02.07.2019

Radiobiology and progress in dose calculation in PT: the FRoG platform

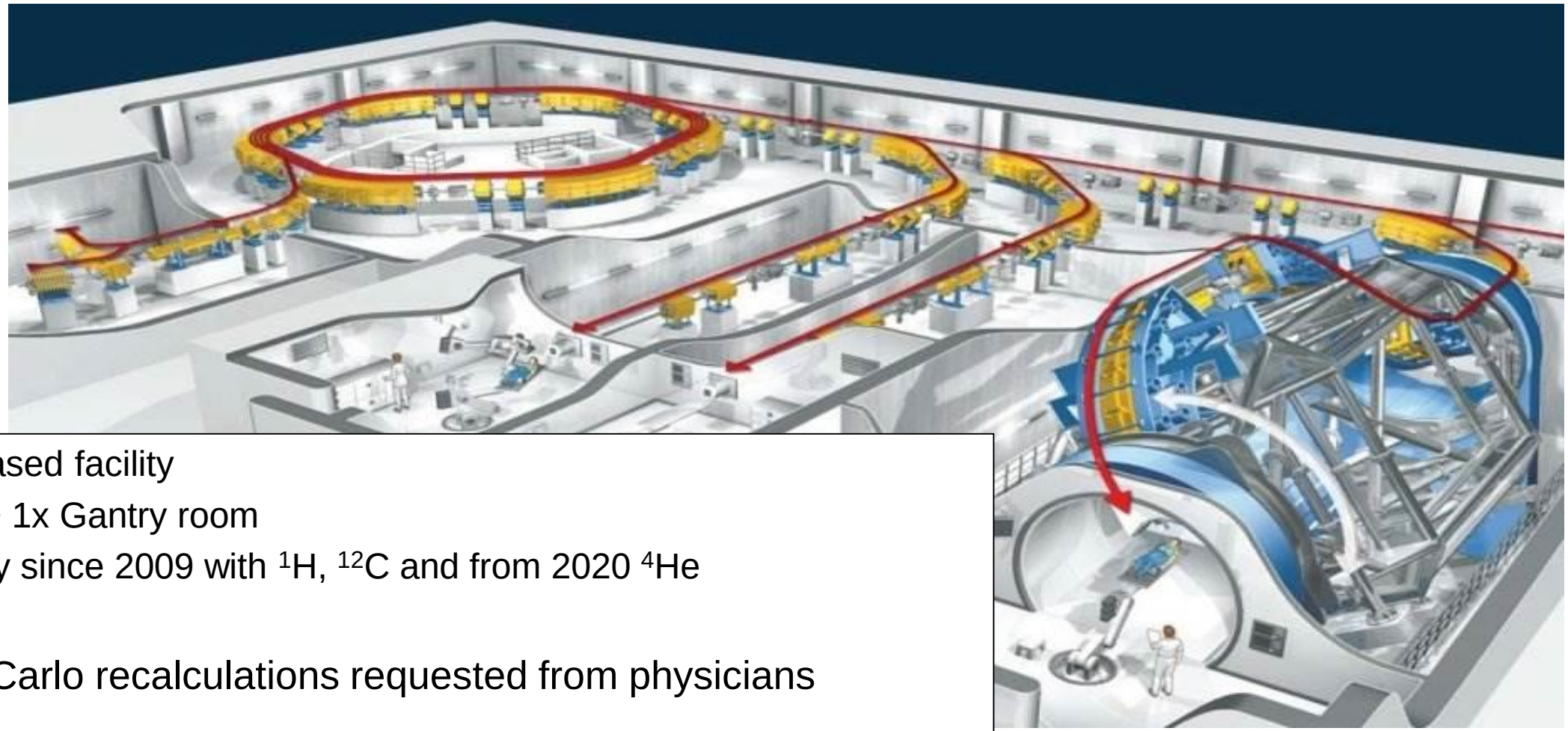
PD Dr. Andrea Mairani
Group Leader, Biophysics in Particle Therapy Group (BioPT)
Heidelberg Ion-beam Therapy Center (HIT), Heidelberg, Germany
National Centre of Oncological Hadrontherapy (CNAO)

ENLIGHT Annual Meeting and Training 2019, Caen, France

BioPT

HEIDELBERG UNIVERSITY HOSPITAL

The Heidelberg Ion-Beam Therapy Center (HIT)



- Synchrotron-based facility
- 2x Horizontal + 1x Gantry room
- Particle therapy since 2009 with ^{1}H, ^{12}C and from 2020 ^{4}He

Patient Monte Carlo recalculations requested from physicians

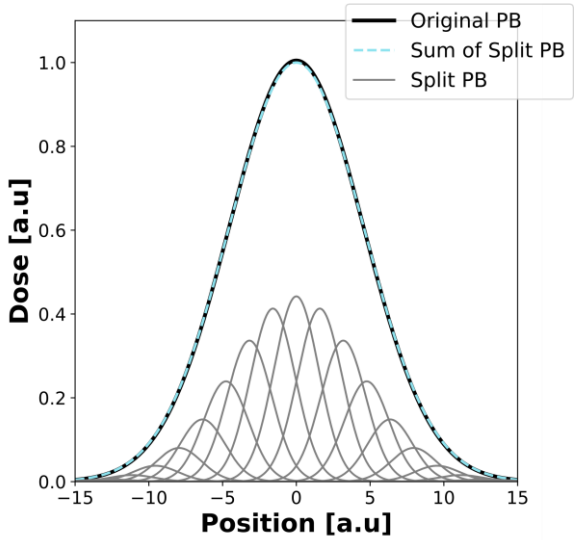
General purpose MC too slow in clinical practice!

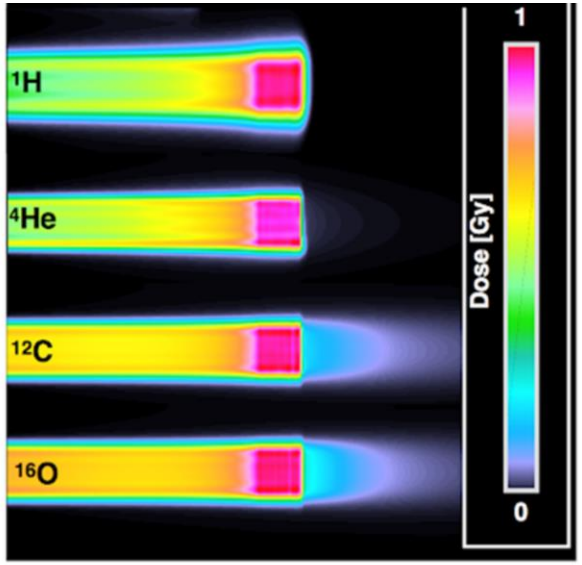
Inflexibility of clinical TPS — precompiled architecture.

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)
- Aims for MC-like accuracy
- Clinical viable calculation times through GPU utilization
- Clinical and research tool





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

FRoG – Code Framework I/II

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

- Pycuda API[1] for GPU link
- Raytracing on GPU
- Dose calculation on GPU
  - Maximise L1/Register usage
- GPGPU (e.g. trilinear interp.)
- …

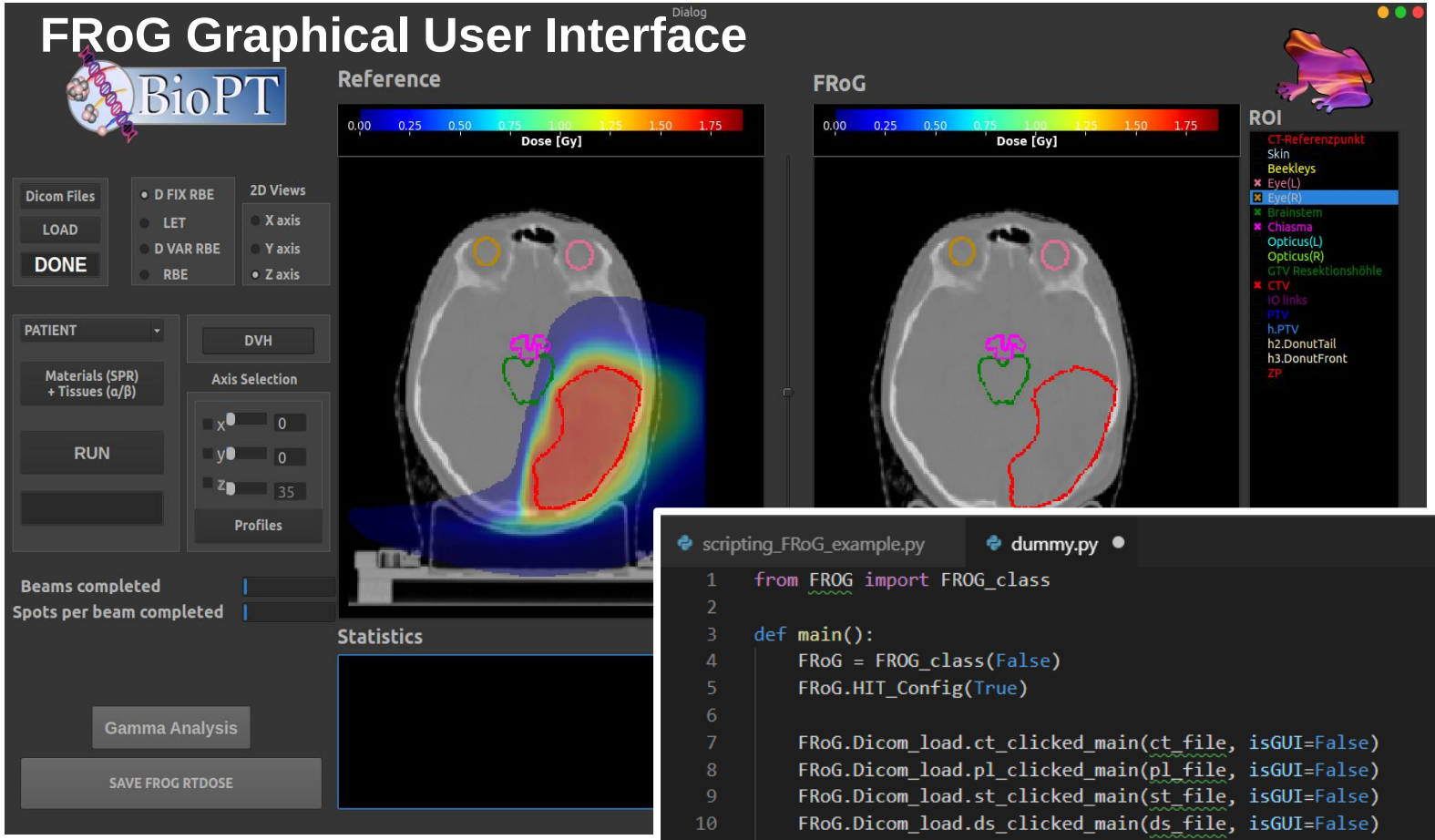
[1]A. Klöckner et al. 2012 Parallel Computing, Volume 38

FRoG – Code Framework II/II

FRoG modules:

- Gamma analysis
- QA routines (Dose readouts)
- Plan robustness analysis
- Automatic cohort analysis
- Dose* Volume Histogram (DVH) analysis
- multi-tissue radio-sensitivity (α/β) assignment

*LET_d, D_{RBE}, RBE…



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=False)
    FRoG.Dicom_load.pl_clicked_main(pl_file, isGUI=False)
    FRoG.Dicom_load.st_clicked_main(st_file, isGUI=False)
    FRoG.Dicom_load.ds_clicked_main(ds_file, isGUI=False)

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

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

FRoG Python Script

Clinical RBE: AAPM TG-256

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

Eleanor Blakely
Biological Systems and Engineering Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA

Alejandro Carabe-Fernandez
Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

David J. Carlson
Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, USA

Indra J. Das
New York University Langone Medical Center & Laura and Isaac Perlmutter Cancer Center, New York, NY, USA

Lei Dong
Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

David Grosshans
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Kathryn D. Held
Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Radhe Mohan
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Vitali Moiseenko
Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA, USA

Andrzej Niemierko
Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Robert D. Stewart
Department of Radiation Oncology, School of Medicine, University of Washington, Seattle, WA, USA

Henning Willers
Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

(Received 6 August 2018; revised 21 November 2018; accepted for publication 13 January 2019; published xx xxxx xxxx)

streamline clinical access to variable RBE / LET computation

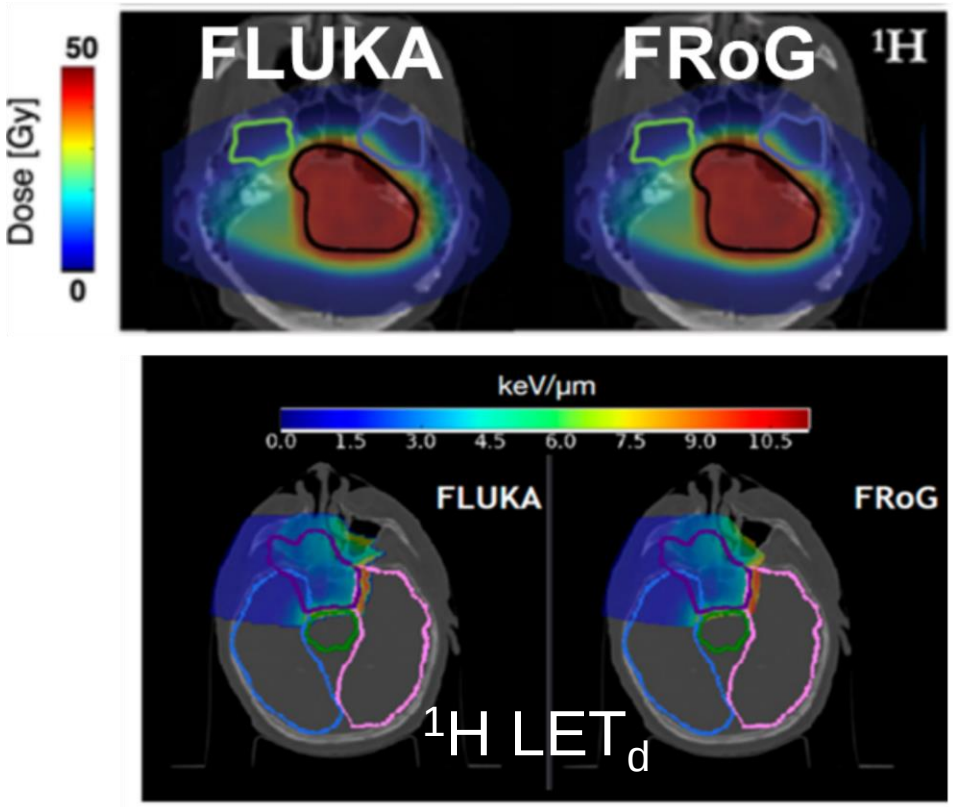
(Received 6 August 2018; revised 21 November 2018; accepted for publication 13 January 2019; published xx xxxx xxxx)

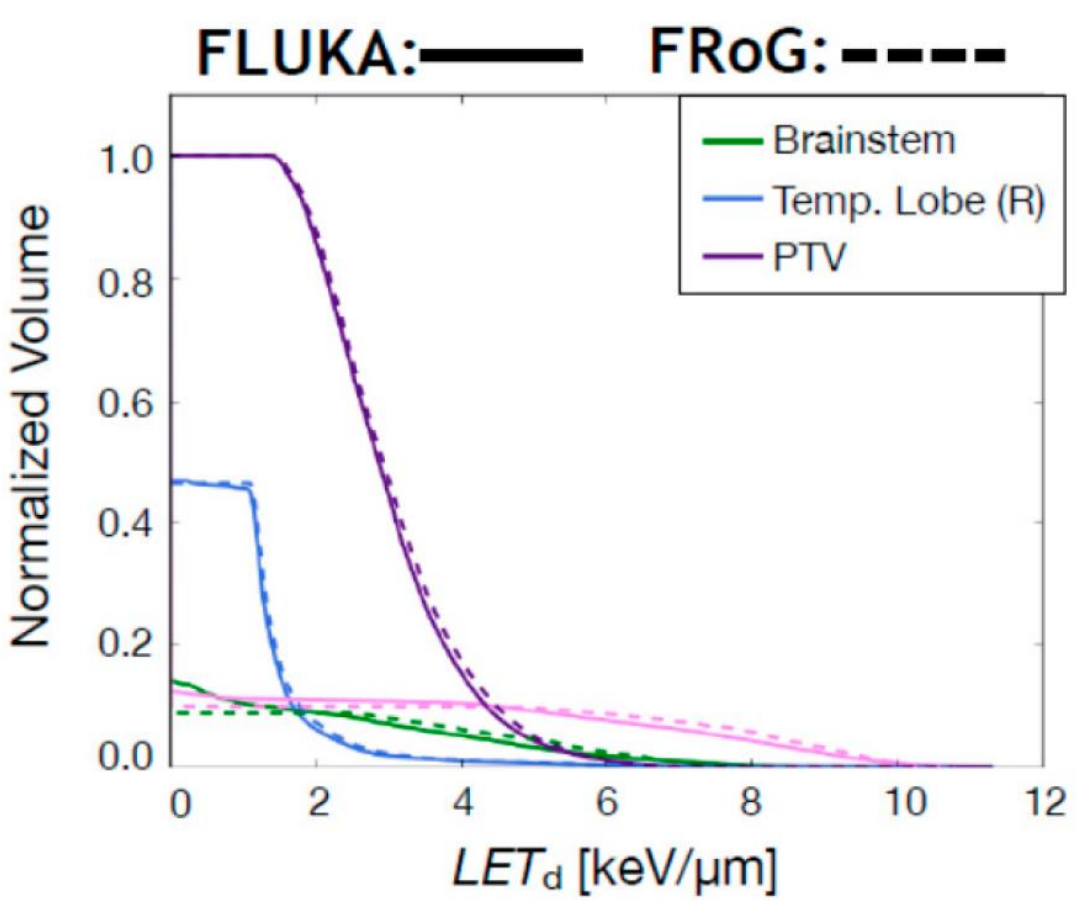
The biological effectiveness of proton beams relative to photon beams in radiation therapy has been taken to be 1.1 throughout the history of proton therapy. While potentially appropriate as an average value, actual relative biological effectiveness (RBE) values may differ. This Task Group report outlines 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]

FRoG – Validations

in silico





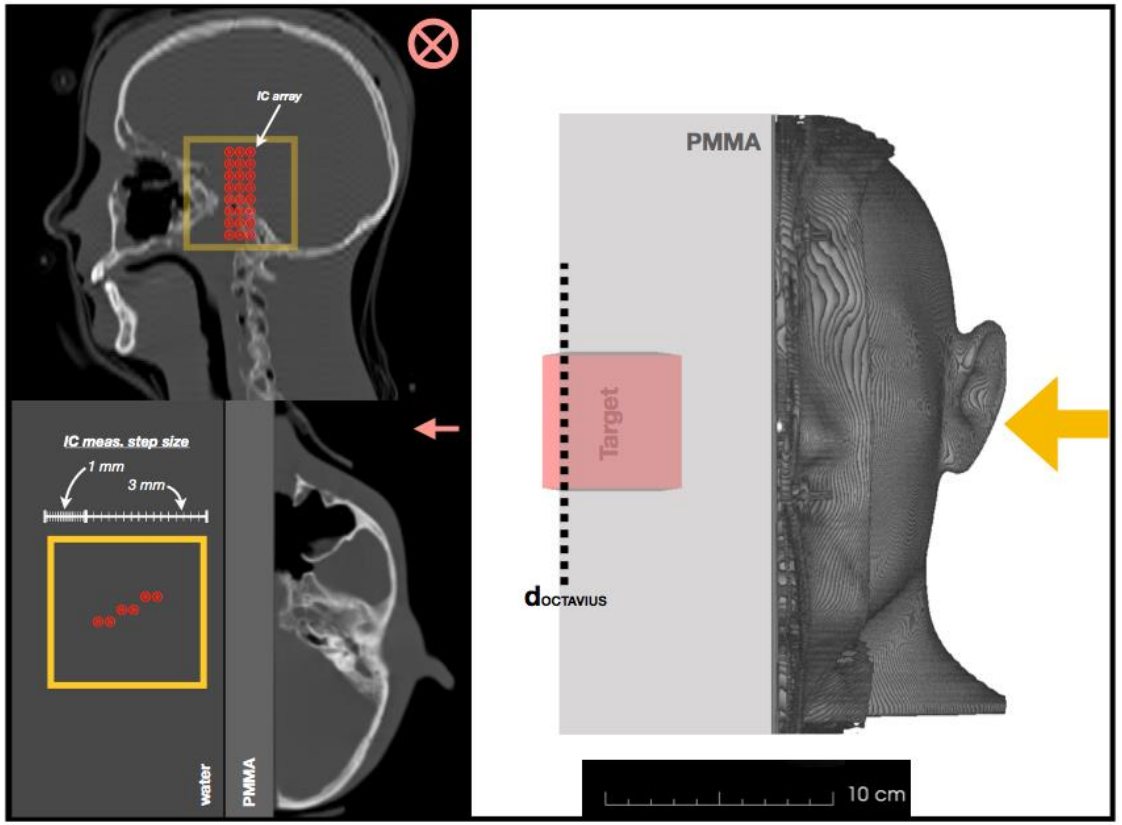
On average: FRoG matches FLUKAs D_{95}, D_{50}, D_5 within 2%. Measurements are ~2% difference.

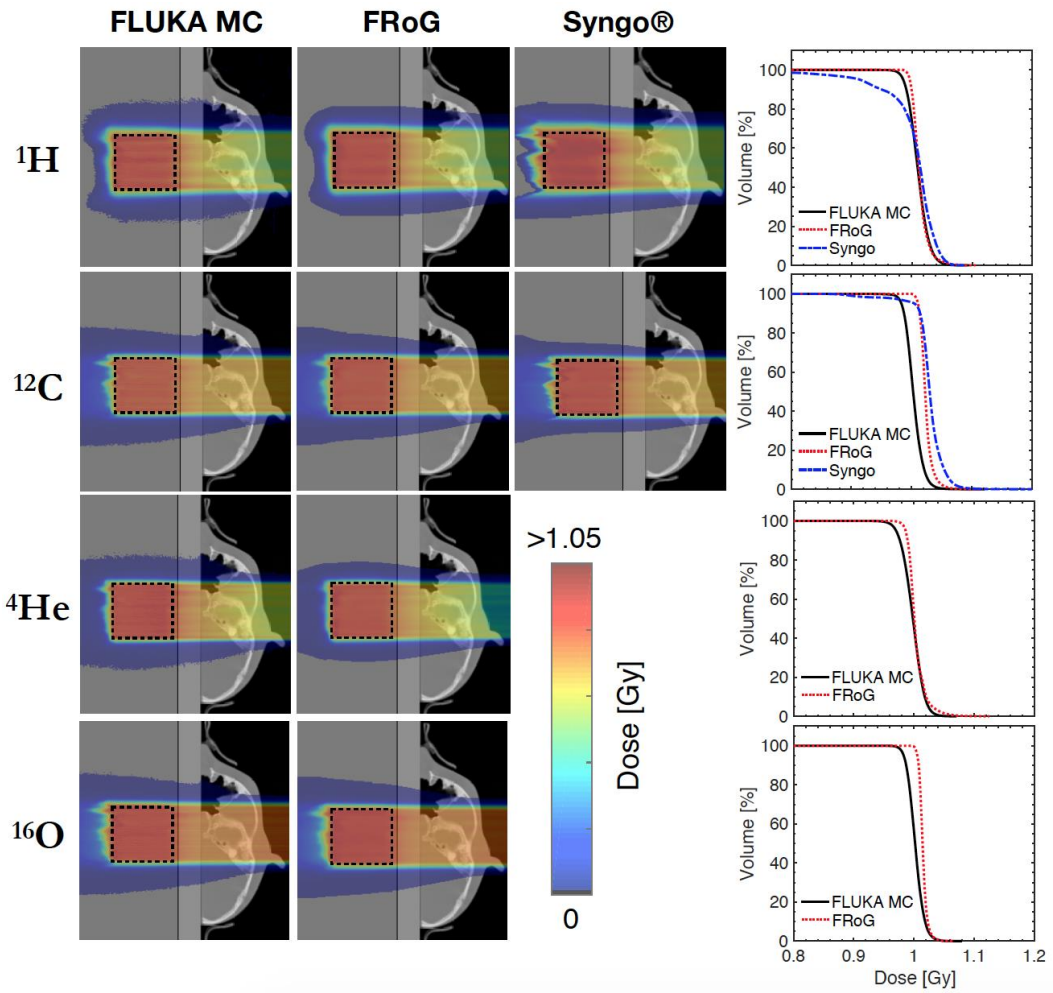
→ Calculation times are up to 200 times shorter than FLUKA at HIT

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

FRoG – Validations

experimental





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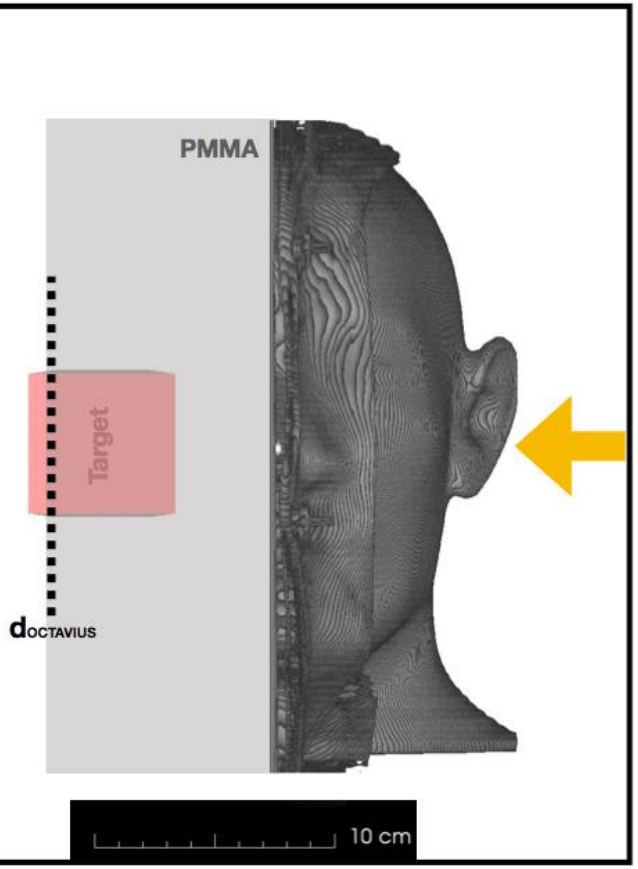
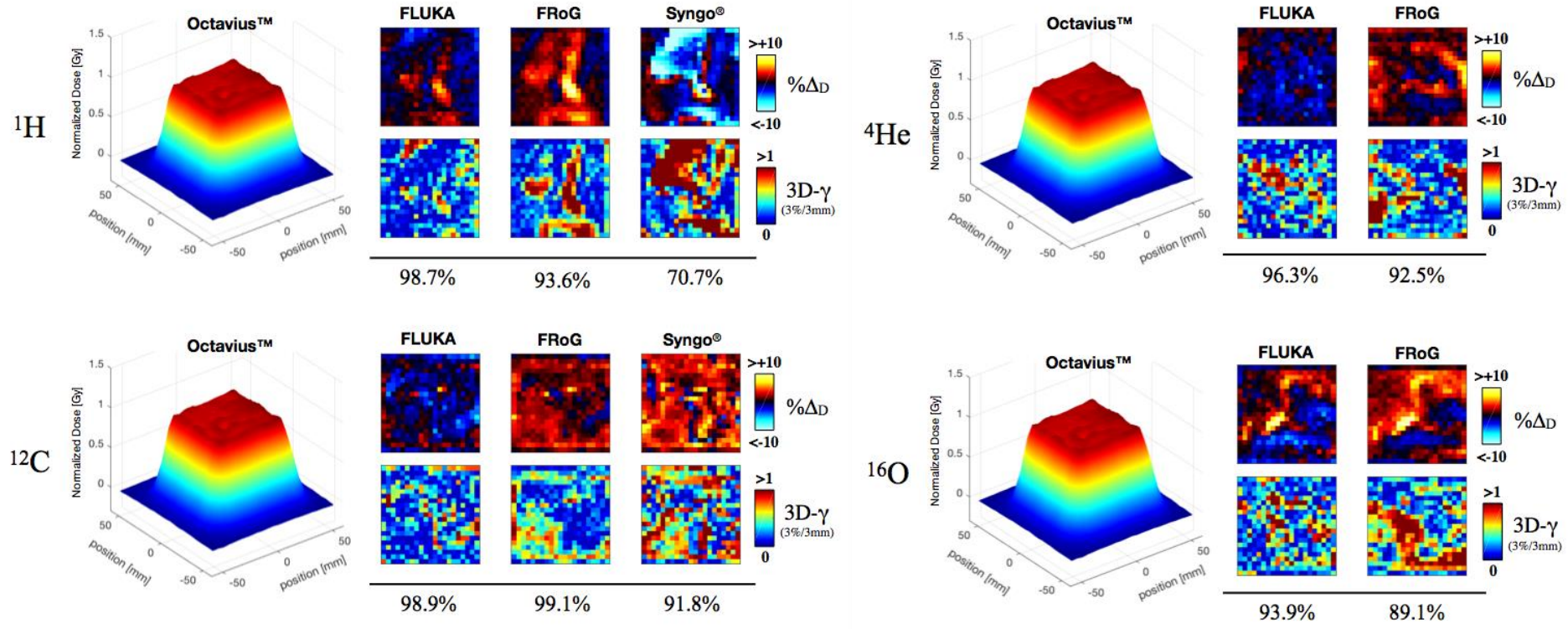
S. Mein et al 2019 Phys. Med.

FRoG – Verification

MC vs. FRoG vs. clinical TPS (AA)





S. Mein et al 2019 Phys. Med.

FRoG – Verification

MC vs. FRoG vs. clinical TPS (MC)

Physics Contribution

Pencil Beam Algorithms Are Unsuitable for Proton Dose Calculations in Lung

Paige A. Taylor, MS, Stephen F. Kry, PhD, and David S. Followill, PhD

The Imaging and Radiation Oncology Core Houston Quality Assurance Center, The University of Texas MD Anderson Cancer Center, Houston, Texas

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Received Jan 23, 2017, and in revised form May 16, 2017. Accepted for publication Jun 5, 2017.

Summary

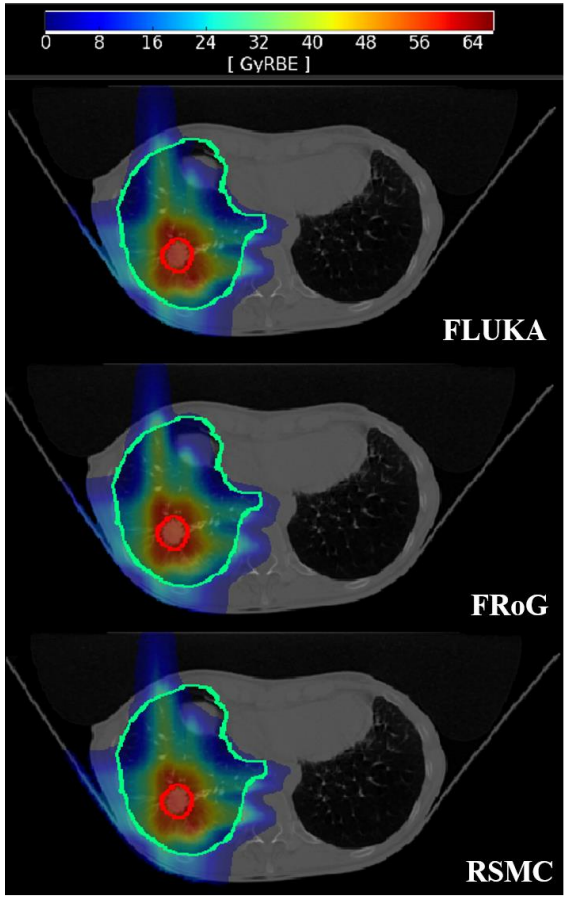
Commercial analytic proton algorithms were compared with measurements and Monte Carlo–based algorithms in a multi-institution phantom study. The analytic algorithms dramatically and consistently overestimated delivered dose up to 31% in the iGTV and 46% in the PTV. Monte Carlo algorithms and measurements showed considerably better agreement. Proton therapy centers should implement Monte Carlo–based (or other more advanced) algorithms in proton therapy for thoracic malignancies. Pencil beam algorithms for proton dose calculation in lung are unacceptable.

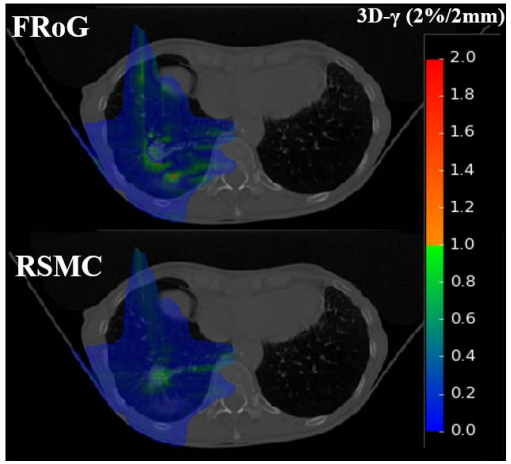
Purpose: To compare analytic and Monte Carlo–based algorithms for proton dose calculations in the lung, benchmarked against anthropomorphic lung phantom measurements.

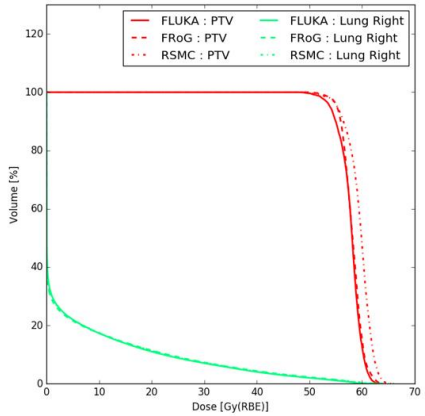
Methods and Materials: A heterogeneous anthropomorphic moving lung phantom has been irradiated at numerous proton therapy centers. At 5 centers the treatment plan could be calculated with both an analytic and Monte Carlo algorithm. The doses calculated in the treatment plans were compared with the doses delivered to the phantoms, which were measured using thermoluminescent dosimeters and film. Point doses were compared, as were planar doses using a gamma analysis.

Results: The analytic algorithms overestimated the dose to the center of the target by an average of 7.2%, whereas the Monte Carlo algorithms were within 1.6% of the physical measurements on average. In some regions of the target volume, the analytic algorithm calculations differed from the measurement by up to 31% in the internal gross target volume (iGTV) (46% in the planning target volume), over-predicting the dose. All comparisons showed a region of at least 15% dose discrepancy within the iGTV between the analytic calculation and the measured dose. The Monte Carlo algorithm recalculations showed dramatically improved agreement with the measured doses, showing mean agreement within 4% for all cases and a maximum difference of 12% within the iGTV.

Conclusions: Analytic algorithms often do a poor job predicting proton dose in lung tumors, over-predicting the dose to the target by up to 46%, and should not be used unless extensive validation counters the consistent results of the present study. Monte Carlo algorithms showed dramatically improved agreement with physical measurements and should be implemented to better reflect actual delivered dose distributions.



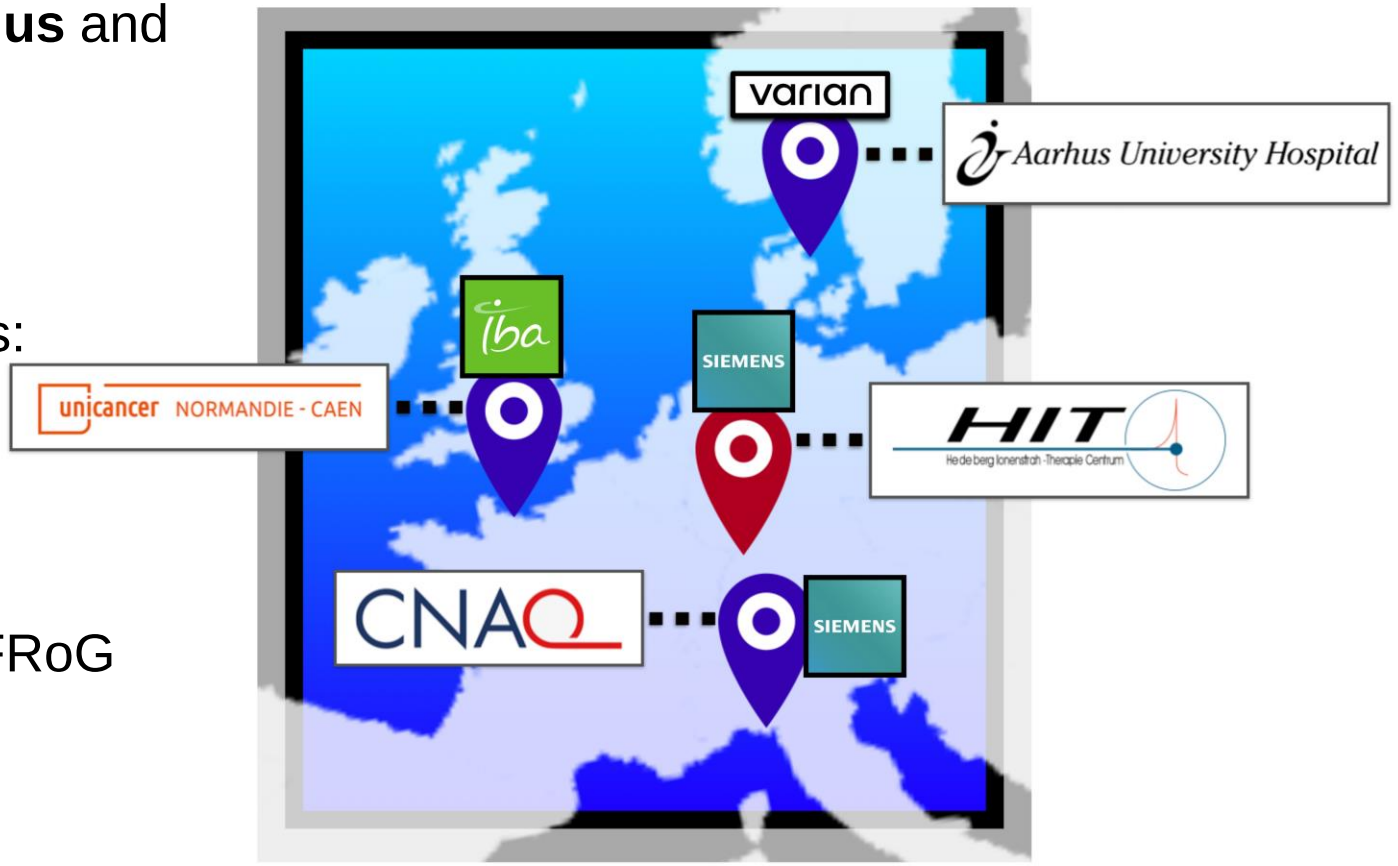




3D-γ passing rate (2mm/2%): RS-MC = 98%, FRoG = 94%

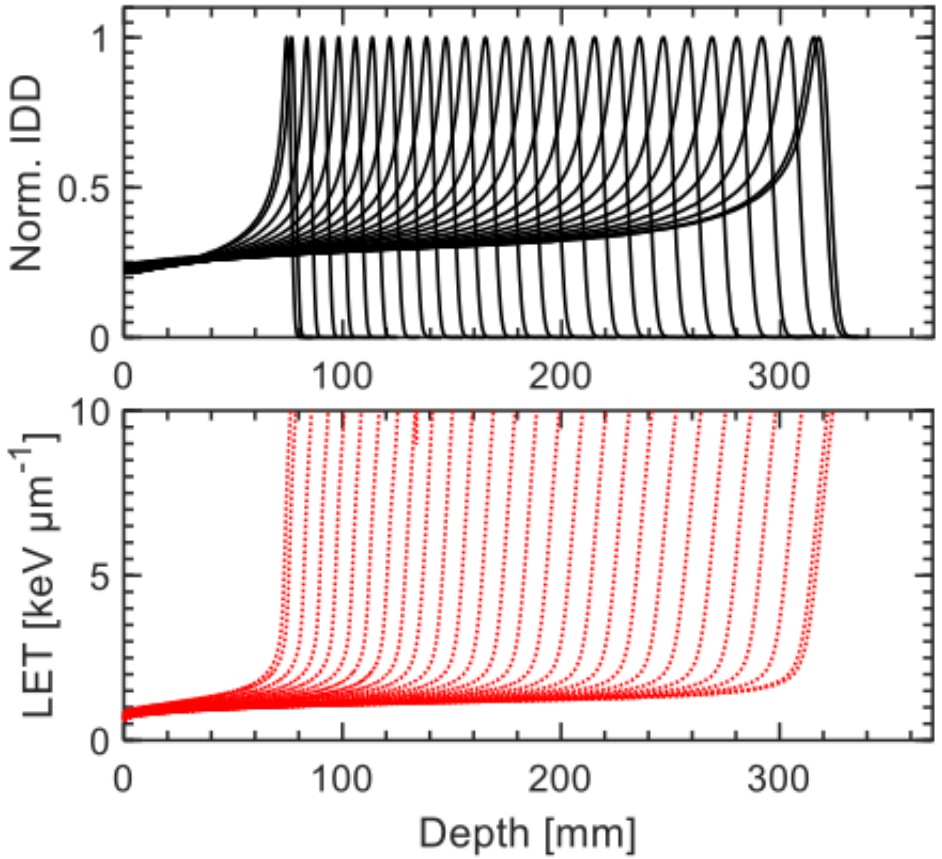
FRoG in 2019+

- FRoG installed at two new facilities (**Aarhus** and **Caen**)
- FRoG coupled with external optimizer
- Explore/Support new treatment modalities:
  - Helium ions (^{4}He)
  - Multi-ion optimization framework
- New biological models (e.g. Hypoxia) to FRoG



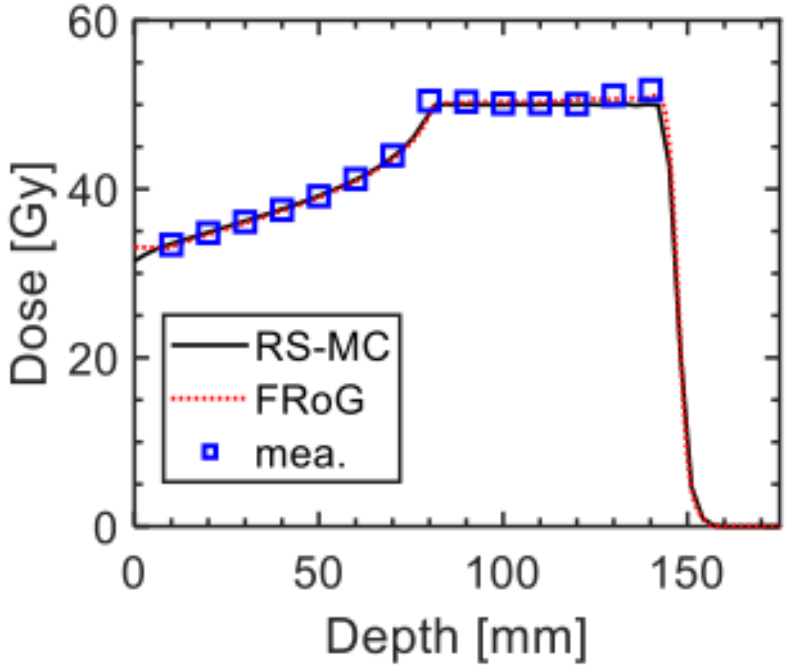
FRoG in Caen

- **Beam model + calibration**



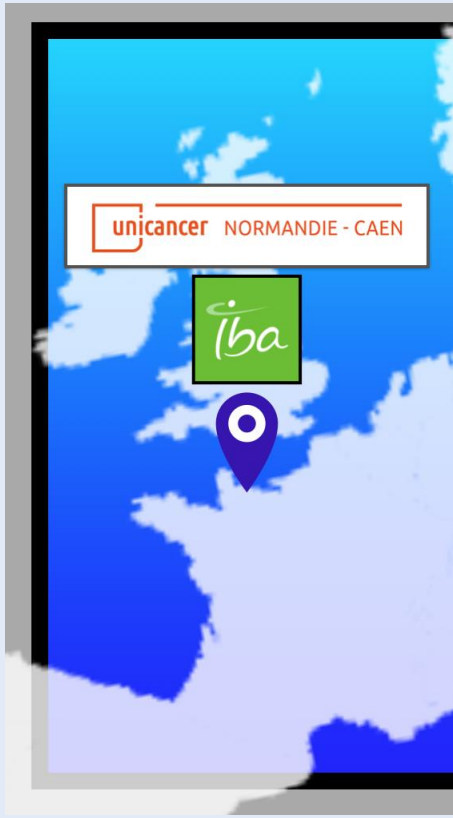
- **Physical dose validation**

SOBPs: 6x6x6 cm^3
depths [cm]: [5, 11, 15, 25]



$|\Delta_{FRoG}|$ = 1.03(±0.98)%

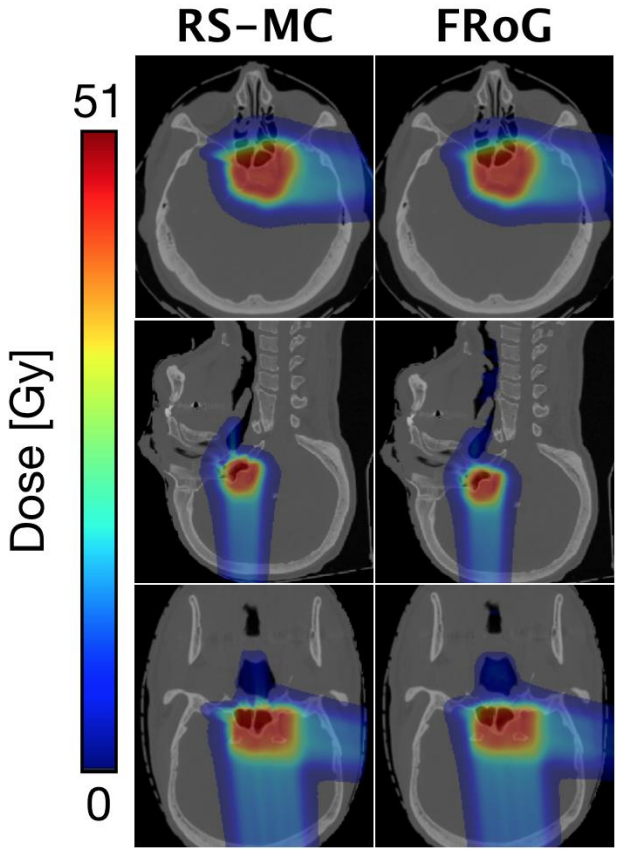
$|\Delta_{RSMC}|$ = 1.31(±1.36)%

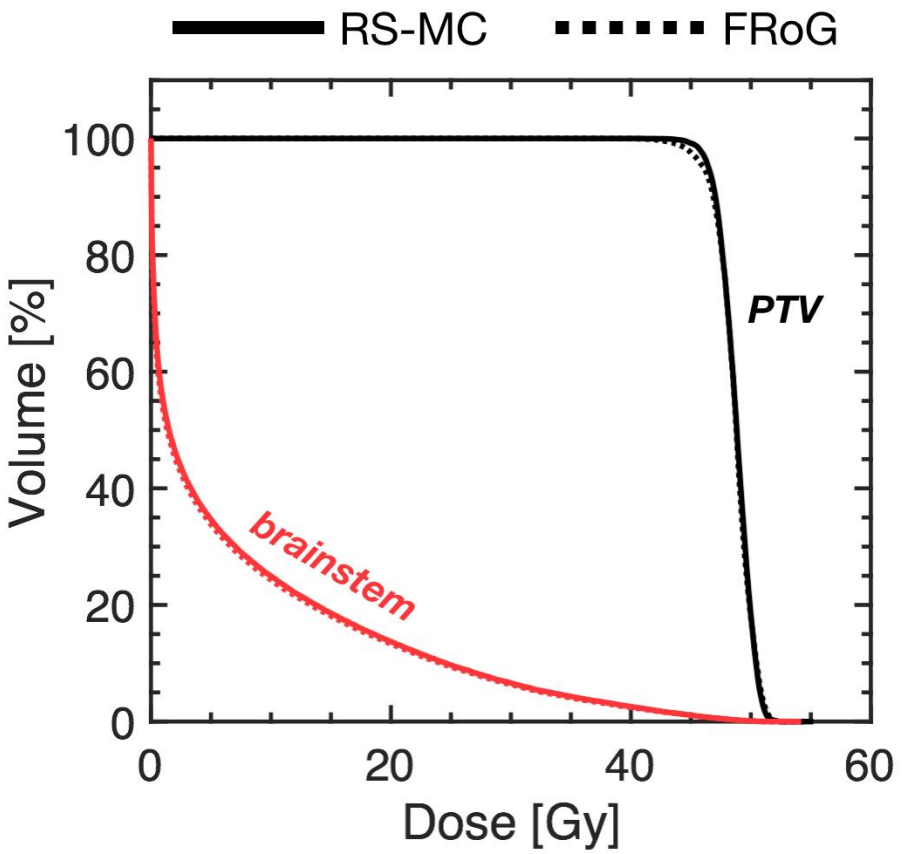


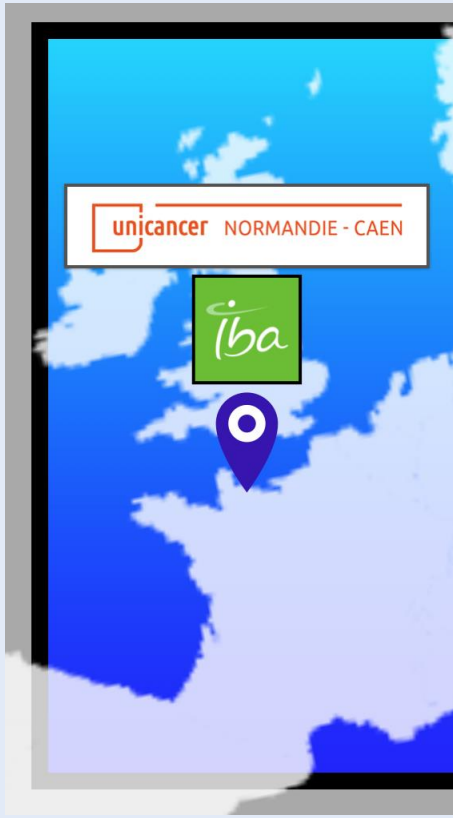
Mein & Tessonnier et al. 2019 (drafted)

FRoG in Caen

- **Physical dose validation (patients):**





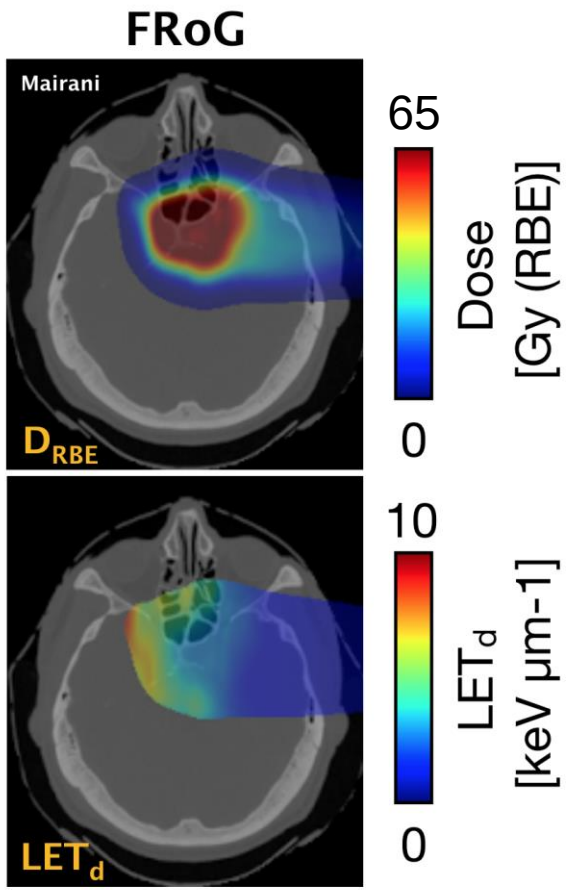


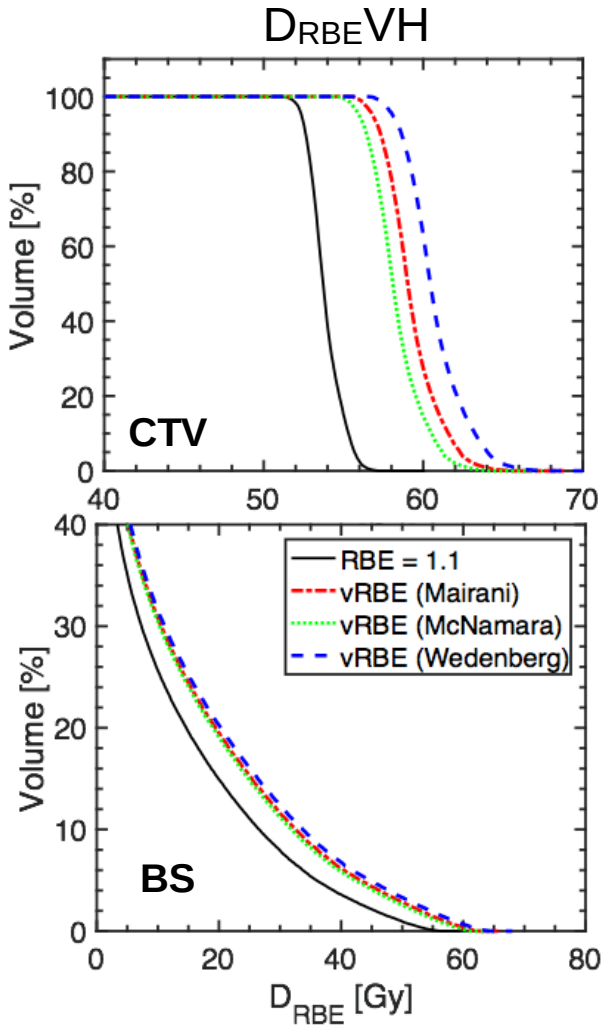
- Secondary dose engine for IBA-based facility

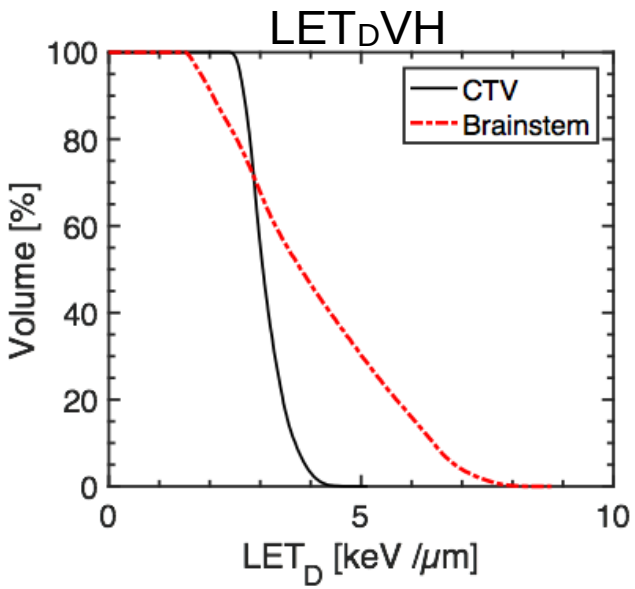
Mein & Tessonnier et al. 2019 (drafted)

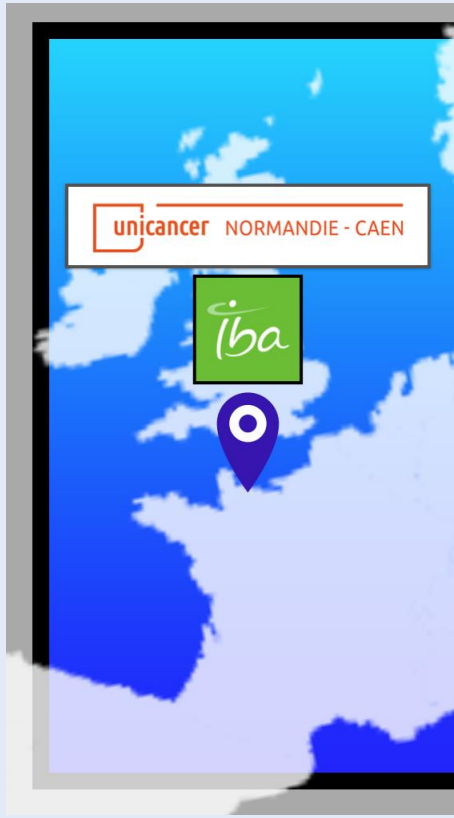
FRoG in Caen

- **Streamline access to LET_D / innovative biophysical dose computation**







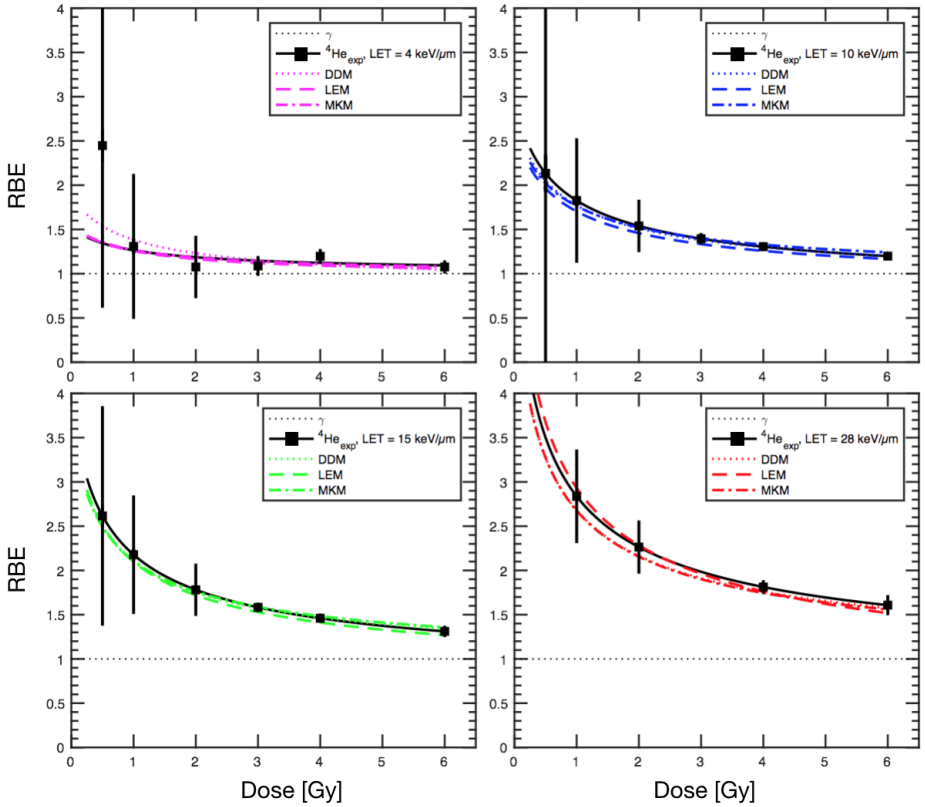


α/β = 2 Gy

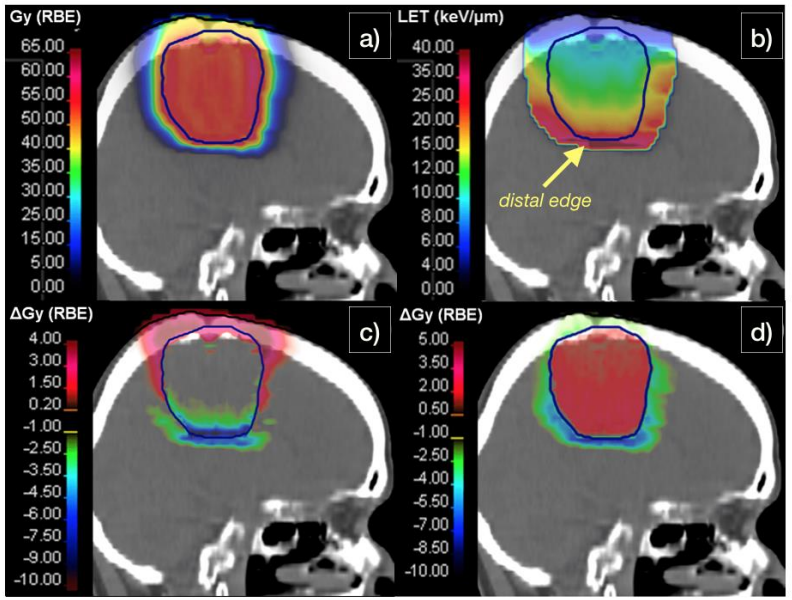
Mein & Tessonnier et al. 2019 (drafted)

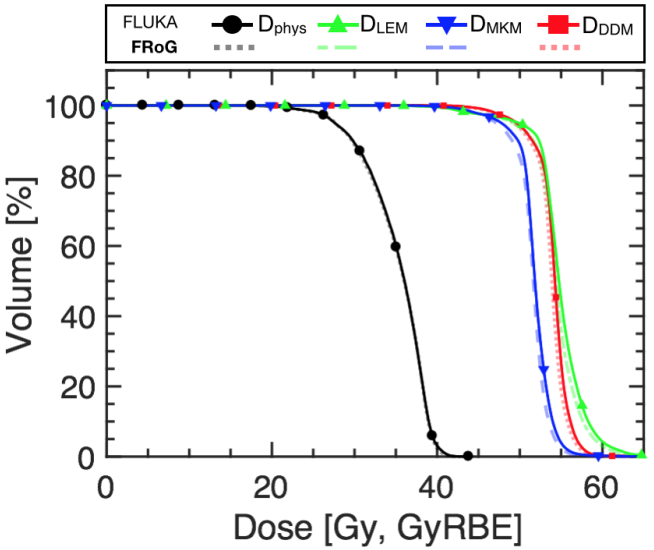
FRoG for ^{4}He

- **Validate reference biophysical dose computation (MC & FRoG) for developing first commercial TPS**



in silico vs. *in vitro*
Renca (α/β = 2 Gy)



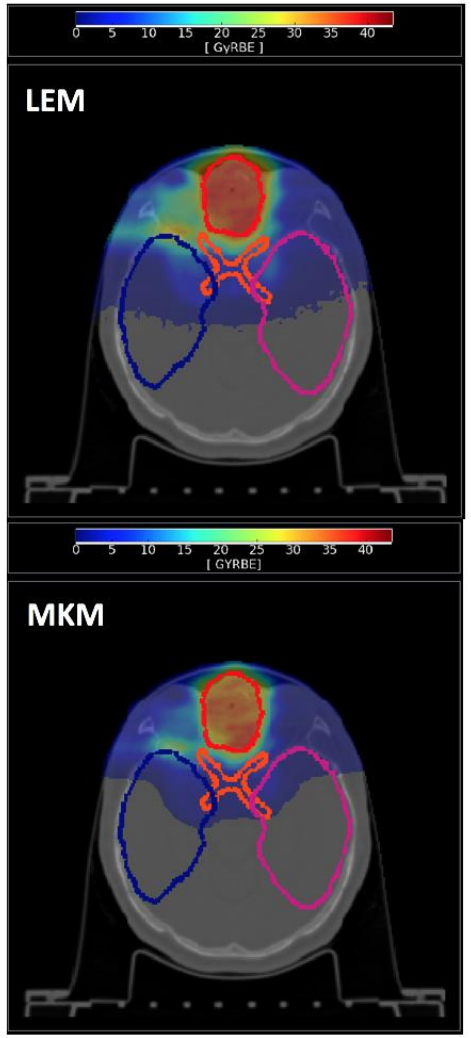


D_{RBE} calculations for glioma patient: MC vs. FRoG
D98, D50, D2 within ~1%

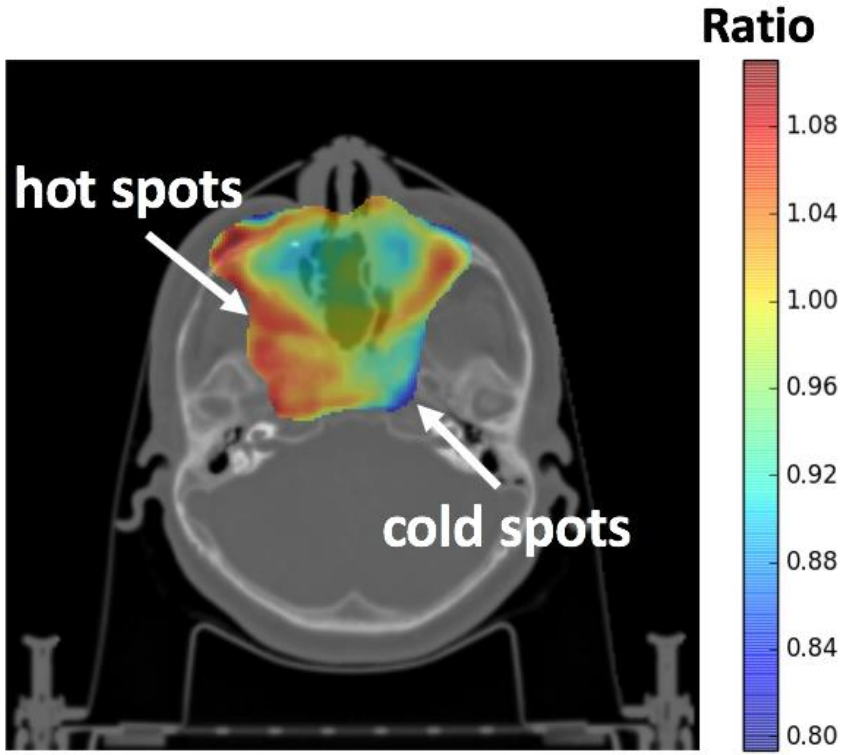
S. Mein 2019 Rad. Onc. (2019)

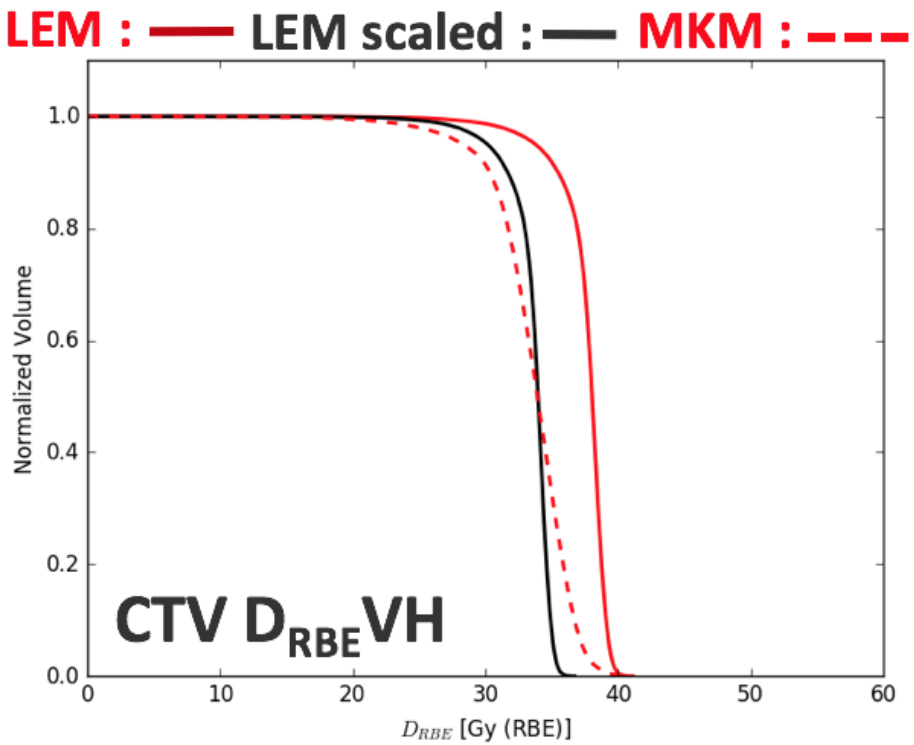
Biological uncertainties: ^{12}C ions

RBE model comparison: LEM vs. MKM



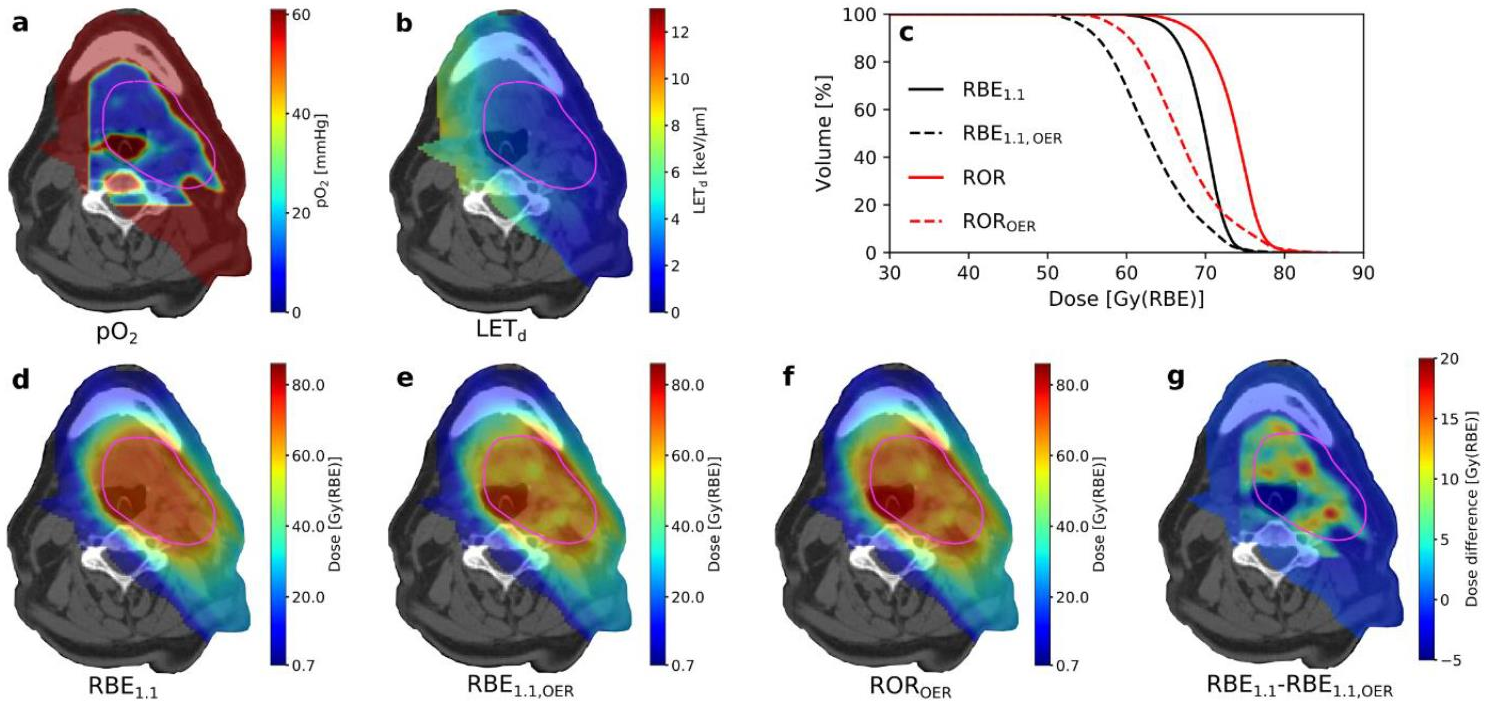
K. Choi,...,A. Mairani Cancers, 2018, 10, 395





PRECISE TPS: hypoxia

estimating the impact of hypoxia on the biological dose



$$\alpha_h = \alpha_a / \mathrm{OER}(L, p_h),$$

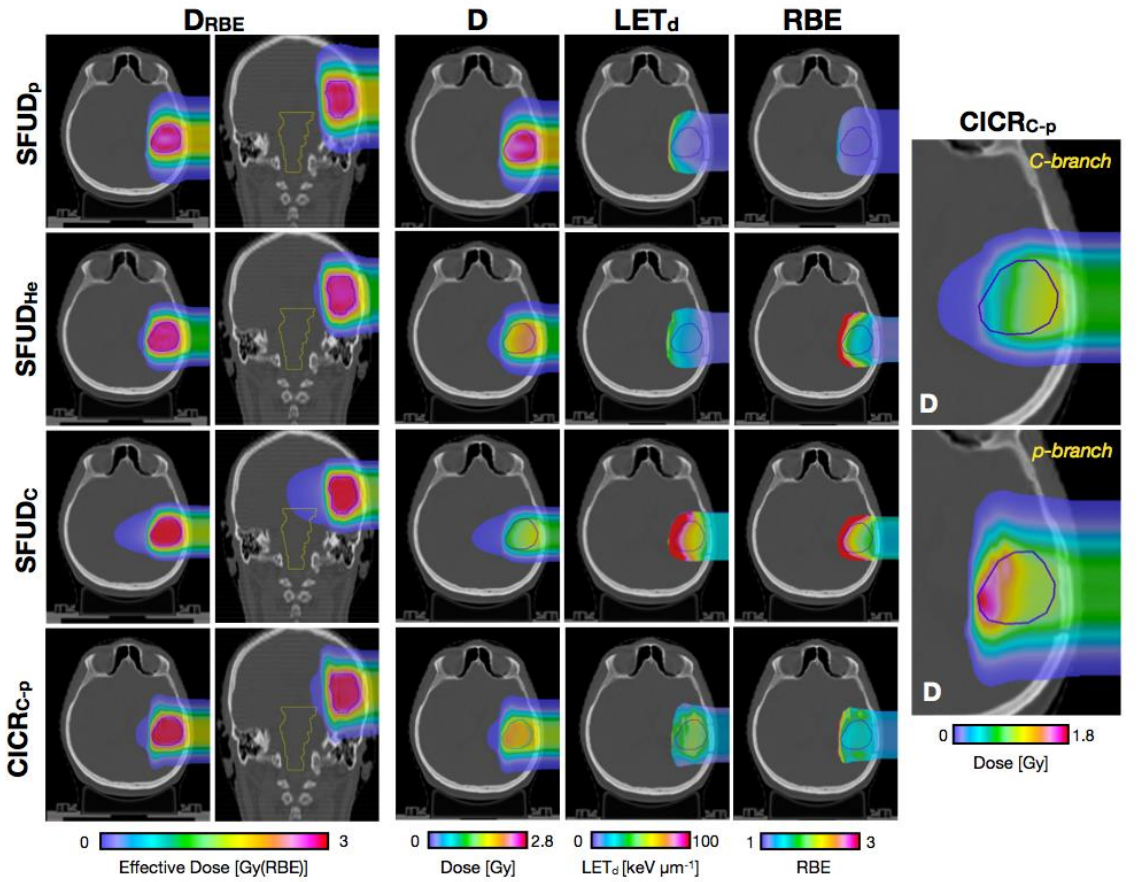
$$\beta_h = \beta_a / \mathrm{OER}^2(L, p_h),$$

$$D_{\mathrm{OER}} = \frac{D}{D_p}\left(\sqrt{\left(\frac{\alpha_x}{2\beta_x}\right)^2 + \frac{\alpha_h D_p + \beta_h D_p^2}{\beta_x}} - \frac{\alpha_x}{2\beta_x}\right),$$

T. Dahle et al. 2019 (under review)

PRECISE TPS

PaRticle thErapy using single and Combined Ion optimization StratEgies



robustness:

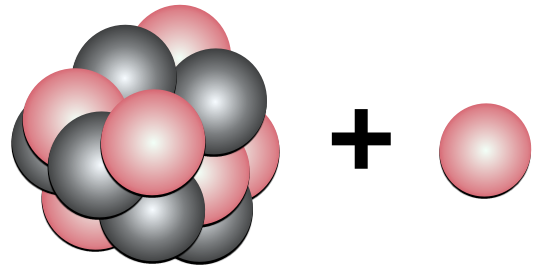
↑phys. ↑bio.

↑stablility:

D_{phys} LET_d

RBE D_{bio}

proximal branch | distal branch



^{12}C + p

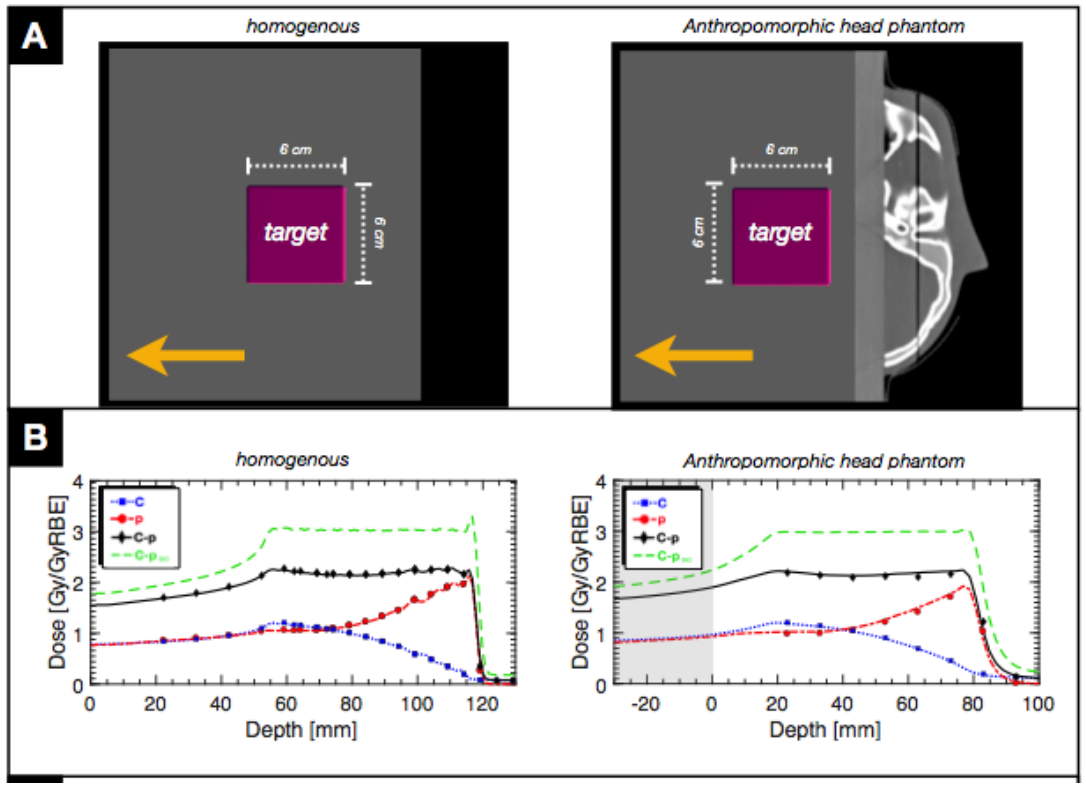
B. Kopp & S. Mein et al. IJROBP (under review)

S. Mein et al. ENLIGHT POSTER #14

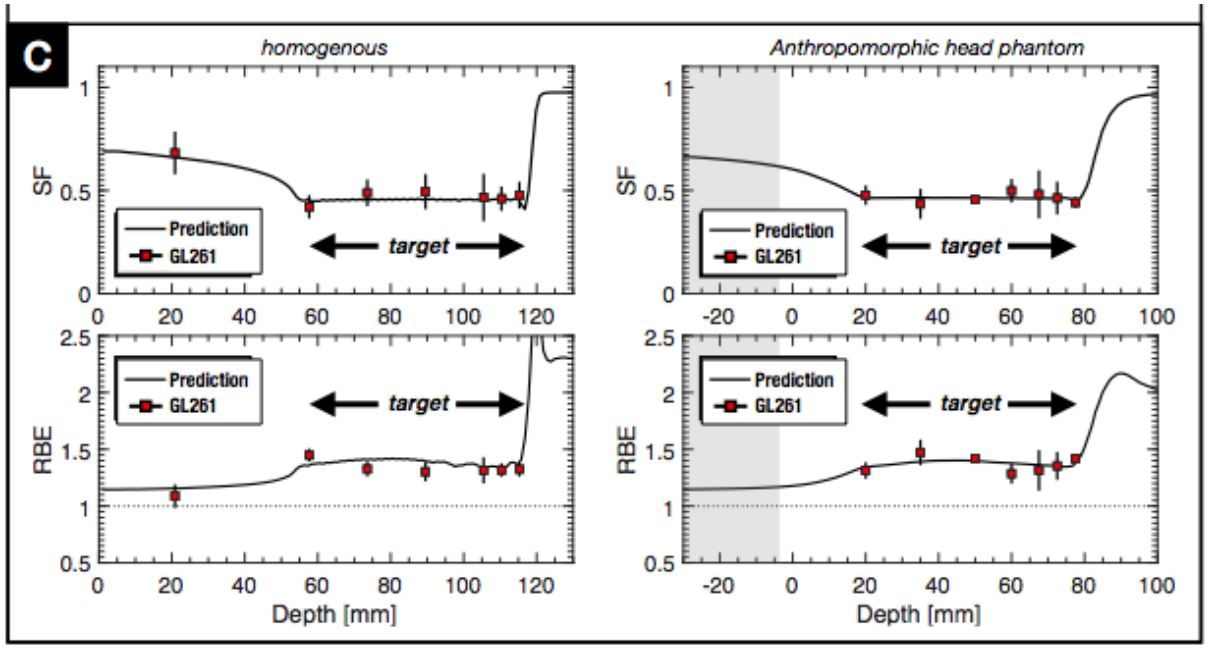
PRECISE TPS

Combined Ion Constant RBE (CICR):

Dosimetric validation



in vitro validation



GL261: α/β = 3.1 Gy

B. Kopp & S. Mein et al. IJROBP (under review)

S. Mein et al. ENLIGHT POSTER #14

Conclusion

- D, LET_d, D_{RBEp}, D_{LEM}, D_{MKM}
- MC-like accuracy
- ~200x faster than FLUKA MC
- Validated
  - In-silico against FLUKA
  - Experimental
- Sandbox environment (RBE models, multi-ion, hypoxia, etc.)
- Since 2019 installed at four clinical facilities in Europe

Thank you for your attention!

HEIDELBERG UNIVERSITY HOSPITAL

The FRoG Development Team

Dr. Andrea Mairani, Group leader

Kyungdon Choi, PhD Candidate

Stewart Mein, PhD Candidate

Benedikt Kopp, PhD Candidate

Questions?

E-mail about FRoG:

andrea.mairani@med.uni-heidelberg.de

HIT Heidelberger Ionenstrahl-Therapiezentrum

CNAO