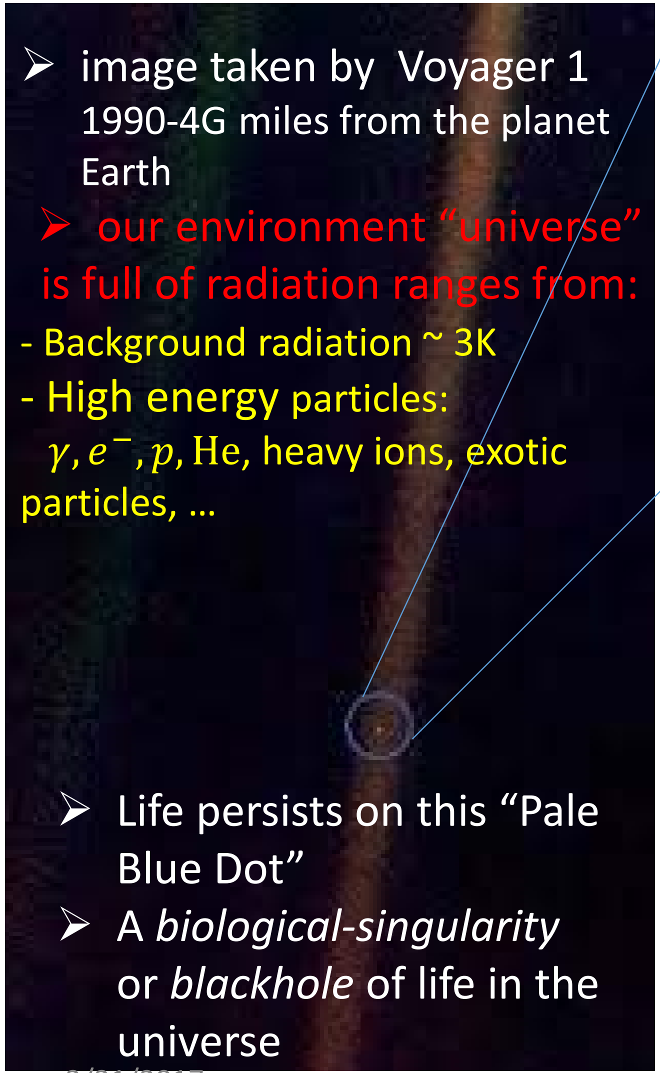
Modeling Biological Responses of Therapeutic Ionizing Radiation

Ramin Abolfath

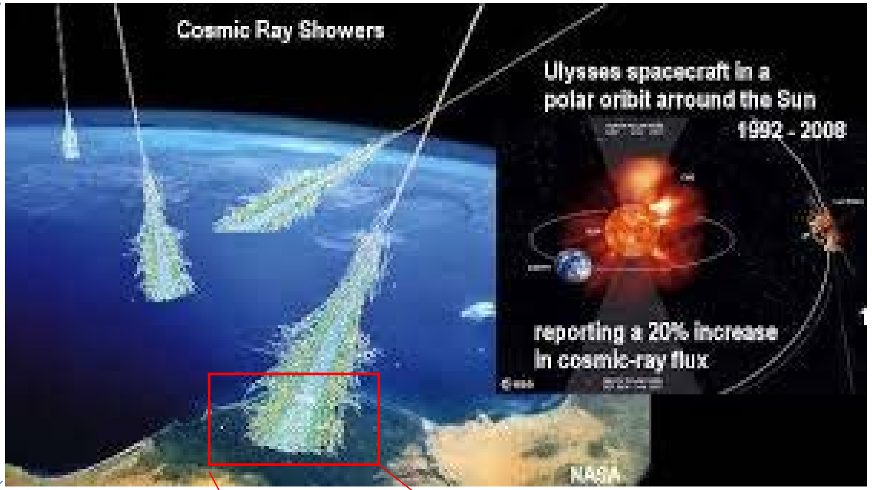
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

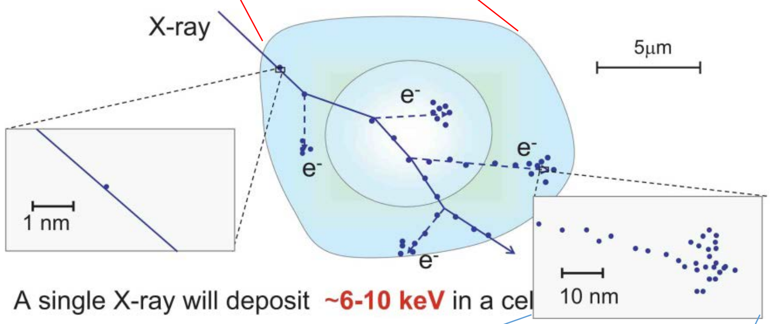
Making Cancer History®

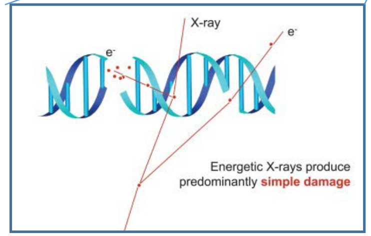


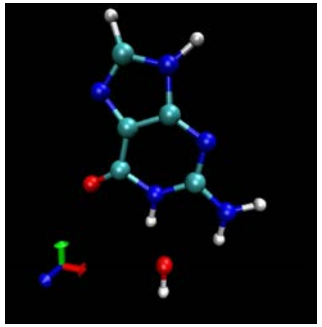
- image taken by Voyager 1 1990-4G miles from the planet Earth
  - our environment “universe” is full of radiation ranges from:
- - Background radiation ~ 3K
- - High energy particles: γ, e^-, p, He, heavy ions, exotic particles, …

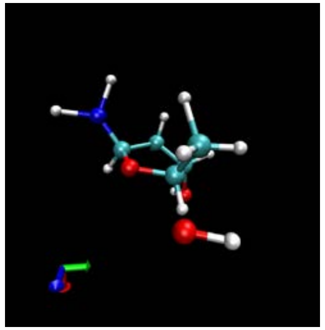
- Life persists on this “Pale Blue Dot”
- A *biological-singularity* or *blackhole* of life in the universe

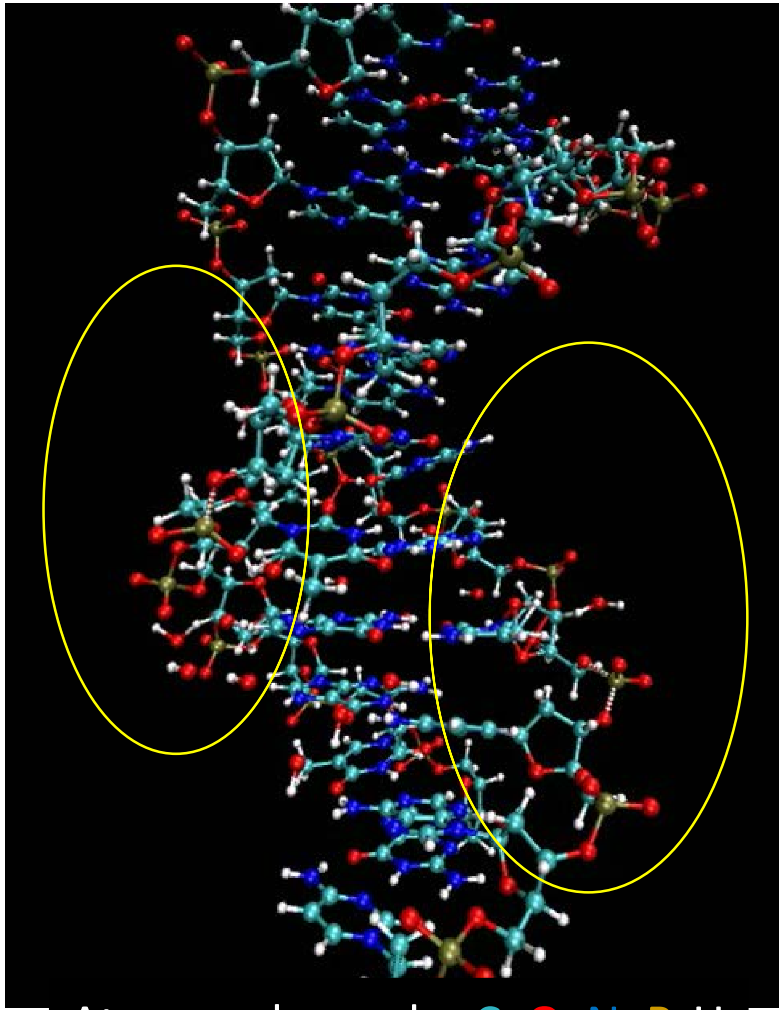










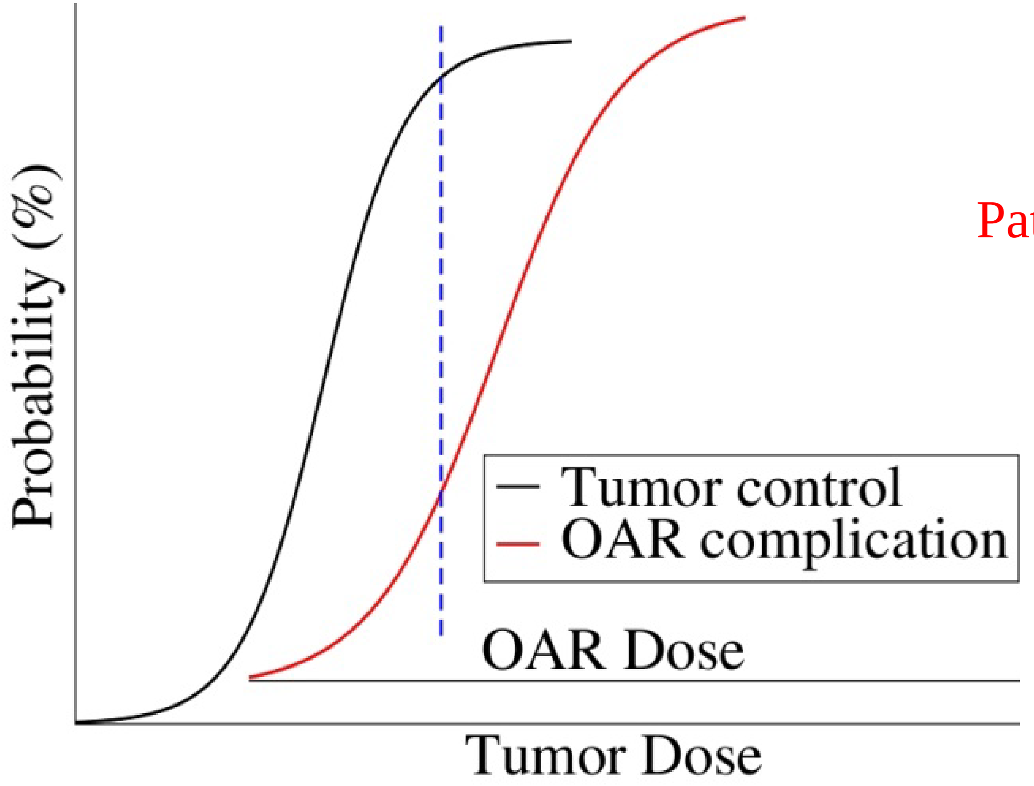


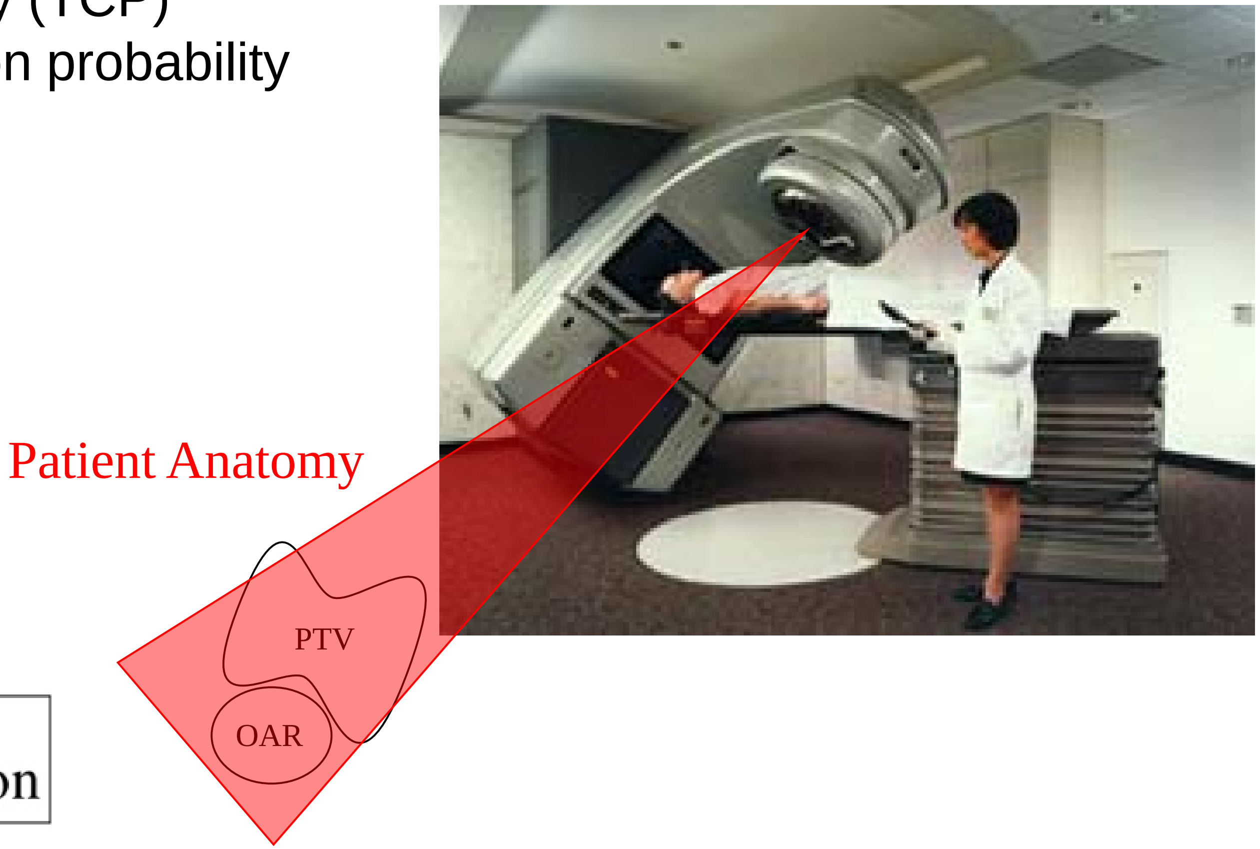
Atoms color code: C, O, N, P, H

Optimization in Radiation Therapy

- Maximize tumors control probability (TCP)
- Minimize normal tissue complication probability (NTCP)

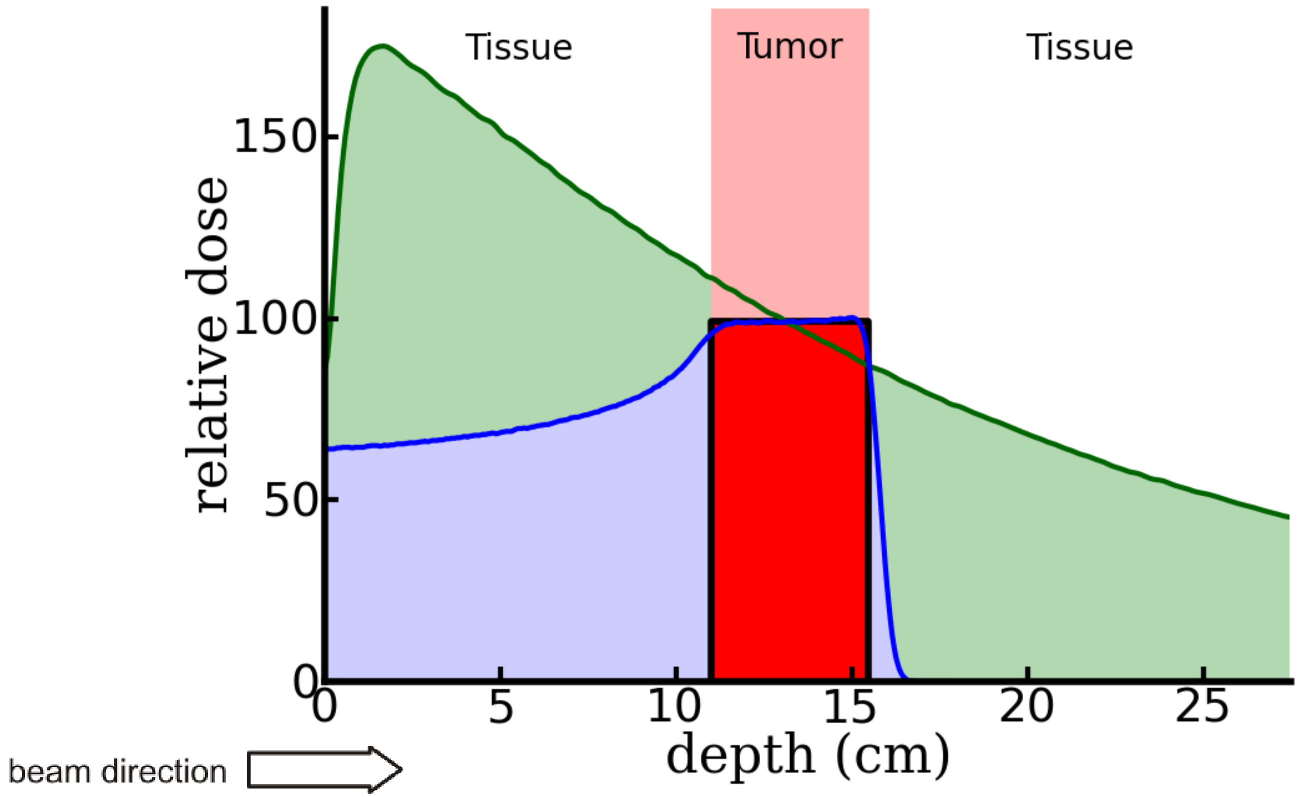
Prescription dose

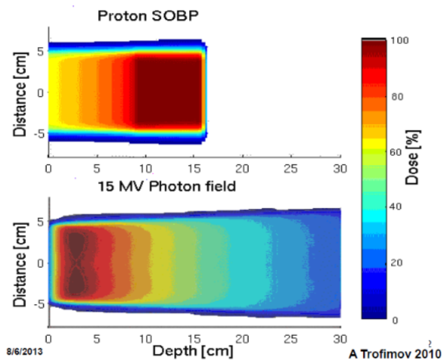


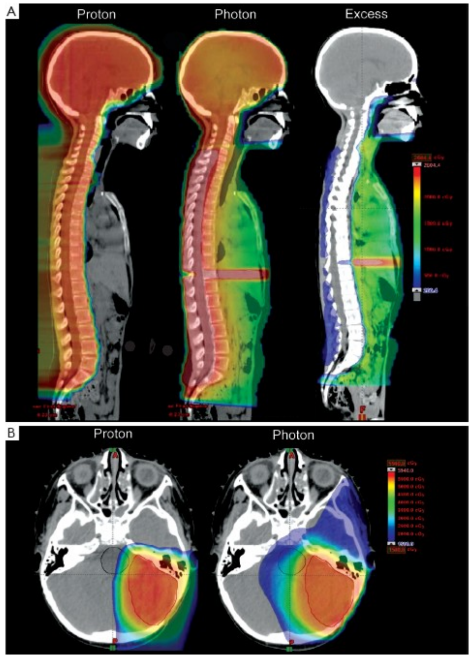


Pros and Cons of Ions (Proton/He/C/…) over Photon

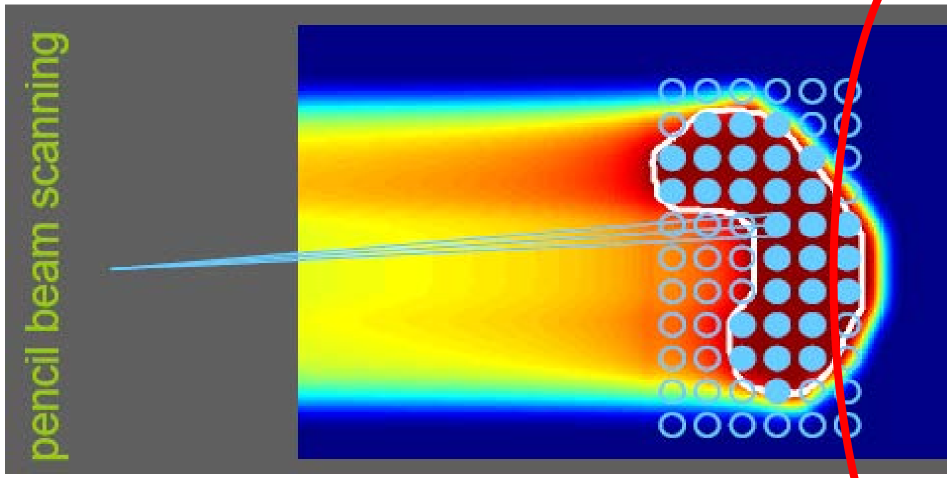
- Dose fall off sharply in the distal edge
  - o Higher target coverage
  - o Protect normal tissues
- However more complex biological responses



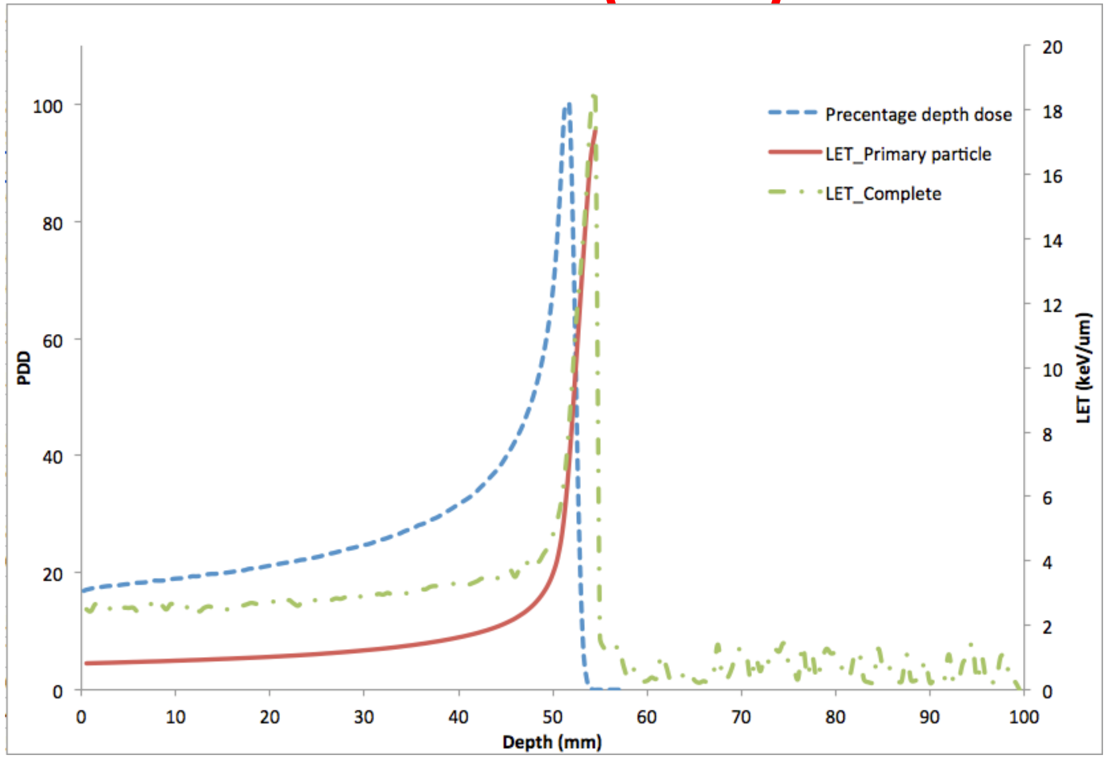




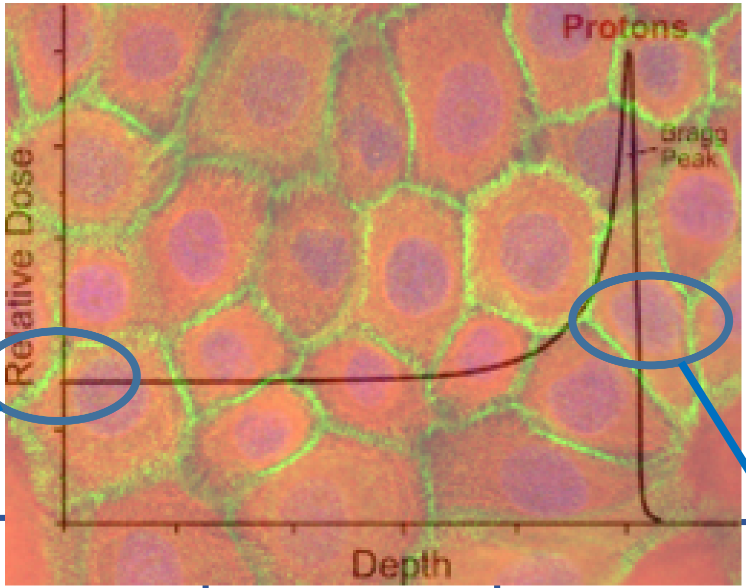
PB-IMPT / multienergy scanning technique



Do we know RBE accurately in the end of proton range

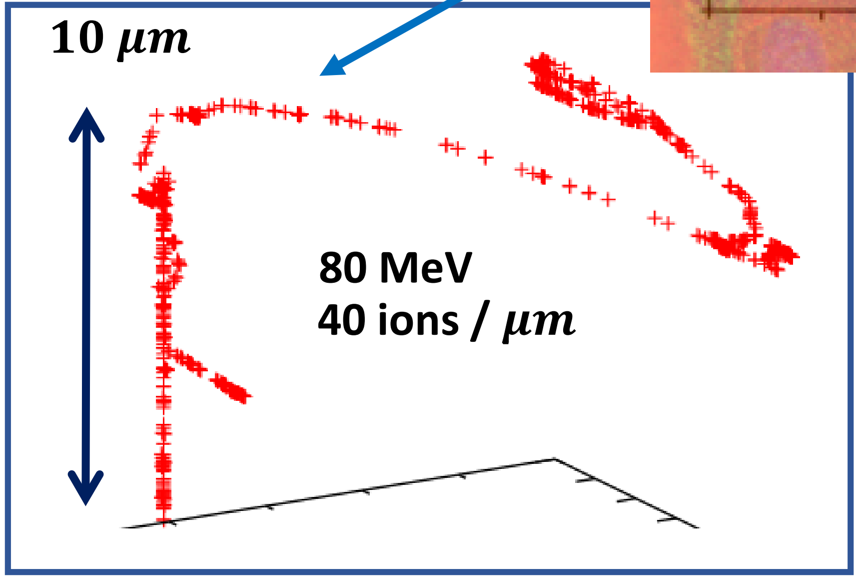


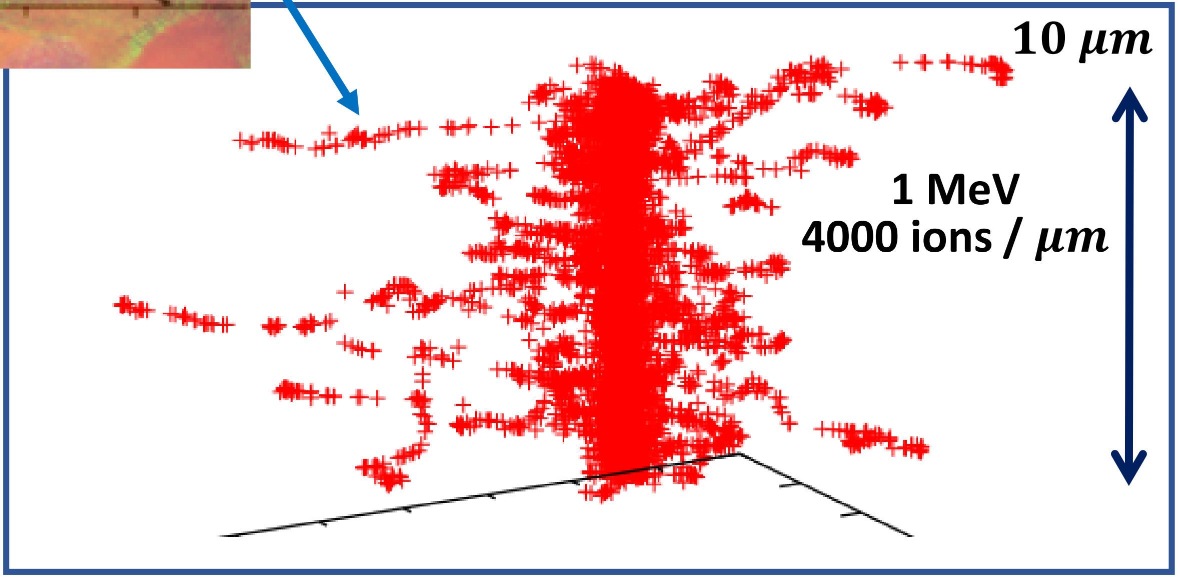
Variable RBE



Low RBE
Sparse ionization

High RBE
Dense Ionization





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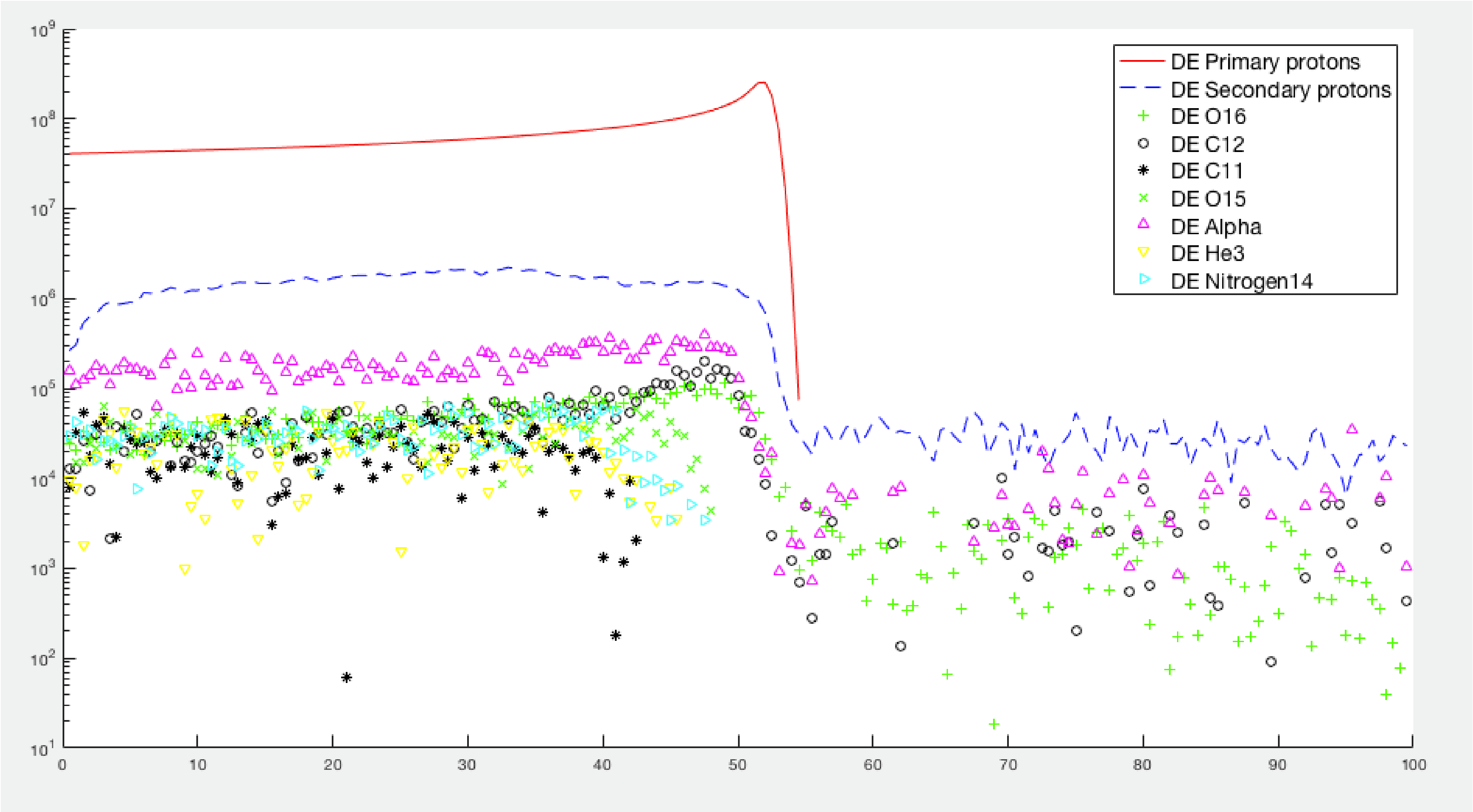
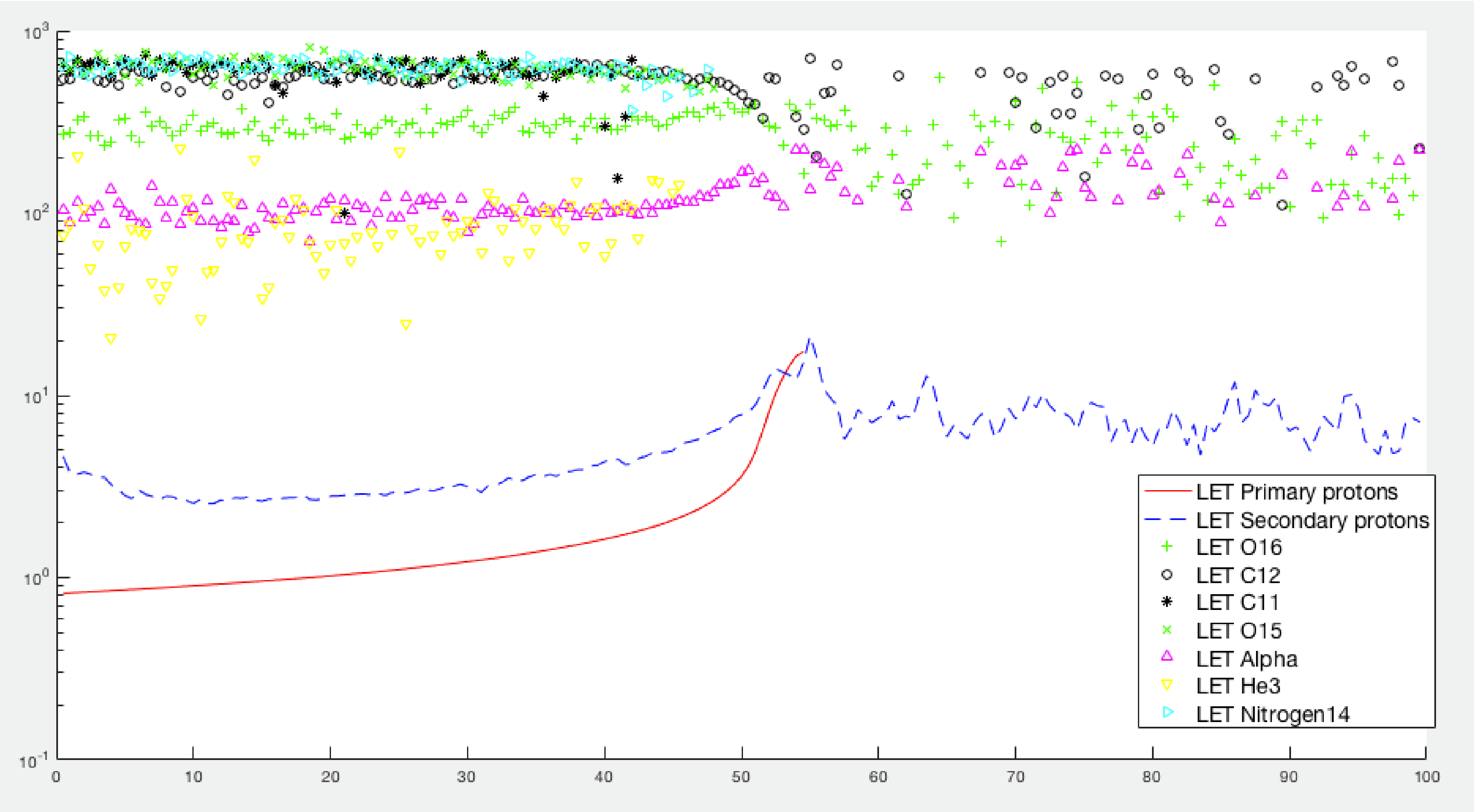
Energy deposition of primary and secondary particles



LET of primary and secondary particles



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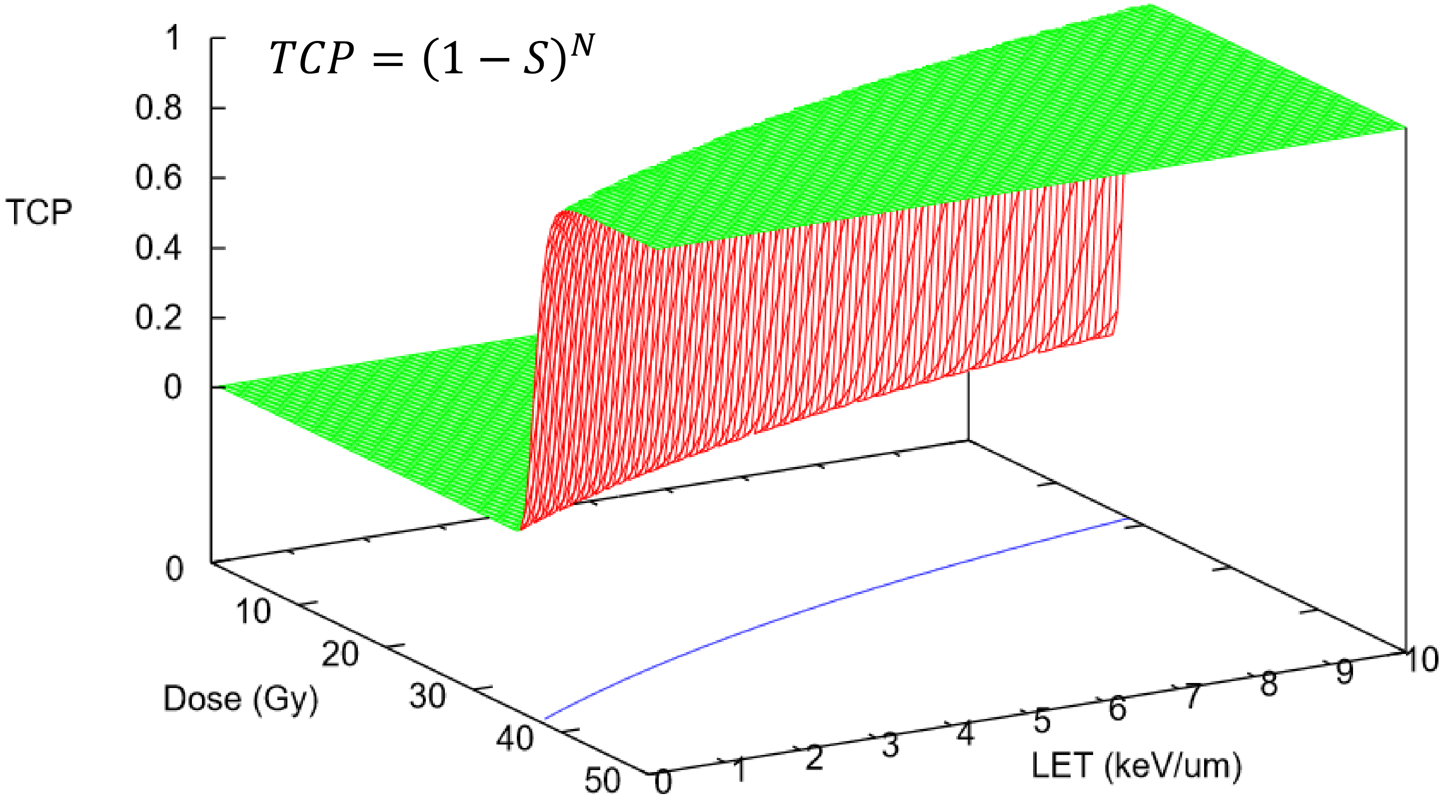
Is the current proton TPS biologically optimized?

$$S = exp\left(-[\alpha_0 + \alpha_1 LET_d]D + \beta_p D^2\right)$$

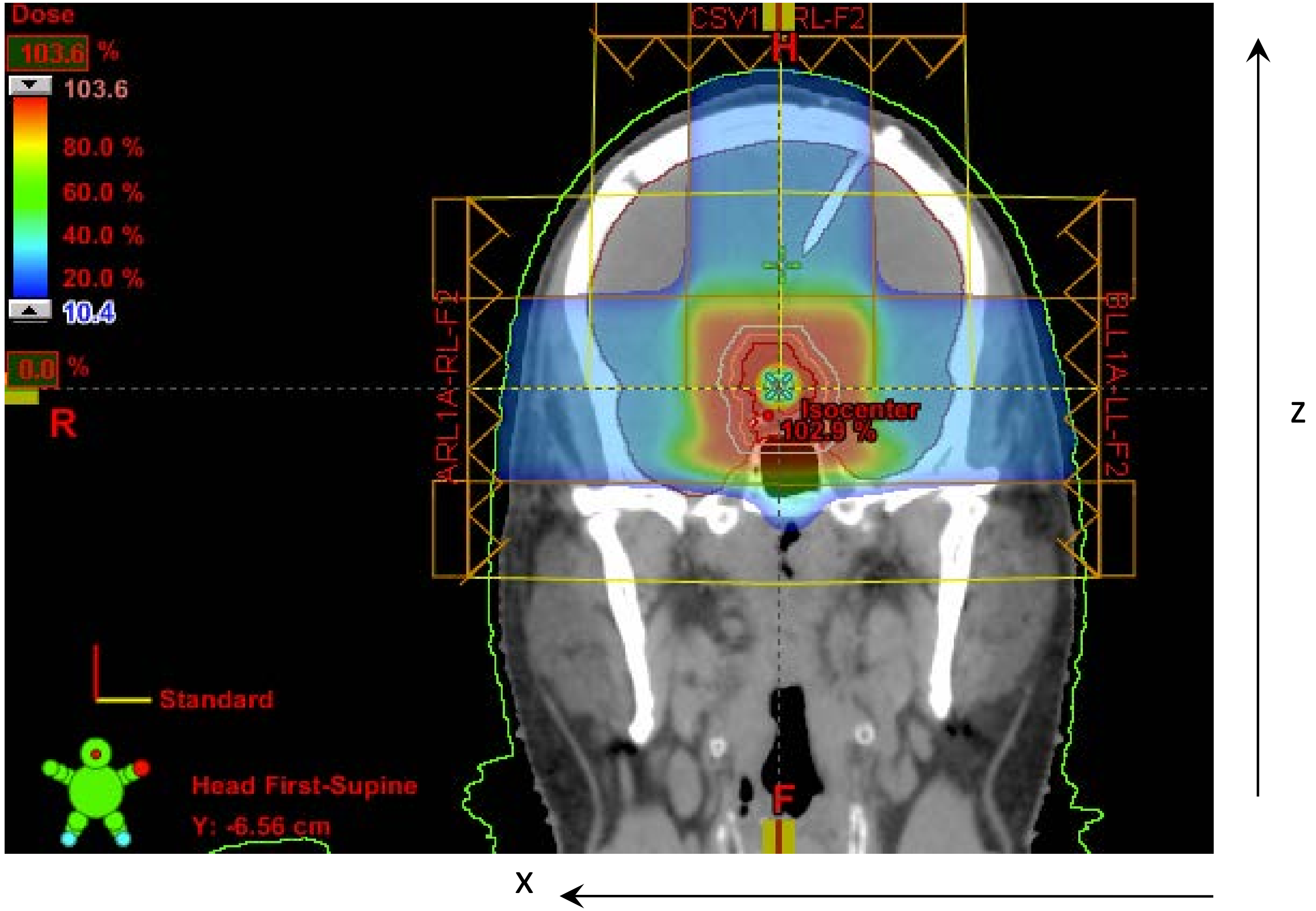
$$TCP = (1 - S)^N$$



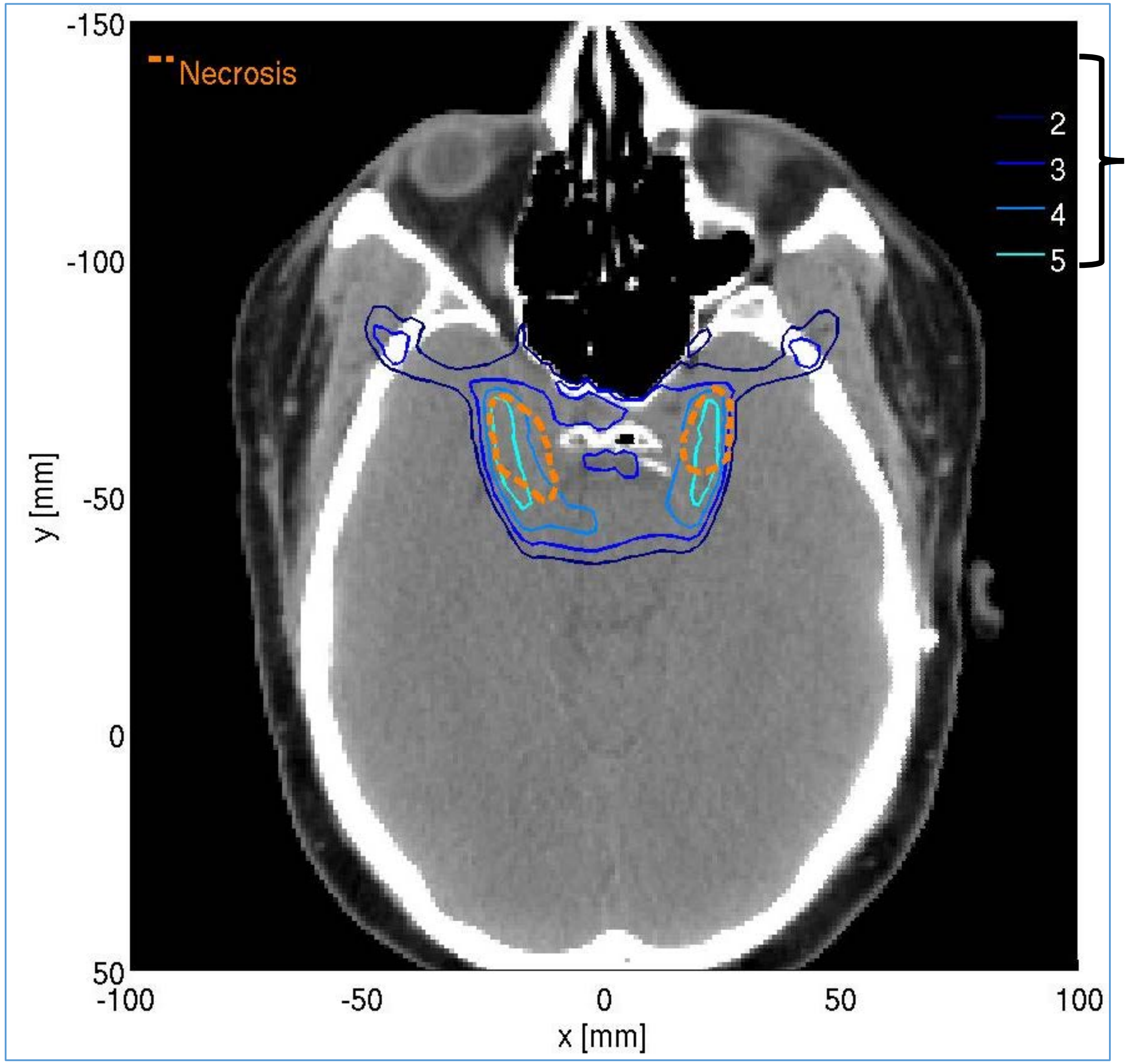
- Considering a uniform RBE 1.1 in proton therapy allows optimization of plans and employing TPS techniques developed in photon therapy
- Is constant RBE a reality?

Brain Necrosis in CNS Patients
- Possible Consequences of Variable RBE

40 year old male with craniopharyngioma



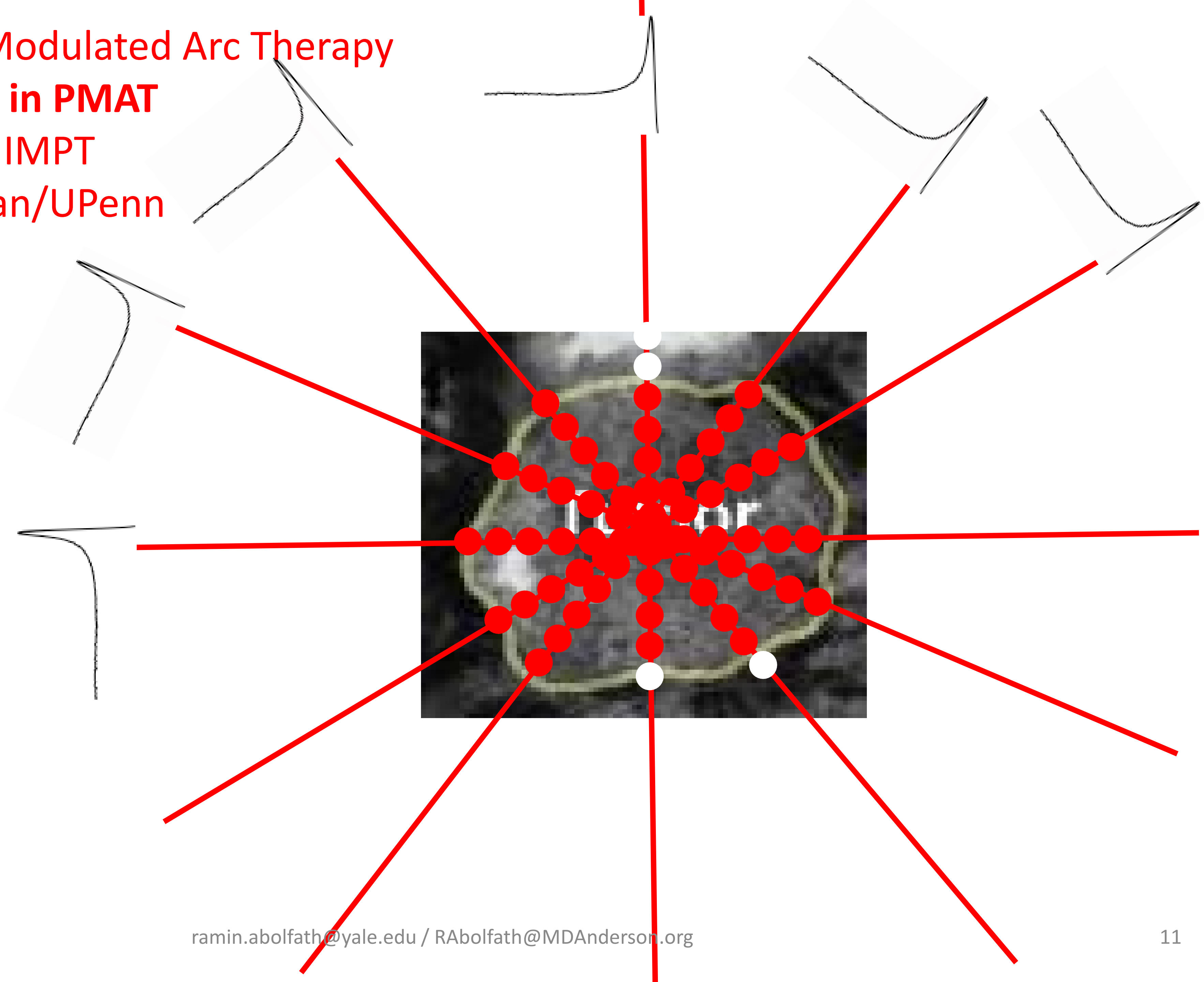
Possible Consequences of Variable RBE - Brain Necrosis in CNS Patients



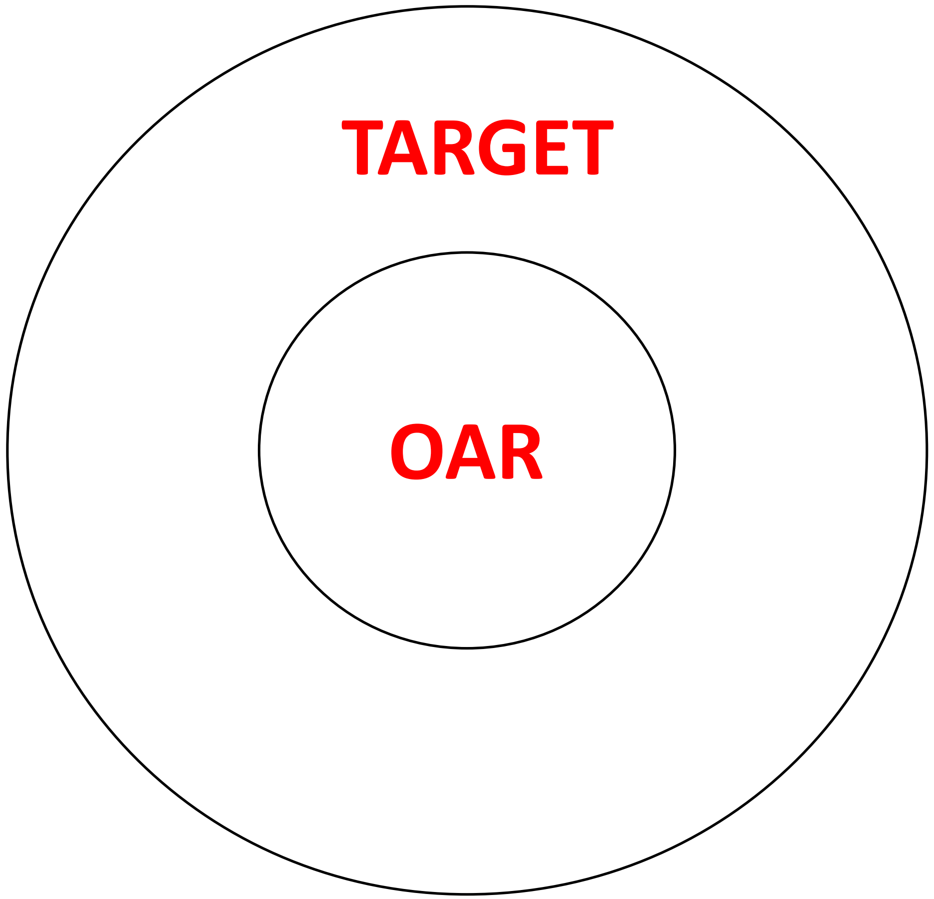
Excess dose with variable RBE - Prescription 52 Gy(RBE)

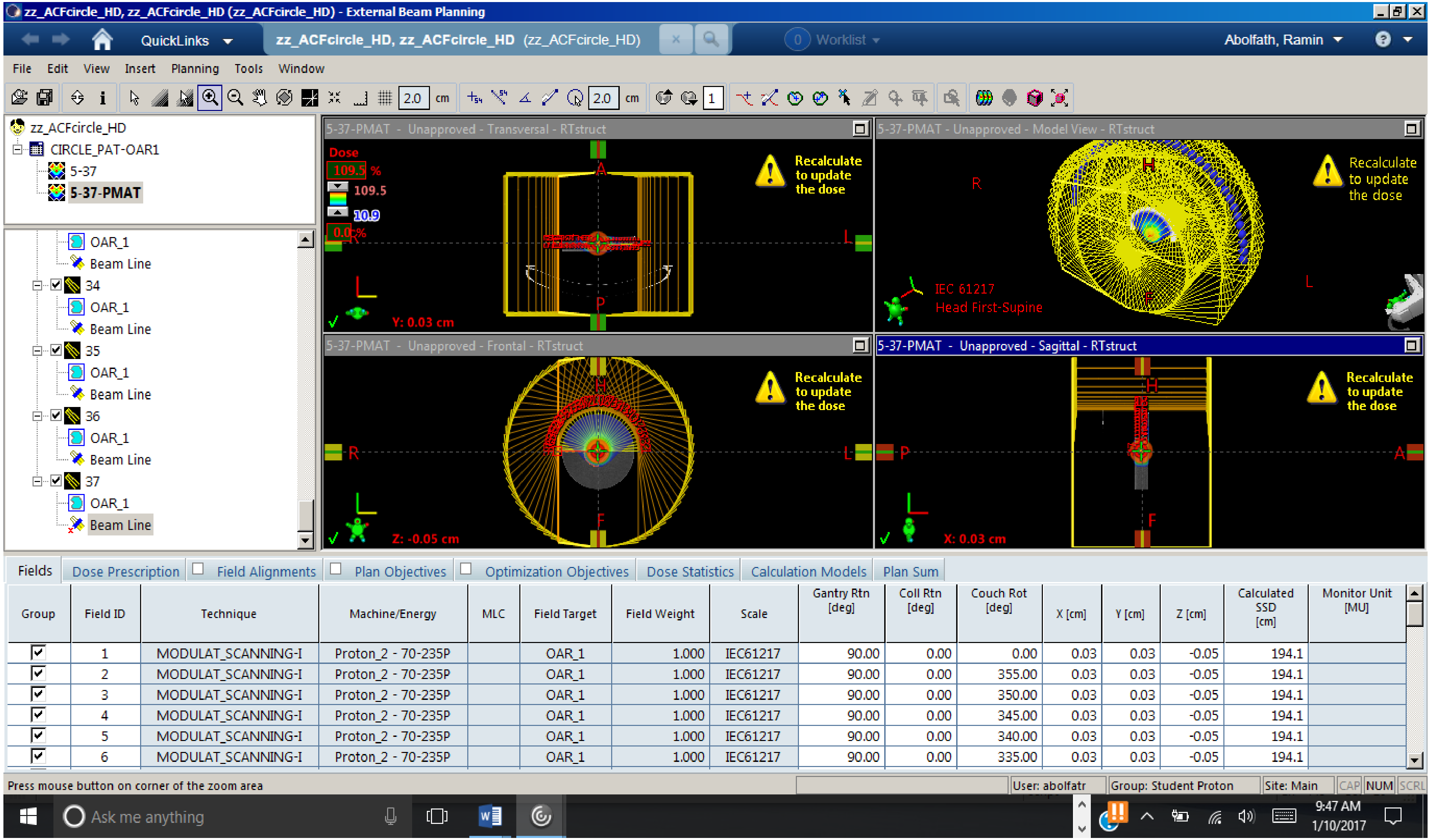
Spot-scanning Proton Modulated Arc Therapy

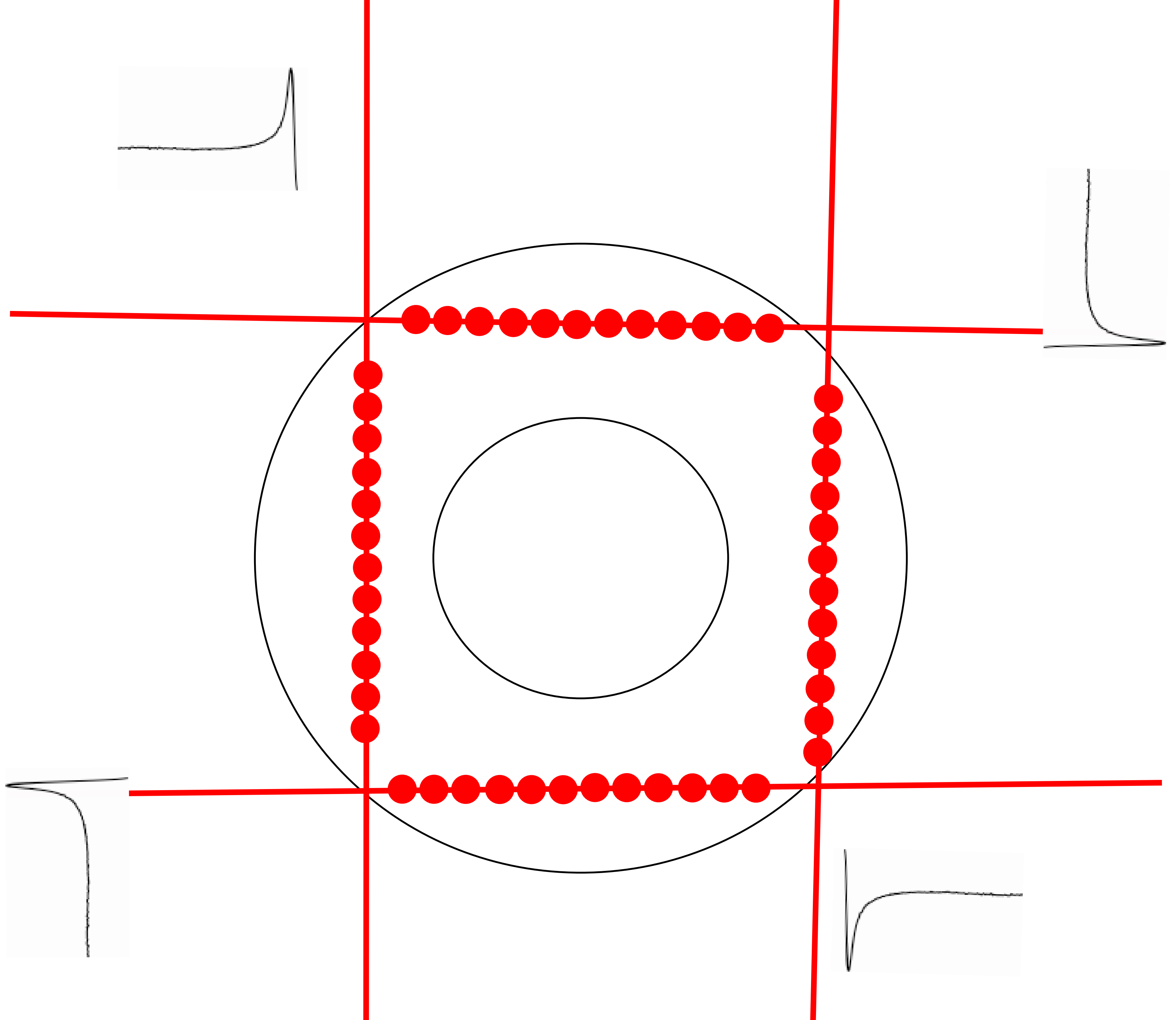
- Use of **single energy in PMAT** vs. multi-energies in IMPT
- Under progress Varian/UPenn



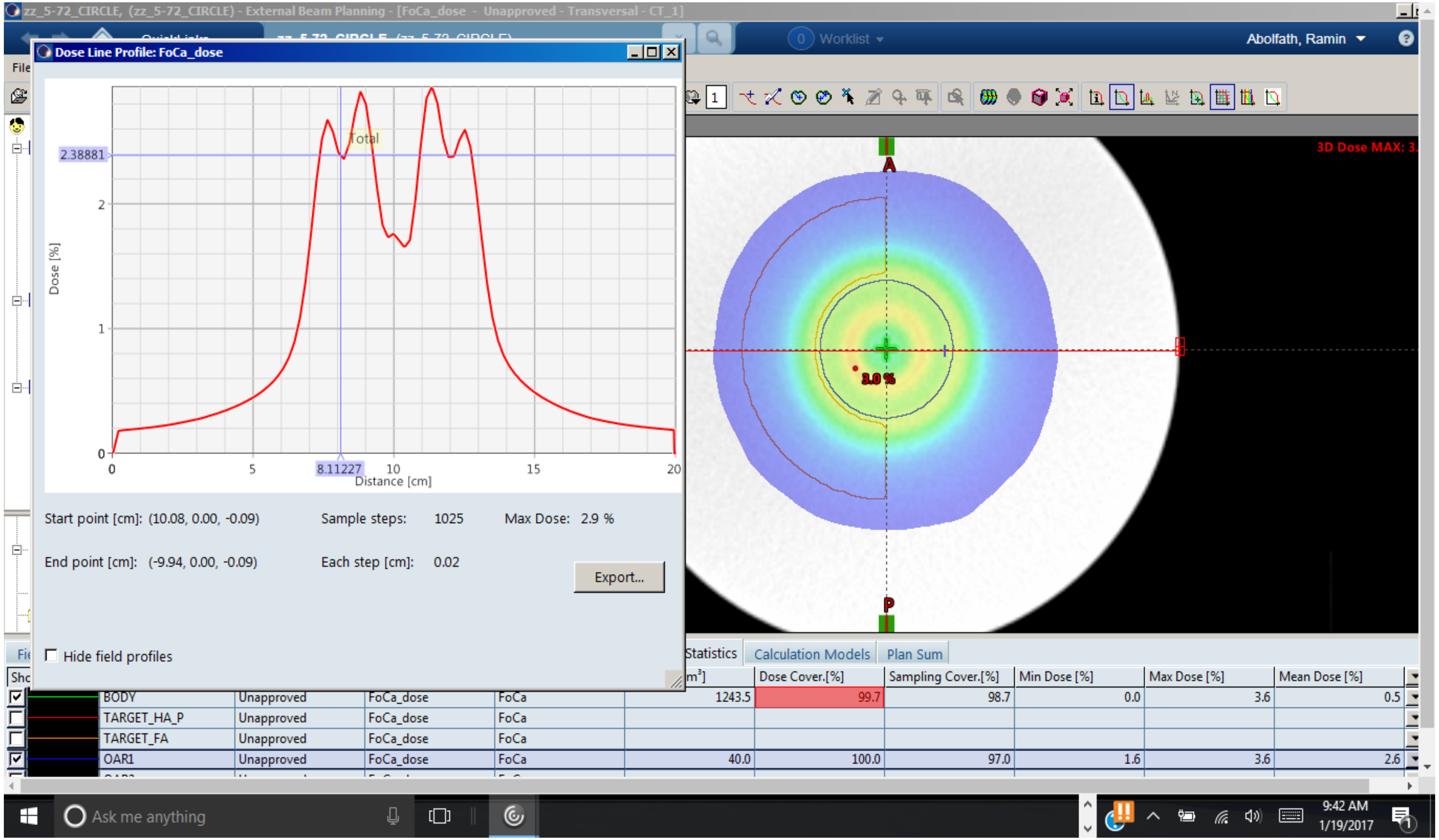
A simple case study for ARC therapy applicable in H&N




zz_ACFcircle_HD, zz_ACFcircle_HD (zz_ACFcircle_HD) - External Beam Planning
QuickLinks
zz_ACFcircle_HD, zz_ACFcircle_HD (zz_ACFcircle_HD)
Worklist
Abolfath, Ramin
File Edit View Insert Planning Tools Window
2.0 cm
2.0 cm
zz_ACFcircle_HD
CIRCLE_PAT-OAR1
5-37
5-37-PMAT
OAR_1
Beam Line
34
OAR_1
Beam Line
35
OAR_1
Beam Line
36
OAR_1
Beam Line
37
OAR_1
Beam Line
5-37-PMAT - Unapproved - Transversal - RTstruct
Dose
109.5 %
109.5
10.9
0.0 %
Recalculate to update the dose
Y: 0.03 cm
5-37-PMAT - Unapproved - Model View - RTstruct
Recalculate to update the dose
IEC 61217
Head First-Supine
5-37-PMAT - Unapproved - Frontal - RTstruct
Recalculate to update the dose
Z: -0.05 cm
5-37-PMAT - Unapproved - Sagittal - RTstruct
Recalculate to update the dose
X: 0.03 cm
Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum
Group | Field ID | Technique | Machine/Energy | MLC | Field Target | Field Weight | Scale | Gantry Rtn [deg] | Coll Rtn [deg] | Couch Rot [deg] | X [cm] | Y [cm] | Z [cm] | Calculated SSD [cm] | Monitor Unit [MU]
1 | MODULAT_SCANNING-I | Proton_2 - 70-235P | OAR_1 | 1.000 | IEC61217 | 90.00 | 0.00 | 0.00 | 0.03 | 0.03 | -0.05 | 194.1
2 | MODULAT_SCANNING-I | Proton_2 - 70-235P | OAR_1 | 1.000 | IEC61217 | 90.00 | 0.00 | 355.00 | 0.03 | 0.03 | -0.05 | 194.1
3 | MODULAT_SCANNING-I | Proton_2 - 70-235P | OAR_1 | 1.000 | IEC61217 | 90.00 | 0.00 | 350.00 | 0.03 | 0.03 | -0.05 | 194.1
4 | MODULAT_SCANNING-I | Proton_2 - 70-235P | OAR_1 | 1.000 | IEC61217 | 90.00 | 0.00 | 345.00 | 0.03 | 0.03 | -0.05 | 194.1
5 | MODULAT_SCANNING-I | Proton_2 - 70-235P | OAR_1 | 1.000 | IEC61217 | 90.00 | 0.00 | 340.00 | 0.03 | 0.03 | -0.05 | 194.1
6 | MODULAT_SCANNING-I | Proton_2 - 70-235P | OAR_1 | 1.000 | IEC61217 | 90.00 | 0.00 | 335.00 | 0.03 | 0.03 | -0.05 | 194.1
Press mouse button on corner of the zoom area
User: abolfatr
Group: Student Proton
Site: Main
CAP NUM SCRL
Ask me anything
9:47 AM
1/10/2017

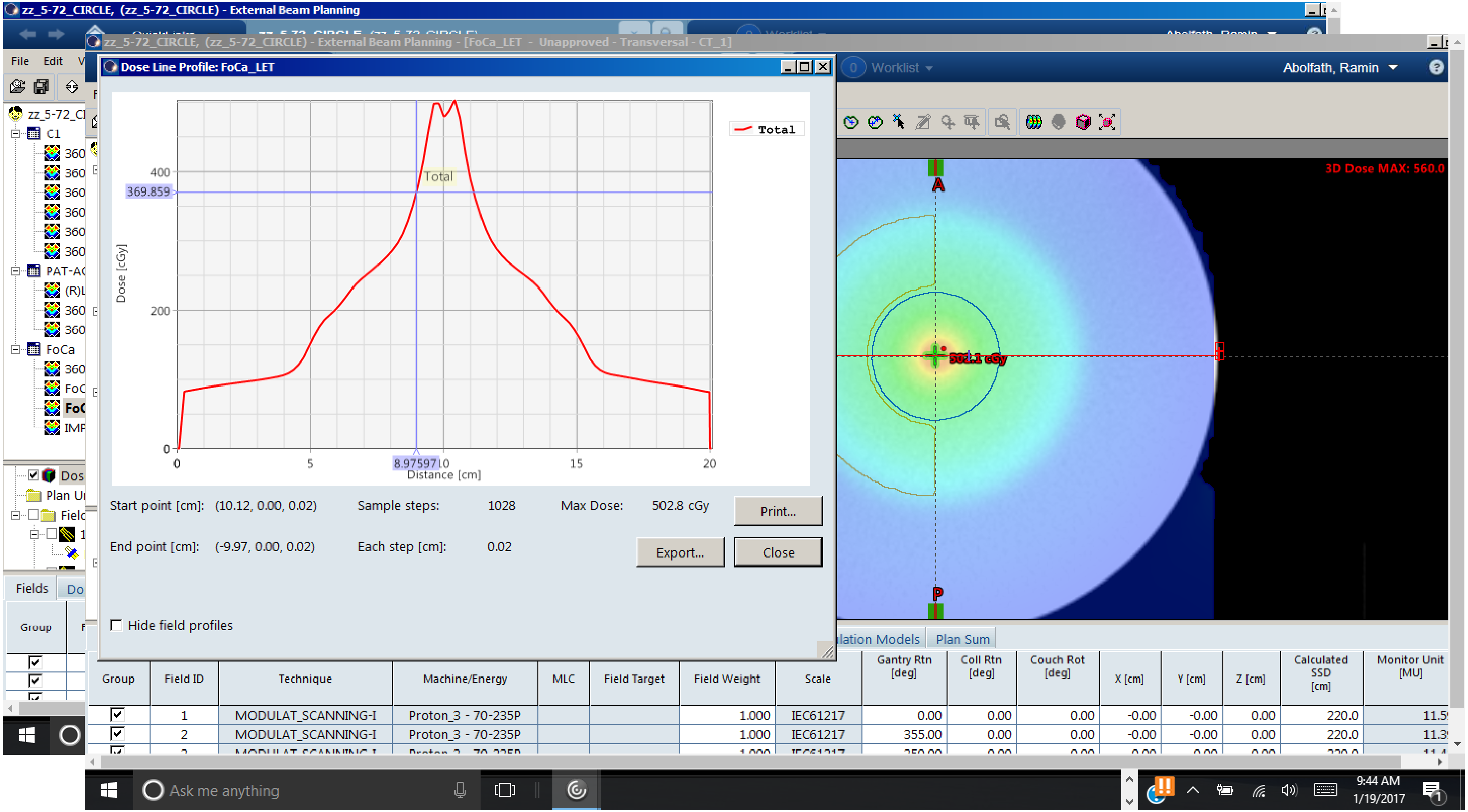


dose



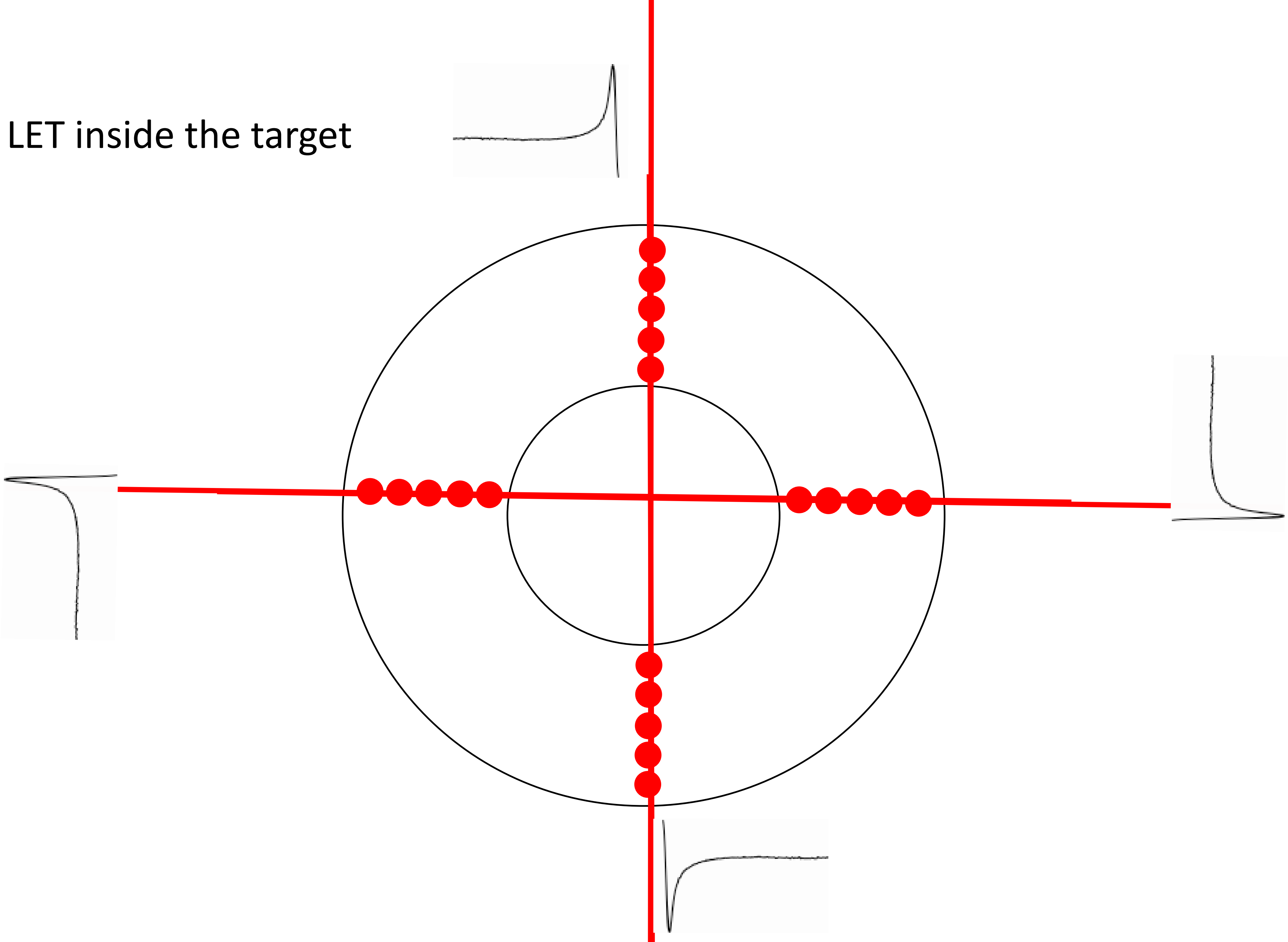
C:\Users\abolf\Desktop\HP Desktop3\4-UPenn\4-FoCa\FoCa_patients\zz_5-72_CIRCLE_RBE\PMAT

LET



zz_5-72_CIRCLE, (zz_5-72_CIRCLE) - External Beam Planning
zz_5-72_CIRCLE, (zz_5-72_CIRCLE) - External Beam Planning - [FoCa_LET - Unapproved - Transversal - CT_1]
Dose Line Profile: FoCa_LET
Total
400
369.859
200
0
Dose [cGy]
0
5
8.97597
10
15
20
Distance [cm]
Start point [cm]: (10.12, 0.00, 0.02)
End point [cm]: (-9.97, 0.00, 0.02)
Sample steps: 1028
Each step [cm]: 0.02
Max Dose: 502.8 cGy
Print...
Export...
Close
Hide field profiles
Worklist
Abolfath, Ramin
3D Dose MAX: 560.0
A
P
502.1 cGy
Plan Sum
Fields
Group
Field ID
Technique
Machine/Energy
MLC
Field Target
Field Weight
Scale
Gantry Rtn [deg]
Coll Rtn [deg]
Couch Rot [deg]
X [cm]
Y [cm]
Z [cm]
Calculated SSD [cm]
Monitor Unit [MU]
1 MODULAT_SCANNING-I Proton_3 - 70-235P 1.000 IEC61217 0.00 0.00 0.00 -0.00 -0.00 0.00 220.0
2 MODULAT_SCANNING-I Proton_3 - 70-235P 1.000 IEC61217 355.00 0.00 0.00 -0.00 -0.00 0.00 220.0
Ask me anything
9:44 AM
1/19/2017

To paint LET inside the target



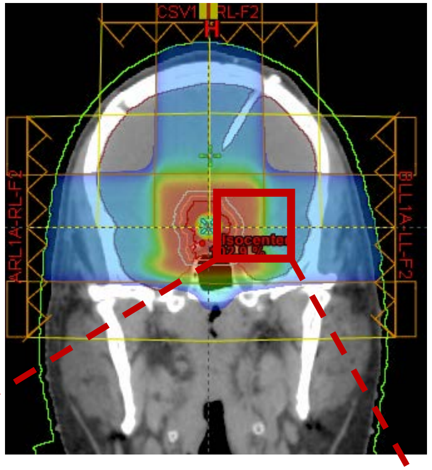
How can we account for the variability in RBE?

What would be appropriate model?

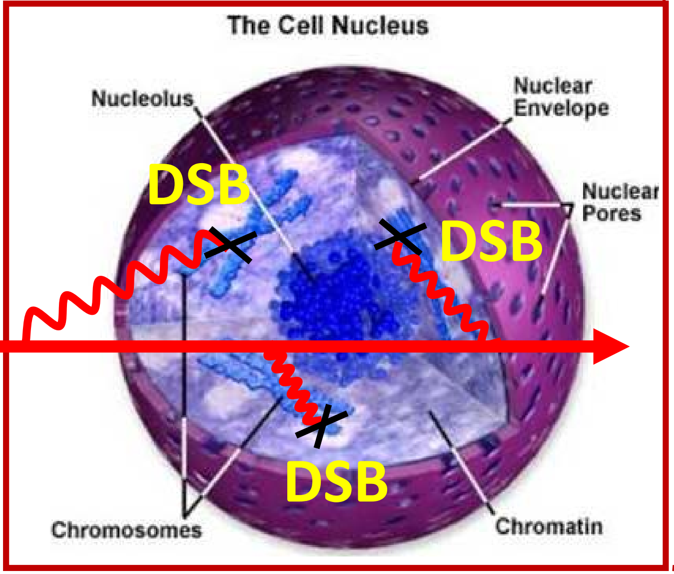
Multi-Scale RBE Modeling: $cm \rightarrow \mu m \rightarrow nm$

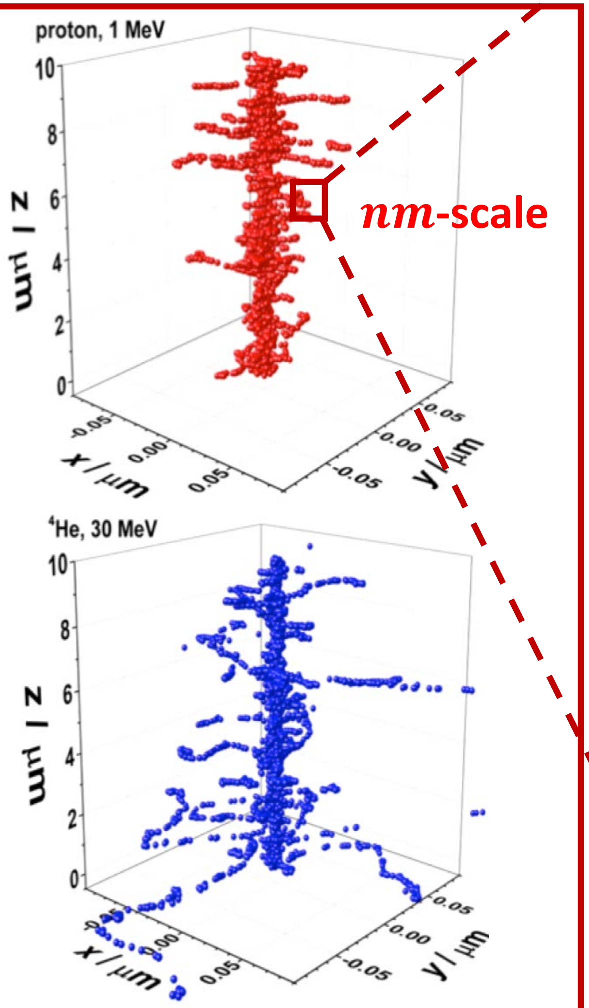
Radio-biological response is a collective macroscopic phenomenon that is resemblance of microscopic energy deposition events; like superconductivity and magnetism so we would start from nm-track structure

Atoms color code: C, O, N, P, H



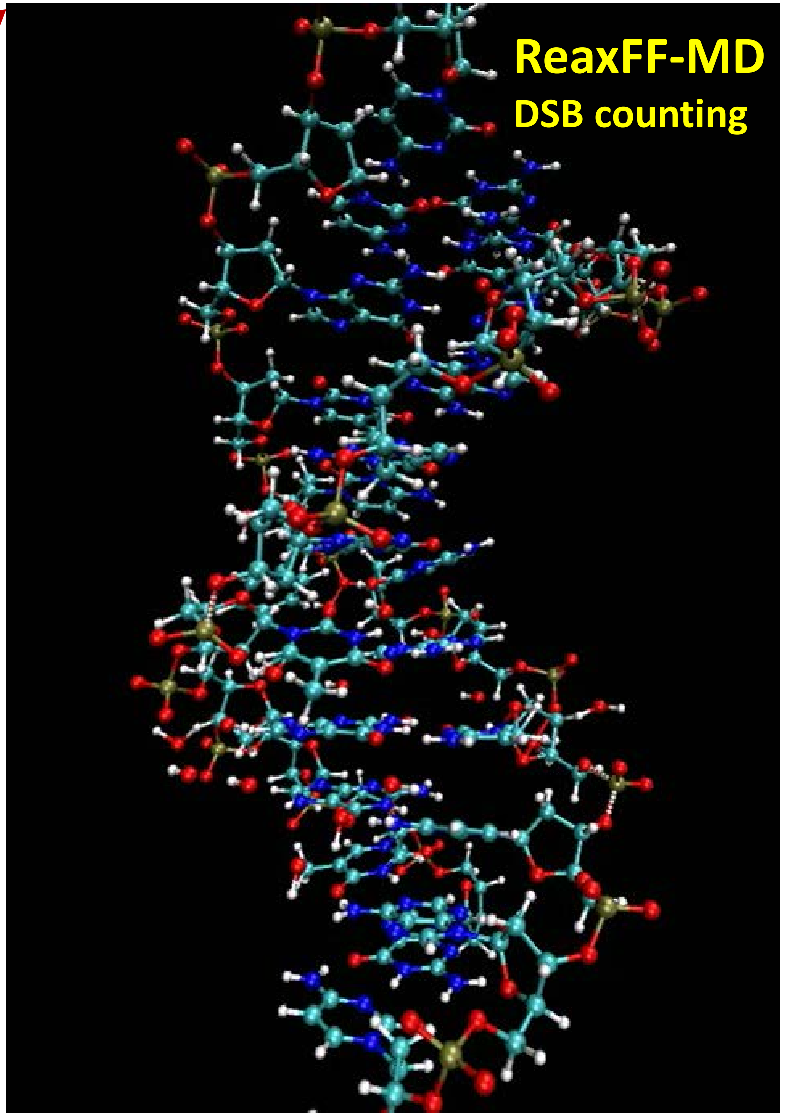
μm-scale



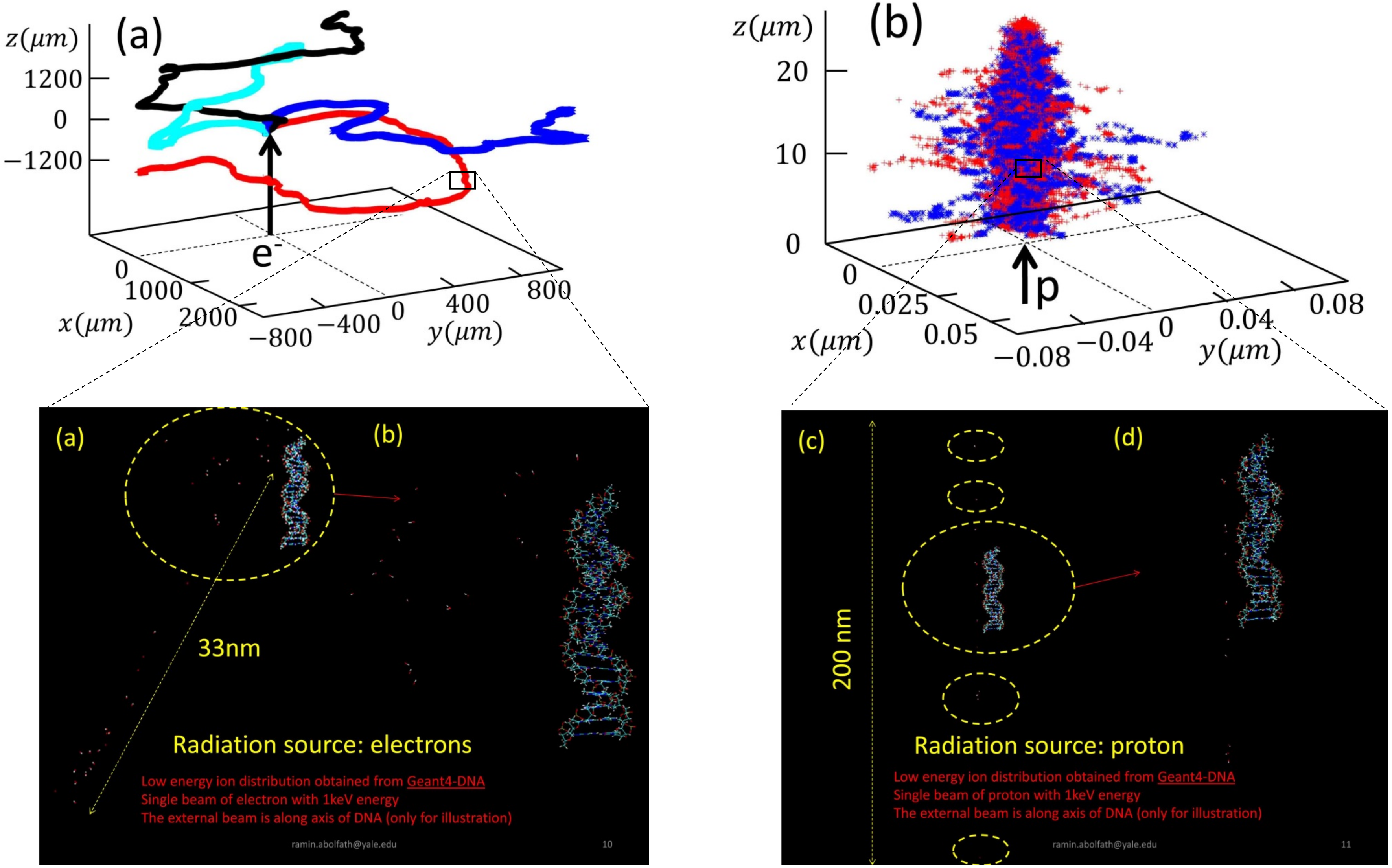


nm-scale

Geant4-DNA



Track structures and ion coordinates calculated by MC (Geant4-DNA)



Computational challenges – requires data mining

- A single track of 1MeV electron/proton contains ~ 50,000 ion-coordinates

RBE from first principle multi-scale modeling – data mining

IOP Publishing — Physics in Medicine and Biology

Phys. Med. Biol. 58 (2013) 7143–7157 doi:10.1088/0031-9155/58/20/7143

A molecular dynamics simulation of DNA damage induction by ionizing radiation

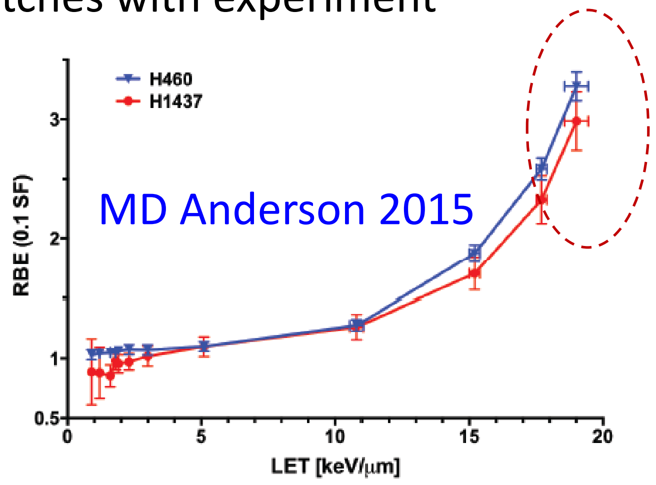
Ramin M Abolfath, David J Carlson, Zhe J Chen and Ravinder Nath

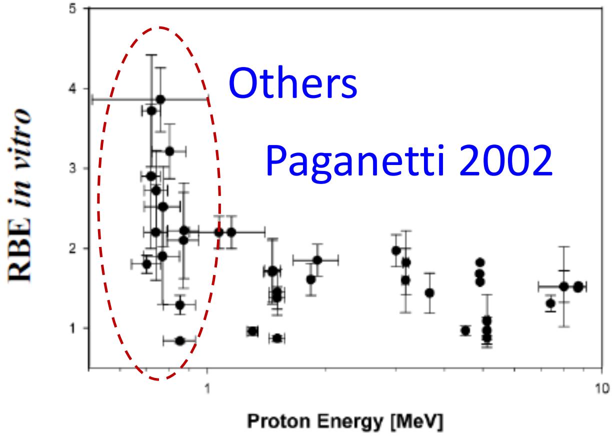
Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT 06520-8040, USA

$$RBE_{DSB} \sim 4$$

Experiments

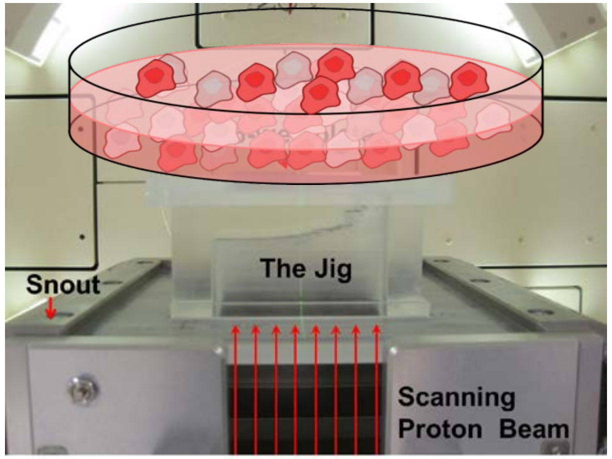
Prediction matches with experiment

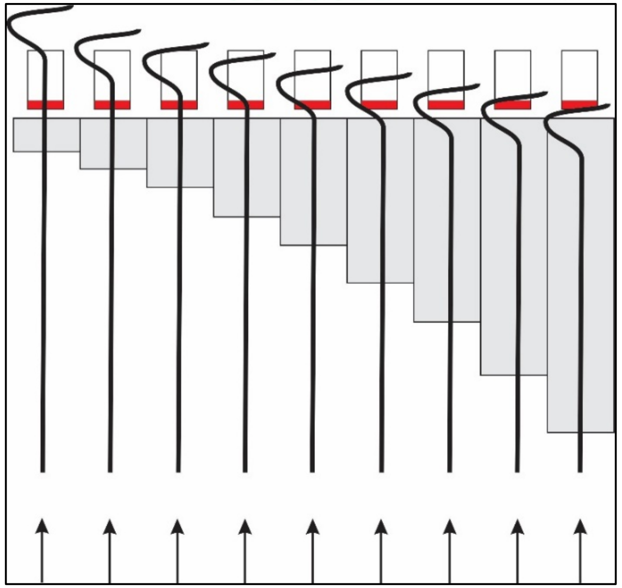


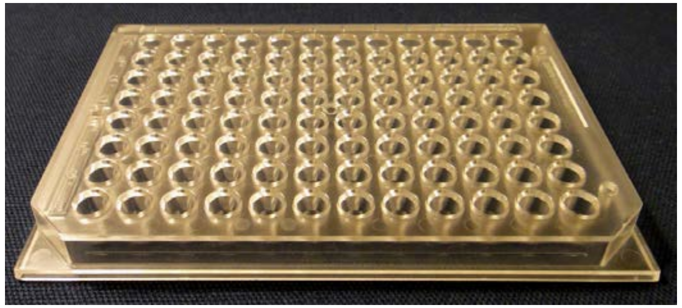


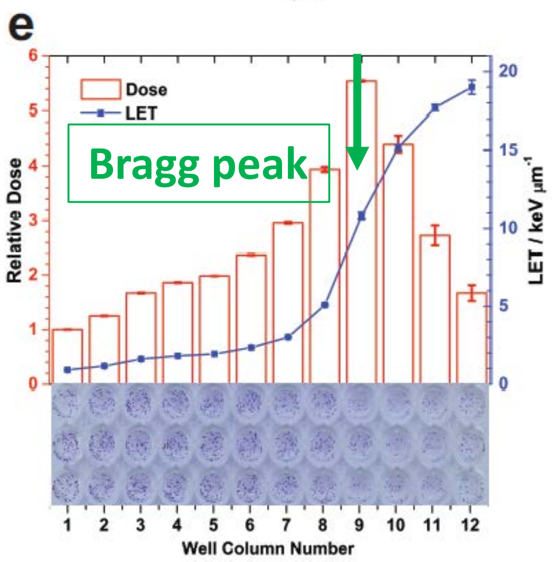
Spatial Mapping of the RBE of Scanned Particle Beams

High Precision, High Throughput Experiments (Guan, et al 2015)

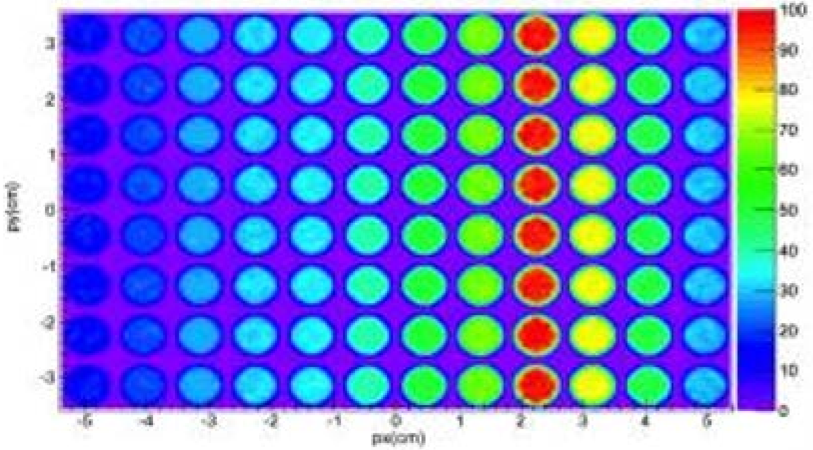








96-well plates



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Spatial mapping of the biologic effectiveness of scanned particle beams: towards biologically optimized particle therapy

Fada Guan[1]*, Lawrence Bronk[2]*, Uwe Titt[1], Steven H. Lin[2,3], Dragan Mirkovic[1], Matthew D. Kerr[1], X. Ronald Zhu[1], Jeffrey Dinh[2], Mary Sobieski[4], Clifford Stephan[4], Christopher R. Peeler[1], Reza Taleei[1], Radhe Mohan[1] & David R. Grosshans[2,3]

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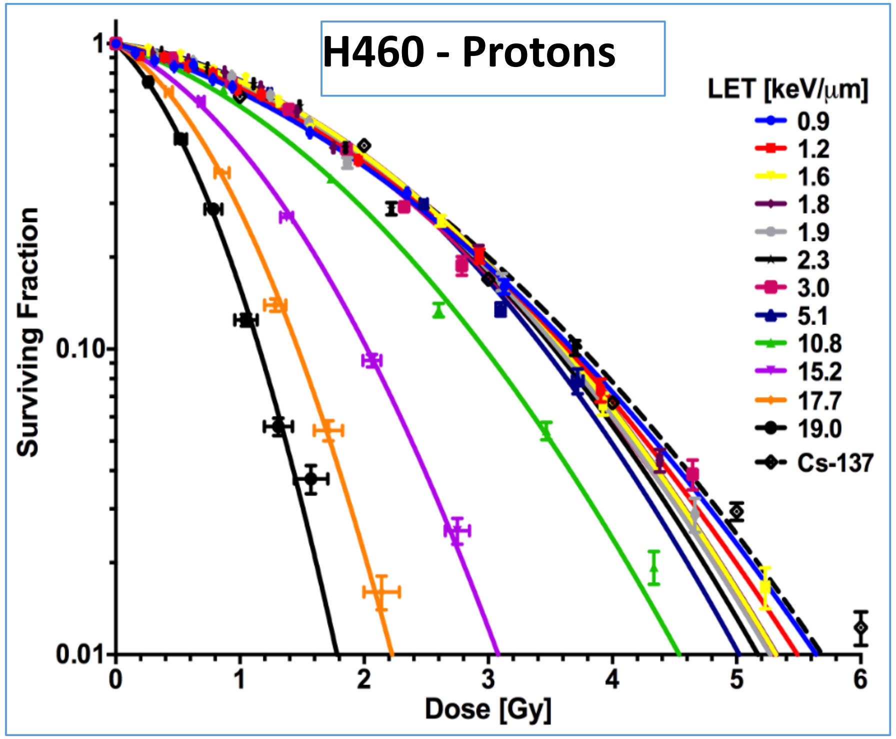
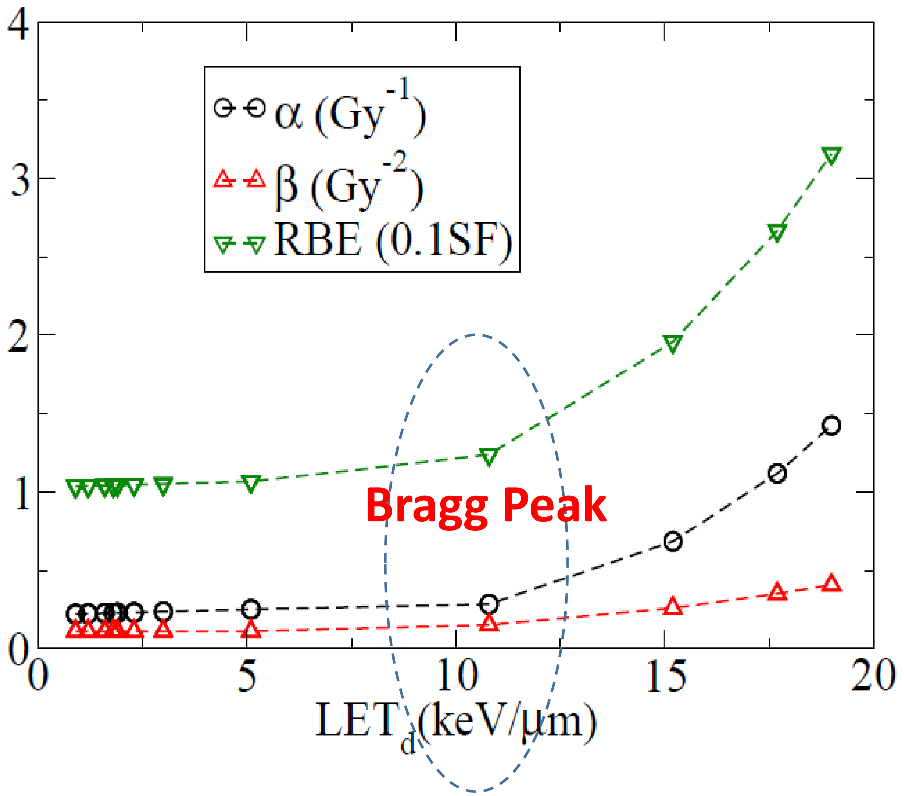


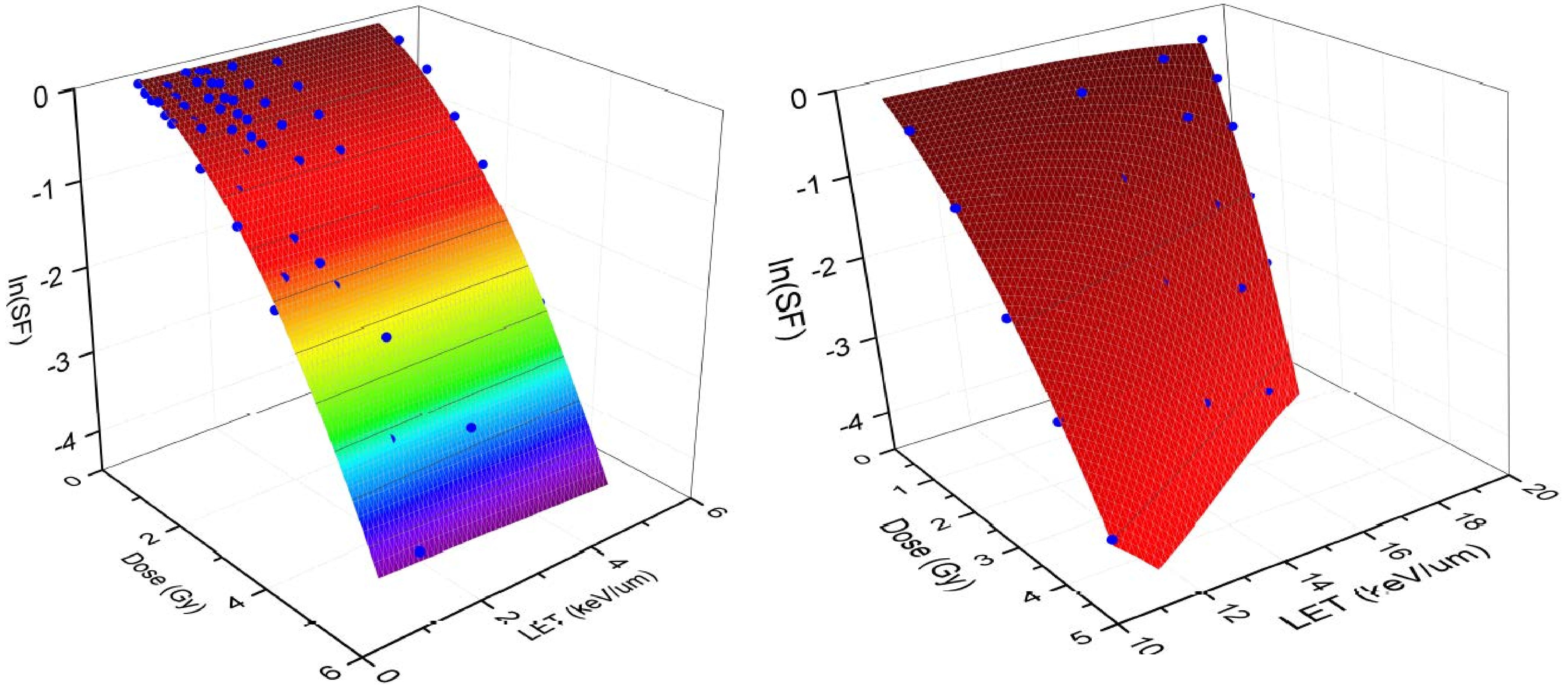


$$-\ln(S) = \alpha D + \beta D^2$$

$$\alpha(LET) = \alpha_0 + \alpha_1 \times LET + \alpha_2 \times LET^2 + \alpha_3 \times LET^3 + \cdots$$
$$\beta(LET) = \beta_0 + \beta_1 \times LET + \beta_2 \times LET^2 + \cdots$$

Fitting the experimental data – Global 3D surface fitting

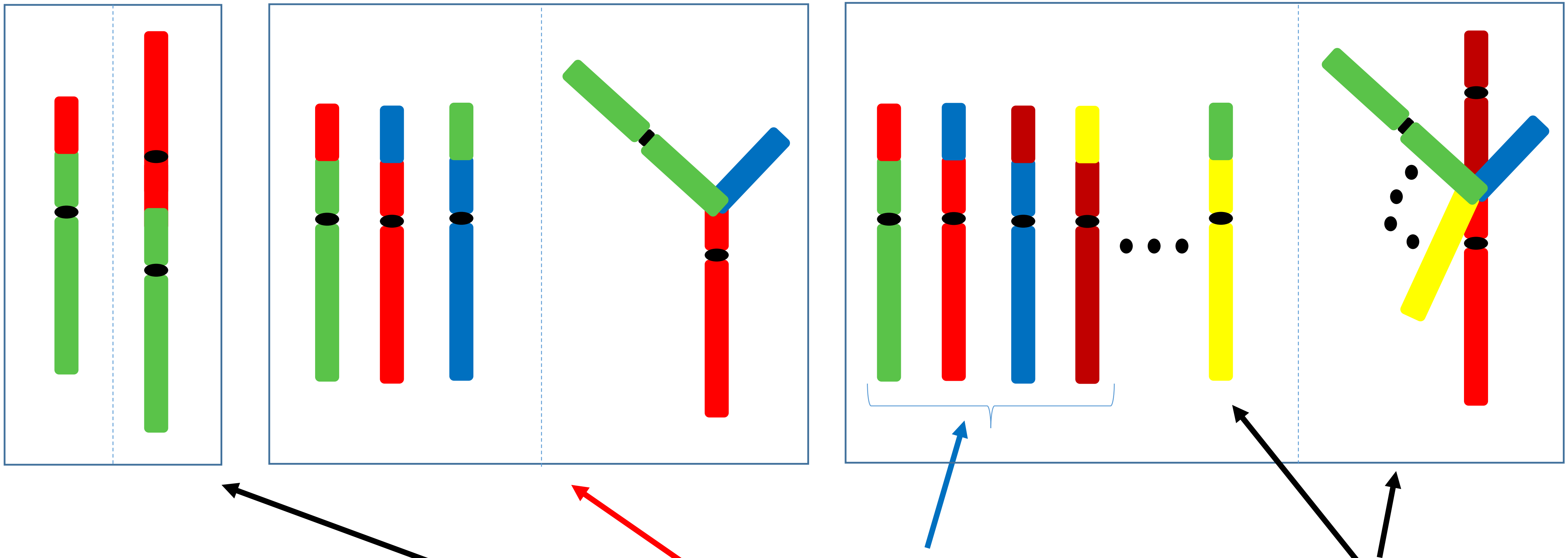
- Making correlation among the curves



Cell survival fraction for low (left panel) and high (right panel) LETs. The blue dots are the experimental data.

Non-linearity in RMF model

Diagrammatic Representation of non-linear LETs terms; perturbative expansion



Pair   Triple   Quadruple $+ \cdots$ N-tuple end-joining

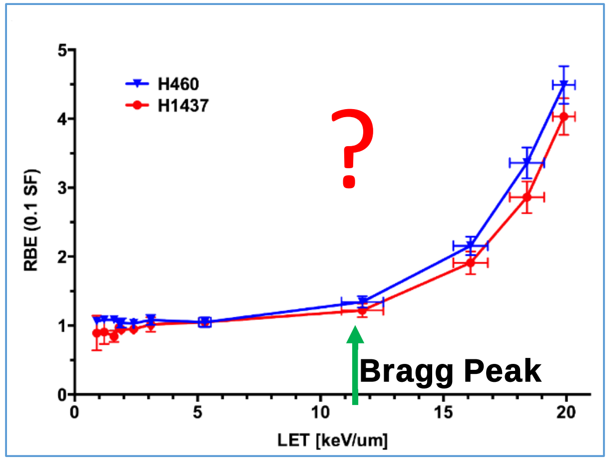
$$\alpha = \alpha_0 + \alpha_1 \times LET + \alpha_2 \times LET^2 + \alpha_3 \times LET^3 + \cdots$$

$$\beta = \beta_0 + \beta_1 \times LET + \beta_2 \times LET^2 + \cdots$$

Abolfath *et al.* unpublished

Summary
Limitations of Current Proton RBE Models

- Based on insufficient and inconsistent data and fitting procedures
- Assumption of RBE as linear (or near linear) function of LET
- LET dependence on averaged dose or fluence



Current Models Likely Underestimate RBE Especially at Points Around the Bragg Peak

Recommendation if RBE $\neq$ 1.1; variable RBE

- Avoidance of beam directions for which distal edge is in or close to a sensitive critical normal structure
- Deliver conformal dose and LET distribution within the target
- To achieve these goals direct measurement of LET is needed
- A direct measurement and modeling to establish accurate correlation between RBE and LET

Acknowledgements

My past mentors:

Radhe Mohan & Lech Papiez

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- Rob Stewart, Dave Carlson, Alejandro Carabe, Ravi Nath, Harald Paganetti, Uwe Titt , Jan Schuemann, …

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- Michael Story, David Chen, Bob Timmerman, Peter Glazer, Sara Rockwell, Reinhard Kodym, David Grosshans, …

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- Varian – PMAT project
- St. Vincent’s hospital at Bridgeport, CT

Our work submitted recently to Sci. Rep. is available
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A model for relative biological effectiveness of therapeutic proton beams based on a global fit of cell survival data

Ramin Abolfath[1], Christopher R. Peeler[1], Mark Newpower[1], Lawrence Bronk[1], David Grosshans[2], and Radhe Mohan[1]

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Thank You