Mechanisms and Clinical Significance of Particle RBE

Variable RBE (vRBE) Models are the Future of Particle Therapy Treatment Planning

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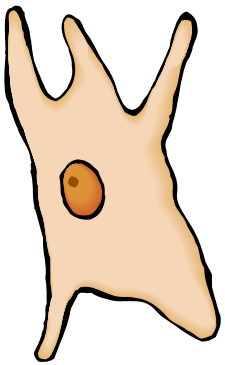


Presented: 2020 Joint AAPM/COMP Meeting (July 12-16)
Date and Time: Tuesday July 14 from 3:30 PM - 4:30 PM
Location: Virtual

Disclaimer

- Co-investigator on a Research Collaboration Agreement with RaySearch Inc.
- Have an unapologetic bias towards the use of vRBE models for outcome assessment and plan optimization

Learning Objectives

- Understand the relationship between the RBE for DNA double strand break (DSB) induction (RBE_{DSB}) and the RBE for reproductive cell survival
- Gain an appreciation for the strengths and weaknesses of RBE modeling as useful predictive tools for the analysis of laboratory and clinical studies
  - Do mechanism-inspired RBE models **capture *more* biology** than LET-based models? From a clinical perspective, do we care more about LET or biology?
- Provoke discussion and ***debate*** on forward-looking strategies to more fully exploit the potential of hadron therapy using RBE-based plan optimization
  - Is plan optimization based on LET more accurate and less risky than **robust planning** using a mechanistic RBE model?

RBE for DSB Induction (RBE_{DSB})

DSB are the most critical form of initial molecular damage created by ionizing radiation

Pairs of mis-rejoined DSB create chromosome aberrations that are often lethal or highly mutagenic.

RBE_{DSB} closely related to the RBE for cell survival.

Monte Carlo models reflect and synthesis a large body of measurements, i.e., they are the "gold standard" for RBE_{DSB}

Published models for RBE_{DSB} are in good agreement with each other for a wide range of particle types and energies.

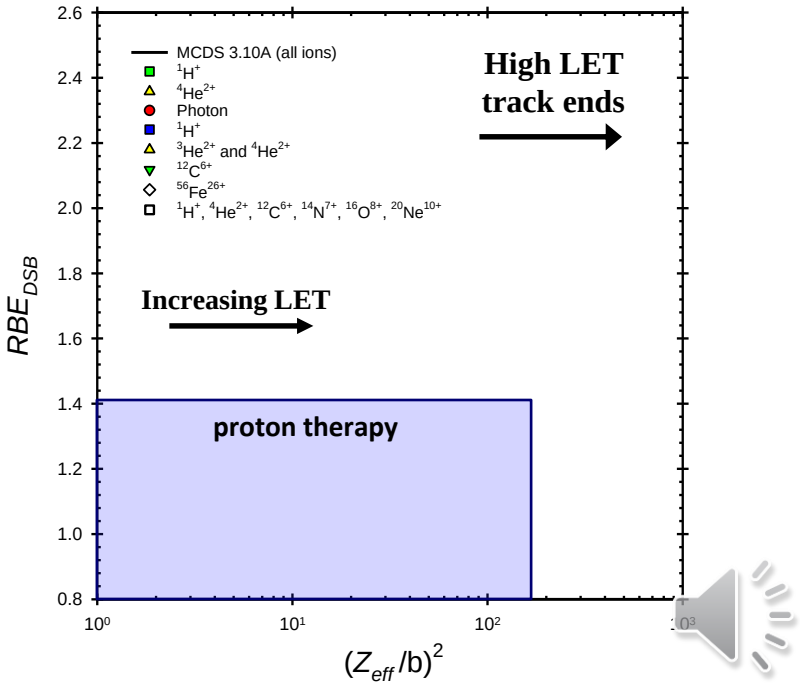


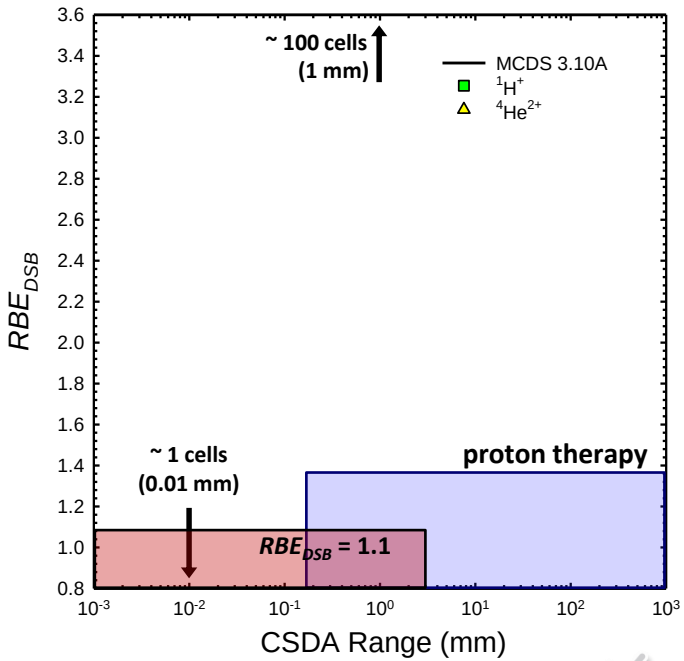
Figure adapted from data presented in Stewart *et al.* (2011, 2015, and 2018). Open and filled symbols are published data from *track structure simulations*. **Solid lines** are for the Monte Carlo Damage Simulation (MCDS).

Track-end radiobiology and RBE_{DSB}

Monte Carlo models are in very good agreement for $^{1}H^{+}$ and $^{4}He^{2+}$ ions with even a sub-millimeter range.

RBE_{DSB} only exceeds 1.1 in the last 2 mm of a proton track–track-end effects only have an impact on a few tens or hundreds of cells per proton (*i.e., it's a small volume effect*)!

For therapeutic protons, RBE_{DSB} only exceeds 1.4 well beyond the tip of a pristine Bragg peak (range ~ 1-2 mm**).**



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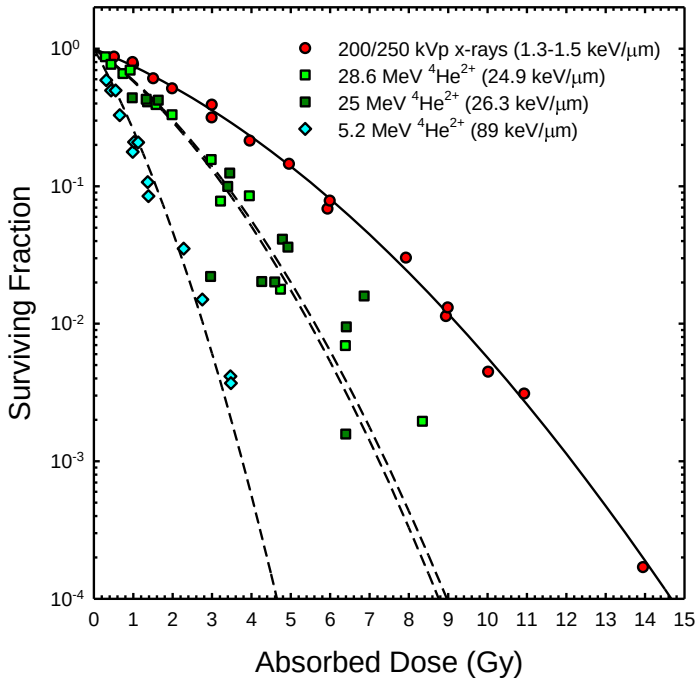
Is RBE_{DSB} Predictive of Trends in Cell Survival with LET?



Repair-Misrepair-Fixation (RMF) Model (Carlson *et al.* 2008, Stewart *et al.* 2018)

1. Estimate α_R and $(\alpha/\beta)_R$ from a fit to kV x-ray data (**red** filled circles)
2. Use MCDS to compute ion- and energy-specific value for RBE_{DSB}
3. Compute ion-specific value for α_{ion} and β_{ion} using RMF formula

$$\alpha_{ion} = \alpha_R \cdot RBE_{DSB}\left(1 + \frac{2\bar{z}_F RBE_{DSB}}{(\alpha/\beta)_R}\right)$$

$$\beta_{ion} = \beta_R \cdot RBE_{DSB} \cdot RBE_{DSB}.$$

$$\bar{z}_F \cong LET / \rho d^2$$

d is effective diameter of cell nucleus (~ few μm)

4. Compute cell survival: $S(D) = \exp\left(-\alpha_{ion} D - \beta_{ion} D^2\right)$

(dashed lines in figure are *predictions* and not fits!)

Figure is from Stewart *et al.* Med Phys. 45(11):e925-e952. doi: 10.1002/mp.13207 (2018). PMID: 30421808

RBE_{DSB} → RBE for Reproductive Cell Survival

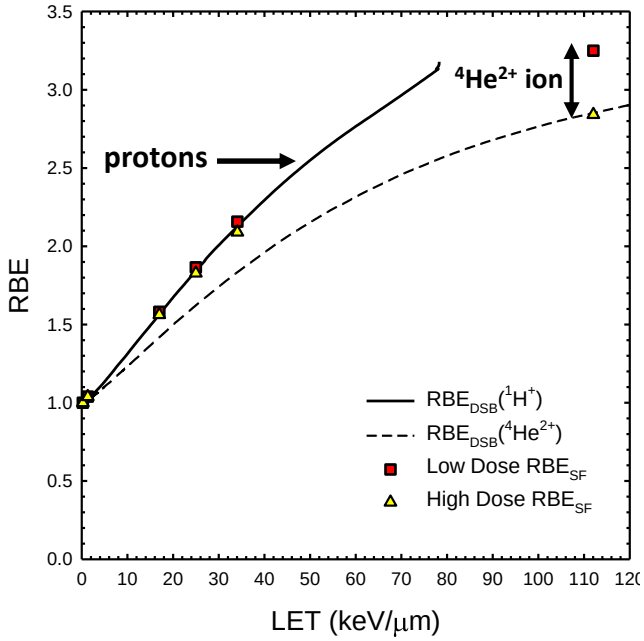
In the MCDS + RMF system of models, the RBE for cell survival is always greater than or equal to the RBE for DSB induction.

Low dose RBE: $$RBE_{LD} \equiv \frac{\alpha_{ion}}{\alpha_R} = RBE_{DSB}\left(1+\frac{2\bar{z}_F RBE_{DSB}}{(\alpha/\beta)_R}\right) \geq RBE_{DSB}$$

High dose RBE: $$RBE_{HD} \equiv \sqrt{\frac{\beta_{ion}}{\beta_R}} = RBE_{DSB} \geq 1.$$

For ion dose *D*, RBE for cell survival only depends on $(\alpha/\beta)_R$ and the asymptotic value for RBE_{LD} and RBE_{HD}.

$$RBE(D) = \frac{(\alpha/\beta)_R}{2D}\left\{-1+\sqrt{1+\frac{4D}{(\alpha/\beta)_R}\left(1+\frac{D}{(\alpha/\beta)_R}\frac{(RBE_{HD})^2}{RBE_{LD}}\right)RBE_{LD}}\right\}$$



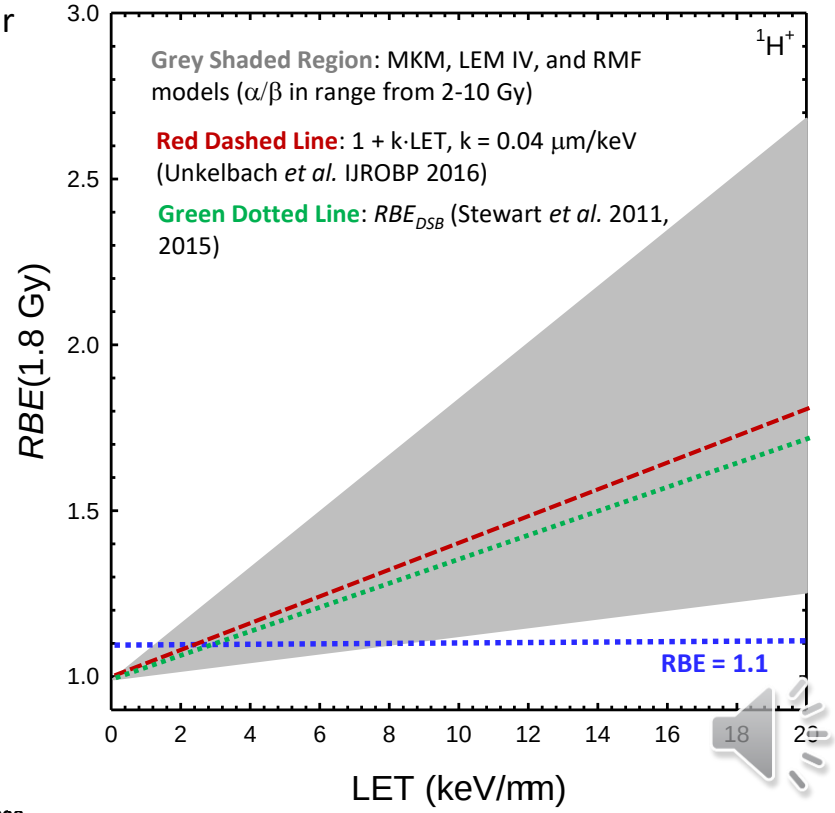
For protons, the RBE for cell survival is in good agreement with RBE_{DSB} (red squares and yellow triangles are within a few %). For $^4He^{2+}$ and other massive ions, RBE_{LD} can be much larger than RBE_{DSB}.

Reviewed in Stewart *et al.* Med Phys. 45(11):e925-e952. doi: 10.1002/mp.13207 (2018). PMID: 30421808

Is LET an effective alternative to RBE modeling?

Laboratory studies provide overwhelming evidence that molecular and cellular damage tends to (*1*) increase with increasing LET, (*2*) decreases with increasing dose, and (*3*) increases with decreasing tumor and tissue (α/β)

- LET-based approach of Unkelback *et al.* (2016) is effectively the same as plan optimization using a Monte Carlo model (Stewart *et al.* 2011, 2015) for proton RBE_{DSB}
- Optimization based on LET and RBE_{DSB} does not capture the dose-dependence nor the tissue-specific aspects of particle RBE
  - **Parameter "k" depends on (α/β) and dose.**
- Neglecting the dose- and tissue-specific aspects of particle RBE is potentially more risky than robust planning (**e.g., Kamp presentation**) using RBE models that capture fundamental molecular and cellular mechanisms.



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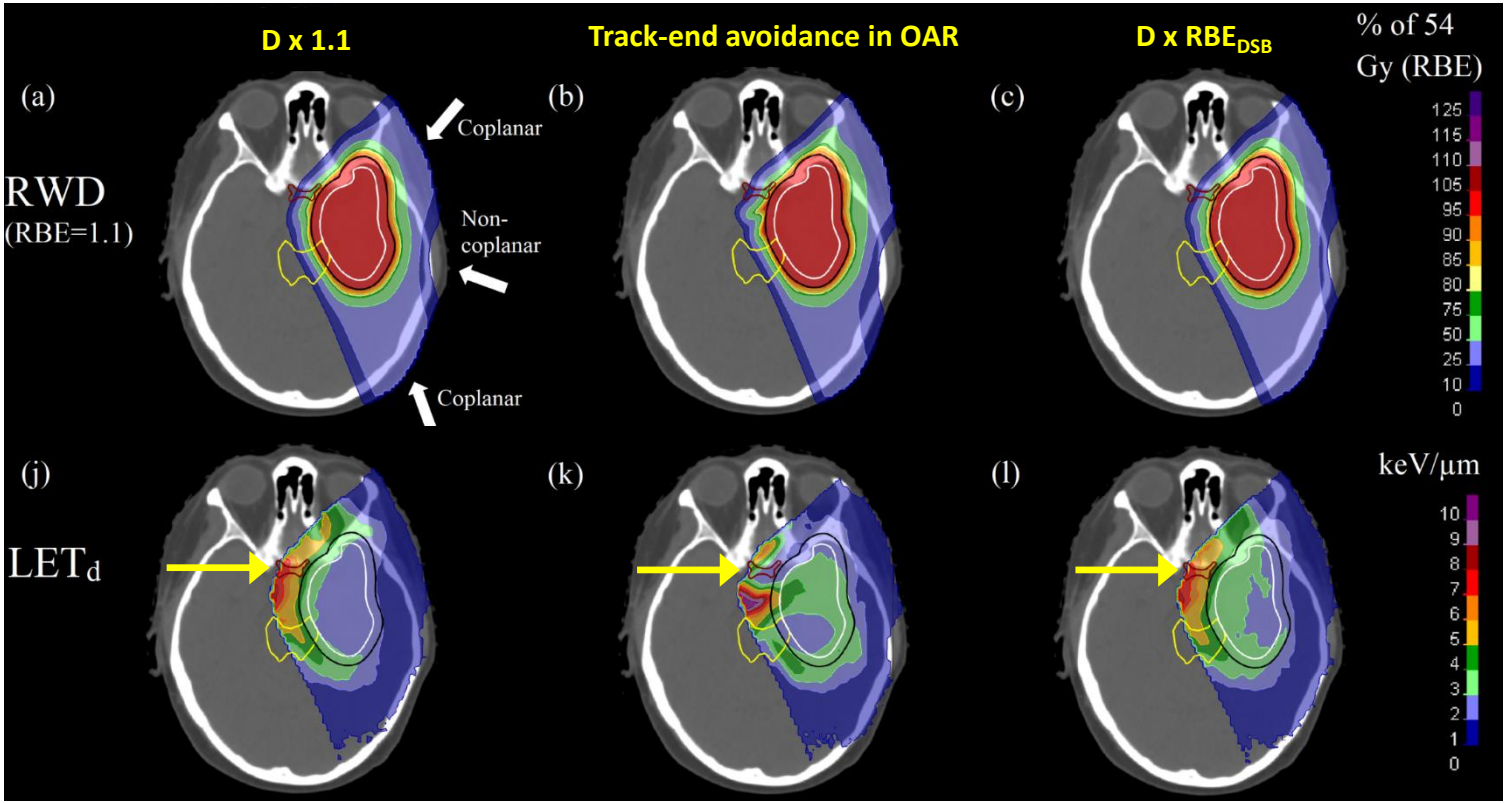
Representative plan optimized for dose (RBE = 1.1), track-end avoidance in a critical OAR, and RWD (= dose × RBE_{DSB})



Conclusions

- Mechanism-inspired RBE models for the endpoint of cell survival may not capture all of the relevant biology. ***But…*** they do capture **more** fundamental molecular and cellular biology than LET-based methods
  - LET-based approach of Unkelback *et al.* (2016) is effectively the same as using RBE_{DSB} for plan optimization, ***if*** selective applied to contoured (*critical*) OAR
  - Track-end based optimization is ***much more aggressive*** about pushing biological hot spots out of **contoured** critical OAR and into adjacent (**non-specific**) tissue than global RBE-based optimization. **Which approach is more risky?**
- RBE modeling has been effective for high LET carbon ions and fast neutron therapy – Why not use it for proton plan optimization too?
  - Uncertainties in vRBE modeling can be mitigated through robust planning (**e.g., Kamp presentation**). Plans could also be re-scaled to ensure tumor coverage is not compromised.
- RBE-based plan optimization is no more risky than LET-based optimization and, regardless, arguably superior to a constant clinical RBE = 1.1 for plan optimization.