An Introduction to the Problem of RBE in Particle Therapy

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Motivation

Biologically Guided Radiation Therapy (BGRT)
- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- Optimize treatment conditions based on biological objectives

Learning Objectives
1. Review of biological mechanisms and RBE models
2. Modeling RBE in proton and heavy ion RT
3. Should variable RBE models be used for proton therapy plan optimization?

Physical and Biological Aspects of Particle Therapy

RBE Depends on Many Factors

\[ \text{RBE} = \frac{\text{Dose Required for Given Effect with Reference Radiation}}{\text{Dose Required for Same Effect with Test Radiation}} \]

- Biological Endpoint
  - In vitro (e.g., DSB induction, clonogenic cell death) or in vivo (e.g., tumor growth delay)
  - Clinical endpoints (e.g., local tumor control, normal tissue toxicity)
- Particle type and energy
- Physical Dose
- Tissue Radiosensitivity
- Many other biological factors

Complex function of many variables!
Empirical RBE Models

- Estimate RBE for protons based on linear energy transfer (LET), dose per fraction, and reference radiosensitivity
- Wilkens and Oelfke model (2004):
  \[ RBE = \frac{D_{\text{physical}}}{D_{\text{ref}}} \]
  for same biological endpoint & effect

\[ RBE = \frac{\alpha}{D_{\text{ref}}} + \frac{\beta}{D_{\text{ref}}^{2}} \]

Additional Models:

\[ \Sigma_{\text{LET}} = \sum_{i} \alpha_{i} + p_{\text{LET}_{i}} \]

\[ \beta_{\text{LET}} = \beta_{1} + p_{\beta} \text{LET}_{i} \]

Comparison of Mechanistic RBE Models

Common aspects of MK, LEMIV, and RMF models:

- Induction and biological processing of DSB (sublethal or potentially lethal damage)
- MK and RMF models have conceptual and mathematical roots in the repair–misrepair (RMR) model (Tobias, 1985) and the lethal and potentially lethal (LPL) model (Curtis, 1986)

Conceptual differences:

- RMF trends in RBE arise from changes in (1) # of DSB Gy^cell and (2) # of DSB track + cell
- Impact of nearby DSB on kinetics and accuracy of the DSB rejoicing process: intra- and inter-track DSB interactions
- Considers entire cell nucleus for DSB interactions

- LEM/MKM: interaction of DSB within same subcellular domain (e.g., a chromatin loop) different from DSB interactions among adjacent or nearby domains

Assumptions for RBE<sub>DISK</sub> and predictions of \( \beta \text{(Gy)} \)

Challenge: biological model selection

How do we predict changes in biological effects in particle therapy?

1. Other physical surrogates such as dose-averaged LET (LET_{av}) (reasonable approximation for protons!)
2. Empirical LET-based RBE models, e.g.,
   - Wilkens and Oelfke (2004)
   - Carabe et al. (2002)
   - Wedenberg et al. (2013)
   - McNamara et al. (2015)
3. Mechanistic RBE models
   - Local effect model (LEM-LEMIV)
   - Microdosimetric kinetic model (MMK)
   - Repair-misrepair-fixation model (RMF)
Implementation of 3-D treatment plan optimization

- Autotally plan optimized on 3 Gy(RBE)
- Spot scanning, dose-to-water pencil beam algorithm uses pre-calculated reference tables of depth-dose, lateral spread, \(a\) and \(b\) for 32 initial carbon ion energies
- Simplified range shifter used to generate necessary peaks


Biological dose-volume histograms (DVHs)

- RBE in PTV ranges from 2.2 to 4.9 (mean 2.8)
- \(a\), \(b\), and \(\beta\) increase with depth (lower particle E) toward distal edge of PTV w/ max values outside PTV at target edge
- \(a = 0.4\) Gy\(^{-1}\), \(b = 0.05\) Gy\(^{-1}\) for optimization
- Tools can be used to:
  - Evaluate clinical differences and correlation with clinical endpoints for various RBE models
  - Perform sensitivity analysis performed by changing \((a/b) = 2\) Gy by \(\pm 50\%
- Biological model is decoupled from physical dose
- Extremely fast changes of \(\alpha\) and \(\beta\) (full biological modeling in 1-4 ms)


Where is the clinical evidence?

In conclusion, the spatial distribution of late treatment induced MR image changes in the brain following passive scattering proton therapy was highly non-uniform. A correlation with dose, LET and the PVR was shown demonstrating the relevance of variable dose-response modeling for proton therapy in the brain.

Therapy Education Symposium

Mechanisms and Clinical Significance of Particle RBE

An Introduction to the Problem of RBE in Particle Therapy
David J. Carlson, PhD, FAAPM, University of Pennsylvania

Track-End Objectives in Intensity Modulated Proton Therapy to Reduce LET
Jakob Ödén, PhD, Raysearch Laboratories

Uncertainty and Sensitivity Analysis of Biological Modeling in Proton and Carbon Ion Treatment Planning
Florian Kamp, PhD, LMU Munich

Proton Therapy and Variations in RBE - A Clinical Perspective
Harald Paganetti, PhD, FAAPM, MGH & Harvard

Variable RBE Models are the Future of Particle Therapy Treatment Planning
Robert D. Stewart, PhD, University of Washington

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