Update from MoVe IT: recent insights in the biological impact of target fragments

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The MoVeIT experiment

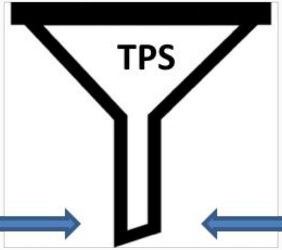
Physics

- Depth dose distributions
- Nuclear fragment spectra (including target)
- Stopping power data

Radiobiology

(= Biological effects + micro/nanoscale physics)

- RBE (eg. LEMx, MKM)
- OER
- SER

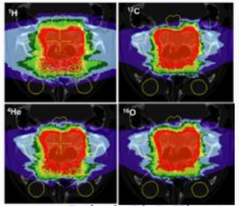


Beamline specifics

Patient Imaging data

Including intratumor heterogeneity

Effective Dose profile

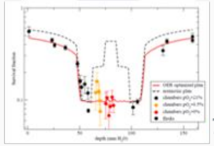


Sokol PhD Thesis

Verification

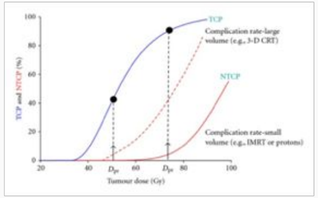
advanced beam monitoring

“Bio”-dosimetry



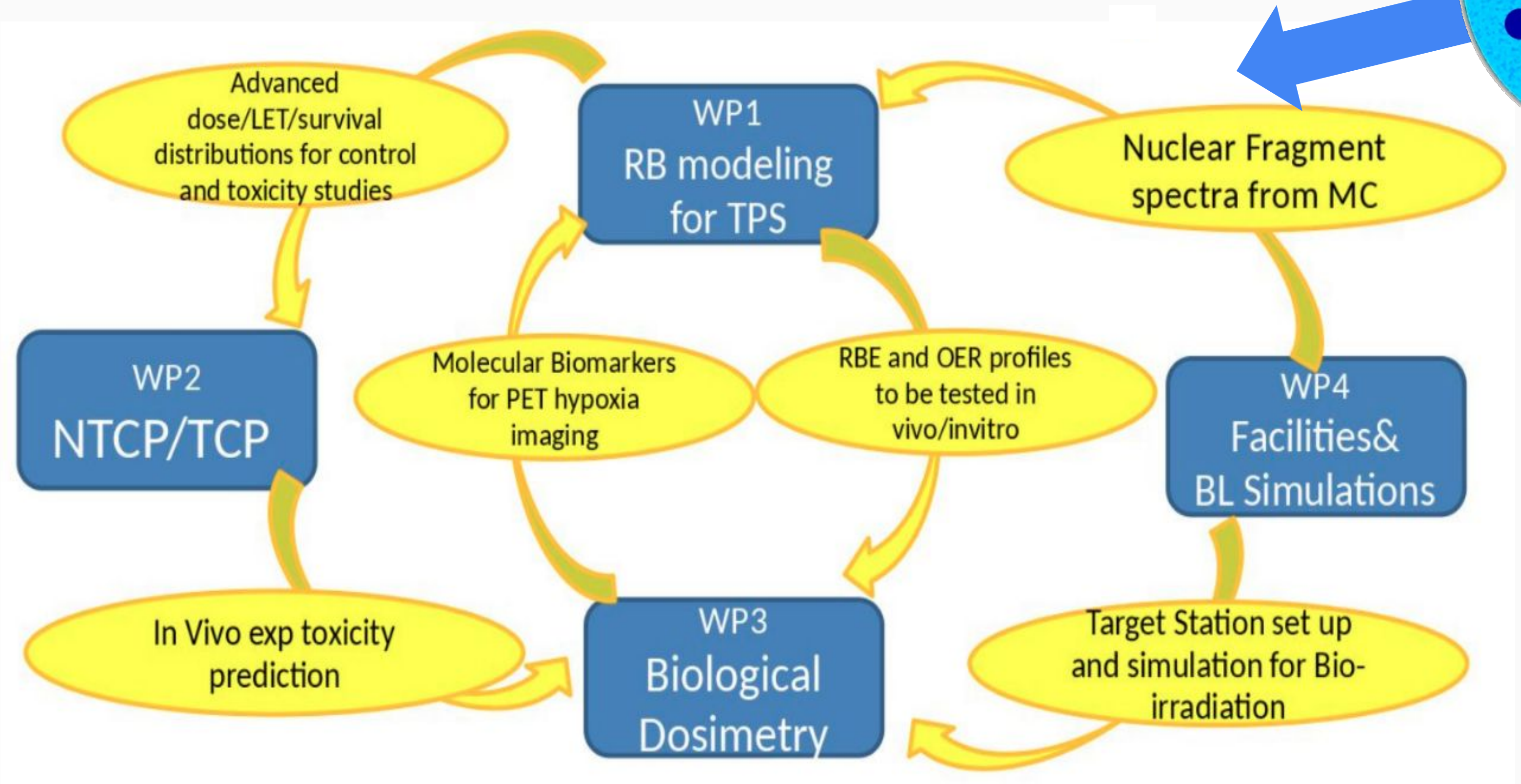
Tinganelli et al Sci Rep 2015

Clinical Impact

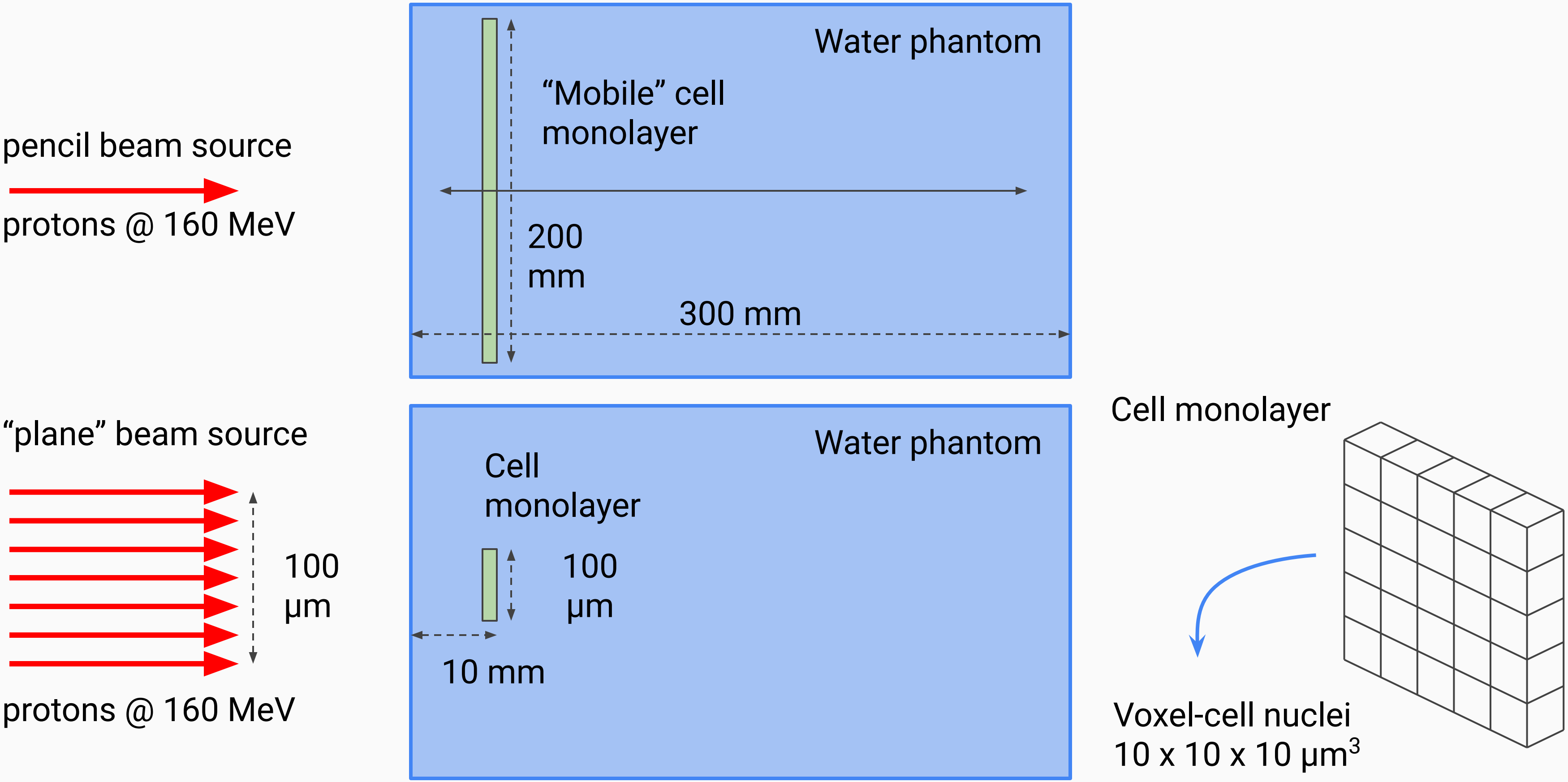


TCP/NTCP

MoVe IT structure and links



FragmentatiOn Of Target simulations - Geometry



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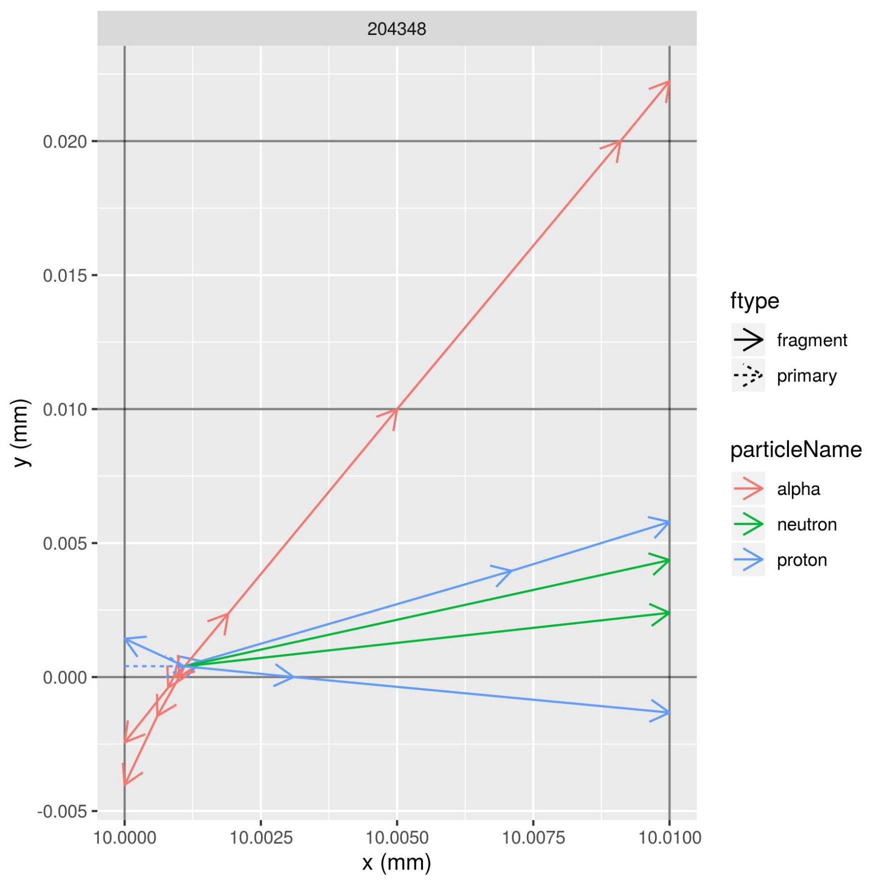
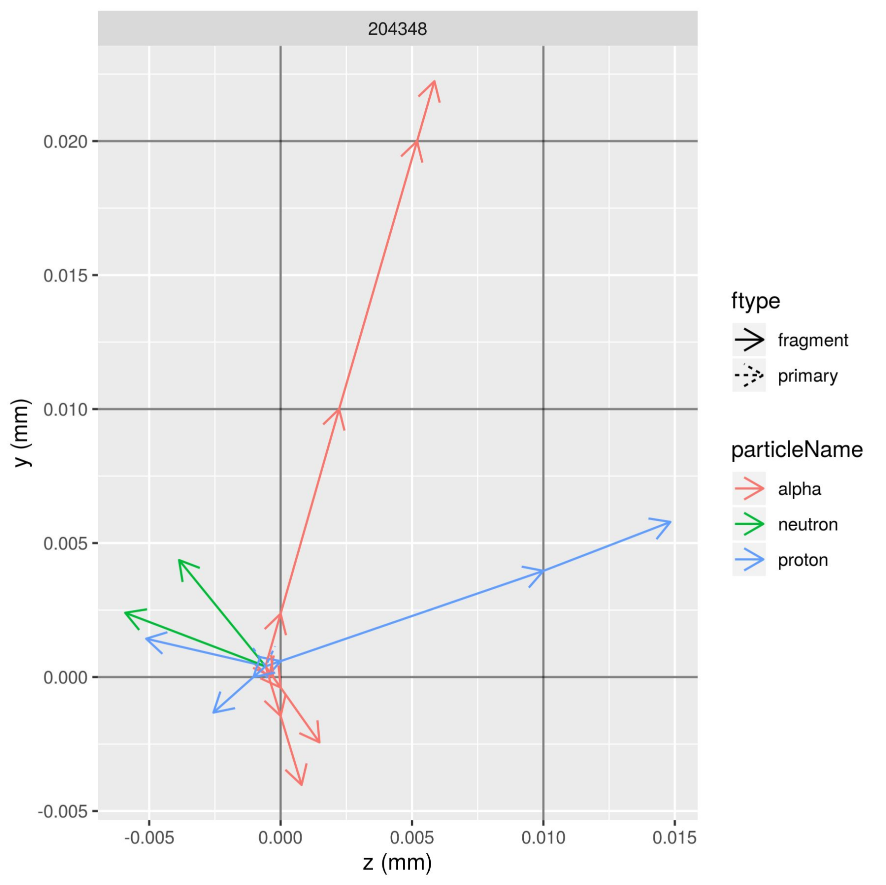
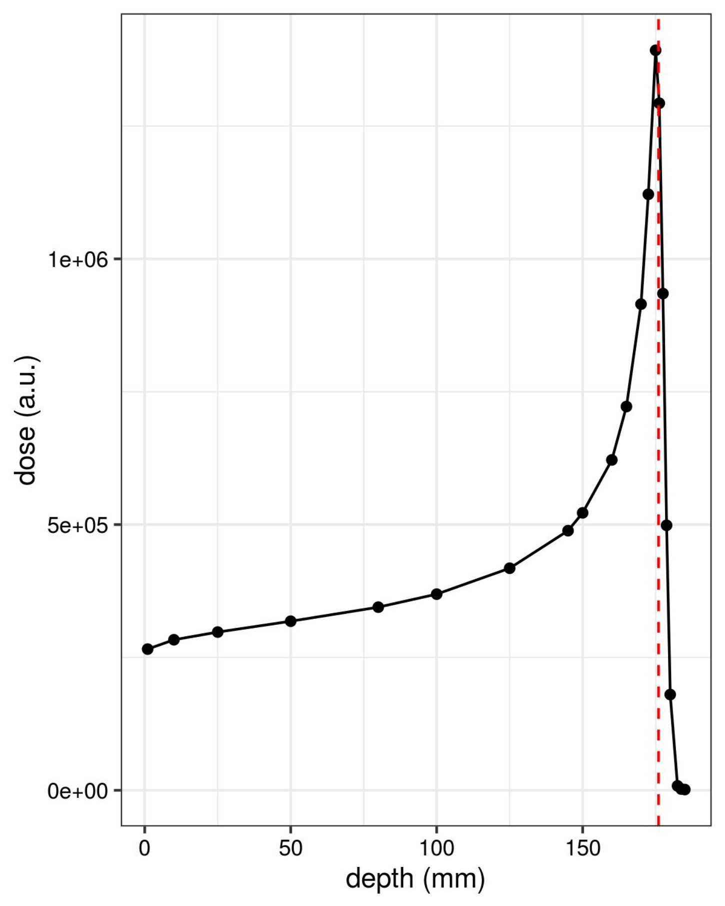
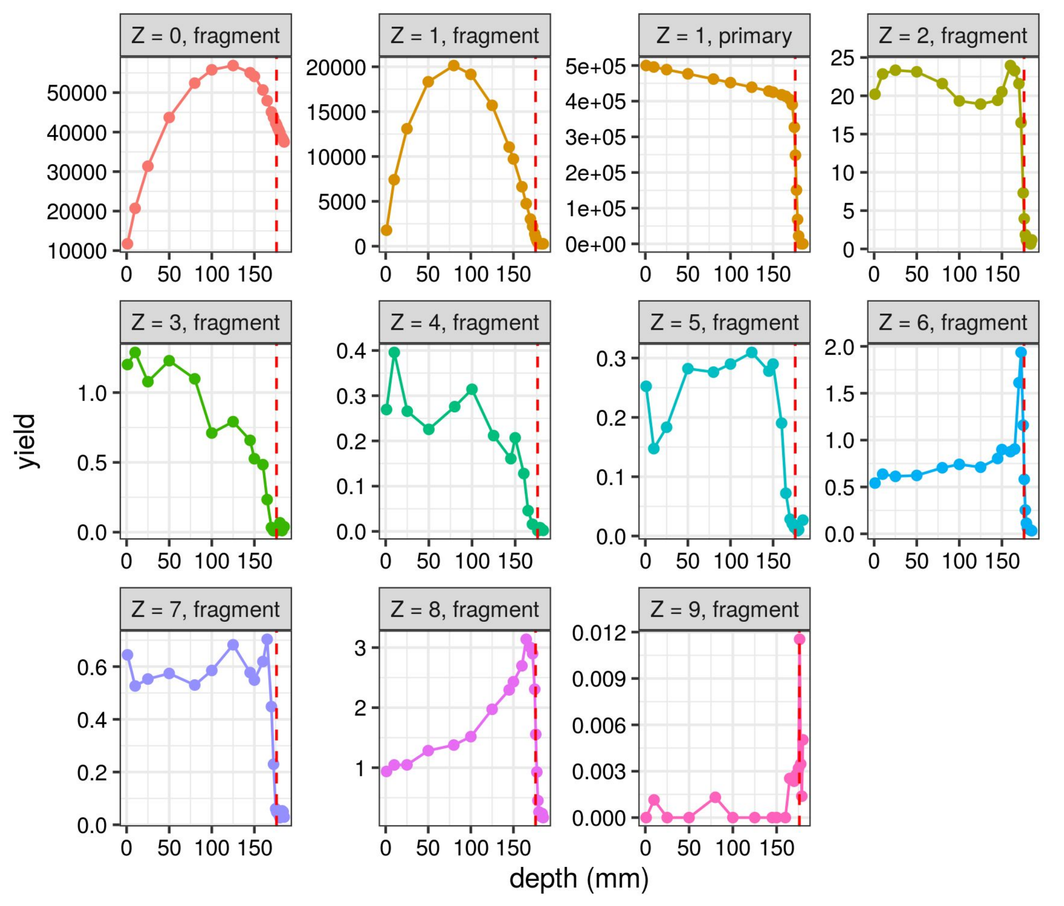


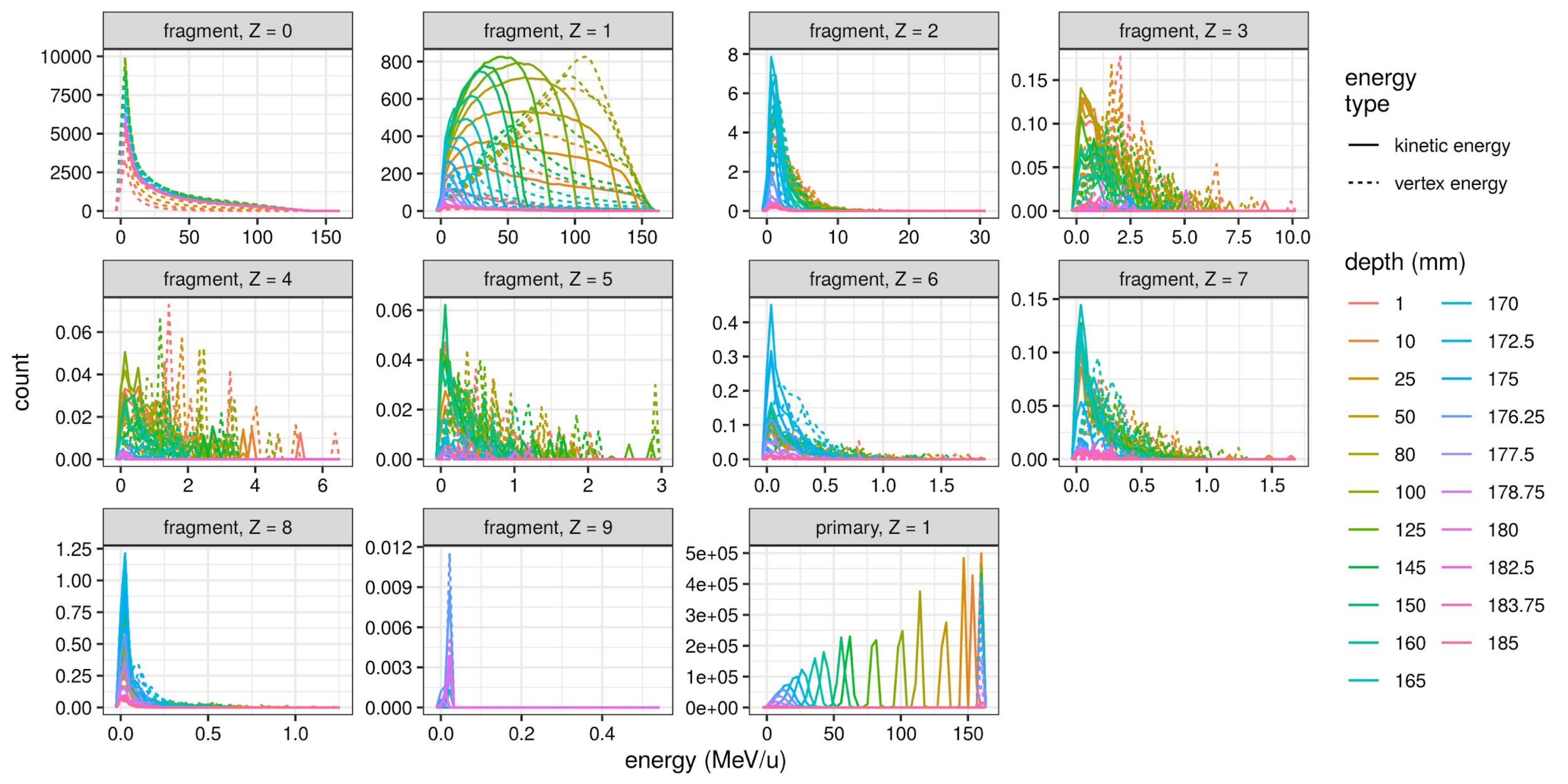


Dose & yield vs. depth (proton beam @ 160 MeV)





Kinetic and “vertex” energy (proton beam @ 160 MeV)



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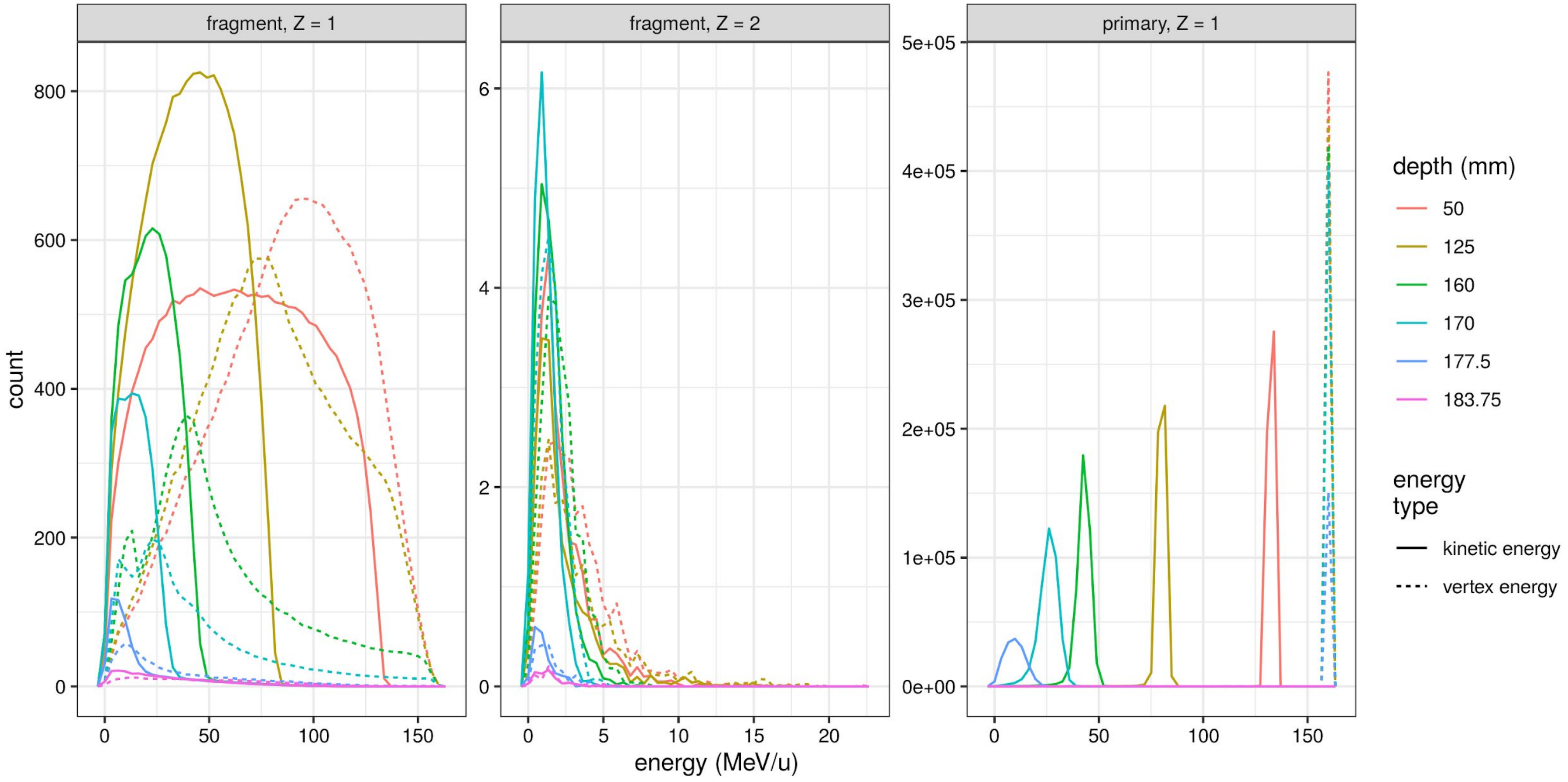
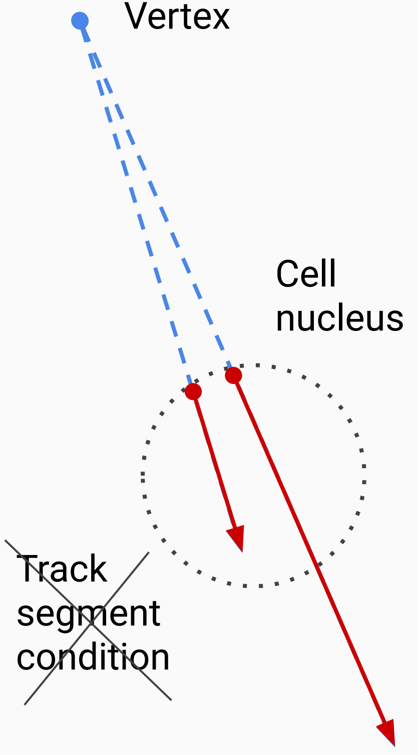
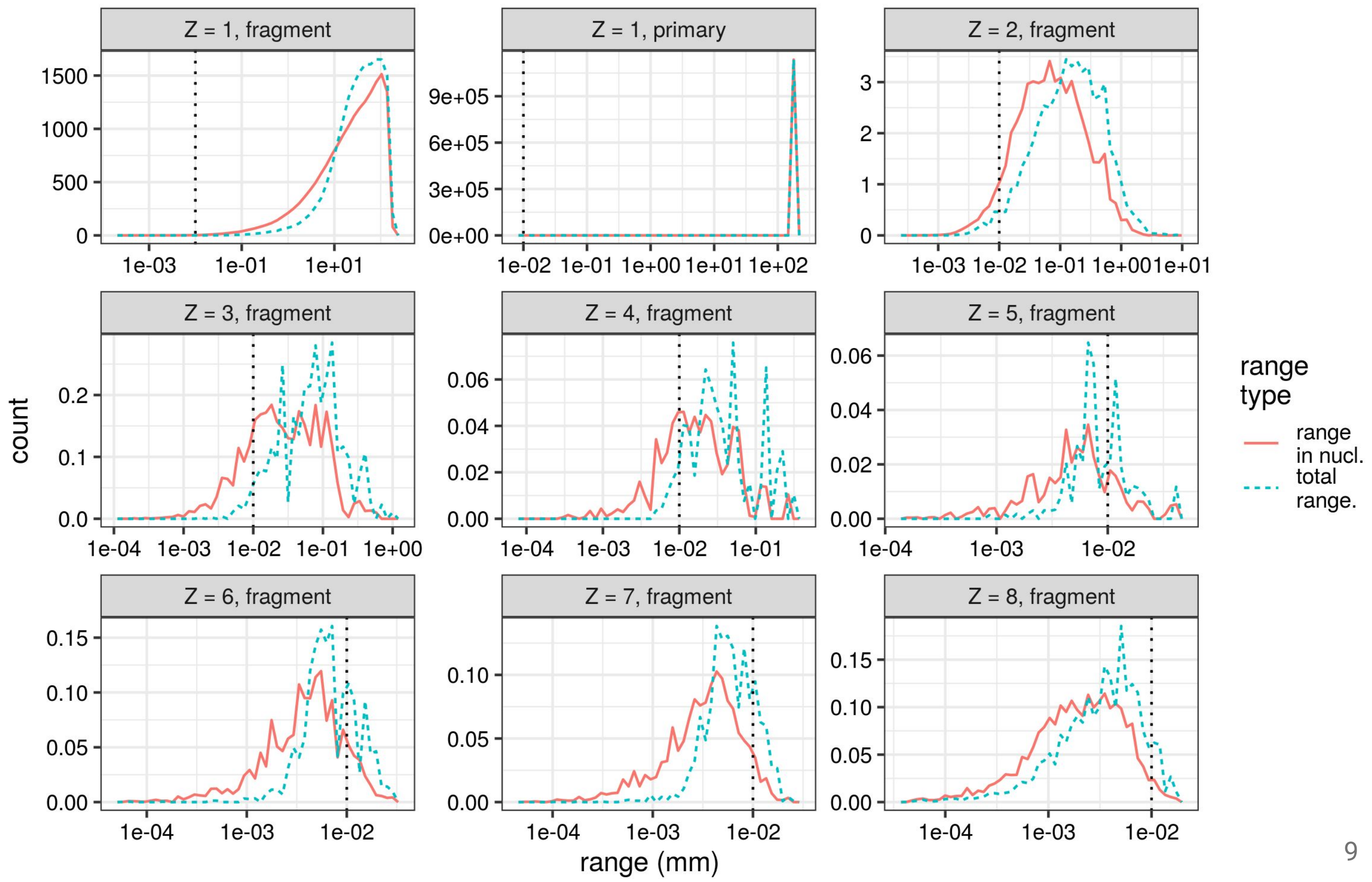


Residual range in cell nucleus considerations





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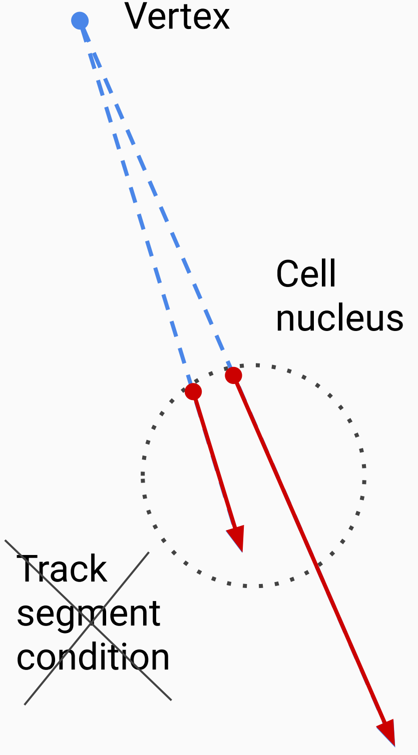
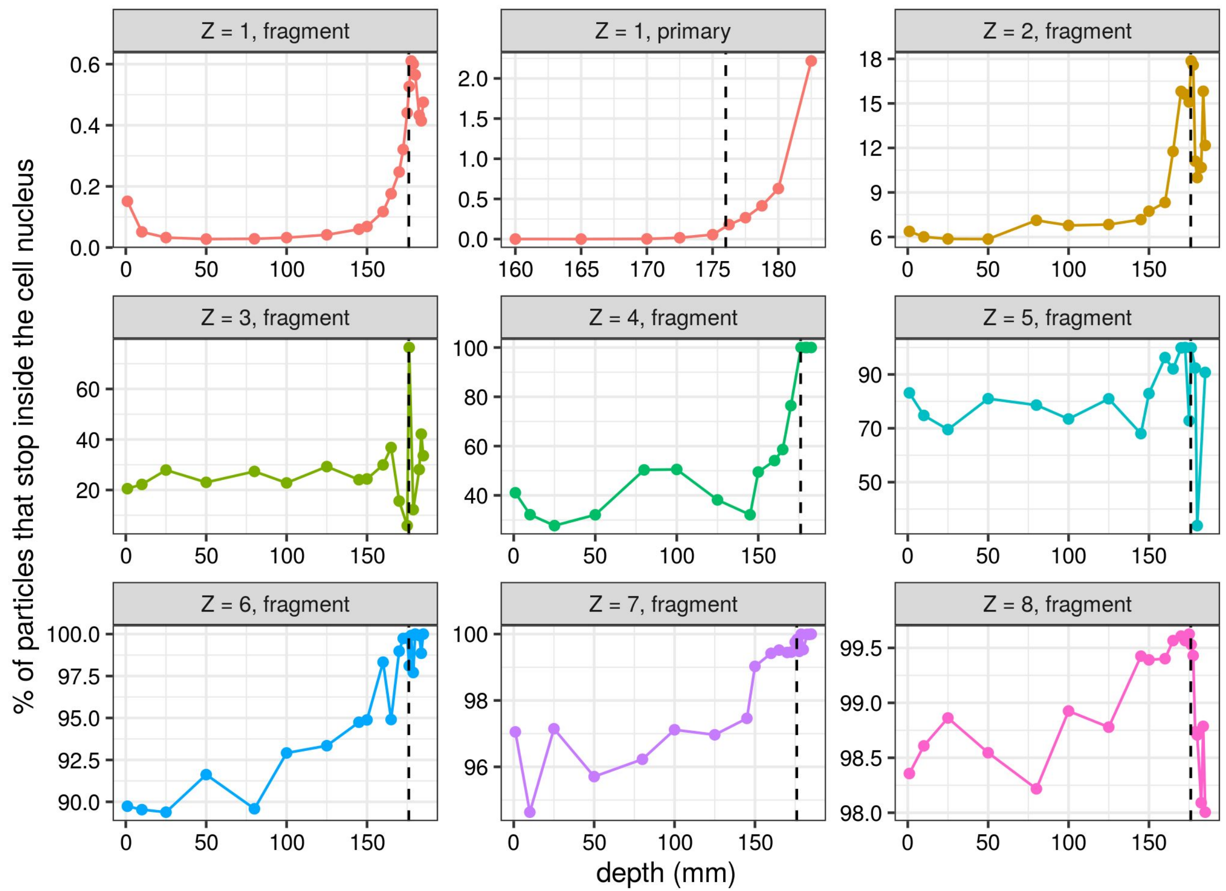




Biological impact - The relative Biological Effectiveness (RBE)

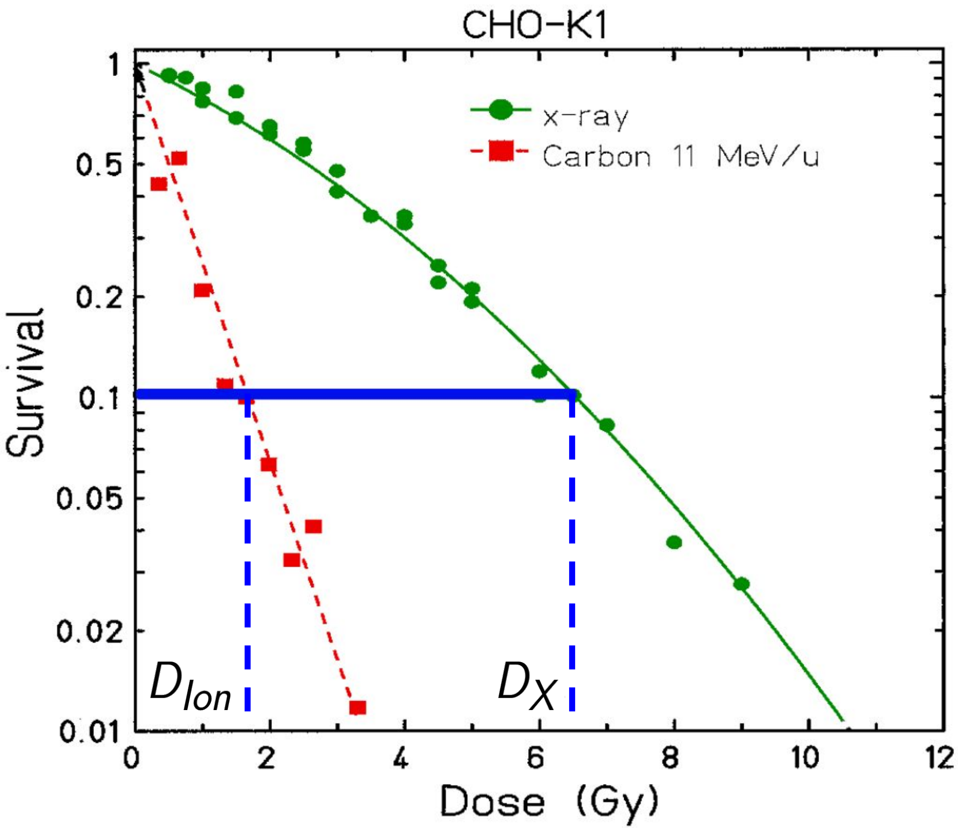
Relative Biological Effectiveness

RBE

$$RBE_n = \left.\frac{D_X}{D_{Ion}}\right|_{S_X=S_{Ion}=n}$$

RBE ~ 1.1 for protons
RBE > 1 for ions

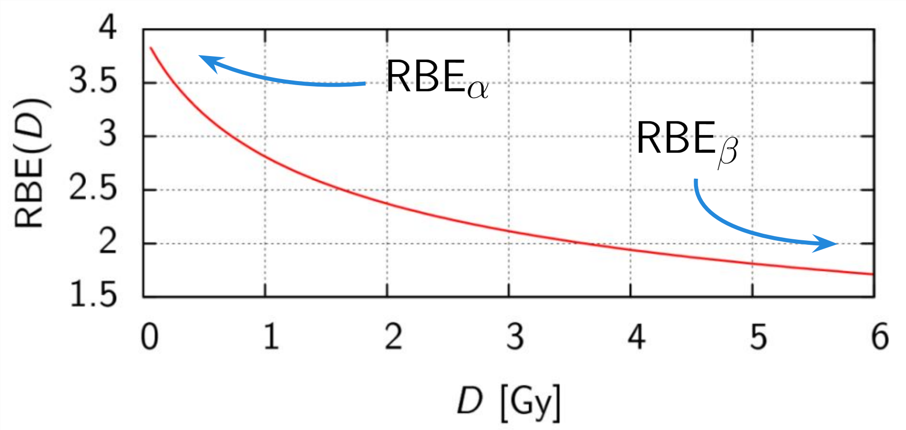
RBE-Weighted Dose (RWD):
RWD = *D* x RBE

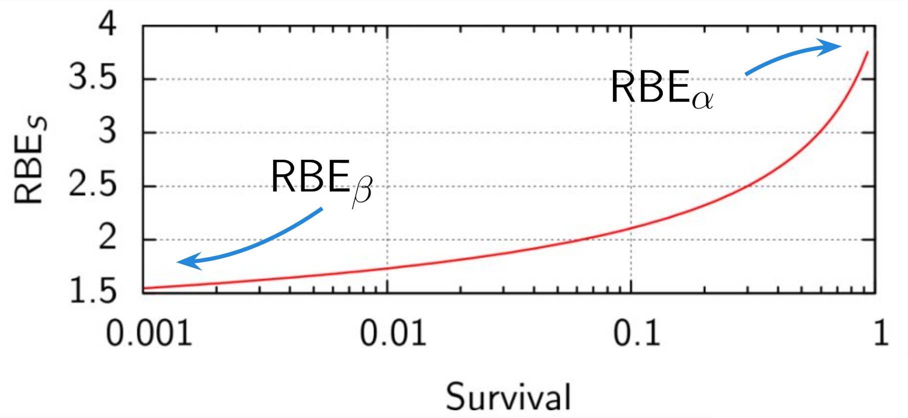


WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

Biological impact - The relative Biological Effectiveness (RBE)

$$\begin{cases} \mathrm{RBE}_\alpha = \alpha/\alpha_X \\ \mathrm{RBE}_\beta = \sqrt{\beta/\beta_X} \\ R = \alpha_X/\beta_X \end{cases} \Rightarrow \quad \mathrm{RBE} = R\left(-1+\sqrt{1+\frac{4}{R}\left(\mathrm{RBE}_\alpha D + \frac{(\mathrm{RBE}_\beta D)^2}{R}\right)}\right)/2D$$



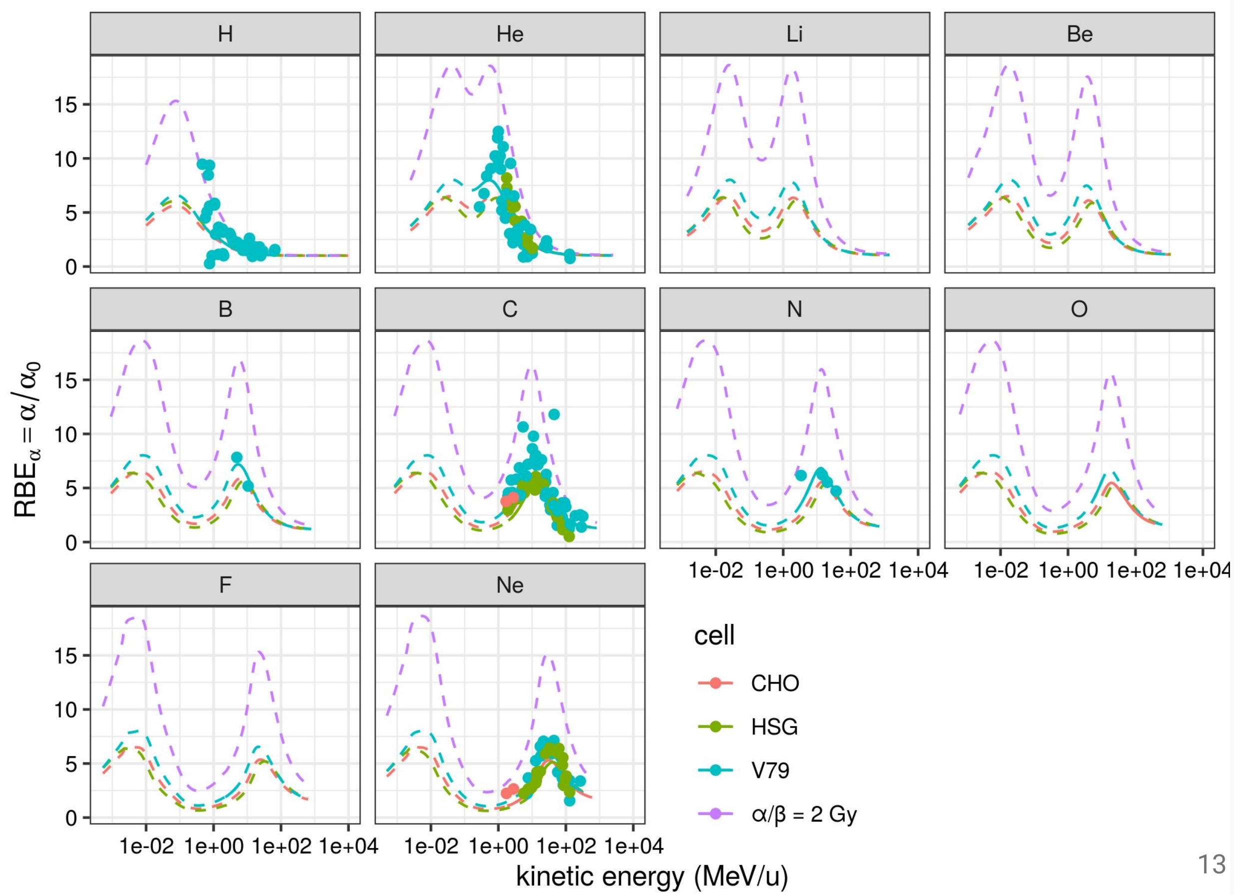


Choice of cell/model parameterization

cell	α0 ~ αx (Gy^-1)	β0 ~ βx (Gy^-2)	rN (μm)	rd (μm)
α/β = 2 Gy	0.1	0.05	4.5	0.35
HSG	0.313	0.0615	4.1	0.34
V79	0.184	0.02	4.1	0.26
CHO	0.3698	0.0706	5	0.3698

[Parameters from: Kase, Y., *et al*. (2008). Biophysical calculation of cell survival probabilities using amorphous track structure models for heavy-ion irradiation. *Phys. Med. Biol.*, 53(1), 37–59.

Experimental data taken from PIDE v3.1 (Friedrich, T. *et al*., 2019)]



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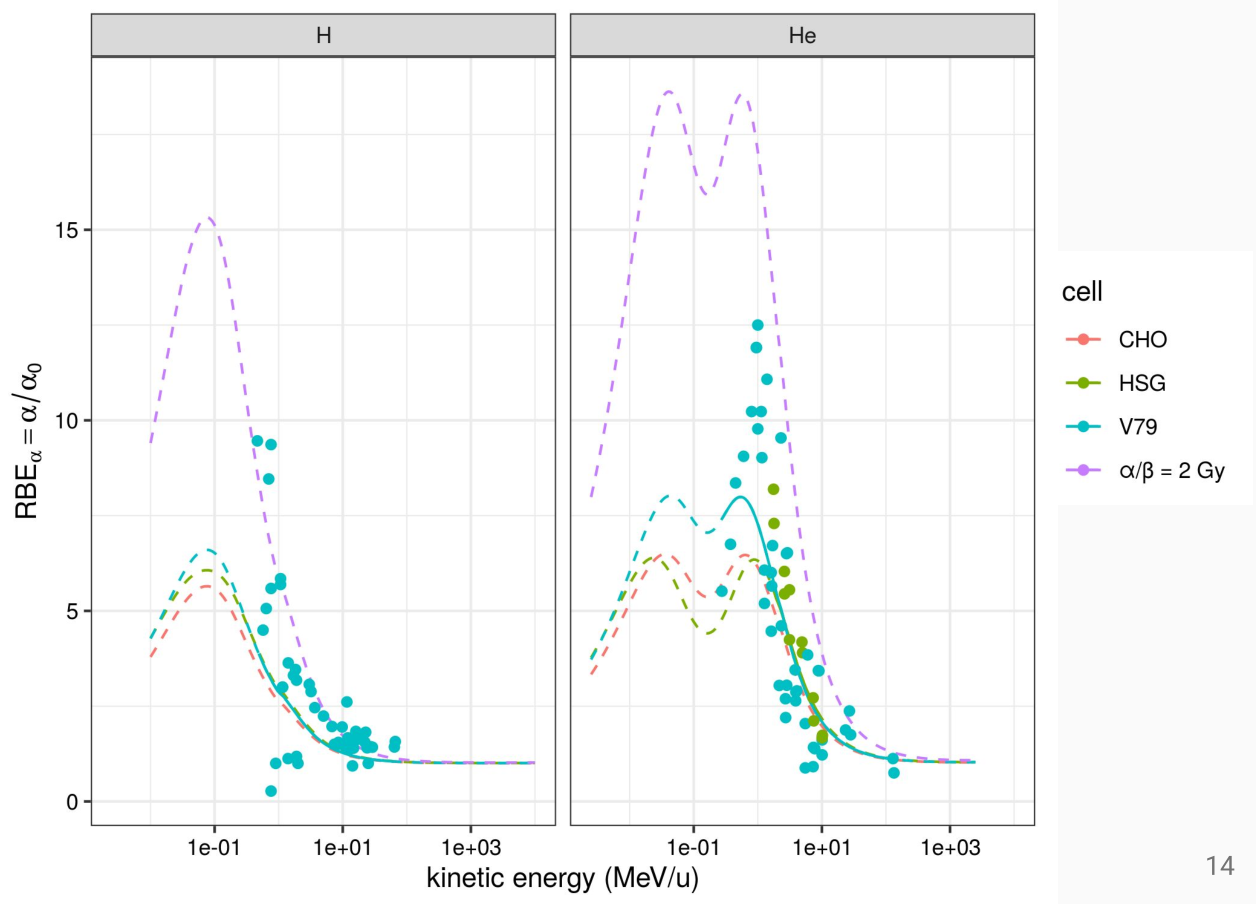
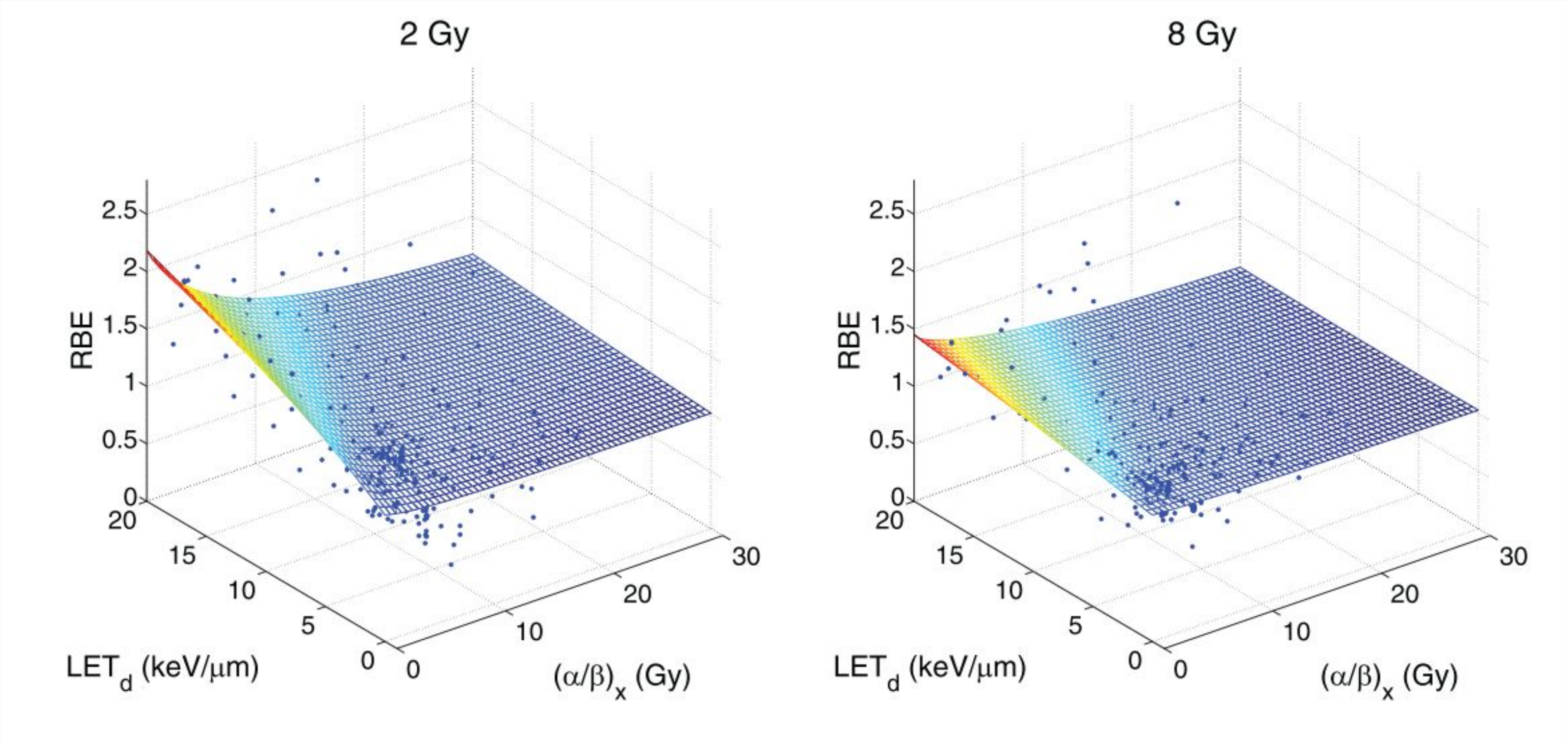
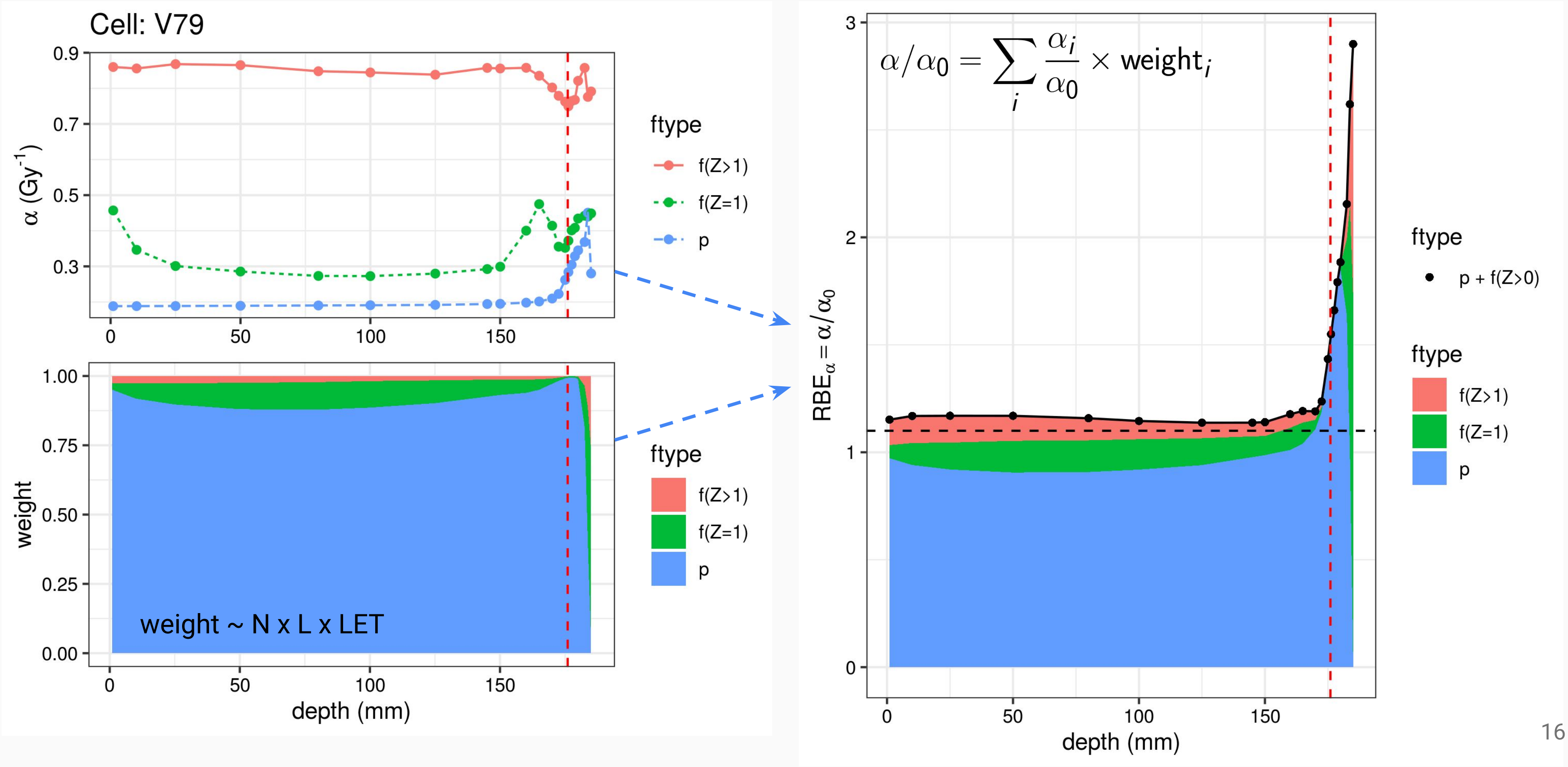


RBE vs. LET and α/β ratio

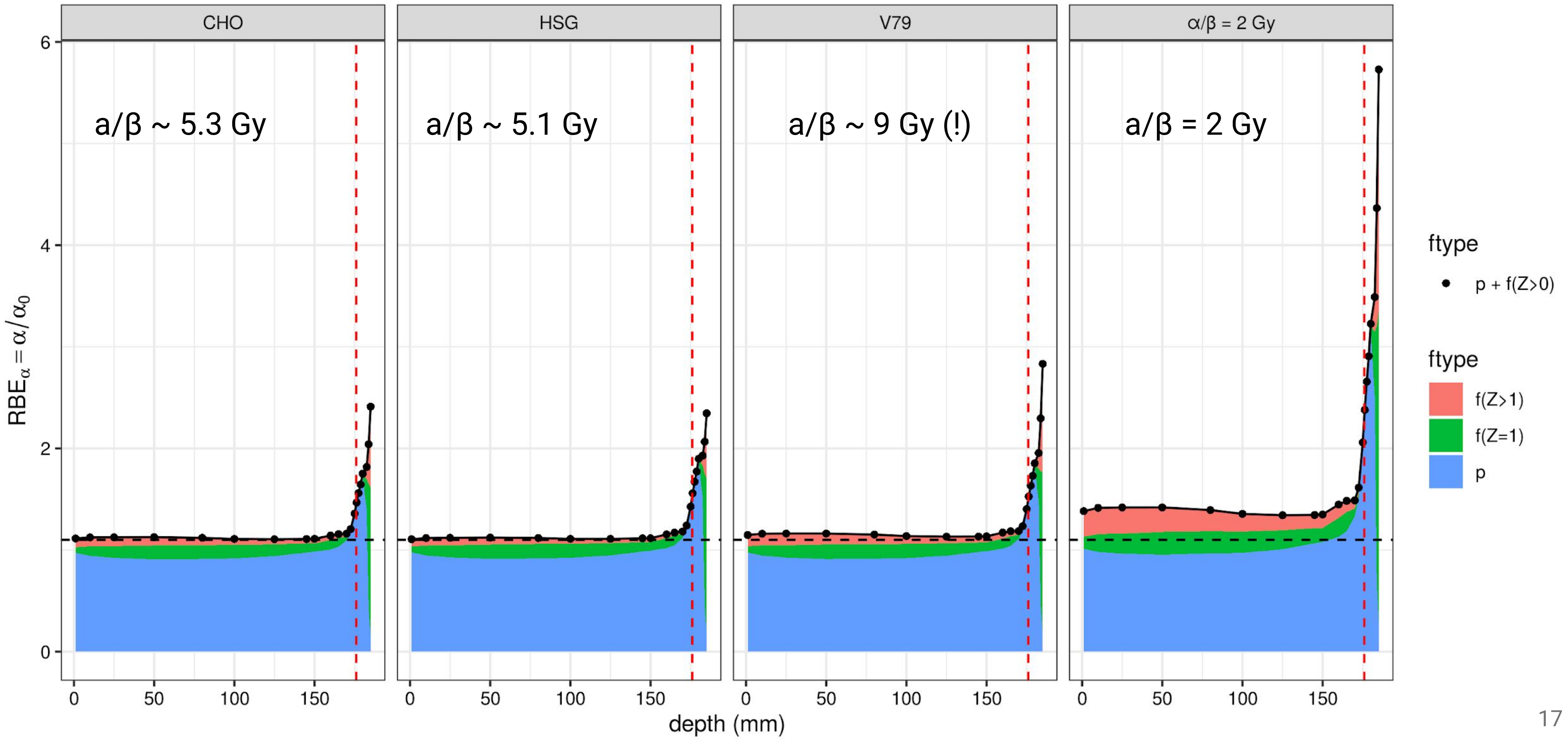


McNamara, A. L., Schuemann, J., & Paganetti, H. (2015). A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data. *Physics in Medicine and Biology*, *60*(21), 8399–8416.

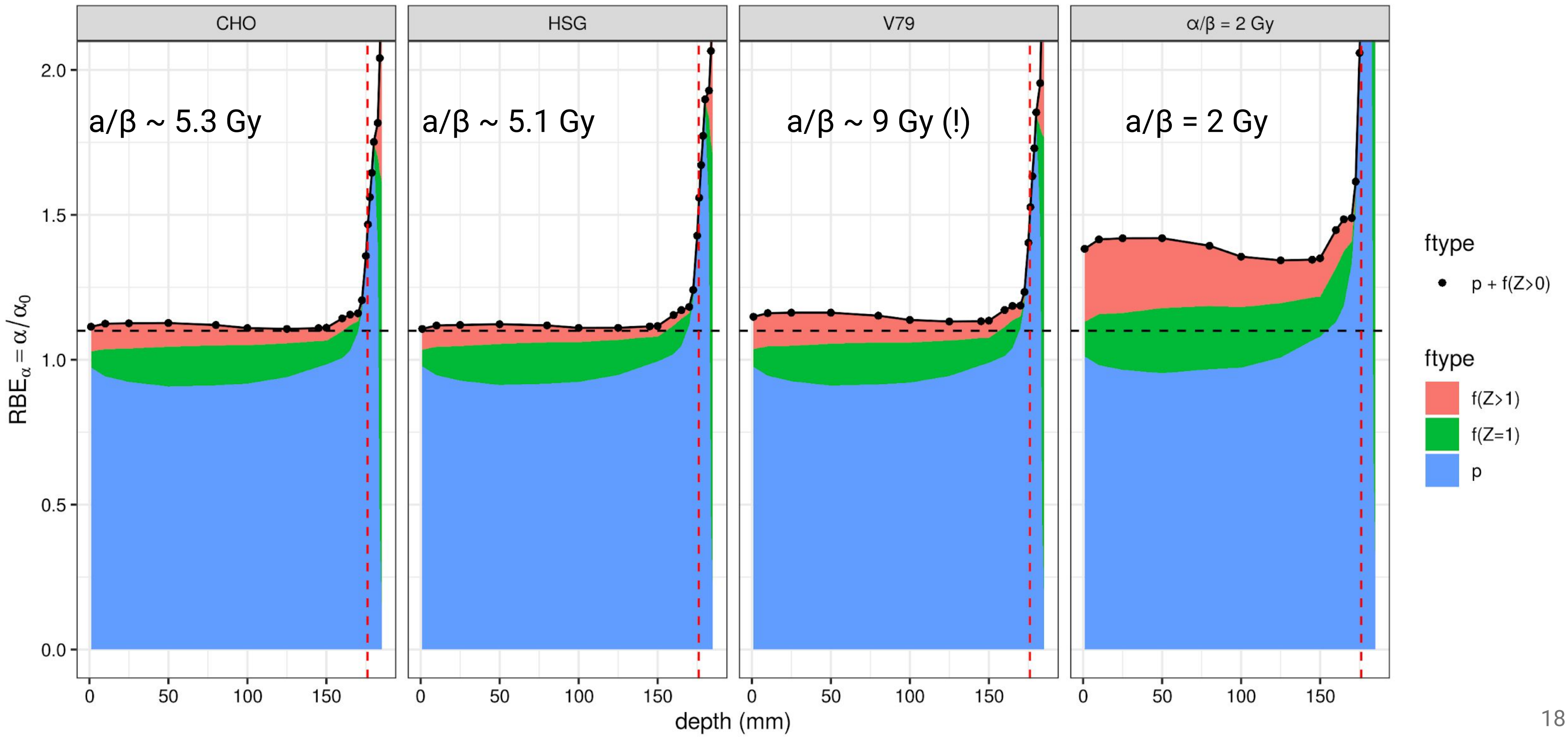
RBE contributions vs. depth (proton beam @ 160 MeV)



RBE contributions vs. depth, different cells



RBE contributions vs. depth, different cells (zoom in)



RBE, different cells (160 MeV proton beam, 10 mm)

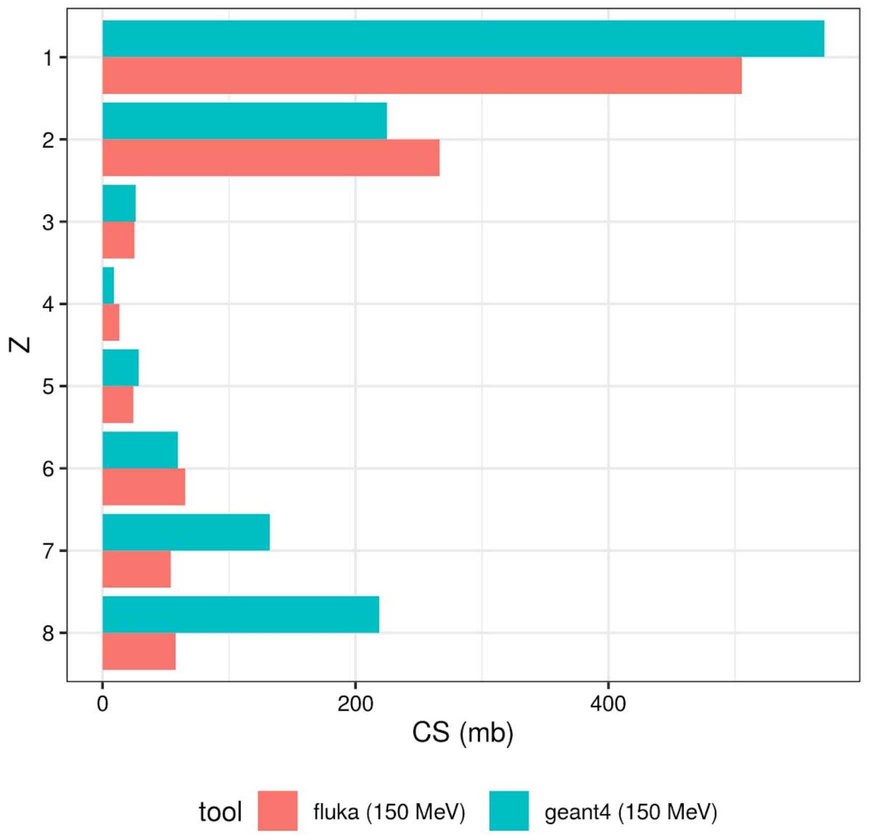
Cell	ftype	weight	RBEα
HSG	f(Z>1)	0.03	2.97
	f(Z>0)	0.08	2.20
	f(Z=1)	0.05	1.81
	p + f(Z>0)	1.00	1.12
	p + f(Z=1)	0.97	1.07
	p	0.92	1.03

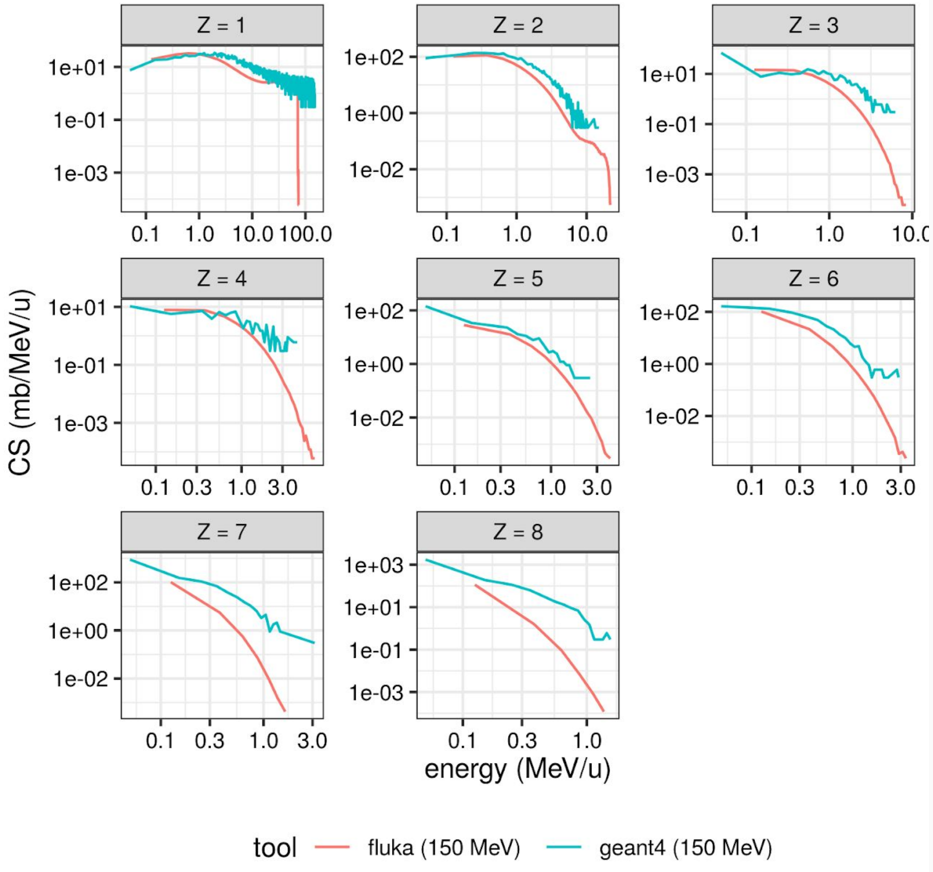
Cell	ftype	weight	RBEα
CHO	f(Z>1)	0.03	3.55
	f(Z>0)	0.08	2.34
	f(Z=1)	0.05	1.74
	p + f(Z>0)	1.00	1.13
	p + f(Z=1)	0.97	1.06
	p	0.92	1.02

Cell	ftype	weight	RBEα
V79	f(Z>1)	0.03	4.65
	f(Z>0)	0.08	2.80
	f(Z=1)	0.05	1.88
	p + f(Z>0)	1.00	1.17
	p + f(Z=1)	0.97	1.07
	p	0.92	1.02

Cell	ftype	weight	RBEα
α/β = 2 Gy	f(Z>1)	0.03	10.49
	f(Z>0)	0.08	5.68
	f(Z=1)	0.05	3.28
	p + f(Z>0)	1.00	1.44
	p + f(Z=1)	0.97	1.19
	p	0.92	1.06

Cross Section (CS) estimates





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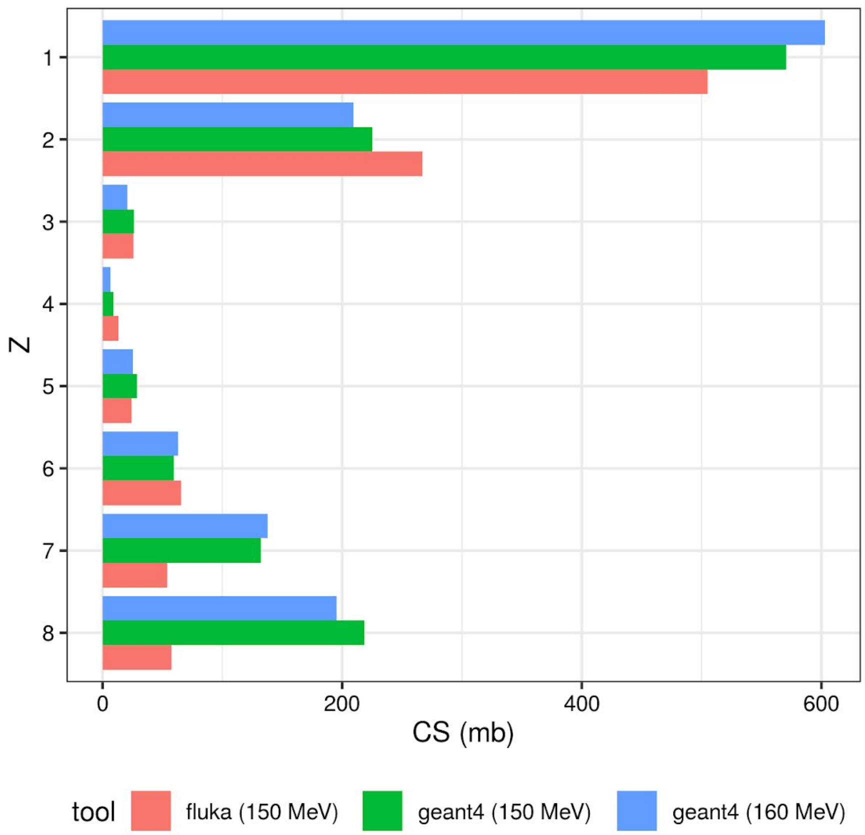
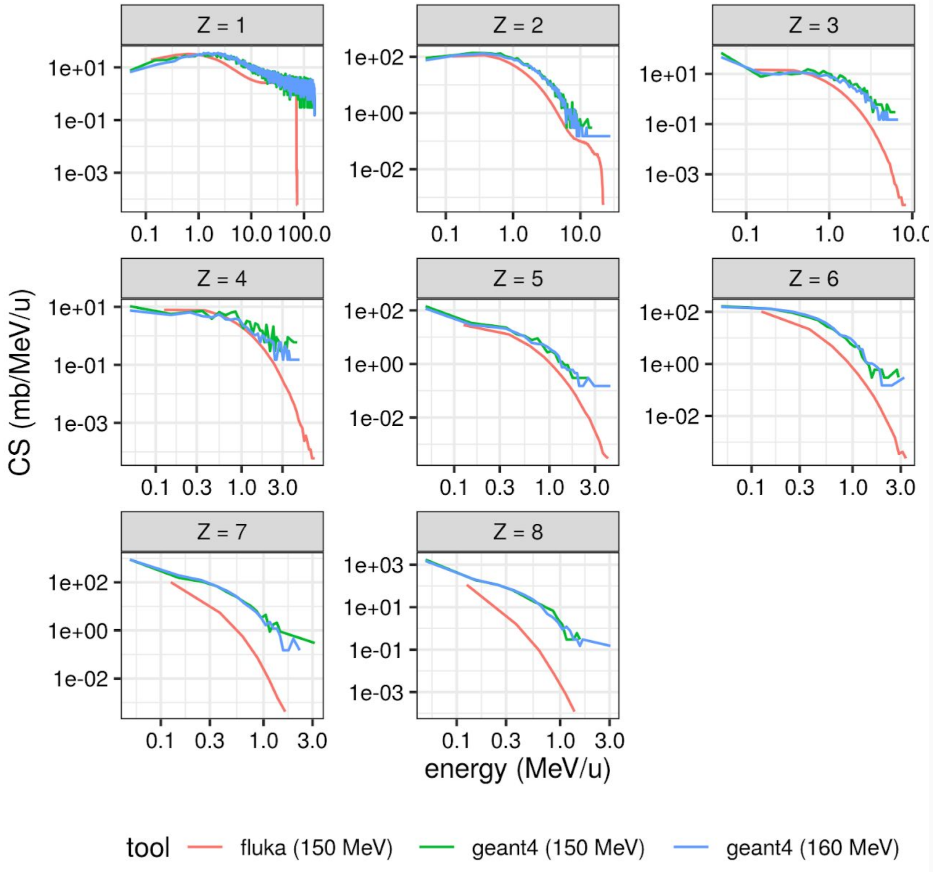
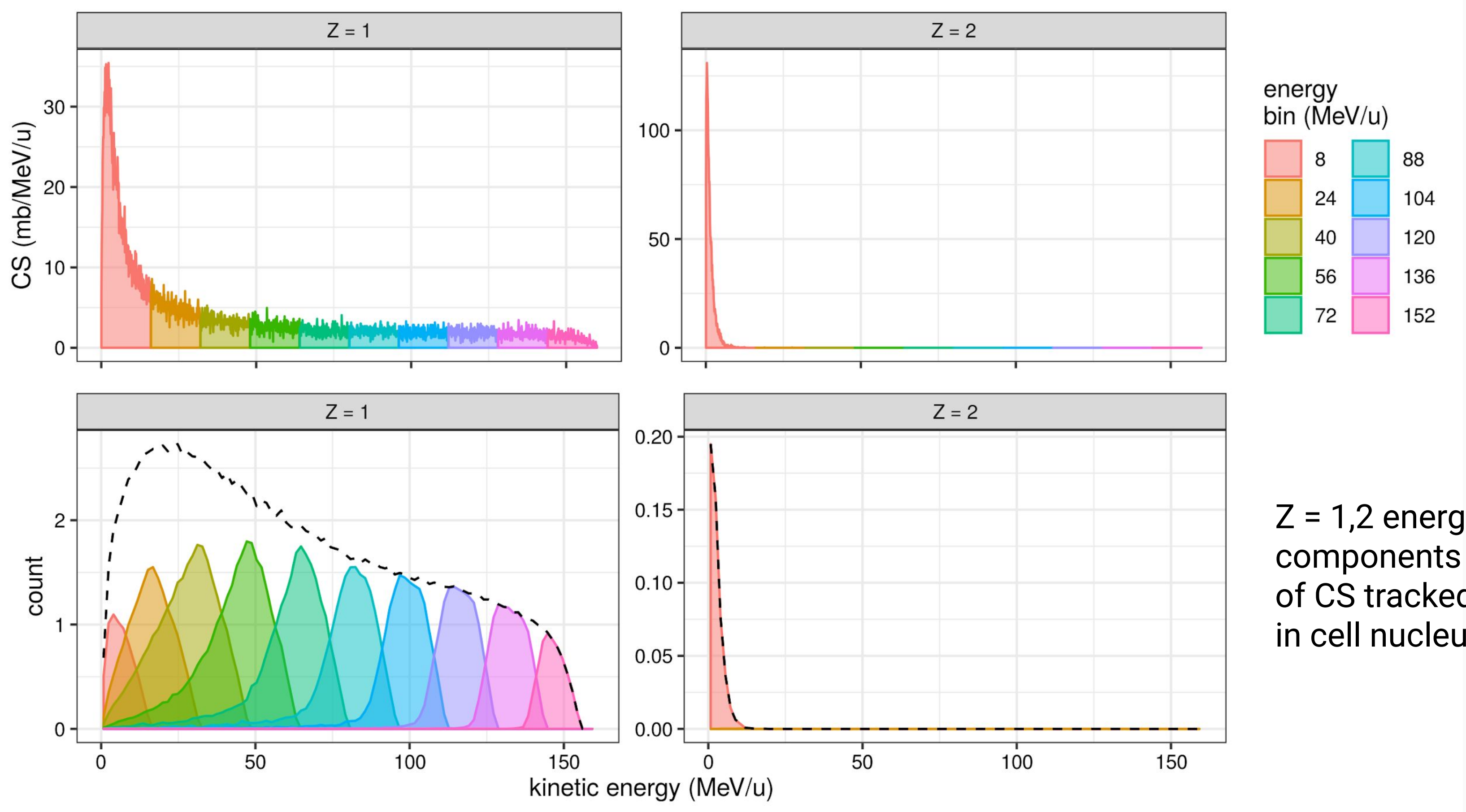


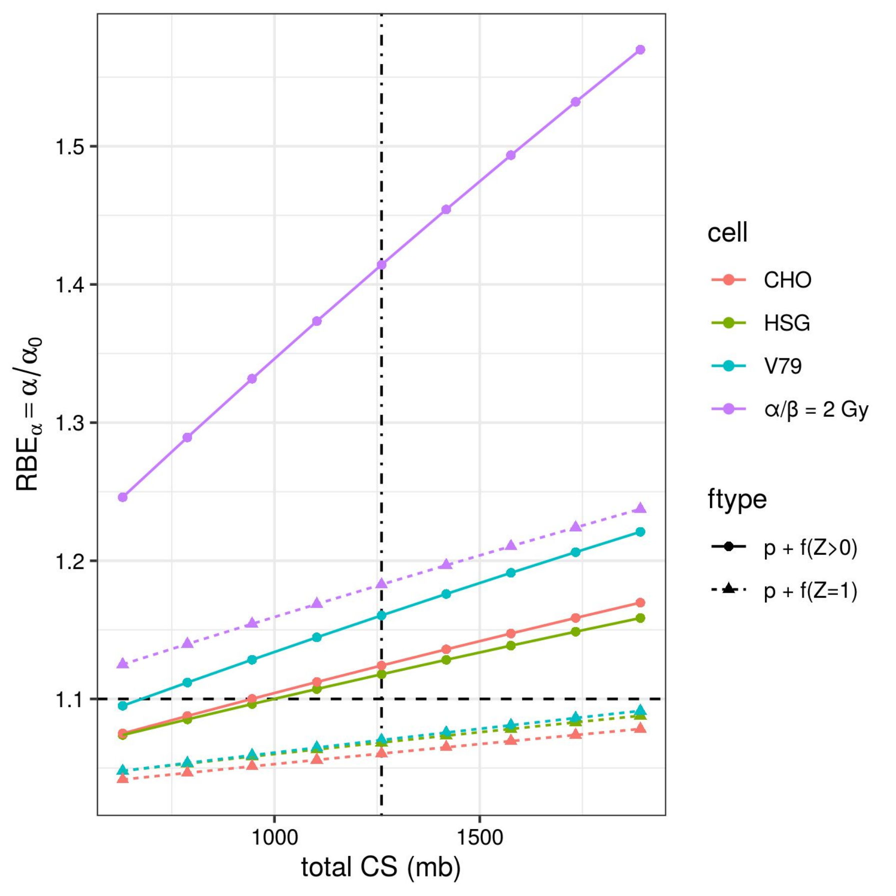


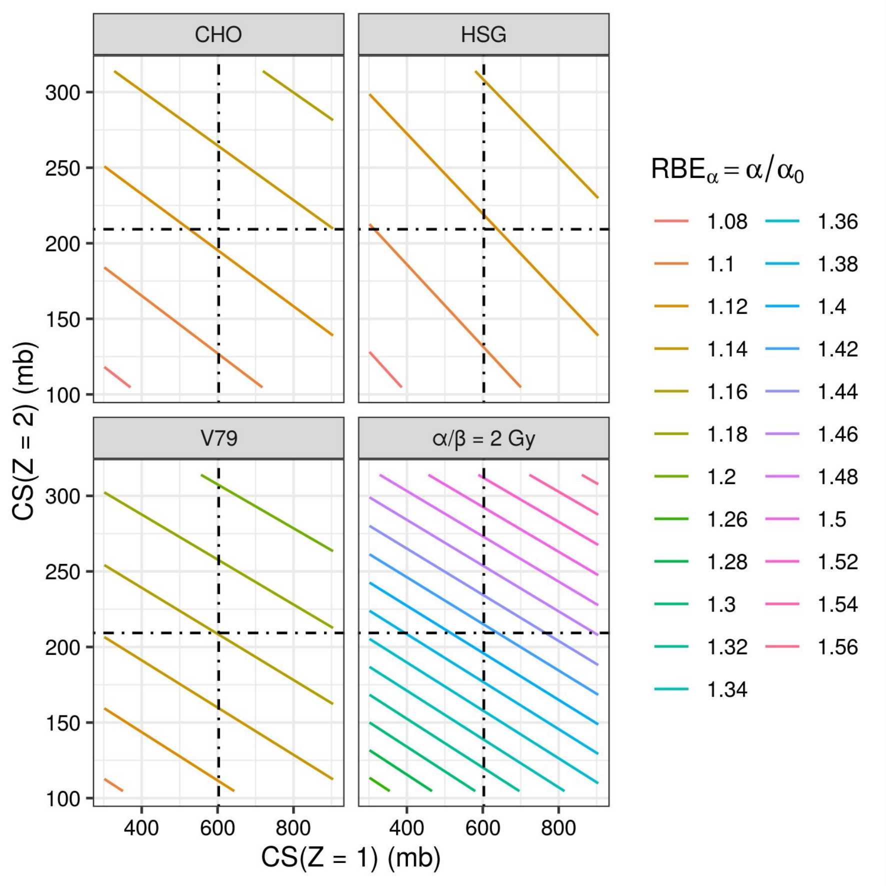
RBE vs. CS - energy components (evaluated at 10 mm)



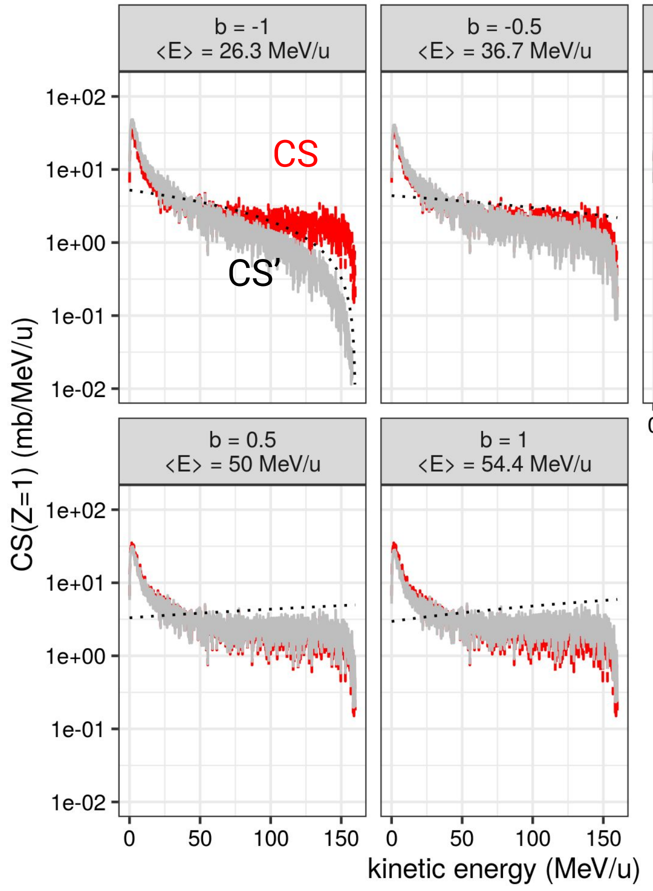
Z = 1,2 energy components of CS tracked in cell nucleus

RBE vs. total and partial CS (evaluated at 10 mm)

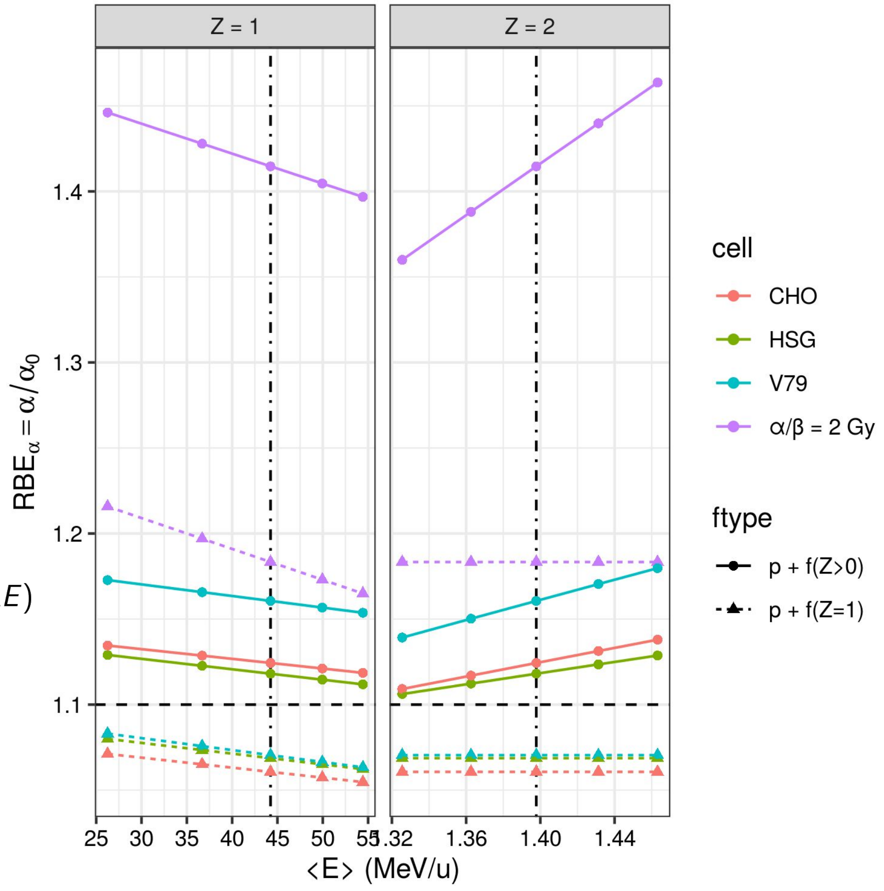




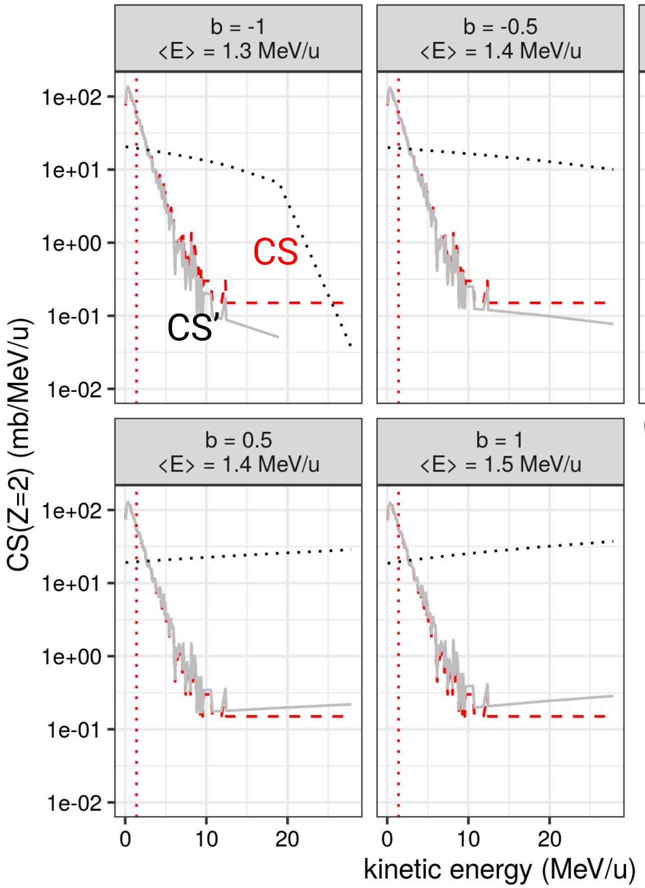
RBE vs. differential CS (evaluated at 10 mm)



$$CS' = CS(k + kb \times E/\Delta E)$$
$$b \in [-1, 1]$$
$$k = \int CS\, dE / \int CS'\, dE$$



RBE vs. differential CS (evaluated at 10 mm)



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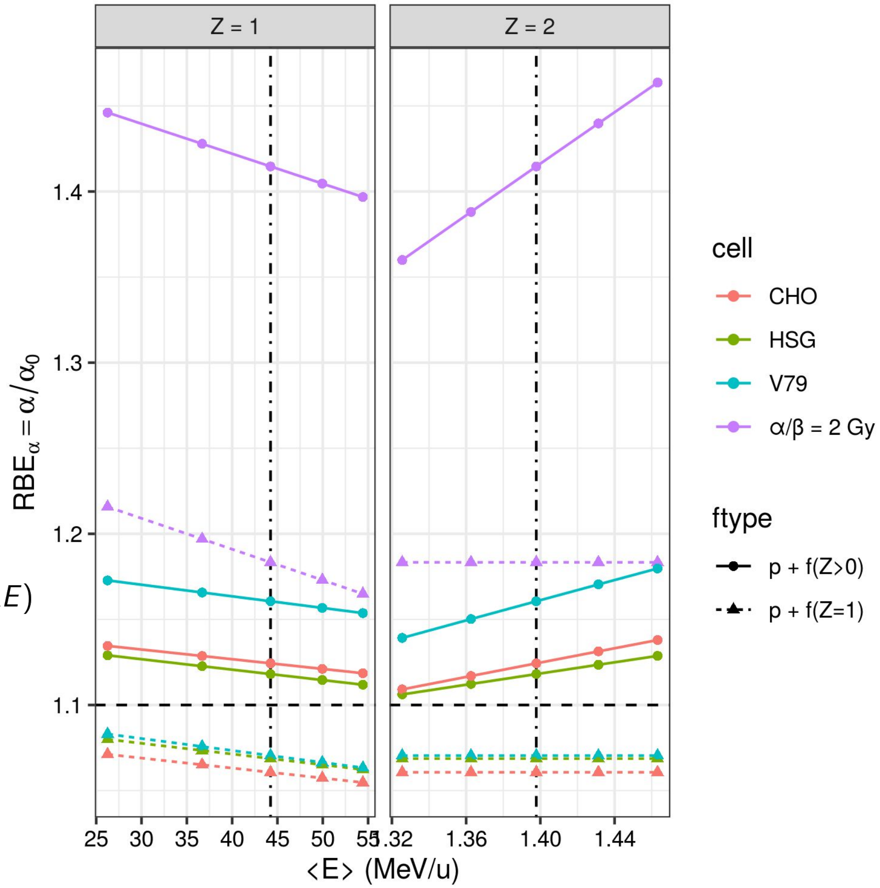


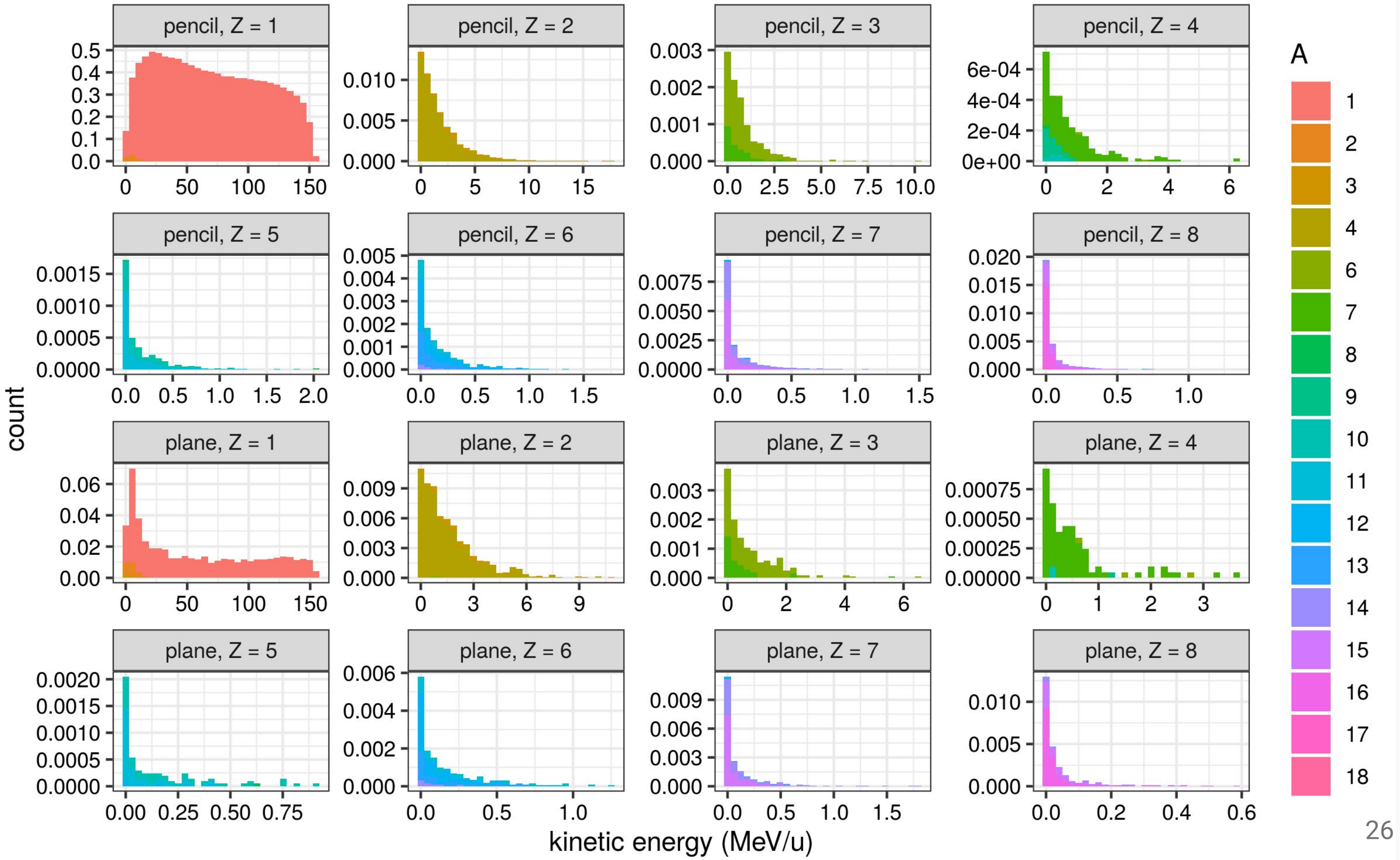
Field size effects on the RBE (evaluated at 10 mm)

pencil beam source

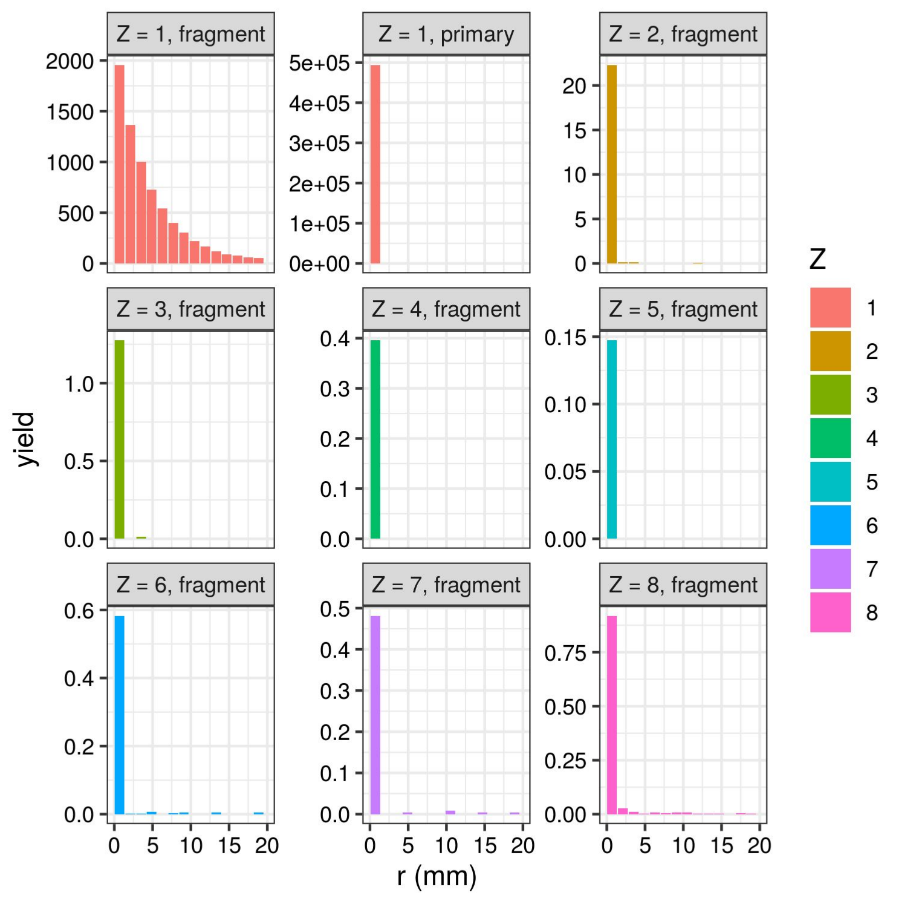
protons @ 160 MeV

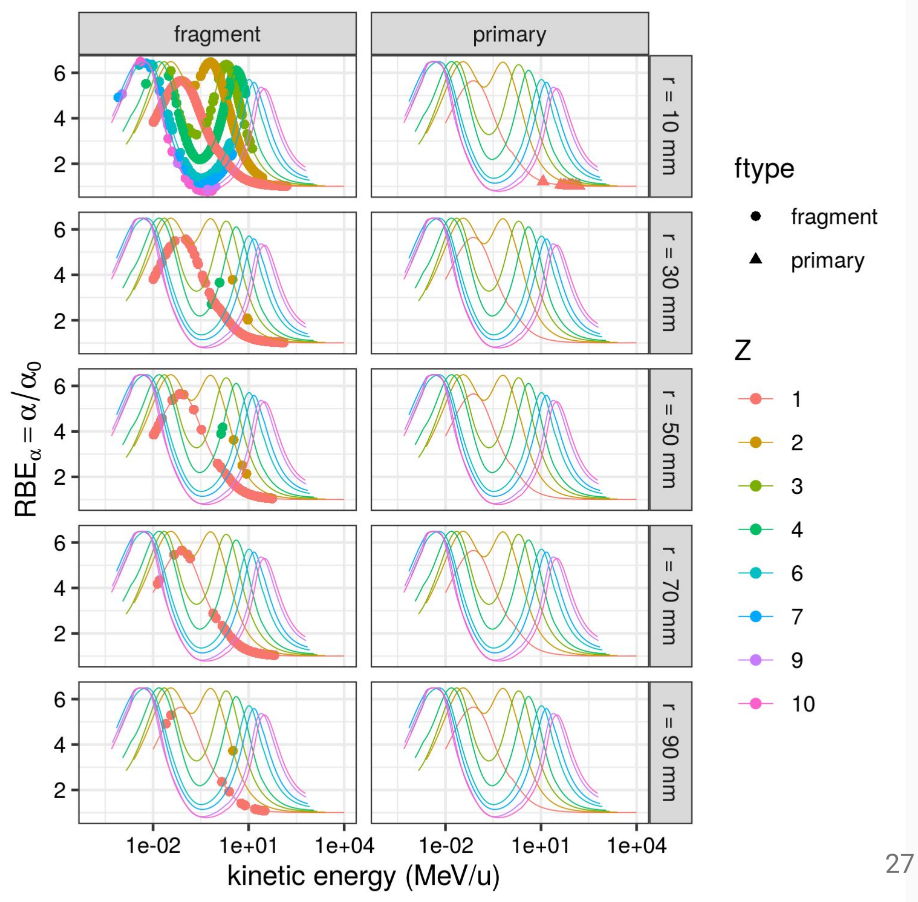
“plane” beam source

protons @ 160 MeV

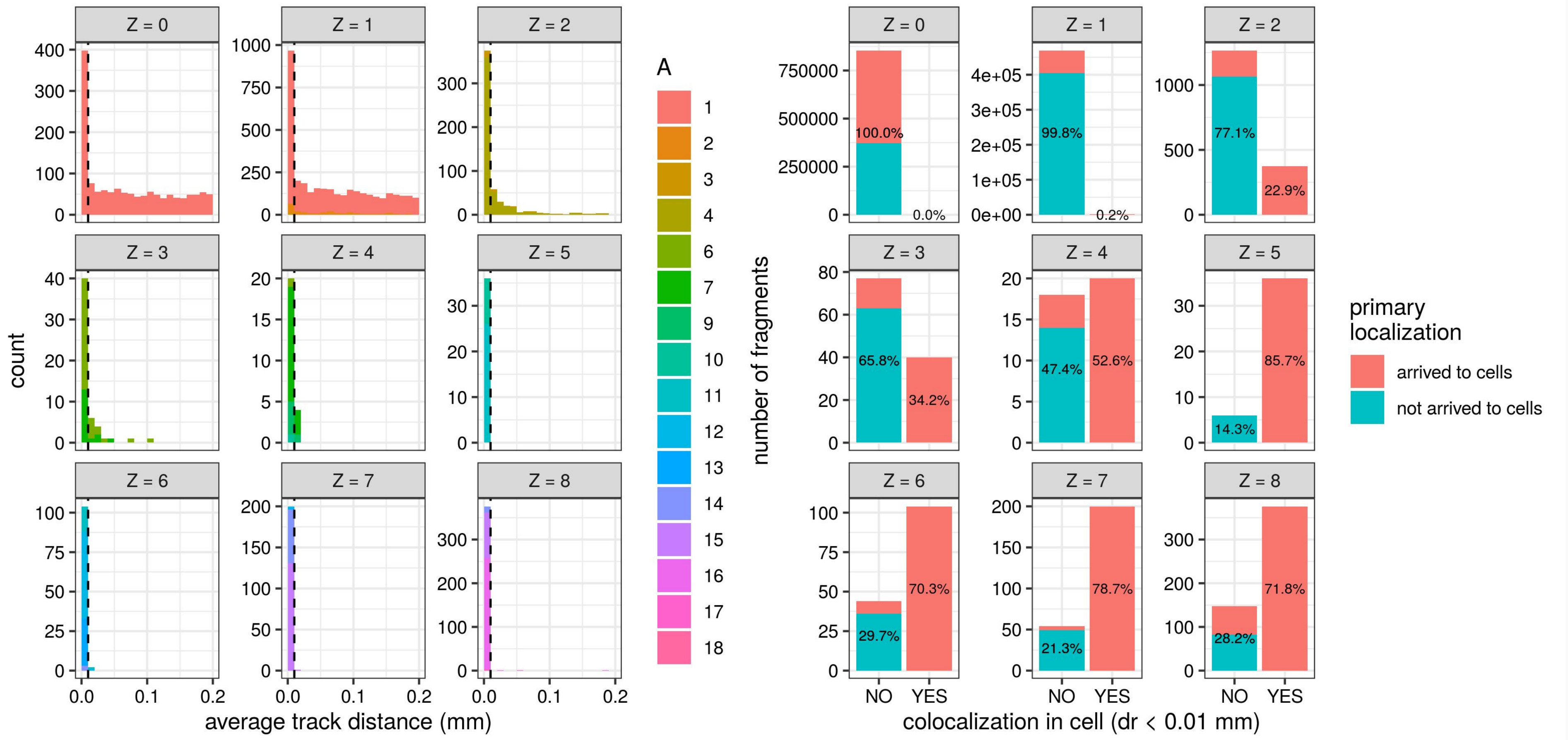


RBE radial dependence (evaluated at 10 mm)





Pair distribution for tracks (evaluated at 10 mm)



Conclusions

- We implemented a “MICRO” MC simulation using a thin mobile monolayer of voxels (10 x 10 x 10 μm^3) to sample the microscopic energy deposition in cell nuclei volumes.
- We have observed a sensible RBE contribution (RBE=1.12-1.44) from target fragmentation (Z=1 and Z>1, from water molecules) using 160 MeV protons and the “nominal” CSs implemented in MC codes (geant4 & fluka) combined with a MKM-based radiobiological evaluation.
- A RBE sensitivity analysis on the production CS (total and differential) shows:
  - interplay between LET and range of fragments.
  - dependence on the specific cell line.
  - higher sensitivity for cells with low α_X/β_X ratio.
- Geometrical conditions of the irradiation and the field size effects might play a role.

Next steps

- Extension of existing radiobiological models to better account for:
  - inapplicable track segment conditions (inclusion of track length in LEM and MKM).
  - tracks colocalization in cell (MC approach for both LEM and MKM).
- Study of Oxygen fragmentation.
- RBE vs. total and differential CS for complete irradiated 3D volume (monoenergetic beams, SOBP → patient, using Trip98/RPlanit).

↓

- Later on...substitution of "nominal" CSs implemented in MC codes with the experimental CSs from FOOT experiment.