Planned measurements at FLUTE

Dosimetry and radiochemical measurements at ultra-high dose rates for medical applications

PhD topic and experiments at FLUTE

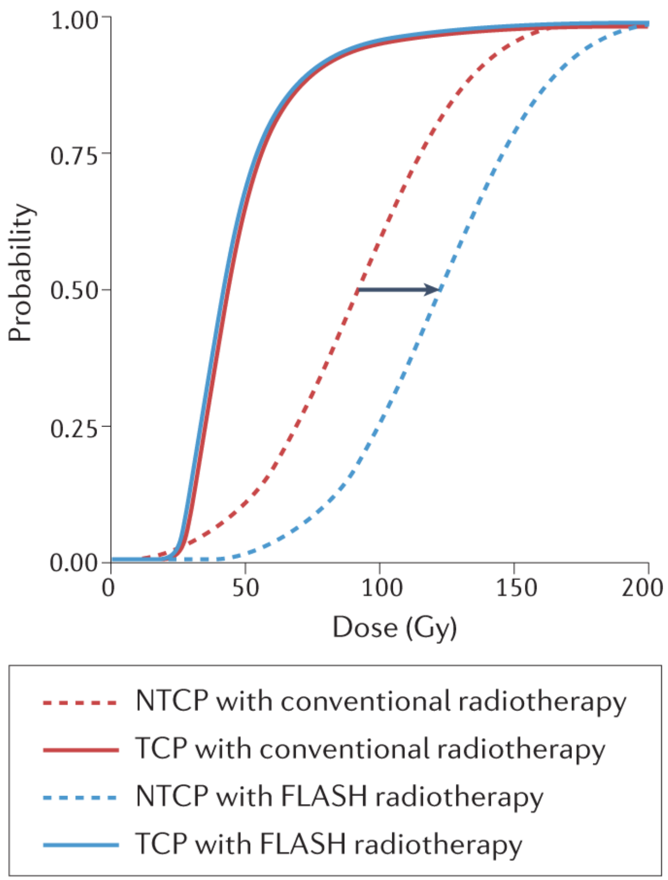
- Working title: Untersuchung zur Auswirkung der Pulsstruktur auf den Sauerstoffverbrauch (unter ultra-hohen Dosisleistungen) und dadurch resultierende biologische Reaktionen

- Experimental and accompanying simulation-based investigations into radiation-induced chemical and radiobiological phenomena at ultra-high dose rates

- Influence of beam pulse structure on:
  - Oxygen depletion
  - Radical-radical recombination

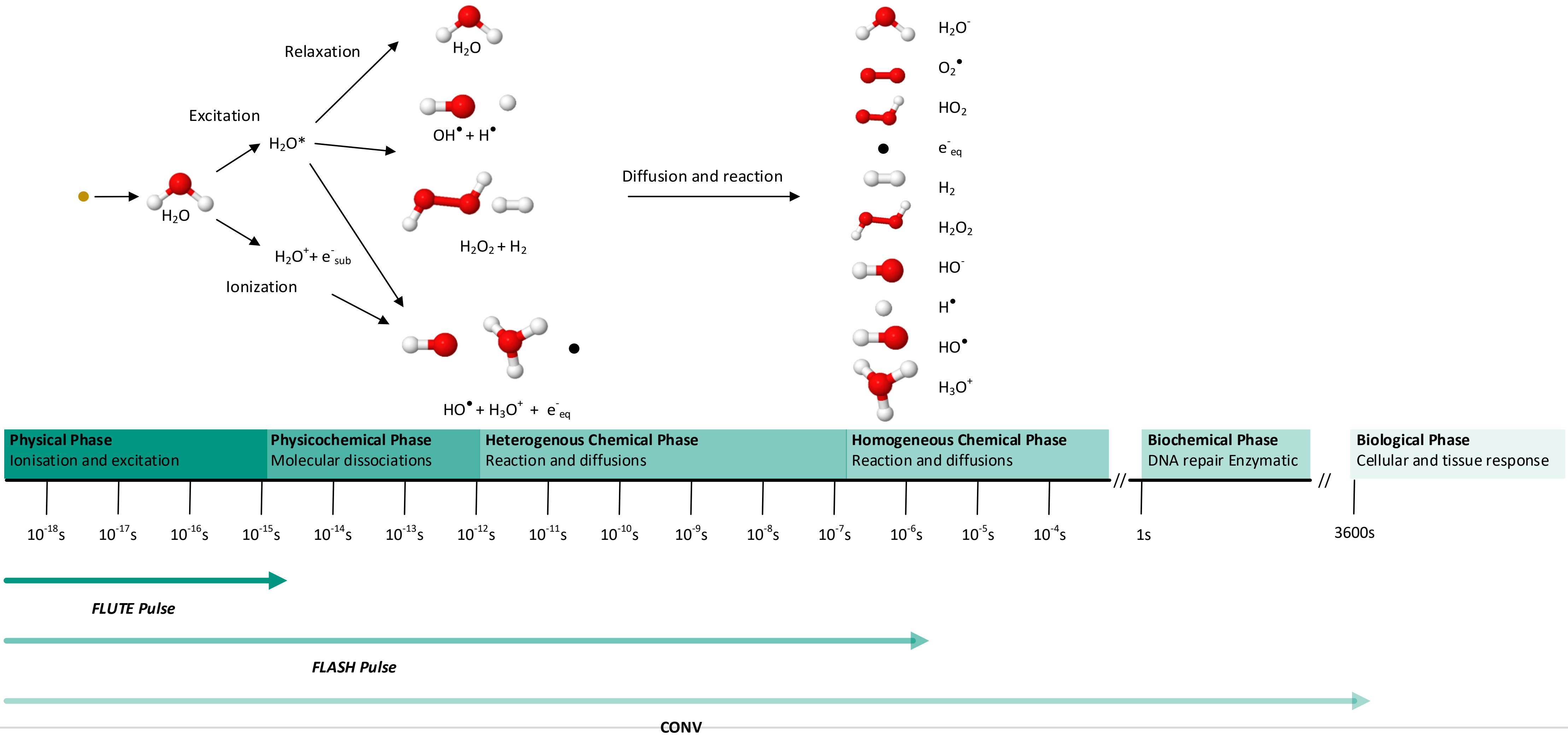
FLASH radiotherapy / FLASH effect

- Ultra-high dose rate (≥ 40 Gy/s)
- Sparing of normal tissue
- Same tumour control
- What leads to…
  - The increased normal-tissue protection?
  - The differential effect?



Vozenin, MC., Bourhis, J. & Durante, M. Towards clinical translation of FLASH radiotherapy. *Nat Rev Clin Oncol* **19**, 791–803 (2022).

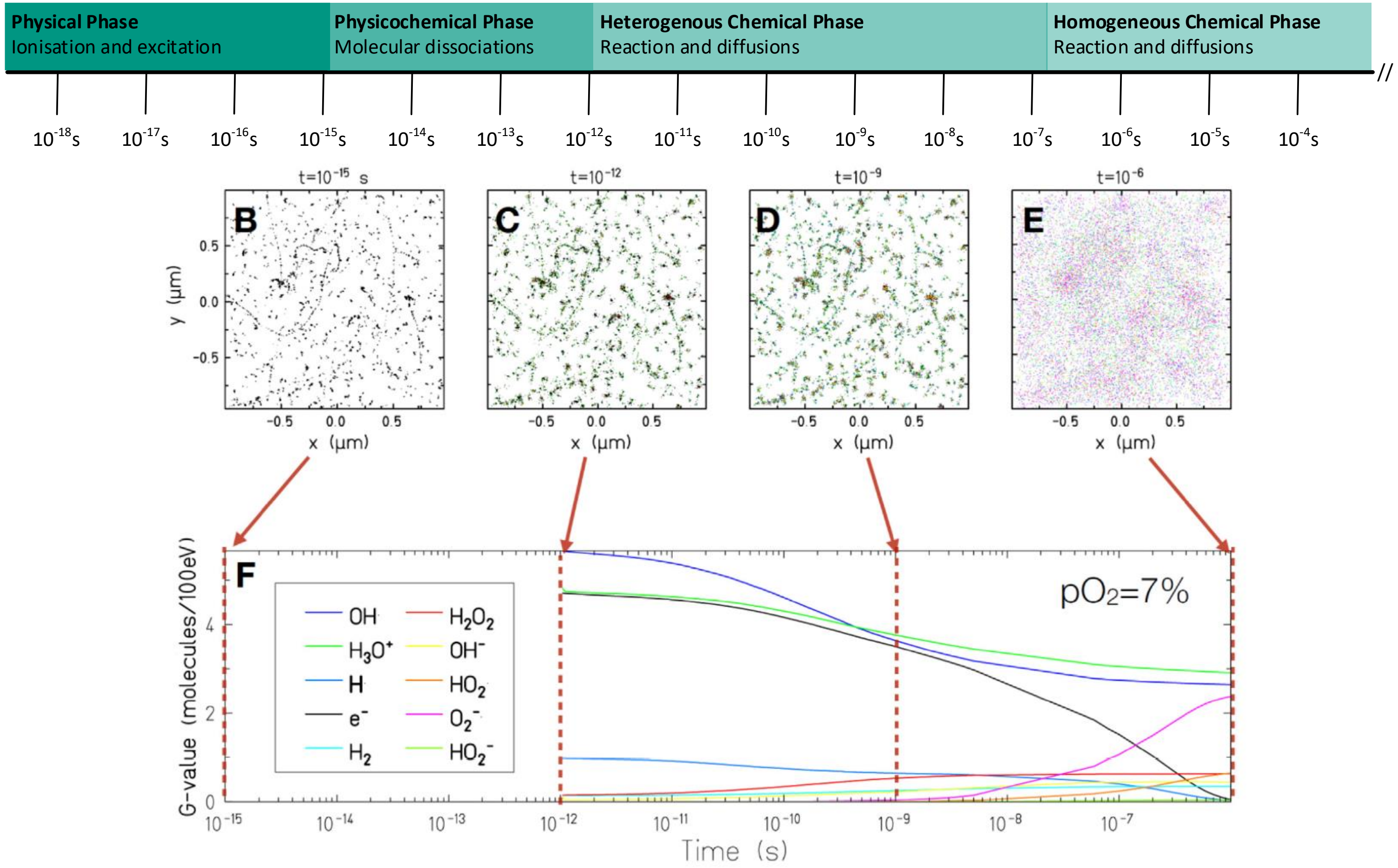
Radiolysis of water



Reaction kinetics

	Reaction		Products	$k(10^{10}\ dm^3\ mol^{-1}\ s^{-1})$
(i)	$OH^{\bullet} + OH^{\bullet}$	→	H_2O_2	0.6
(ii)	$OH^{\bullet} + e^-_{aq}$	→	OH^-	2.2
(iii)	$OH^{\bullet} + H^{\bullet}$	→	H_2O	2.0
(iv)	$OH^{\bullet} + H_2$	→	$H^{\bullet} + H_2O$	0.0045
(v)	$OH^{\bullet} + H_2O_2$	→	$HO_2^{\bullet} + H_2O$	0.0023
(vi)	$e^-_{aq} + e^-_{aq} + H_2O + H_2O$	→	$H_2 + OH^- + OH^-$	0.55
(vii)	$e^-_{aq} + H^{\bullet} + H_2O$	→	$H_2 + OH^-$	2.5
(viii)	$e^-_{aq} + H_3O^+$	→	$H^{\bullet} + H_2O$	1.7
(ix)	$e^-_{aq} + H_2O_2$	→	$OH^{\bullet} + OH^-$	1.0
(x)	$H^{\bullet} + H^{\bullet}$	→	H_2	1.0
(xi)	$H^{\bullet} + H_2O_2$	→	$OH^{\bullet} + H_2O$	0.01
(xii)	$H^{\bullet} + OH^-$	→	$e^-_{aq} + H_2O$	0.002
(xiii)	$H_3O^+ + OH^-$	→	$H_2O + H_2O$	10.0
(xiv)	$e^-_{aq} + O_2$	→	$O_2^{\bullet -}$	1.9
(xv)	$H^{\bullet} + O_2$	→	$HO_2^{\bullet}$	2.0
(xvi)	$OH^{\bullet} + HO_2^{\bullet}$	→	O_2	1.0
(xvii)	$OH^{\bullet} + O_2^{\bullet -}$	→	$O_2 + OH^-$	0.9
(xviii)	$OH^{\bullet} + HO_2^-$	→	$HO_2^{\bullet} + OH^-$	0.5
(xix)	$e^-_{aq} + HO_2^{\bullet}$	→	HO_2^-	2.0
(xx)	$e^-_{aq} + O_2^{\bullet -}$	→	$OH^- + HO_2^-$	1.3
(xxi)	$H^{\bullet} + HO_2^{\bullet}$	→	H_2O_2	2.0
(xxii)	$H^{\bullet} + O_2^{\bullet -}$	→	HO_2^-	2.0
(xxiii)	$H_3O^+ + O_2^{\bullet -}$	→	$HO_2^{\bullet}$	3
(xxiv)	$H_3O^+ + HO_2^-$	→	H_2O_2	2.0
(xxv)	$HO_2^{\bullet} + HO_2^{\bullet}$	→	$H_2O_2 + O_2$	0.000076
(xxvi)	$HO_2^{\bullet} + O_2^{\bullet -}$	→	$O_2 + HO_2^-$	0.0085

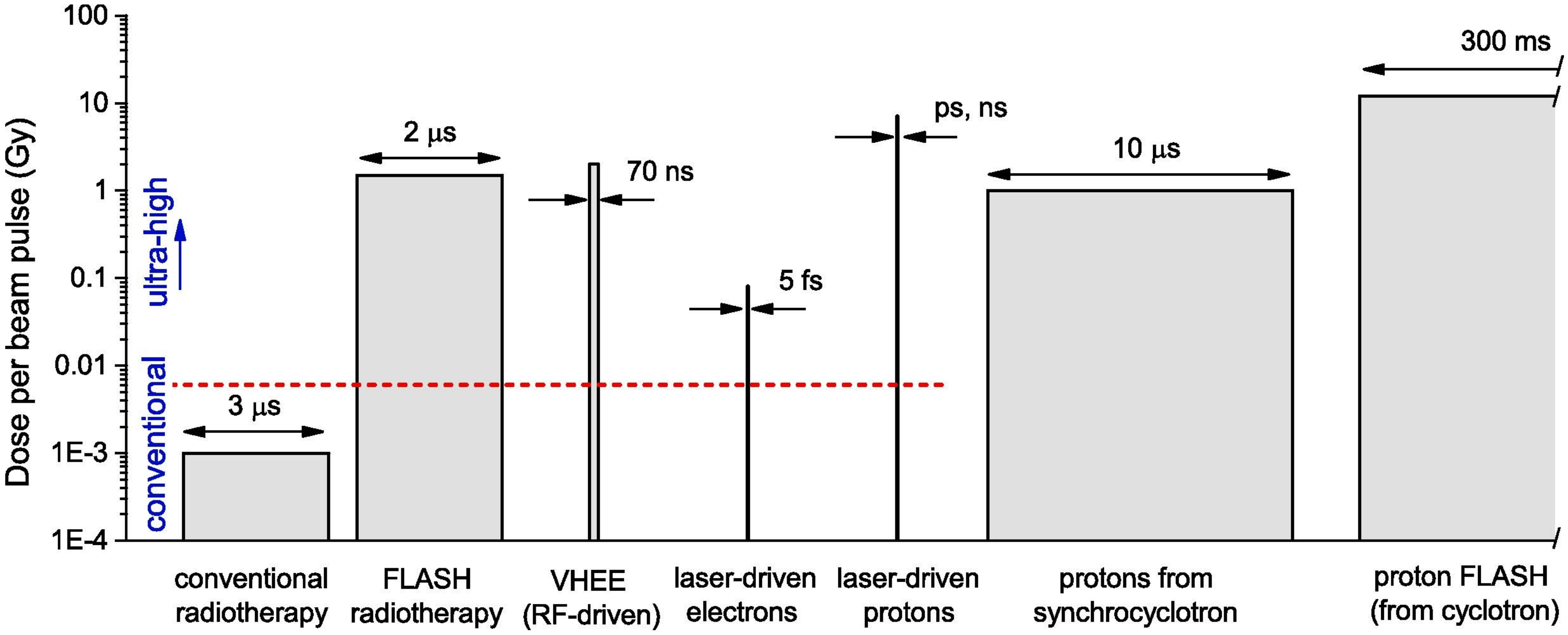
Boscolo, D.; Krämer, M.; Fuss, M.C.; Durante, M.; Scifoni, E. Impact of Target Oxygenation on the Chemical Track Evolution of Ion and Electron Radiation. Int. J. Mol. Sci., **2020**



Daria Boscolo et. al. , May oxygen depletion explain the FLASH effect? A chemical track structure analysis, Radiotherapy and Oncology, Volume 162, 2021

Beam pulse structure

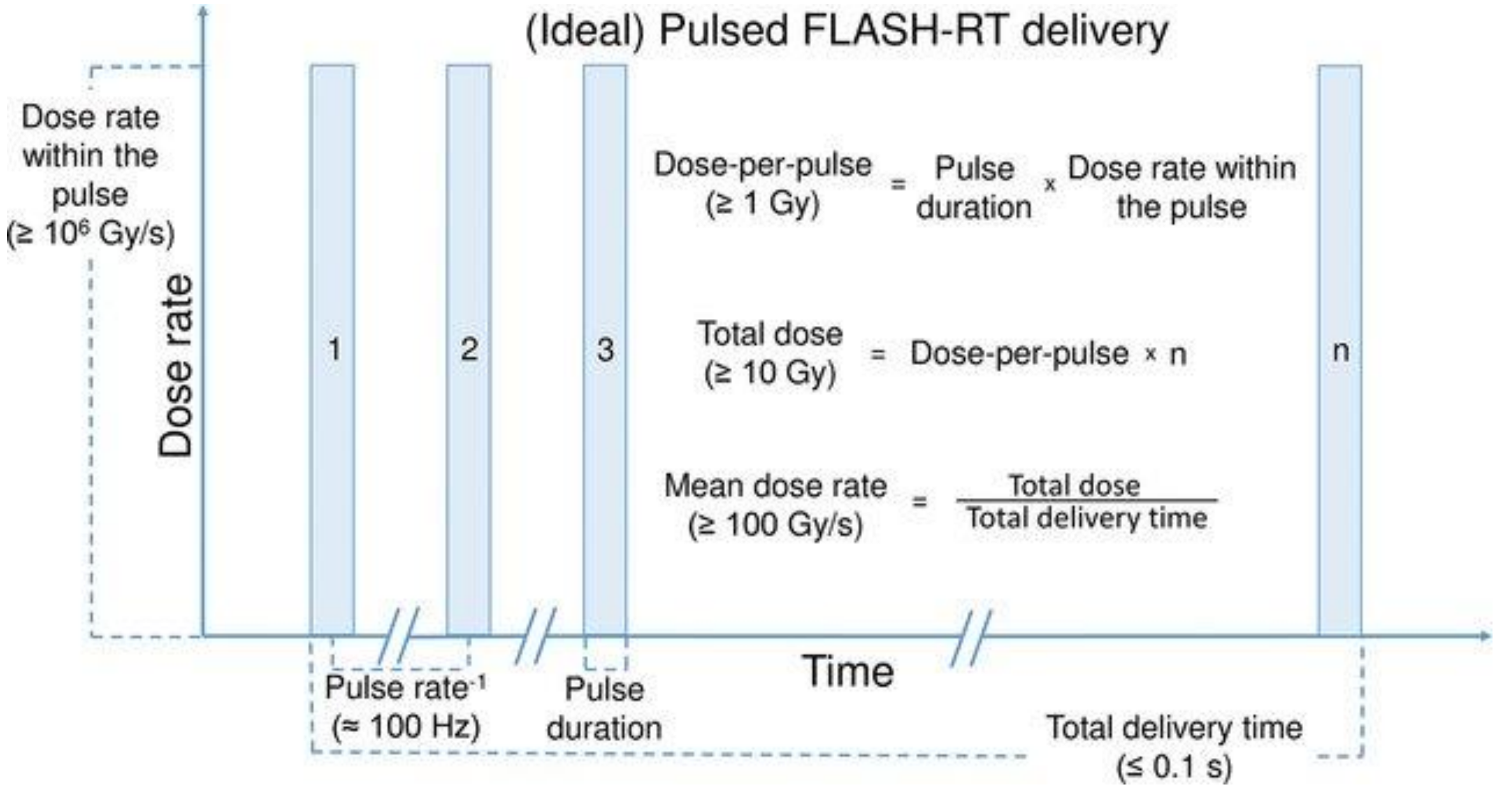
- Pulse dose rate



Andreas Schüller et. al. The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates, Physica Medica, Volume 80, 2020

Beam pulse structure

- Pulse dose/ Pulse dose rate
- Average dose rate
- Pulse frequency
- Pulse length
- Macro pulse structure
- Total dose
- Irradiation time



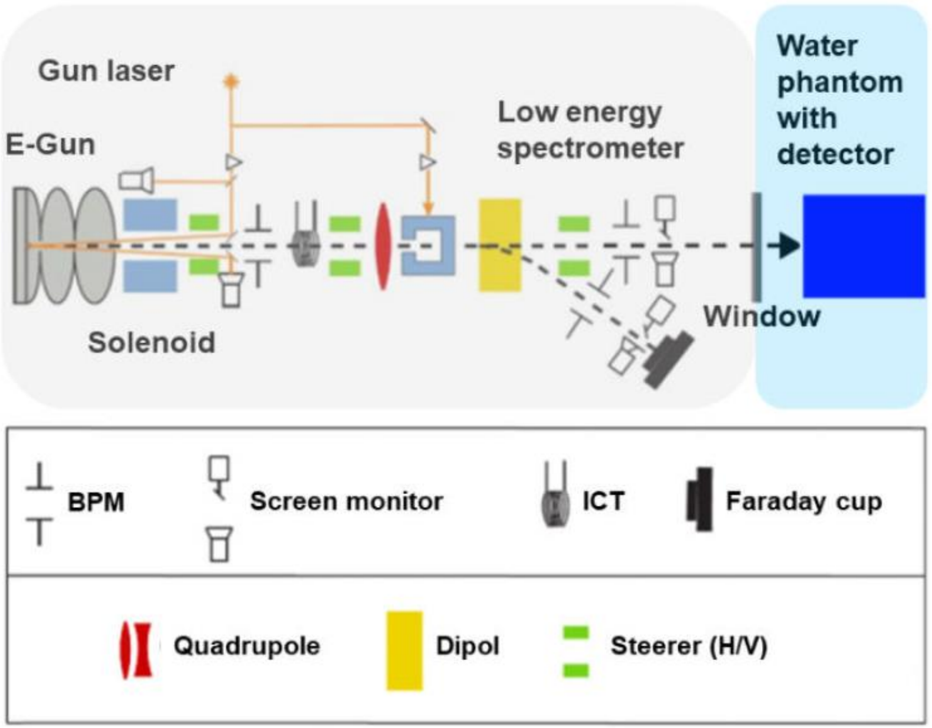
Wilson, Joseph & Hammond, Ester & Higgins, Geoff & Petersson, Kristoffer. Ultra-High Dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool's Gold?. Frontiers in Oncology. 9. 1563. 10.3389/fonc.2019.01563., 2020

Dosimetry @FLUTE

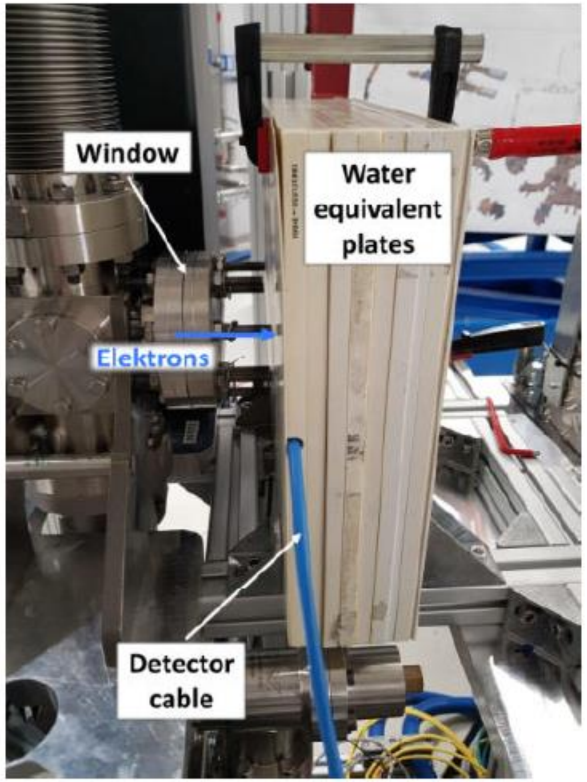
- Electrons
- Energy: > 5 MeV

- Dosimetry
  - Roos Camber
  - Advanced Markus Chamber
  - flashDiamond

  - Passive Dosimetry
    - TLD
    - OSL
    - EBX-Film?



Mayer, K. *Irradiation Studies at IBPT Accelerators.* KIT, 2023

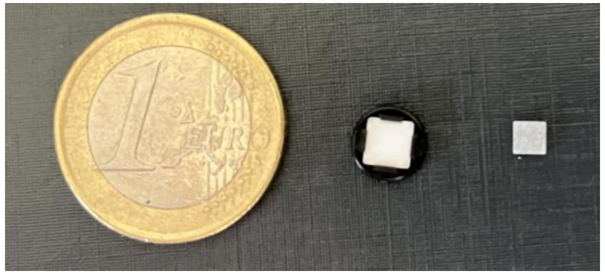


Mayer, K. *Irradiation Studies at IBPT Accelerators.* KIT, 2023

FLASH Dosimetry

TABLE 1 | Dosimeters and their capabilities rated for potential FLASH dose measurement of key parameters.

Response	Detectors	Measurement type	FLASH study	Instantaneous dose-rate/dose per pulse (D_p) dependence	Spatial resolution	Time-resolution	Energy dependence
Luminescence	TLD/OSLD	**1D**, 2D	e [15, 37, 71]	Independent (~10^9 Gy/s) [80, 137]	~ 1 mm	Passive	Tissue-equivalent
	Scintillators	1D, **2D**, 3D	p [13, 18]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ns	Tissue-equivalent
	Cherenkov	**1D**, 2D, 3D	e [29]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ps	Energy dependent
	FNTD	2D	NA	Independent (~10^8 Gy/s) [85]	~ 1 µm	Passive	Energy dependent
Charge	Ionization chambers	**1D**, **2D**	p [13, 18, 19] e [15, 37, 71] ph [16, 17]	Dependent on D_p [48, 52] (>1 Gy/pulse),	~3–5 mm	~ms	Energy dependence shows up > 2 MeV
	Diamonds	**1D**	p [18]	Dependent on D_p (>1 mGy/pulse) [49]	~ 1 mm	~µs	Tissue-equivalent
	Si diode	**1D**, 2D	NA	Dependent on D_p [54] (Independent ~0.2 Gy/s) [138]	~ 1 mm	~ms	Energy dependent
Chemical	Alanine pellets	**1D**	e [12, 15, 37, 139]	Independent (10^8 Gy/s) [69]	~ 5 mm	Passive	Tissue-equivalent
	Methyl viologen/fricke	**1D**	e [29, 48]	Depends on the decay rate and diffusion of radiation induced species	~ 2 mm	~ns	Tissue-equivalent
	Radiochromic film	**2D**	p [18, 19] e [10–12, 15, 30, 37, 71, 140] ph [16]	Independent (10^9 Gy/s) [70, 71]	~1 µm	Passive	Tissue-equivalent
	Gel dosimeters	3D	NA	Strong dependence below 0.001 Gy/s [141] and above 0.10 Gy/s [142]	~1 mm	Passive	Tissue-equivalent



Roos Chamber, PTW Freiburg

Advanced Markus Chamber, PTW Freiburg

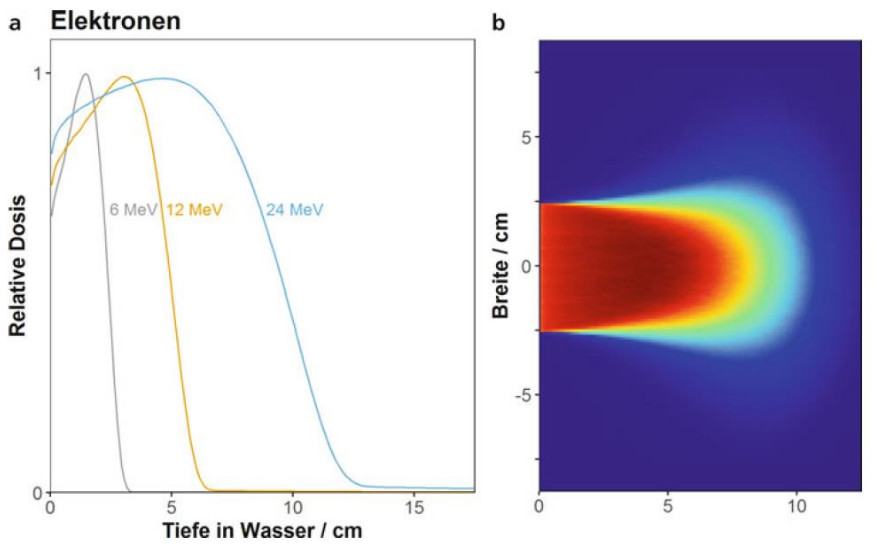
flashDiamon, PTW Freiburg

Ashraf, M.Ramish & Rahman, Mahbubur & Zhang, Rongxiao & Williams, Benjamin & Gladstone, David & Pogue, Brian & Bruza, Petr. Dosimetry for FLASH Radiotherapy: A Review of Tools and the Role of Radioluminescence and Cherenkov Emission. Frontiers in Physics. 8. 328. 10.3389/fphy.2020.00328. 2020

Determine the maximum dose and dose rate

- Depth dose measurements
  - Advanced Markus Ionization Chamber
  - TLD / (OSLD)
  - Solid water RW3 Phantom

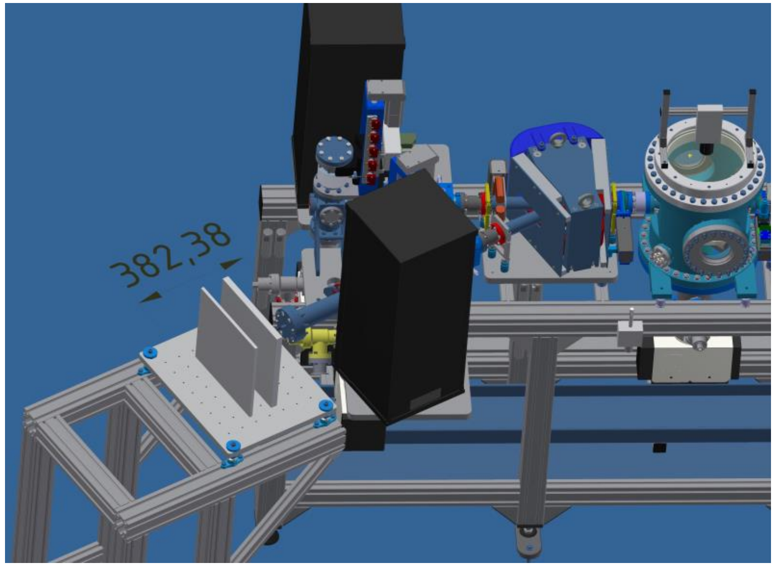
- Considerations:
  - Dose rate dependance
  - Homogenity
  - Field size



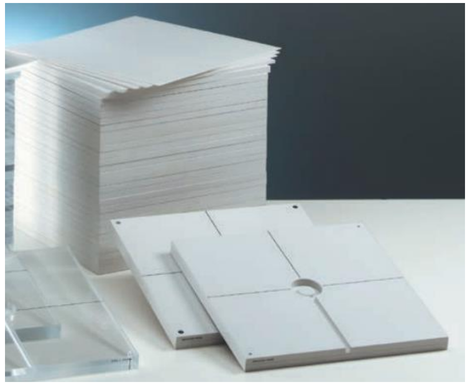
Greilich, S., Osinga-Blättermann, JM. Strahlenphysik. In: Schlegel, W., Karger, C., Jäkel, O. (eds) Medizinische Physik. Springer Spektrum, Berlin, Heidelberg, 2018

→Calibrate ICT for dose at specific position and field size
→Define Isocenter → Point with max. dose

FLASH Dosimetry @ FLUTE

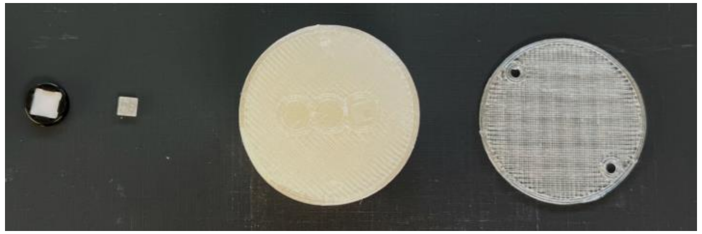


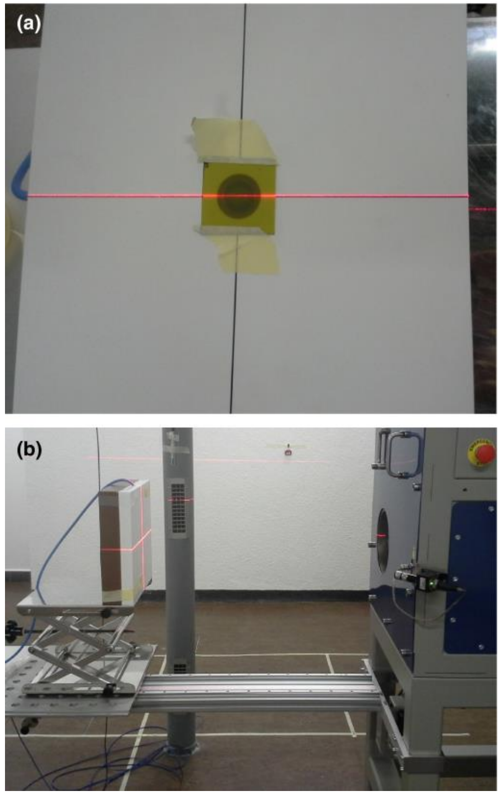
Till Borkowski, KIT- IBPT



PTW Freiburg

PTW Freiburg

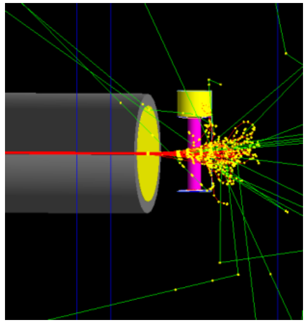


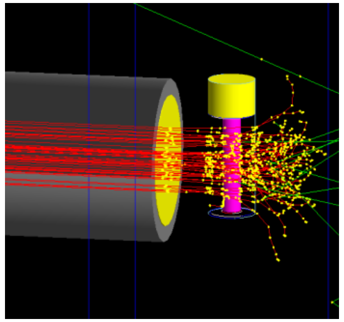


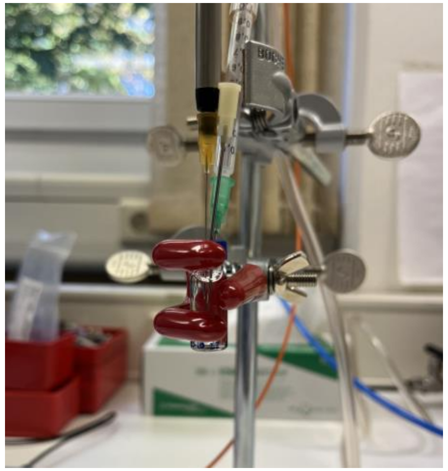
Petersson, K., et. al. High dose-per-pulse electron beam dosimetry — A model to correct for the ion recombination in the Advanced Markus ionization chamber. Med. Phys., 44: 1157-1167, 2017

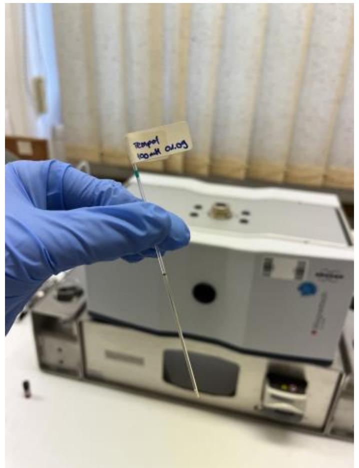
Radical Measurements

- Homogeneous energy distribution in the sample volume
- Different beam pulse structures
- Electron Spin Resonance (ESR) measurements ~ 5 min. after irradiation
- Measurements with high and low oxygen concentrations in the water sample









Measurements at FLUTE

	Measurement system	Beam characteristics	Time
Beam position and field homogeneity	EBT-XD Film or AdvaPix	• Highest and lowest charge per bunch, bunch duration? • Repetitions at (3?) different distances (SSD)	1-2 days
Depth dose measurements	Advanced Markus IC TLD / OSLD	• Highest and lowest dose rate (bunch charge, repetition rate, bunch length) • 8 measurement points at different depths	2-3 days
Radical / Oxygen concentrations	Water, ESR, spin trap oxygen sensor	• Testing max./min. bunch charge, repetition rate, bunch length • consider useful steps	5 days
Alternative spin traps? Biology? Scavengers, cells ?			

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Beam settings

Karlsruhe Institute of Technology

- ELBE (Phantom 2,5mm diameter, 5mm length)

Configuration	Dose [Gy]	Irr. time [s]	Mean dose rate [Gy/s]	Bunch dose rate [Gy/s]
(i)	31.5 ± 0.6	240	0.13	2.0×10^3
(ii)	32.3 ± 0.6	0.160	201.9	1.6×10^9
(iii)	31.9 ± 0.5	0.100	319.0	4.9×10^6
(iv)	32.1 ± 0.6	0.0003	1.1×10^5	1.6×10^9

Jansen et. al. Changes in Radical Levels as a Cause for the FLASH effect: Impact of beam structure parameters at ultra-high dose rates on oxygen depletion in water, Radiotherapy and Oncology, Volume 175, 2022

- FLASHlab@PITZ (1mm² spot size)

Options @PITZ	Low dose case	High dose case
Bunch charge [pC]	0.1	5 000
Individual bunches OR train	Single bunch	1 ms train, (i.e.1000 bunches)
RF pulse rep. rate [Hz]	1	10
Bunch length [ps]	<1	~30
Dose (D_{bunch}) **per bunch** [Gy]	0.02	1000
Dose rate ($\dot{D}_{bunch}$) **per bunch** [Gy/s]	>2E+10	4E+13
Dose (D_{train}) **per train (ms)** [Gy]	0.02	1E+6
Dose rate ($\dot{D}_{train}$) **per train (ms)** [Gy/s]	20	1E+9
Dose **per second** ($\langle\dot{D}\rangle$) [Gy/s]	0.02	1E+7

Stephan F, Gross M, Grebinyk A, et al. FLASHlab@PITZ: New R&D platform with unique capabilities for electron FLASH and VHEE radiation therapy and radiation biology under preparation at PITZ. *Phys Med*. 2022;104:174-187. doi:10.1016/j.ejmp.2022.10.026

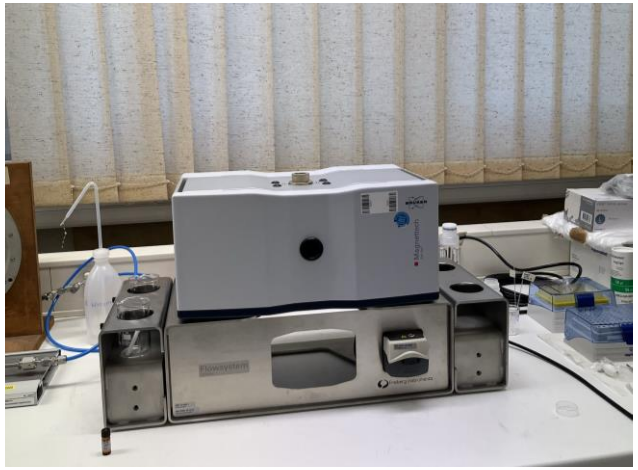
Measurement of radicals

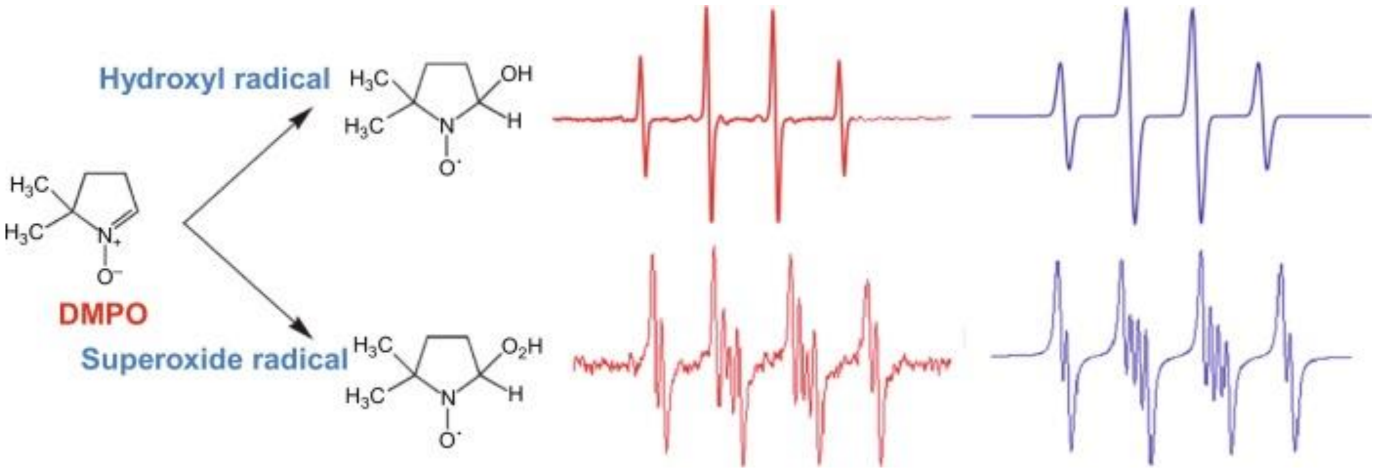
- Electron Spin Resonance (ESR) / Electron Paramagnetic Resonance (EPR)
- Spin trap / Spin probe

Reactive Oxygen Species (ROS)

Radicals:	
$O_2^{\bullet-}$	Superoxide
$HO^{\bullet}$	Hydroxyl
$ROO^{\bullet}$	Peroxyl
$RO^{\bullet}$	Alkoxyl
$HOO^{\bullet}$	Hydroperoxy
$^1O_2$	Singlet oxygen

Non-Radicals:	
H_2O_2	Hydrogen peroxide
HOCl	Hypochlorous acid
O_3	Ozone
$ONOO^-$	Peroxynitrite

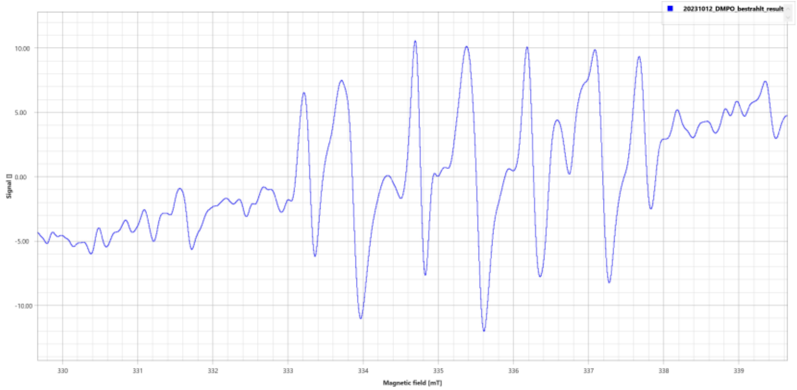


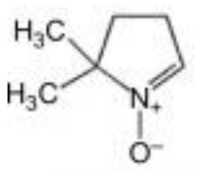


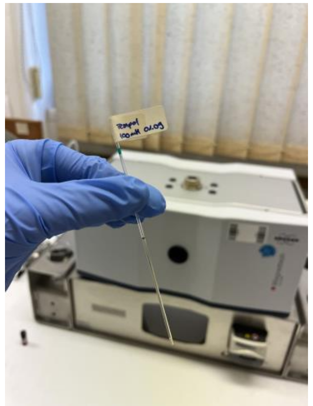
Janusz M. Dąbrowski, in Advances in Inorganic Chemistry, 2017

Development of measurement method

- Concentration of reagents
- Stability
- Oxygen concentration (stability)
- EPR parameter
- Setup in the beam







Sample preparation → Add spin trap → Adjust oxygen concentration → Irradiate sample → Transfer the sample → Acquire EPR spectrum and process the data

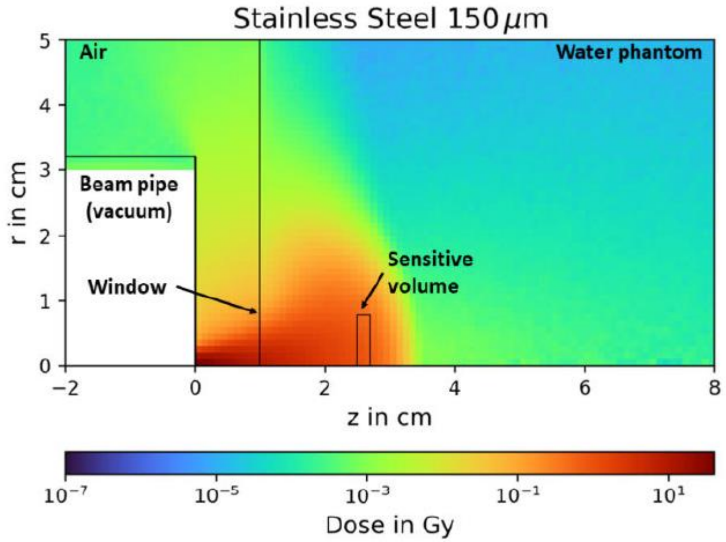
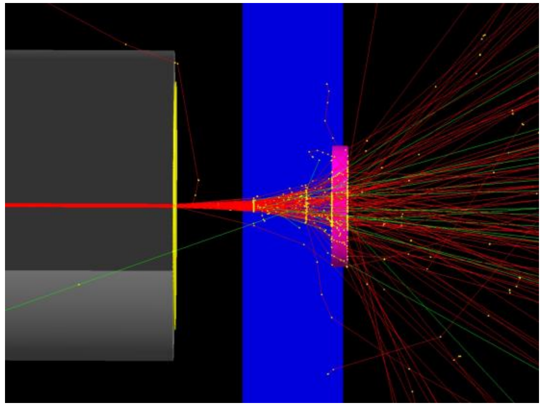
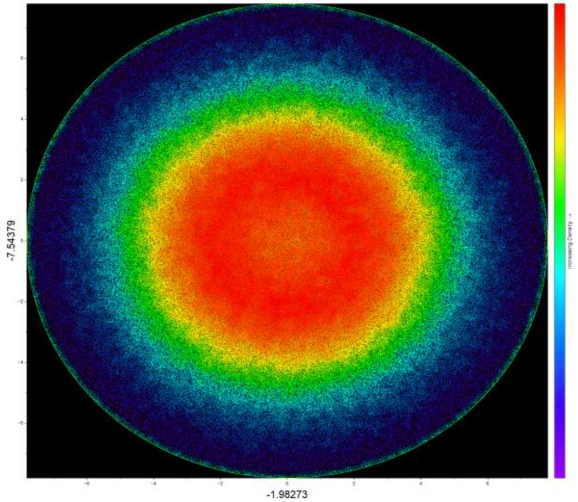
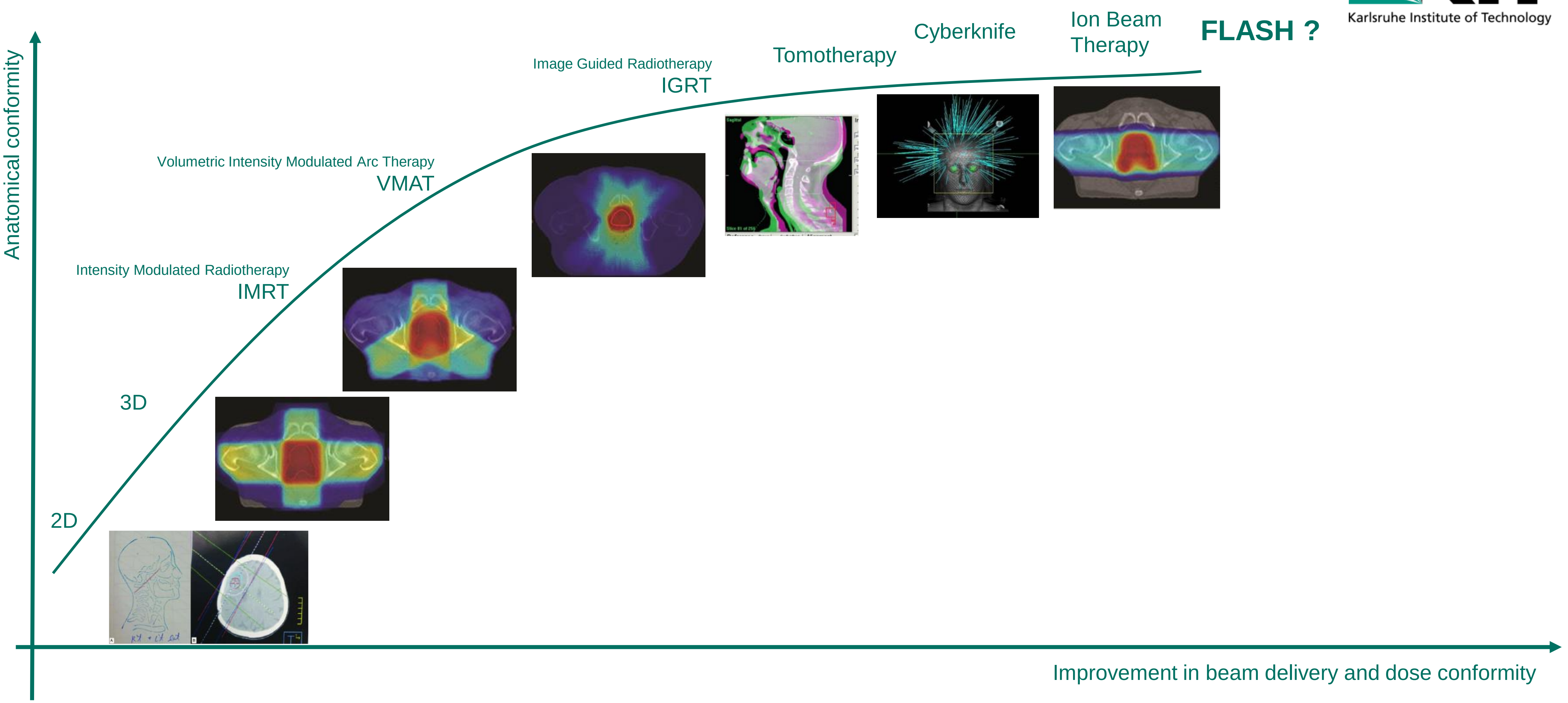


Figure 4.11.: 2D absorbed dose plot (side view) in logarithmic scale assuming rotational symmetry around the z-axis. Accumulated absorbed dose over 1 s, assuming five bunches per second and a bunch charge of 348 pC. Accelerator beam pipe, water phantom, and imitated Roos Chamber are marked separately. No dose deposition takes place inside the beam pipe under vacuum conditions as shown in white.

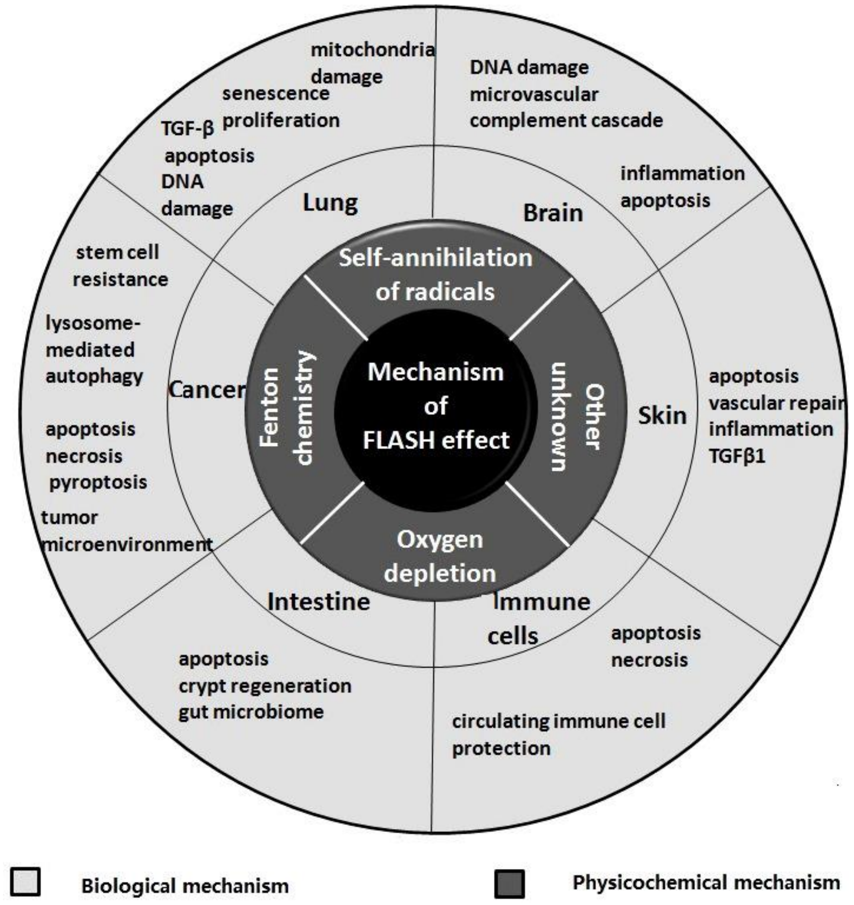






Reprinted from Herrmann, H., Seppenwoolde, Y., Georg, D. *et al.* Image guidance: past and future of radiotherapy. *Radiologie* **59** (Suppl 1), 21–27 (2019).

Possible FLASH Mechanisms



Lin, Binwei et al. "Mechanisms of FLASH effect." *Frontiers in oncology* vol. 12 995612. 23 Sep. 2022, doi:10.3389/fonc.2022.995612