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Inverse problems and machine learning in medical physics

Treatment planning -
Machine learning in treatment planning

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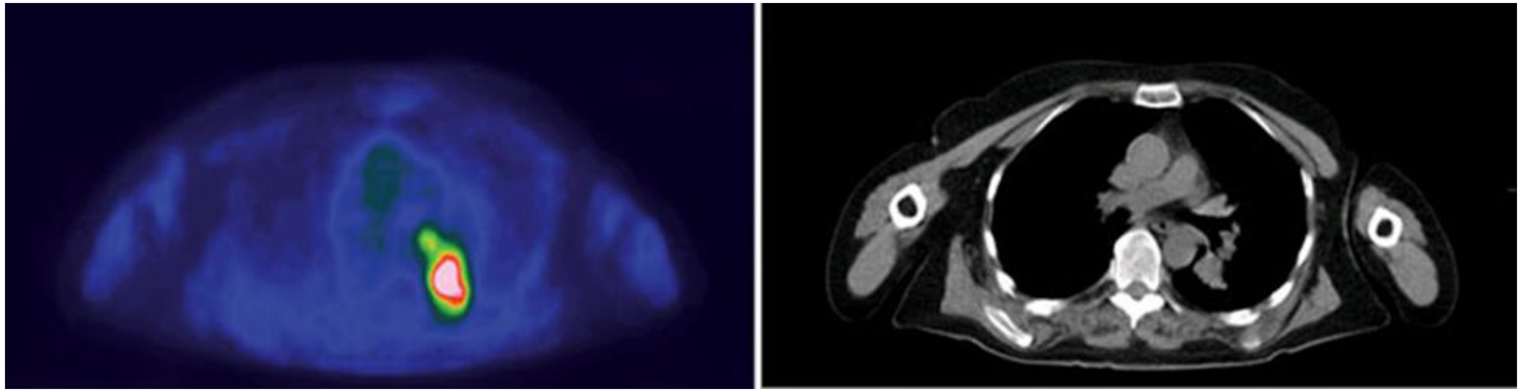
Imaging in treatment planning

- The anatomical identification of the target is typically based on X-ray imaging, or Computed Tomography (CT)
    - Functional information based on Positron Emission Tomography (PET) and anatomical or functional information based on Magnetic resonance imaging (MRI) can complement the anatomical target identification (i.e., secondary imaging)

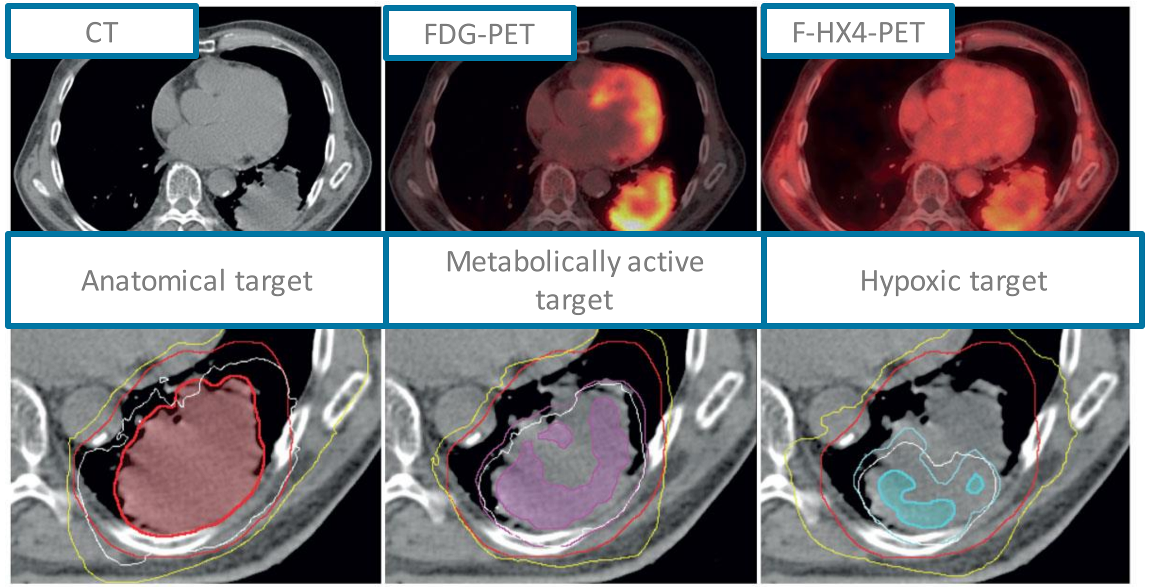
PET image | CT image



Bussink et al. *Nat. Rev. Clin. Oncol.* 2011

Imaging in treatment planning

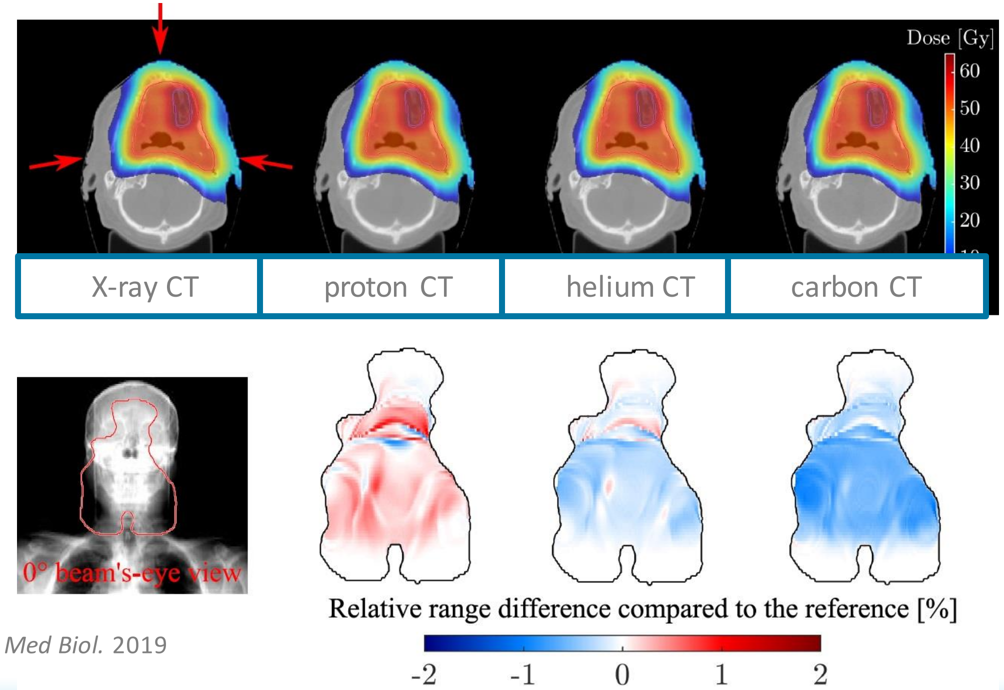
- The functional identification of the target can be used for "dose painting"
  - ^{18}FDG-PET: glucose uptake and metabolism
  - ^{18}F-HX4-PET: molecular retention correlated to tumor hypoxia



Grootjans et al. *Nat. Rev. Clin. Oncol.* 2015

Fundamentals in treatment planning

- The treatment planning is an inverse problem and requires numerical optimization to define the beam parameters (i.e., inverse treatment planning), based on:
  - Definition of the treatment geometry (i.e., target and critical organs identification)
  - Physical characterization of the patient (i.e., tomographic image reconstruction of the properties of the radiation in tissue)
    - photon attenuation (X-ray CT)
    - ion stopping power relative to water (ion CT)

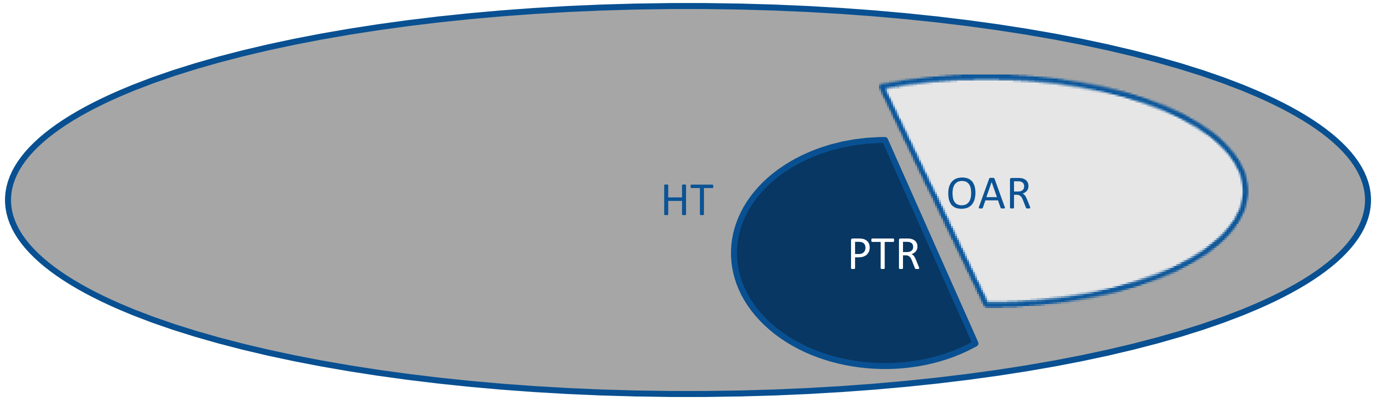


Meyer et al. *Phys Med Biol.* 2019

Fundamentals in treatment planning

- Treatment planning aims to match the dose value of the PTR (*planning target region*) to its prescribed value while limiting dose values in the surrounding OAR (*organ at risk*) and HT (*healthy tissue*) to tolerable limits

- In particular, OARs are highly sensitive to radiation exposure and require lower dose values than HT



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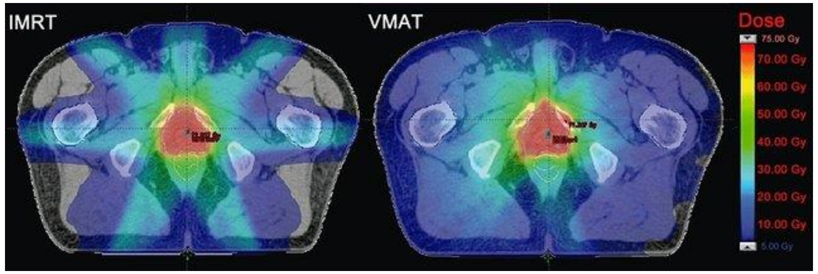
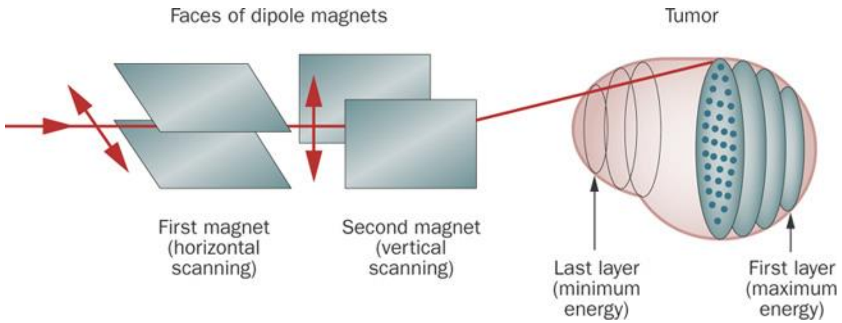
Fundamentals in treatment planning

- Intensity modulated radiation treatment (IMRT) and volumetric modulated arc therapy (VMAT)
  - High precision conformation as overlay of multiple discrete (IMRT) or continuous (VAMT) 3D dose distributions
  - The intensity of the radiation beam is subdivided in multiple beam-lets
- Ion beam therapy
  - High precision conformation as stack of multiple iso-energy 2D dose distributions
  - The intensity of the radiation beam is subdivided in multiple pencil beams



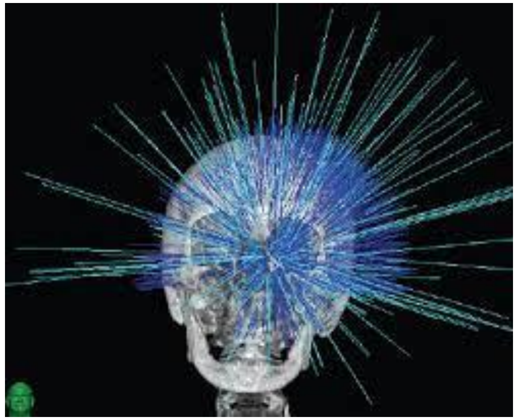
Nguyen, B. T., Hornby, C., Kron, T., Cramb, J., Rolfo, A., Pham, D., ... & Foroudi, F. (2012). Optimising the dosimetric quality and efficiency of post-prostatectomy radiotherapy: A planning study comparing the performance of volumetric-modulated arc therapy (VMAT) with an optimised seven-field intensity-modulated radiotherapy (IMRT) technique. *Journal of Medical Imaging and Radiation Oncology*, 56(2), 211-219.

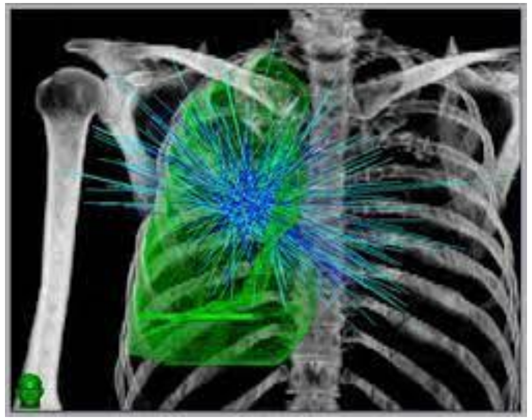


Durante, M., & Loeffler, J. S. (2010). Charged particles in radiation oncology. *Nature reviews Clinical oncology*, 7(1), 37-43.

Fundamentals in treatment planning

- Stereotactic radiation therapy (cranial SRT) and stereotactic body radiation therapy (SBRT)
    - High precision and high dose conformation as overlay of multiple 3D dose distributions, delivered from fixed points in space called nodes, arranged in spherical (intracranial applications) or ellipsoidal (extracranial applications) configurations
        - The combination of nodes and pointing vectors provides a set of "elementary beams" to plan the treatment

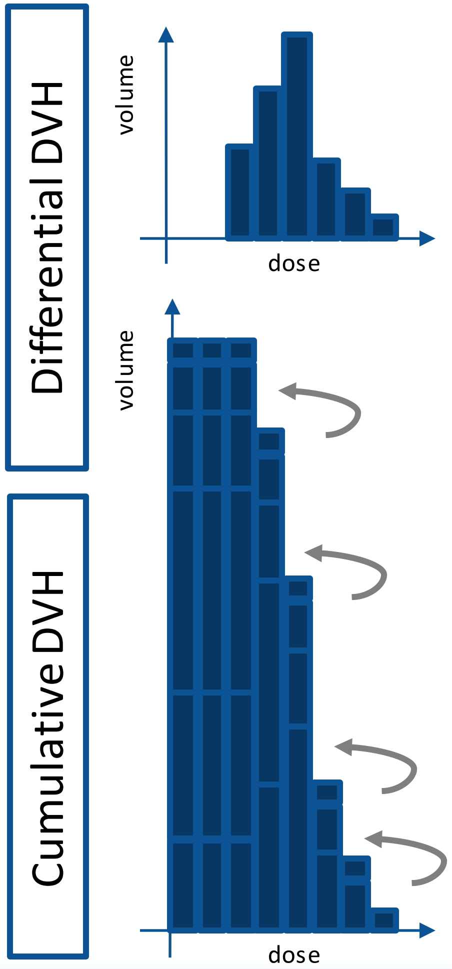


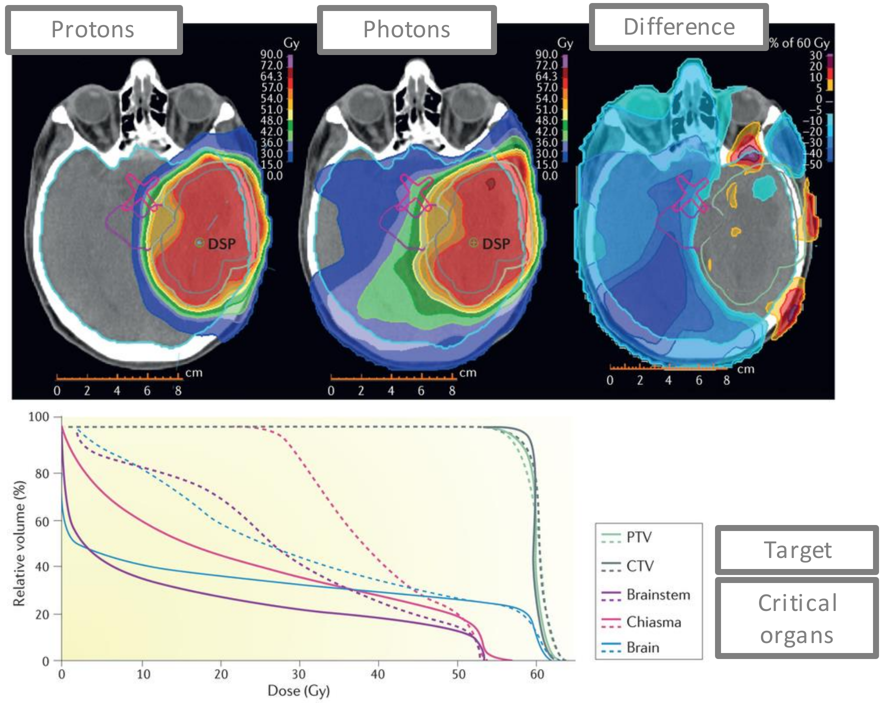


http://www.cyberknifendc.com

Fundamentals in treatment planning

- The dose-volume histogram (DVH) is a treatment plan evaluating tool
- DVH summarizes a 3D dose distribution in a graphical 2D format
- The volumes reported in the DVH are the PTR and OAR
  - Differential DVH
    - the relative volume of PTR or OAR that receives the indicated dose
  - Cumulative DVH
    - the integral relative volume of PTR or OAR that receives at least the indicated dose





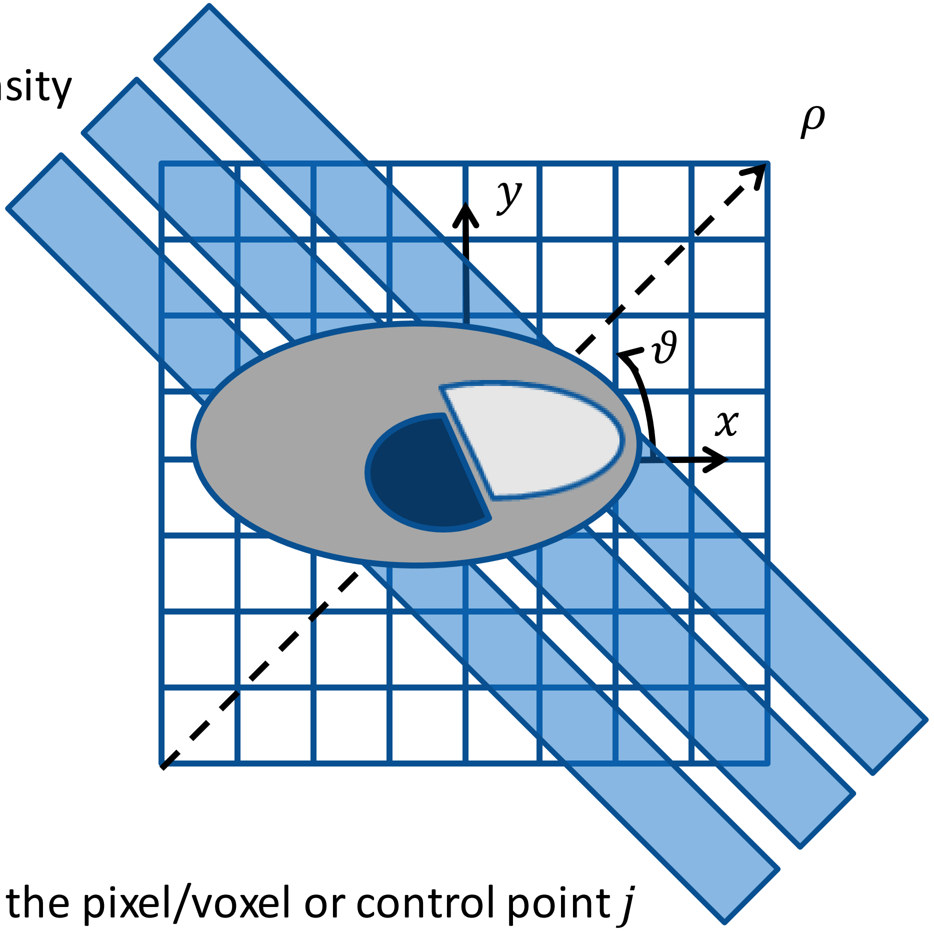
Baumann, M., Krause, M., Overgaard, J., Debus, J., Bentzen, S. M., Daartz, J., ... & Bortfeld, T. (2016). Radiation oncology in the era of precision medicine. *Nature Reviews Cancer*, 16(4), 234-249.

Fundamentals in treatment planning

- Discretization of the dose distribution into a grid of dose points
  - Beam-let or pencil beam: elementary radiation beam with fixed intensity
  - Beam: beam-lets or pencil beams with fixed angle ϑ or fixed energy
- Modeling of the inverse problem of treatment planning as matrix-vector product:

$$\bar{f}_j = \sum_i a_{ji} g_i$$

  - $\bar{f}_j$ is the dose distribution in the pixel/voxel or control point j
  - g_i is the unknown weight of the beam-let or pencil beam i
  - a_{ij} is the dosimetric contribution of the beam-let or pencil beam i to the pixel/voxel or control point j



Fundamentals in treatment planning

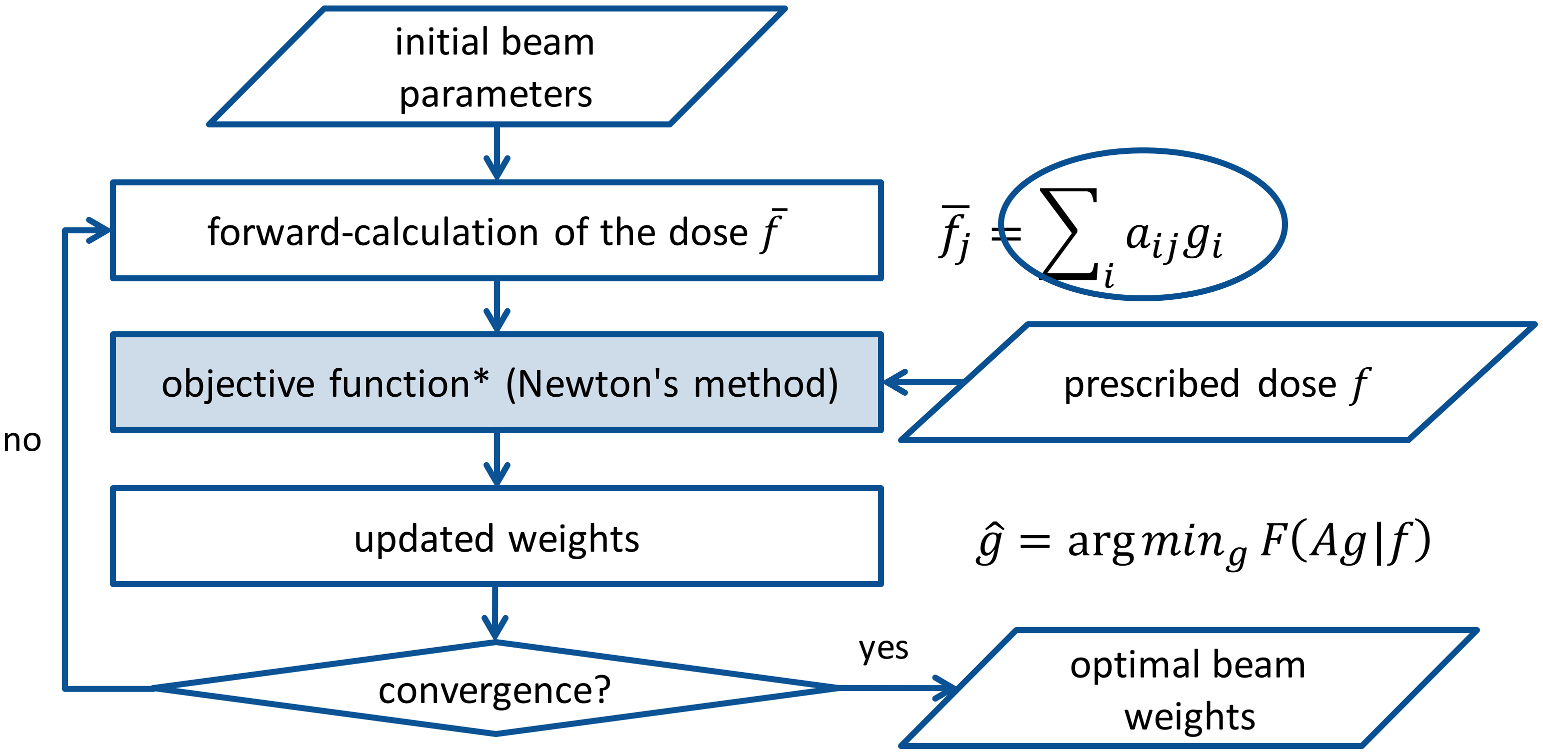
- The inverse problem of treatment planning is concerned with determining the non-negative weights g_i that results in optimal dose distribution f_j
  - a_{ij} can be interpreted as the dose per unit of time deposited at pixel or control point j by the beam-let or pencil beam i, and g_i is the time the beam-let or pencil beam i is kept on
  - a_{ij} is referred to as the dose calculation matrix
    - model-based algorithms (convolution-superposition methods based on dose kernels scaled according to the electron density or relative stopping power of the heterogeneity)
    - correction-based algorithms (semiempirical approaches to account for tissue heterogeneity)
    - Monte Carlo simulations

Oelkfe, U., & Scholz, C. (2006). Dose calculation algorithms. In New technologies in radiation oncology (pp. 187-196). Springer, Berlin, Heidelberg.

Fundamentals in treatment planning

- In photon beam therapy (IMRT), M beams (different angles) are needed to conform the dose distribution to the target
- In ion beam therapy, M beams (different energies) are needed to conform the dose distribution to the target
- The model of the inverse problem becomes a $F = AG$ matrix-matrix product with:
  - F is the matrix of optimal dose distribution for each *m=1:M* (*JxM* matrix)
  - A is the matrix of the geometrical contribution of the beam-let or pencil beam to the pixel (*JxI* matrix), referred to as dose calculation matrix
  - G is the unknown (intensity) weight matrix of each beam-let or pencil beam, for each *m=1:M* (*IxM* matrix)
- The inverse problem of treatment planning is concerned with determining the non-negative weight matrix G that results in optimal dose distribution F

Fundamentals in treatment planning



* the objective function can be either voxel-based or organ/DVH-based, the violation of the DVH constraints can an be adopted as penalty function

Treatment planning

- Newton's method of objective function minimization is based on the approximation of ψ(f) as a quadratic function in the neighborhood of the minimum f_{min}
  - The objective function can be approximated by its Taylor series expansion as:

$$\psi(f_{\min}+f) \approx \psi(f_{\min}) + f^T \nabla_f \psi(f_{\min}) + \frac{1}{2} f^T \nabla^2{}_f \psi(f_{\min}) f$$

where the Gradient vector and the Hessian matrix (H) are defined as:

$$\nabla_f \psi(f_{\min}) = \begin{pmatrix} \dfrac{\partial \psi}{\partial f_1} \\ \dots \\ \dfrac{\partial \psi}{\partial f_N} \end{pmatrix}_{f=f_{\min}} \qquad \nabla^2{}_f \psi(f_{\min}) = \begin{pmatrix} \dfrac{\partial^2 \psi}{\partial {f_1}^2} & \dots & \dfrac{\partial^2 \psi}{\partial f_N \partial f_1} \\ \dots & \dots & \dots \\ \dfrac{\partial^2 \psi}{\partial f_1 \partial f_N} & \dots & \dfrac{\partial^2 \psi}{\partial {f_N}^2} \end{pmatrix}_{f=f_{\min}}$$

- Implementations of inverse treatment planning differ from objective function approximations

Treatment planning

- Newton's method finds the minimum f_{min} when the gradient of ψ(f) is equal to zero:

$$\nabla_f \psi(f_{\min}) + \nabla^2{}_f \psi(f_{\min}) f = 0$$

$$f = -\left(\nabla^2{}_f \psi(f_{\min})\right)^{-1} \nabla_f \psi(f_{\min})$$

  - The inverse Hessian matrix can be not exact ($HH^{-1} \neq$ identity matrix)
  - Iterative algorithms are adopted to compute an approximation of the inverse Hessian matrix (quasi-Newton methods)

$$f_{n+1} = f_n - \overline{H}^{-1} \nabla_f \psi(f_n)$$

- Implementations of inverse treatment planning differ from inverse Hessian matrix approximations

Treatment planning

- Being $f=Ag$, and therefore $g=A^{-1}f$, the objective function minimization is expressed as:

$$f_{n+1} = f_n - \overline{H}^{-1}\nabla_f \psi(f_n)$$

$$g_{n+1} = g_n - \overline{A}^{-1}\overline{H}^{-1}\nabla_f \psi(f_n) = g_n - \overline{A}^{-1}\overline{H}^{-1}\overline{A}^{-1}\nabla_g \psi(f_n)$$

  - A^{-1} is the inverse dose calculation matrix
  - The two gradient vectors are related according to:

$$\nabla_g \psi(f) = \frac{\partial f}{\partial g}\frac{\partial \psi(f)}{\partial f} = A\nabla_f \psi(f)$$

- Implementations of inverse treatment planning differ from inverse dose calculation matrix approximations

Treatment planning

- Closed-form least square optimization

$$g_{min} = argmin \left\| f_j - \sum_i a_{ji} g_i \right\|^2$$

$$g_{\min} = (\underbrace{\boxed{A^T A}}_{\text{Hessian}})^{-1} \underbrace{\boxed{A^T f_j}}_{\text{Gradient}}$$

- Numerical (iterative) optimization or iterative inverse treatment planning

$$g_i^{\,n+1} = g_i^{\,n} + \frac{f_j - \sum_i a_{ji} g_i^{\,n}}{\sum_i a_{ji}^{\,2}} \cdot a_{ji}$$

Xing, L., & Chen, G. T. (1996). Iterative methods for inverse treatment planning. Physics in Medicine & Biology, 41(10), 2107.

Machine learning in treatment planning

- Conventional radiotherapy treatment planning consists of inverse optimization to determine the radiation beam weights (i.e., g_i) based on the treatment planning X-ray CT image and the dose prescription (i.e., f_j)

- The optimized radiation beam parameters need to be manually adjusted with trial and error (time-consuming and labor-intensive)

- Artificial intelligence, including machine learning and deep learning, has been recently proposed to automate radiotherapy treatment planning and improve treatment planning quality and efficiency

- Automated treatment planning includes
    - Automated beam orientation selection (i.e., pre-defined angles of the beam-lets)
    - Automated dose distribution prediction (i.e., forward-calculation of the dose)
    - Automated radiation beam parameters estimation (i.e., the weights)

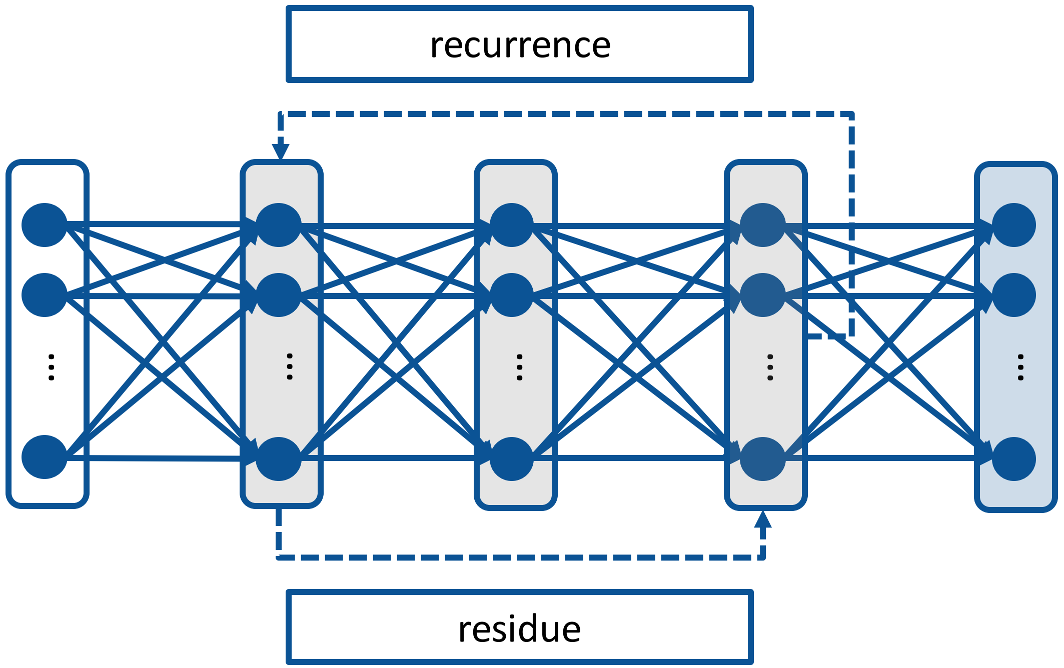
Wang, M., Zhang, Q., Lam, S., Cai, J., & Yang, R. (2020). A review on application of deep learning algorithms in external beam radiotherapy automated treatment planning. *Frontiers in oncology*, 10, 2177.

Recurrent and residual neural networks

- In recurrent neural networks, outputs from the current layers are taken as inputs for the previous layer or the current layer itself (i.e., feedback networks)

    - Considering subsequent layers as a temporal sequence, recurrent neural networks process time-dependent inputs

    - A fully recurrent neural network, once unfolded through time, can be seen as a very deep feed-forward network in which all the layers share the same weights



- In residual neural networks, skip or residual connections are added to connect neurons in non-adjacent layers to preserve features as the network depth increases

    - Residual networks are an approximation of recurrent networks

Dose distribution prediction

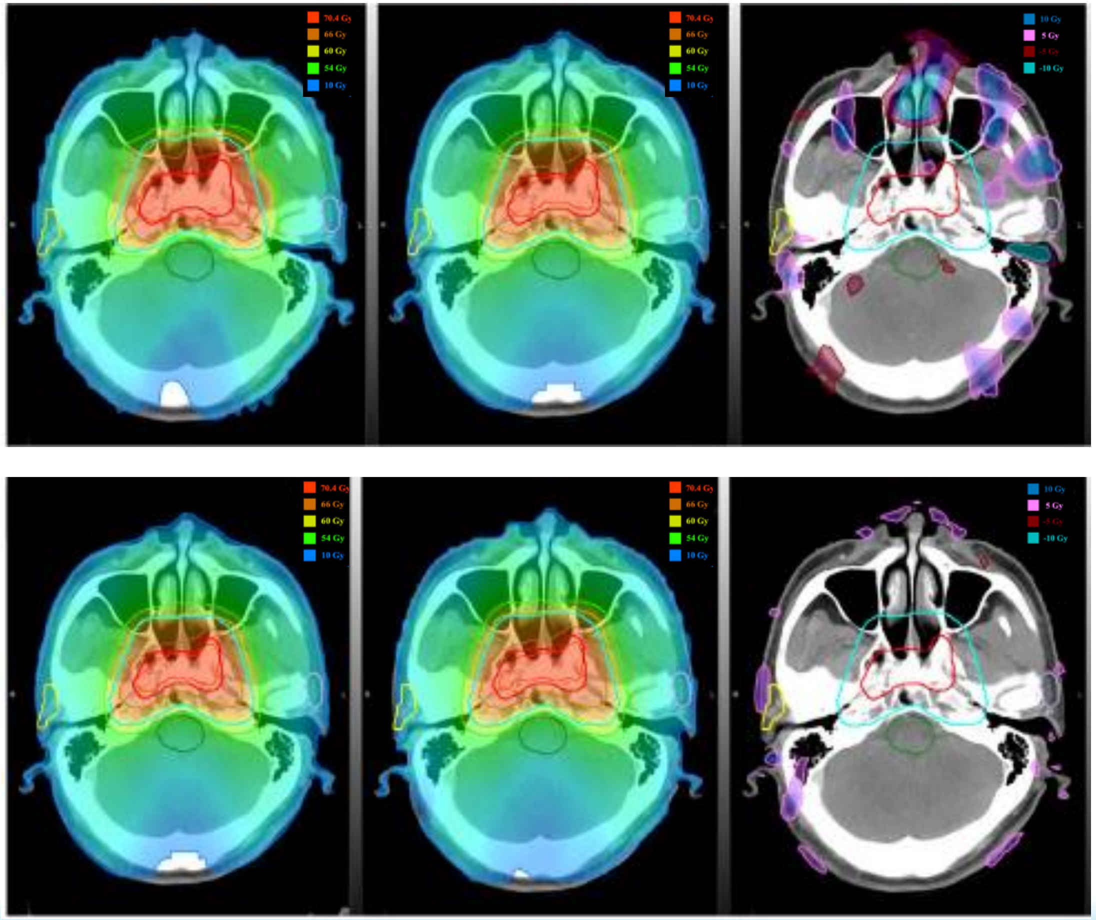
- A 3D dose prediction is obtained based on a deep residual neural network (“Res-Net”), trained on images describing patient geometry (input) and manually optimized dose distribution (target)

- The output is used to optimize the treatment plan (i.e., beam-let angles and intensities) based on a voxel-by-voxel optimization, instead of a dose-volume histogram optimization based on the prescribed dose distribution

    - The predicted dose distribution *per se* does not account for the physics of the beamlets

Prescribed dose → DVH-based optimization of the treatment planning

Predicted dose → Voxel-based optimization of the treatment planning



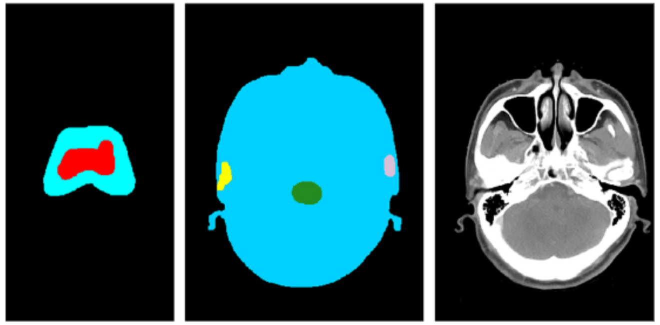
Manually optimized dose distribution vs. predicted dose distribution

Predicted dose distribution vs. Automatically optimized dose distribution

Fan, J., Wang, J., Chen, Z., Hu, C., Zhang, Z., & Hu, W. (2019). Automatic treatment planning based on three-dimensional dose distribution predicted from deep learning technique. *Medical physics*, 46(1), 370-381.

Dose distribution prediction

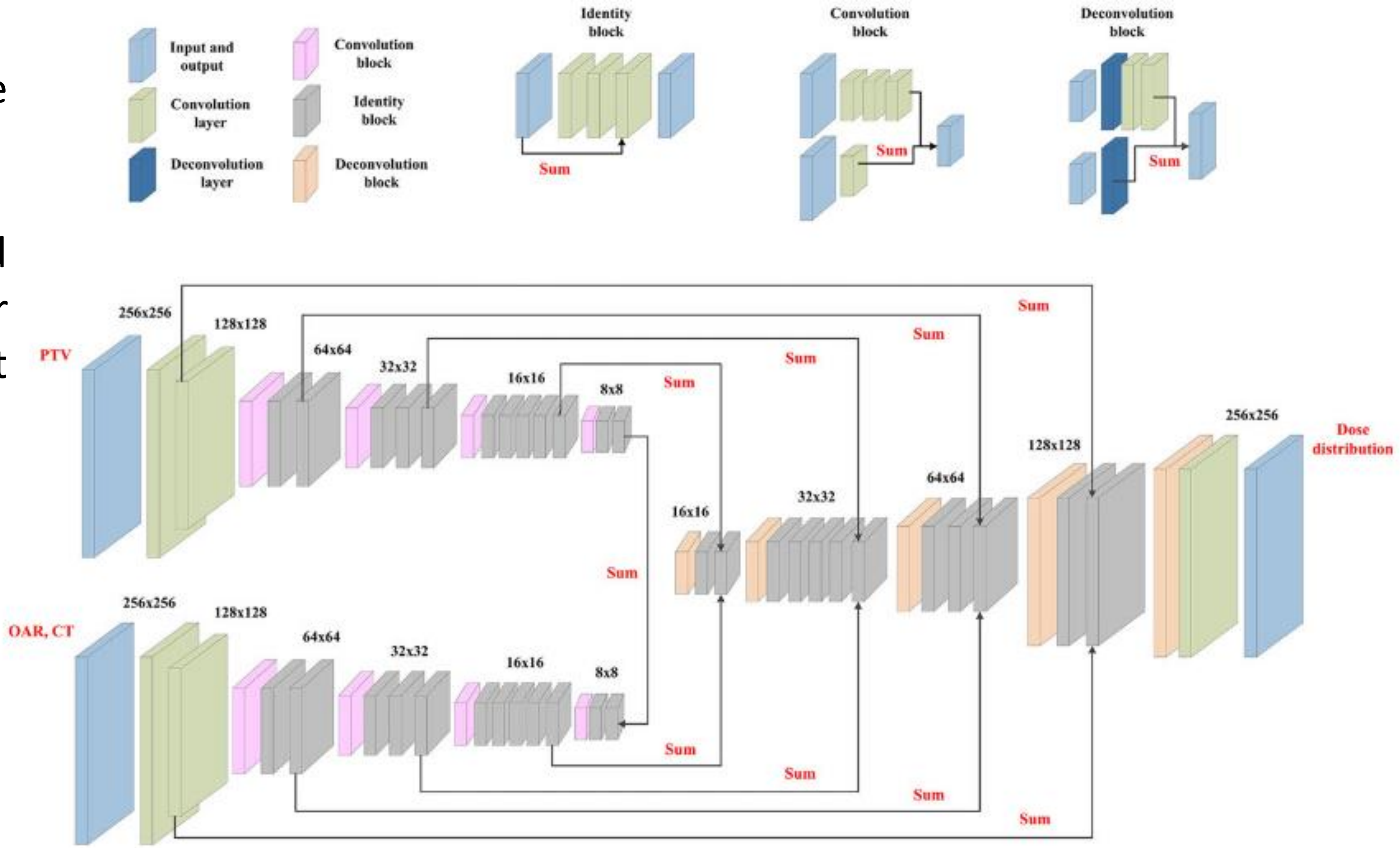
- Convolutional layers to down-sample the feature maps
- Deconvolutional layers to up-sample the feature maps and recover the image details
- Links between convolutional and deconvolutional layers with multiple skip-layer connections (tackling the problem of gradient vanishing and passing of image details)



PTV (prescribed dose)

OAR (label)

CT



Dose distribution prediction

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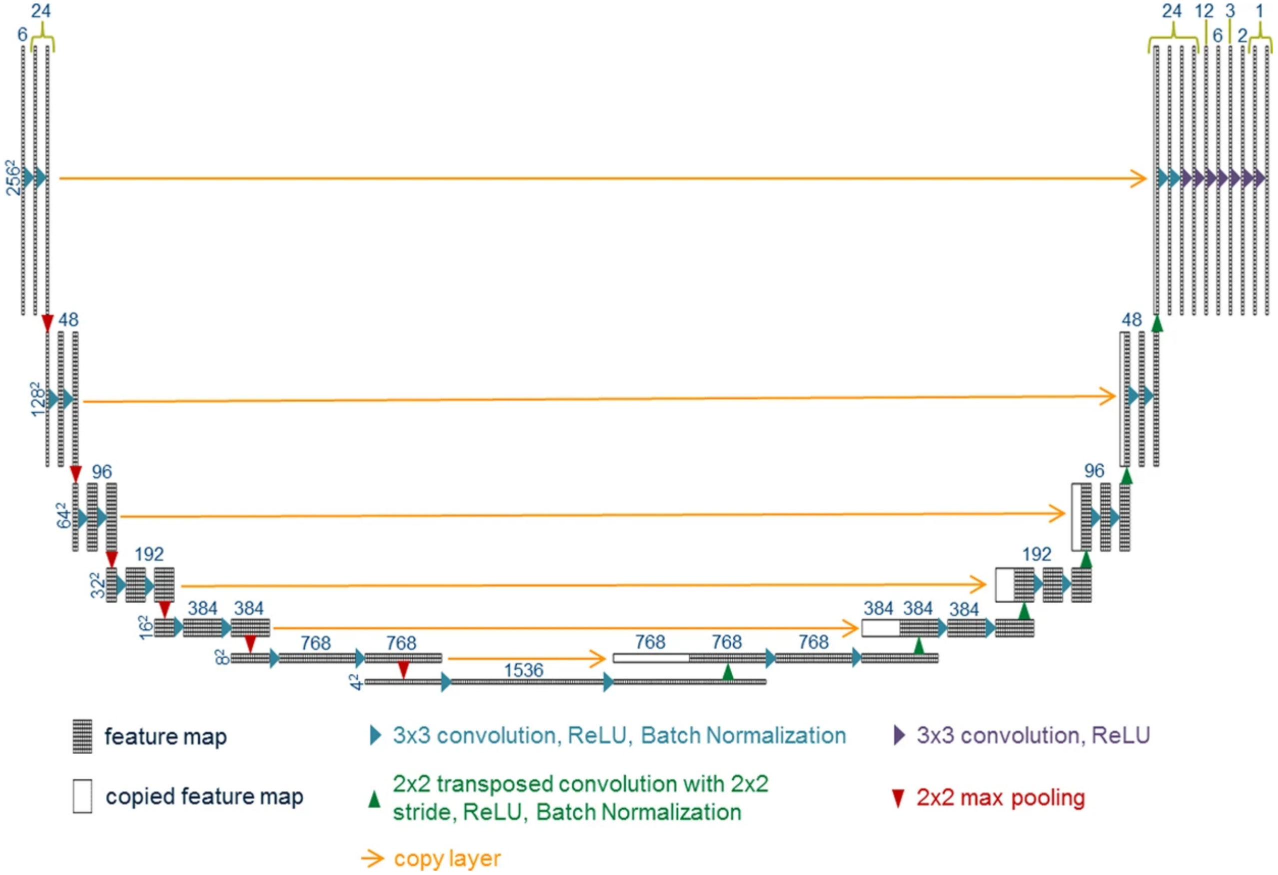
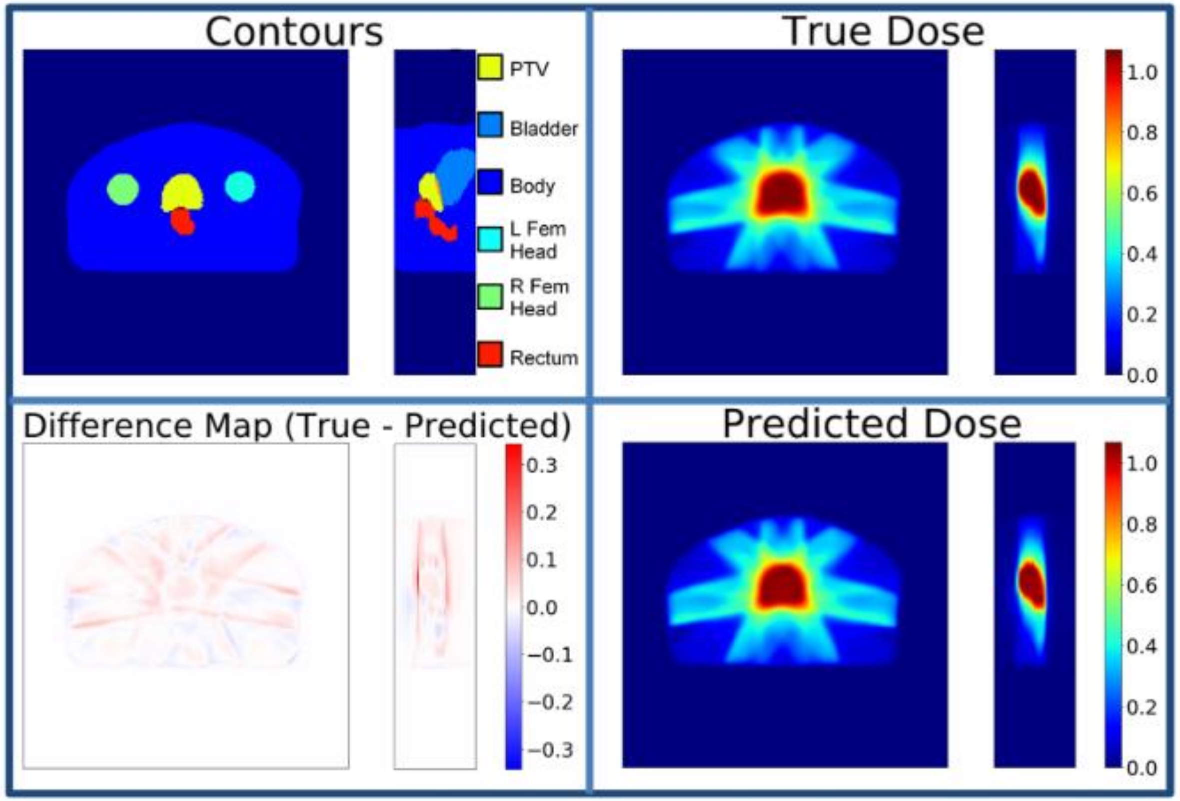
- A modified seven-level hierarchy U-Net architecture is trained to predict 2D dose distribution using the treatment planning CT image, labeled PTV and OARs for IMRT of prostate cancer patients
  - Contours of PTV and OARs treated as channels
  - Fully convolutional network, originally designed for segmentation purposes
  - Large number of max pooling operations to allow for the convolution filters to find higher level global features
  - Transposed convolution operations (i.e., deconvolution or up-convolution) to return the image to its original size
  - Copying the maps from the first half of the U-net in order to preserve the lower-level local features



Nguyen, D., Long, T., Jia, X., Lu, W., Gu, X., Iqbal, Z., & Jiang, S. (2019). A feasibility study for predicting optimal radiation therapy dose distributions of prostate cancer patients from patient anatomy using deep learning. *Scientific reports*, 9(1), 1-10.

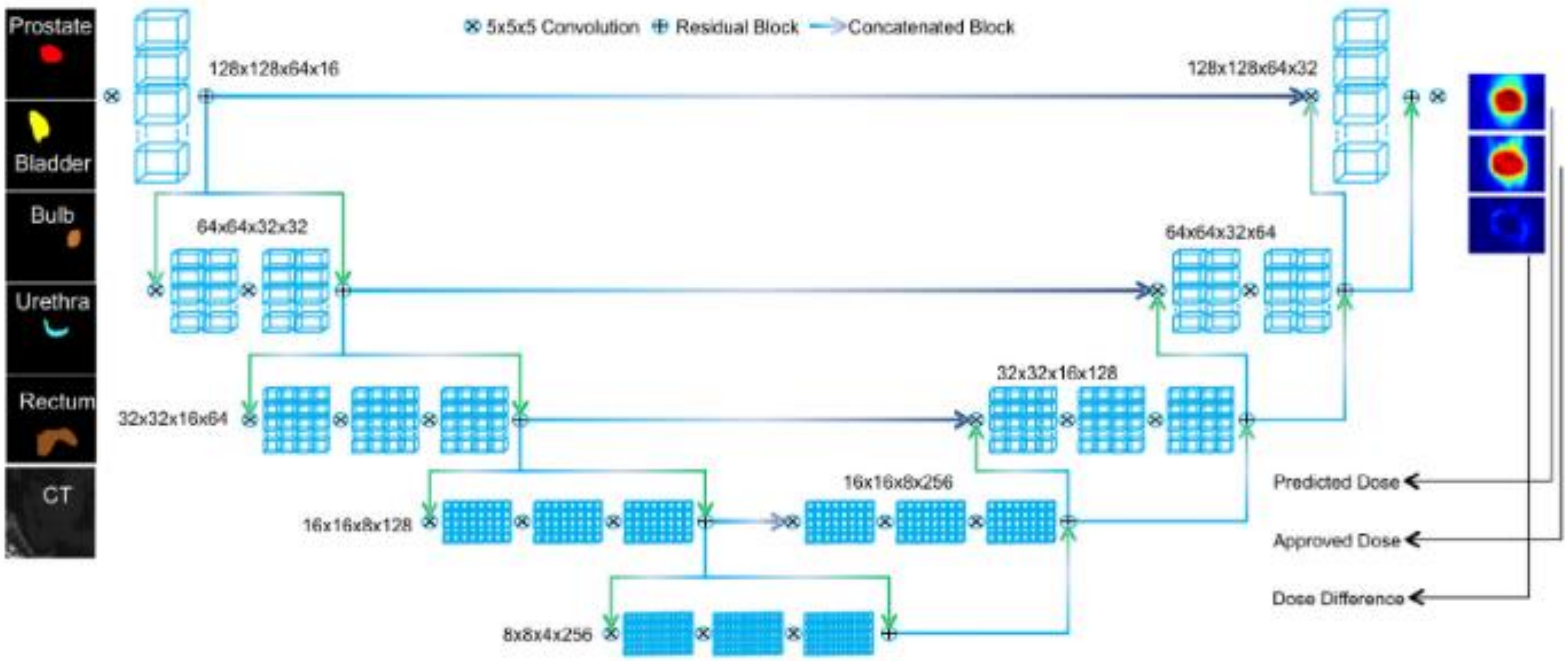
Dose distribution prediction

- The true dose is the dose distribution explicitly informed about the physics of the beamlets
- The predicted dose is informed by treatment planning data



Dose distribution prediction

- A fully convolutional residual network (DoseNet) is trained to predict 3D dose distribution for non-coplanar prostate stereotactic body radiotherapy patients
  - Treatment planning CT image, structures and dose prescription as input



Kearney, V., Chan, J. W., Haaf, S., Descovich, M., & Solberg, T. D. (2018). DoseNet: a volumetric dose prediction algorithm using 3D fully-convolutional neural networks. *Physics in Medicine & Biology*, 63(23), 235022.

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Dose distribution prediction

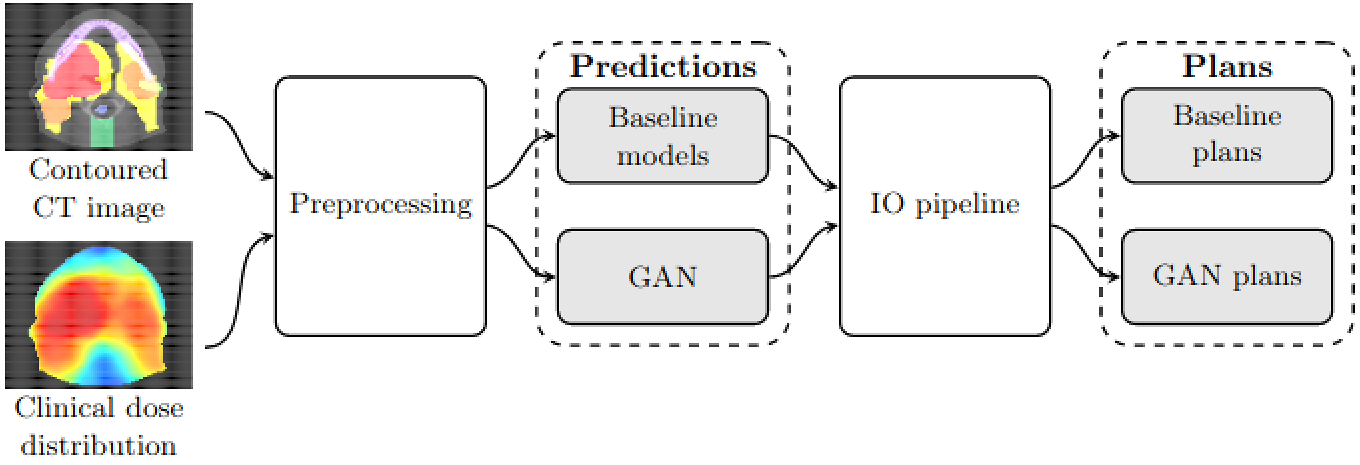
- A 3D dose distribution can be predicted by training artificial neural networks based on patient-specific geometric (i.e., based on CT image and structures) and planning (i.e., the closest distance to planning target volume (PTV) and organ-at-risks (OARs), number of beams irradiating the voxel …) parameters
  - Feed-forward networks with a limited number of layers and nodes
    - Two-layer feed-forward network, ten nodes in the first layer, one single node in the second layer[1]
    - Multiple feed-forward networks with 1-3 hidden layers, each layer with 10-50 nodes[2]
  - Two separated artificial neural networks are trained for voxels within and outside the PTV due to very different dose distribution patterns in the two regions
    - Weak generalizability

Parameters → ANN → Dose value

[1]Shiraishi, S., & Moore, K. L. (2016). Knowledge-based prediction of three-dimensional dose distributions for external beam radiotherapy. *Medical physics*, 43(1), 378-387.
[2]Campbell, W. G., Miften, M., Olsen, L., Stumpf, P., Schefter, T., Goodman, K. A., & Jones, B. L. (2017). Neural network dose models for knowledge-based planning in pancreatic SBRT. *Medical physics*, 44(12), 6148-6158.

Dose distribution prediction

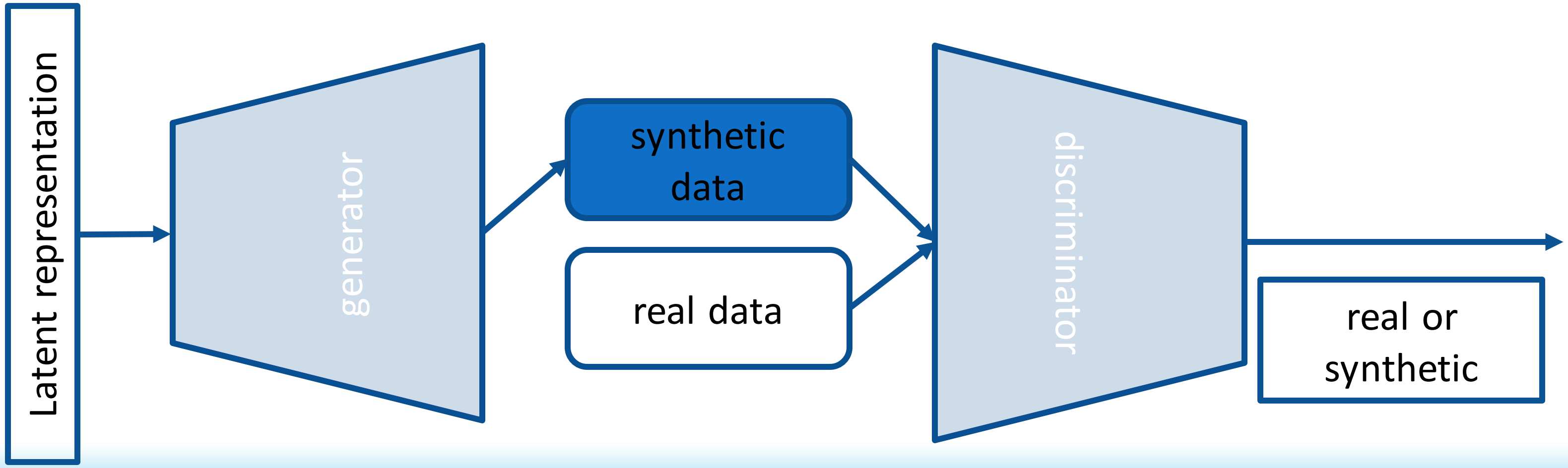
- A GAN is trained using contoured CT images and clinically acceptable dose distribution from the treatment plans of oropharyngeal cancer patients
  - Recasting the dose prediction problem as an image colorization problem solved with two neural networks
    - a generator performing the task (planner)
    - a discriminator evaluating the performance of the generator (radiation oncologist)



Mahmood, R., Babier, A., McNiven, A., Diamant, A., & Chan, T. C. (2018, November). Automated treatment planning in radiation therapy using generative adversarial networks. *In Machine Learning for Healthcare Conference* (pp. 484-499). PMLR.

Semi-supervised learning

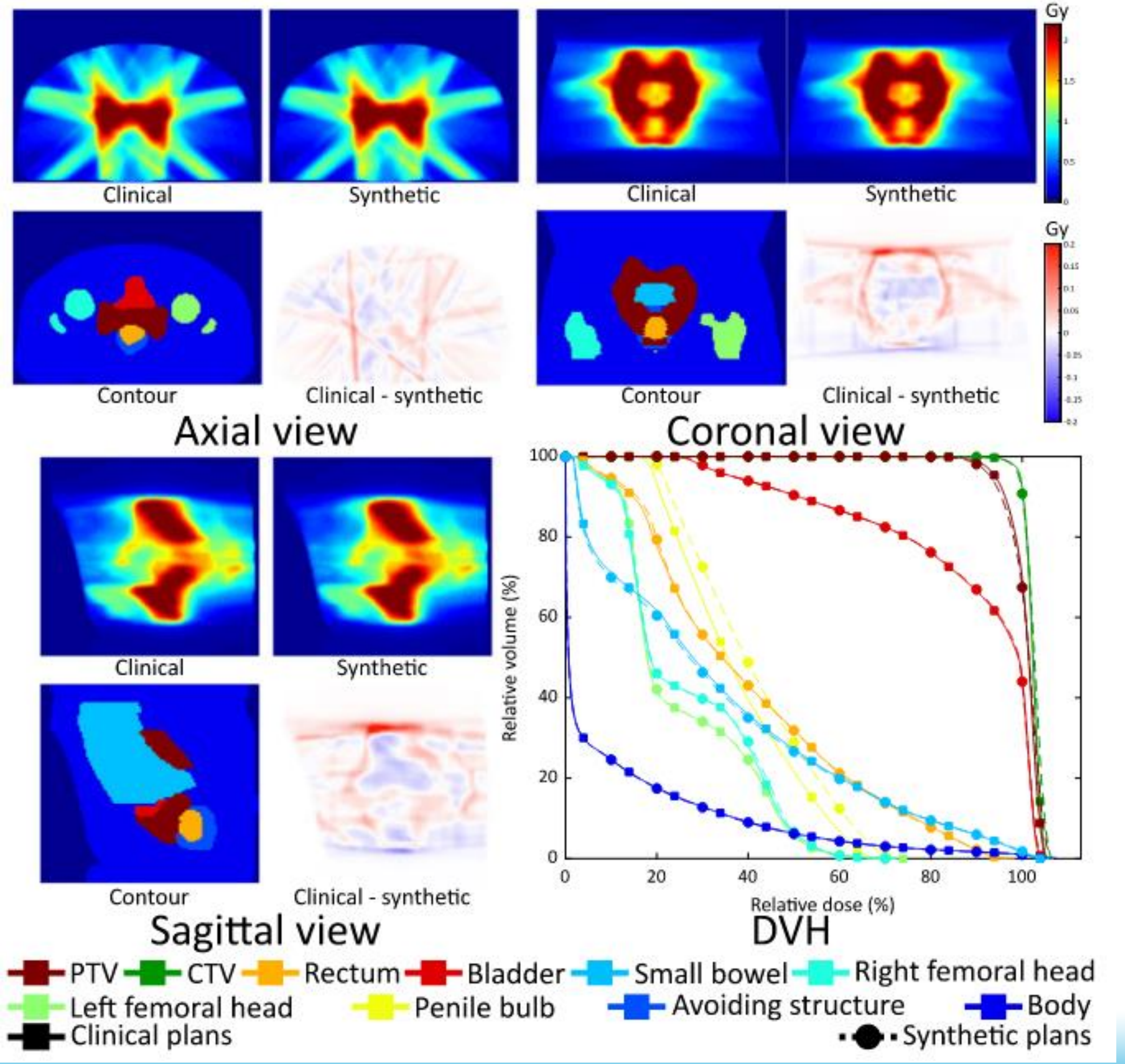
- The model is trained by relying on target information only partially available
- The generative adversarial network (GAN) is one of the most widely used
    - A generative network (generator, encoder) and a discriminative network (discriminator, decoder) are trained simultaneously to fight against each other
        - The discriminator is trained to distinguish real and synthetic samples
        - The generator is trained to produce examples that are realistic enough to fool the discriminator



Fluence map and delivery parameters generation

- A residual neural network is trained to directly generate beam fluence/intensity maps (i.e., the weights g_i for each a_{ij}) from the organ contours and a volumetric dose distributions, without inverse planning

  - The clinically-acceptable dose distribution is predicted with a deep neural network (modified U-Net architecture) from organ contours for intensity-modulated radiotherapy of prostate patients

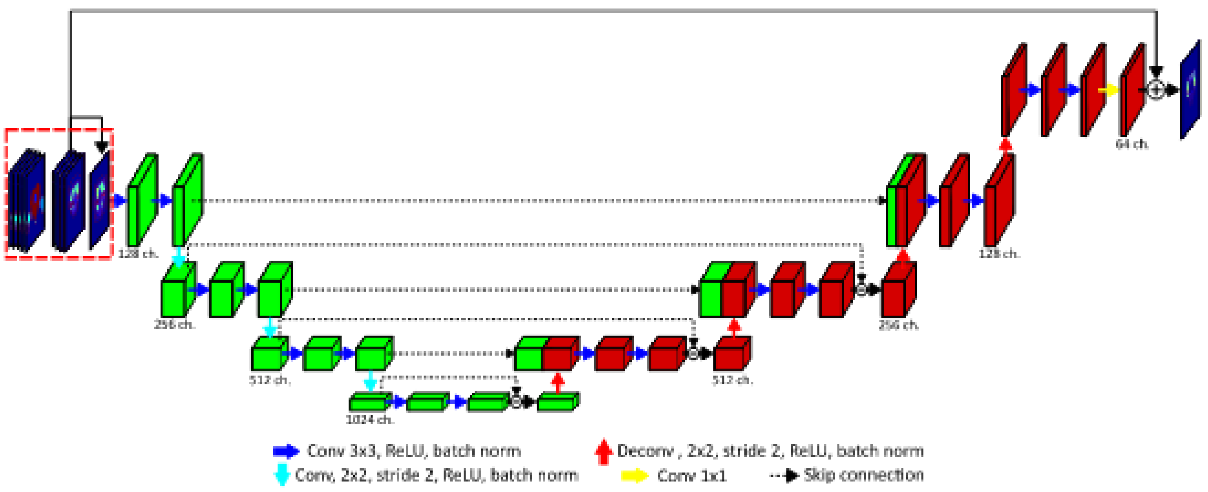


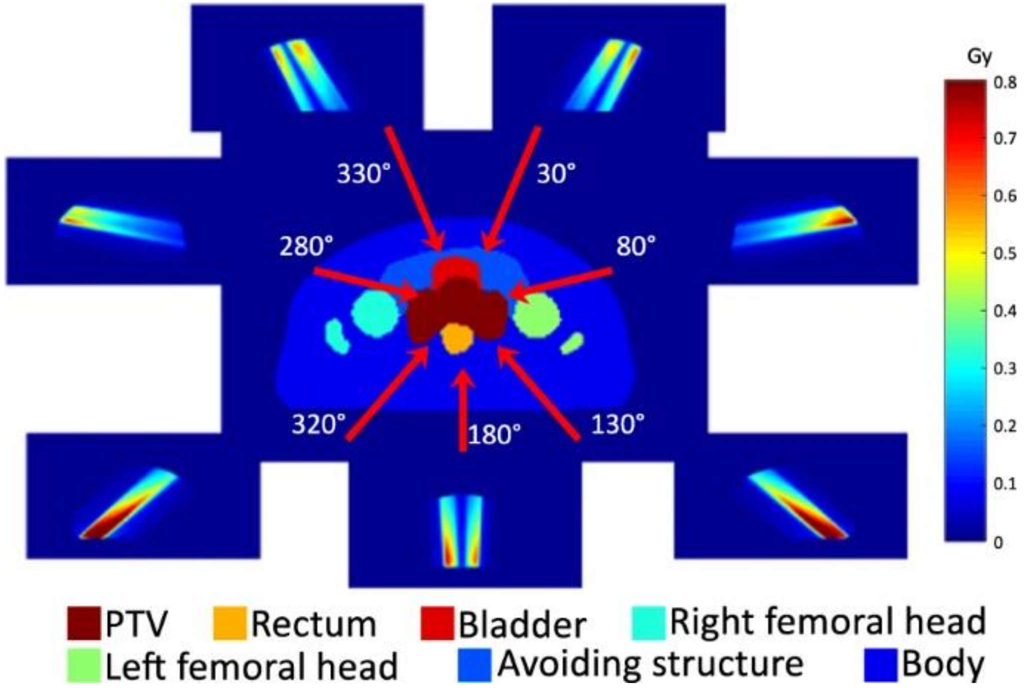
Lee, H., Kim, H., Kwak, J., Kim, Y. S., Lee, S. W., Cho, S., & Cho, B. (2019). Fluence-map generation for prostate intensity-modulated radiotherapy planning using a deep-neural-network. *Scientific reports*, 9(1), 1-11.

Fluence map and delivery parameters generation

- Organ contours, containing PTV and OARs, and the volumetric dose distributions viewed from the beam's eye view (BEV) of a single beam are used as input data

- Fluence map at each corresponding beam direction are adopted as desired output data





Outlook

- Treatment planning consists in the solution of an inverse problem
- Treatment planning in high precision 3D conformal radiotherapy relies on optimization algorithms
  - Analytical methods can only be applied to geometrically simple cases
  - Numerical methods are required for geometrically complex cases
    - Many degrees of freedom
    - Many beam-lets or pencil beams
    - High degree of flexibility in dose distribution
- The role of machine learning in treatment planning is relevant to the automation of tasks to support (or accomplish) the inverse treatment planning

Exam

- Day: February 23rd
- Time:10.00-14.00
- Room: tbd