Heavy Ion Therapy Research Integration

Introduction to Treatment Planning

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Radiation therapy

- Patient fixation
- Imaging (esp. CT, but also MRT or PET)
- Identification & delineation of tumor volume and organs on 3D image
- Treatment planning
- Verification & quality assurance
- Patient positioning
- Irradiation (several “fractions“)

Adapted from W. Schlegel & A. Mahr: 3D Conformal Radiation Therapy Springer Multimedia DVD

A treatment plan should …

- ... fulfil clinical requirements (“The physician prescribes”) …
- ... based on biological processes (cell death) …
- ... induced by chemical & physical processes (reactions & interactions) …
- ... by means of numerical simulation (dose calculation / optimization)

→ Interdisciplinary **inverse problem**

Imaging: X-ray

[1]

[2]

[3]

8/11/1895

22/12/1895

1901

[1] anonym (https://commons.wikimedia.org/wiki/File:Roentgen2.jpg), „Roentgen2“, marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-EU-no author disclosure
[2] Wilhelm Röntgen; current version created by Old Moonraker. (https://commons.wikimedia.org/wiki/File:X-ray_by_Wilhelm_Röntgen_of_Albert_von_Kölliker's_hand_-_18960123-02.jpg), „X-ray by Wilhelm Röntgen of Albert von Kölliker's hand - 18960123-02“, marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-old
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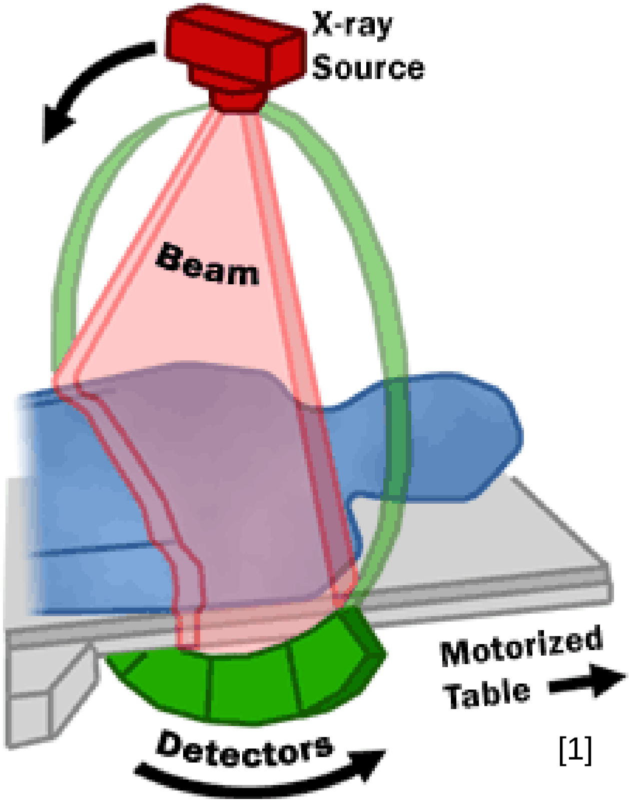
Imaging: Computed tomography

"3D X-ray"



[1]

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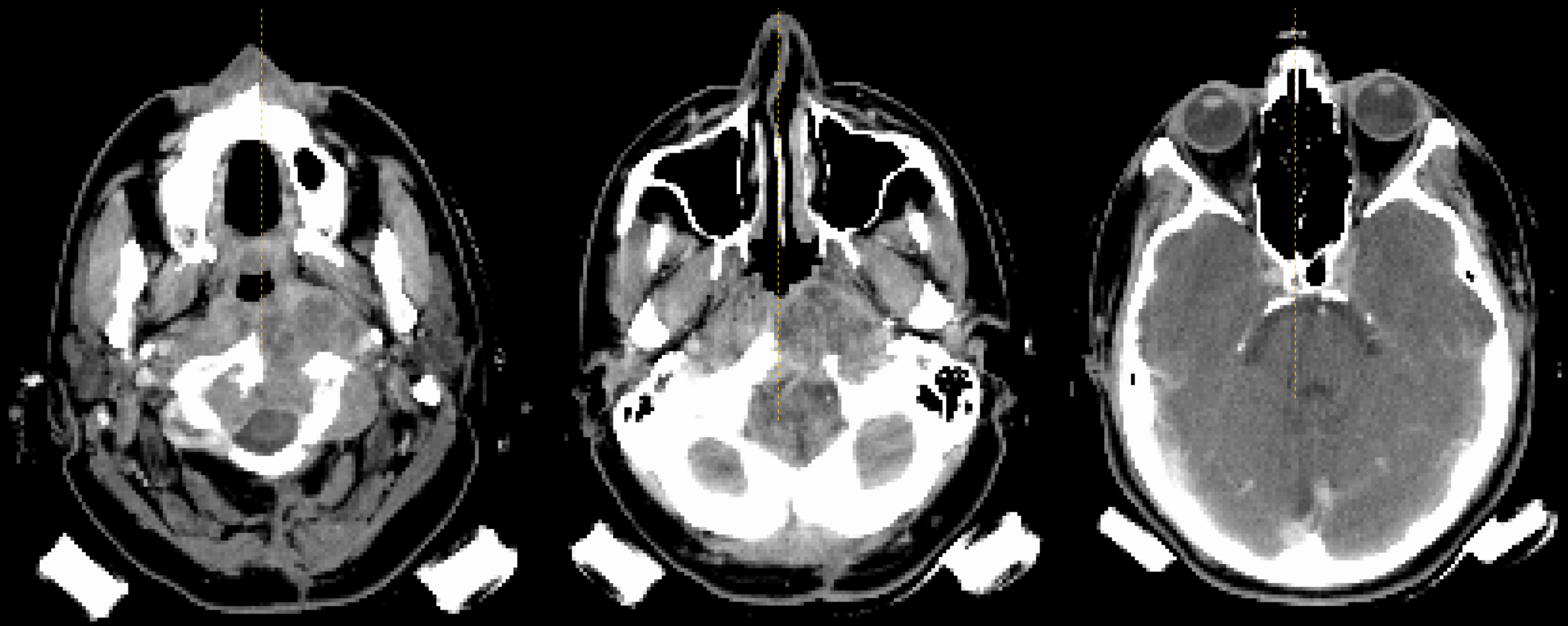
[1] FDA – Radiation emitting products – Medical X-ray Imaging – What is Computed Tomography? - Accessed from https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/what-computed-tomography on 15.02.2021.
[2] daveynin from United States (https://commons.wikimedia.org/wiki/File:UPMCEast_CTscan.jpg), „UPMCEast CTscan", https://creativecommons.org/licenses/by/2.0/legalcode

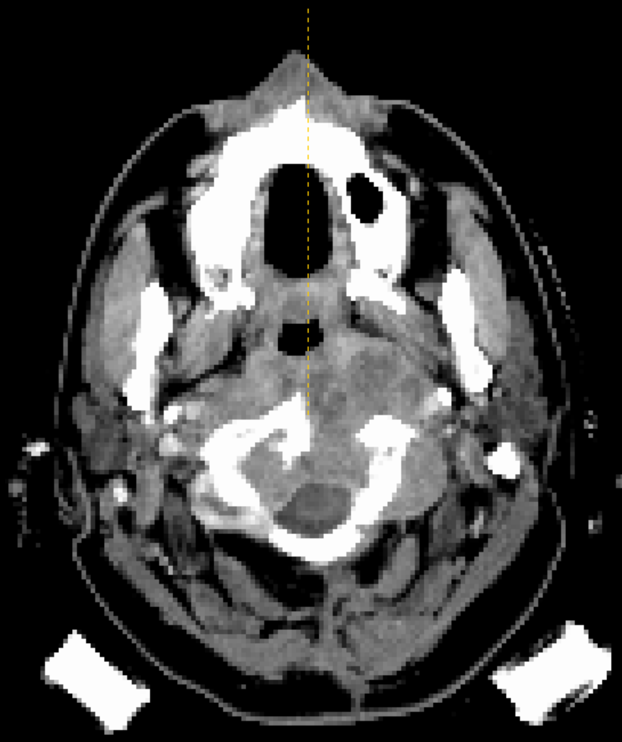
CT scans for treatment planning



transversal slices

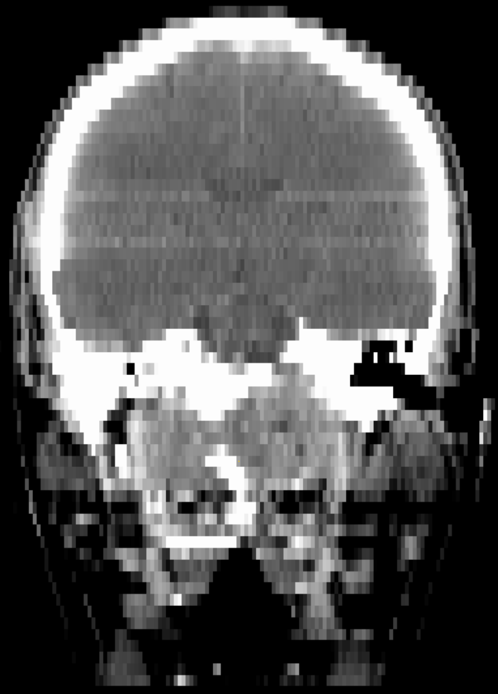
Slide by courtesy of Dr. Simeon Nill

CT scans for treatment planning



transversal/axial

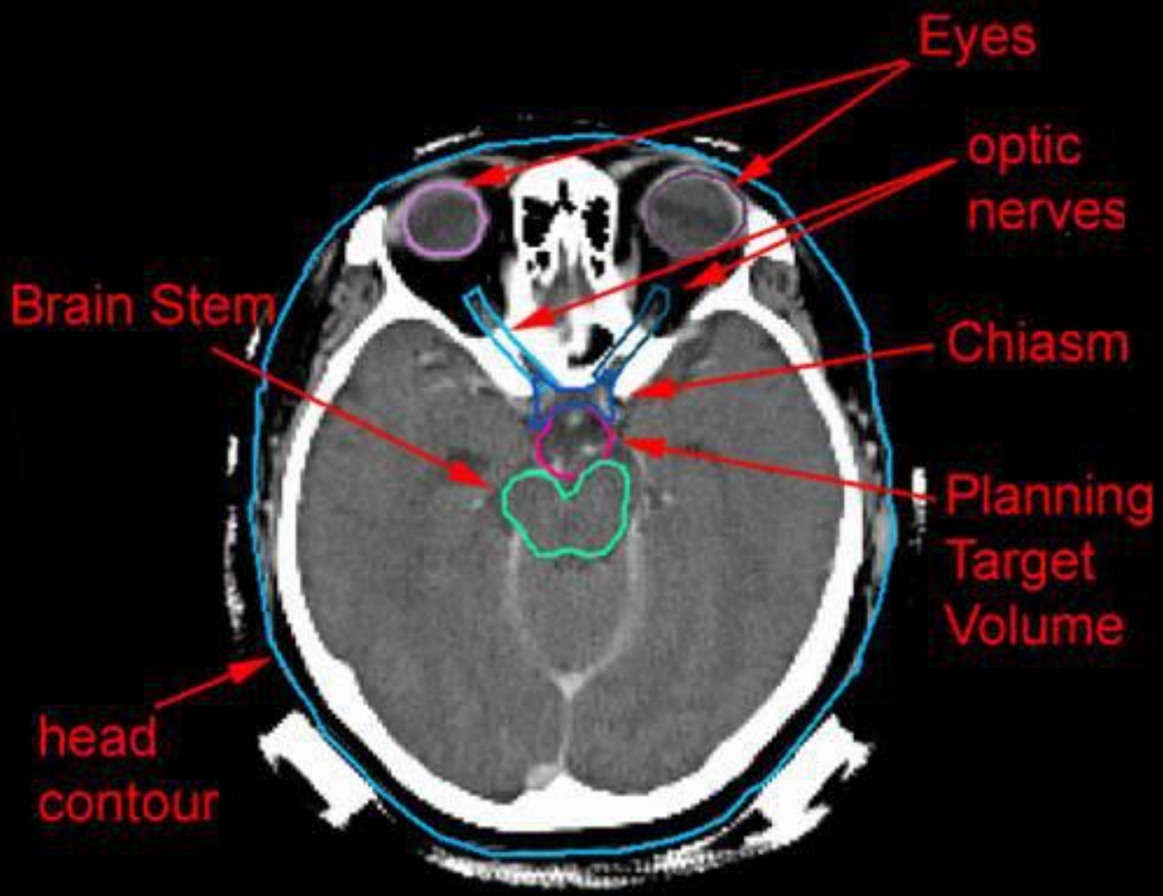
sagittal



frontal/coronal

Slide by courtesy of Dr. Simeon Nill

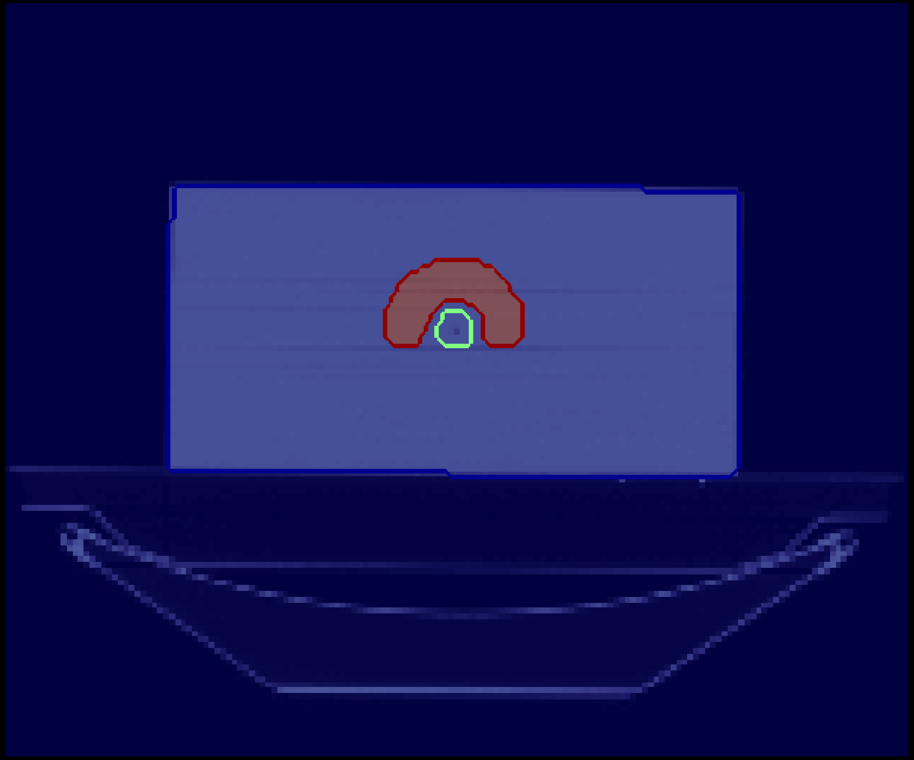
Delineating volumes of interest



W. Schlegel & A. Mahr: 3D Conformal Radiation Therapy Springer Multimedia DVD

Slide by courtesy of Dr. Simeon Nill

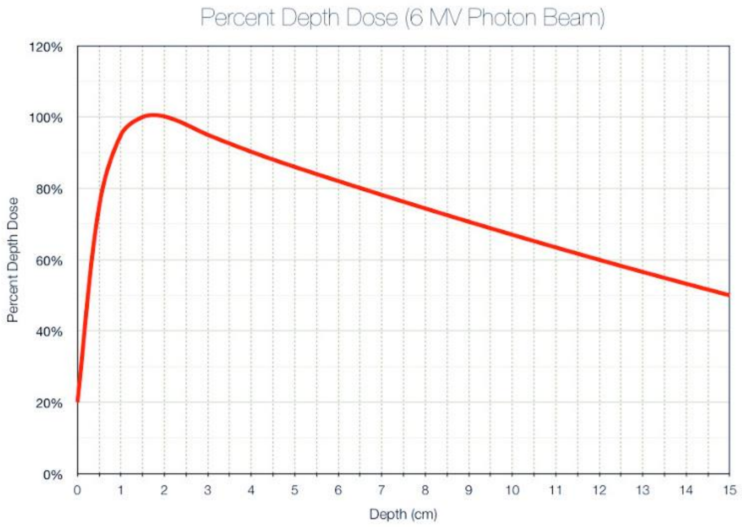
The ideal dose distribution



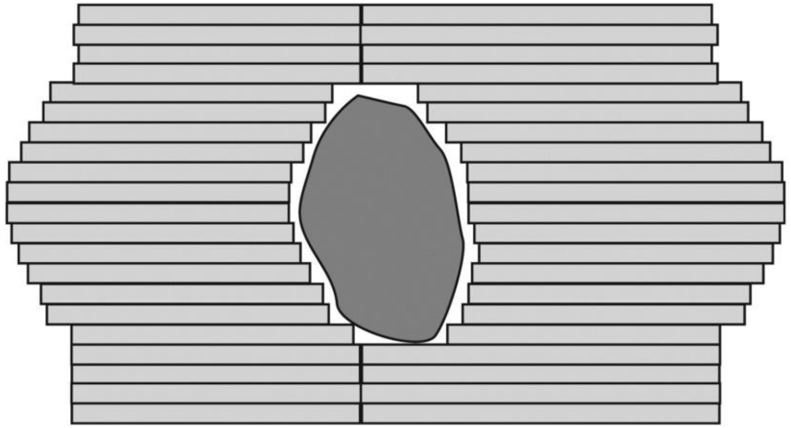
- High / prescribed dose in the tumor
- No dose in normal tissue

Modern 3D-planning with photons

Photon beam

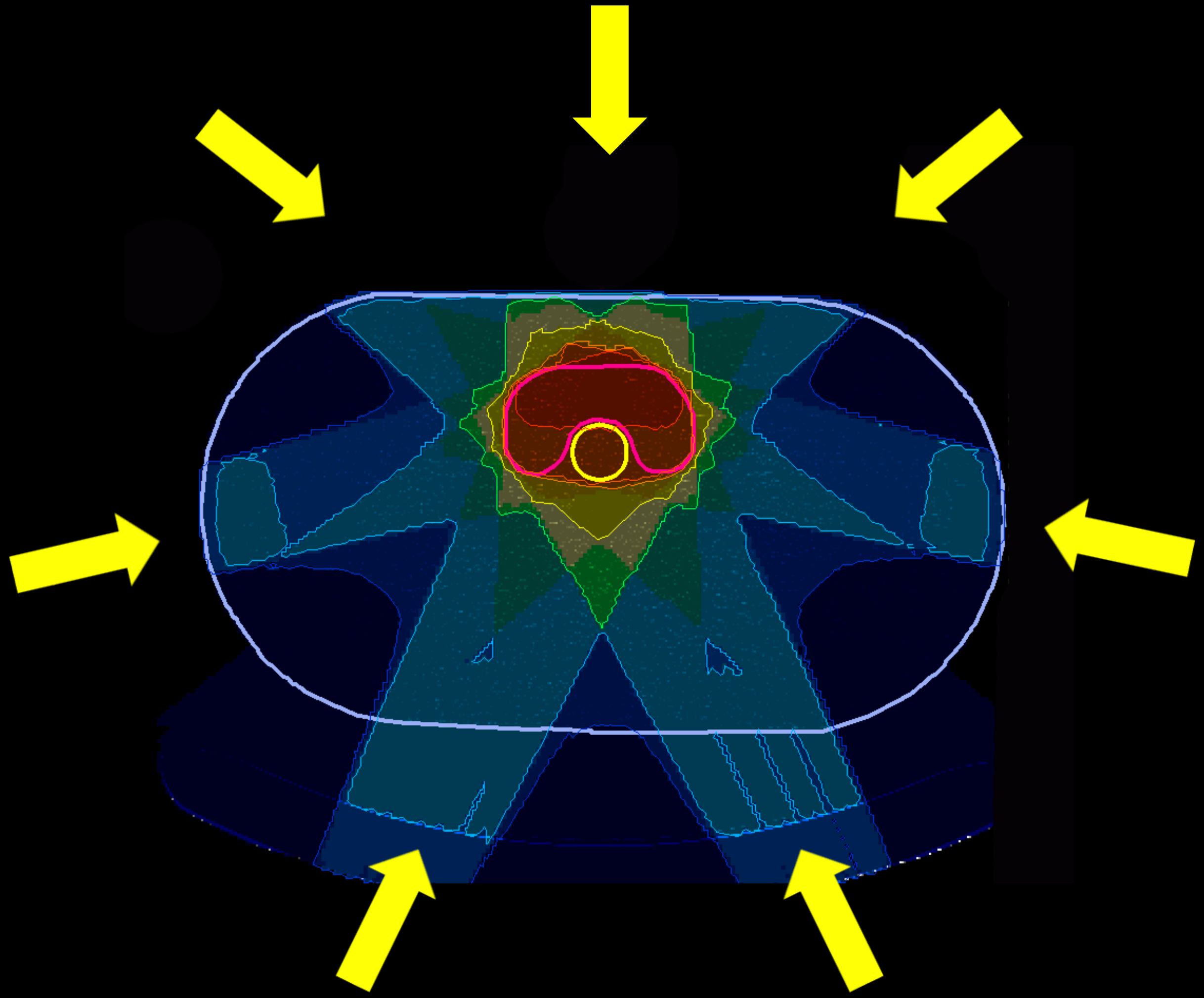


Collimator



→ Adaptation of the photon beam to the tumor shape

A realistic dose distribution



Slide by courtesy of Mark Bangert

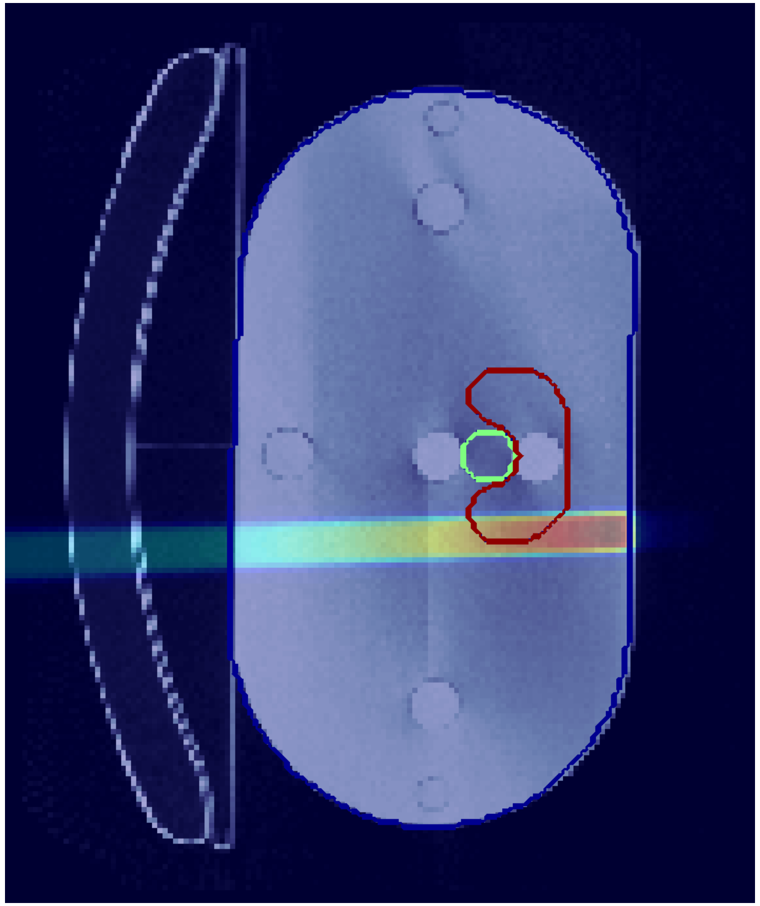
Can we do better?

The concept of the „beamlet“

- „Multi-leaf“ collimator are able to generate fine beams (let’s call them beamlets)

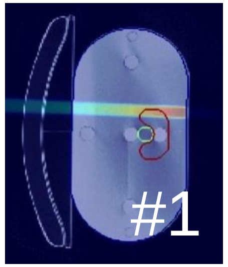
- We calculate their dose for unit intensity using various algorithms, e.g.:
  - **Analytical Pencil beam**
    Precomputed / measured dose curves in water are “scaled” to the patient
    → deterministic, very quick, but inaccurate
  - **Monte Carlo**
    Simulation of individual particle trajectories (“histories”) through the patient
    → stochastic, slow, but mostly more accurate

#4



→ we are able to simulate and “modulate” our beams

Intensity-modulation with pencil-beams



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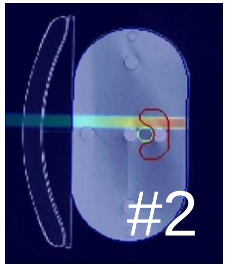

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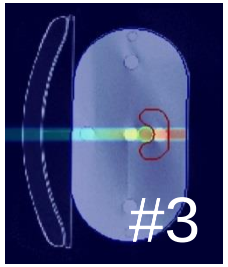

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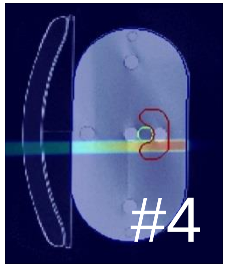

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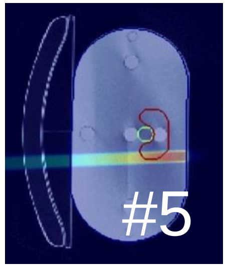

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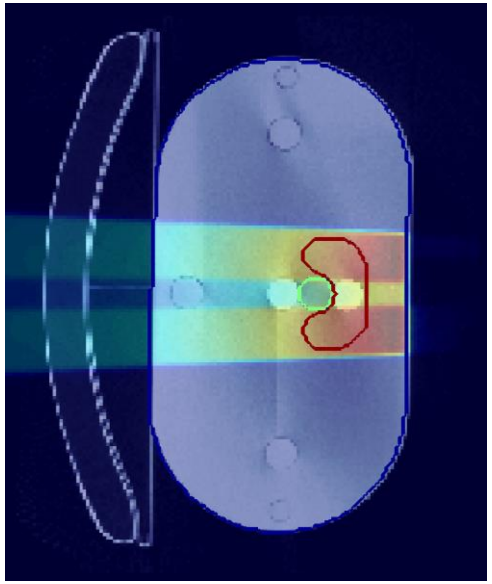
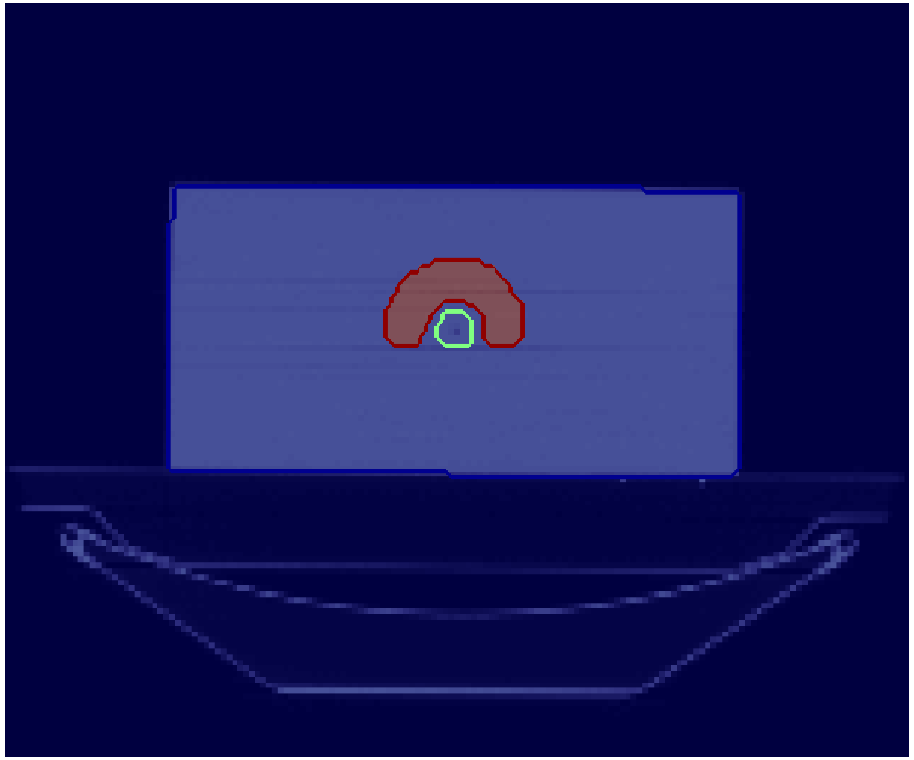


Different beamlet weights w
= Intensity-modulated field

- Number of beamlets: ~100-1000 per field
- Number of fields: 5 to 12

→ We can‘t do it by hand

The ideal dose distribution (again)



- Write ideal dose as a vector:

$$d^* = (\dots, 0, \dots, d^p, \dots)^T \in \mathbb{R}_+^I$$

I = number of voxels

- Put the beamlets in a *dose influence matrix:*

$$D \in \mathbb{R}_+^{J \times I}$$

J = number of beamlets

- Fluence weight vector:

$$w \in \mathbb{R}_+^J$$

→ We would like to solve $d^* = Dw$ for w

Finding the right vector w^*

- $d^* = Dw$ has no solution: $d^* = Dw + \epsilon$
- Approximate d^* → We need to minimize ϵ!
- An exemplary straightforward optimization approach:

  weighted/penalized least squares

$$\mathrm{w}^* = \arg\min_{w} (Dw - d^*)^T P(Dw - d^*)$$

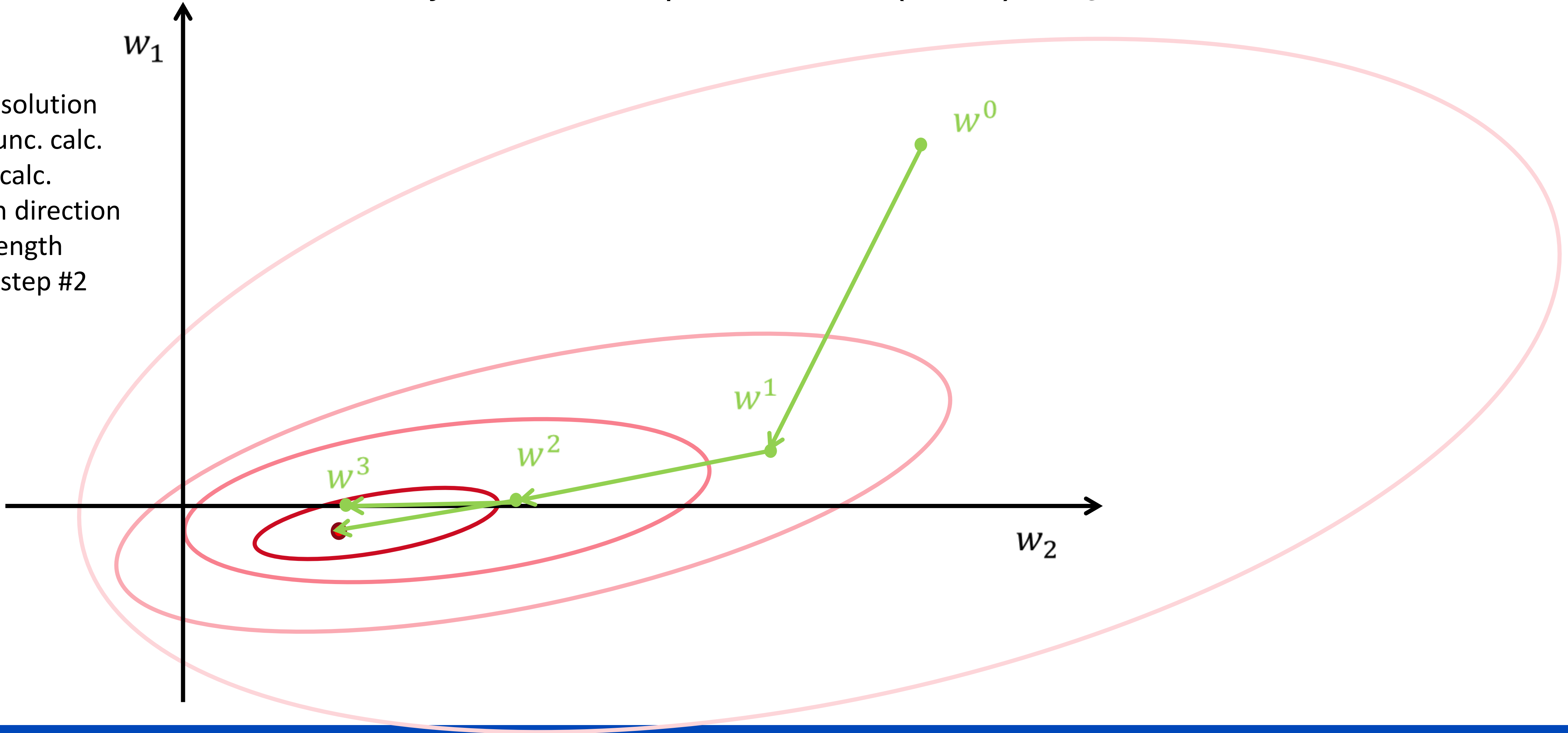
$$\text{s.t.} \quad w \geq 0$$

$$P = \mathrm{diag}(p_1, p_2, \ldots, p_I)$$

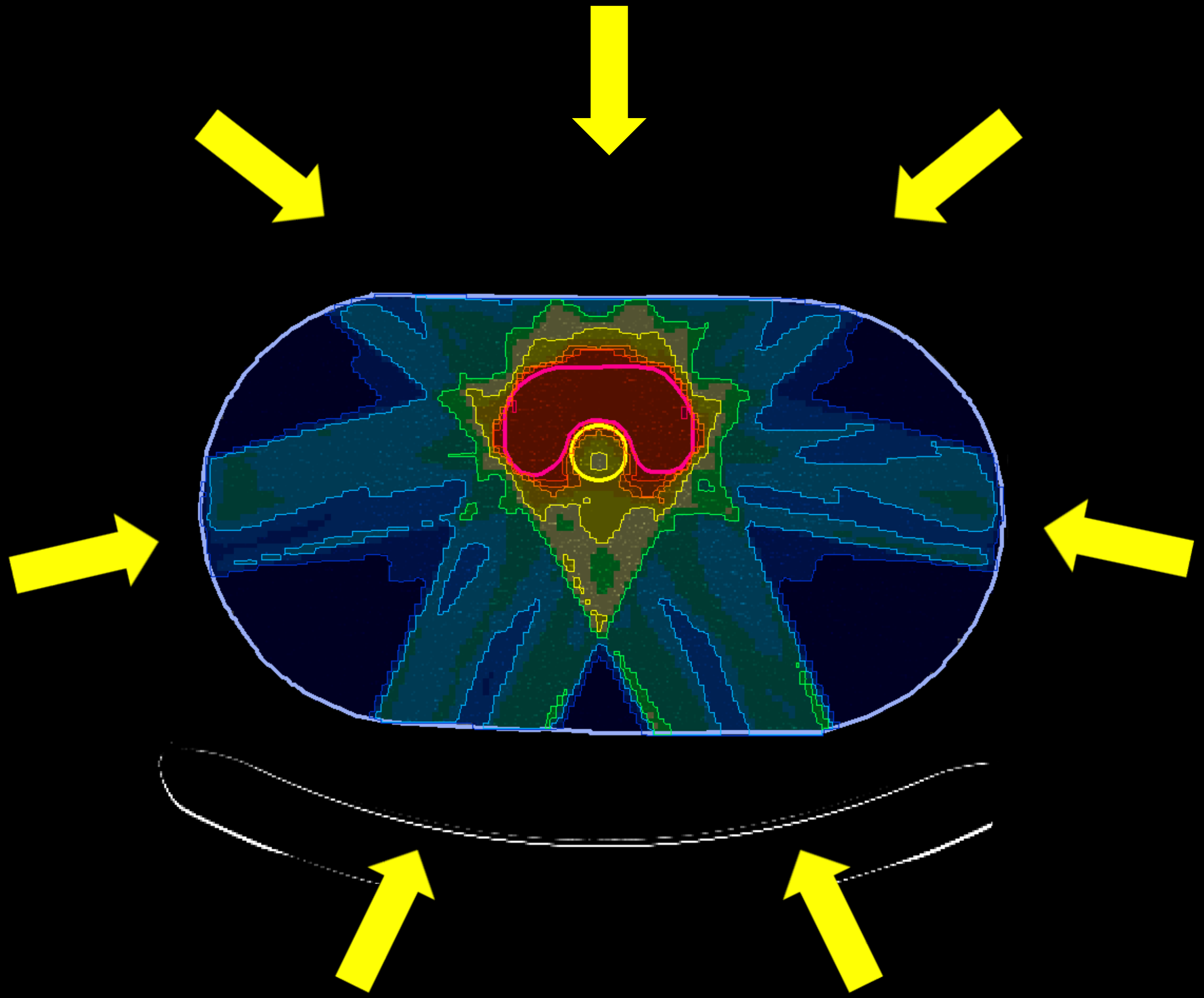
Optimize for w^*

dimensionality = number of pencil beams (~$10^{3\text{-}4}$) → Quasi-Newton Method

1. Initial solution
2. Obj. func. calc.
3. Grad. calc.
4. Search direction
5. Step length
6. Go to step #2

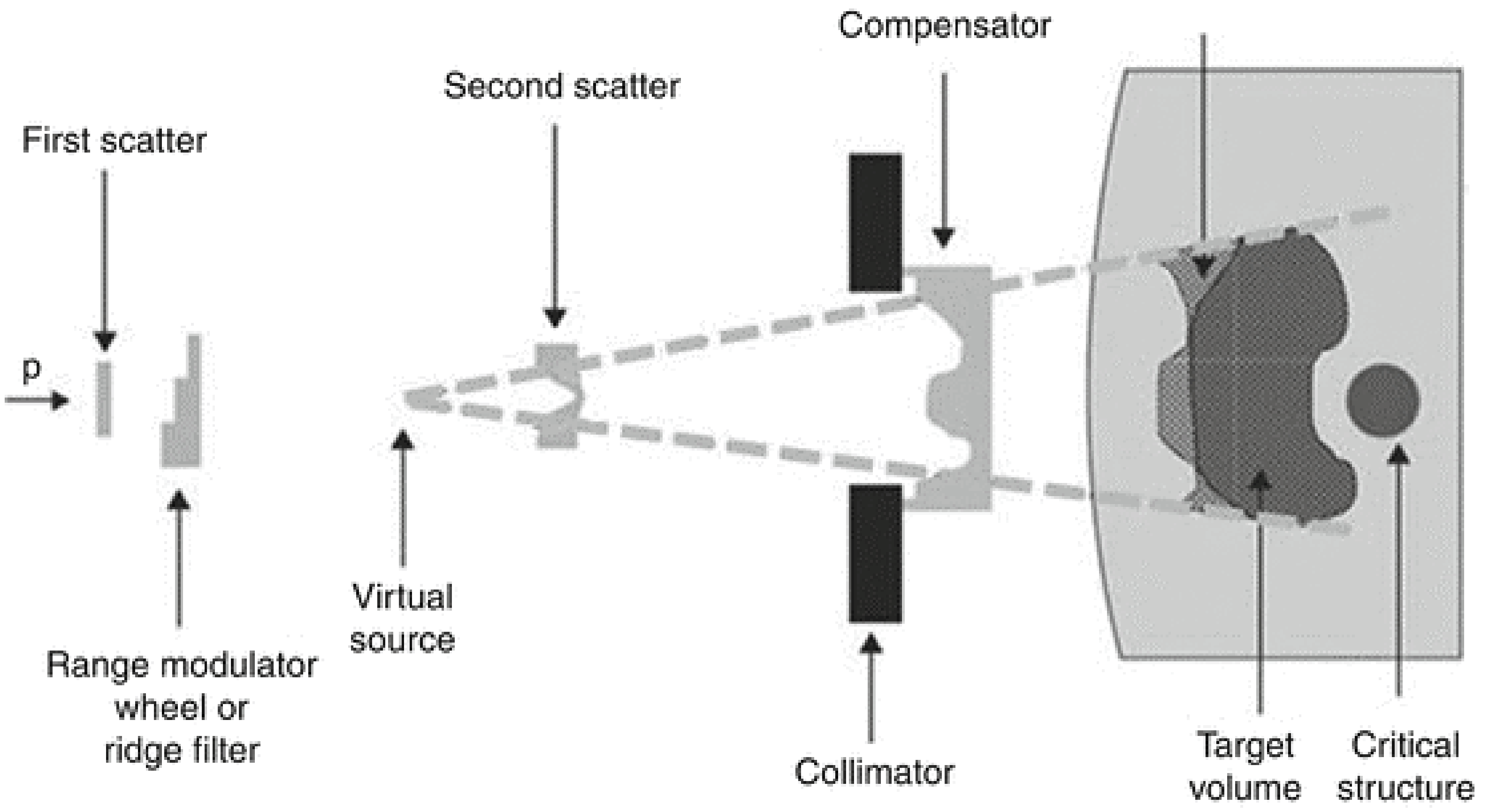


Intensity modulated treatment plan – dose distribution



Let‘s move to hadrons & ions…

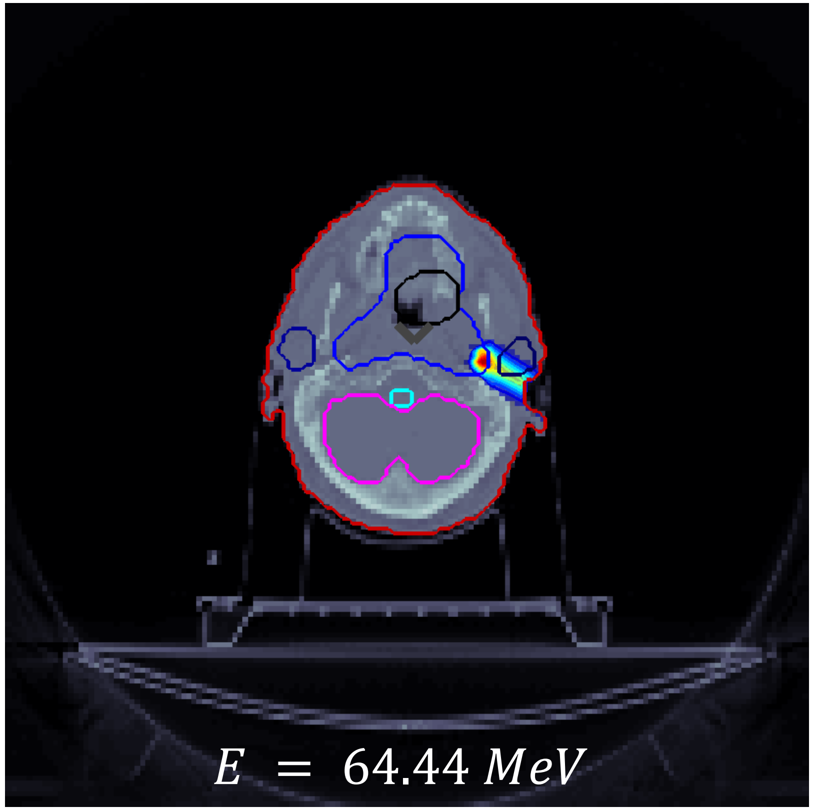
The “old” way: Passive Scattering



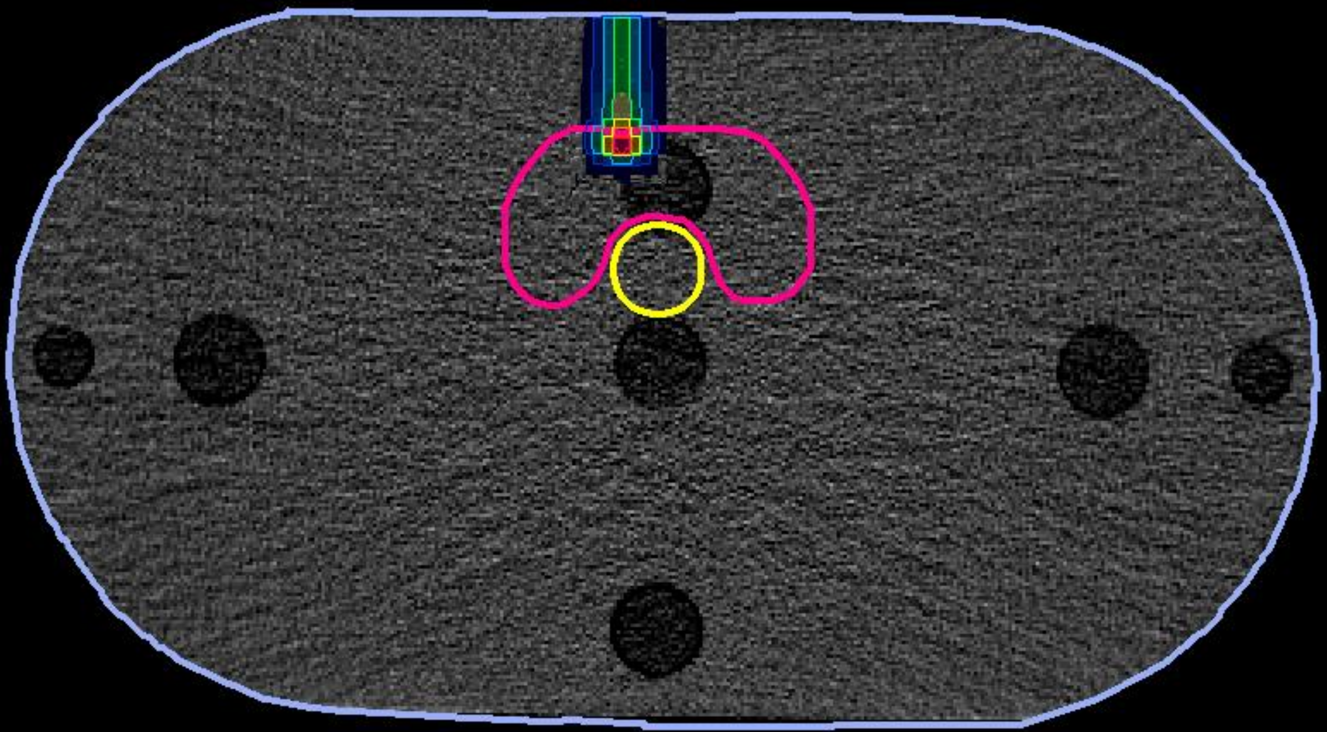
RL Maughan, MJ Hardy, MJ Taylor, J Reay, R Amos: Radiation Shielding and safety for particle therapy facilities, IPEM Report 75 Ed. 2

Translation to intensity-modulated particle therapy (IMPT)
→ We do not need a collimator

- Hadron / ion accelerators (synchrotrons / cyclotrons) produce “natural“ beamlets
- improved dose distribution (Bragg-Peak)
- can also be simulated with deterministic or MC algorithms
- additional modulation in depth
  → much higher number of beamlets per beam



The “new” way: Fluence Modulation → intensity-modulated particle therapy



Lateral Scanning

Energy Change

103 MeV protons

(x_3, y_3)

Weighted sum of pencil beams with different energies and lateral position

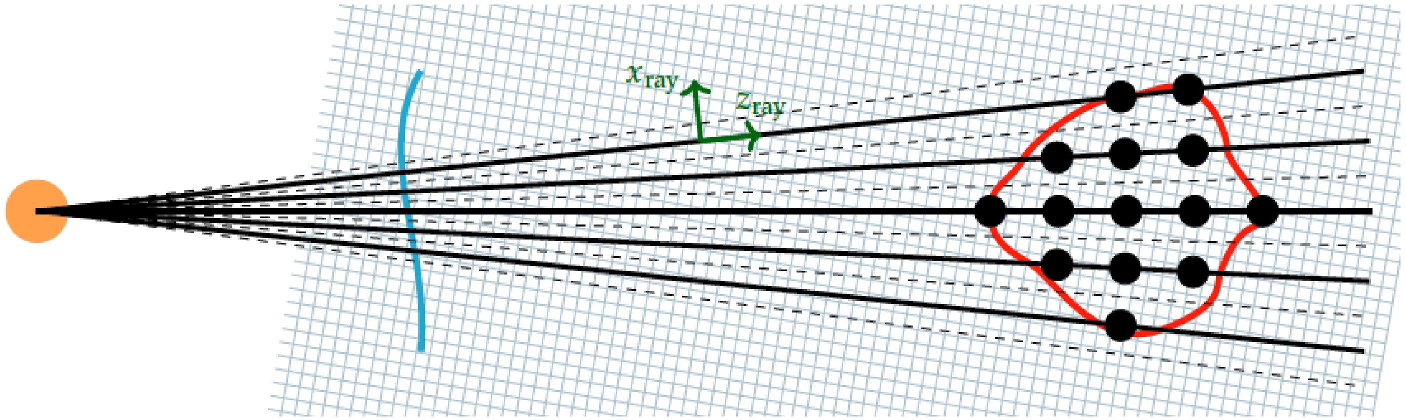
→ Dose optimization = finding the weights of pencil beams

Slide courtesy of Mark Bangert (adapted)

Dose Influence Matrix D: Analytical Dose Calculation

- separate depth dose from lateral dose component
- based on pre-computed / measured dose distributions in water
- fast but inaccurate in heterogeneous tissues

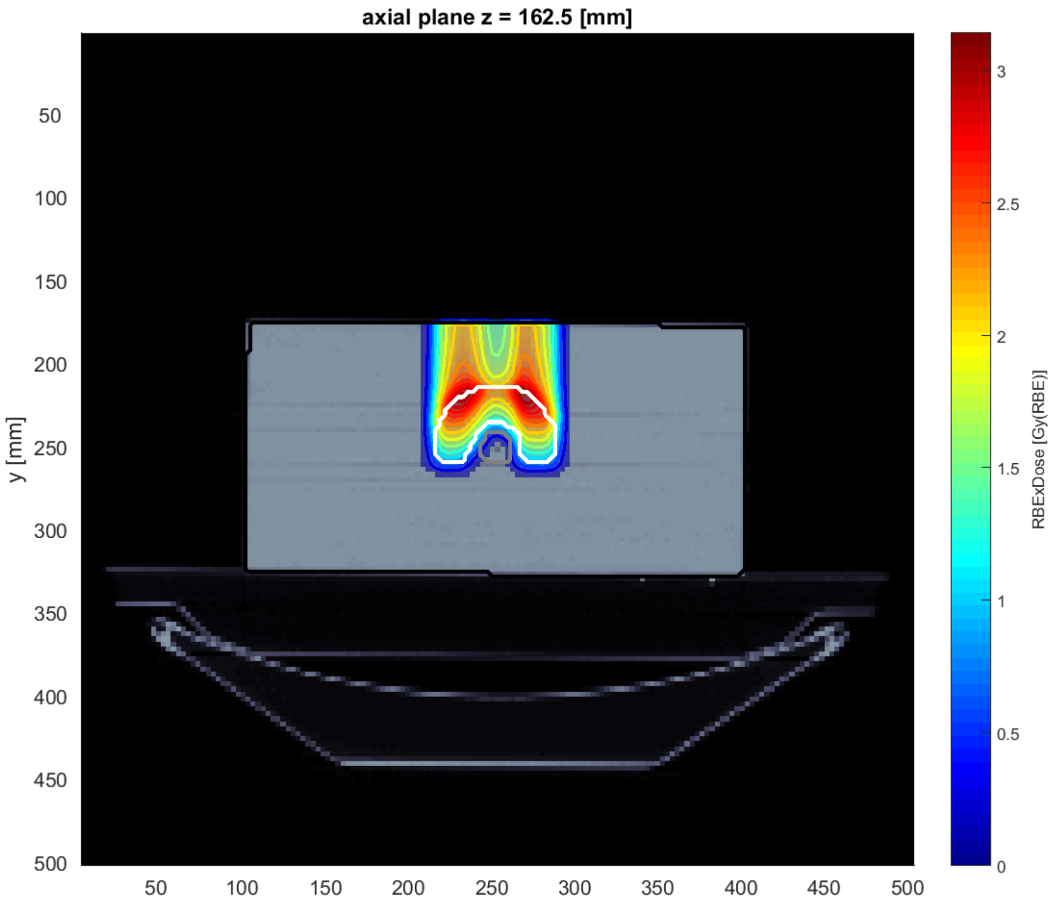
$$d_i = \sum_{j=1}^{B} w_j D_{ij} = \sum_{j=1}^{B} w_j \, L_{ij}^{x} L_{ij}^{y} Z_{ij}^{z}$$

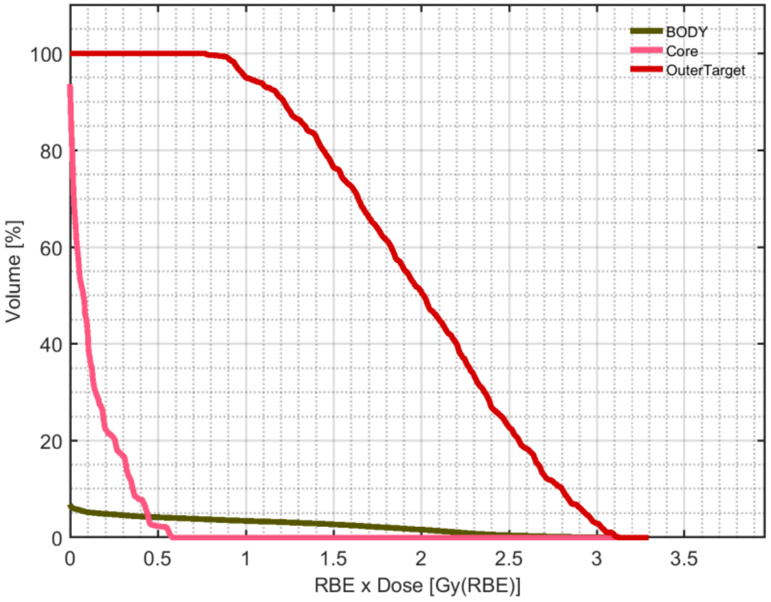


geometry and ray-casting for “radiological depth” / Water-equivalent path length (WEPL) computation

- particles: lateral Gaussian, depth tabulated

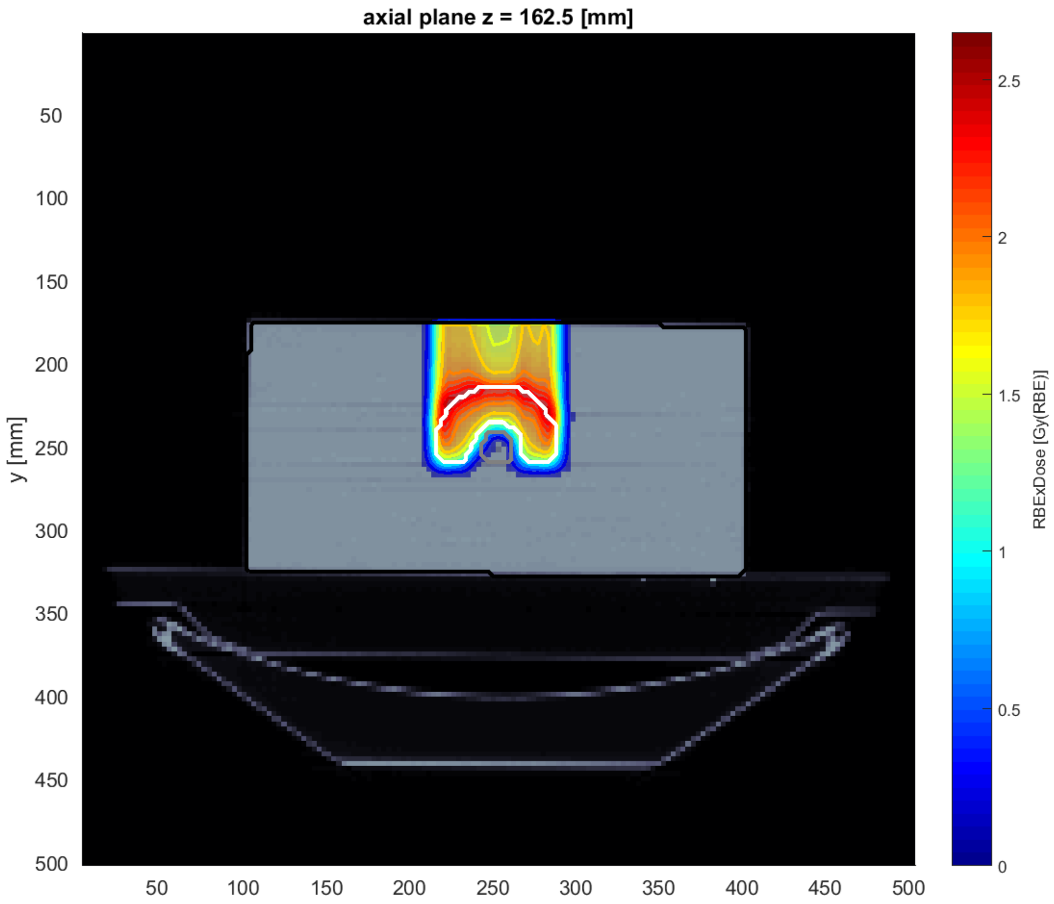
Example: TG119 phantom – iteration 1

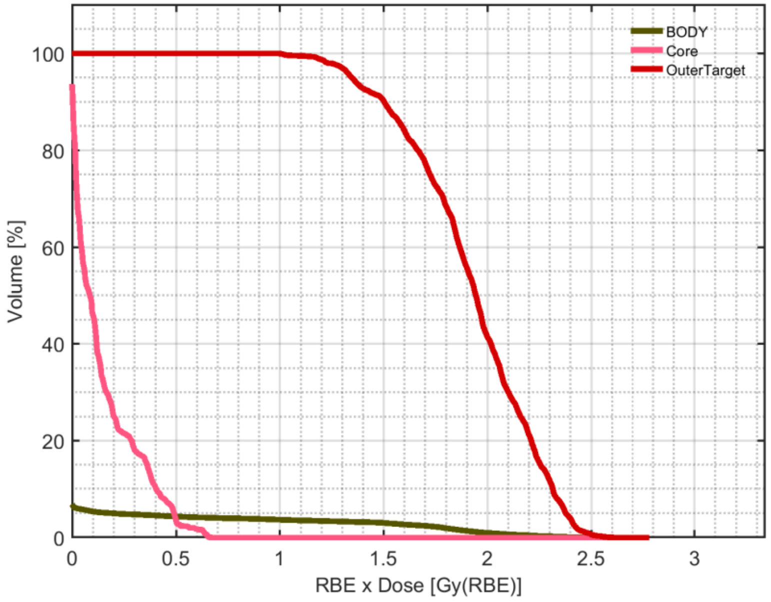




Slide courtesy of Mark Bangert (adapted)

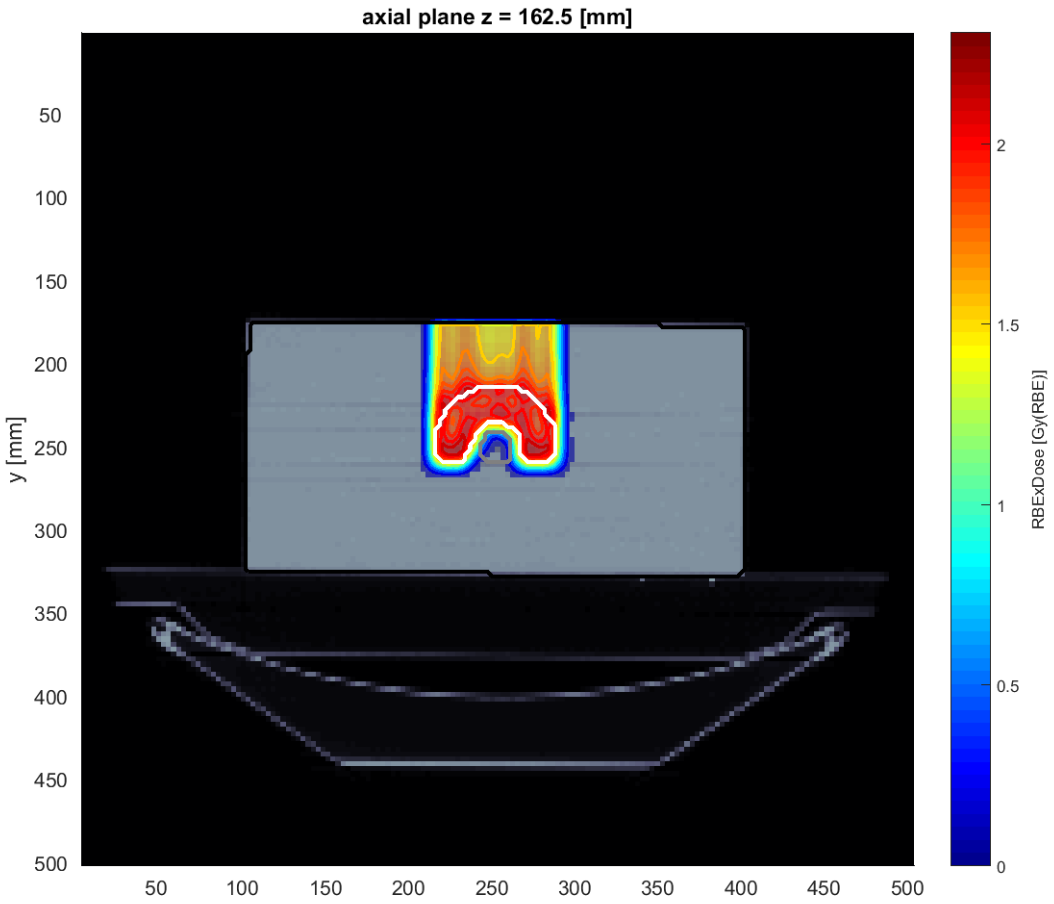
Example: TG119 phantom – iteration 5

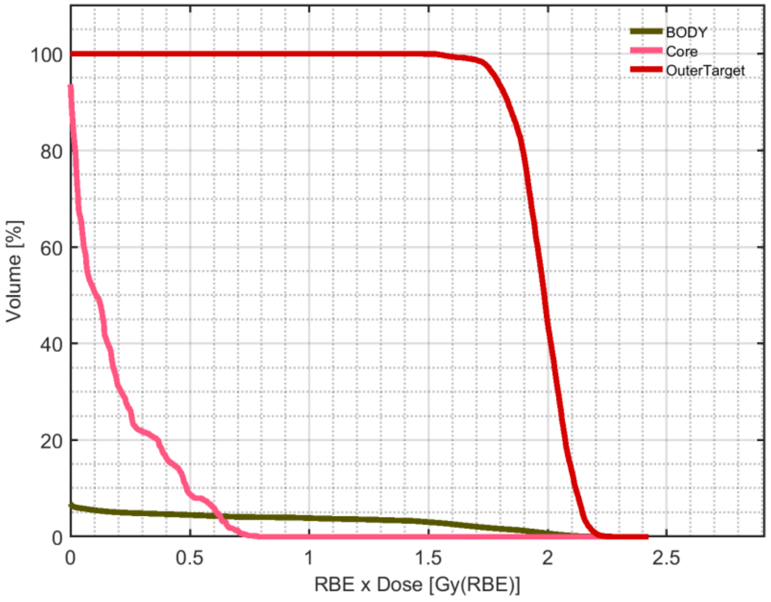




Slide courtesy of Mark Bangert (adapted)

Example: TG119 phantom – iteration 10





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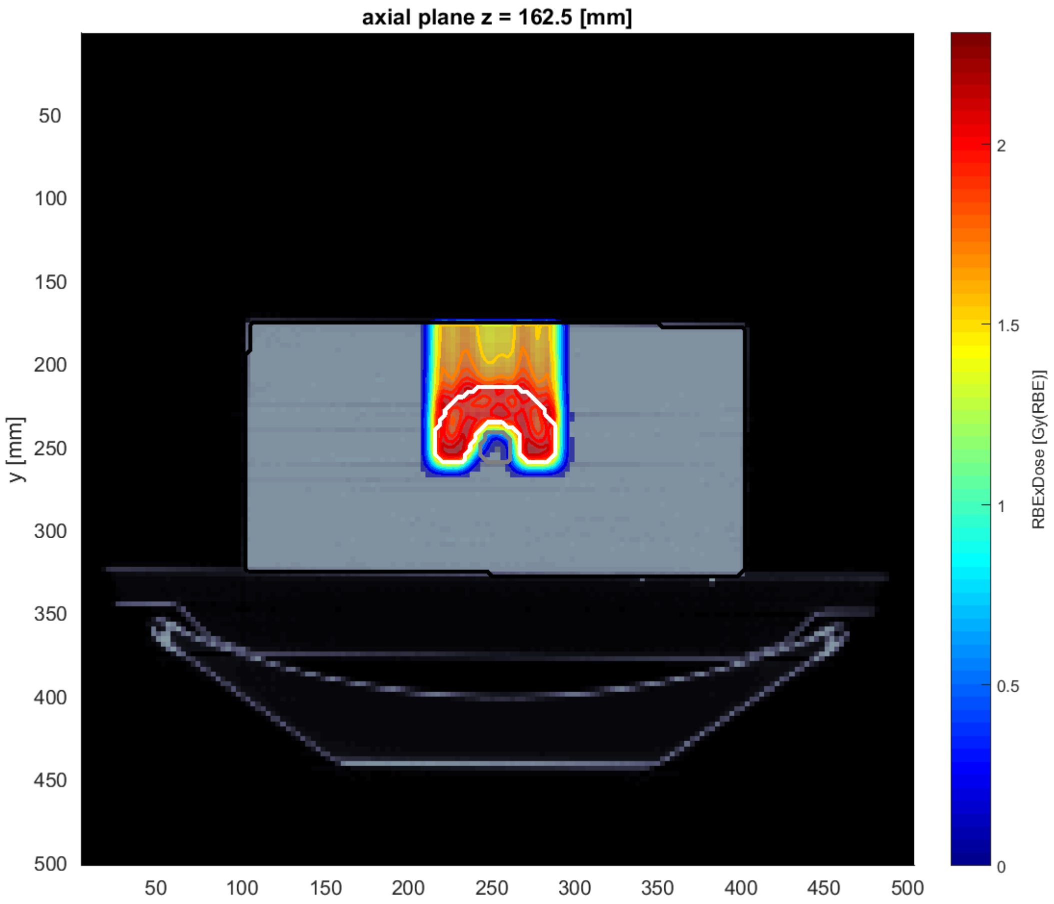
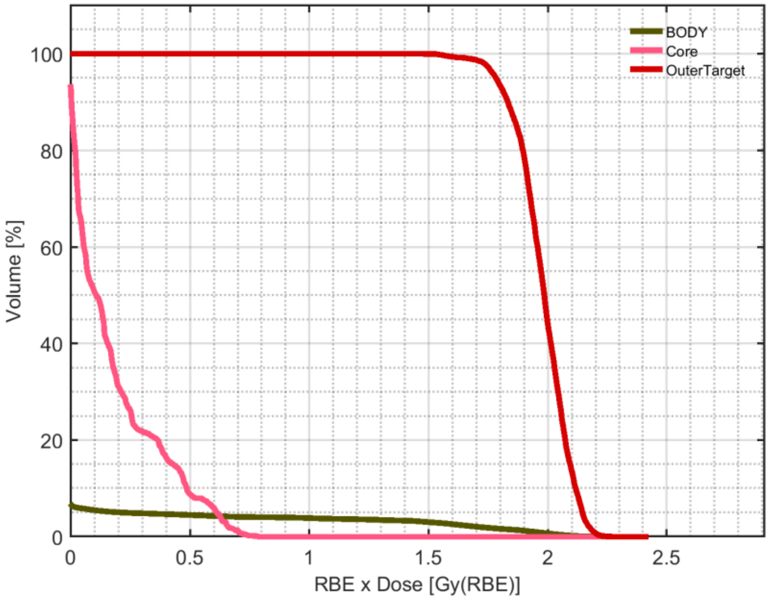
Example: TG119 phantom – iteration 10





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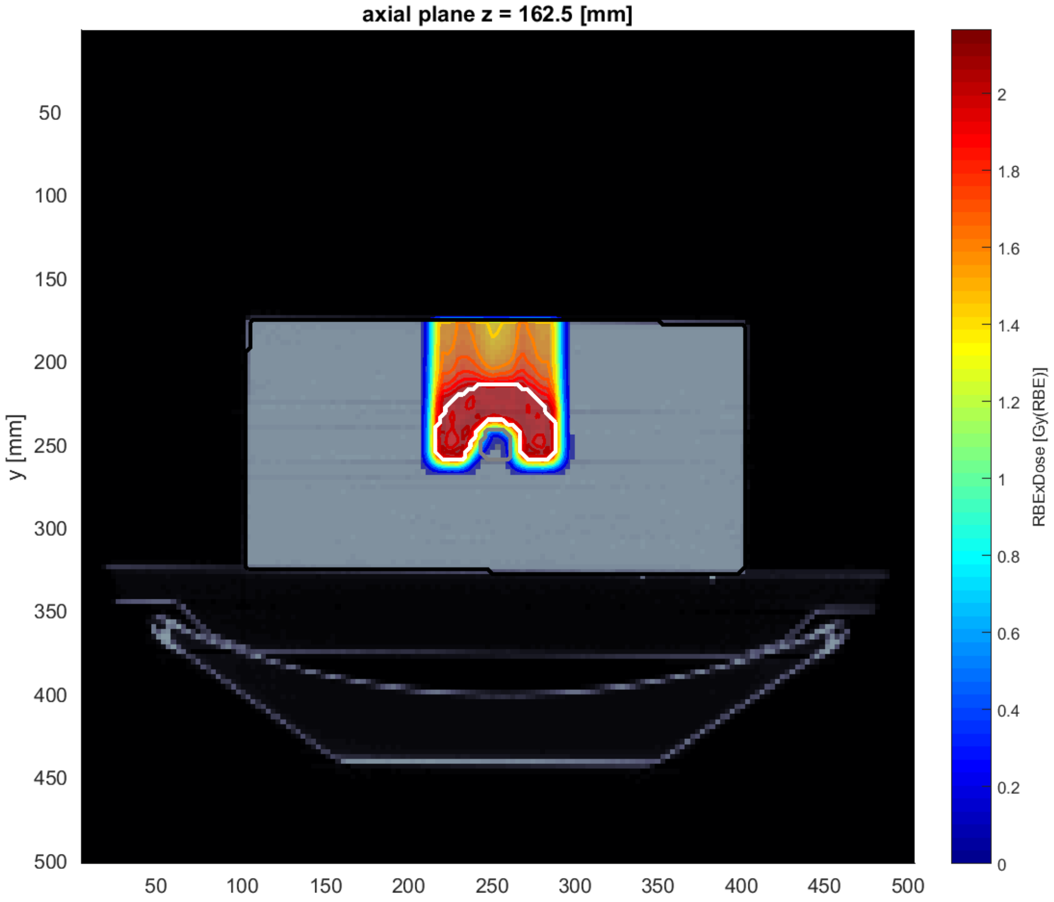
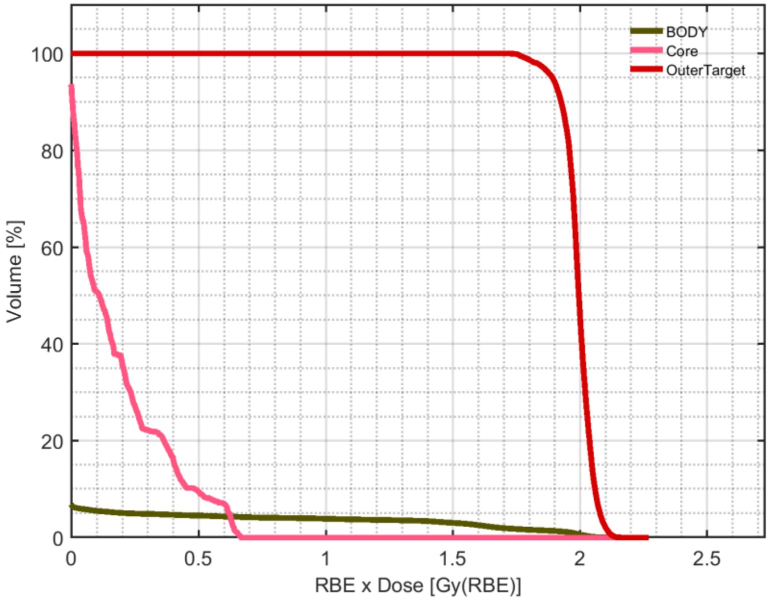
Example: TG119 phantom – iteration 30





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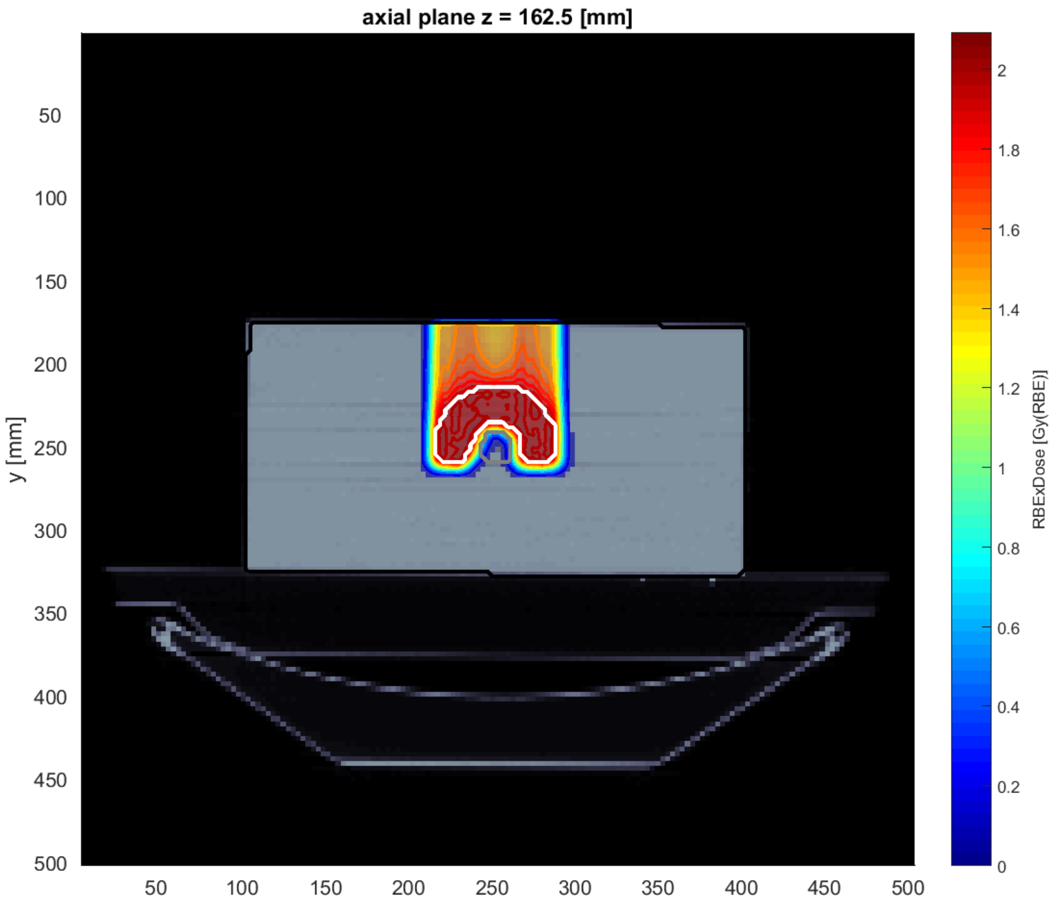
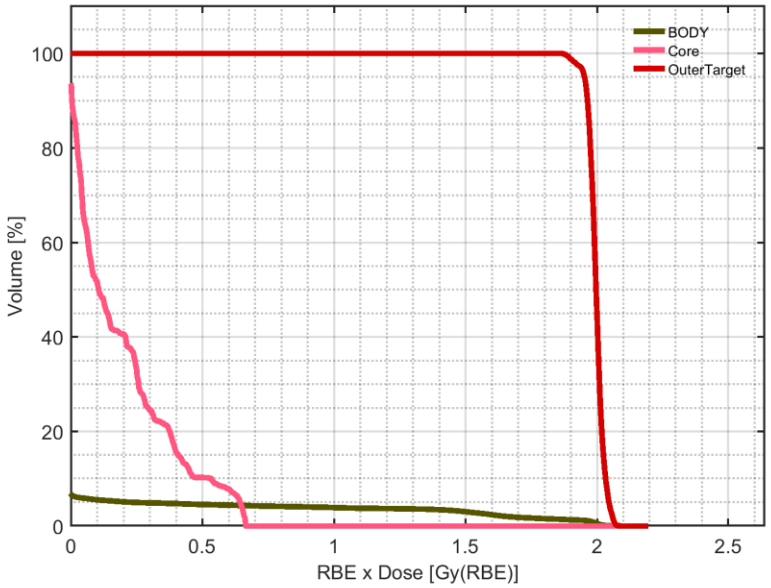
Example: TG119 phantom – iteration 97





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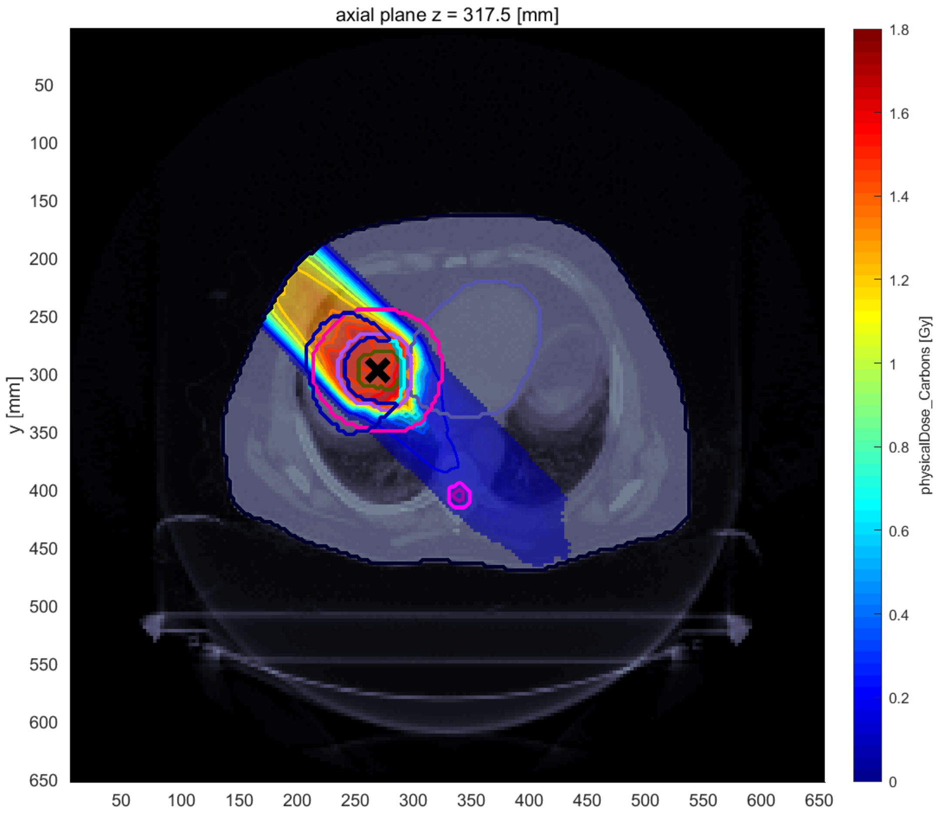
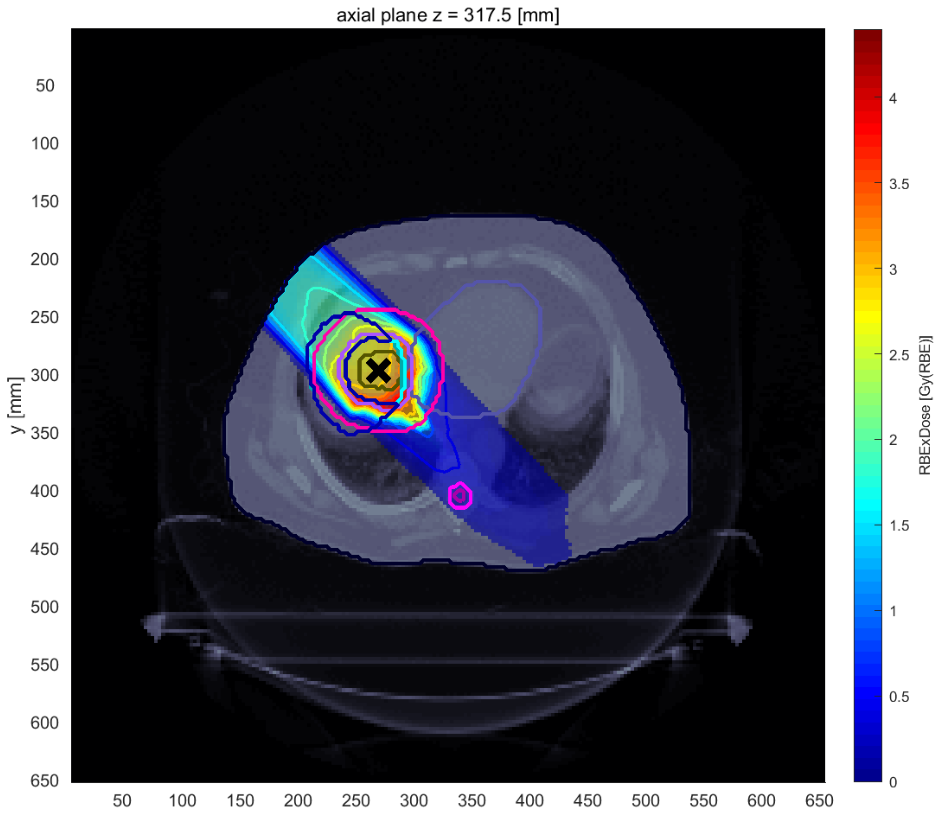
Example Liver Case – Carbons

Physical dose



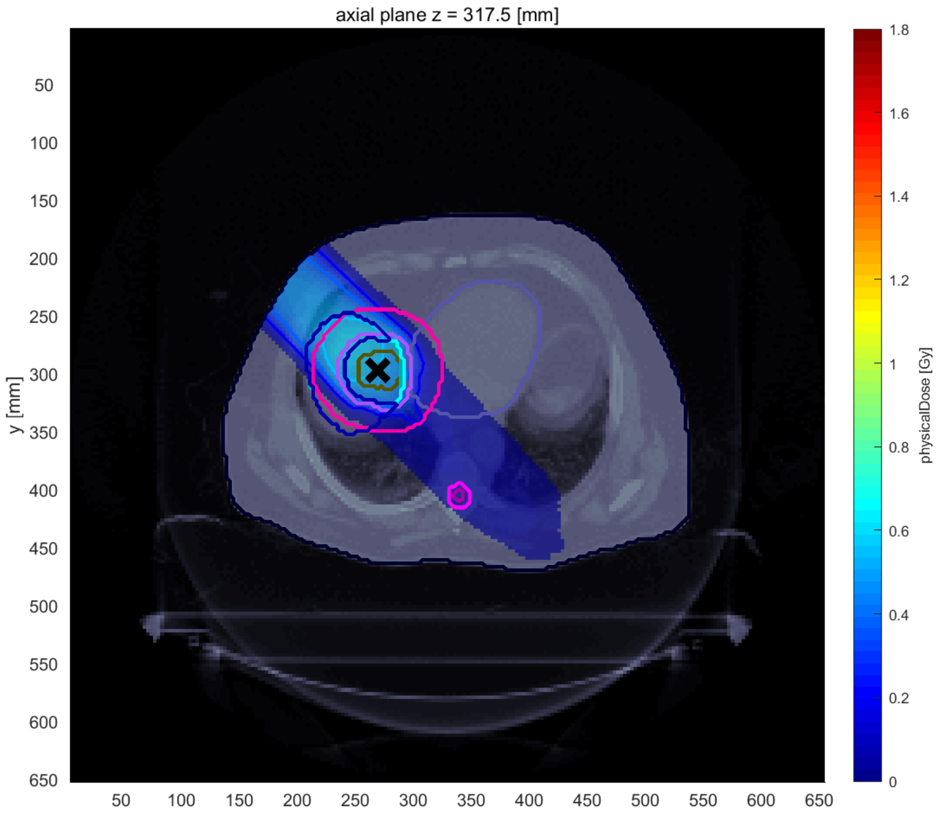
Physical dose



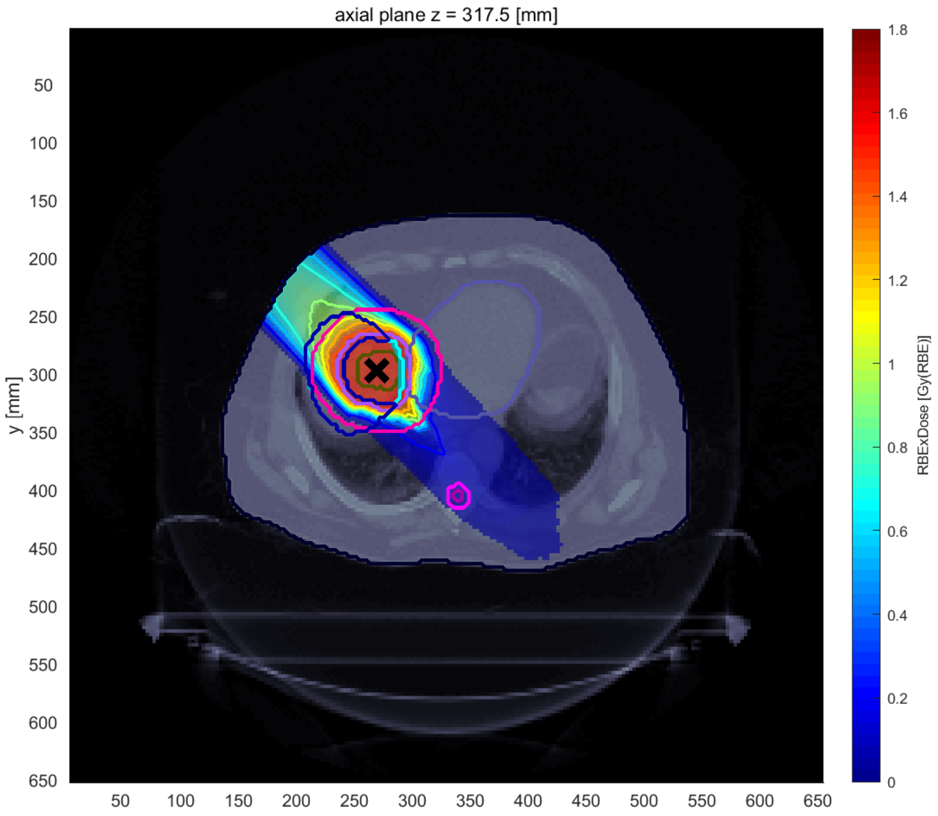
→ The same physical dose induces different biological effect!

Example Liver Case – Carbons

physical dose



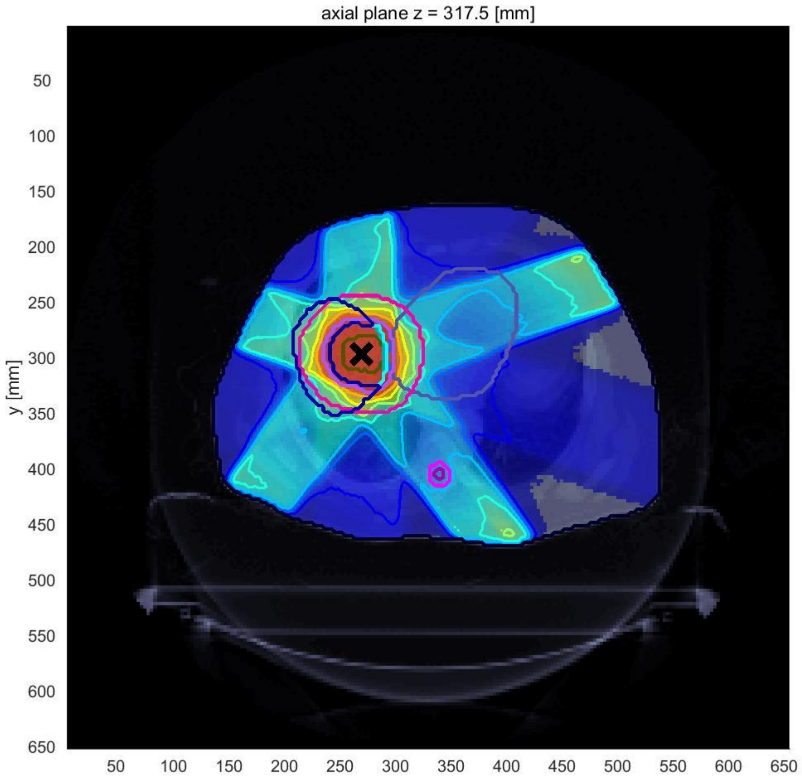
Biologically effective dose



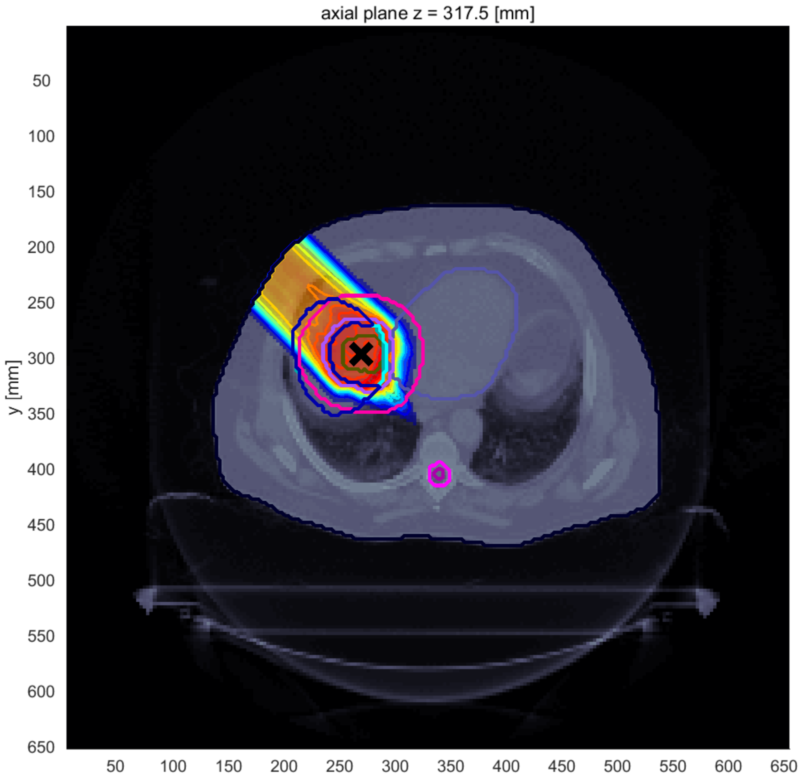
→ Optimize for biology (i.e. RBE) directly instead of dose

Examples: Liver patient

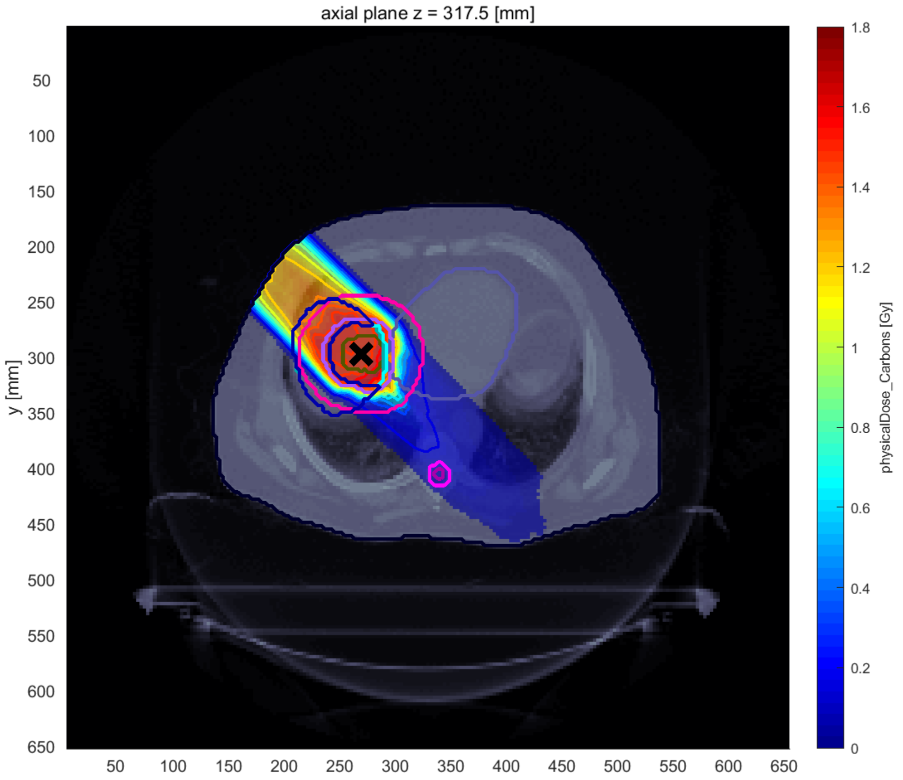
photons



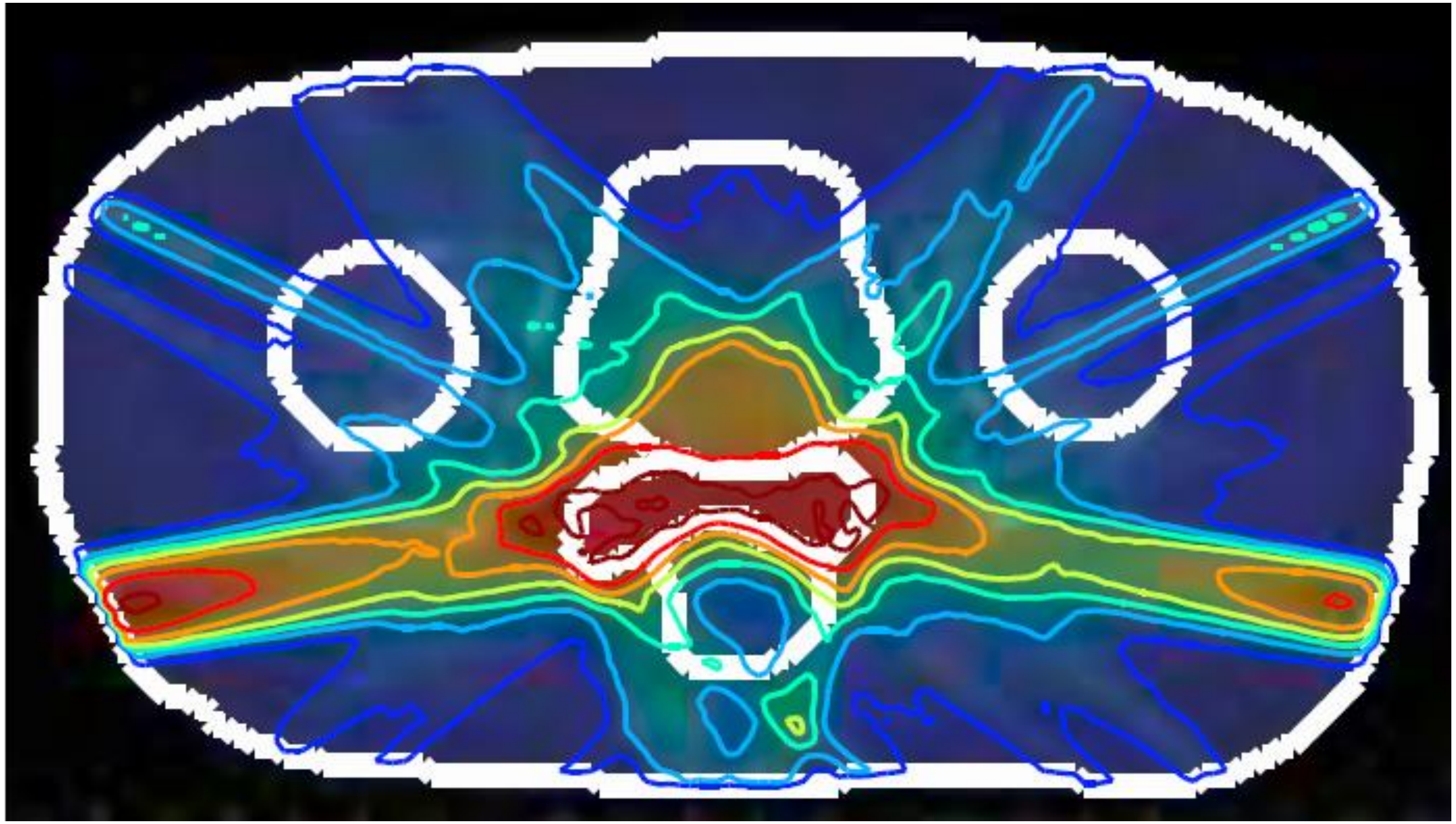
protons



carbon ions



How do we analyze a dose / quantify a plan?



Evaluation of the
2D tomographic images

Dose statistics:

Mean, maximum, minimum dose

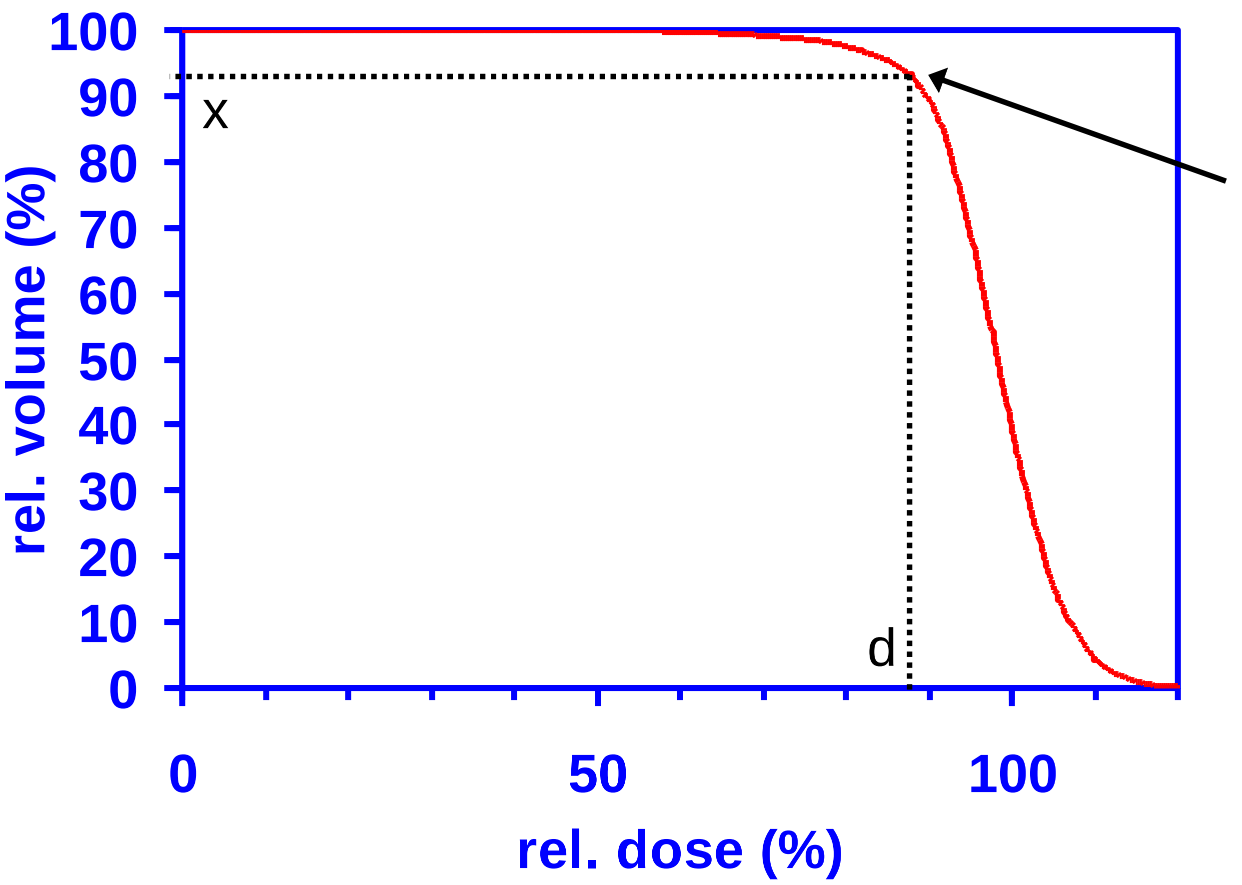
Dose-volume histograms

2D display of the 3D dose distribution

Complication / Control Models

(N)TCP, mostly derived empirically

Dose-volume histograms



x% of the volume obtains at least d% of the prescribed dose

TCP / NTCP models

- Tumor control & normal tissue complication often modeled with logistic functions
  → Lyman-Kutcher-Burman – LKB
- Empirically determined, more recently often ML/AI-driven
- May be used directly in planning, but more commonly used to assess plan quality and “design” prescriptions

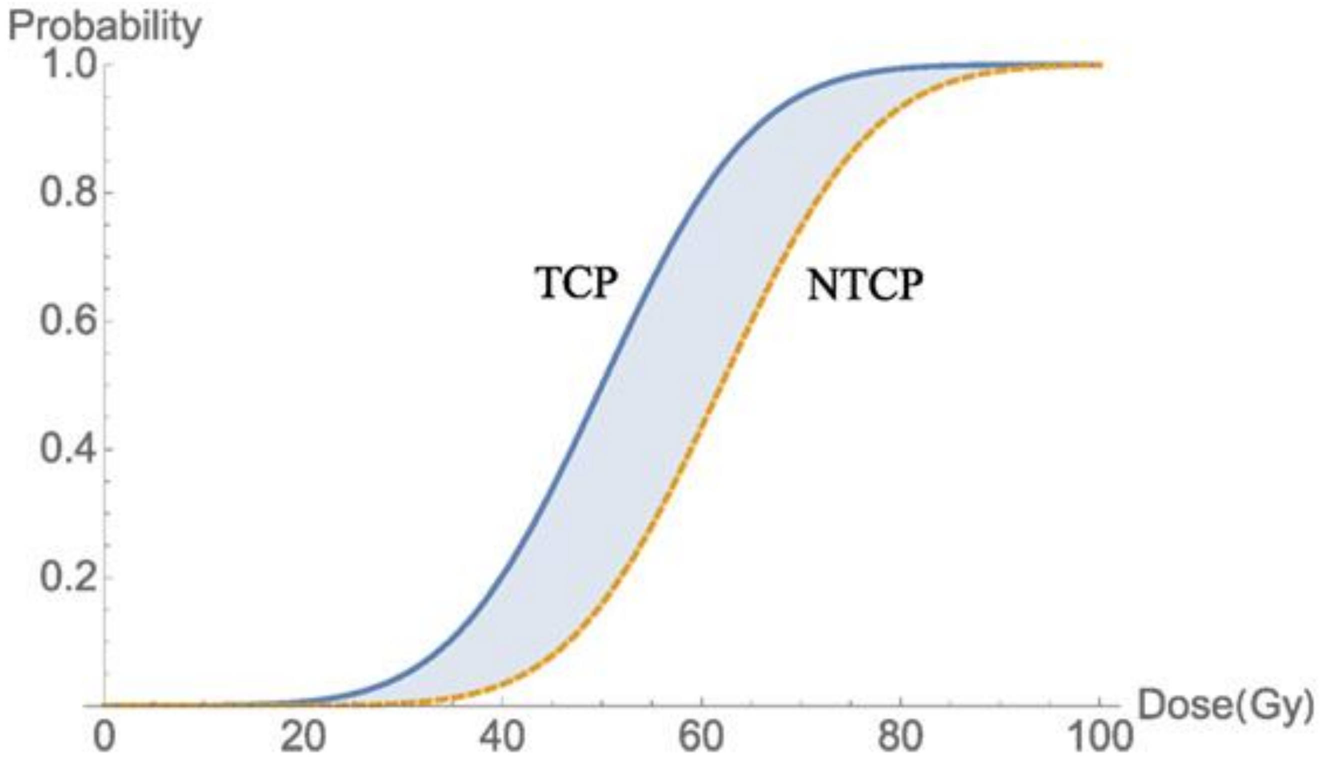


Image from Tseng H-H, Luo Y, Ten Haken RK and El Naqa I (2018) The Role of Machine Learning in Knowledge-Based Response-Adapted Radiotherapy. *Front. Oncol.* 8:266. doi: 10.3389/fonc.2018.00266

More complex prescriptions…

- The prescription can be much more complex / abstract than the initial example
- Prescriptions need to be translated into the language of the optimizer (math)

„Keep the mean dose to the parotid gland low....“

„while achieving a coverage with 60 Gy in the tumor“

„do not exceed a dose of 10 Gy in the brainstem“

…require more complex optimization problems

„Keep the mean dose to the parotid gland low....“

Objective (minimize) $$f_1 = \frac{1}{N_S} \sum_{i \epsilon S} d_i$$

„while achieving a coverage with 60 Gy in the tumor“

Objective (minimize) $$f_2 = \frac{1}{N_S} \sum_{i \epsilon S} \left(d_i - \hat{d}\right)^2$$

„do not exceed a dose of 10 Gy in the brainstem“

Constraint (enforce) $$c_1 = d_{max} + \kappa \log \left(\sum_{i \epsilon S} \frac{d_i - d_{max}}{\kappa} \right)$$

- Optimizers:
  - interior-point method
  - Sequential quadratic programming (e.g. in RayStation)

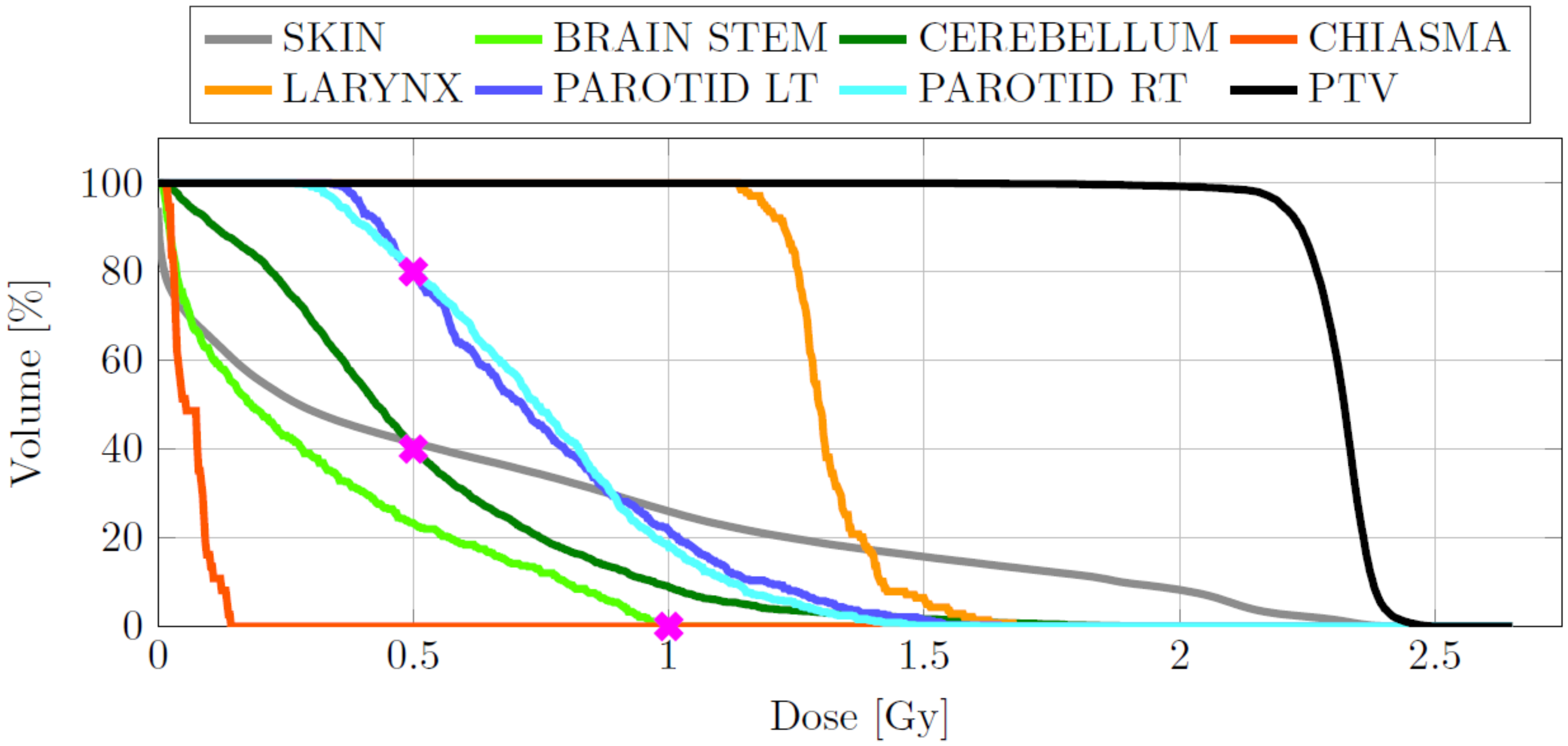
$$\min_{w \in \mathbb{R}^B} f(w) = \sum_n p_n f_n(w)$$

$$\text{s.t.} \quad c_k^l \leq c_k(w) \leq c_k^u$$

$$0 \leq w$$

Example of fulfilled constraints in a DVH

- DVH constraints on cerebellum & parotid glands
- Maximum dose constraint on brainstem



In practice: „Sea“of objective functions for targets and healthy tissue

- Non-linear constrained optimization problem

$$w^* = \arg\min f(d(w)) = \sum_k^K p_k f_k(d(w))$$
$$\text{s. t.} \quad c_q^L \leq c_q\big(d(w)\big) \leq c_q^U$$
$$w \geq 0$$

- Example from matRad paper:

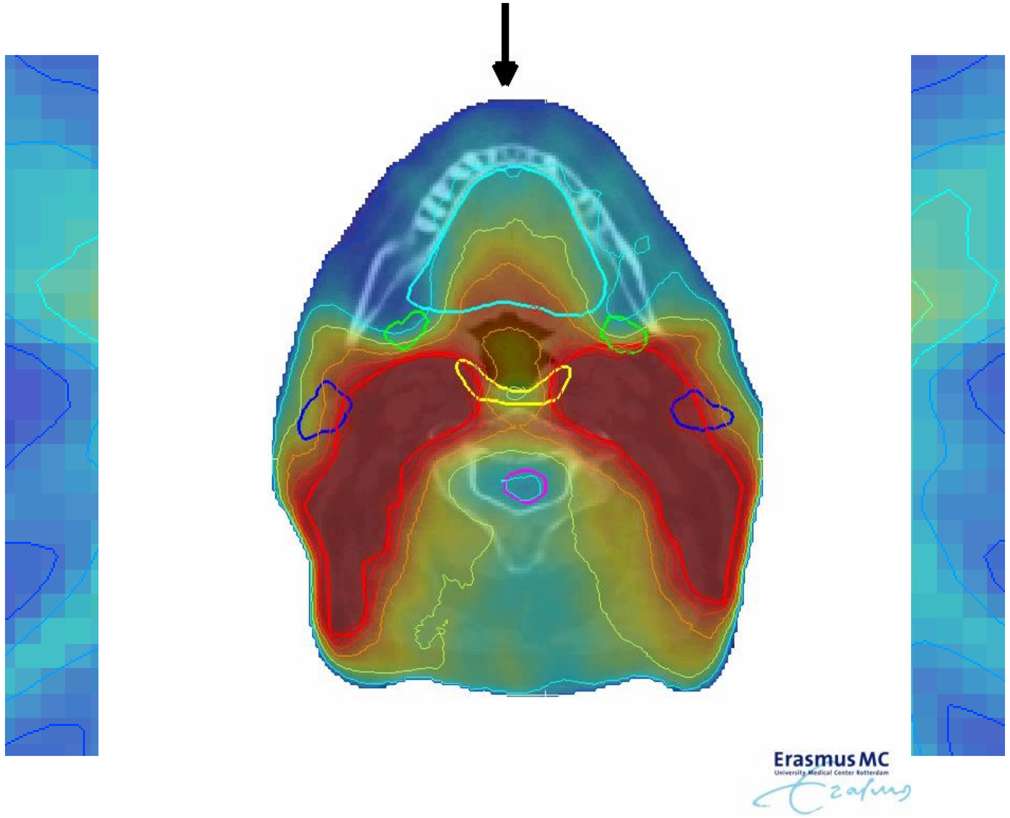
objectives		constraints	
$f_{sq\,deviation}$	$= \frac{1}{N_S}\sum_{i\epsilon S}(d_i - \hat{d})^2$		
$f_{sq\,under\,dosage}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(\hat{d} - d_i)(d_i - \hat{d})^2$	$c_{min\,dose}$	$= d_{min} - \kappa\, log\left(\sum_{i\epsilon S} e^{\frac{d_{min}-d_i}{\kappa}}\right)$
$f_{sq\,over\,dosage}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(d_i - \hat{d})(d_i - \hat{d})^2$	$c_{max\,dose}$	$= d_{max} + \kappa\, log\left(\sum_{i\epsilon S} e^{\frac{d_i-d_{max}}{\kappa}}\right)$
f_{mean}	$= \frac{1}{N_S}\sum_{i\epsilon S} d_i$	c_{mean}	$= \frac{1}{N_S}\sum_{i\epsilon S} d_i$
f_{EUD}	$= \left(\frac{1}{N_S}\sum_{i\epsilon S} d_i^a\right)^{\frac{1}{a}}$	c_{EUD}	$= \left(\frac{1}{N_S}\sum_{i\epsilon S} d_i^a\right)^{\frac{1}{a}}$
$f_{min\,DVH}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(\hat{d} - d_i)\Theta(d_i - \tilde{d})(d_i - \hat{d})^2$	$c_{min\,DVH}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(\hat{d} - d_i)$
$f_{max\,DVH}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(d_i - \hat{d})\Theta(\tilde{d} - d_i)(d_i - \hat{d})^2$	$c_{max\,DVH}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(d_i - \hat{d})$

Most important thing to never forget: It‘s a trade-off

- Trade-off between target coverage and sparing of normal tissues
- Trade-off between sparing of different organs at risk

Multicriteria decision/planning/optimization problem

More options to solve this problem, e.g., with Pareto surface approximation & exploration



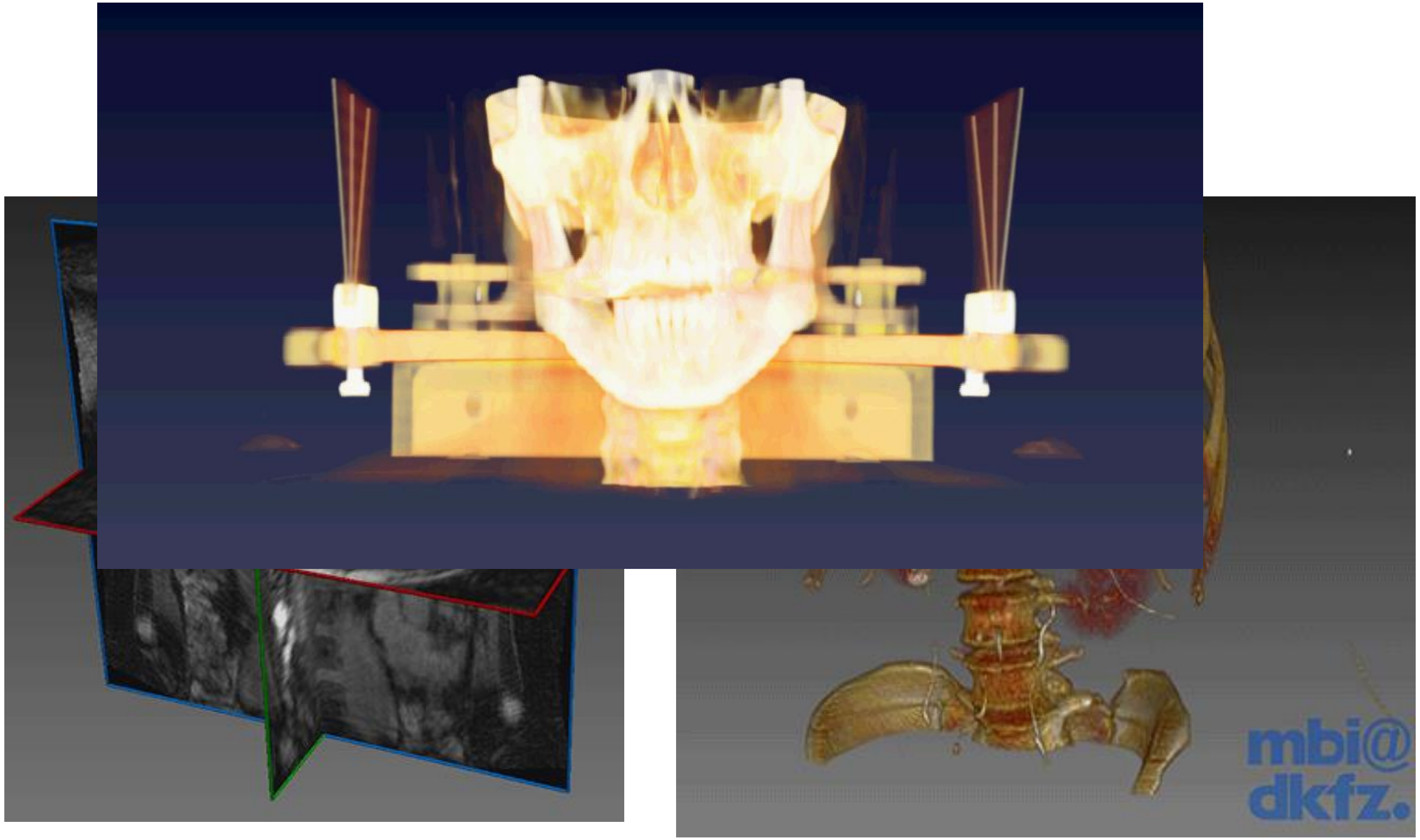
Head and neck animation courtesy of Dr. Sebastiaan Breedvelt @ Erasmus MC Cancer Institute Rotterdam

https://sebastiaanbreedveld.nl/rt_tradeoffs.html

Now we have fully understood and solved the problem of inverse treatment planning using intensity modulation for photons & ions?

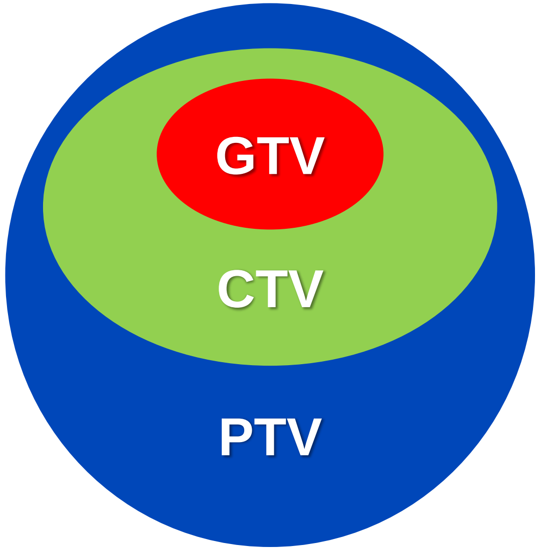
dkfz.

Problem: Dealing with uncertainties



Animations courtesy of Paul Merca & Markus Stoll

Margins in treatment planning

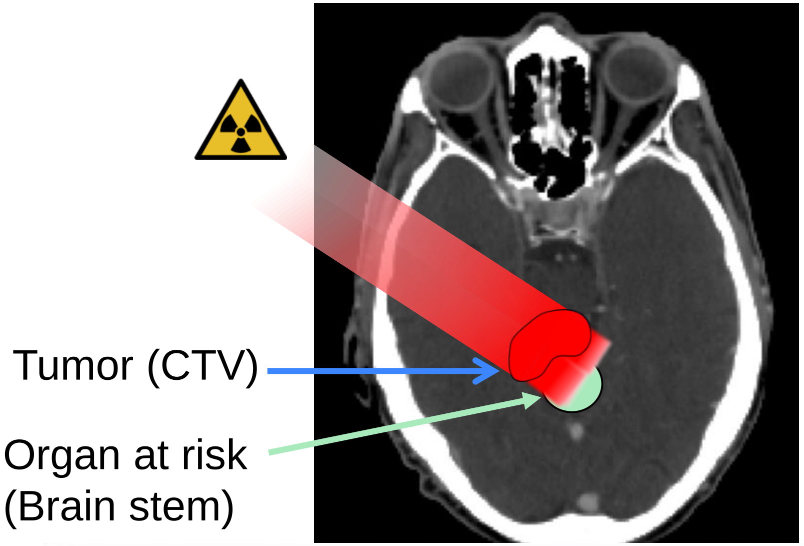


- GTV = Gross tumor volume
  tumor volume that is visible on the images
- CTV = Clinical target volume
  includes the GTV and regions where invisble tumor tissue is expected
- PTV = Planning target volume
  safety margin to take uncertainties into account

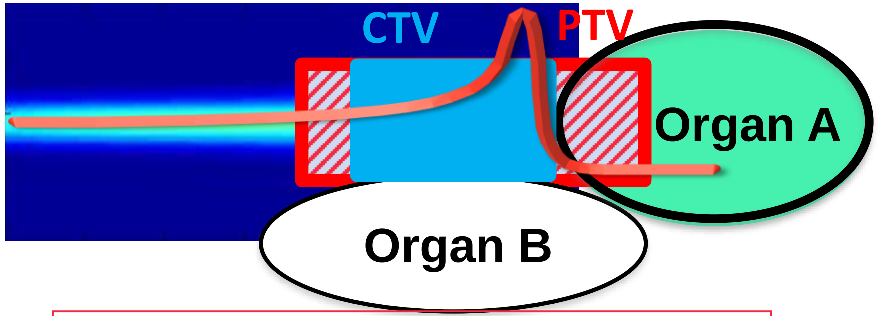
W. Schlegel & A. Mahr: 3D Conformal Radiation Therapy Springer Multimedia DVD

ICRU report 50

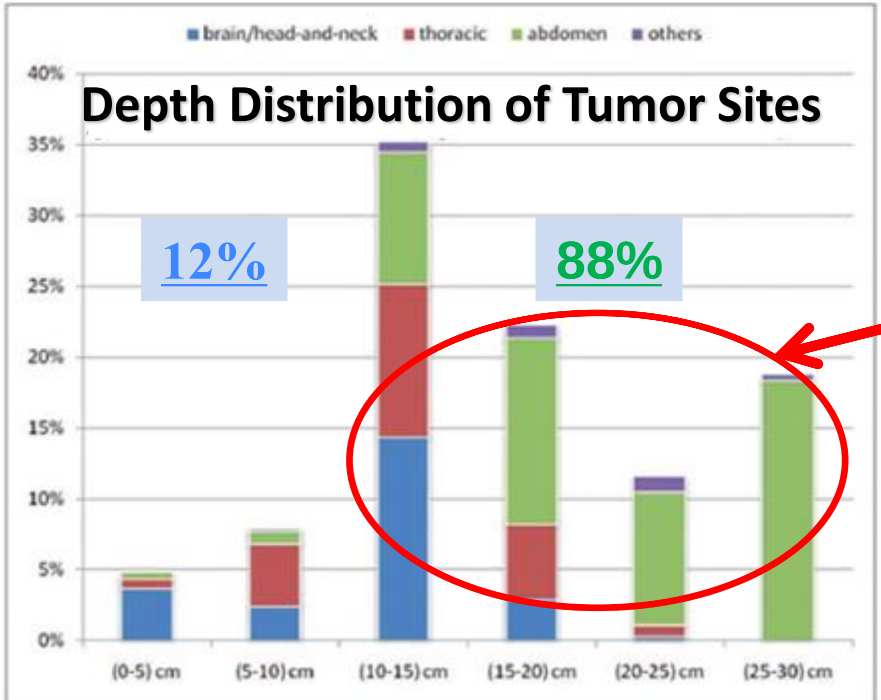
“Bragg Peak” Range Uncertainty

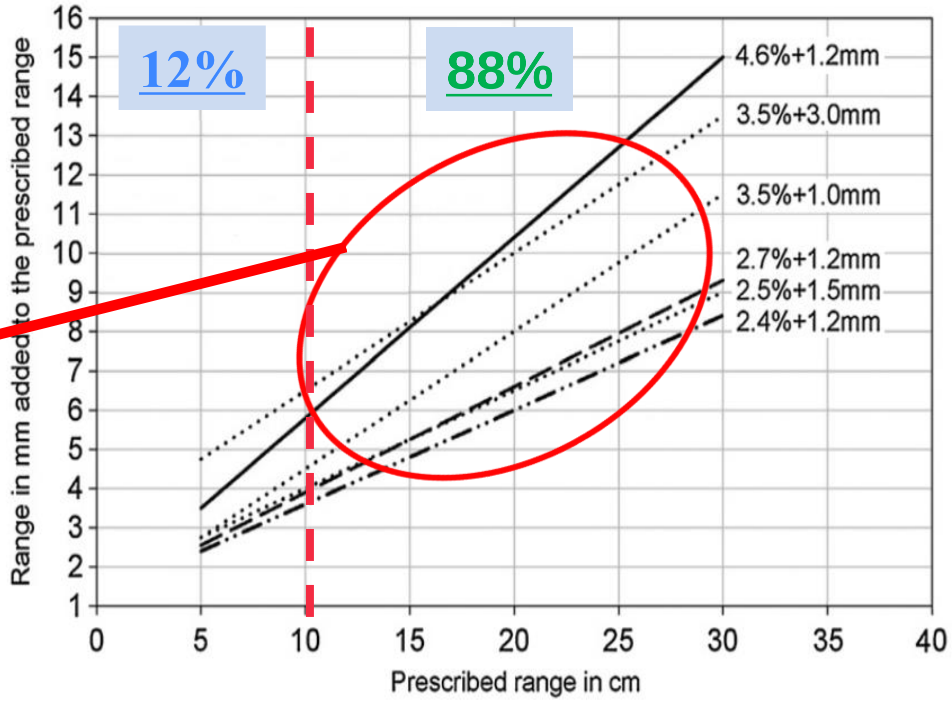


TUMOR (CTV) and PLANNING TARGET (PTV)



Range Margin recipes in use

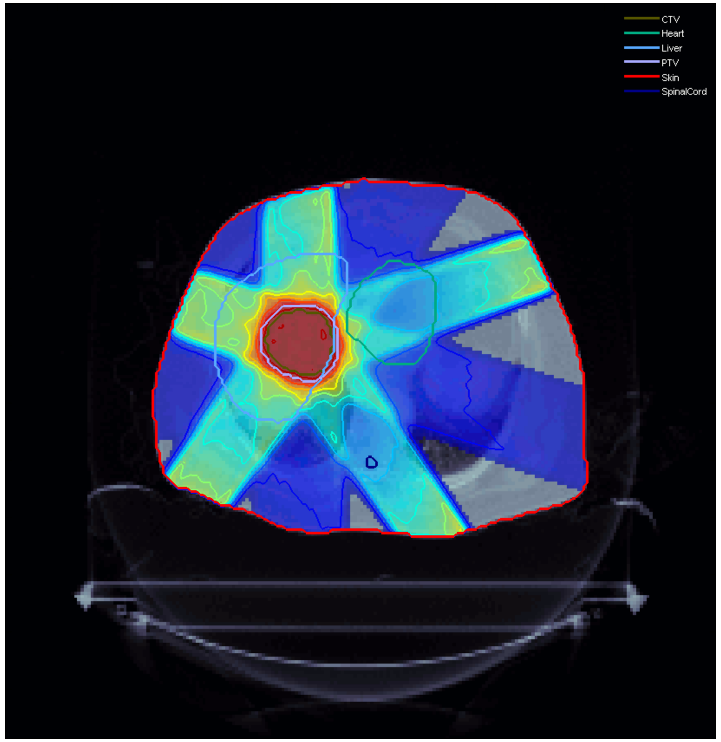


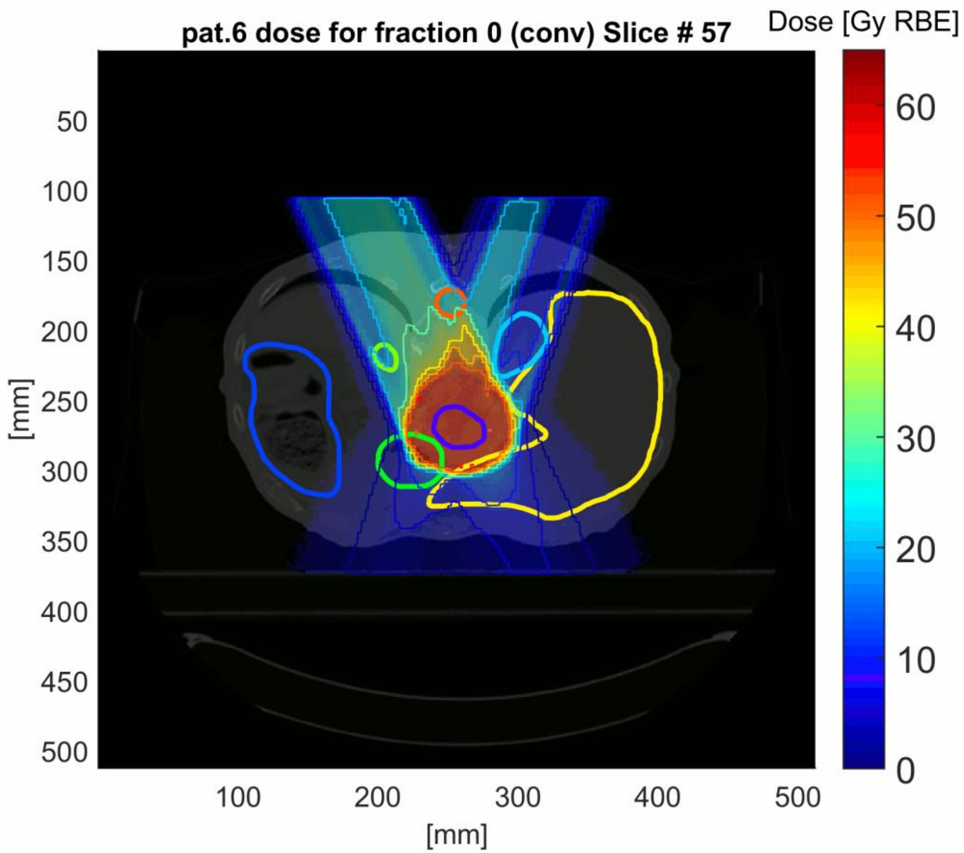


dkfz.

Margins – really?

- The “original” margin recipe for photon therapy:
  “**Minimum dose to CTV is 95% for 90% of population**” $2.5\,\sigma_{\text{sys}} + 0.7\sigma_{\text{rand}} - 3\text{mm}$



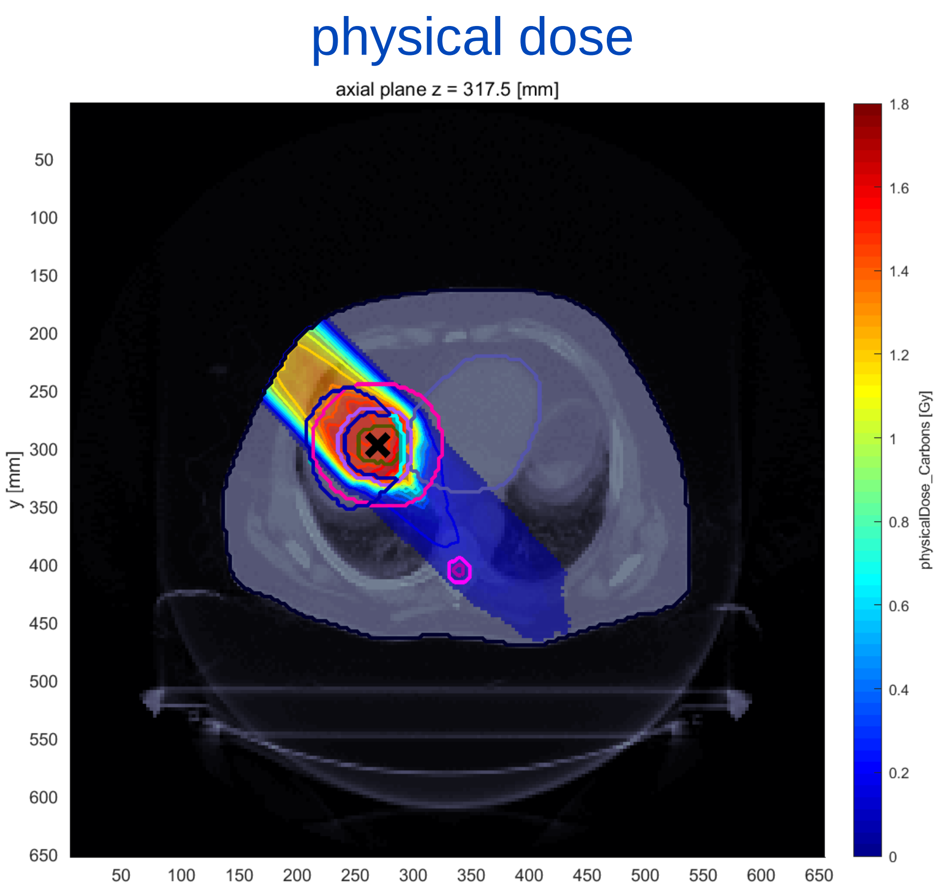


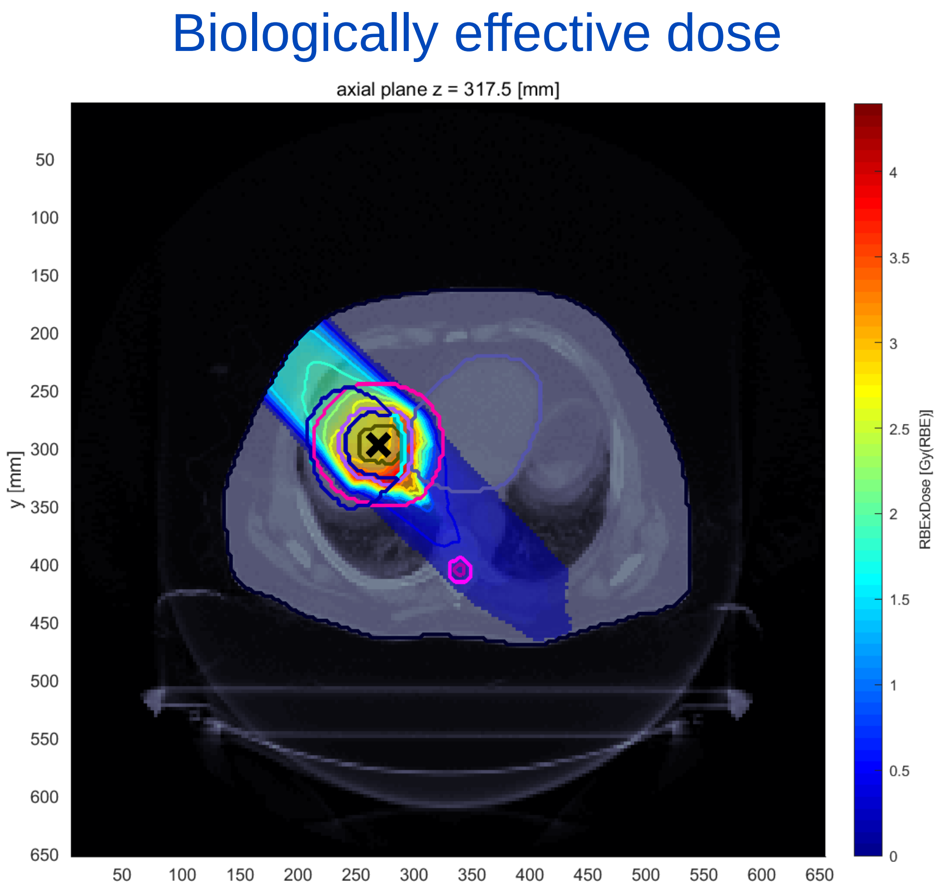
[3] Steitz et al., *Radiation Oncology 2016,* **11**:134

→ Not applicable for protons / ions!

van Herk et al., *IJRBOP 2000,* **57**(4):1121

Difference in biological effect





→ Physical doses similar to photons induce different biological effect!

dkfz.

Robust/worst case optimization

- Describe uncertainty with scenarios π from a discrete uncertainty set
- All scenarios may contribute to a voxel-wise combination of a worst case dose distribution

$$d_i^{WC} = \begin{cases} \min(d_i^{\pi}), i \in target \\ \max(d_i^{\pi}), i \in rest \end{cases}$$

Optimization problem

$$\boldsymbol{w}^* = \arg\min\ F(\boldsymbol{d}^{WC})$$

subject to

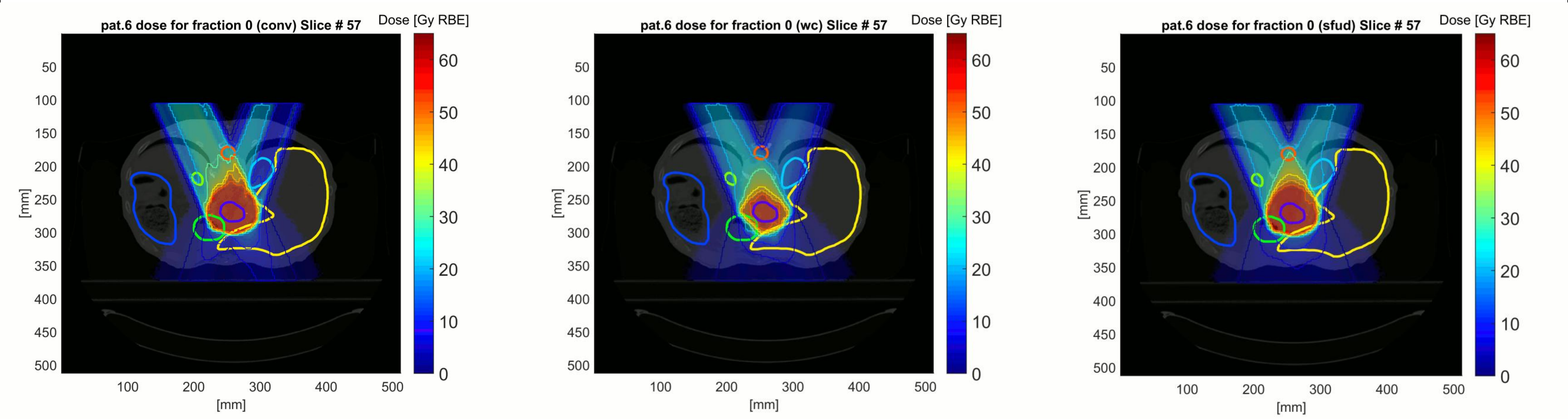
$$\boldsymbol{c}^l \leq C(\boldsymbol{d}^{WC}) \leq \boldsymbol{c}^u$$

„while the minimum (worst-case) PTV dose is above 54 Gy in all scenarios“

„Minimize the maximum (worst-case) mean lung dose....“

Robust/worst case optimization

conventional | Worst case | SFUD



J Steitz, P Naumann, S Ulrich, MF Haefner, F Sterzing, U Oelfke & M Bangert. (2016). Worst case optimization for interfractional motion mitigation in carbon ion therapy of pancreatic cancer. *Submitted to Radiation Oncology*

Summary

- In treatment planning we try to find the best approximation to an ideal dose distribution / prescription
  → Multiple factors (biology, importance of objectives / organs, etc.)
- The problem is approached by optimization techniques (inverse planning)
- It is a multicriteria problem that let's the planner choose trade-offs
- Ion therapy has its advantages but also pitfalls during planning, most notably
  - Biology
  - Localization (NT sparing & tumor coverage) ⇔ Uncertainties
  - Robustness of treatment plan

THANK YOU

Heavy Ion Therapy Research Integration

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