IMAG/e

TU/e Technische Universiteit **Eindhoven** University of Technology

Deep learning for (deformable) medical image registration

Ruisheng Su

Maureen van Eijnatten

Outline for today:

- First hour:
  - Introduction non-parametric / deformable image registration
  - Deep learning for medical image registration:
    - Deep iterative registration
    - Supervised methods
    - Unsupervised (optimization-based) methods

- Second hour:
  - Recap of medical image registration
  - Example exam questions

Learning goals of this lecture

The students should be able to:

- Explain the difference between parametric and non-parametric image registration models
- Formulate deformable image registration as an optimization problem
- Understand displacement vector fields
- Explain the difference between supervised and unsupervised learning
- Understand why deep learning is an interesting technique to solve medical image registration tasks
- Understand the different ways in which deep learning can be used to perform (deformable) image registration

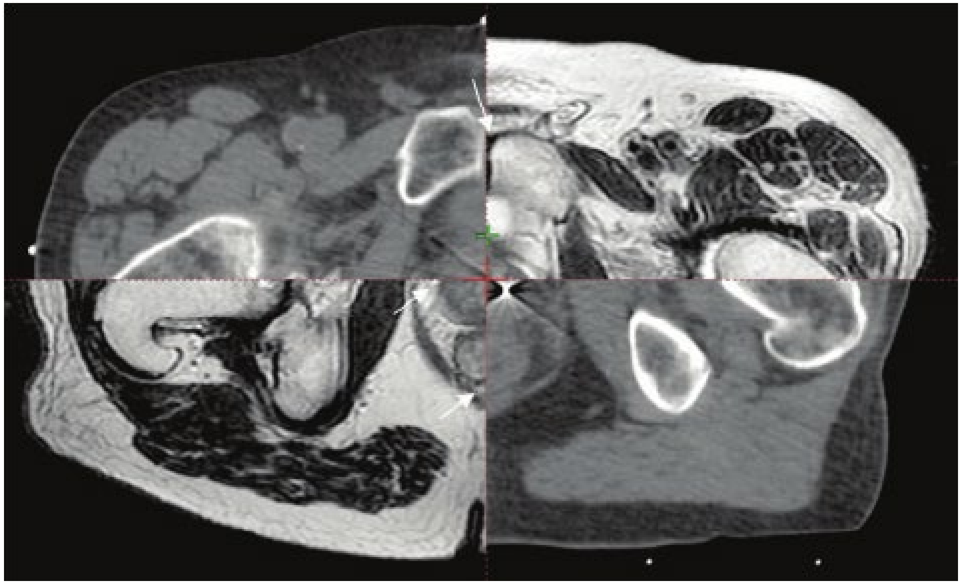
Medical image registration

Why important?

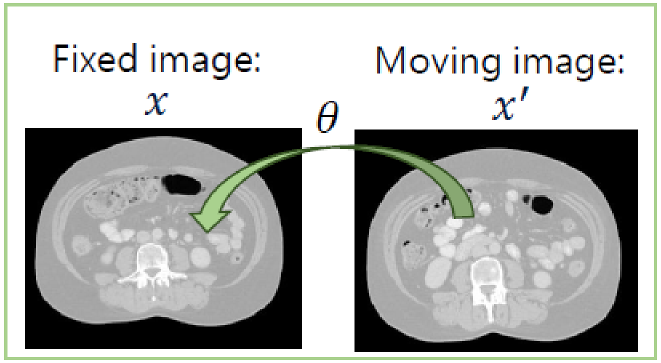
- Multi-modal registration (e.g. CT on MRI)
- Inter-subject (e.g. atlas registration)
- Longitudinal (e.g. treatment evaluation)

Remaining challenges:

- Large 3D volumes
- Accuracy vs. efficiency (speed)
- Intensity inhomogeneities and discontinuities
- Outlier rejection



Medical image registration: general “recipe”



Transformation model:
(e.g., rigid, affine, deformable)

$$T(x', \theta)$$

Image registration

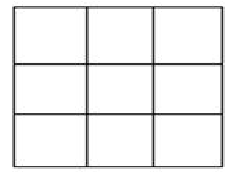
Similarity measure:
(e.g. SSD, CC, MI, MSE)

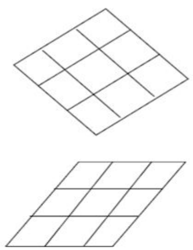
$$S(x, x')$$

Optimization:

$$\hat{\theta} = \max_{\theta} S\big(x, T(x', \theta)\big)$$

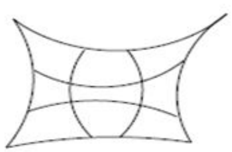
Transformation models





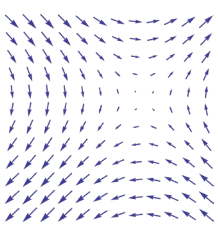
Rigid & Affine

- Point or feature-based (e.g. landmarks, fiducials)
- Intensity-based
- Gradient/edge-based



Non-linear

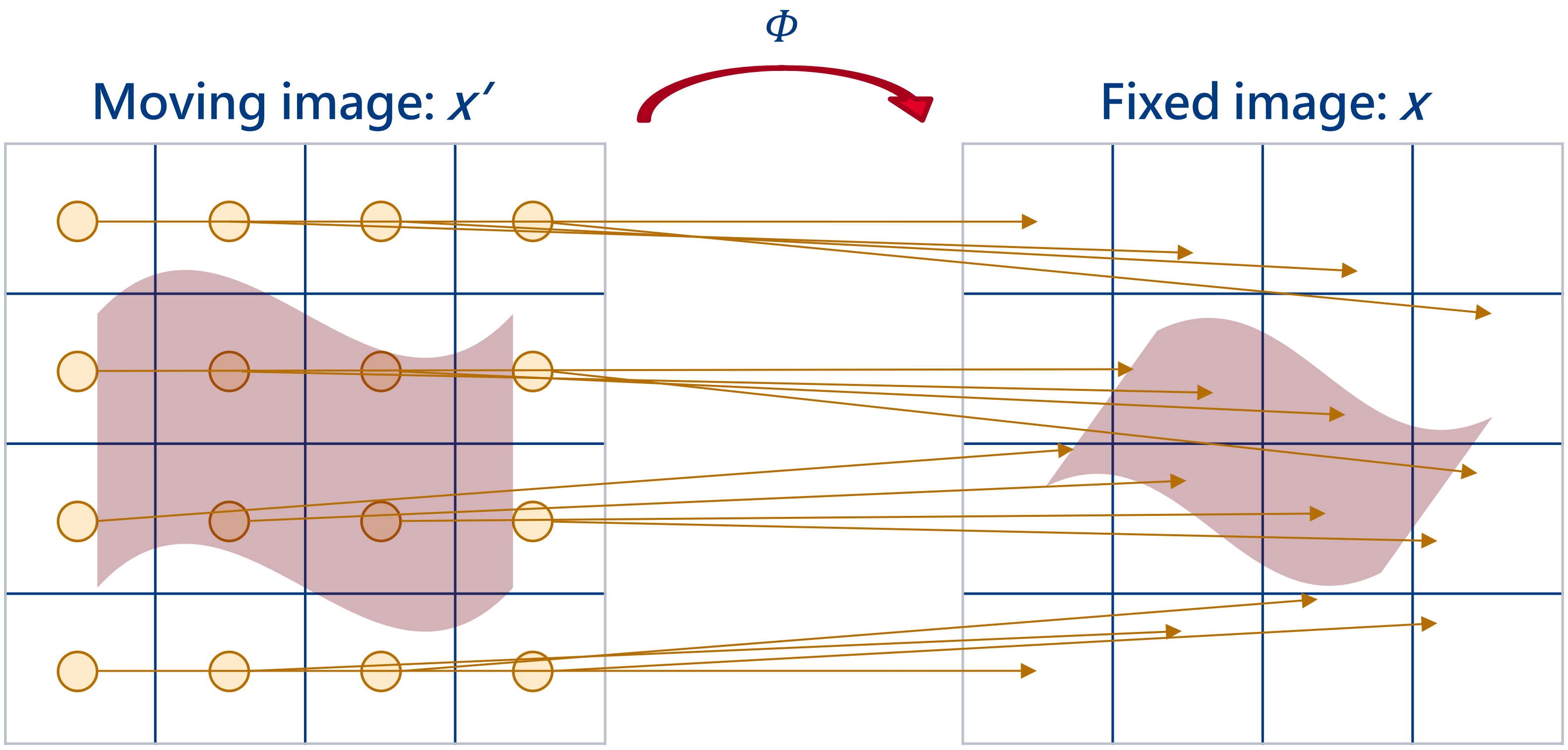
- Linear or higher order polynomials
- Spline-based



Non-parametric / deformable

- Allowing each image element to be displaced arbitrarily

Displacement (vector) field (DVF) = Dense set of vectors representing the displacement in a given spatial domain



How to find such a DVF?

1. Write the error as a function of the DVF.
2. Find the minimum of the error function w.r.t. the transformation.

Formulation of deformable image registration

Images (fixed image x, moving image x'): $x : \Omega \rightarrow \mathbb{R}$

Image domain: $\Omega \rightarrow \mathbb{R}^d, d = 2{,}3$

Transformed moving image:

Regularization

$$u' = \underset{u \in H}{\arg\min}\ E_D\left(x, \boxed{x'(\varphi)}\right) + \lambda\, E_R(u)$$

Difference measure

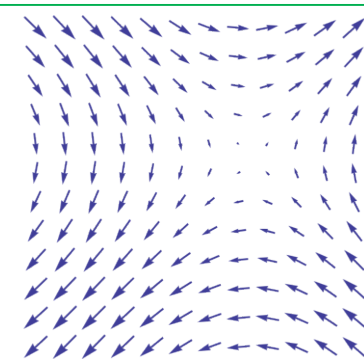
Deformation: $\varphi = \mathrm{Id} + u, \qquad \varphi : \Omega \rightarrow \mathbb{R}^d$

or point-wise: $\varphi(x) = x + u(x)$

Displacement:

$u : \Omega \rightarrow \mathbb{R}^d$

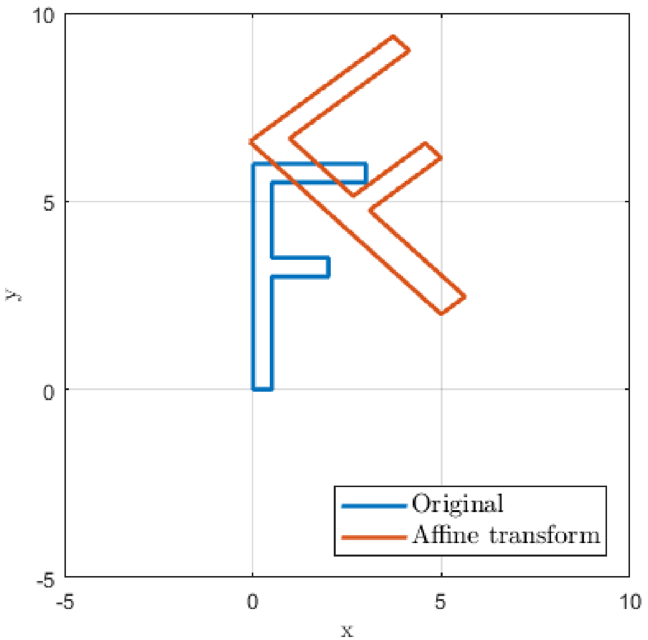
e.g. $u = [u_x, u_y, u_z]$



Affine transformation (no restriction on the transformation parameters):

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} t_x \\ t_y \end{bmatrix}$$

$$\mathbf{x}' = \mathbf{A}\mathbf{x} + \mathbf{t}$$



It can be considered as a composition of any combination of rotations, scalings, shearings, reflections + translations.

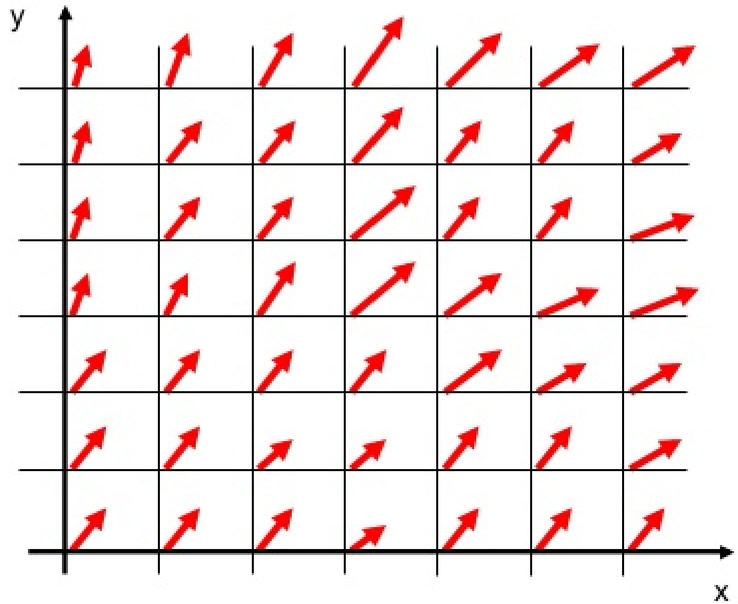
How many parameters in 2D?

And in 3D?

Affine transformation in 3D:

$$\begin{bmatrix} x' \\ y' \\ z' \\ 1 \end{bmatrix} = \begin{bmatrix} a & b & c & t_x \\ d & e & f & t_y \\ g & h & i & t_z \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \\ 1 \end{bmatrix}$$

Deformable image registration: how many free parameters (DOF) in 3D?



Typical spatial resolution of a 3D medical image
(MRI: e.g. 1.5×1.5×4 mm^3 voxels)

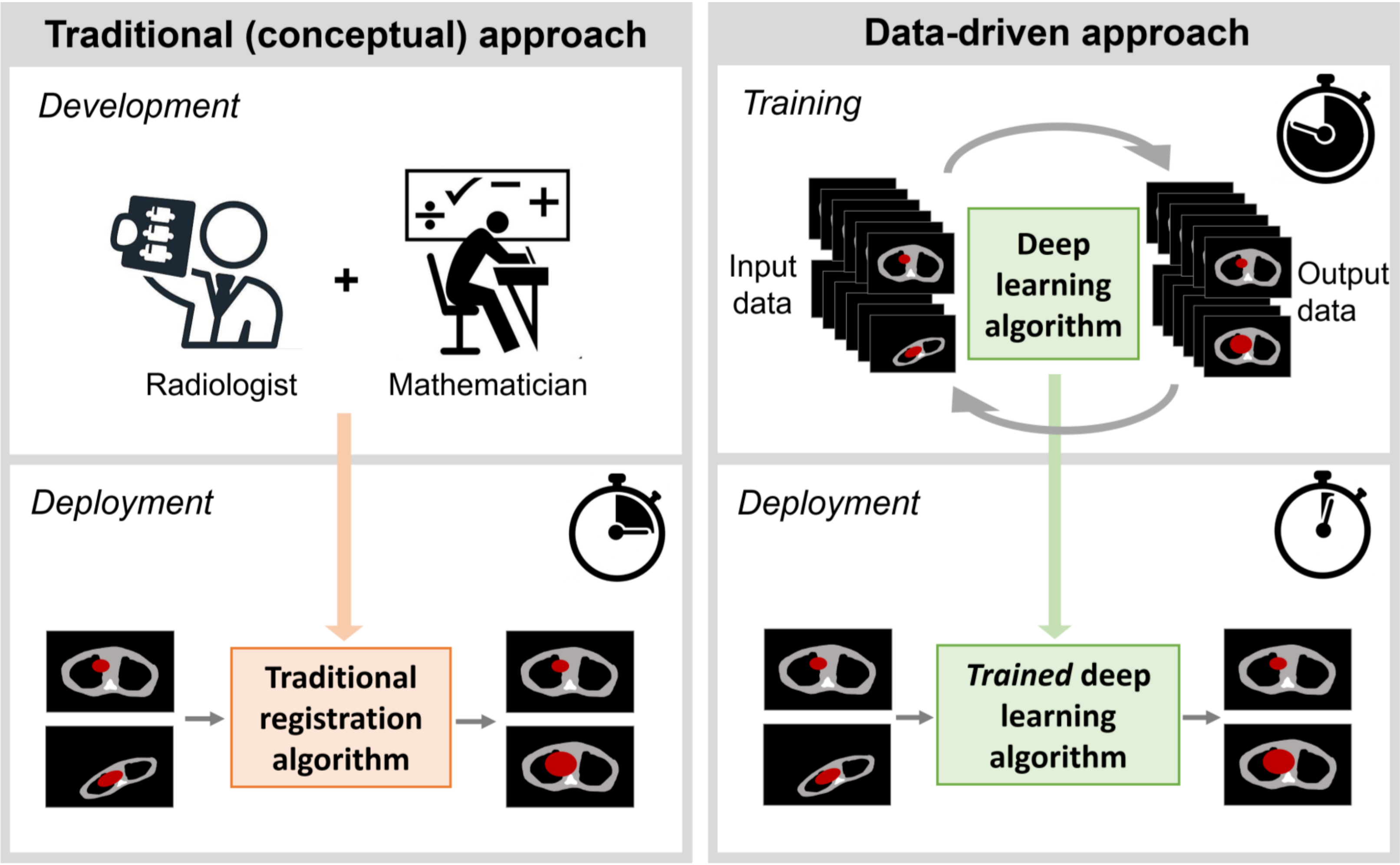
DOF = 3*Nx*Ny*Nz (!)

Deformable image registration is still a very active area of research, and many different deformable registration models exist:

- Free-form deformation model
- Optical flow
- Demons
- Fluid flow
- Diffeomorphisms
- …

Note that the details of these models and their implementations are beyond the scope of this course.

Why focus on deep learning for medical image registration?



Machine learning – different training strategies

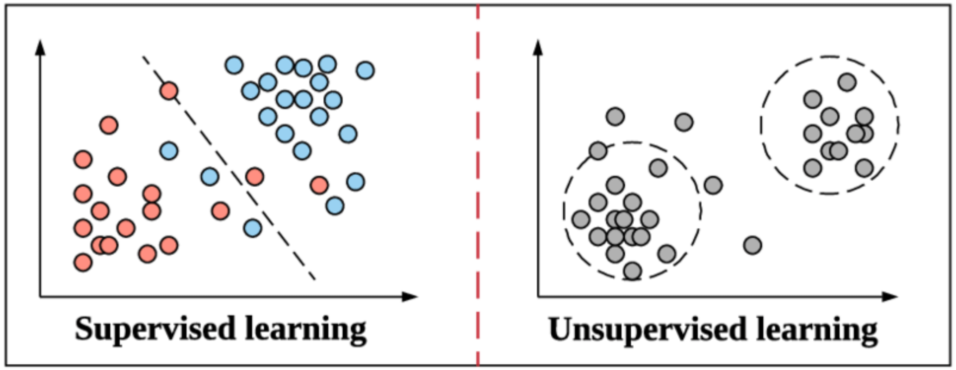
Supervised learning = develop predictive model based on input and output data (i.e., ground truth, "labels")

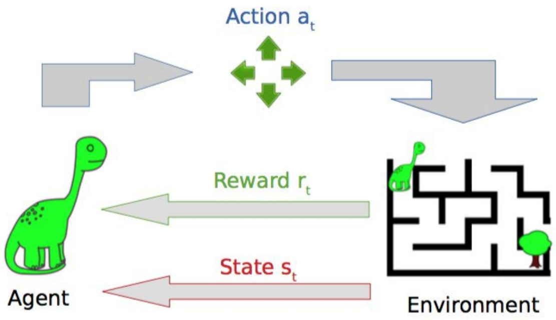
Examples: classification (e.g., skin lesion classification), regression (segmentation of vessel structures)

Unsupervised learning = group or interpret data based on input data alone

Example: clustering (e.g., k-means)

NB: also semi-supervised learning and reinforcement learning, not part of this course.





Reinforcement learning

Image 1 source: Qian et al. (2019). Orchestrating the Development Lifecycle of Machine Learning-Based IoT Applications: A Taxonomy and Survey.
Image 2 source: https://twimlai.com/whats-hot-in-ai-deep-reinforcement-learning-edition/

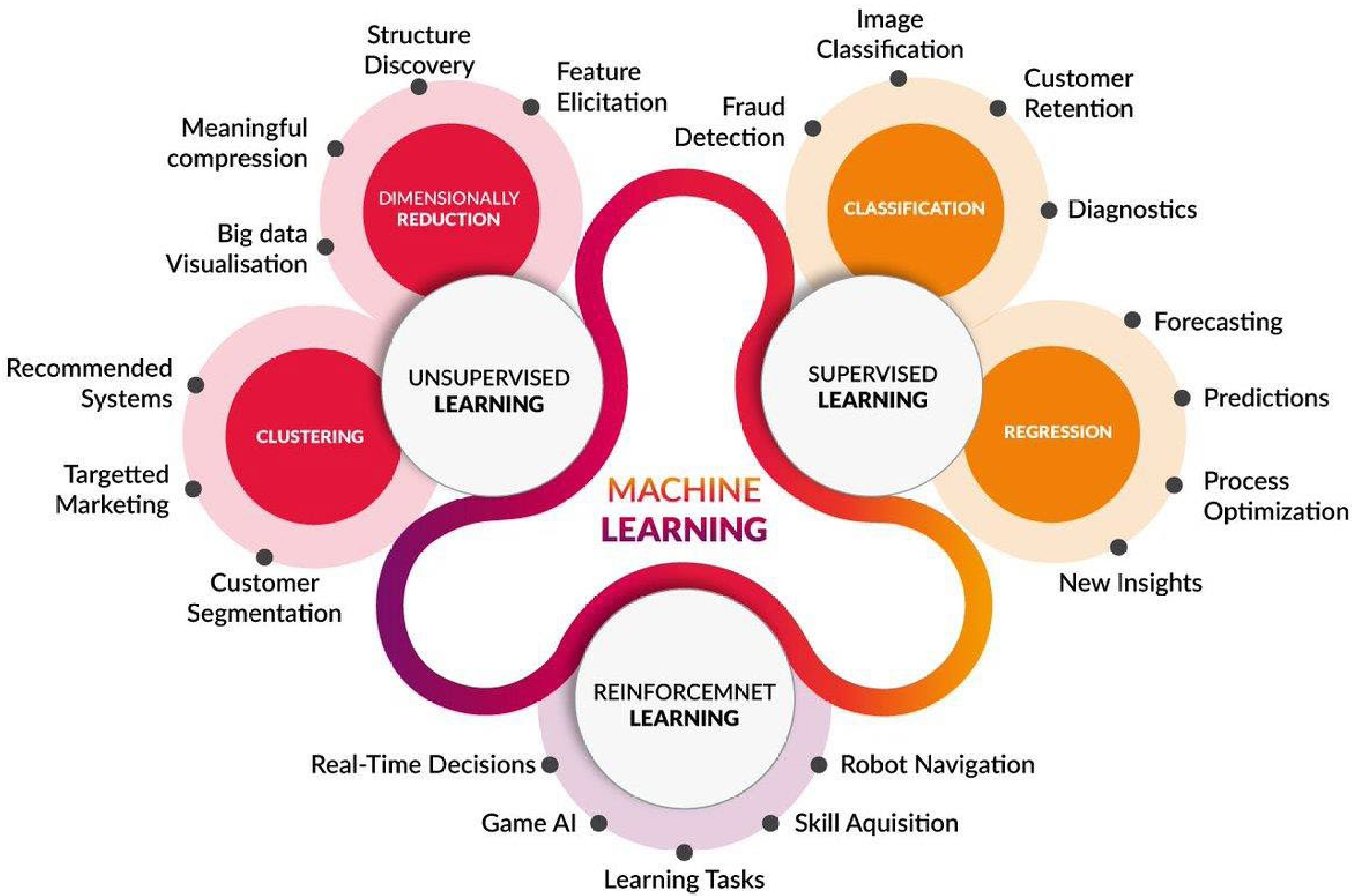


Image source: http://www.cognub.com/index.php/cognitive-platform/

Learning image registration: how does it work?

A. Deep iterative registration

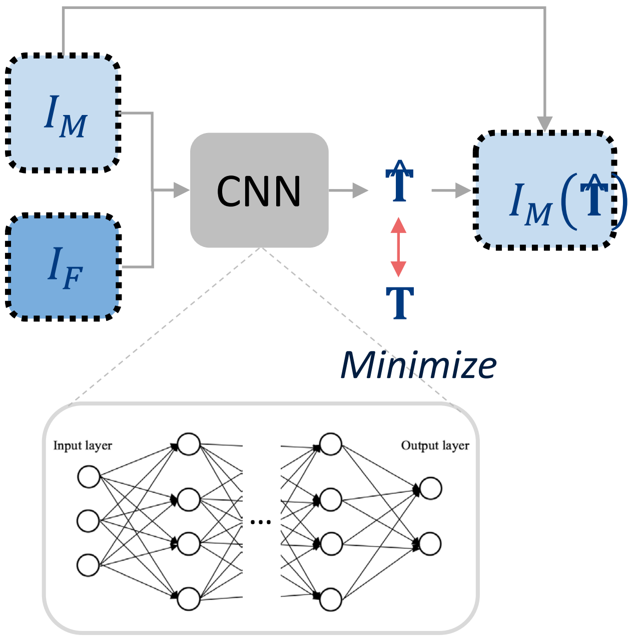
- Learn a component of a classical registration method

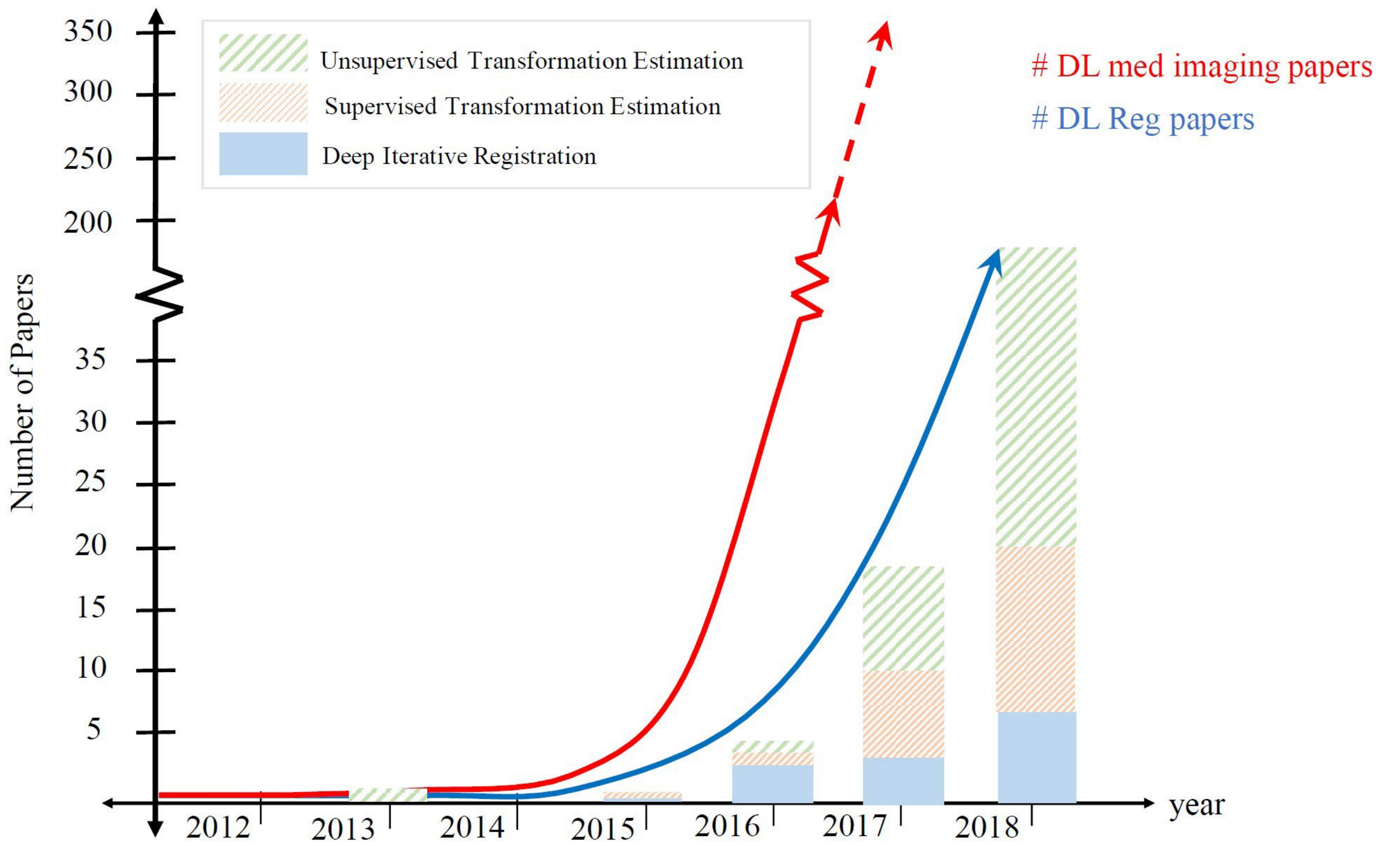
B. Supervised transformation estimation

- Obtain using classical registration method
- or make synthetic ground truth

C. Unsupervised transformation estimation

- Use similarity metric to judge





Haskins et al. (2019) Deep Learning in Medical Image Registration: A Survey. arXiv:1903.02026v1

A. Deep iterative registration

Use a traditional registration method and learn one component

Automatically extract (learn) similarity features

- *Unimodal*: Wu et al. (2013) Unsupervised deep feature learning for deformable registration of mr brain images (MICCAI); Wu et al. (2016) Scalable high-performance image registration framework by unsupervised deep feature representations learning (IEEE Transactions on Biomedical Engineering); Eppenhof et al. (2018) Error estimation of deformable image registration of pulmonary ct scans using convolutional neural networks (Journal of Medical Imaging)
- *Multimodal*: Mostly *rigid registration*; learn a similarity metric to evaluate or register multimodal images using gradient descent. E.g. Cheng et al. (2016&2018) Deep similarity learning for multimodal medical images (MICCAI)

Reinforcement learning

Mostly used for *rigid registration*

- Low-resolution transformation model for deformable registration

  Krebs et al. (2017) Robust non-rigid registration through agent-based action learning (MICCAI)

Where are we in the image registration "recipe"?

Transformation model:
(e.g., rigid, affine, deformable)

$$T(x', \theta)$$

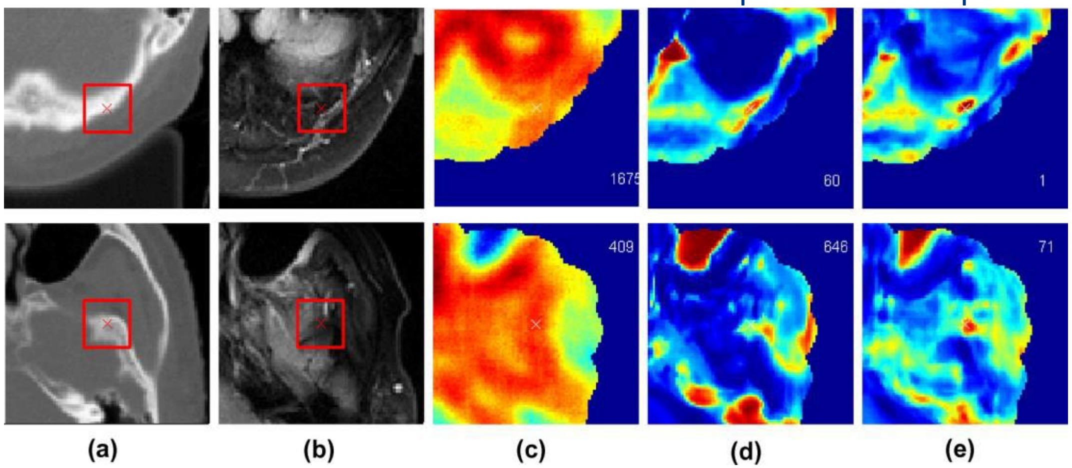
Similarity measure:
(e.g. SSD, CC, MI, MSE)

$$S(x, x')$$

Optimization:

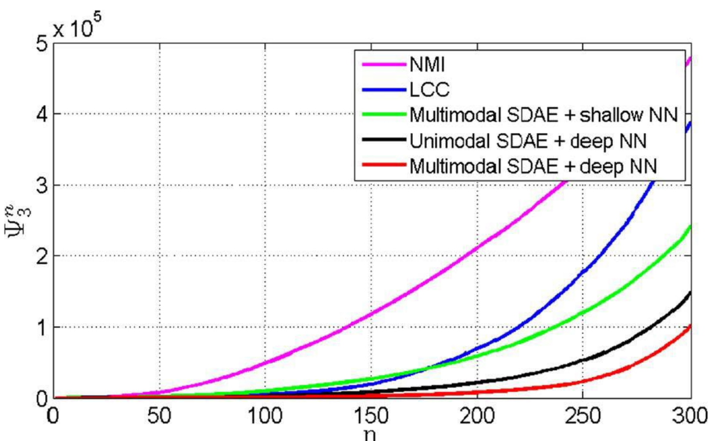
$$\hat{\theta} = \max_{\theta} S\big(x, T(x', \theta)\big)$$

Example 1: *Learning multimodal feature extraction (Haskins et al., 2019)*



Similarity maps

Cumulative sum of prediction errors



No. of patches

Cheng, Xi, Li Zhang, and Yefeng Zheng. "Deep similarity learning for multimodal medical images." *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization* 6.3 (2018): 248-252

Where are we in the image registration "recipe"?

Transformation model:
(e.g., rigid, affine, deformable)

$T(x', \theta)$

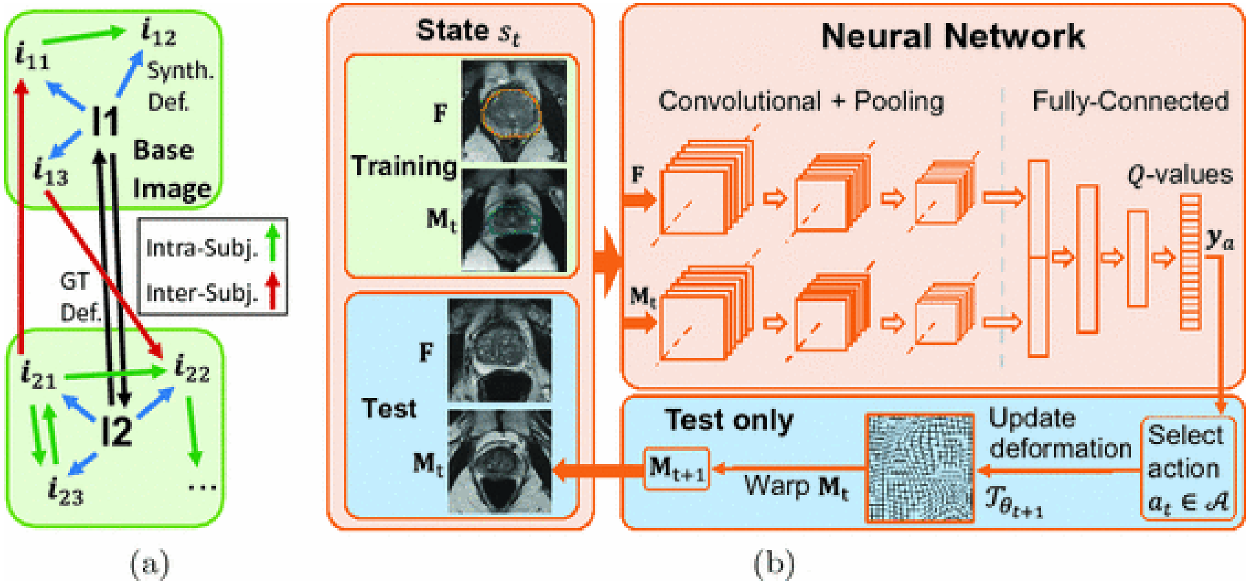
Similarity measure:
(e.g. SSD, CC, MI, MSE)

$S(x, x')$

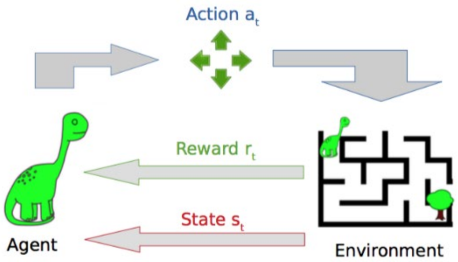
Optimization:

$$\hat{\theta} = \max_{\theta} S\big(x, T(x', \theta)\big)$$

Example 2: *Reinforcement learning for image registration*



(a) Training Data Generation: **Synthetic deformations** (blue arrows) and inter-subject GT deformations (black) are used for intra- (green) and inter-subject (red) image pairs for training. (b) Dual-stream network used for Q-value prediction including complete single-stage Markov Decision Process for testing (blue background).



Krebs, Julian, et al. "Robust non-rigid registration through agent-based action learning." *International Conference on Medical Image Computing and Computer-Assisted Intervention*. Springer, Cham, 2017.

B. Supervised methods

Require many known transformations for training, use ground truth labels to calculate the loss

Fully supervised

2D (FlowNet) vs. 3D approaches (e.g. 3D U-net); mostly patch-based (e.g. 128^3)

- *Generation of ground truth transformations* ➔ many, e.g. Eppenhof et al. (2018)
  Pulmonary ct registration through supervised learning with convolutional neural networks (IEEE trans. on med. imaging)
- *Large Deformation Diffeomorphic Metric Mapping (LDDMM)* ➔Yang et al. (2017)
  Quicksilver: Fast Predictive Image Registration - a Deep Learning Approach (NeuroImage)

Weakly supervised

Use overlap between segmentations or a similarity metric between *M* and *F* combined with ground truth

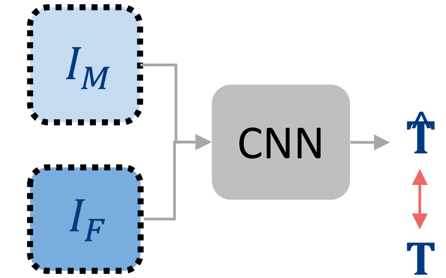
- MR-US registration
  - *CNN* ➔ Hu et al. (2018) Weakly-supervised convolutional neural networks for multimodal image registration (Medical Image Analysis)
  - *Generative Adversarial Networks (GANs)* ➔ Yan et al. (2018) Adversarial image registration with application for mr and trus image fusion (arXiv preprint: 1804.11024)

Supervised learning of the transformation requires a ground truth!

Questions:

- What is the ground truth of an image registration task?
  - Parametric?
  - Non-parametric?

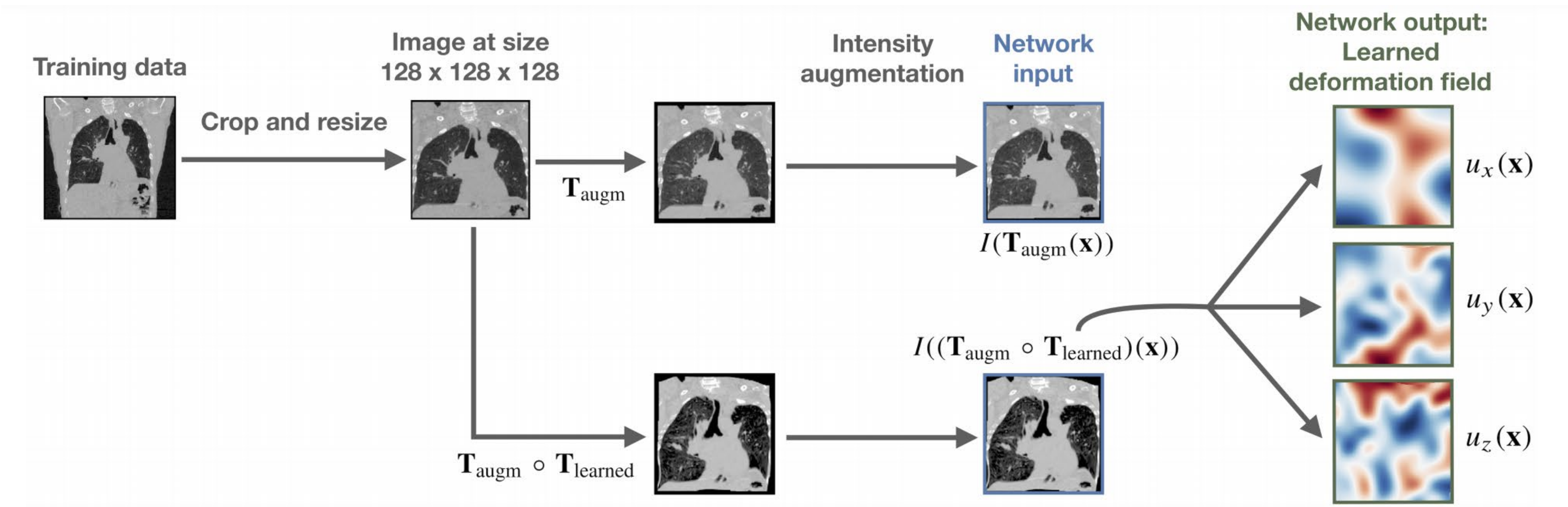
- How can we acquire this?



B. Supervised transformation estimation

Requires many known transformations for training, use ground truth labels to calculate the loss

Example 1: *"On-the-fly" simulation of displacement fields: T_{augm} (Eppenhof & Pluim, 2018)*



Eppenhof, Koen AJ, and Josien PW Pluim. "Pulmonary CT registration through supervised learning with convolutional neural networks." *IEEE transactions on medical imaging* 38.5 (2018): 1097-1105.

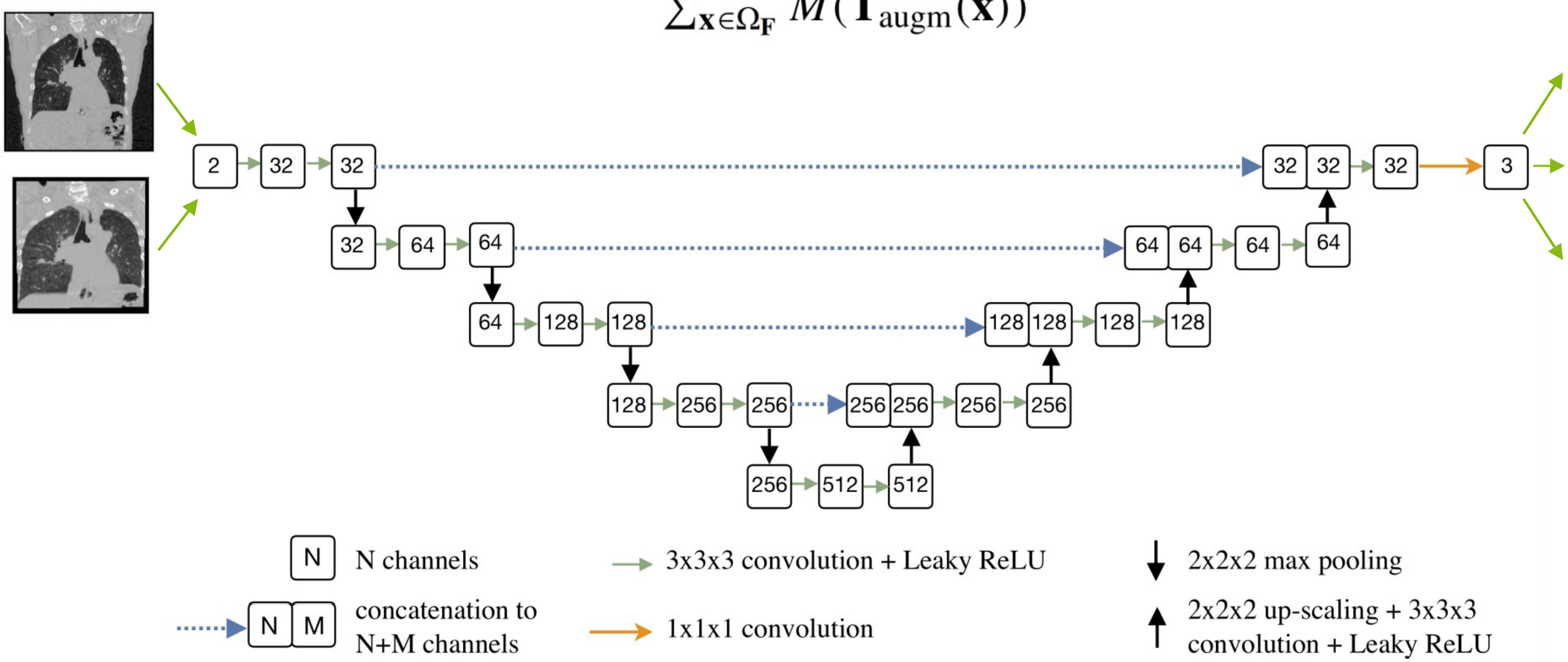
Learning the displacement vector field (Eppenhof & Pluim, 2018)

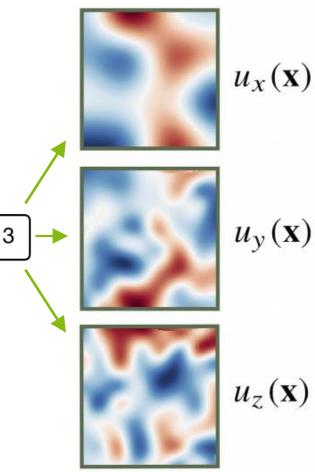
Binary mask of the lungs

True vector field

Estimated vector field

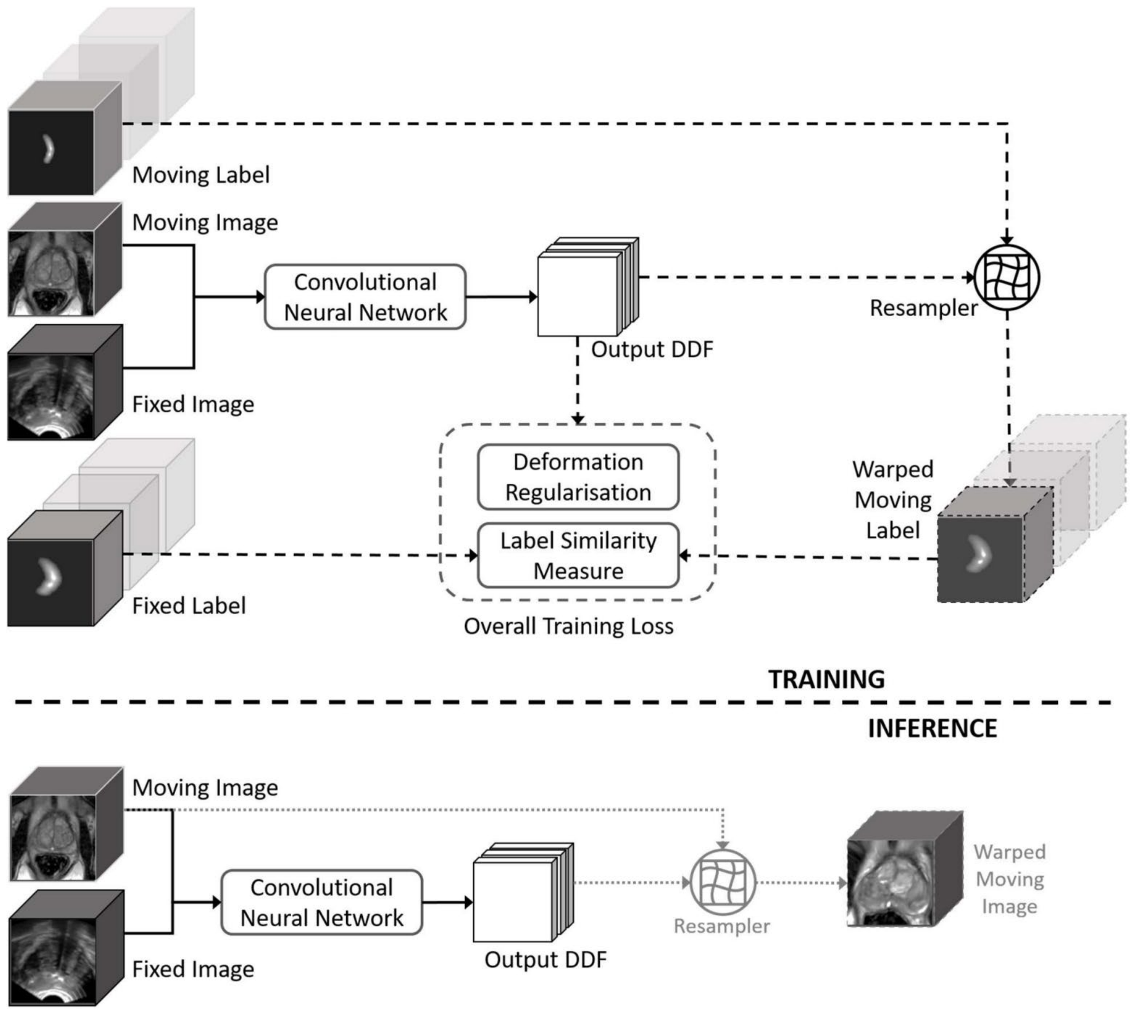
$$L = \frac{\sum_{\mathbf{x}\in\Omega_\mathbf{F}} M(\mathbf{T}_{\text{augm}}(\mathbf{x}))\,|\mathbf{u}(\mathbf{x}) - \hat{\mathbf{u}}(\mathbf{x})|}{\sum_{\mathbf{x}\in\Omega_\mathbf{F}} M(\mathbf{T}_{\text{augm}}(\mathbf{x}))}$$





Eppenhof, Koen AJ, and Josien PW Pluim. "Pulmonary CT registration through supervised learning with convolutional neural networks." *IEEE transactions on medical imaging* 38.5 (2018): 1097-1105.

Example 2: *Weakly-supervised* *CNN for MR-US registration*



Hu, Yipeng, et al. "Weakly-supervised convolutional neural networks for multimodal image registration." *Medical image analysis* 49 (2018): 1-13.

C. Unsupervised methods

No ground truth needed. Often use a spatial transformer layer.

Variational autoencoders ➔ Krebs et al. (2018) Unsupervised Probabilistic Deformation Modeling for Robust Diffeomorphic Registration. (DLMIA)

Generative Adversarial Networks (GANs) ➔ Tanner et al. (2018) Generative Adversarial Networks for MR-CT Deformable Image Registration (CVPR) & Hu et al. (2018) Adversarial Deformation Regularization for Training Image Registration Neural Networks (MICCAI)

Multi-scale methods:

- **RegNet** ➔ Sokooti et al. (2017) Nonrigid Image Registation Using Multi-scale 3D Convolutional Neural Networks (MICCAI). NB: dual path
- **ConvNet** ➔ De Vos et al. (2018) A deep learning framework for unsupervised affine and deformable image registration (Medical Image Analysis). NB: chain
- **pgCNN** ➔ Eppenhof et al. (2019) Progressive Growing Convolutional Networks for End-to-End Deformable Image Registration (SPIE medical imaging)

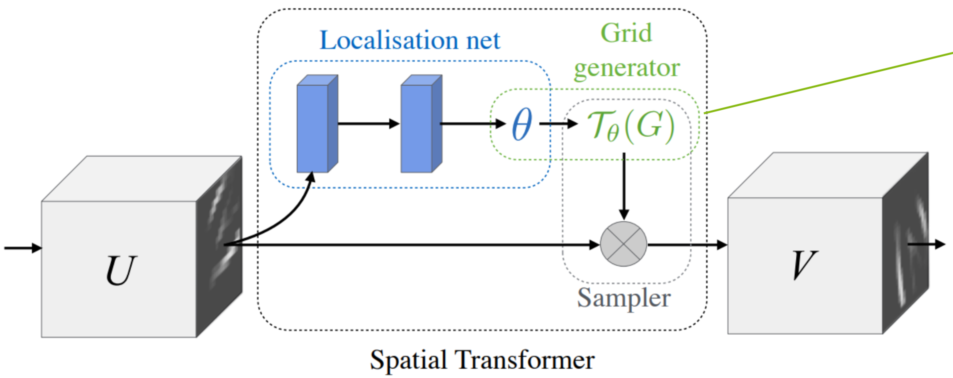
VoxelMorph (U-net) ➔ Balakrishnan et al. (2019) VoxelMorph: A Learning Framework for Deformable Medical Image Registration (IEEE tran.med.imaging)

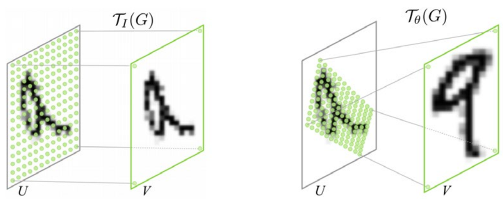
- **Cycle-consistent VoxelMorph** ➔ Kim et al. (2019) Unsupervised Deformable Image Registration Using Cycle-Consistent CNN (MICCAI)

Spatial transformer networks (Jaderberg et al., NIPS 2015)

Spatial transformer = a learnable module that explicitly allows the spatial manipulation of data within the network

- *Differentiable*
- Can be inserted into existing convolutional neural networks
- Actively transforms feature maps (conditional on the feature map itself)



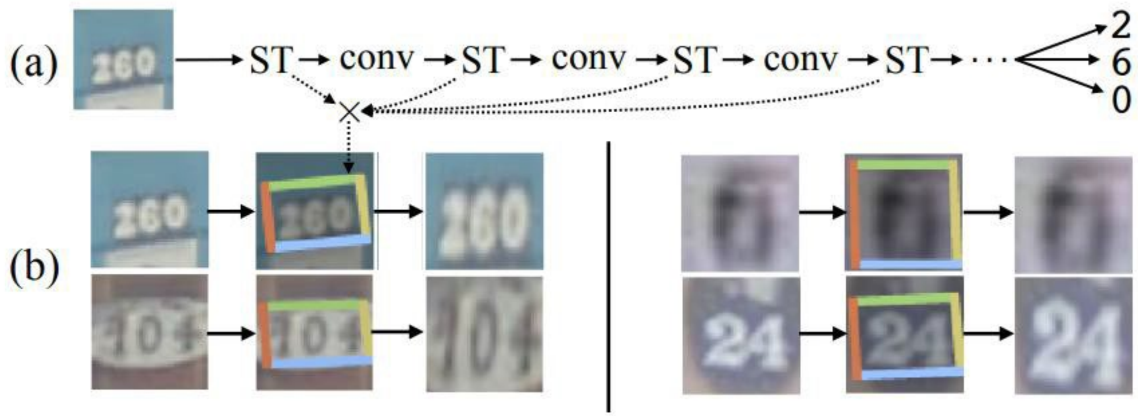


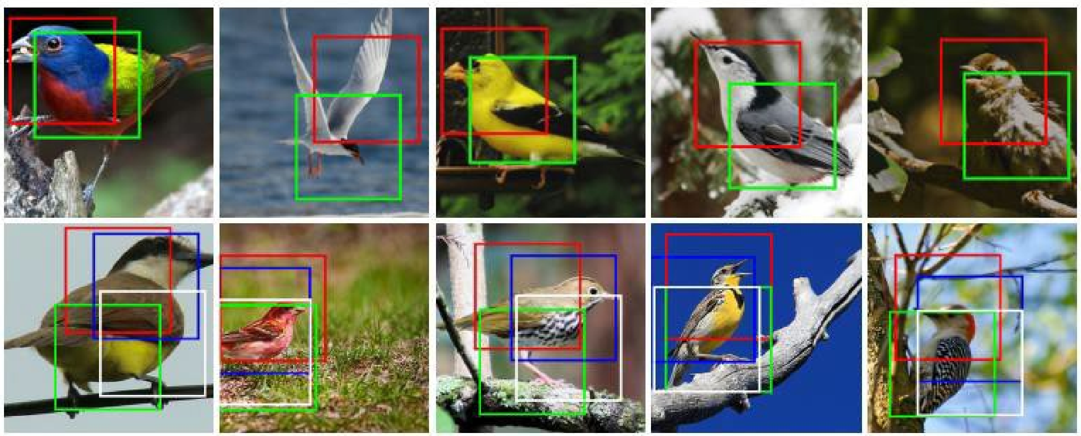
Example $T_\theta(G)$ for an affine transformation:

$$\begin{pmatrix} x_i^s \\ y_i^s \end{pmatrix} = \mathcal{T}_\theta(G_i) = \mathtt{A}_\theta \begin{pmatrix} x_i^t \\ y_i^t \\ 1 \end{pmatrix} = \begin{bmatrix} \theta_{11} & \theta_{12} & \theta_{13} \\ \theta_{21} & \theta_{22} & \theta_{23} \end{bmatrix} \begin{pmatrix} x_i^t \\ y_i^t \\ 1 \end{pmatrix}$$

Jaderberg, Max, Karen Simonyan, and Andrew Zisserman. "Spatial transformer networks." *Advances in neural information processing systems*. 2015.

CNNs are in essence not invariant to translation, scale, rotation and more generic warping of the input data

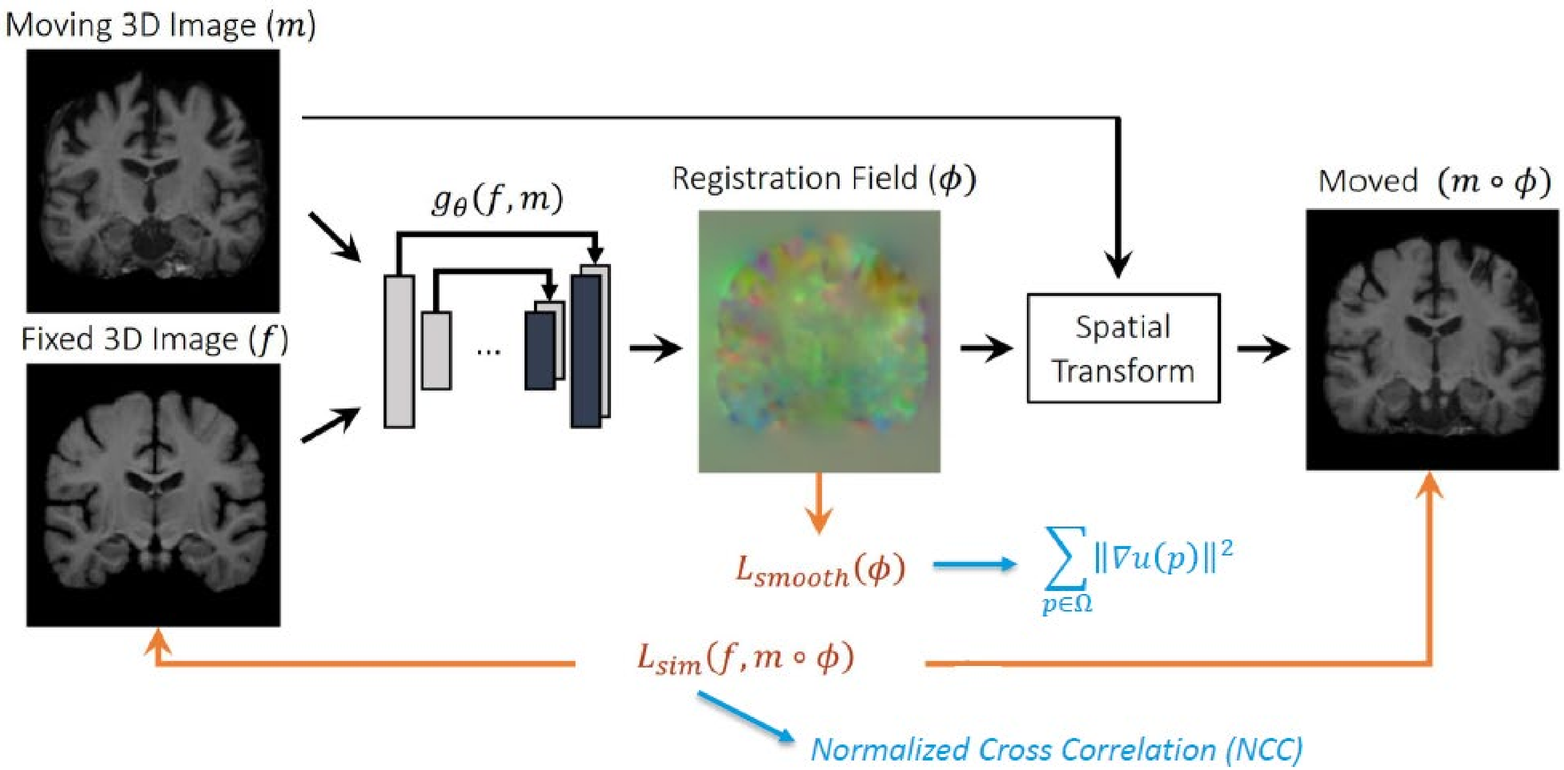




Jaderberg, Max, Karen Simonyan, and Andrew Zisserman. "Spatial transformer networks." *Advances in neural information processing systems*. 2015.

VoxelMorph

Example of a popular unsupervised framework for deformable image registration



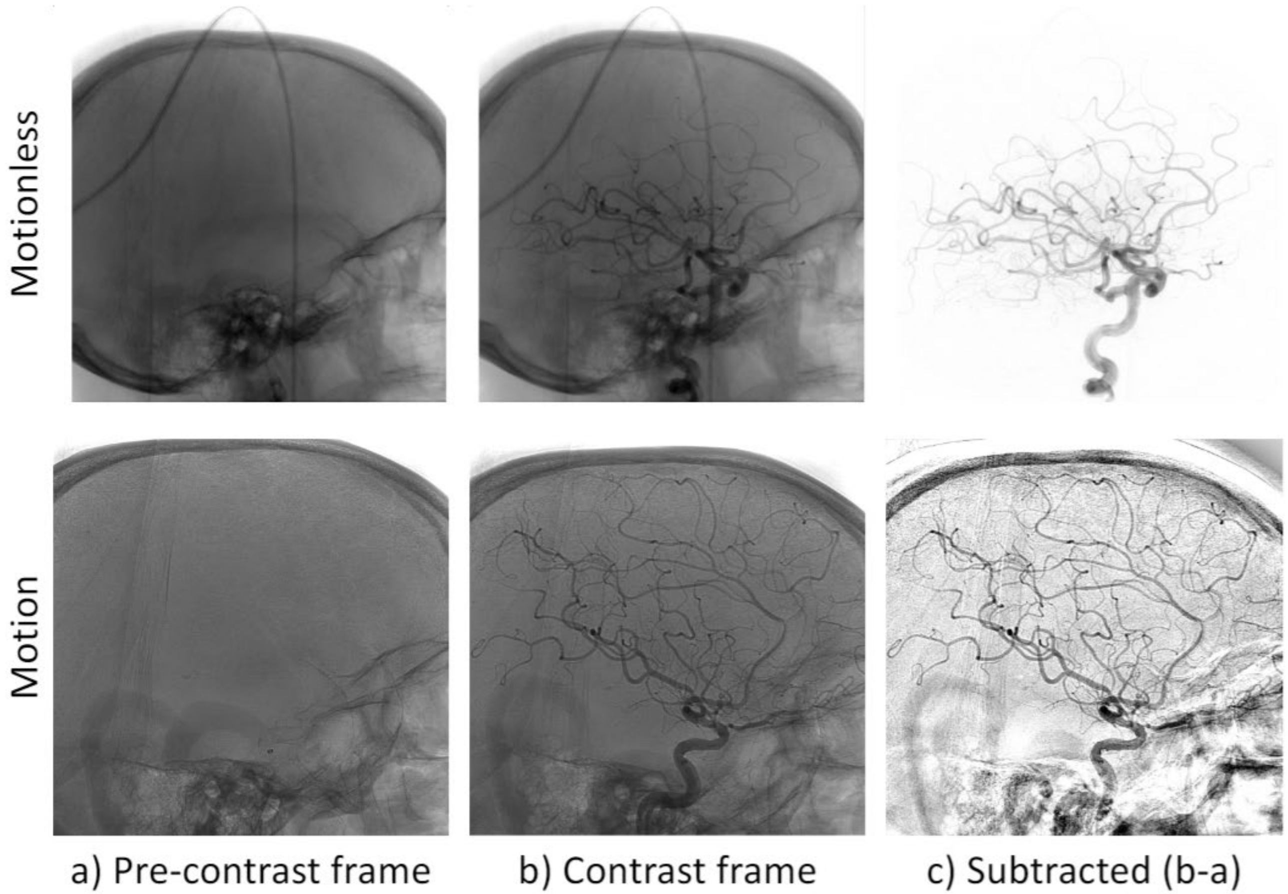
$$\hat{\Phi} = \underset{\Phi}{\operatorname{argmin}}\, L_{sim}(f, m \circ \Phi) + \lambda L_{smooth}(\Phi)$$

Balakrishnan et al. (2018): VoxelMorph: A Learning Framework for Deformable Medical Image Registration. arXiv:1909.05231v3

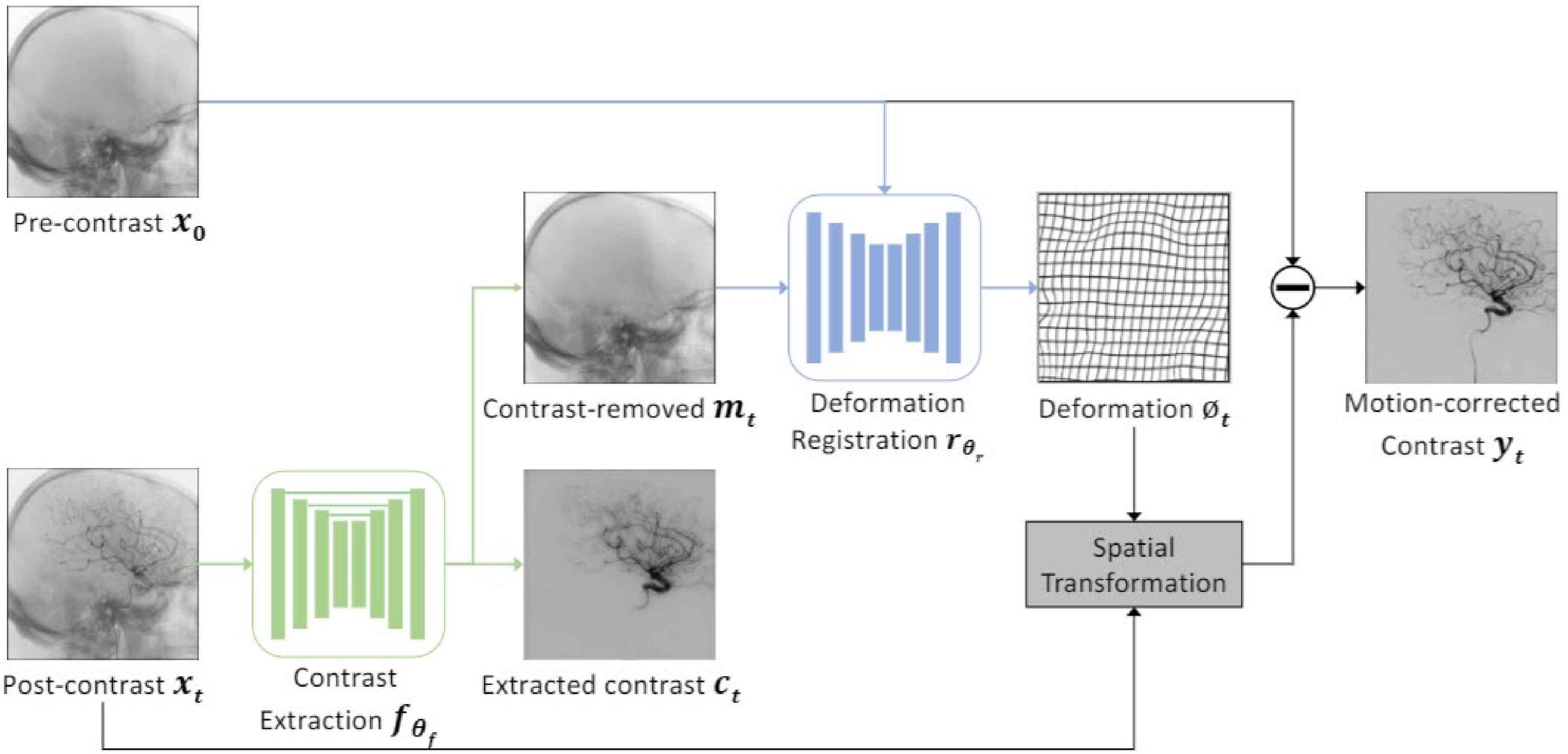
IMAG/e TU/e Technische Universiteit Eindhoven University of Technology

Example from my own research:

Deformable registration of motion correction in brain digital subtraction angiography



Su et al. (2023): AngioMoCo: Learning-based Motion Correctionin Cerebral Digital Subtraction Angiography. arXiv:2310.05445



Su et al. (2023): AngioMoCo: Learning-based Motion Correctionin Cerebral Digital Subtraction Angiography. arXiv:2310.05445

Summary

- Parametric vs. non-parametric image registration
  - Displacement vector fields
- Formulation of deformable image registration
- Different ways to use deep learning for image registration
  - Deep iterative registration
  - Supervised learning
  - Unsupervised learning
- Disadvantages of deep learning for image registration (performance, # of training data, ground truth, …)

IMAG/e

TU/e Technische Universiteit Eindhoven University of Technology

Recap & Preparing for the exam

IMAG/e TU/e Technische Universiteit Eindhoven University of Technology

How can I prepare for the exam?

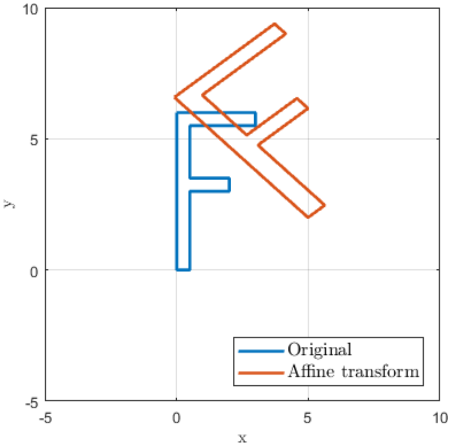
- (Re)study all the lecture slides, intended learning outcomes
- (Re)study all exercises, example exam, and reader questions
  - Answers on Canvas
- Questions in the lecture slides
- Some example exam questions on next slides

Rigid transformations $\mathbf{x}' = \mathbf{R}\mathbf{x} + \mathbf{t}$

- Translation $\mathbf{t} = \begin{bmatrix} t_x \\ t_y \end{bmatrix}$
- Rotation $\mathbf{R} = \begin{bmatrix} \cos(\phi) & -\sin(\phi) \\ \sin(\phi) & \cos(\phi) \end{bmatrix}$

Affine transformations: translation, rotations and $\mathbf{x}' = \mathbf{A}\mathbf{x} + \mathbf{t}$

- Scaling $\mathbf{S} = \begin{bmatrix} s_x & 0 \\ 0 & s_y \end{bmatrix}$
- Shearing $\mathbf{H} = \begin{bmatrix} 1 & h_x \\ h_y & 1 \end{bmatrix}$



A transformation matrix and a translation vector can be combined when using homogeneous coordinates:

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} t_x \\ t_y \end{bmatrix}$$

$$\begin{bmatrix} x' \\ y' \\ 1 \end{bmatrix} = \begin{bmatrix} a & b & t_x \\ c & d & t_y \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ 1 \end{bmatrix}$$

This largely simplifies the notation and implementation of complex transformations.

Example exam question

The sequence of transformations that registers a moving to a fixed image is the following: scaling by 0.5 in the x-direction and by 2 in the y-direction, followed by counterclockwise rotation by π/4 radians.

Which of the following sequence of transformation matrices should be applied to the grid G of the output (transformed) image when performing inverse mapping? Motive your answer.

(a)

$$\begin{bmatrix} \cos(\frac{\pi}{4}) & -\sin(\frac{\pi}{4}) \\ \sin(\frac{\pi}{4}) & \cos(\frac{\pi}{4}) \end{bmatrix} \begin{bmatrix} 2 & 0 \\ 0 & 0.5 \end{bmatrix} \mathbf{G}$$

(b)

$$\begin{bmatrix} \cos(\frac{\pi}{4}) & -\sin(\frac{\pi}{4}) \\ \sin(\frac{\pi}{4}) & \cos(\frac{\pi}{4}) \end{bmatrix} \begin{bmatrix} 0.5 & 0 \\ 0 & 2 \end{bmatrix} \mathbf{G}$$

(c)

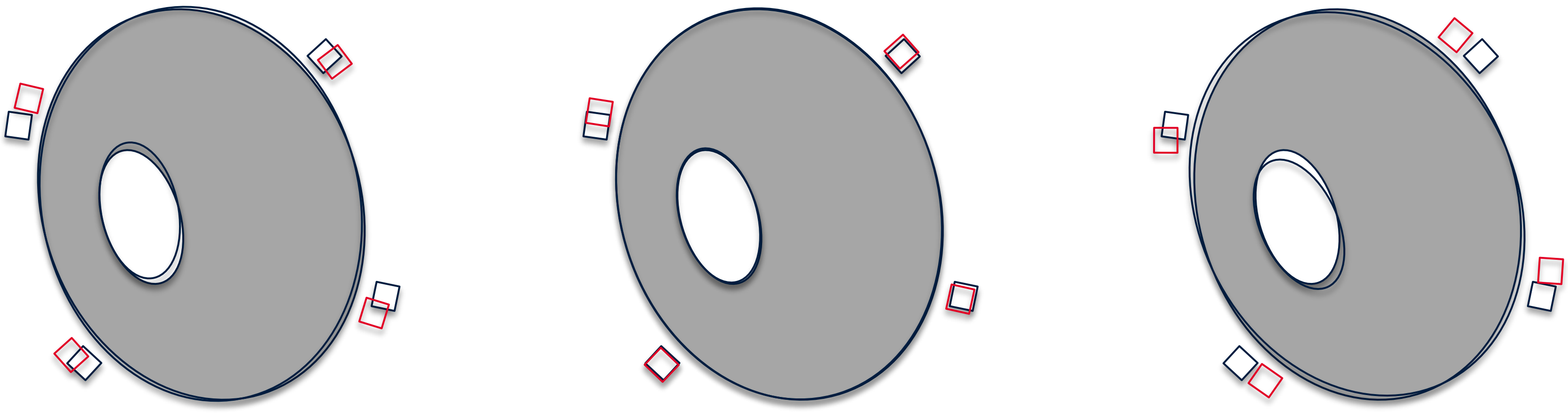
$$\begin{bmatrix} 2 & 0 \\ 0 & 0.5 \end{bmatrix} \begin{bmatrix} \cos(-\frac{\pi}{4}) & -\sin(-\frac{\pi}{4}) \\ \sin(-\frac{\pi}{4}) & \cos(-\frac{\pi}{4}) \end{bmatrix} \mathbf{G}$$

(d)

$$\begin{bmatrix} 0.5 & 0 \\ 0 & 2 \end{bmatrix} \begin{bmatrix} \cos(-\frac{\pi}{4}) & -\sin(-\frac{\pi}{4}) \\ \sin(-\frac{\pi}{4}) & \cos(-\frac{\pi}{4}) \end{bmatrix} \mathbf{G}$$

How to find such a transformation?

1. Write the error as a function of the transformation.
2. Find the minimum of the error function w.r.t. the transformation.



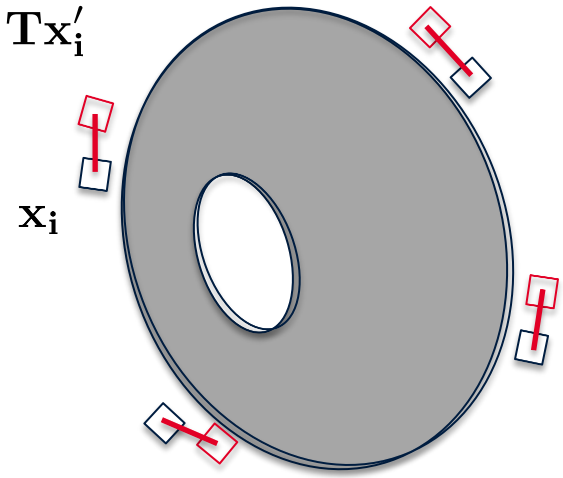
Different transformations will result in different errors.
Our goal: find the transformation that results in the lowest error.

Step 1, affine registration:

$$E(\mathbf{T}) = \sum_{i=1}^{n} ||\mathbf{T}\mathbf{x_i'} - \mathbf{x_i}||_2^2$$

$$\mathbf{T} = \begin{bmatrix} a & b & t_x \\ c & d & t_y \\ 0 & 0 & 1 \end{bmatrix}$$

Error as a function of the transformation T



Step 2, find the minimum of the error w.r.t. to the parameters.

$$\hat{\mathbf{T}} = \arg\min_{\mathbf{T} \in A} \sum_{i=1}^{n} ||\mathbf{T}\mathbf{x}'_{\mathbf{i}} - \mathbf{x}_{\mathbf{i}}||_2^2 \qquad \mathbf{T} = \begin{bmatrix} a & b & t_x \\ c & d & t_y \\ 0 & 0 & 1 \end{bmatrix}$$

The optimal T is the one that minimizes the error

T belongs to the set of all affine transformations

Evaluation:

1. Perform image registration (compute the transformation matrix T)
2. Annotate some target corresponding point pairs in the fixed and moving images. These must be different from the corresponding points used to compute T and at locations that are relevant for some treatment or diagnosis.
3. Transform the points from the moving image
4. Compute the target registration error as the average distance between the points in the fixed image and the transformed moving points.

Example exam question

- What is the minimum number of fiducial points needed for affine transformation in 2D?
- FRE vs TRE
- Describe the steps to evaluate the point-based image registration

Intensity-based similarity measures:

- Sum of square differences
- Cross-correlation
- Mutual information

Optimization for intensity-based registration:

- Gradient ascent (descent)

General procedure (for maximization of a similarity function):

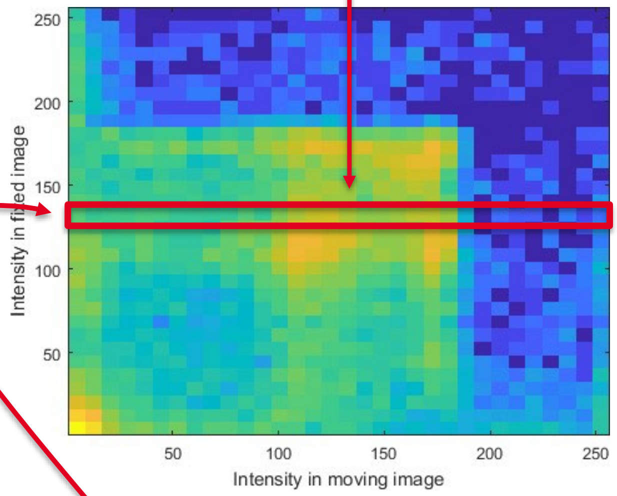
1. Start with some initial values for the parameters (in this case the transformation $\mathbf{T}$).
2. Slightly update the parameters in such a wat that the similarity will slightly increase.
3. Repeat until the similarity stops increasing.

Example exam question

Which pair of images is better aligned according to the joint histogram?

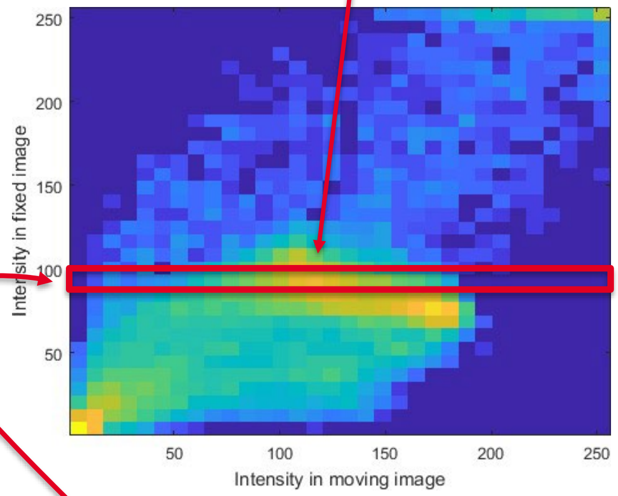
Which histogram is more “compact”?

There are many probable values.



One value is “fixed”.

There are a few values with very high probability.



One value is “fixed”.

Important characteristics to consider when evaluating medical image analysis methods:

- **Accuracy** = deviation of results from known ground truth.
- **Precision**, **reproducibility, reliability** = extent to which equal or similar input produces equal or similar results.
- **Robustness** characterizes the change of analysis quality if conditions deviate from assumptions made for analysis (e.g., when noise level increases or if object appearance deviates from prior assumptions).
- **Efficiency** = effort necessary to achieve an analysis result.

Evaluation metrics

- Image segmentation
  - Accuracy
  - Dice score
  - Hausdorff distance
- Image registration
  - Target registration error
  - Segmentation mask
- CAD
  - Sensitivity, Specificity (trade-off)
  - ROC, AUC

Active shape models

Train

1. Gather training images and label landmarks consistently

2. Align all shapes to remove variations due to position, size, and orientation.

3. Build a statistical model from the aligned shapes using PCA.

4. Find the mean shape and the deviation of each point of the mean shape.

Test

1. Place the mean shape in a new image to start the fitting process.

2. Iterative Fitting: adjust landmark positions and shape parameters based on local appearance and shape constraints.

3. Stop fitting when the convergence criteria are met, or max iterations are reached.