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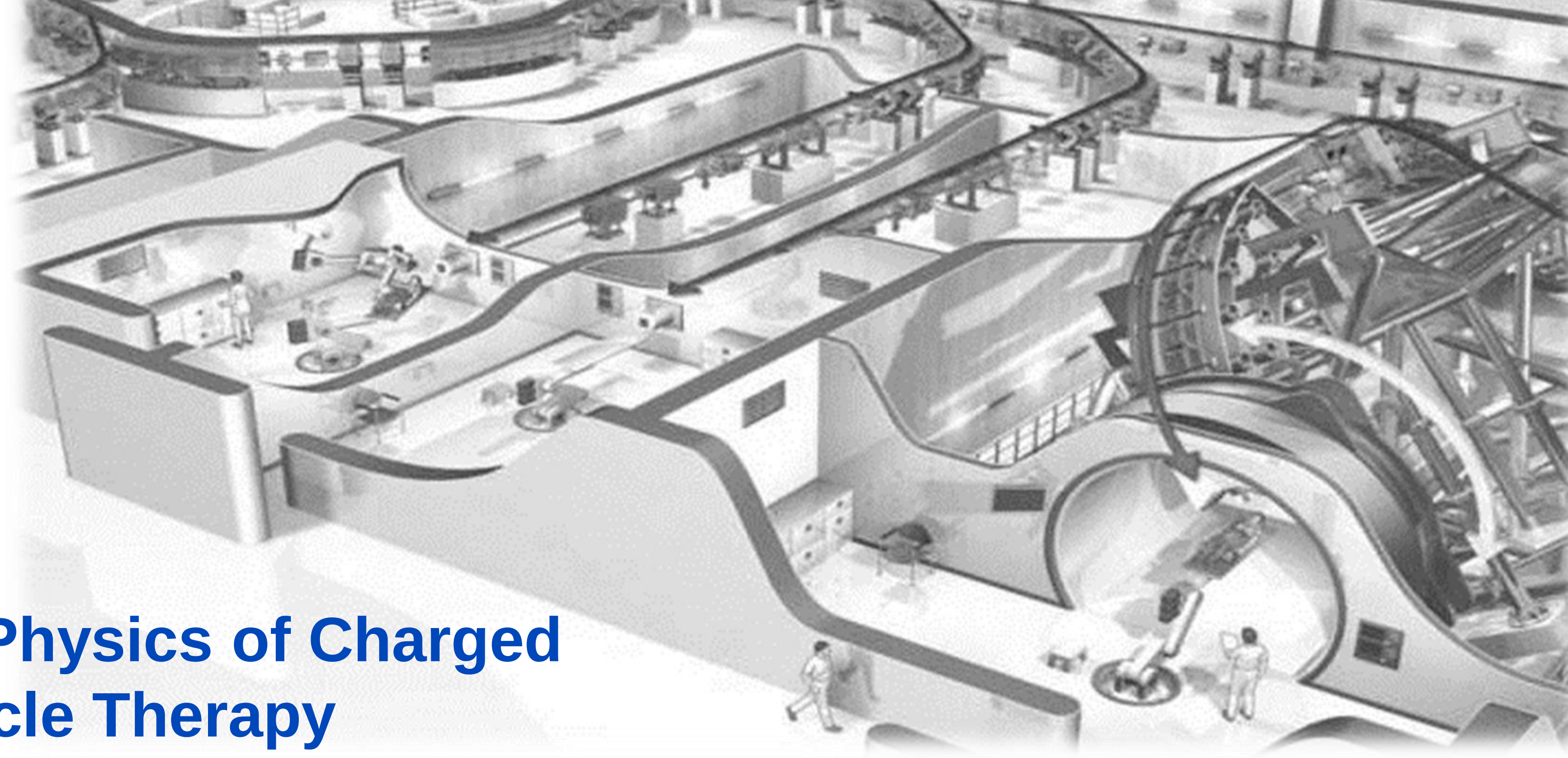


The Physics of Charged Particle Therapy

Introduction to Particle Therapy

Part II/II – HIT, Introduction to Biological Dose and Research of the BioPT Group

Benedikt Kopp
PhD Candidate
Biophysics in Particle Therapy Group (BioPT), Heidelberg, Germany

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer
HEIDELBERG UNIVERSITY HOSPITAL

!! Disclaimer !!

All (most) slides courtesy of

Dr. Stewart Mein

BioPT Group - Heidelberg

Additional Literature

- Schardt, Dieter, Thilo Elsässer, and Daniela Schulz-Ertner. "*Heavy-ion tumor therapy: Physical and radiobiological benefits.*" Reviews of modern physics 82.1 (2010): 383.
- Paganetti, Harald, et al. "*Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy.*" Medical physics 46.3 (2019): e53-e78.
- Haberer, T., Debus, J., Eickhoff, H., Jäkel, O., Schulz-Ertner, D., & Weber, U. (2004). *The Heidelberg ion therapy center*. Radiotherapy and Oncology, 73, S186-S190.

Overview Part II/II

I. **Introduction to the Heidelberg Ion-Beam Therapy Center (HIT)**

II. Introduction to Radiation Biology

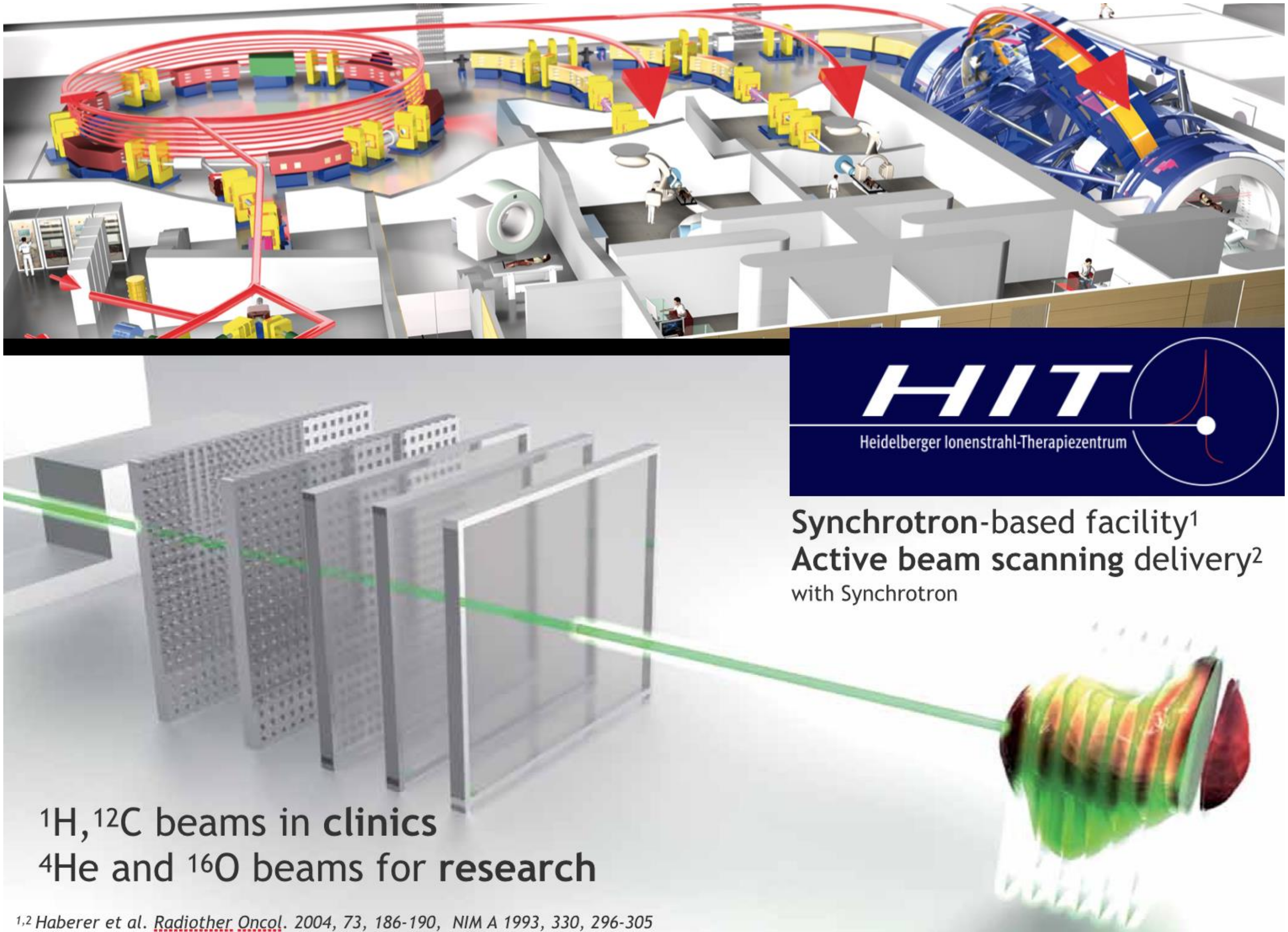
III. Ongoing Research at HIT

a) FRoG

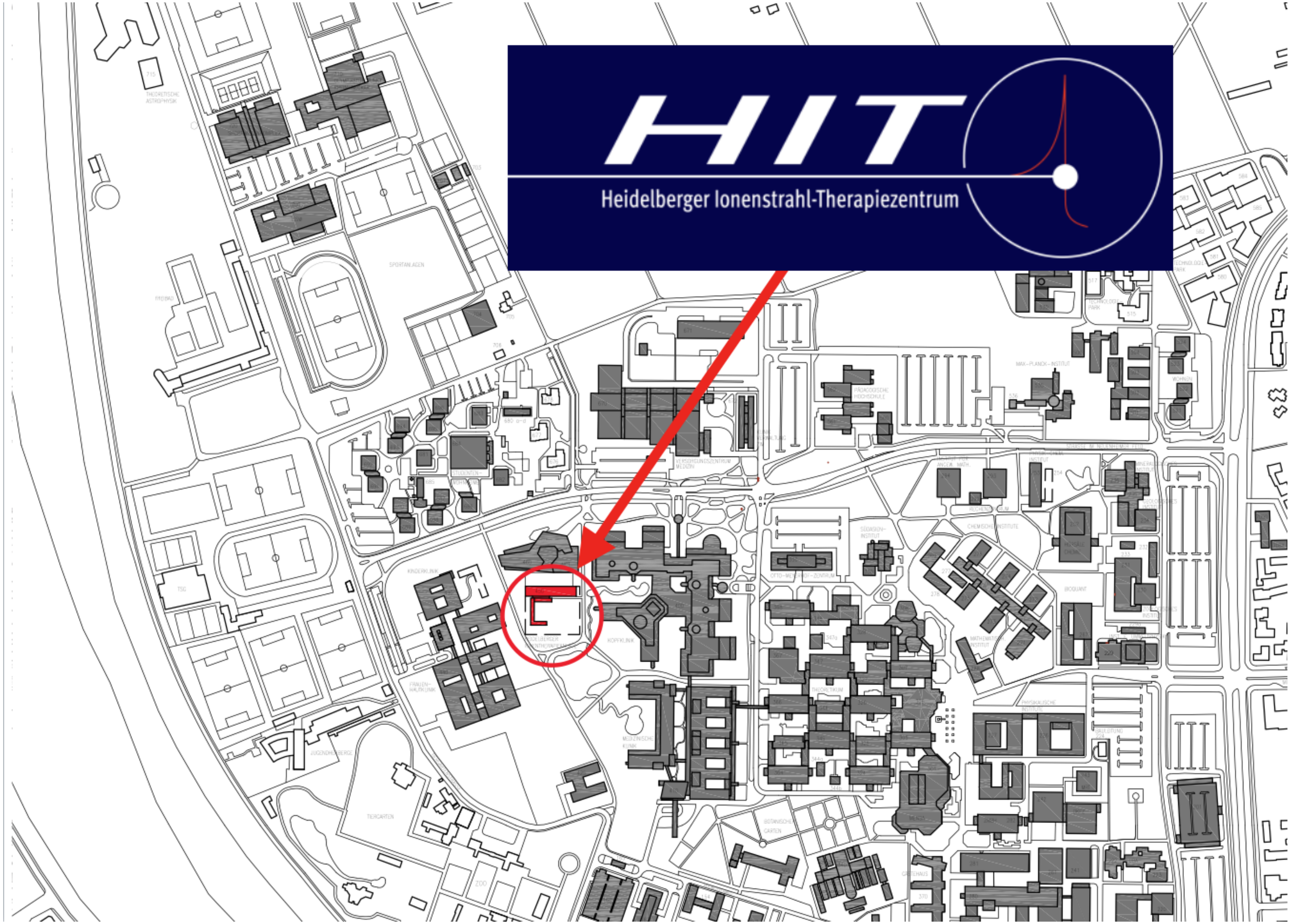
b) Multi-ion particle treatments

c) Other research

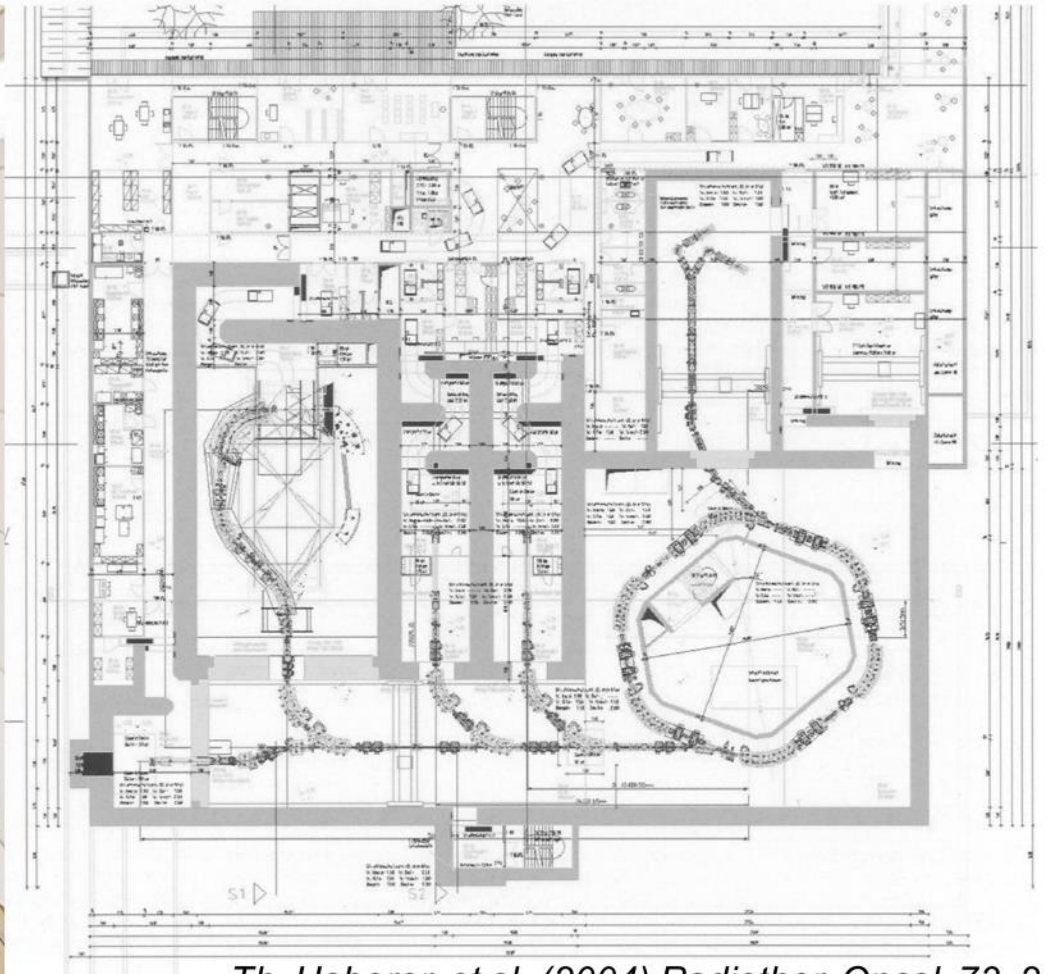
What is HIT?


HIT
Heidelberger Ionenstrahl-Therapiezentrum
Synchrotron-based facility[1]
Active beam scanning delivery[2]
with Synchrotron
^{1}H, ^{12}C beams in clinics
^{4}He and ^{16}O beams for research
[1,2] Haberer et al. Radiother Oncol. 2004, 73, 186-190, NIM A 1993, 330, 296-305

Where is HIT?

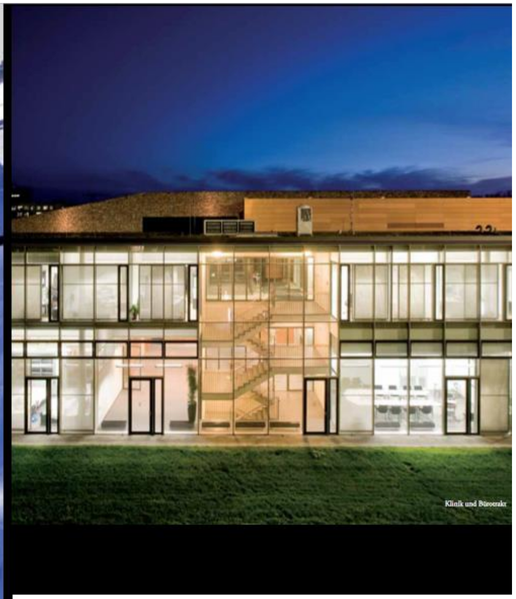


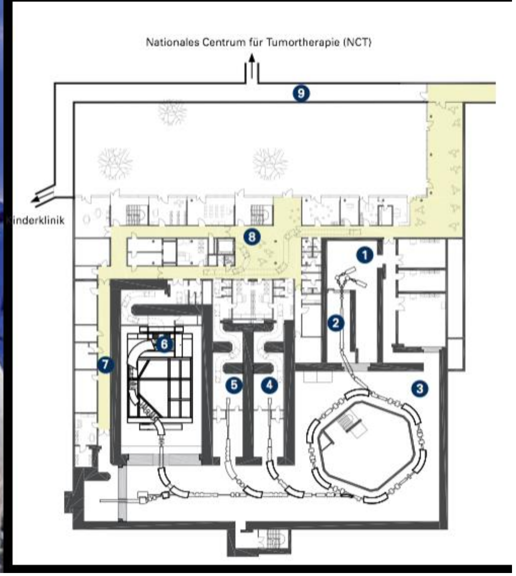
Active Beam Delivery - HIT



Th. Haberer. et al, (2004) Radiother. Oncol. 73, 2

What makes HIT unique I/II?





Tumorbekämpfung mit der Gantry

8.522 Aufrufe • 11.04.2014

44 1 TEILEN SPEICHERN ...

AuswaertigesAmtDE
6500 Abonnenten

ABONNIEREN

Serie "Wissenschaftsstandort Deutschland"

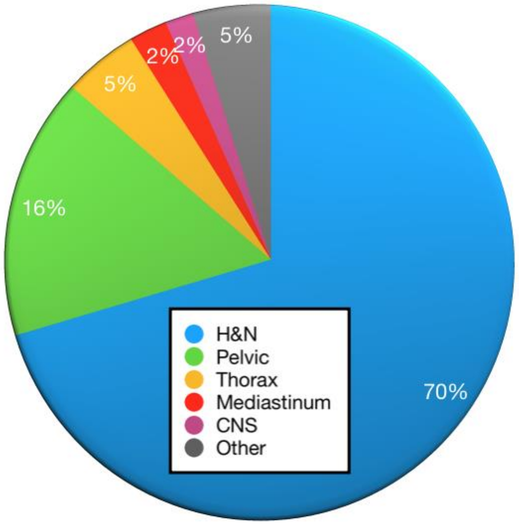
What makes HIT unique II/II?

About HIT

2009 - present: ~5000 patients
40%/60% C/p

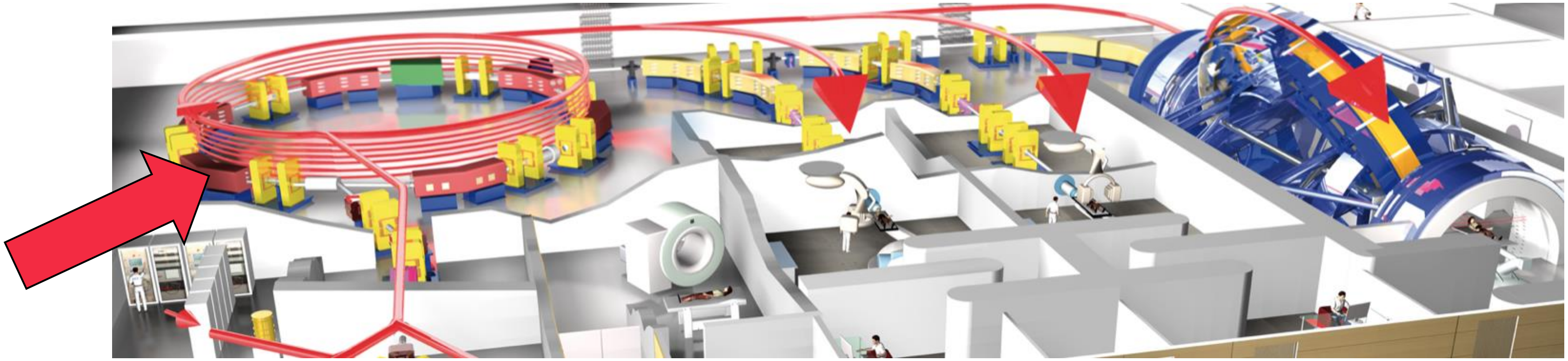
Clinical Physicians: ~10

Accelerator Physics & Medical Physicists: ~30



other: liver, abdominal, extremities, pancreatic, etc.

Synchrotron



Pulsed Beam (i.e. off – on – off – on...)

→ Can complicate irradiating moving targets (for example in lung)

Multiple ion species can be delivered to various energies

Almost no material needed upstream the particle beam (except sometimes for range shifters on the patient)

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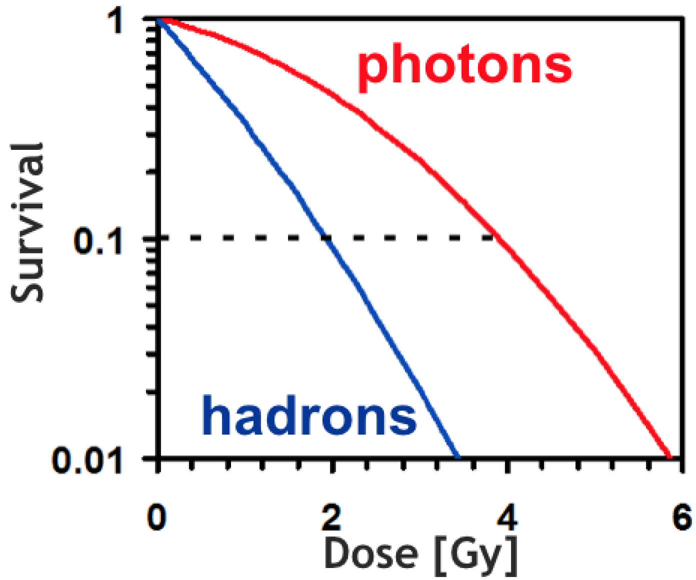
Relative Biological Effectiveness

Biology



RBE (relative biological effectiveness):

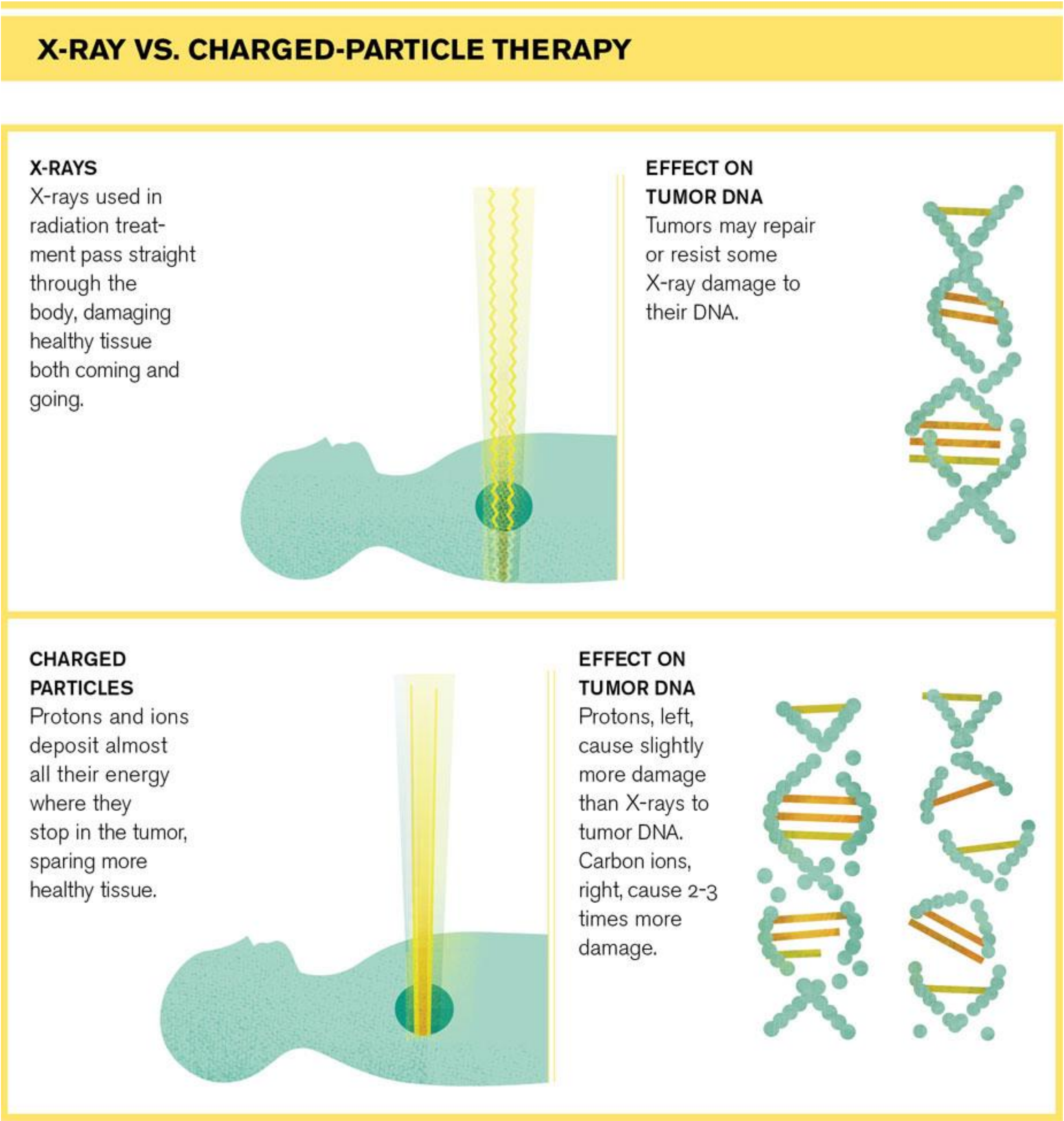
tumor control (TC)
normal tissue constraints (NTC)

TCγ ➜ TC [p, C]
NTCγ ➜ NTC [p, C]

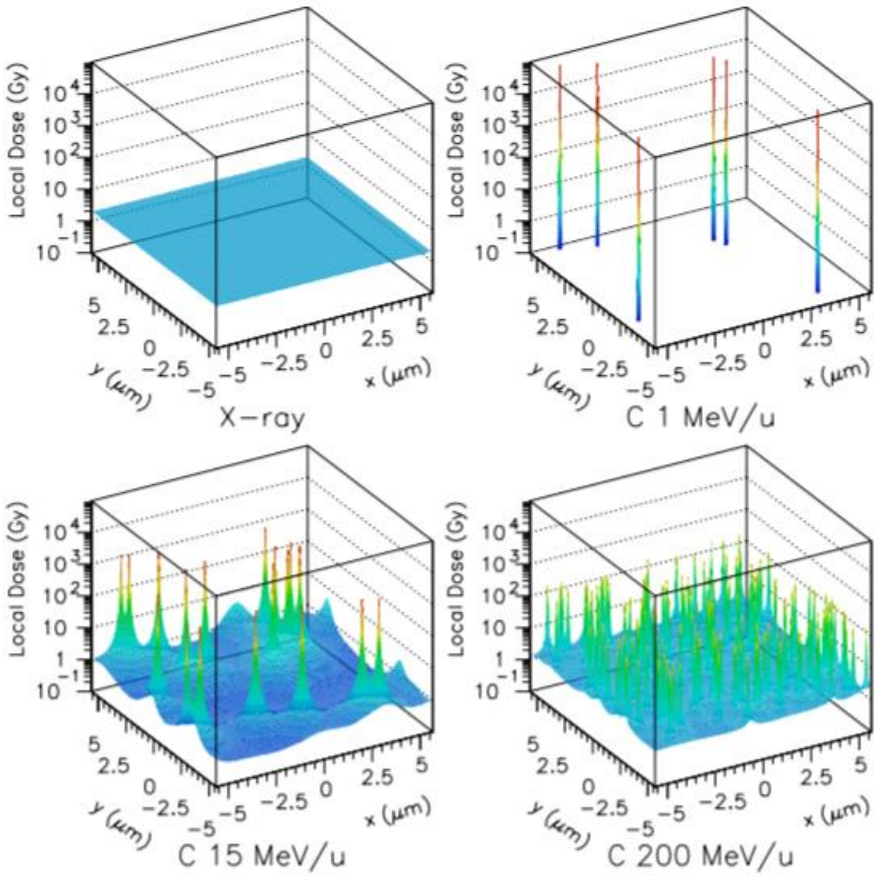
In clinic:

p RBE = 1.1
^{12}C variable RBE models

Cell Survival and RBE



Track Structure of Radiation



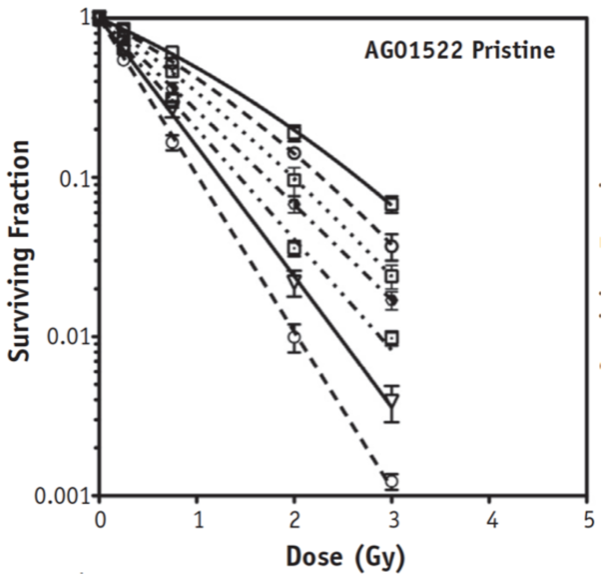
Scholz 2003

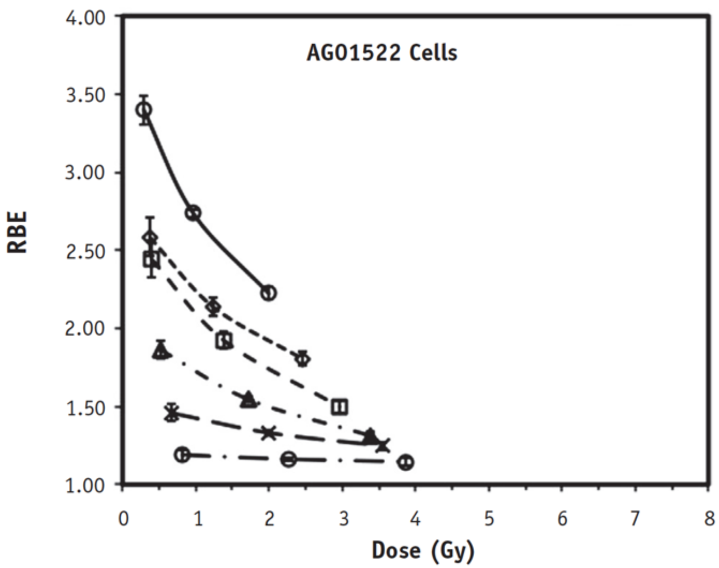
X-rays homogenously deposit local dose

Depending on the energy ^{12}C ions have different track structures

Cell Survival and RBE

model surviving fraction (SF)



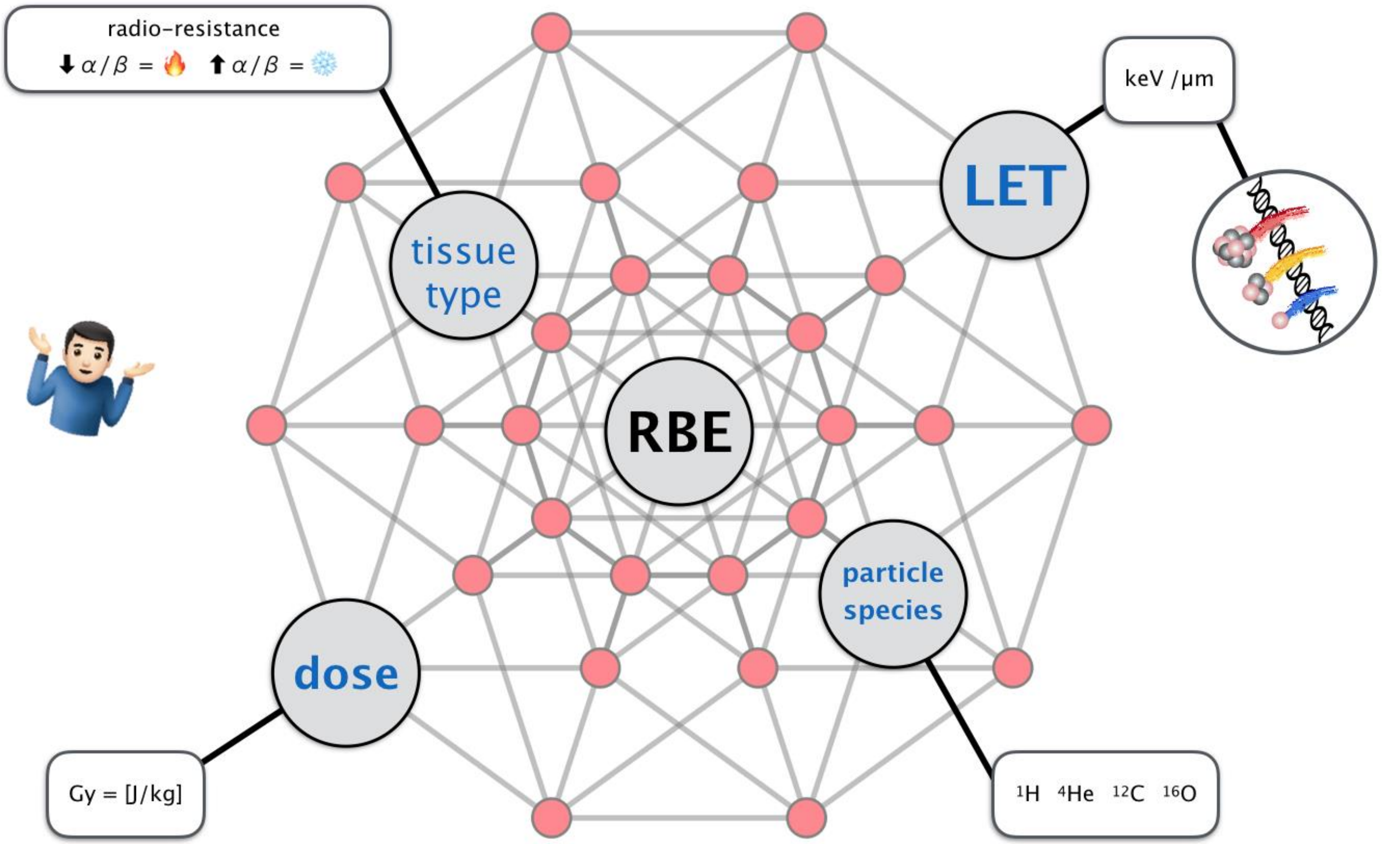


$$SF = e^{-\left(\alpha D + \beta D^2\right)}$$

$$RBE_{SF} = \frac{D_{SF}^{X}}{D_{SF}^{P}}$$

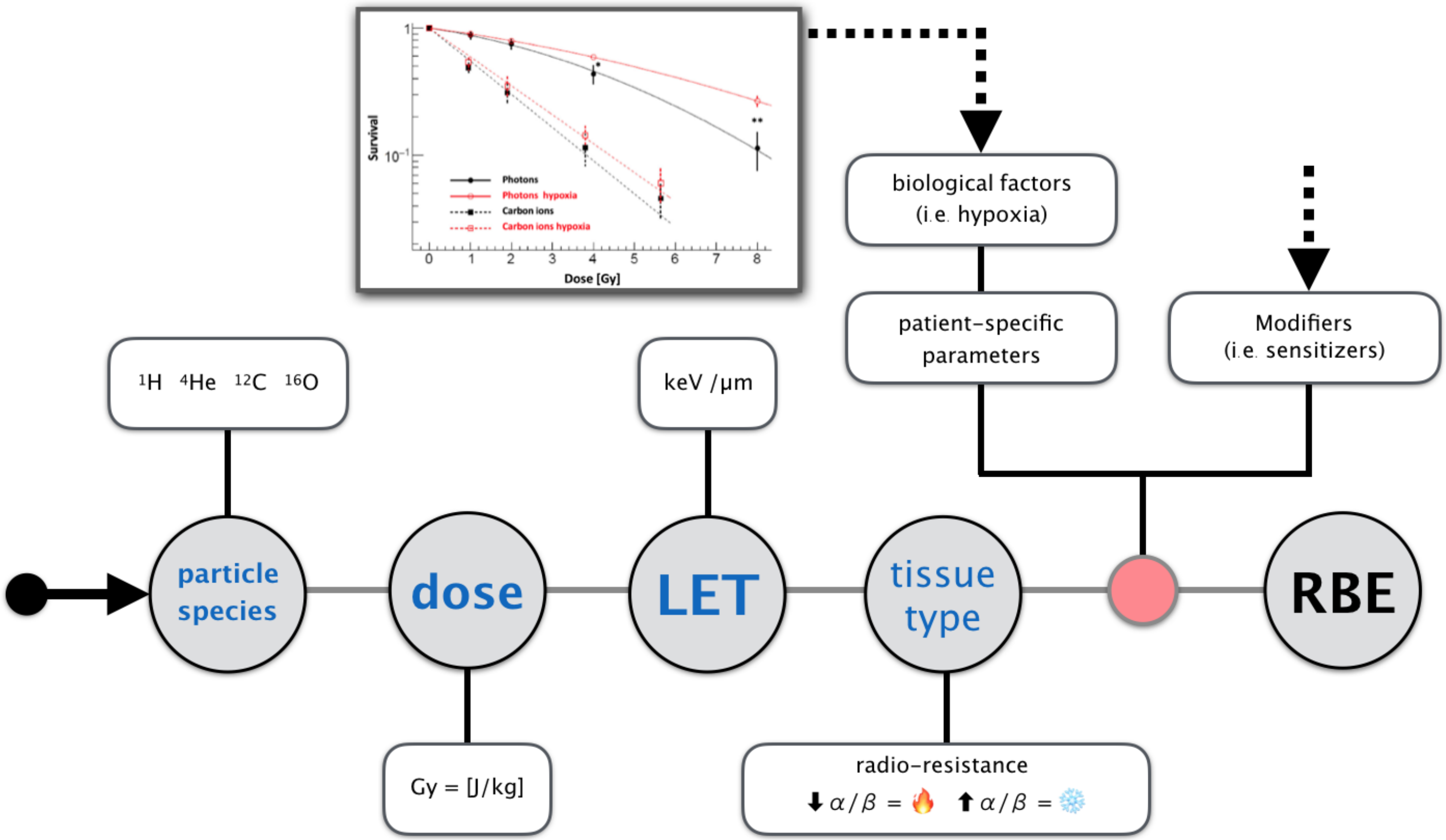
RBE(Dose, LET, [α/β]γ)

RBE is dependent on ??



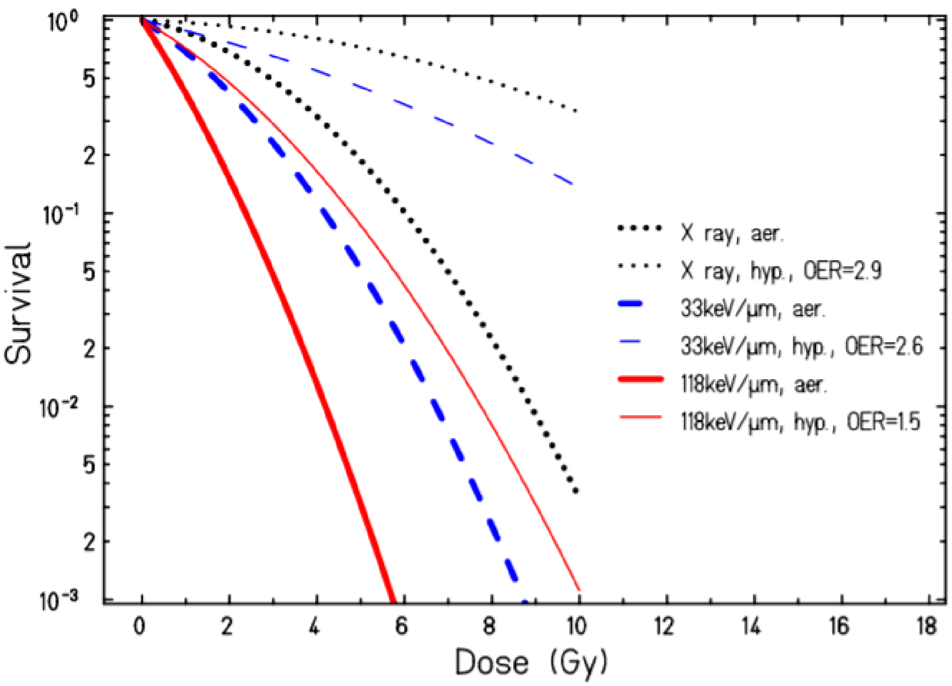
$$\mathrm{RBE} = f\left({}^{A}_{Z}\mathrm{X}, \mathrm{D}, \mathrm{LET}, \alpha/\beta, \ldots \right)$$

RBE is dependent on ??



$$\mathrm{RBE} = f\left({}^{A}_{Z}\mathrm{X}, \mathrm{D}, \mathrm{LET}, \alpha/\beta, \ldots \right)$$

Oxygen Enhancement Ratio



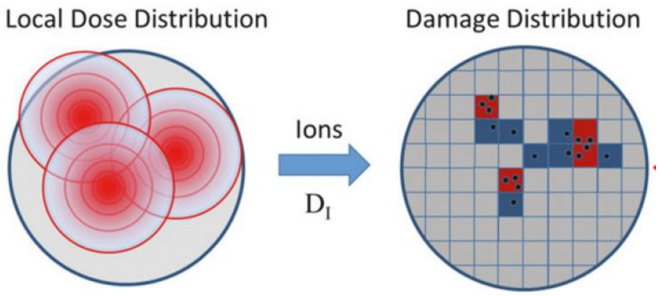
A lack of oxygen (hypoxia) makes a tumor more radiation resistant

Heavy ions can be used to treat hypoxic tumors!

How to calculate RBE

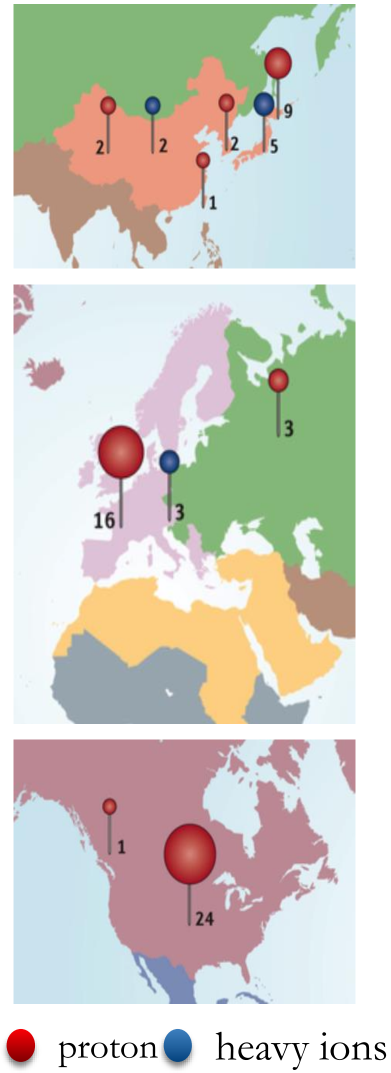
1) Biophysical/Mechanistic (Theoretical)

- **MKM** = Microdosimetric Kinetic Model
- **LEM** = Local Effect Model



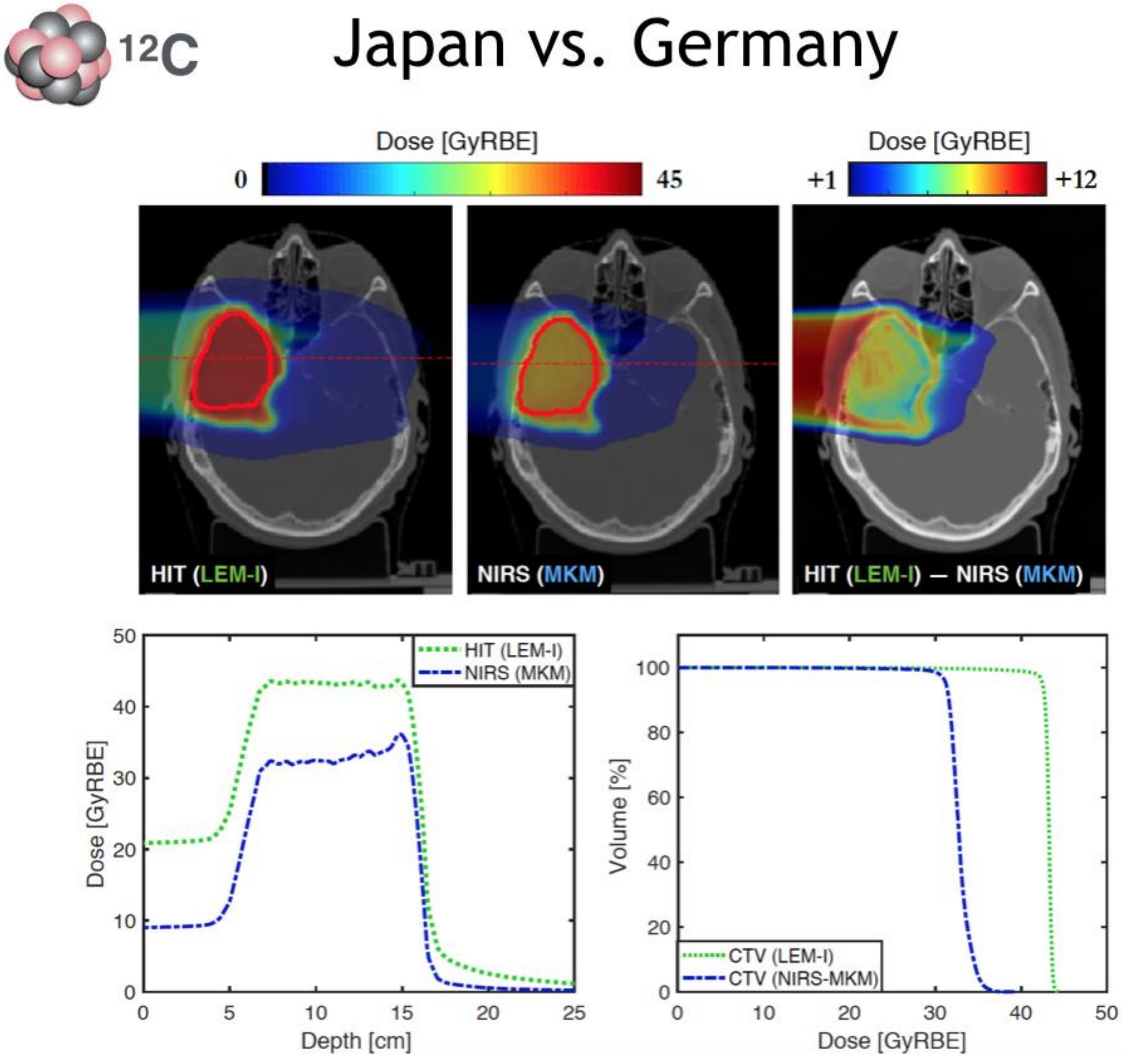
2) Phenomenological (Experimental)

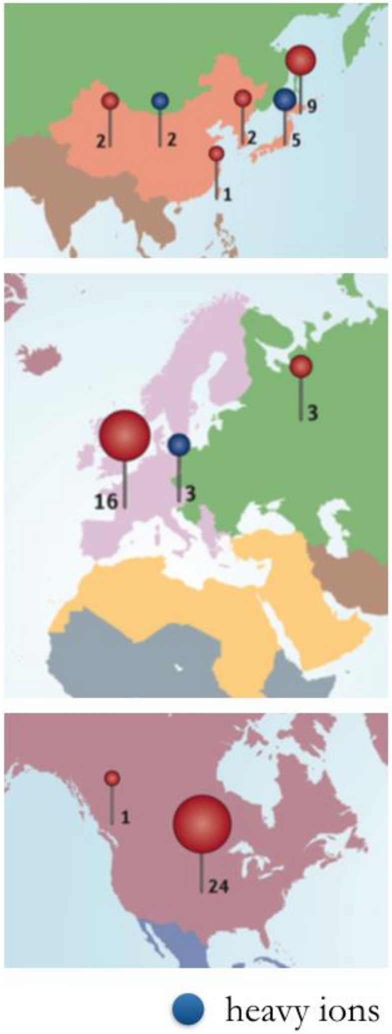
- "Data-driven"
- Interpretation of collected data from the literature



Durante et al 2017

How to calculate RBE

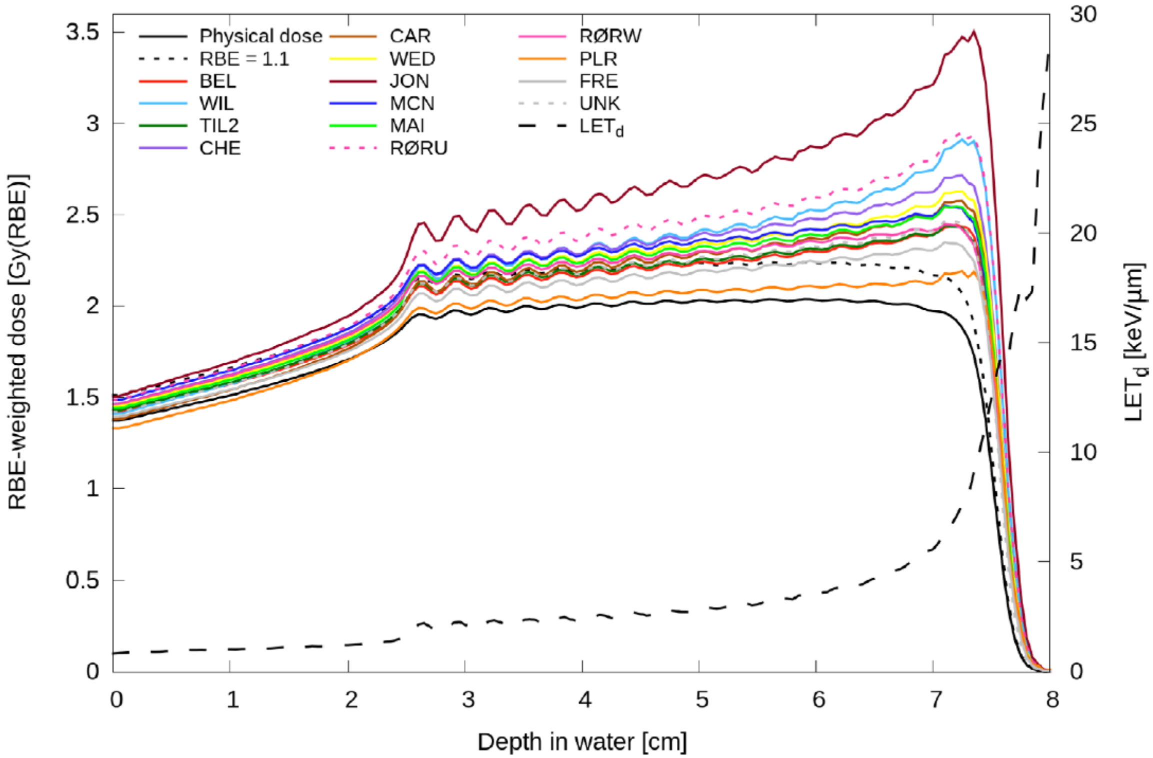




Durante et al 2017

How to calculate RBE for protons?

^{1}H



Rorvik et al 2018

Figure 3. Depth dose distribution of an SOBP in water with model estimates in colour curves. Uppermost curves represent the RBE-weighted dose given by the left axis, while the dashed black curve represents the LET_d given by the right axis. $(\alpha/\beta)_x$ value of 3.76 Gy was applied in the calculations.

RBE = 1.1 assumed in the clinic worldwide

Proton RBE = 1.1?

^{1}H

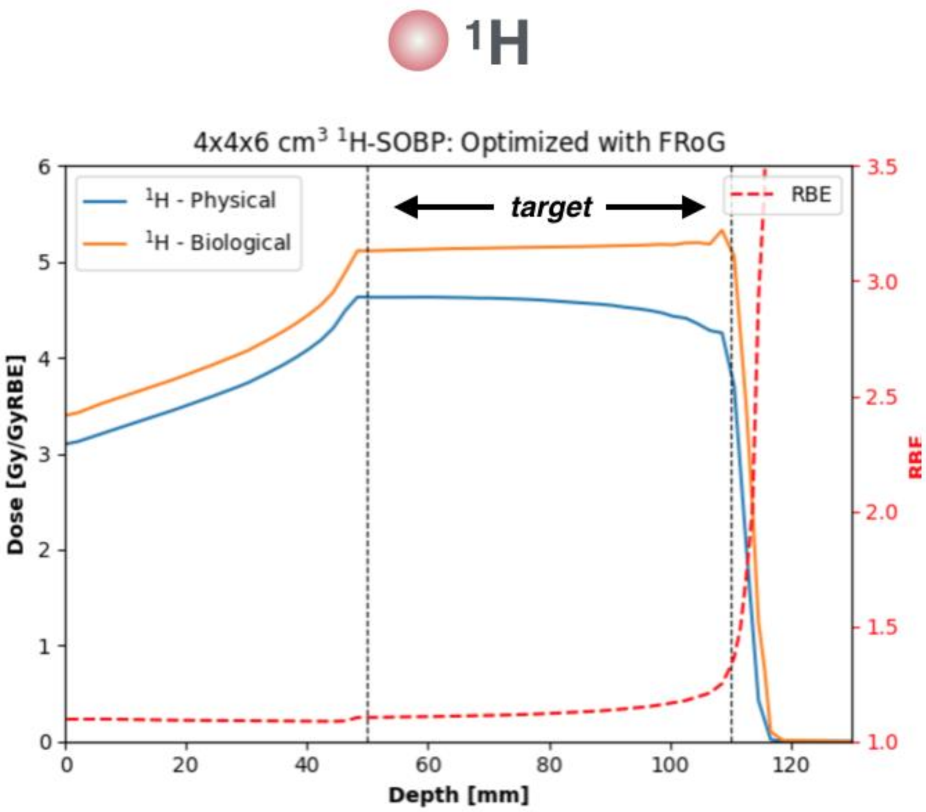
Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy

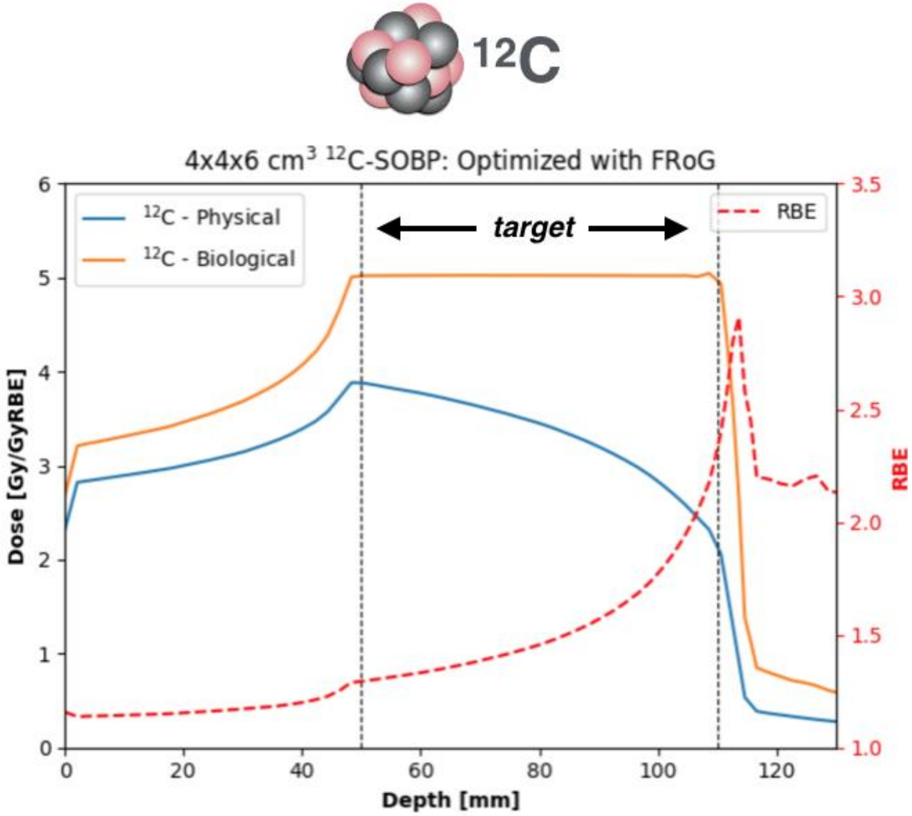
Harald Paganetti[a)]
Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

The biological effectiveness of proton beams relative to photon beams in radiation therapy has been taken to be 1.1 throughout the history of proton therapy. While potentially appropriate as an average value, actual relative biological effectiveness (RBE) values may differ. This Task Group report outlines the basic concepts of RBE as well as the biophysical interpretation and mathematical concepts. The current knowledge on RBE variations is reviewed and discussed in the context of the current clinical use of RBE and the clinical relevance of RBE variations (with respect to physical as well as biological parameters). The following task group aims were designed to guide the current clinical practice:

1. Assess whether the current clinical practice of using a constant RBE for protons should be revised or maintained.
2. Identifying sites and treatment strategies where variable RBE might be utilized for a clinical benefit.
3. Assess the potential clinical consequences of delivering biologically weighted proton doses based on variable RBE and/or LET models implemented in treatment planning systems.
4. Recommend experiments needed to improve our current understanding of the relationships among in vitro, in vivo, and clinical RBE, and the research required to develop models. Develop recommendations to minimize the effects of uncertainties associated with proton RBE for well-defined tumor types and critical structures. [https://doi.org/10.1002/mp.13390]

Proton RBE


1H
4x4x6 cm3 1H-SOBP: Optimized with FRoG
1H - Physical
1H - Biological
RBE
target
Dose [Gy/GyRBE]
Depth [mm]
RBE


12C
4x4x6 cm3 12C-SOBP: Optimized with FRoG
12C - Physical
12C - Biological
RBE
target
Dose [Gy/GyRBE]
Depth [mm]
RBE

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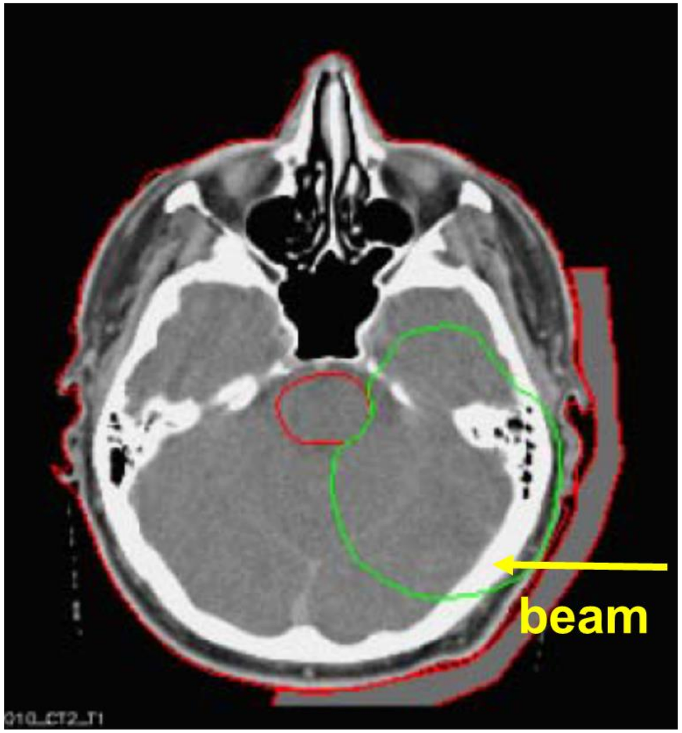
Treatment Planning Systems

- Acquisition of imaging data (CT, MRI, PET)
- Delineation of regions of interest
- Selection of proton/ion beam directions
- Design of each beam
- Optimization of the plan

main input for dose calculation:

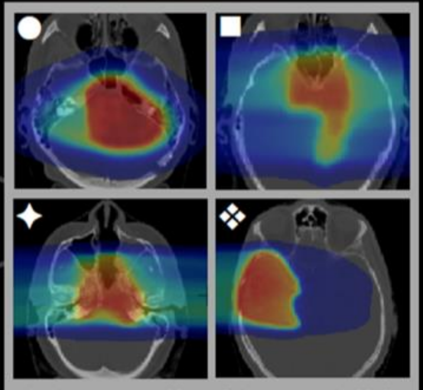
dosimetric description of the interaction of the beam in water



FRoG

●proton ■helium ✦carbon ❖oxygen

Rapid
Robust



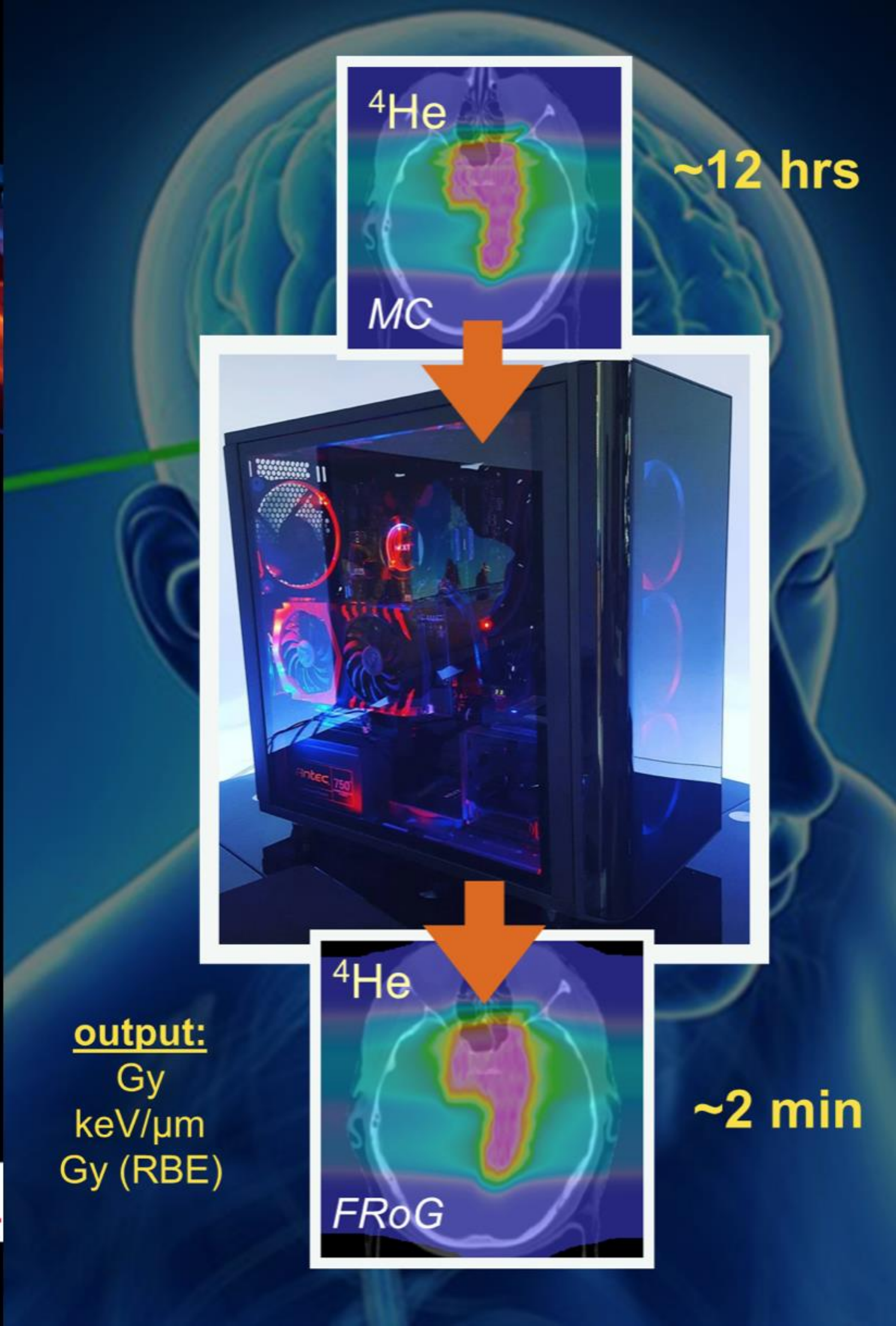
Validation against Monte Carlo (submitted, 2018)

next generation
dose engine in particle therapy

HIT dkfz. NCT DKTK HIRO CNAO

S Mein, K Choi, B Kopp, T Tessonnier, J Bauer, A Ferrari, T Haberer, J Debus, A Abdollahi, A Mairani*

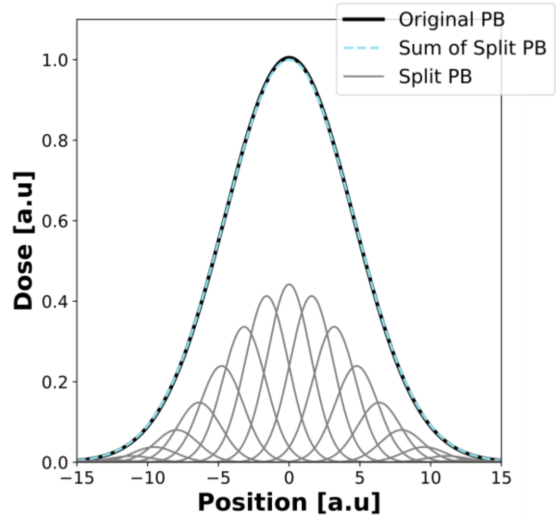
andrea.mairani@med.uni-heidelberg.de

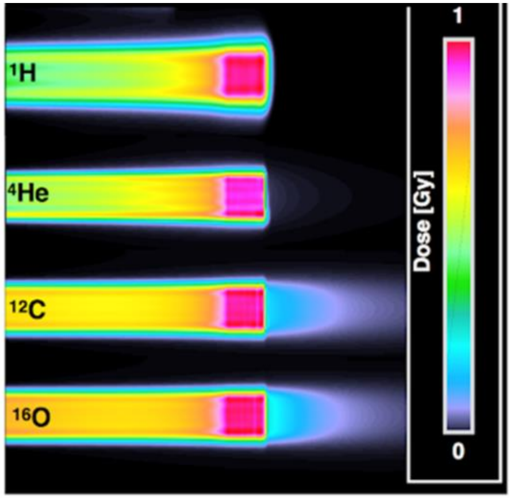


FRoG – Philosophy and Goals

FRoG was developed at HIT and CNAO in 2017

- Analytical dose calculation engine with pencil beam splitting approach (N ≈ 350/700)
- Provides more than just physical dose (LET_d, D_{RBEp}, D_{LEM}, D_{MKM})
- For all available ions at HIT (^{1}H, ^{4}He, ^{12}C, ^{16}O)
- Clinical and research tool
- Aims for Monte Carlo-like accuracy
- Short calculation times through GPU utilization





S. Mein et al. 2018 Sci Rep.; K. Choi et al. 2018 Cancers 10, 395

FRoG – Code Framework I/II

python™

- DICOM files handling
- Pre/Post processing
- Graphical User Interface (GUI)
- Sandbox environment
- Scripting language
- …

NVIDIA®

- Pycuda API[1] for GPU link
- Raytracing on GPU
- Dose calculation on GPU
- GPGPU (e.g. trilinear interp.)
- …

[1] A. Klöckner et al. 2012 Parallel Computing, Volume 38

FRoG – Code Framework II/II

FRoG Graphical User Interface

scripting_FRoG_example.py | dummy.py

```python
from FROG import FROG_class

def main():
    FRoG = FROG_class(False)
    FRoG.HIT_Config(True)

    FRoG.Dicom_load.ct_clicked_main(ct_file, isGUI=Fa
    FRoG.Dicom_load.pl_clicked_main(pl_file, isGUI=Fa
    FRoG.Dicom_load.st_clicked_main(st_file, isGUI=Fa
    FRoG.Dicom_load.ds_clicked_main(ds_file, isGUI=Fa

    FRoG.exec_clicked()
    FRoG.Dose_cal_TG_clicked()
    FRoG.dosedcmsave_clicked()

if __name__ == "__main__":
    main()
```

FRoG Python Script

FRoG – Paper

2

cancers MDPI

Article

FRoG—A New Calculation Engine for Clinical Investigations with Proton and Carbon Ion Beams at CNAO

KyungDon Choi [1,2], Stewart B Mein [3,4], Benedikt Kopp [4,5], Giuseppe Magro [1], Silvia Molinelli [1], Mario Ciocca [1] and Andrea Mairani [1,6,*]

Received: 28 August 2018; Accepted: 16 October 2018; Published: 23 October 2018

Abstract: A fast and accurate dose calculation engine for hadrontherapy is critical for both routine clinical and advanced research applications. FRoG is a graphics processing unit (GPU)-based forward calculation tool developed at CNAO (Centro Nazionale di Adroterapia Oncologica) and at HIT (Heidelberg Ion Beam Therapy Center) for fast and accurate calculation of both physical and biological dose. FRoG calculation engine adopts a triple Gaussian parameterization for the description of the lateral dose distribution. FRoG provides dose, dose-averaged linear energy transfer,

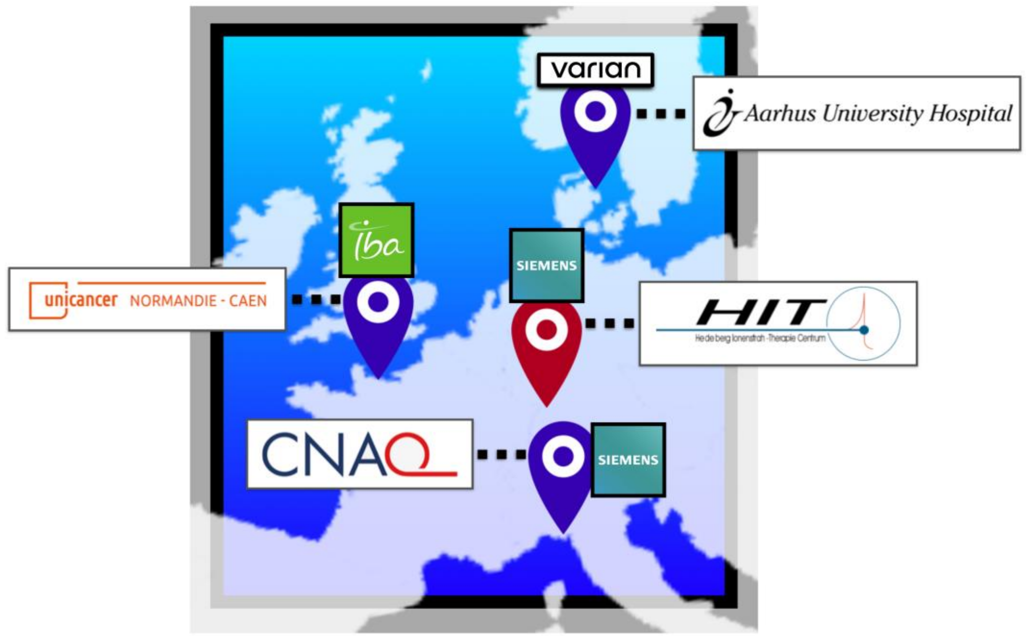
1

SCIENTIFIC REPORTS

Fast robust dose calculation on GPU for high-precision ^{1}H, ^{4}He, ^{12}C and ^{16}O ion therapy: the FRoG platform

Stewart Mein[1,2,3,4,5], Kyungdon Choi[6,7], Benedikt Kopp[2,5], Thomas Tessonnier[8], Julia Bauer[2], Alfredo Ferrari[9], Thomas Haberer[2], Jürgen Debus[1,2,3], Amir Abdollahi[1,2,3,4] & Andrea Mairani[2,6]

Radiotherapy with protons and heavier ions landmarks a novel era in the field of high-precision cancer therapy. To identify patients most benefiting from this technologically demanding therapy, fast assessment of comparative treatment plans utilizing different ion species is urgently needed. Moreover, to overcome uncertainties of actual *in-vivo* physical dose distribution and biological effects elicited by different radiation qualities, development of a reliable high-throughput algorithm is required. To this end, we engineered a unique graphics processing unit (GPU) based software architecture allowing rapid and robust dose calculation. FRoG, Fast Recalculation on GPU, currently operates with four particle beams available at Heidelberg Ion Beam Therapy center, i.e., raster-scanning proton (^{1}H), helium (^{4}He), carbon (^{12}C) and oxygen ions (^{16}O). FRoG enables comparative analysis of different models for estimation of physical and biological effective dose in 3D within minutes and in excellent agreement with the gold standard *Monte Carlo (MC)* simulation. This is a crucial step towards development of next-generation patient specific radiotherapy.



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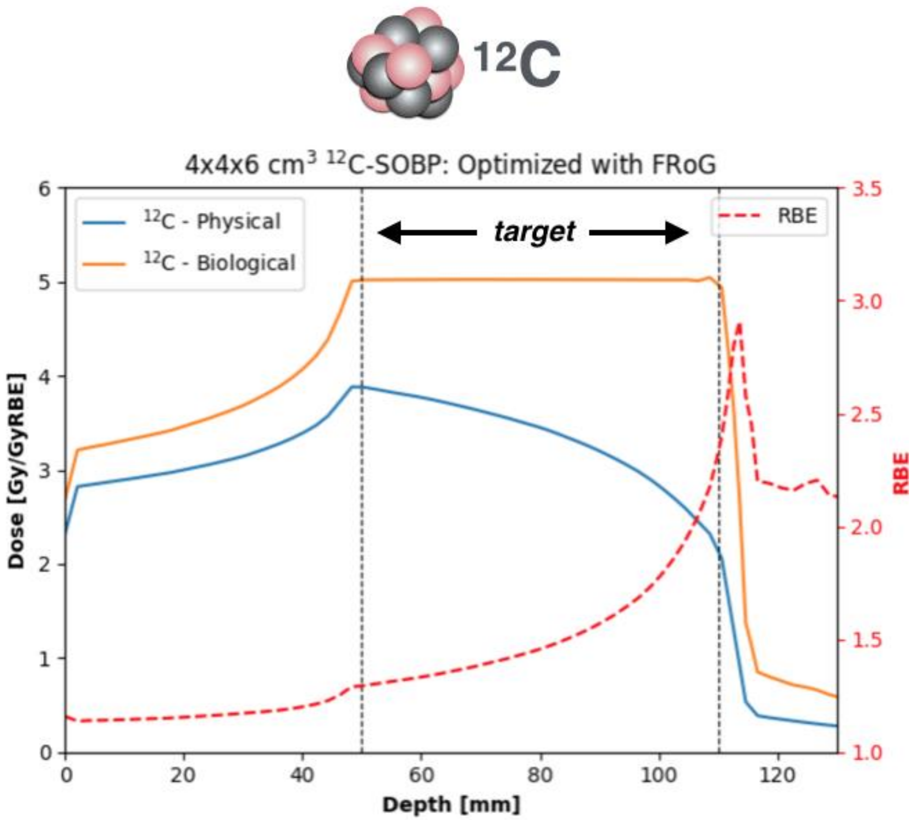
Quick Callback on ^{12}C RBE



Multi-Ion Particle Therapy

International Journal of
Radiation Oncology
biology • physics
Official Journal of the American Society for Radiation Oncology
ASTRO

Physics Contribution

Development and Validation of Single Field Multi-Ion Particle Therapy Treatments

Check for updates

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Ivana Dokic, PhD,[*,†,‡,§] **Semi Harrabi, MD,**[§,¶,#,**,††]
Till Tobias Böhlen, PhD,[‡‡] **Thomas Haberer, PhD,**[††]
Jürgen Debus, MD, PhD,[‡,§,‖,¶,#,**,††] **Amir Abdollahi, MD, PhD,**[*,†,‡,§]
and Andrea Mairani, PhD[††,§§]

**Clinical Cooperation Unit Translational Radiation Oncology, National Center for Tumor Diseases (NCT), Heidelberg University Hospital (UKHD) and German Cancer Research Center (DKFZ); [†]Division of Molecular and Translational Radiation Oncology, Department of Radiation Oncology, Heidelberg Faculty of Medicine (MFHD) and Heidelberg University Hospital (UKHD), Heidelberg Ion-Beam Therapy Center (HIT), 69120; [‡]German Cancer Consortium (DKTK) Core-Center Heidelberg, German Cancer Research Center (DKFZ); [§]Clinical Cooperation Unit Radiation Oncology, Heidelberg Institute of Radiation Oncology (HIRO), National Center for Radiation Oncology (NCRO), Heidelberg University and German Cancer Research Center (DKFZ); [‖]Department of Physics and Astronomy, Heidelberg University; [¶]Department of Radiation Oncology, Heidelberg University Hospital; [#]Heidelberg Institute of Radiation Oncology (HIRO); **National Center for Tumor diseases (NCT); [††]Heidelberg Ion-Beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany; [‡‡]Center for Proton Therapy, Paul Scherrer Institute (PSI), Villigen, Switzerland; and [§§]National Centre of Oncological Hadrontherapy (CNAO), Medical Physics, Pavia, Italy*

Received May 14, 2019, and in revised form Aug 23, 2019. Accepted for publication Oct 1, 2019.

Summary

We introduce a particle therapy modality producing a constant relative biological effectiveness (RBE) in the target by combining multiple

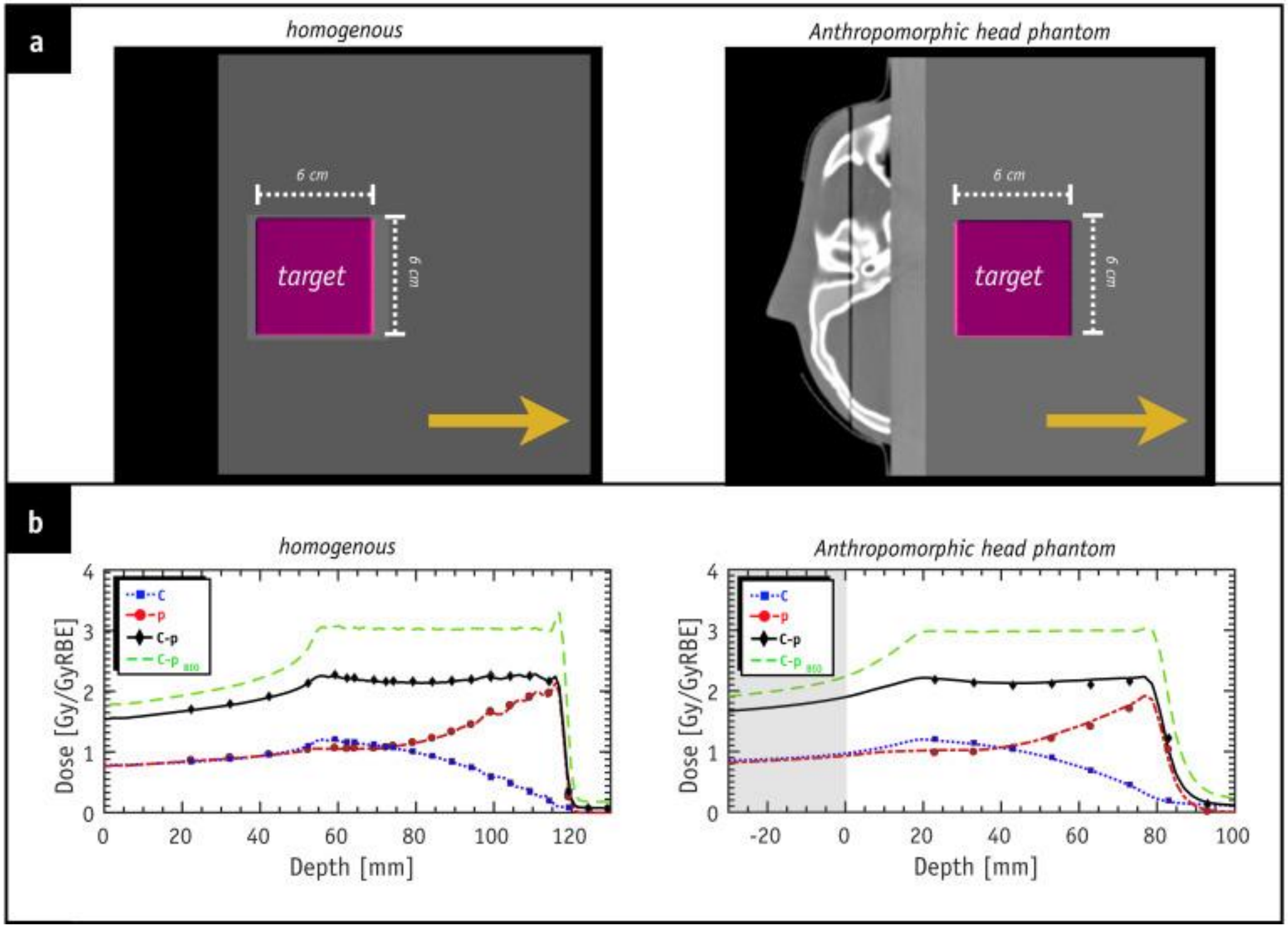
Purpose: To develop and validate combined ion-beam with constant relative biological effectiveness (RBE) (CICR) particle therapy in single field arrangements for improved treatment efficacy, robustness, and normal tissue sparing.

Methods and Materials: The PRECISE (PaRticle thErapy using single and Combined Ion optimization StratEgies) treatment planning system was developed to investigate clinical viability of CICR treatments. Single-field uniform dose (SFUD) with a single

What happens if we mix multiple ions in the same field?

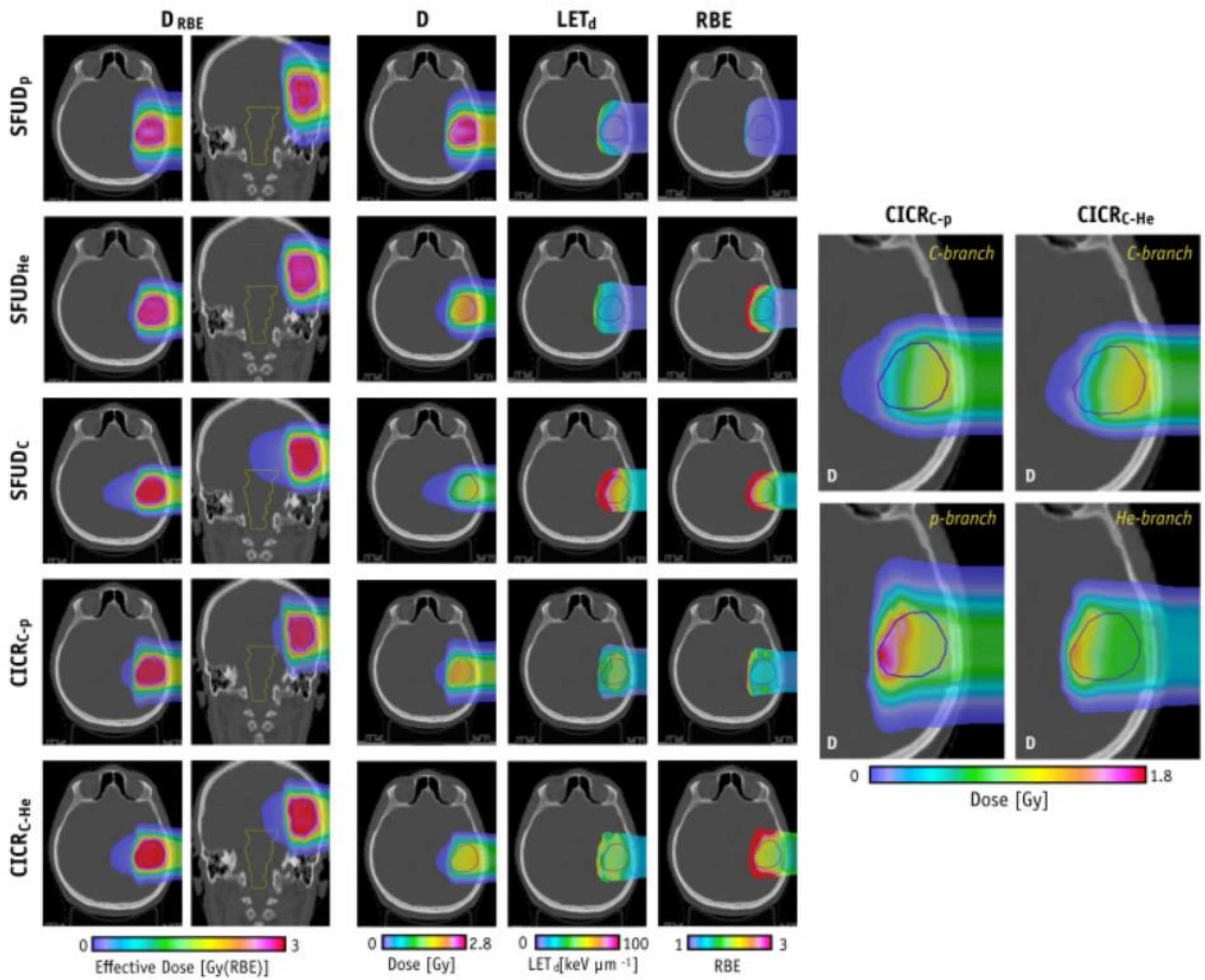
For example:

Mixing ^{1}H and ^{12}C RBE



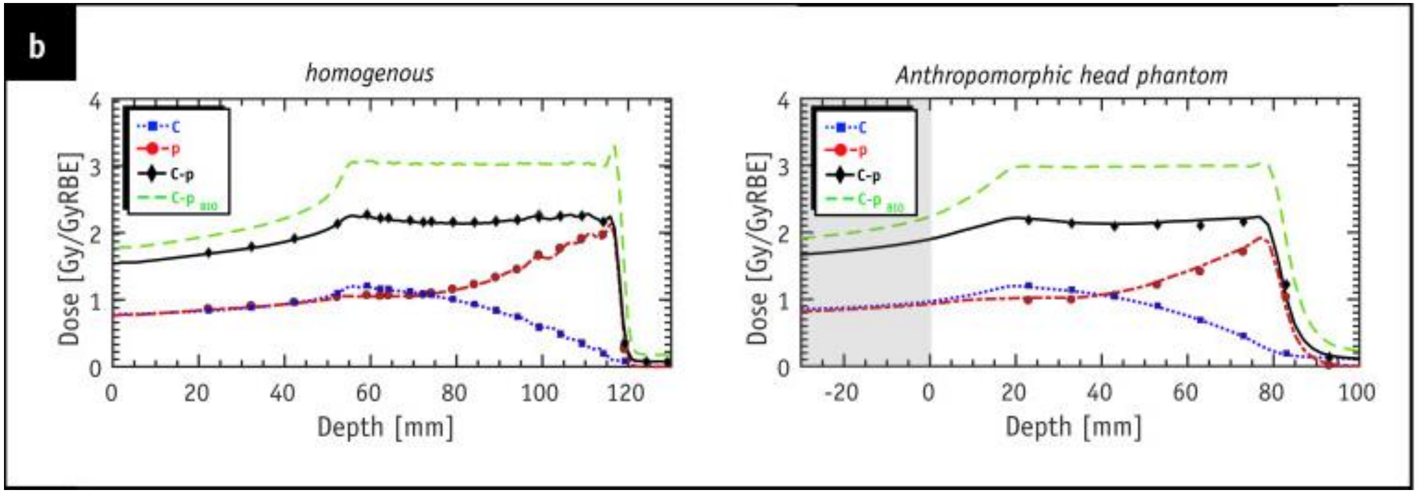
Kopp et al. 2020 IJROBP

Mixing
^{1}H and ^{12}C RBE



Kopp et al. 2020 IJROBP

Mixing
^{1}H and ^{12}C RBE



Adapted from Kopp et al. 2020 IJROBP

Mixing multiple ions in the same field can reduce biological uncertainties accompanied with heavy ion therapy!

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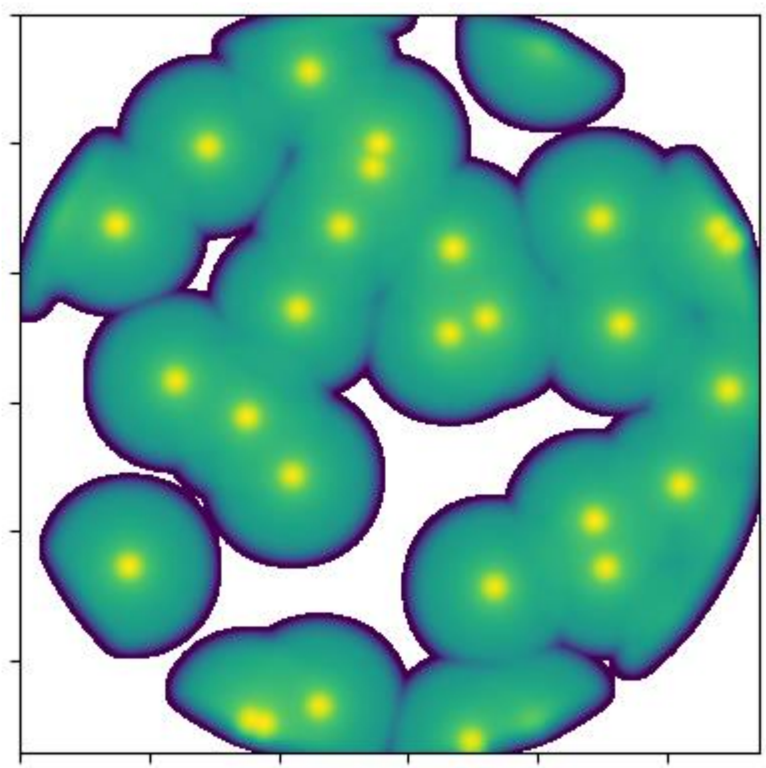
UNIVERSE



"UNIfied and VERSatile bio response Engine" (UNIVERSE) (Liew et al. 2019)

GPU Based Monte Carlo

Cell survival simulation engine

Used for all available ions + photons and cell types

Unpublished Data - Courtesy of Hans Liew (BioPT group)

BioPT Website

https://www.klinikum.uni-heidelberg.de/radiologische-klinik/radioonkologie-und-strahlentherapie/forschung/forschungsschwerpunkte/biophysik-in-der-partikeltherapie

End of Part III/II

HEIDELBERG UNIVERSITY HOSPITAL

Any Questions?

Send me an E-mail: **B.Kopp@dkfz-heidelberg.de**