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Low-pressure gas detector for radiotherapy:

Applications of nanodosimetry in proton and ion beam therapy

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Proton therapy center
Krakow, Poland
Greenland
Iceland
Finland
Canada
Ukraine
Kazakhstan
Mongolia
China
Italy
Spain
Türkiye
Iran
Afghanistan
Pakistan
North
Atlantic
Ocean
Mexico
Algeria
Libya
Egypt
Saudi Arabia
Mali
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Sudan
Chad
Nigeria
Ethiopia
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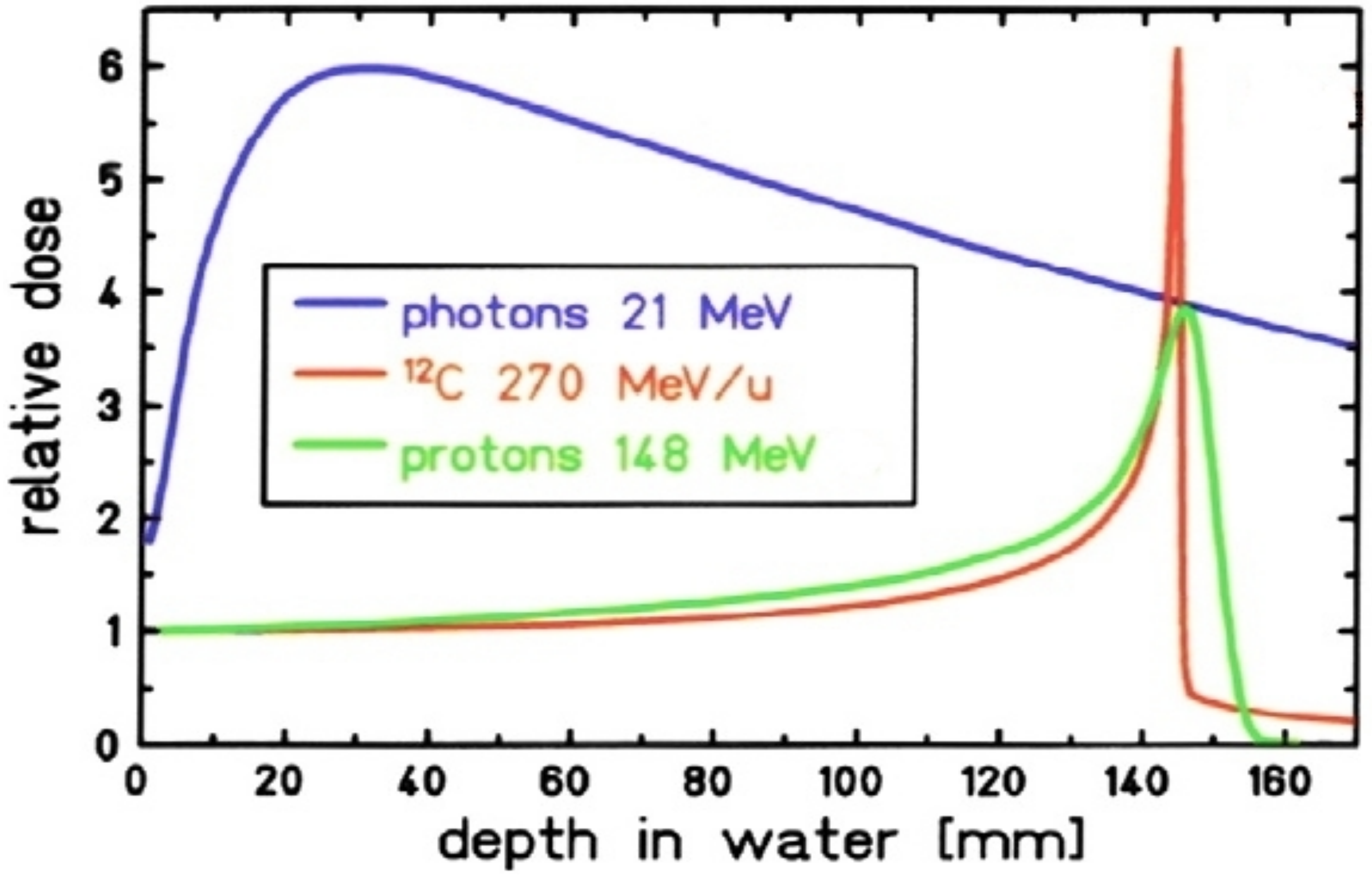
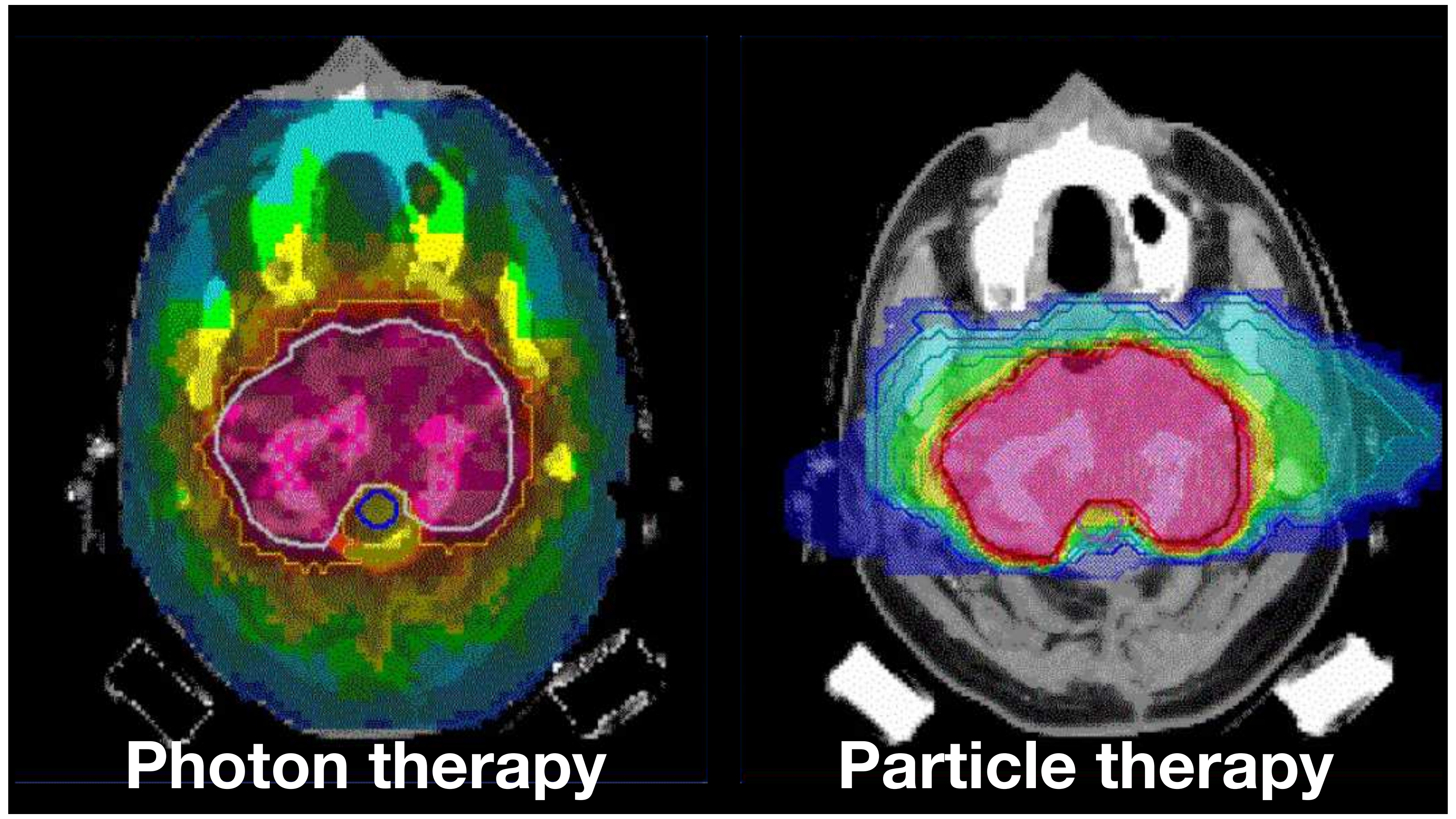
Radiation therapy with photons and ions





Radiation therapy

- Maximize the dose in the tumor, minimize the dose in normal tissue

Ions exhibit

- Inverted depth-dose profile
- Finite range
- Reduced integral dose (~2-3)

Ions allow

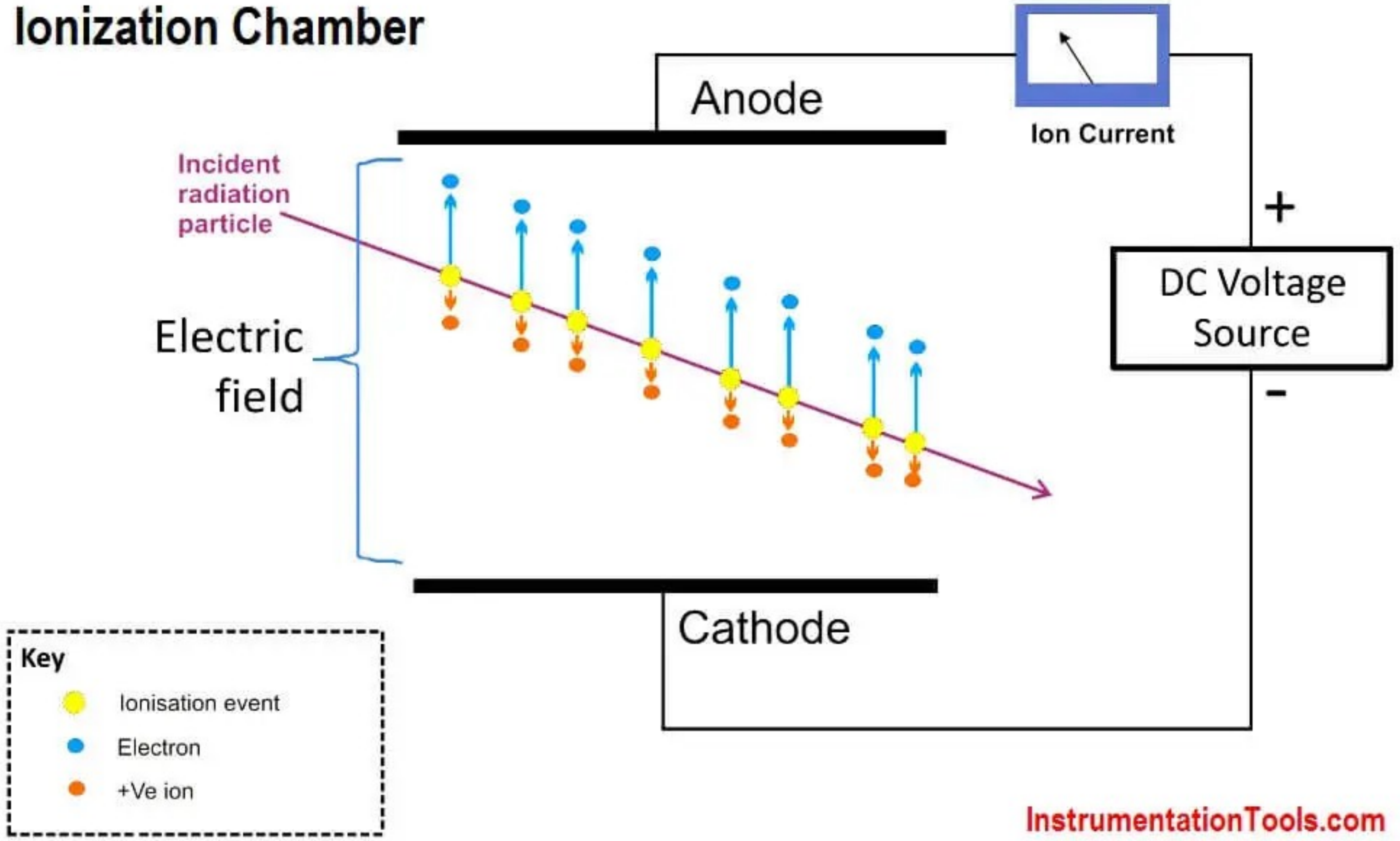
- Superior tumor dose conformity

Ions introduce

- Increased sensibility to range uncertainties

Ionization chamber

From: http://www.ptw.de



Ionization events are integrated over time

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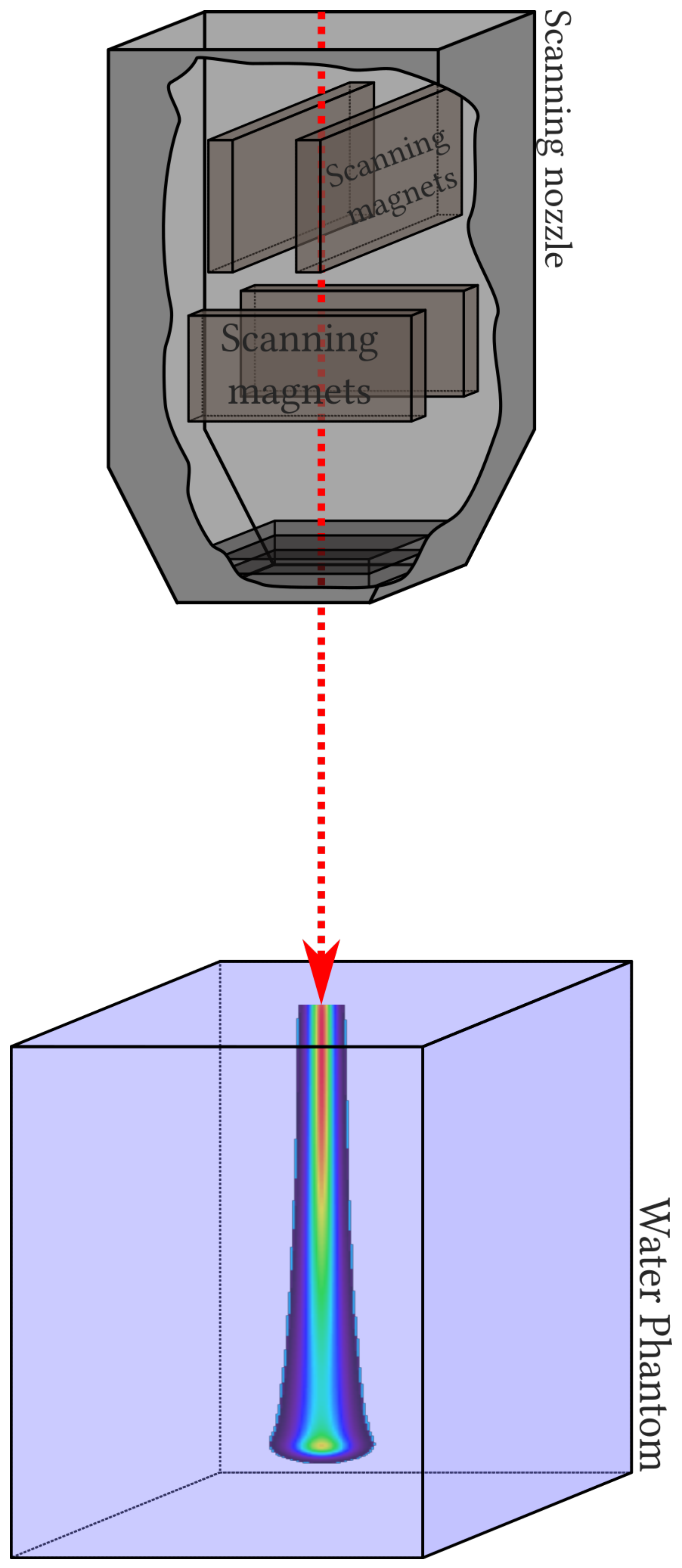
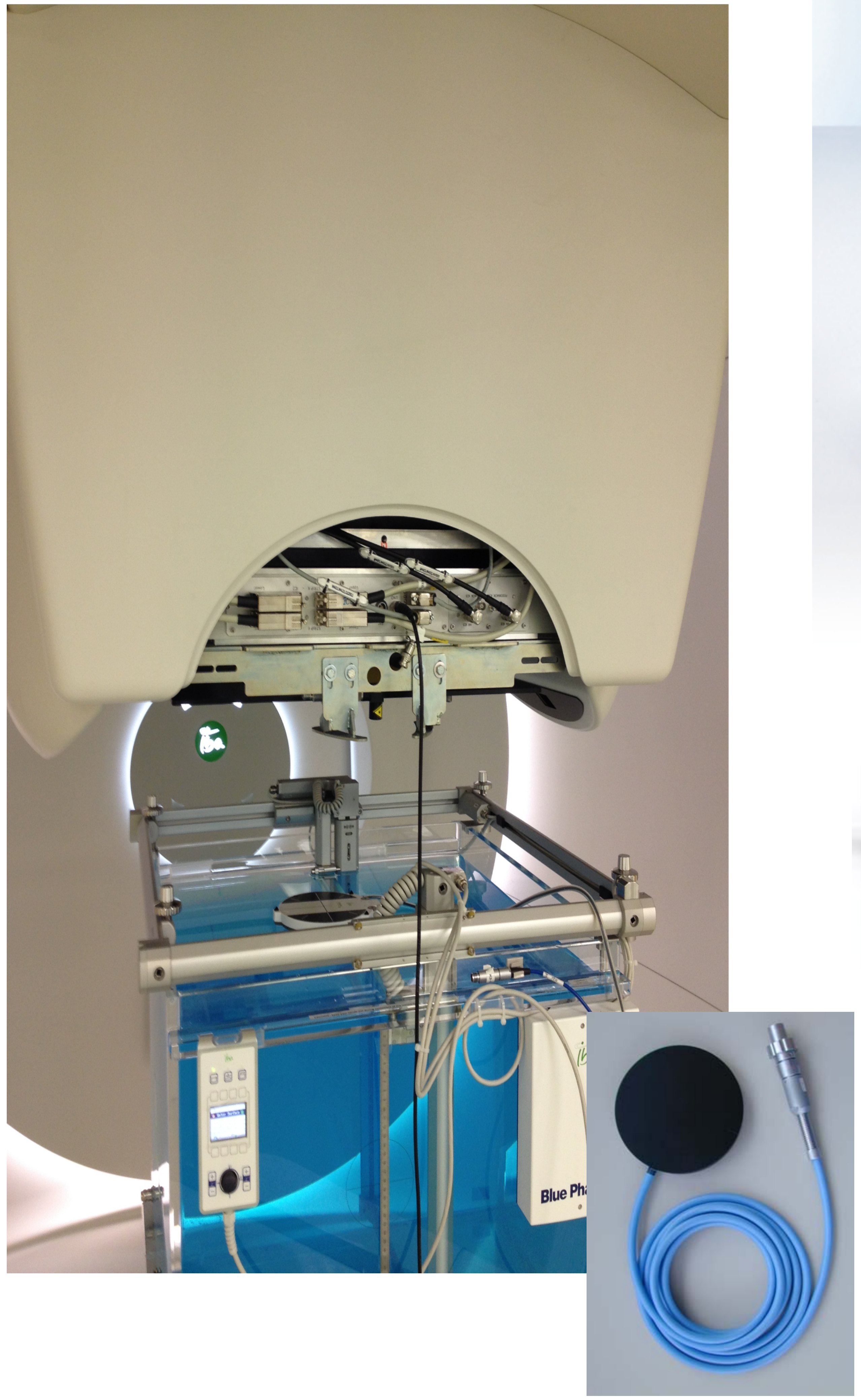
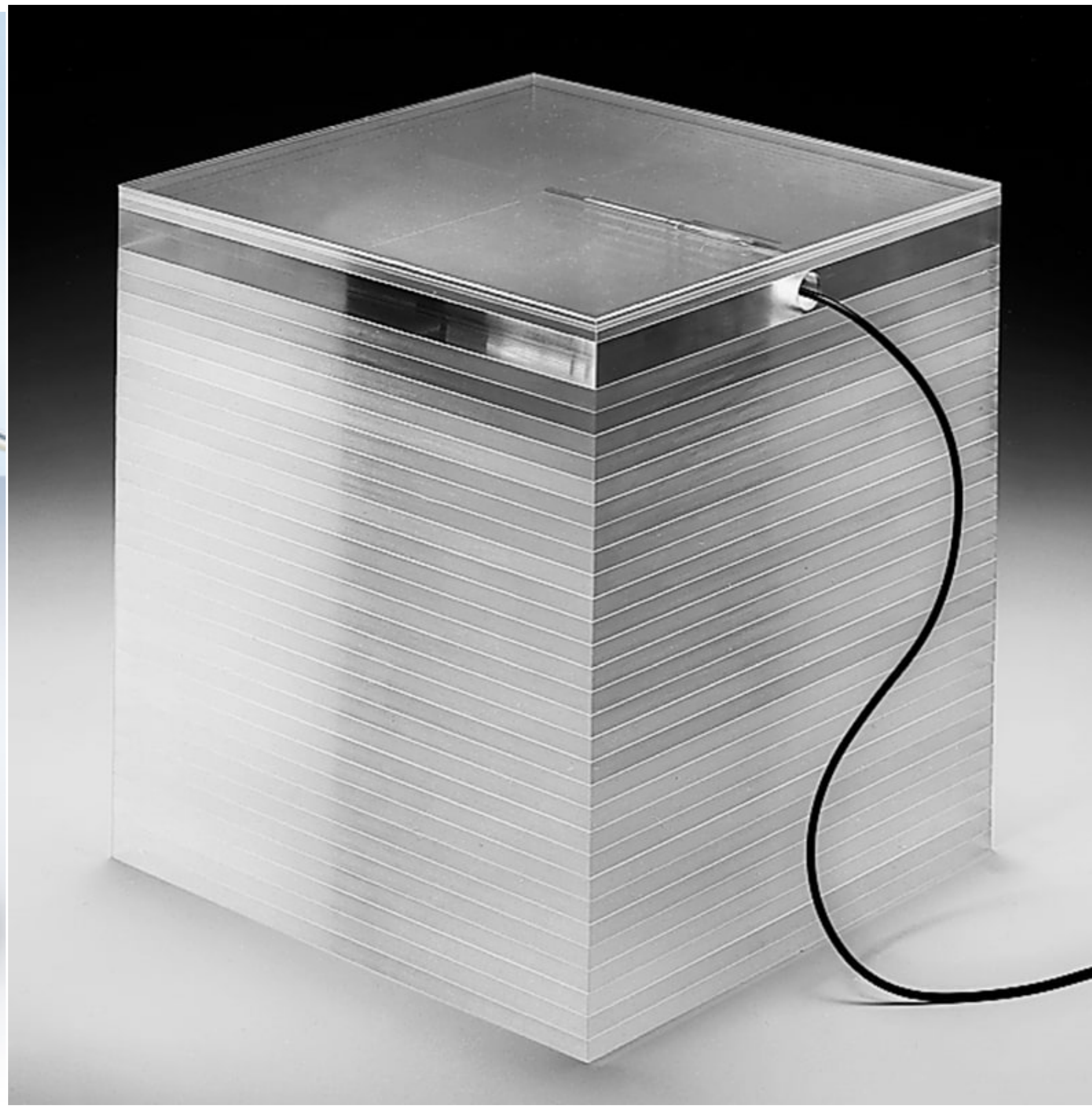
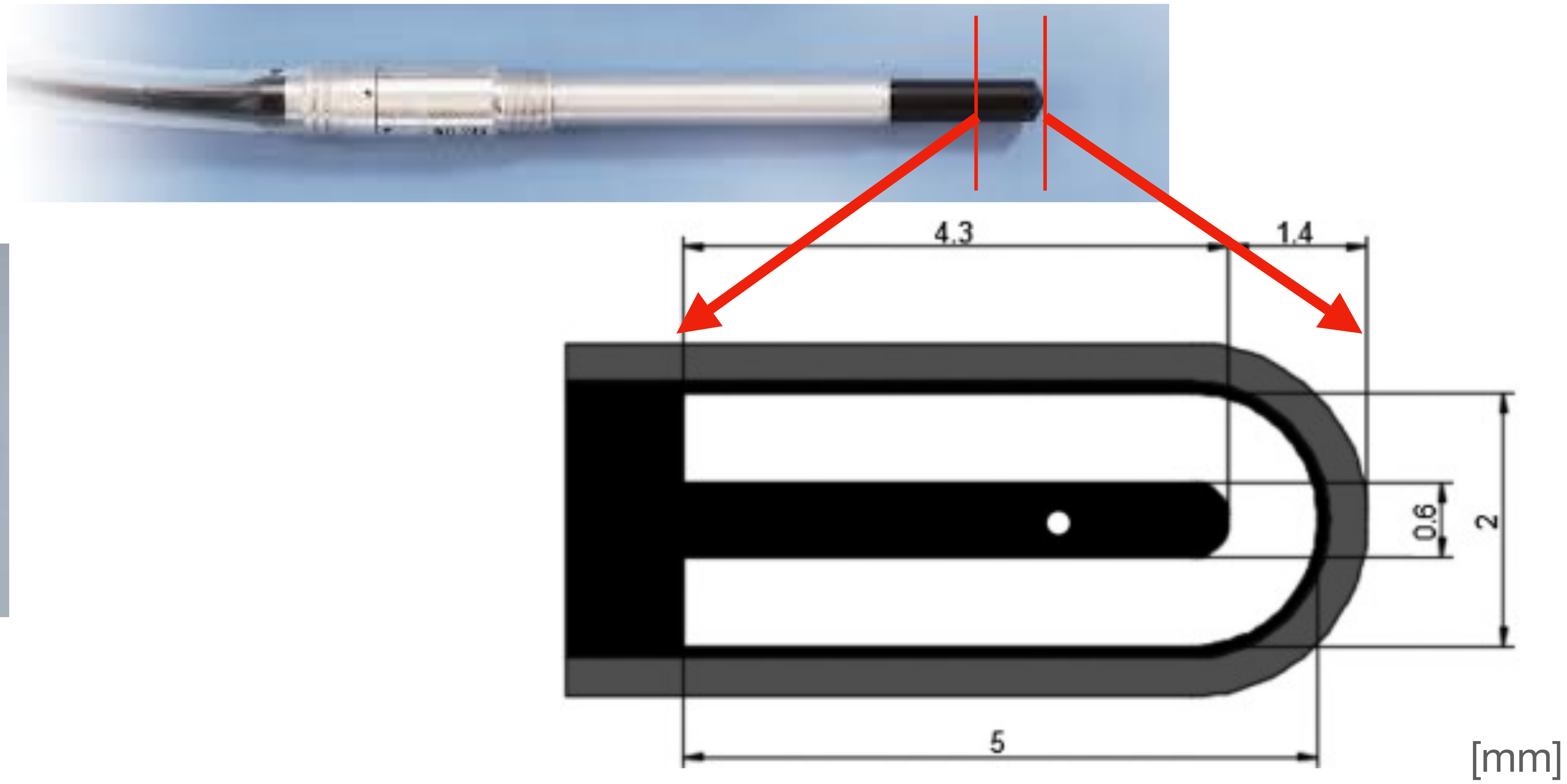
Beam characterization









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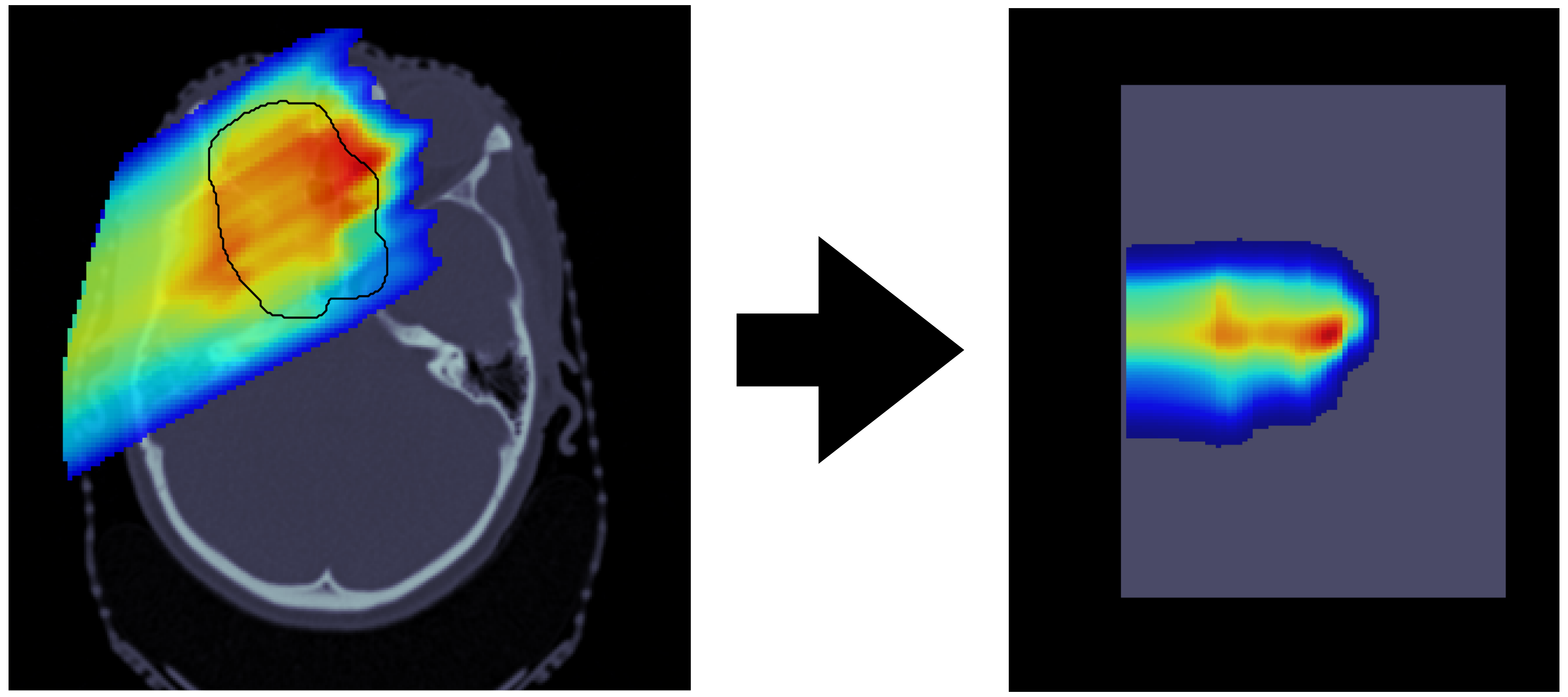
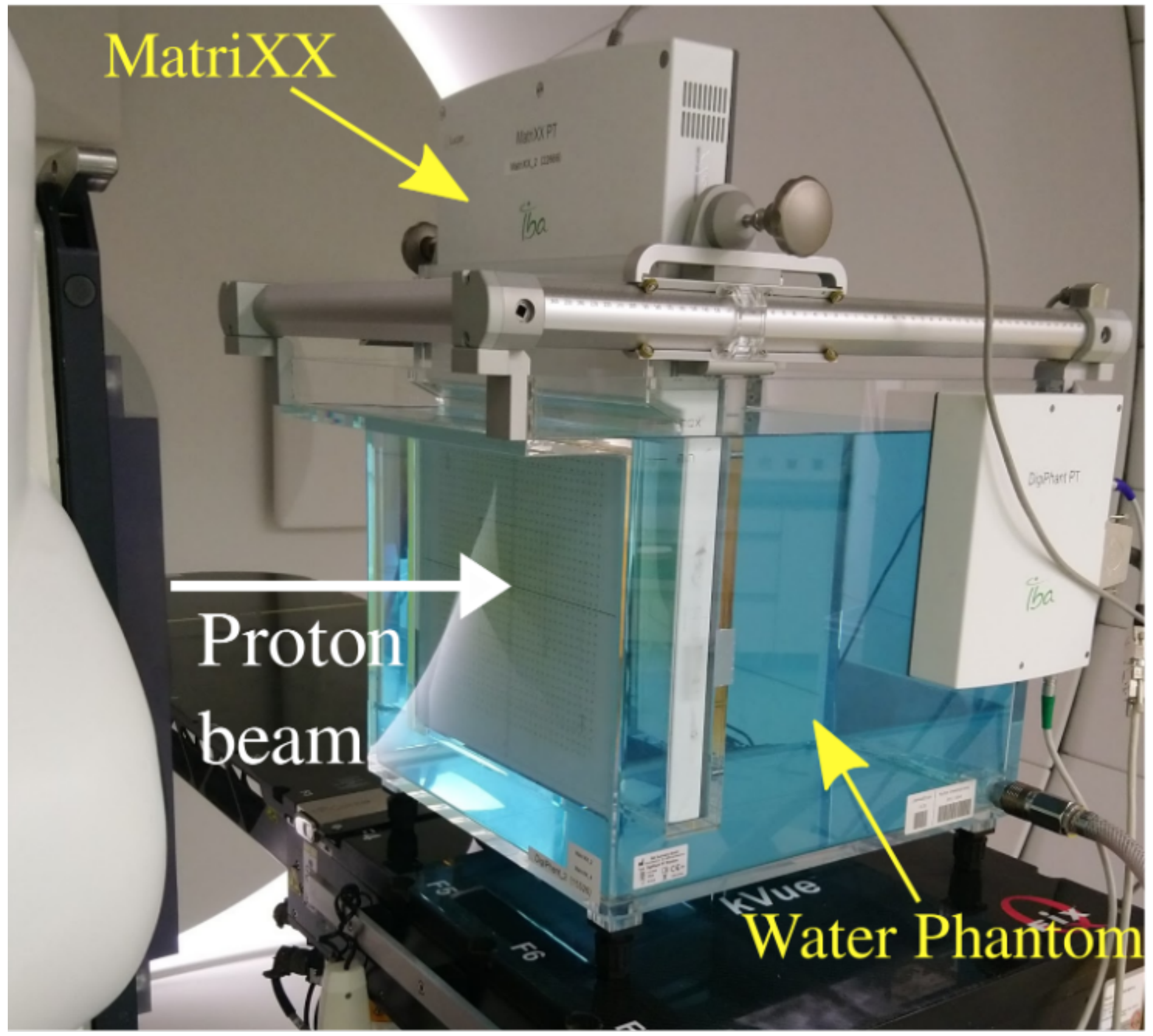
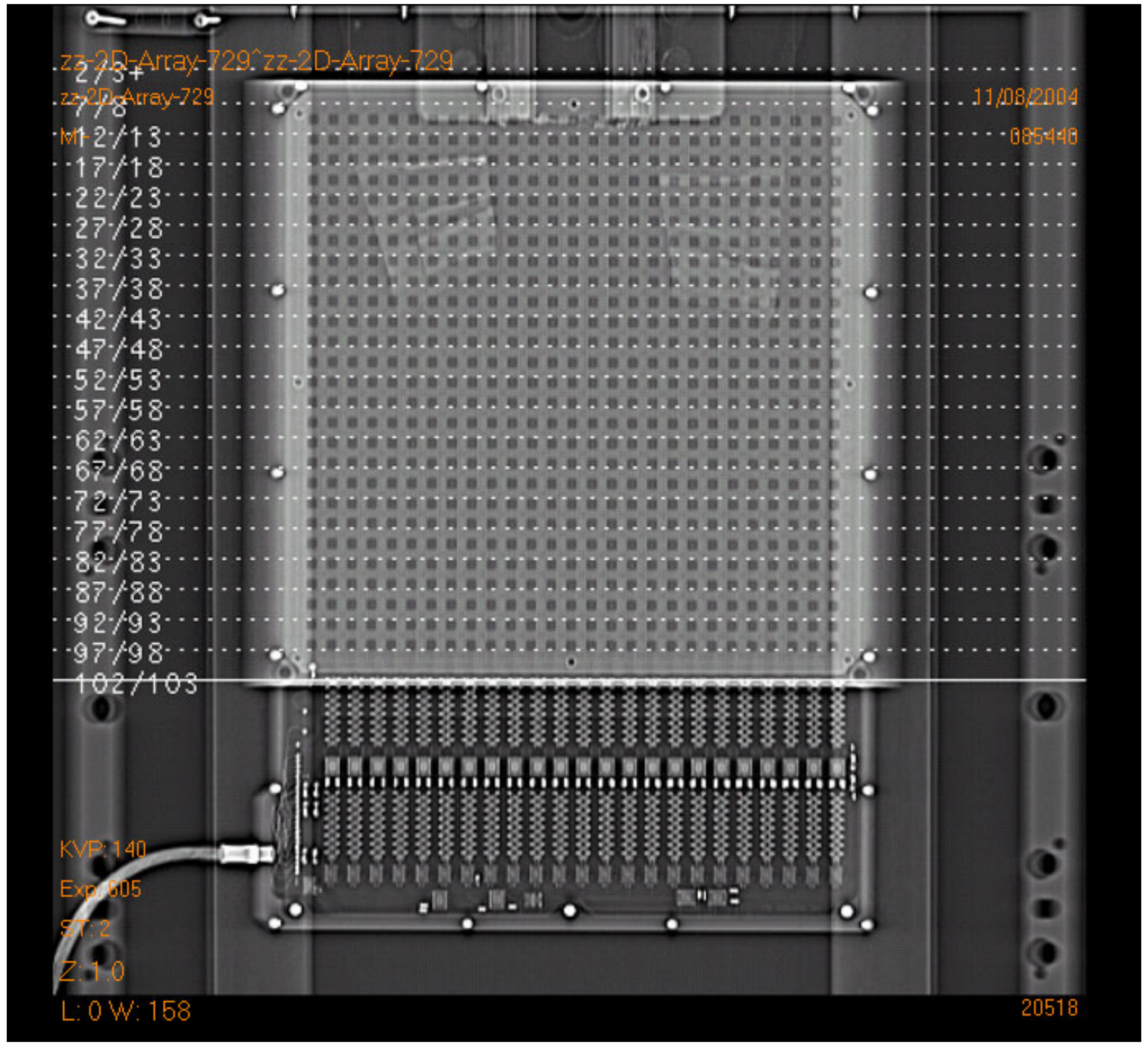
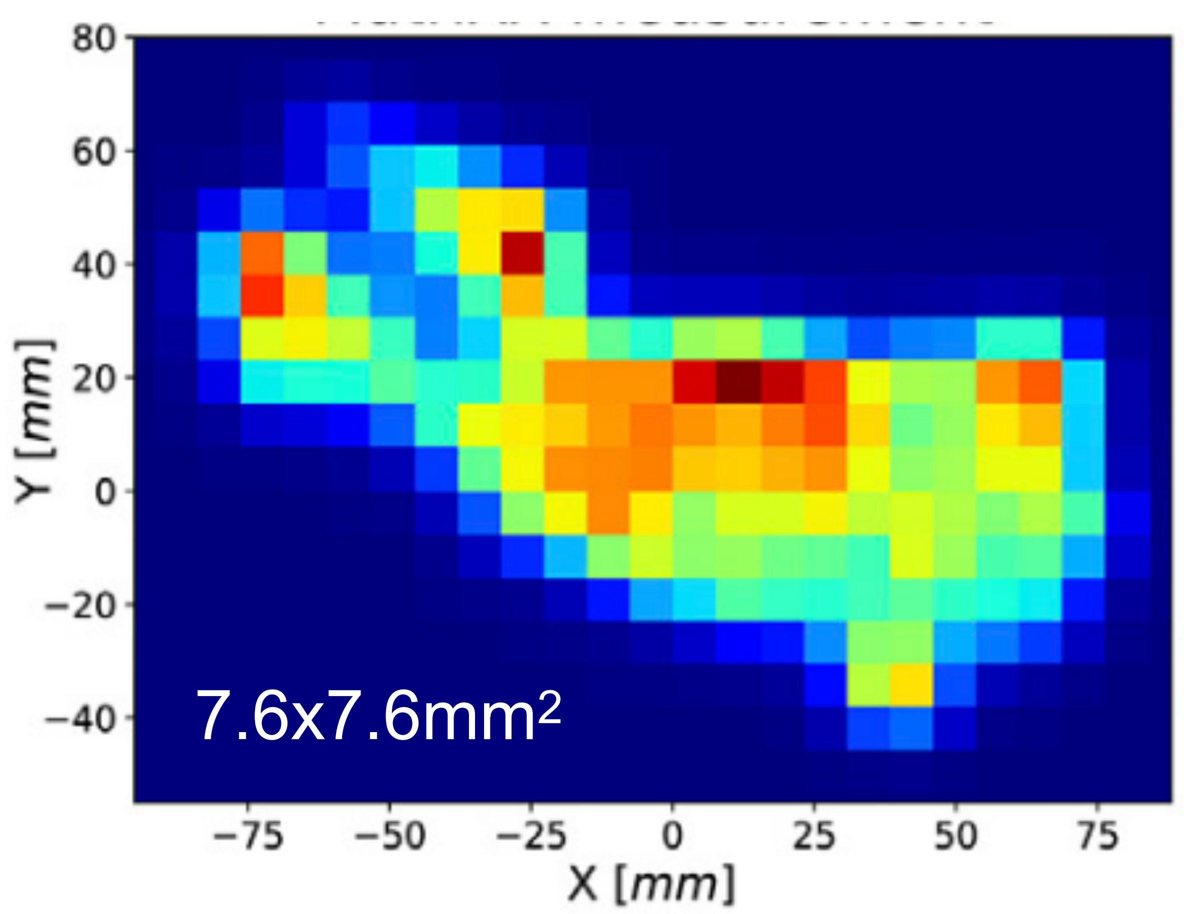
Treatment plan verification

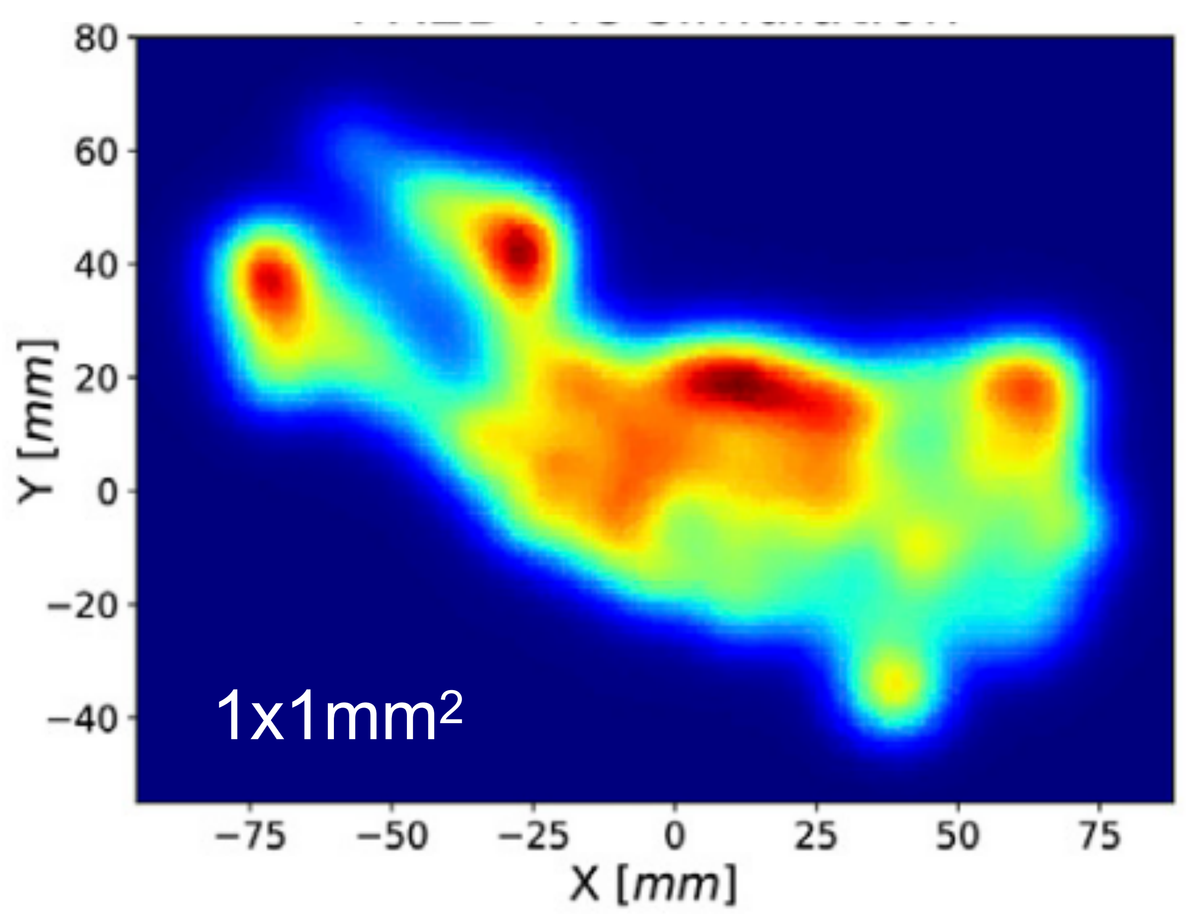


Pixel size of 1-3mm3









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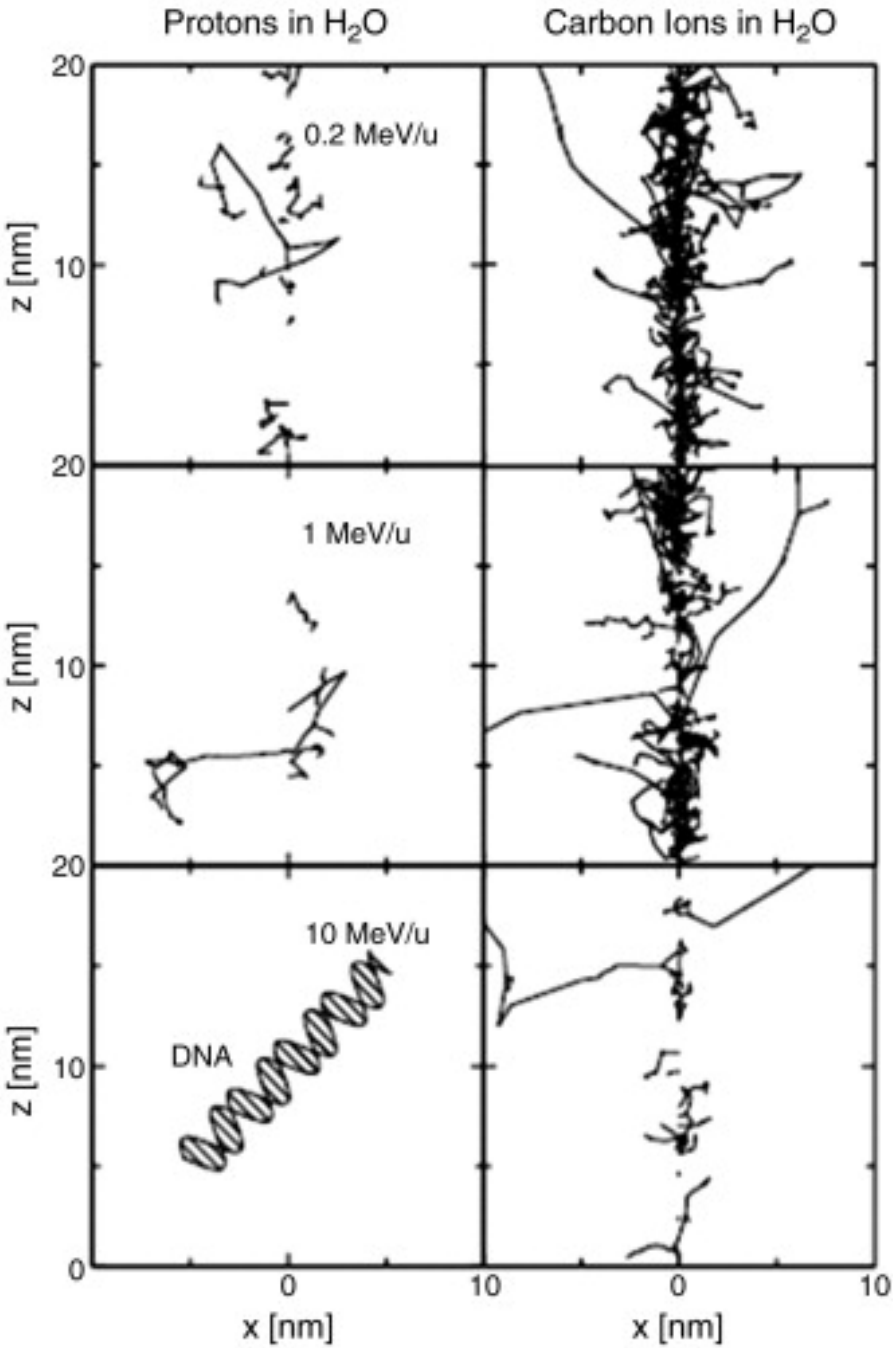
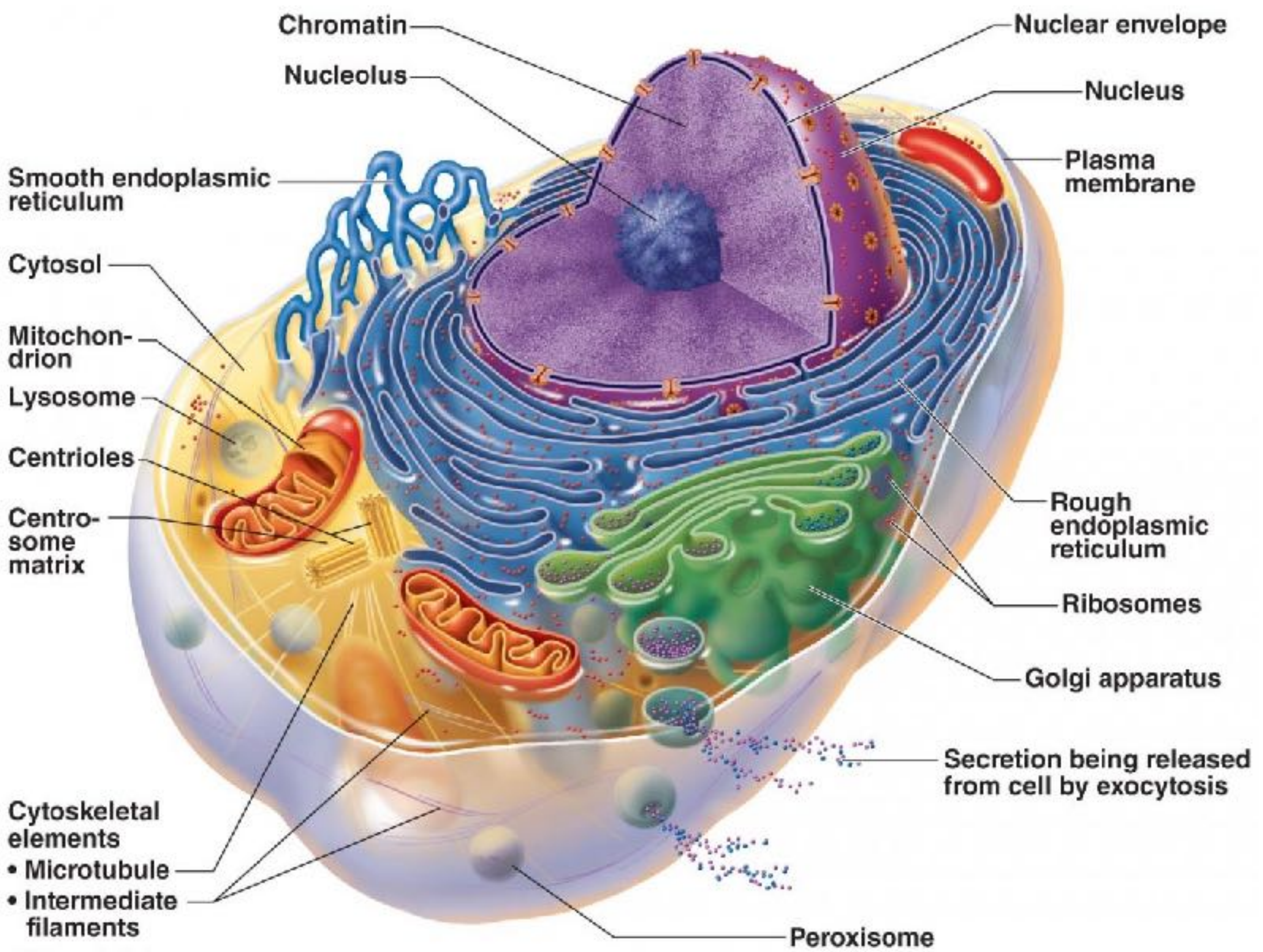
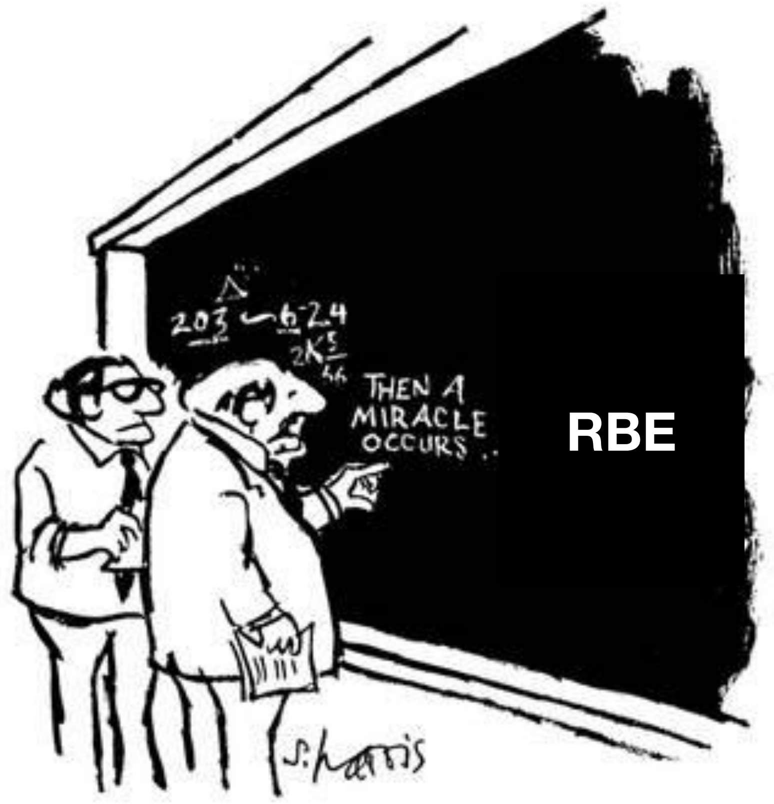


M. Kramer, G. Kraft Calculations of heavy-ion track structure
Radiat. Environ. Biophys., 33 (1994), pp. 91-109

Dose becomes inadequate at microscopic levels

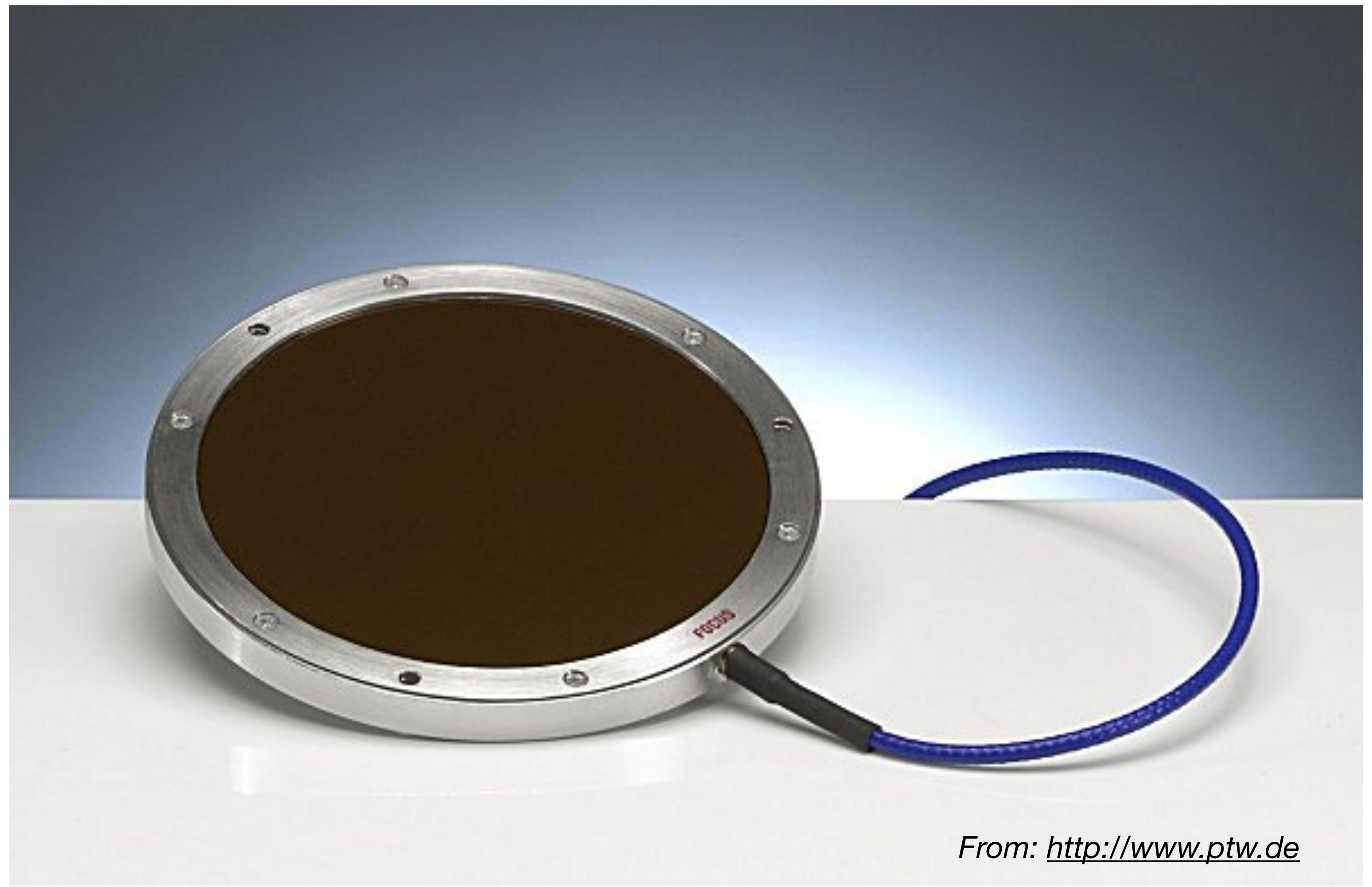
Cell/DNA damage: Micro/nano-scopic concepts





"I think you should be more explicit here in step two."

Dose: Macroscopic concept



From: http://www.ptw.de

- **The state-of-the-art particle RT treatment planning:**
  - Is based on the RBE models dependent on dose, and LET or microdosimetric quantities
  - Does not directly take into account the knowledge on nanoscopic patterns created by particles

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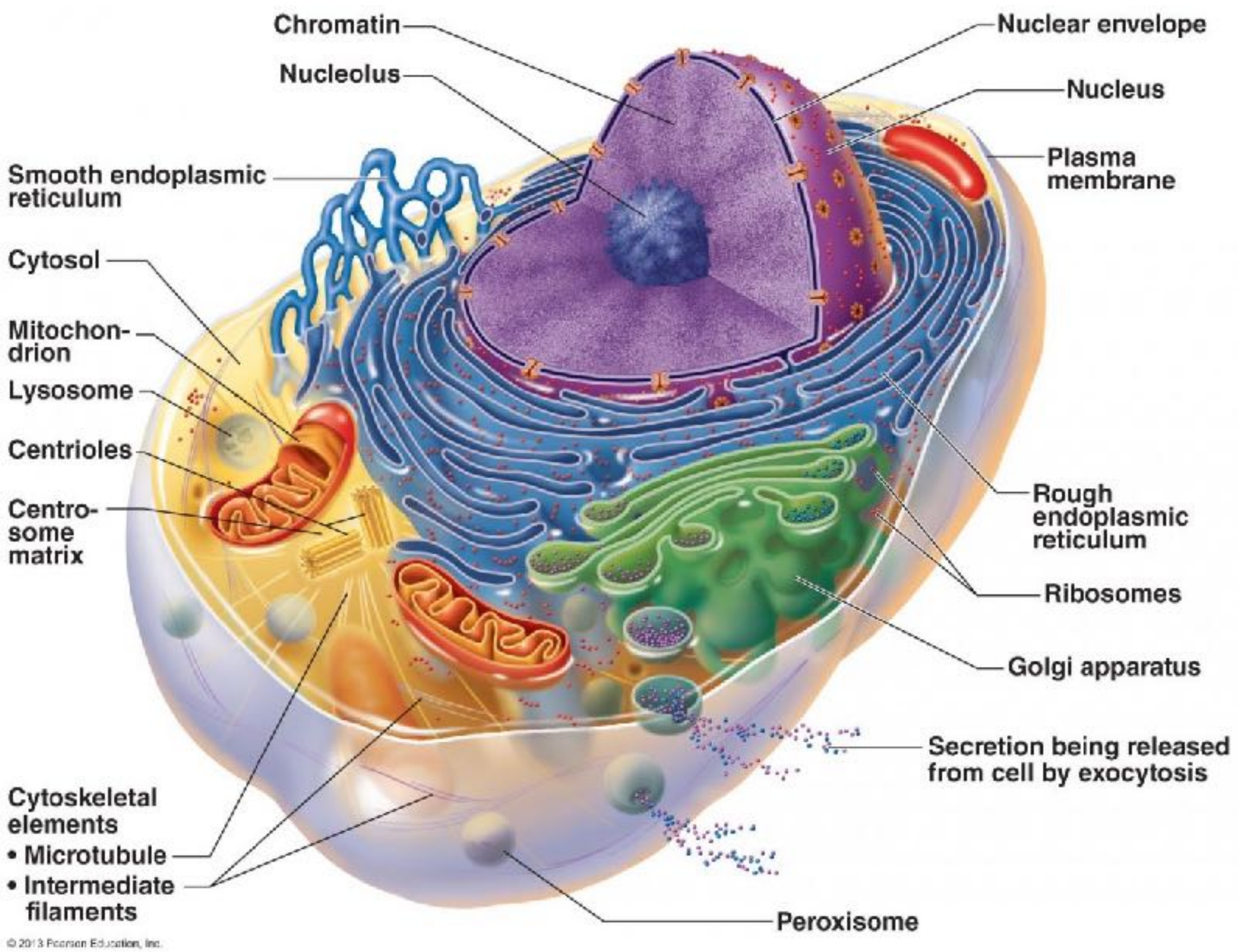
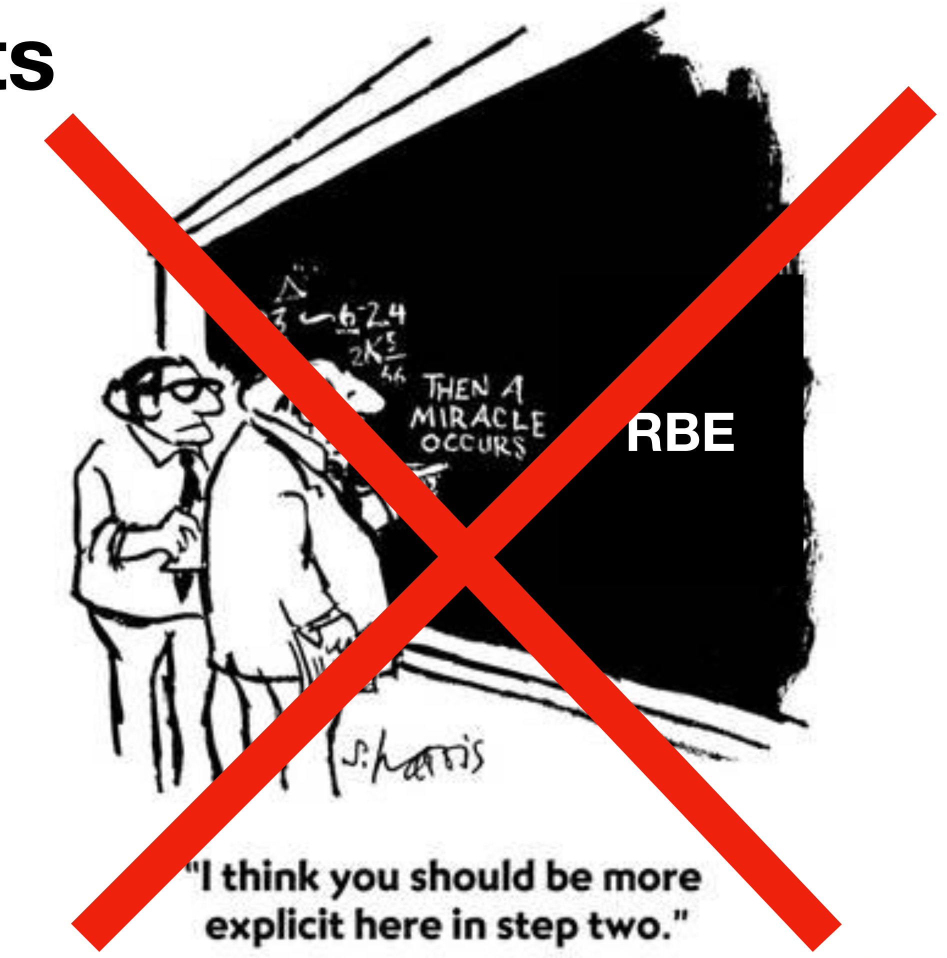
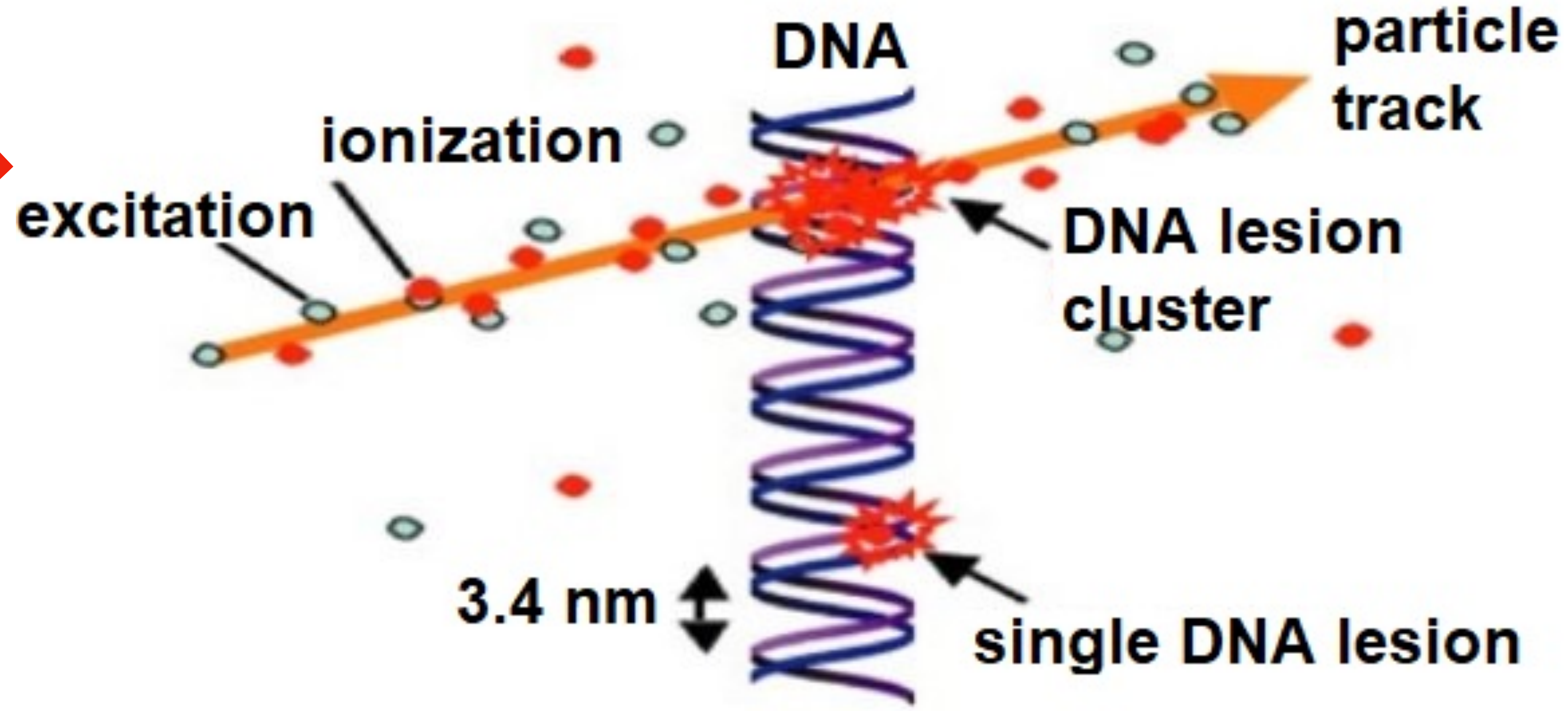
Dose becomes inadequate at microscopic levels

Cell/DNA damage: Micro/nano-scopic concepts





Ionisation clusters and DNA lesion clusters



- **Radiation damage is a stochastic quantity on the micro- and nanoscopic level, there fore the modeling solution must use micro- and/or nanodosimetric distrbutions rather than average quantities (LET, absorbed dose).**

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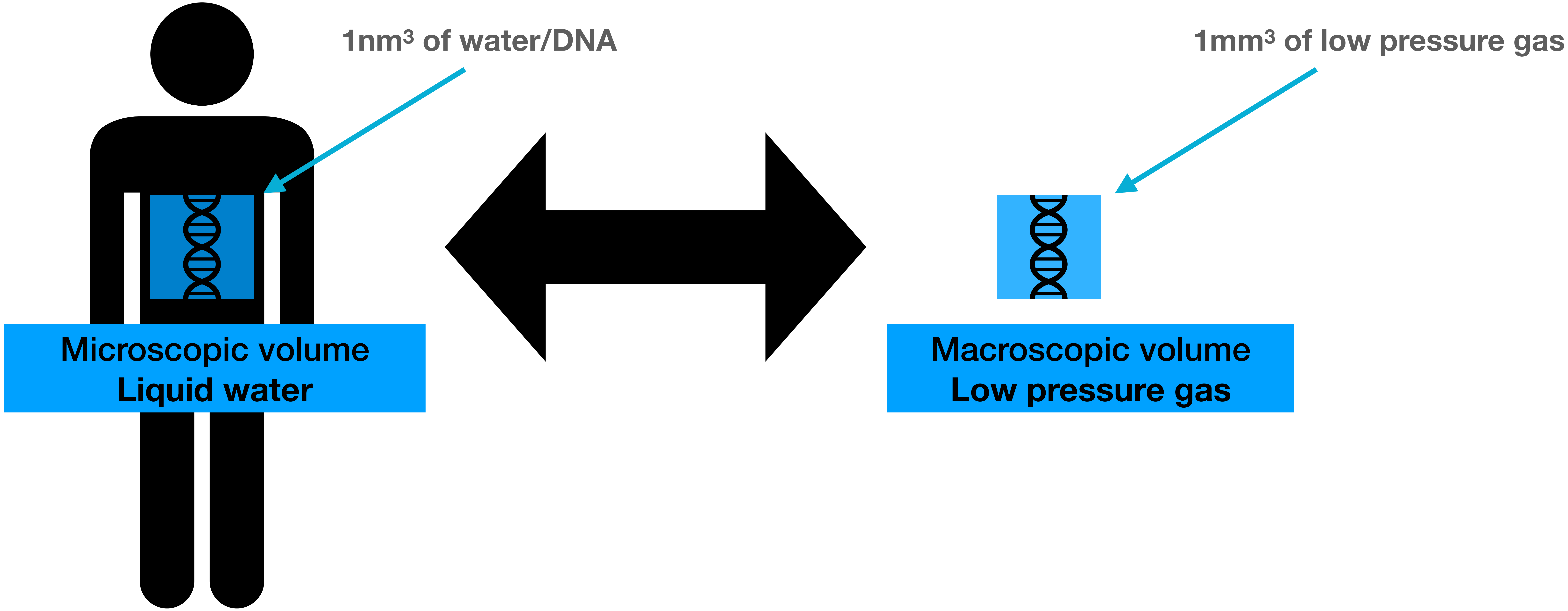
Principles of nanodosimetry

How can we measure on a nanometer scale?

Equivalence principle



Grosswendt et al 2004

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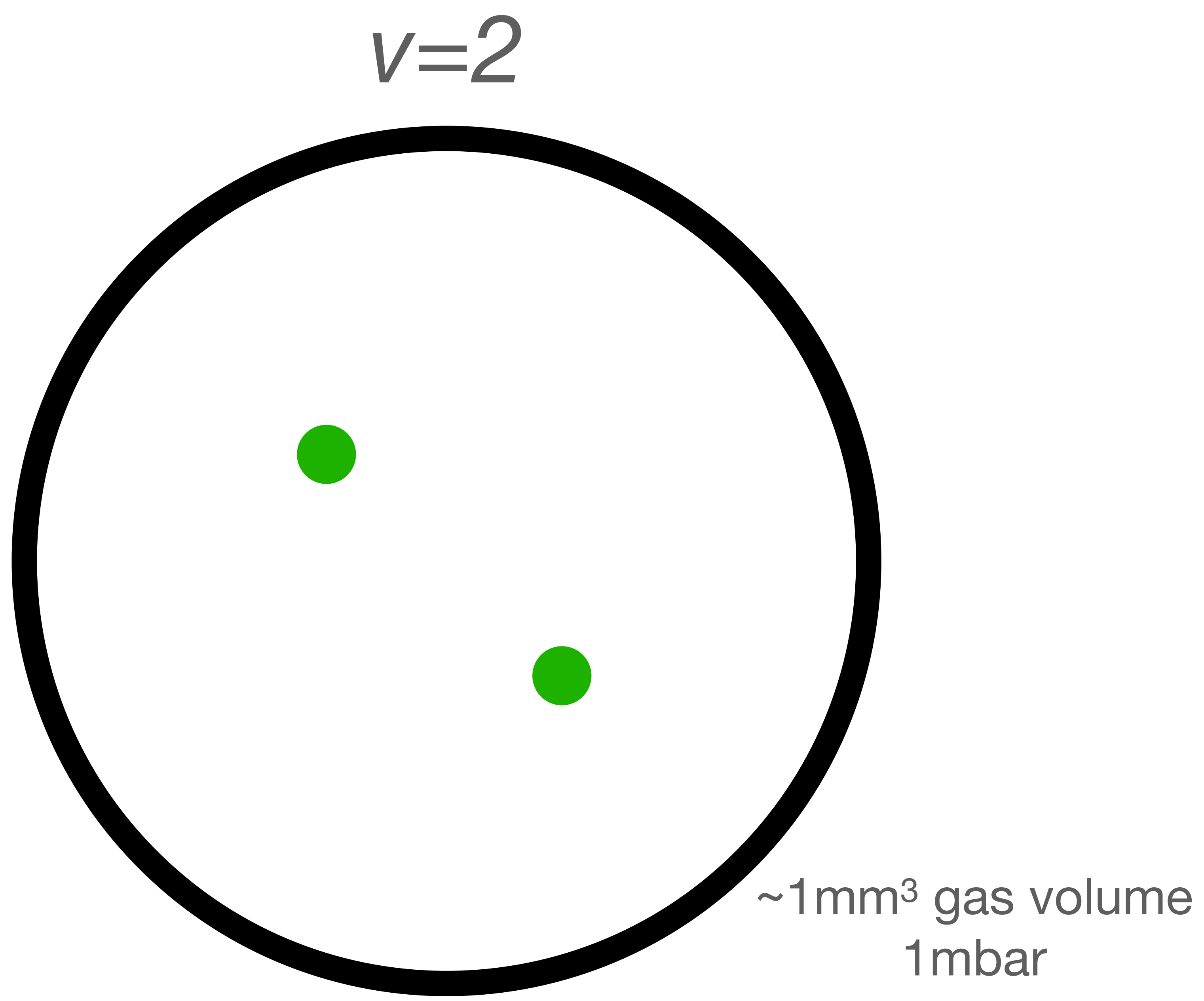
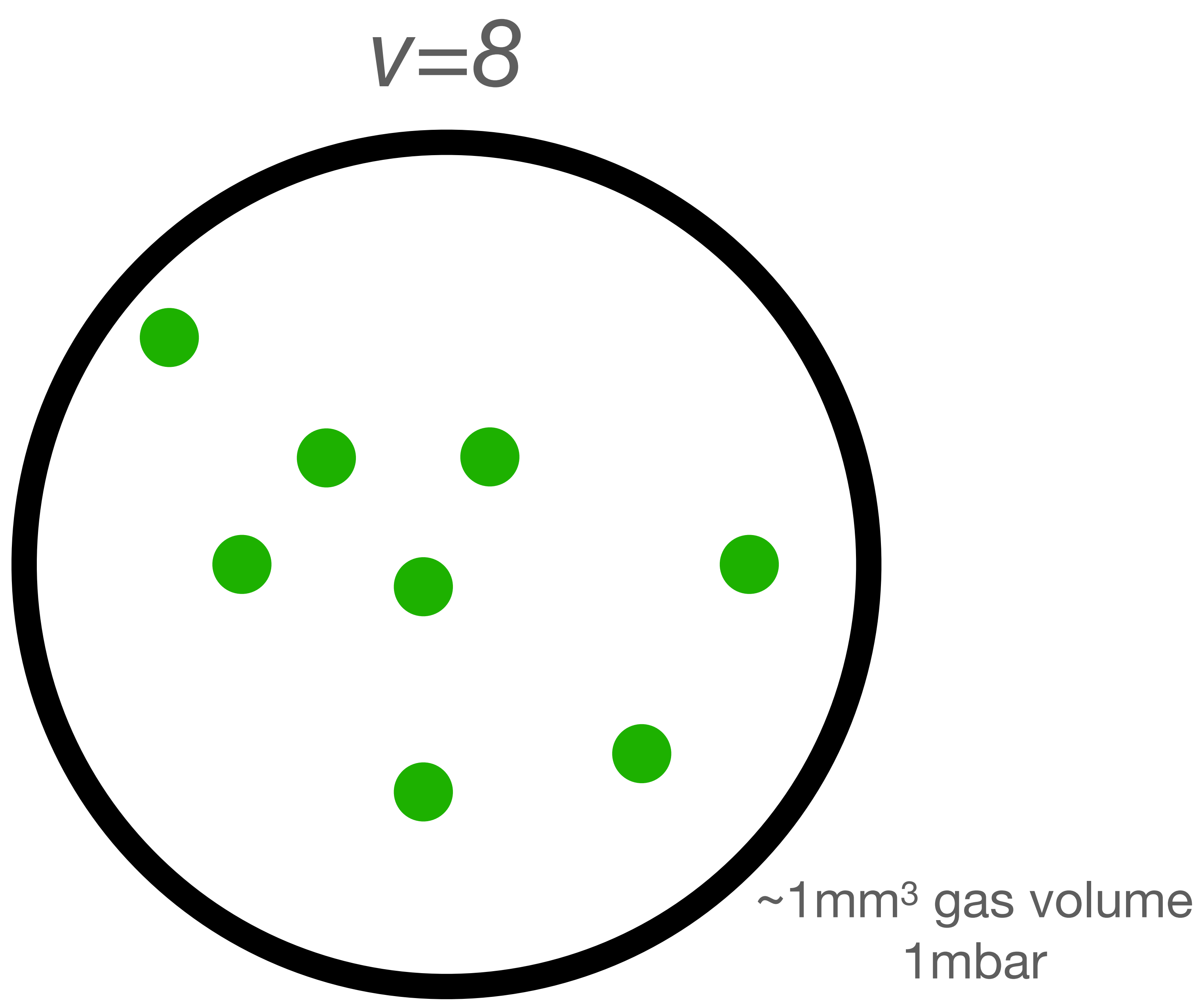
Ionization cluster SIZE: *ν*

Primary physics quantity to replace dose



Small cluster



Large cluster

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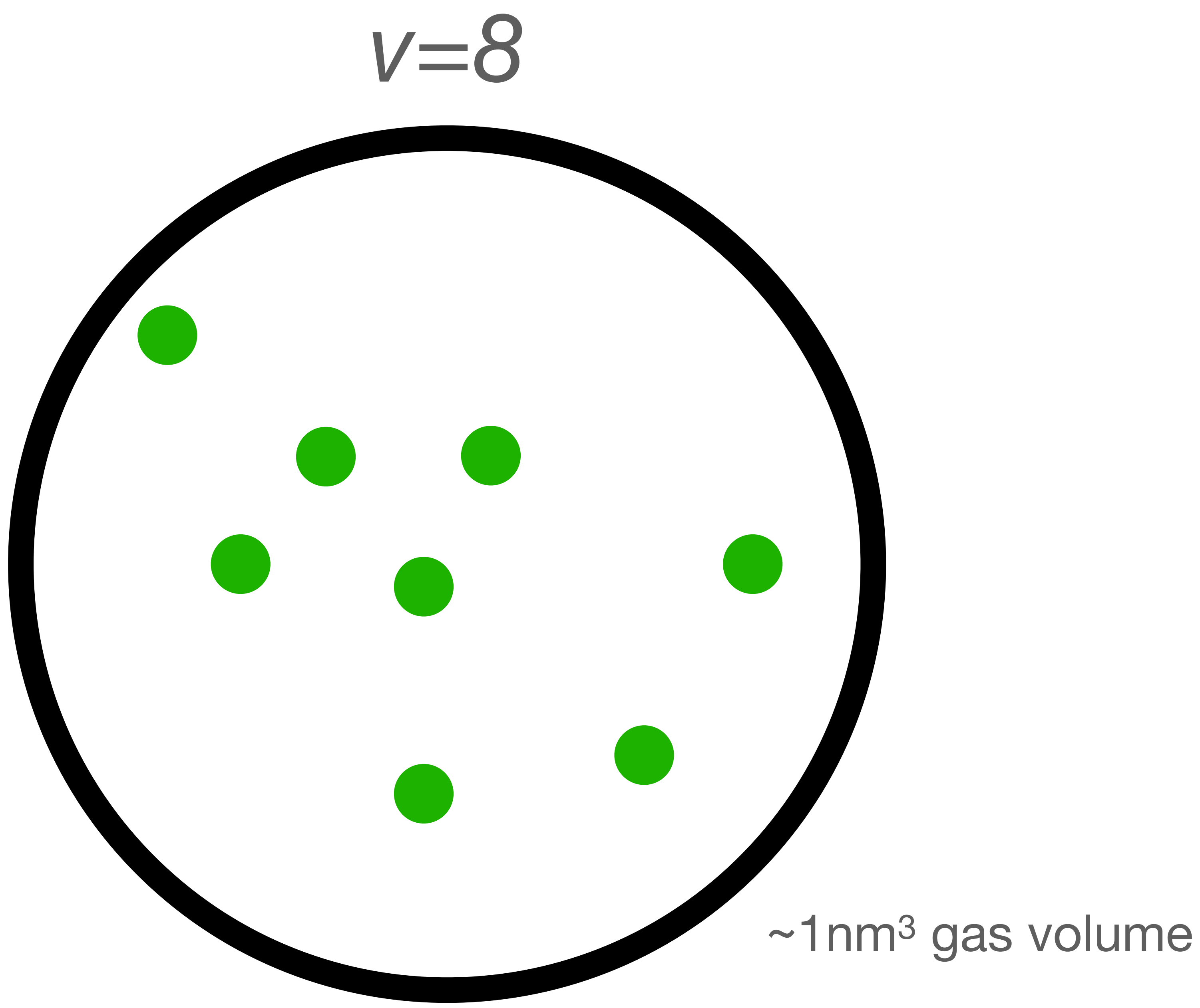
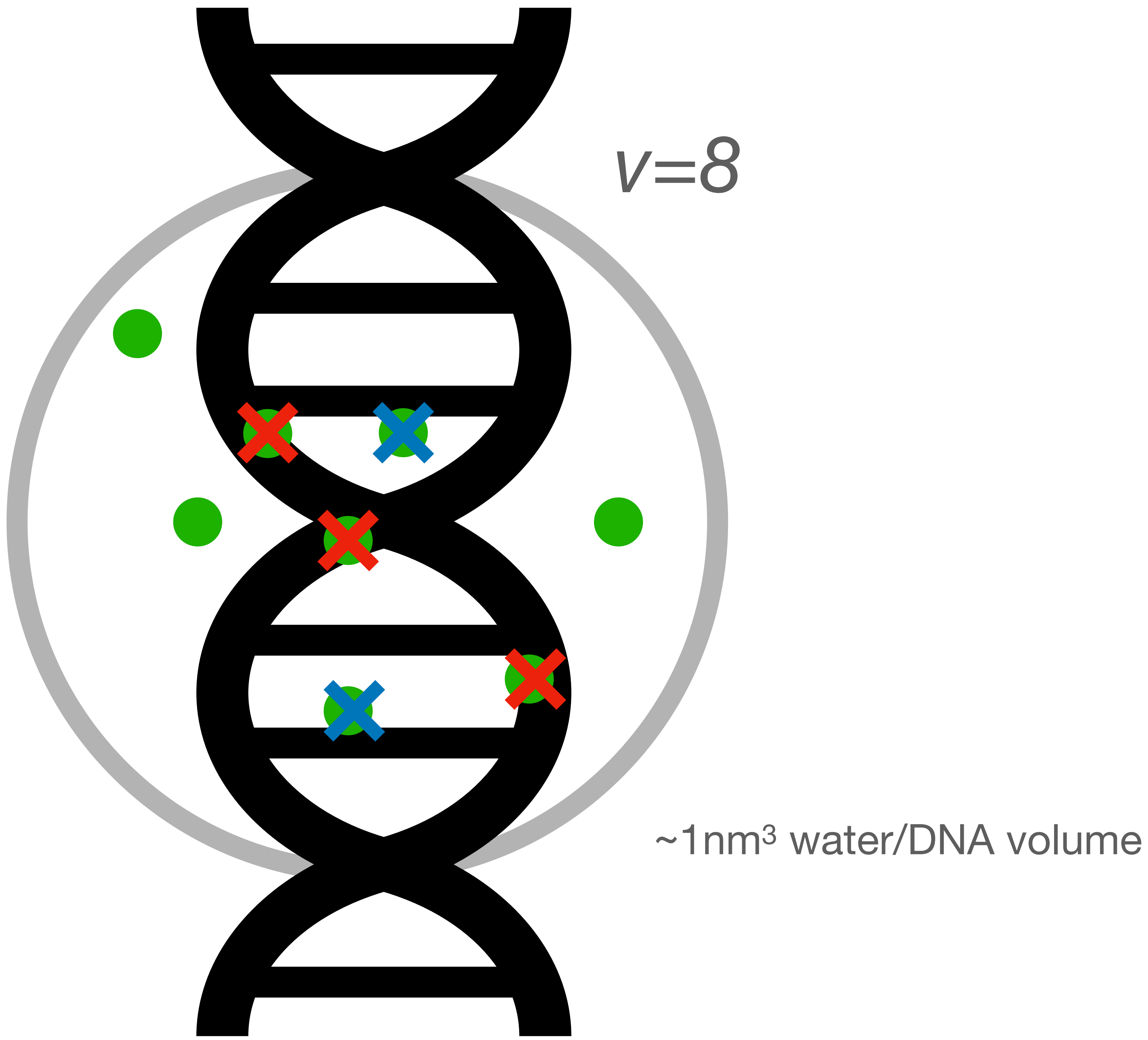
Ionization cluster size *v*



Lesion cluster size



The **ionization cluster size** is directly proportional to **DNA lesion cluster size**

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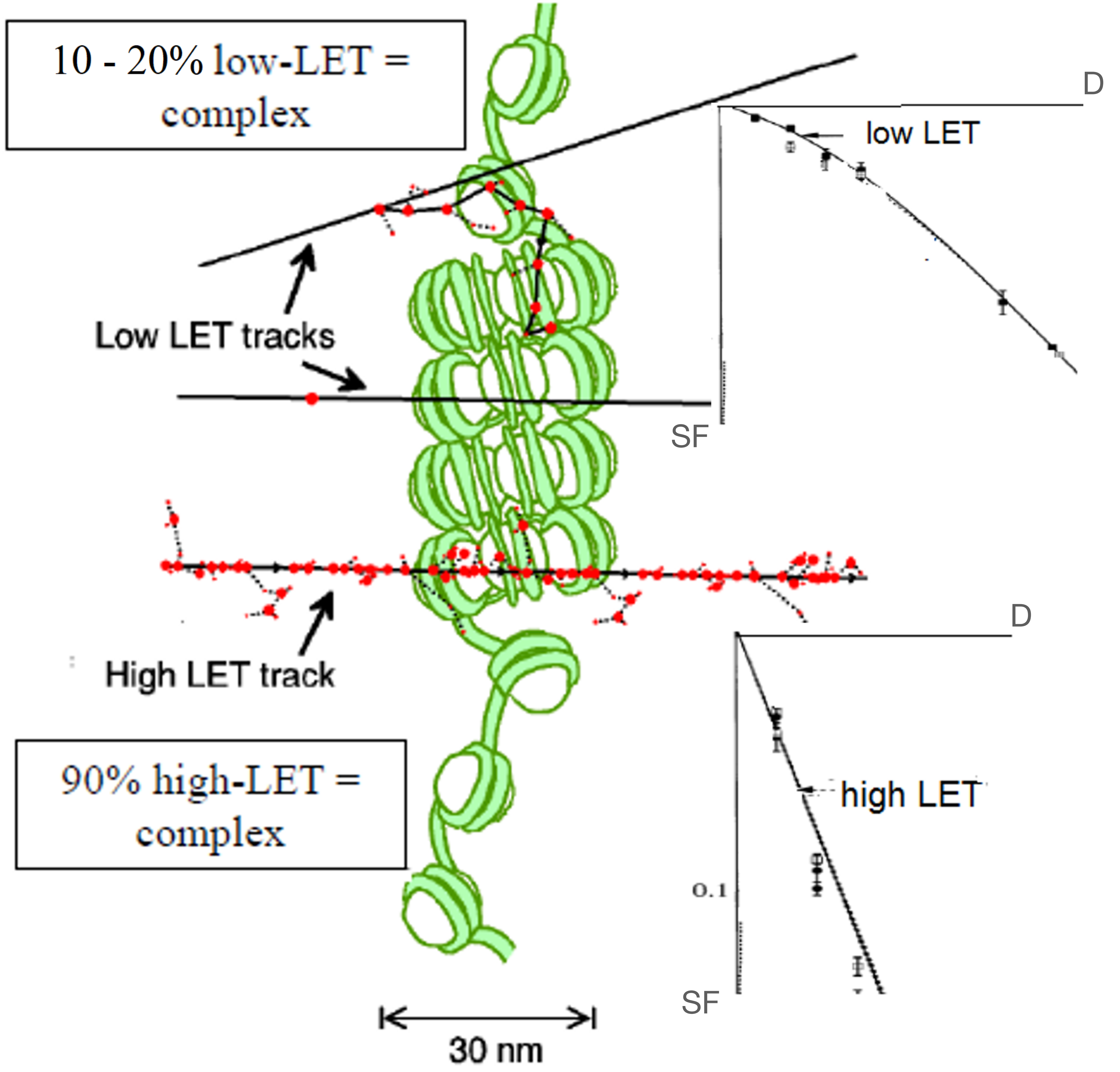
<u>The hypothesis</u>: Similar clustering leads to similar biological effect

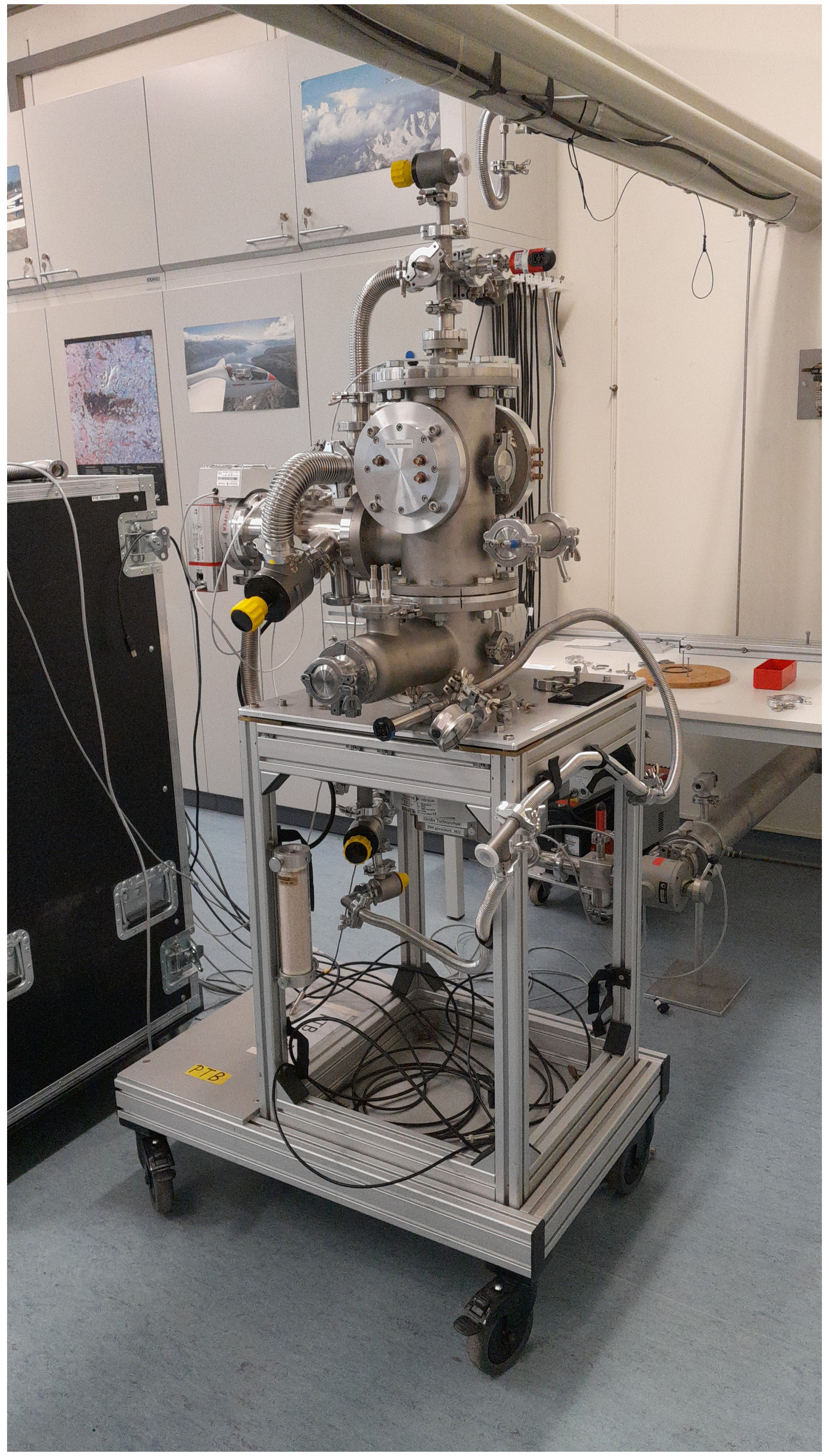
- Local **ionization cluster size** on the nanometer scale is the starting condition for all subsequent processes that lead to the observed DNA damage
- The **complexity of the damage** <u>determines</u> the **repair pathways** chosen by cells and, in turn, will <u>dictate</u> the **final biological outcomes** that are important for RT
- **Complex DNA damage** caused by ionization clusters in short DNA segments <u>is responsible</u> for **cell death/dysfunction/DNA mutation**



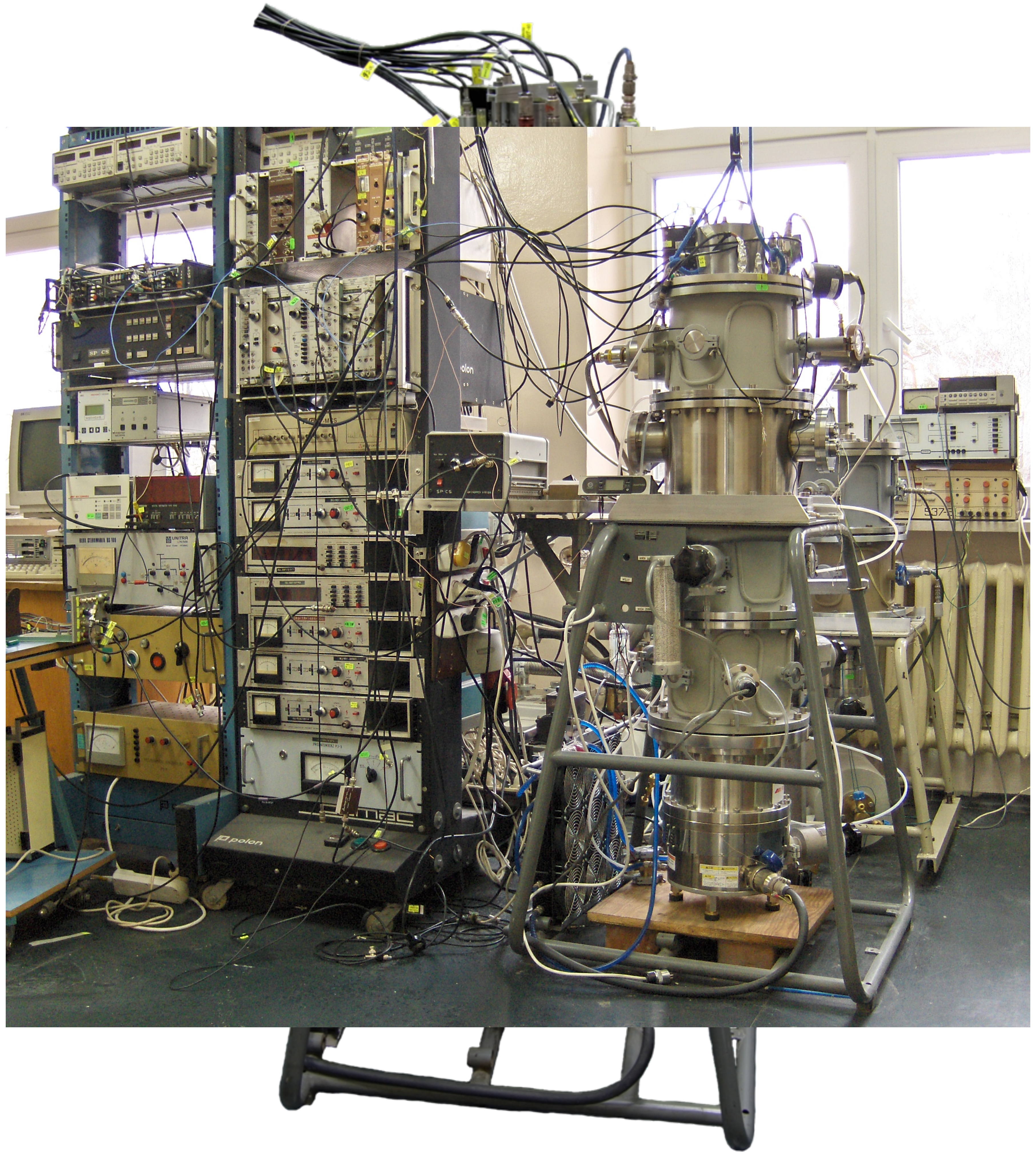
Courtesy of Dudley Goodhead

Reference nanodosimeters

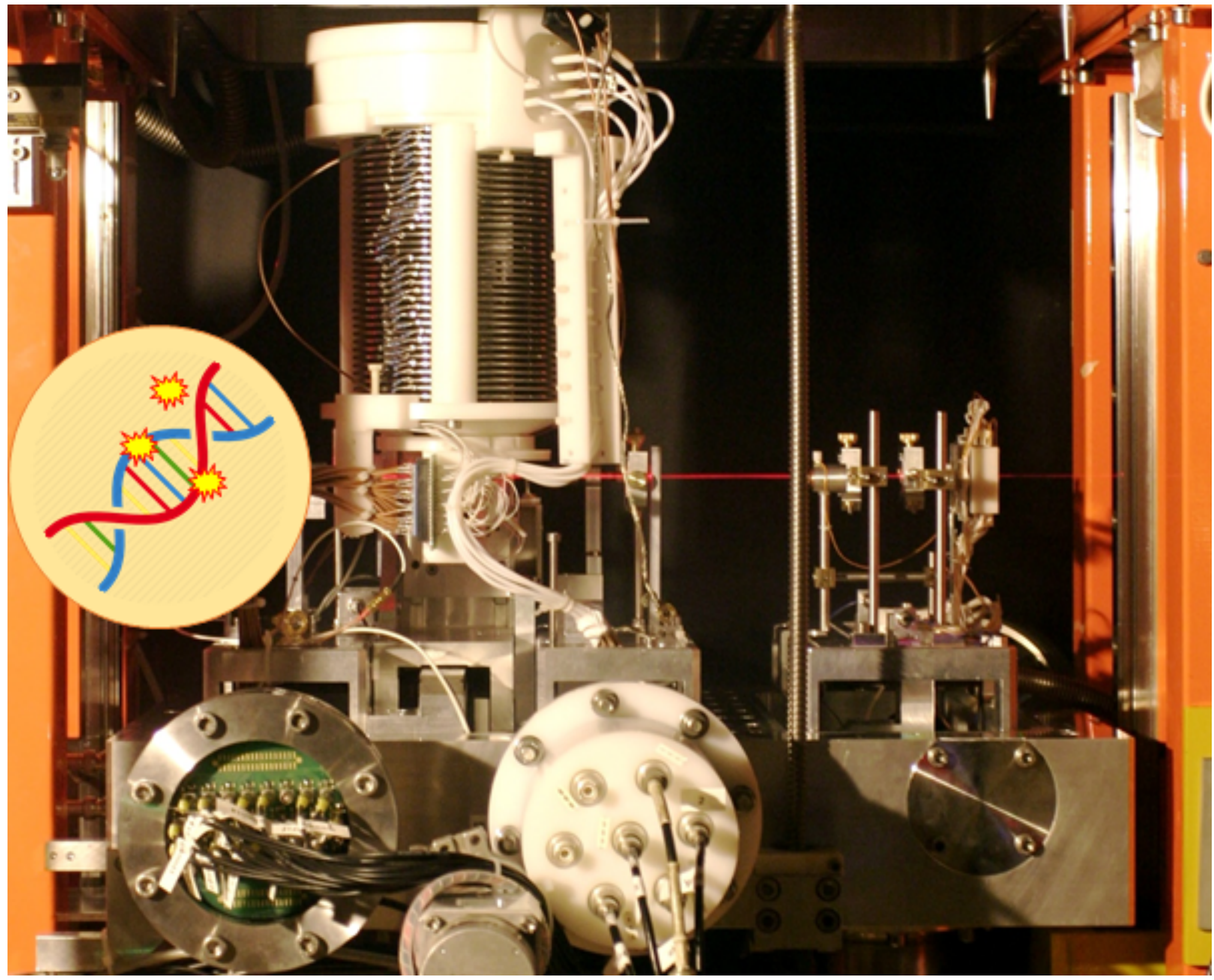
PTB IC ND
Ion Counting Nanodosimeter



NCBJ Jet Counter



INFN Startrack
Structure of hadronic track



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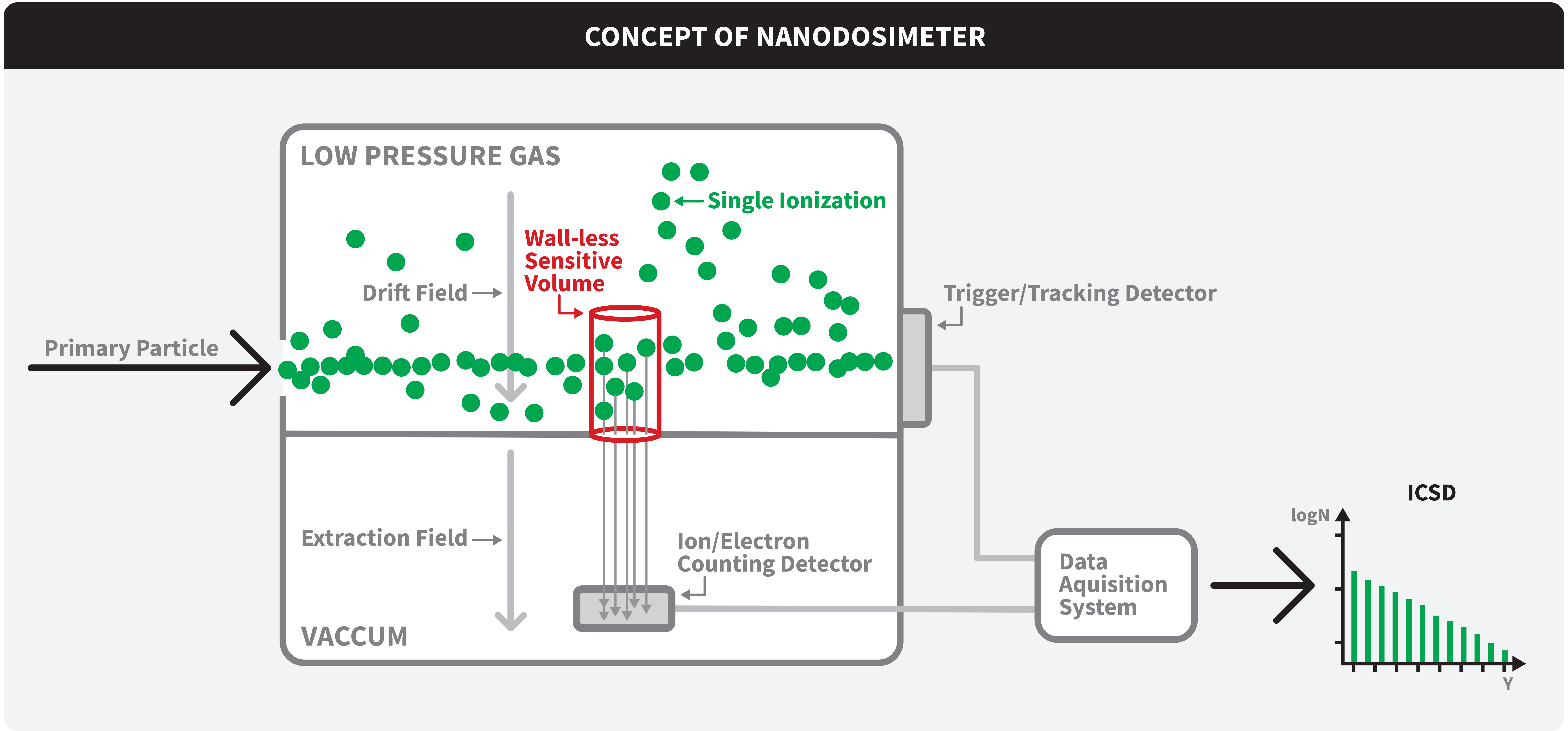
Experimental nanodosimetry



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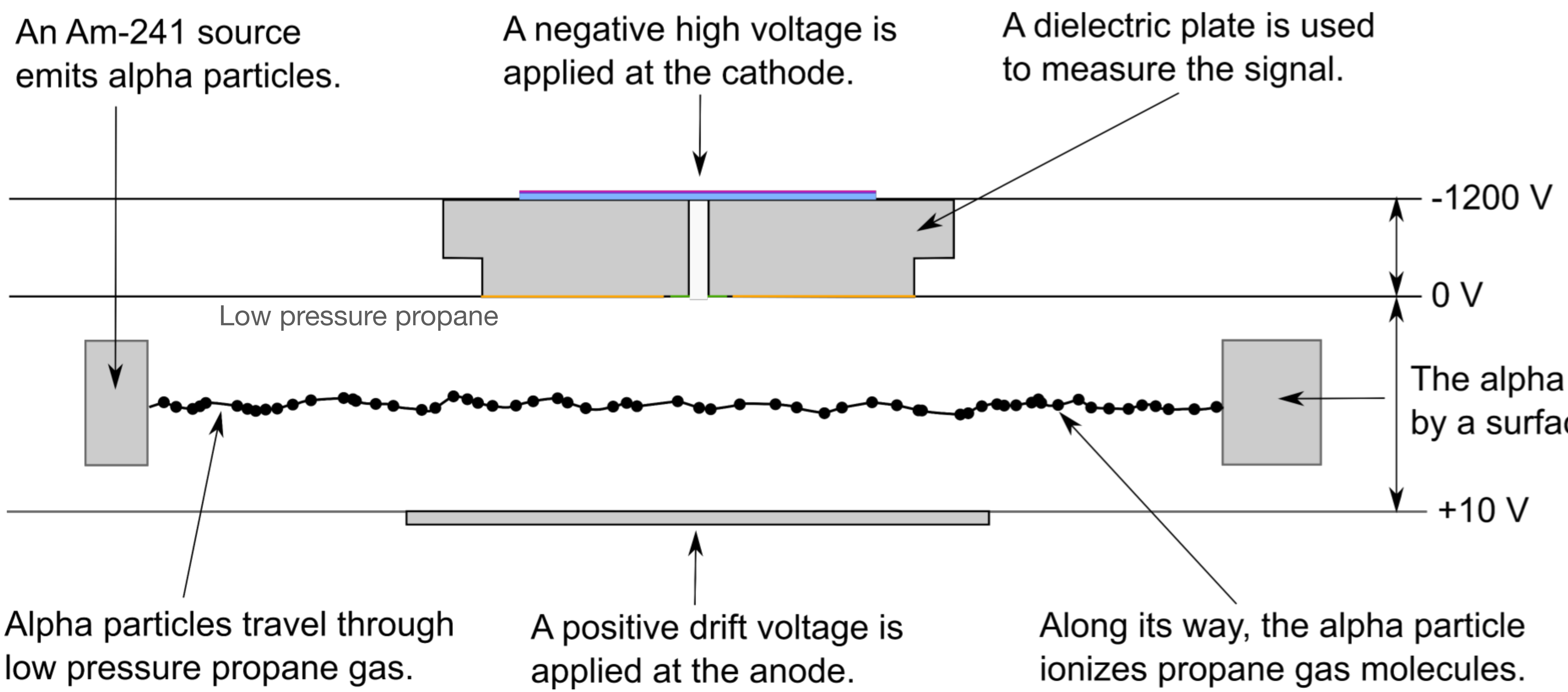
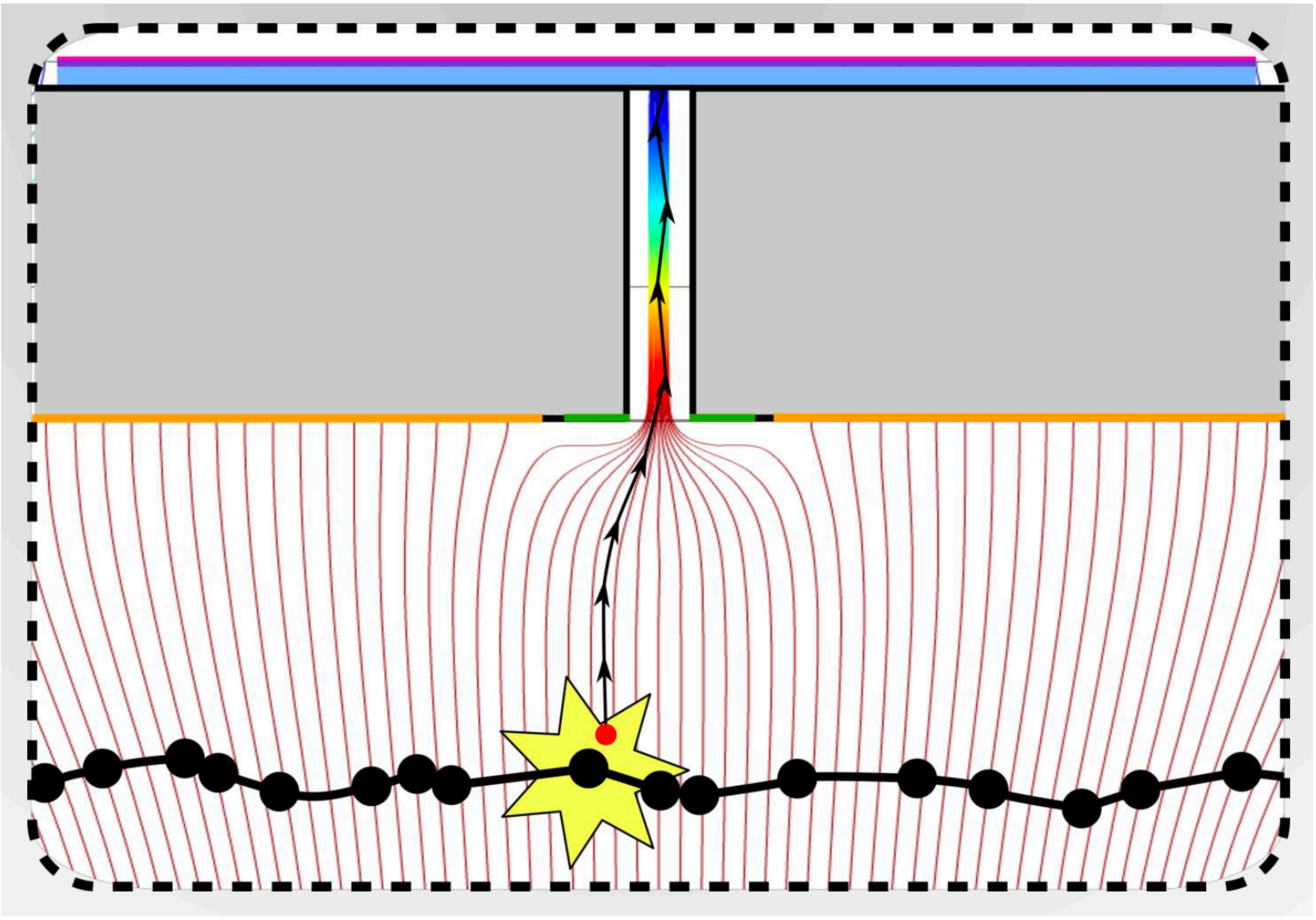
Rucinski, *Biernacka, Schulte 2021, PMB*, doi: https://doi.org/10.1088/1361-6560/ac35f1

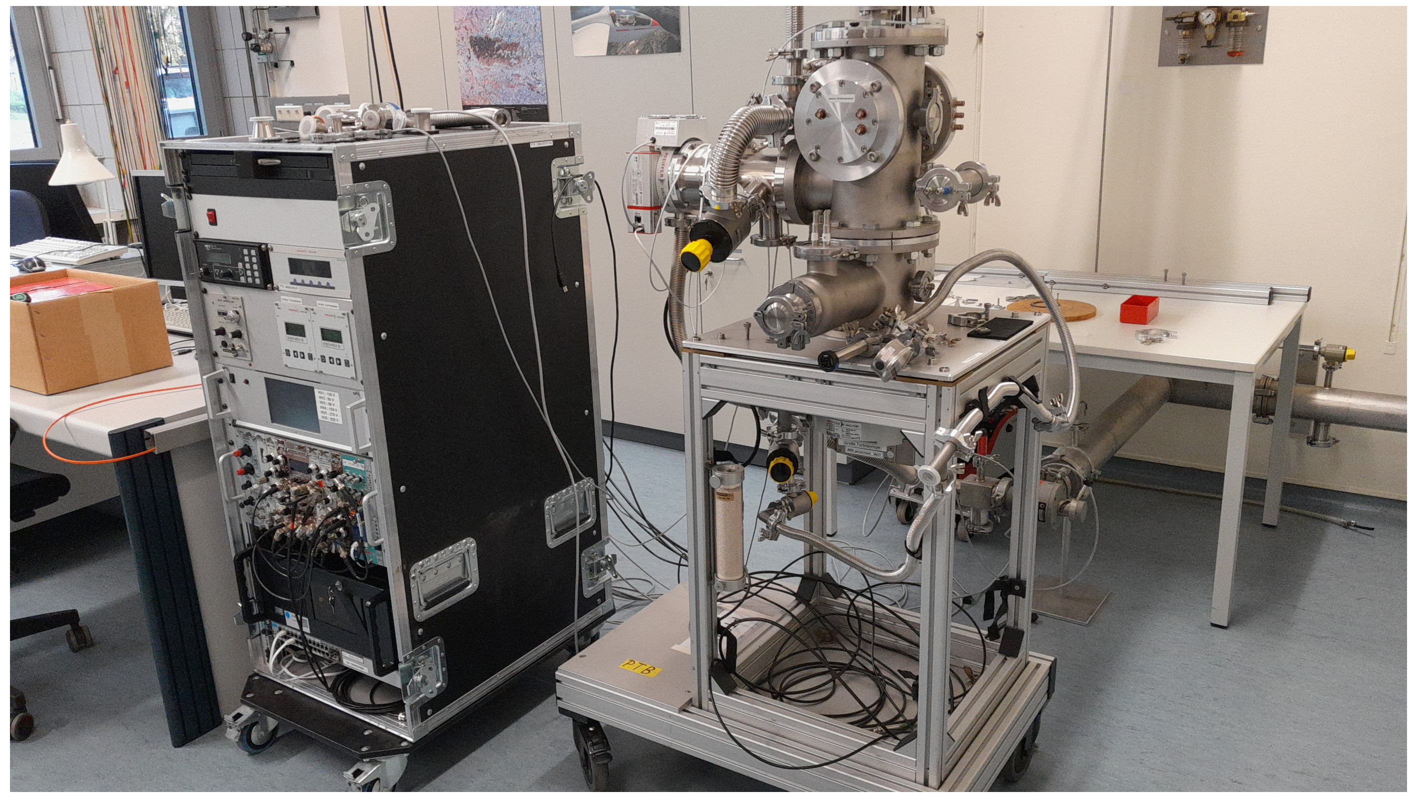
GEM based nanodosimetric detector



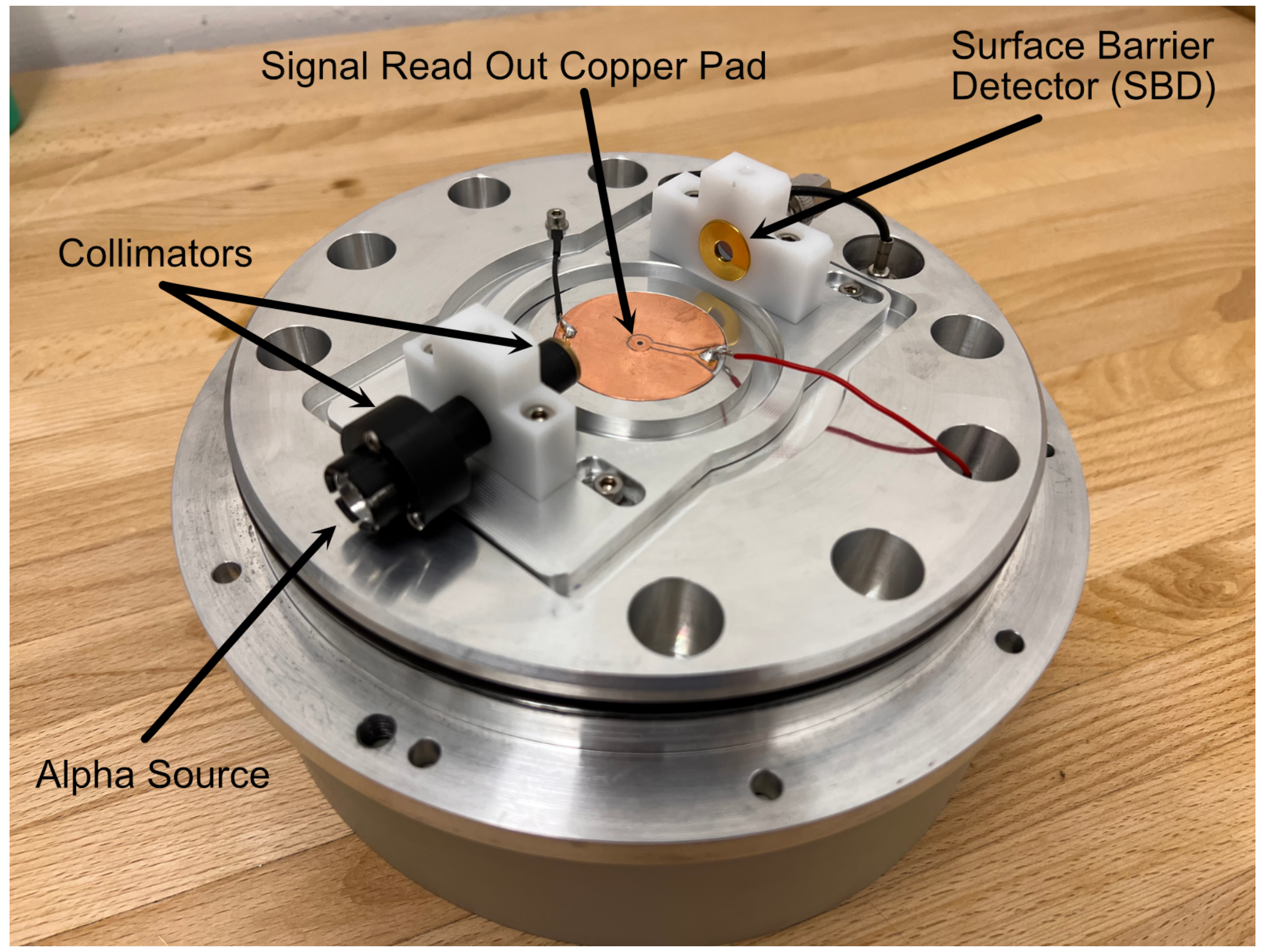


Experimental nanodosimetry lab at IFJ PAN

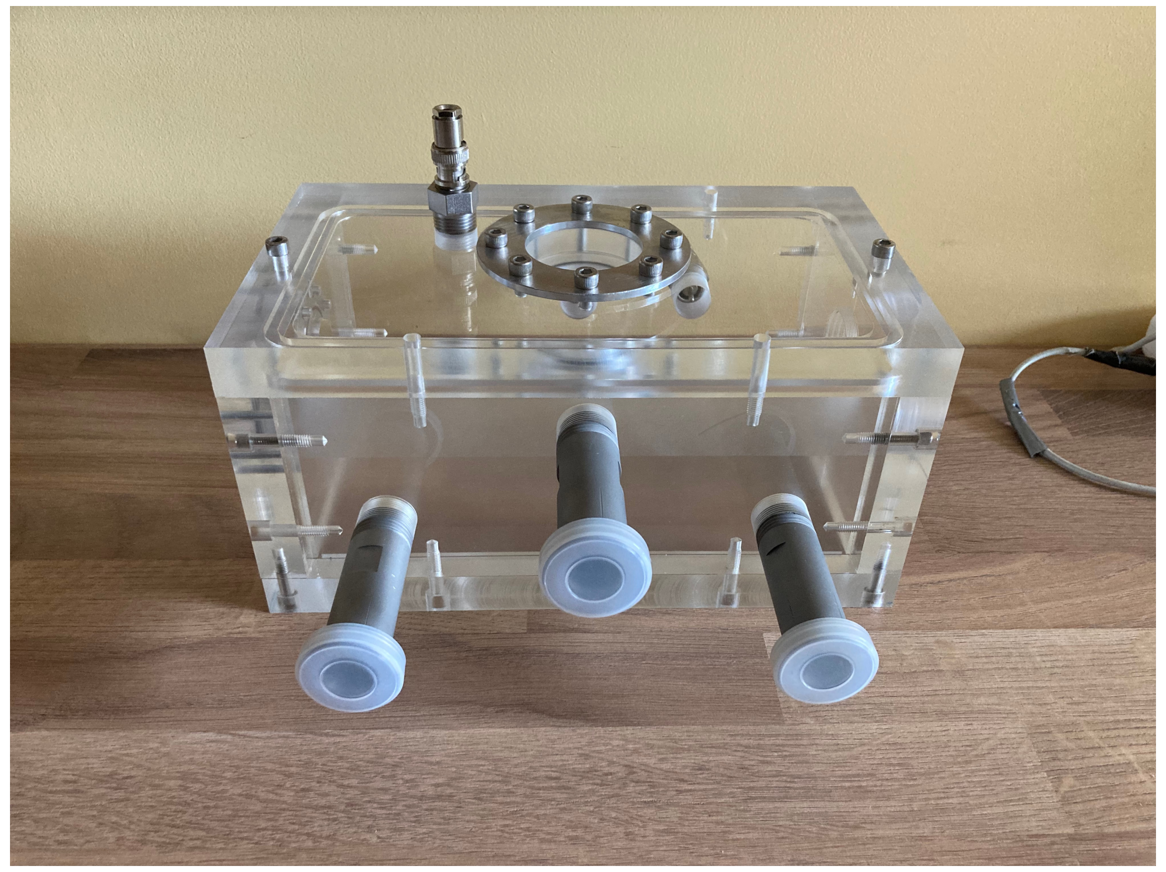
PTB IC ND
Ion Counting Nanodosimeter

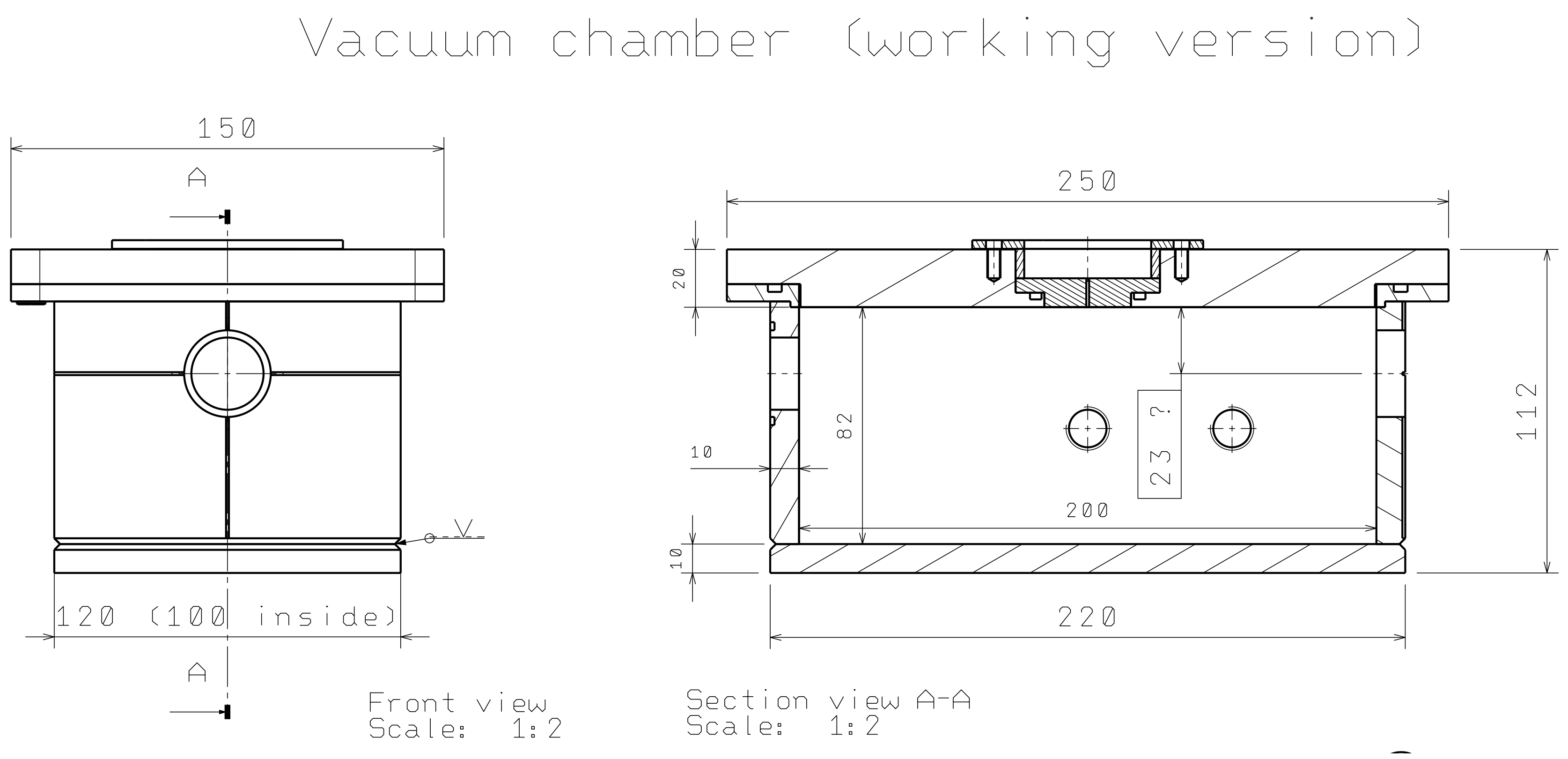


University of Zurich
FIRE-V2 Prototype



CCB prototype





Victor Merza
ProtoTera Association/FCT

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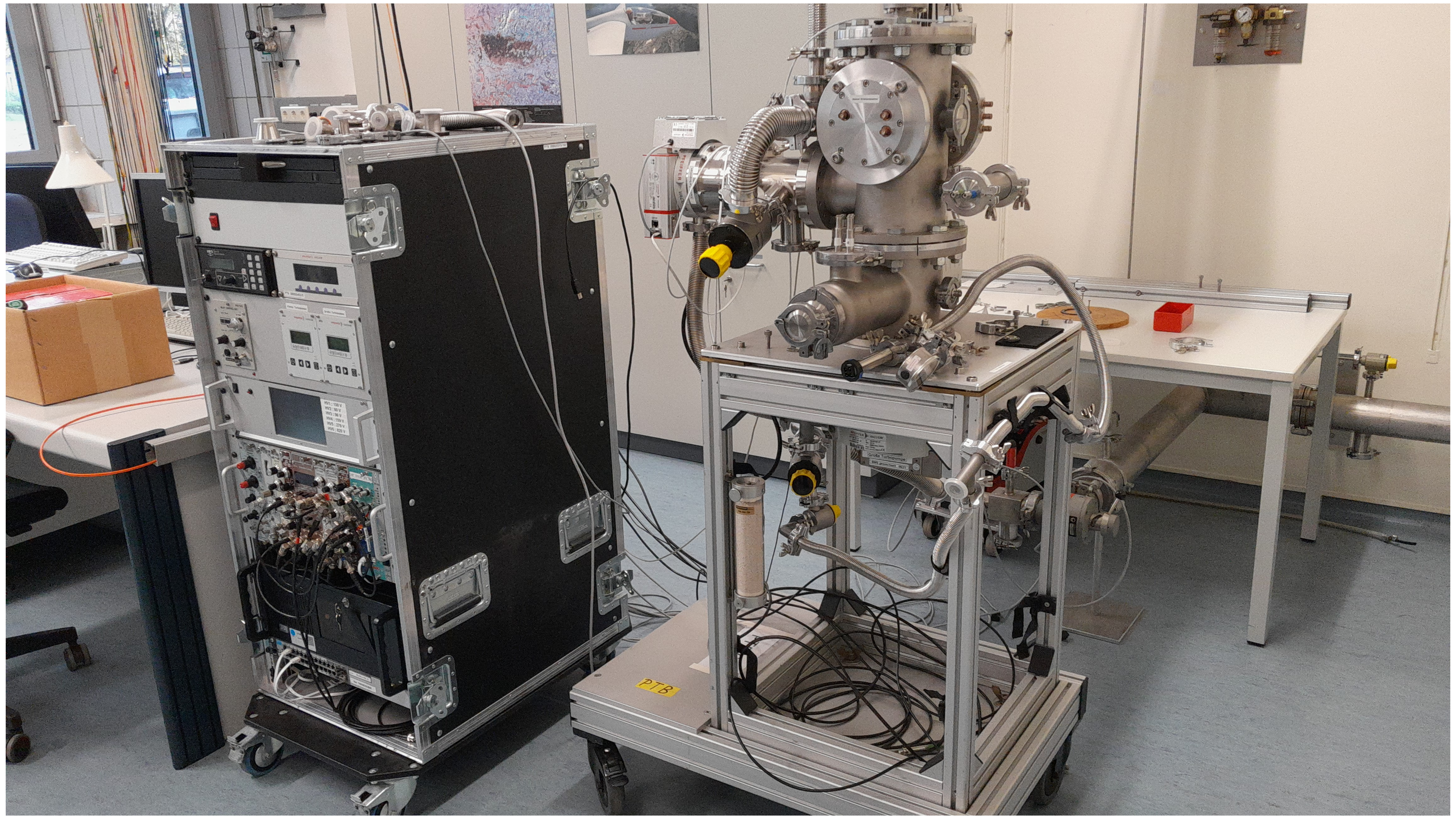
Vision for nanodosimetry

Detector miniaturization and sealing



?

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Requirements and last DRD1 online meeting

Discussion after Irina's slides

- Detection of electrons instead of ions
- Can we measure ionization cluster size with a one cell device? Why not to use multihole device?
    - Multi-hole single channel approach
    - Single hole device with single channel
    - Track imaging detector: Multi-hole multi channel
- Why we are using propane? -> because it is easy to ionize. It is more difficult to create electron avalanche in Nitrogen, much higher electric field is required. Cluster size is 4 times higher in propane than in nitrogen, for the same gas density.
- Deadtimes:
    - Deadtime after each avalanche, determined by beam intensity, required to be below the beam intensities.
    - Deadtime how you can distinguish if the signal was from primary particle 1 or primary particle 2. Avoiding overlaps/pile-ups.

DRD1 online meeting

Discussion after Irina’s slides

- Is the „signal“ simply a discharge? (This came up when Irina mentioned that they didn’t use a preamp for the THGEM signal as it was already strong enough)
- A possible solution to gain more information from the measurement: „Mirroring“ of the detector geometry. The electrons provide information (charge), and there may be a combination of a THGEM and other electron detector elements.
- „Multi Mesh“ THGEMs might be an inspiration
- GEMpix detectors were also discussed
- Propane at around 1 Torr: at the minimum of the proportionality curve

Collaboration: Europe

- **Nanodosimetry Seminars** joining “old” players, mainly from Andante and BioQuart grants:
    - V. Conte (INFN Legnaro), H. Rabus and G. Hilgers (PTB), and others
- **University of Zurich**
    - U. Schneider: Sharing know-how and equipment (FIRE v2 prototype) with PhD students
- The Faculty of Physics at the **University of Warsaw** (FUW) and the **National Center of Nuclear Research** (NCBJ)
    - B. Brzozowska (FUW), M. Pietrzak (NCBJ, now at Curie), A. Banstar (NCBJ) and students
- **CERN DRD1 Collaboration**, joined FUW and CCB initiative to include nanodosimetry as a Working Package task. In progress.

Collaboration: US

- **Loma Linda University**
    - Prof. Reinhard Schulte and Dr. Vladimir Bachkirov
- **NIH Grant** 1R01CA266467-01A1 "*Ionization Detail - Biologically based treatment planning for particle therapy beyond LET-RBE*" University California San Francisco (UCSF), CA, Prof. Bruce Faddegon, Ph.D., FCCPM, FAAPM, Dr. Rucinski is an unpaid consultant.
- **Students**
    - Victor Merza and Khaled Katmah from ProtoTera program, University of Lisabon,
    - A few other PhD students funded by own University funds and co-supervised by Prof. Schulte and myself.

Submitted grants

- MSCA GF: “Investigating Complex DNA Lesions and their Repairability Using Plasmid Assays and DNA Repair Extracts (CLEOPATRA)”
- OPUS 24, 26 “Portable GEM-based detector for nanoscale characterization of radiation quality in proton therapy”

Grant opportunities

- National Science Center OPUS
- NASA Artemis program
- ERC Consolidator

Conclusions

- Experimental nanodosimetry and track structure simulation methods for radiation therapy and radiation protection applications is an old field of science that started dating to 1970s
- Measurement of the number of ionizations in a sensitive volume seems to be a basic nanoscale physics quantity that is well correlated with the biological effect
- The most explored technique for decreasing the dimensions of nanodosimeters is THGEM
- **Miniaturization** of nanodosimeter to the size of a pinpoint ionization chamber is necessary to pursue the approach toward clinical practice
- DRD1 expertise is essential for rethinking and redesigning miniaturized detector

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  A mathematical model for employing nanodosimetric quantities in treatment planning for charged particle radiotherapy, Physics in Medicine and Biology 68:175013, URL: https://doi.org/10.1088/1361-6560/acea16
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Acknowledgement

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National Center for Nuclear Research
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CERN
Piotr Gasik

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Prof. Stanisław Pszona: Father of experimental nanodosimetry

From 1958: National Centre for Nuclear Research

Education LinkedIn

Warsaw University of Technology
MSc, Electronics
1952 - 1959
Grade: 1959

AGH University of Krakow
Ph D in engineering
Grade: 1970

1972-73 - **Columbia University**, Radiological Research Laboratory, Columbia University, postdoc, Fulbright Scholar

A TRACK ION COUNTER

S.Pszona
Radiation Protection Department,
Institute of Nuclear Research,
Swierk, Poland

Abstract

A method to measure the frequency of production of various number of ions in a gas domain is described. The characteristics of a device, which is termed a "track ion counter, are presented. The counter consists of two cylindrical volumes separated by a diaphraqme with 500μm dia. orifice. The device is connected to an oil diffusion pump with high pumping speed. The gas flow through the orifice determines the pressure in the upper and the lower volumes of the device. The positive ions produced in a cylindrical volume above an orifice by charged particles traversing that volume move in a constant electric field. Some of these ions pass through the orifice are accelerated and detected by an electron multiplier. The absolute efficiency of ions detection from the domain above the orifice as well as the extention the domain from which ions are collected have determined. The measurements were carried out for single charged ions of N_2, H_2, CH_4, CO_2. The preliminary measurements of the frequency of variuos number of ions created within cylindrical gas domain equivalent to 0.15 nm dia. and 7.6 nm height tissue cylinder are reported.

Reprinted from the Proceedings
Fifth Symposium on
MICRODOSIMETRY
Verbania Pallanza (Italy), September 22-26, 1975

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Beam conditions

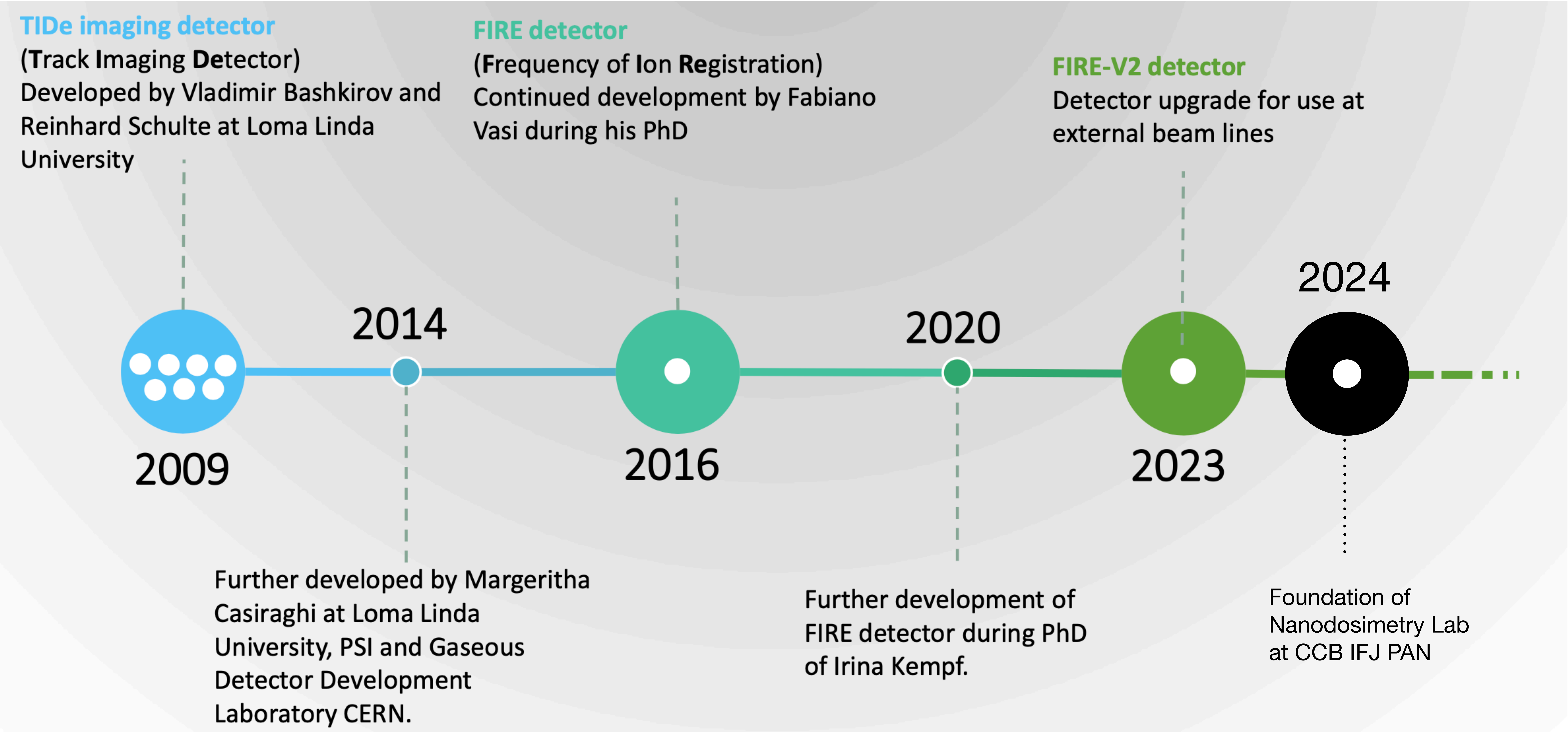
Clinical radiation qualities and beam conditions (including pencil beam):

- Protons (70 MeV to 230 MeV), flux from 10e8 to 10e10 protons/s
- Carbon ions (120 MeV to 400 MeV), flux from 10e7 to 10e9 ions/s
- Gamma-, x- and beta-radiation qualities are not of particular interest for the time being

Track structure simulations and experimental nanodosimetry

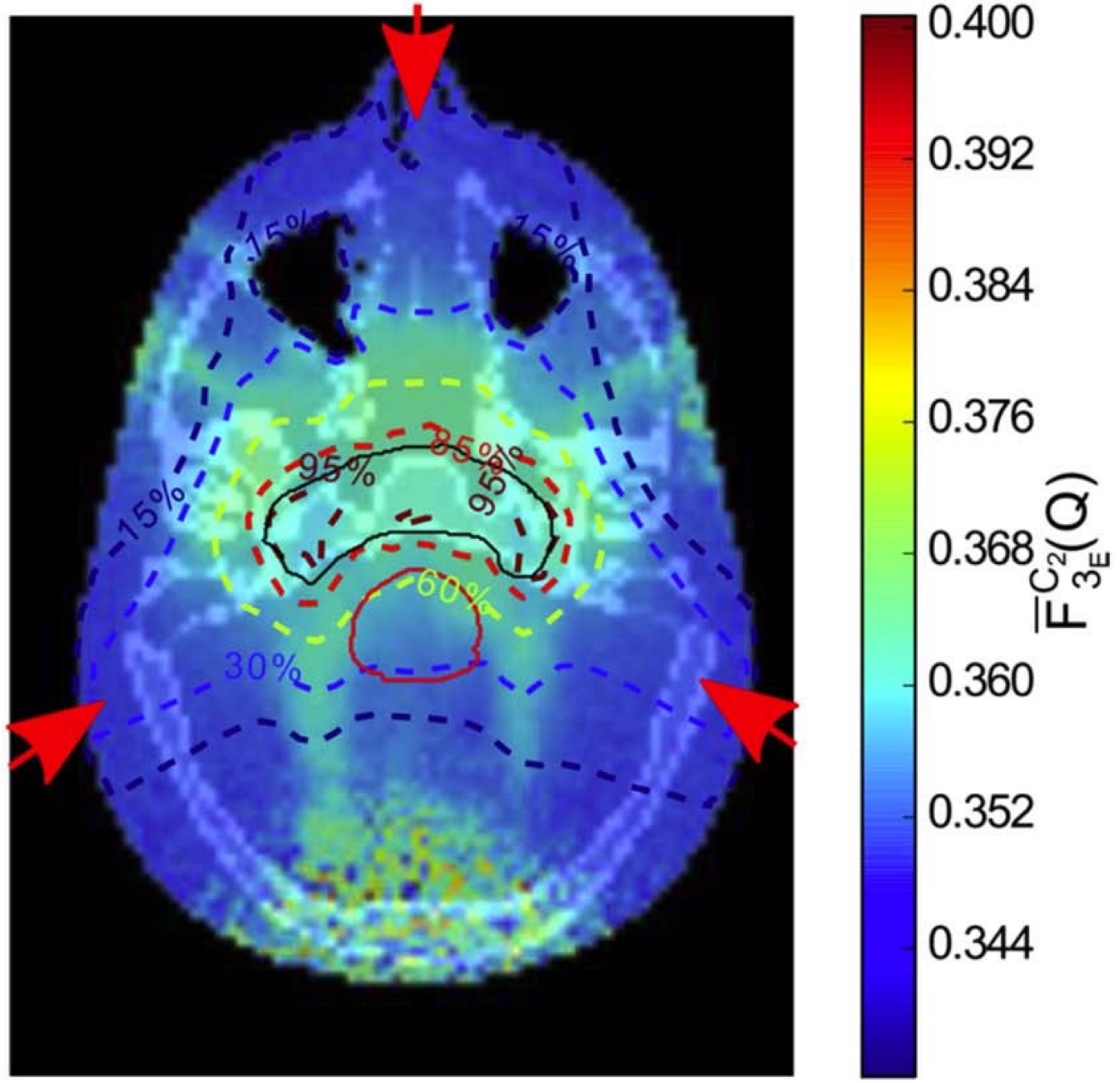
- Track structure simulations
  - Started in 1970s:
    availability of ionization and excitation cross-sections of water vapour
    Paretzke HG 1974 Proceedings. 4. Symposium on microdosimetry, Verbania-Pallanza, Italy:
    Comparison of track structure calculations with experimental systems
  - Constantly developing until today:
    improved cross-sections of liquid water and the increasing computational speed, e.g.,
    PTra, PARTRACK, Geant4-DNA, TOPAS-nBIO, PHITS-KURBUC
- Experimental nanodosimetry
  - Proposed in 1970s
    Pszona S 1976 Proceedings. 5. Symposium on microdosimetry. Verbania Pallanza, Italy: ***A track ion counter***
  - Practical implementation in 1990s:
    jet-counter, ion-counting nanodosimeter, Startrack

Recent history of experimental nanodosimetry



Forward calculation of ID parameters in patient

Proton treatment plan



Carbon ion treatment plan