An Introduction to the Problem of RBE in Particle Therapy

2020 Joint Meeting of the AAPM | COMP

David J. Carlson, PhD, DABR, FAAPM
Associate Professor & Director of Clinical Operations, Physics Division

PENN RADIATION ONCOLOGY
Penn Medicine

14 July 2020

0

Motivation

Biologically Guided Radiation Therapy (BGRT)

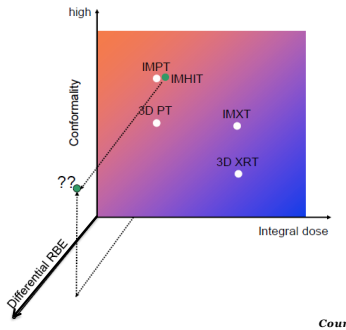
- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- Optimize treatment conditions based on *biological objectives*

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?**

1

Physical and Biological Aspects of Particle Therapy



Courtesy Prof. Uwe Oelfke (ICR, London)

2

RBE Depends on Many Factors

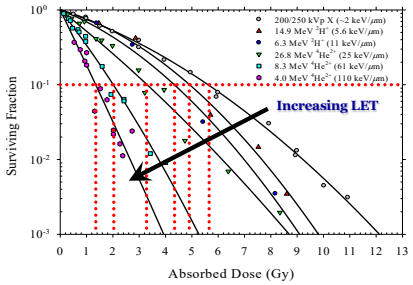
$$\text{RBE} = \frac{\text{Dose Required for Given Effect with Reference Radiation}}{\text{Dose Required for Same Effect with Test Radiation}}$$

- **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!

3

RBE for clonogenic Survival



Definition of RBE:

$$\mathrm{RBE} = D_{\mathrm{photon}}/D_{\mathrm{ion}}$$

for same biological endpoint & effect

or

$$RBE = \frac{-\alpha_x + \sqrt{\alpha_x^2 + 4d_p\beta_x\left(\alpha_p + \beta_p d_p\right)}}{2\beta_x d_p}$$

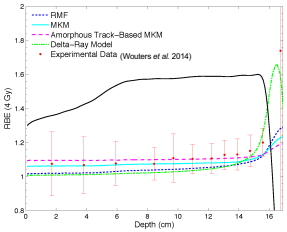
Barendsen *et al.* (1960, 1963, 1964, 1966): *In vitro* survival data for human kidney T-1 cells

4

Challenge: biological model selection

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

Proton SOBP with 160 MeV max. E
RBE values for clonogenic survival of V79 cells



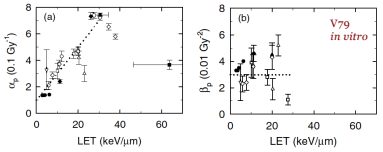
Polster *et al.* Extension of TOPAS for the simulation of proton radiation effects considering molecular and cellular endpoints. *PMB* 60: 5053–5070 (2015).

1. Other physical surrogates such as dose-averaged LET [LET_d] (reasonable approximation for protons?)
2. Empirical LET-based RBE models, e.g.,
   - Wilkens and Oelfke (2004)
   - Carabe *et al.* (2012)
   - Wedenberg *et al.* (2013)
   - McNamara *et al.* (2015)
3. Mechanistic RBE models
   - Local effect model (LEMI-LEMIV)
   - Microdosimetric kinetic model (MKM)
   - Repair-misrepair-fixation model (RMF)

5

Empirical RBE Models

- **Estimate RBE for *protons* based on linear energy transfer (LET), dose per fraction, and reference radiosensitivity**
- Wilkens and Oelfke model (2004):
  - $\boldsymbol{\alpha = \alpha_\gamma + p_1 LET_d}$ *and* $\boldsymbol{\beta = \beta_\gamma}$



(o Perris *et al* 1986; Δ Goodhead *et al* 1992; ∇ Blomquist *et al* 1993; ■Belli *et al* 1993; □ Folkard *et al* 1996; • Wouters *et al* 1996; ◊ Belli *et al* 1998; ♦Schettino *et al* 2001)

Wilkins and Oelfke. A phenomenological model for the relative biological effectiveness in therapeutic proton beams. *PMB* 49: 2811–2825(2015).

Additional Models:

$$\alpha(LET_d) = \alpha_\gamma\left(p_0 + p_1\frac{LET_d}{(\alpha/\beta)_\gamma}\right)$$

$$\beta(LET_d) = \beta_\gamma[p_2 + p_3 h(LET_d)]$$

$$h(LET_d) = \begin{cases} \frac{LET_d}{(\alpha/\beta)_\gamma}, & \text{Carabe } et\ al.\ (2007, 2012) \\ 1, & \text{Wedenberg } et\ al.\ (2013) \\ LET_d\sqrt{(\alpha/\beta)_\gamma}, & \text{McNamara } et\ al.\ (2015). \end{cases}$$

TABLE I. Recommended parameters for selected empirical proton RBE models. The fits by Wedenberg et al. and Carabe et al. are based on a subset of the experimental cell survival data used by McNamara et al.

Model	p_0	p_1	p_2	p_3
McNamara[37]	0.99064	0.35605	1.1012	−0.00387
Wedenberg[36]	1.0	0.434	1.0	0.0
Carabe[12]	0.843	0.413644	1.09	0.01612

Paganetti et al. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. *Med. Phys.* 2019 46(3): e53–e78.

6

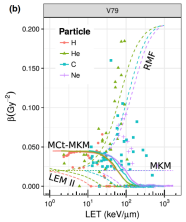
Comparison of Mechanistic RBE Models

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^{-1} cell^{-1} and (2) # of DSB track^{-1} cell^{-1}
  - →Impact of nearby DSB on kinetics and accuracy of the DSB rejoining process: intra- and inter-track DSB interactions
  - →Considers entire cell nucleus for DSB interactions
- LEM/MKM: interaction of DSB within same sub-cellular domain (e.g., a chromatin loop) different from DSB interactions among adjacent or nearby domains
- Assumptions for RBE_{DSB} and predictions of β (Gy^{-2}),



Manganaro *et al. Med. Phys.* 44: 1577-1589 (2017)

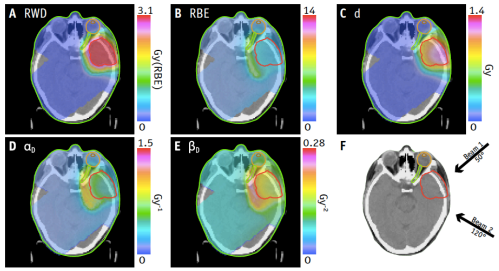
Stewart RD, Carlson DJ, Butkus MP, Hawkins R, Friedrich T, Scholz M. A comparison of mechanism-inspired models for particle relative biological effectiveness. *Med. Phys.* 45: e925–e952 (2018).

7

Implementation of 3-D treatment plan optimization

Multi-field biological optimization with RMF model for carbon ion RT in extension of research TPS CERR (Deasy et al. 2003)

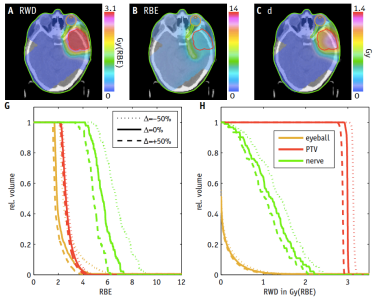
- Astrocytoma plan optimized on 3 Gy(RBE)
- Spot scanning, dose-to-water pencil beam algorithm uses pre-calculated reference tables of depth-dose, lateral spread, α_0 and β_0 for 32 initial carbon ion energies
- Simplified range shifter used to generate necessary peaks



Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, **Carlson DJ**. Fast biological modeling for voxel-based heavy ion therapy treatment planning using the mechanistic repair-misrepair-fixation (RMF) model and nuclear fragment spectra. *Int. J. Radiat. Oncol. Biol. Phys.* 93: 557–568 (2015).

8

Biological dose-volume histograms (DVHs)

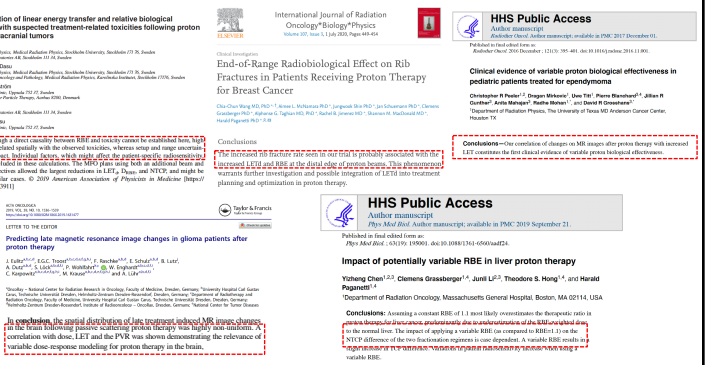


- RBE in PTV ranges from 2.2 to 4.9 (mean 2.8)
- RBE, α_0, and β_0 increase with depth (lower particle E) toward distal edge of PTV w/ max values outside PTV at target edge
- α_X = 0.1 Gy^{-1}, β_X = 0.05 Gy^{-2} for optimization
- Tools can be used to :
  - Evaluate clinical differences and correlation with clinical endpoints for various RBE models
  - Perform Sensitivity analysis performed by changing (α/β)x = 2 Gy by ±50%
    - Biological model is decoupled from physical dose
    - Extremely fast changes of α_X and β_X (full biological modeling in 1-4 ms)

Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, **Carlson DJ**. Fast biological modeling for voxel-based heavy ion therapy treatment planning using the mechanistic repair-misrepair-fixation (RMF) model and nuclear fragment spectra. *Int. J. Radiat. Oncol. Biol. Phys.* 93: 557–568 (2015).

9

Where is the clinical evidence?


Spatial correlation of linear energy transfer and relative biological effectiveness with suspected treatment-related toxicities following proton therapy for intracranial tumors

International Journal of Radiation Oncology*Biology*Physics

End-of-Range Radiobiological Effect on Rib Fractures in Patients Receiving Proton Therapy for Breast Cancer

HHS Public Access
Author manuscript

Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma

Predicting late magnetic resonance image changes in glioma patients after proton therapy

HHS Public Access
Author manuscript

Impact of potentially variable RBE in liver proton therapy

10

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*

11