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

Andreas Schüller
Department 6.2 “Dosimetry for Radiation Therapy and Diagnostic Radiology”
on behalf of the UHDpulse consortium

WP2 EPTN, Workshop “Ultra-high dose rate dosimetry: what’s going on?”
6.5.21, virtual
Overview of the EMPIR project UHDpulse - “Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

Contents
- EMPIR program, Partners & Collaborators
- Ultra-high dose per pulse, metrological challenges
- Objectives, Work Package structure
- Current progress in ultra-high dose rate dosimetry
EMPIR project UHDpulse

Type: Joint Research Project
Duration: Sep/2019-Feb/2023
Start: 1. Sept. 2019
Funding: 2.1 M €
Coordinator: Andreas Schüller (PTB)
Topic: tools for traceable dose measurements for:
• FLASH radiotherapy
• VHEE radiotherapy
• laser driven medical accelerators

http://uhdpulse-empir.eu/

The European Metrology Programme for Innovation and Research (EMPIR):
- metrology-focused programme of coordinated R&D
- enables European metrology institutes, industrial and medical organisations, and academia to collaborate
# UHDpulse Partners and Collaborators

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<th>Metrology Institutes</th>
<th>Irradiation facility provider</th>
<th>Radiation detector developer</th>
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<td>CHUV</td>
<td>ADVACAM</td>
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<td>Central Office of Measures</td>
<td>Centre hospitalier universitaire vaudois</td>
<td>Imaging the Unseen</td>
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<td>National Physical Laboratory</td>
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<td>Czech Metrology Institute</td>
<td>HZDR</td>
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<td>MedAustron</td>
<td>THE DOSIMETRY COMPANY</td>
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<td>Detector Devices and Technologies Toshiba</td>
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</table>

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

Interested institutes that want to contribute to the goals of the project may join the as **collaborator**
FLASH radiotherapy

- ultra-high dose rate $\rightarrow$
  - reduction of the normal tissue complications (NTC)
  - same tumour control level (TC)
  - Less side effects, or higher dose for better chance of cure

$\rightarrow$ FLASH effect
FLASH radiotherapy

• The number of institutes interested in FLASH radiotherapy and the number of FLASH papers published per year increasing exponentially.

• 2021: 1 paper/week

• Regardless of whether FLASH will play a significant role in radiotherapy in the future or not, there is just now an urgent need for tools for traceable dose measurements for FLASH.
“Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

electrons, protons (no photons)

ultra-high dose per pulse, ultra-short pulse duration or both

Dose per beam pulse (Gy)

conventional radiotherapy
FLASH radiotherapy (RF-driven)
VHEE electrons
laser-driven electrons
laser-driven protons
protons from synchrocyclotron
proton FLASH (from cyclotron)

300 ms
10 μs
70 ns
5 fs
ps, ns
2 μs
3 μs

ultra-high
ultra-short
Ultra-high dose per pulse at FLASH radiotherapy

Mice brain irradiation with 10 Gy

Mean 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
Ultra-high dose per pulse at FLASH radiotherapy

Conventional and FLASH Irradiation (with same total dose)

36 weeks post-RT

Conventional (5 Gy/min)

34 Gy 31 Gy 28 Gy

necrotic lesions

FLASH (300 Gy/s)

34 Gy 31 Gy 28 Gy

normal appearance of skin

Vozenin et al., Clin Cancer Res 25 (2019) 35
http://dx.doi.org/10.1158/1078-0432.CCR-17-3375
Ultra-high dose per pulse at FLASH radiotherapy

human Patient:
lymphoma on skin

FLASH-RT:
10 pulses (of 1 μs duration) in 90 ms with 1.5 Gy/pulse

Day 0

3 weeks
(max. of skin reactions)

5 months

DOI: 10.1016/j.radonc.2019.06.019
Ultra-high dose per pulse at FLASH radiotherapy

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<tr>
<th>Parameters</th>
<th>FLASH</th>
<th>CONV</th>
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<tr>
<td>e-beam energy</td>
<td>~16 MeV</td>
<td>~16 MeV</td>
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<tr>
<td>Repetition rate</td>
<td>108 Hz</td>
<td>72 Hz</td>
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<tr>
<td>Dose per pulse</td>
<td>2.0 Gy</td>
<td>0.00109 Gy</td>
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<tr>
<td>Average dose rate</td>
<td>216 Gy/s</td>
<td>0.07863 Gy/s (4 Gy/min)</td>
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<tr>
<td>Instantaneous dose rate (pulse length 5 μs)</td>
<td>4.0E5 Gy/s</td>
<td>218.5 Gy/s</td>
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Levy et al. Scientific Reports (2020) Abdominal FLASH irradiation …

https://doi.org/10.1038/s41598-020-78017-7
Due to ultra-high dose rates and pulsed structure of the beams, tools and methods established in dosimetry for conventional radiotherapy are not suitable for FLASH radiotherapy.

There are

- no active dosimeters for real-time measurements
- no formalism (Codes of Practice) for reference dosimetry
- no corresponding primary standards

Losses due to ion recombination increase with increasing dose per pulse.
Objectives, WPs

to establish traceability in absorbed dose measurements of ultra-high pulse dose rate beams.

The specific aims of the project are:

- Development of primary and secondary absorbed dose standards and reference dosimetry methods
- Characterization of state-of-the-art detector systems
- Development of methods for relative dosimetry and for the characterization of stray radiation
- Providing of input data for future Code of Practice

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

WP3: Detectors for primary beam
- Active detection techniques for pulsed mixed radiation fields of stray radiation and pulsed neutrons
- Methods with passive detectors

WP4: Detectors and methods outside primary beam

WP5: Impact, WP6: Coordination
The UHDpulse consortium wrote an overview paper describing the goals of the project, providing details on the state-of-the-art of radiotherapy using particle beams with ultra-high pulse dose rates and introducing promising candidates as suitable dosimeters for ultra-high dose rate dosimetry to be investigated within UHDpulse.

(currently number 7 on the list of most downloaded articles of the last 90 days of this journal)
• Review the uncertainty in determining the dose and need for standardization in dosimetry for FLASH beams to be used in experiments, research and potentially in pre-clinical applications.

• Assess the suitability of radiation measurement equipment (ion chambers, film, diodes, Faraday cap, etc) for FLASH mode.

• Provide general guidelines on calibration, dosimetry and reporting of beams in FLASH mode.

Objective 5: to facilitate the uptake of the project’s achievements by standards developing organizations and end users.

Objective 2: to characterise the response of available detector systems.

Objective 4: provide the input data for Codes of Practice.

https://www.aapm.org/org/structure/default.asp?committee_code=TG359
AAPM-ESTRO joint Task Group No. 359

Liaison

<table>
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<tr>
<th>Member Name</th>
<th>Role</th>
<th>Term Dates</th>
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<tr>
<td>Malcolm R. McEwen</td>
<td>PhD</td>
<td>1/1/2021 - 12/31/2021 Member</td>
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<td>Moyed Mitter</td>
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<td>1/1/2021 - 12/31/2021 Member</td>
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<td>Dimitris N. Mihalidis</td>
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<td>1/1/2021 - 12/31/2021 Task Group Chair</td>
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<td>Raphael Moeckli</td>
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<td>2/19/2021 - 12/31/2021 Member</td>
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<tr>
<td>Paige A. Taylor</td>
<td>MS</td>
<td>1/1/2021 - 12/31/2021 Member</td>
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**NON-VOTING Appointments**

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<td>Faustino Gomez</td>
<td>Cons (nonvoting)</td>
<td>1/1/2021 - 12/31/2021</td>
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<tr>
<td>Sophie Heinrich</td>
<td>Cons (nonvoting)</td>
<td>1/1/2021 - 12/31/2021</td>
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<td>Jessica Lye</td>
<td>Consultant (nonvoting)</td>
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<td>Kristoffer Petersson</td>
<td>Consultant (nonvoting)</td>
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<td>Yolanda Prezado</td>
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<tr>
<td>Anna Subiel Ph.D.</td>
<td>Consultant (nonvoting)</td>
<td>1/1/2021 - 12/31/2021</td>
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https://www.aapm.org/org/structure/default.asp?committee_code=TG359
PTB’s Research electron accelerator

$E = 0.5 - 50 \text{ MeV}$

Beam line with water phantom

**up to 7 Gy/pulse** (SSD 0.7 m, 20 MeV)
PTB’s electron reference field for UHD dosimetry

Non-destructive absolute beam pulse charge measurement (uncertainty < 0.1 % @70 nC/pulse)

Alanine pellets at reference depth in water phantom

Dose traceable to primary standard
PTB’s electron reference field for UHD dosimetry

Detector under test at reference depth in water phantom

A Bourgouin et al., Calorimeter for Real-Time Dosimetry of Pulsed Ultra-High Dose Rate Electron Beams
https://doi.org/10.3389/fphy.2020.567340
Within the framework of UHDpulse theoretical models for the calculation of the charge collection efficiency of plane parallel ionization chambers at ultra-high dose per pulse are developed, with the aim of to provide an ion recombination correction function.

F. Gomez et al., The Challenge of Dosimetry in Flash Radiotherapy
https://indico.ific.uv.es/event/5983/contributions/13896/
Within UHDpulse the performance of plane parallel ionization chamber prototypes with different electrode distance at ultra-high dose per pulse are investigated. Reduction of the electrode distance helps to increase the charge collection efficiency at ultra-high dose per pulse.

Rafael Kranzer et al., Medical Physics 2021, https://doi.org/10.1002/mp.14620
Dosimetry for FLASH RT with ion chambers

Within UHDpulse USC builds an ultra-thin plane parallel ionization chamber prototype in order to enable reliable ionization chamber measurements up to 5 Gy/pulse.

Simulated ion recombination correction factor for plane parallel ionization chambers at 300 V for 5 Gy/pulse

USC’s ultra-thin chamber prototype

PPC05

Advanced Markus

Roos, Markus, PPC40, NACP

https://doi.org/10.1016/j.ejmp.2020.09.020
Dosimetry for FLASH RT with ion chambers

Within UHDpulse the response of different types of commercially available ionization chambers as well as their intra-type variations are characterized.

Alexandra Bourgouin et al., to be published
Within UHDpulse the performance of the Graphite Probe Calorimeter prototype “Aerrow” is investigated. The detector shows linear response in the FLASH range.

Aerrow (and Exradin A12 ionization chamber for size reference). The internal structure of Aerrow is shown as a blended rendering.

Detector response vs. dose reference from alanine/monitor.

Alexandra Bourgouin et al., to be published
Dosimetry for FLASH RT by diamond detectors

Within UHDpulse the performance of microDiamond detectors are investigated at ultra-high dose per pulse. Adapted prototypes show linear response in the FLASH range. -> currently under test at PTB’s proton beam at UHD

Rafael Kranzer et al., to be published
Dosimetry for proton FLASH by ML Faraday Cup

- PTB developed a portable Multi-leaf Faraday Cup (MLFC)
- Measuring principle is independent of the dose rate
- to be used in FLASH proton beams
A test of the MLFC for proton beams was carried out at UHDpulse Collaborator MedAustron (at conventional dose rates).

From energy and charge the dose rate can be determined.
Within the framework of UHDpulse NPL has conducted an experimental campaign at Cincinnati’s Children Proton Therapy Centre, where traceability to the NPL portable graphite primary standard has been provided for their FLASH proton beam. The centre was then allowed to start the first clinical trial of FLASH proton therapy in human patients.
NPL primary standard graphite calorimeter

- developed to facilitate calibration in proton beams primarily for scanned (but also for scattered beam) delivery modes
- Graphite core 2 mm thick and 16 mm diameter
- Surrounded by a graphite inner and outer jacket, and a graphite mantle, arranged in a nested construction
- New UK IPEM code of practice is being delivered to deliver an uncertainty on reference dosimetry for protons of approx. 2% (k=2) → against 4.6% (k=2) for proton beams currently suggested by IAEA TRS-398 and based on an ionization chamber calibrated in a $^{60}$Co beam → beam quality correction factor.

Fig. 1: NPL’s primary standard graphite calorimeter.
Traceable graphite calorimetry of UHDR proton beam

to be published
Dosimetry for proton FLASH stray radiation

• ADVACAM developed a new prototype detector for the real-time measurement of pulsed stray radiation. The device was tested in a FLASH proton beam at HZDR (pencil PB, 160 Gy/s, 220 MeV, 2 ms pulseduration).

MiniPIX TPX3 Flex in a water phantom in an ultra-high dose rate proton beam

to be published
UHDpulse co-organizes the 3-day conference “FLASH Radiotherapy & Particle Therapy” (FRPT2021).

The conference will include the 3rd FLASH Workshop, the workshops of UHDpulse and INSPIRE (integrating activity for European research in proton therapy).

There will be dedicated Sessions for dosimetry and QA at ultra-high dose rates.

https://frpt-conference.org/
FRPT Conference

All abstracts accepted to FRPT 2021 will be published in a supplement of the “Physica Medica” Journal.

Moreover, the full papers of the best abstracts presented at the Conference will be published in a special issue of:

- The “Physica Medica” Journal – for technology/dosimetry related work
- The “Radiotherapy and Oncology” Journal – for clinical application and biology related research

Submit your abstract and gain maximum exposure for your work.

Deadline: 12 May 2021
FRPT Conference

FRPT 2021 will be held at the Austria Center Vienna and Online

Sponsors:

[Images of sponsors' logos]
“A wealth of future studies are waiting to be done at all levels of physical, chemical, molecular, biological, and clinical endeavors.”

Jolyon Hendry, Taking Care with FLASH Radiation Therapy
https://doi.org/10.1016/j.ijrobp.2020.01.029

However, if there is an error in dosimetry, then the difference in tissue response between conventional and ultrahigh-dose rate irradiation at seemingly equal total dose may be due to this error and not due to the FLASH effect.

This project (18HLT04) has received funding from the EMPIR programme co-financed by the Participating States and from the European Union’s Horizon 2020 research and innovation programme.

http://uhdpulse-empir.eu/