INTRODUCTION TO PARTICLES

Lars Glimelius, Senior product manager, RaySearch Laboratories

UPLIFT School #1, Lyon, 2025-11-18

ADVANCING CANCER TREATMENT

RaySearch Laboratories

AGENDA

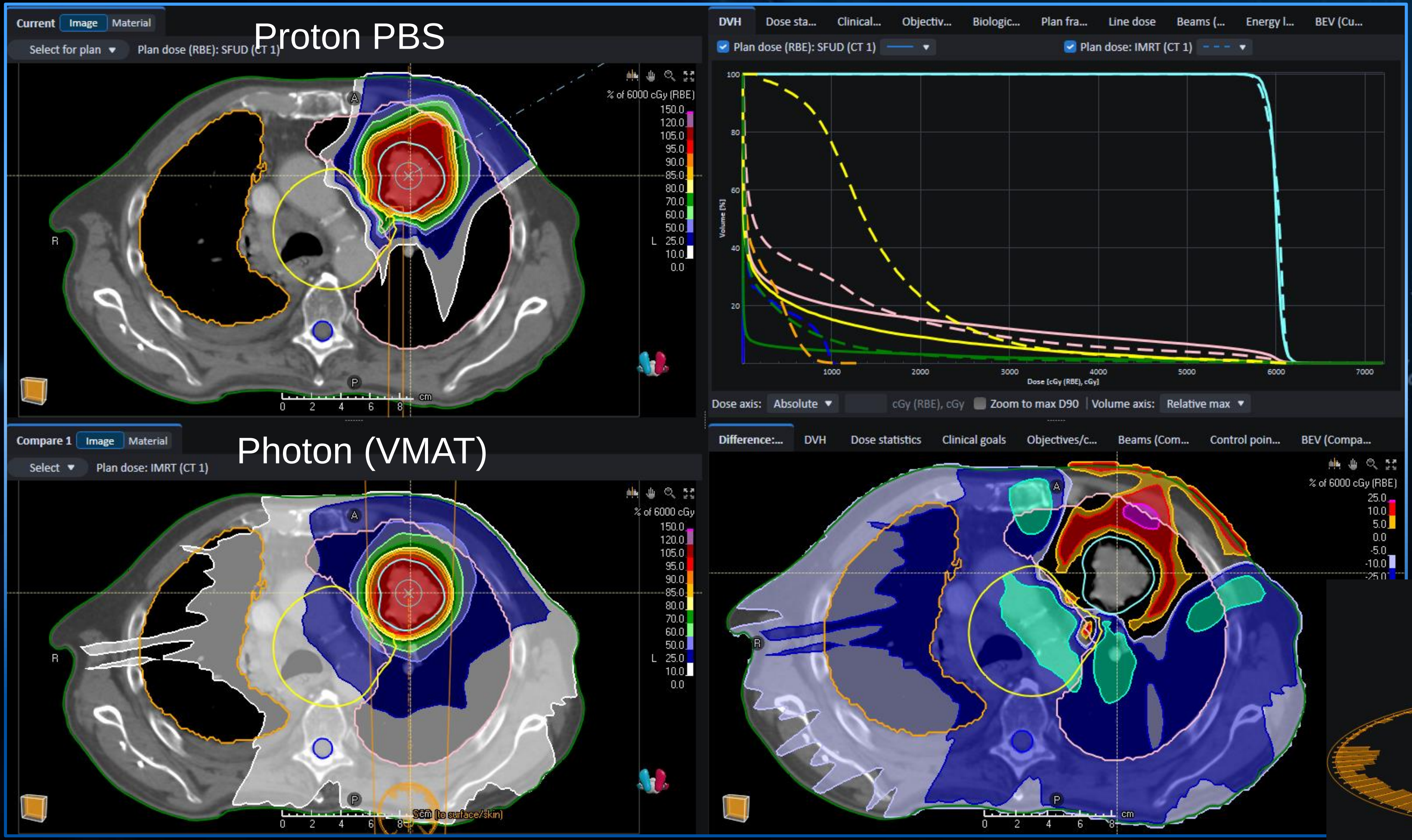
- Why use particles?
- A little bit of physics
- Delivery techniques
- Dose computation algorithms
- Uncertainties and robustness

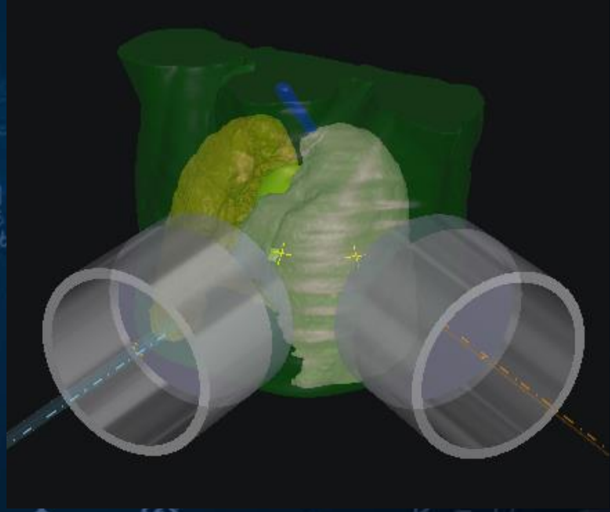
EXTERNAL RADIATION THERAPY AROUND THE WORLD

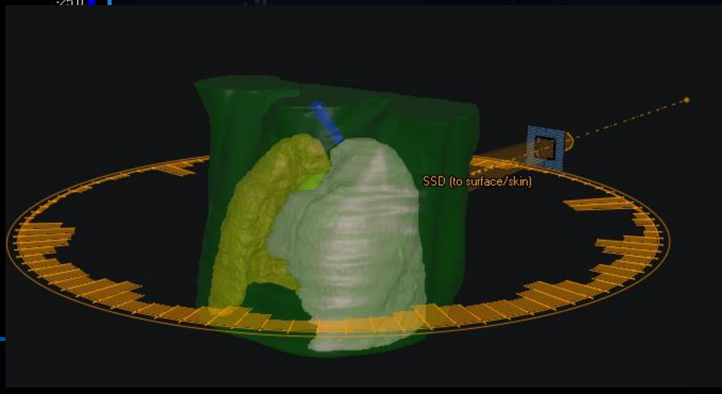
Modality	Nb of clinics
Conventional radiotherapy (photons and electrons)	~9000
Protons	~150
Helium ions	1
Carbon ions	~15
Oxygen & neon ions	1
Fast neutrons	A few (declining)
Boron neutron capture therapy (BNCT)	~10

WHY USE PARTICLES?

Because the dose distribution looks so nice!

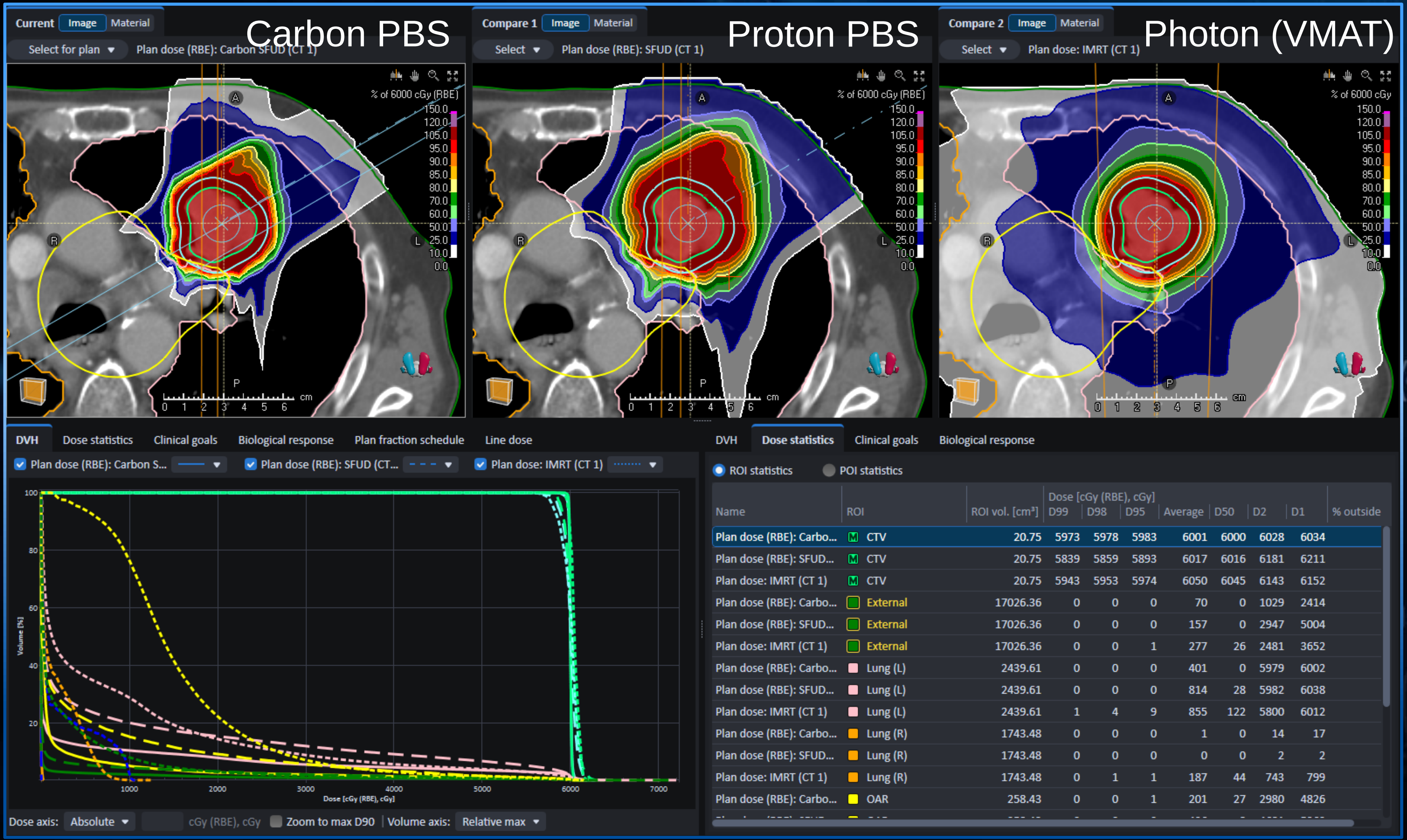






WHY USE PARTICLES?

Heavier ions look even nicer!

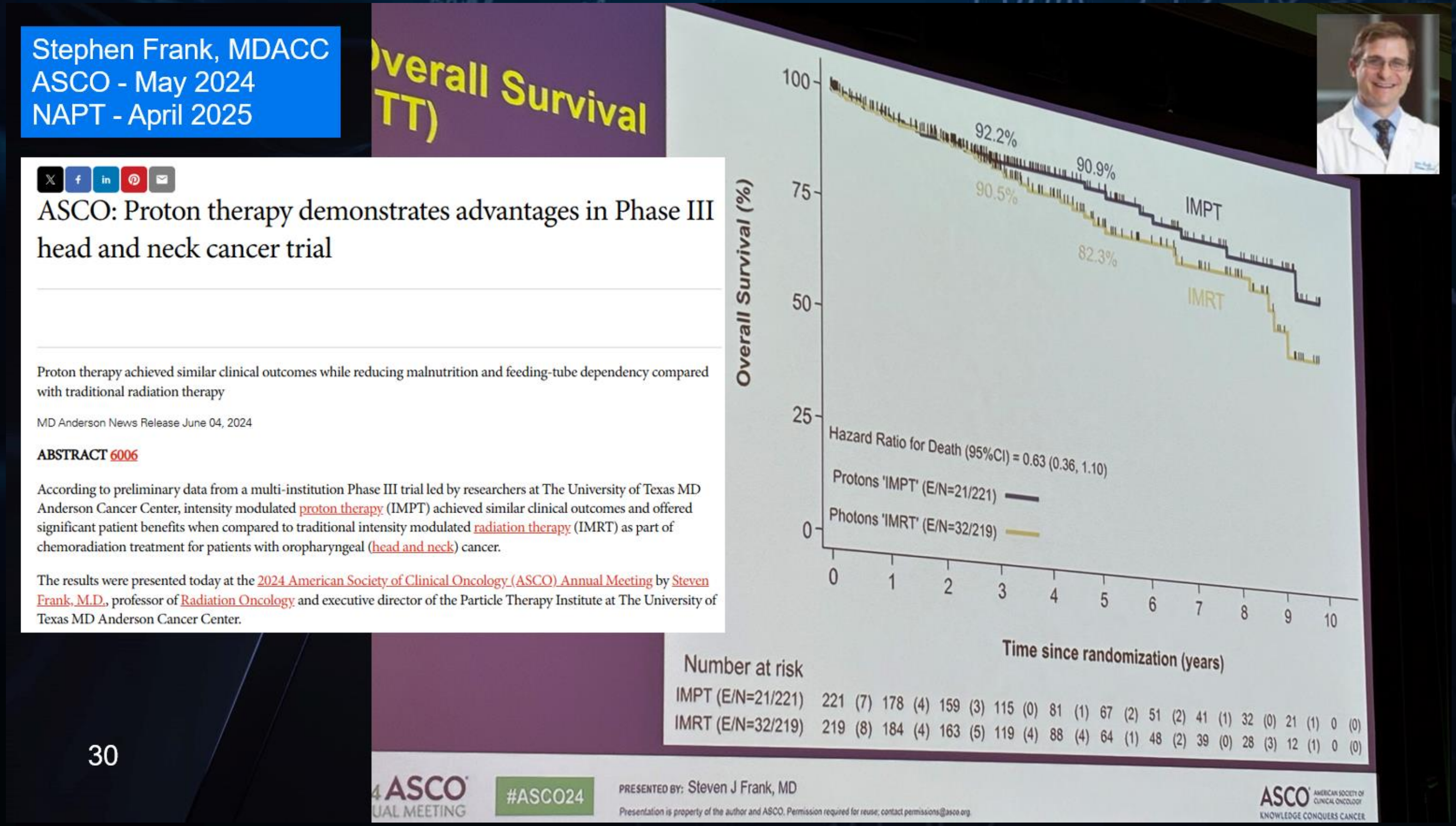


RaySearch Laboratories

CLINICAL EVIDENCE?

IMPT vs IMRT

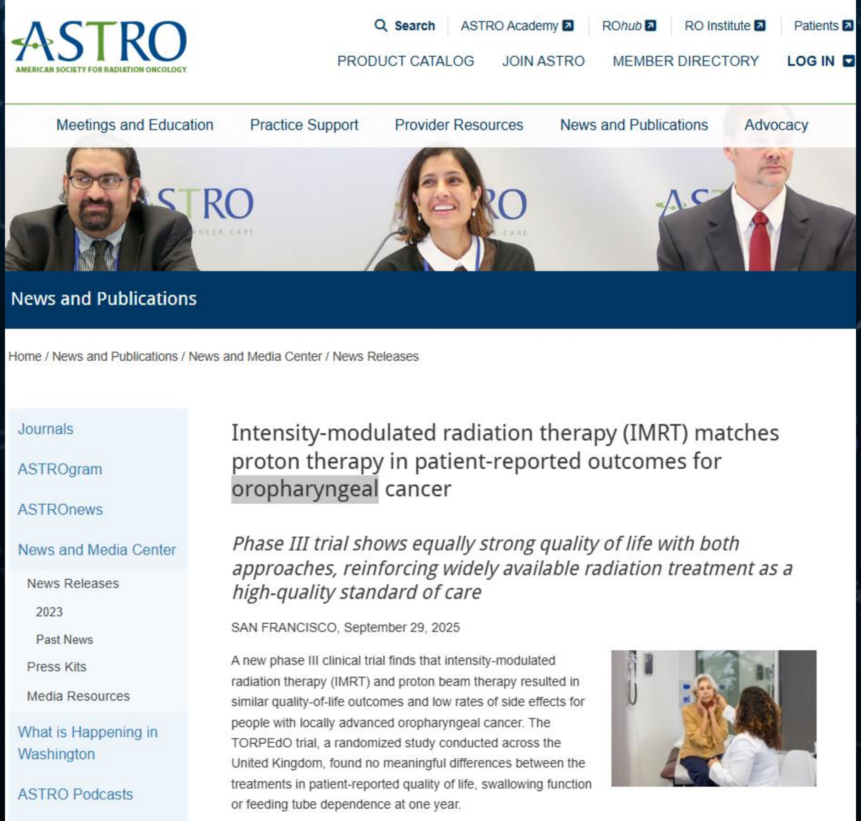
- The MD Andersson trial
  - Randomized phase III oropharyngeal cancer trial
  - Non-inferior to IMRT
  - Less side effects (e.g. less need of feeding tubes)
  - Better 5-year overall survival
  - Still not published!?



CLINICAL EVIDENCE?

IMPT vs IMRT

- The TORPEdO trial
  - Randomized phase III head and neck trial
  - Does not show a benefit for proton PBS
  - Not as long follow-up as MDA trial (2.6 years)
- There are differences between UK and US and between the trials
- Technology always improving (both for protons and photons)
- Multiple clinical trials coming...



ASTRO
AMERICAN SOCIETY FOR RADIATION ONCOLOGY

Search | ASTRO Academy | ROhub | RO Institute | Patients

PRODUCT CATALOG | JOIN ASTRO | MEMBER DIRECTORY | LOG IN

Meetings and Education | Practice Support | Provider Resources | News and Publications | Advocacy

News and Publications

Home / News and Publications / News and Media Center / News Releases

Journals
ASTROgram
ASTROnews
News and Media Center
News Releases
2023
Past News
Press Kits
Media Resources
What is Happening in Washington
ASTRO Podcasts

Intensity-modulated radiation therapy (IMRT) matches proton therapy in patient-reported outcomes for oropharyngeal cancer

Phase III trial shows equally strong quality of life with both approaches, reinforcing widely available radiation treatment as a high-quality standard of care

SAN FRANCISCO, September 29, 2025

A new phase III clinical trial finds that intensity-modulated radiation therapy (IMRT) and proton beam therapy resulted in similar quality-of-life outcomes and low rates of side effects for people with locally advanced oropharyngeal cancer. The TORPEdO trial, a randomized study conducted across the United Kingdom, found no meaningful differences between the treatments in patient-reported quality of life, swallowing function or feeding tube dependence at one year.

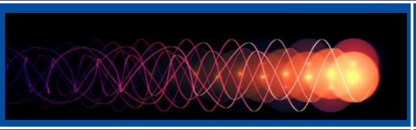
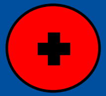
CLINICAL EVIDENCE?

Carbon ions

- What about carbon ions?
  - ETOILE
    - Radioresistant tumors (sarcomas, carcinomas etc.)
  - HIT-1
    - Skull-based chordoma
  - CARE trial
    - Recurrent head and neck cancer
  - ...

A BIT OF PHYSICS

DIFFERENCES BETWEEN MODALITIES

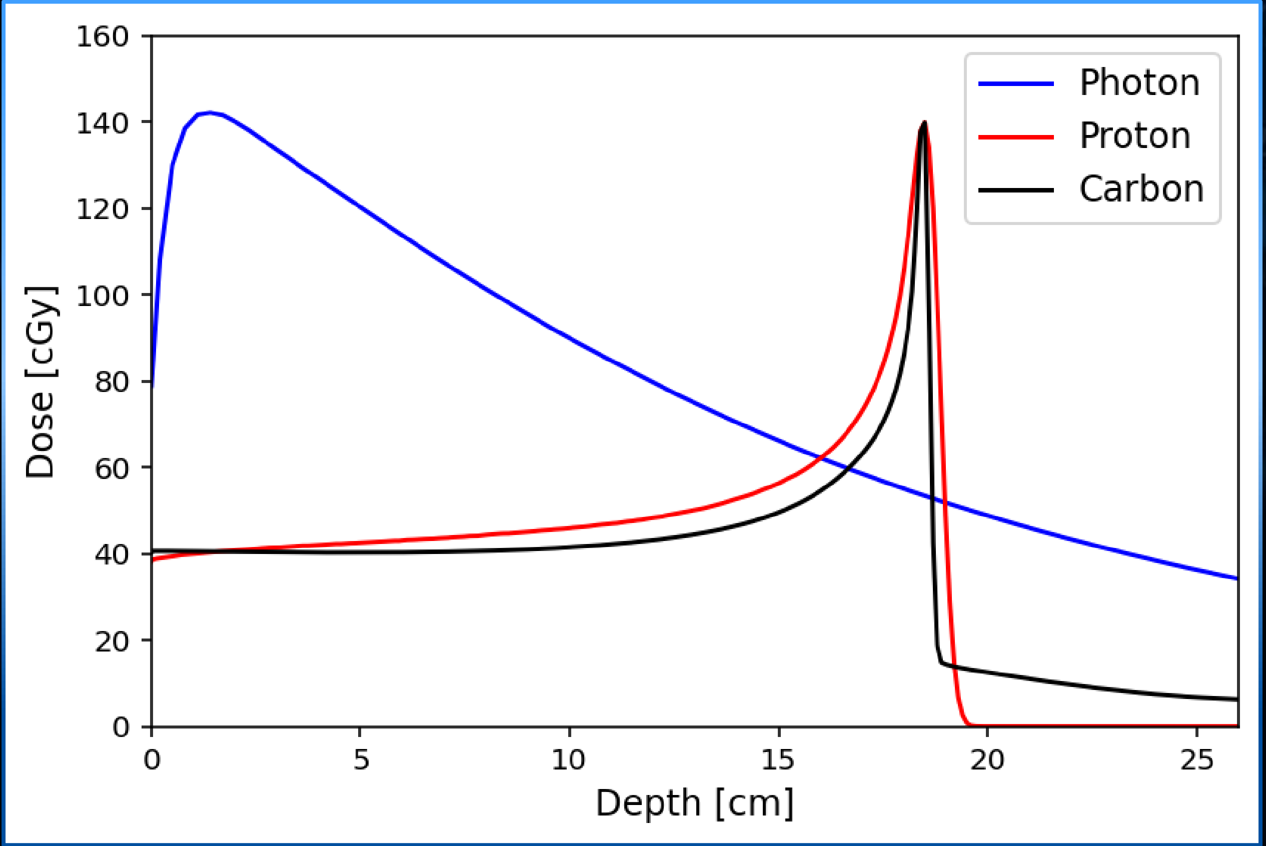
Photons 	Protons 	Light ions 
Neutral	Positively charged	Positively charged
No mass	Medium	Heavy
$	$$	$$$

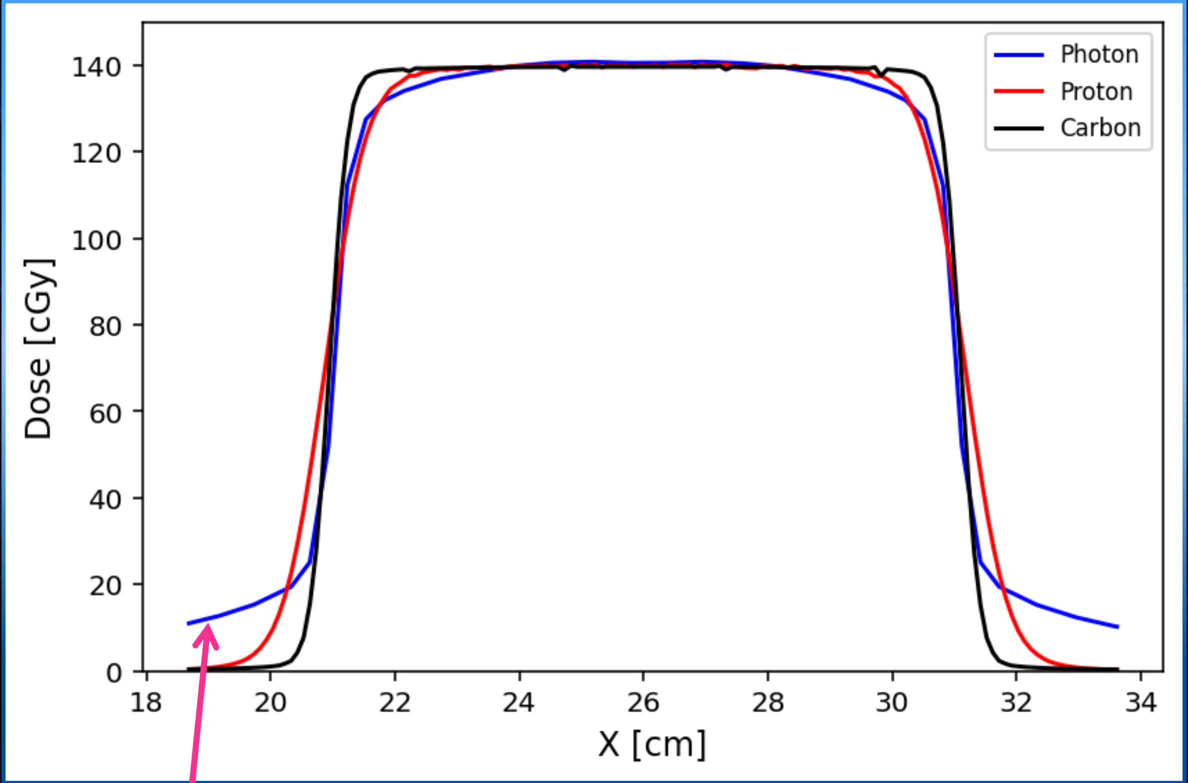
RaySearch Laboratories

PHYSICAL DOSE CHARACTERISTICS

For a 5x5 cm field

The classic depth dose comparison





The lateral penumbra comparison

MLC leakage

RaySearch Laboratories

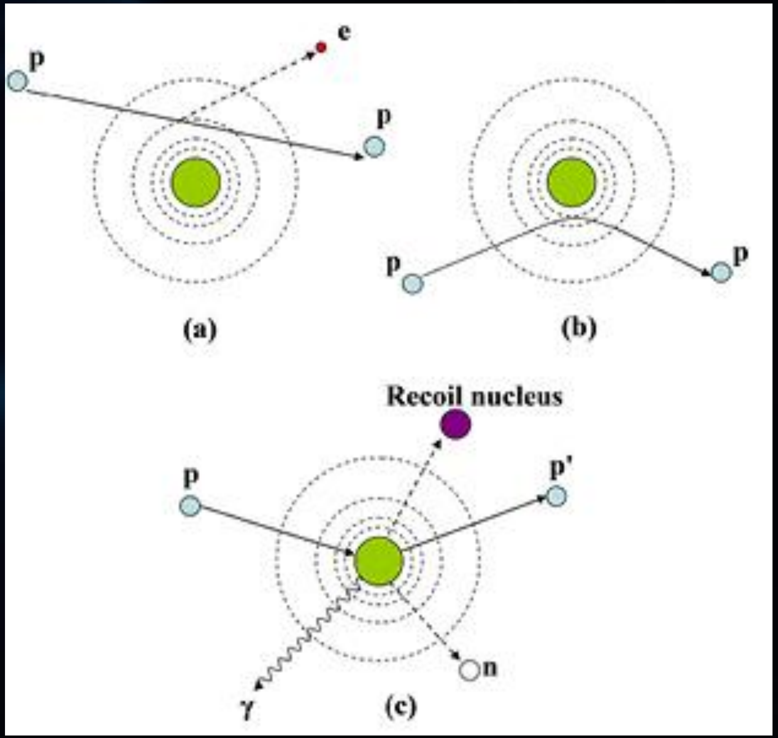
PHYSICAL INTERACTIONS

What happens when we irradiate a target with high energy particles?

Coulomb force

Interactions with atomic electrons

- ➡ particle looses energy (slows down)
- ➡ electron is ejected (and cause damage)



Elastic scattering on target nuclei

- ➡ particle changes direction (only slightly)

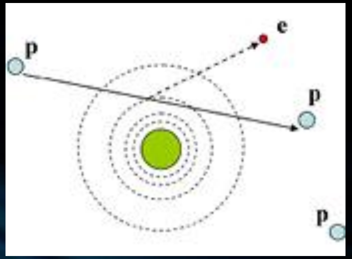
Inelastic scattering (nuclear interaction)

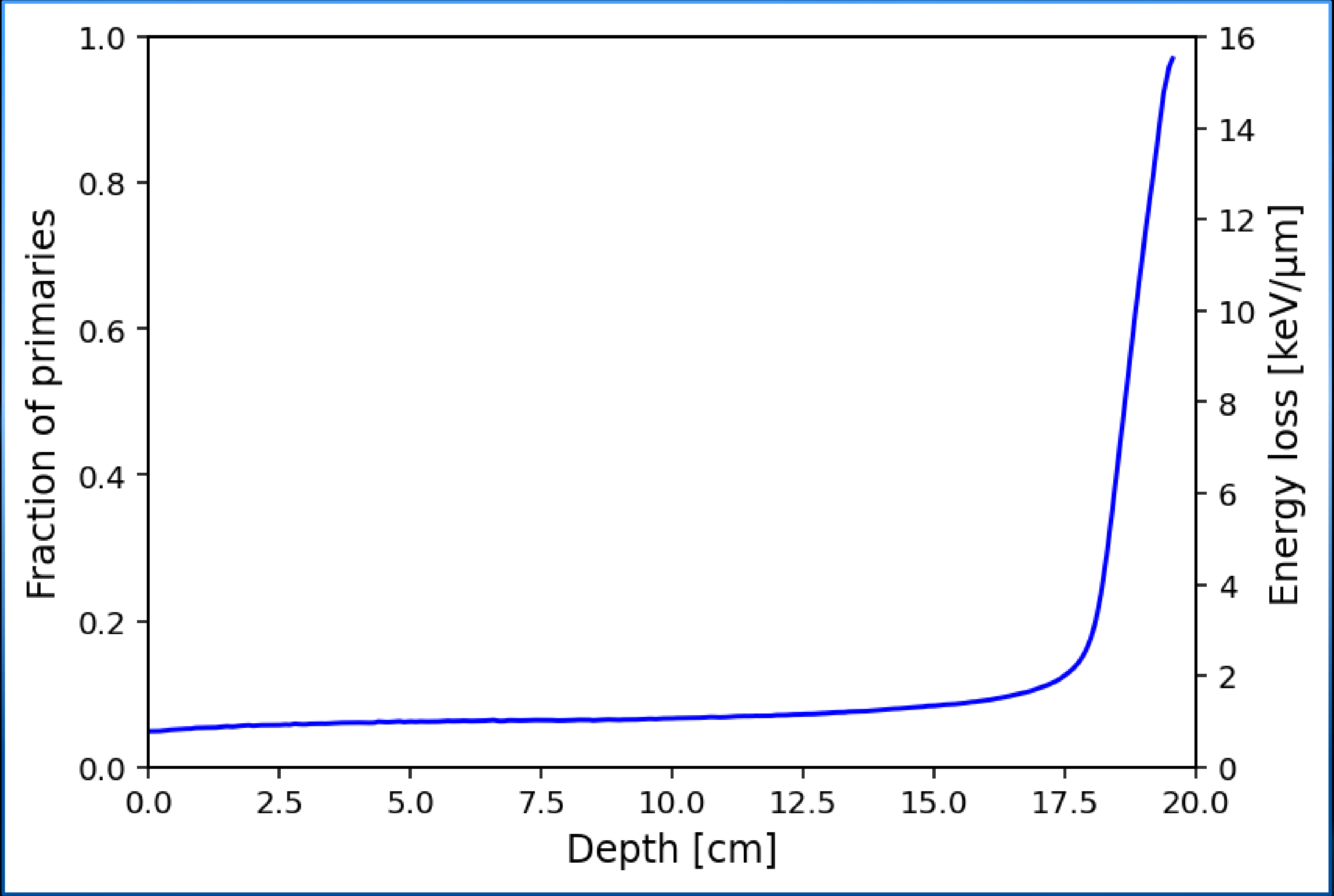
- ➡ primary particle is “removed” and fragments are created

THE BRAGG PEAK

For protons

$$-\left\langle \frac{dE}{dx} \right\rangle = \frac{4\pi}{mc^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0} \right)^2 \cdot \left[\ln\left(\frac{2mc^2\beta^2}{I \cdot (1-\beta^2)} \right) - \beta^2 \right]$$

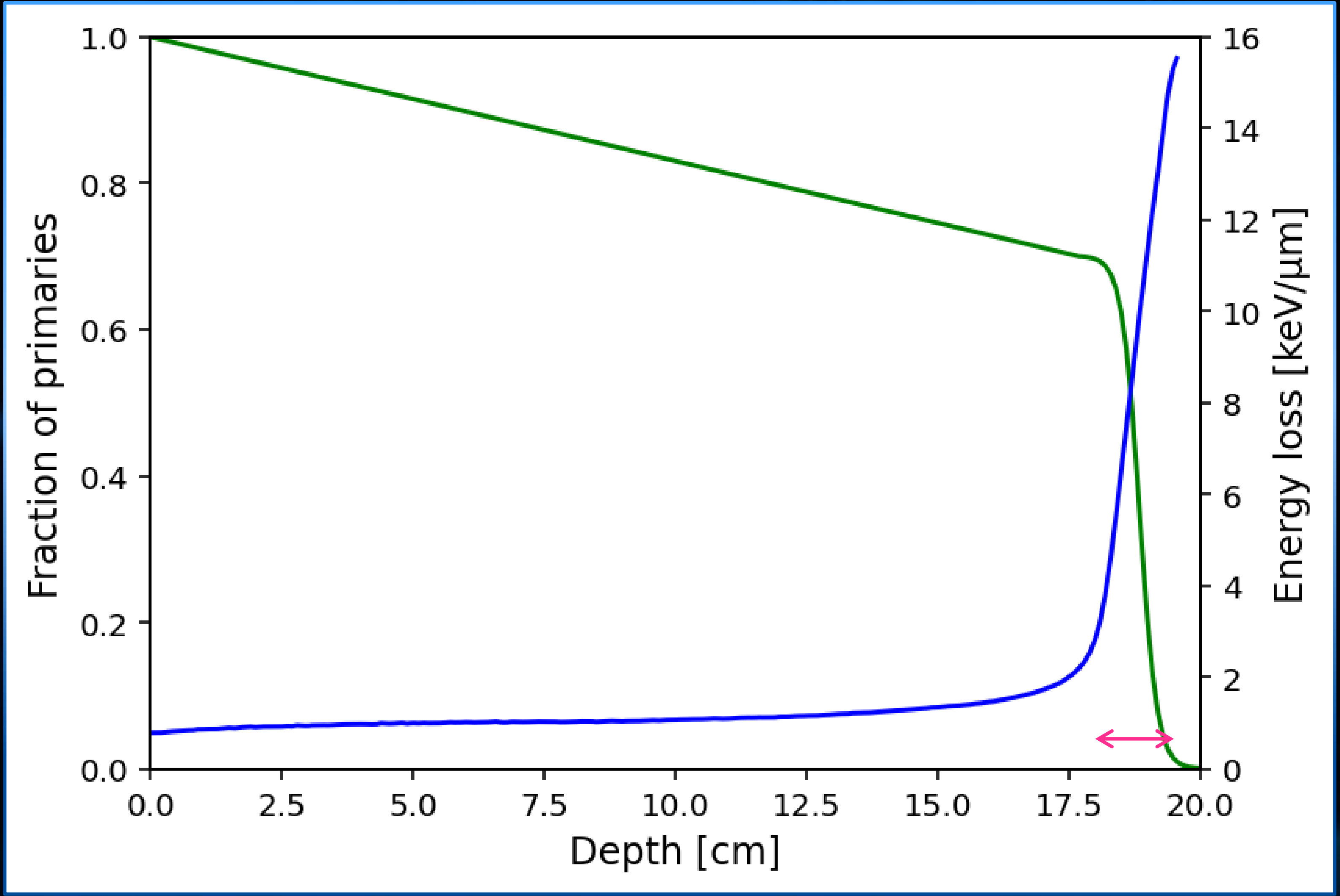


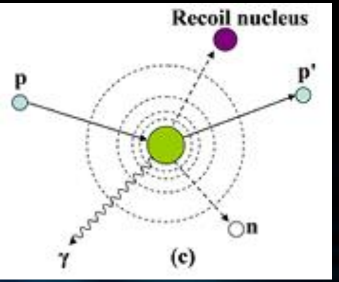


- Energy loss (deposition) increases with decreasing speed (energy)
- Linear energy transfer (LET)
- Bethe-Bloch formula
  - dE/dx ~ 1/v2

THE BRAGG PEAK

For protons



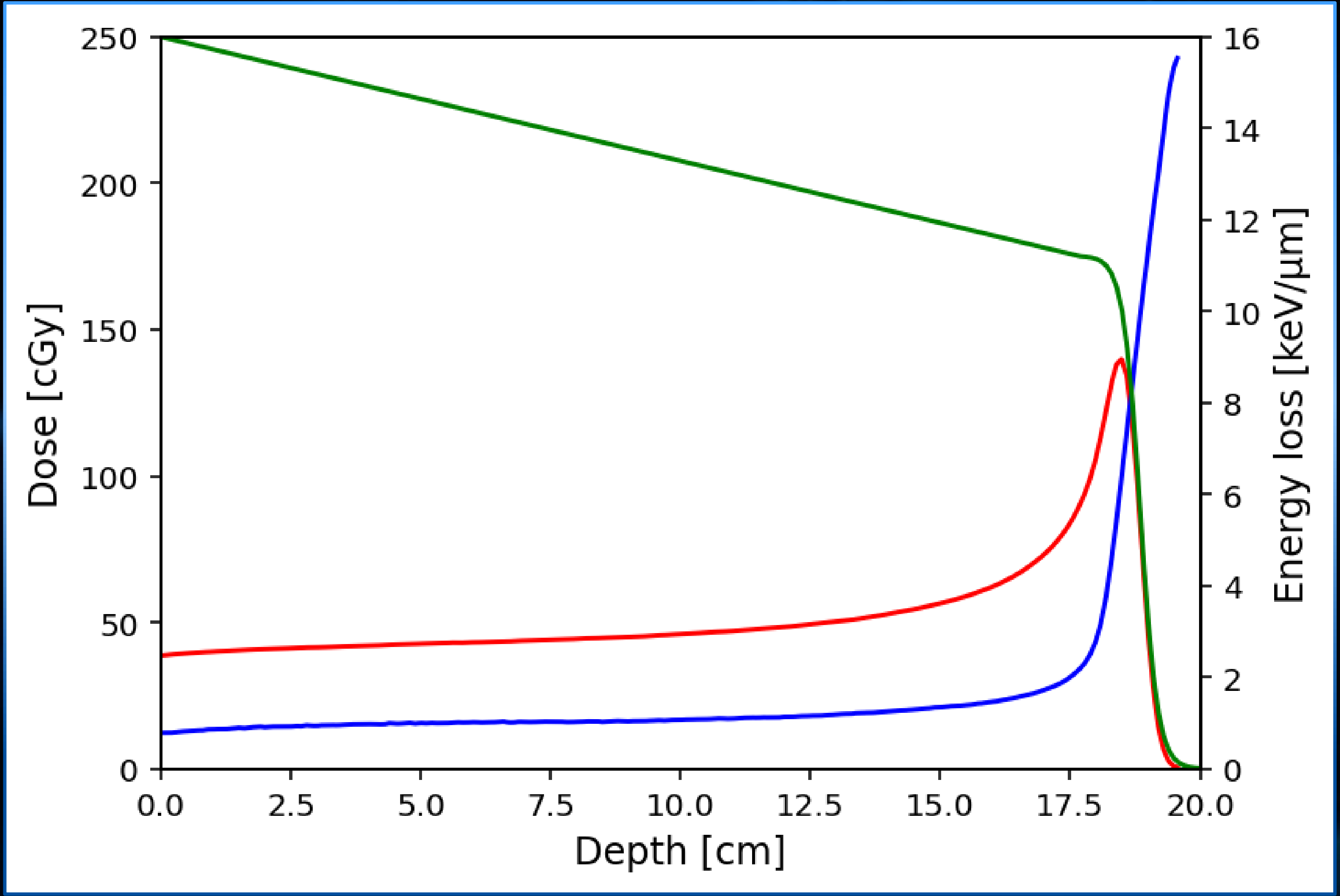


- The number of primary ions (fluence) decreases, until they all stop.
- (Mainly) caused by nuclear interactions (inelastic scattering).
  - Secondary protons, ^{2}H, ^{3}H, α etc. are produced
- Note that energy loss is a stochastic process, i.e. all particles don't stop in the same place. This is known as energy/range straggling.

RaySearch Laboratories

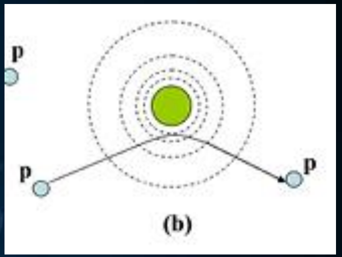
THE BRAGG PEAK

For protons

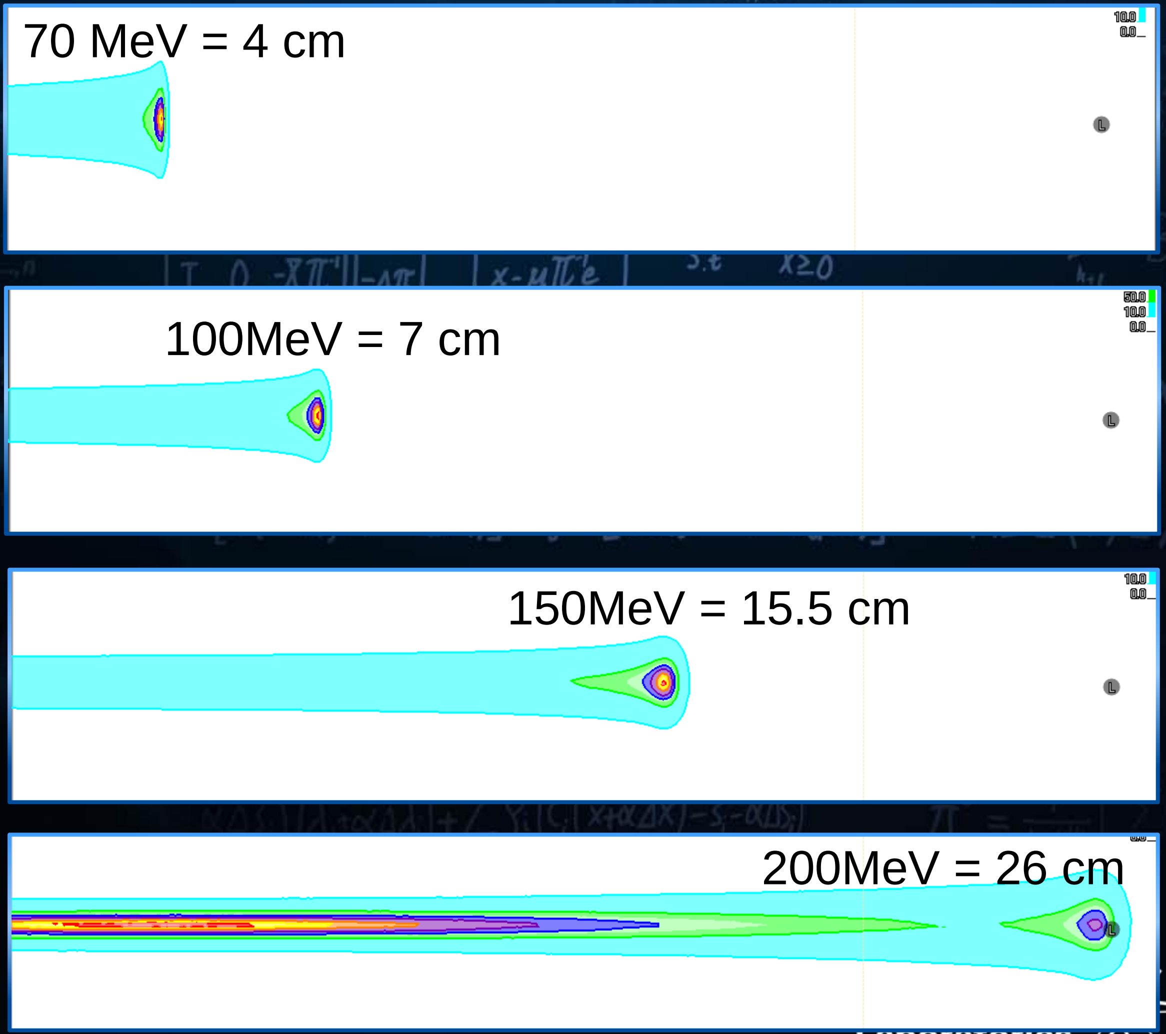


- Dose = deposited energy x fluence / mass
  - [J/kg] = [Gy]

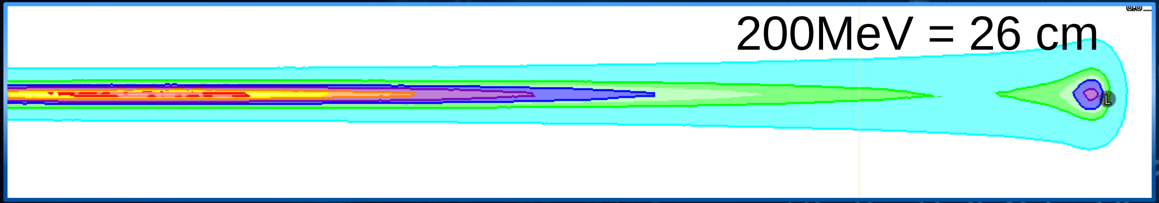
PROTON PENCIL BEAM SPOTS

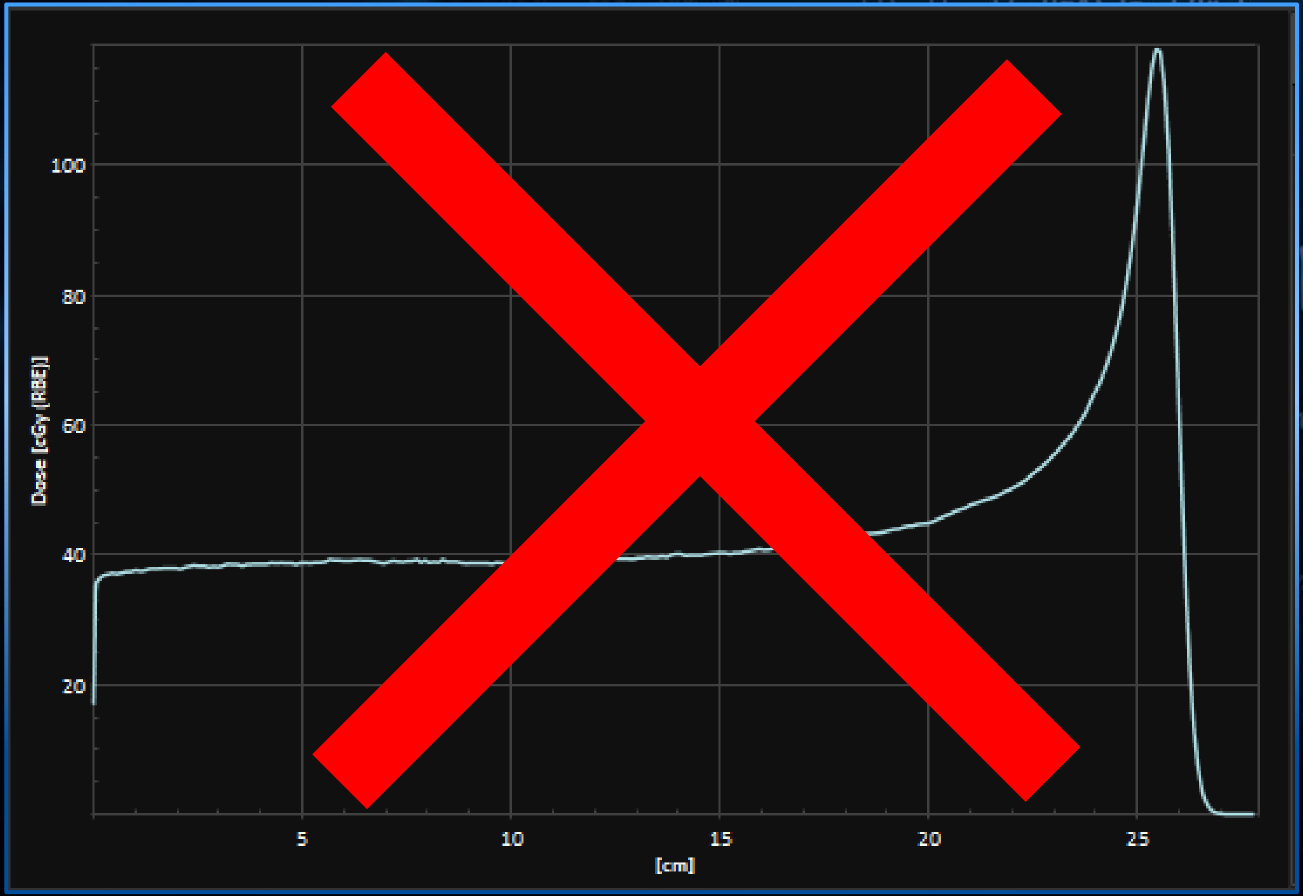


- A proton spot is a thin pencil beam
  - σ =~ 0.5 – 2 cm
- The depth is controlled by the energy (velocity)
  - Range shifters are needed for depths smaller than ~4 cm. This significantly increases the spot width!
- The spot is spread out due to multiple Coulomb scattering (MCS) and initial divergence

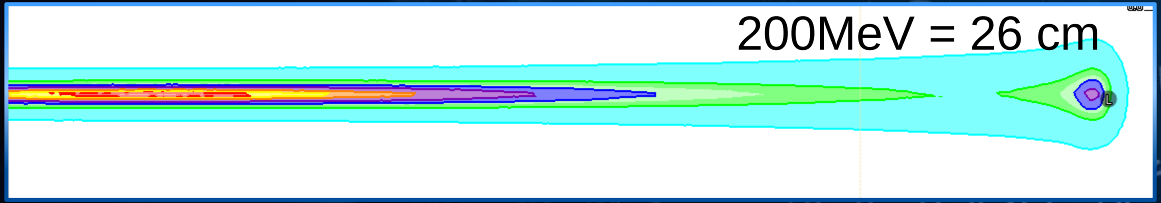


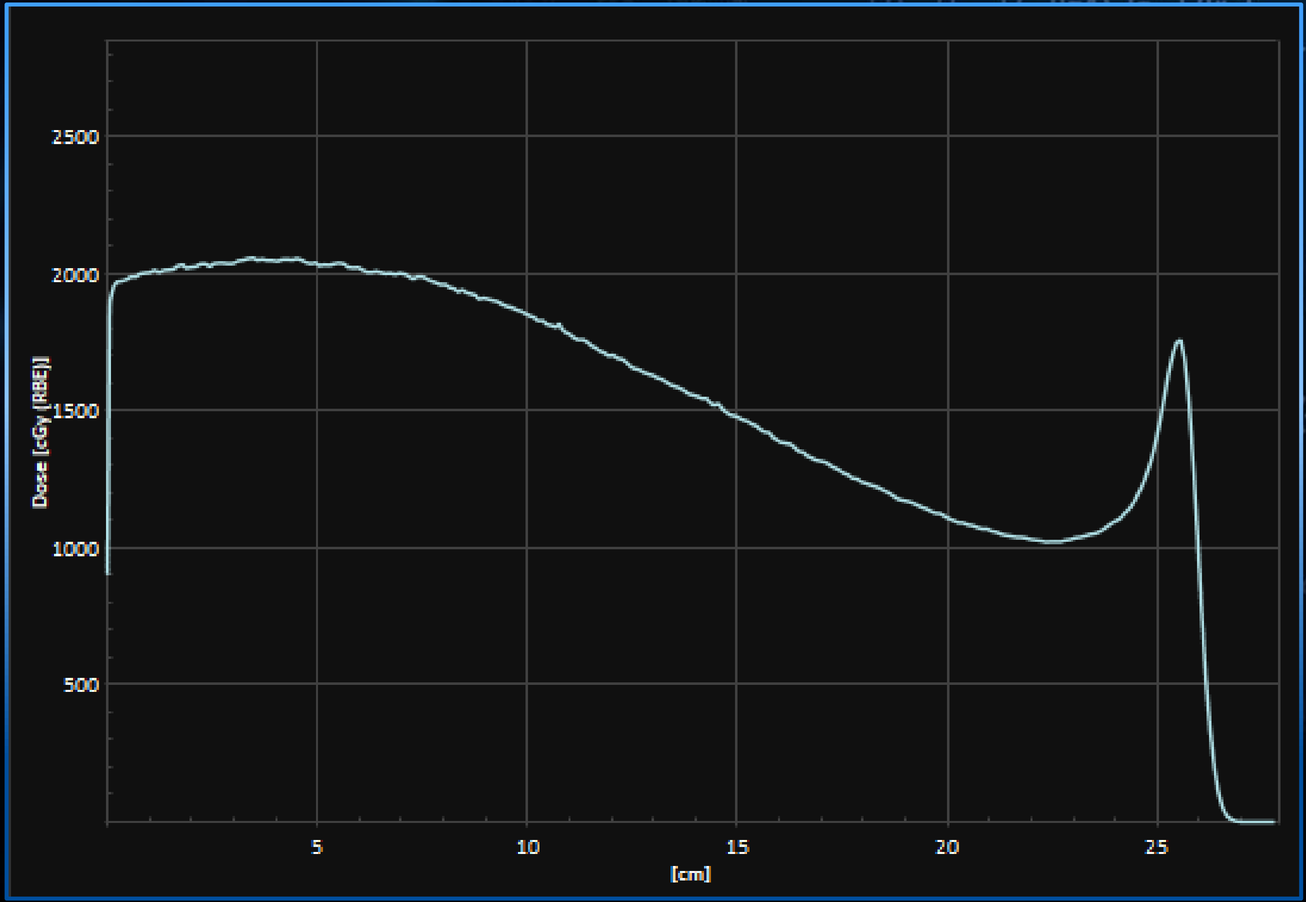
PROTON PENCIL BEAM SPOTS





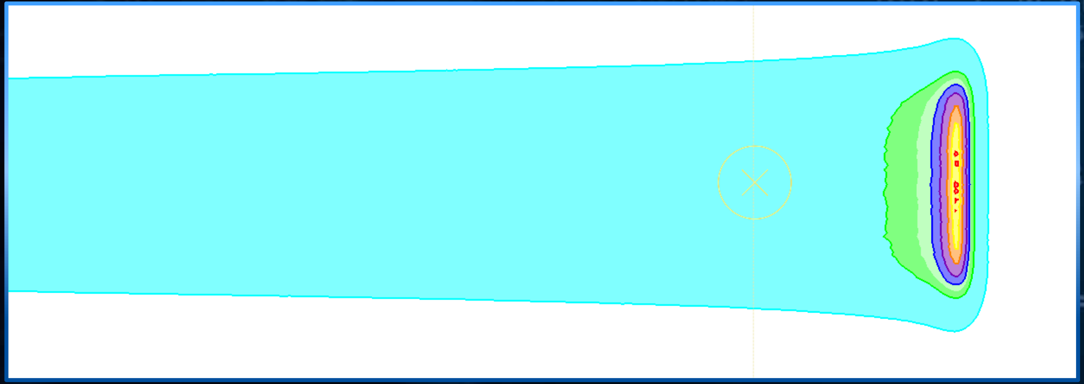
PROTON PENCIL BEAM SPOTS

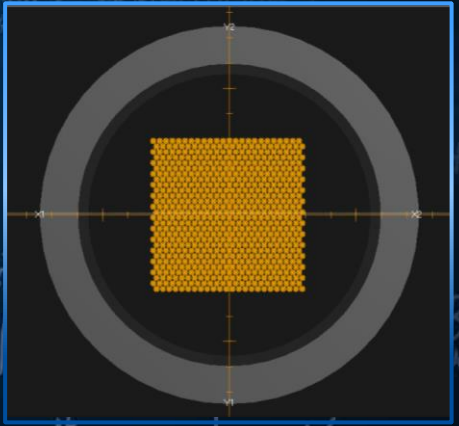


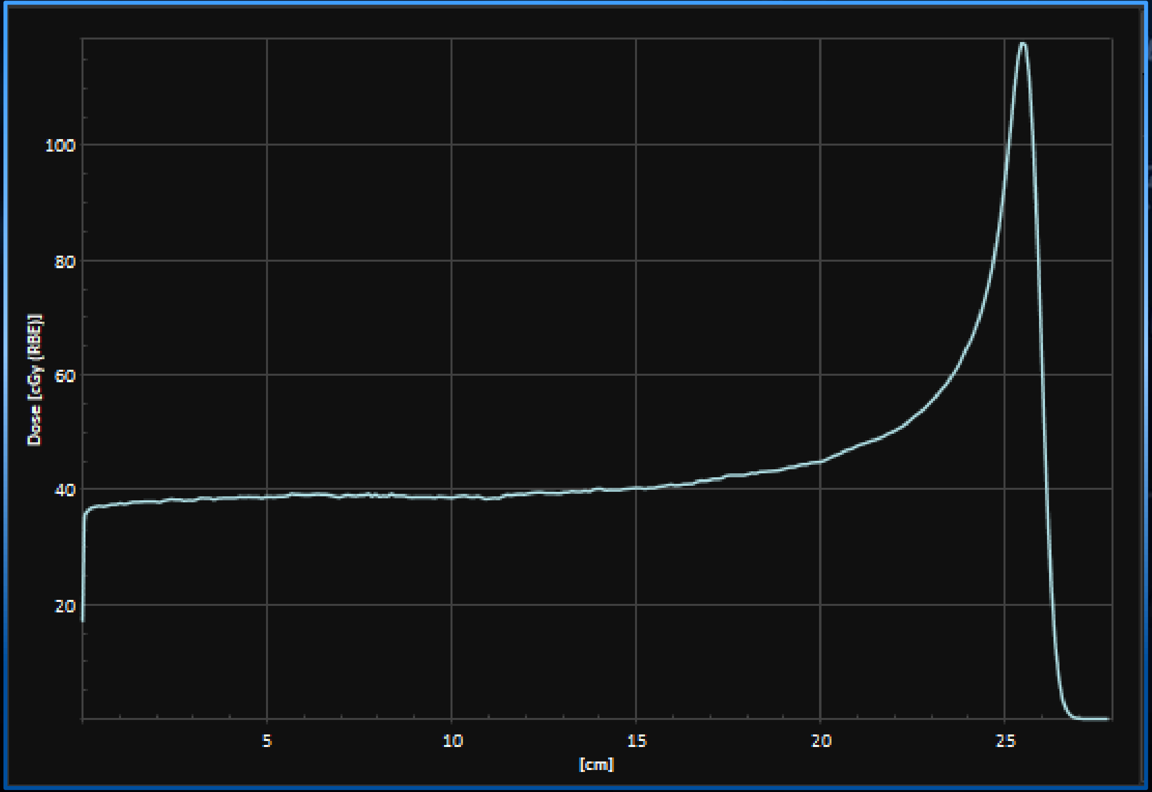


200MeV = 26 cm

PROTON PENCIL BEAM SPOTS



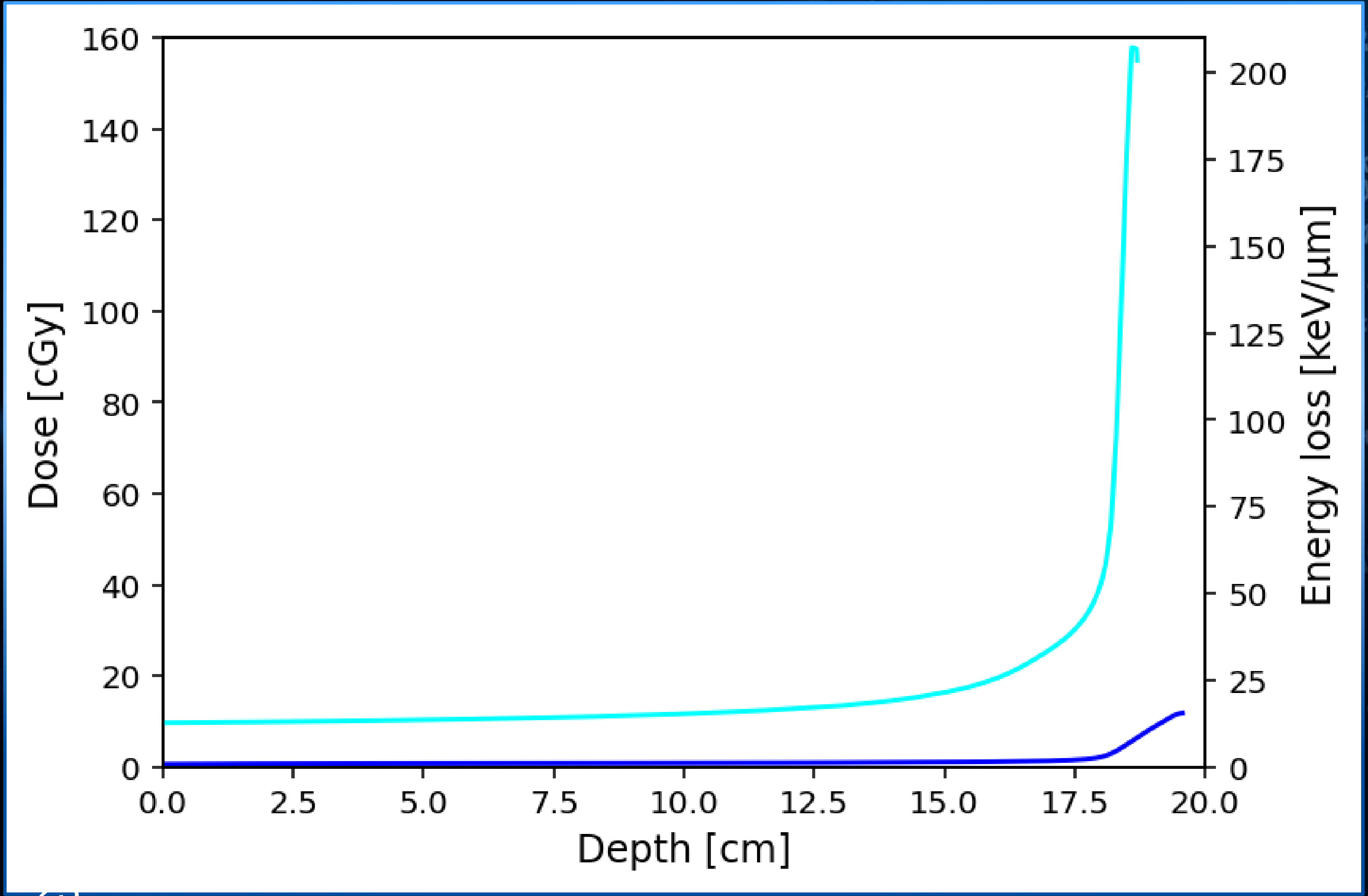




200MeV = 26 cm

THE BRAGG PEAK

For carbon ions



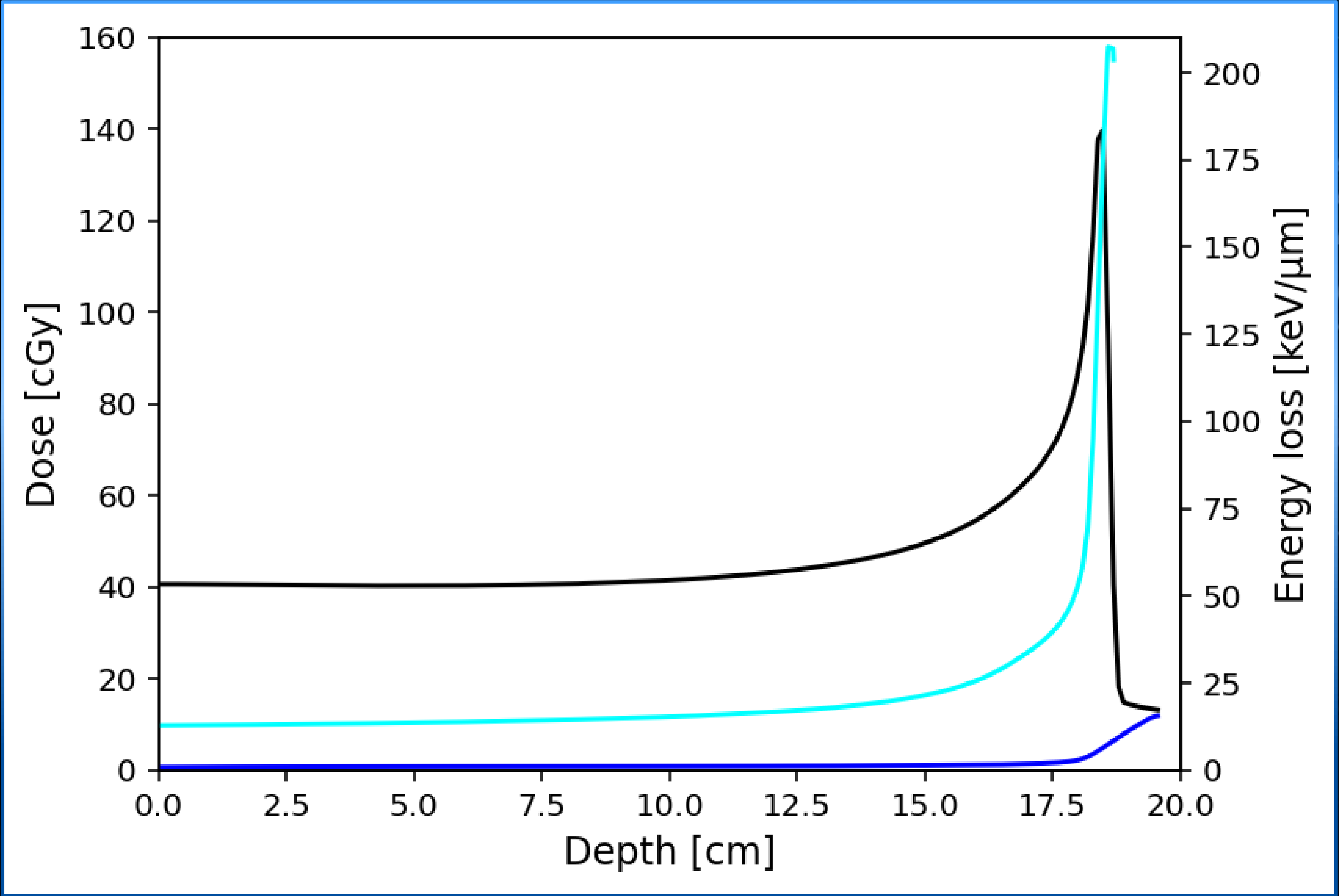
- Carbon ions are 12 times heavier than protons

➡ LET significantly higher

THE BRAGG PEAK

For carbon ions

It's actually even sharper than this. So-called ripple filters are used to spread out the Bragg peak to reduce the number of energy layers.

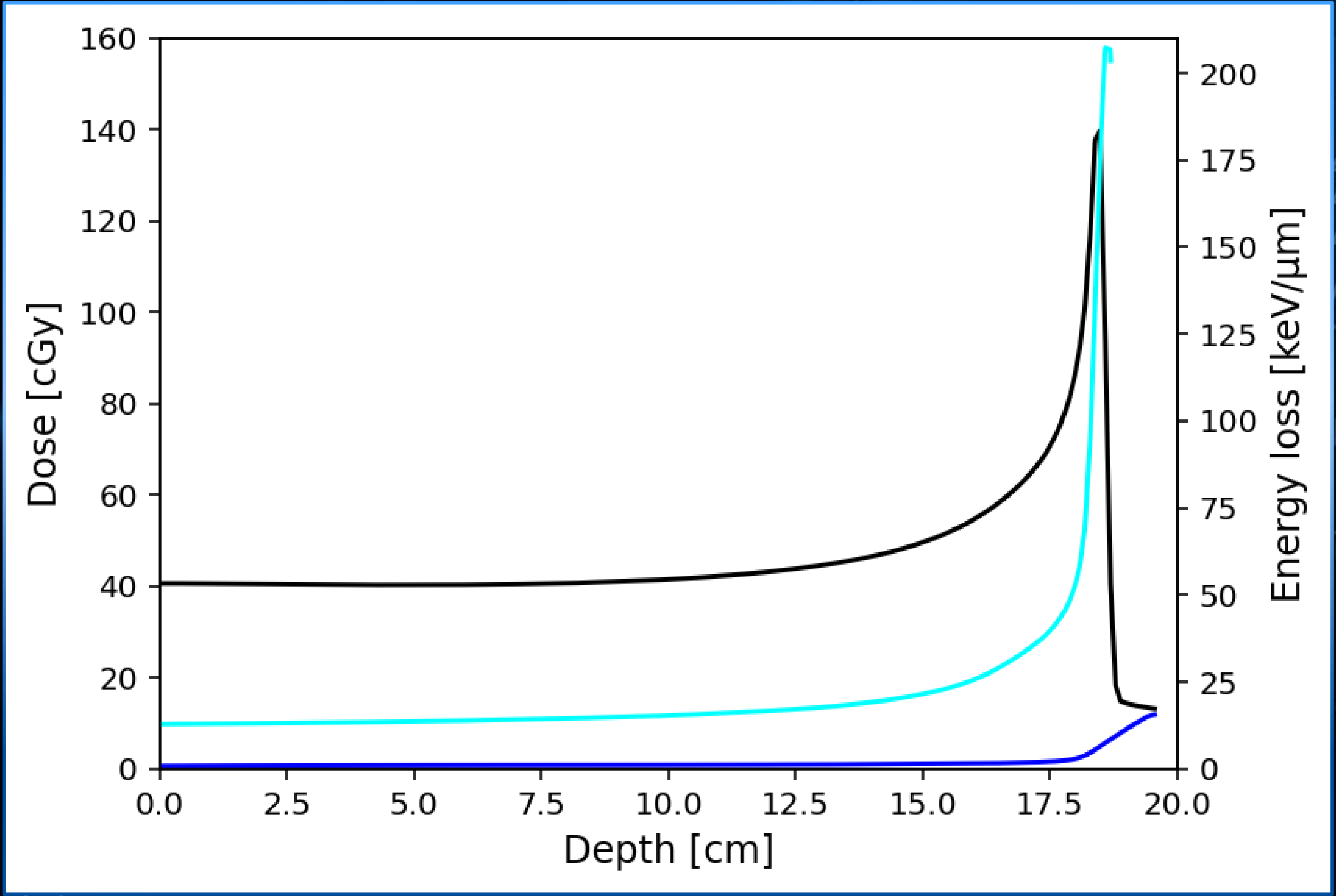


- Carbon ions are 12 times heavier than protons
  - ⇨ LET significantly higher
  - ⇨ Sharper Bragg peak

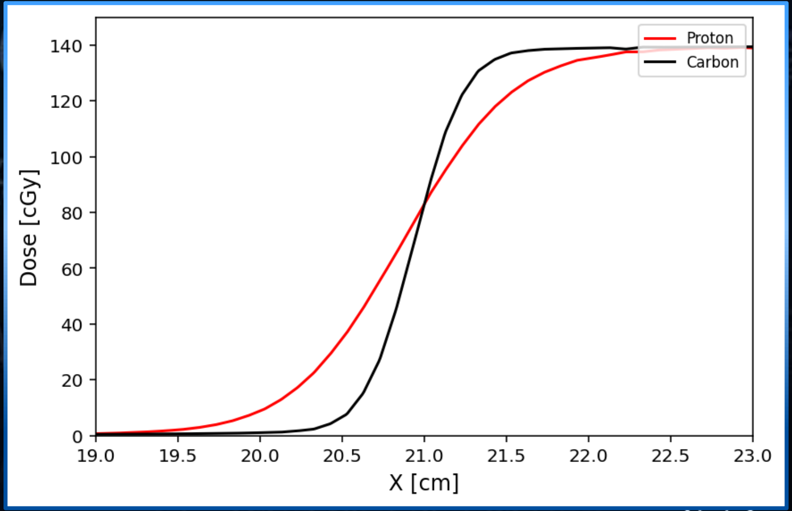
RaySearch Laboratories

THE BRAGG PEAK

For carbon ions

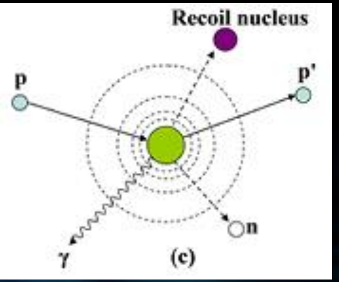


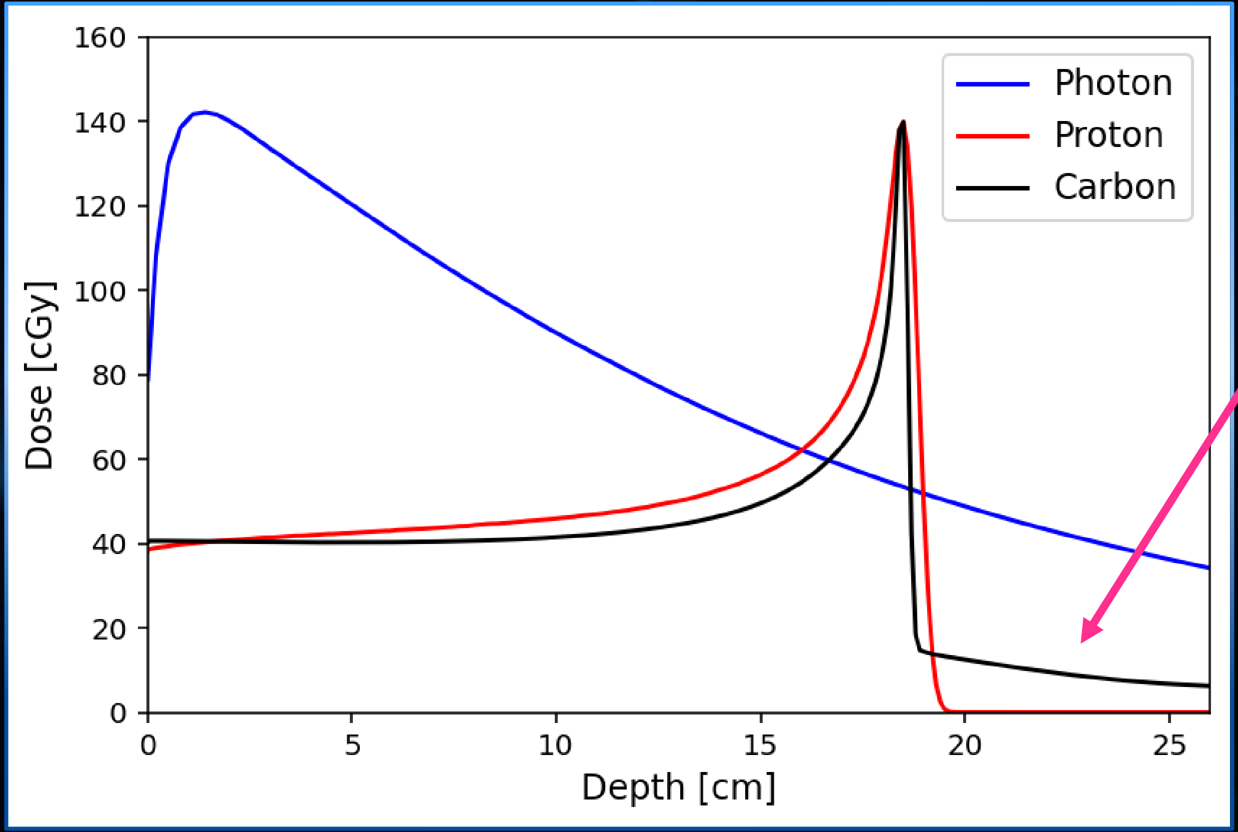
- Carbon ions are 12 times heavier than protons
  - ➡ LET significantly higher
  - ➡ Sharper Bragg peak
  - ➡ Sharper penumbra



RaySearch Laboratories

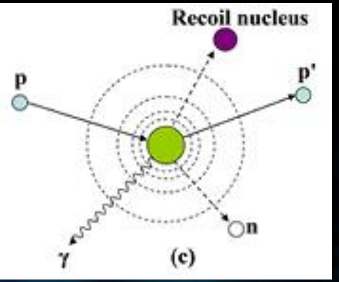
THE FRAGMENT TAIL



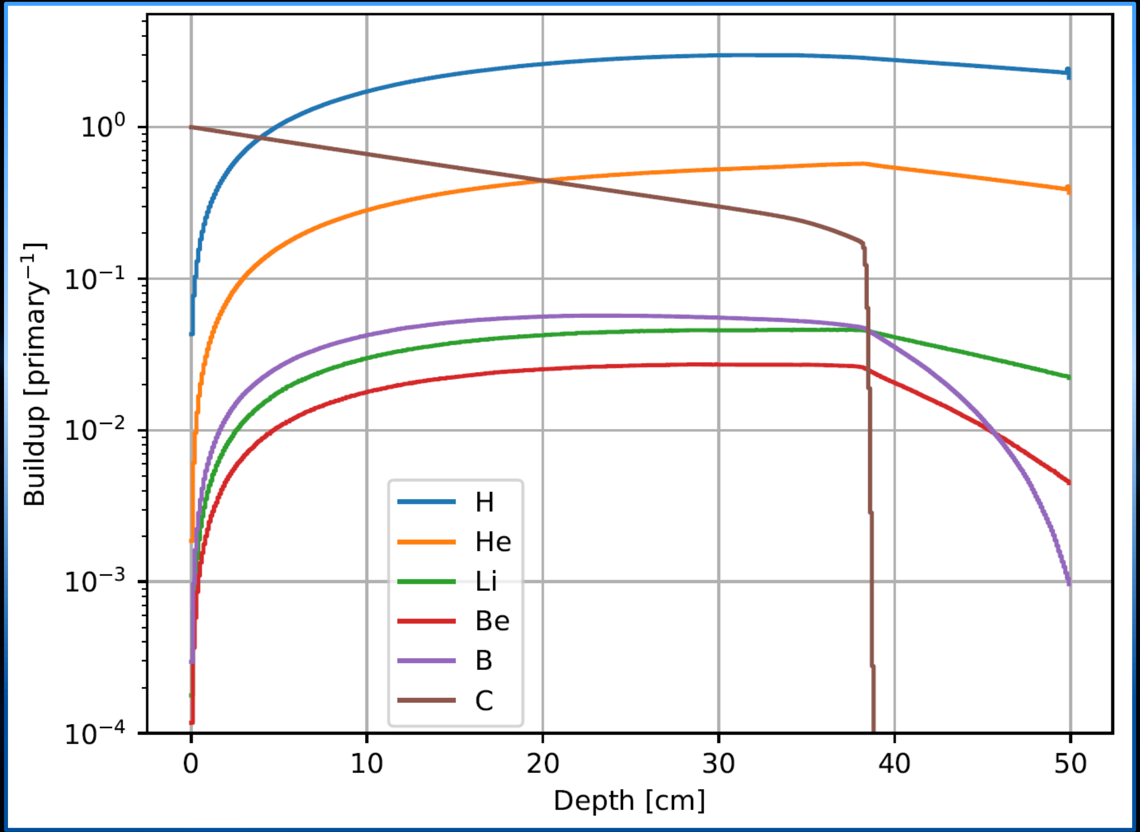


The fragment tail, caused by light fragments from nuclear interactions with the target material

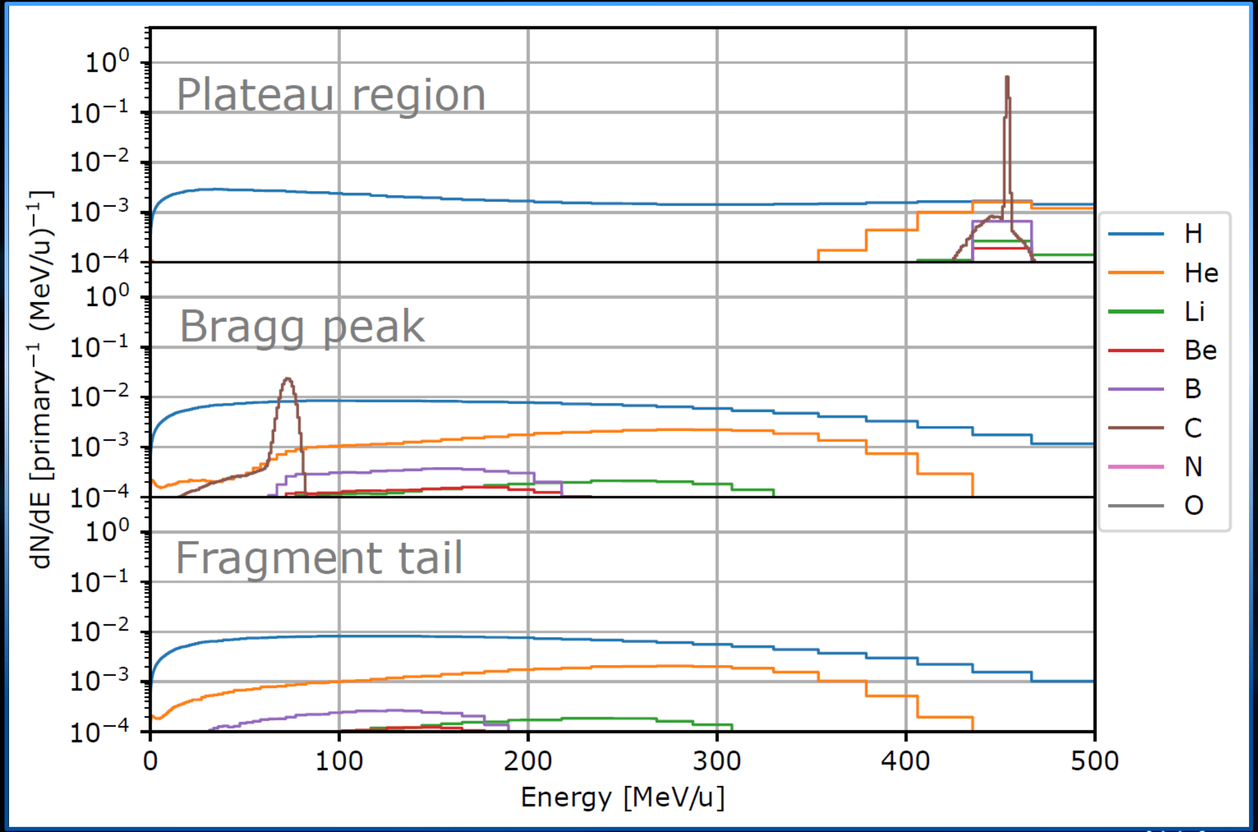
THE FRAGMENT TAIL



Fragment build-up



Differential energy spectra



RADIOBIOLOGY

Do we know what is going on now???

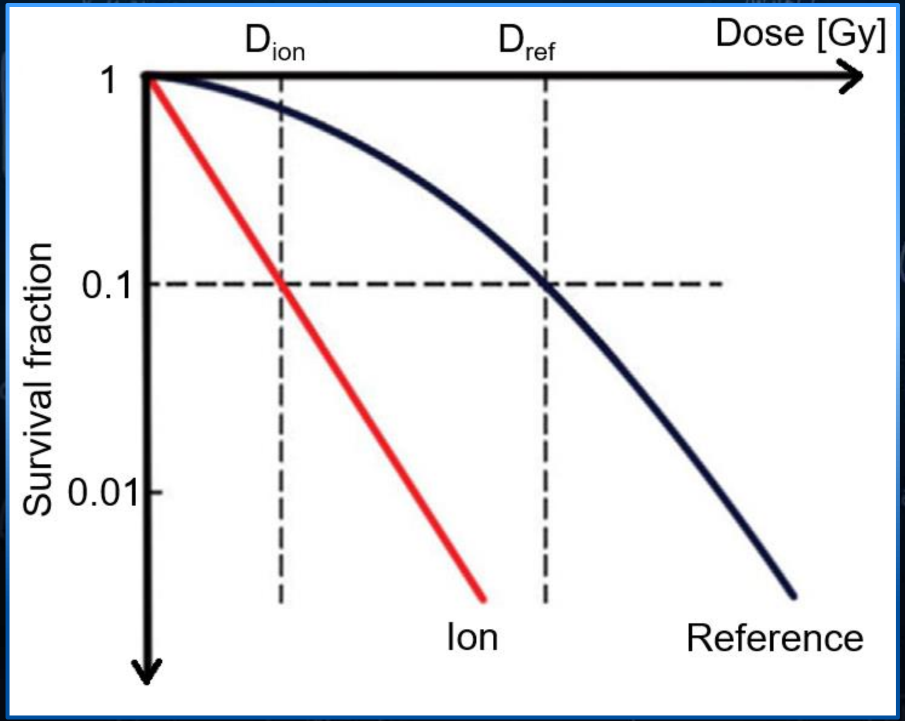
RaySearch Laboratories

RADIOBIOLOGY

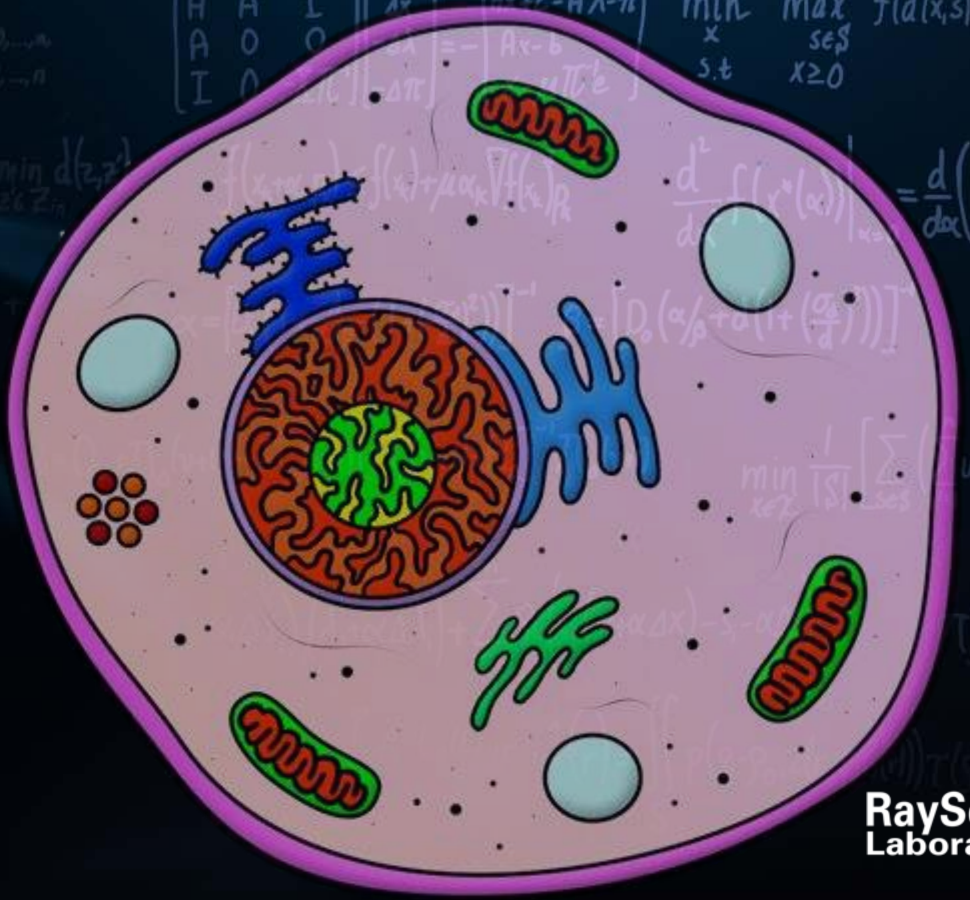
- Radiobiology is largely based on clinical experience from 100+ years of radiotherapy
- Protons are about 10% more effective at killing cells compared to photon radiation
- Carbon (and other high LET particles) are much more effective compared to low LET radiation

Linear quadratic (LQ) model

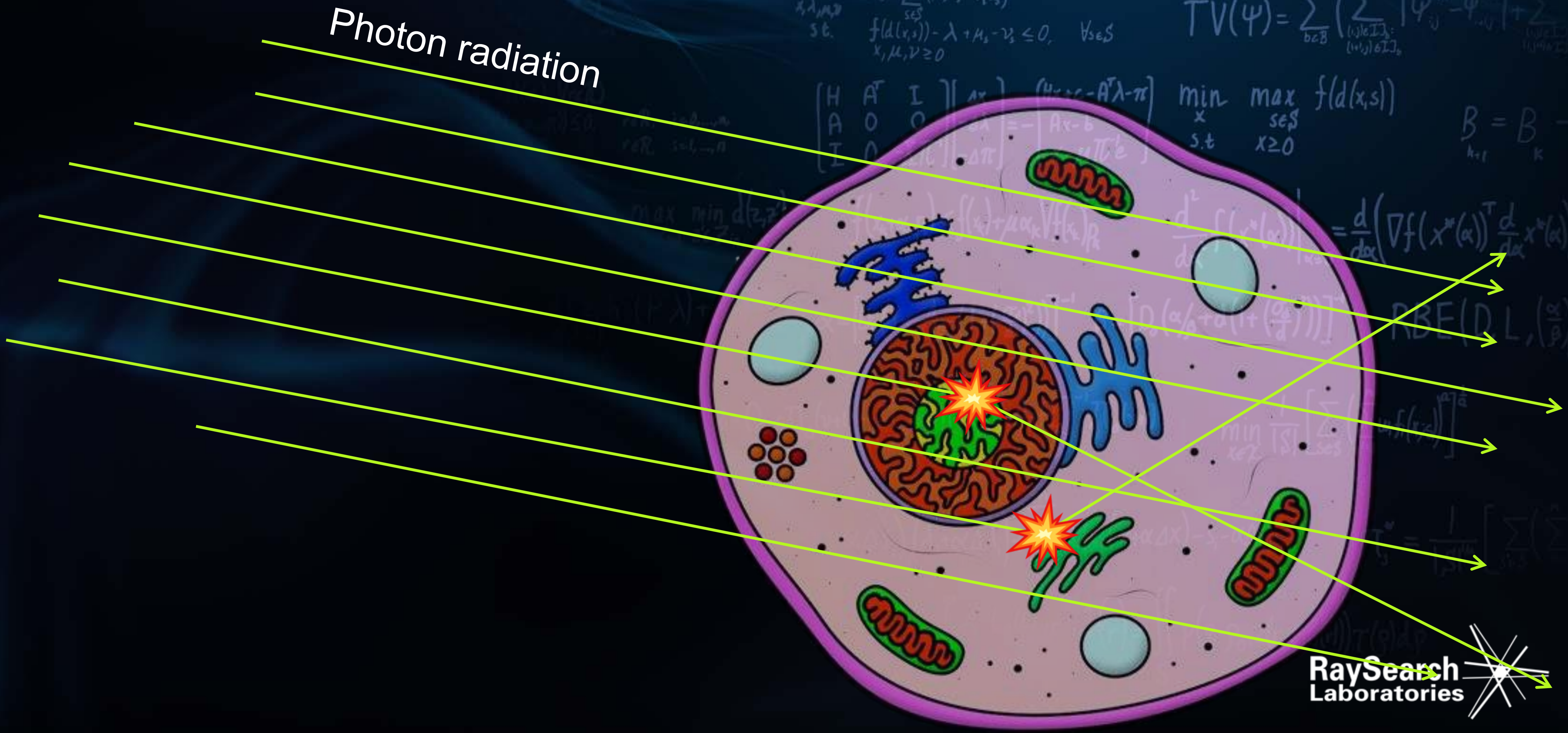
Survival $S = e^{-\alpha D - \beta D^2}$



RADIOBIOLOGY FOR IONS

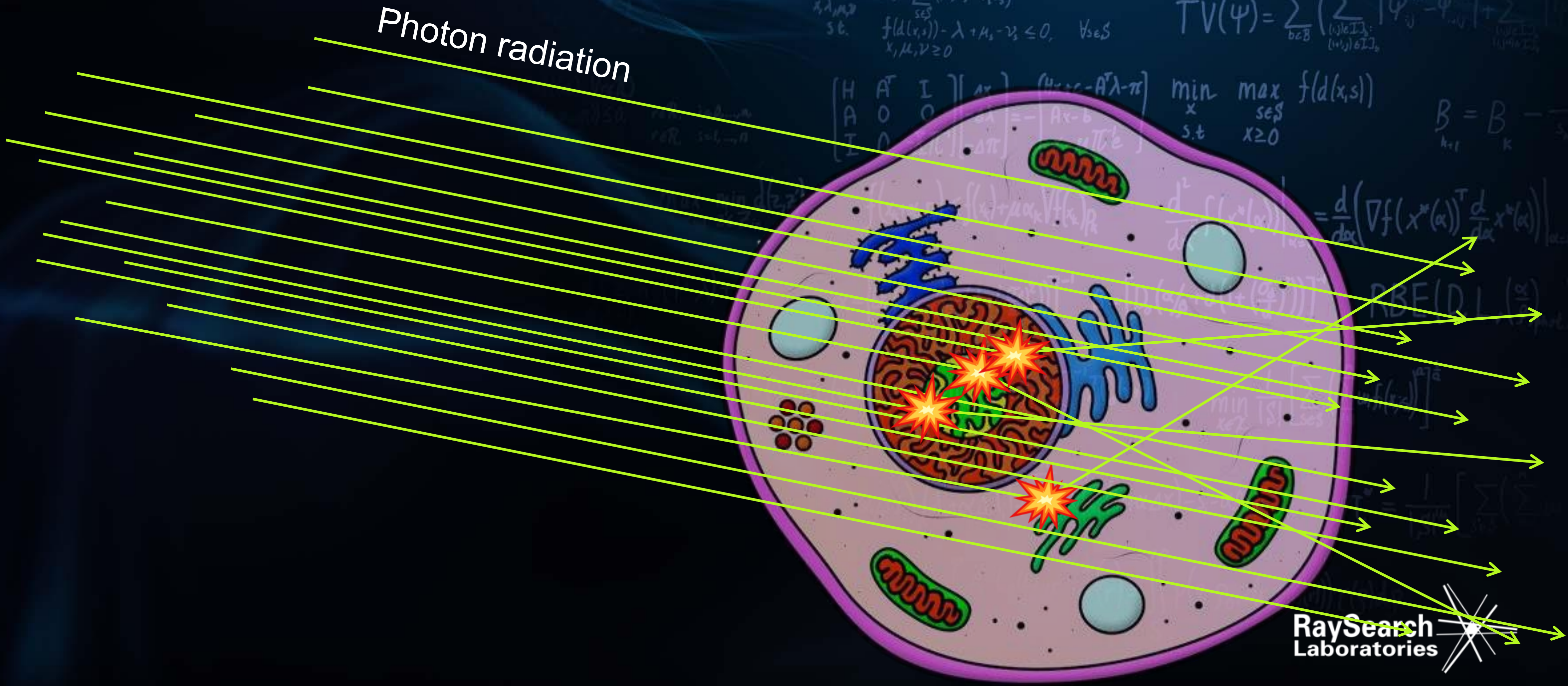


RADIOBIOLOGY FOR IONS

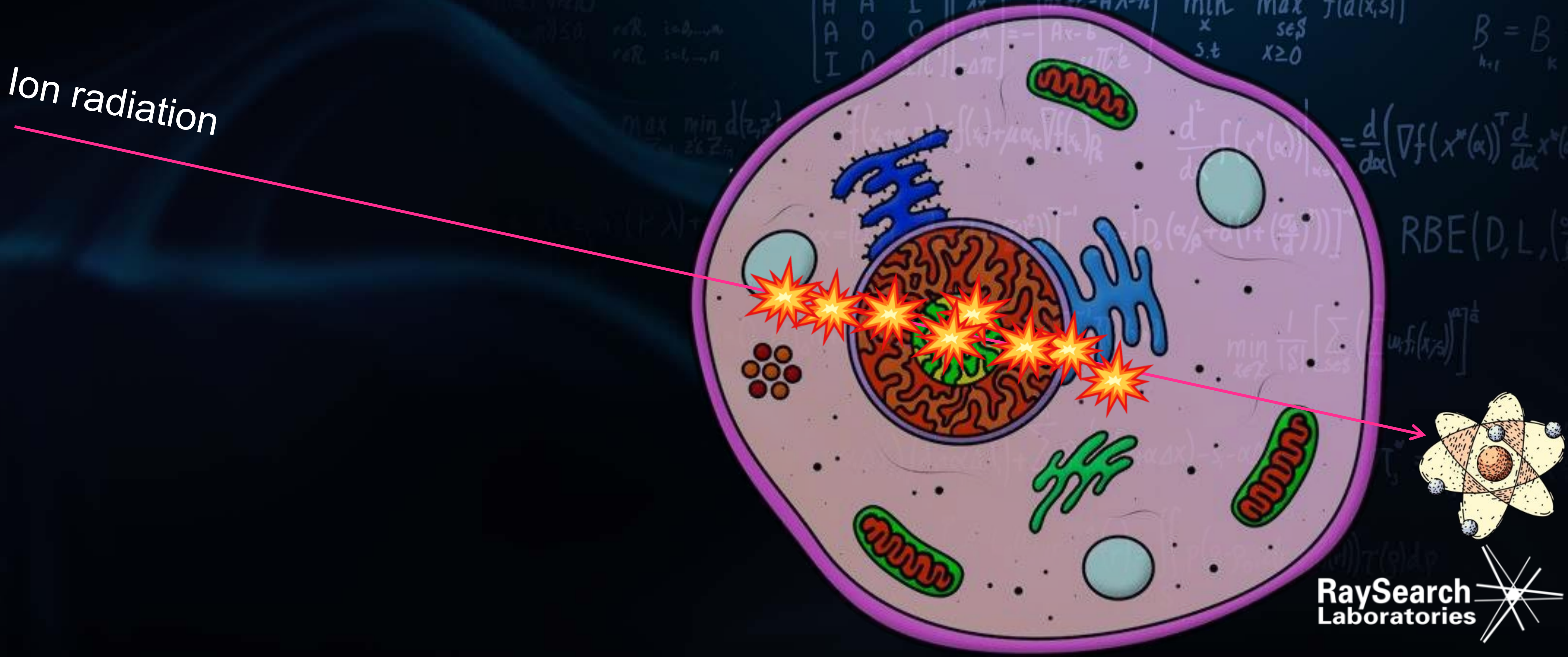


RaySearch Laboratories

RADIOBIOLOGY FOR IONS



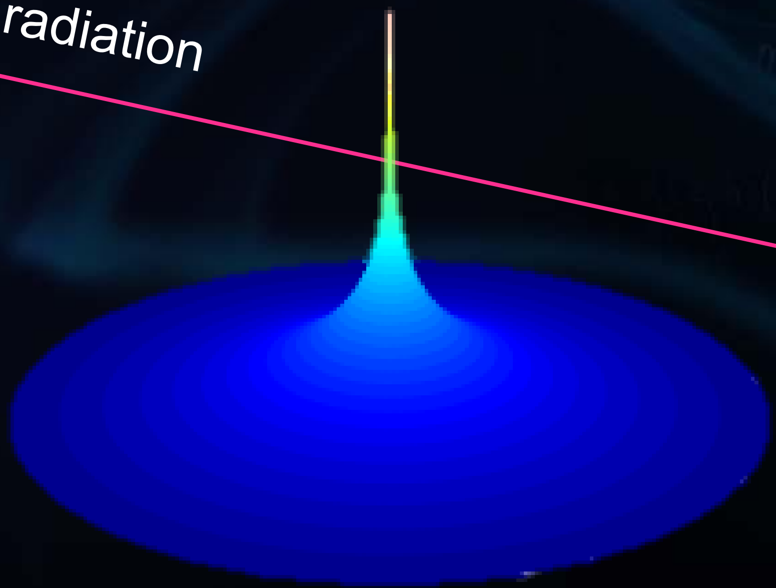
RADIOBIOLOGY FOR IONS



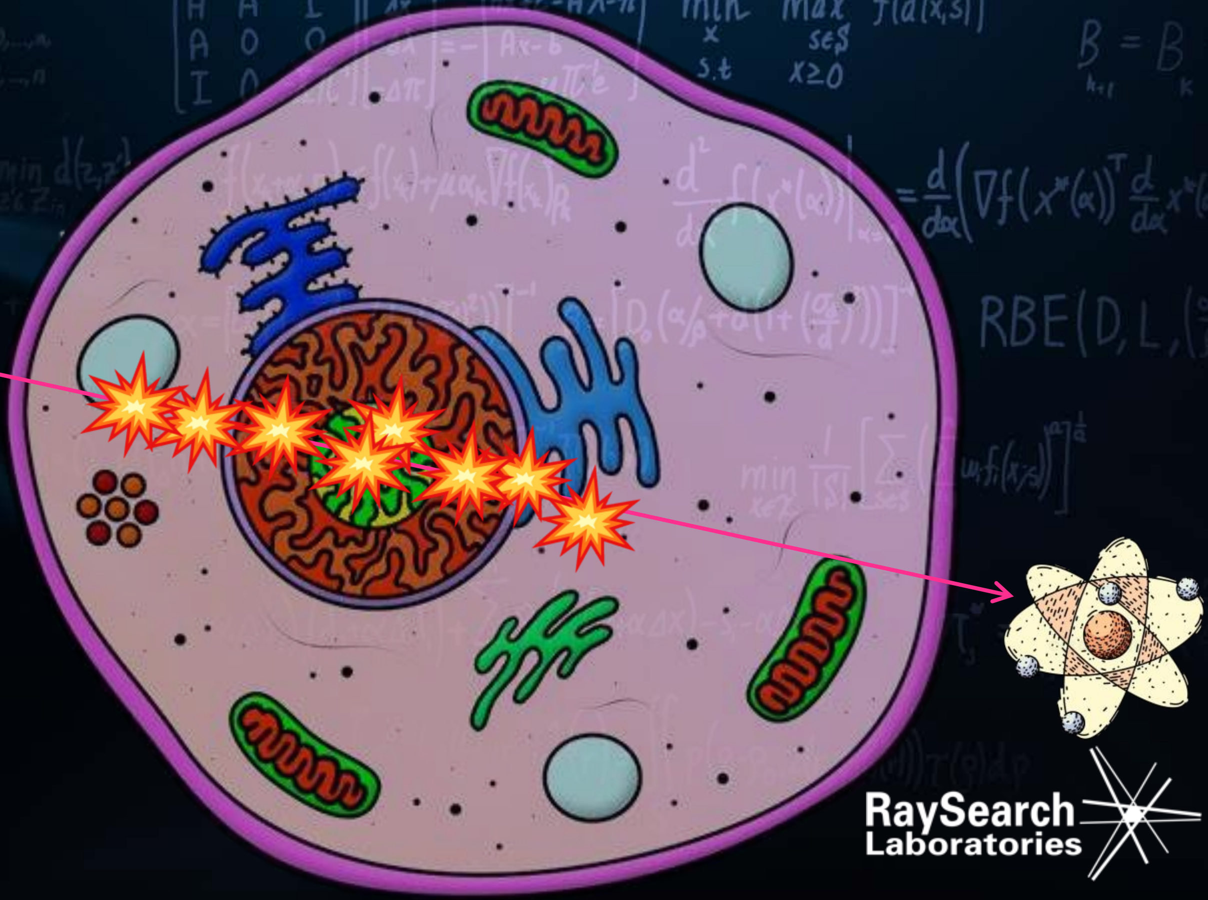
RADIOBIOLOGY FOR IONS

- Local dose extremely high => more complex damage => cell death

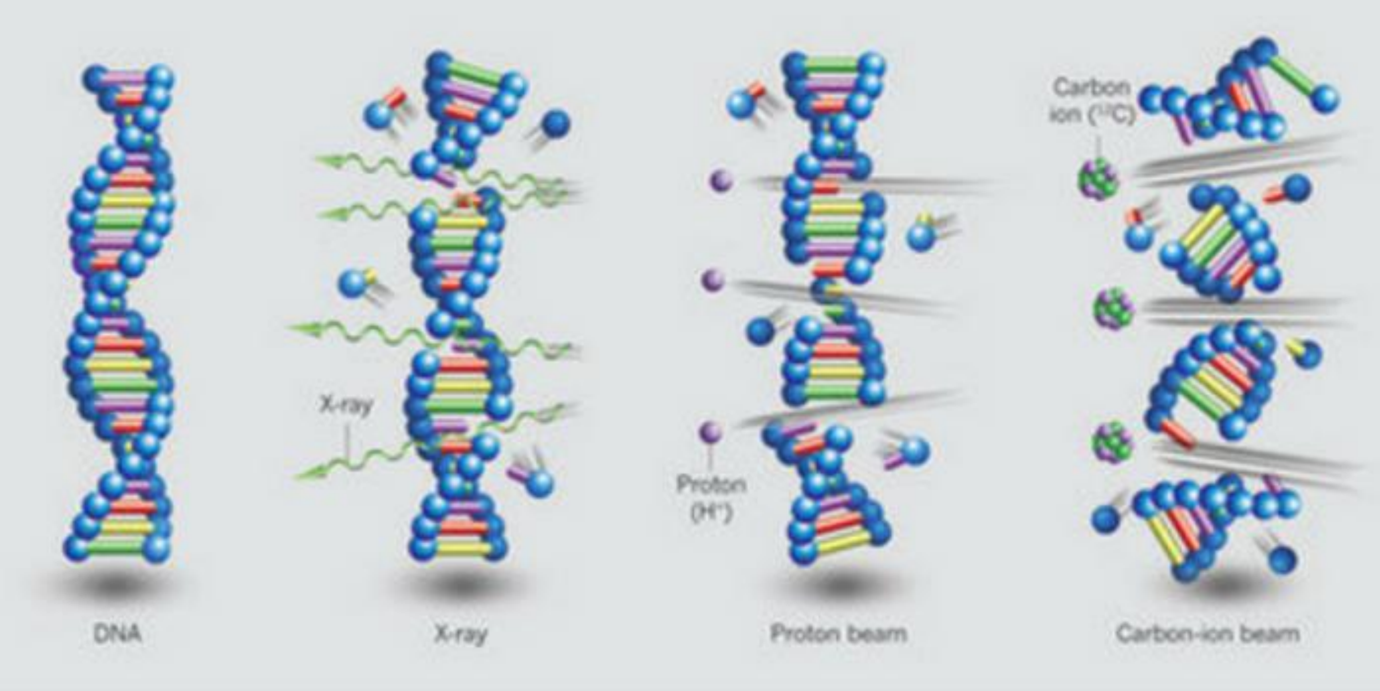
Ion radiation



Dose distribution used in
the local effect model (LEM)



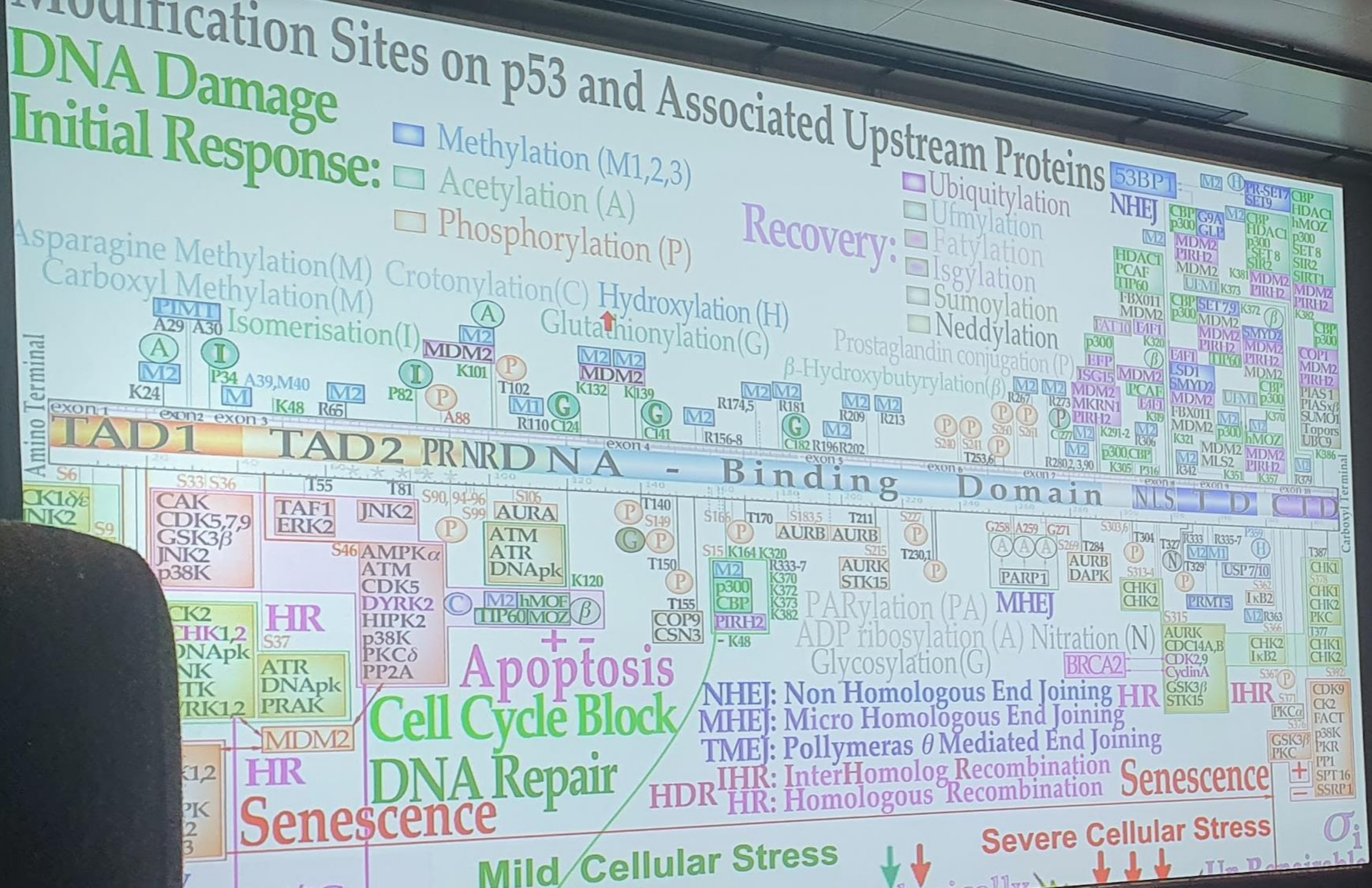
RADIOBIOLOGY FOR IONS



Radiation types and their damage to DNA; Photo Source: Nature

RADIOBIOLOGY

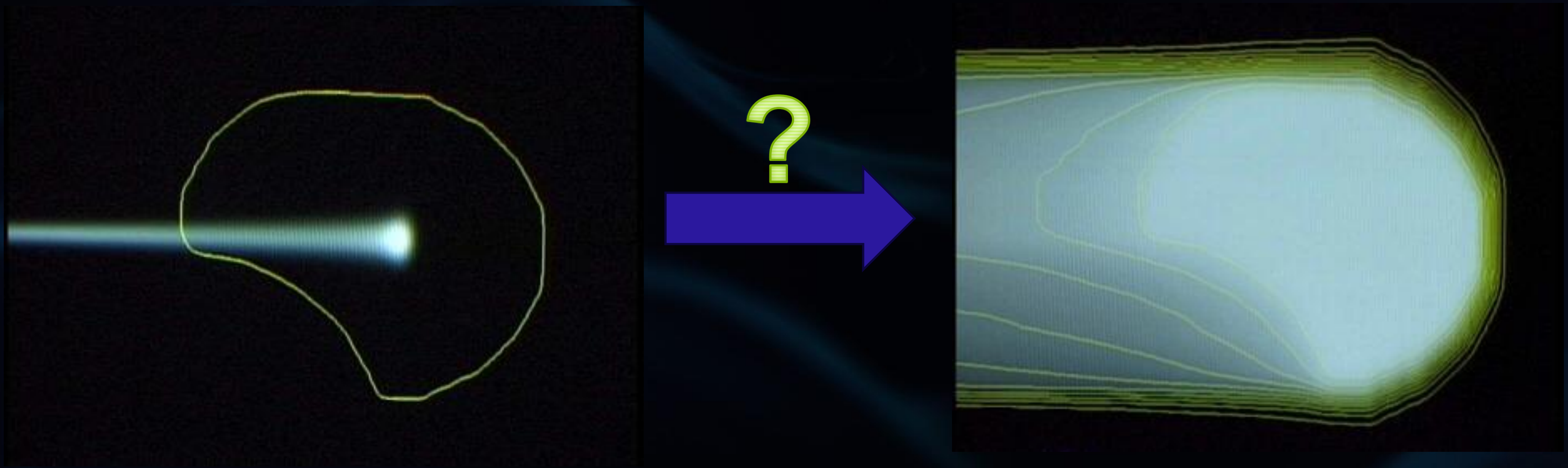
So how does it actually work???



Modification Sites on p53 and Associated Upstream Proteins
DNA Damage
Initial Response:
Methylation (M1,2,3)
Acetylation (A)
Phosphorylation (P)
Asparagine Methylation(M)
Carboxyl Methylation(M)
Crotonylation(C)
Hydroxylation (H)
Glutathionylation(G)
Isomerisation(I)
Prostaglandin conjugation (P)
β-Hydroxybutyrylation(β)
Recovery:
Ubiquitylation
Ufmylation
Fatylation
Isgylation
Sumoylation
Neddylation
53BP1
NHEJ
Amino Terminal
Carboxyl Terminal
TAD1
TAD2
PR
NRD
DNA - Binding Domain
NLS
TD
CTD
PIMT
MDM2
CAK
CDK5,7,9
GSK3β
JNK2
p38K
TAF1
ERK2
AURA
ATM
ATR
DNApk
AMPKα
CDK5
DYRK2
HIPK2
PKCδ
PP2A
hMOF
TIP60
MOZ
COP9
CSN3
p300
CBP
PIRH2
AURB
AURK
STK15
PARP1
MHEJ
DAPK
CHK1
CHK2
PRMT5
USP7/10
IκB2
CDC14A,B
CDK2,9
CyclinA
BRCA2
PRAK
HR
IHR
HDR
PARylation (PA)
ADP ribosylation (A) Nitration (N)
Glycosylation(G)
NHEJ: Non Homologous End Joining
MHEJ: Micro Homologous End Joining
TMEJ: Pollymeras θ Mediated End Joining
IHR: InterHomolog Recombination
HR: Homologous Recombination
Apoptosis
Cell Cycle Block
DNA Repair
Senescence
CDK9
CK2
FACT
p38K
PKR
PP1
SPT16
SSRP1
PKCα
Mild Cellular Stress
Severe Cellular Stress

PENCIL BEAM SCANNING

HOW TO CREATE A UNIFORM DOSE IN THE TARGET?



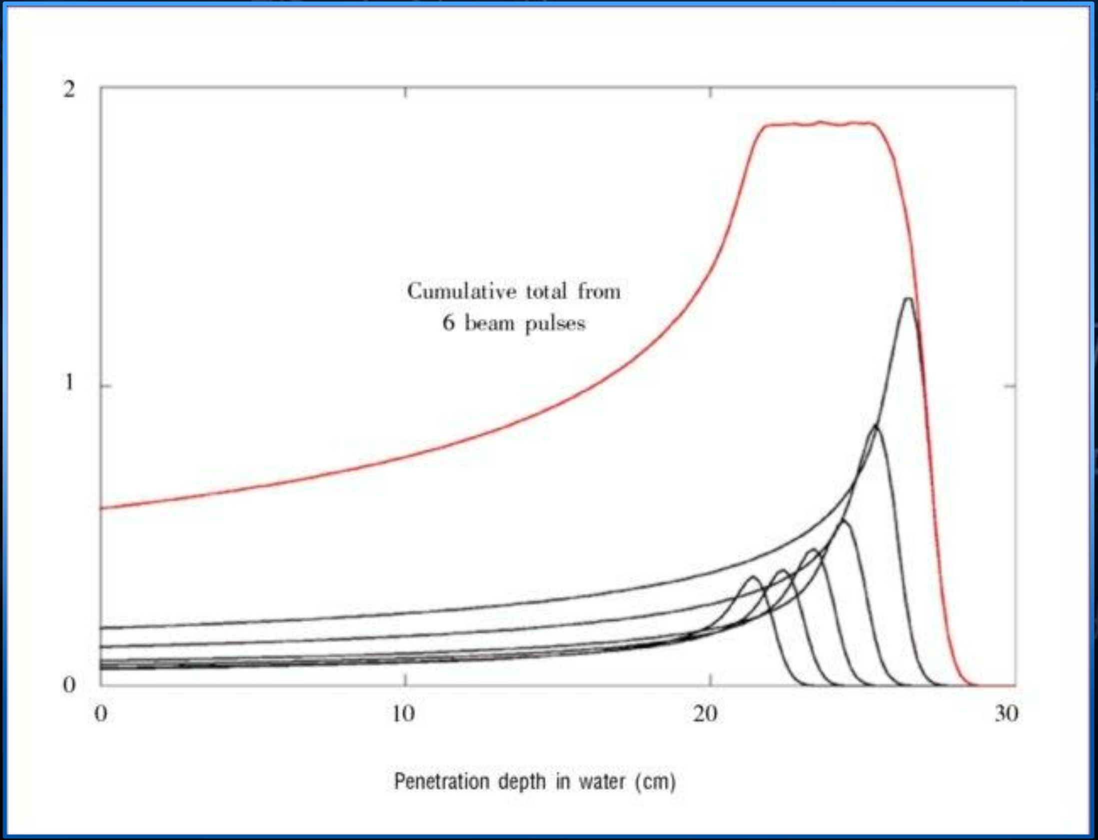
The particles have to be spread out laterally and in depth to cover the entire target.

RaySearch Laboratories

HOW TO CREATE A UNIFORM DOSE IN THE TARGET?

Uniform dose in depth

- A single Bragg peak is too narrow to cover the target
- By combining several energy layers with different weight, a spread out Bragg peak (SOBP) is created.
- Entrance dose is increased (but there is still an advantage compared to photons)!

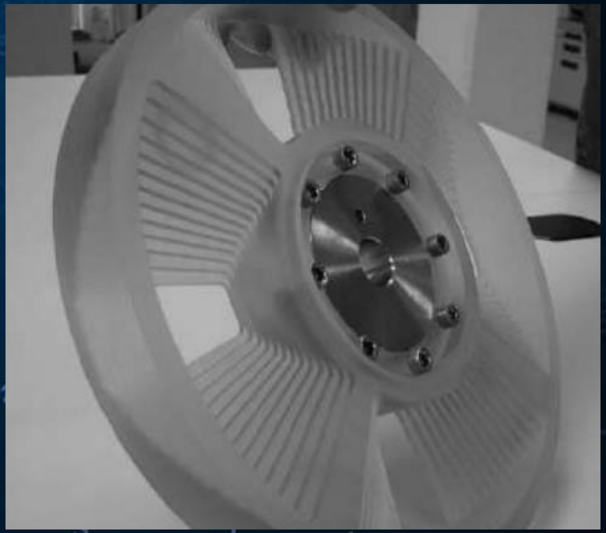


A FEW HISTORICAL TECHNIQUES

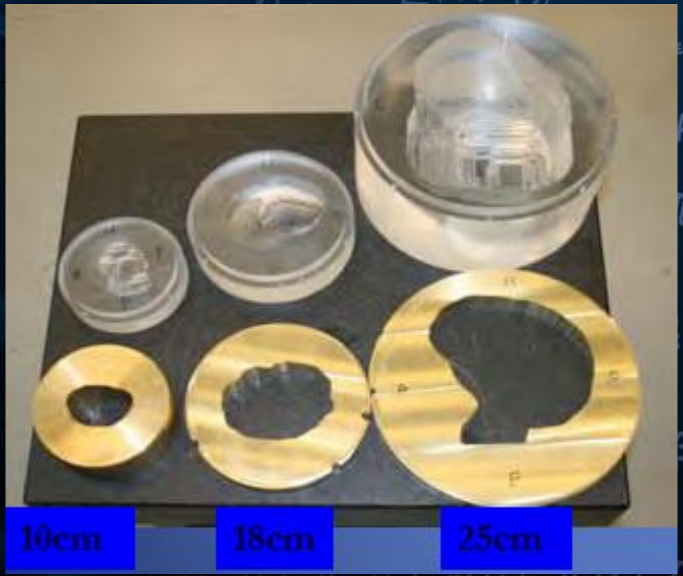
That we don't really need to care about

- Broad beam techniques
  - Single scattering (non-uniform fluence)
  - Double scattering (uniform fluence)
  - Uniform scanning
- Energy layers
  - Range modulator or ridge filter
- Beam shape
  - Aperture block or MLC
- Distal edge
  - Range compensator

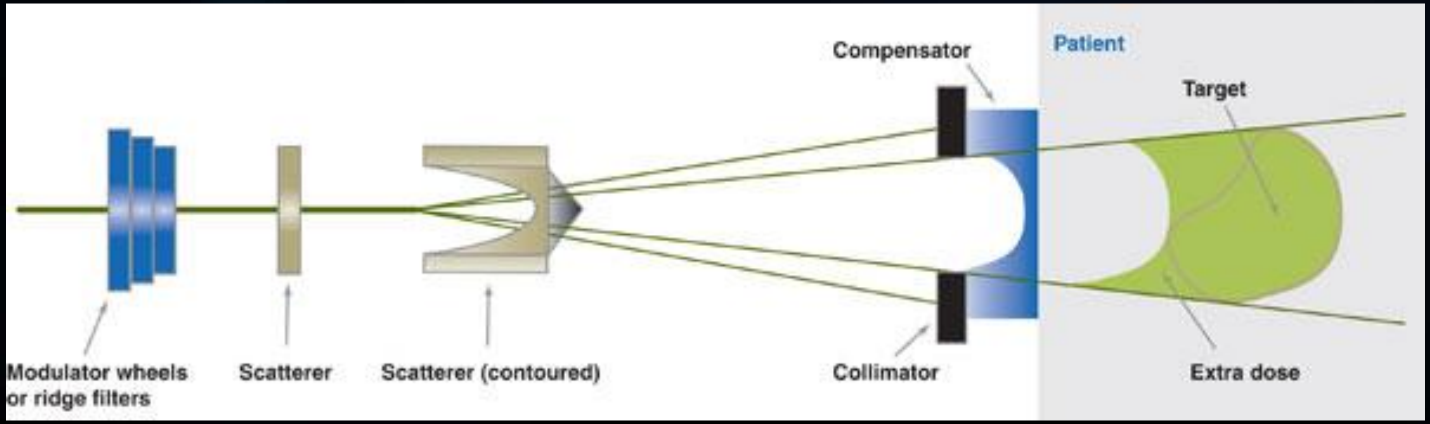
Range modulator wheel



Brass block and range compensators



Passive proton beamline

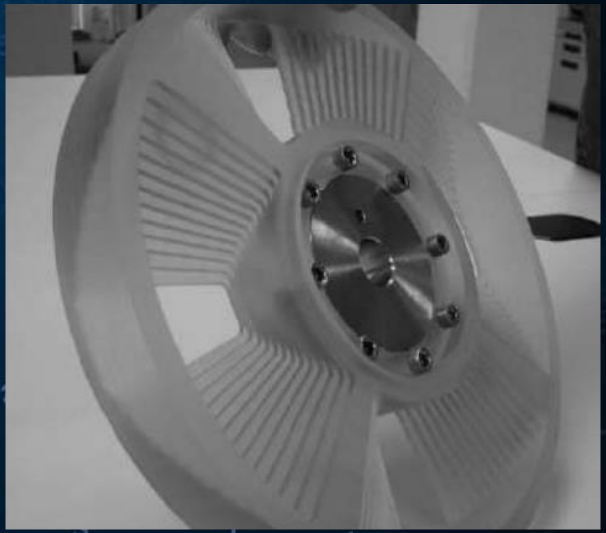


A FEW HISTORICAL TECHNIQUES

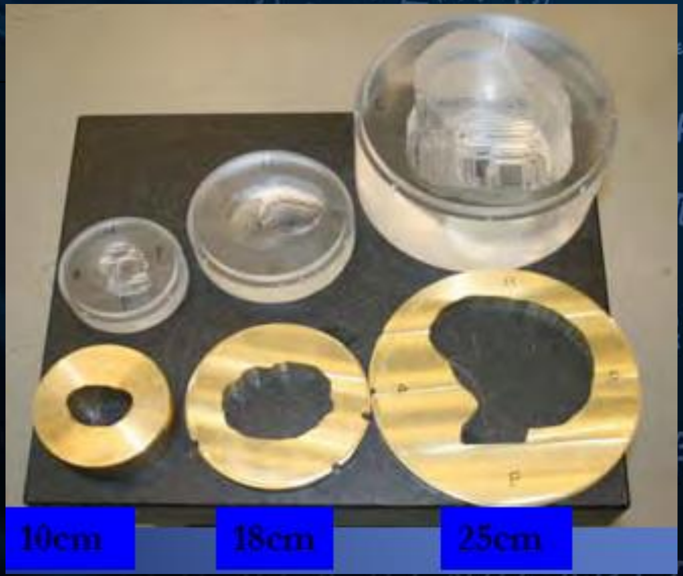
That we don’t really need to care about

- Broad beam techniques
  - Single scattering (non-uniform fluence)
  - Double scattering (uniform fluence)
  - Uniform scanning
- Energy layers
  - Range modulator or ridge filter
- Beam shape
  - Aperture block or MLC
- Distal edge
  - Range compensator

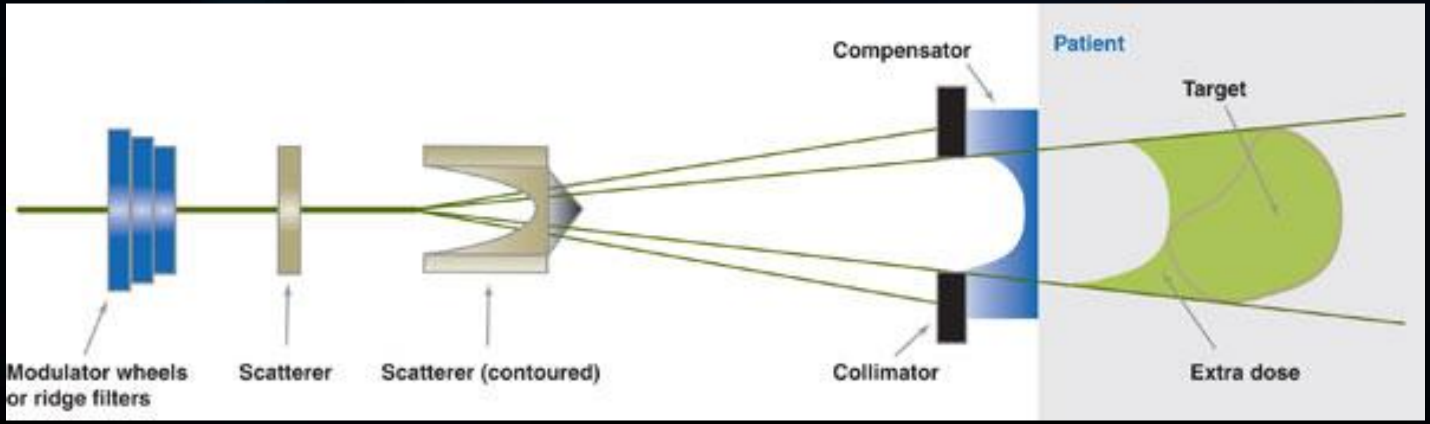
Range modulator wheel



Brass block and range compensators



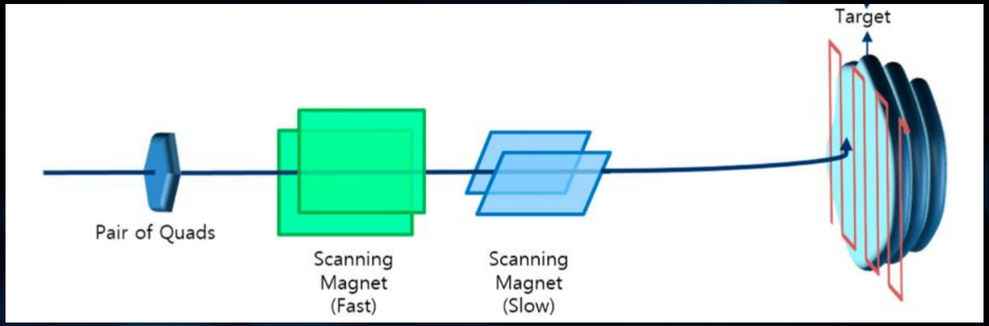
Passive proton beamline



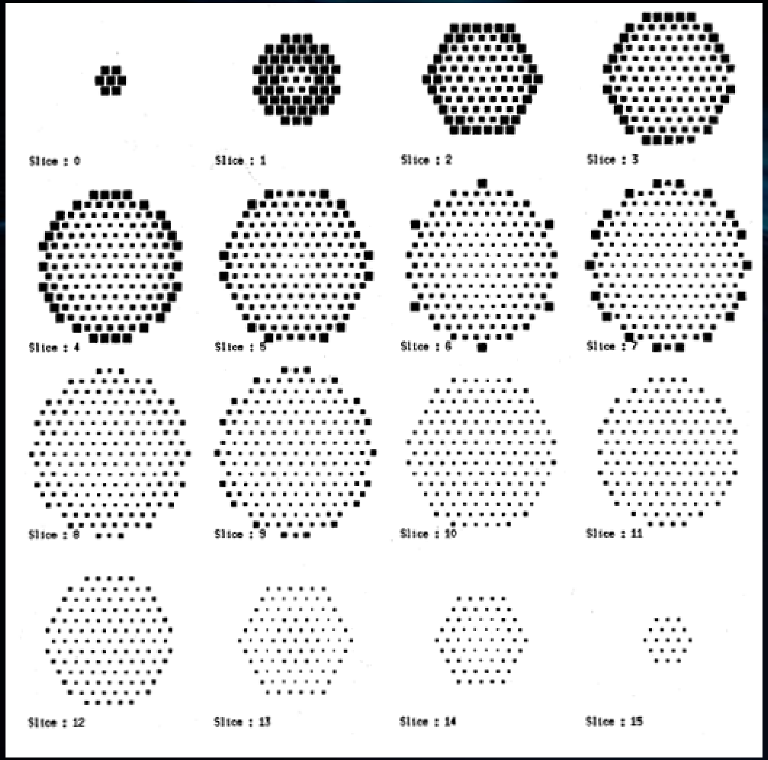
PENCIL BEAM SCANNING

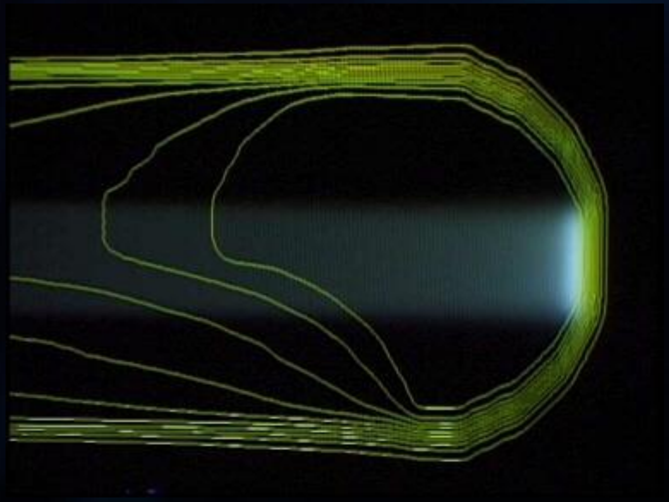
Almost exclusively used today

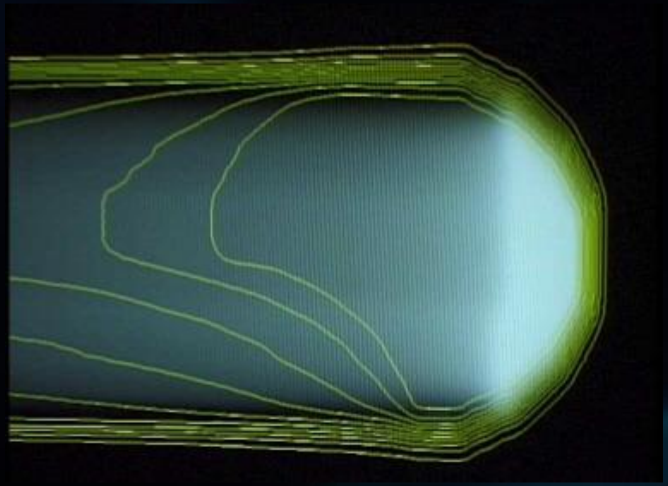
The pencil beam or spot is scanned (using bending magnets) over the tumor one energy at the time

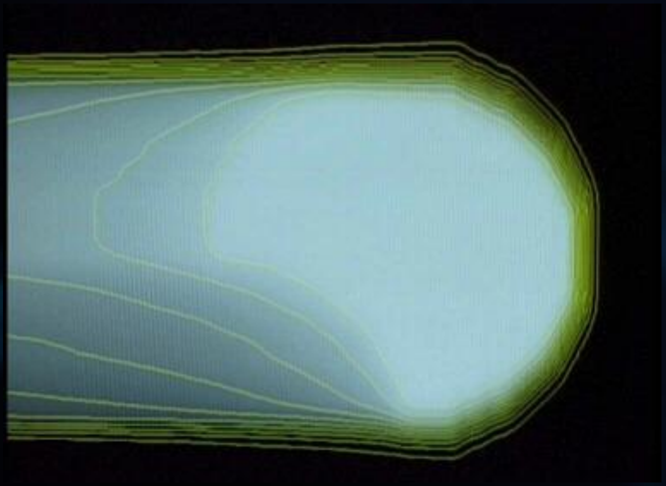


Spot pattern for a spherical target





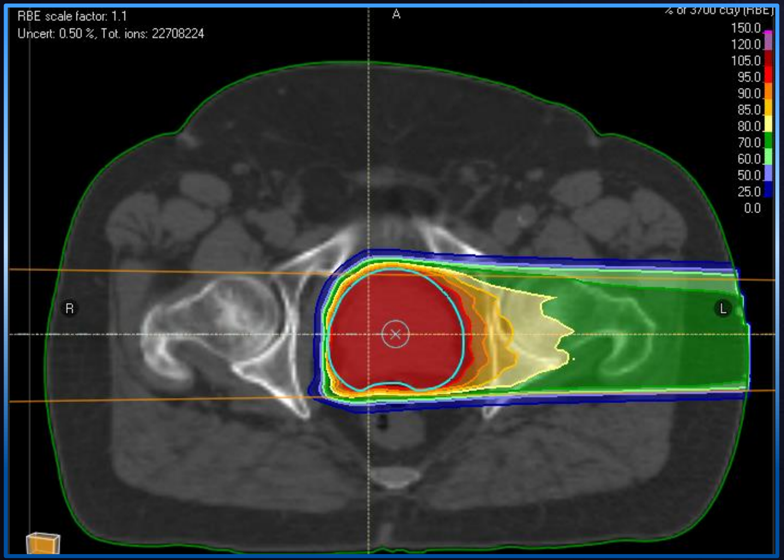


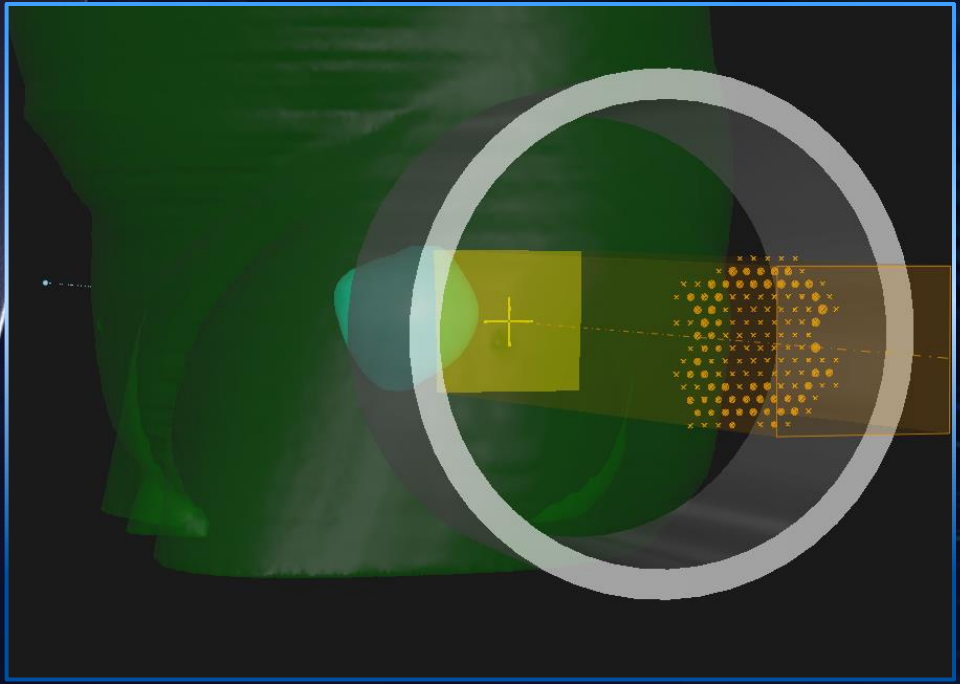


PENCIL BEAM SCANNING

Planning aspects

- Treatment planning system (TPS)
  - Select energy layers for each beam
  - Select initial spot pattern for each layer
  - Optimize spot weights
  - Plan evaluation (robustness analysis)

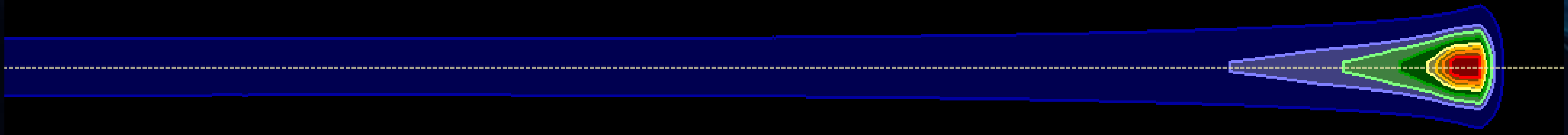




DOSE COMPUTATION

ANALYTICAL DOSE COMPUTATION ALGORITHMS

Pencil beam dose approximation

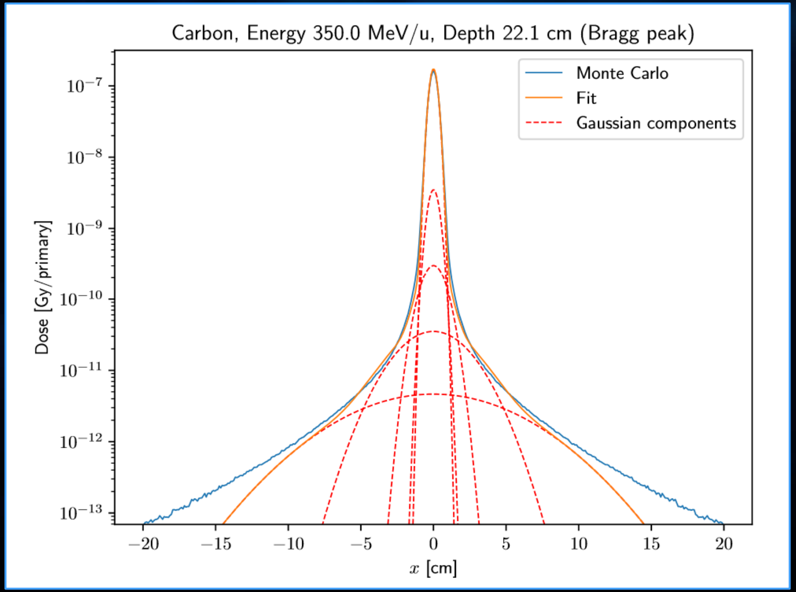


Depth in patient

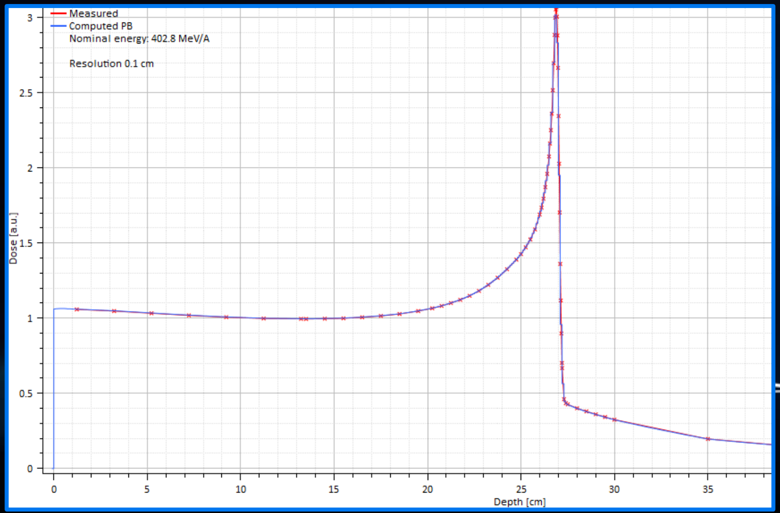
Distance to central axis

$$dose(z,r) = \Phi(z,r)IDD(z)$$

Lateral fluence (cylinder symmetric)



(longitudinal) Integrated Depth Dose



ANALYTICAL DOSE COMPUTATION ALGORITHMS

Pencil beam dose approximation

- Total dose computed as sum of all spots in all energies in all beams

$$d(x,y,z) = \sum_b \sum_e \sum_j w_{bej} dose_{bej}(x,y,z)$$

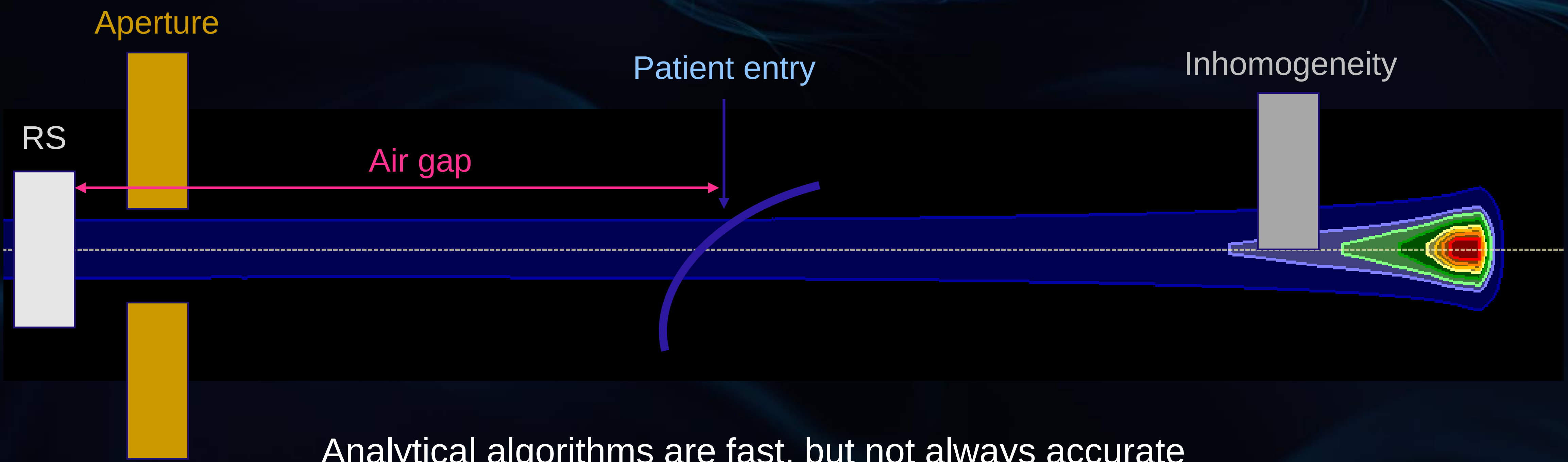
b – beam
e – energy layer
j – spot

- Note! Do not confuse the pencil beam approximation with pencil beam scanning

RaySearch Laboratories

ANALYTICAL DOSE COMPUTATION ALGORITHMS

Pencil beam dose approximation

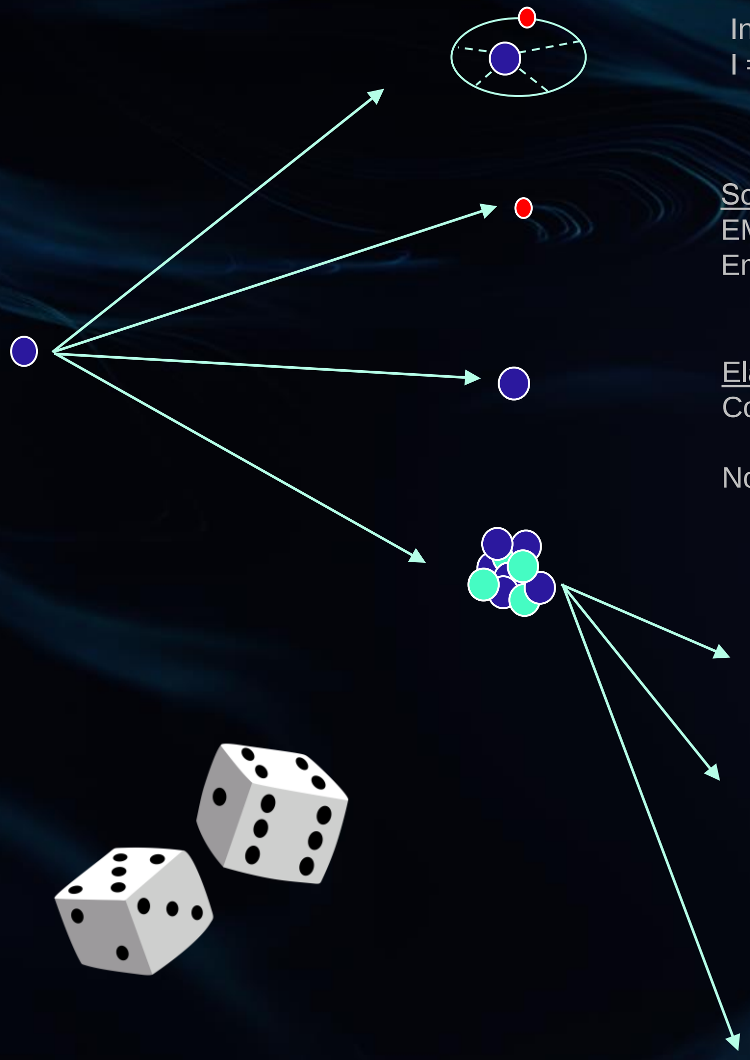


Analytical algorithms are fast, but not always accurate

- Cylinder symmetry disregards lateral inhomogeneities
- Analytical models not accurate e.g. in large air gaps

MONTE CARLO

- Tracking of individual particles using random sampling (throwing dice)
- Very accurate, but potentially slow
  - General purpose MC (FLUKA, Geant) can take hours or even days
- Commonly used for proton planning
- Not (yet) clinically available for light ions
  - Complicated nuclear interactions
  - RBE



Interaction with bound electrons -> Ionisation
I = average ionisation potential = <optical dipole o

Scattering on quasi ”free” atomic electrons
EM process described by Rutherford or Bhabha cro
Emission of recoil electron → ”Delta rays”

Elastic p+p scattering
Coulomb force + nuclear force

Note: Threshold for reaction p+p → p + p + π^0 is
p+p → p+p+γ bremstrahlung cross section

Elastic p+A scattering
Coulomb + nuclear force
Energy transferred to recoil nucleus according t
Nucleus left in ground state

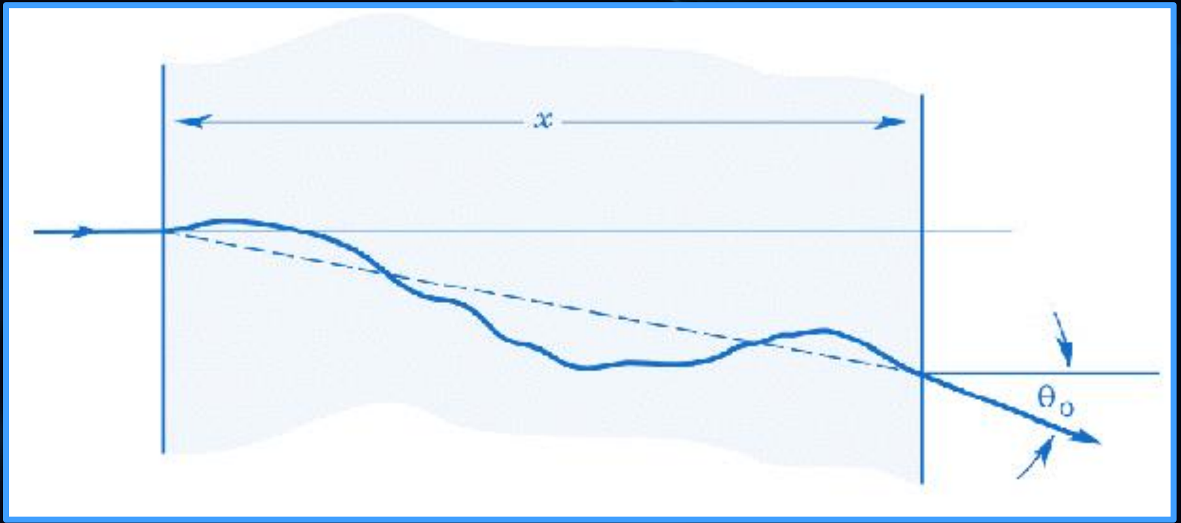
Inelastic p+A scattering
Coulomb + nuclear force
Energy transferred to recoil nucleus according t
Nucleus left in excited state

Nuclear reaction (”Non-elastic”)
Incoming energy transferred to recoil and ejectile
manner.

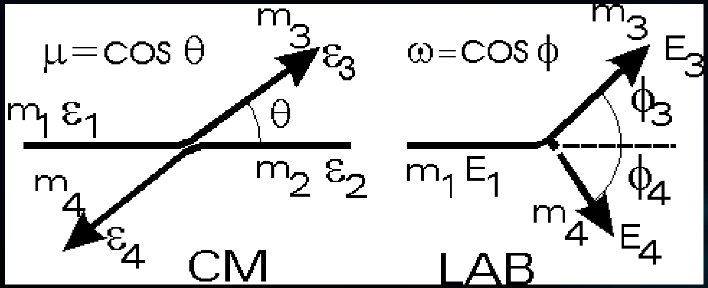
RaySearch Laboratories

MONTE CARLO

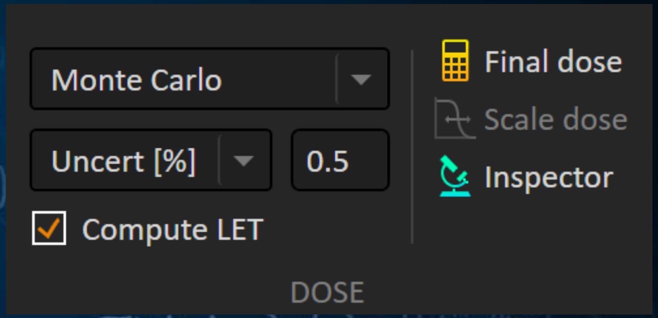
Class II condensed history Monte Carlo

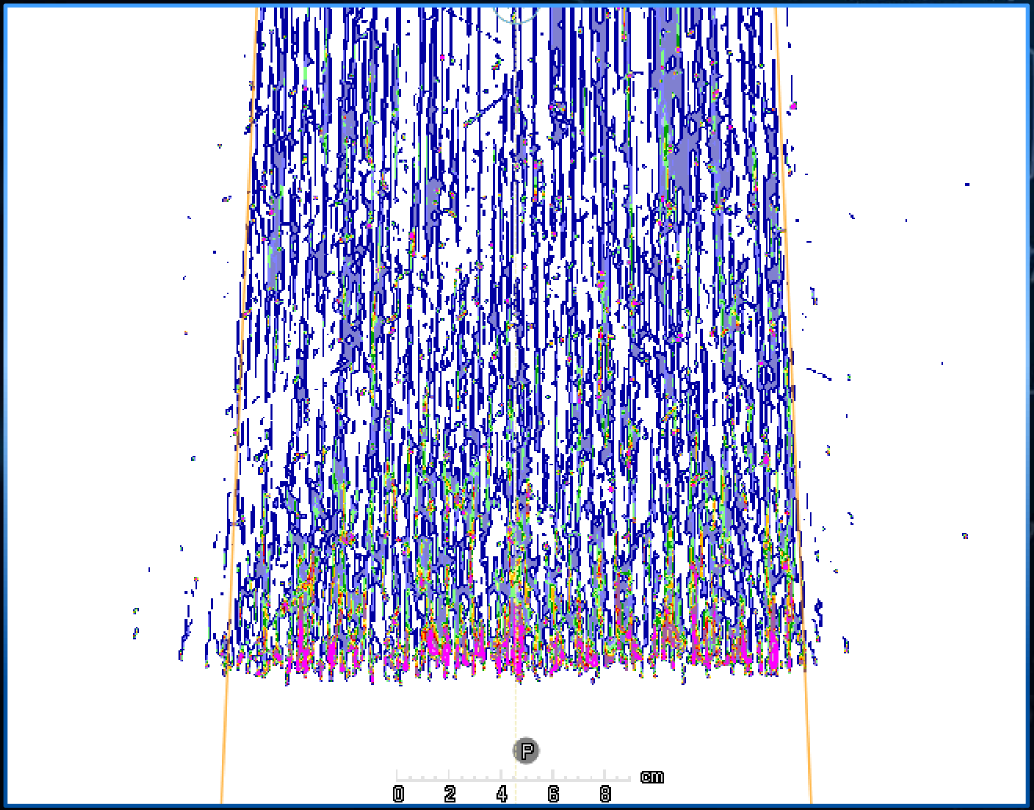


With catastrophic events (nuclear interactions)

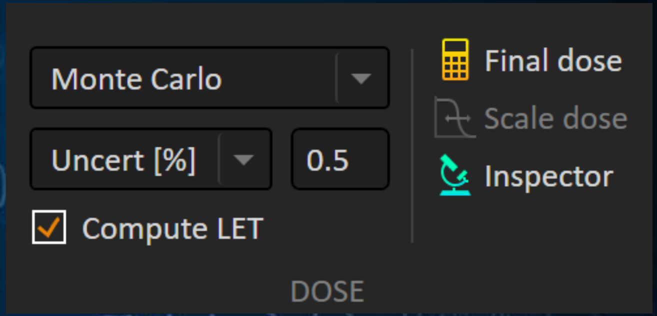


MONTE CARLO

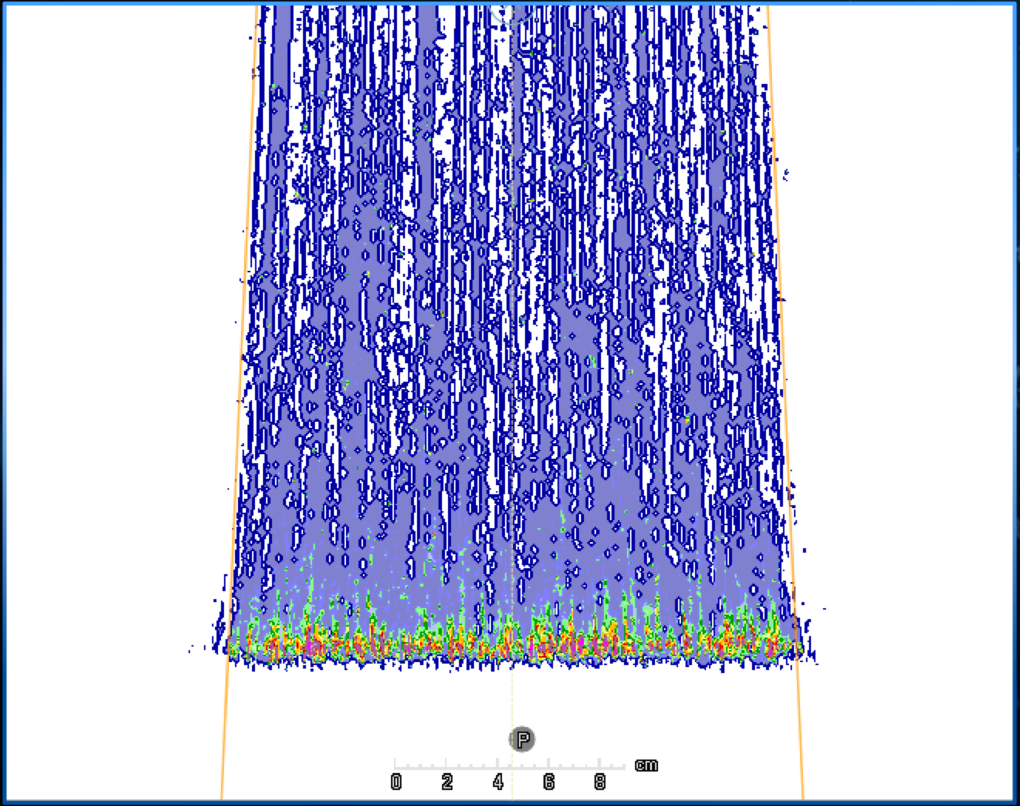

Monte Carlo
Final dose
Uncert [%]
0.5
Scale dose
Inspector
Compute LET
DOSE


P
0 2 4 6 8
cm

MONTE CARLO

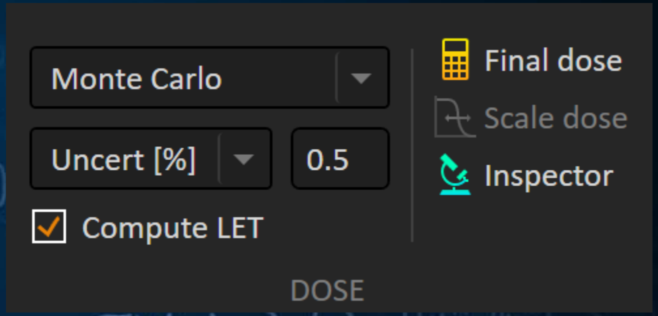


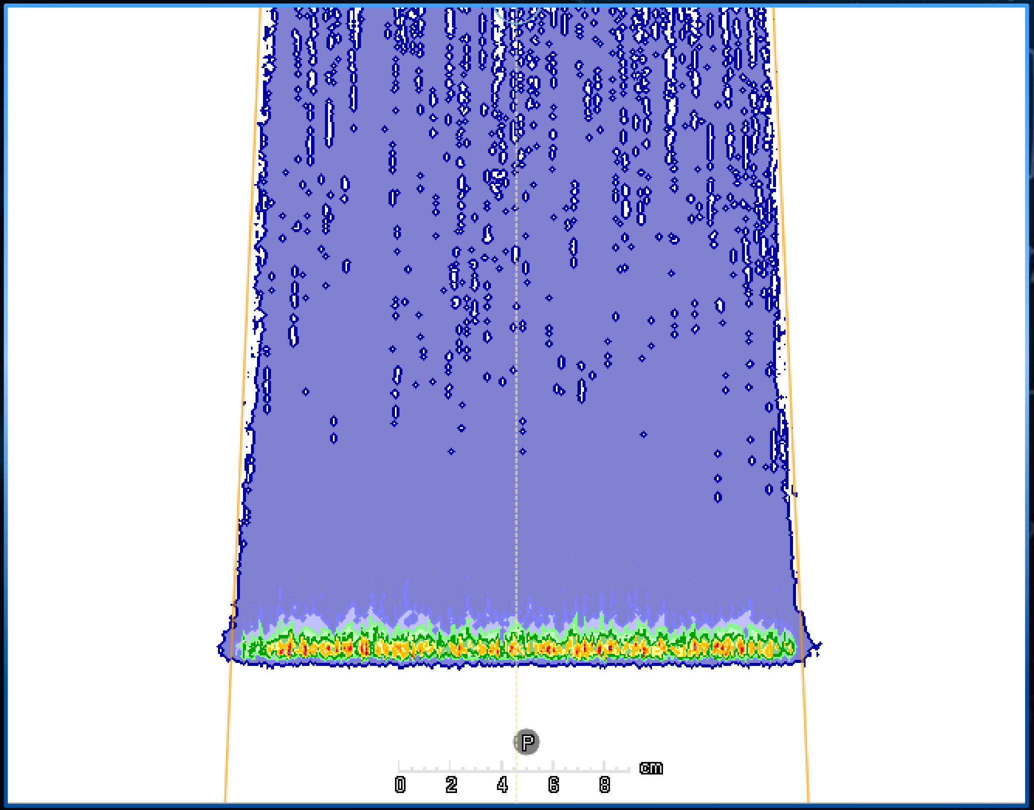
Monte Carlo
Final dose
Uncert [%]
0.5
Scale dose
Inspector
Compute LET
DOSE



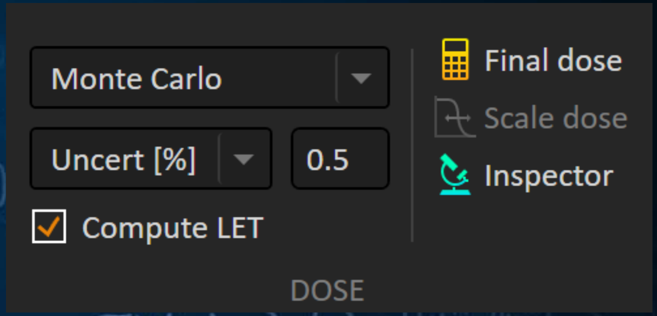
P
0 2 4 6 8
cm

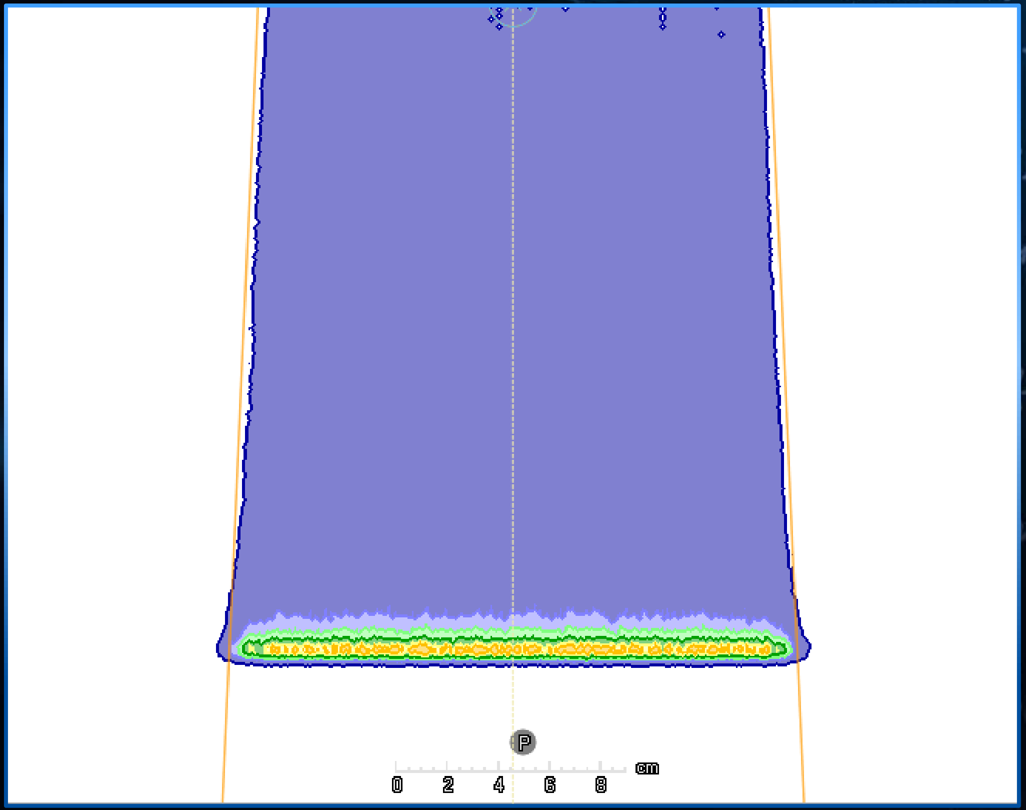
MONTE CARLO


Monte Carlo
Uncert [%]
0.5
Compute LET
DOSE
Final dose
Scale dose
Inspector

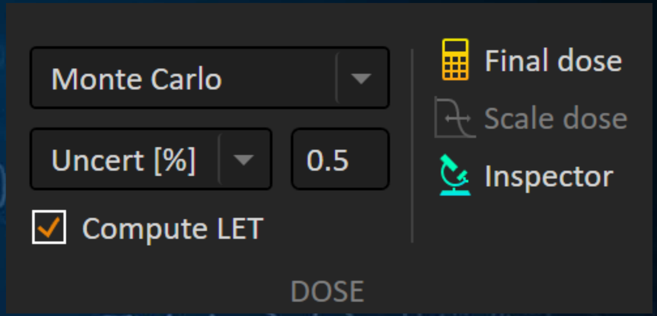

P
0 2 4 6 8
cm

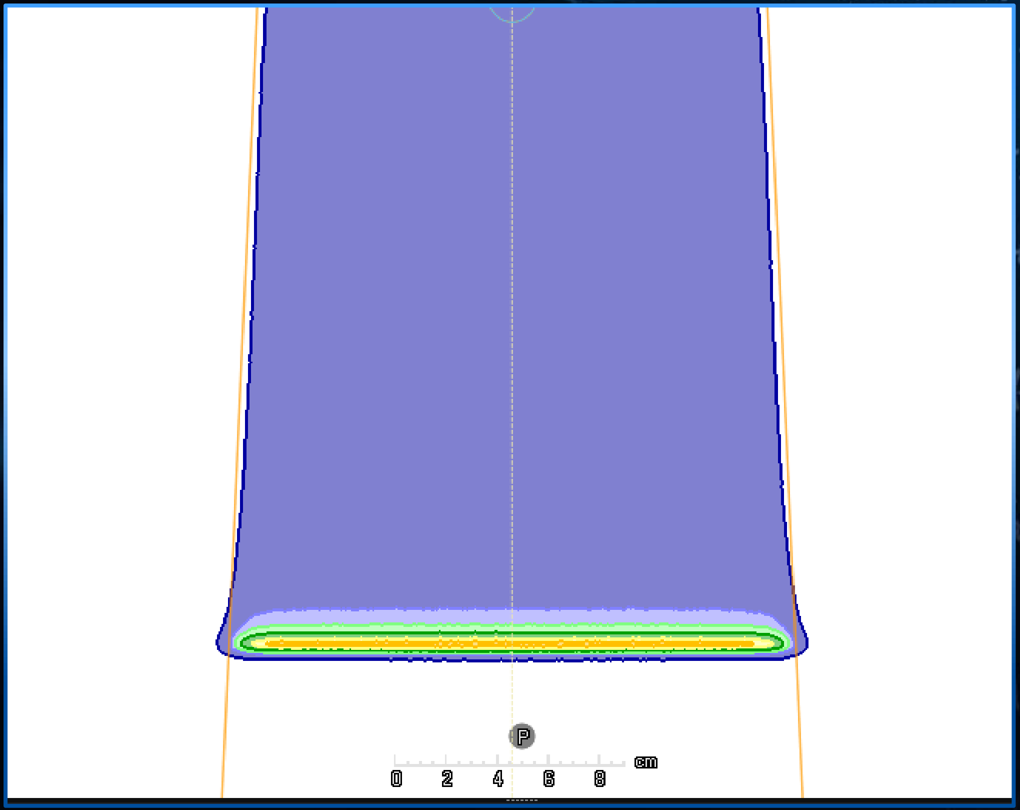
MONTE CARLO


Monte Carlo
Uncert [%]
0.5
Compute LET
Final dose
Scale dose
Inspector
DOSE


P
0
2
4
6
8
cm

MONTE CARLO


Monte Carlo
Final dose
Scale dose
Uncert [%]
0.5
Inspector
Compute LET
DOSE


P
0 2 4 6 8
cm

ROBUSTNESS IN PARTICLE THERAPY

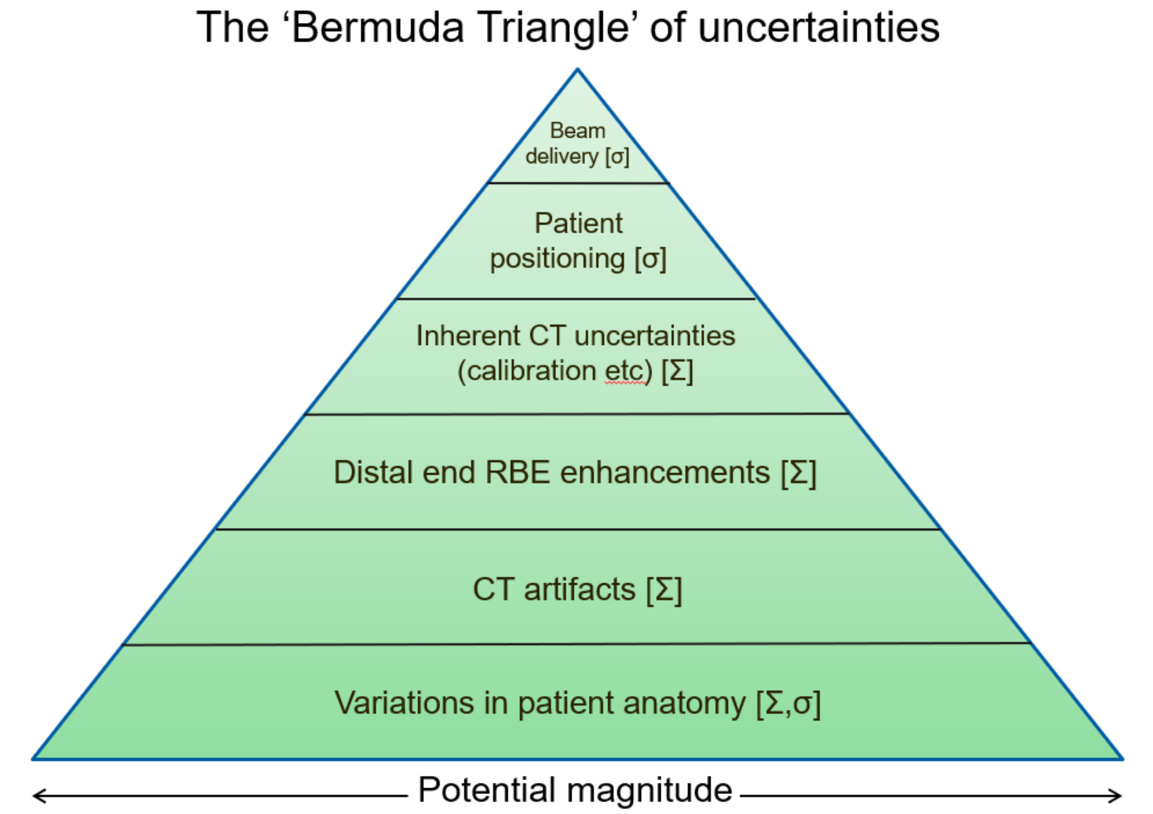
Dealing with uncertainties

UNCERTAINTIES IN RADIOTHERAPY

The Bermuda triangle of uncertainties

Also:

- Dose computation accuracy
- Biological uncertainties
  - RBE very uncertain for light ions
- Human errors (e.g. contouring)
- ...



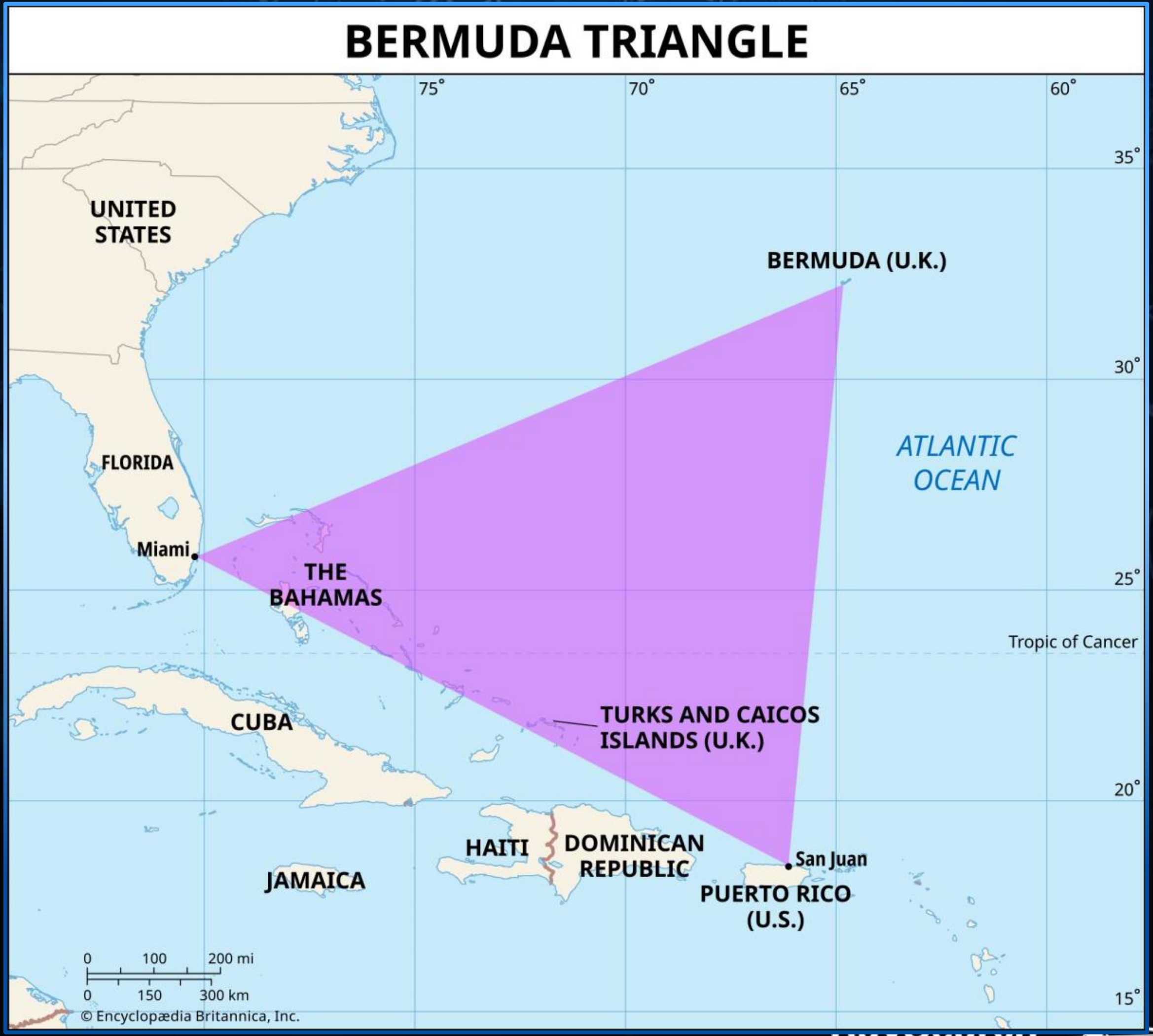
RaySearch Laboratories

UNCERTAINTIES IN RADIOTHERAPY

The Bermuda triangle of uncertainties

Also:

- Dose computation accuracy
- Biological uncertainties
  - RBE very uncertain for light ions
- Human errors (e.g. contouring)
- ...

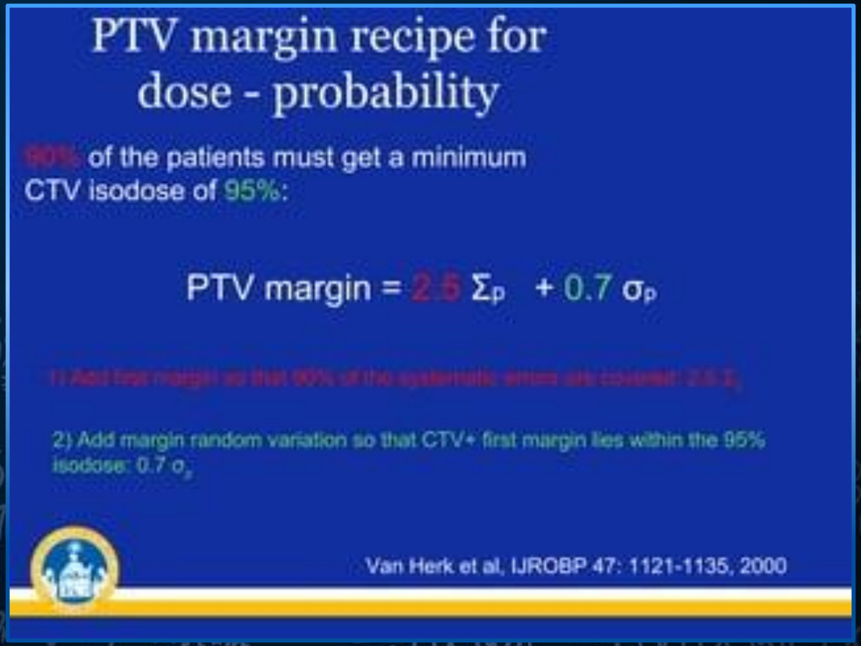


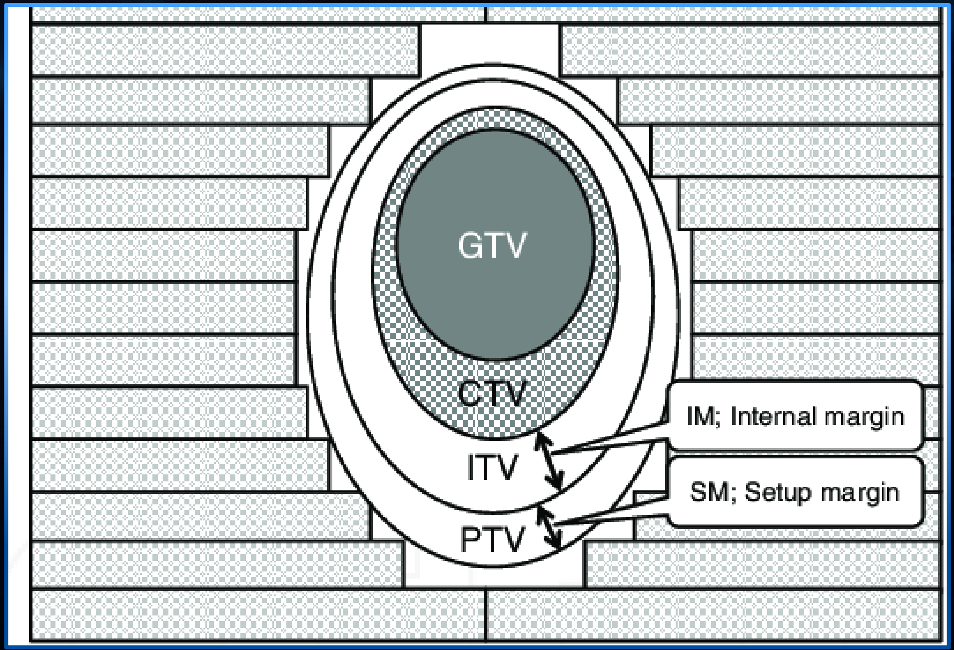
Laboratories

UNCERTAINTIES IN RADIOTHERAPY

The van Herk recipe

- GTV – gross target volume (what you can ”see”)
- CTV – clinical target volume (microinfiltration of tumor)
- ITV – integrated target volume (organ motion)
- PTV – planning target volume (setup errors)

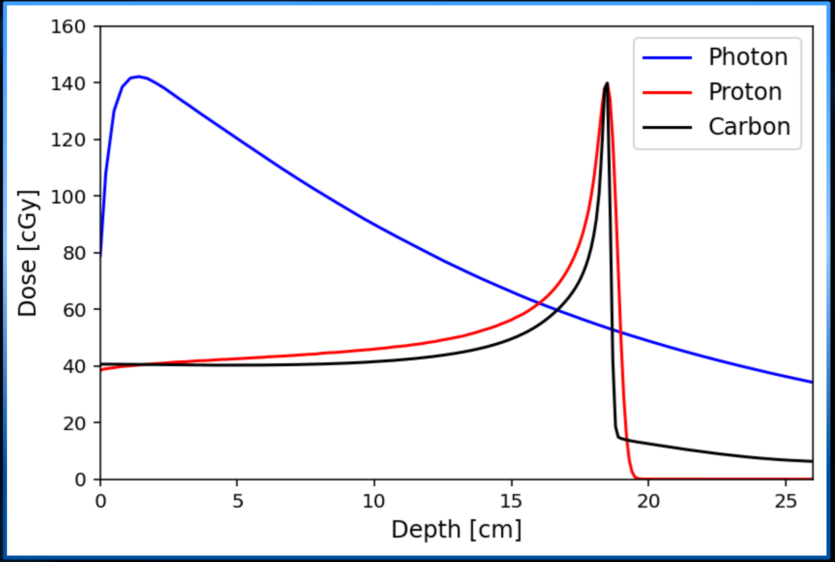


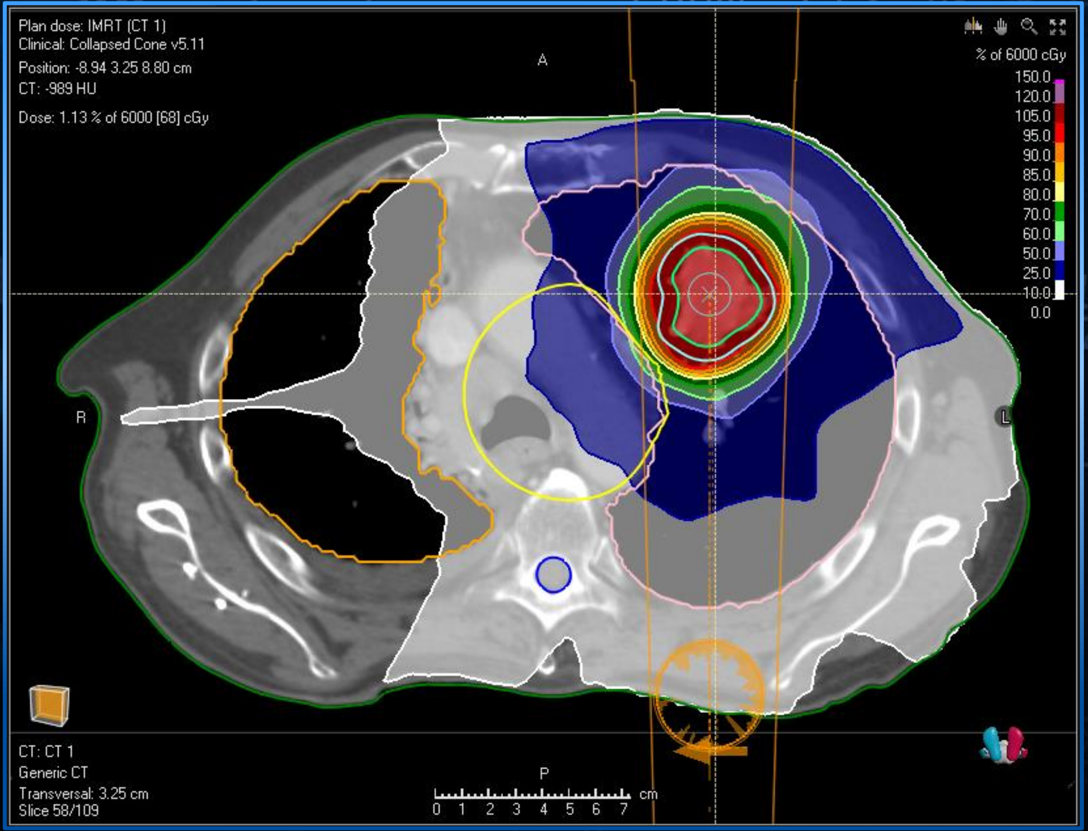


If the van Herk recipe is followed, 90% of all patients will receive at least 95% of the prescribed dose to the CTV

CREATING A ROBUST PLAN

- Conventional treatment planning typically performed on the PTV
- Photon radiation not so sensitive to range errors

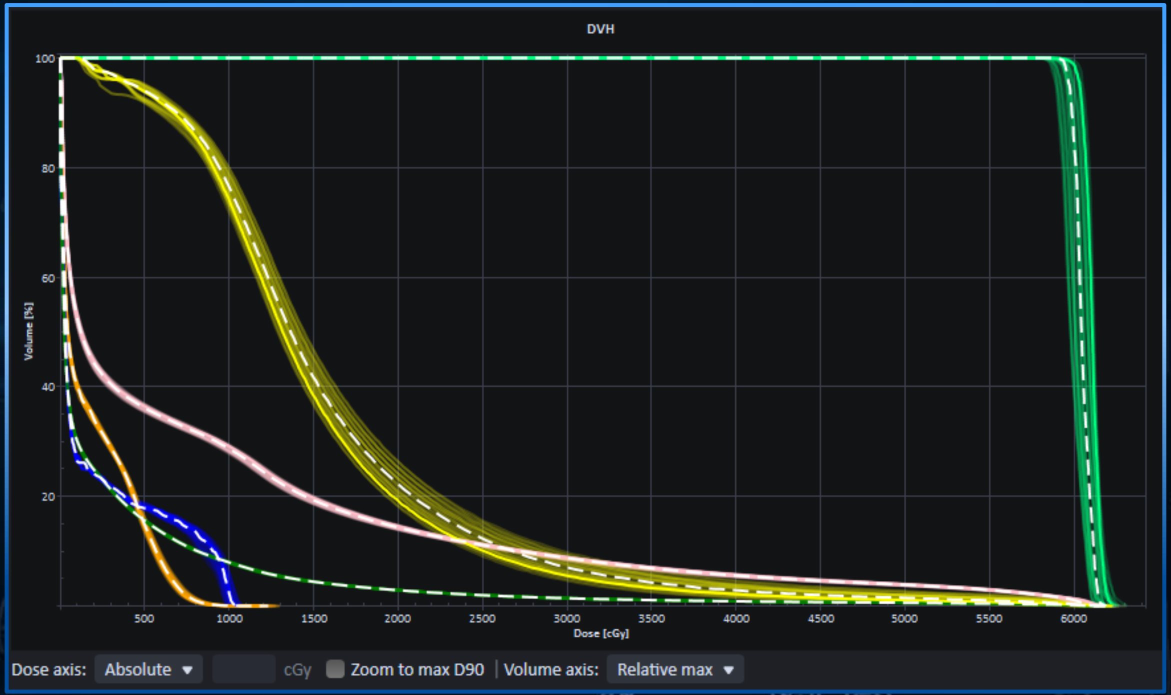


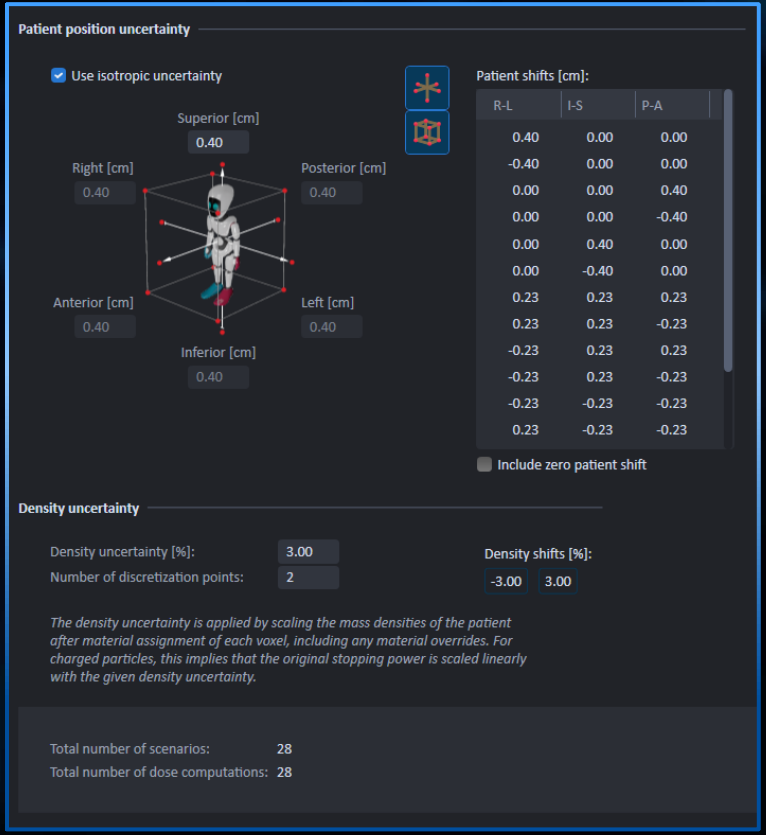


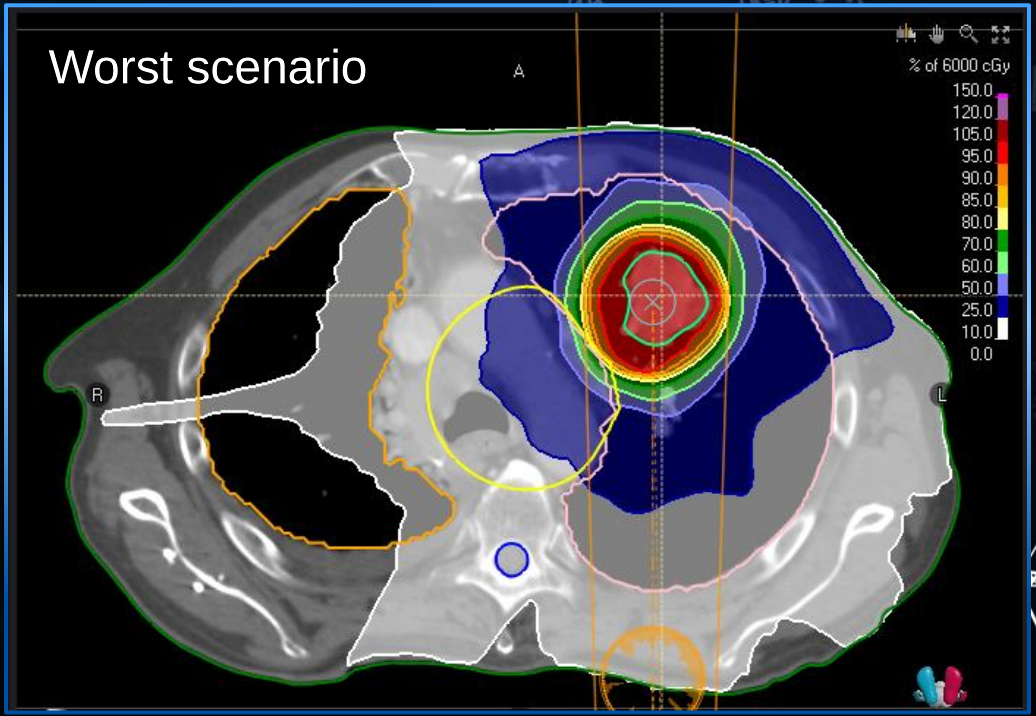
RaySearch Laboratories

ROBUST EVALUATION

- Robust evaluation assuming 4 mm setup and 3% range uncertainty (28 dose computations)







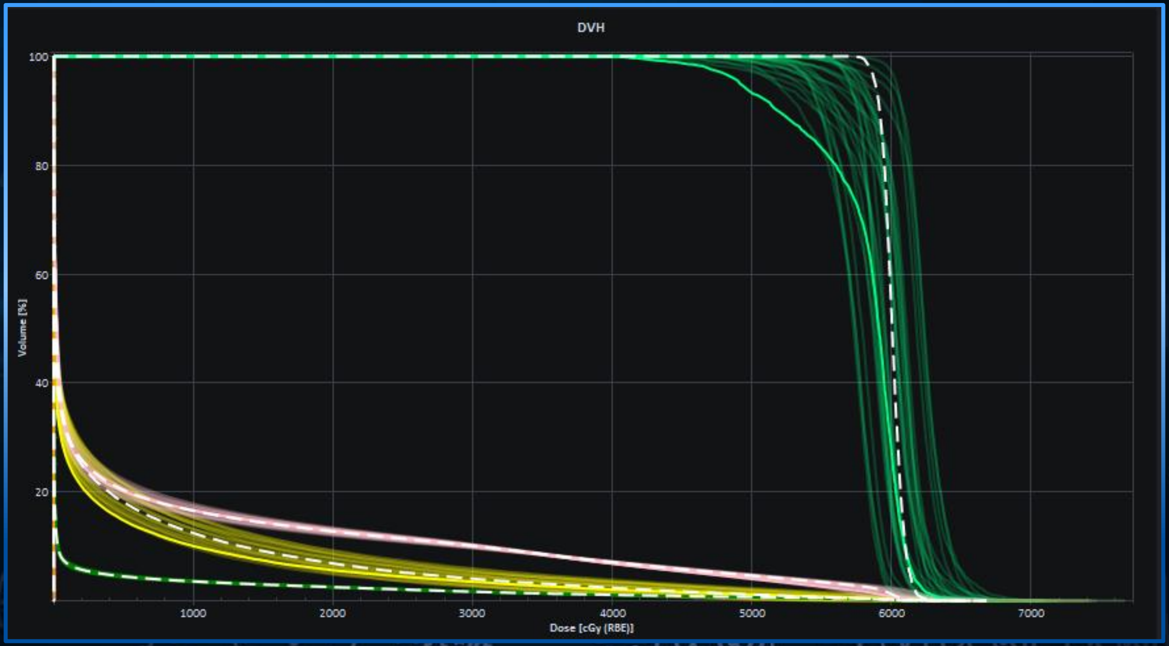
THE PROBLEM OF ROBUSTNESS

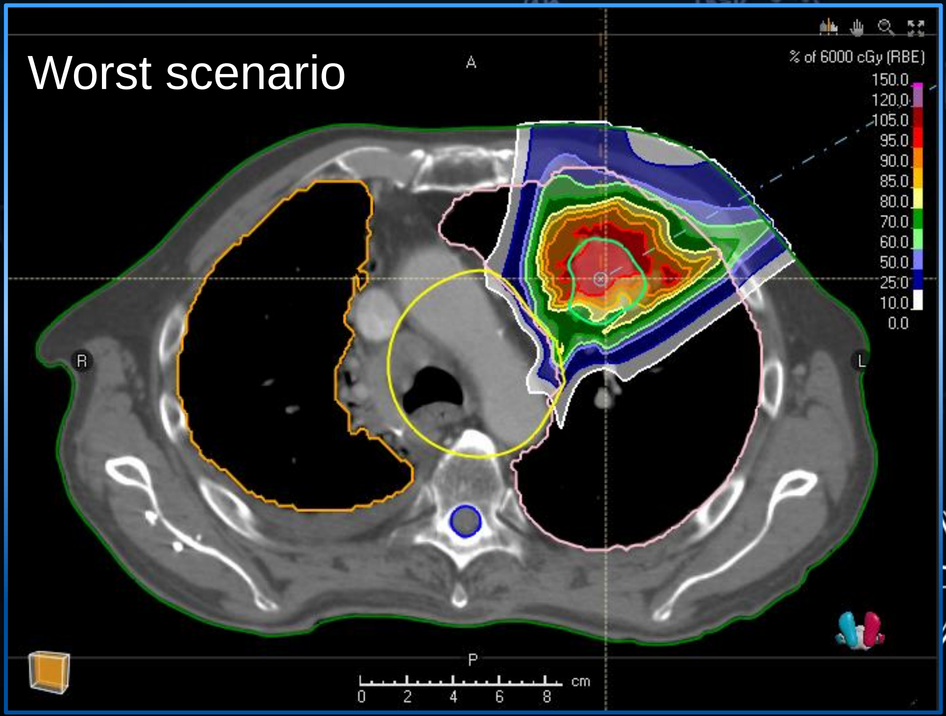
The good thing about particles is that they stop!
The problem is that we don’t know where…

ROBUST EVALUATION

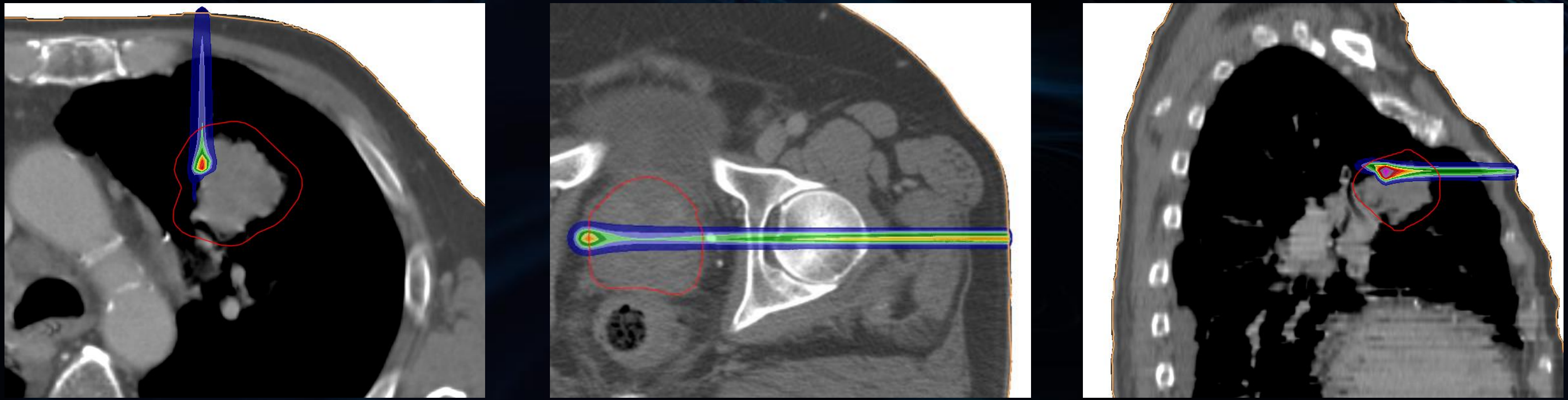
Lets do a similar robust evaluation for the proton plan

- Large cold spots in the target for a majority of the error scenarios

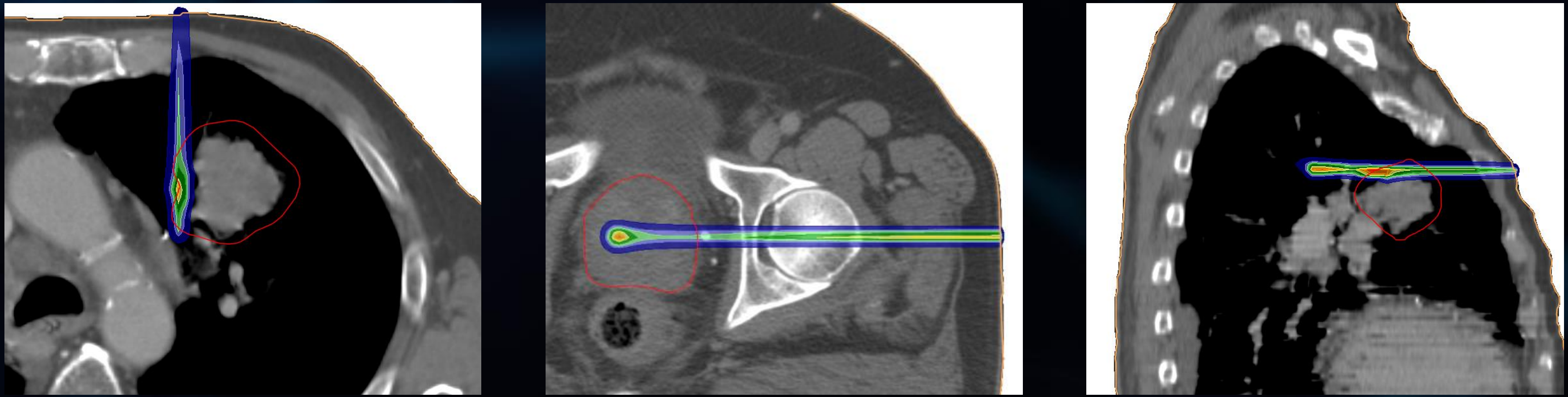




THE EFFECTS OF ERRORS ON A PBS BEAM



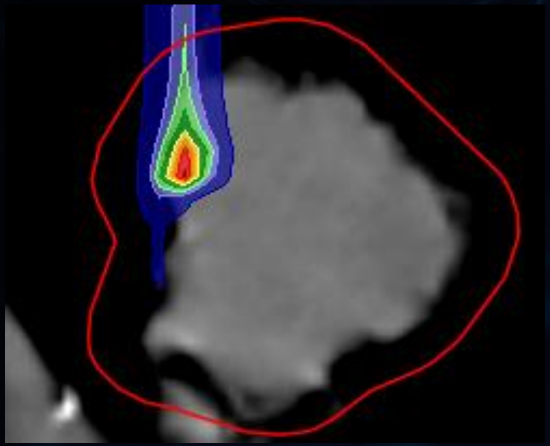
(a) Nominal setup (c) Nominal density (e) Nominal tumor position



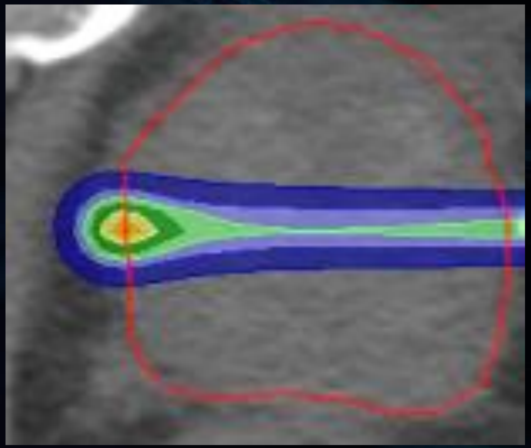
(b) Shifted setup (d) Scaled density (f) Shifted tumor position

RaySearch Laboratories

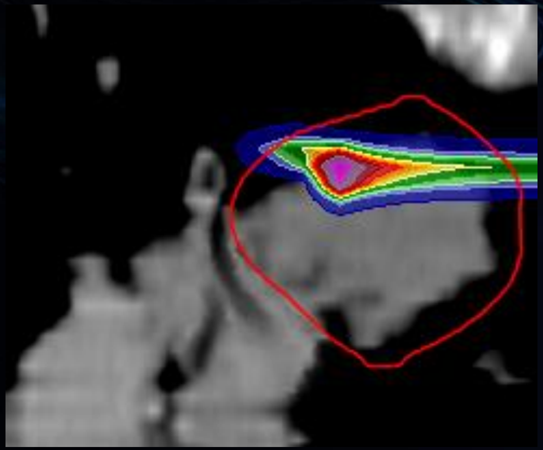
THE EFFECTS OF ERRORS ON A PBS BEAM



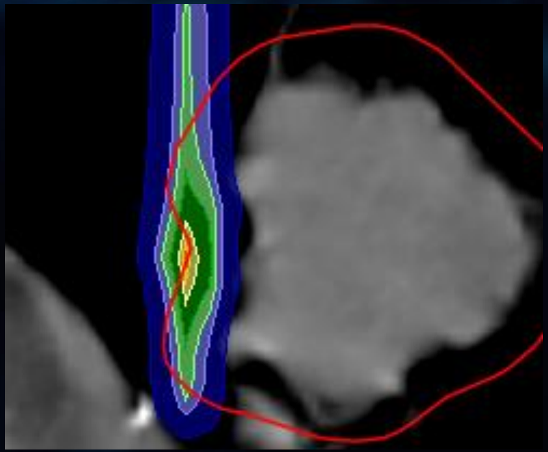
(a) Nominal setup



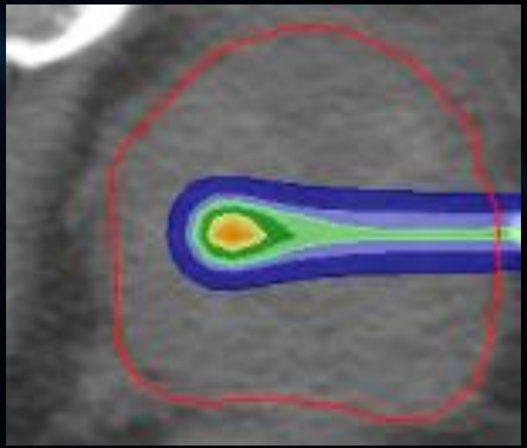
(c) Nominal density



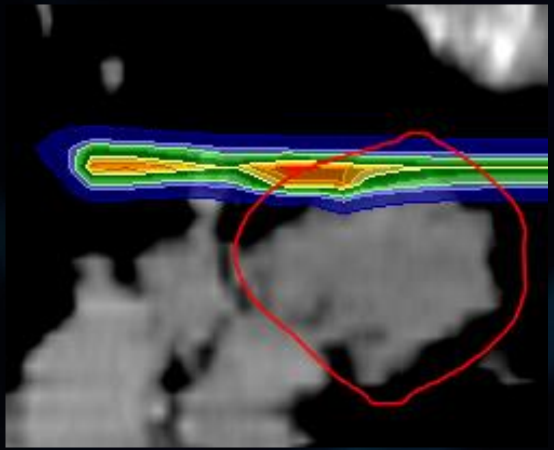
(e) Nominal tumor position



(b) Shifted setup



(d) Scaled density



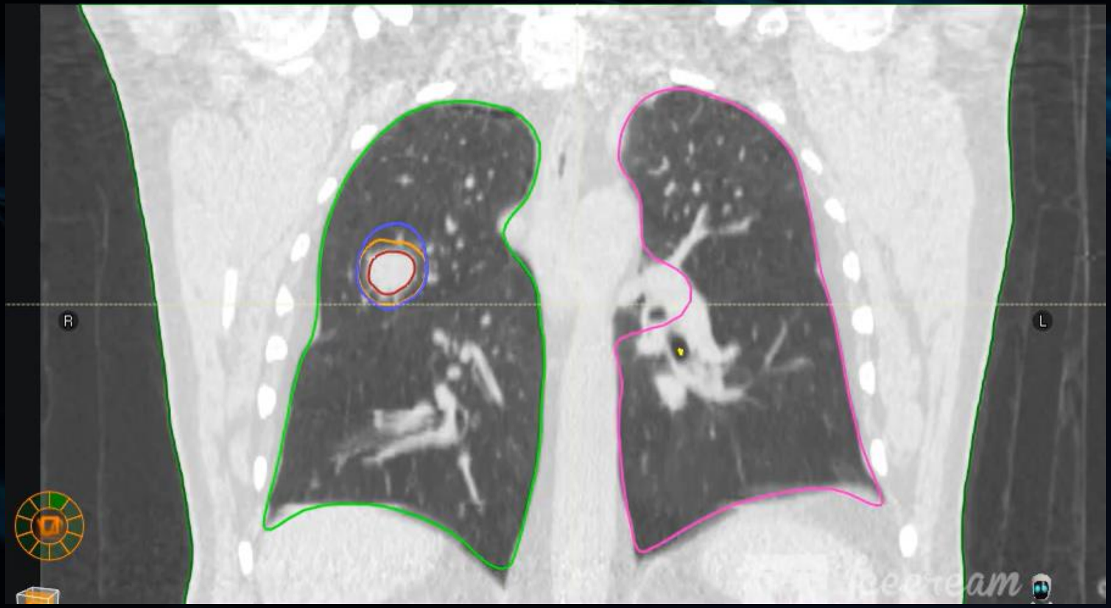
(f) Shifted tumor position

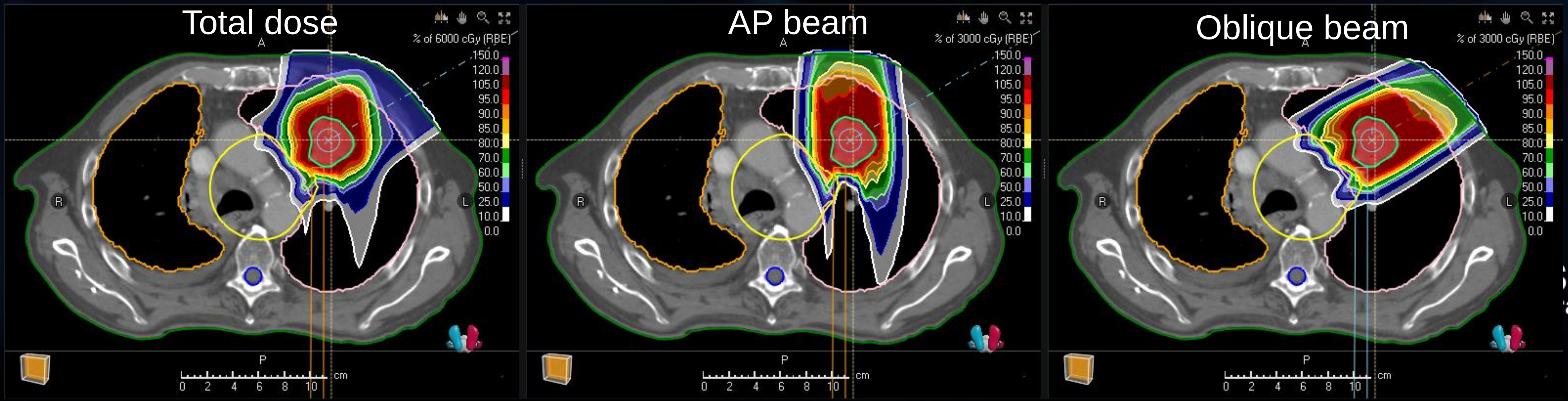
RaySearch Laboratories

CREATING A ROBUST PLAN

A suboptimal workflow

- So how do we solve this problem?
  - ITV + PTV margins
  - Material override in PTV – GTV
    - Which we remove after optimization
  - Single field uniform dose (SFUD)
    - Each beam completely covers the target by itself
  - Dose computation on average CT

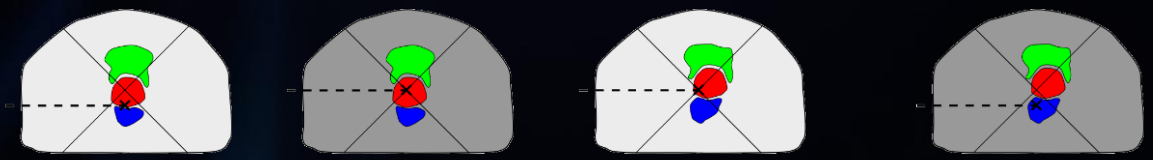




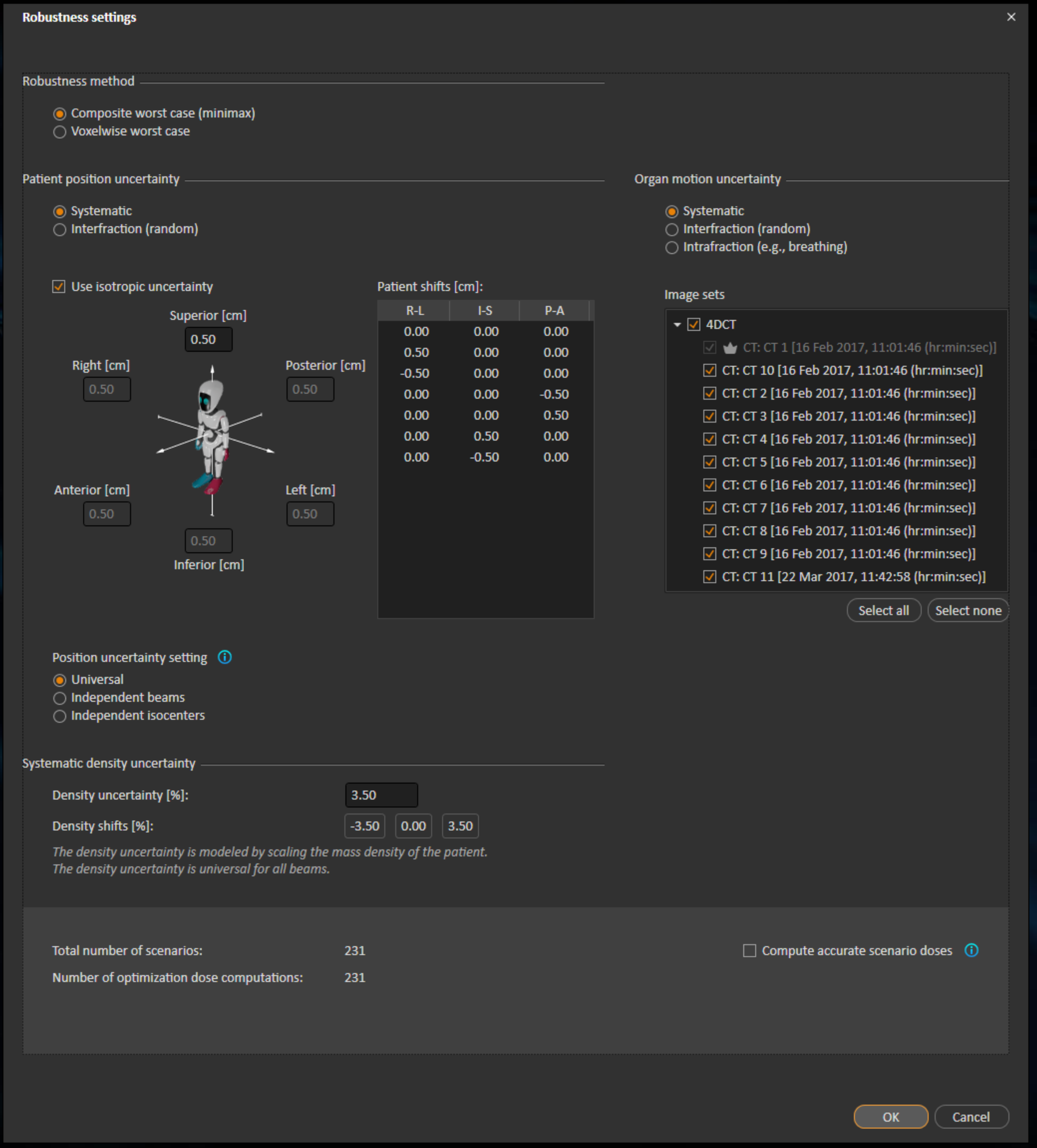
ROBUST 4D OPTIMIZATION

A better solution

- Composite worst-case optimization (minimax)
- Scenario based optimization
  - Patient position
  - Density uncertainty
  - Patient image (4D)
- Dose is computed and evaluated in all scenarios during plan optimization
  - Can take a long time for many scenarios

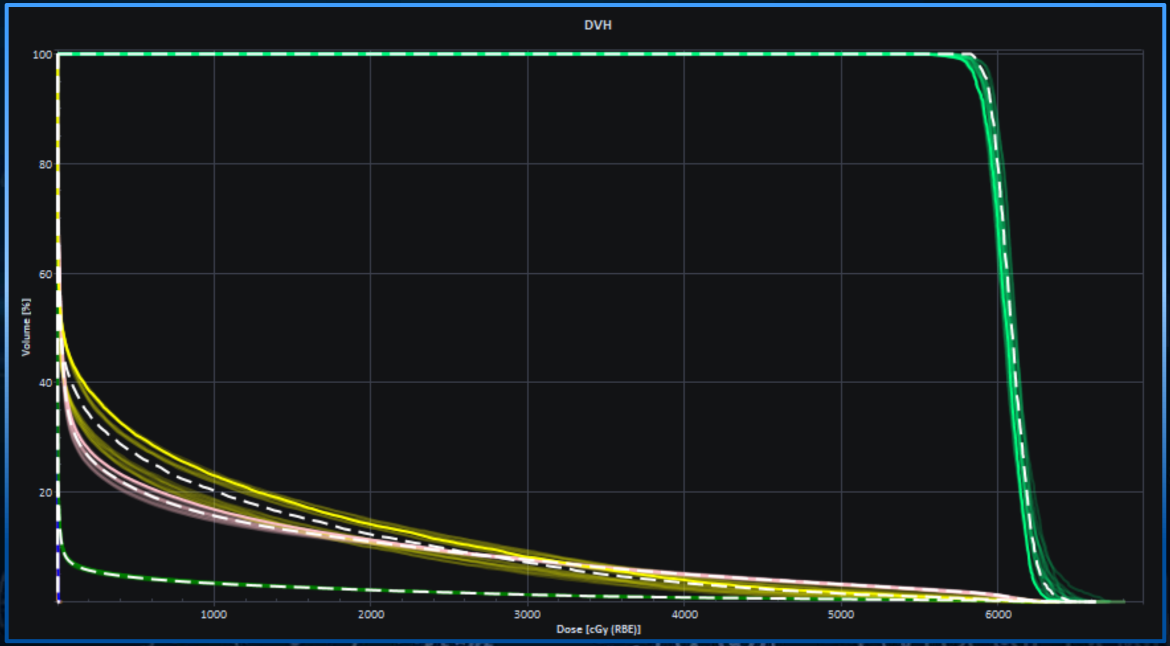


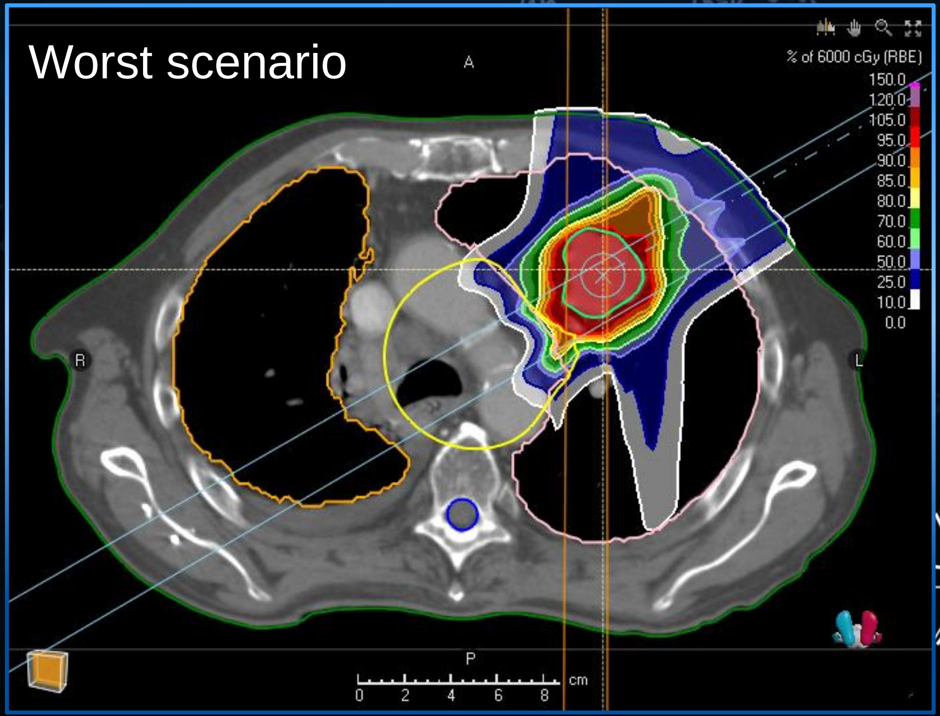
Shifted setup + Scaled density + Patient image = Scenario



ROBUST EVALUATION

- A similar robust evaluation for the robustly optimized proton plan have sufficient target coverage in all scenarios.
- Dose to OARs is slightly higher. Robustness always comes with a price.

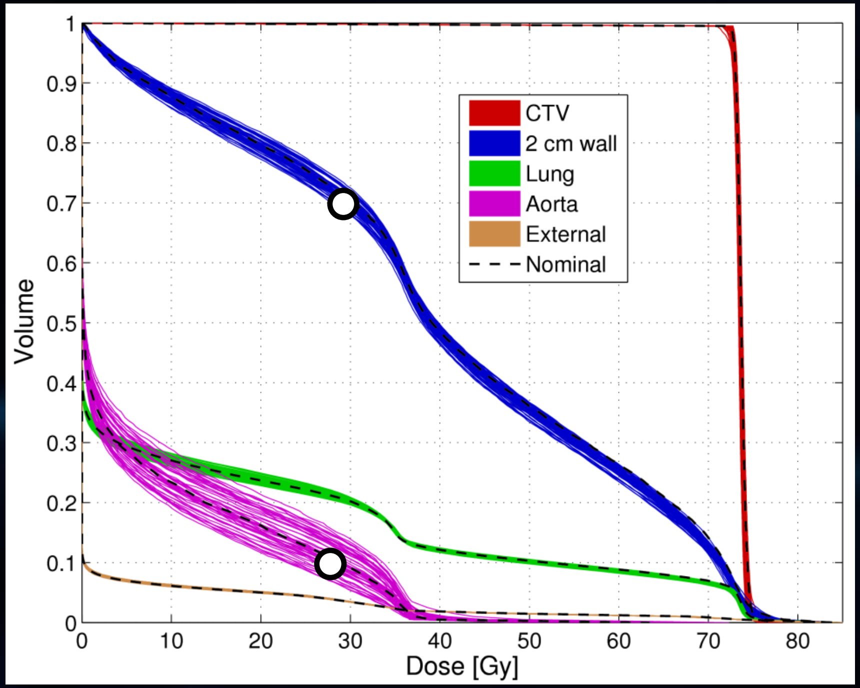


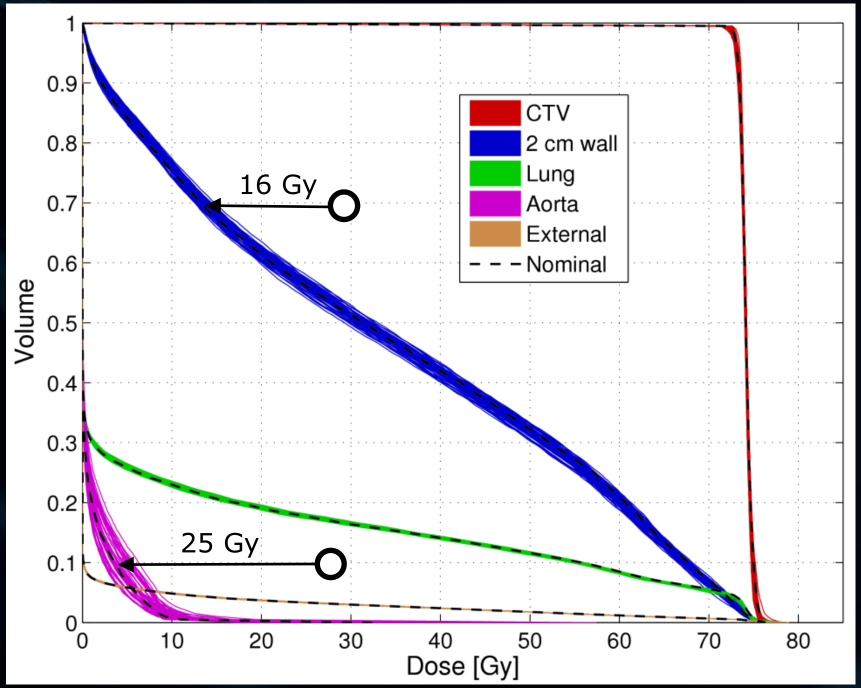


CONVENTIONAL VS ROBUST OPTIMIZATION

For a similar lung case

Evaluation over 50 scenarios:





Conventional planning

- Single field uniform dose
- Material override
- Margins for setup errors
- ITV for breathing motion

Robust optimization

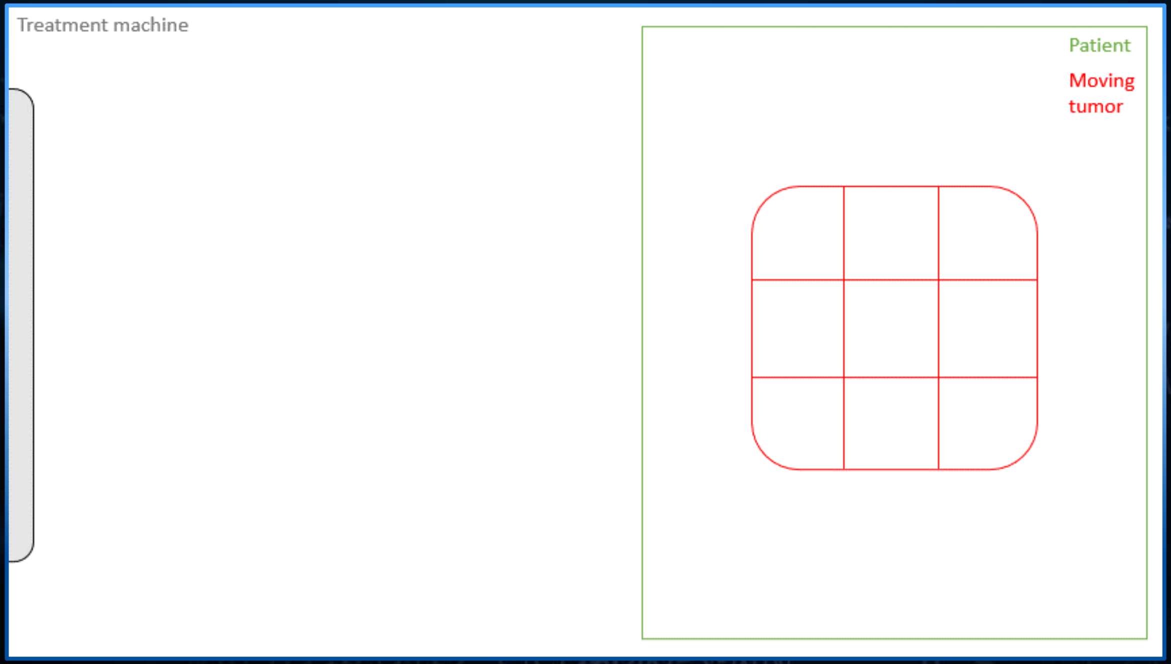
- 4D-CT, range, and setup scenarios

INTERPLAY ROBUSTNESS

Are we done yet?

THE INTERPLAY EFFECT

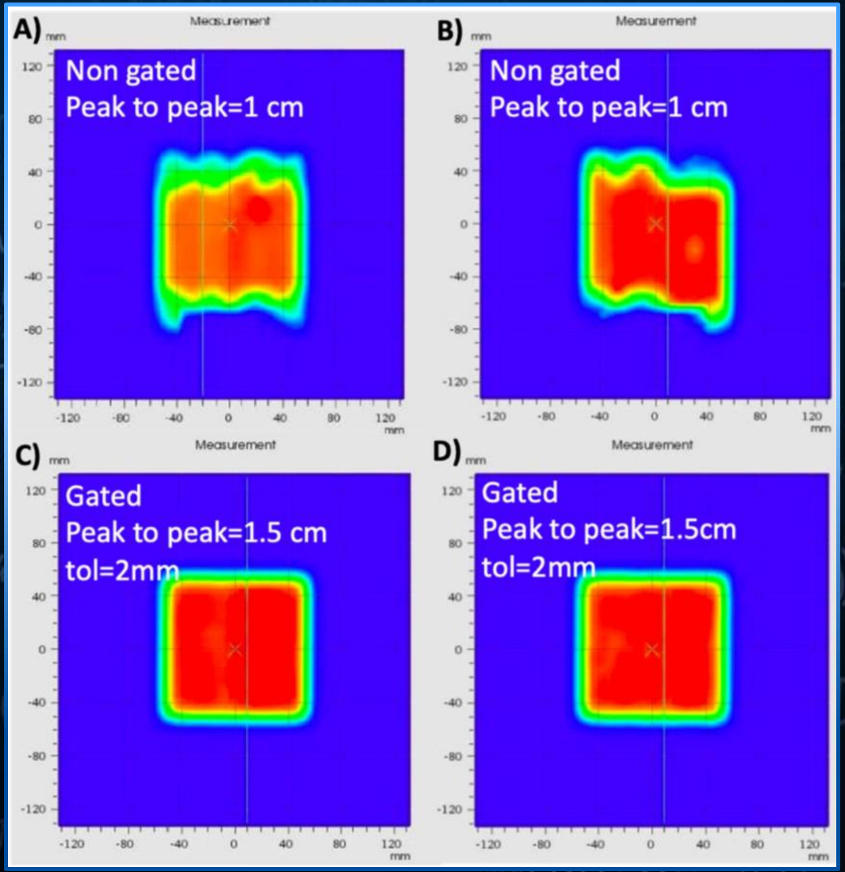
- A particle beam is not delivered instantaneously, but spot by spot
  - Time to deliver spots and redirect the beam between spots
  - Time to switch energy on the machine (~2 s)
- The interplay between the time structure of the machine and the breathing cycle affects the dose delivered to the patient
  - Some spots are delivered in during inhale, some during exhale and so on
- Note that 4D optimization does not take this into account



RaySearch Laboratories

THE INTERPLAY EFFECT

Tan, Hong Qi et al. (2024)



- Mitigation techniques:
  - Gating (only deliver the beam during a part of the breathing cycle)
  - Breath hold
  - Repainting – deliver each energy layer
  - Fractionation (interplay effect is random)
- Robust optimization with time structures

Med Phys. 2018 Jul 16. doi: 10.1002/mp.13094. Online ahead of print.

4D robust optimization including uncertainties in time structures can reduce the interplay effect in proton pencil beam scanning radiation therapy

Erik Engwall [1], Albin Fredriksson [1], Lars Glimelius [1]

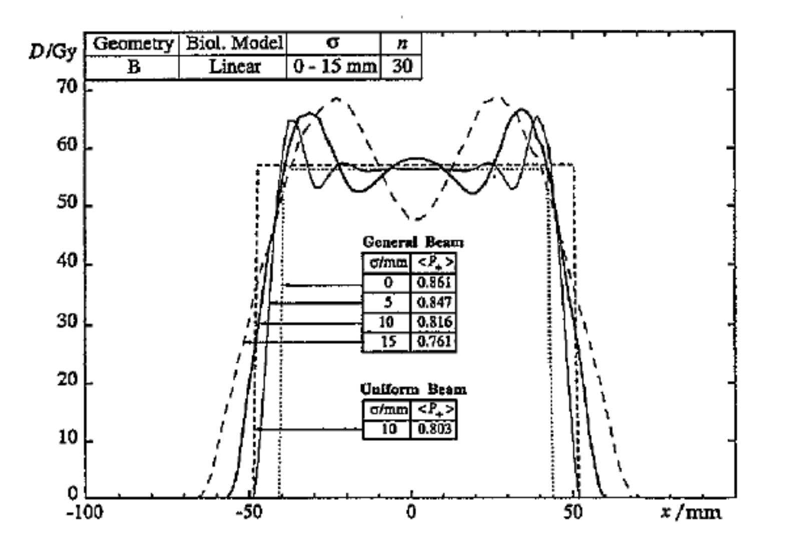
Interplay-robust optimization for treating irregularly breathing lung patients with pencil beam scanning

Ivar Bengtsson*[1,2], Anders Forsgren[1], Albin Fredriksson[2], and Ye Zhang[3]

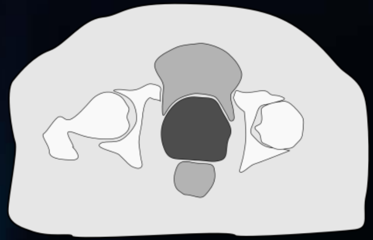
November 26, 2024

SOME FINAL WORDS ABOUT ROBUSTNESS

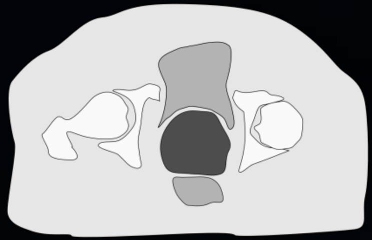
- Robust planning is needed for particles
- But don’t be overly robust. Assuming large systematic errors in all fractions may cause unnecessary dose to the OARs.
- Interfractional robustness simulates the treatment course, and can handle random errors and reduce margins.
  - Although don’t forget about biological effects
  - Typically not used clinically



Löf et al. (1995)

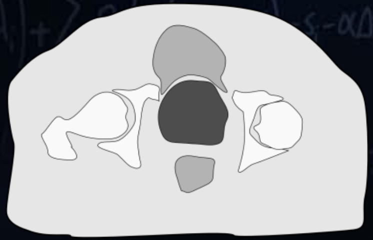


Planning CT



Fraction 1

. . .



Fraction *n*

RaySearch Laboratories

SOME FINAL WORDS ABOUT ROBUSTNESS

Instead of creating a plan that is robust against all uncertainties for 30 consecutive days of treatments, perhaps we can change the plan instead?

Adaptive radiotherapy

- Offline – reoptimize plan between fractions
  - In regular clinical use
- Online – reoptimize plan just before treatment
  - In clinical use at PSI
- Realtime – reoptimize plan during treatment

RaySearch Laboratories

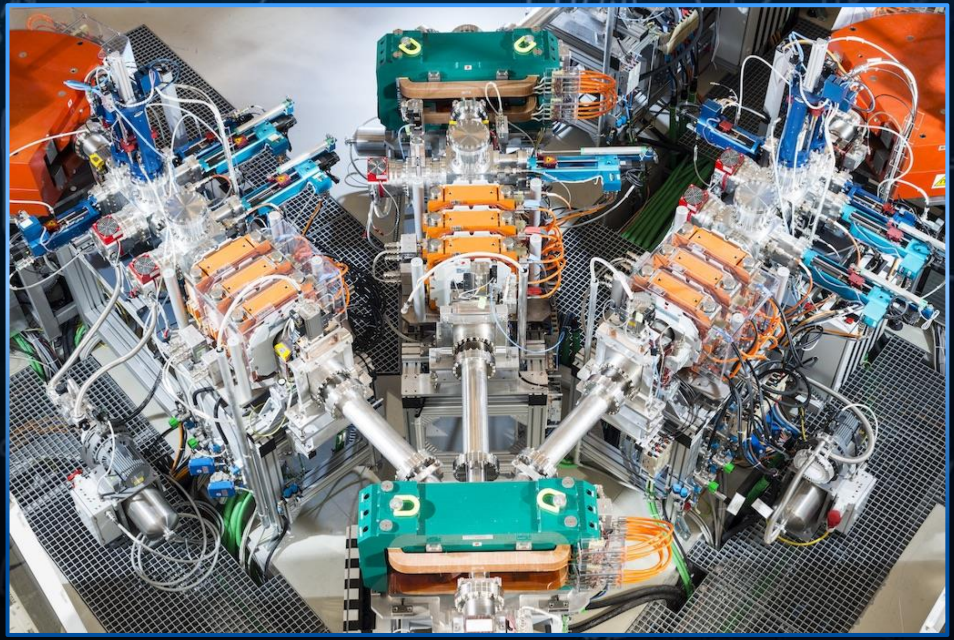
THANK YOU FOR YOUR ATTENTION

lars.glimelius@raysearchlabs.com

RaySearch Laboratories

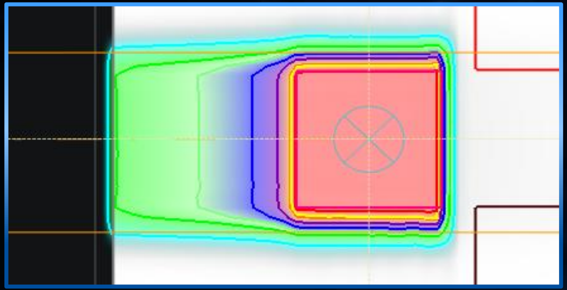
MULTI IONS

- Support for multiple ions
  - Proton – validation in progress ⚠
  - Helium – in clinical use ☑
  - Carbon – in clinical use ☑
  - Oxygen – validation in progress ⚠
  - Neon – implementation in progress ⚠
- Co-optimized and delivered in the same fraction



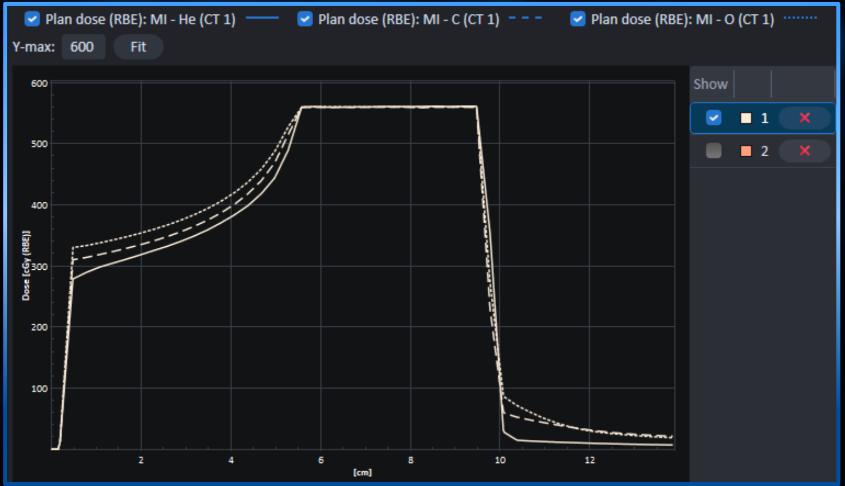
RaySearch Laboratories

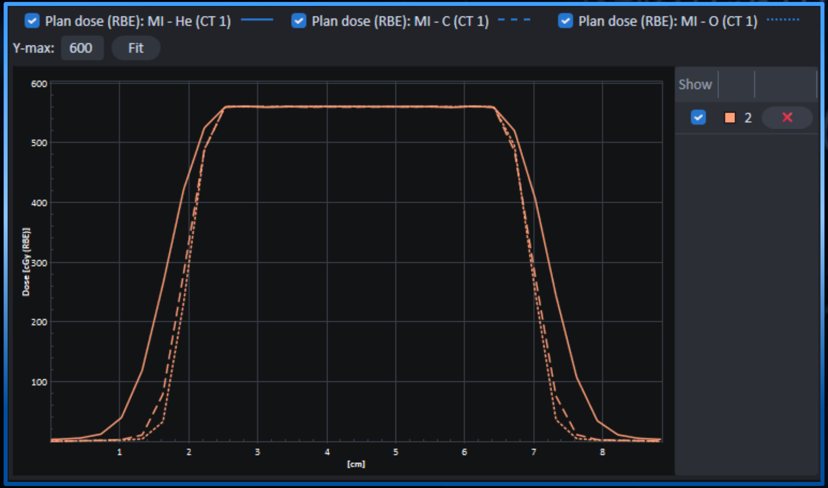
MULTI IONS

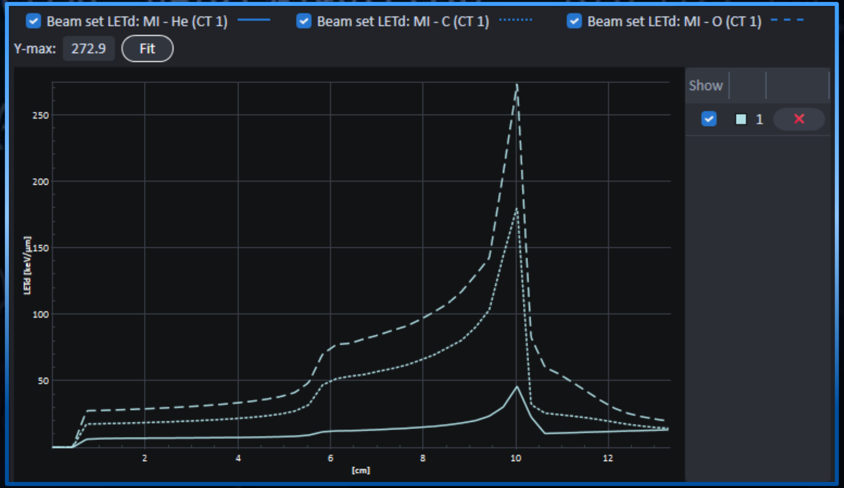


Particle	Entry dose	Fragmentation Tail	Penumbra	LET/RBE
Proton	✓ Medium	✓ No	Large	✓ ? Very low
Helium	✓ Medium	✓ Small	Medium	✓ ? Low
Carbon	Large	Large	✓ Small	Medium
Oxygen	Large	Large	✓ Small	✓ High
Neon	Very large	Very large	✓ Very small	✓ Very high

——— He
- - - - - - C
---------- O





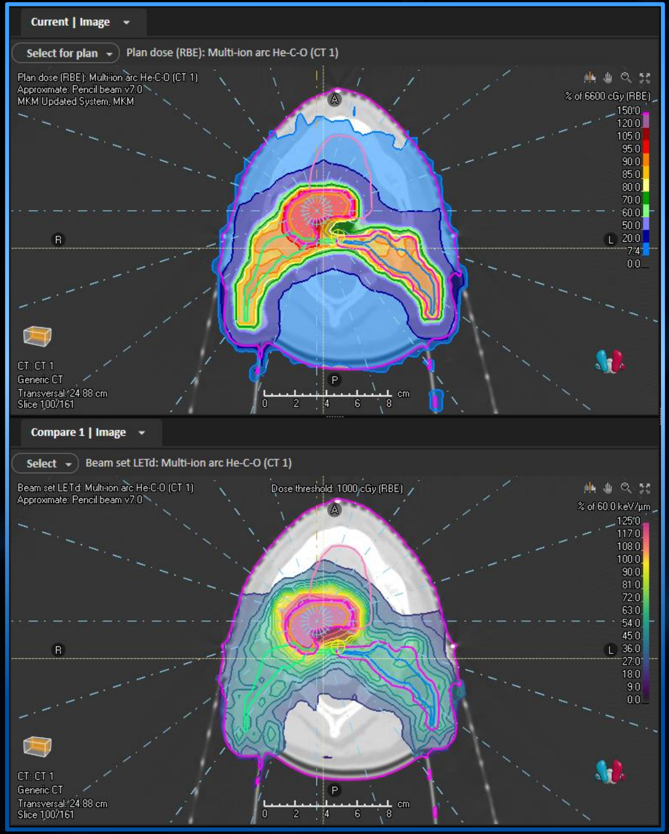


Depth dose

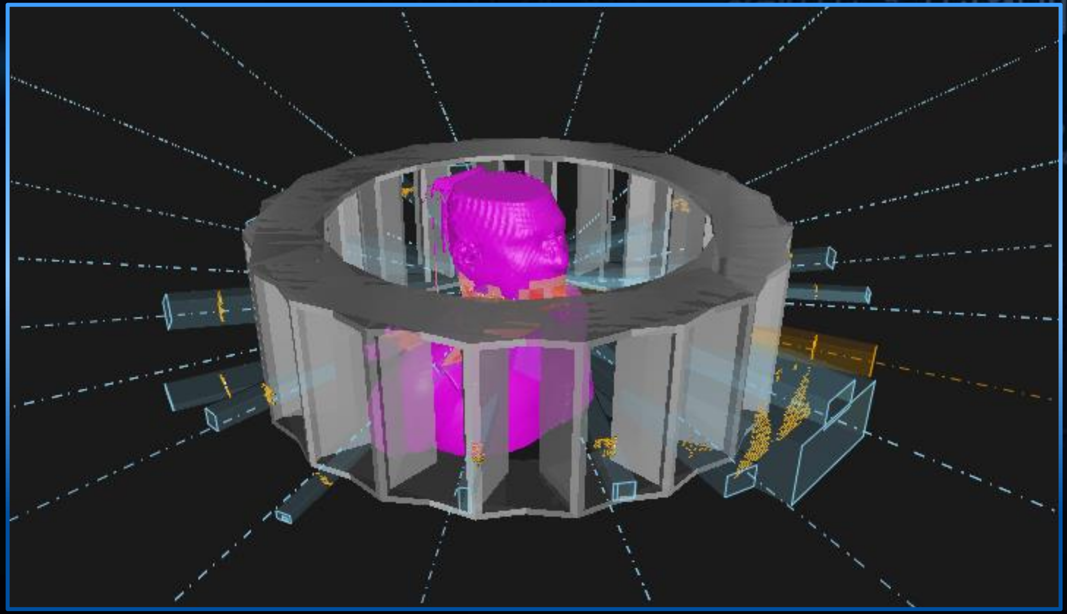
Lateral penumbra

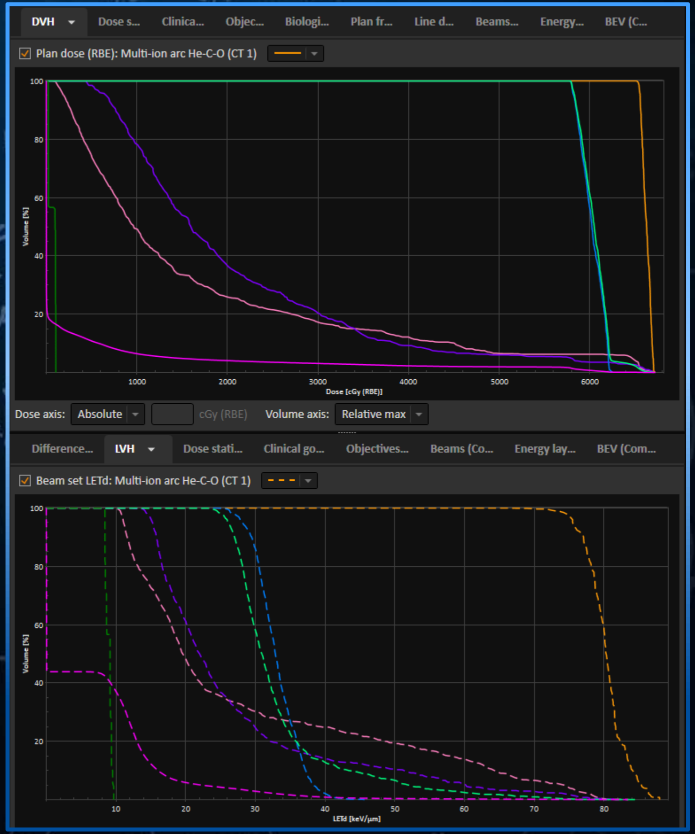
Dose-averaged LET

MULTI ION ARCS



- Helium – carbon – oxygen
- 3 x 10 discrete arc directions
- LET-boosted primary CTV: 80 keV/um





RaySearch Laboratories