Ultra-high dose rate: Transforming Radiotherapy in a FLASH?

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Institute of Physics, London, UK

The role of NPL in supporting the traceability for dosimetry in emerging techniques - FLASH Radiotherapy

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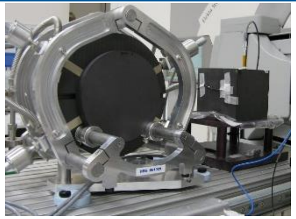
The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement

2. The realization of units of measurement by scientific methods

primary standard



secondary standard

working standard

3. The establishment of **traceability** chains

property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty

Measurement uncertainty

$$\boldsymbol{M = m \pm U \quad (k = 1)}$$

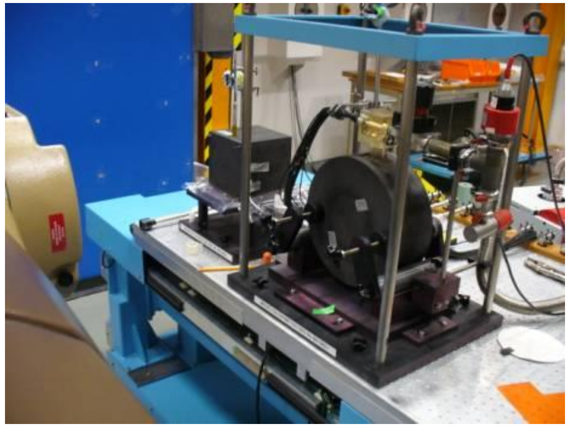
measurand

coverage factor

Traceability chain in Radiotherapy

- **MV photon dosimertry under reference conditions**

NPL **primary standard** → **calibration** → NPL reference chambers → **calibration** → Hospital **secondary standard** → **calibration** → Hospital **working standard**



σ: 0.50 % (k=1) | 0.7 % (k=1) | 1.5 % (k=1)

Traceability chain in Radiotherapy

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- **MV photon dosimertry under reference conditions**

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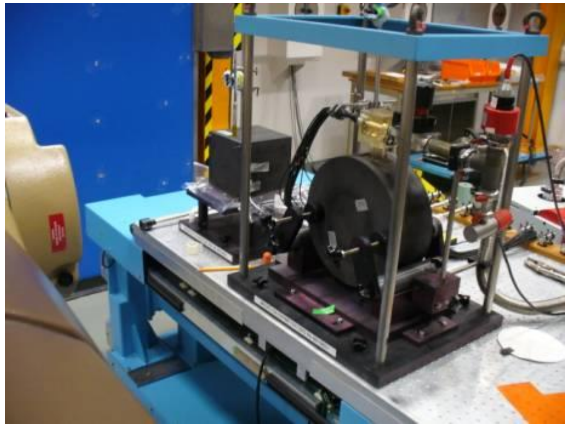


σ: 0.50 % (k=1) | 0.7 % (k=1) | 1.5 % (k=1)

← **TRACEABILITY**

Why do we need metrology in FLASH RT?

- To compare different measurements carried out in space and time

Timeline of FLASH RT…

Timeline of FLASH RT…

National Physical Laboratory

Published: 19 August 1967

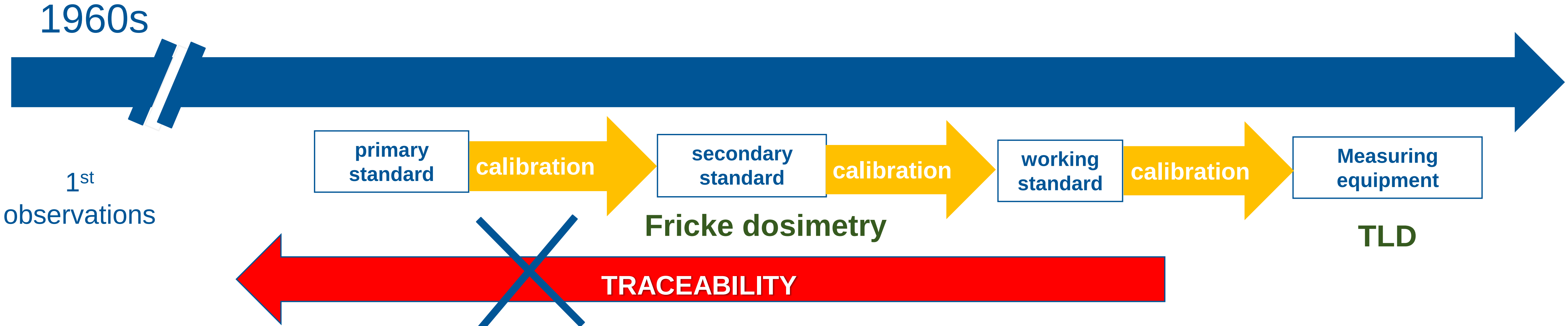
Effect of High Dose Rates on Survival of Mammalian Cells

C. D. TOWN

Nature **215**, 847–848 (1967) | Cite this article

The dose delivered was measured by using lithium fluoride thermoluminescence dosimetry; this was checked by ferrous sulphate and red 'Perspex' dosimetry[2]. The error in the dose delivered, chiefly caused by the spatial distribution of the beam, was 2 per cent at 200 rads, rising to 10 per cent at 5,000 rads.

Is the dose measurement traceable?



Fricke dosimetry in UHDR pulsed e-beams

Change in absorbance
$A_{irradiated} - A_{unirradiated}$

$$D_W = \frac{\Delta A \cdot f_{F/W}}{\rho \cdot l \cdot \varepsilon(\lambda) \cdot G}$$

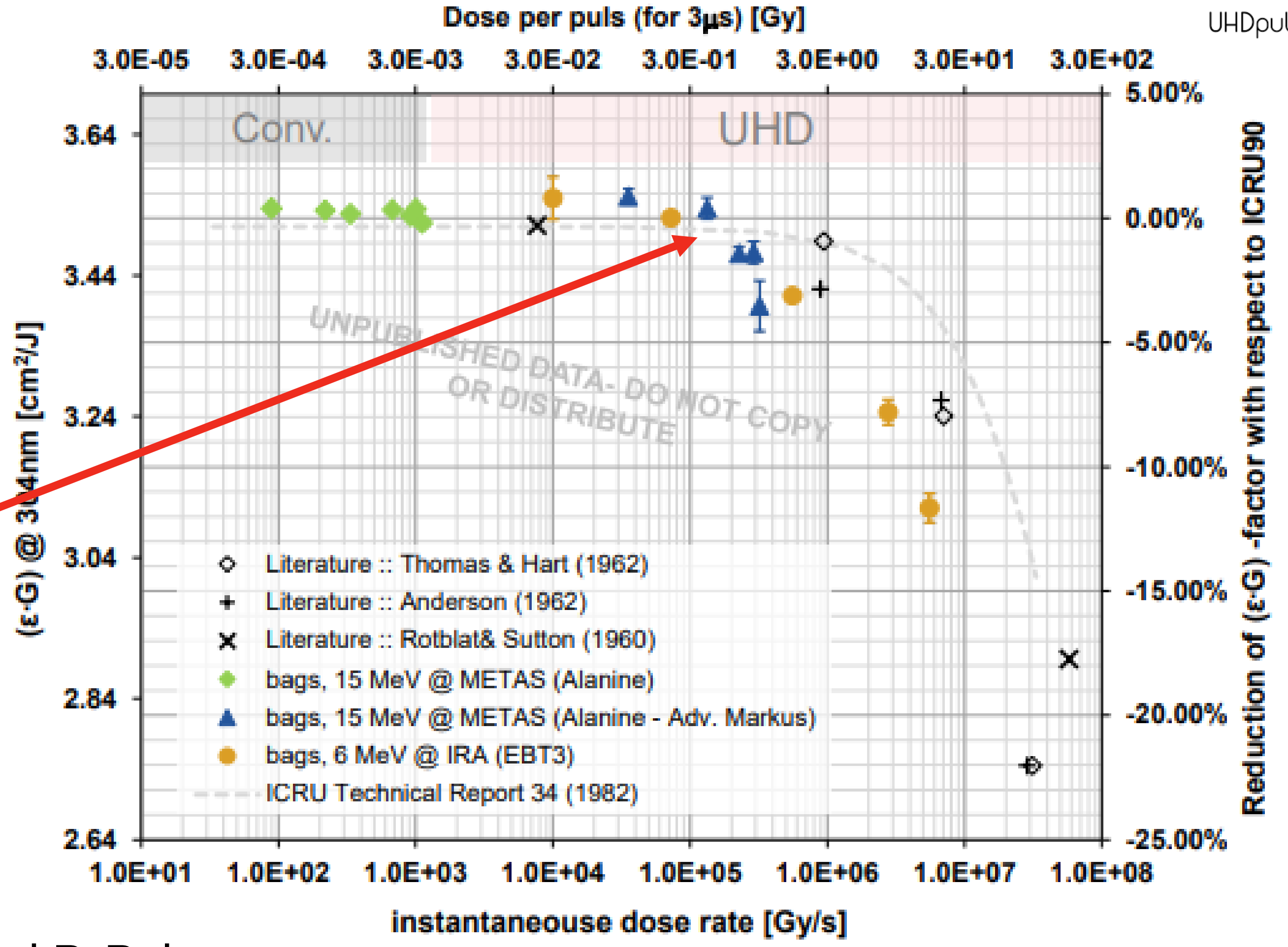
Chemical yield in mol/J

Density of Fricke solution in kg/l

Path length through cuvette in cm

Molar extinction coefficient in l/cm/mol

- At ~> 1Gy/pulse (of 3us) radical-radical reactions start to reduce the value of radiation yield G.



Fricke dosimetry not a primary standard for UHDR e-beam

Courtesy of F. Frei and P. Peier

NOTE: ICRU Rep.34 Fricke solution without NaCl

Timeline of FLASH RT…

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Hypoxia in mouse intestine induced by electron irradiation at high dose-rates

SHIRLEY HORNSEY
M. R. C. Experimental Radiopathology Unit, Hammersmith Hospital, Ducane Road, London W.12

and D. K. BEWLEY
Medical Research Council Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W.12

(*Received* 17 *February* 1971; *accepted* 4 *March* 1971)

Effects of dose-rate on the radiation response of rat skin

S. B. FIELD and D. K. BEWLEY
Medical Research Council, Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS, U.K.

(*Received* 13 *May* 1974; *accepted* 12 *June* 1974)

In studies of the effects of varying dose-rates, it is essential that the response of the monitor and the dose-distribution within the animal should be independent of dose-rate. The experiments reported here were made using 7 MeV electrons from the M.R.C. linear accelerator. The mice were irradiated two at a time in a Perspex box having compartments of internal dimensions 6 × 3 × 3 cm with the entrance window 0·6 mm thick. The dose and dose-rate were monitored with a pair of collector monitors, as described by Bewley (1971). This type of monitor gives a signal proportioned to fluence (or fluence-rate). Absorbed dose bears a constant relation to fluence at a given electron energy, and the constant of proportionality varies only slowly with electron energy at a few MeV. The monitor was calibrated at 100 rads/min with a Farmer–Baldwin chamber to give the dose at the centre of the compartments of the box. The linear accelerator

1970s

Is the dose measurement traceable?

1st observations

primary standard → calibration → secondary standard → calibration → working standard → calibration → Measuring equipment

Farmer chamber

fluence monitor

TRACEABILITY

Timeline of FLASH RT…

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]

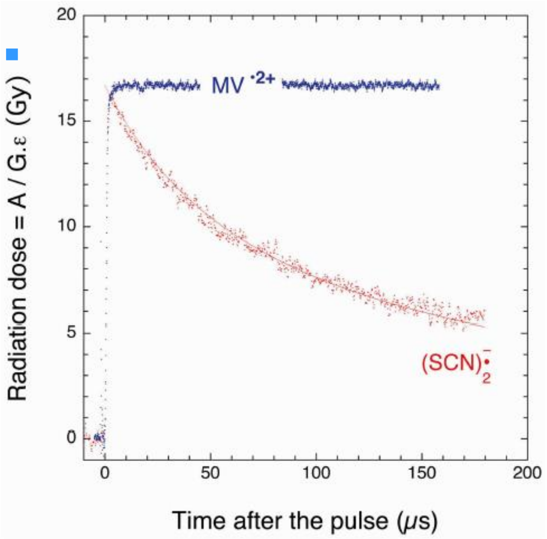


Fig. S4. Time course of the evolution of the methyl viologen MV^{2+} and thiocyanate $(SCN)_2^{-\bullet}$ radicals. The evolution of these radicals was measured after a 1.0 μs pulse of 4.5 MeV electrons (16.6 ± 0.1 Gy). The decay of the $(SCN)_2^{-\bullet}$ radical occurs by recombination and was fitted (continuous line) to the second-order equation $1/A(t) = 1/A_0 + kt$. Found: $k = 3.74 \times 10^5\ s^{-1}$.

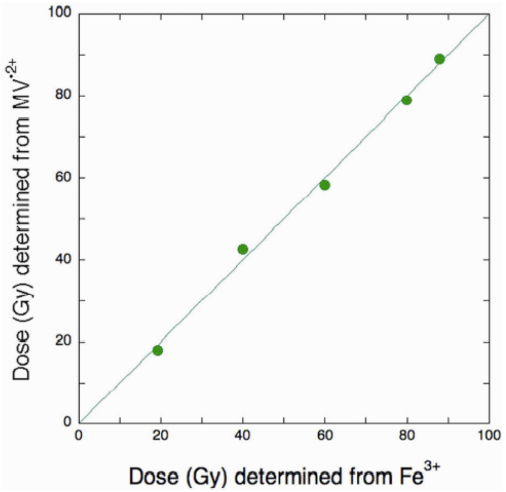


Fig. S5. Correlation between methyl viologen and ferrous sulfate (Fricke) dosimeters. Correlation was established at conventional dose-rate (0.031 Gy/s, ^{137}Cs γ-rays). Fe^{3+} (ε_{304} = 2,204 $M^{-1}.cm^{-1}$, G = 1.61 $\mu mol.J^{-1}$) and $MV^{\bullet 2+}$ (ε_{603} = 13,300 $M^{-1}.cm^{-1}$, G = 0.625 $\mu mol.J^{-1}$) were measured by optical absorption using a Cary-3E spectrophotometer.

1.3 - Dosimetry

Current methods used for the dosimetry of radiation at conventional dose-rate, such as ionisation chambers, do not work at ultra-high dose-rate. For this reason, we used chemical dosimeters long established for pulse radiolysis studies and operating at the submicrosecond time scale. These techniques are described below.

Is the dose measurement traceable?

1960s — 1st observations

2014 — pre-clinical study (mouse model)

calibration → secondary standard → calibration → working standard → calibration → Measuring equipment

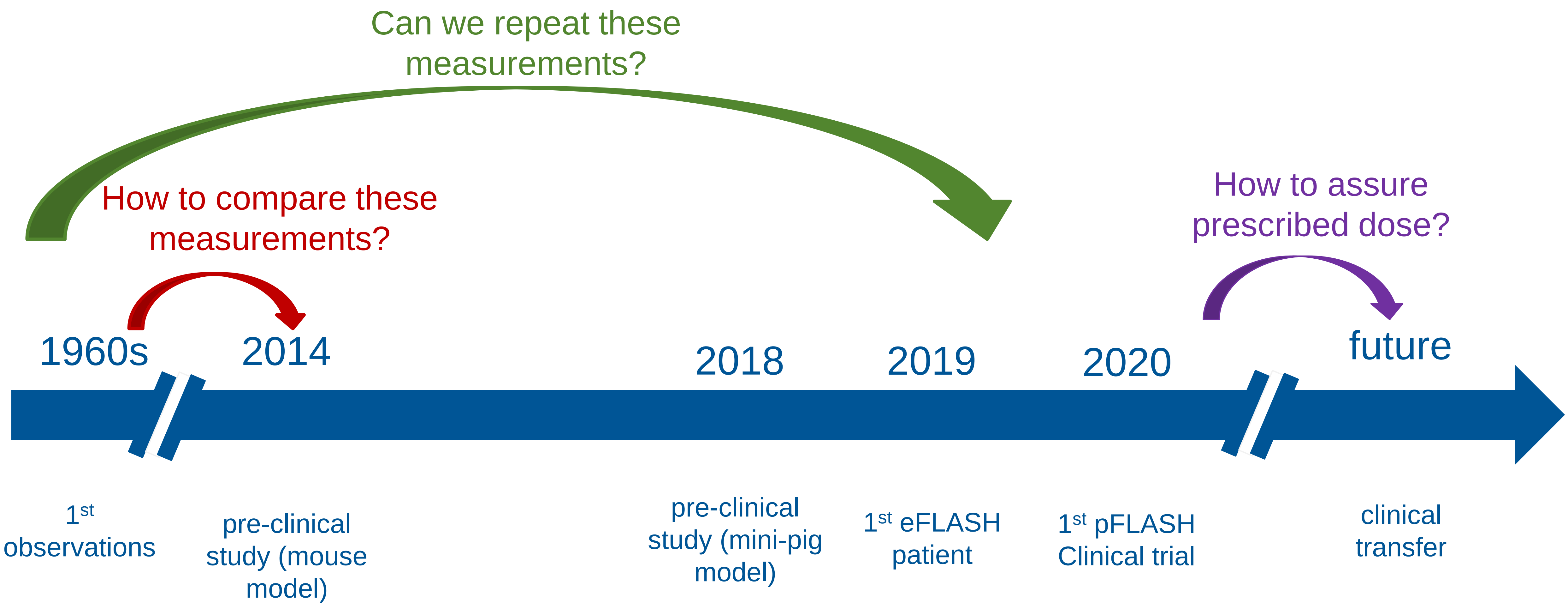
Fricke dosimetry

Methyl vilogen

~~TRACEABILITY~~

Timeline of FLASH RT…

TRACEABILITY IN DOSIMETRY of UHDR beams



Role of National Metrology Institutes

- FLASH community had no support from NMIs with provision of traceability for the UHDR beams
- No standards available
- Developing science and technology that defines the NEED for developments in metrology for UHDR exposures

The support needs to come form NMIs

to provide traceable dissemination of D_w to clinics

Requirement for accuracy in dosimetry

- The ICRU Rep.24 (1976) states:

*An uncertainty of **5% (k=1)** is tolerable in the delivery of absorbed dose to the target volume*

This is an **OVERALL UNCERTAINTY**
(incl. dose delivery, dose calculations, patient positioning etc.)

Dose measurement at the reference conditions
should to be **<u>less than 1% (k=1)!</u>**

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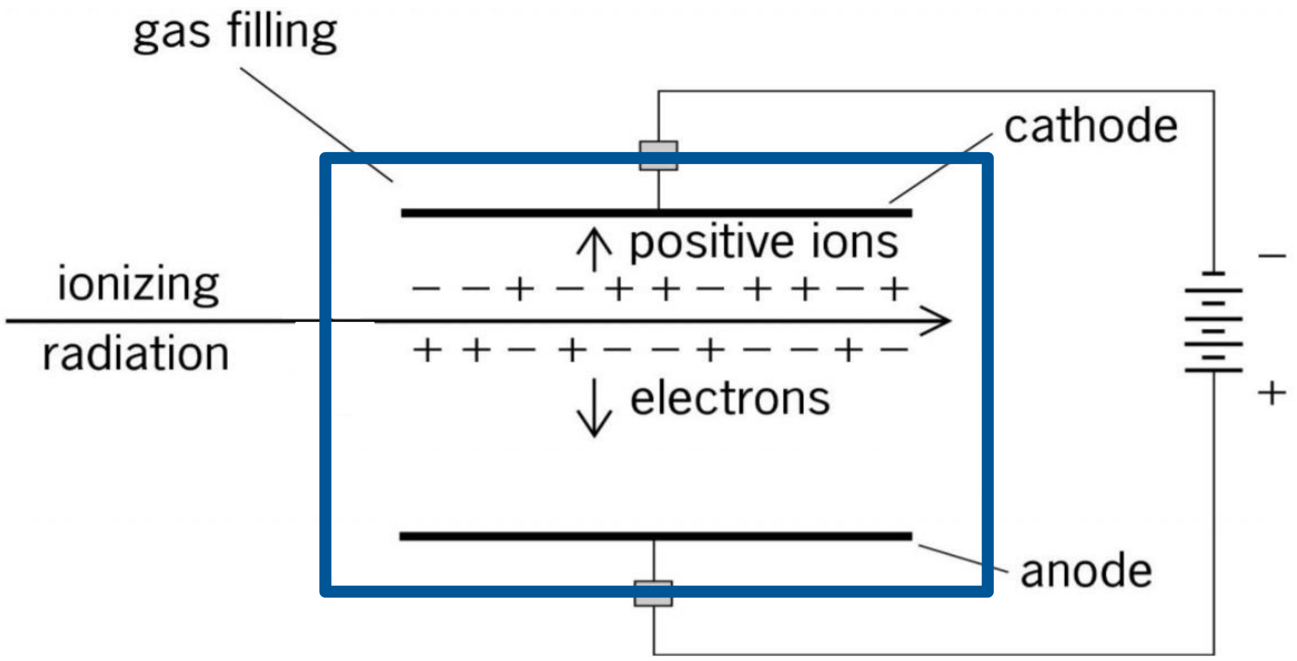
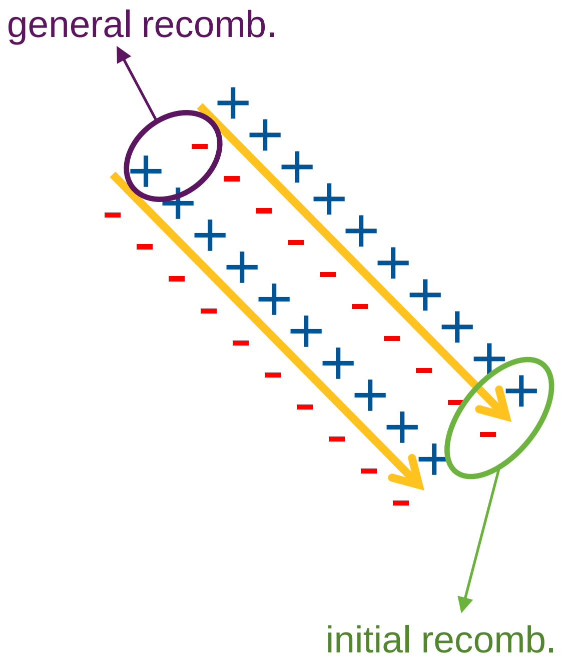
Dosimeters for UHDR

Ionization chambers

Ionization chamber – principle of operation





Initial Recombination

- Recombination along a single charged particle track.
- **Independent of dose and dose-rate.**
- More pronounced in highly ionising particles such as alpha-particles.

General Recombination

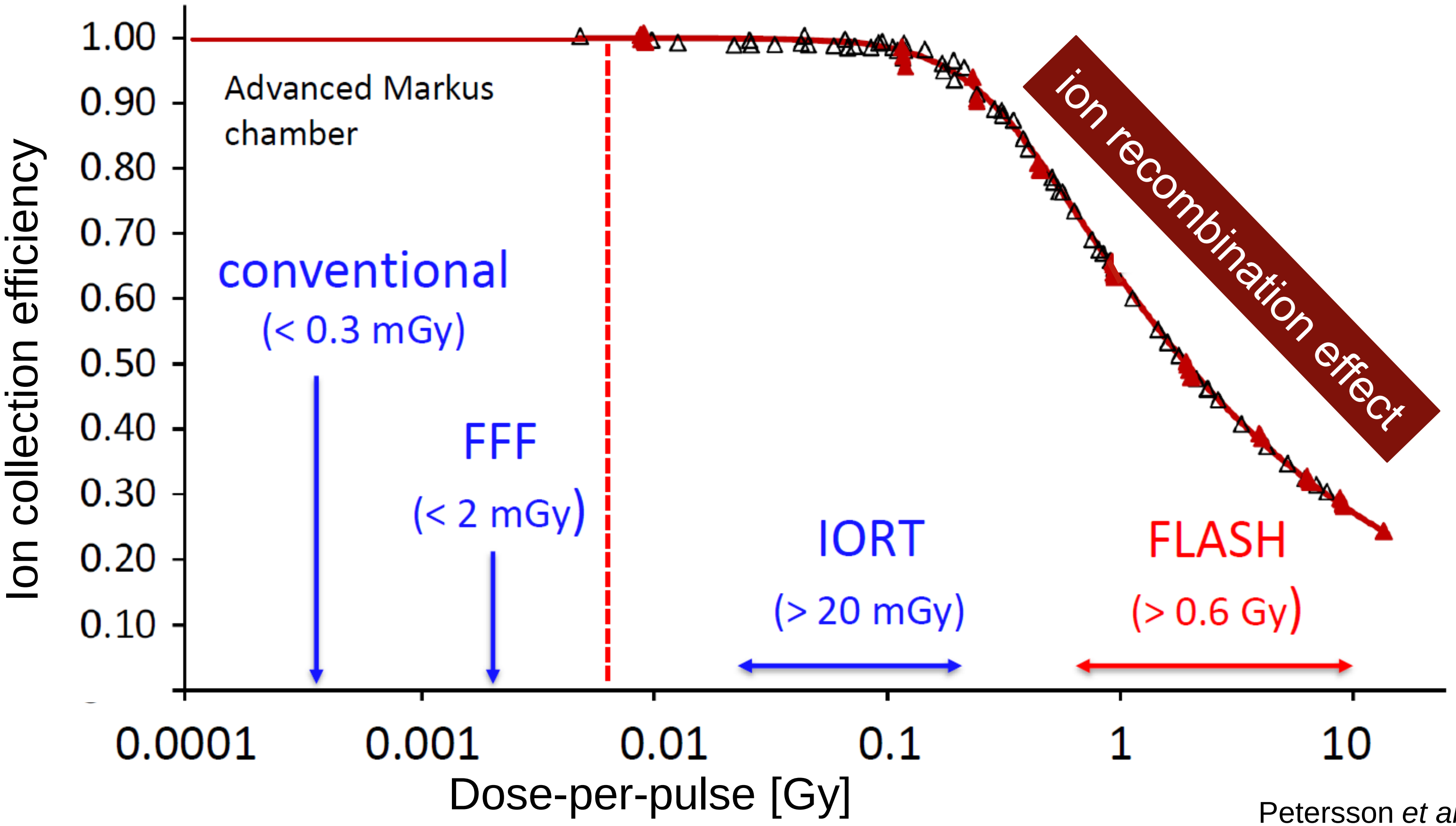
- Recombination between separate charged particle tracks.
- Directly dependent on charge density i.e the number of ions produced per unit volume.
- **Dose-rate dependent.**

General recombination is likely to play a much larger role in recombination effect in UHDR pulsed beams

IC: Metrological challenges of dosimetry at UHDR

Typical behaviour of an IC at UHDR dose rates for **pulsed electron beams**

6 MeV e-beam



PTW Advanced Markus
(1 mm electrode separation)

Petersson *et al.*, Med Phys 44 (2017) 1157

IC: Metrological challenges of dosimetry at UHDR

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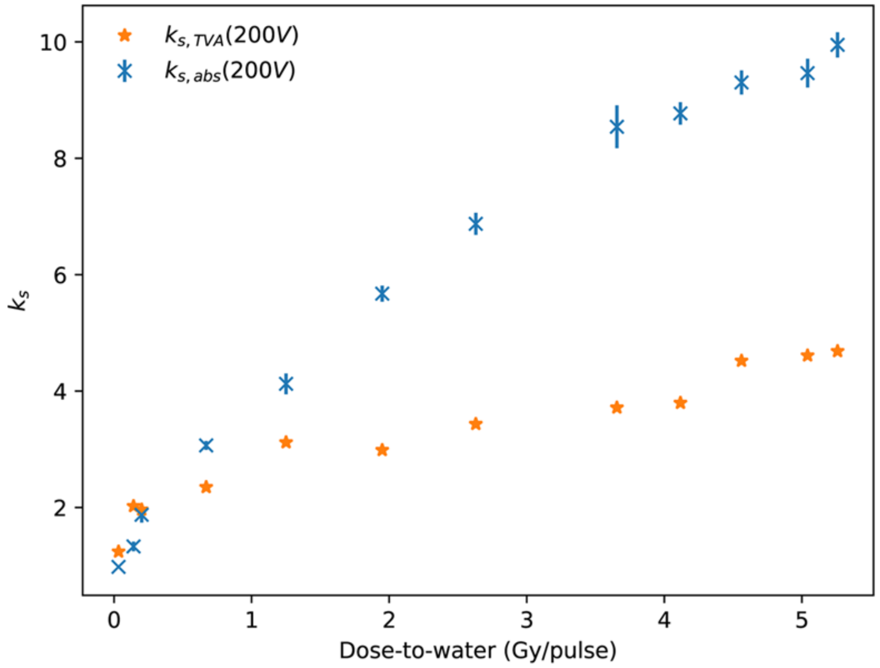
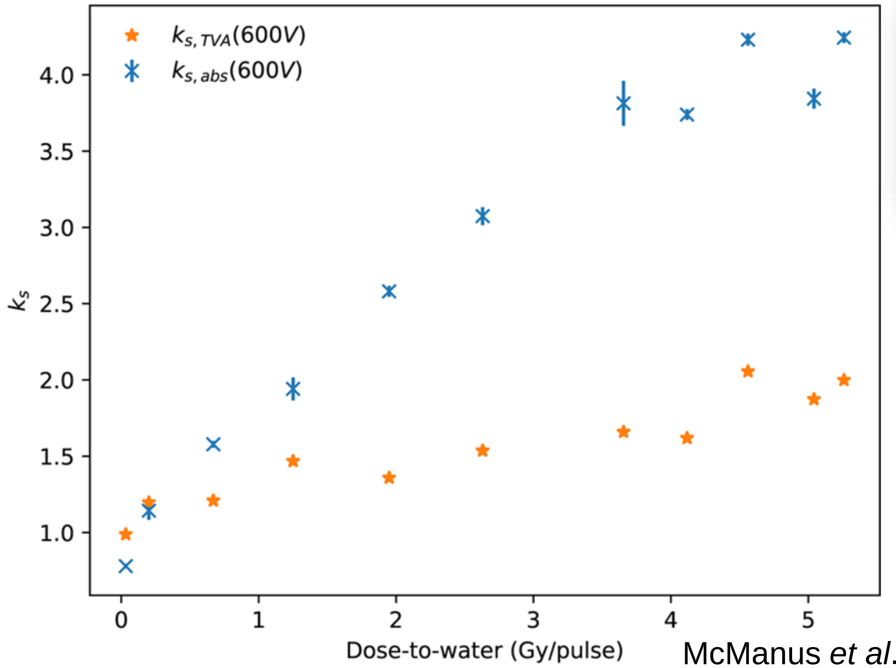




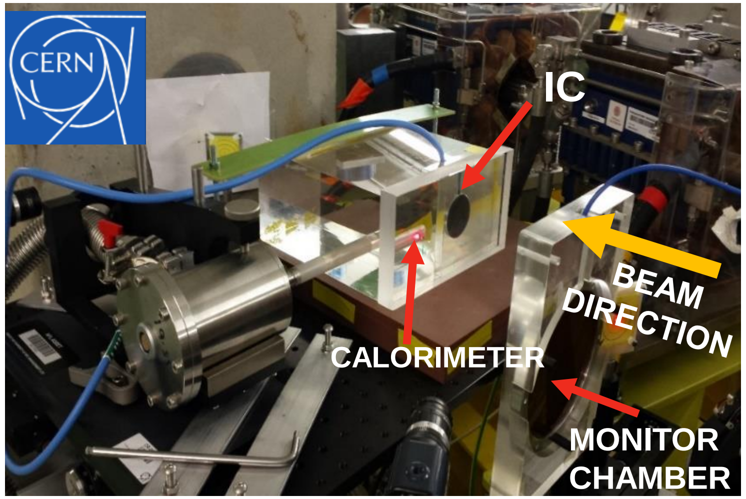
PTW Roos
(2 mm electrode separation)

- 200 MeV VHEE beam
- DPP: 0.03 – 5.3 Gy/pulse
- Graphite calorimeter employed as reference detector

$$k_{s,abs} = \frac{D_{w,cal}}{M k_{pol} k_{TP} k_{Q,Q_0} N_{D,w,Q_0}}$$

McManus *et al*., Sci. Rep. (2020)

- k_s up to 10 (V = 200 V) → **collection eff. 10%**
- k_s up to 4 (V = 600 V) → **collection eff. 25%**
- $k_{s,abs}$ compared with $k_{s,TVA}$ (two-voltage method)
- Available **analytical ion recombination models cannot predict chamber behaviour** for such a high DPP



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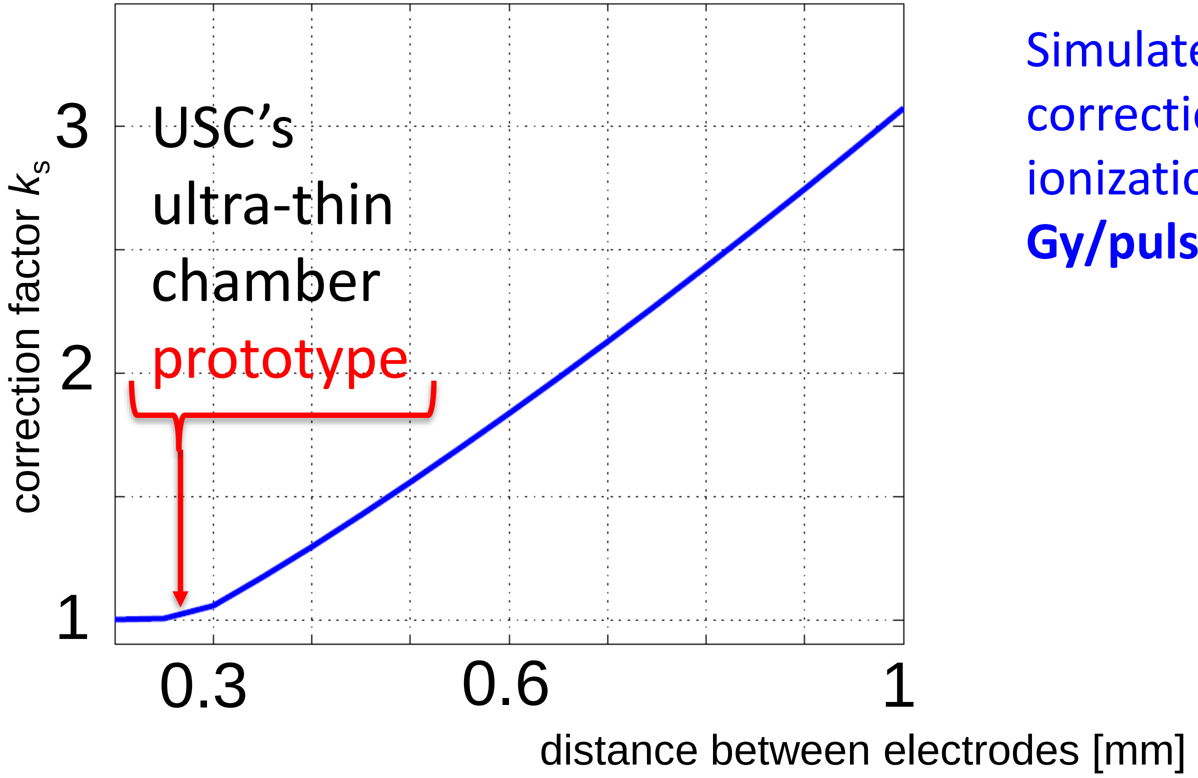
Ionization chambers – possible solutions

Possible solution for UHDR beams

USC's prototype ionization chambers for ultra-high DPP

Fig. Ionization chamber prototype (0.27 mm)



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

Courtesy of Faustino Gomez

Schüller *et al.*, Phys.Med. 80 (2020)

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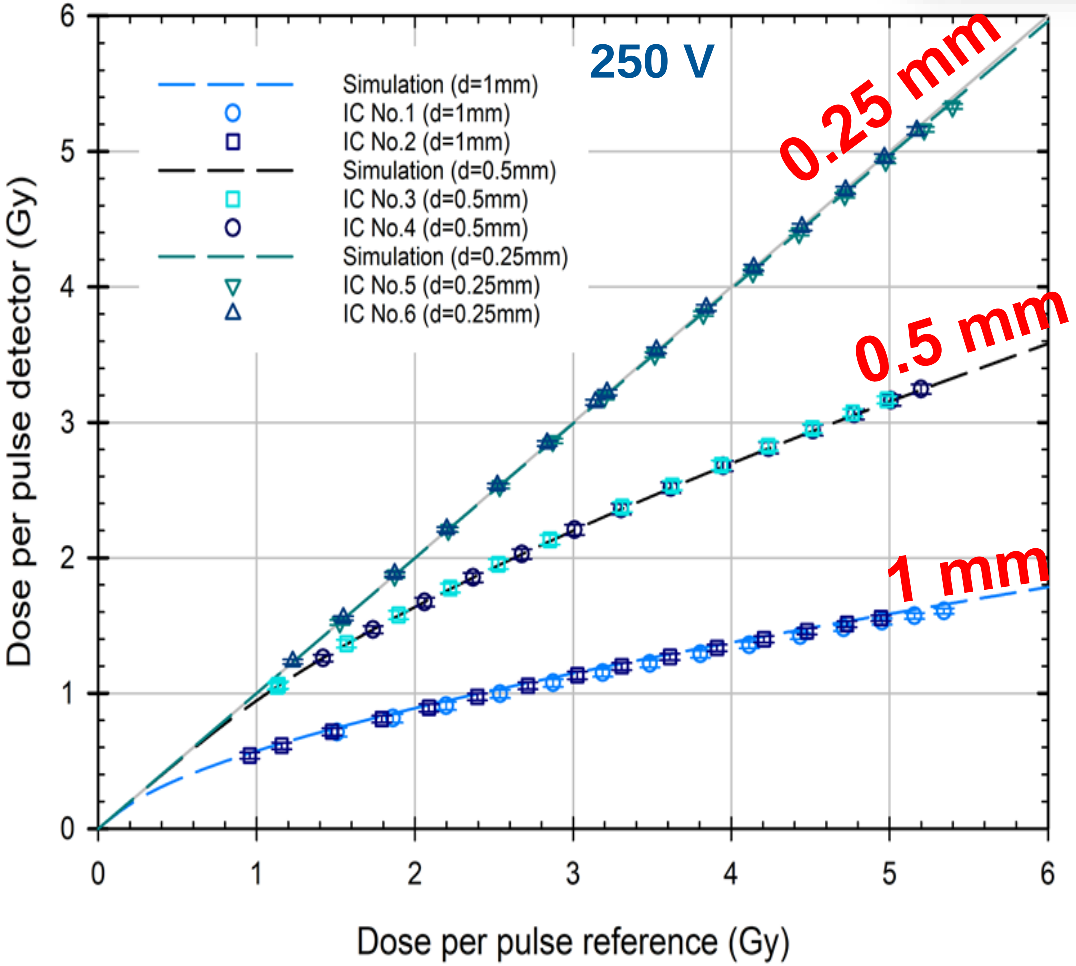
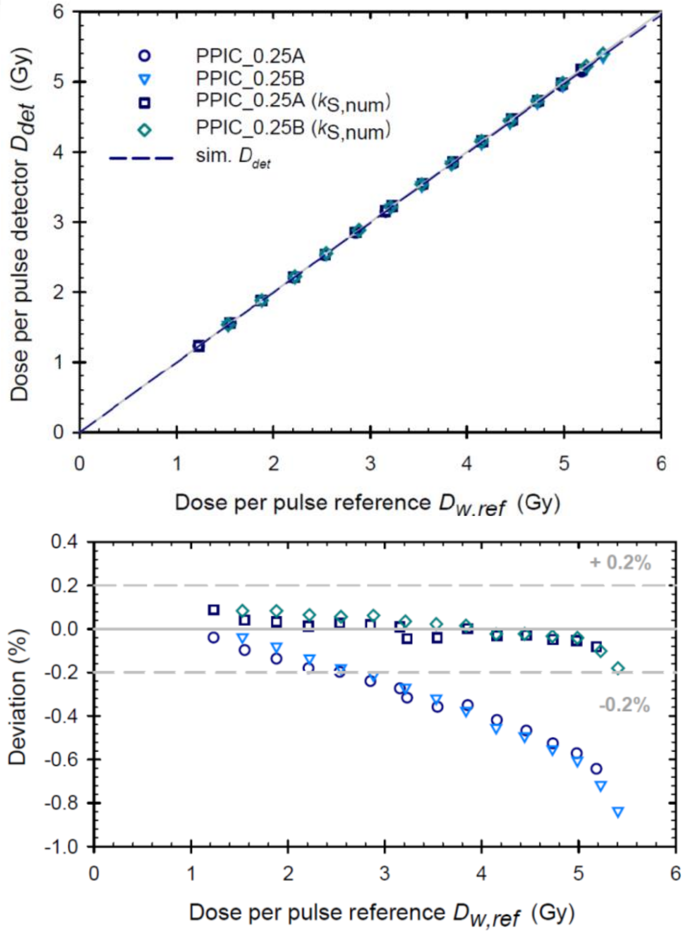
Possible solution for UHDR beams

PTW THE DOSIMETRY COMPANY

PTW’s prototype ionization chambers for ultra-high DPP

Fig. PTW IC prototype (0.25 mm)





Kranzer *et.al.* Phys.Med. 104, 10-17

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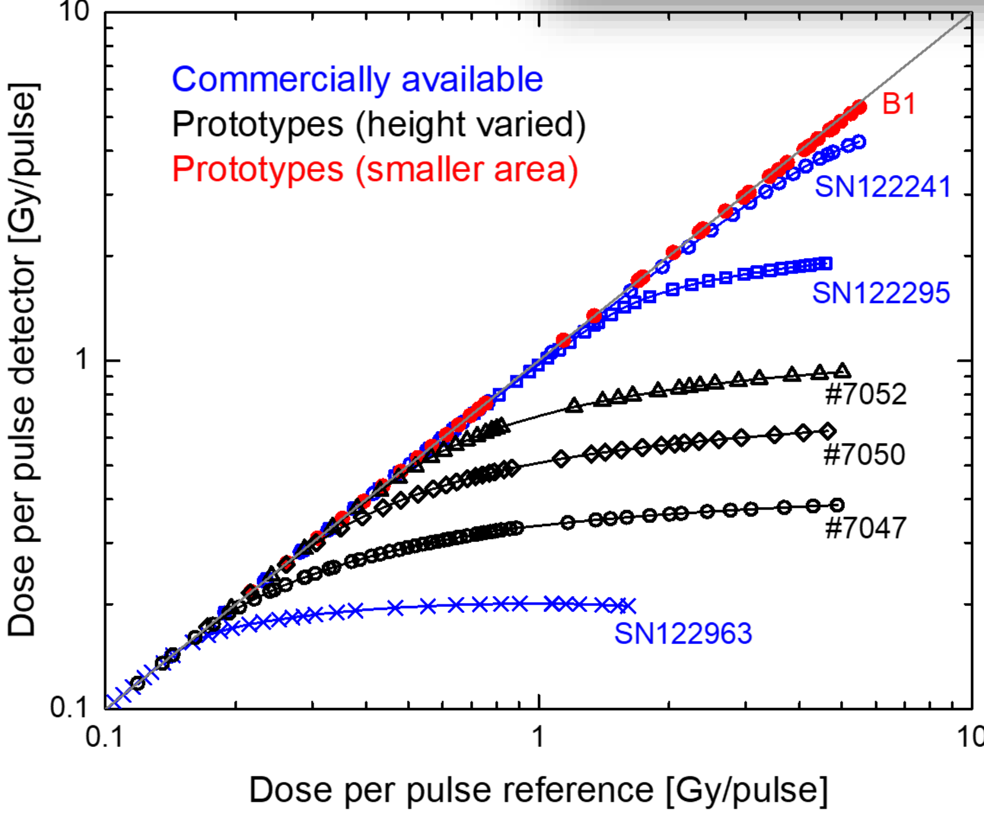
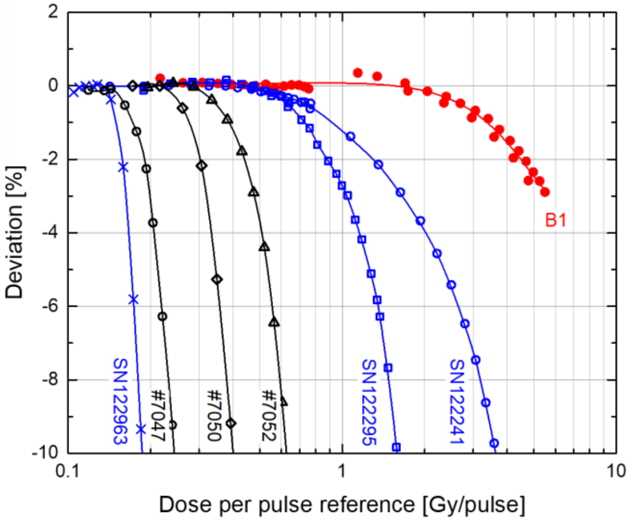
Diamond detectors

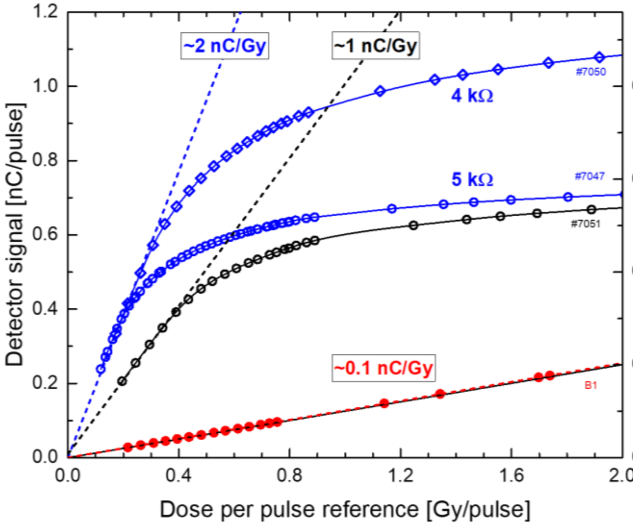
Possible solution for UHDR beams

PTW's microDiamond for ultra-high DPP

Fig. microDiamond





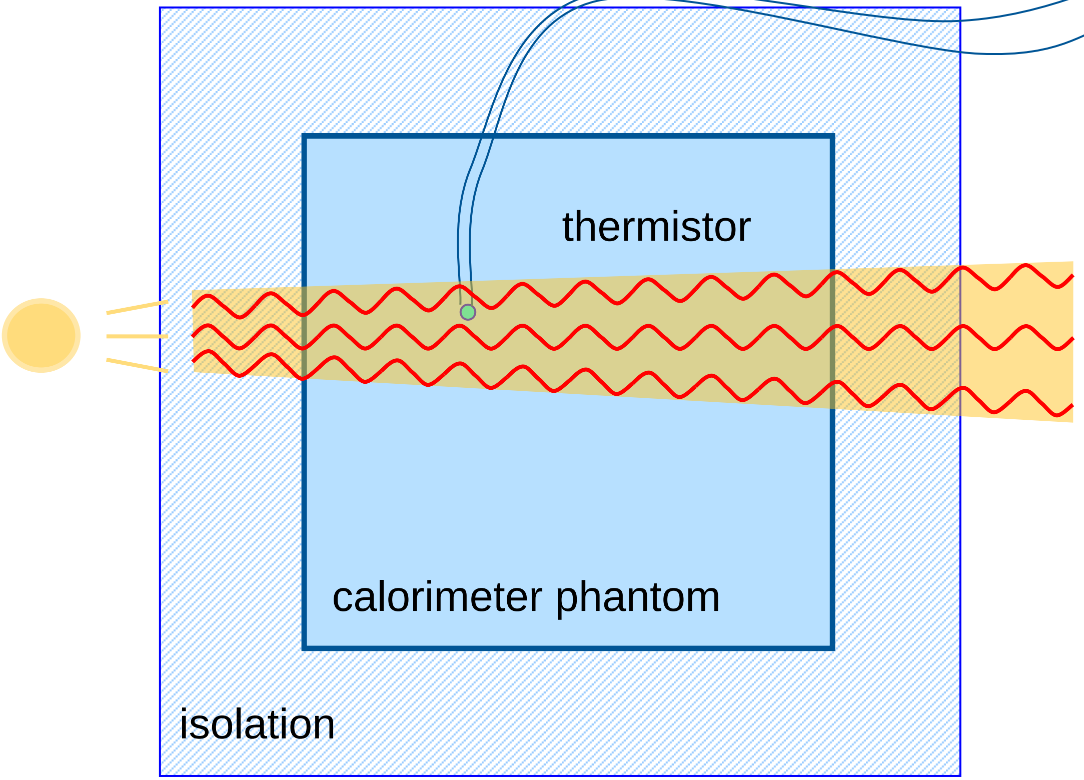


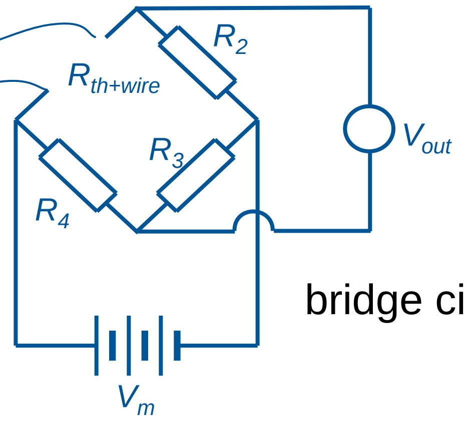
- Commercially available microDiamond detectors show saturation effects at different DPP levels.
- The linear range can be extended to the ultra-high DPP range by reduction of sensitivity and resistance.

Kranzer *et al.*, *PMB 67 (2022)*

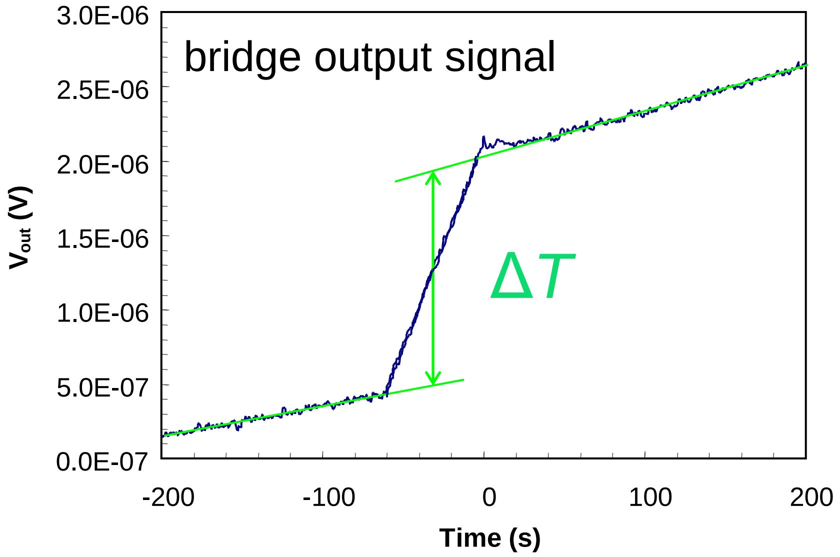
Calorimeters

Calorimeters used as prim. standards in high energy beams





$$D = c \cdot \Delta T$$



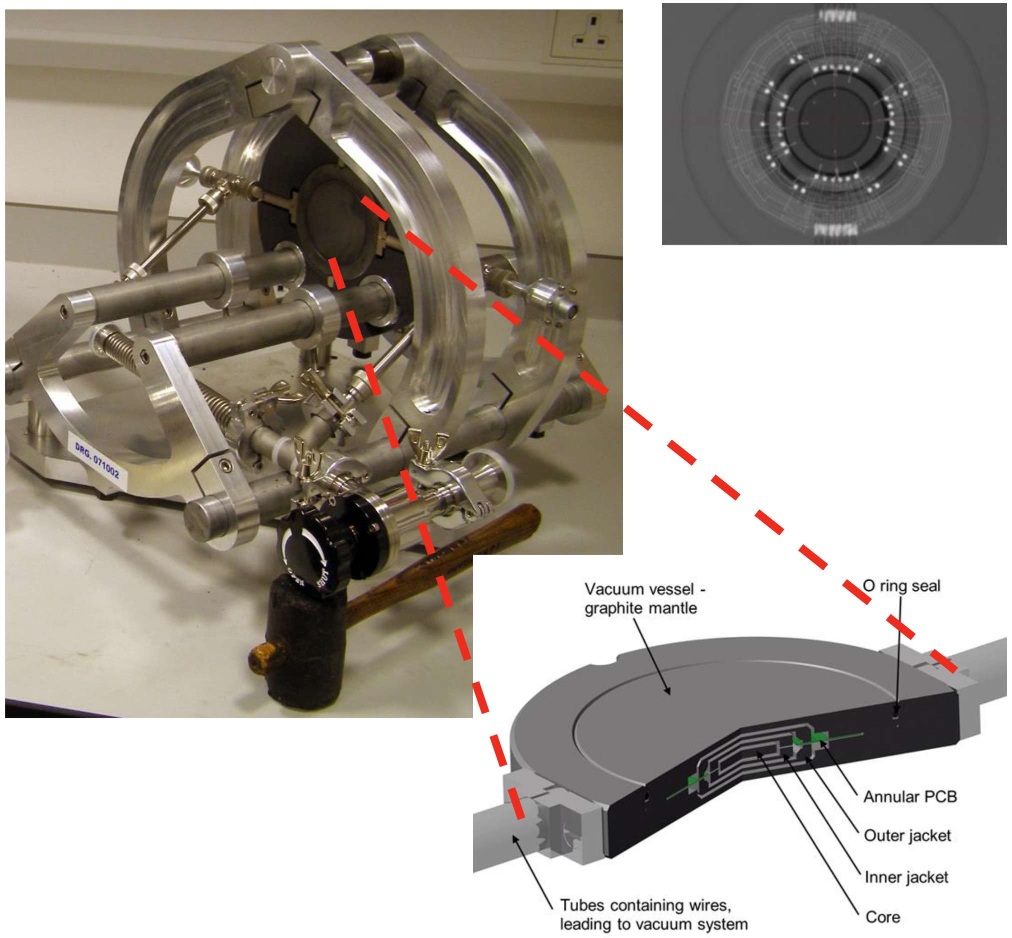
ADVANTAGES

- independent of dose-rate
- linear with dose in UHDR range
- independent of pulse structure
- real-time readout

Calorimetry in UHDR beams

NPL primary standard graphite calorimeter

- the control and analysis software was reconfigured to enable it to be used with UHDR particle beams
- Operated in quasi-adiabatic mode, thermistors detect changes in temperature of the graphite created by energy absorbed from the radiation beam allowing derivation of absorbed dose



NPL's primary standard graphite calorimeter.

Calorimetry in UHDR beams

NPL primary standard graphite calorimeter

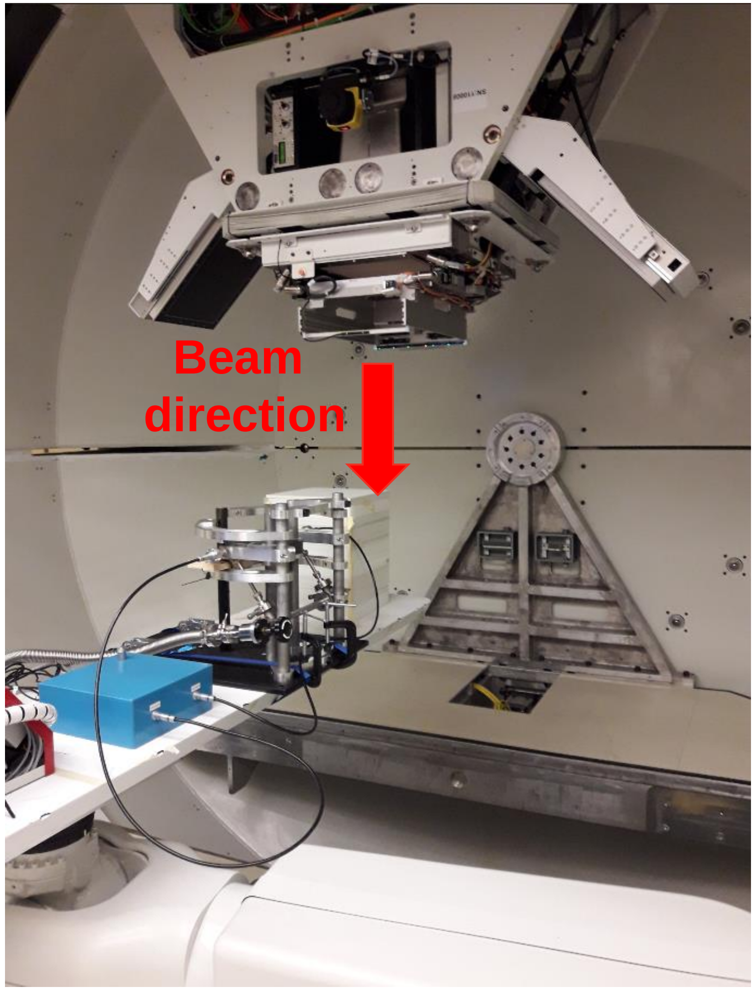
- 250 MeV (Varian ProBeam® operating in research mode) at ~65 Gy/s
- The core of the calorimeter was positioned at the isocentre with graphite plates placed in front to position the core at a WET of 5 gcm^{-2}

	Proton calorimeter					dose to water	
Field size, cm	5 x 6	5 x 8	5 x 10	5 x 12		6 x 5	12 x 5
Mean Dose, Gy	**7.654**	**7.690**	**7.726**	**7.736**		**7.666**	**7.741**
SDOM, %	0.04%	0.04%	0.04%	0.04%		0.04%	0.03%

Parameter	Value
c (J·kg^{-1}·K^{-1})	651.57+2.74· (T-273.15)
k_{imp}	1.0016
k_{gap}	1.0029
$s_{w,g}$	1.1210
k_{fl}	0.9713
$k_{z,cal}$	1.0000

Sources of uncertainties (%)	Type A	Type B
Physical dimensions	<0.01	0.09
Electrical calibrations	0.20	0.06
Specific heat capacity	0.08	0.26
k_{imp}, k_{gap}	0.01	0.11
$s_{w,g}$, k_{fl}	0.07	0.71
$k_{z,cal}$	-	0.10
Positioning on beam axis and reference depth	0.06	0.13
PCB	-	0.25
Calorimeter measurements and analysis	0.04	0.15
Total	0.24	0.84
Overall (1σ)	0.9	

Lourenço *et al. Sci.Rep*. under review



Calorimetry in UHDR proton beams

Cincinnati Children's

UHDpulse

NPL National Physical Laboratory

→ First ever calorimetry measurements in UHDR proton beam

- Established the correction factors required for absolute dosimetry of FLASH proton beam radiotherapy (Lourenço et al., 2022 (under review))
- Measurement uncertainty of 0.9% (k=1) – in line with clinical requirement
- **Underpinned the FDA approval and provided the hospital with confidence to commence clinical implementation of this novel technology**

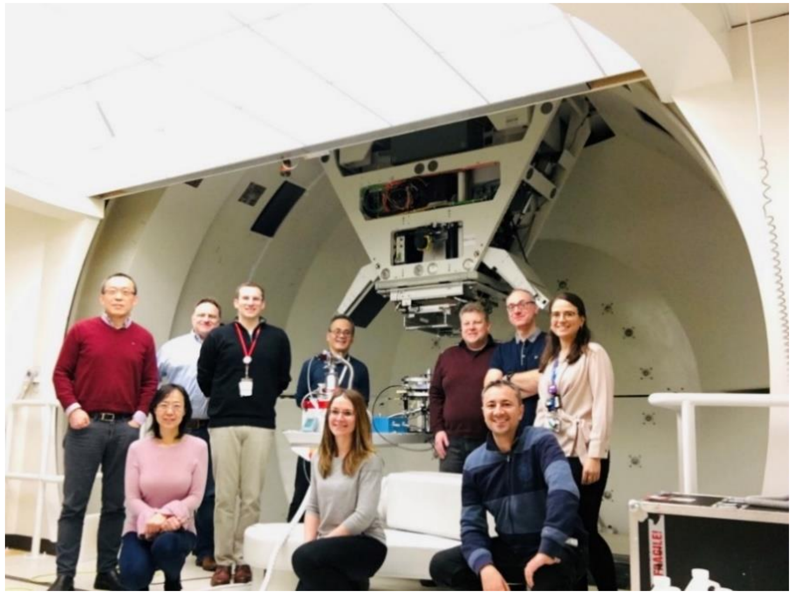
NIH U.S. National Library of Medicine

ClinicalTrials.gov

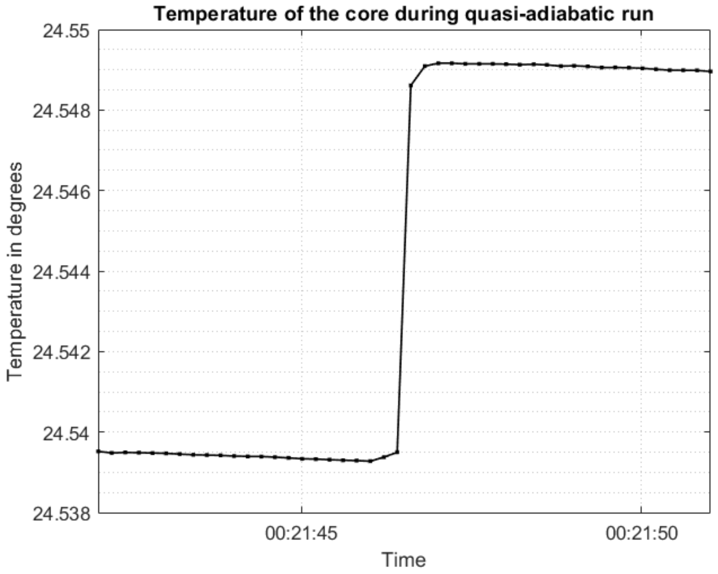
Feasibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01)

ClinicalTrials.gov Identifier: NCT04592887

Recruitment Status : Active, not recruiting
First Posted : October 19, 2020
Last Update Posted : November 1, 2021



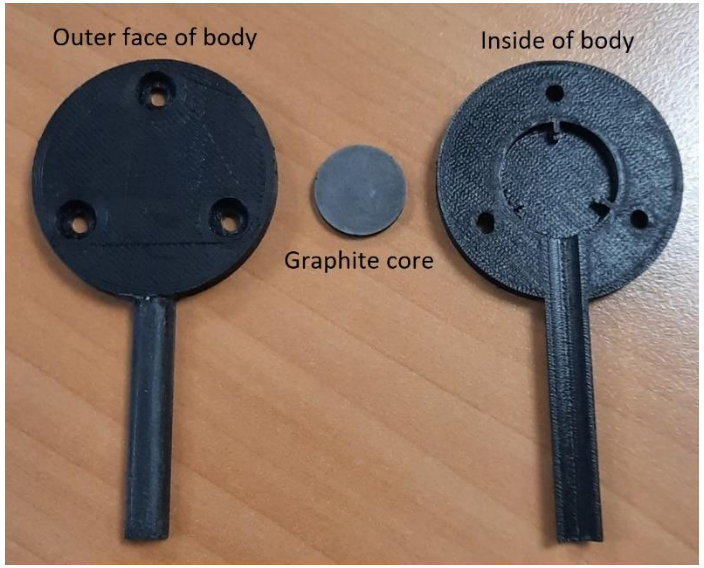
NPL and Cincinnati Teams



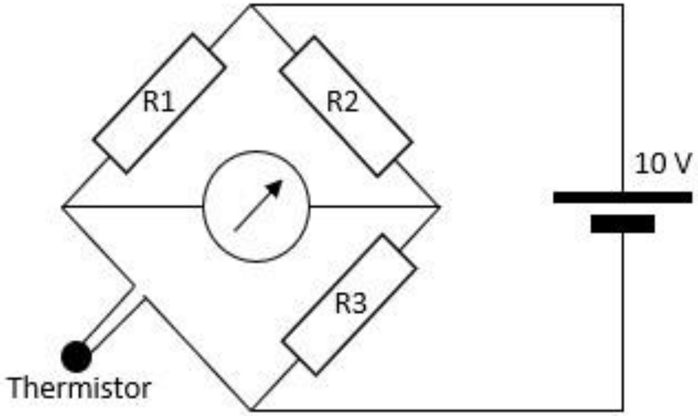
Simple Design Calorimeters as secondary standards for FLASH RT

Secondary standard calorimeter:
basic design & measurement system

- Shaped like a Roos or PPC05 IC
- Solid graphite or aluminium core 16 mm Ø, 2 mm thick, supported on 3 plinths, surrounded by air gap
- Single thermistor embedded in core, 10 kΩ at 25 °C
- 3D-printed body, in two halves
- Can be lacquered to be waterproof



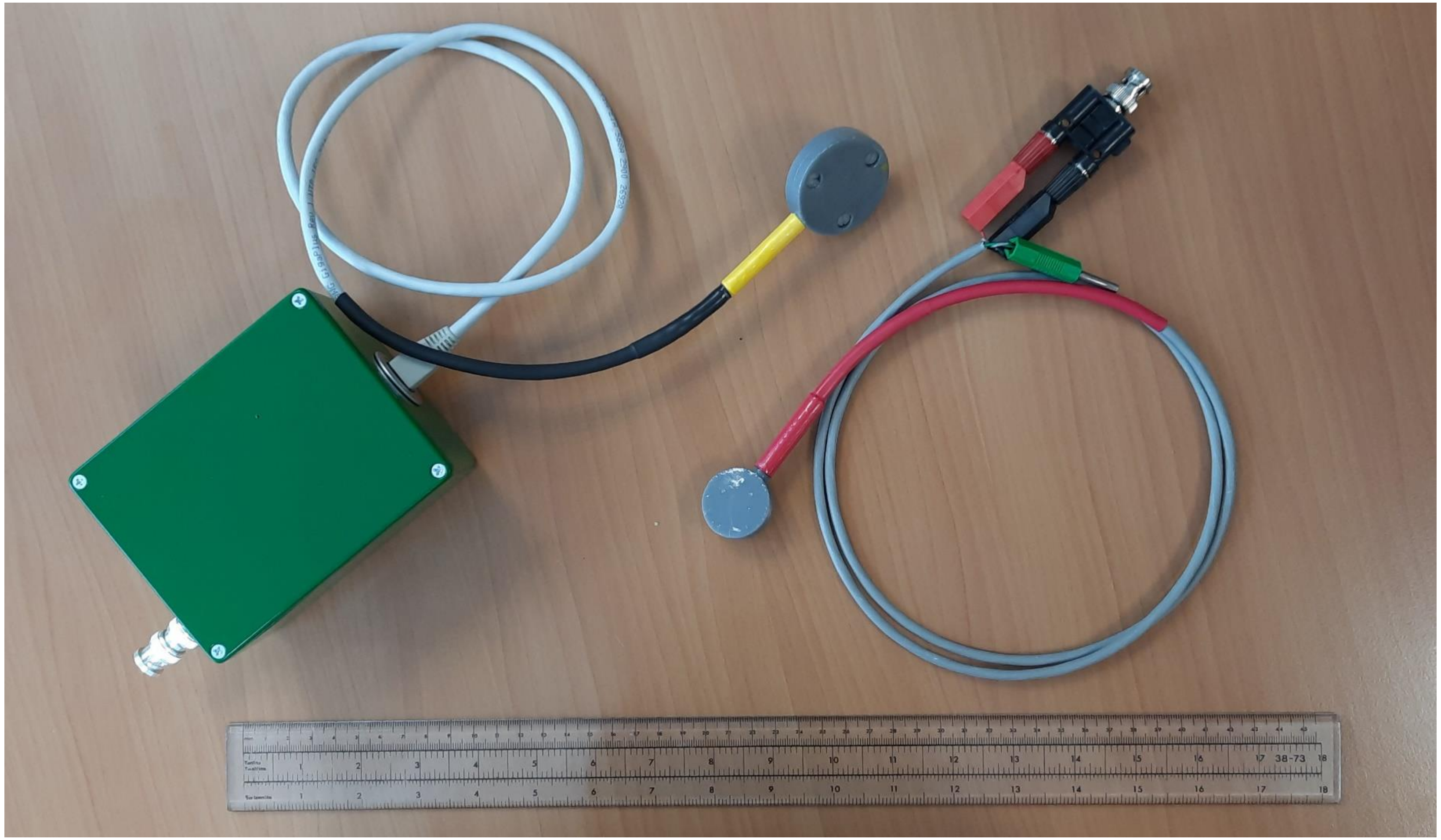
- Simple DC Wheatstone bridge
- Sensing thermistor in one arm
- Resistors 10 kΩ ± 0.01 %, ± 2 ppm/°C
- 10 V supply voltage



Courtesy of R. Thomas

Bass et al., *Br J Radiol* (2022) 10.1259/bjr.20220638.

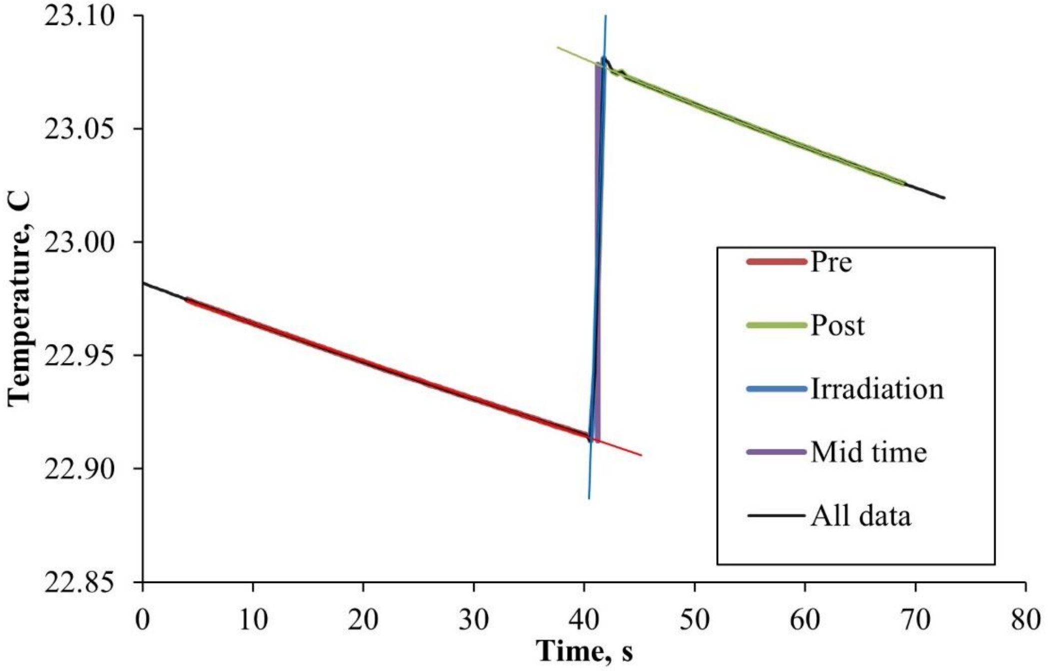
Secondary standard calorimeter: *built examples*



Courtesy of R. Thomas

Secondary standard calorimeter:
UHDR beam response

- test in research 28 MeV proton beam
- ~100 Gy beam delivery in < 0.5s
- Much higher SNR compared to conv. delivery
- Extrapolation of pre- and post-irradiation drifts over much shorter duration → resulting in lower uncertainty



- Investigations planned in
  - UHDR high energy proton beam
  - UHDR electron beam
  - and more..

Courtesy of R. Thomas

How to ensure traceability in FLSH RT?

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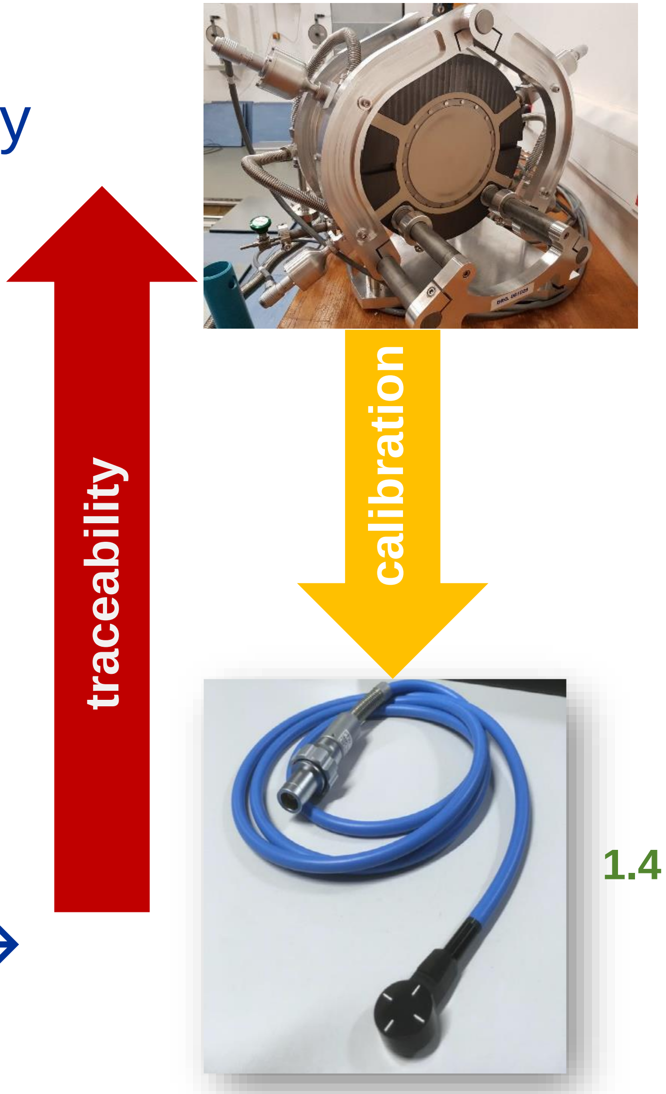
1. Disseminate the D_w in the UHDR beam with a primary standard

2. Use adequate detectors as a s/s and calibrate them against primary standard under the reference conditions



0.9% (k=1)

1.4 % (k=1)

- The reference conditions need to be specified (TBC) → these will depend on the UHDR radiation device

Summary

- Metrology is essential for **safe** and efficient clinical translation of FLASH RT

This requires:

- Definition of reference beam conditions
- Dissemination of D_w through a primary standard
- Establishment for adequate secondary standard devices (thin gap IC, fDiamond or ssCal)

- To enable provision of traceability chains in FLASH RT

NOTE: if we move away from IC dosimetry → the dosimetry CoP need to be adjusted for FLASH RT

National Physical Laboratory

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Thank you

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http://uhdpulse-empir.eu/