

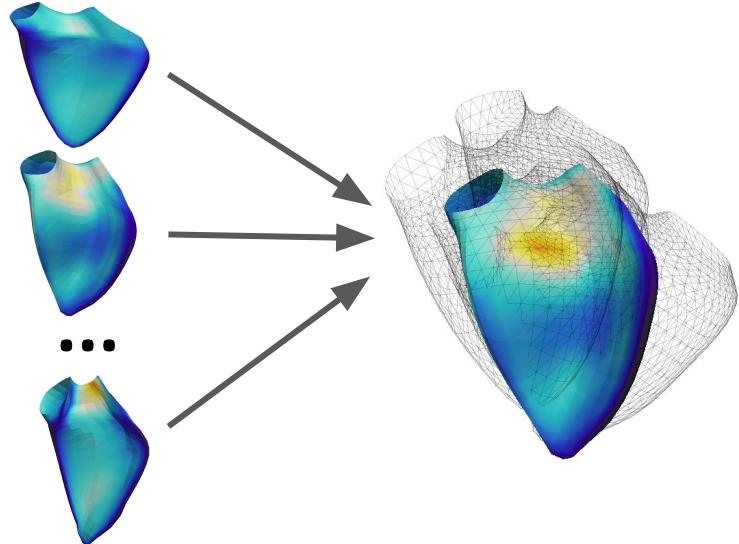
# **Representation learning and fusion of multi-modal data for the statistical analysis of medical imaging populations**

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Institut Universitaire de France

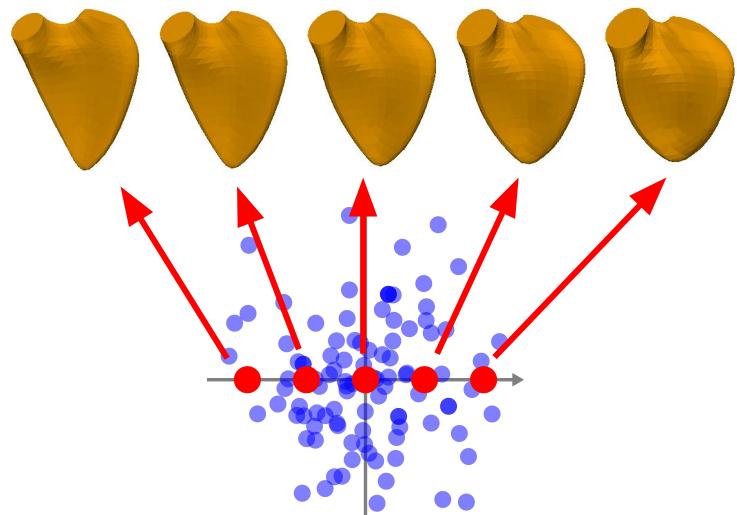
## Statistical atlases

= “aligned” data



## Representation learning

= “simplified” view of a population

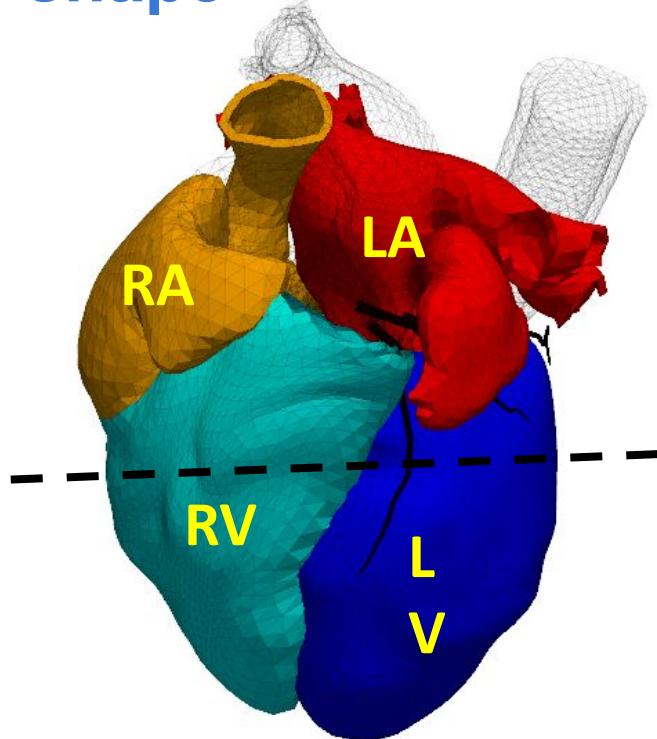


## Clinical (cardiac) questions

- Abnormality quantification
- Phenotyping
- Longitudinal follow-up

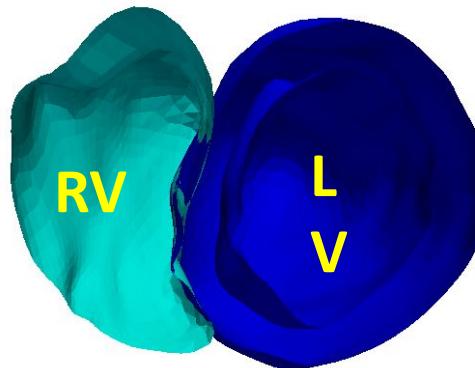
# Cardiac shape

1



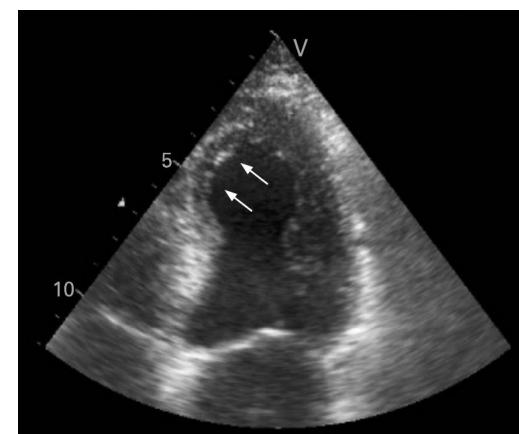
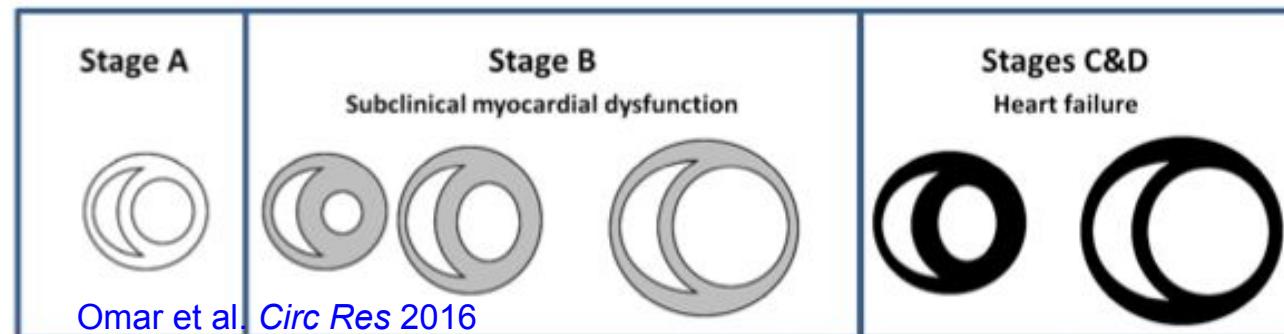
3D atlas from:

Hoogendoorn et al. *IEEE T Med Imaging* 2013



Disease: global remodelling

local remodelling  
ex: infarct



Displacement	$0 \rightarrow t$	vector
Velocity	$t \rightarrow t+1$	vector
Strain	$0 \rightarrow t$	tensor
Strain rate	$t \rightarrow t+1$	tensor

## Deformation:

- $\neq$  motion
- partially reflects contractility
- tensor... often simplified

Eject enough blood...

= ejection fraction

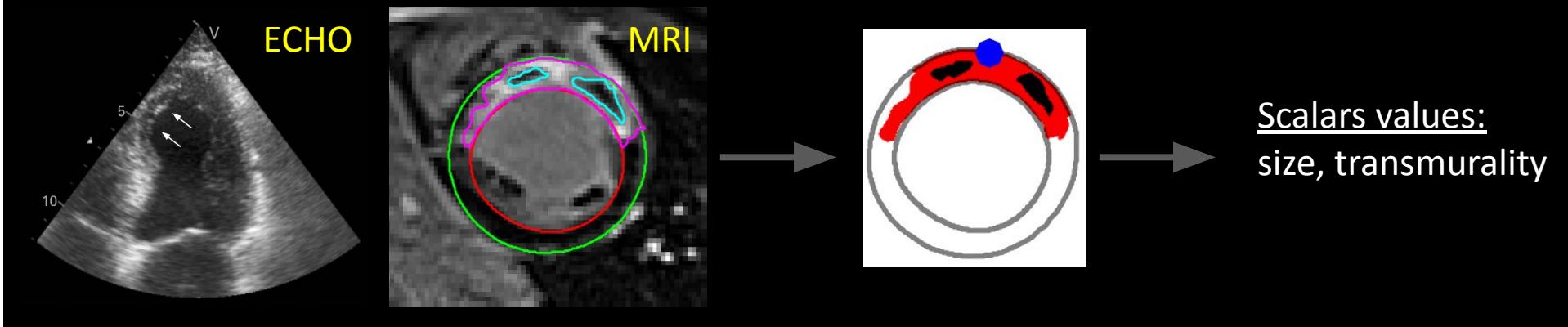
$$\frac{V_{ED} - V_{ES}}{V_{ED}}$$

## + complementary factors:

- Interactions between shape + fibers vs. deformation
- Valves / flow
- Electrical activation
- Patient characteristics (age, sex, etc.)
- External factors, effort, etc.

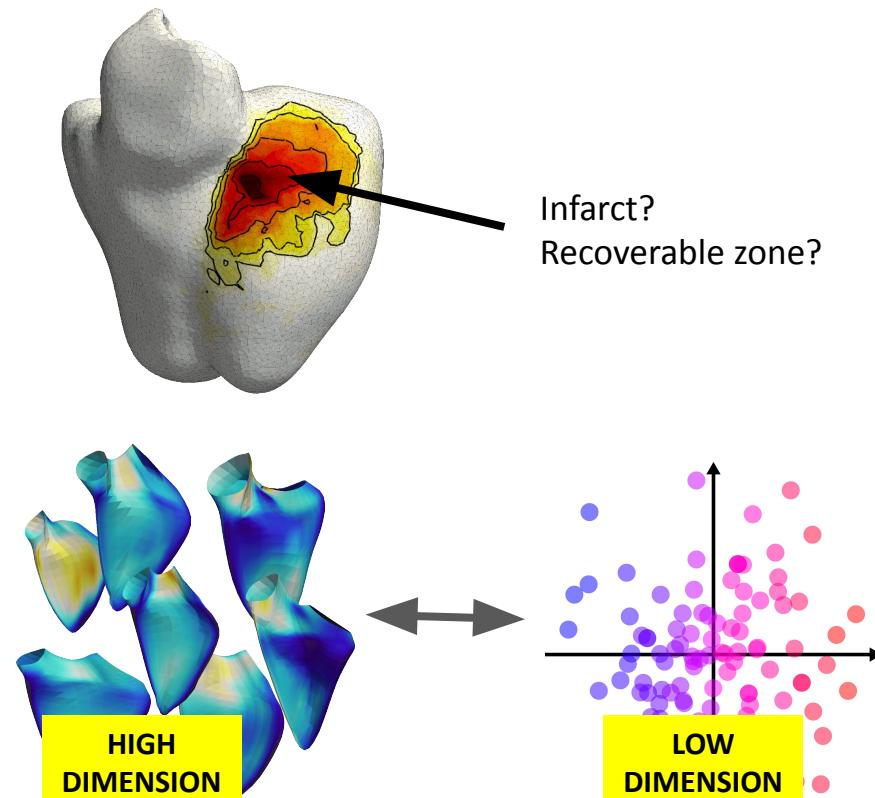
Imaging is useful...

... but “truncated” analysis in the clinic !



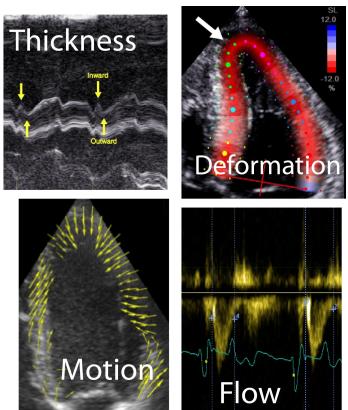
## Where can we contribute ?

- Need for precise **AND** reliable biomarkers
- And a statistically-relevant framework to analyze them



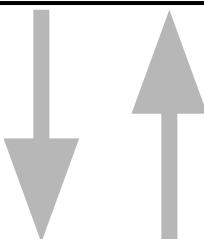
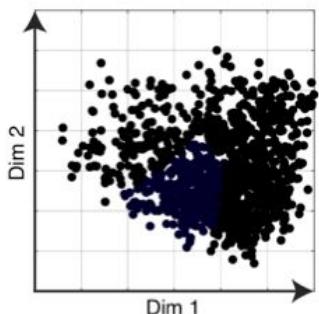
Idea = better represent the data space

- lower dimensional space
- unsupervised (?)



Inputs =

- **Single high-dimensional** descriptors
- **Multiple** scalars
  - ...or **Multiple high-dimensional** descriptors



Output =

- **Low-dimensional** representation

# Representation learning

5

Idea = better represent the data space

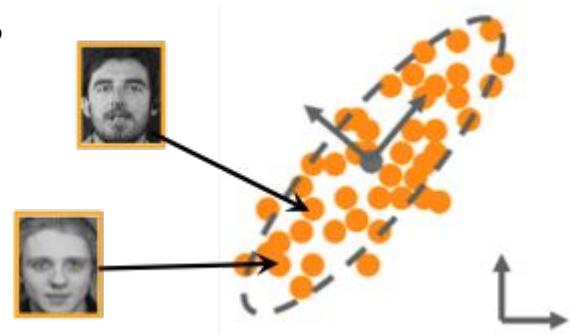
- lower dimensional space
- unsupervised (?)



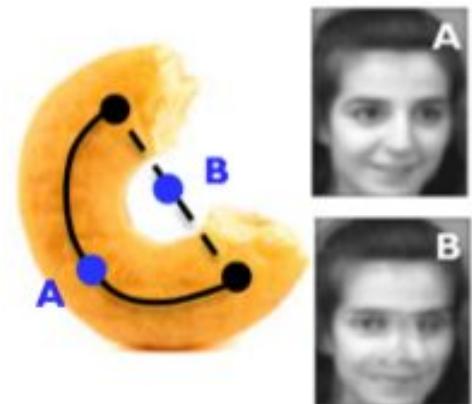
ex: average face for a given person = ?



Linear ?

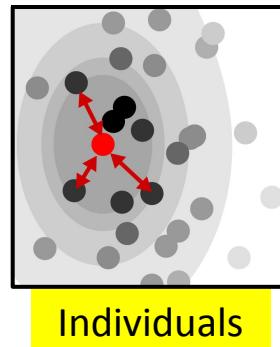


Non-linear !!!

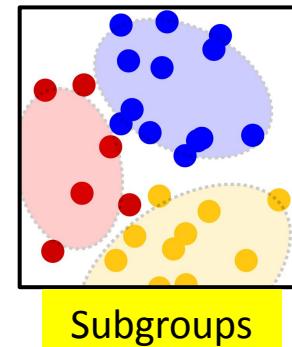


## Medical images/descriptors = warnings !!!

- Non linear data space
- Exploitable latent space
  - Distances
  - Reconstruction (interpretation)



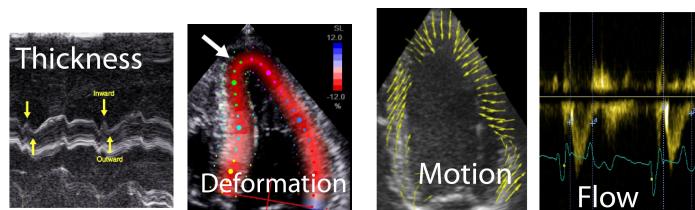
Individuals



Subgroups

- Unsupervised: validation = ?

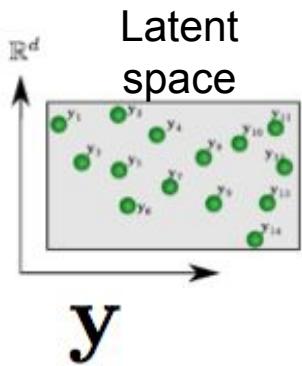
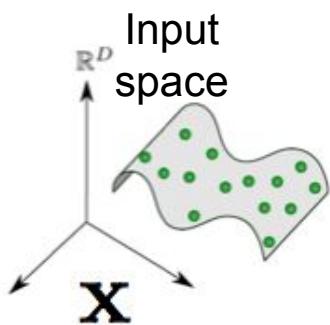
- Heterogeneous types of data



- Not millions of samples
  - No deep?
  - Pre-normalization?
  - Better metrics?

Dimensionality reduction:  $D \gg d$

Input space      Latent space



Inputs =

- Single high-dimensional descriptors
- Multiple scalars
- ...or Multiple high-dimensional descriptors

1) Embedding / encoding

3) Reconstruction / decoding

Output =

- Low-dimensional representation

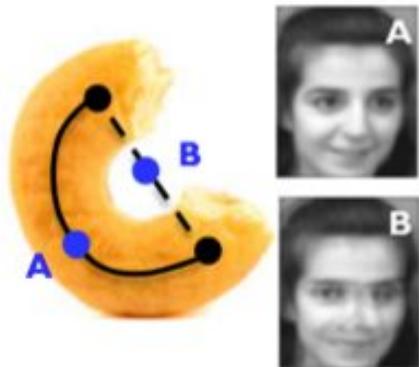
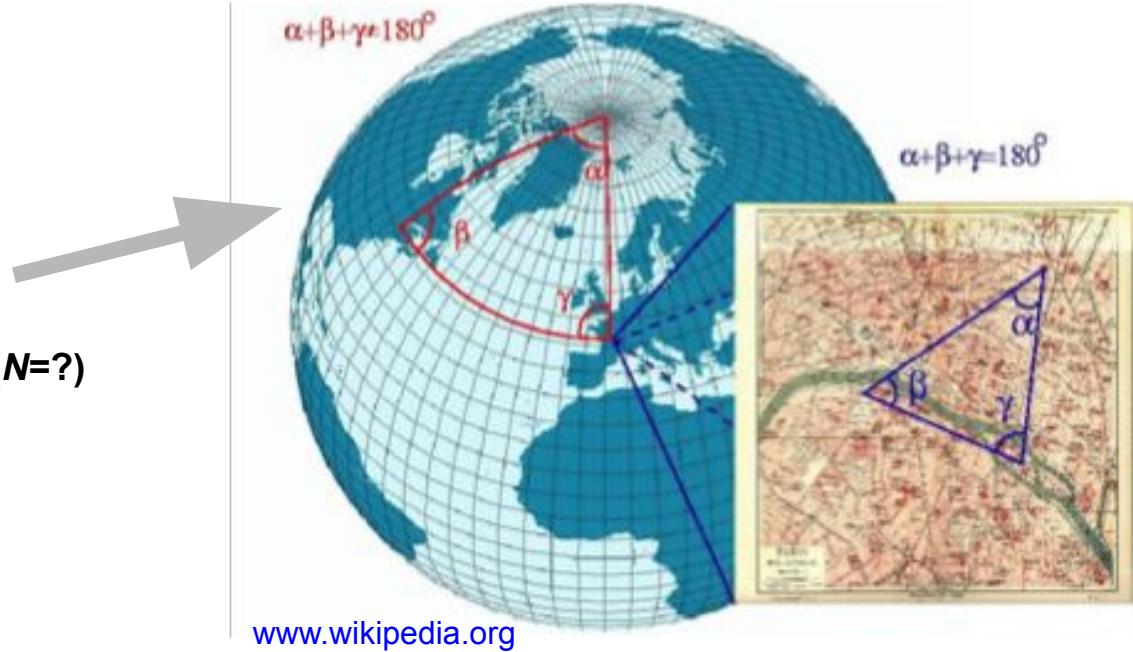
2) Manifold / latent space

**Manifold of dimension  $N$**  = topological space that near each sample resembles  
(is homeomorphic to) a  $N$ -dimensional Euclidean space

ex: - lines and circles ( $N=1$ )

- plane, sphere, surfaces ( $N=2$ )

- brain images, cardiac shapes ( $N=?$ )



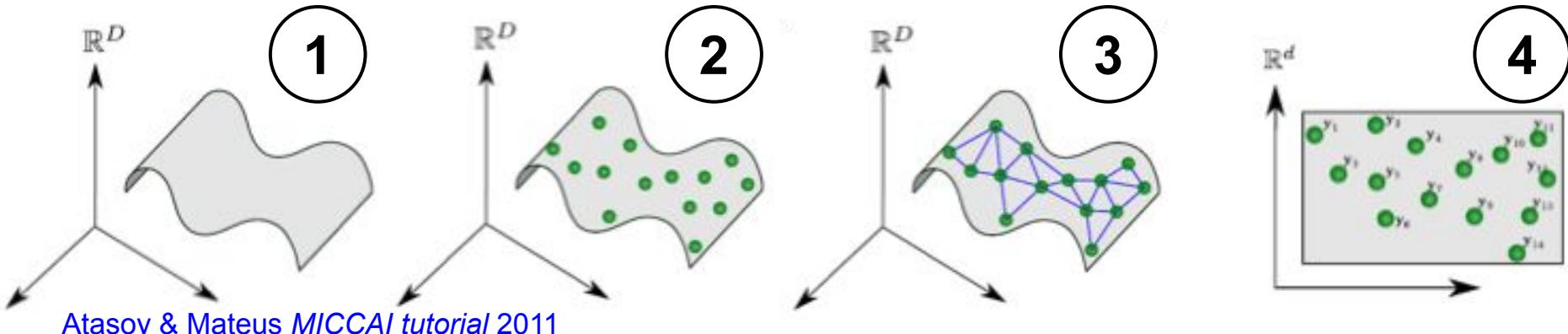
**Interesting for medical data:**  
(specific) distance in the high-dimensional space  
= Euclidean distance in the low-dimensional space

# Manifold learning

## Manifold of dimension $N$

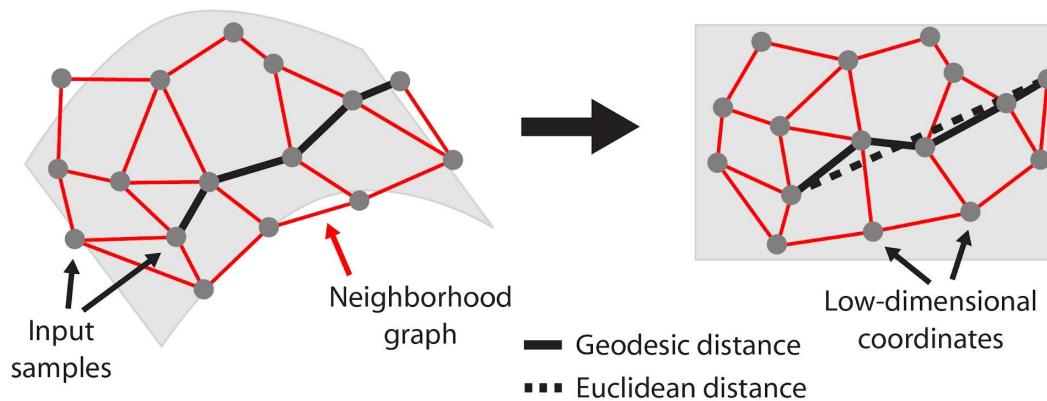
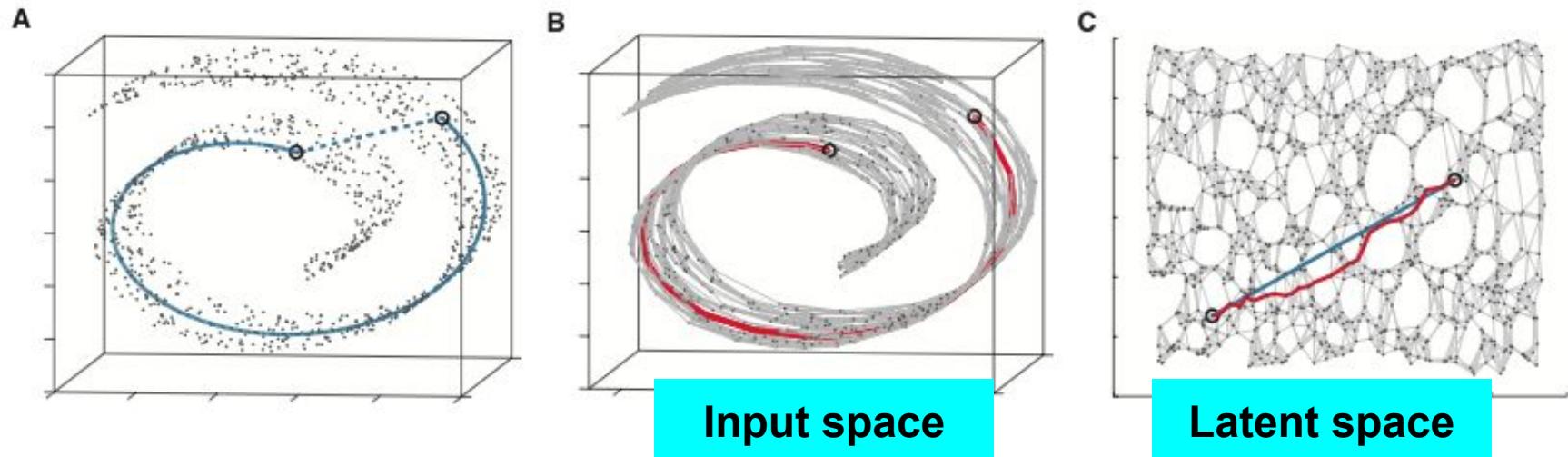
- ◆ In some cases = **known structure**
- ◆ Otherwise = **learn it from data !**

- ↓
1. Assumption = data **lies on / close to a manifold**
  2. **Few samples** (on the manifold) available
  3. **Neighborhood graph** = approximation of the manifold
  4. Dimensionality reduction = **spectral decomposition** of...?

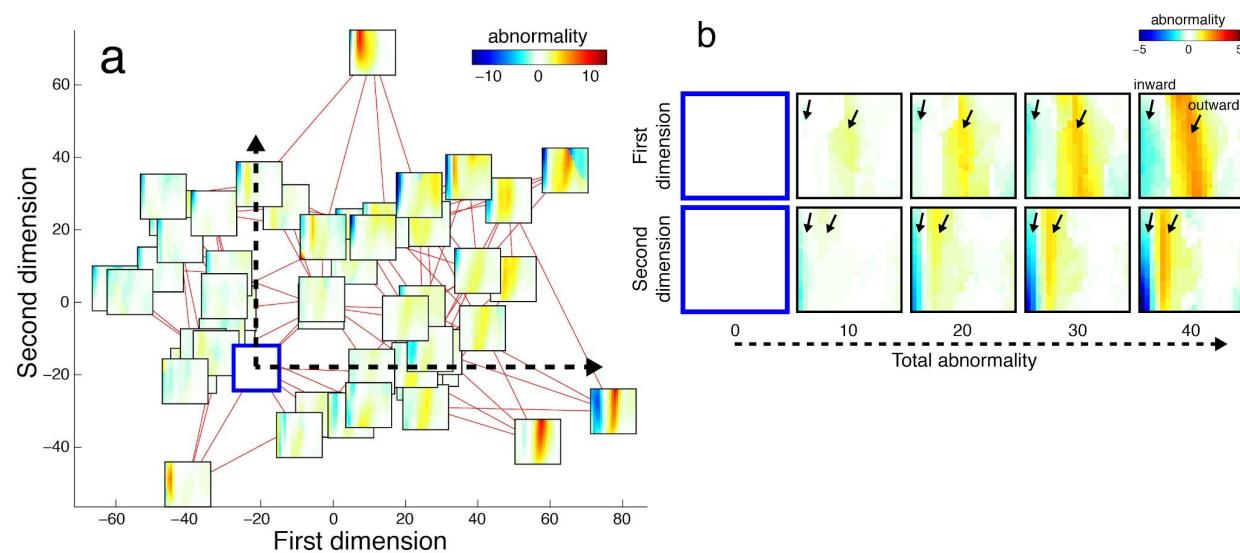


Tenenbaum et al. *Science* 2002

Idea = approximate **geodesic distances** / shortest path along the graph



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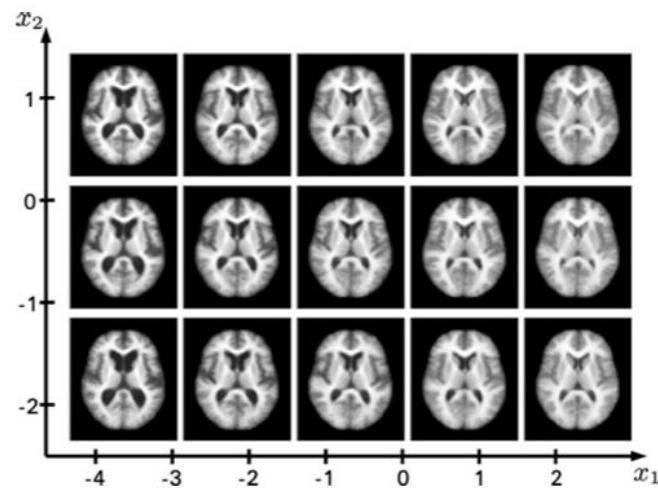
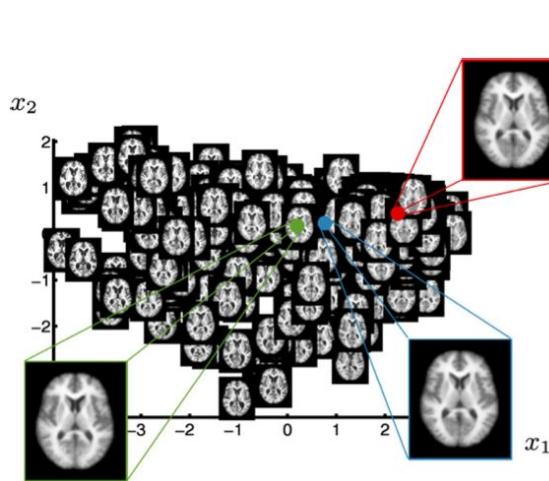


**ex: disease evolution**  
(cardiac velocity patterns)

Duchateau et al. *Med Image Anal* 2012

**ex: preprocessing for regression** (brain images)

Gerber et al. *Med Image Anal* 2010



Belkin & Niyogi *Neur Comput* 2003

Idea = diagonalize the graph Laplacian

$$\hat{\mathbf{Y}} = \underset{\mathbf{Y}}{\operatorname{argmin}} \sum_{i,j} w_{ij} \|\mathbf{y}_i - \mathbf{y}_j\|^2 = \underset{\mathbf{Y}}{\operatorname{argmin}} \mathbf{Y}^T \mathbf{LY}$$

Constraint:  $\mathbf{Y}^T \mathbf{D} \mathbf{Y} = 1$

Graph Laplacian  $\mathbf{L} = \mathbf{D} - \mathbf{W}$

Parameter = kernel bandwidth

$$w_{ij} = k(\mathbf{x}_i, \mathbf{x}_j) = \exp\left(-\frac{\|\mathbf{x}_i - \mathbf{x}_j\|^2}{2\sigma^2}\right)$$

- Close inputs  $\rightarrow w_{ij} \approx 1 \rightarrow$  close outputs
- Far inputs  $\rightarrow w_{ij} \approx 0 \rightarrow$  minor influence

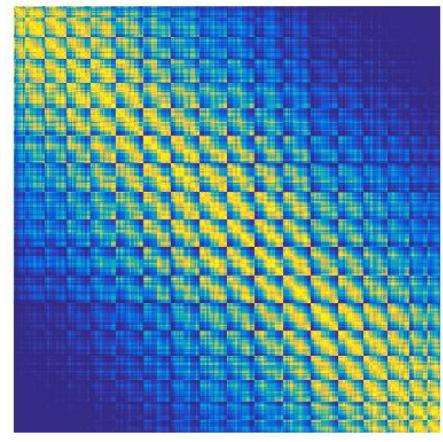
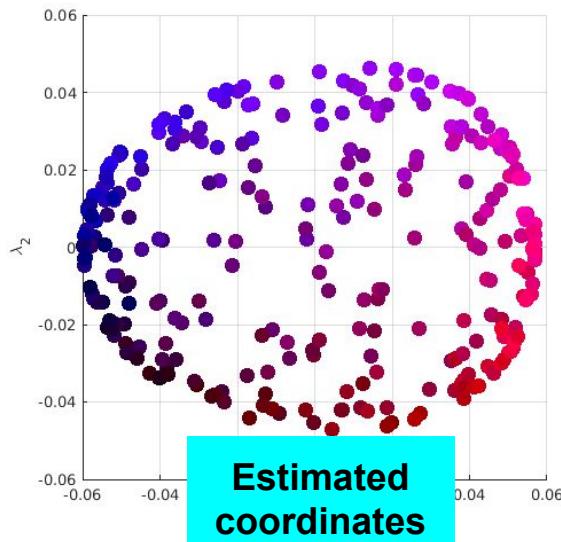
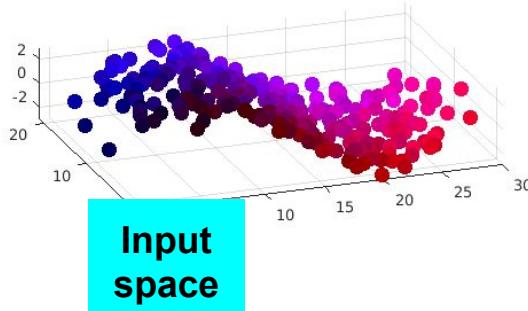
Belkin & Niyogi *Neur Comput* 2003

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Eigendecomposition problem:  $\mathbf{L}\mathbf{v} = \lambda \mathbf{D}\mathbf{v}$

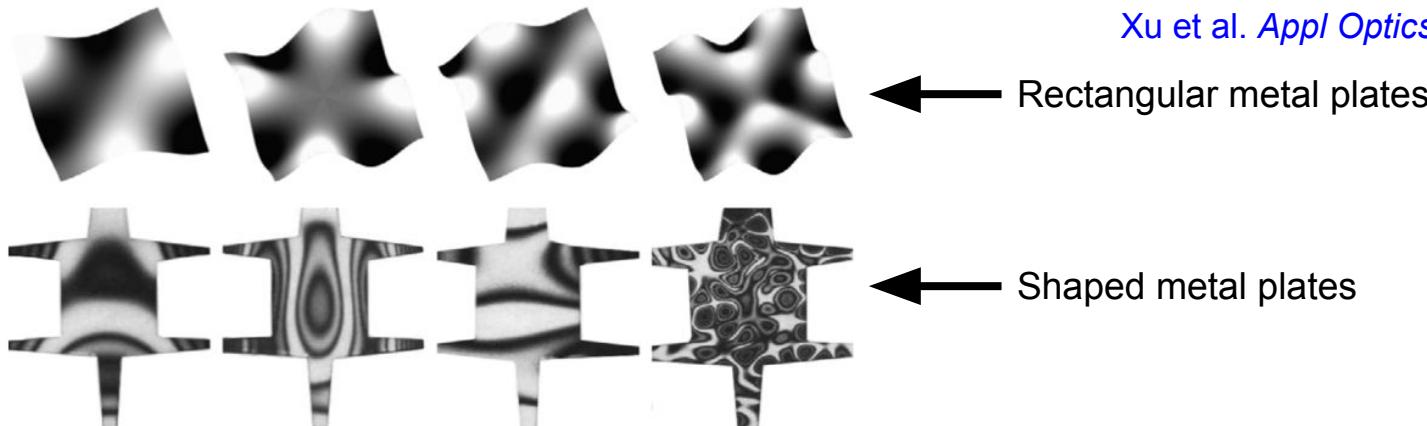
$$\mathbf{D}^{-1/2} \mathbf{W} \mathbf{D}^{-1/2} \mathbf{v} = (1 - \lambda) \mathbf{v}$$



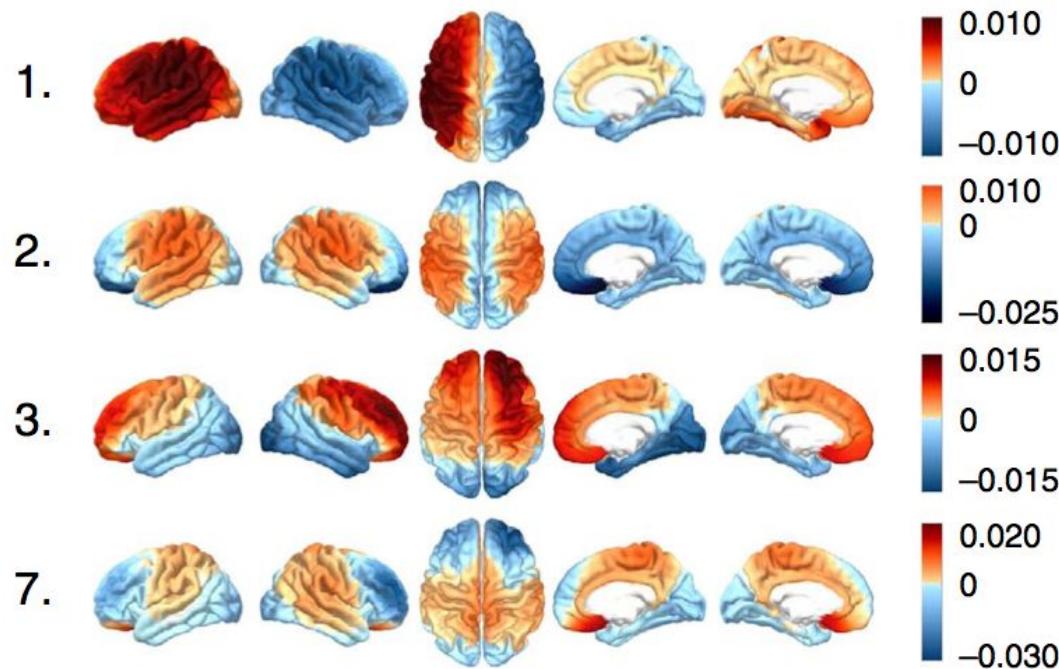
$\mathbf{W}$

## Imaged vibrations (interferometry)

Xu et al. *Appl Optics* 1983



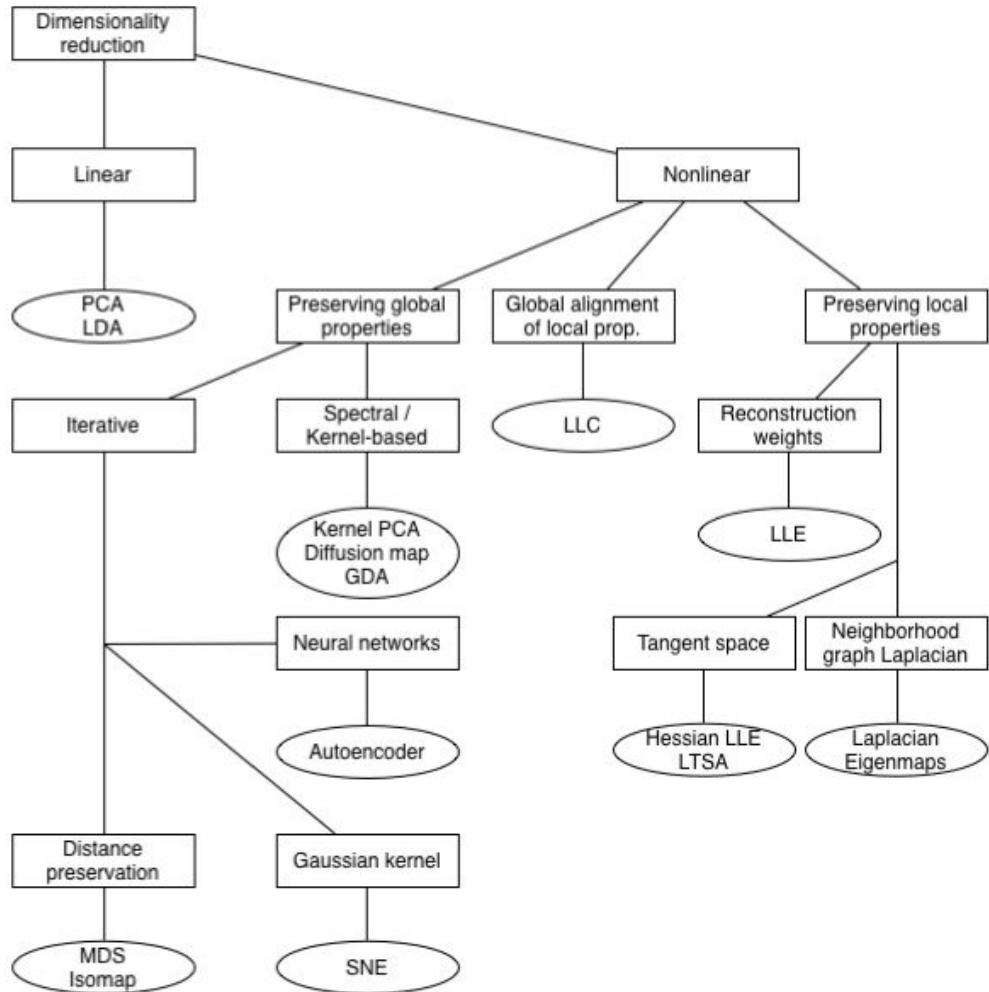
**Learnt embedding:**  
ex: connectome harmonics



van der Maaten et al. 2009

## Depends on:

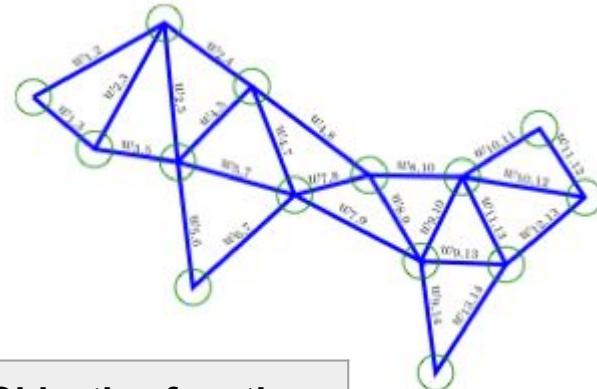
- Your knowledge on data
- Your objectives (distance=?)



# Unified framework?

16

$$\mathbf{W} = \begin{bmatrix} 0 & w_{1,2} & w_{1,3} & w_{1,4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ w_{1,2} & 0 & w_{2,3} & w_{2,4} & w_{2,5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ w_{1,3} & w_{2,3} & 0 & 0 & w_{3,5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ w_{1,4} & w_{2,4} & 0 & 0 & w_{4,5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & w_{2,5} & w_{3,5} & w_{4,5} & 0 & w_{5,6} & w_{5,7} & w_{5,8} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & w_{3,6} & 0 & w_{6,7} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{6,7} & w_{6,8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{6,8} & 0 & w_{7,8} & w_{7,9} & w_{7,10} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & w_{8,9} & w_{8,10} & w_{8,11} & w_{8,12} & 0 & w_{9,13} & w_{9,14} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & w_{9,10} & w_{9,11} & w_{9,12} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & w_{10,11} & w_{10,12} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & w_{11,12} & w_{11,13} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & w_{12,13} & w_{12,14} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & w_{13,14} & 0 & 0 & 0 & 0 \end{bmatrix}$$



Method	Operator / Matrix	Preserved	Objective function
PCA	Covariance matrix	Variance of the dataset / Euclidean distances between data points	$\mathbf{u}^T \Sigma \mathbf{u}$
Laplacian eigenmaps	Graph Laplacian	Distances within the local neighborhood of each data point	$\mathbf{u}^T L \mathbf{u}$
Isomap	Geodesic distance matrix	Geodesic distances between data points	$\mathbf{u}^T D_G \mathbf{u}$
LLE	Reconstruction weighs	Reconstruction weights within the local neighborhood of each data point	$\mathbf{u}^T W \mathbf{u}$

Yan et al. *IEEE PAMI* 2007

(cf. Laplacian eigenmaps...)

$$\hat{\mathbf{Y}} = \underset{\mathbf{Y}}{\operatorname{argmin}} \sum_{i,j} w_{ij} \|\mathbf{y}_i - \mathbf{y}_j\|^2 = \underset{\mathbf{Y}}{\operatorname{argmin}} \mathbf{Y}^T \mathbf{L} \mathbf{Y}$$

Yan et al. *IEEE PAMI* 2007

(cf. Laplacian eigenmaps...)

$$\hat{\mathbf{Y}} = \operatorname{argmin}_{\mathbf{Y}} \sum_{i,j} w_{ij} \|\mathbf{y}_i - \mathbf{y}_j\|^2 = \operatorname{argmin}_{\mathbf{Y}} \mathbf{Y}^T \mathbf{LY}$$

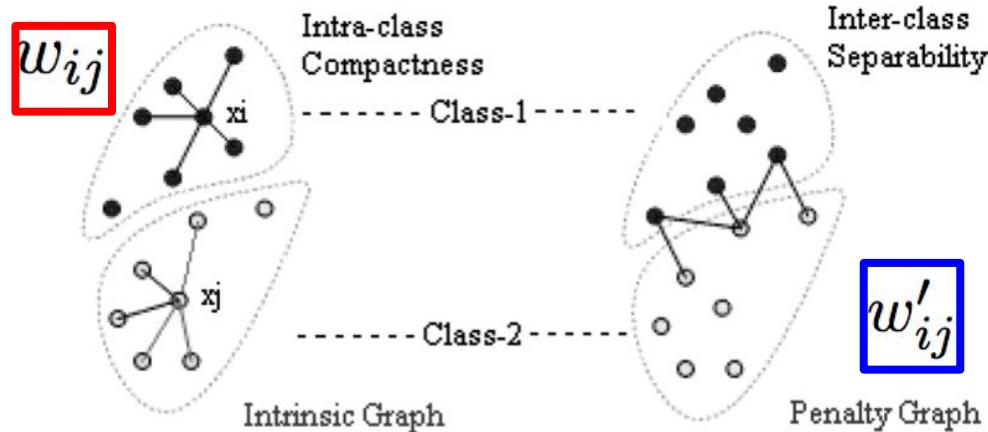
Under the constraint:

Supervised

$$\sum_{i,j} \|\mathbf{y}_i - \mathbf{y}_j\|^2 w'_{ij} = 1$$

Unsupervised

$$\sum_i \|\mathbf{y}_i\|^2 d_{ii} = 1$$



$$d_{ii} = \sum_j w_{ij}$$

Yan et al. *IEEE PAMI* 2007

$$\hat{\mathbf{Y}} = \underset{\mathbf{Y}}{\operatorname{argmin}} \sum_{i,j} w_{ij} \|\mathbf{y}_i - \mathbf{y}_j\|^2 = \underset{\mathbf{Y}}{\operatorname{argmin}} \mathbf{Y}^T \mathbf{LY}$$

Under the constraint:

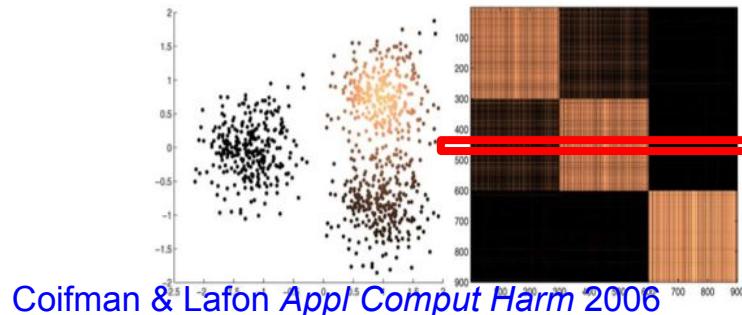
Supervised

$$\sum_{i,j} \|\mathbf{y}_i - \mathbf{y}_j\|^2 w'_{ij} = 1$$

Unsupervised

$$\sum_i \|\mathbf{y}_i\|^2 d_{ii} = 1$$

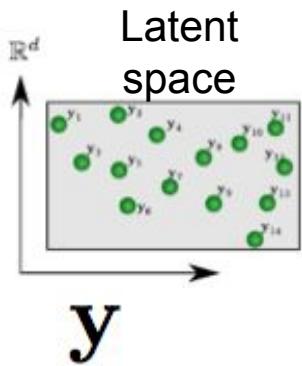
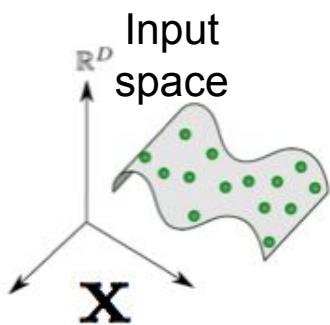
$$d_{ii} = \sum_j w_{ij}$$



Coifman & Lafon *Appl Comput Harm* 2006

Dimensionality reduction:  $D \gg d$

Input space      Latent space



Inputs =

- Single high-dimensional descriptors
- Multiple scalars
- ...or Multiple high-dimensional descriptors

1) Embedding / encoding



3) Reconstruction / decoding = ?

Output =

- Low-dimensional representation

2) Manifold / latent space



x  
↓  
↑  
y

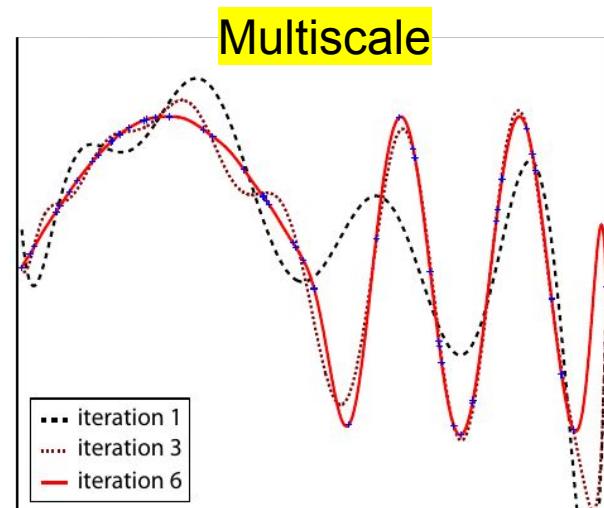
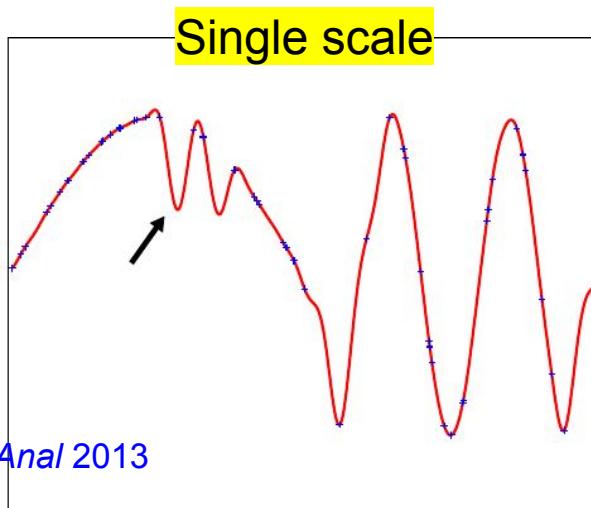
In many cases, no analytical formula !  
= out-of-sample extension / interpolation

ex: **kernel** regression:

- Close to existing samples
- Smooth enough

$$\operatorname{argmin}_f \|f\|_{\mathcal{F}}^2 + \gamma \sum_{i=1}^N \|f(\mathbf{y}) - \mathbf{x}_i\|^2$$

Multiscale version = more robust to density of samples



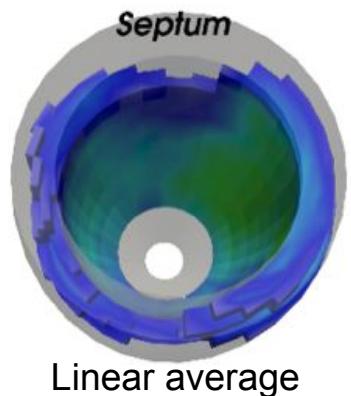
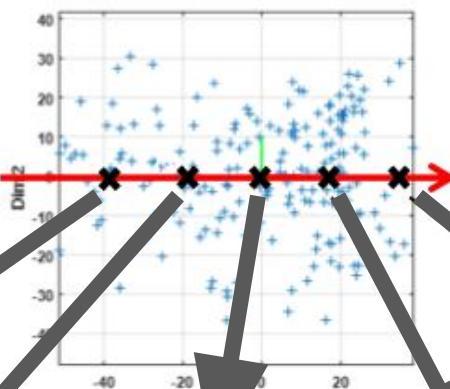
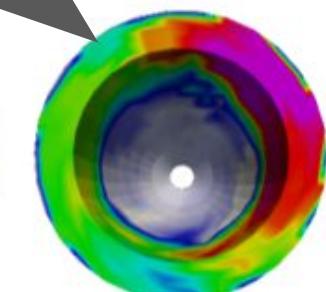
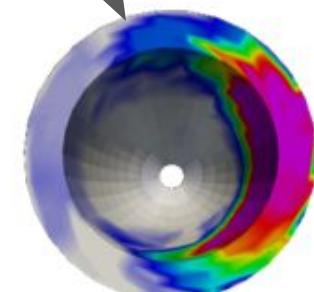
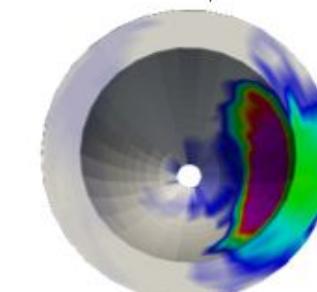
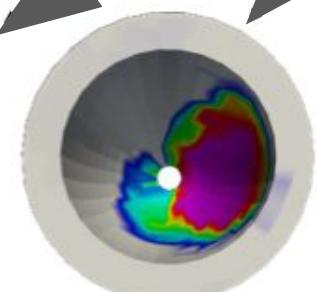
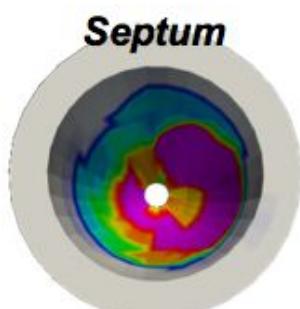
# Reconstruction (a-posteriori)

22

ex: variability in myocardial infarcts

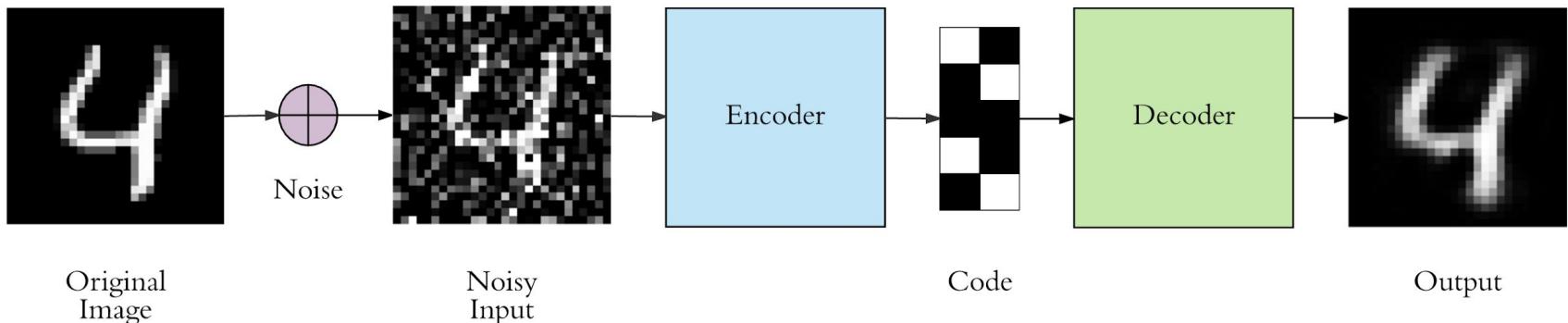
Di Folco et al. CNIV 2019

x  
↓  
↑  
y



## → Autoencoders

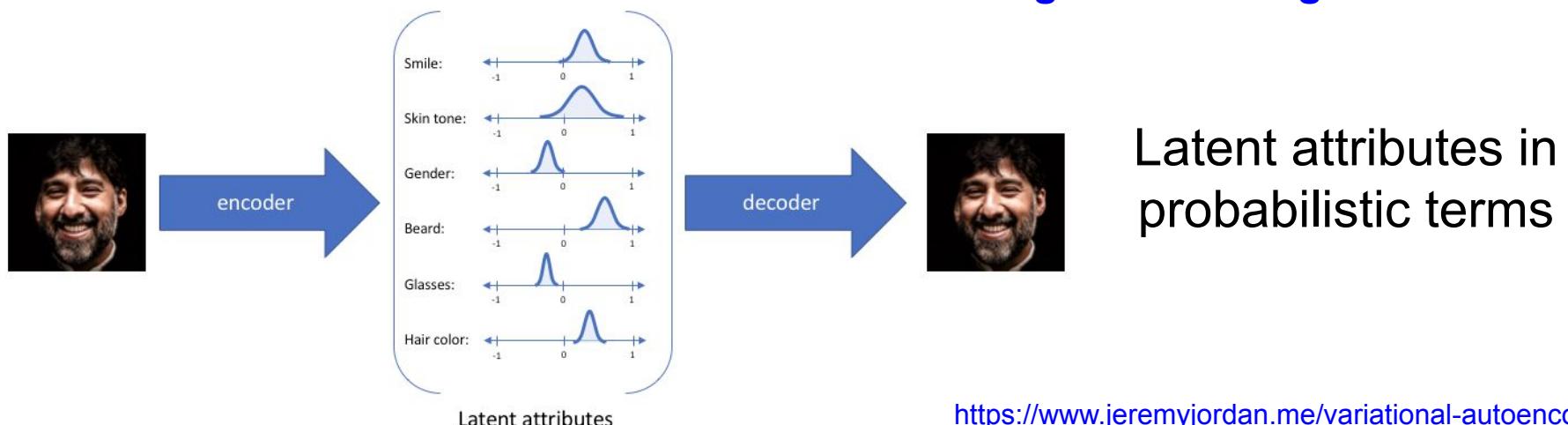
LeCun et al. *PhD* 1987  
Hinton & Zemel *NIPS* 1994



<https://towardsdatascience.com/applied-deep-learning-part-3-autoencoders-1c083af4d798>

## → Variational autoencoders

Kingma & Welling *ICLR* 2014

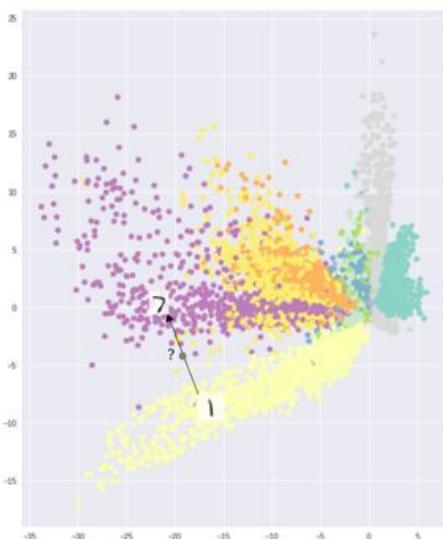


Kingma & Welling *ICLR 2014*

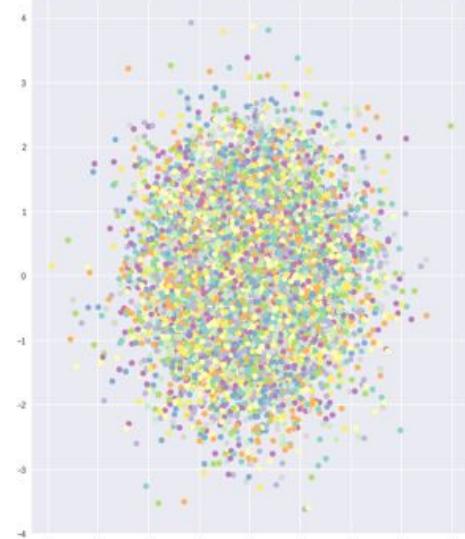
## → Variational autoencoders

$$\mathcal{L}(x, \hat{x}) + \sum_j KL(q_j(z|x) || p(z))$$

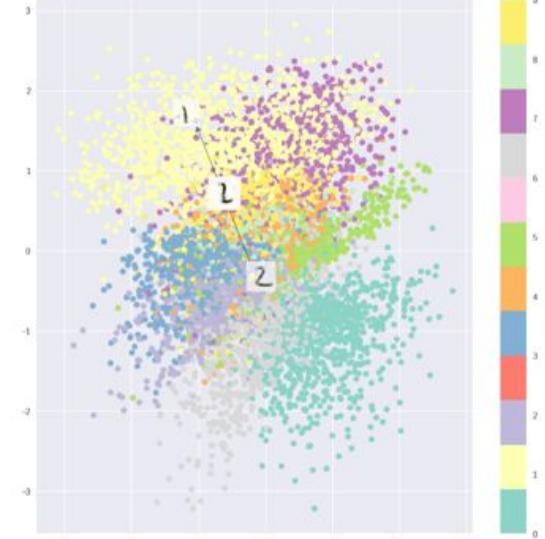
Only reconstruction loss



Only KL divergence



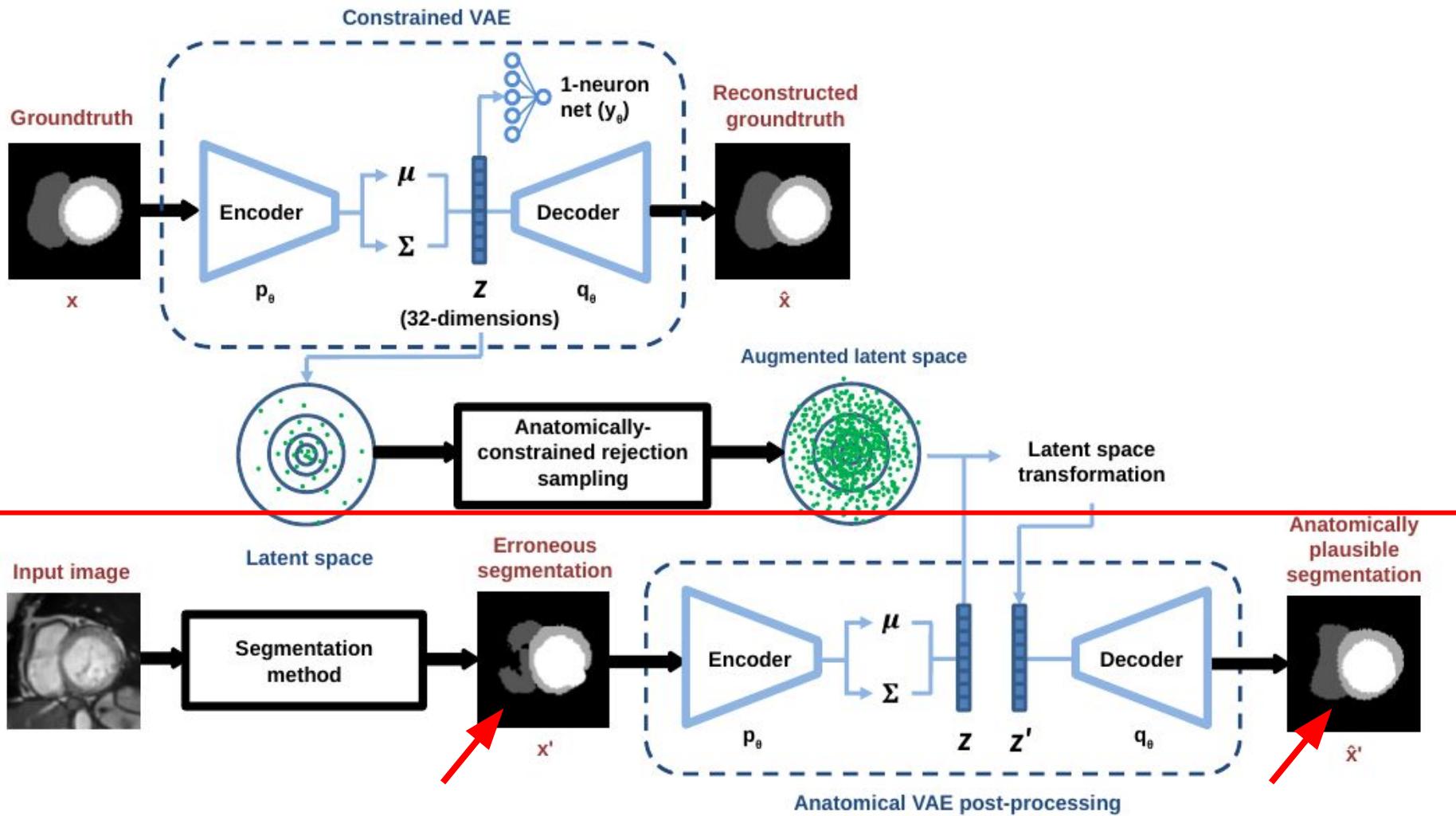
Combination



ex: variational autoencoders

## Anatomical consistency ?

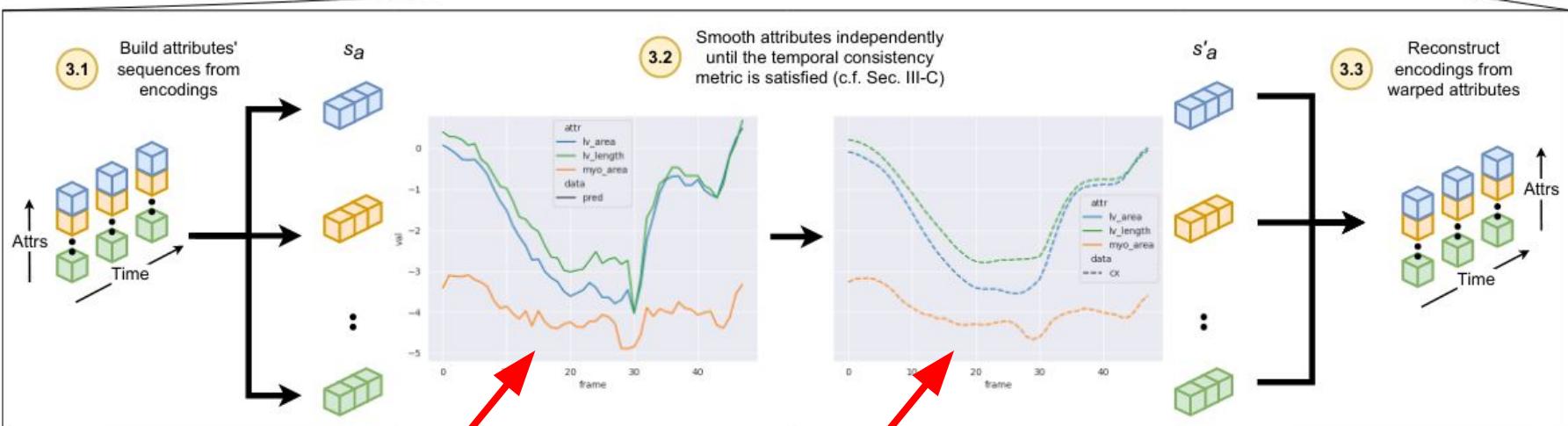
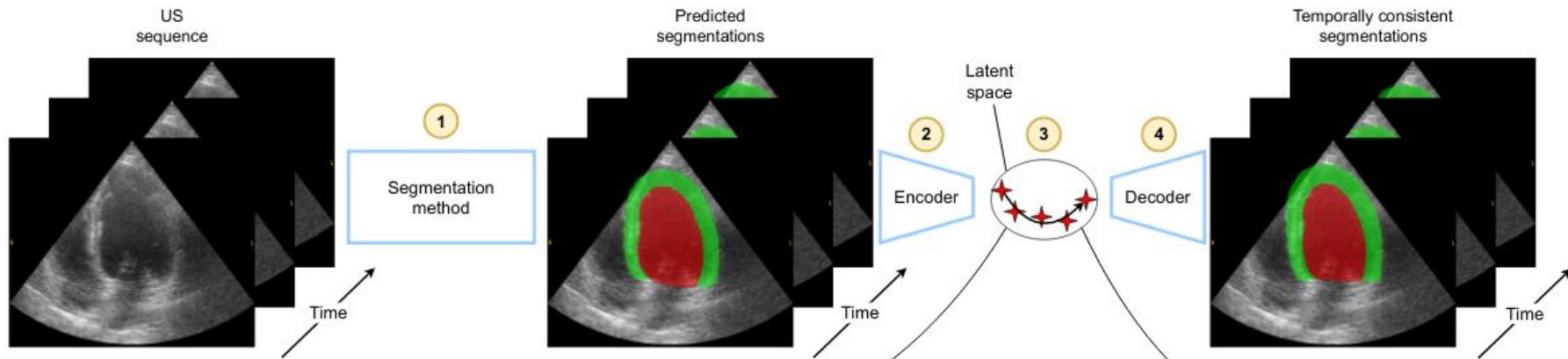
Painchaud et al. IEEE TMI 2020



ex: variational autoencoders

Temporal consistency ?

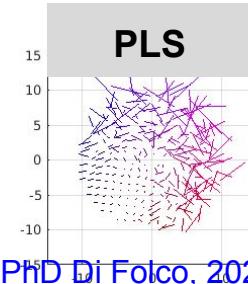
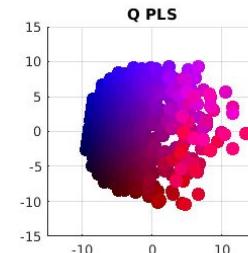
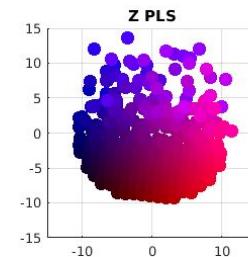
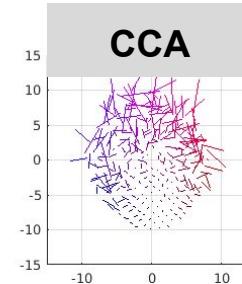
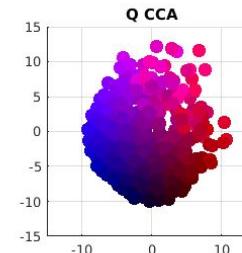
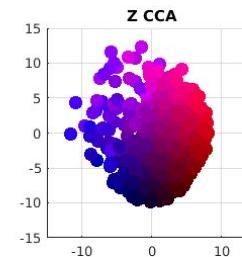
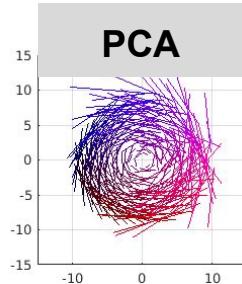
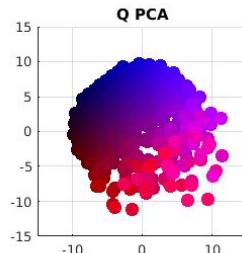
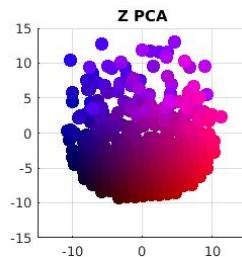
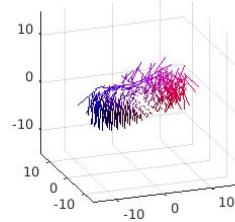
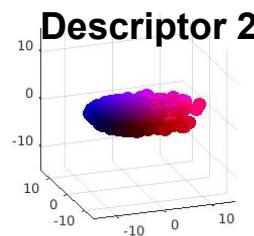
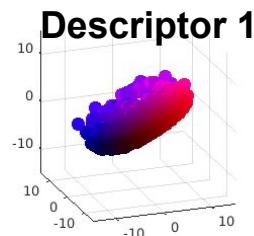
Painchaud et al. arXiv 2021



# Multiple descriptors

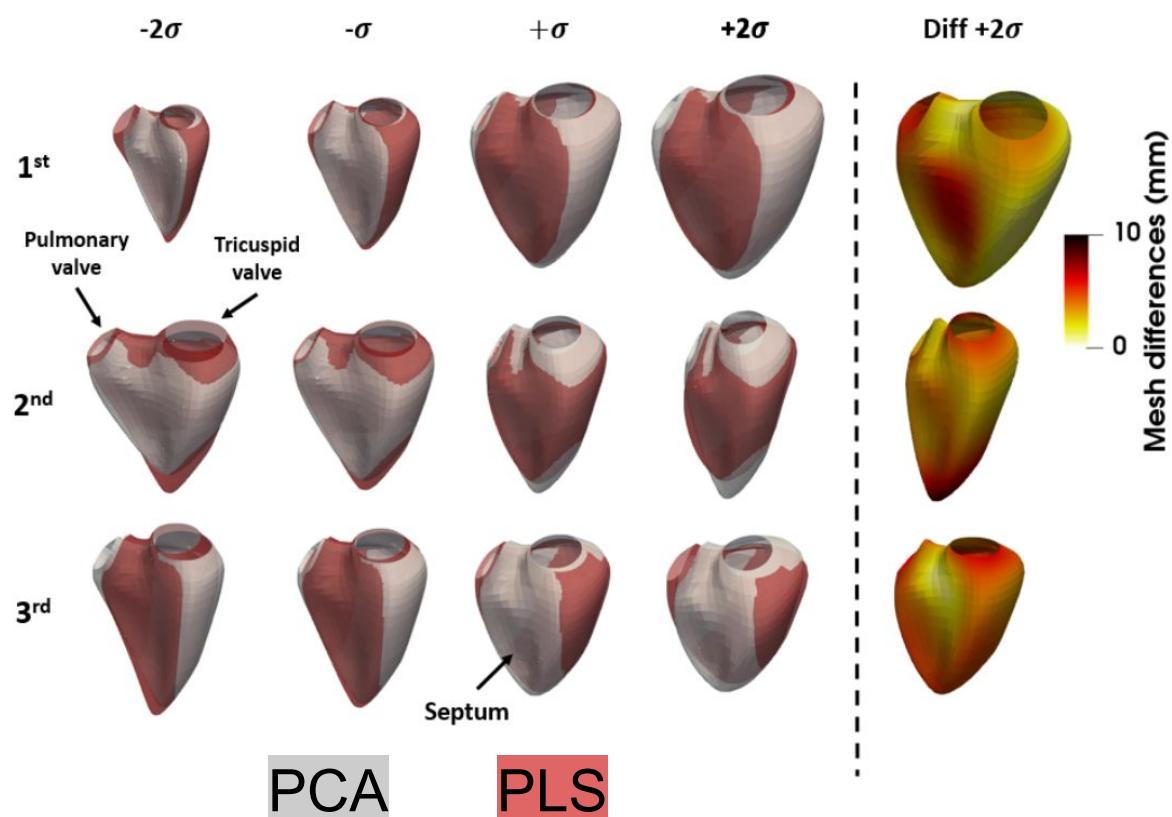
27

		Nb descriptors	Maximizes...	
<b>Principal Component Analysis</b>	PCA	1	Variance	
<b>Partial Least Squares</b>	PLS	2+	Covariance	Wold et al. <i>Chemo</i> 1984
<b>Canonical Correlation Analysis</b>	CCA	2+	Correlation	Hotelling <i>Biometr</i> 1936



		Nb descriptors	Maximizes...	
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<b>Canonical Correlation Analysis</b>	CCA	2+	Correlation	Hotelling <i>Biometr</i> 1936

Strong differences  
in disease-relevant  
zones !



- Interesting extensions of “standard” manifold learning:
  - **Multiple kernel learning (MKL)** Lin et al. *PAMI* 2011  
with Sergio Sanchez + Gemma Piella (UPF Barcelona)
  - **Manifold alignment** Ham et al. *AISTATS* 2005 + Clough et al. *PAMI* 2020
  - **Multiple manifold learning (MML)** Valencia et al. *CIARP* 2011 + Lee et al. *Patt Rec* 2016  
with Maxime Di Folco (CREATIS)
  - **Similarity network fusion (SNF)** Wang et al. *CVPR* 2012 + *Nat Meth* 2014

- Interesting extensions of variational auto-encoders:
  - **Multi-channel VAE** Antelmi et al. *PMLR* 2019

Idea = mixing kernels

How to mix  
heterogeneous data ?

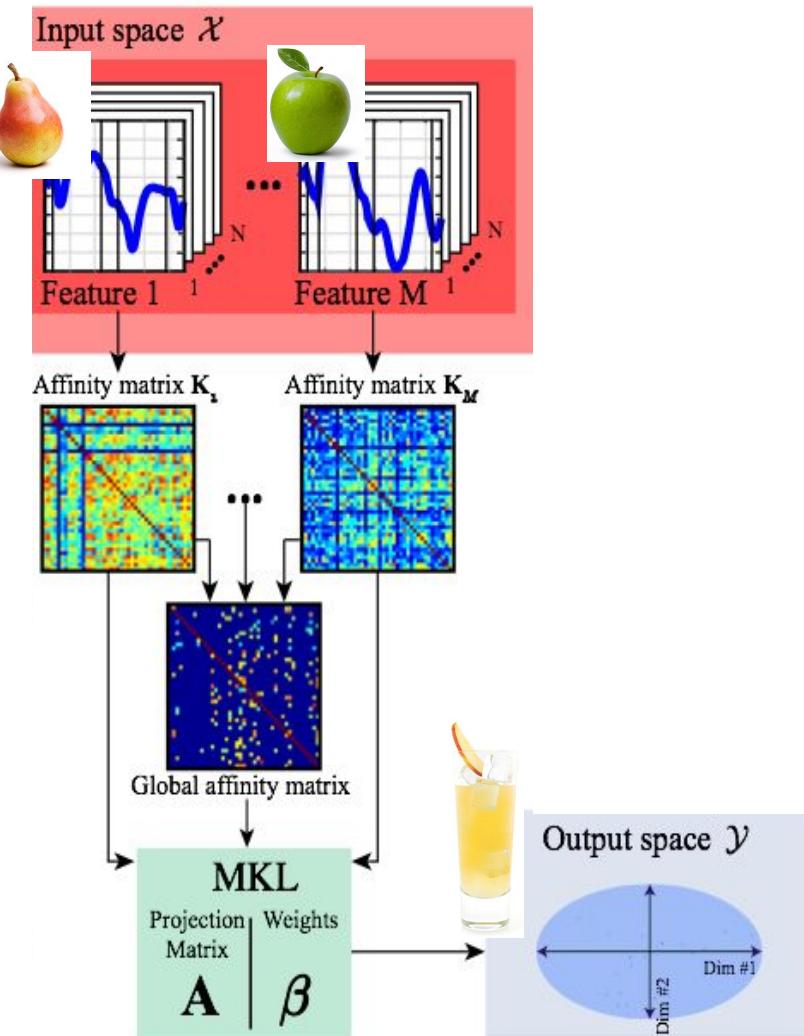


Normalization  
+ concatenation



Kernels

Lin et al. *IEEE PAMI* 2011  
Sanchez et al. *Med Image Anal* 2017



Linear, 1 descriptor:  $y_i = \mathbf{v}^t \mathbf{x}_i$

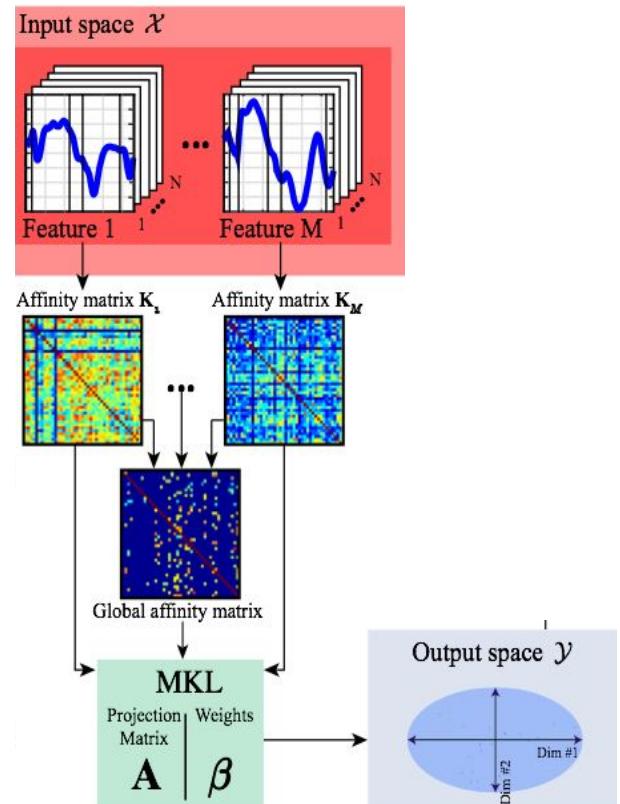
$$\hat{\mathbf{v}} = \underset{\mathbf{Y}^t \mathbf{B} \mathbf{Y} = \delta}{\operatorname{argmin}} \sum_{i,j} \|\mathbf{v}^t \mathbf{x}_i - \mathbf{v}^t \mathbf{x}_j\|^2 w_{ij} = \underset{\mathbf{Y}^t \mathbf{B} \mathbf{Y} = \delta}{\operatorname{argmin}} \mathbf{v}^t \mathbf{X} \mathbf{L} \mathbf{X}^t \mathbf{v}$$

Non-linear, multiple descriptors:

$$\underset{\boxed{\mathbf{A}, \beta}}{\operatorname{argmin}} \sum_{i,j=1}^N \|\mathbf{A}^t \mathbb{K}^{(i)} \beta - \mathbf{A}^t \mathbb{K}^{(j)} \beta\|^2 w_{ij}$$

Lin et al. *IEEE PAMI* 2011

Sanchez et al. *Med Image Anal* 2017



Linear, 1 descriptor:  $y_i = \mathbf{v}^t \mathbf{x}_i$

$$\hat{\mathbf{v}} = \operatorname{argmin}_{\mathbf{Y}^t \mathbf{B} \mathbf{Y} = \delta} \sum_{i,j} \|\mathbf{v}^t \mathbf{x}_i - \mathbf{v}^t \mathbf{x}_j\|^2 w_{ij} = \operatorname{argmin}_{\mathbf{Y}^t \mathbf{B} \mathbf{Y} = \delta} \mathbf{v}^t \mathbf{X} \mathbf{L} \mathbf{X}^t \mathbf{v}$$

Non-linear, multiple descriptors:

$$\operatorname{argmin}_{\boxed{\mathbf{A}, \beta}} \sum_{i,j=1}^N \|\mathbf{A}^t \mathbb{K}^{(i)} \beta - \mathbf{A}^t \mathbb{K}^{(j)} \beta\|^2 w_{ij}$$

In practice: alternate optimization

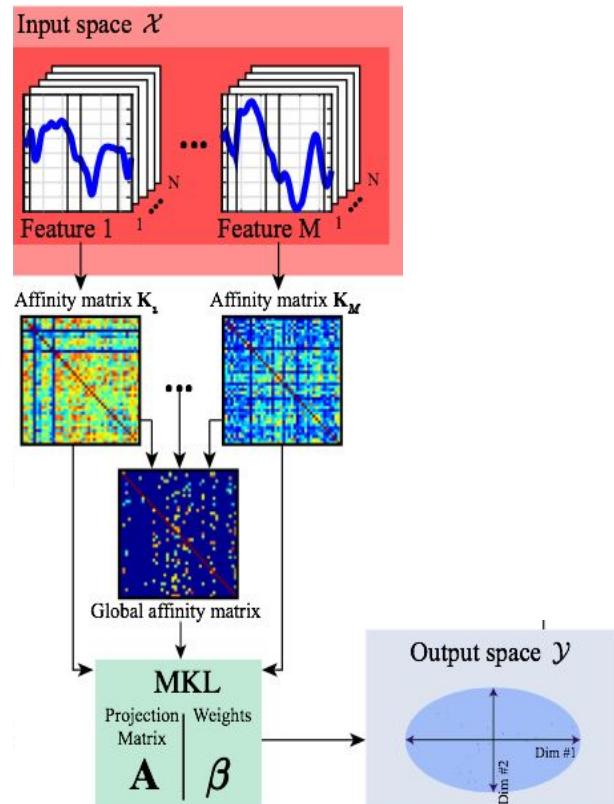
1. Fix  $\mathbf{A}$  and optimize  $\beta$

= solving a trace-ratio problem

2. Fix  $\beta$  and optimize  $\mathbf{A}$

= not anymore a generalized eigenvalue problem due to  $\beta_m \geq 0$   
 Problem: non-convex, hard to solve  
 > Can be relaxed and solved by semidefinite programming

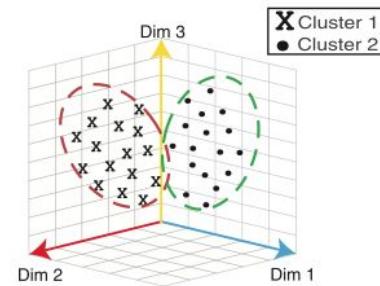
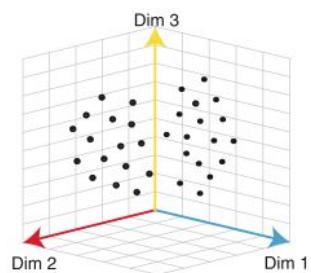
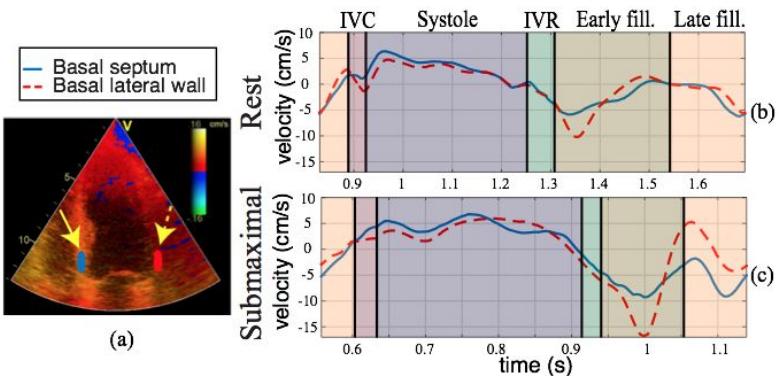
Lin et al. *IEEE PAMI* 2011  
 Sanchez et al. *Med Image Anal* 2017



# Multiple kernel learning (fusion)

34

ex: Heart Failure with Preserved Ejection Fraction (HFpEF)



Sanchez et al. *Med Image Anal* 2017  
Sanchez et al. *Circ-Imaging* 2018

Why unsupervised?

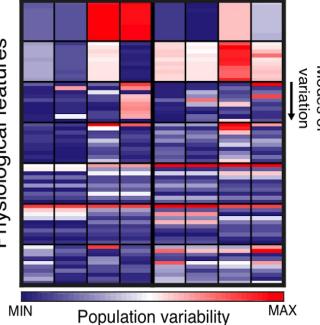
Continuum from normal to diseased

/ no trust in the [normal/HFPEF] labels

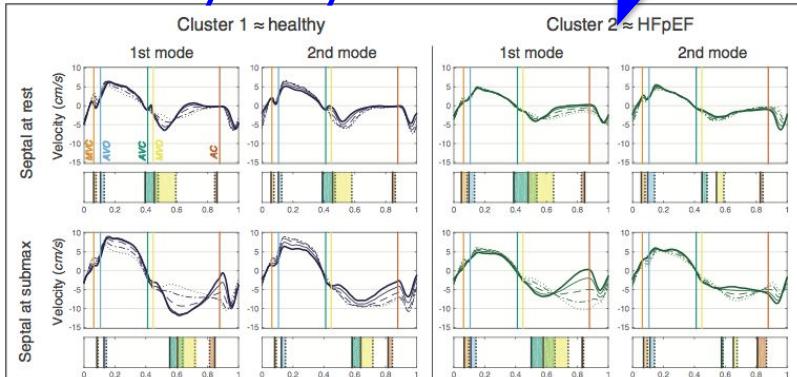
## Phenotyping

Input descriptors

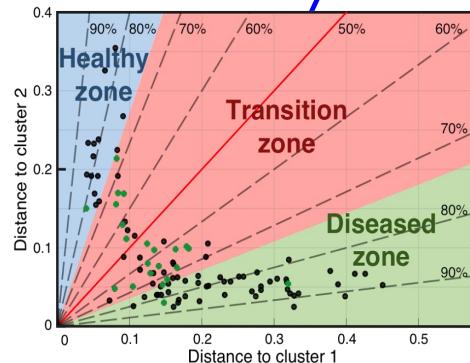
Group 1 (healthy) Group 2 (diseased)



## Variability analysis



## Risk analysis

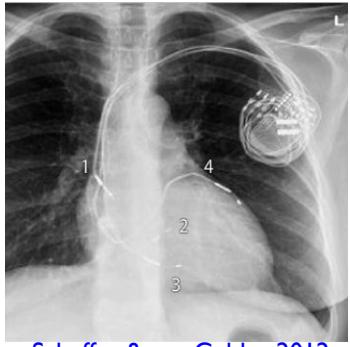


# Multiple kernel learning (fusion)

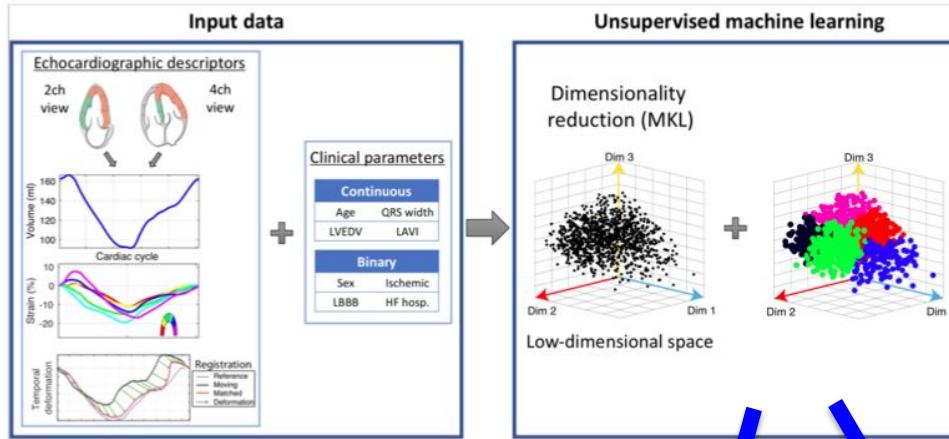
35

ex: Cardiac Resynchronization Therapy (CRT)

Cikes et al. Eur J Heart Fail 2019



Scheffer & van Gelder 2012

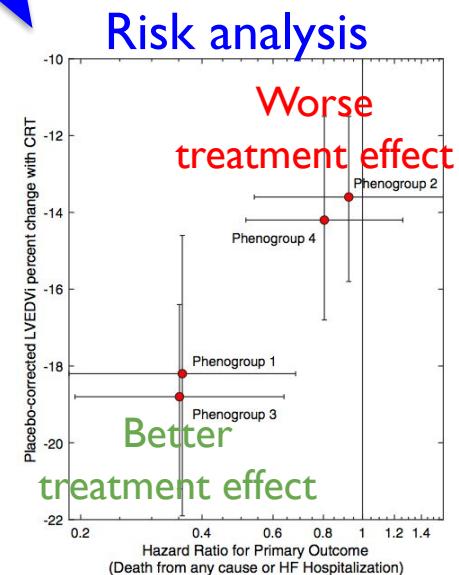
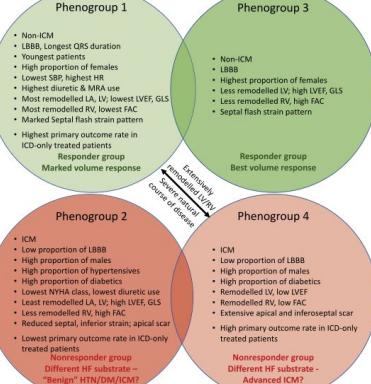


Why unsupervised?

30% of non-responders with current selection

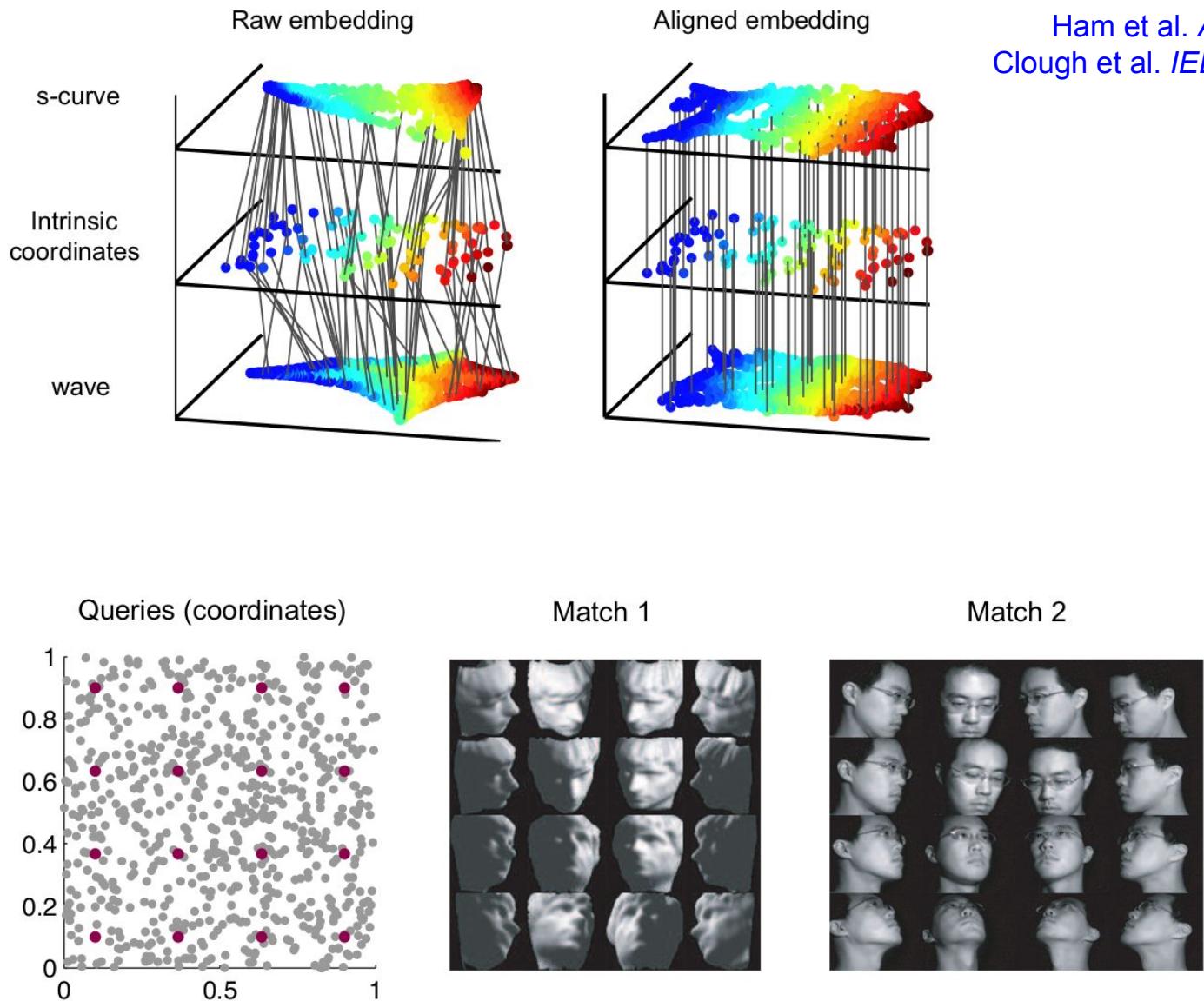
+ Limits of supervised formulation

Phenotyping



# Multiple manifold learning (alignment)

36



Ham et al. AISTATS 2005  
Clough et al. IEEE PAMI 2020

Ham et al. AISTATS 2005  
Clough et al. IEEE PAMI 2020

$$\text{tr}(\mathbf{Y}^T \mathbf{L}_A \mathbf{Y}) = \sum_{i,j=1}^K \|\mathbf{y}_i^{(1)} - \mathbf{y}_j^{(1)}\|^2 W_{ij}^{(1)} + \sum_{i,j=1}^K \|\mathbf{y}_i^{(2)} - \mathbf{y}_j^{(2)}\|^2 W_{ij}^{(2)} + \mu \sum_{i,j=1}^K \|\mathbf{y}_i^{(1)} - \mathbf{y}_j^{(2)}\|^2 M_{ij}$$

$$\mathbf{L}_A = \mathbf{D}_A - \mathbf{A} \quad \text{with}$$

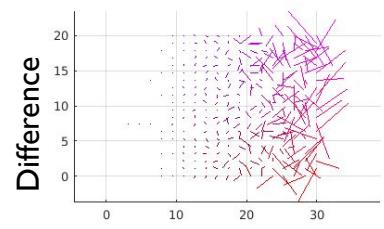
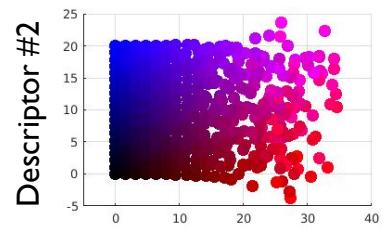
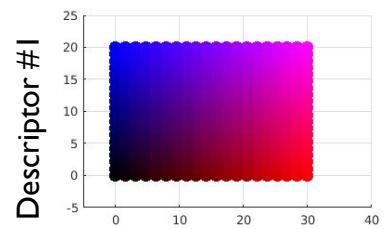
$$\mathbf{A} = \left[ \begin{array}{c|c} \mathbf{W}^{(1)} & \mu \mathbf{M} \\ \hline \mu \mathbf{M}^T & \mathbf{W}^{(2)} \end{array} \right]$$

$$\text{and } \mathbf{D}_A = \begin{bmatrix} \ddots & & 0 \\ & \sum_{j=1}^K A_{ij} & \\ 0 & & \ddots \end{bmatrix}$$

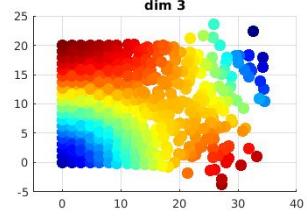
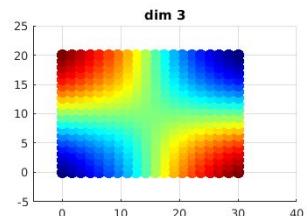
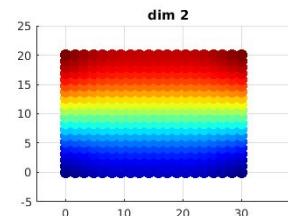
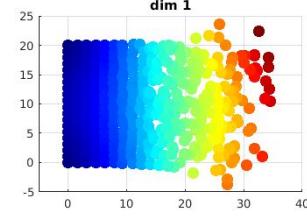
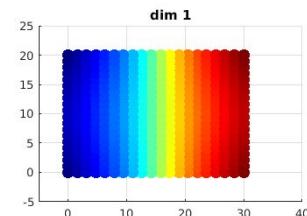
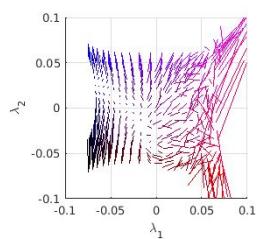
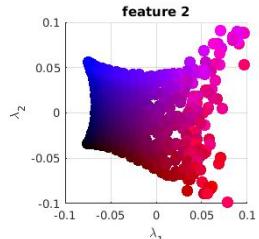
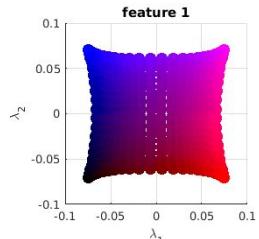
In practice:  $\mathbf{M}$  sparse

Specific case:  $\mathbf{M} = \mathbf{I}$   
= pairwise alignment

Input (high dimensional) data



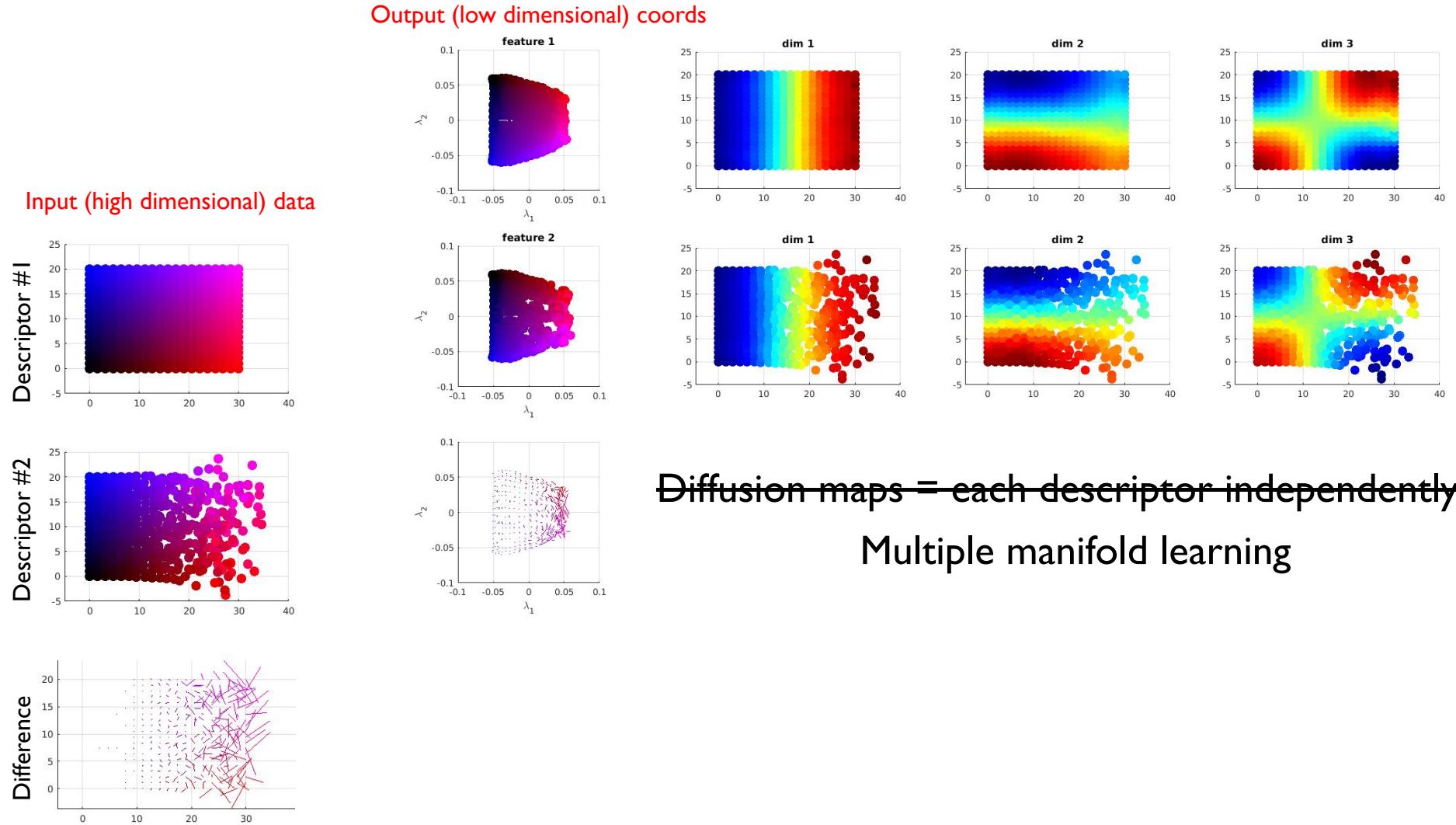
Output (low dimensional) coords



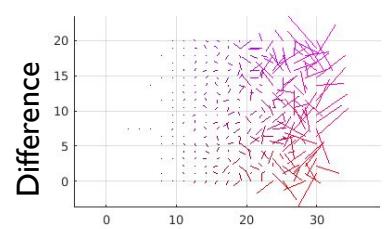
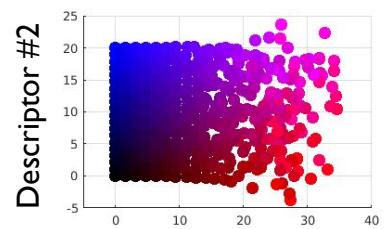
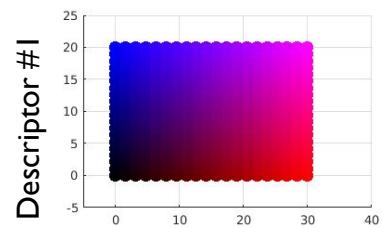
Diffusion maps = each descriptor independently

# Multiple manifold learning (alignment)

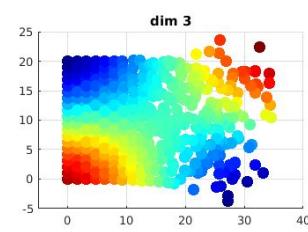
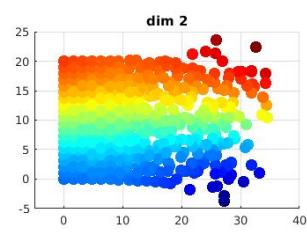
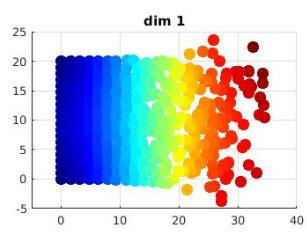
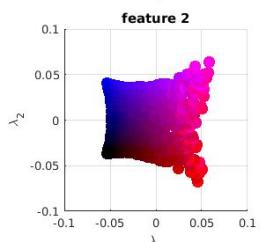
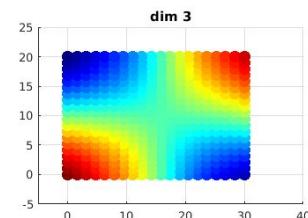
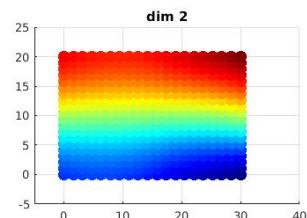
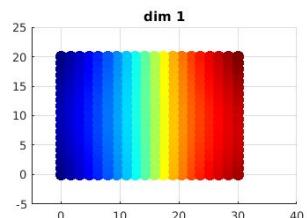
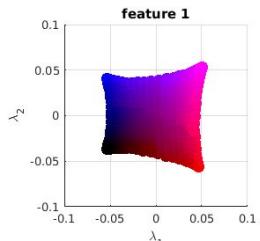
39



Input (high dimensional) data



Output (low dimensional) coords



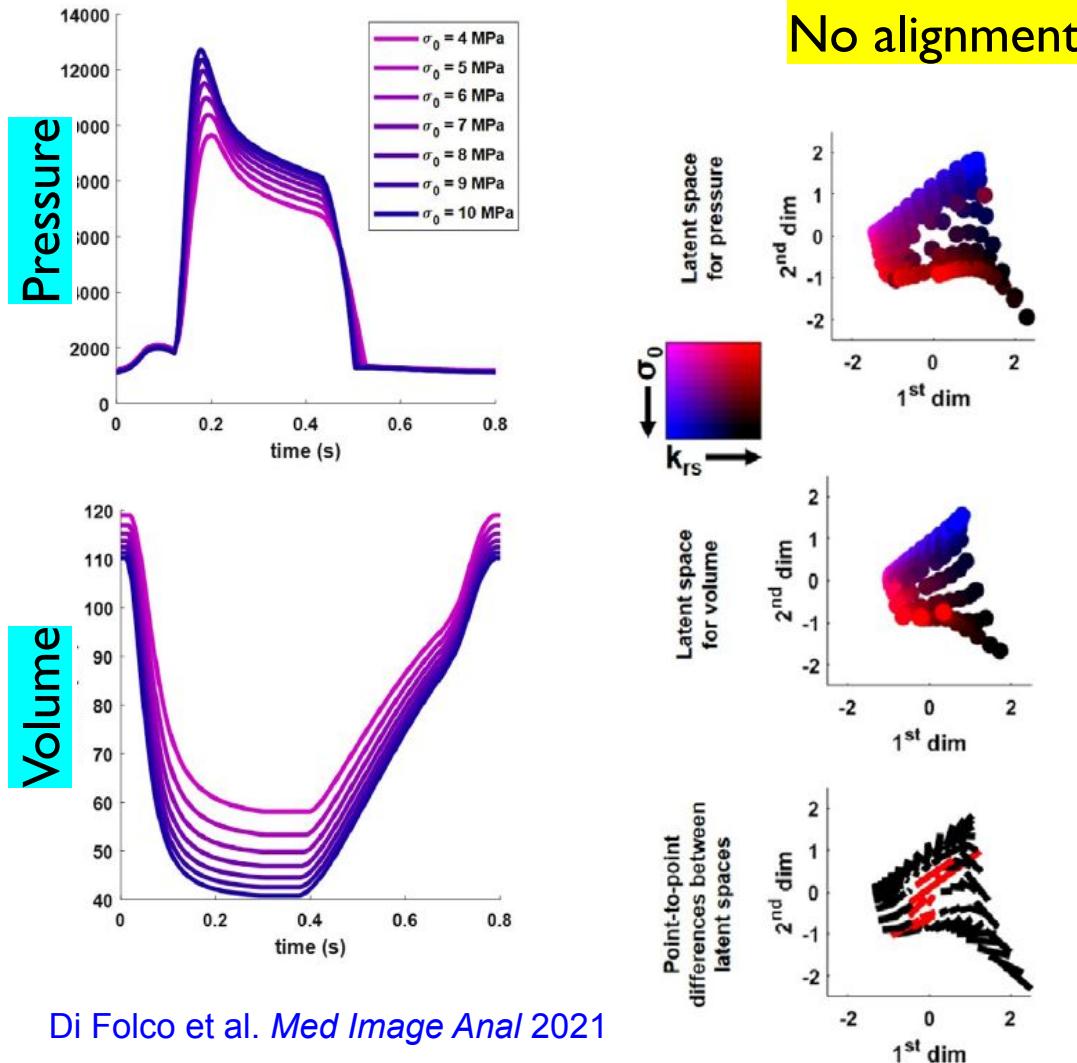
~~Diffusion maps = each descriptor independently~~

~~Multiple manifold learning~~

Concatenated descriptors (= ground truth)

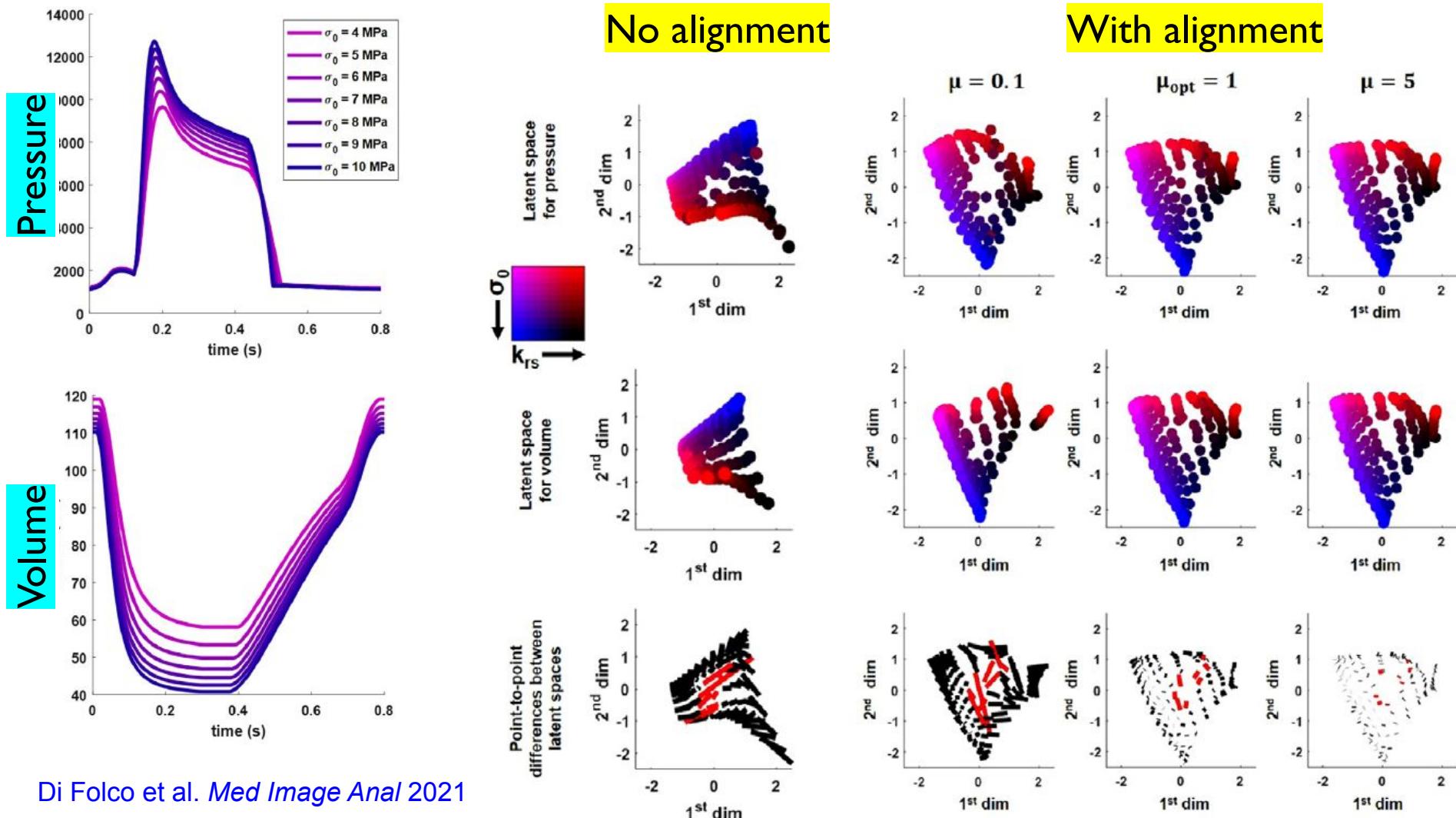
## ex: synthetic data

- 0D model = pressure + volume (Mollero et al. Biomech Model Mechanobiol 2018)
- deteriorated link on some samples



## ex: synthetic data

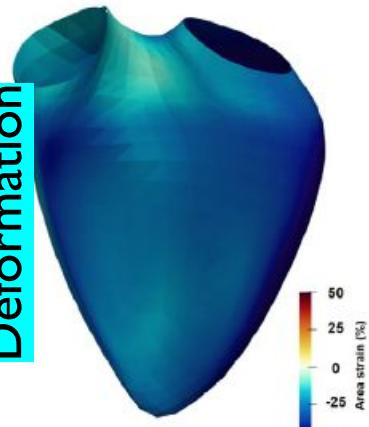
- 0D model = pressure + volume (Mollero et al. Biomech Model Mechanobiol 2018)
- deteriorated link on some samples



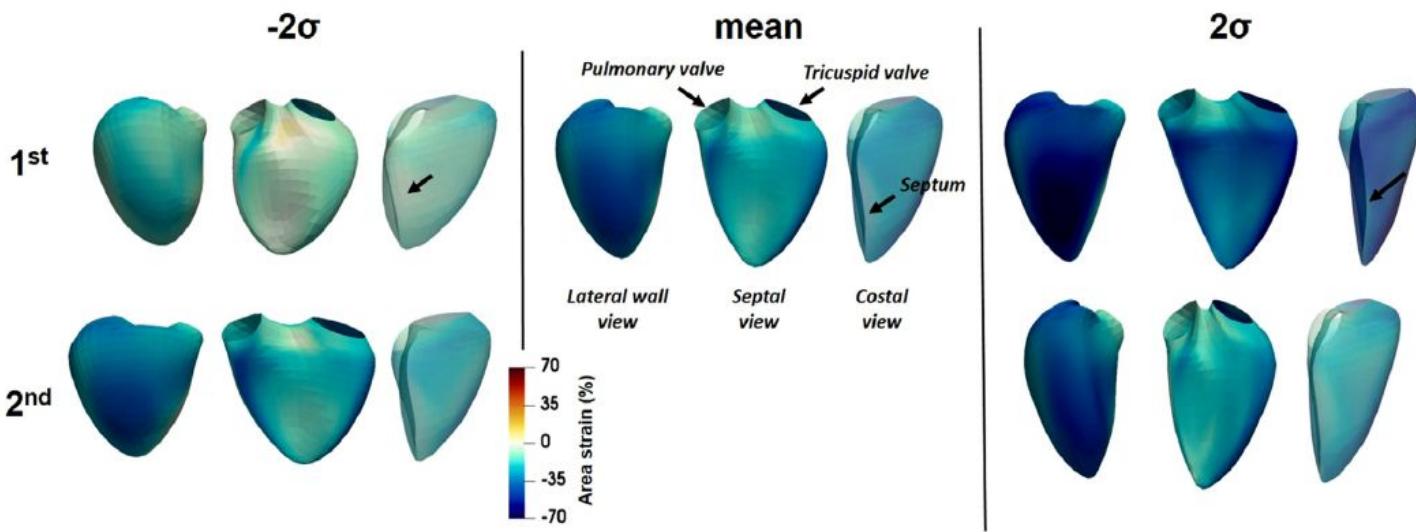
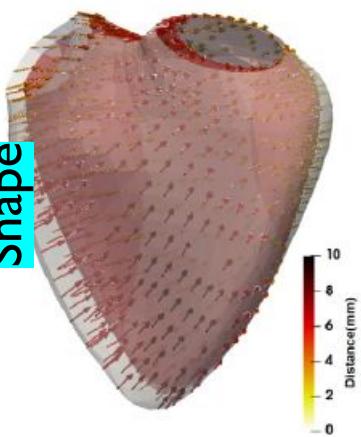
## ex: real data

- 3D RV meshes (Moceri et al. *Eur Heart J Cardiovasc Imaging* 2018, 2020)
- Varying shape/deformation interactions depending on disease

Deformation



Shape



- Consistent shape/deformation patterns
- Fusion vs. alignment
- “Pairwise” vs. “relaxed” alignment

# Similarity network fusion

Idea = non-linear fusion (iterative cross-diffusion until...)

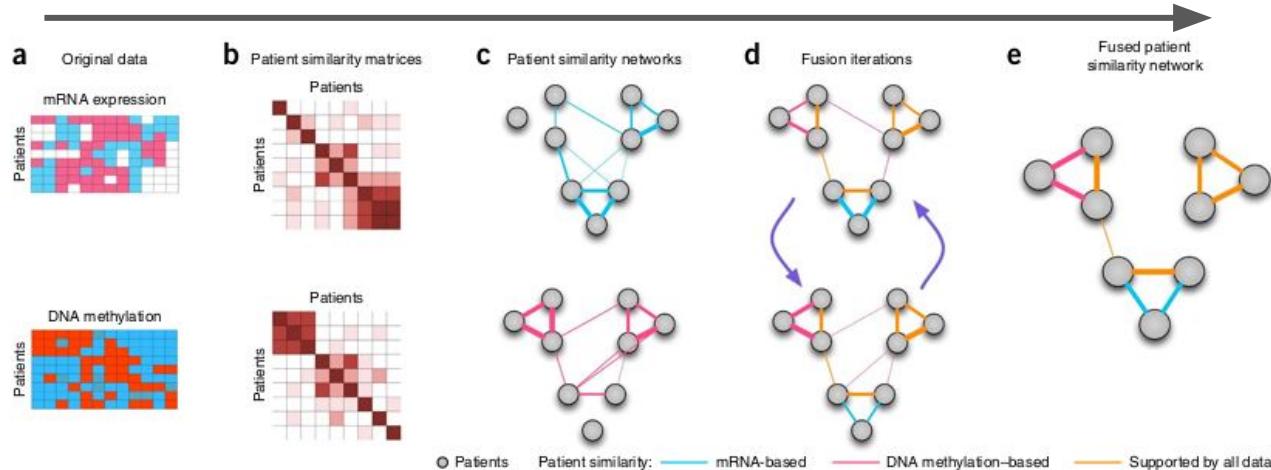
$$\mathbf{P}_{t+1}^{(1)} = \mathbf{S}^{(1)} \times \mathbf{P}_t^{(2)} \times (\mathbf{S}^{(1)})^T$$

$$\mathbf{P}_{t+1}^{(2)} = \mathbf{S}^{(2)} \times \mathbf{P}_t^{(1)} \times (\mathbf{S}^{(2)})^T$$

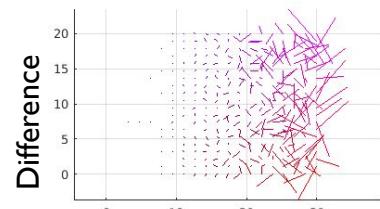
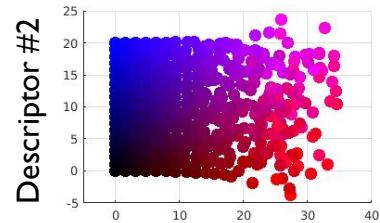
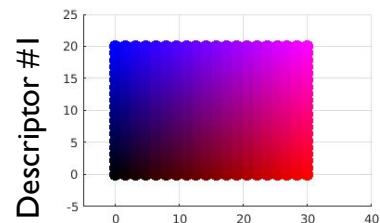
$$\mathbf{P}(i,j) = \begin{cases} \frac{\mathbf{W}(i,j)}{2\sum_{k \neq i} \mathbf{W}(i,k)}, & j \neq i \\ 1/2, & j = i \end{cases}$$

$$\mathbf{S}(i,j) = \begin{cases} \frac{\mathbf{W}(i,j)}{\sum_{k \in N_i} \mathbf{W}(i,k)}, & j \in N_i \\ 0 & \text{otherwise} \end{cases}$$

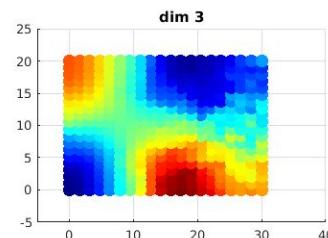
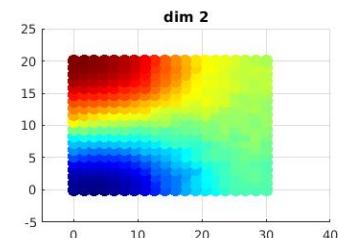
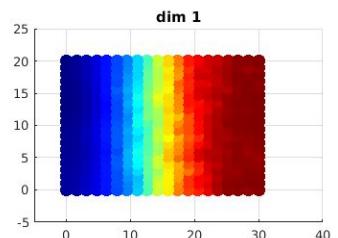
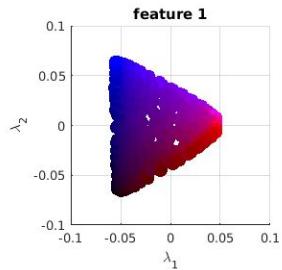
Wang et al. CVPR 2012  
Wang et al. Nat Meth 2014



Input (high dimensional) data



Output (low dimensional) coords



Similarity network fusion

$$\mathbf{x} = \{\mathbf{x}_1, \dots, \mathbf{x}_C\}$$

Multiple channels

Latent space:

$$\mathbf{z} \sim p(\mathbf{z}),$$

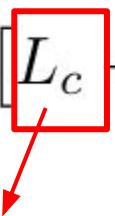
$$\mathbf{x}_c \sim p(\mathbf{x}_c | \mathbf{z}, \boldsymbol{\theta}_c),$$

Antelmi et al. *PMLR 2019*

$$\mathcal{L}(\boldsymbol{\theta}, \boldsymbol{\phi}, \mathbf{x}) = \mathbb{E}_c [ L_c - \boxed{\mathcal{D}_{KL}(q(\mathbf{z} | \mathbf{x}_c, \boldsymbol{\phi}_c) || p(\mathbf{z}))} ]$$

Fit to distribution

Reconstruction error



$$\mathbb{E}_{q(\mathbf{z} | \mathbf{x}_c, \boldsymbol{\phi}_c)} \sum_{i=1}^C \ln p(\mathbf{x}_i | \mathbf{z}, \boldsymbol{\theta}_i)$$

$$\mathbf{x} = \{\mathbf{x}_1, \dots, \mathbf{x}_C\}$$

Multiple channels

Latent space:

$$\mathbf{z} \sim p(\mathbf{z}),$$

$$\mathbf{x}_c \sim p(\mathbf{x}_c | \mathbf{z}, \theta_c),$$

Antelmi et al. PMLR 2019

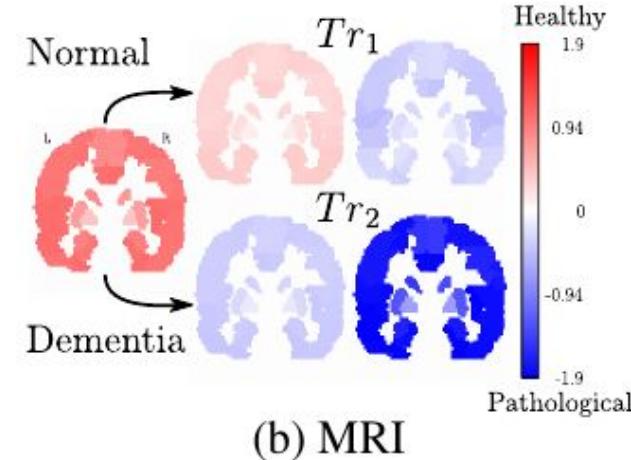
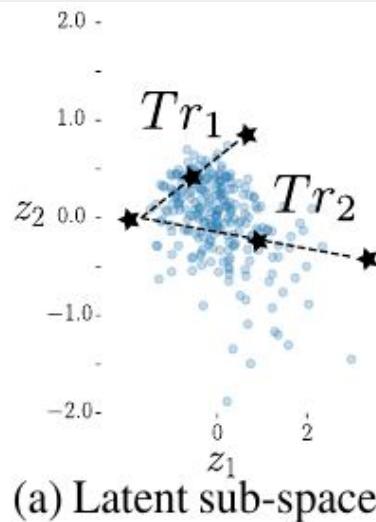
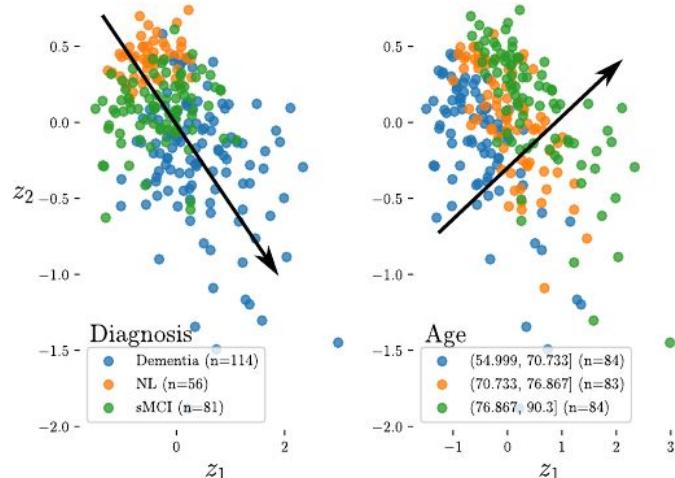
$$\mathcal{L}(\theta, \phi, \mathbf{x}) = \mathbb{E}_c [L_c - \text{Fit to distribution}]$$

$$- \mathbb{E}_{q(\mathbf{z}|\mathbf{x}_c, \phi_c)} \sum_{i=1}^C \ln p(\mathbf{x}_i | \mathbf{z}, \theta_i)$$

Reconstruction error

1 clinical channel (6 scalar variables)

+ 3 imaging channels (structural = MRI, functional = FDG-PET + Amyloid-PET)

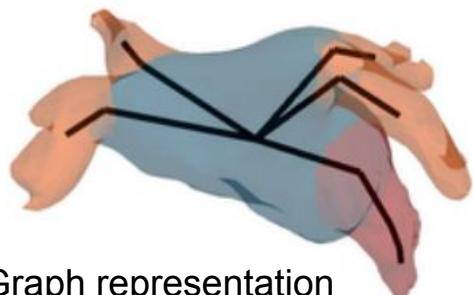


## Interesting extension: meta-learning for heterogeneous datasets

Harrison et al. MICCAI 2021

Reconstruction error = on labels !

$$\mathcal{L}(x, y, \theta, \phi) = \frac{1}{N} \sum_{k=1}^N \mathbb{E}_{z \sim q_{\phi_k}(z|x_k, y_k)} \left[ \sum_{k=1}^N \ln p_{\theta}(y_k|z, x_k) \right] - \mathcal{D}_{KL}[q_{\phi_k}(z|x_k, y_k) || p_{\theta}(z|x)]$$

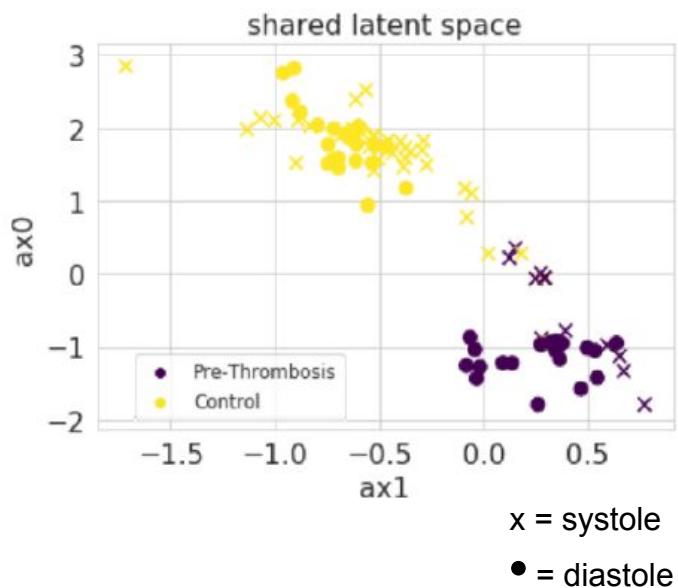
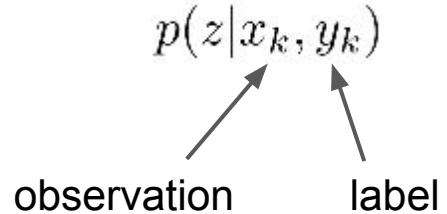


Graph representation  
of the left atrium

Datasets:

$$D = \{D_k\}_{k=1}^N$$

Single latent space:



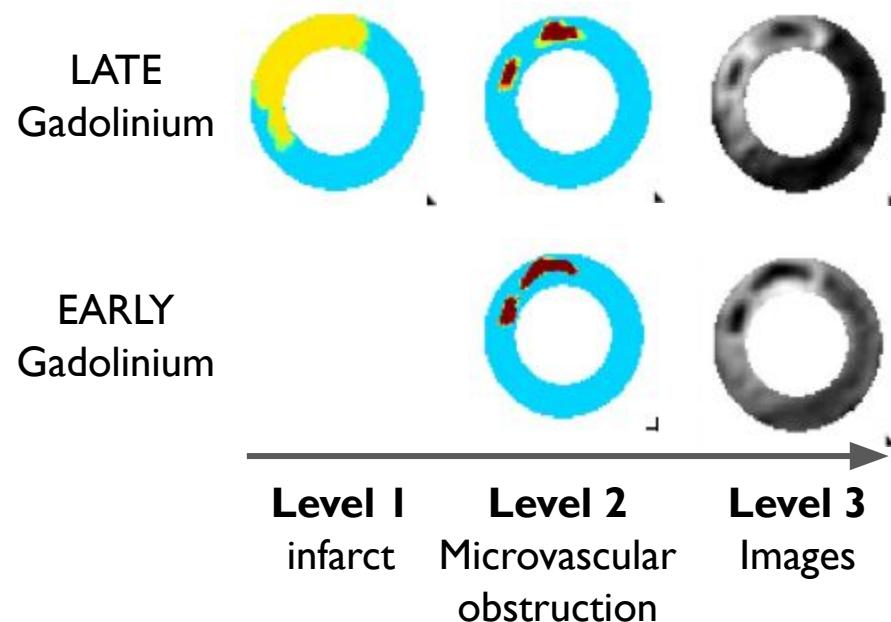
- Interesting extensions of “standard” manifold learning:
  - **Multiple kernel learning (MKL)** Lin et al. *PAMI* 2011  
with Sergio Sanchez + Gemma Piella (UPF Barcelona)
  - **Manifold alignment** Ham et al. *AISTATS* 2005 + Clough et al. *PAMI* 2020
  - **Multiple manifold learning (MML)** Valencia et al. *CIARP* 2011 + Lee et al. *Patt Rec* 2016  
with Maxime Di Folco (CREATIS)
  - **Similarity network fusion (SNF)** Wang et al. *CVPR* 2012 + *Nat Meth* 2014

- Interesting extensions of variational auto-encoders:
  - **Multi-channel VAE** Antelmi et al. *PMLR* 2019

→ **What about not merging all data at once ?**

# Imposed data hierarchy

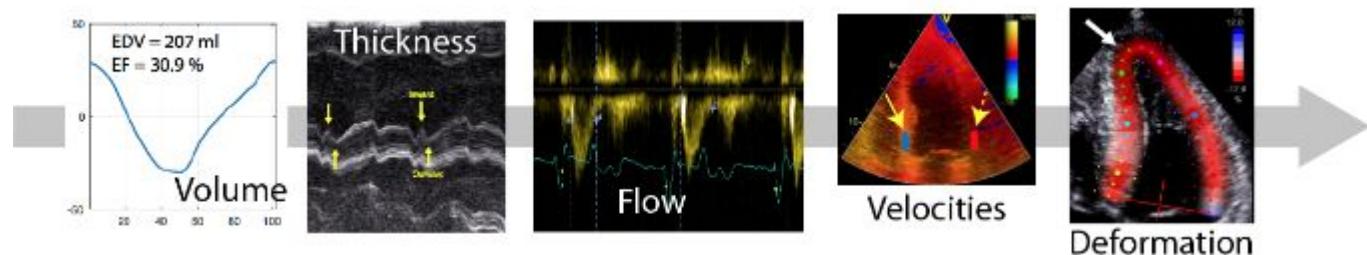
50



**Ischemia-reperfusion with MRI:**  
→ Value of non-truncated images ?

PhD of B. Freiche (CREATIS)

**Imaging protocol:**  
→ Which acquisition is recommended next ?



Postdoc of G. Bernardino (CREATIS)

Zhou et al. *Knowl Based Syst* 2019

$$\min_{\mathbf{K}_b^{(1)}, \dots, \mathbf{K}_b^{(m)}, \mathbf{K}^{(t)}} \sum_{i=1}^m \|\mathbf{K}^{(t)} - \mathbf{K}_b^{(i)}\|_F^2 + \|\mathbf{K}^{(t)} - \mathbf{K}_c^{(t)}\|_F^2$$

Evolution of consensus kernel

$$+ \lambda_1 \sum_{i=1}^m \|\mathbf{K}_b^{(i)} - \hat{\mathbf{K}}_b^{(i)}\|_F^2$$

Evolution of base kernels

$$+ \lambda_2 \left( \text{rank}(\mathbf{K}^{(t)}) + \sum_{i=1}^m \text{rank}(\mathbf{K}_b^{(i)}) \right),$$

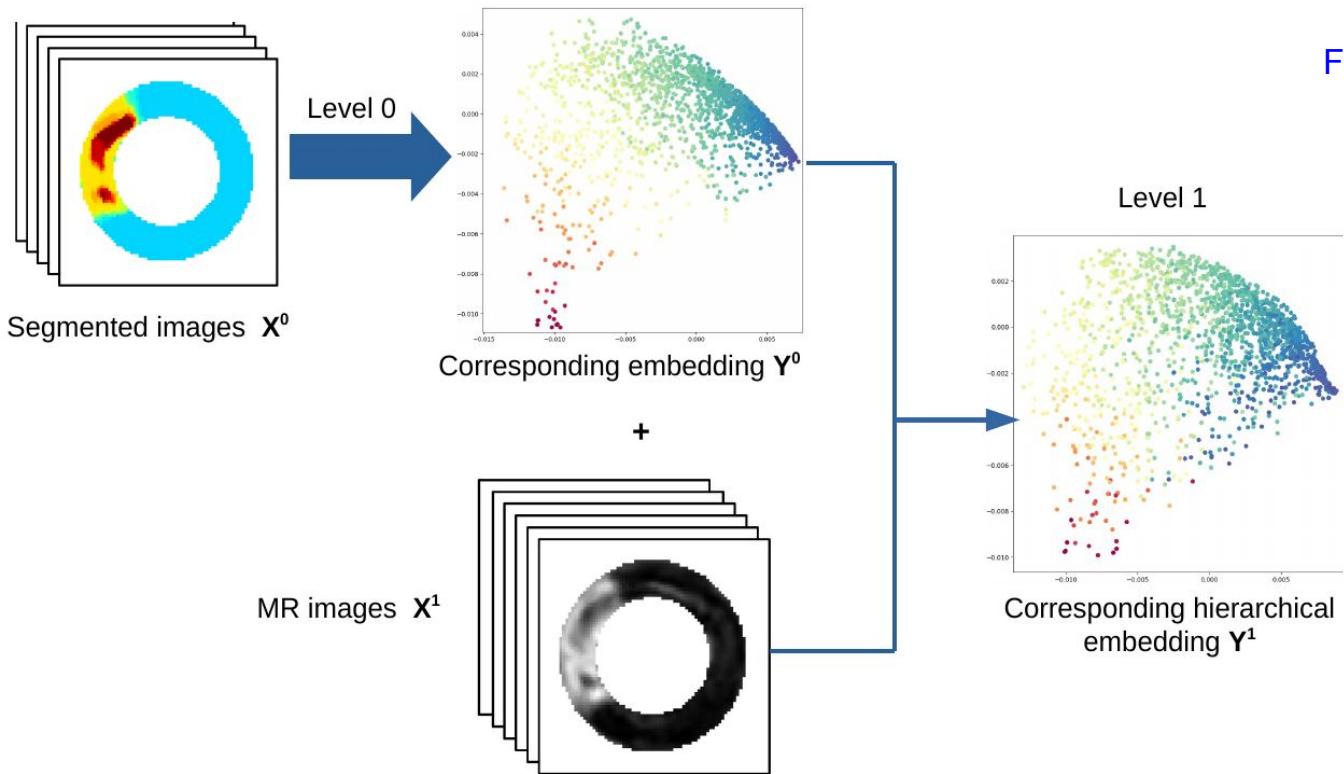
Regularization

Yin et al. *Neural Networks* 2021

$$\min_{\tilde{\mathbf{W}}_{t+1}} \underbrace{\|\tilde{\mathbf{W}}_{t+1} - \tilde{\mathbf{W}}_t\|_F^2 + \|\tilde{\mathbf{W}}_{t+1} - \mathbf{W}^{(t+1)}\|_F^2}_{\text{Evolution of consensus kernel}} + \underbrace{\lambda \|\tilde{\mathbf{W}}_{t+1}\|_1}_{\text{Regularization}}$$

# Imposed data hierarchy

52



Bhatia et al. IEEE TMI 2014  
Freiche et al. STACOM-MICCAI 2021

Hierarchical cost function :

$$\arg \min_{\mathbf{Y}^1} (1 - \mu) \sum_i \sum_j \|\mathbf{y}_i^1 - \mathbf{y}_j^1\|^2 W_{ij} + \mu \sum_i \|\mathbf{y}_i^1 - \mathbf{y}_i^0\|^2$$

Analytic solution :

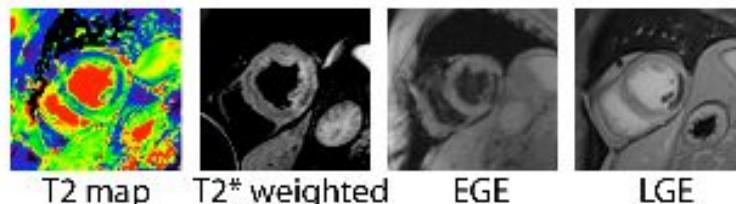
$$\mathbf{Y}^1 = (\mu \mathbf{I} + 2(1 - \mu) \mathbf{L}^1)^{-1} \mu \mathbf{Y}^0$$

## Going further:

- More descriptors ?

Postdoc of F. Zheng

Multi-parametric imaging



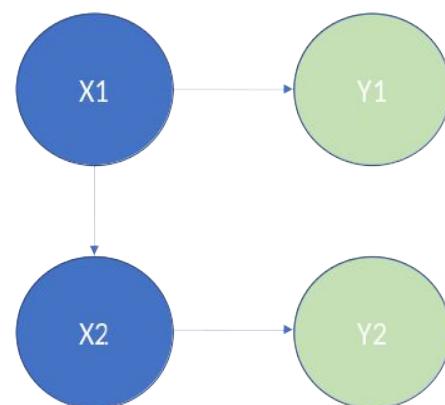
Multiple descriptors



- More generic / probabilistic formulation ?

Bernardino & Freiche *Work in progress*

$$\sum_i d(\mathbf{y}_i^1, f(\mathbf{y}_j^2))$$



## Estimating the need of acquiring new data:

Bernardino et al. STACOM-MICCAI 2021

$$P(Y|\mathbf{X}_0, \mathbf{X}_1) = \left( \prod_i (w^i P(Y^i|X_0^i, \theta_0) + (1 - w^i) P(Y^i|X_1^i, \theta_1)) \right) P(\mathbf{w}|\mathbf{X}_0)$$

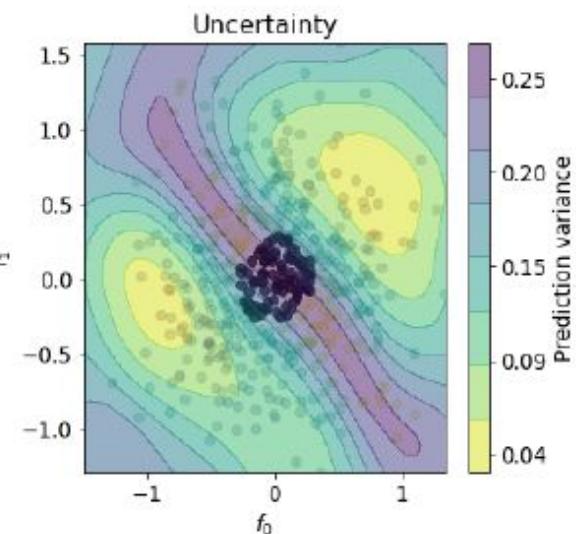
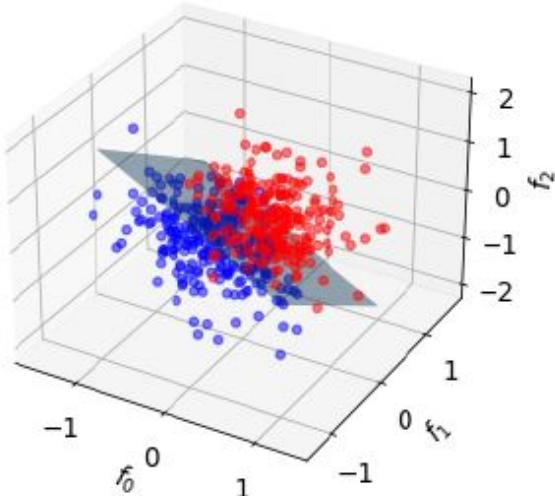
↓  
weights

single view  
classification

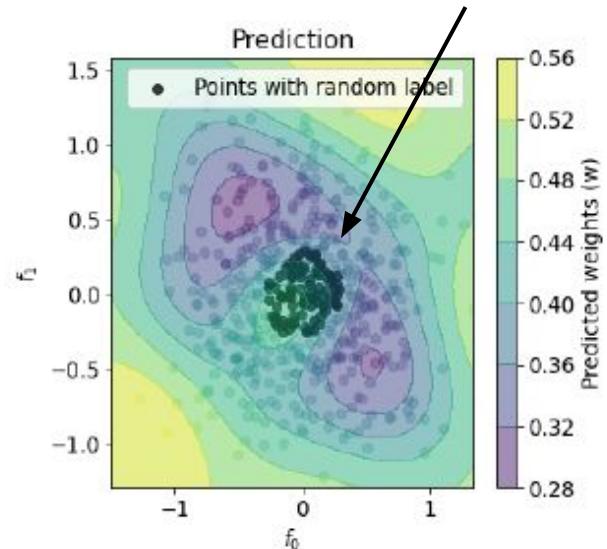
## Prediction:

$$P(Y^i|X_0^i, X_1^i) = \begin{cases} P(Y^i|X_0^i) & w^i \geq k, \\ w^i P(Y^i|X_0^i) + (1 - w^i) P(Y^i|X_1^i) & w^i < k. \end{cases}$$

ex: synthetic data (label =  $\mathbf{X}_1$  + noise)

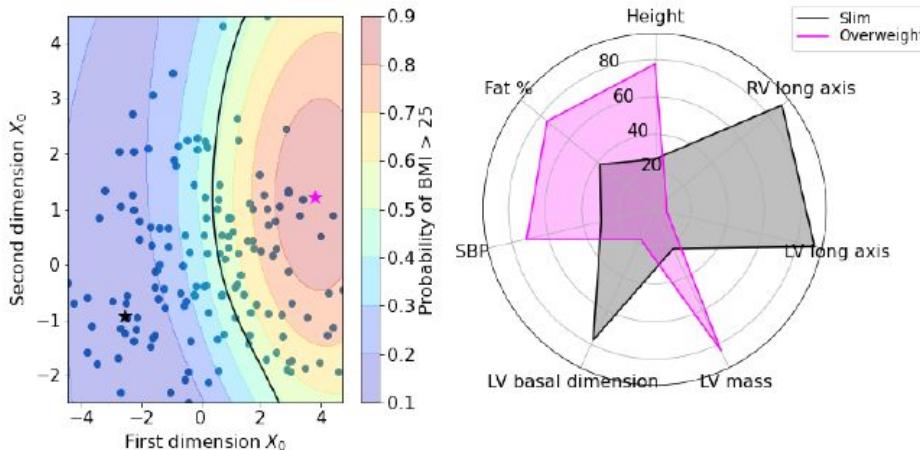


No further acquisition required



ex: real data = ECHO measurements ( $X_0$ ),  $N=480$   
 MRI cardiac shape ( $X_1$ ),  $N=159$

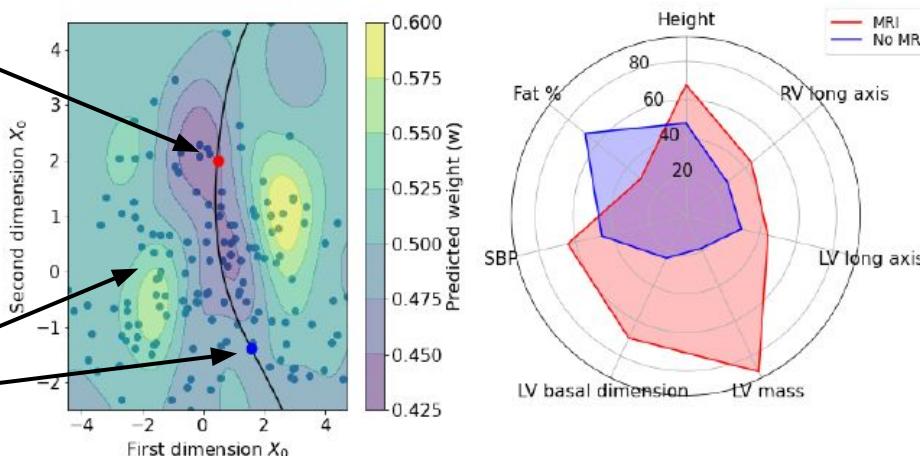
Bernardino et al. STACOM-MICCAI 2021



(a) Overweight

MRI more  
valuable

MRI less  
valuable



(b) Predicted weights

## Reinforcement learning:

Bernardino et al. *Work in progress*  
Wang et al. *NIPS 2015*

Learning a policy, an optimal sequences of actions done by an actor to maximise a reward.

→ RL estimates the value of taking actions (long term instantaneous reward).

**Actor:** clinician

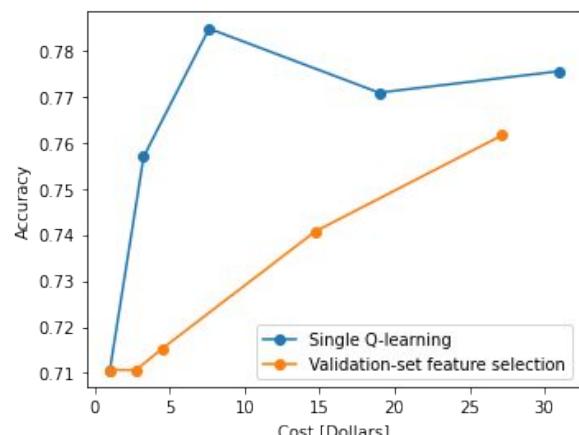
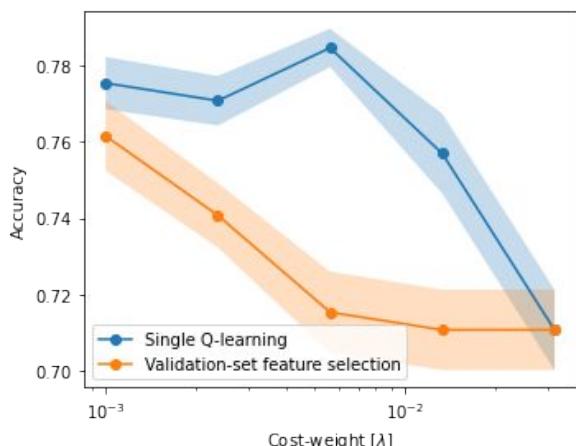
**Action:** acquiring new modality / finish and do diagnosis

**Reward:** accuracy + cost

**States:** Which modalities have been acquired + its measurements.

## ex: Cleveland ICU dataset

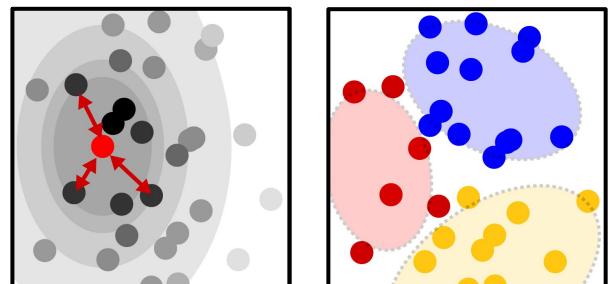
- Predict CAD in patients admitted to ICU. Prevalence ~60%
- 11 variables, in 4 groups (demographic, admission data, exercise test, laboratory). Each has a different cost.



	Embedding space	Reconstruction
<b>Manifold learning</b>	<b>Meaningful</b> distances between <i>input</i> samples ~ Euclidean distance between <i>output</i> coordinates	Interpolation ?
<b>Auto-encoders</b>	Limited statistical meaning Limited for “non convolutionable” data ?	Optimized encoding/decoding

## Nice statistical framework for analysis + extensions...

- Exploitable latent space
- Heterogeneous types of data
- Better metrics



... keeping in mind the clinical question

# Thanks... questions?



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