LOMA LINDA UNIVERSITY HEALTH

Introduction: The Clinical and Radiobiological Perspective

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Disclosure/Conflict of Interest

Nothing to disclosure/no conflict

My Perspective

- 20+ years clinical experience in proton therapy including proton radiosurgery (1990-2014), Dept. Radiation Medicine, LLUMC
- 30+ years of experience in medical physics research related to proton therapy
- Previous Grant Funding: Nanodosimetry (U.S. Army, 1998-2003), Biologically weighted Quantities in Radiation Therapy (BioQuaRT, EMRP, 2012-2015)
- Future NIH Grant Funding 2022-2026: Ionization Detail – Biologically based treatment planning for particle therapy beyond (R01, 4th percentile)

Outline

- A short history of RBE in proton treatment planning
- Why we do not live in an ideal proton planning world
- The best we can do today and what we may do in the future

What I assume you know

- The definition of RBE
- How RBE depends on LET and dose
- How RBE depends on LQ model parameters, which depend on tissue type
- That RBE/LET increases with decreasing particle energy
- That particles with the same LET have different RBE

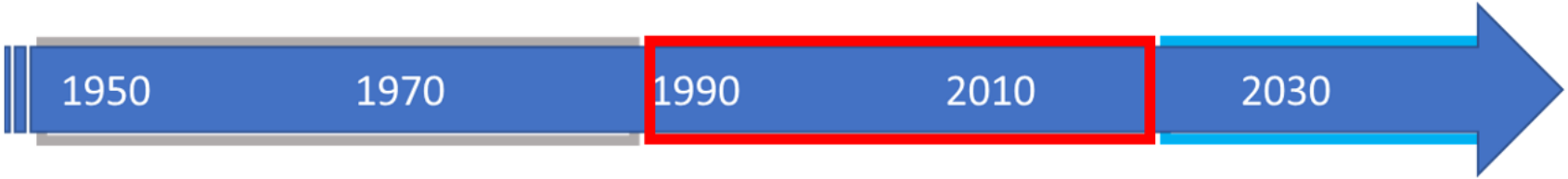
Biologically Weighted Radiation Dosimetry is Important!

"The onus, …, rests with the research community to conduct thorough and systematic dosimetry and radiobiology inter-comparisons between different centers to facilitate a meaningful comparison of all the experimental and clinical results accrued at each center. " Peter Binns, 2004

Binns PJ, et al Appl Radiat Isot. 2004
doi: 10.1016/j.apradiso.2004.05.044
PMID: 15308159

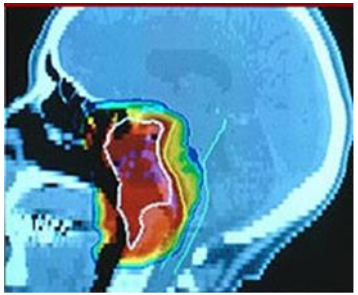
History of clinical RBE in Proton Therapy

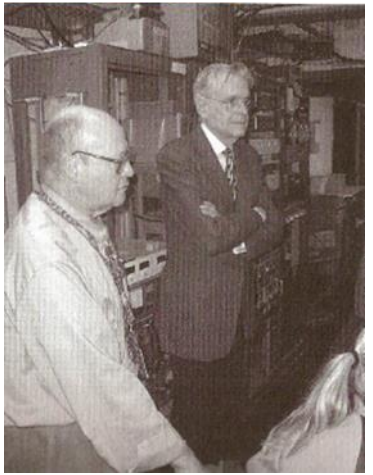
- The past (early history of RBE and proton therapy)
- The present (RBE = 1.1, but are aware of variable RBE)
- The future (treatment planning based on biological weighting)



Harvard Cyclotron goes Medical: MGH (1970-2001), RBE = 1.1

- With fading Harvard Cyclotron physics research, medical physicists and radiation oncologists took over in the early 1970s, initially with radiobiology studies (RBE), then with first clinical trials in chordomas/chondrosarcomas of the base of skull, and treatment planning technology
- Herman Suit (seen with John Munzenrider on the right) opted for a 'clinical' RBE of 1.1 based on the exist-ng radiobiological evidence
- He argued that a higher RBE, while safer, would risk that we underdose tumors and miss the benefit

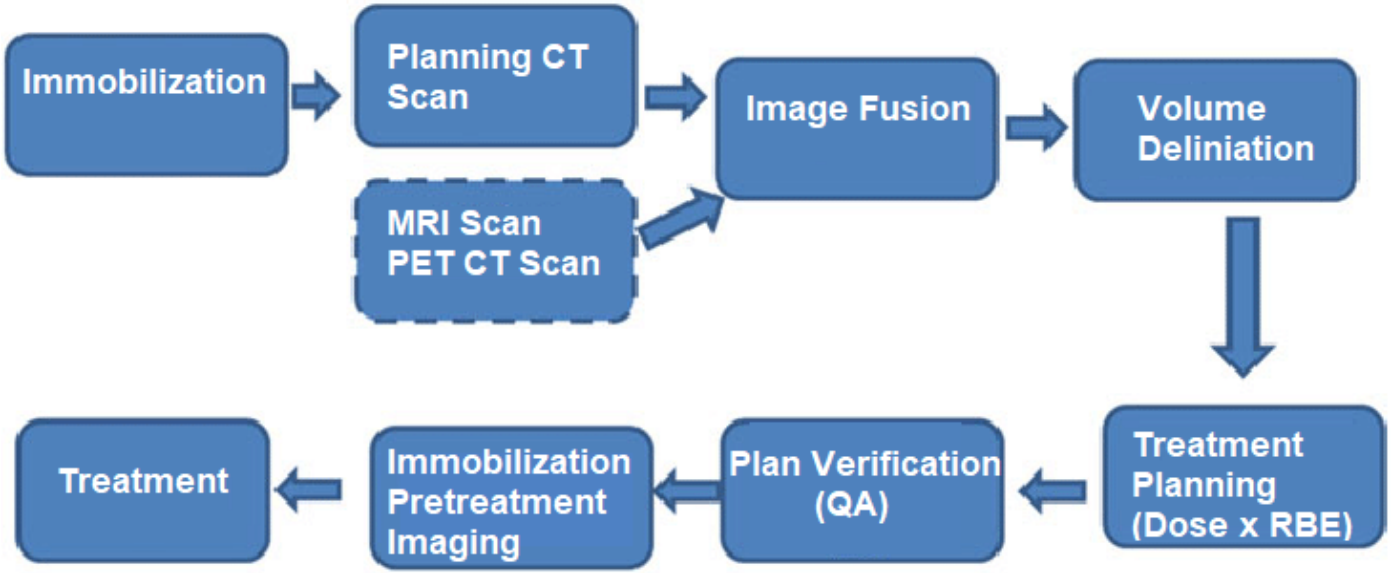




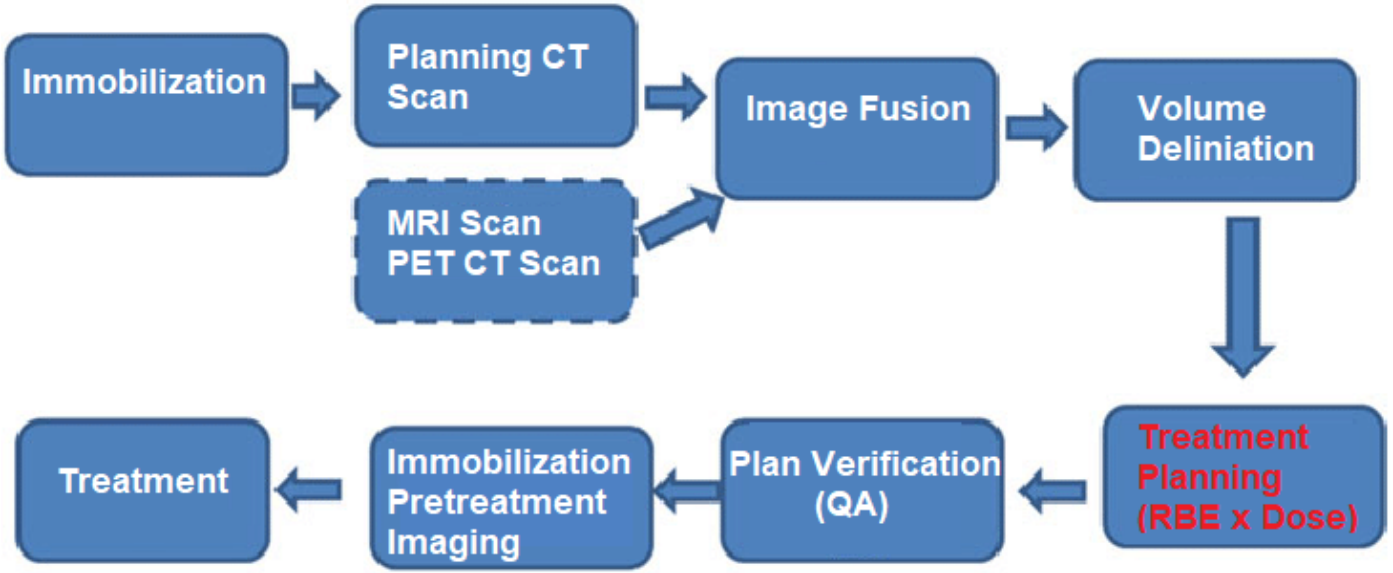
1985-1990 – Proton Therapy Moves to Loma Linda University Medical Center

- In 1985, Dr. Phil Livdahl, Director of Fermilab, embraced the idea of proton therapy in a hospital. He wrote a detailed proposal and hosted a week-long workshop with about 100 physicians, physicists and engineers to discuss a medical facility.
- His efforts led Dr. James M. Slater of the Loma Linda University Medical Center to petition the DOE to build the LL medical proton synchrotron, that is still in operation
- Treatment planning continued with a constant RBE of 1.1

Proton Treatment Planning Workflow

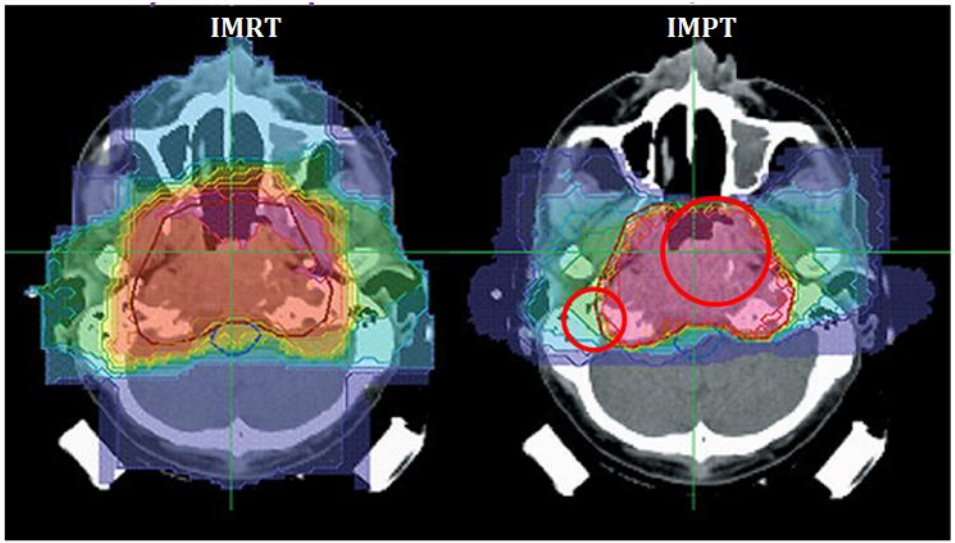


Proton Treatment Planning Workflow



RBE = 1.1.

Treatment Planning Example



~ Is the IMPT dose really biologically uniform?

~ Are there hot or cold spots in biologically-weighted dose?

~ Is the dose distributions geometrically accurate?

Proton Treatment Planning in the Ideal World

- The treatment planning system (TPS) must be approved for clinical use (FDA approval in the U.S.)
- Ideally the treatment plan would be taking into account changes in biologically weighted dose (RBE weighting) with beam depth
- Dose distributions from all beams (typically 2-4) need to be combined and optimized for biologically weighted dose planning
- Treatment planning should optimize the microscopic dose, ideally at the DNA level (nanoscopic dose) for uniform effect in a uniform biological system (tumor or normal tissue)
- A critical constraint is a minimal biological effective dose in the tumor and subthreshold dose for complications in serial OARs or a subthreshold number of FSUs receiving above threshold dose in parallel OARs

Proton Treatment Planning in the Real World

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Clinical use and future requirements of relative biological effectiveness: Survey among all European proton therapy centres

Lena Heuchel[a], Christian Hahn[a,b,c], Jörg Pawelke[b,d], Brita Singers Sørensen[e,f], Manjit Dosanjh[g,h], Armin Lühr[a,*]

» Biologically weighted TP is currently a ‘hot topic’, discussed in publications and at medical physics meetings

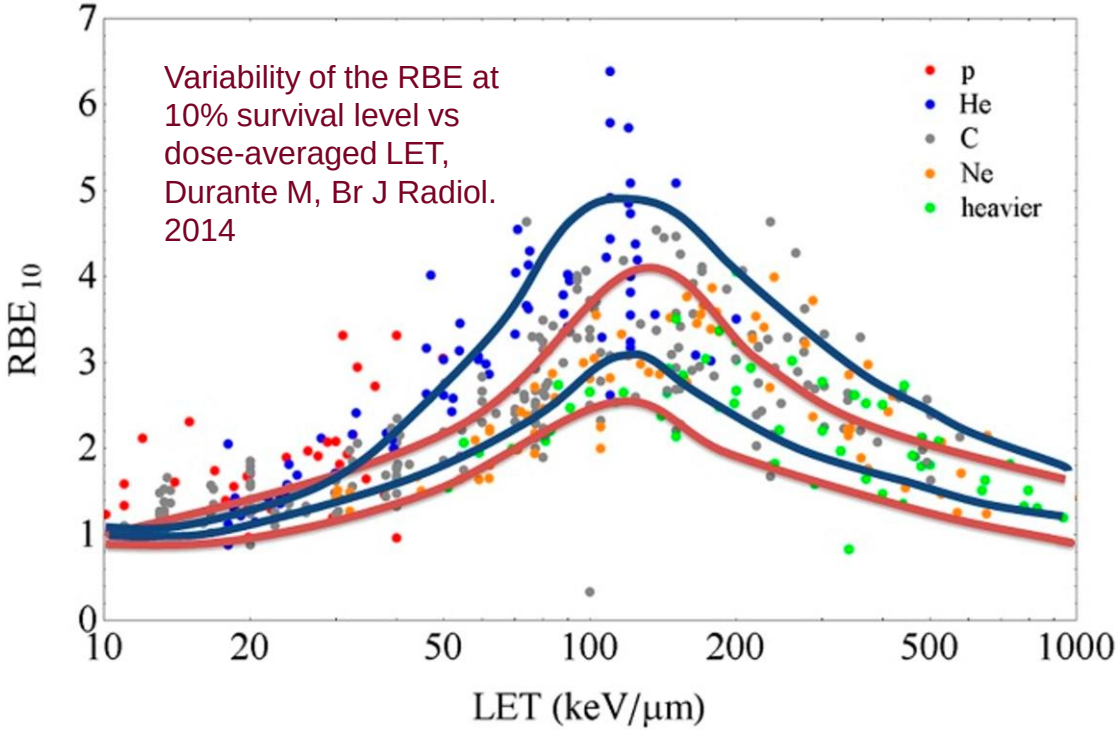
» Discussed solutions range from using RBE models to physical quantities of radiation quality such as linear energy transfer (LET)

Biologically Weighted Robust Planning of Proton Therapy: Knowledge Gaps, Controversies and Solutions

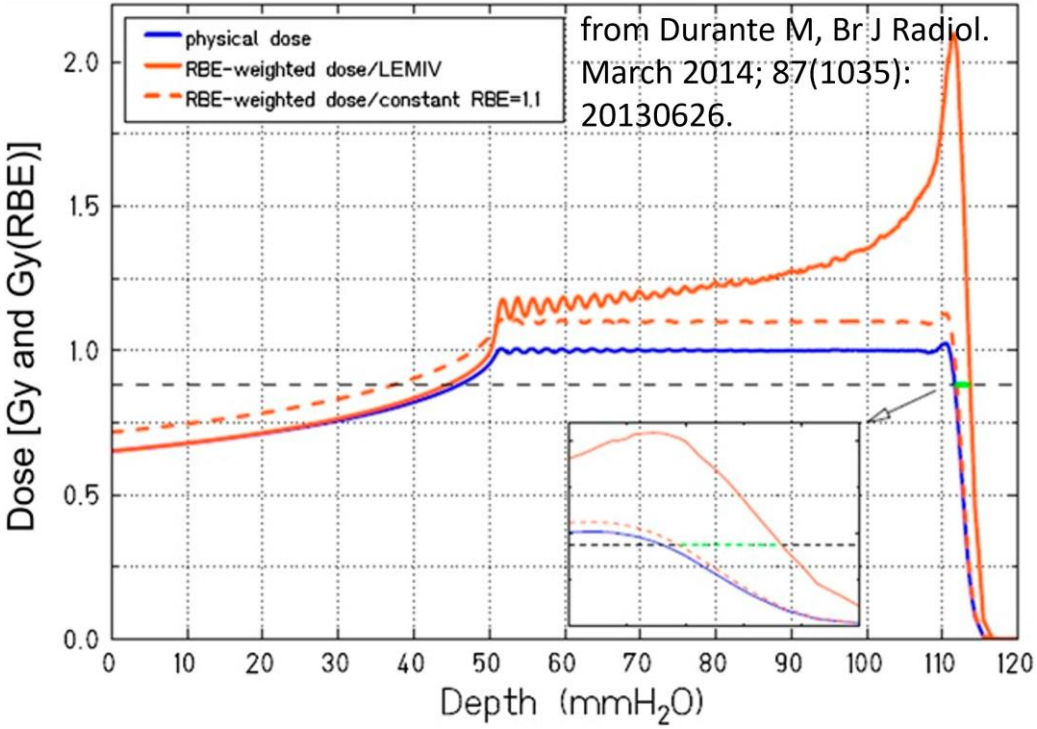
W Liu[1]*, R Schulte[2]*, R Mohan[3]*, K Parodi[4]*, A McNamara[5]*, (1) Mayo Clinic Arizona, Phoenix, AZ, (2) Loma Linda University, Grand Terrace, CA, (3) UT MD Anderson Cancer Center, Houston, TX, (4) Ludwig-Maximilians-Universitat Munchen, Garching B. Munich,DE, (5) Harvard / MGH, Boston, MA

W Liu R Schulte R Mohan K Parodi A McNamara

RBE vs. LET is (Very) Uncertain

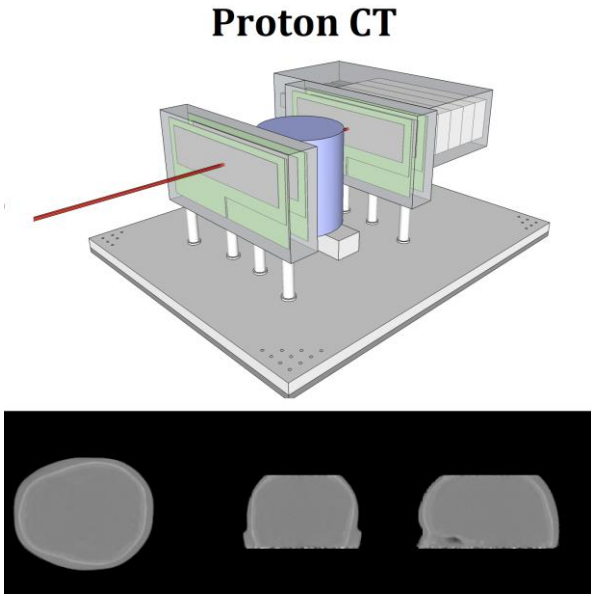


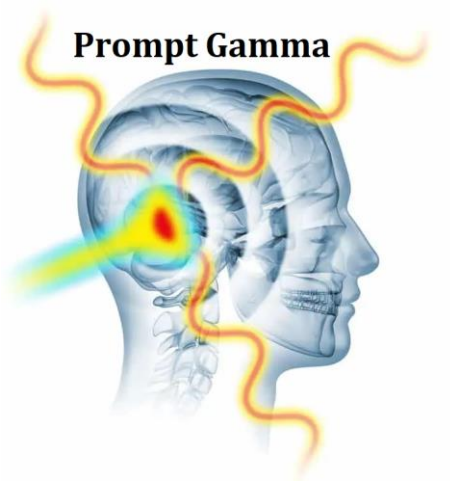
RBE and Range Uncertainties Interact



from Durante M, Br J Radiol. March 2014; 87(1035): 20130626.

Range Uncertainty Mitigation





~ New approaches to mitigate range uncertainties before or during treatment are under development

~ Prompt gamma in vivo monitoring and proton CT (pCT) are 2 examples

~ This will allow better geometric accuracy of the dose distribution

Cellular Dose Response is Non-linear and Depends on Radiation Quality

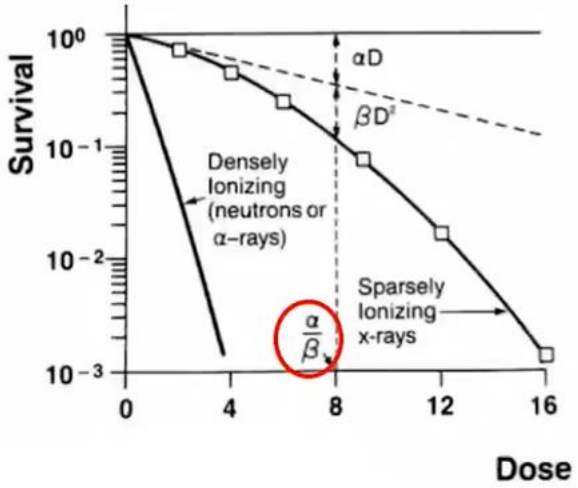
Linear Quadratic (LQ) Model

Aimee McNamara 2020

Assumption – two components to cell killing by IR
One (α) proportional to dose
One (β) proportional to square of the dose

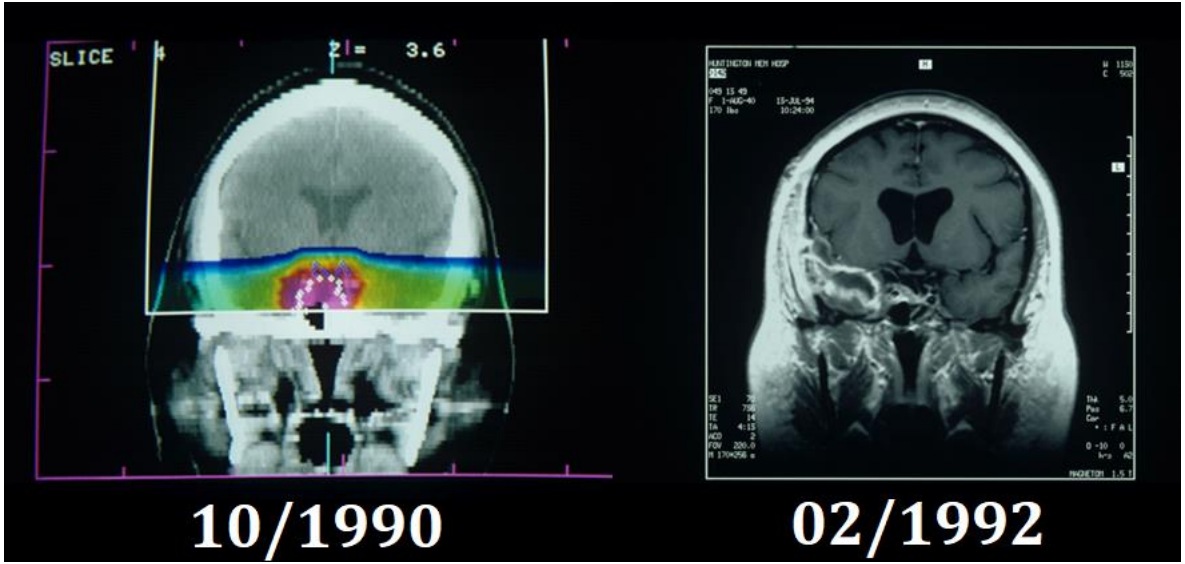
$$SF = e^{-(\alpha D + \beta D^2)}$$

α = initial slope at low doses
β = slope at high doses
α/β ratio = dose at which linear and quadratic components are equal (describes the "curviness" of the survival curve)



Phenomenological models can predict RBE as function of cell-type, O2 status, LET, and dose per fraction, however their prediction for individual patients is uncertain. A mechanistic modeling approach may increase accuracy.

RBE Uncertainty – Clinical Consequences

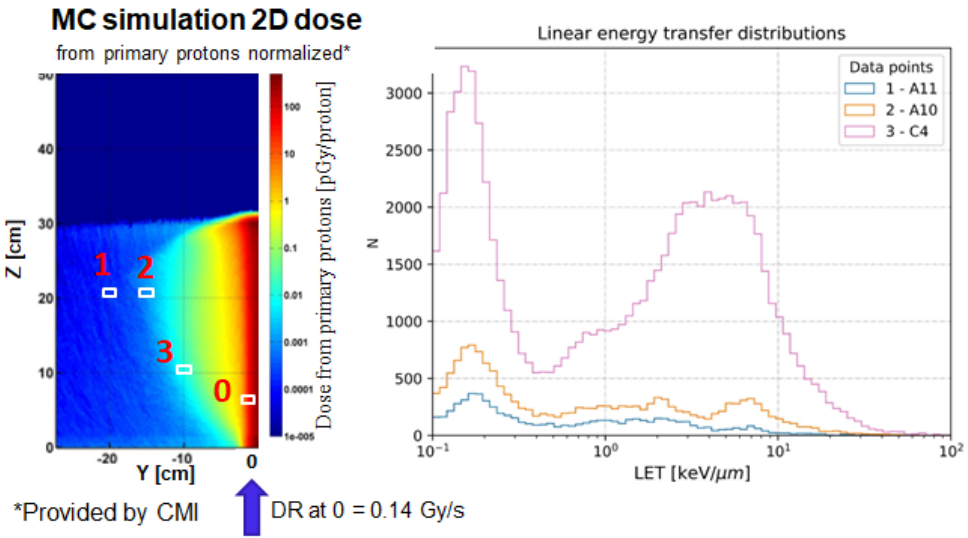


Pituitary adenoma, 50 Gy (RBE), 25 fx)

From Absorbed Dose to Microscopic Dose Quantities in Proton Planning

- Absorbed dose to water is the anchor of external radiation dosimetry, but known to have different biological effects according mean energy deposited per track length (LET) or the stochastic spatial distribution of deposited energy in
  - ~ Cells -> *Microdosimetry*
  - ~ Subcellular volumes (in particular DNA) -> *Nanodosimetry*
- These physical quantities that can be quantified (measure and MC-simulated) will increasingly ‘infiltrate’ the biologically weighted planning process and lead to more robust (less sensitive to RBE uncertainties) plan optimization

New Technology for Benchmarking LET Simulations

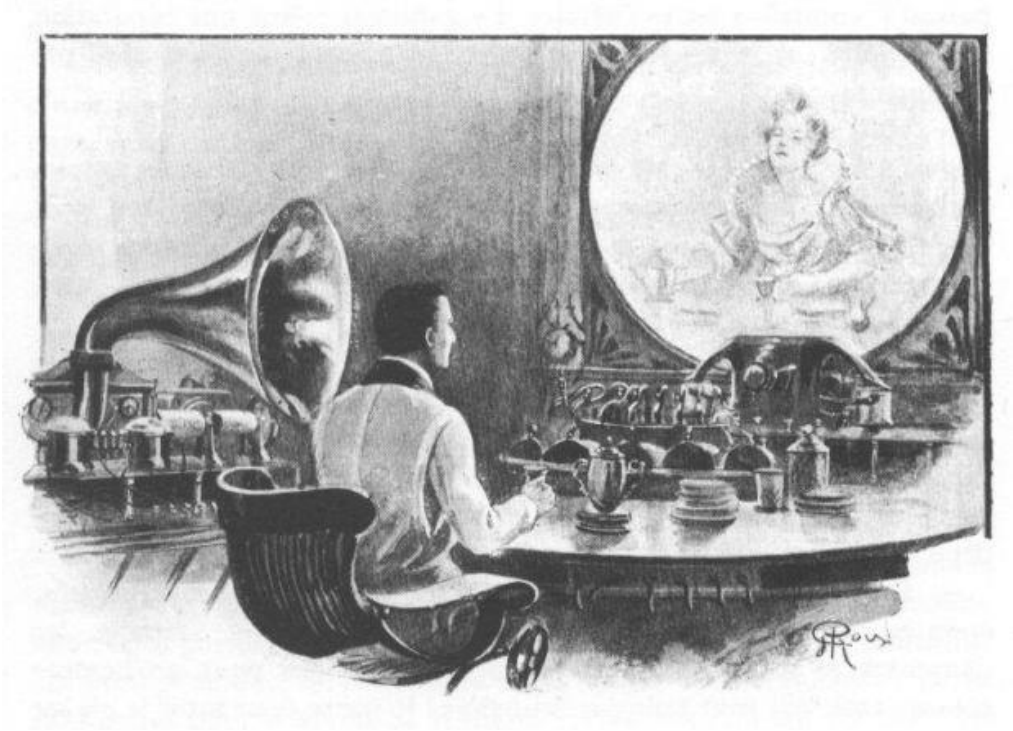


Cristina Oancea, PTCOG 60, June 2022, Miami USA

~ Dose, flux and LET measurements in and out of field in proton therapy is possible with Timepix3 detector technology

~ Single particle identification and energy deposition permits accurate bench marking of treatment planning MC codes

“The best predictor of the future is what you imagine today”



In his short story “In the Year 2889”, Jules Verne predicted video conferencing (Zoom)