Radiobiology applications of Nuclear Physics simulations

from track structure to biological treatment planning

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MoVe IT
Modeling and Verification for Ion beam Treatment planning

INFN Istituto Nazionale di Fisica Nucleare
CSN5

Outline

- **Basics of Ion beam Radiobiology**
- **Biological Treatment planning (Bio-TPS):**
  - **RBE-weighted dose optimization and beyond**
  - **Adaptive Bio-TPS including hypoxia**
- **Nuclear physics data need and their impact**
- **Bio-TPS with different/multiple ions**

The basics of Treatment Planning

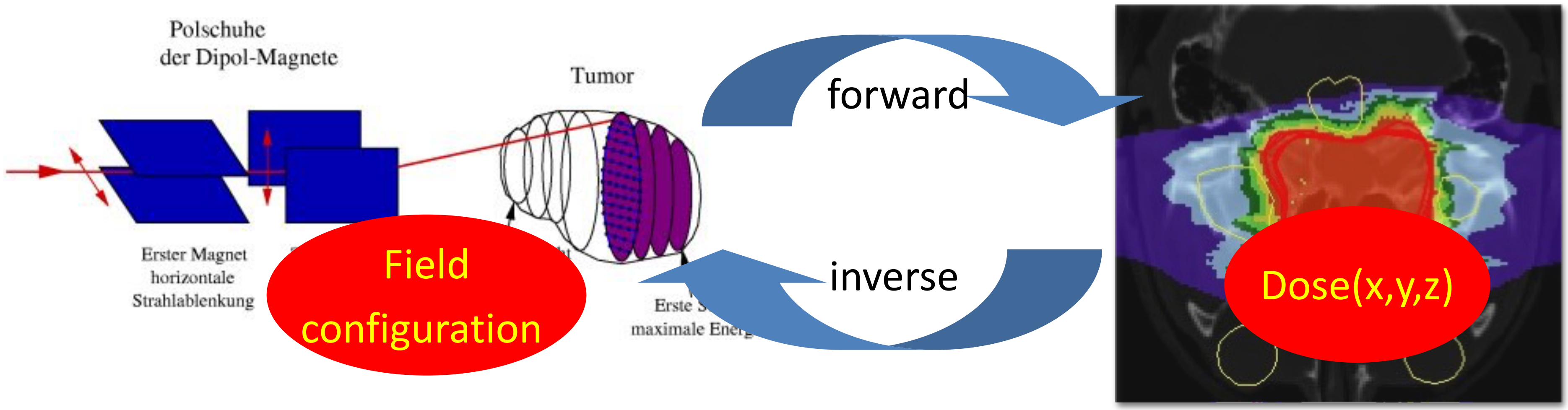
- A Treatment Planning System (TPS)

  Relates dose on the target and the whole irradiated area

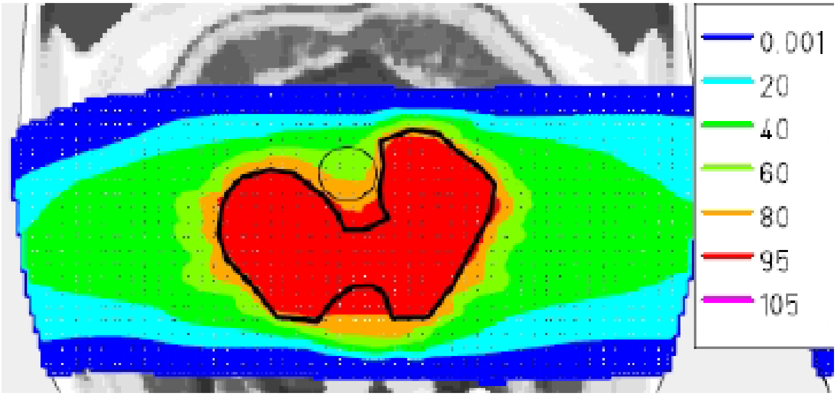
  to the technical delivery of the irradiation field(s) and can perform:

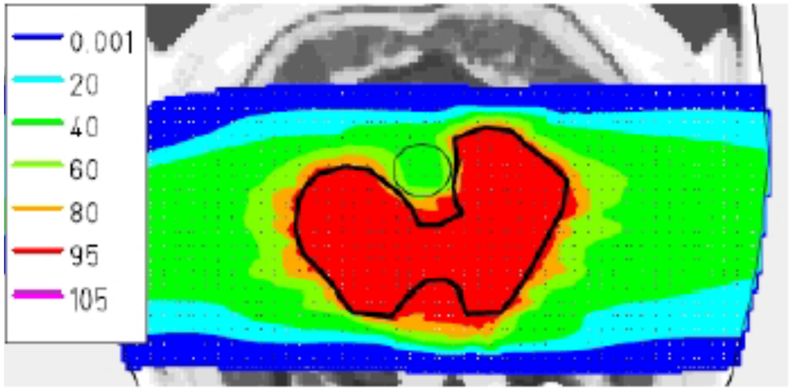
  – **Forward Planning**: from radiation field setup to expected dose

  – **Inverse Planning:** from requested dose on target to irradiation protocol. Requests an **optimization** algorithm



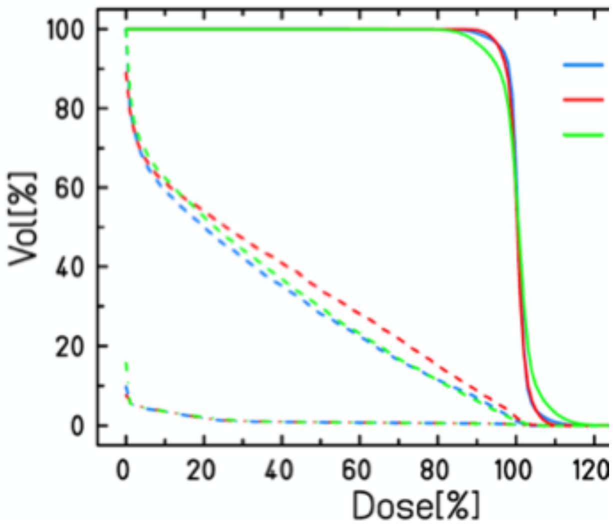
Dose Optimization





In particle raster scanning

Optimization step: Determination of appropriate particle
numbers for every single raster spot.



The Cost function

$$\chi^2(\vec{N}) = \sum_{i \in target} \frac{[D^i_{pre} - D^i_{act}(\vec{N})]^2}{\Delta D^2_{pre}} + \sum_{i \in OAR} \frac{[D^i_{max} - D^i_{act}(\vec{N})]^2}{\Delta D^2_{max}} \Theta(D^i_{act}(\vec{N}) - D^i_{max})$$

$\vec{N}$: vector that contains the particle numbers

i : voxel which belongs to target - or OAR - volume

D^i_{pre} : prescribed dose within target voxel i

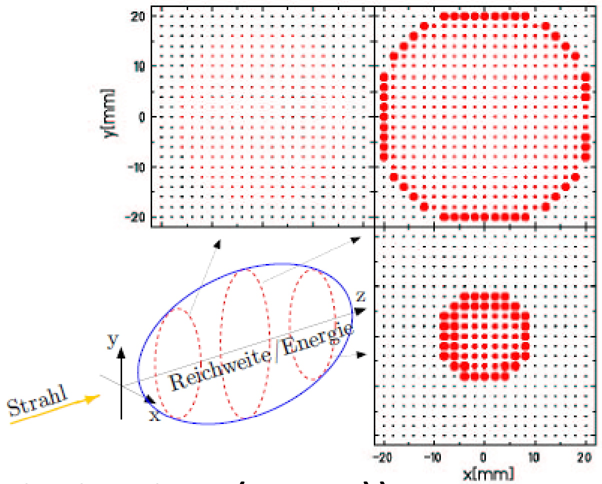
D^i_{act} : actual dose at voxel i

ΔD^2 : weight factor

D^i_{max} : maximum dose within OAR - voxel i

Θ : Heaviside function

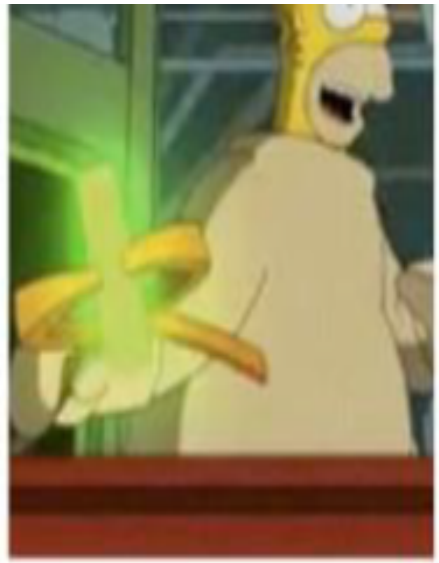
$$\Theta\left(D^i_{act}(\vec{N}) - D_{max}\right) = \begin{cases} 1 & : D^i_{act}(\vec{N}) > D_{max} \\ 0 & : D^i_{act}(\vec{N}) \leq D_{max} \end{cases}$$

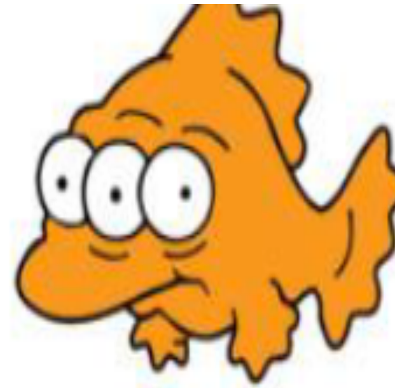


- All fields are included in the function (Multiple Field Optimization (IMPT)).

- # voxels and rasterspots 20.000-80.000

Why “Bio”-TPS





Bequerel [Bq]
How brightly your Cesium glows

ACTIVITY

Gray [Gy]
How brightly Cesium will make you glow

ABSORBED DOSE

Sieverts [Sv]
How many extra eyes will you have after glowing?

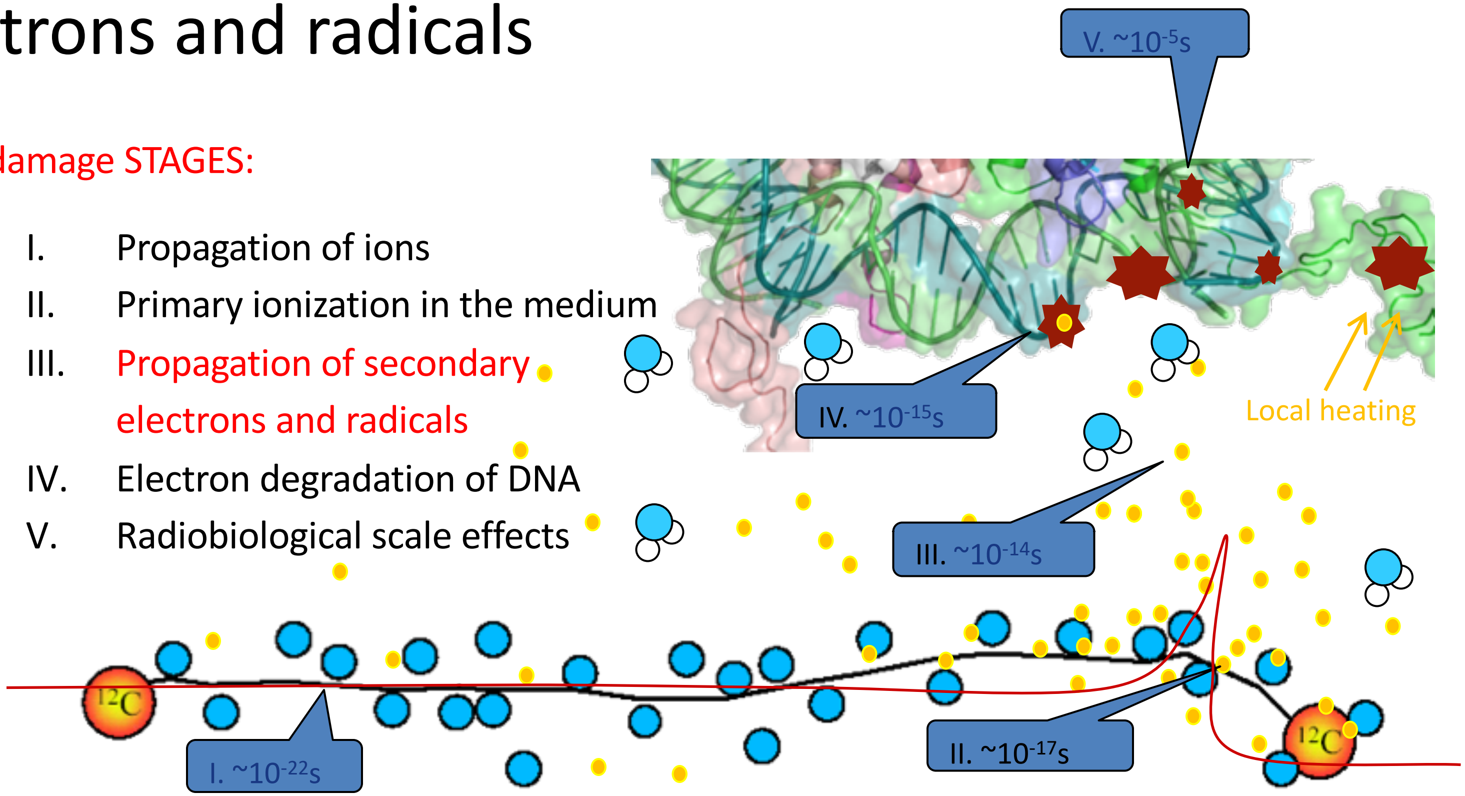
(BIOLOGICAL) EFFECTIVE DOSE

The mechanism of biological damage with ions

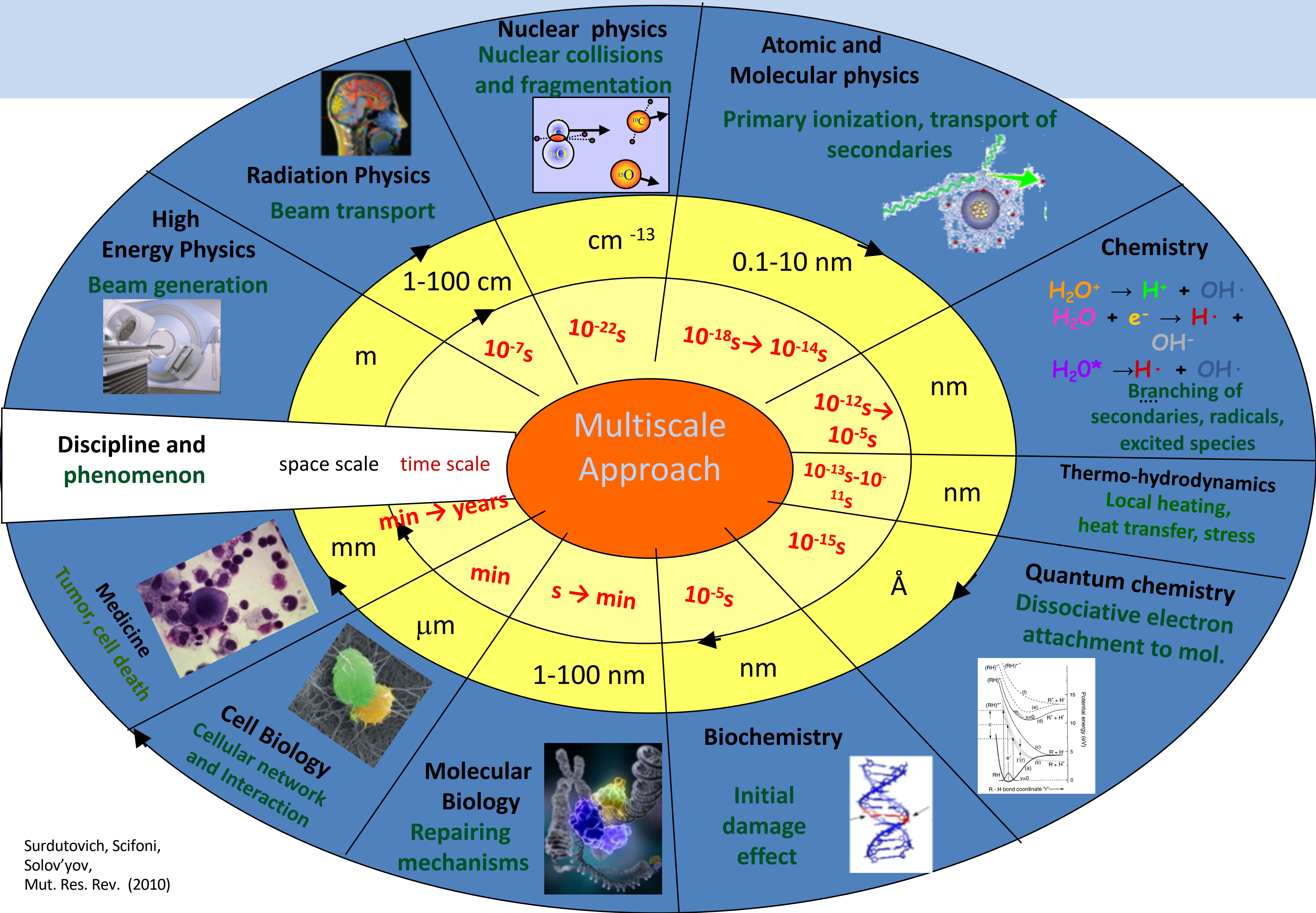
La Largest part of the damage comes from secondary electrons and radicals

Ion beam damage STAGES:

I. Propagation of ions
II. Primary ionization in the medium
III. Propagation of secondary electrons and radicals
IV. Electron degradation of DNA
V. Radiobiological scale effects



Spatiotemporal scales of Radiation Damage

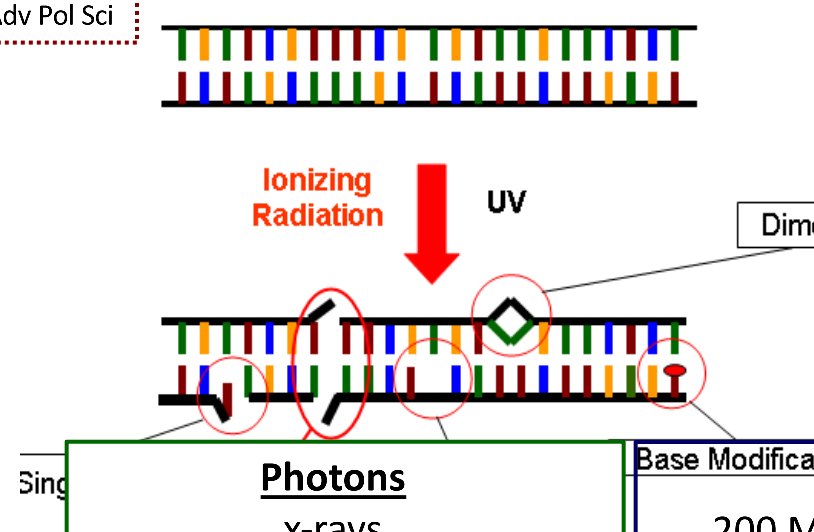


Surdutovich, Scifoni, Solov'yov,
Mut. Res. Rev. (2010)

DNA Damage

Basic concepts of radiation biophysics

Scholz 2006
Adv Pol Sci

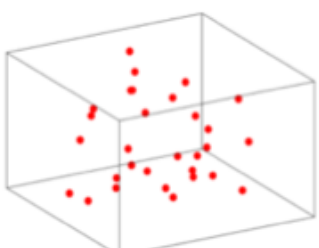


- The DNA **Double Strand Break (DSB)** is considered the type of lesion most directly related to cell killing
- Different radiation qualities produce the same spectrum of DNA lesions
- **BUT** the distribution of lesions inside the target can be very different

Photons

x-rays

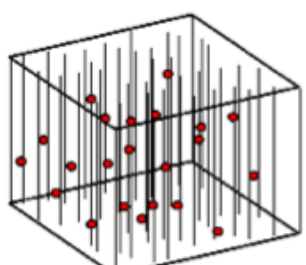
Random
DSB distribution



^{12}C Low LET

200 MeV/u, ≈ 16 keV/μm

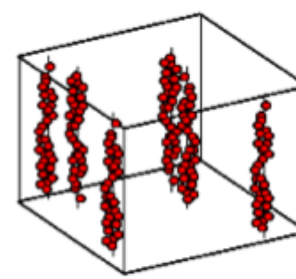
Random
DSB distribution
(photon-like)



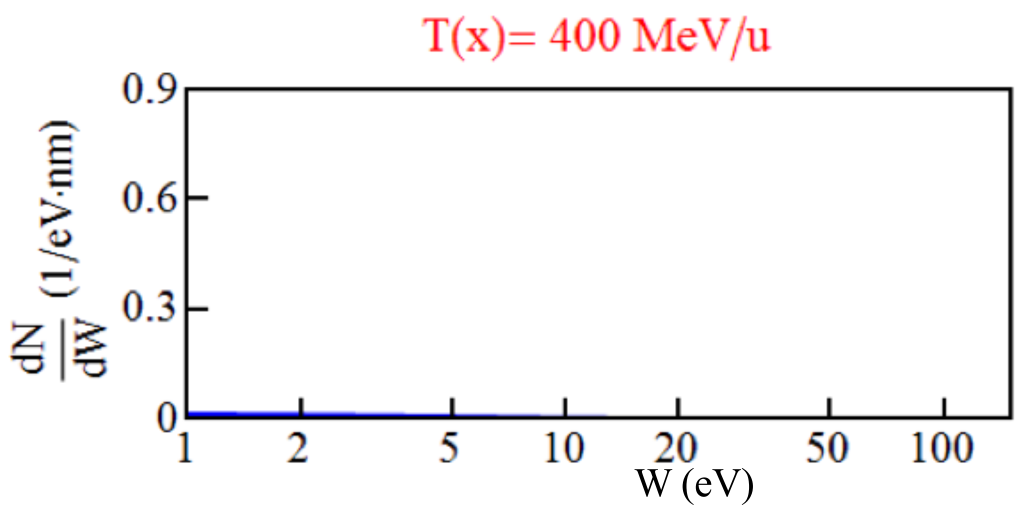
^{12}C High LET

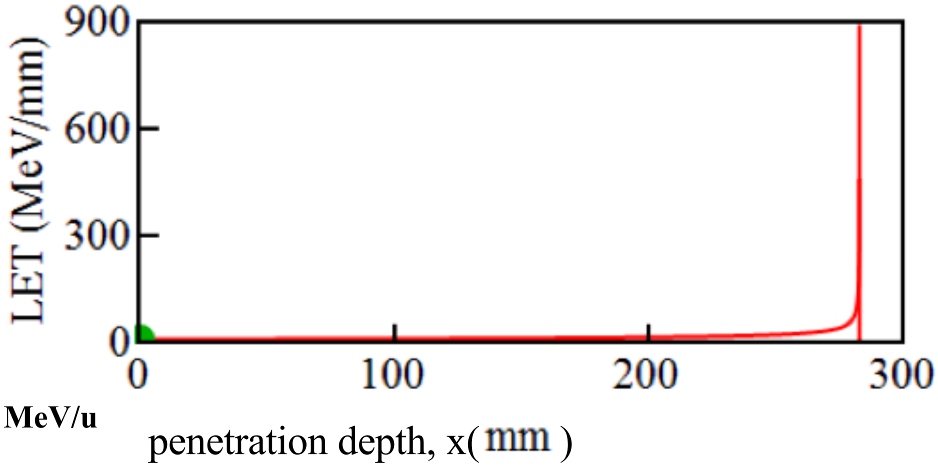
1 MeV/u, ≈ 690 keV/μm

Non-random
DSB distribution
(RBE>>1)



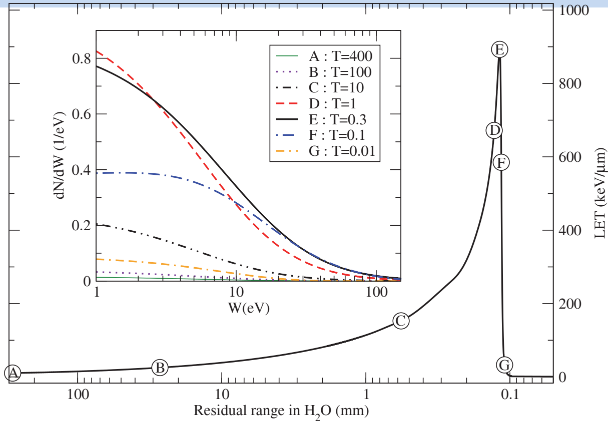
Secondary Electrons produced by an ion along a Bragg Peak



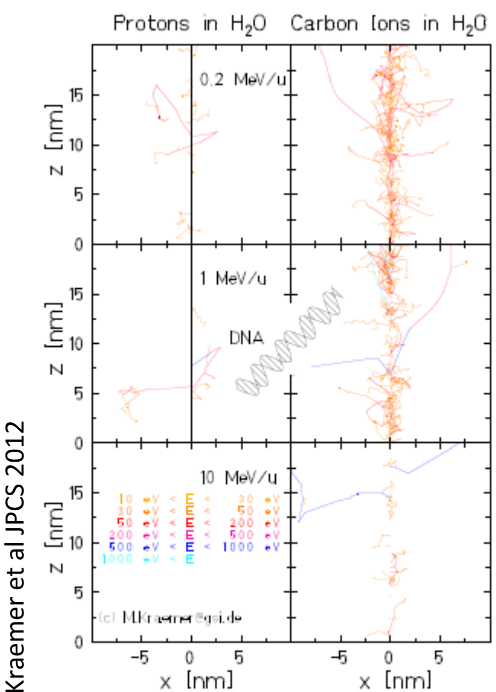


Scifoni,et al., PRE 2010

T_0=400 MeV/u



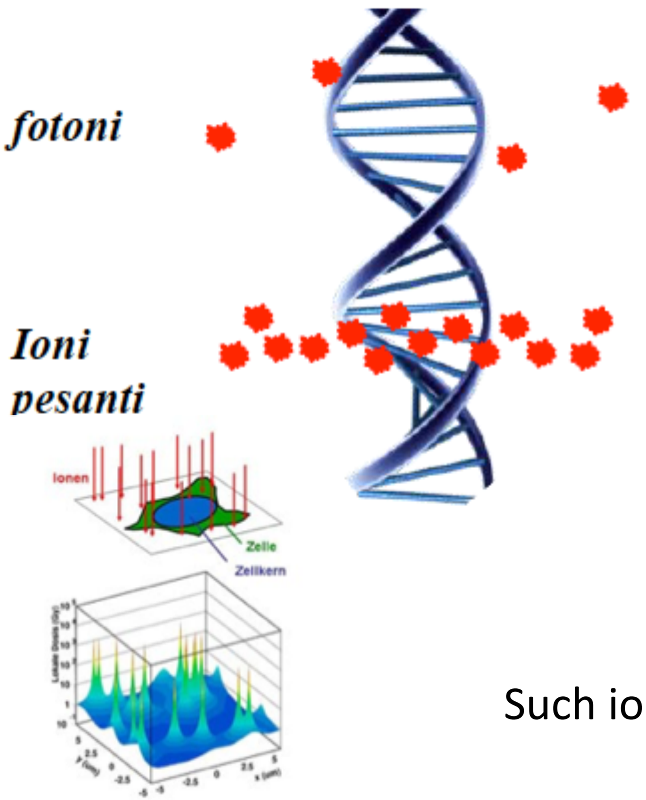
Scifoni,et Mod Phys Lett. 2015



Kraemer et al JPCS 2012

Track Structure simulation

RBE: Relative Biological Effectiveness



Photons

Ions

Such ionization density may be described by **Track structure** codes

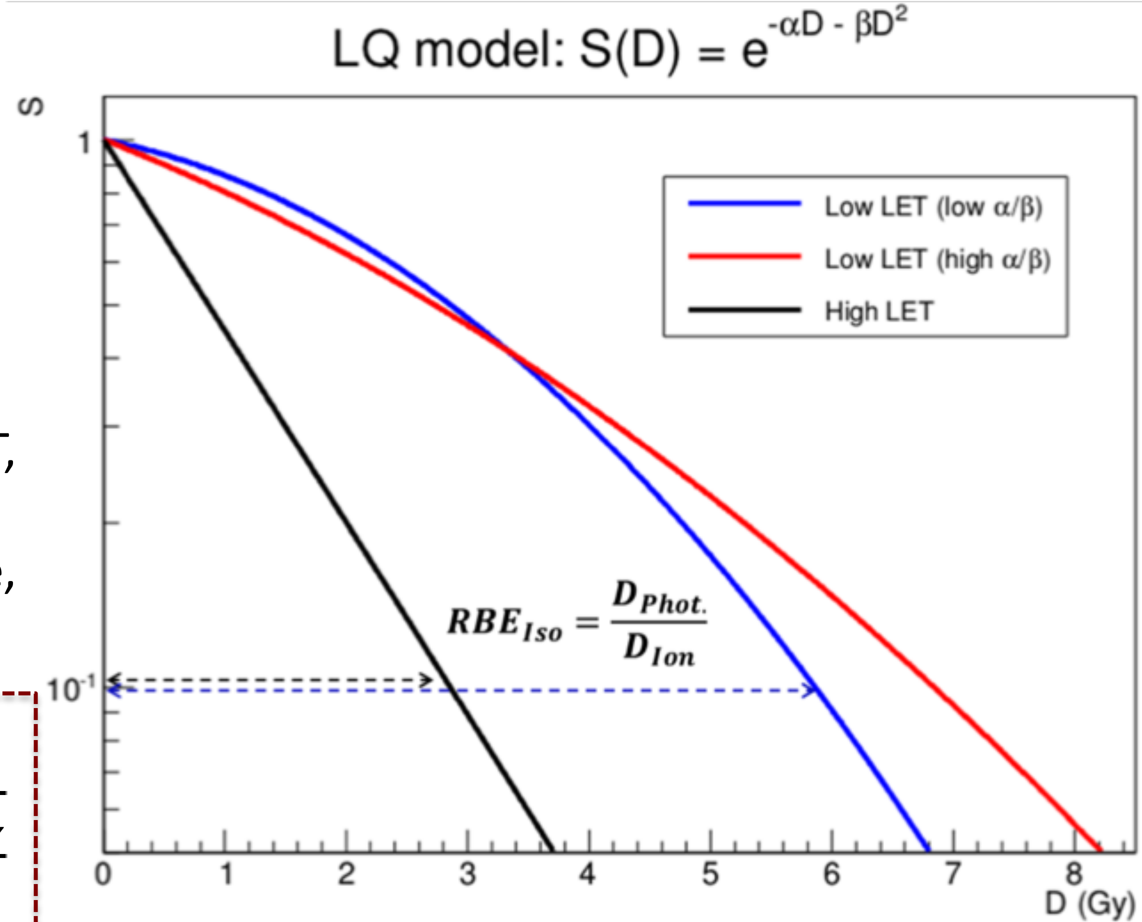
Relative Biological Effectiveness (RBE):

$$RBE = \frac{D_\gamma}{D_{Ion}}\bigg|_{Isoeffect}$$

RBE depends on:

- Physical parameters (dose, LET, fractionation).
- Biological parameters (cell cycle, oxygenation, end-point).

$$RBE(\alpha_\gamma, \beta_\gamma, \alpha_I, \beta_I, S) = \\ = \frac{-(\alpha/\beta)_\gamma \pm \sqrt{(\alpha/\beta)_\gamma^2 - 4(\ln\, S/\beta)_\gamma}}{-(\alpha/\beta)_I \pm \sqrt{(\alpha/\beta)_I^2 - 4(\ln\, S/\beta)_I}}$$



See A. Attili's talk

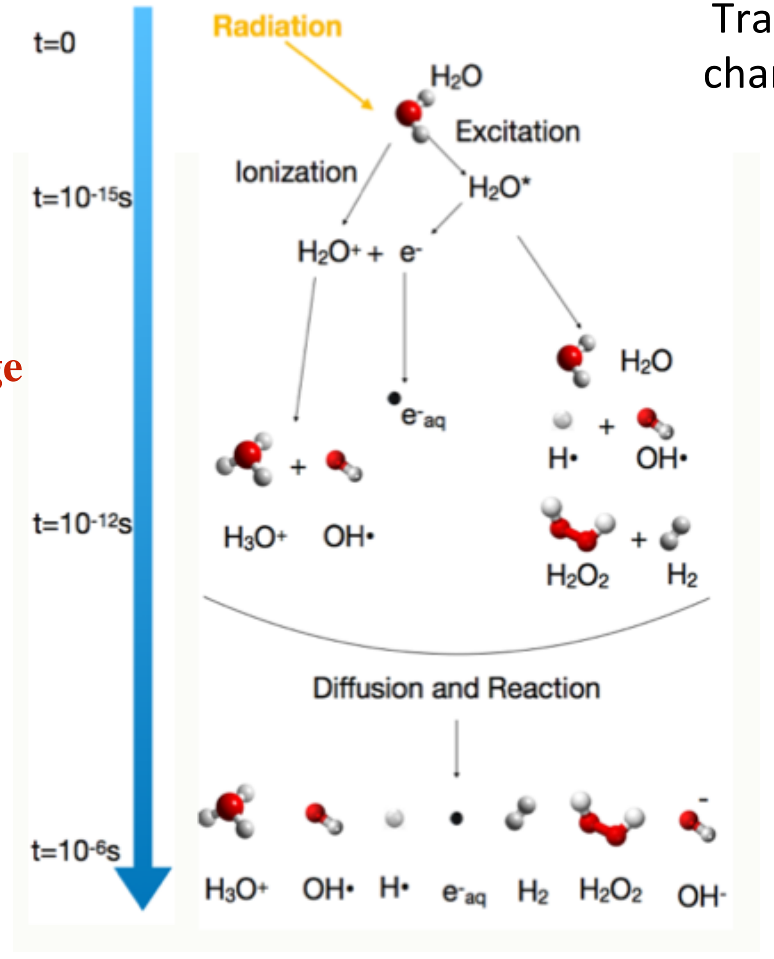
MC Track structure simulations

Track evolution: **three stage process** characterised by different time scales

1)Physical stage

2)Pre-chemical stage

3)Chemical stage



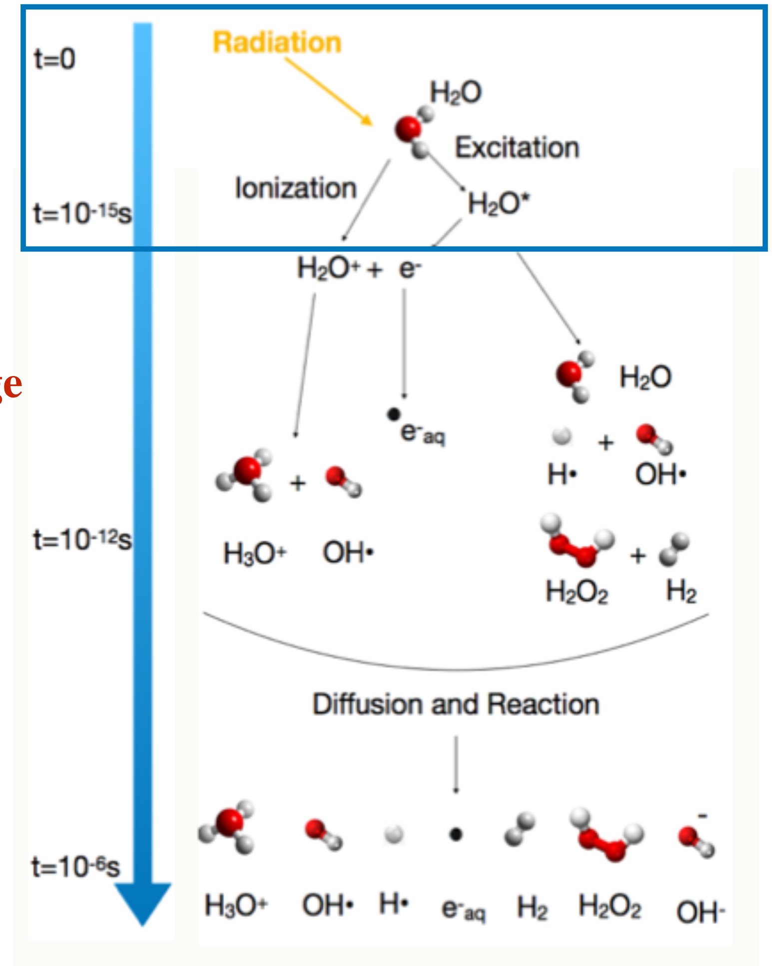
D. Boscolo PhD thesis TUD

From TRAX to TRAX CHEM:

1)Physical stage

2)Pre-chemical stage

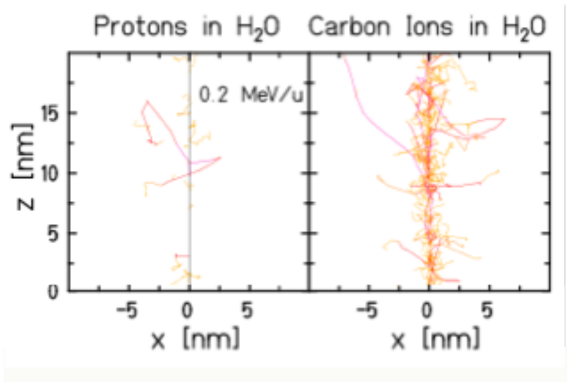
3)Chemical stage



D. Boscolo PhD thesis TUD

Classical version TRAX

Monte Carlo track structure code.
Passage of ion and electron tracks



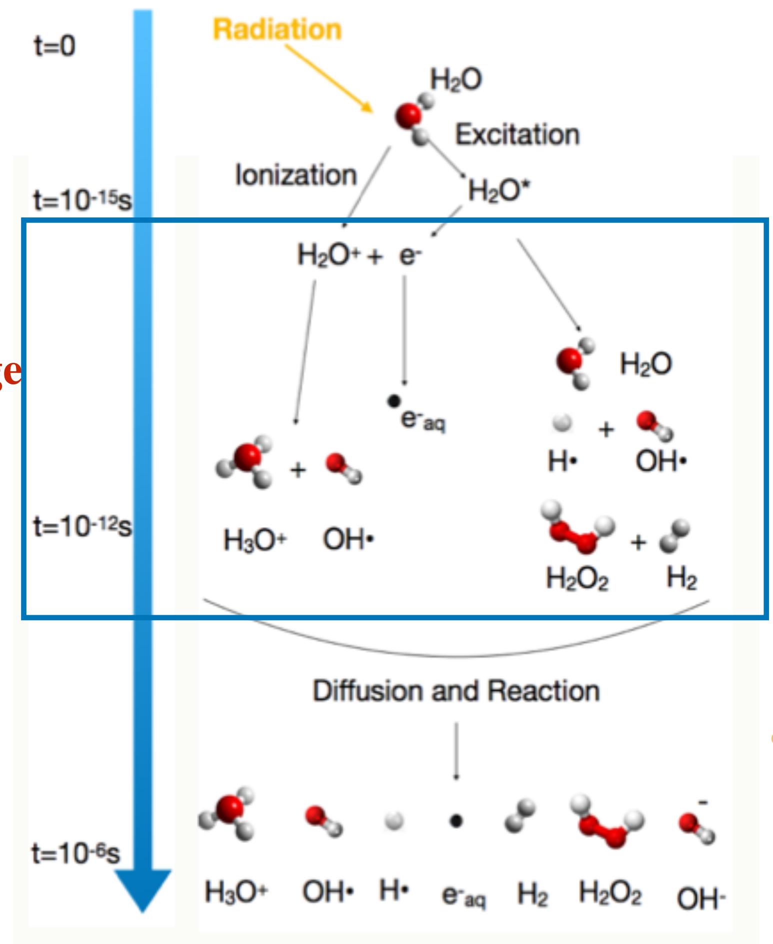
- *Wälzlein et al. 2014*
- *Kraemer et al.1994*

Pre-chemical stage

1)Physical stage

2)Pre-chemical stage

3)Chemical stage



D. Boscolo PhD thesis TUD

- **Molecular dissociation:**

  Excited and ionized water molecules **dissociate or relax to the ground state**.

	Dissociation channel	Probability(%)
Ionization	$H_3O^+ + OH^\bullet + e^-_{aq}$	100
Excitation		
A^1B_1	H_2O	25
	$OH^\bullet + H^\bullet$	75
B^1A_1	H_2O	15
	$H_3O^+ + OH^\bullet + e^-_{aq}$	55
	$H_2 + H_2O_2$	30
Ryd(A+B), Ryd(C+D)	H_2O	23
	$OH^\bullet + H^\bullet$	20
	$H_3O^+ + OH^\bullet + e^-_{aq}$	57
diffuse bands, H^* *Lymanα*, H^* *Balmerα*, OH^*	$H_3O^+ + OH^\bullet + e^-_{aq}$	100
e^-_{sub}	e^-_{aq}	100

- **Thermalisation model:**

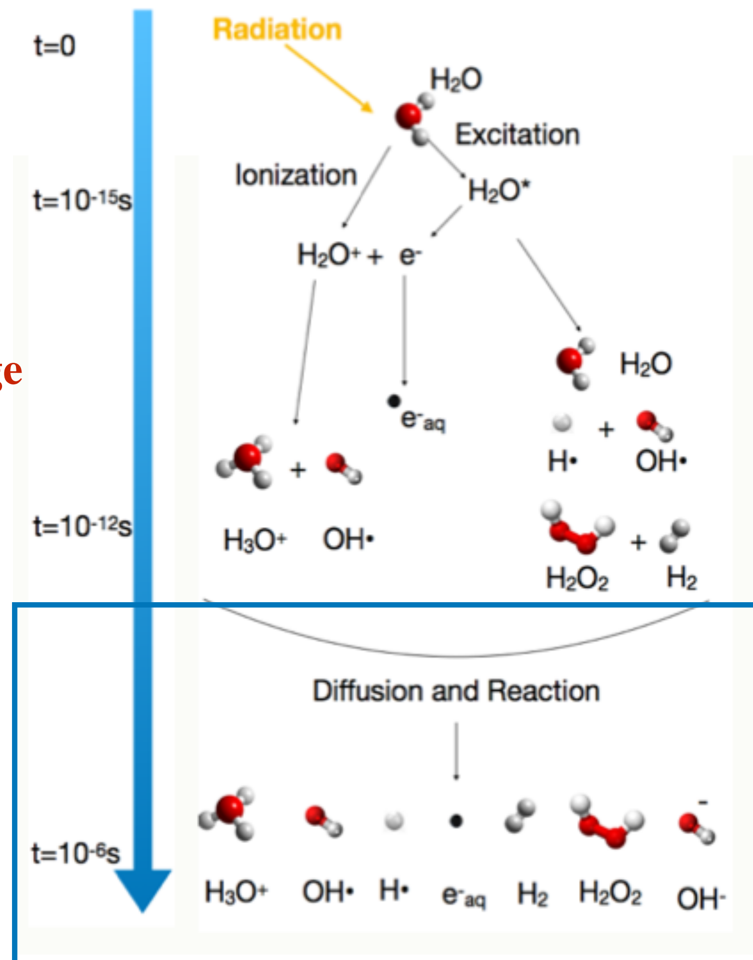
  Products of molecular dissociation thermalise with the solvent

Chemical stage

1)Physical stage

2)Pre-chemical stage

3)Chemical stage



D. Boscolo PhD thesis TUD

- **Diffusion:**

Jump in a **random direction**
Einstein Smoluchowski eq.:

$$\lambda = \sqrt{6D\Delta t}$$

D the diffusion coefficient
Δ**t** the time step

- **Reaction:**

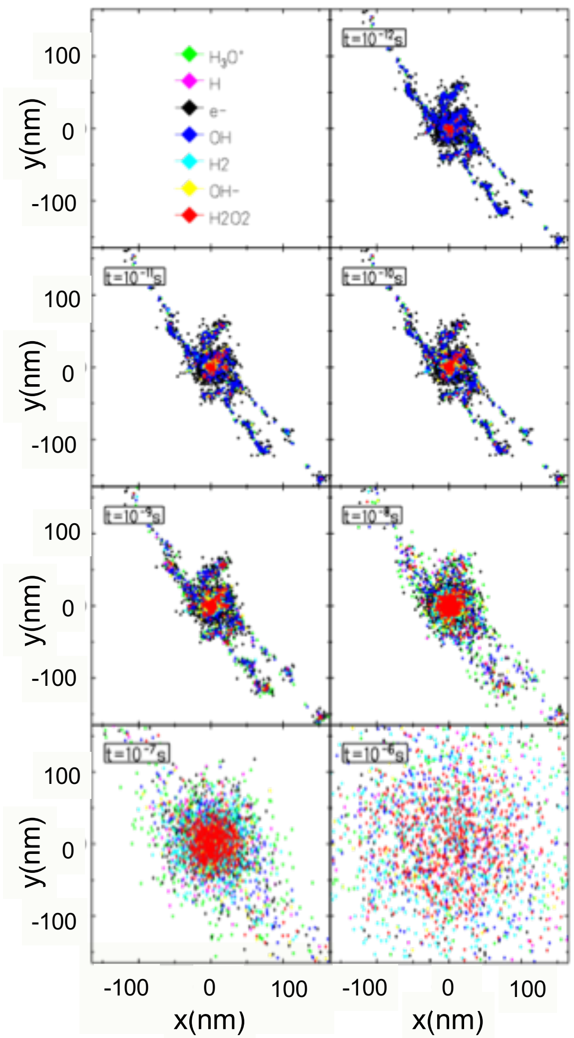
Described with a proximity parameter

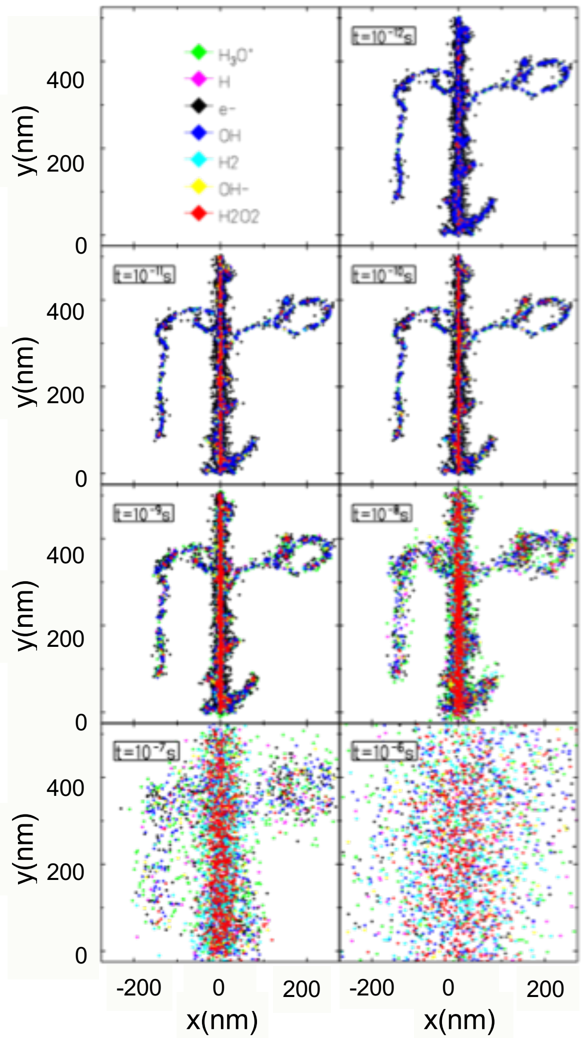
- a_{AB} reaction radius

$$a_{AB} = \frac{k_{AB}}{4\pi(D_A + D_B)}$$

Water radiolysis (TRAX-CHEM)

Boscolo, Scifoni, Fuss, Kraemer, Durante, Chem Phys Lett .(2018)

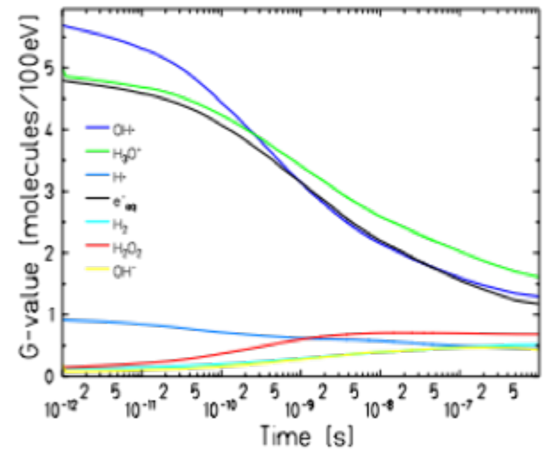




Carbon 8MeV/u

$t=10^{-6}$ s

End of the Chemical stage



G-value = molecules/ 100eV

See also Geant4DNA (S.. Incerti.s talk), mTOPAS-bio (Ramos et al.2018), PARTRAC (Friedland), RITRACK (Plante)

Biological-based treatment planning

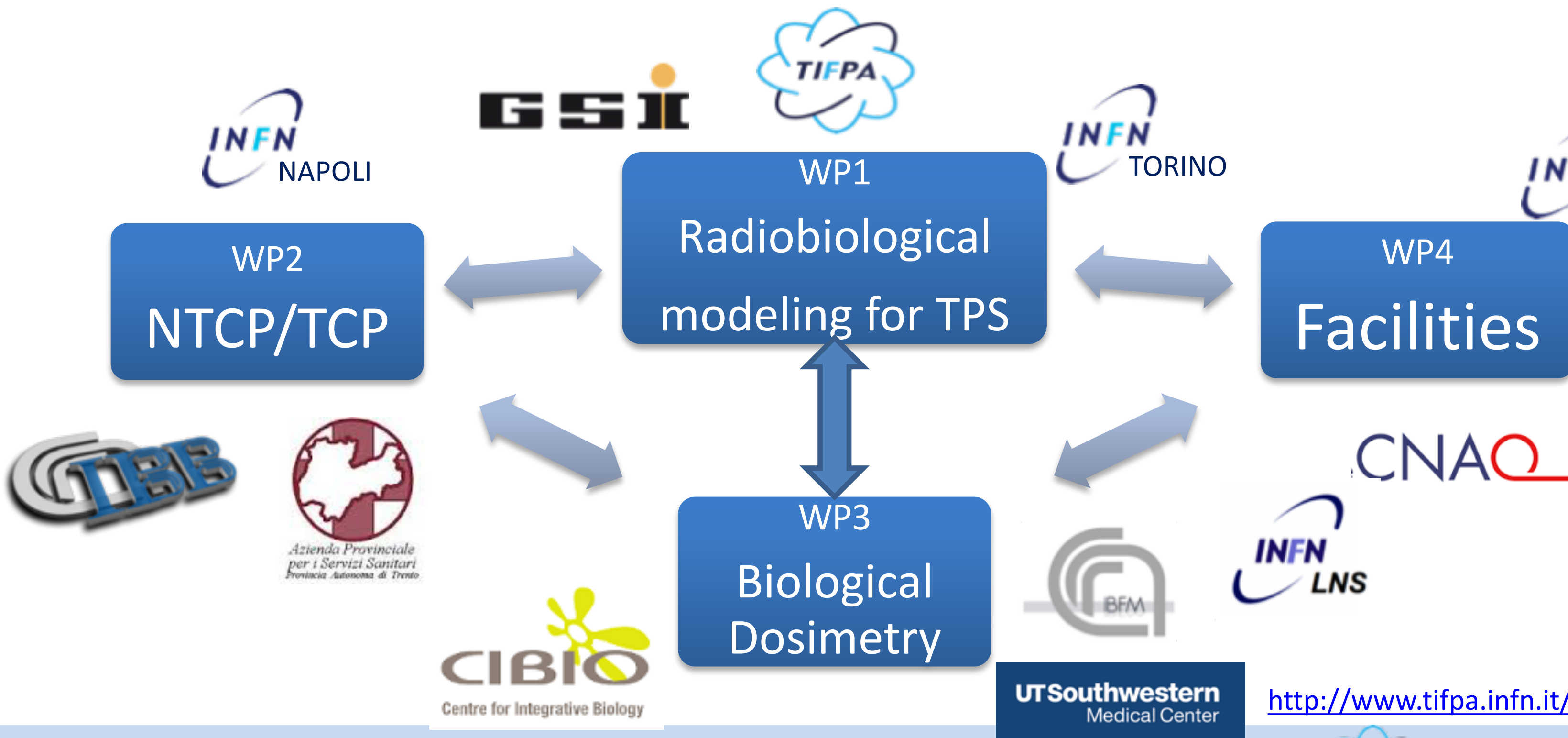
- Bio-TPS for ion beams aims to include as much as possible biological effect information in the planning strategy.
- Relevant for plan recalculation but ideally needed for inverse planning.
- Substantial e.g., for assessing differential benefits of different irradiation modalities and selecting the most suitable choice for a given patient case.
- **Additional physics data** needed, since the different components (E,Z) of the mixed field in a beam should be properly accounted in order to get an overall biological effect.

MoVe IT

Modeling and Verification for Ion beam Treatment planning

INFN Network - Call group V - funded 2017-2019- Coordinator: E. Scifoni

- Advancing biolological treatment planning (e.g. impact of full nuclear spectra (including target fragments from FOOT) on RBE, hypoxia, intra-tumour heterogeneities)
- Developing new systems and tools for biological verification



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

INFN TIFPA Trento Institute for Fundamental Physics and Applications

Advancing clinical prescription for Particle therapy

optimized quantity:

- Absorbed Dose

⬇

- Biologically effective Dose (RBE weighted)

Optimization of the RBE-Weighted Dose

$$\chi^2_{Bio}(\vec{N}) = \sum_{i \in target} \frac{[D^i_{pre} - D^i_{Bio}(\vec{N})]^2}{\Delta D^2_{pre}} + \sum_{i \in OAR} \frac{[D^i_{max} - D^i_{Bio}(\vec{N})]^2}{\Delta D^2_{max}} \Theta(D^i_{Bio}(\vec{N}) - D^i_{max})$$

RBE-weighted dose:

Biophysical model

$$D^i_{act}(\vec{N}) = D^i_{bio}(\vec{N}) = D^i_{abs}(\vec{N}) \cdot RBE^i(\vec{N})$$

Optimization Task

$$\chi^2_{Bio}(\vec{N}) \rightarrow \min$$

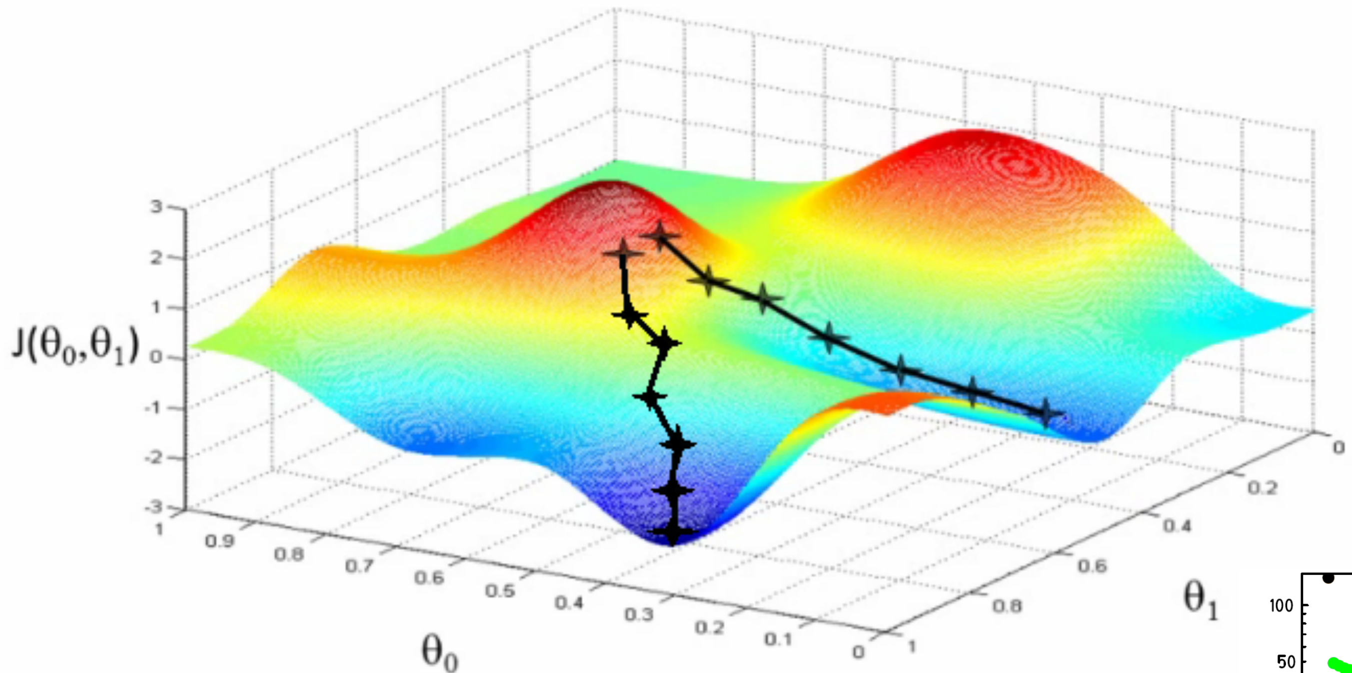
nonlinear RBE-weighted dose

-> nonlinear objective function

-> nonlinear optimization task

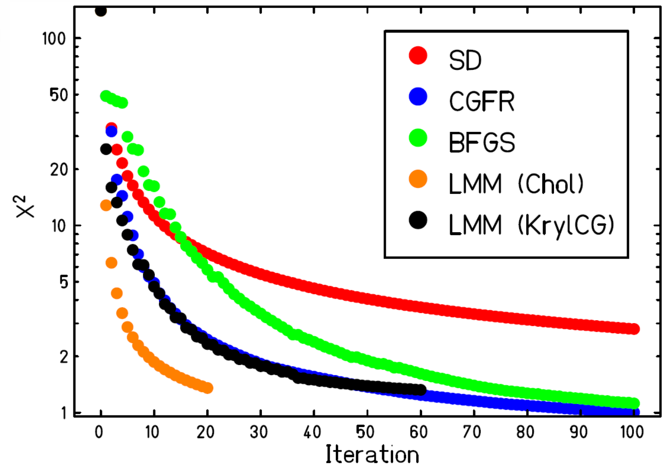
-> solution only with numerical methods

The Optimization task

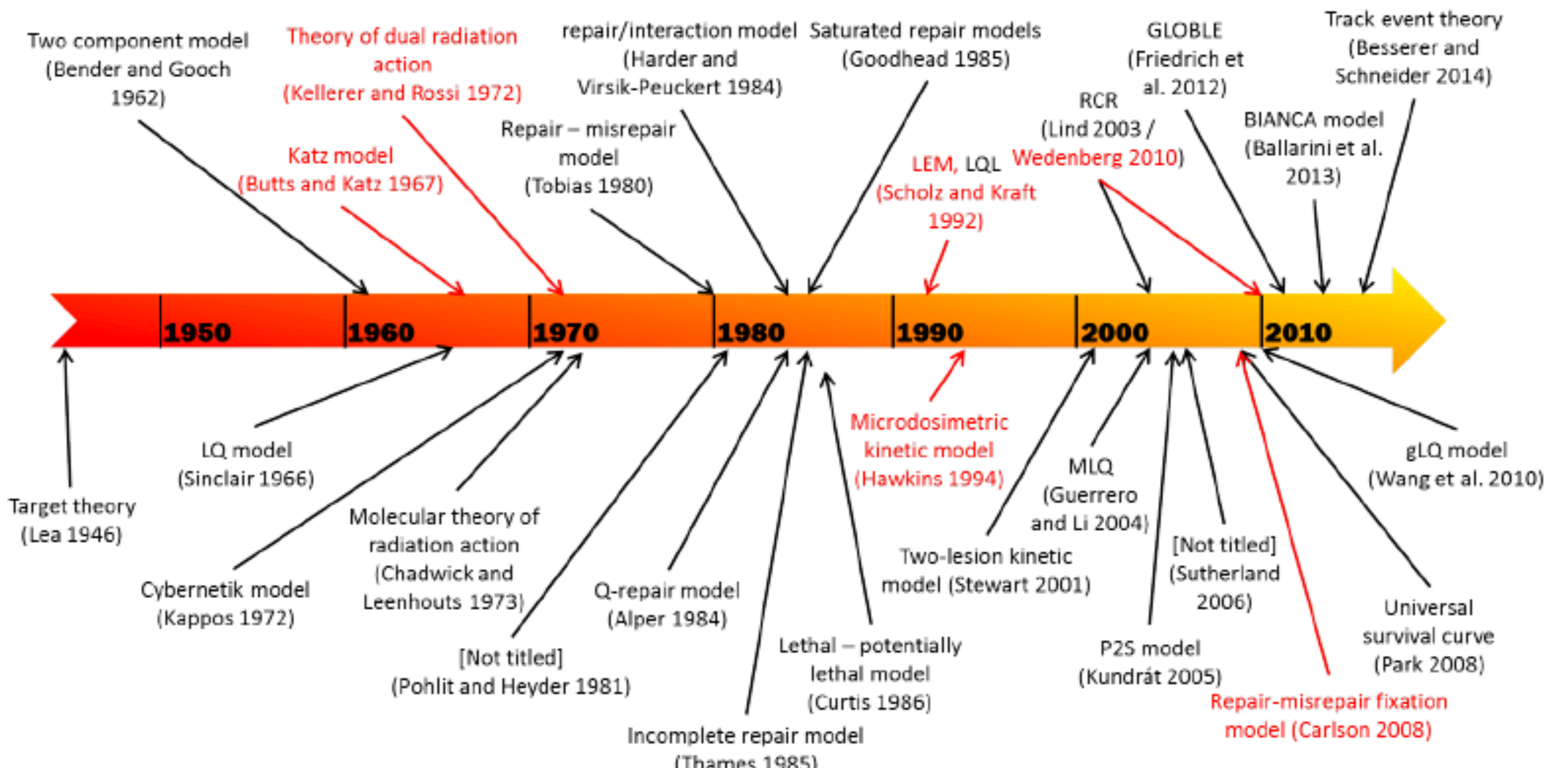


Algorithms for the optimization of RBE-weighted dose in particle therapy

Horcicka et al. PMB 2013



History of biophysical modeling



Red=also high LET radiation

T. Friedrich (Habil Thesis) TUD 2016

Clinically applied models

- MKM – Microdosimetric Kinetic Model (Japan)
- LEM– Local Effect Model (Europe)

Microdosimetric Kinetic Model

Extension of the Dual Radiation Action Model.

Cell nucleus divided into a number *q* of microscopic sites called *domains*.

Survival fraction s_d of a domain after a dose *z* is absorbed:

$$-\ln s_{\mathrm{d}} = Az + Bz^2$$

Independent of the radiation quality.

Number of hits to a domain: Poisson distribution.

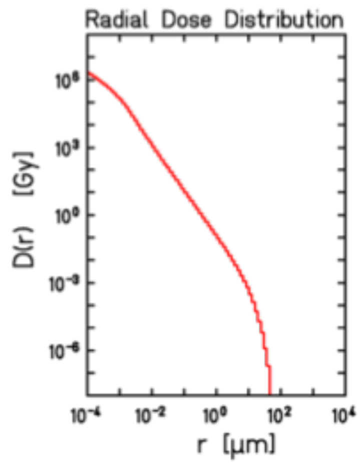
Survival fraction of a cell: *S*.

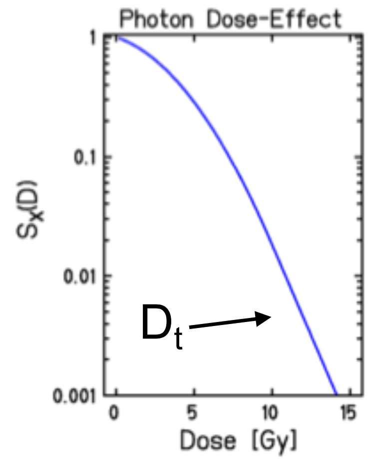
A cell survives if all domain survive.

See A. Attili's talk

LEM I: Three Ingredients

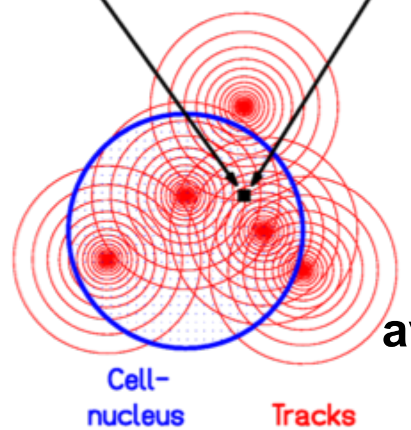
Physics
Radial Dose Distribution:
Monte-Carlo (TRAX),
Experimental Data,
Semi-empirical
(Amorphous Track model)





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

Geometry
Target (cell nucleus):
Experimental Data



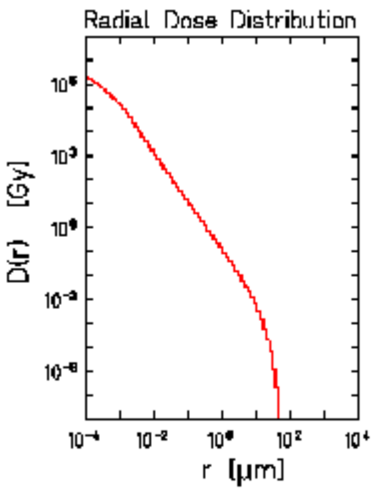
$$S = e^{-(\alpha D + \beta D^2)}, \quad D < D_t$$

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

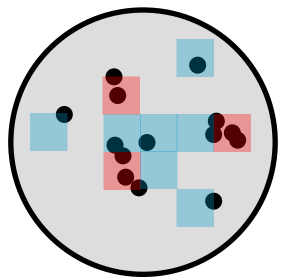
average number of lethal events

Scholz&Kraft 1996

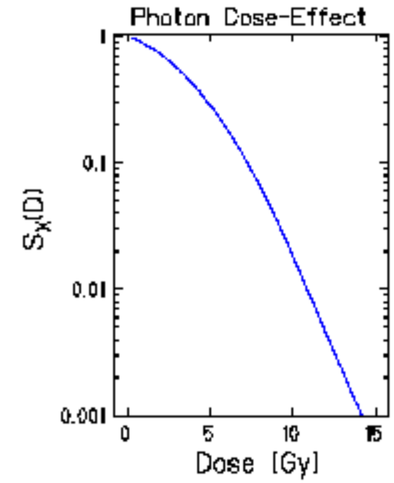
LEM IV: Photon equivalent lesion distribution



Amorphous track structure



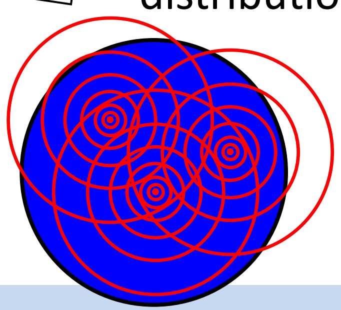
Local lesion distribution



Photon equivalent situation

Local dose distribution

Elsaesser 2010
Friedrich 2012



Lesion statistics

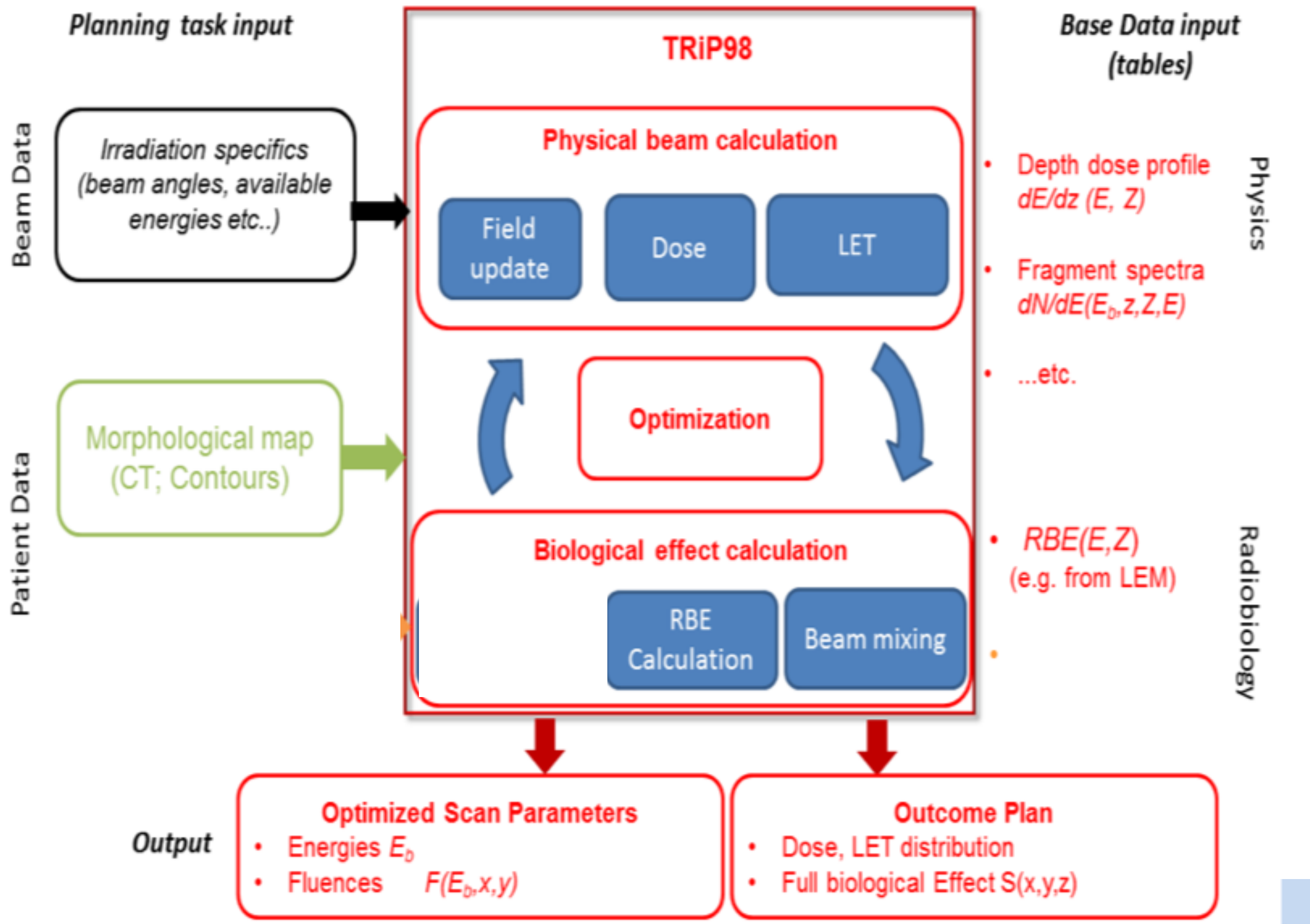
: 7
: 3

RBE

Courtesy.of T. Friedrich

TRiP98 – Treatment planning for Particles

Clinical use in pilot project, Research use in GSI, HIT, Aarhus, Lyon etc.
Reference for: Siemens SynGo/PT, RayStation Carbon



Beam-mixing models

TDRA based beam-mixing, Zaider & Rossi (1980):

in principle, the same derivation as single beam (mean calculation for microdosimetric quantities),

now for two beams: (α_1, β_1), (α_2, β_2)

no further model assumption needed

result again linear-quadratic:

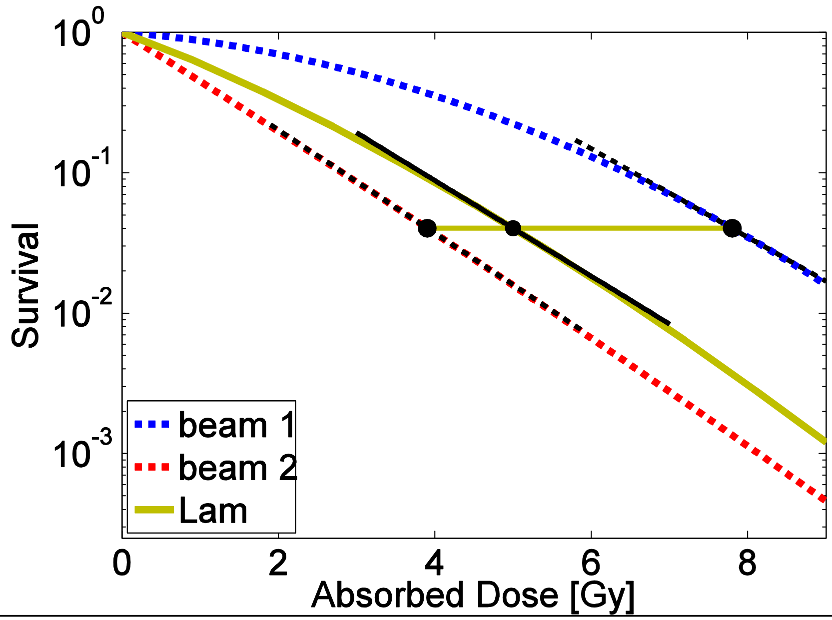
$$\epsilon(D) = \bar{\alpha} D + \bar{\beta} D^2$$

mixed-beam α and β:

$$\bar{\alpha} = \frac{\alpha_1 D_1 + \alpha_2 D_2}{D}, \sqrt{\bar{\beta}} = \frac{\sqrt{\beta_1} D_1 + \sqrt{\beta_2} D_2}{D}$$

applied e.g. in Kraemer&Scholz 2006

Beam-mixing models



Lam model (Lam 1987):

dose-mean of the *slopes* of the monoenergetic beams at the *same effect*

mixed beam:

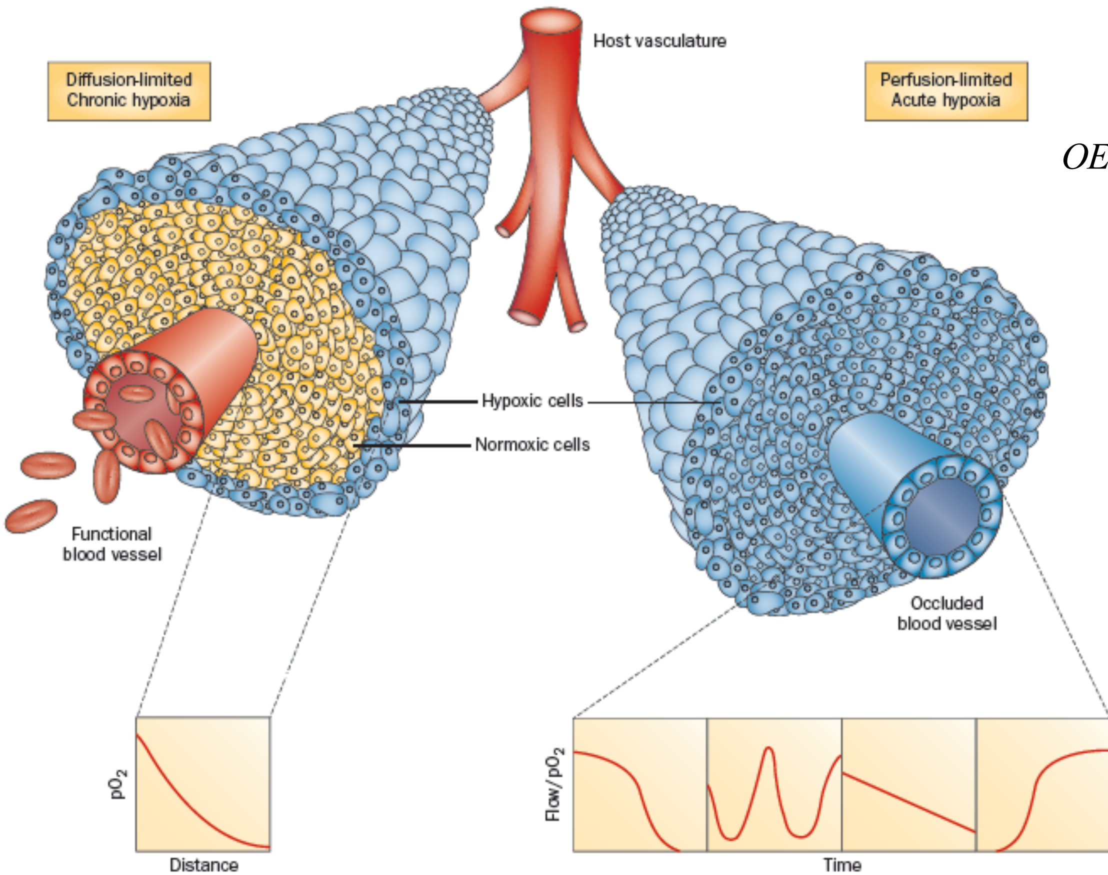
effect : ϵ,

slope: $$\frac{d\epsilon}{dD}(D) = \frac{\frac{d\epsilon_1}{dD}(\epsilon_1^{-1}(D))D_1 + \frac{d\epsilon_2}{dD}(\epsilon_2^{-1}(D))D_2}{D}$$

Steinstraeter et al. 2015

Adaptive Bio-TPS

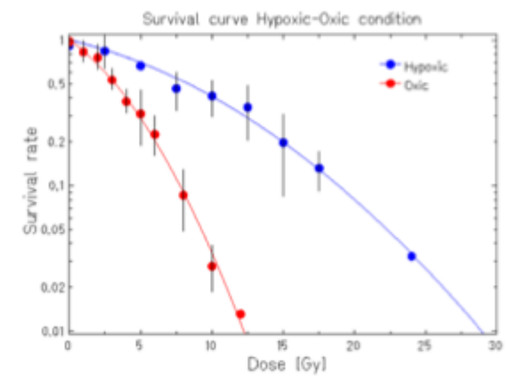
Intratumor heterogeneity: Hypoxia

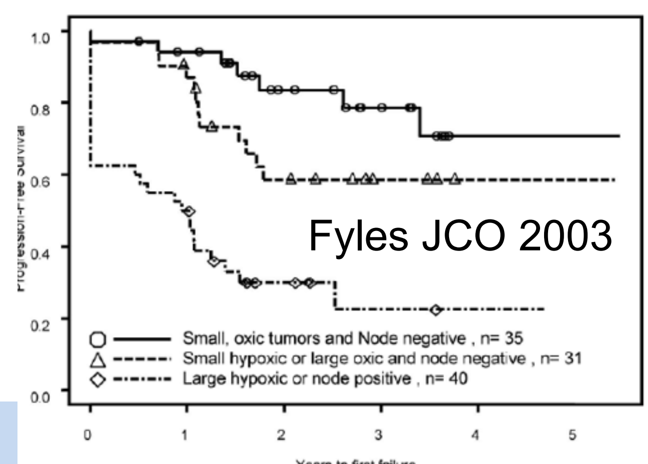


Horsman et al *Nat. Rev. Clin. Oncol.* (2012)

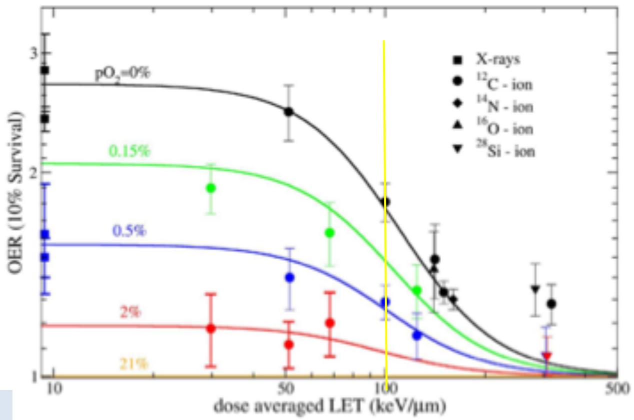
Oxygen Enhancement Ratio

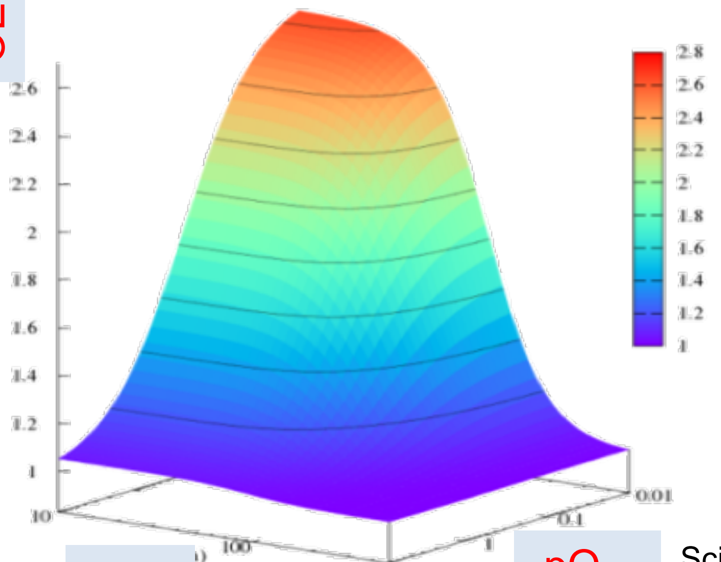
$$OER = \left.\frac{D_{hypoxic}}{D_{normoxic}}\right|_{same effect} \quad ; \quad OER(p) = \left.\frac{D(p)}{D_{normoxic}}\right|_{same effect}$$

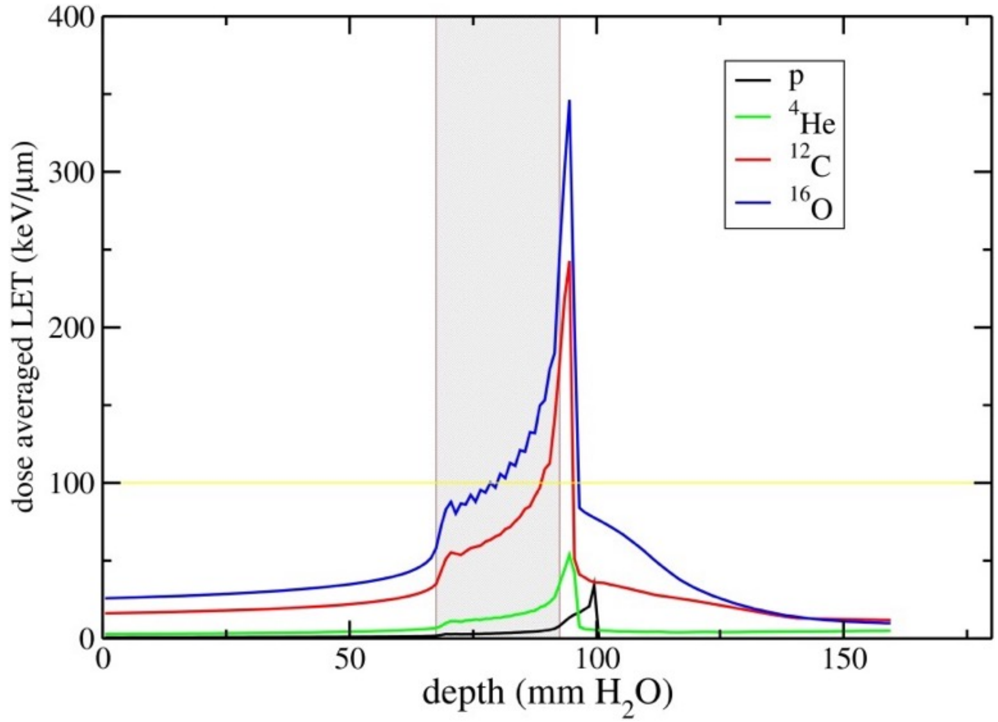




OER (pO2,LET)







Tommasino Scifoni Durante Int J Part Ther 2015

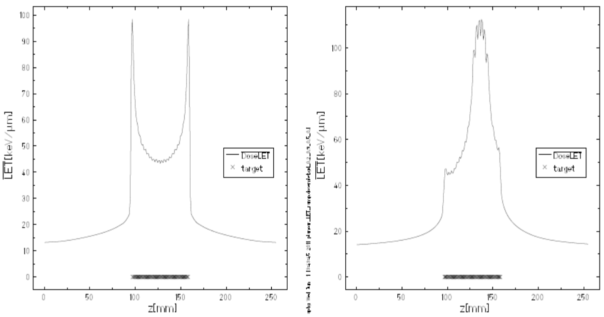
Scifoni et al PMB 2013

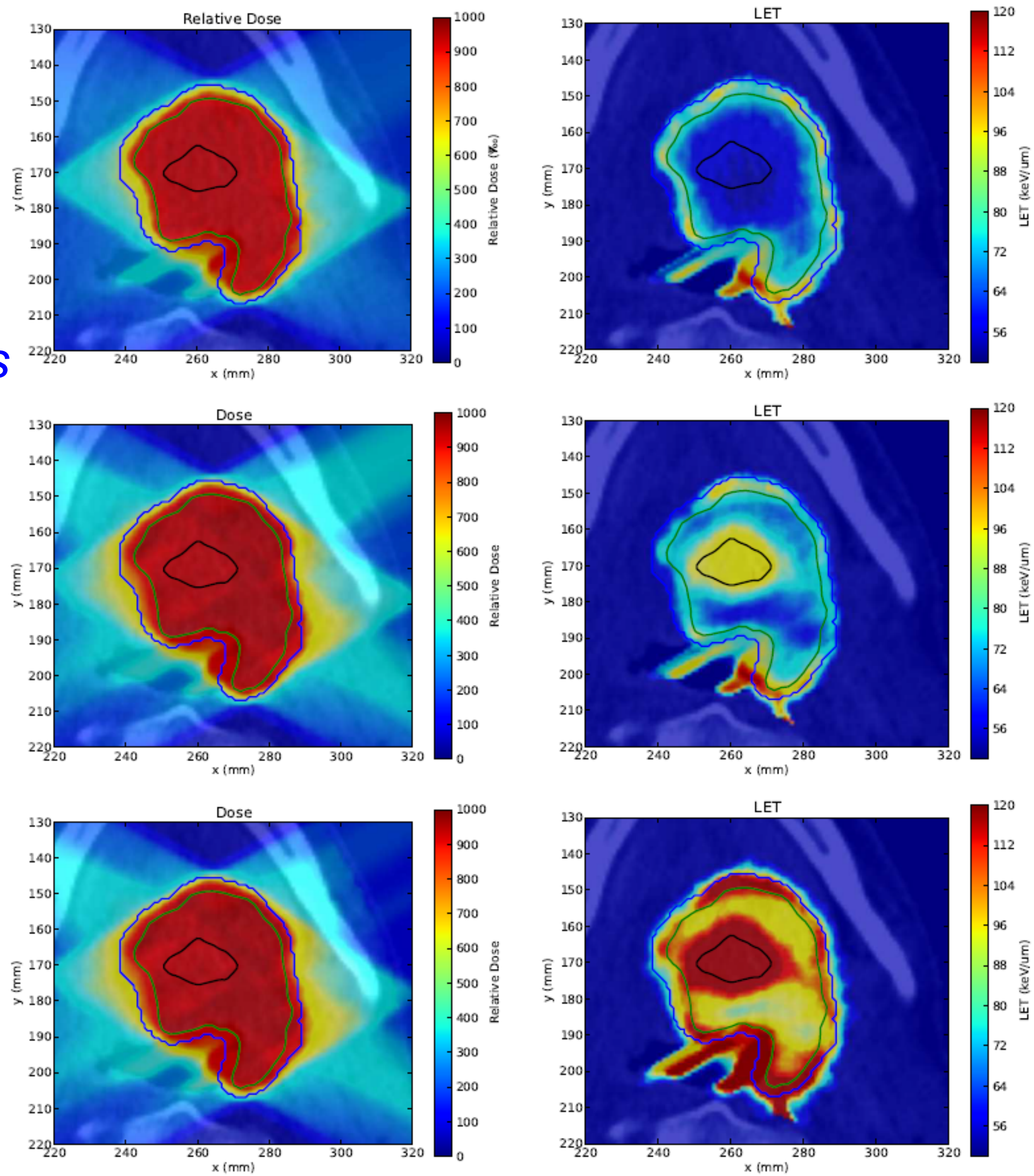
Tinganelli et al. Sci Rep 2015

LET painting

- Redistribution of LET, to be maximized in a target volume,

using TRiP98 with dose ramps





Bassler et al. Acta Oncol 2014

The kill painting basic idea

optimized quantity:

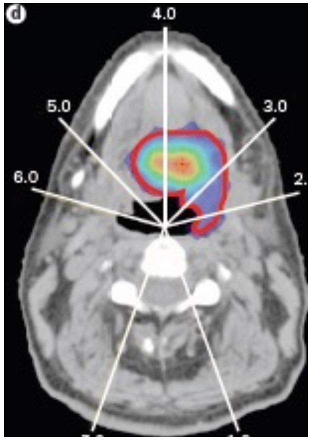
- Absorbed Dose

↓

- Biologically effective Dose (RBE weighted)

↓

- Biologically isoeffective Dose in the local microenvironment

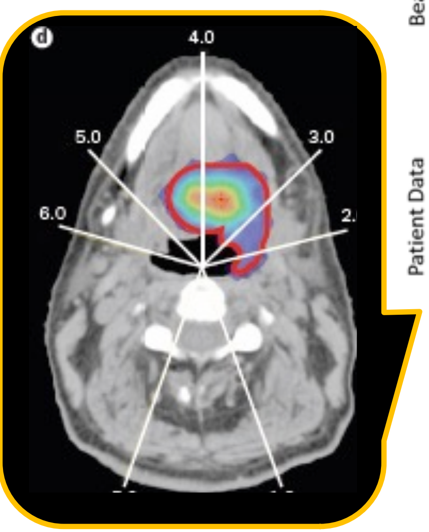


Intra-tumour
Heterogeneity
revealed by functional imaging
e.g. CT/PET(FMISO)
Horsman NRCO 211

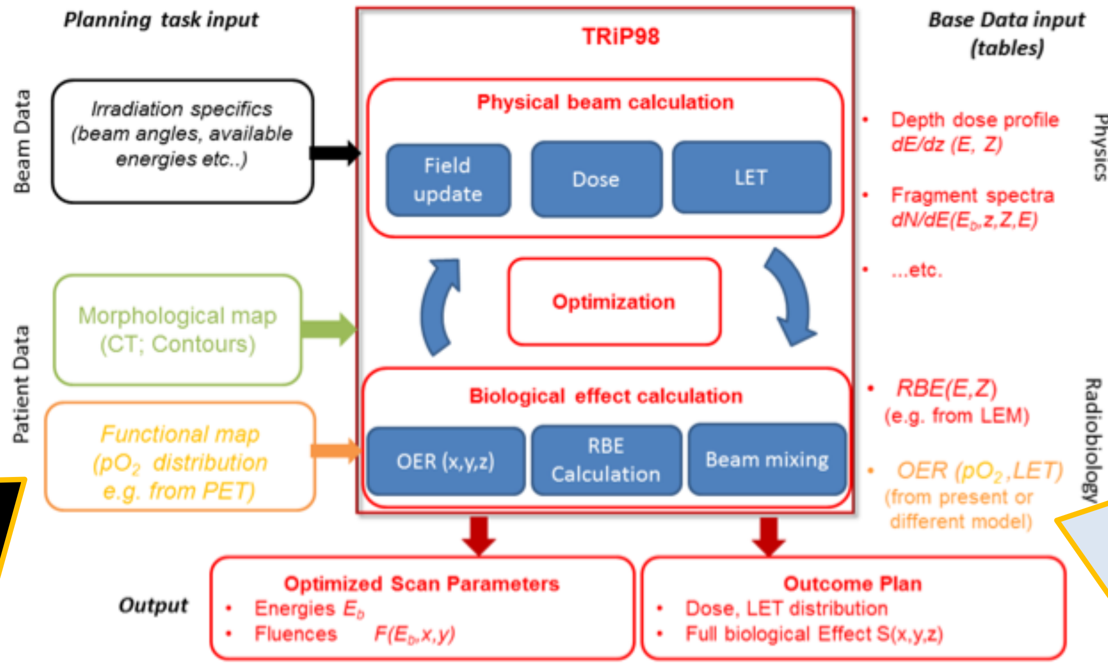
What is needed:

- ✓ Physical beam modeling
- ✓ RadioBiological modeling
- ✓ Implementation in TPS
- ✓ Experimental Verification

Kill painting implementation in TPS

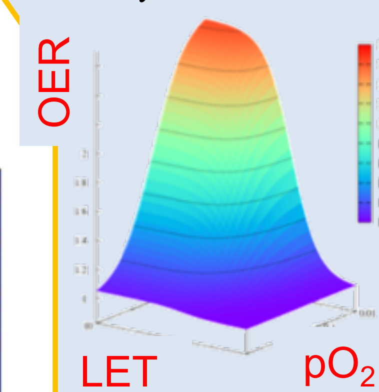


Horsman et al
Nat. Rev. Clin. Oncol. (2012)

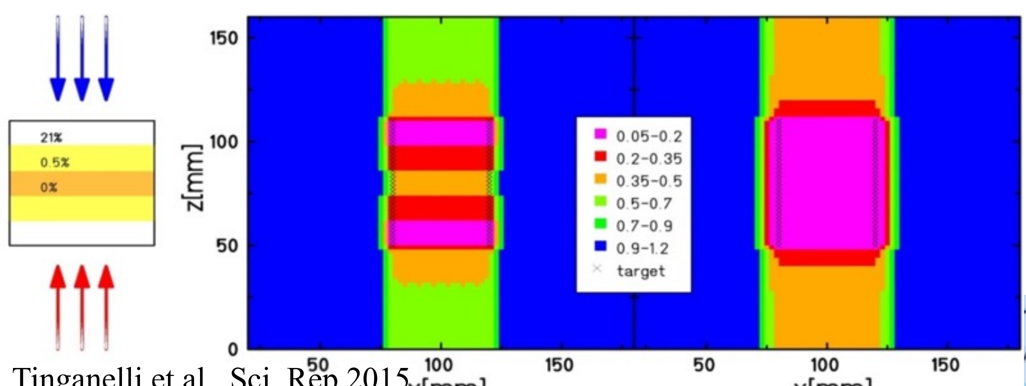


Semi-empirical model for OER (pO_2,LET)

Scifoni et al . Phys Med Biol 2013



LET and dose distribution of the particle fields automatically adjusted from the optimization to the oxygen distribution

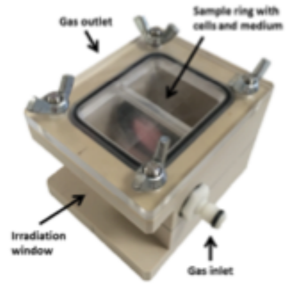


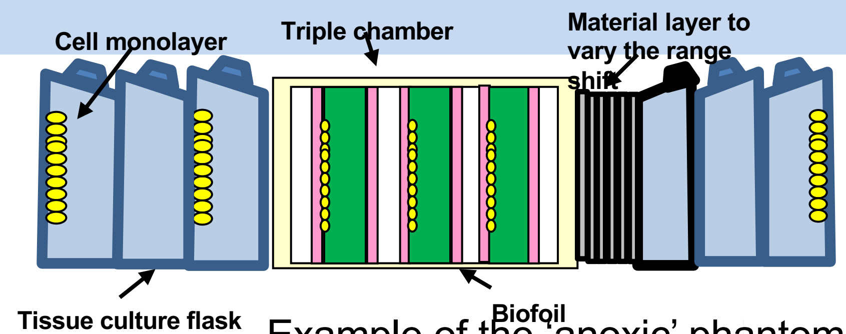
Tinganelli et al . Sci Rep 2015

Trento Institute for Fundamental Physics and Applications

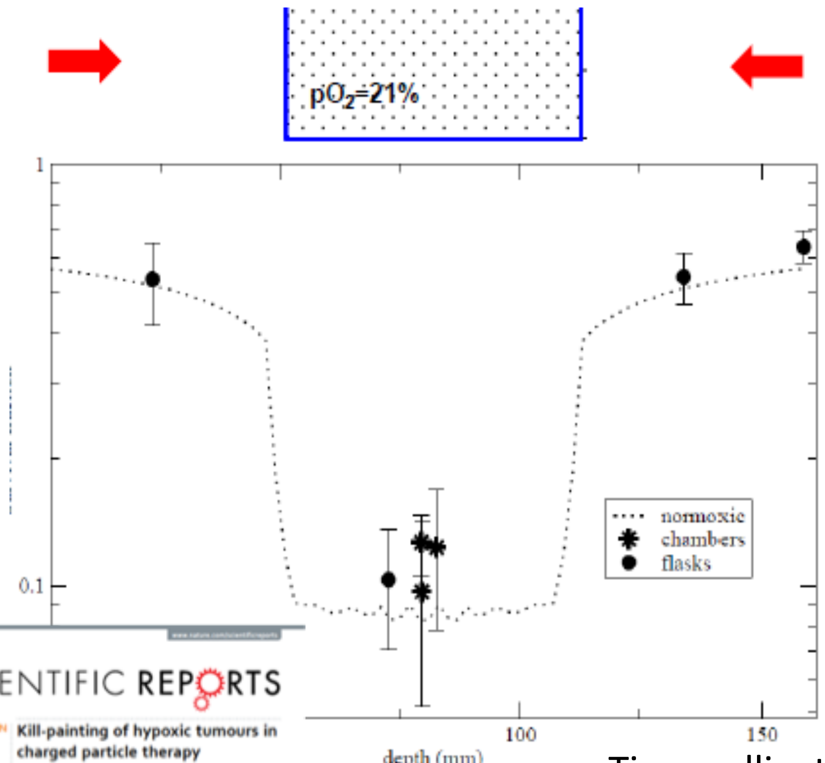
Experimental verification: Hypoxic cell chambers

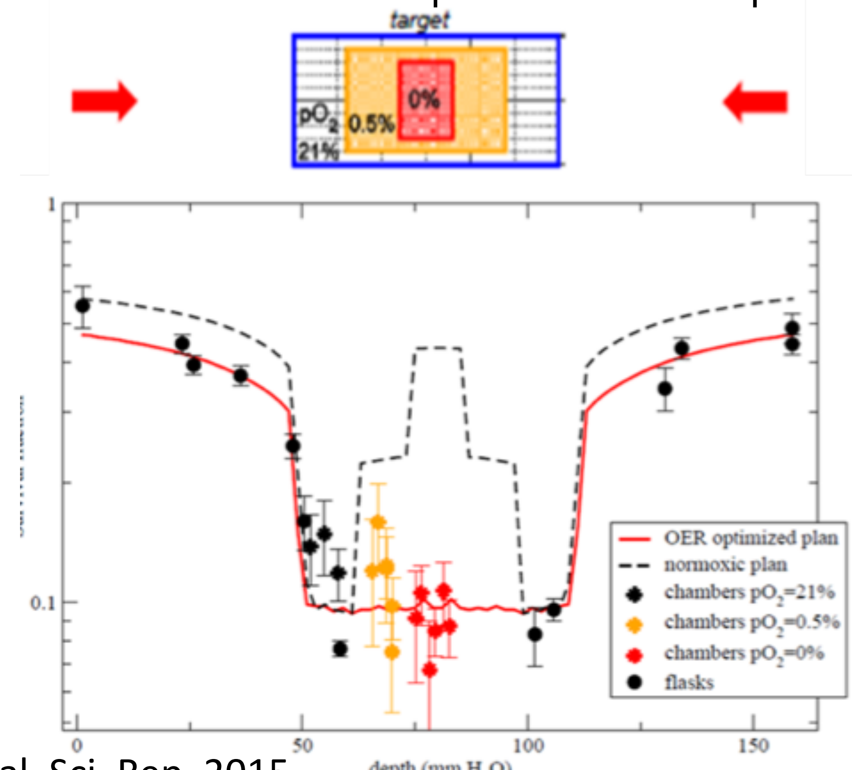
2 Fields C ions@GSI





Example of the 'anoxic' phantom





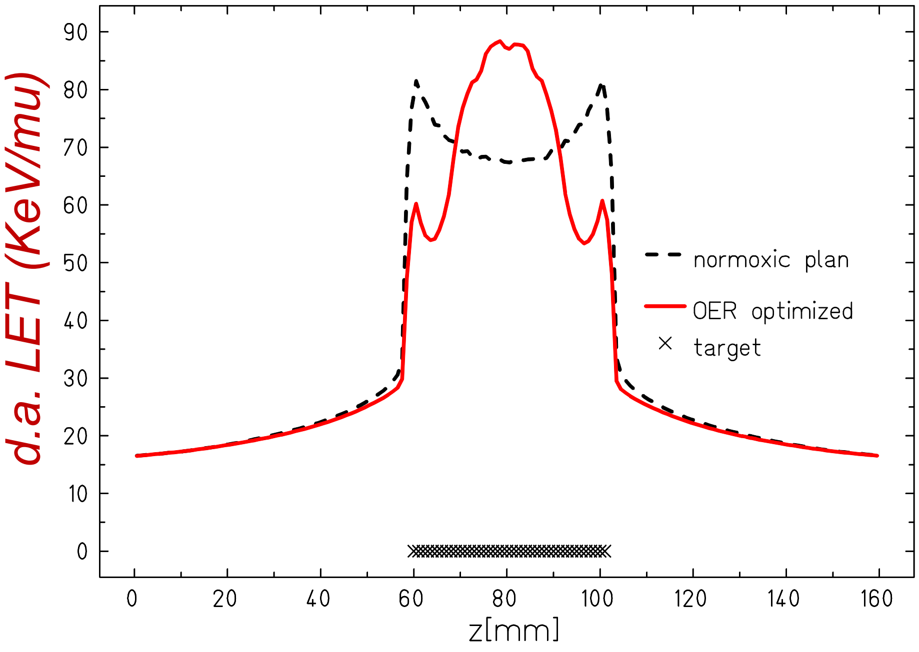
SCIENTIFIC REPORTS

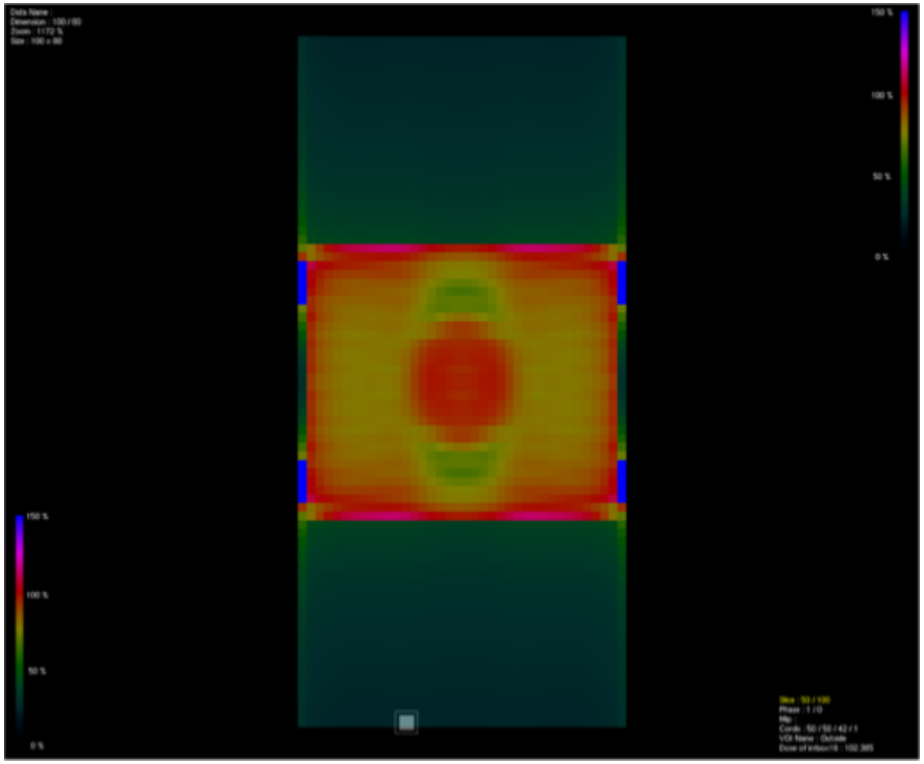
OPEN Kill-painting of hypoxic tumours in charged particle therapy

Tinganelli et al. Sci. Rep. 2015.

Proof of principle of 3D kill painting

Automatic optimal LET distribution

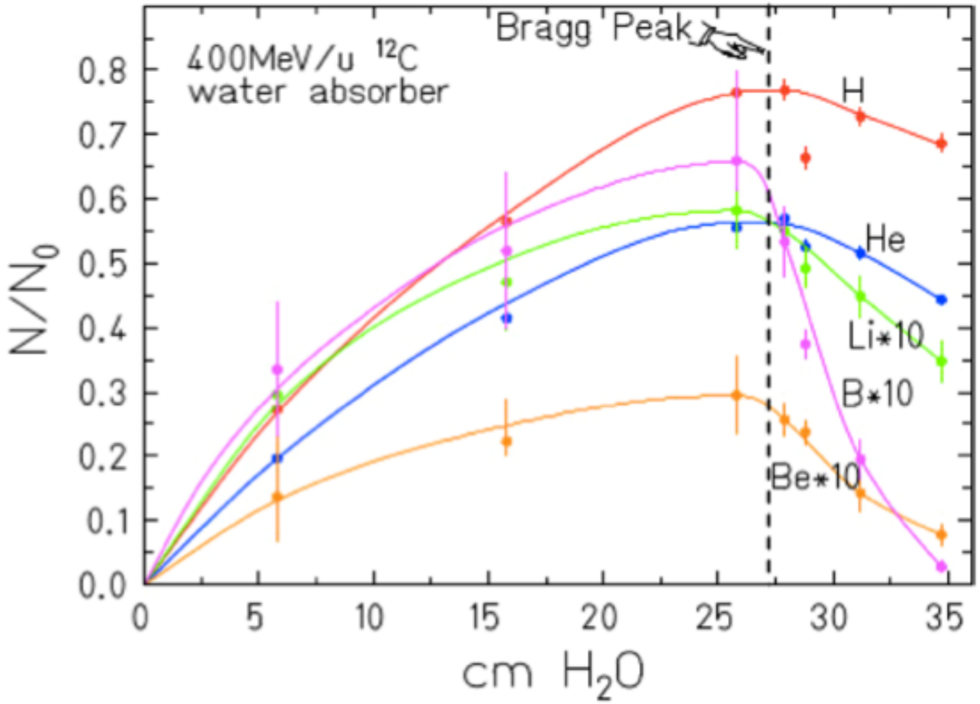




Bio-TPS with ^{12}C

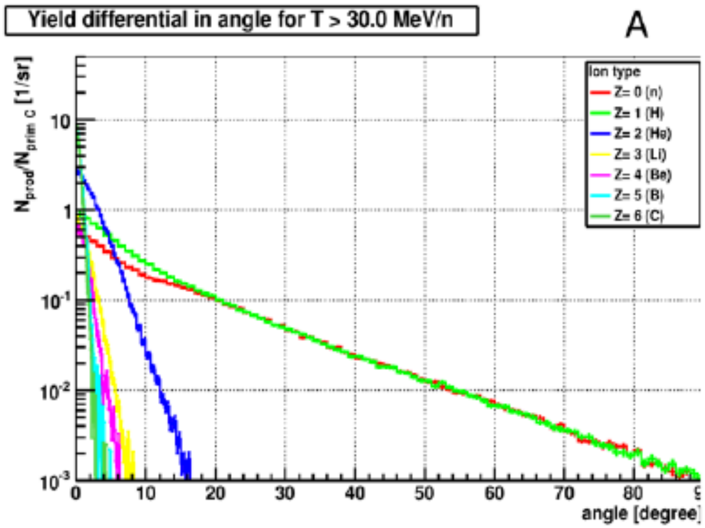
C fragmentation data

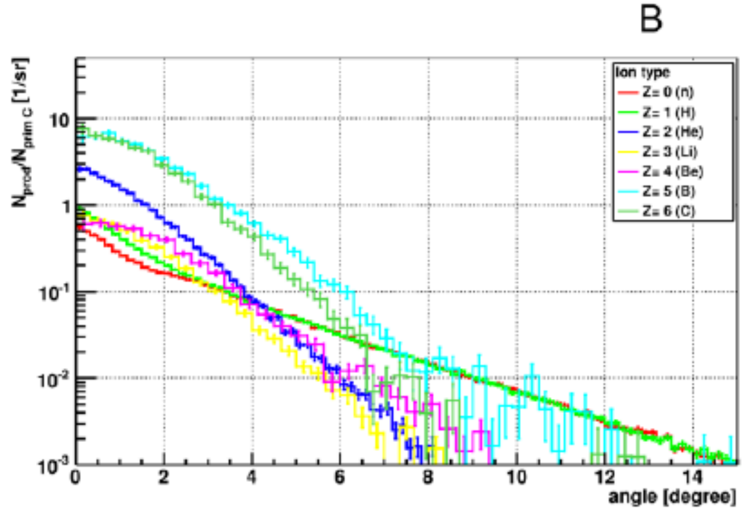
Fragments Build up

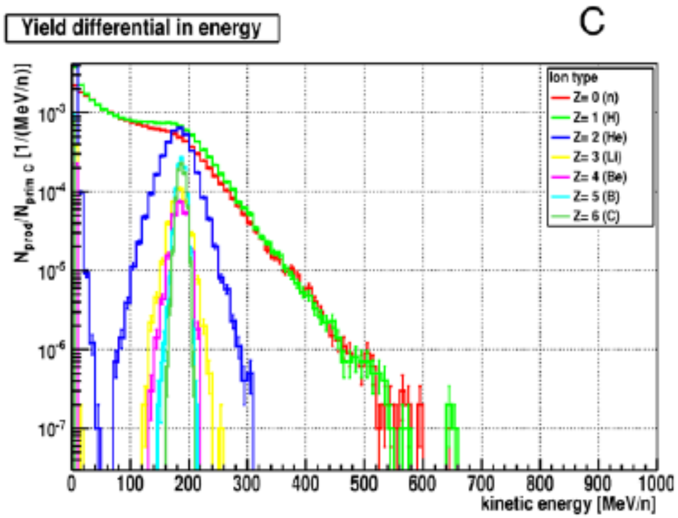


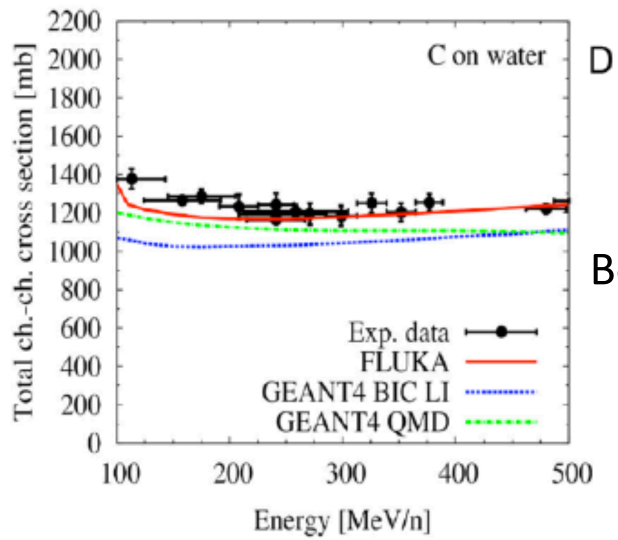
Schardt et al .2010

C fragmentation data









Bohlen 2010

Impact of C Fragmentation on RBE

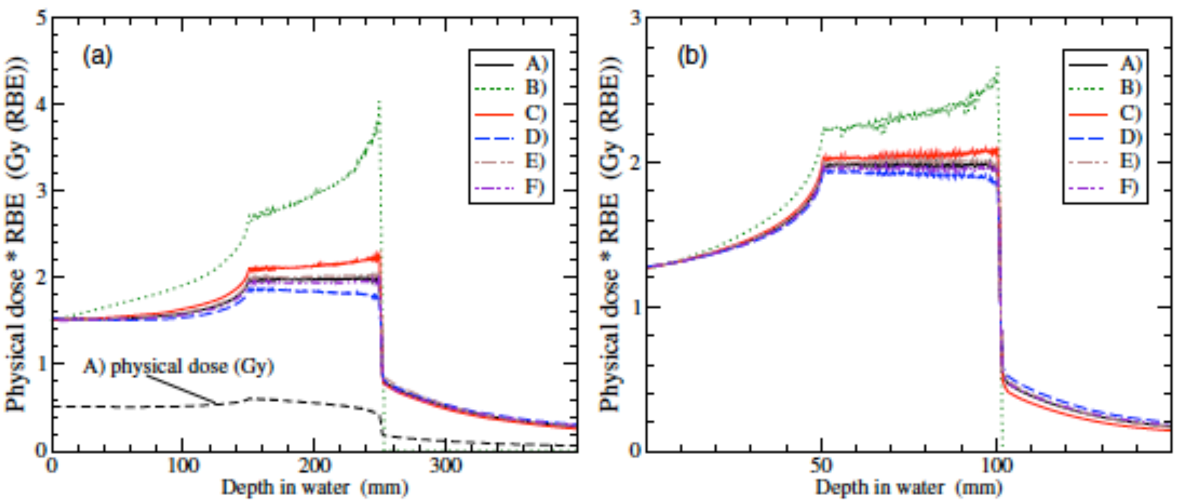
IOP PUBLISHING — PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. 57 (2012) 5169–5185 — doi:10.1088/0031-9155/57/16/5169

The impact of modeling nuclear fragmentation on delivered dose and radiobiology in ion therapy

Armin Lühr[1,2,3], David C Hansen[1,2], Ricky Teiwes[2], Nikolai Sobolevsky[4], Oliver Jäkel[5,6] and Niels Bassler[1,2]

- SHIELD-HIT (MC) + TRiP98
- C beam
- 20% in xs => only 3% in RBE

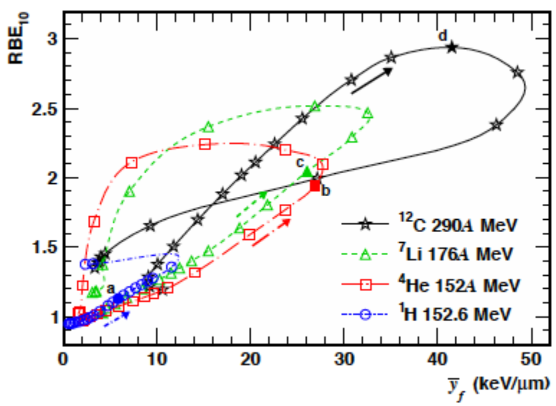


***A**: Reference nuclear models of SHIELD-HIT10A;*
***B**: Turning off entirely nuclear reactions;*
***C,D**: +,- 20% of all inelastic cross sections,*
***E,F**: different parameters in the Fermi-breakup model*

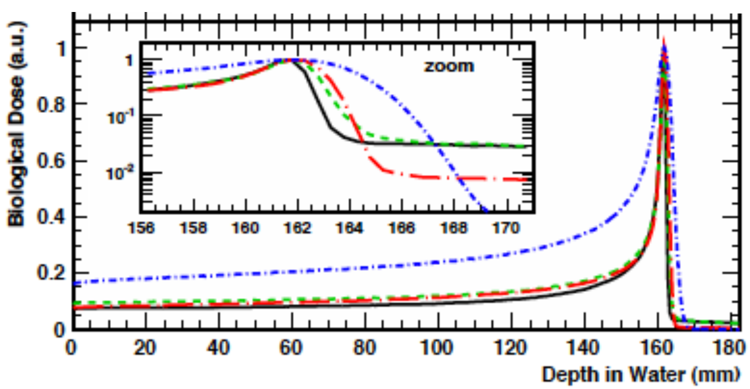
Microdosimetric spectra

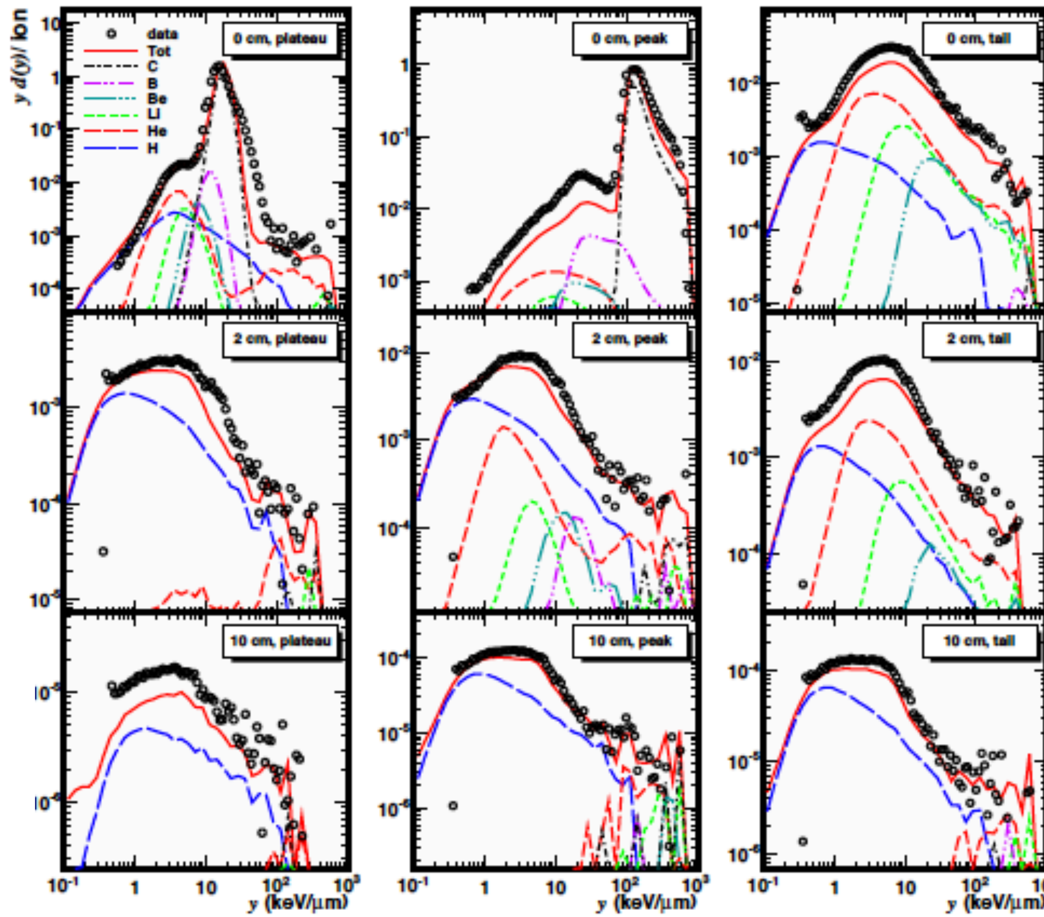
Burigo et al. NIMB(2014)

Exp: Martino et al. PMB (2010)



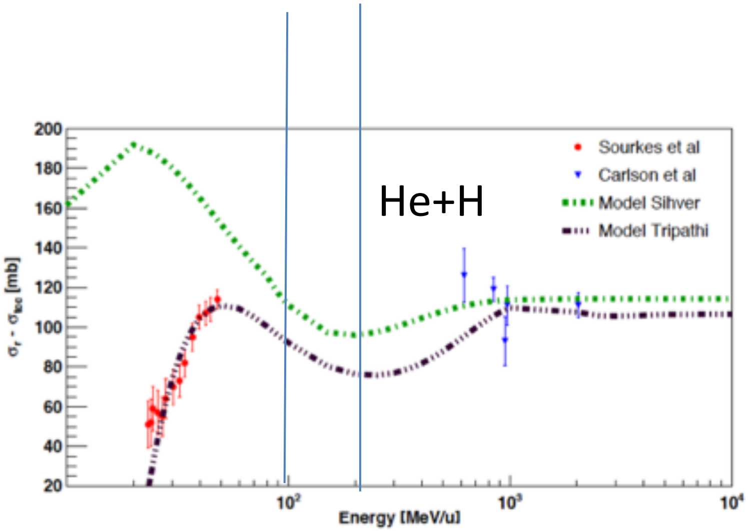
+ MKM

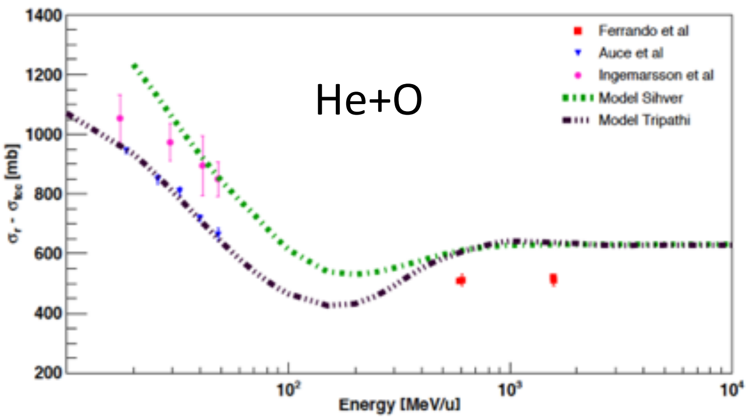


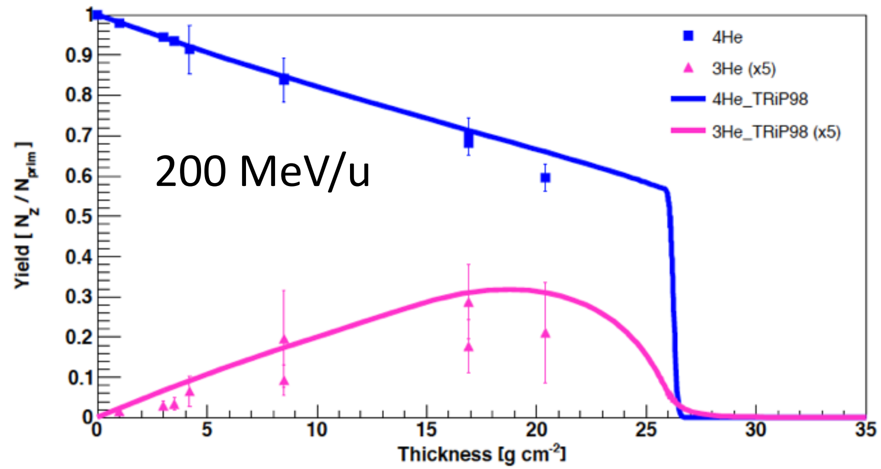


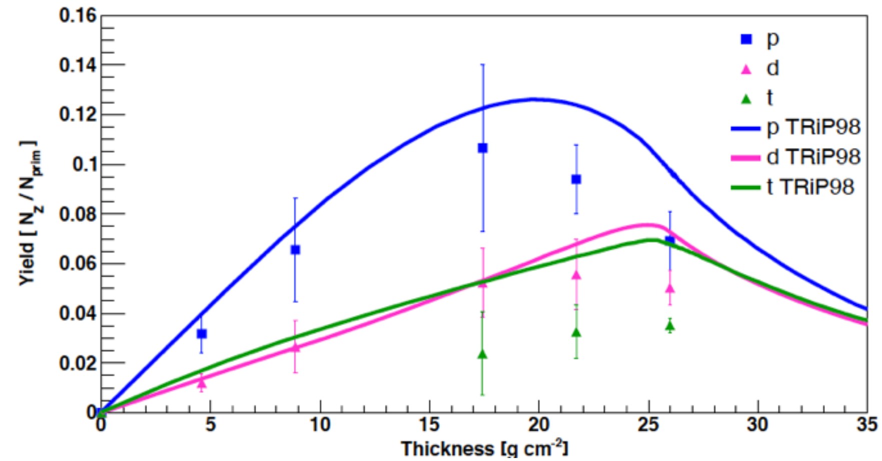
Bio-TPS with ^{4}He

^{4}He beam fragmentation







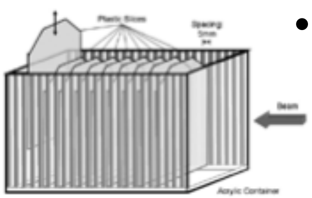


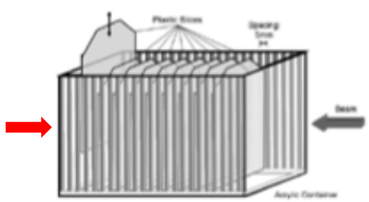
Kraemer et al. Med Phys 2016

Rovituso et al. PMB 2017

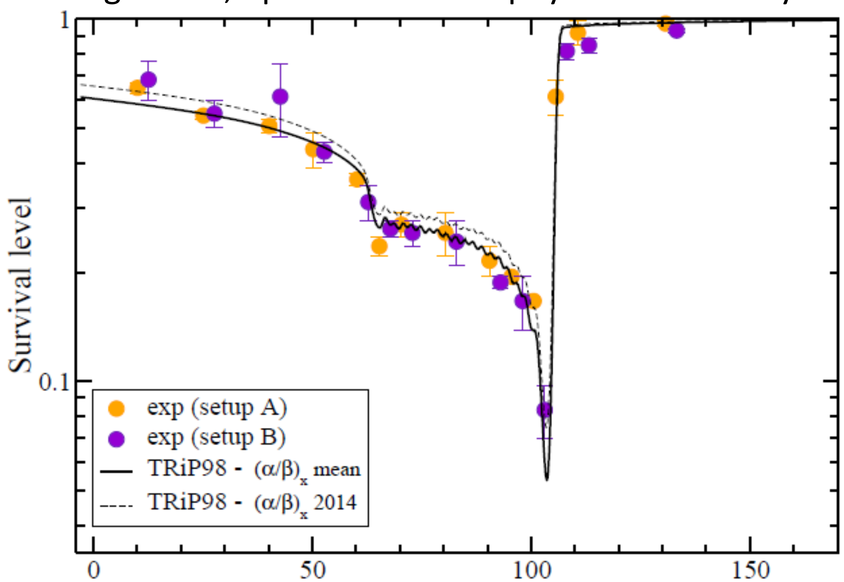
^{4}He biological verification

- New Beam model + LEMIV
    - CHO cells Survival on a He planned extended volume
    - spatial resolution : 2.5 mm



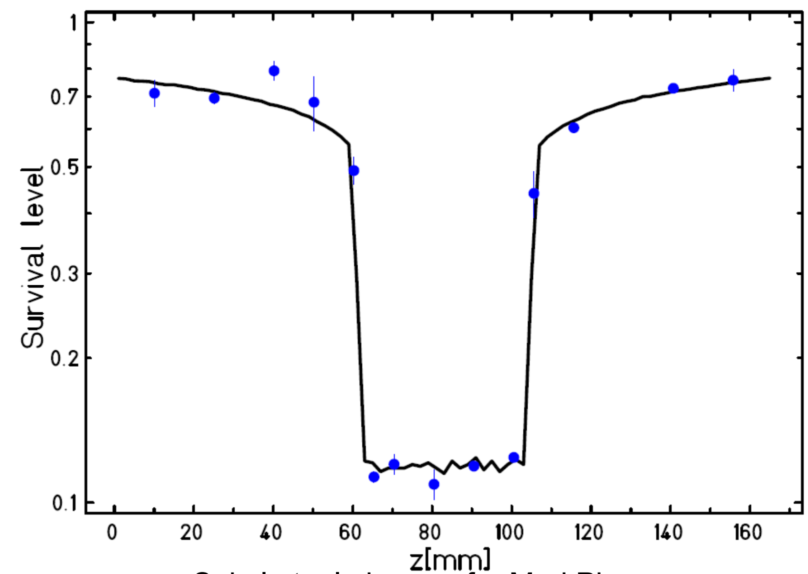


- Single field, optimized on flat physical dose =4Gy



Krämer et.al. Med. Phys. 43, 2016

- 2 Fields bio-optimized (MFO) on uniform survival

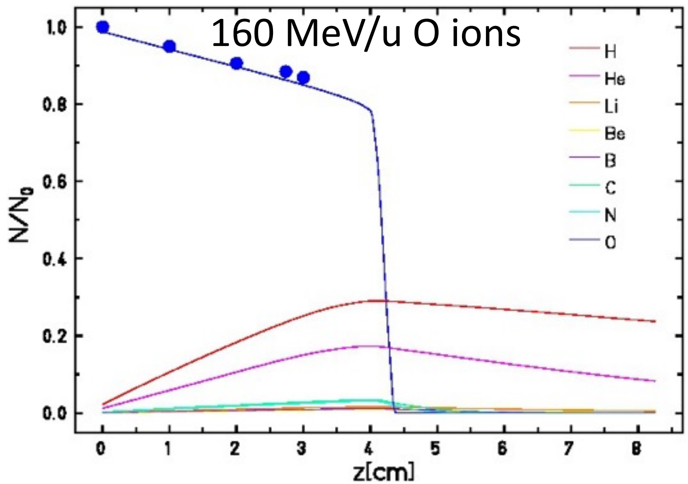


Sokol et. al. in prep for Med Phys.

Bio TPS with ^{16}O

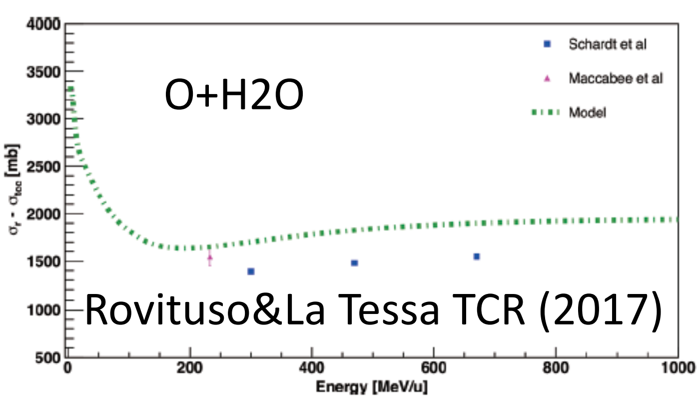
^{16}O beam fragmentation

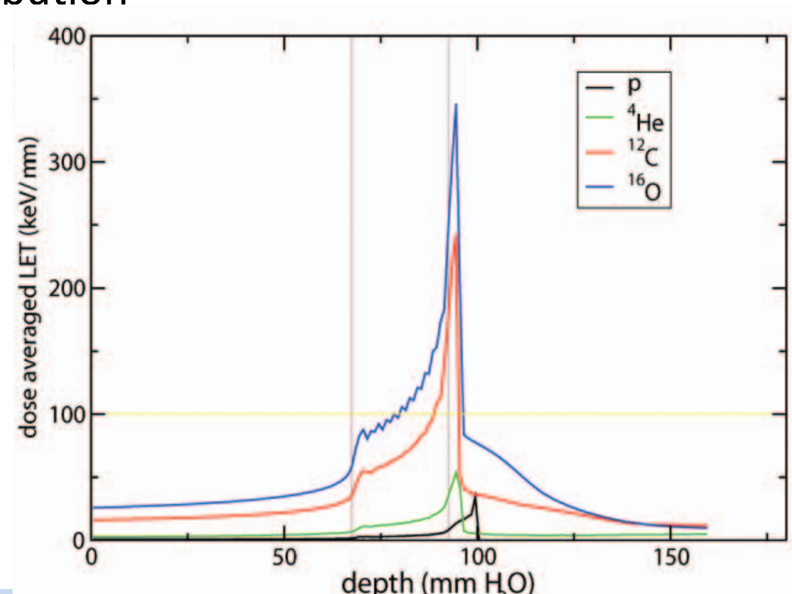
- Large number of fragments
- Few solid data available
- High need of additional data especially for light fragments.
- Relevant for hypoxic targets for broad high LET distribution



(TRiP98) Yield of secondary particles in water

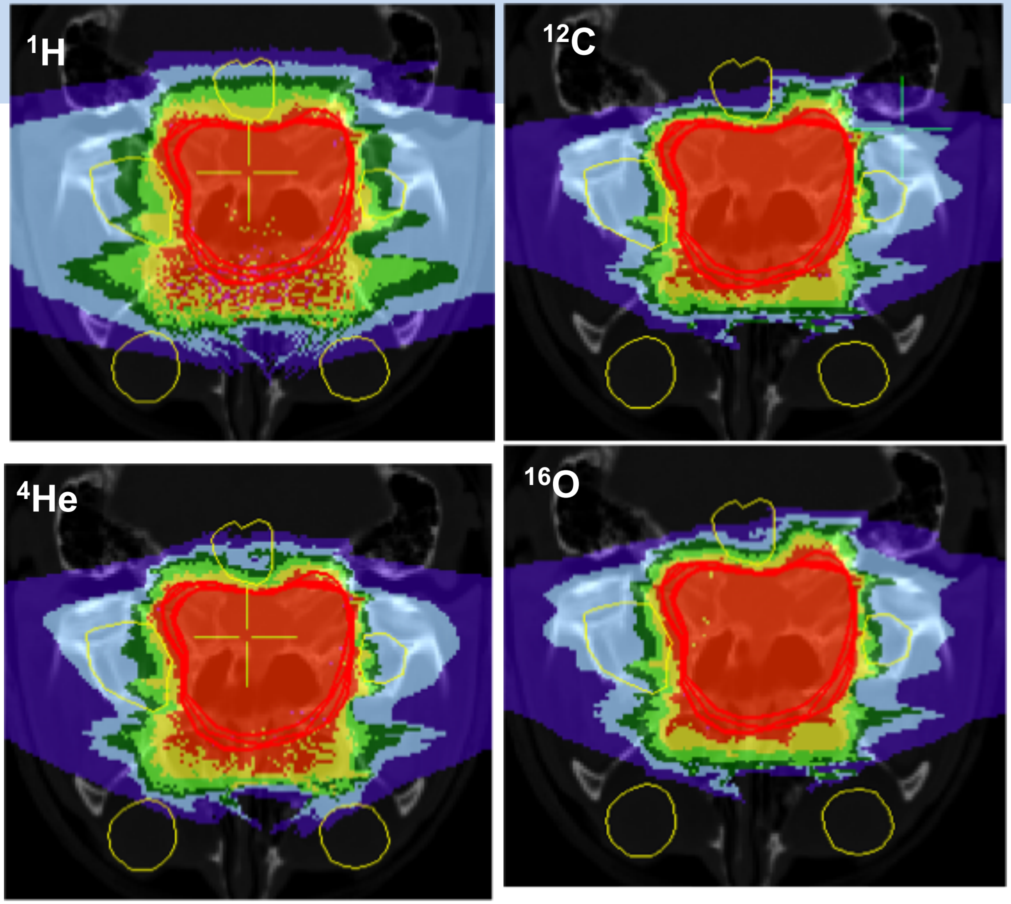
Exp attenuation C. La Tessa (@BNL)





Trento Institute for Fundamental Physics and Applications

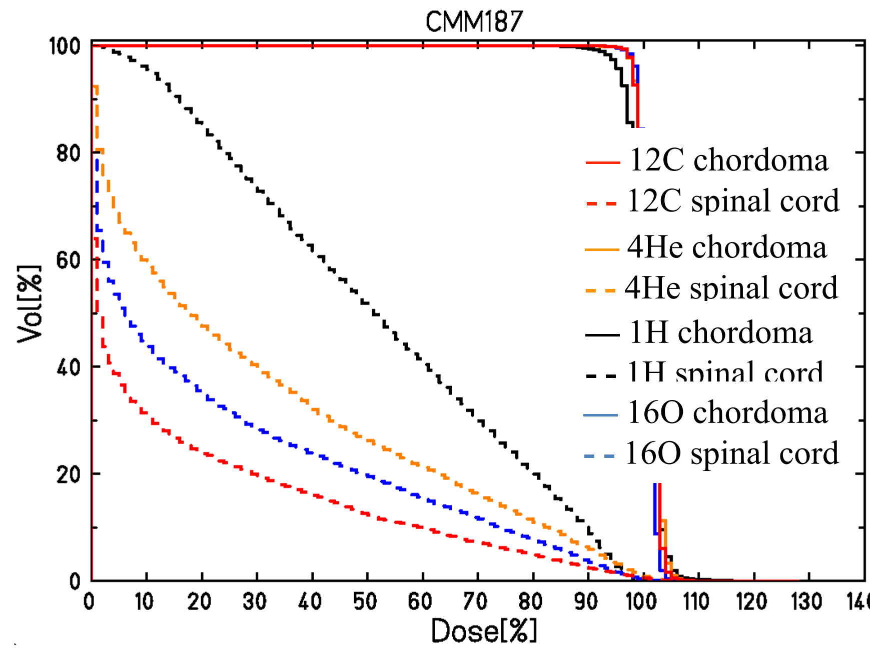
Treatment plans comparison - a patient example



Two-dimensional dose distributions for GSI pilot project patient CT slice
Plans for double-field irradiation of chordoma with ^{1}H, ^{4}He, ^{12}C

R. Grün et al, Med.Phys. 42, 1037 (2015)

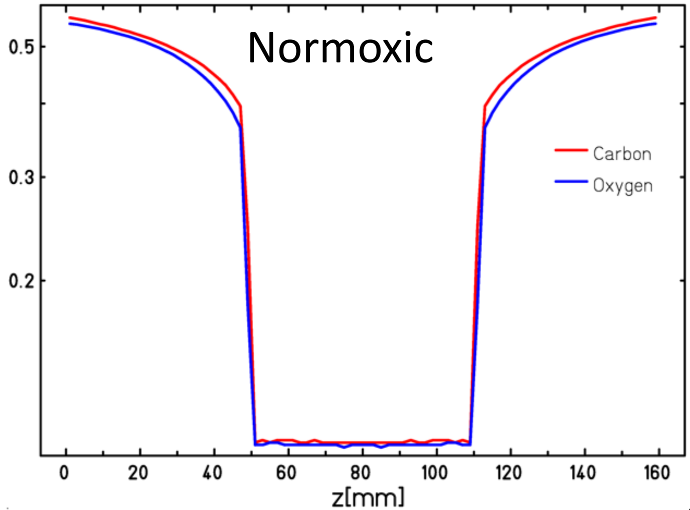
Extended + ^{16}**O** (Sokol et al. PTCOG 2017)

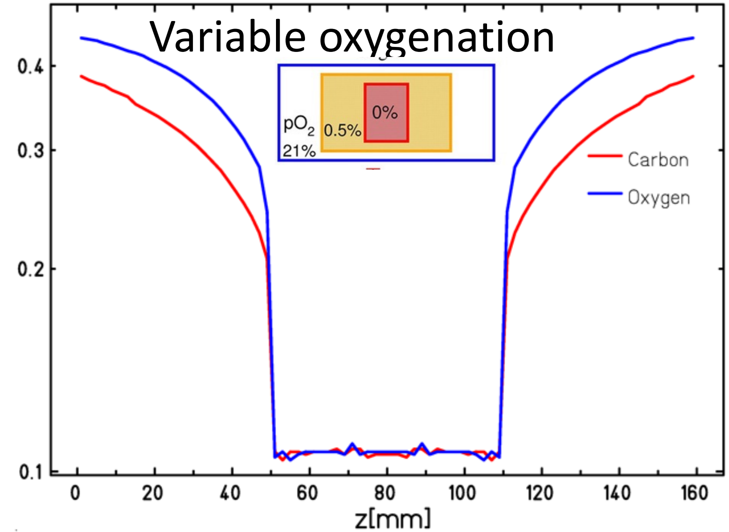


- RBE –weighted dose (LEMIV)
Helium: a promising alternative for carbon and protons

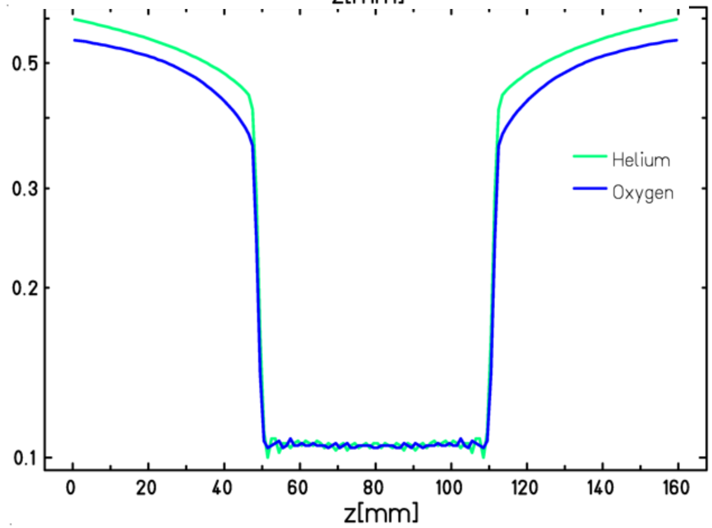
Kill painting with O:
Inverted peak-to-base ratios

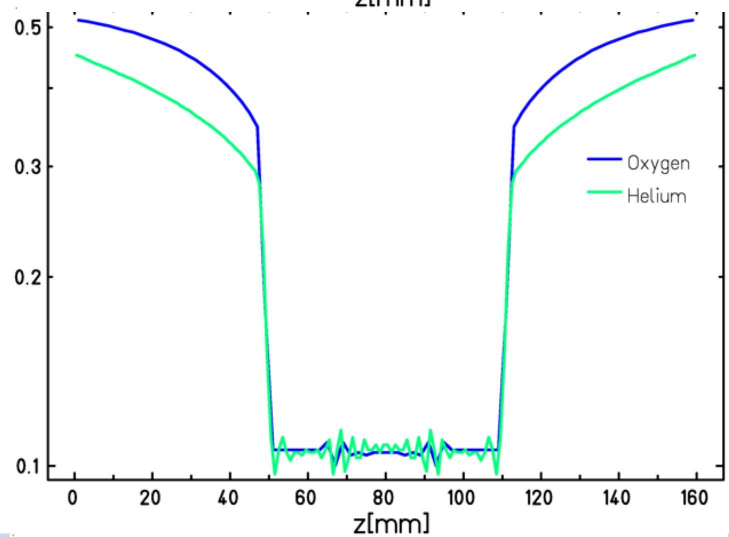
O vs C





O vs He



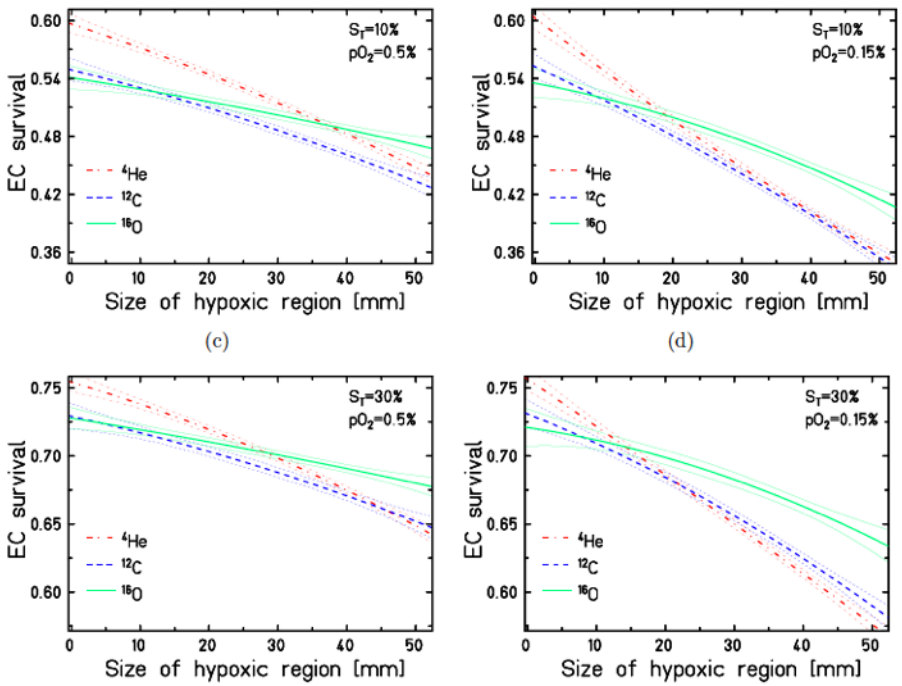


^{16}O beam bio-TPS in hypoxia

Oxygen beams for therapy: advanced biological treatment planning and experimental verification

O Sokol[1], E Scifoni[1,2], W Tinganelli[1,2], W Kraft-Weyrather[1], J Wiedemann[1], A Maier[1], D Boscolo[1], T Friedrich[1], S Brons[3], M Durante[1,2] and M Krämer[1]

Phys Med Biol 2017



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- MRI could be 'game changer' for cardiac arrest survivors
- Synthetic hydrogels aim to repair intestinal injuries
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- From photo, to 3D model, through to wound healing

More news articles

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- Hadron minibeams: a less toxic treatment
- 'Kill-painting' tackles hypoxic tumours
- Introducing new ions into the clinic

RESEARCH

Oct 11, 2017

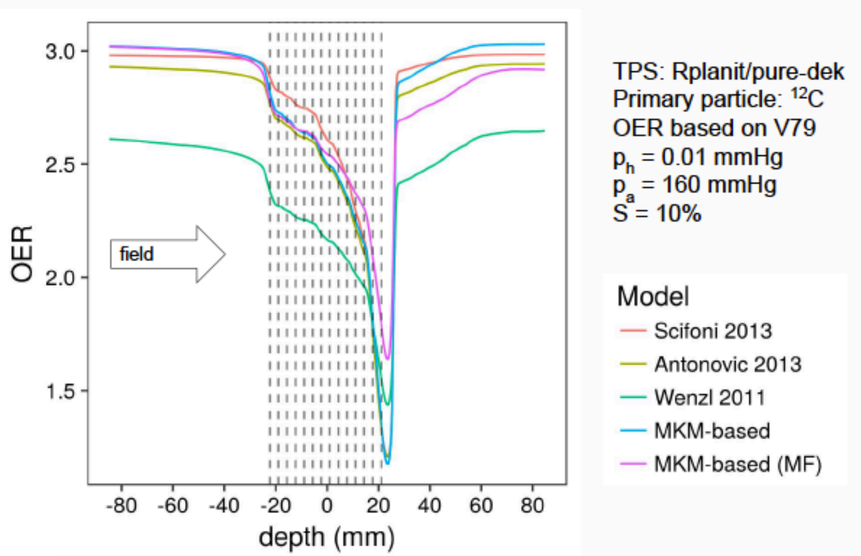
Where will oxygen ion therapy help the most?

As proton and carbon therapy become increasingly entrenched in the cancer treatment armoury, interest is also growing in the use of heavier ions, such as ^{16}O, for therapy. Oxygen ions have a higher linear energy transfer (LET), which increases their relative biological effectiveness (RBE) and provides more effective tumour kill, particularly for hypoxic targets.

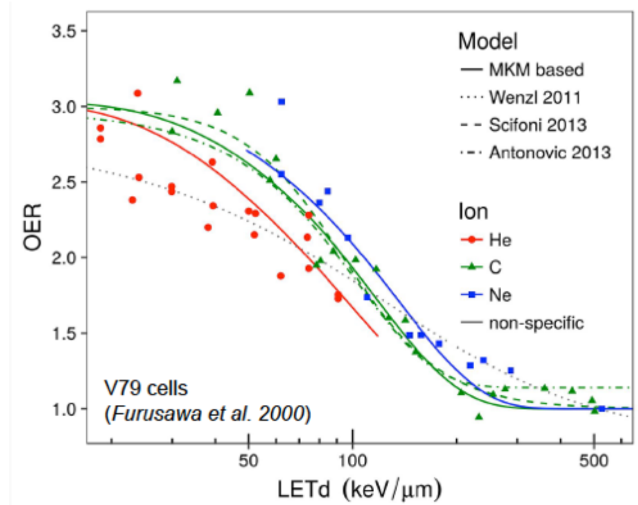
High-LET radiation, however, also increases RBE in surrounding tissue, while increased fragmentation can damage normal tissue surrounding the target. To investigate these trade-offs, researchers from the GSI Helmholtz Centre for Heavy Ion Research and the Trento Institute for Fundamental Physics and Application have performed experimental verification of biologically optimized treatment plans, and determined the range of plans where ^{16}O ions could provide benefit over lighter particle beams (*Phys. Med. Biol.* **62** 7798).

- Differential advantage of Oxygen beams with respect to other ions is a
- Trade-off between better **LET distribution** and worse **Fragmentation** in entrance and tail. Thus fragmentation description is crucial

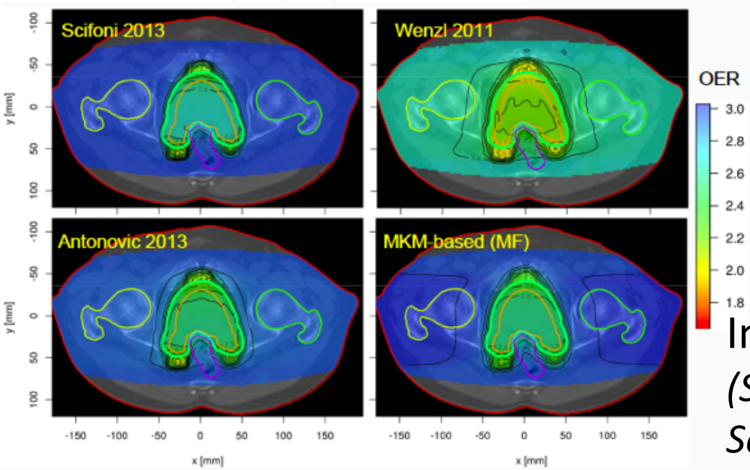
OER Modeling with modified MKM (RPlanIT)



- *Development of a new mechanistic model based on MKM, explicitly accounting for partcle dependence and dose fraction*



- *comprehensive inclusion of OER from different models into RPlanIT and systematic comparison*



Impact of different OER models on a prostate tumor

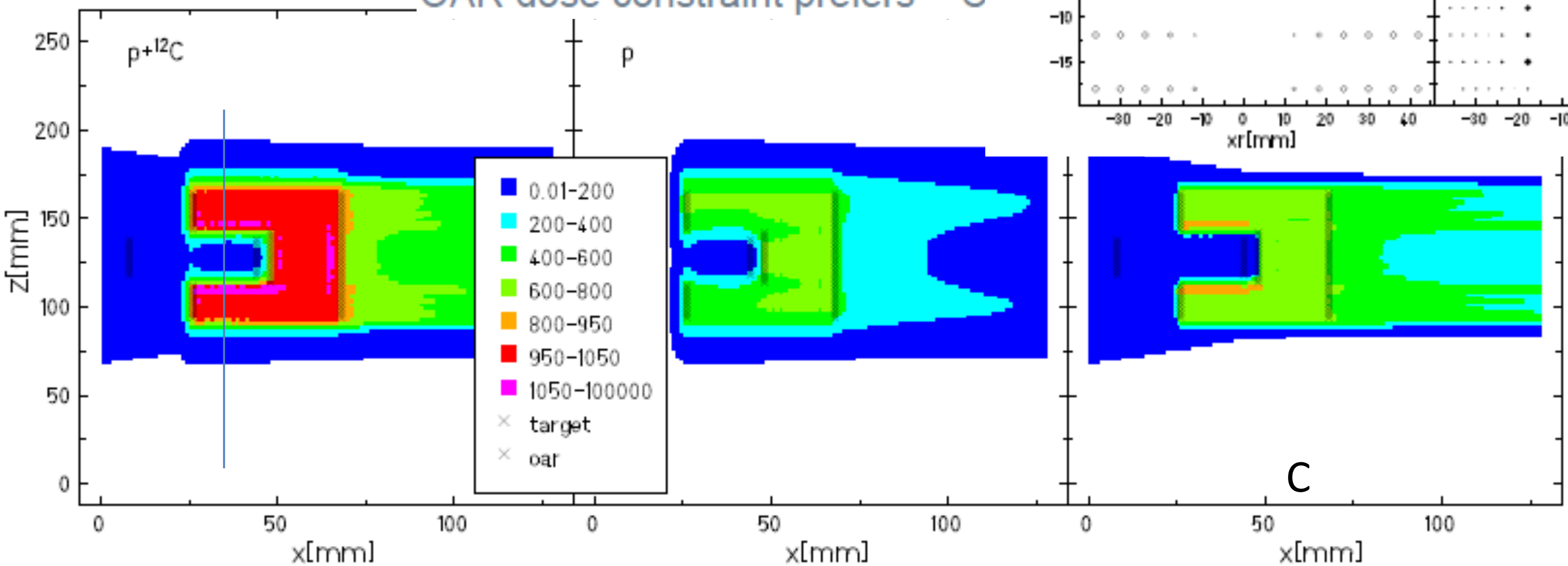
(Strigari,Attili et al.PMB 2017)

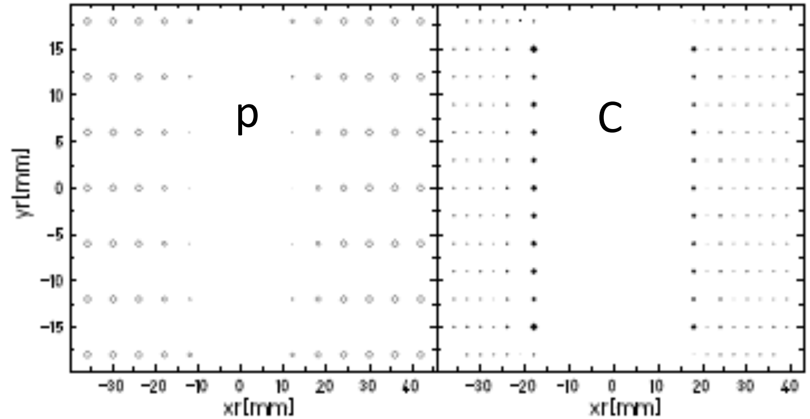
See also Bopp et al. 2016

Multi-ion treatment planning

- TRiP version for a biologically optimised multi-ion treatment plan
- TPS enhanced to handle more modalities at once

OAR dose constraint prefers ^{12}C





Switching times ~minutes

Krämer, Scifoni, ,Schmitz, Sokol, Durante, *EPJD 68 (2014)*

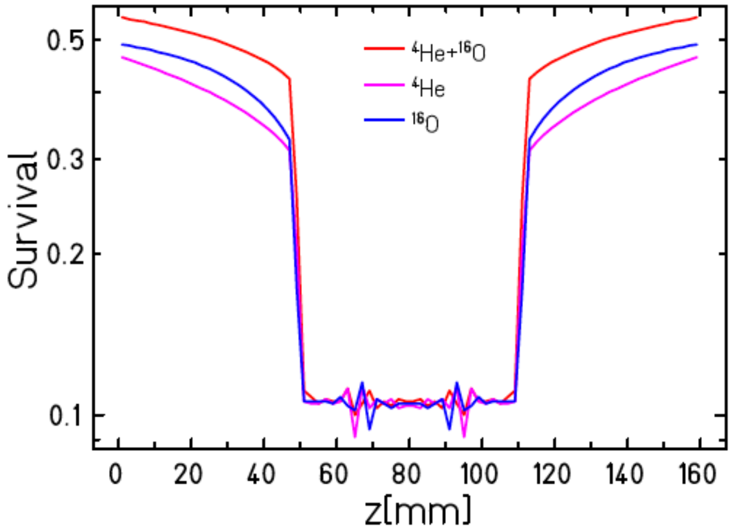
Multi-ion + Hypoxia

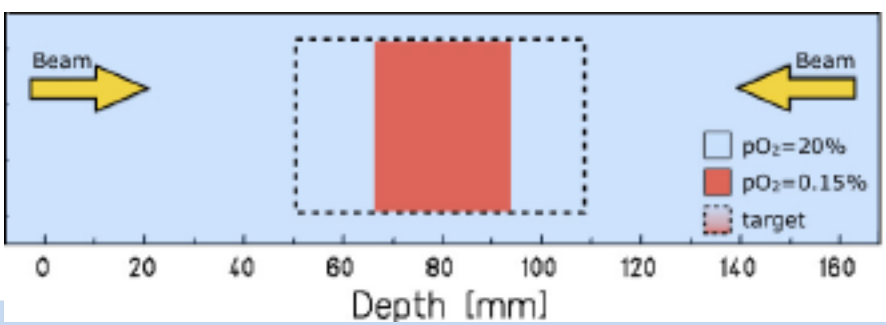
T1.2

Towards the multi-ion treatment planning with ^{16}O beams

O. Sokol[1,2], E. Scifoni[1,3], S. Hild[1,3], M. Krämer[1,2], and M. Durante[2]*

GSI Sci Rep. (2017)
Sokol et al. PTCOG '17





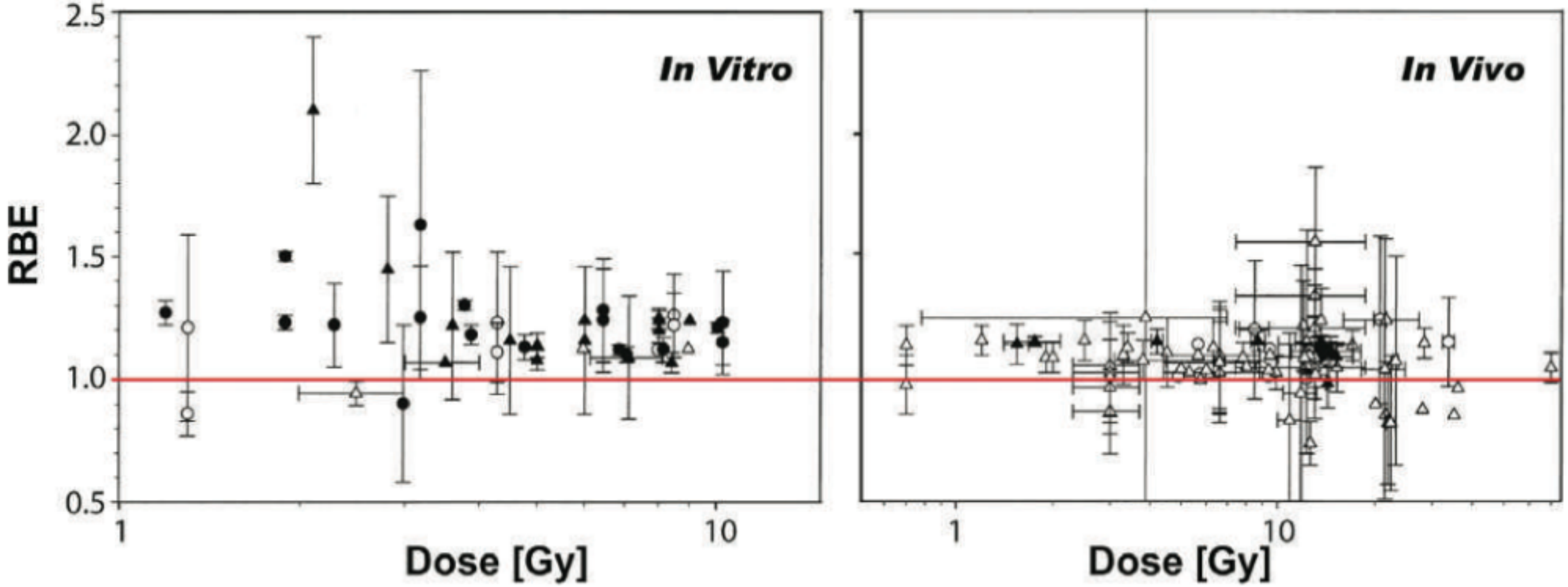
Survival distributions for single-ion double-field optimizations (^{4}He + ^{4}He and ^{16}O + ^{16}O), and multiion quadruple-field optimization (^{16}O + ^{16}O + ^{4}He + ^{4}He).

pO_2 =20%: z < 6.6 & z > 9.4
pO_2 = 0.5%: 6.6 < z < 9.4

Depth (mm)	EC survival, %		
	O	He	O+He
5	48.4	45.4	54.3
45	34.3	32.3	43.5

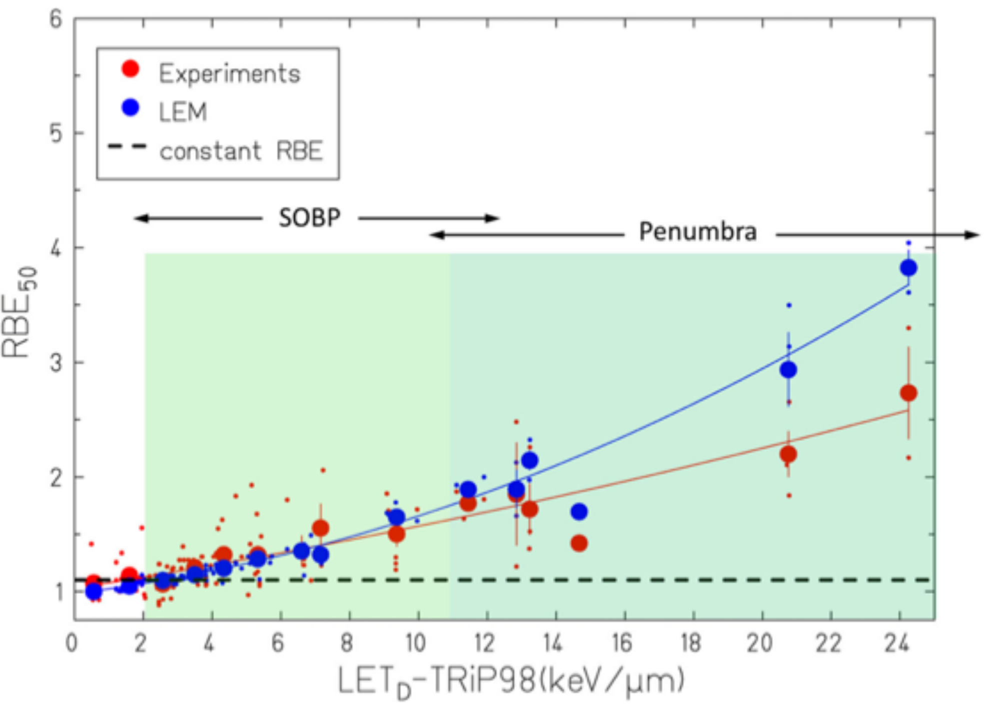
BioTPS with protons

RBE=1.1 for protons in radiation therapy
(ICRU recommendations)

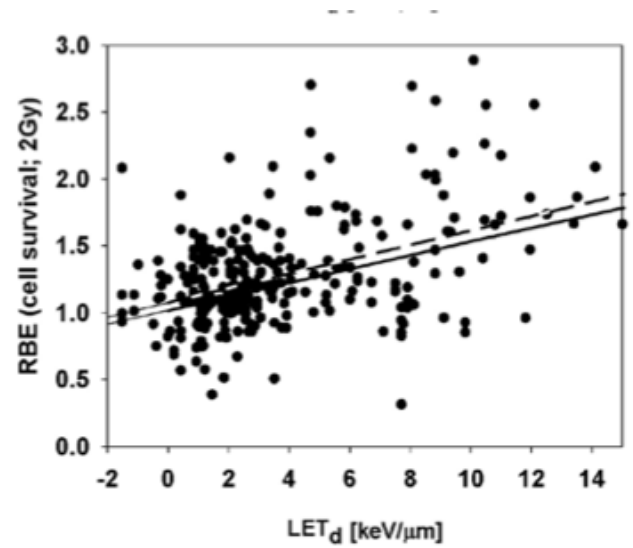


Paganetti 2002 PMB

RBE(LETd) for protons

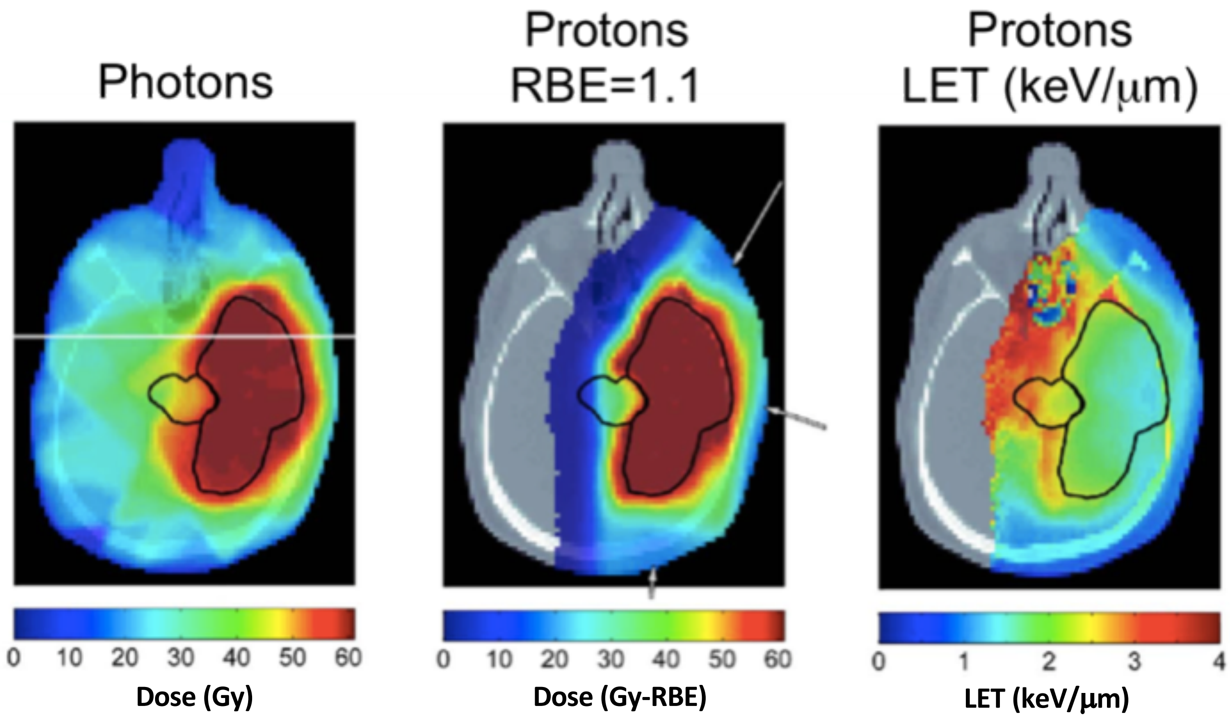


Gruen et al. 2017



Paganetti. 2014

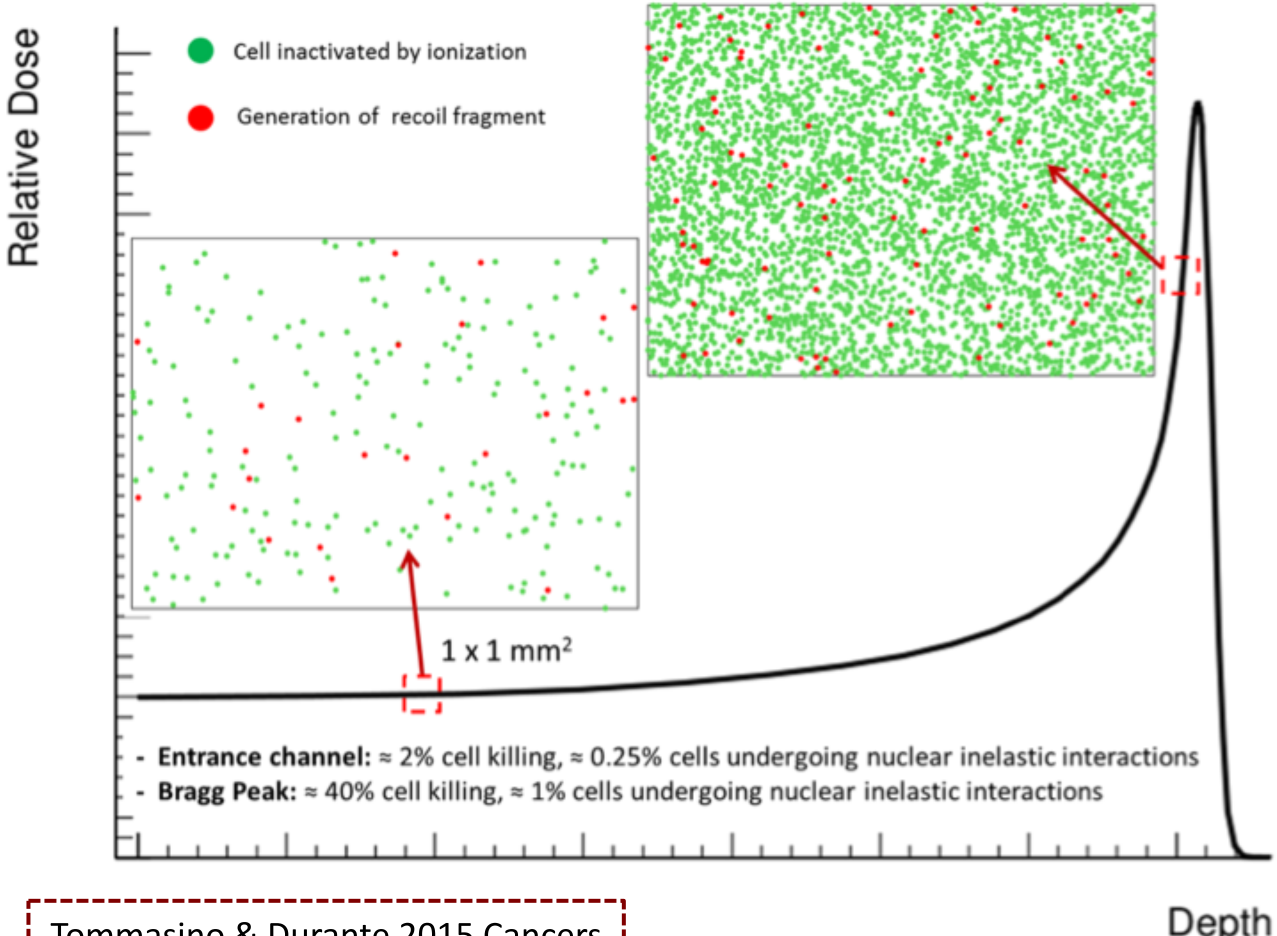
…are deviations from 1.1 of **clinical relevance**?



- **Potential improvements offered by biological optimization**
- **Possible bias when neglecting variable RBE**
- **Sensitivity to RBE model**
- **Only 3 patients considered!**

Wedenberg 2014 Med Phys

Role of Target fragmentation in proton therapy



Tommasino & Durante 2015 Cancers

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**

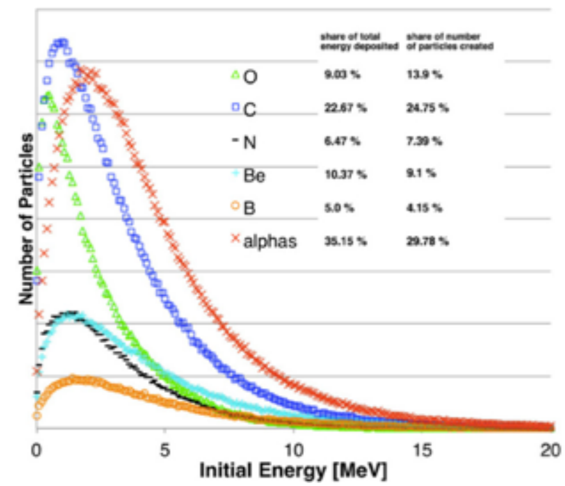
↓

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

Role of Target fragmentation in proton therapy

Differently from Projectile fragments, their Energy distribution being peaked at very low E
Combines with the peak of RBE at low E

Fragment	E (MeV)	LET (keV/μm)	Range (μm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

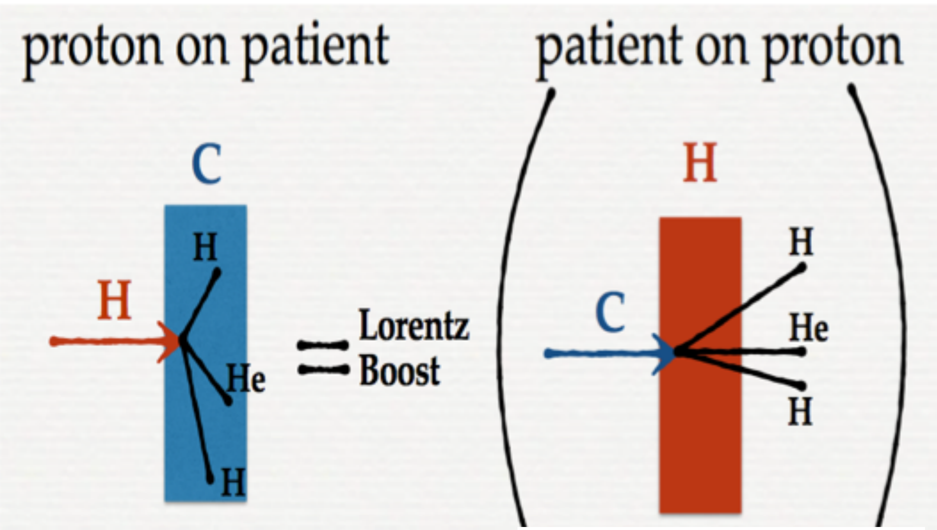


Grassberger et al. 2011

Tommasino & Durante 2015 Cancers

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

FOOT exp: Inverse kinematic approach



Fragments with low energy and short range

Fragments with higher energy and longer range

courtesy of V.Patera

CSN-3

- Protons @ E_{kin}= 200 MeV (β~0.6) on a "patient" (98% C, O, and H nucleus)

- can be replaced by ^{16}O, ^{12}C ion beams (E_{kin} ~ 200 MeV/n β~0.6) impinging on a target made of protons
- by applying the Lorentz transformation (well known β) it is possible to switch from the ***lab. frame*** to the ***patient frame***

Expected results from FOOT

This approach allows for a robust measurement program:

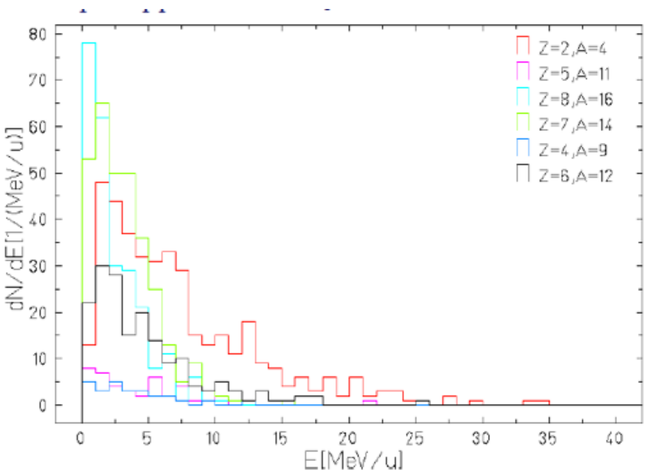
a) Target fragmentation of p on O,C @100-200 MeV/u

b) Projectile fragmentation of O on C @200-400 MeV/u

c) Projectile fragmentation of C on C @200-350 MeV/u

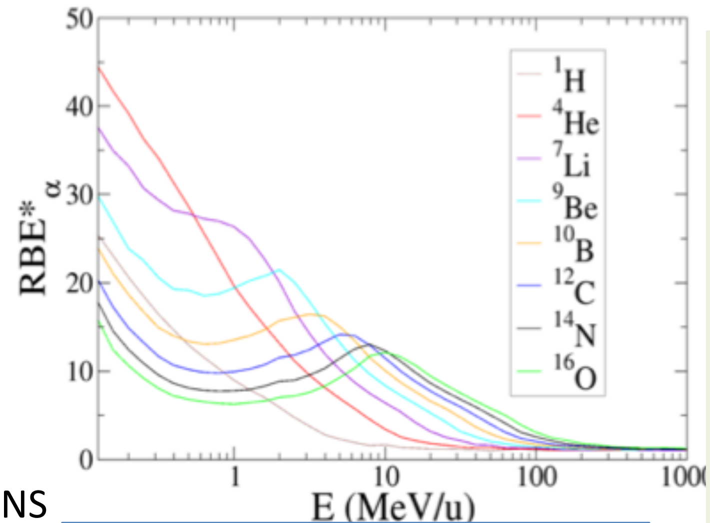
d) Evaluation of the β+ emitters production (8B production) from C,O on C @200-400 MeV/u

Initial RBE description with initial (MC) cross sections for target fragments



G.Petringa LNS

Simulated spectra for p@160MeV provided wih GEANT4 and SHIELD-HIT



Typical single particle RBE* distribution input in TRiP98 (from LEM)

Resolution requirement for FOOT.

Initial figures for p:

- spectrum E resolution ≈1 MeV/u
- cross section< 5%
- charge ID ~ 2-3%
- Isotopic ID ~ 5%

$$\langle\xi\rangle = \frac{C}{D_{abs}} \sum_{i} N_i \sum_{Z,E} \frac{dN}{dE}(E_0^i, E,, Z, z)\Delta E \frac{dE}{dz}(Z,E)\xi(Z,E)$$

Beam mixing algorithm in TRiP

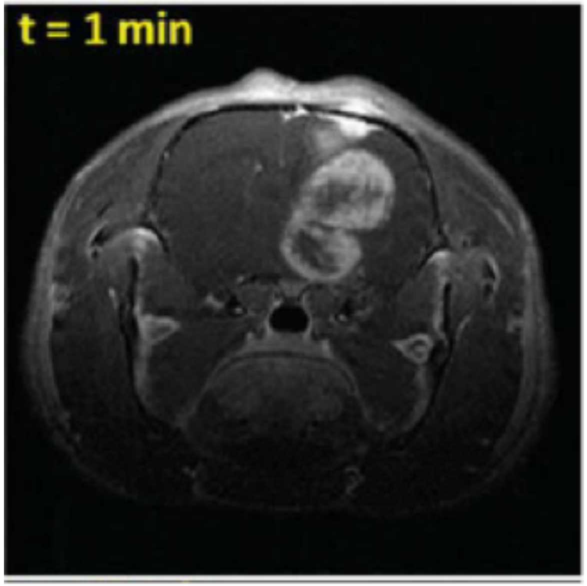
$\xi = \alpha$ or $\sqrt{\beta}$

Concluding..

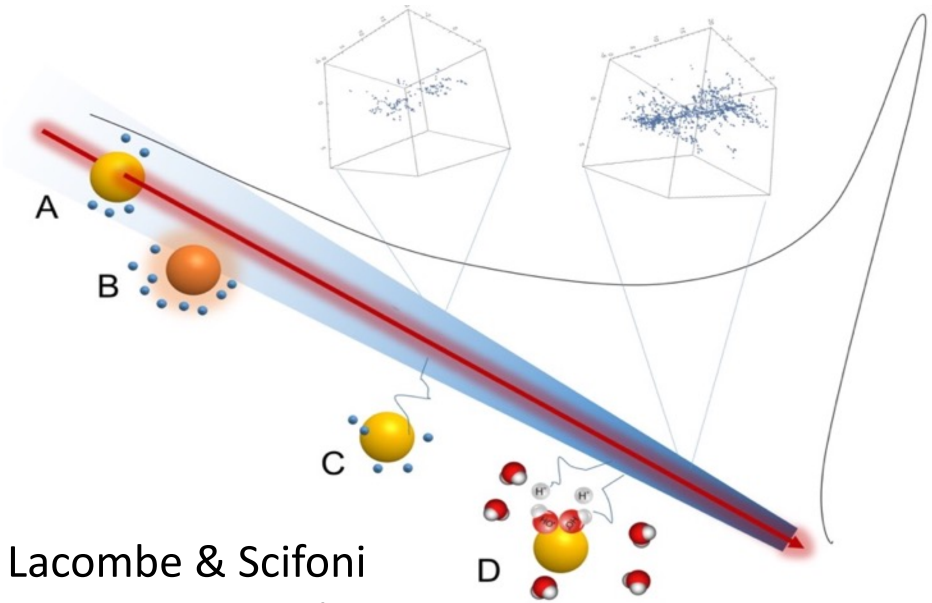
Radiosensitization

Sensitized regions (e.g. with Metallic Nanoparticles)
MRI can visualize differential uptake with striking resolution

also in this case DEF would depend on the LET
DEF(LET, C), for differential uptake...



GdNP distribution in mouse tumor
Tillement et al.



Lacombe & Scifoni
Cancer Nanotech. 2017

LET dependence of radiosensitization?

Nuclear process driven radiosensitization?

SCIENTIFIC REPORTS

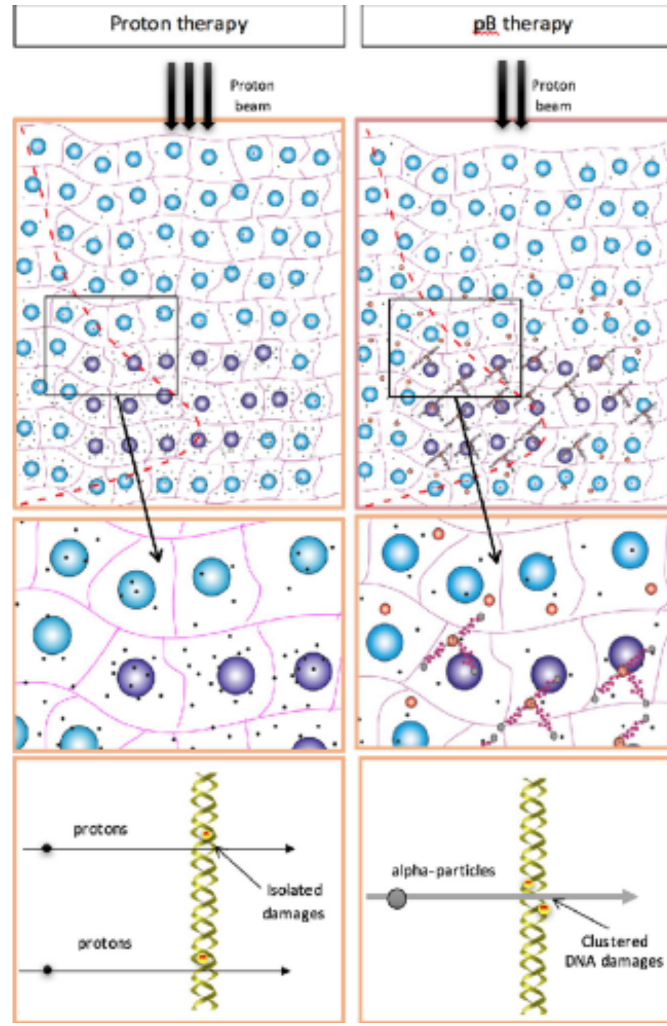
OPEN

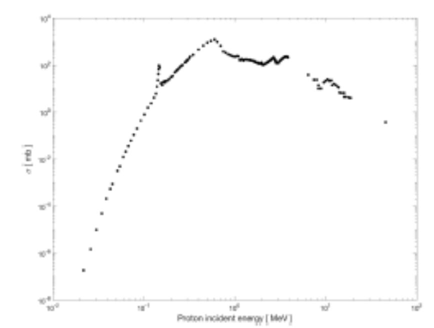
First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness

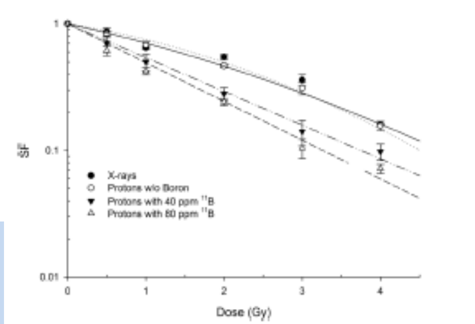
ceived: 26 January 2017
cepted: 27 December 2017
blished online: 18 January 2018

G. A. P. Cirrone[1], L. Manti[2,3], D. Margarone[4], G. Petringa[1,5], L. Giuffrida[4], A. Minopoli[2], A. Picciotto[6], G. Russo[7,1], F. Cammarata[7,1], P. Pisciotta[1,5], F. M. Perozziello[2,3], F. Romano[8,1], V. Marchese[1], G. Milluzzo[1,5], V. Scuderi[1,4], G. Cuttone[1] & G. Korn[4]

- Large SER found: 1.46!!
- **Evidence of DNA damage**
- Evidence of **complex** DNA damage= high LET signature
- Despite low number of produced alphas







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Trento Institute for Fundamental Physics and Applications

Advancing biological treatment planning: a graphical summary

Physics

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

TPS

Radiobiology

(= Biological effects + micro/nanoscale physics)

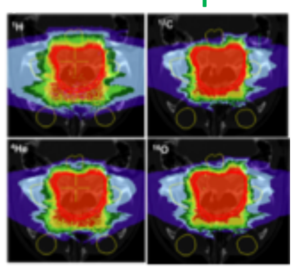
- RBE (eg. LEMx, MKM)
- OER
- DEF

Beamline specifics

Patient Imaging data

Including intratumor heterogeneity

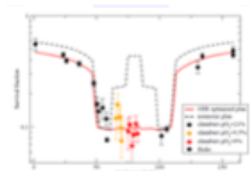
Effective Dose profile



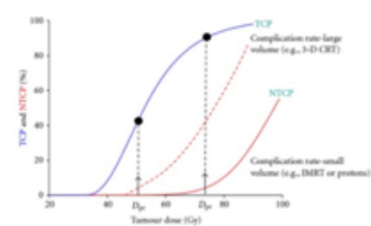
Verification

advanced beam monitoring

"Bio"-dosimetry



Clinical Impact



TCP/NTCP

Summary

- Active scanned Particle therapy offer a maximum flexibility for bio-optimization of a target
- Biologically optimized TPS needs accurate physics description e.g. for exploiting the different ion beams merits.
- **Monte Carlo simulation softwares** can provide input on several scales
- New Ions may present specific biological advantages for selected cases or fractions
- Use of larger LET ions (**^{16}O**) quantitatively assessed and encouraged for hypoxic boosts
- Multi-ion optimization may exploit combination of different ions peculiarities for specific biological scenarios

...in case you didn‘t get enough:

(a few) **References - general**

- Durante M, Orecchia R, Loeffler JS (2017) Charged-particle therapy in cancer: clinical uses and future perspectives. Nat Rev Clin Oncol. doi: 10.1038/nrclinonc.2017.30
- Schardt D, Elsässer T, Schulz-Ertner D (2010) Heavy-ion tumor therapy: Physical and radiobiological benefits. Rev Mod Phys 82:383–425.
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- Tommasino F, Durante M (2015) Proton radiobiology. Cancers (Basel) 7:353–381.
- Tommasino F, Scifoni E, Durante M (2015) New Ions for Therapy. Int J Part Ther IJPT-15-00027.1

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Thanks for your attention!