HITRI plus

Heavy Ion Therapy Research Integration

Marburg Ion-Beam Therapy Center (MIT)

KILIAN-SIMON BAUMANN

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

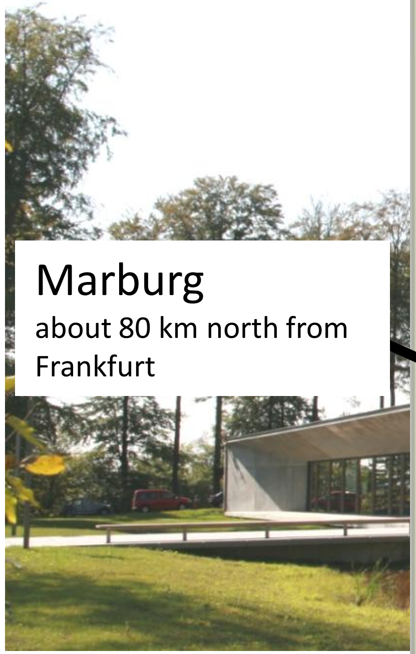
Marburg Ion-Beam Therapy Center (MIT)

Kilian-Simon Baumann

- Postdoctoral Researcher at Philipps-University Marburg
- Medical Physicist at MIT

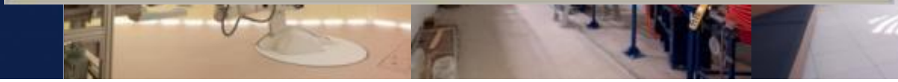
- Overview of the Marburg Ion-Beam Therapy Center

- Physics research performed at our working group



Marburg

about 80 km north from Frankfurt



History of MIT

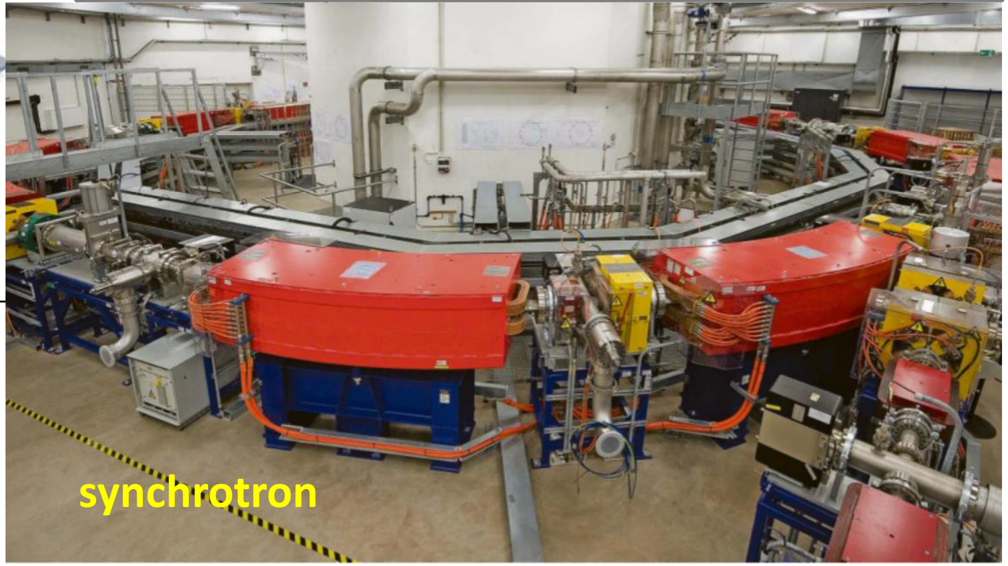
Constructed by Siemens Healthineers

2 facilities in operation: Marburg and Shanghai

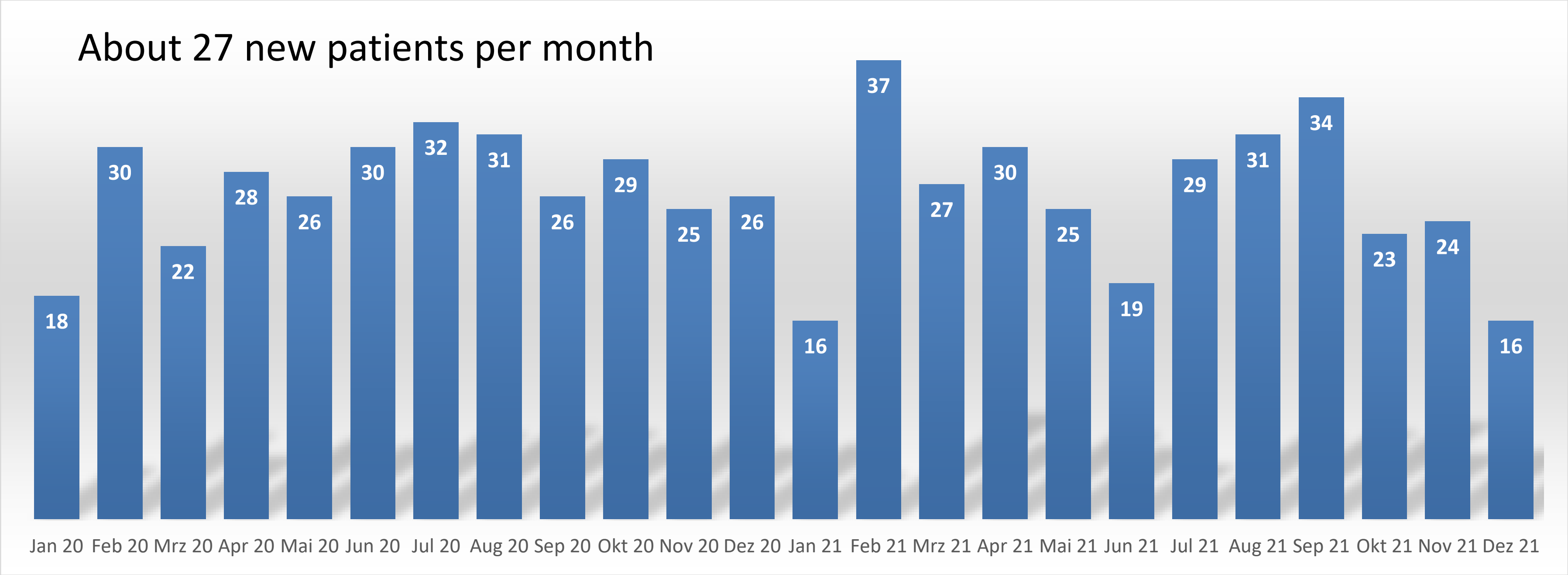
Start of construction:	09/2007
End of construction:	04/2009
Installation accelerator:	08/2008
First beam in treatment room:	02/2010
First patient treatment: (planned)	2011
Shut down:	2011
Restart (leadership HIT):	2015
First patient treated:	2015
Change of ownership HIT -> UKGM:	**08/2019**

Technical Equipment

- Synchrotron:
  - up to 430 MeV/u ^{12}C
  - up to 250 MeV protons
- active raster scanning
- 3 treatment rooms with horizontal beam
- 1 treatment room with 45° beam line



Patient statistics

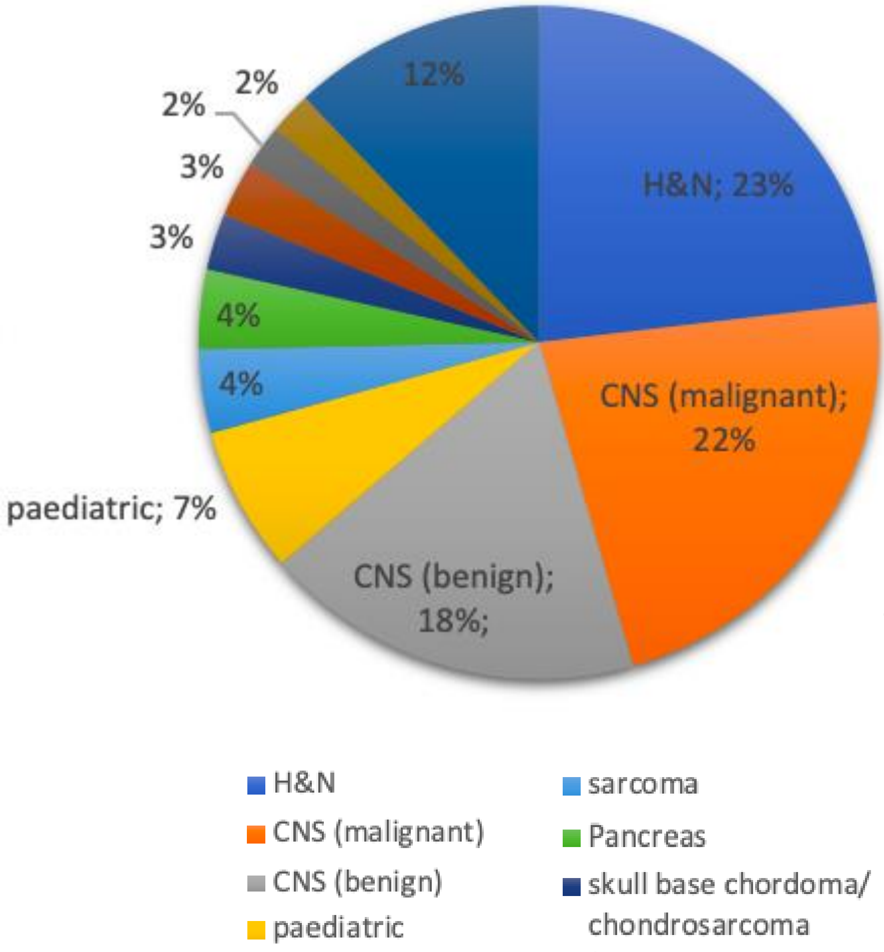


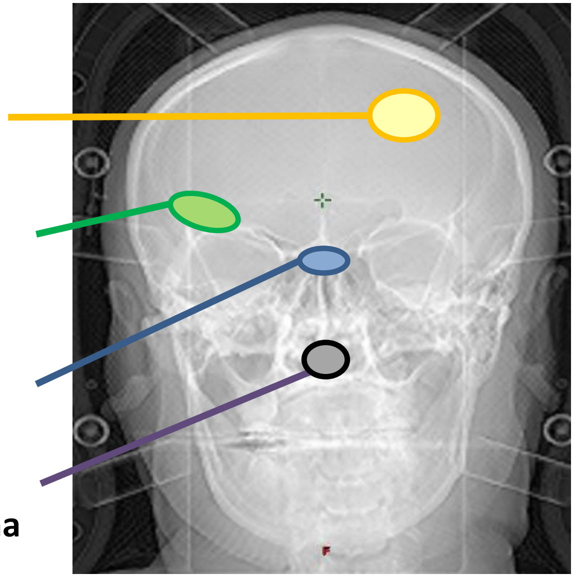
year	number of patients
2018	251
2019	293
2020	323
2021	311

Treatments:
- 66% Primary
- 34% Boost

Treatments:
- 40% ^{12}C
- 60% Protonen

Treated tumor entities





Glioma

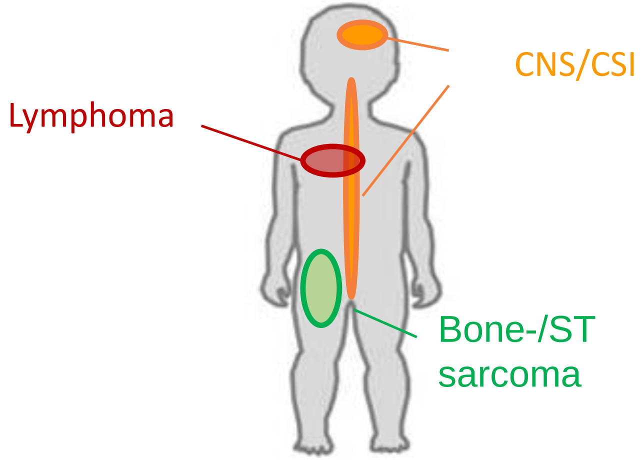
Meningioma

Pituitary gland adenoma

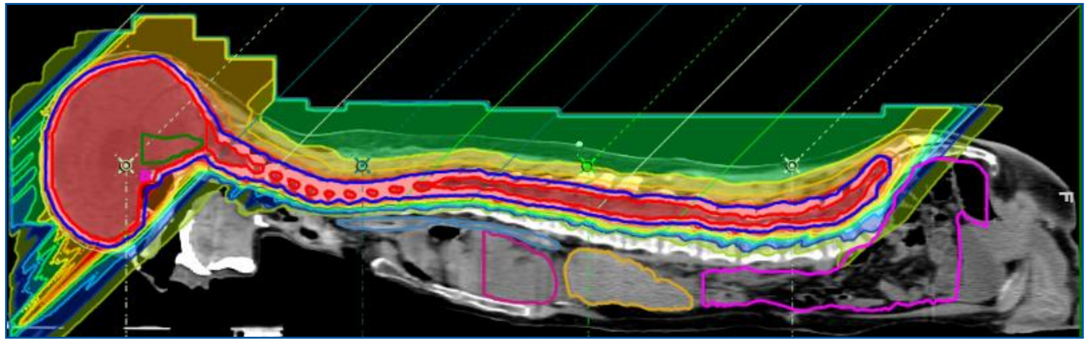
Chordomas/ Chondrosarkoma

Re-irradiation (Meningioma, Glioma)

Pediatric tumors

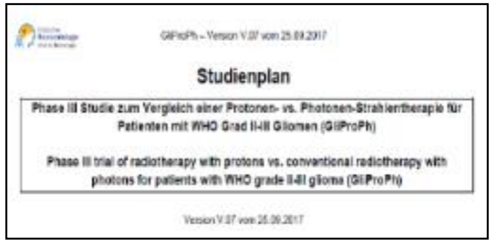


Treatment of neuro axis with protons at MIT



Clinical trials initiated by MIT

GliProPh (phase III)



GliProPh – Version V.07 vom 25.09.2017

Studienplan

Phase III Studie zum Vergleich einer Protonen- vs. Photonen-Strahlentherapie für Patienten mit WHO Grad II-III Gliomen (GliProPh)

Phase III trial of radiotherapy with protons vs. conventional radiotherapy with photons for patients with WHO grade II-III glioma (GliProPh)

Version V.07 vom 25.09.2017

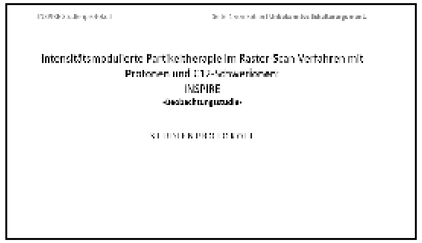
grade 2 and 3 glioma

protons vs. photons

multicentric
prospective randomised

recruiting

INSPIRE



Intensitätsmodulierte Partikeltherapie im Raster-Scan Verfahren mit Protonen und C12-Schwerionen
INSPIRE
-Beobachtungsstudie-

STUDIENPROTOKOLL

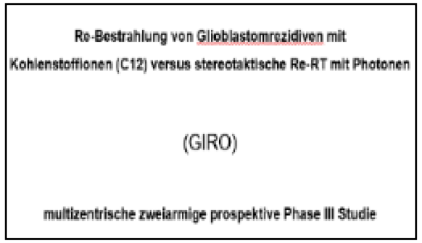
registry

all patients out of prospective trials

monocentric
prospective

recruiting

GIRO (phase III)



Re-Bestrahlung von Glioblastomrezidiven mit Kohlenstoffionen (C12) versus stereotaktische Re-RT mit Photonen

(GIRO)

multizentrische zweiarmige prospektive Phase III Studie

recurrent glioblastoma

C^{12} vs. photons

multicentric
prospective
randomised

start in Q3/2021

KOENIG (phase I/II)

Klinisches Studienprotokoll

Kohlenstoffionentherapie beim primären Glioblastom

Die KOENIG Studie

Version 1.0

26.8.2019

glioblastoma

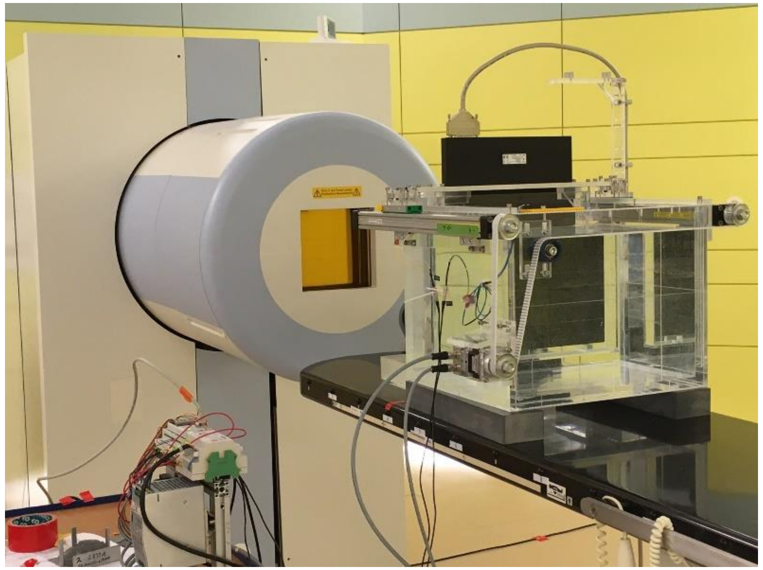
C^{12}

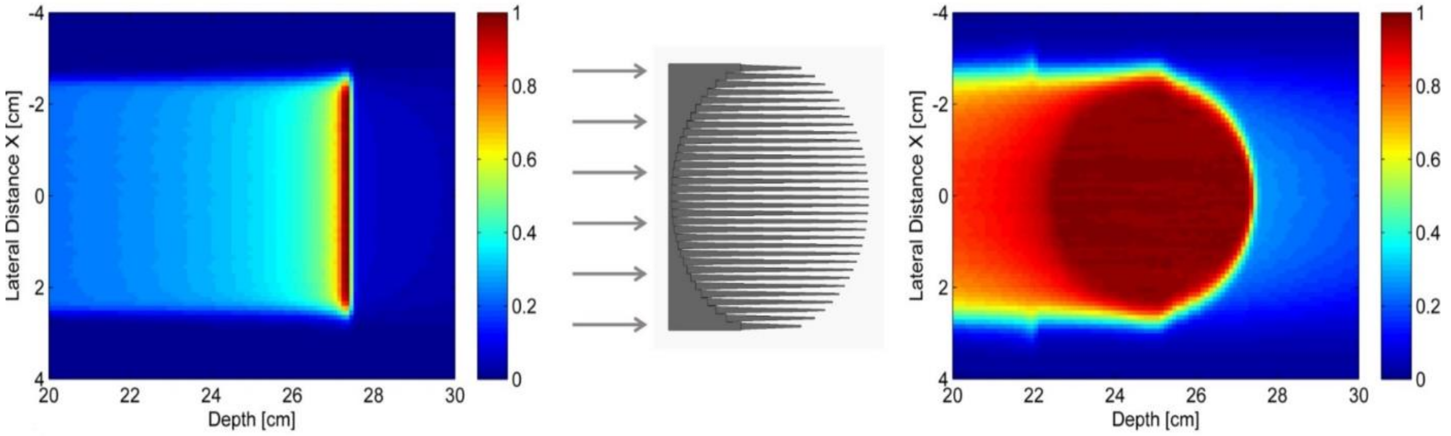
monocentric
prospective
one armed

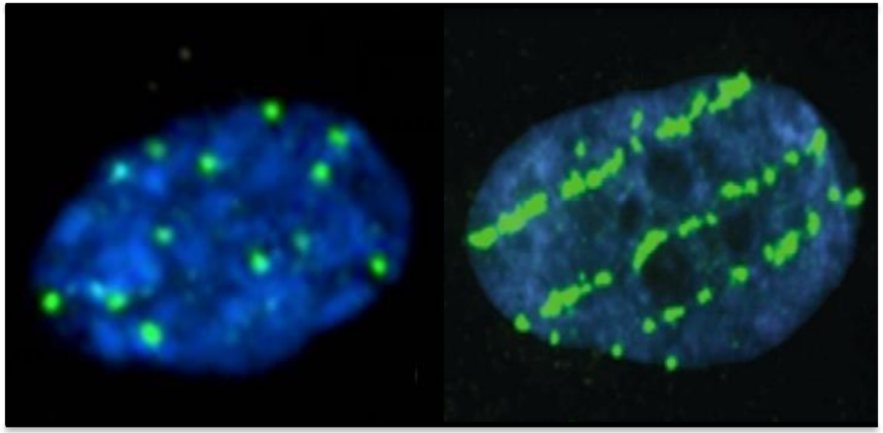
start in Q1/2022

Research@MIT

- Since 2018 MIT hosted about 18 scientific projects and groups
    - Radiobiology
    - Medical physics
    - Particle physics
- Annual grants for beamtime for hessian research groups



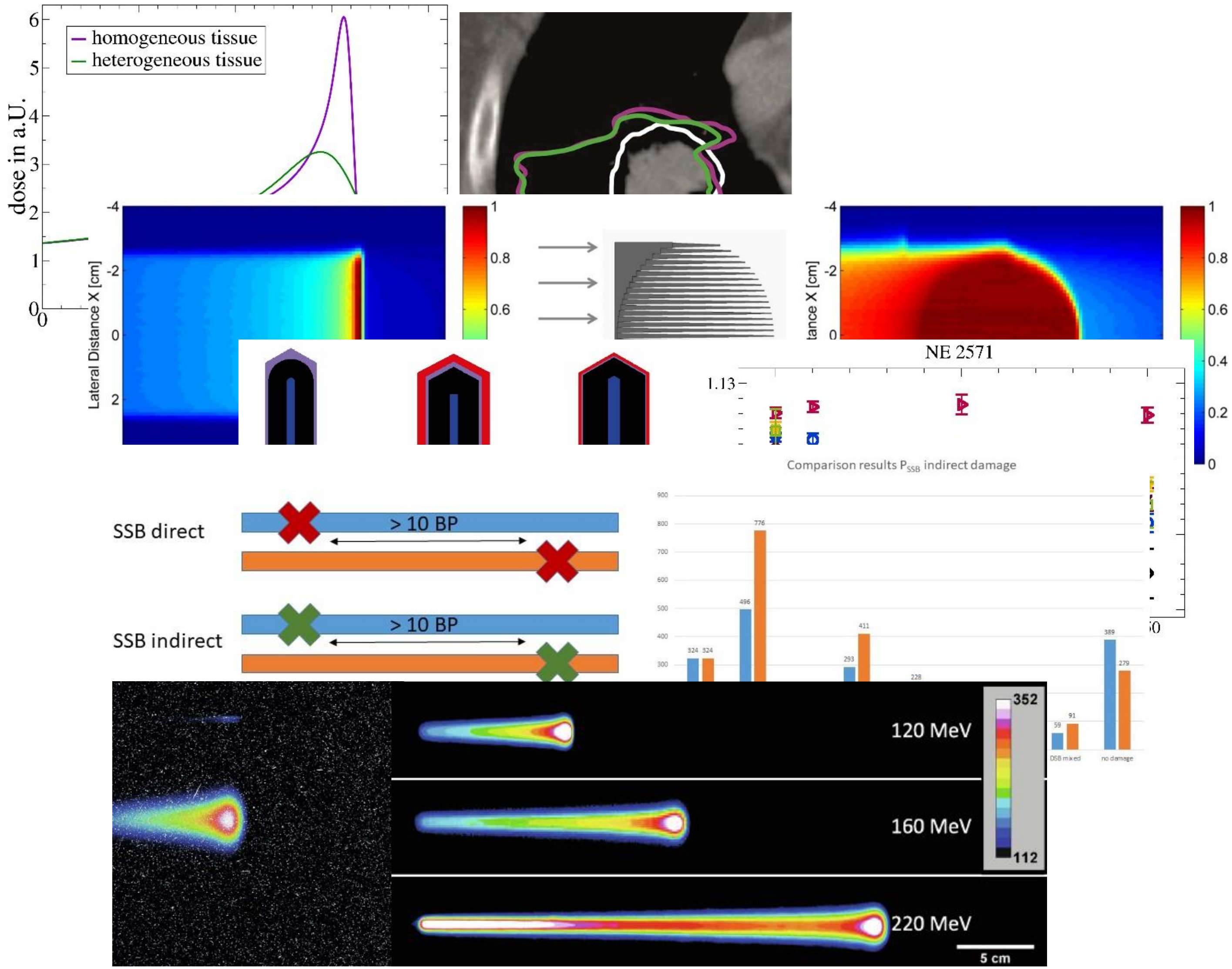




Medical Physics Research at MIT

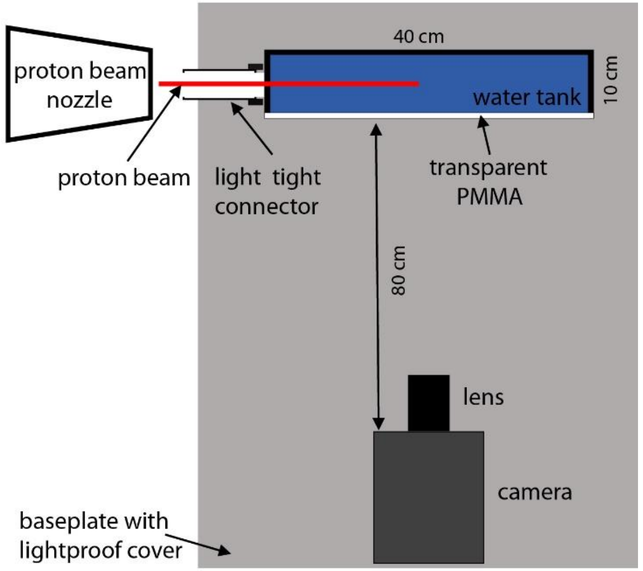
Research topics:

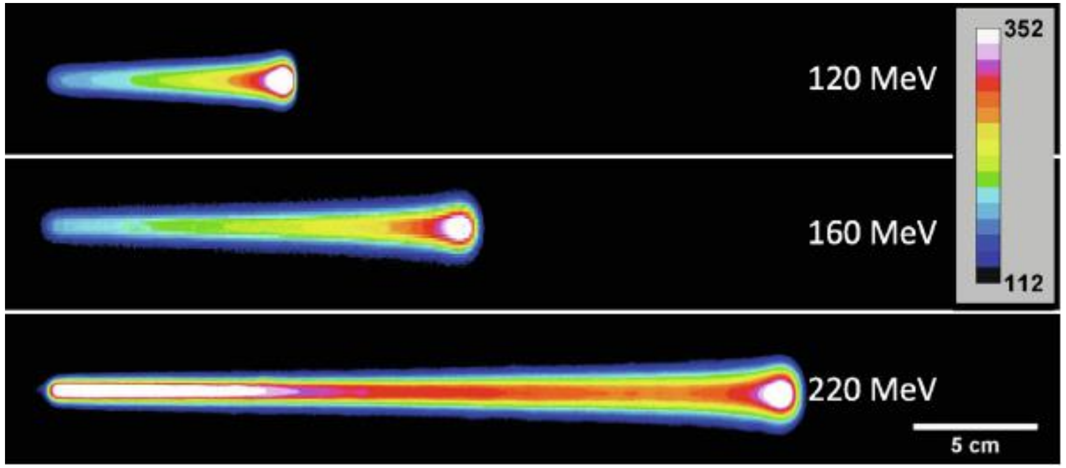
- Particle therapy of lung cancer patients
    - Investigation of lung modulation effects
    - Development of 3d range modulator
- Monte-Carlo based dosimetry on microscopic and macroscopic scales
    - Calculation of beam quality correction factors for air-filled ionization chambers
    - Track structure simulation on cellular scales using Geant4-DNA
- Optical range verification

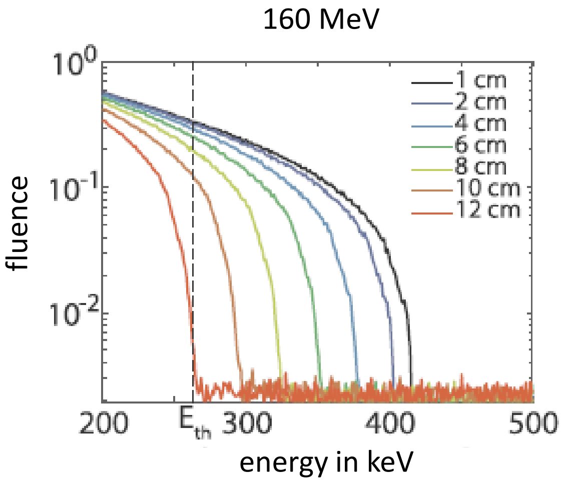


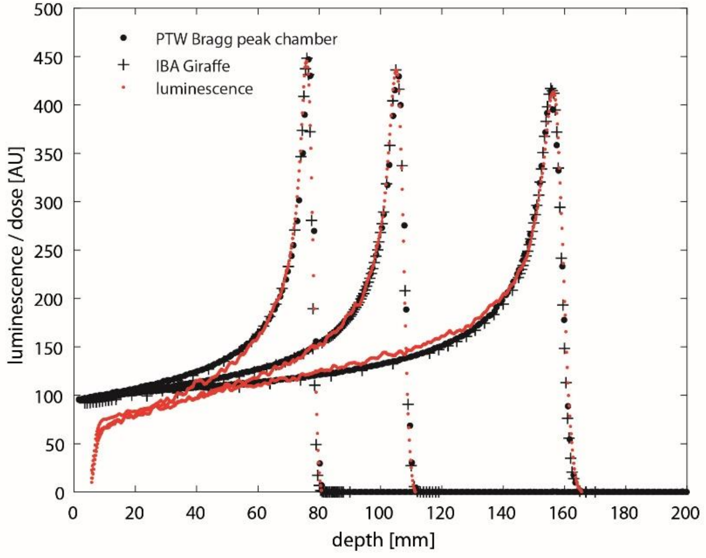
Optical range verification

- CMOS camera is used to collect light emitted by protons
- Range of protons can be determined on the sub-millimetre scale
- Results verified against PTW Bragg peak chamber and IBA Giraffe
- Changes in energy smaller than 0.5 MeV detectable
- Source of light:
    - Cherenkov radiation only at entrance region
    - Measurements of spectral fluence



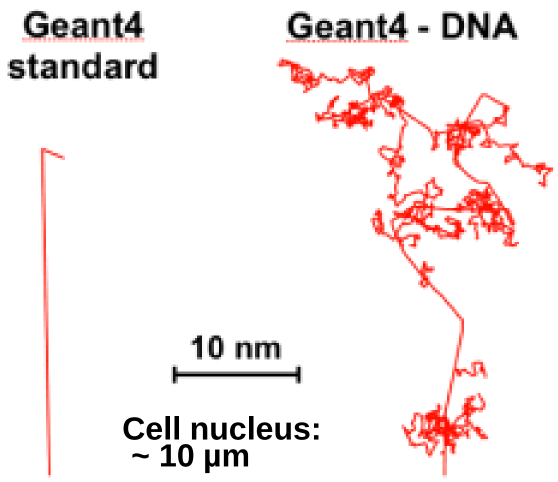


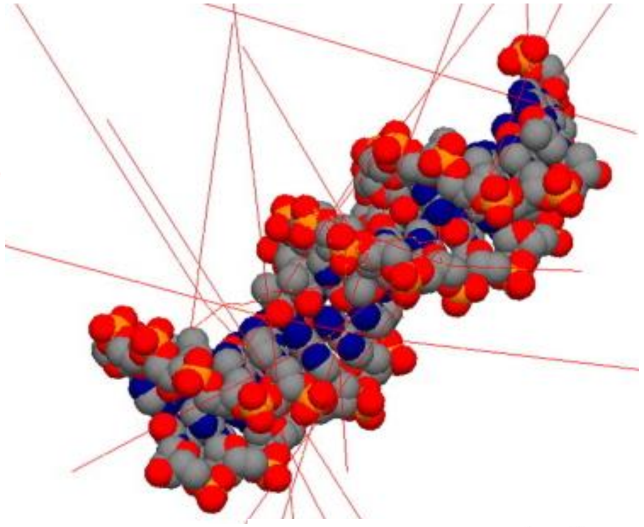


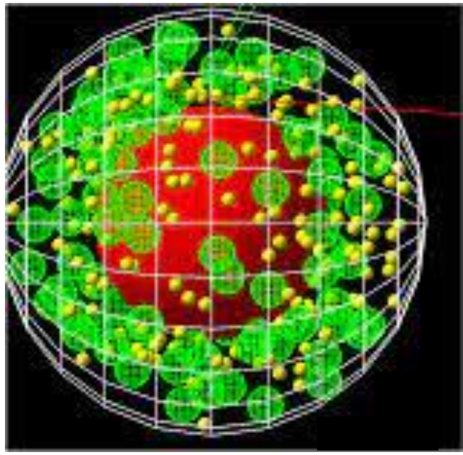


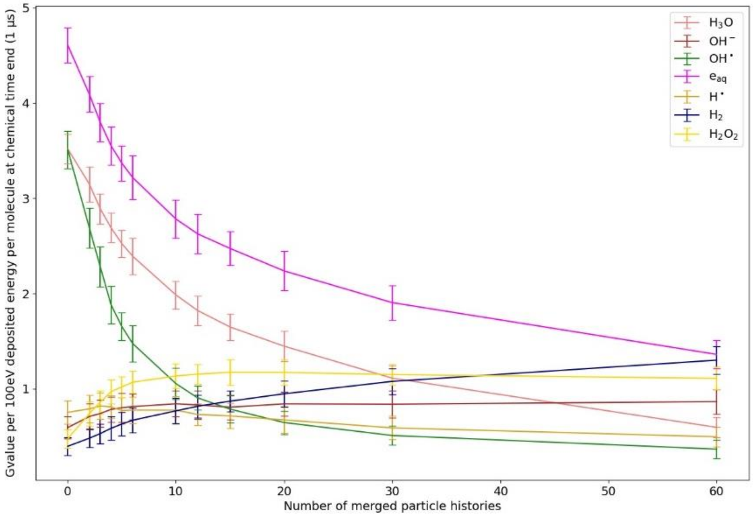
Track structure simulations

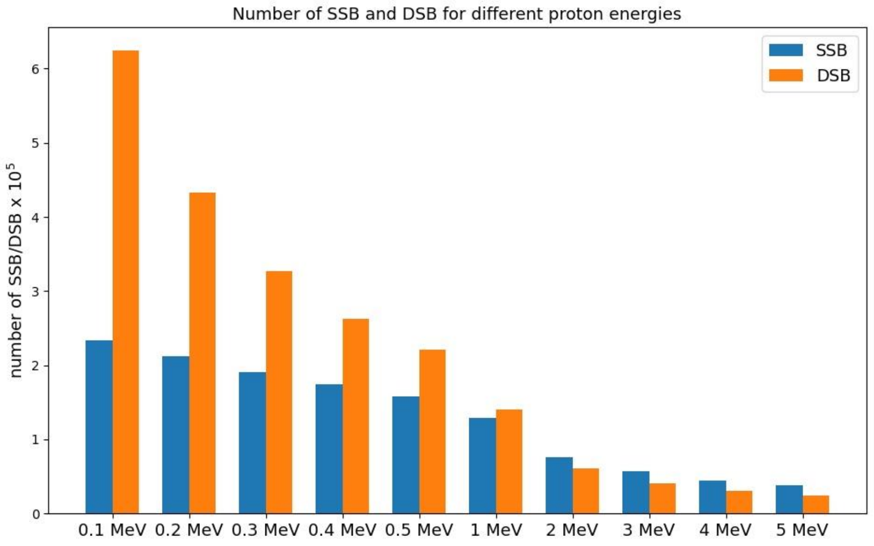
- Geant4-DNA is able to simulate track structures on the nm scale and dose deposition down to several eV
- Simulation of chemical stage as well as biological stage
- Determination of quantity and quality of DNA damage
- Influence of FLASH irradiation
- Simulations will be used to support cell experiments
- Overall goal is optimization of RBE models





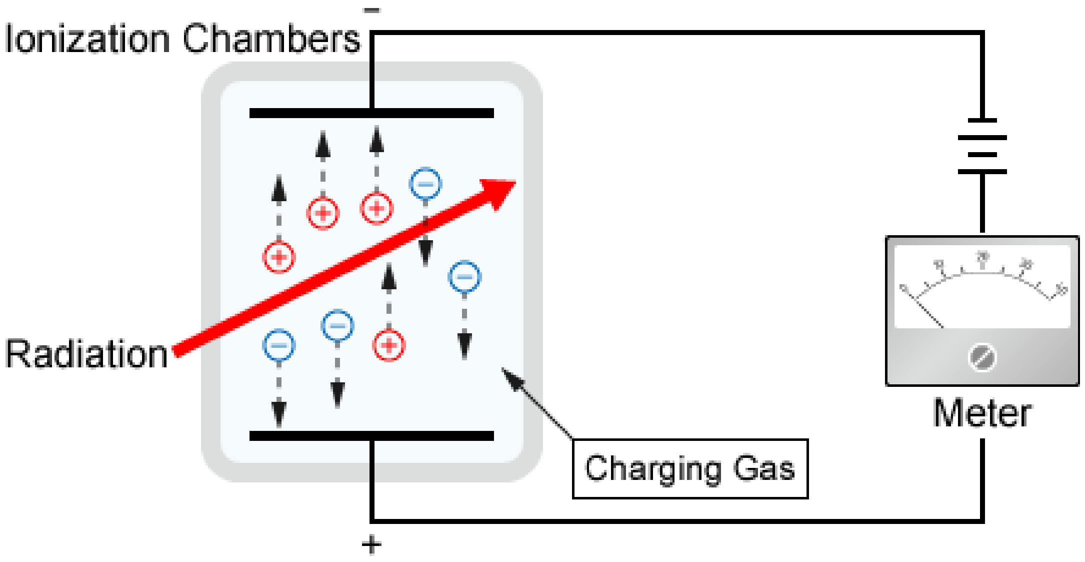


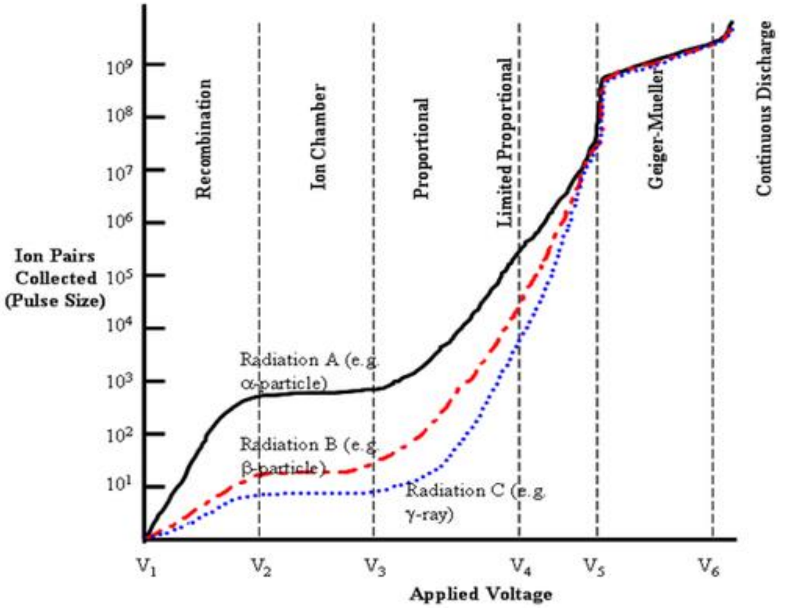




Macroscopic dosimetry

- Clinical dosimetry with air-filled ionization chambers
- Ionizing radiation creates ion-electron pairs in cavity
- Applied voltage accelerates ions and electrons to cathode and anode
- Measured charge proportional to deposited dose





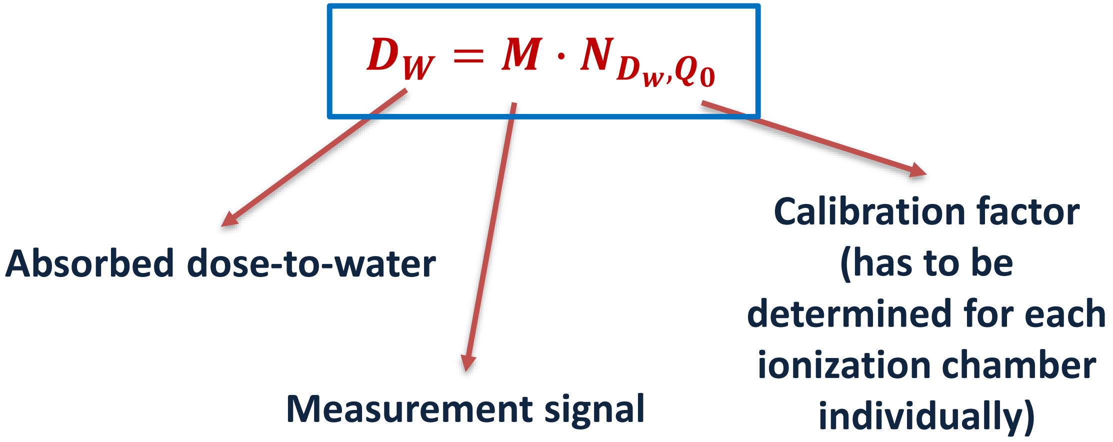
$$D = \frac{\mathrm{d}E}{\mathrm{d}m} = \frac{Q \cdot W_{\mathrm{air}}}{\rho \cdot \boxed{V}}$$

The volume of the air-filled cavity is not known with a sufficient accuracy!

Macroscopic dosimetry

- Calibration of air-filled ionization chambers

- Connection between measured charged and deposited dose under well-defined conditions



$$\boxed{D_W = M \cdot N_{D_w,Q_0}}$$

Absorbed dose-to-water

Measurement signal

Calibration factor (has to be determined for each ionization chamber individually)

PTW 30013 Farmer

PTW 34001 Roos

Parameter	Condition
Beam quality	^{60}Co γ-radiation
Measurement medium	Water
Measurement depth	10 cm
Beam size	10 cm x 10 cm
Temperature	293.15 K
Pressure	101.325 hPa

Macroscopic dosimetry

- If measurement conditions differ from calibration conditions each deviation has to be accounted for!
  - Background: $\boldsymbol{M_0}$
  - Change in air temperature and pressure: $\boldsymbol{k_{p,t}}$
    Air temperature and pressure influence the number of air molecules and, hence, the amount of created charge in the air cavity
  - Response of the chamber to different beam qualities Q: $\boldsymbol{k_Q}$
    Beam quality correction factor

$$\boxed{D_W = (M - M_0) \cdot N_{D_W,Q_0} \cdot k_Q \cdot \prod_i k_i}$$

Beam quality correction factor $\boldsymbol{k_Q}$

Further correction factors:

- Applied voltage
- Saturation effects
- Humidity
- Effective point of measurement
- …

Macroscopic dosimetry

- Beam quality correction factor accounts for different response of the ionization chamber between calibration beam quality Q_0 and used beam quality Q

- Ideally, should be determined for each ionization chamber individually and for each beam quality employed!

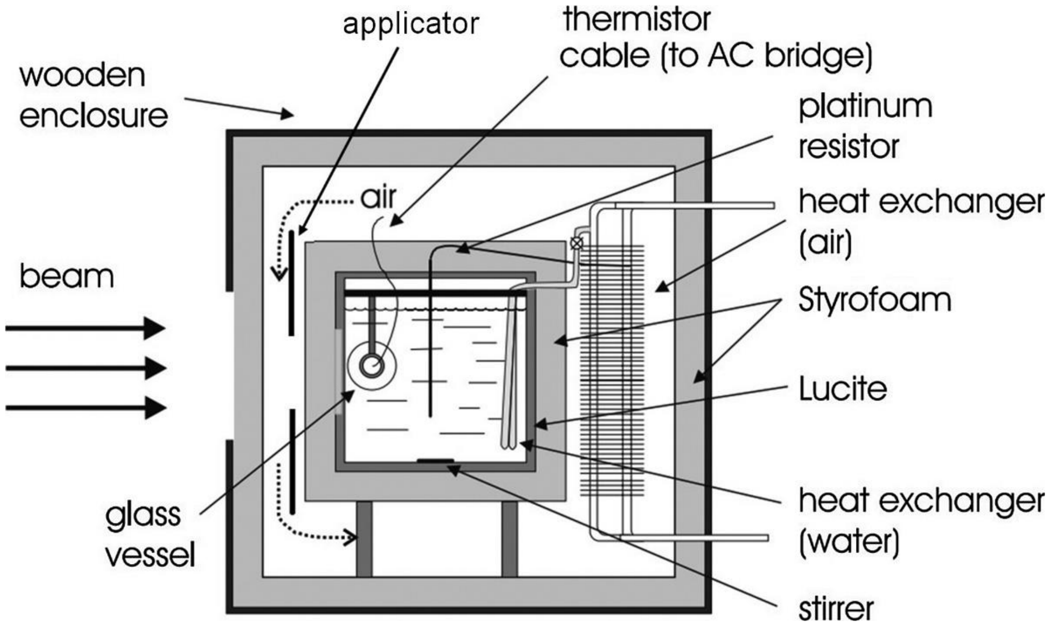
- But how?

- Option 1: Measurement-based determination:

$$k_{Q,Q_0} = \frac{N_{D_\mathrm{w},Q}}{N_{D_\mathrm{w},Q_0}} = \frac{(D_\mathrm{w})_Q/M_Q}{(D_\mathrm{w})_{Q_0}/M_{Q_0}}$$

- Measurement with calorimetry

- High experimental effort
- Not convenient for clinical routine



Macroscopic dosimetry

- Beam quality correction factor accounts for different response of the ionization chamber between calibration beam quality Q_0 and used beam quality Q
- Ideally, should be determined for each ionization chamber individually and for each beam quality employed!
- But how?
- Option 2: Theoretical calculation:

$$k_{Q,Q_0} = \underbrace{\frac{\left(s_{\mathrm{w,air}}\right)_Q}{\left(s_{\mathrm{w,air}}\right)_{Q_0}}}_{\text{Stopping power ratios water-to-air}} \cdot \underbrace{\frac{P_Q}{P_{Q_0}}}_{\text{Fluence perturbation correction}} \cdot \underbrace{\frac{\left(W_{\mathrm{air}}\right)_Q}{\left(W_{\mathrm{air}}\right)_{Q_0}}}_{\text{Energy needed to create electron-ion-pair in air}}$$

Stopping power ratios water-to-air

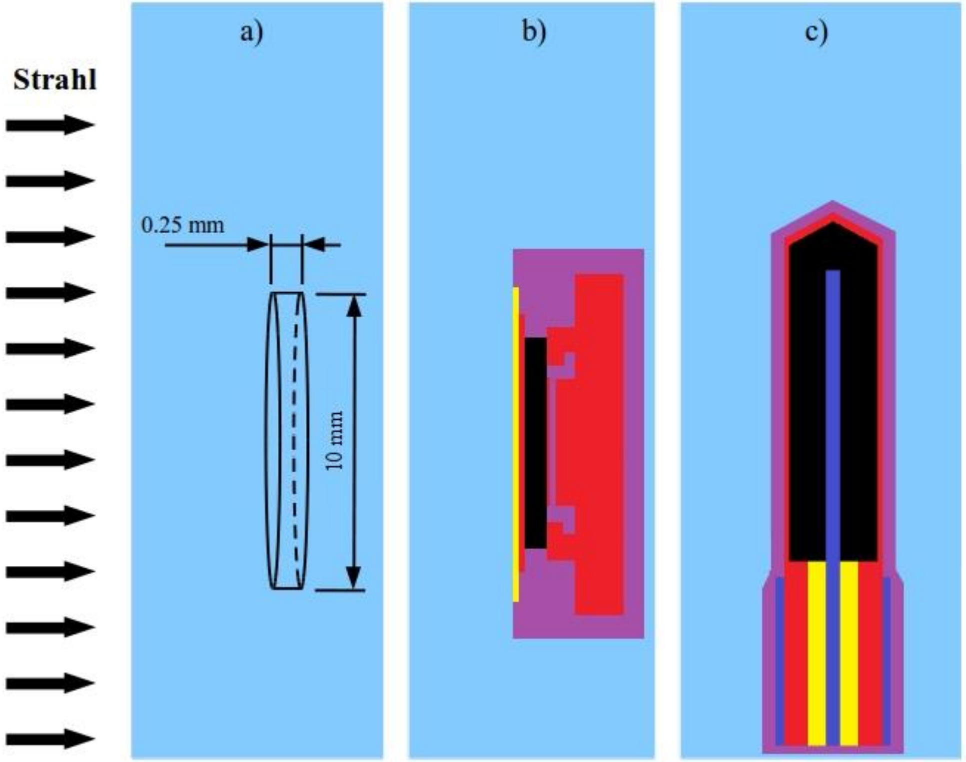
Fluence perturbation correction

Energy needed to create electron-ion-pair in air

Theoretically calculated k_Q factors are tabulated in dosimetry protocols like the IAEA TRS-398 Code of Practice

Macroscopic dosimetry

- Beam quality correction factor accounts for different response of the ionization chamber between calibration beam quality Q_0 and used beam quality Q
- Ideally, should be determined for each ionization chamber individually and for each beam quality employed!
- But how?
- Option 3: Calculation with the Monte Carlo method:
  - Calculation of absorbed dose-to-water $\boldsymbol{D_W}$ in reference volume
  - Modelling of ionization chamber geometry in Monte Carlo code
  - Calculation of dose $\boldsymbol{D_{det}}$ absorbed in air cavity of ionization chamber
  - Calculation of doses for calibration beam quality and user beam quality



Macroscopic dosimetry

- Beam quality correction factor accounts for different response of the ionization chamber between calibration beam quality Q_0 and used beam quality Q

- Ideally, should be determined for each ionization chamber individually and for each beam quality employed!

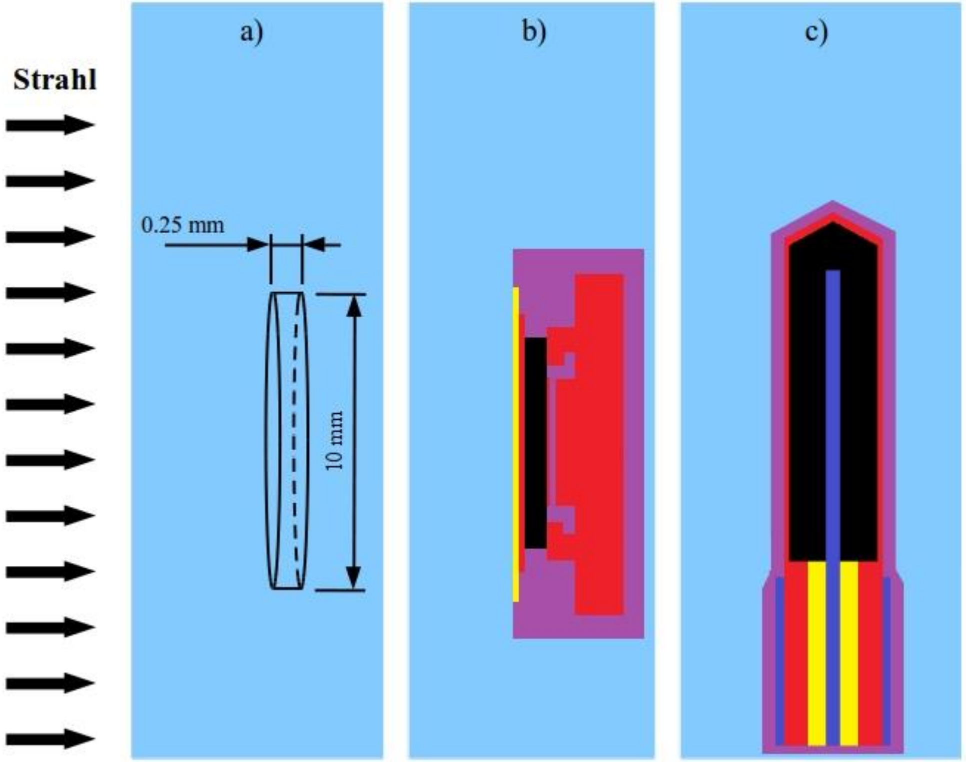
- But how?

- Option 3: Calculation with the Monte Carlo method:
  - Determination of f_Q factor (overall response of chamber):

$$f_Q = \left(\frac{D_\mathrm{w}}{D_\mathrm{det}}\right)_Q = \left(s_\mathrm{w,air}\right)_Q \cdot P_Q$$

  - Calculation of k_Q factor:

$$\boxed{k_Q = \frac{f_Q}{f_{Q_0}} \cdot \frac{(W_\mathrm{air})_Q}{(W_\mathrm{air})_{Q_0}}}$$



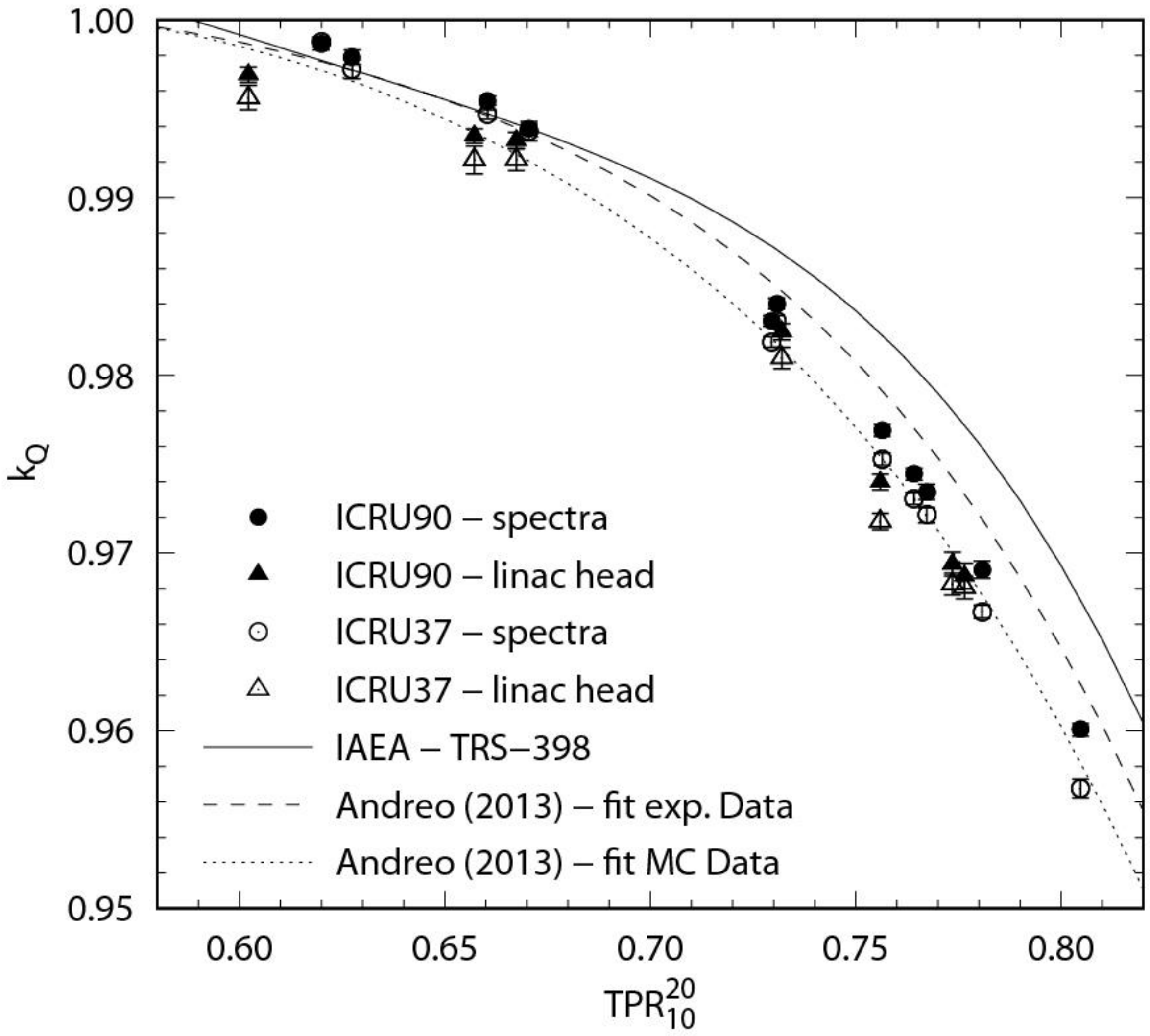
Macroscopic dosimetry

- For clinical photon beams, experimentally as well as Monte Carlo calculated values for k_Q factors exist

- Agreement between experimentally determined and Monte Carlo calculated k_Q factors on the 1%-level

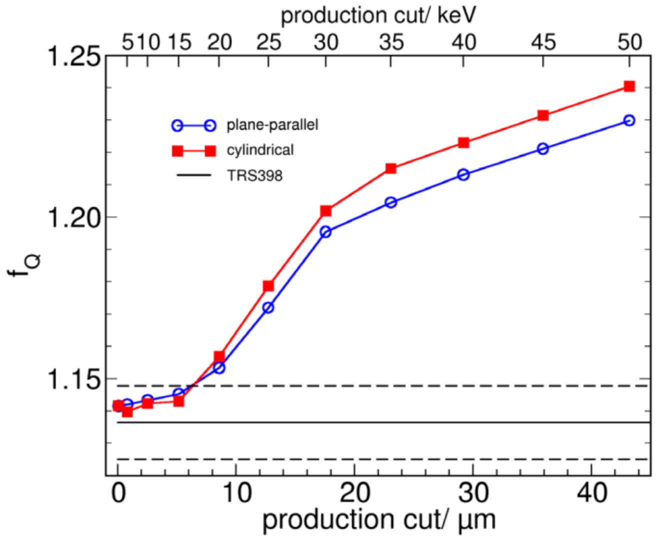
- For protons, data are scarce

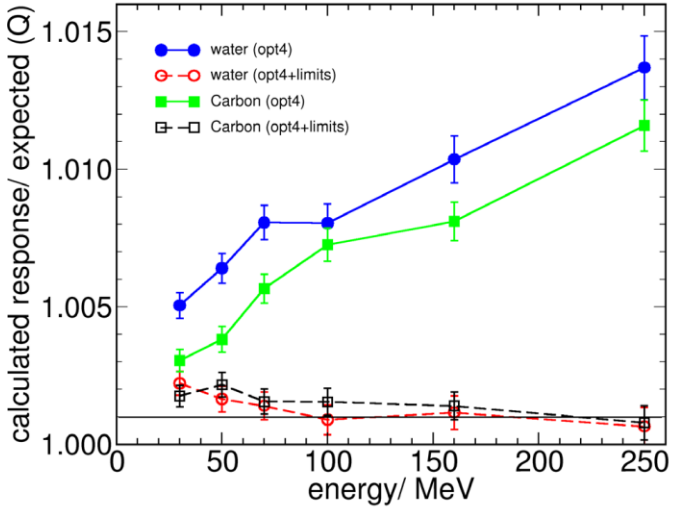
- Hence, for the update of the IAEA TRS-398 Code of Practice, experimental as well as Monte Carlo calculated values will be created and included



Macroscopic dosimetry

- Used Monte Carlo codes: PENH, FLUKA and Geant4
- PENH values from Carles Gomà (Hospital Cliníc de Barcelone)
- FLUKA and Geant4 values produced at our working group
- First step: Optimization of codes
  (production cut and length of a condensed-history step)

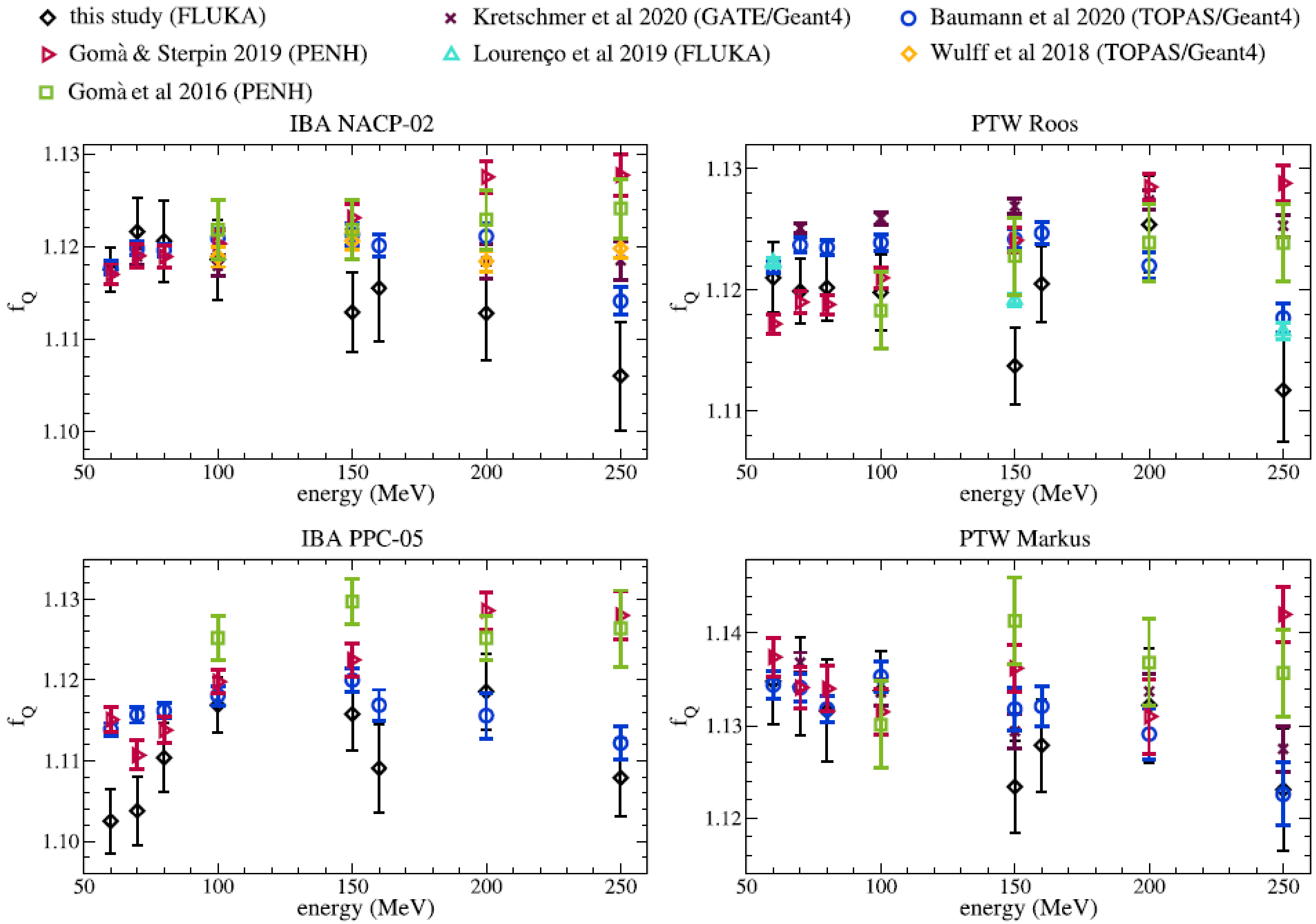




A SIMULATION TOOLKIT

Macroscopic dosimetry

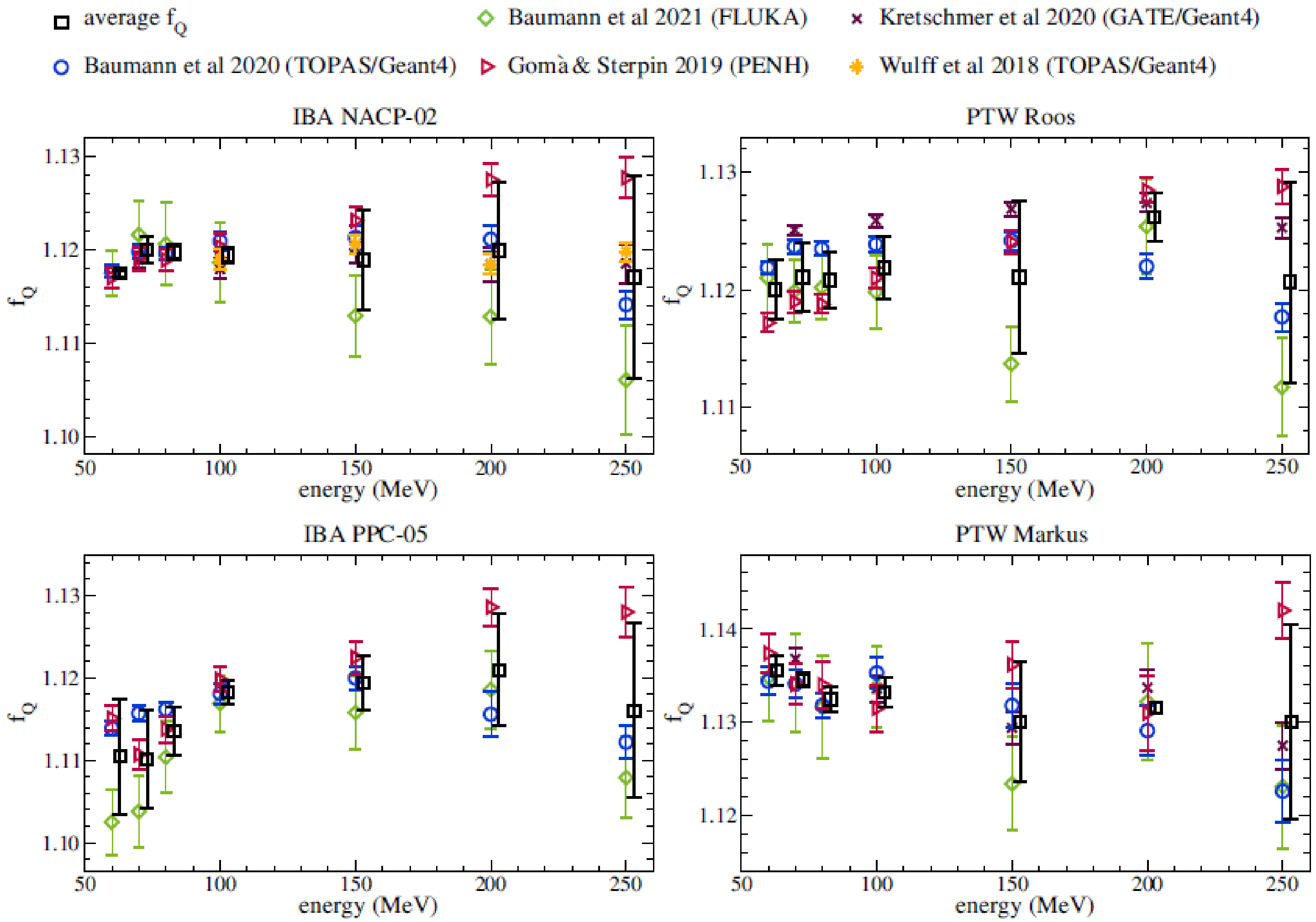
- Comparison of Monte Carlo calculated f_Q factors in proton beams
- Good agreement (~1%) for low energies
- Larger differences (up to 2%) for high energies
  - Role of nuclear interactions?
- FLUKA leads to smallest values, PENH to largest



Macroscopic dosimetry

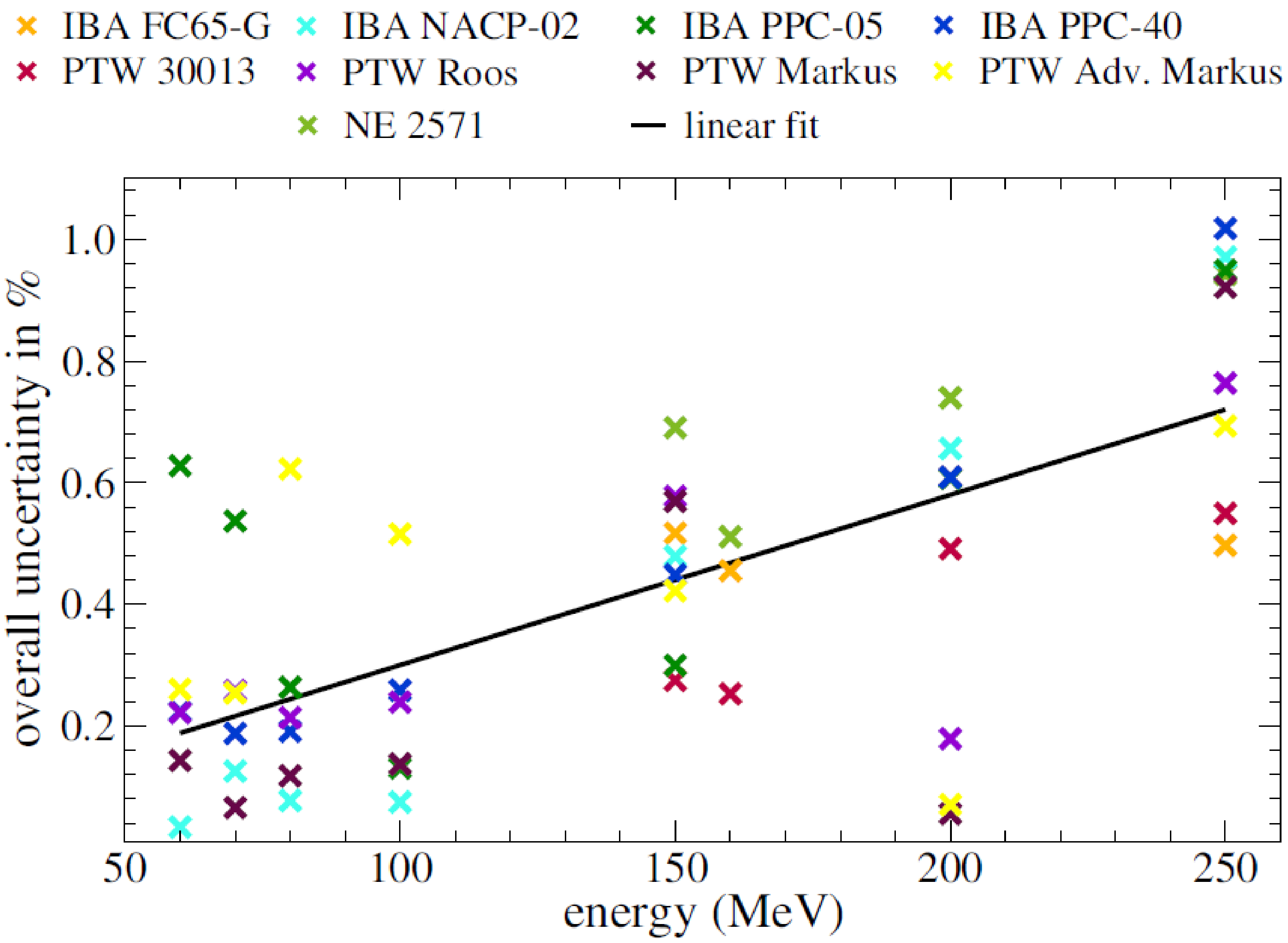
- Determination of average Monte Carlo calculated $\boldsymbol{f_Q}$ factors in proton beams

- Average Monte Carlo calculated $\boldsymbol{f_Q}$ factors are constant over the energy regime within ~1%



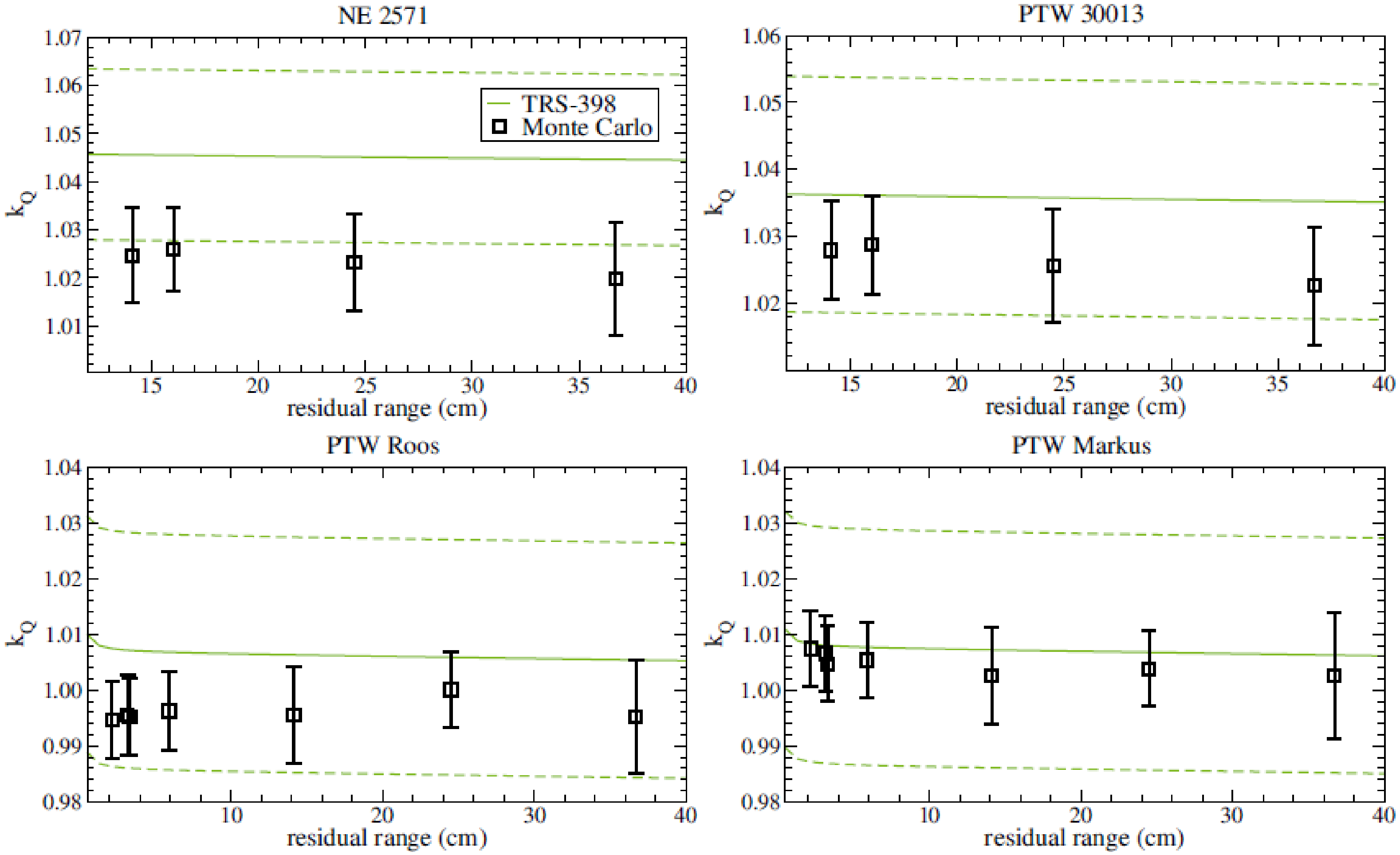
Macroscopic dosimetry

- Determination of average Monte Carlo calculated $\boldsymbol{f_Q}$ factors in proton beams
- Average Monte Carlo calculated $\boldsymbol{f_Q}$ factors are constant over the energy regime within ~1%
- Overall uncertainty for low energies relatively small (~0.3%)
- Overall uncertainty increases with proton energy up to ~1%



Macroscopic dosimetry

- Comparison of Monte Carlo calculated beam quality correction factors k_Q with values from IAEA TRS-398
- Values agree within one standard uncertainty
- Monte Carlo calculated values are smaller than values from IAEA TRS-398
- Differences up to 2.4%
- Uncertainty of Monte Carlo calculated values is smaller

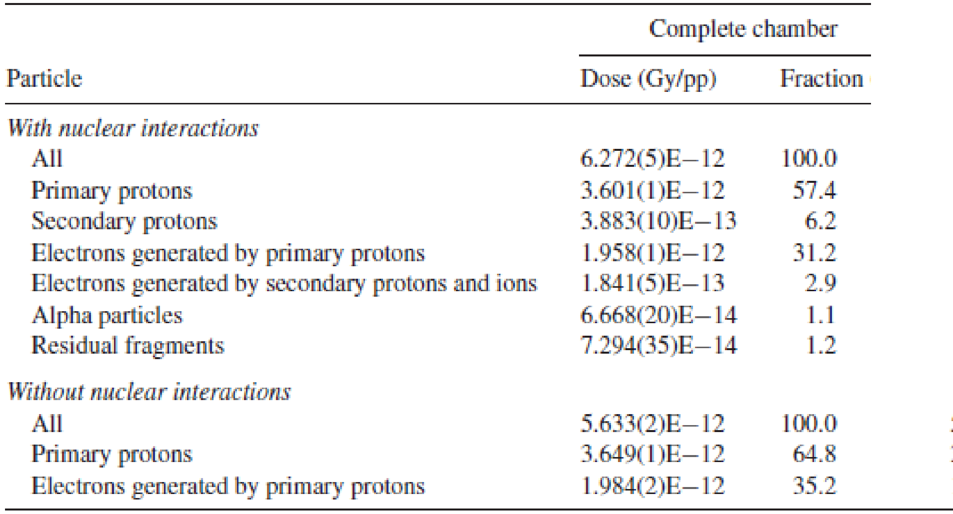


Macroscopic dosimetry

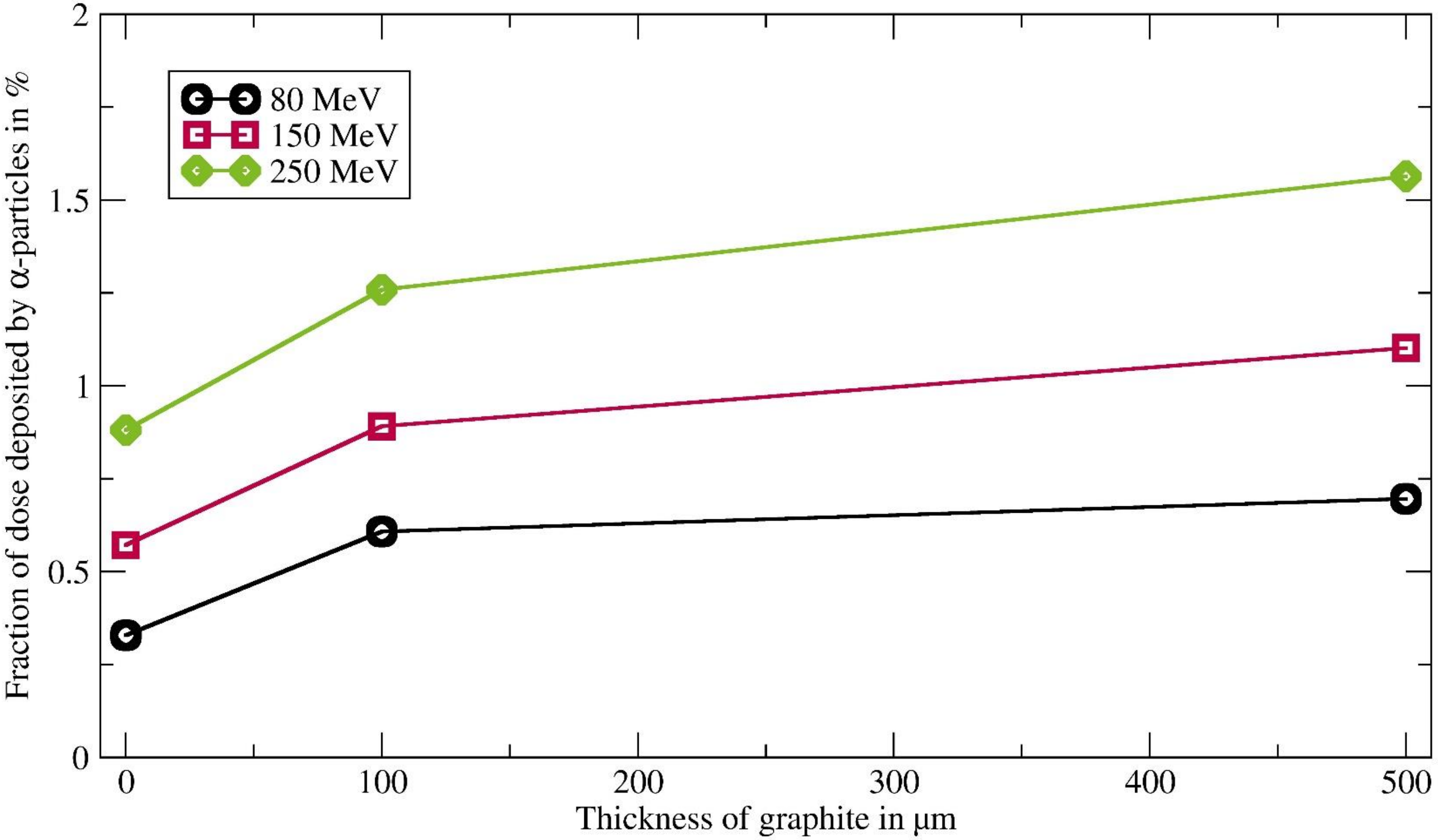
- Potential role of nuclear interactions

- Modelling of nuclear interactions complex and might be different between individual Monte Carlo codes

- Impact increases with energy which might explain the difference at high energies



Particle	Complete chamber				
	Dose (Gy/pp)	Fraction			
With nuclear interactions					
All	6.272(5)E−12	100.0			
Primary protons	3.601(1)E−12	57.4			
Secondary protons	3.883(10)E−13	6.2			
Electrons generated by primary protons	1.958(1)E−12	31.2			
Electrons generated by secondary protons and ions	1.841(5)E−13	2.9			
Alpha particles	6.668(20)E−14	1.1			
Residual fragments	7.294(35)E−14	1.2			
Without nuclear interactions					
All	5.633(2)E−12	100.0	5.618(2)E−12	100.0	−0.3
Primary protons	3.649(1)E−12	64.8	3.647(1)E−12	65.0	<0.1
Electrons generated by primary protons	1.984(2)E−12	35.2	1.971(2)E−12	35.1	−0.7



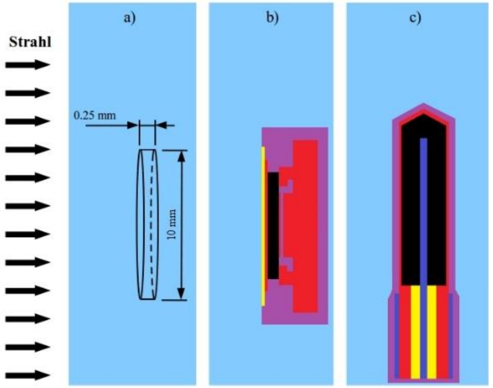
Macroscopic dosimetry

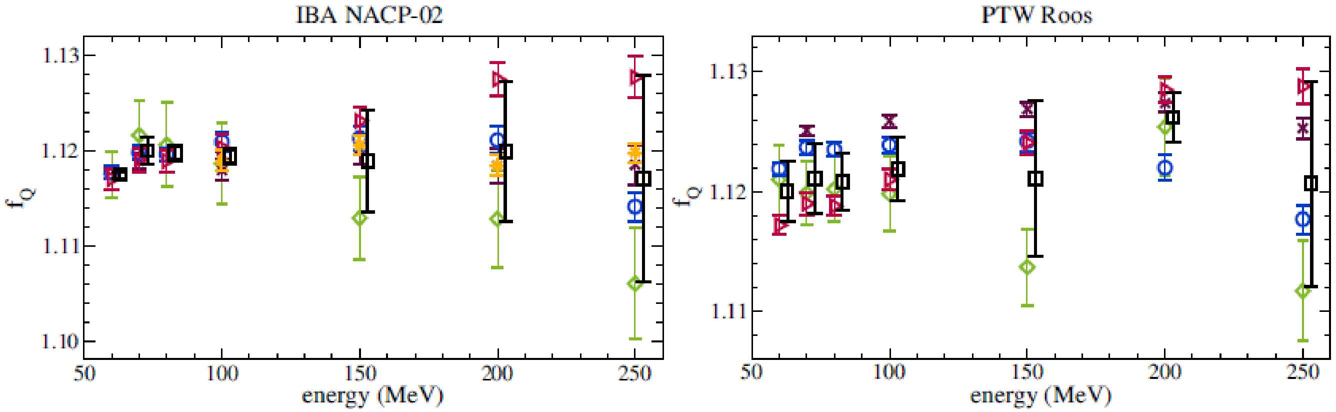
- Conclusion:

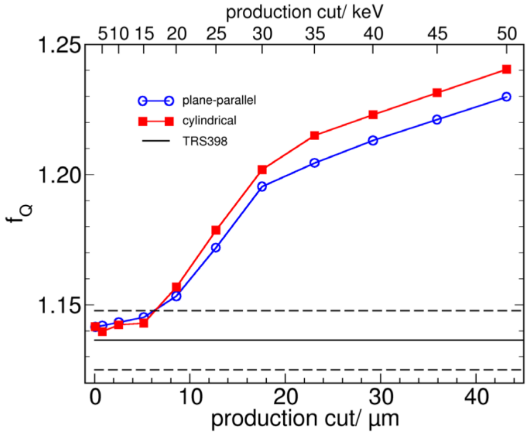
- Monte Carlo calculations are an efficient tool for dosimetry calculations

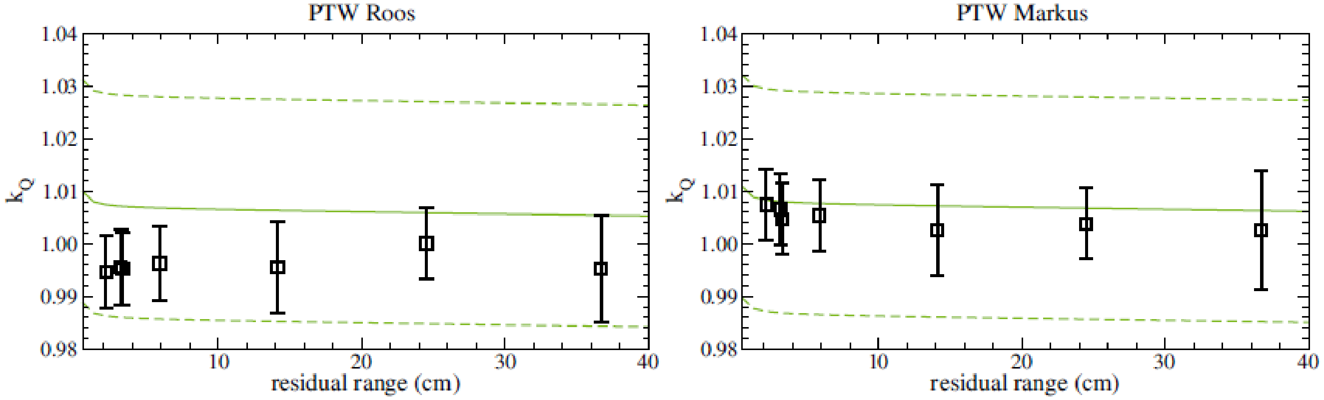
- Physics models and transport parameters have to be optimized

- Difference between codes for high energies most likely due to nuclear interactions



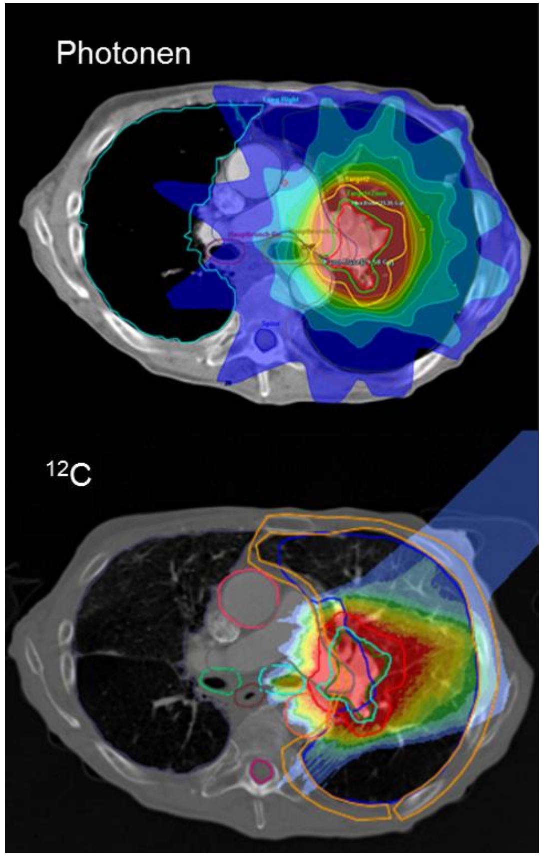


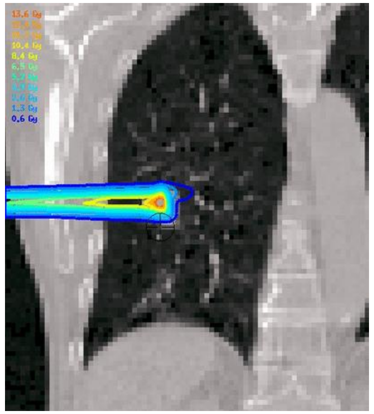




PT of thoracic tumors

- Particle therapy promising alternative to photon-based radiotherapy for lung cancer patients
    - Conformal dose deposition in tumor and significantly better sparing of normal tissue
    - Higher biological effectiveness for carbon ion
- However: major challenges!
    - Motion
    - Lung modulation effects





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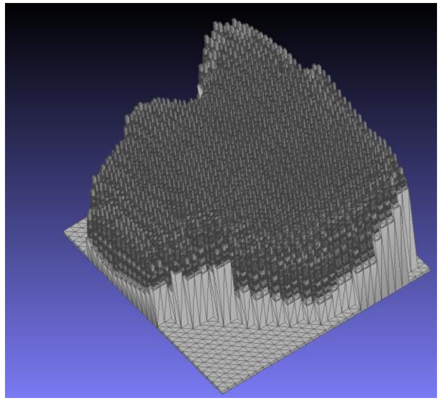
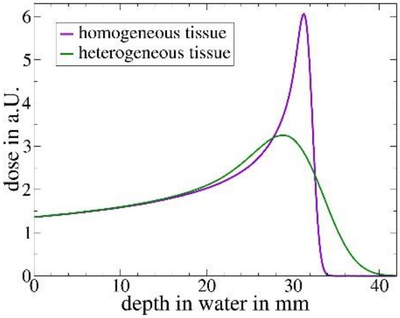
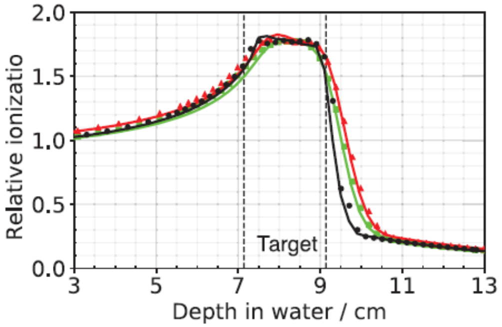


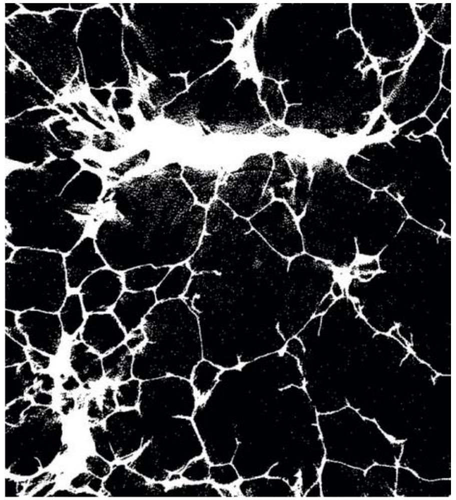


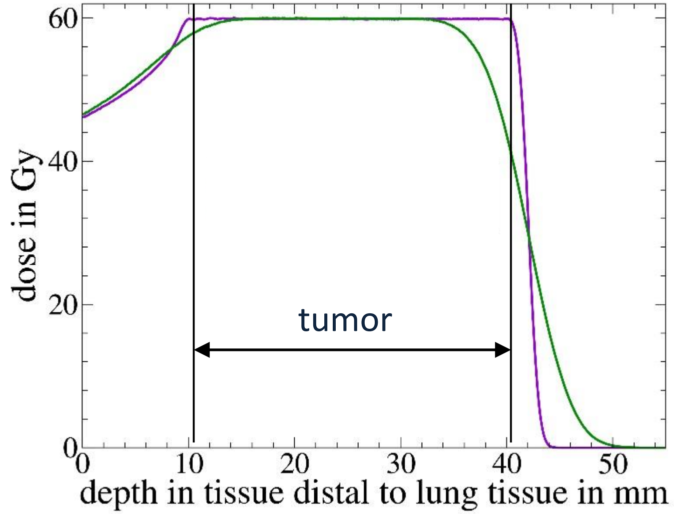


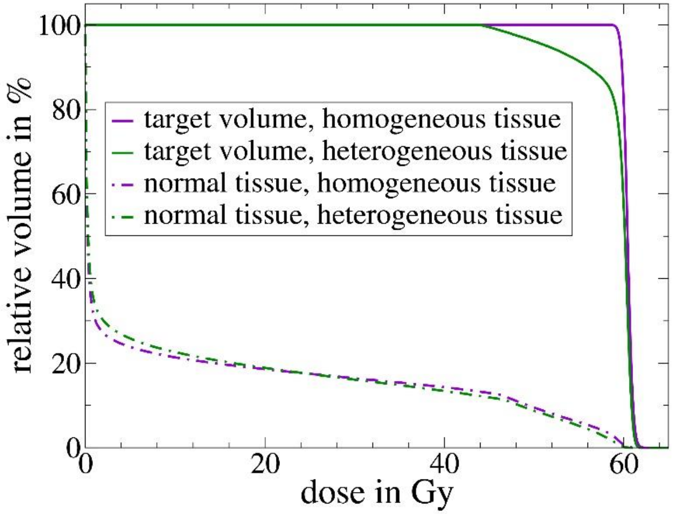
Lung modulation effects

- Heterogeneous structure of lung tissue leads to degradation of Bragg peak
- Potential underdosage of target volume and overdosage of distal normal tissue
- Effect should be considered in treatment planning
- Problem: Structure of lung tissue is not sufficiently resolved in treatment-planning CTs
    - More homogeneous
    - Consideration of effects hardly possible

beam







Lung modulation effects

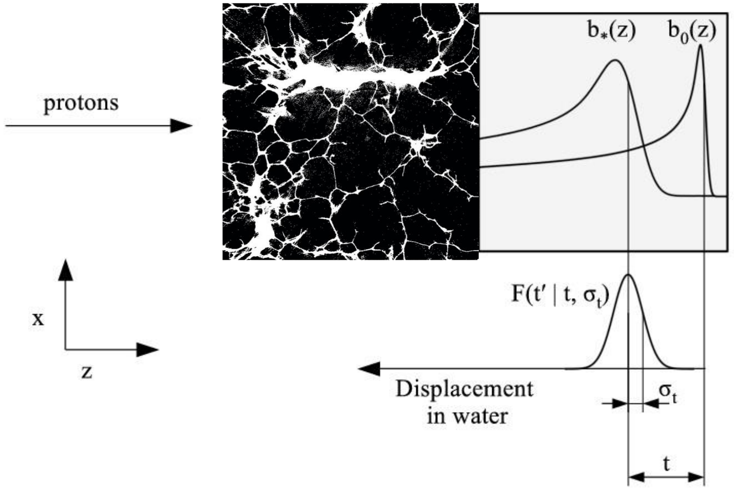
- Mathematical description of Bragg peak degradation by convolution with normal distribution

- Definition of material characteristics **modulation power** P_{mod}

- Modulation power can be determined experimentally

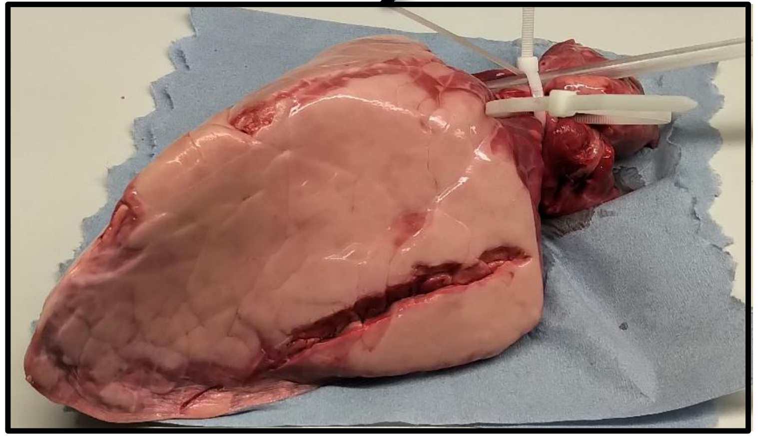
  - Applicability for human lung tissue?

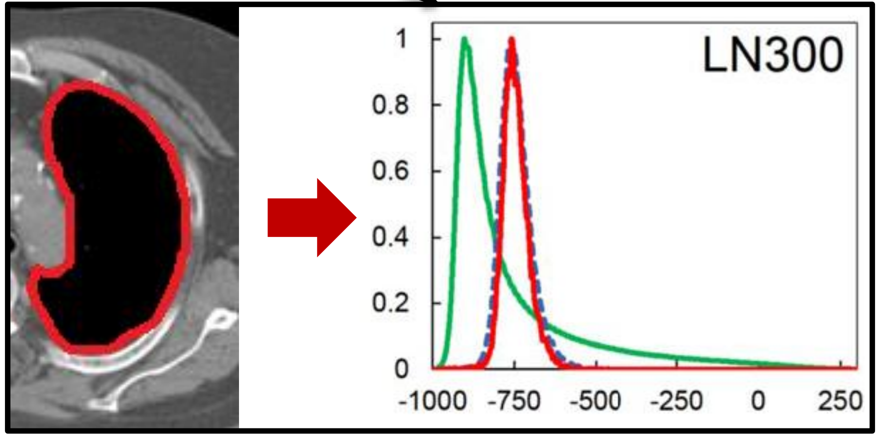
- Estimation of modulation power on basis of clinical CT-images with the help of a histogram analysis



$$b_*(z) = (F \times b_0)(z) = \\ = \int_{-\infty}^{\infty} F(t'|t,\sigma_t) b_0(z+t')\, dt'$$

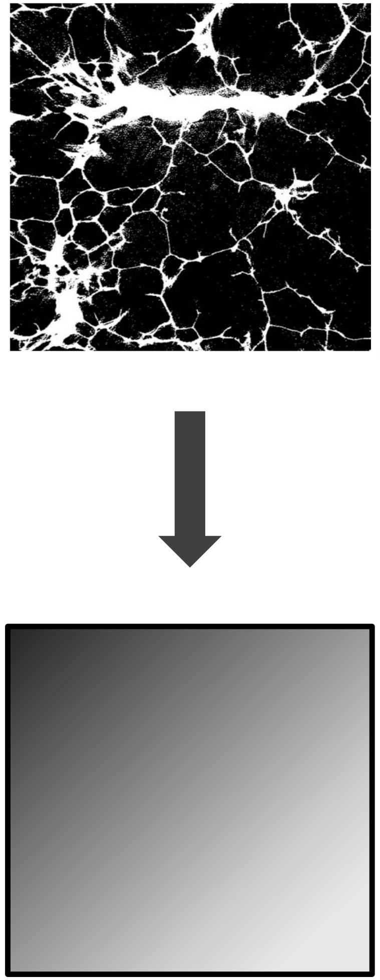
$$P_{\text{mod}} \equiv \frac{\sigma_t^2}{t}$$





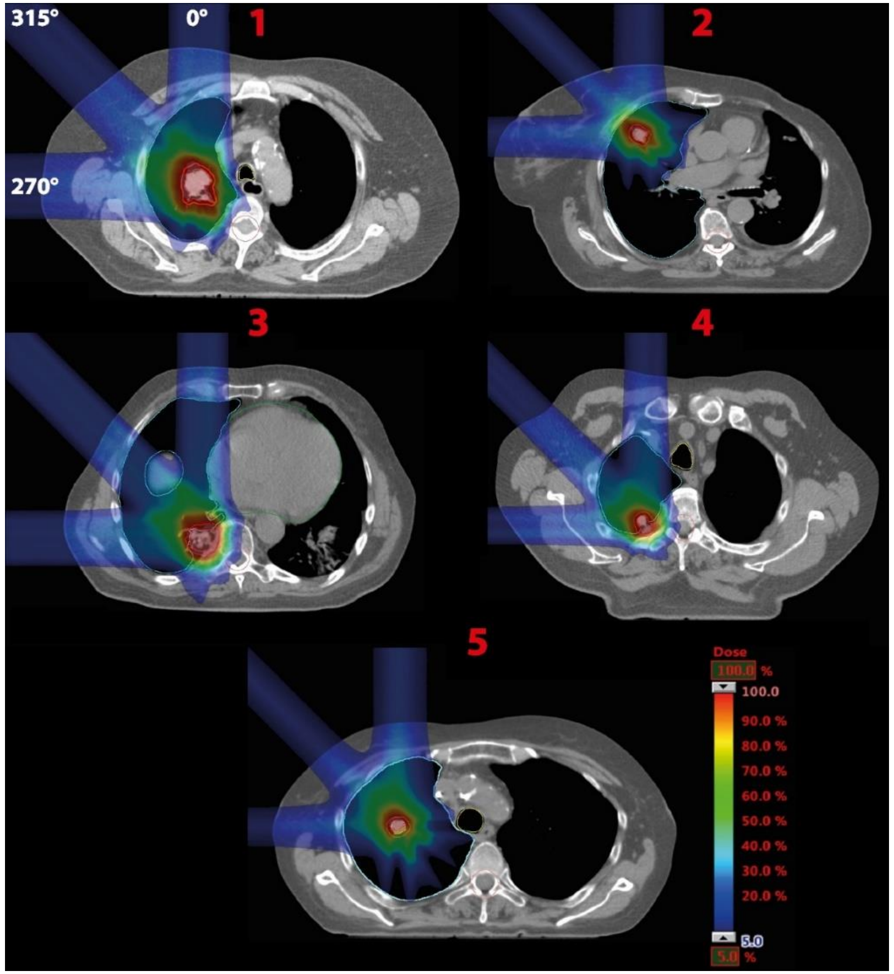
Lung modulation effects

- Monte-Carlo based solution to reproduce lung modulation effects on clinical CT-images
- Modulation of physical density of lung voxels
- Investigation of dose uncertainties for clinical treatment plan
- Different tumor volumes, positions within the lung, and irradiation strategies



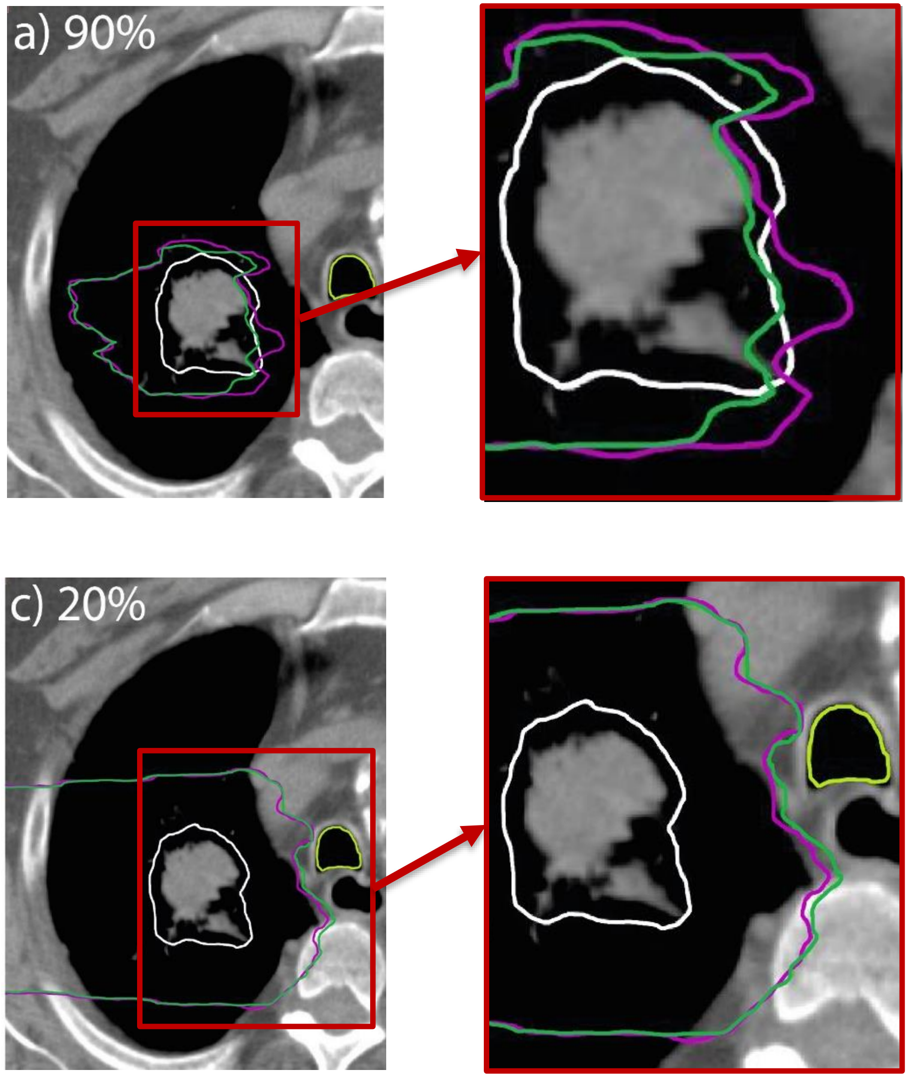
- Binary density distribution
- Heterogeneous fine structure not depicted in CT-images

- Rougher structure (CT-voxel)
- Modulation of mass density



Lung modulation effects

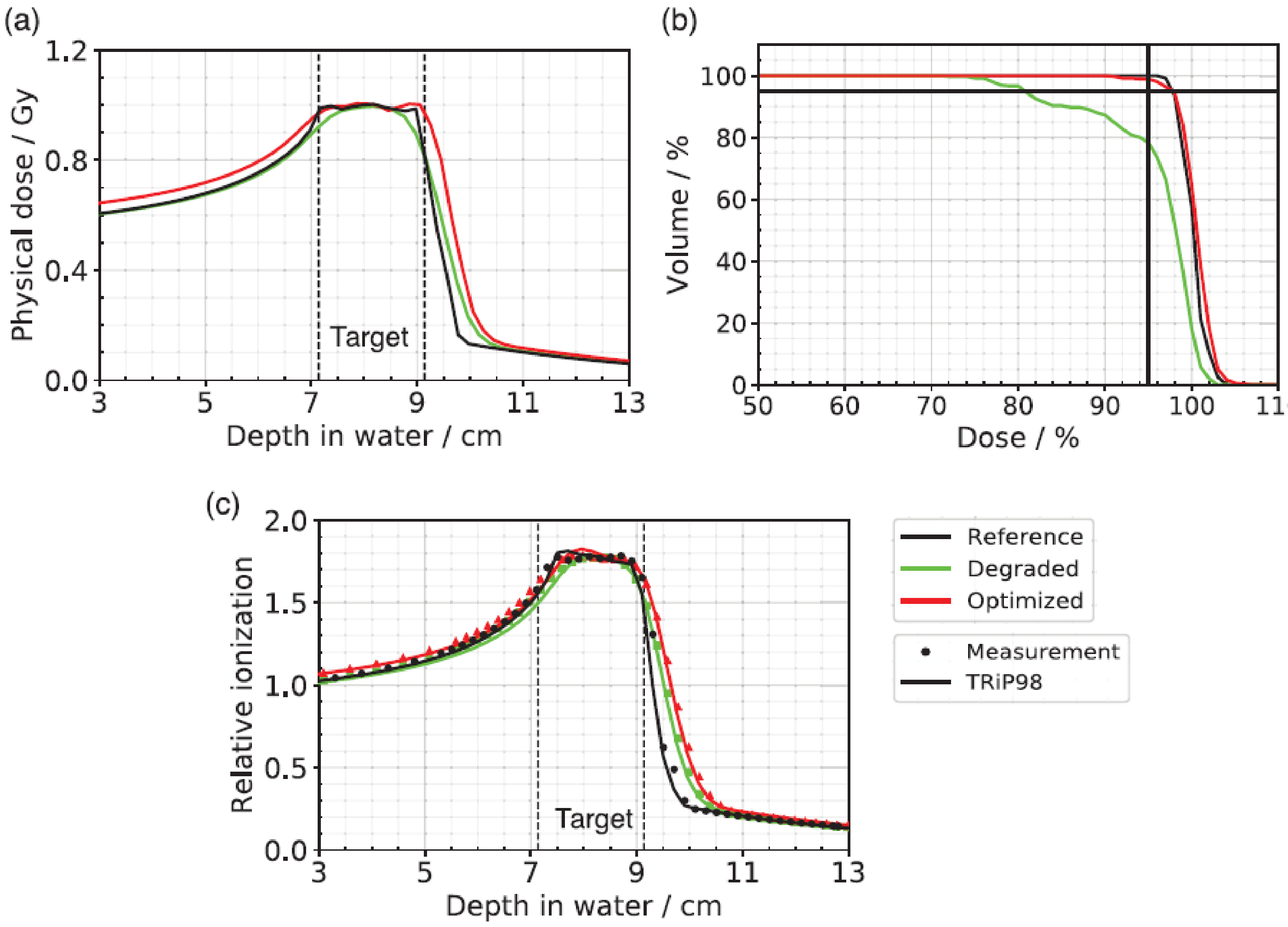
- Lung modulation effects lead to smaller region of high dose
  - Range uncertainties of up to 10 mm
- The region of low dose is smaller and reaches farther
  - Range uncertainties of up to 5 mm
- Underdosage of CTV up to -5% for protons
- Effects significantly more pronounced for carbon ions



Patient	Underdosage in terms of average dose in CTV
1	**-2.1%**
2	**-3.1%**
3	**-1.8%**
4	**-2.2%**
5	**-4.9%**

Lung modulation effects

- Consideration of lung modulation effects in treatment planning
- Degradation of base data depth dose curves for dose calculation and optimization
    - Reference plan optimized without consideration of lung modulation effects
    - Lung modulation effects lead to underdosage of target volume
    - Improved optimization reduces dose uncertainties to <0.5%

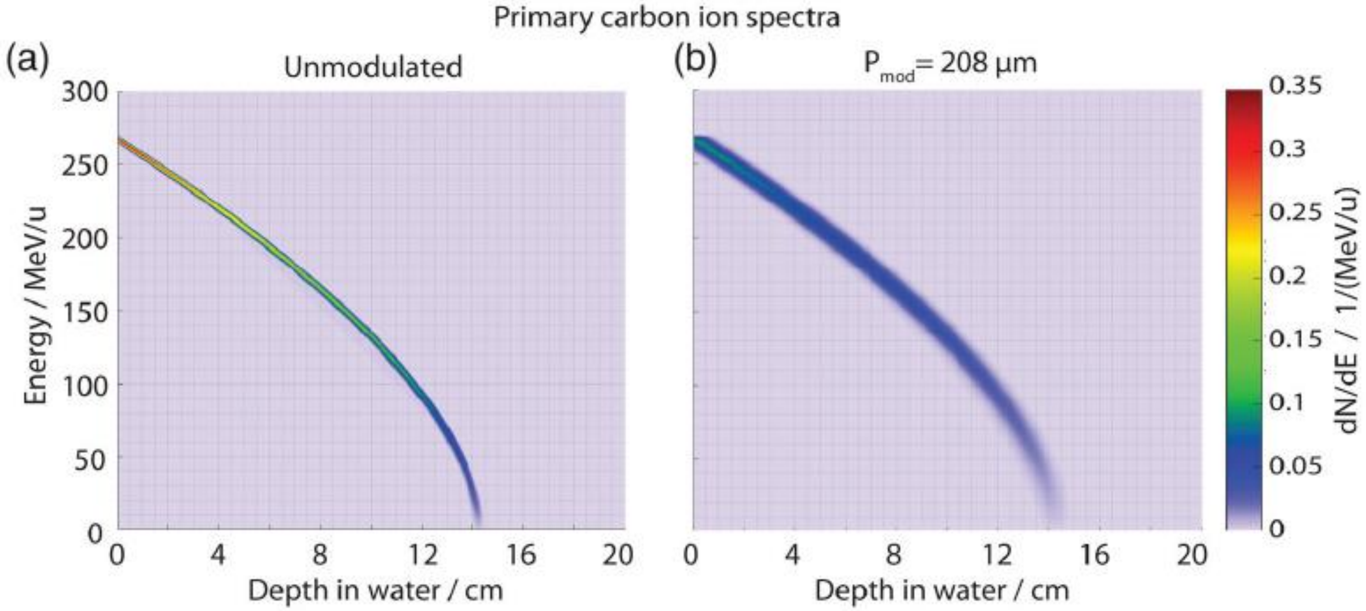


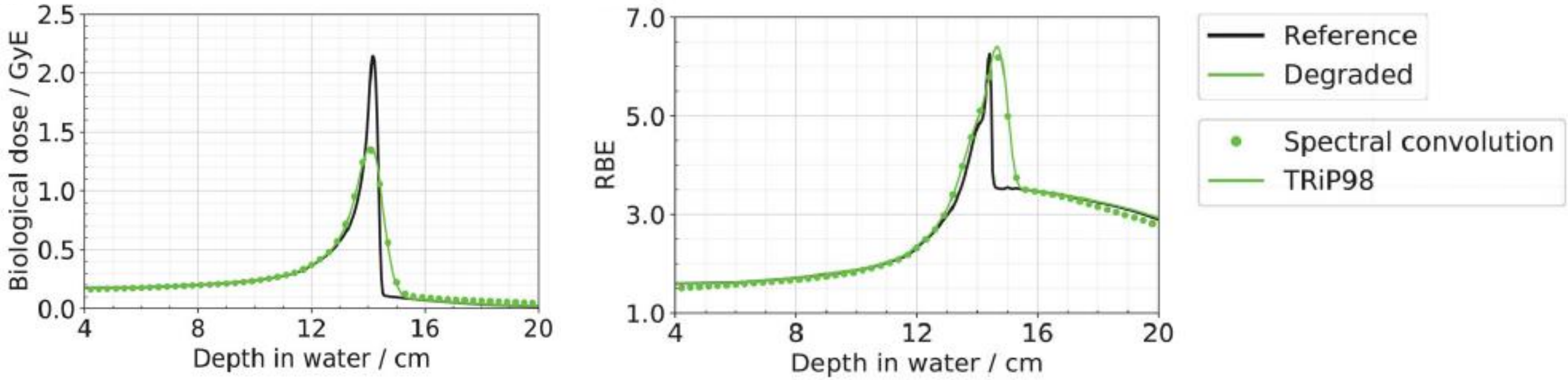
Lung modulation effects

Outlook:

- Investigation of lung modulation effects on biological effectiveness of carbon ions
- Implementation of determination of modulation power
- Automatic determination of modulation properties and compensation for lung modulation effects patient-individually

Primary carbon ion spectra





Range Modulator

- Background: Particle therapy of lung cancer patients

- For active scanning interference between tumor motion and movement of the particle beam
  → Interplay effects

- Potential hot and cold spots negatively influencing therapy outcome

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Can we achieve a sufficient reduction in irradiation time enabling an irradiation under breath hold?

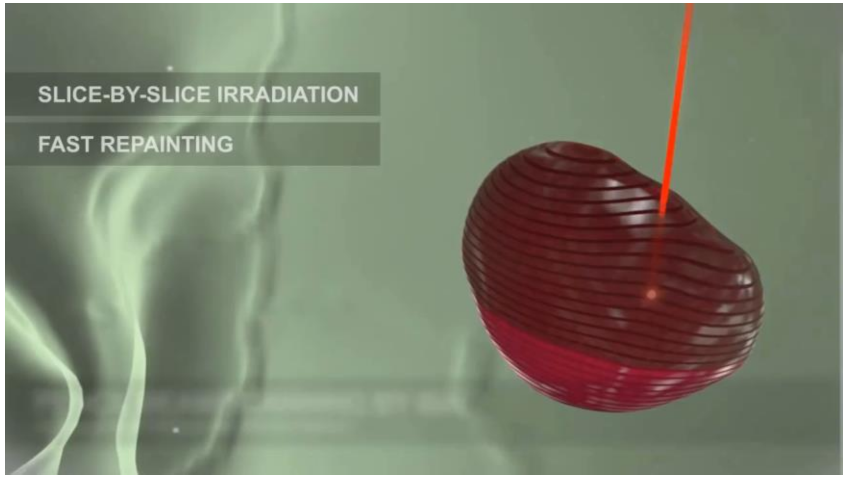
Range Modulator

- For synchrotron-based facilities an acceleration of particles is necessary for each iso-energy layer that is being irradiated

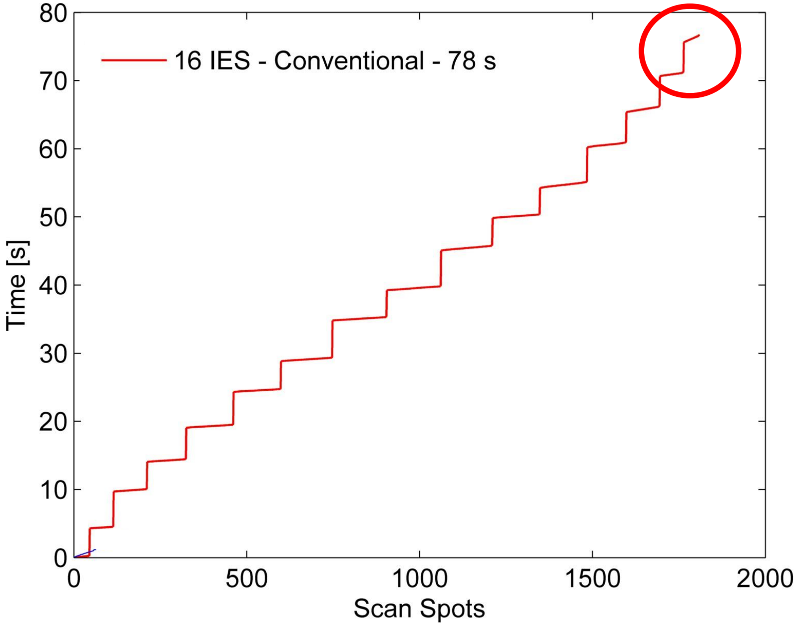
- Acceleration takes time in the order of seconds

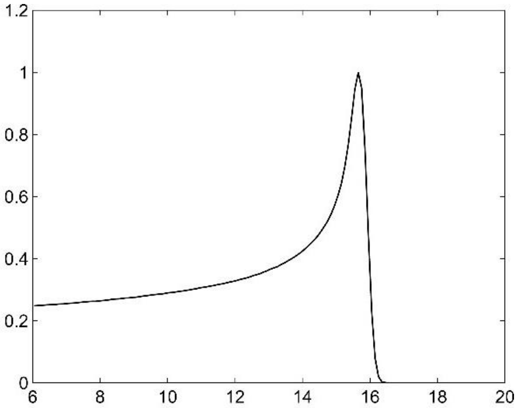
- For an exemplary treatment plan with 16 iso-energy layers, the total irradiation time is 78 seconds

- Is there a possibility to enlarge high-dose region of depth dose curve?



With courtesy of IBA





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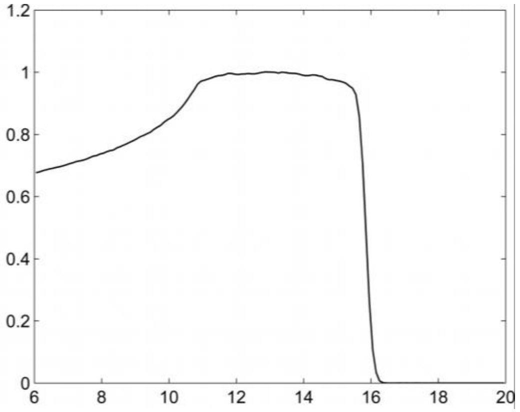
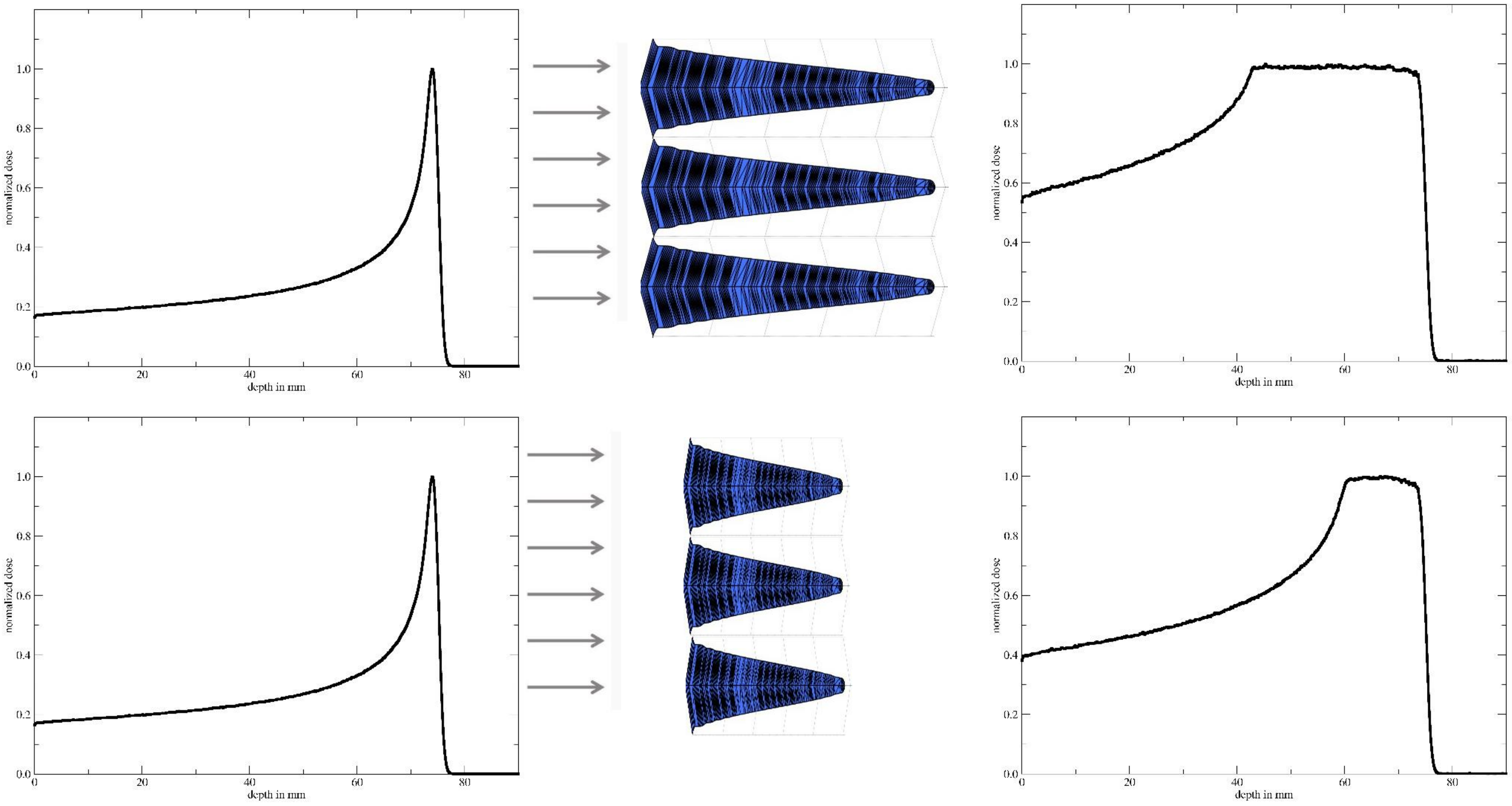


Range Modulator

- Approach: Use passive Range Modulator similar to Ripple Filter to enlarge Bragg Peak
- Range Modulator consists of Pins
- Energy loss and hence range depend on the particle's trajectory through the pin
- Length of Pin defines width of Spread-Out Bragg Peak
- Only 1 energy needed to apply Spread-Out Bragg Peak

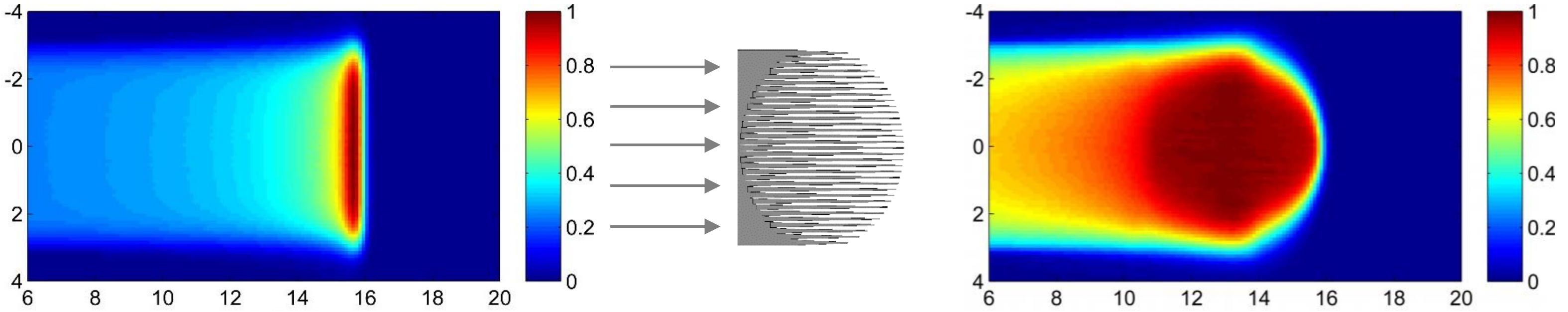


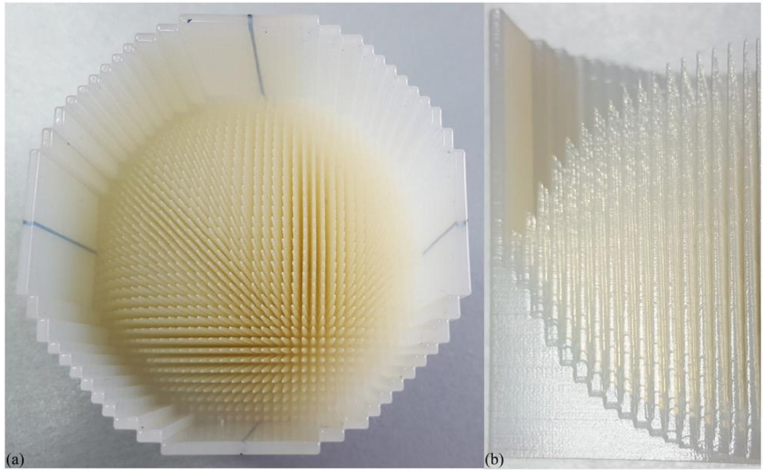
Range Modulator

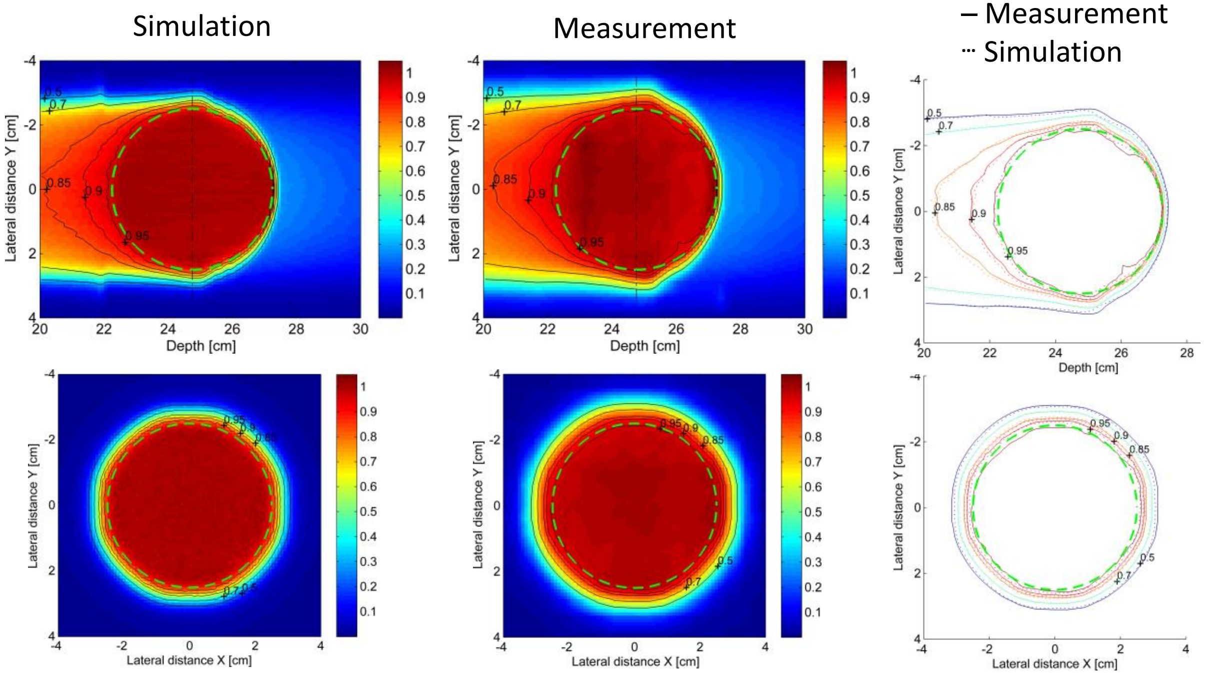
- By arranging different pins, 3D dose distributions can be created

- 3D Range Modulators can easily be 3D-printed

- Verification with measurements at MIT

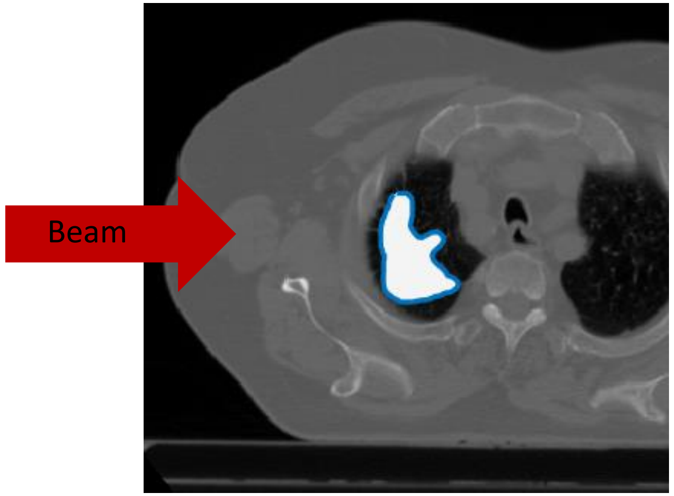


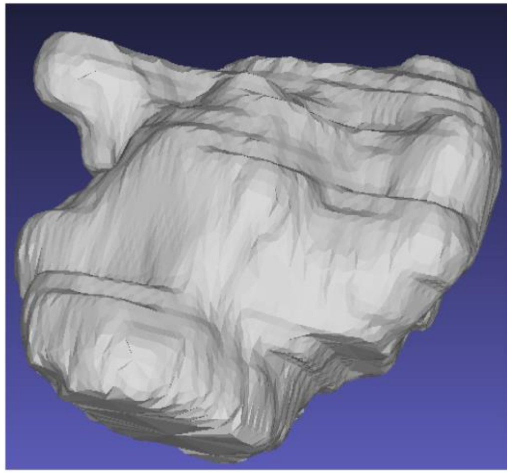


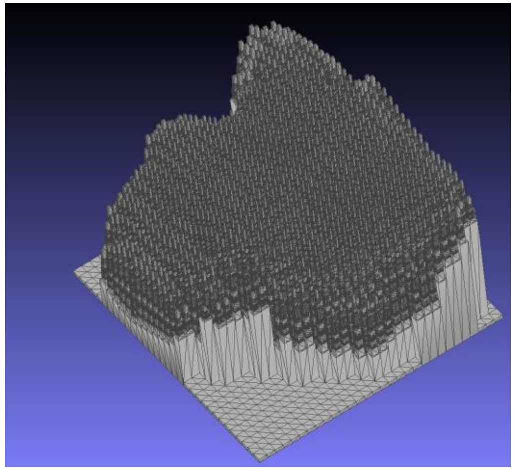


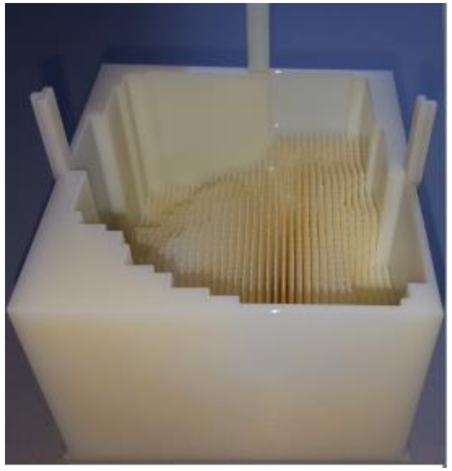
Range Modulator

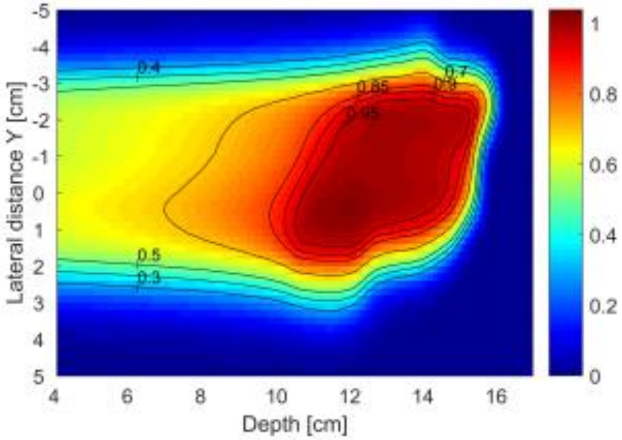
- 3D Range Modulator for complex tumor geometries designed patient individually

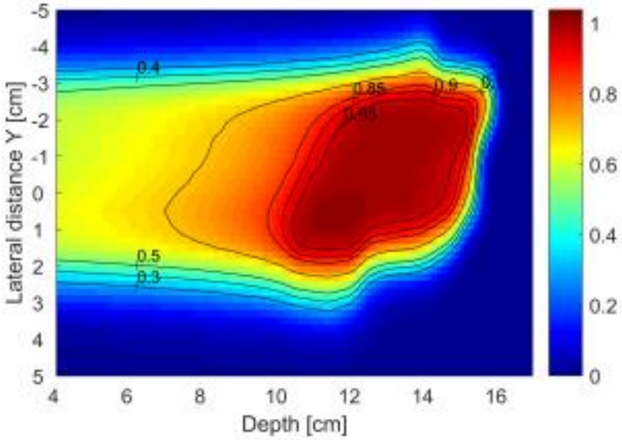


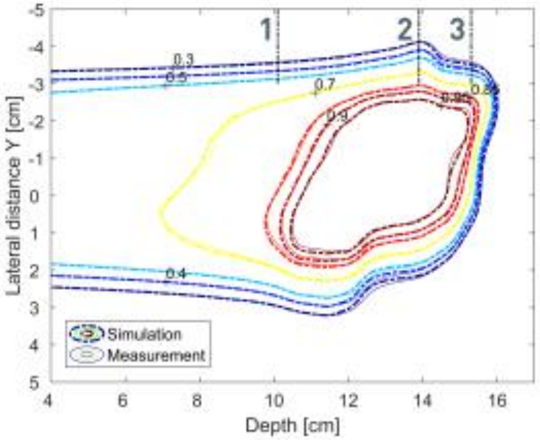


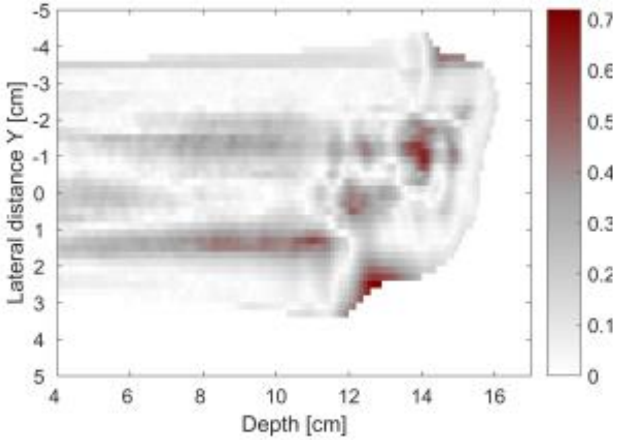










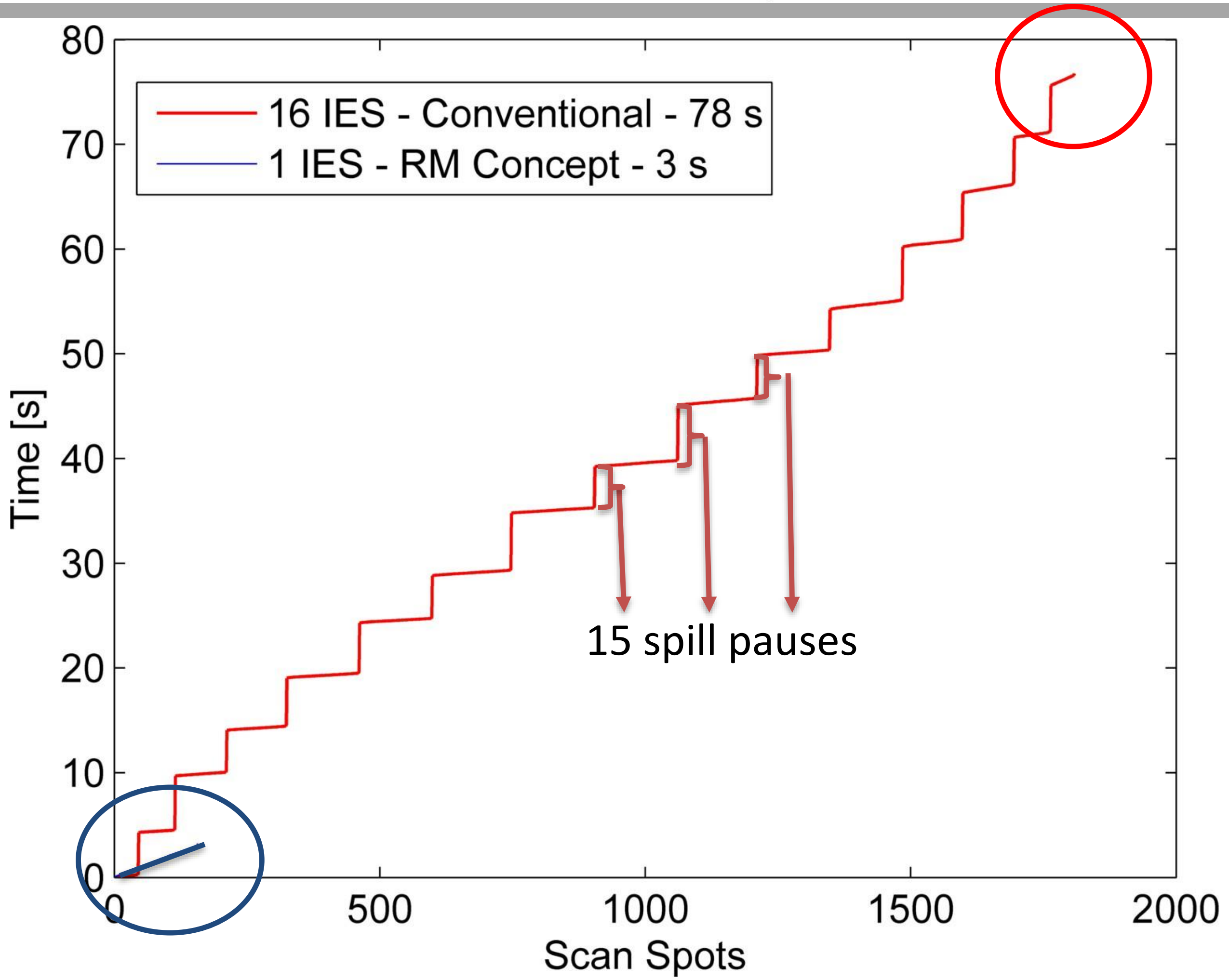


Range Modulator

- Reduction in treatment time due to 3D Range Modulator:

  - 78 seconds without RM
  - 3 seconds with RM

Pencil Beam Scanning	**3D Range modulator**
Very good dose conformity	Dose conformity comparable to PBS
Slow due to energy switching	Only one energy needed
Interplay effects in moving target	Treatment time in order of seconds



3D Range Modulator also essential for FLASH irradiation with active scanning and "slow" energy selection!

Thank you very much for your attention!

This material was prepared and presented within the HITRIplus **Specialised Course on Heavy Ion Therapy Research,** and it is intended for personal educational purposes to help students; people interested in using any of the material for any other purposes (such as other lectures, courses etc.) are requested to please contact the authors:
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