EURADOS SCHOOL 2022 – Belgrade 20-24/6

New developments in radiotherapy treatment planning with particle beams:

Advancing in Biological Treatment Planning

Emanuele Scifoni

BiMeR Bio-Medical Radiation physics lab

TIFPA Trento Institute for Fundamental Physics and Applications

INFN

UNIVERSITÀ DI TRENTO

Outline

- **Basics of Biological Treatment Planning with Particle beams**

- **Latest Advancements:**
  - **Multiion/Multifraction**
  - **NTCP based planning**
  - **FLASH planning (outlook)**

INFN TIFPA Trento Institute for Fundamental Physics and Applications

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 a proper overall biological effect.

INFN TIFPA Trento Institute for Fundamental Physics and Applications

Dose modifying factors

- in general a „dose modifying factor“ (DMF) is defined as a ratio of doses compared to normal conditions (n.c.) giving **a Same biological effect**

-more properly called `Dose effectiveness factor (DEF)-

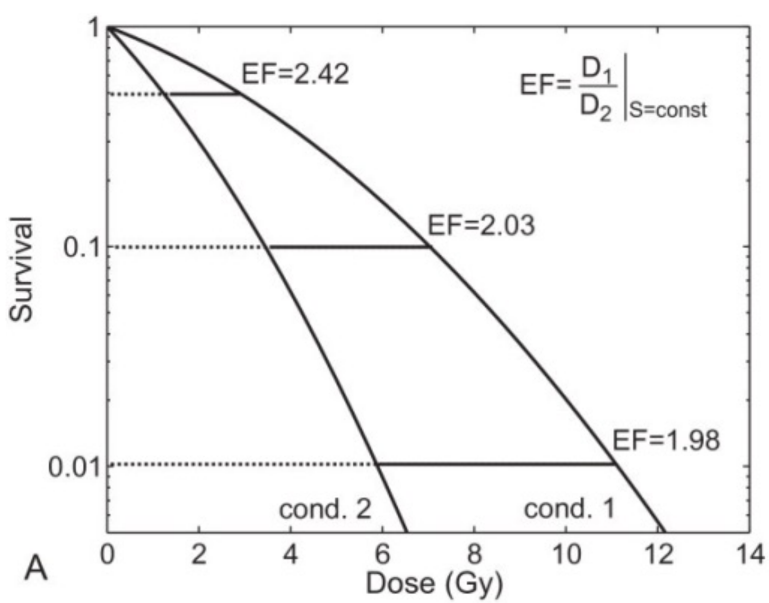
$$DEF = \left. \frac{D_{special\,conditions}}{D_{n.c.}} \right|_{same\,effect(S)} \quad ; \quad DEF([C]) = \left. \frac{D([C])}{D_{n.c.}} \right|_{same\,effect(S)}$$

- Can be a radiation quality related feature like **RBE**, or a more target related property (like e.g. **OER**)

- it is called properly a „dose modifying factor“ if independent on S (or D)

Depending on several parameters, in particular LET

$$DEF(LET,[C]) = \left. \frac{D(LET,[C])}{D_{n.c.}} \right|_{same\,effect(S)}$$



Wenzl&Wilkens 2011

The Optimization problem

Optimal particle numbers $\vec{N}_{opt}$ **for all rasterpoints in order to obtain a 3D dose distribution that respects the constraints imposed.**

TRiP98 cost function $\longrightarrow$ **formalizes the treatment goals**:

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

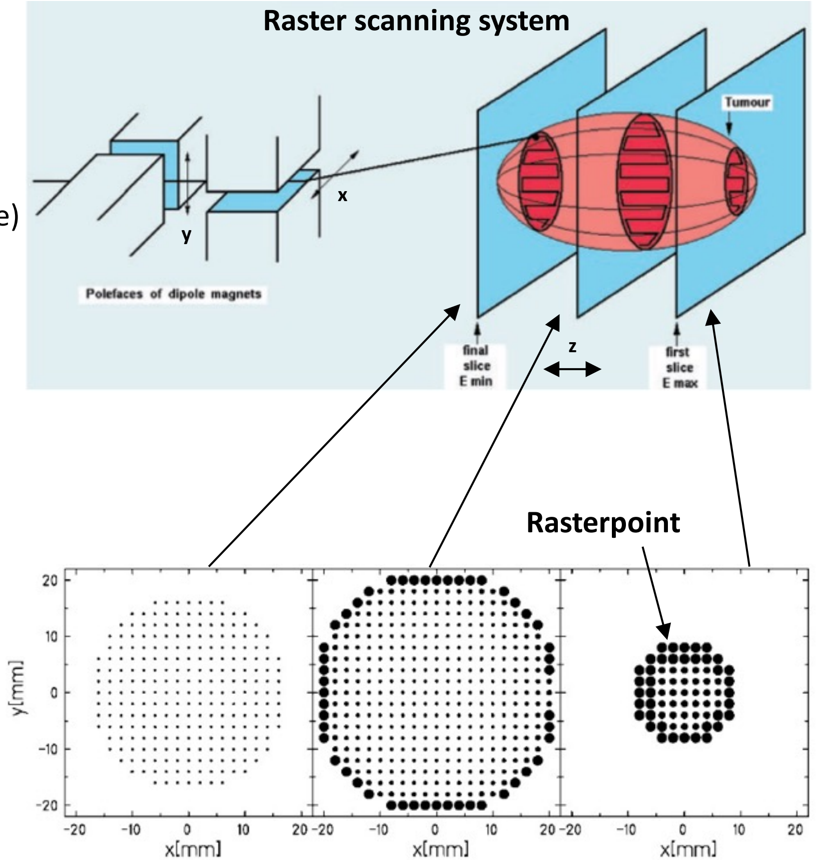
Target (uniform dose)

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

OAR (maximum dose)

Where in order to account for bio effects, the "bio" dose is obtained through scaling the physical dose by the specific DMF

Aim: searching the **minimum** of $\chi^2(\vec{N})$ for **all fields simultaneously (multiple field optimization)**.



Krämer et al. (2000)

Krämer et al. (2000)

Treatment Planning Codes for Particles

Some examples including Z>1:

Analytical

- TRiP98: first for Z>1
- MatRad
- FROG (GPU based)
- RPLANIT/PLANKIT

Monte Carlo

- FRED (GPU based)
- FLUKA
- TOPAS
- RayStation (comm.)

Nanodosimetry based treatment planning

Research Article

Nanodosimetry-Based Plan Optimization for Particle Therapy

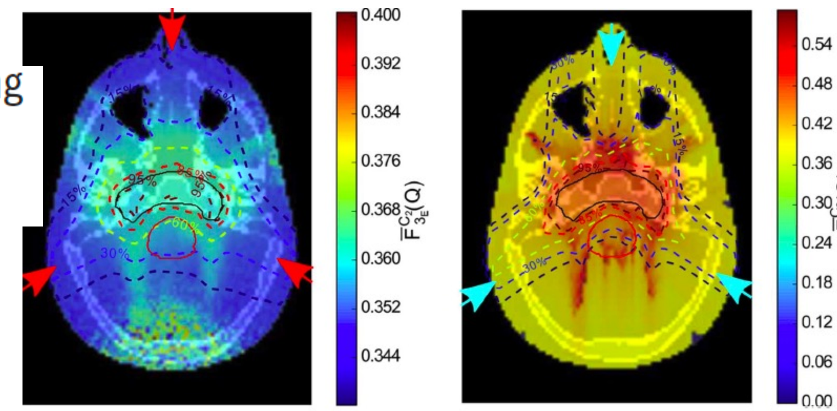
Comp Math Meth Med 2015

Margherita Casiraghi[1] and Reinhard W. Schulte[2]

Fast calculation of nanodosimetric quantities in treatment planning of proton and ion therapy

José Ramos-Méndez[1,5], Lucas N Burigo[2,3], Reinhard Schulte[4], Cynthia Chuang[1] and Bruce Faddegon[1]

PMB 2018



TOPICAL REVIEW

Applications of nanodosimetry in particle therapy planning and beyond

PMB 2021

Antoni Rucinski[1,*], Anna Biernacka[2] and Reinhard Schulte[3]

The kill painting basic idea

optimized quantity:

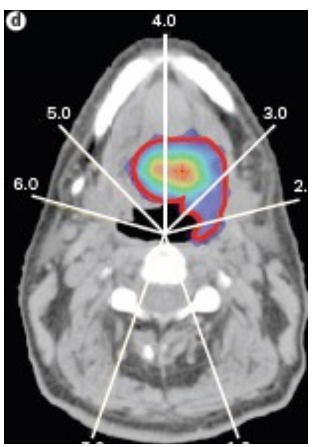
SCIENTIFIC REPORTS

OPEN **Kill-painting of hypoxic tumours in charged particle therapy**

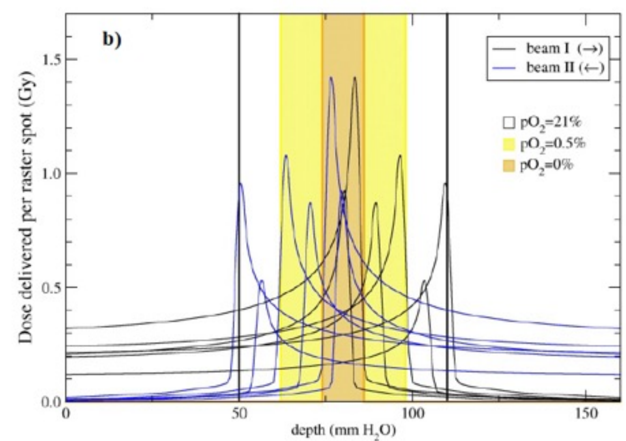
Walter Tinganelli[1,2], Marco Durante[1,3], Ryoichi Hirayama[2], Michael Krämer[1], Andreas Maier[1], Wilma Kraft-Weyrather[1], Yoshiya Furusawa[2], Thomas Friedrich[1] & Emanuele Scifoni[1]

Received: 03 July 2015

- Absorded Dose
- Biologically effective Dose (RBE weighted)
- Biologically isoeffective Dose in the local microenvironment (OER weighted)



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



Tinganelli et al. Sci Rep. 2015

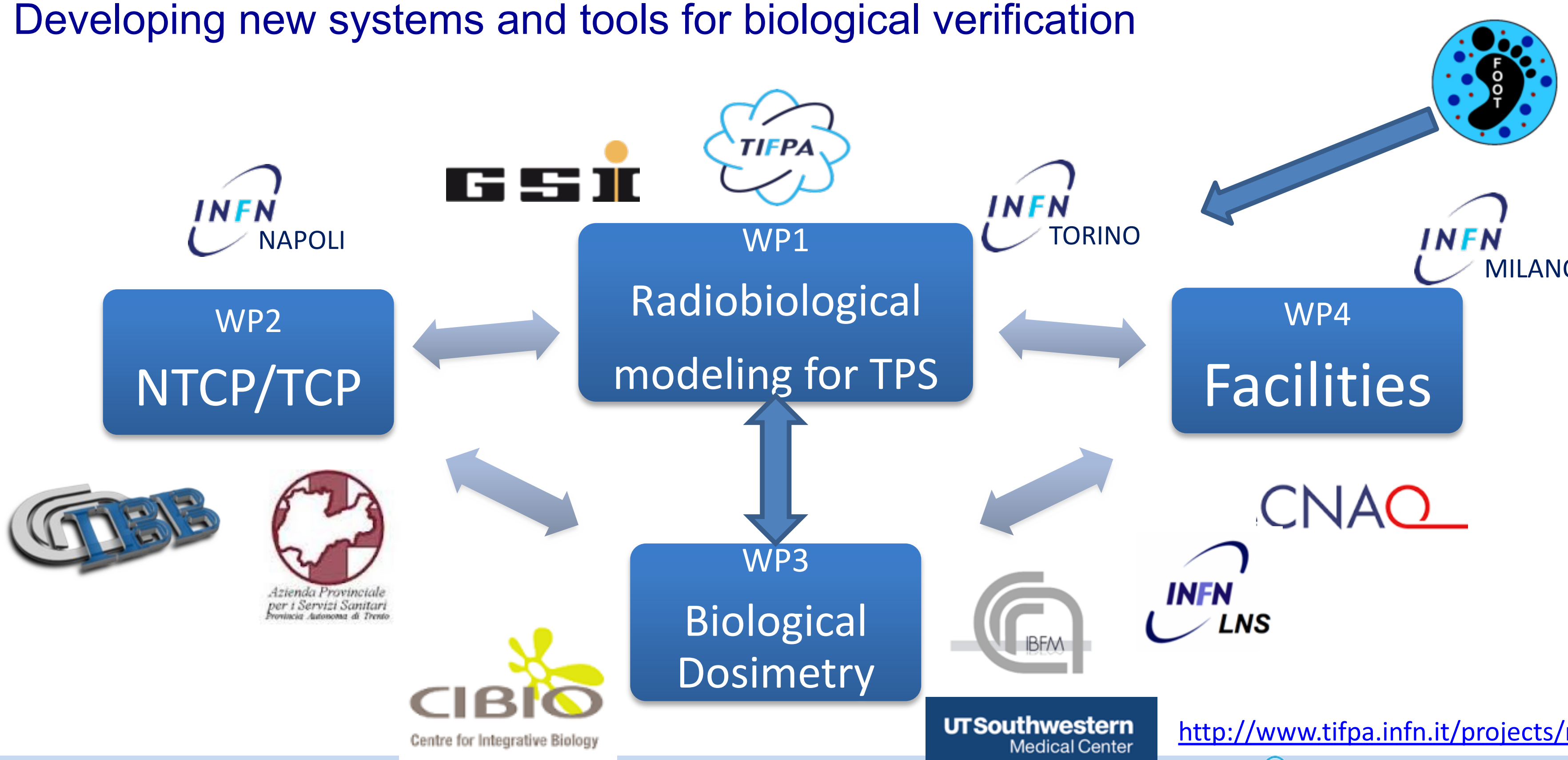
Trento Institute for Fundamental Physics and Applications

MoVe IT

Modeling and Verification for Ion beam Treatment planning

INFN Network - Call group V - funded 2017-2020- 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

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)

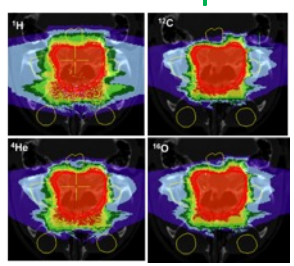
- RBE (eg. LEMx, MKM)
- OER
- any other DMF…

TPS

Beamline specifics

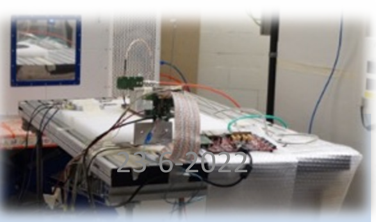
Patient Imaging data
Including intratumor heterogeneity

Effective Dose profile

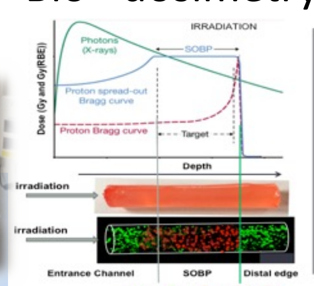


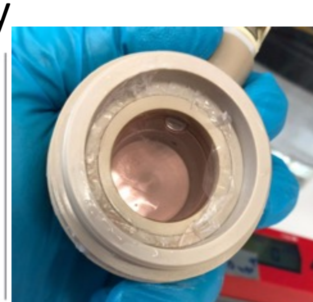
Verification

advanced beam monitoring

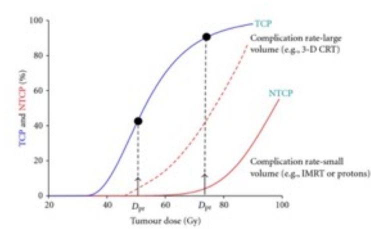


"Bio"-dosimetry





Clinical Impact

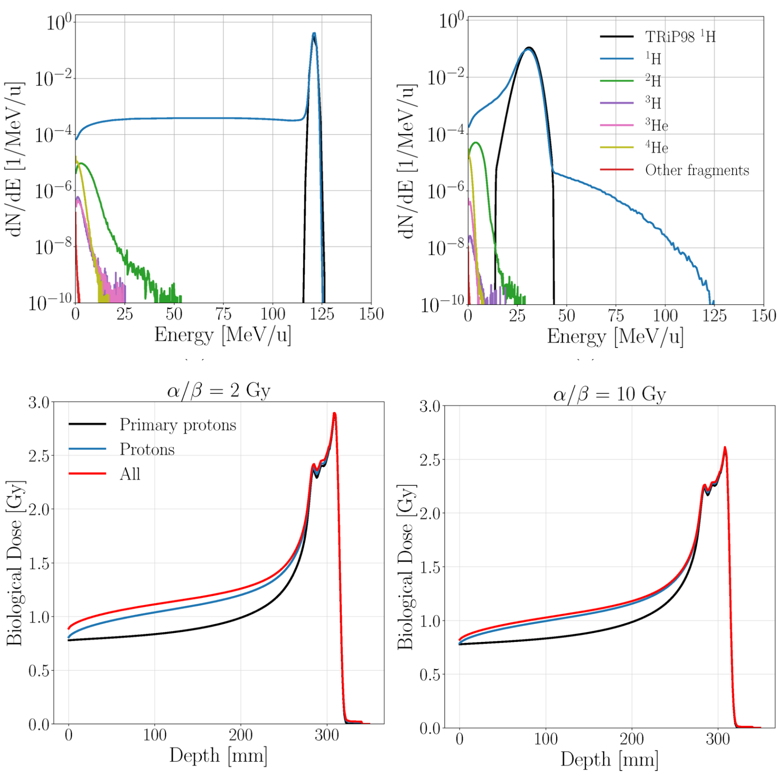


TCP/NTCP

INFN
TIFPA
Trento Institute for Fundamental Physics and Applications

Biological impact of fragmentation

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



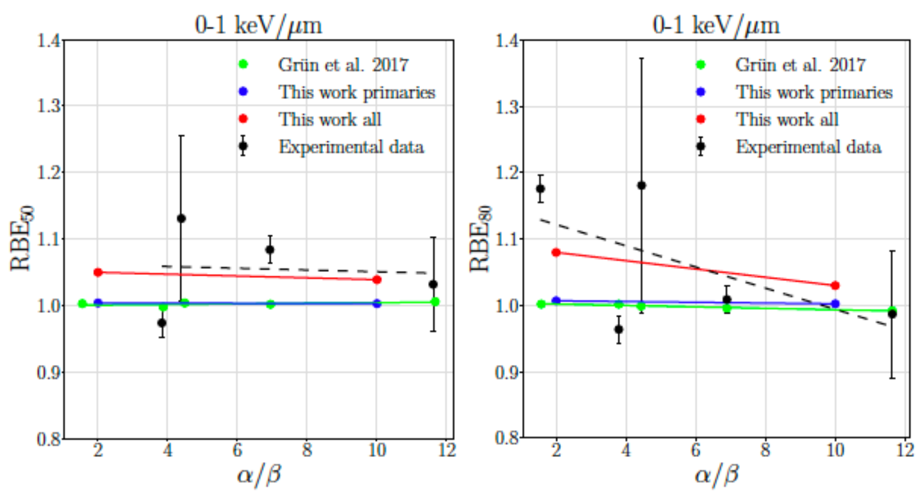
cancers 2021

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

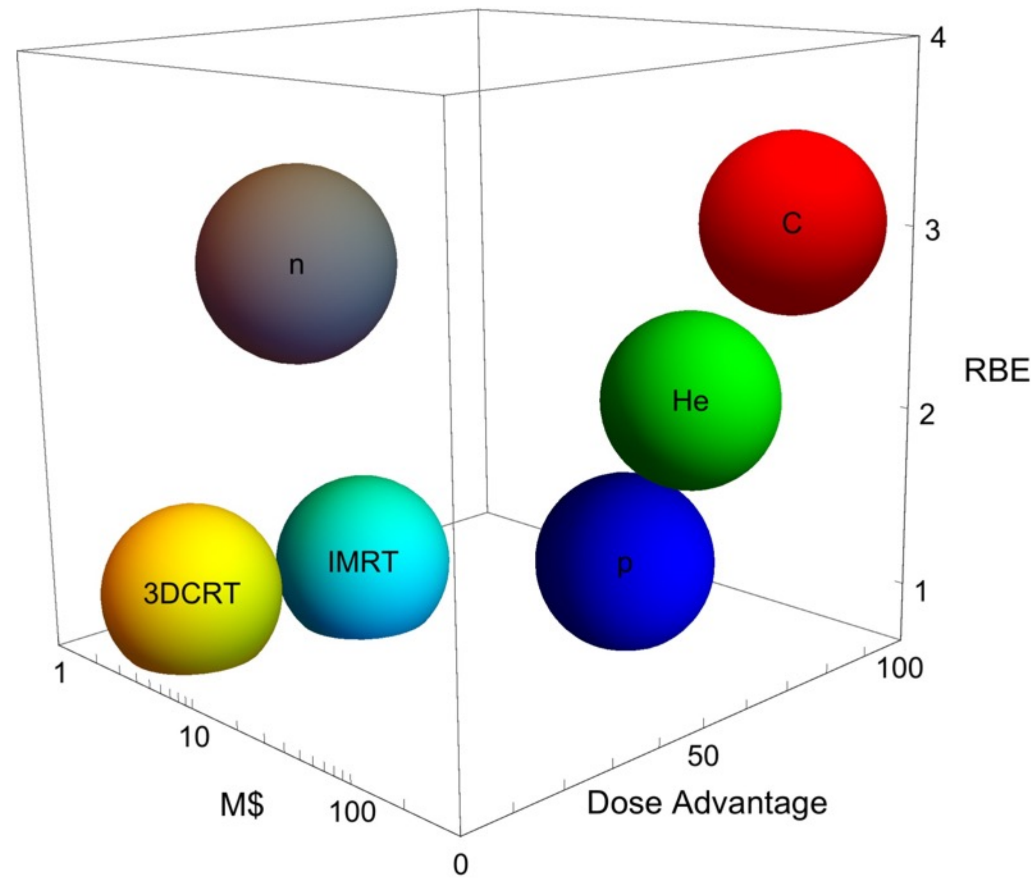
Elettra Valentina Bellinzona [1,2], Leszek Grzanka [3], Andrea Attili [4], Francesco Tommasino [1,2], Thomas Friedrich [5], Michael Krämer [5], Michael Scholz [5], Giuseppe Battistoni [2], Alessia Embriaco [6], Davide Chiappara [7,†], Giuseppe A. P. Cirrone [7], Giada Petringa [7,‡], Marco Durante [5,8]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



INFN TIFPA Trento Institute for Fundamental Physics and Applications

What's the best ion?

- What means the best?
- Most probably no unique choice
- The choice depend on morphological and biological features
- We need specific (Bio)-TPS studies



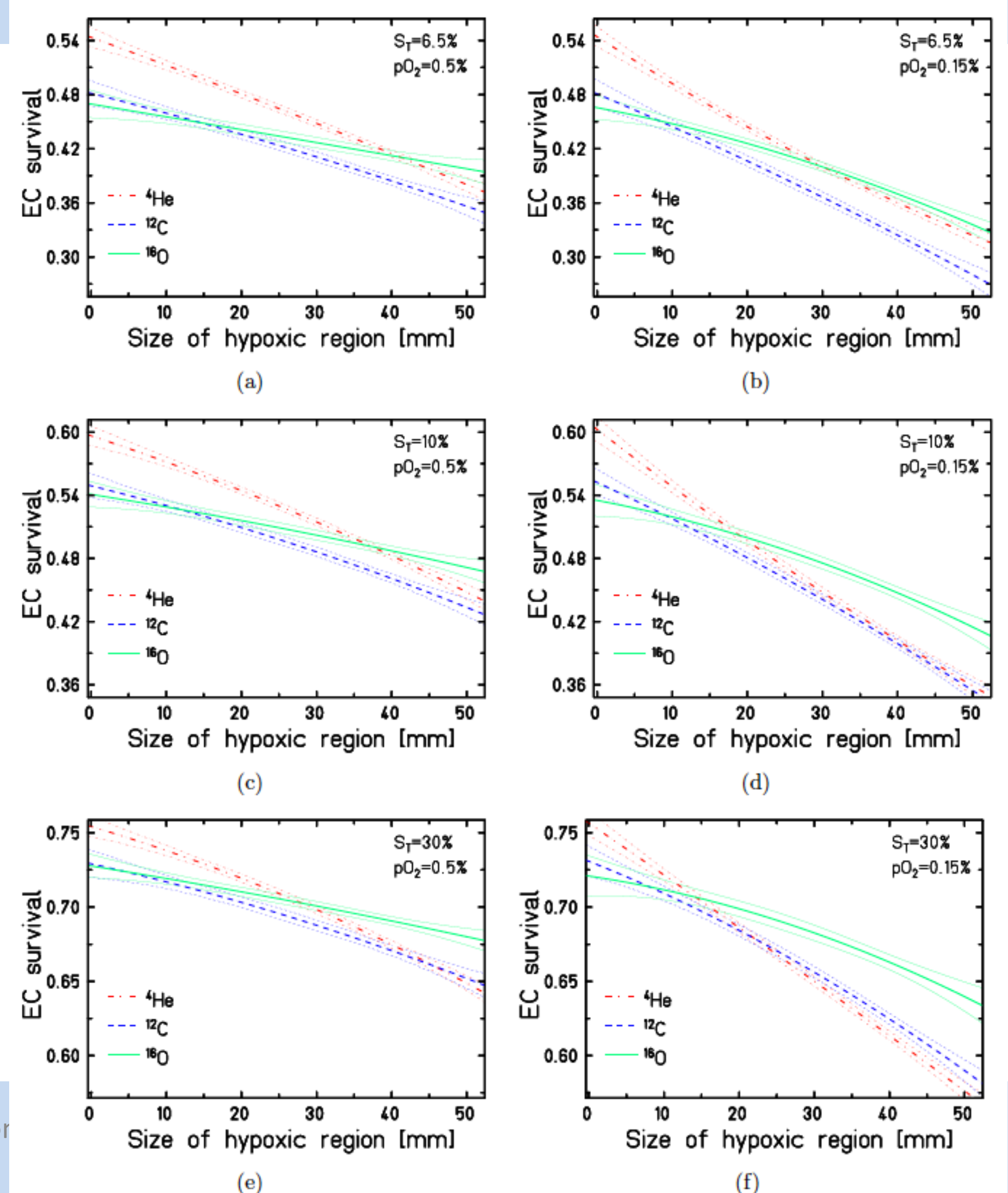
Kill painted plans with different ions

Sokol et al. PMB 2017

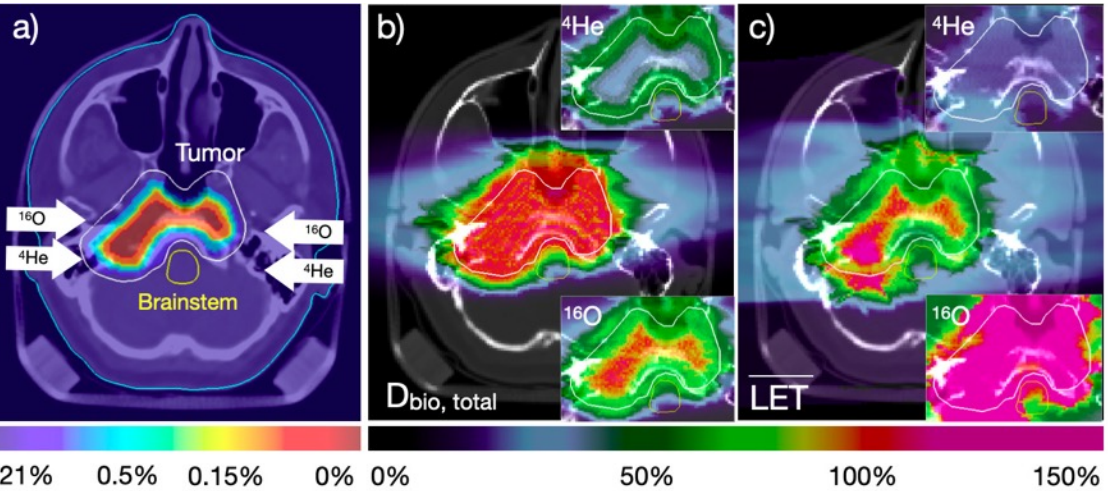
- In case of hypoxia, proper optimization accounting for OER may lead to **Inverted peak-to-entrance ratios** as compared to a normoxic case

- Trade off analysis (peak-to entrance survival ratio) among differerent optimized ions, first time considering explicity oxygenation

- Trade-off between better **LET distribution** and worse **Fragmentation** in entrance and tail



Exploiting degrees of freedom in Biological Ion beam TPS: Multiple ions



Physics in Medicine & Biology 2019

IPEM Institute of Physics and Engineering in Medicine

PAPER

Kill painting of hypoxic tumors with multiple ion beams

O Sokol[1], M Krämer[1], S Hild[2,3], M Durante[1,4] and E Scifoni[2]

Towards Multiple Ion Applications in Particle Therapy

Taku Inaniwa
National Institutes for Quantum and Radiological Science and Technology (QST)
Chiba, Japan

Andrea Mairani
Heidelberg Ion-Beam Therapy Center (HIT)
Heidelberg, Germany

Benedikt Kopp
Heidelberg Ion-Beam Therapy Center (HIT)
Heidelberg, Germany

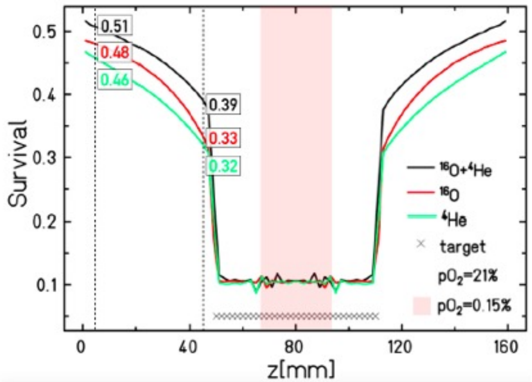
Stewart Mein
Heidelberg Ion-Beam Therapy Center (HIT)
Heidelberg, Germany

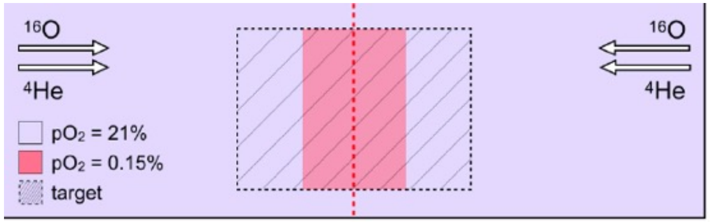
Michael Krämer
GSI Helmholtz Centre for Heavy Ion Research
Darmstadt, Germany

Olga Sokol
GSI Helmholtz Centre for Heavy Ion Research
Darmstadt, Germany

Emanuele Scifoni
TIFPA Trento Institute for Fundamental Physics and Applications
Trento, Italy

T&F chapter submitted





Exploiting degrees of freedom in Ion beam TPS: Multi-fraction TPS

…Planning different fractions differently

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

CrossMark

RECEIVED
9 November 2021

REVISED
13 January 2022

ACCEPTED FOR PUBLICATION
27 January 2022

PAPER

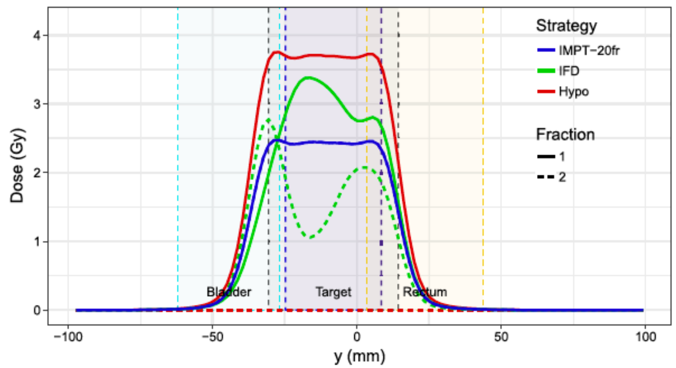
Spatiotemporal optimisation of prostate intensity modulated proton therapy (IMPT) treatments

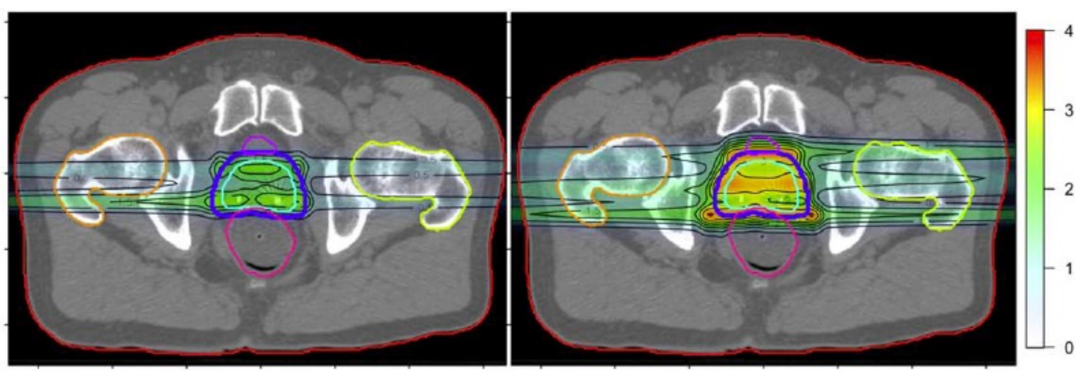
2022

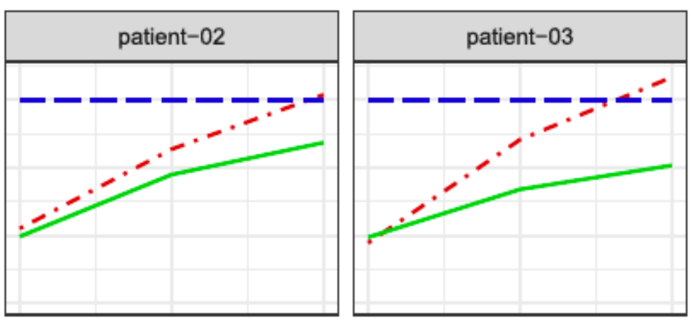
L Manganaro[1,2,3,4,5], A Attili[4], T Bortfeld[1,2] and H Paganetti[1,2]

[1] Department of Radiation Oncology, Massachusetts General Hospital (MGH), Massachusetts, United States of America

[2] Harvard Medical School, Massachusetts, United States of America

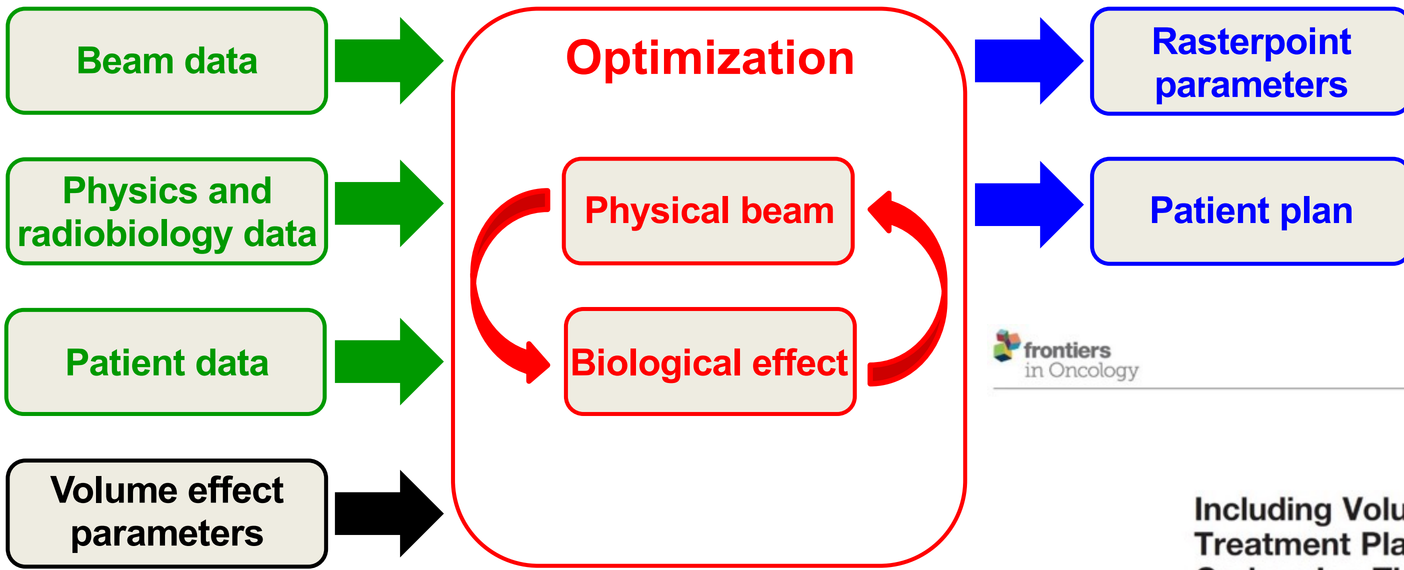


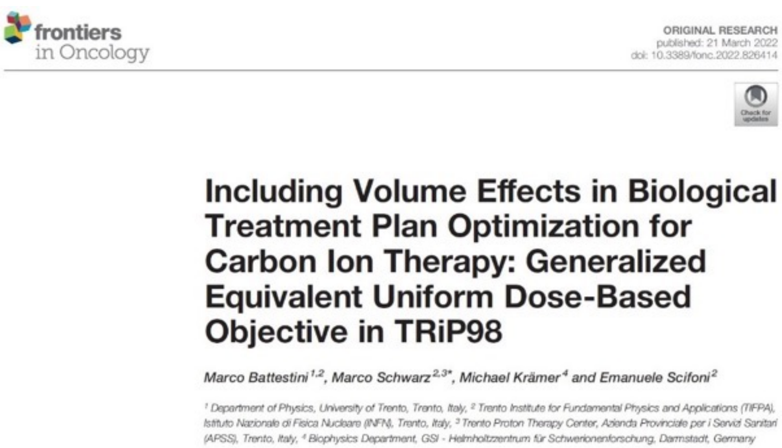




INFN TIFPA Trento Institute for Fundamental Physics and Applications

Including Volume effects





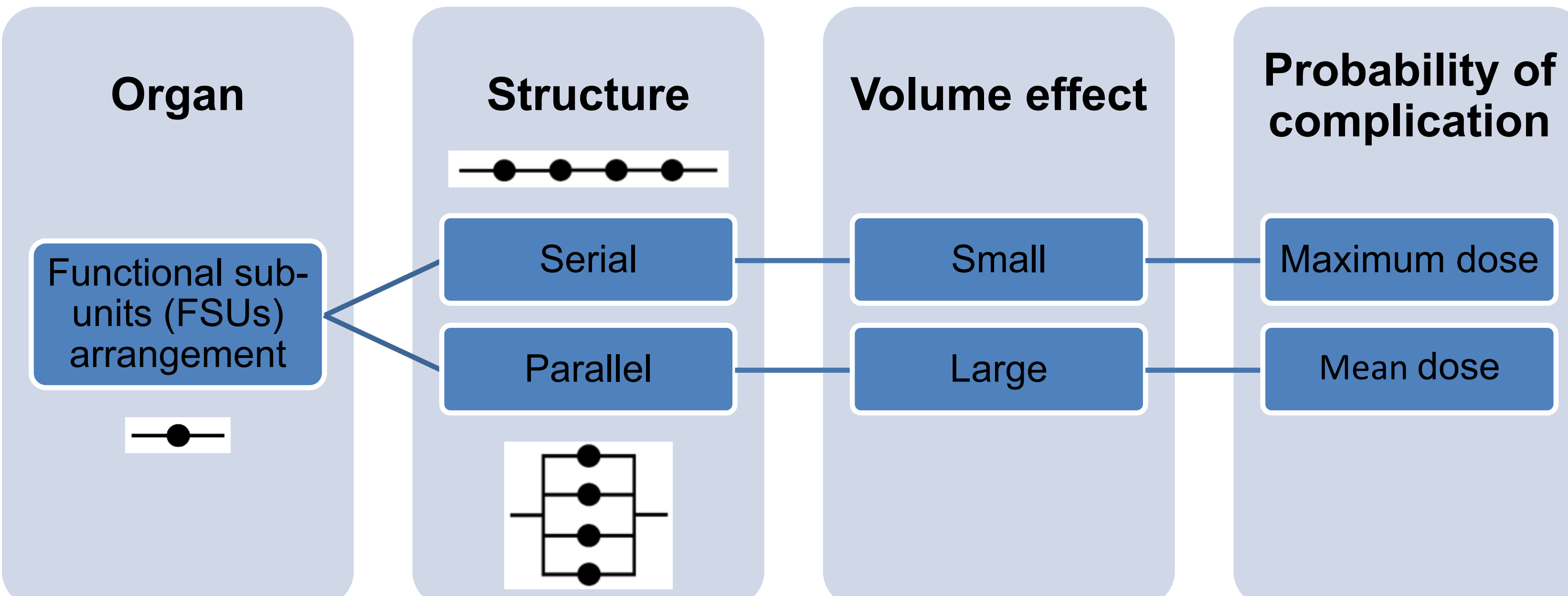
frontiers in Oncology
ORIGINAL RESEARCH
published: 21 March 2022
doi: 10.3389/fonc.2022.826414

Including Volume Effects in Biological Treatment Plan Optimization for Carbon Ion Therapy: Generalized Equivalent Uniform Dose-Based Objective in TRiP98

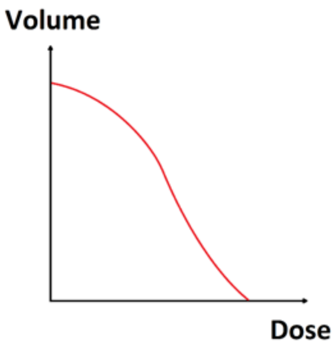
Marco Battestini[1,2], Marco Schwarz[2,3*], Michael Krämer[4] and Emanuele Scifoni[2]

[1] Department of Physics, University of Trento, Trento, Italy, [2] Trento Institute for Fundamental Physics and Applications (TIFPA), Istituto Nazionale di Fisica Nucleare (INFN), Trento, Italy, [3] Trento Proton Therapy Center, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy, [4] Biophysics Department, GSI - Helmholtzzentrum für Schwerionenforschung, Darmstadt, Germany

What is the volume effect?



Generalized Equivalent Uniform Dose (gEUD)



Niemierko (1999)

$$gEUD[Gy] = \left(\frac{1}{M}\sum_{i=1}^{N} D_i^a\right)^{\frac{1}{a}} = \begin{cases} D_{min} & a \to -\infty \\ D_{mean} & a = 1 \\ D_{max} & a \to +\infty \end{cases}$$

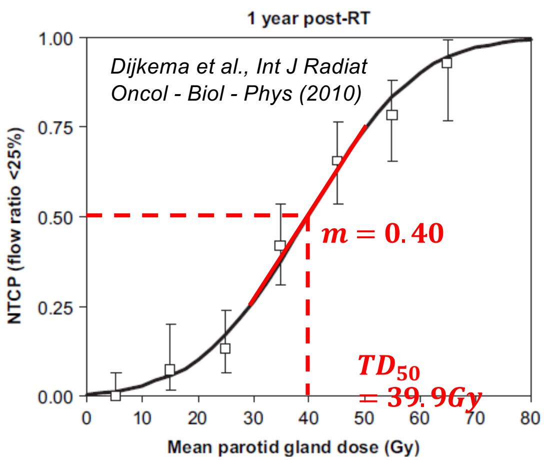
Large volume effect

Small volume effect

$$NTCP\,(u) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2} dt$$

$$u = \frac{gEUD - TD_{50}}{m \cdot TD_{50}}$$

Lyman–Kutcher–Burman (LKB) model (1989)



New optimization approach

$$D_i^{bio}(\vec{N}) = D_i^{phys}(\vec{N}) \cdot RBE_i(\vec{N})$$

TRiP98 cost function

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

Target (uniform dose)

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

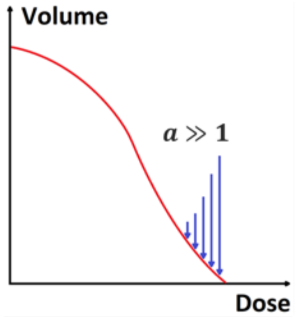
OAR (maximum dose)

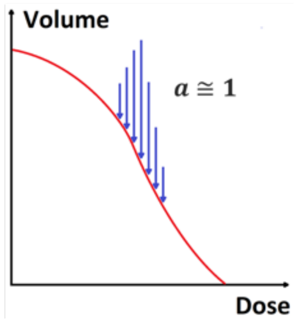
$$+\left(w_{OAR}^{gEUD_0}\right)^2 \frac{\left(gEUD_0 - gEUD(\vec{N})\right)^2}{\Delta gEUD_0^2} \cdot \theta\left(gEUD(\vec{N}) - gEUD_0\right)$$

OAR (gEUD)

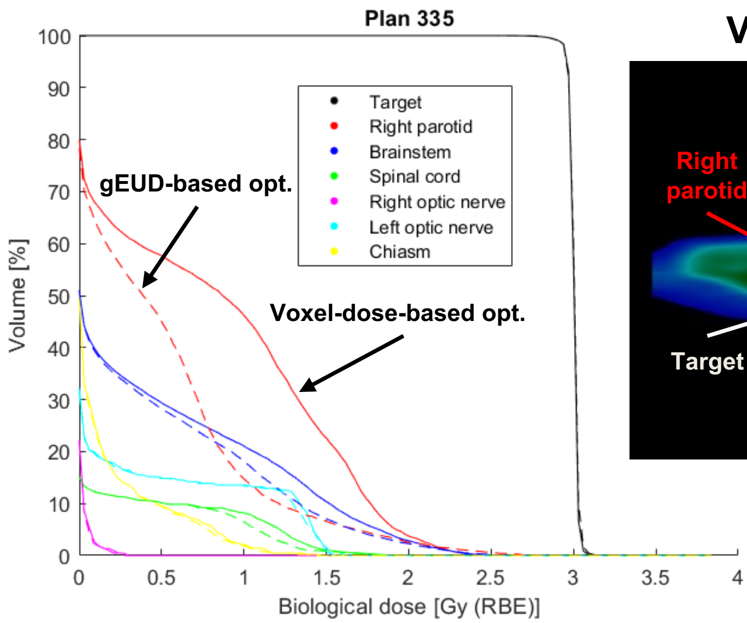
RBE-weighted dose

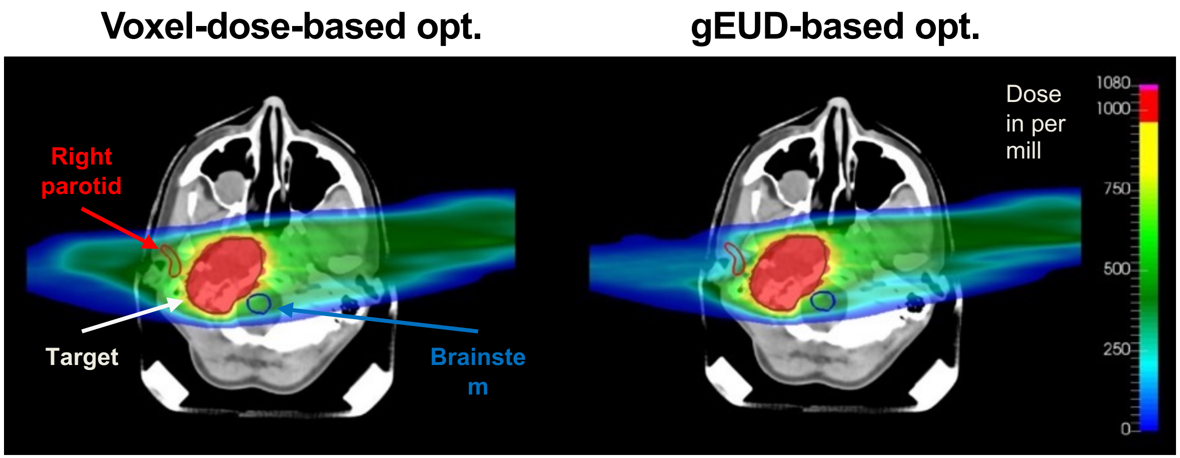
$$gEUD = \left(\frac{1}{M}\sum_{i=1}^{N}\left(D_i^{bio}(\vec{N})\right)^a\right)^{\frac{1}{a}}$$





Optimization results





Target $D_{pre} = 3\ \text{Gy}$
OARs D_{max}

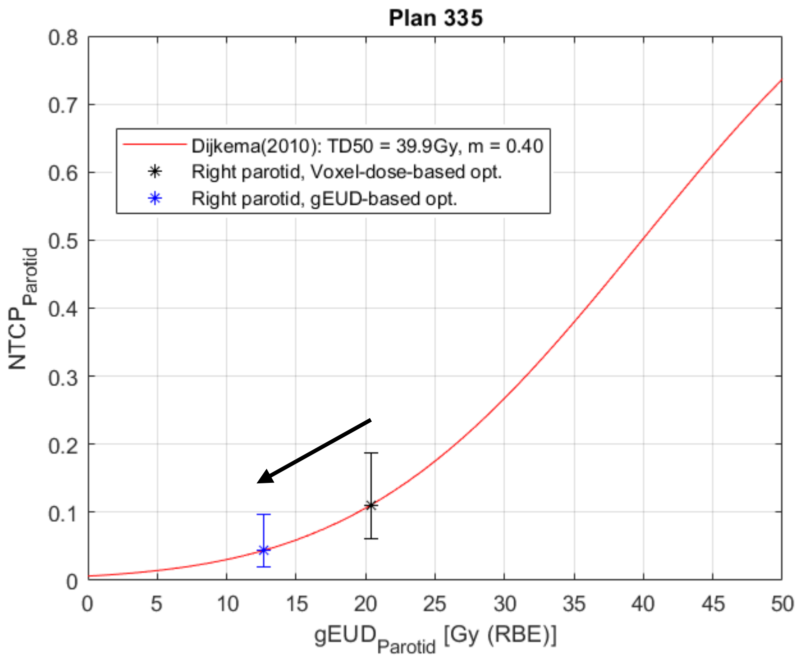
Target $D_{pre} = 3\ \text{Gy}$
Serial OARs $gEUD(a = 20)$
Right parotid $gEUD(a = 1)$

Battestini et al., Front. Oncol. (2022)

Normal Tissue Complication Probability (NTCP)

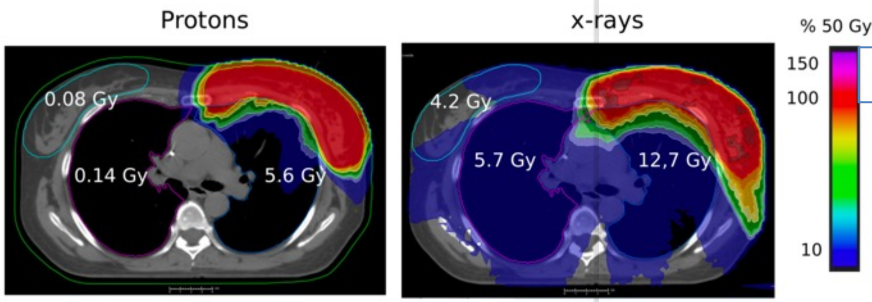
Parameter	Voxel-dose-based opt.	gEUD-based opt.
	Right parotid	
$gEUD\ (a=1)$	$0.82\ Gy$	$0.50\ Gy$
$NTCP$	$11.09\ \%$	$4.37\ \%$
D_{max}	$2.51\ Gy$	$2.80\ Gy$

Battestini et al., Front. Oncol. (2022)



Secondary Cancer risk modeling: particles vs X-rays

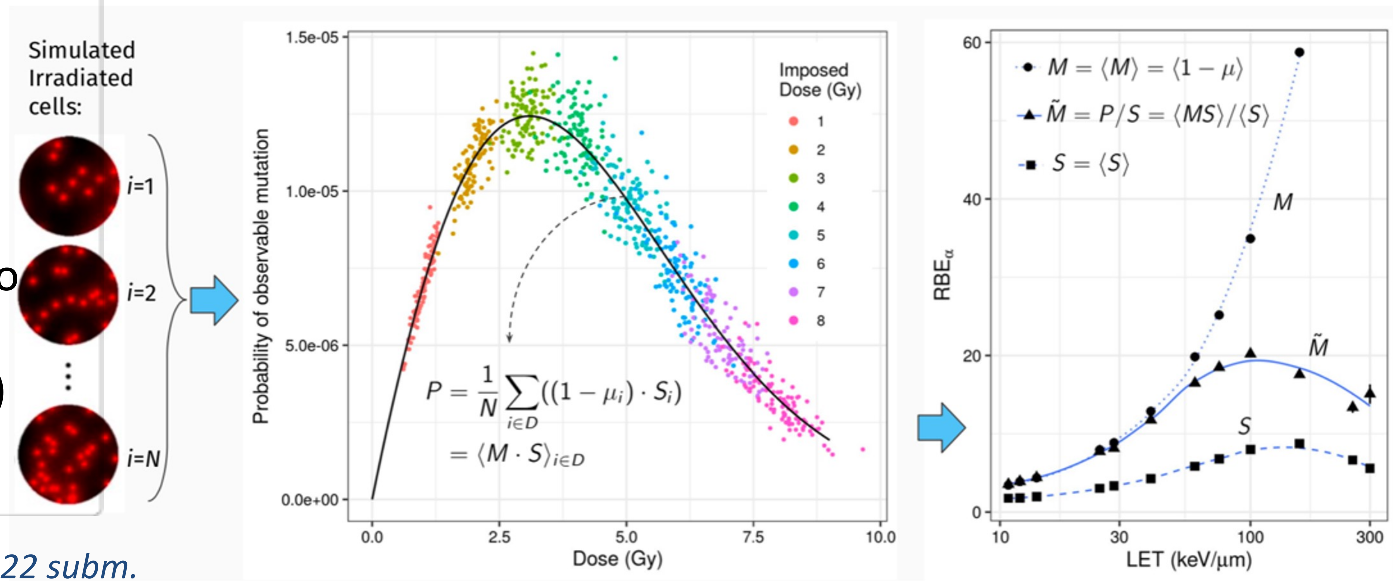
- Dosimetric studies : strong reduction of Excess Relative Risk (EAR) in **p** vs **X** –rays plans according to different models



EAR(cases/10000 persons/year:	VMAT			PT		
	Linear	Lin-exp	Lin-plat	Linear	Lin-exp	Lin-plat
Ipsilateral Lung	131±17	40±3	37±3	63±5	20±3	18±2
Contralateral Lung	55±8	35±3	30±2	2±2	1±1	1±1
Contralateral Breast	44±6	35±4	31±3	0±0	0±0	0±0

Cartechini et al. *Radiot. Oncol.2020*

- Biophysical modeling: New **MKM** based model for **Mutation Induction RBE** (RBE_M) of particles versus X-rays in analogy to the standard RBE for clonogenic survival (RBE_S)



Attili et al. *PTCOG 2021, PMB 2022 subm.*

Secondary Cancer risk modeling: proton versus carbon

Modeling Radiation-Induced Neoplastic Cell Transformation *In Vitro* and Tumor Induction *In Vivo* with the Local Effect Model

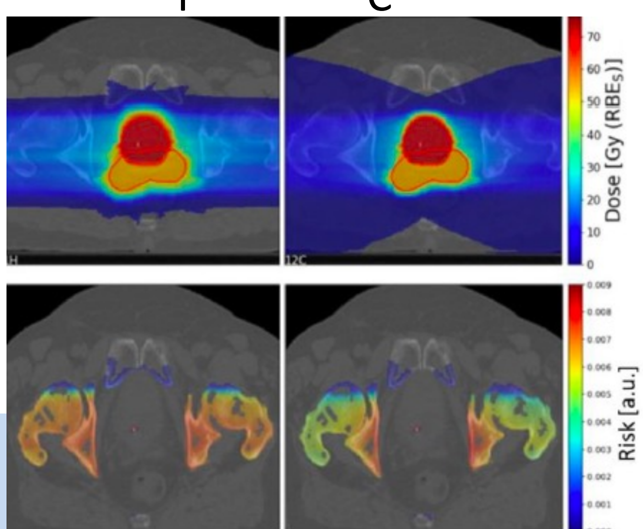
Antonia Hufnagl,[1] Michael Scholz and Thomas Friedrich[2]

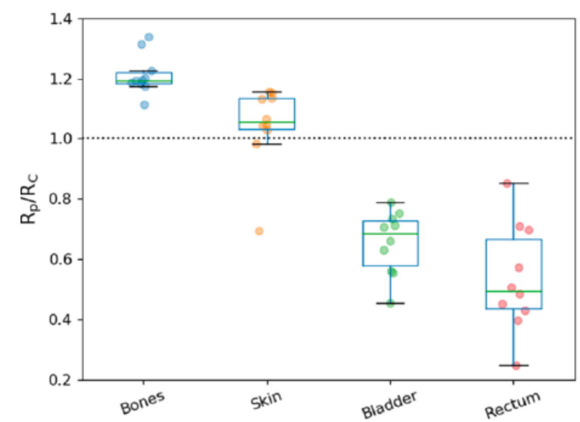
Rad Res 2021

Modelling secondary cancer risk ratios for proton vs. carbon ion beam therapy: A comparative study based on the Local Effect Model

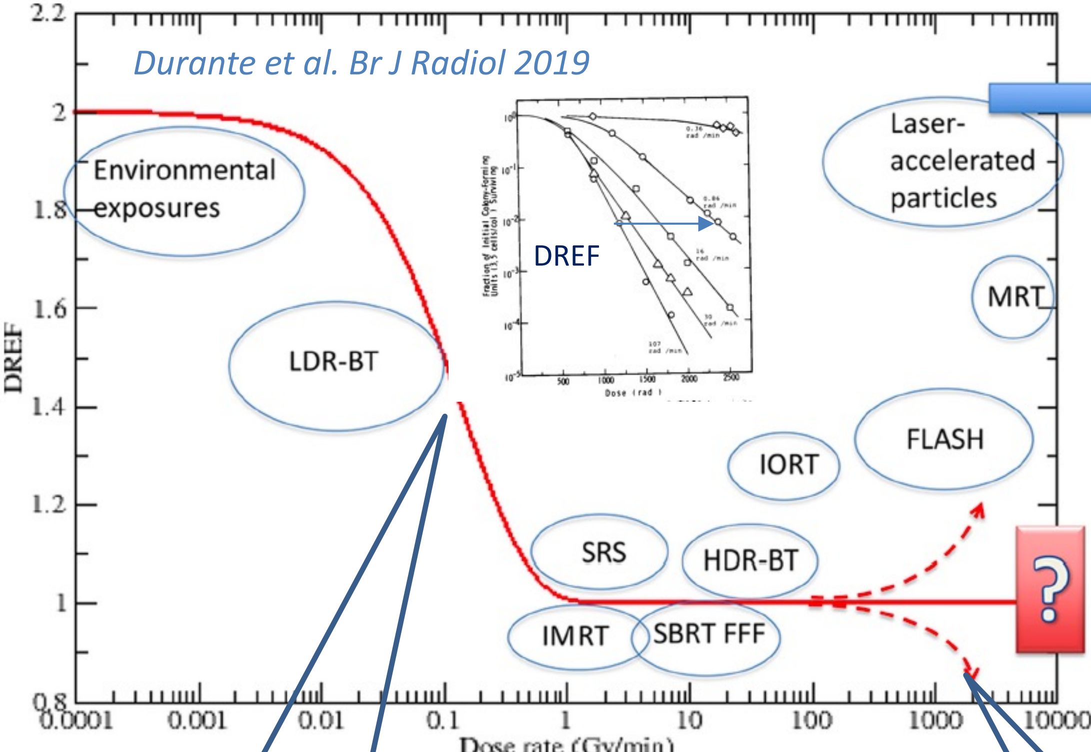
Antonia Hufnagl[1], Gracinda Johansson[2], Albert Siegbahn[2,3], Marco Durante[1,4], Thomas Friedrich[1], Michael Scholz[1,*]

Med Phys 2022



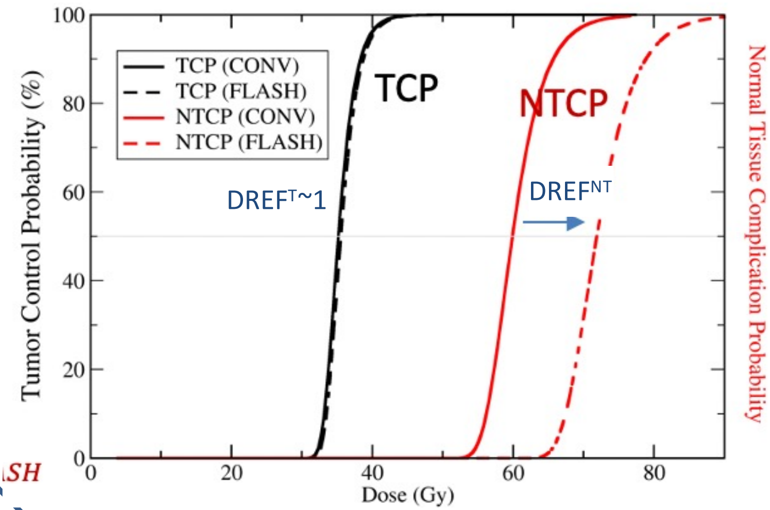


Ultrahigh Dose Rate Response and FLASH

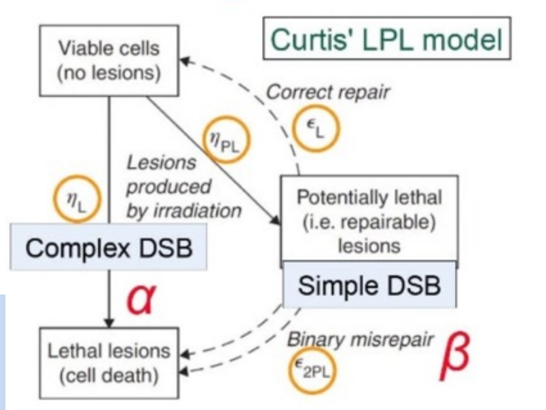


$$DREF = \frac{D(\dot{D})}{D(\dot{D}_{ref})}\bigg|_{same\ effect}$$

Dose-Rate Effectiveness Factor



This we understand (sublethal damage repair etc..) e.g.:



This we presently **DON'T** understand

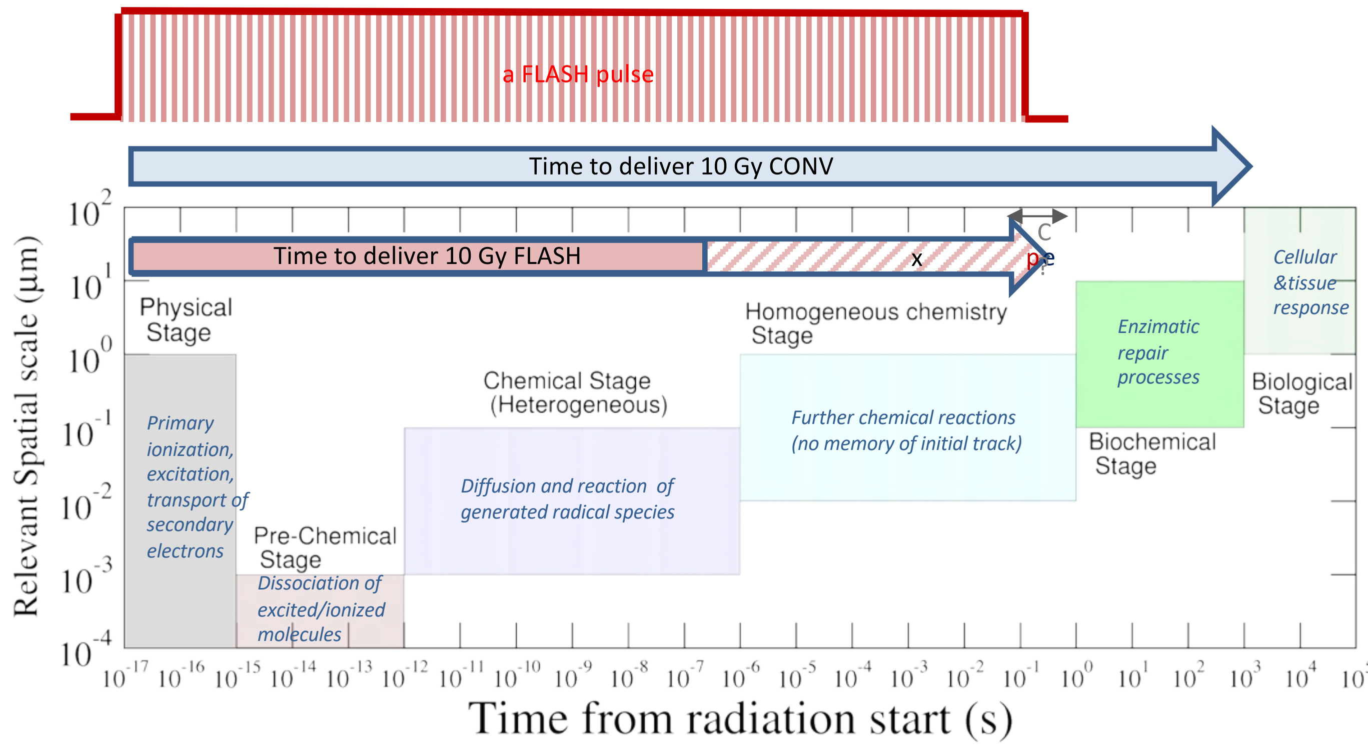
Despite plenty of accumulating exp evidence….

FLASH Basic questions:

- **WHY** this happens?
- How is it possible to justify an "inverse" protective effect with increasing dose rate?
- How is it possible to justify having it selectively for NT while maintaining unchanged tumor control?

- **WHEN** (for which irradiation parameters) this happens?
- **HOW** can we optimize it in a plan?

FLASH and spatiotemporal scales of Radiation Damage



Weber, Scifoni, Durante Med Phys 2022

FRIDA - FLASH Radiotherapy with hIgh Dose-rate particle beAms project

INFN-CSNV Call 2022-2024

WP1
The FLASH mechanism
E. Scifoni (modeling)
G. Forte (bio experiments)

WP2
Beam delivery
A. Mostacci (e-)
G. A. P. Cirrone (p)

WP0
Coordination
A. Sarti

WP3
Beam/dose monitoring
A. Vignati (Beam monitoring)
G. Bisogni (Dose monitoring)

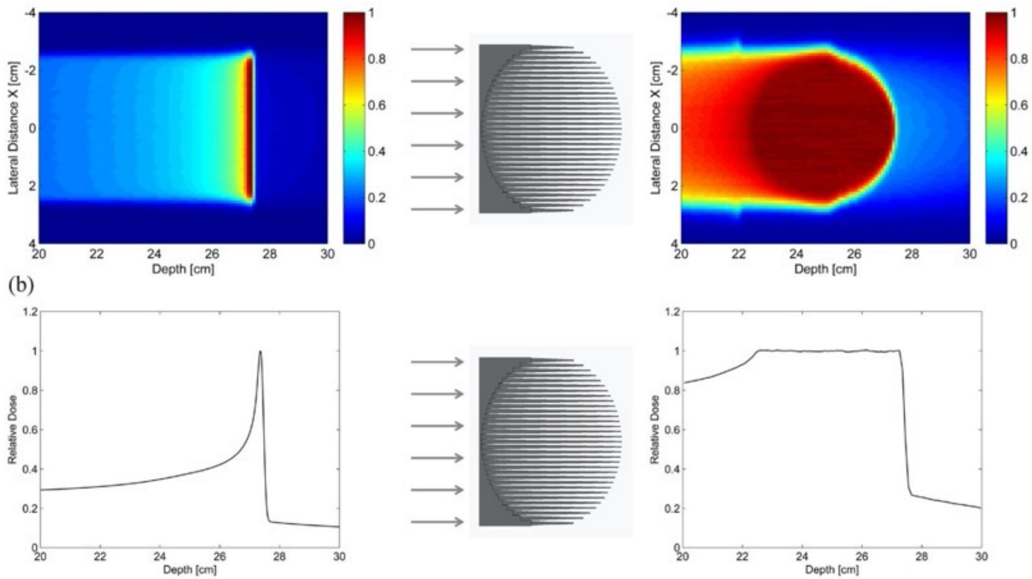
WP4
Treatment planning
A. Schiavi (Dose sim/optim.)
M. Schwarz (Treatment planning)

INFN
units
CT – F. Romano
LNS – G. Cirrone
MI – D. Giove
PI – G. Bisogni
RM1 – A. Sarti
TIFPA – E. Scifoni
TO – A. Vignati

Partners:

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA
GSI
eli beamlines
HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF
QUEEN'S UNIVERSITY BELFAST
UNIVERSITY OF SURREY
Consiglio Nazionale delle Ricerche

3D Range Modulators

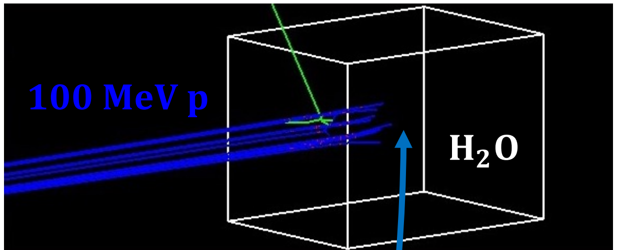


Y. Simeoneov et al, 3D range-modulator for scanned particle therapy: development, Monte Carlo simulatons and experimental validation, PMB 2017

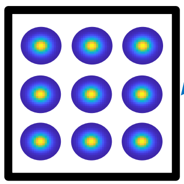
- All pins need to be **optimized**
- Increased number of degrees of freedom required
- Need to control **beam scattering** and **optical divergence**
- Up to several thousands of optimization variables
- Linear combination of **full dose distributions** instead of single depth dose profiles

Dose Rate scoring

M. Battestini

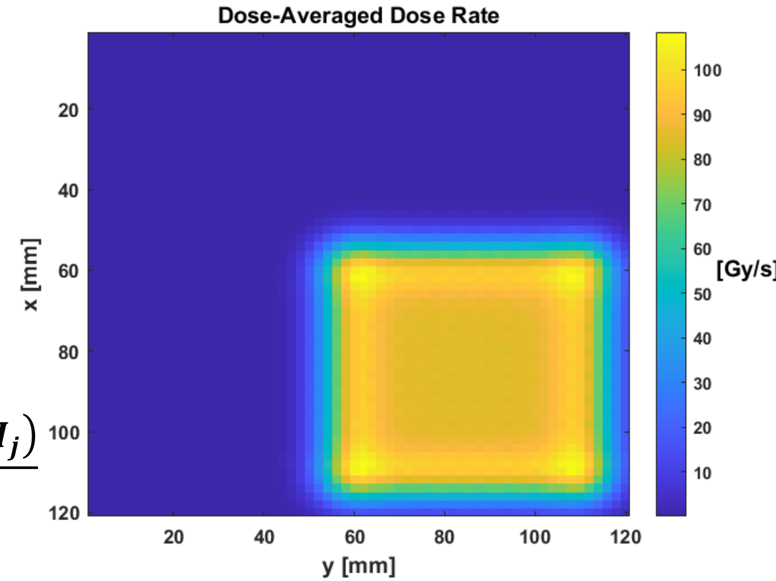


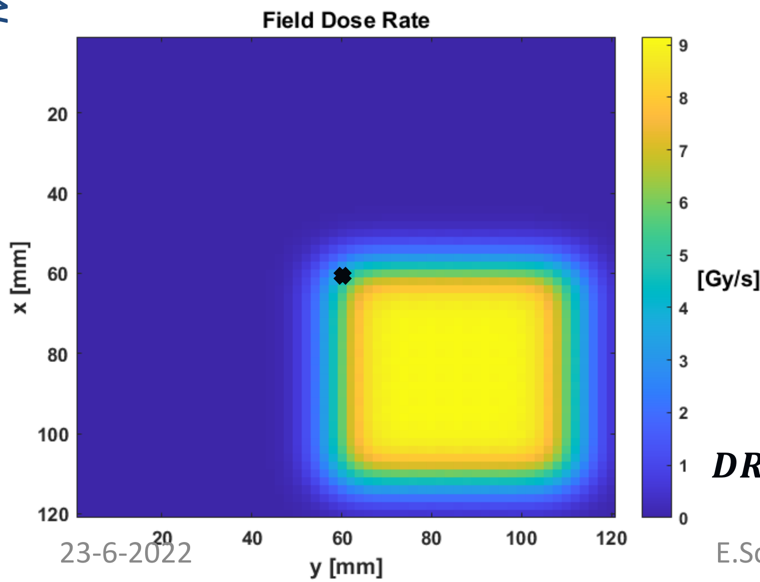
Tumor



Essential
for BioTPS

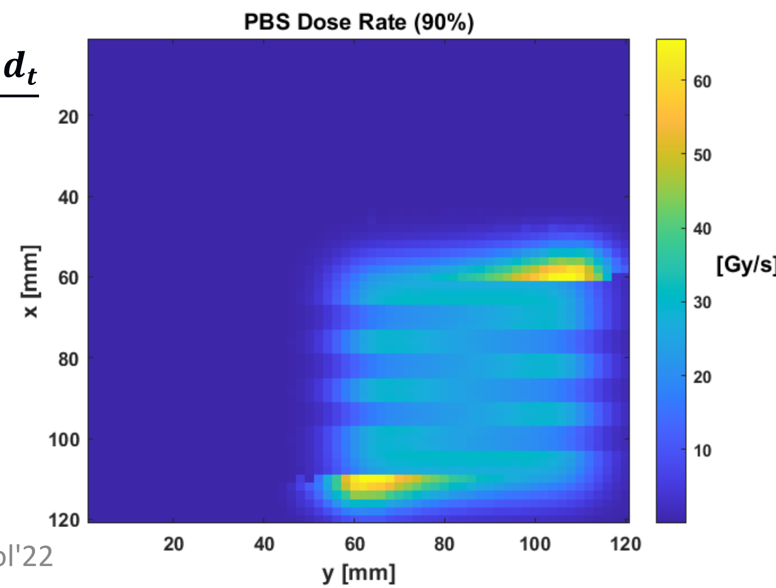
$$DADR_i = \sum_{j=1}^{n} \frac{(d_{ij}w_j)(d_{ij}BI_j)}{\sum_{j=1}^{n} d_{ij}w_j}$$





$$DR_i^{PBS} = \frac{D_i - 2d_t}{T_i}$$

$$DR_i^{field} = \frac{D_i}{t_f}$$



Summary

- Biological Treatment planning, BioTPS, i.e. including as much as possible information from physics and biological effects in inverse treatment planning, exploiting beam delivery degrees of freedom is a growing field with many expansion directions

- Biophysical modeling at different scales can help providing insights in mechanism and predictive description of different types of bio-effects (DMFs)

- The different DMFs could be implemented on turn in TPS, as “driving forces” for inverse planning

BiMeR @TIFPA team

Bio-Medical Radiation Physics Research Team in Trento

TIFPA Trento Institute for Fundamental Physics and Applications · INFN · University of Trento · Azienda Provinciale per i Servizi Sanitari, Provincia Autonoma di Trento

- E. Scifoni, Primo Ricercatore INFN
- **C. La Tessa**, Prof Ass UniTN
- **F. Tommasino**, RTDB UniTN
- **F. Cordoni,** RTDB UniTN
- M. Missiaggia, Postdoc
- L. Petrolli, PhD student
- G. Cartechini, PhD student
- E. Pierobon. PhD student
- M. Battestini PhD student
- E. Fogazzi, PhD student
- E. Verroi, Technical Resp Exp Cave

- S. Lorentini Head of Medical Physics staff @ Trento PTC
- A. Bisio, CIBIO (Biologist)

MAIN COLLABORATORS

M. Durante, M. Krämer, M. Fuss, D. Boscolo, W. Tinganelli, O. Sokol	GSI
M. Schwarz	University of Washington
A. Attili	INFN RM3
P. Cirrone, G. Petringa	INFN LNS
V. Conte	INFN LNL
L. Grzanka	IFJ
V. Patera	Sapienza

Thanks for your Attention!

..and friends