J. Bundesmann, A. Denker, T. Damerow, A. Dittwald, T. Fanselow, D. Hildebrand, I. Ja, I. Kailouh, M. Kang, G. Kourkafas, S. Ozierenski, R. Pena Freitas Mendes, J. Röhrich, C. Zimmer

HZB Helmholtz Zentrum Berlin

D. Cordini, J. Heufelder, S. Seidel, R. Stark, A. Weber

CHARITÉ

A. Akin

BHT Berliner Hochschule für Technik

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Universität der Bundeswehr München

Operation of the HZB Cyclotron

Medical Application and its Challenges

Experimental Mode and Special Features

Extension Plans

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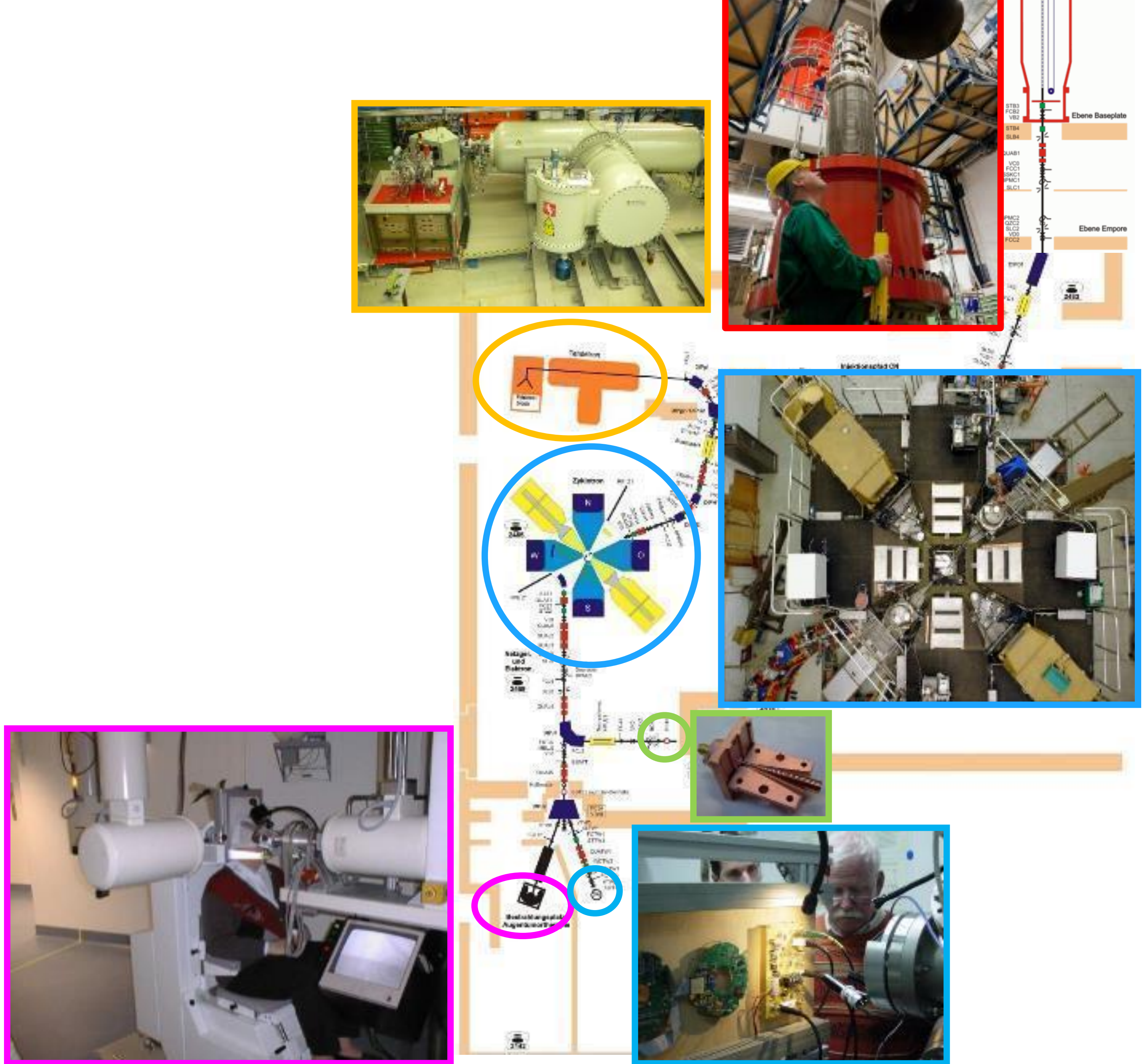
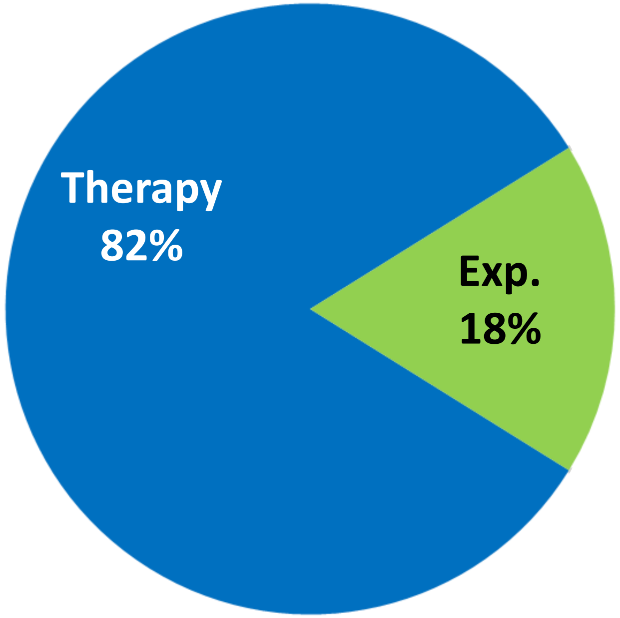
Layout of the accelerator complex

- k = 130 isochronous sector cyclotron
  10 – 20 MHz
- two injectors:
  - 2 MV Tandetron™
  - 6 MV Van-de-Graaff,
    backup, time structures
- three target stations:
  - treatment room
  - experimental station
  - beam line end for tests in
    cyclotron vault



Beam Time Distribution

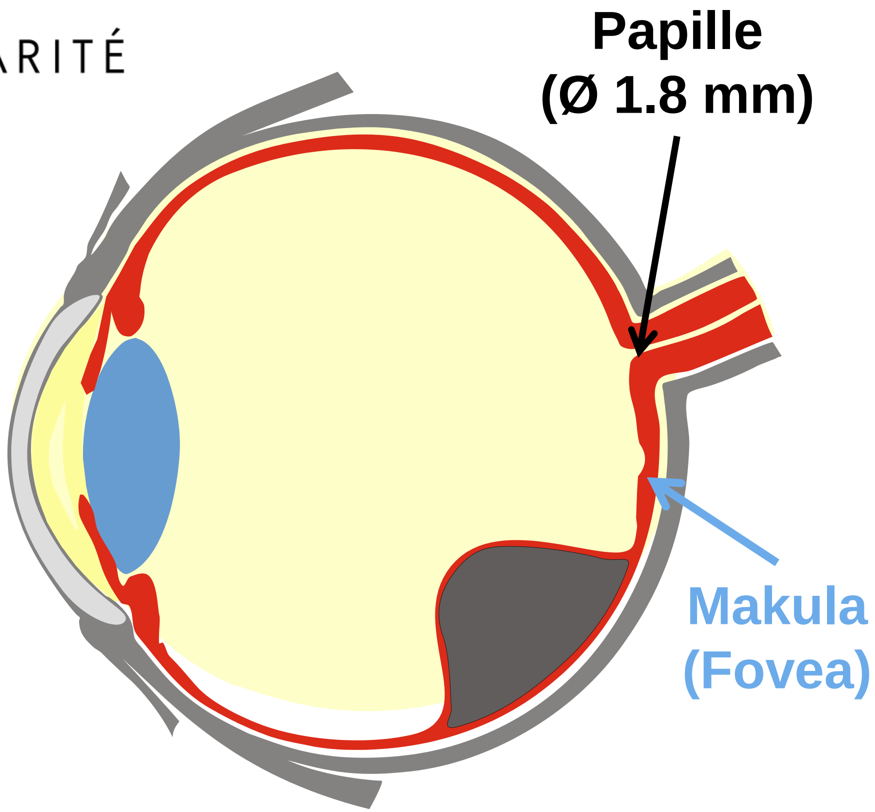
- **main user:**
  Charité – Universitätsmedizin Berlin for proton therapy of ocular melanoma

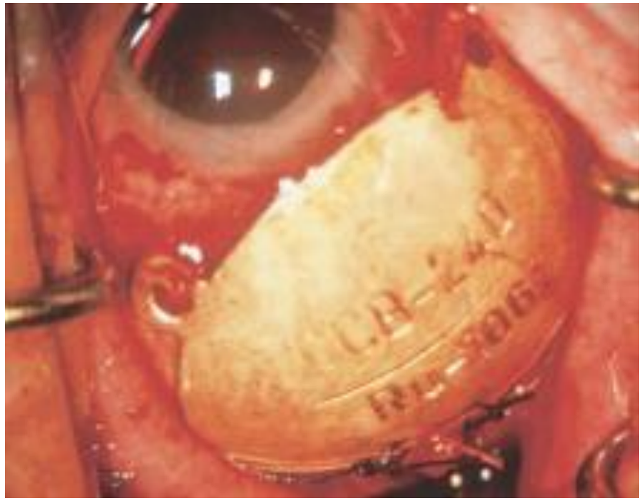


Ocular Melanoma

Treatment Possibilities:

- enucleation (removal of the eye)
  if tumour is too large
- irradiation with radioactive plaques
  (small tumours, away from critical structures)
- stereotactic irradiation (e.g. Cyberknife)
  high radiation level for eye, macula,
  and optic nerve
- proton therapy





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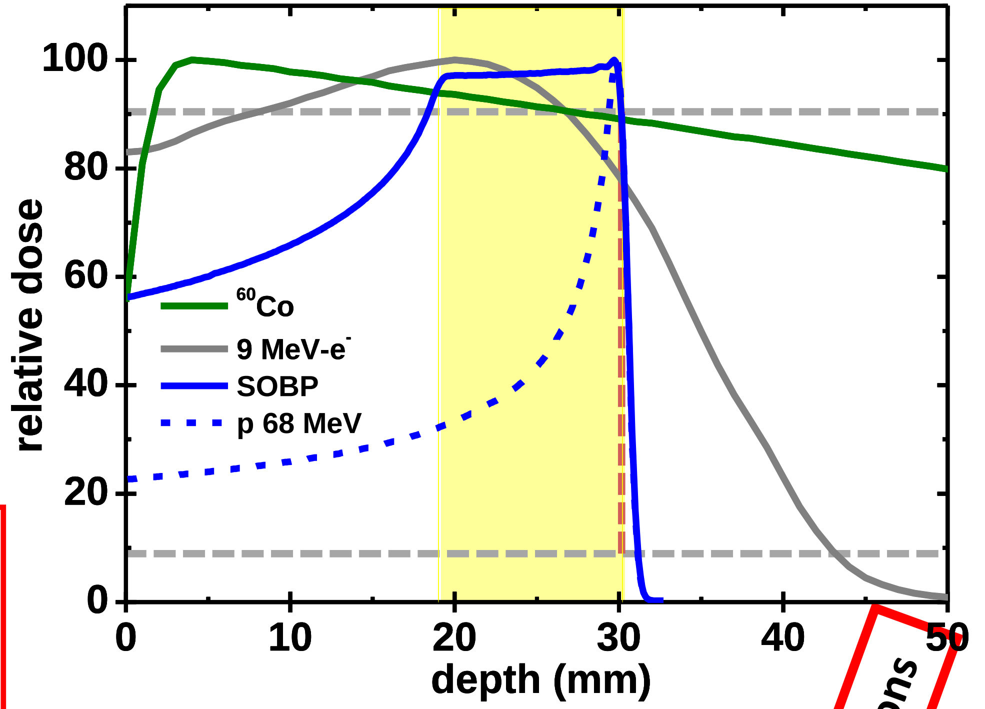
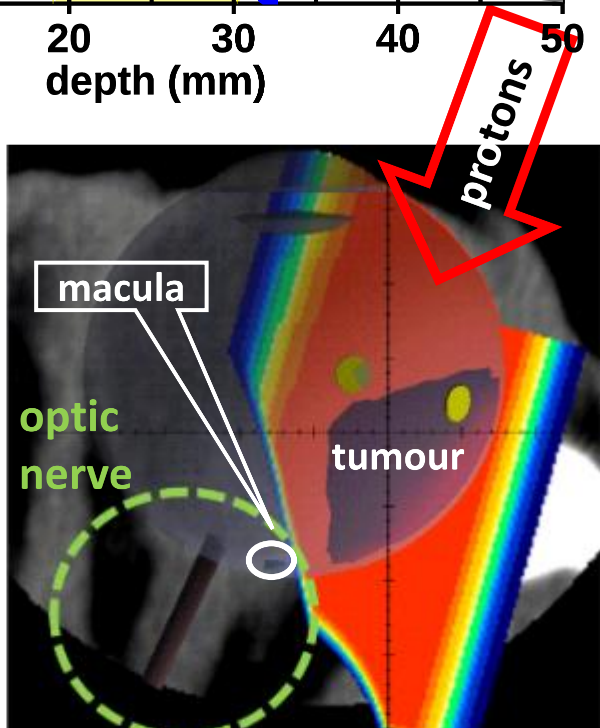
Proton Therapy of Ocular Melanoma

- **photons:**
  increase of dose after skin due to build-up effect
  exponential reduction after maximum (infinite range)
- **electrons:**
  build-up of dose due to secondary electrons
  finite range (charged particle)
- **protons:**
  low dose in entrance channel
  no dose after proton has stopped
- **HZB: proton energy of 68 MeV**
- **well adapted energy:**
  sharp distal fall-off, less than 1 mm 90% - 10% of dose
- **enough beam current, treatment time < 1 minute/fraction**

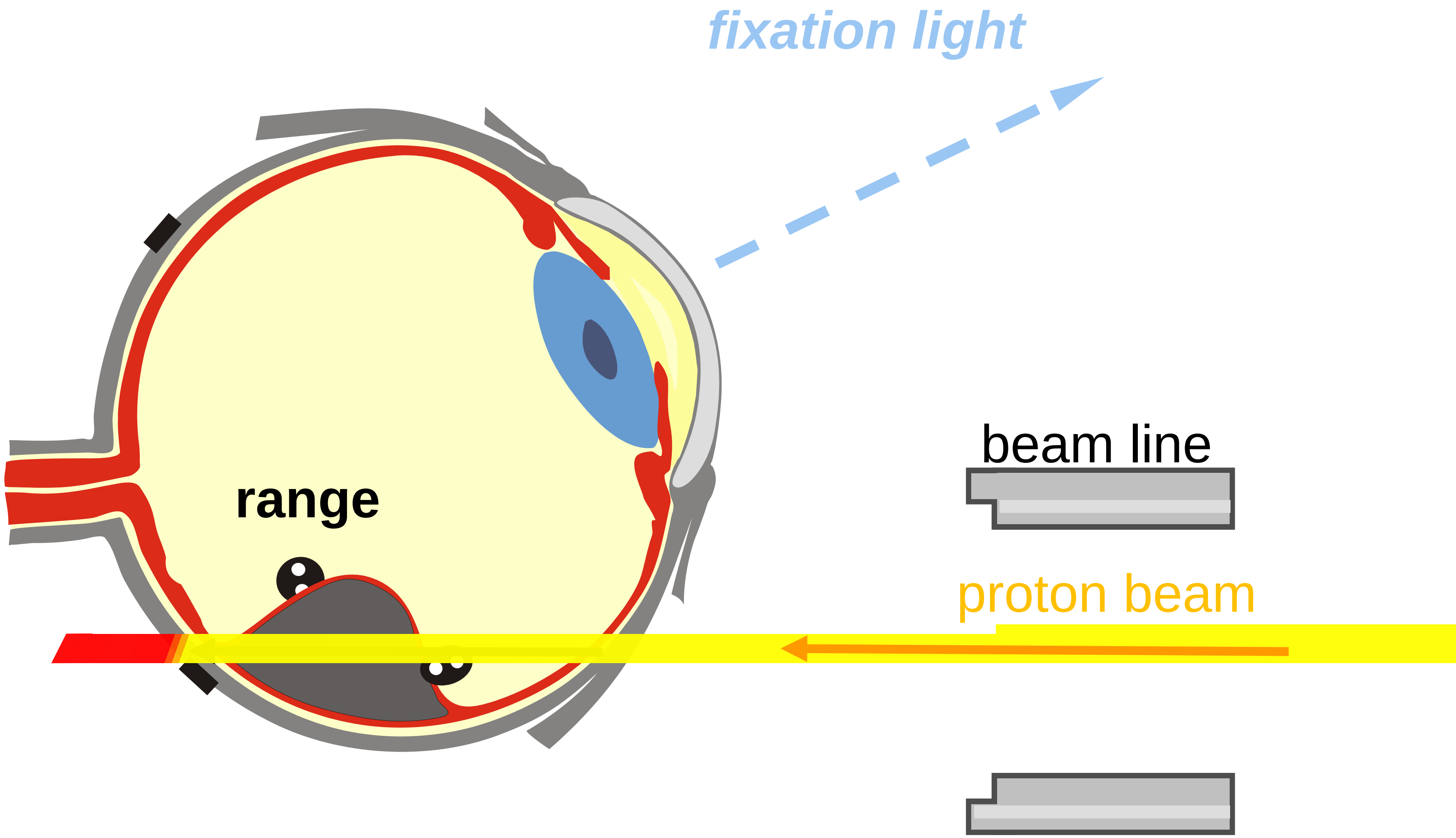
protons permit confinement of dose to tumour





Proton Therapy: Beam Adaptation

- monoenergetic focussed proton beam from accelerator



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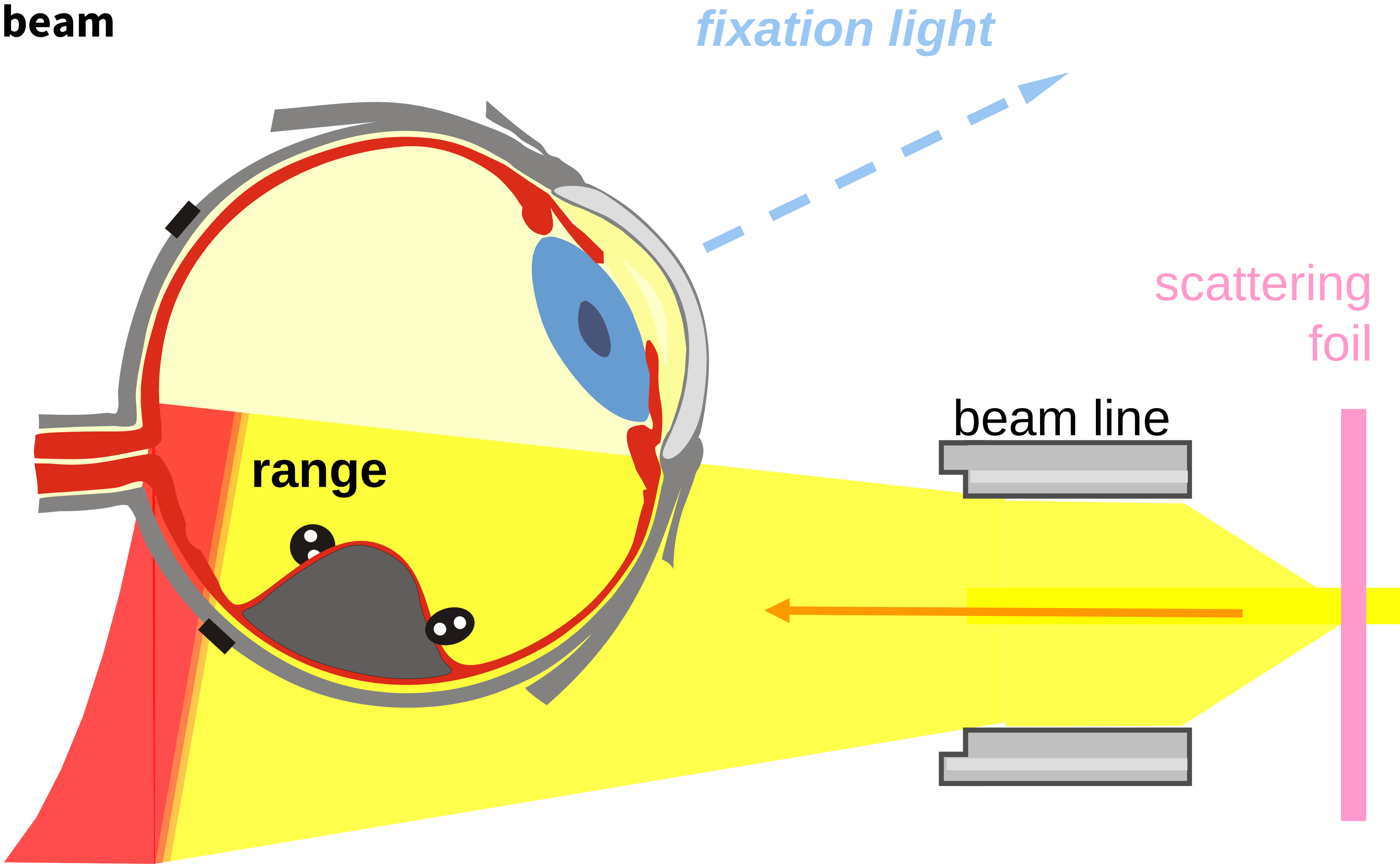
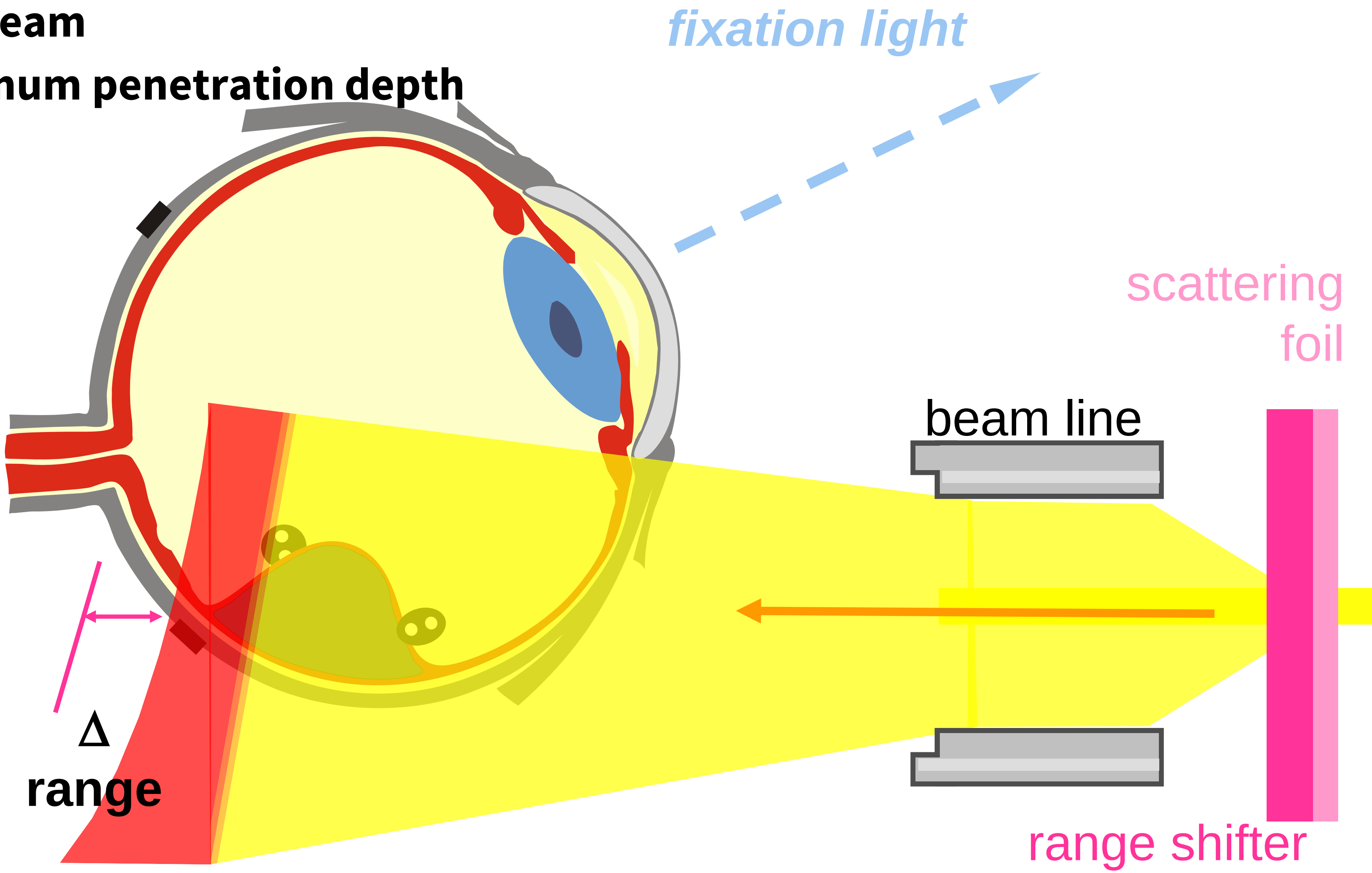
Proton Therapy: Beam Adaptation

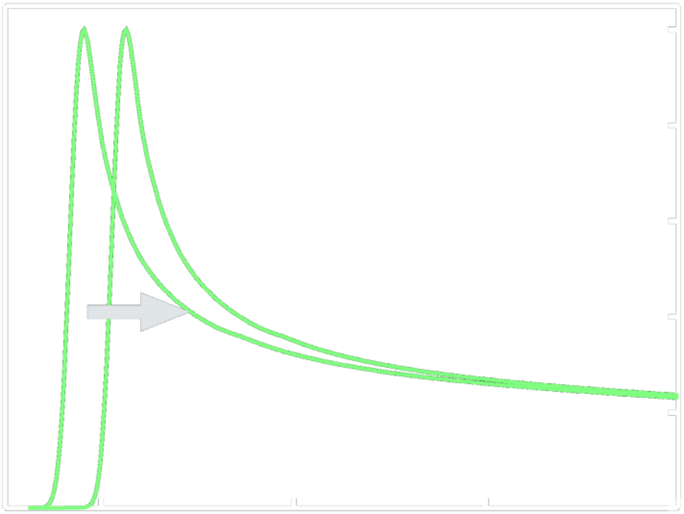
- monoenergetic focussed proton beam from accelerator
- scattering foil widens the beam



Proton Therapy: Beam Adaptation

- **monoenergetic focussed proton beam from accelerator**
- **scattering foil widens the beam**
- **range shifter defines maximum penetration depth**





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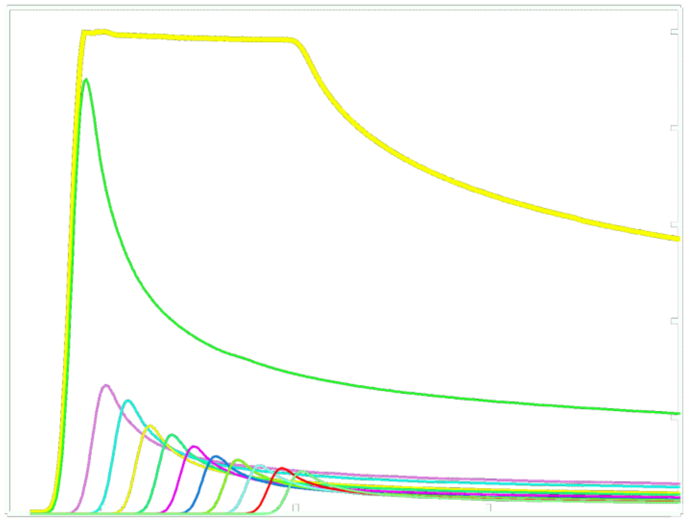
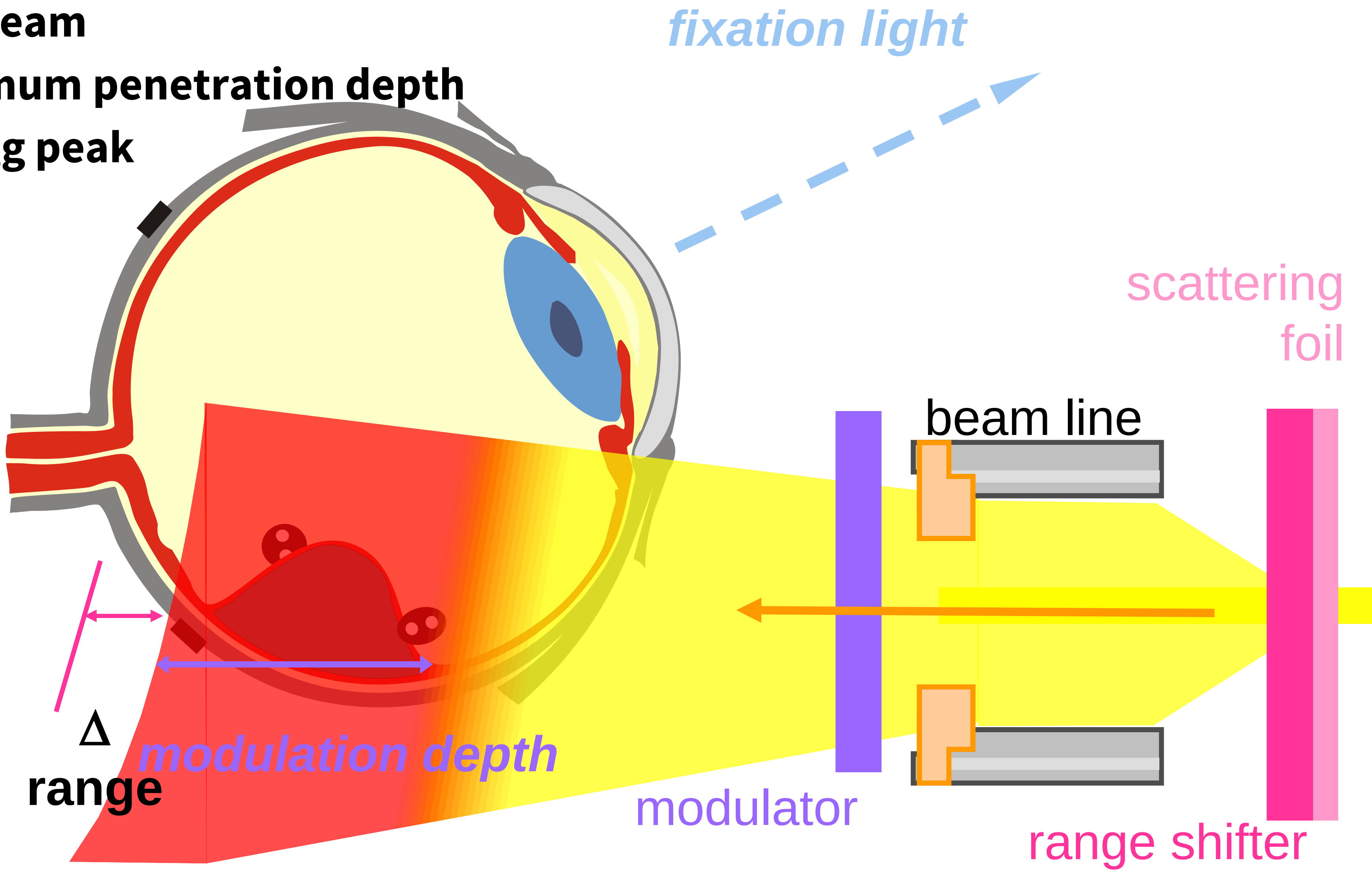
Proton Therapy: Beam Adaptation

- monoenergetic focussed proton beam from accelerator
- scattering foil widens the beam
- range shifter defines maximum penetration depth
- modulator widens the Bragg peak





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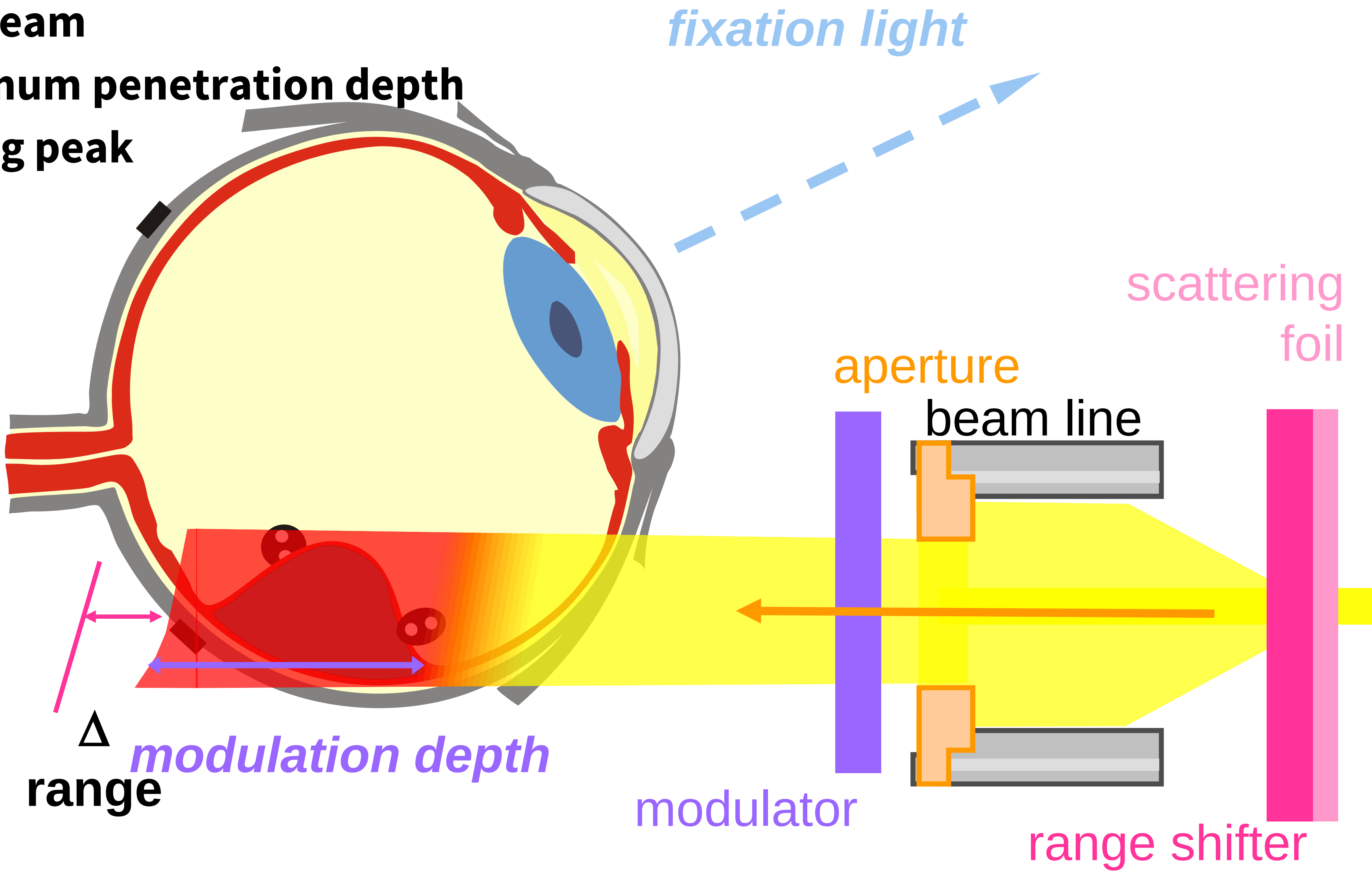
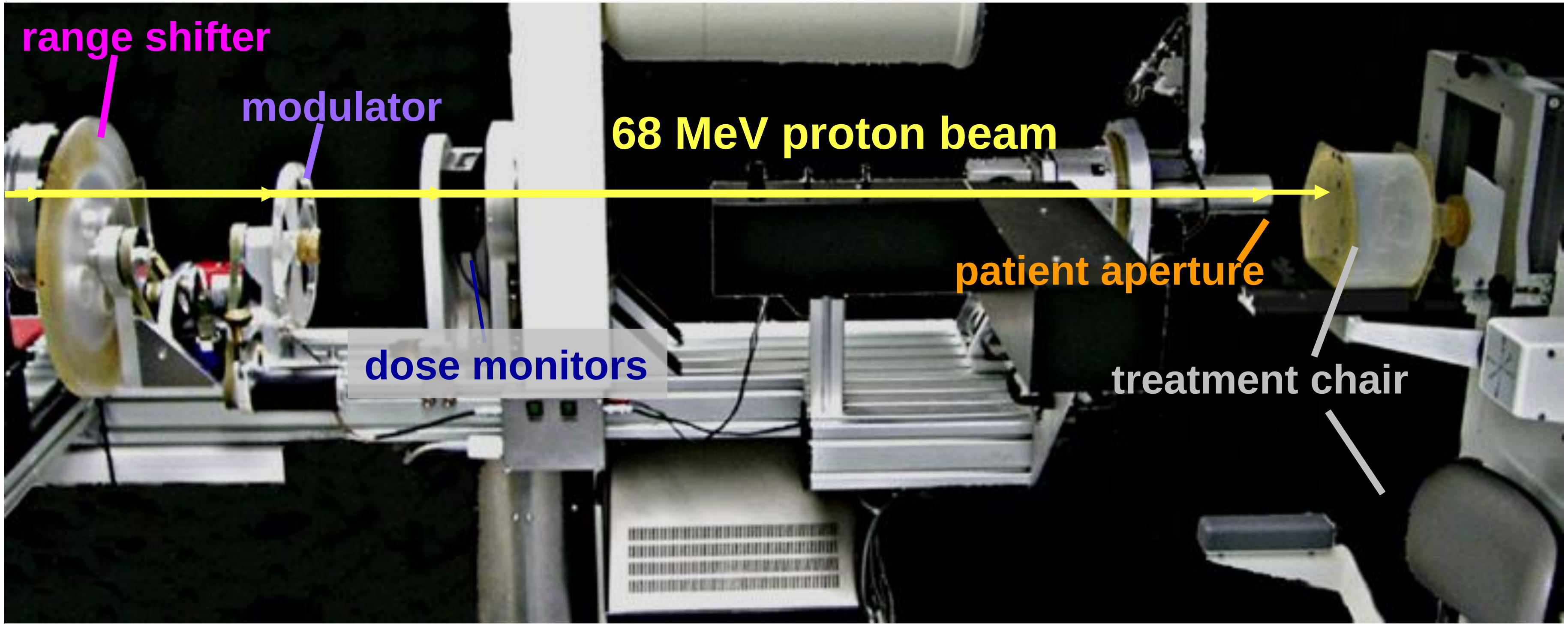
Proton Therapy: Beam Adaptation

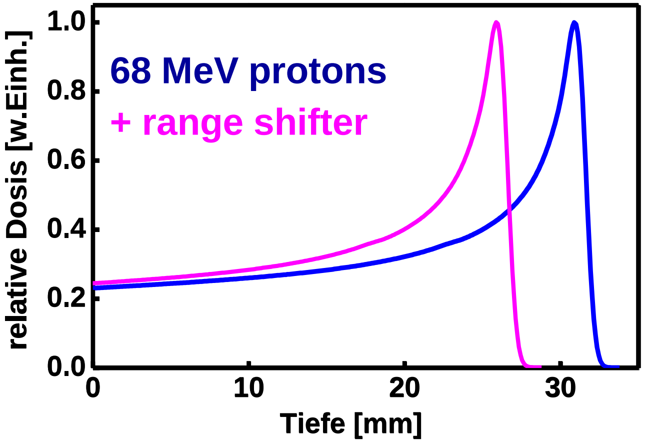
- monoenergetic focussed proton beam from accelerator
- scattering foil widens the beam
- range shifter defines maximum penetration depth
- modulator widens the Bragg peak
- individual aperture defines proton field in x and y

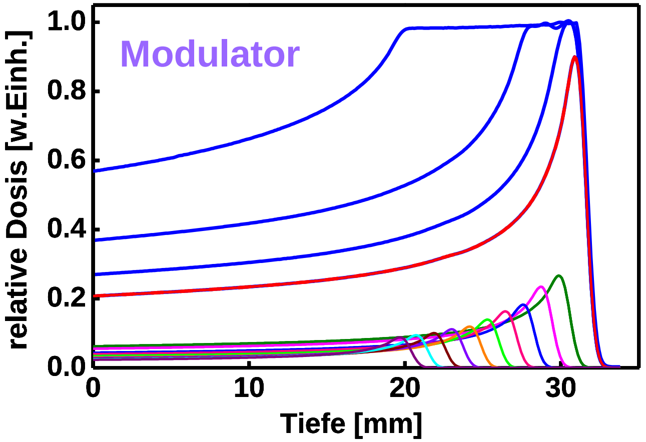


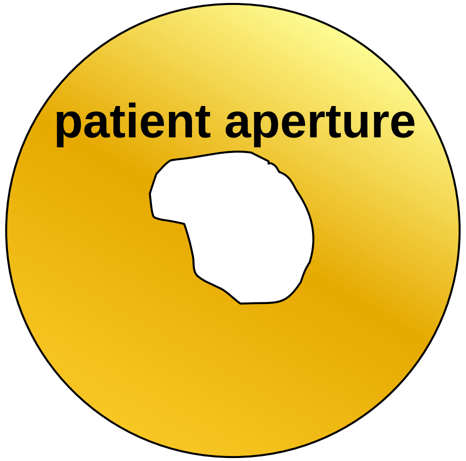
Proton Therapy: Beam Adaptation

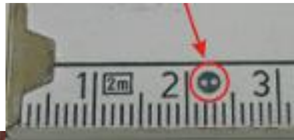
- protons from the left





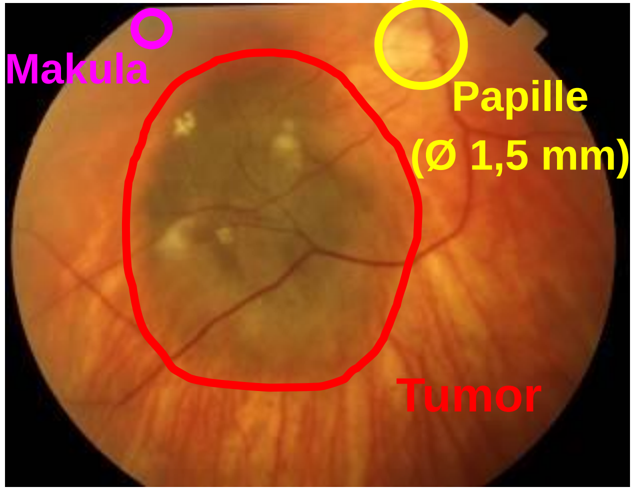


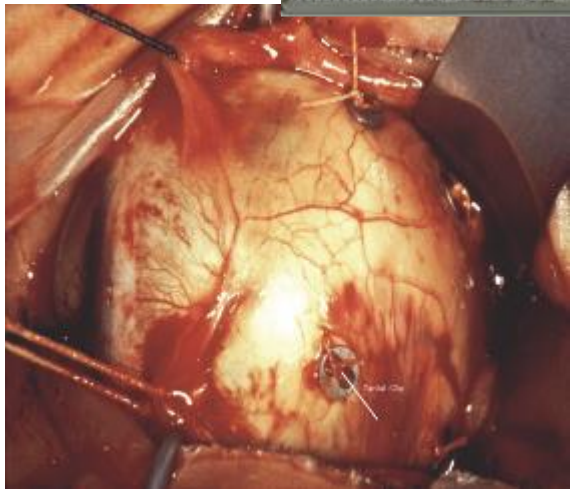


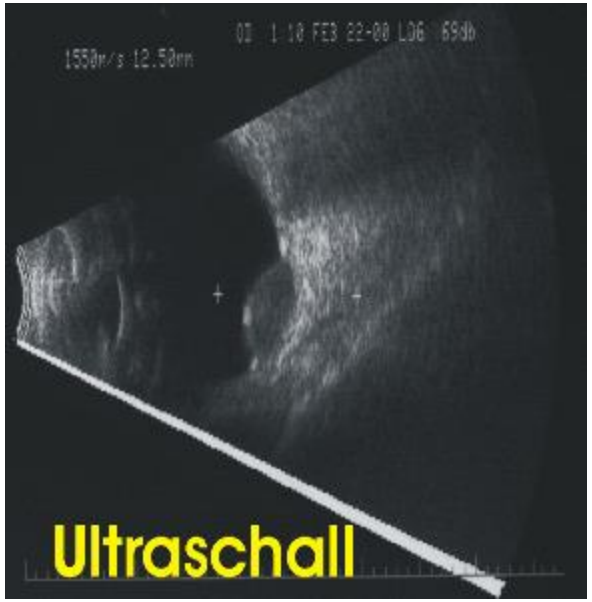


Proton Therapy: Imaging

- *Fundus photo*
  - shape of tumour
  - tumour position
  - tumour-macula-distance
  - tumour-papilla-distance
- *Operation: suturing of clips*
  - clip-tumour distance
  - clip-limbus distance
- *Ultrasound of eye*
  - length of eye
  - tumour thickness
  - tumour length and width
  - clip-papilla-distance
- *eye-CT / MRT*
  - verification of eye and tumour geometry







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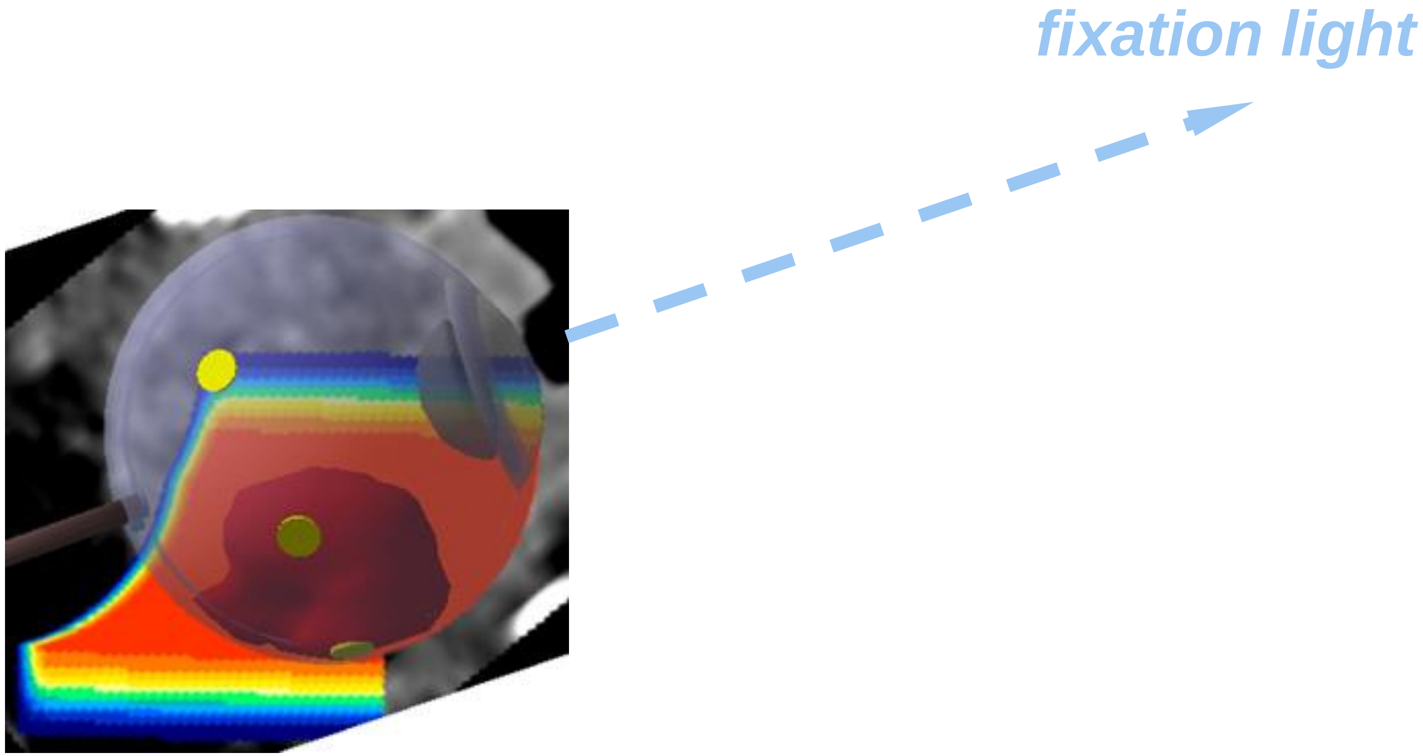
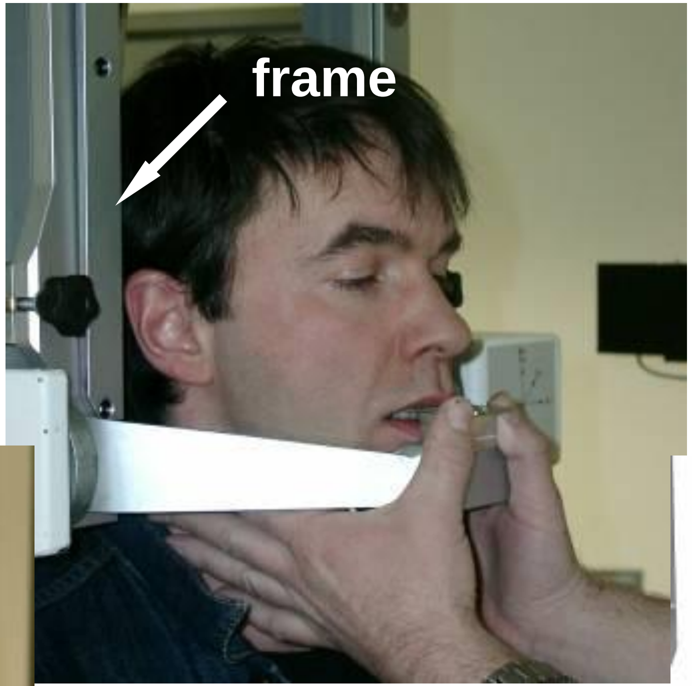
Proton Therapy: Treatment Plan

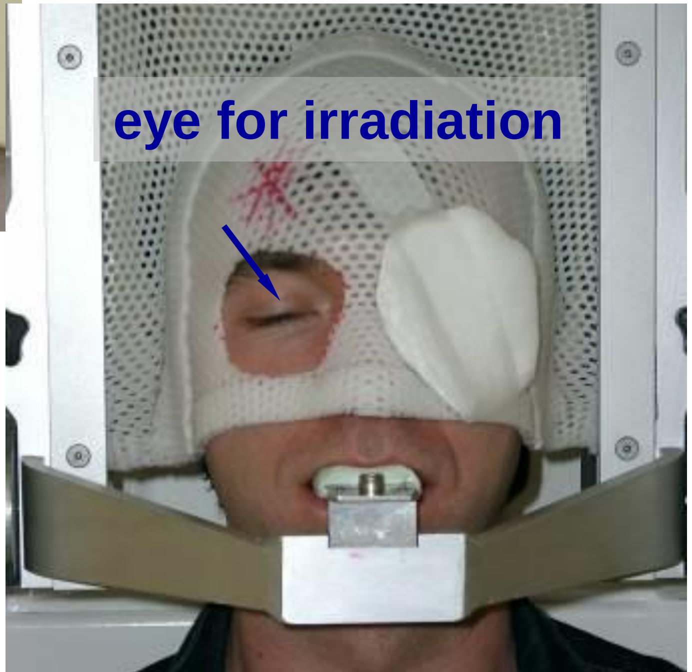
- from imaging: digital eye model adapted to real shape of the eye
- permits the calculation of the dose distribution with a treatment planning system (Octopus, developed jointly with the DKFZ)
- treatment plan provides information necessary information
  - position of clips in space
  - range shifter
  - modulator
  - line of vision to fixation light
- treatment plan provides dose distribution



Proton Therapy: Patient Preparation

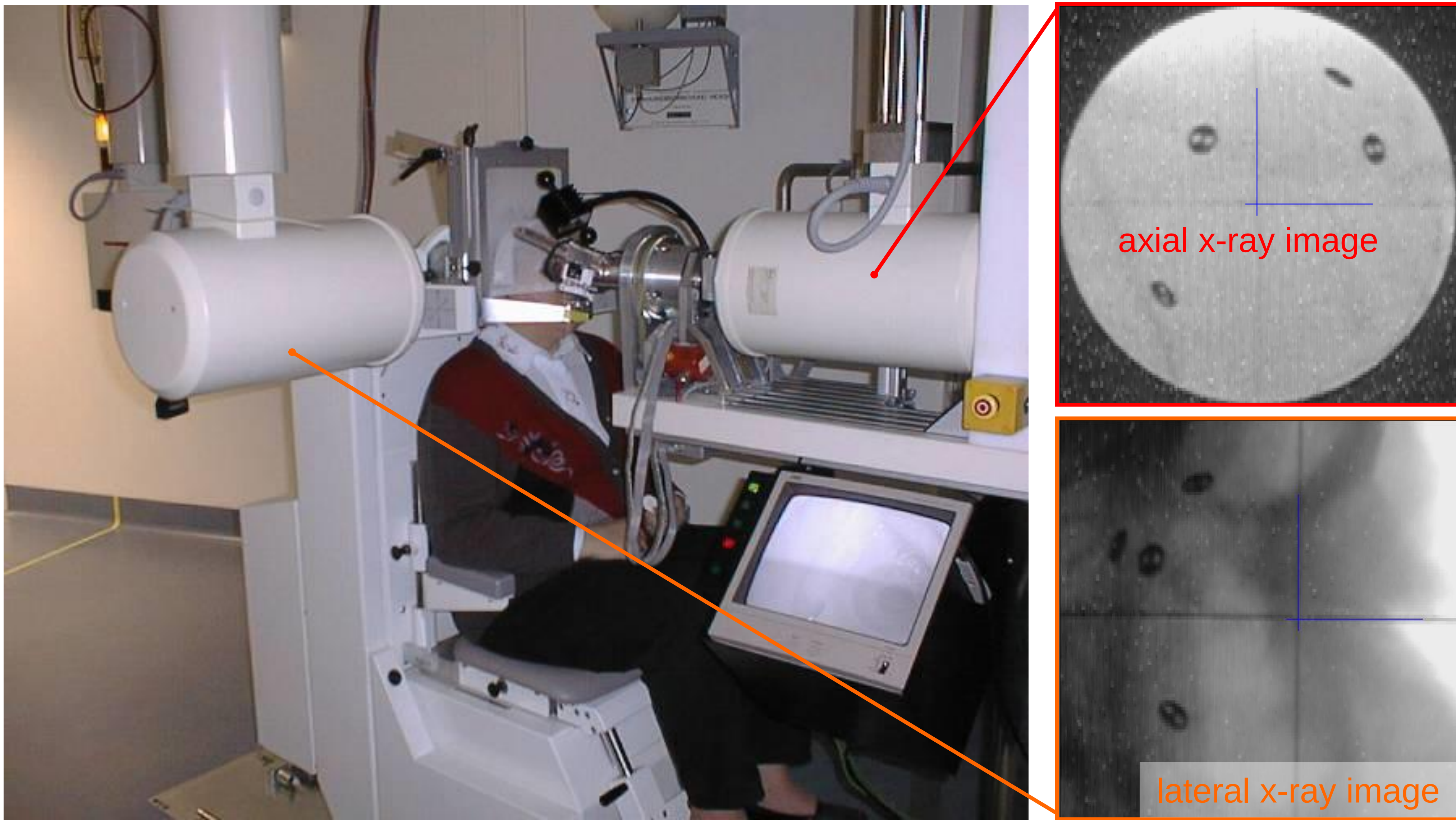
- **mask and bite block on high-precision adjustable chair**





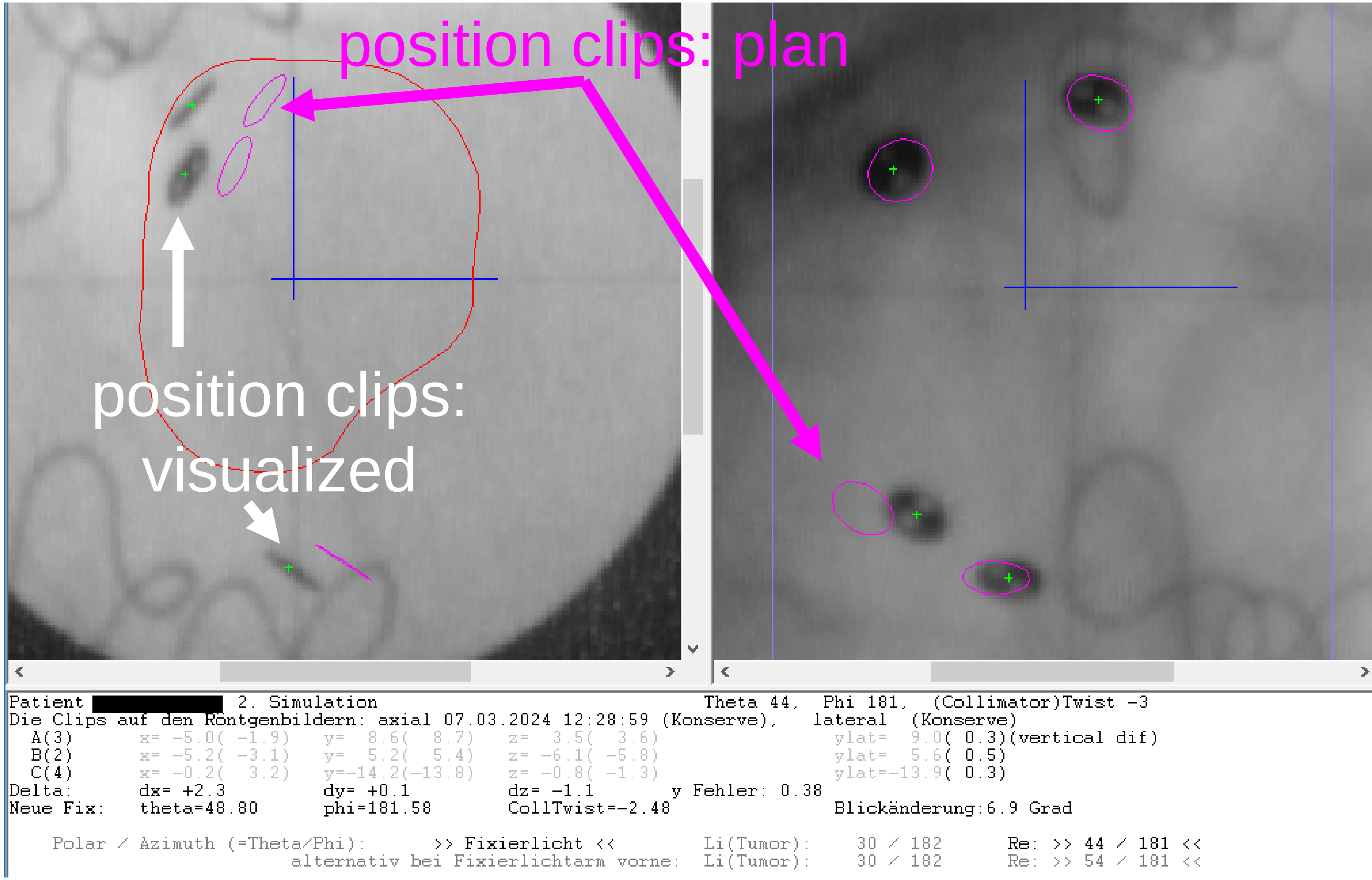
Proton Therapy: Verification of Patient Positioning

- **digital X-ray system the first in ocular proton therapy (1998)**



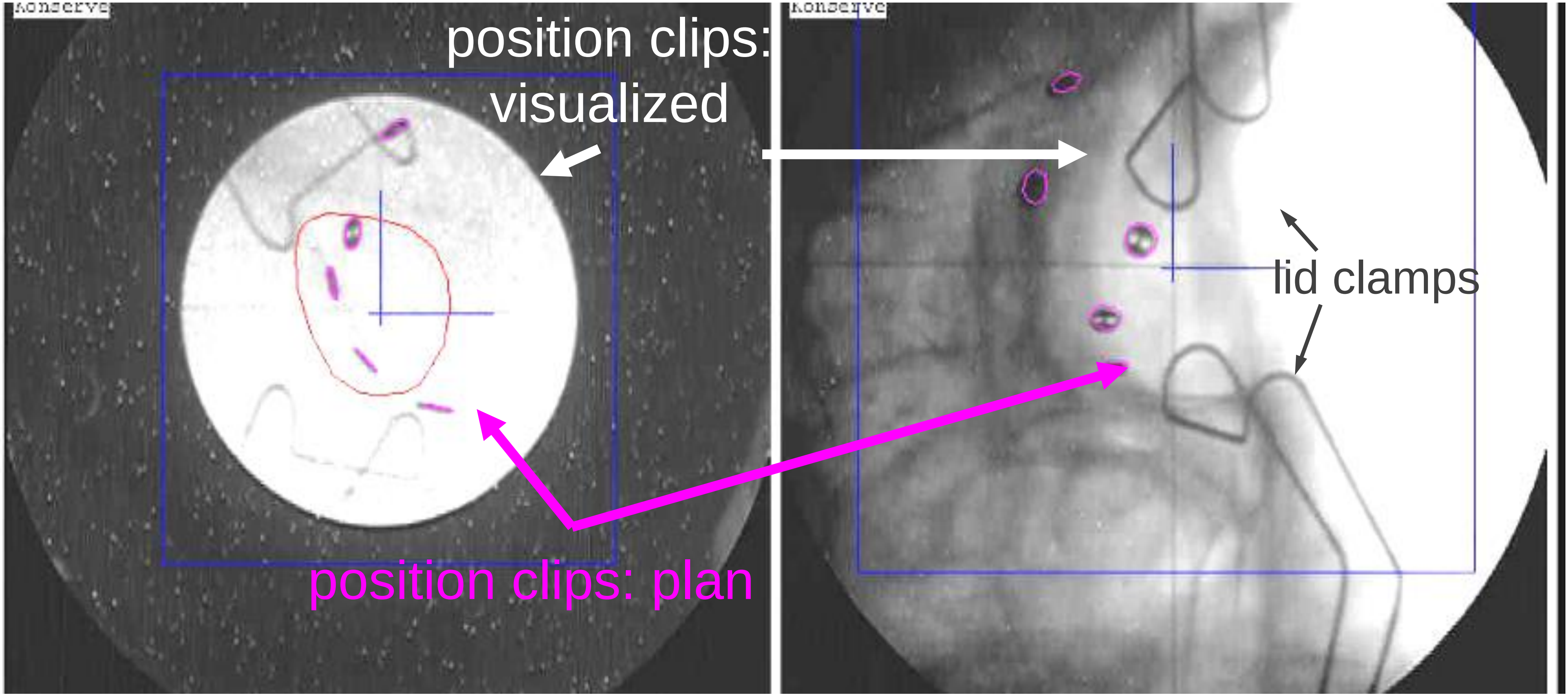
Proton Therapy: Verification of Patient Positioning

- **automatic calculation of the correction vector for patient positioning in 6 DOF:**
  - 3 translations (left/right, up/down, forward/backward)
  - 3 rotations of the eye (polar, azimuthal, twist/collimator)

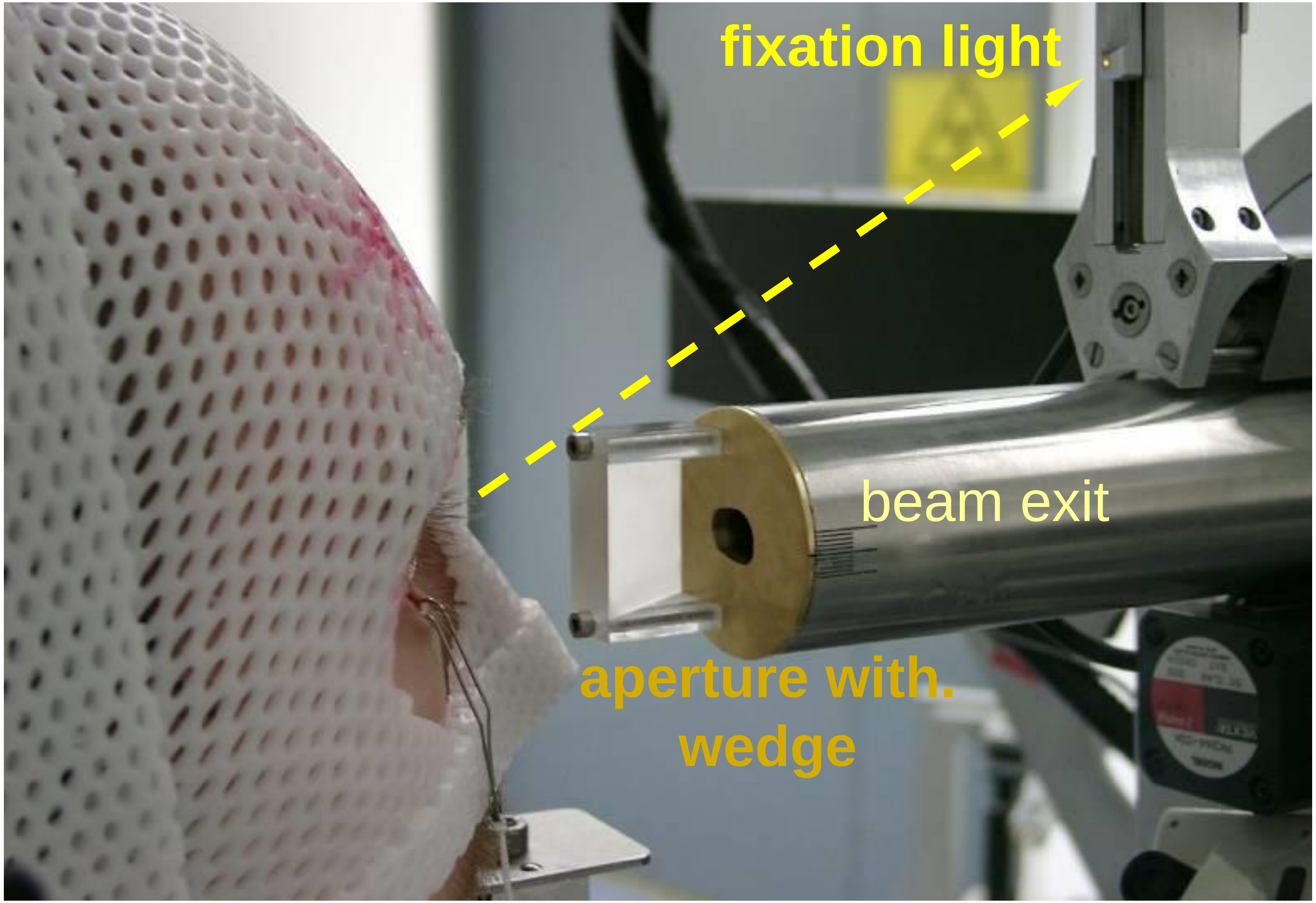


Proton Therapy: Verification of Patient Positioning

- **after correction of patient position**



Proton Therapy: Patient Preparation



Proton Therapy: Patient Irradiation

- prescribed dose is applied in 4 sessions:
- choroidal melanoma 4 times 15,0 CGE = 60 CGE
- iris melanoma 4 times 12,5 CGE = 50 CGE
- choroidal haemangioma 4 times 5,0 CGE = 20 CGE

  (CGE = Cobalt Gray Equivalent, with RBE = 1.1 $\Rightarrow$ 1 CGE = 1.1 Gy)

- 1 fraction ~ 30 seconds – 60 seconds

- high intensities required

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Proton Therapy: Results

- Tumor control after 5 years:
  - Ru-106: 80 – 98% weighted average: 91%[1] (Charité: ca. 92%[7])
  - I-125: 82 – 99% weighted average: 91%[1]
  - Protons: 90 – 99% weighted average: 96%[1,2] (Charité: ca. 96%[3])
  - LINAC (SRT): 85 – 96% weighted average: 94%[1,9]
  - Cyberknife: 71 – 84% weighted average: 81%[4,5]

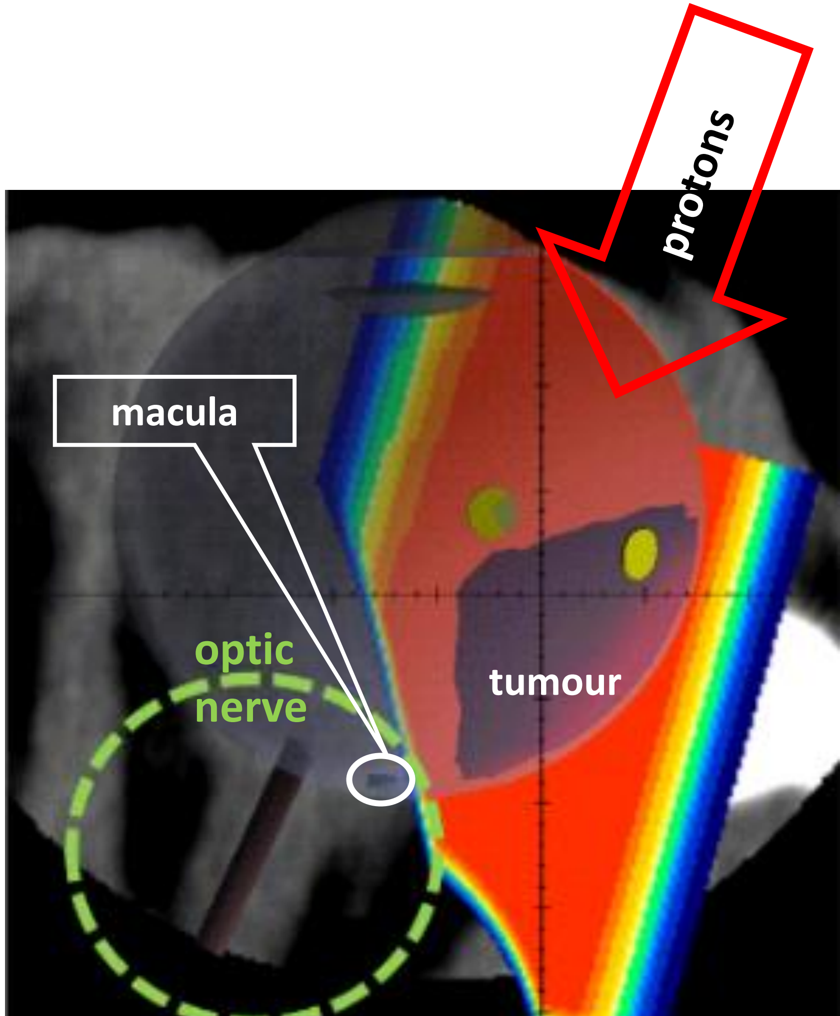
- Eye preservation after 5 years:
  - Ru-106: >90%[10] (Charité: ca. 95%[7])
  - I-125: ~90%[8]
  - Protons: >90%[2,6] (Charité: ca. 95%[3])
  - LINAC (SRT): ~78%[9]
  - Cyberknife: ~81%[4,5]

- Literatur (Auswahl):

[1]Chang: Brit J Ophthalmol. 2013; [2]Egger: Int J Radiat Oncol Biol Phys 2001; [3]Seibel: Am J Ophthalmol 2015; [4]Liegl: Am J Ophthalmol 2023; [5]Yazici: Int J Radiat Oncol Biol Phys 2017; [6]Mishra: CCO 2016; [7]Krause: Diss.2015; [8]Vonk: Brachytherapy 2015; [9]Dunavoelgyi: Int J Radiat Oncol Biol Phys 2011; [10]Verschueren: Radiother Oncol 2010

Proton Therapy: Challenges for the Accelerator - Energy

- **HZB: proton energy of 68 MeV**
- **well adapted energy:**
  sharp distal fall-off, less than 1 mm for 90% - 10% of dose
- **ideal for small structures like eyes**
  (~ 24 mm diameter)
- **high-energy accelerators (230 MeV – 250 MeV) with commercial ocular treatment line:**
  1.8 mm up to 4.4 mm for 90% - 10% of dose
  (based on PTCOG ocular proton therapy survey 2022)

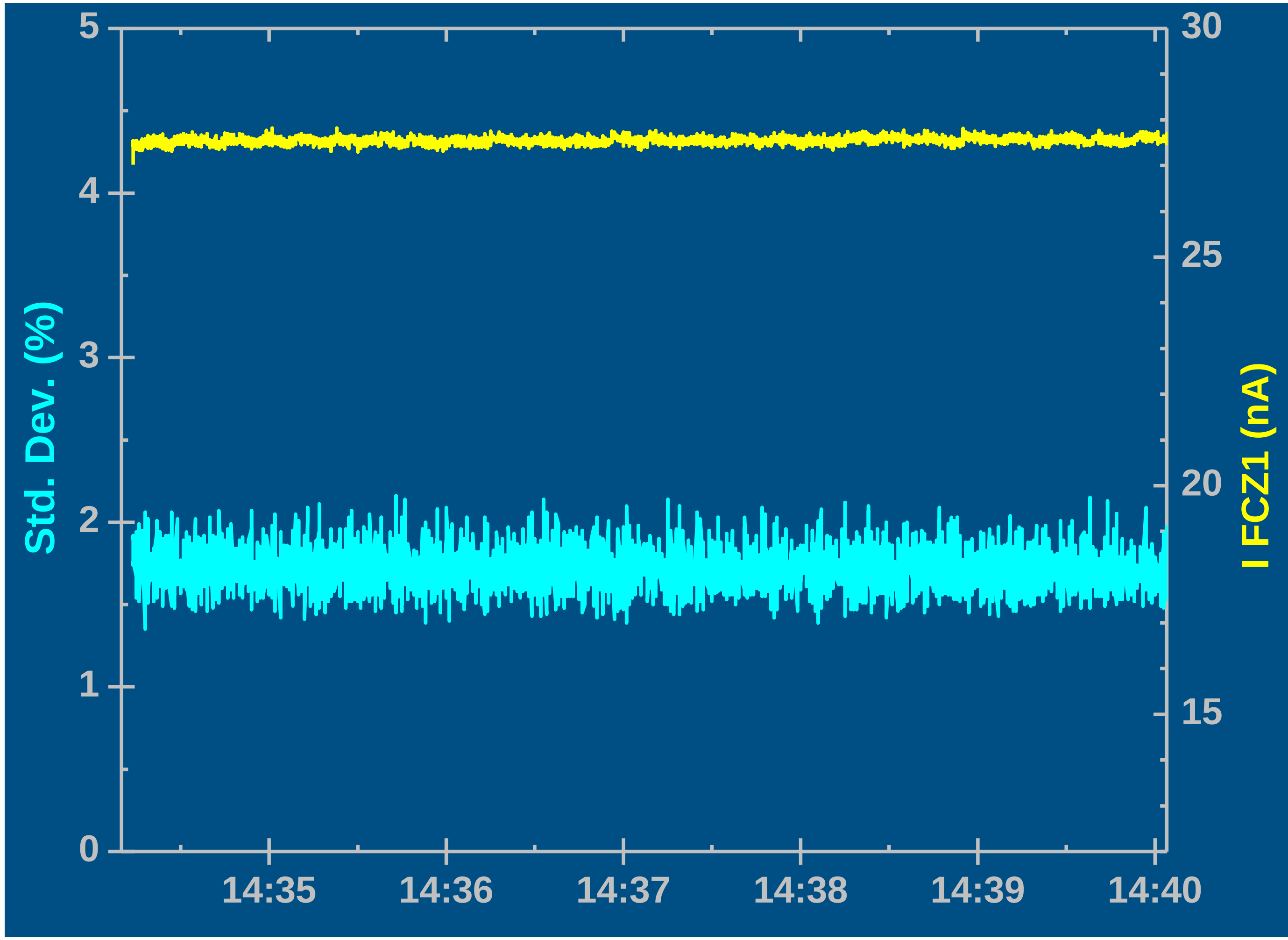


Proton Therapy: Challenges for the Accelerator - Intensity

- **HZB: proton energy of 68 MeV**
- **due to adapted energy: efficient beam adaptation**
- **high intensities in the treatment room**
  - ⇨ **dose rates up to 35 Gy/min**
  - ⇨ **comfortable short irradiation times for the patient**
- **high-energy accelerators (230 MeV – 250 MeV) with commercial ocular treatment line:**
  one exception, all other between 3 Gy/min and 15 Gy/min
  (based on PTCOG ocular proton therapy survey 2022)

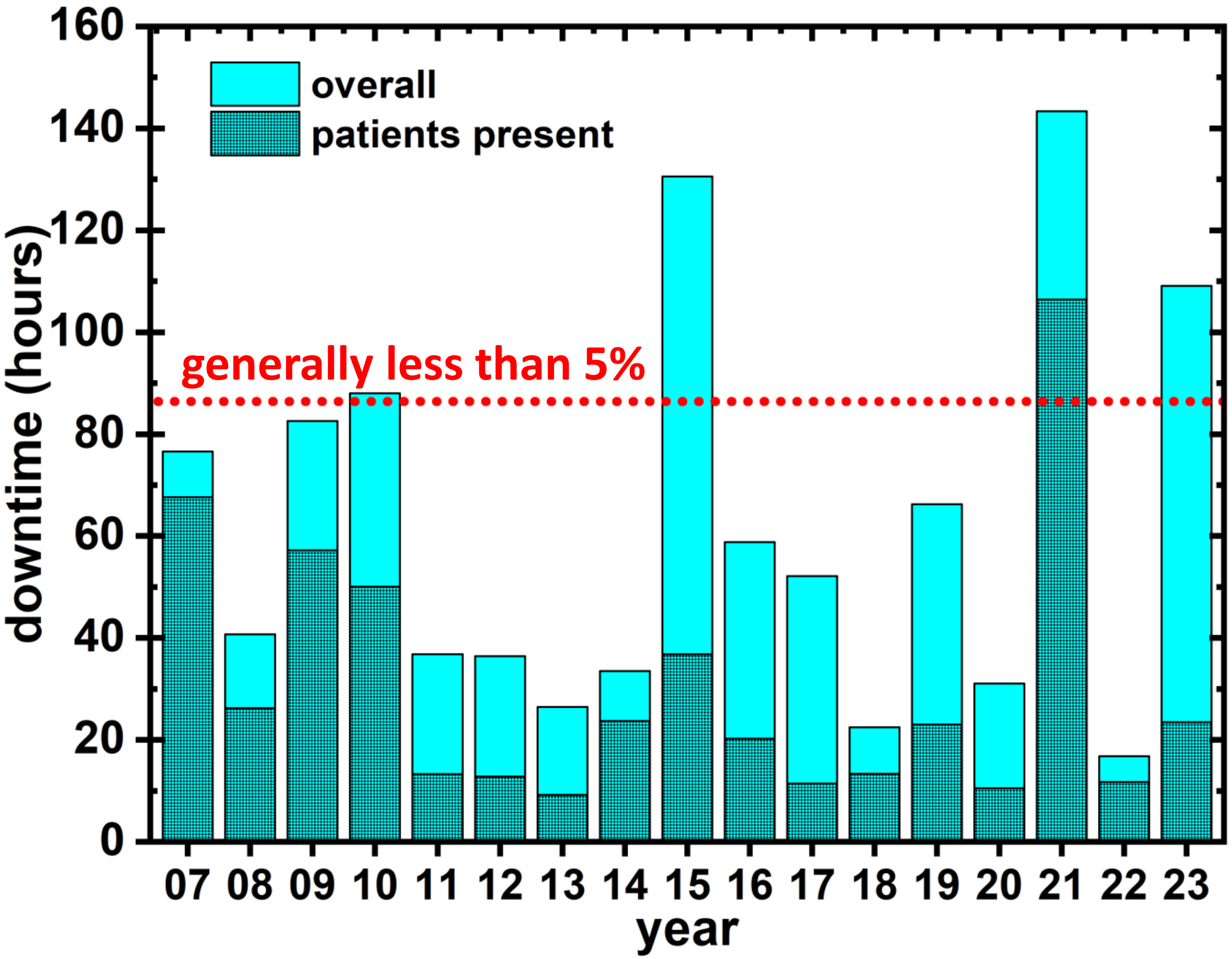
Proton Therapy: Challenges for the Accelerator - Stability

- beam intensity is monitored on-line during the treatment
- fast beam intensity changes lead to automatic interruption of the beam
- measured on Faraday cup after the cyclotron: less than 2%



Proton Therapy: Challenges for the Accelerator - Availability

- only 1700 hours of scheduled beam time: major events → huge impact on statistics
- most errors appear during start-up of accelerator
- with few exceptions: downtime < 5%
- good performance in spite of:
  - problems with suppliers (main issue: ultra long delivery times)
  - new safety regulations, requiring exchanges of perfectly working parts
- good performance thanks to huge efforts of the staff



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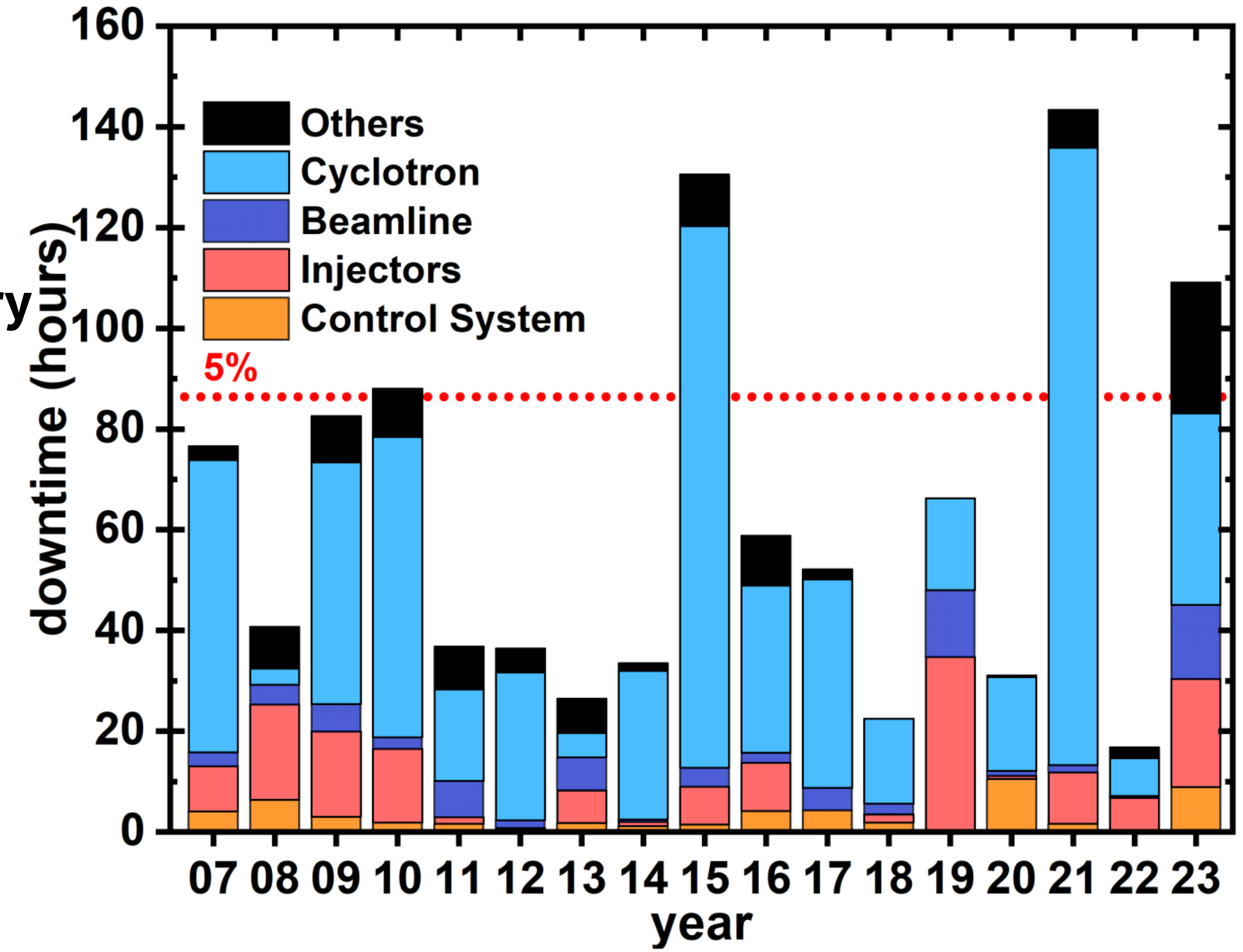
Proton Therapy: Challenges for the Accelerator - Reliability

- major events: cyclotron
- 2015: human error
  – increase of injector voltage too fast
- 2021: high power coaxial feedthrough leaking – shifting of therapy week necessary
  (shifting counts as downtime)
- 2023: severe cyber attack

- control system extremely stable

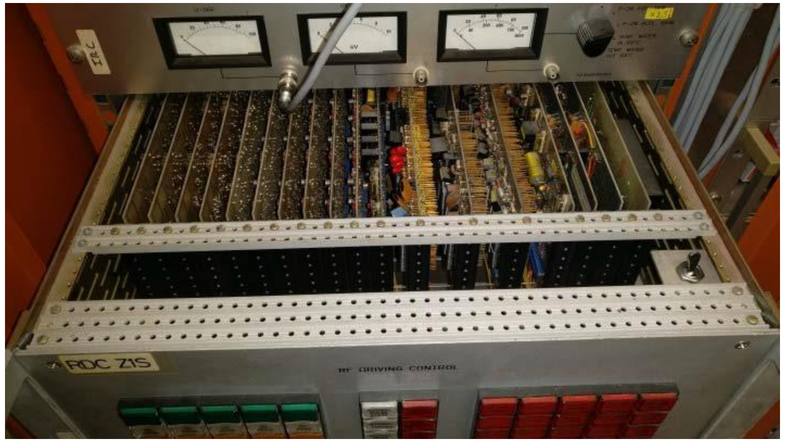


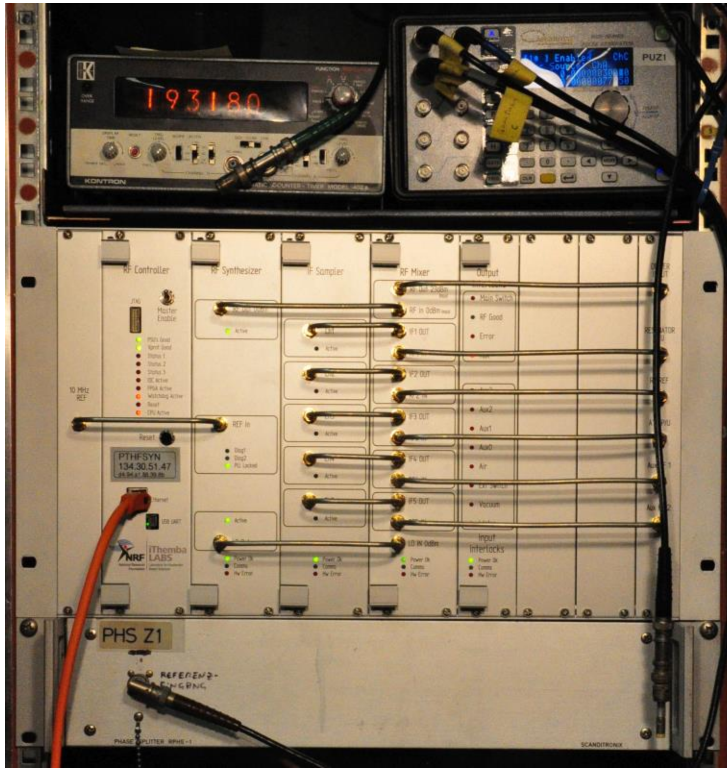
Proton Therapy: Challenges for the Accelerator – Control System

- origins of the accelerator date back to the 70s: PDP 11, MUMTI (Multi User – Multi Task – Interface) with touchscreens!!
- decision in the 90s: create new control system using V-Systems (the commercial version of EPICS)
- challenge: installation of new control system parallel to accelerator operation, no long shut-downs available
- over the years: different control systems moved in
  - Tandetron: own control-system from accelerator supplier
  - Low Level RF control: based on EPCIS
  - beam diagnostics and experimental control: based on LabVIEW
- need to communicate to each other
- lock parameters when treatment operation

Low Level RF Control

- old low level RF control based on wire wrapped cards relatively compact despite the large number of components repair and maintenance more difficult
- in-house development was rejected due to lack of personnel and time
- collaboration with iThemba Labs
- signals are read or output via Beckhoff EtherCAT terminals
- two server PCs with Linux
- EPICS based user interface
- reduction in downtime of the RF





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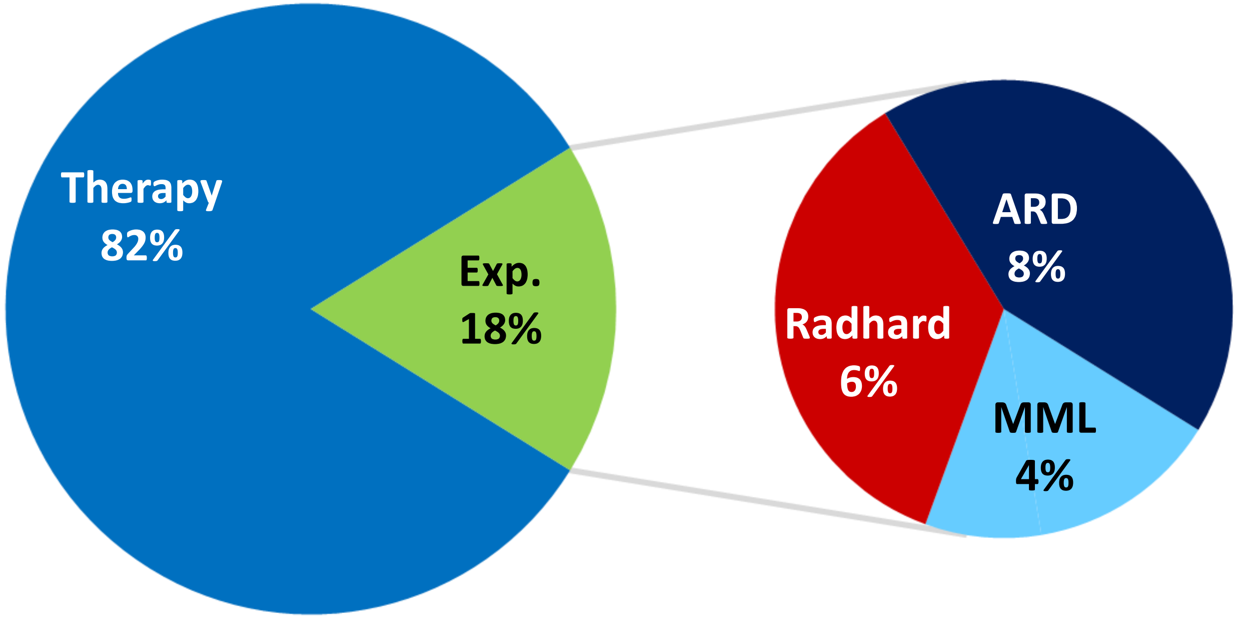
Beam Time Distribution

- **main user:**
  Charité – Universitätsmedizin Berlin for proton therapy of ocular melanoma
- **accelerator R & D (ARD):**
  - **beam delivery for Flash irradiations (extremely high doses in short times)**
  - **beam profile monitors "behind" the cyclotron**
  - **„Cocktail beams“: 90 MeV $^{4}He^{2+}$ and 45 MeV H_2^{+}**
- **Dosimetry and Medical Physics (MML):**
  - **irradiation of cells and organoids under conventional and FLASH conditions collaboration with Charité and others**
- **Radiation hardness tests (Radhard):**
  - **external users, e.g. DLR, universities, industry**



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FLASH experiments

- parallel to tumour treatment: ongoing research and development
- wish: reduction of side effects
  (e.g. radiation induced retinopathy 1 -2 years after treatment)
- one idea: increase dose rate = so called FLASH irradiations
- standard for ocular tumours: 15 Gy in 30 s to 60 s → dose rate less than 0.5 Gy/s
- definition of FLASH irradiations: dose rate > 40 Gy/s, irradiation time < 1 s
- currently ideal combination irradiation time versus dose rate unknown
- medical physicists: precision of dose delivery must be better than 3%

- challenges:
  - dosimetry: linearity, saturation effects, …
  - reliable beam delivery: beam stability, same dose from shot to shot, …

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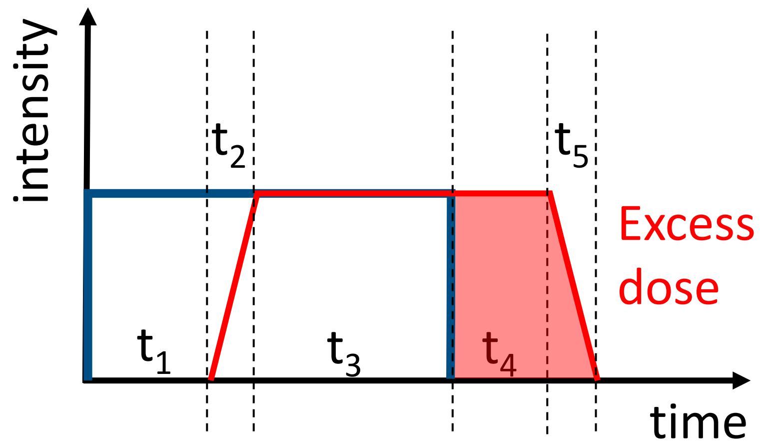
Timing Issues

- **ideal: instant opening and closing of the beam shutter and no delays**
  → instantaneous, rectangular intensity (dose rate) curve
- **reality:**
  - **t_1 = delay from open command to start opening**
  - **t_2 = opening time**
  - **t_3 = closing command**
  - **t_4 = delay from closing command to start closing**
  - **t_5 = closing time**



Beam intensity stable = Excess dose constant

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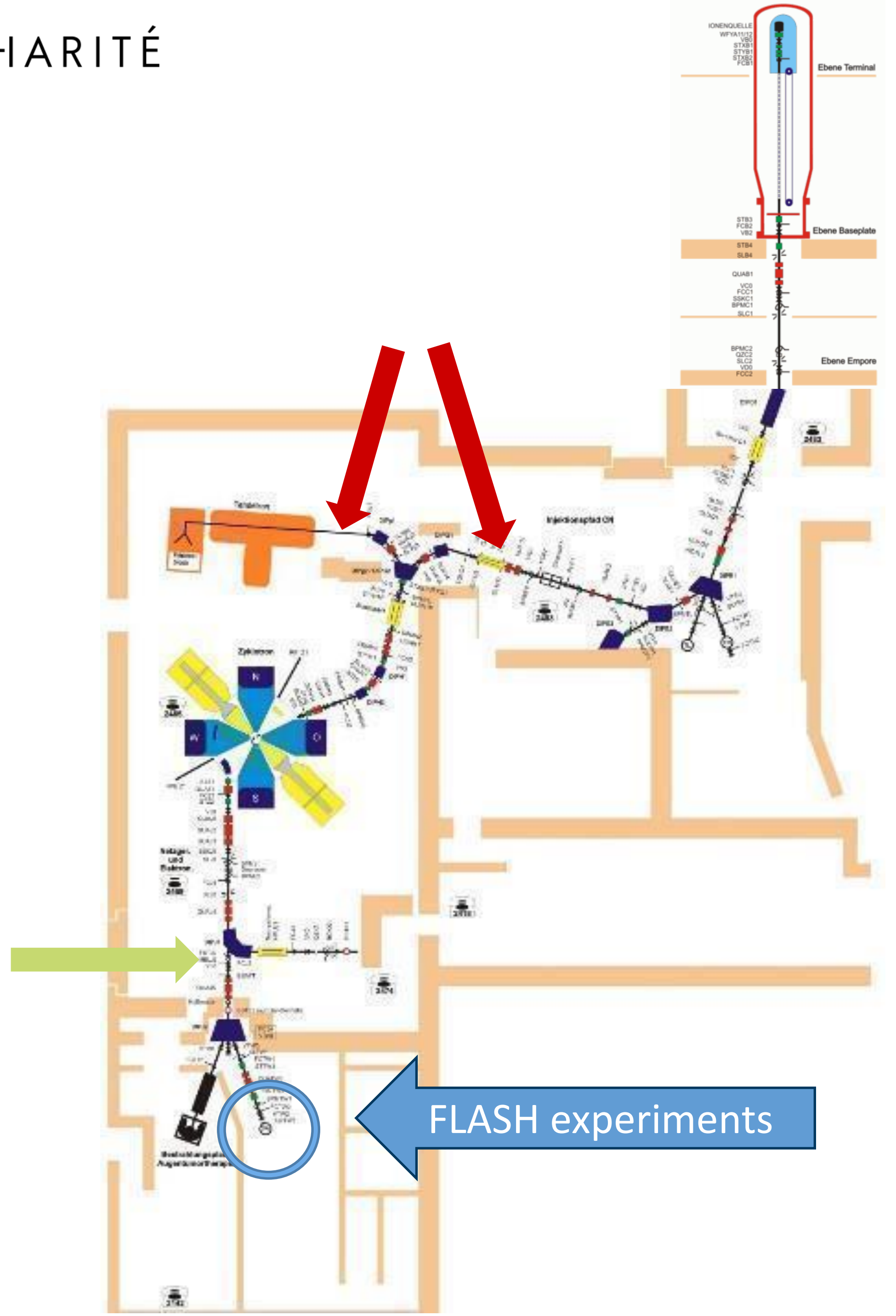
Possible Beam Shutters

- normal Faraday Cups
  (in total 16 at various positions):
  - opening/closing time ~ 150 ms (50 mm stroke)
  - >>too slow
- mechanical shutter in front of treatment room:
  - opening time 20 ms/delay 40 ms
  - closing time 10 ms /delay 40 ms
  - no issue for conventional irradiation (30 s to 60 s)
- electrostatic kicker
  - opening / closing time : < 1 µs
  - delay ~ 100 µs



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Experimental Set-up

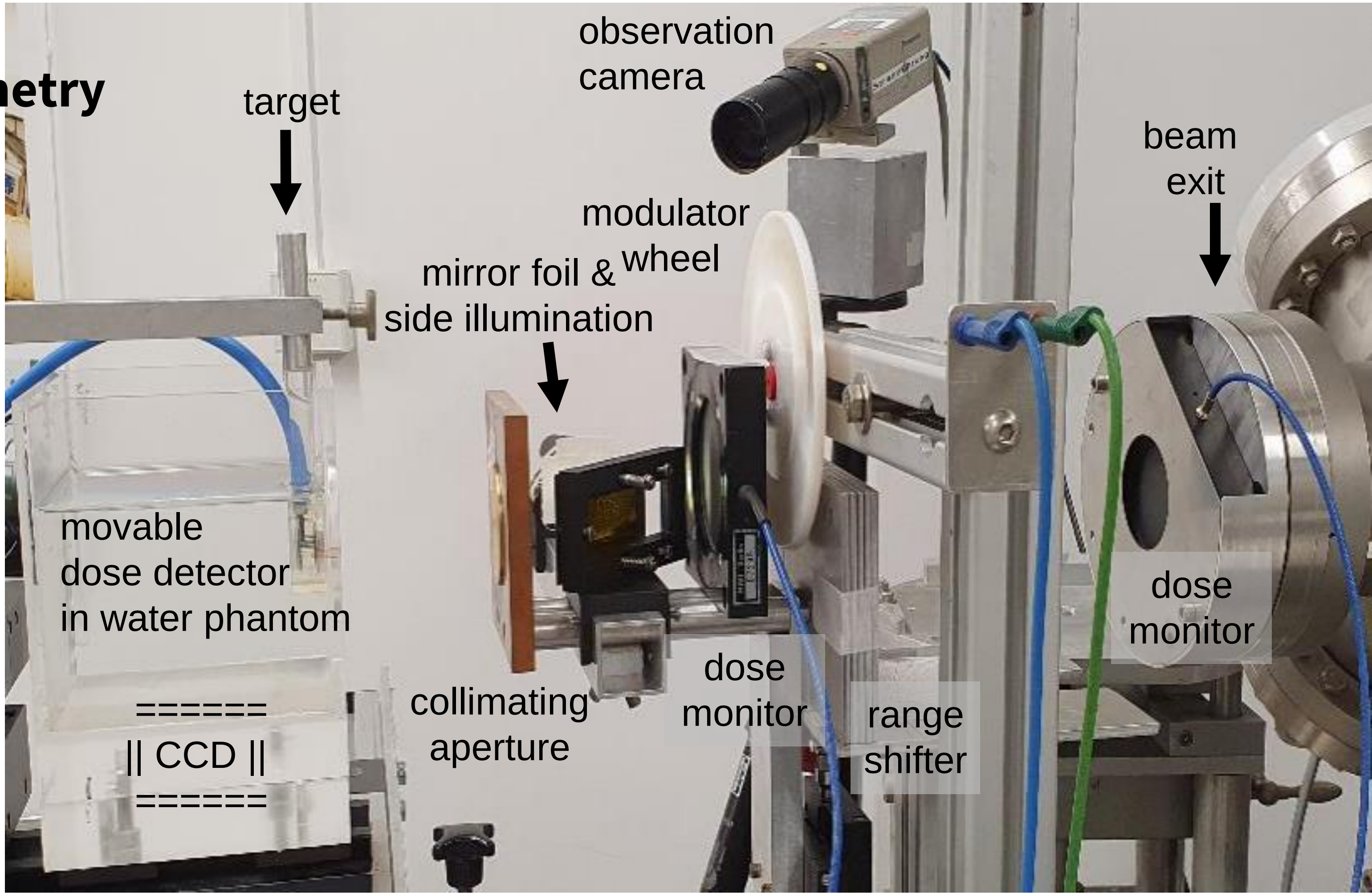
- **Faraday cup with interlocks, e.g. radiation safety (not in image)**
- **either mechanical shutter OR electrostatic kicker (not in image)**

a) two ionisation chambers for dose monitoring (>>redundancy)

b) Advanced Markus chamber in water phantom for absolute dosimetry

OR

sample to be irradiated



Important:

use of spread out Bragg peak

(modulator wheel for 6.4mm)

No shoot through with full energy!!

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Hardware

- Embedded system: sbRIO 9637 from NI
- Ionization chamber 7861 from PTW Freiburg with I/U-Converter DPLCA 200 from FEMTO

Software

- LabVIEW from NI

Absolute Dosimetry

- Unidos with Advanced Markus chamber, both from PTW Freiburg (medical device for dose / dose rate)

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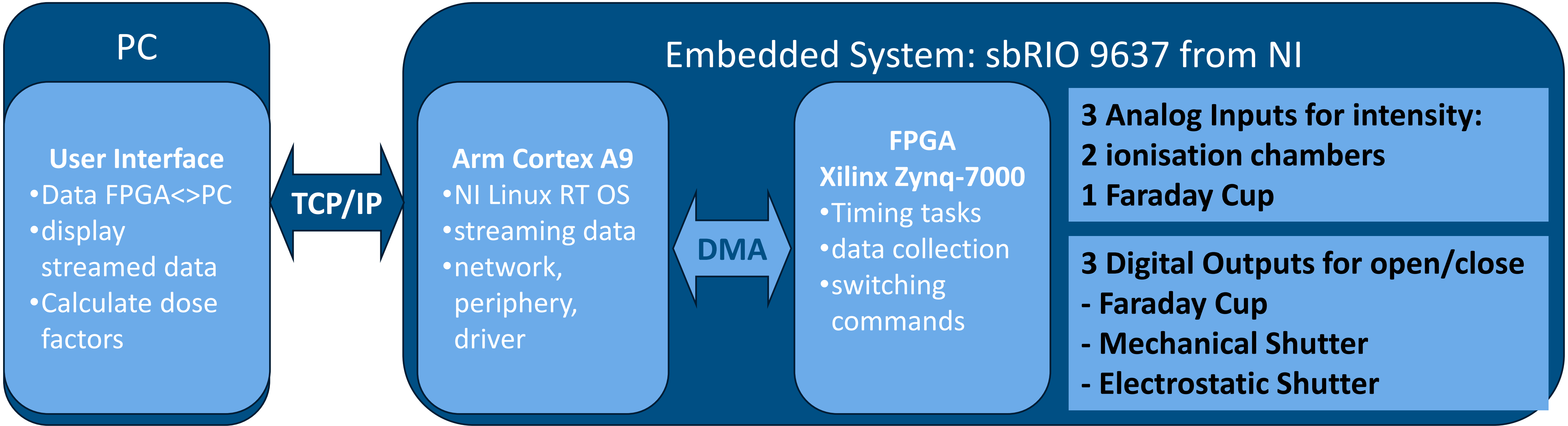
Distributed Tasks

- **PC: receives / displays streamed data, generates start signal, saves streamed data in file after start, calculates dose factors**

- **embedded system:**
- **ARM CORTEX: communication PC<>FPGA, streaming data every 100 ms**
- **FPGA: 10kHz sampling rate, all timing tasks and data collection**



Timing Issues

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- **reality:**
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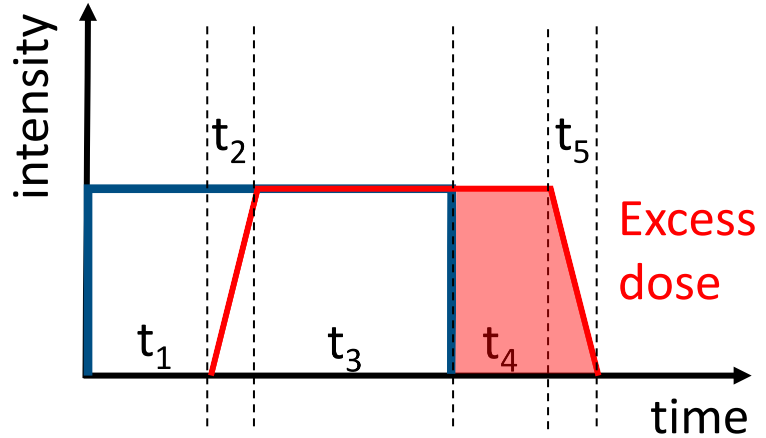
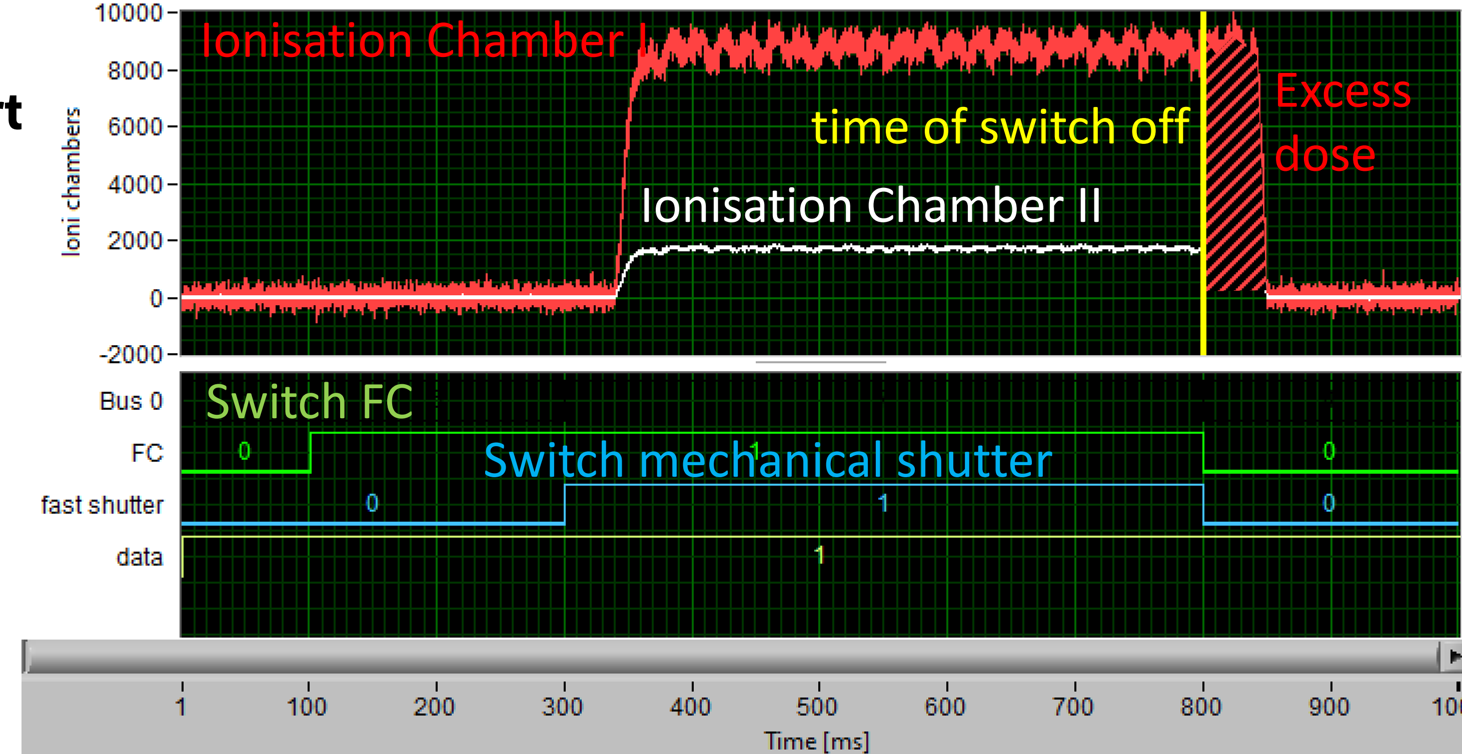
  - **t_2 = opening time**
  - **t_3 = closing command**
  - **t_4 = delay from closing command to start closing**
  - **t_5 = closing time**
- **real signal from ionisation chamber here: fixed time of 500 ms**





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Workflow

1. **CALIBRATION (setup with absolute dosimetry)**
   1. **set beam intensity to desired dose rate**
   2. **select fixed time window T_{Cal} (10ms to 500ms)**
   3. **start Beam Pulse [switch off is given by Time] and measure calibration dose D_{cal} (Gy)**

2. **VERIFICATION (setup with absolute dosimetry)**
   1. **set Dose D to applicate (must be smaller than calibration dose)**
   2. **start Beam Pulse [Switch off is given by Dose - excess Dose] and measure Dose D (Gy)**
   3. **repeat it (several trial runs for statistics)**

Takes only a few minutes

3. **„TREATMENT“ (replace water phantom with sample)**
   1. **same dose D as during verification**
   2. **irridiate your samples**

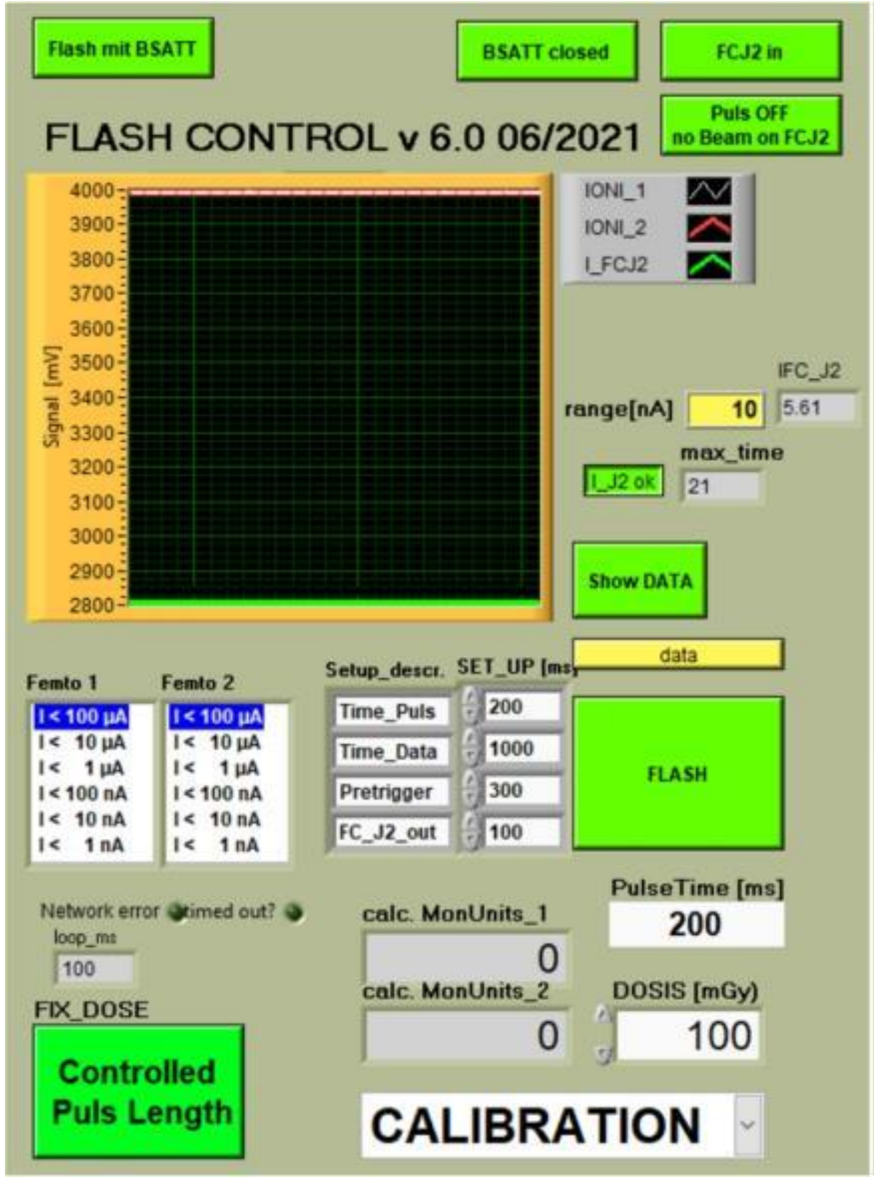
Safety Measures

- **if beam intensity changes for more than 5%: verification and „treatment“ is vetoed -> new calibration and verification is necessary**

- **both ionisation chambers are integrating dose independently: the first chamber reaching the dose equivalent switches off beam**

- **in case both ionisation chambers fail: after the time used during calibration the beam is switched off**

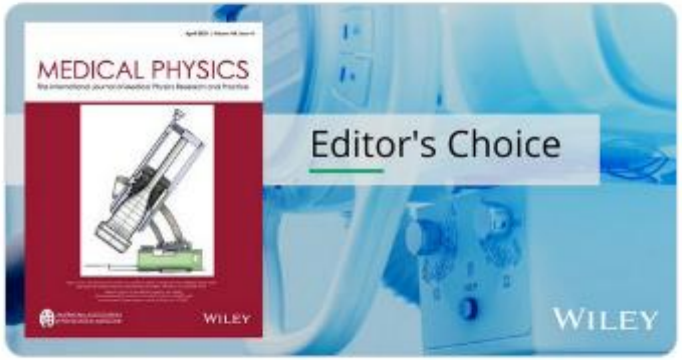
- **BUT: no medical device – not yet certified**



Scientific results: FLASH irradiation of single mice eyes

- control group: conventional irradiation mode, 0.25 Gy/s, 60 s total irradiation time = 15 Gy, statistically no fluctuations in dose,
- FLASH , dose rate 75 Gy/s , 200ms, 30 trial runs to estimate error:
  14.9 Gy with a standard deviation of 0.6%
- first publications with mechanical shutter: G. Kourkafas et al., FLASH proton irradiation set-up with a modulator wheel for a single mouse eye, Medical Physics 48 (2021) 1839-1845

- work in progress with electrostatic shutter



WILEY
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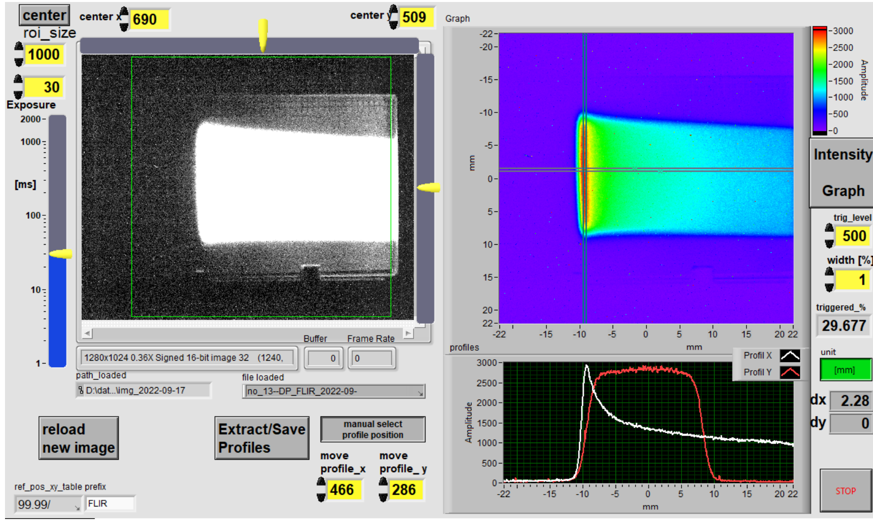
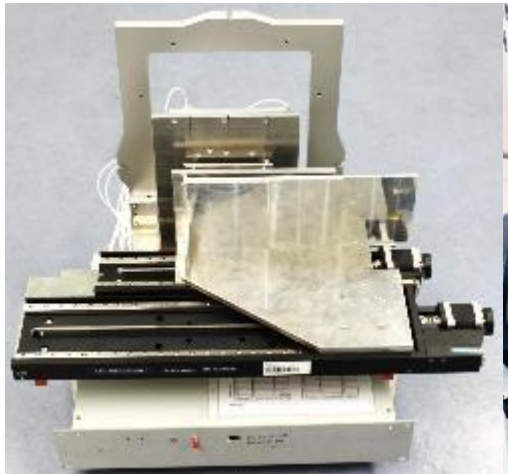
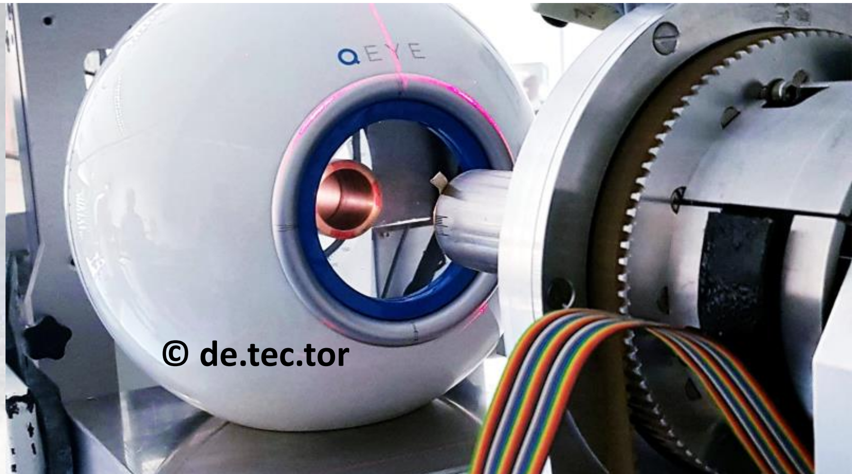
Dosimetry

- investigating linearity of dosemeters
- development of a transmission ionization chamber which is linear up to 1 kGy/s
- development of a depth profile camera
- development of a Multi-Leaf Faraday Cup, PhD Thesis C. Kunert
- company de.tec.tor licensed the MLFC and made a full certified medical device







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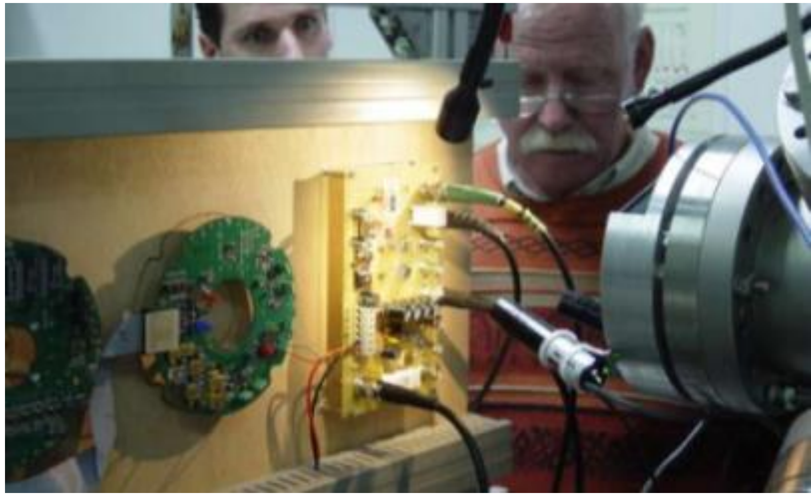
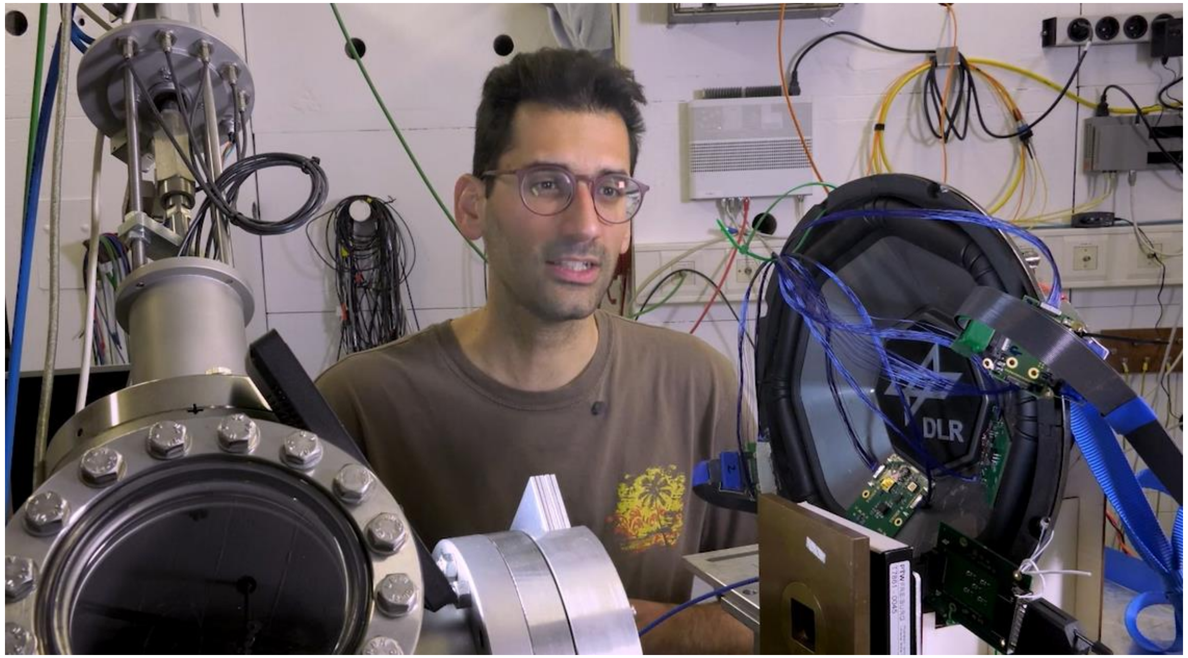
Radiation Hardness Tests – External Users

- beam in air
- quasi DC or pulsed
- 0.1 pA to 10 nA (DC) on target (above: special rad. safety required)
- 0.5 mm < ø < 45 mm
- 25 MeV < E < 68 MeV (rapid: insertion of Al plates)
- on-line-dosimetry with transmission ionisation chamber
- beam shape visualized via 2D-camera
- well suited for radiation hardness tests often in conjunction with tests on in-house ^{60}Co-source



2004 parts of the Rosetta electronics irradiated
2014: successful end of hibernation

movement sensor of DLR – moved during irradiation



New Target Stations

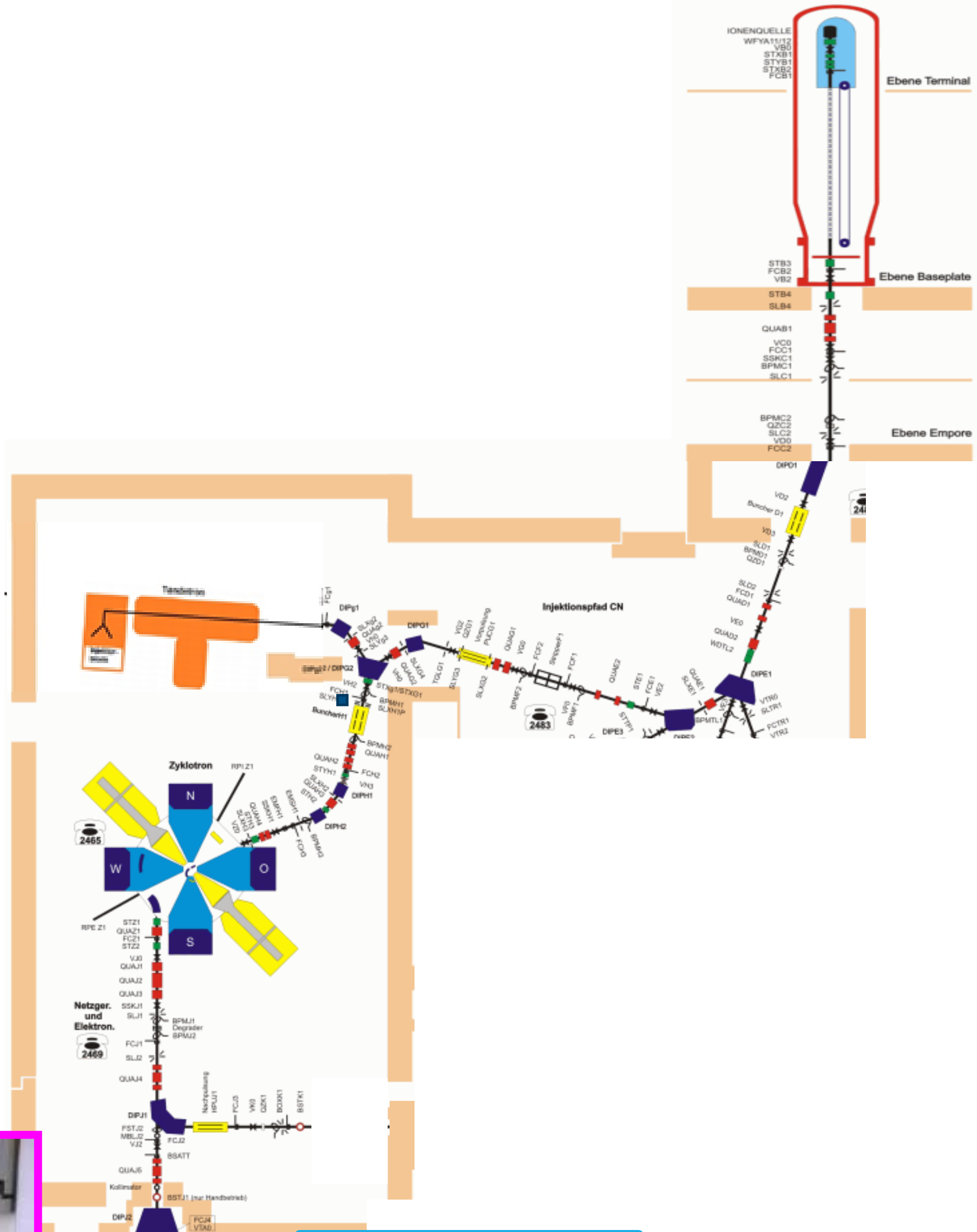
- increased demand on beam time
- increased variety of experiments
- beam time not used due to change of experiment set-up

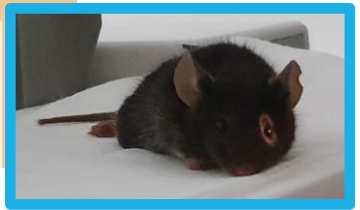
→ new target station dedicated to radiation hardness test: In-Operando-beam line

→ more time for experiment preparation

- collaboration with Universität der Bundeswehr München:

new target station for minibeams





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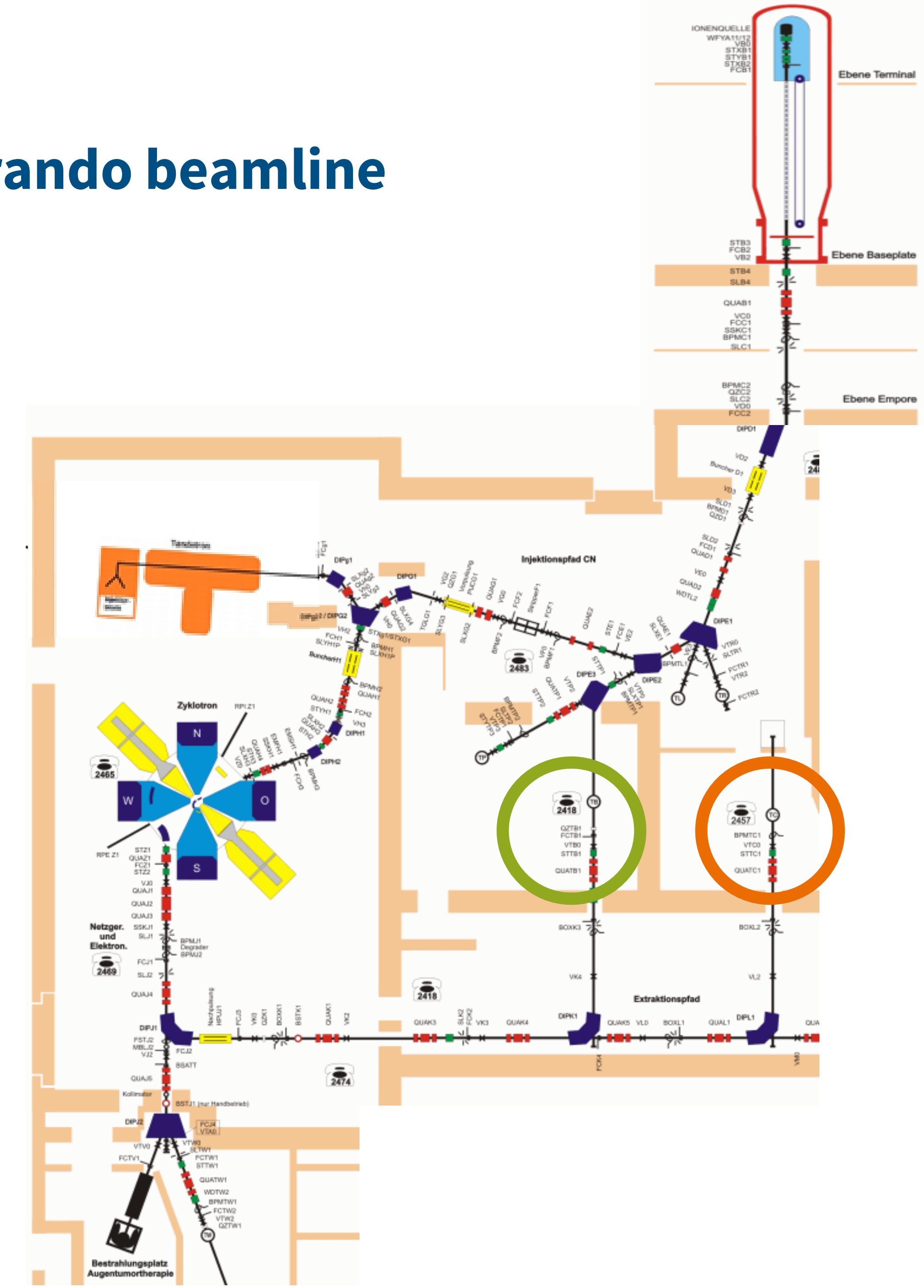
Target Station for Radiation Hardness Tests: In-Operando beamline

- provide more space for accompanying equipment, e.g. sun simulator
- after irradiation:
  additional off-line measurements possible
  samples can stay in control area
- to do:
  - open wall between cyclotron vault and beam line room
  - check for radiation safety
  - enhance system of dose meters
  - perform beam line simulations
  - install beam line
  - install control system
  - commissioning
- applies also for 2nd target station with minibeam



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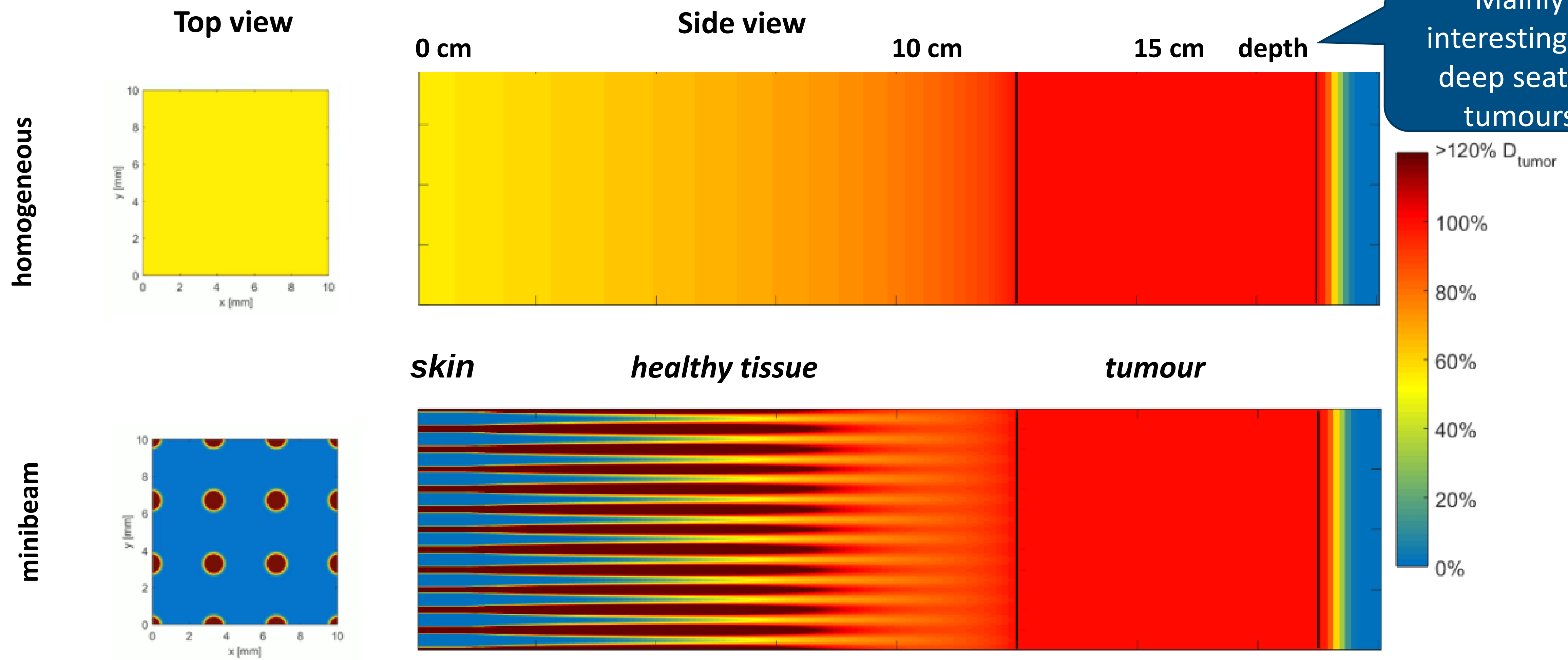
Universität der Bundeswehr München

Proton Minibeam Radiotherapy (pMBRT) - the concept of spatial fractionation

Mainly interesting for deep seated tumours



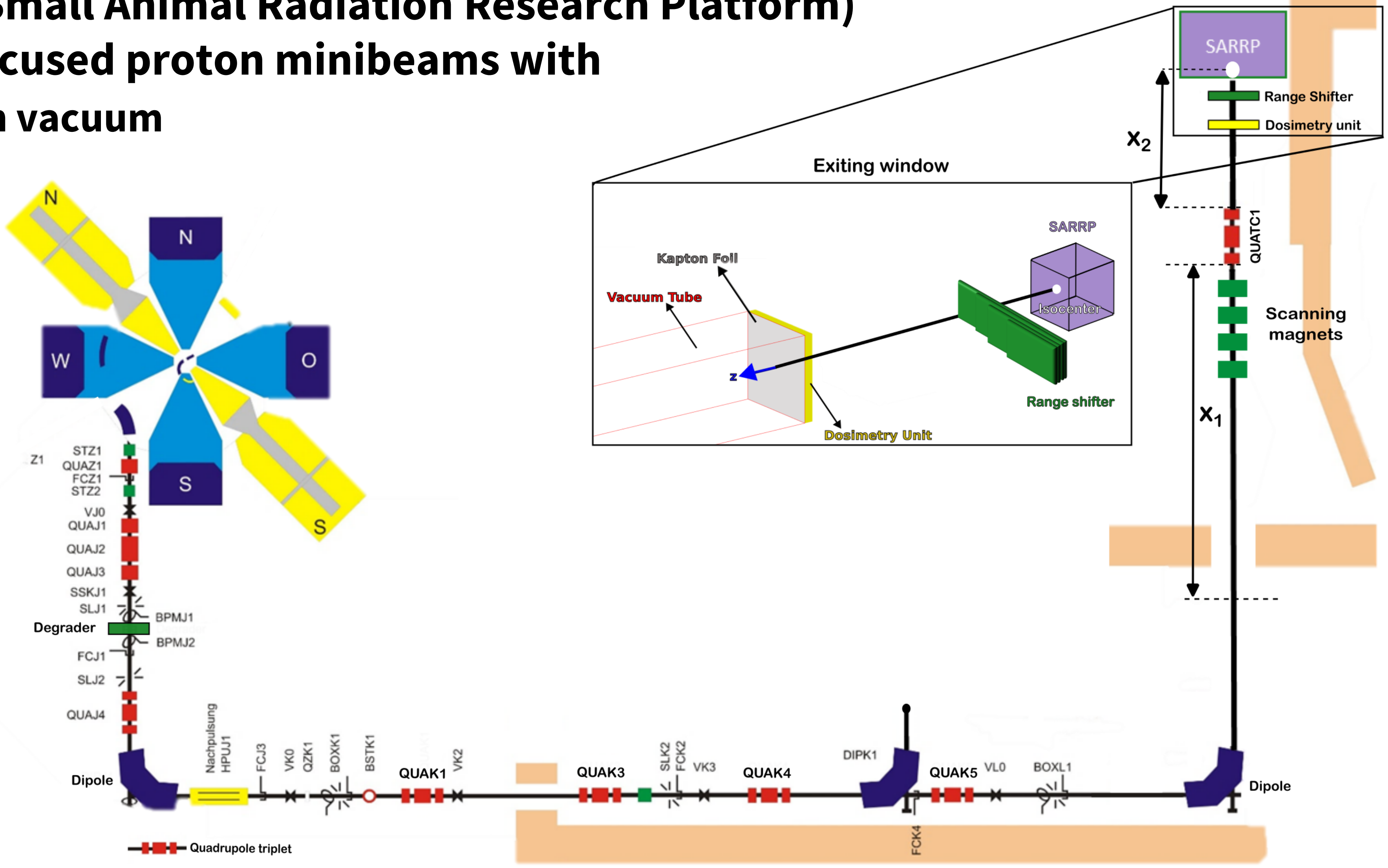
Beam sizes σ: 100 µm to 1mm
Centre-to-centre distance mm range

- Tissue sparing, reduced side effects
- Normal tumour control

Slide by Prof. Dr. Judith Reindl judith.reindl@unibw.de

Proton Mini-Beamline: MINIBEE

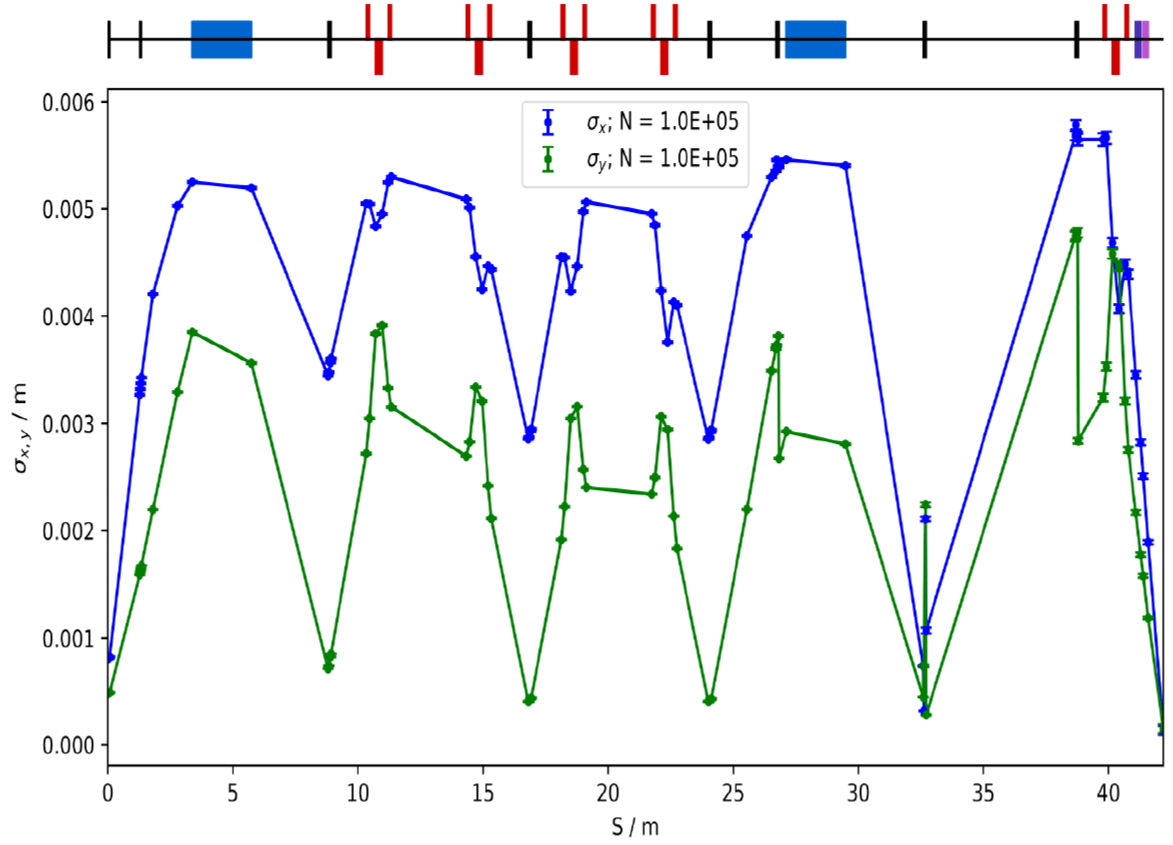
- installation of a SARRP (Small Animal Radiation Research Platform)
- generate magnetically focused proton minibeams with
  - a beam size (σ) of 50 µm in vacuum
  - a centre-to-centre distance in the mm range
  - current of ~ 1 nA

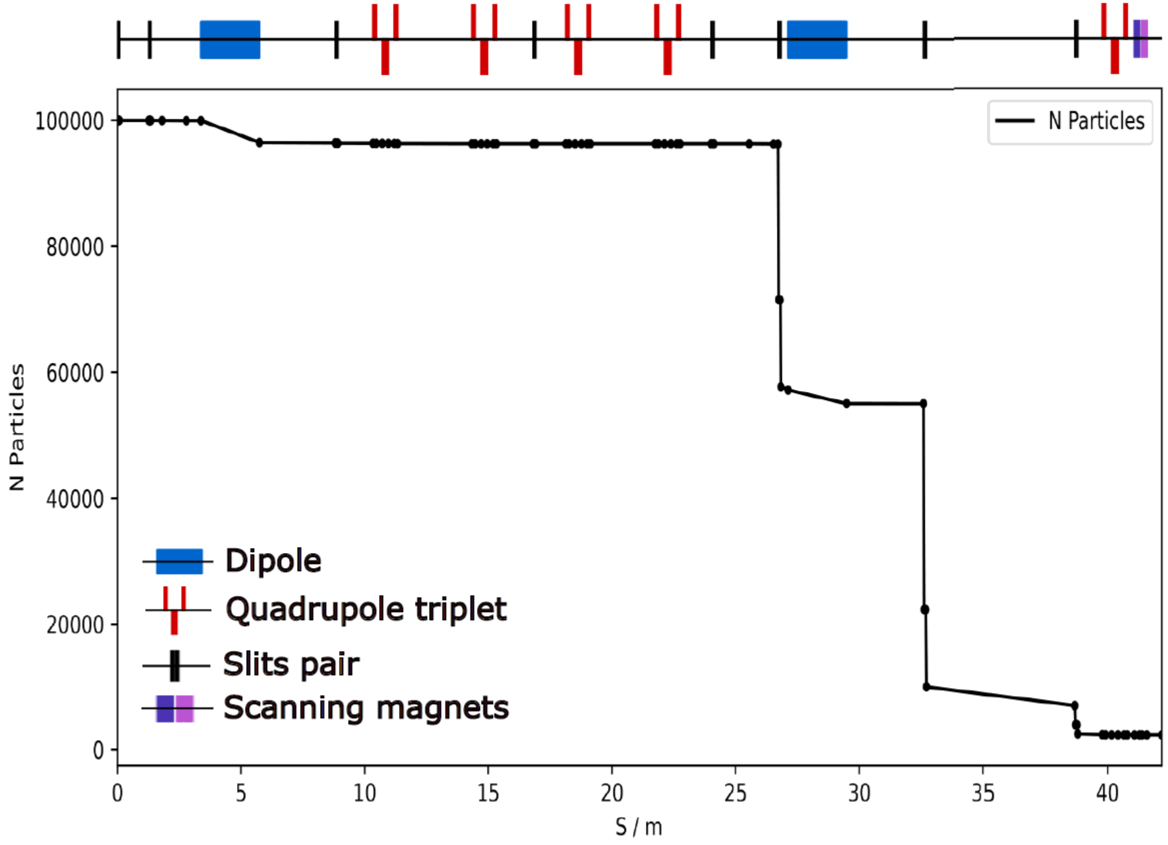


Proton Mini-Beamline: MINIBEE

- **Beam line simulations performed with BDSIM:**

  Current Status of MINIBEE – Minibeam Beamline for Preclinical Experiments on Spatial Fractionation in the FLASH Regime
  A. Rousseti , G. Dollinger, M. Mayerhofer, J. Neubauer, J. Reindl, Universität der Bundeswehr München
  J. Bundesmann, A. Dittwald, A. Denker , M. Kang, G. Kourkafas, HZB
  IPAC 2024

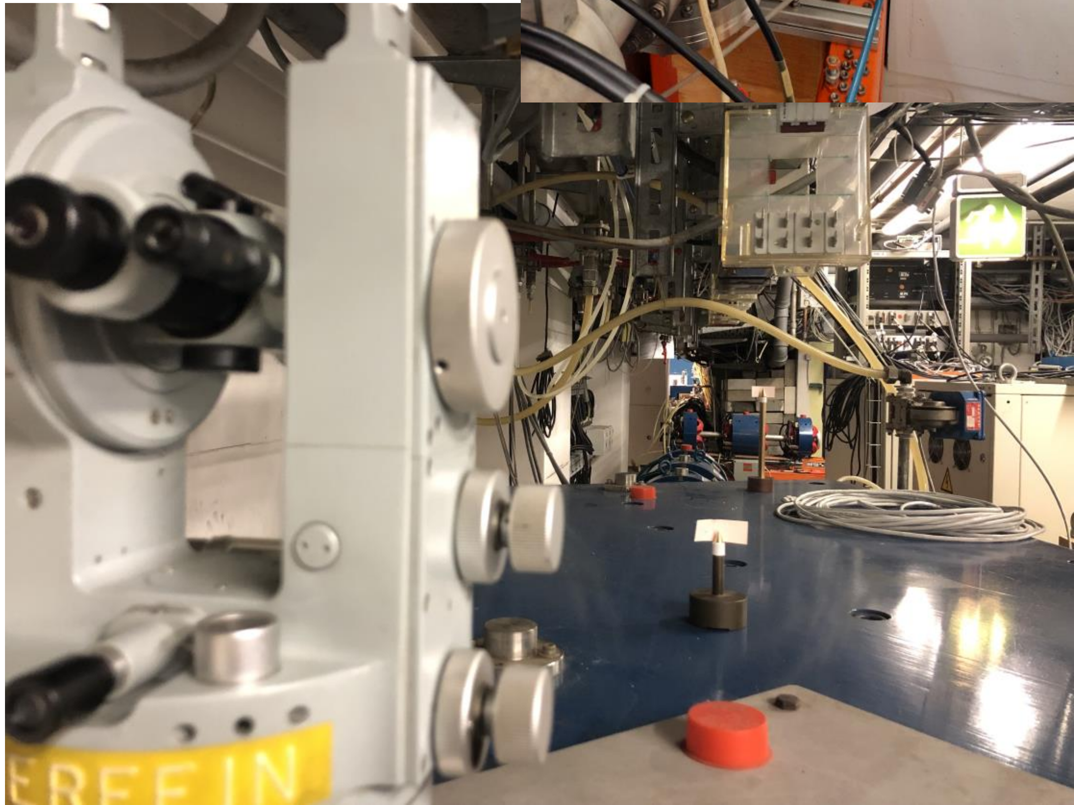




Installation of New Beamlines: To do

- **open wall between cyclotron vault and beam line room** ☑
- **check for radiation safety** ☑
- **perform beam line simulations** ☑
- **install beam line** — **on-going**
- **enhance system of dose meters** — **on-going**
- **install control system:**
  after excellent experiences with LLRF: EPICS

- **commissioning planned for winter 2024**
  last quadrupole for minibeam coming later



Conclusion

- medical application: more than 4700 patients treated
  = 10% of the worldwide ocular melanomas irradiated with protons
- lively research and development program
- new target stations under construction: In-Operando beam line and MINIBEE
- control system for new beam lines: EPICS

Thank you for your attention!

patient statistics based on the apertures used

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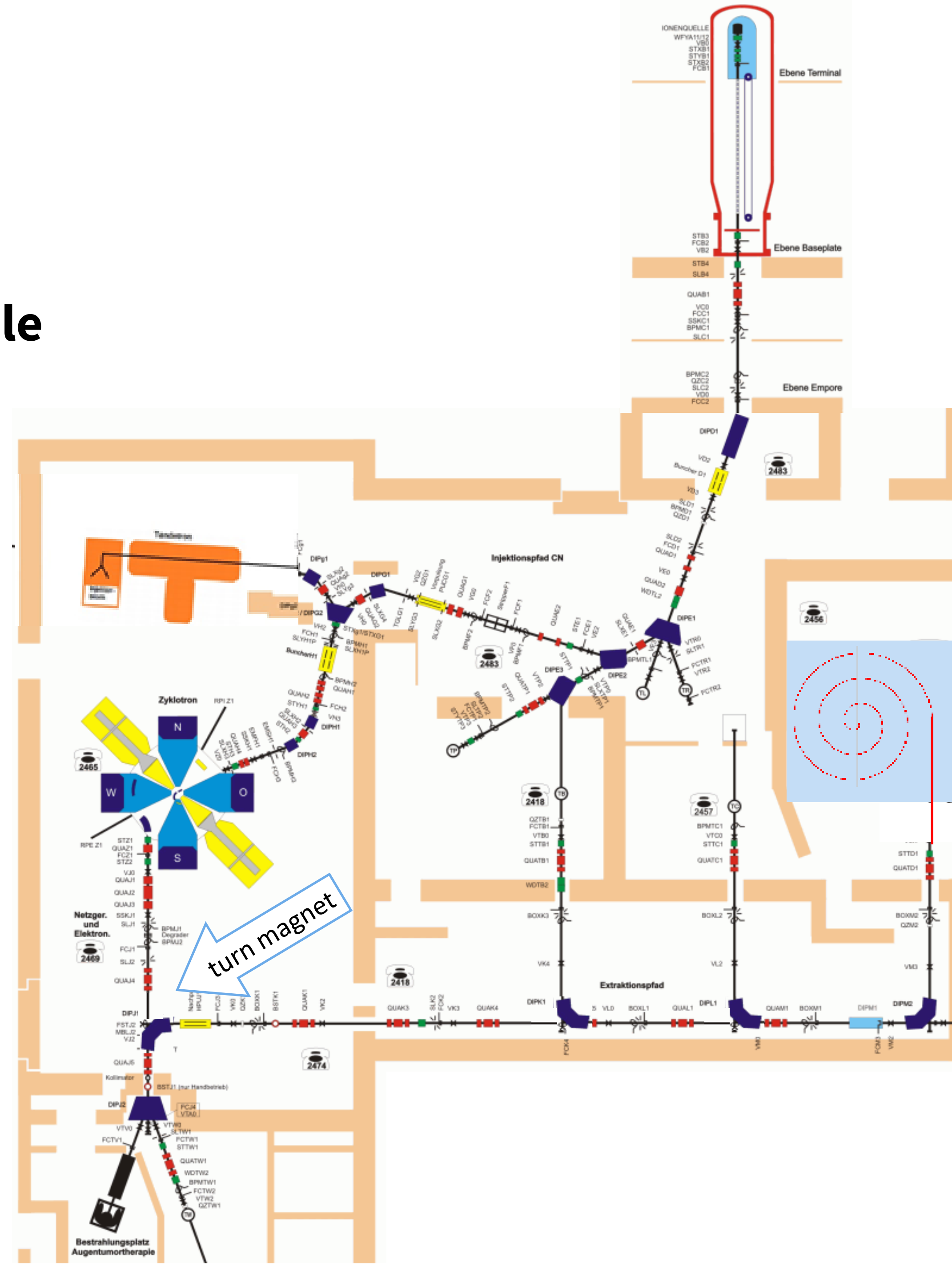
Modernization of Accelerator Complex: Ideas

- use existing building to install a new cyclotron
  → parallel installation to accelerator operation possible
  → adapt existing beam line
- wishlist: about 70 MeV protons, 280 MeV He
  - maintain sharp distal fall-off
  - enhance possibilities for radiobiological research
- experiments with "Cocktail-beams"
  ⇨ 140 MeV H_2^+ and 280 MeV He^{2+}
  ⇨ same magnetic field, adjust RF frequency



Modernization of Accelerator Complex: Tasks

- **cyclotron:**
  - concept study assigned to AIMA development
- **building:**
  - architect evaluated existing building and estimated modernization costs
  - comparison to costs of new building
- **beam line design:**
  - investigate necessary changes
- **write down research programme:**
  - radiation hardness tests
  - radiobiology
  - dosimetry
  - therapy
- **autumn 2024: present conceptual design report to directors**

AIMA DEVELOPPEMENT
Accelerators for Industrial and Medical Applications

fun facts: new building might be cheaper!

Universität Potsdam

Deutsches Zentrum DLR für Luft- und Raumfahrt

CHARITÉ

BHT Berliner Hochschule für Technik

Universität der Bundeswehr München

+ others

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HZB Overview and Research Topics

- former research reactor BERII, out of operation since 12/2019
- cyclotron
- electron synchrotron BESSY II
- core labs
- ~ 1200 people at two scientific locations

- photon science
- photovoltaics
- solar fuels / catalysis
- electrochemical energy storage
- quantum and functional materials
- accelerator research