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

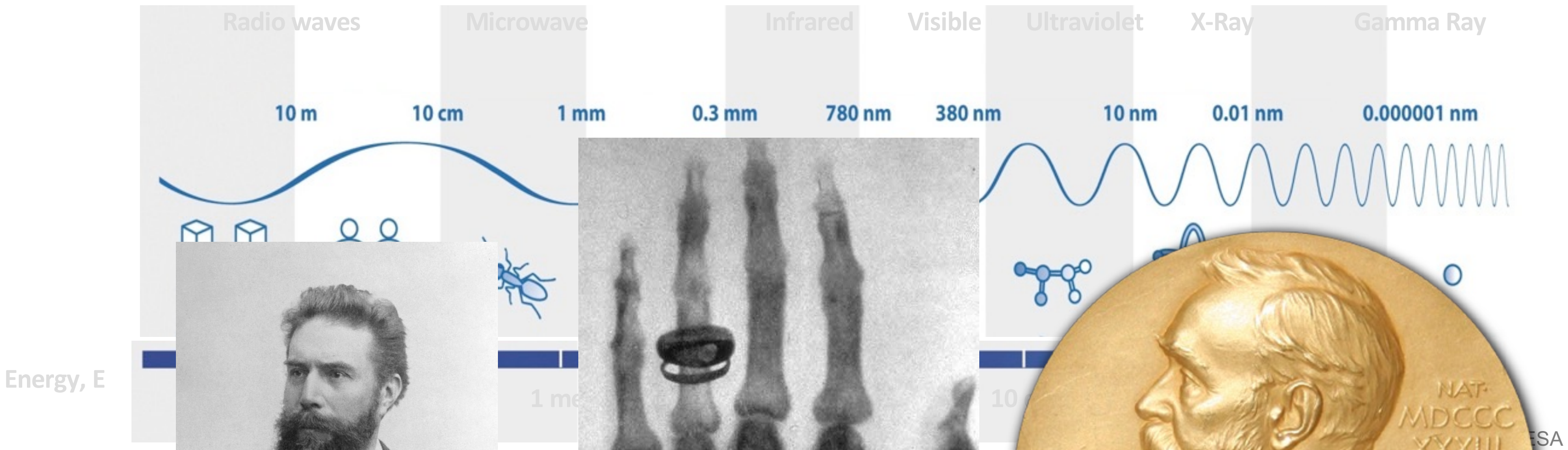
A treatment plan should …

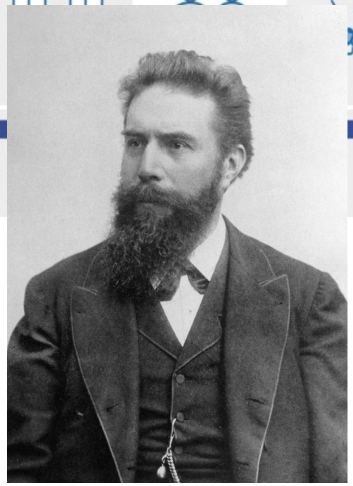
- ... fulfil clinical requirements ("The physician prescribes") …
- ... based on biological processes (cell death) …
- ... induced by chemical & physical processes (reactions & interactions) …
- ... by means of numerical simulation (dose calculation / optimization)

→ Interdisciplinary **inverse problem**

dkfz.

Imaging: X-ray





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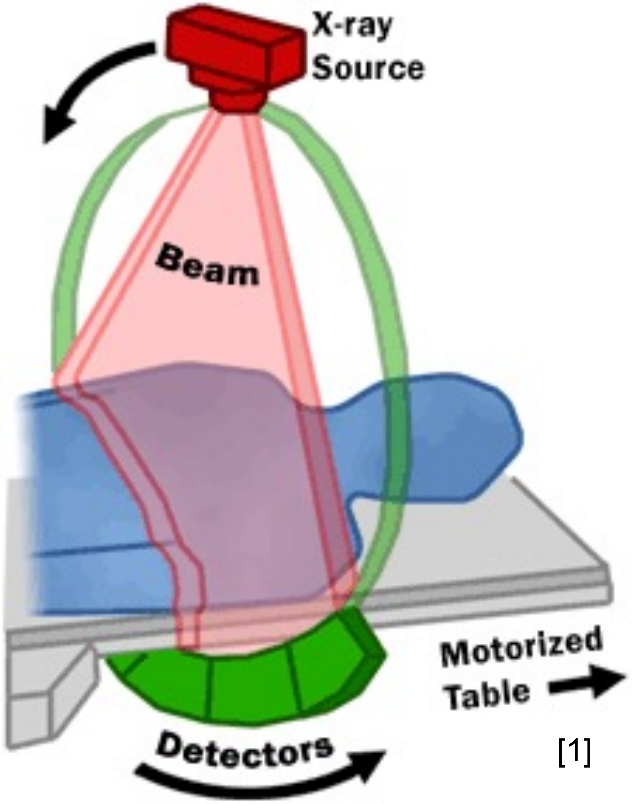
[1] anonym (https://commons.wikimedia.org/wiki/File:Roentgen2.jpg), „Roentgen2“, marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-EU-no author disclosure
[2] Wilhelm Röntgen; current version created by Old Moonraker. (https://commons.wikimedia.org/wiki/File:X-ray_by_Wilhelm_Röntgen_of_Albert_von_Kölliker'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
[3] Photograph: JonathunderMedal: Erik Lindberg (1873-1966) (https://en.wikipedia.org/wiki/File:Nobel_Prize.png), „Nobel Prize“, marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-US

Imaging: Computed tomography

"3D X-ray"



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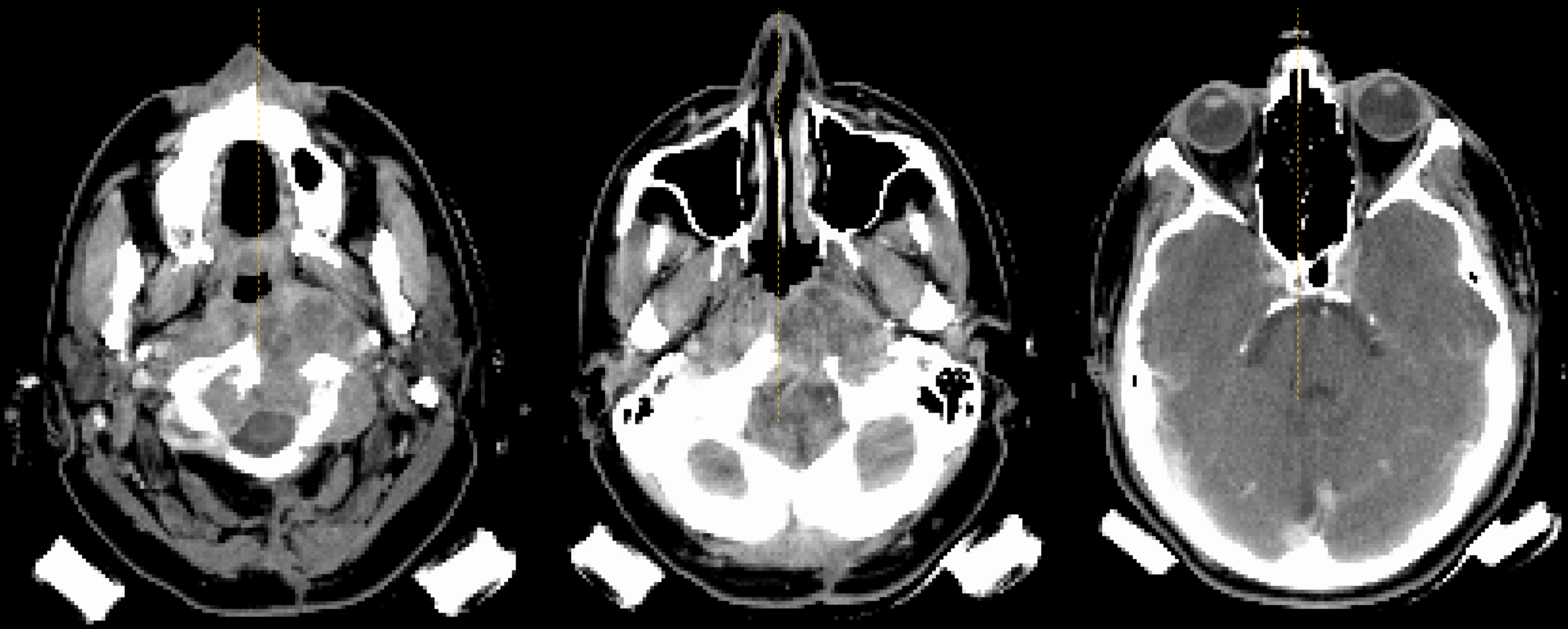
[1] FDA – Radiation emitting products – Medical X-ray Imaging – What is Computed Tomography? - Accessed from https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/what-computed-tomography on 15.02.2021.
[2] daveynin from United States (https://commons.wikimedia.org/wiki/File:UPMCEast_CTscan.jpg),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

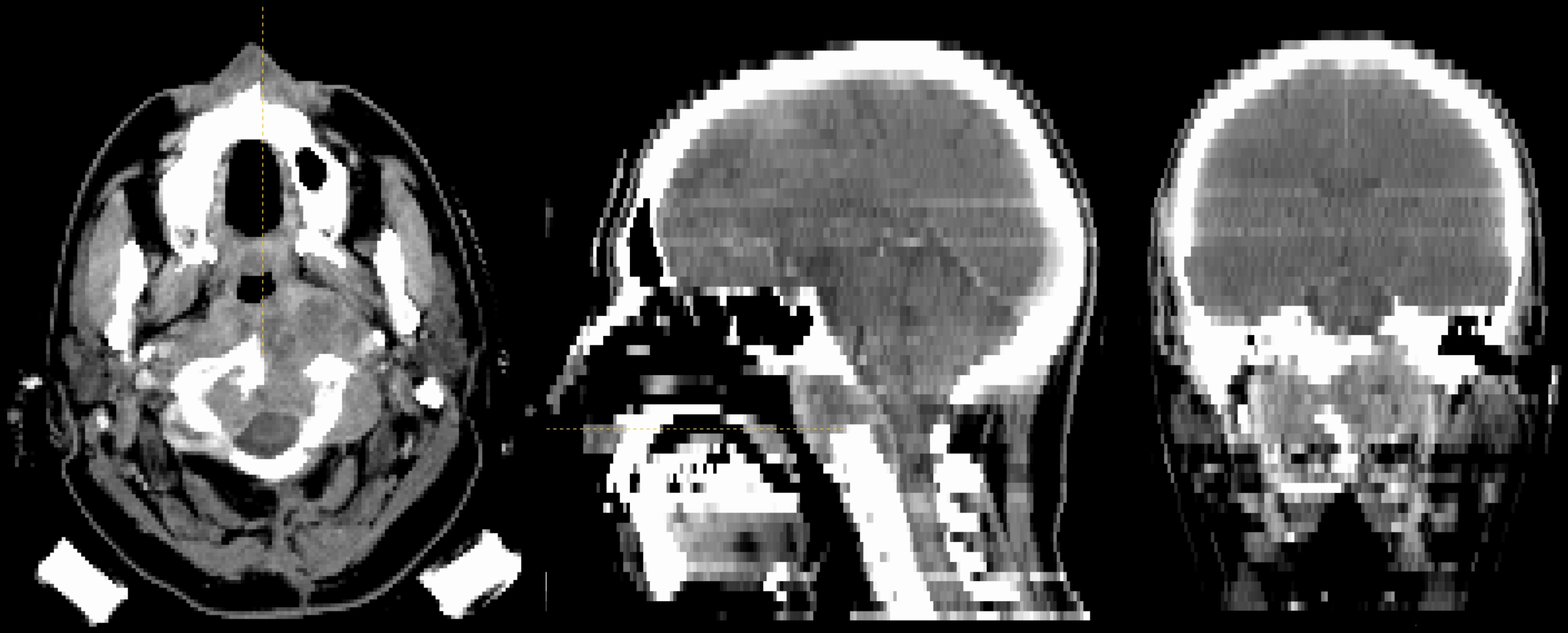
CT scans for treatment planning



transversal slices

Slide by courtesy of Dr. Simeon Nill

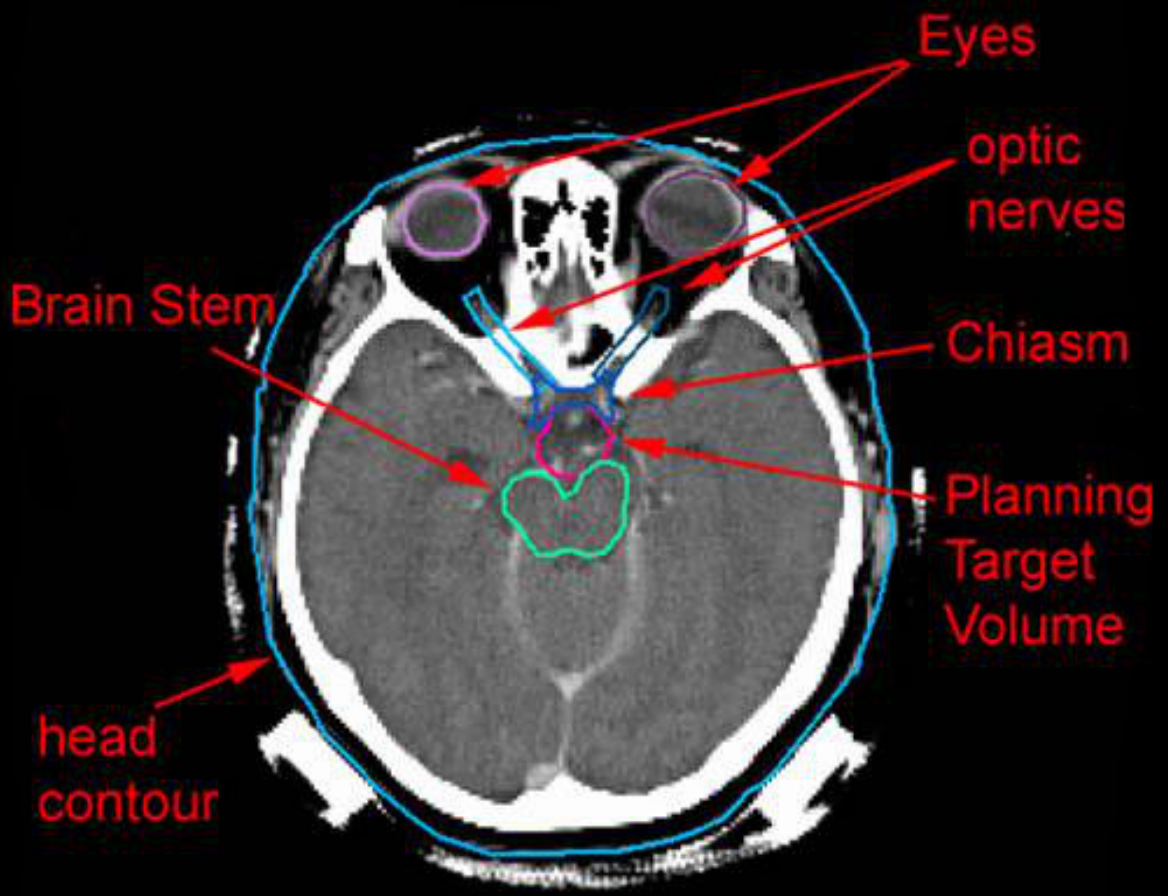
CT scans for treatment planning



transversal sagittal frontal

Slide by courtesy of Dr. Simeon Nill

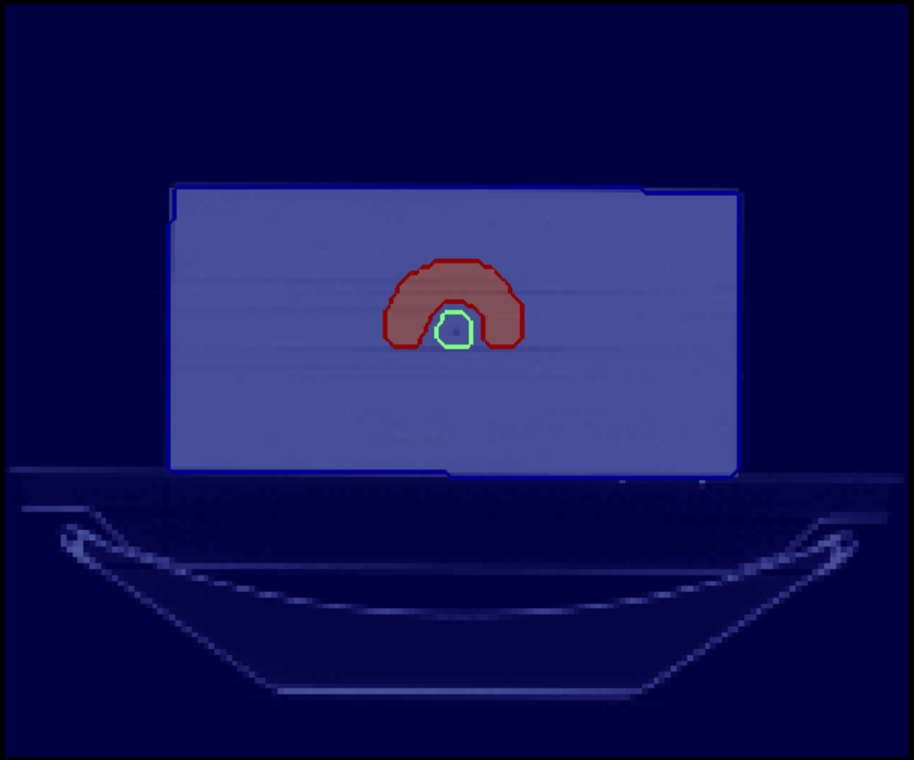
Delineating volumes of interest



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

Slide by courtesy of Dr. Simeon Nill

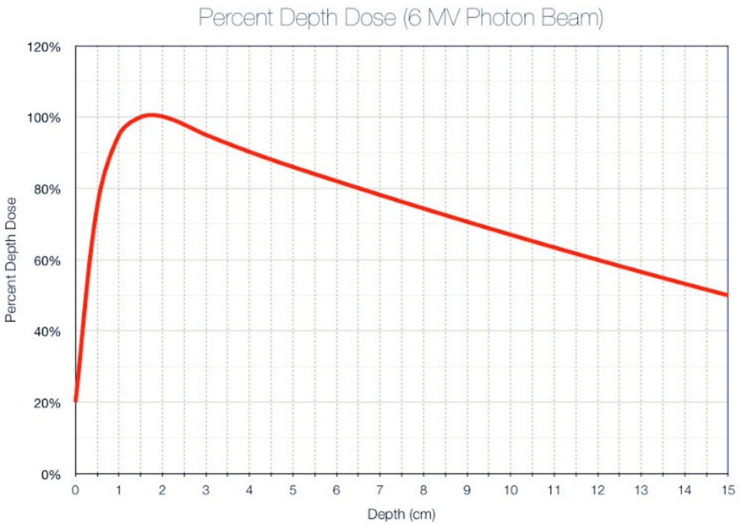
The ideal dose distribution



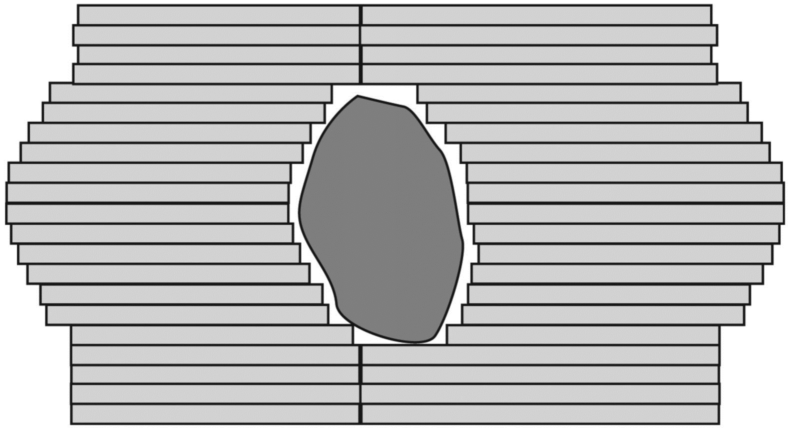
- High / prescribed dose in the tumor
- No dose in normal tissue

Modern 3D-planning with photons

Photon beam

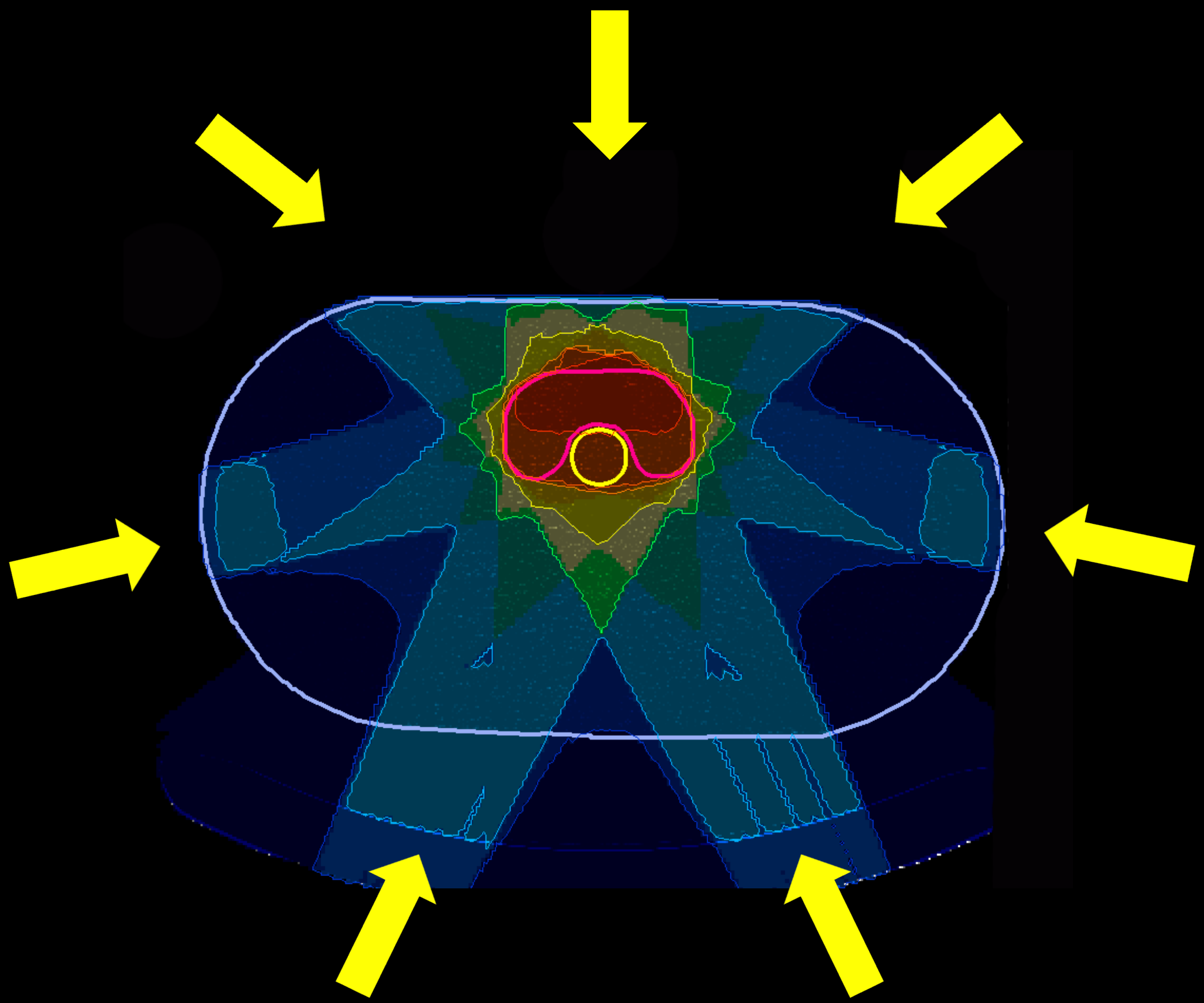


Collimator



→ Adaptation of the photon beam to the tumor shape

A realistic dose distribution



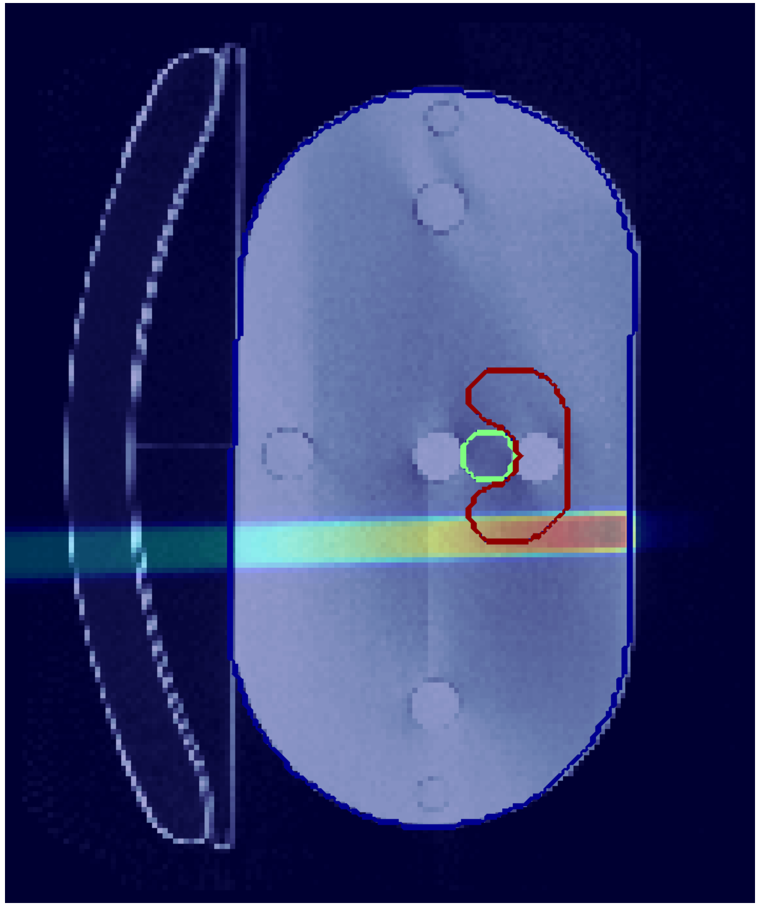
Slide by courtesy of Mark Bangert

Can we do better?

The concept of the „beamlet“

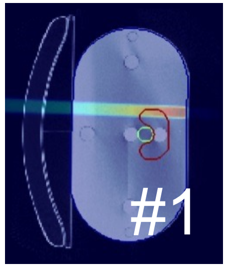
- „Multi-leaf“ collimator are able to generate fine beams (let’s call them beamlets)

- 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



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

Intensity-modulation with pencil-beams



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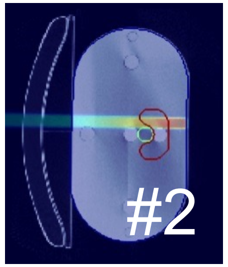

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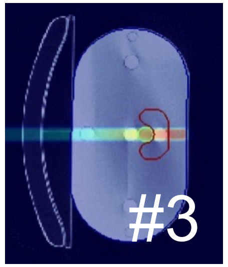

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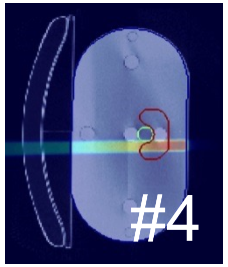

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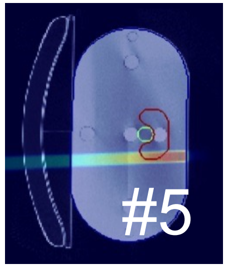

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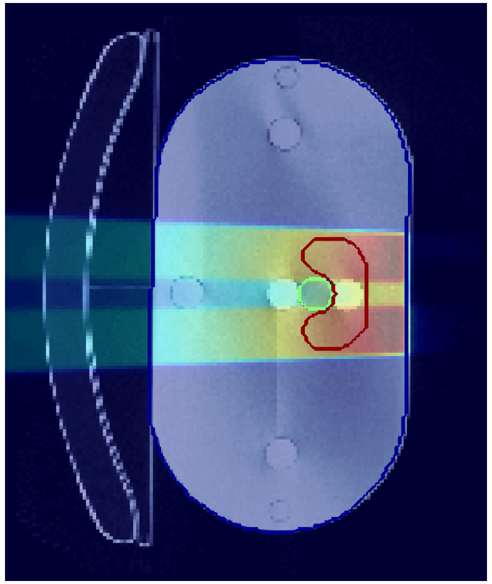
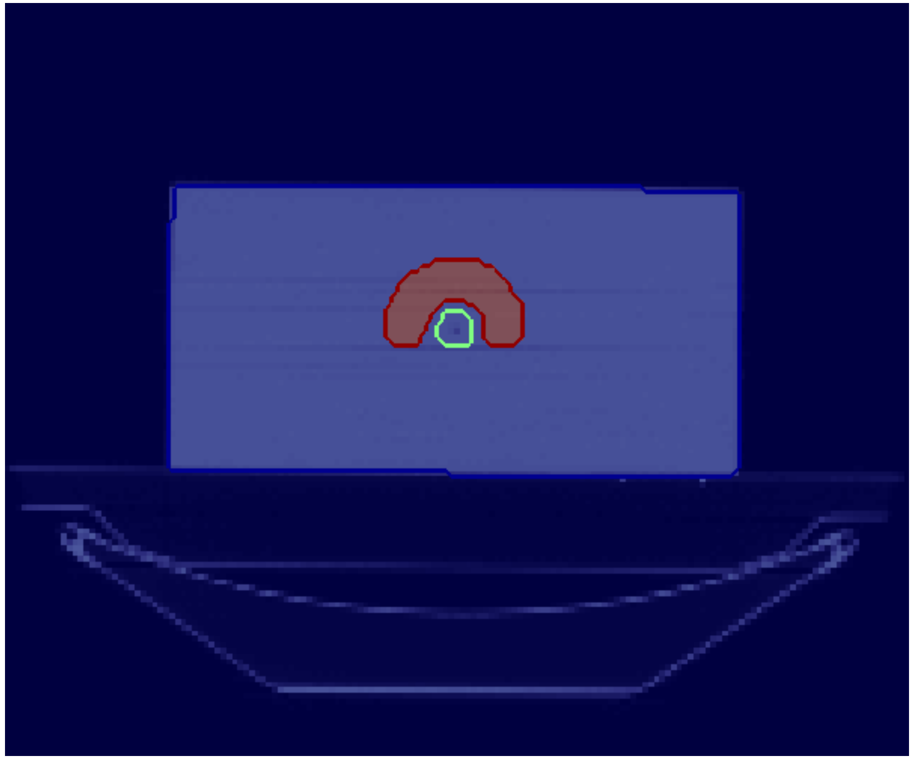


Different beamlet weights w
= Intensity-modulated field

- 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

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

$$\mathrm{s.t.} \;\; w \geq 0$$

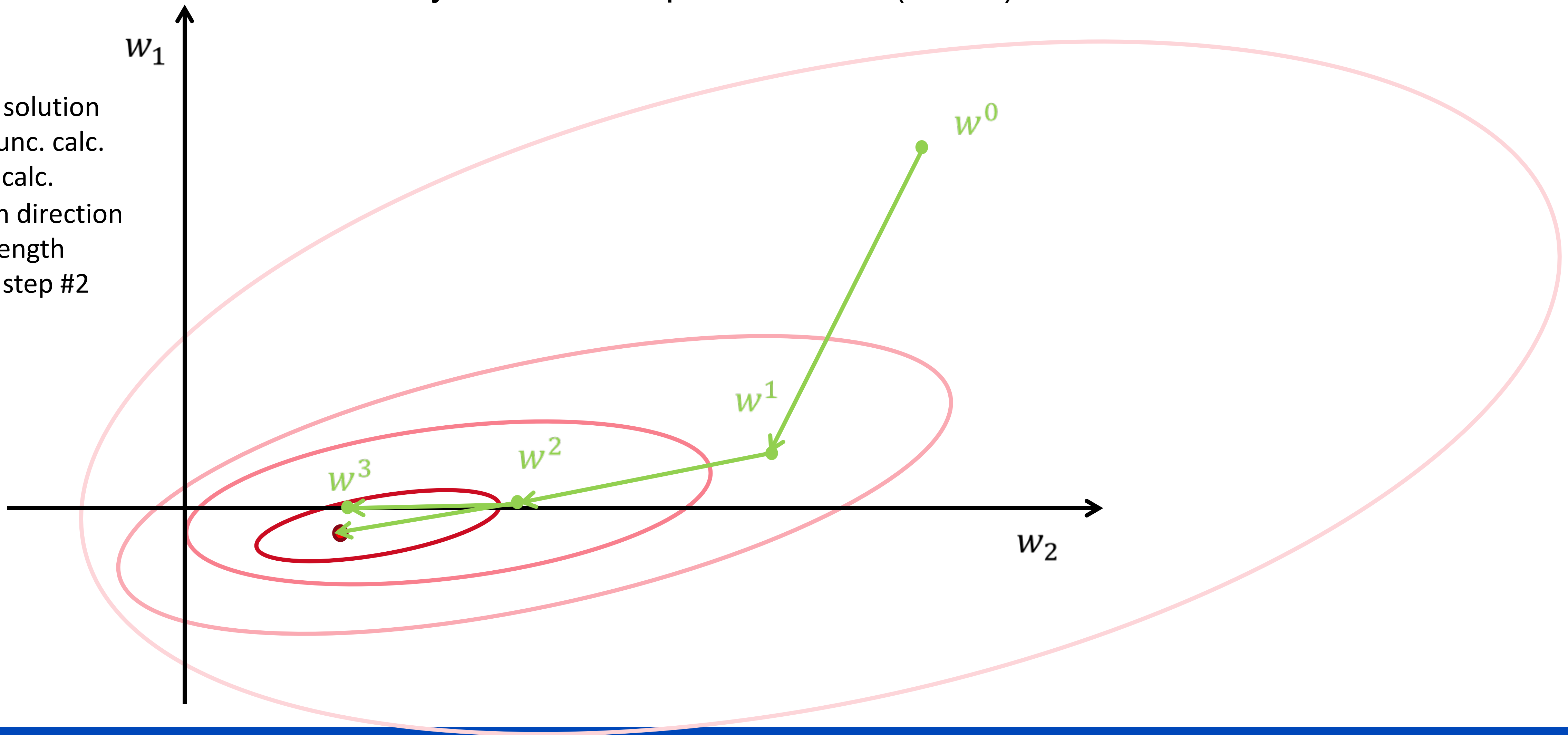
$$P = \mathrm{diag}(p_1, p_2, \dots, p_I)$$

dkfz.

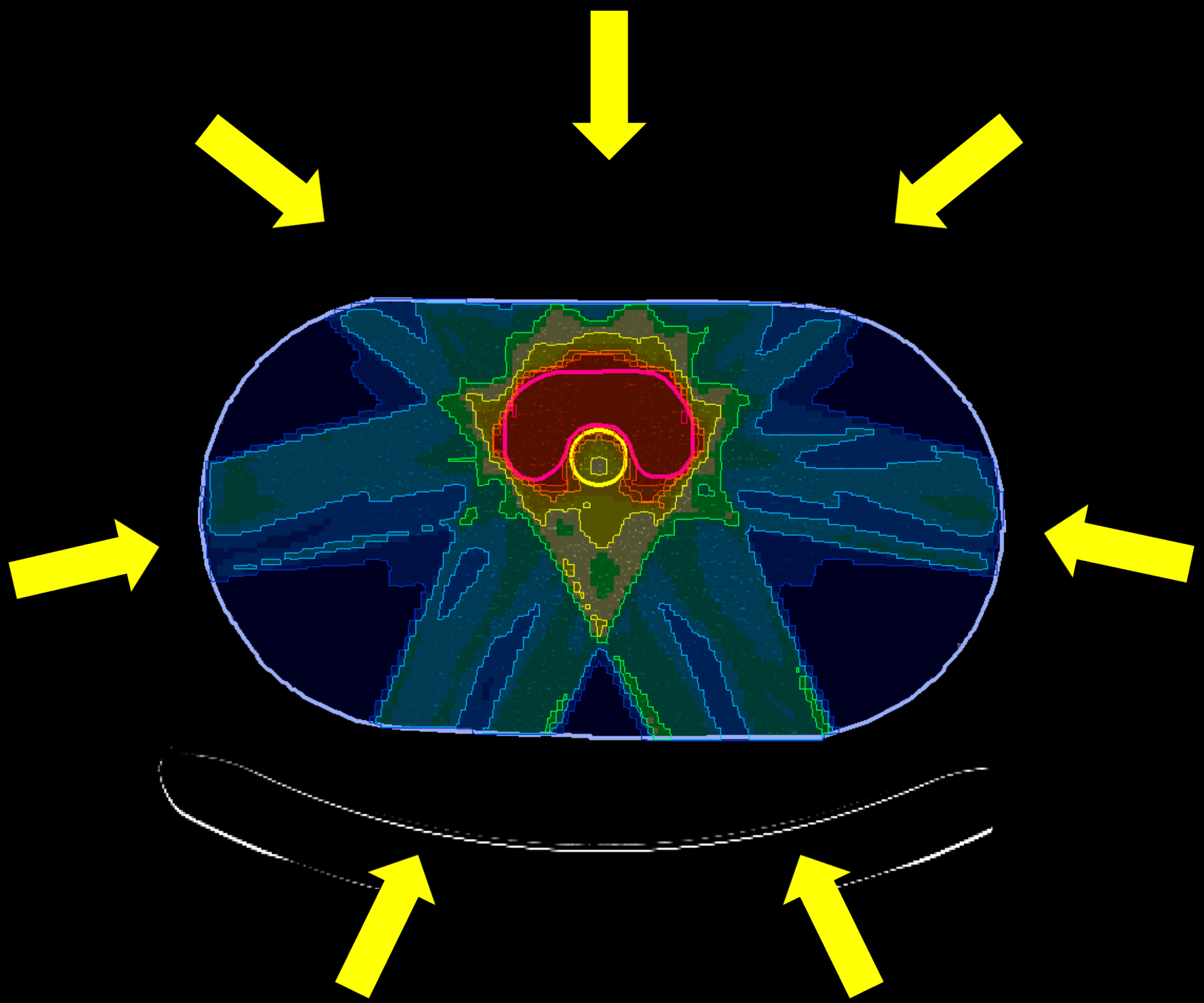
Optimize for w^*

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

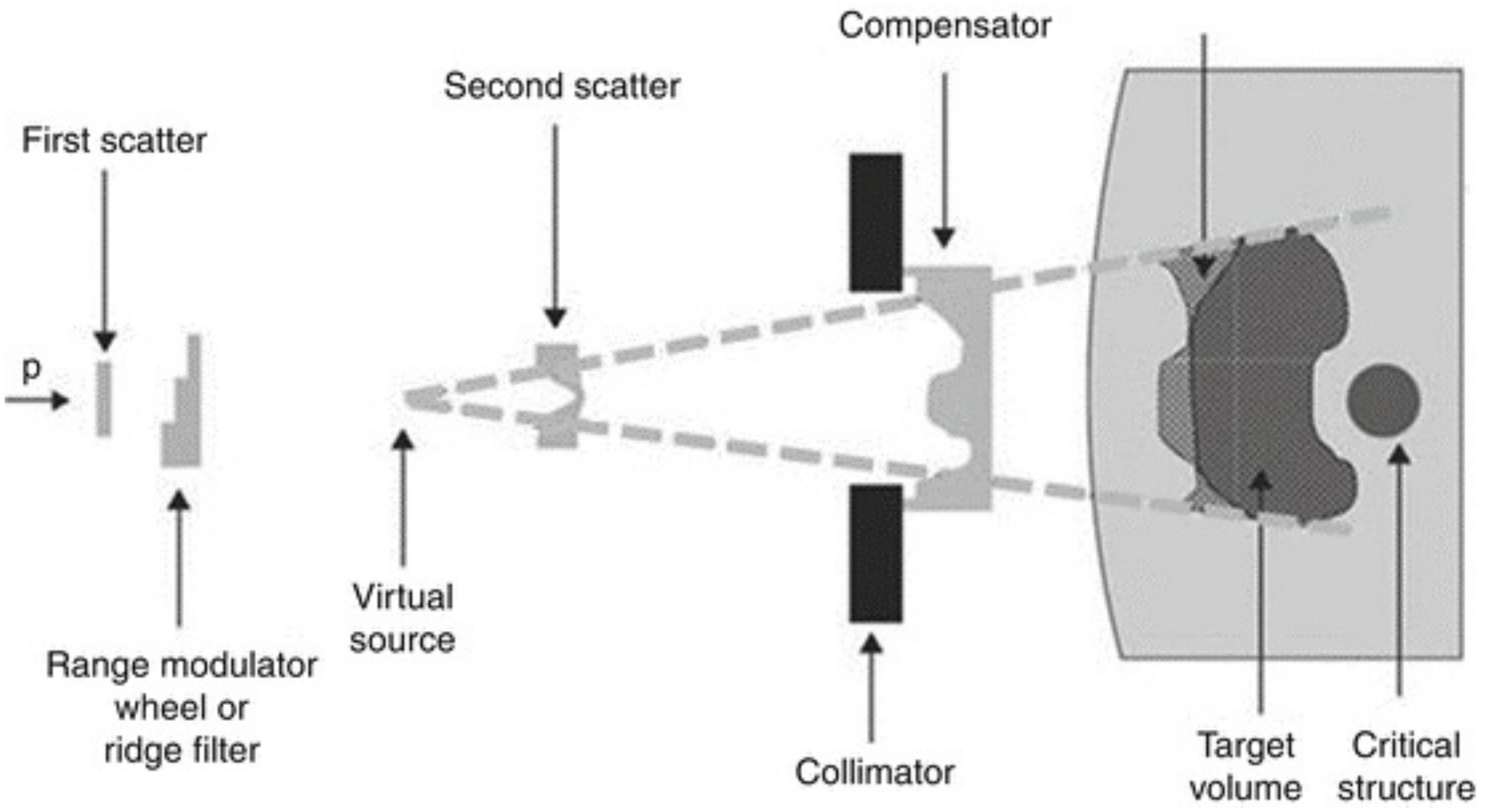


Intensity modulated treatment plan – dose distribution



Let‘s move to hadrons & ions…

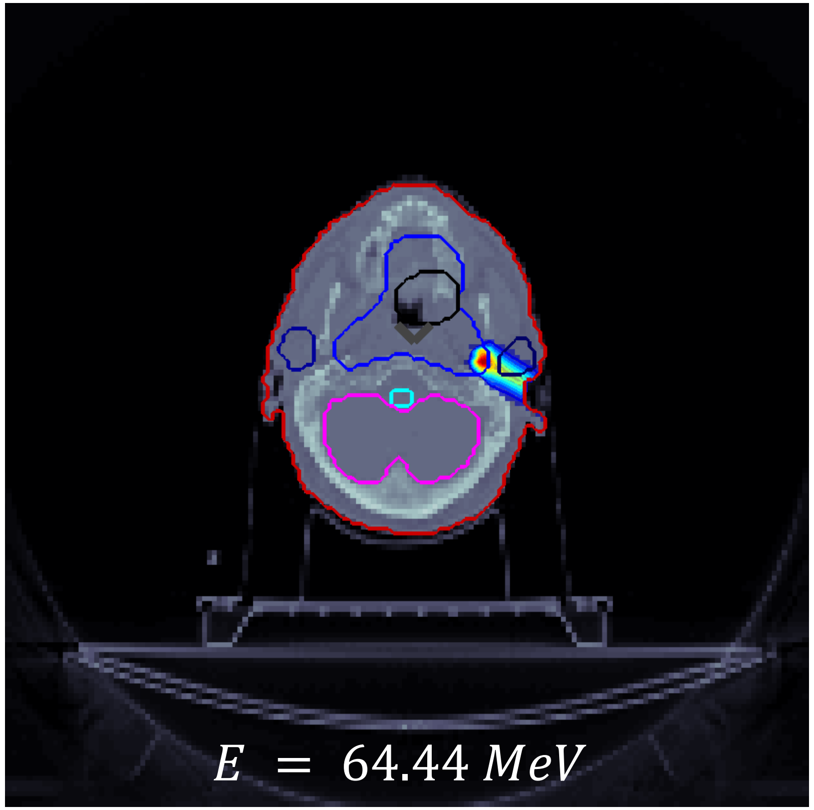
The “old” way: Passive Scattering



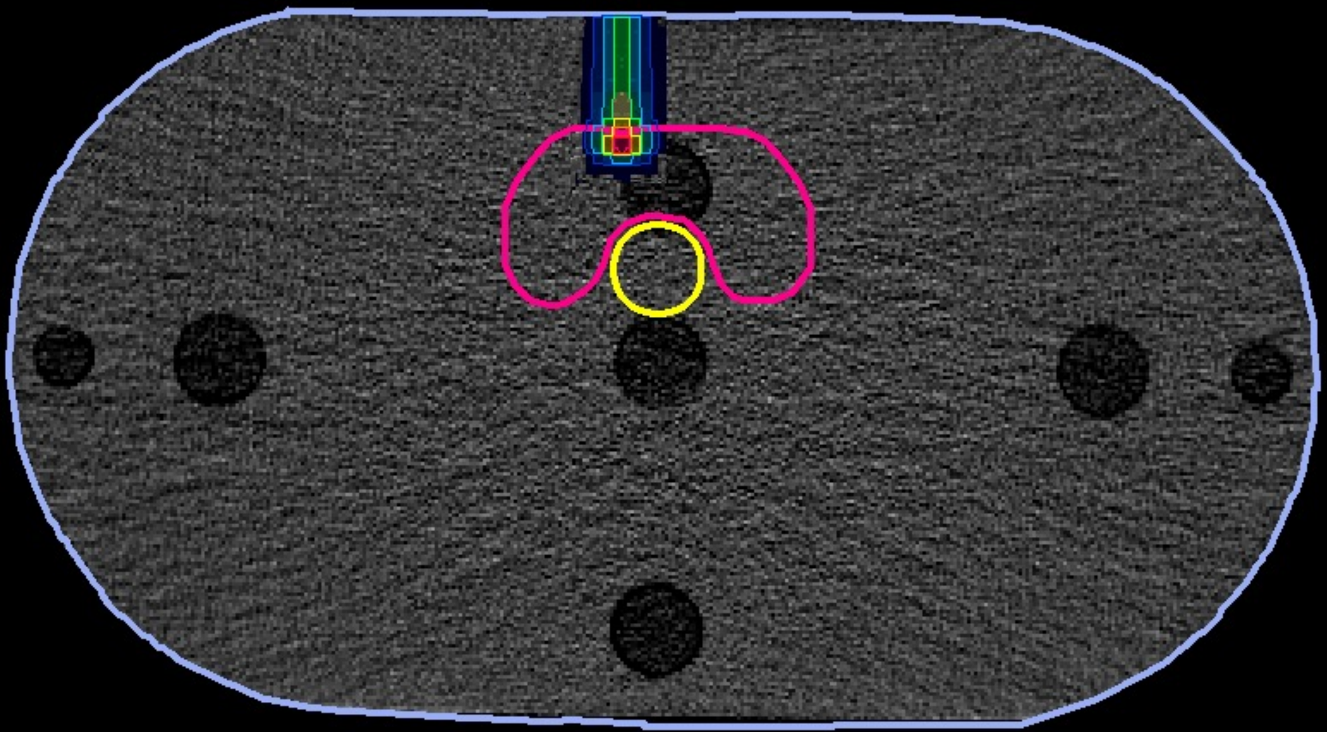
RL Maughan, MJ Hardy, MJ Taylor, J Reay, R Amos: Radiation Shielding and safety for particle therapy facilities, IPEM Report 75 Ed. 2

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_B, y_B)

Weighted sum of pencil beams with different energies and lateral position

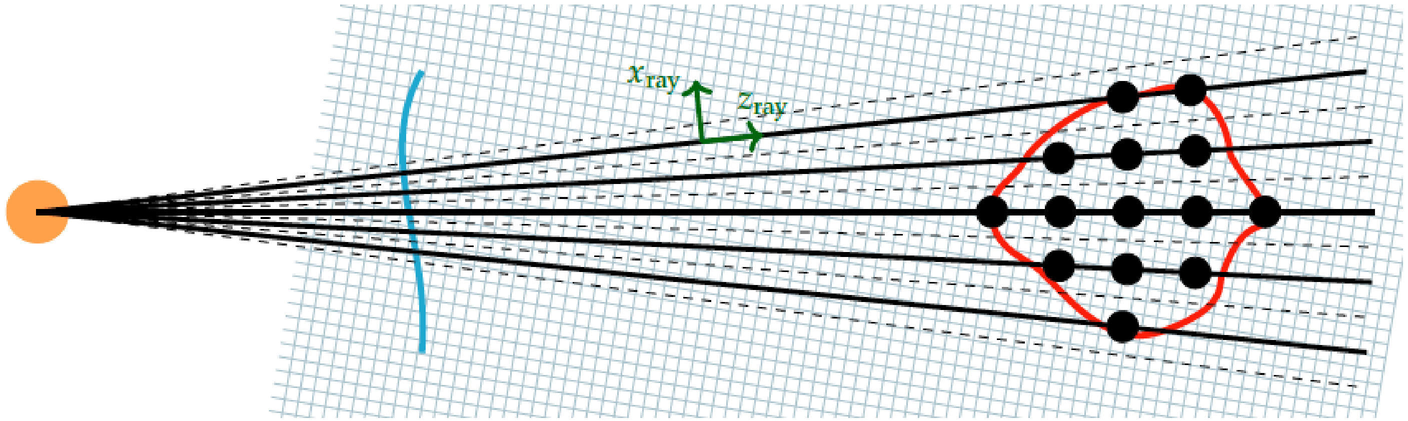
→ Dose optimization = finding the weights of pencil beams

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

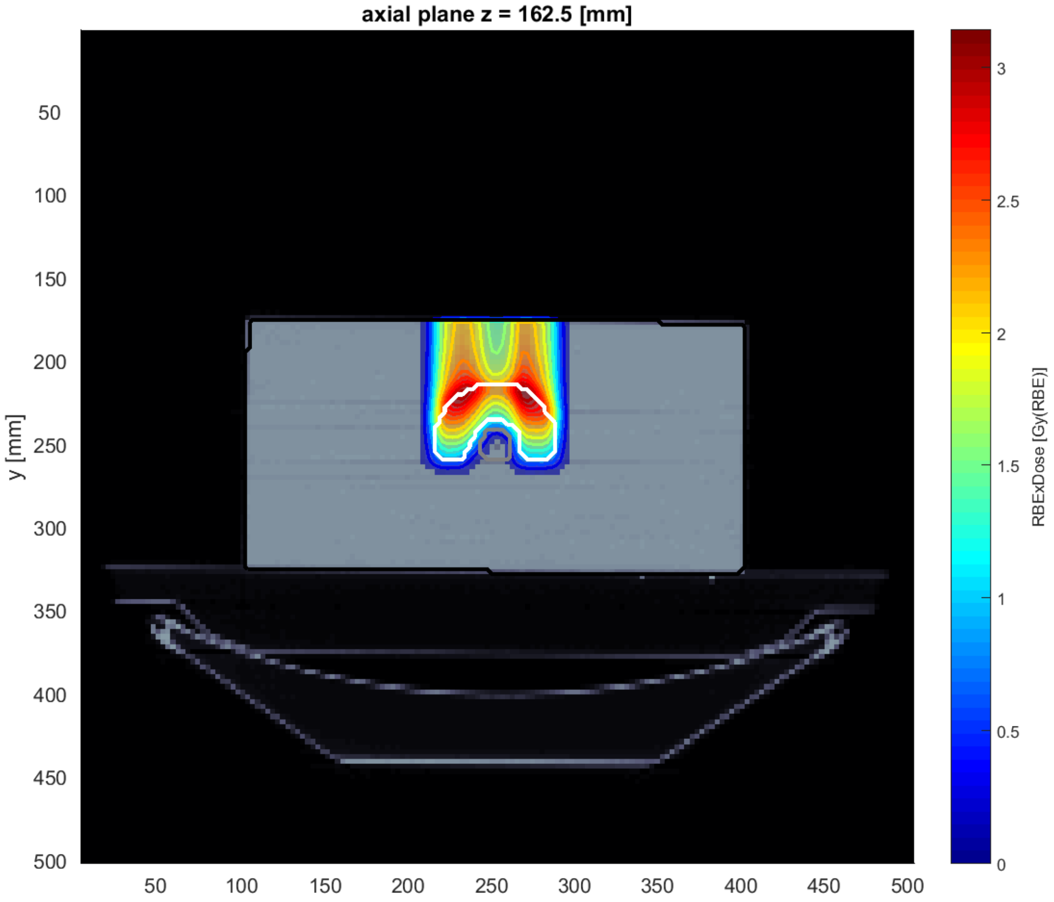
$$d_i = \sum_{j=1}^{B} w_j D_{ij} = \sum_{j=1}^{B} w_j \, L_{ij}^{x} L_{ij}^{y} Z_{ij}^{z}$$

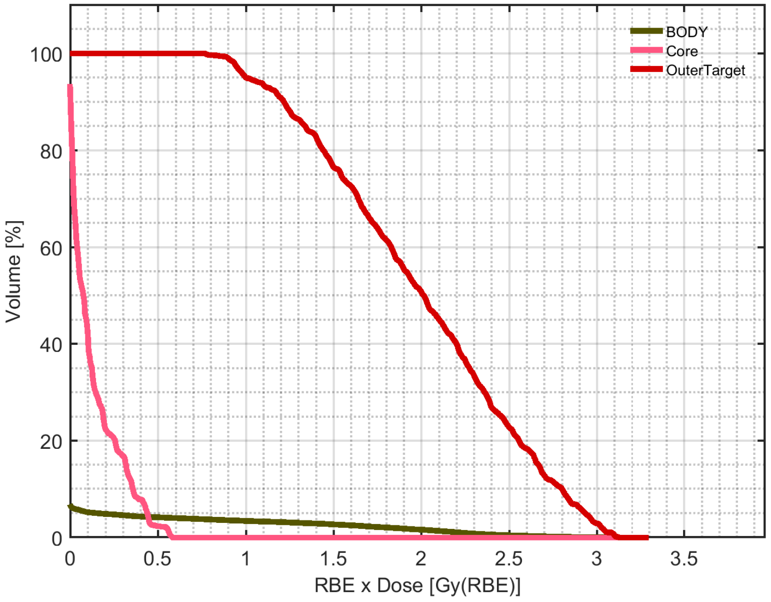


geometry and ray-casting for “radiological depth” / Water-equivalent path length (WEPL) computation

- particles: lateral Gaussian, depth tabulated

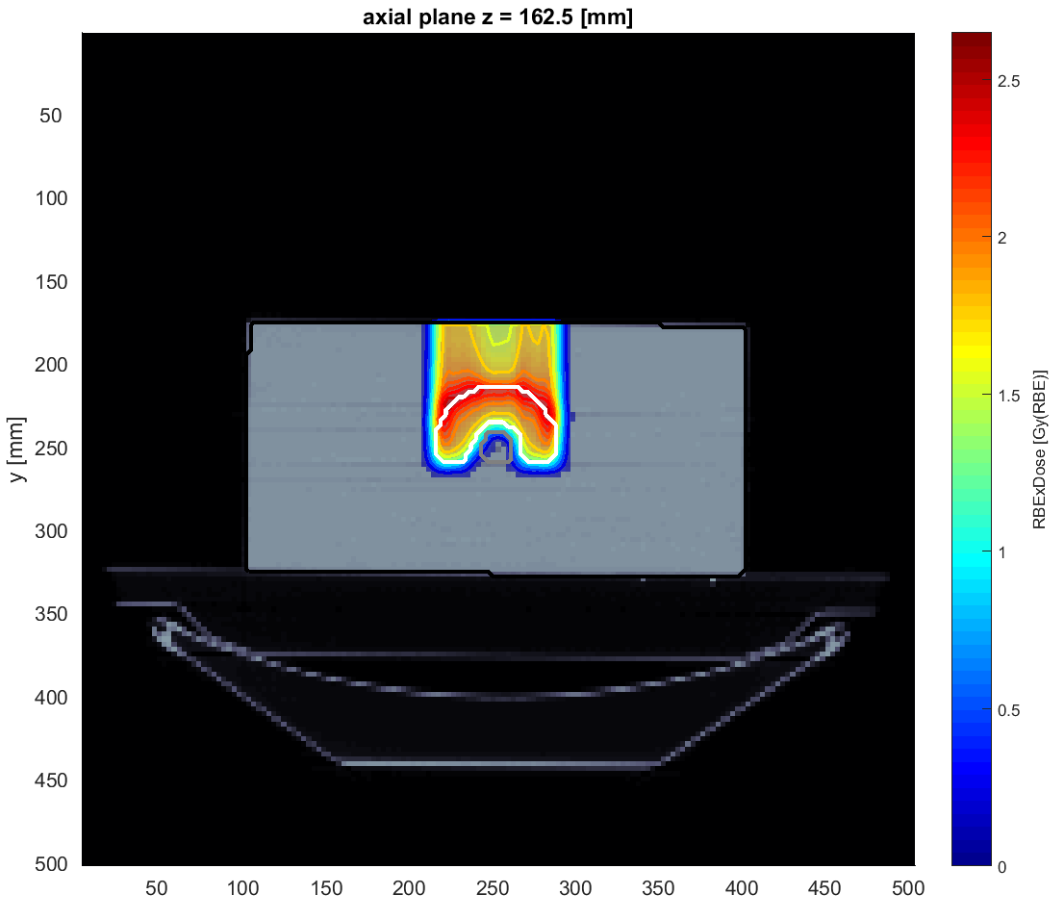
Example: TG119 phantom – iteration 1

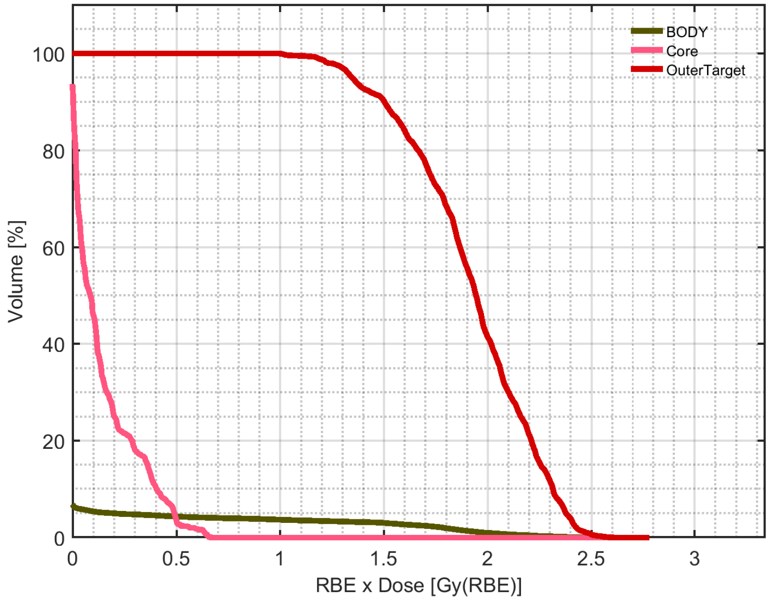




Slide courtesy of Mark Bangert (adapted)

Example: TG119 phantom – iteration 5





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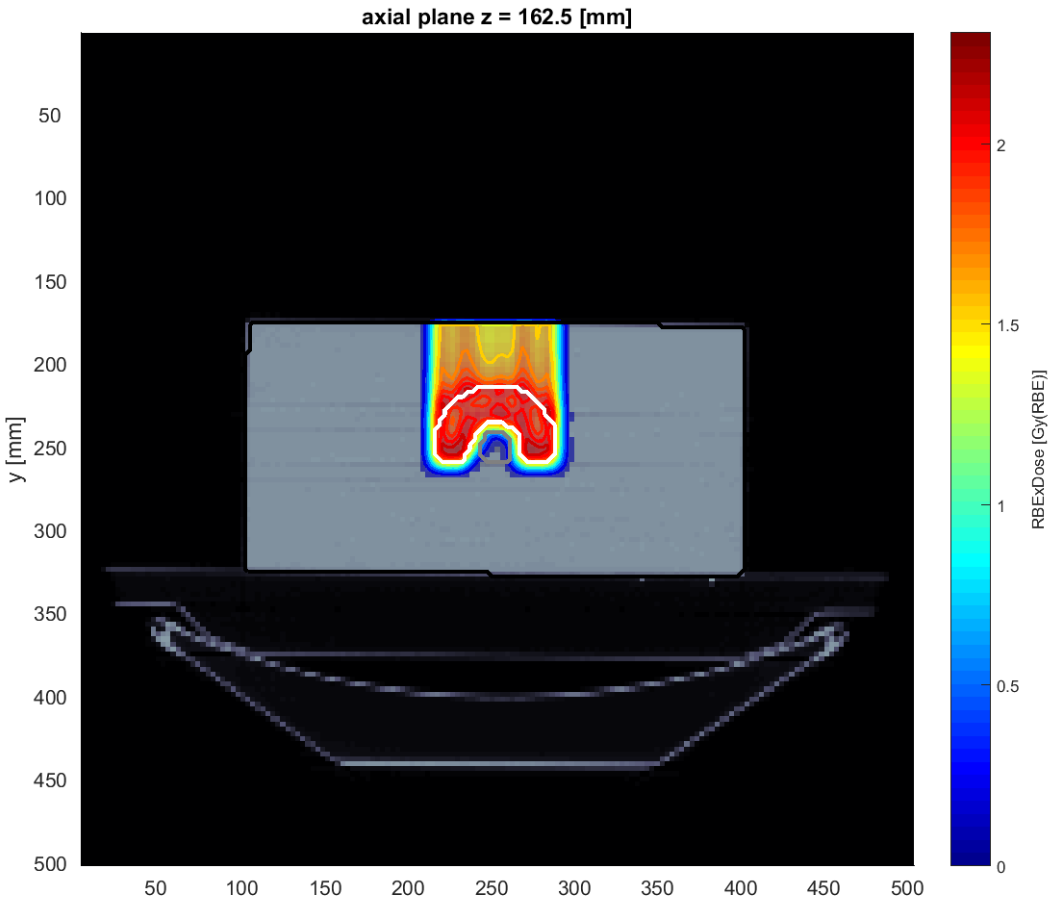
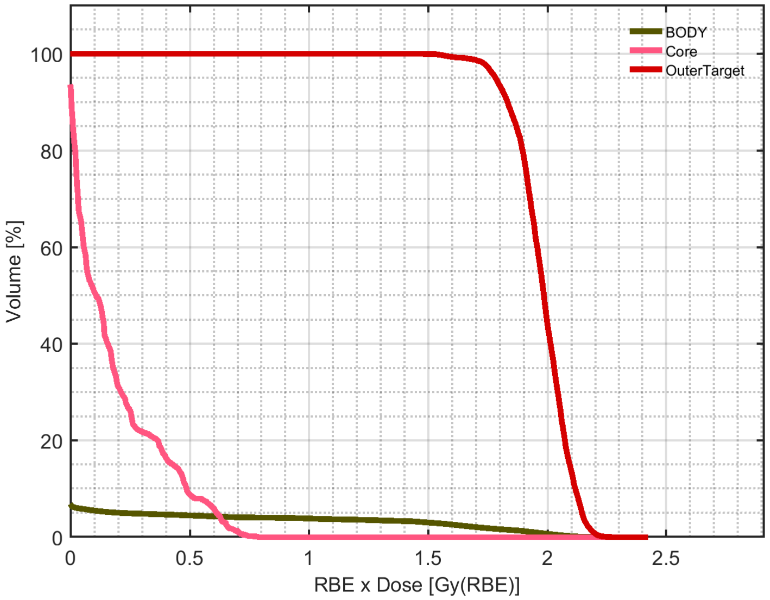
Example: TG119 phantom – iteration 10





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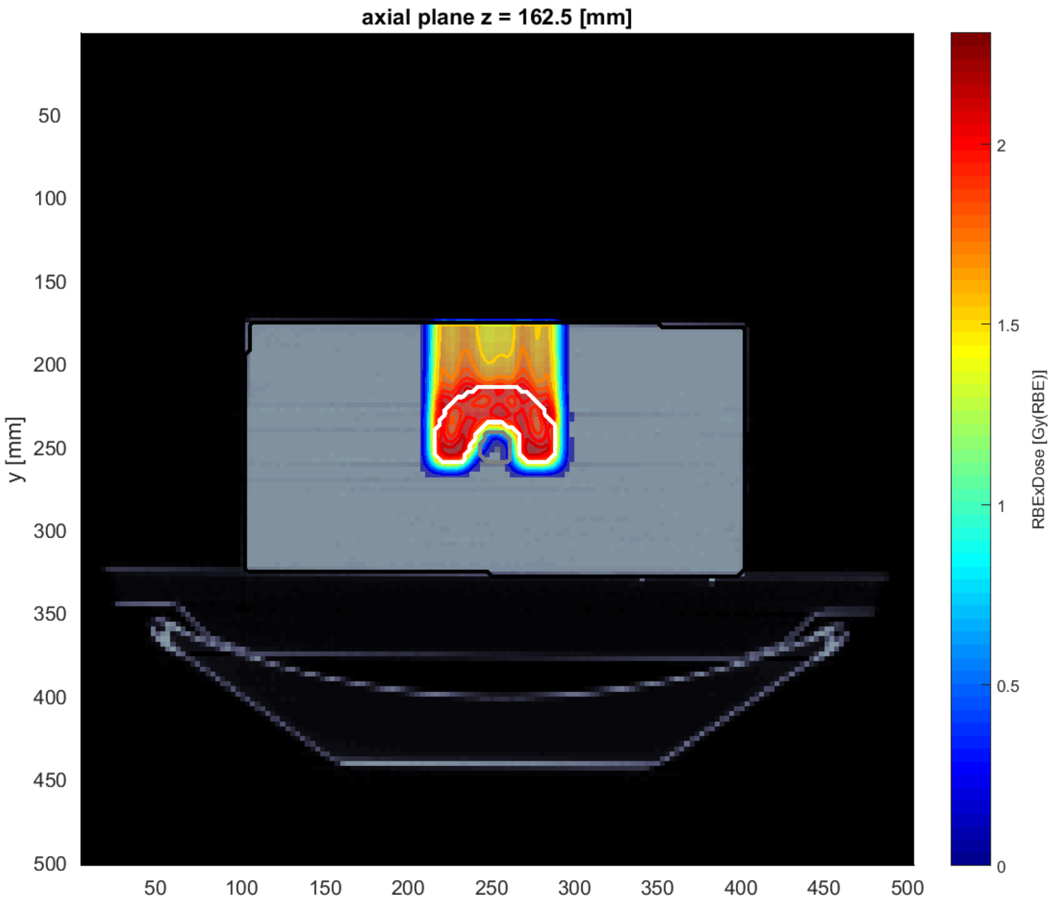
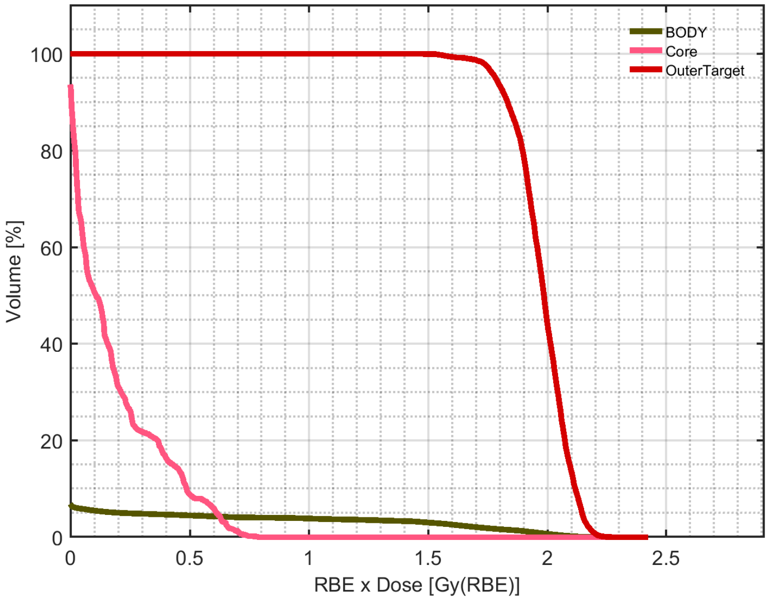
Example: TG119 phantom – iteration 10





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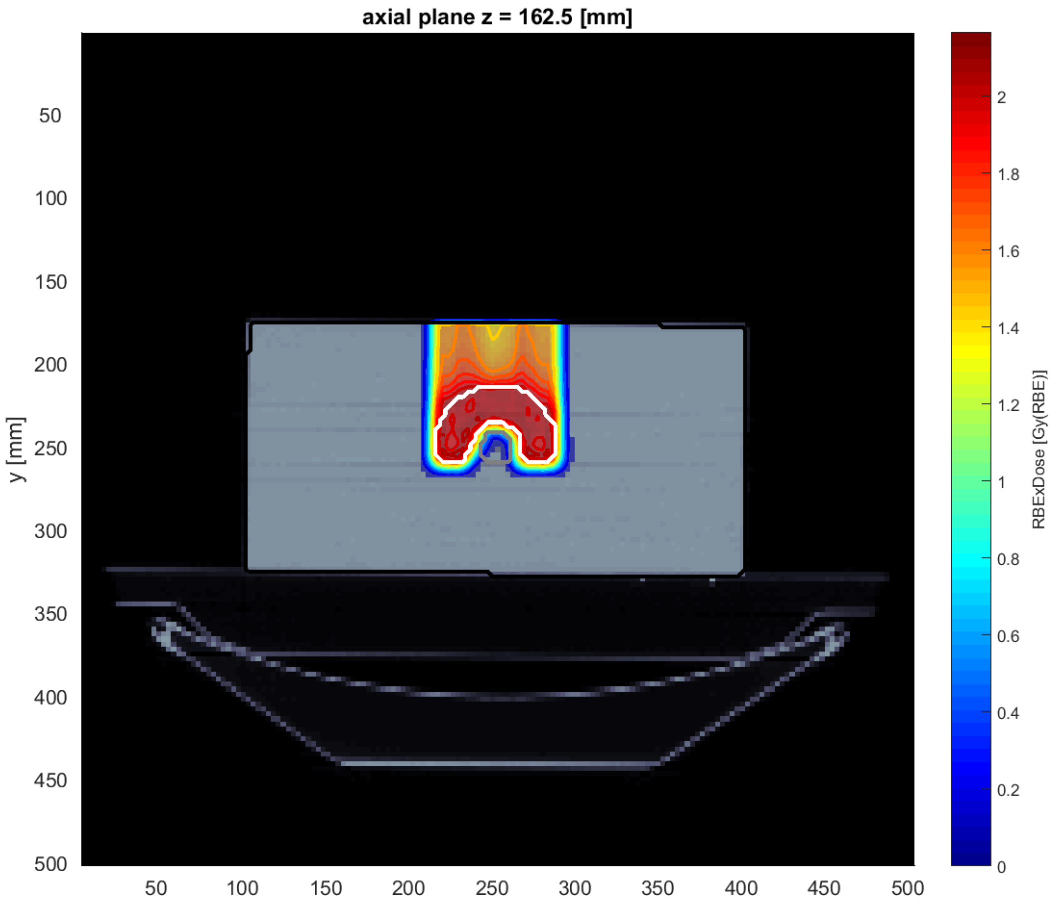
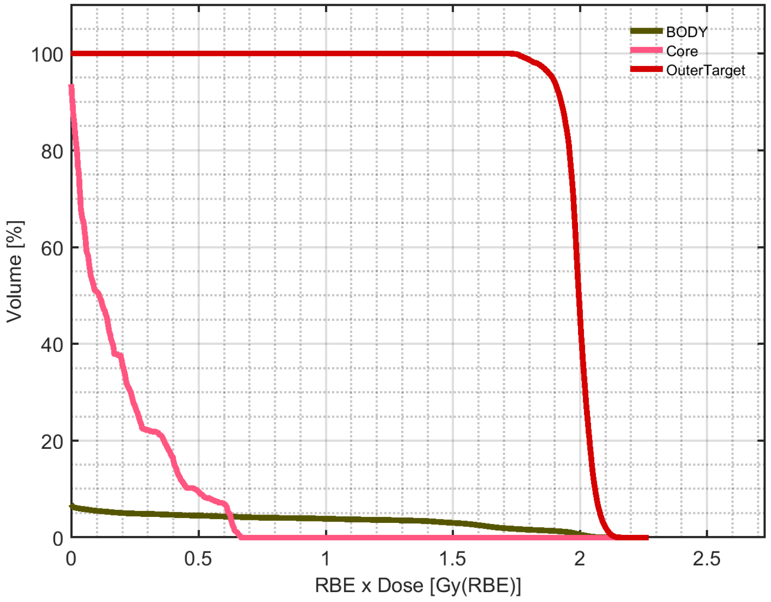
Example: TG119 phantom – iteration 30





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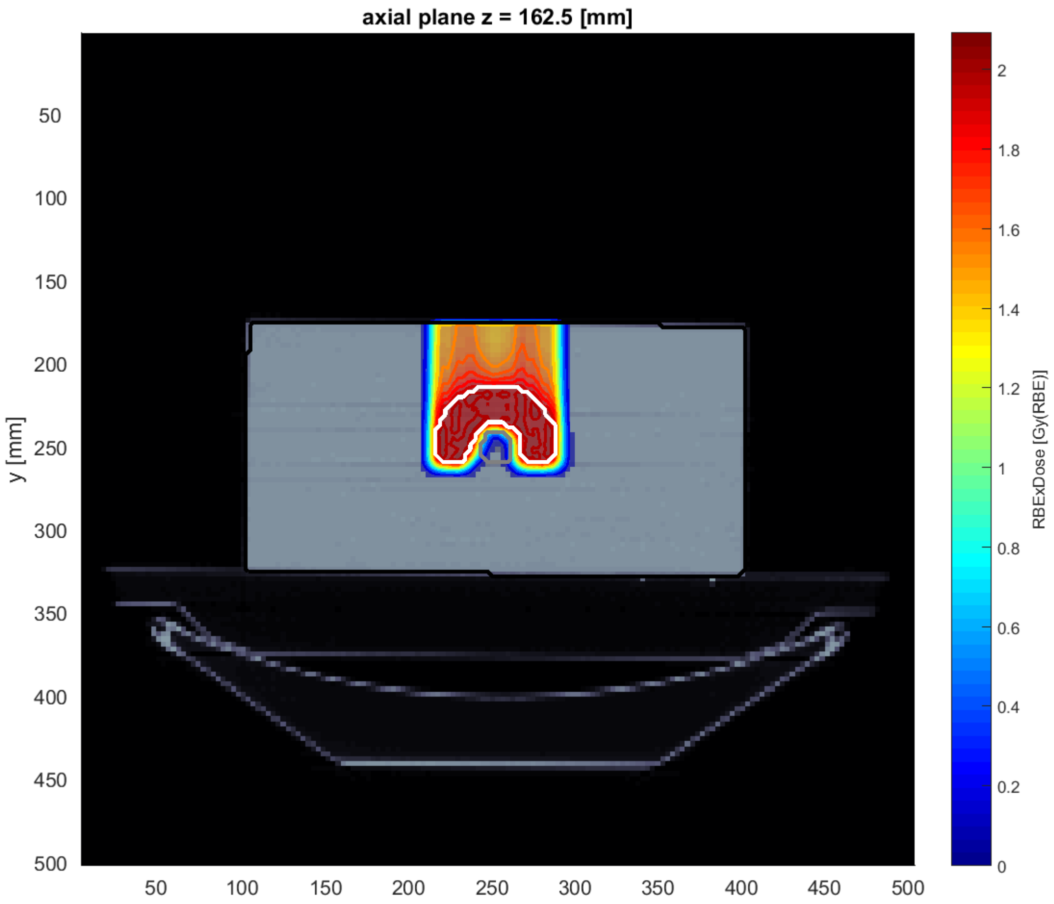
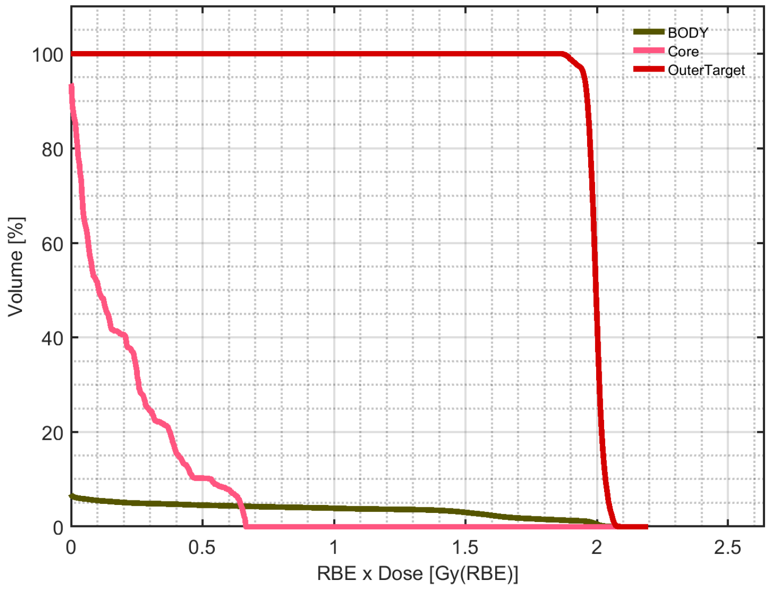
Example: TG119 phantom – iteration 97





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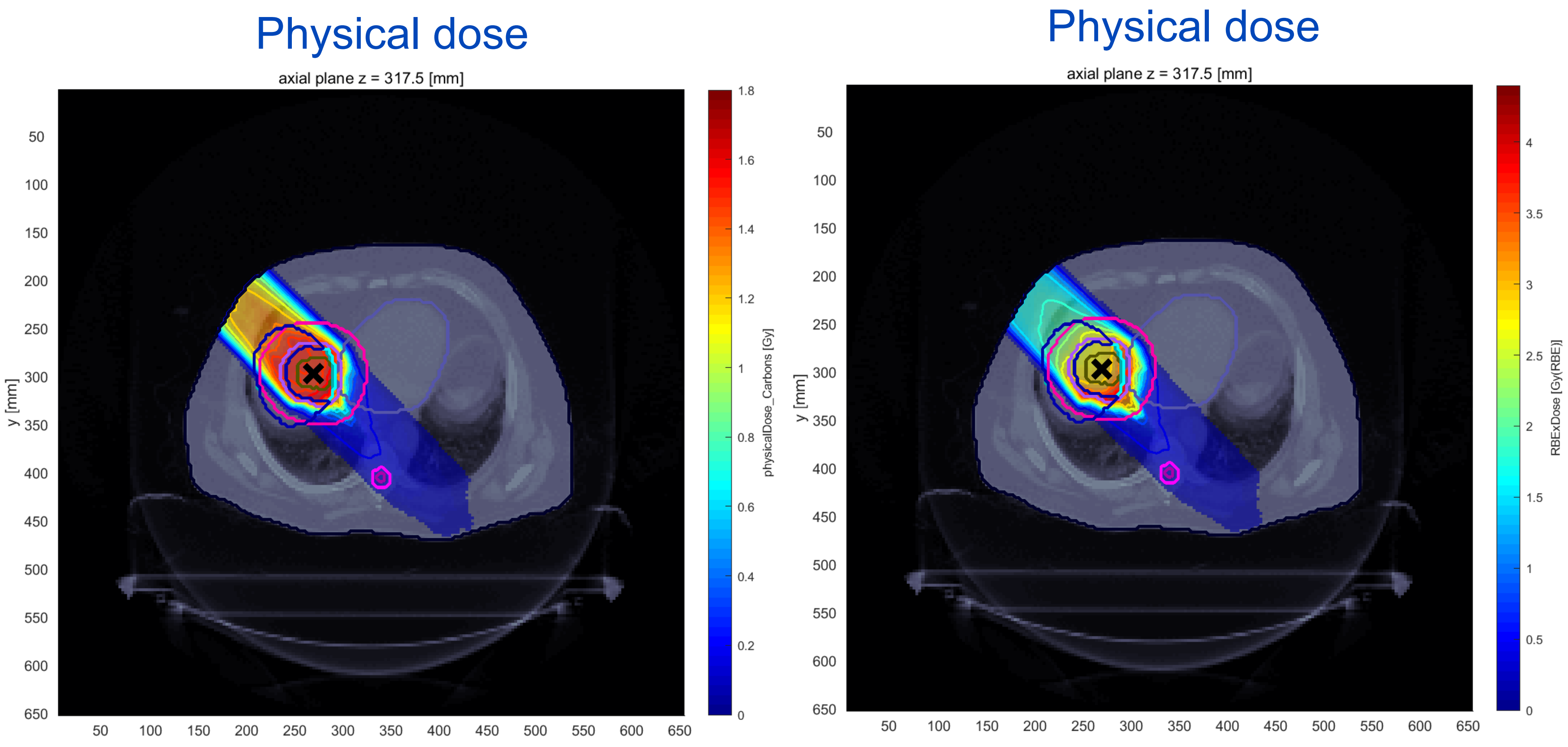
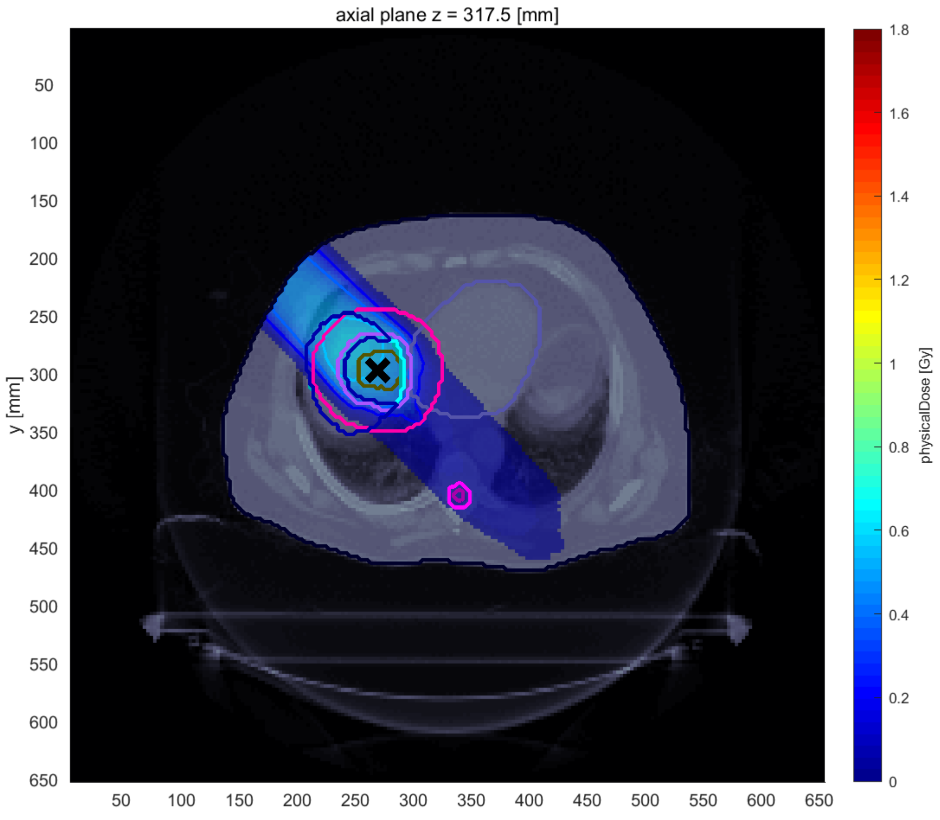
Example Liver Case – Carbons



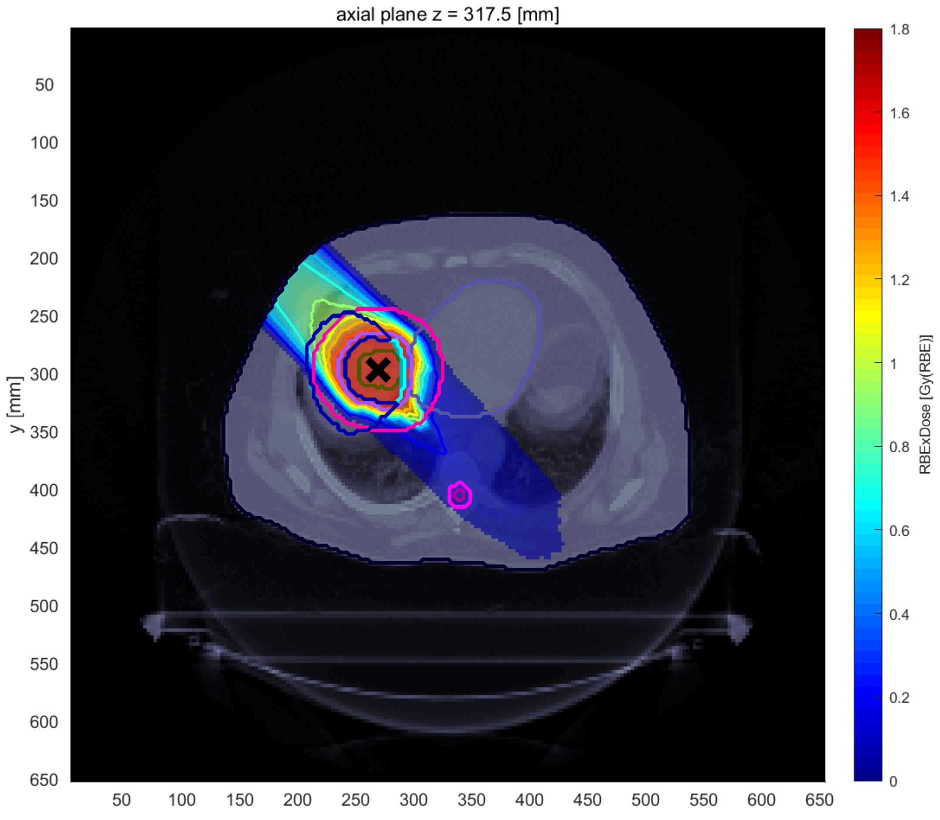
→ The same physical dose induces different biological effect!

Example Liver Case – Carbons

physical dose

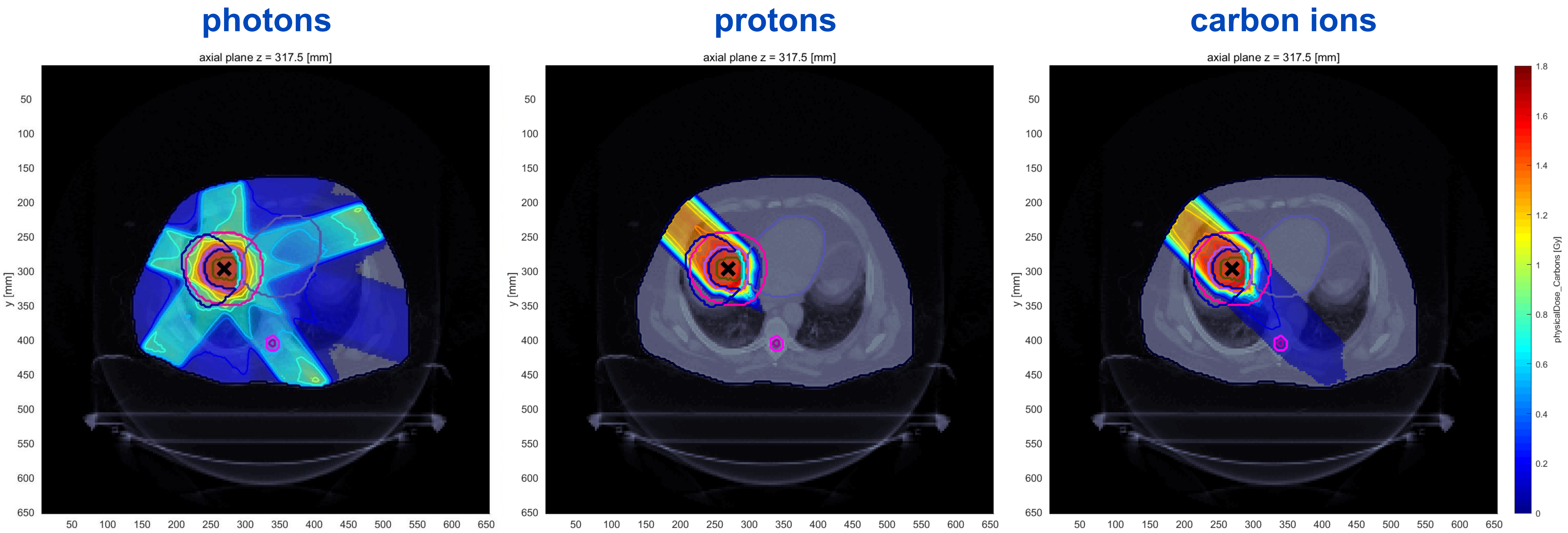


Biologically effective dose



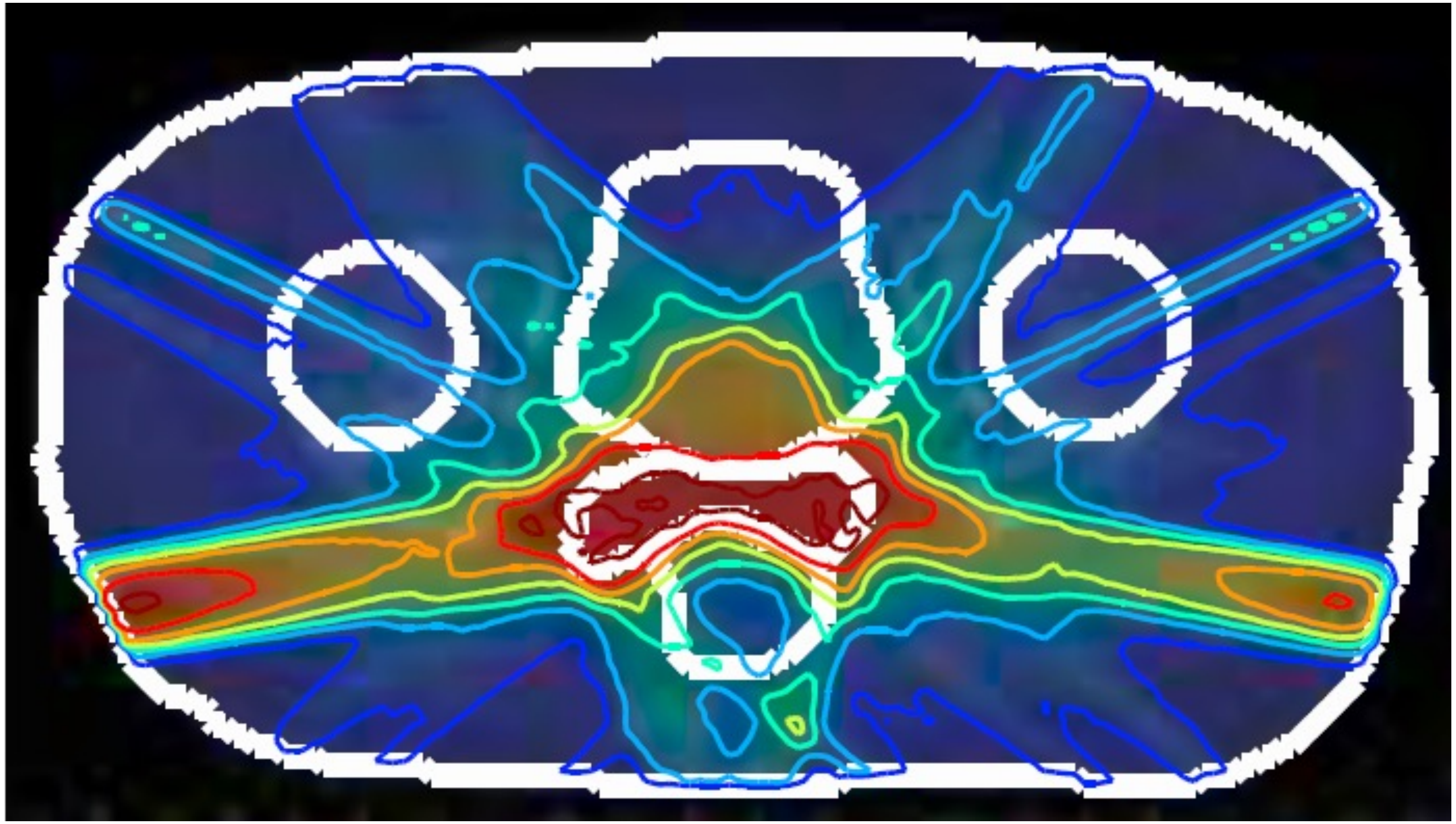
→ Optimize for biology (i.e. RBE) directly instead of dose

Examples: Liver patient



How do we analyze a dose / quantify a plan?

Evaluation of the
2D tomographic images



Dose statistics:

Mean, maximum, minimum dose

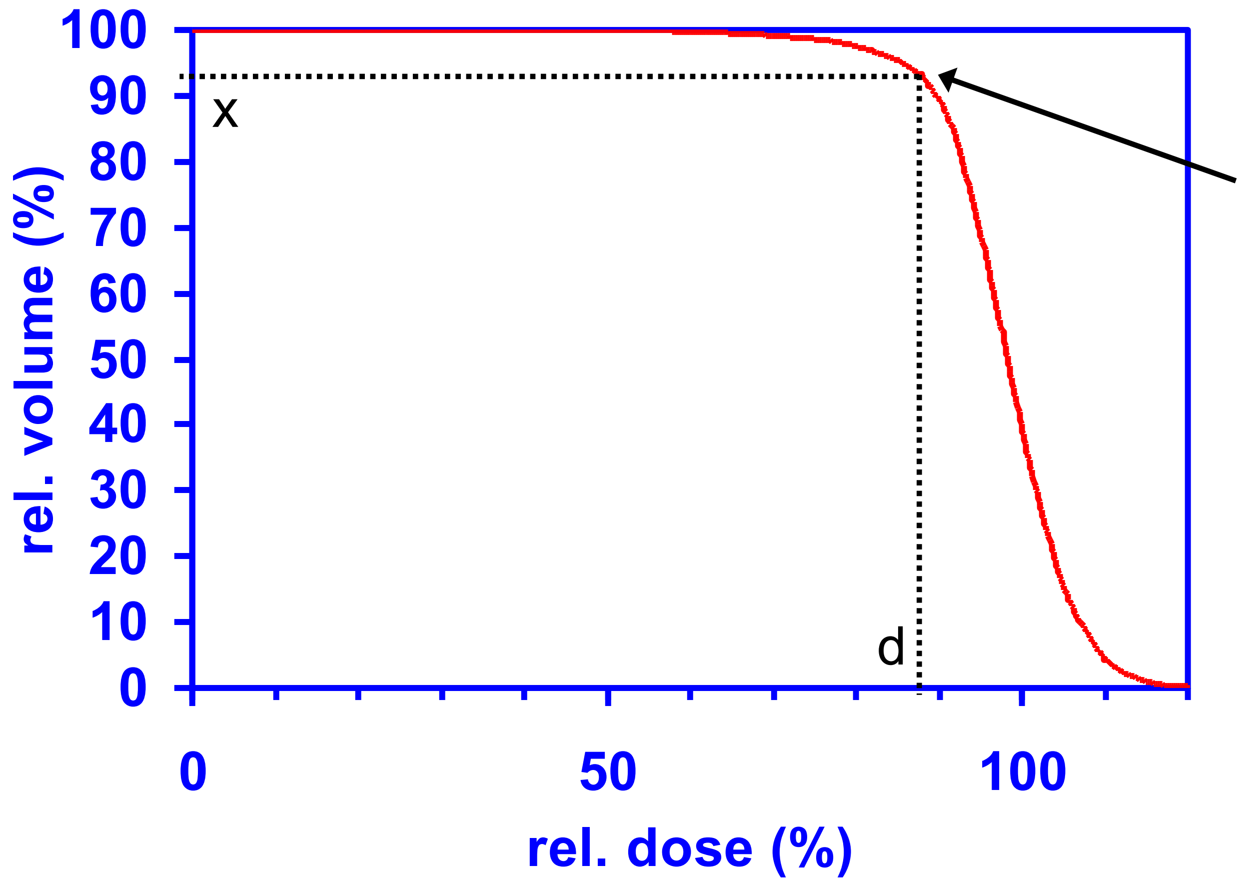
Dose-volume histograms

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

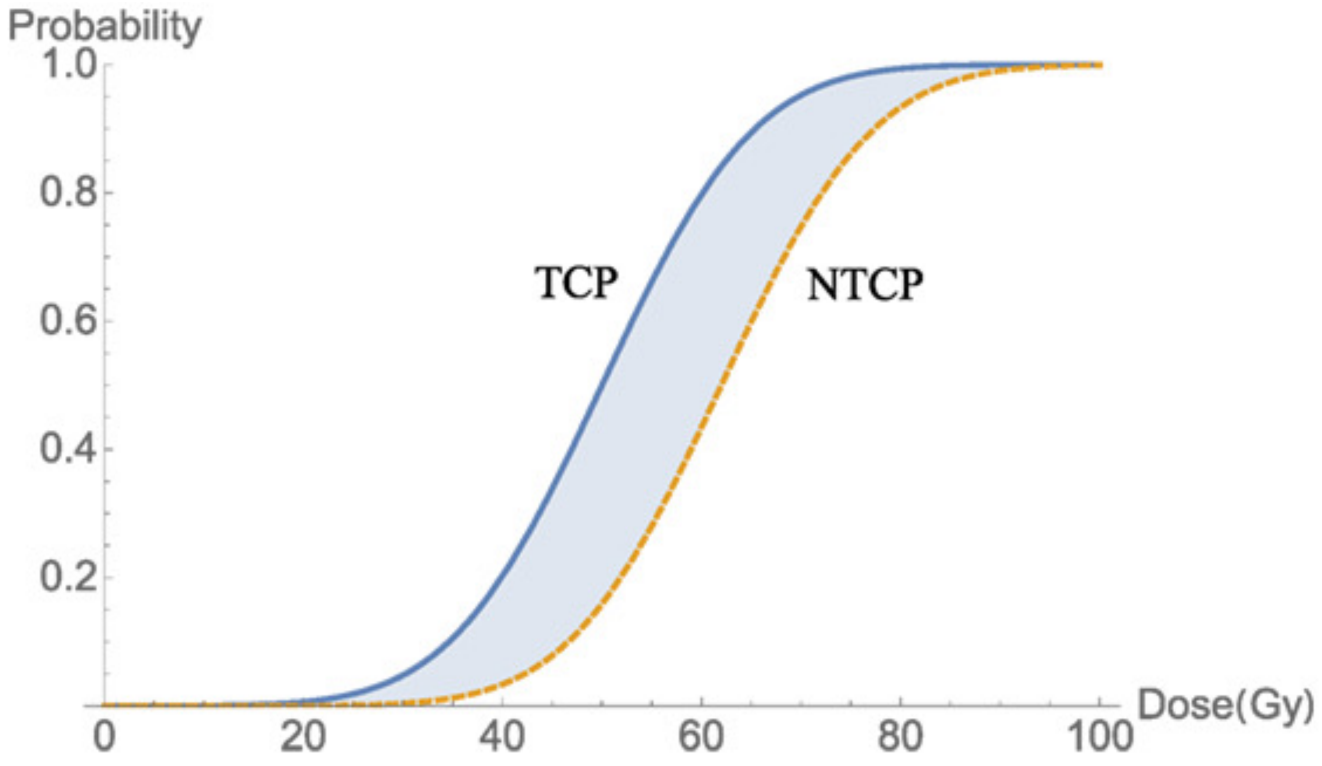


Image from Tseng H-H, Luo Y, Ten Haken RK and El Naqa I (2018) The Role of Machine Learning in Knowledge-Based Response-Adapted Radiotherapy. *Front. Oncol.* 8:266. doi: 10.3389/fonc.2018.00266

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)

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

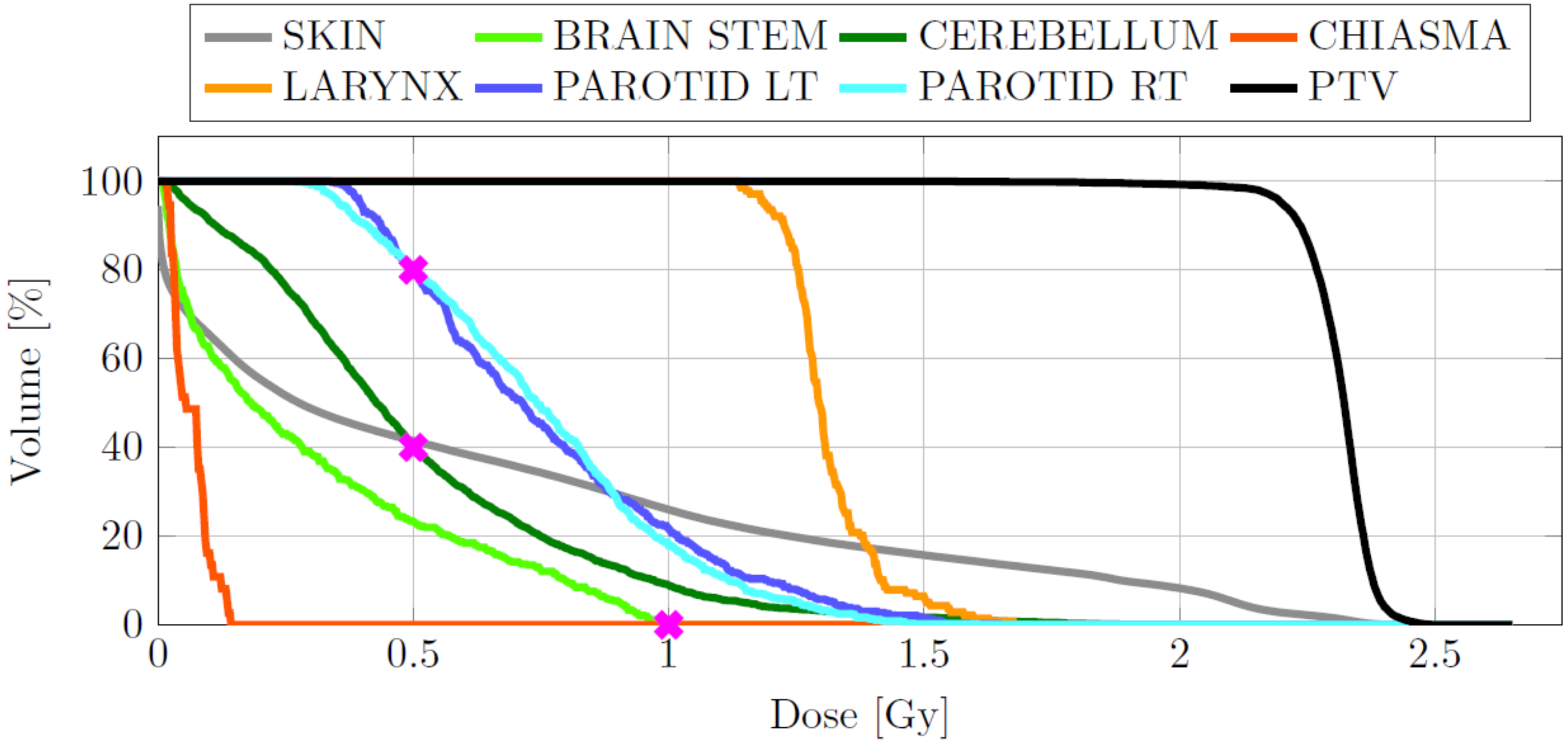
$$\text{s.t.} \quad c_k^l \leq c_k(w) \leq c_k^u$$

$$0 \leq w$$

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

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

- Example from matRad paper:

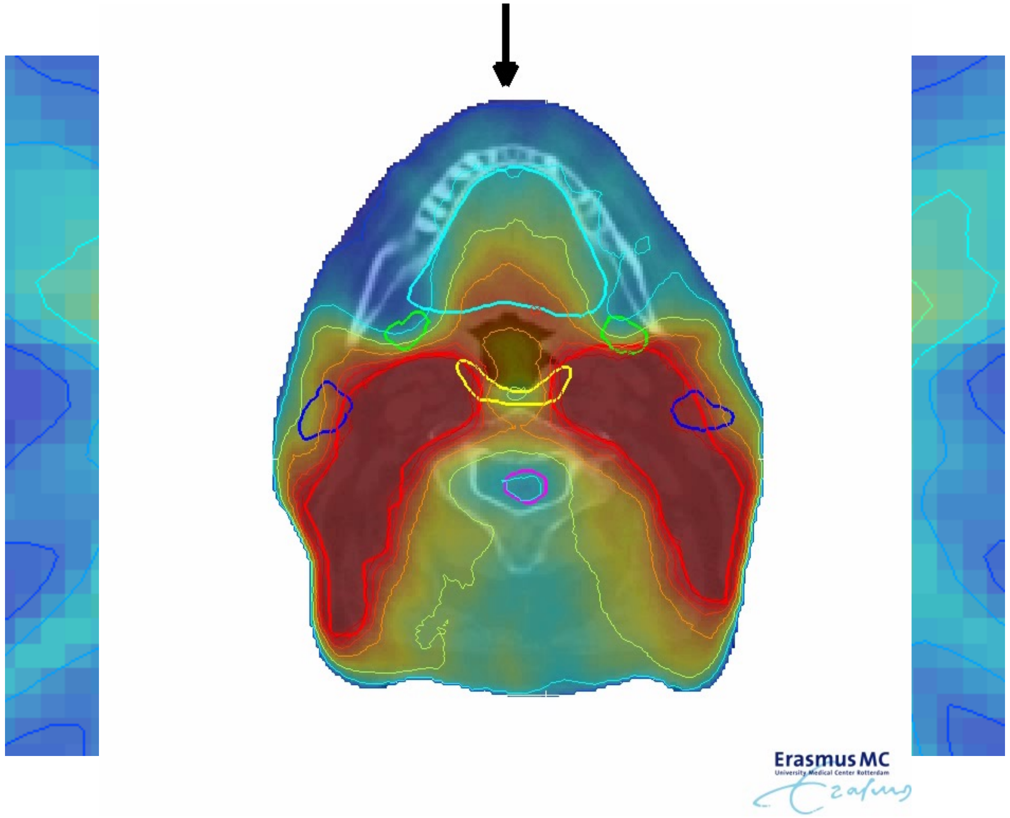
objectives		constraints	
$f_{sq\,deviation}$	$= \frac{1}{N_S}\sum_{i\epsilon S}(d_i - \hat{d})^2$		
$f_{sq\,under\,dosage}$	$= \frac{1}{N_S}\sum_{i\epsilon S}\Theta(\hat{d} - d_i)(d_i - \hat{d})^2$	$c_{min\,dose}$	$= d_{min} - \kappa\, log\left(\sum_{i\epsilon S} e^{\frac{d_{min}-d_i}{\kappa}}\right)$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

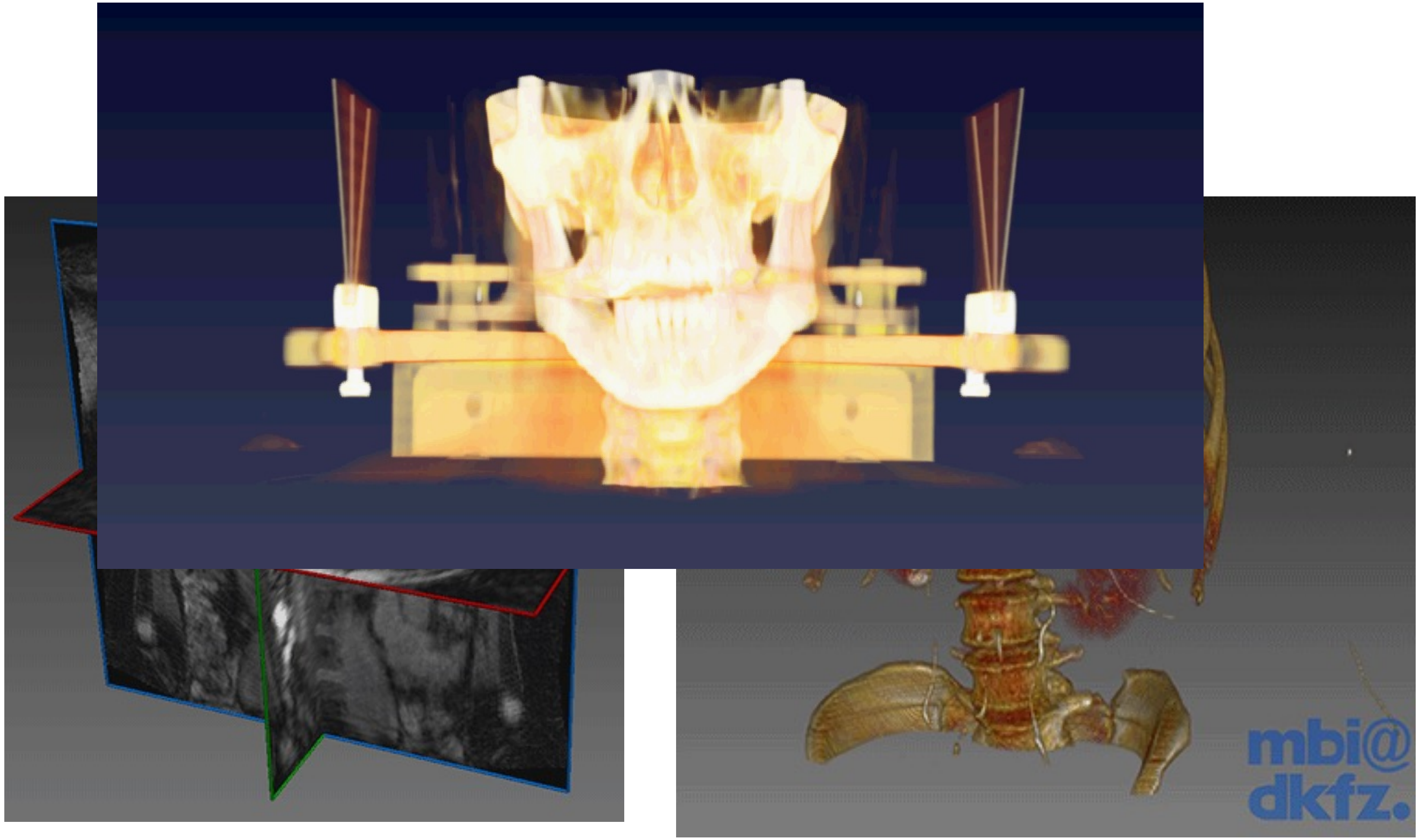
More options to solve this problem, e.g., with Pareto surface approximation & exploration



Head and neck animation courtesy of Dr. Sebastiaan Breedvelt @ Erasmus MC Cancer Institute Rotterdam
https://sebastiaanbreedveld.nl/rt_tradeoffs.html

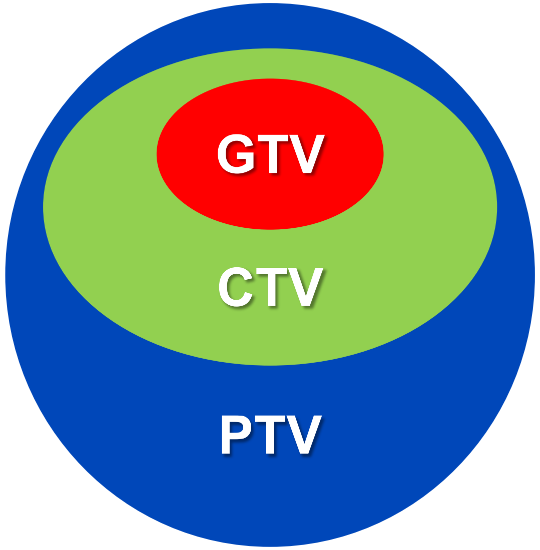
Now we have fully understood and solved the problem of inverse treatment planning using intensity modulation for photons & ions?

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

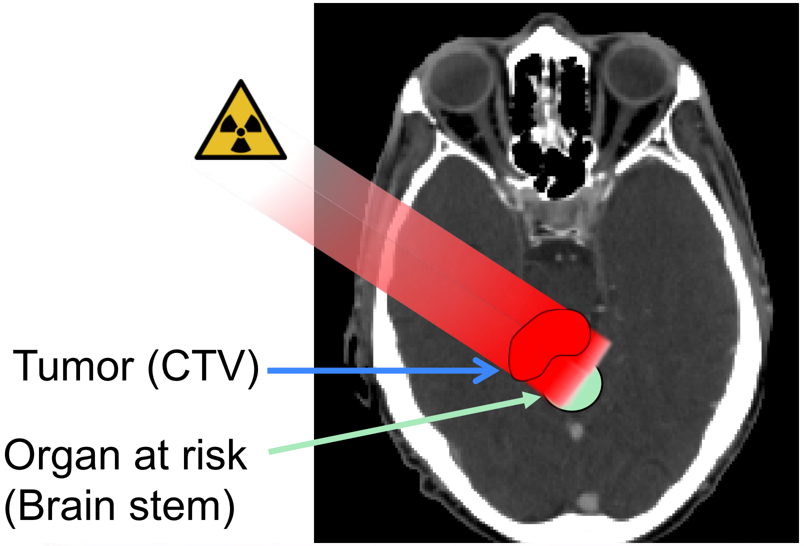
- PTV = Planning target volume

  safety margin to take uncertainties into account

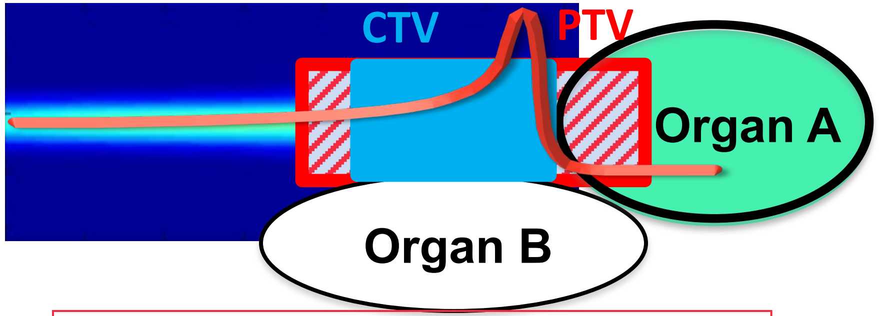
W. Schlegel & A. Mahr: 3D Conformal Radiation Therapy Springer Multimedia DVD

ICRU report 50

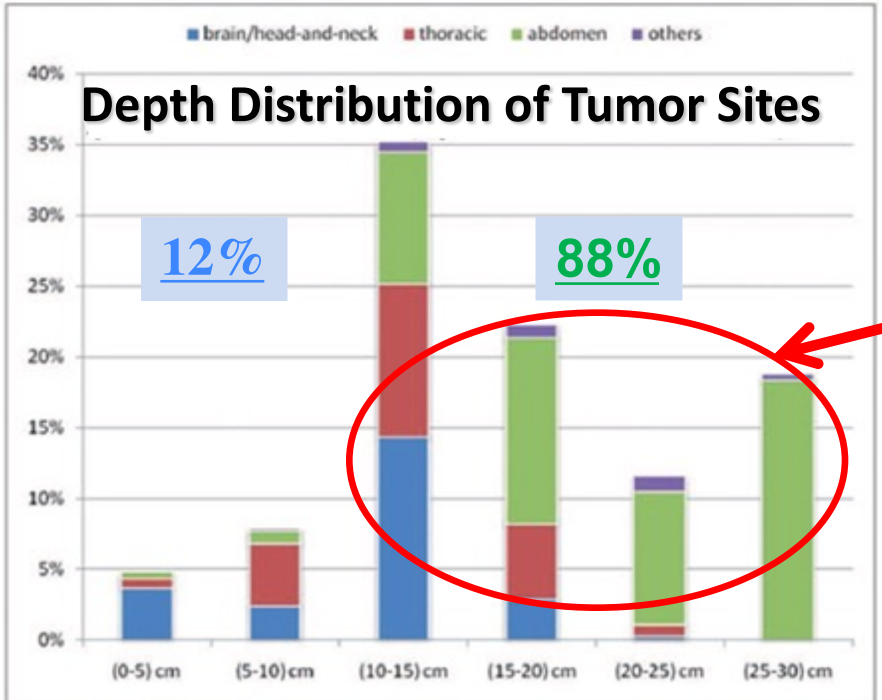
"Bragg Peak" Range Uncertainty

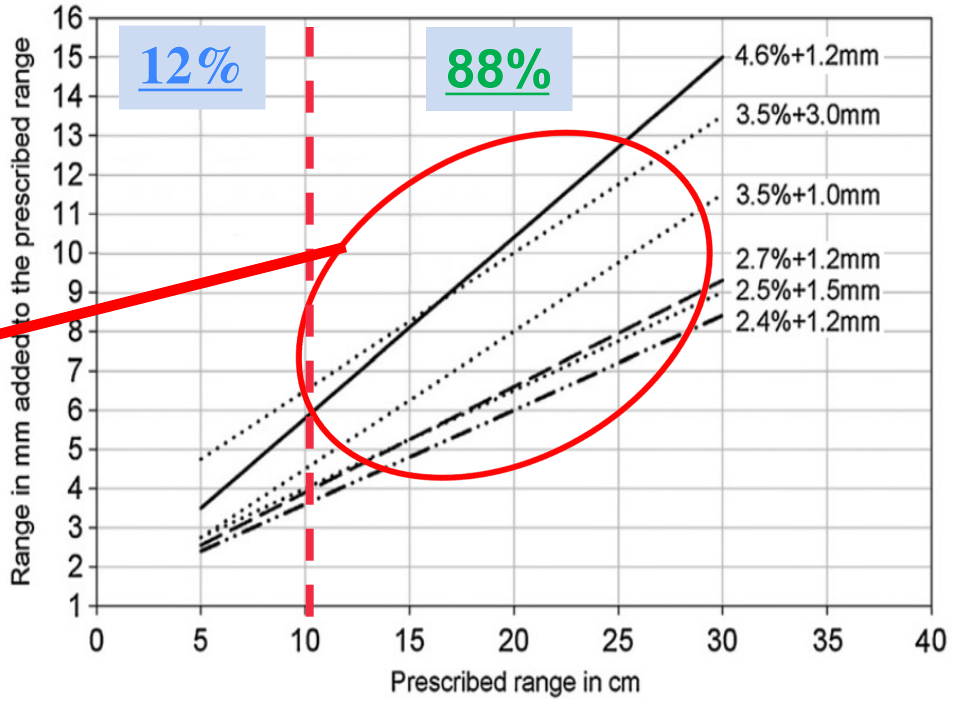


TUMOR (CTV) and PLANNING TARGET (PTV)



Range Margin recipes in use

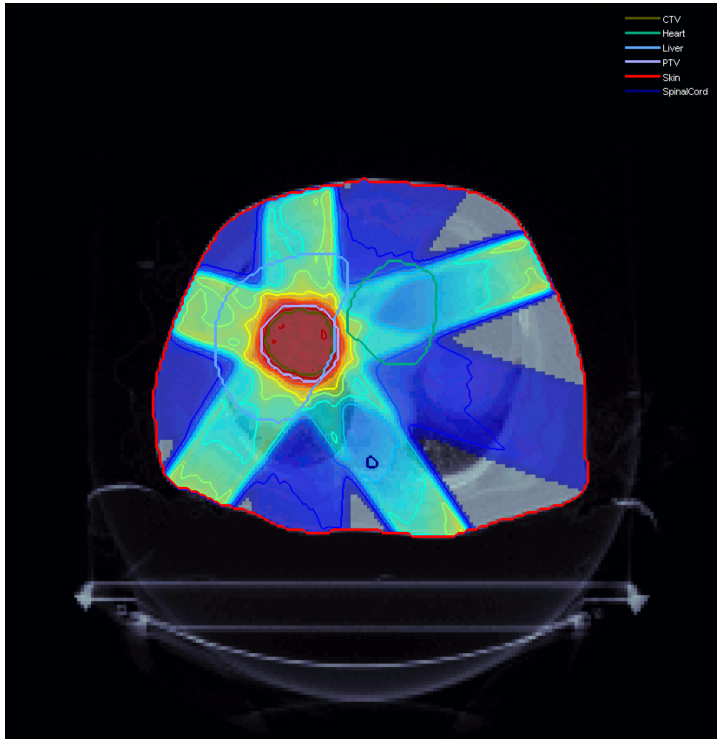


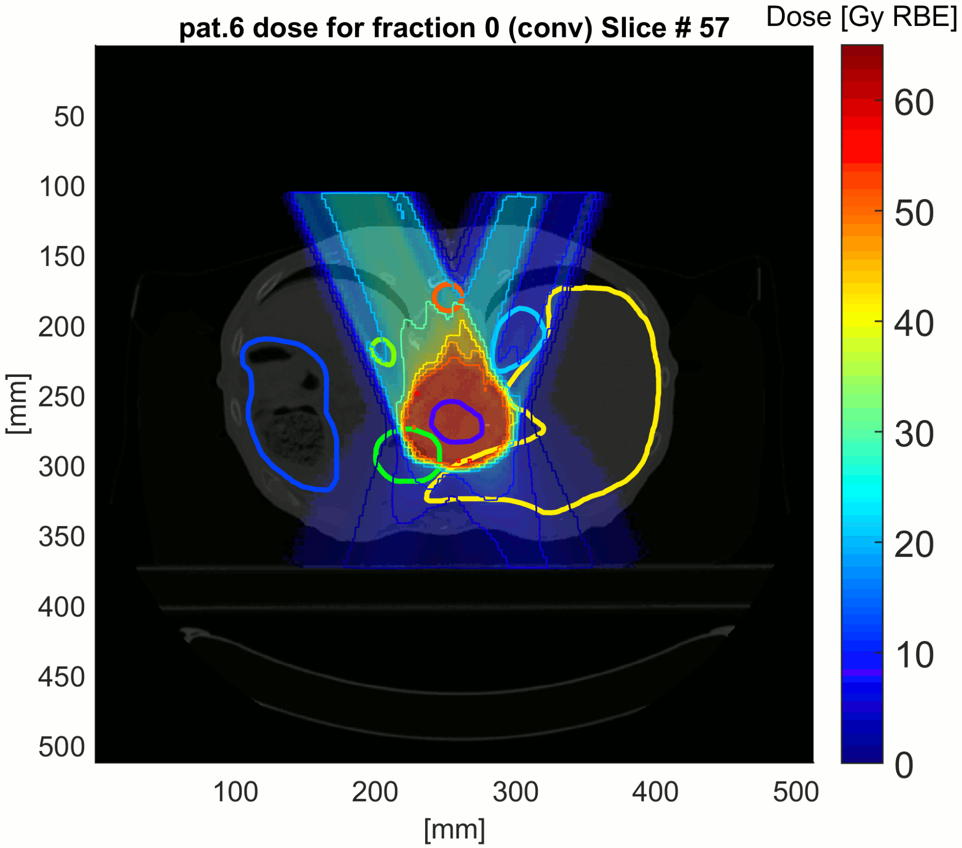


dkfz.

Margins – really?

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





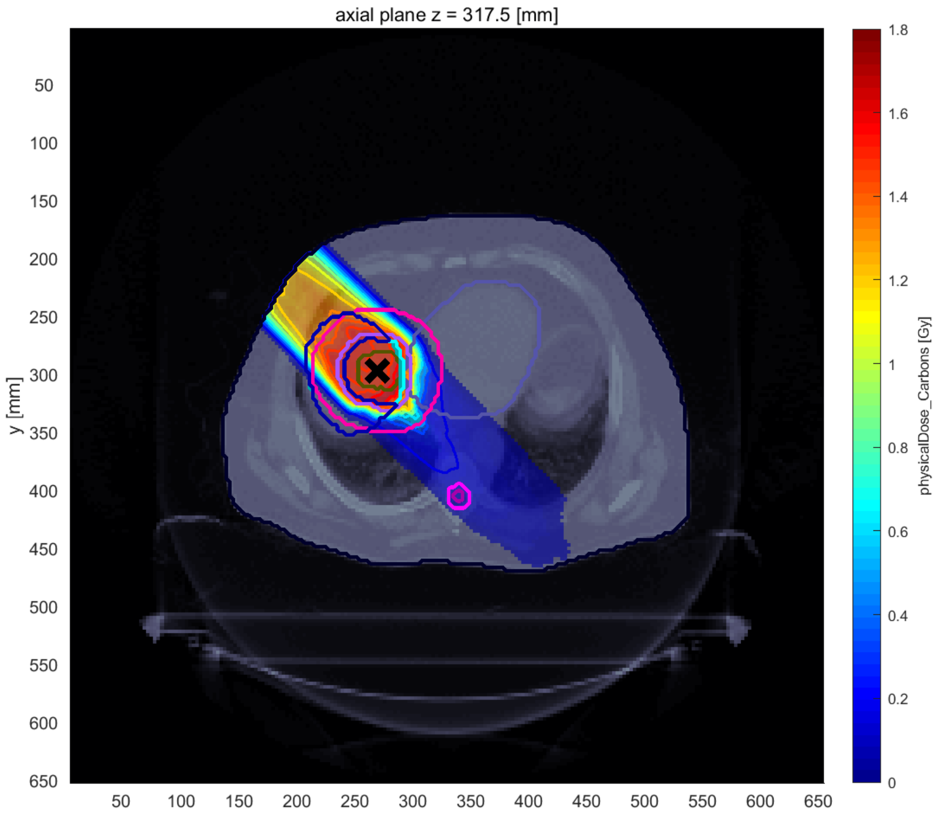
→ Not applicable for protons / ions!

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

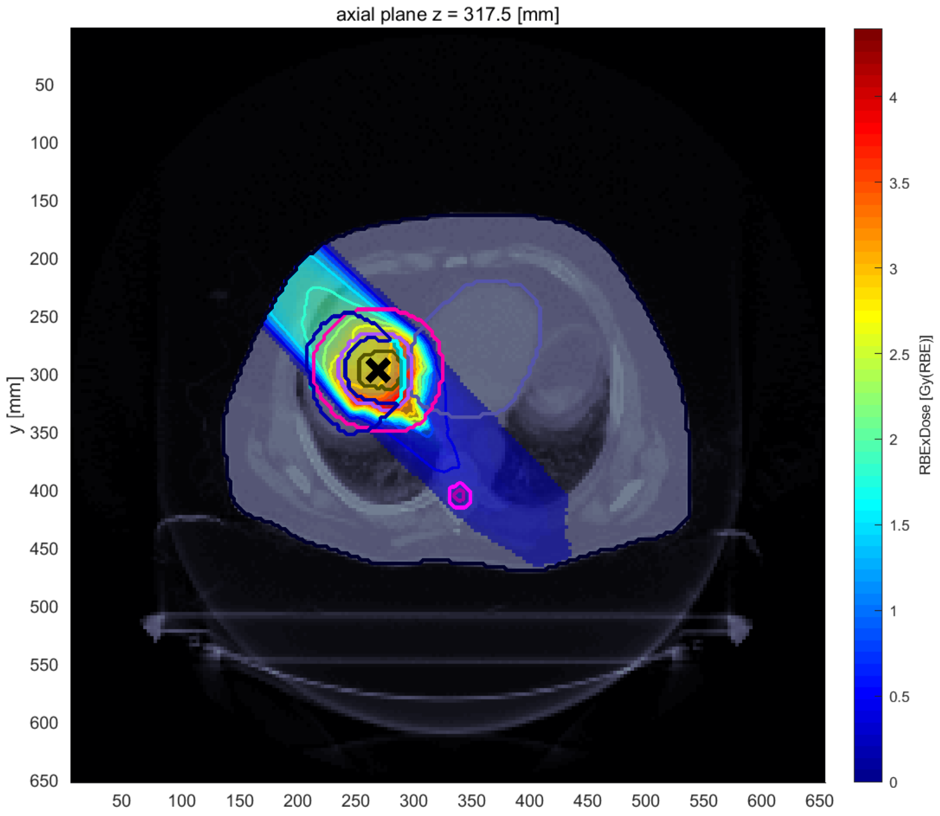
[3] Steitz et al., *Radiation Oncology 2016,* **11**:134

Difference in biological effect

physical dose



Biologically effective dose



→ Physical doses similar to photons induce different biological effect!

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

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

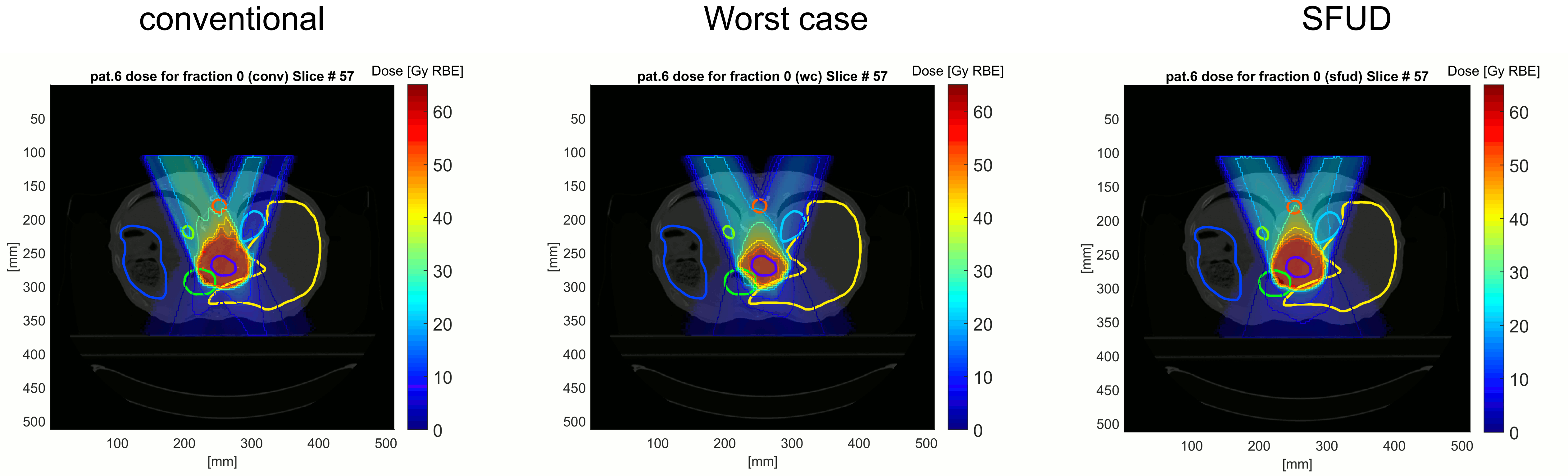
subject to

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

„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



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

HITRI plus
Heavy Ion Therapy Research Integration

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