24th International Workshop on Radiation Imaging Detectors

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Instrumentation for FLASH Radiotherapy

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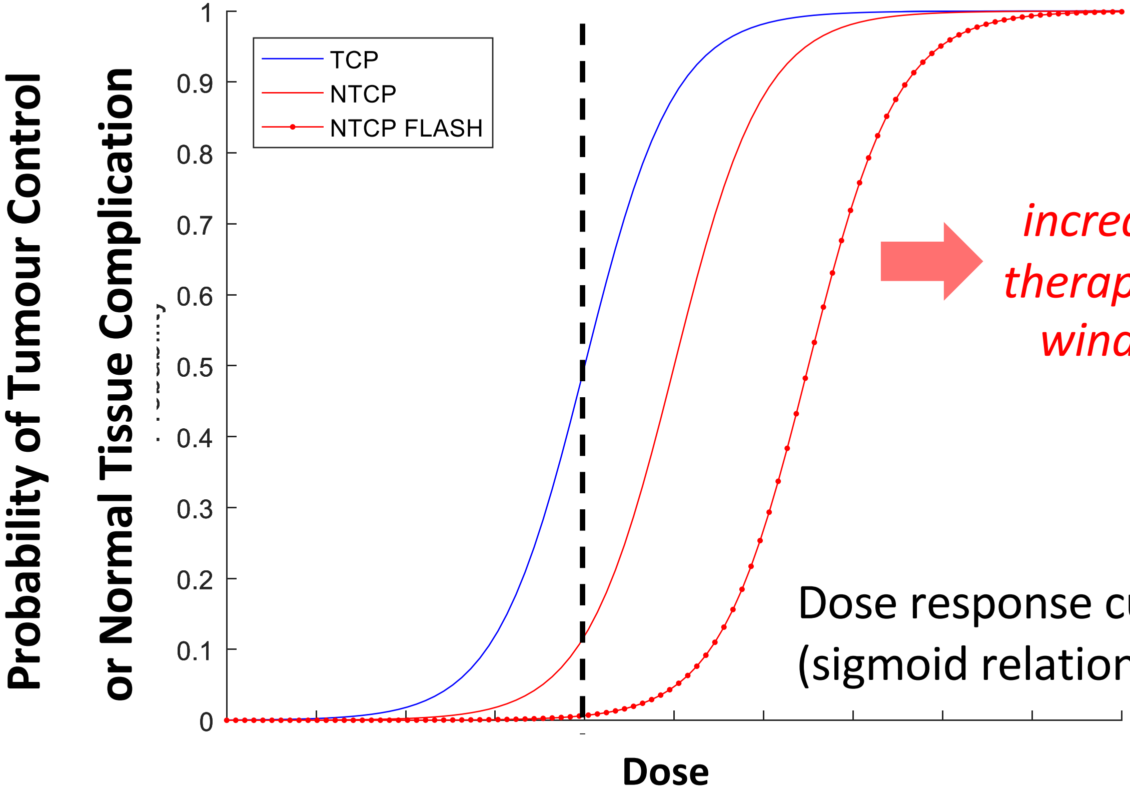
Decreasing toxicity maintaining tumor control: FLASH effect

- **FLASH radiotherapy:** a promising cancer treatment modality under development → almost instantaneous delivery of a high radiation dose in a few radiation **pulses** of **ultra-high dose rate** (**UHDR**)



increased therapeutic window

Dose response curves (sigmoid relationship)

TCP = Tumour Control Probability

NTCP = Normal Tissue Complications Probability

36 weeks post-RT

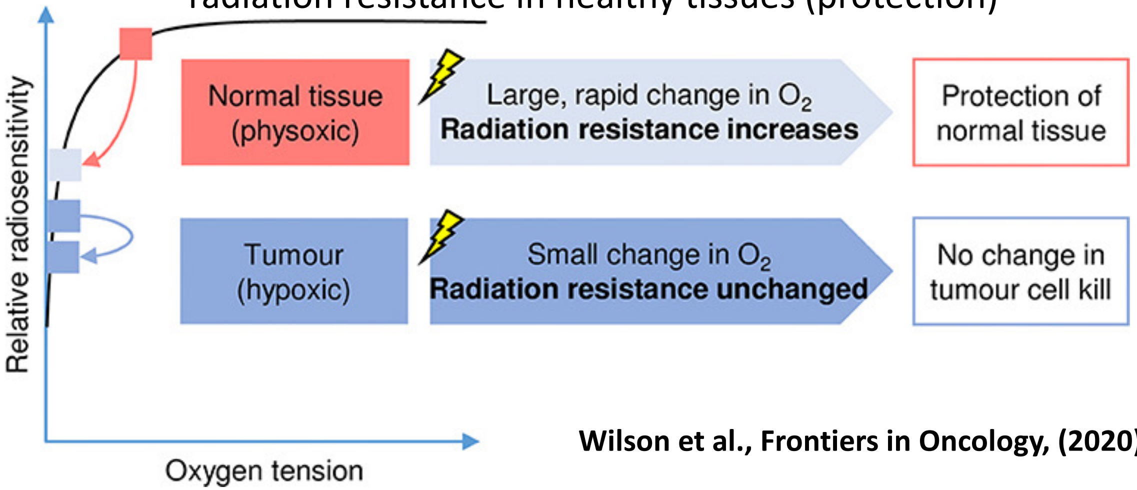
FLASH (300 Gy/s) **Conventional (5 Gy/min)**

normal appearance of skin *necrotic lesions*

Vozenin et al., Clin Cancer Res 25 (2019) 35

FLASH radiation consume the local oxygen faster than reoxygenation

Transient radiation induced hypoxia in healthy tissues → transient radiation resistance in healthy tissues (protection)



Wilson et al., Frontiers in Oncology, (2020)

Numbers of FLASH radiotherapy

CONVENTIONAL RADIOTHERAPY

<u>*Dose:*</u> ~2 Gy/fract. (x 30 fractions)
<u>*Dose Rate:*</u> ~ Gy/min
<u>*Irradiation Time:*</u> few minutes

FLASH RADIOTHERAPY

<u>*Dose:*</u> > 8 Gy (x 1 fraction?)
<u>*Dose Rate:*</u> > 40 Gy/s
<u>*Irradiation Time:*</u> <200 ms

Are these numbers telling the whole story?

Realization of FLASH radiation beams

Year	Radiation type	Machine	Energy (MeV)	Average dose rate (Gy/s)	Dose per pulse (Gy/pulse)	Pulse repetition rate (Hz)	Field size	Purpose	Dosimetry method
1995	Photon[30]	Brookhaven National Laboratory (USA)	0.08 mean	310–620	Not provided	52 MHz	4 × 0.02/0.04 mm 0.075/0.2 × 7 mm	Rat neuro-study	IC, RCF, TLD
2014	Electron[4]	Kinetron Linac[37] (Switzerland)	4.5	60	5×10^6	19	Ø 1.2 cm 1.8 cm × 2.0 cm	Mouse study (bilateral thorax irradiation)	Chemical dosimetry with blue methyl viologen
2017	Electron[5]	Oriatron 6e Linac (Switzerland)	6	100	5×10^6	100	Ø 1.7 cm	Mouse study (brain irradiation)	TLD
2017	Electron[17]	Varian 21EX (USA)	9 and 20	35–210	1.7×10^6	182	1–5 cm @ 90%	Feasibility study	EBT2 RCF
2018	Photon[7]	European Synchrotron Radiation Facility (France)	0.102 mean	37	1.2×10^4 Gy/s instantaneous	Continuous	2 × 2 cm (reference size)	Mouse study (brain irradiation)	IC[39]
2018	Proton[20]	IBA isochronous cyclotron (France)	138–198	40	N/A	106.14 MHz (quasi-continuous)	~1.2 cm @ 90%	Feasibility study	Cylindrical IC, EBT3 RCF
2019	Electron[18]	ELEKTA Precise Linac (Sweden)	8	30–300	Not provided	200	Ø 2 cm (at the highest dose rate)	Feasibility study	EBT3 RCF
2019	Electron[6]	Kinetron Linac and Oriatron 6e (Switzerland)	4.5 and 6	300	5×10^6	Not provided	Ø 2.6 cm or 1.8–4.5 cm rectangular	Mini-pig (skin) and cat (nasal tumor) study	TLD, alanine pellets, EBT3 RCF
2019	Electron[31]	Oriatron ERT6 Linac (Switzerland)	5.6	150	1×10^6	100	Ø 3.5 cm 1.3 depth @ 90%	Human patient treatment (skin)	Alanine pellets, EBT3 RCF
2019	Proton[21]	Varian isochronous cyclotron (USA)	245	40	N/A	Quasi-continuous	1 cm × 3 cm	Mouse study (whole thorax irradiation)	Not provided
2020	Proton[22]	IBA isochronous cyclotron (USA)	230	80	N/A	106.14 MHz (quasi-continuous)	~2 cm FWHM	Mouse study (abdomen irradiation)	Plane-parallel IC
2020	Proton[24]	Mevion synchrocyclotron (USA)	70	100–200	0.16–0.32 Gy/pulse (8–16×10^3 Gy/s instantaneous)	648	~1.2 cm FWHM (5 mm @ 90% isodose)	Feasibility study	Plane-parallel IC, FC, MC simulation, and RCF

> 40 Gy/s

e- Modified clinical LINACs

e- Research LINACs

p Isochronous cyclotrons

p Synchro cyclotrons

γ ions Synchrotrons

F. Romano *et al*. Med. Phys. (2022)

Realization of FLASH radiation beams

Year	Radiation type	Machine	Energy (MeV)	Average dose rate (Gy/s)	Dose per pulse (Gy/pulse)	Pulse repetition rate (Hz)	Field size	Purpose	Dosimetry method
2020	Proton[32]	IBA isochronous cyclotron (USA)	227.5	130	N/A	106 MHz (quasi-continuous)	1.6 × 1.2 cm^2 ellipse	Mouse (partial abdomen irradiation)	Plane-parallel IC, FC, MC simulation, EBT3 RCF
2020	Photon[33]	ANSTO Australian Synchrotron	0.07 and 0.09 mean	40–350 (at treat-ment depth and fil-tration)	200 (at 20 mm reference depth and filtration)	Continuous	2 × 2 cm (reference dosimetry size)	Rat study (brain cancer irradiation)	Pinpoint IC (reference), silicon semiconductor, and MC
2021	Proton[25]	Mevion synchrocyclotron (USA)	60	120–160	0.22 Gy/pulse (9.3 × 10^3 Gy/s instantaneous)	750	Ø 1.1 cm FWHM (5 mm @ 90% isodose)	Feasibility of SOBP beam using a synchrocyclotron	IC, FC, MC simulation, and EBT-XD RCF
2021	Electron[34]	Varian Clinac 2100 C/D (USA)	10	240–260	0.81 Gy/pulse	360	Ø 1–1.5 cm	Feasibility of UHDR at the machine's isocenter	EBT-XD RCF
2021	Proton[35]	Research isochronous cyclotron (Germany)	68	75	N/A	20 MHz	Ø 1.3 cm	Preclinical setup for mouse irradiation	IC and RC
2021	Proton[36]	COMET[38] isochronous cyclotron (Switzerland)	170—250	9000 (for a single spot)	N/A	72.85 MHz	~2.3–5 mm (16 × 1.2 cm^2 by scanning)	Feasibility study	FC
2021	Helium ion[26]	Synchrotron (Germany)	145.74 MeV/u	185	N/A	Quasi-continuous	1 cm^2 (by spot scanning)	In vitro study of dose, LET, and O_2 concentration	Parallel-plate IC
2021	Carbon ion[27]	Synchrotron (Germany)	280 MeV/u	70	N/A	Quasi-continuous	1 cm^2 (by spot scanning)	Dosimetry and in vitro study	IC and EBT3 RCF

> 40 Gy/s

e- Modified clinical LINACs

e- Research LINACs

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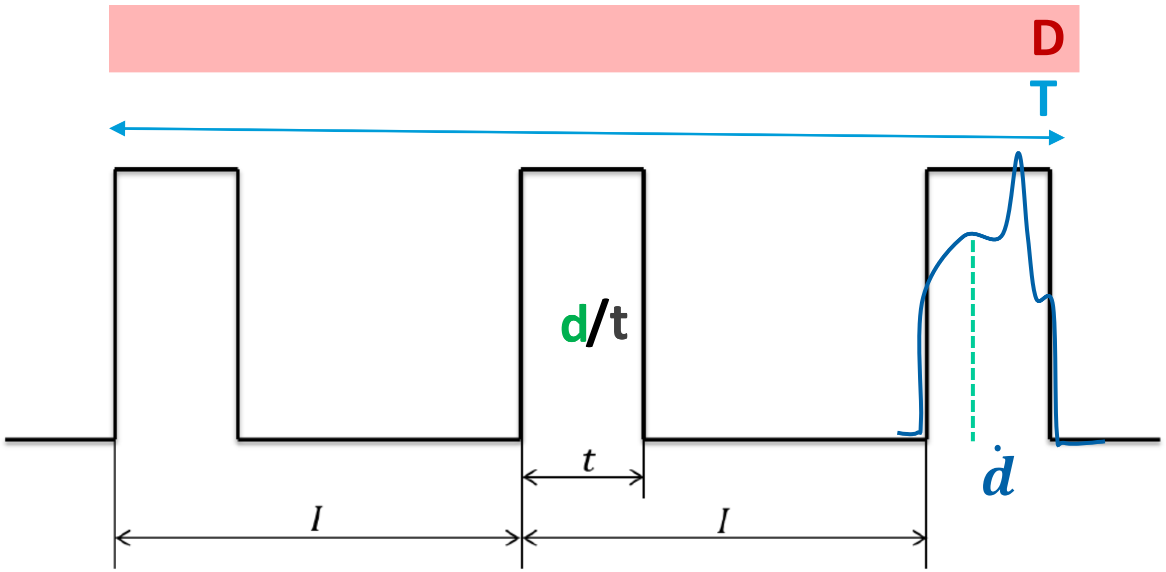
F. Romano *et al*. Med. Phys. (2022)

FLASH Radiotherapy: open questions

Is the FLASH effect only dependent on the **average dose-rate** along the irradiation duration?

Which physical parameters could be more relevant?

- Total dose → **D (>8 Gy)**
- **T** (<200ms) → Average dose rate → **D/T** (> 40 Gy/s)
- Dose-per-pulse? → **d** (→ relevant for ion chambers)
- Dose rate (averaged) in the pulse? → **d/t (< MGy/s)**
- Instantaneous dose rate? → $\dot{d}$



….open questions (for physicists):

Are we able to accurately perform absorbed dose measurements for FLASH Radiotherapy with the level of accuracy required for ***clinical translations****?*

All relevant parameters? Which detectors? For different beam pulse structures?

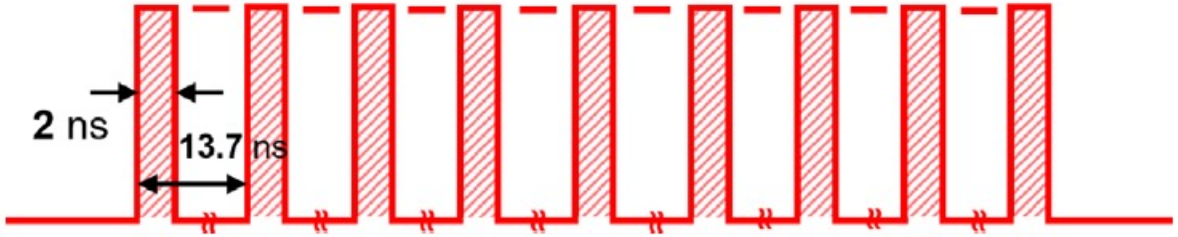
Are we able to accurately real-time monitor the dose delivery at the irradiation point?

Pulse duration and instantaneous dose for different accelerators at UHDRs

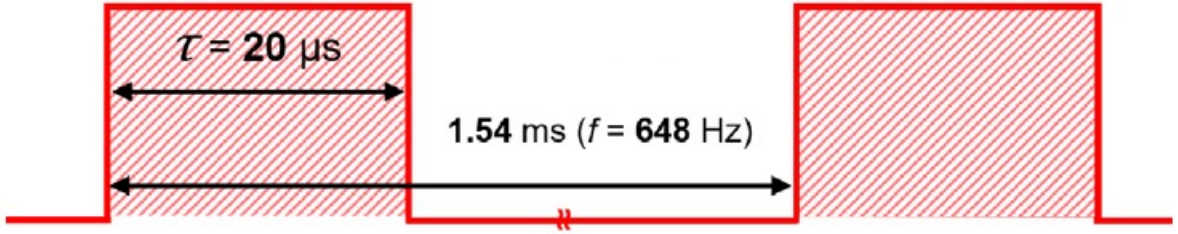
protons

$\dot{d}$ < 500 Gy/s

Isochronous cyclotron (quasi-continuous radiation)
(f=72.8 MHz, 2nd Harmonic)



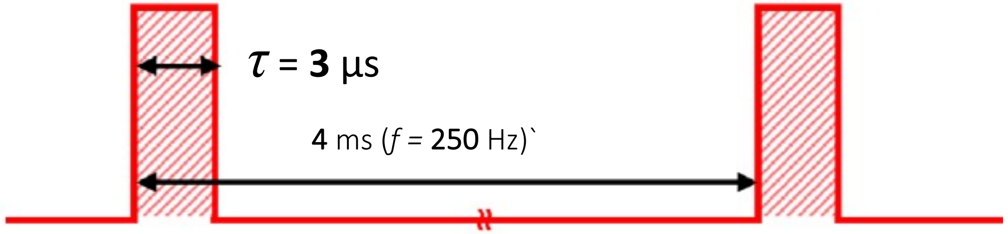
Synchrocyclotron (FLASH dose rate) $\dot{d}$ < 10 kGy/s



electrons

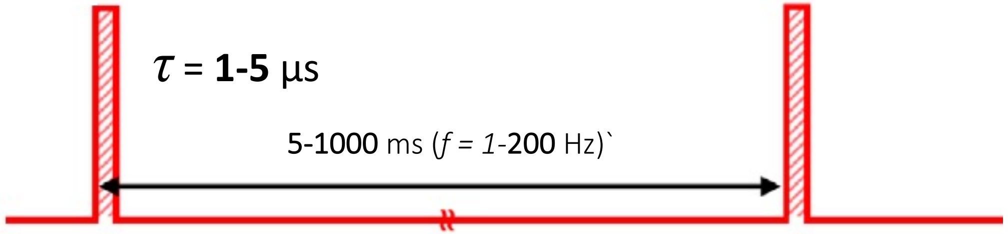
$\dot{d}$ < 100 kGy/s

Clinical LINAC for Radiotherapy (modified)



$\dot{d}$ < 5 MGy/s

Research LINAC for pre-clinical studies

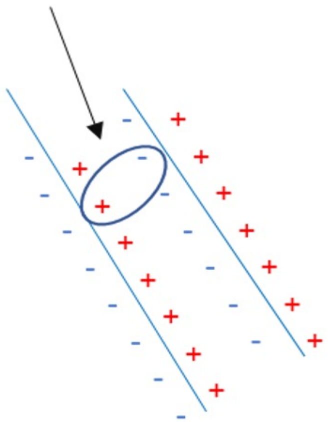


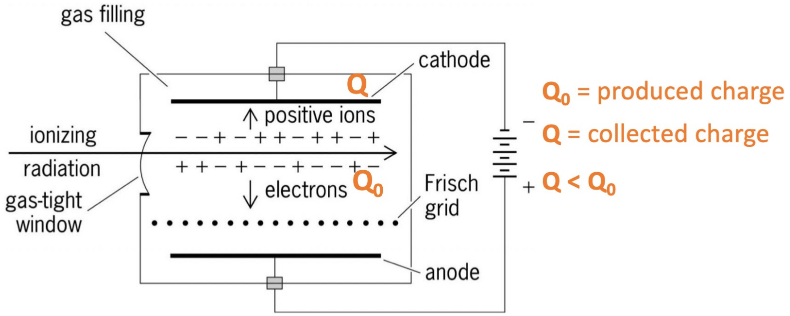
F. Romano *et al*. Med. Phys. (2022)

Reference dosimetry in Radiotherapy

The present Code of Practice fulfils the need for a systematic and internationally unified approach to the calibration of ionization chambers in terms of absorbed dose to water and to the use of these detectors in determining the absorbed dose to water for the radiation beams used in radiotherapy. The Code of Practice provides a methodology for the determination of absorbed dose to water in the low-, medium- and high-energy photon beams, electron beams, proton beams and heavy-ion beams used for external radiation therapy. The structure of this Code of Practice differs from TRS-277 and more closely resembles TRS-381 in that the practical recommendations and data for each radiation type have been placed in an individual section devoted to that radiation type. Each essentially forms a different Code of Practice including detailed procedures and worksheets.

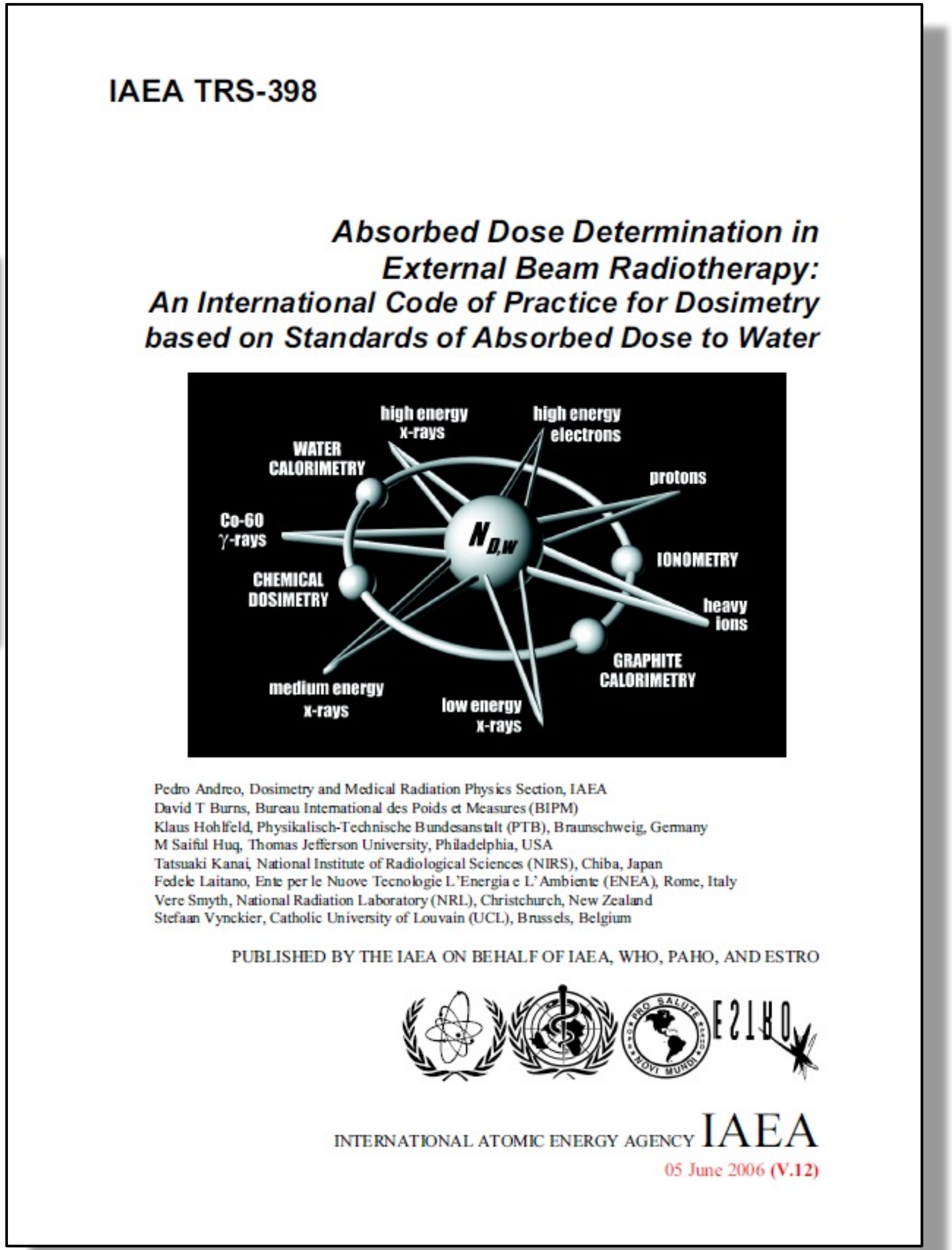
General Recom.





Depending on the dose rate:

- Ion recombination processes
- Ion collection efficiency ***f*** decreases
- For conv: 97%-100%



IAEA TRS-398

Absorbed Dose Determination in External Beam Radiotherapy: An International Code of Practice for Dosimetry based on Standards of Absorbed Dose to Water

Pedro Andreo, Dosimetry and Medical Radiation Physics Section, IAEA
David T Burns, Bureau International des Poids et Measures (BIPM)
Klaus Hohlfeld, Physikalisch-Technische Bundesanstalt (PTB), Braunschweig, Germany
M Saiful Huq, Thomas Jefferson University, Philadelphia, USA
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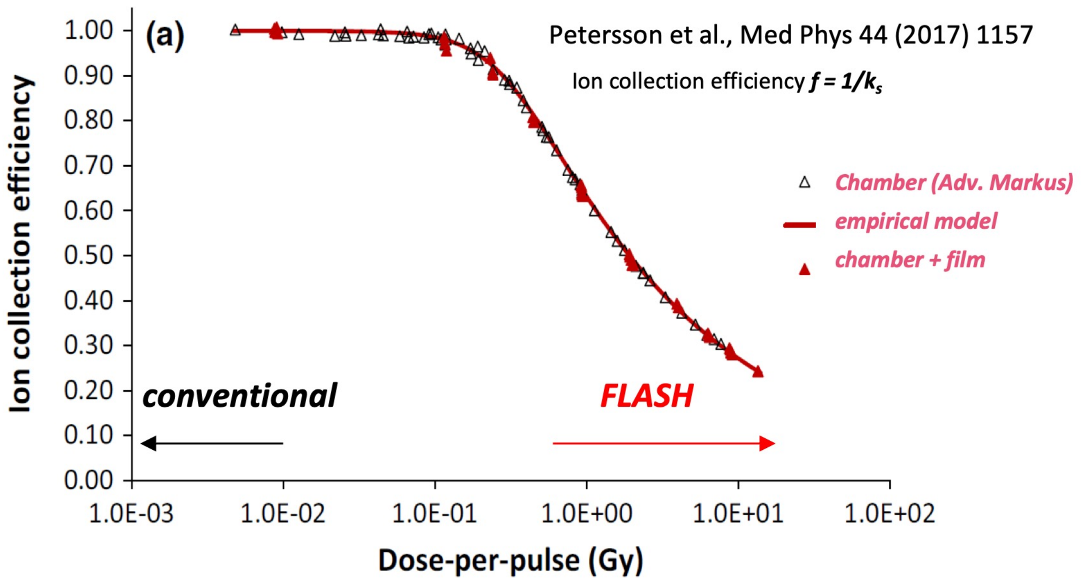
INTERNATIONAL ATOMIC ENERGY AGENCY IAEA
05 June 2006 (V.12)

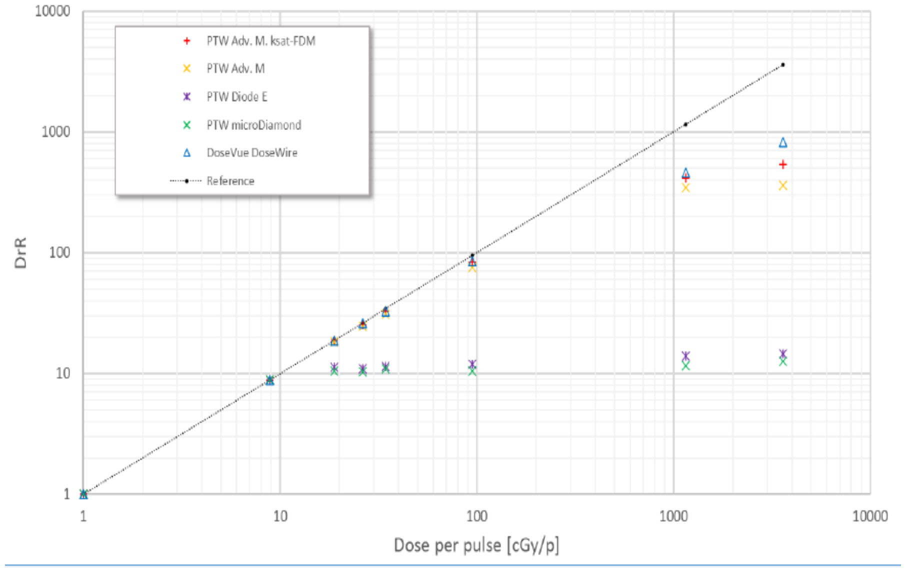
FLASH Radiotherapy: dosimetric challenges

Ionization chamber collection efficiency



Ionization chambers: recommended by protocols for reference dosimetry for Radiotherapy

Di Martino et al., Front. Phys. (2020)



Other commercially available detectors

Tools and methods established in dosimetry for conventional RT are not suitable for FLASH-RT:

- Alternative active detectors to be developed
- New protocols for reference dosimetry

Uncertainties in dosimetry:

→ under/over/not estimate different biological response between conventional irradiation and ultra-high dose rate irradiation

→ no proper assessment and investigation of the FLASH effect.

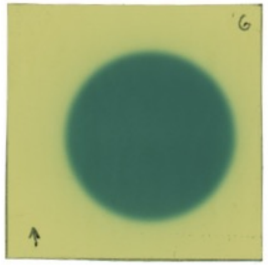
Possible dosimetric approaches for FLASH RT: passive detectors

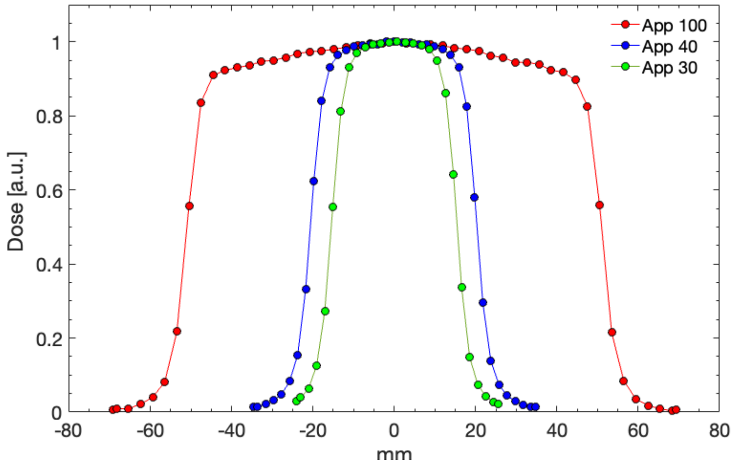
Dosimeter	Real time	In vivo dosimetry	Absolute/ reference dosimetry	Beam monitoring	Spatial resolution	Temporal resolution	2D dosimetry	Accuracy at conventional dose rates[a]	Other considerations
Ion chamber	Yes	No	Yes	Yes	Several mm	10–200 μs	Array	1%–2%	Significant ion recombination at UHDRs
Semiconductor	Yes	Yes	No	Yes	Sub-mm (or μm)	1–10 ns	Yes	2%–5%	Angular dependency, radiation damage, LET dependence
TLD	No	Yes	Yes	No	Several mm	N/A	No	3%–10%	Energy dependence, time consuming, LET dependence
OSLD	No	Yes	Yes	No	Sub-mm to mm	N/A	Array	3%–5%	Energy dependence, quenching in high LET fields
Scintillator	Yes	Yes	Potentially	Potentially	Sub-mm to mm	ns to μs	Array and sheet	3%–5%	Quenching in high LET fields, Cherenkov radiation
Gas scintillator	Yes	No	No	Yes	Sub-mm	N/A	Yes	1%	Beam centroid measurement
Calorimeter	Yes	No	Yes	No	cm to several mm	ms–10 ms	No	<1% at the primary standard level	Bulky, not easy to use, correction factors, time consuming
Film	No[b]	Yes	Potentially	No	Tens of μm	N/A	Yes	3%–5%	Quenching in high LET fields
Fricke	No	No	Yes	No	cm to sub-mm	N/A	Potentially	<1% at primary standard level	Time consuming, complexity
Faraday cup	Yes (for charge measurements)	No	Yes	No	N/A	<μs	No	2%–5% for commercial devices; 1%–2% for dedicated equipment[c]	Measures the total collected charge (other detectors are required for dose determination)
Nuclear track detector	No	Yes	No	No	mm; sub-mm with specialized equipment	N/A	Yes	5%–7%	Time consuming, energy dependence, LET dependence
Alanine	No	Yes	Yes	No	mm	N/A	No	2%–7% for doses larger than 10 Gy	Decreased accuracy for doses less than 10 Gy (minimum 2 Gy)
Integrated current transformer	Yes	Potentially	No	Yes	N/A	sub-μs	No	<1% for charge measurements	Lack of 2D measurements, only charge measurements

F. Romano *et al*. Med. Phys. (2022)

Possible dosimetric approaches for FLASH RT: passive detectors

Radiochromic films

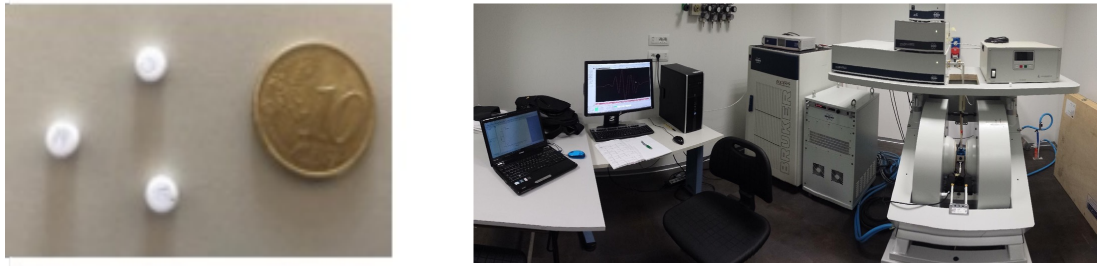


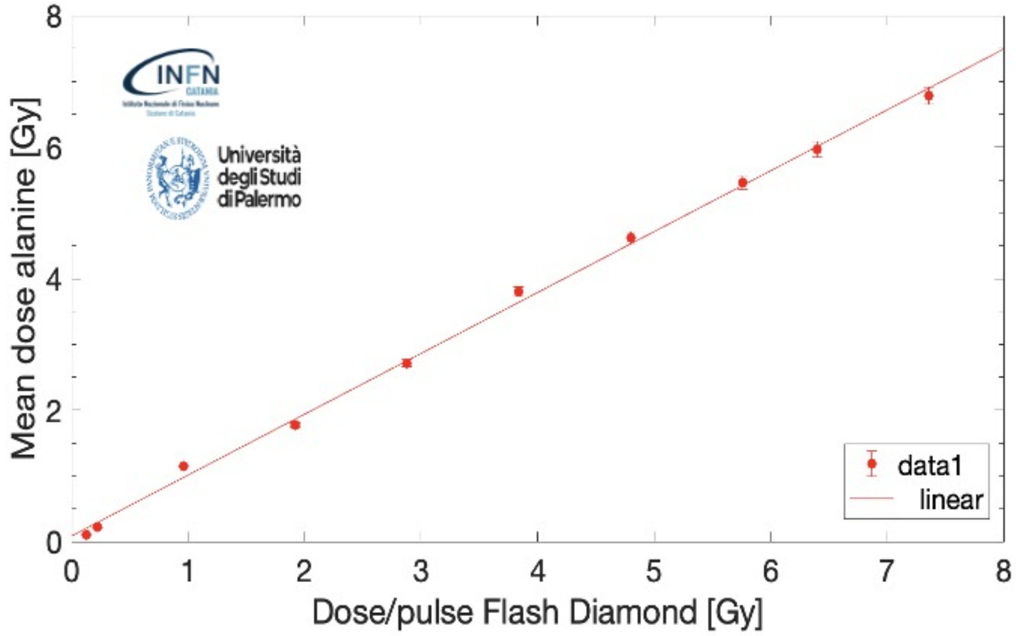


Relative dosimetry

Not suitable for clinical routine

Alanine



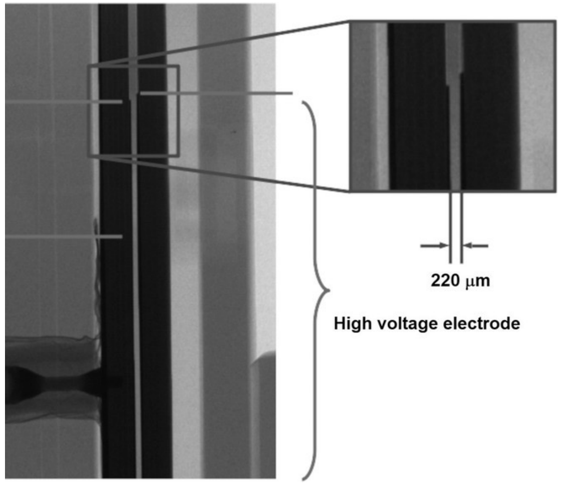


Absolute dosimetry

Possible dosimetric approaches for FLASH RT: ionization chambers

Dosimeter	Real time	In vivo dosimetry	Absolute/ reference dosimetry	Beam monitoring	Spatial resolution	Temporal resolution	2D dosimetry	Accuracy at conventional dose rates[a]	Other considerations
Ion chamber	Yes	No	Yes	Yes	Several mm	10–200 μs	Array	1%–2%	Significant ion recombination at UHDRs
Semiconductor	Yes	Yes	No	Yes	Sub-mm (or μm)	1–10 ns	Yes	2%–5%	Angular dependency, radiation damage, LET dependence
TLD	No	Yes	Yes	No	Several mm	N/A	No	3%–10%	Energy dependence, time consuming, LET dependence
OSLD	No	Yes	Yes	No	Sub-mm to mm	N/A	Array	3%–5%	Energy dependence, quenching in high LET fields
Scintillator	Yes	Yes	Potentially	Potentially	Sub-mm to mm	ns to μs	Array and sheet	3%–5%	Quenching in high LET fields, Cherenkov radiation
Gas scintillator	Yes	No	No	Yes	Sub-mm	N/A	Yes	1%	Beam centroid measurement
Calorimeter	Yes	No	Yes	No	cm to several mm	ms–10 ms	No	<1% at the primary standard level	Bulky, not easy to use, correction factors, time consuming
Film	No[b]	Yes	Potentially	No	Tens of μm	N/A	Yes	3%–5%	Quenching in high LET fields
Fricke	No	No	Yes	No	cm to sub-mm	N/A	Potentially	<1% at primary standard level	Time consuming, complexity
Faraday cup	Yes (for charge measurements)	No	Yes	No	N/A	<μs	No	2%–5% for commercial devices; 1%–2% for dedicated equipment[c]	Measures the total collected charge (other detectors are required for dose determination)
Nuclear track detector	No	Yes	No	No	mm; sub-mm with specialized equipment	N/A	Yes	5%–7%	Time consuming, energy dependence, LET dependence
Alanine	No	Yes	Yes	No	mm	N/A	No	2%–7% for doses larger than 10 Gy	Decreased accuracy for doses less than 10 Gy (minimum 2 Gy)
Integrated current transformer	Yes	Potentially	No	Yes	N/A	sub-μs	No	<1% for charge measurements	Lack of 2D measurements, only charge measurements

Possible dosimetric approaches for FLASH RT: ionization chambers

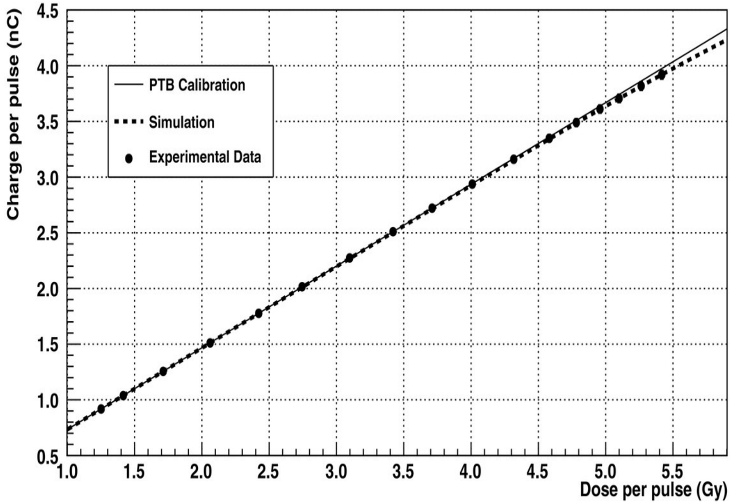


F. Gomez et al. Med Phys. 2022

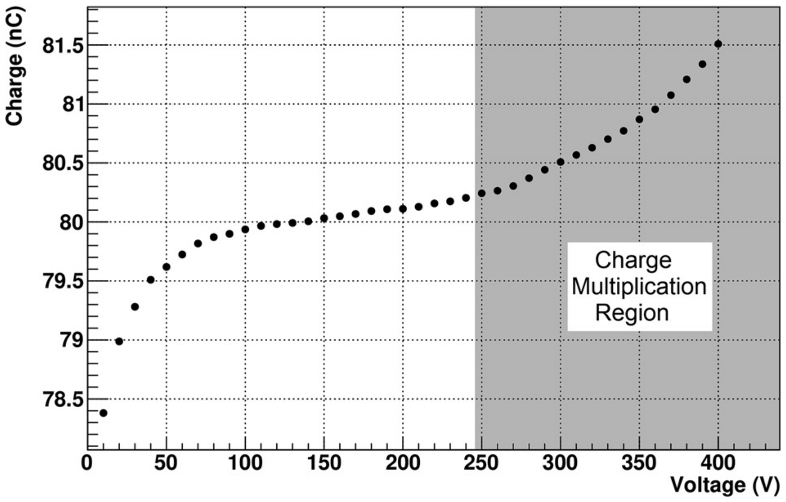
Which solutions for ion recombination at UHDRs?

- *Still using ionization chambers → k_{sat} to be decreased and/or properly determined*

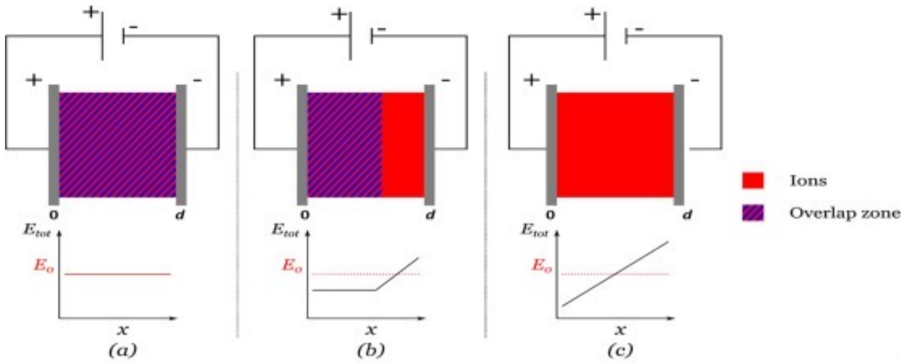
New chamber design with ultra-thin gap thickness (F. Gomez et al., Med. Phys. 2022)



Increasing applied V



Possible dosimetric approaches for FLASH RT: ionization chambers



Which solutions for ion recombination at UHDRs?

- *Still using ionization chambers → k_{sat} to be decreased and/or properly determined*

Decreasing the gas pressure and changing the mixture (F. Di Martino et al., EJMP 2022)

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A new solution for UHDP and UHDR (Flash) measurements: Theory and conceptual design of ALLS chamber

Fabio Di Martino [a,b,d,*], Damiano Del Sarto [b], Maria Giuseppina Bisogni [b,c,d], Simone Capaccioli [b,c], Federica Galante [e], Alessia Gasperini [f,g], Stefania Linsalata [a], Giulia Mariani [e], Matteo Pacitti [e], Fabiola Paiar [b,d,h], Stefano Ursino [b,d,h], Verdi Vanreusel [f,g], Dirk Verellen [f,g], Giuseppe Felici [e]

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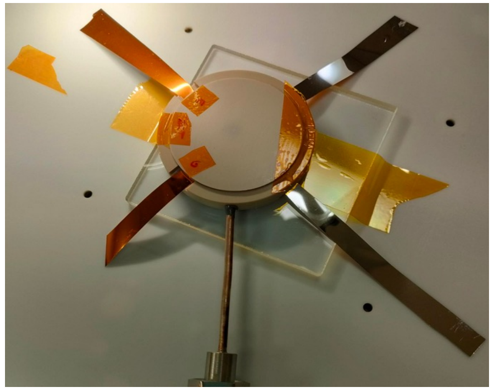

Possible dosimetric approaches for FLASH RT: calorimeters

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OSLD	No	Yes	Yes	No	Sub-mm to mm	N/A	Array	3%–5%	Energy dependence, quenching in high LET fields
Scintillator	Yes	Yes	Potentially	Potentially	Sub-mm to mm	ns to μs	Array and sheet	3%–5%	Quenching in high LET fields, Cherenkov radiation
Gas scintillator	Yes	No	No	Yes	Sub-mm	N/A	Yes	1%	Beam centroid measurement
Calorimeter	Yes	No	Yes	No	cm to several mm	ms–10 ms	No	<1% at the primary standard level	Bulky, not easy to use, correction factors, time consuming
Film	No[b]	Yes	Potentially	No	Tens of μm	N/A	Yes	3%–5%	Quenching in high LET fields
Fricke	No	No	Yes	No	cm to sub-mm	N/A	Potentially	<1% at primary standard level	Time consuming, complexity
Faraday cup	Yes (for charge measurements)	No	Yes	No	N/A	<μs	No	2%–5% for commercial devices; 1%–2% for dedicated equipment[c]	Measures the total collected charge (other detectors are required for dose determination)
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Integrated current transformer	Yes	Potentially	No	Yes	N/A	sub-μs	No	<1% for charge measurements	Lack of 2D measurements, only charge measurements

Possible dosimetric approaches for FLASH RT: **calorimeters** → *expertise of PSDLs*

Charge liberated in the medium results in an energy cascade - the liberated energy ends up as heat → measured as a temperature rise

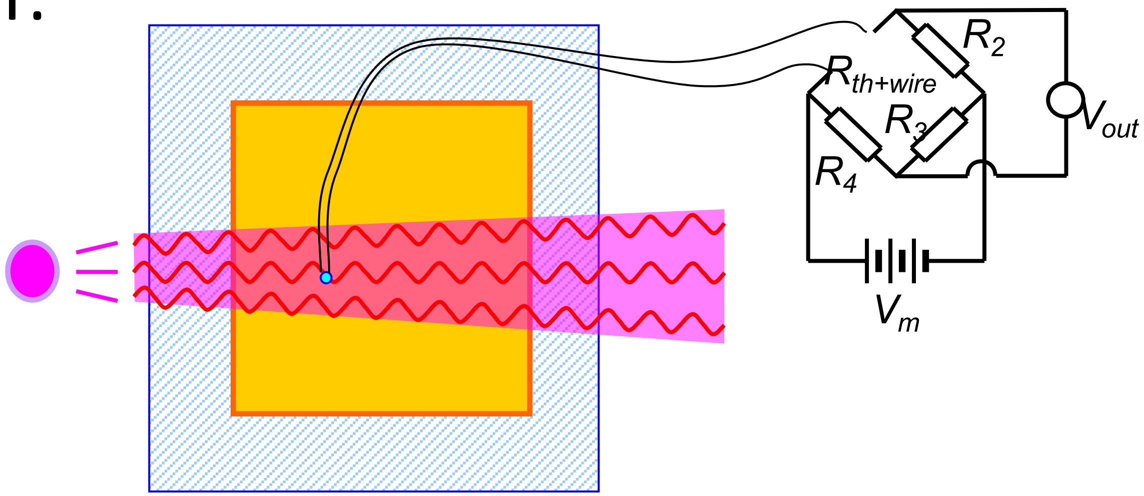
$$D_m = c_m \Delta T$$

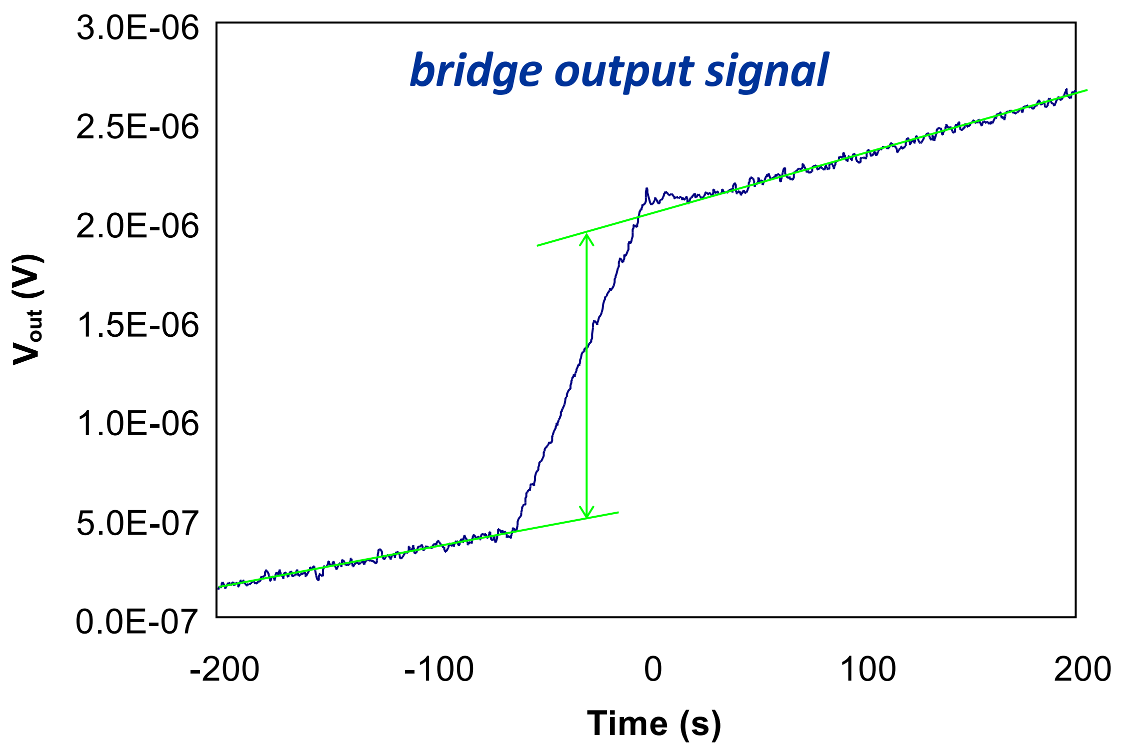
Where c_m stands for the specific heat capacity of the material and ΔT for the temperature rise.

- Water calorimeters: bulky systems typically used as a primary standard for metrology
- The temperature rise of water is **very small**:

$$\Delta T\ (water) = 2.4 \times 10^{-4}\ \text{K/Gy}$$

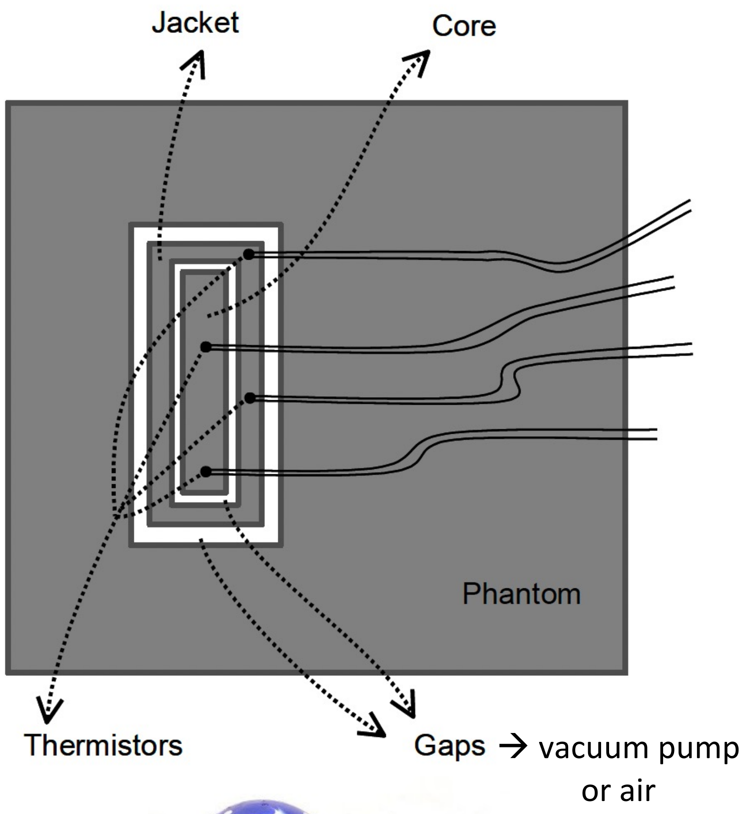
- **Graphite** calorimeters: higher temperature rise as respect to **water** (**c_m** six times smaller)

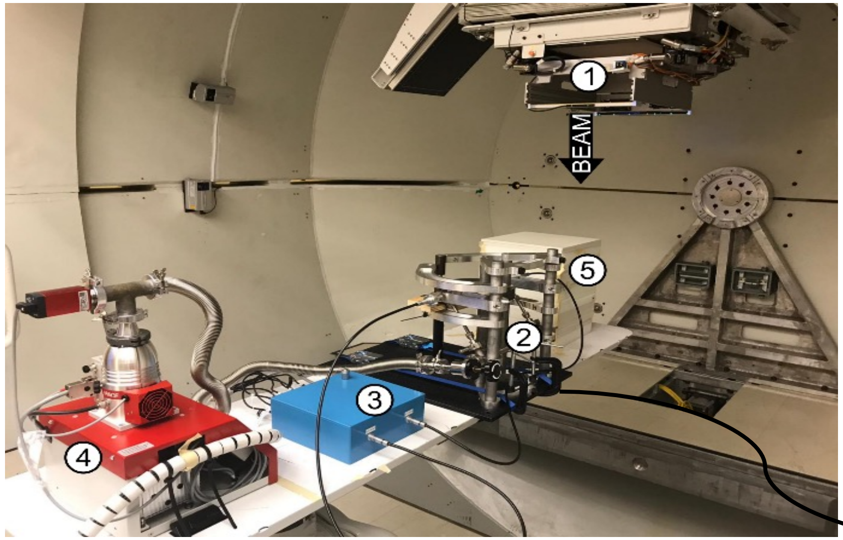




Graphite calorimeters

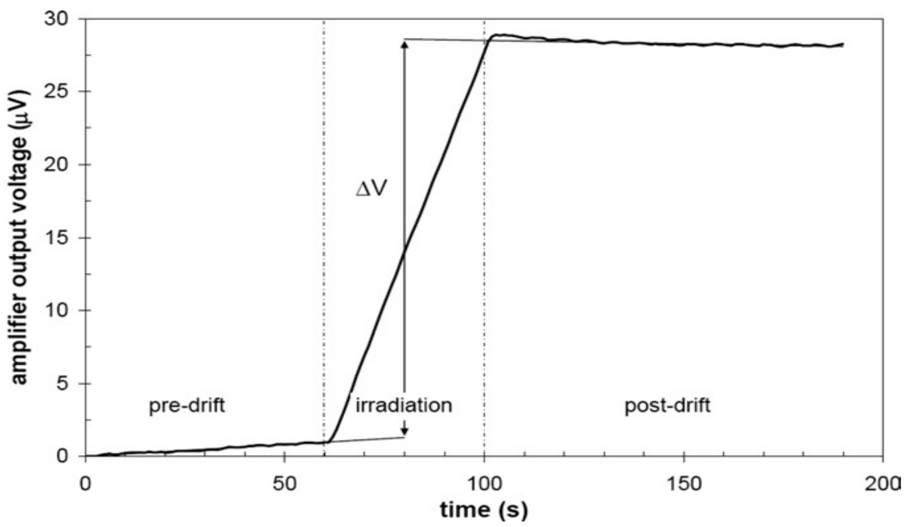
- A **core** needs to be thermally isolated from the surrounding graphite by one or more air or vacuum gaps → **nested configuration**
- Correction factor to be applied:
    - for the effect of gaps (vacuum or air)
    - Volume average correction factor due to the finite size of the core
    - heat transfers
    - pre- post- drift extrapolation



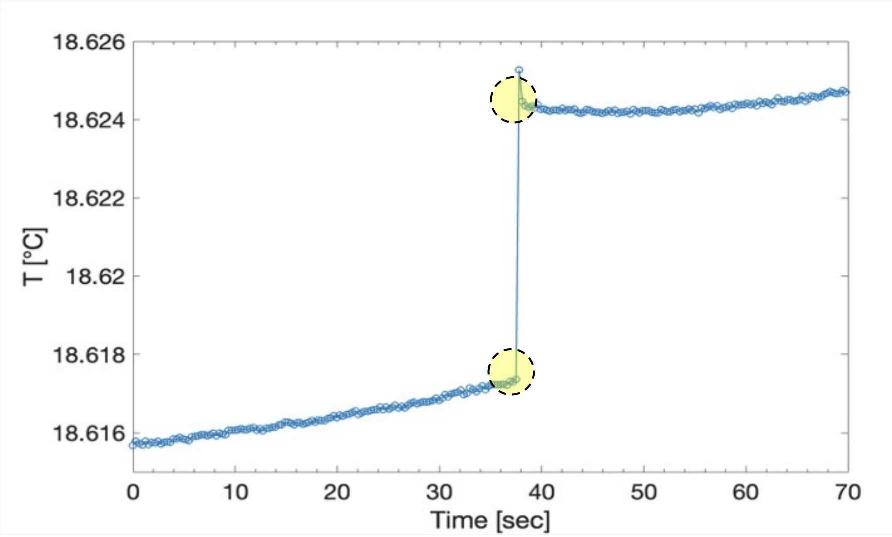


rack of DMMs!

Calorimeters for FLASH RT: portable!



Conventional Radiotherapy



FLASH Radiotherapy

A. Subiel and F. Romano, Br. J. Radiol. (2023)

Calorimeter type	Beam & energy	Average dose rate	Dose-per-pulse	Pulse duration	Uncertainty ($k = 1$)
Transfer standard graphite calorimeter	200 MeV electrons	0.2–50 Gy/s	0.03–5.3 Gy/pulse	Approx. 100 ns	1.2% (no uncert. budget)
Small portable graphite calorimeter	15–40 MeV laser-driven protons	10^9 Gy/s (one ps pulse delivered)	1–3 Gy/pulse	Approx. ns	Not stated
Aluminium calorimeter*	50 MeV electrons	1–9 Gy/s	0.2–1.8 Gy/pulse	2.5 μs	0.5% (no uncert. budget)
Aerrow graphite calorimeter*	20 MeV electrons	3–28 Gy/s	0.6–5.6 Gy/pulse	2.5 μs	1.06 %
Al-core secondary standard calorimeter	6 MeV electrons	180 Gy/s	Approx. 0.45 Gy/s	4 μs	1.25%

References

McManus et al. Scientific Reports (2020)

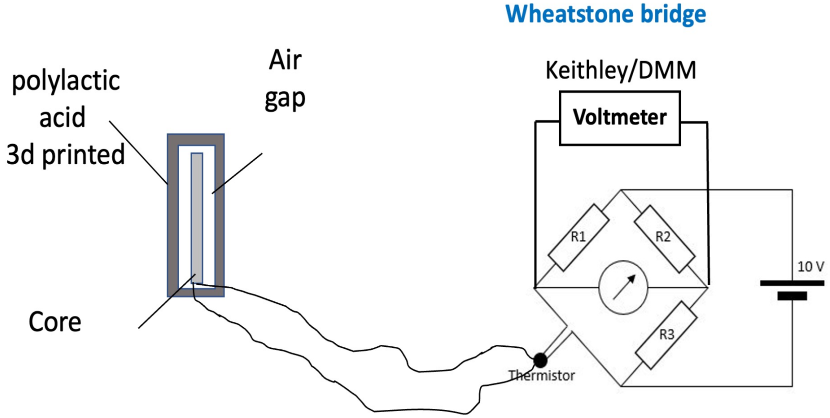
H. Palmans et al. PMB (2009)
F. Romano et al. Journal of Physics (2020)

A. Bourgouin, Frontiers in Physics (2020)

A. Bourgouin, Med. Phys. (2022)

G. Bass et al., Br. J. Radiol. (2023)

Secondary standard calorimeter

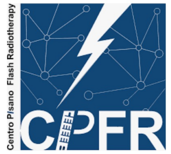


- Developed by NPL
- Simple usage and low cost
- 2 mm graphite core
- 1 single termistor connected to the Wheatstone bridge to measure the temperature increase
- IBA PPC05 ion chamber geometry (same holders)
- Tested at CPFR in Pisa (SIT e_FLASH linac)

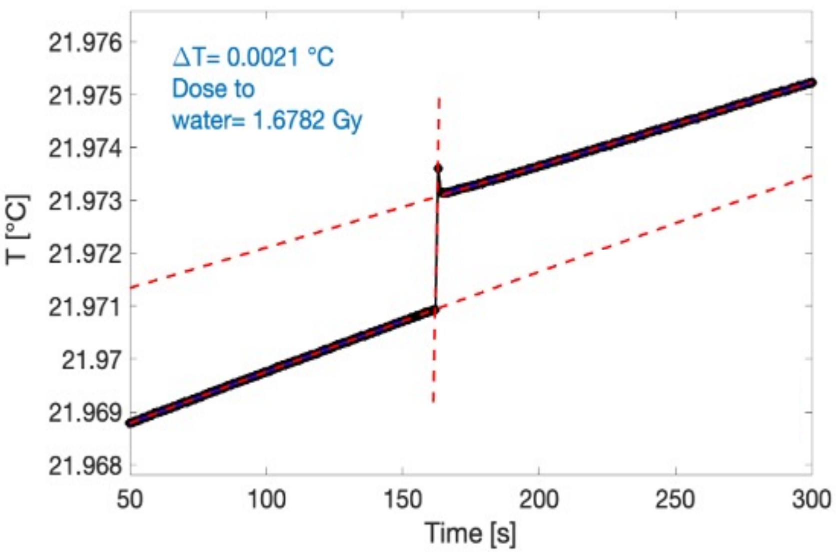
NPL National Physical Laboratory

INFN CATANIA Istituto Nazionale di Fisica Nucleare Sezione di Catania

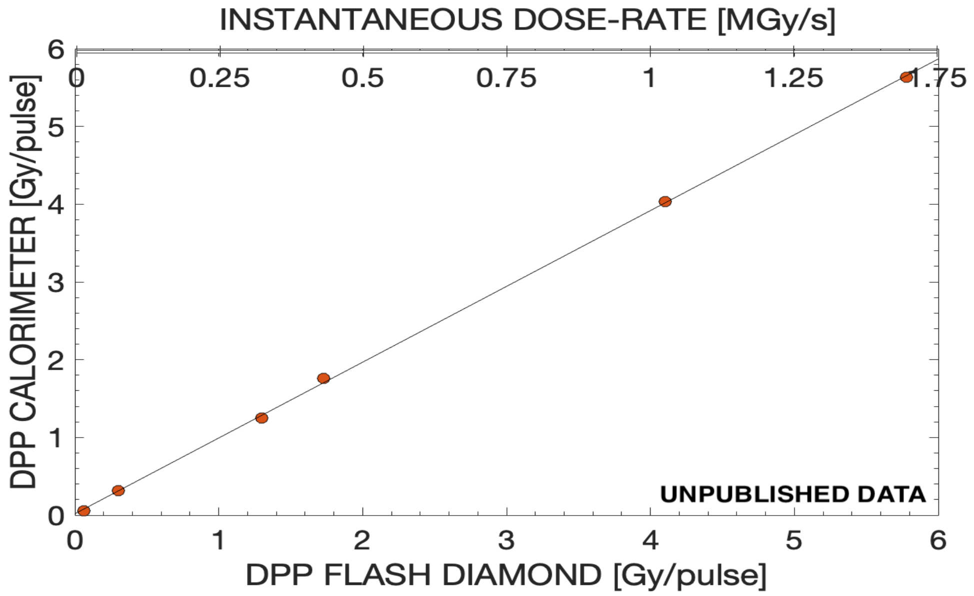
INFN FRIDA



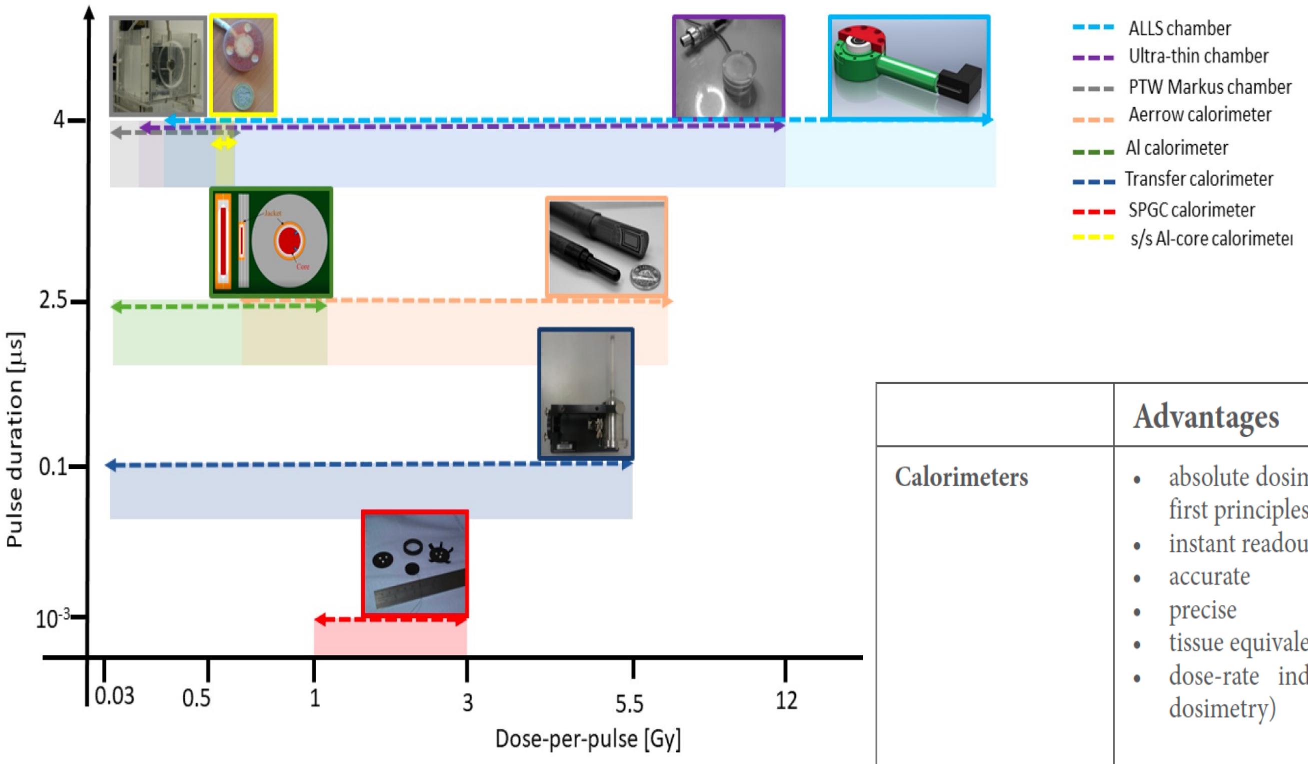
SINGLE PULSE TEMPERATURE RISE



App 100-40, pulse length= 4 us



Possible dosimetric approaches for FLASH RT: calorimeters vs ion chambers



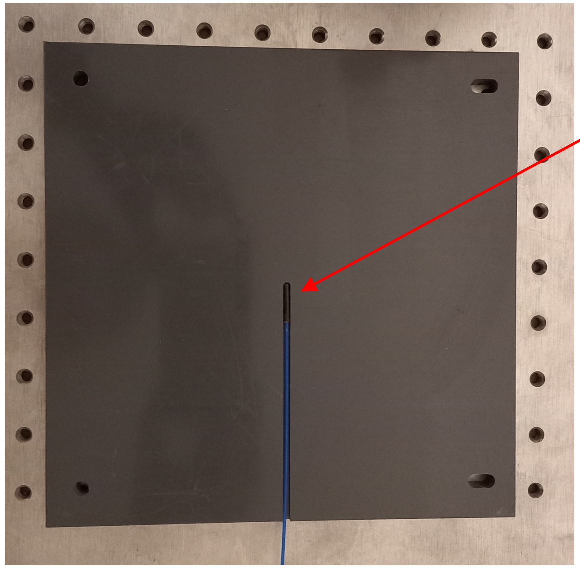
A. Subiel and F. Romano, Br. J. Radiol. (2023)

	Advantages	Disadvantages
Calorimeters	• absolute dosimeter (absorbed dose determination from first principles) • instant readout • accurate • precise • tissue equivalence (water and graphite calorimeters) • dose-rate independent detector (ideal for UHDR dosimetry)	• typically complex devices normally used in primary standard laboratories • require post-processing to retrieve the absorbed dose • several correction factors required • conversion to dose to water required for non-water calorimeters • low sensitivity (for water calorimeters) • expensive devices (particularly when maintained as a primary standard)
Ionization chambers	• simplicity • easy operation • instant readout • precise • recommended by international protocols for beam calibration • long-term usage for radiation dosimetry in radiotherapy • less expensive than calorimeters	• require calibration for determination of absorbed dose • low density medium • high voltage supply required from associated electrometer • require many correction factors • significant ion recombination effects in high dose-per-pulse beams

Possible dosimetric approaches for FLASH RT: scintillators

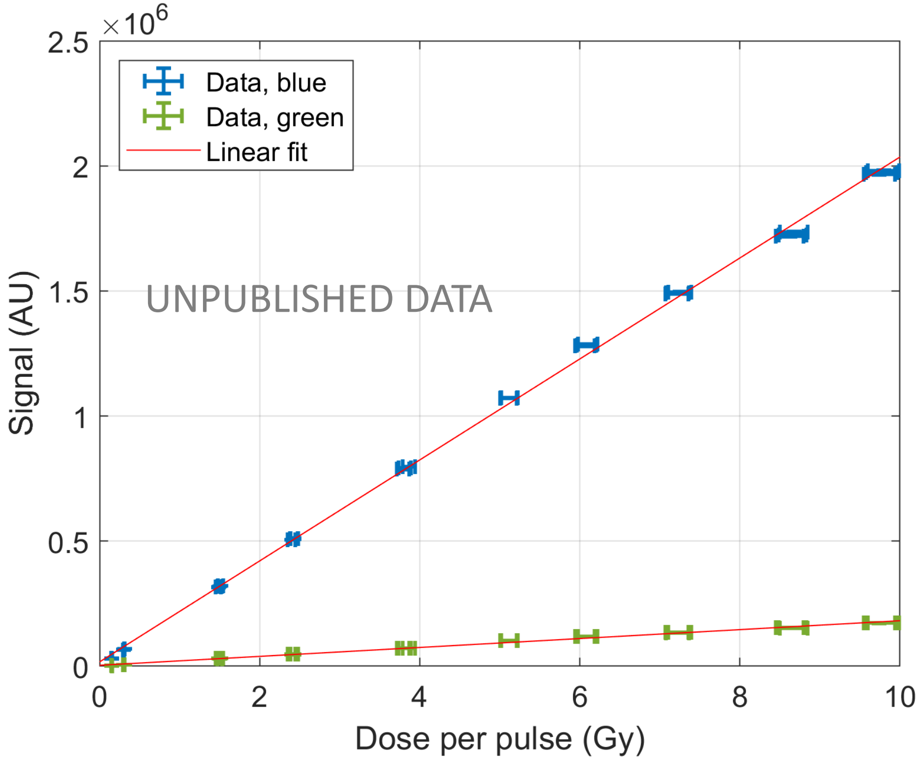
Dosimeter	Real time	In vivo dosimetry	Absolute/reference dosimetry	Beam monitoring	Spatial resolution	Temporal resolution	2D dosimetry	Accuracy at conventional dose rates[a]	Other considerations
Ion chamber	Yes	No	Yes	Yes	Several mm	10–200 μs	Array	1%–2%	Significant ion recombination at UHDRs
Semiconductor	Yes	Yes	No	Yes	Sub-mm (or μm)	1–10 ns	Yes	2%–5%	Angular dependency, radiation damage, LET dependence
TLD	No	Yes	Yes	No	Several mm	N/A	No	3%–10%	Energy dependence, time consuming, LET dependence
OSLD	No	Yes	Yes	No	Sub-mm to mm	N/A	Array	3%–5%	Energy dependence, quenching in high LET fields
Scintillator	Yes	Yes	Potentially	Potentially	Sub-mm to mm	ns to μs	Array and sheet	3%–5%	Quenching in high LET fields, Cherenkov radiation
Gas scintillator	Yes	No	No	Yes	Sub-mm	N/A	Yes	1%	Beam centroid measurement
Calorimeter	Yes	No	Yes	No	cm to several mm	ms–10 ms	No	<1% at the primary standard level	Bulky, not easy to use, correction factors, time consuming
Film	No[b]	Yes	Potentially	No	Tens of μm	N/A	Yes	3%–5%	Quenching in high LET fields
Fricke	No	No	Yes	No	cm to sub-mm	N/A	Potentially	<1% at primary standard level	Time consuming, complexity
Faraday cup	Yes (for charge measurements)	No	Yes	No	N/A	<μs	No	2%–5% for commercial devices; 1%–2% for dedicated equipment[c]	Measures the total collected charge (other detectors are required for dose determination)
Nuclear track detector	No	Yes	No	No	mm; sub-mm with specialized equipment	N/A	Yes	5%–7%	Time consuming, energy dependence, LET dependence
Alanine	No	Yes	Yes	No	mm	N/A	No	2%–7% for doses larger than 10 Gy	Decreased accuracy for doses less than 10 Gy (minimum 2 Gy)
Integrated current transformer	Yes	Potentially	No	Yes	N/A	sub-μs	No	<1% for charge measurements	Lack of 2D measurements, only charge measurements

Scintillators



Plastic scintillator fiber (d = 1 mm)

UHDR e- beams



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- **Plastic scintillators:**

✓ Minimal to no saturation at high dose per pulse (DPP) and dose rates

✓ Water and tissue-equivalent

✓ Allow sampling the pulse time structure

✓ **Fibers**: compact, easy-to-use, cost-effective, real-time detector prototypes for precise local dose measurements

Air fluorescence

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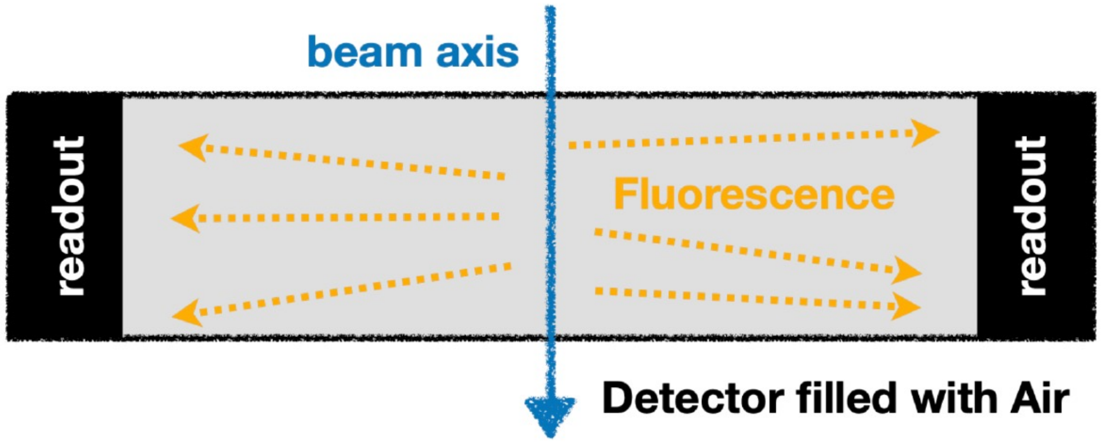

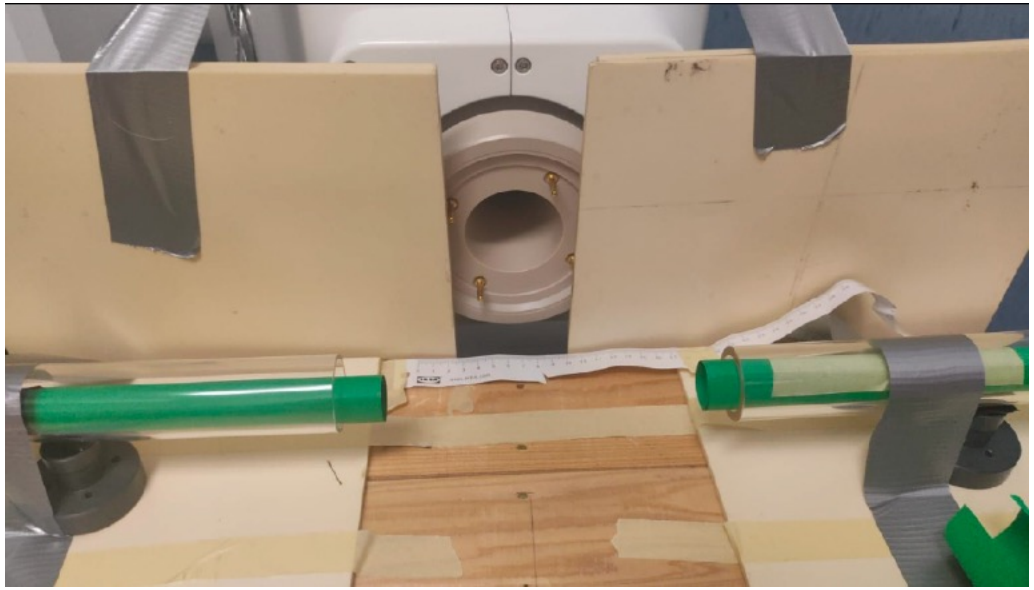

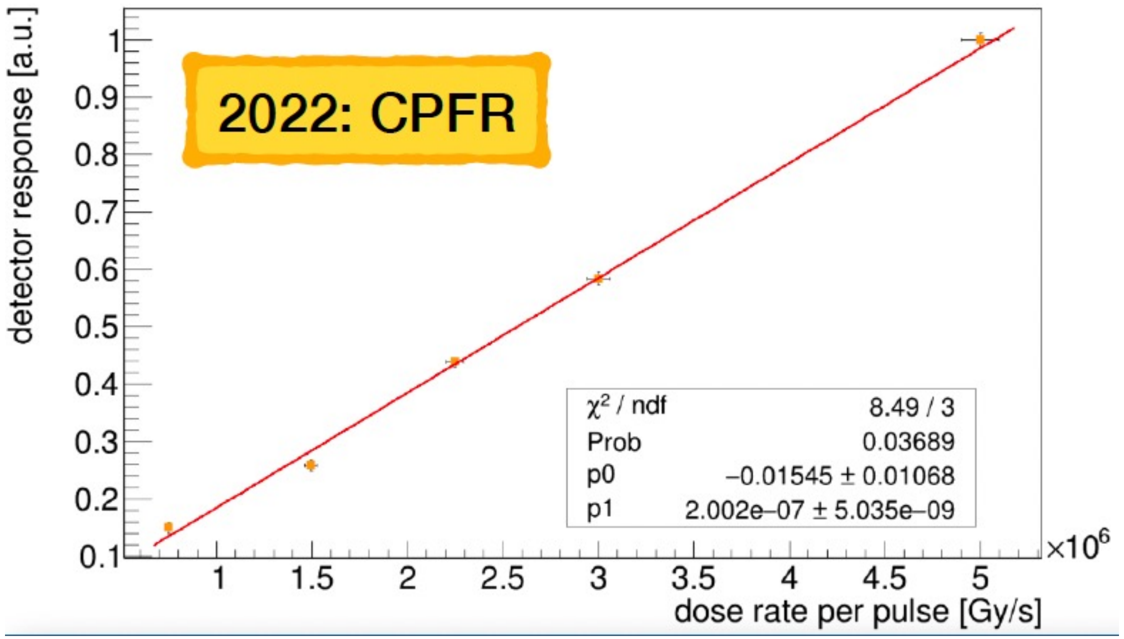

Possible dosimetric approaches for FLASH RT: semiconductors

Dosimeter	Real time	In vivo dosimetry	Absolute/ reference dosimetry	Beam monitoring	Spatial resolution	Temporal resolution	2D dosimetry	Accuracy at conventional dose rates[a]	Other considerations
Ion chamber	Yes	No	Yes	Yes	Several mm	10–200 μs	Array	1%–2%	Significant ion recombination at UHDRs
Semiconductor	Yes	Yes	No	Yes	Sub-mm (or μm)	1–10 ns	Yes	2%–5%	Angular dependency, radiation damage, LET dependence
TLD	No	Yes	Yes	No	Several mm	N/A	No	3%–10%	Energy dependence, time consuming, LET dependence
OSLD	No	Yes	Yes	No	Sub-mm to mm	N/A	Array	3%–5%	Energy dependence, quenching in high LET fields
Scintillator	Yes	Yes	Potentially	Potentially	Sub-mm to mm	ns to μs	Array and sheet	3%–5%	Quenching in high LET fields, Cherenkov radiation
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Calorimeter	Yes	No	Yes	No	cm to several mm	ms–10 ms	No	<1% at the primary standard level	Bulky, not easy to use, correction factors, time consuming
Film	No[b]	Yes	Potentially	No	Tens of μm	N/A	Yes	3%–5%	Quenching in high LET fields
Fricke	No	No	Yes	No	cm to sub-mm	N/A	Potentially	<1% at primary standard level	Time consuming, complexity
Faraday cup	Yes (for charge measurements)	No	Yes	No	N/A	<μs	No	2%–5% for commercial devices; 1%–2% for dedicated equipment[c]	Measures the total collected charge (other detectors are required for dose determination)
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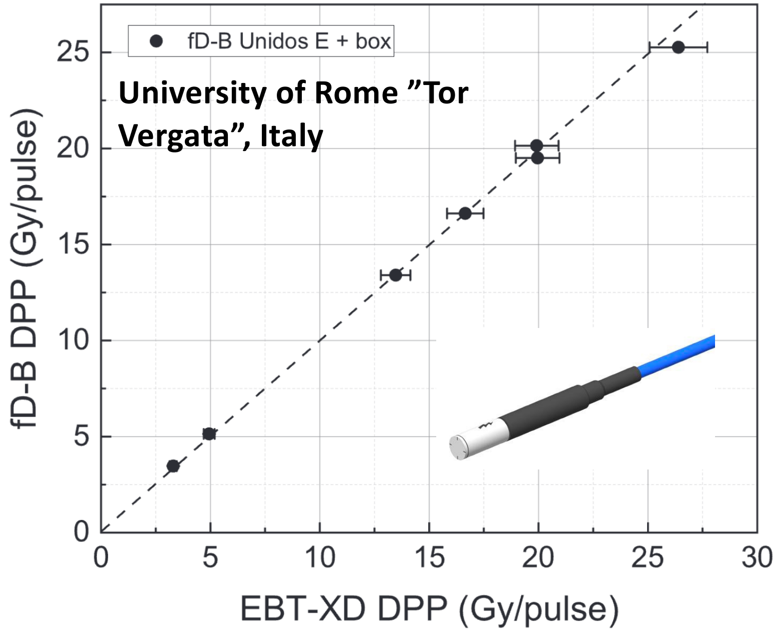
Alanine	No	Yes	Yes	No	mm	N/A	No	2%–7% for doses larger than 10 Gy	Decreased accuracy for doses less than 10 Gy (minimum 2 Gy)
Integrated current transformer	Yes	Potentially	No	Yes	N/A	sub-μs	No	<1% for charge measurements	Lack of 2D measurements, only charge measurements

Solid state detectors: semiconductors

UHDR e- beams

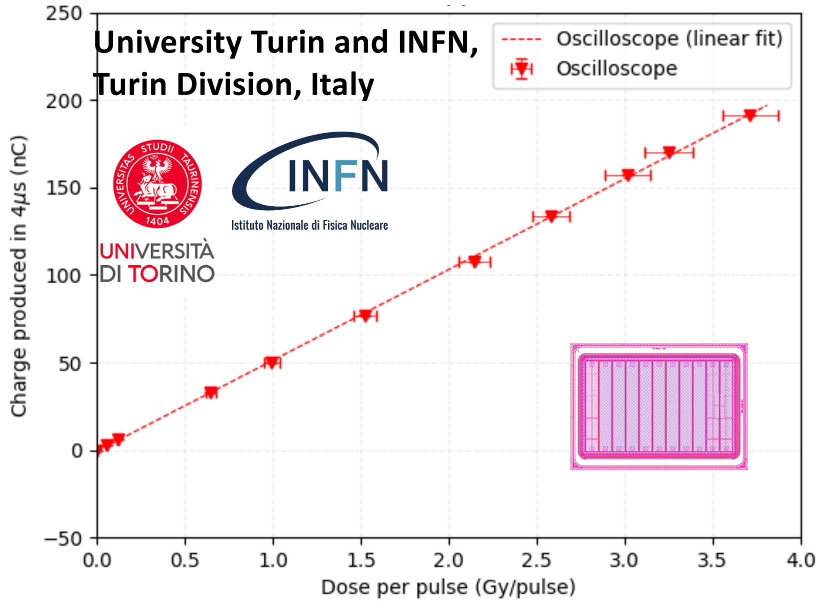
Diamond detectors (FLASH diamond)



M. Marinelli *et al*. Med. Phys. (2022)
G. Verona Rinati *et al*. Med. Phys. (2022)

- Linear response at UHDR
- Good stability (long-term response stability?)
- High spatial resolution (< 1 mm)
- Water equivalent
- Commercialized by PTW

Silicon detectors

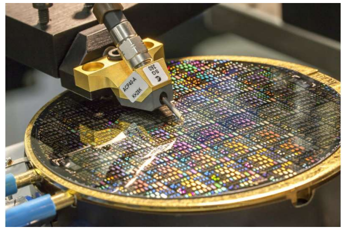


- More mature technology
- Linear response at UHDR
- Good stability (long-term response stability?)
- High spatial resolution (< 500 um)
- Pixellated and strip geometries

FRIDA

Silicon carbide detectors for dosimetry and monitoring

Silicon



+

Diamond

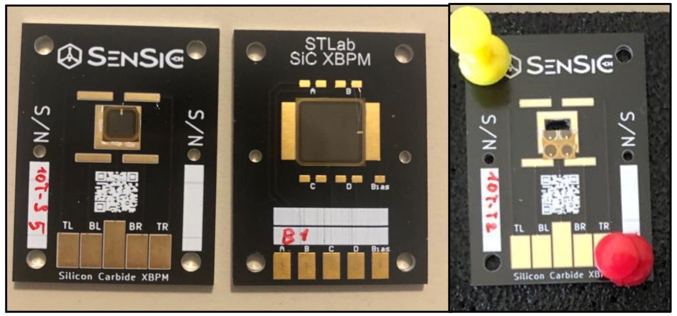
SiC

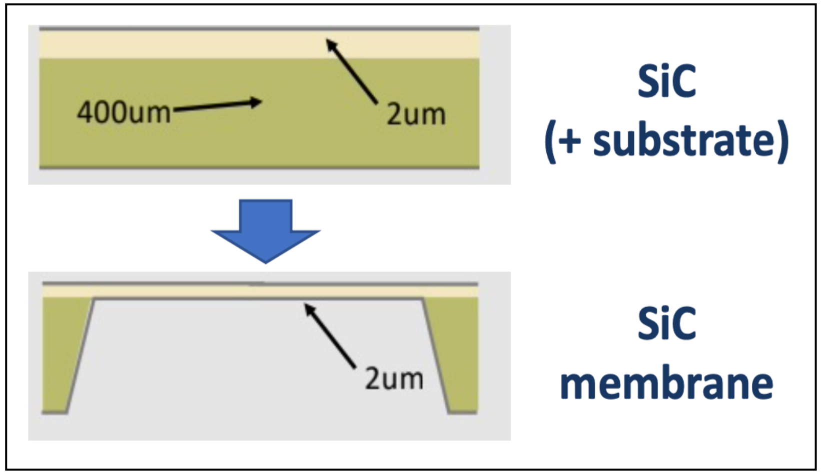
Radiation **hardness**
High signal to noise ratio
High **time resolution (ns)** and fast collection time
Large area devices

STLAB ↔ INFN CATANIA Istituto Nazionale di Fisica Nucleare Sezione di Catania

Standard with bulk devices

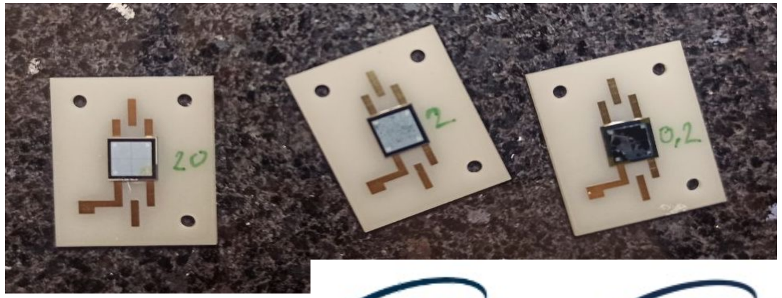
5x5 mm² 10x10 mm ² 2x2 mm ²





Freestanding membranes

20um 2um 0.2um



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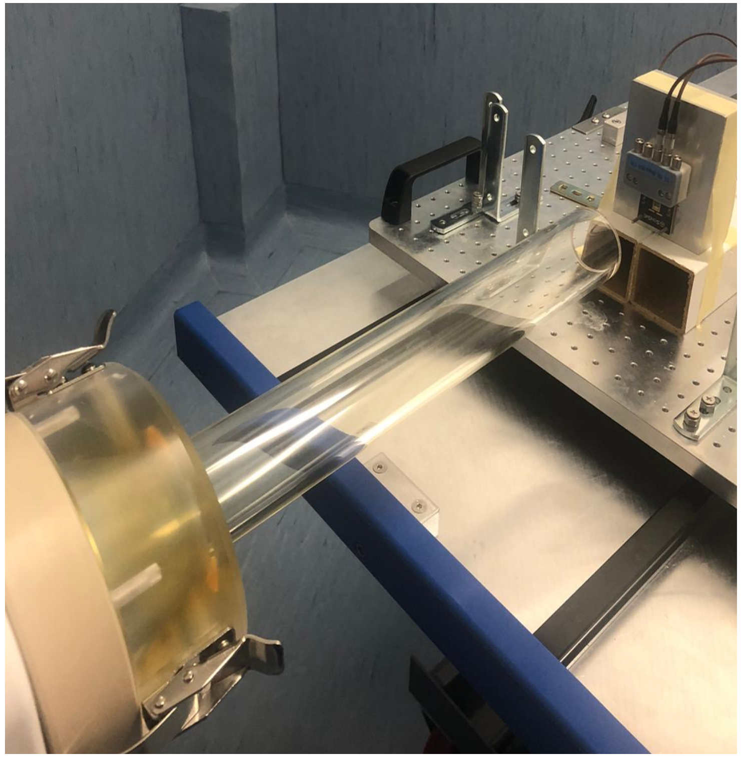
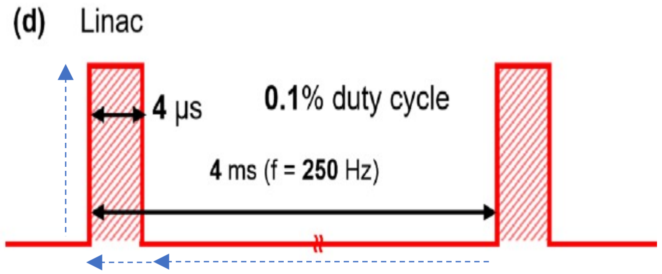
INFN TORINO

Characterization with Electron FLASH Linac accelerator @ CPFR

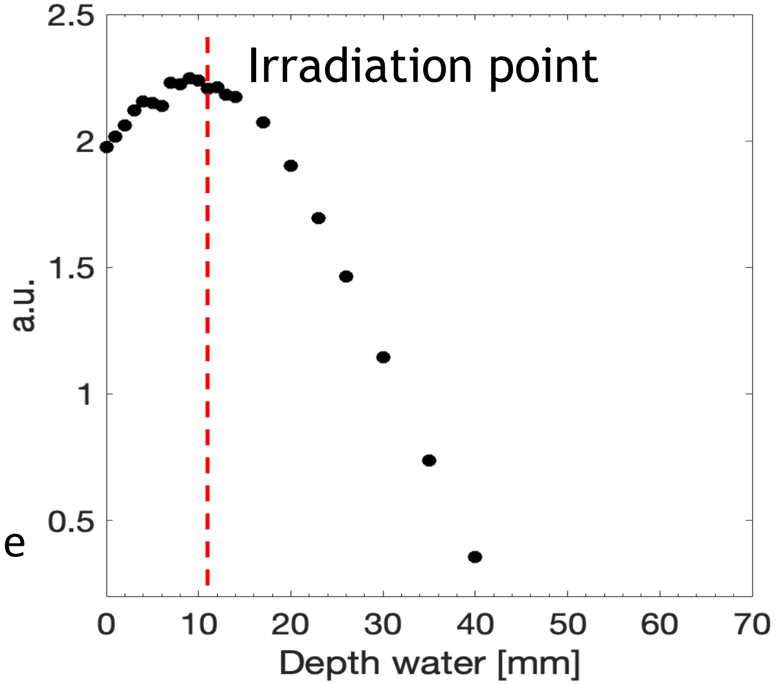


F. Romano *et al*. Med. Phys. (2022)



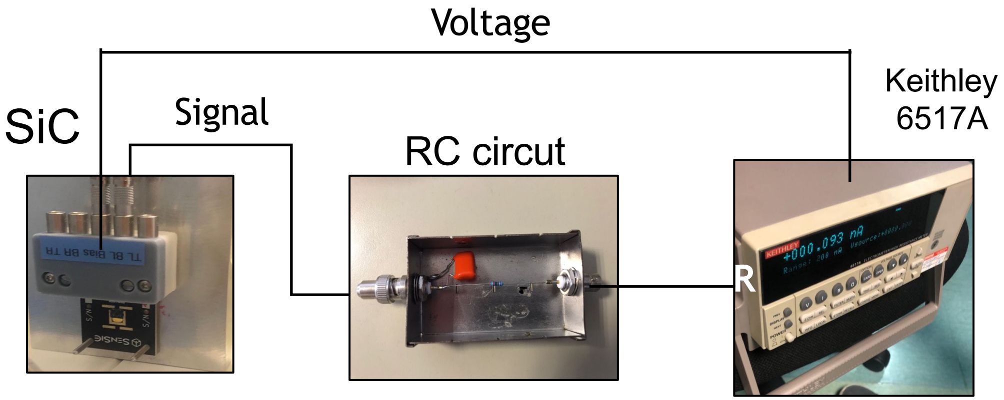
- E = 9 MeV
- **Single pulse duration: 0-5-4 us**
- PRF:1-245 Hz
- **Dose per pulse: from 0.1-20 Gy**
- Average instantaneous dose rates in the single pulse up to **5 MGy/s**

Depth dose distribution with SiC



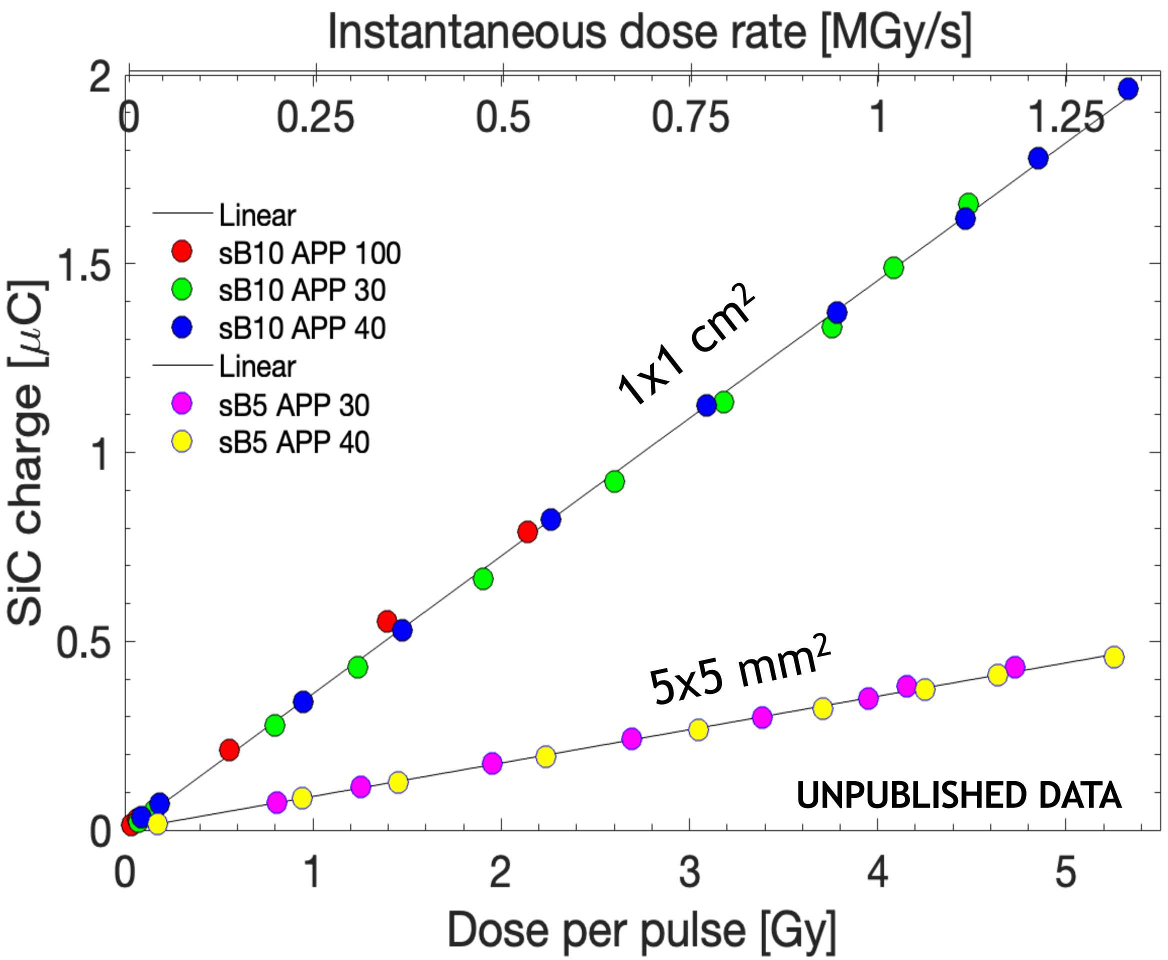
Experimental setup

- 10x10, 5x5, 3 mm^2 10 um thick SiC with and without the substrate placed at the build-up connected to a Keithley electrometer
- Alanine dosimeters at the build-up
- **30,40,100 Applicator and Open Field**
- RC circuit connected to the detector

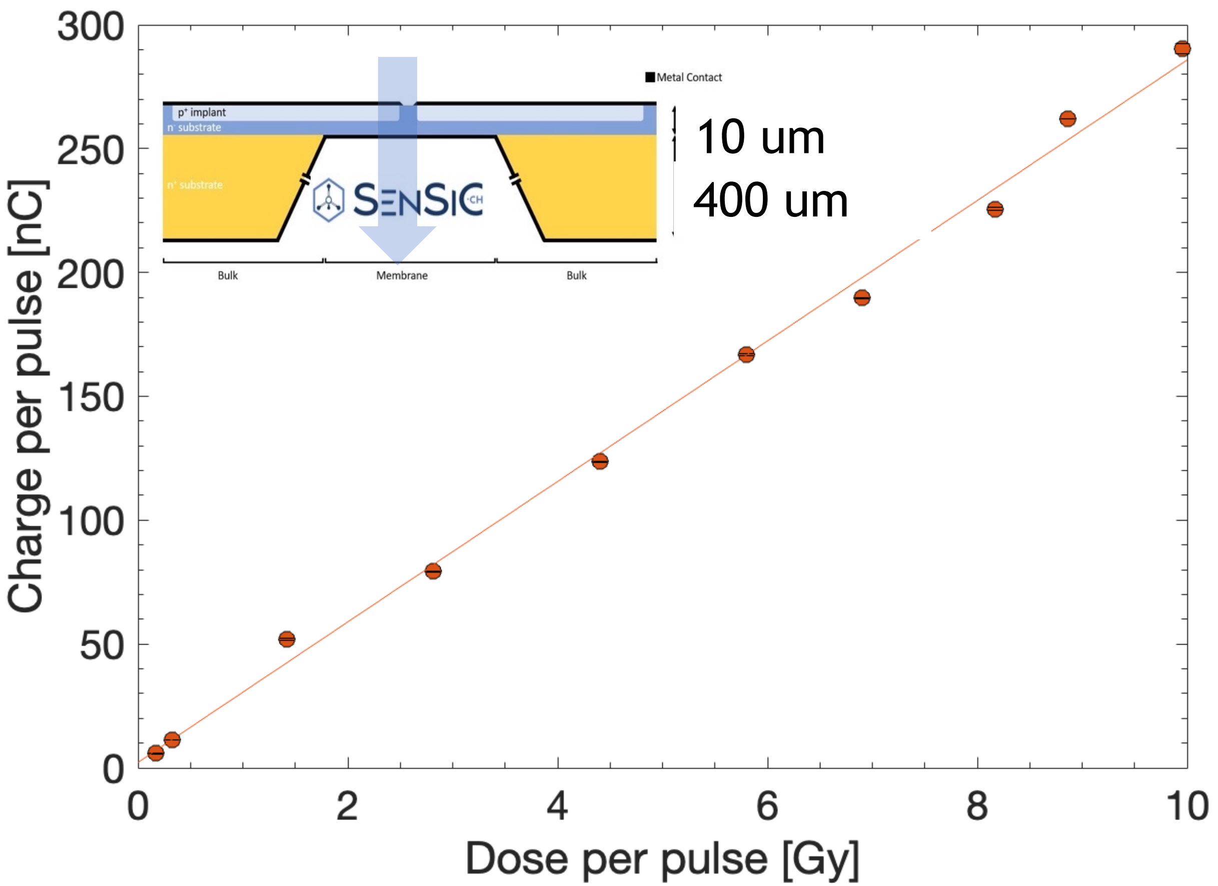


Independence with the instantaneous dose rate and dose per pulse

1x1 cm^2- 5x5 mm^2 Bias Voltage: 200 V

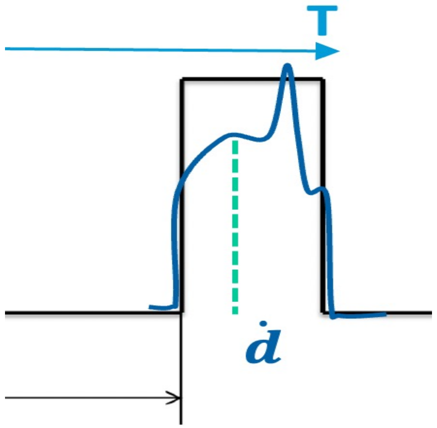


10 um thick free-standing membrane



F. Romano, G. Milluzzo* et al., First Characterization of Novel Silicon Carbide Detectors with Ultra-High Dose Rate Electron Beams for FLASH Radiotherapy. Appl. Sci. 2023, 13, 2986.
E. Medina et al., Radiation Hardness Study of Silicon Carbide Sensors under High-Temperature Proton Beam Irradiations. Micromachines 2023, 1, 0.
G. Milluzzo et al., in prep for Medical Physics

Instantaneous dose rate measurements for FLASH?

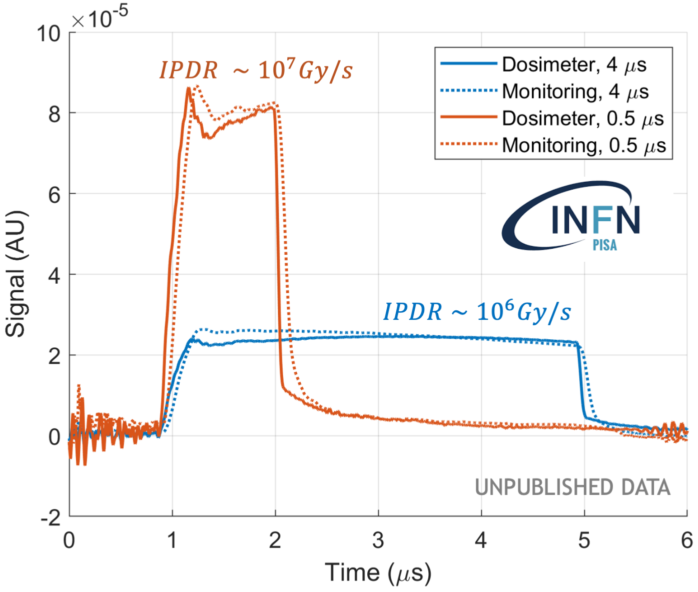


- *Temporal resolution from 1 to tens of ns, allowing for "intra-pulse" instantaneous dose rate measurements*
- *Different doses per pulse*
- *Different pulse duration*

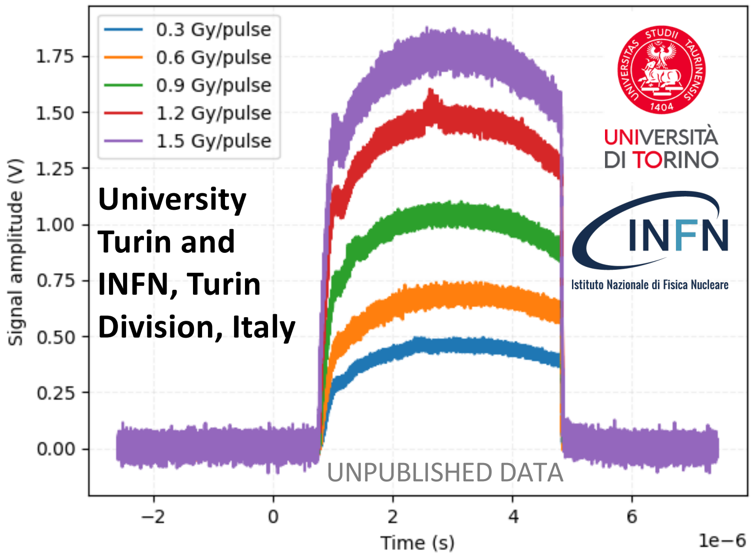
FRIDA

UHDR e- beams

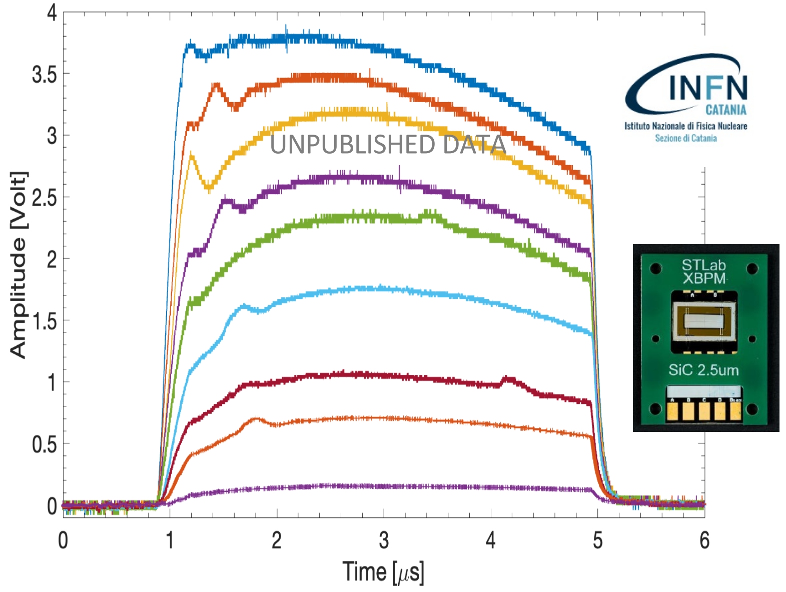
Scintillators



Silicon detectors



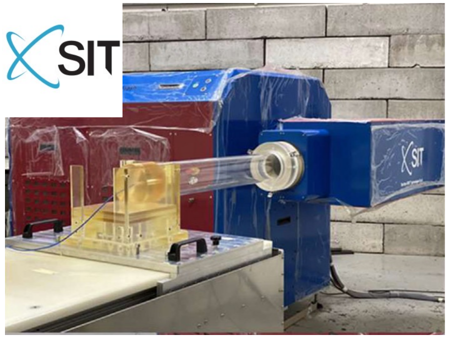
Silicon carbide (SiC)



Real-time beam monitoring (@ SIT in Aprilia)

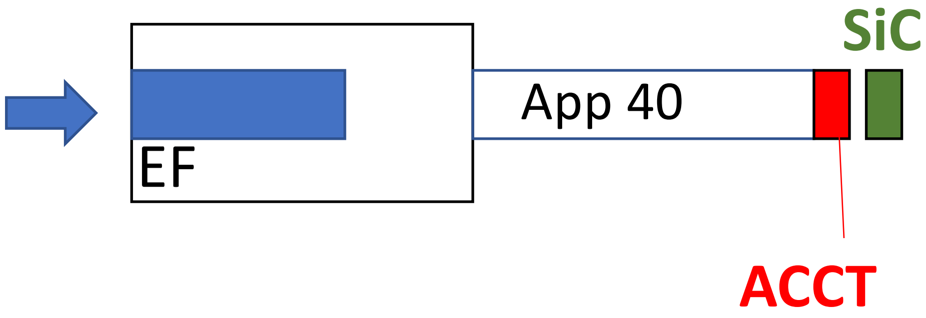
- Fast signals
- High temporal resolution
- **Low beam perturbation**

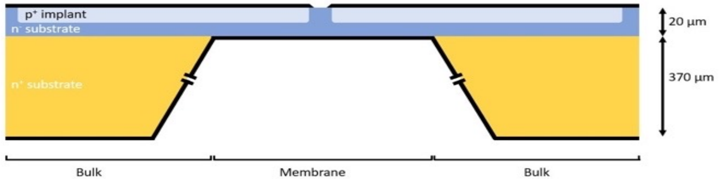
For UHDR **electron** beams in transmission ion chambers cannot be used → new approaches!

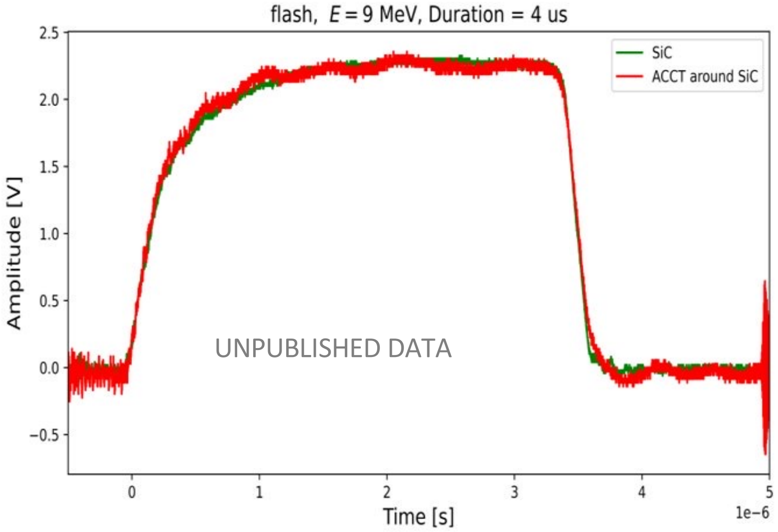


ACCT (AC current transformer)

(no position sensitive)





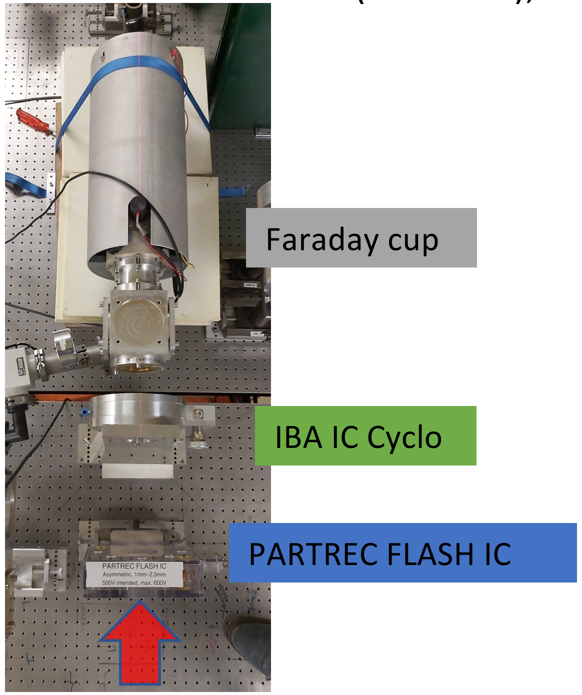


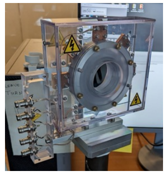
Real-time beam monitoring for UHDR protons

For UHDR **proton** beams, modified ionization chambers can still work!

Particle Therapy Research Center (PARTREC), NL

R.J.C. de Koster, PhD Thesis (UMCG, NL)





thin ion chambers used

- Research facility

-Radiotherapy department - University Medical Center Groningen

-Proton FLASH beams: up to 190 MeV

FLASH **Twin Beam** - Reproduce clinical beams

- Mimic the beam temporal structure
- Flexible dose delivery system @ PARTREC
  - Flexible field/spot size, scanning speed, dose-rate
  - Scattered CW and pulsed beams
  - Pencil Beam Scanning
- Reproduce the Groningen Proton Therapy Center gantries
  - IBA Proteus Plus (230 MeV, PBS only)

Summary and conclusions

- Radiochromic films to asses 2D dose distributions and alanine dose rate independent but passive detectors
- Ionization chambers still reference dosimeters for routine beam calibration measurements?
- Small portable calorimeters as an alternative reference instrument?
- Alternative dosimetric approaches with scintillators, silicon, diamond and SiC detectors for relative dosimetry (and beam monitoring?)
- Real-time beam monitoring needs additional challenges to be addressed
- 2D configurations for both real-time beam monitoring and dosimetry to be developed in the perspective of a clinical translation of FLASH radiotherapy
- New protocols and guidelines for beam dosimetry and characterization to be delivered and verified (international and national initiatives)

Thank you for your attention

Acknowledgements:

G. Milluzzo (INFN-CT), C. Okpuwe (INFN-CT),M. Camarda (STLab), N. Amato (STLab), S. Both (UMCG), A. Gerbershagen (UMCG), M.-J. van Goethem (UMCG), S. Brandenburg (UMCG), F. Di Martino (CPFR), J. Pensavalle (SIT), D. Del Sarto (CPFR), L. Masturzo (SIT), G. Felici (SIT), S. McCallum (QUB), M. McManus (NPL), A. Vignati (INFN-TO), E. Medina (INFN-TO), G. Bisogni (INFN-PI), E. Ciarrocchi (INFN-PI), A. Subiel (NPL), R. Thomas (NPL), H. Palmans (NPL)

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European initiatives

UHDpulse EMPIR project

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

Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

Type:	Joint Research Project
Duration:	2019-2023
Start:	1. Sept. 2019
Funding:	2.1 M €
Coordinator:	Andreas Schüller (PTB)
Topic:	Tools for traceable dose measurements for:

UHDpulse

- **FLASH radiotherapy**
- **VHEE radiotherapy**
- **Laser driven accelerators**

http://uhdpulse-empir.eu/

EMPIR EURAMET

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):

- **traceable reference standards** and **validated reference methods** for dose measurements at ultra-high pulse dose rates
- characterization of detector systems, development of traceable and validated methods **for relative dosimetry**
- contribution to **codes of practice**

Follow-up normative project submitted soon

Courtesy of A. Schueller

Italian initiatives

The INFN "FRIDA" project

Istituto Nazionale di Fisica Nucleare

WP1
The FLASH mechanism

WP2
Beam delivery

WP3
Beam/dose monitoring

WP4
Treatment planning

Units
CT – F. Romano
LNS – G. Cirrone
MI – D. Giove
PI – G. Bisogni
RM1 – A. Sarti (PI)
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Goal of "FRIDA" (FLASH Radiotherapy with hIgh Dose-rate particle beAms) **is to make a step forward in all the crucial areas... Four WPs** [mechanism modelling & rad-bio experiments; beam delivery; beam monitoring; treatment planning] **working in parallel, >25 FTEs, 7 INFN units with know-how in the fields and a solid international network of research centres and companies (SIT, STLab) are the resources to accomplish the research program.**

- **Test few promising techniques for FLASH beam monitoring and dosimetry applications**
  - **Adapting existing techniques for FLASH conditions**
  - **Developing from scratch some other novel approaches.**

Task 1 Development and test of new Beam Monitoring systems
- Task 3.1.1: Air Fluorescence monitor (Roma1)
- Task 3.1.2: Integrating Current Transformer (LNS)
- Task 3.1.3: Silicon/Diamond detectors (To)
- Task 3.1.4: SiC detectors (in-kind) (CT)

Task 2 Development and test of new dosimetric systems
- Task 3.2.1: Portable Calorimeter (CT)
- task 3.2.2: Scintillator based dosimeter (PI)
- Task 3.2.3: SiC for relative dosimetry (in-kind) (LNS)

Task3 Intercomparisons, calibrations and codes of practice
- Task 3.3.1Dosimetric characterization of the beams with available BM systems (dual gap chamber, SEM, FC) and reference dosimeters (Faraday cup, alanine, RCF, IC))
- Task 3.3.2 Intercomparisons and calibrations of the developed BMs and dosimeters
- Task.3.3.3 Dosimetric codes of practice for the dosimetry of FLASH beams