RDH-WP1
IRPT-M3

February 2017

RDH/IRPT “TPS” Research Activities

IRPT (Innovative Radio- and Particle-Therapy)
RDH (Research and Development in Hadrontherapy)
- nATT (nano Amplified Targeted Therapy)
- RIDOS (Real-Time Ion Dose Planning and Delivery System)

1. Innovative treatment planning systems for ion beam therapy
2. Radiobiological Modeling
3. Treatment simulations and clinical analysis
4. (on-line) dose reconstruction and adaptive radiotherapy with ion beams

“TPS” Research Activities - Updates

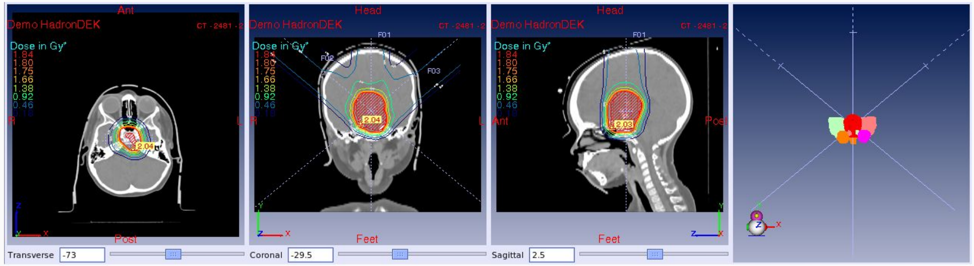
- Nell'ultimo periodo ci siamo occupati soprattutto di finalizzare e a sottomettere articoli dei risultati ottenuti (1 articolo è stato già accettato, 3 sono stati sottomessi e sono in revisione, un'altro lo stiamo per sottomettere, vedi penultima slide).
- Alcune delle attività "TPS" di RDH/IRPT, in particolare la modellizzazione dell'OER e degli effetti temporali e l'implementazione di approcci adattativi al TPS continueranno in **MOVIT** e nella collaborazione eventuale con Paganetti nel progetto di ricerca associato allo stage di L. Manganaro (PhD) a MGH.

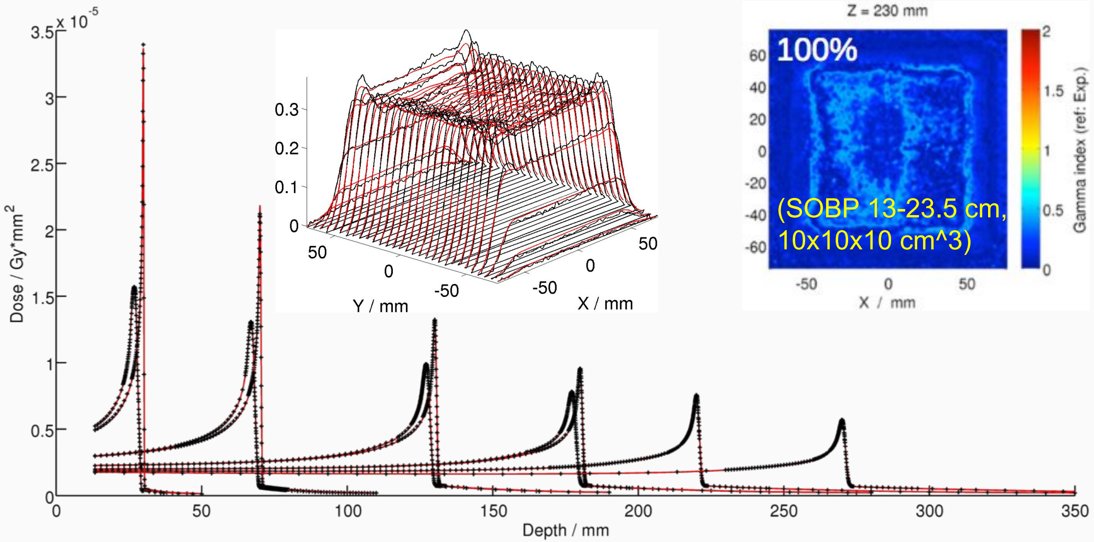
Some highlights of RDH/IRPT deliveries, potentially relevant for next research projects related to TPS in INFN (MOVIT):

- Developed tools: PlanKit/R-planit & “Survival”
- Methods to account to uncertainties in TPS.
- Implementation of irradiation with different ions and study of ion type optimality in treatments.
- Clinical data-driven RBE modelization feasibility studies.
- OER modeling and TPS implementation for hypoxia.
- MKM based model (MC*t*-MKM) accounting for stochastic spatio-temporal and dose-LET correlations and its implementation in TPS.

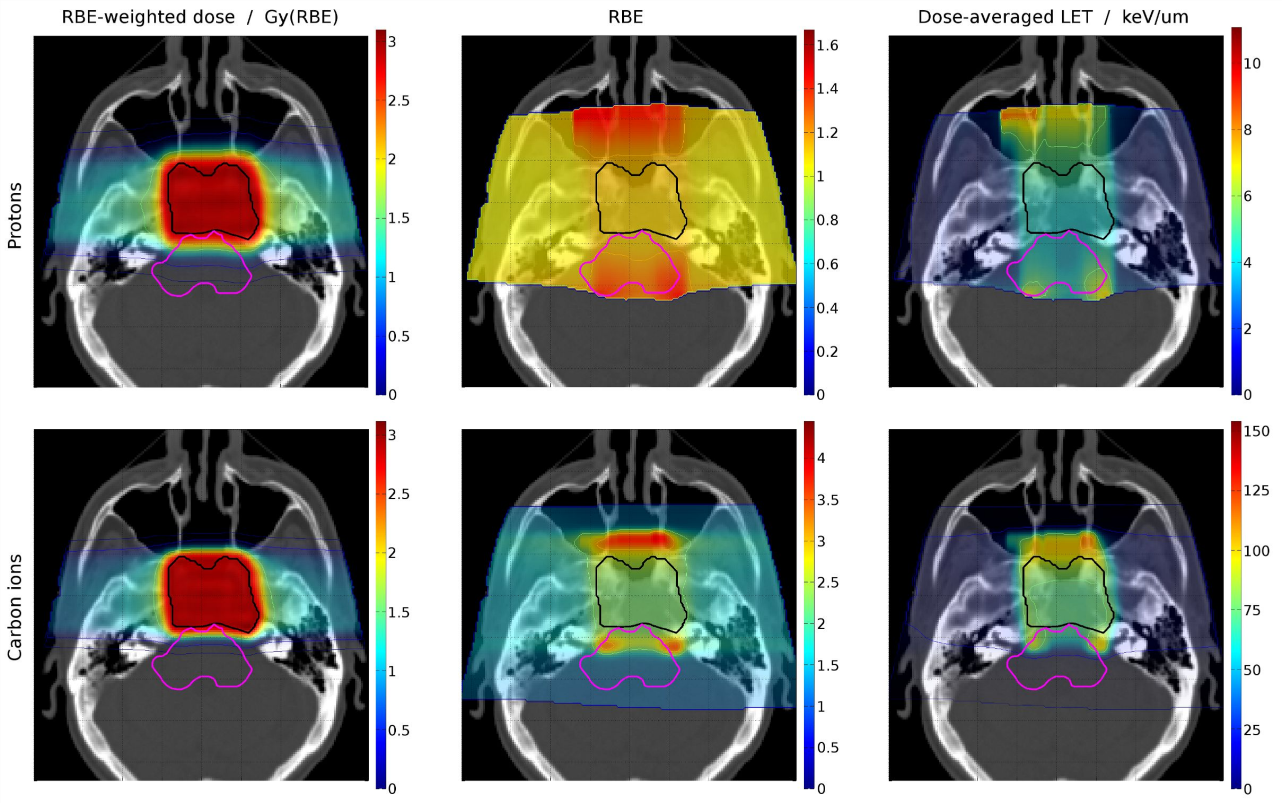
“PlanKIT”: TPS kernel for Ion Beam Therapy

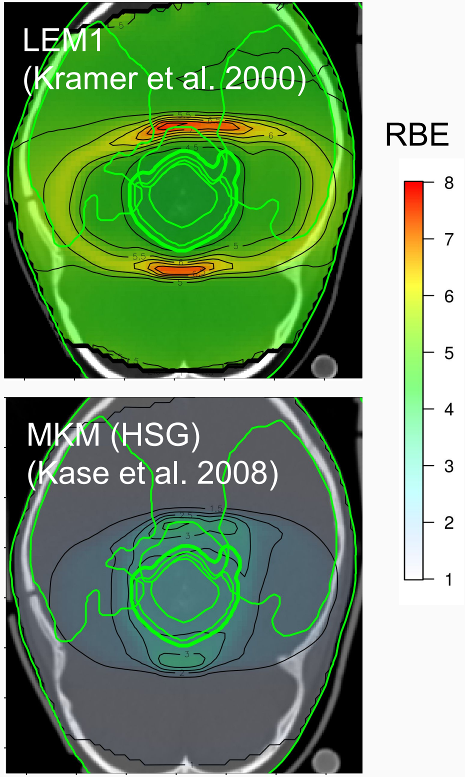
- **Plan**ning **K**ernel for **I**on **T**herapy.
- Original TPS kernel (12-2012) developed in a **collaboration INFN/IBA** (Ion Beam Application, BE).
- Clinical validation performed at **CNAO**.
- Innovative aspects:
  - Multi-Ion (H, He, Li, C, O, ...)
  - Radiobiological models: LEM/MKM, etc...
  - Simultaneous evaluations of different quantities: dose, RBE, LET, RWD, cell survival, etc…
- EU **Patent** pending (INFN/IBA/I-See)
- To be included as EM in Raystation (**Raysearch**)





“PlanKIT” - Example of evaluations



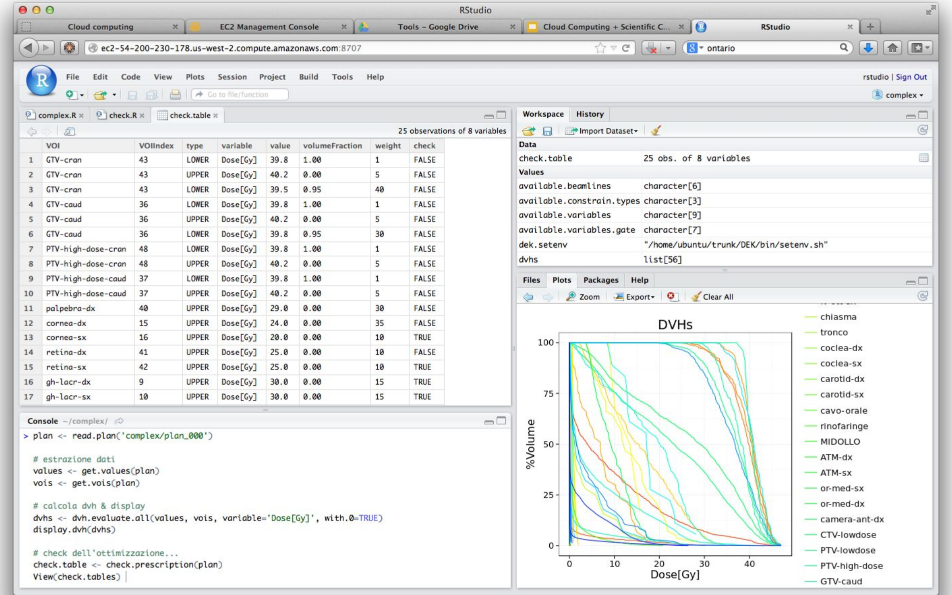


“Reproducible research” - Developed and published tools

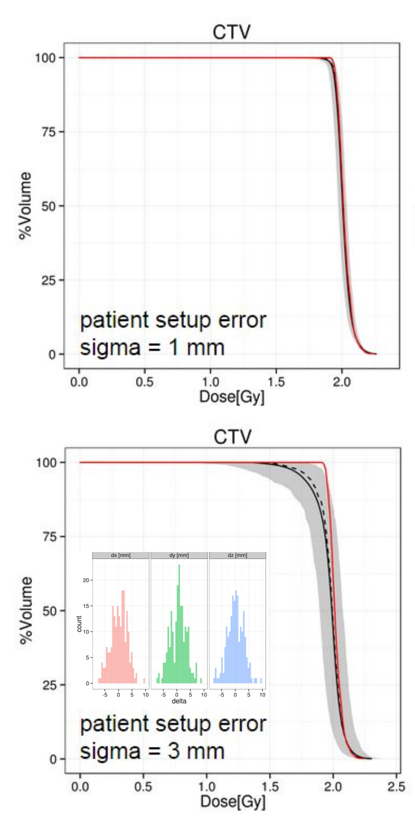
- Open source codes
  - **Survival**: Implementation of radiobiological models (LEM, MKM & variations) to predict the cell survival after irradiation with ion beams. (https://github.com/batuff/Survival)
  - **R-Planit**: A collection of methods and procedures to perform simulations and analysis related to radiotherapy treatment planning with ion beams. It includes a set of radiobiological evaluations and display possibilities (https://github.com/planit-group/Rplanit.) It uses:
    - **p-DEK** and **Gate/Geant4** for TPS evaluations,
    - **Survival** for radiobiological evaluations
- Compiled codes
  - **p-DEK**: (*“pure” Dose Engine Kernel*) TPS for ion beam therapy with active scanning (fork of **PlanKIT**, *Planning Kernel for Ion Therapy*, property of IBA/INFN).

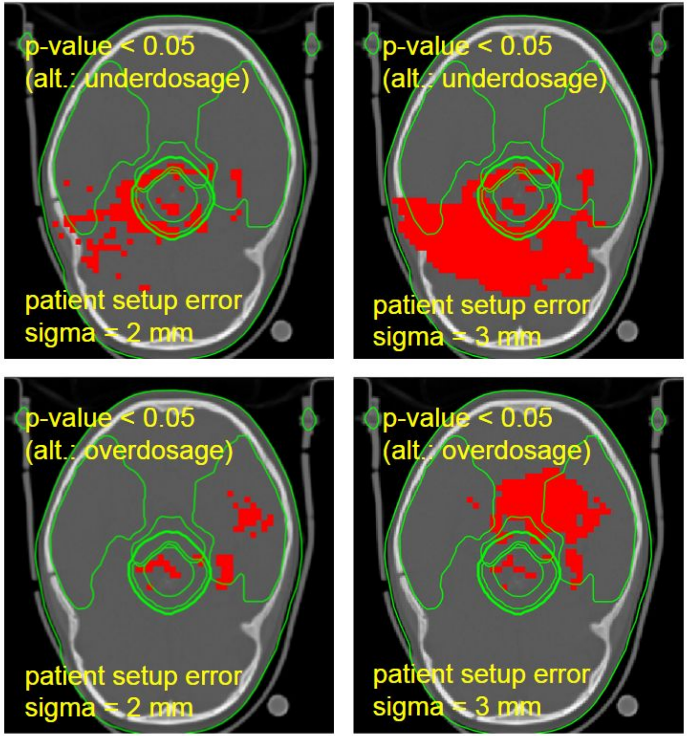
R-Planit: programmable TPS computing platform

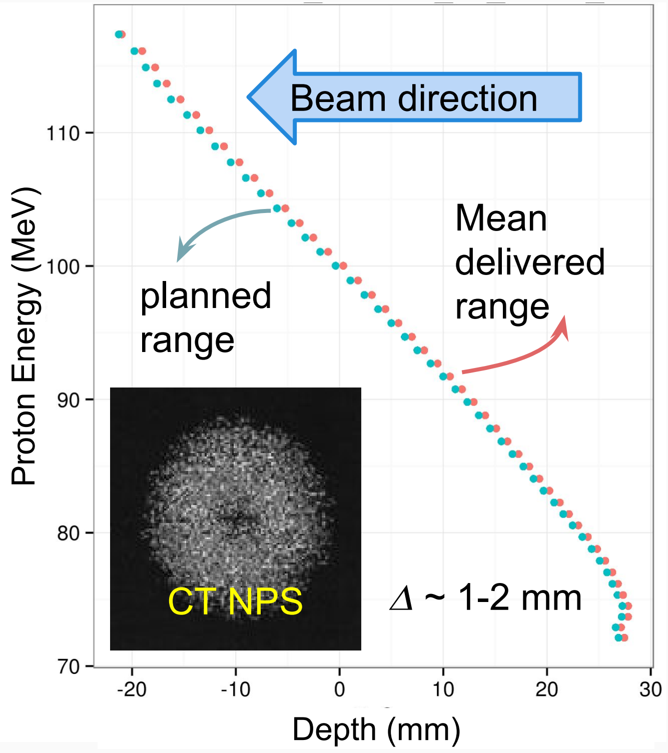
- Based on "**R**" language
- TPS simulations (via "**p-DEK**", fork of "**PlanKIT**")
- Biological simulations (**LEM**, **MKM**, **TCP/NTCP**, etc...)
- MC simulations (**Gate/Geant4**)
- Several **data analysis** and **visualization** methods (2D/3D/4D)
- Managing and **sharing** data (databases, DICOM, etc...)
- **Flexibility** and **ease to extend** due to the programmable approach
- Accessible also via web-browser (can run on remote servers: no need of installation)
- Github & tutorials (github.com/planit-group/Rplanit)



Probabilistic approach to evaluate the impact of uncertainties/errors

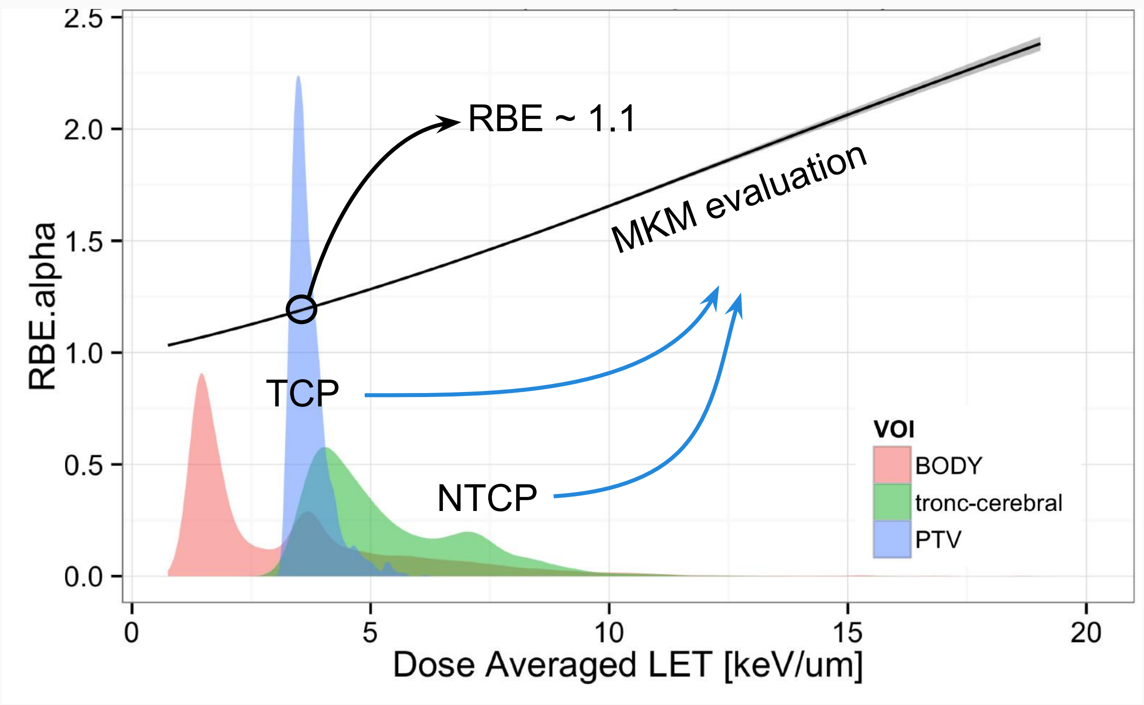






Clinical data-driven RBE evaluation & model training

Proton treatment (H&N)



Adaptive Bayesian framework

log-likelihood:

$$LL'(\theta | D_k, \mathrm{LET}_{d_k}, e_k) =$$

$$\ln\left(p\left(D_k, \mathrm{LET}_{d_k}, e_k | \theta\right)\right) + \ln\left(p_0\left(\theta\right)\right)$$

PDF from clinical followups

in-vitro & *in-vivo* PDF

$$\sum_k e_k \cdot \ln\left(\pi_k\left(D_k,\ \mathrm{LET}_{d_k} | \theta\right)\right) +$$

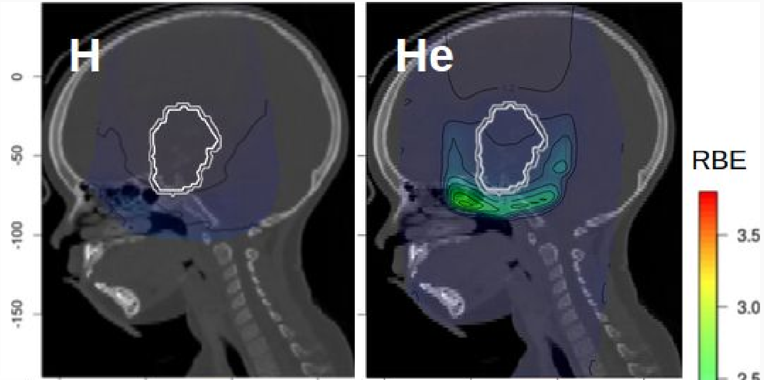
$$+ \left(1 - e_k\right) \cdot \ln\left(1 - \pi_k\left(D_k,\ \mathrm{LET}_{d_k} | \theta\right)\right)$$

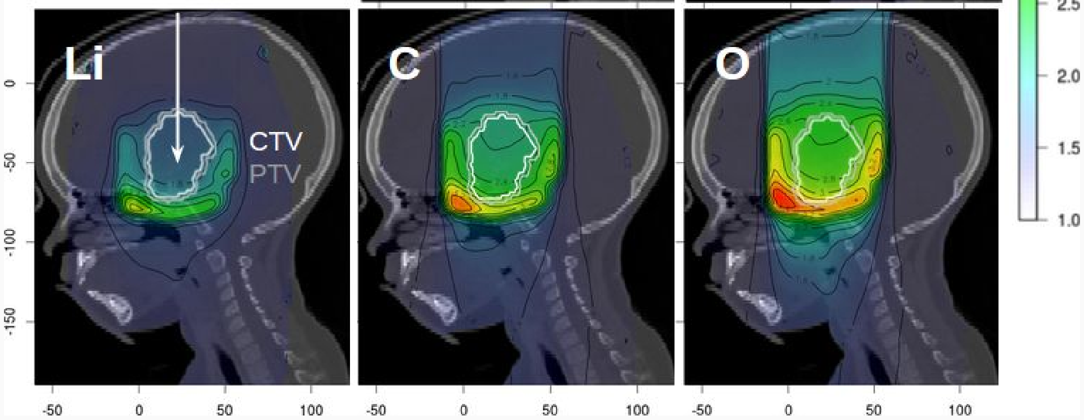
Therapeutic index vs. ion type

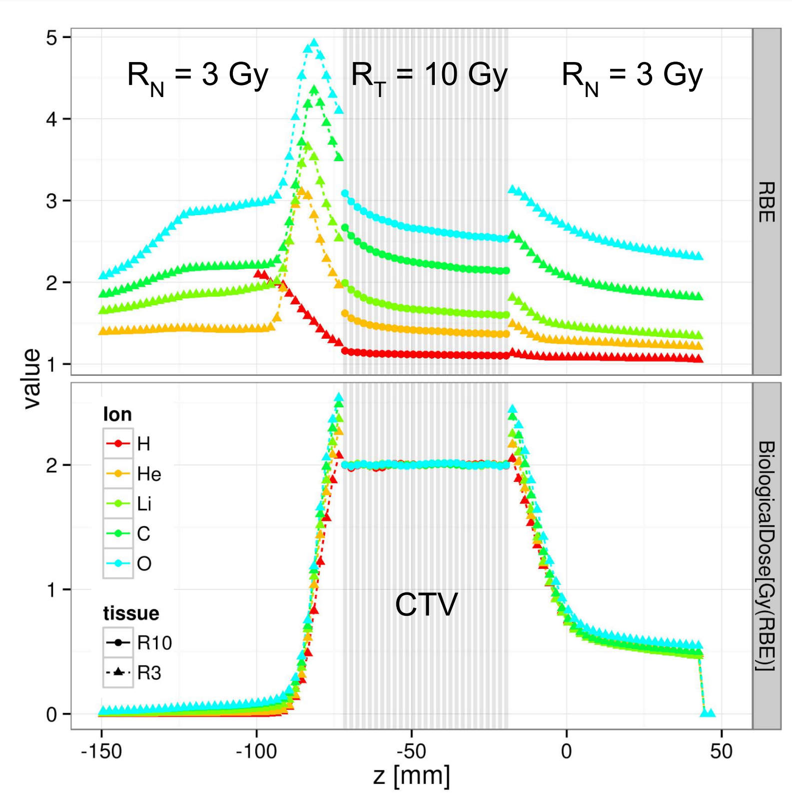
Pediatric brain tumor case

RBE distribution

(evaluated for R = 10 Gy using MKM)

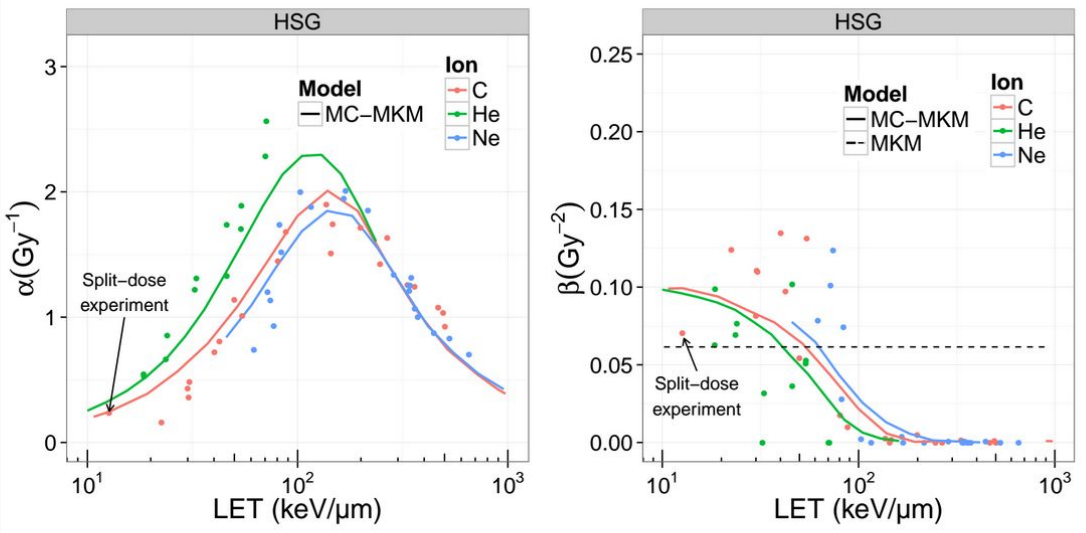


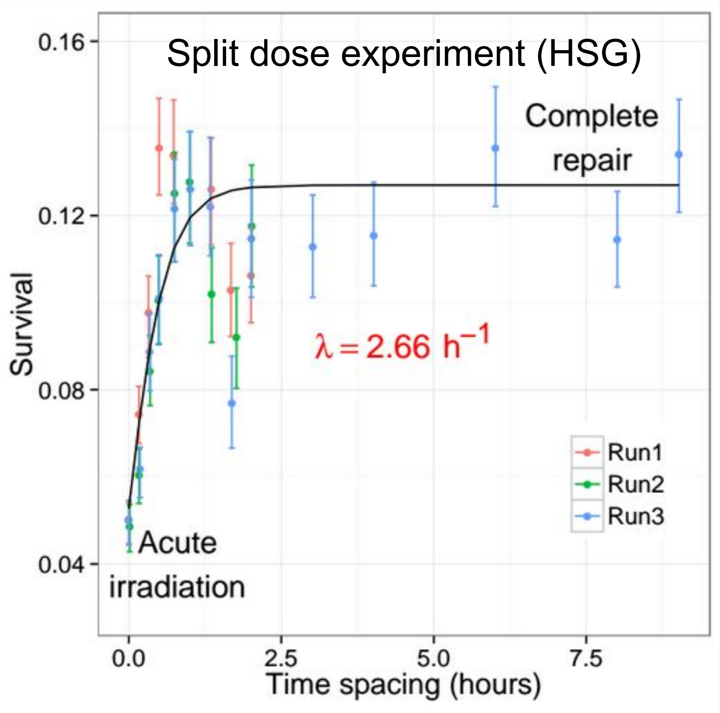




MC*t*-MKM: Stochastic Microdosimetric Kinetic Model

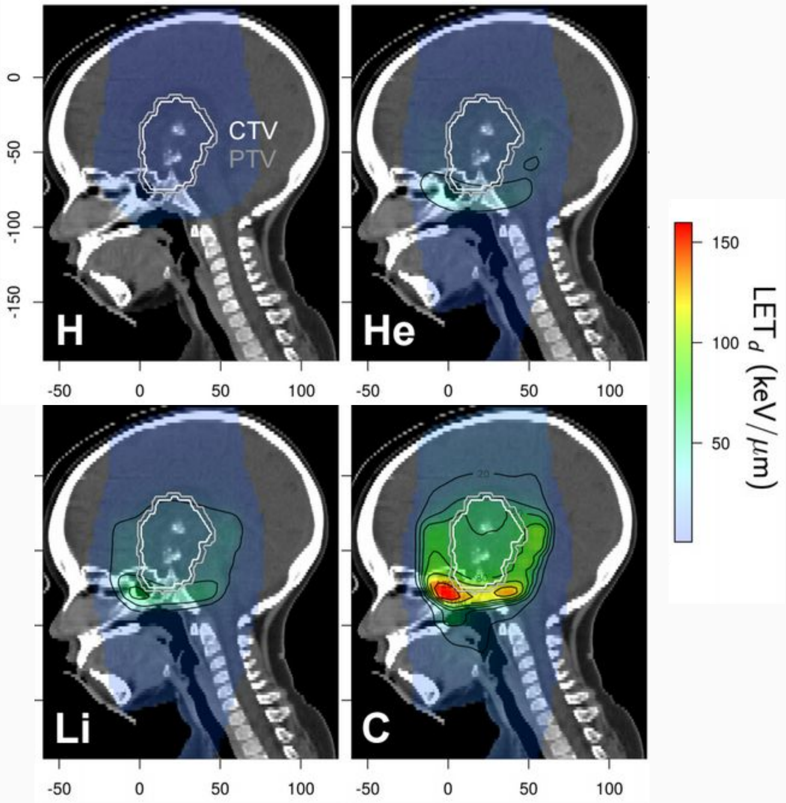
Acute irradiation

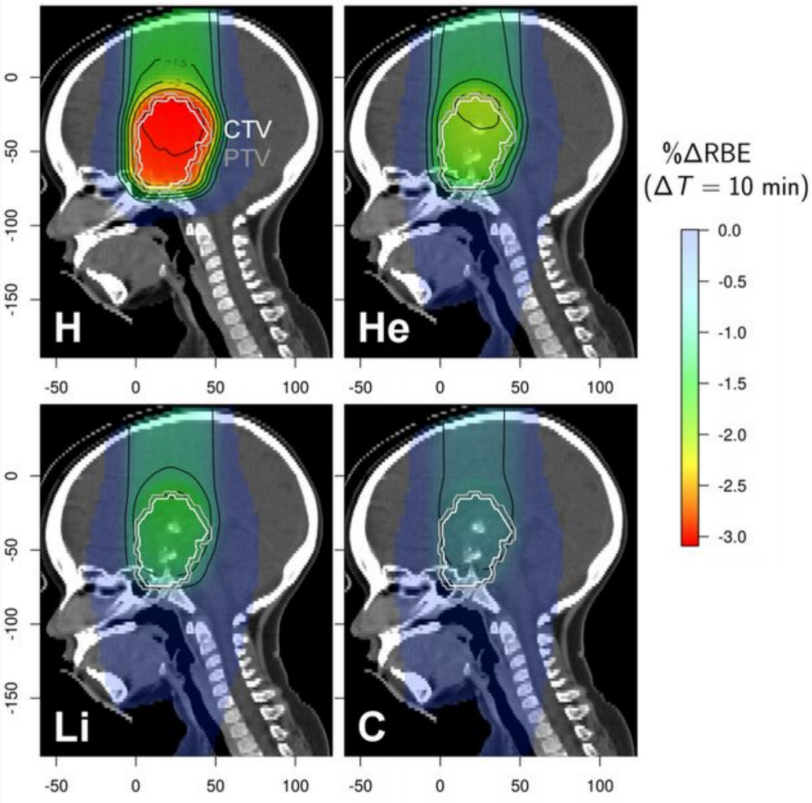




data from Furusawa et al (2000) and Inaniwa et al. (2013)

Brain tumor case - Protracted irradiation effects predictions via MC*t*-MKM

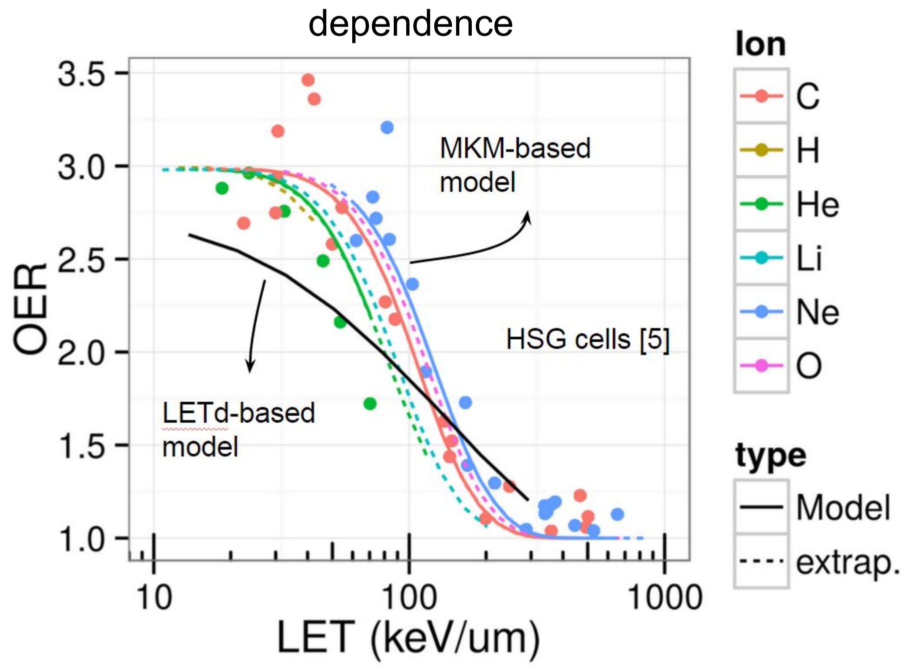




Oxygen Enhancement Ratio (OER) modeling for ion therapy

- Implementation of a MKM-based model, that includes the dependences:
  - Tissue type
  - LET spectra and particle type
  - Partial oxygen pressure
  - Dose per fraction
- The model was benchmarked on exp. data reported in literature (He, C, Ne).
- It was included in the TPS to perform methodological studies (fractionation, hypoxia level, size effects, etc...).
- Preliminary study of the impact of different ions over tumor control in presence of hypoxia.

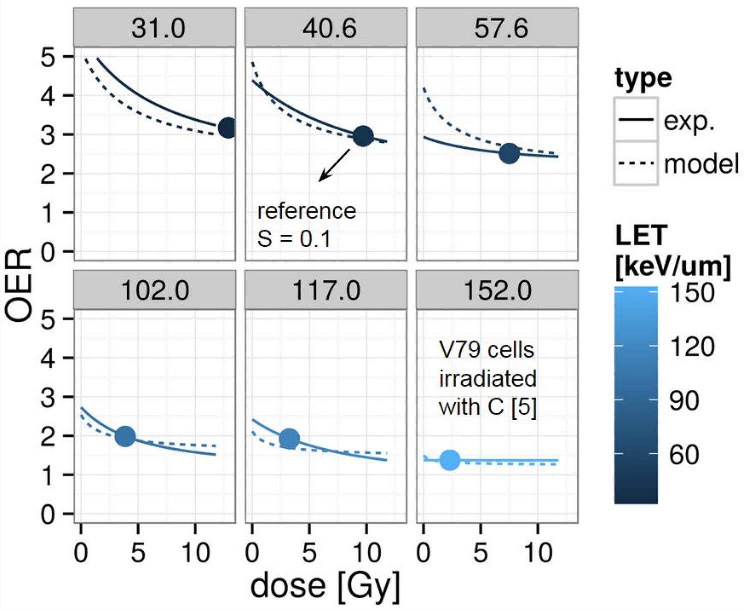
LET and particle type dependence



data from Furusawa et al (2000)

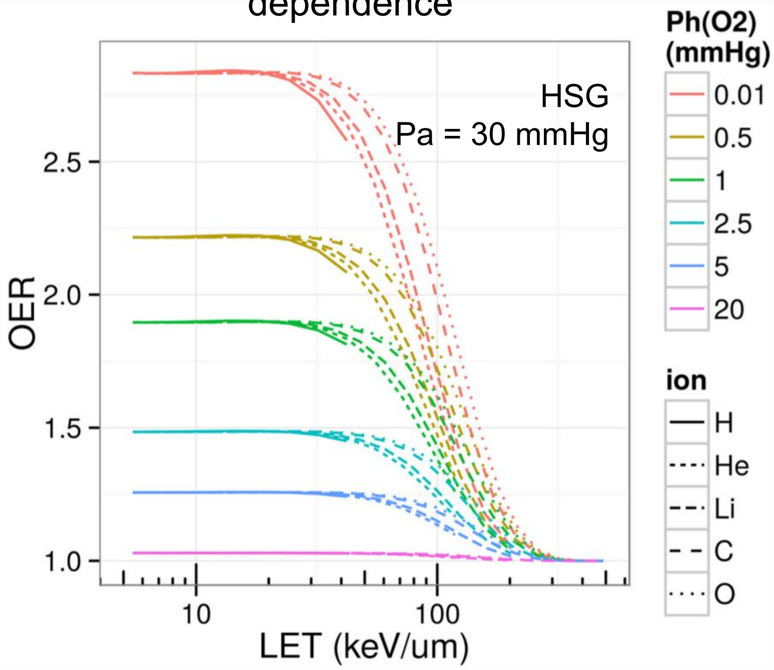
Oxygen Enhancement Ratio (OER) modeling for ion therapy

Dose per fraction dependence

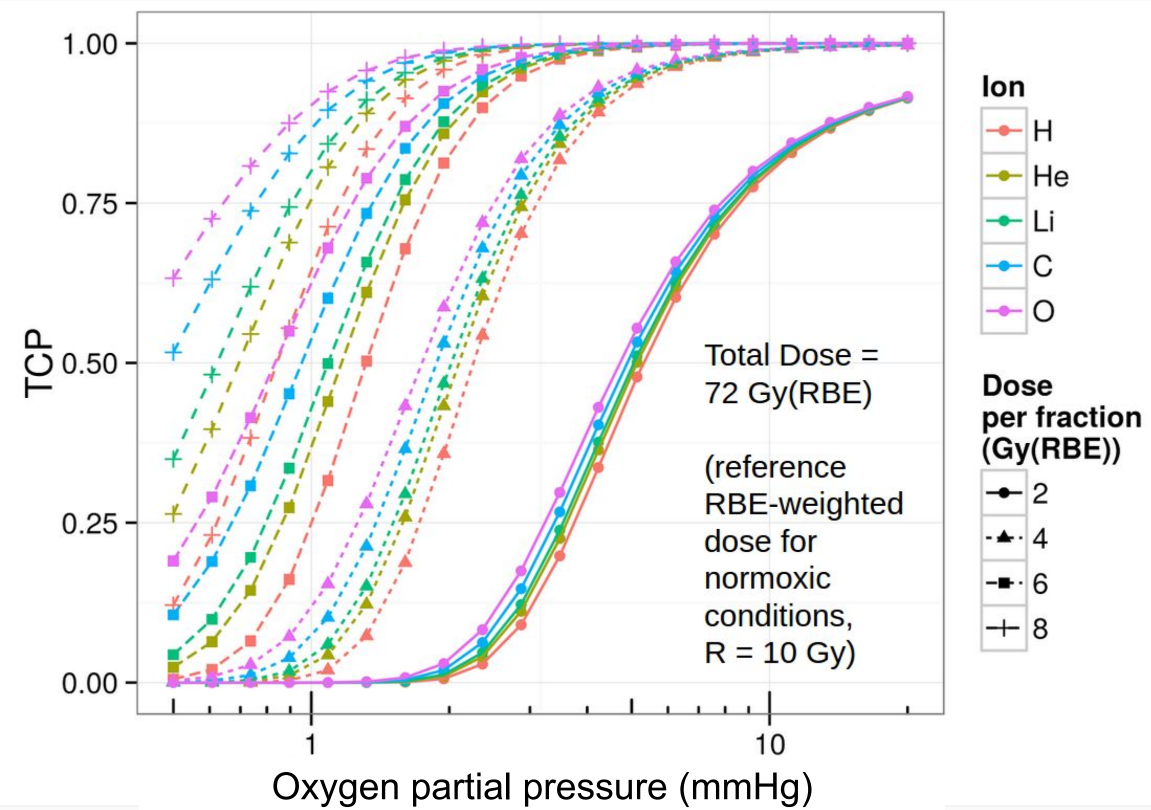


data from Furusawa et al (2000)

Oxygen partial pressure dependence



Tumor control with different ions in presence of hypoxia (brain tumor case)



The treatment plans were optimized assuming a normoxic condition for the tumor (HSG cells).

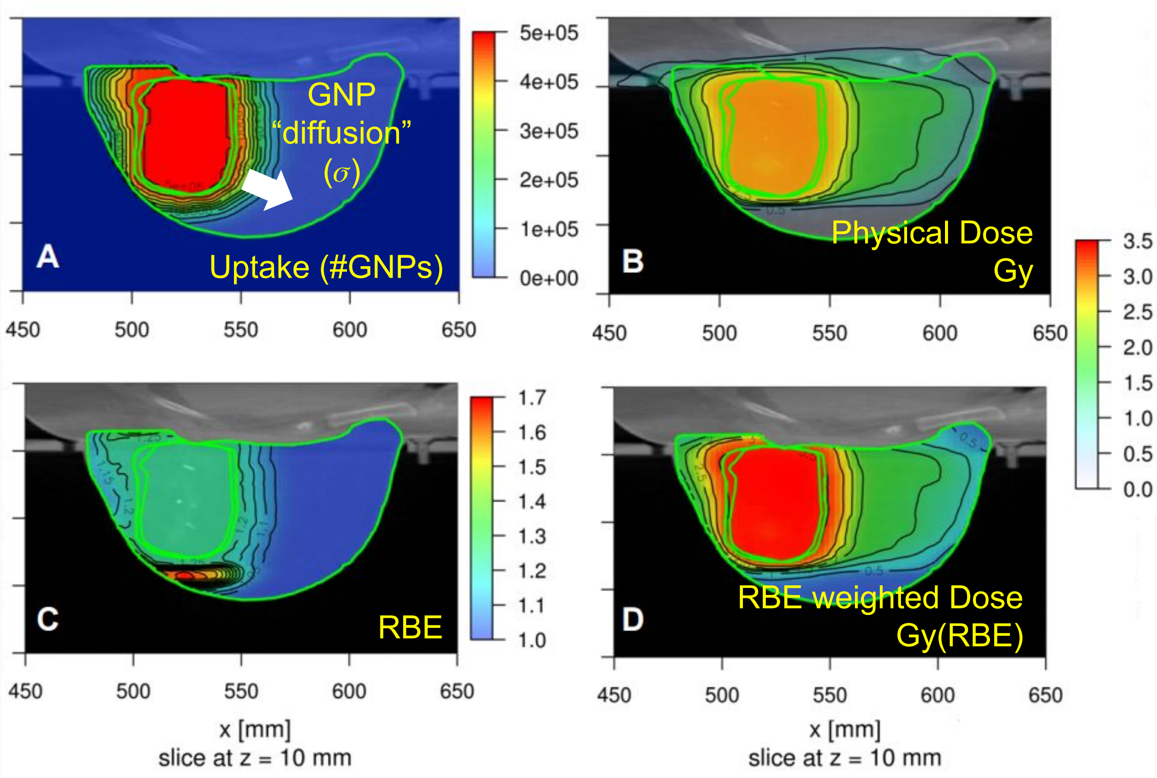
An uniform oxygen partial pressure was then assumed in the HTV.

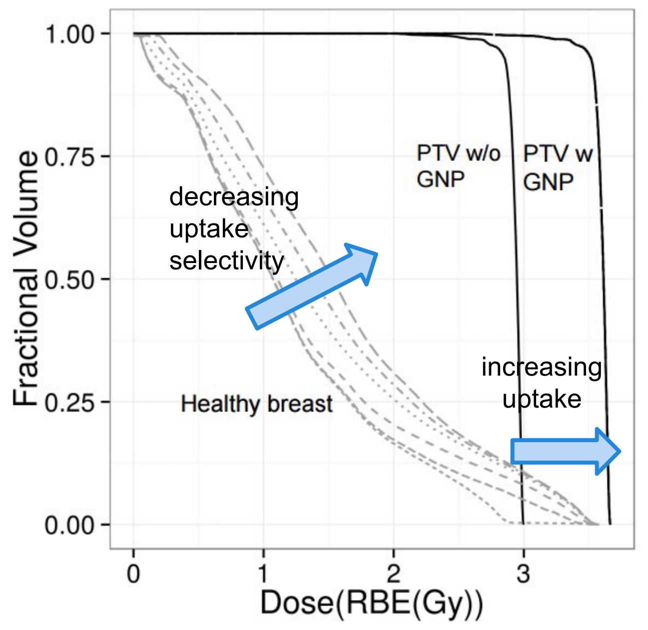
An “equivalent dose” isoeffective to the normoxic conditions was used to evaluate TCP curves in presence of hypoxia.

RBE.h(D,p) = RBE(D) / OER(D,p)
D.eq = D x RBE.h(D,p)

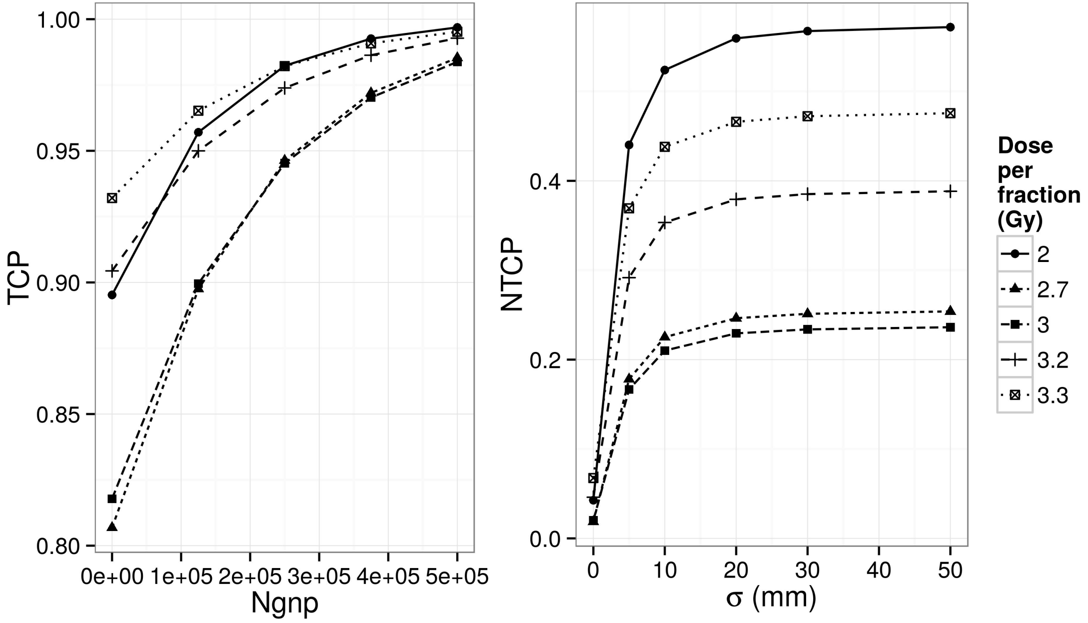
Where RBE is evaluated in reference normoxic conditions (p = 30 mmHg).

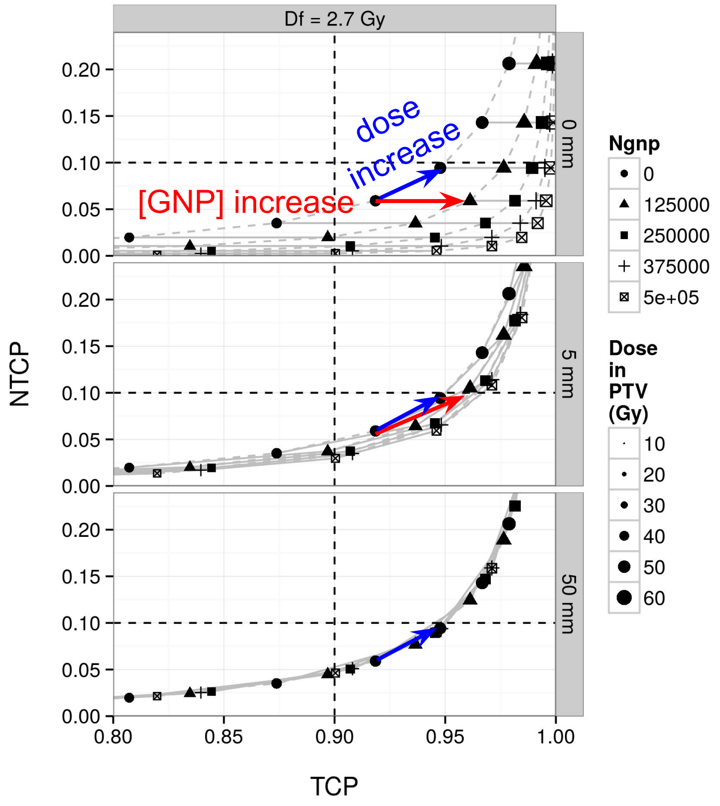
Simulation of breast tumor treatment in presence of targeted gold nanoparticle (GNP)





Therapeutic index vs. GNP concentration
Breast cancer radiotherapy with GNP





Relevant papers in RDH/IRPT

- Cometto A, Russo G, Bourhaleb F, Milian FM, Giordanengo S, Marchetto F, Cirio R, Attili A, “Direct evaluation of radiobiological parameters from clinical data in the case of ion beam therapy: an alternative approach to the relative biological effectiveness”, Phys. Med. Biol. 59 (2014) 7393-7417(25)
- L. Polster, J. Schuemann, I. Rinaldi, L. Burigo, A. McNamara, R. Stewart, A. Attili, D. Carlson, T. Sato, J. Ramos-Mendez, B. Faddegon, J. Perl and H. Paganetti, “Extension of TOPAS for the simulation of proton radiation effects considering molecular and cellular endpoints”, Phys. Med. Biol. 60 (2015) 5053–5070
- G. Russo, A. Attili, G. Battistoni, D. Bertrand, F. Bourhaleb, F. Cappucci, M. Ciocca, A. Mairani, F.M. Milian, S. Molinelli, M.C. Morone, S. Muraro, T. Orts, V. Patera, P. Sala, E. Schmitt, G. Vivaldo, F. Marchetto, “A novel algorithm for the calculation of the physical and biological irradiation effect in scanned ion beam therapy: the beamlet superposition approach", Phys. Med. Biol. 61(1) (2016) 183–214
- L. Manganaro, G. Russo, R. Cirio, F. Dalmasso, S. Giordanengo, V. Monaco, S. Muraro, R. Sacchi, A. Vignati, A. Attili, “A Monte Carlo approach to the microdosimetric kinetic model to account for dose-delivery time structure effects in ion beam therapy with application in treatment planning simulations”, submitted to Med. Phys. (Accepted)
- V. Ferrero, G. Visonà, F. Dalmasso, A. Gobbato, P. Cerello, S. Visentin, L. Strigari, A. Attili, “Targeted dose enhancement in radiotherapy for breast cancer using gold nanoparticles, part 1: a radiobiological model study”, submitted to Med. Phys. (Minor Revisions)
- L. Strigari, V. Ferrero, G. Visonà, F. Dalmasso, A. Gobbato, P. Cerello, S. Visentin, A. Attili, “Targeted dose enhancement in radiotherapy for breast cancer using gold nanoparticles, part 2: a treatment planning study”, submitted to Med. Phys. (Minor Revisions)
- F. Torriani, L. Manganaro, T. Inaniwa, L. Strigari, F. Dalmasso, R. Cirio, A. Attili, “Tumor control in ion beam radiotherapy with different ions in presence of hypoxia: an oxygen enhancement ratio model based on the microdosimetric kinetic model” submitted to Phys. Med. Biol (Major revisions).
- L. Manganaro, G. Russo, F. Bourhaleb, et al. ““Survival”: a modular code for radiobiological simulations for ion irradiation” to be submitted in Phys. Med. Biol.