LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Inverse problems and machine learning in medical physics

Image registration - Machine learning for image registration

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30/1/2024
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Introduction to deformable image registration

- Deformable image registration is a numerical optimization that aims at determining a spatial transformation that relates positions in one image (reference or fixed image) to the corresponding positions in another image (target or moving image)

- The aim is to compare and integrate the information given by different images

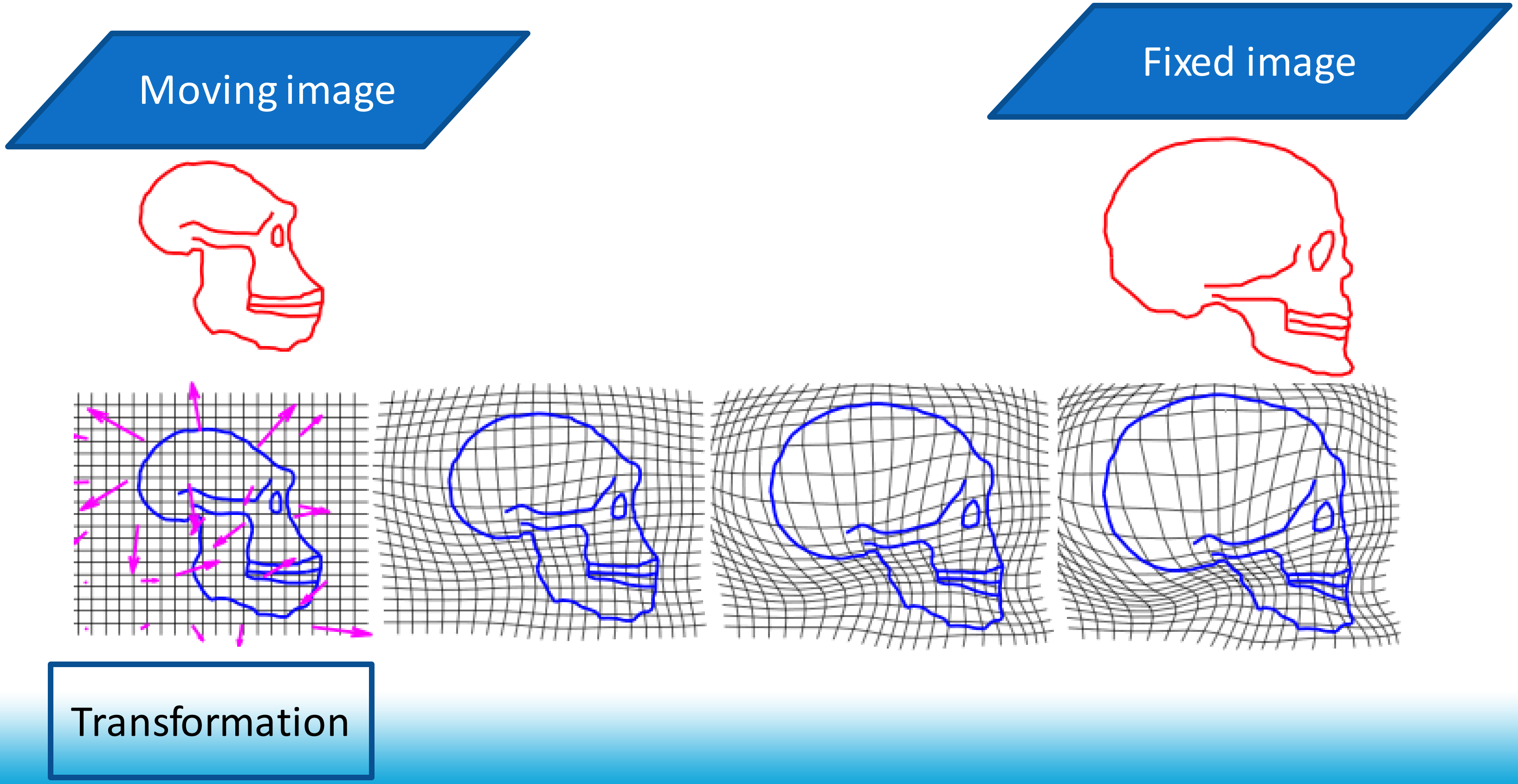
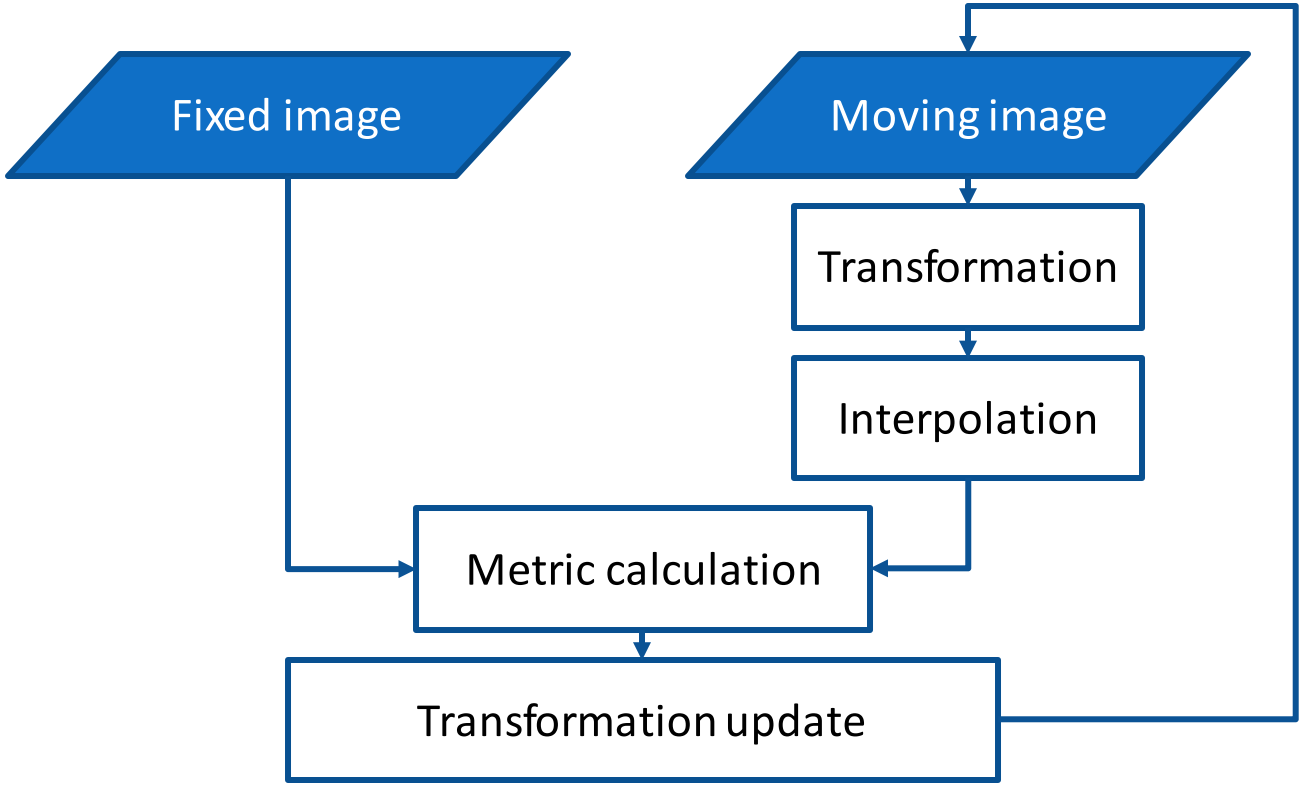


Image registration algorithm

- The numerical optimization is based on the metric, chosen according to the two image modalities, and iterative updates of the transformation parameters
  - Input: fixed image and moving image
  - Output: transformation parameters



- The moving image (undergoing transformation) requires interpolation based on the voxel grid of the fixed image

Metric calculation

- The metric is defined on the gray levels of the two images
  - The gray levels of mono-modality images expresses the same information and they are directly comparable (image differences, mean square errors, root mean square errors, correlation coefficients…)

$$MSE(x,y) = \frac{1}{IJK}\sum_{i,j,k}\left(x_{i,j,k} - y_{i,j,k}\right)^2$$

$$CC(x,y) = \frac{\sum_{i,j,k}\left(x_{i,j,k} \cdot y_{i,j,k}\right)}{\sqrt{\sum_{i,j,k} {x_{i,j,k}}^2 \cdot \sum_{i,j,k} {y_{i,j,k}}^2}}$$

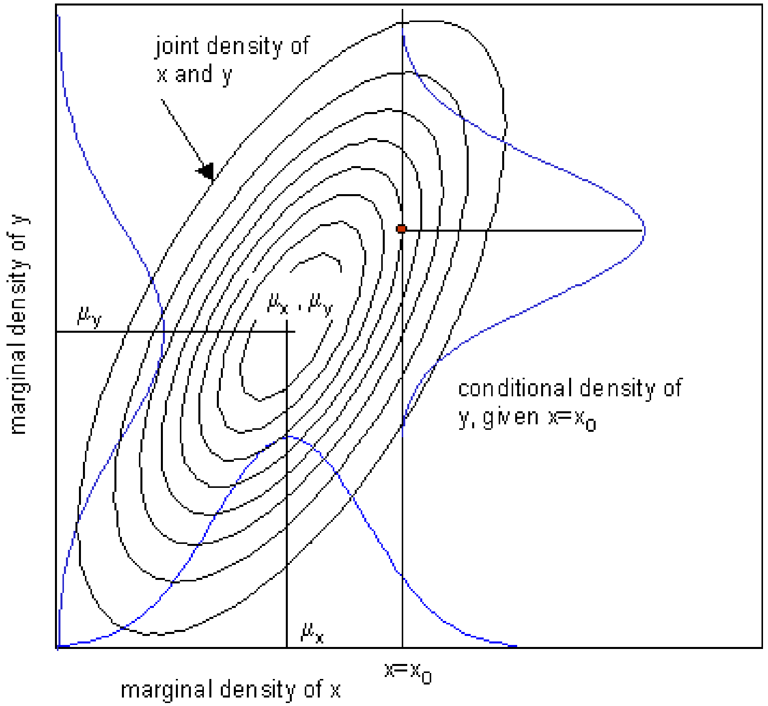
  - The gray levels of multi-modality images expresses different information and "information processing" is need to compare them
    - Mutual information (MI)
    - Normalized Mutual Information (NMI)

Mutual information

- In information theory, the mutual information of two random variables X and Y, $I(X;Y)$, is a measure of the mutual dependence between the two variables

- Mutual information quantifies the "amount of information" (in bit, if the logarithm base is 2) obtained about one random variable through observing the other random variable

$$MI = I(X;Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log(\frac{p(x,y)}{p(x)p(y)})$$



  - $p(x)$ and $p(y)$ are the marginal probability functions of X and Y, respectively

  - $p(x,y)$ is the joint probability function of X and Y

- $I(X;Y) = I(Y;X) \geq 0$ symmetric and non-negative

- $I(X;Y) = 0$ if X and Y are independent random variables, so that $p(x,y) = p(x)p(y)$

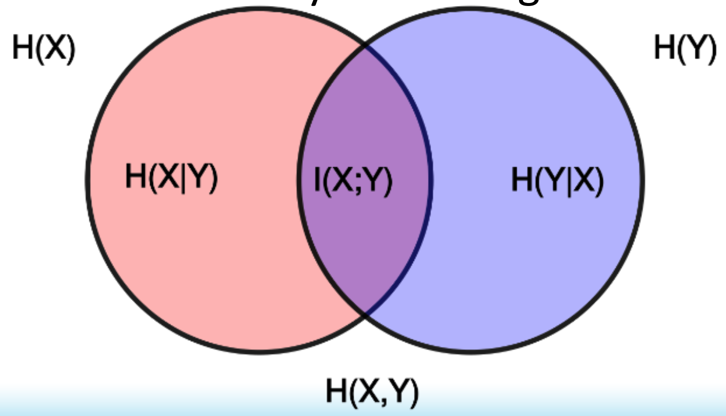
Mutual information

- The mutual information can be expressed in terms of Shannon entropy $H(X)$ as a measure of uncertainty of a random variable

$$H(X) = -\sum_{x \in X} p(x)\log\big(p(x)\big) = \sum_{x \in X} p(x)\log(\frac{1}{p(x)})$$

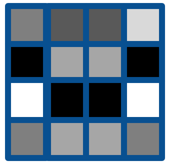
$$I(X;Y) = H(X) - H(X|Y) = H(Y) - H(Y|X) = H(X) + H(Y) - H(X,Y)$$

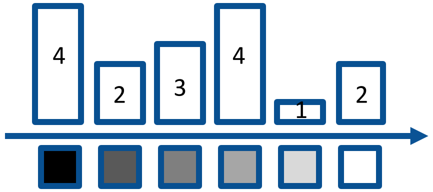
  - $H(X)$ and $H(Y)$ are the marginal entropies
  - $H(Y|X)$ is the conditional entropy of Y given X measuring the amount of uncertainty remaining about Y after X is known (and *vice versa*)
    - $p(y|x)$ and $p(x|y)$ are the conditional probability functions
    - The conditional probability functions and the joint probability function are related according to: $p(x,y) = p(y|x)p(x)$ and $p(x,y) = p(x|y)p(y)$



Mutual information

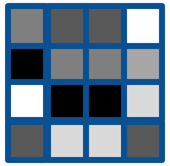
- $p(x)$ (to calculated $H(X)$) is the histogram of gray level occurrences of the fixed image

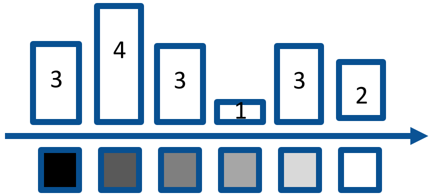




$$x = (1, \ldots N)$$

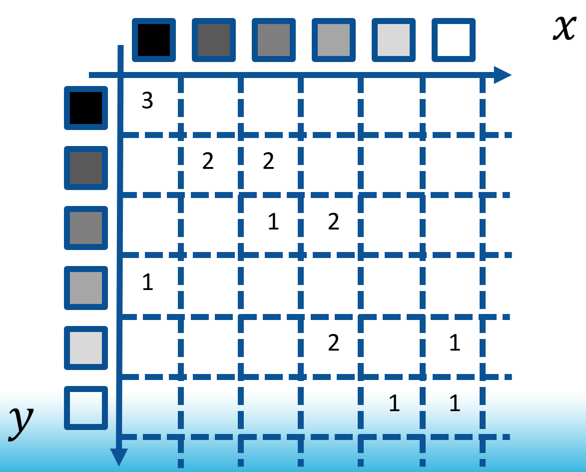
- $p(y)$ (to calculated $H(Y)$) is the histogram of gray level occurrences of the moving image

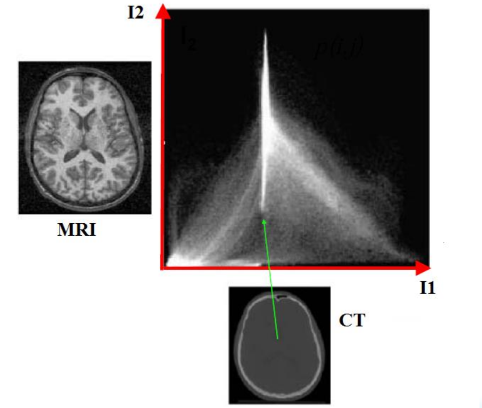




$$y = (1, \ldots N)$$

- $p(x, y)$ (to calculate $H(X, Y)$) is the joint histogram of the gray level occurrences of the two images

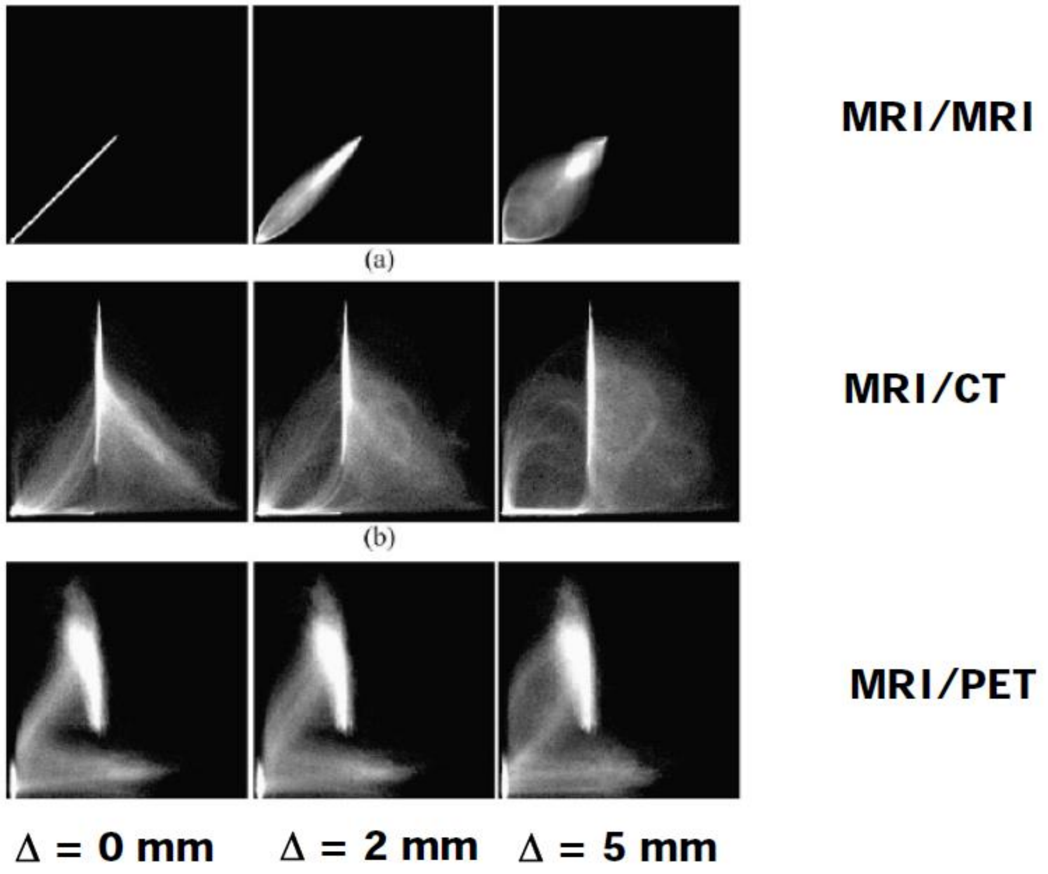




Mutual information

- Realistic joint histograms for different rigid translations (Δ)
- The mutual information is a measure of the joint histogram dispersion
- To reduce the influence of background, the normalized mutual information can be calculated

$$NMI = \frac{H(X) + H(Y)}{H(X,Y)}$$



Transformation parameters

- The parametrization for rigid registration is given by 6 parameters (3 for translation and 3 for rotations)

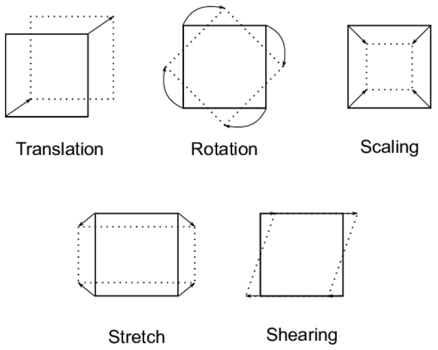
$$T=\left(\begin{array}{ccc|c} & R(\Omega,\Phi,K) & & \begin{array}{c}X\\Y\\Z\end{array} \\ \hline 0 & 0 & 0 & 1\end{array}\right)$$

$$\begin{pmatrix}1&0&0&X\\0&1&0&Y\\0&0&1&Z\\0&0&0&1\end{pmatrix}\begin{pmatrix}1&0&0&0\\0&\cos(\Omega)&\sin(\Omega)&0\\0&-\sin(\Omega)&\cos(\Omega)&0\\0&0&0&1\end{pmatrix}\begin{pmatrix}\cos(\Phi)&0&\sin(\Phi)&0\\0&1&0&0\\-\sin(\Phi)&0&\cos(\Phi)&0\\0&0&0&1\end{pmatrix}\begin{pmatrix}\cos(K)&\sin(K)&0&0\\-\sin(K)&\cos(K)&0&0\\0&0&1&0\\0&0&0&1\end{pmatrix}$$

Translation Rotation across x Rotation across y Rotation across z

  - The order of operations (translation and rotations) matters…

- The parametrization for affine transformation is given by 12 parameters (3 for translation, 3 for stretching/scaling, 3 for shearing and 3 for rotations)



Translate

$$\begin{bmatrix}1&0&T_x\\0&1&T_y\\0&0&1\end{bmatrix}$$

Rotate

$$\begin{bmatrix}\cos(\Theta)&-\sin(\Theta)&0\\\sin(\Theta)&\cos(\Theta)&0\\0&0&1\end{bmatrix}$$

Scale

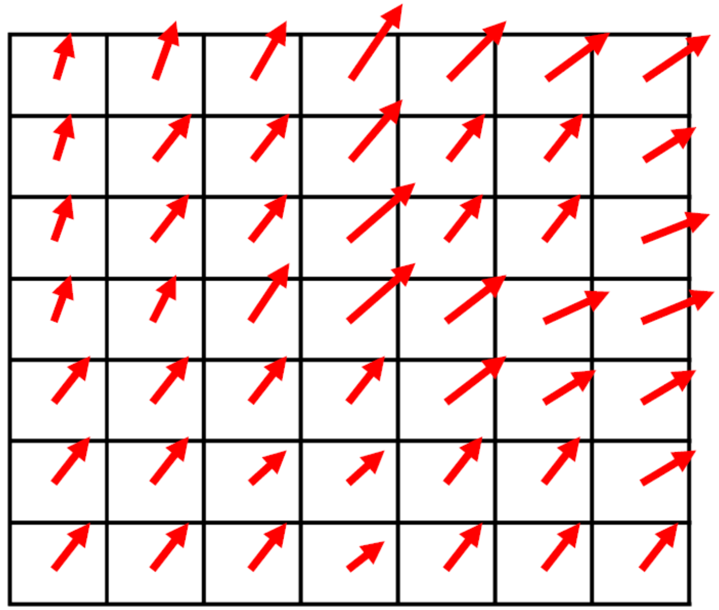
$$\begin{bmatrix}S_x&0&0\\0&S_y&0\\0&0&1\end{bmatrix}$$

Shear

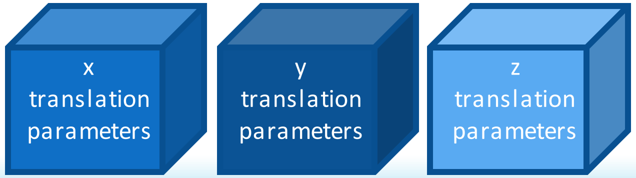
$$\begin{bmatrix}1&Sh_x&0\\Sh_y&1&0\\0&0&1\end{bmatrix}$$

Transformation parameters

- The parametrization for deformable registration is given by 3 translational parameters for each voxel (2 translational parameters for each pixel)

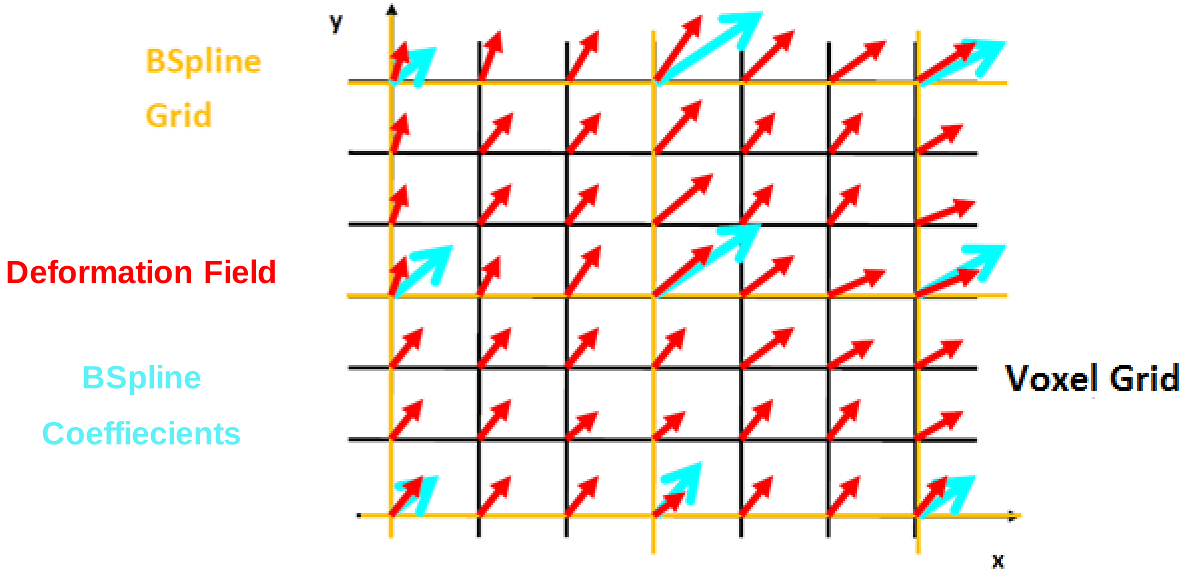


- The parameter matrix, provided with and additional dimension with respect to the image, is typically referred to as "deformation field"



Transformation parameters

- To reduce the amount of parameters, the deformation field can be defined in control points (grid coarser than the voxel grid) and modeled elsewhere in terms of coefficients and basis functions

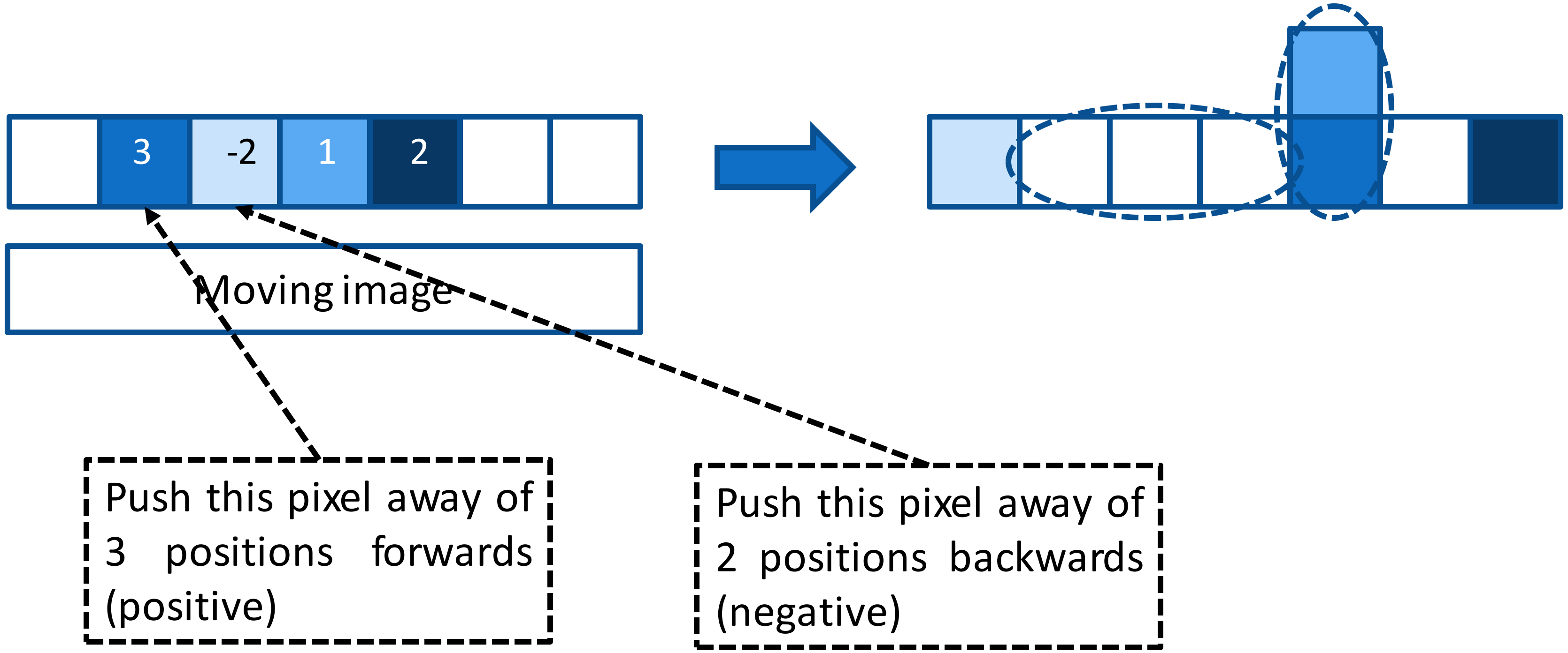


- The B-spline coefficients $P(i,j,k)$ are optimized on the B-spline grid in (i,j,k) and subsequently calculated according to the B-spline basis functions (pre-calculated) in (x,y,z)

$$v(x,y,z) = \sum_{i=1}^{4} \sum_{j=1}^{4} \sum_{k=1}^{4} P(i,j,k) B_i(x) B_j(y) B_k(z)$$

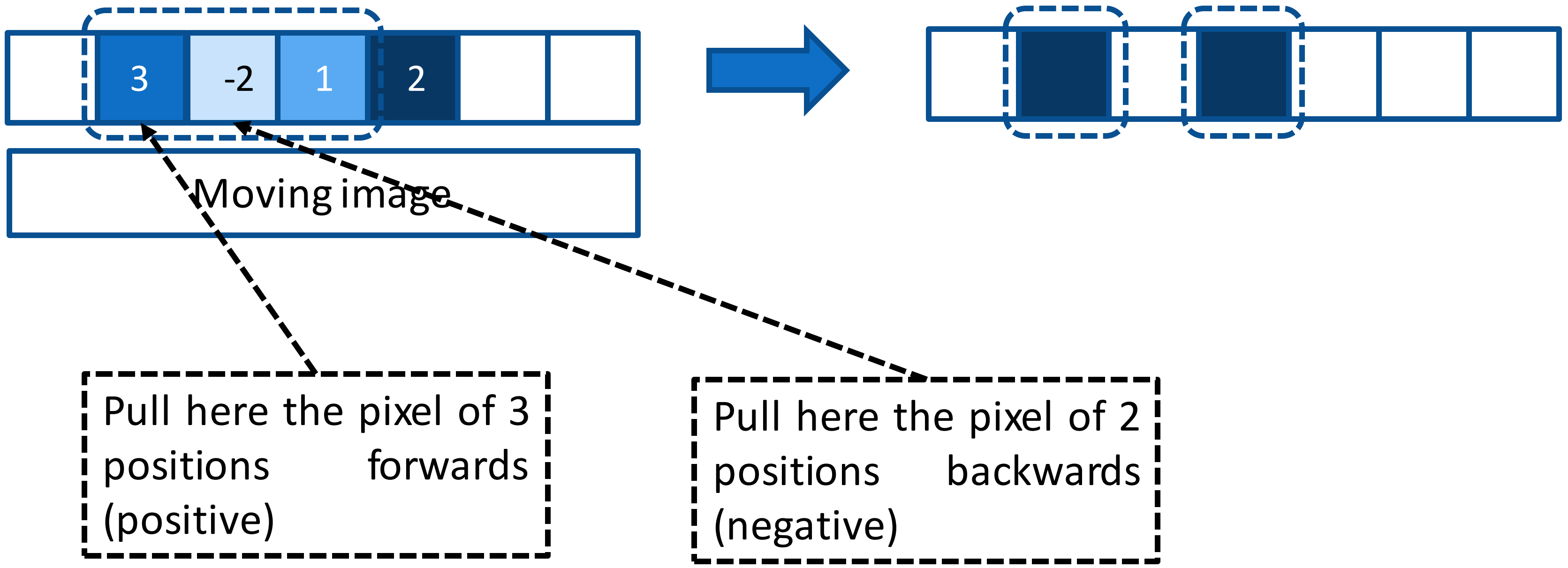
Formalism in parameterization

- Push-forward formalism: the deformation indicates the voxel of the moving image to be pushed-forward
    - The gray levels of the moving image are maintained but can create hole and overlap



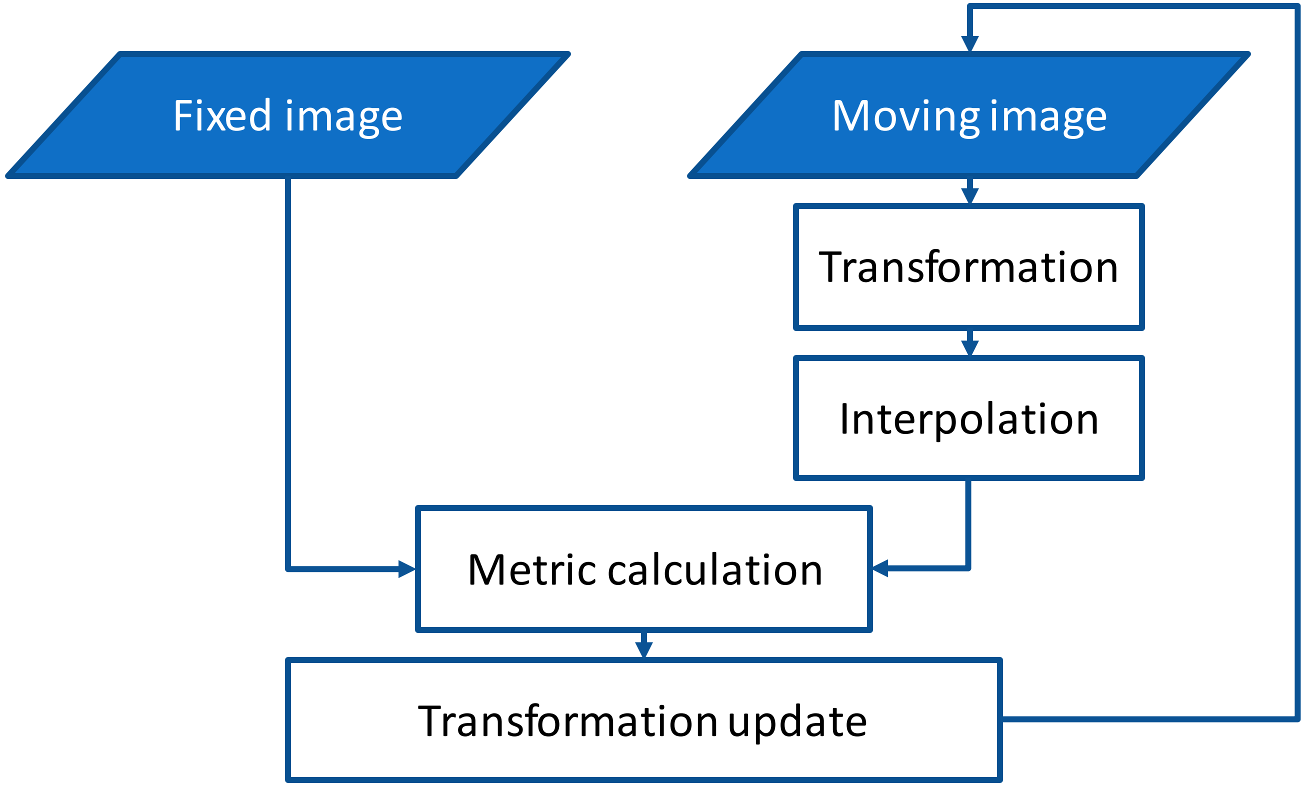
Formalism in parameterization

- Pull-back formalism: the deformation field indicates the voxel of the moving image to be pulled-back
  - The gray levels of the moving image are not maintained as they can be repeated or missed (hole and overlap are excluded) but no hole and overlap are created



Optimization

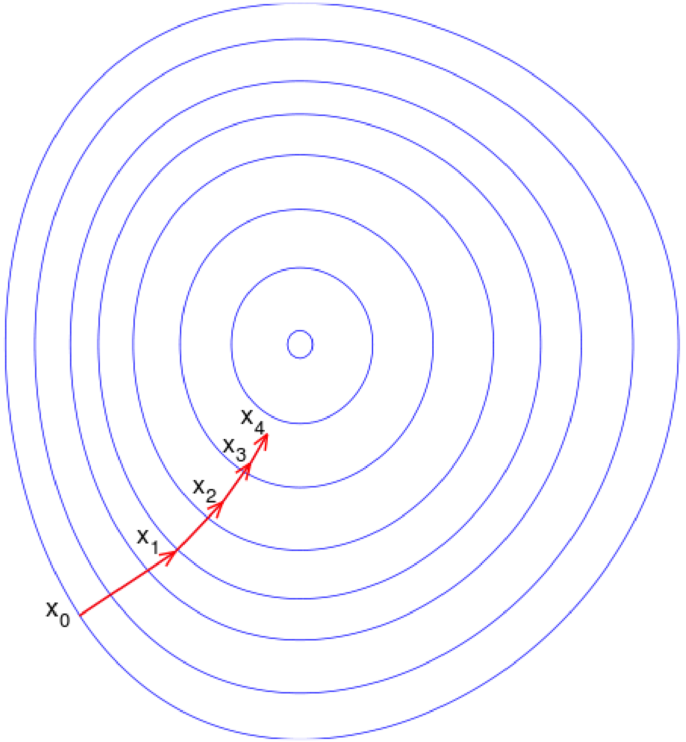
- The numerical optimization aims at finding the "best" transformation parameters according to an objective function defined by the chosen metric



- Different numerical optimization algorithms can be adopted for deformable image registration

Gradient descent

- First-order iterative optimization algorithm for finding the local minimum of the objective function using gradient descent
- Update steps proportional to the negative of the gradient (or approximate gradient) of the objective function at the current point
  - Initialize x_0
  - Compute $\nabla f(x_n)$
  - Update $x_{n+1} = x_n - \alpha \nabla f(x_n)$ (α is the step size)
  - Stop (stopping criteria on n or x_n and x_{n+1})



Newton method

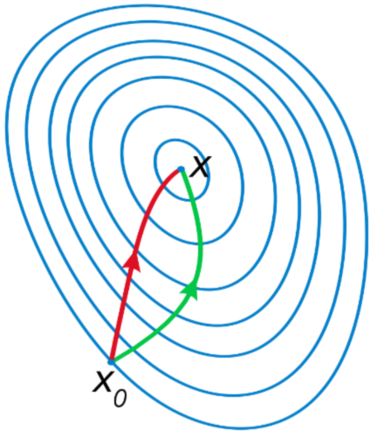
- Second-order iterative optimization algorithm for finding the local minimum of the objective function using first and second derivatives of the objective function

$$f(x_n + \Delta x) \approx f(x_n) + f'(x_n)\Delta x + \frac{1}{2} f''(x_n)\Delta x^2$$

$$\frac{d\left(f(x_n) + f'(x_n)\Delta x + \frac{1}{2} f''(x_n)\Delta x^2\right)}{d\Delta x} = f'(x_n) + f''(x_n)\Delta x = 0$$

$$\Delta x = -\frac{f'(x_n)}{f''(x_n)}$$

$$x_{n+1} = x_n + \Delta x$$

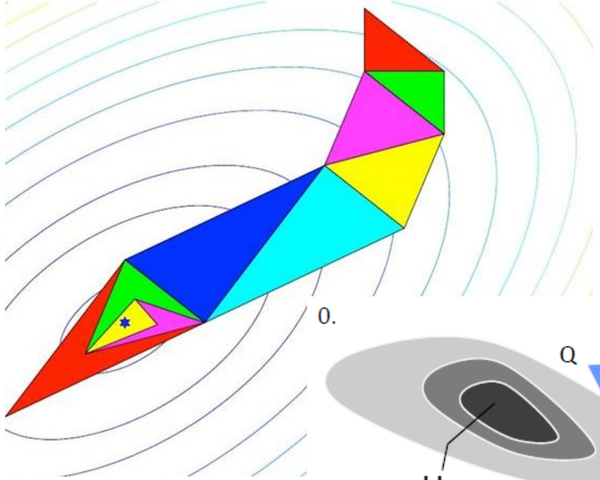


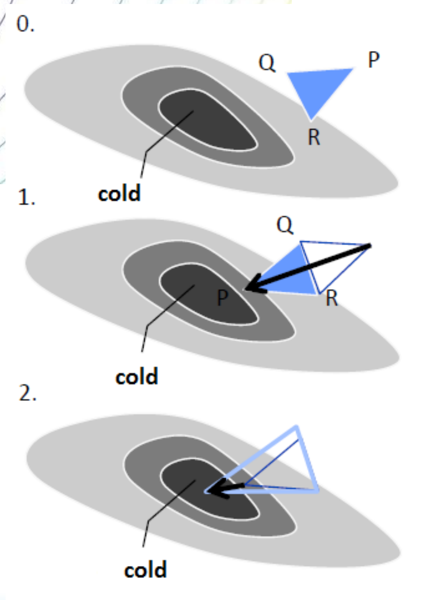
- Update steps account for also for curvature (second derivative) of the objective function at the current point

Nedler-Mead algorithm

- “Direct” (without derivative calculation) iterative optimization algorithm for finding the local minimum of the objective function based on adjustment of the simplex

  - Simplex has $n + 1$ vertices, each vertex is described by $x_n \in R^n$
  - Update of the vertex position x_n based on the evaluation of the objective function $f: R^n \rightarrow R$ at each vertex position
  - Replacement of the worst vertex by the reflected centroid of the remaining n vertices across the opposite best face of the simplex
  - Expansion or contraction and shrinkage
  - The simplex moves towards the minimum of the objective function





The role of imaging in radiation oncology

- The clinical use of image registration in radiotherapy can be classified according to the following applications
  - Treatment planning
  - Patient positioning
  - Treatment adaptation
  - Long-term treatment verification

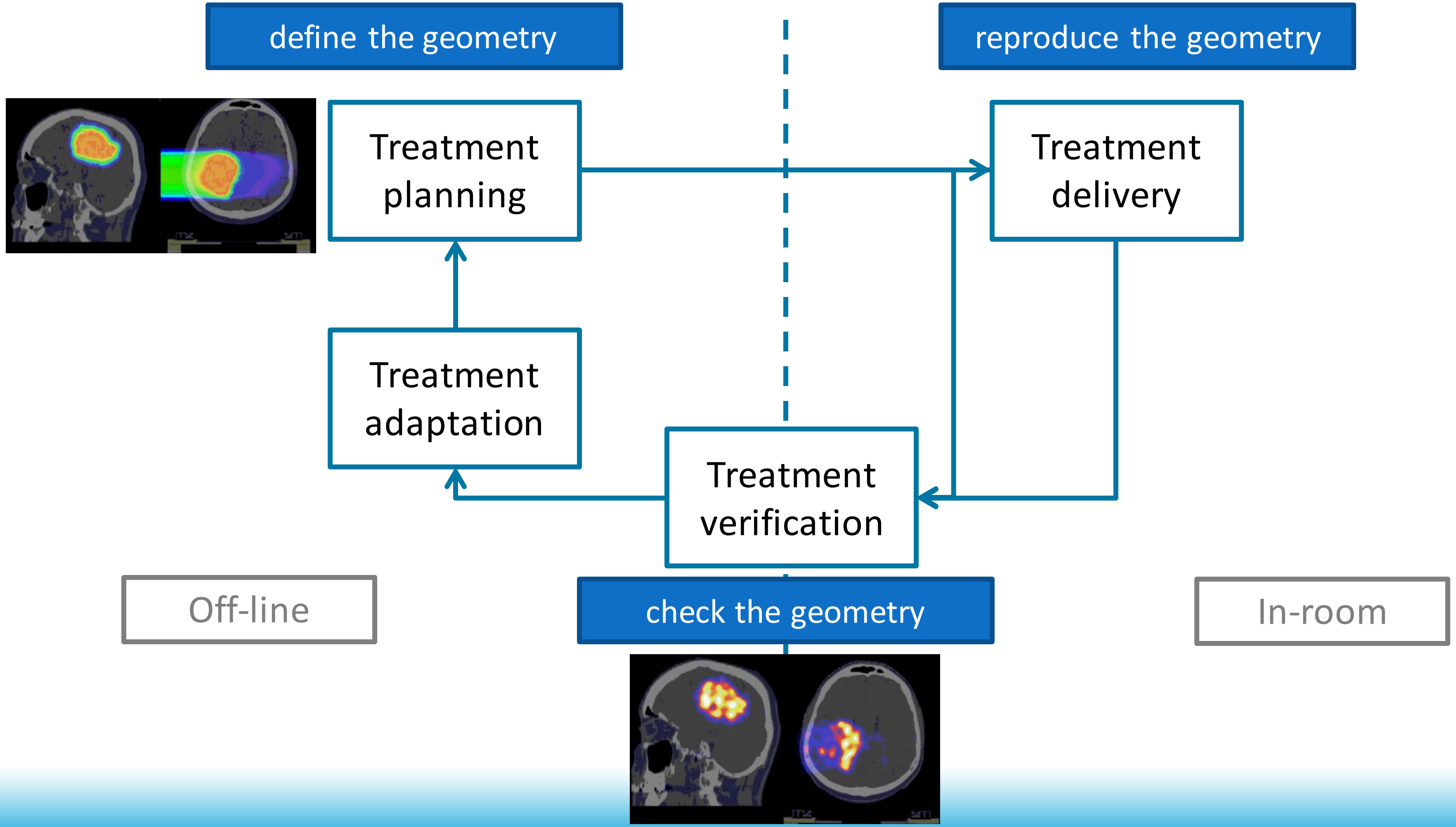
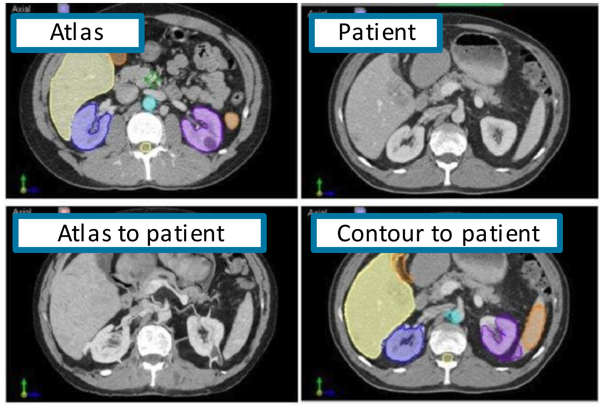
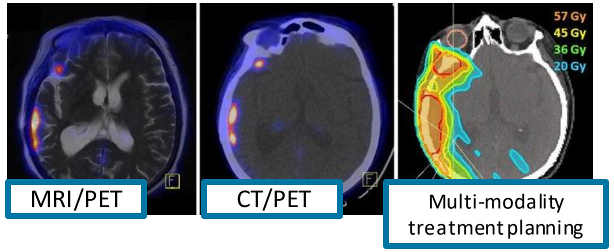


Image registration in treatment planning

- Between the image of the patient and anatomical atlases (i.e., organ segmentation in treatment planning)
  - Same image modality (mono-modal), different patients (inter-patient)
- Between images of the patient from different imaging modalities such as CT and MRI, PET/CT and PET/MRI (i.e., multi-modality treatment planning)
  - Different image modalities (multi-modal), same patient (intra-patient)



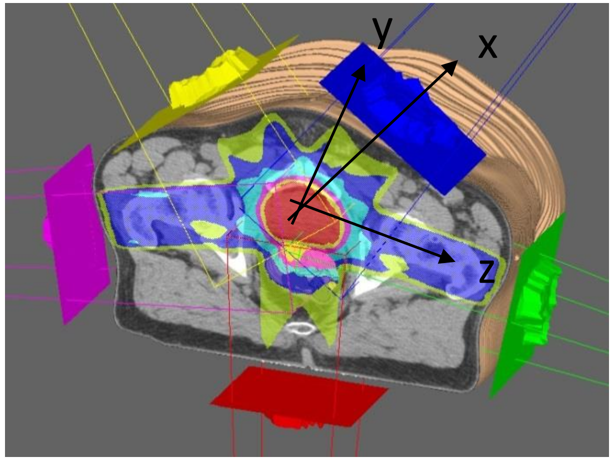


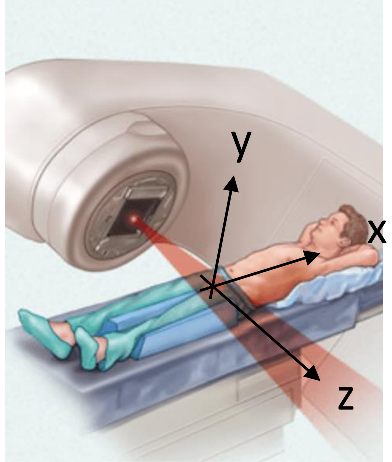
Thorwarth, D., Leibfarth, S., & Mönnich, D. (2013). Potential role of PET/MRI in radiotherapy treatment planning. Clinical and Translational Imaging, 1, 45-51.

Rigid registration for patient positioning

- The in-room patient anatomy (treatment delivery scenario) is matched to the (model of) patient anatomy of the treatment planning CT (treatment planning scenario)
- The patient position in treatment delivery is rigidly aligned to the treatment planning scenario prior to treatment delivery

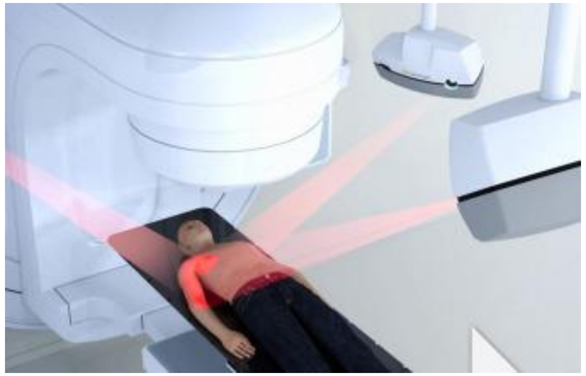
Treatment planning → Treatment delivery

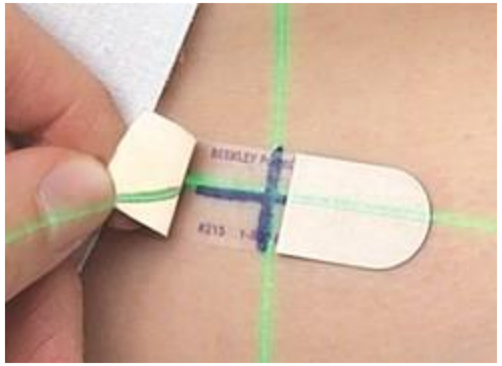




Rigid registration for patient positioning

- Patient positioning can rely on in-room optical systems enabling surface alignment or point alignment of external landmarks placed directly on patient skin (referenced with tattoo) or on immobilization devices





Rigid registration for patient positioning

- Patient positioning can rely on in-room X-ray imaging, thus enabling point alignment ("feature-based", requiring image processing for feature/point identification) or anatomical alignment ("intensity-based", directly exploiting the image intensities)

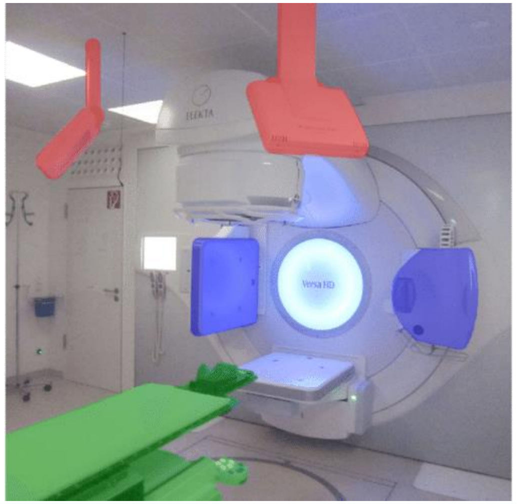
Rigid registration for patient positioning

- Patient positioning can rely on in-room X-ray imaging, thus enabling point alignment ("feature-based", requiring image processing for feature/point identification) or anatomical alignment ("intensity-based", directly exploiting the image intensities)

  - Point alignment of internal (implanted) and external landmarks as imaged by 2D MeV/KeV "continuous" fluoroscopic imaging (dynamic treatment delivery)

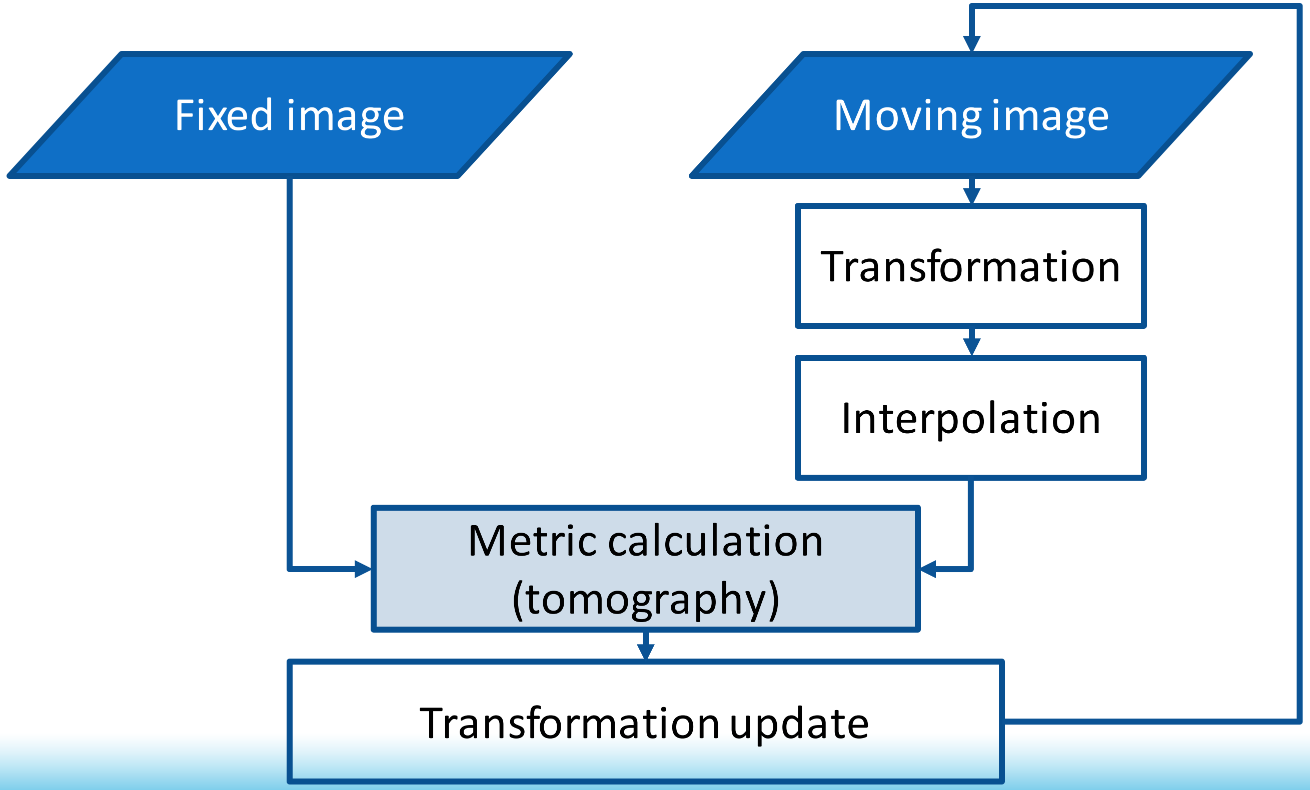
  - Anatomical alignment based on 2D or 3D MeV ("mega-voltage") electronic portal imaging in photon therapy (the X-ray source coincides with the therapeutic radiation source)

  - Anatomical alignment based on 2D or 3D KeV ("kilo-voltage") imaging from auxiliary imaging systems (i.e., cone beam CT)



3D-3D rigid registration algorithm

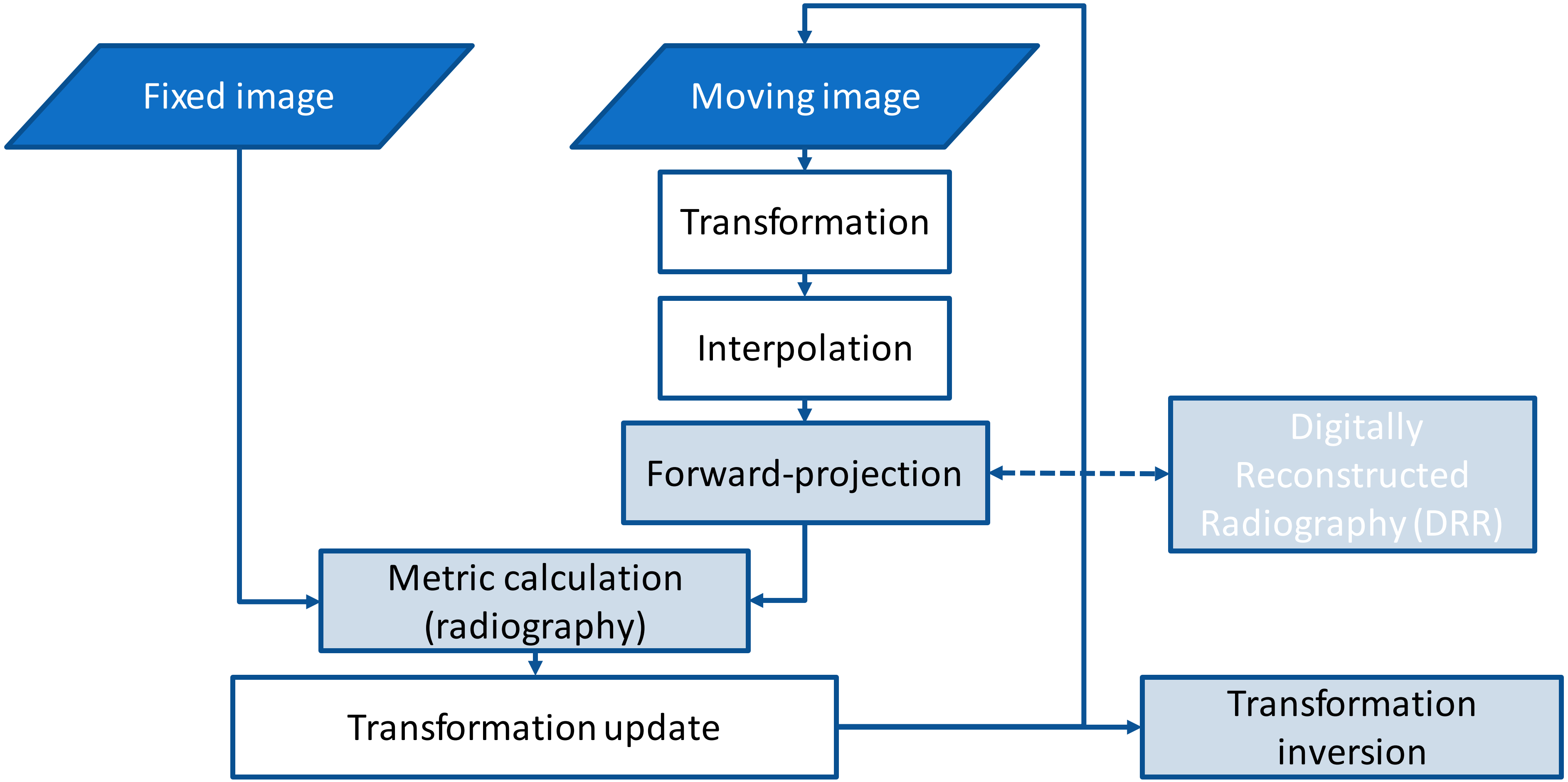
- When 3D in-room X-ray imaging is available, the anatomical alignment is based on 3D-3D rigid image registration algorithm
  - The treatment planning scenario is adopted as reference (fixed image) and the treatment delivery scenario is adopted as target (moving image)



2D-3D rigid registration algorithm

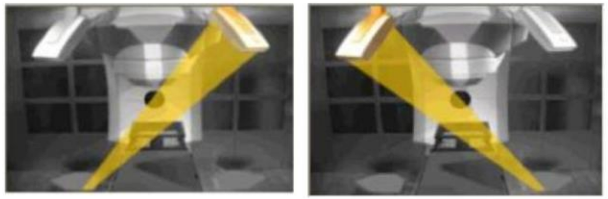
- When relying on 2D in-room X-ray imaging, the anatomical alignment requires 2D-3D rigid image registration algorithm
  - The treatment planning scenario (3D X-ray image) *must be* adopted as moving image, thus undergoing transformation (roto-translation) during numerical optimization
    - In static treatment delivery the inverse rigid transformation is applied to the treatment couch prior to treatment delivery
      - The inverse transformation converts the treatment planning scenario into the reference (fixed image)
    - In dynamic treatment delivery the direct rigid transformation is applied to the radiation source during treatment delivery
      - The treatment delivery scenario is actually the reference (fixed image)

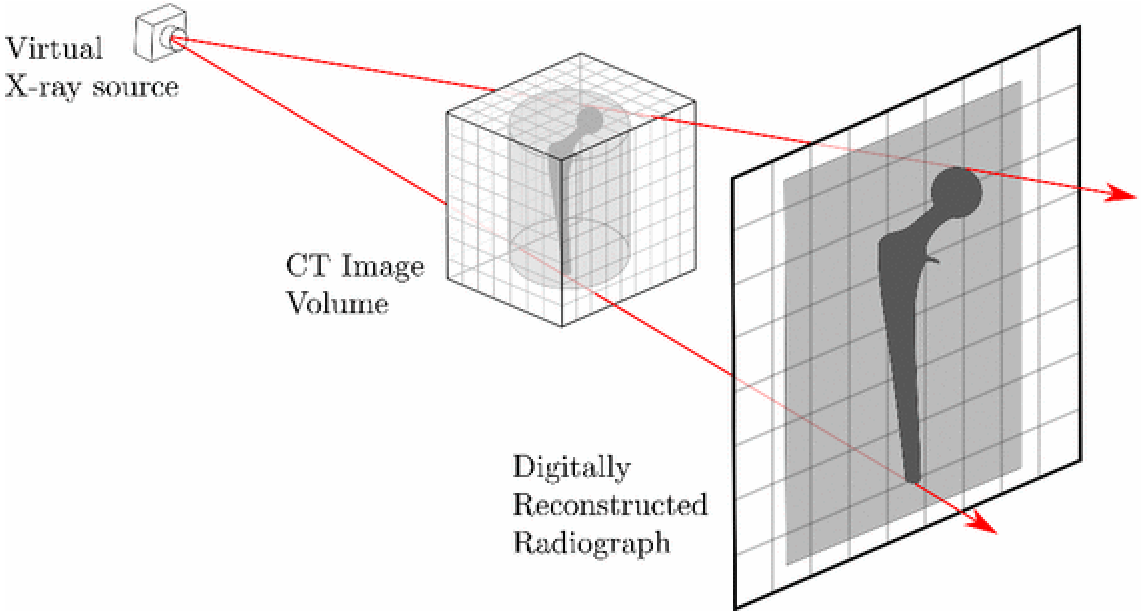
2D-3D rigid registration algorithm



Digitally Reconstructed Radiography (DRR)

- The DRR is defined as the forward-projection of the treatment planning CT
- When 2D in-room X-ray imaging is available, the DRRs (a minimum of 2 DRRs is required!) is used for patient positioning based on 2D-3D rigid registration but can have also a role in treatment verification

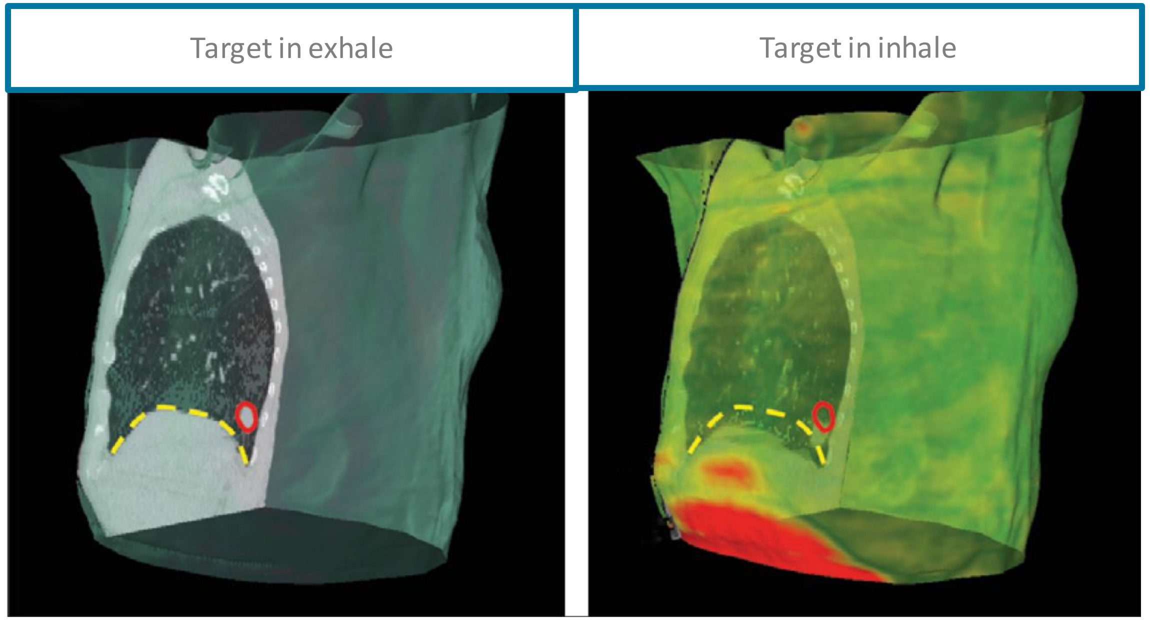




- Treatment is eventually adapted based on a re-planning CT (if 3D in-room X-ray imaging is not available)

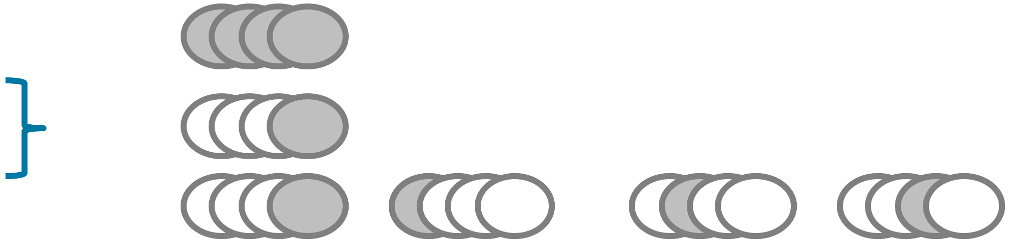
Insights about static/dynamic treatment

- Motion managements in treatment planning, delivery and verification of moving targets



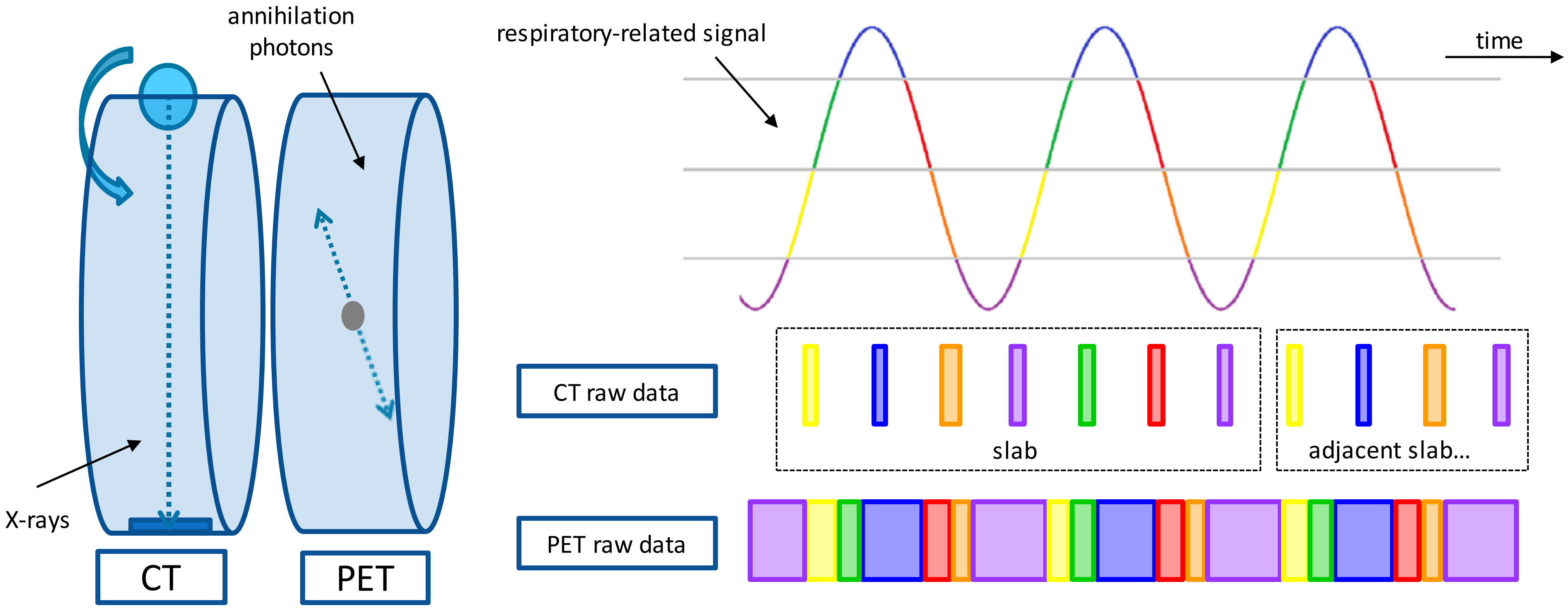
Riboldi, M., Orecchia, R., & Baroni, G. (2012). Real-time tumour tracking in particle therapy: technological developments and future perspectives. The lancet oncology, 13(9), e383-e391.

- Motion encompassing
- Gating
- Breath hold
- Tumor tracking



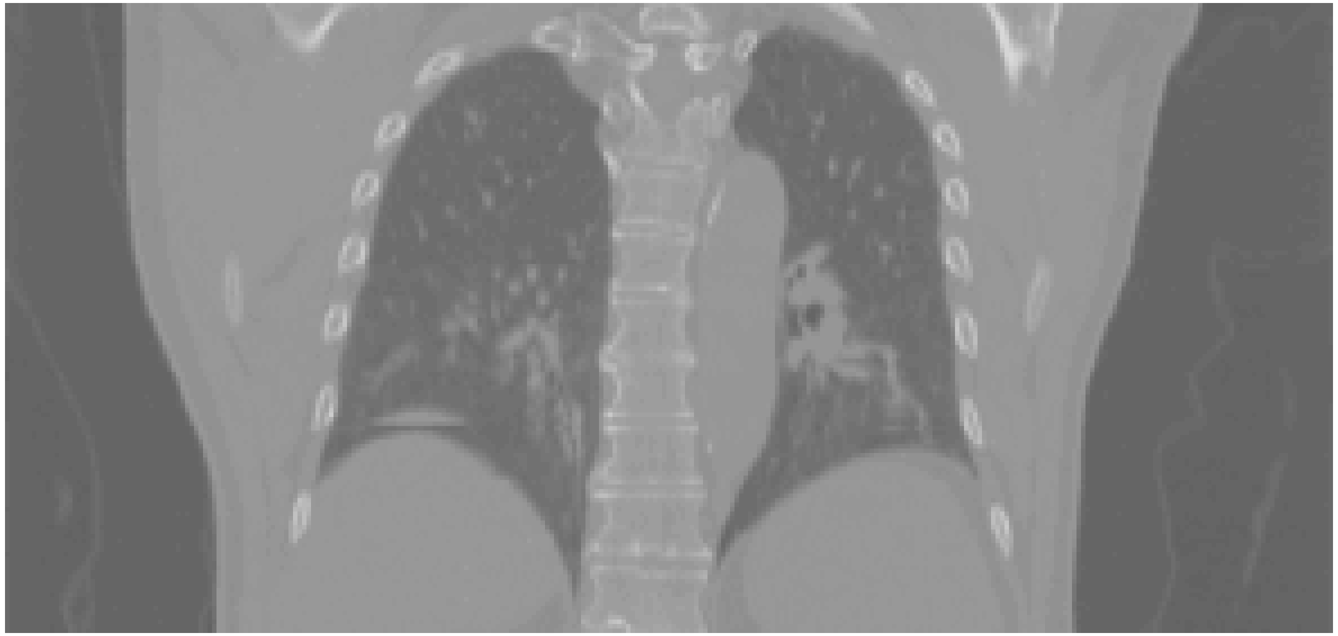
Insights about dynamic treatment

- Image acquisition synchronized with a respiratory-related signal, as provided by infrared localization of a marker(s)
- Time-labelled CT raw data (slab projections) and PET raw data (annihilation counts) classified into different breathing phases, namely PET gating and CT sorting, respectively



Insights about dynamic treatment

4D CT clinical data



Insights about dynamic treatment

- Dynamic treatment planning for moving targets requires time-resolved imaging and deformable image registration
    - Same image modality (mono-modal), same patient (intra-patient)
- The geometry is defined on a reference breathing phase and deformable image registration is used to map the same geometry on the different breathing phases
- The treatment planning is calculated on each breathing phase
- The dose is then calculated on the reference breathing phase by means of *dose warping* (pull-back or push-forward?) and time weighted summation

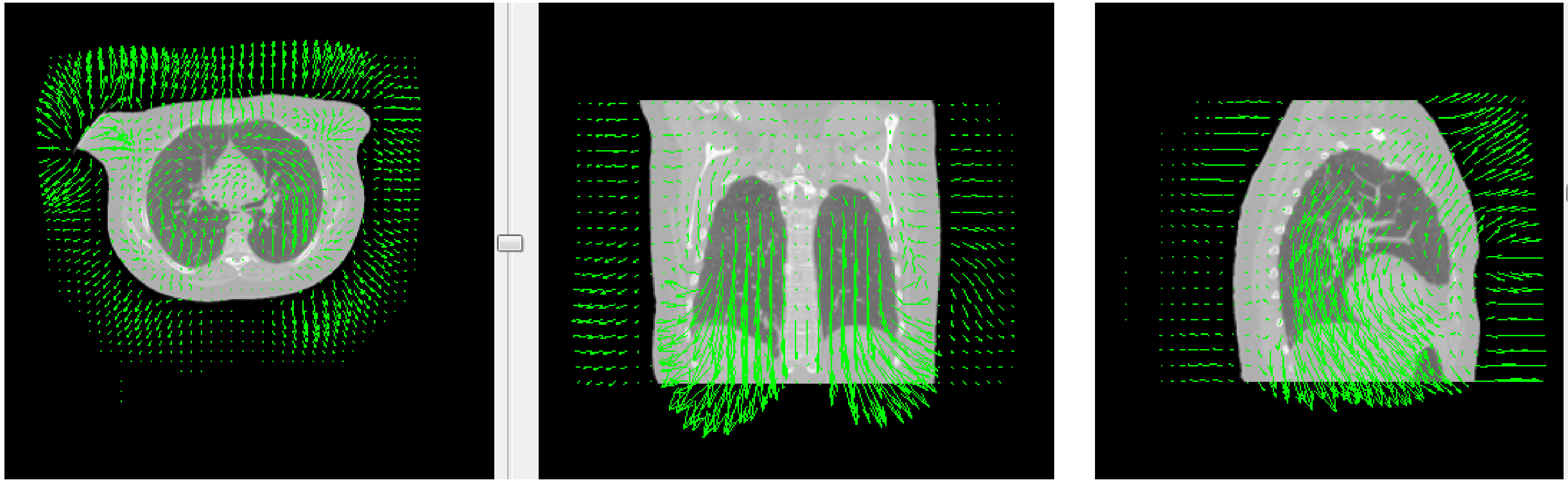
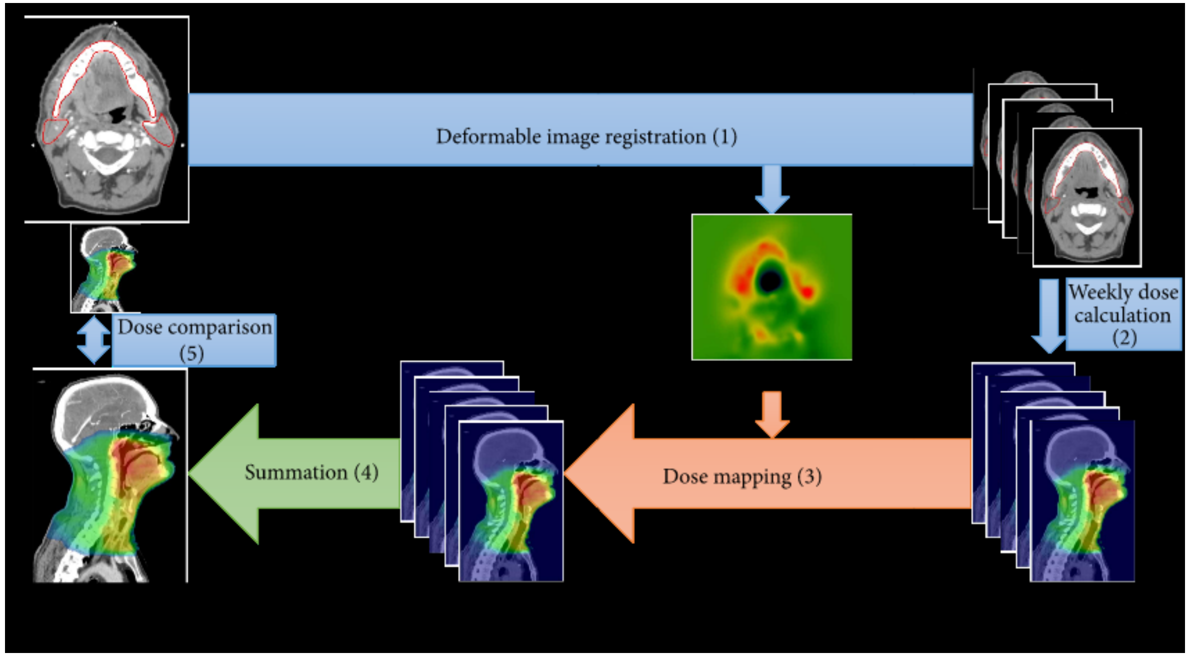


Image registration in treatment adaptation

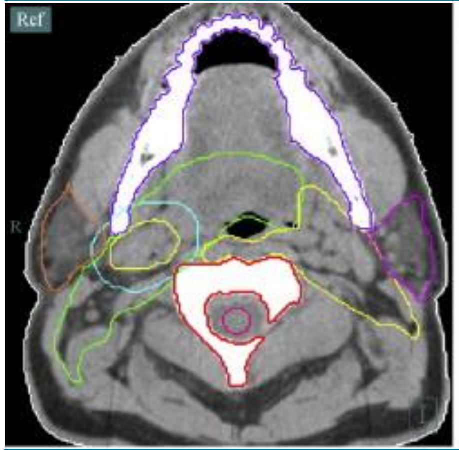
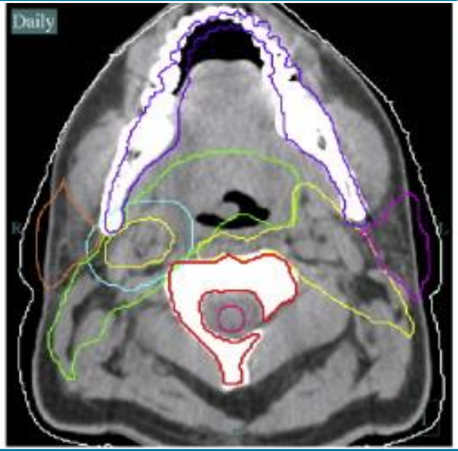
- Between images of the same patient in the treatment planning scenario and in the treatment delivery scenario
  - To provide an up-to-date estimation of the delivered dose
  - To eventually provide an up-to-date image for treatment re-planning, along with the up-to-date contours



Rigaud, B., Simon, A., Castelli, J., Gobeli, M., Ospina Arango, J. D., Cazoulat, G., … & De Crevoisier, R. (2015). Evaluation of deformable image registration methods for dose monitoring in head and neck radiotherapy. BioMed research international, 2015.

Image registration in treatment adaptation

- Treatment adaptation and *contour propagation*
  - Deformable image registration of the treatment planning CT (moving image) to the "CT of the day" (fixed image) to obtain a deformation field to be applied to contours (time consuming)

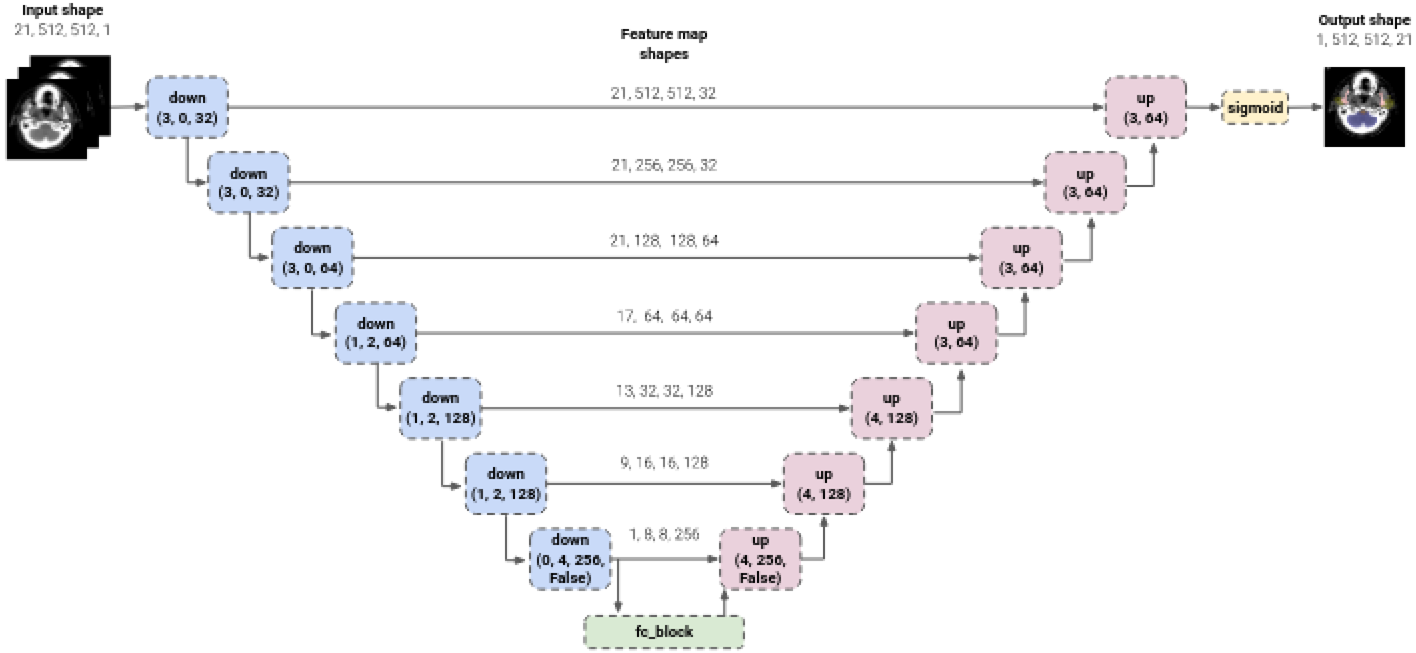
Treatment planning	CT of the day	CT of the day
		
Contours	Rigid alignment of contour	Contour propagation

Machine learning in treatment planning and adaptation

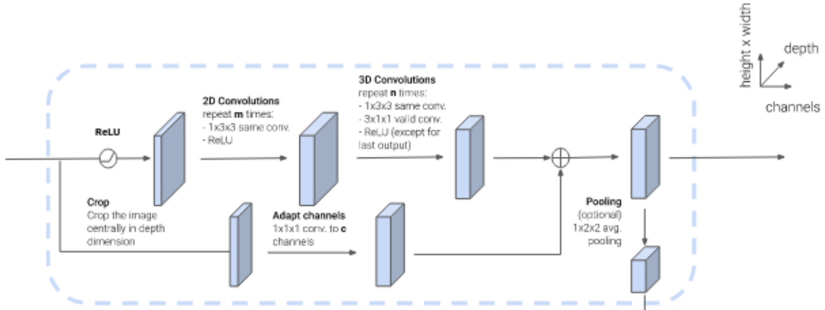
- Machine learning has been recently proposed in radiation oncology
  - Automatic contouring (i.e., auto-segmentation) of targets and organs at risks for treatment planning
  - Treatment adaptation as "virtual CT generator"
    - Based on CBCT for treatment adaptation
      - Deformable image registration maps the treatment planning CT (i.e., treatment planning scenario) onto the CBCT (i.e., treatment delivery scenario)
        - Image quality of the CBCT is inappropriate for treatment planning (compromised by artifacts and scattering effects)
    - Based on MRI also for treatment planning (i.e., "MRI-only radiotherapy")

Auto-segmentation

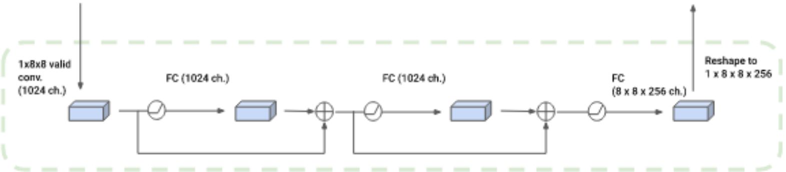
- 3D U-Net architecture with 8 levels, taking the CT (single channel) as input and giving the segmentation masks (21 channels) as output



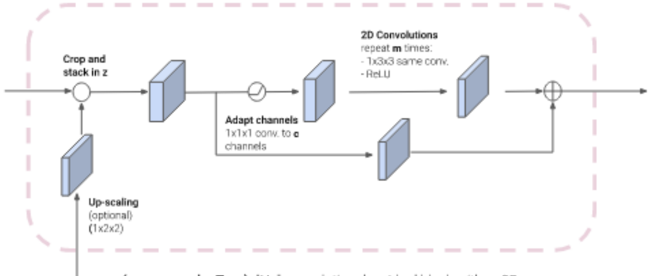
Nikolov, S., Blackwell, S., Zverovitch, A., Mendes, R., Livne, M., De Fauw, J., ... & Ronneberger, O. (2018). Deep learning to achieve clinically applicable segmentation of head and neck anatomy for radiotherapy. arXiv preprint arXiv:1809.04430.



down(m, n, c, pool=True): "Down" convolutional residual block with **m** 2D convolutions, **n** 3D convolutions, and **c** output channels. Optional pooling.



fc_block: Fully connected, residual block at the bottom of the U-Net.



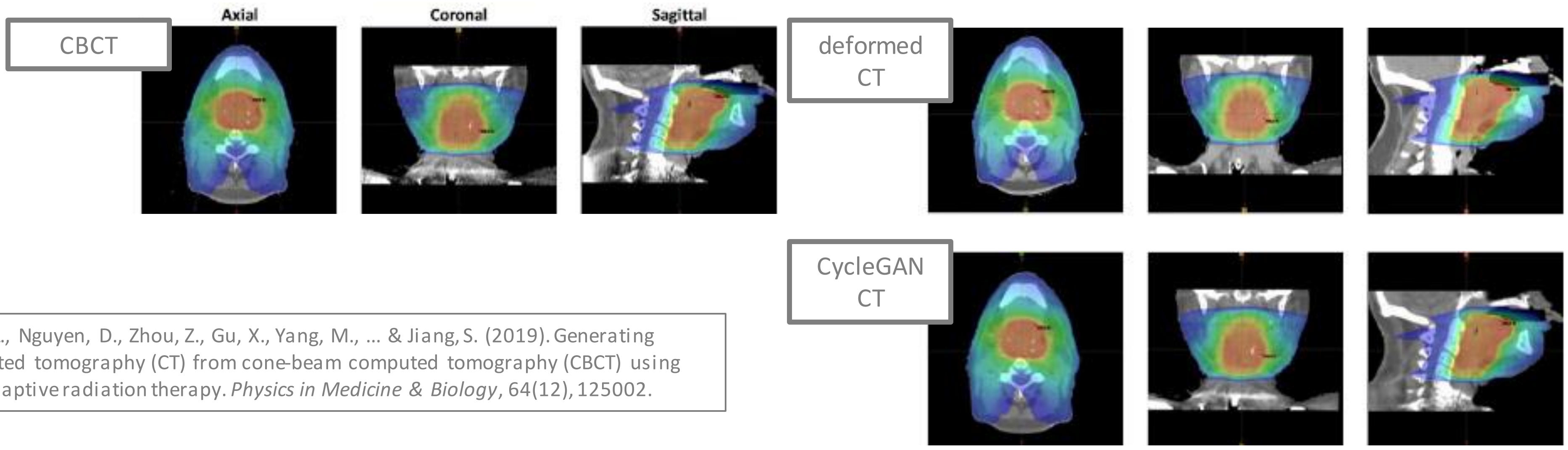
up(m, c, upscale=True): "Up" convolutional residual block with **m** 2D and **c** output channels. Optional upscaling.

Virtual CT generation

- A cycle generative adversarial network (CycleGAN) is proposed as unsupervised learning without fully relying on paired CT-CBCT images (supervised training is very difficult in these scenarios)

- Synthesized CT images are obtained from CBCT images for adaptive radiation therapy with artifacts removed or greatly reduced and intensities corrected while keeping the anatomical accuracy

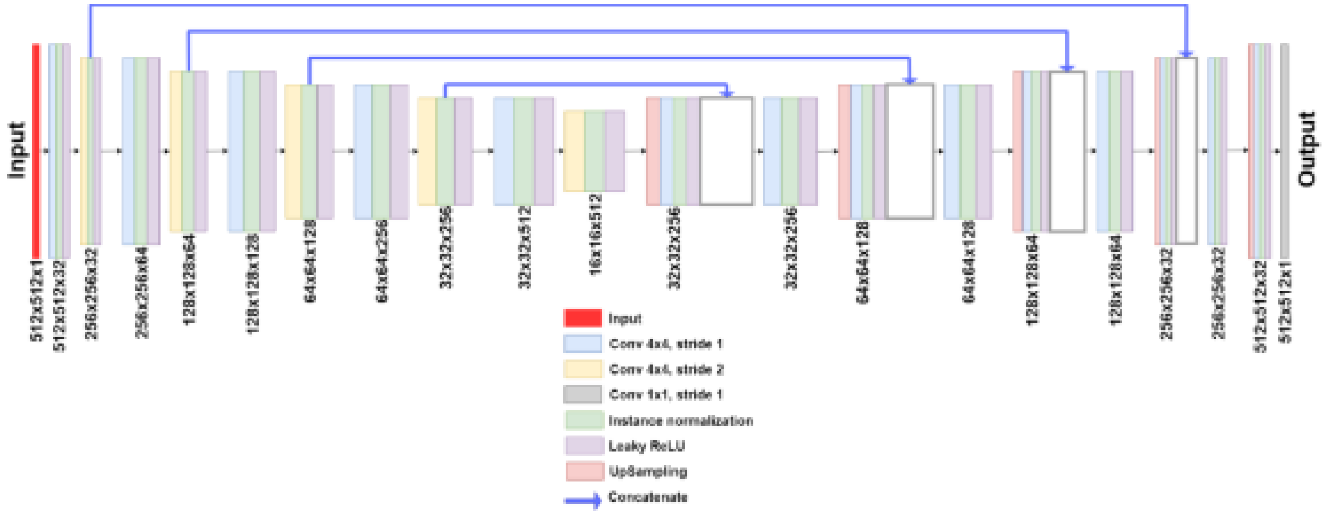
  - The synthesized CT images are used for dose calculation in adaptive radiation therapy



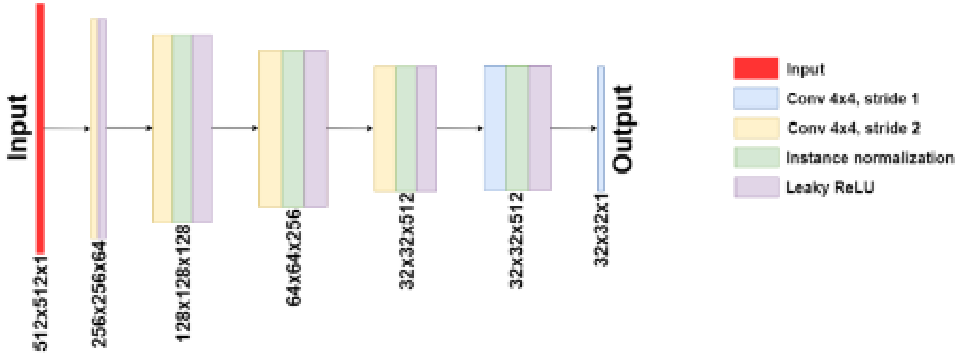
Liang, X., Chen, L., Nguyen, D., Zhou, Z., Gu, X., Yang, M., ... & Jiang, S. (2019). Generating synthesized computed tomography (CT) from cone-beam computed tomography (CBCT) using CycleGAN for adaptive radiation therapy. *Physics in Medicine & Biology*, 64(12), 125002.

Virtual CT generation

- Generator (U-Net)
  - U-Net-type architectures with encoder/decoder arms
  - Fully convolutional framework provided with skip connections



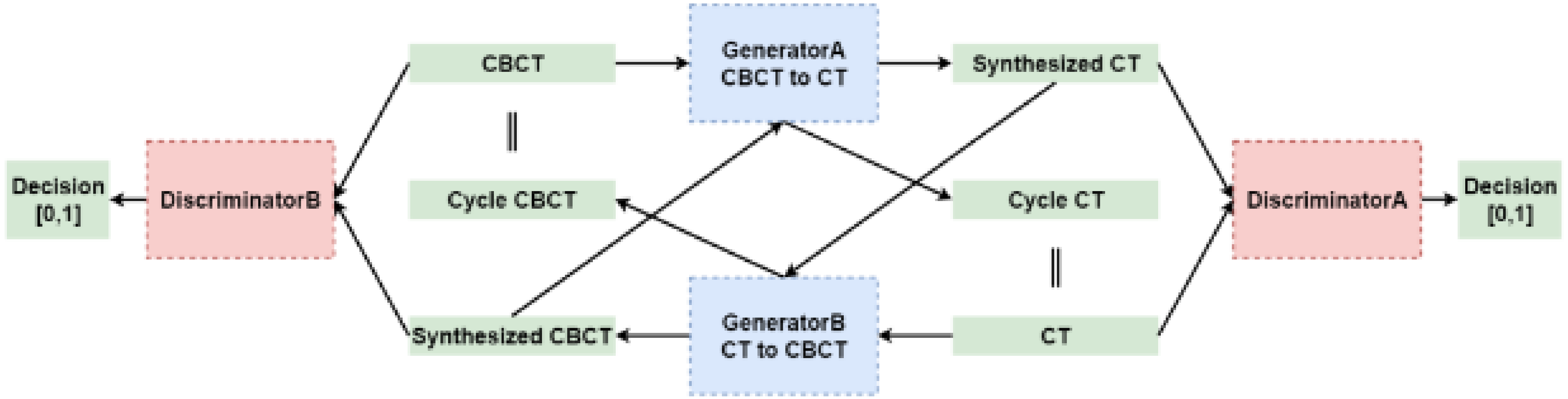
- Discriminator (patchGAN)
  - Encoder classifiers



Virtual CT generation

- Cycle-GAN includes two generators
  - mapping from CBCT to CT
  - mapping from CT to CBCT

- Cycle-GAN includes two discriminators
  - The first aims to distinguish real CT from fake CT
  - The second aims to distinguish real CBCT from fake CBCT



Virtual CT generation

- Two cycles are included in Cycle-GAN
  - In the first cycle, the CBCT is used as input to the first generator, which generates the synthetized CT. Then, the second generator takes the synthetized CT as input and generates the cycle CBCT, which is supposed to be equal to the CBCT
    - Meanwhile, the first discriminator identifies real and synthetized CT images
      - The CT label is 1 and the synthetized CT label is 0
  - In the second cycle, the CT is used as input to the second generator which generates the synthetized CBCT. Then, the first generator takes the synthetized CBCT as input and generates the cycle CT, which is supposed to be equal to the CT
    - Meanwhile, the second discriminator identifies real and synthetized CBCT images
      - The CBCT label is 1 and the synthetized CBCT label is 0

Virtual CT generation

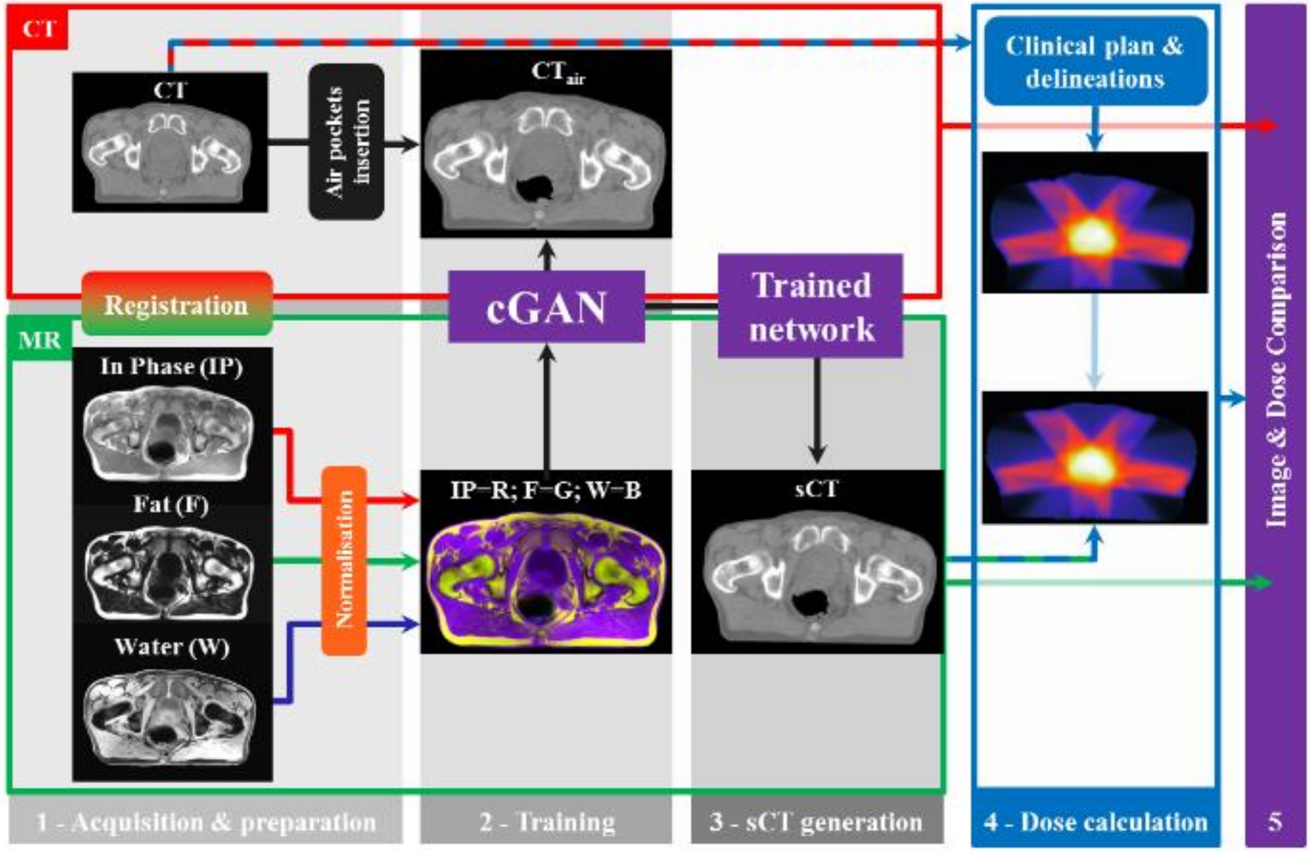
- The Cycle-GAN is a variant of the GAN that introduces a cycle-consistency loss using two generators and two discriminators
- GAN training proceeds in alternating:
  - (1) the discriminator is trained for one or more epochs while keeping the generator constant (i.e., minimization of the discriminator loss) to optimize the faking capability of the generator
  - (2) the generator is trained for one or more epochs while keeping the discriminator constant (i.e., maximization of the adversarial loss) to optimize the fooling capability of the discriminator
  - Repeat (1) and (2)

MRI-only radiotherapy

- The soft tissue contrast offered by MRI is exploited without recurring to inter-modality image registration
- The patient exposure to ionizing radiation is reduced, along with treatment cost and workload, thus enabling on-line daily re-planning in MR-guided radiotherapy systems

Tenhunen, M., Korhonen, J., Kapanen, M., Seppälä, T., Koivula, L., Collan, J., ... & Visapää, H. (2018). MRI-only based radiation therapy of prostate cancer: workflow and early clinical experience. Acta Oncologica, 57(7), 902-907.

- Conditional generative adversarial network (cGAN) as supervised version of GAN based on paired images (i.e., DIR)
  - Generator based on U-Net architecture
  - Discriminator based on convolutional “PatchGAN” classifier



Maspero, M., Savenije, M. H., Dinkla, A. M., Seevinck, P. R., Intven, M. P., Jurgenliemk-Schulz, I. M., ... & van den Berg, C. A. (2018). Dose evaluation of fast synthetic-CT generation using a generative adversarial network for general pelvis MR-only radiotherapy. Physics in Medicine & Biology, 63(18), 185001.

Outlook

- Image registration is used at different stages in radiation oncology
  - Patient positioning is based on rigid registration
  - Multi-modality treatment planning, atlas-based segmentation in treatment planning and treatment adaptation are based on deformable image registration
- Deep learning is adopted to replace the role of deformable image registration with advantages in term of quality and efficiency