Proton Therapy

From Quarks to Cancer Treatment

Pablo Yepes

Medical Physics Workshop

May 22, 2024

Outline

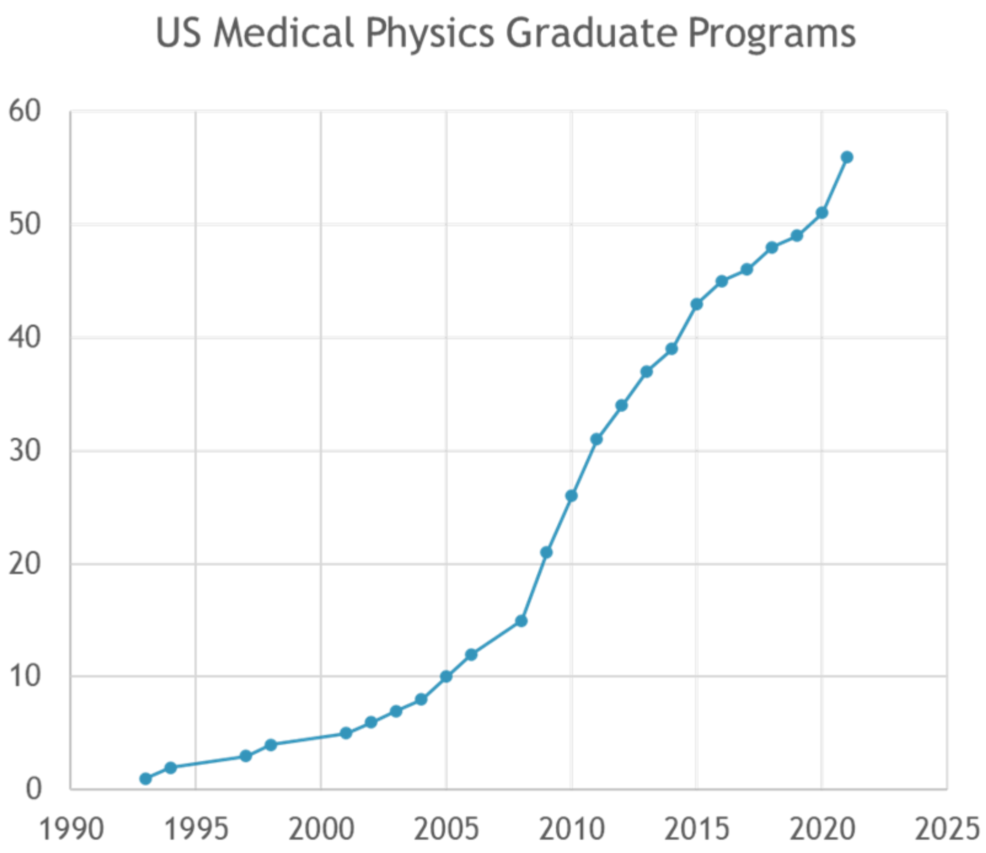
- Medical Physics
  - Radiation Therapy
    - Proton Therapy
- Proton Therapy Challenges:
  - Dose Calculations
  - Handling biological uncertainties, LET Optimization
- Exciting developments: Flash Therapy

No effort was made to include all contributions to Rice effort in Proton Therapy from many people: Q. Wang, M. Fassnacht, A. Adair, A. Higuera, H. Mao, E. Moran, D. Cristancho….

Medical Physics

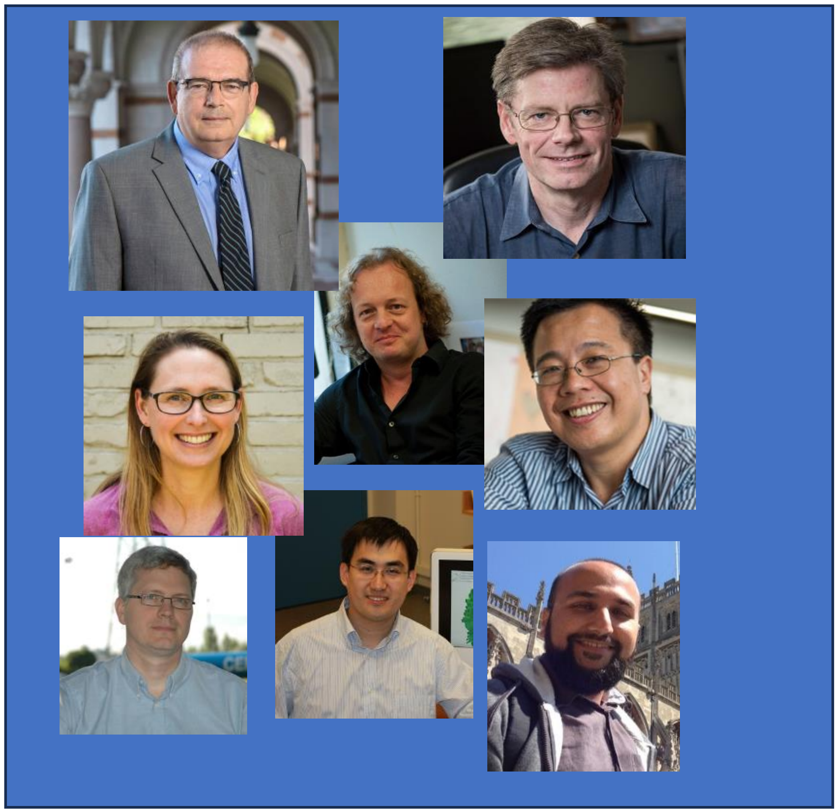
Medical physics is the field that applies principles of physics to medicine and healthcare.

- ❑Radiation Therapy: Use of radiation for cancer treatment
- ❑ Diagnostic Imaging: All the techniques to visualize the human body for medical purposes
- ❑ Nuclear Medicine: Handling radioactive substances for diagnostic imaging and therapeutic purposes.

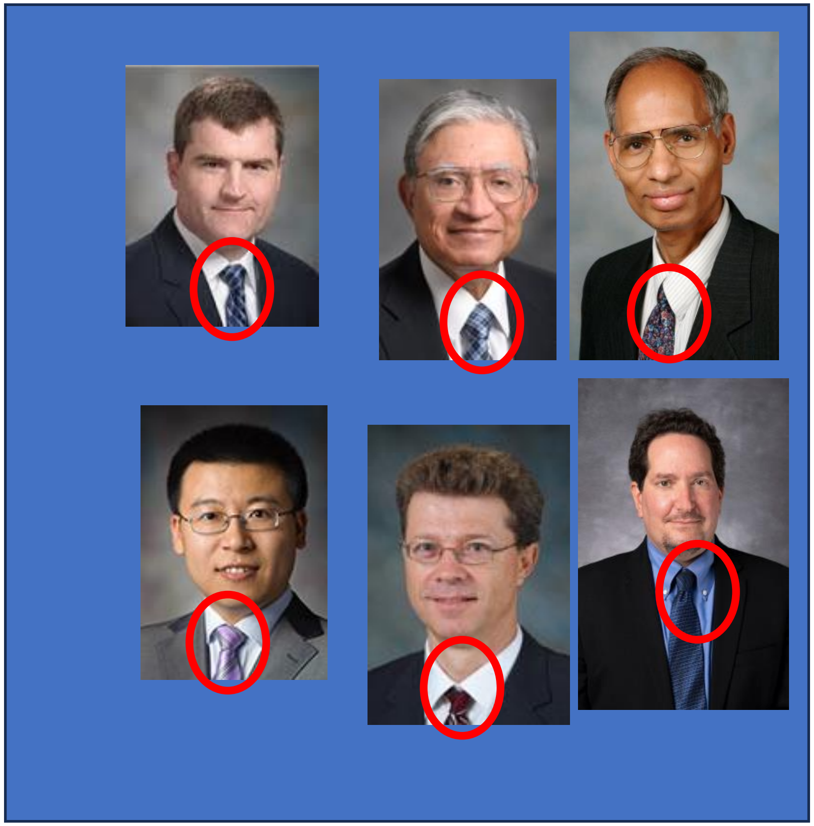


Medical Physics is a Different Culture

Rice Physicists

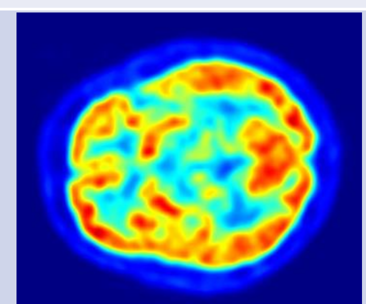


MD Anderson Physicists



$\rho_T^{MDA} \gg \rho_T^{Rice}$ where $\rho_T = Tie\ Density, \quad even\ though\ \rho_T^{Rice}>0$

Diagnostic Imaging

		Energy	Physical Property	Purpose	Example
X Rays **C**omputerized **T**omography	CT	X-Rays	Absorption	Morphology	
Magnetic **R**esonance **I**magine	MRI	Radio Waves	Magnetic Resonance	Morphology/function	
Positron **E**mission **T**omography	PET	γ-Rays	Positron Annihilation	Function	

Radiation Therapy (RT), Significance

- 40% of population will be diagnosed with cancer during their lifetimes (https://www.cancer.gov/about-cancer/understanding/statistics)
- 50% of all cancer patients receive radiation therapy (RT) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298009)

Types of Ionizing Radiation in Therapy

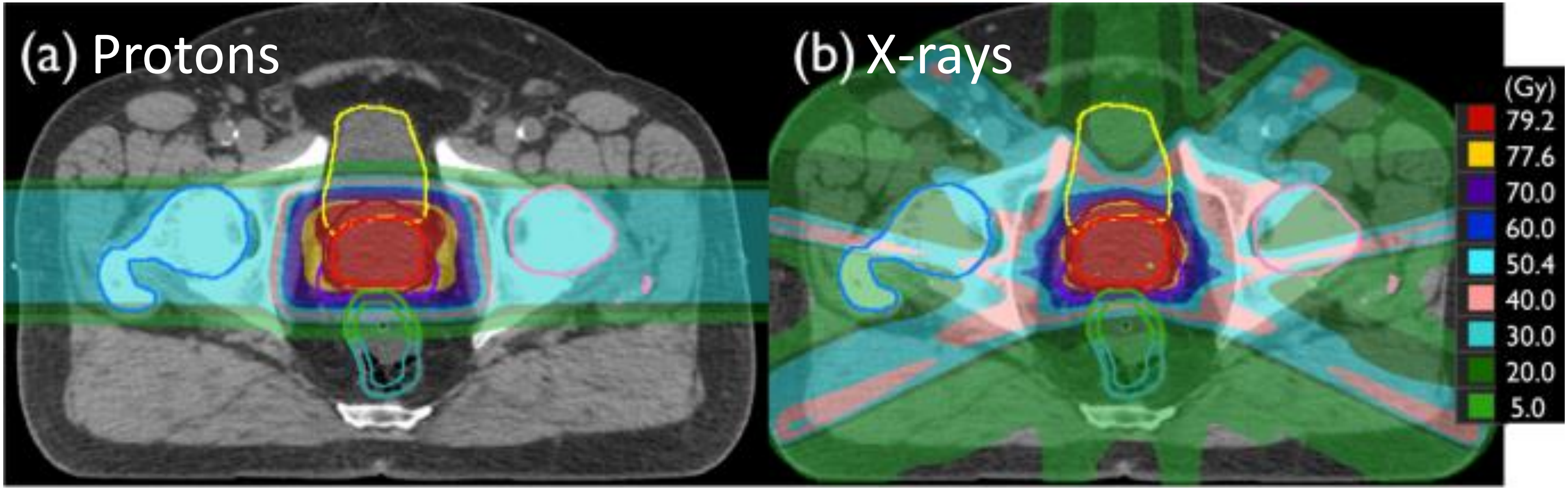
- Photons: X-rays in the energy domain used in Radiation Therapy.
  - Energy given by electron beam: 4-25 MV
- Charged particles: electrons, protons, ions (Carbon, Helium, Oxygen).
  - Referred to as “particle therapy”
  - Proton beams: 70-250 MeV
- “Exotic”: neutrons, pions, kaons, anti-protons.

Physical Dose

- When ionizing radiation traverses a medium, it transfers energy to it.
- Physical dose (D), is defined as the amount energy deposited in the medium per unit mass: 1 Gy = 1 Joule/Kg (100 rads)
- The dose depends on the material properties (density, Ionization potential, etc) and the radiation characteristics (species and energy)

Radiation Therapy: The Name of the Game

- ❑Maximize the dose delivered to the cancerous tumor (target).
- ❑Minimize the dose received by any healthy tissue, and especially OAR (organs at risk)
- ❑Example of prostate case treated with protons (a) and X-rays (b):



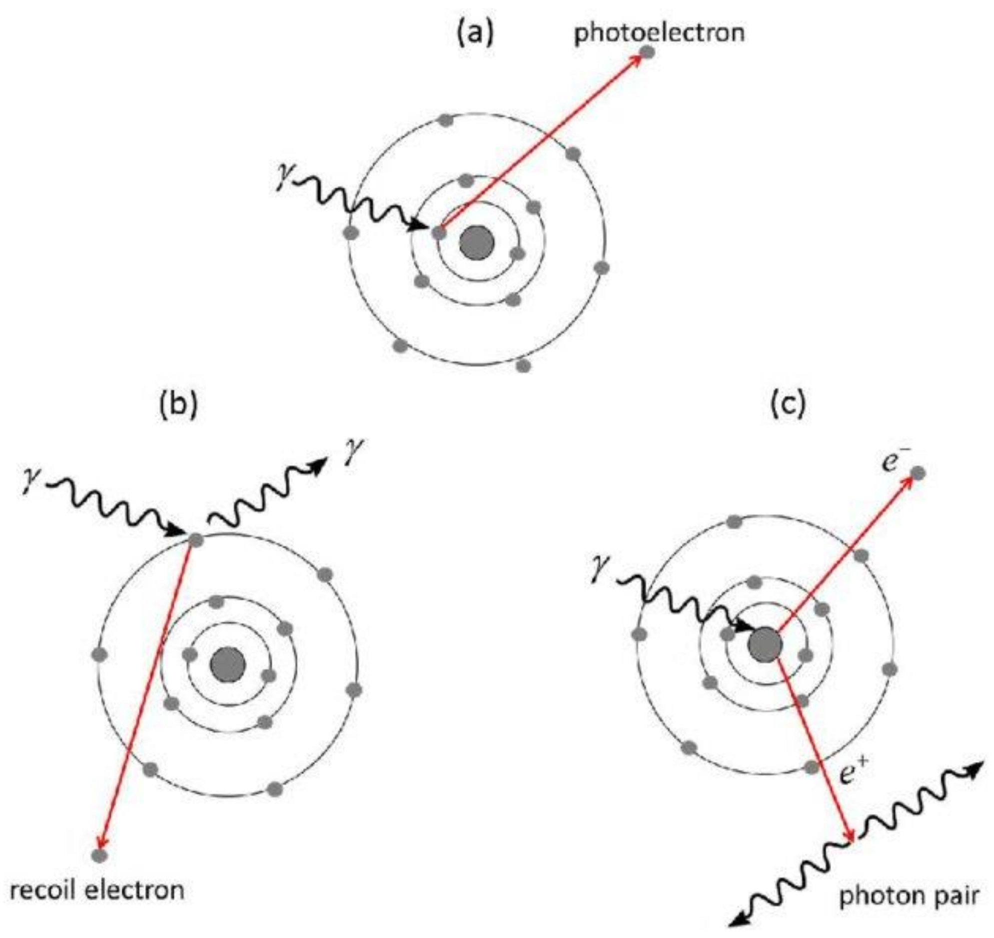
Interactions of X-rays With Matter in Nutshell

- X-rays (photons) interact with matter in a variety of ways: Compton, pair production, photo disintegration
- Since all processes significantly affect the X-rays, the beam attenuation can be expressed:

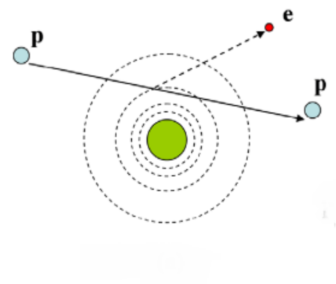
$$dN_{photons} = -\lambda(E)\, N_{photons}\, dL\ ;$$

λ: interaction probability,

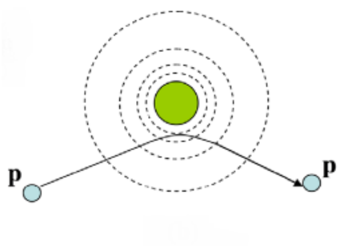
L: distance traveled in the medium



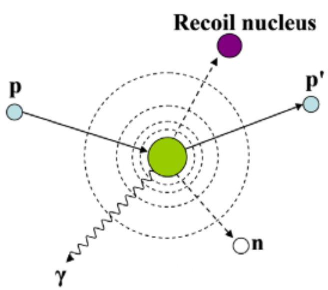
Proton and Ion Interactions



Electromagnetic interactions with atomic electrons. Occur very often and produce a continuous energy loss.



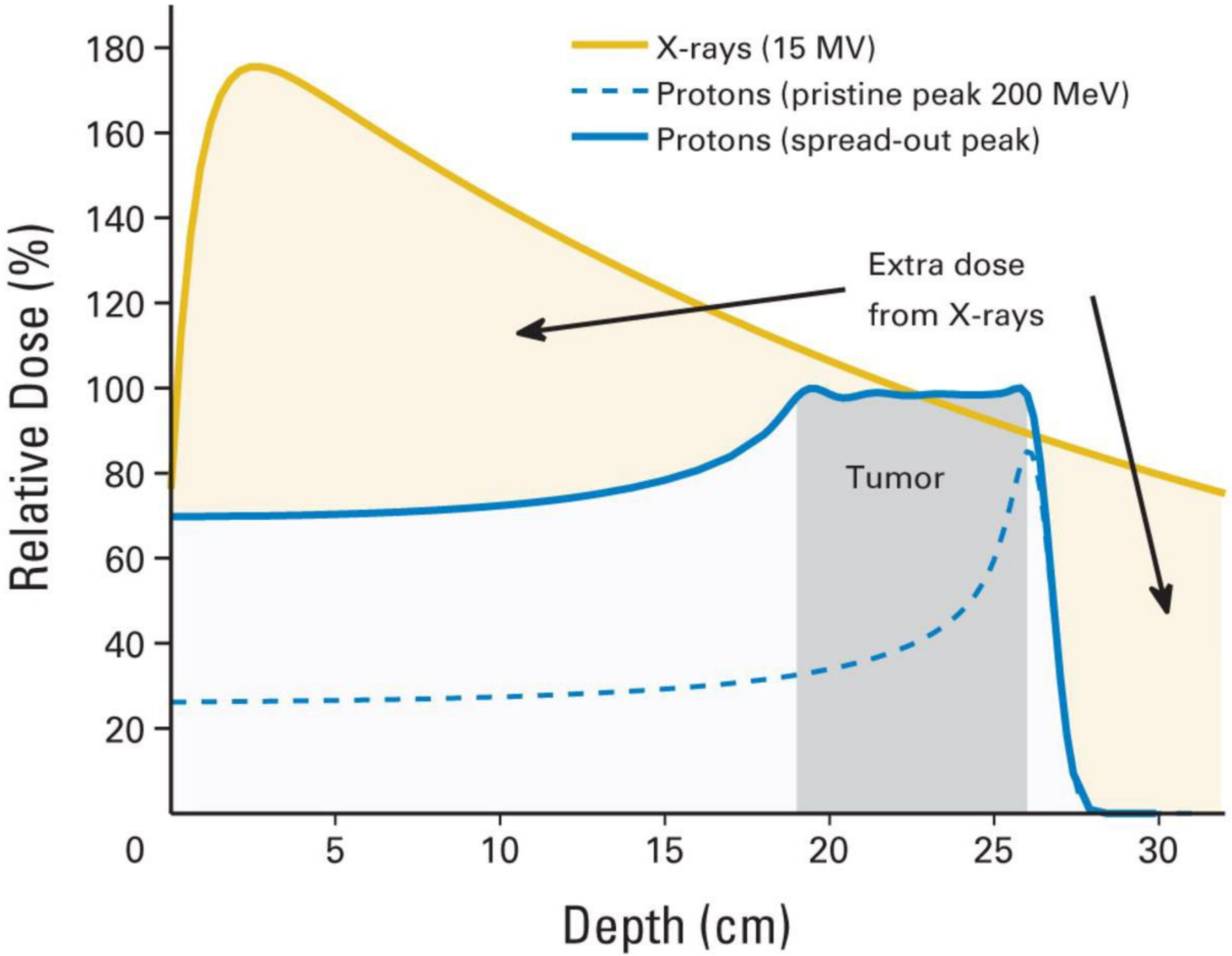
Electromagnetic Interactions with nuclei. Proton/ion gets close to the nucleus, but it does not "touch" it. Trajectories are bent. "Cone effect"



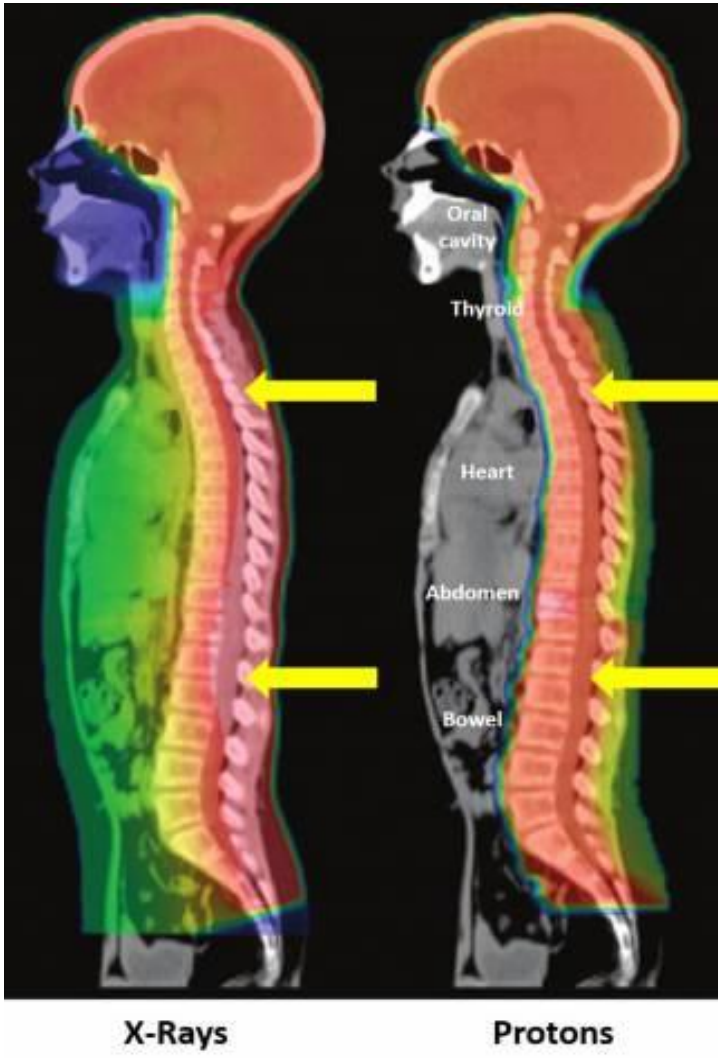
Strong/hadronic/nuclear proton/ion and nucleus interaction. Most often proton is "destroyed", nucleus may be split. A few per cent of interactions.

Features of Proton Dose

https://www.ilcn.org/proton-beam-therapy-versus-photon-beam-therapy-the-debate-continues/

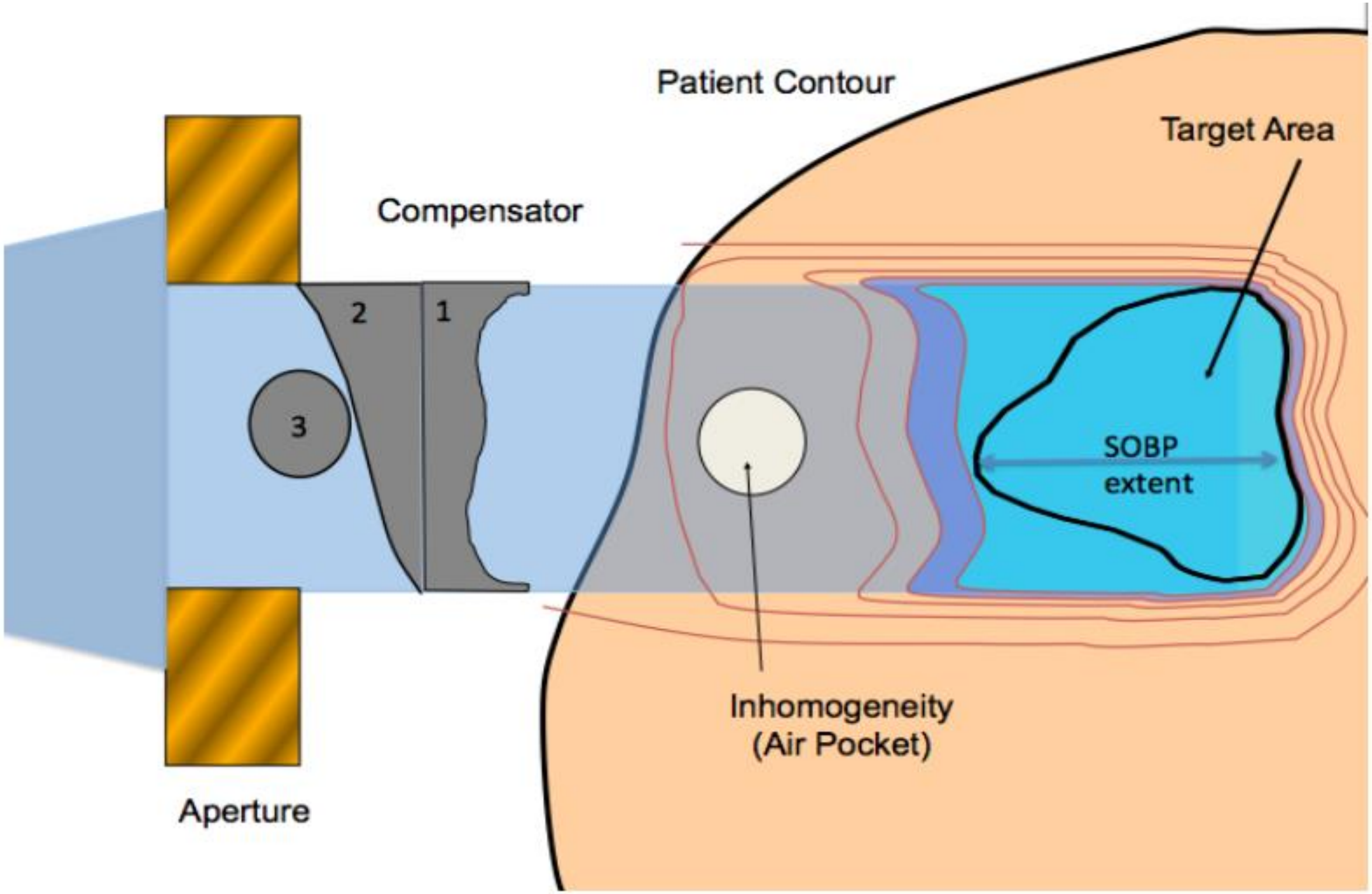


Advantages of Protons over X-Rays

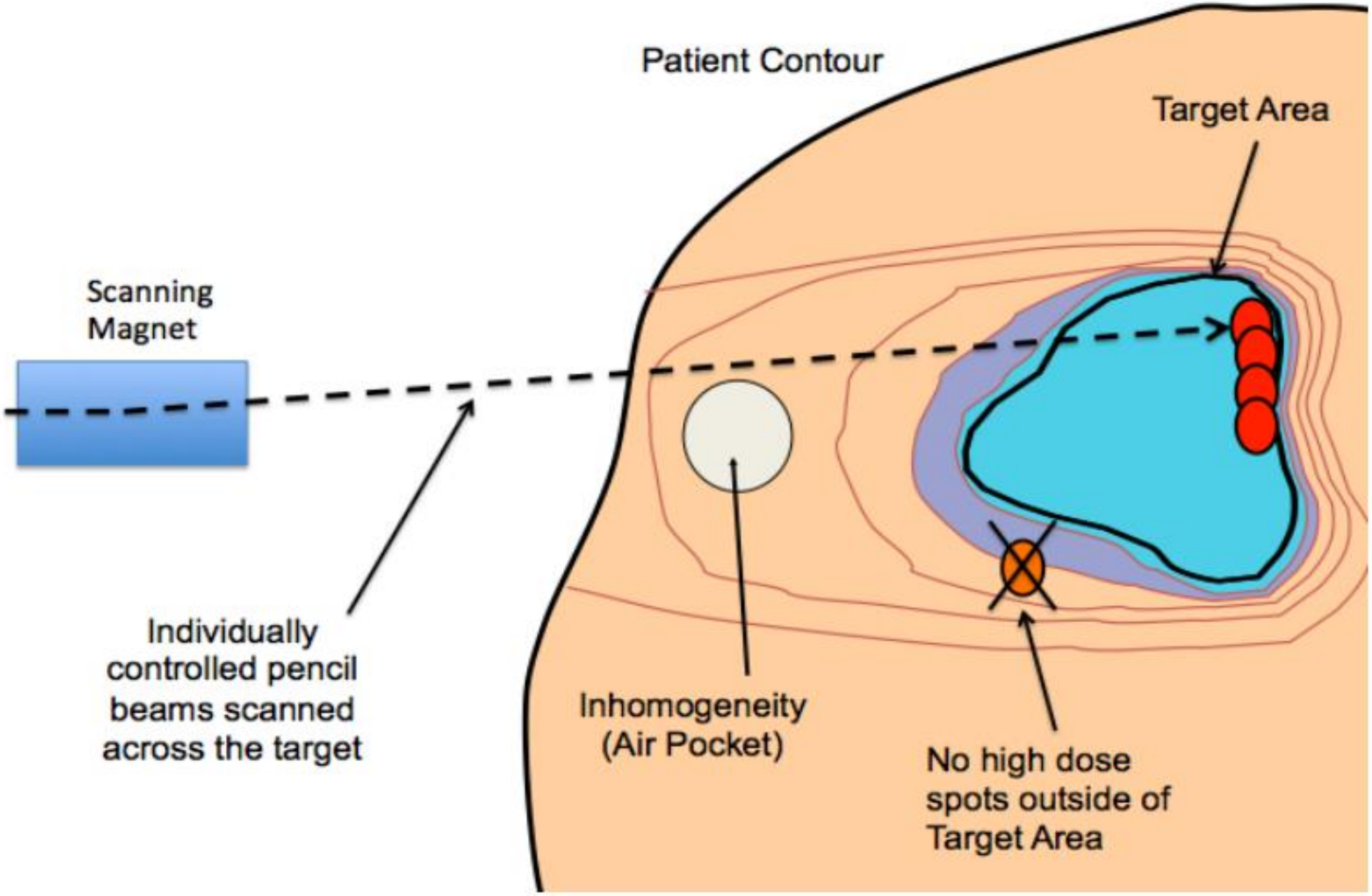


- ❑Example of a pediatric patient with a medulla cancer (https://www.ucl.ac.uk)
- ❑Protons spare organs at risk: heart, bowel, abdomen

Passive Scattering Proton Therapy (PSPT)

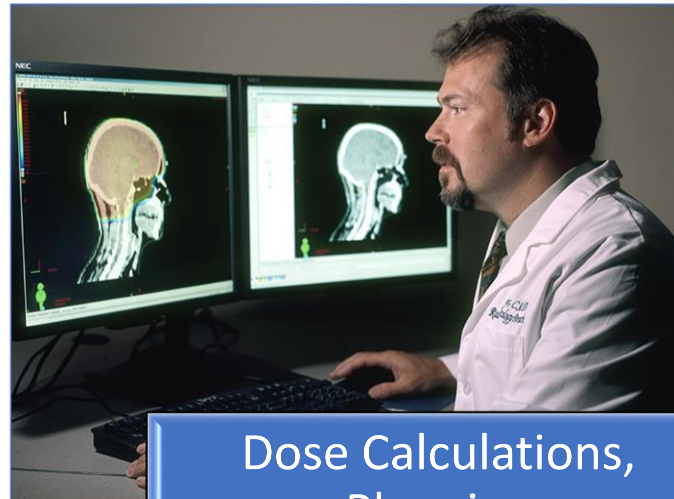


Intensity Modulated Proton Therapy (IMPT)



How It Happens in Real Life?

Positioning and Imaging



Dose Calculations, Planning

Quality Assurance

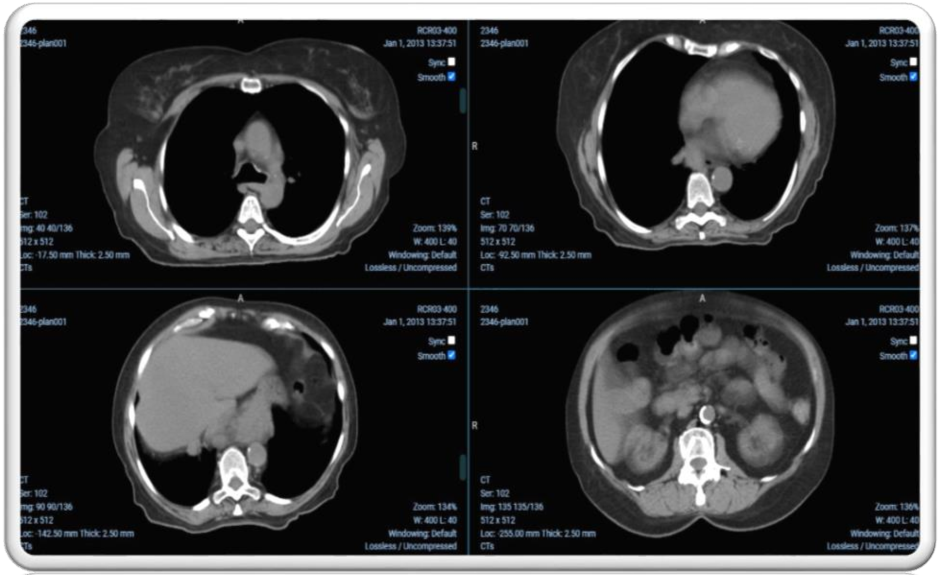
Treatment

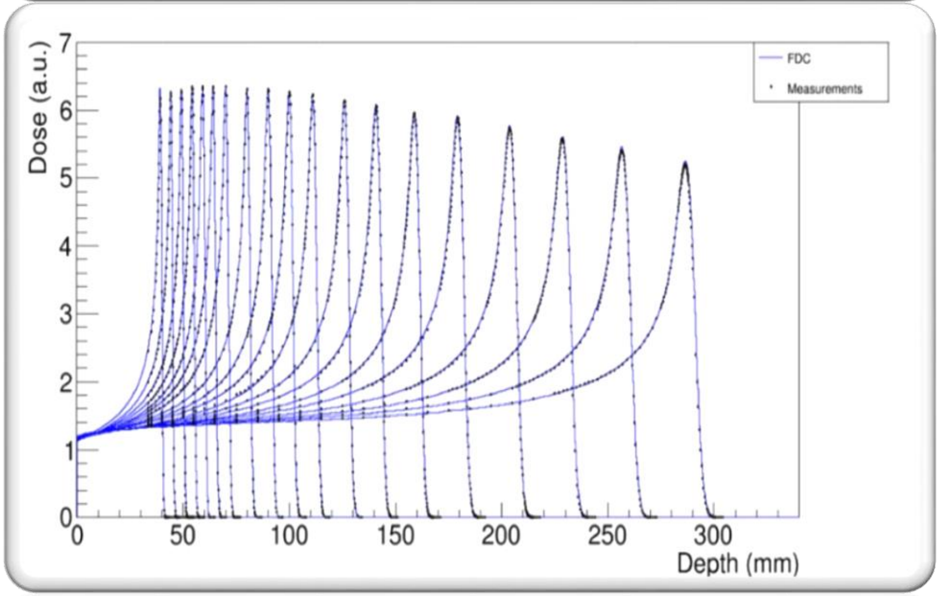
Challenge I: Dose Calculations

Proton more sensitive to the medium than X-rays

Solution: Monte Carlo

Ingredients for Proton Dose Calculations





Patient Anatomy Description: 3D and 4D/5D (time variation)

Beam Description: Longitudinal (energy) and transverse (mainly geometry)

Dose Engine: Analytical or Monte Carlo

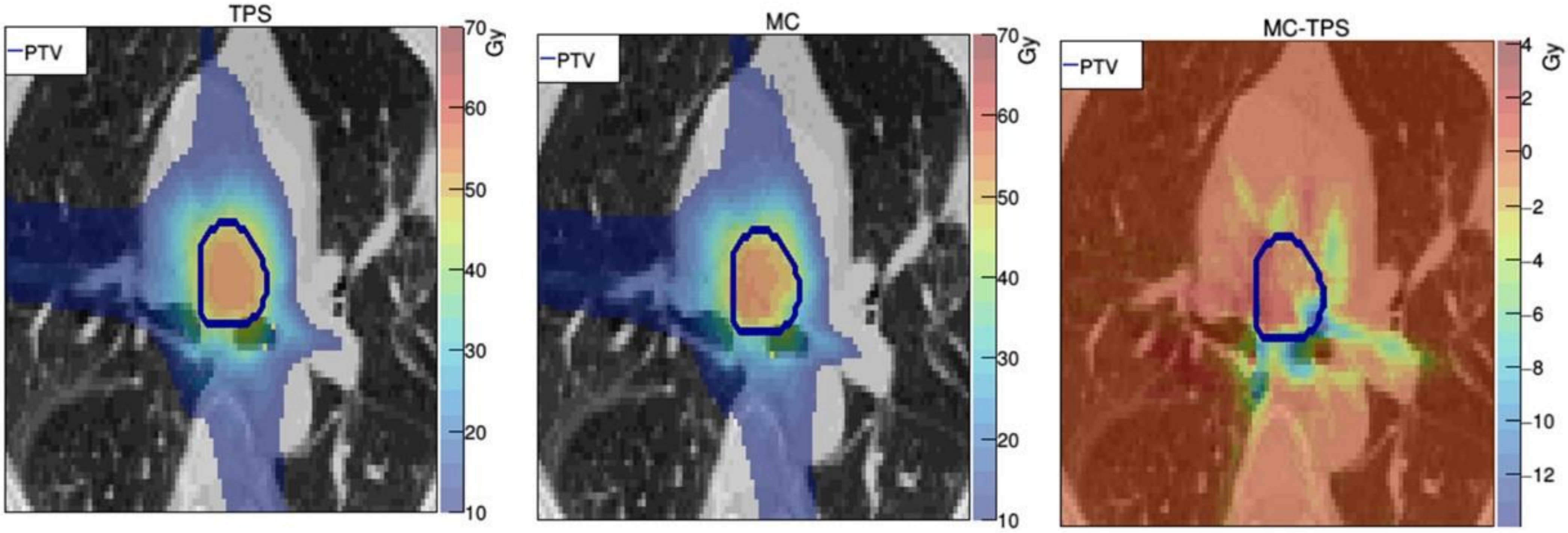
Monte Carlo vs Analytical Calculations

- Analytical approaches (AA) are not accurate in heterogeneous areas, i.e.: head-and-neck, thorax
- Sources of inaccuracies:
  - Transport of protons under the influence of lateral scattering, Multiple Coulomb Scattering (MCS), in different media
  - Secondary particles generated by nuclear non-elastic scattering in both beam shaping devices and the patient itself.
- For example:
  - In lung patients, point dose can be under-estimated by up to 46% (AAPM report)
  - In some cases (Range Shifters), the dose on the surface and entrance regions can be overestimated up to 10% for setups with large air gaps

Monte Carlo vs Analytical Calculations

(Yepes et al, Phys. Med. Biol. 63(2018) 04500)

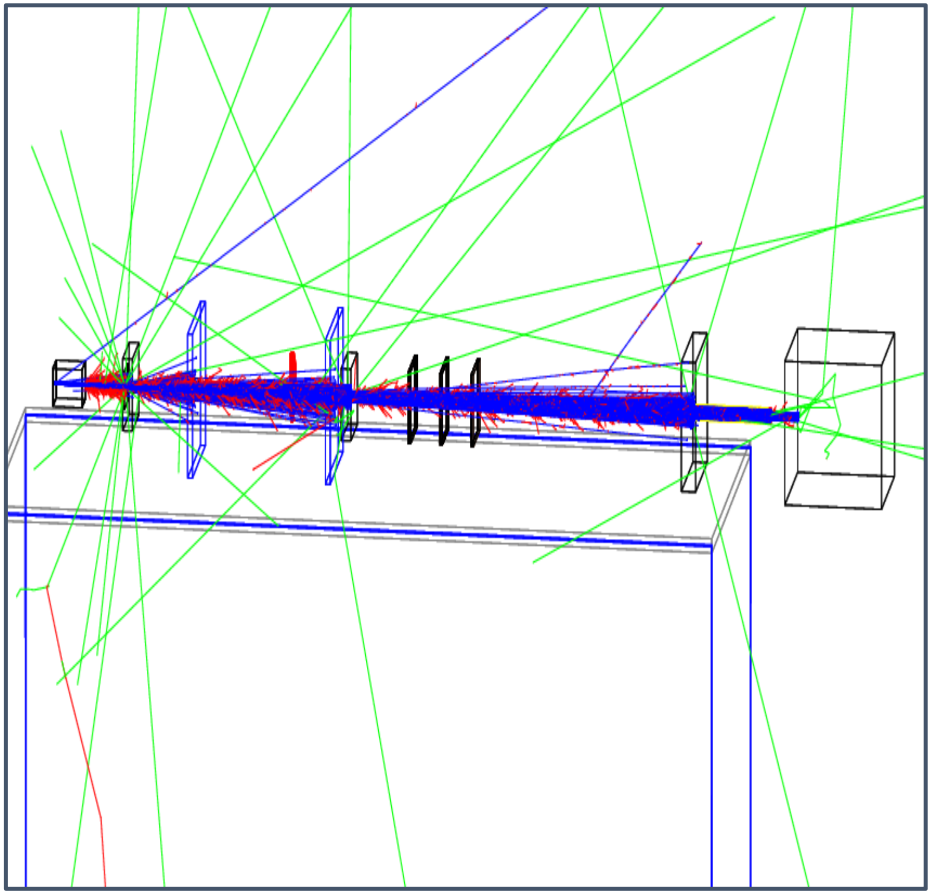
- ❑ Analytical approaches are not accurate in heterogeneous areas, i.e.: head-and-neck, thorax
- ❑ Treatment plan obtained with the Treatment Planning System (TPS) using Analytical Calculations



Analytical Calculations (TPS) may lead to incomplete coverage of the target!

Full Monte Carlos for Proton Therapy

- Monte Carlos to simulate the interaction of radiation with matter have been available for decades
- Millions of lines of code
- Very detailed physics simulation with many physical processes included
- Full Monte Carlos (open source):
  - GEANT4: Nucl. Inst. Meth. A. 506 (2003), 250.
  - MCNPX (restricted): Los Alamos 2002.
  - FLUKA: Nuovo Cimento C. 31 (2008) 69, Phys Med Biol. 64 (2019) 075012.
- Dose Calculation for a typical treatment plan:
  - $\sim 10^8$ protons to be simulated
  - $\sim 10^3$ CPU hours

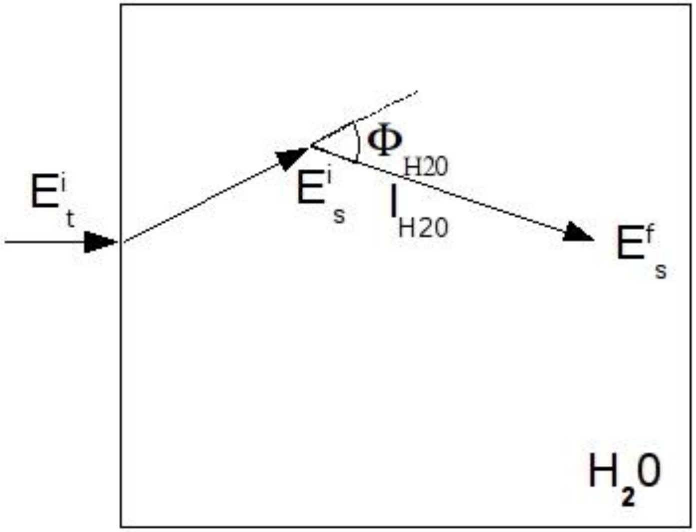


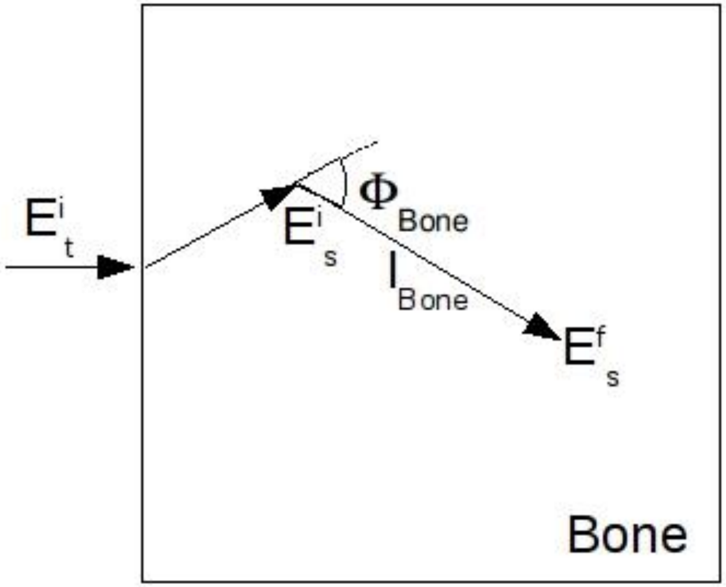
Proton tracks
https://web.infn.it/Geant4-INFN/

Fast Dose Calculator (FDC) in a nutshell

Yepes et al, Phys Med Biol. 55 (2010) 7107

- Monte Carlo based on track-repeating algorithm
- Trajectories of primary and secondary particles in water are simulated with GEANT4, and stored in a database in discrete steps
- Trajectories are re-tracked in any voxelized medium by scaling the length and angle of each step according to the medium
- For each step, the length (l) and angle (ϕ) are scaled:
  - Length: $l_M = \alpha\,(E)\; l_{H2O}$
  - Scattering Angles: $\phi_M = \beta \phi_{H2O}$





FDC (Fast Monte Carlo) Evaluation

- ❑Compare to a full Monte Carlo (GEANT4), considered the calculation *Gold Standard*
- ❑FDC came in two flavors: CPU and GPU (Graphic Processor Units)
- ❑ Exactly same algorithm is run for both versions
- ❑ S, Speed up factor relative to GEANT4:
  - ❑ $S_{CPU} > 100$
  - ❑ $S_{GPU} > 1000$

Phys. Med. Biol. **61** (2016) 2633 P P Yepes *et al*

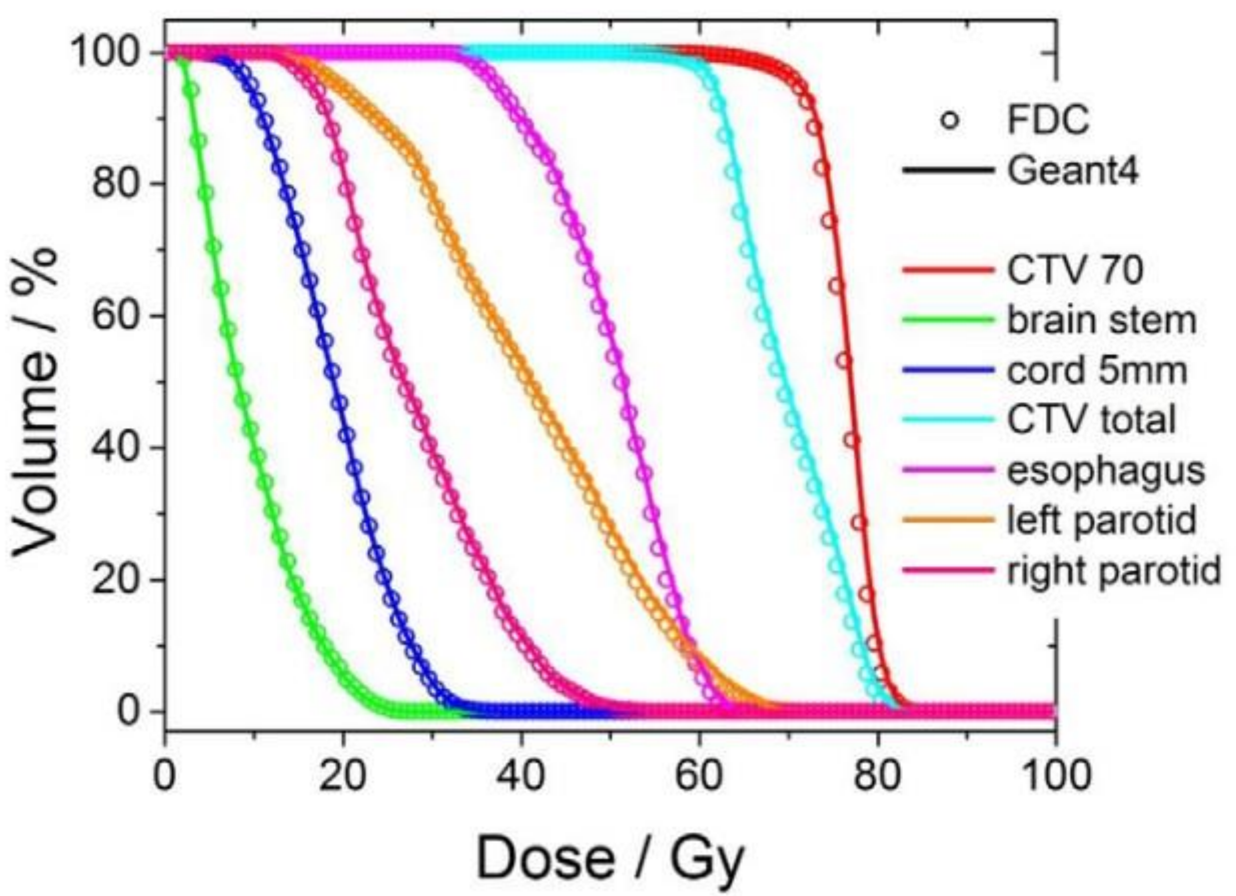
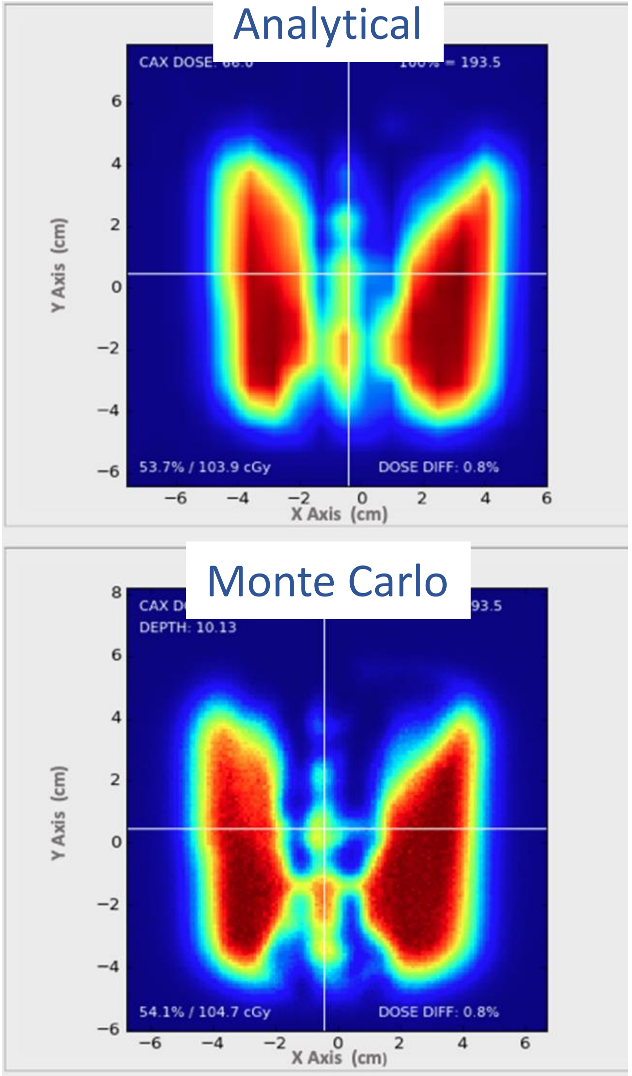


Figure 3. Proton therapy dose-volume histograms of a head-and-neck patient calculated with FDC and G4.

Proton Monte Carlos in the Market

- ❑ Fast Monte Carlos for Proton Therapy
  - ❑ FDC: Rice, Phys Med Biol. 55(2010):7107
  - ❑ gPMC: Jia et al, Phys Med Biol. 57 (2012) 7783.
  - ❑ gMC: Wan et al, Med Phys. 42 (2015) 2967.
  - ❑ MCsquare: Souris et al, Med Phys. 43 (2016) 700. (Open Source: http://www.openmcsquare.org/).
  - ❑ FRED: Schiavi et al, Phys Med Biol. 62 (2017) 7482.
- ❑ Commercial (restricted):
  - ❑ **RayStation**: Saini et al, Phys Med Biol. 62 (2017) 7659.
  - ❑ Eclipse: Lin et al, J Appl Clin Med Phys. 18 (2017) 44.
  - ❑ Monaco (Elekta)

Comparison RayStation Analytical/Monte Carlo



Animal Model [Med. Phys. 20 (2019) 160]

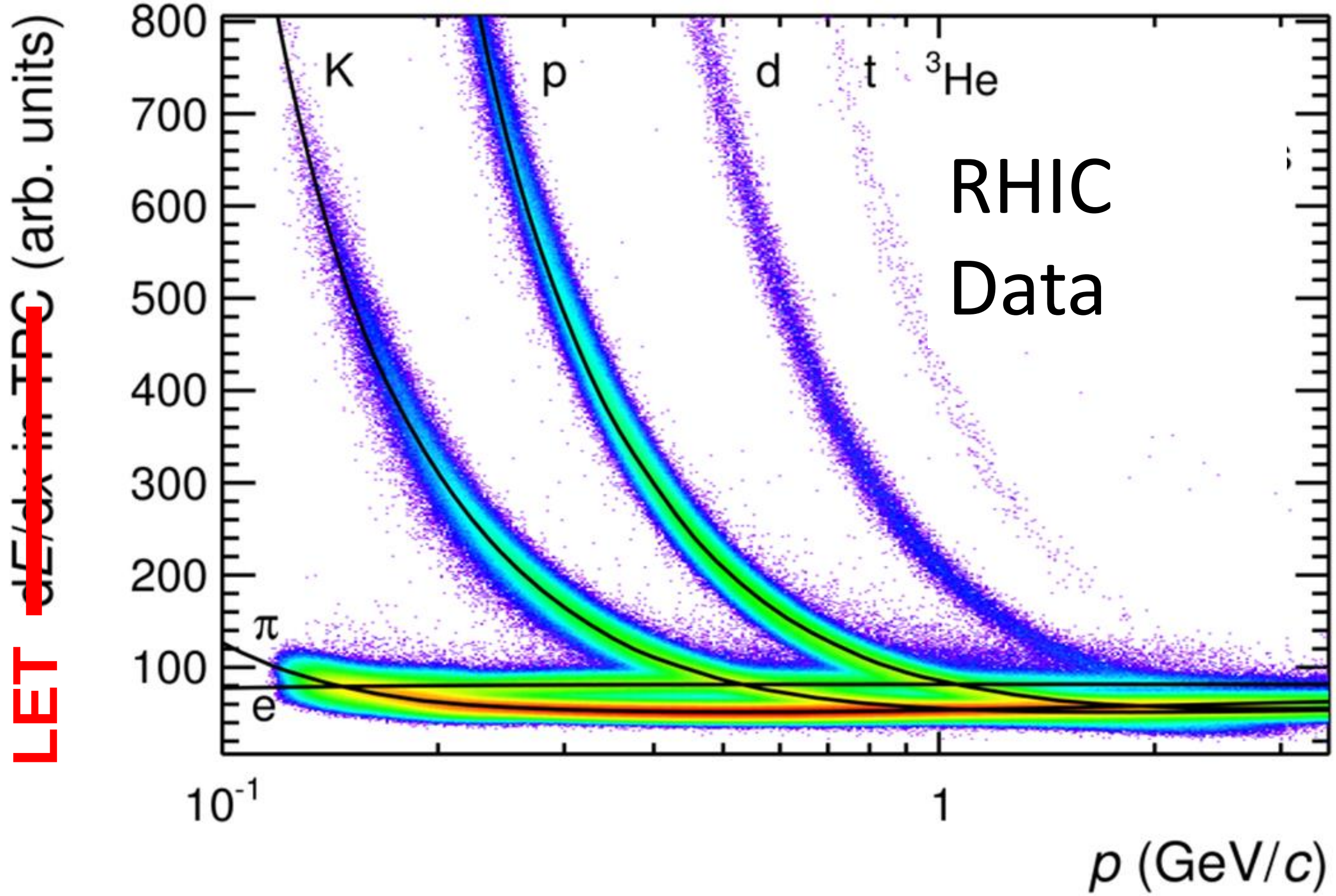
Challenge II: Handling Biological Uncertainties
Solution: LET Optimization

Relative Biological Effectiveness (RBE)

- ❑Radiotherapy seeks biological effects:
  - ❑Control (eliminate) the tumor
  - ❑Minimize toxicity (side-effects: pneumonitis, necrosis, etc)
- ❑The same amount of physical dose delivered by two different types of radiation (i.e. X-rays and protons) has different biological effects
- ❑Proton RBE is the ratio of the dose of a reference radiation (typically X-rays) and the proton dose when both produce the same biological effect.
  - ❑ RBE=1.1 for protons, a tumor is treated with 55 Gy with X-rays, and with 50 Gy with protons.
- ❑There are many phenomenological RBE models.
  - ❑large uncertainties (10-20%) because of the great variety of biological variables.
- ❑RBE depends on:
  - ❑Biological end-point: Many, many variables. i.e.: cell survival, type of toxicity, in-vivo/in-vitro, etc. (α_γ,β_γ)
  - ❑Physical variables: species, energy, etc (LET).

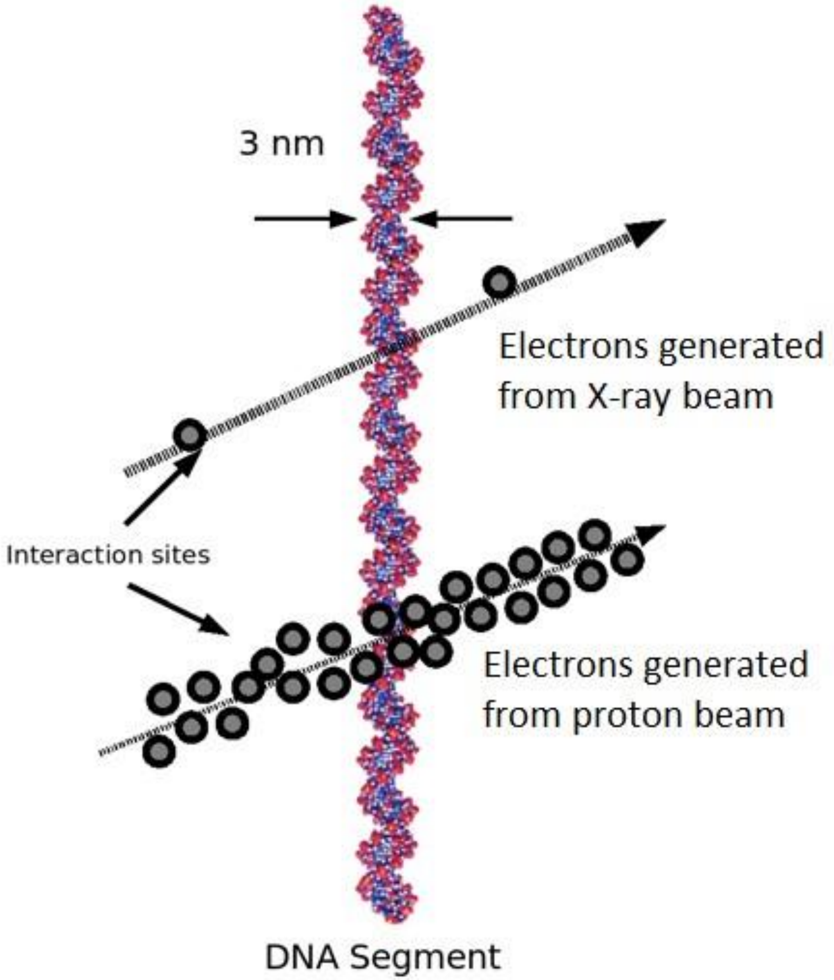
Linear Energy Transfer (LET)

- ❑LET is the amount of energy deposited per unit length by a specific type of radiation
- ❑Nuclear/particle physicists call it dE/dx
- ❑Biological effect is clearly dependent on LET
- ❑Low LET particles: photons (X-rays), electrons
- ❑High LET particles: protons, ions (C, He, etc.)



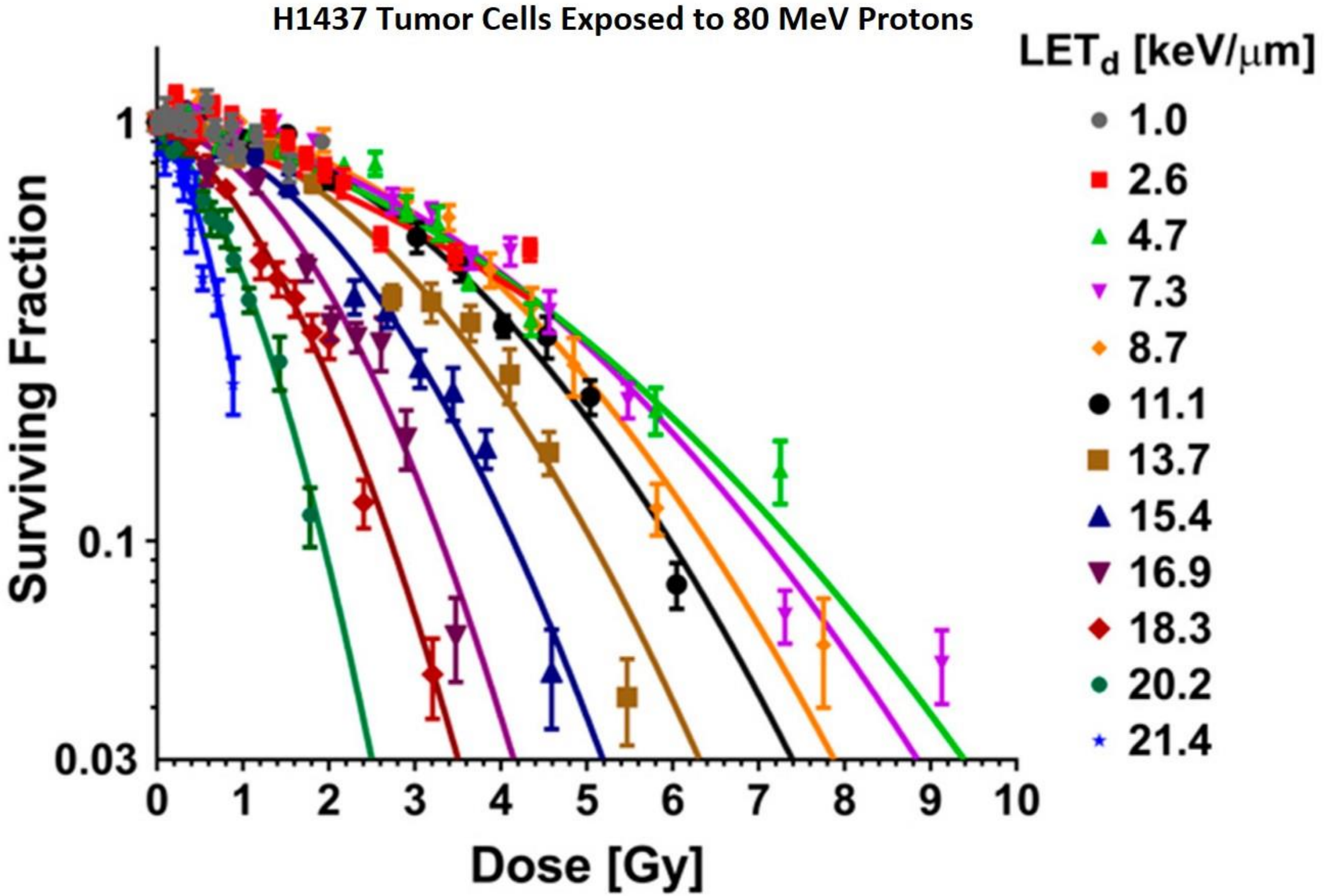
Why RBE depends on LET

- ❑ Biological effect of radiation is related to DNA
- ❑ DNA is made of two linked strands that wind around each other as a double helix.
- ❑ Radiation damages the DNA directly or indirectly by breaking one or both strands
- ❑ Cell repairs most of the broken strands. The larger the break, the more difficult to repair.
- ❑ The larger the LET, the worse the break



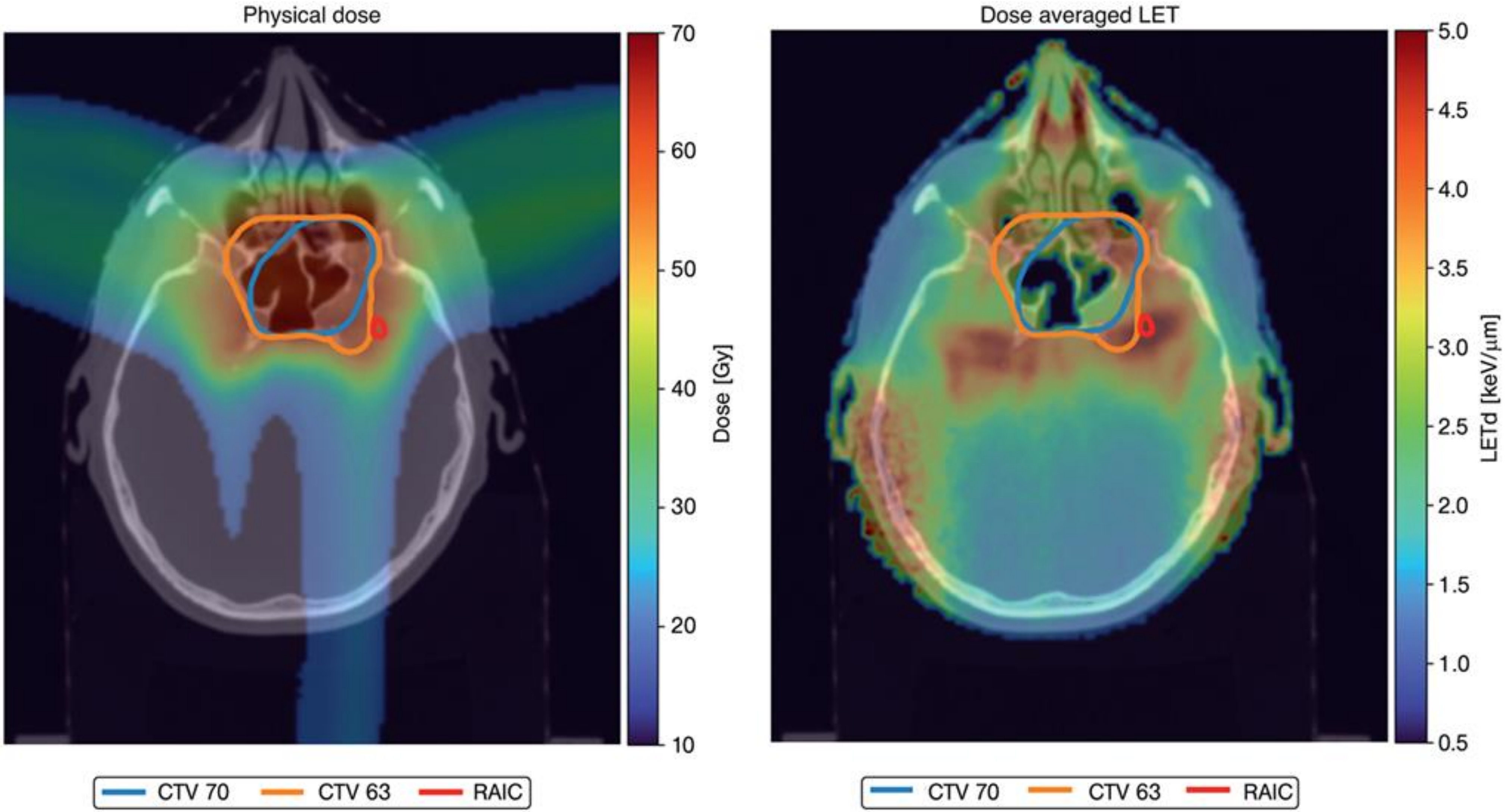
Measuring RBE for Tumor Control

Bronks et al, Cancers 12 (2020), 3658



Challenge: LET and Unexpected Necrosis!

Engeseth,..Yepes, et al, Int J Radiat Oncol Biol Phys 111(2021)684.

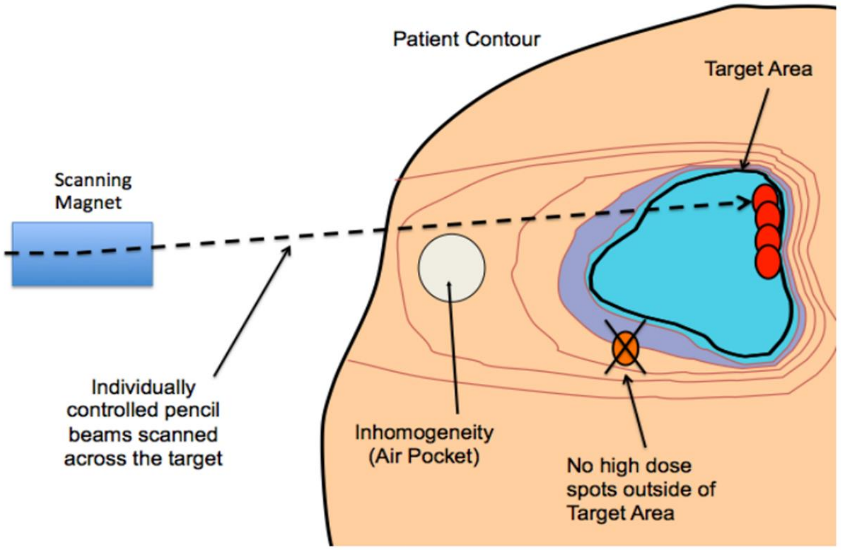


RAIC: Radiation Associated Image Change = Necrosis

Addressing the Problem: LET Optimization

Cao…,Yepes et al, Phys Med Biol. 63(2017) 015013

- Treatment plan optimization: Get the beam intensity for each position for optimal target coverage and minimum OAR dose by minimizing f_D (cost function).
- Take into account not only the dose but also the dose distribution

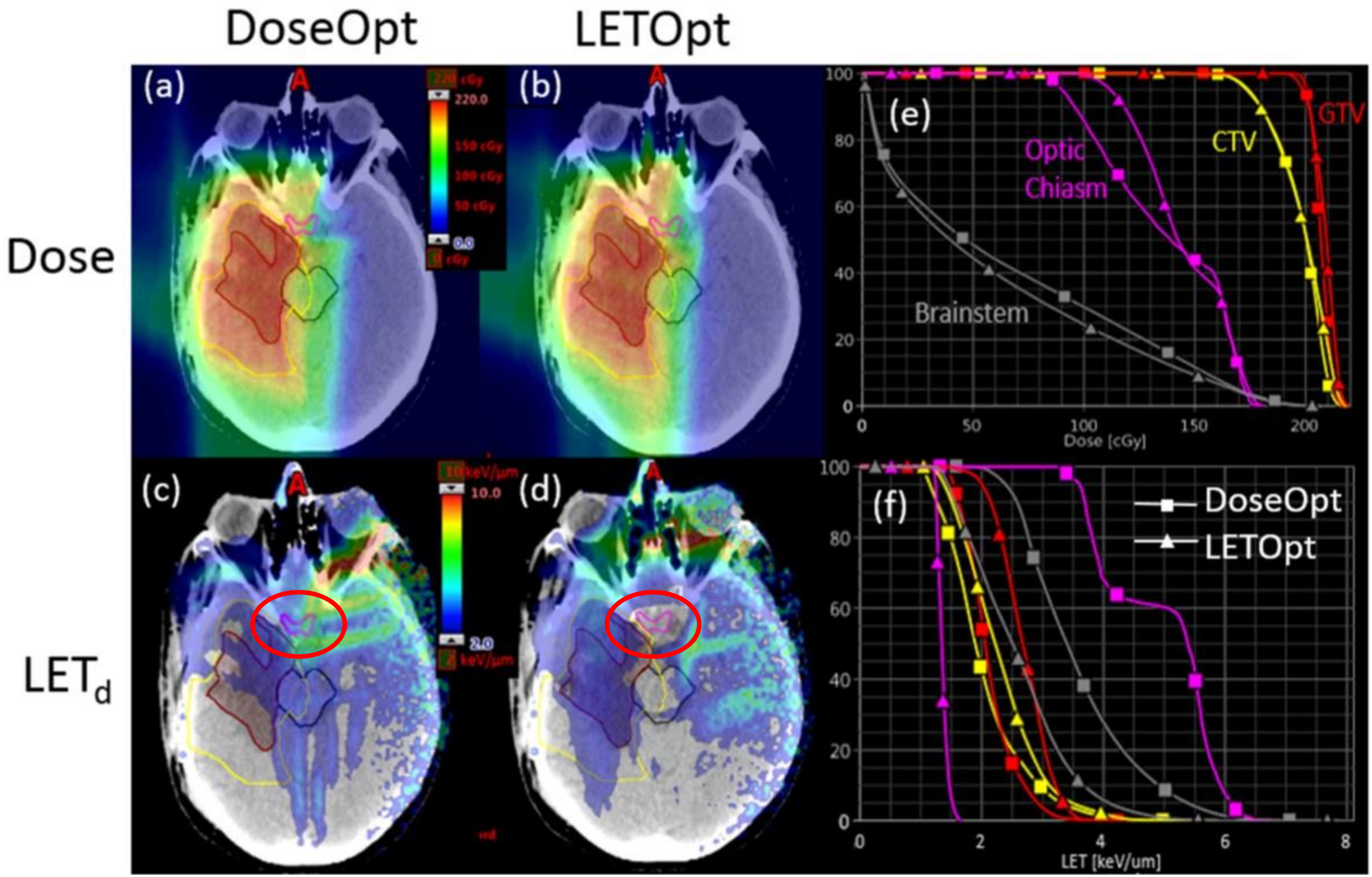


Dose **LET**

$$f_D(w) = \sum_{S\in Struct} \frac{\lambda_S^-}{|S|} \left\| \left(D_{i\in S}^P - D(w)_{i\in S}\right)_+ \right\| + \sum_{S\in Struct} \frac{\lambda_S^+}{|S|} \left\| \left(D(w)_{i\in S} - D_{i\in S}^P\right)_+ \right\| + \sum_{S\in Struct} \frac{\lambda_S^L}{|S|} LET(w)_{i\in S}$$

Where: w is the vector of beam intensities, D is the dose, S are structures (organs: tumor, heart, etc.), D_P is the "prescribed" dose for the structure, i is the voxel index.

Same Dose with different LET!



RaySearch Laboratories

BOOK A DEMO   > EN   MENU

and innovations in oncology software solutions. Recent advancements include LET optimization, discrete proton arcs* and dose computation on converted CBCTs for protons and light ions, plus the latest developments in RayCare* and RayIntelligence*.

Promo by lead software company in proton-therapy at latest Particle Therapy conference

RayStation®* is the next generation of treatment planning systems. Recent advancements include LET optimization, discrete proton arcs* and dose computation on converted CBCTs for protons and light ions.

RayCare® is an innovative oncology information system designed to support comprehensive cancer care. RayCare connects all oncology disciplines, enabling you to fluidly coordinate tasks to ensure optimal use of resources. Patient chart improvements, extension of summary workspace, and increased support for radiotherapy processes are all included in the latest version.

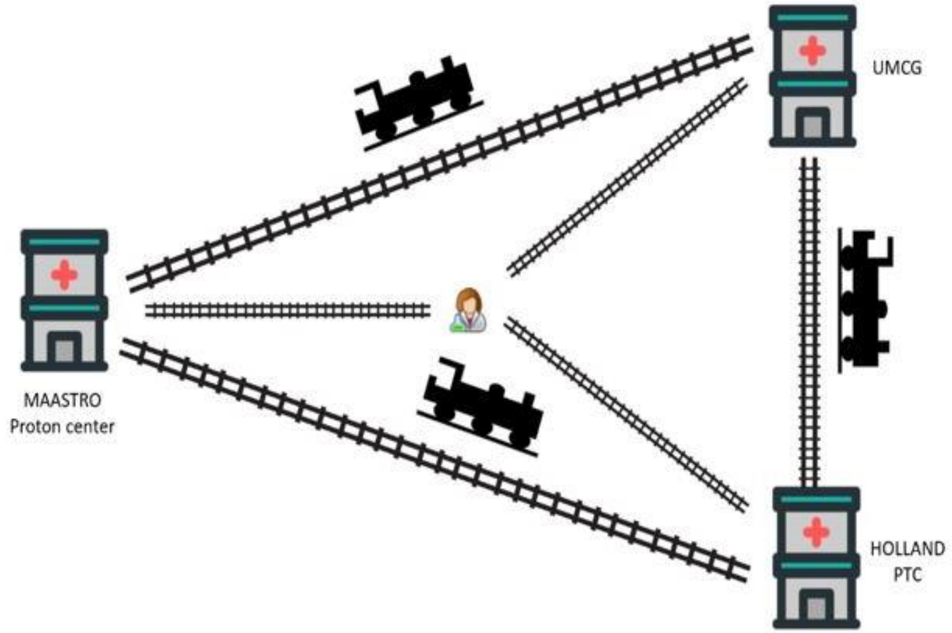
RayIn…
analy…
your …
cancer ca…
oncology, and surg…

Only now becoming available in commercial products

*Subject to regulatory clearance in some markets

Larger Cohorts to Tackle RBE Challenge

- ❑ Problem:
  - ❑ RBE depends on many biological factors
  - ❑ Ideally better RBE models from patient data
  - ❑ However we are often limited by statistics: not enough patients, not even at MD Anderson
- ❑ Possible Solution:
  - ❑ Share data from multiple-institutions
  - ❑ Difficulties with patient confidentiality (anonymization)
  - ❑ Federated Learning (FL): Share algorithm rather than the data.



Our group is currently collaborating with:

- ❑ Dutch group with ample FL experience
- ❑ Harvard (MGH) in the context of an NIH grant on proton therapy

Exciting Developments: Flash Therapy

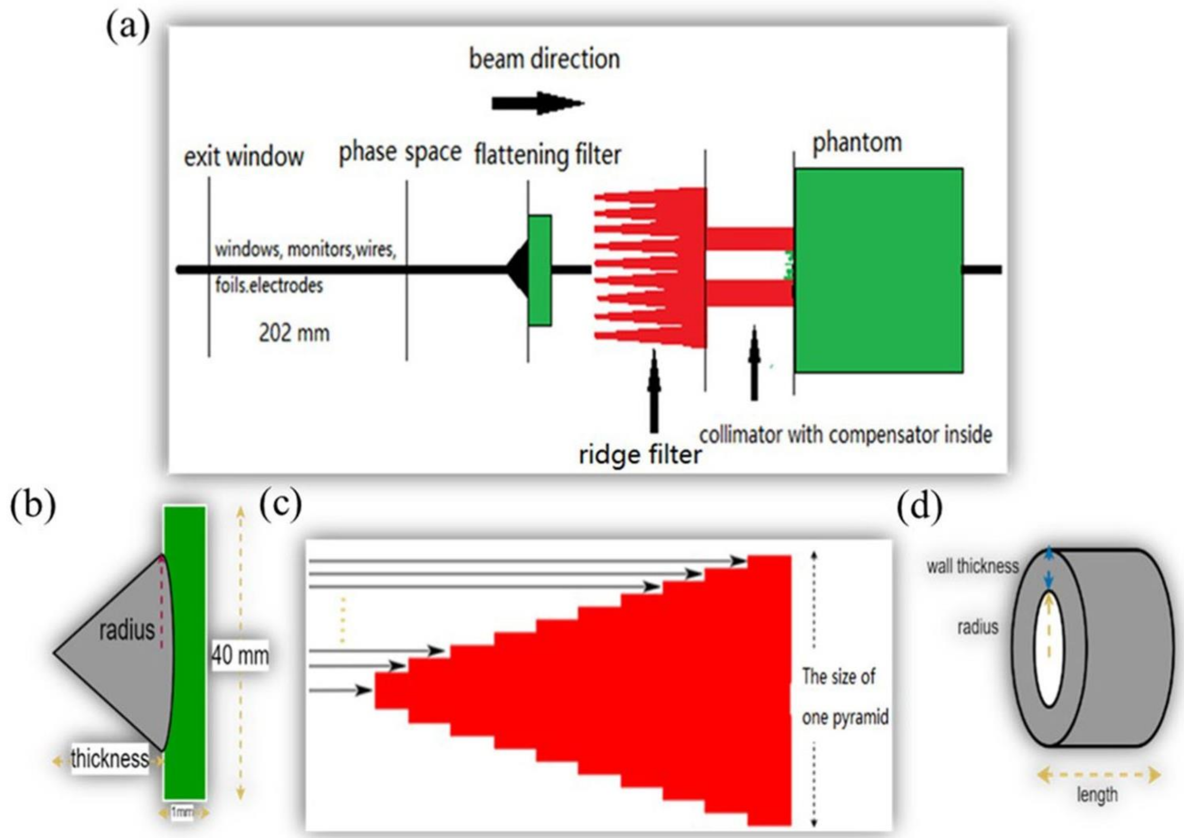
Flash Therapy

- ❑ It may revolutionize Radiotherapy!
- ❑ Present for all types ionizing radiation (x-rays, protons, etc)
- ❑ Fast delivery of dose:
  - ❑ Flash: 40 Gy/s
  - ❑ Conventional: 0.5-5 Gy/min
- ❑ Effects:
  - ❑ Similar on tumors
  - ❑ Lesser or no effects on healthy tissue
- ❑ Effect depends on: dose, dose rate, time structure.
- ❑ Lot of areas need improvement, i.e.:
  - ❑ Accelerator delivery
  - ❑ Dose measurements
  - ❑ Biological understanding (oxygen depletion)
- ❑ Technical challenges particularly acute for x-ray traditional therapy. Protons may have technical advantages. Going back to PSPT?

Going Back to PSPT to achieve Flash?

Q. Wang,...,P Yepes, Med Phys. 49 (2022) 6684.

- ❑MD Anderson is using its soon-to-be-retired Proton Therapy Center to carry out experiments in Flash
- ❑Necessary component appropriate proton beam covering a large enough volume
- ❑We developed an automatic procedure to design necessary components to provide a homogeneous FLASH proton beam.



Summary

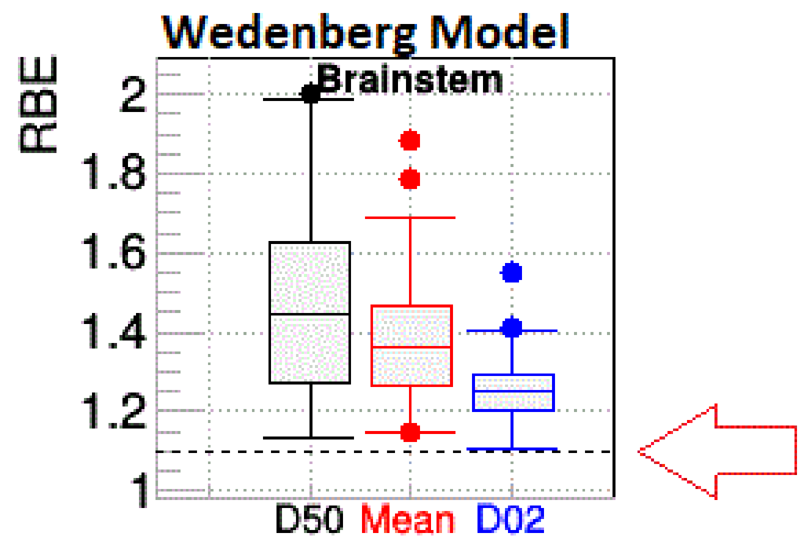
- Radiation therapy physics have a large overlap with that of particle and nuclear physics.
- Proton Therapy (PT) is a rapidly growing modality of cancer treatment because of its capability to achieve tumor control while better preserving healthy tissue.
- However, PT is a relatively new technique compared to traditional therapy. Many challenges remain to fully exploit it. Accurate dose calculations and LET handling are developments to overcome them.
- Flash therapy presents a new an exciting possibility for radiation therapy, almost too good to be true. PT presents technical advantages to implement it.

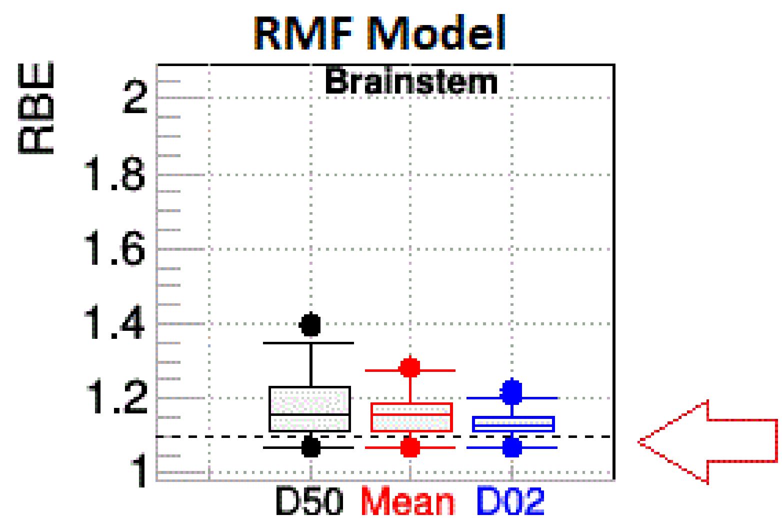
Additional Materials

RBE Effect on Patient Treatment Plans

Yepes et al., Adv Radiat Oncol. (2019)156

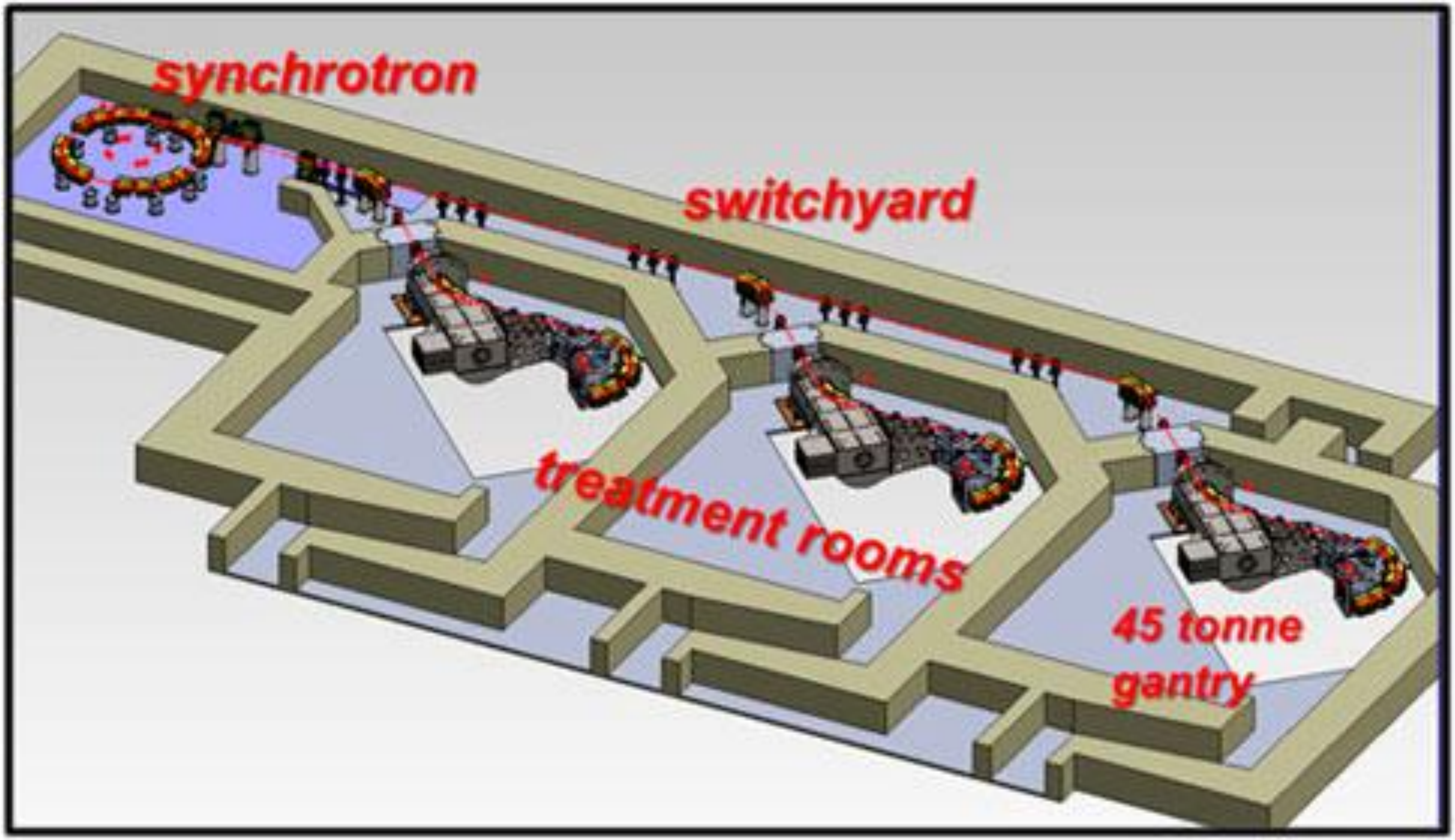
- ❑In the clinic to treat patients an RBE=1.1 is used for protons
- ❑There are many models of variable RBE (≠1.1), many based on cell survival measurements
- ❑ What is the uncertainty/inaccuracy introduced by RBE=1.1
- ❑Study of largest cohort of patients (400) on the impact of variable RBE on dosimetric information (indices) used to evaluate treatment plans.





10-20% differences found on dose with variable RBE models

Proton Therapy Center



Proton Therapy Center

Ion Beam Therapy

Increasing interest in Ion Beam therapy

Sharper beams (less Coulomb scattering)

Apparently less danger of metastasis, more efficient immunological systems triggered with ions.

A few centers around the world (Germany, Japan, China, none in the US)

Even more expensive, because gantries need to be larger (when they are used)

More talk about ion therapy in US.