DCE-imaging biomarker construction in cancer treatment

Statistical tools

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1 Medical framework and goal

2 Automatic clustering DCE image sequences

3 Tissue microvascular circulation estimation

4 A complex global framework involving registration

5 Testing in convolution models
Medical framework and goal

1. Automatic clustering DCE image sequences
2. Tissue microvascular circulation estimation
3. A complex global framework involving registration
4. Testing in convolution models
Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

**Angiogenesis**: growth of new blood vessels from pre-existing vessels.
Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

IDEA: An early 90’s point of view

\[
\text{tumor} \iff \text{growth} \iff \text{energy} \iff \text{glucose} \iff \text{vascularization} \iff
\]

“Reducing angiogenesis will asphyxiate the tumor”. 
Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

IDEA: An early 90’s point of view

\[
\text{tumor} \Leftrightarrow \text{growth} \Leftrightarrow \text{energy} \Leftrightarrow \text{glucose} \Leftrightarrow \text{vascularization}
\]

“Reducing angiogenesis will asphyxiate the tumor”.

An interesting but unfortunately wrong idea

However, penalizing angiogenesis induces:

- a regularization of the tumor blood pathways,
- an improvement of the tumor vessel efficiency.
Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

IDEA: An early 90’s point of view

\[
\text{tumor} \rightleftharpoons \text{growth} \oplus \rightleftharpoons \text{energy} \rightleftharpoons \text{glucose} \rightleftharpoons \text{vascularization} \oplus
\]

“Reducing angiogenesis will asphyxiate the tumor”.

However, penalizing angiogenesis induces:
- a regularization of the tumor blood pathways,
- an improvement of the tumor vessel efficiency.

Current point of view

At least anti-angiogenesis treatments may help to bring chemical weapons inside the tumor.

“Anti-angiogenesis treatments help to fight tumors from inside”.
Materials

A Dynamic Contrast Enhancement - CT (DCE-CT) example

Axial CT image of the abdomen showing a liver metastasis. Follow-up of a 80ml injection from Xénétix as contrast agent.
DCE-CT experiment with C-A Cuénod (HEGP - LRI)
Follow-up of a contrast agent bolus injection via DCE Computerized Tomography
About 50 images in 100 seconds with very low X-ray dose

before injection

\[ t=0 \text{ s} \]
DCE-CT experiment with C-A Cuénod (HEGP - LRI)

Follow-up of a contrast agent bolus injection via DCE Computerized Tomography

About 50 images in 100 seconds with very low X-ray dose

arterial phase
DCE-CT experiment with C-A Cuénod (HEGP - LRI)
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DCE-CT experiment with C-A Cuénod (HEGP - LRI)

Follow-up of a contrast agent bolus injection via DCE Computerized Tomography
About 50 images in 100 seconds with very low X-ray dose
Building biomarker in cancer treatment

Discriminating between “responder” and “not responder”

**Responder**

<table>
<thead>
<tr>
<th>t=0</th>
<th>t=1</th>
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</thead>
<tbody>
<tr>
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<td>16/06/05</td>
</tr>
<tr>
<td>BF: 130</td>
<td>BF: 18</td>
</tr>
</tbody>
</table>

**Not-Responder**

<table>
<thead>
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<th>t=0</th>
<th>t=1</th>
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<tbody>
<tr>
<td>03/01/05</td>
<td>12/04/05</td>
</tr>
<tr>
<td>BF: 250</td>
<td>BF: 230</td>
</tr>
</tbody>
</table>
1. Medical framework and goal

2. Automatic clustering DCE image sequences

3. Tissue microvascular circulation estimation

4. A complex global framework involving registration

5. Testing in convolution models
A noisy problem

Typical enhancements

Model: 

\[ Q^x(t_i) = q^x(t_i) + \sigma \varepsilon_i^x, \ i = 1 \ldots n, \]

Image made of time-series
Automatic clustering for DCE with Fuchen Liu (PhD)

**Problem:** We assume that the image $\mathcal{X}$ is made of few clusters that we aim at recover
- $\mathcal{X} = C_1 \cup \ldots \cup C_K$;
- if $x \in C_k$ for $k = 1, \ldots, K$, then $\mathbb{E}(Q^x) = q^x =: q_k$;
- if $k \neq \ell$, then $C_k \cap C_\ell = \emptyset$ and $q_k \neq q_\ell$. 

**Key idea:** Build a test such that "=" should be the research hypothesis $H_1$. 

**Intersection-Union Test:** (Where $\pi_k$ is the projection on a time-partition with $2^k$ bins)

- $H_0^k = \{H_k^0 : \parallel \pi_k(d_{xy}) \parallel_{2^k} \leq 0\}$ versus $H_1^k = \{H_k^1 : \parallel \pi_k(d_{xy}) \parallel_{2^k} > 0\}$.

**Th. (Berger and Hsu, 1996):** If $R_J$ are $\alpha$-level rejection regions of $H_k^0$, then $R = \bigcup_k R_k$ is a $\alpha$-level rejection region for $H_0$. It follows that if $p_k$ is the $p$-value for $H_k^0$, then the rejection region $R = \bigcup_k R_k$ has max $k(p_k)$ for $p$-value.

**Idea:** Use $p(x : y) = \max_k p_{xy}^k$ as a dissimilarity measure in a hierarchical approach.
Automatic clustering for DCE with Fuchen Liu (PhD)

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Key idea: Build a test such that "\(=\)" should be the research hypothesis $H_1$.

$$H_0^{xy} : d^{xy} \neq 0 \quad \text{v.s.} \quad H_1^{xy} : d^{xy} = 0$$

where $d^{xy} = q^y - q^x$. 
Automatic clustering DCE image sequences

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where $d^{xy} = q^y - q^x$

**Intersection-Union Test:**

$H_0 = \bigcup_k (H_0^k : \|\pi_k(d^{xy})\|^2 \neq 0)$

versus

$H_1 = \bigcap_k (H_1^k : \|\pi_k(d^{xy})\|^2 = 0)$.  

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Automatic clustering for DCE with Fuchen Liu (PhD)

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**Intersection-Union Test:** ($\pi_k$ is the projection on a time-partition with $2^k$ bins)

$$H_0 = \bigcup_k (H_0^k : \|\pi_k(d^{xy})\|^2 \neq 0) \text{ versus } H_1 = \bigcap_k (H_1^k : \|\pi_k(d^{xy})\|^2 = 0).$$

**Th. (Berger and Hsu,1996):** If $R_J$ are $\alpha$-level rejection regions of $H_0^k$, then $R = \bigcap_k R_k$ is a $\alpha$-level rejection region for $H_0$. It follows that if $p_k$ is the $p$-value for $H_0^k$, then the rejection region $R = \bigcap_k R_k$ has $\max_k(p_k)$ for $p$-value.

**Idea:** Use $p(x : y) := \max_k(p_k^{xy})$ as a **dissimilarity measure** in a hierarchical approach.
Automatic clustering for DCE with Fuchen Liu (PhD)

using multiple equivalence test

Model: \( Q^X(t_i) = q^X(t_i) + \sigma \varepsilon^X_i, \quad i = 1 \ldots n, \) with i.i.d. \( \varepsilon^X_i \). together with \( Q^X = \sum_{x \in X} Q^x/n \)

Rejection Area: \( \exists k \text{ s.t. } \| \pi_k D^{XY} \|^2 \leq 2^K + \delta^2 - 2\sqrt{(2^K/n + 2\delta^2)\ln \alpha^{-1}} \) with \( D^{XY} = \frac{Q^X - Q^Y}{\sigma\sqrt{1/|X| + 1/|Y|}} \)

ensures that if \( \| \pi_k d^{XY} \|^2 \leq n\delta \), \( X \) and \( Y \) are clusterized with probability \( 1 - \alpha \).

Hierarchical clustering with \( p \)-values are used as dissimilarity measure

- clustering stops automatically by ensuring that the minimum \( p \)-value of \( s \) different clusters is smaller than \( c_\alpha(s) \) with small probability \( \alpha \) (type I error):

\[
c_\alpha(s) = \left(1 - (1 - \alpha)^{2/s(s-1)}\right)^{1/(K_0 + 1)}.
\]
Automatic clustering for DCE with Fuchen Liu (PhD)

A two steps procedure to take into account local and global properties of the tissue/image

**Local clustering:**
- Starts from a partition made of all voxels as singletons;
- only consider **neighbors** in four directions: north, south, east, west;
- At each iteration, merge two neighbor clusters with minimal dissimilarity measure.
Automatic clustering for DCE with Fuchen Liu (PhD)

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- the neighbors of the neighbors
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Take away message

Testing equality of dynamics helps to clusterize homogeneous tissue and improve signal to noise ratio!
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A parametric model for tissue microvascular circulation.

Quantities of interest are NOT related to
- blood input,
- contrast agent characteristics.

but are related to bio-medical descriptions of the microvascular circulation.
Parametric model for tissue microvascular circulation.
Parametric model for tissue microvascular circulation.

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Parametric model for tissue microvascular circulation.

Red blood cells

O$_2$

Contrast Agent

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Parametric model for tissue microvascular circulation.

![Diagram of microvascular circulation]

- Artery
- Blood
- Capillary plasma
- Interstitium
- Cells
- Vein
- Contrast Agent

Red blood cells and oxygen are depicted within the tissue microvasculature.
Parametric model for tissue microvascular circulation.

- Artery
  - Red cells
  - Plasma

- Blood
  - Red blood cells
  - Capillary plasma
  - Interstitium
  - Cells

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O₂
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Y. Rozenholc (USPC - UPD)

Statistical tools for DCE-imaging biomarker construction

SMAC Cancéropôle GS0 7/4/16
Parametric model for tissue microvascular circulation.
Parametric model for tissue microvascular circulation.

The diagram illustrates the flow of blood through the tissue microvasculature, starting from the Artery, moving through the Capillary plasma, and ending with the Contrast Agent. Oxygen ($O_2$) is also depicted, indicating the exchange of oxygen between the blood and the tissue cells.
Parametric model for tissue microvascular circulation.
Tissue microvascular circulation estimation


\[
\begin{align*}
\frac{dQ_P(t)}{dt} &= \frac{\alpha}{1-h} AIF(t-\delta) - \frac{k}{V_P} Q_P(t) + \frac{k}{V_I} Q_I(t) - \frac{\alpha}{V_P} Q_P(t) \\
\frac{dQ_I(t)}{dt} &= \frac{k}{V_P} Q_P(t) - \frac{k}{V_I} Q_I(t)
\end{align*}
\]

A simple vision of an inverse problem:

Given AIF and \( Q = Q_P + Q_I \) noisily observed at \( t_0, \ldots, t_n \):

\( \alpha, k, V_I, V_P \) do not depend on AIF.
A non parametric complex modelization

\[ g(t) = \beta AIF(t - \delta) \]

Body axis

CT voxel x

Arterial enhancement

Blood flow with contrast agent

Imaging slice thickness

Imaging cross section

Tissue enhancement

AIF(t)

Y. Rozenholc (USPC - UPD) Statistical tools for DCE-imaging biomarker construction
Laplace convolution model for microvascularization

Queuing system with one entrance \( /G/\infty\)-type and one exit \((t \in \mathbb{R}_+)\).

- \(AIF(t)\) number of arrivals in aorta voxels at time \(t\), \(AIF(0) = 0\)
- \(g(t) := \beta AIF(t - \delta)\) number of arrivals in tissue voxel \(x\) at time \(t\)
- \(Q(t)\) number of particles in tissue voxel \(x\) at time \(t\)
- \(S_i\) \(i.i.d.\) particle sojourn times in tissue voxel \(x\) with c.d.f. \(F\)

Link between arrivals and sojourn times:

\[
\mathbb{E} Q(t) = \int_0^t g(\tau) \, d\tau - \int_0^t g(t - \tau) \ast P(S_1 \leq \tau) \, d\tau = \int_0^t g(t - \tau)(1 - F(\tau)) \, d\tau.
\]

\(\underbrace{\int_0^t g(\tau) \, d\tau}_{\text{arrived before time } t}\) \(\underbrace{\int_0^t g(t - \tau) \ast P(S_1 \leq \tau) \, d\tau}_{\text{left before time } t}\)
Laplace convolution model for microvascularization

Queuing system with one entrance $/G/\infty$-type and one exit ($t \in \mathbb{R}_+$).

- $AIF(t)$: number of arrivals in aorta voxels at time $t$, $AIF(0) = 0$
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$$\mathbb{E} Q(t) = \int_0^t g(\tau) \, d\tau - \int_0^t g(t - \tau) \ast P(S_1 \leq \tau) \, d\tau = \int_0^t g(t - \tau)(1 - F(\tau)) \, d\tau.$$ 

Discrete Laplace convolution model with noisy observations:

$$AIF(t_i) \quad \text{and} \quad Q(t_i) = AIF \otimes \beta(1 - F)(t_i - \delta) + \sigma \varepsilon_i,$$

for $i = 1, \ldots, n$ with $\varepsilon_i$ independent and identically distributed $\mathcal{N}(0, 1)$ and $0 \leq t_1 \leq \ldots \leq t_n = T_n$.

$R := \beta(1 - F)$ unknown function to estimate $\rightarrow$ ill-posed pb
Laplace deconvolution using Laguerre functions
with F. Comte, C.-A. Cuénod, M. Pensky in JRSS-B 2016

- Consider the $L_2(\mathbb{R}^+) \text{ orthonormal basis of the Laguerre functions } \phi_k(t) = e^{-t/2}L_k(t)$ for $k \in \mathbb{N}$.
- Consider the decompositions of the functions $R$, $A$ et $Q$ on this basis:

\[
R(t) = \sum_{k=0}^{\infty} r_k \phi_k(t), \quad A(t) = \sum_{k=0}^{\infty} a_k \phi_k(t), \quad Q(t) = \sum_{k=0}^{\infty} Q_k \phi_k(t)
\]

- Thanks to Abramovitz, Stegun (1972, 22.13.14):

\[
\int_0^t \phi_k(x) \phi_j(t-x) \, dx = \phi_{k+j}(t) - \phi_{k+j+1}(t)
\]

and we have

\[
Q(t_i) = \int_0^{t_i} A(s)R(t_i - s) \, ds + \sigma \epsilon_i \iff \tilde{Q}_\infty = A_\infty \tilde{R}_\infty + \sigma \tilde{e}_\infty
\]

with:

\[
\begin{pmatrix}
Q_0 \\
Q_1 \\
\vdots \\
Q_m
\end{pmatrix} =
\begin{pmatrix}
a_0 & 0 & \ldots & 0 \\
a_1 - a_0 & a_0 & \ldots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
a_m - a_{m-1} & \ldots & \ldots & a_0
\end{pmatrix}, \quad
\begin{pmatrix}
r_0 \\
r_1 \\
\vdots \\
r_m
\end{pmatrix} =
\begin{pmatrix}
0 \\
0 \\
\vdots \\
0
\end{pmatrix}
\]

⇒ Provide a theoretical solution

\[
\hat{R}_\infty = A_\infty^{-1}\tilde{Q}_\infty \quad \ldots \text{unfortunately not usable.}
\]
Laplace deconvolution using Laguerre functions

... going from theoretical to practical solution

Consider the truncations at size $m$ of the previous expansions

$$
\hat{Q}_m = \begin{pmatrix}
Q_0 \\
Q_1 \\
\vdots \\
Q_m
\end{pmatrix},
A_m = \begin{pmatrix}
a_0 & 0 & \cdots & 0 \\
a_1 - a_0 & a_0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
am_m - a_{m-1} & \cdots & \cdots & a_0
\end{pmatrix},
$$

and their linear least-square estimates $\hat{Q}_m$, $\hat{A}_m$ using design matrix $\Phi_m = (\phi_k(t_j))_{1 \leq j \leq n, 0 \leq k \leq m}$.

Using

$$
\hat{R}_m := \hat{A}_m^{-1} J_{m,M} \hat{Q}_M \quad \text{and} \quad \hat{R}_m(x) := \sum_{k=0}^m \hat{R}_m[k] \phi_k(x)
$$

the following bias-variance decomposition of the risk holds:

$$
\mathbb{E}(\| R - \hat{R}_m \|^2) \leq \| R - R_m \|^2 + \text{Tr}(\Sigma_m) \left[ \sigma^2 + \frac{C}{3n} \right]
$$

with $\Sigma_m = \left[ (\Phi_M^T \Phi_M)^{-1} \right]_m \left[ (A_M A_M^T)^{-1} \right]_m$ and $J_{m,M} = (I_{dm}, O_{m,M-m})$.

Choose $m$ using penalized least-squares
Real examples from two DCE-MRI

![Graphs showing tissue microvascular circulation estimation](image)

a.hat=2.65

a.hat=1.9

a.hat=2.6

a.hat=1.45

a.hat=2.3

before treatment starts

after 15 days of treatment
Medical framework and goal

Automatic clustering DCE image sequences

Tissue microvascular circulation estimation

A complex global framework involving registration

Testing in convolution models
Dealing with non-rigid movements

slide from Nikos Paragios

Intensity-based Image Registration

source image $I_T$

transformation $\phi$

transf. source $I_s \circ \phi$

target image $I_T$

difference image

difference image

Compute deformation $\phi$, such that the transformed source $I_s \circ \phi$ matches target $I_T$ by minimizing the image-based difference measure $E_D$. 
Dealing with non-rigid movements
slide from Nikos Paragios

Intensity-based Deformable Registration as Energy Minimization

\[
\phi' = \arg \min_{\phi} \left[ E_D(I_S \circ \phi, I_T) + \lambda E_R(\phi) \right]
\]

Transformation \( \phi \) can be assumed as element of:
- Can be modeled as element of a Hilbert space (\( L^2 \), Sobolev space) or group/manifold (group of diffeomorphisms)
- Has to be parametrized for digital representation (B-Spline FFDs, DCT, RBFs)

Difference Measure between:
- Target image \( I_T \)
- Warped source image \( I_S \circ \phi \)
Examples:
- Sum of squared differences (SSD)
- Sum of absolute differences (SAD)
- Correlation Coefficient (CC)
- Correlation Ratio (CR)
- Mutual Information (MI)

Regularization term:
- Models the behaviour of underlying elastic model (internal energy)
- Incorporates prior knowledge
- Can be required to constrain problem
Examples:
- Diffusion (1st-order) (in-)homogeneous, (an-)isotropic
- Curvature/Bend. Energy (2nd-order)
- Linear Elasticity
Dealing with non-rigid movements

figure from Nikos Paragios

A complex but reasonable problem for corresponding intensities

A more complex but still reasonable problem for multi-modalities

Need to
- infer one modality from the other one
- apply sophisticated similarity measures

!!! HOWEVER IMPOSSIBLE WHEN GRAY LEVELS CHANGE DYNAMICALLY !!!
Take home message

Tools to build good DCE imaging biomarkers are available.
Tools to solve noise and movement issues are available.
However each previous tool fails separately.

PROBLEMS ARE DEEPLY INTERMINGLED:

- Feature extraction needs registration.
- Registration requires similarity measure between dynamics.
- Without deconvolution dynamics change with AIF.
- Deconvolution requires registration.
A complex global framework involving registration

Dictionary for integrated registration and labeling
going from not so large to complex problem

- Grade DCE sequences from low to high motion.
- Clusterize low motion DCE sequences and retrieve denoised cluster dynamics.
- Deconvolve cluster dynamics with respect to AIF to get reproducible parameters of the microcirculation.
- Reduce the set of all reproducible parameters to build a smaller dictionary $D$.
  (using mixture models, unsupervised classification, etc)

- For a DCE sequence showing movements
  - Find AIF (easy),
  - Realize $AIF \otimes D$ to get a personalized dictionary of enhancement $D_{AIF}$,
  - Use $D_{AIF}$ as input of the $AIF$-adapted similarity measure

- Improve $D$ with registered DCE sequences iteratively.

When $D$ is optimized, registration of new DCE sequence provides an association “voxel to microcirculation parameter” !!!

$D$ can be large if hierarchical: ensure small registration cost at each level of the hierarchy.
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Direct clustering between DCE as follow-up biomarkers

Example - Responder

Follow-up and prospective Biomarker in cancer treatment

$t_0$: Before treatment — $t_1$: 1 week — $t_2$: 3 months
Direct clustering between DCE as follow-up biomarkers

Example - Not Responder

Follow-up and propective Biomarker in cancer treatment

t₀: Before treatment — t₁: 1 week — t₂: 3 months
Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one?

Model:

\[ Q^x(t_i) = q^x(t_i) + \sigma \varepsilon^x_i, \quad i = 1 \ldots n, \]

Image made of time-series

Tools:

\[ H_{0}^{xy} : q^x - q^y \equiv 0, \]

Direct test of nullity
Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one?

Model: \( Q^x(t_i) = q^x(t_i) + \sigma \varepsilon_i^x, \ i = 1 \ldots n, \)  
Tools: \( H_{xy}^0 : q^x - q^y \equiv 0, \)

Image made of time-series

Direct test of nullity

Discrete Laplace convolution model with noisy observations:

\[
AIF(t_i) \quad \text{and} \quad Q(t_i) = AIF \otimes \beta (1 - F)(t_i - \delta) + \sigma \varepsilon_i,
\]

for \( i = 1, \ldots, n \) with \( \varepsilon_i \) independent and identically distributed \( \mathcal{N}(0, 1) \) and \( 0 \leq t_1 \leq \ldots \leq t_n = T_n. \)

Should we prefer an indirect test for \( H_{xy}^0 : R^x - R^y \equiv 0 \) ???
Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one?
Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one?

Theorem 3.1 Let \((Y_j)_{j \geq 1}\) a sequence obeying to model (3). Let \(\alpha, \beta \in (0, 1)\) be fixed. Let \(E_{\alpha,2}(R)\) the ellipsoid defined in (4). We assume that \(0 < \sigma < 1\). Then, in the four cases displayed in Table 1, we have:

- Every level-\(\alpha\) test minimax for \(H_0^{DP}\) on \(E_{\alpha,2}(R)\) is also minimax for \(H_0^{IP}\) on \(E_{\alpha,2}(R)\),
- There exist level-\(\alpha\) tests minimax for \(H_0^{IP}\) on \(E_{\alpha,2}(R)\) but not for \(H_0^{DP}\) on \(E_{\alpha,2}(R)\),

where for all \(k \geq 1\), \(c_k = a_k b_k^{-1}\).

Note that under ellipsoid constraint, previous results hold both for mildly and severely ill-posed problems. Hence the conclusion of this theorem is that testing in the space of observations should be preferred rather than building specific tests designed for inverse problem which will not improve the rates and will introduce additional difficulties.
Direct clustering between DCE images: Is that possible?
How to deal with the non reproducibility of the kernel?

DCE images don’t have the same AIF (convolution kernel)!
How to realize direct comparison i.e. without deconvolution?
Cross-testing in Laplace convolutions
with R. Castro and I. Dattner

We observe
\[
\begin{align*}
Q_j(t_i) &= q_j(t_i) + \sigma_j \varepsilon_j, \\
A_j(t_i) &= a_j(t_i) + \tau_j \nu_j,
\end{align*}
\]
for \( i = 1, \ldots, n. \)

with \( q_j = a_j \otimes R_j, \) for two DCE sequences indexed by \( j = 1, 2. \)

We aim at testing \( H_0 : R_1 = R_2 \) versus \( H_1 : R_1 \neq R_2. \)

**Classical approach**

Step 1: **Deconvolution** to get \( \hat{R}_1 \) and \( \hat{R}_2; \) Step 2: **Comparison** of \( \hat{R}_1 \) and \( \hat{R}_2. \)

However, direct comparison avoids ill-posedness difficulties and should be preferred.
Testing in convolution models

Cross-testing in Laplace convolutions

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Step 1: Deconvolution to get \( \hat{R}_1 \) and \( \hat{R}_2 \); Step 2: Comparison of \( \hat{R}_1 \) and \( \hat{R}_2 \).

However direct comparison avoids ill-posedness difficulties and should be preferred.

IDEA for direct comparison in between sequences:

\[
a_1 \otimes q_2 - a_2 \otimes q_1 = a_1 \otimes a_2 \otimes R_2 - a_2 \otimes a_1 \otimes R_1 = a_1 \otimes a_2 \otimes (R_2 - R_1).
\]

Thanks to associative and commutative properties of Laplace convolution!
Cross-testing in Laplace convolution models: statistic

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with \( q_j = a_j \otimes R_j, \) for two DCE sequences indexed by \( j = 1, 2. \)

Given some projection estimators \( \tilde{a}_j \) of \( a_j \) and \( \tilde{q}_j \) of \( q_j, \) for \( j = 1, 2, \) we consider

\[
\tilde{h} : = \tilde{a}_1 \otimes \tilde{q}_2 - \tilde{a}_2 \otimes \tilde{q}_1
\]
\[
= a_1 \otimes q_2 - a_2 \otimes q_1 + (\bar{a}_1 - a_1) \otimes q_2 - (\bar{a}_2 - a_2) \otimes q_1
\]
\[
+ \tilde{a}_1 \otimes (\bar{q}_2 - q_2) - \tilde{a}_2 \otimes (\bar{q}_1 - q_1) + (\bar{a}_1 - a_1) \otimes q_2 - (\bar{a}_2 - a_2) \otimes q_1
\]
bias
\[
+ \tilde{a}_1 \otimes (\bar{q}_2 - q_2) - \tilde{a}_2 \otimes (\bar{q}_1 - q_1)
\]
stochastic error

where \( \bar{f} \) denotes the projection of \( f. \)