Unsupervised clustering under spatial constraints using multiple equivalence tests

An application to DCE imaging

Fuchen Liu - Université Paris Descartes & Intrasense
Yves Rozenholc - Université Paris Descartes & INRIA Select
Charles-André Cuénod - Université Paris Descartes & HEGP

Workshop
« Traitement, Analyse, Indexation en Imagerie du Vivant »
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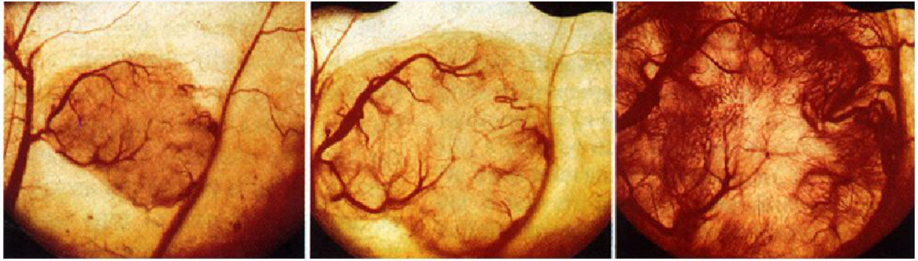
Micro-vascularization

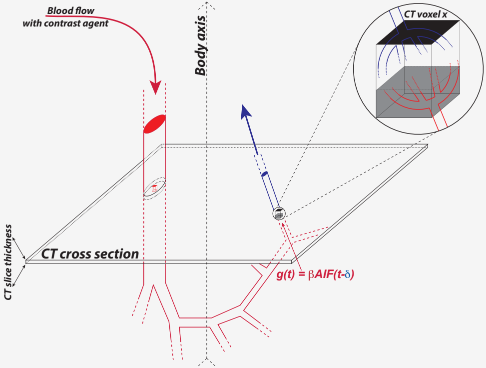


Tumors may have pathologic angiogenesis leading to abnormal vascularization.

Perfusion imaging gives access to functional modification of micro-vascularization.

Include DCE-CT, DCE-MRI, or DCE-US.

Perfusion imaging
Experimental design



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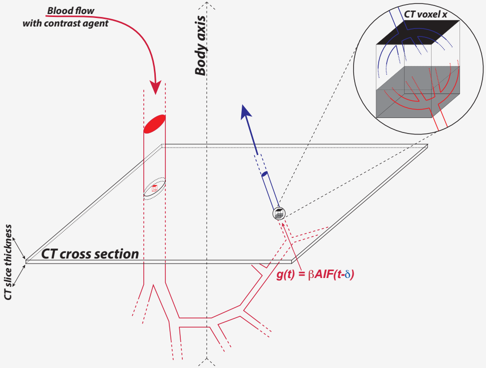

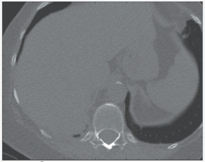

t = 0

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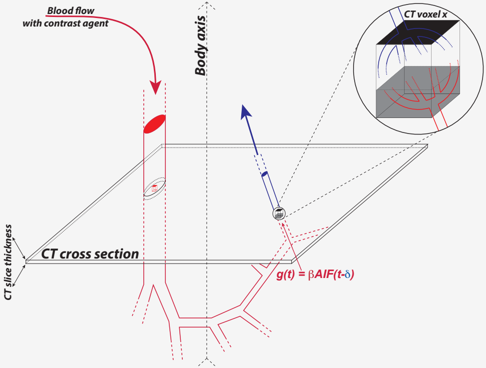

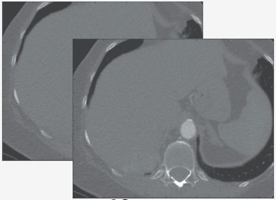

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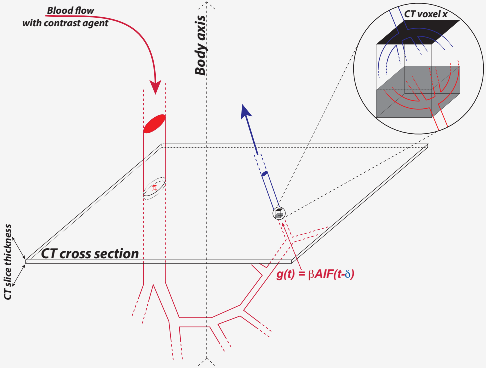

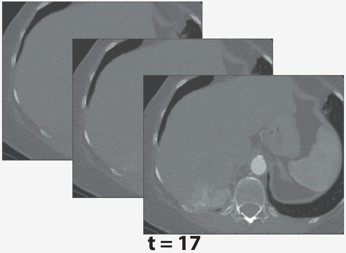

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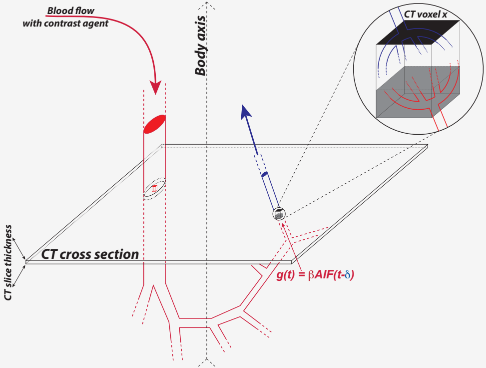

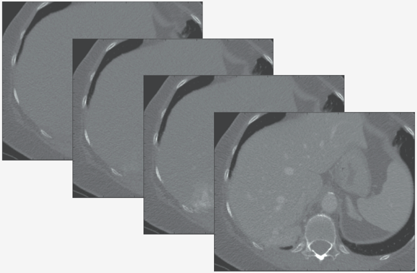

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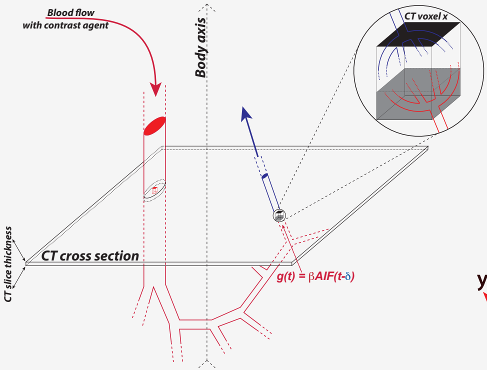

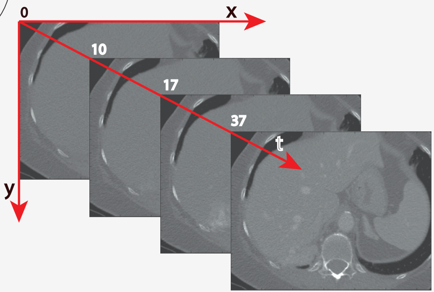

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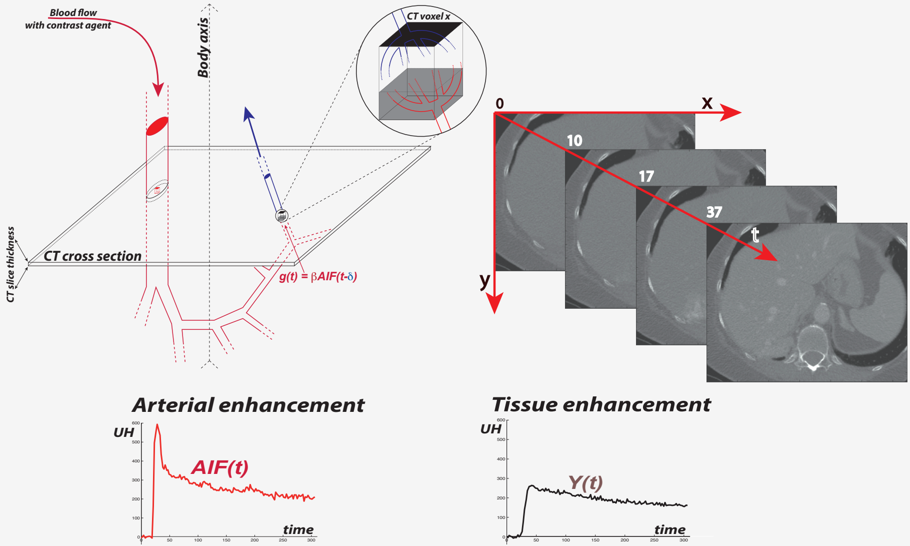

Perfusion analysis

Quantitative analysis uses either

- descriptors from direct evaluation on the dynamic curves;
- compartmental models / system of PDE's;
- blood flow model / Volterra equation of the first type or Laplace deconvolution.

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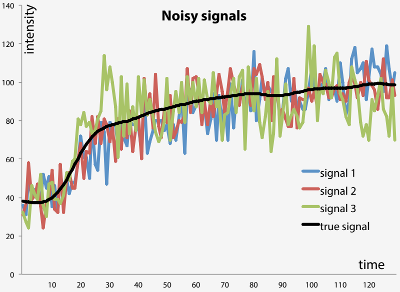
However

all methods suffer from
LOW Signal to Noise Ratio
and
movements

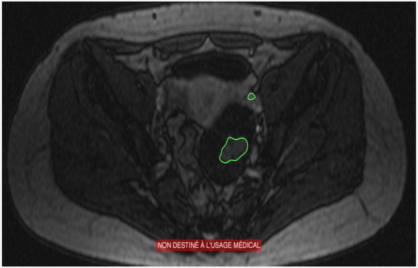


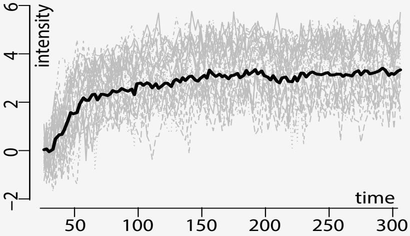
LOW Signal to Noise Ratio is due to instrumental noise of imaging devices:

- X-radiation control in DCE-CT;
- trade-off between spatial and time resolution in DCE-MRI.

Region Of Interest (ROI)

Averaging signals by building ROIs of multiple voxels improves Signal to Noise Ratio





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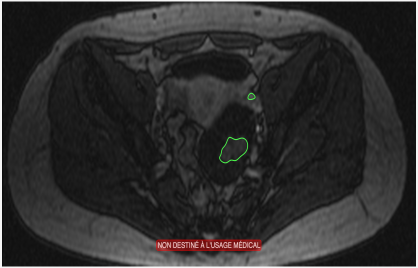
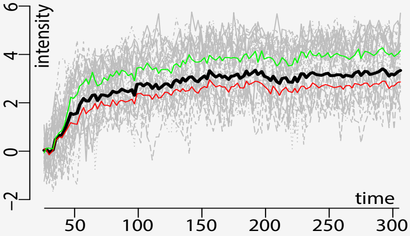




However may suffer from bad homogeneity

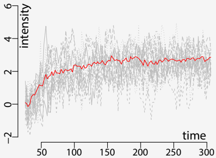
due to mixing different tissues / signals because of :

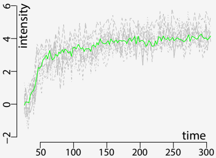
- hard visual perception when drawing manual ROIs ;
- bad comparisons when building automatic ROIs:
  - BAD representation (PCA, basis decomposition, etc) or modelization;
  - BAD choice of distance.

Medical objective

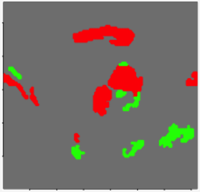
Improve Signal to Noise Ratio by building automatic ROIs

- **controlling temporal homogeneity without prior**





- **controlling spatial homogeneity** $\begin{cases} \textbf{locally} \\ \textbf{at large distance.} \end{cases}$



GOAL: Realize a spatial clusterization which protects temporal structures taking into account that images show neighborhood properties: smoothness, piecewise constant, etc.

Statistical context and statistical objective

Statistical context

We observe a random vector of $\mathbb{R}^n$, $I^x = i^x + \varepsilon^x$ at each location $x \in \mathcal{X}$. Assuming

- ε^x i.i.d. and $\mathbb{E}(\varepsilon^x) = 0$;
- $\mathcal{X} = C_1 \cup \ldots \cup C_K$;
- if $x \in C_k$ for $k = 1, \ldots, K$, then $\mathbb{E}(I^x) := i^x = i_k$;
- if $k \neq \ell$, then $C_k \cap C_\ell = \varnothing$ and $i_k \neq i_\ell$.

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Examples:

- $\mathcal{X}$ is a spatial grid of pixels (image) and I^x is a grey-level intensity vector;
- $\mathcal{X}$ is a geographic grid of area and I^x is utility (electricity, water) consumption;
- $\mathcal{X}$ is internet graph and I^x is traffic intensity on node.

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Objective

Realize a unsupervised classification to recover the partition $C_1, \ldots, C_K$ such that

$$\boxed{x, y \in \mathcal{X} \text{ belong to the same cluster if and only if } i^x = i^y.}$$

State of the arts of unsupervised classification methods

Main categories:

- **Model-based methods**:
  - Mixture of Gaussians or more complex distributions.
- **Distance-based methods**:
  - K-means;
  - Hierarchical clustering.

Choice of the number K of clusters:

- **penalization techniques like GAP** (Tibshirani, Walther, Hastie, '01)

Actual limitations:

- **Difficulty to select the number K of clusters**:
  - Repeat the same method for different values of K: time consuming;
  - Need assumptions on the distribution inside a cluster (e.g. log-concave).
- **Choice of distance** (e.g. Euclidean distance, Correlation coefficient);
- **Choice of representation** (e.g. PCA, spectral embedding, basis decomposition);
- **Seeds in K-means;**
- **Generic methods which don't take into account spatial regularity.**

Unsupervised classification under spatial constraint: Motivations

Idea 1: Highlight equality

- Build a test such that "=" should be the research hypothesis that is $\mathcal{H}_1$.

Idea 2: Build a universal dissimilarity measure

- Dissimilarity measure derived from the "=" multi-comparison p-value.

Idea 3: Use local spatial homogeneity

- Use neighboring information through a greedy aggregation (low complexity) to take into account the regularity of $x \mapsto i^x$ over the grid $\mathcal{X}$.

Idea 4: Deal with global spatial homogeneity

- Ensure global structure recognition by changing the neighboring information (higher complexity but with less information).

Main tool: Equivalence testing

Notations

Given two subsets X and Y of $\mathcal{X}$, $X \cap Y = \varnothing$,

- Empirical mean over X (resp. Y) is denoted I^X (resp. I^Y);
- $D^{XY} := I^X - I^Y$;
- $d^{XY} := \mathbb{E}(D^{XY})$.

We want to compare i^x and i^y and we test $d^{xy} := i^x - i^y = \vec{0}$ or not.

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Traditional test:

$$\mathcal{H}_0 : d^{xy} = \vec{0} \qquad \text{v.s.} \qquad \mathcal{H}_1 : d^{xy} \neq \vec{0}$$

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Equivalence test: reverse the hypothesis

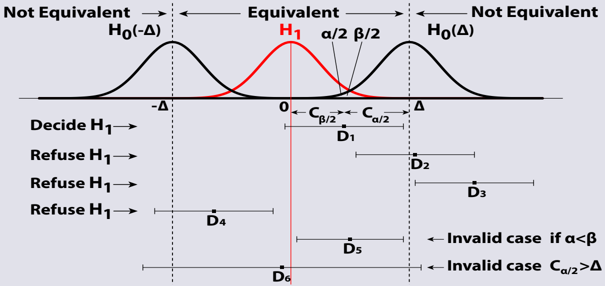
$$\mathcal{H}_0 : d^{xy} \neq \vec{0} \qquad \text{v.s.} \qquad \mathcal{H}_1 : d^{xy} = \vec{0}$$

Equivalence is the research hypothesis: **OUR PURPOSE**.

Equivalence test does not provide strict equivalence but an equivalence up to a given "margin" Δ.

An example of equivalence test: TOST

Gaussian example: Two One-Side Tests (Walker and Nowacki 2011), $n = 1$



Observations not having their confidence interval in $[-\Delta, +\Delta]$ are declared under $\mathcal{H}_1$

Multiple equivalence tests

Multiple equivalence test

Given V_J, $J = 1, \ldots, J_0$ strict linear subspaces of $\mathbb{R}^n$, we consider the **equivalence tests**

$$\mathcal{H}_0^J : d^{XY} \in V_J \setminus \{\vec{0}\} \qquad \text{v.s.} \qquad \mathcal{H}_1 : d^{XY} = \vec{0}.$$

We denote $p_1(X:Y), \ldots, p_{J_0}(X:Y)$ the corresponding **p-values**.

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Universal dissimilarity measure

The universal dissimilarity measure is $\max_J(p_J)$.

Neighboring clustering with universal dissimilarity measure $\max_J(p_J)$.

An image with 25 pixels

5x5 grid image

1	6	11	16	21
2	7	12	17	22
3	8	13	18	23
4	9	14	19	24
5	10	15	20	25

- grid $\mathcal{X} := \{1, \ldots, 25\}$.

Neighboring clustering with universal dissimilarity measure $\max_J(p_J)$.

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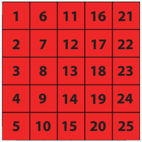
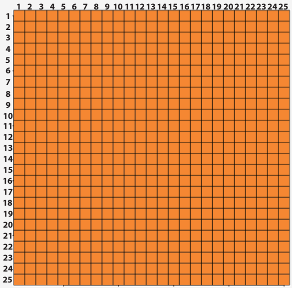


25x25 dissimilarity sparse matrix $\mathbf{P}^{(0)}$:



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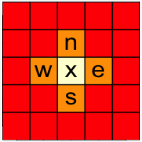
Initialization

5x5 grid image



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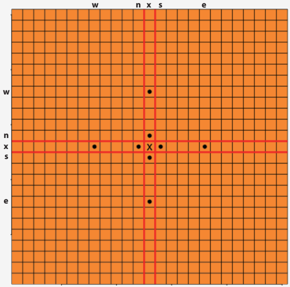

- $\mathcal{P}^{(0)} := \mathcal{X} = \{1, \ldots, 25\}$;
- $\mathcal{V}^{(0)}(x) := \{\{n\}, \{s\}, \{e\}, \{w\}\}$ for $x \in \mathcal{X}$;
- $\mathbf{P}^{(0)}(x, y) := p(x : y)$ for $y \in \mathcal{V}^{(0)}(x)$;
- $\dim(\mathbf{P}^{(0)}) = 25x25$ BUT less than $4x25$ non-zero elements.

Neighboring clustering with universal dissimilarity measure $\max_J(p_J)$.

Iteration t to $t+1$: example of $t = 0$

5x5 grid image

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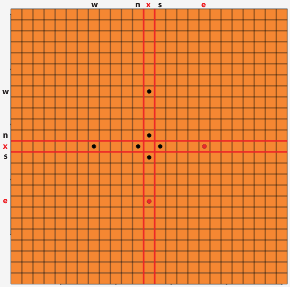

Optimization step

$$(X, Y) = \arg\min(\mathbf{P}^{(t)}) \qquad \text{for } t = 0: \quad X = \{x\} \text{ and } Y = \{e\}$$

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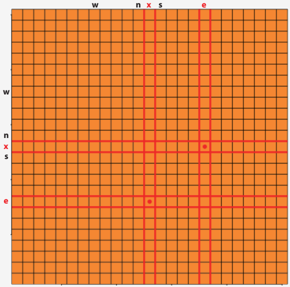

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Update phase 1 - downsizing by 2

Remove two columns and two lines of $\mathbf{P}^{(t)}$ corresponding to X and Y.

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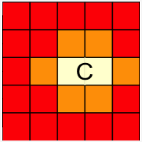
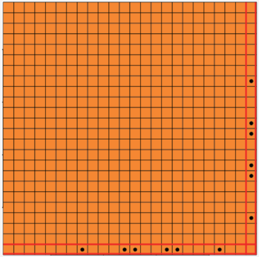


24x24 dissimilarity sparse matrix $\mathbf{P}^{(1)}$:



Update phase 2 - upsizing by 1: Update partition, neighbors and dissimilarity matrix

- $C := X \cup Y$; **new cluster**
- $\mathcal{P}^{(t+1)} := \mathcal{P}^{(t)} \setminus X \setminus Y \cup C$; **new partition**
- $\mathcal{V}^{(t+1)}(C) := \mathcal{V}^{(t)}(X) \cup \mathcal{V}^{(t)}(Y) \setminus X \setminus Y$; **new neighbors**
- $\boxed{\mathbf{P}^{(t+1)}(C, Z) = p(C : Z) \text{ for } Z \in \mathcal{V}^{(t+1)}(C)}$ **new dissimilarities**

From local to global clustering with universal dissimilarity measure

Local clustering — uses spatial regularity

- Starts from a partition made of all voxels as singletons;
- Builds, iteratively, successive partitions by aggregating two clusters at each step;
- Provides a hierarchical sequence of partitions with decreasing sizes from N to 1.

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Global clustering

When local clustering stops, process continues by changing the neighborhood structure:

- neighbors of neighbors

$$\mathcal{V}(X) := \bigcup_{Y \in \mathcal{V}(X)} \mathcal{V}(Y) \setminus \{X\}.$$

- all other clusters

$$\mathcal{V}(X) := \mathcal{P} \setminus \{X\}.$$

Automatic selection of number of clusters

With s clusters, we fix type I error to α and search for $c_\alpha(s)$ s.t.

$$\mathbb{P}[\min \mathbf{P}^{(N-s)} \leqslant c_\alpha(s)] = \mathbb{P}\left[\min_{1\leqslant k,\ell\leqslant s}\left\{p(C_k^{(N-s)} : C_\ell^{(N-s)})\right\} \leqslant c_\alpha(s)\right] = \alpha$$

Automatic selection of number of clusters

With s clusters, we fix type I error to α and search for $c_\alpha(s)$ s.t.

$$\mathbb{P}[\min \mathbf{P}^{(N-s)} \leqslant c_\alpha(s)] = \mathbb{P}\left[\min_{1\leqslant k,\ell\leqslant s}\left\{p(C_k^{(N-s)} : C_\ell^{(N-s)})\right\} \leqslant c_\alpha(s)\right] = \alpha$$

As $p(X : Y) := \max_{J=1,\dots,J_0} p_J(X : Y)$

Control function

If p-values p_J are uniform (abs. cont. tests), assuming independence of the p-values:

$$c_\alpha(s) = (1-(1-\alpha)^{2/s(s-1)})^{1/J_0}, \quad \text{for all } s = N, \dots, 1.$$

Automatic selection of number of clusters

With s clusters, we fix type I error to α and search for $c_\alpha(s)$ s.t.

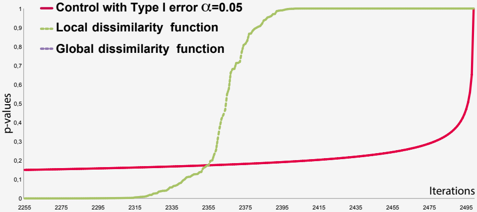
$$\mathbb{P}[\min \mathbf{P}^{(N-s)} \leqslant c_\alpha(s)] = \mathbb{P}\left[\min_{1\leqslant k,\ell\leqslant s}\left\{p(C_k^{(N-s)} : C_\ell^{(N-s)})\right\} \leqslant c_\alpha(s)\right] = \alpha$$

$$\text{As } p(X:Y) := \max_{J=1,\dots,J_0} p_J(X:Y)$$

Control function

If p-values p_J are uniform (abs. cont. tests), assuming independence of the p-values:

$$c_\alpha(s) = (1-(1-\alpha)^{2/s(s-1)})^{1/J_0}, \quad \text{for all } s = N, \dots, 1.$$



Note that $c_\alpha(.)$ does not depend on Δ. Only p-values depend on Δ.

Automatic selection of number of clusters

With s clusters, we fix type I error to α and search for $c_\alpha(s)$ s.t.

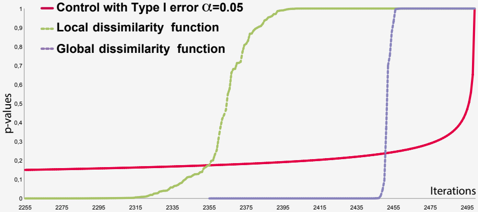
$$\mathbb{P}[\min \mathbf{P}^{(N-s)} \leqslant c_\alpha(s)] = \mathbb{P}\left[\min_{1\leqslant k,\ell\leqslant s}\left\{p(C_k^{(N-s)} : C_\ell^{(N-s)})\right\} \leqslant c_\alpha(s)\right] = \alpha$$

$$\text{As } p(X:Y) := \max_{J=1,\ldots,J_0} p_J(X:Y)$$

Control function

If p-values p_J are uniform (continuous tests), assuming independence of the p-values:

$$c_\alpha(s) = (1-(1-\alpha)^{2/s(s-1)})^{1/J_0}, \quad \text{for all } s = N, \ldots, 1.$$



Note that $c_\alpha(.)$ does not depend on Δ. Only p-values depend on Δ.

Statistical framework

Notations

Given two sets of voxels X and Y, $X \cap Y = \varnothing$

$$D^{XY} := \frac{\frac{1}{|X|}\sum_{x\in X} I^x - \frac{1}{|Y|}\sum_{y\in Y} I^y}{\rho(X:Y)} \sim \mathcal{N}(d^{XY}, Id_n),$$

where

$$d^{XY} := \frac{\frac{1}{|X|}\sum_{x\in X} i^x - \frac{1}{|Y|}\sum_{y\in Y} i^y}{\rho(X:Y)}, \qquad \rho^2(X:Y) := \frac{1}{|X|} + \frac{1}{|Y|}.$$

$\Pi_J(D^{XY})$ **denotes the projection of** D^{XY} **over the** 2^J**-bins piecewise constant vectors.**

Multi-resolution equivalence tests for dynamics comparison

$$\mathcal{H}_0^J : \|\Pi_J(D^{XY})\|^2 \neq 0 \quad \text{v.s.} \quad \mathcal{H}_1 : \|\Pi_J(D^{XY})\|^2 = 0.$$

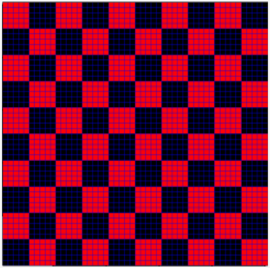
in this case :

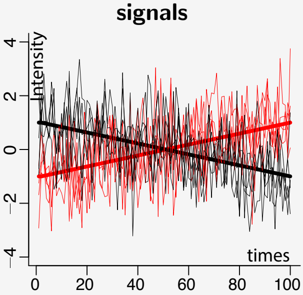
$$p_J(X:Y) := \mathbb{P}\left(\chi^2(2^J, \Delta^2 n) \leqslant \|\Pi_J(D^{XY})\|^2\right).$$

see Baraud et al (2003) for traditional test.

Simulation: chess board

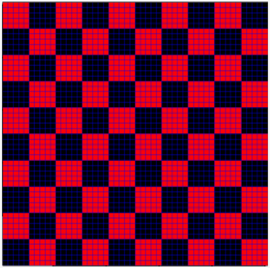
2 clusters in a 50×50 image



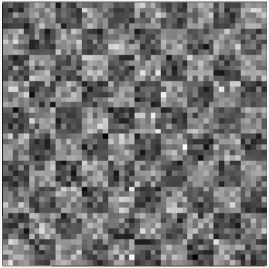


Simulation: chess board

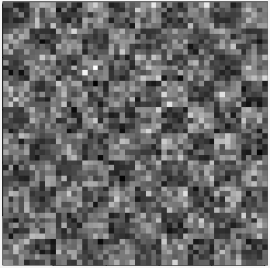
2 clusters in a 50×50 image



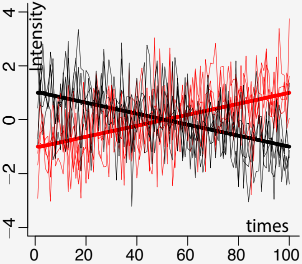
$t = 1$



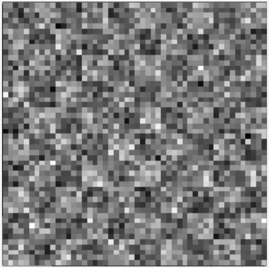
$t = 10$



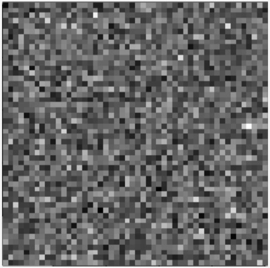
signals



$t = 20$



$t = 50$



Simulation: chess board

Data information

- Spatial resolution: 50×50 voxels;
- Temporal resolution: 100 times points;
- Noise level: $\sigma = 1$.

Parameter setting

- $\Delta = \mathbf{1}$; margin
- $\alpha = 0.05$. Type I error

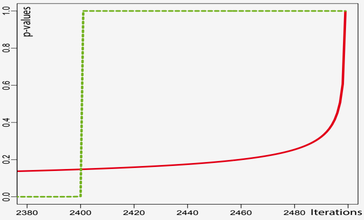
Simulation: chess board

Data information

- Spatial resolution: 50×50 voxels;
- Temporal resolution: 100 times points;
- Noise level: $\sigma = 1$.

Parameter setting

- $\Delta = \mathbf{1}$; margin
- $\alpha = 0.05$. Type I error



Type I error control

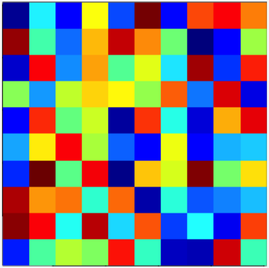
Simulation: chess board

Data information

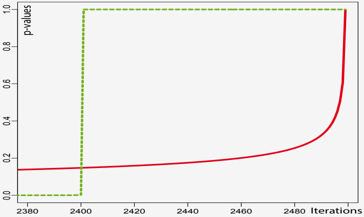
- Spatial resolution: 50×50 voxels;
- Temporal resolution: 100 times points;
- Noise level: $\sigma = 1$.

Parameter setting

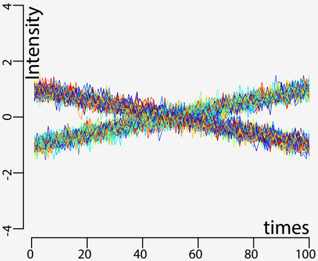
- $\Delta = \mathbf{1}$; margin
- $\alpha = 0.05$. Type I error



Local step: 100 clusters



Type I error control



Estimated curves

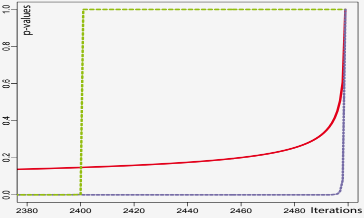
Simulation: chess board

Data information

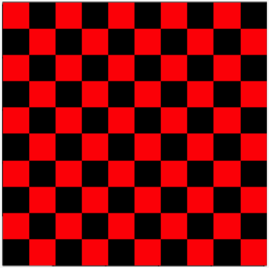
- Spatial resolution: 50×50 voxels;
- Temporal resolution: 100 times points;
- Noise level: $\sigma = 1$.

Parameter setting

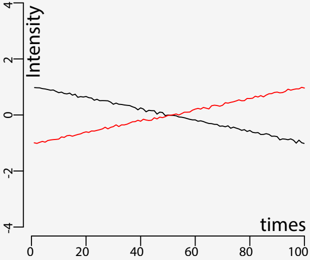
- $\Delta = \mathbf{1}$; margin
- $\alpha = 0.05$. Type I error



Type I error control



Global step: 2 clusters

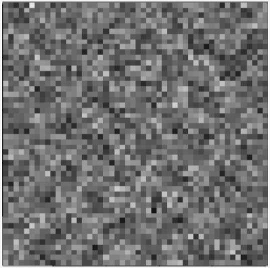


Estimated curves

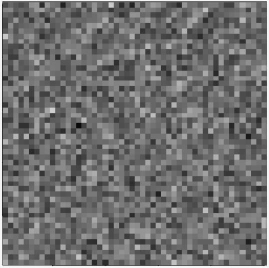
Simulation: chess board

A much harder case

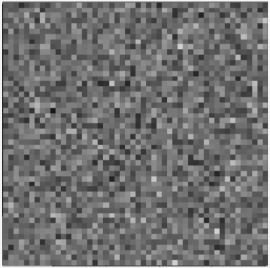
$t = 1$



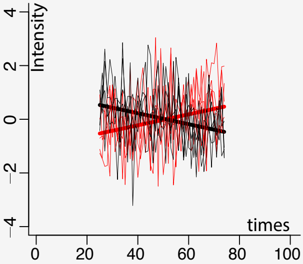
$t = 13$



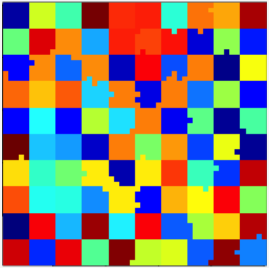
$t = 26$



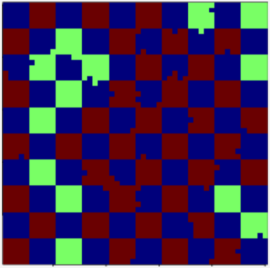
Shrinken signals



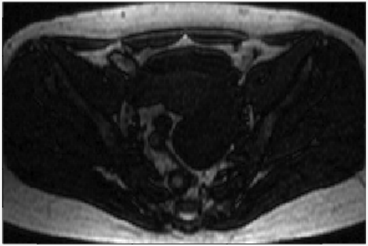
Local: 89 clusters



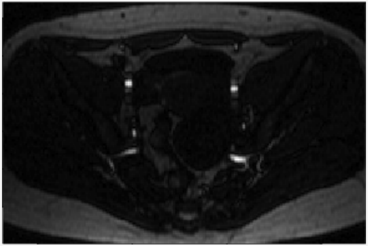
Global: 3 clusters



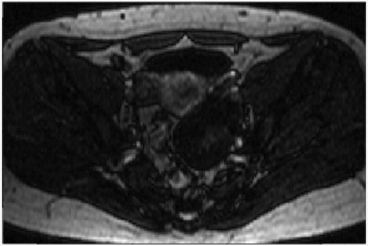
DCE-MRI: Ovarian malignant tumor (192×128 voxels, 119 times points)



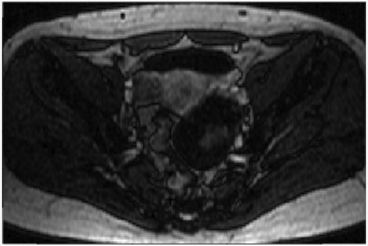
$t = 2$



$t = 14$

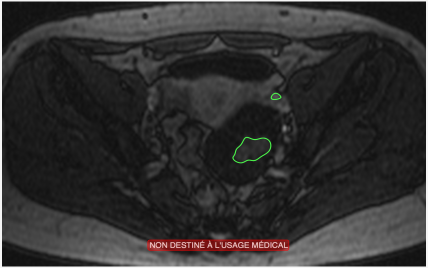


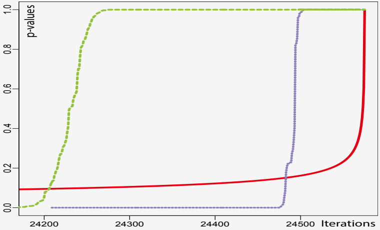
$t = 20$



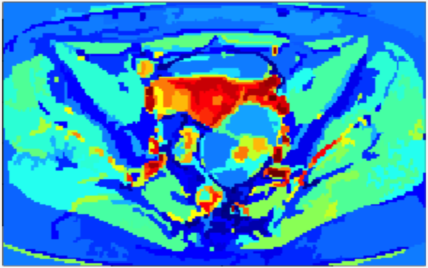
$t = 40$

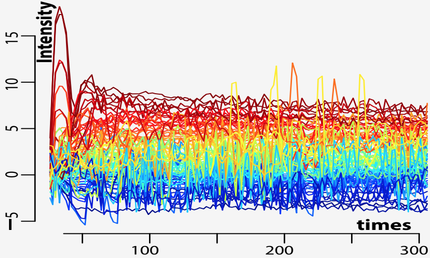
DCE-MRI: Ovarian malignant tumor ($\Delta = \mathbf{3}^2 \times 119$, $\alpha = 0.05$)





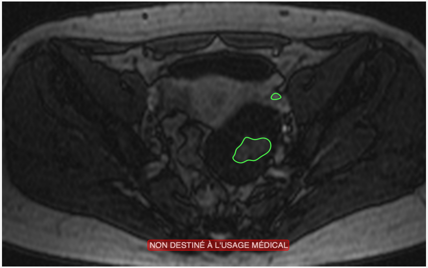
Type I error control

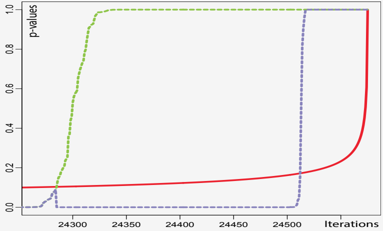




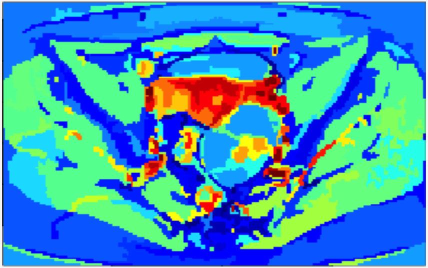
Global step: 94 clusters

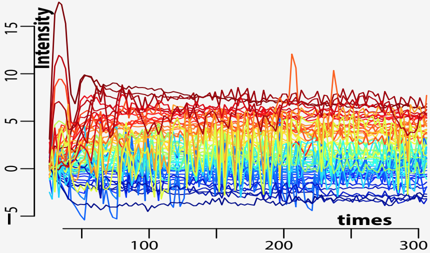
DCE-MRI: Ovarian malignant tumor ($\Delta = \mathbf{3.5}^2 \times 119$, $\alpha = 0.05$)





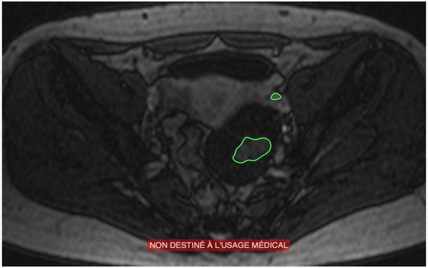
Type I error control

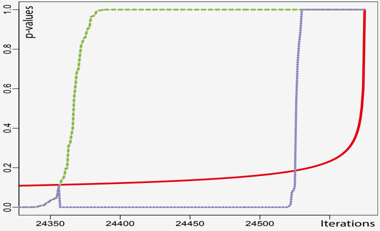




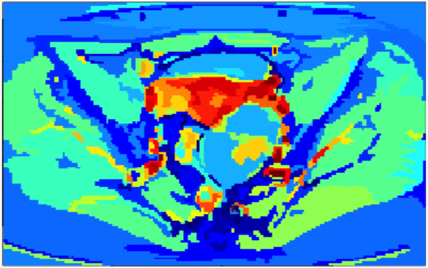
Global step: 64 clusters

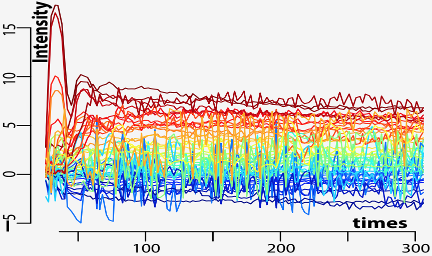
DCE-MRI: Ovarian malignant tumor ($\Delta = \mathbf{4}^2 \times 119$, $\alpha = 0.05$)





Type I error control



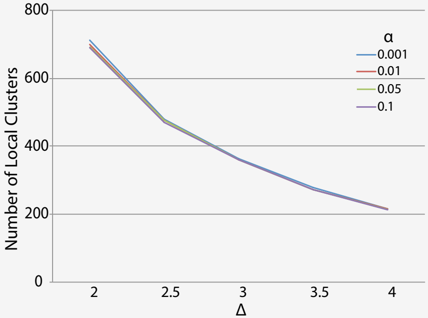


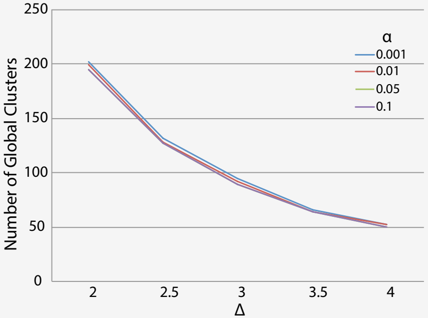
Global step: 51 clusters

Influence of the parameters

Parameter tuning

- Δ : from 2 to 4;
- α : from 0.001 to 0.1;





Only Δ has a major contribution on the number of clusters !

References

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