Uncertainty and Sensitivity Analysis of Biological Modeling in Proton and Carbon Ion Treatment Planning

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Disclaimer

- Research and development funds from ViewRay
Learning objectives

- Linear-quadratic model as basis for RBE modeling
  - Parameters
  - Isoeffective RBE definition

- Differences in RBE modeling between proton and carbon ions
  - Fragmentation
  - RBE prediction for carbon ions

- Uncertainties in RBE modeling
  - Origin, impact and analysis
  - Variance-based uncertainty and sensitivity analysis
Relative biological effectiveness (RBE)

Linear-quadratic (LQ) model:

\[ S(d) = \exp \left( -\alpha d - \beta d^2 \right) \]

Relative biological effectiveness:

\[
RBE = \frac{d_x}{d_p} \Bigg|_{S=\text{const}}
\]

\[
RBE = \frac{-\alpha_x + \sqrt{\alpha_x^2 + 4d_p\beta_x(\alpha_p + \beta_p d_p)}}{2\beta_x d_p}
\]

Biological dose-response modeling:

\[
\alpha_p(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, \text{cell})
\]

\[
\beta_p(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, \text{cell})
\]

RBE-weighted dose:

\[
RWD = RBE \cdot d_p
\]

\[
RWD = RBE(\alpha_p(...), \beta_p(...), \alpha_x, \beta_x, d_p) \cdot d_p
\]

\[ C^6+ (p^+) \]
Differences between $p^+$ and $C_6^+$

Fragmentation

$p^+$

$C_6^+$

E = 200 MeV

$z = 24.0 \text{ cm}$

E = 200 MeV/μ

$z = 8.0 \text{ cm}$

Courtesy of K. Parodi and G. Dedes, LMU Munich

Kamp et al., IJROBP 2015
Influence of fragmentation on RBE and RWD

- Accounting for fragmentation reduces RBE
- It is crucial: underestimation of needed dose of up to 30% without fragmentation
- General: RBE is a main factor for carbon ion RT

Kamp et al., IJROBP 2015
Uncertainties in RBE modeling

\[ \alpha_p(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, cell) \]
\[ \beta_p(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, cell) \]

- Many factors:
  - Determination of radiosensitivity parameters
  - Validity of the LQ-model
  - Extrapolation from in-vitro experiments to the human body
  - Uncertainties in the biological models and their parameters / assumptions
  - …
  - Every model is wrong, some are useful*

*George Box, https://en.wikipedia.org/wiki/All_models_are_wrong
Example: Impact of uncertainties

Change one biological modeling ($\Sigma/\Sigma_X$) parameter by 10%

$$RWD = RBE \cdot d$$

- Multi-field biological optimization with RMF model for carbon ion RT
- $$(\alpha_X/\beta_X) = 2 \text{ Gy}$$

5% deviation in $RWD$
Uncertainty and sensitivity analysis
Teaser

- All RBE model predictions are uncertain
- Uncertainty and sensitivity analysis mostly done by changing one parameter at a time in the model.

- Variance-based uncertainty and sensitivity analysis to combine "physical" uncertainties in
  - range
  - setup (isocenter shifts)

- with uncertainties in RBE prediction originating from:
  - $\alpha_x$ and $\beta_x$ (or $(\alpha_x/\beta_x)$)
  - RBE model input parameters

e.g. Böhlen et al., PMB 2012
Variance-based uncertainty analysis
Add uncertainties to treatment planning

- Execute RWD calculation many times ($10^3$-$10^4$) with randomly and simultaneously changed:
  - Isocenter
  - Range
  - Biological model parameters

- Requirements:
  - Fast RBE model execution given changed input*
  - Fast RWD calculation

Hofmaier et al., conditionally accepted Med. Phys.

*e.g. Wedenberg et al. Acta Oncol, 2013, or RMF model as described in Kamp et al. PMB, 2017
Variance-based sensitivity analysis
Break down resulting uncertainties into impact of the input uncertainties

Missing sectors of pie chart:
Interactions between different uncertainties

Preliminary results, courtesy of Jan Hofmaier, LMU Munich
Literature

RBE for carbon ion therapy
- Scholz et al., *Radiat Environ Biophys* 1997; 36:59-66
- Grün et al., *PMB* 2012; 57:7261-7274
- Frese et al., *IJROBP* 2012; 83(1):442-450
- Kamp et al., *IJROBP* 2015; 93(3):557-568
- Inaniwa et al., *PMB* 2010; 55 6721–37
- Mein et al., *IJROBP* 2020. in press
- Karger et al, *PMB* 2018; 63 01TR02

RBE for proton therapy
- See other talks in this session

Variance-based uncertainty and sensitivity analysis
- Kamp et al., *Med Phys* 2018; 46(2):437-447
- Kamp et al., *Phys Medica* 2014; 30(5):583-587
- Hofmaier et al., cond. accepted *Med Phys*

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