Progress on the R&D platform FLASH*lab*@PITZ:

→ we aim to provide unique R&D capabilities for studying electron FLASH radiation therapy and radiation biology

for you !

Frank Stephan (frank.stephan@desy.de) for the PITZ team,

Head of the Photo Injector Test facility at DESY in Zeuthen (PITZ)

Faculty Disclosure

I am only employed by DESY, a public research center in Germany, so there are

No Disclosures

Outline of the talk

Extremely flexible & tightly controlled high brightness electron beams for cancer research

Introduction: FLASH RT, DESY + PITZ

Beam parameters details are important

FLASH*lab*@PITZ capabilities

Status of realization:

A) Commissioning of mother beamline → tight control of beam properties

B) Start-up beamline for FLASH*lab*@PITZ → first experiments done

C) Design of full beamline for FLASH*lab*@PITZ

D) Preparing *in vivo* lab

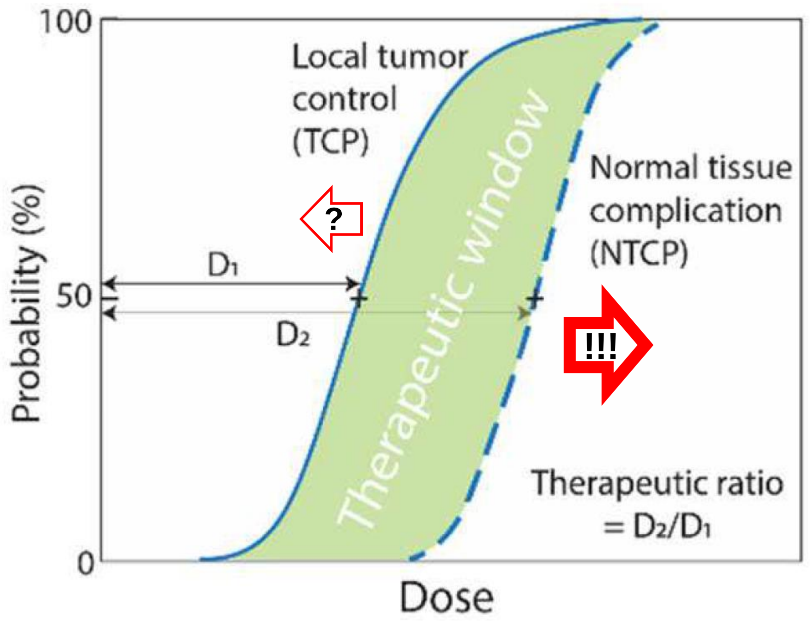
E) Idea to detect tumor location and treat it within 1 ms

Summary: you are invited to come and exploit the unique PITZ beam parameter range

What is FLASH radiation therapy ?

FLASH effect is an experimental observation (Favaudon, 2014), underlying mechanism still under study

- Medical/biological definition of the FLASH effect (**in vivo**):
  - **Sparing of healthy tissue** by radiation with **short, high intensity pulses** (e^-, p, ion, x-ray) while having at least the **same tumor control** as with conventional radiation



Basic sketch from M.R. Ashraf et al., Frontiers in Physics, 2020, doi: 10.3389/fphy.2020.00328

→ **Opening therapeutic window**

→ **Strongly reduce treatment time, simply life for patients**

→ **Treating radiation resistant cancer**

→ **With online imaging (e.g. via XFI): confine dose to moving cancer (e.g. lung)**

DESY

Largest accelerator center in Germany, one lab - two locations: Hamburg + Zeuthen (near Berlin)

(ARES: single e^- bunches, 50Hz, **160 MeV)**

Facts and Figures

- publicly funded national research centre of the Helmholtz Association
- **Employees** at DESY
  - approximately **2700**, including 1180 scientists
- Interdisciplinary research, international cooperation
- Research at DESY in 4 areas:
  - **Accelerators**
  - Photon Science (focus in Hamburg)
  - Particle Physics
  - Astroparticle Physics (focus in Zeuthen)

PITZ

Courtesy of Ulrike Behrens

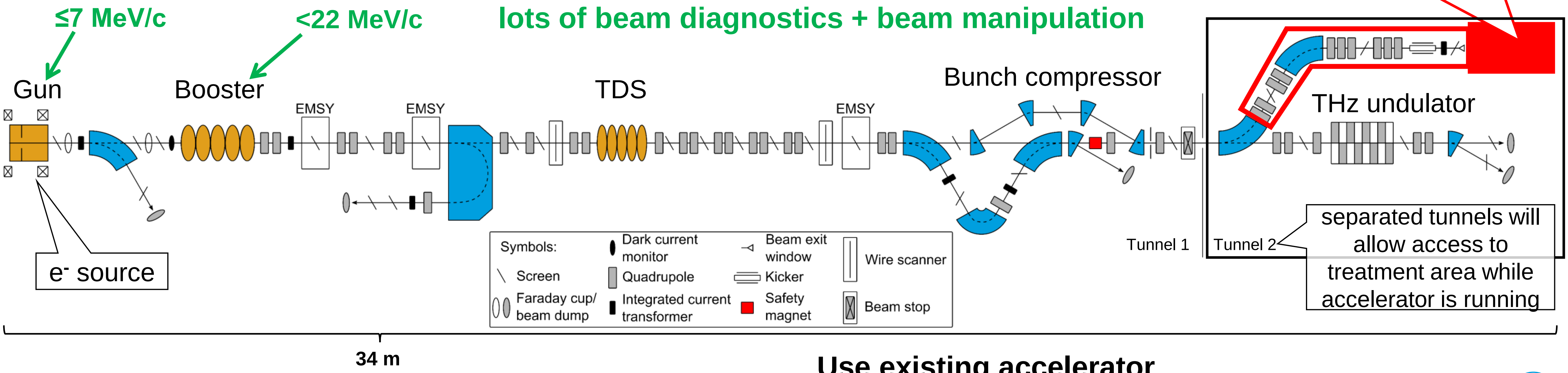
New activity: → FLASH*lab*@PITZ

Where we come from and where we go ?

- The **P**hoto **I**njector **T**est facility at DESY in **Z**euthen (**PITZ**) was+is used to **test** and **optimize** high brightness **electron sources** for Free-Electron-Laser **user facilities** (**FELs**) like the European XFEL in Hamburg

- We also do general accelerator R&D + applications of high brightness beams
  → R&D on electron FLASH radiation therapy (FLASH*lab*@PITZ)

free space for FLASH*lab*@PITZ area:
> 6 x 2 x 3 m³ (l x w x h)



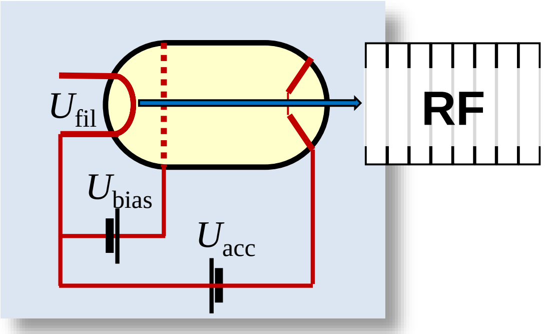
Use existing accelerator
+ own + external resources

Thermionic electron source versus photo injector

e.g. CLARA, CLEAR, PITZ, SRFgun@HZDR

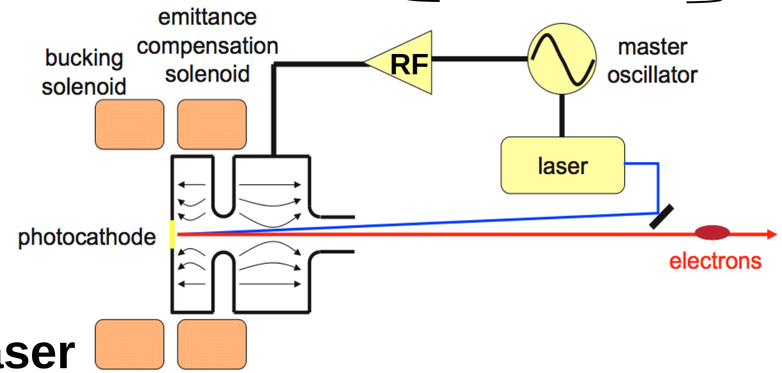
Electron source type has key impact on the achievable beam parameters

Standard:
thermionic electron source



- Heating + **grid** defines **length** of radiation pulse
- **RF frequency** of accelerating cavity defines **micro structure** inside radiation pulse

High brightness photo injector:



- Photocathode **laser** defines **time structure** of electron beam
- Length of **RF** pulse defines **maximum length** of radiation pulse

- **Repetition rate of RF** defines repetition of **radiation pulse + ** total **irradiation time** during session

This results in very different

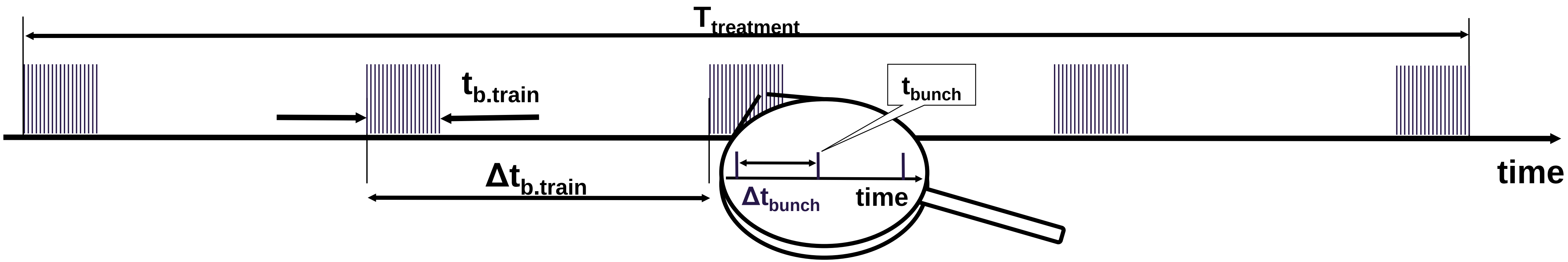
- time structure of radiation pattern
- possibilities to change the time structure flexible

} ➔ experimentally study very different time scales in RT

- bunch charge ➔ instantaneous dose and dose rate
- beam quality ➔ capability to focus beam for mico beam RT + scanning

Definition of relevant beam parameters

Here: concentrate on **timing parameters** for one application period (treatment session / positioning of patient)

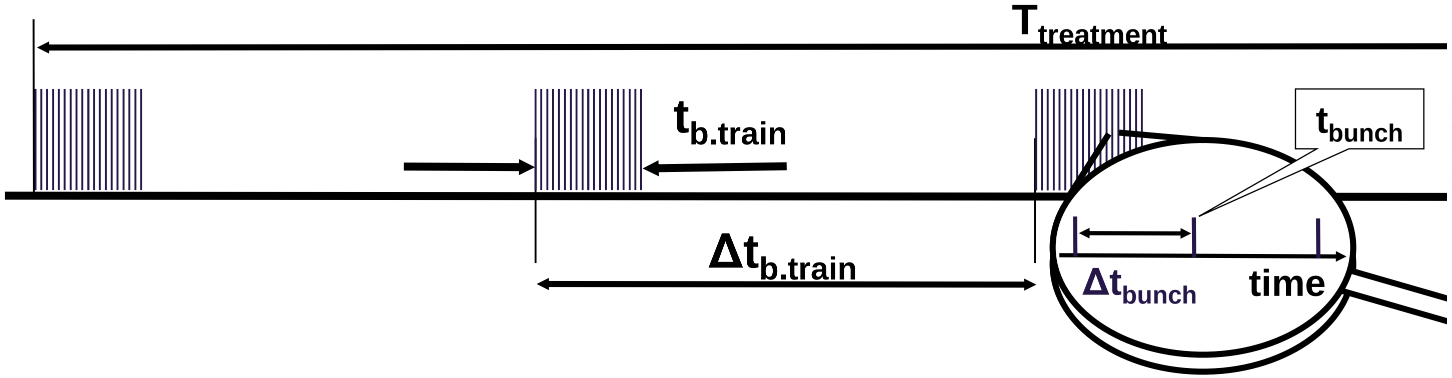


quantity	description	mainly used till now 3 GHz linac, therm. emission	e.g. PITZ 1.3 GHz linac, photo emission
$T_{treatment}$	Time needed for one treatment session	< 200 ms for FLASH	< 1 ms possible
$t_{b.train}$	Length of **bunch train** (in RT commonly called **'pulse'**)	e.g. 0.5 – 4 **µ**s	0 – 1 **m**s
$\#_{bunch}$	Number of bunches in bunch train	e.g. 1500 – 12000	**1** – 4500
$\Delta t_{b.train}$	Separation of 2 neighboring bunch trains	e.g. 0.003 – **0.1 s**	**0.1** – 1 **s**
Δt_{bunch}	Separation of 2 neighboring bunches	0.3 **n**s	0.2 – 10 **µ**s
t_{bunch}	Length of individual electron bunch, FWHM	e.g. ~30 **ps**	**0.1** – 60 **ps**
q_{bunch}	Charge per bunch = average current in train * $t_{b.train}$ / $\#_{bunch}$	e.g. 0.1 – 100 pC	0.1 **– 5000** pC

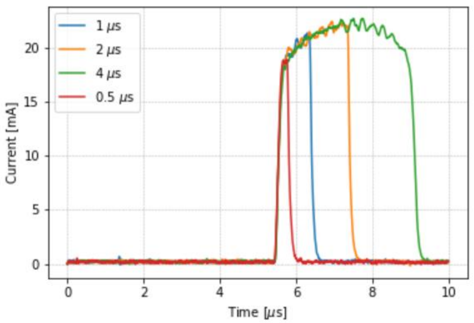
Definition of relevant beam parameters

General: characterize beams used as precise as possible !!!

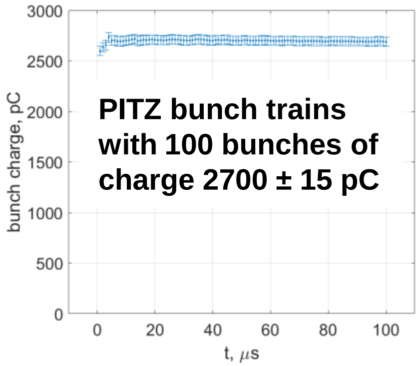
Here: concentrate on timing parameters for one application period



Examples for bunch trains ('pulses'):



C. Bailat, private communication derived from R. Oesterle at al, DOI: 10.1002/acm2.13433



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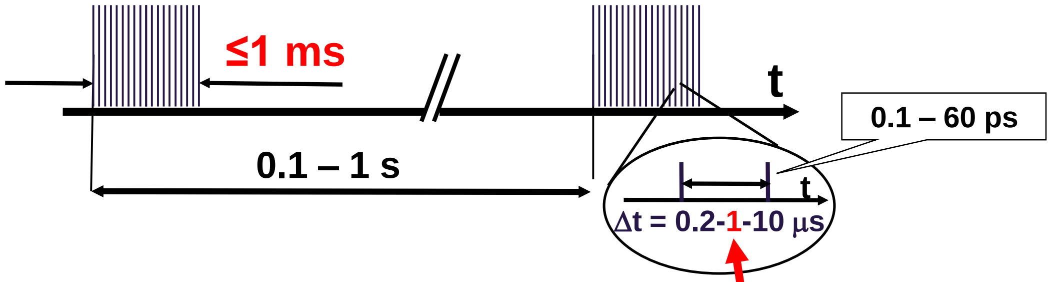
Unique beam properties at PITZ

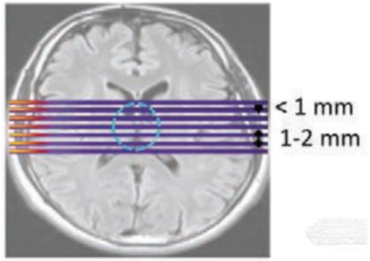
allow extremely flexible treatment parameters and dose distribution (in space + time)

- Possibility of **bunch trains** with **up to 1 ms** length:
  - Bunch repetition rate within train 0.1 – **1 MHz** (opt. 4.5 MHz)



- **Kicker** can be used to distribute the bunches of the bunch train (1ms) over treatment area
  ➔ **"painting" tumor** with mini beams **within 1 ms**
  ➔ **~no organ motion**
  - Kicker system is already existing

  → **possibility of spatially fractionated radiation therapy (SFRT)**



Courtesy of Angeles Faus-Golfe

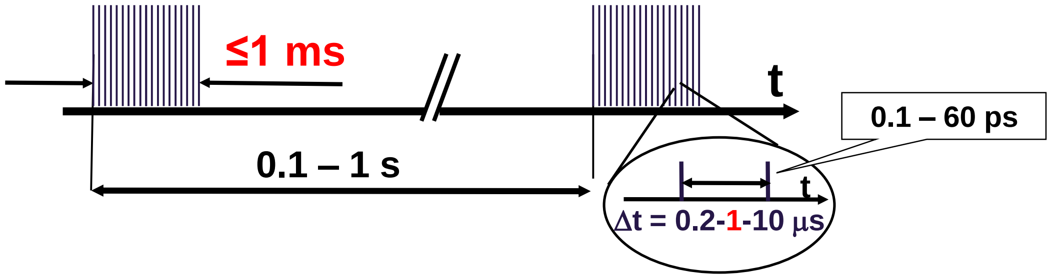
This is **not** science fiction !

Similar kicker system is in every day operation at European XFEL !!!

Unique beam properties at PITZ

allow extremely flexible treatment parameters and dose distribution (in space + time)

- Possibility of **bunch trains** with **up to 1 ms** length:
  - Bunch repetition rate within train 0.1 – 1 MHz (opt. 4.5 MHz)
  - Trains can be repeated with up to 10 Hz
  - ➔ **1 – 1000 bunches in 1 ms (opt. up to 4500)**
  - ➔ 1 – 10 000 bunches in 1 s (opt. up to 45 000)
  - Depending on **bunch charge (fC – 5nC)** indiv. bunches have
    a) **length** of **~0.1 – 60 ps** (bunch compressor)
    b) **spot size** down to **~100µm**



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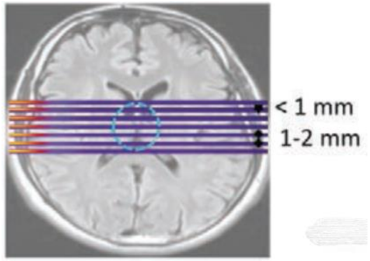


Courtesy of Angeles Faus-Golfe

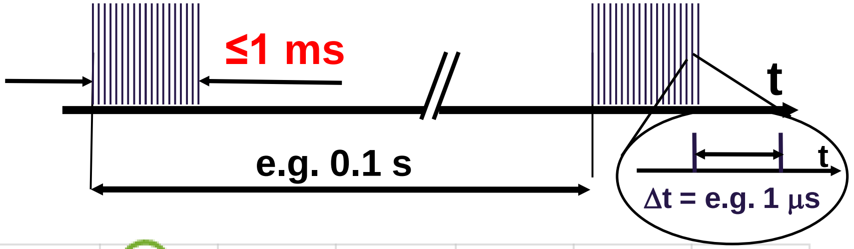
Two examples:

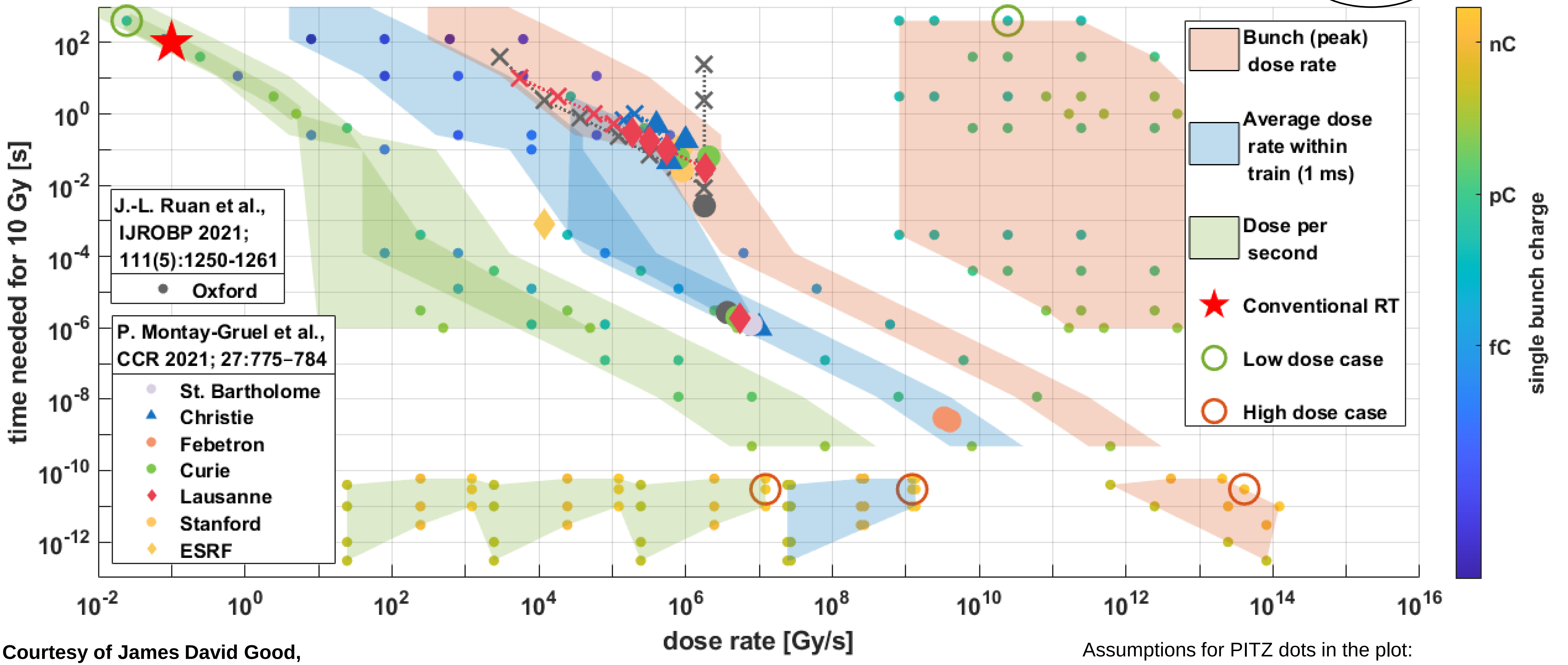
Options @PITZ:	low dose case	high dose case
Bunch charge	**0.1 pC**	**5 000 pC**
Single bunch OR train	**single bunch**	**1ms train** (1MHz)
RF pulse rep. rate	1 Hz	10 Hz
Bunch length	<1 ps	~30 ps
Dose **per bunch**	**0.02 Gy**	**1000 Gy**
Dose rate **per bunch**	**$2\bullet10^{10}$ Gy/s**	**$4\bullet10^{13}$ Gy/s**
Dose **per train(ms)**	0.02 Gy	**$1\bullet10^{6}$ Gy**
Dose rate **per train(ms)**	20 Gy/s	$1\bullet10^{9}$ Gy/s
Dose **per second**	0.02 Gy/s	$1\bullet10^{7}$ Gy/s

Assumptions for table:
~20 MeV e-beam in water with **1mm³** irradiation volume.

Parameter space available at PITZ

In comparison with the state-of-the-art up to now



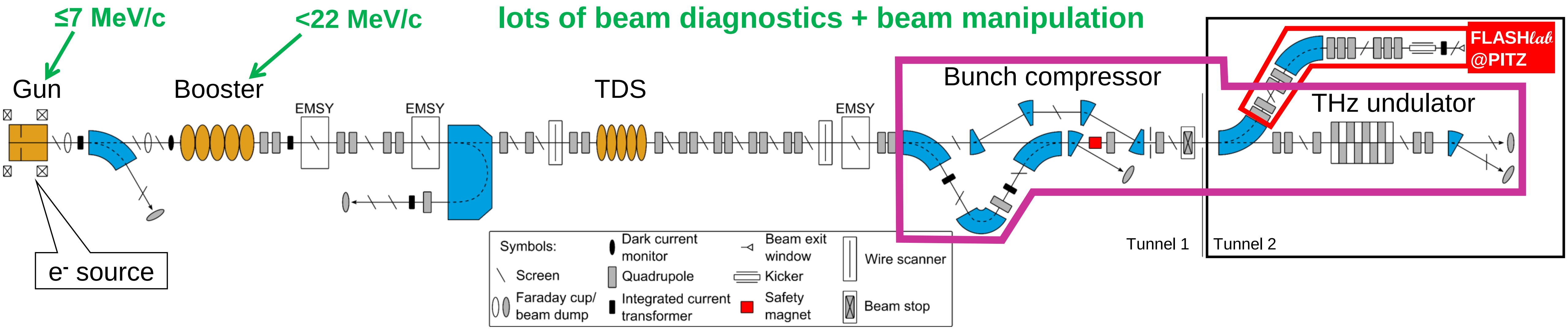


Courtesy of James David Good, Marie-Catherine Vozenin, Jean-Francois Germond

Assumptions for PITZ dots in the plot: ~20 MeV electron beam in water with **1mm³** irradiation volume.

Status of realizing FLASH*lab*@PITZ

A) Commissioning of mother beamline: lasing at THz SASE FEL, → tight control of beam properties



Mother beamline → THz SASE FEL:

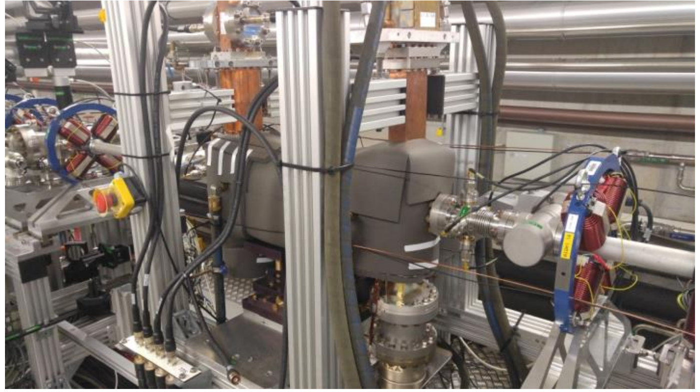
- Mother beamline for FLASH*lab*@PITZ → **17m new beamline were built** + commissioned → **lasing**
- Uses bunch charges up to 4 nC + bunch trains
- Needs tight control of beam properties
- Needs high reproducibility

FLASH*lab*@PITZ uses strong synergy

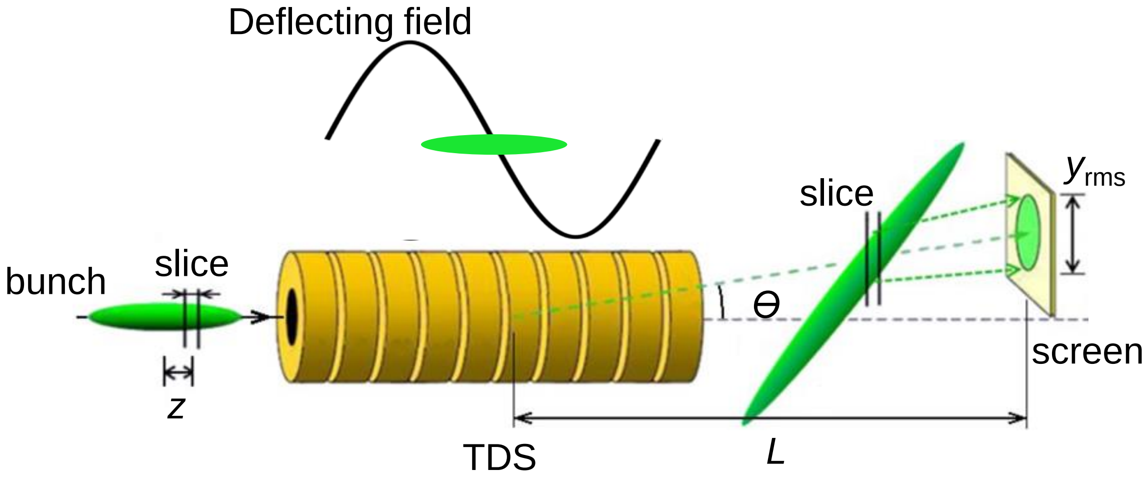
→ Beam properties measurements:
bunch length, bunch charge,
transverse beam distribution, beam position

Bunch length measurement

Using transverse deflecting structure (TDS) to reach <ps time resolution



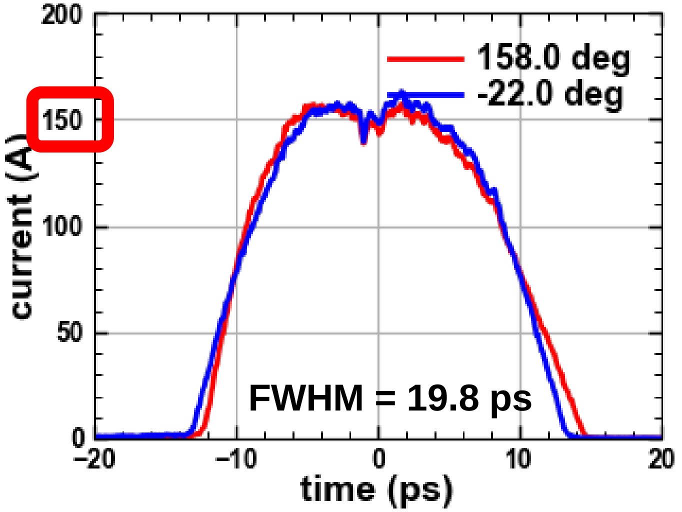
- **Measuring principle:**



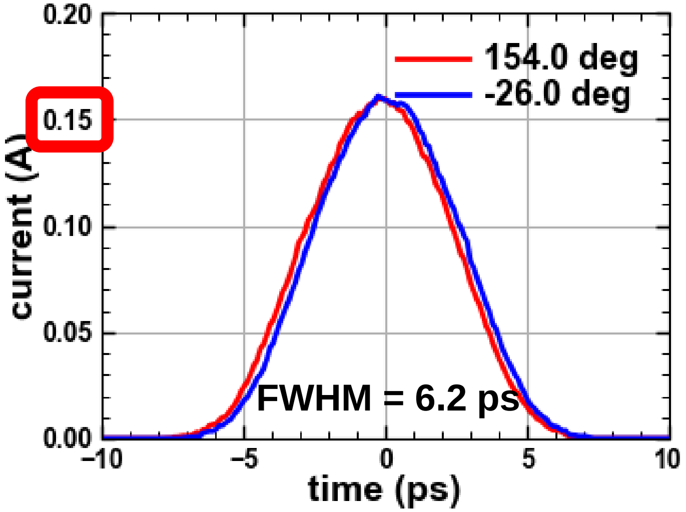
D. Malyutin, Ph.D. thesis, Universität Hamburg, (2014)

- **Measurement results:**

a) 3 nC



b) 1 pC



⇨ **Peak dose distribution !**

Courtesy of Raffael Nienczyk, Xiangkun Li

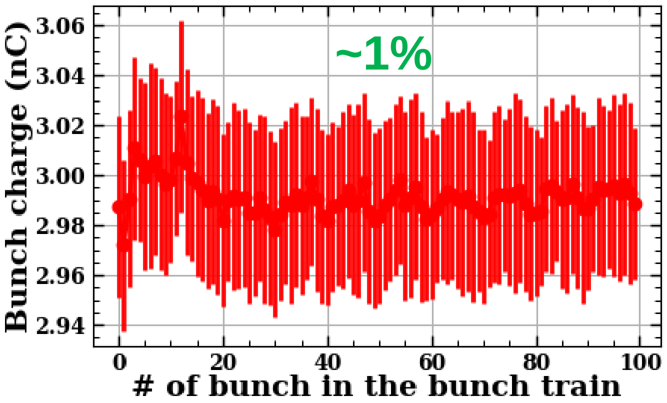
Typical beam properties from current PITZ beamline

	Charge along bunch train	Beam distributions for different focusing conditions	Beam position stability along bunch train
3nC	see below	see below	see below
≤1pC	see below	see below	see below

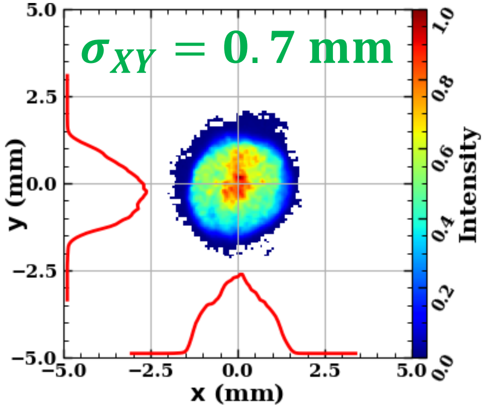
3nC

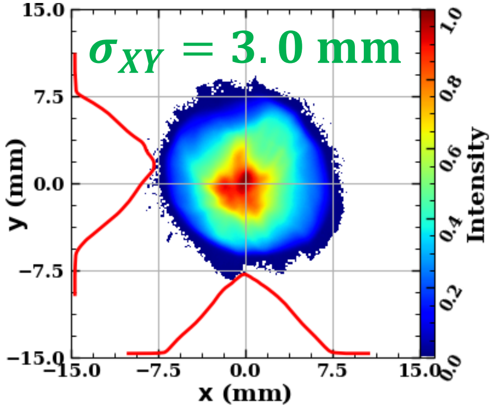
Charge along bunch train

ICT measurement

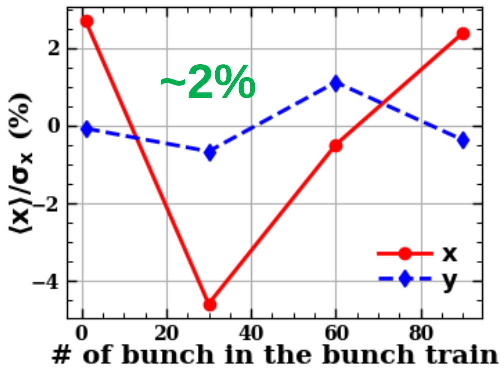


Beam distributions for different focusing conditions





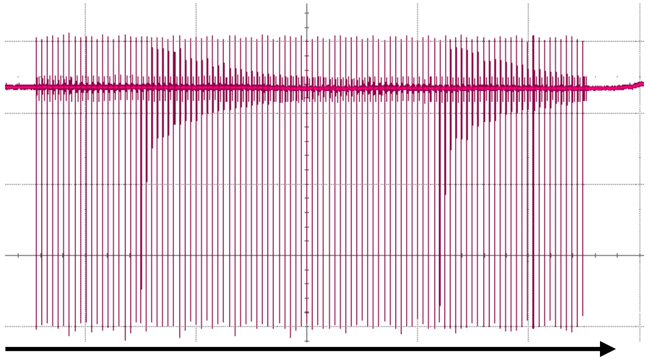
Beam position stability along bunch train



≤1pC

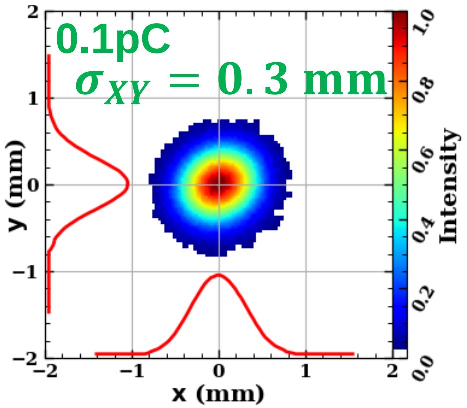
Charge along bunch train

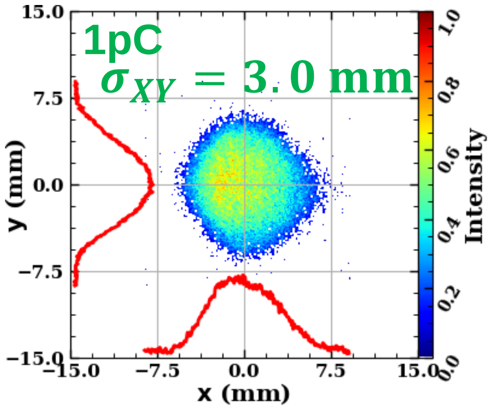
Scope signal Faraday cup for 1 pC



100 bunches in the bunch train

Beam distributions for different focusing conditions





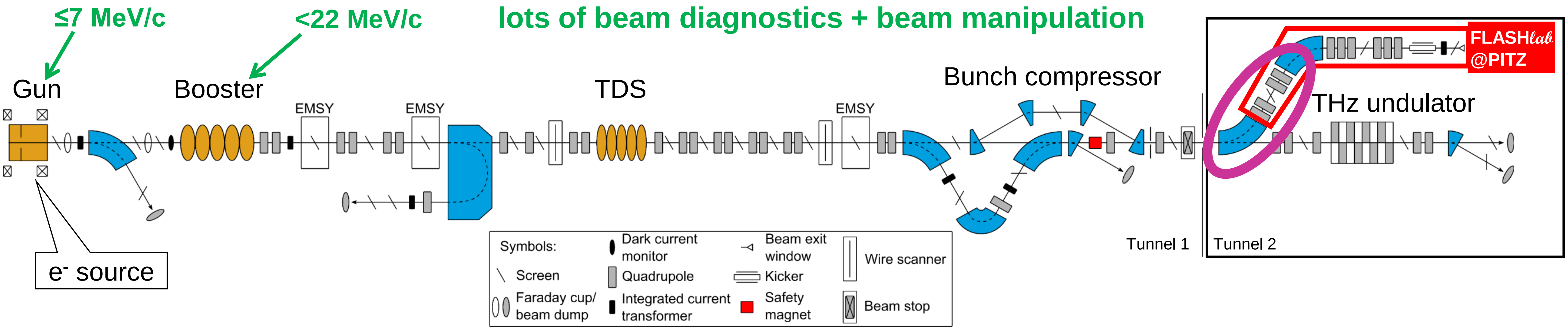
Beam position stability along bunch train

smaller + bigger beam sizes are reachable

Courtesy of Xiangkun Li

Status of realizing FLASHlab@PITZ

B) Start-up beamline for FLASHlab@PITZ → first experiments are done

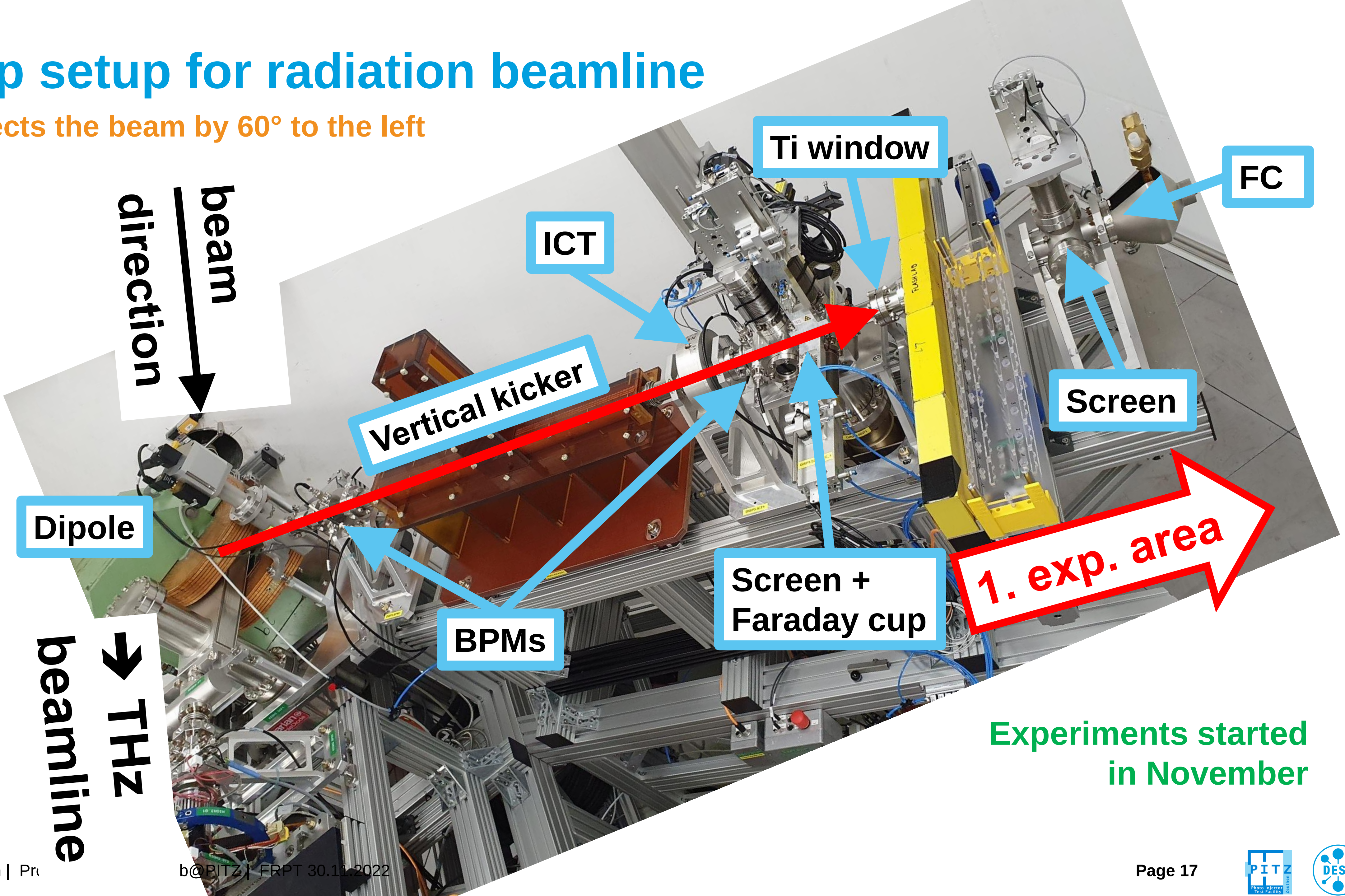


Start-up beamline for FLASHlab@PITZ:

- Allows early experiments on FLASH RT R&D
  - Beam characterization
  - Dosimetry
  - First experiments with chemical, biochemical and biological samples
- Dispersion limits minimum horizontal beam size, only vertical kicker installed

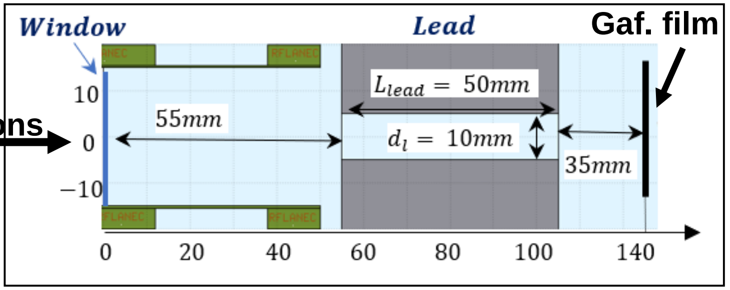
Start-up setup for radiation beamline

Dipole deflects the beam by 60° to the left



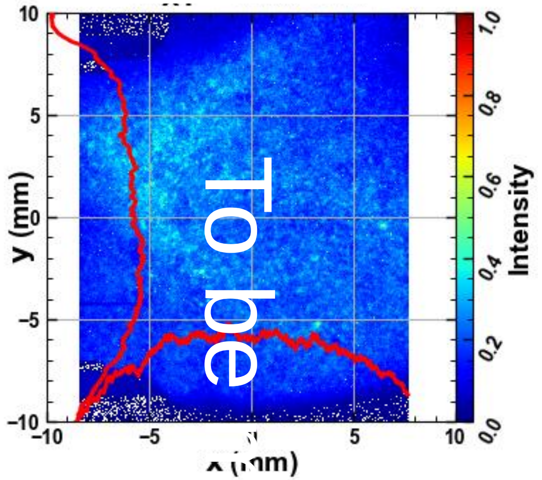
Experiments started in November

Electron beam and dose distributions

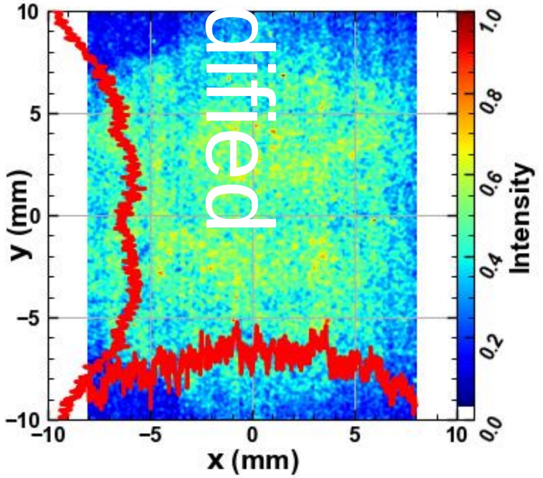


Beam measurements:

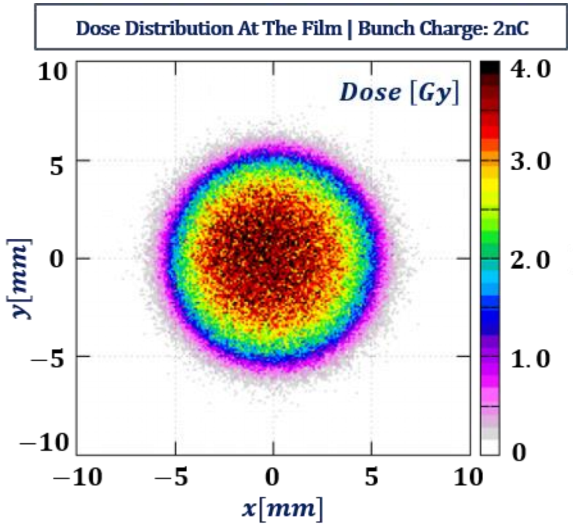
2 nC, $\sigma_{XY} = 4.7$ mm

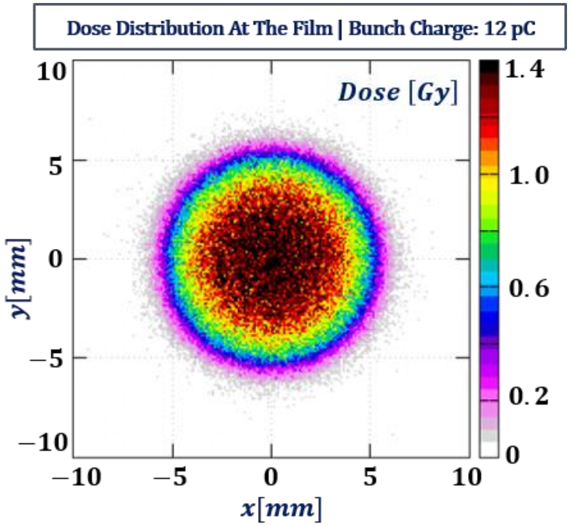


10 pC, $\sigma_{XY} = 4.9$ mm

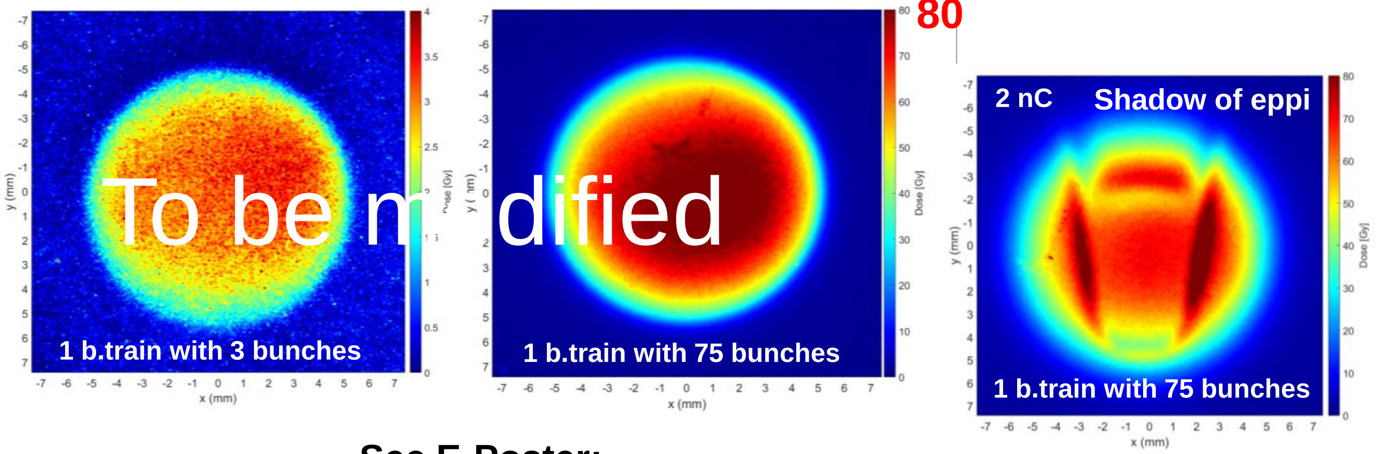


Dose simulations:

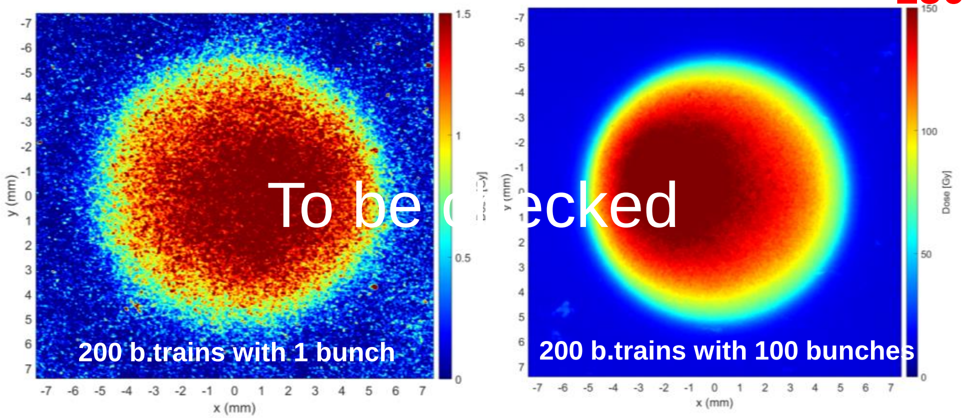




Dose measurements:



See E-Poster:
"First dosimetry tests at PITZ" by Felix Riemer

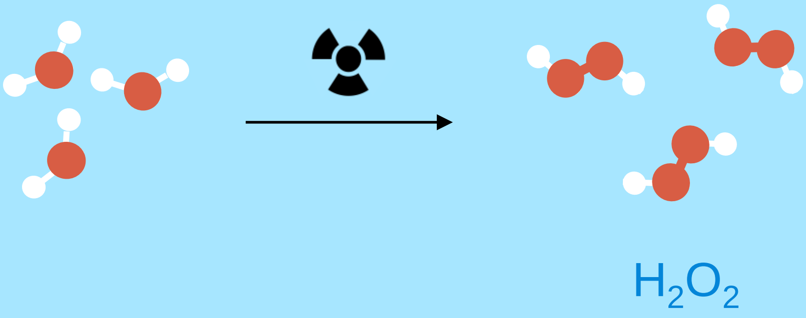


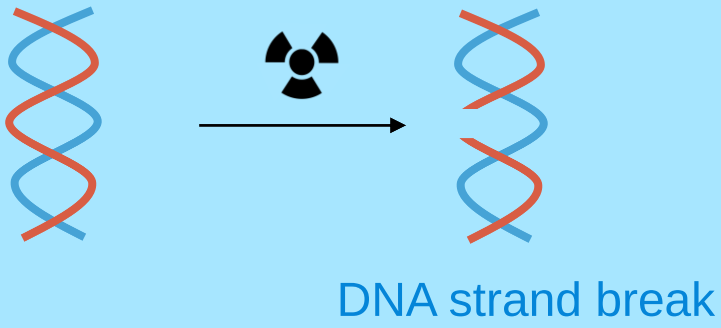
Courtesy of Xiangkun Li, Zohrab Amirkhanyan, Felix Riemer

First chemical / biochemical experiments at FLASHlab@PITZ

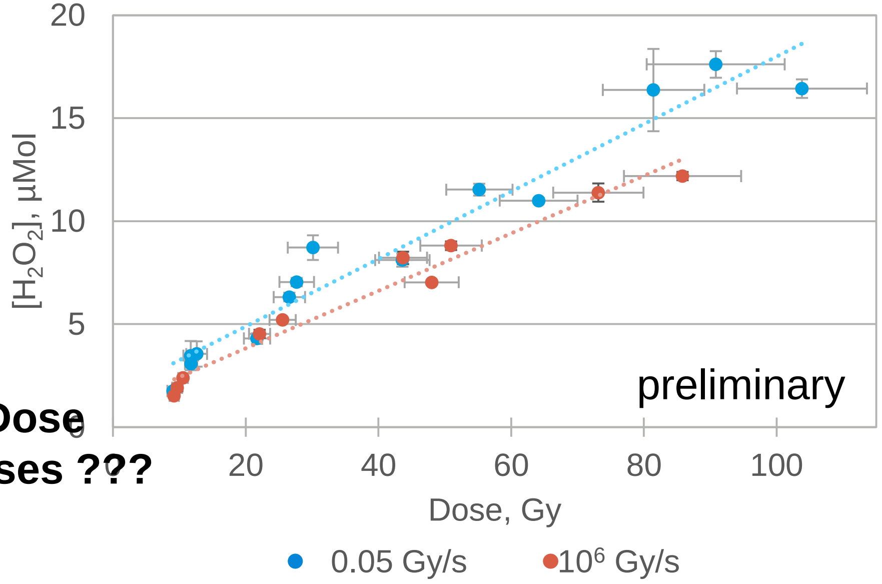
First proof-of-concept for doing chemical and biological research at PITZ

in water



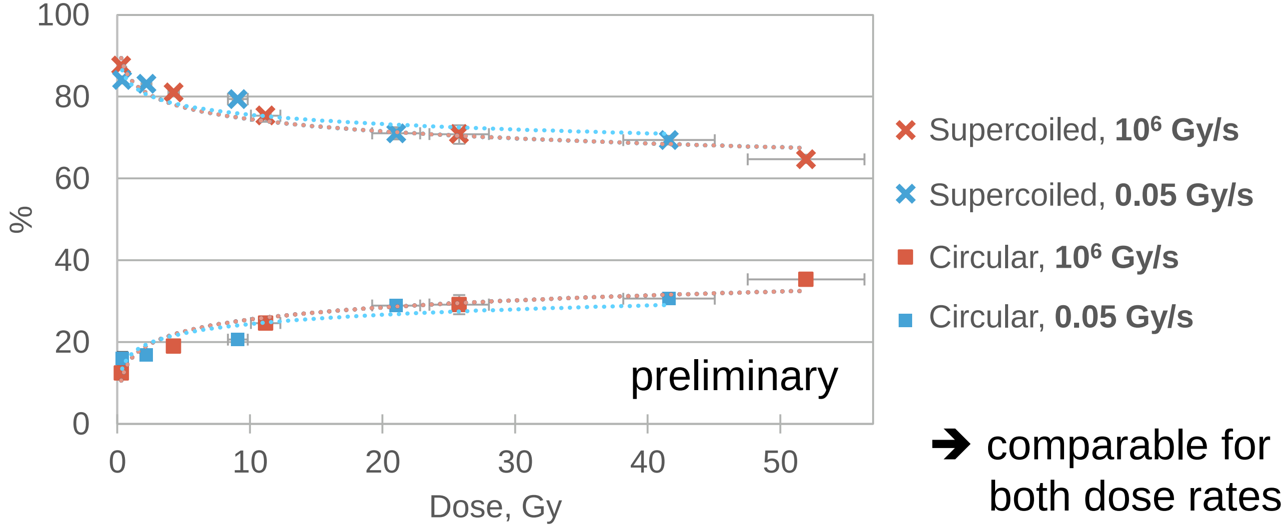


H_2O_2 generation



0 Dose cases ???

DNA plasmid conformation

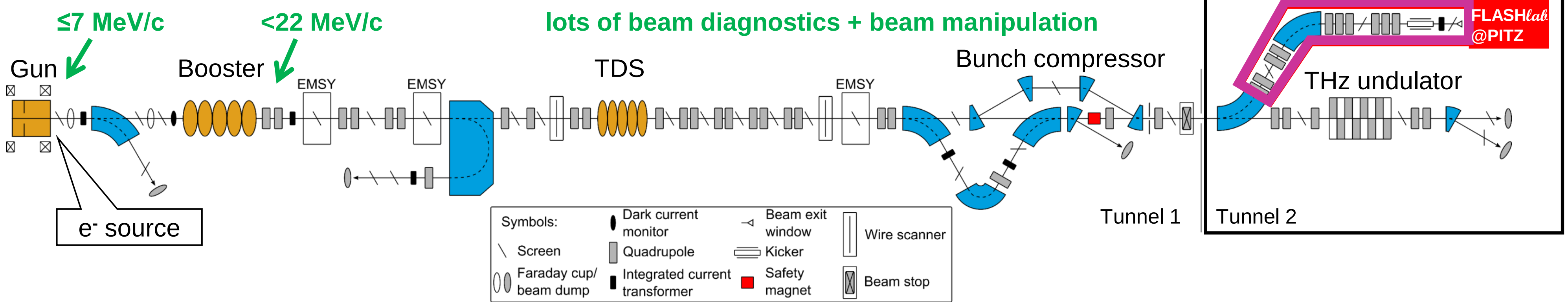


➔ comparable for both dose rates

Status of realizing FLASHlab@PITZ

Courtesy of Xiangkun Li

C) Design update of full beamline FLASHlab@PITZ + laser system upgrade

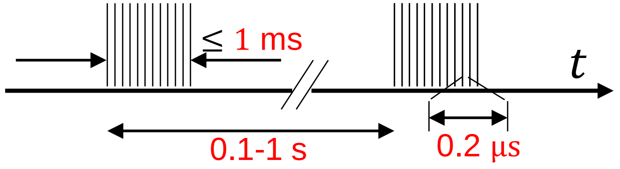


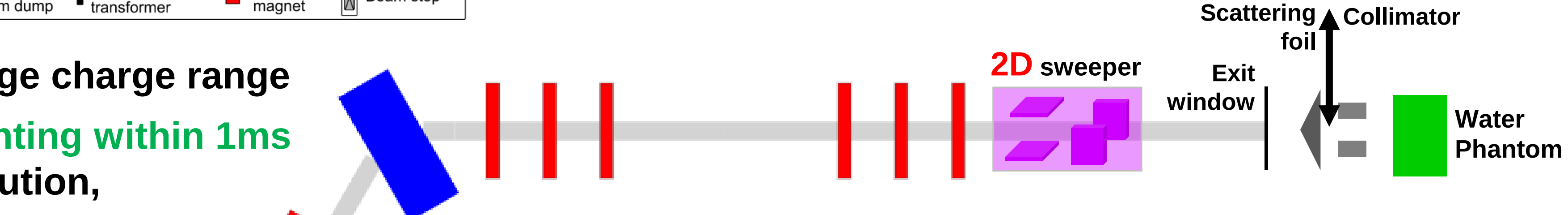
- **new** photo cathode **laser system** to be installed in **2023**

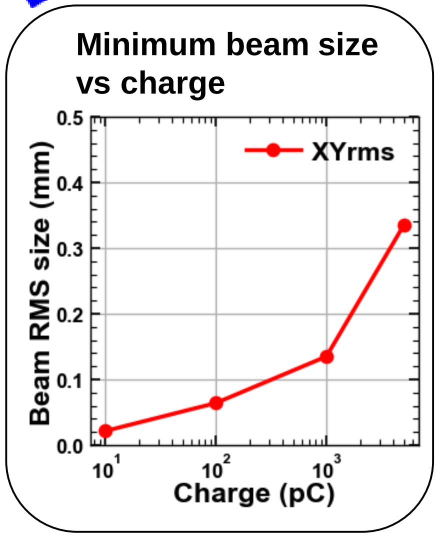
→ **even tighter beam control**
+ higher flexibility

- **Tiny beam size** reachable in **huge charge range**
- **Sweeper system** allows **2D painting within 1ms**
  ➔ **arbitrary transverse distribution,**
  no loss from flattening
- **Scattering system** allows generation of **symmetric beam of several cm width**, ~50 % loss due to flattening

Electron beam from PITZ injector

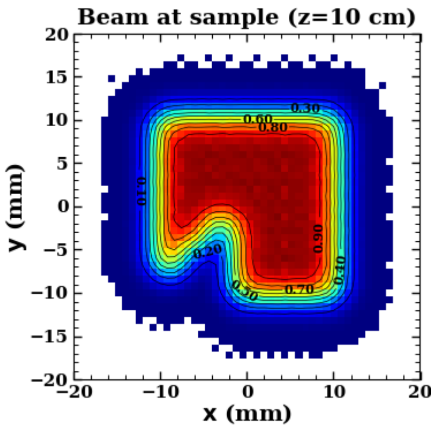




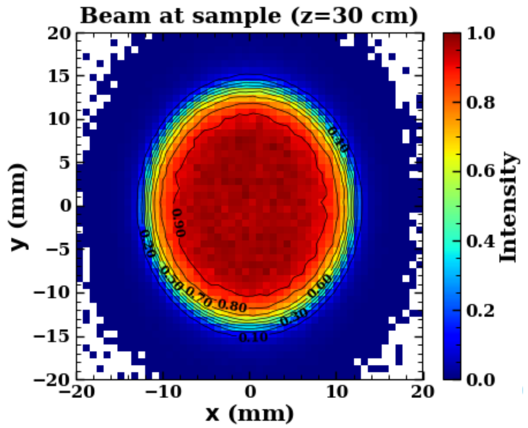


Example beams (the beam field size is easy scalable):

a) From 2D sweeper



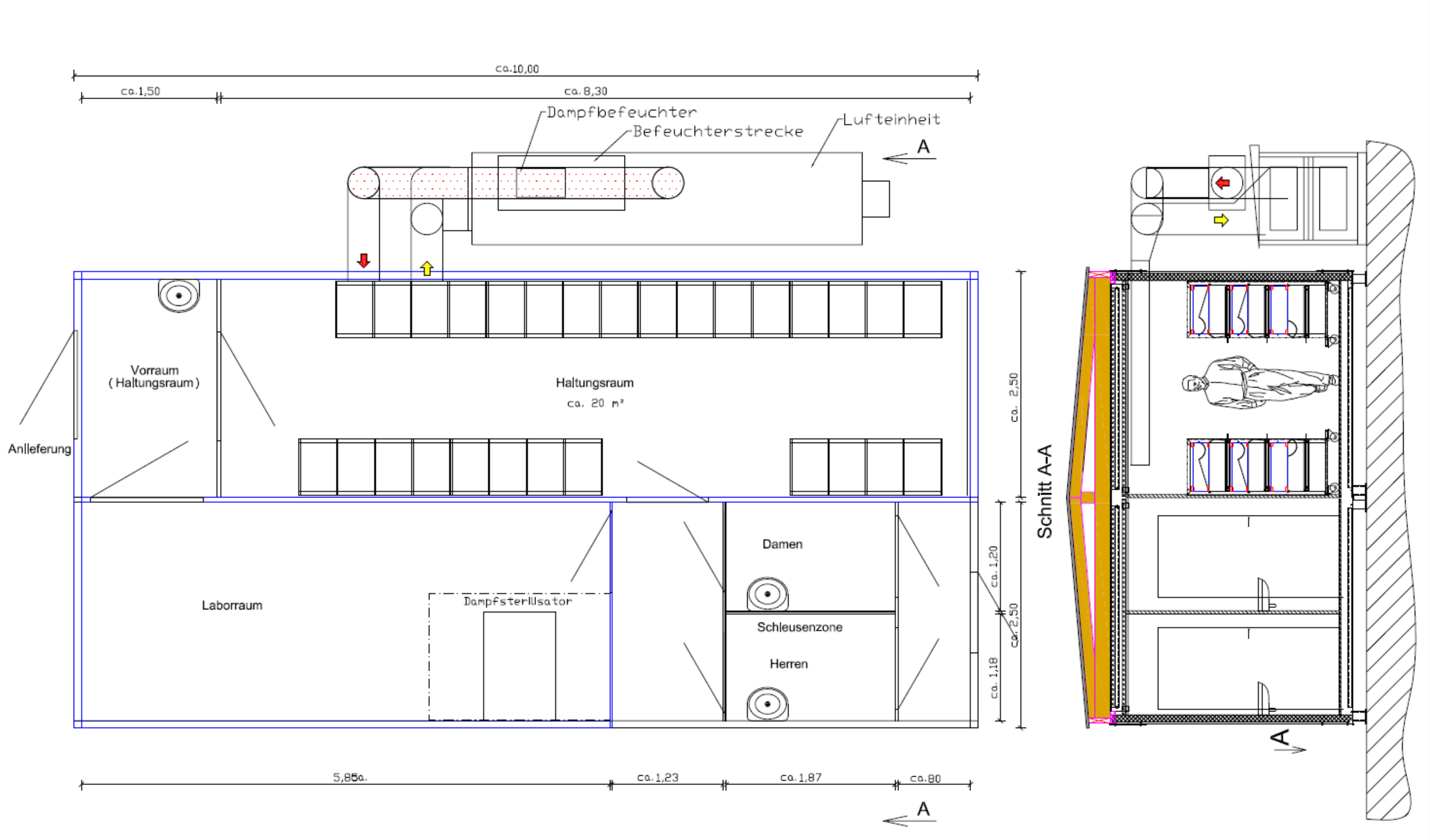
b) from scattering foil



Status of realizing FLASH*lab*@PITZ

Courtesy of Michael Köpke

D) Preparing an *in vivo* laboratory for animal experiments at PITZ



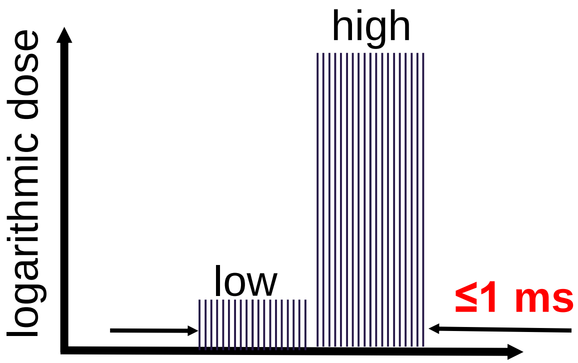
- A **container solution** is the **quickest way** of allowing **in vivo experiments** at PITZ
- Money was allocated
- In contact with building companies
- Operation of *in vivo* lab planned in close collaboration with MDC, TH Wildau and local partners

Status of realizing FLASHlab@PITZ

Courtesy of Florian Grüner, Theresa Staufer

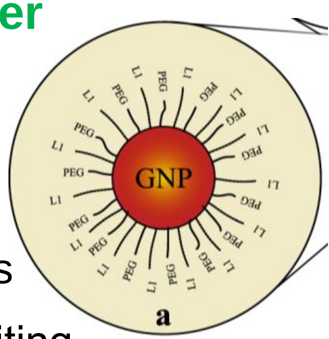
Universität Hamburg
DER FORSCHUNG | DER LEHRE | DER BILDUNG

E) Idea to detect tumor location and treat it within 1 ms → tightly confine dose to moving cancer

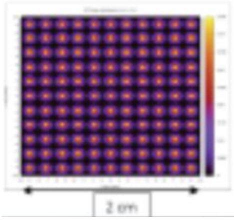


Principle:

- **detect tumor location by X-ray fluorescence imaging (XFI):**
  - gold nanoparticles (GNPs) are accumulated in tumor by tumor markers
  - **Pencil electron** beam **scans** object and creates „**X-ray echos**" by exciting fluorescence of these **labels**



F. Grüner et al., Sci. Rep. **8**, 16561 (**2018**)

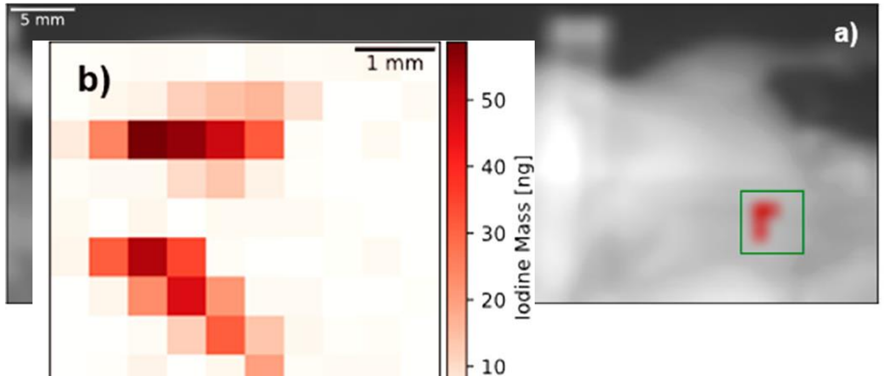


Realization: use bunch train

- first part (**low dose**) → scan narrow pencil beams over sample by x-y kicker
  → Check **XFI signal** for each **kicker setting**: yes = tumor, no = no tumor
- second part (**high dose**) → send it exactly to those kicker settings where XFI signal was found during scanning in first step → **kill tumor**
- should be possible within 1 ms → ~no organ motion at this time scale

→ tightly confine dose to moving cancer (e.g. in the lung)

Example of non-invasive, high sensitive and quantitative analysis:
measurement of natural iodine concentration in the thyroid of a mouse via XFI



→ try @PITZ

C. Sanchez-Cano et al., *ACS Nano* **2021**, 15, 3754−3807
C. Körnig et al., *Scientific Reports* 12, 2903, **2022**

Current cooperation partners of FLASH*lab*@PITZ :

HZDR
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

dkfz.

IJCLab
Irène Joliot-Curie
Laboratoire de Physique des 2 Infinis

Universität der Bundeswehr München

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

UHH
Universität Hamburg
DER FORSCHUNG | DER LEHRE | DER BILDUNG

CHUV
Lausanne

MANCHESTER 1824
The University of Manchester

PTB
Physikalisch-Technische Bundesanstalt
Braunschweig und Berlin
+ UHDpulse

DESY.

TH WILDAU

UKRI Science and Technology Facilities Council
ASTeC

ICR The Institute of Cancer Research

FLASH RT

VHEE RT

rad. biology

TOPAS / NAPTA:
LBNL, UCSF, LLU

CANDLE
Yerevan

Work strongly supported by DESY directorate

With FLASH*lab*@PITZ we …

offer

- worldwide uniquely wide **parameter space** to study FLASH radiation therapy
- extremely flexible **pulse structure** of the radiation (ps → µs → ms → s, min) ➔ to be chosen by user
- tight **control** and high **stability** of radiation (feedback algorithms)
- **access** for all scientifically interested groups

aim to (together with cooperation partners)

- systematically study under which **conditions** the **FLASH effect** is present
- understand the **mechanism** of the **FLASH effect**
- push the R&D on FLASH radiation therapy on the **next level**
- **finally find the optimum treatment conditions for curing different types of tumor**

Summary

FLASH*lab*@PITZ with unique parameter range under commissioning and will be extended further

- Currently **collecting interests from FLASH RT community** about doing experiments or model tests at PITZ
  - to check that we are on the right path
  - to align research capabilities to the interests of the FLASH RT community

➔ If you are interested to exploit the unique beam parameter range by doing experiments or model testing (theory/simulations) at FLASH*lab*@PITZ and have not been contacted yet

➔ send email to frank.stephan@desy.de

➔ I send you short description of capabilities at FLASH*lab*@PITZ and questions for feedback

➔ **Deadline** for feedback **15.12.2022**

Thank you for your attention