FLASH experiments at the “Dresden platform for high dose rate radiobiology”

Felix Horst, Elke Beyreuther, Jörg Pawelke
Dresden platform for high dose rate radiobiology

Dresden platform provides possibility to perform radiobiological experiments

- Clinical and experimental electron and proton beams
- Huge range of dose rates covering physical, chemical and biological reaction times
- Experience with cell and animal studies at accelerators

Dosimetry for such experiments depends on the individual requirements and beam properties of the different facilities.
University Proton Therapy Dresden

IBA Proteus Plus system:
- isochronous cyclotron
- 230 MeV primary proton energy
- down to 70 MeV from degrader-based energy selection system
- Max. cyclotron current: 500 nA (radiation protection limit)

Experiments in parallel with patient treatment
EMPIR

Experiments performed by UHDpulse partners:
- NPL: graphite calorimetry, ionization chamber dosimetry, CMOS detector tests
- Advacam: dosimetry using pixel sensors

Experiments performed by externals within MRgRT-DOS:
- NPL, PTB: alanine and ionization chamber dosimetry in magnetic fields
University Proton Therapy Dresden: fixed beam line

IBA Proteus Plus system:
- isochronous cyclotron
- 230 MeV primary proton energy
- down to 70 MeV from degrader-based energy selection system
- Max. cyclotron current: 500 nA (radiation protection limit)

In-house developed beam control for static pencil beam delivery

45% transmission at 225 MeV

Segmented ionisation chamber (in-house/PTW)

Transmission

<table>
<thead>
<tr>
<th>Protons/MU</th>
<th>Proton energy / MeV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5E+10</td>
<td>225 MeV</td>
</tr>
<tr>
<td>4E+10</td>
<td></td>
</tr>
<tr>
<td>3E+10</td>
<td></td>
</tr>
<tr>
<td>2E+10</td>
<td></td>
</tr>
<tr>
<td>1E+10</td>
<td></td>
</tr>
</tbody>
</table>

Recombination effects at high beam currents

<table>
<thead>
<tr>
<th>Target beam current / nA</th>
<th>Protons/MU</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>1E+10</td>
</tr>
<tr>
<td>1</td>
<td>2E+10</td>
</tr>
<tr>
<td>10</td>
<td>3E+10</td>
</tr>
<tr>
<td>100</td>
<td>4E+10</td>
</tr>
<tr>
<td>225 MeV</td>
<td>5E+10</td>
</tr>
</tbody>
</table>
Recombination effects in ionization chambers at UHDr

2 mm air gap: 2000 V/cm @ 400 V

1.45 mm radius: 2750 V/cm @ 400 V

max. voltage according to manual: 500 V
University Proton Therapy Dresden: further developments

- Generation of SOBP from single pencil beam
- Proton energy: 225 MeV
- Dose rates in the SOBP up to 700 Gy/s

![3D-printed range modulator](image)

Simeonov et al., Zeitschrift für Med. Phys. 2020

Modulator provided by Uli Weber, GSI
UHDR experiments at HZDR: ELBE and DRACO

**Electron accelerator ELBE**
- 30 MeV electron beams with flexible adjustable pulse structure
- Mean dose rates up to 10,000 Gy/s

**Laser accelerator DRACO**
- High power laser: 20 J in 30 fs
- Mean proton dose rates up to $10^9$ Gy/s
Experimental setup at ELBE

- PMMA scatterer
- ICT
- Transmission IC
- Markus IC
- Sample
  - Eppi with zebrafish embryos
- RCF
- Mirror
- Lanex
- Camera
- Flash
  - 300 µs

- Electron beam
- Be window
- 10 mm = ~11% dose build-up

Beam position changes for different regimes
UHDR experiments at ELBE – Pulse structures

LET independent investigation of beam pulse structure influence at research electron linear accelerator ELBE

Variable pulse time structure and tunable bunch charge over broad range allow to mimic pulse structure of clinical proton accelerators (isochronous and synchrocyclotron)

<table>
<thead>
<tr>
<th>Dose</th>
<th>100 ms</th>
<th>164 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 µs</td>
<td>100 ms</td>
<td>164 ms</td>
</tr>
</tbody>
</table>

**Flash\textsubscript{cyclo}** (290 Gy/s | 10\textsuperscript{6} Gy/s)  
**Flash\textsubscript{synchro}** (177 Gy/s | 10\textsuperscript{9} Gy/s)

**Flash\textsubscript{max}**  
Reference (0.12 Gy/s | 10\textsuperscript{3} Gy/s)  
(10\textsuperscript{5} Gy/s | 10\textsuperscript{9} Gy/s)

Karsch et al.: Radiother Oncol 2022
Zebrafish experiments at ELBE

Model: Wildtype zebrafish embryo, 24 hours old
- Small vertebrate in vivo model for normal tissue response

~ 1mm

4 days

Unirradiated control

Irradiated embryo

Endpoint: radiation induced length reduction

Mean embryo length of controls: 3950 µm

L. Karsch et al. Radiother Oncol 173:49-54 (2022)

Szabo et al. PLoS One 2018;
Beyreuther et al. Radiother Oncol 2019

Mean body length of the embryos / µm

Average dose rate / Gy/s
Zebrafish experiments at ELBE

Model: **Wildtype zebrafish embryo**, 24 hours old
- Small vertebrate *in vivo* model for normal tissue response

~ 1mm

4 days

Unirradiated control

Irradiated embryo

Endpoint: radiation induced length reduction


F. Horst et al, In Regard to Boehlen et al., accepted in IJROBP (2023)
DRACO laser: proof-of-concept animal study

- Pilot campaign with 92 mice prove applicability for preclinical *in vivo* studies, incl. all necessary controls and reference irradiation at clinical proton accelerator

<table>
<thead>
<tr>
<th>UPTD</th>
<th>Draco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy spectrum</td>
<td>Monoenergetic, 70 – 230 MeV</td>
</tr>
<tr>
<td>Pulse frequency</td>
<td>100 MHz</td>
</tr>
<tr>
<td>Dose per pulse</td>
<td>10^-8 Gy</td>
</tr>
<tr>
<td>Pulse dose rate</td>
<td>~ Gy/s</td>
</tr>
</tbody>
</table>


Beyreuther et al. PLoS One 2018
Dresden platform provides possibility to perform high dose rate experiments

- Clinical and experimental electron and proton beams that provide a huge range of dose rates for physical, chemical and biological experiments
- Challenges for dosimetry (small fields, high dose rates): specific solutions realized for several experimental setups
Thanks for your attention!

Related publications

... on dose rate dependence of different dosimeters

Karsch et al.: Z Med Phys 21 (2011) 4
Karsch Med Phys 43 (2016) 6154

... and on dose rate dependence of biological response in vitro

Laschinsky et al.: Radiat Environ Biophys 55 (2016) 381

... and on FLASH effect in-vivo (zebrafish)

Pawelke et al.: Radiother Oncol 158:7-12 (2021)
Kroll et al., Nature Physics 18:316–22 (2022)
Karsch et al.: Radiother Oncol 173:49-54 (2022)
Jansen et al.: Radiother Oncol 175:193-196 (2022)
Horst et al.: accepted in IJROBP (2023)