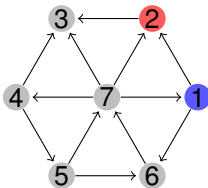
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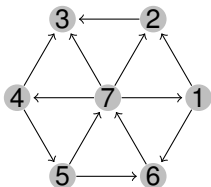
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$$\ell_{13} = 2 \Rightarrow \text{efficiency}_{13} = \frac{1}{\ell_{13}} = \frac{1}{2}$$

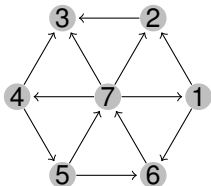
$$\ell_{21} = \infty \Rightarrow \text{efficiency}_{21} = \frac{1}{\ell_{21}} = 0$$

$$E_{glob}[i] = \text{average}_{j \neq i} \left(\frac{1}{\ell_{ij}} \right)$$

$$E_{glob}[\mathbf{G}] = \text{average}_i (E_{glob}[i])$$

Global efficiency (GE)

- **Definition:** How efficient a node communicates with the rest of graph.
- **Measuring GE?**
- we count the paths, but their related information are not considered.



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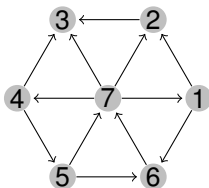
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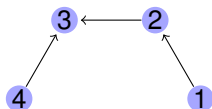
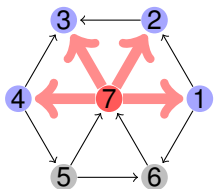
Local efficiency (LE)

- **Definition:** How efficient a node communicates with its neighbors.
- **Measuring LE ?**



Local efficiency (LE)

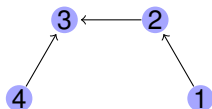
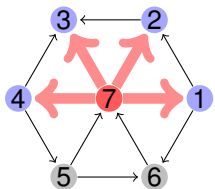
- **Definition:** How efficient a node communicates with its neighbors.
- **Measuring LE?**



$$L_{G_7^-} = \begin{pmatrix} \infty & 1 & 2 & \infty \\ \infty & \infty & 1 & \infty \\ \infty & \infty & \infty & \infty \\ \infty & \infty & 1 & \infty \end{pmatrix}$$

Local efficiency (LE)

- **Definition:** How efficient a node communicates with its neighbors.
- **Measuring LE ?**
- a node whose LE is high is not necessarily a source
- amount of information is not considered

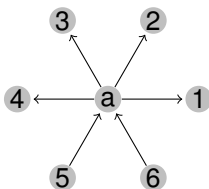


$$L_{G_7} = \begin{pmatrix} \infty & 1 & 2 & \infty \\ \infty & \infty & 1 & \infty \\ \infty & \infty & \infty & \infty \\ \infty & \infty & 1 & \infty \end{pmatrix}$$

Local information

Local information (L): amount of information passes through each node locally.

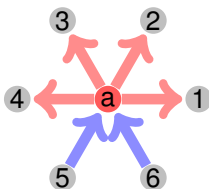
$$LI[a] = \sum_{\mathbf{v}_{a \rightarrow b}} MI(d_a[k], d_b[k - \tau_{ab}^*]) - \sum_{\mathbf{v}_{b \rightarrow a}} MI(d_a[k], d_b[k - \tau_{ab}^*])$$



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- the greater positive LI values, the greater relevance of node as a source.
- total degree of a weighted digraph.

Local information

- **Advantages of L_I over classic measures**

- weighted measure
- the information carried by each edge

- **Disadvantages of L_I**

- local measure
- computationally heavy

Outline

1 Directed differential connectivity graph (dDCG)

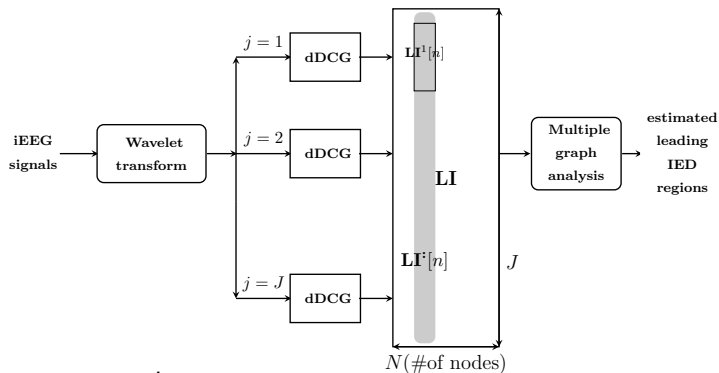
- Basic idea of DCG
- DCG calculation
- Characterization of dDCG
- **Multiple graph analysis**

2 Experimental results

- dDCG
- Leading IED regions

3 Conclusion and Perspectives

Multiple graph analysis



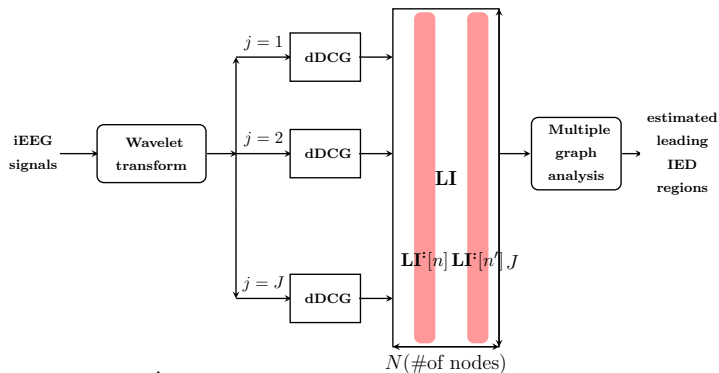
One measure value
for node n
at frequency level j

$$\Rightarrow \mathbf{LI}^i[n] = \{L^{j=1}[n], L^{j=2}[n], \dots, L^{j=J}[n]\}$$

a vector of J components

How to compare the relevance of two nodes $\mathbf{LI}^i[n]$ and $\mathbf{LI}^i[n']$?

Multiple graph analysis



One measure value
for node n
at frequency level j

$$\Rightarrow \mathbf{LI}^j[n] = \{L^{j=1}[n], L^{j=2}[n], \dots, L^{j=J}[n]\}$$

a vector of J components

How to compare the relevance of two nodes $\mathbf{LI}^j[n]$ and $\mathbf{LI}^j[n']$?

How to consider the L values of all the frequency bands simultaneously?

- scalarization of $\mathbf{L}^i[n]$ into a single scalar value: e.g.
 $\max \|\mathbf{L}^i[n]\|_2$
- solutions depend on the importance of the frequency bands
- the preference between different frequency bands is unknown

Multi-objective optimization methods (Pareto optimization)

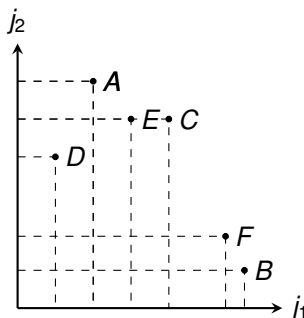
- Multiple objective functions are optimized simultaneously

[Deb, 1999]: $\max \left\{ L^{j=1}[n], L^{j=2}[n], \dots, L^{j=J}[n] \right\}$

- providing a set of optimal solutions: Pareto front = most relevant nodes = leading IED regions
 - Pareto (1848-1923)
 - Pareto optimization: in economics, and social science

Multi-objective optimization (MOP) methods

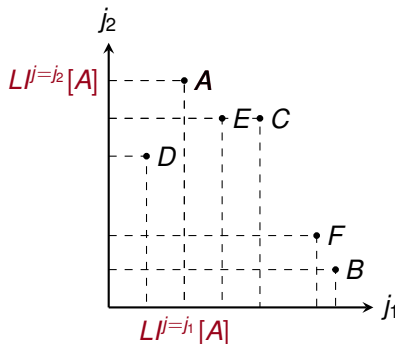
Dominancy



- nodes or points in 2 dimensions: 2 frequency bands j_1 and j_2
- the basic concept of MOP: Definition of dominance
- node A dominates node D : $\forall j \quad \mathbf{L}^j[A] \geq \mathbf{L}^j[D]$ & $\exists j \quad \mathbf{L}^j[A] > \mathbf{L}^j[D]$
- node C dominates node E
- We can reject nodes D and E

Multi-objective optimization (MOP) methods

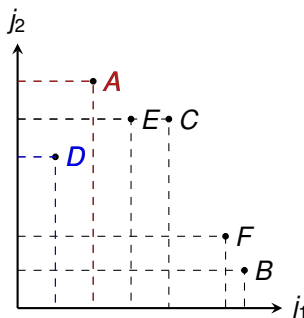
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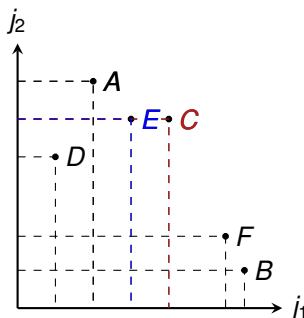
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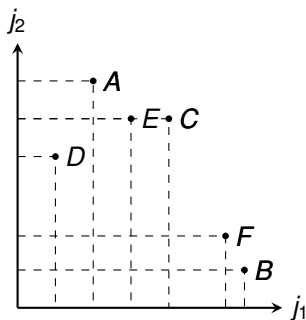
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Multi-objective optimization methods

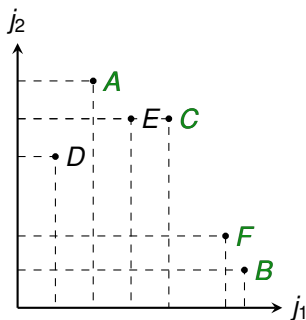
Pareto front



- nodes A , C , F , and B : Pareto front
 - there is no node dominating these nodes
 - these nodes do not dominate each other
- Pareto front: the set of non-dominated nodes

Multi-objective optimization methods

Pareto front



- nodes A, C, F, and B: Pareto front
 - there is no node dominating these nodes
 - these nodes do not dominate each other
- Pareto front: the set of non-dominated nodes

Multi-objective optimization methods

Estimation of ℓ IED regions

- Nodes $\in J$ -dimensional search space
- maximize $\{L^{j=1}[n], L^{j=2}[n], \dots, L^{j=J}[n]\}$
- Pareto front or estimated ℓ IED regions:
 - Pareto optimization algorithm (classic)
 - Neighbor-Pareto optimization algorithm (new)

Outline

1 Directed differential connectivity graph (dDCG)

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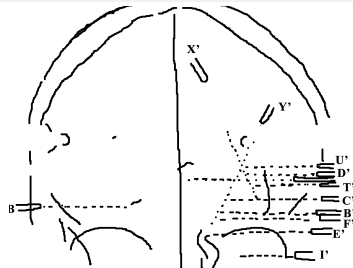
3 Conclusion and Perspectives

Parameters of the patients' iEEG

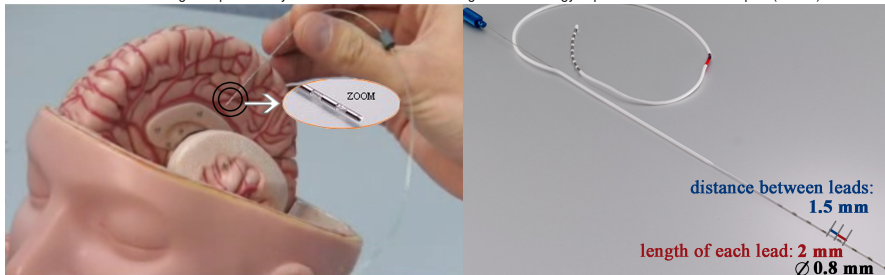
Parameters of the five patients' iEEG

	min	max	mean
iEEG bipolar channels	104	111	106
possible number of connections	4950	6105	5551
length of data (minutes)	42	90	55.44 $\approx 2 \times 10^6$ samples
number of IED time intervals	160	614	304
number of non-IED time intervals	143	200	174

Implantation scheme of iEEG electrodes for patient 3



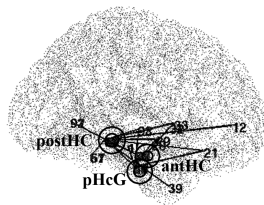
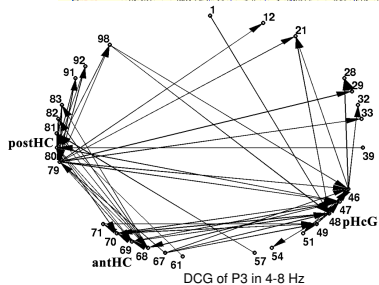
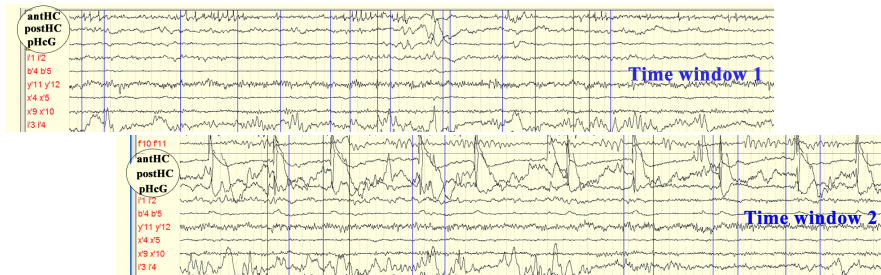
The iEEG recordings are provided by Prof. P. Kahane and his colleagues in Neurology department of Grenoble hospital (CHUG).



<http://www.diximedical.net>

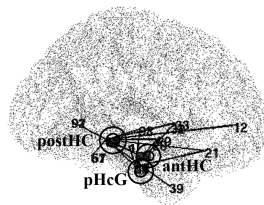
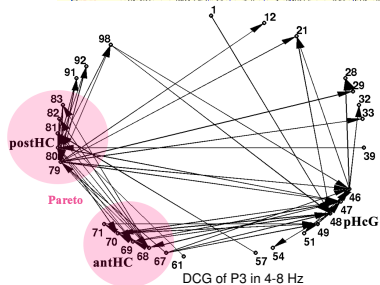
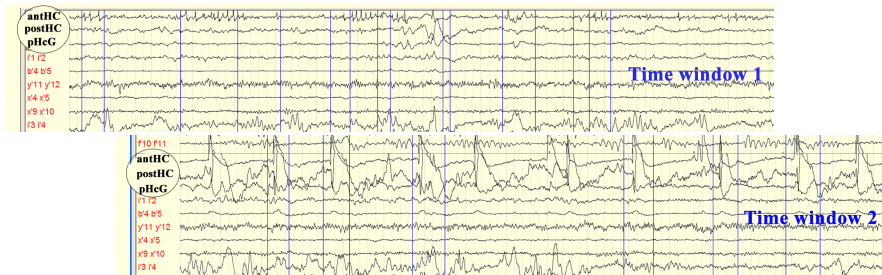
dDCG

iEEG recordings of patient 3 (P3) for two time windows



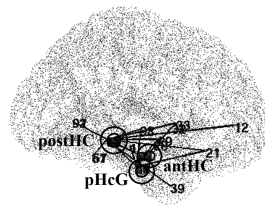
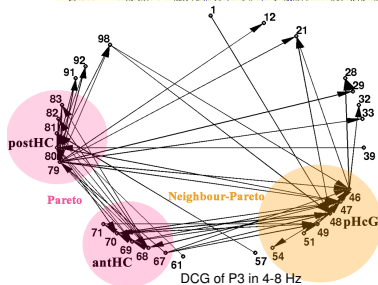
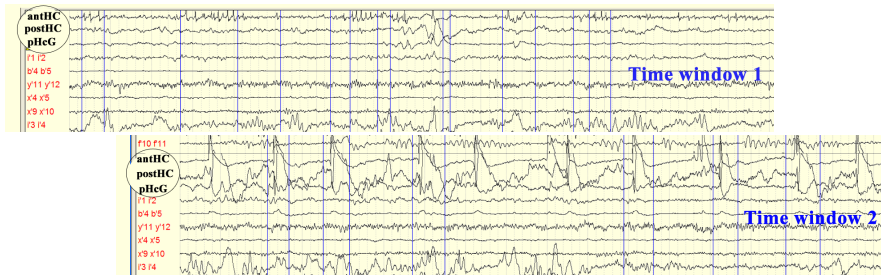
dDCG

iEEG recordings of patient 3 (P3) for two time windows



dDCG

iEEG recordings of patient 3 (P3) for two time windows



DCG overlaid on anatomical mesh

Outline

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3 Conclusion and Perspectives

Qualitative comparison between *L* and classic measures

P1	antHC	postHC	amyg	pHcG	mTP	
global efficiency			x	x	x	
local efficiency*	x	x	x	x	x	
total degree			x	x		
local information using Pareto opt	x		x	x		
visually inspected SOZ	x	x	x	x	x	
P2	antHC	postHC	amyg	pHcG		
global efficiency	x					
local efficiency	x	x		x		
total degree	x			x		
local information using Pareto opt	x					
visually inspected SOZ	x	x	x	x		
P3	antHC	postHC	pHcG			
global efficiency	x	x	x			
local efficiency	x	x	x			
total degree	x	x				
local information using Pareto opt	x	x				
visually inspected SOZ	x	x	x			
P4	antHC	postHC	amyg	entCx	mTP	at
global efficiency	x	x	x	x		x
local efficiency	x	x		x		
total degree		x	x	x		
local information using Pareto opt	x	x	x	x		
visually inspected SOZ	x	x	x	x		x
P5	midInsG					
global efficiency	x					
local efficiency	NA					
total degree	x					
local information using Pareto opt	x					
visually inspected SOZ	x					

amyg: amygdala; ant/post/m: anterior/posterior/mesial; CG: cingulate gyrus; entCx: entorhinal cortex; HC: hippocampus; Ins: insula; midInsG: middle short gyrus of insula; pHcG: parahippocampal gyrus; T: temporal; TP: temporal pole; NA: not applicable; opt: optimization.

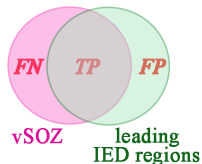
Quantitative comparison between L_I and classic measures

Definition (Assumption: vSOZ are ground truth)

- TP = No. common regions between ℓ IED regions and vSOZ
- FN = No. uncommon regions
- FP = No. ℓ IED regions not included in vSOZ

$$\text{Precision} = \frac{TP}{TP+FP}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$



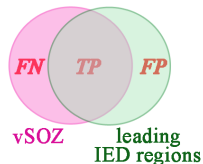
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Interpretation

- $\text{Precision} = 1$ if $FP = 0$; $FP \neq 0$: extra regions are provided.
- $\text{Sensitivity} = 1$ if $FN = 0$; $FN \neq 0$: some regions are missed.
- trade off between FP and FN .

Quantitative comparison between LI and classic measures

Definition (Assumption: vSOZ are ground truth)

- TP = No. common regions between $lIED$ regions and vSOZ
- FN = No. uncommon regions
- FP = No. $lIED$ regions not included in vSOZ

$$Precision = \frac{TP}{TP+FP}$$

$$Sensitivity = \frac{TP}{TP+FN}$$

Interpretation

- $Precision = 1$ if $FP = 0$; $FP \neq 0$: extra regions are provided.
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Remarks

- LI : more precise and informative
- Neighbor-Pareto optimization: relevance of $lIED$ regions

P3	antHC	postHC	pHcG
global efficiency	x	x	x
local efficiency	x	x	x
total degree	x	x	
local information Pareto	x	x	
visually inspected SOZ	x	x	x

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P3	antHC	postHC	pHcG
global efficiency	x	x	x
local efficiency	x	x	x
total degree	x	x	
local information N-Pareto	x	x	x
visually inspected SOZ	x	x	x

Comparison between proposed method and other classic methods

P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	x	x	x	x	x	
removed region	x	x	x	x	x	x
electrically stimulated SOZ		x				
<i>ℓ</i> IED using <i>LI</i> and Pareto opt	x		x	x		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	x	x	x	x		
removed region	x	x	x	x	x	
electrically stimulated SOZ	x	x				
<i>ℓ</i> IED using <i>LI</i> and Pareto opt	x					
P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	x	x	x			
removed region	x	x	x	x		
electrically stimulated SOZ	x					
<i>ℓ</i> IED using <i>LI</i> and Pareto opt	x	x				
P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	x	x	x	x	x	
removed region	x	x	x	x	x	
electrically stimulated SOZ	-					
<i>ℓ</i> IED using <i>LI</i> and Pareto opt	x	x	x	x		
P5	midInsG					
visually inspected SOZ	x					
removed region	x					
electrically stimulated SOZ	NA					
<i>ℓ</i> IED using <i>LI</i> and Pareto opt	x					

amyg: amygdala; ant/post/m/sup: anterior/posterior/mesial/superior; CG: cingulate gyrus; entCx: entorhinal cortex; G: gyrus; HC: hippocampus; Ins: insula; midInsG: middle short gyrus of insula; pHcG: parahippocampal gyrus; T: temporal; TP: temporal pole; NA: not applicable.

Methods

- **vSOZ** and **removed regions**: by epileptologists
- **eSOZ**: by [David et al., 2008]
- ***ℓ*IED using *LI* and Pareto opt**: our method

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P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	x	x	x	x	x	
removed region	x	x	x	x	x	x
electrically stimulated SOZ		x				
ℓ IED using <i>LI</i> and Pareto opt	x		x	x		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	x	x	x	x		
removed region	x	x	x	x	x	
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P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	x	x	x			
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electrically stimulated SOZ	x					
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P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	x	x	x	x	x	
removed region	x	x	x	x	x	
electrically stimulated SOZ	-					
ℓ IED using <i>LI</i> and Pareto opt	x	x	x	x		
P5	midInsG					
visually inspected SOZ	x					
removed region	x					
electrically stimulated SOZ	NA					
ℓ IED using <i>LI</i> and Pareto opt	x					

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P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	×
electrically stimulated SOZ		×				
ℓIED using <i>LI</i> and Pareto opt	×		×	×		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	×	×	×	×		
removed region	×	×	×	×	×	
electrically stimulated SOZ	×	×				
ℓIED using <i>LI</i> and Pareto opt	×					
P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	×	×	×			
removed region	×	×	×	×		
electrically stimulated SOZ	×					
ℓIED using <i>LI</i> and Pareto opt	×	×				
P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	
electrically stimulated SOZ	-					
ℓIED using <i>LI</i> and Pareto opt	×	×	×	×		
P5	midInsG					
visually inspected SOZ	×					
removed region	×					
electrically stimulated SOZ	NA					
ℓIED using <i>LI</i> and Pareto opt	×					

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P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	×
electrically stimulated SOZ		×				
ℓIED using LI and Pareto opt	×		×	×		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	×	×	×	×		
removed region	×	×	×	×	×	
electrically stimulated SOZ	×	×				
ℓIED using LI and Pareto opt	×					
P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	×	×	×			
removed region	×	×	×	×		
electrically stimulated SOZ	×					
ℓIED using LI and Pareto opt	×	×				
P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	
electrically stimulated SOZ	-					
ℓIED using LI and Pareto opt	×	×	×	×		
P5	midInsG					
visually inspected SOZ	×					
removed region	×					
electrically stimulated SOZ	NA					
ℓIED using LI and Pareto opt	×					

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P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	×
electrically stimulated SOZ		×				
ℓIED using LI and Pareto opt	×		×	×		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	×	×	×	×		
removed region	×	×	×	×	×	
electrically stimulated SOZ	×	×				
ℓIED using LI and Pareto opt	×					
P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	×	×	×			
removed region	×	×	×	×		
electrically stimulated SOZ	×					
ℓIED using LI and Pareto opt	×	×				
P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	
electrically stimulated SOZ	-					
ℓIED using LI and Pareto opt	×	×	×	×		
P5	midInsG					
visually inspected SOZ	×					
removed region	×					
electrically stimulated SOZ	NA					
ℓIED using LI and Pareto opt	×					

amyg: amygdala; ant/post/m/sup: anterior/posterior/mesial/superior; CG: cingulate gyrus; entCx: entorhinal cortex; G: gyrus; HC: hippocampus; Ins: insula; midInsG: middle short gyrus of insula; pHcG: parahippocampal gyrus; T: temporal; TP: temporal pole; NA: not applicable.

Comparison between proposed method and other classic methods

Methods

- **vSOZ** and **removed regions**: by epileptologists
- **eSOZ**: by [David et al., 2008]
- **ℓIED using LI and Pareto opt**: our method

P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	×
electrically stimulated SOZ		×				
ℓIED using LI and Pareto opt	×		×	×		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	×	×	×	×		
removed region	×	×	×	×	×	
electrically stimulated SOZ	×	×				
ℓIED using LI and Pareto opt	×					
P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	×	×	×			
removed region	×	×	×	×		
electrically stimulated SOZ	×					
ℓIED using LI and Pareto opt	×	×				
P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	×	×	×	×	×	
removed region	×	×	×	×	×	
electrically stimulated SOZ	-					
ℓIED using LI and Pareto opt	×	×	×	×		
P5	midInsG					
visually inspected SOZ	×					
removed region	×					
electrically stimulated SOZ	NA					
ℓIED using LI and Pareto opt	×					

amyg: amygdala; ant/post/m/sup: anterior/posterior/mesial/superior; CG: cingulate gyrus; entCx: entorhinal cortex; G: gyrus; HC: hippocampus; Ins: insula; midInsG: middle short gyrus of insula; pHcG: parahippocampal gyrus; T: temporal; TP: temporal pole; NA: not applicable.

Remarks

- **ℓIED**: congruent with vSOZ, removed regions, and eSOZ
- **ℓIED**: reliable results for presurgery evaluations

Comparison between proposed method and other classic methods

Methods

P1	antHC	postHC	amyg	pHcG	mTP	antsupTG
visually inspected SOZ	x	x	x	x	x	
removed region	x	x	x	x	x	x
electrically stimulated SOZ		x				
<i>l</i> IED using <i>LI</i> and Pareto opt	x		x	x		
P2	antHC	postHC	amyg	pHcG	TP	
visually inspected SOZ	x	x	x	x		
removed region	x	x	x	x	x	
electrically stimulated SOZ	x	x				
<i>l</i> IED using <i>LI</i> and Pareto opt	x					
P3	antHC	postHC	pHcG	TP		
visually inspected SOZ	x	x	x			
removed region	x	x	x	x		
electrically stimulated SOZ	x					
<i>l</i> IED using <i>LI</i> and Pareto opt	x	x				
P4	antHC	postHC	amyg	entCx	mTP	antCG
visually inspected SOZ	x	x	x	x	x	
removed region	x	x	x	x	x	
electrically stimulated SOZ	-					
<i>l</i> IED using <i>LI</i> and Pareto opt	x	x	x	x		
P5	midInsG					
visually inspected SOZ	x					
removed region	x					
electrically stimulated SOZ	NA					
<i>l</i> IED using <i>LI</i> and Pareto opt	x					

amyg: amygdala; ant/post/m/sup: anterior/posterior/mesial/superior; CG: cingulate gyrus; entCx: entorhinal cortex; G: gyrus; HC: hippocampus; Ins: insula; midInsG: middle short gyrus of insula; pHcG: parahippocampal gyrus; T: temporal; TP: temporal pole; NA: not applicable.

- **vSOZ** and **removed regions**: by epileptologists

- **eSOZ**: by [David et al., 2008]

- ***l*IED using *LI* and Pareto opt**: our method

Remarks

- ***l*IED**: congruent with vSOZ, removed regions, and eSOZ

- ***l*IED**: reliable results for presurgery evaluations

- ***l*IED**: without using seizures.

Outline

1 Directed differential connectivity graph (dDCG)

- Basic idea of DCG
- DCG calculation
- Characterization of dDCG
- Multiple graph analysis

2 Experimental results

- dDCG
- Leading IED regions

3 Conclusion and Perspectives

Conclusion

- **Methodological point of view**
 - Development of DCG: identify the reliable discriminated connections between two states [Amini et al., 2010b]
 - Local information [Amini et al., 2010a]
 - Integration of advanced/reliable methods
 - Pareto optimization [Deb, 1999]
 - Permutation [Pollard & van der Laan, 2003]
- **Application point of view**
 - ℓ IED regions (based on IEDs) congruent with vSOZ (based on seizures)

Perspective

- **Methodological point of view**
 - Automatic IED labelling
 - Estimating ℓ IED regions from scalp EEG (noninvasive)
 - General application of DCG
- **Application point of view**
 - Using larger number of patients for the relationship ℓ IED/SOZ.

List of Related Publications

Journals

- 1 L. Amini, C. Jutten, S. Achard, O. David, P. Kahane, L. Vercueil, L. Minotti, G. A. Hossein-Zadeh, and H. Soltanian-Zade, Comparison Of Five Directed Graph Measures For Identification Of Leading Interictal Epileptic Regions, *Physiological Measurements, Physiol. Meas.*, vol. 31, pp. 1529-1546, 2010.
- 2 L. Amini, C. Jutten, S. Achard, O. David, H. Soltanian-Zadeh, G. A. Hossein-Zadeh, P. Kahane, L. Minotti, and L. Vercueil, Directed Differential Connectivity Graph Of Interictal Epileptiform Discharges, *accepted in IEEE Trans. Biomed. Eng.*.

Conferences

- 1 L. Amini, R. Sameni, C. Jutten, G. A. Hossein-Zadeh, and H. Soltanian-Zadeh, MR Artifact Reduction in the Simultaneous Acquisition of EEG and fMRI of Epileptic Patients, *Proc. of 16th European Signal Processing Conference (EUSIPCO), Lausanne, Switzerland, August 25-29, 2008.*
- 2 L. Amini, S. Achard, C. Jutten, G.A. Hossein-Zadeh, and H. Soltanian-Zadeh, Connectivity Analysis of EEG Recordings for Epileptic Patients, *The 10th International Conference On Cognitive Neuroscience (ICON X), Bodrum, Turkey, September 1-5, 2008.*
- 3 L. Amini, S. Achard, C. Jutten, H. Soltanian-Zadeh, G. A. Hossein-Zadeh, O. David, and L. Vercueil, Sparse Differential Connectivity Graph of Scalp EEG for Epileptic Patients, *Proc. of the 17th European Symposium on Artificial Neural Networks (ESANN), Bruges, Belgium, April 22-24, 2009.*
- 4 L. Amini, C. Jutten, S. Achard, O. David, H. Soltanian-Zadeh, G. A. Hossein-Zadeh, P. Kahane, L. Minotti, and L. Vercueil, Directed Epileptic Network From Scalp And Intracranial EEG Of Epileptic Patients, *Proc. of the IEEE International Workshop On Machine Learning For Signal Processing (MLSP), Grenoble, France, September 2-4, 2009.*

Outline

4 Appendix

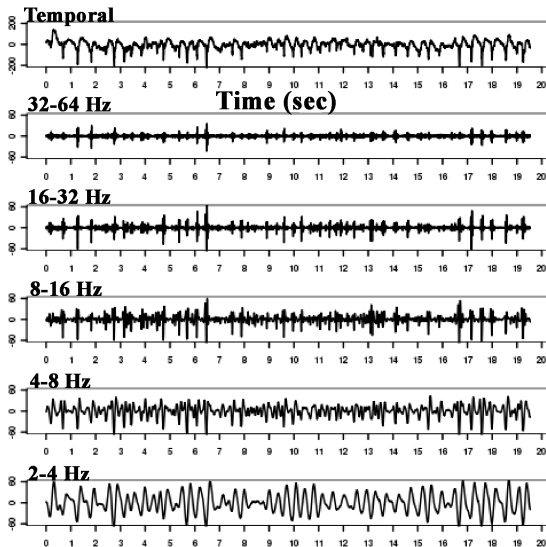
Graphs

- Graph is a set pair of nodes (associated with iEEG bipolar channels or bipolar electrode leads) and edges (or connections).
- Particular directed graph (digraph): oriented graphs.



Wavelet transform

Wavelet coefficients of a typical iEEG channel in different frequency bands



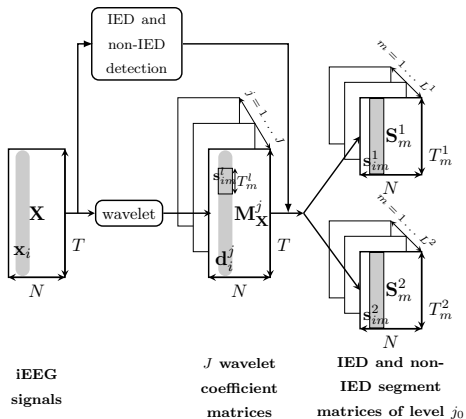
Wavelet transform

$$c_i^{j+1}[k] = h^j[-k] * c_i^j[k], \quad j = 0, \dots, J-1$$

$$d_i^{j+1}[k] = g^j[-k] * c_i^j[k], \quad j = 0, \dots, J-1$$

$$h^{j+1}[k] = \begin{cases} h^j[\frac{k}{2}], & k \text{ even} \\ 0, & k \text{ odd} \end{cases}$$

IED and non-IED segment matrices



Multiple testing

$$\begin{cases} H_0^n : \mu_n^1 = \mu_n^2 \\ H_1^n : \mu_n^1 \neq \mu_n^2 \end{cases}$$

$$t_n = \frac{\hat{\mu}_n^1 - \hat{\mu}_n^2}{\sqrt{\frac{(\hat{\sigma}_n^1)^2}{L^1} + \frac{(\hat{\sigma}_n^2)^2}{L^2}}}$$

$$p[n] = \frac{\text{card}(\{n_p \mid |t_n^{n_p}| > |t_n|\})}{N_p}$$

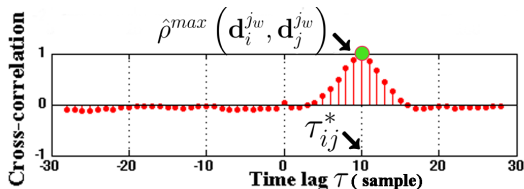
$$\begin{cases} a[i] = \max(a[i-1], 1 - (1 - p[i])^{N_c - i + 1}) & 2 \leq i \leq N_c \\ a[1] = 1 - (1 - p[1])^{N_c} & i = 1 \end{cases}$$

Time delay estimation

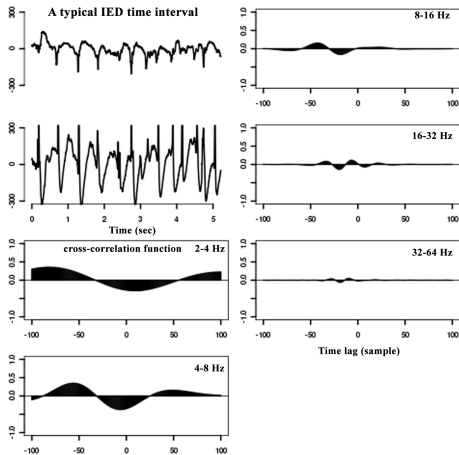
- nodes i and $j \in \text{DCG}$
- \mathbf{d}_i^{jw} and \mathbf{d}_j^{jw} : wavelet coefficients of signal pair (i, j) in frequency band related to j_w for the *whole* selected time for processing.

$$\hat{\rho}(\mathbf{d}_i^{jw}, \mathbf{d}_j^{jw}, \tau) = \frac{\widehat{\text{cov}}\{d_i^{jw}[k], d_j^{jw}[k - \tau]\}}{\sqrt{\widehat{\text{var}}(d_i^{jw}[k])\widehat{\text{var}}(d_j^{jw}[k - \tau])}}$$

$$\tau_{ij}^{*jw} = \arg \max_{\tau} \left| \hat{\rho}(\mathbf{d}_i^{jw}, \mathbf{d}_j^{jw}, \tau) \right|$$



Reliability of time delay estimation



Reliability of time delay estimation

● Jackknife method:

- For $N_w = 100$ windows of length $W = 20$ minutes, the time delay τ_{ij}^{*jw} is estimated.
- W is large enough to include enough number of IEDs.
- $\bar{\tau}_{ij}^{*jw} = \arg \max_u (\hat{p}_{\tau_{ij}^{*jw}}(u))$
- $\#(\bar{\tau}_{ij}^{*jw} \times \tau_{ij}^{*jw} > 0) / \#(\text{edges})$ is in the range [78 95]% for different frequency bands.

● Remarks

- τ_{ij}^{*jw} can provide reliable estimation of the most probable time lag if:
 - significant couplings
 - length of signal pairs are long enough for a proper estimation of CCF
 - τ^{max} is chosen properly.

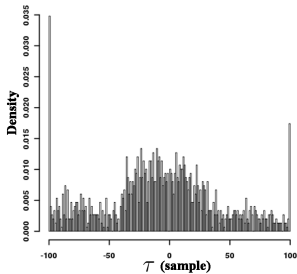
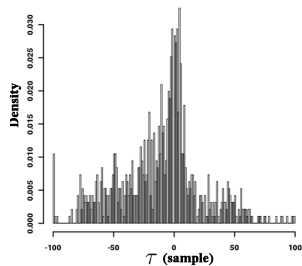
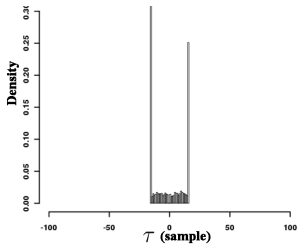
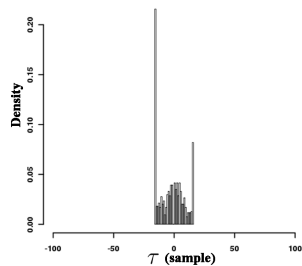
Reliability of time delay estimation

Jackknife method:

Frequency (Hz)	2-4	4-8	8-16	16-32	32-64
$\#(\bar{\tau}_{ij}^{*jw} \times \tau_{ij}^{*jw} > 0) / \#(\text{edges})$	94/110	74/82	41/43	18/23	8/9
percentage (%)	85	90	95	78	88

Choice of τ^{max} in dDCG

- increase of $\tau^{max} \Rightarrow$ increases the bias & variance (length of overlapped signals) of time delay estimation.
- decreasing τ^{max} less than the true time delay \Rightarrow missing the time delay
- τ^{max} : the smallest value of the maximum physiological constraint.
- We need to know the range of physiological constraints (IED propagation delay $< [50\ 200]$ msec).

(a) 2-4 Hz, $\tau^{max} = 100$ samples(b) 4-8 Hz, $\tau^{max} = 100$ samples(c) 2-4 Hz, $\tau^{max} = 16$ samples(d) 4-8 Hz, $\tau^{max} = 16$ samples

Pretest for testing the significance of each edge of DCG

- The effect of adding a pretest
- Connections whose couplings are significantly greater than the threshold for both IED and non-IED states are entered the multiple testing.

$$\begin{cases} H_0^n : & \mu_n^I \leq 0.3 \\ H_1^n : & \mu_n^I > 0.3 \end{cases}$$

Pretest for testing the significance of each edge of DCG

Comparison

- Similarity percentage: the normalized sum of common number of significant or non-significant t-values over number of possible connections.

Remarks

- most of the connections of the DCG have significantly large couplings in both IED and non-IED time intervals
- DCG is designed to detect the connections whose couplings change significantly between IED and non-IED time intervals

Similarity percentage	2-4	4-8	8-16	16-32	32-64
P1	96.83	92.53	94.45	97.65	99.27
P2	100	99.95	99.54	99.69	99.87

Different frequency bands

Why wavelet transform?

- Wavelet transforms are well adapted for the analysis of non-stationary EEG signals [Clark et al., 1995, Senhadji & Wendling, 2002, Adeli et al., 2003, Yamaguchi, 2003, Indiradevi et al., 2008, Conlon et al., 2009].
- Provide automatic frequency selection.
- Narrower bands for lower frequencies.
- Daubechies mother wavelets are a proper choice for filtering IED signals [Adeli et al., 2003].
- We calculated DCGs for different frequency bands using wavelet transform.

DCG construction

- **Problem statement:**

- Classic graph inference methods are threshold dependent.
- Variance of MMCC estimation:
 - estimation error
 - non-stationarity of the couplings in time
- The reliability of inferred graphs

- **Solution:**

- Testing if the couplings during IED and non-IED change
- Using permutation based multiple testing

$$\begin{cases} H_0 : & \text{no significant change} \\ H_1 : & \text{significant change} \end{cases}$$

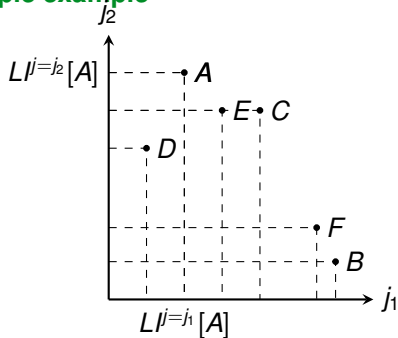
- Uncertainty of the edges of graph

Problem statement

- Global efficiency (GE), local efficiency (LE), and node degree
- Total degree = outgoing degree - ingoing degree
 - the importance of each edge is not considered.
- LE
 - a node whose LE is high is not necessarily a source
 - neither the amount of information of each edge
 - nor the incoming paths
- GE
 - GE is more global than LE.
 - neither the amount of information of each edge
 - nor the incoming paths
 - GE is preferred between other classic measures

Multi-objective optimization methods

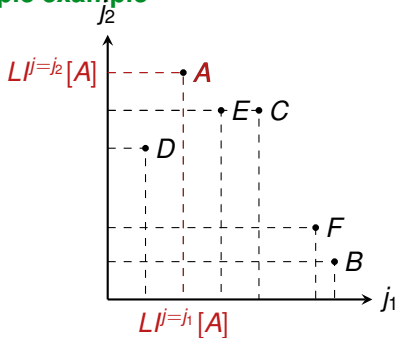
Model building: simple example



- nodes or points in 2 dimensions: 2 frequency bands j_1 and j_2

Multi-objective optimization methods

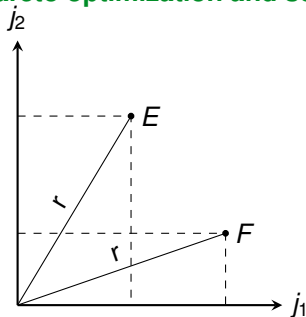
Model building: simple example



- nodes or points in 2 dimensions: 2 frequency bands j_1 and j_2

Multi-objective optimization methods

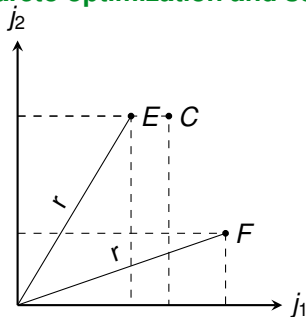
Comparison between Pareto optimization and scalarizing multi-objective functions



- if there exist nodes E and F with equal norms:
 - Pareto front: nodes E , and F
 - Scalarizing: nodes E , and F

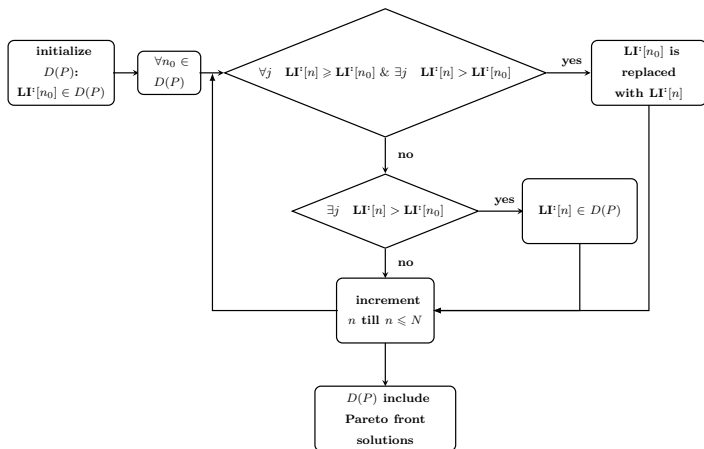
Multi-objective optimization methods

Comparison between Pareto optimization and scalarizing multi-objective functions

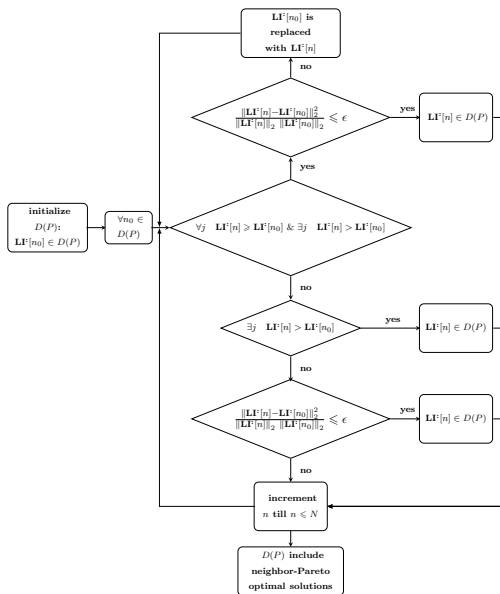


- if there exist nodes E and F with equal norms:
 - Pareto front: nodes E , and F
 - Scalarizing: nodes E , and F
- if node C exists:
 - Pareto front: nodes C , and F
 - Scalarizing: node C

Pareto optimization algorithm

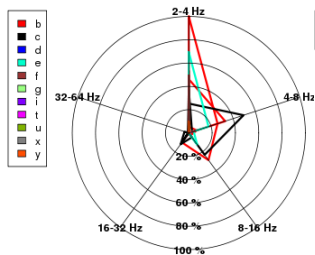


Neighbour-Pareto optimization algorithm

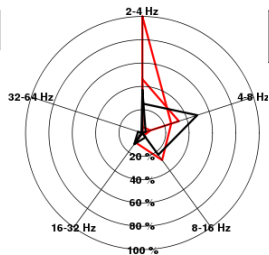


Multi-objective optimization methods

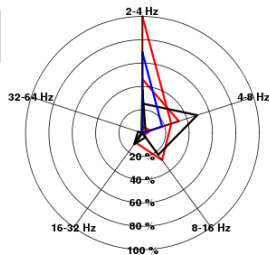
Pareto and neighbor-Pareto optimization solutions



$LI^2[n]$ for bipolar iEEG channels



Pareto solutions



neighbor-Pareto solutions

Processing time

Shared 3 GHz, 4 core Xeon 64 bits processor

processing time	min	max	mean	sum
Coupling computation for all of IED/non-IED time intervals and signal pairs (hours)	2.93	3.4	3.15	15.76
Multiple testing (hours)	4.57	7.6	6.1	30.33
Direction estimation + <i>LI</i> computation + Pareto (minutes)	1.97	15.23	5.9	29.53
sum (hours)				46.58

Patients

patient	focal epilepsy
P1	LT
P2	LT
P3	LT
P4	RT
P5	RmidInsG

Parameters

	P1	P2	P3	P4	P5	mean
N	104	105	111	109	100	106
T (minutes)	61	56	42	90	66	55.44
N_c	5356	5460	6105	5886	4950	5551
L^1	298	614	223	160	223	304
L^2	143	200	195	183	148	174







Parameters

Method parameter	
Wavelet filter	'la8'
Number of wavelet levels	5
False positive error (α)	0.05
α_{fW} (familywise α)	0.05
τ^{max} for DCG (samples)	27
τ^{max} for dDCG (samples)	100
f_s (Hz)	512
N_p for DCG	10^6
N_p for SP	10^4
N_w	100
N_b	10^4
W for reliability test of τ^* (minutes)	20
W for reliability test of LI and SP (minutes)	33






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