Challenges and opportunities for implementing biological optimization in particle therapy

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Overview of Talk

**Biologically Guided Radiation Therapy (BGRT)**
- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- Problem: derived prescriptions may have large uncertainties
  - Incomplete understanding of physical and biological factors (experimental and clinical) that influence tumor and normal tissue response

**Brief introduction of radiobiological concepts and RBE models**
- Repair-misrepair-fixation (RMF) model: kinetic reaction-rate model relates DSB induction and processing to cell death
  - Provides formulas linking LQ parameters to DSB induction and repair

**Modeling RBE in proton, helium, and carbon ion RT**
- RMF and Monte Carlo Damage Simulation (MCDS) models used to predict trends in biological response with particle type and energy
- Derive practical estimates of the RBE for cell death for clinically-relevant charged particle therapy
- Application of RBE-weighted dose (RWD): implementation and implications for particle therapy

Comparison of photons versus protons

Protons allow reduction of integral dose and lower dose outside target:

![Comparison of photons versus protons](image_url)
Physical and Biological Aspects of Particle Therapy

Biological effects of radiation quality

**Definition of RBE:**

$$RBE = \frac{D_{\text{photon}}}{D_{\text{ion}}}$$

**for same biological endpoint & effect**

with

$$RBE = \frac{\beta_1 + \beta_2 (\beta_3 + \beta_4)}{\beta_5}$$


**Increasing LET**

**Major Challenge: biological model selection**

- How do we predict changes in biological effects in particle therapy?
  1. Empirical LET-based RBE models, e.g.,
     - Wilkins and Oelfke (2004)
     - Carabe et al. (2015)
     - Wedenberg et al. (2013)
     - McNamara et al. (2015)
  2. Mechanistic RBE models
     - Local effect model (LEMI-LEMIV)
     - Microdosimetric kinetic model (MKM)
     - Repair-repair-fusion model (RMF)
  3. Other physical surrogates such as dose-averaged LET ([LET]_d) (may provide a reasonable approximation for protons)

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

Wouters et al. (2014)

Lethal lesions are created by the actions of one or two radiation tracks:

1 track damage ($\alpha D$)
- Lethal DSB misrepair, unreparable damage

2 track damage ($\alpha D^2$)
- Pairwise interaction of two DSBs

Repair-misrepair-fixation (RMF) Model

Cell death related to fatal lesions:

\[ Z_c = \left[ 1 - e^{-1.25 \frac{D_c}{T_m}} \right] \]

1. Unrejoinable and lethal damage
2. Intra-track DSB interaction

\[ \alpha = (1 - \beta C) + \beta C \sum f \frac{1}{2} \frac{T_m}{2} \]

3. Lethal misrepair and fixation

\[ \beta = \left( \frac{1}{2} \frac{T_m}{2} \right) \pi f \frac{1}{2} \]

4. Inter-track DSB interaction

Monte Carlo Damage Simulation (MCDS)

Effect of charge:

\[ Z_c = \left[ 1 - e^{-1.25 \frac{D_c}{T_m}} \right] \]

\[ \beta = \left( \frac{1}{2} \frac{T_m}{2} \right) \pi f \frac{1}{2} \]

MCDS reproduces trends in DNA damage yields from more detailed track structure simulations for electrons, protons, and heavy ions over a wide range of energies.

References:
Particle Irradiation Data Ensemble (PIDE)

- Comparisons of RMF predictions with experimentally measured carbon ion RBE values reported by multiple institutions (www.gsi.de/bio-pide) for two biological endpoints (RBE_α and RBE at a survival level of S = 10%) and a range of LET and (α/β) values.

- Data calculated with d_{Tar} = 5 μm and a focus on LET variations.

Method to determine RBE for cell killing

- RMF-derived predictions of α and β are used to estimate the RBE for cell killing in clinically-relevant ion therapies:

1. Estimate cell-specific model constants: 
   \[ \kappa = \frac{2D_\alpha}{\Sigma F_i}, \quad \theta = \frac{\Sigma F_i}{\Sigma (\alpha/\beta)}, \]

2. Calculate radiosensitivity parameters for ion of given energy E_i:
   \[ \alpha_i = 4E_i + \alpha, \quad \beta_i = (\alpha + \beta)E_i \]

3. Calculate dose-averaged mean values of α and β as a function of penetration depth for a mixed field of ions of different energy:
   \[ \alpha_D = \frac{1}{D} \sum \alpha_i D_i, \quad \beta_D = \frac{1}{D} \sum \beta_i D_i \]

4. Calculate RBE for cell killing relative to reference treatment (simply an isoeffect calculation using D = RBE × D):
   \[ \text{RBE}(\alpha, \beta, \alpha', \beta') = \frac{\sum_i \alpha_i D_i + \beta_i D_i \cdot \frac{1}{\Sigma D} - \alpha'}{\Sigma D} \]

Clinically-relevant pristine Bragg peaks

- Dose & LET calculated using analytical approximations (Bortfeld 1997, Wilkens and Oldfield 2003)
- DSB yields simulated with MC6
- α and β calculated assuming chordoma reference parameters
- All calculations include Gaussian particle spectrum

Physical and biological properties of proton and carbon ion pristine Bragg peaks:

- Dose & LET calculated using analytical approximations (Bortfeld 1997, Wilkens and Oldfield 2003)
- DSB yields simulated with MC6
- α and β calculated assuming chordoma reference parameters
- All calculations include Gaussian particle spectrum

References:
RBE for cell killing in Proton SOBP

Conditions:
1. Normoxic chordoma cells: \( \alpha_x = 0.1 \text{ Gy}, (\alpha/\beta)_x = 2.0 \text{ Gy} \)
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 5 cm
5. \# of Bragg peaks: 17

Results:
1. Entrance RBE ~ 1.0
2. RBE ranges from 1.03 to 1.34 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP ~ 1.11

Potential for biological hot and cold spots within proton SOBP

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RBE for cell killing in Carbon Ion SOBP

Conditions:
1. Normoxic chordoma cells: \( \alpha_x = 0.1 \text{ Gy}, (\alpha/\beta)_x = 2.0 \text{ Gy} \)
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 5 cm
5. \# of Bragg peaks: 17

Results:
1. Entrance RBE ~ 1.3
2. RBE ranges from 1.8 to 5.4 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP ~ 2.8

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Physical dose optimization

Clinical objective is to deliver a uniform biological effect (UWD)

Physical dose optimization

Spread out Bragg peaks consisting of pristine Bragg peaks whose fluences were optimized to yield a constant RBE-weighted absorbed dose of 3 Gy (RBE) using method of Wilkens and Oelfke (2006)
Challenge: accurate physics modeling of fragments

- Simulation of clinical carbon ion beam line using Monte Carlo code FLUKA (Parodi et al. 2012)
- In our example, 32 carbon ion beams with energies from 90 to 400 MeV/u in 10 MeV/u steps in a homogeneous water phantom
- Panel A: characteristic depth-dose dependency (Bragg peak) of carbon ions for an initial energy of 200 MeV/u
- Panel B: relative number of particles. H and He are most prominent fragments
- Panel C: spectra of six considered fragments at a depth of 8 cm, close to the Bragg peak, where the impact of fragmentation is highest

Impact of nuclear fragmentation on RBE for carbon

- RMF predictions of RBE-weighted dose w/ and w/o FLUKA-generated nuclear fragments and an analytical approach w/o fragmentation (Owen et al. 2015)
- SOBPs optimized for target in water at depth of 10-15 cm with RWD = 3 Gy(RBE)–Squared differences optimization (Wilkens and Oelfke 2006)
- RBE is over-estimated when neglecting nuclear fragments (especially in distal edge of SOBP)
- If fragments are neglected, estimated physical dose required to obtain a constant RWD could be underestimated by up to 32%

Comparison to LEM1 and LEM4

(Grün et al. 2012, PMB)
Implementation of 3-D treatment plan optimization

**Multi-field biological optimization**
with RMF incorporation into the planning platform CERR (Deasy et al. 2003)

- Antennomytoma plan with a carbon ion field optimized on 3 Gy(RBE)
- Spot scanning, dose-to-water pencil beam algorithm for dose calculation
- Pre-calculated reference tables of depth-dose, beam spread, $\alpha_D$ and $\beta_D$
- Initial carbon ion energy range covers > 27 cm in water (with mean distance of 8 mm between single Bragg peaks)
- Simplified range shifter used to generate necessary peaks in between


**Biological dose-volume histograms (DVHs)**

- PTV shown in red
- Organs: LT optic nerve (green), LT eye (orange)
- RBE in PTV ranges from 2.2 to 4.9 (mean 2.8)
- $\alpha_D$ and $\beta_D$ increase with depth (lower particle E) toward distal edge of PTV w/ max. values outside PTV at target edge
- $\alpha_D = 0.1$ Gy$^{-1}$, $\beta_D = 0.5$ Gy$^{-2}$ for optimization
- Sensitivity analysis performed by changing $(\alpha_D/\beta_D)$ to 0.5 Gy$^{-1}$
- Biological model is decoupled from physical dose
- Extremely fast changes of $\alpha_D$ and $\beta_D$


**Comparing model predictions**

- RBE predictions by LEM1 are generally larger than the RMF model predictions as expected
- Deviations between the two implemented models are large but not surprising given the uncertainties in the biological modeling process
- Disagreement is reduced when comparing RMF to LEM4 version (not shown)
- Differences in RBE and RWD of the OARs need to be carefully evaluated in order to apply dose constraints for OARs and to predict normal tissue complication probabilities
- More 3-D model comparisons are necessary

Is there a more optimal particle type for RT?

- Potential advantages and disadvantages depend on interplay of physical and biological properties
  - For protons:
    - No observable fragmentation tail
    - Larger lateral scattering
    - Wider Bragg peak
  - For carbon ions:
    - Decreased lateral scattering and narrower Bragg peak
    - Higher entrance to peak dose ratio
    - Higher and longer nuclear fragmentation tail
    - Lateral dose halo effect is greater than other ions
  - What about helium ions?
    - Less lateral scattering than protons and smaller fragmentation tail than carbon ions


Optimized D_{RBE}, FLUKA simulated absorbed dose D, and LET_{D} values plotted as a function of the depth in water


Objective: to perform studies on biological effect of raster-scanned helium ion beams with experimental verification before clinical application.

Integration of data-driven biological models into Monte Carlo treatment planning (MCTP) tool based on FLUKA (Mairani et al. 2013)

Consider primary He-4 ions and secondary particles: He-3 and He-3 (Z=2) fragments, and protons, deuterons, and tritons (Z=1)

4 cm SOBP optimized and delivered at Heidelberg Ion Beam Therapy Center (HIT)
Predicting RBE effects in helium ion therapy


• Human lung adenocarcinoma cells A549 (\(\alpha/x = 0.173\) Gy\(^{-1}\), \(\beta/x = 0.032\) Gy\(^{-2}\))
• Cell survival and RBE as function of the depth in water for the forward re-calculated plan using the RMF model as an empirical approach
• Implementation of RMF model only needed \(\alpha/x\) and \(\beta/x\) as input parameters – not previously adjusted to match light ion data.

Summary of mean survival absolute deviation (\(\mu S\)) between model predictions and experimental data

RMF model not fit to data or adjusted using other helium ion data.

Conclusions and Future Opportunities

• Biological models can be used for optimization in particle therapy
  - RMF model, combined with independently benchmarked MCDS, provides quantitative & mechanistic method to efficiently predict RBE-weighted dose distributions in carbon ion RT in real patient cases
  - RMF and MCDS approach can also be used to investigate oxygenation effects

• Limitations of existing RBE models
  - May not explicitly capture many important biological factors, e.g., low dose hyper-radiosensitivity, possibility of other biological targets (e.g., vasculature and immune responses, etc.)
  - Uncertainty in experimental data, variation in patient radiosensitivity, and differences between RBE model predictions present real challenges for the heavy ion therapy community
  - Need reliable methods to quantify patient variability in radiosensitivity and RBE as function of genomic heterogeneity (e.g., DNA repair defects could result in enhanced RBE)

• Best to practice evidence-based medicine
  - Clinical data is gold standard – must be skeptical of simplified models and understand limitations
  - Potential to improve outcomes in particle RT through optimization based on biological objective functions in addition to dose-based surrogates

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