Trento Institute for Fundamental Physics and Applications

FOOT Annual Meeting Bergamo 2023

Biological impact of proton target fragments: where do we stand

Emanuele Scifoni, Francesco Tommasino and Andrea Attili
on behalf of the MoVe IT collaboration

Outline

- Introduction
  - RBE in a mixed field
    - The MoVe IT Task 1.1
- The standard approach (Bellinzona 2021)
- Additional analysis
- Derivated approach (pB fragmentation)
- Outlook: Impact on other projects

Biological impact - The relative Biological Effectiveness (RBE)

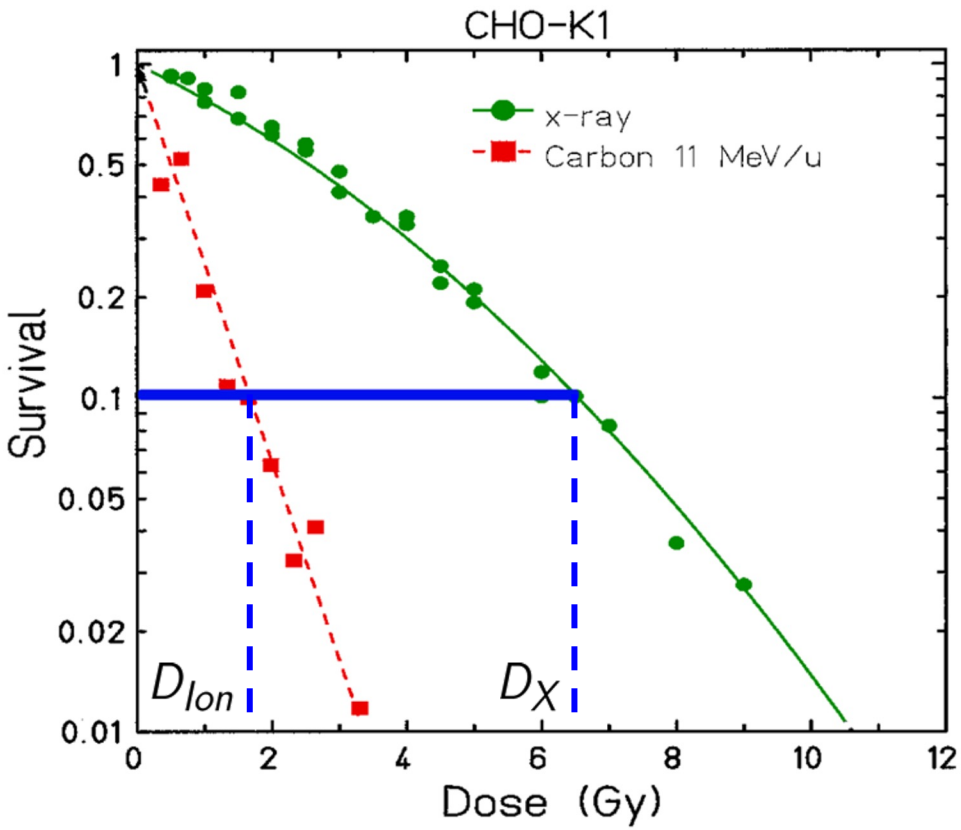
Relative Biological Effectiveness

RBE

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

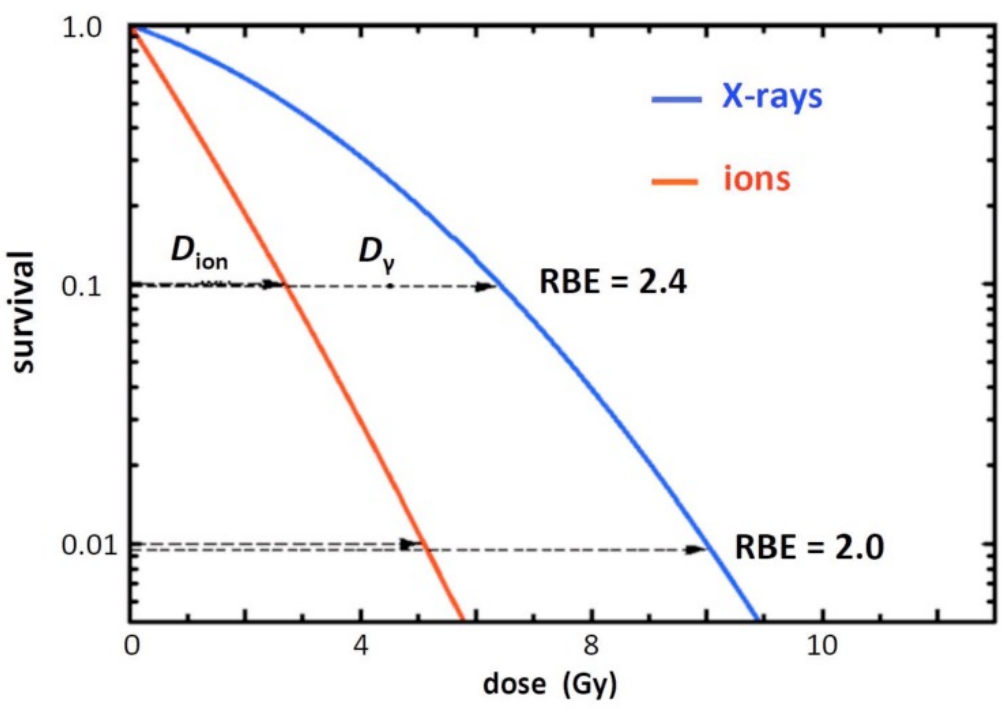
RBE ~ 1.1 for protons
RBE > 1 for ions

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



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

Biological impact - The relative Biological Effectiveness (RBE)



$$RBE = \frac{D_{reference}}{D_{radiation}}\Big|_{isoeffect}$$

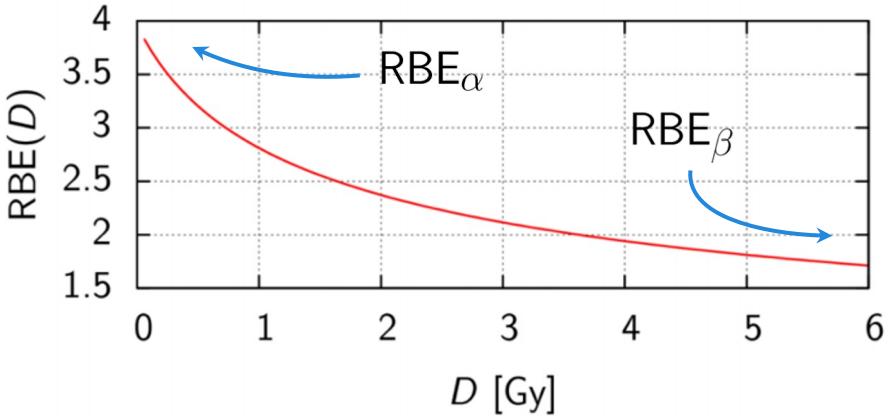
$$RBE_{10} = \frac{D_{reference}}{D_{radiation}}\Big|_{S=10\%}$$

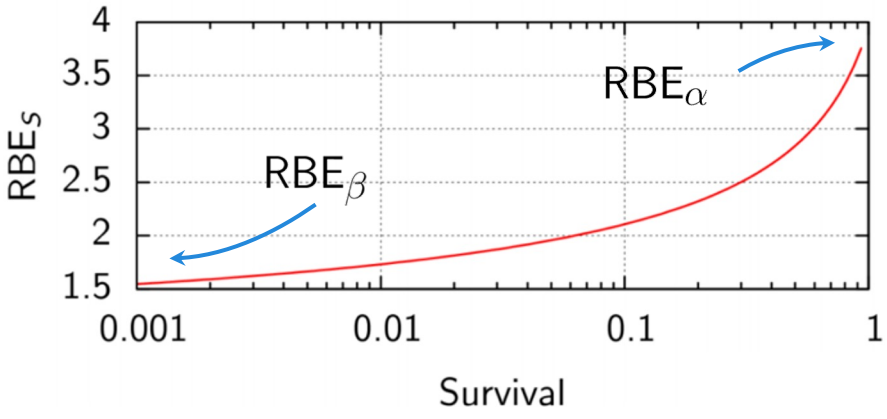
Amaldi U. et.al. (2019)

$$s(D) = \begin{cases} e^{-\alpha D - \beta D^2} & : D \le D_t \\ e^{-\alpha D_t - \beta D_t^2} e^{S_m (D - D_t)} & : D > D_t \end{cases}$$

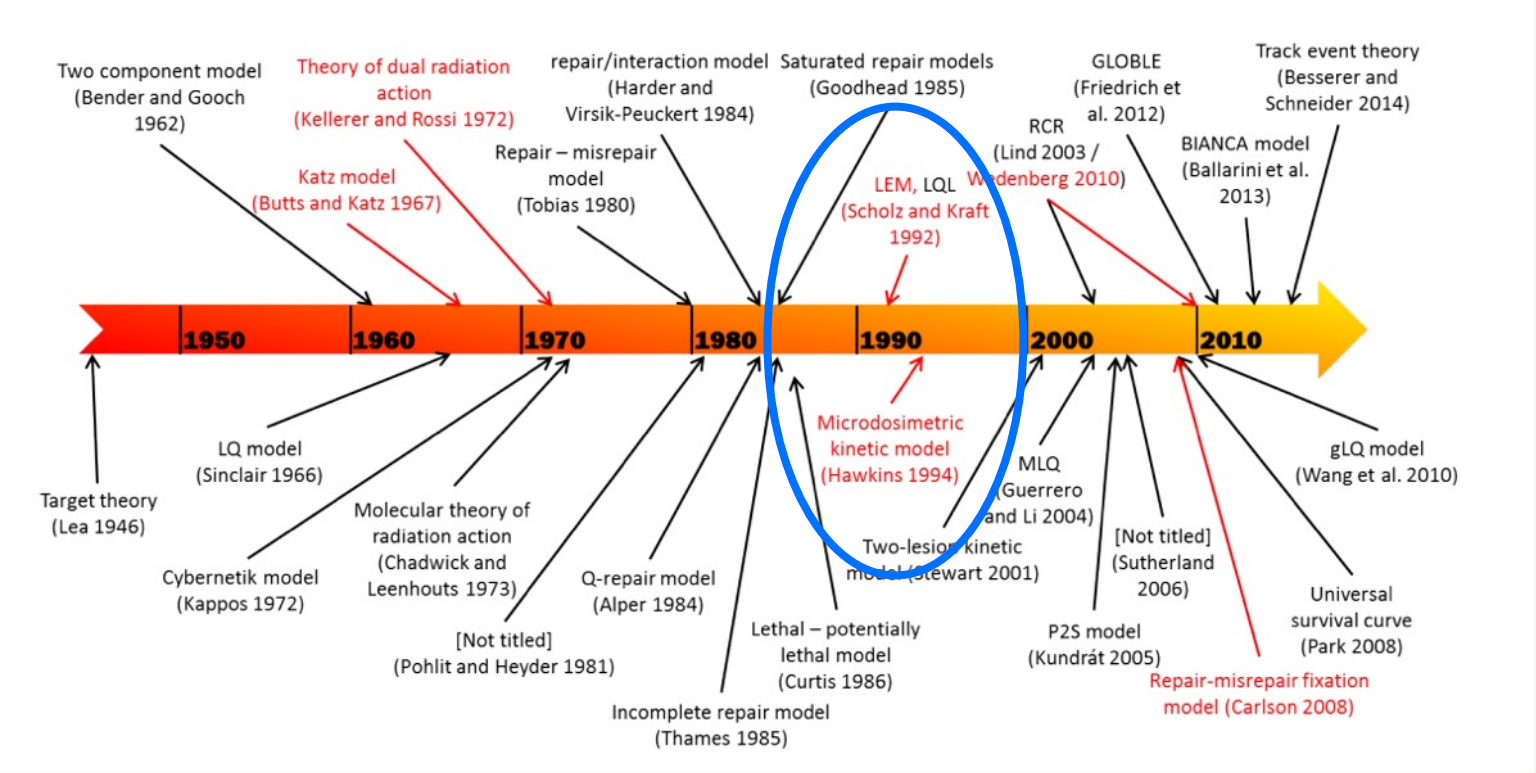
Biological impact - The relative Biological Effectiveness (RBE)

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





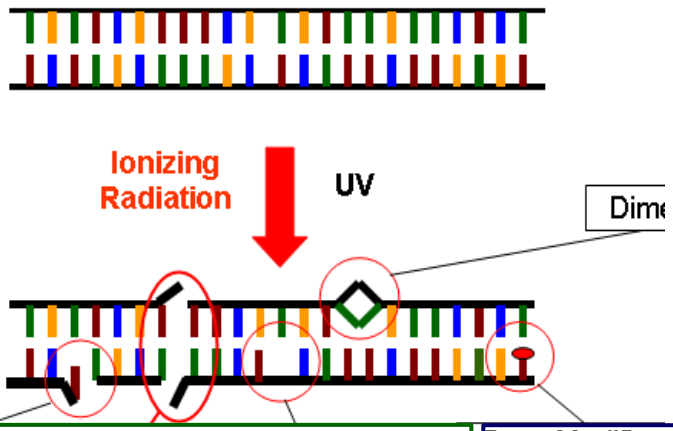
Mechanistic RBE models



Friedrich T. Hab. Thesis(2016)

Differential DNA Damage

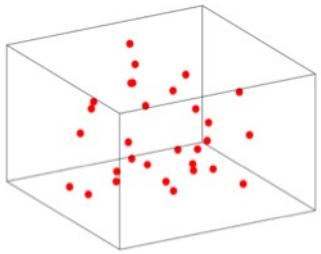
Scholz 2006
Adv Pol Sci



- The DNA **Double Strand Break (DSB)** is considered the type of lesion most directly related to cell killing
- Different radiation qualities produce the same spectrum of DNA lesions
- **BUT** the distribution of lesions inside the target can be very different

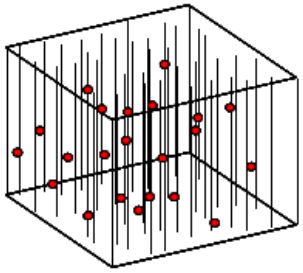
Photons
x-rays

Random
DSB distribution



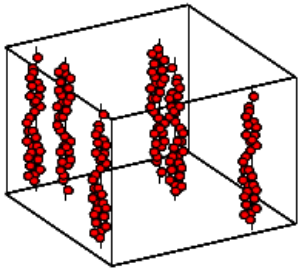
^{12}C Low LET
200 MeV/u, ≈ 16 keV/µm

Random
DSB distribution
(photon-like)

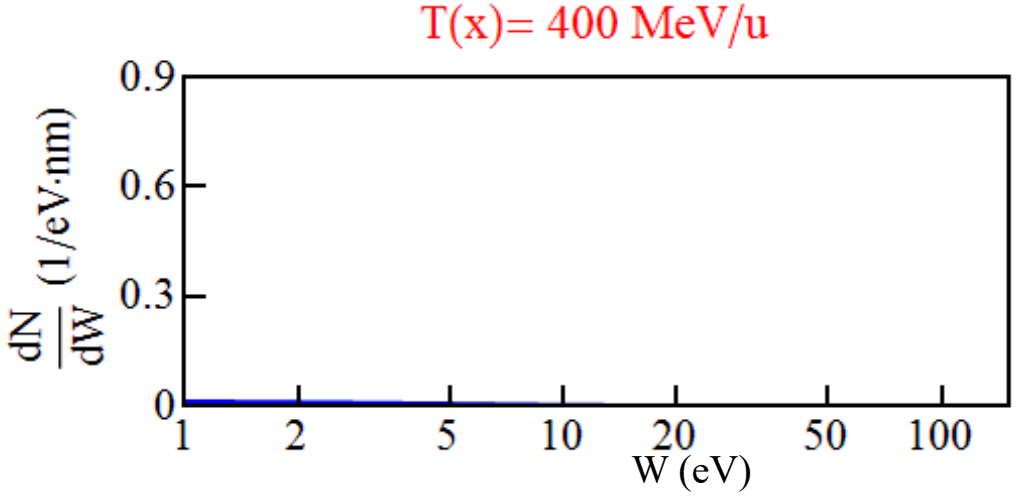


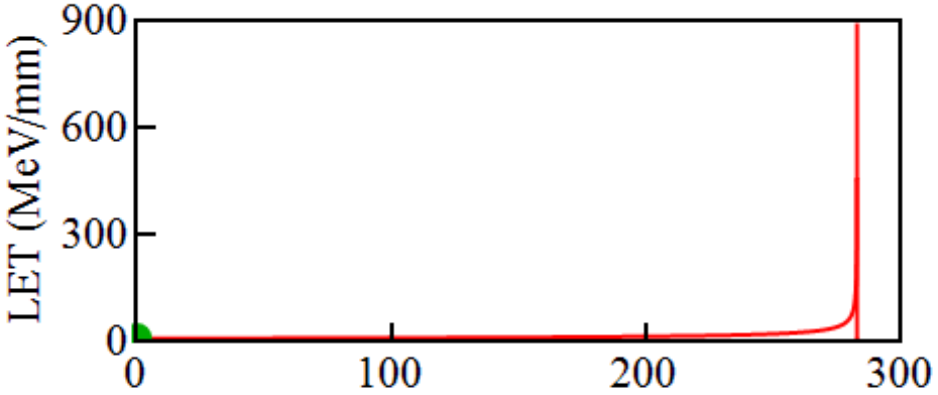
^{12}C High LET
1 MeV/u, ≈ 690 keV/µm

Non-random
DSB distribution
(RBE>>1)



Secondary Electrons produced by an ion along a Bragg Peak

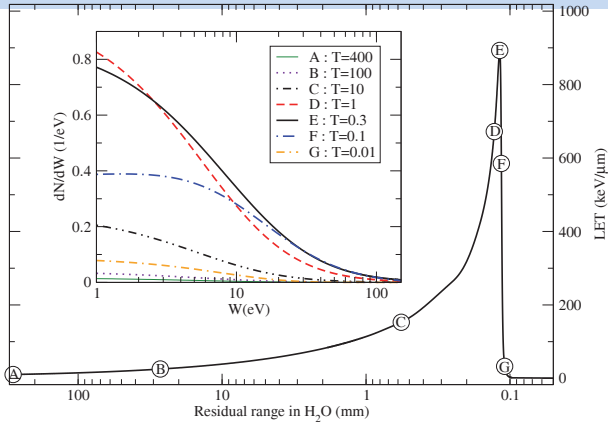




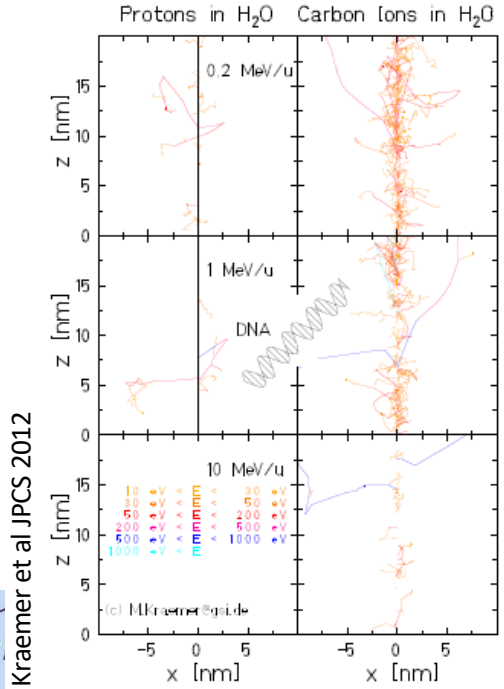
Scifoni,et al., PRE 2010

T_0=400 MeV/u

Track Structure simulation



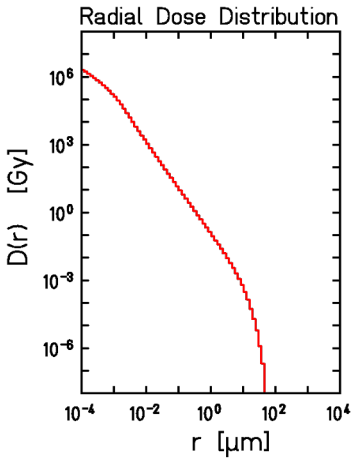
Scifoni,et Mod Phys Lett. 2015

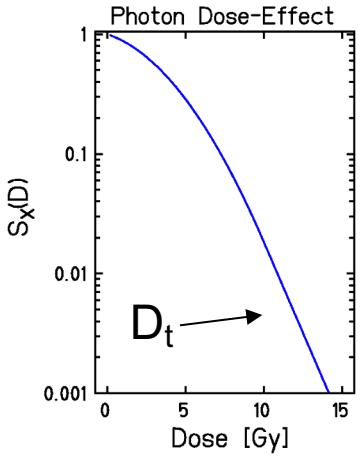


Kraemer et al JPCS 2012

LEM I: Three Ingredients

Physics
Radial Dose Distribution:
Monte-Carlo (TRAX),
Experimental Data,
Semi-empirical
(Amorphous Track model)

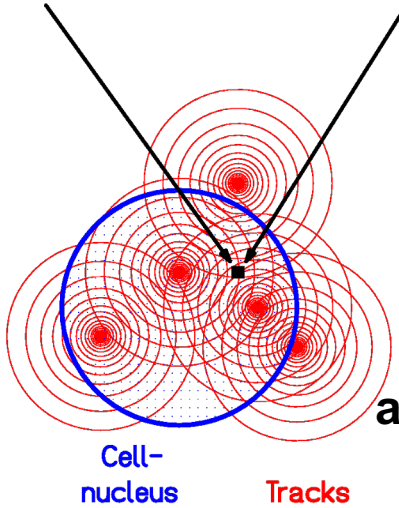




Radiobiology
Photon Survival Curve:
large data base available
linear-quadratic-linear:
LQL

Geometry
Target (cell nucleus):
Experimental Data

Scholz&Kraft 1996

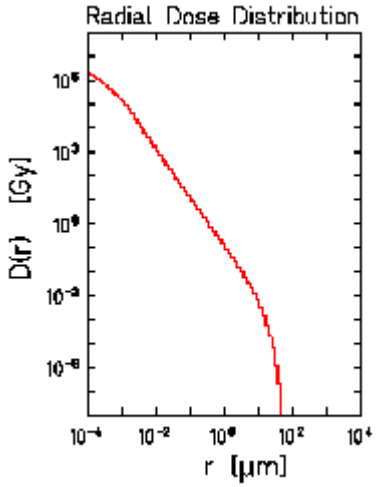


$$S = e^{-(\alpha D + \beta D^2)}, \quad D < D_t$$

$$S = e^{-s_{\max}\eta(D - D_t)}, \quad D \geq D_t$$

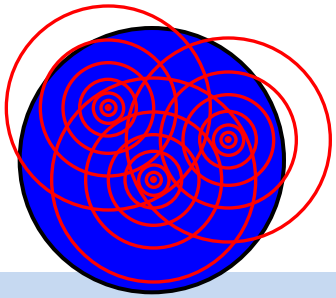
average number of lethal events

LEM IV: Photon equivalent lesion distribution

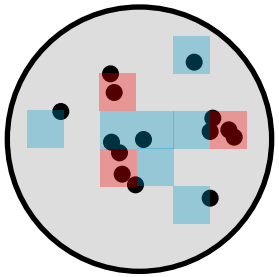


Amorphous track structure

Local dose distribution



Elsaesser 2010
Friedrich 2012

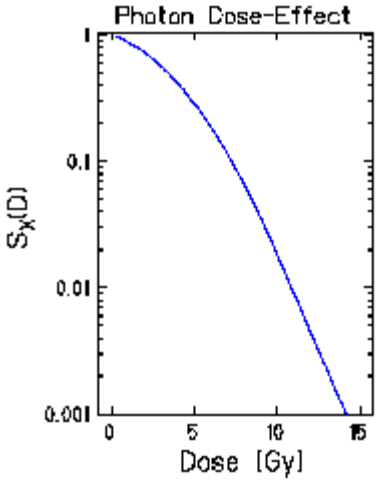


Local lesion distribution

Lesion statistics

: 7

: 3



Photon equivalent situation

RBE

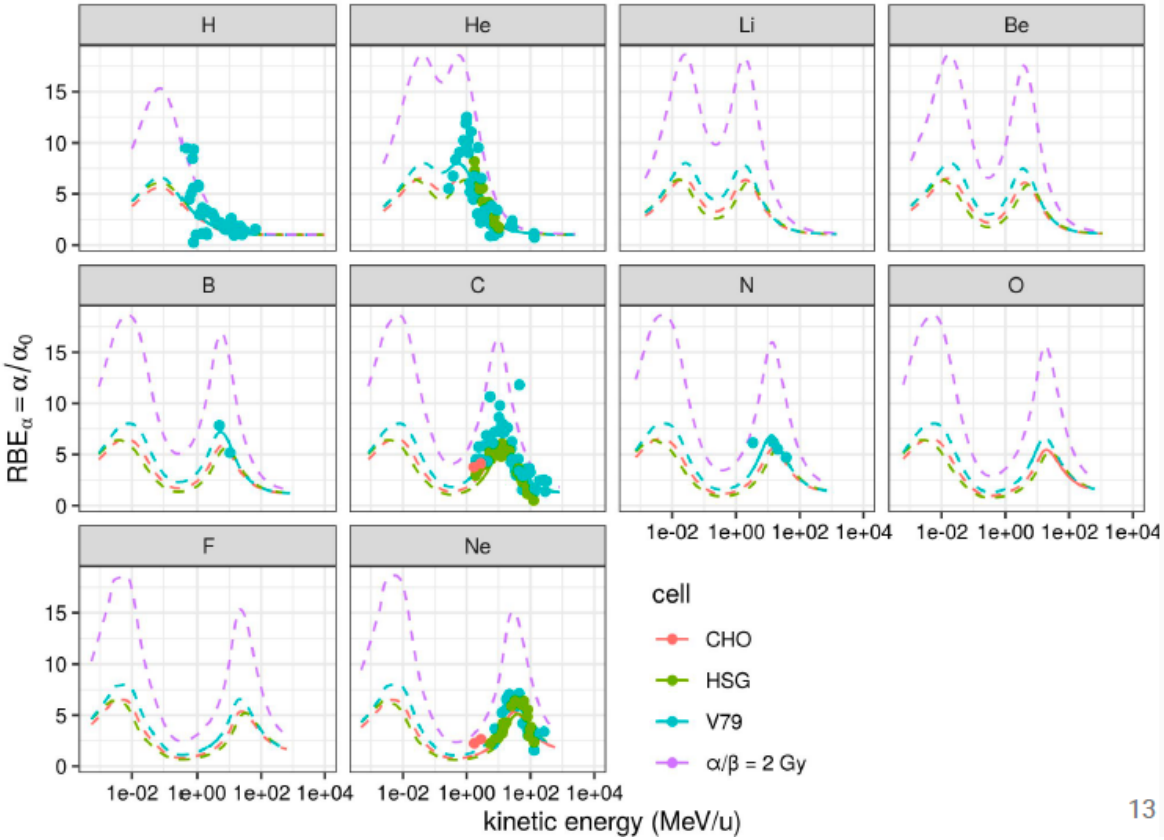
Courtesy.of T. Friedrich

PARTICLE DEPENDENT RBE

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

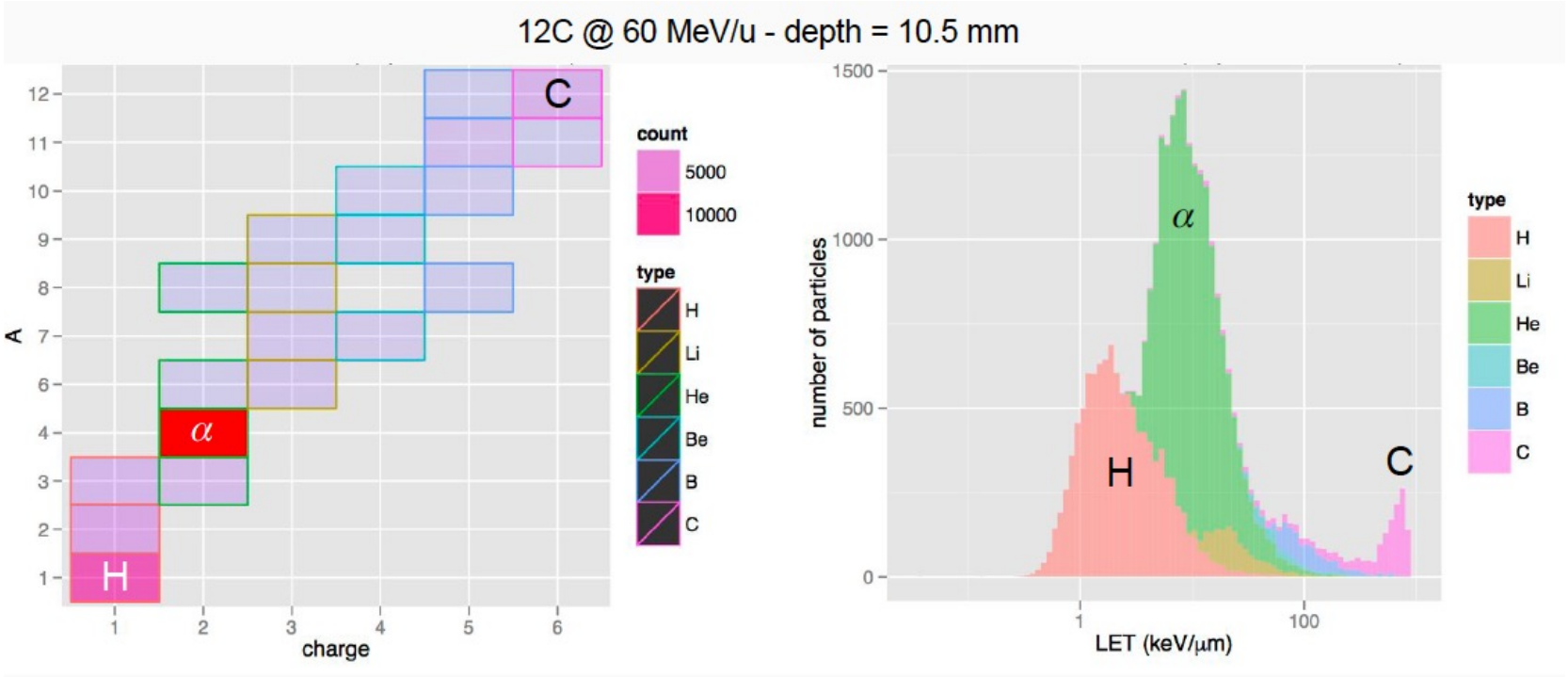
[Parameters from: Kase, Y., *et al.* (2008). Biophysical calculation of cell survival probabilities using amorphous track structure models for heavy-ion irradiation. *Phys. Med. Biol.*, 53(1), 37–59.

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



13

MIXED PARTICLE FIELD

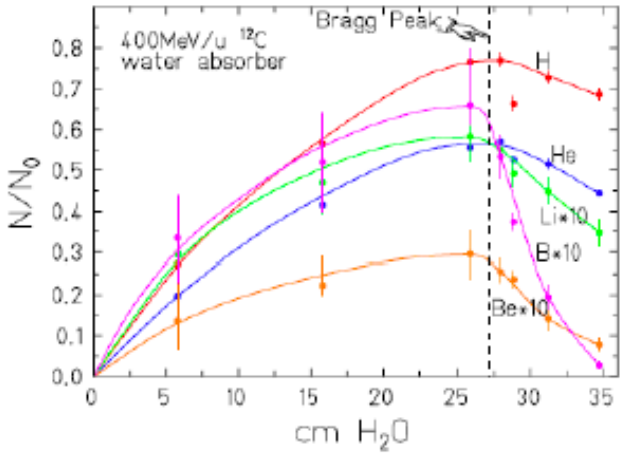


Mixed Field RBE

Primary proton's fragments are considered as secondary particles; each single spectra of those fragments is evaluated separately, considering its impact on the RBE. The total RBE is evaluated by using mixed field algorithm[3] [4] and LEM IV model.

$$\bar{\alpha} = \left(\sum_l w_l \frac{dE}{dx}(l) \right)^{-1} \sum_l w_l \frac{dE}{dx}(l) \alpha_l$$

$$\sqrt{\bar{\beta}} = \left(\sum_l w_l \frac{dE}{dx}(l) \right)^{-1} \sum_l w_l \frac{dE}{dx}(l) \sqrt{\beta_l}$$



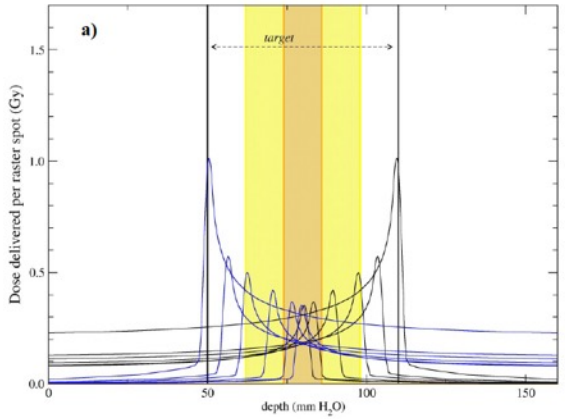
where w_l denotes the relative weight of the radiation component l and

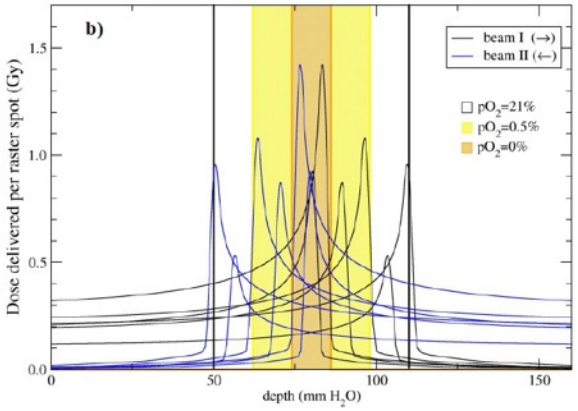
α_l, β_l are the α_D, β_D values in low dose approximation

[3] M. Zaider and H.H. Rossi 1980 Rad. Res. 83:732–9

[4] M. Krämer and M. Scholz 2006 Phys. Med. Biol. 51:1959–1970

Exploiting degrees of freedom in Ion beam TPS





$$\chi^2(\vec{N}) = (w_t)^2 \sum_{i=1}^{N_T} \frac{\left(D_{pre} - D_i(\vec{N})\right)^2}{\Delta D_{pre}^2}$$

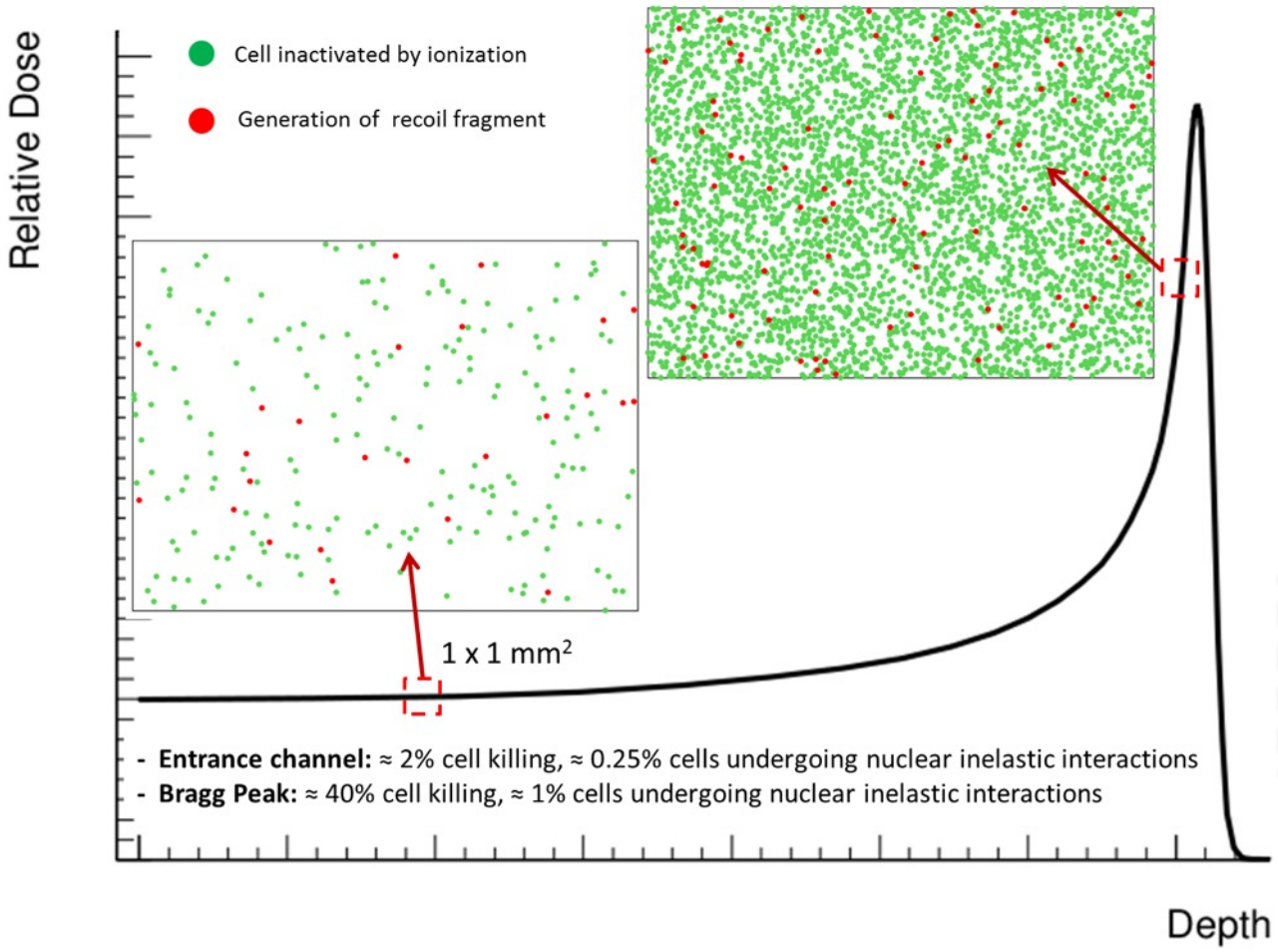
Target (uniform dose)

$$+\left(w_{OAR}^{Dmax}\right)^2 \sum_{i=1}^{N_{OAR}^{Dmax}} \frac{\left(D_{max} - D_i(\vec{N})\right)^2}{\Delta D_{max}^2} \cdot \theta\left(D_i(\vec{N}) - D_{max}\right)$$

OAR (maximum

Tinganelli et al. Sci Rep. 2015

Target fragmentation in proton therapy?



About 10% of biological effect in the entrance channel due to secondary fragments

↓

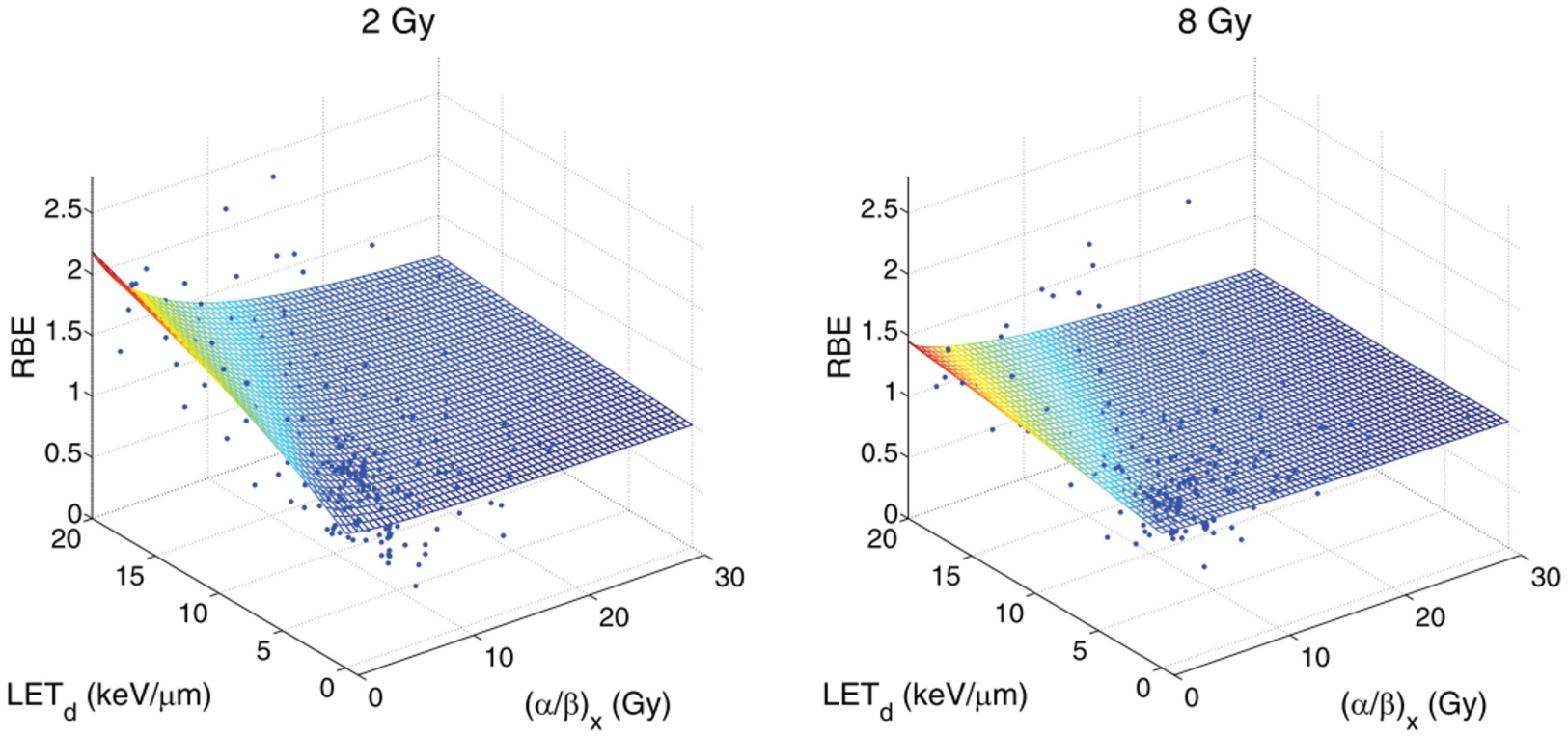
Largest contributions of recoil fragments expected from **He, C, Be, O, N**

↓

Heavy fragments have low residual energies and release low doses -> high RBE!!

Tommasino et al 2015

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.

MoVe IT

Modeling and Verification for Ion beam Treatment planning

A Graphycal summary

Physics

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

Radiobiology

(= Biological effects + micro/nanoscale physics)

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

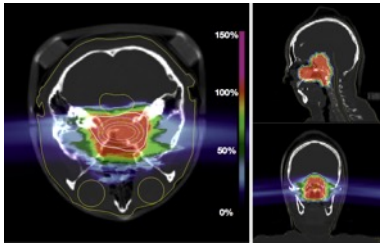
TPS

Beamline specifics

Patient Imaging data

Including intratumor heterogeneity

Effective Dose profile

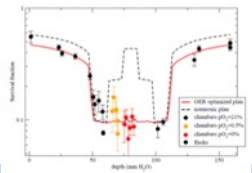


Sokol PhD Thesis

Verification

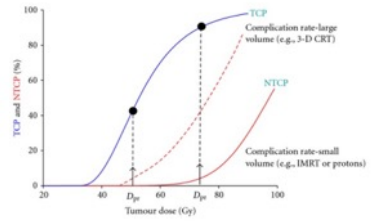
advanced beam monitoring

"Bio"-dosimetry



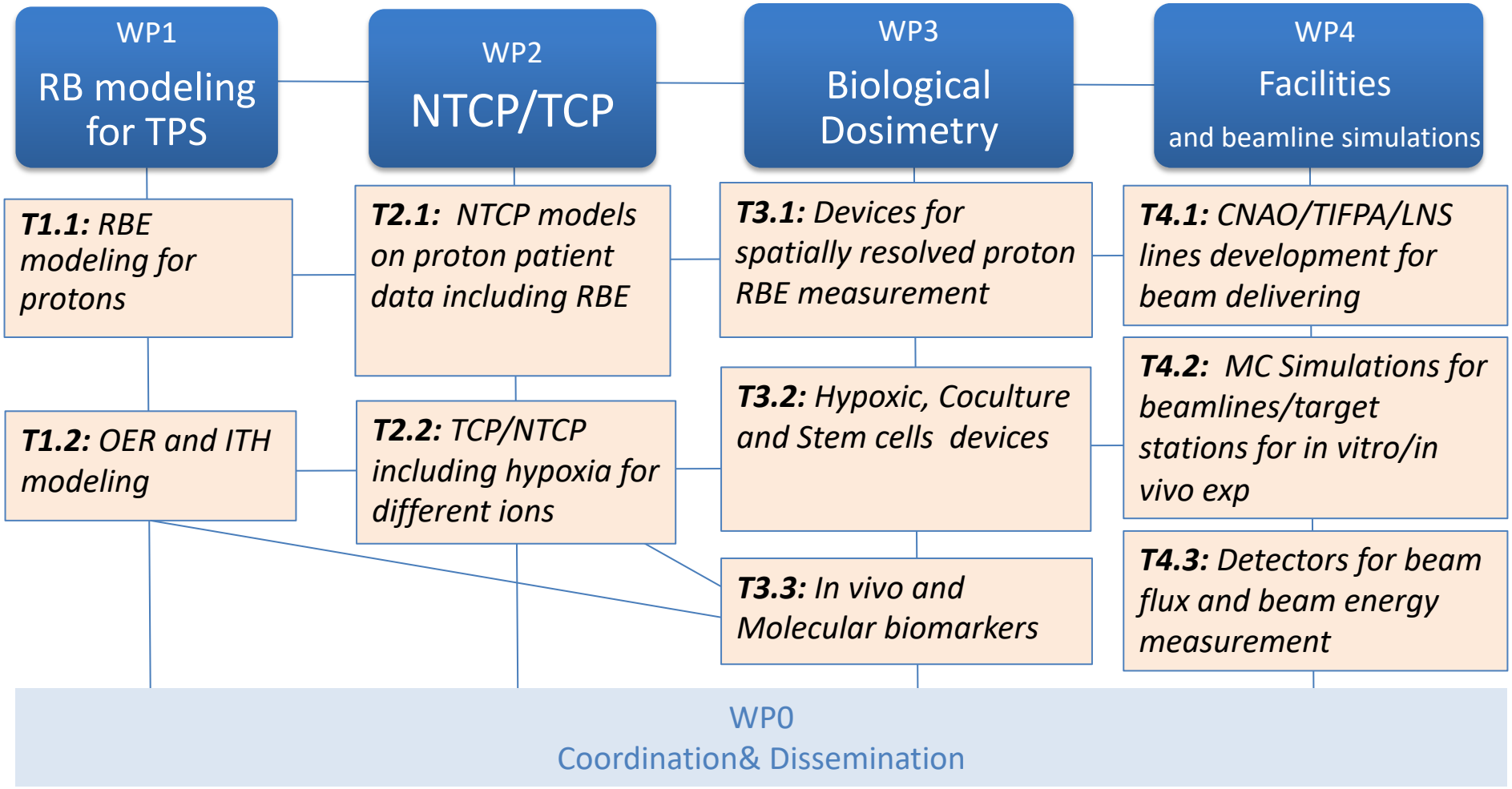
Tinganelli et al Sci Rep 2015

Clinical Impact

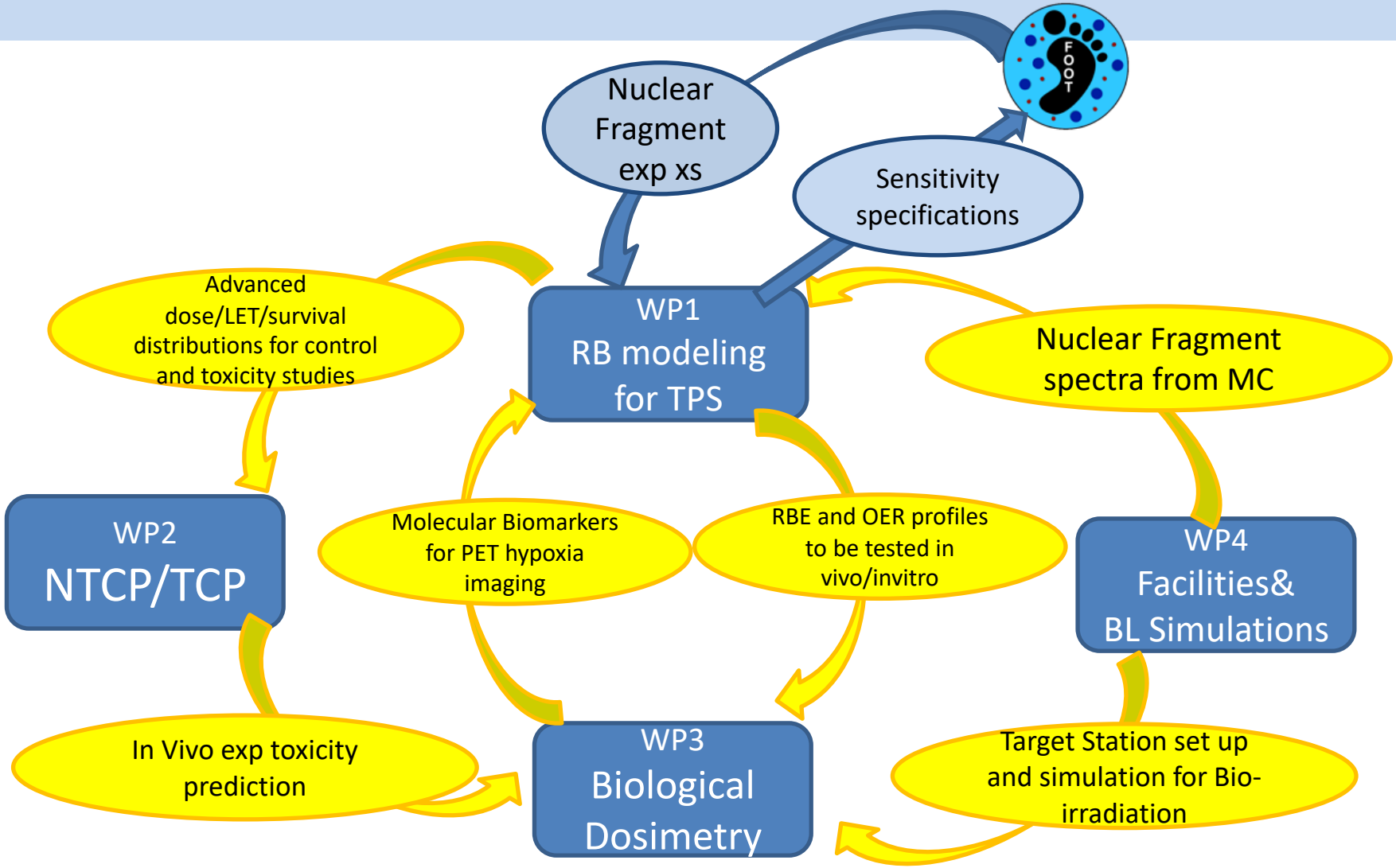


TCP/NTCP

WP Structure and Tasks Breakdown



Main WP connections



First approach – LETd based

Contents lists available at ScienceDirect

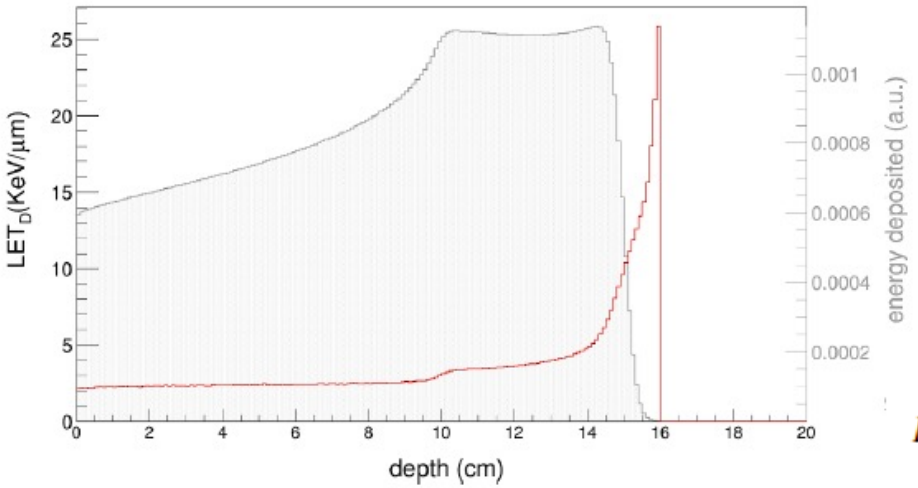
Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

FLUKA simulation of target fragmentation in proton therapy

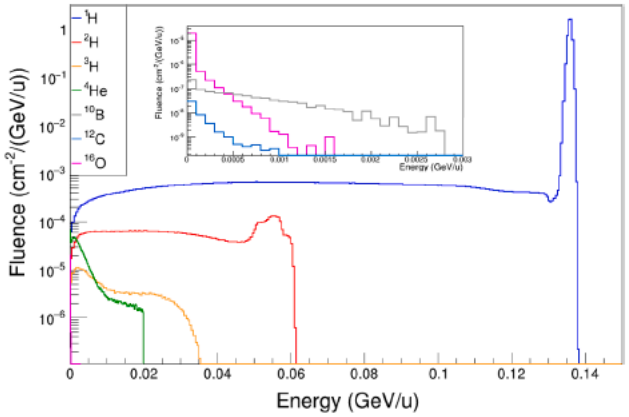
A. Embriaco [a,*], A. Attili [b], E.V. Bellinzona [c,d], Y. Dong [a,e], L. Grzanka [f], I. Mattei [a], S. Muraro [a], E. Scifoni [d], F. Tommasino [c,d], S.M. Valle [a], G. Battistoni [a,d]



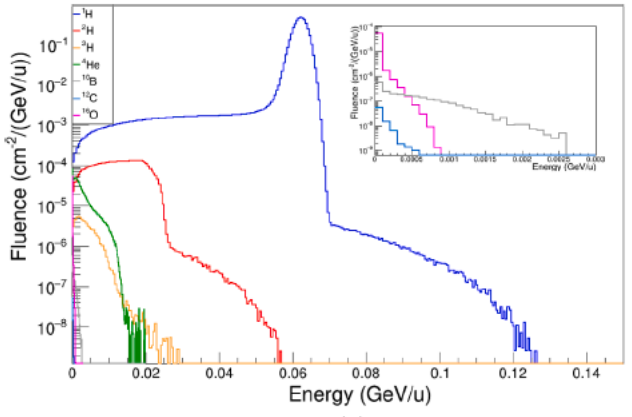
$$LET_D(z) = \frac{\Sigma_i \int LET_i(E) D_i(E,z) dE}{\Sigma_i \int D_i(E,z) dE} = \frac{\Sigma_i \int LET_i^2(E) \phi_i(E,z) dE}{\Sigma_i \int LET_i(E) \phi_i(E,z) dE}$$

FLUKA computed spectra

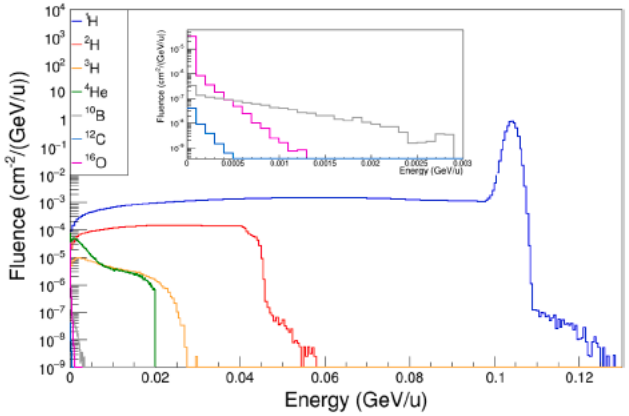
Physica Medica 80 (2020) 342–346

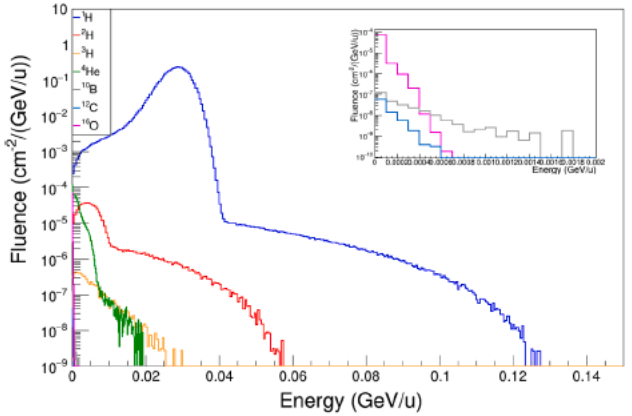


(a)



(a)

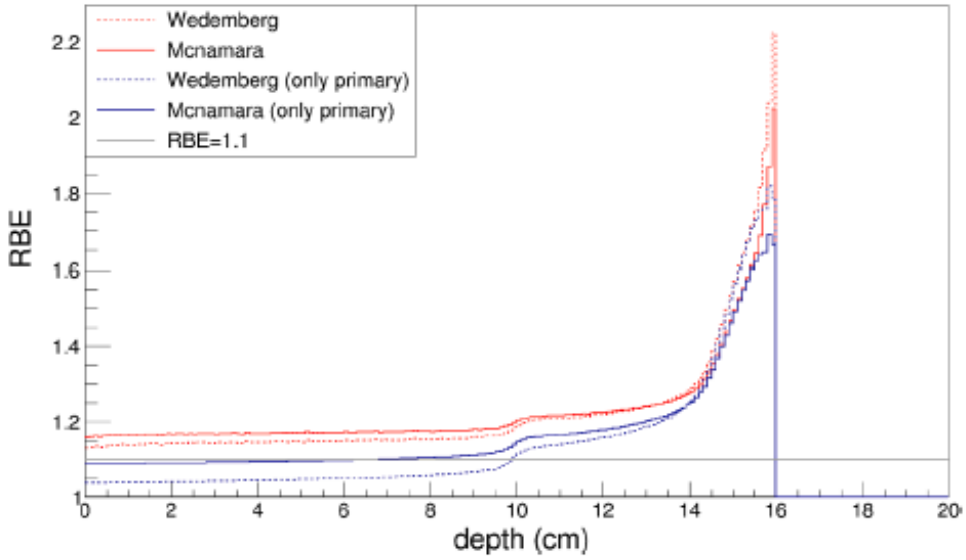




Impact on RBE

McManara and Wedemberg LETd based approaches

Embriaco et al. 2020



$$RBE(LET_D, D, (\alpha/\beta)_{ph}) = \frac{1}{2D}\left(\sqrt{\left(\frac{\alpha}{\beta}\right)_{ph}^2 + 4D\left(\frac{\alpha}{\beta}\right)_{ph}\left(p_0 + \frac{p_1}{(\alpha/\beta)_{ph}} LET_D\right) + 4D^2\left(p_2 + p_3\sqrt{\left(\frac{\alpha}{\beta}\right)_{ph}} LET_D\right)^2} - \left(\frac{\alpha}{\beta}\right)_{ph}\right)$$

$$RBE(LET_D, D, (\alpha/\beta)_{ph}) = -\frac{1}{2D}\left(\frac{\alpha}{\beta}\right)_{ph} + \frac{1}{D}\sqrt{\frac{1}{4}\left(\frac{\alpha}{\beta}\right)_{ph}^2 + \left(qLET_D + \left(\frac{\alpha}{\beta}\right)_{ph}\right)D + D^2}$$

Biological impact of fragmentation with a full mixed field

2022

cancers

MDPI

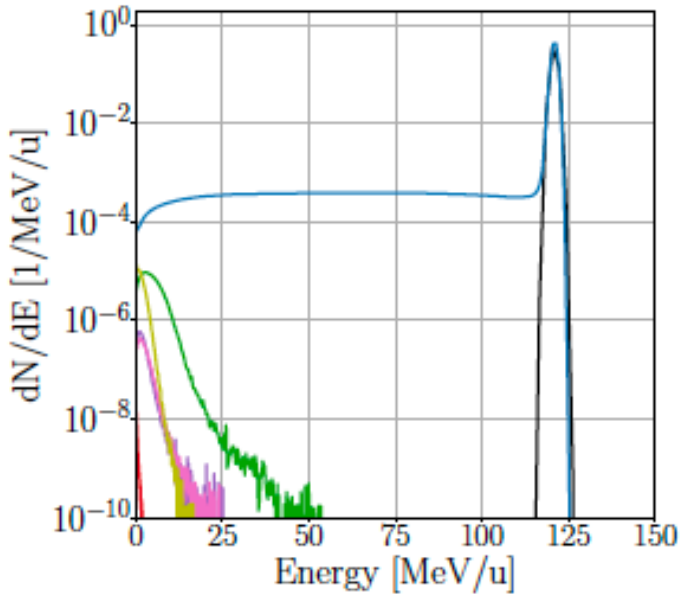
Article

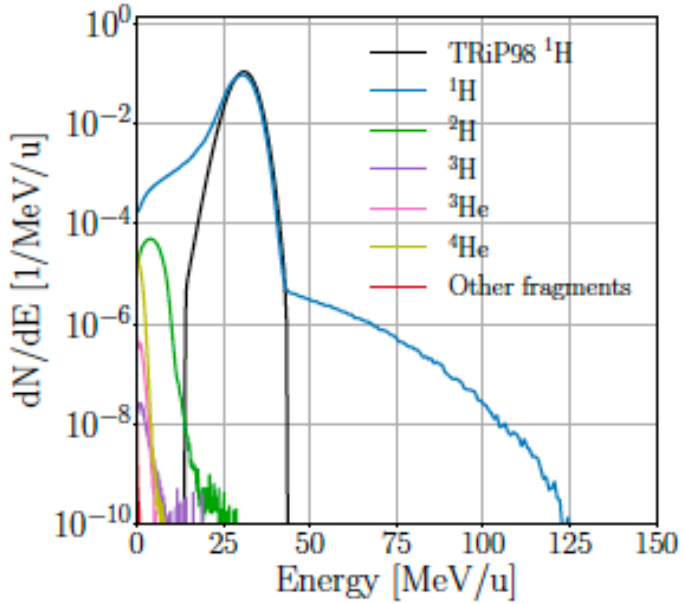
Biological Impact of Target Fragments on Proton Treatment Plans: An Analysis Based on the Current Cross-Section Data and a Full Mixed Field Approach

Elettra Valentina Bellinzona [1,2], Leszek Grzanka [3], Andrea Attili [4], Francesco Tommasino [1,2], Thomas Friedrich [5], Michael Krämer [5], Michael Scholz [5], Giuseppe Battistoni [2], Alessia Embriaco [6], Davide Chiappara [7,†], Giuseppe A. P. Cirrone [7], Giada Petringa [7,‡], Marco Durante [5,8] and Emanuele Scifoni [1,2,*]

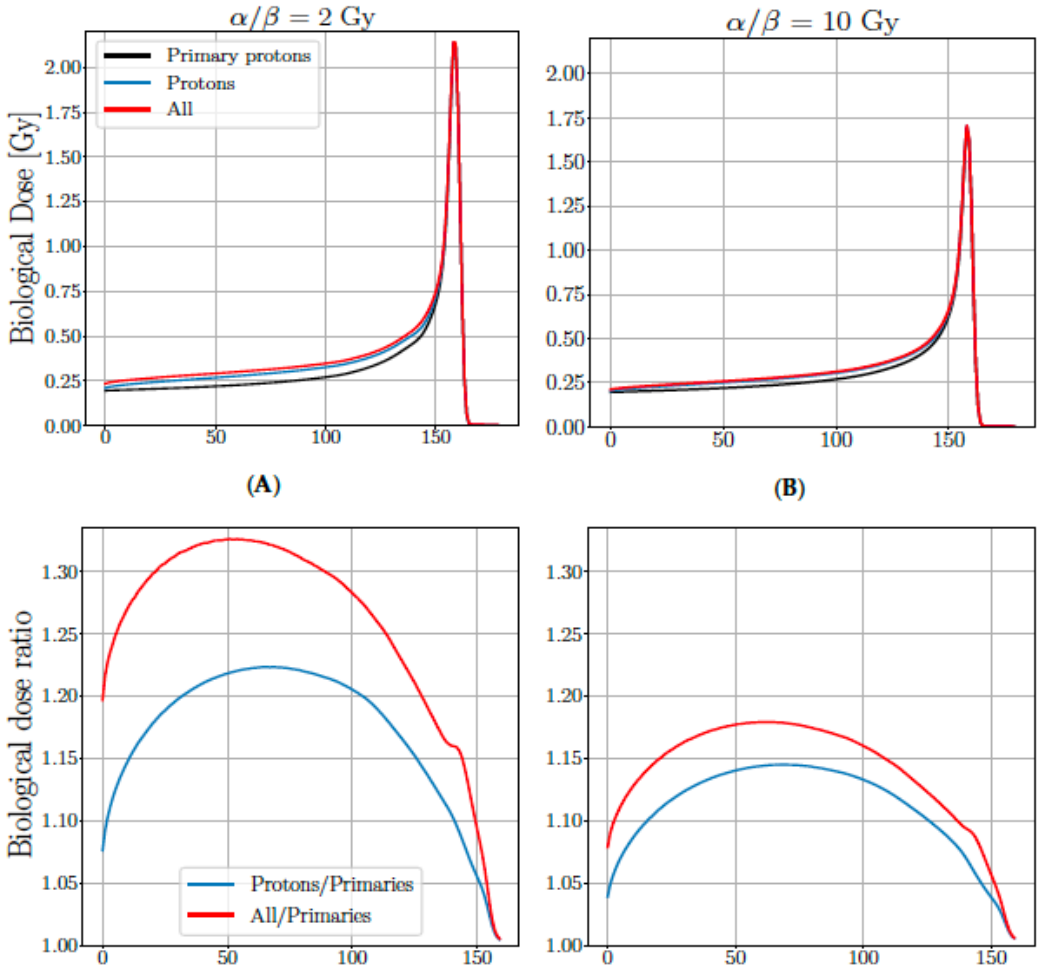
Computed Spectrum

TOPAS 3.3
-standard Geant4 Electromagnetic module version opt4
– high precision QGSP_BIC_HP model
– ion binary cascade model
– decay physics model
– stopping physics model
– high precision neutron transport model, with G4NDL4.5 data

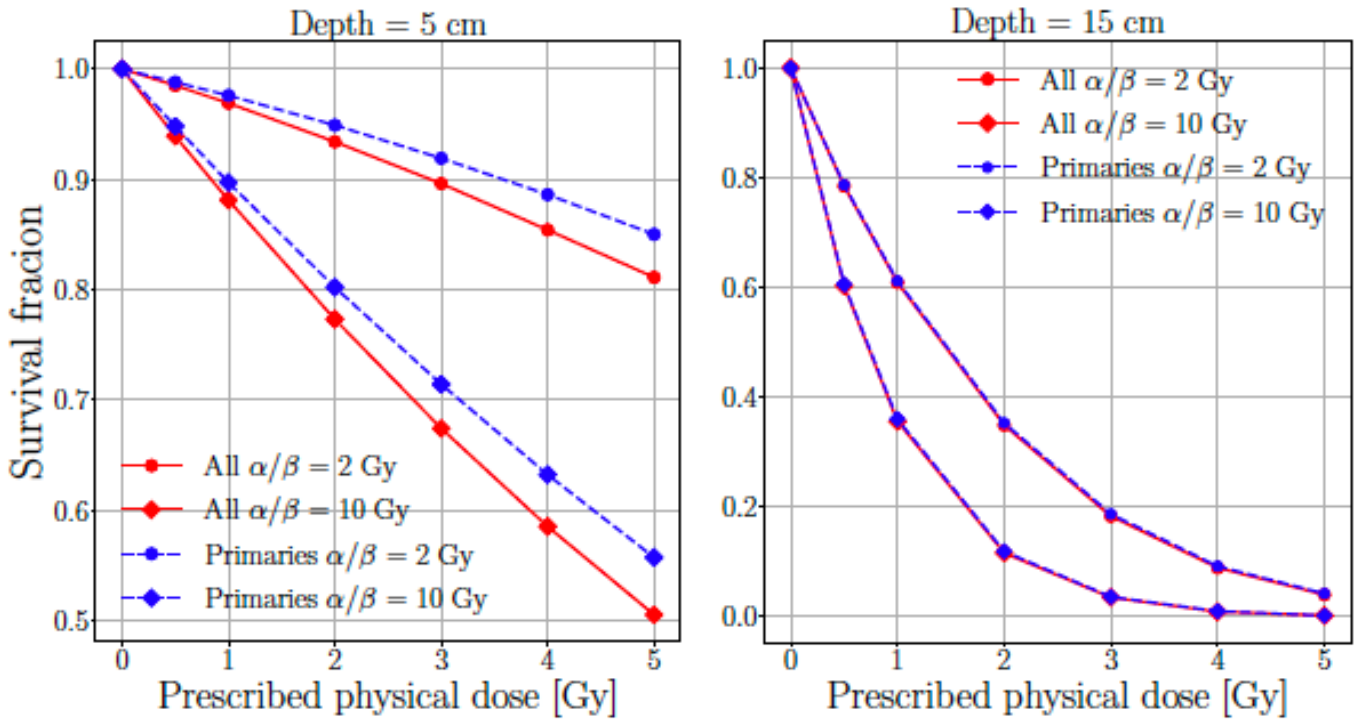




Impact on a pristine peak RBE

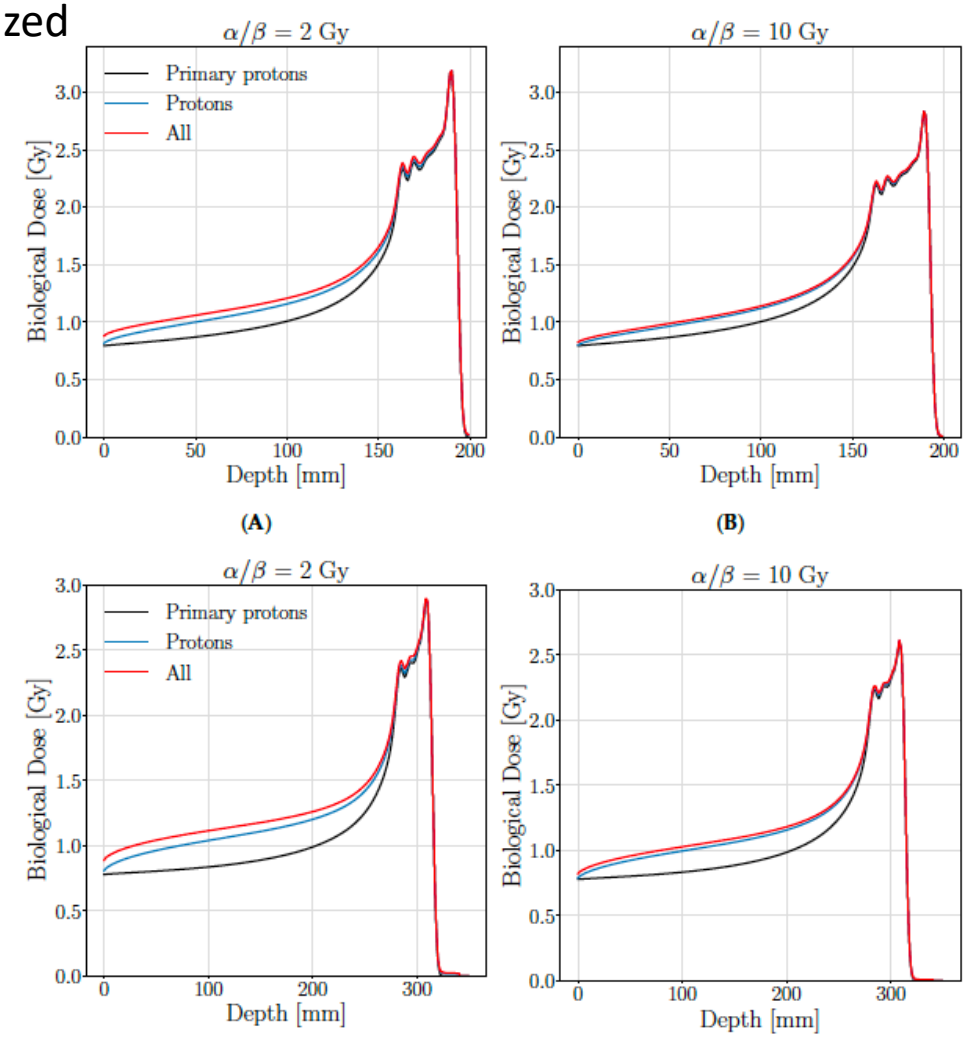


Impact on survival level

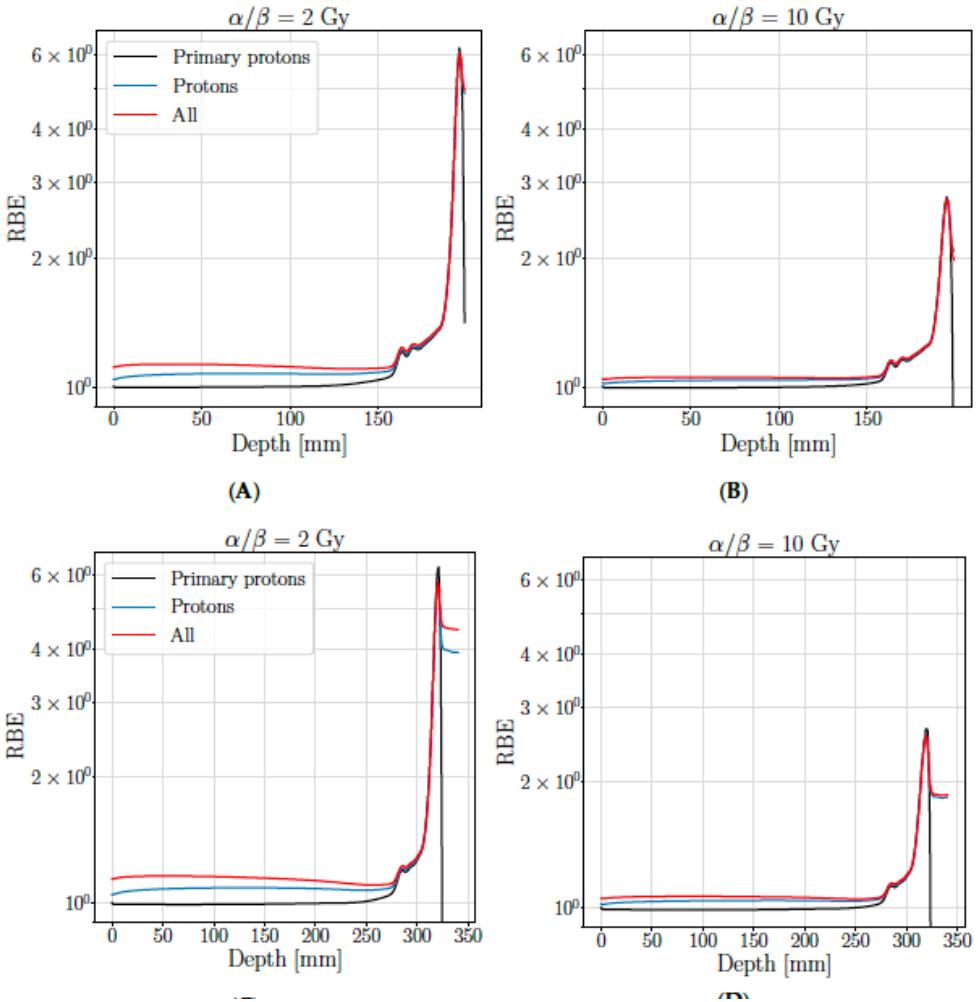


Impact on a SOBP

Flat Physical dose optimized

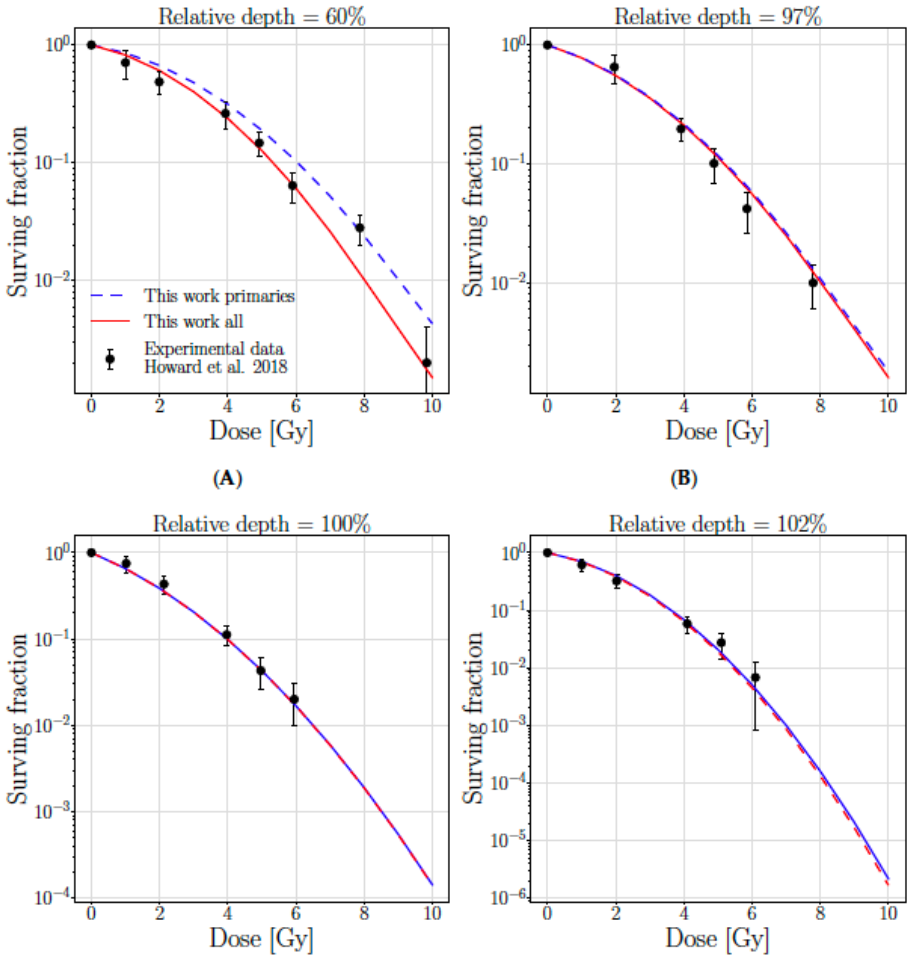


Impact on a SOBP



Biological impact of fragmentation

Comparison of plans including target fragments with experimental *in vitro* data



Biological impact of fragmentation

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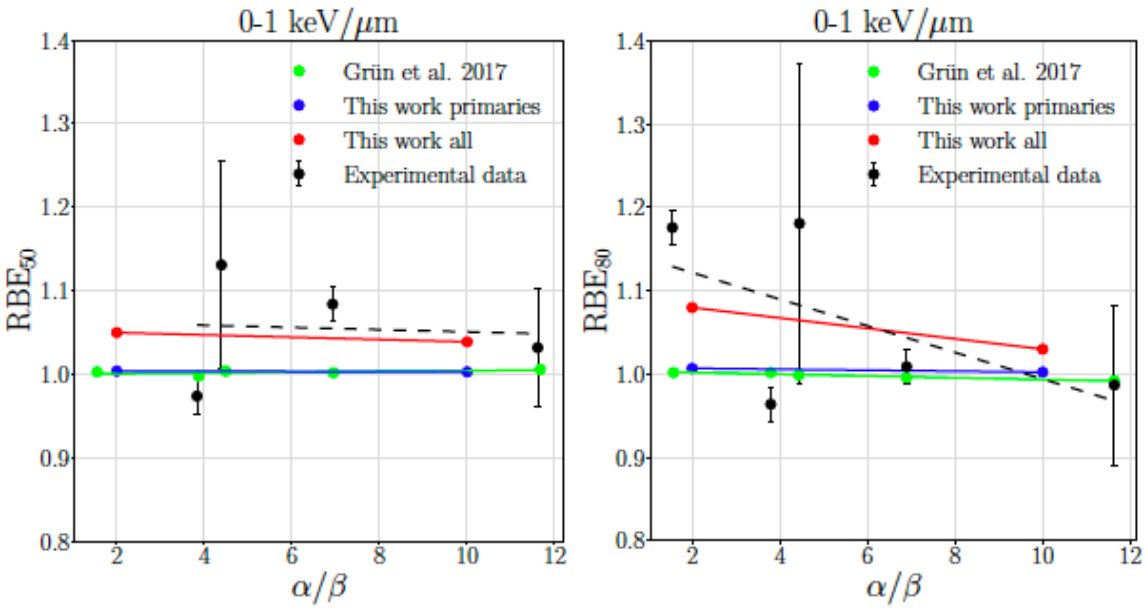
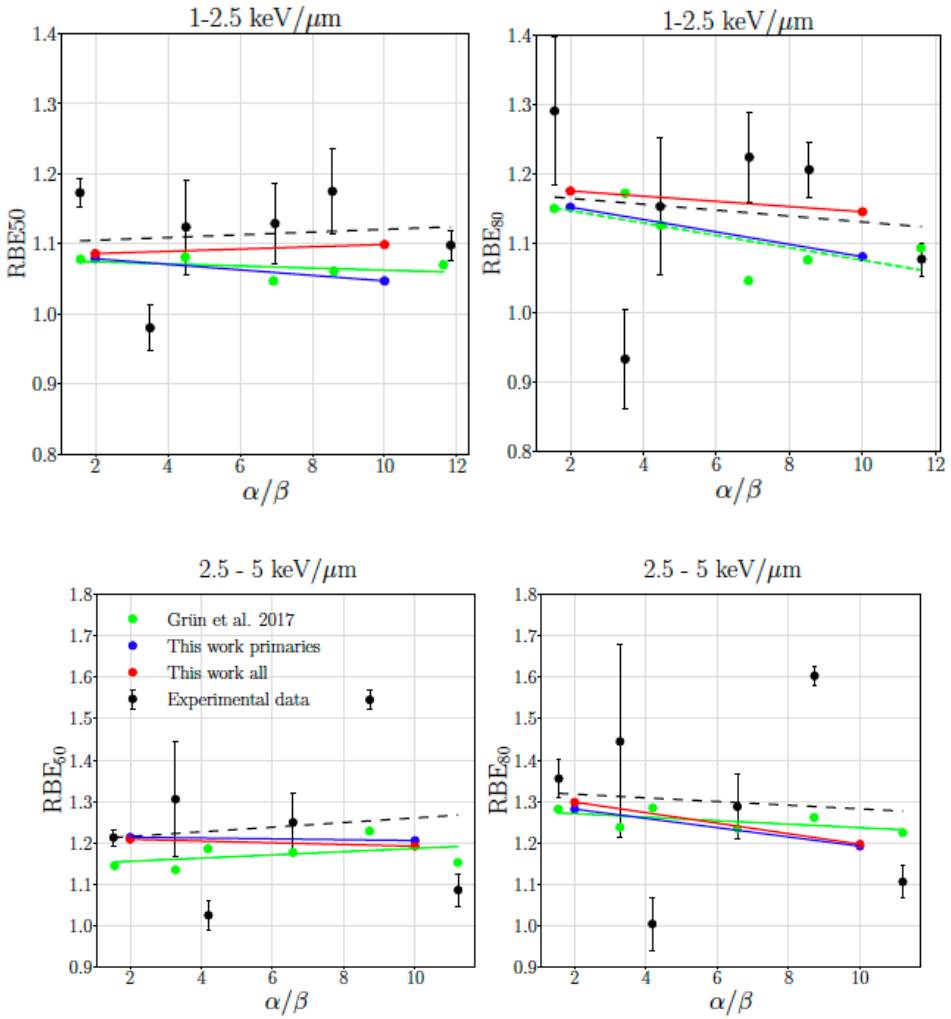


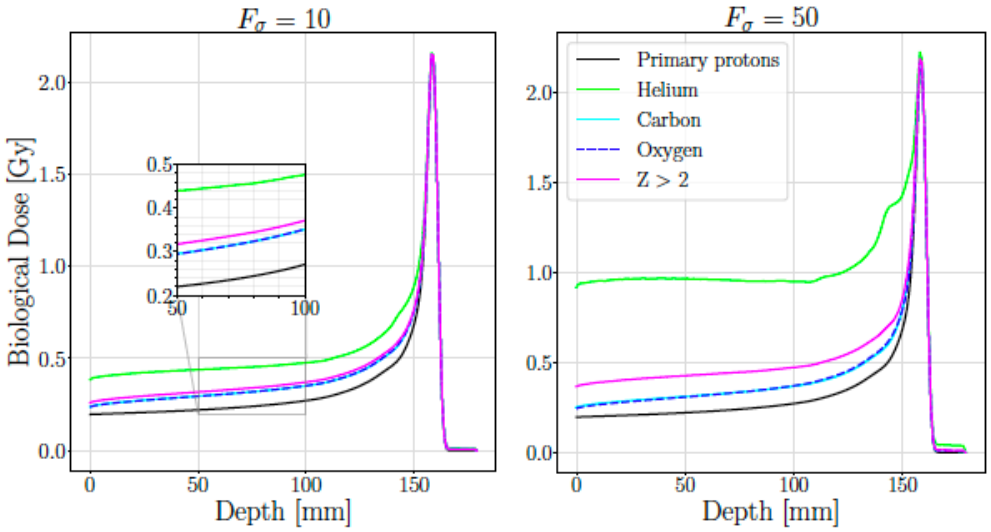
Biological impact of fragmentation

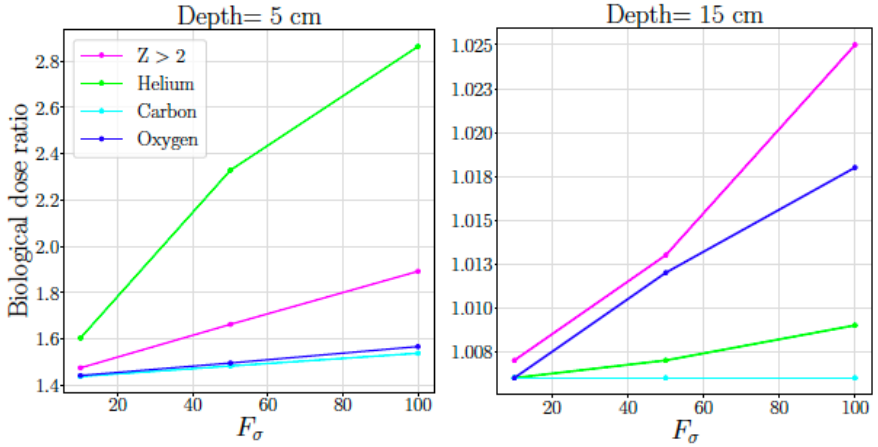
Comparison of plans including target fragments with experimental *in vitro* data

Increasing LET range, less important correction



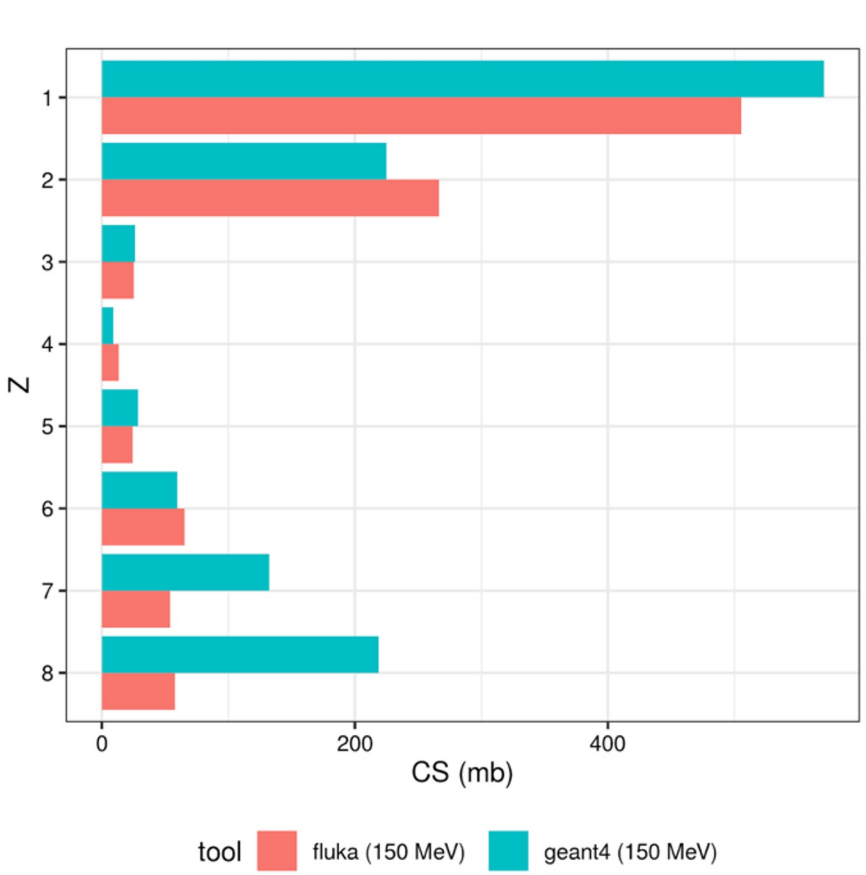
Scaling the xs..

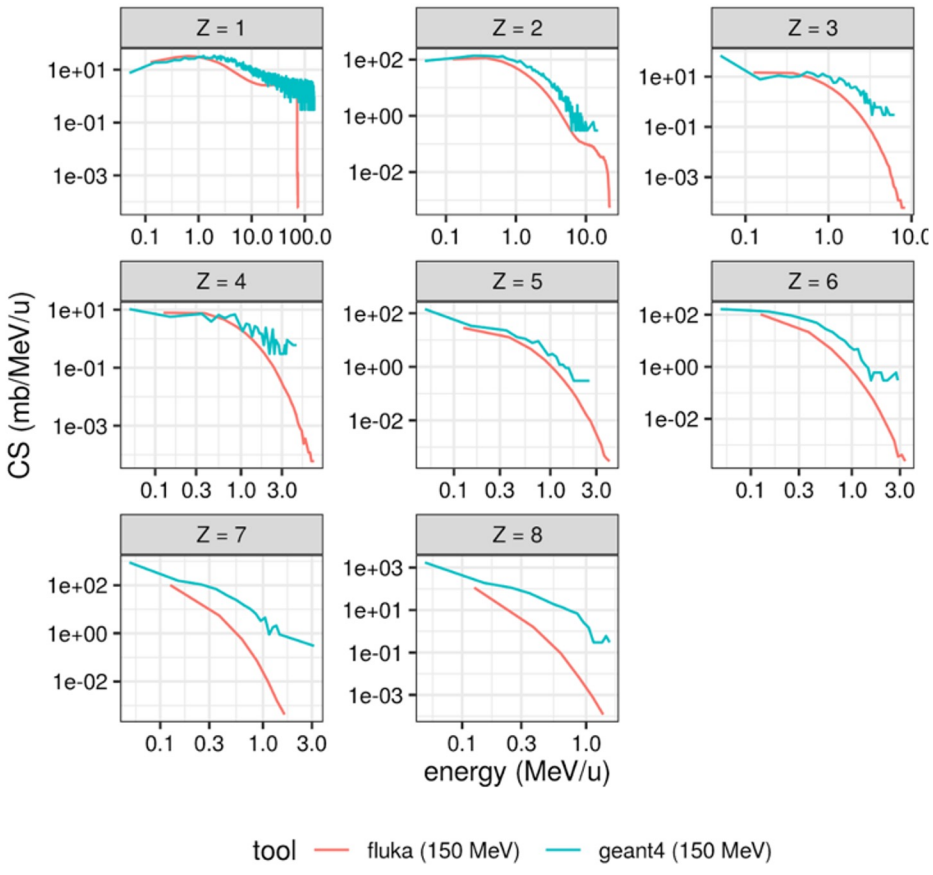




How much should we correct the available cross sections to get a relavant impact on the High Z contributions?

Cross Section (CS) estimates from MC codes



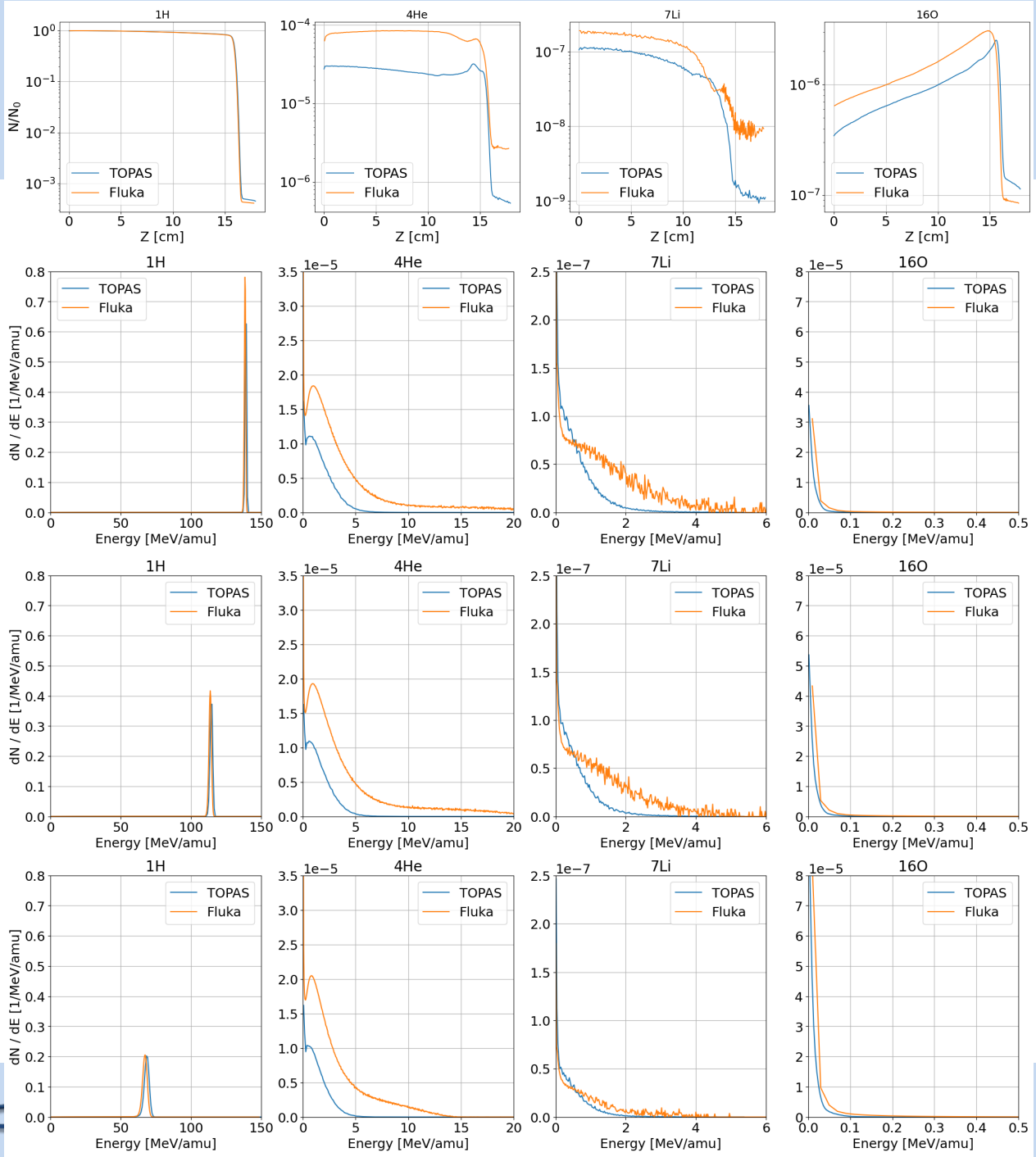


150 MeV p @

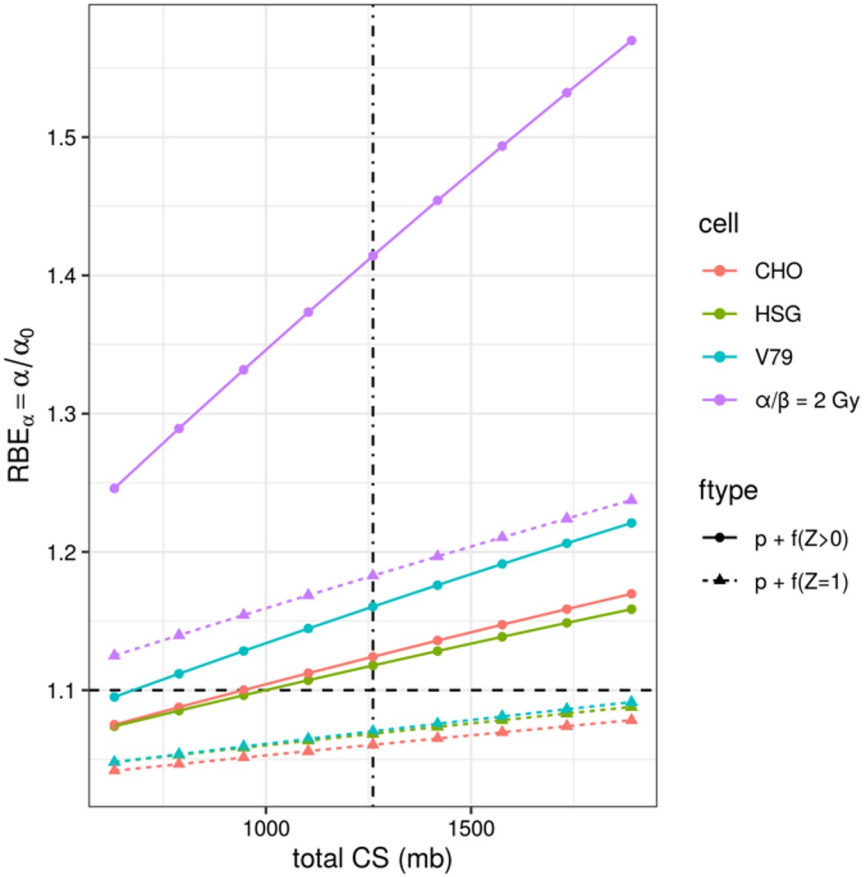
2cm

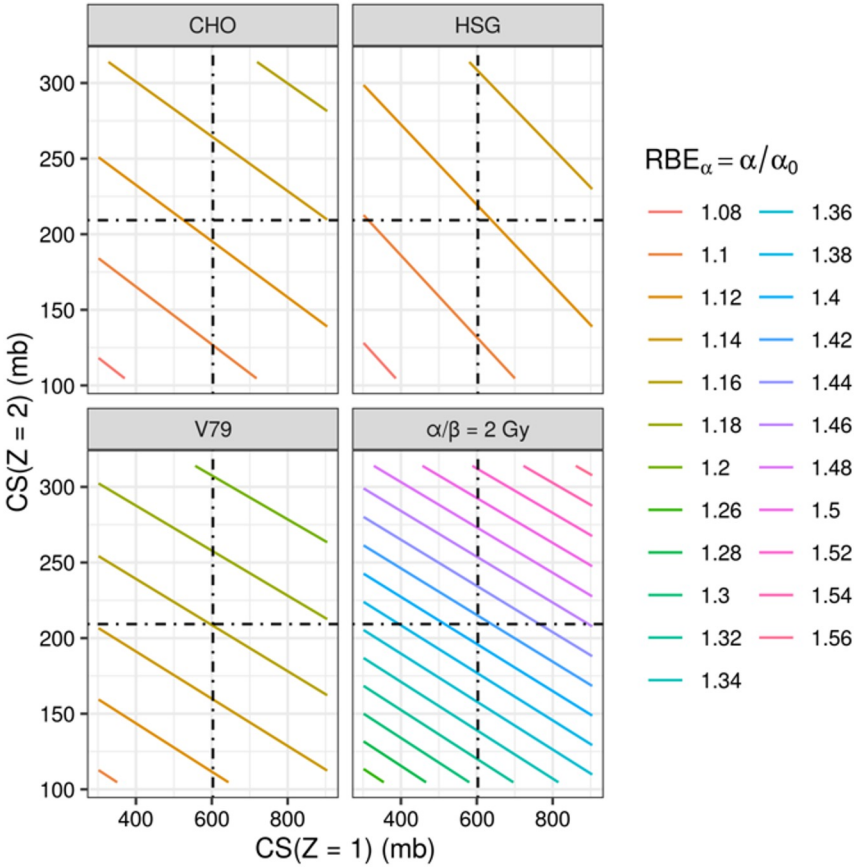
4cm

12cm

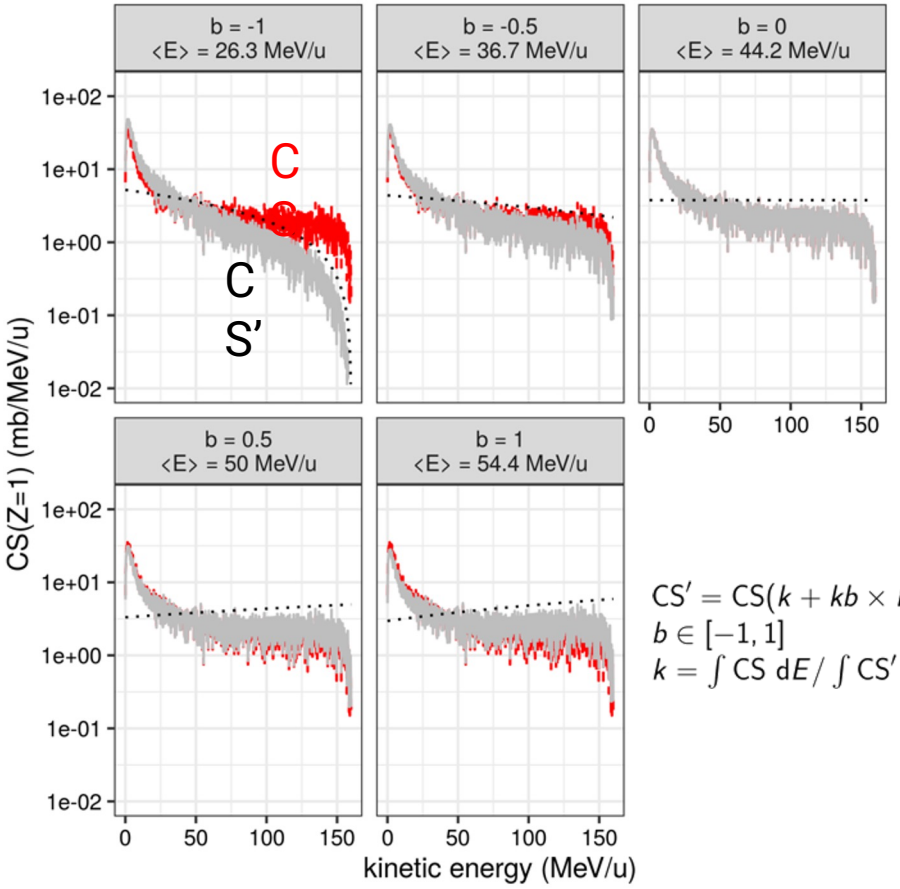


RBE vs. total and partial CS (evaluated at 10 mm)

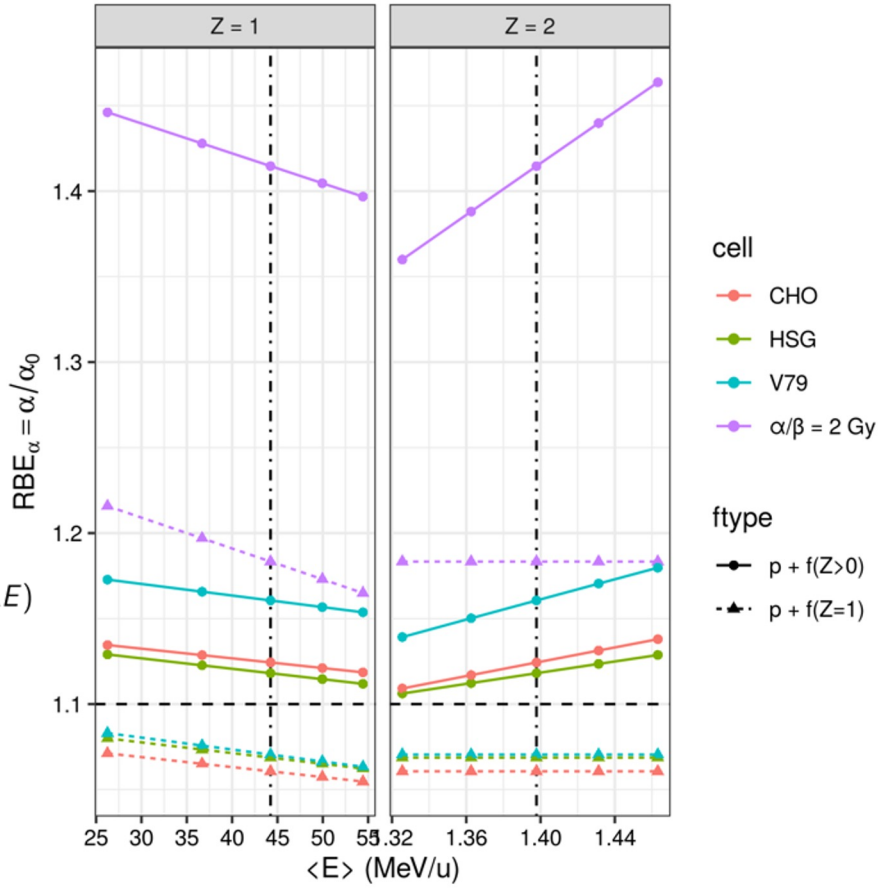




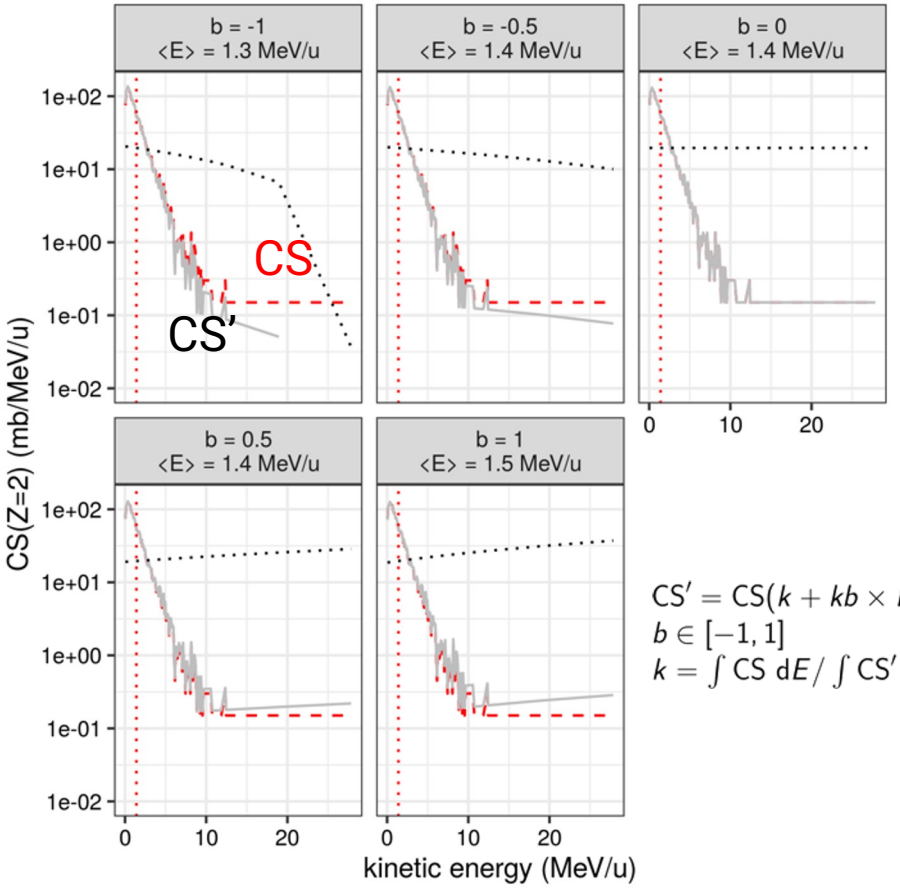
RBE vs. differential CS (Z = 1, evaluated at 10 mm)



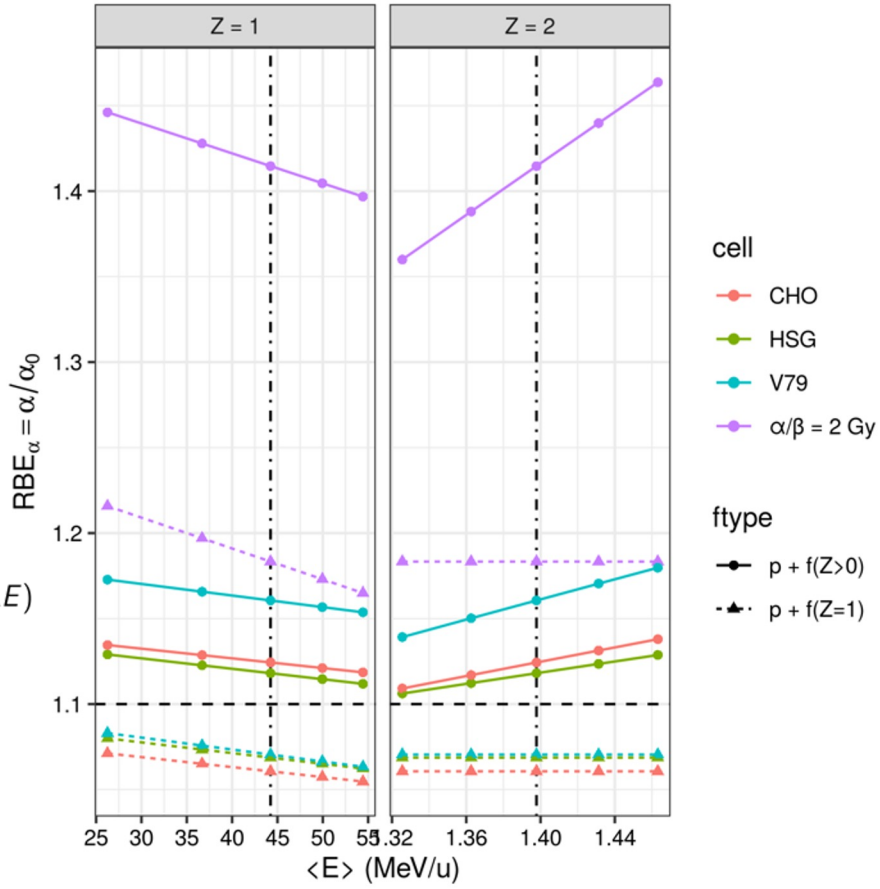
$$CS' = CS(k + kb \times E/\Delta E)$$
$$b \in [-1, 1]$$
$$k = \int CS\, dE / \int CS'\, dE$$



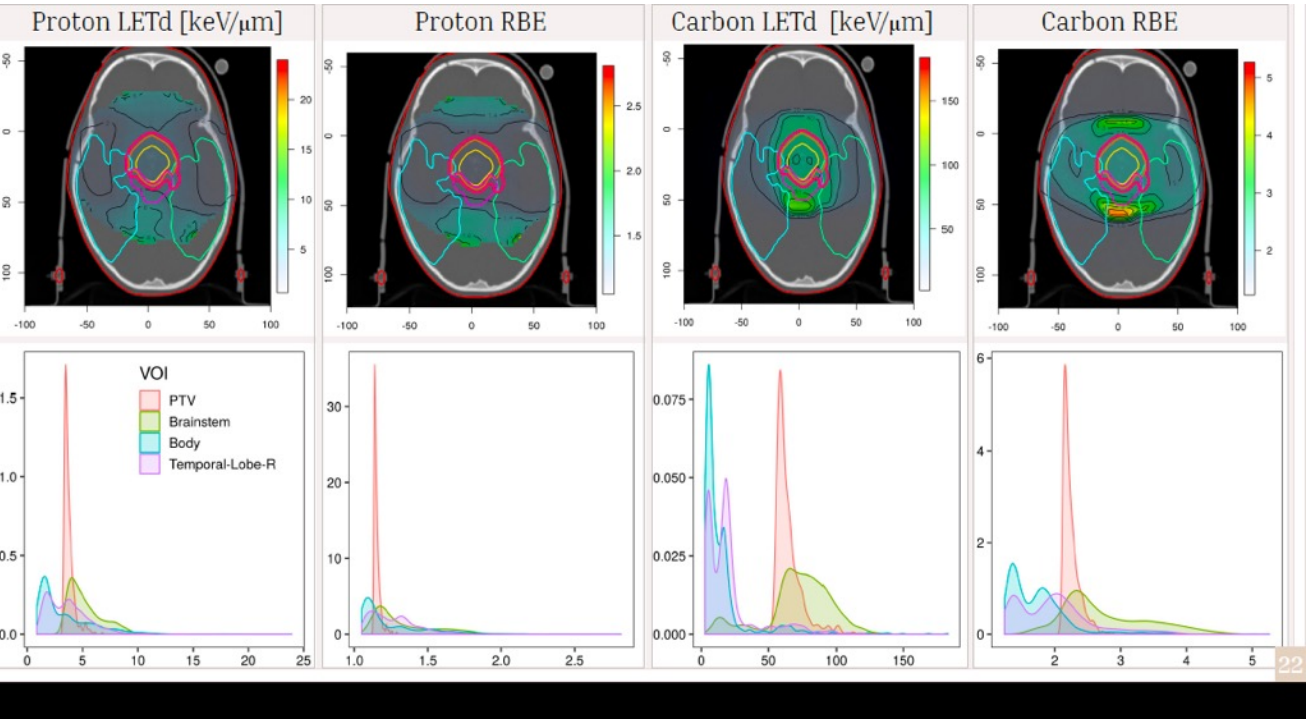
RBE vs. differential CS (Z = 2, evaluated at 10 mm)

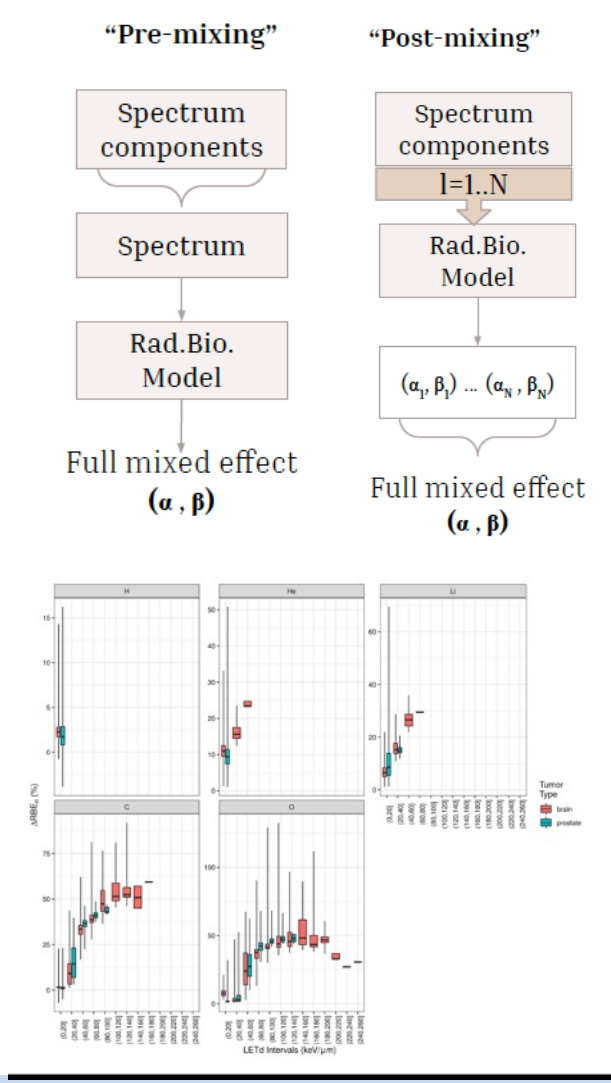


$$CS' = CS(k + kb \times E/\Delta E)$$
$$b \in [-1, 1]$$
$$k = \int CS\, dE / \int CS'\, dE$$



Beam mixing and LET





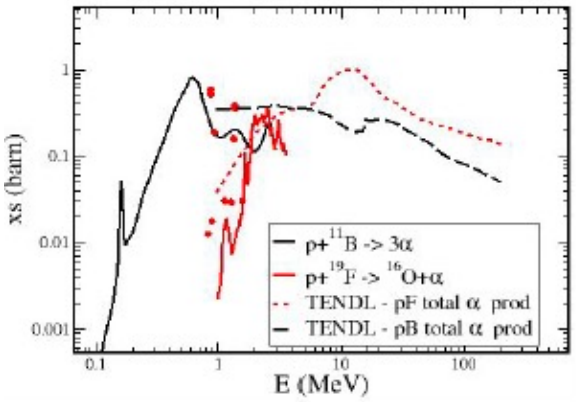
Impact of different weighting of beam components in their biological effect, as compared to. LETd based approaches,

Attili et al. NeuDos, ***2022, in prep.***

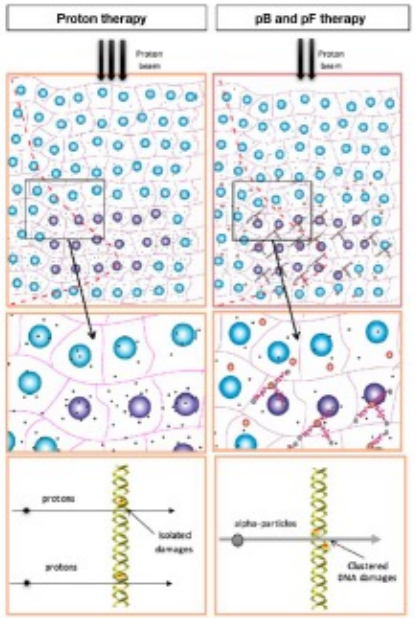
A similar question: pB fragmentation matters biologically? The NEPTUNE puzzle

One shortcoming of protontherapy is its inability to treat radioresistant cancers. Heavier particles, such as 12C ions, can overcome radioresistance but they present radiobiological and economic issues.

Goal: to investigate the use of nuclear reactions triggered by protons (p + ^{11}B and p + ^{19}F) generating short-range high-LET alpha particles inside the tumours, thereby allowing a highly localized DNA-damaging action.



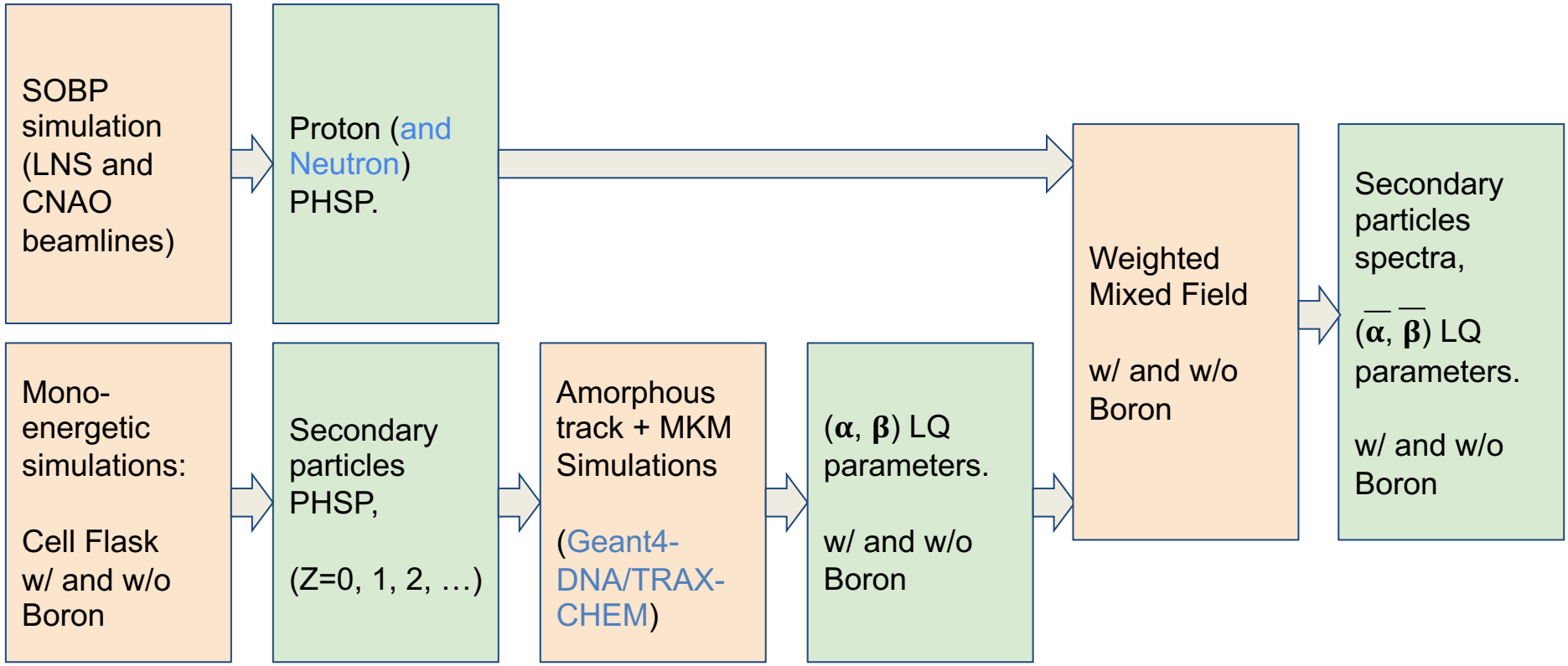
Comparison of cross sections for alpha production of the 2 processes exploited in the NEPTUNE project.



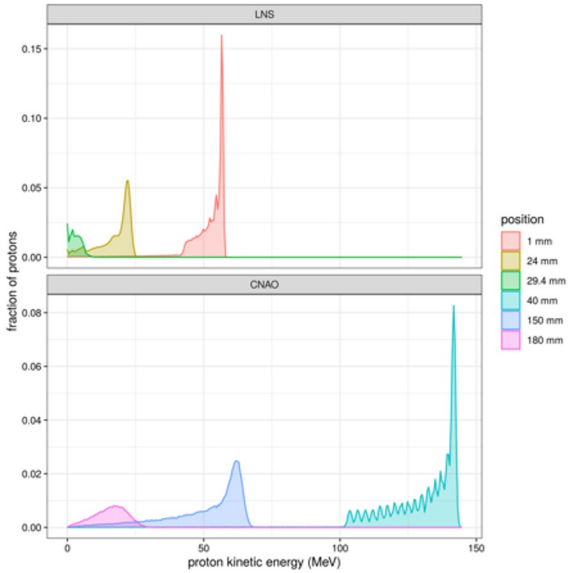
Schematic representation of "conventional" protontherapy with low-LET proton beams (left) and the rationale for boron/fluorine enhanced protontherapy (right).

pB Bio impact Modeling:

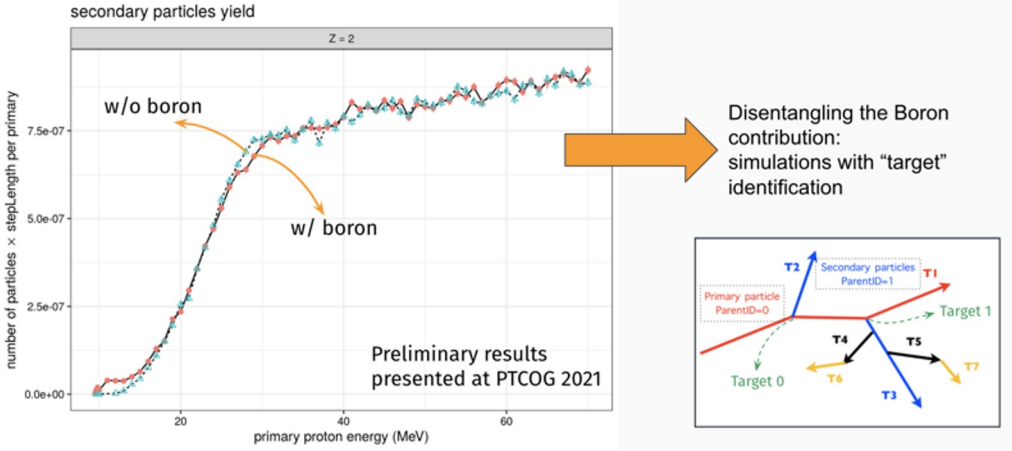
Biophysical effect modeling scheme

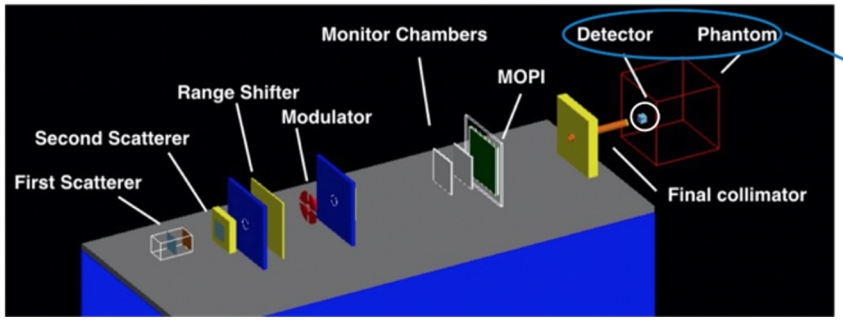


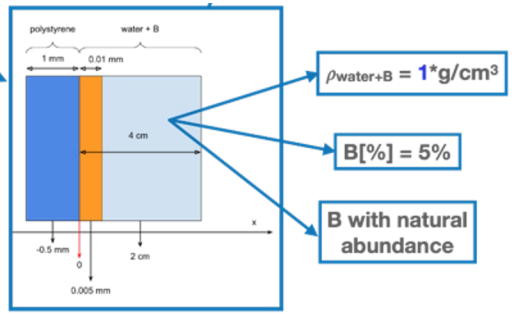
Reproduction of experimental irr. conditions

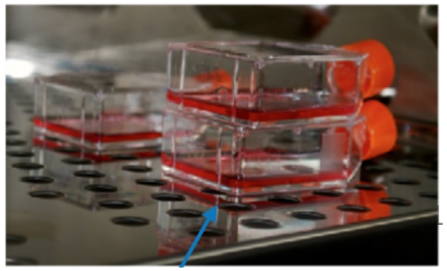


All the different experimental proton fields at CNAO/LNS have been reproduced, including



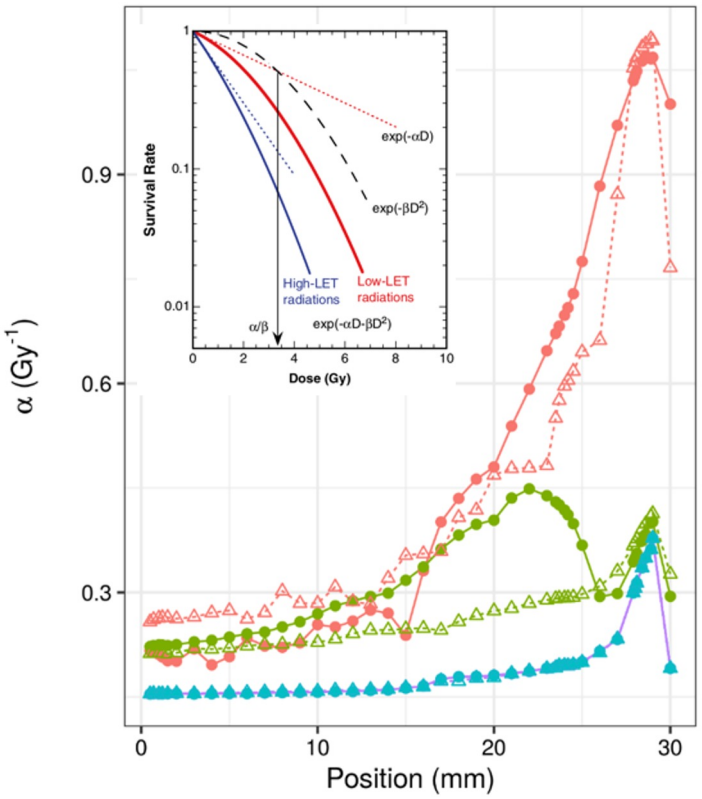


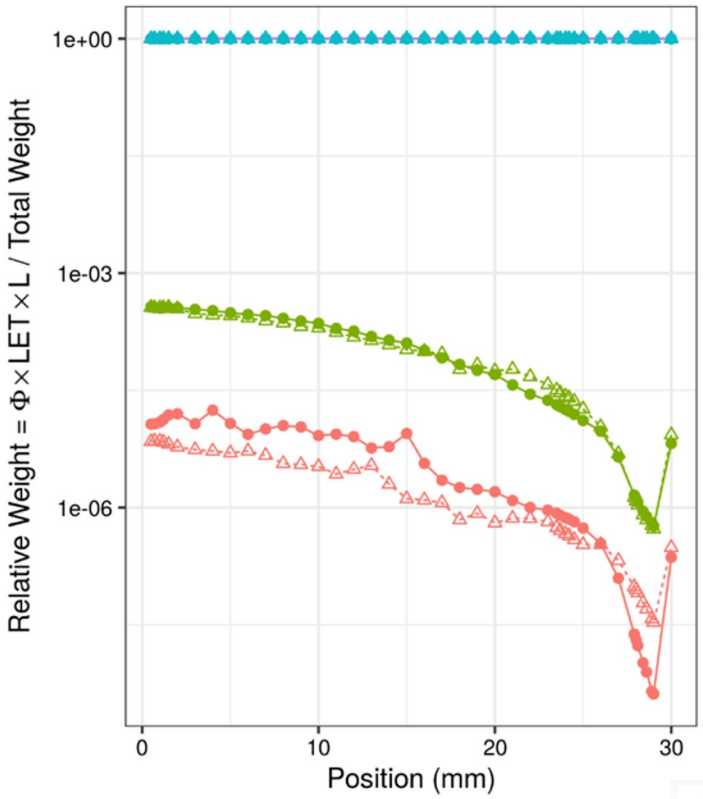




SOBP simulations (MKM for DU145) - α

parameter & relative weight





Particle Type

- f(Z>0) [Boron interaction]
- f(Z>0) [No Boron interaction]
- p (primary)
- p + f(Z>0)

Physics List

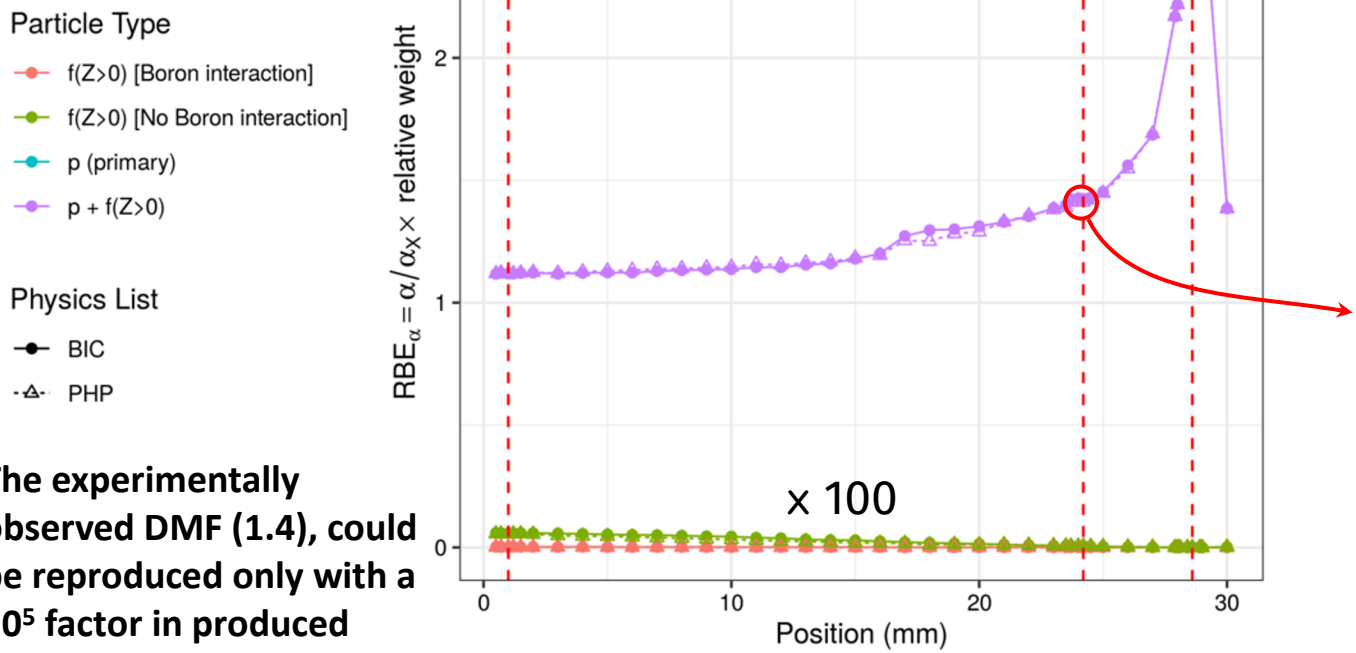
- BIC
- PHP

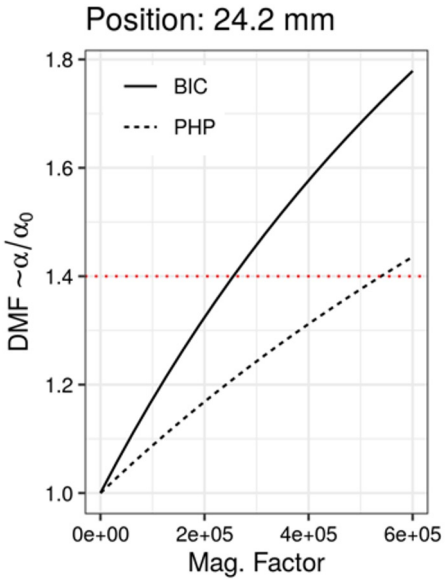
NEPTUNE

Nuclear process driven Enhancement of Proton Therapy UNravElled

Radiobiological impact and Comparison with experimental DMF

$RBE_\alpha = \alpha \times$ relative weight / α_x





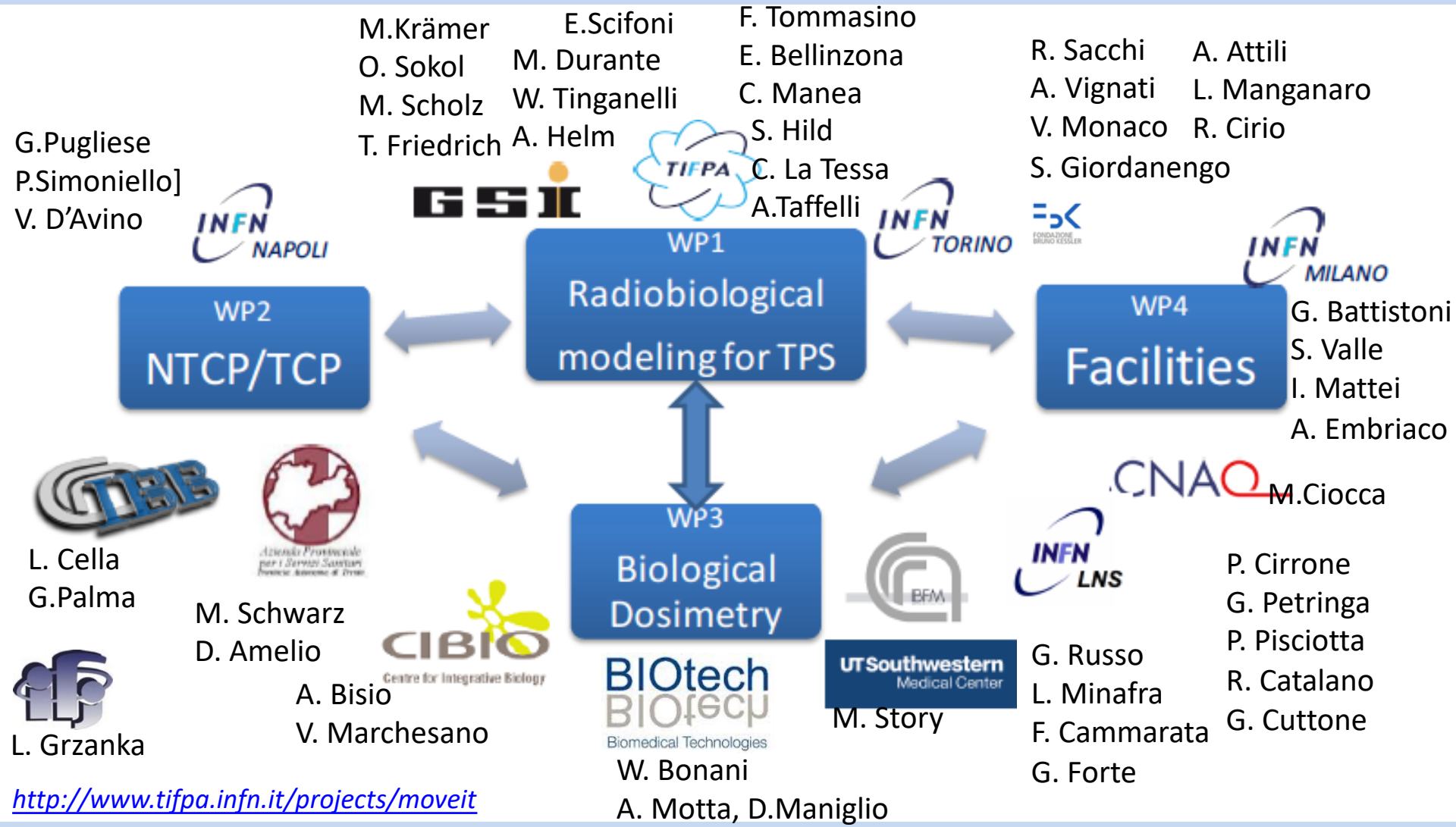
The experimentally observed DMF (1.4), could be reproduced only with a 10^5 factor in produced fragments

Attiil et al. in prep for PMB

Summary

- RBE in a mixed field of a particle beam should be computed accounting for all components
- According to the obtained results secondary protons have a relevant impact in proton particle fields
- Helium component is the major contributor for Z>1
- But its role, according to the present available cross sections is limited to a small contibution
- A correction on a factor larger than an order of magnitude on the xs would impact the role of Z>1 frags
- The present correction is enough to provide good agreement with the experimental in vitro data
- Even the energy distribution will not affect importantly the resulting RBE

Thanks!



http://www.tifpa.infn.it/projects/moveit