Physikalisch-Technische Bundesanstalt
Braunschweig and Berlin
National Metrology Institute

Overview of the EMPIR project UHDpulse – "Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates"

UHDpulse

Andreas Schüller

Working Group 6.21 "Dosimetry for radiotherapy"

on behalf of the UHDpulse consortium

AIFM webinar "Ultra-high dose rate radiotherapy: dosimetric challenges", 19.5.2022

Physikalisch-Technische Bundesanstalt
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Overview of the EMPIR project UHDpulse – “Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

Contents

- Ultra-high dose rate (FLASH) radiotherapy
- Ultra-high dose rate electron beams
- Ultra-high dose rate / ultra-high dose per pulse
- Dosimetric challenges
- The EMPIR project UHDpulse
- PTB’s ultra-high pulse dose rate reference electron beam
- Some solutions for dosimetry for FLASH RT

Traceable dosimetry for clinical electron beams

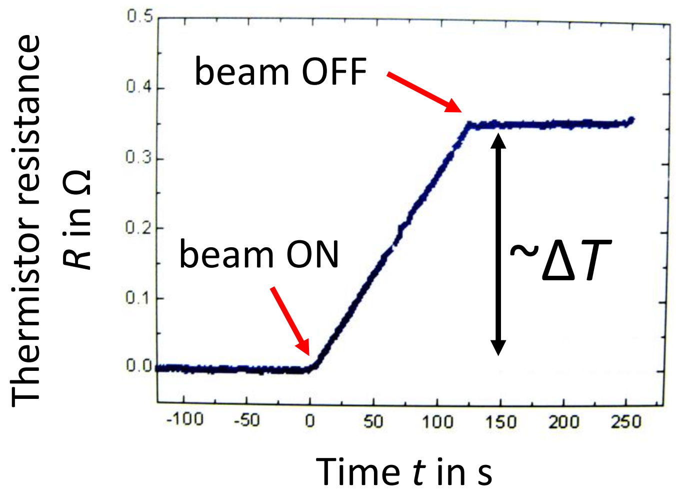
PTB's primary standard of the unit Gy for absorbed dose to water

$\boxed{D_w = d\varepsilon/dm}$ 1 Gy = 1 J/Kg

ε: energy deposit in medium, *m:* mass of medium (water)

$\boxed{D_w = c_p \cdot \Delta T \cdot \Pi k_i}$ ΔT = 0.24 mK/Gy

c_p: Heat capacity of water, ΔT: Radiation-induced temperature rise
Πk_i: corrections for perturbations (heat transport, etc.)



PTB water calorimeter at a medical LINAC

Ultra-high dose rate (FLASH) radiotherapy

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

In vitro studies suggested that sub-millisecond pulses of radiation elicit less genomic instability than continuous, protracted irradiation at the same total dose. To determine the potential of ultrahigh dose-rate irradiation in radiotherapy, we investigated lung fibrogenesis in C57BL/6J mice exposed either to short pulses (≤500 ms) of radiation delivered at ultrahigh dose rate (≥40 Gy/s, FLASH) or to conventional dose-rate irradiation (≤0.03 Gy/s, CONV) in single doses. The growth of human HBCx-12A and HEp-2 tumor xenografts in nude mice and syngeneic TC-1 Luc+ orthotopic lung tumors in C57BL/6J mice was monitored under similar radiation conditions. CONV (15 Gy) triggered lung fibrosis associated with activation of the TGF-β (transforming growth factor–β) cascade, whereas no complications developed after doses of FLASH below 20 Gy for more than 36 weeks after irradiation. FLASH irradiation also spared normal smooth muscle and epithelial cells from acute radiation-induced apoptosis, which could be reinduced by admin-

(May 2022)

treatment time

average dose rate
(delivered dose/treatment time)

delivered dose

Science Translational Medicine 6 (2014) 245, pp. 245ra93
http://dx.doi.org/10.1126/scitranslmed.3008973

Ultra-high dose rate (FLASH) radiotherapy

(May 2022)

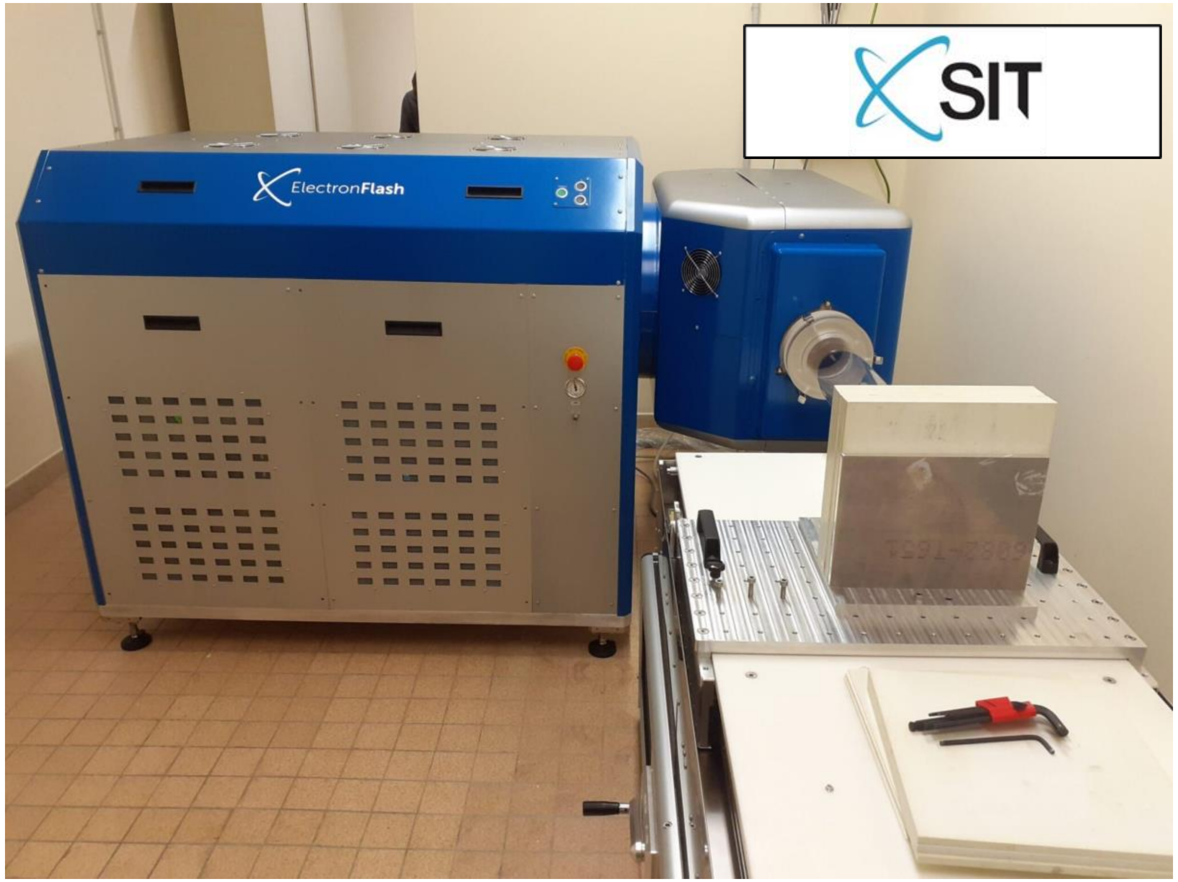
- increasing interest in FLASH RT
- **2021: 1.4 paper/week about** "FLASH" or "ultra-high dose rate"
- just now an urgent need for dosimetry for FLASH RT

Ultra-high dose rate electron beams

Dedicated FLASH LINACs

PMB eRT6

Centre hospitalier universitaire vaudois



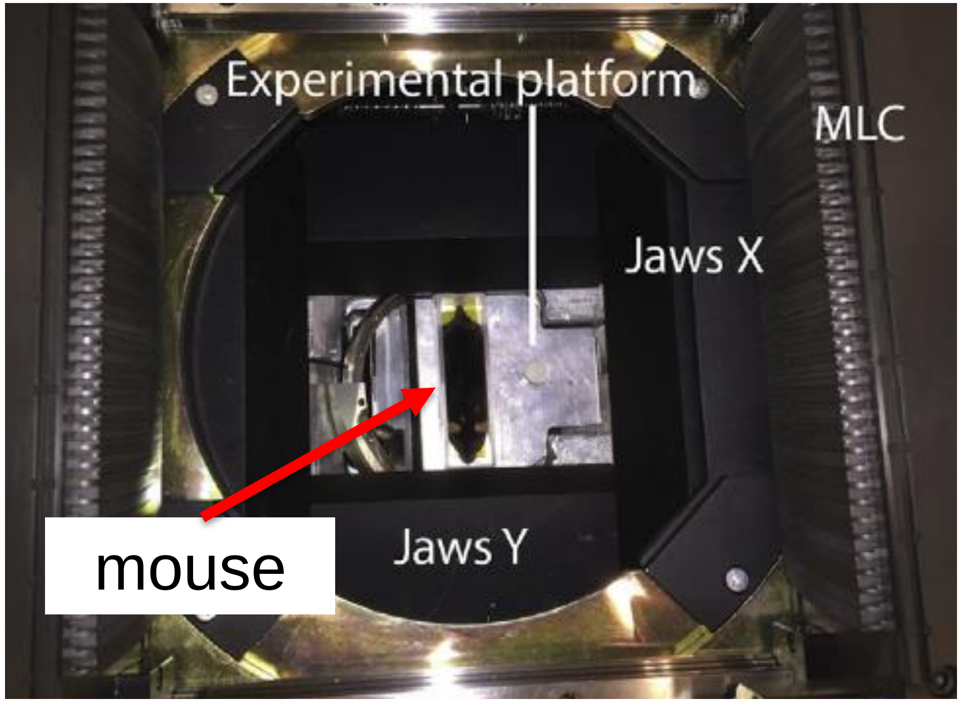
SIT ElectronFlash

institutCurie

Ultra-high dose rate electron beams

modified medical LINACs

modified Varian Clinac



view into the head of the LINAC

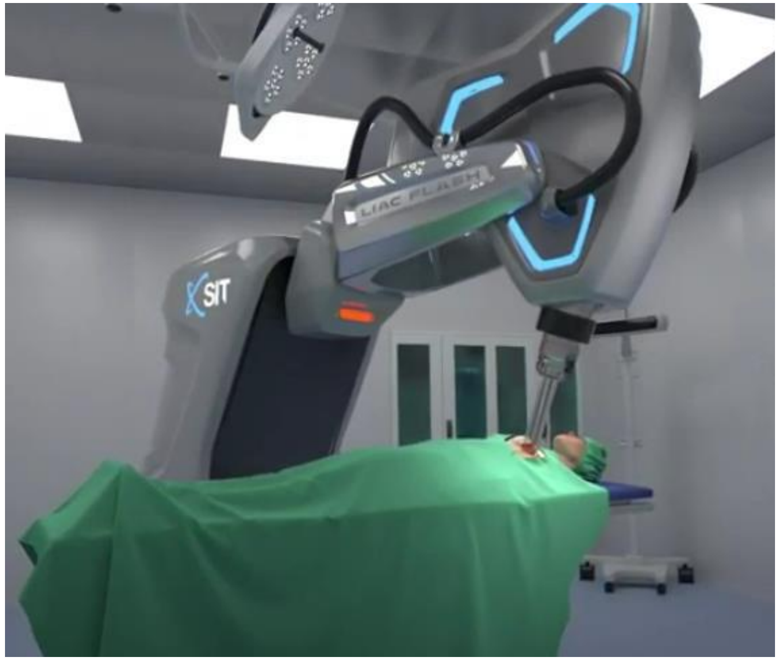
E. Schüler et al.
"Experimental Platform for Ultra-high Dose Rate FLASH …"
Int J Radiation Oncol Biol Phys **97** (2017) 195
https://doi.org/10.1016/j.ijrobp.2016.09.018

Ultra-high dose rate electron beams

Dedicated FLASH IOeRT LINACs

IntraOp Mobetron
With FLASH-IQ™

PMB ALCEN FLASHKNiFE:

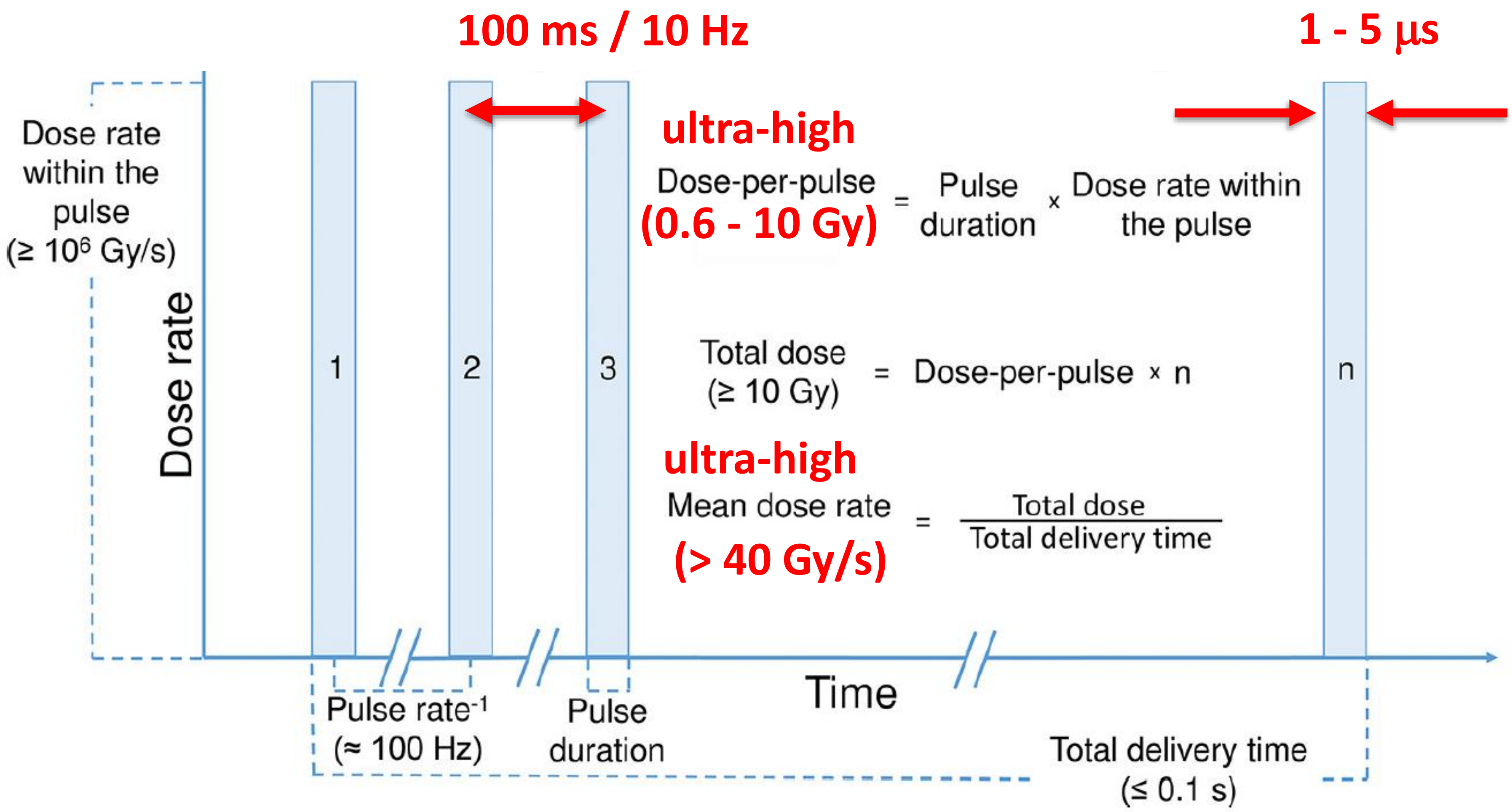


LIAC FLASH: life changing IOeRT FLASH device.

SIT
Sordina IORT Technologies

Ultra-high dose rate electron beams

Pulsed electron beam from LINACs



Wilson et al., *Front. Oncol.* **9** (2020) 1563.
http://dx.doi.org/10.3389/fonc.2019.01563

Ultra-high dose rate electron beams

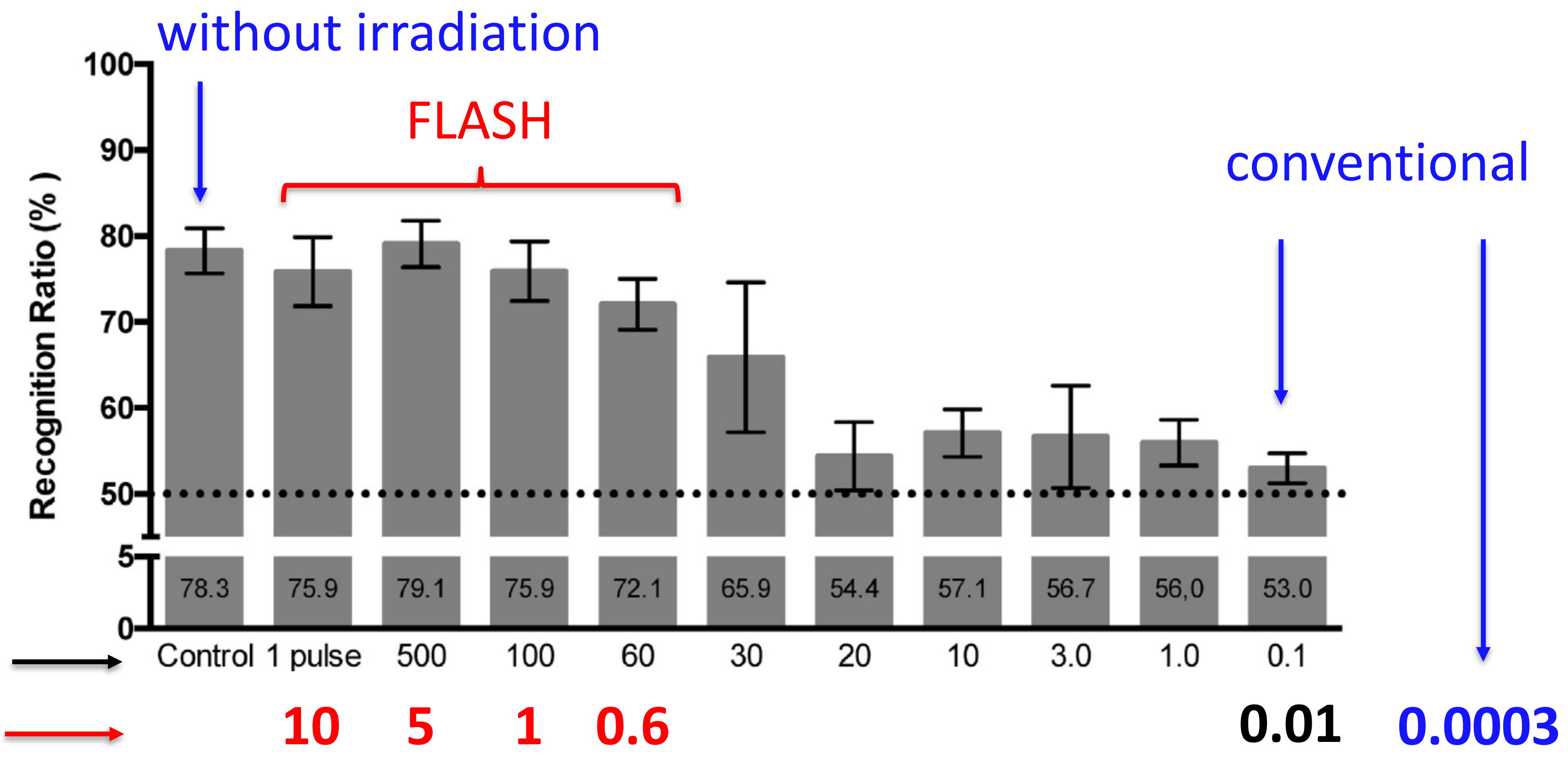
Comparison FLASH vs. conventional irradiation

	FLASH (LINAC beam)	conventional
average dose rate	**> 40 Gy/s**	**5 Gy/min**
treatment time	< 500 ms	4 min
pulse width	2 μs	4 μs
pulse repetition frequency	10 Hz	300 Hz
pulse dose rate (within pulse)	~ MGy/s	< 100 Gy/s
dose per pulse (DPP)	0.6 – 10 Gy	0.3 mGy

ultra-high dose per pulse

FLASH irradiation: Ultra-high dose rate / dose per pulse

<u>Mice brain irradiation with 10 Gy</u>



average dose rate [Gy/s]

dose per pulse [Gy]

Montay-Gruel *et al.*, Radiotherapy and Oncology 124 (2017) 365
http://dx.doi.org/10.1016/j.radonc.2017.05.003

FLASH irradiation: Ultra-high dose rate / dose per pulse

<u>FLASH irradiation of the skin of a pig</u>

Conventional and FLASH Irradiation
(with same total dose)

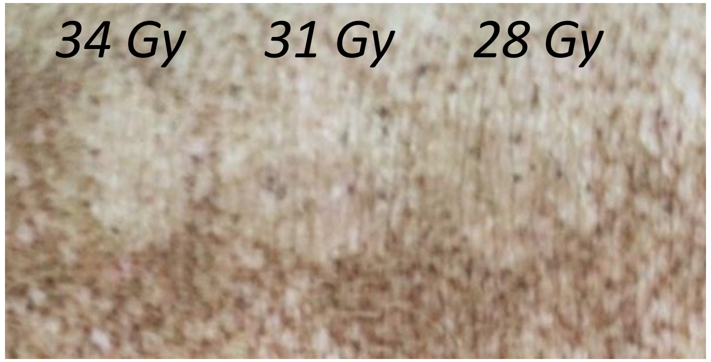
36 weeks post-RT

Conventional
(5 Gy/min)

necrotic lesions

FLASH
(300 Gy/s)

3 Gy/pulse



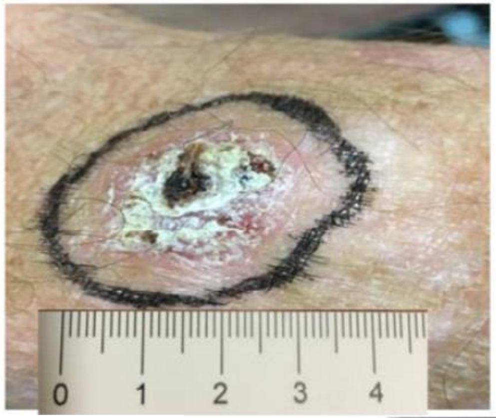
normal appearance of skin

Vozenin et al., *Clin Cancer Res* **25** (2019) 35
http://dx.doi.org/10.1158/1078-0432.CCR-17-3375

FLASH irradiation: Ultra-high dose rate / dose per pulse

<u>FLASH treatment of a human patient</u>
(lymphoma on skin)

- delivered total dose: 15 Gy
- 10 pulses (of 1 μs duration)
- treatment time: 90 ms
- **Dose per pulse: 1.5 Gy**



Day 0

3 weeks

5 months

Bourhis et al., *Radiother. Oncol.* (2019)
http://dx.doi.org/10.1016/j.radonc.2019.06.019

FLASH irradiation: Ultra-high dose rate / dose per pulse

FLASH treatment of canine patients

- Delivered total dose: 15 – 35 Gy in 7-16 pulses
- Treatment time: < 75 ms
- Mean dose rates: > 400 Gy/s
- **Dose per pulse: 2 Gy**

treatment of leg

Konradsson et al., *Front. Oncol.* **11** (2021) 658004
https://doi.org/10.3389/fonc.2021.658004

Ultra-high dose rate radiotherapy: dosimetric challenges

<u>Ionization chambers</u>

Advanced Markus®
Chamber
Type 34045

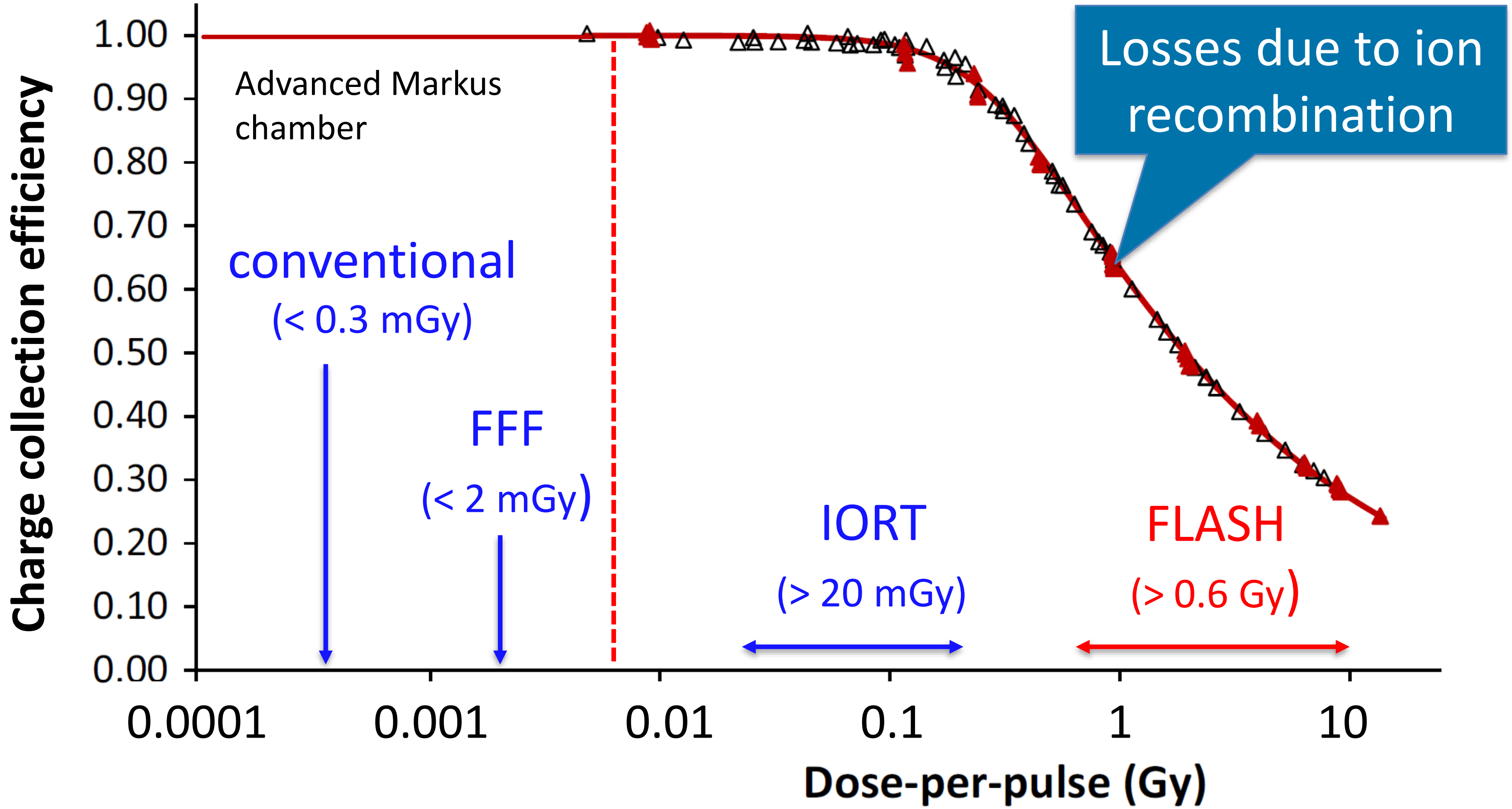
Well-guarded plane-parallel chamber for the dosimetry of high-energy electron beams, especially for high dose per pulse values

Ion collection efficiency at nominal voltage	
Ion collection time	22 µs
Max. dose rate for	
≥ 99.5 % saturation	187 Gy/s
≥ 99.0 % saturation	375 Gy/s
Max. dose per pulse for	
≥ 99.5 % saturation	2.78 mGy
≥ 99.0 % saturation	5.56 mGy

Ranges of use	
Chamber voltage	± (50 ... 300) V
Radiation quality	(2 ... 45) MeV electrons

Ultra-high dose rate radiotherapy: dosimetric challenges

<u>Ionization chambers</u>



There are

- **no** active dosimeters for real-time measurements
- **no** formalism (CoP) for reference dosimetry
- **no** primary standard

Petersson et al., *Med Phys* **44** (2017) 1157
https://doi.org/10.1002/mp.12111

EMPIR project UHDpulse

Duration: Sep/2019-Feb/2023

Funding: 2.1 M €

Coordinator: Andreas Schüller (PTB)

Topic: dosimetry for

- **FLASH radiotherapy**
- VHEE radiotherapy
- laser driven beams

http://uhdpulse-empir.eu/

The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

The European Metrology Programme for Innovation and Research (EMPIR):

- enables European metrology institutes to collaborate with industrial and medical organisations, and academia

EMPIR project UHDpulse

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- FLASH radiotherapy

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- laser driven beams

UHDpulse

http://uhdpulse-empir.eu/


Outline

Highlights

Abstract

Keywords

1. Introduction

2. Overview of novel radiotherapy techniques using ultra-...

3. Metrological challenges and possible solutions for dosi...

4. The UHDpulse project

5. Conclusion

Acknowledgements

References

Show full outline

Figures (15)

ELSEVIER

Physica Medica

Volume 80, December 2020, Pages 134-150

Original paper

The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

Andreas Schüller [a], Sophie Heinrich [b], Charles Fouillade [b], Anna Subiel [c], Ludovic De Marzi [b, d], Francesco Romano [e, c], Peter Peier [f], Maria Trachsel [f], Celeste Fleta [g], Rafael Kranzer [h, i], Marco Caresana [j], Samuel Salvador [k], Simon Busold [l], Andreas Schönfeld [m], Malcolm McEwen [n], Faustino Gomez [o], Jaroslav Solc [p], Claude Bailat [q] ... Marie-Catherine Vozenin [q]

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Highlights

- Ultra-high dose rate reduces adverse side effects in radiotherapy (FLASH effect).
- Studies and implementation in practice requires accurate dose measurements.
- An European joint research project was started to develop a measurement framework.
- Tools for dosimetry of ultra-high pulse dose rate beams will be provided.

Schüller et al.,
The European Joint Research Project UHDpulse ...
Physica Medica **80** (2020) 134-150
https://doi.org/10.1016/j.ejmp.2020.09.020

Partners and Collaborators

Metrology Institutes

Irradiation facilities / providers

Detector developers

7 Metrology institutes
6 Hospitals
7 Universities
6 Research institutes
10 Companies
+ Proton therapy network

WPs

UHDpulse

WP1: Primary standards

- Definition of reference conditions
- Reference radiation fields
- Adapting primary standards (water calorimeter, Fricke dosimeter)
- Prototype graphite calorimeters

WP2: Secondary standards, relative dosimetry

- Transfer from primary standards
- Characterizing established detector systems
- Formalism for reference dosimetry for future Code of Practice

WP5: Impact, WP6: Coordination

WP4: Detectors and methods outside primary beam

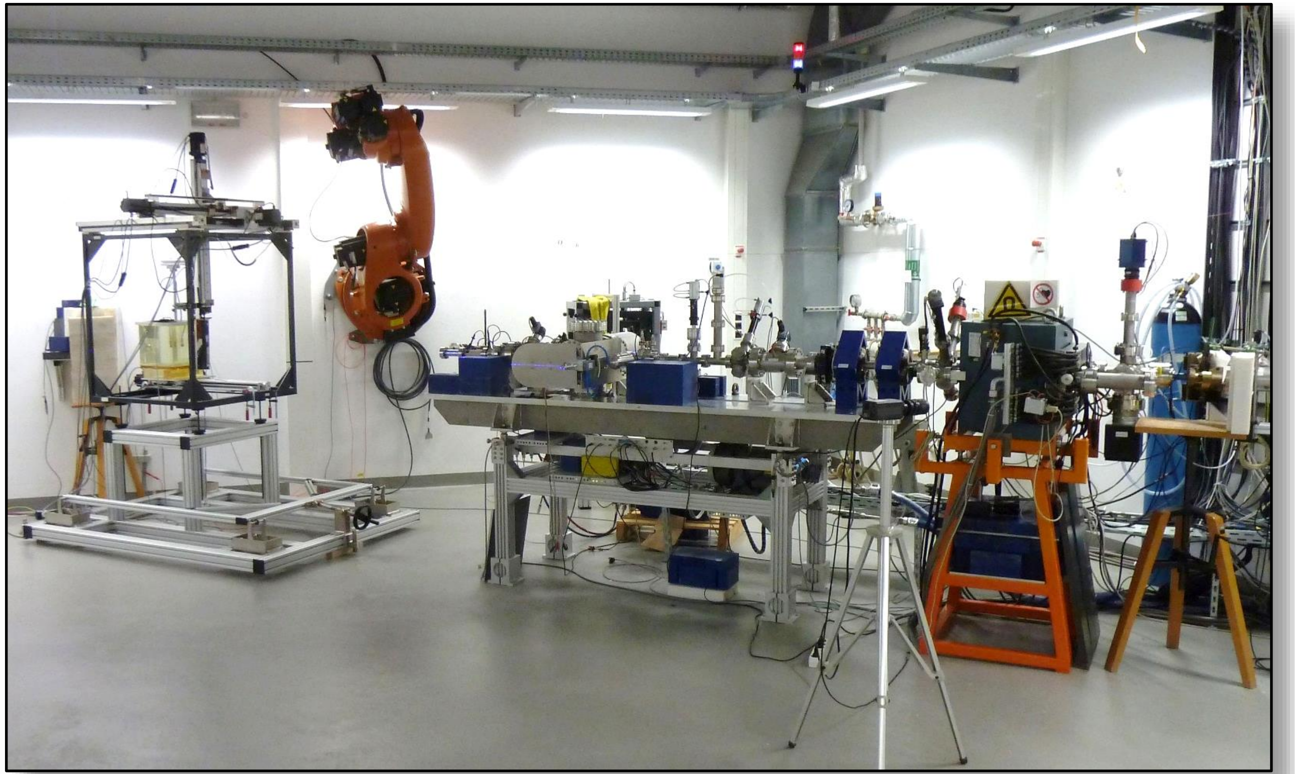
- Active detection techniques for pulsed mixed radiation fields of stray radiation and pulsed neutrons
- Methods with passive detectors

WP3: Detectors for primary beam

- Novel and custom-built active dosimetric systems
- Beam monitoring systems

PTB ultra-high pulse dose rate reference electron beam

PTB's Research electron accelerator



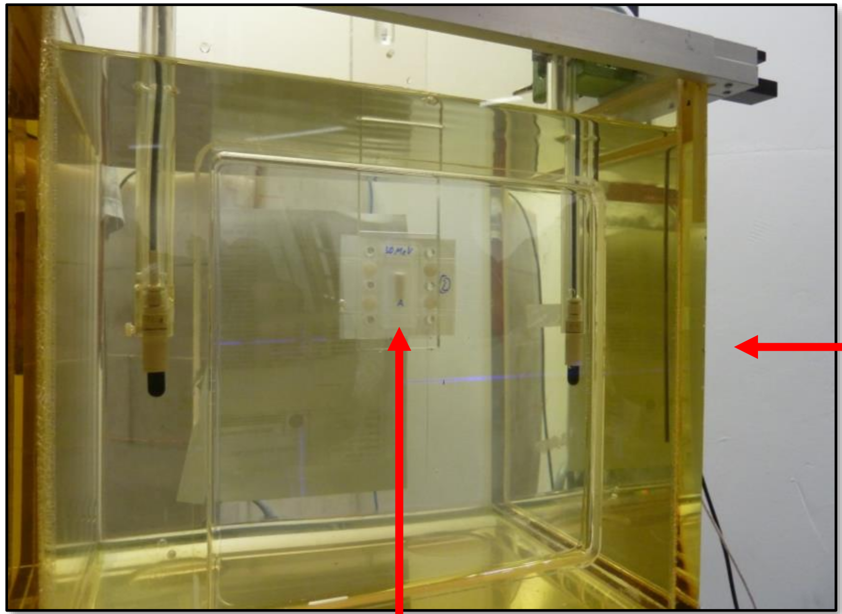
Beam line with water phantom

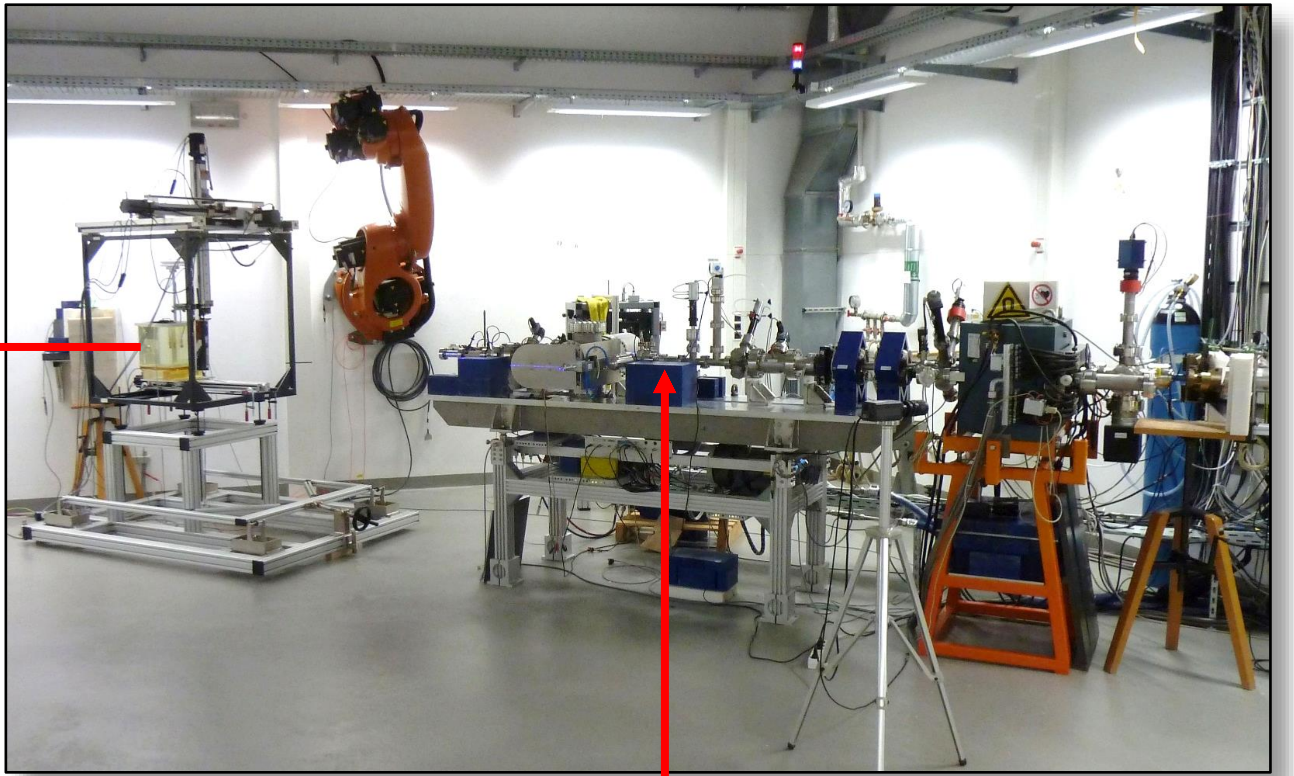
$E = 0.5 - 50$ MeV, $t_{pulse} = 0.1 - 3$ us
up to **15 Gy per pulse** (SSD 0.5 m, 20 MeV)

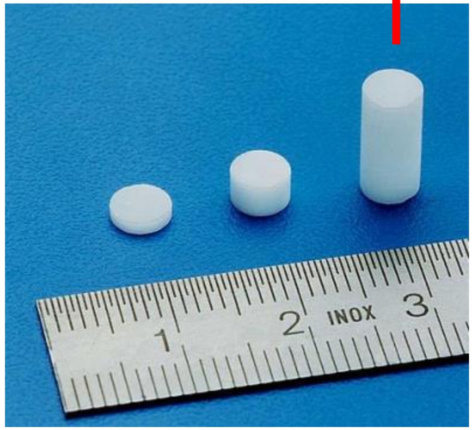
A. Bourgouin et al. "Characterization of the PTB ultra-high …"
Phys. Med. Biol. **67** (2022) 085013
https://doi.org/10.1088/1361-6560/ac5de8

UHDpulse

PTB ultra-high pulse dose rate reference electron beam





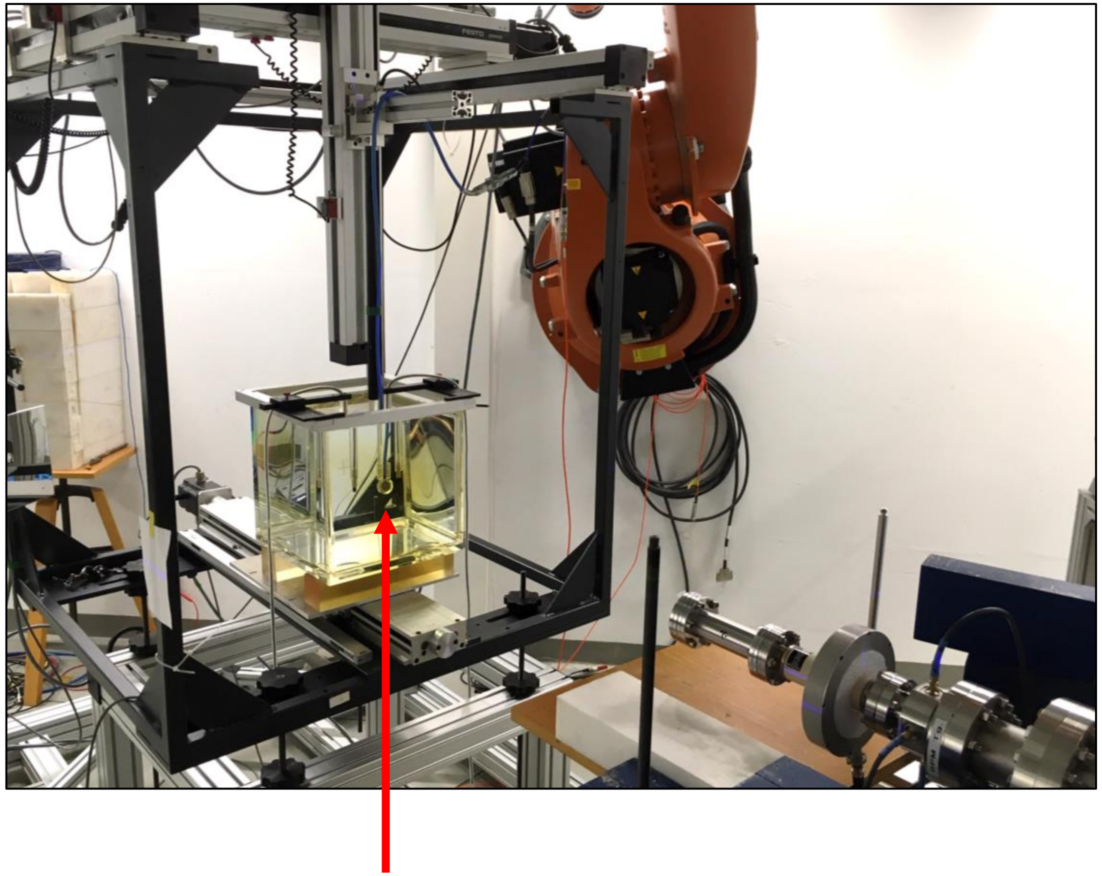


Alanine pellets at reference depth in water phantom

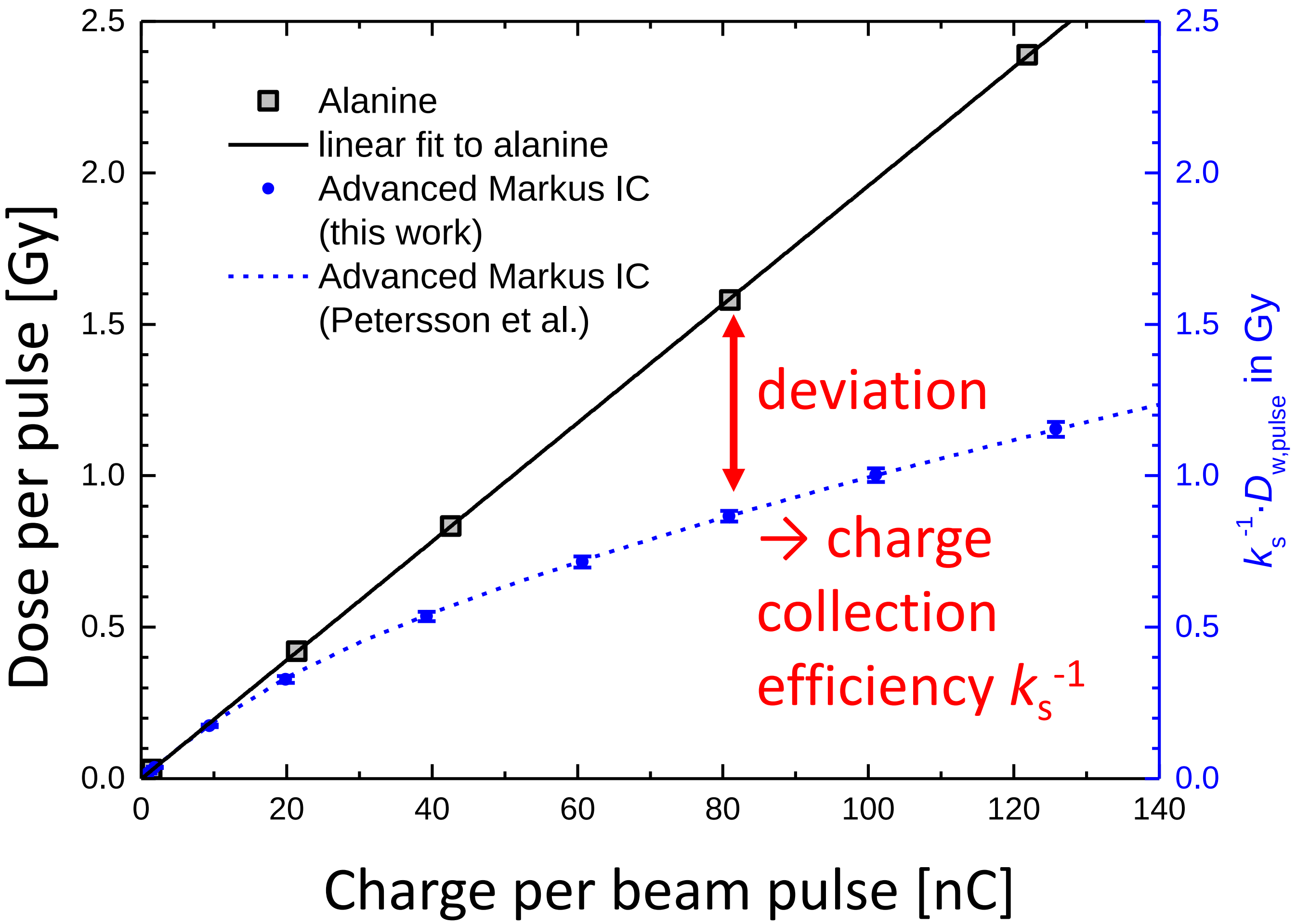
Dose traceable to PTB's primary standard

Current transformer (Bergoz ICT): Non-destructive absolute beam pulse charge measurement (uncertainty < 0.1 % @70 nC per pulse)

PTB ultra-high pulse dose rate reference electron beam

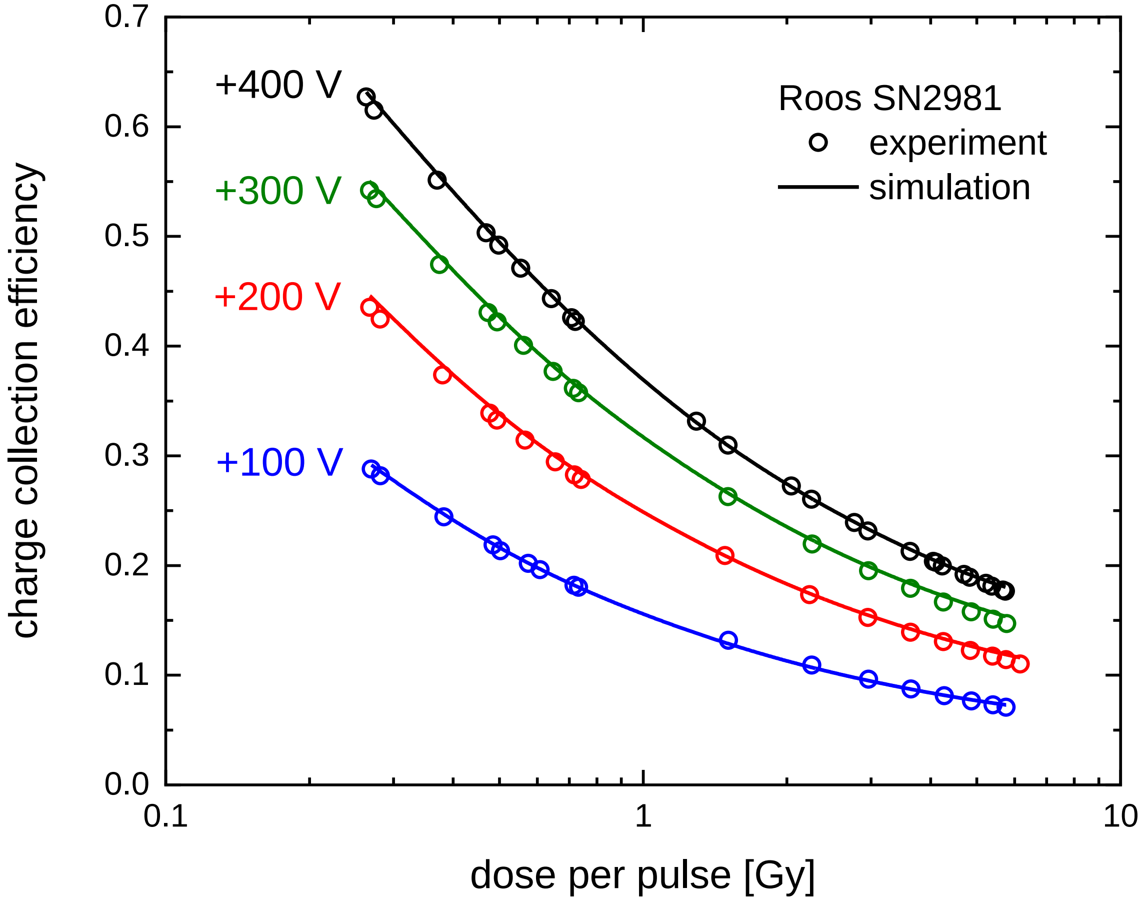


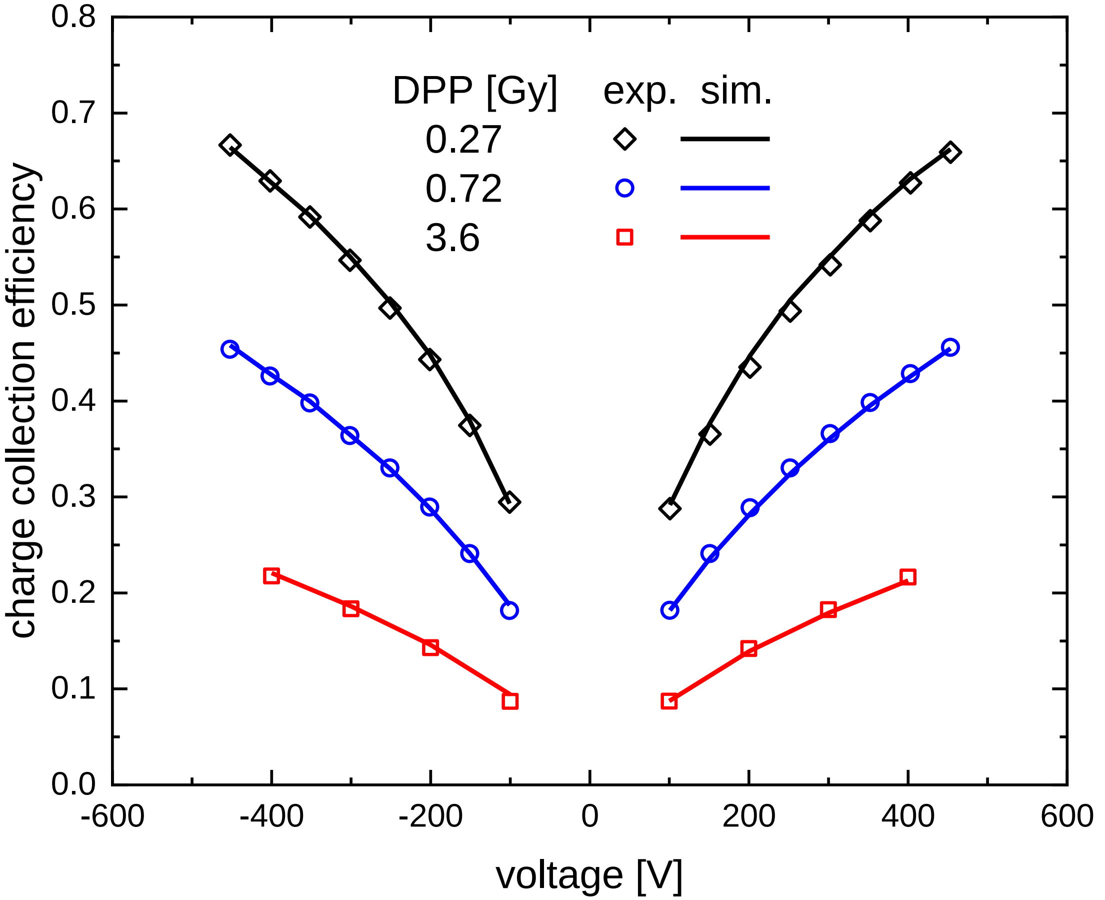
Detector under test at reference depth in water phantom



A Bourgouin et al., "Calorimeter for Real-Time Dosimetry …" *Front. Phys.* **8** (2020) 567340
https://doi.org/10.3389/fphy.2020.567340

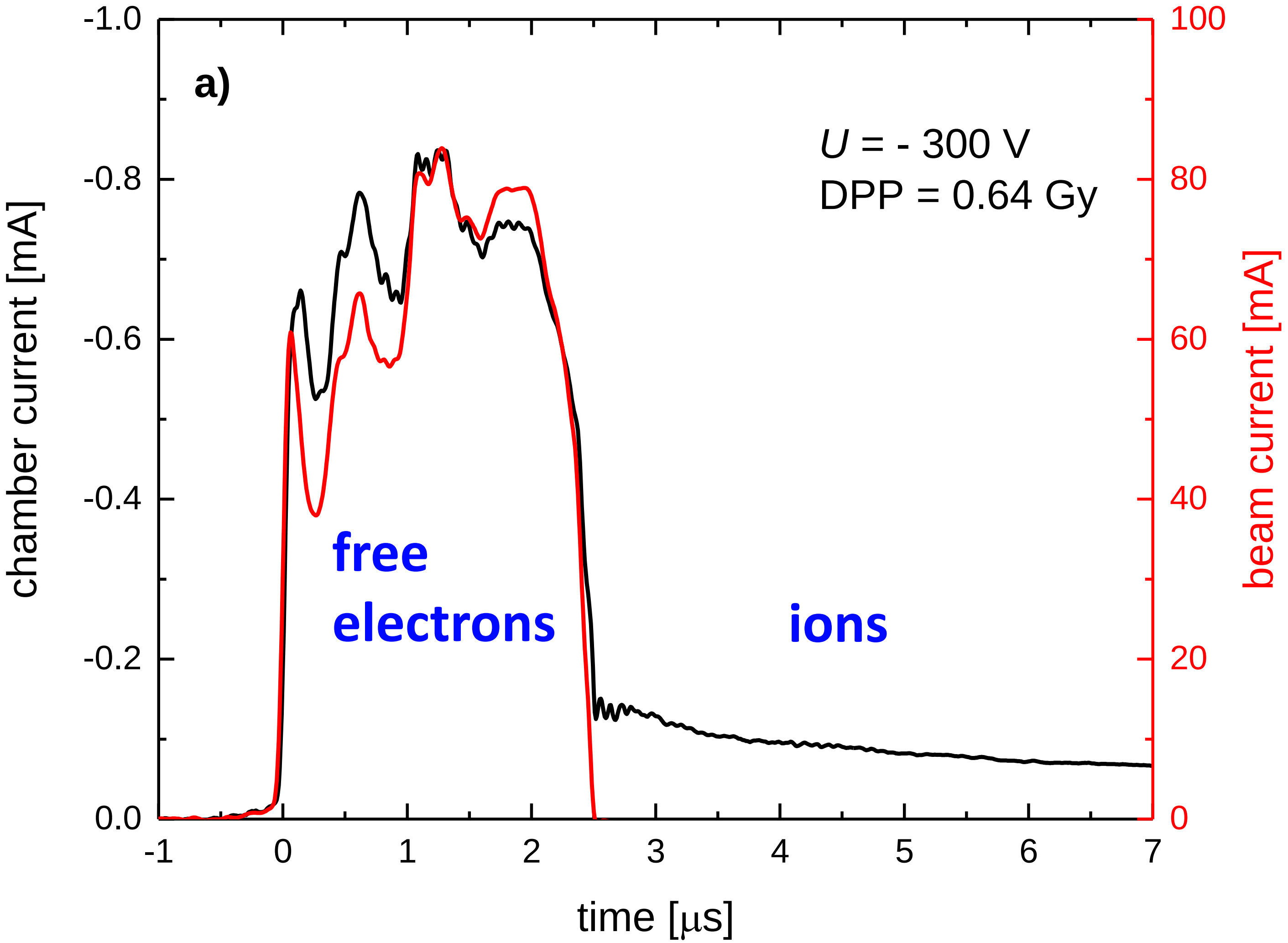
Calculation of charge collection efficiency





J. Paz-Martín et al.
"Numerical modelling of air-vented parallel plate ionization chambers for ultra-high dose rate applications"
Physica Medica, submitted

Calculation of charge collection efficiency



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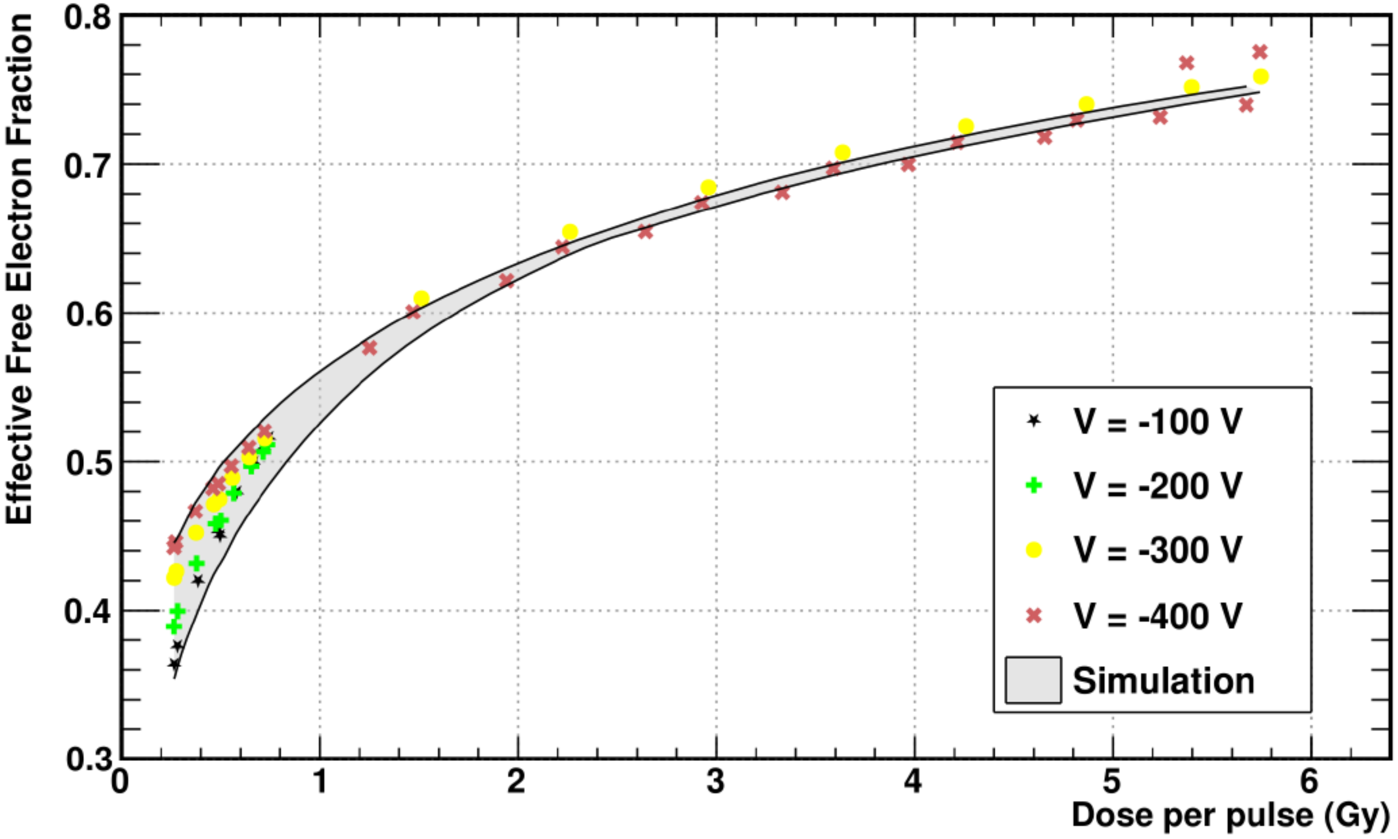
Physica Medica, submitted

210705-35

Calculation of charge collection efficiency



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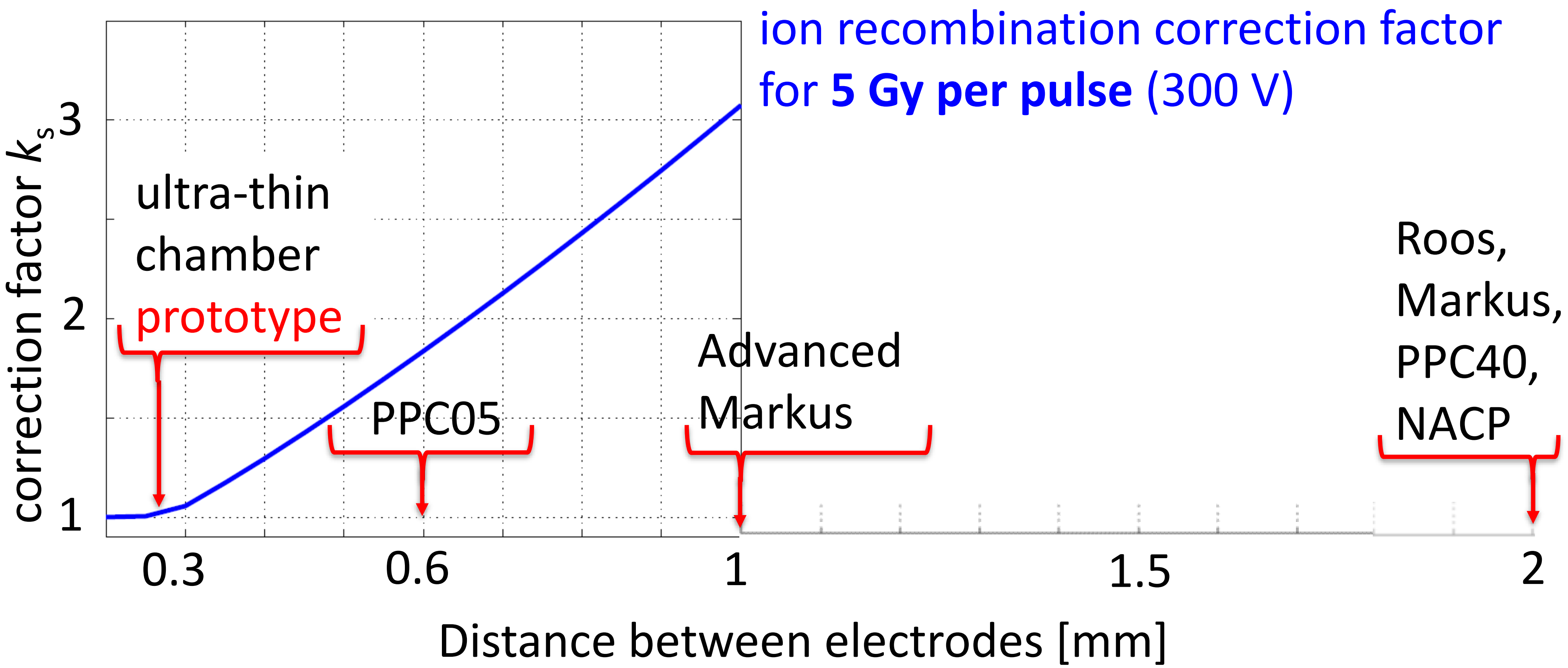
Calculation of charge collection efficiency

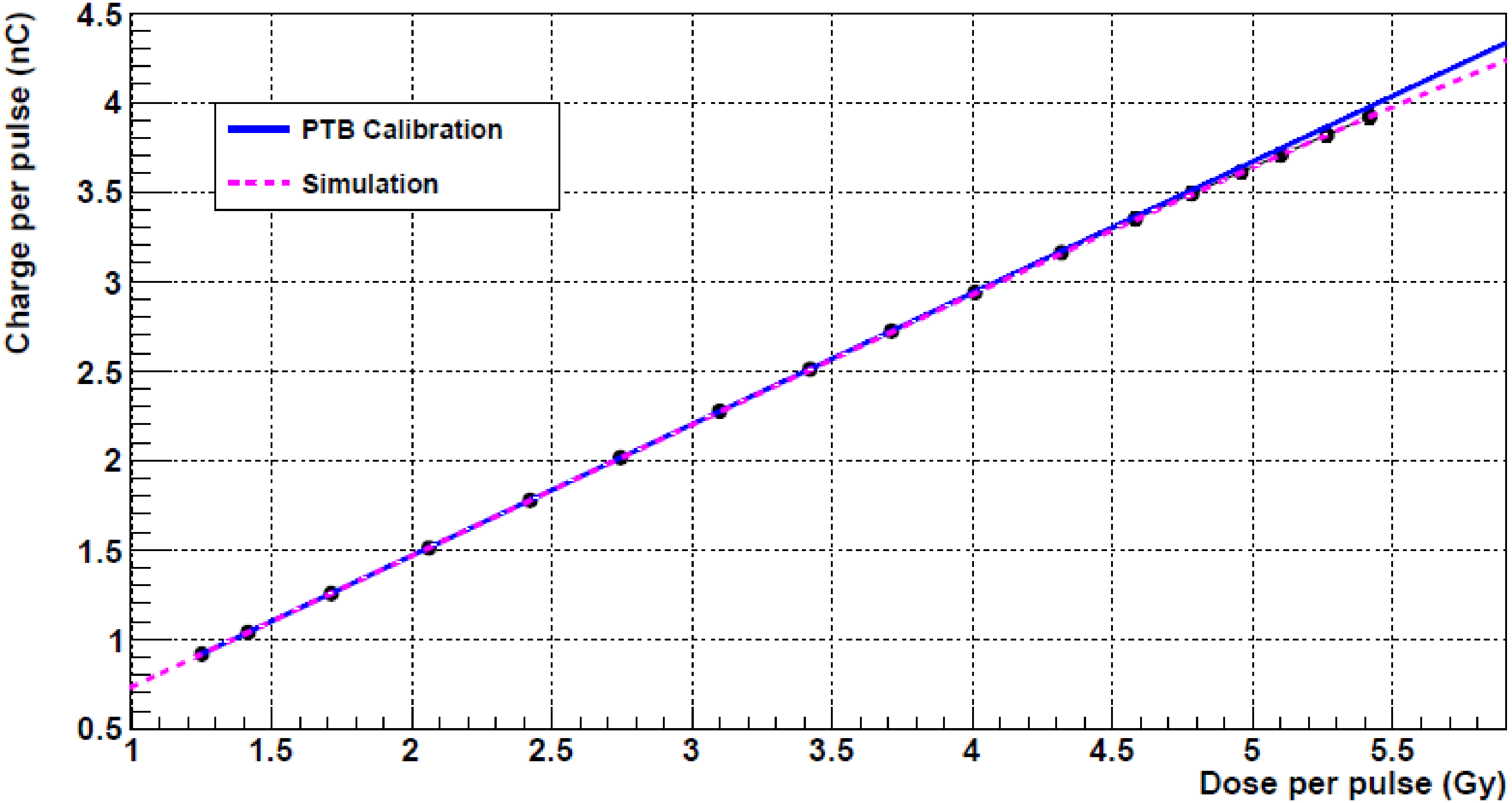


Faustino Gomez

https://doi.org/10.1016/j.ejmp.2020.09.020

Prototype ionization chambers for FLASH RT dosimetry

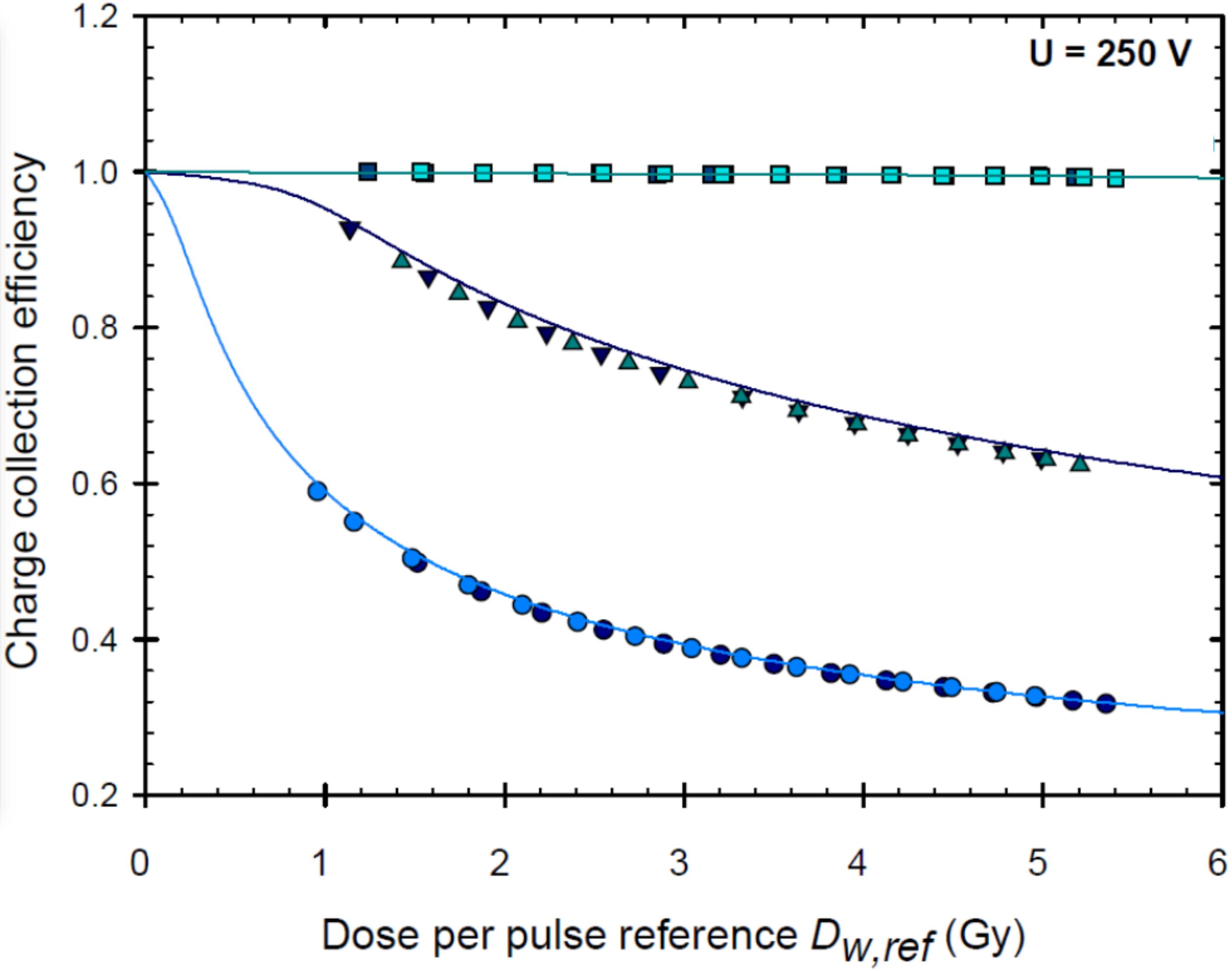
Ionization chamber prototype electrode distance: 0.27 mm



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Faustino Gomez et al.,
"Development of an ultra-thin parallel plate ionization chamber for dosimetry in FLASH radiotherapy"
Medical Physics (2022)
https://doi.org/10.1002/mp.15668

Prototype ionization chambers for FLASH RT dosimetry



electrode distance

0.25 mm

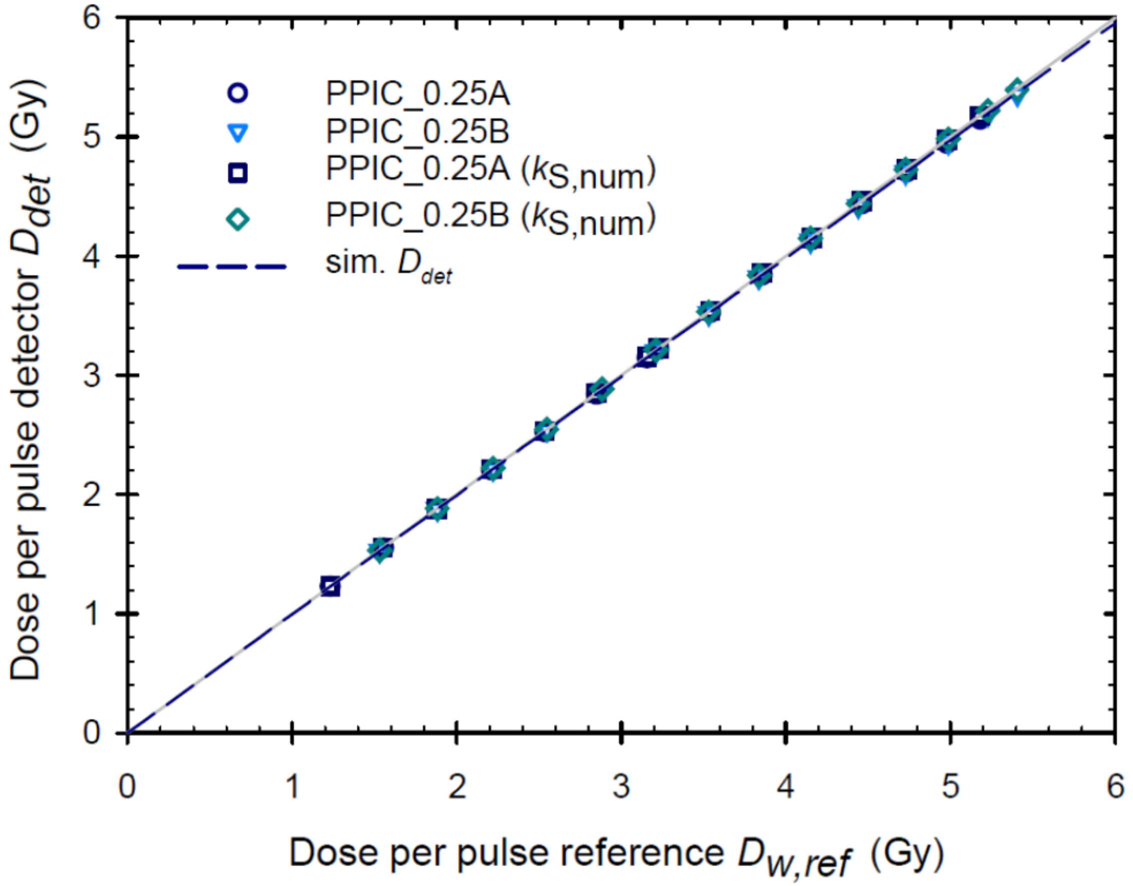
0.5 mm

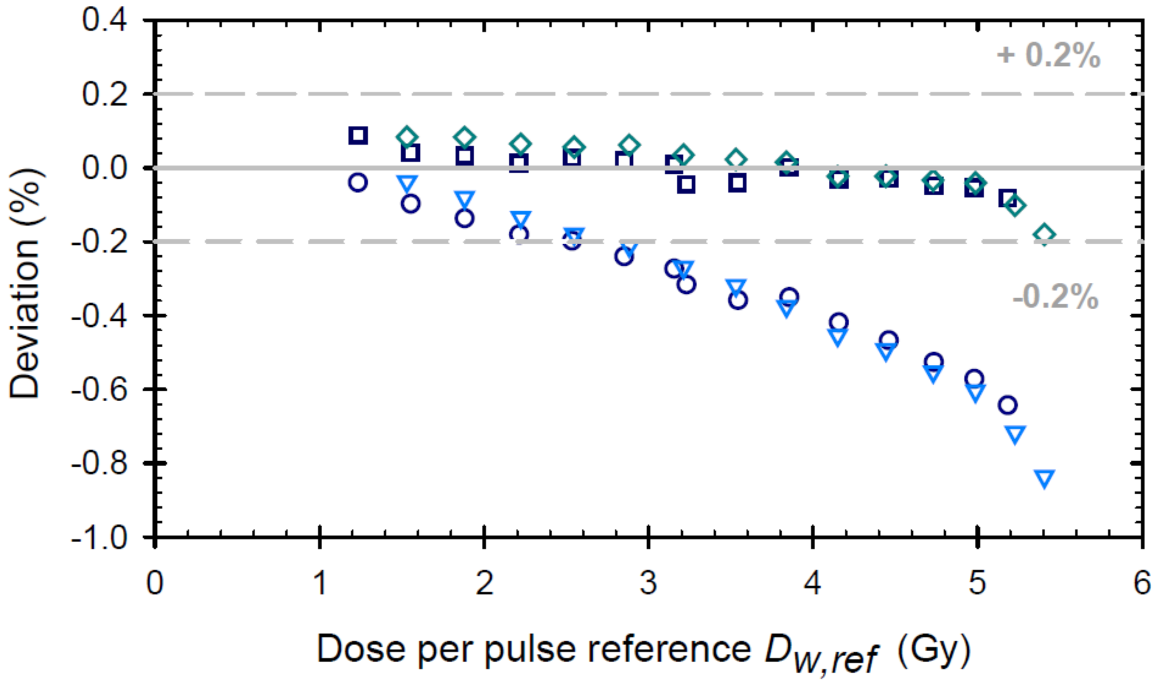
1 mm

PTW THE DOSIMETRY COMPANY

R. Kranzer et al.
"Charge collection efficiency, underlying recombination mechanisms, and the role of electrode distance …"
Physica Medica, submitted

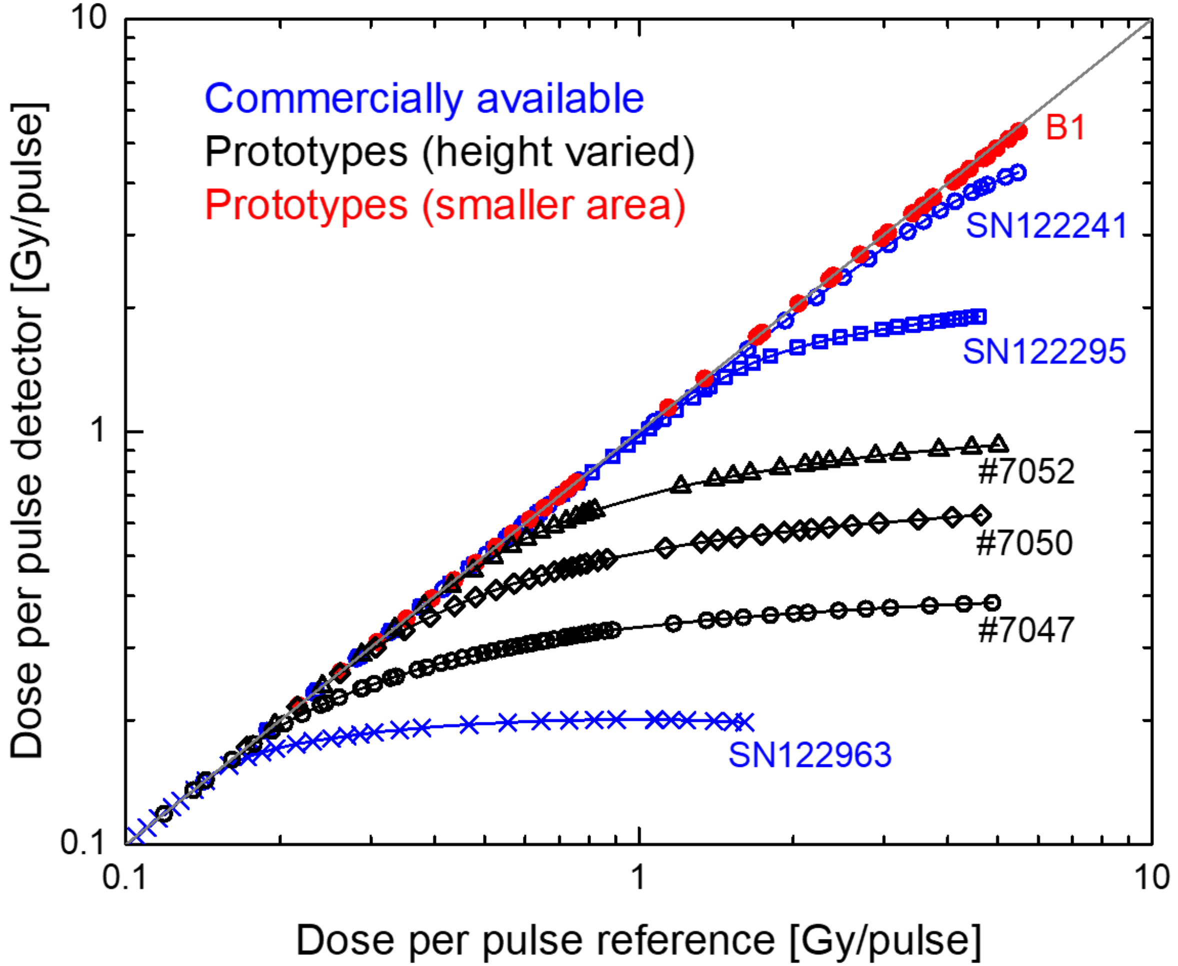
Prototype ionization chambers for FLASH RT dosimetry





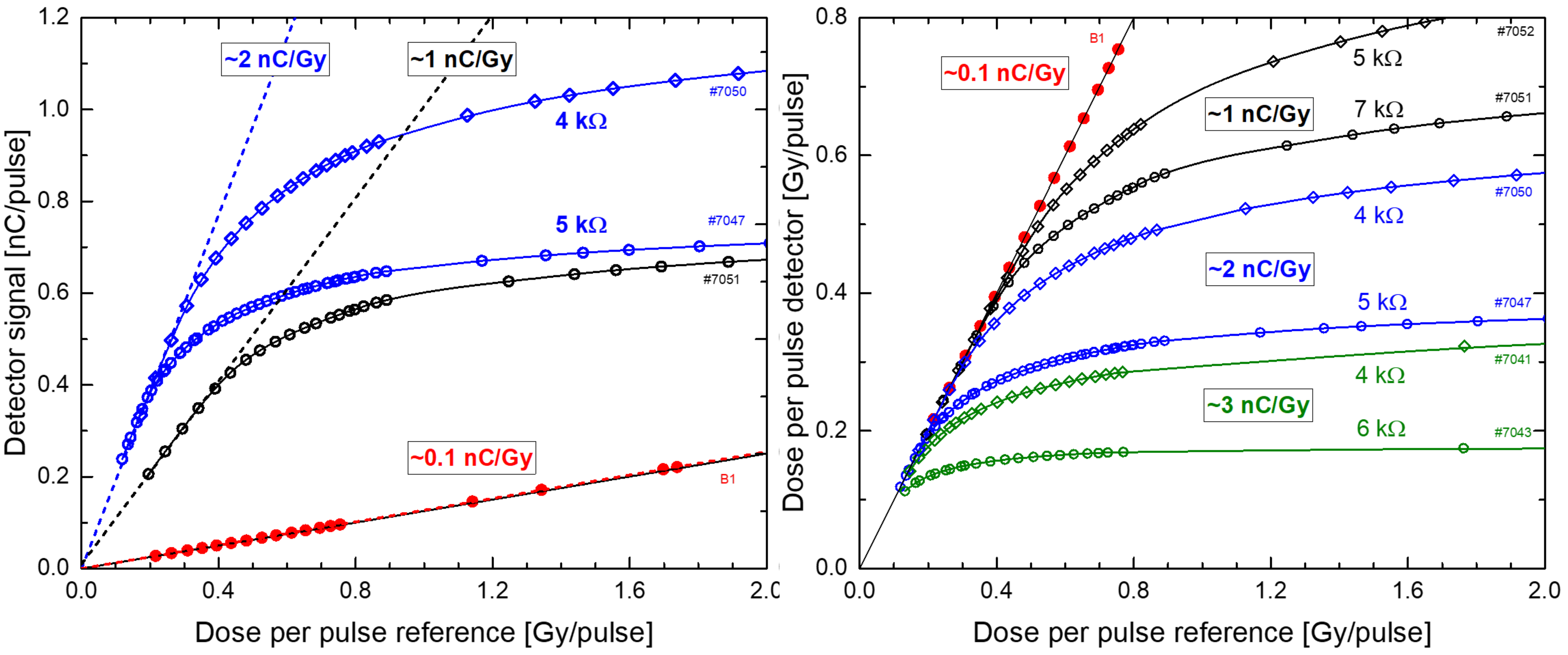
R. Kranzer et al.
"Charge collection efficiency, underlying recombination mechanisms, and the role of electrode distance …"
Physica Medica, submitted

Diamond detector prototype for FLASH RT dosimetry

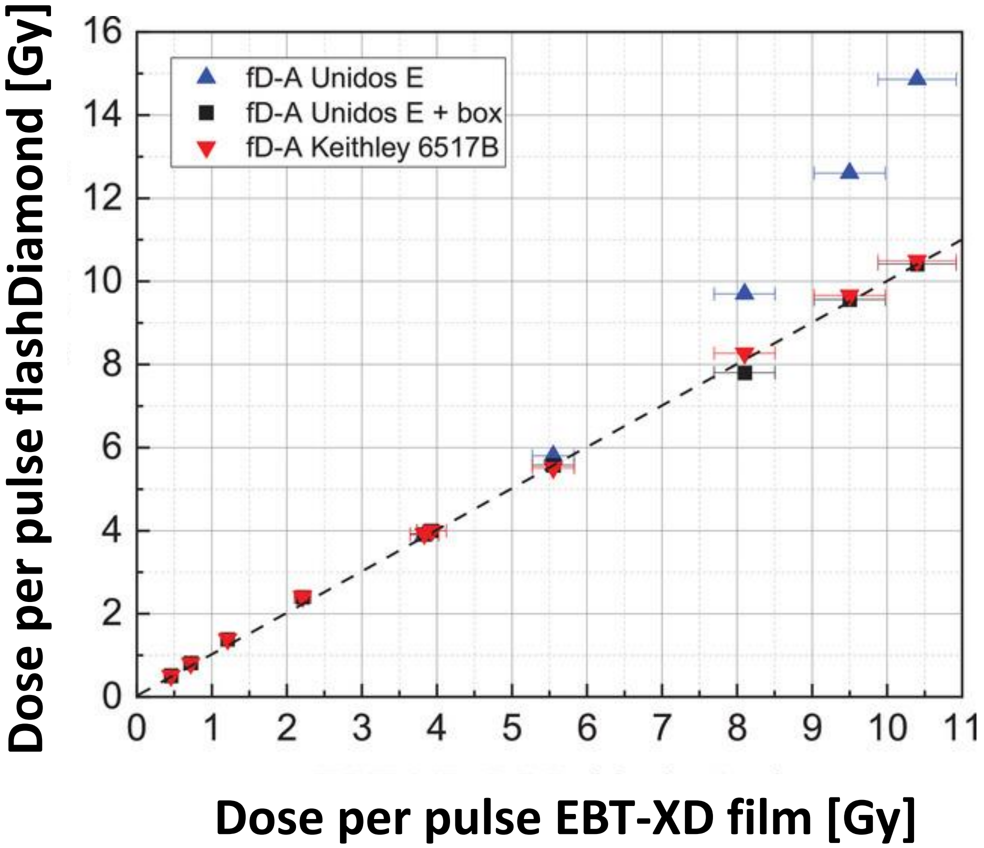


R. Kranzer et al.
"Response of diamond detectors in ultra-high dose-per-pulse electron beams for dosimetry at FLASH radiotherapy"
Phys. Med. Biol. **67** (2022) 075002
https://doi.org/10.1088/1361-6560/ac594e

Diamond detector prototype for FLASH RT dosimetry

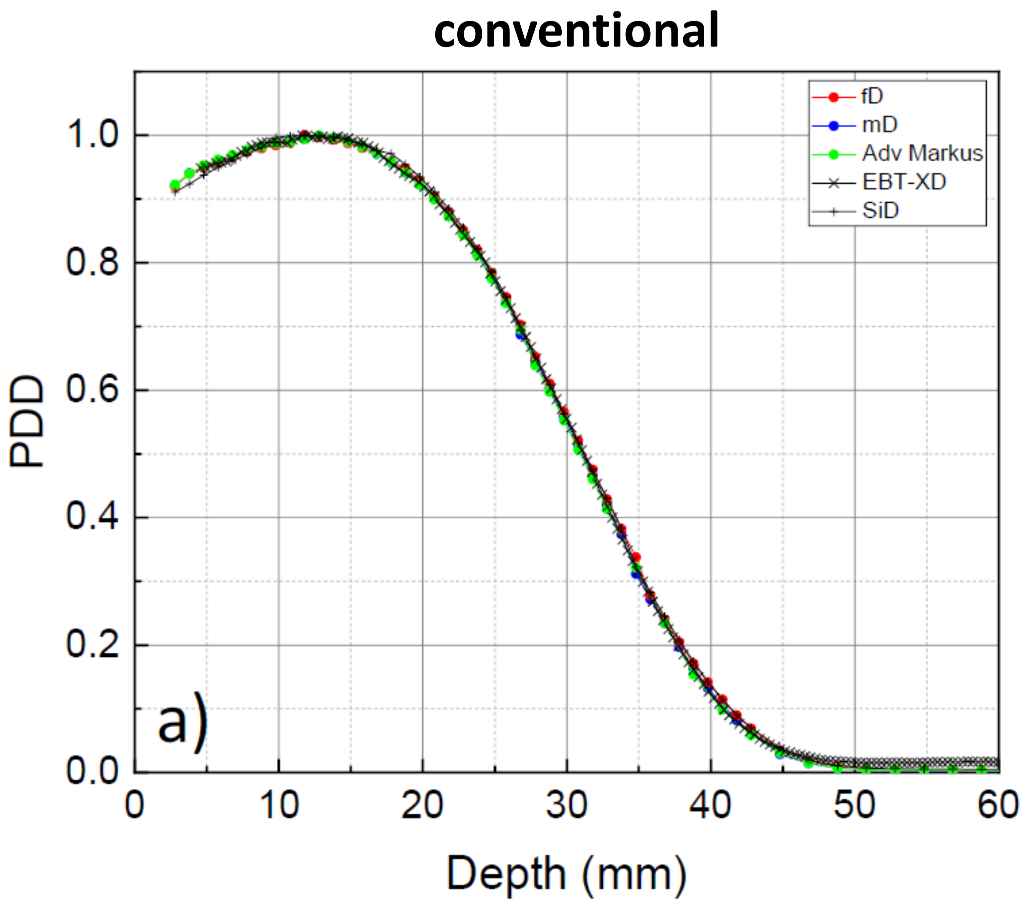


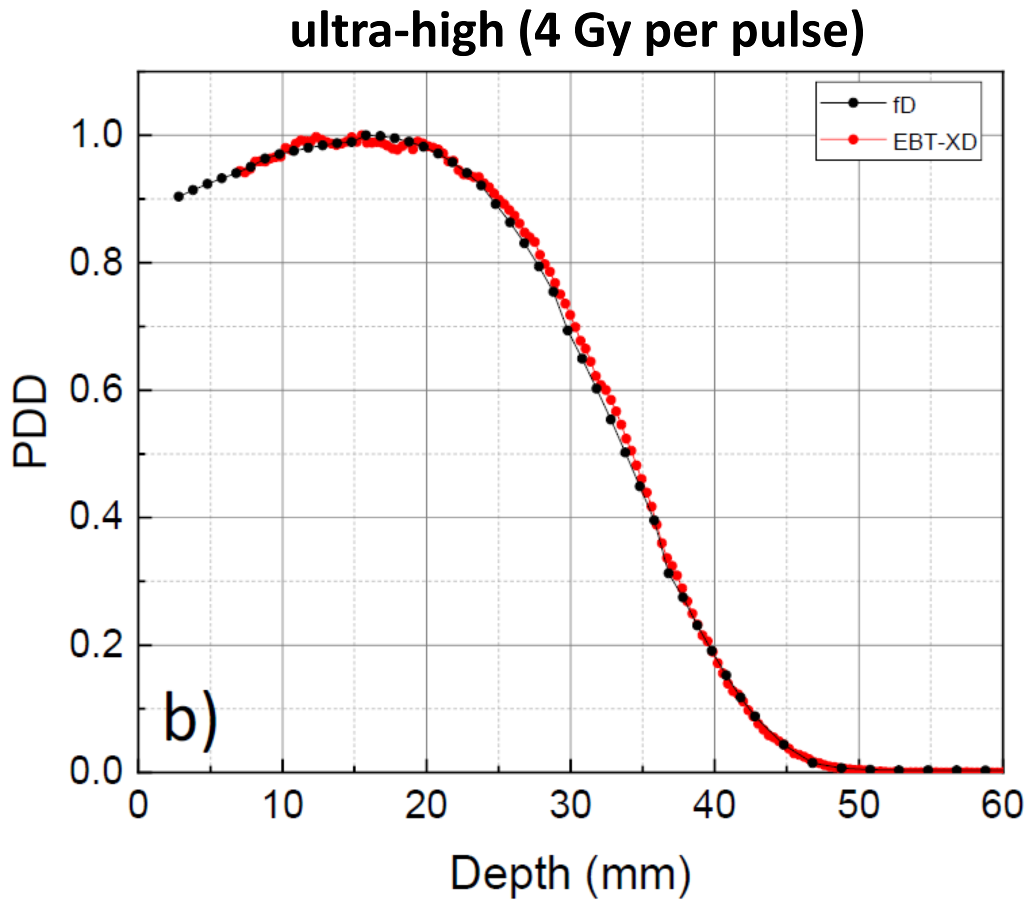
Diamond detector prototype for FLASH RT dosimetry



M. Marinelli et al.
"Design, realization, and characterization of a novel diamond detector prototype for FLASH radiotherapy dosimetry."
Med. Phys. **49** (2022) 1902.
https://doi.org/10.1002/mp.15473

Diamond detector prototype for FLASH RT dosimetry



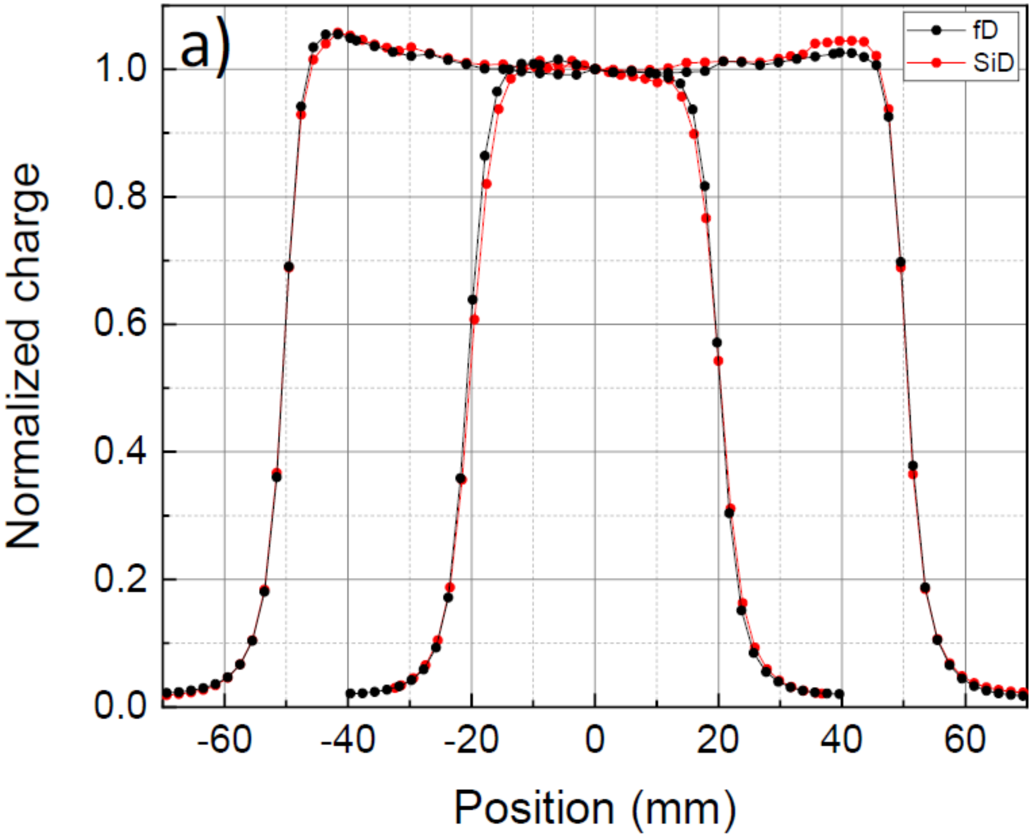


9 MeV, 100 mm applicator

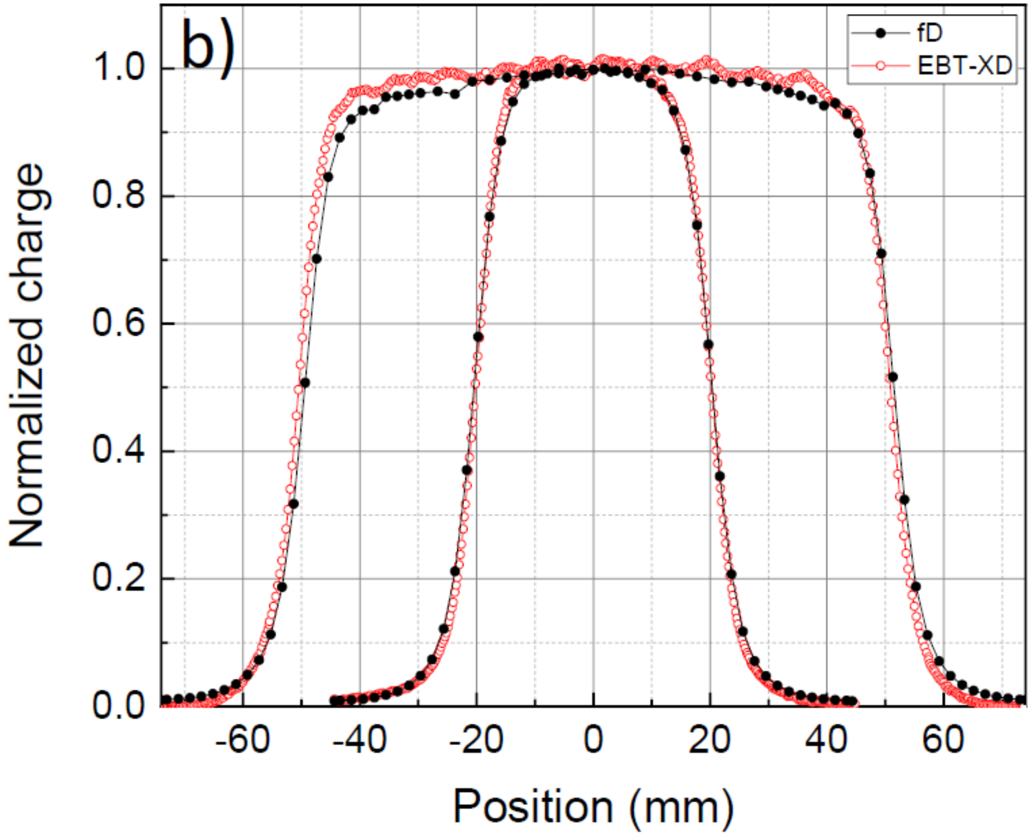
G. Verona Rinati et al.
“A diamond detector prototype for commissioning of FLASH radiotherapy electron beams”
submitted to *Medical Physics*

Diamond detector prototype for FLASH RT dosimetry

conventional



ultra-high (11 and 4 Gy per pulse)

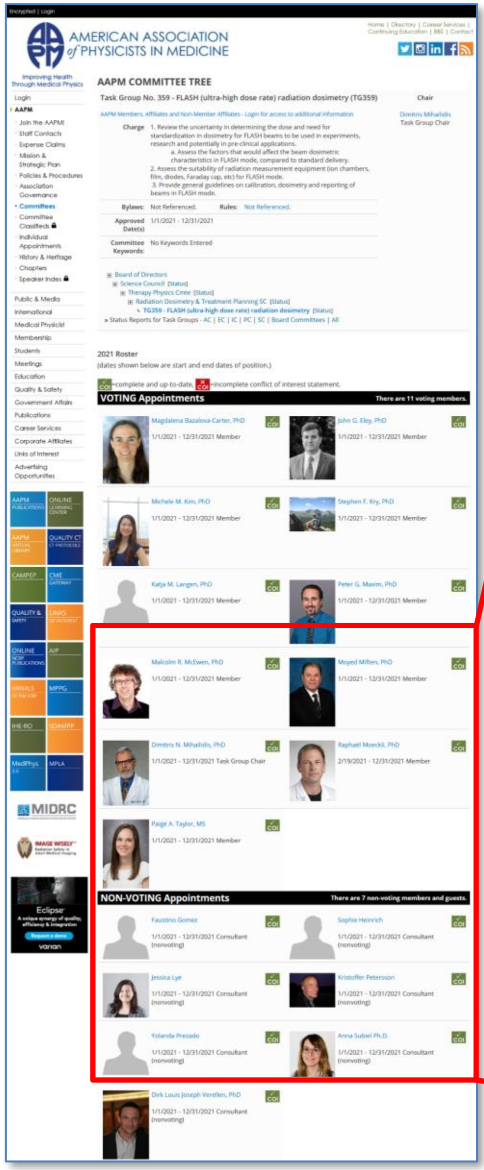


9 MeV, 100 mm and 40mm applicator

G. Verona Rinati et al.
“A diamond detector prototype for commissioning of FLASH radiotherapy electron beams”
submitted to *Medical Physics*

AAPM TG 359 “FLASH radiation dosimetry”

UHDpulse



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Moyed Miften, PhD
1/1/2021 - 12/31/2021 Member

Dimitris N. Mihailidis, PhD
1/1/2021 - 12/31/2021 Task Group Chair

Raphaël Moeckli, PhD
2/19/2021 - 12/31/2021 Mem

Paige A. Taylor, MS
1/1/2021 - 12/31/2021 Member

NON-VOTING Appointments There are 7 non-voting members and guests.

Faustino Gomez
1/1/2021 - 12/31/2021 Consu
(nonvoting)

Sophie Heinrich
1/1/2021 - 12/31/2021 Consul
(nonvoting)

Jessica Lye
1/1/2021 - 12/31/2021 Consultant
(nonvoting)

Kristoffer Petersson
1/1/2021 - 12/31/2021 Consultant
(nonvoting)

Yolanda Prezado
1/1/2021 - 12/31/2021 Consultant
(nonvoting)

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1/1/2021 - 12/31/2021 Consul
(nonvoting)

https://www.aapm.org/org/structure/default.asp?committee_code=TG359

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NRC·CNRC Canada

CHUV Centre hospitalier universitaire vaudois

USC Universidade de Santiago de Compostela

institut Curie

NPL National Physical Laboratory

SIT

netwerk iridium Topzorg in radiotherapie

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iba Dosimetry Protect, Enhance and Save Lives

UHDpulse stakeholder workshop

All abstracts are published in in Physica Medica 94 Supplement S1-S132

https://www.physicamedica.com/issue/S1120-1797(22)X0003-3

Summary

- There is no real-time dosimetry system for FLASH RT with electrons commercially available up to now.
- Commercially available ionization chambers show large deviations at ultra-high dose per pulse (DPP) due to ion recombination.
- Calculation of charge collection efficiency agree with experimental results.
- Prototypes of parallel plate ionization chambers with very small electrode distances show linear response in the ultra-high DPP range.
- microDiamond detectors show saturation effects at different DPP levels.
- Prototype Diamond detectors show linear response in the ultra-high DPP range.

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