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

Department of Radiation Oncology
July 14, 2020| Dr. Florian Kamp

Disclaimer

- Research and development funds from ViewRay

Learning objectives

C^{6+}

p^{+}

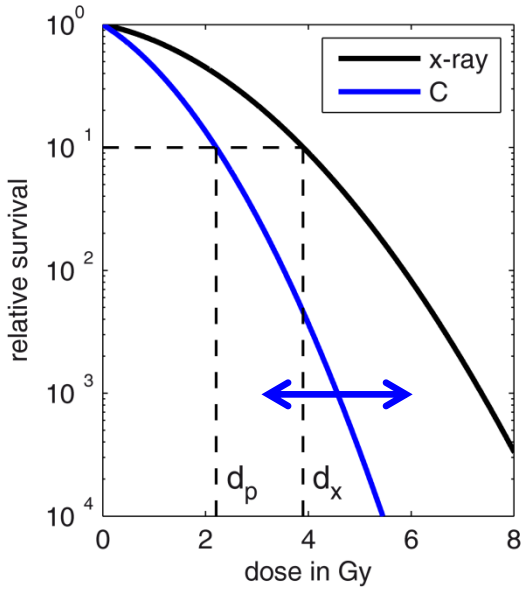
- Linear-quadratic model as basis for RBE modeling
  - Parameters
  - Isoeffective RBE definition

- 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)

C^{6+}
(p^{+})



Linear-quadratic (LQ) model:

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

Relative biological effectiveness:

$$RBE = \left.\frac{d_x}{d_p}\right|_{S=const}$$

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

biological dose-response modeling:

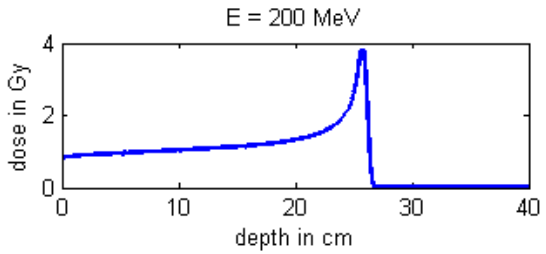
$$\alpha_p\left(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, cell\right)$$
$$\beta_p\left(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, cell\right)$$

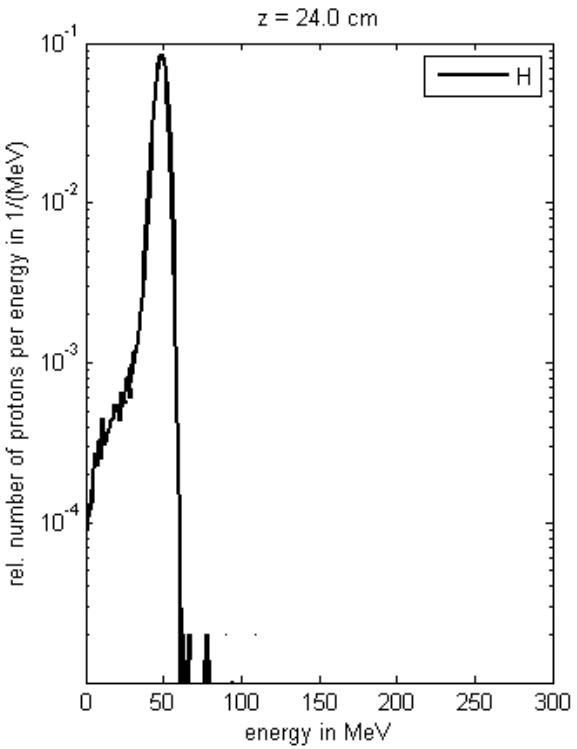
RBE-weighted dose:

$$RWD = \boldsymbol{RBE} \cdot d_p$$
$$RWD = \boldsymbol{RBE}\left(\alpha_p(\ldots), \beta_p(\ldots), \alpha_x, \beta_x, d_p\right) \cdot d_p$$

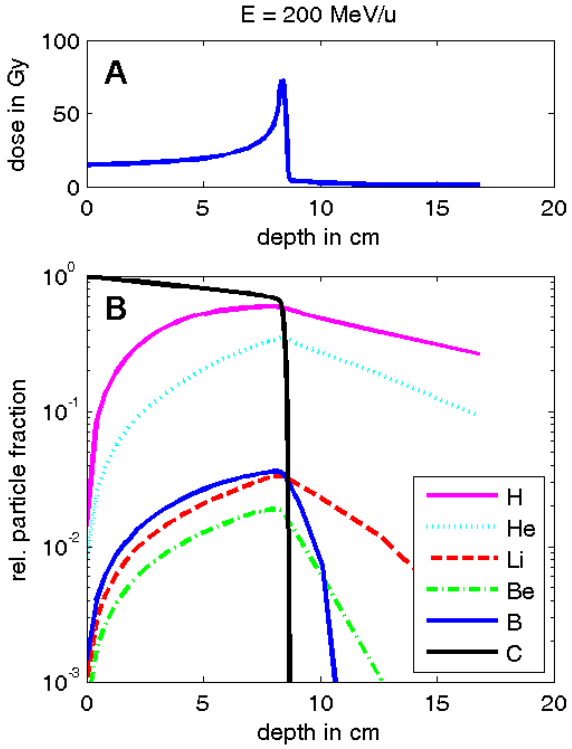
Differences between p^+ and C^{6+}
Fragmentation

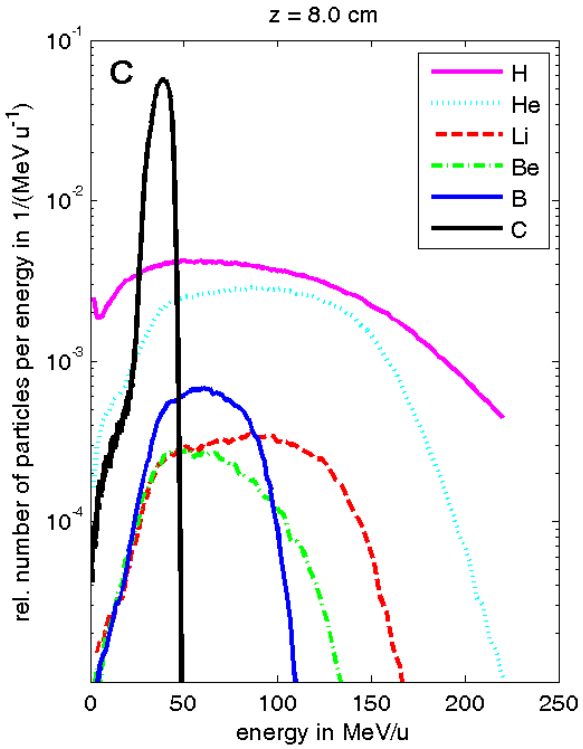
p^+





C^{6+}



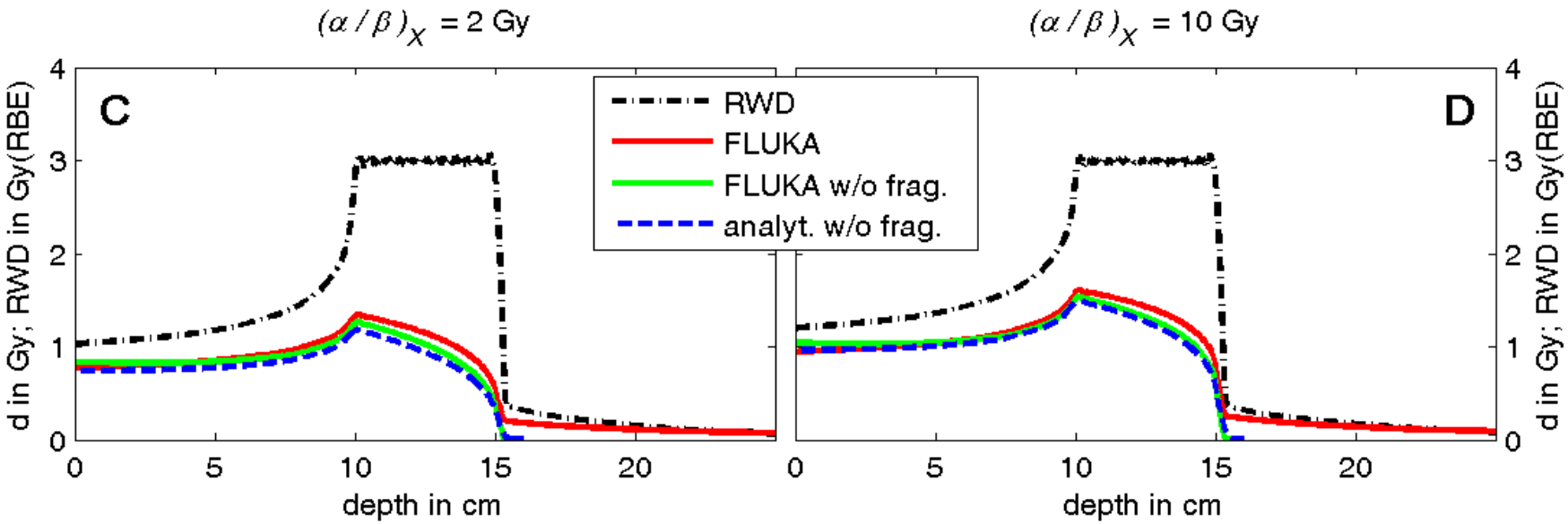


Courtesy of K. Parodi and G. Dedes, LMU Munich

Kamp et al., IJROBP 2015

Influence of fragmentation on RBE and RWD

C^{6+}



- 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

$$\alpha_p\left(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, cell\right)$$

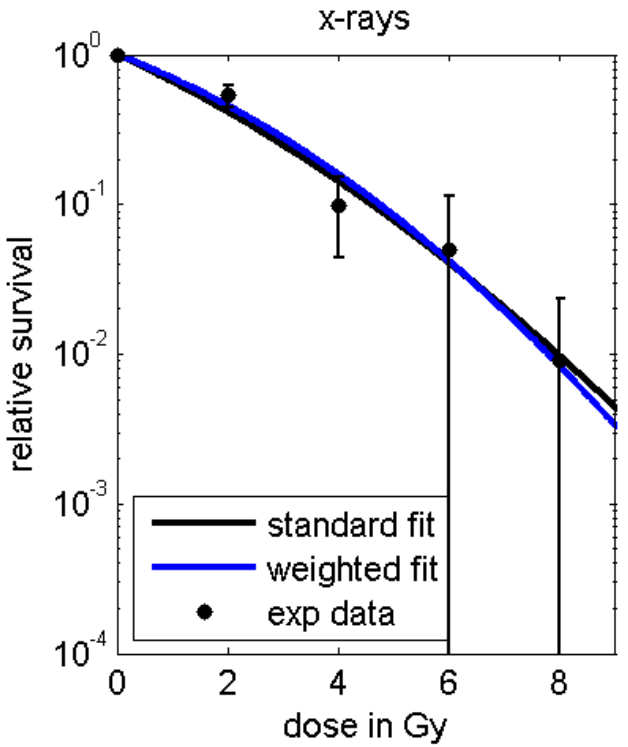
$$\beta_p\left(\alpha_x, \beta_x, Z_{ion}, LET_{ion}, cell\right)$$

- 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 usefull*

*George Box, https://en.wikipedia.org/wiki/All_models_are_wrong

C^{6+}

p^{+}



	α_x in Gy^{-1}	β_x in Gy^{-2}
standard fit	0.397 ± 0.129	0.023 ± 0.019
weighted fit	0.323 ± 0.123	0.034 ± 0.021

68.3% confidence interval of the fit

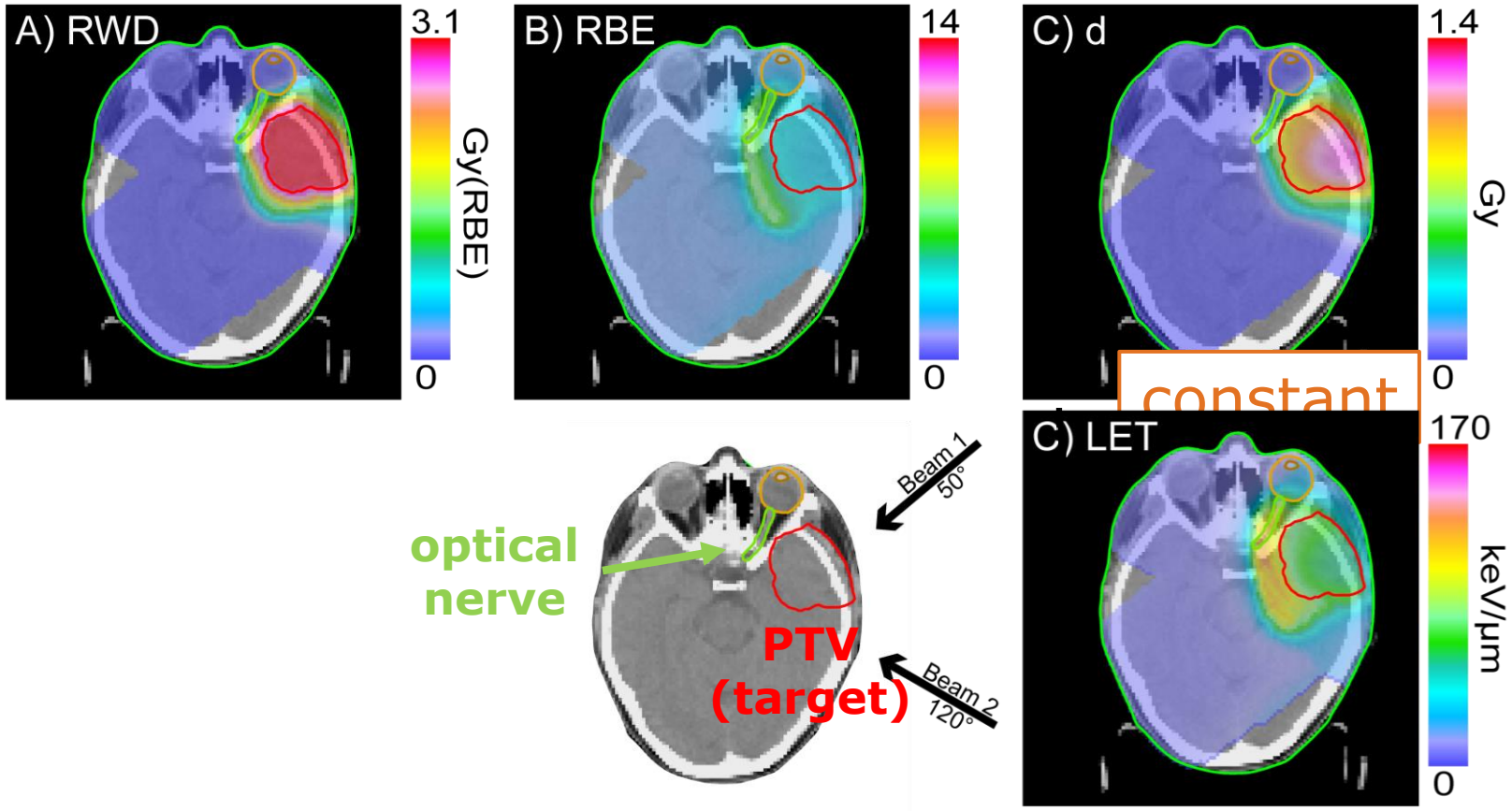
Experimental data courtesy of D. Habermehl

Example: Impact of uncertainties

C^{6+}

Change one biological modeling (Σ/Σ_X) parameter by **10%**

$RWD = RBE \cdot d$

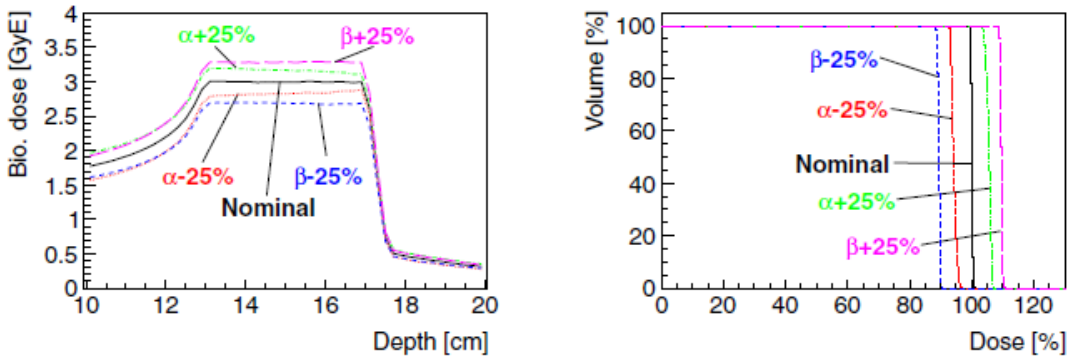


- Multi-field biological optimization with RMF model for carbon ion RT
- (α_X/β_X) = 2 Gy

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.



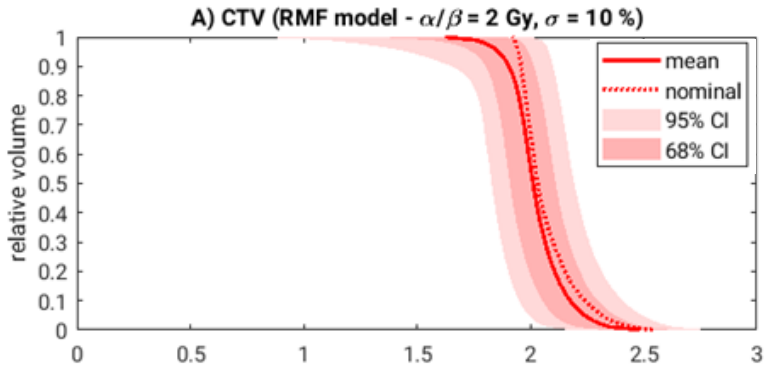
e.g. Böhlen et al., PMB 2012

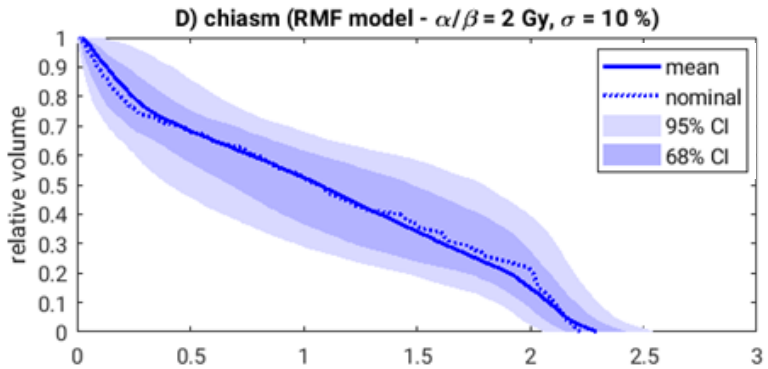
- Variance-based uncertainty and sensitivity analysis to combine „physical" uncertainties in
  - **range**
  - **setup** (isocenter shifts)
- with uncertainties in RBE prediction originating from:
  - α_X and β_X (or (α_X/β_X))
  - RBE model **input parameters**

Variance-based uncertainty analysis
Add uncertainites 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



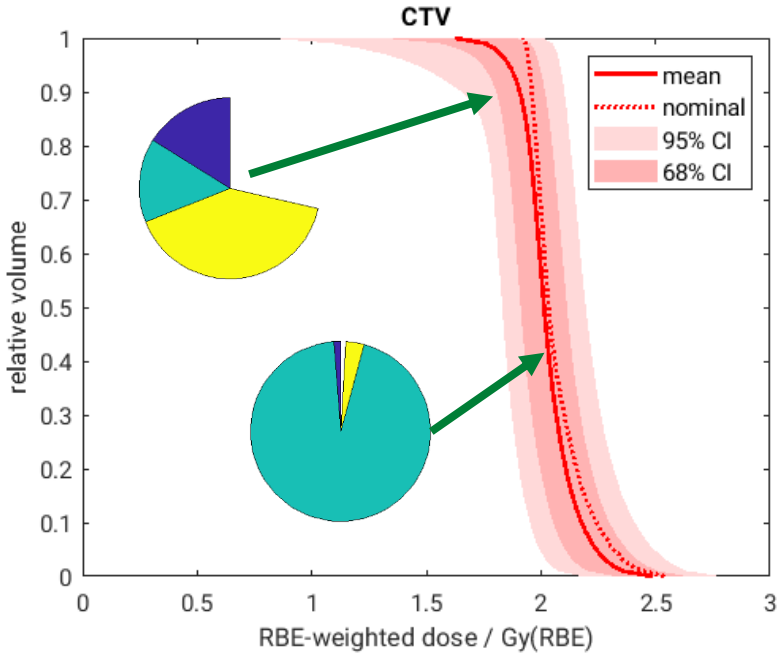


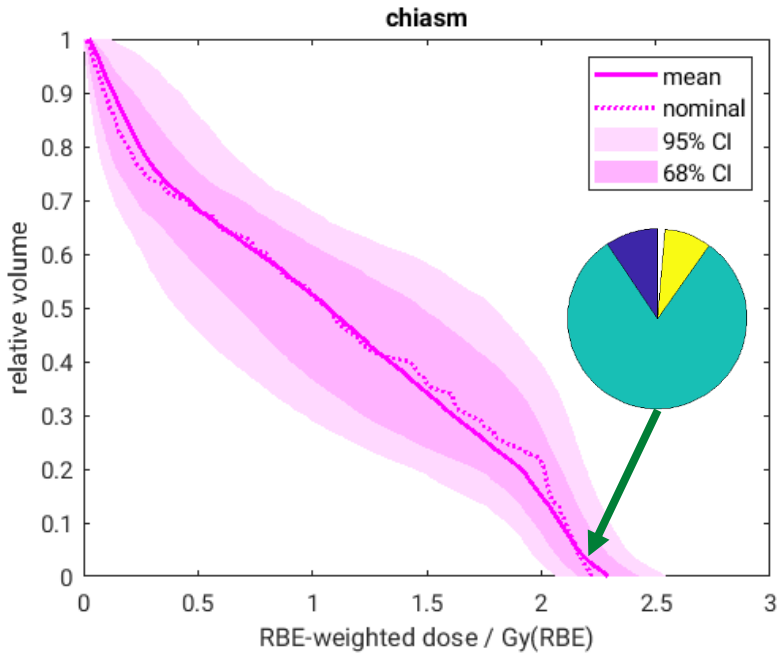
Hofmaier et al., conditionally accepted Med. Phys.

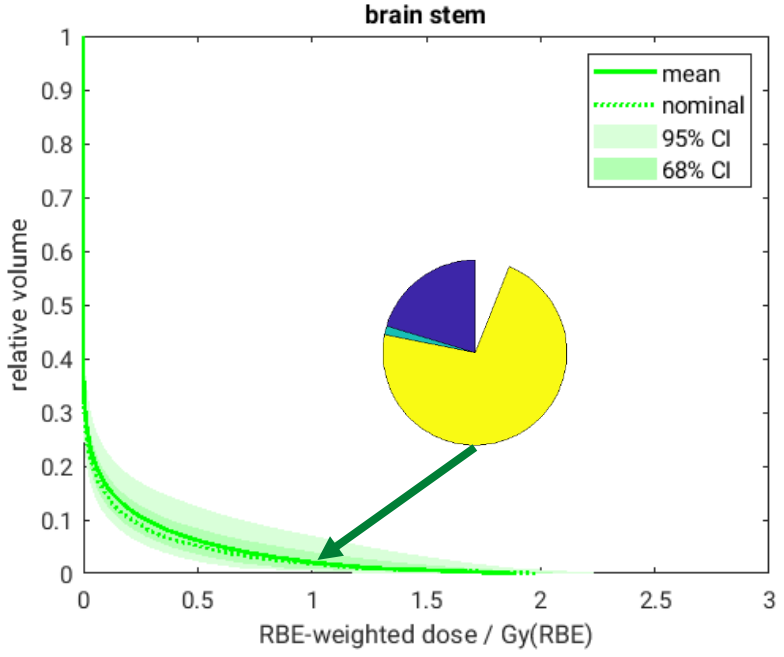
*e.g. Wedenberg et al. Acta Oncol, 2013 , or RMF model as described in Kamp et al. PMB, 2017

Variance-based sensitivity analysis

Break down resulting uncertainties into impact of the input uncertainties







Biology
Setup
Range

Missing sectors of pie chart:
Interactions between different uncertainties

Preliminary results, courtesy of Jan Hofmaier, LMU Munich

Literature

C^{6+}

- 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

p^{+}

- RBE for proton therapy
  - See other talks in this session

C^{6+}/p^{+}

- Variance-based uncertainty and sensitivity analysis
  - Saltelli et al., *Comput Phys Commun* 2010;181(2):259-270.
  - 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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