Statistical Atlases of Motion and Deformation for the Characterization of CRT Responders

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Abnormal motion / deformation?
Brief overview

- New patient
- Normality
- Known (?) pathologies

- Learning process
- Huge amount of information

Where computational methods can be useful? = QUANTIFICATION

In the scope of this thesis, application to CRT:

Initial problem: Understanding CRT response

Methods design: Atlases and manifold-learning

Clinical impact: CRT clinical studies
Abnormal motion / deformation: what to look at

2D US  MRI  t-MRI  CT

Tobon-Gomez et al., STACOM 2011
Tobon-Gomez et al., 2012. Under review.

Hoogendoorn et al., 2012. Under review.

Velocity  Displacement  Strain rate  Strain

Mor-Avi et al., EJE, 2011
Abnormal motion / deformation: what to look at

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interval</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displacement</td>
<td>$0 \rightarrow t$</td>
<td>Vector</td>
</tr>
<tr>
<td>Velocity</td>
<td>$t \rightarrow t+1$</td>
<td>Vector</td>
</tr>
<tr>
<td>Strain</td>
<td>$0 \rightarrow t$</td>
<td>Tensor</td>
</tr>
<tr>
<td>Strain Rate</td>
<td>$t \rightarrow t+1$</td>
<td>Tensor</td>
</tr>
</tbody>
</table>

Velocities

*Duchateau et al., MedIA, 2011*

Strain

*De Craene et al., MedIA + ISBI, 2012*
Abnormal motion / deformation: what to look at

2-stages approach:
1. Finding a population-wise representation
2. Comparing a new patient to this population

ATLAS = geometry + labels built from a population

Peyrat et al., TMI, 2007

Atlas of shape
Ordas et al., ISPA, 2006

Fiber structure
Peyrat et al., TMI, 2007

Strain
De Craene et al., MediA + ISBI, 2012

Velocities
Duchateau et al., MediA, 2011
Clinical motivation: CRT

Ho et al., Anesth. Analg. 2010

Hare et al., N. Engl. J. Med. 2002

Reuters Pictures, Medtronic Inc. 2008
Clinical motivation: CRT

Healthy volunteer

Pre-CRT

Follow-up (6 months)
Clinical motivation: CRT

- **Current guidelines for selecting patients** [1]
  - Decreased LV function → Ejection fraction < 35%
  - Electrical abnormalities → QRS duration > 120ms
  - Symptomatic heart failure → NYHA class (II)-III-IV

- **Definition of response to the therapy**
  - Clinical = improvement of patient condition
  - Volume = reverse remodelling

- **Non-responders with current guidelines** [2]
  - 30% (clinical response)
  - 44% (volume response)

[1] Dickstein et al., EHJ 2010
Improving CRT patient selection

- **Measurements of dyssynchrony**
  - Electrical → invasive (electroanatomical mapping)
  - Mechanical
    - Conventional imaging: 2D/3D US, MRI, t-MRI, CT
    - Advanced imaging: Tissue Doppler, Strain rate imaging
    - Image-based tracking

*EPI + ENDO mappings during LBBB*  
*Hospital Clínic, Barcelona*

*Speckle tracking*  
*Mor-Avi et al., EJE, 2011*
Improving CRT patient selection

- **Limits of dyssynchrony analysis**
  - No consensus within the clinical community
    - Can CRT candidates without dyssynchrony worsen?[1]
    - Dyssynchrony as predictor of response?[2]

- **Towards a change of strategy?**
  - Measuring the right thing = is there a magic index?
    - Single measurements of dyssynchrony
    - Dyssynchrony alone

  - Why doing so? → lack of reproducibility / quantification tools

- **Understanding cardiac dyssynchrony**

Understanding mechanical dyssynchrony

- **Classes of mechanical dyssynchrony**

  - **C1**: Intra DYS
  - **C2**: Inter DYS
  - **C3**: Long AV
  - **C4**: Short AV
  - **C5**: Other

  Parsai et al. EHJ, 2009.

http://www.texasheartinstitute.org
Understanding mechanical dyssynchrony

- Does it make sense?

- **Pigs experiments at HCPB**[1]
  1. “normal” heart
  2. Left Bundle Branch Block (LBBB)
  3. CRT pacing

- Getting popular: Septal flash / rebound stretch, apical rocking

---

Understanding mechanical dyssynchrony

- Our strategy:

  New patient

  - Normality
  - Known (?) pathologies

New patient

- Normality

  - C1 = Intra DYS
  - C2 = Inter DYS
  - C3 = Long AV
  - C4 = Short AV
  - C5 = Other

“known” response rate
Quantification of abnormalities in myocardial tissue velocities: statistical atlas of motion

Adapted from:

A spatiotemporal statistical atlas of motion for the quantification of abnormalities in myocardial tissue velocities

Atlas-based quantification of myocardial motion abnormalities: added-value for understanding the effect of CRT
Quantifying dyssynchrony

Which comparison?

- Event timing = time-to-peak measurements
- Shape of the curves = cross-correlation
- Curve matching + voxel-wise comparison

Time-to-peak velocity
Anderson et al., Circ., 2008.

Fourier analysis of strain curves
Bertola et al., JASE, 2009.

Spatial uniformity of strain

Cross-correlation of TDI displacements
Silva et al., JCE, 2009.
Quantifying dyssynchrony

- Some important questions:
  - Reference for normal motion?
  - Which reference system of coordinates?
  - Temporal alignment?

Non-aligned and aligned velocity curves.
De Craene et al., ISBI, 2012.
Statistical atlas of motion

Atlas of motion

Healthy subjects

Patient to study

Radial velocity (mm/s)

Long. velocity (mm/s)

ECG

variance

average

d = ???
Construction of an atlas of “normality”

Registration-based tracking

- Parametric?
- Diffeomorphic?
- Other properties?
Construction of an atlas of “normality”

Registration-based tracking

Healthy subjects

Radial velocity ($mm/s$)

FFD: Rueckert et al. MICCAI, 2006
TDFFD: De Craene et al., MedIA, 2012
Construction of an atlas of “normality”

Registration-based tracking

Spatio-temporal normalization

Healthy subjects

Initial ECG

Normalized timescale

REFERENCE SPACE

SUBJECT SPACE
Statistical distance to “normality”

Statistical distance = \textit{p-value} associated to Mahalanobis distance

LOW \textit{p-value} = HIGH abnormality
Data representation

Temporal evolution at a given anatomical point

Spatiotemporal maps of abnormality

Local maps at a given time t
Validation

- **Reference population**
  - Size, statistical distribution

- **Atlas steps**
  - Tracking quality
  - Spatiotemporal normalization (spatial alignment, temporal resolution, reference choice)
  - Abnormality maps: agreement with clinical observations
Added-value for understanding the effect of CRT

Adapted from:

A spatiotemporal statistical atlas of motion for the quantification of abnormalities in myocardial tissue velocities

Atlas-based quantification of myocardial motion abnormalities: added-value for understanding the effect of CRT
Patient population

21 Healthy volunteers

≈ 60 frames/s
0.24 x 0.24 mm²

88 candidates OFF / ON / FU (11±2 months)

≈ 30 frames/s
0.25 x 0.25 mm²

2D echo, 4-chamber view
Predictive value at baseline?

Follow-up

CRT #9
Septal flash

CRT #8
Septal flash

CRT #12
Left-right interaction

OFF

IVC  Systole  Diastole

ECG

0  0.2  0.4  0.6  0.8 (s)
Evolution of motion abnormalities?

CRT #9
Septal flash

CRT #8
Septal flash

CRT #12
Left-right interaction

OFF

Follow-up

ECG

0 0.2 0.4 0.6 0.8 (s)

IVC Systole Diastole
**Correction of motion abnormalities**

![Graph showing motion abnormalities](image)

<table>
<thead>
<tr>
<th></th>
<th>OFF</th>
<th>FU</th>
<th><strong>p-value</strong></th>
<th>OFF</th>
<th>FU</th>
<th><strong>p-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responde</strong>rs</td>
<td><strong>BI</strong></td>
<td>1.02 (0.84-1.27)</td>
<td>0.74 (0.64-0.99)</td>
<td><strong>&lt; 0.001</strong></td>
<td>0.96 (0.72-1.16)</td>
<td>0.81 (0.73-0.97)</td>
</tr>
<tr>
<td></td>
<td><strong>MI</strong></td>
<td>1.15 (0.97-1.74)</td>
<td>0.86 (0.66-1.22)</td>
<td><strong>0.001</strong></td>
<td>1.26 (0.81-1.58)</td>
<td>1.03 (0.80-1.30)</td>
</tr>
<tr>
<td></td>
<td><strong>AS</strong></td>
<td>0.82 (0.65-0.99)</td>
<td>0.78 (0.63-1.06)</td>
<td><strong>NS</strong></td>
<td>0.68 (0.54-1.10)</td>
<td>0.78 (0.66-0.99)</td>
</tr>
<tr>
<td><strong>Non-responders</strong></td>
<td><strong>BI</strong></td>
<td>0.76 (0.52-1.22)</td>
<td>0.76 (0.52-1.22)</td>
<td><strong>0.014</strong></td>
<td>0.65 (0.51-0.89)</td>
<td>0.57 (0.47-0.74)</td>
</tr>
<tr>
<td></td>
<td><strong>MI</strong></td>
<td>0.96 (0.62-1.71)</td>
<td>0.68 (0.52-1.20)</td>
<td><strong>0.013</strong></td>
<td>0.78 (0.55-1.62)</td>
<td>0.77 (0.53-0.94)</td>
</tr>
<tr>
<td></td>
<td><strong>AS</strong></td>
<td>0.90 (0.62-1.23)</td>
<td>0.66 (0.51-1.03)</td>
<td><strong>0.030</strong></td>
<td>0.84 (0.46-1.45)</td>
<td>0.70 (0.51-1.04)</td>
</tr>
</tbody>
</table>

**p-value** corresponds to the discrimination score between baseline and follow-up abnormalities.

**BI**: Basal Inferoseptal; **MI**: Mid Inferoseptal; **AS**: Apical Septal; **SYS**: Systole; **DIA**: Diastole.
Predictive value: whole population

<table>
<thead>
<tr>
<th></th>
<th># CRT</th>
<th># R</th>
<th>Response rate</th>
<th>6min walking test increase ≥ 10% OR NYHA reduction ≥ 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUR STUDY</td>
<td>88</td>
<td>72</td>
<td>0,82 (clinical)</td>
<td>LVESV reduction ≥ 15%</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td></td>
<td>0,60 (volume)</td>
<td></td>
</tr>
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</table>

Response rate with the current guidelines:
- 0.7 (clinical response)
- 0.5 (echo response)

1. **Baseline characteristics unable to predict response**
2. **Predominance of SF (resp.) and LR/other (non-resp.)**

![Graph showing response rate with CRT and R](image-url)
Predictive value: SF only

- **Evolution with therapy:**
  1. Reduction of abnormal motion
  2. Clinical improvement (clinical response)
  3. Reverse remodelling (volume response)

- **Reduction of SF abnormalities**

- **Non-responders, other factors?**
  - Presence of local infarct
  - Advanced heart failure (NYHA IV)
  - Atrial fibrillation
  - Lack of contractile reserve


### Predictive value: SF only

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- **Presence of SF at baseline:** NOT the new magic index

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<th># SF</th>
<th>Response rate</th>
<th>LVESV reduction ≥ 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>60</td>
<td>0,73</td>
<td>NYHA Class reduction ≥ 1 OR LVESV reduction ≥ 10%</td>
</tr>
<tr>
<td>161</td>
<td>87</td>
<td>0,89</td>
<td>LVESV reduction ≥ 10%</td>
</tr>
<tr>
<td>52</td>
<td>36</td>
<td>1</td>
<td>LVESV reduction ≥ 10%</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>1</td>
<td>LVESV reduction ≥ 10%</td>
</tr>
<tr>
<td>80</td>
<td>35</td>
<td>0,8</td>
<td>EF increase ≥ 6% OR ED diameter reduction ≥ 15%</td>
</tr>
<tr>
<td>34</td>
<td>23</td>
<td>0,61</td>
<td></td>
</tr>
</tbody>
</table>

- **Maybe a less naive analysis?**
Characterization of pathological deviations from normality

Adapted from:

Constrained manifold learning for the characterization of pathological deviations from normality
Atlas-based distance to normality

- Some “nice” questions:
  - Is this a detector of SF?
  - If we detect SF, it will respond
  - A clinician sees the same with his eye
  - Another new magic index
  - I don’t believe in SF

- What about the pattern analysis problem?

```
C1 = Intra DYS
C2 = Inter DYS
C3 = Long AV
C4 = Short AV
C5 = Other
```

New patient

Normality

“known” response rate
How to compare dyssynchrony patterns?

- Which statistics?
  1. Population modelling
  2. Comparison of individuals to a population

$$d = ???$$
Pattern modelling: linear? non-linear?

- **Average over a population**
  - Linear: same for healthy or specific pattern?
  - Non-linear?

- **Individuals vs. modelled pattern**

Trouvé, SAMSI, 2007
Distance from a specific population

- **Objective:** each pathology is modelled as a deviation from normality along a manifold structure

1. **INPUT = 2D motion abnormality maps**
2. **Manifold-learning problem**
   - Training = one specific population (SF)
   - Tested patients = new CRT candidates, volunteers
3. **How to include origin for normality?**
Manifold-learning from training set

- Geodesic distances = isomap  
  Tenenbaum et al., Science, 2000
- Local linear embedding  
  Roweis and Saul, Science, 2000
- Laplacian eigenmaps  
  Belkin and Niyogi, Neur. Comp., 2003
- Kernel PCA  
  Schölkopf et al., Neur. Comp., 1998

Atasoy, MICCAI tutorial, 2011
Mateus, MICCAI tutorial, 2011

1. Assumption = data lies on / close to a manifold
2. Few samples (on the manifold) available
3. Neighbourhood graph = approximation of the manifold
4. Dimensionality reduction (e.g. spectral decomposition)
Manifold-learning from training set

Training set $\mathcal{I} = \{I_i\}_{i \in [0,N]} \subset \mathcal{A}$

$k$-NN graph

Isomap

Low dimension Coordinate space

High dimension Ambient space

Swiss roll ($P=3$)

$2D$ embedding ($M=2$)

$N+1$ images, $P$ pixels

$2D$ embedding (e.g.)

Synthetic dataset

CRT dataset
Mapping new subjects

Pre-image problem:  

Principal curves:  
Hastie and Stuetzle, JASA, 1989.

Ambient-to-coordinate spaces mappings:  
Gerber et al., ICCV, 2009; Bengio et al., NIPS, 2004; Meinicke et al., PAMI, 2005; Gerber et al., MedIA, 2010; ...

- Exact / inexact interpolation problems
- Formulation on a RKHS
Mapping new subjects

- **A-to-C Exact matching:**

\[
\arg\min_{f \in \mathcal{F}} \left( \frac{1}{2} \| f \|_{\mathcal{F}}^2 \right),
\]

under the constraint \( f(I_i) = x_i, \forall i \in [0, N] \).

**With solution:**

\[
\begin{align*}
  f(I) &= \sum_{i=0}^{N} K_{\mathcal{F}}(I, I_i) \cdot a_i, \\
  \text{with } A &= K_{\mathcal{A}}^{-1} \cdot X,
\end{align*}
\]
Mapping new subjects

- **A-to-C Exact matching:**

  \[
  \arg\min_{f \in \mathcal{F}} \left( \frac{1}{2} \| f \|_F^2 \right),
  \]

  under the constraint \( f(I_i) = x_i, \forall i \in [0, N]. \)

  **With solution:**
  \[
  \left\{ \begin{array}{l}
  f(I) = \sum_{i=0}^{N} K_{\mathcal{F}}(I, I_i) \cdot a_i, \\
  \text{with } A = K^{-1}_A \cdot X,
  \end{array} \right.
  \]

- **A-to-C Inexact matching:**

  \[
  \arg\min_{f \in \mathcal{F}} \left( \frac{1}{2} \| f \|_F^2 + \frac{\gamma_f}{2} \sum_{i=0}^{N} S_C(f(I_i), x_i)^2 \right),
  \]

  **With solution:**
  \[
  \left\{ \begin{array}{l}
  f(I) = \sum_{i=0}^{N} K_{\mathcal{F}}(I, I_i) \cdot a_i, \\
  \text{with } A = \left( K_A + \frac{1}{\gamma_f} I_d_{N+1,N+1} \right)^{-1} \cdot X,
  \end{array} \right.
  \]
Mapping new subjects

- **A-to-C Constrained inexact matching**

\[
\begin{align*}
\arg\min_{f \in \mathcal{F}} & \left( \frac{1}{2} \| f \|^2_{\mathcal{F}} + \frac{\gamma_f}{2} \sum_{i=1}^{N} S_C(f(I_i), x_i)^2 \right), \\
\text{under the constraint} & \quad f(I_0) = x_0.
\end{align*}
\]

With solution:

\[
\begin{align*}
f(I) &= \sum_{i=0}^{N} K_{\mathcal{F}}(I, I_i) \cdot a_i, \\
\text{with} & \quad A = (K_A + \frac{1}{\gamma_f} M)^{-1} \cdot X,
\end{align*}
\]

where \( M = (M_{i,j})_{(i,j) \in [0,N]^2} \in M_{N+1,N+1} \), with \( M_{i,i} = 1 \) for all \( i \neq 0 \) and 0 otherwise.
Mapping new subjects

- **C-to-A Constrained inexact matching**

\[
\arg\min_{g \in \mathcal{G}} \left( \frac{1}{2} \|g\|_G^2 + \frac{\gamma_g}{2} \sum_{i=1}^{N} S_A(g(x_i), I_i)^2 \right),
\]

under the constraint \( g(x_0) = I_0, \)

**With solution:**

\[
\begin{align*}
g(x) &= \sum_{i=0}^{N} K_g(x, x_i) \cdot b_i, \\
\text{with } B &= (K_C + \frac{1}{\gamma_g} M)^{-1} \cdot Y,
\end{align*}
\]
Adjusting kernel size

- RKHS = Kernel-based interpolation
  \[ K_F(I, J) = \exp \left( -\frac{S_A(I, J)^2}{\sigma_F^2} \right), \]
  \[ \sigma_F = \frac{1}{N+1} \sum_{i=0}^{N} S_A(I_i, \text{nn}_k(I_i)), \]

- Fixed bandwidth

- Varying bandwidth
  \[ \sigma_F(I) = \frac{1}{K^2} \sum_{k=1}^{K} \sum_{l=1}^{K} S_A(\text{nn}_k(I), \text{nn}_l(I)), \]
Distance computation

1. Distance to the manifold
2. Distance to normality along the manifold

Reconstructed image: \( \hat{I} = g(f(I)) \).
Experiments
Experiments: synthetic data

Number of $k$-NN

Tenenbaum et al., Science 2000
Experiments: CRT data

Learning set
- 50 CRT with SF
- 1 “true” normal

Tested set
- 7 CRT with SF
- 31 CRT without SF
- 21 volunteers

- Number of k-NN?
- Dimensionality N?
- Interpolation weights?
Is non-linear REALLY necessary?

- Compactness / Generalization ability / Specificity + interpretation
- Evolution along the first principal directions
Is non-linear REALLY necessary?

(a) Non-linear (ML)

(b) Linear (PCA)
General conclusions: back to the beginning

New patient

- Learning process
- Huge amount of information

> Where computational methods can be useful?

= QUANTIFICATION
Future work

- Registration-based motion and deformation

- Voxel-based vs. pattern based comparison

- Going beyond Parsai’s paper
  - Value of SF
  - Baseline comparison to specific patterns
    - How?
    - Which patterns?
  - A threshold for CRT response?

- Application to other modalities and mechanisms
Publications

6 journal papers:


+ 8 conference papers
+ 8 conference abstracts / communications
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EuHeart, cvRemod, CDTeam, Stimath
Thanks !!! Any questions...?