

Methods for improving the precision of proton beam radiation therapy of cancer

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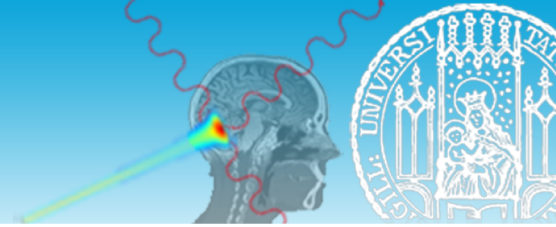


- Cancer as a disease
- Radiation therapy
- Physics of proton therapy

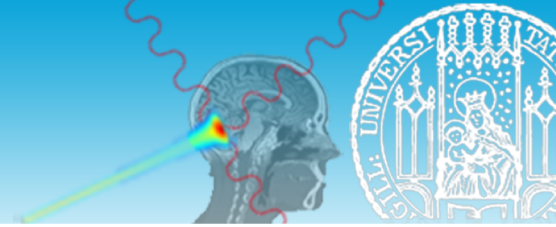
Part I

- Proton therapy and its associated uncertainties
- Investigated solutions for reducing uncertainties
 - Proton imaging
 - Relative biological effectiveness
 - In-vivo range verification
- Concluding remarks

Part II

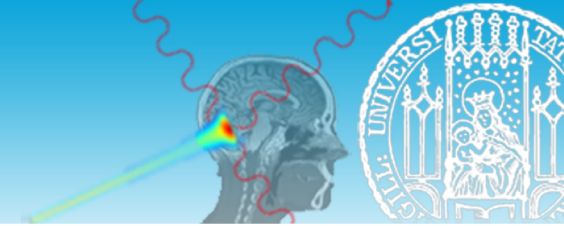


Part I

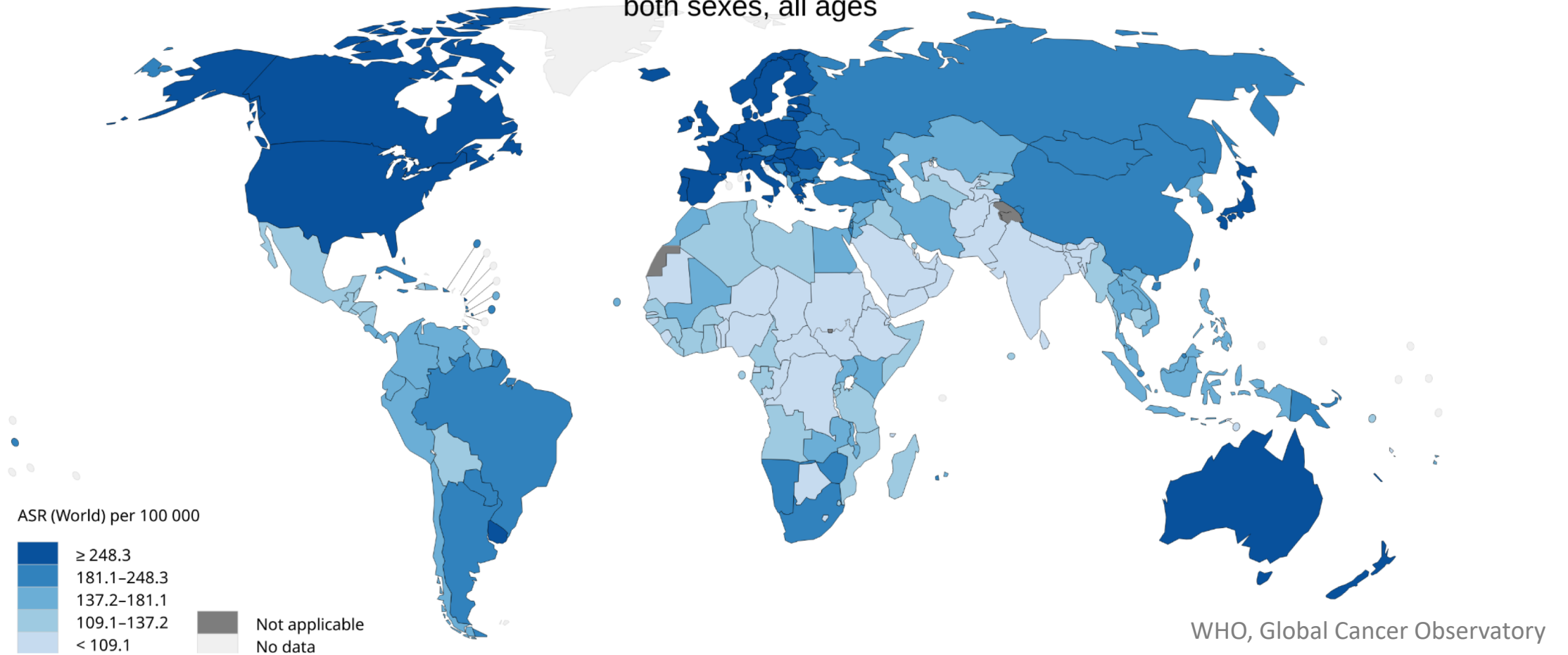


- Leading causes of death:
 - US: 23% heart disease (700k), 21% cancer (600k) – total $8 \cdot 10^{-3}$ deaths/million
 - Germany: 35% heart disease (340k), 24% cancer (240k) – total $1.1 \cdot 10^{-2}$ deaths/million

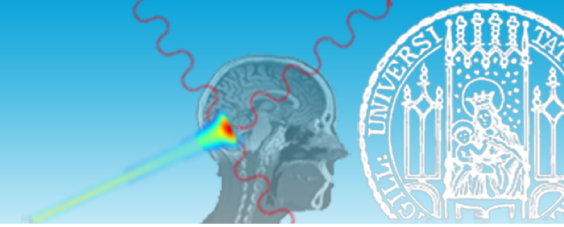
Cancer statistics



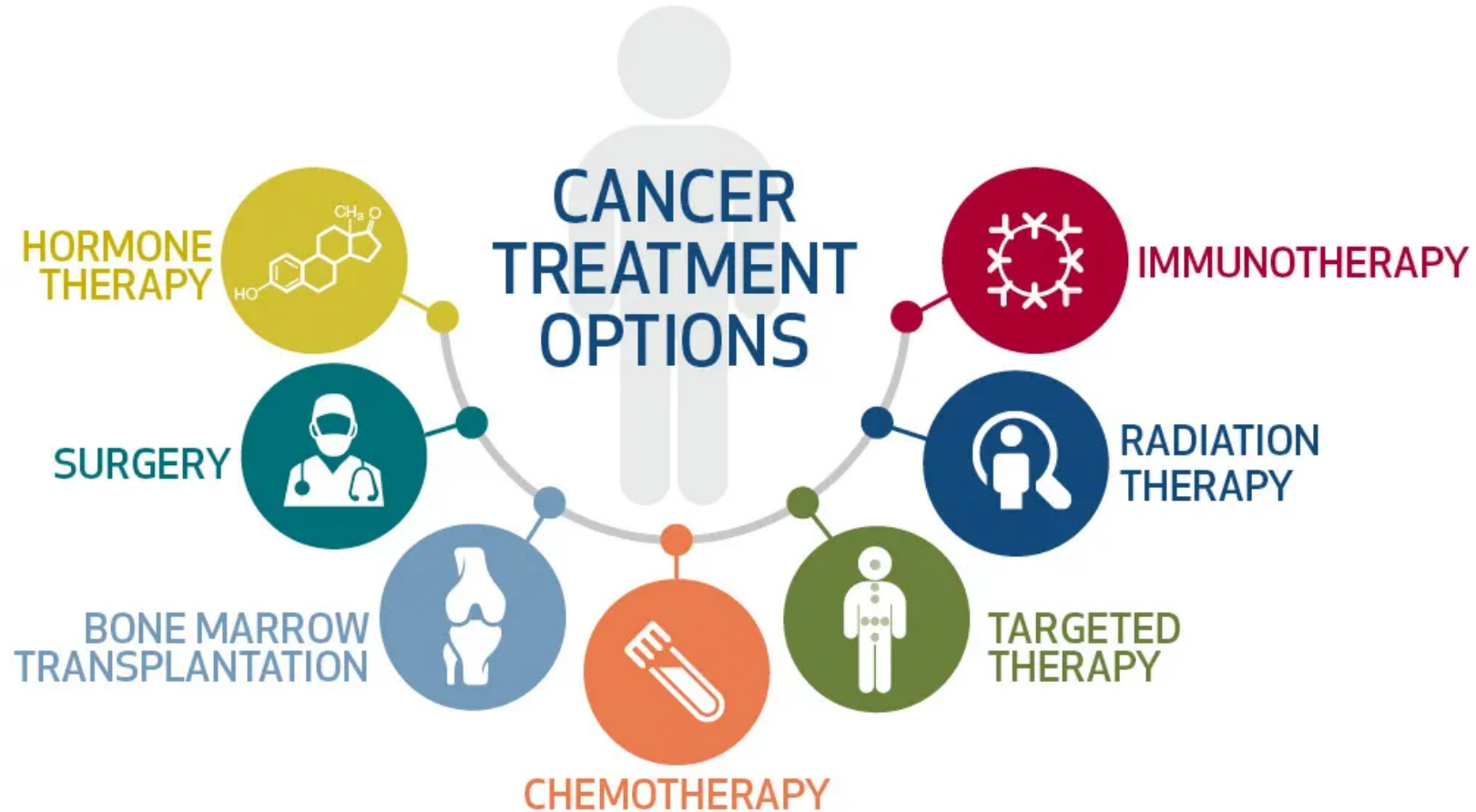
Estimated age-standardized incidence rates (World) in 2020, all cancers excl. non-melanoma skin cancer, both sexes, all ages



- For a city like Munich (1.472M) approximately 3680 new cases every year

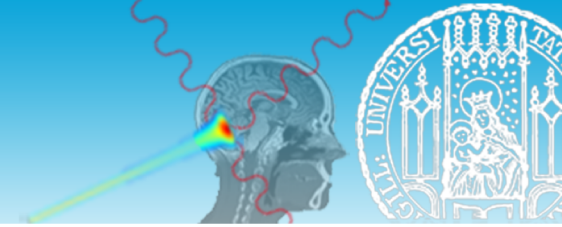


- Many and in most cases synergistic treatment modalities

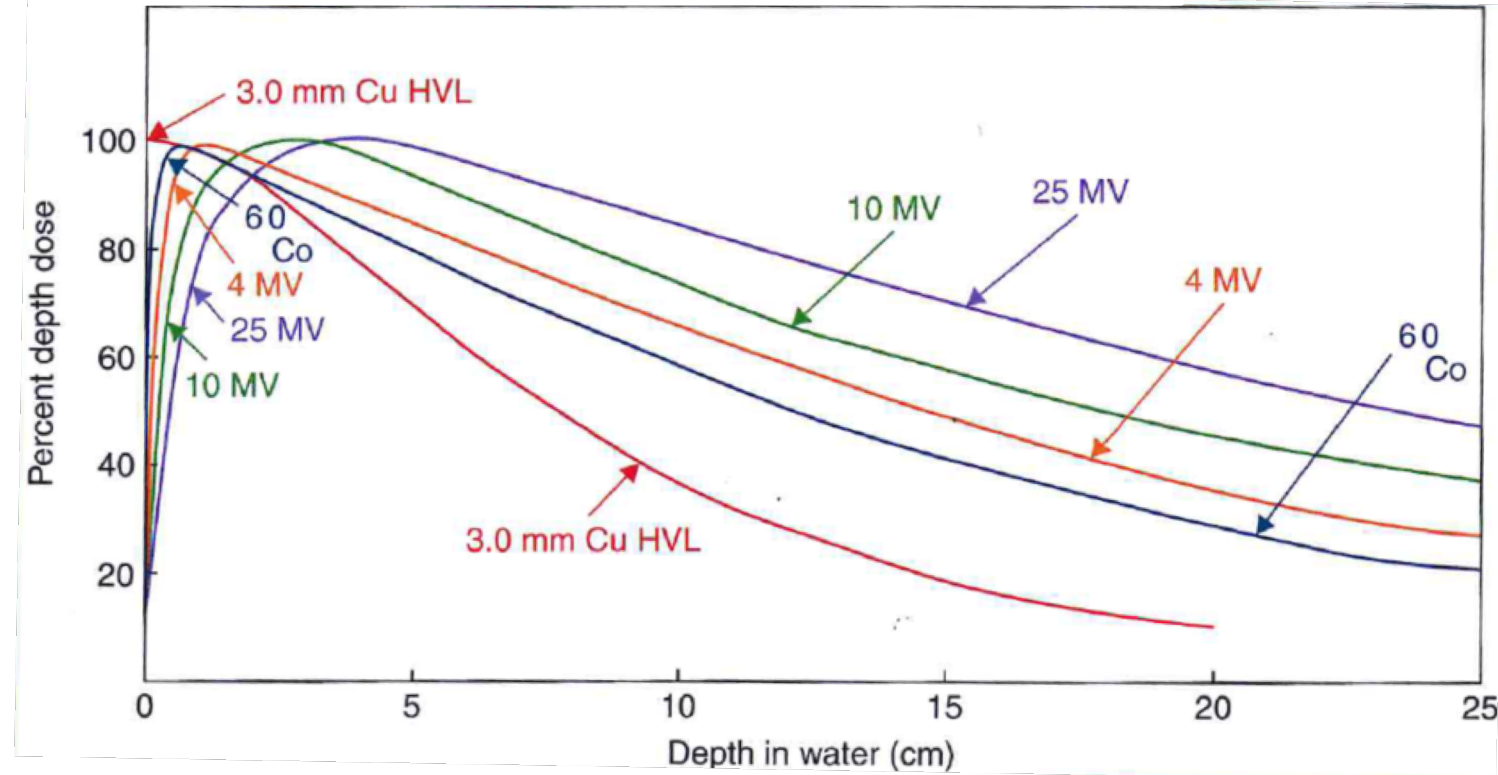


- Radiation therapy will be the conceptual basis of this talk

Radiation therapy – photons

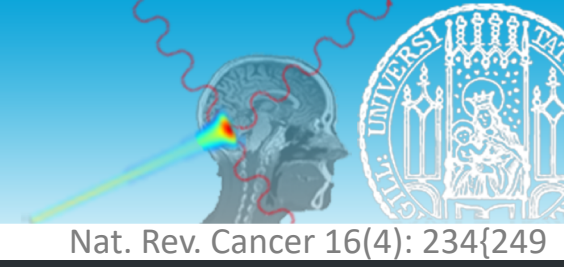


- Ionizing radiation -> DNA damage -> cell death
- Photons attenuate in matter and indirectly ionize: $I = I_0 \cdot e^{-\mu x}$
- Dose maximum at shallow depths
- A single photon beam:
no clinically useful dose distribution



Br J Radiol. 1978;(suppl 11);

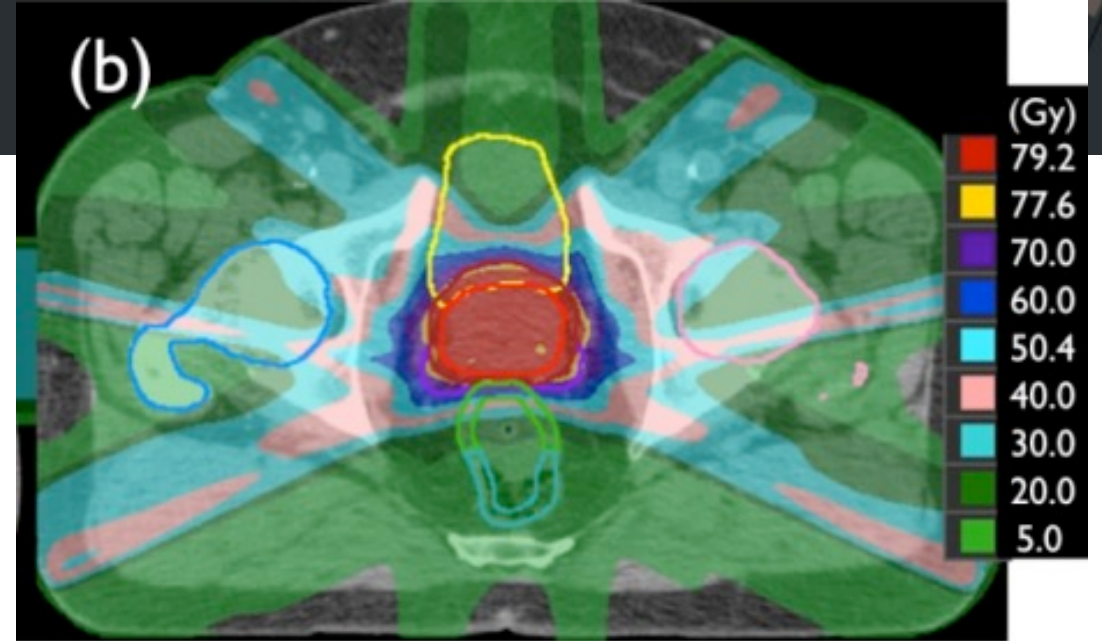
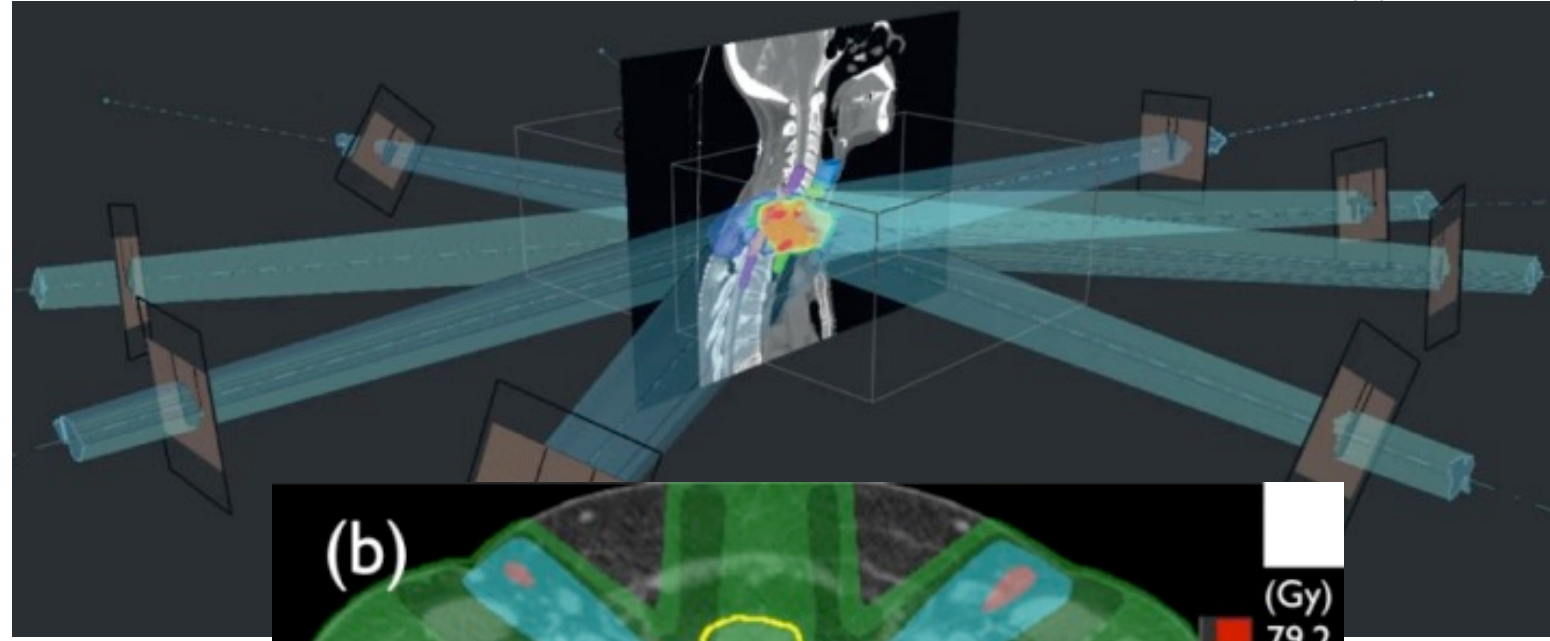
Radiation therapy – photons

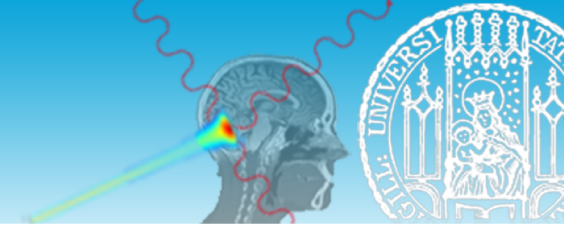


Nat. Rev. Cancer 16(4): 234{249

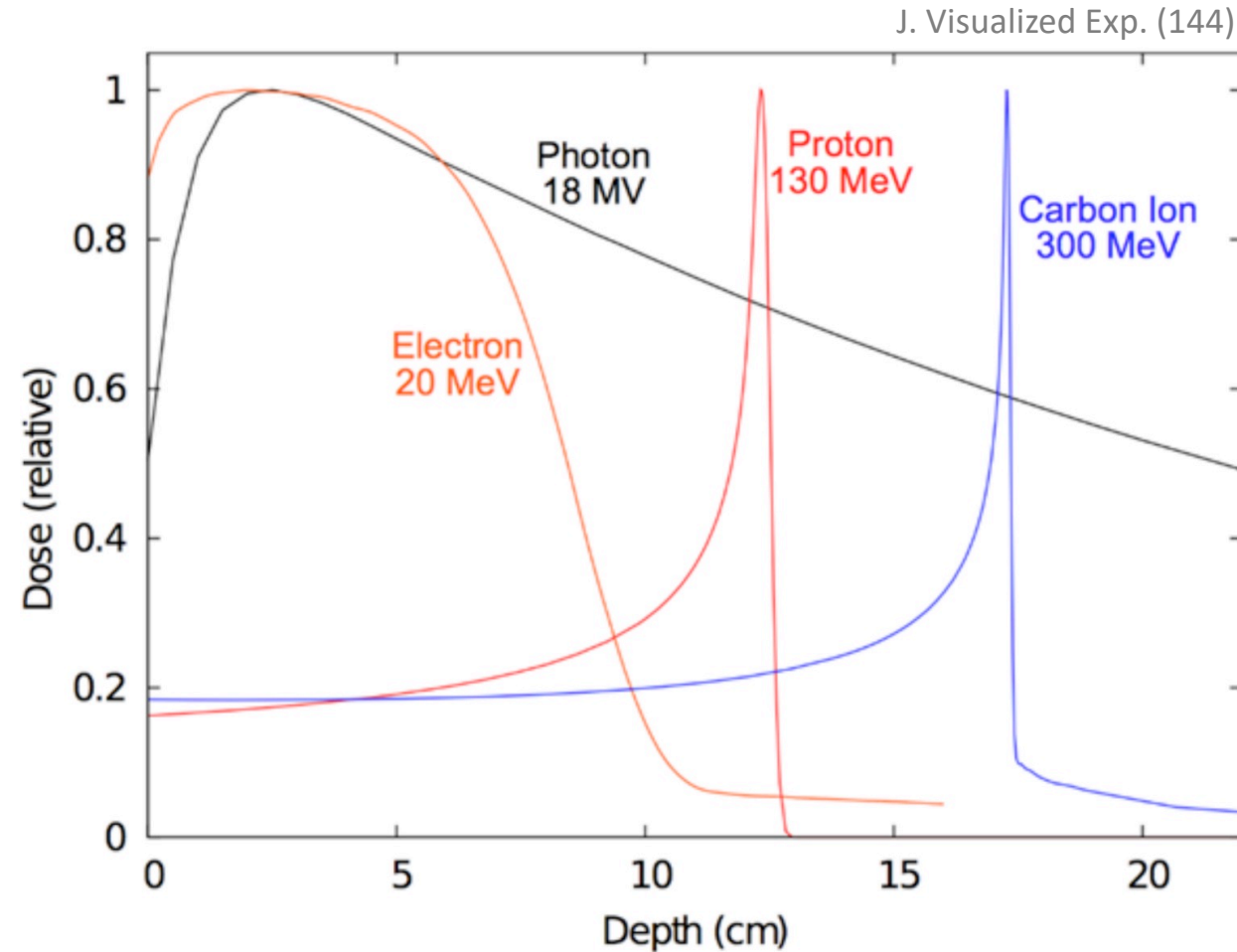
- Multiple fields superimposed
- High dose to the tumor
- Low dose bath around it

- Clinical dose distribution example:

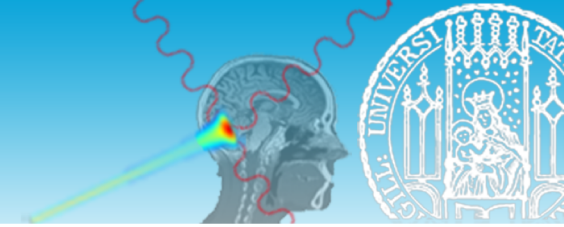




- More favorable depth-dose shape
- Maximum dose Bragg peak (BP) near end-of-range
- Low entrance and almost no exit dose
- Position of maximum regulated by particle energy
- Bragg curve: named after WH Bragg (1903)

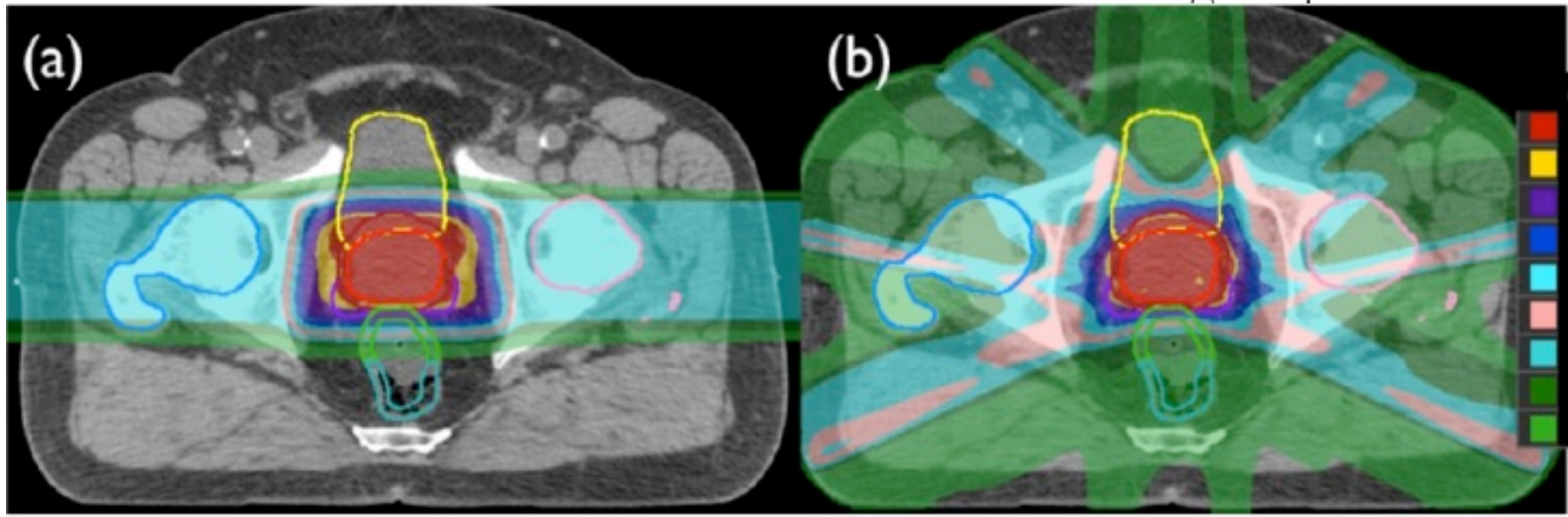
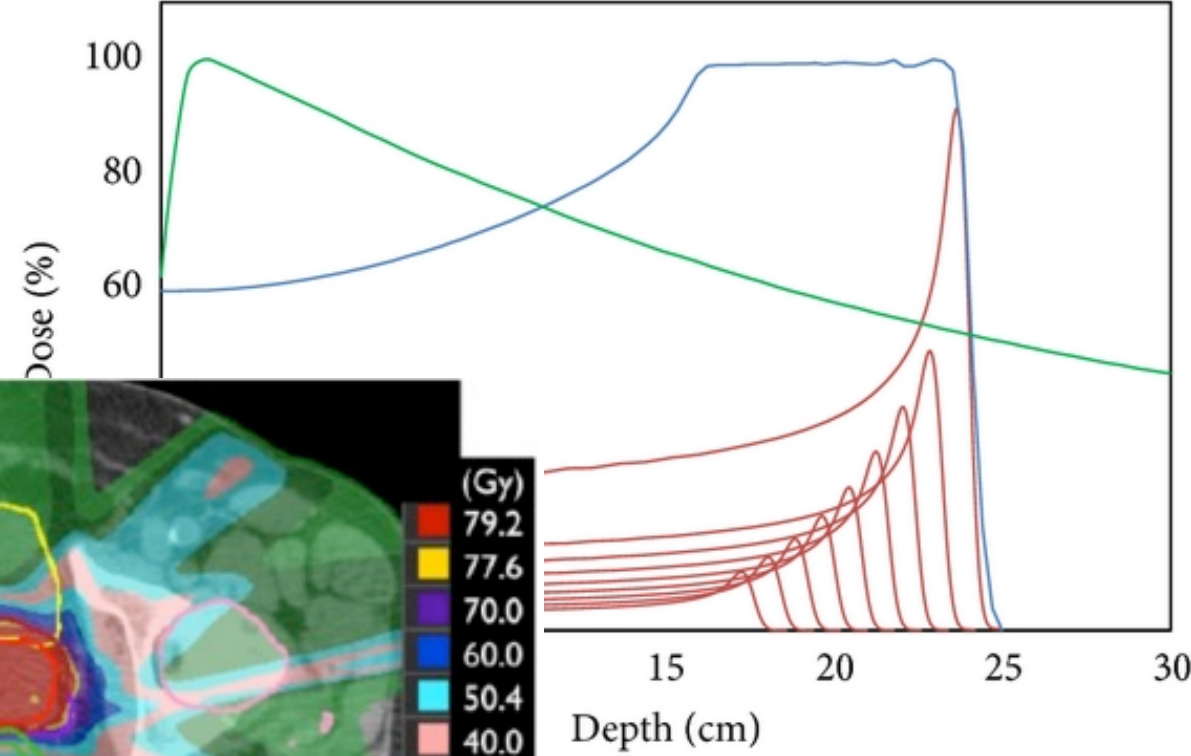


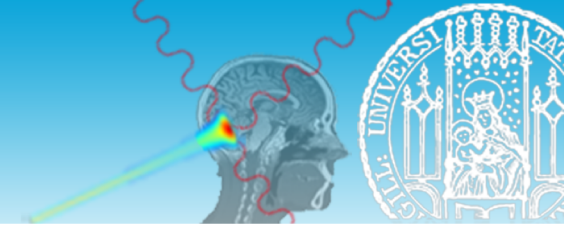
Radiation therapy – ions



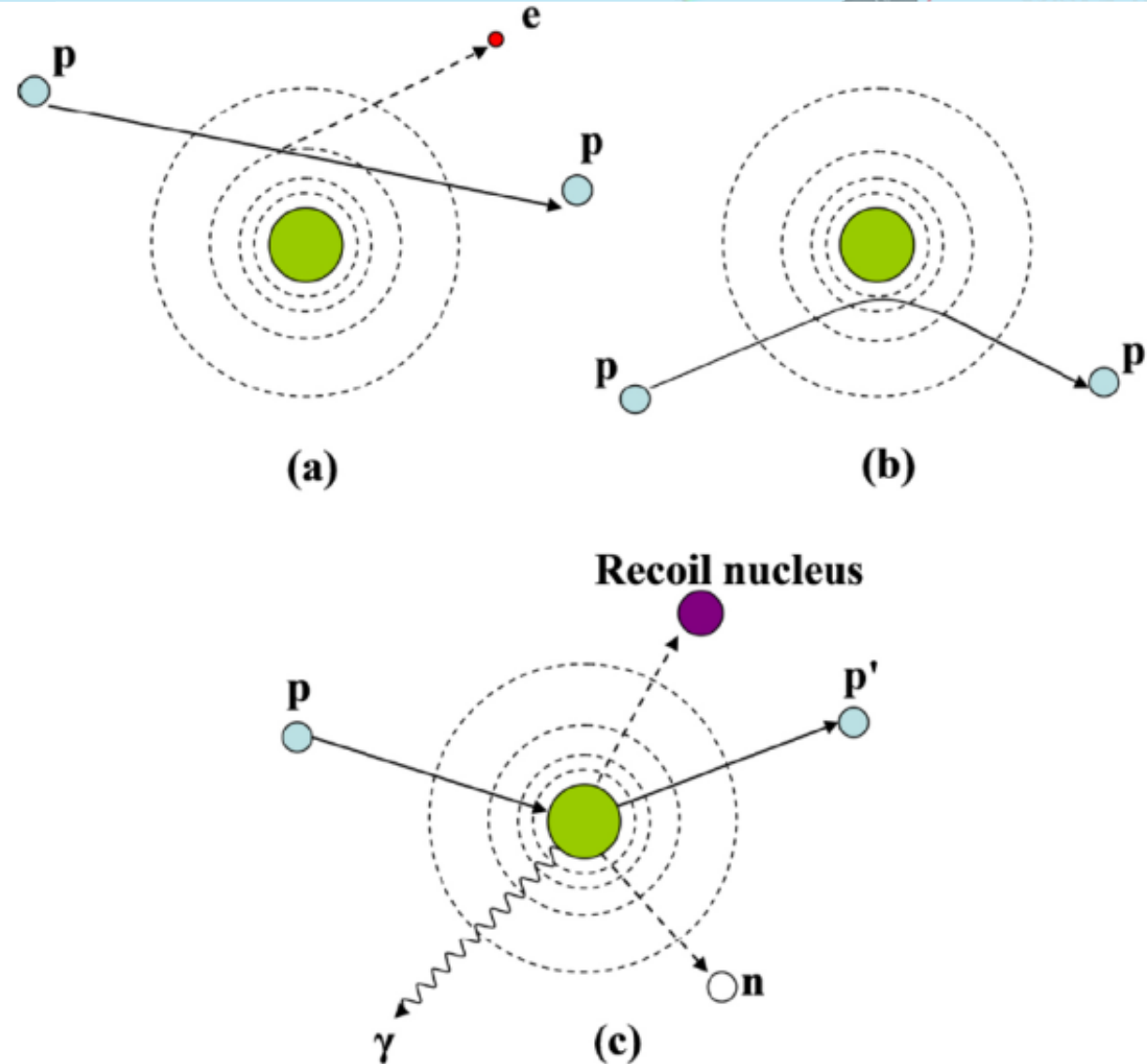
- Spread-out Bragg Peak (SOBP) for extended tumors
- Reduced peak to plateau dose ratio
- Fewer fields required - Reduced low dose bath

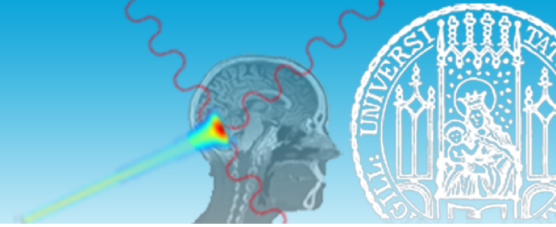
BioMed Research International, 2014, 389048



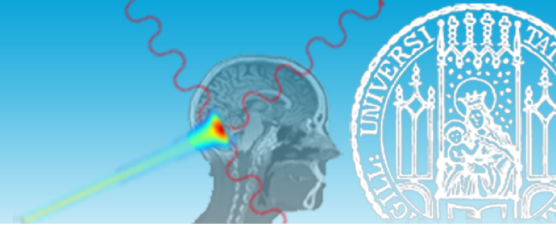


- Brief reminder
- Main mechanisms
 - Ionizations/excitations (a)
 - Elastic scattering with nucleus (b)
 - Non-elastic interactions with nucleus (c)





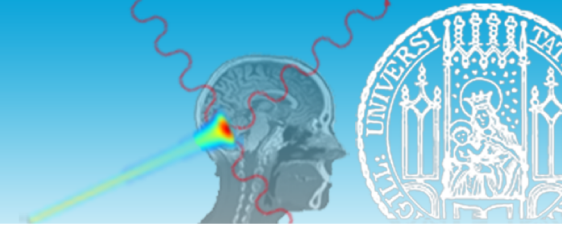
- Ion stopping power:
$$\frac{S}{\rho} = -\frac{dE}{\rho dx} = 4\pi N_A r_e^2 m_e c^2 \frac{Z}{A} \frac{z^2}{\beta^2} \left[\ln \frac{2m_e c^2 \gamma^2 \beta^2}{I} - \beta^2 - \frac{\delta}{2} - \frac{C}{Z} \right]$$
- Energy loss fluctuations: Gaussian (~1% for 200 MeV protons in water)
- To factor out energy dependence:
$$\text{RSP} = \frac{S_{mat}}{S_{water}}$$



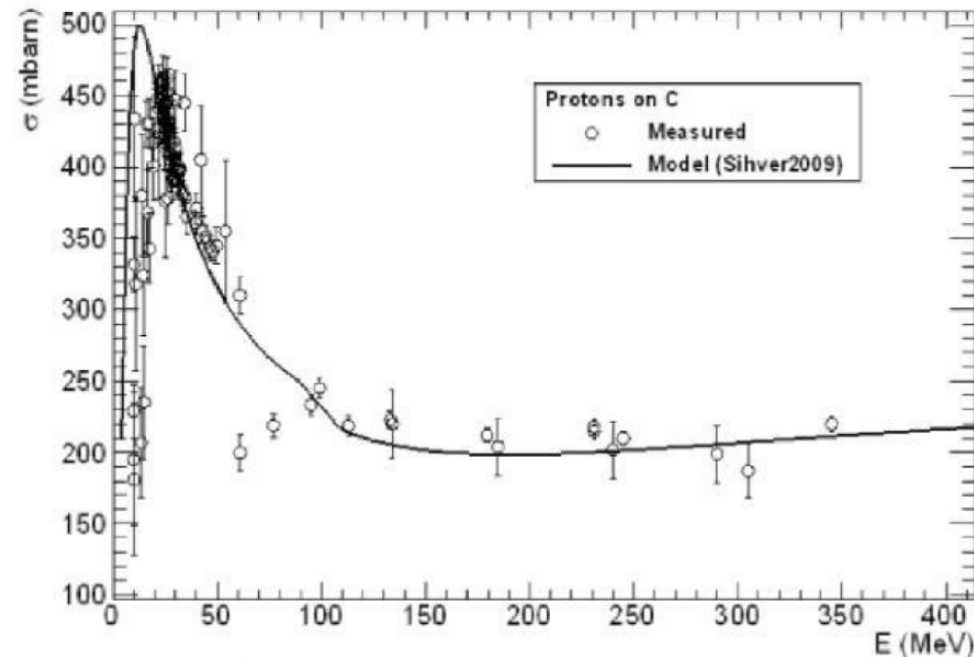
- Coulomb scattering on nuclei
- Angular distribution approximately Gaussian:

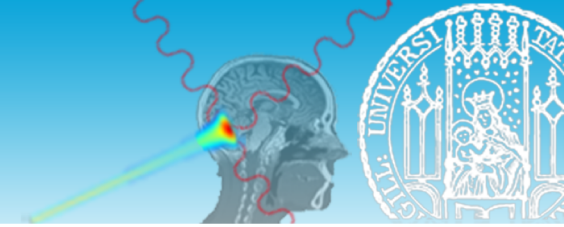
$$\sigma_{\theta} = \frac{E_0}{\beta pc} z \sqrt{\frac{x}{X_0}} \left[1 + 0.038 \ln \left(\frac{x}{X_0} \right) \right]$$

- For ions of the same speed: $\frac{\sigma_{\theta 1}}{\sigma_{\theta 2}} = \frac{M_2 z_1}{M_1 z_2}$ (6 times lower for ^{12}C wrt protons)



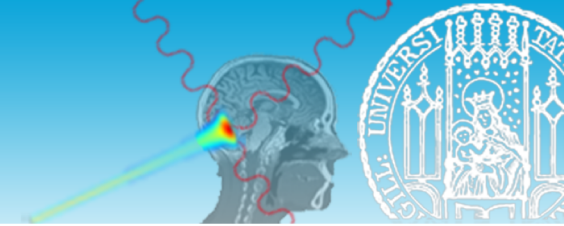
- Nuclear interactions: $\sigma_R(E) = \sigma_0 \cdot f(E, Z_T)$
- Strong energy dependence at low energy



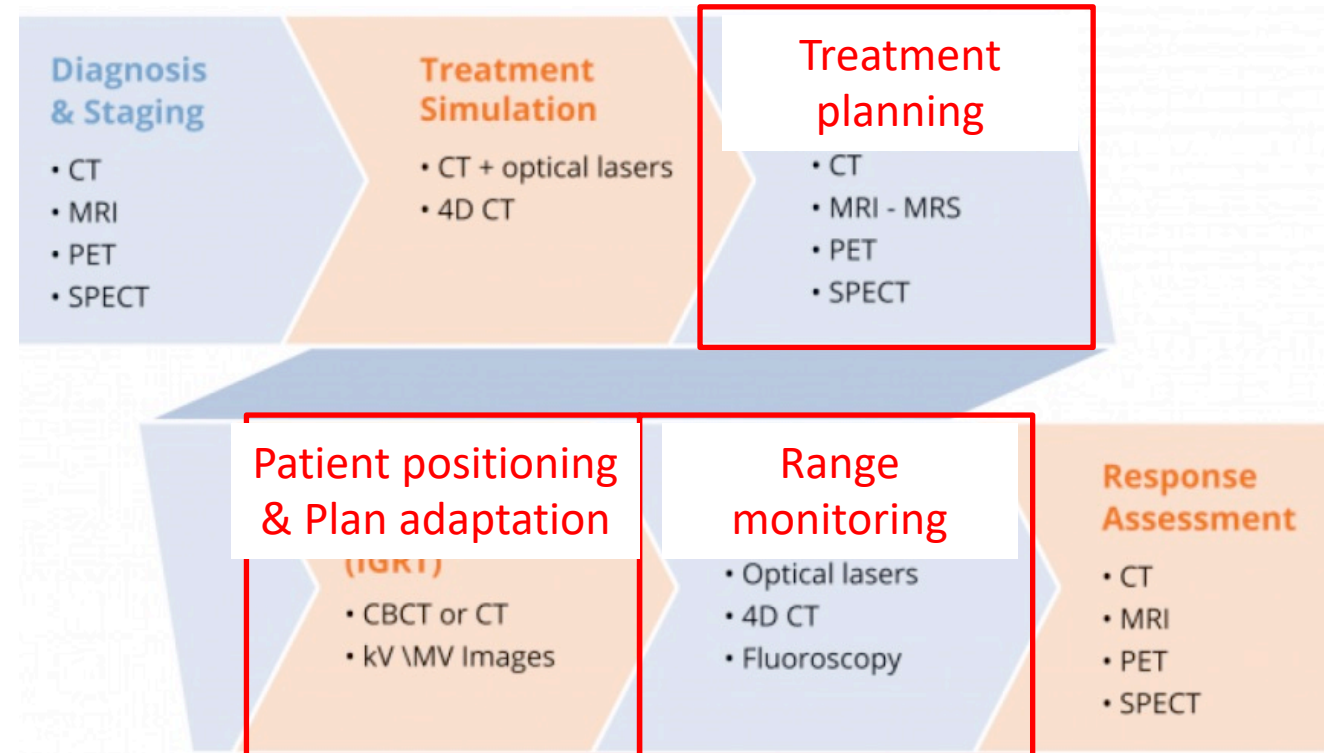


Part II

Ion beam therapy workflow

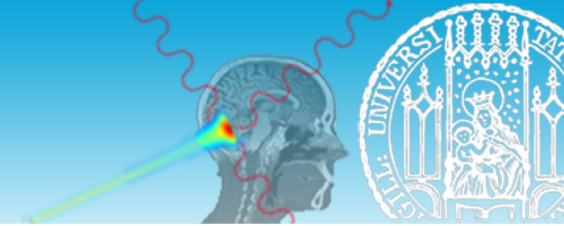


- Several steps leading to treatment delivery
- Numerous imaging modalities involved



www.radiationoncology.com.au/

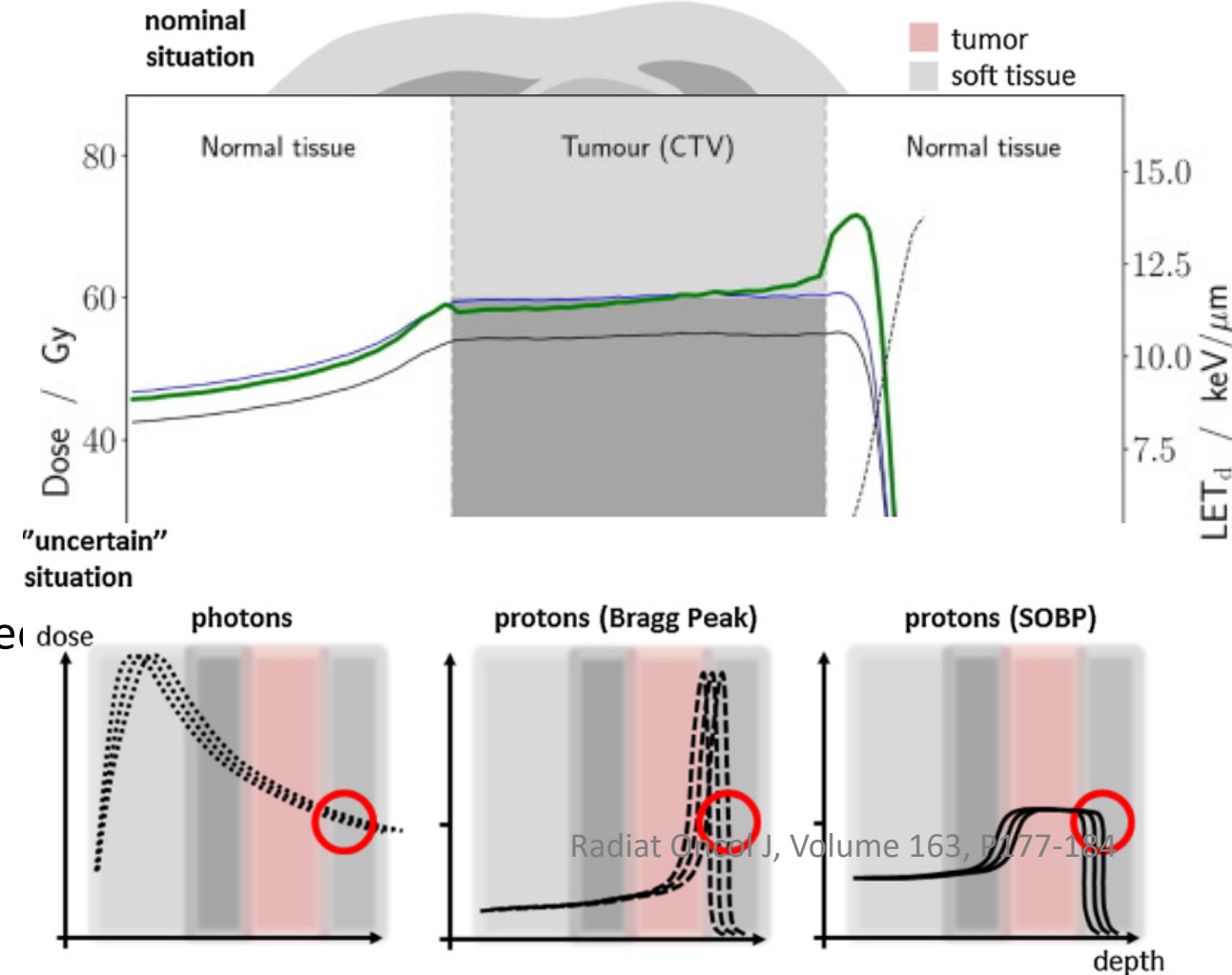
Ion beam therapy uncertainties



Phys Med Biol. 2013 Aug 7;58(15):R131-60

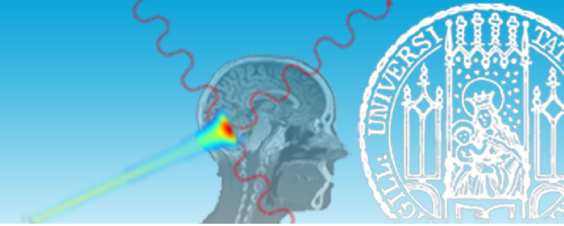
- Treatment planning (TP):

- Need the exact ion range in the patient
- 3D RSP map of the patient via imaging
- RSP uncertainties -> range uncertainty
- Biological rather than absorbed dose is prescribed
- Biological uncertainties -> range uncertainty -> over/under dosage

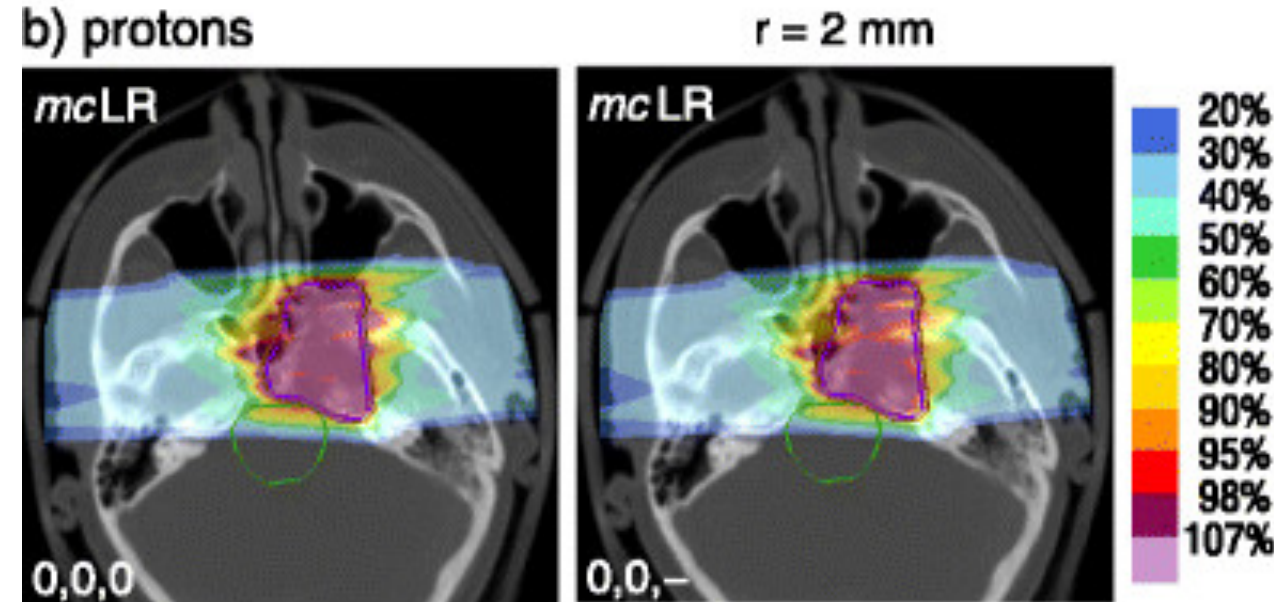


Radiat Oncol J, Volume 163, P177-184

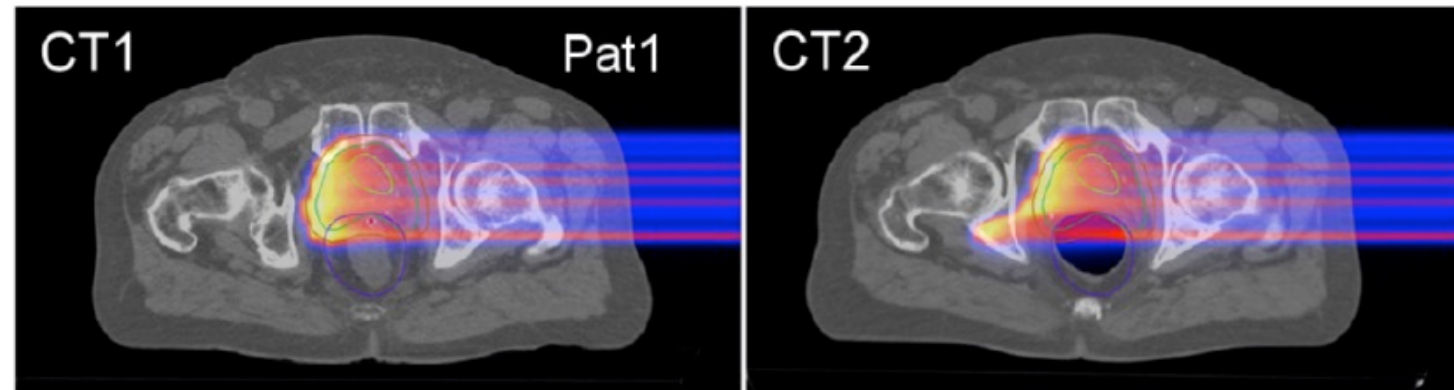
Ion beam therapy uncertainties



- Positioning and anatomical changes
 - Positioning of the patient as on treatment planning day
 - Setup errors -> Altered dose
 - Anatomical changes since the treatment planning day
 - Anatomical changes -> non-valid treatment plans

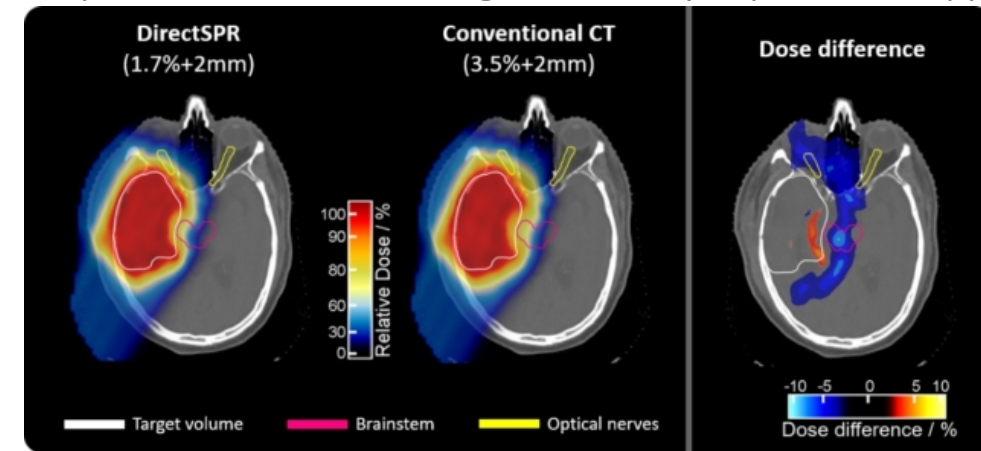


Radiation Oncology. 9. 279. 10.1186/s13014-014-0279-2.

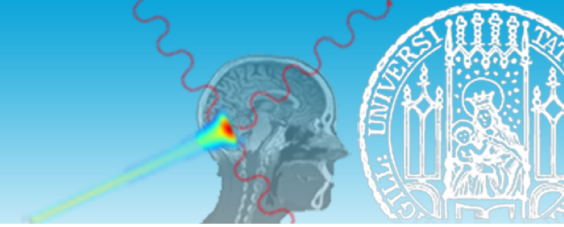


Schmid S., ..., Dedes G. Phys Med Biol. 2015 Nov 18;60(24):9329-934

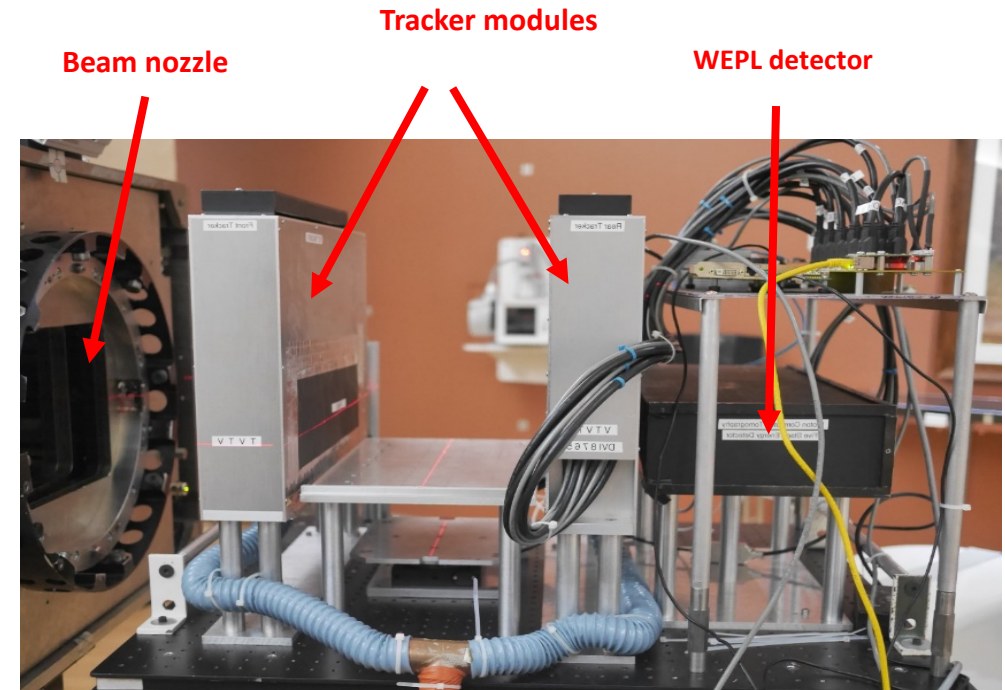
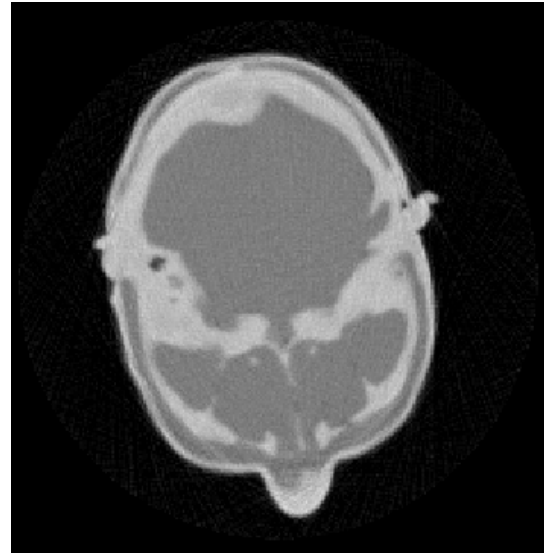
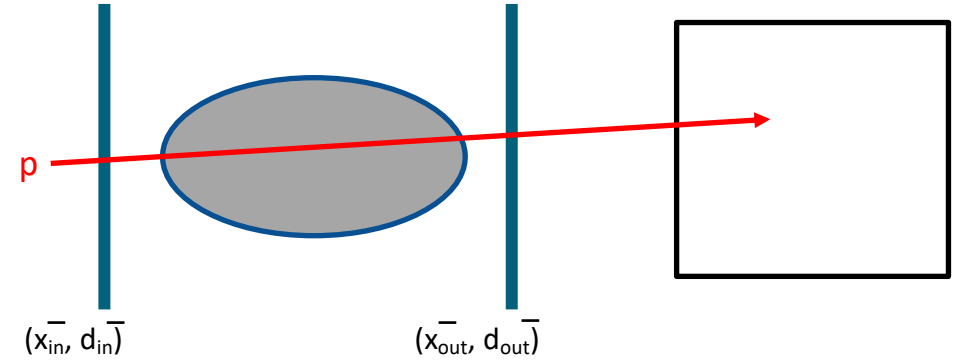
- Treating with protons, imaging with photons
- Proton imaging: direct RSP determination (<1%)
- X-ray imaging:
 - Measure in each projection the integrated (linear) attenuation coefficient along a line
 - Reconstruct from the projections the attenuation coefficient map
- Proton imaging:
 - Measure in each projection the integrated RSP along a line, the water equivalent path length (WEPL)
 - Reconstruct from the WEPL projections the RSP map



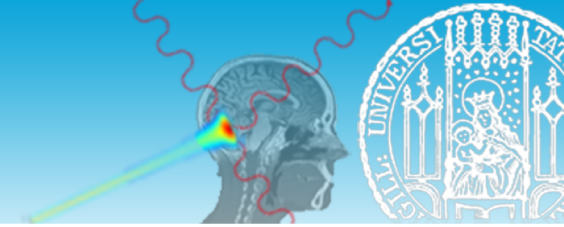
Proton imaging



- Proton's position, direction and energy
- Position and direction -> proton trajectory
- Energy before and after the object -> WEPL



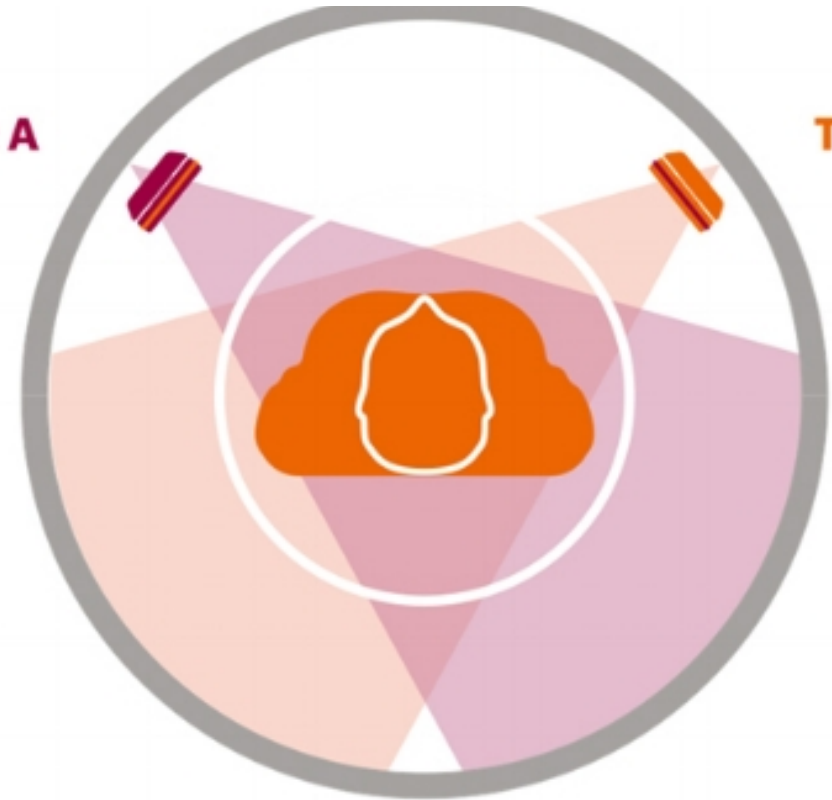
Proton imaging for TP – pCT vs DECT



- Dual energy x-ray CT (DECT): two imaging energies
- Due to $\mu(\rho, Z, E)$, better estimation of RSP with dual energy
- First direct experimental proton CT (pCT) vs. DECT

Tube A

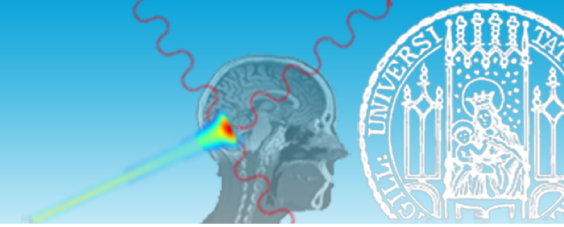
Tube B



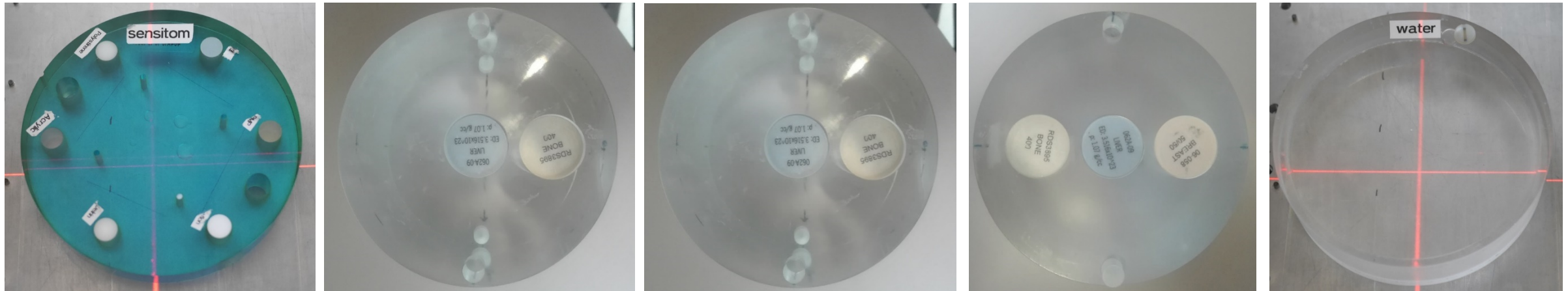
Dual Source CT is equipped with two X-ray tubes and two detectors



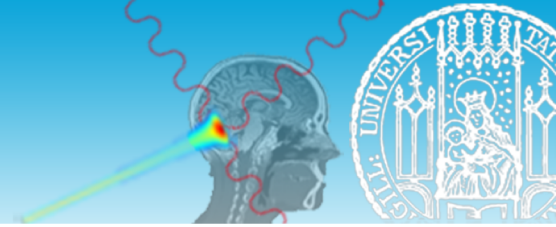
Proton imaging for TP – pCT vs DECT



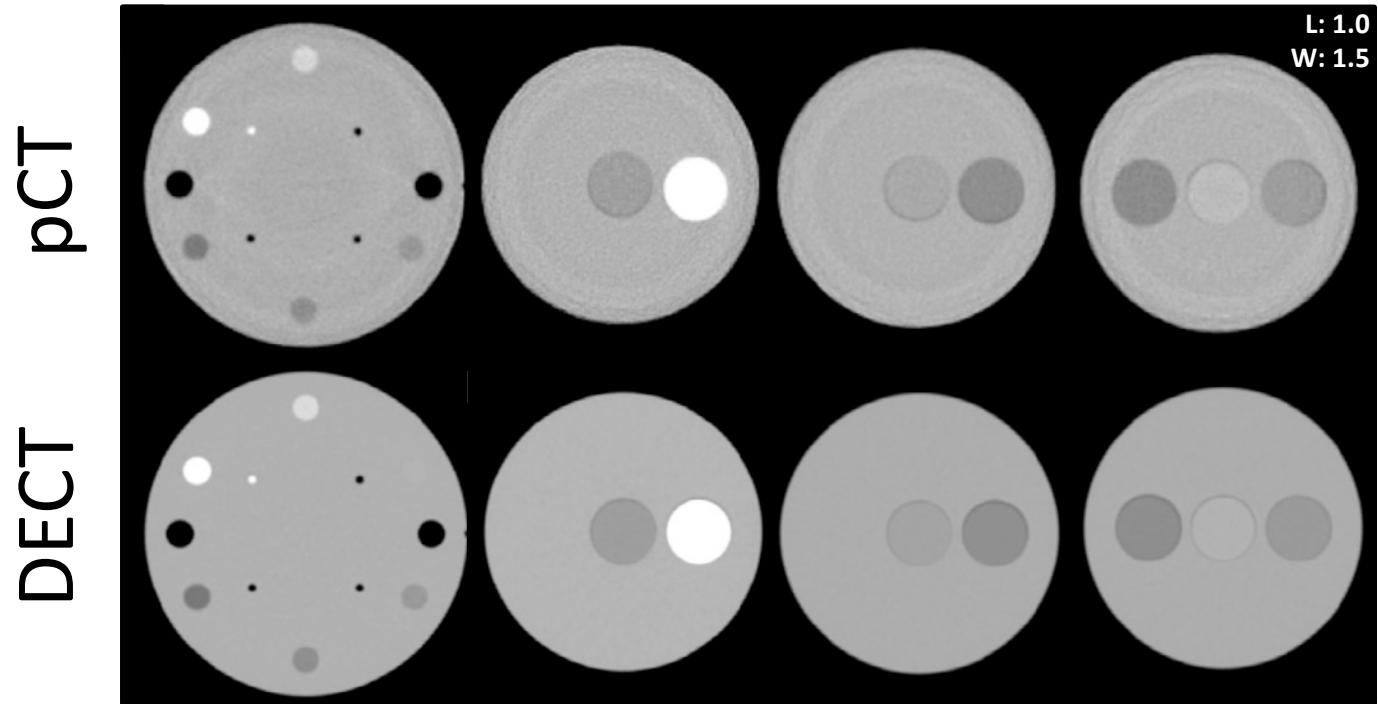
- Scanned objects:



- pCT dose: 1.3 mGy, DECT dose: 35 mGy
- pCT: 6 min, DECT: 14 sec



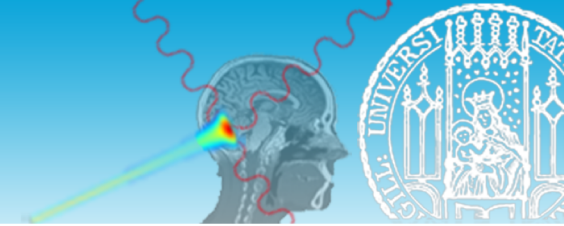
- Reconstructed images:



Dedes G. et al. Phys Med Biol. 2019 Aug 14;64(16):16500

- pCT from prototype scanner: ring shaped artifacts

Proton imaging for TP – pCT vs DECT

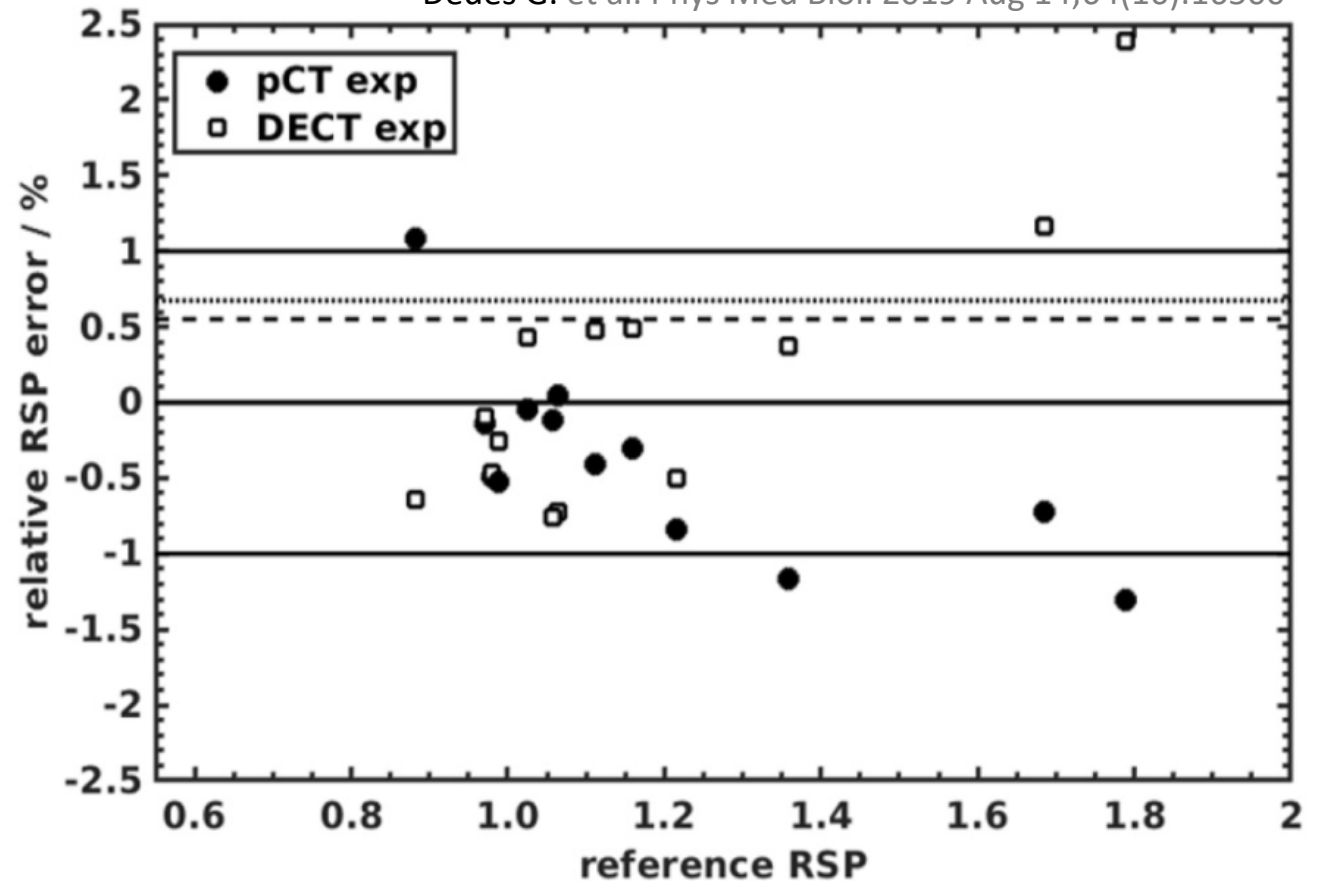


- Quantification of RSP accuracy:

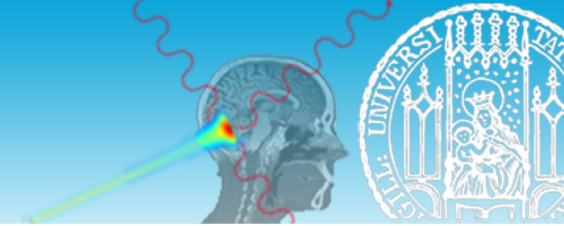
$$RSP_{acc} = 100 \cdot \frac{RSP_{mean} - RSP_{ref}}{RSP_{ref}} \quad \%$$

$$MAPE = \frac{\sum_{i=1}^n |RSP_{acc,i}|}{n}$$

Dedes G. et al. Phys Med Biol. 2019 Aug 14;64(16):16500



Biological uncertainties



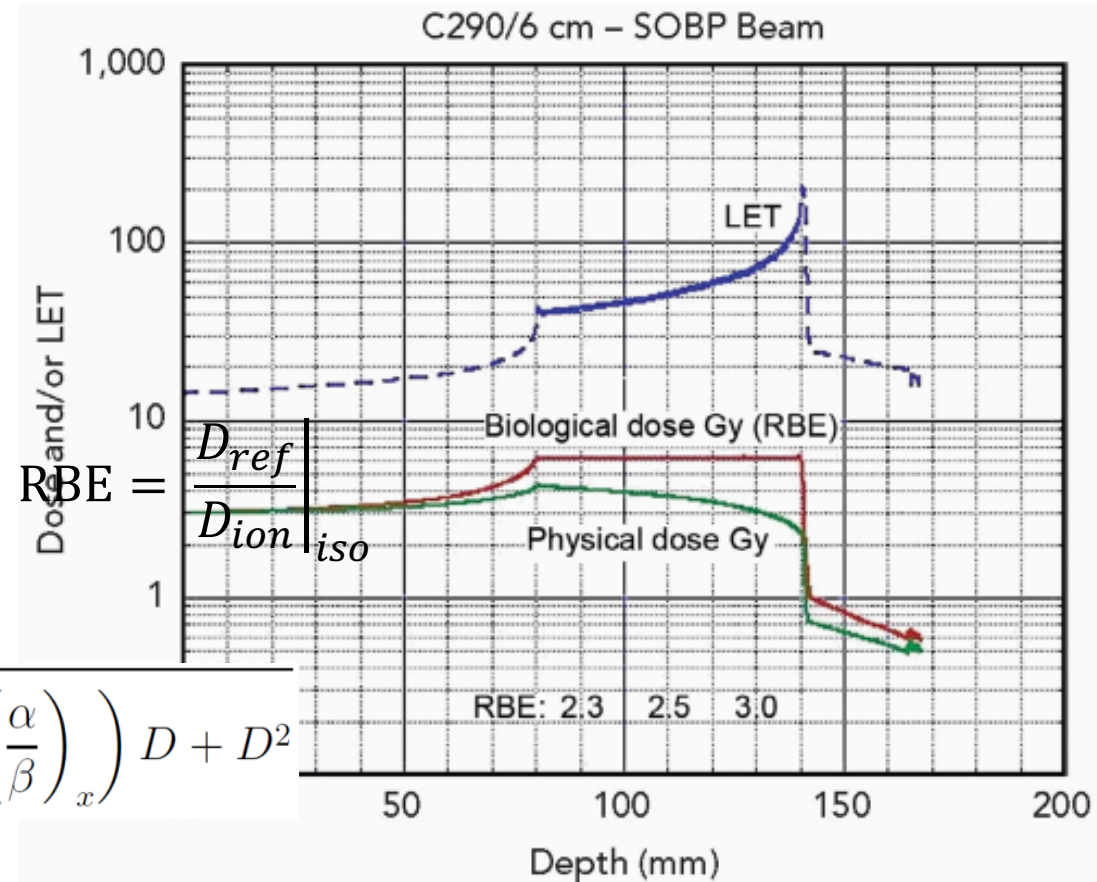
- Increased biological effectiveness at end of range

- Cell survival vs. dose: $S = \exp(-\alpha D - \beta D^2)$

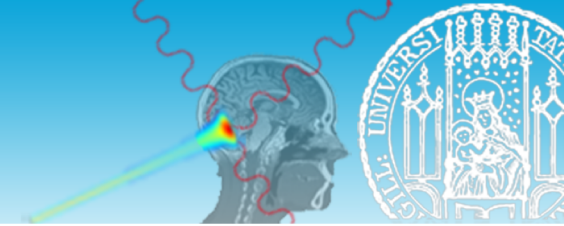
- From photons to protons: $\frac{\alpha_p}{\alpha_x} := 1 + \frac{q}{(\alpha/\beta)_x} \cdot L$

- Relative biological effectiveness (RBE) to photons: $RBE = \frac{D_{ref}}{D_{ion,iso}}$

$$RBE \left(\left(\frac{\alpha}{\beta} \right)_x, L, D \right) = -\frac{1}{2D} \left(\frac{\alpha}{\beta} \right)_x + \frac{1}{D} \times \sqrt{\frac{1}{4} \left(\frac{\alpha}{\beta} \right)_x^2 + \left(qL + \left(\frac{\alpha}{\beta} \right)_x \right) D + D^2}$$

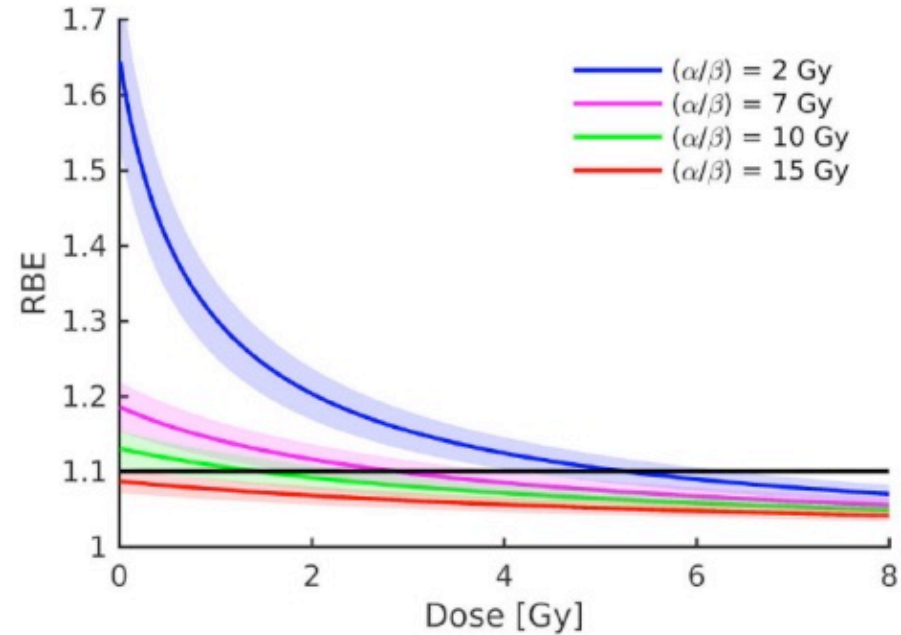
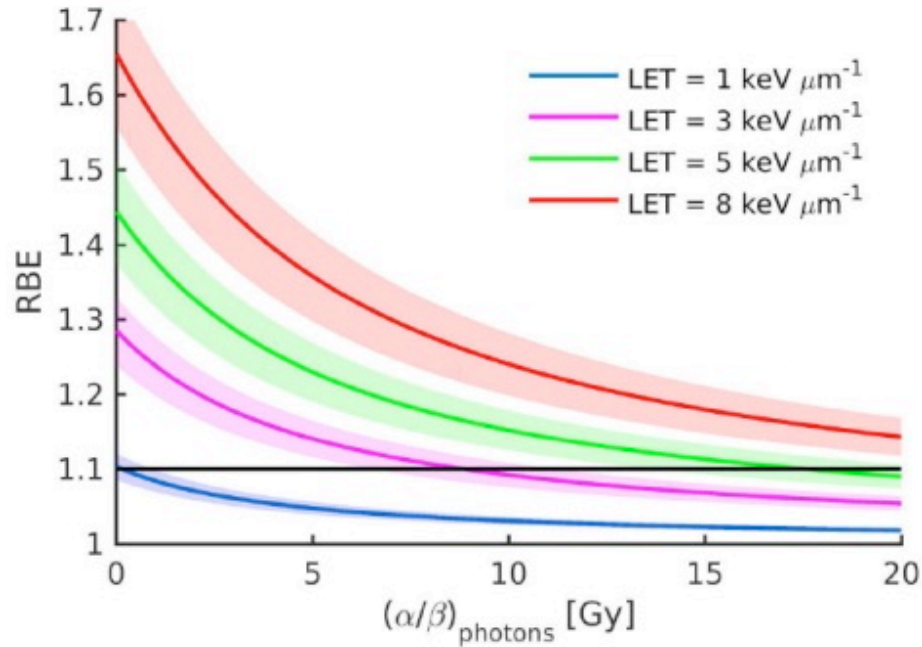


- Protons: almost constant RBE, assumed 1.1



- Radiobiological dependencies and uncertainties (dose, LET, tissue type)

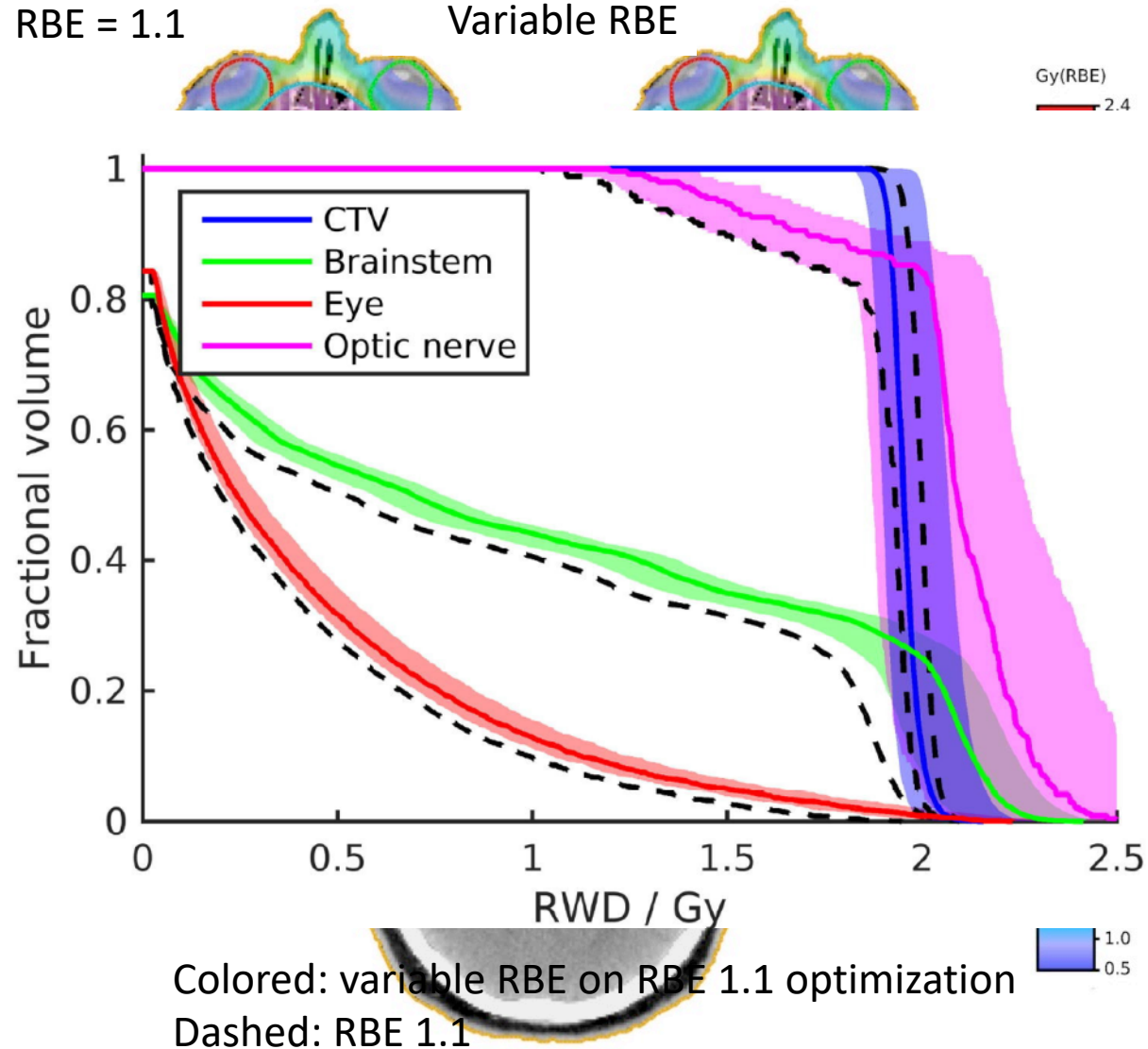
Resch A., ..., Dedes G. Phys Med. 2017 Apr;36:91-102

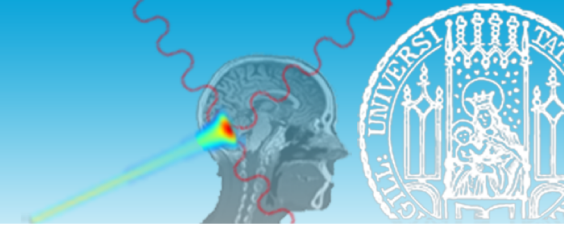


- Uncertainties stem from data based modeling

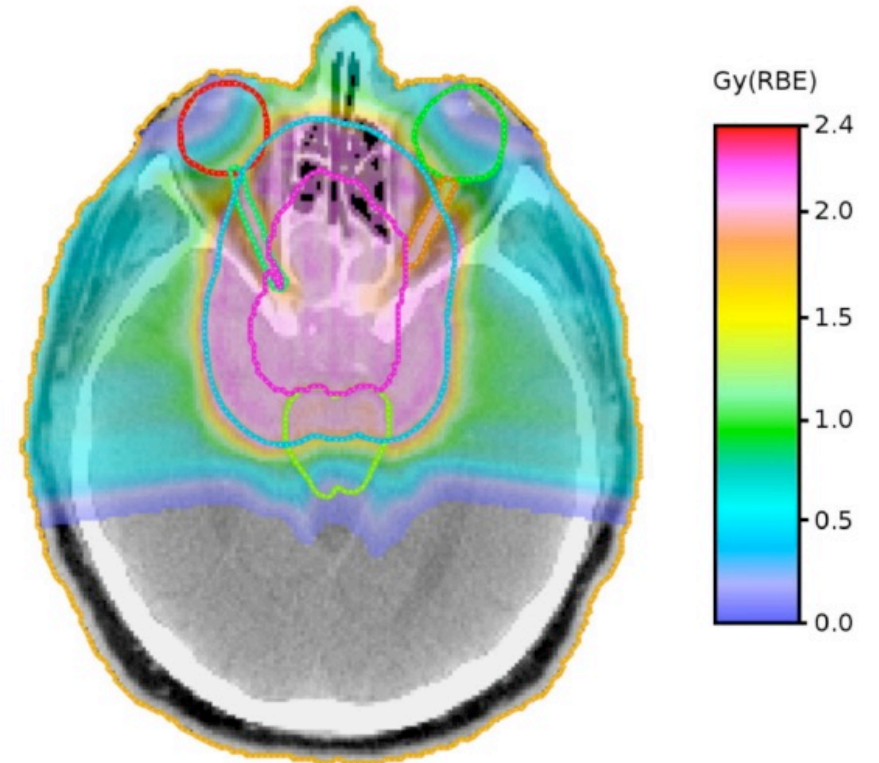
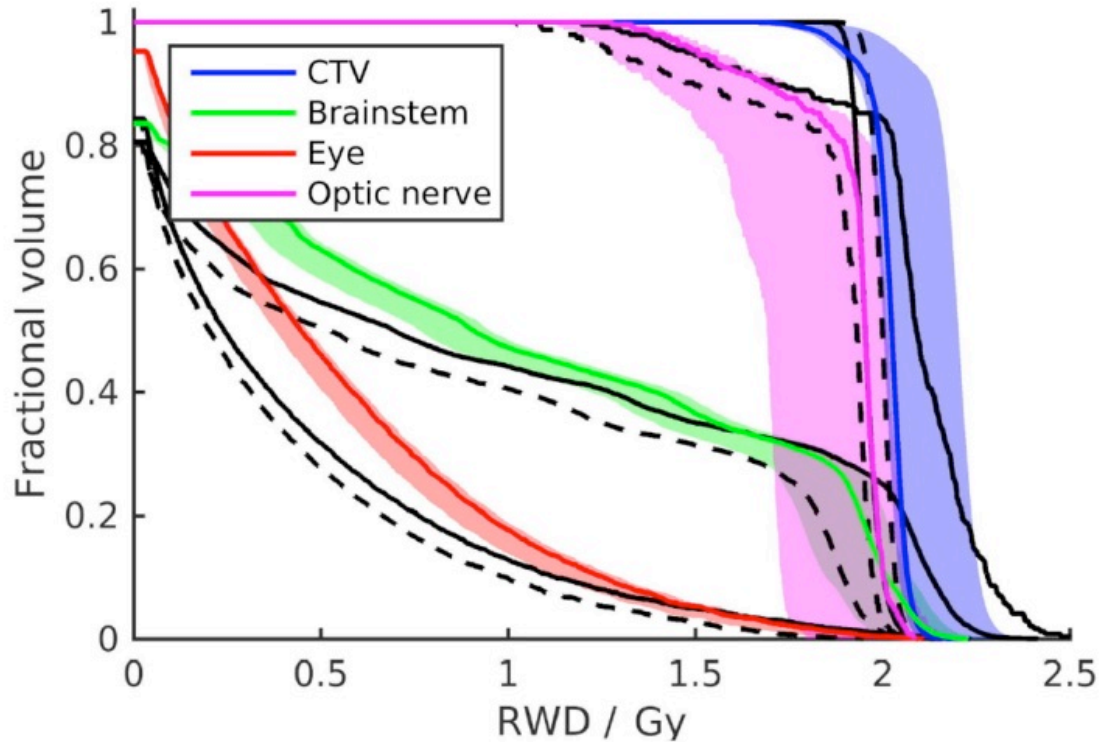


- RBE=1.1 vs variable RBE treatment plans
- Still different when modelling uncertainties included?





- Optimal plans: variable RBE and model uncertainties included



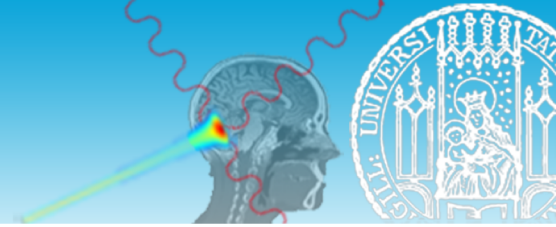
Resch A., ..., Dedes G. Phys Med. 2017 Apr;36:91-102

Colored: biological effect optimization
 Dashed: RBE 1.1 optimization
 Solid: variable RBE on RBE 1.1 optimization

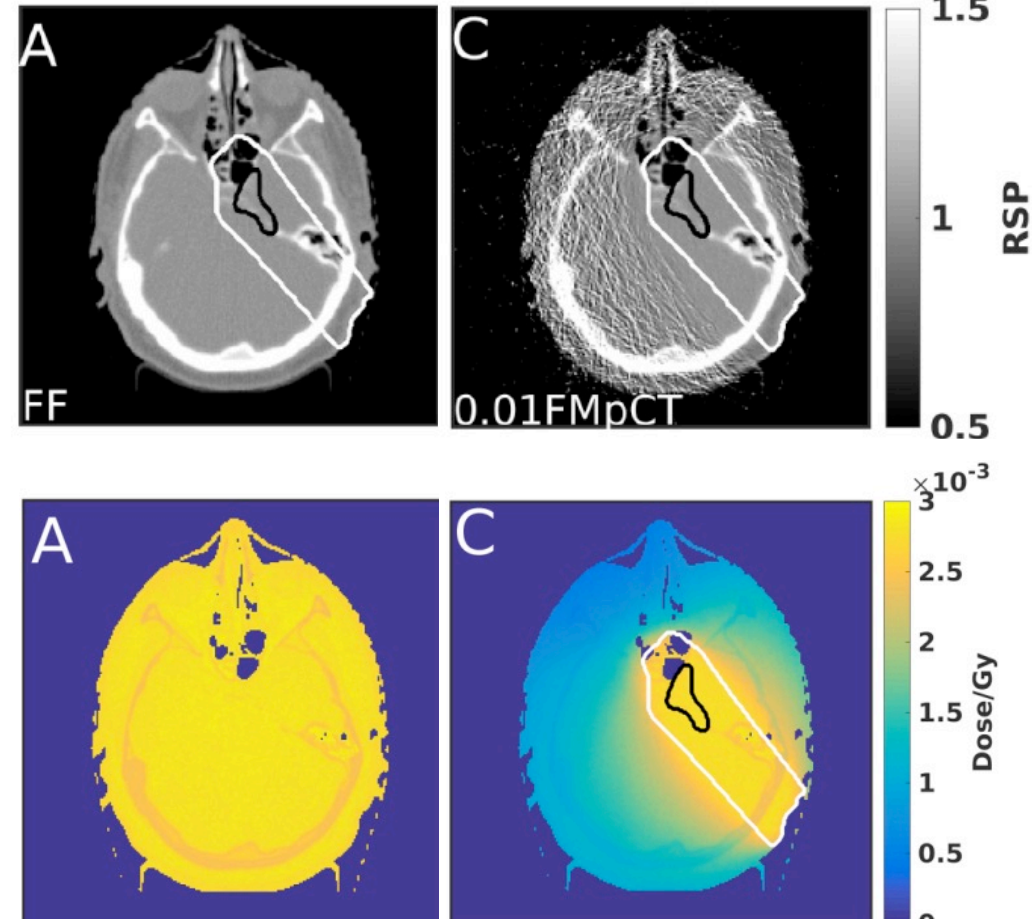
Proton imaging for plan adaptation - general



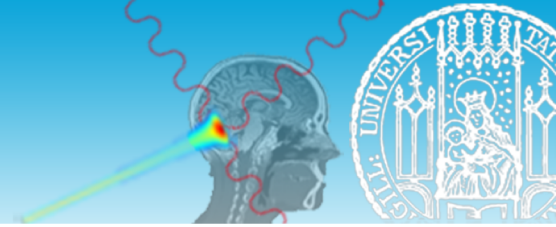
- Patient treatment in ~30 sessions (fractions)
- Image guidance prior each session desirable
- Imaging dose from ~30 pCT/cone beam CT (CBCT) similar to low dose bath from therapy
- Although low (hundreds of mGy), can contribute to second cancer risk
- Reduce dose to healthy tissue/retain image quality?



- Constant imaging fluence:
 - Constant dose
 - Spatially fixed image quality
- Optimized imaging fluence:
 - Retain image quality in a region of interest (ROI)
 - Minimize dose to other regions

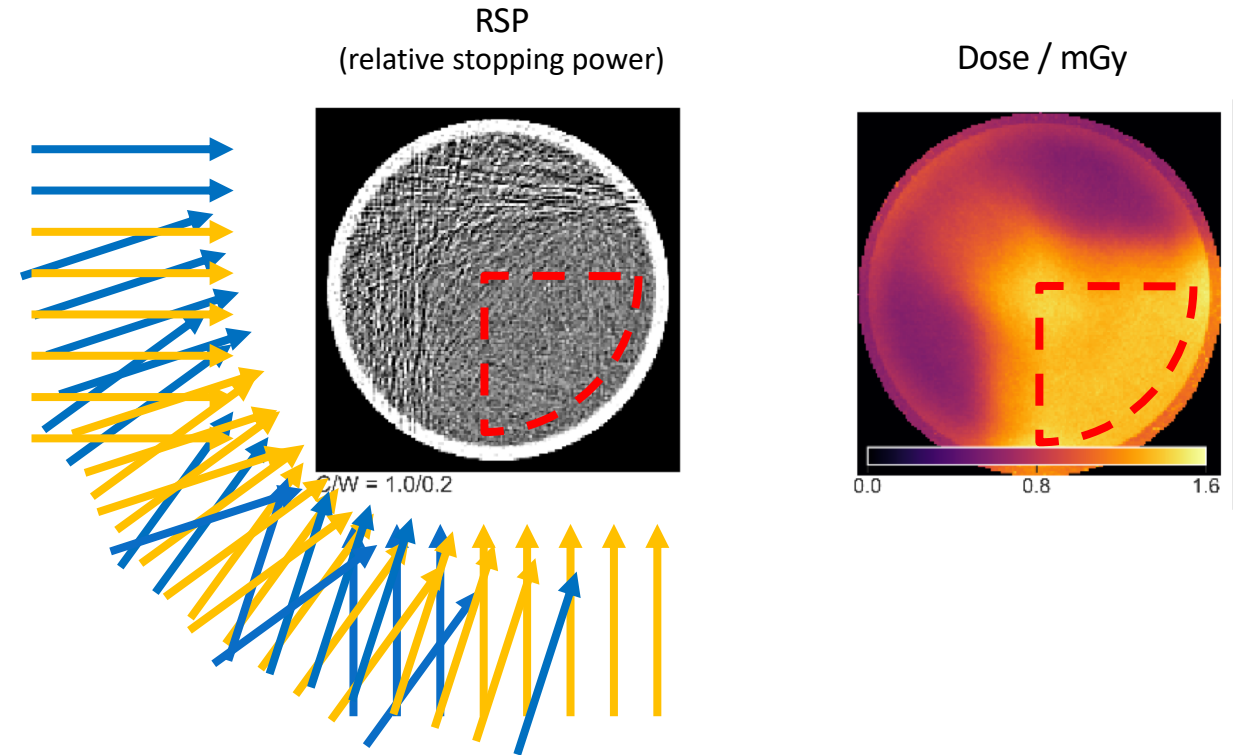


Dedes G., et al. Phys Med Biol. 2017 Jul 12;62(15):6026-604



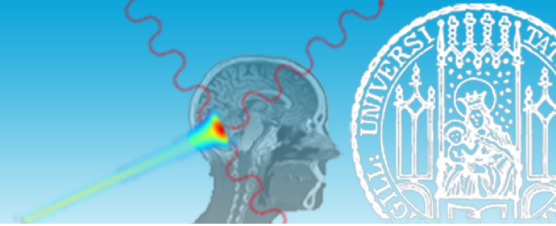
- Basic implementation:

- Clinical facilities: pencil beam (PB) scanning
- Exploit clinical narrow proton beams
- Determine fluence depending on intersection with ROI
- Fluence modulated pCT (FMpCT)

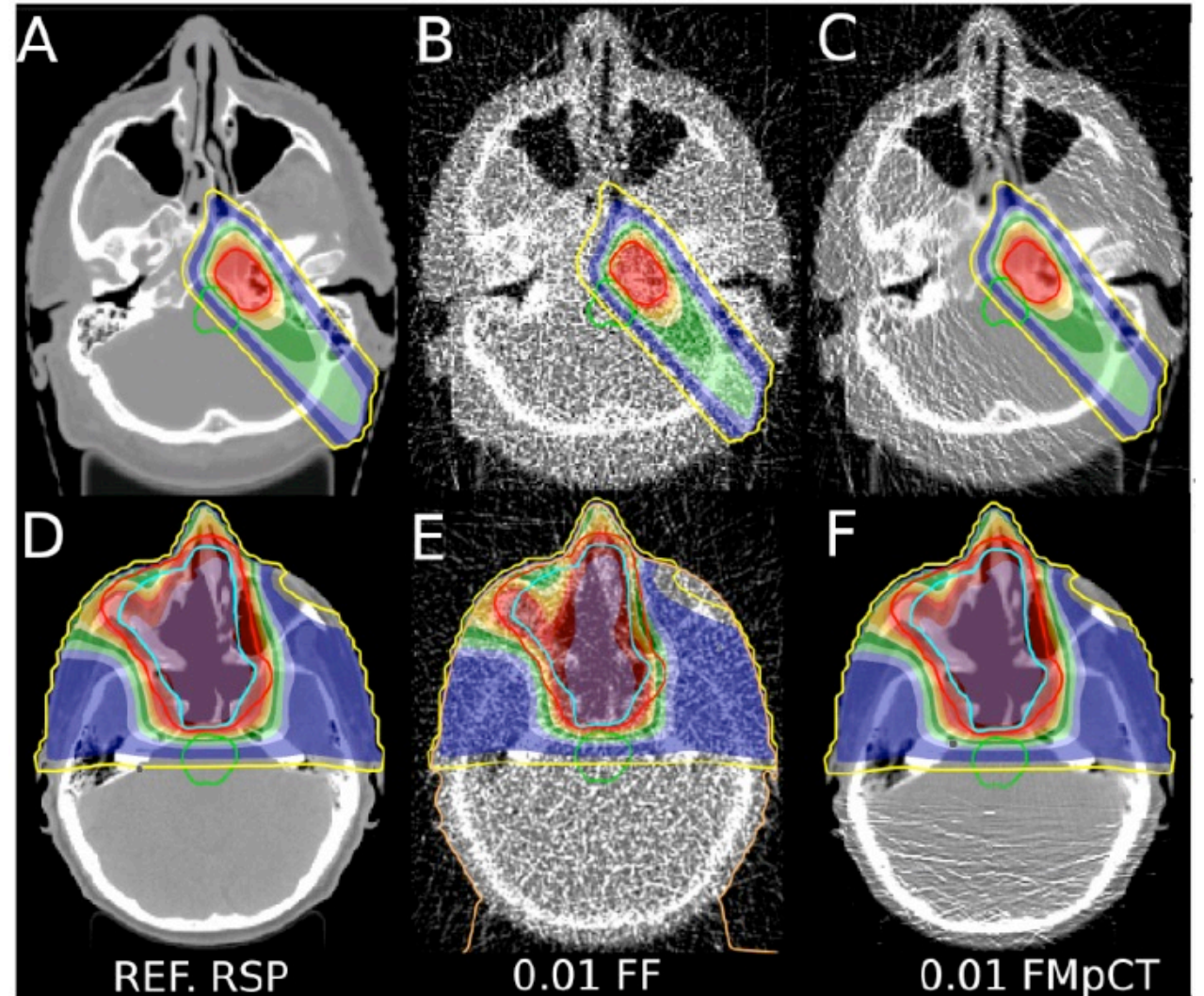


- Disadvantage: non-prescribed image quality

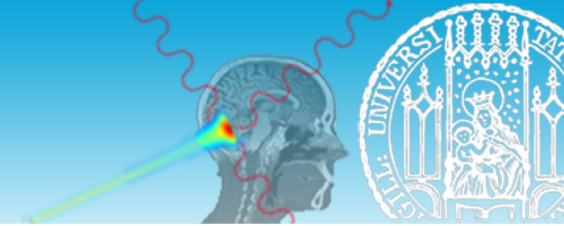
Dickmann J., ..., Dedes G.. Med Phys. 2020 Apr;47(4):1895-190



- Simulated results on patient anatomies
- Dose reduction to healthy tissues:
 - 35 – 55%
- Dependent on ROI size/shape
- Need to understand noise formation and control it

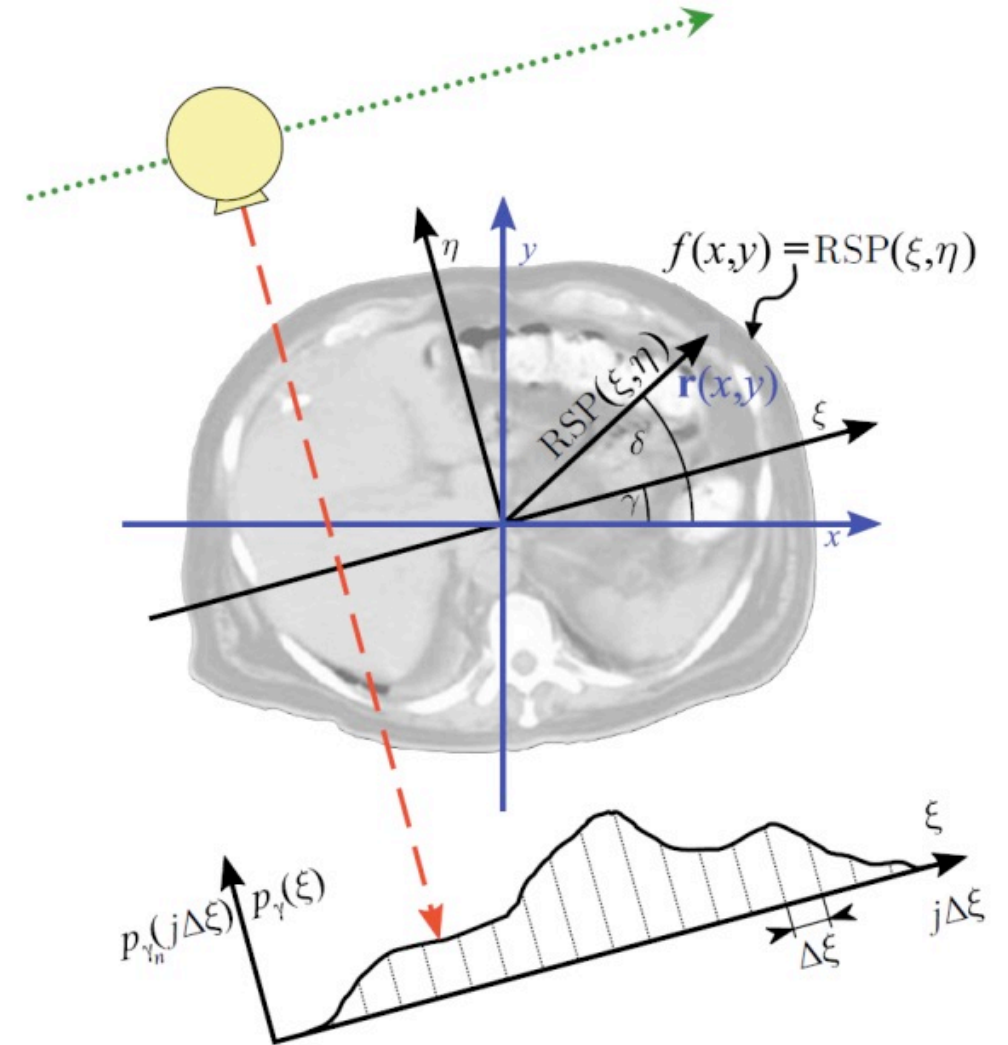


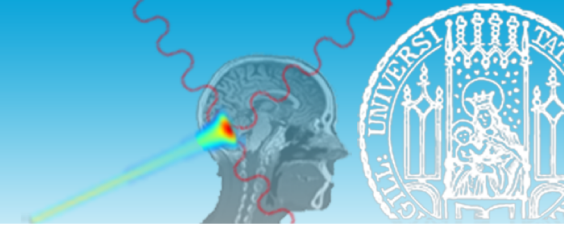
Proton imaging – image reconstruction



- Filtered backprojection:

$$f(x, y) = \frac{\pi}{N_p} \sum_{n=1}^{N_p} h_{\gamma_n} (x \cos(\gamma_n) + y \sin(\gamma_n))$$





- Variance on the projection:

$$\sigma_{\gamma_n}^2(j\Delta\xi) = \frac{\sigma_{\text{WEPL},\gamma_n}^2(j\Delta\xi)}{N_{\gamma_n}(j\Delta\xi)}$$

- WEPL variance:

$$\sigma_{\text{WEPL}}^2 = \left(\frac{\partial \text{WEPL}(\bar{E}_{\text{out}})}{\partial E} \right)^2 \cdot \sigma_{E_{\text{out}}}^2 = \frac{\sigma_{E_{\text{out}}}^2}{S_{\text{W}}^2(\bar{E}_{\text{out}})}$$

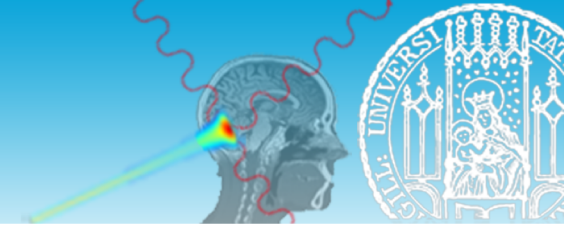
- Final projection variance:

$$\sigma_{\gamma_n}^2(j\Delta\xi) = \frac{\sigma_{E_{\text{out}},\gamma_n}^2(j\Delta\xi)}{N_{\gamma_n}(j\Delta\xi) \cdot S_{\text{W}}^2(\bar{E}_{\text{out},\gamma_n}(j\Delta\xi))}$$

- FBP noise reconstruction:

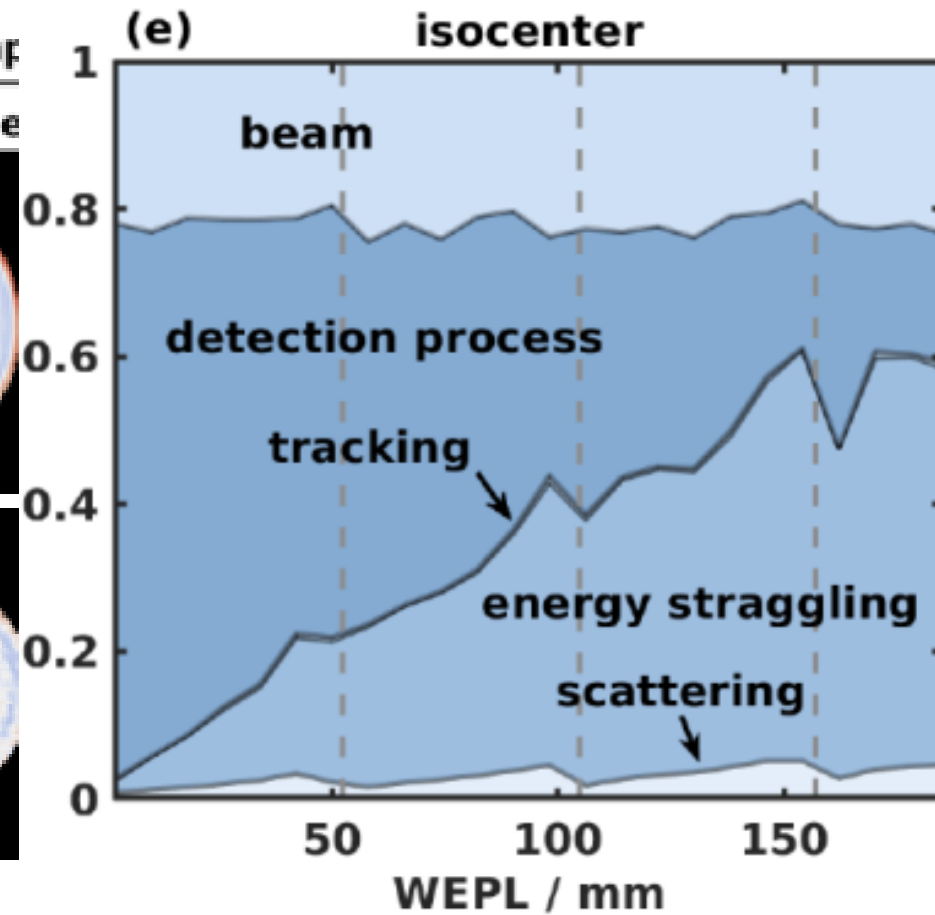
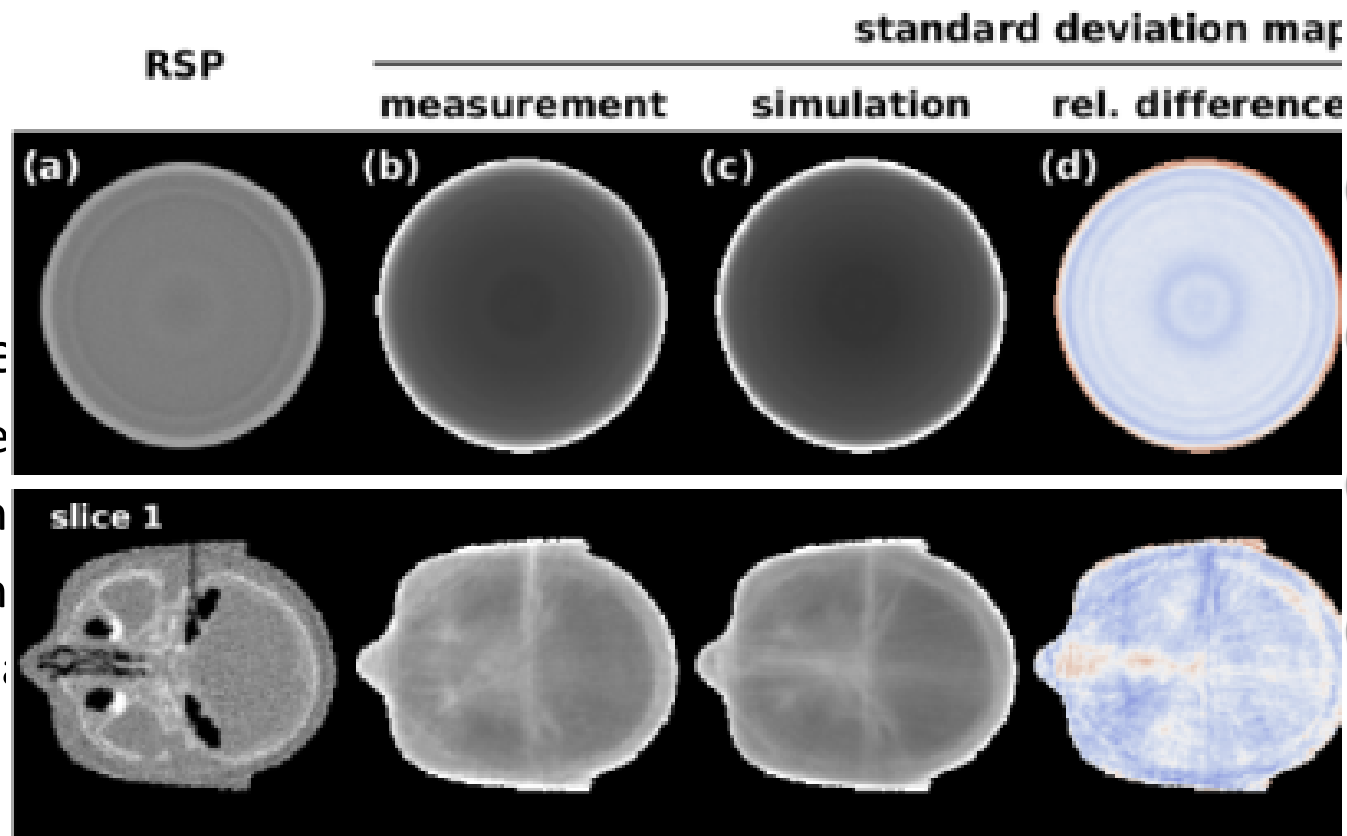
$$\text{Var}[f(x_p, y_p)] = f_{\text{interp},\mu} \left(\frac{\pi}{N_p} \Delta\xi \right)^2 \sum_{n=1}^{N_p} V_{\gamma_n}(j\Delta\xi)$$

Proton imaging – FMpCT noise validation

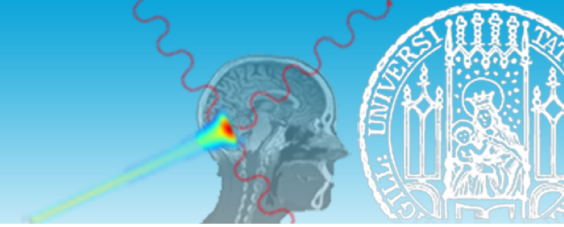


- Experimental and simulated validation of pCT noise theory:

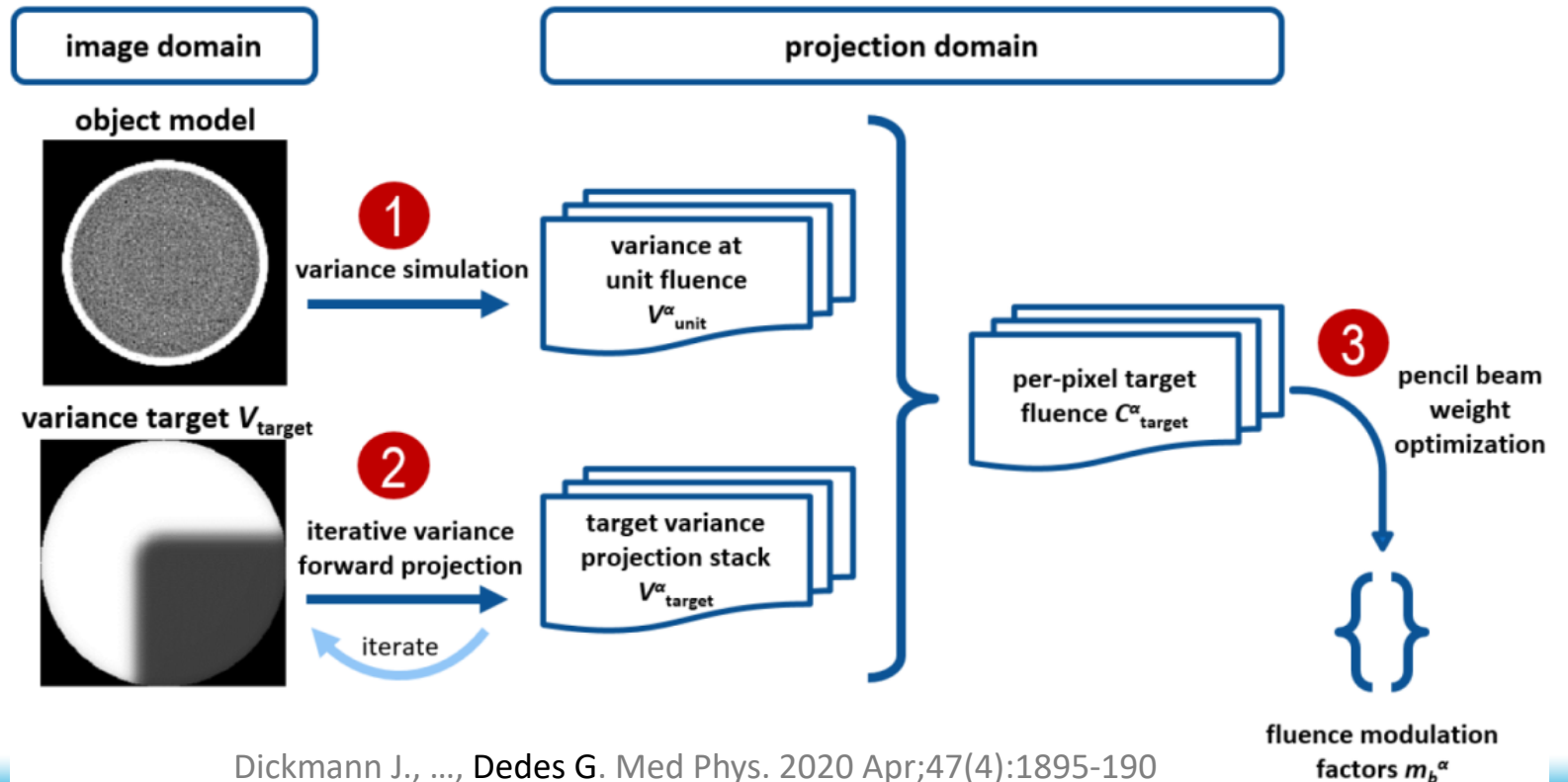
- Noise
 - Beam
 - Energy
 - Energy
 - Scattering



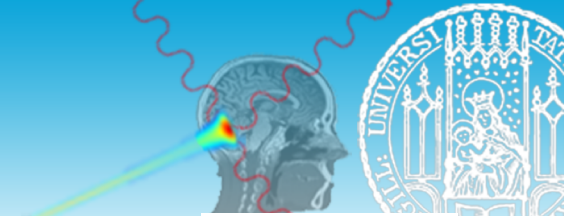
Proton imaging – FMpCT optimization



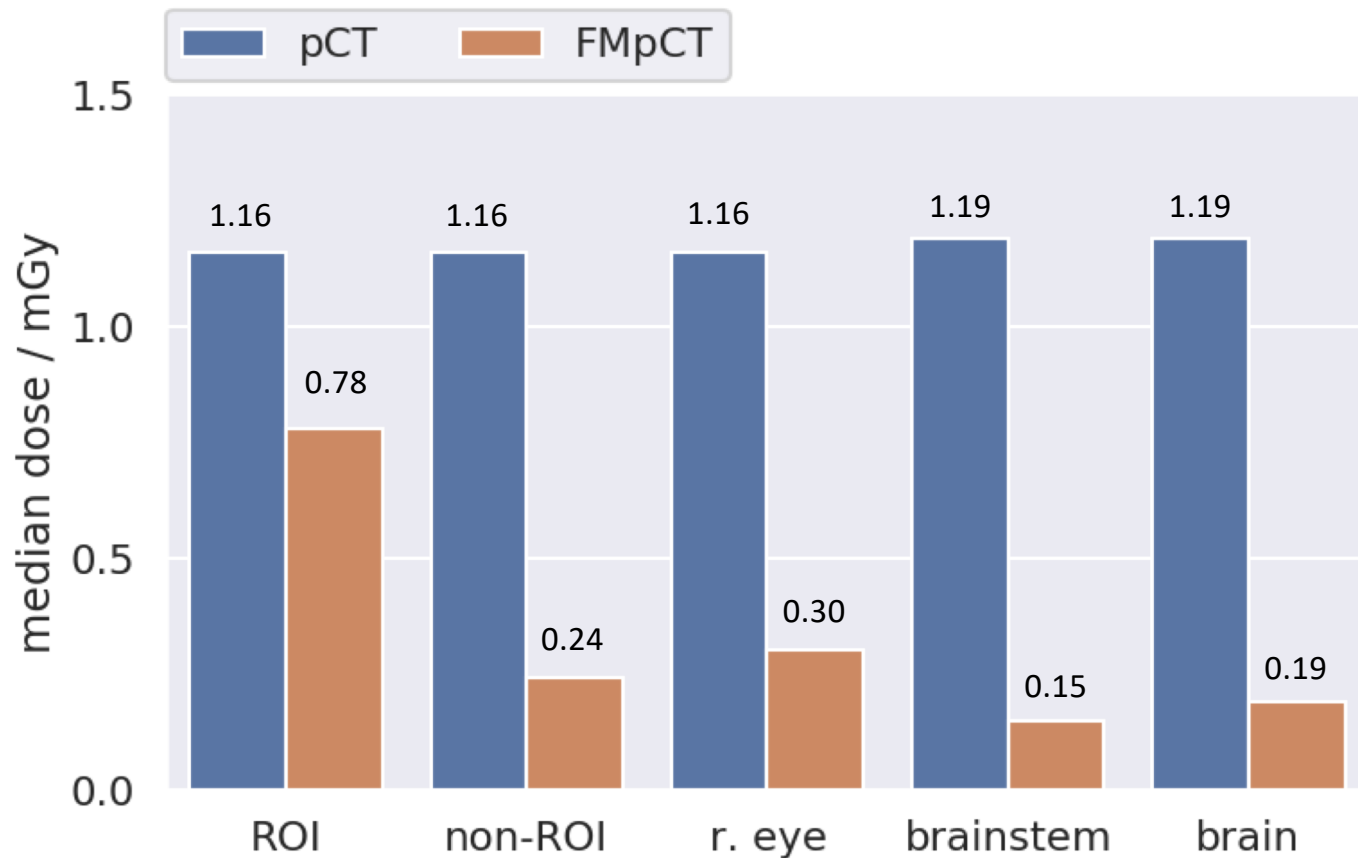
- Using pixel:
$$\sigma_{\gamma_n}^2(j\Delta\xi) = \frac{\sigma_{E_{out},\gamma_n}^2(j\Delta\xi)}{N_{\gamma_n}(j\Delta\xi) \cdot S_W^2(\bar{E}_{out,\gamma_n}(j\Delta\xi))}$$
- Noise target / fluence pattern prescription
- Iterative fluence optimization algorithm



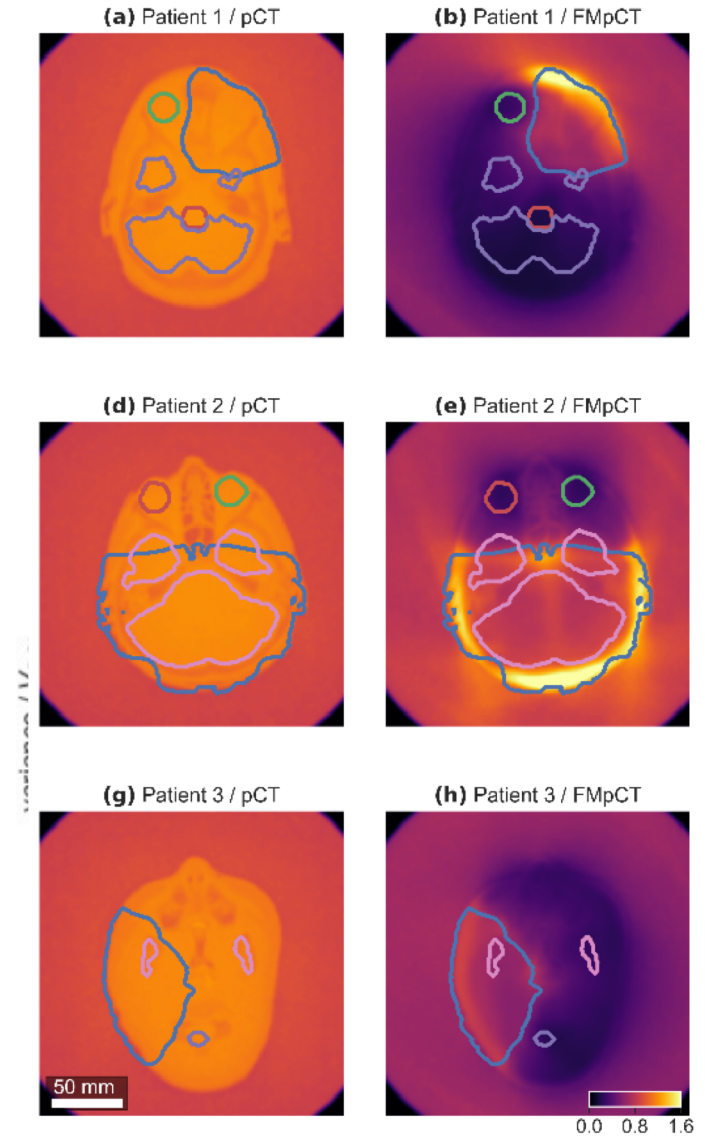
Proton imaging – FMpCT optimization



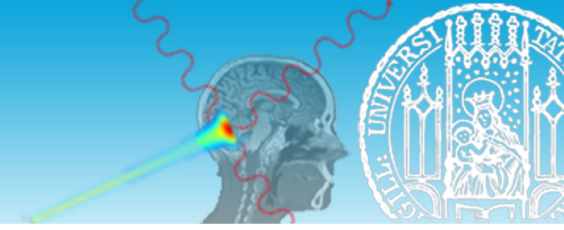
- Optimized fluences applied to simulated acquisitions



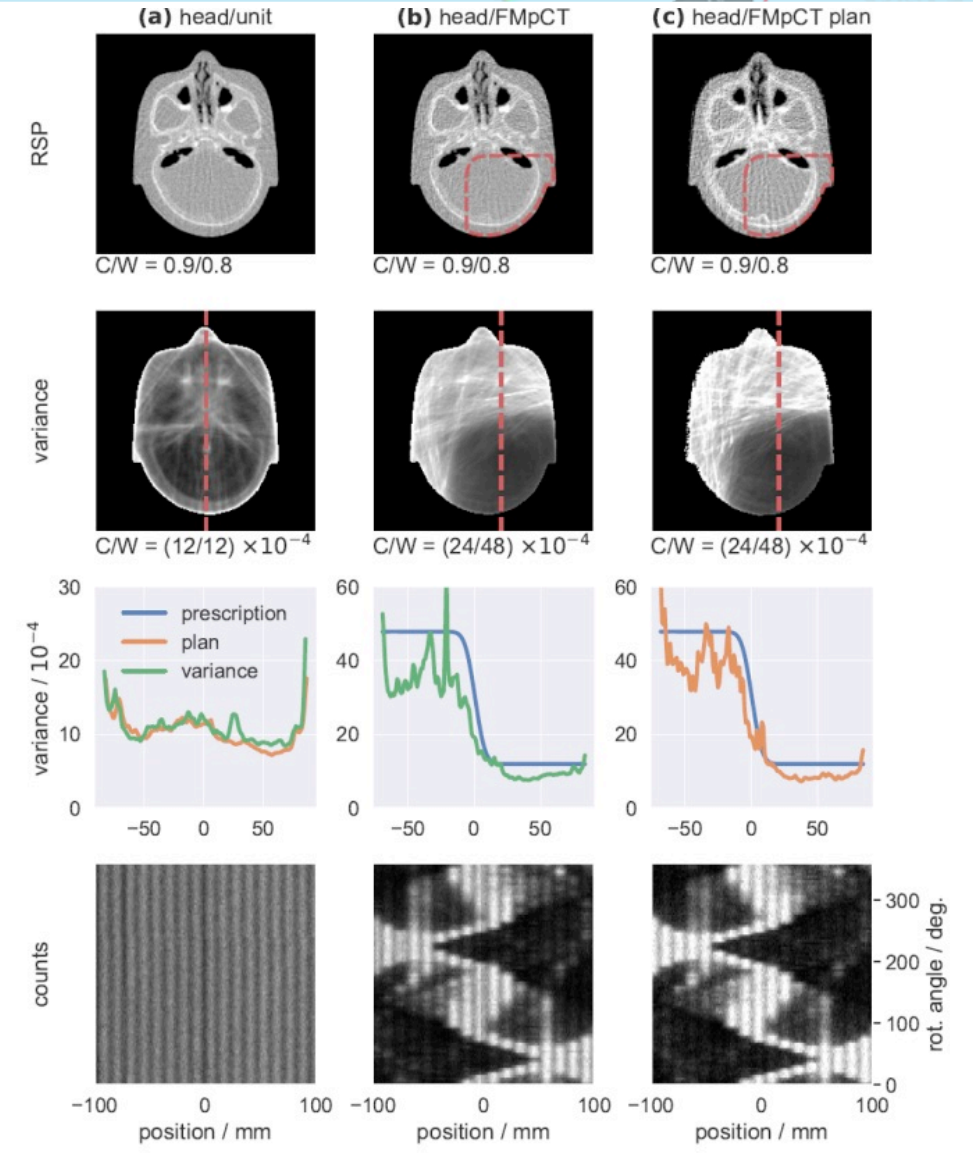
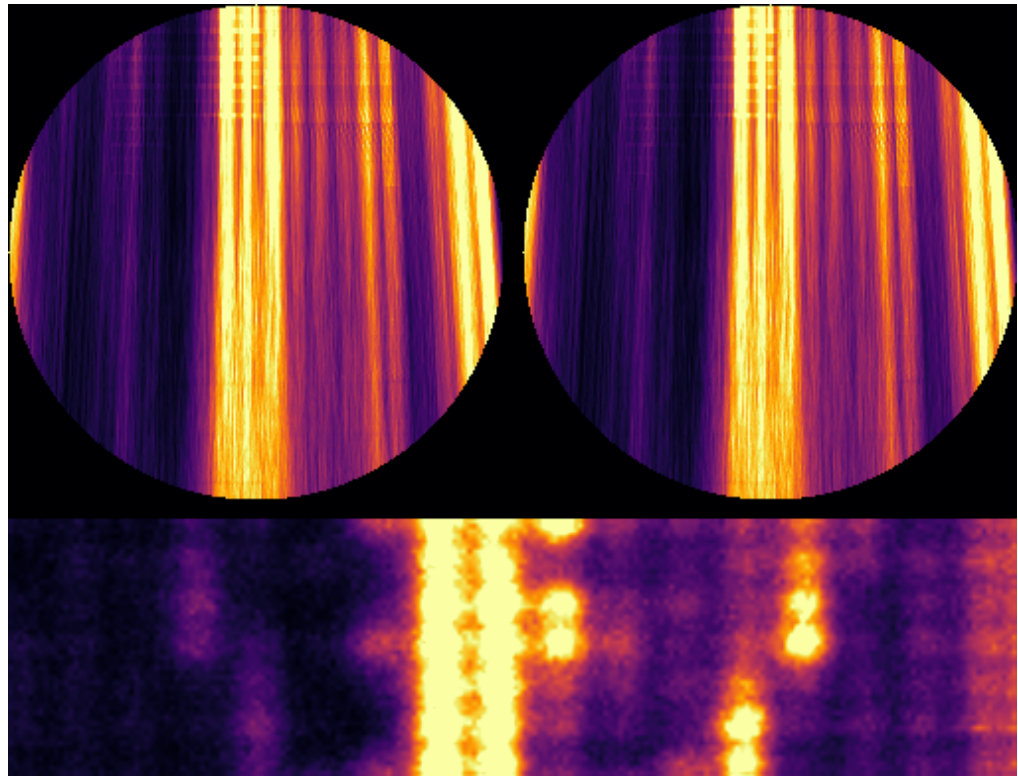
Dickmann J., ..., Dedes G. Med Phys. 2020 Apr;47(4):1895-190



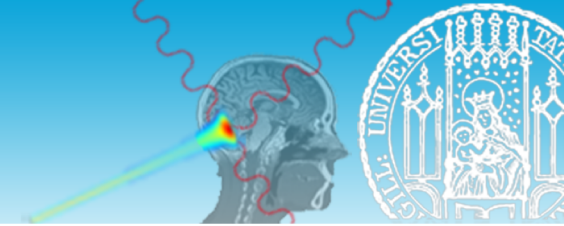
Proton imaging – FMpCT optimization



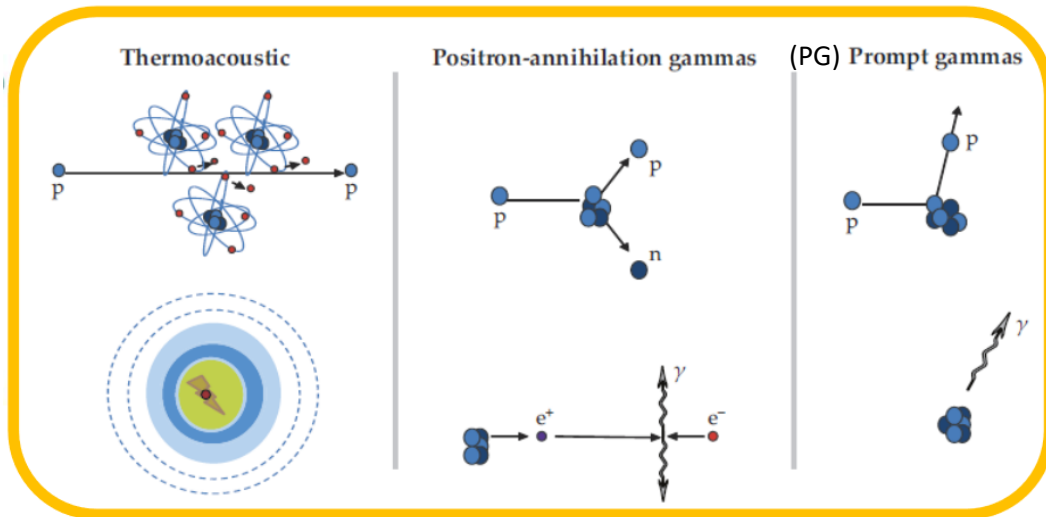
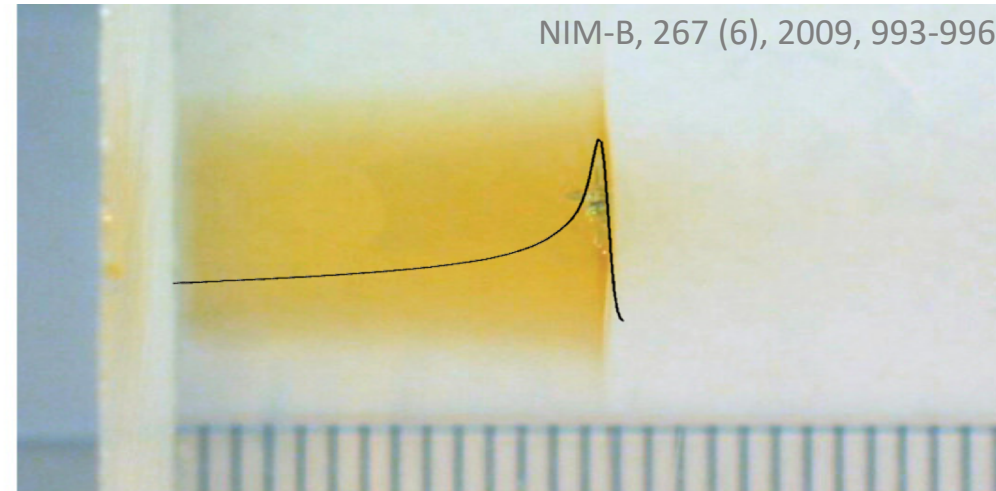
- Experimental implementation of optimized FMpCT



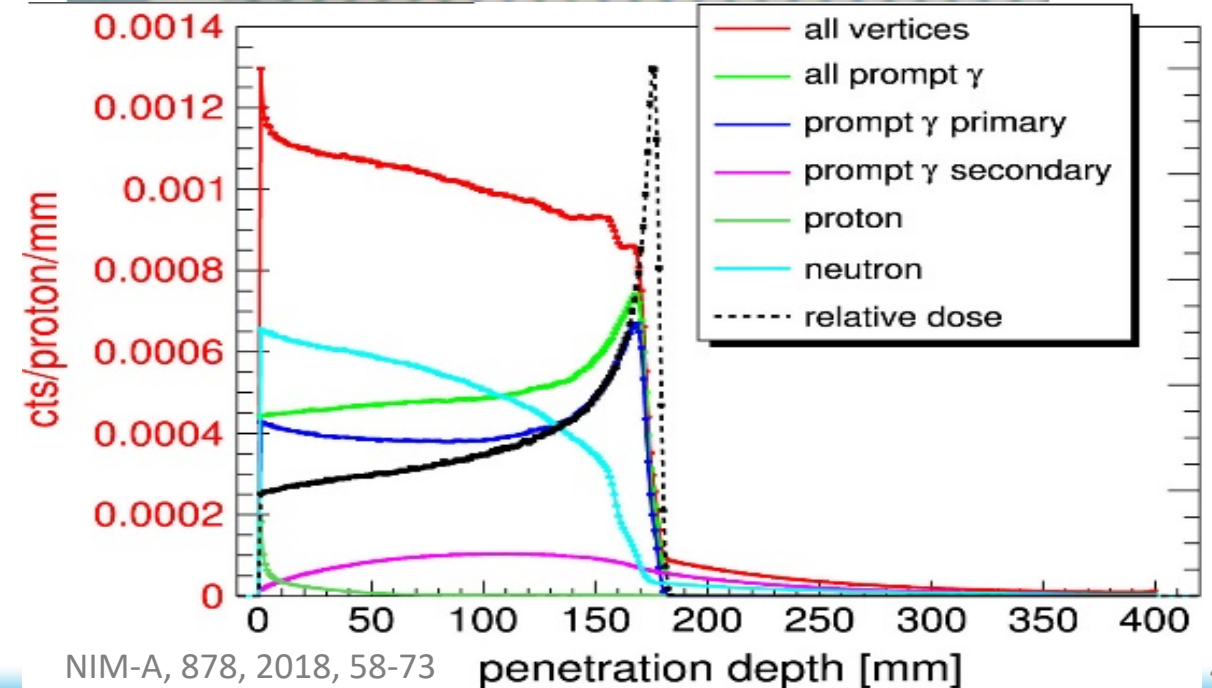
Ion beam range monitoring – general



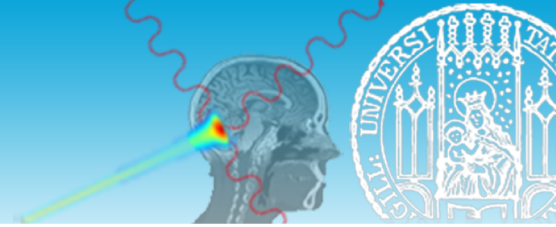
- The ion beam stops in the patient
- How to monitor the Bragg peak position?
 - By means of secondary emission
 - Origin: beam induced nuclear interactions
 - Or thermoacoustic



Physics Today 68(10), 28 (2015)

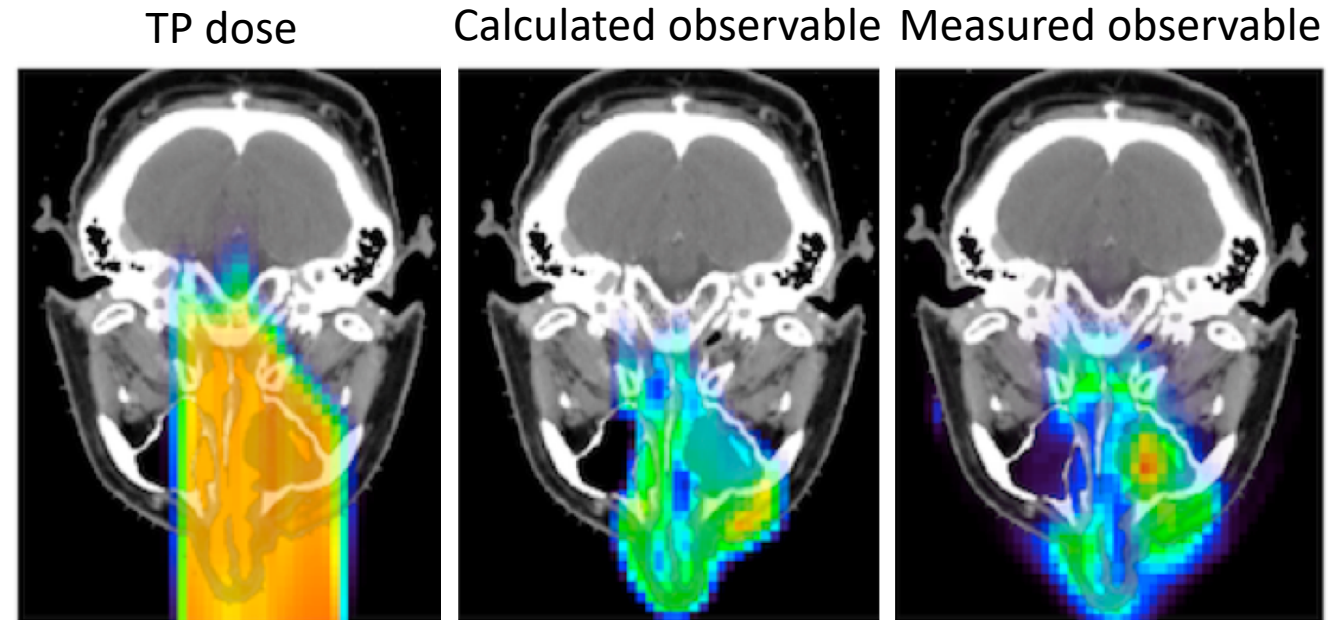


NIM-A, 878, 2018, 58-73



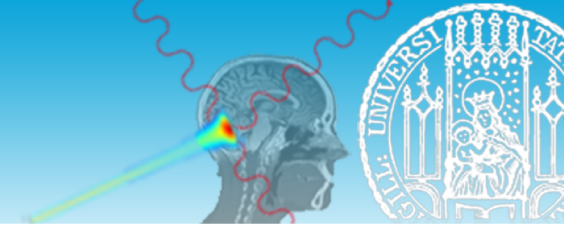
- Workflow:

- Calculate dose in treatment planning system
- Calculate monitoring observable
- Deliver dose
- Measure monitoring observable
- Compare measured and calculated observable

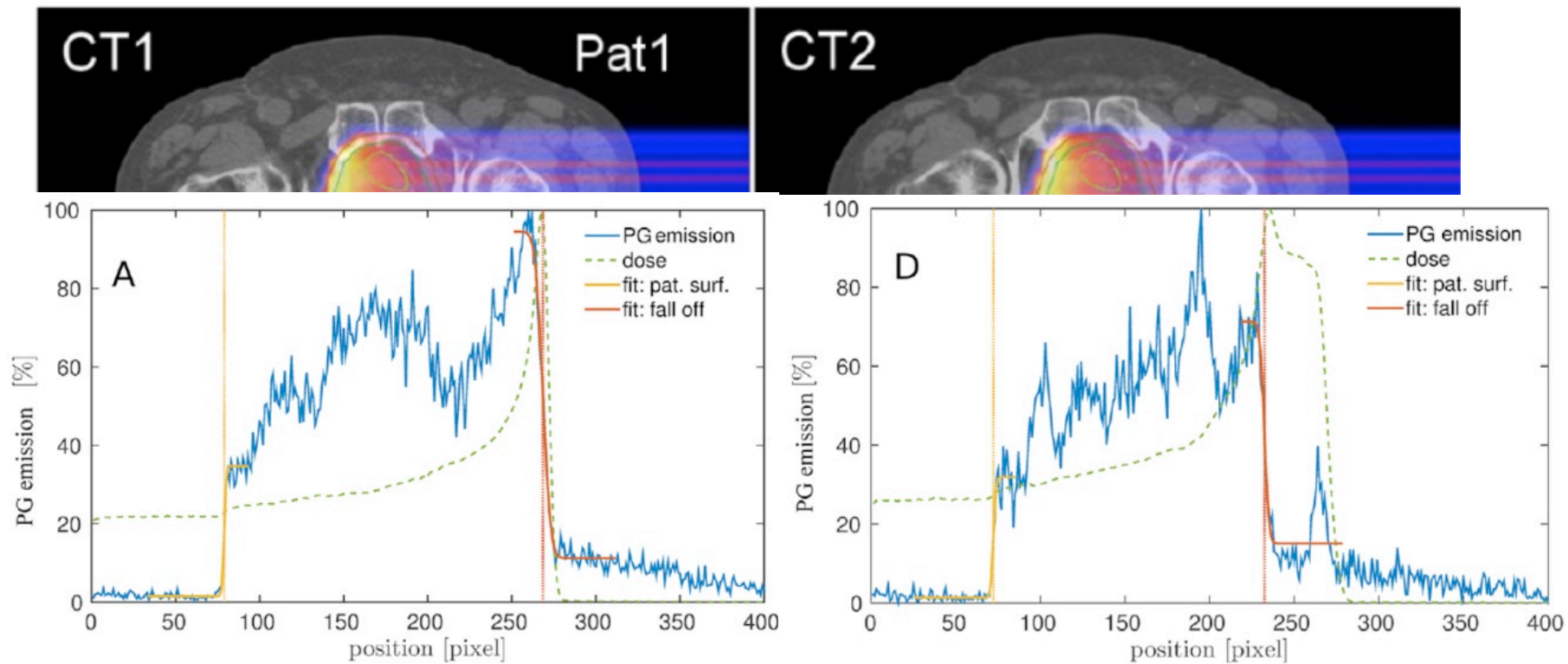


Int. J. Radiat. Oncol. Biol. Phys, 86(1), 2013, 183-189

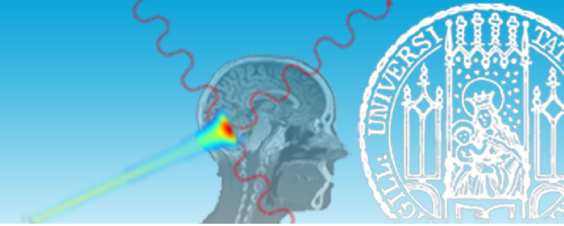
Prompt-gamma range monitoring



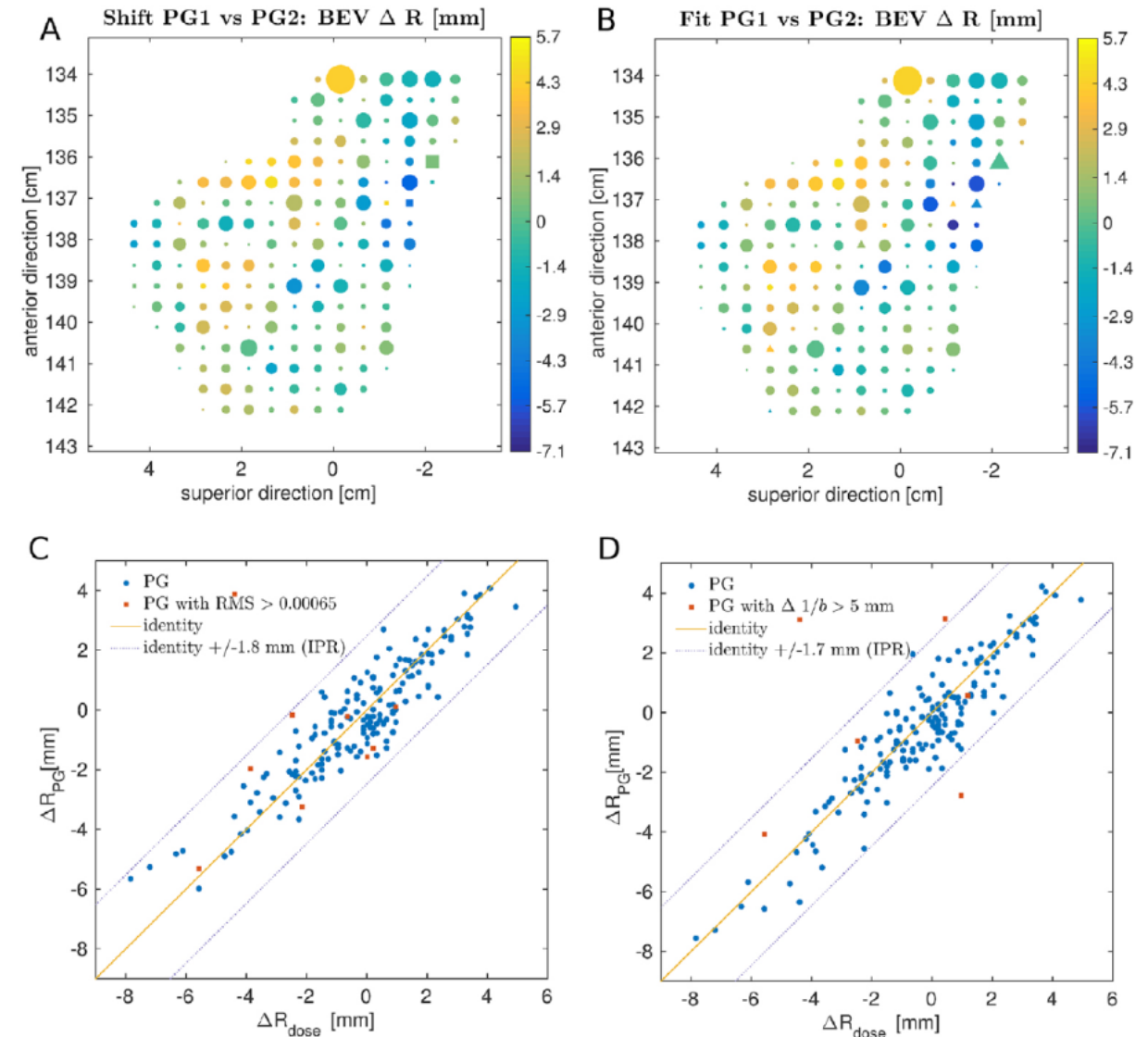
- PG range monitoring in patient anatomies

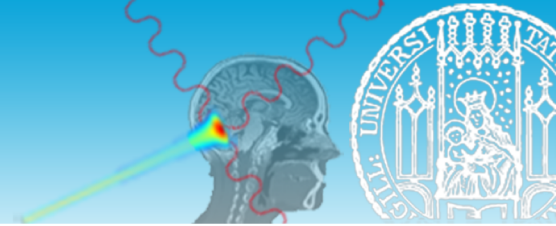


Prompt-gamma range monitoring



- Feasible PG monitoring methodology
- Performance in patient anatomies:
 - 95% of all beams within ± 2 mm
 - Median: < 1 mm
 - Discarded 10% of 1738 spots





- Proton therapy: “sharp” clinical tool, sensitive to uncertainties
- Imaging, biology, accelerator science, math can reduce these uncertainties
- Three aspects presented:
 - Proton imaging as a promising imaging tool for proton therapy
 - Radiobiology as a tool for better understanding proton therapy effectiveness
 - Range monitoring of protons beams as a clinically feasible method

<https://ionimaging2022.sciencesconf.org/>

WELCOME TO THE THIRD ION IMAGING WORKSHOP 2022

The ion imaging workshop 2022 will take place in Munich, Germany. It is the third edition after the workshops in [2018](#) and [2019](#).

Date: October 13-14, 2022

Venue: [LMU Munich](#), Germany

Important dates:

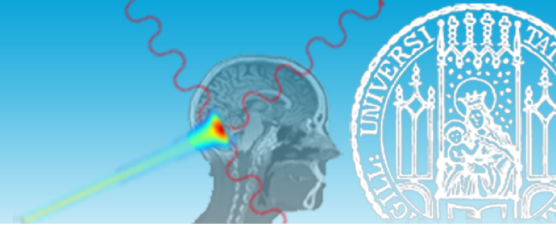
Registration is now open.

Registration fee is 180 Euro including lunches, coffee breaks, and the social dinner.

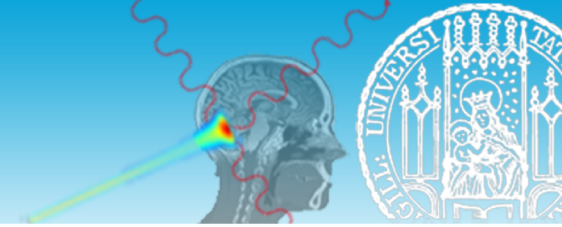
Registration deadline: September 1, 2022.

Abstract submission deadline: ~~July 15, 2022~~, extended to July 27, 2022.

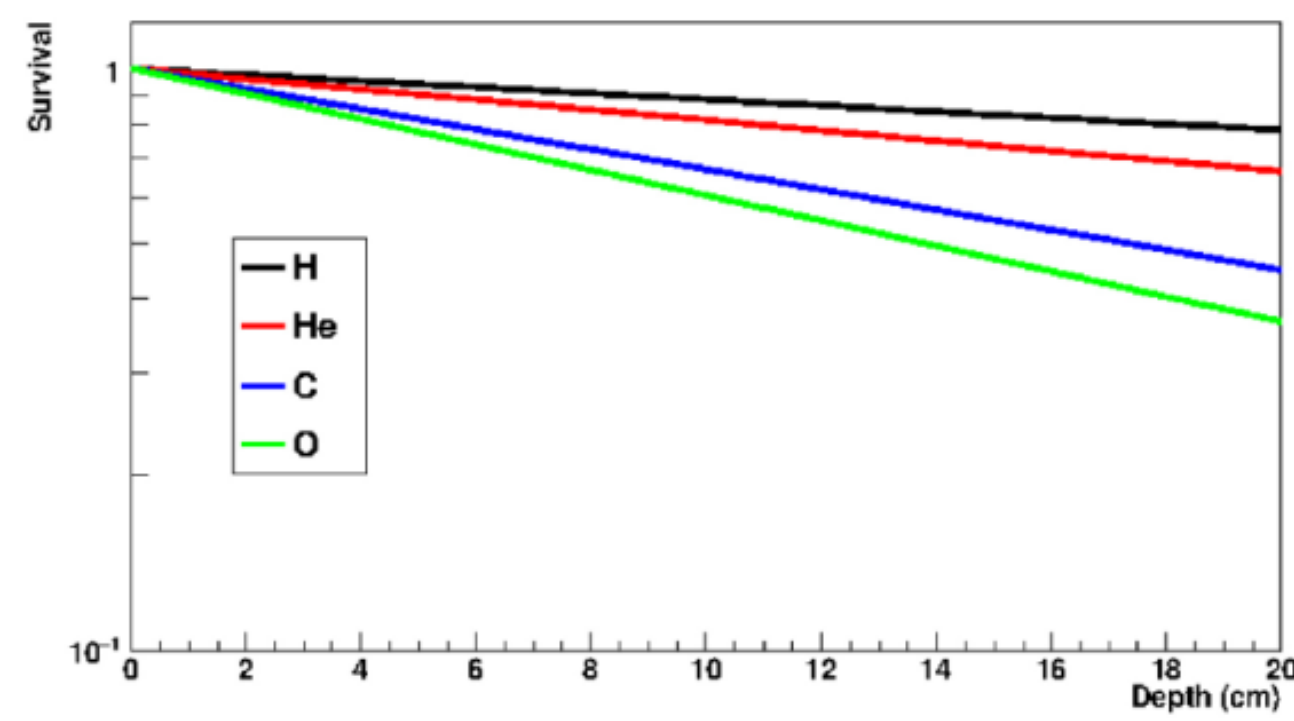
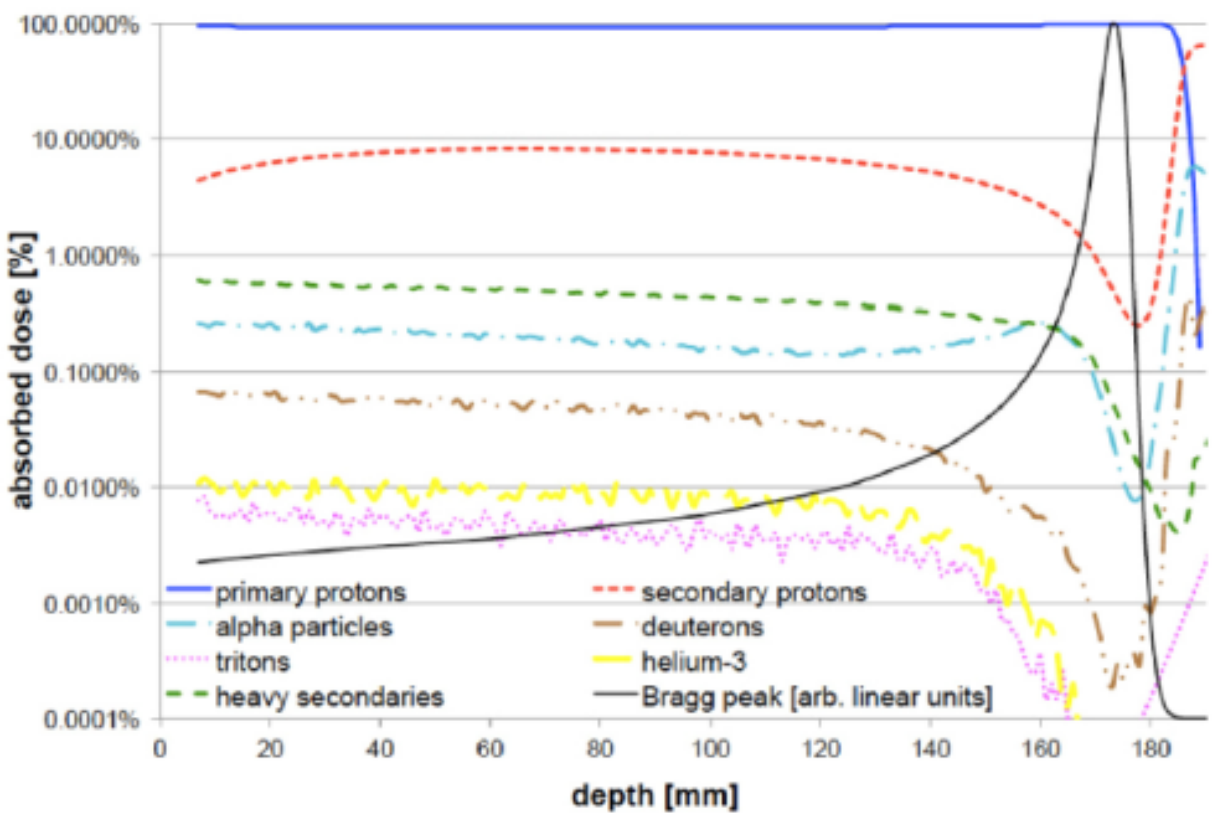
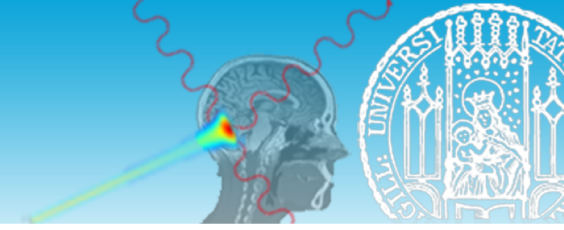
If you want to stay up-to-date about events around ion imaging, **sign up for the [ion imaging researchers mailing list](#)**.

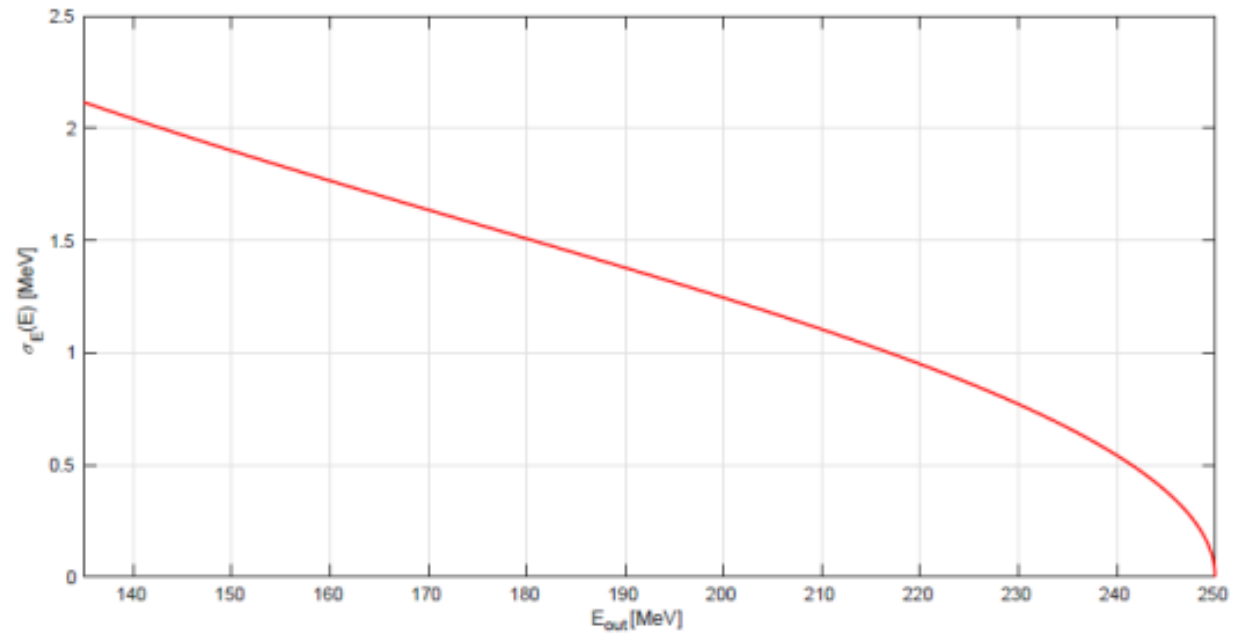
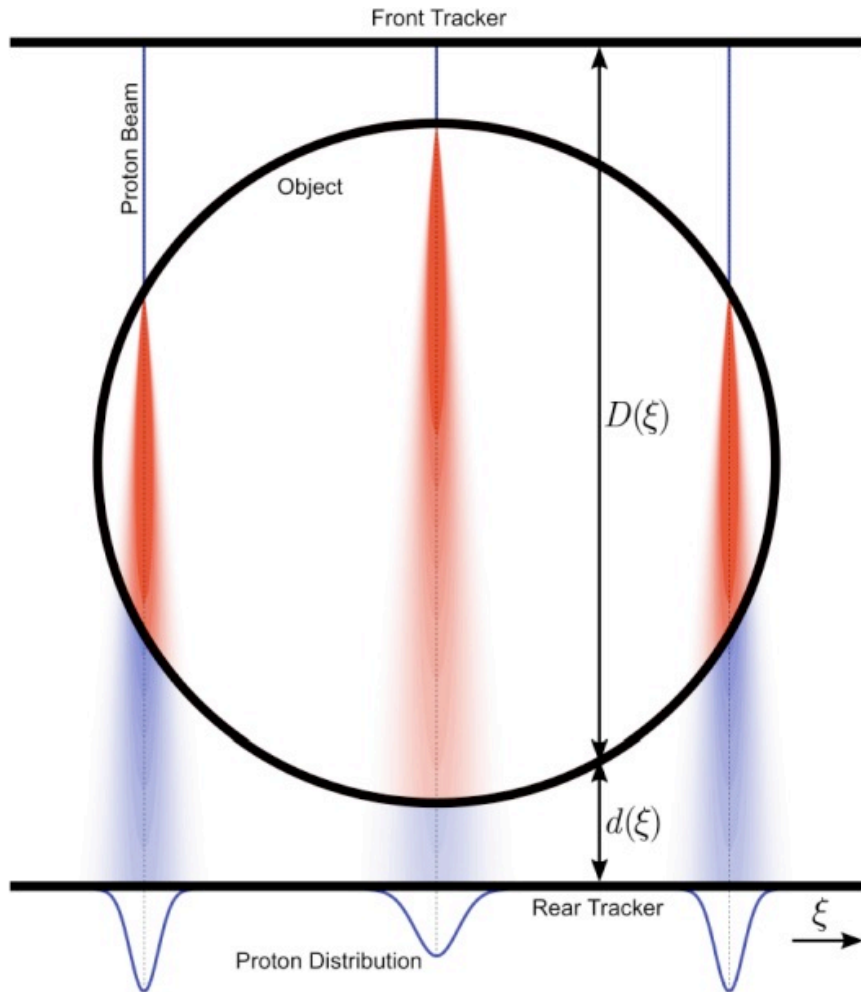
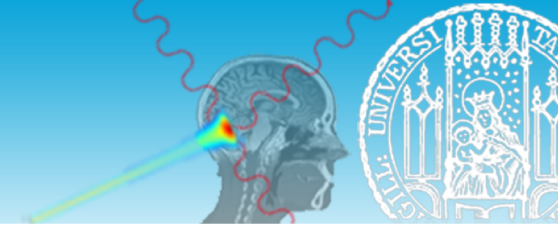


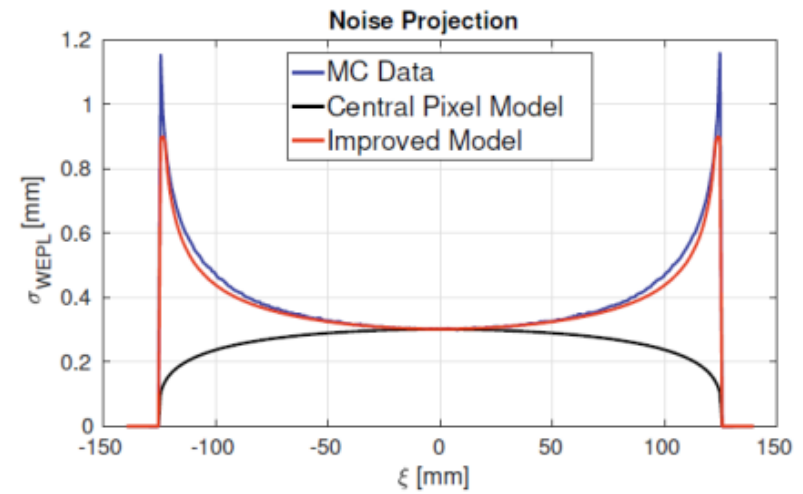
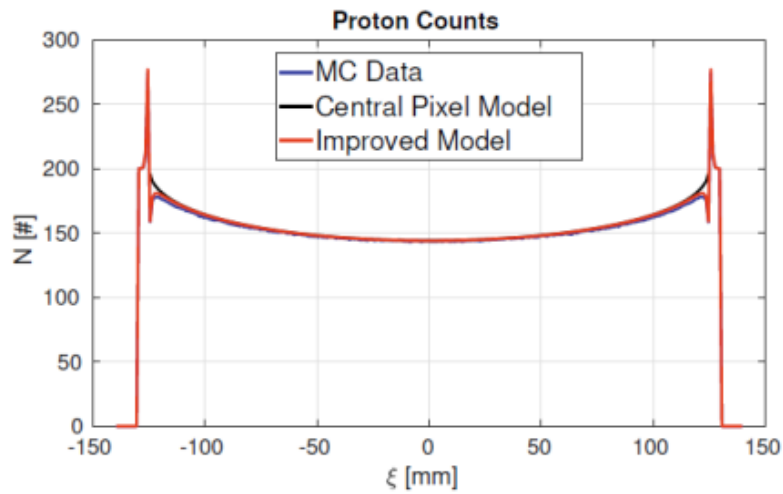
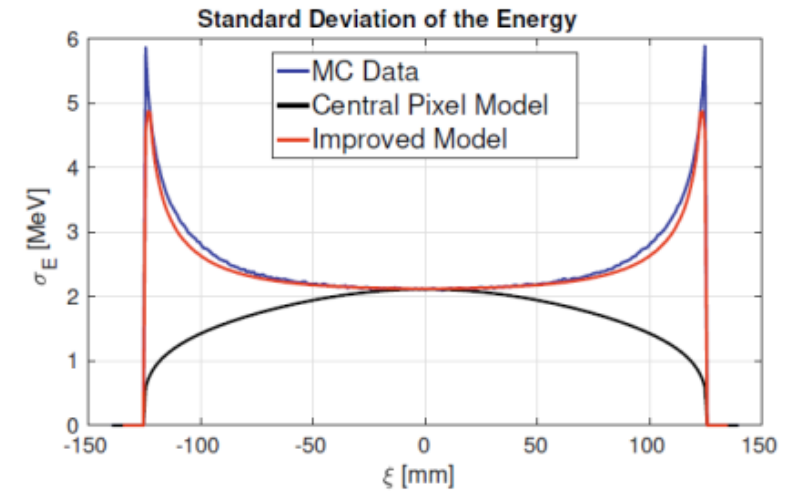
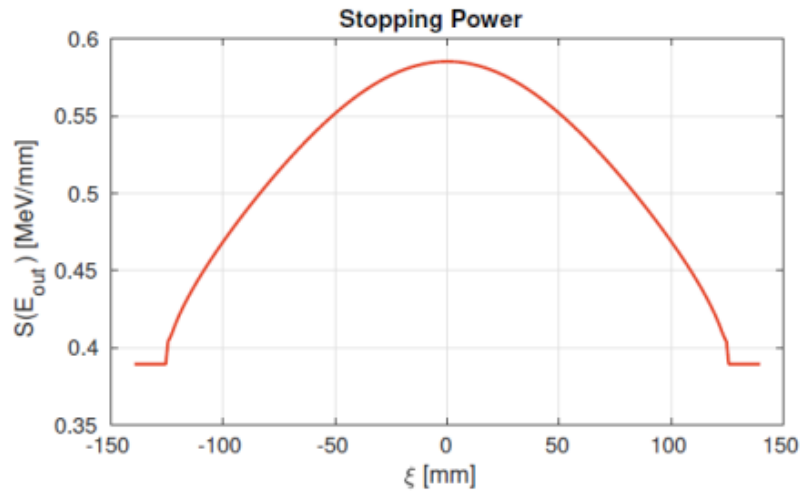
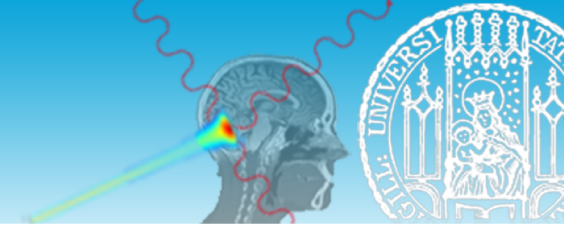
Thank you

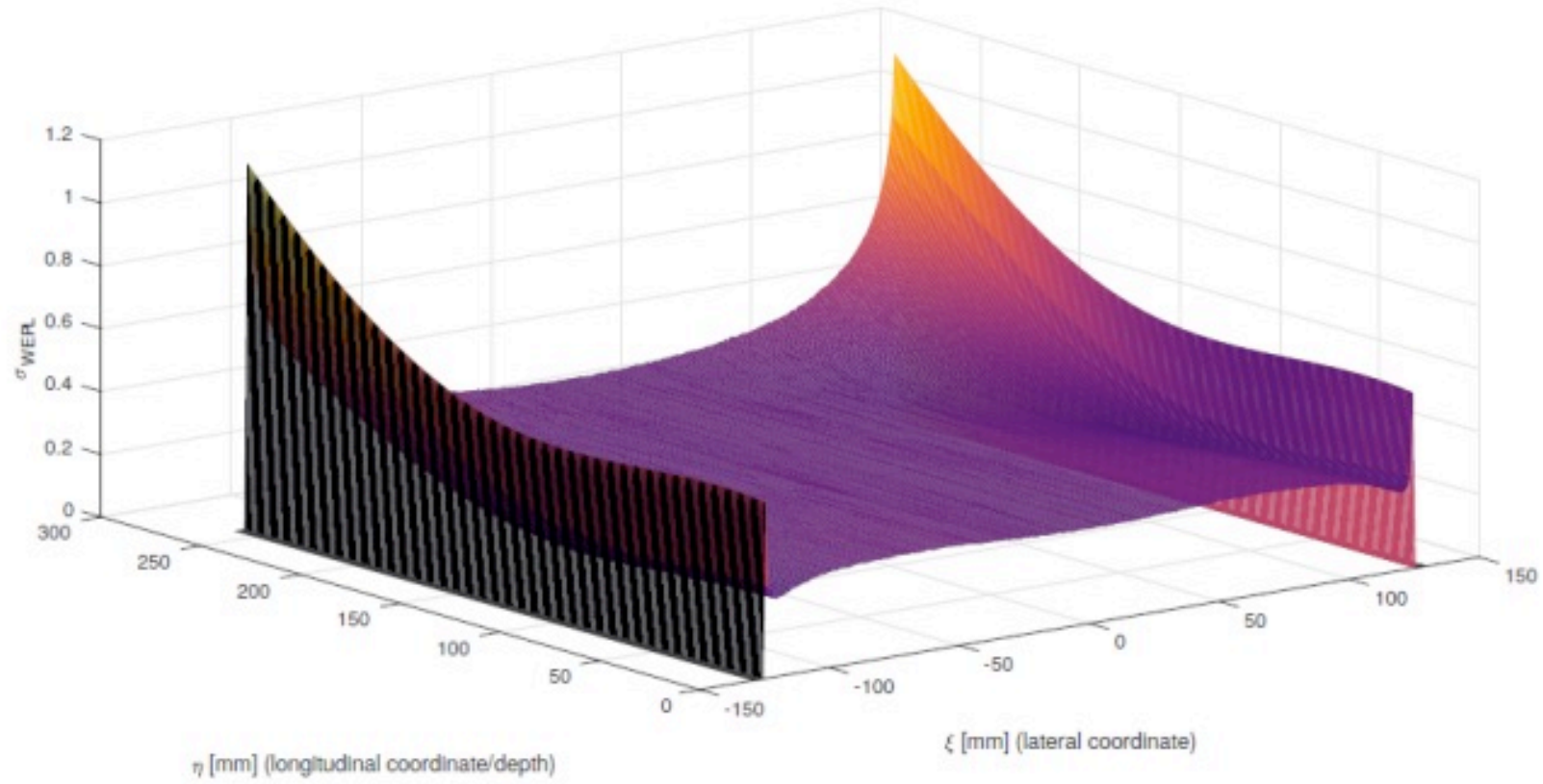
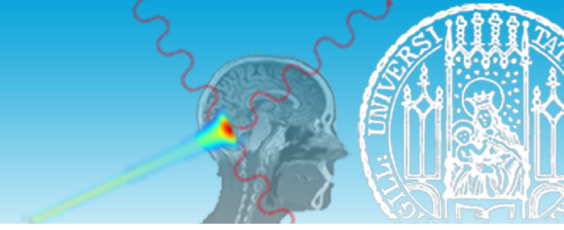


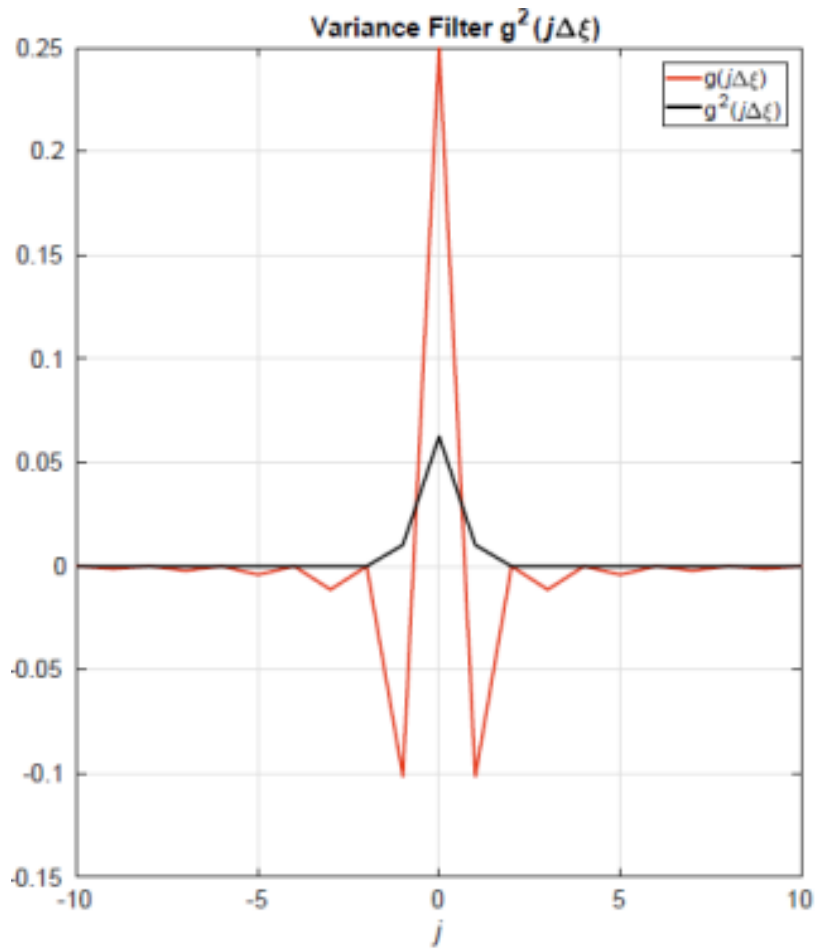
Backup slides



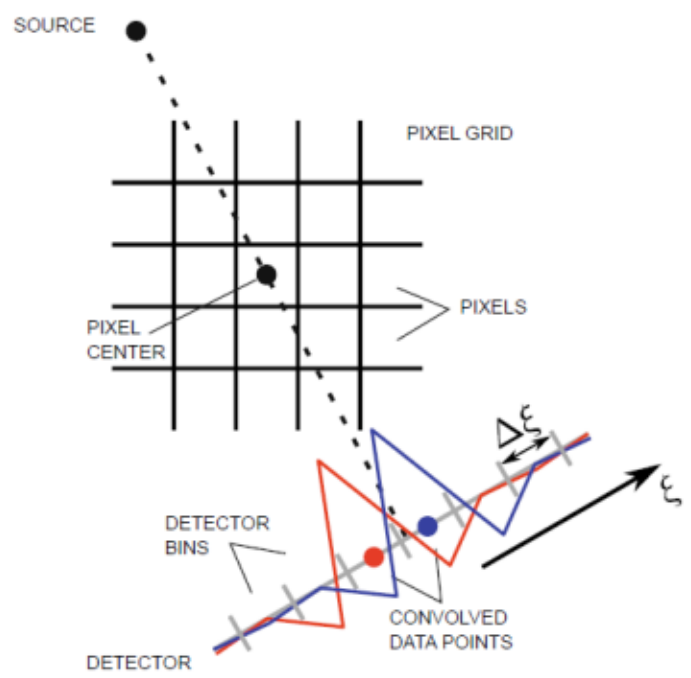




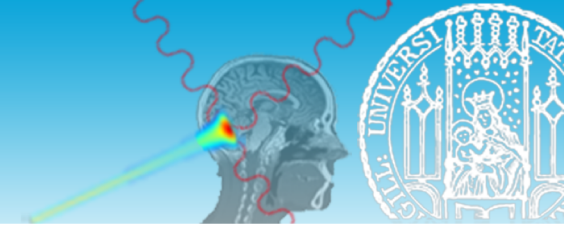




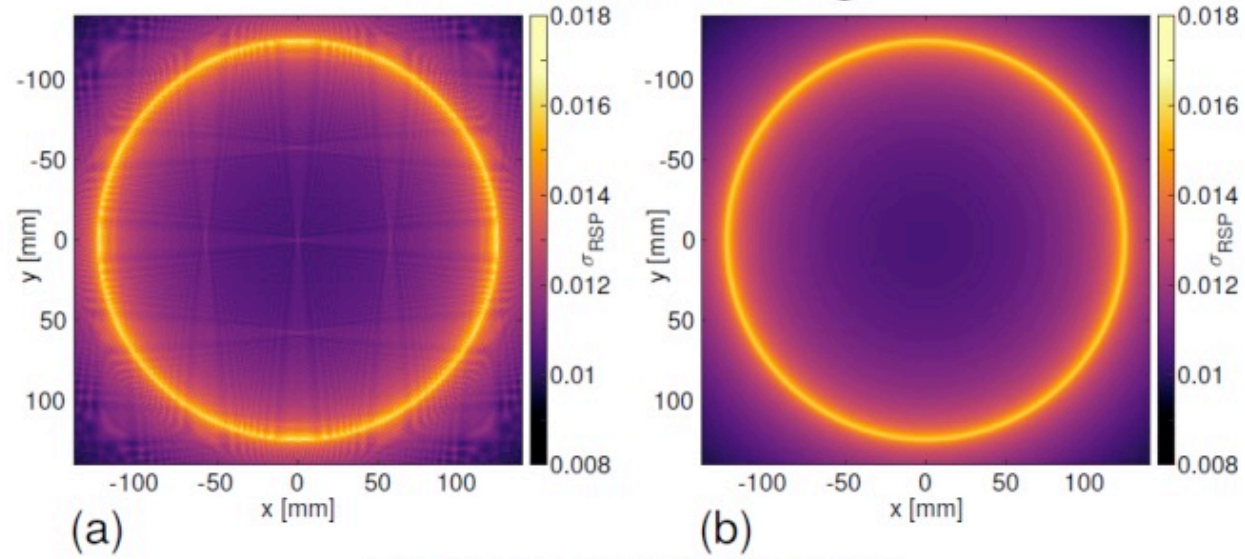
1D INTERPOLATION FOR REAR TRACKER BINNING



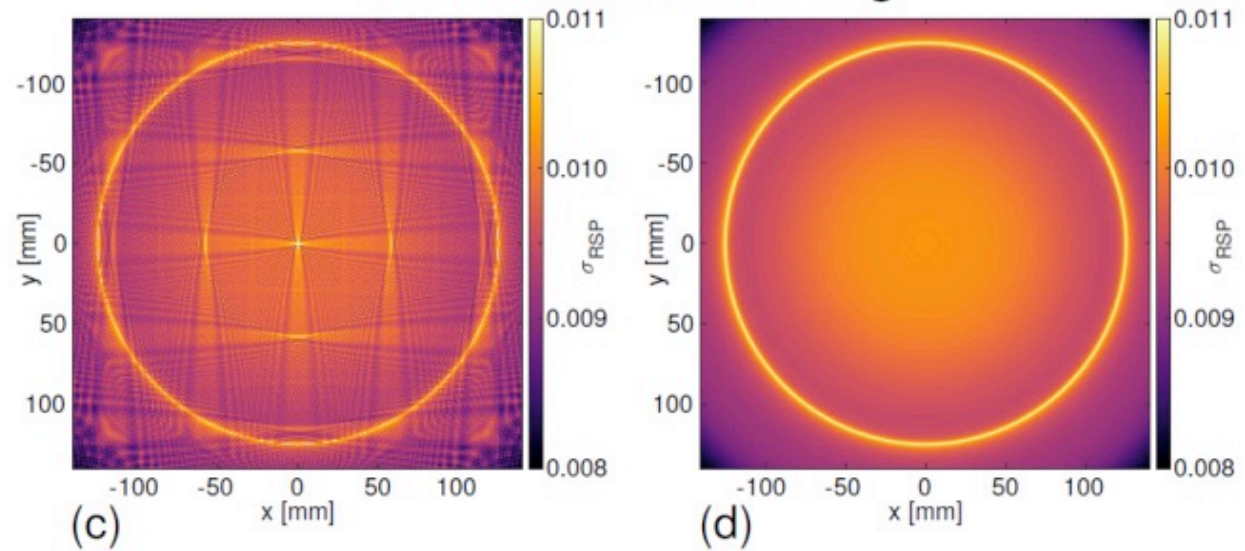
- $h_{\gamma_n}(j\Delta\xi)$
- $h_{\gamma_n}((j+1)\Delta\xi)$



Rear Tracker Binning



Distance Driven Binning





constant variance prescription

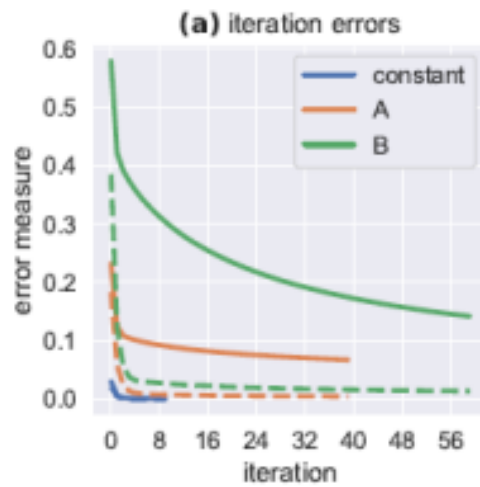
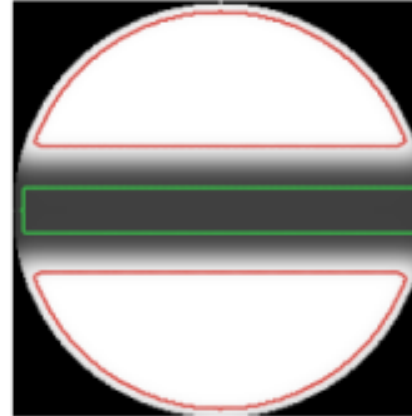


$$C/W = (2/4) V_{ROI}$$

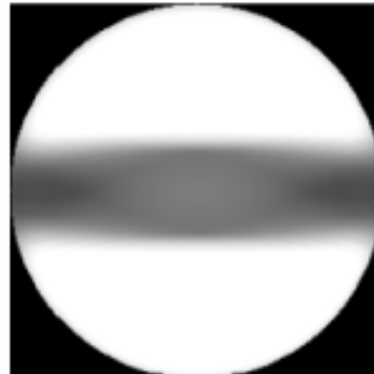
FMpCT prescription A



FMpCT prescription B

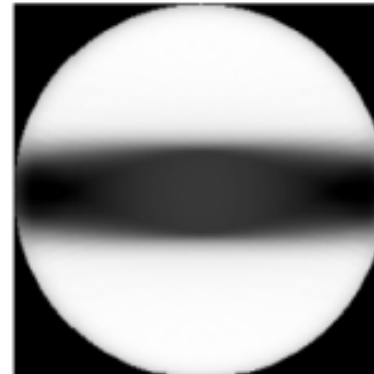


(b) B at iteration 1

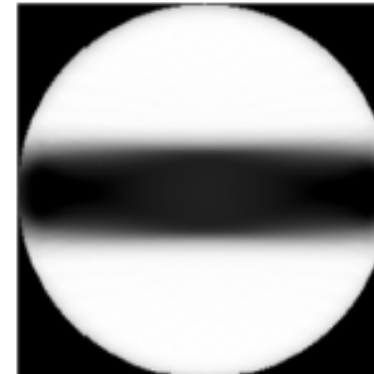


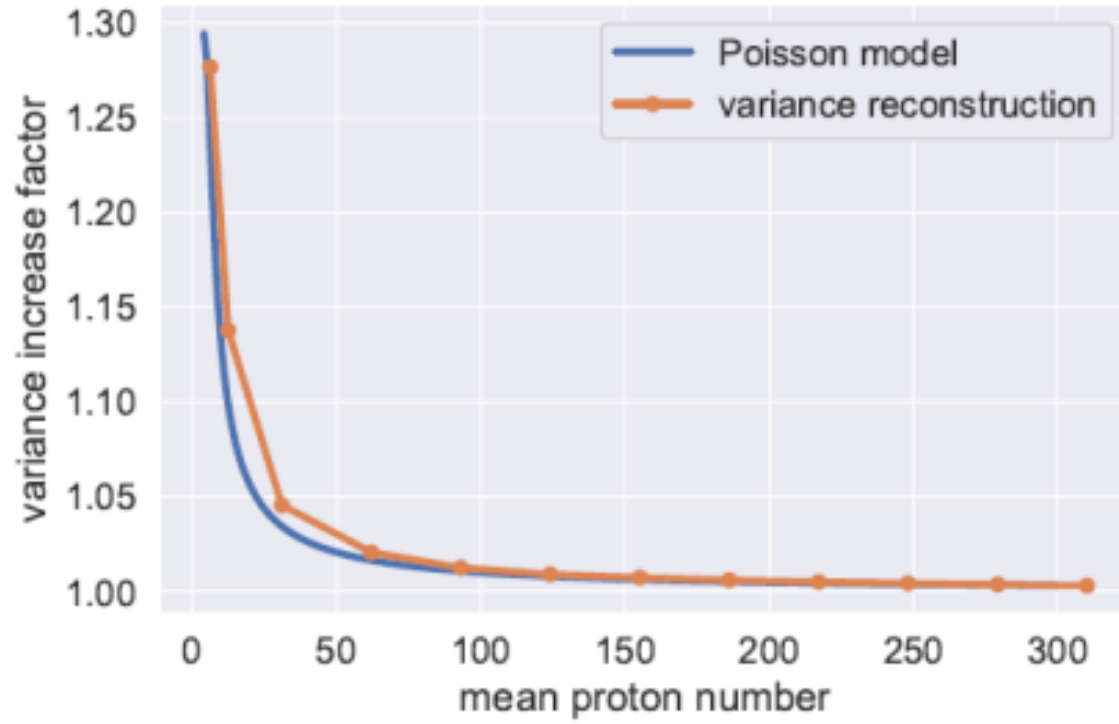
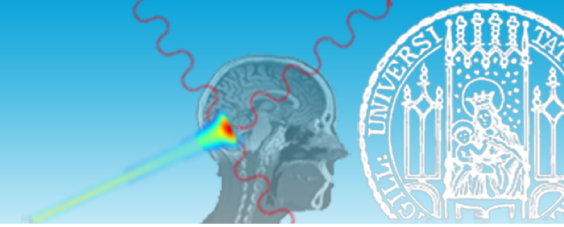
$$C/W = (2.5/3.0) V_{ROI}$$

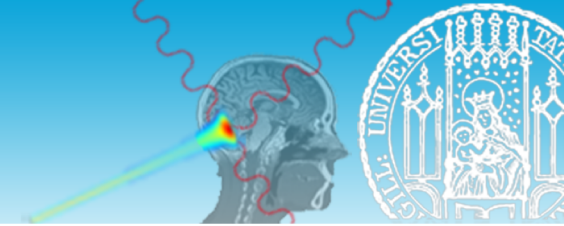
(c) B at iteration 20



(d) B at iteration 60







$$D_w = \frac{\rho_m S_w}{\rho_w S_m} D_m,$$

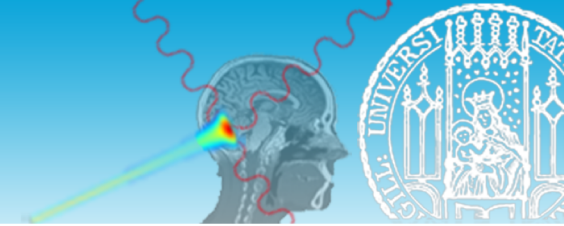
$$L_i = \frac{\sum_{n=1}^N \sum_{s=1}^{S_n} \frac{\epsilon_{sn}^2}{l_{sn}}}{\sum_{n=1}^N \sum_{s=1}^{S_n} \epsilon_{sn}}$$

$$x = r \cos \theta$$

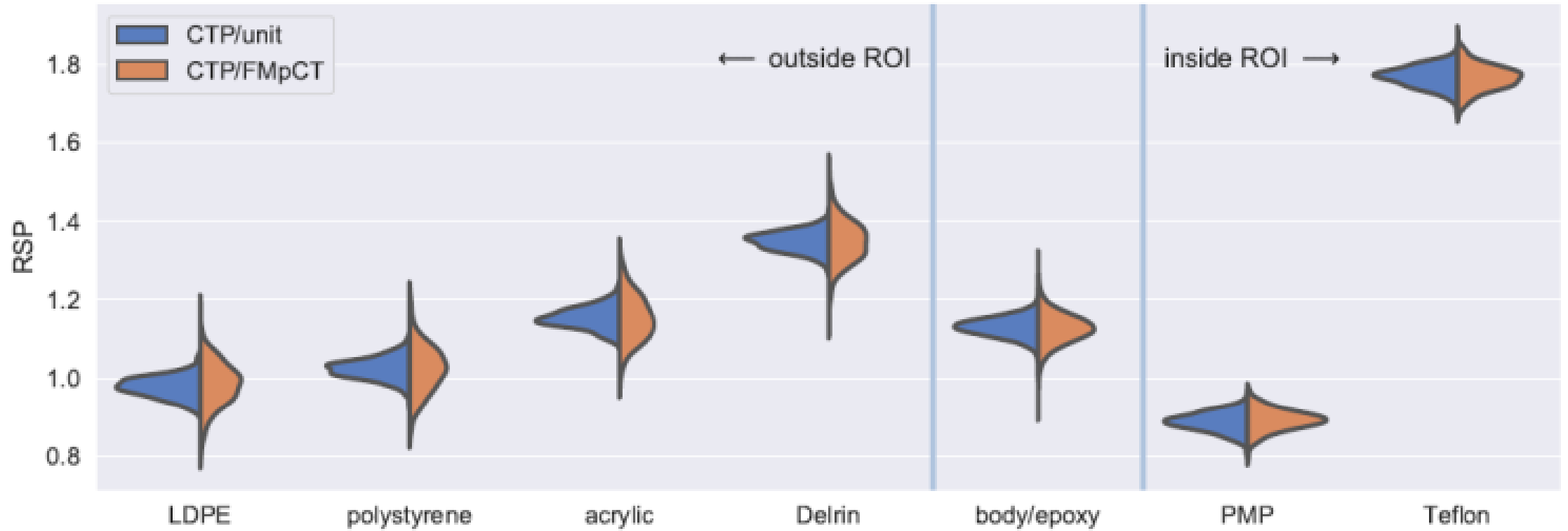
$$y = r \sin \theta$$

$$\frac{\partial(x, y)}{\partial(r, \theta)} = \begin{bmatrix} \cos \theta & -r \sin \theta \\ \sin \theta & r \cos \theta \end{bmatrix}$$

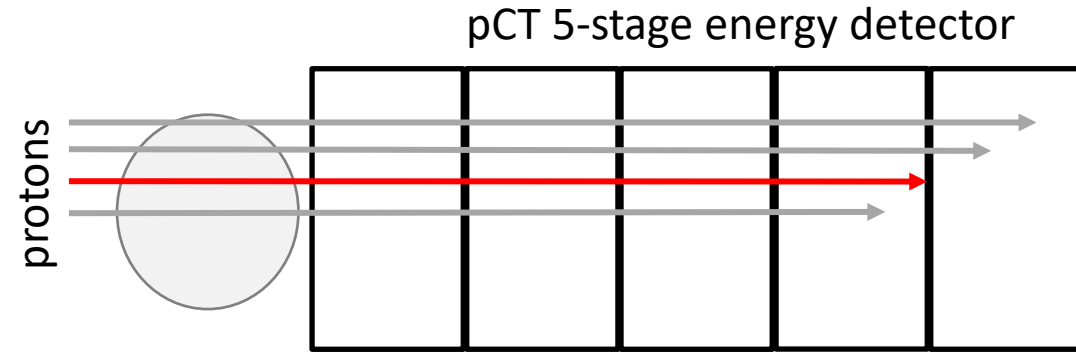
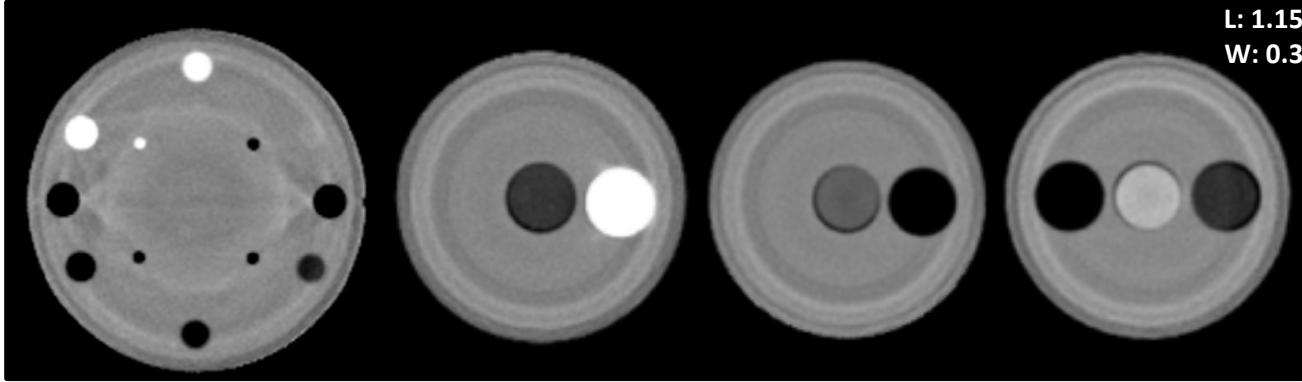
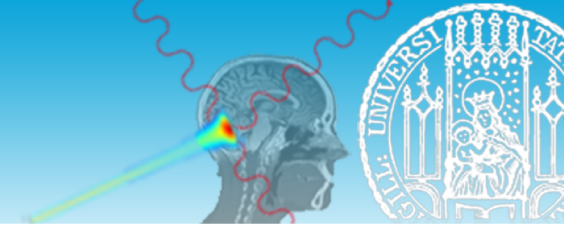
$$\text{Jacobian} = \det \frac{\partial(x, y)}{\partial(r, \theta)} = r$$



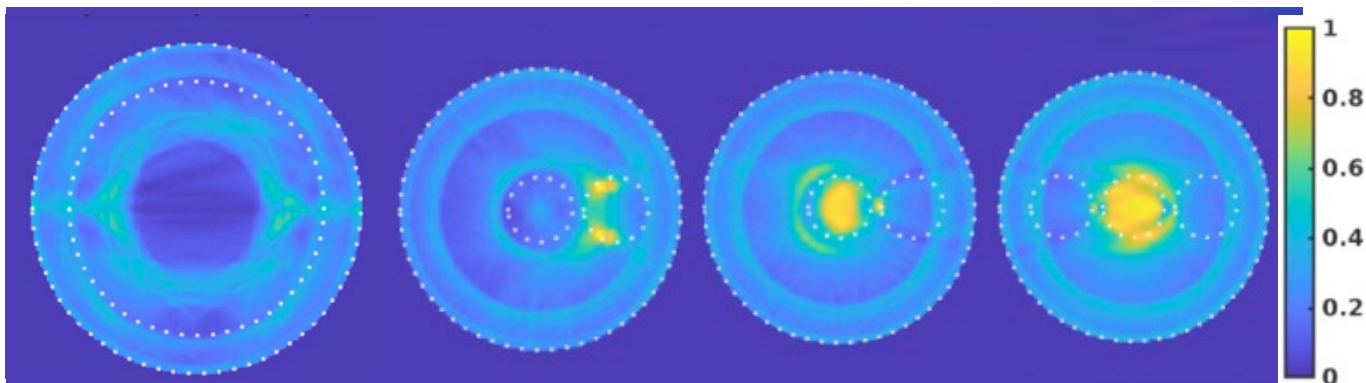
(d) RSP evaluation



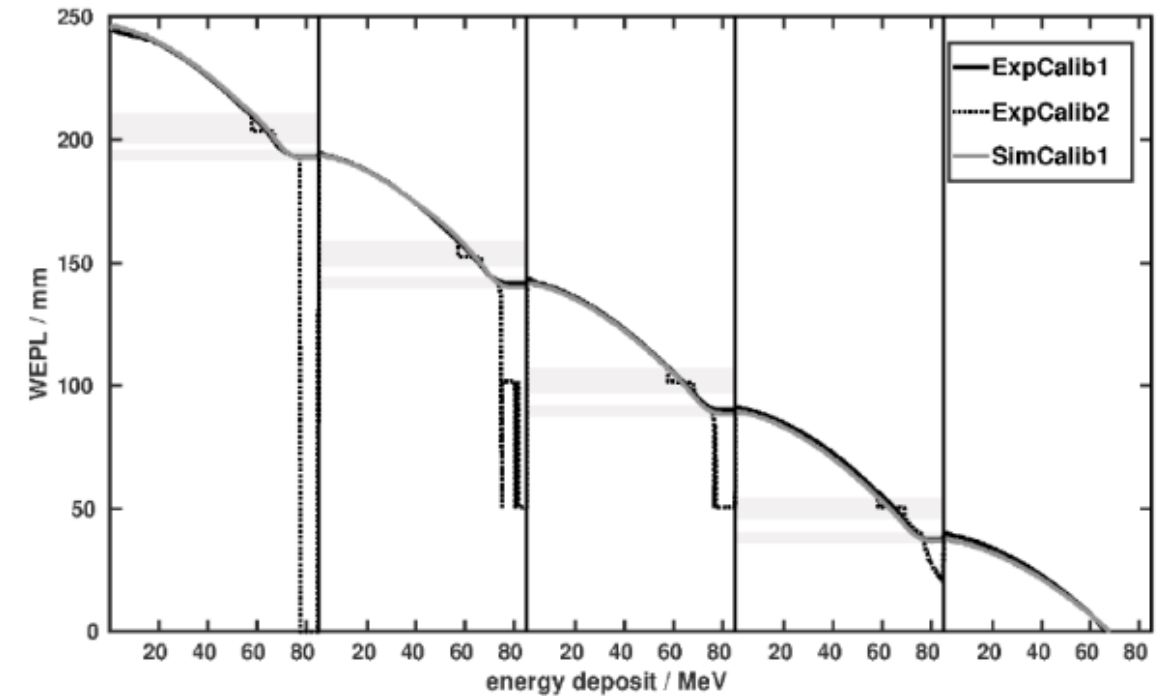
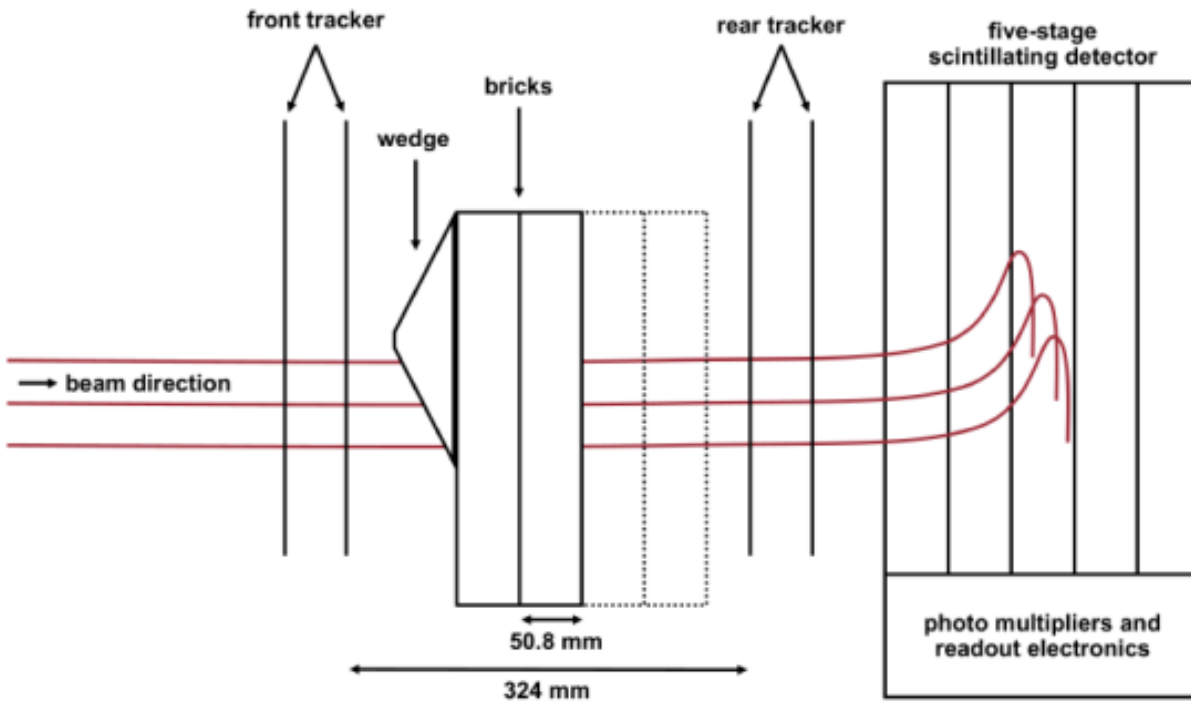
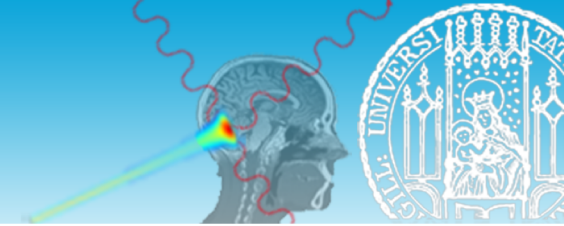
RSP artifacts



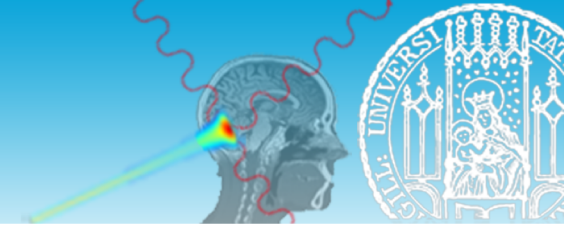
- Protons stopping near stage interfaces yield less accurate information
- In homogeneous cylindrical objects this results in ring artifacts
- Calculating for each voxel, the fraction of protons stopping near stage interfaces



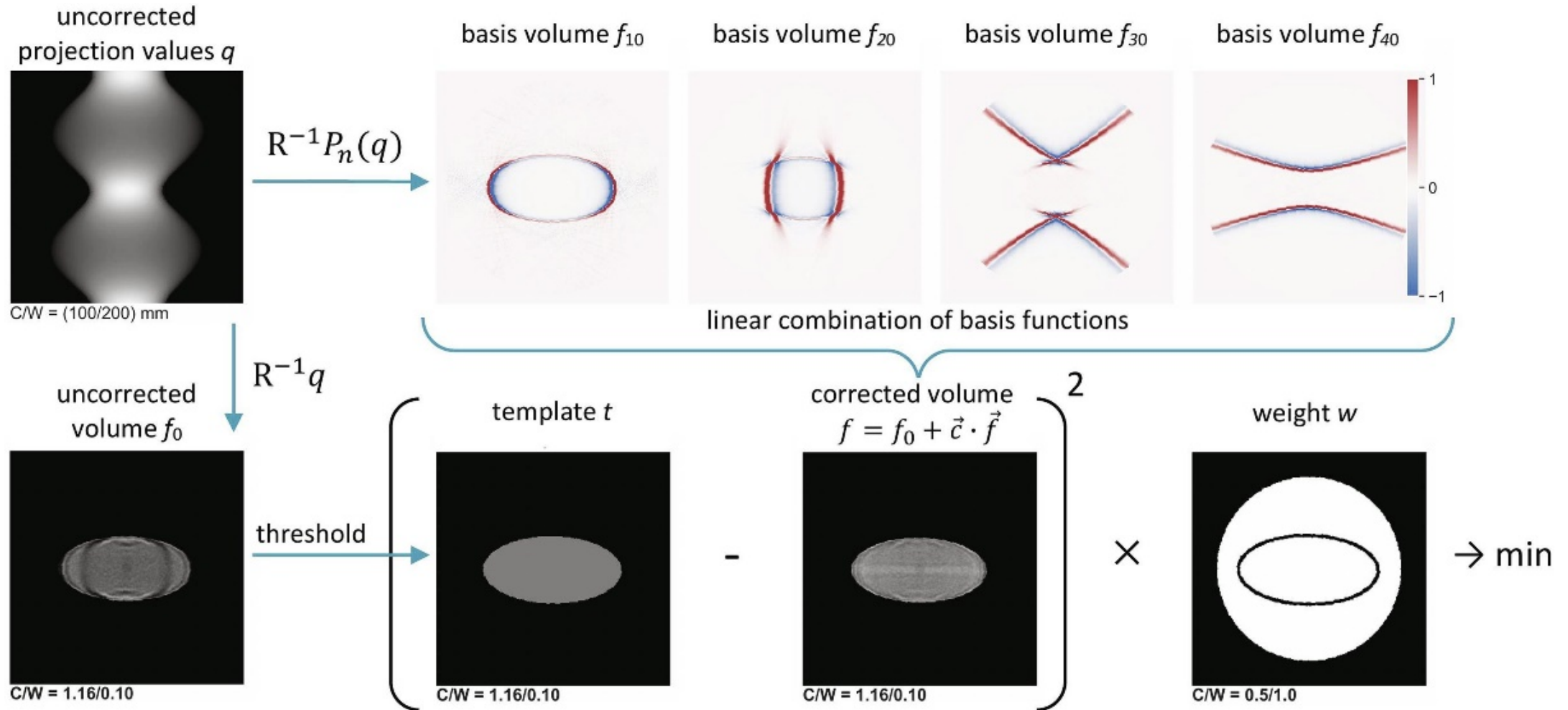
pCT calibration

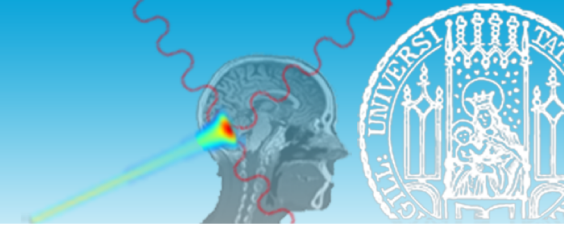


Method (continued)



- The full workflow: Dickmann *et al. Phys Med.* 2021 Jun;86:57-65



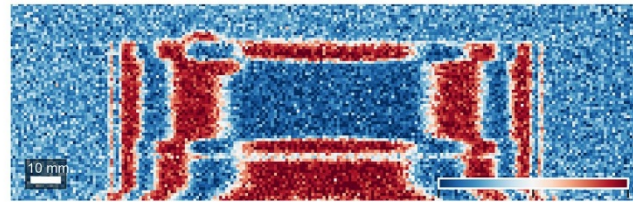


(a) WEPL map



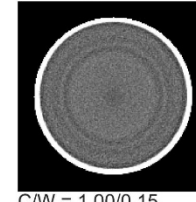
C/W = (80/160) mm

(b) dataset selection A



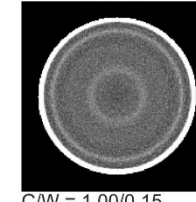
1.0 1.5 2.0

(a) low



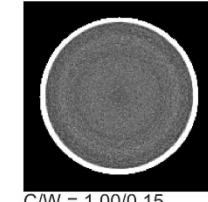
C/W = 1.00/0.15

(b) high



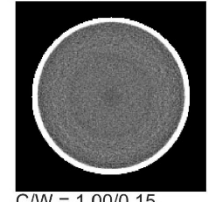
C/W = 1.00/0.15

(c) energy modulation A



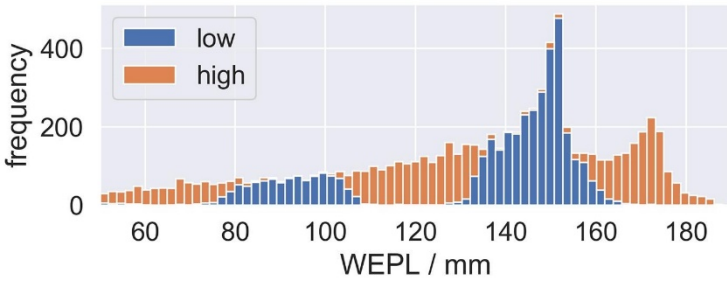
C/W = 1.00/0.15

(d) energy modulation B

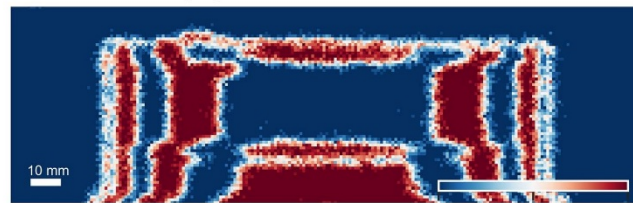


C/W = 1.00/0.15

(c) WEPL distribution for dataset selection B

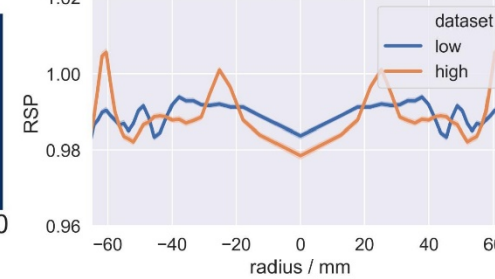


(d) dataset selection B

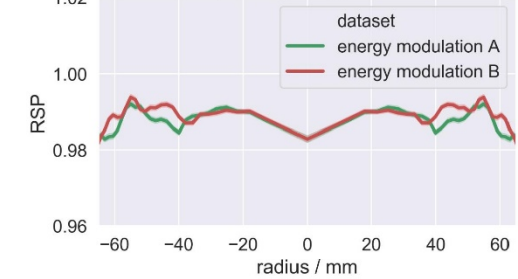


1.0 1.5 2.0

(e) radial RSP profiles (low and high)



(f) radial RSP profiles (energy modulation A and B)



(a) WEPL map (0 deg)



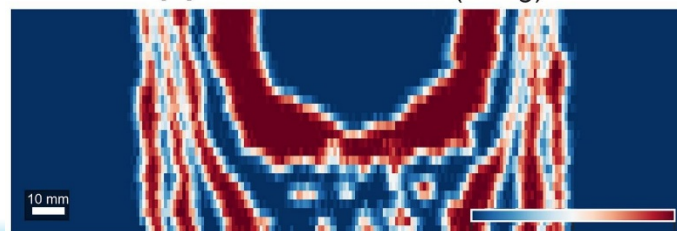
C/W = (100/200) mm

(b) WEPL map (90 deg)



C/W = (100/200) mm

(c) dataset selection B (0 deg)



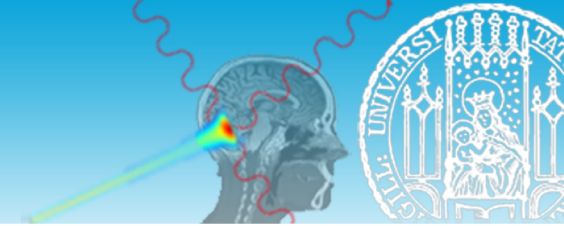
1.0 1.5 2.0

(d) dataset selection B (90 deg)

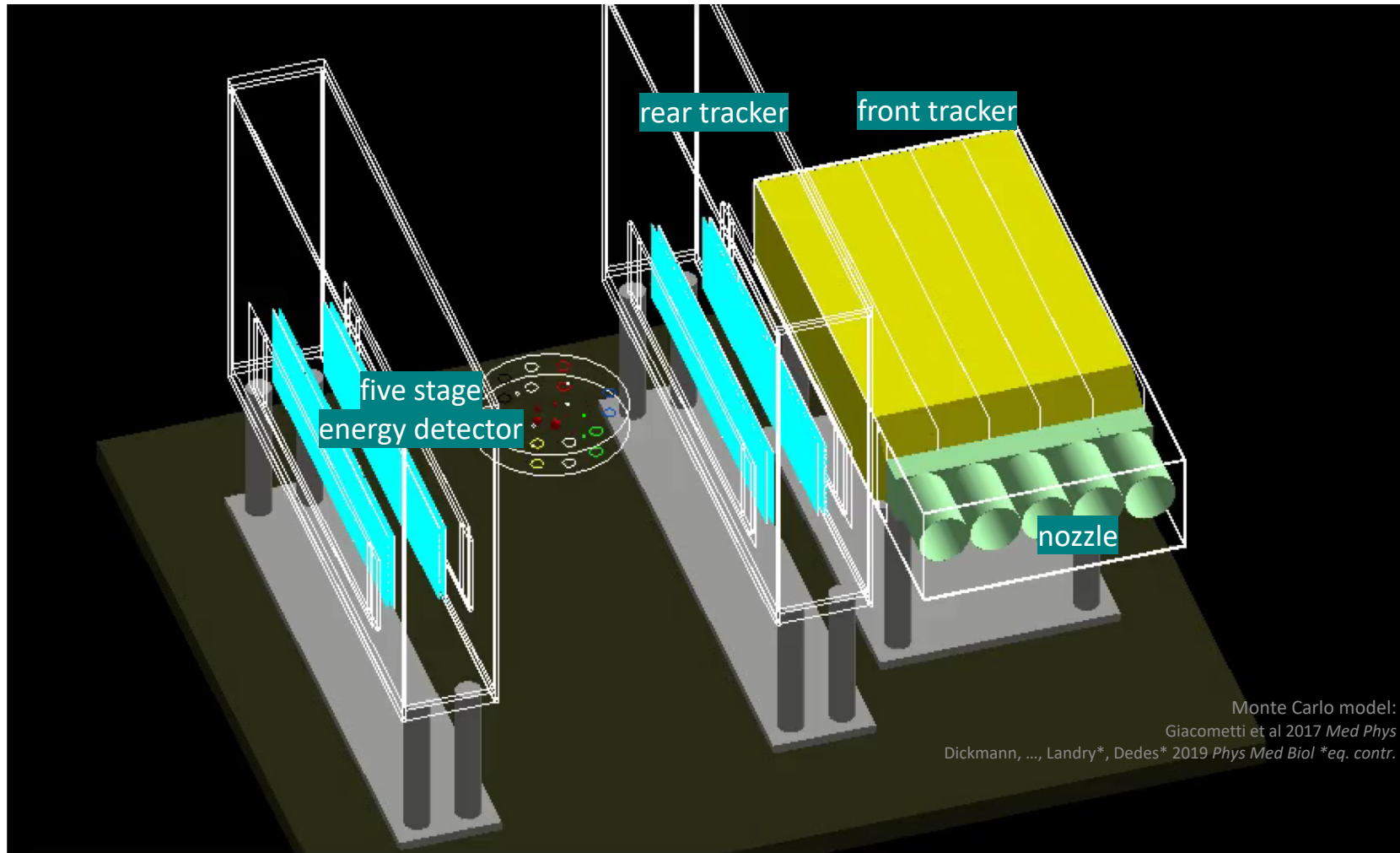


1.0 1.5 2.0

Prototype pCT scanner

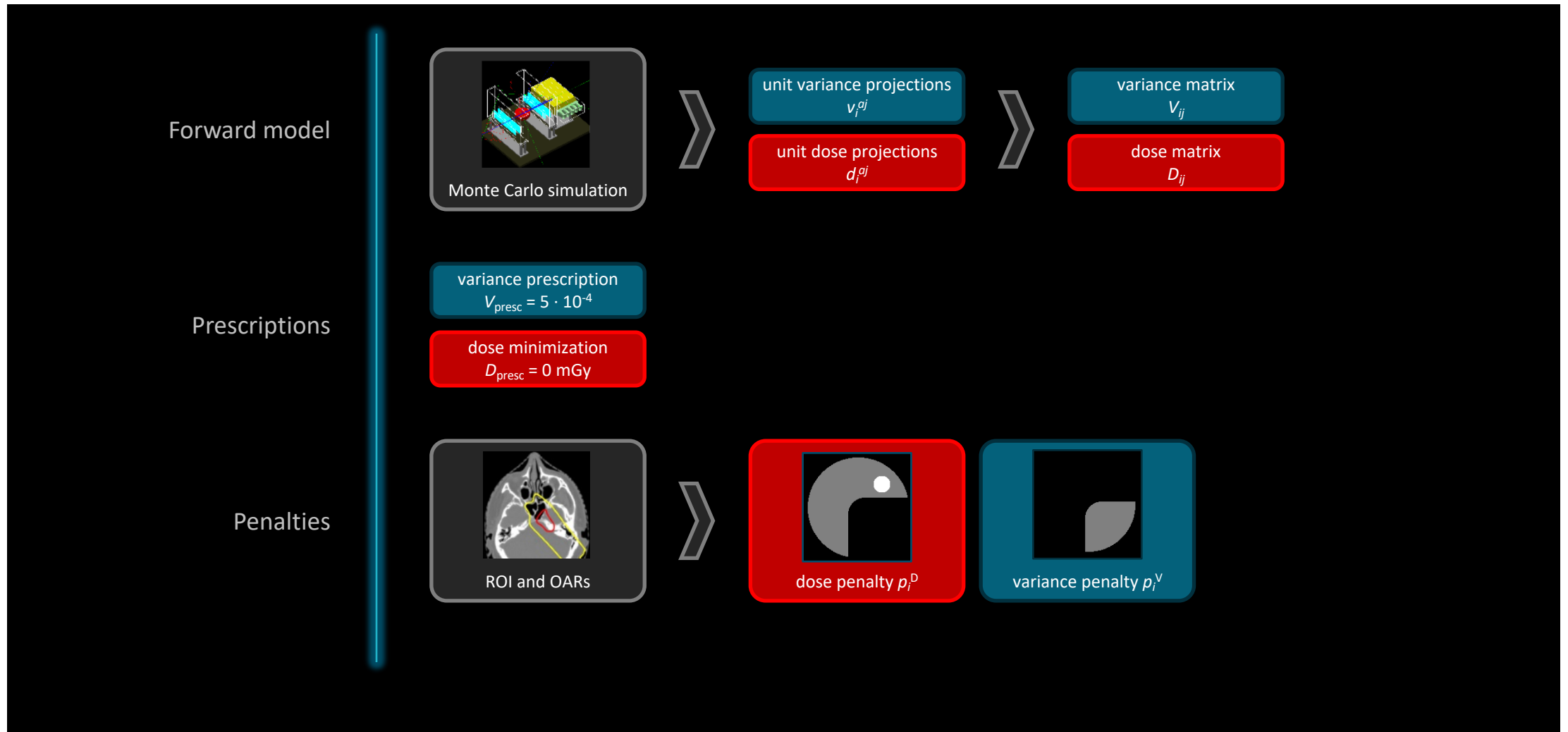


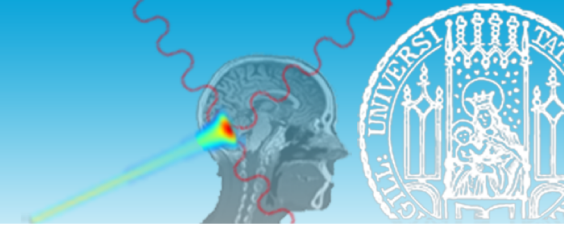
- Validated MC simulation platform, used in this study



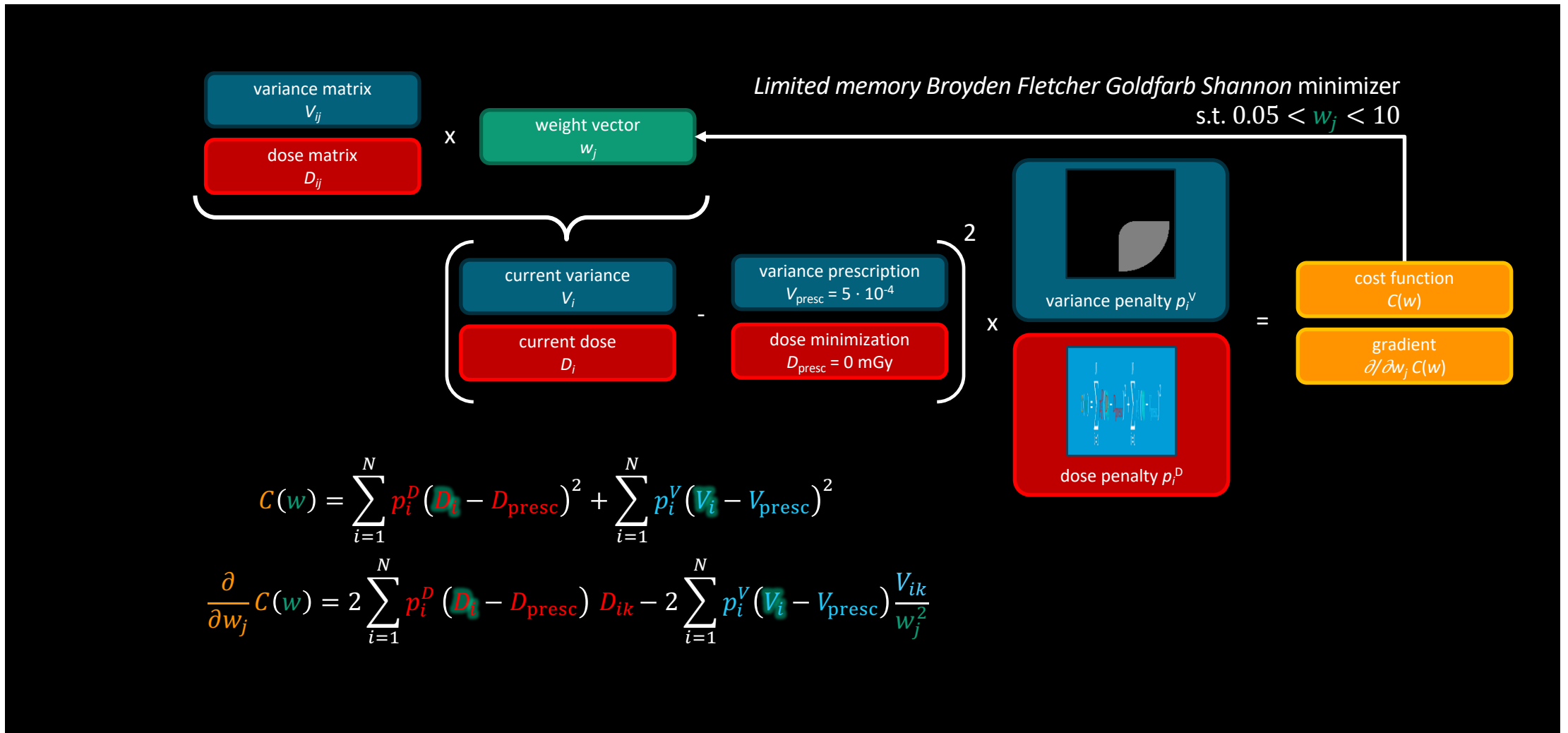


- Dose and variance optimization

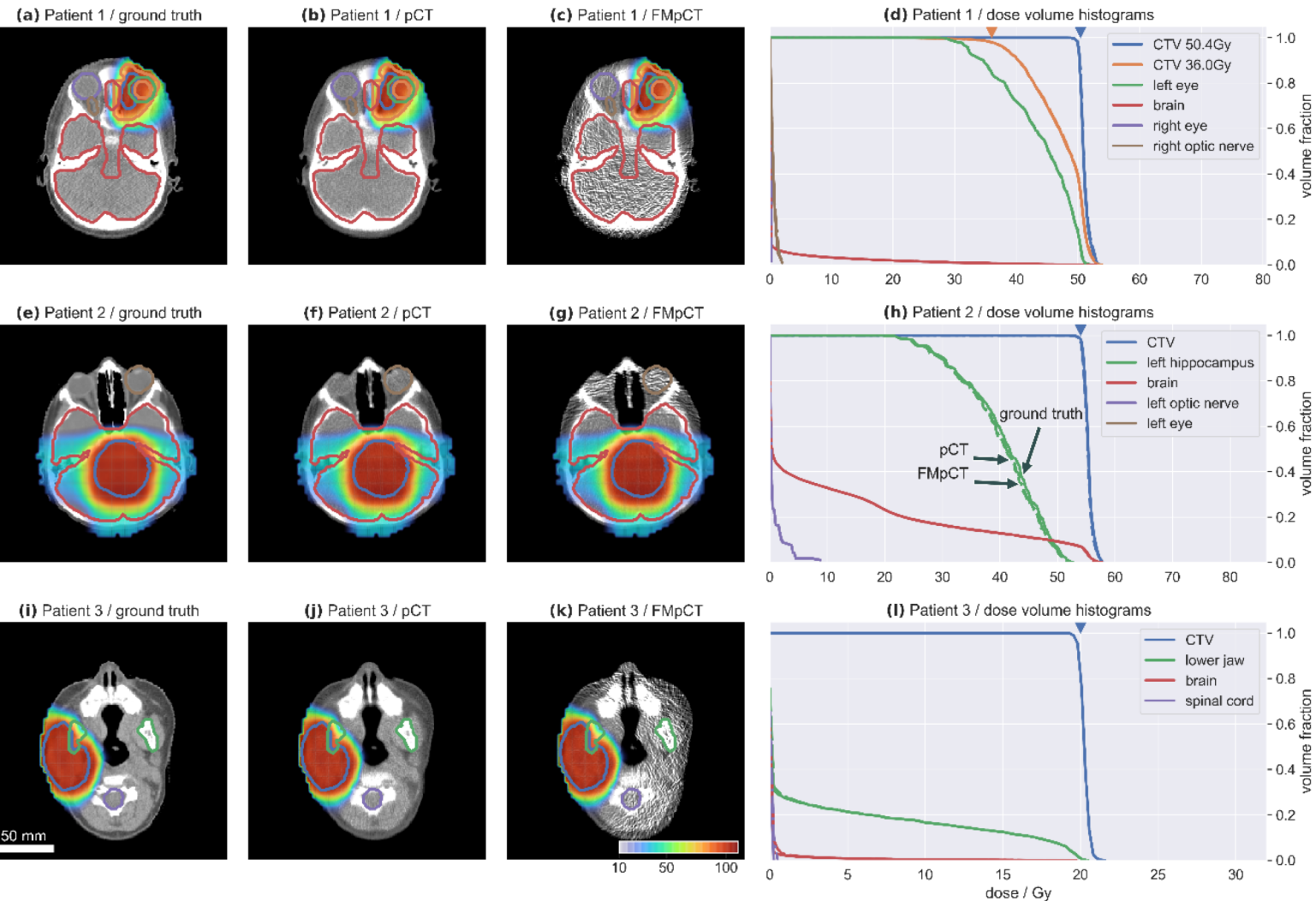
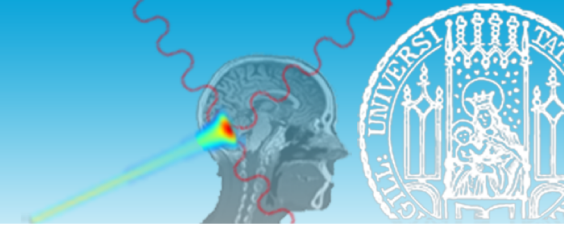




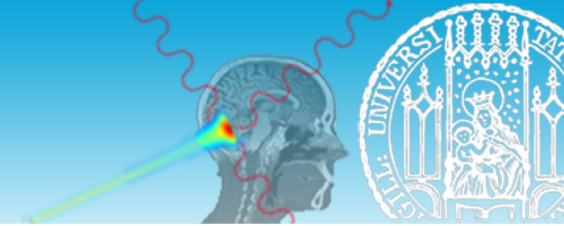
- Bixel-based approach



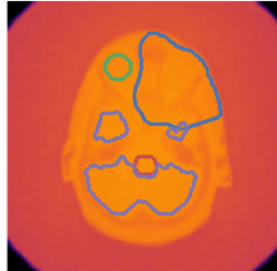
FMpCT in treatment planning



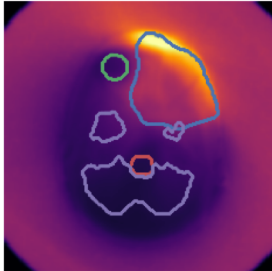
- three **pediatric cases** treated with IMRT selected
- **proton treatment plans** generated on the basis of the IMRT dose distributions using **ground truth RSP**
- **ground truth RSP** from the patient model in the pCT MC **simulation** with **full detector modelling**
- **treatment dose recalculated** on pCT and FMpCT images



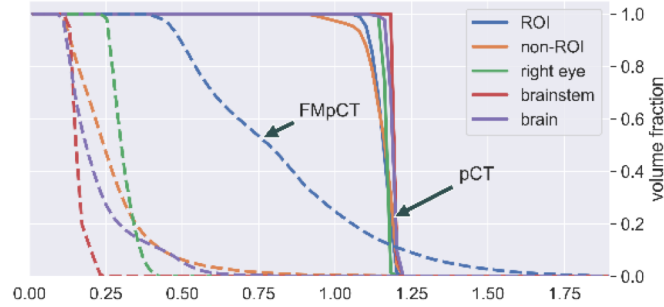
(a) Patient 1 / pCT



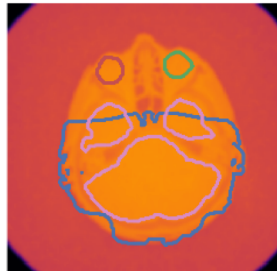
(b) Patient 1 / FMpCT



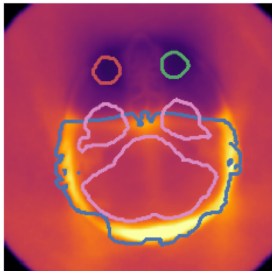
(c) Patient 1 / dose volume histograms



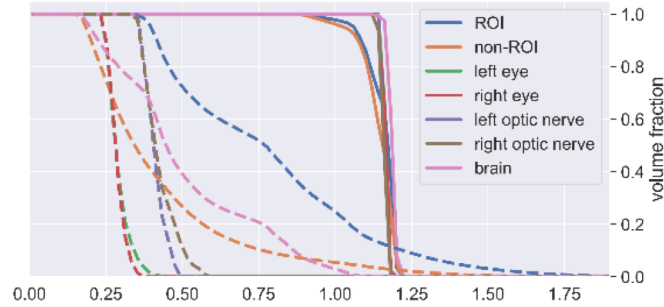
(d) Patient 2 / pCT



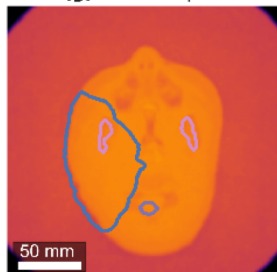
(e) Patient 2 / FMpCT



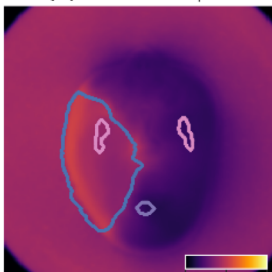
(f) Patient 2 / dose volume histograms



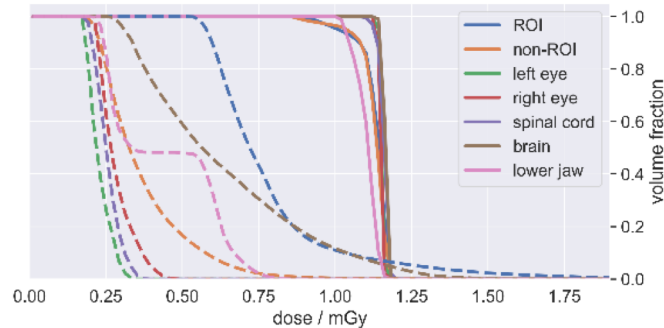
(g) Patient 3 / pCT



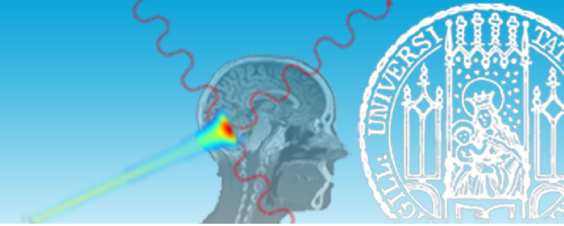
(h) Patient 3 / FMpCT



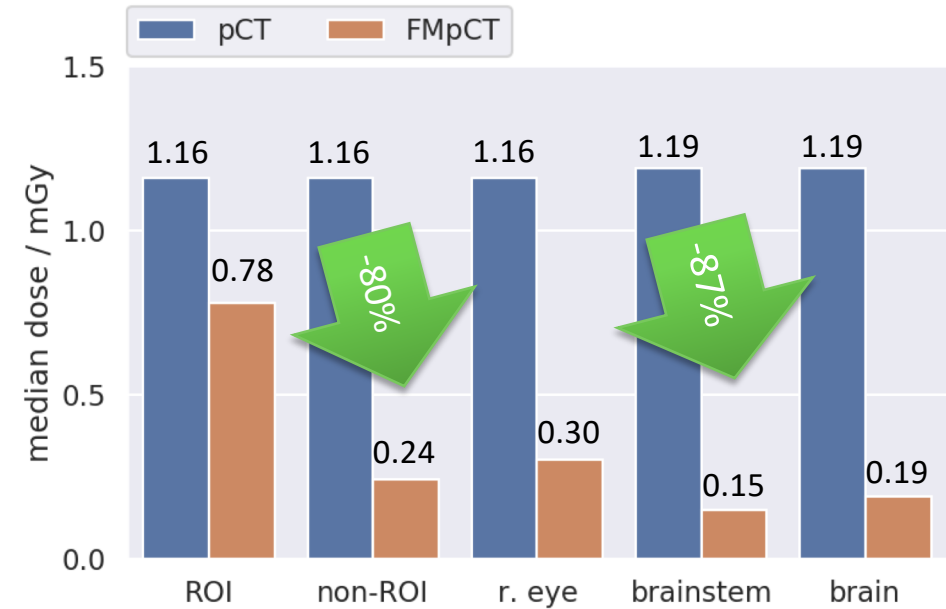
(i) Patient 3 / dose volume histograms



- **DVH for imaging dose**
- **Important dose reduction for all out-of-ROI areas**
- **Dose can be slightly increased in-ROI where treatment dose is also high**
- **OAR dose can be pushed down**



- **Inverse planning** approach yields optimal fluence distributions
- FMpCT allows **substantial imaging dose savings** while preserving dose calculation accuracy
 - **80%** outside the ROI
 - **87%** in some OARs
- Results expected to be **applicable to real world** due to fully realistic simulations
- Previous work showed **imaging plans are deliverable**



Full details:

Physics in Medicine & Biology



PAPER

Fluence-modulated proton CT optimized with patient-specific dose and variance objectives for proton dose calculation

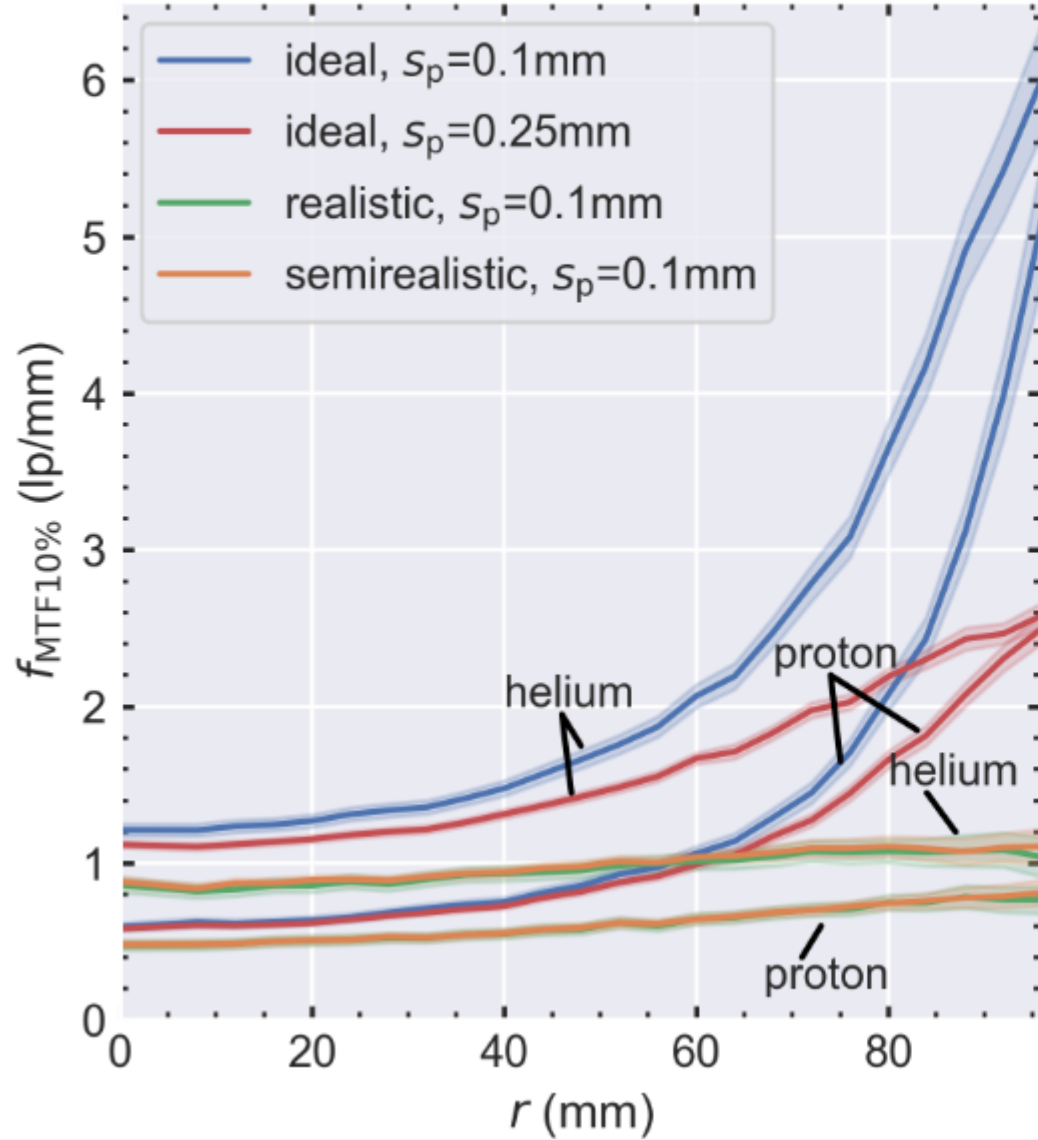
J Dickmann¹, F Kamp^{2,*}, M Hillbrand³, S Corradini², C Belka^{2,4}, R W Schulte⁵, K Parodi¹, G Dedes¹ and G Landry^{1,2}

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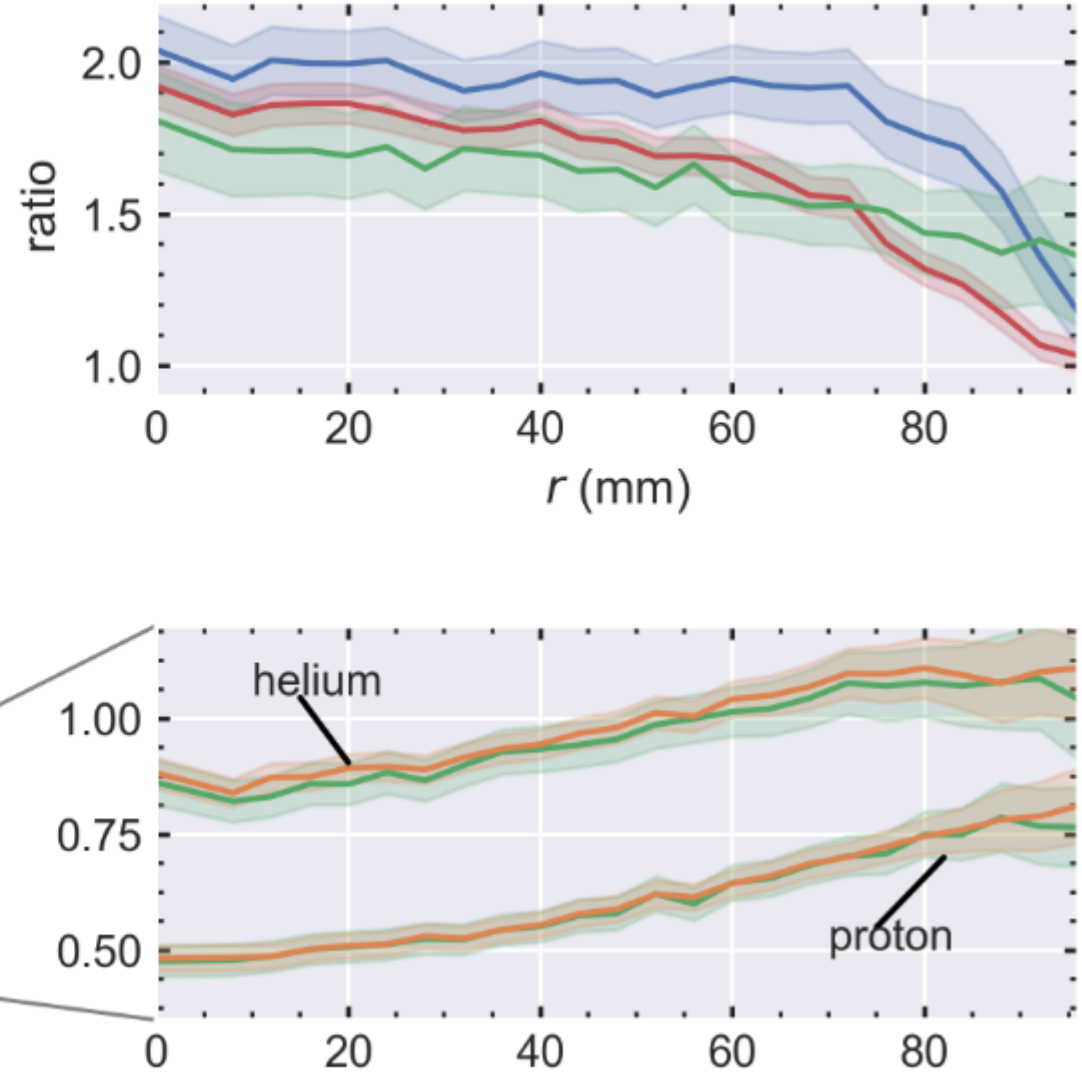
E-mail: guillaume.landry@med.uni-muenchen.de

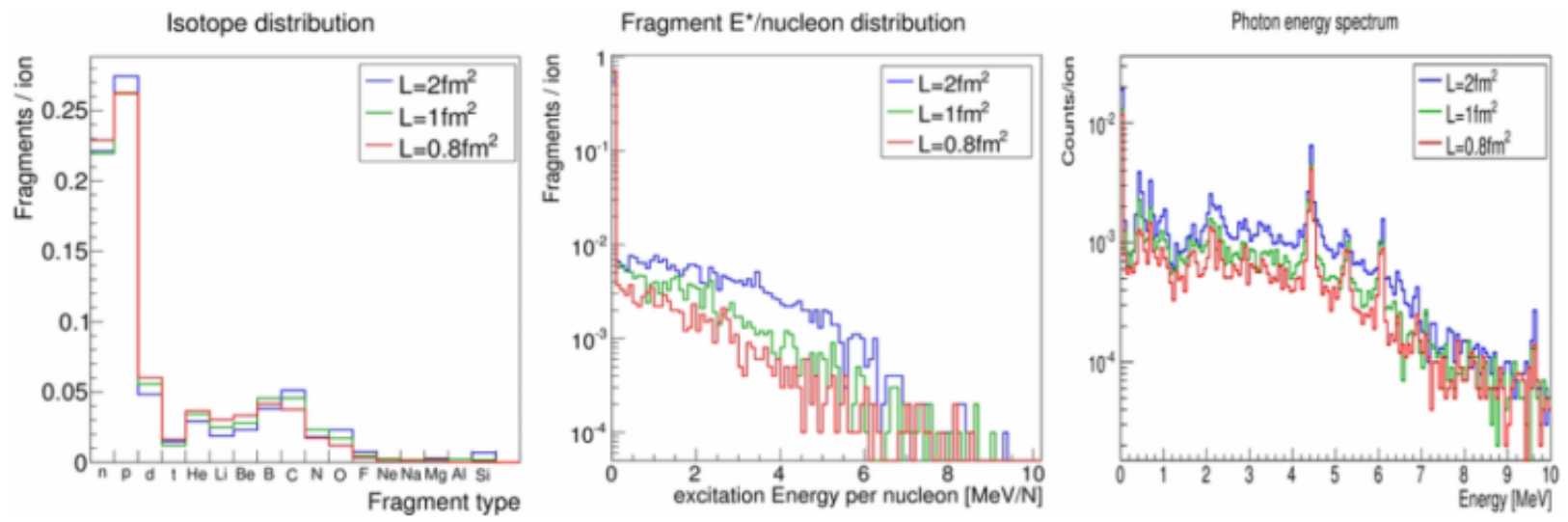


(a) spatial resolution

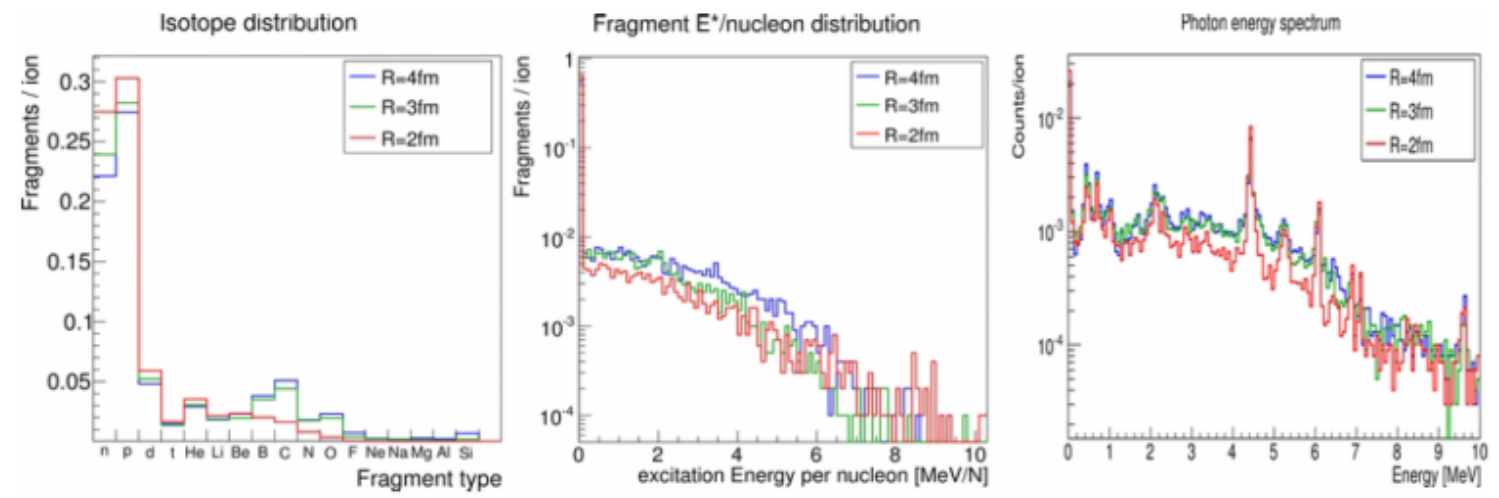
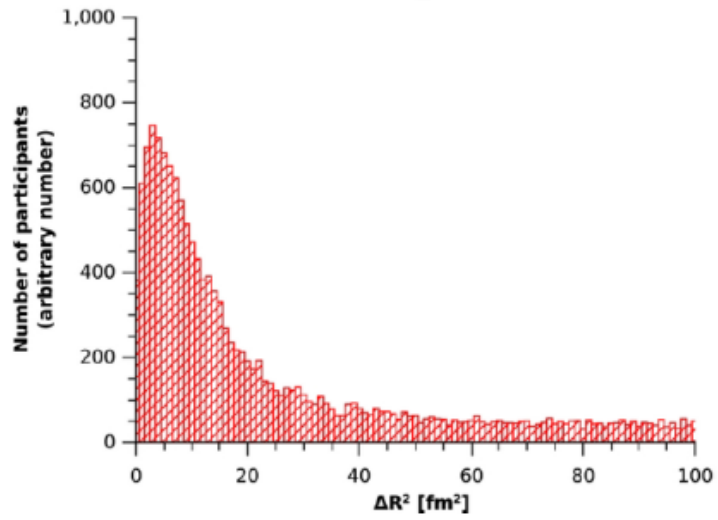


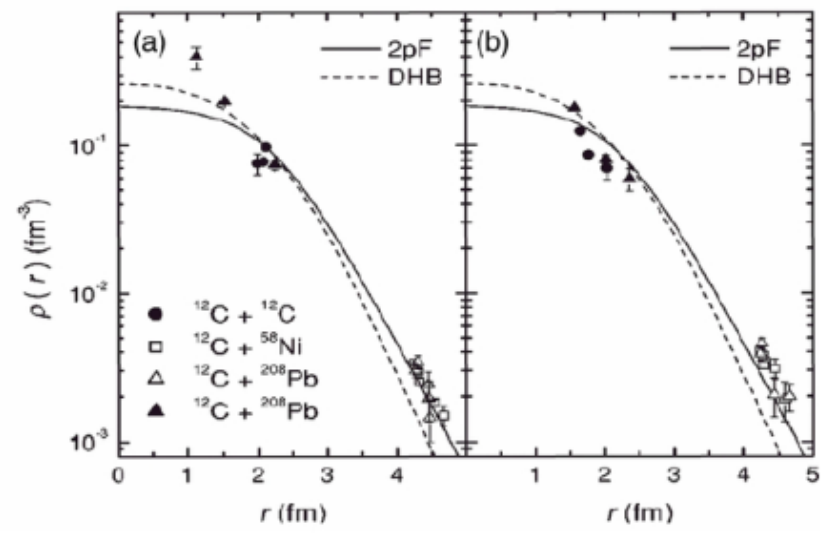
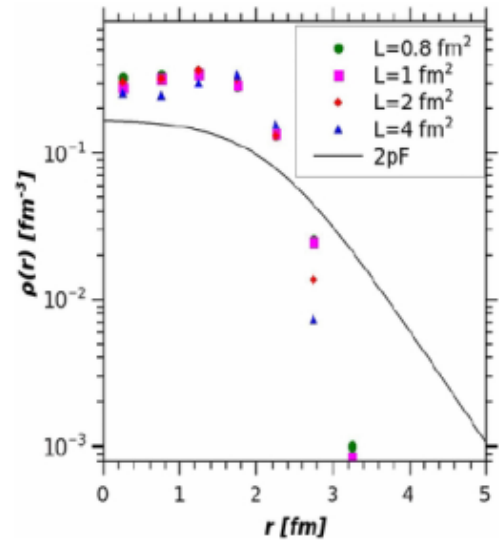
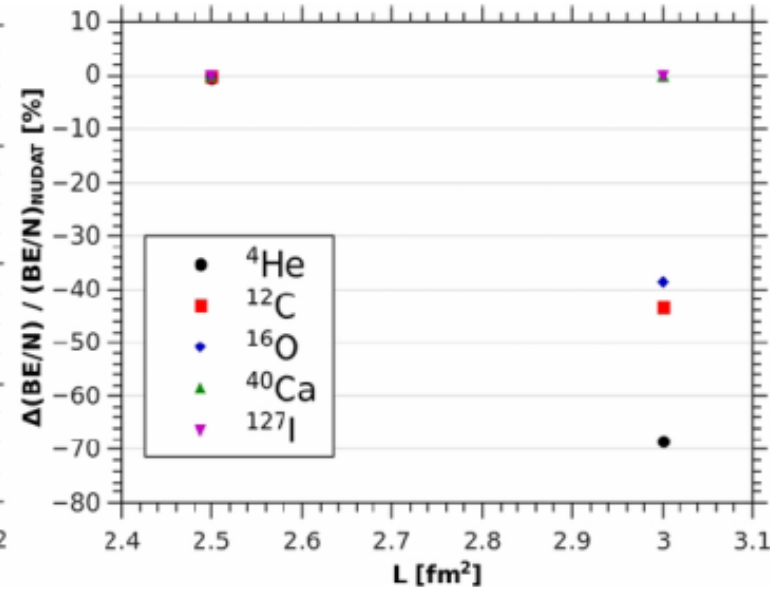
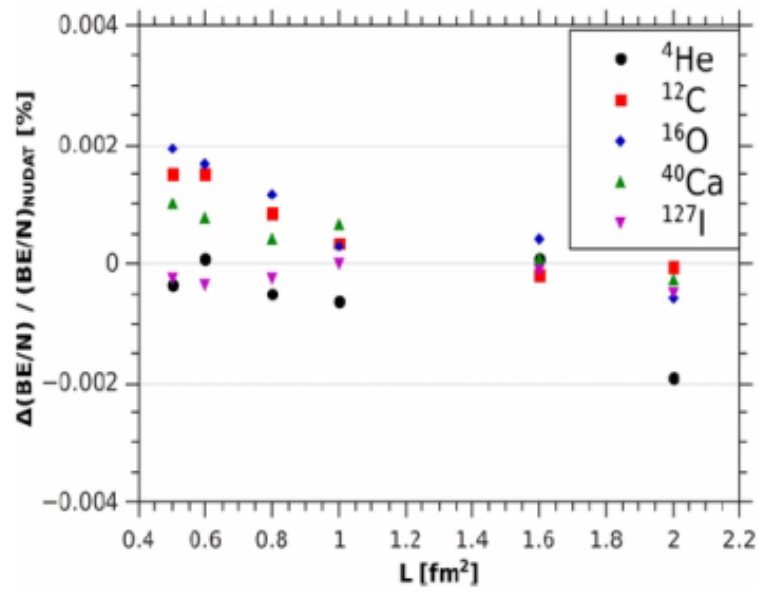
(b) ratio (He/p)

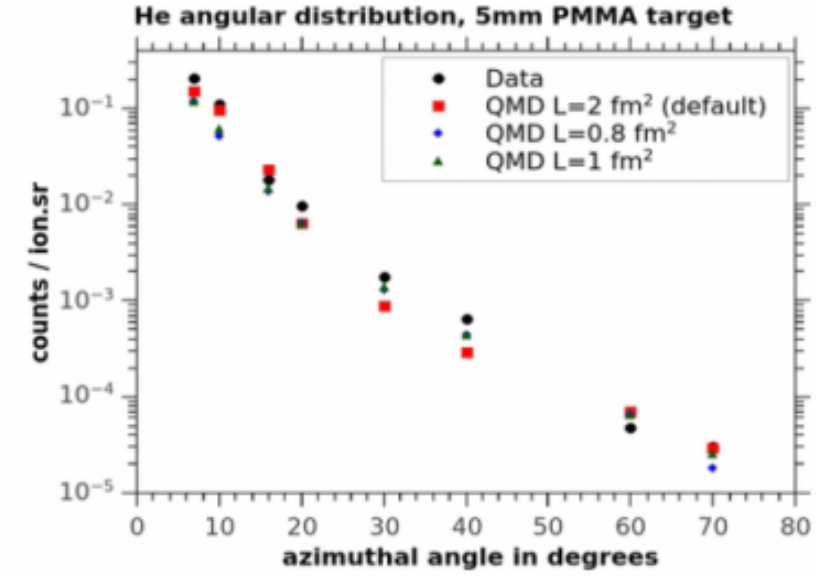
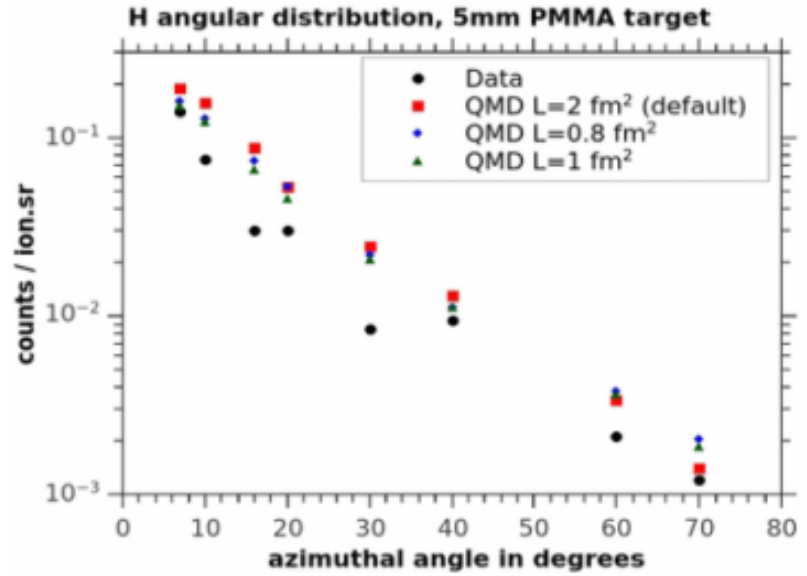
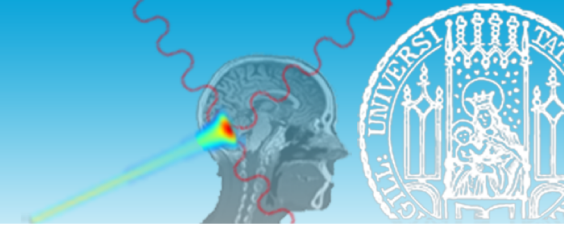




Clustering distance







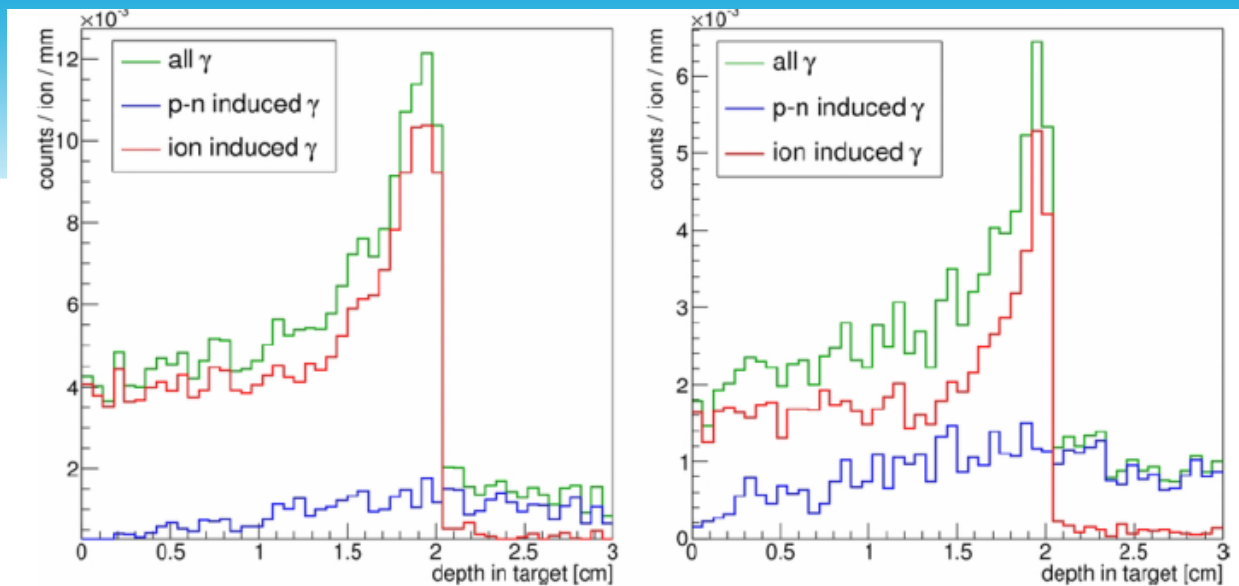
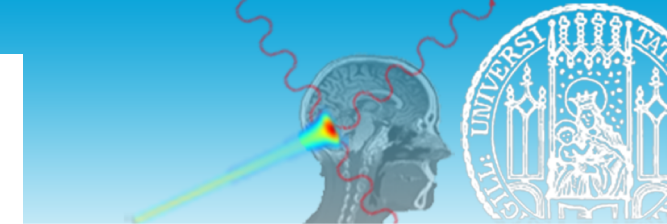


Figure 11.13: $95 \text{ MeV/u } ^{12}\text{C}$ simulated prompt-gamma emission in a PMMA target, for $L = 2 \text{ fm}^2$ (left) and $L = 0.8 \text{ fm}^2$ (right). The total emission profile as well as the contributions from ion induced (QMD) and p/n induced (BIC) reactions are shown.

