Modeling and simulation in radio- and particle-therapy

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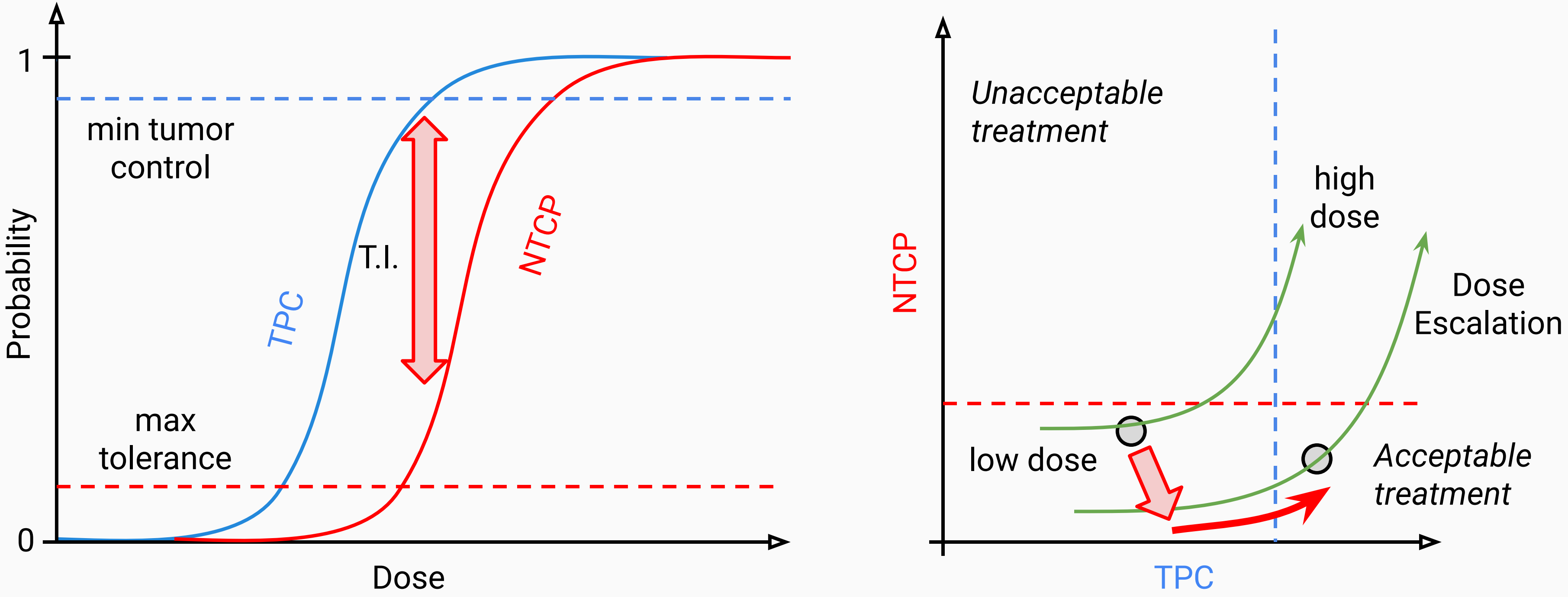
Outline

- A very **short introduction to “hadrontherapy”** (external ion beam therapy)
    - The basic problem in radiotherapy: maximization of the therapeutic index
    - Choice of primary radiation (dose delivery, physical & biological selectivity).
    - The radiobiological problem (RBE/OER)
    - Use of “radio-sensitizer” in hadrontherapy
    - Simulations of treatments & the *Treatment Planning System* (TPS)
- The **NEPTUNE** (**N**uclear process driven **E**nhancement of **P**roton **T**herapy **UN**rav**E**led) experiment
- The **MOVE-IT** (**MO**deling and **VE**rification for Ion beam **T**reatment planning) experiment
- “Appendix”: Implemented and publicly available simulation softwares

Short introduction and some recent research activities in “hadrontherapy”

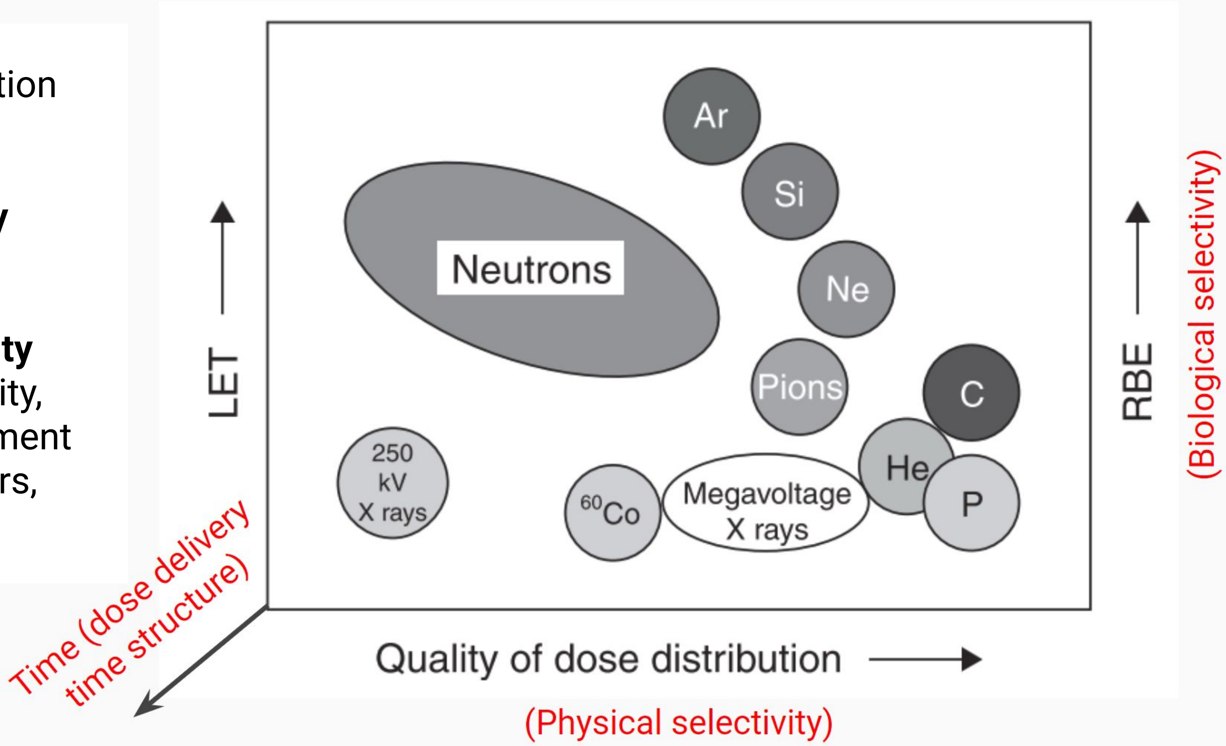
The Radiotherapy problem: increasing the Therapeutic Index



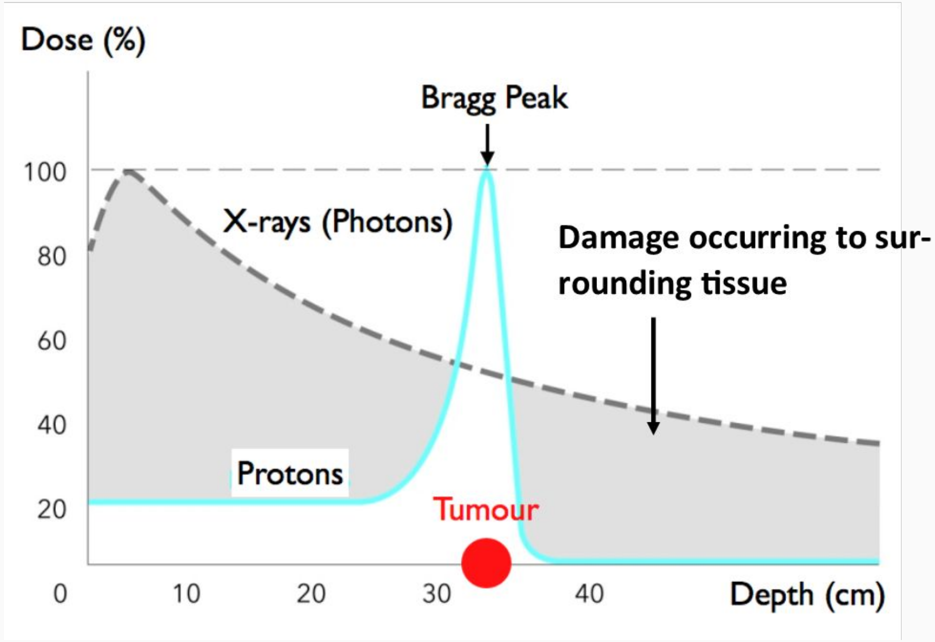
Radiation Type Optimality

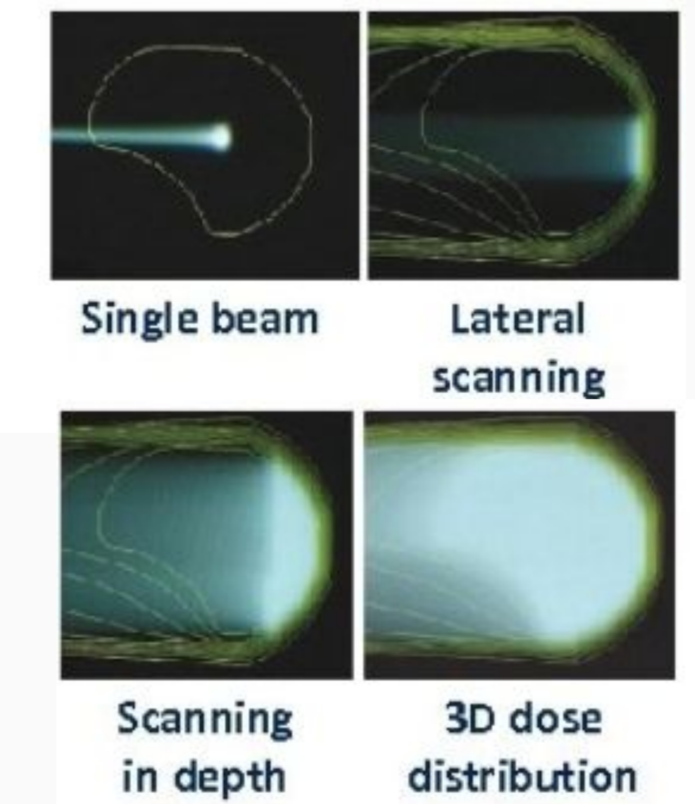
Which is the "best" radiation for radiotherapy?

- **physical selectivity** (dose conformity)
- **biological selectivity** (LET/RBE conformity, Targeted Enhancement with radiosensitizers, etc.)

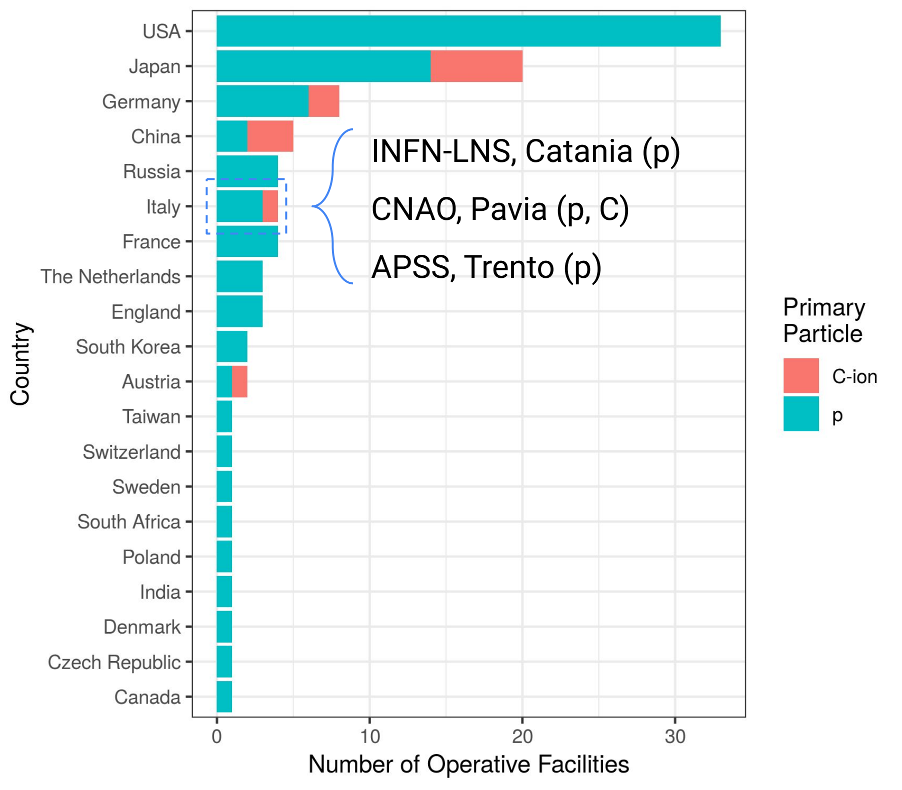


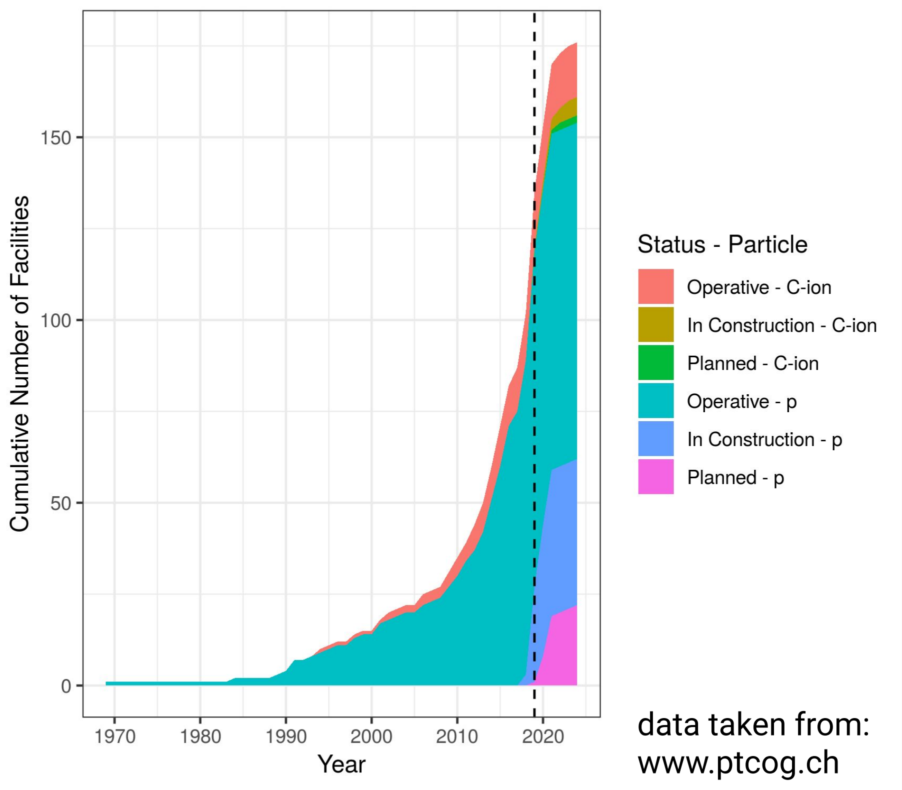
Physical selectivity - Active Raster Scanning





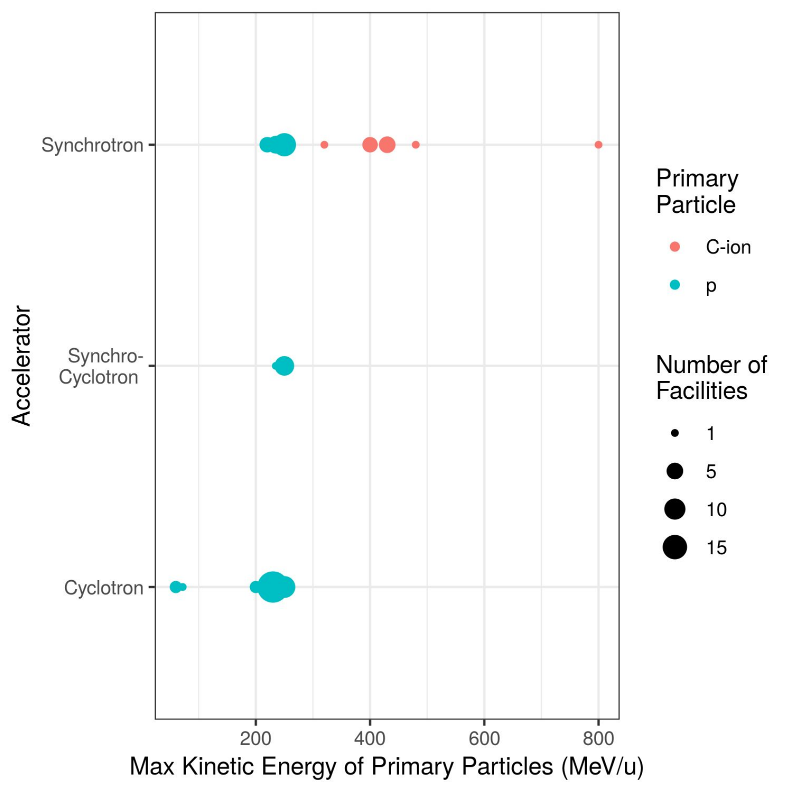
Particle therapy facilities in the world (update: June 2019)





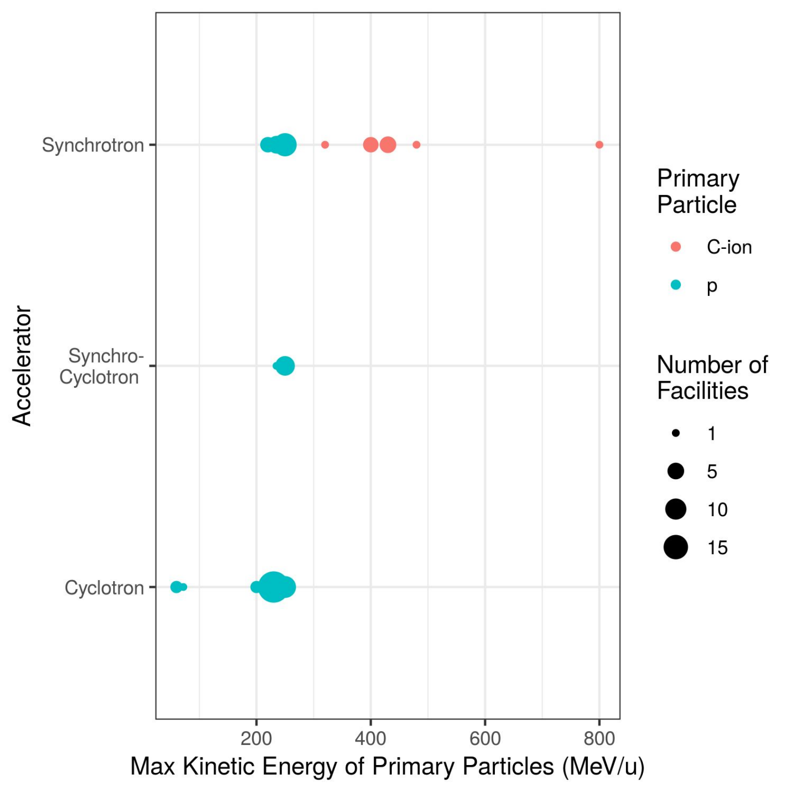
data taken from:
www.ptcog.ch

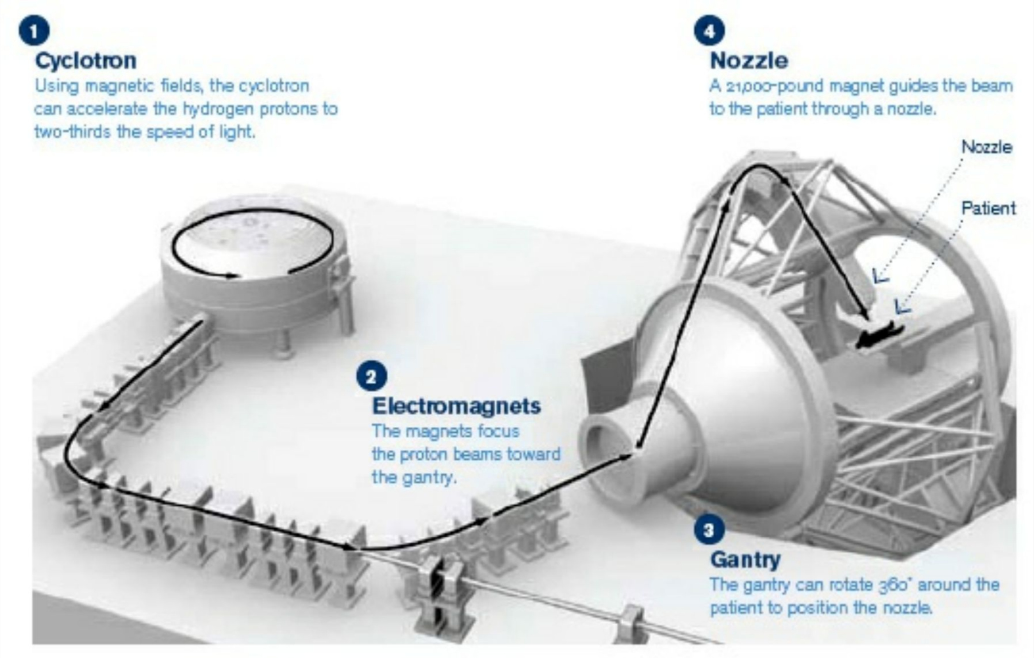
Accelerators for Particle therapy in clinical operation (update: June 2019)



Synchrotron (CNAO, Pavia)

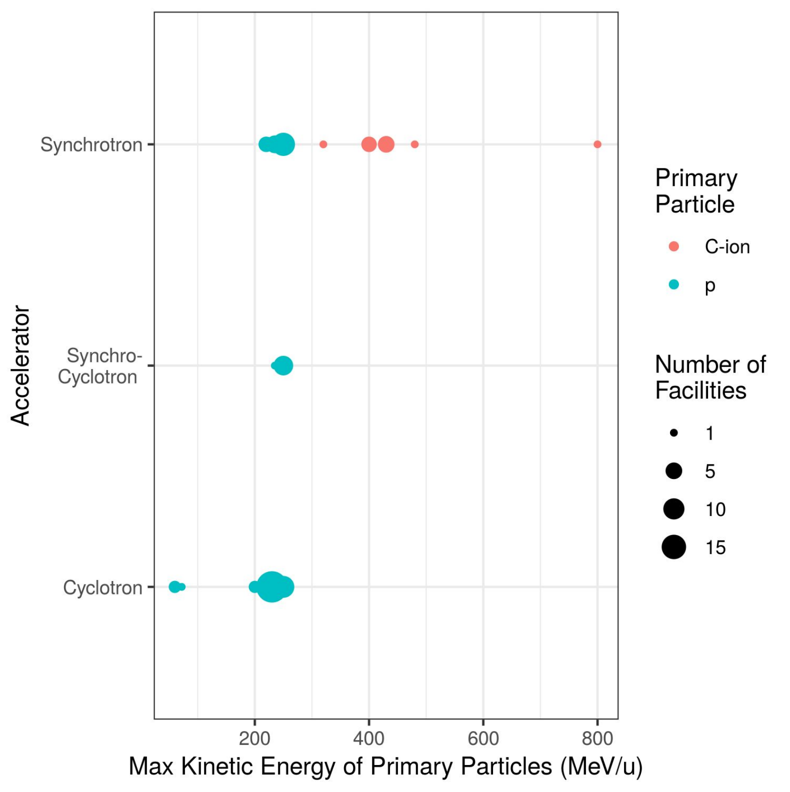
Accelerators for Particle therapy in clinical operation (update: June 2019)

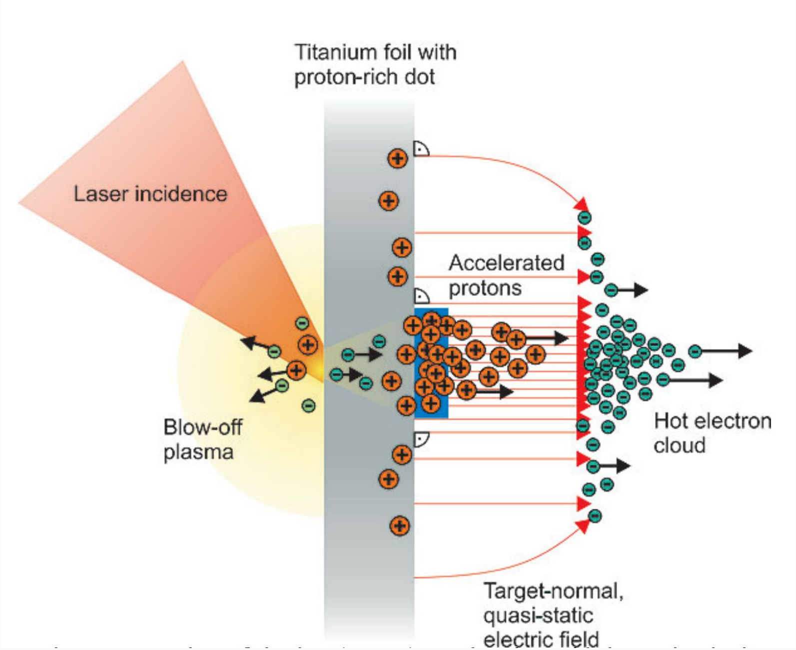




Cyclotron + energy selection + Gantry system

Accelerators for Particle therapy in clinical operation (update: June 2019)





Future directions: Laser accelerated proton therapy (EliMED, INFN-LNS)

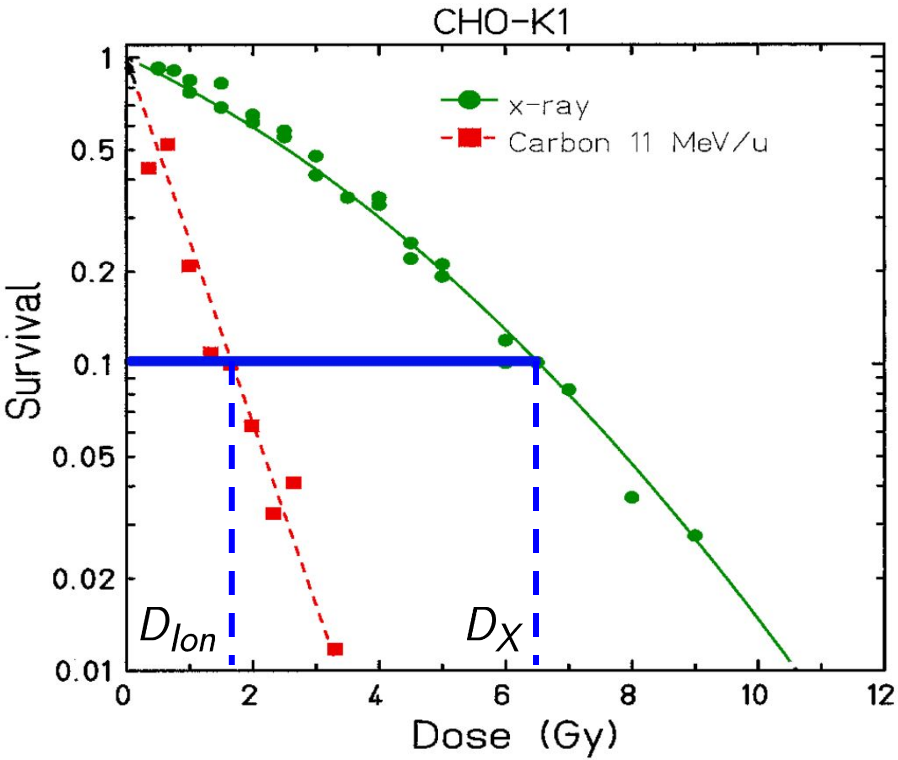
Biological Effect: the Relative Biological Effectiveness (RBE)

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



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

Biological Effect: the Relative Biological Effectiveness (RBE)

Physical Parameters:

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

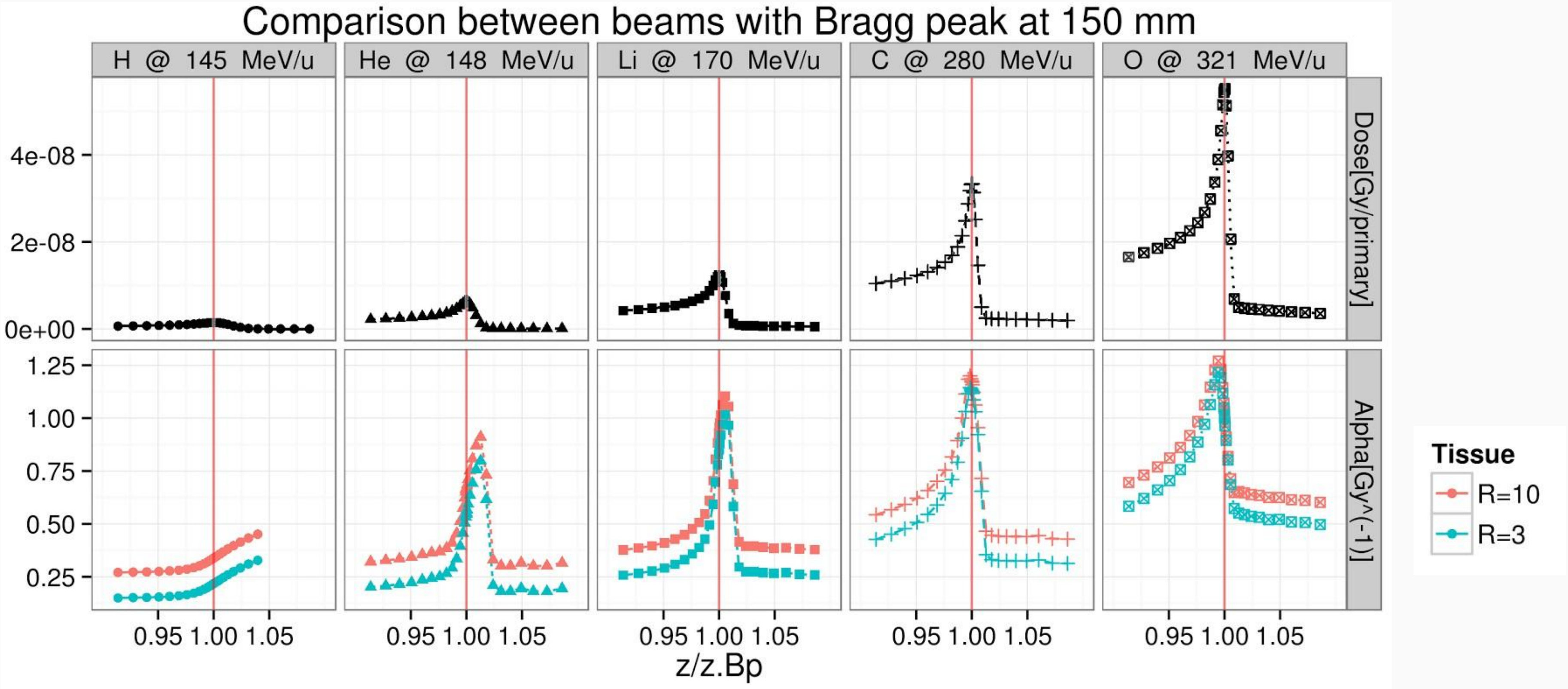
Biological Parameters:

- Cell type
- Oxygenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint

- Local Effect Model (**LEM**)
- Microdosimetric Kinetic Model (**MKM**)
- [...]

"Survival" simulation code (see Appendix)

“Colocalization of High LET / RBE - High Dose” - Ion Optimality

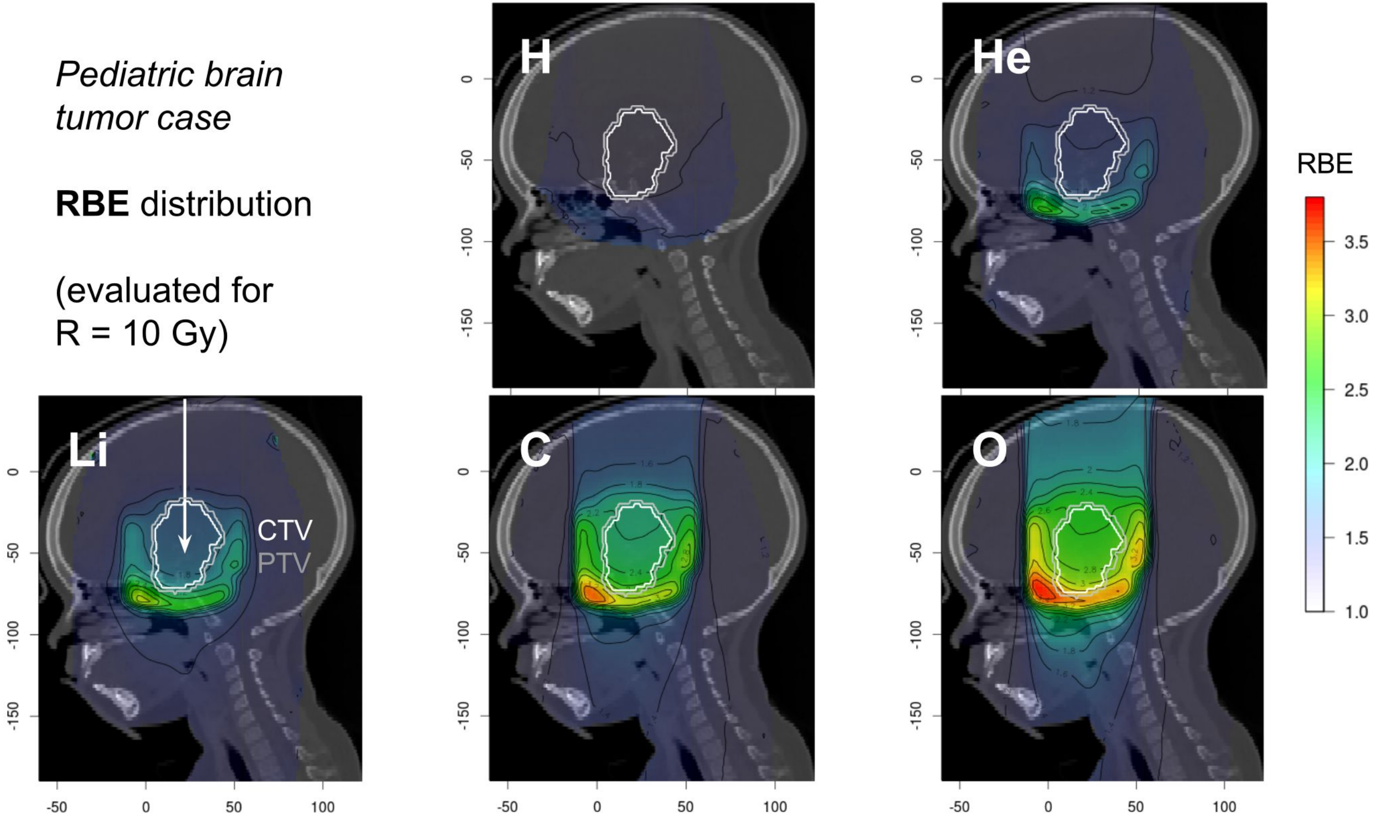


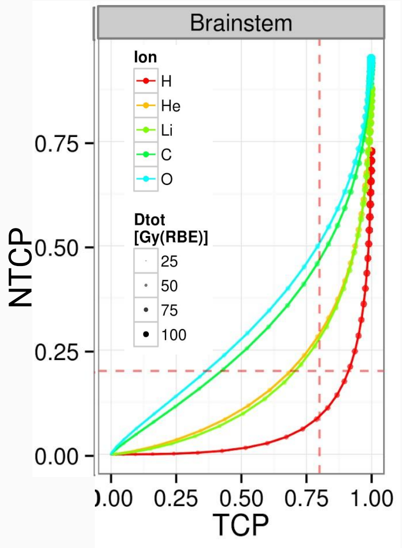
"Colocalization of High LET / RBE - High Dose" - Ion Optimality

Pediatric brain tumor case

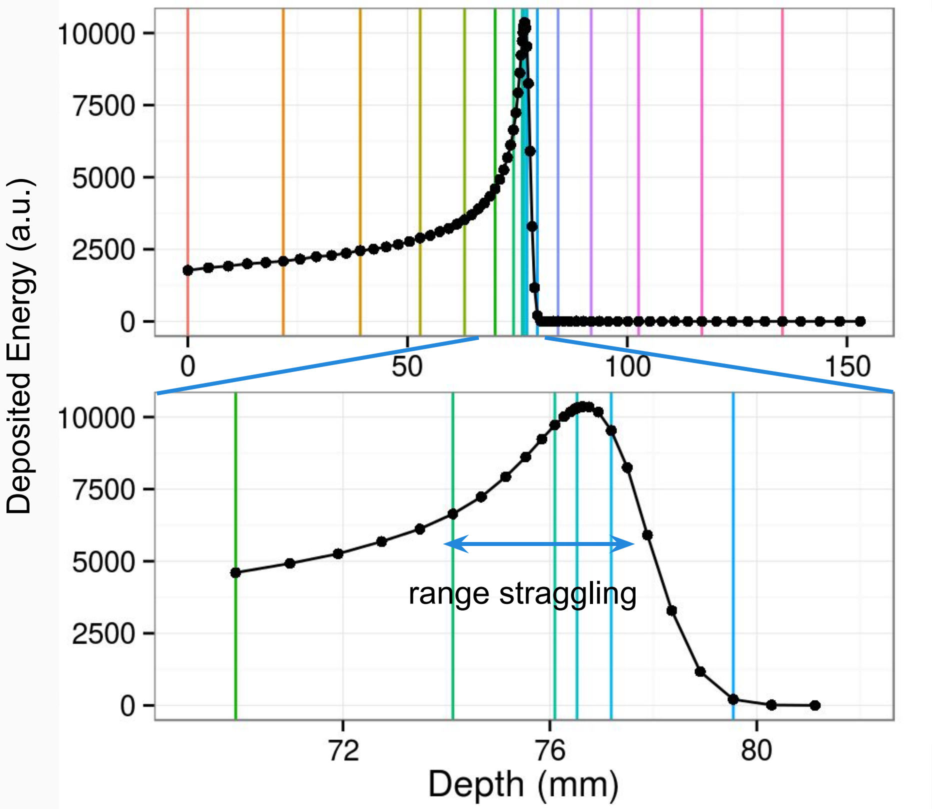
RBE distribution

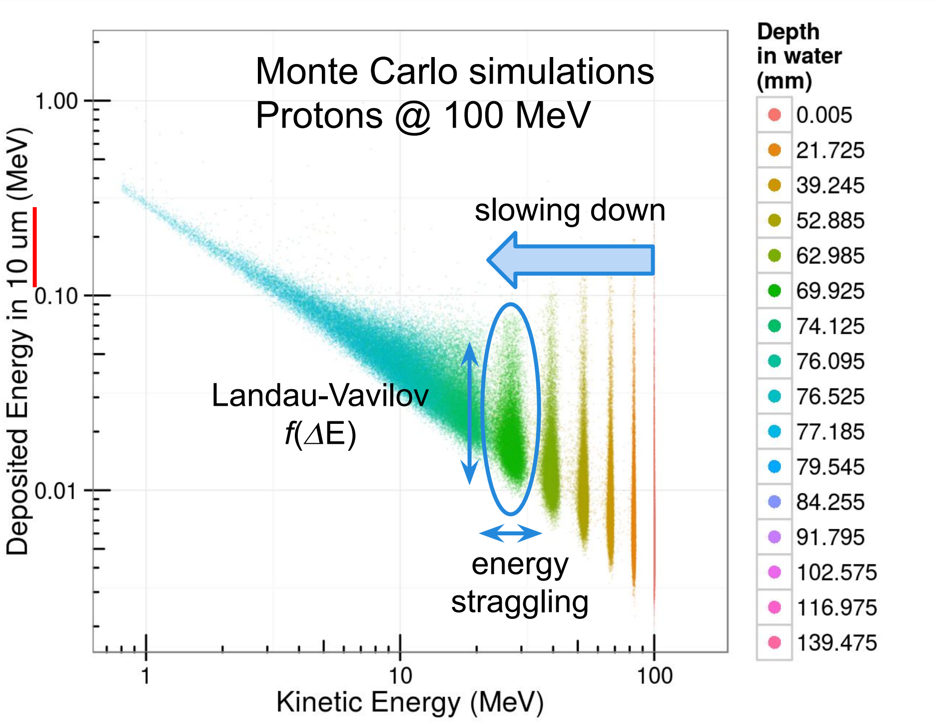
(evaluated for R = 10 Gy)





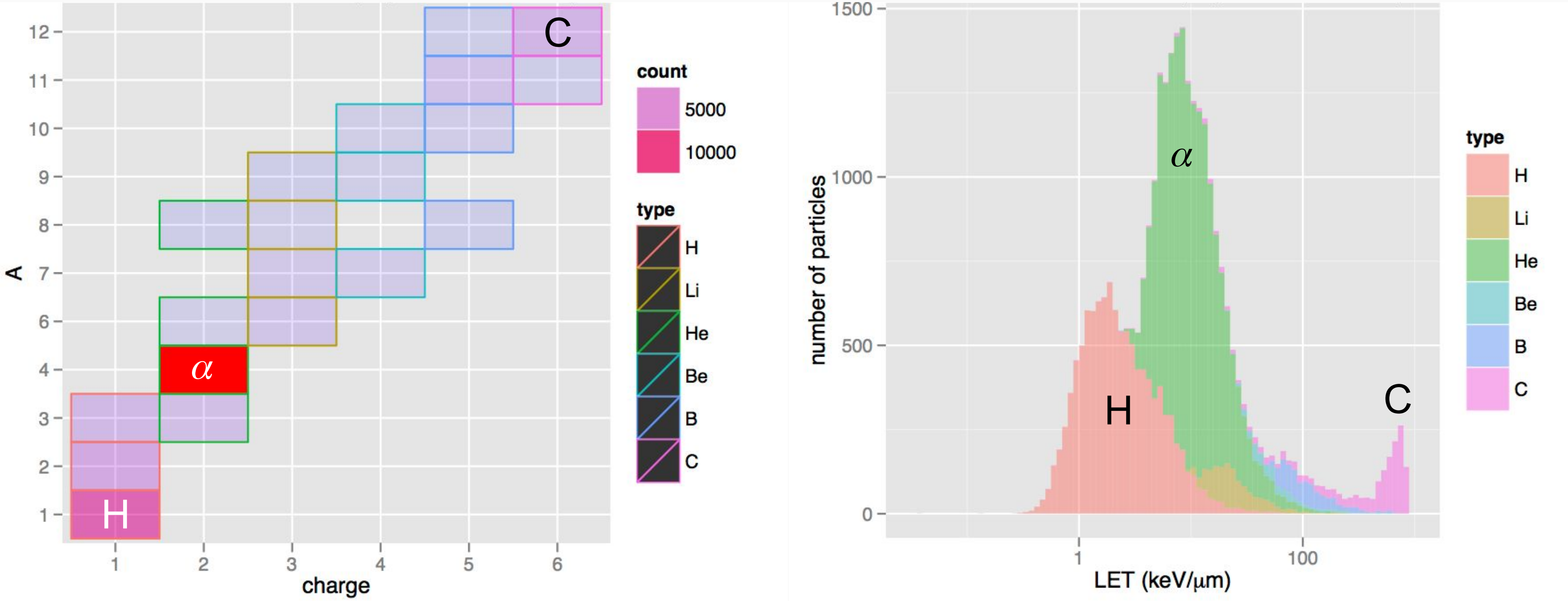
“Mixed field” - Energy straggling



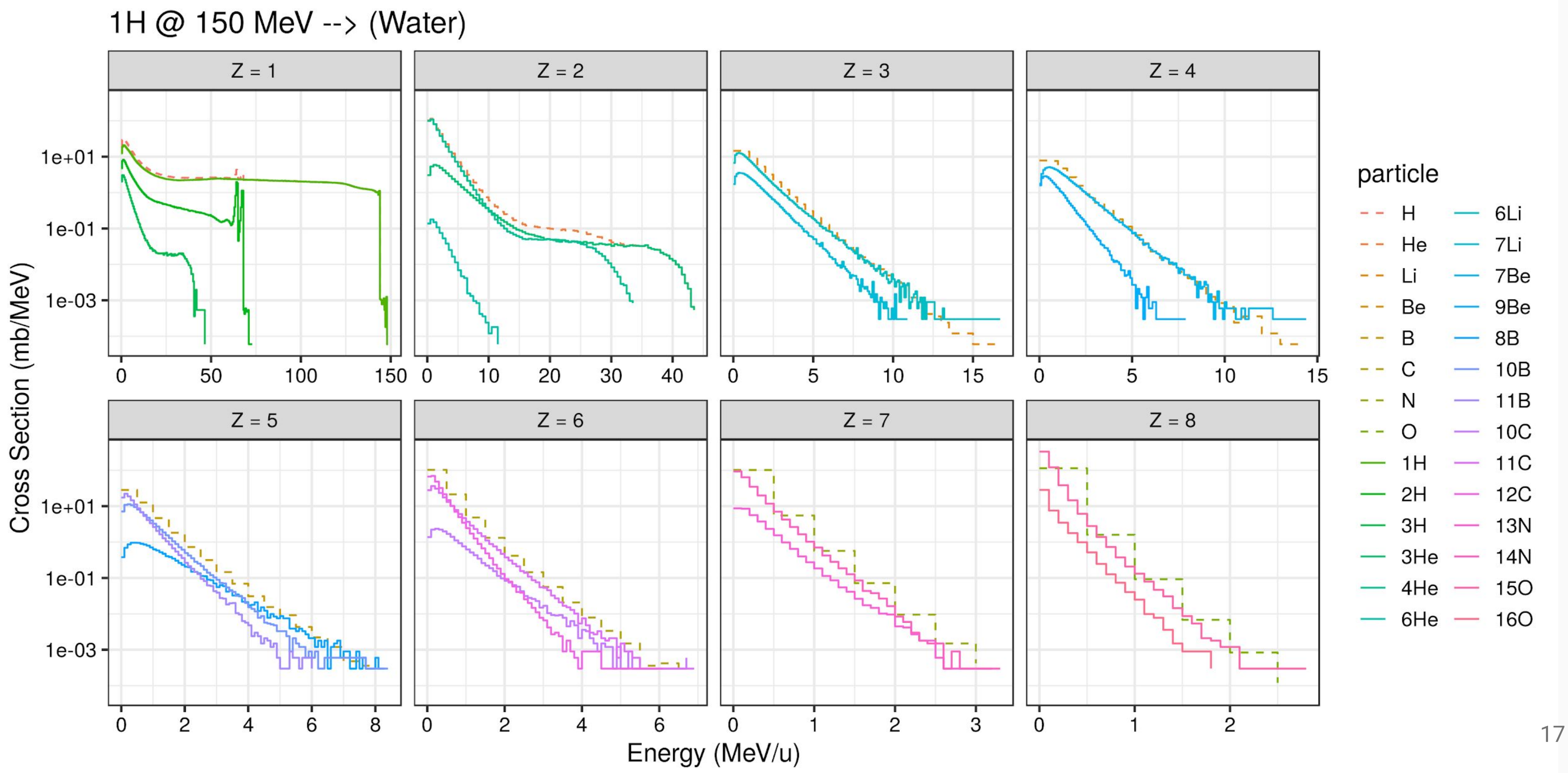


“Mixed field” - Nuclear fragments

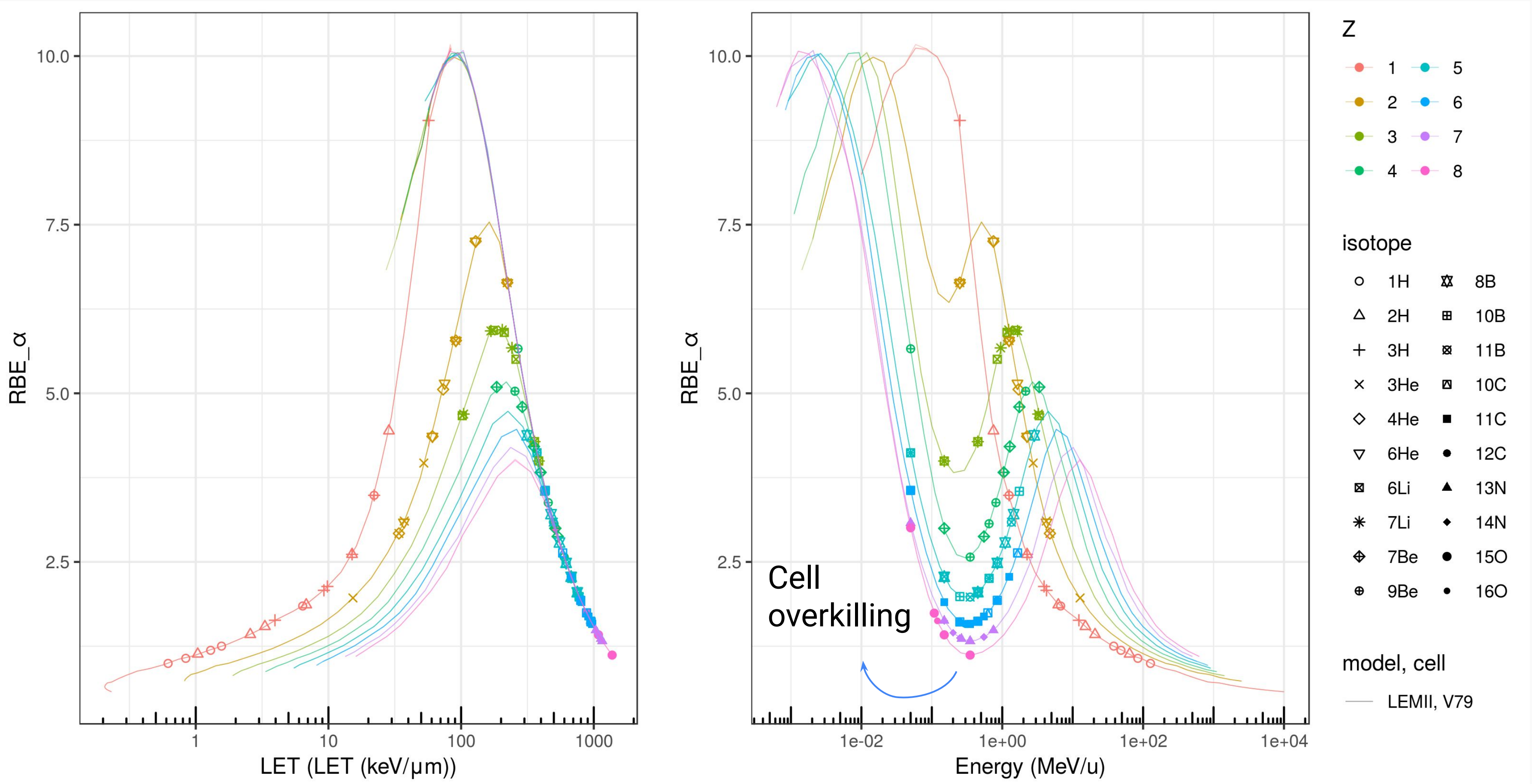
12C @ 60 MeV/u - depth = 10.5 mm



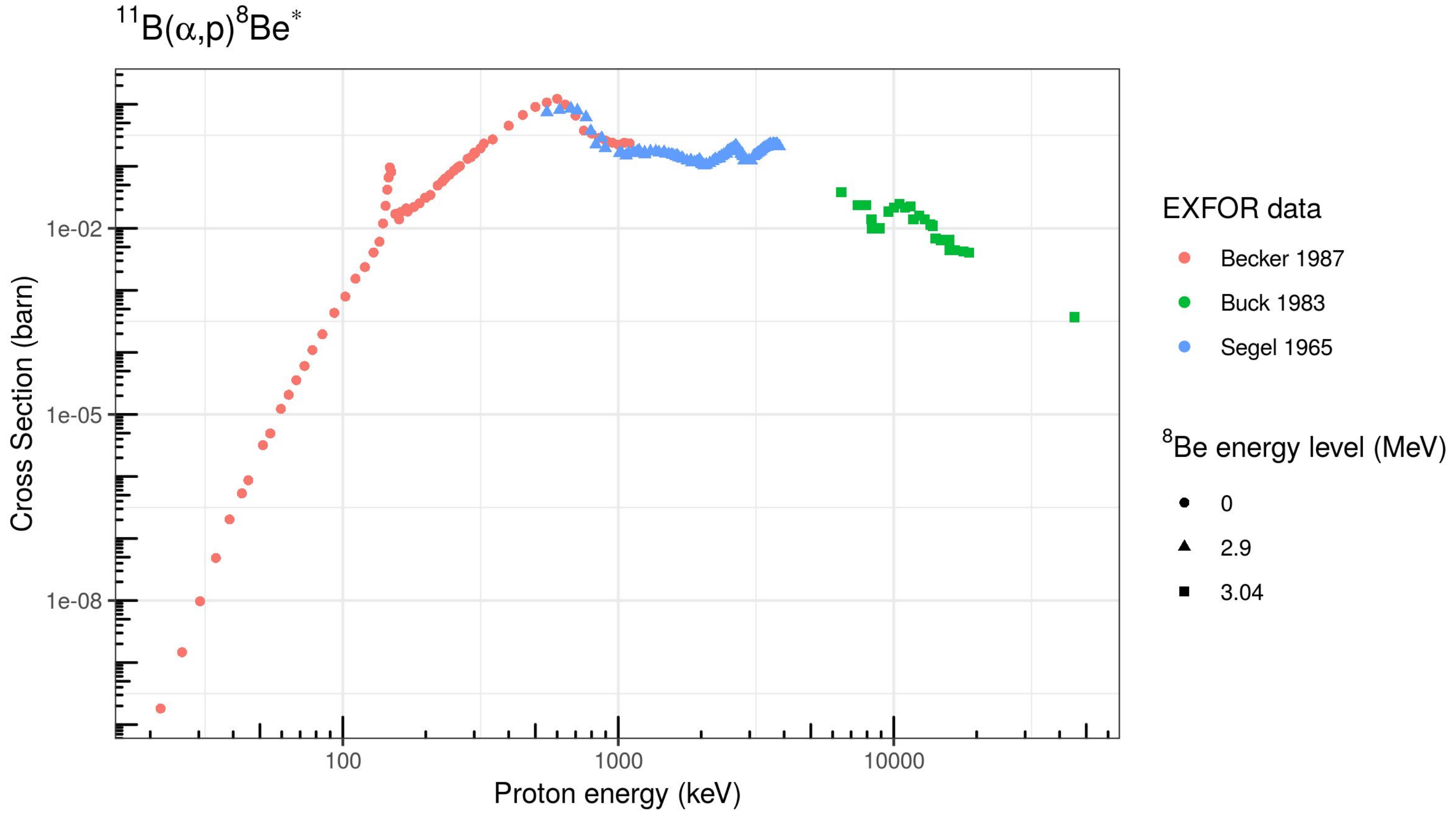
Simulated (Fluka) Differential Cross Sections



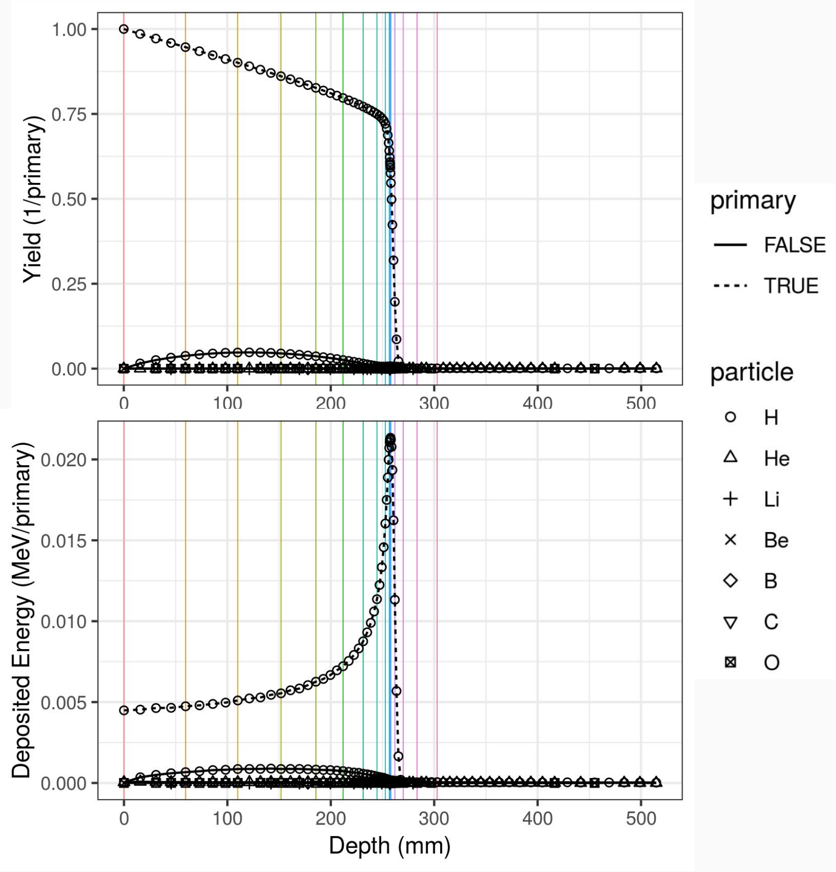
RBEvs. LET for each fragment evaluated with LEM2 (V79 cells)

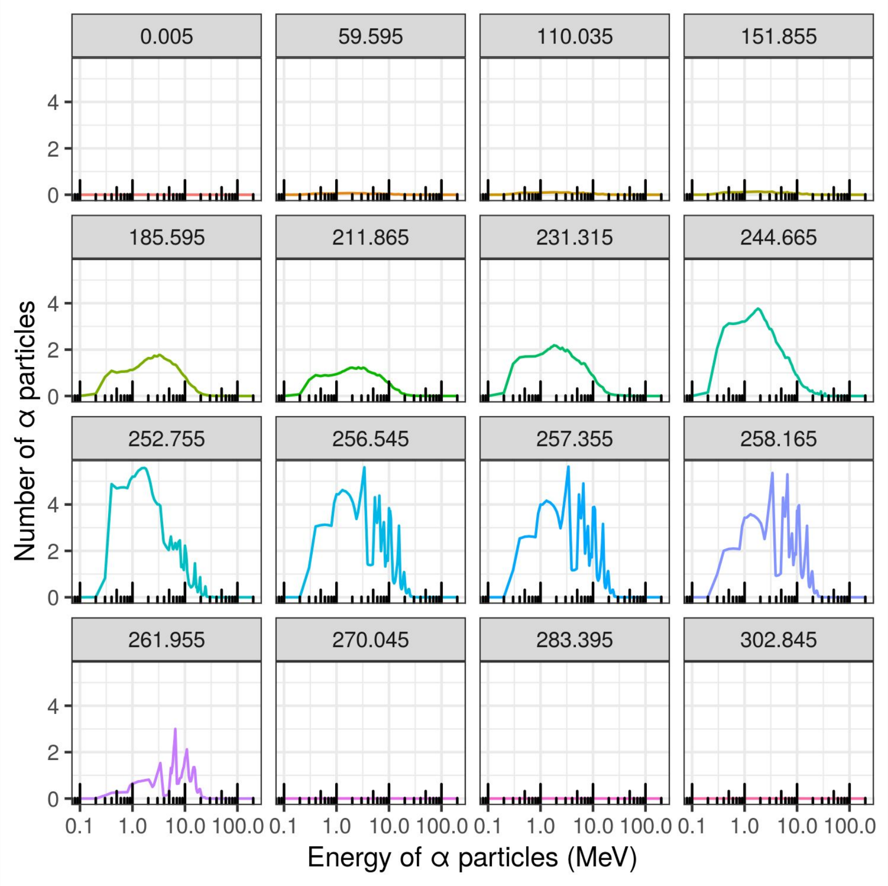


EXFOR data → differential Cross Sections 11B(alpha,p)8Be*

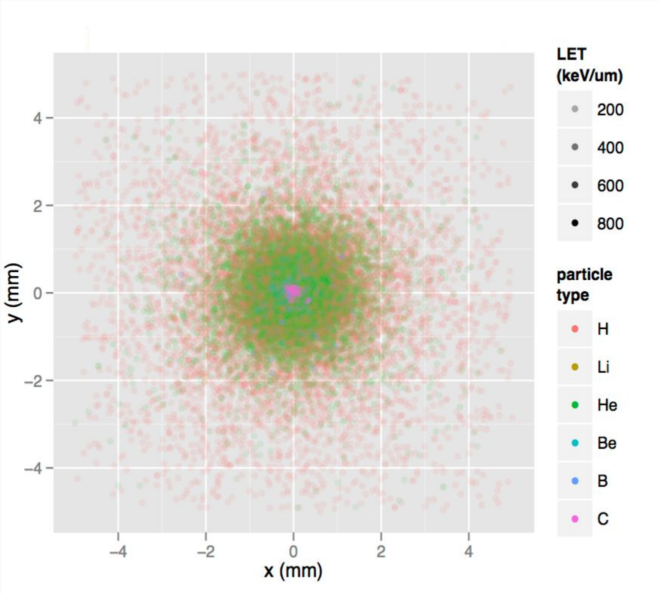


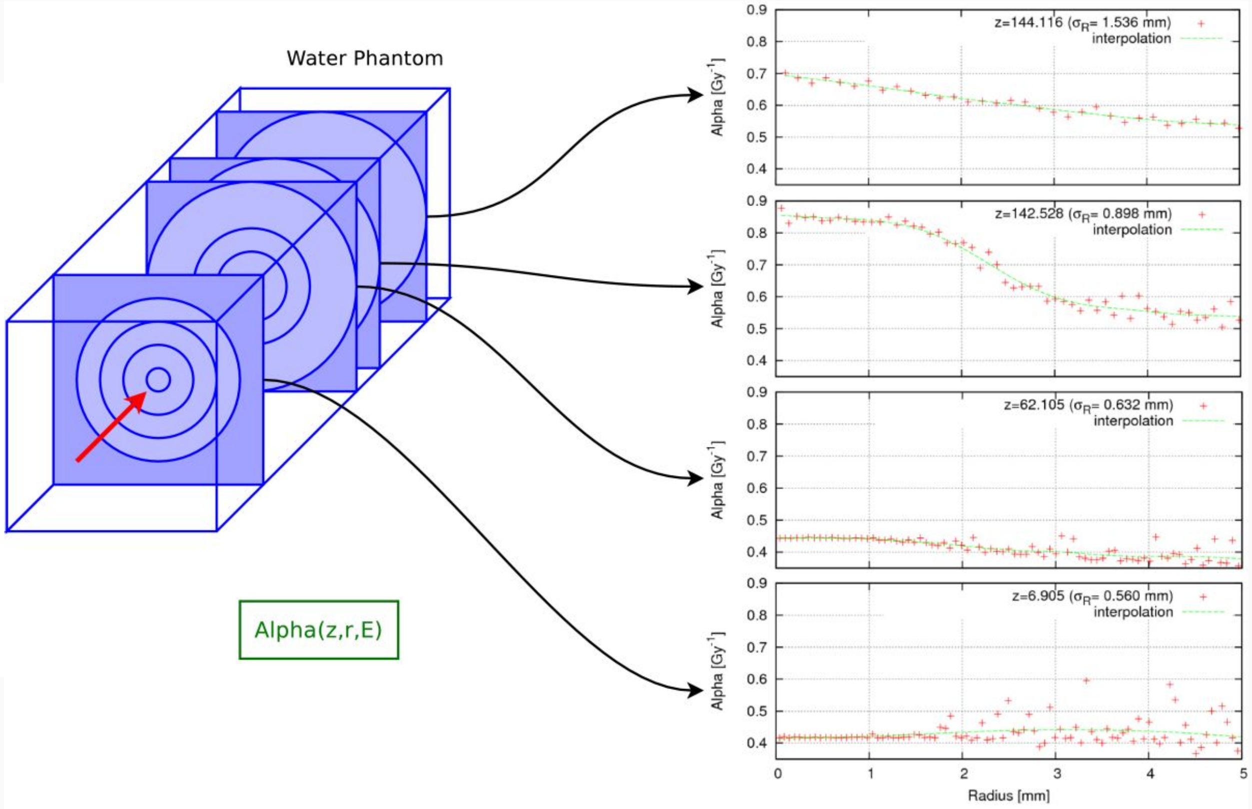
α production vs. depth proton (200 MeV) in a water phantom + ^{11}B



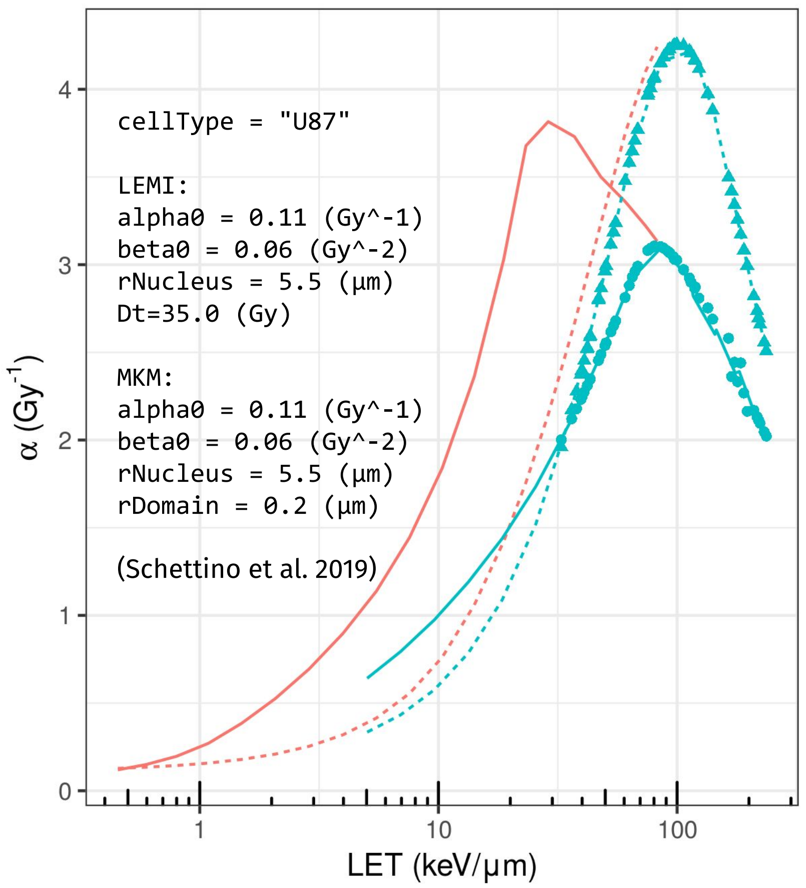


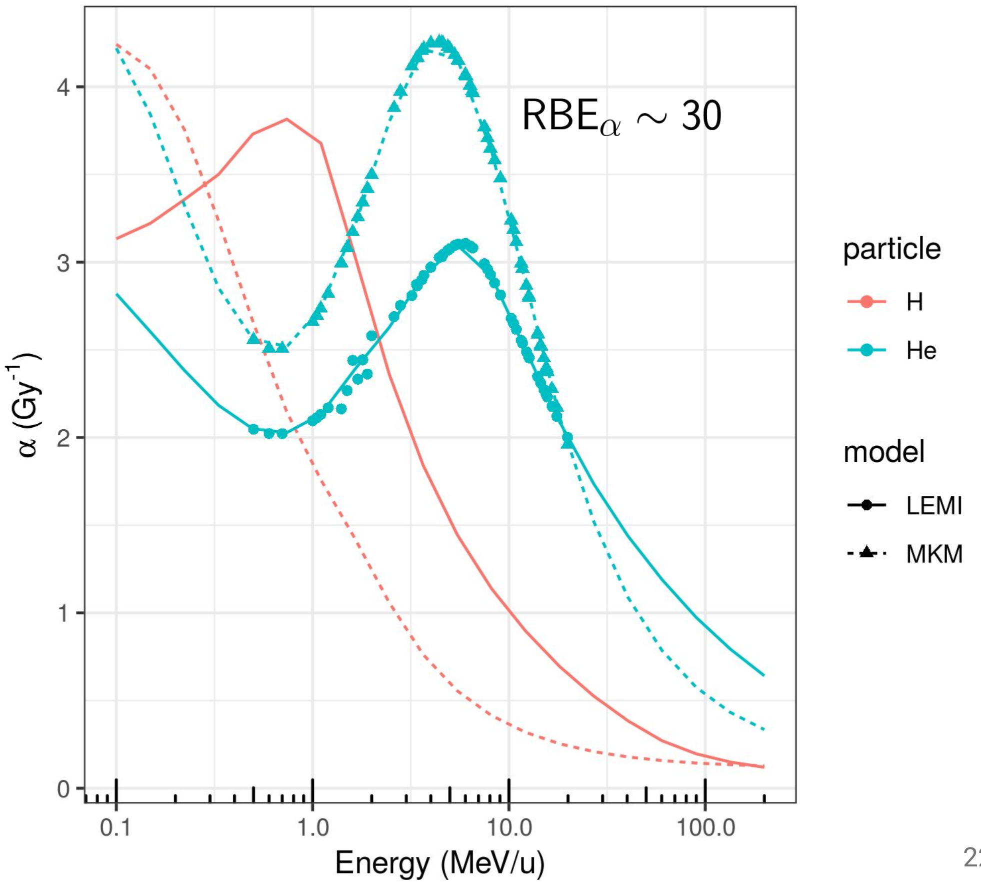
“Mixed field” - Nuclear fragments and radial analysis





(α_f, β_f) evaluations from σ_{pf} (TENDL) + "Survival" (LEM1/MKM)



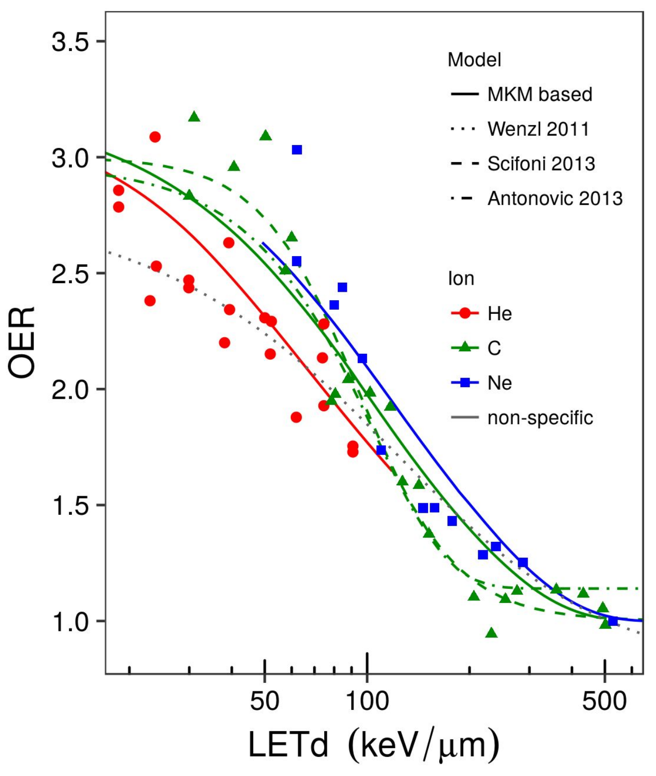


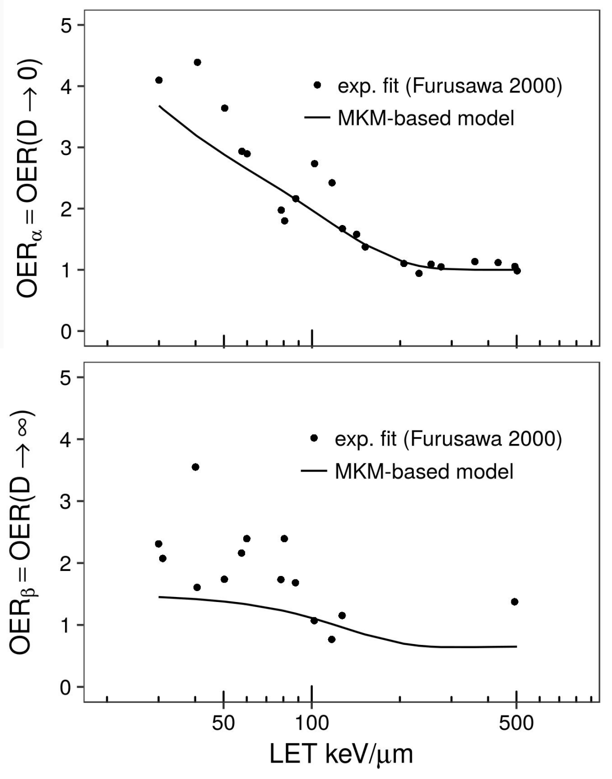
Oxygen Enhancement Ratio: MKM-based modeling

The MKM approach permits to identify an explicit OER dependence on:

- Particle type
- LET spectrum
- Dose/survival level
- Oxygen partial pressure

(Strigari *et al*. 2018)





Inclusion of OER in TPS: estimation of TCP in presence of hypoxia

MoVe IT

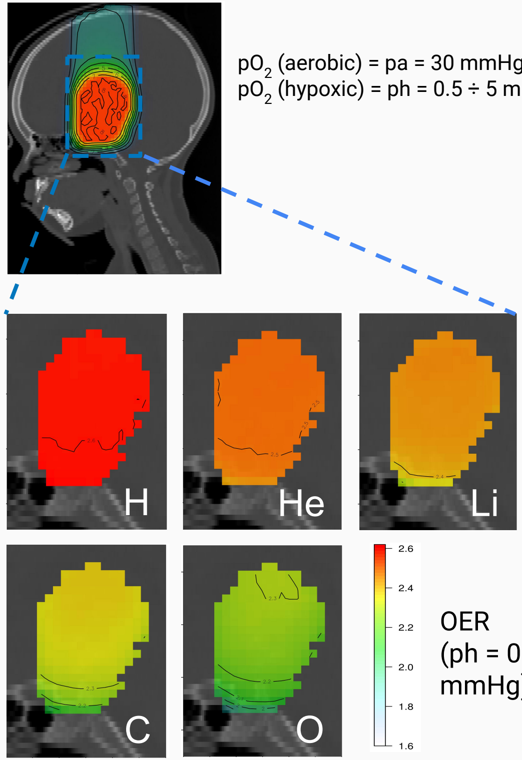
MKM-based OER modelling has been included in a TPS.

The simulation of treatments for a clinical case (brain tumour) using proton, lithium, helium, carbon and oxygen ion beams show a dependence of the OER on oxygen partial pressure, dose per fraction and primary ion type.

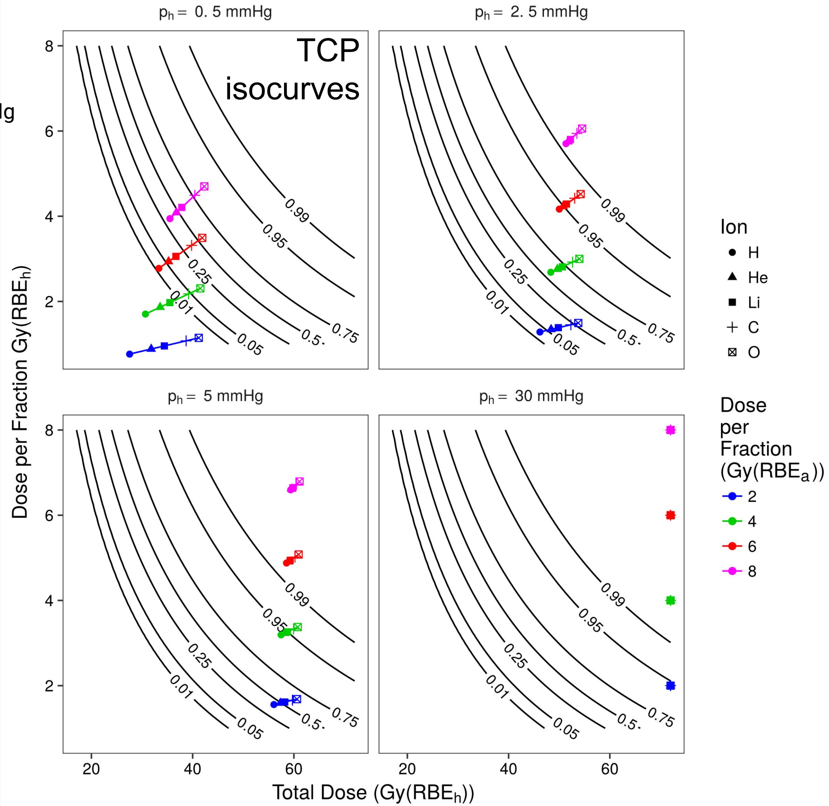
TPS evaluations show also a complex interdependence on these parameters.

(Strigari *et al*. 2018)

pO_2 (aerobic) = pa = 30 mmHg
pO_2 (hypoxic) = ph = 0.5 ÷ 5 mmHg



OER (ph = 0.5 mmHg)

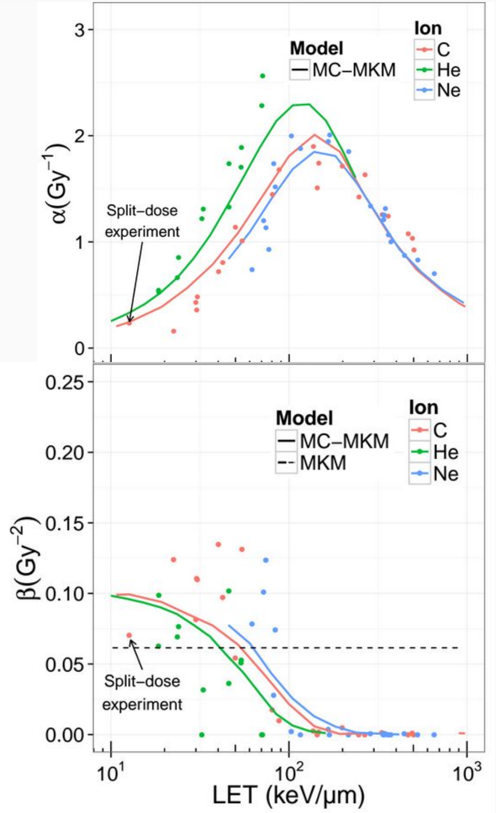


Extensions of MKM - Monte Carlo approach and temporal effects

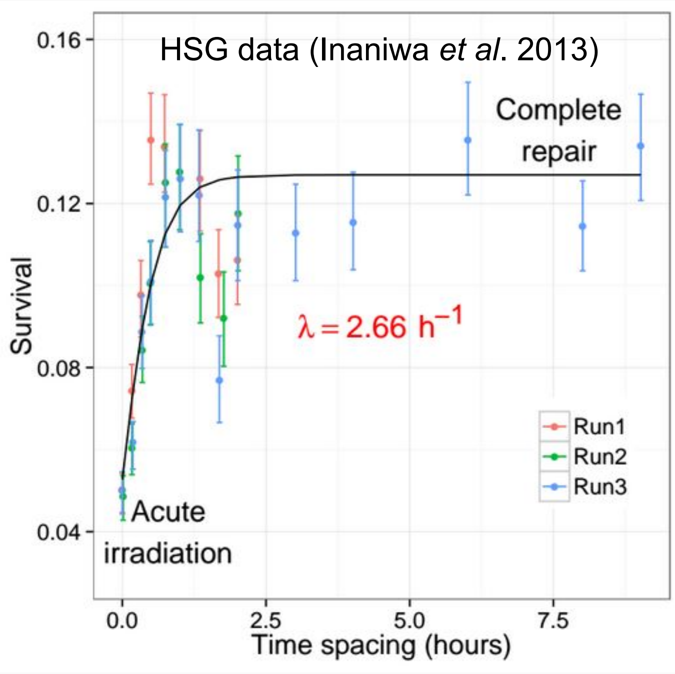
A MC-based formulation of the Microdosimetric Kinetic Model (named MCt-MKM) has been devised to account for spatio-temporal correlations between track energy deposition events (simulated at the nanometer scale in a cell sample) and the cellular repair kinetics.

In contrast to the original MKM formulation, the MCt-MKM explicitly predicts an ion and LET-dependent β compatible with observations. The data from a split-dose experiment were used to experimentally determine the value of the parameters related to the cellular repair kinetics.

(Manganaro *et al*. 2017)



Split dose experiment



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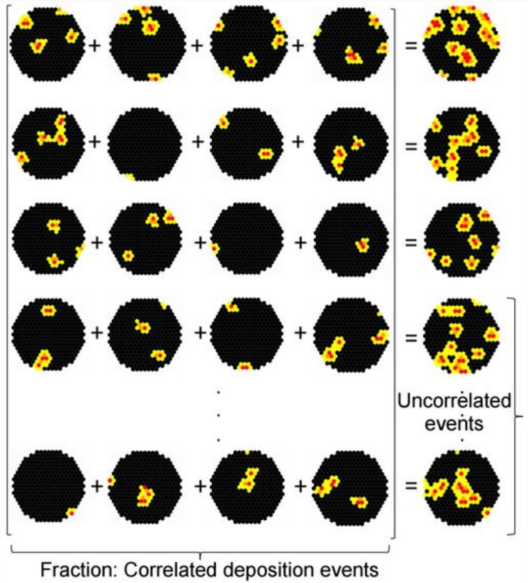
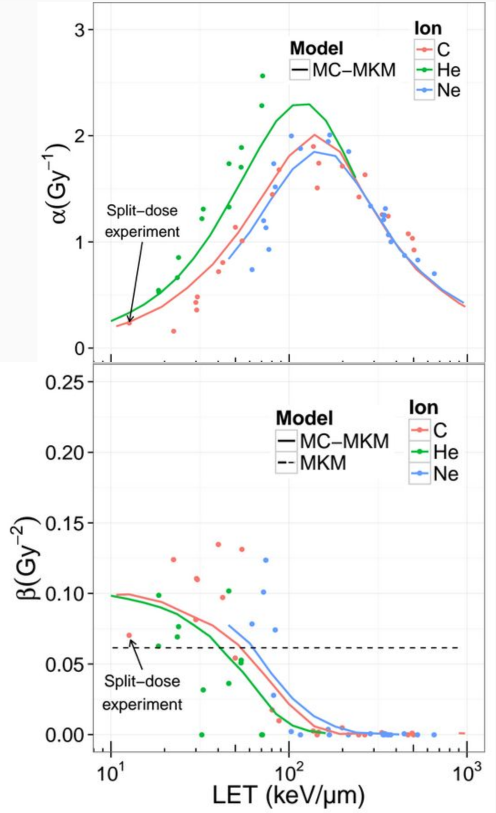
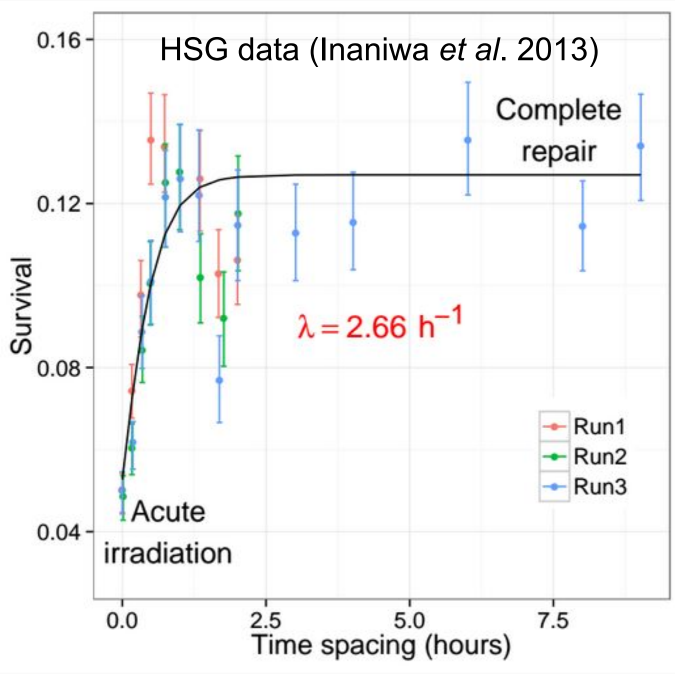
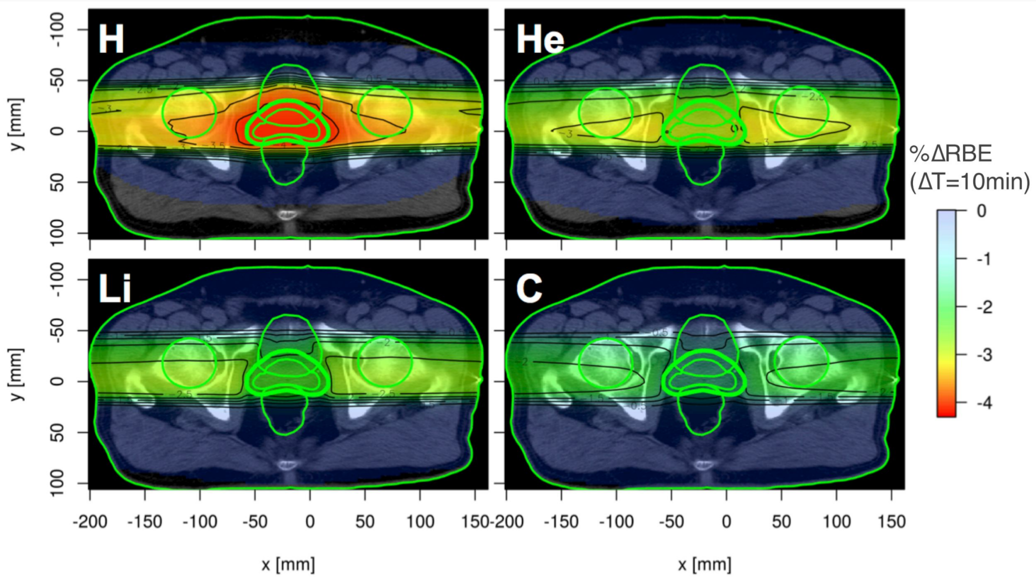


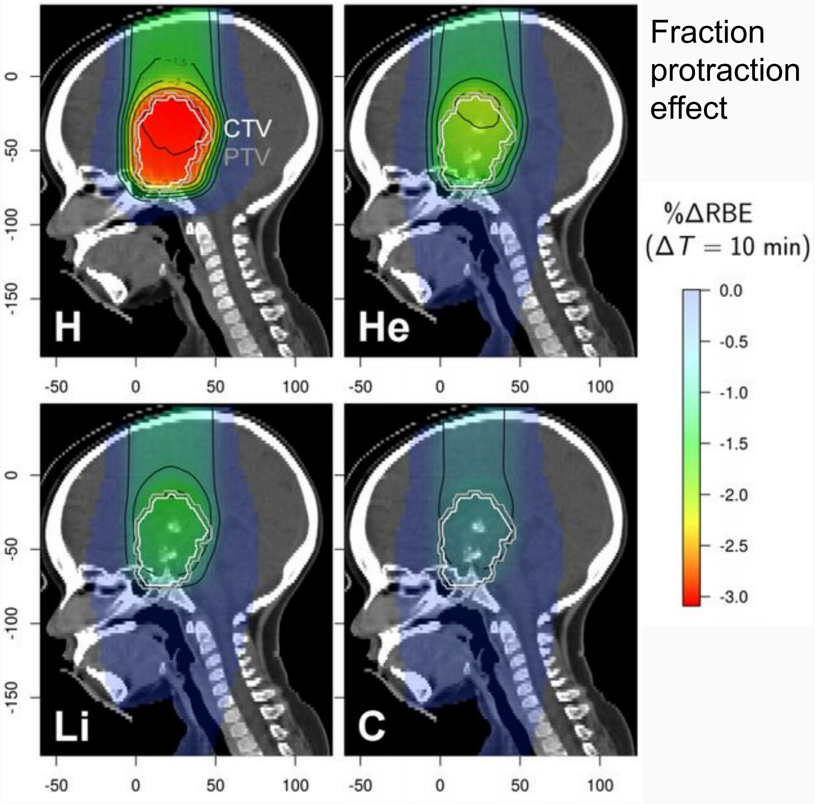


Split dose experiment



Dose delivery temporal effects in treatment





The MCt-MKM has been implemented in a TPS and used to evaluate the effect of dose delivery time structure on the relative biological effectiveness (RBE) in clinical treatments.

(Manganaro *et al*. 2017)

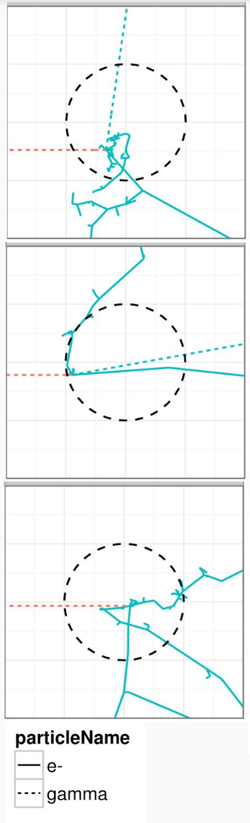
Modelling of radiobiological effects in presence of gold nanoparticles

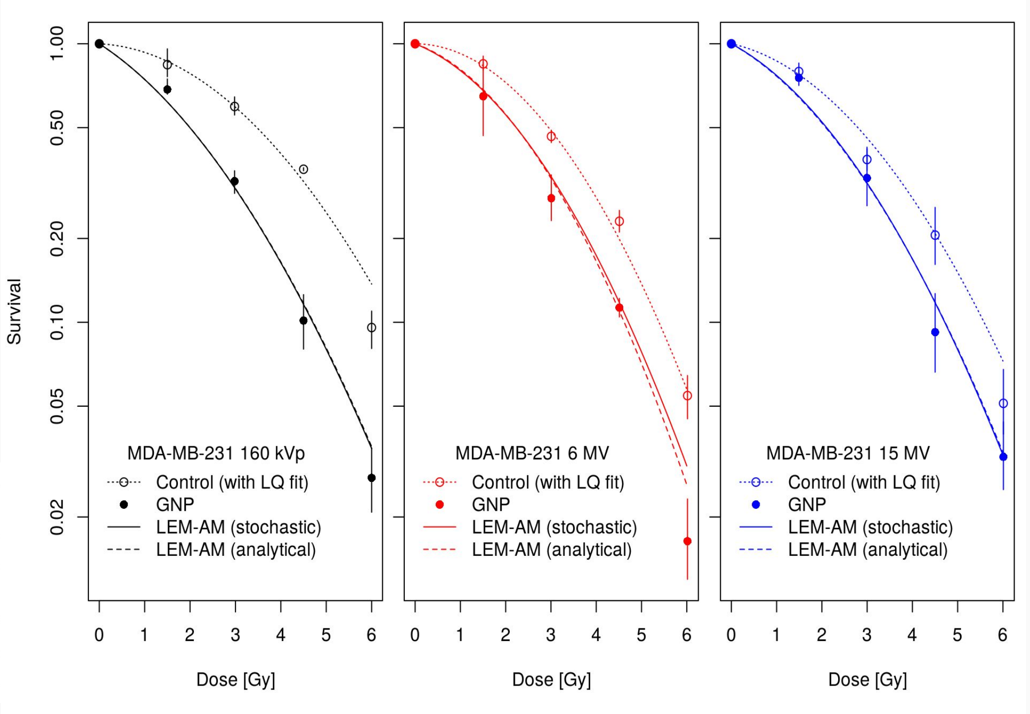
Monte Carlo simulations were carried out using Geant4 + G4DNA extensions.

Auger electrons, photoelectric emission, and interactions of secondaries in nearby atoms were simulated at the nanometer scale.

A stochastic radiobiological model, derived from the Local Effect Model (LEM), was coupled with the MC simulations to estimate the increase in radiosensitivity and validated using in vitro survival data of MDA-MB-231

(Ferrero *et al*. 2017)



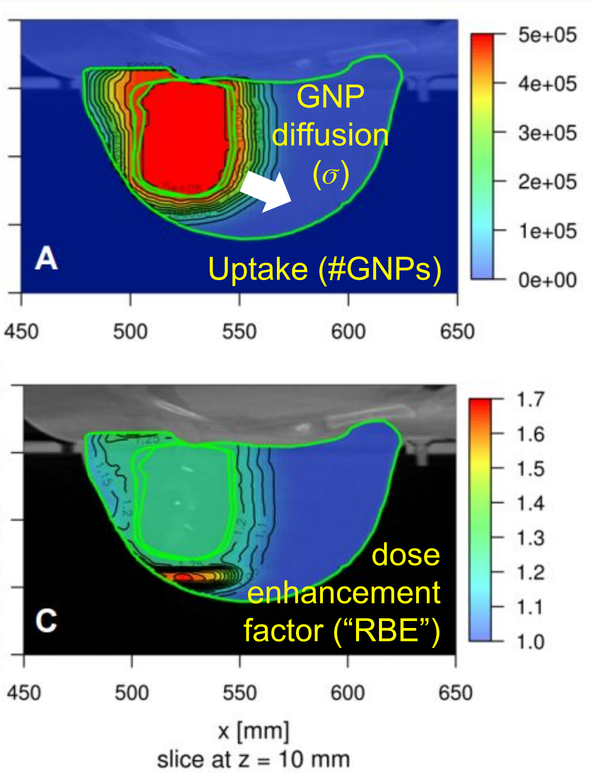


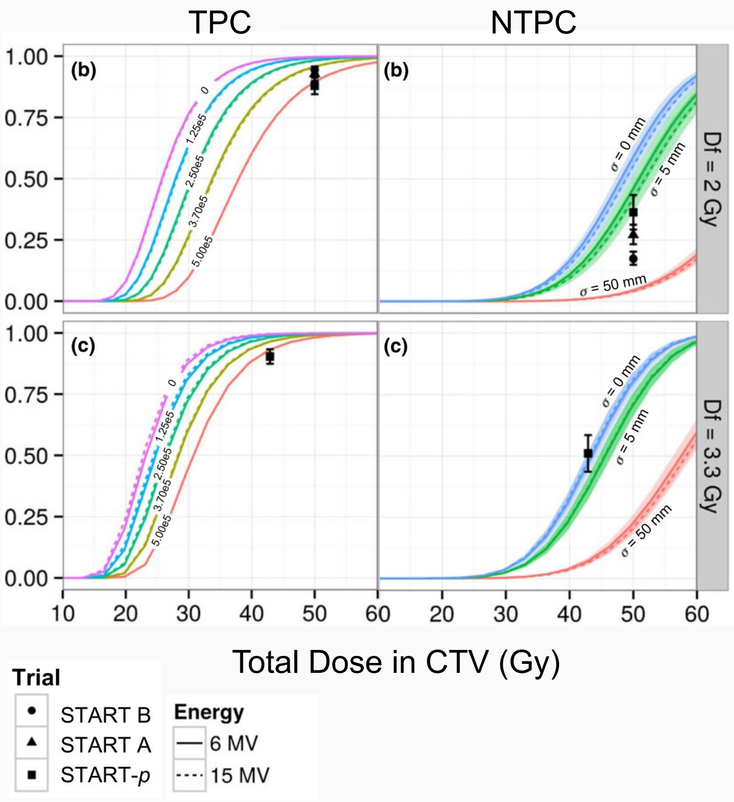
Simulation of clinical treatments in presence of GNPs

A reformulation of the LEM coupled with the estimation of local dose deposited around a GNP has been implemented in a TPS.

The model provides a useful framework to estimate the nanoparticle-driven radiosensitivity, accounting for the complex interplay between dose and GNP uptake distributions.

(Strigari *et al*. 2018)





Neptune experiment

NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled)

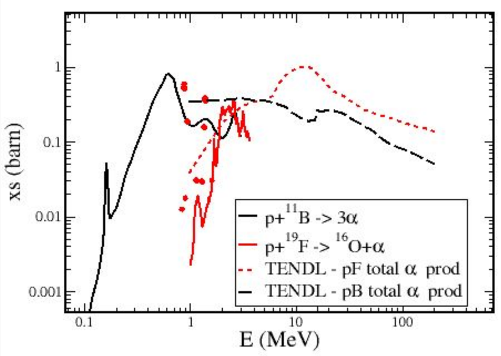
Principal Investigator: Cuttone G (LNS)
INFN Project: Call CSN V
Duration: 3 years (2019 - 2021)

INFN groups:

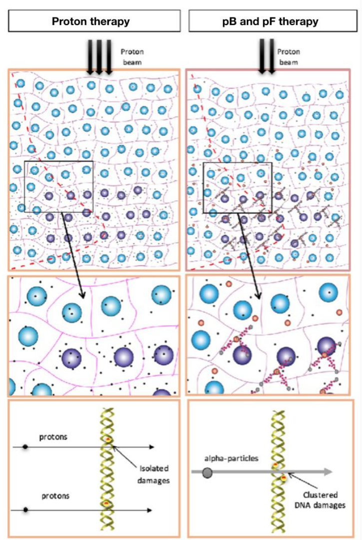
LNS (resp. P Cirrone)
TIFPA (resp. C La Tessa)
Napoli (resp. L Manti)
Roma1 (resp. R Faccini)
Roma3 (resp. A Attili)
Milano (resp. S Agosteo)
Pavia (resp. S Bortolussi)

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).

NEPTUNE WP1: Proton Boron Capture Therapy (PBCT) Modeling

Three main steps have been identified:

S1. The experimental set-up used at INFN-LNS will be simulated with Geant4 to estimate the particle spectra generated by the nuclear reactions. The spectra will be used as an input for the radiobiological simulations based on the *Microdosimetric Kinetic Model* (MKM) & *BIophysical ANalysis of Cell death and chromosome Aberrations* (BIANCA) model.

- Links: microdosimetric data (WP3), B and F cellular uptake (WP2) and cell survival (WP4) measurements.

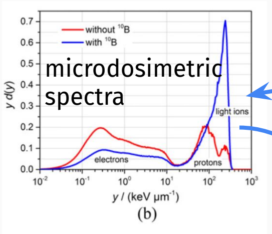
S2. A chemical-physics characterization of the reactive species following p + ^{11}B and p + ^{19}F reactions, will be carried out via two MC codes, Geant4-DNA and TRAX-CHEM.

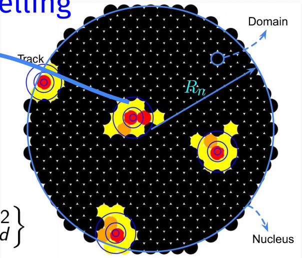
- Links: reactive oxygen species (ROS), rate of double strand breaks (DSBs), chromosomal aberrations (CAs) and foci measurements (WP4).

S3. Other indirect mechanisms, such as non targeted effects (NTEs) will be implemented in the MKM.

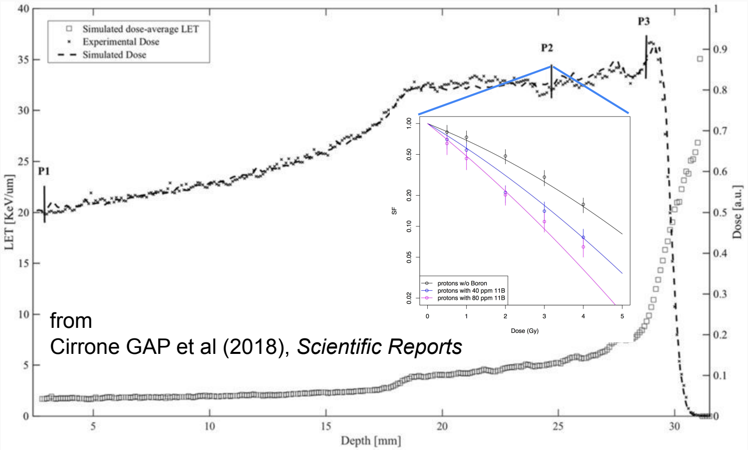
- Links: Bystander effect measurements (WP4)

MKM approach to modelling





$$\bar{N}_{leth} = \sum_d \left\{ (\alpha_0 + \beta_0 \bar{z}_{1d}) D_d + \beta_0 D_d^2 \right\}$$

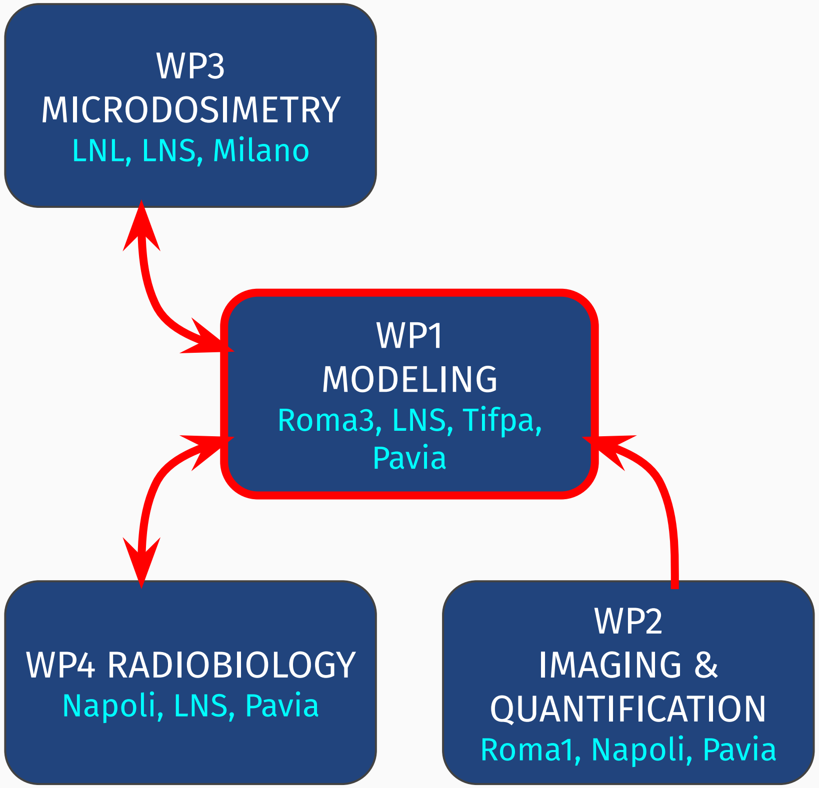


Profile of proton spread out bragg Peak (SOBP). Inset: cell survival fraction vs. dose w/ and w/o ^{11}B @ P2 (measurements & simulations)

NEPTUNE WP1: Proton Boron Capture Therapy (PBCT) Modeling

WP1 (A Attili, P Cirrone) *Modeling*
Roma Tre, LNS, Pavia, TIFPA

- The main aim of the WP1 is the investigation of the radiobiological role of the α particles and other production channel in the p + ^{11}B → 3α and p + ^{19}F → ^{16}O + α by means of computational modelling.
- The WP1 plays a key role in linking the microdosimetric data obtained in (WP3) to the experimental radiobiological outcome (WP4), taking into account the uptake data measured in (WP2).
- This task ultimately will help to untangle the role of the nuclear interactions and to indicate possible further mechanisms that could play a role in PBCT/PFCT.



S1: Milestones/Deliverables for the first year

1st year

	Month	Milestone/Deliverable	
D1.1	1-6	Implementation of MC simulations (Geant4) for p + 11B and p + 19F nuclear reaction spectra generated in the experimental setup.	80%
M1.1	6-12	Integration of the simulated spectra evaluated in D1.1 in the radiobiological simulations (MKM + BIANCA)	50%
...	...	...	
M1.3	24-30	Comparison between simulation data (D1.1) and experimental data (microdosimetric spectra) taken by WP3. Inclusion of the experimental data in the radiobiological simulations (MKM).	
M1.4	24-30	Comparison between simulation data (D1.1, M1.1, M1.6) with the experimental data (cell survival) taken by WP4.	

S2: Milestones/Deliverables for the second year

2nd year

	Month	Milestone/Deliverable
D1.2	12-18	Implementation of Geant4-DNA, and TRAX-CHEM simulations starting from the spectra obtained in D1.1.
M1.4	18-24	Coupling D1.2 simulations with radiobiological models to estimate cell survival, DSB, CA & foci.
...	...	...
M1.5	30-36	Comparison between simulation data (D1.2) and experimental data (ROS production) taken by WP4
M1.6	30-36	Comparison between simulation data from (D1.1, D1.2) + (M1.1, M1.2, M1.3, M1.4) with the experimental data (cell survival, DSB, CA, foci) taken by WP4.

NEPTUNE - Personale e Richieste x Roma Tre (2020)

Richieste finanziarie		
Missioni	Collaboration Activity at LNS	2 k€
	Collaboration Activity at TIFPA	2 k€
	Collaboration Meetings	2 k€
	Conference Participations	2 k€
Inventario	Nessuna	

Personale RM3	FTE
A Attili (Ricercatore INFN)	40 %
P Celio (Tecnico)	20 %
[…] 	

Move -IT experiment

MOVE IT (MOdeling and VErification for Ion beam Treatment planning)

Principal Investigator: Emanuele Scifoni (INFN – TIFPA)
INFN Project: Call CSN V (interdisciplinary)
Duration: 3 years (2017 - 2019)

INFN groups:

TIFPA (resp. E Scifoni)
LNS (resp. P Cirrone),
Torino (resp. R Sacchi),
Napoli (resp. MG Pugliese),
Milano (resp. G Battistoni)

→ ***Roma Tre****?* (A Attili)

Main Goals

1. 1. **Radiobiological Models** implementations in Ion **Treatment Planning System** (TPS):

    a. Increased **Relative Biological Effect** (RBE) of proton beams in the entrance due to high LET fragments and in the end of the range (high LET of primaries).
        i. **Nuclear interactions** (link with FOOT).
    b. Intra-tumor heterogeneity: **hypoxia** and **Oxygen Enhancement Ratio** (OER).
    c. **Tumor Control Probability** (TCP) and **Normal Tissue Complication Probability** (NTCP) models

2. **Experimental Verification**:

    a. **New Devices** for in-vitro and in-vivo irradiation
    b. Development and **Upgrade of INFN accelerator facilities** (Trento, Pavia, Catania)
    c. Development of advanced **beam monitoring systems**

MOVE IT - Working Packages

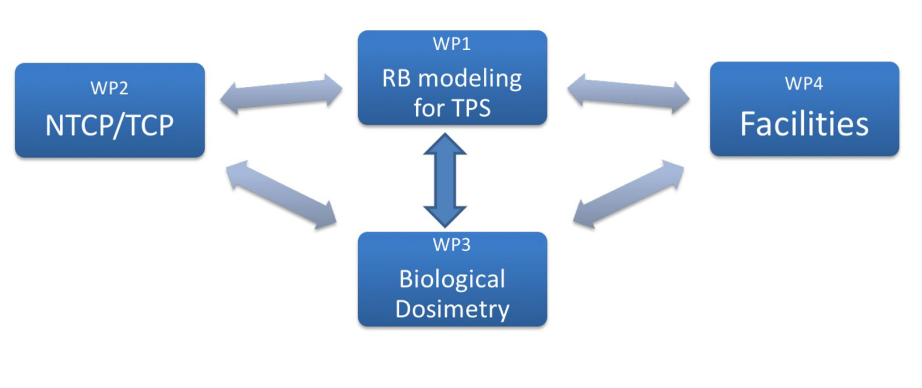
- WP0: Project coordination, results dissemination
  - **TIFPA**, **LNS**, **Torino**, **Napoli**, **Milano**

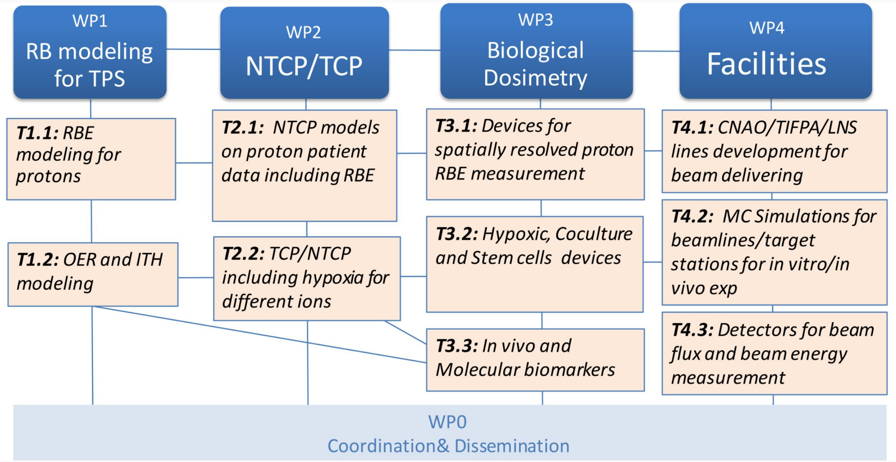
- WP1: Radiobiological modeling for TPS
  - **TIFPA, LNS, Milano, Roma Tre** (*A Attili,* ex attività di Torino)

- WP2: NTCP/TCP modeling
  - **Napoli**, **TIFPA**, **Roma Tre** (*A Attili*, ex attività di Torino)

- WP3: Biological dosimetry
  - **TIFPA**, **LNS**, **Napoli**

- WP4: Facilities and beamline simulations and monitoring
  - **TIFPA**, **LNS**, **Milano**, **Torino**





MOVE IT activities @ Torino/Roma Tre (WP1-2)

WP1-2 activity 2017-2018 - Modelling and TPS in ion beam therapy [Torino / Roma Tre]:

- Modelization of the RBE dependence on dose rate time structure in ion beam therapy and preliminary of interfractional studies in TPS (Manganaro, L, et al. 2017 *Medical Physics*, 44(4); Manganaro et al. to be submitted to *Physics in Medicine and Biology*) [collaboration with Massachusetts General Hospital, Boston]

- Development of a OER model based on the Microdosimetric Kinetic approach (see fig.), inclusion in TPS (Trip98 and RPlanit), and study of the impact of hypoxia on TCP (Strigari, L, et al. 2018, *Physics in Medicine and Biology* 63(6)) [collaboration with IFO - Istituto Nazionale Tumori Regina Elena, Roma]

- Implementation of an open source software for radiobiological simulation in ion beam therapy (Manganaro, L, et al. 2018, *Physics in Medicine and Biology* 63(8))

WP1-2 planned activity (2019-2020) [Roma Tre]:

- Evaluation of the biological impact of fragments in proton beams using data from FOOT experiment.

- Inclusion of the interfractional reoxygenation and repopulation for OER and TCP models in presence of hypoxia [collaboration with IFO - Istituto Nazionale Tumori Regina Elena, Roma]

- Novel dose delivery approach for ion beam therapy: Inhomogeneous Fractional Dose (IFD) [collaboration with Massachusetts General Hospital, Boston]

MOVEIT - Personale e Richieste x Roma Tre

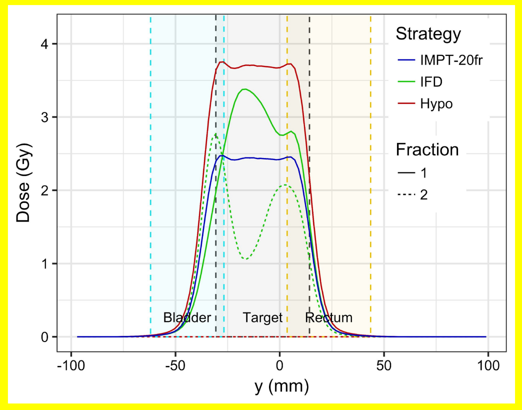
Richieste finanziarie		
Missioni	Collaboration Activity at LNS	2 k€
	Collaboration Activity at TIFPA	2 k€
	Collaboration Meetings	2 k€
	Conference Participations	2 k€
Inventario	Nessuna (Cluster di calcolo @ Torino)	

Personale RM3	FTE
A Attili (Ricercatore INFN)	50 %
[…] 	

WP1-2 activity 2017-2018 @ Torino/Roma Tre

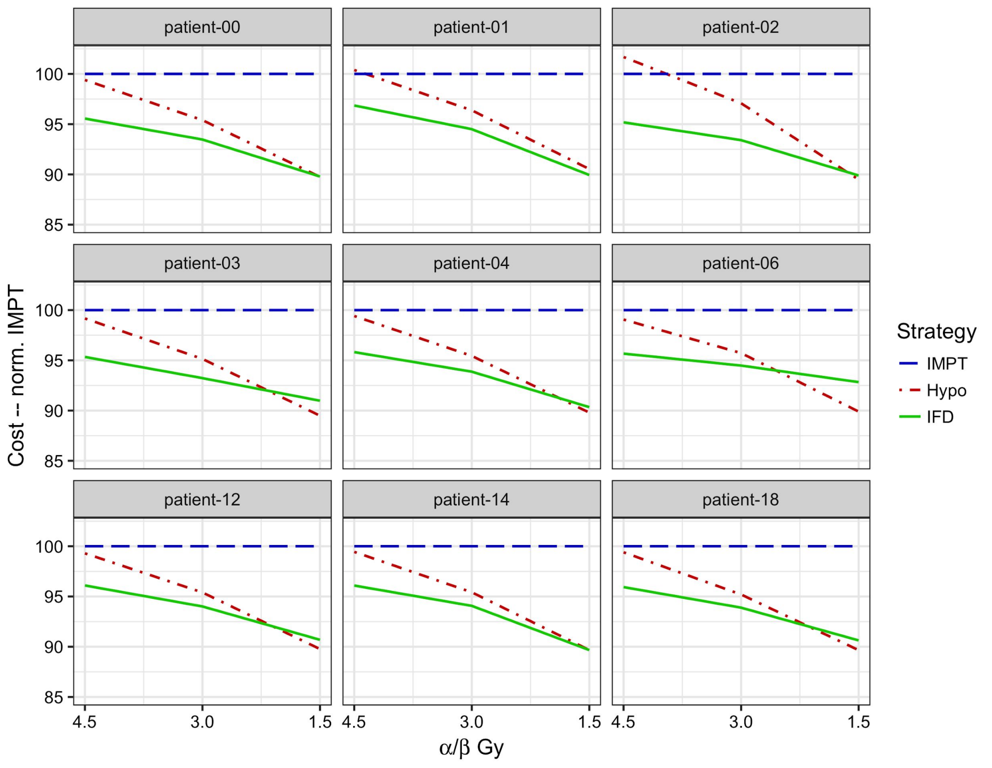
WP1-2 activity 2017-2018 - Modelling and TPS in ion beam therapy [Torino / Roma Tre]:

- Modelling of the RBE dependence on dose rate time structure in ion beam therapy and implementation of inhomogeneous fractional dose optimization in TPS (IFD) (Manganaro, L, et al. 2017 *Medical Physics*, 44(4); Manganaro et al. to be submitted to *Physics in Medicine and Biology*) [collaboration with Massachusetts General Hospital, Boston]



Dose profiles (prostate cancer treatments with protons) for different fractionation schemes

Optimized cost function of the TPS as a function of α/β ratio for different fractionation schemes for proton irradiations



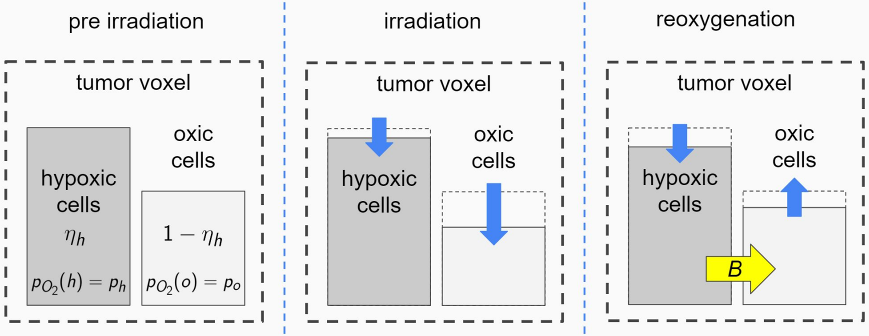
WP1-2 activity 2019-2020 @ Torino/Roma Tre

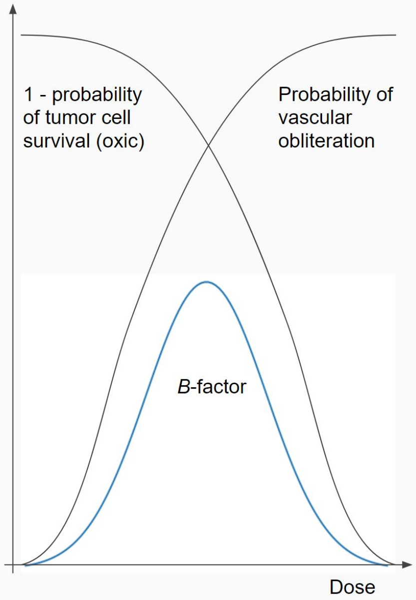
WP1-2 planned activity (2019) - Modelling and TPS in ion beam therapy [Torino / Roma Tre]:

Inclusion of the interfractional reoxygenation and repopulation for OER and TCP models in presence of hypoxia [collaboration with IFO - Istituto Nazionale Tumori Regina Elena, Roma]

$$\begin{cases} \mathrm{TCP} = e^{-N_0(F_o+F_h)} \\ F_o = (1-\eta_h)\cdot S_o^n(d) \\ F_h = \eta_h(1-B)^{n-1}\cdot S_h^n(d)\cdot\left\{1+\dfrac{B}{B-1}\dfrac{S_o(d)}{S_h(d)}\dfrac{1-\left[\frac{1}{1-B}\frac{S_o(d)}{S_h(d)}\right]^{n-1}}{1-\left[\frac{1}{1-B}\frac{S_o(d)}{S_h(d)}\right]}\right\} \end{cases}$$

Two compartment hypothesis: reoxygenation allows some of the surviving hypoxic cells (B) to move into the oxic compartment (i.e., a more sensitive state) before the next irradiation





$B = B(d, D, \{T, E\})$?

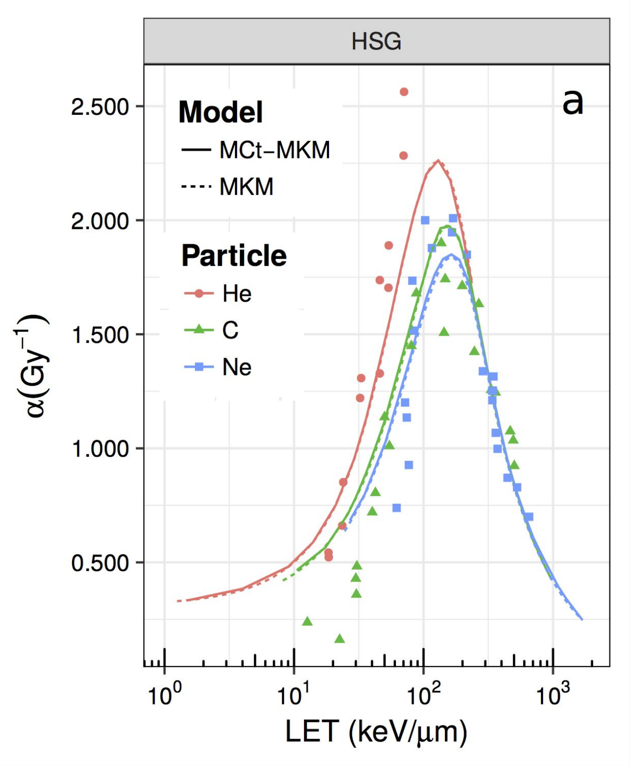
Expected behaviour of *B*: decreasing function of oxic cell survival and vascular obliteration.

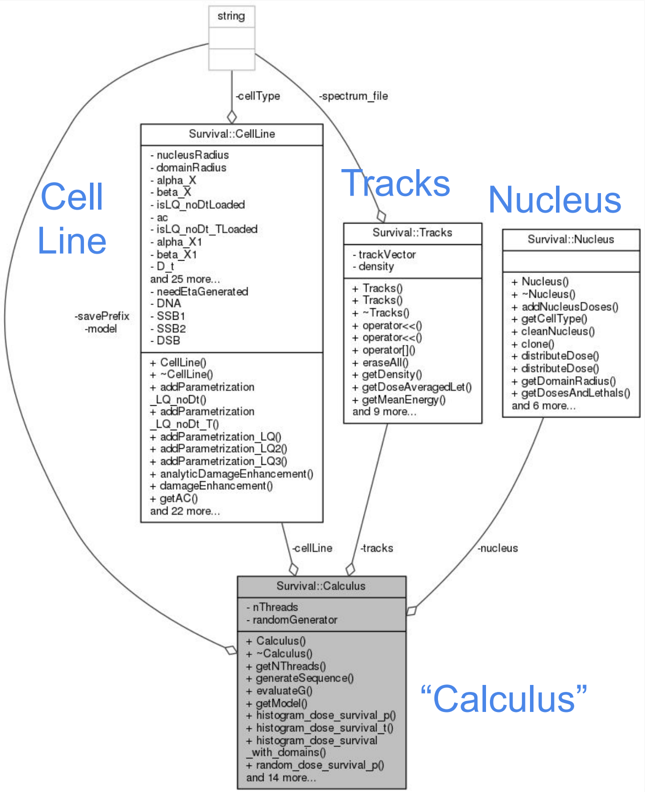
Open question: dependence of *B* on LET/Energy and particle Type.

“Appendix”: Implemented and publicly available simulation softwares

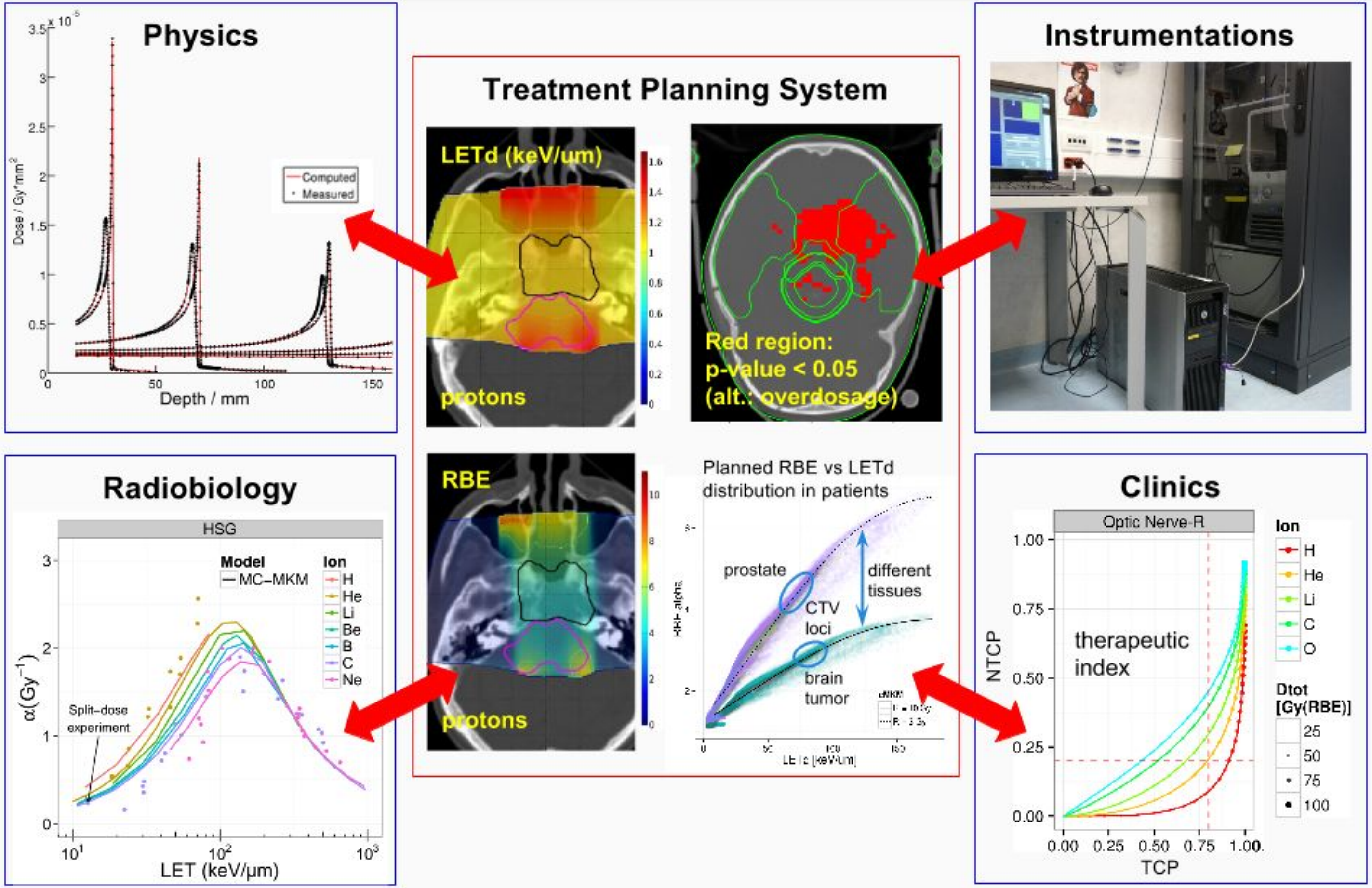
Radiobiological simulations toolkit: “Survival”

- Modular object-oriented approach for radiobiological modelling (C++).
- Implemented models: LEM1-3, MKM, and variants.
- Evaluation of cell survival, LQ parameters, RBE, etc...
- Monte Carlo and fast approximate methods.
- Open source (https://github.com/batuff/Survival)
- Ref: L. Manganaro et al., 2018, *Phys. Med. Biol.* 63





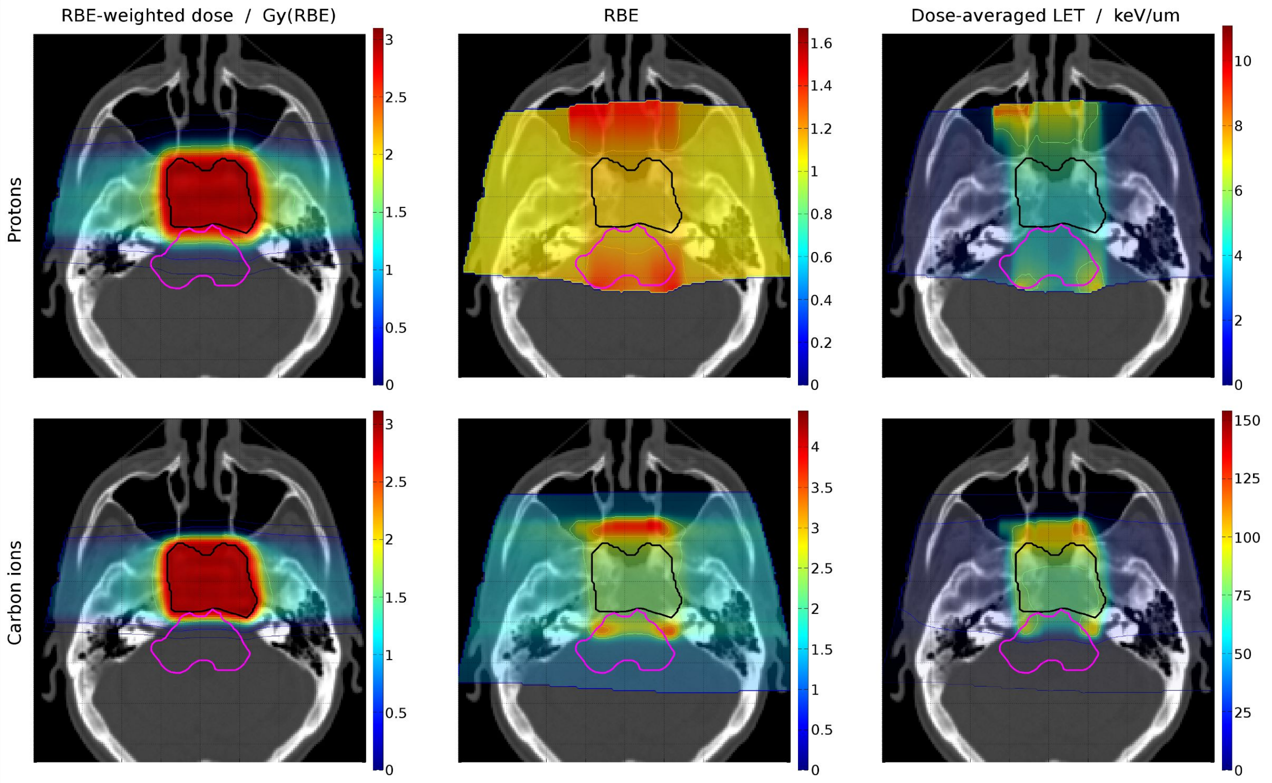
Research activities @ INFN related to Treatment Planning System (TPS) for ion beam therapy (exp.: TPS Project, RDH, IRPT)



Treatment Planning System: “Dose Engine Kernel” *p*-DEK

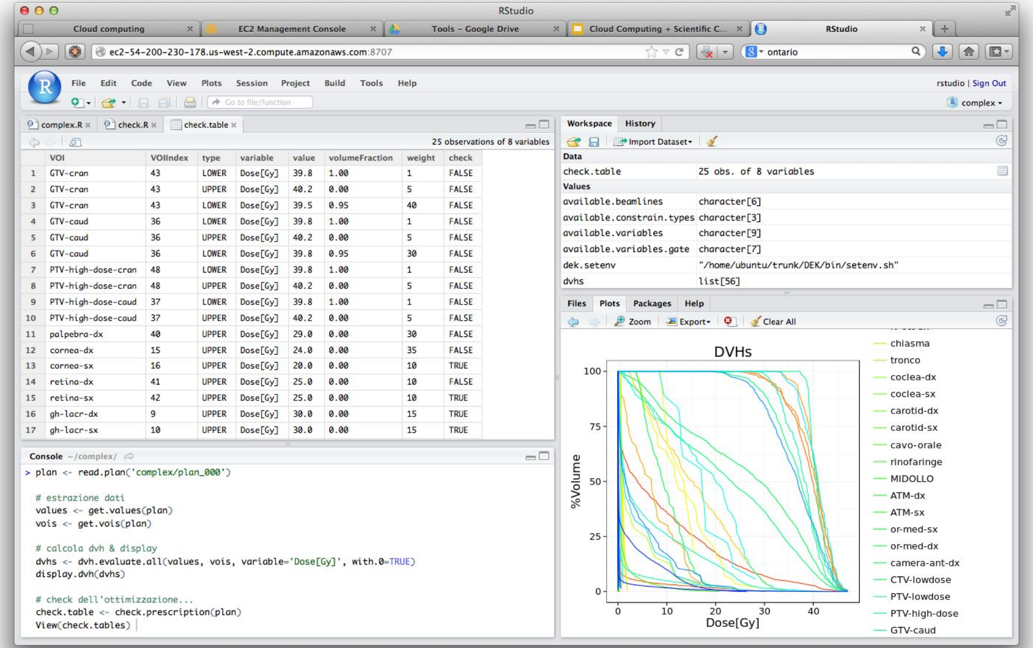
- TPS kernel developed in a collaboration INFN/IBA (Ion Beam Application, BE).
- Clinical validation performed at CNAO.
- Multi-Ion (H, He, Li, C, O, ...)
- Radiobiological models: LEM/MKM, etc.
- Physical/radiobiological evaluations (hybrid MC): dose, LET, RBE, survival, LQ parameters, etc.
- US/EU patents (US9878181B2, EP2992930B1)

(Russo et al. 2016)



Programmable TPS computing platform : “R-Planit”

- Programmable TPS computing platform.
- Based on the “***R***” language.
- TPS evaluations via “***p-DEK***”.
- Biological simulations (LEM, MKM, TCP/NTCP, etc...) via “**Survival**”.
- MC-TPS simulations via **Gate/Geant4**.
- Data analysis and visualization methods (2D/3D/4D).
- Accessible also via web-browser (it can run on remote servers: no need of installation).
- Open source (https://github.com/planit-group/Rplanit)



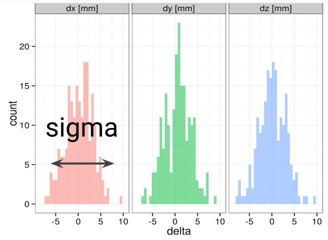
Robust TPS - Impact of uncertainties in ion beam therapy

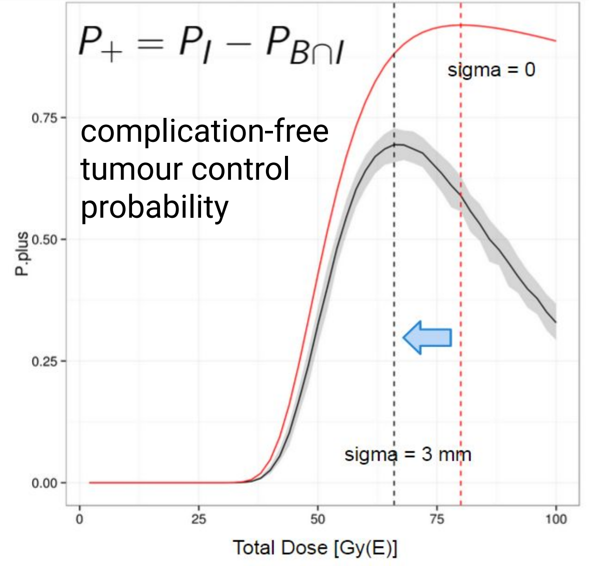
Study of general probabilistic method to evaluate the full dose PDF in presence of uncertainties.

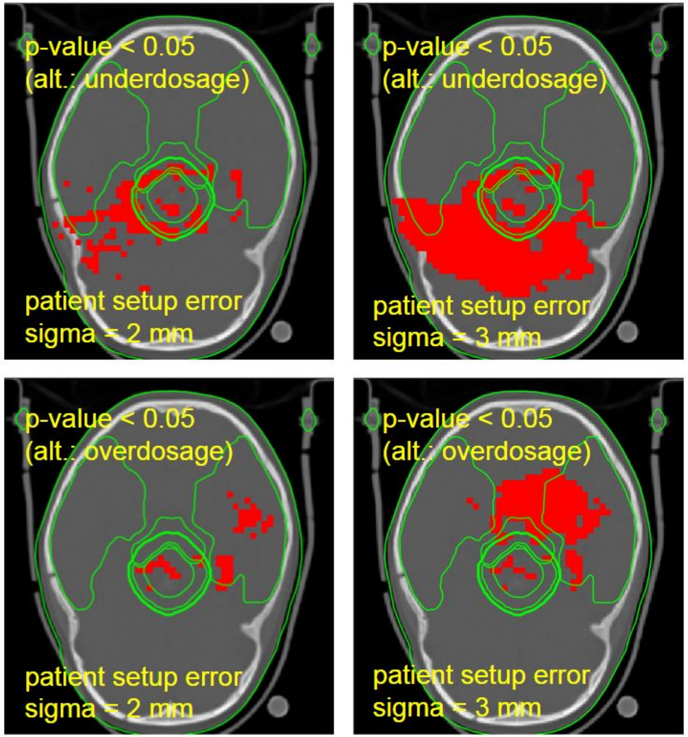
p-value maps for underdosage and ovedosage are automatically evaluated by the TPS along with the expected delivered dose distributions.

The optimality of the full fractionation schedule was also evaluated by means of TPC/NTCP.

Patient set-up errors simulation







Probability density function of radiobiological parameters from clinical data

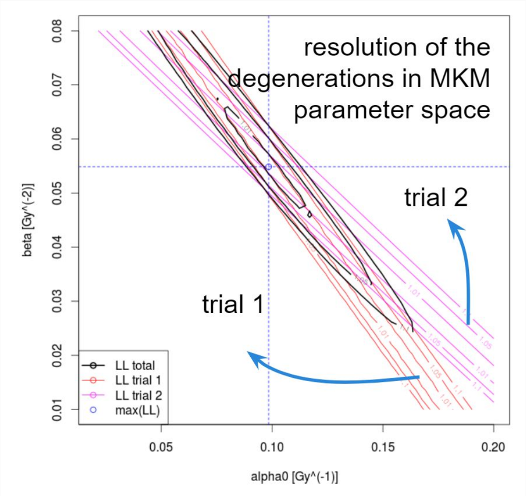
TCP and NTCP models were used to reproduce bNED and TOX data through averages over a set of representative patients. MKM parameters were identified through *LL maximization* using the LET distributions as physical predictors.

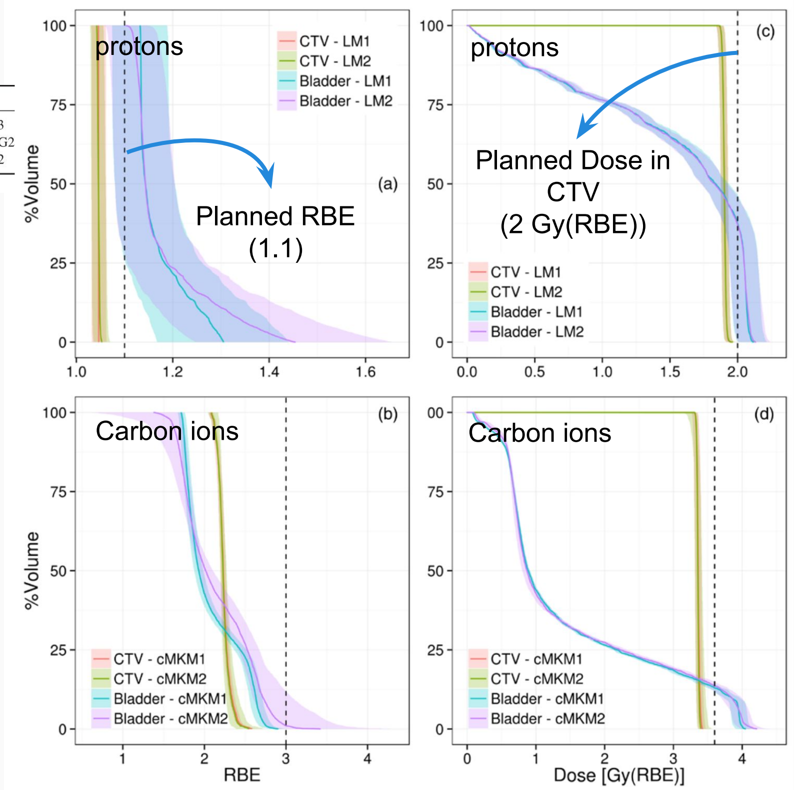
Note: the method is based on the evaluation of the absolute effect, thus it can be used to bypass the RBE approach and the necessity of additional photon data.

(Cometto *et al*. 2014)

Reference	Ion	D_f [GyE]	D_{tot} [GyE]	N_f	RBE	Beam setup	N_p	bRFS	TOX
Mayahara2007	^{1}H	2	74	37	1.1	2 fields	287	81%(5yr)	1% G3
Okada2012	^{12}C	3.15	63	20	3[a]	3 fields	216	90.2%(5yr)	6.5% G2
Okada2012	^{12}C	3.6	57.6	16	3[a]	3 fields	198	88.5%(5yr)	2% G2

[a] In distal SOBP.





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