

Non clinical research and mixed beam developments at CNAO

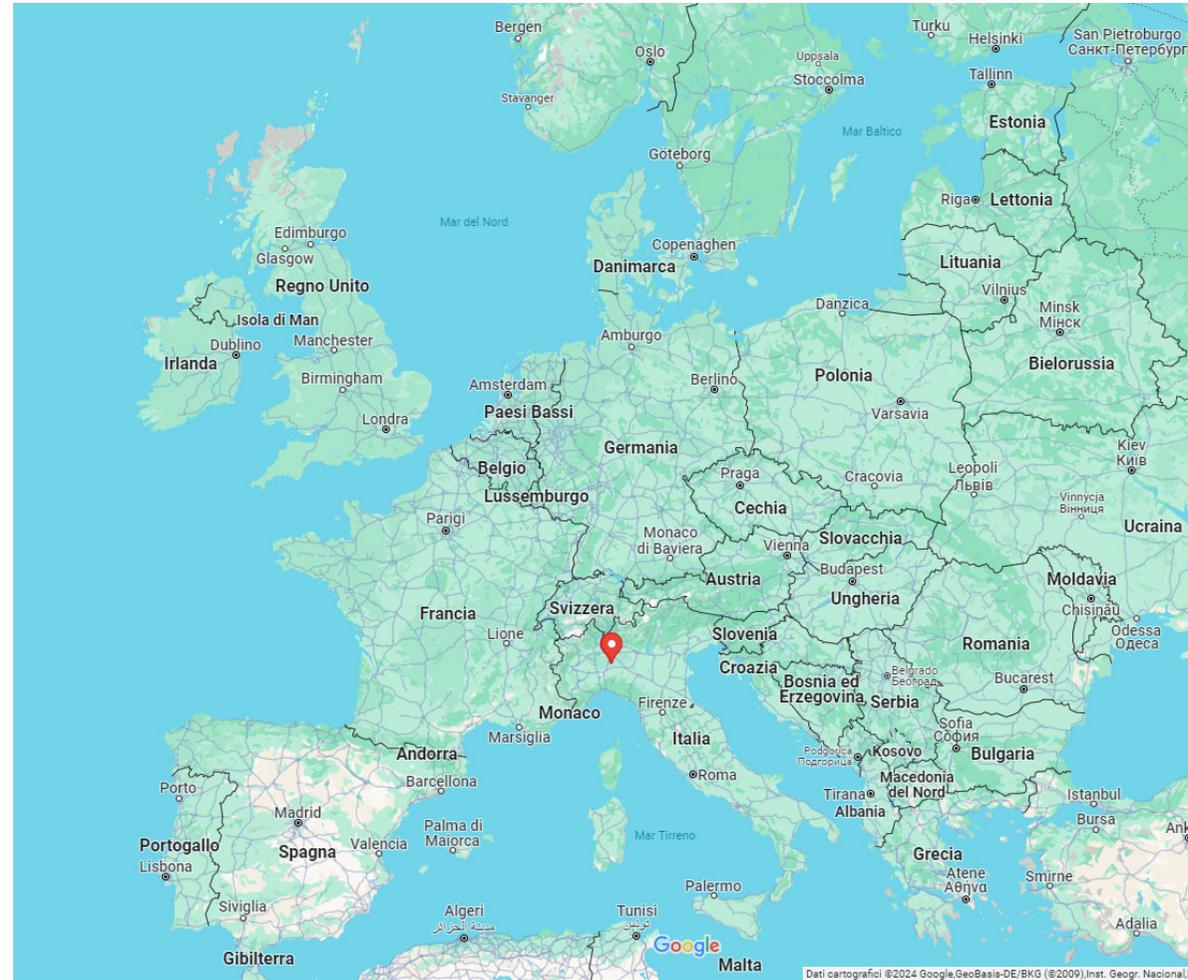
Marco Pullia,
Simone Savazzi, Alessio Mereghetti, Björn Gålnander, Michael Galonska, Ronja Hetzel, M. Chiara Martire, David Ondreka, Andrii Pastushenko, Jens Stadlmann, Lennart Volz, Elisabeth Renner, Katrin Holzfeind, Matthias Kausel, Saad Shaikh, Mikael Simard, Christian Graeff



What is CNAO (National Center for Oncological **Hadrontherapy**)

>5800 patients treated

Not for profit foundation with 3 scopes

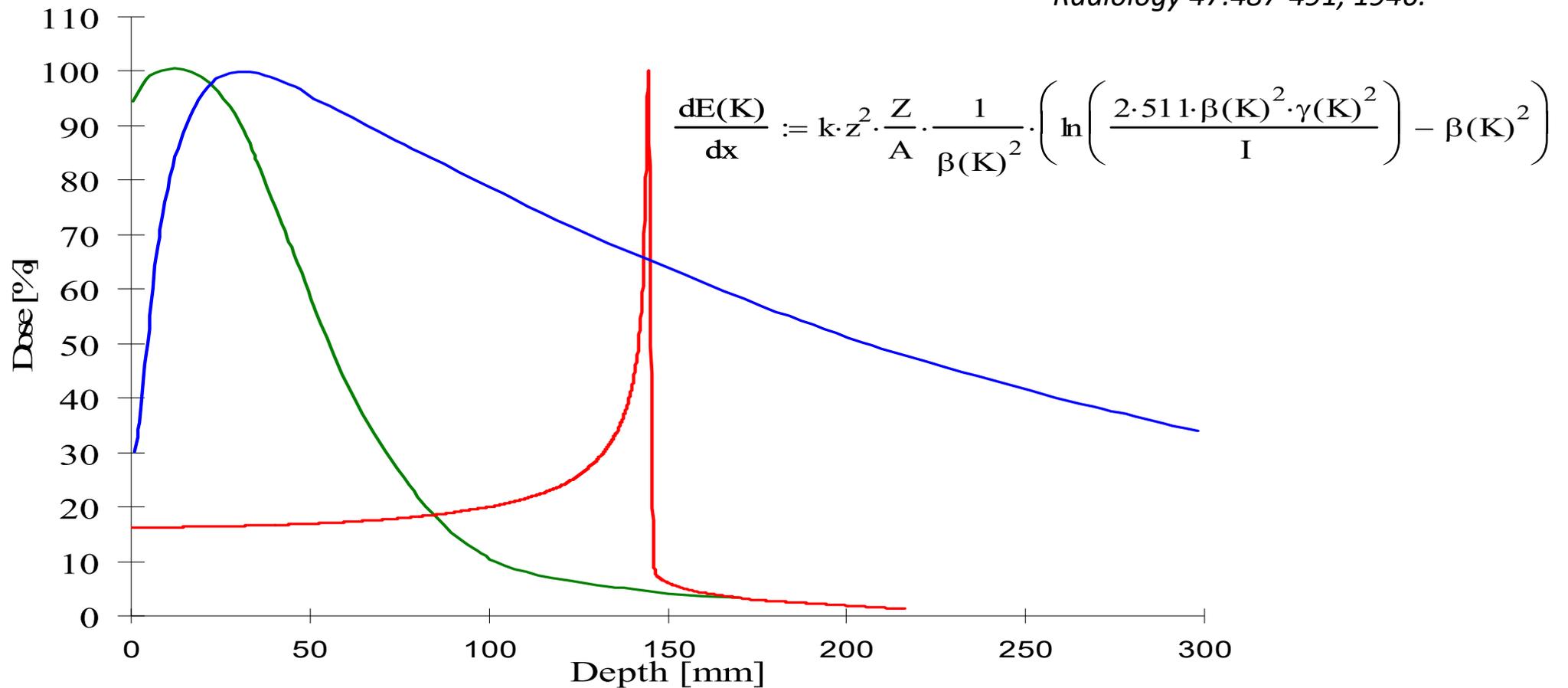


What we do at CNAO

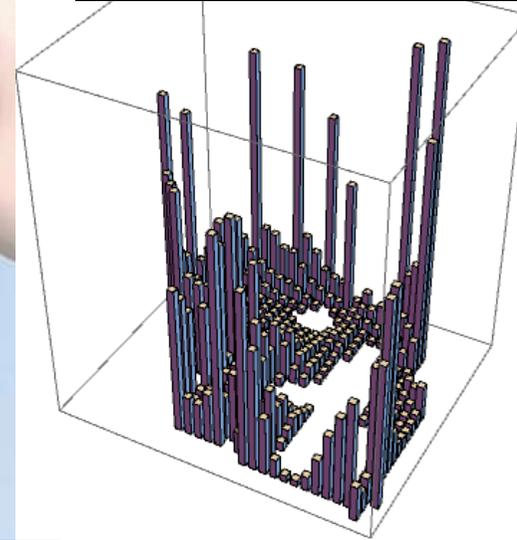
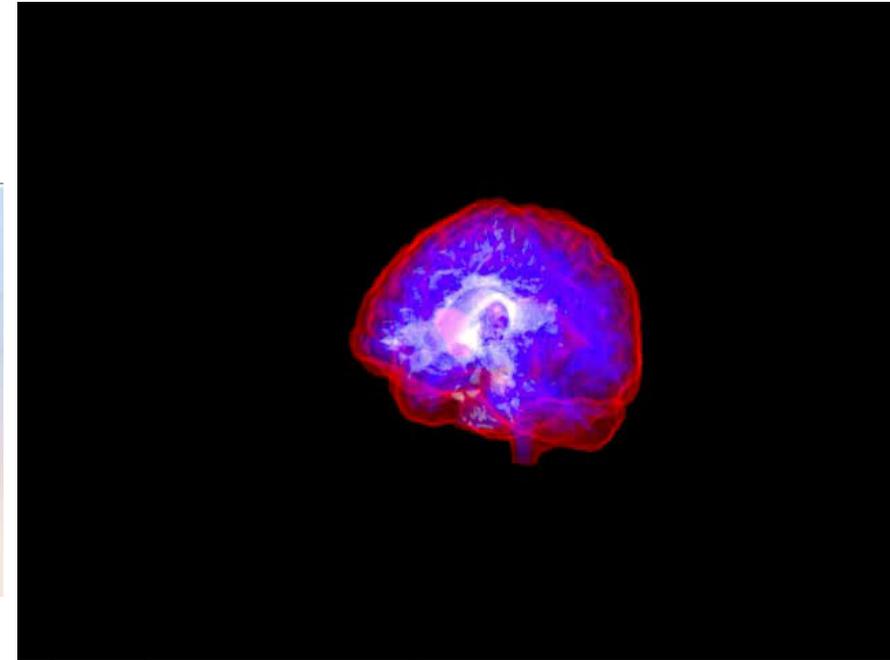
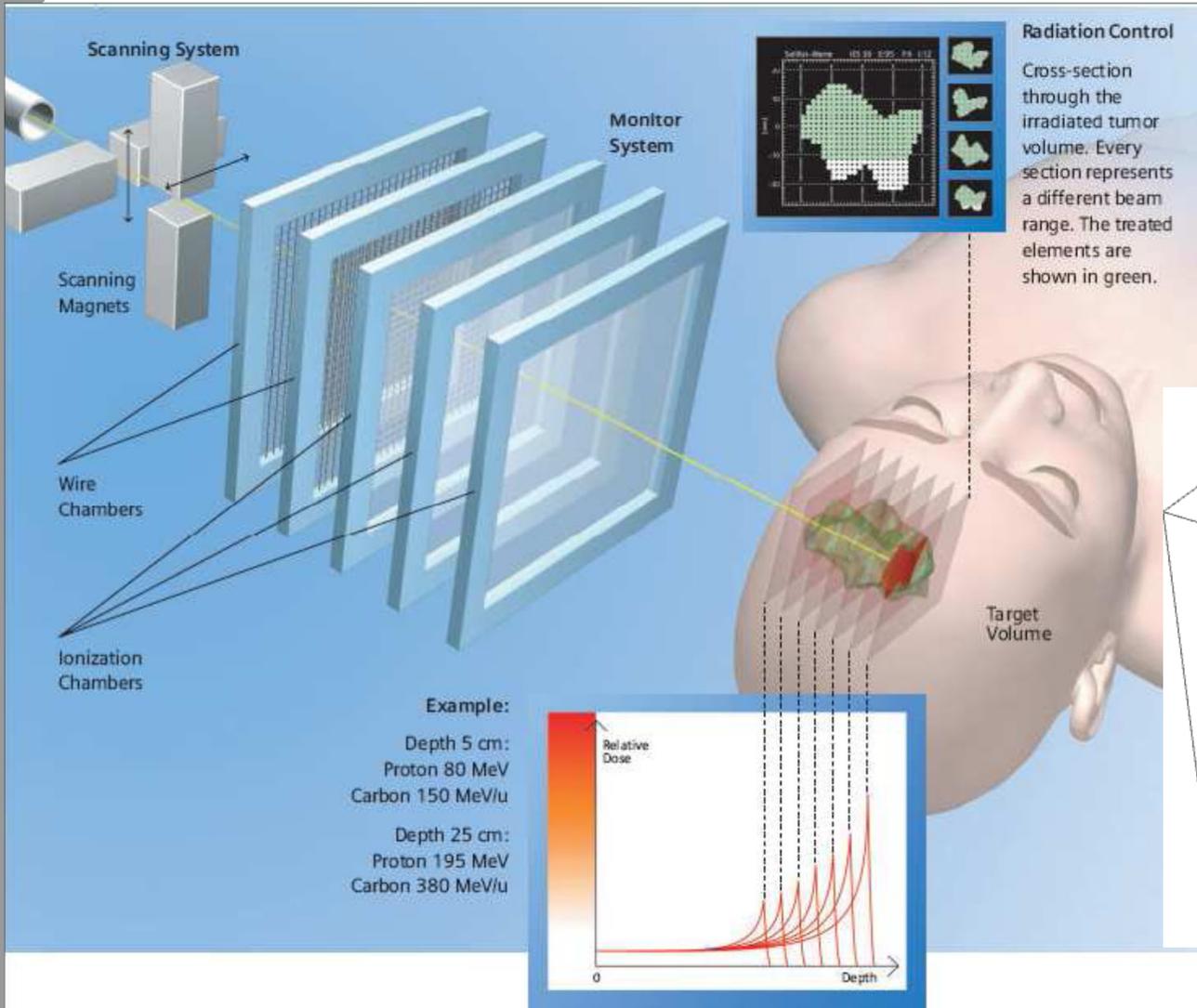
Wilson, R.R.

Radiological use of fast protons.

Radiology 47:487-491, 1946.

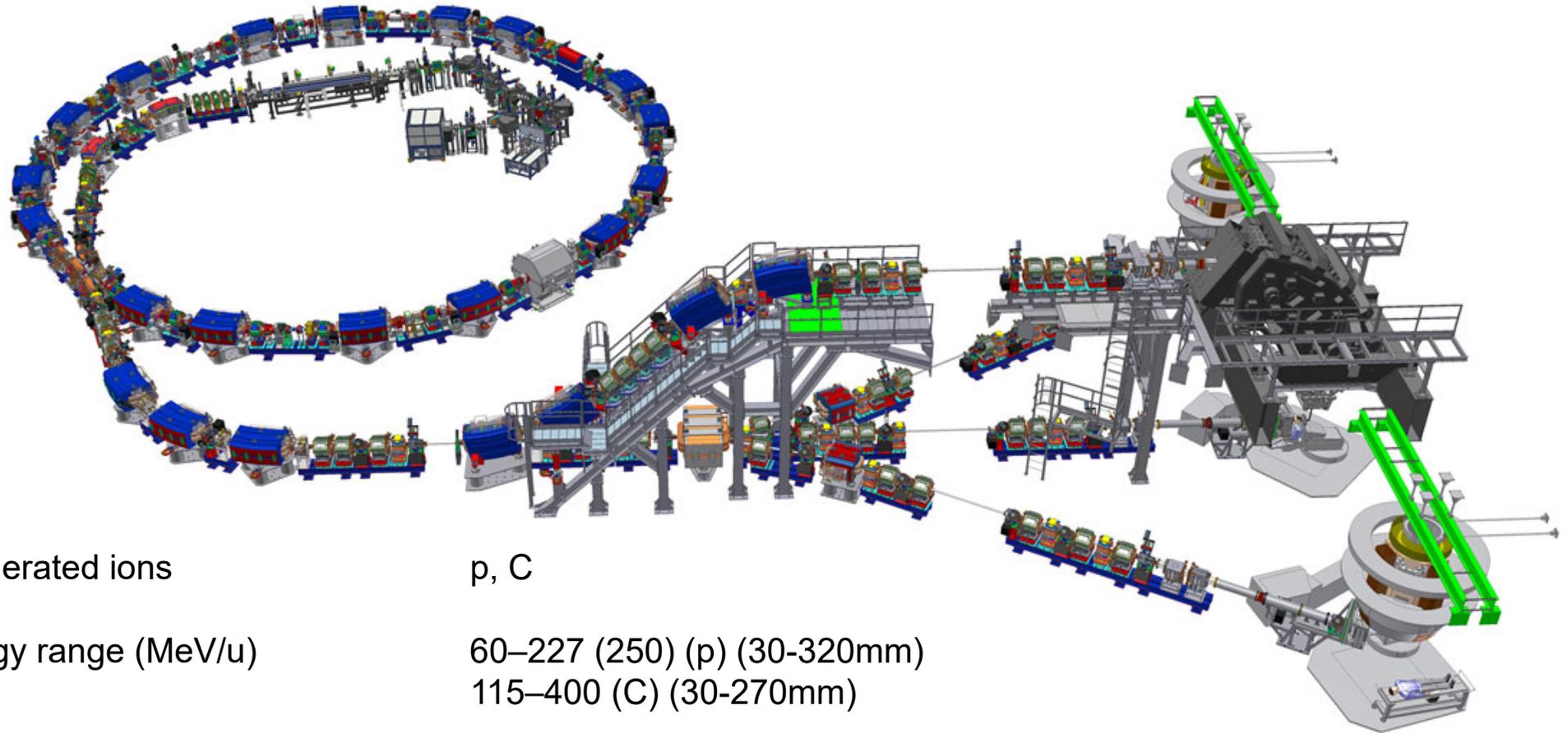


Active dose delivery



The number of particles varies spot by spot

Only 6 facilities in the world offer dual species treatment



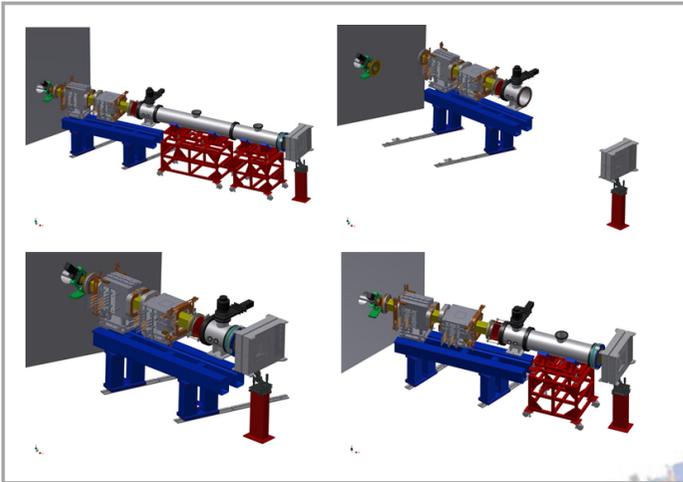
Accelerated ions

p, C

Energy range (MeV/u)

60–227 (250) (p) (30-320mm)
115–400 (C) (30-270mm)

Experimental room

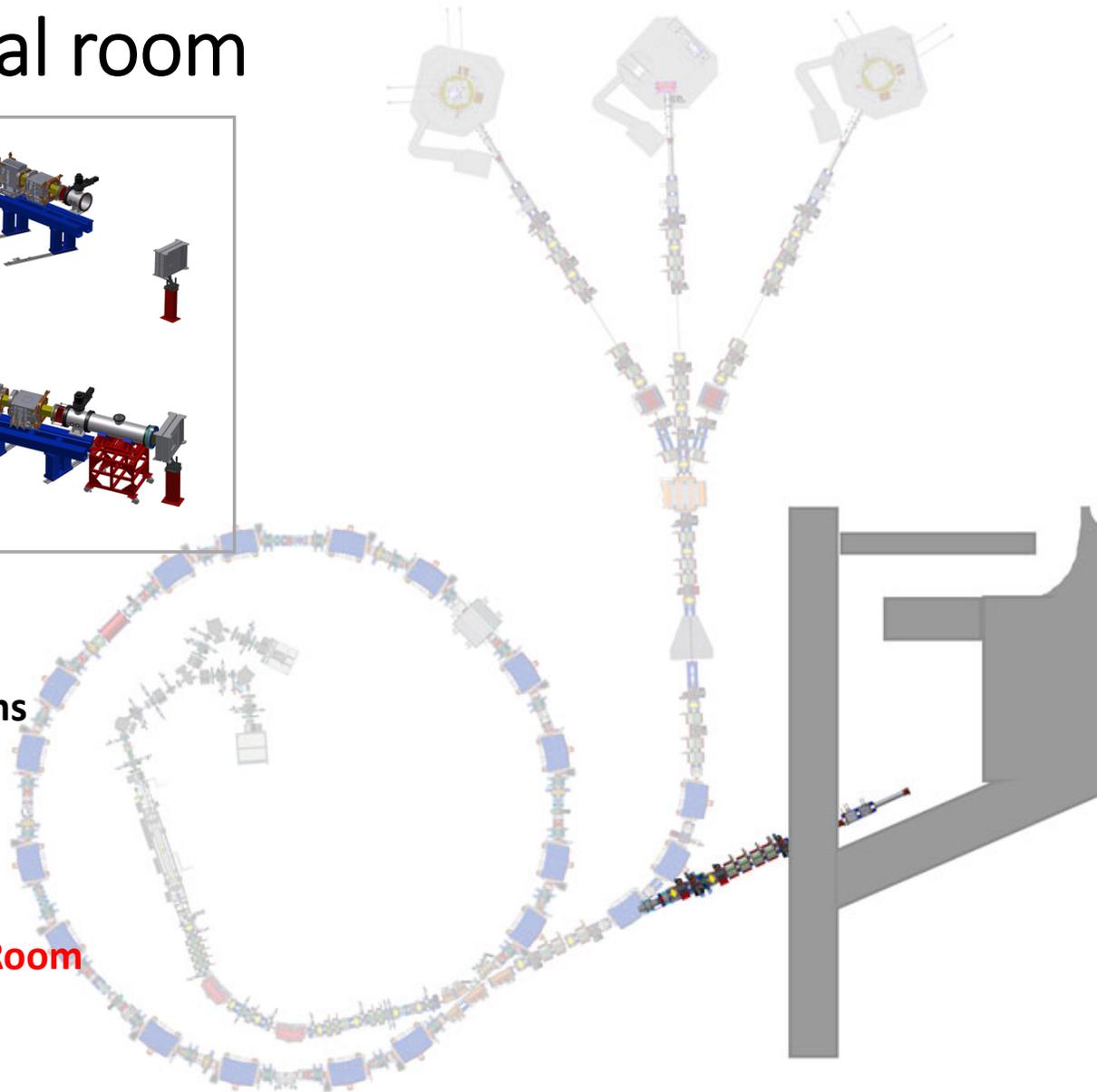


3 Treatment rooms

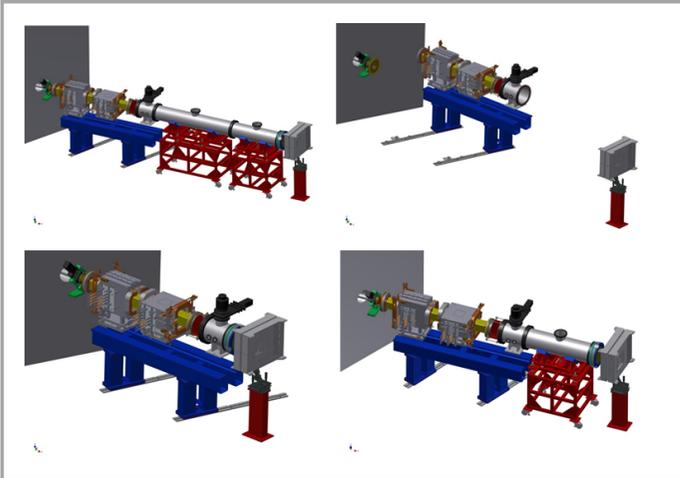
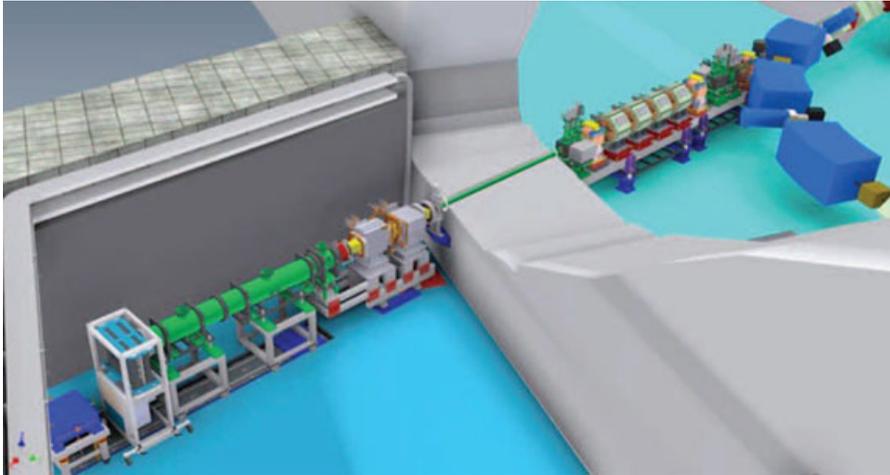
2 H

1 H+V

+1 Experimental Room



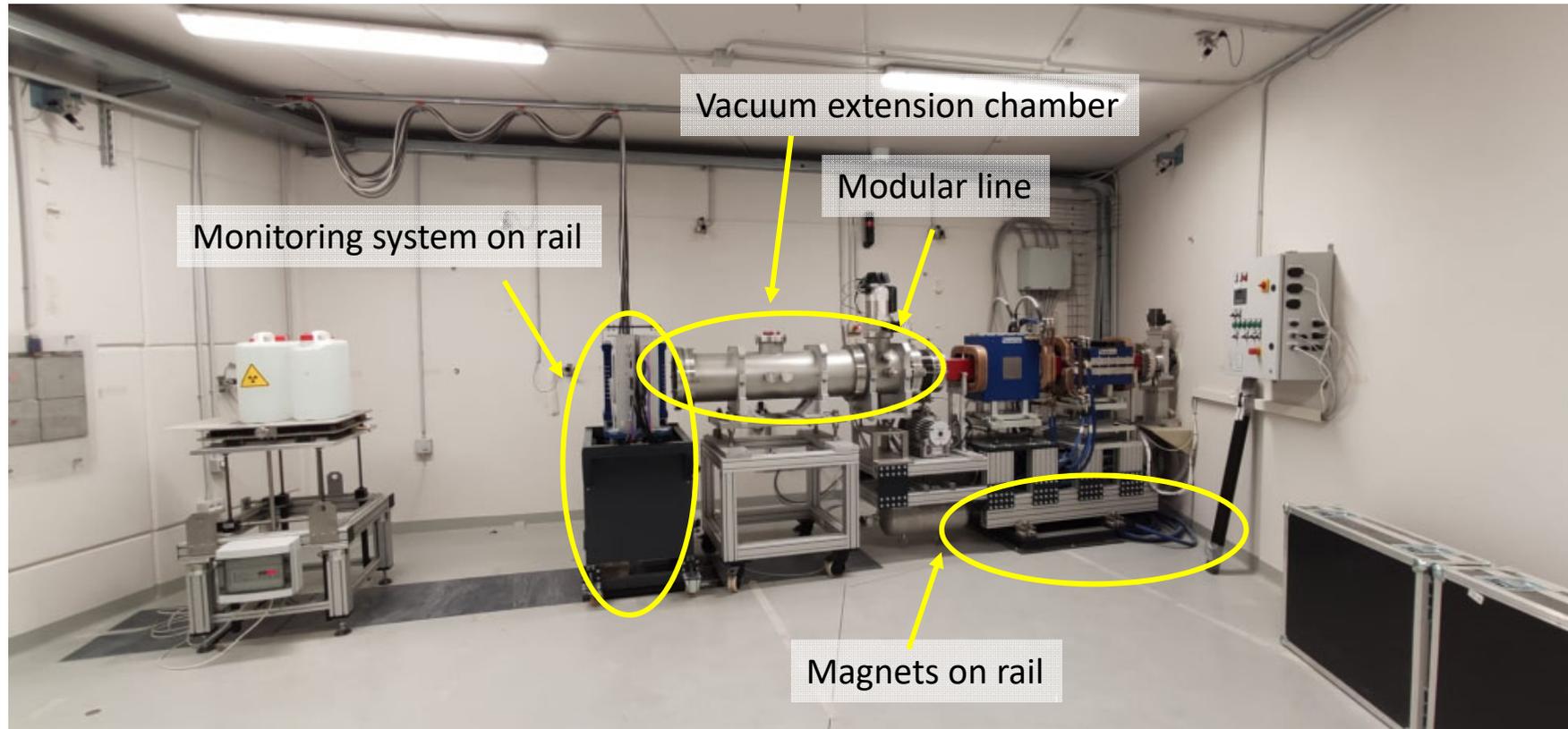
Experimental Facility (XPR + Lab)



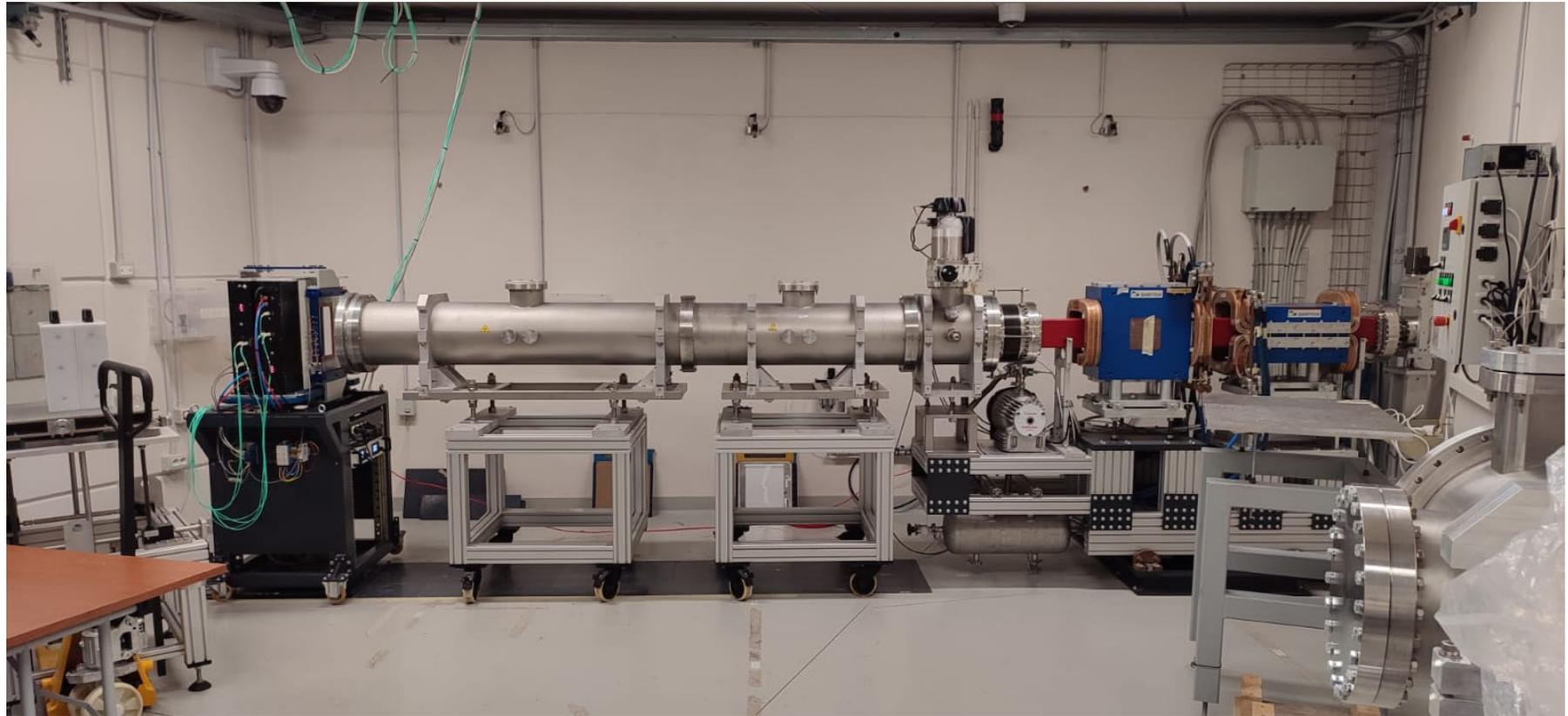
- Multiple configuration
- Accessible during treatment
- Experiments can be installed for many days
- DDS customization possible

Biological laboratory with all the necessary equipment to prepare and process cell samples is available on site. Small animal irradiation is possible taking advantage of the nearby animal house facility of the University of Pavia

Experimental room open to external users



ISO 4



Available beams

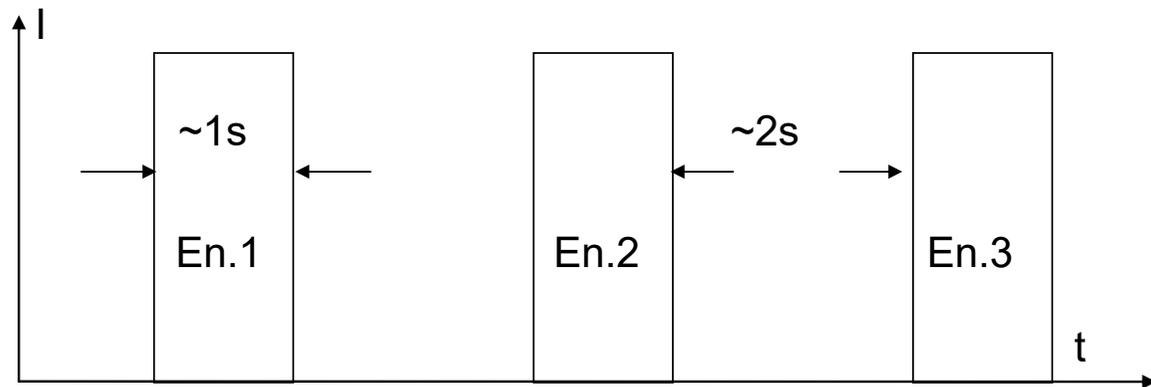
FWHM ~ 10 mm
(particle and energy dependent)

Irradiation field
 $< 200 \times 200$ mm²
[iso4]

Max distance downstream target
 < 5.5 m
[iso1]

Protons
60-227 MeV
 $< 4 \times 10^9$ p/s

Carbon
115-400 MeV/u
 $< 8 \times 10^7$ C/s



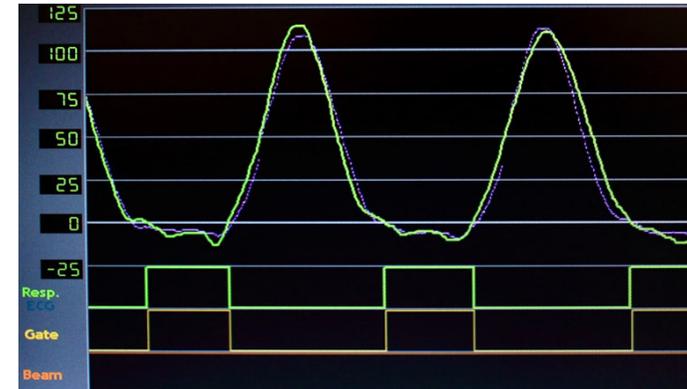
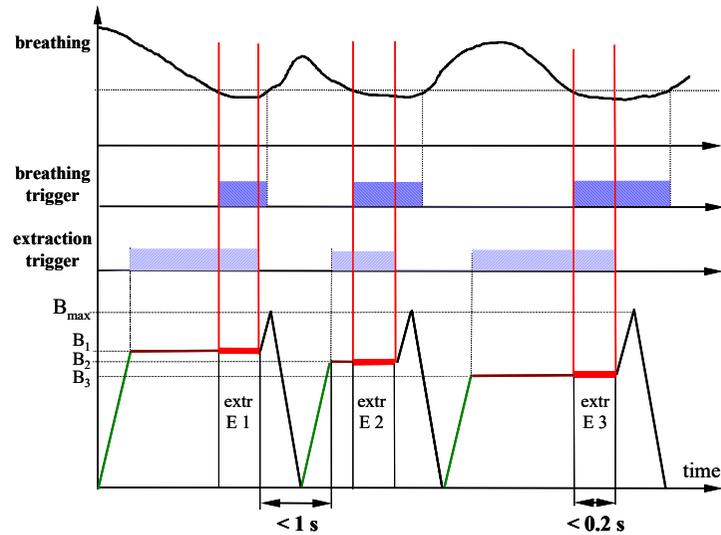
Low intensities (10^3 part/s) possible

Research at CNAO

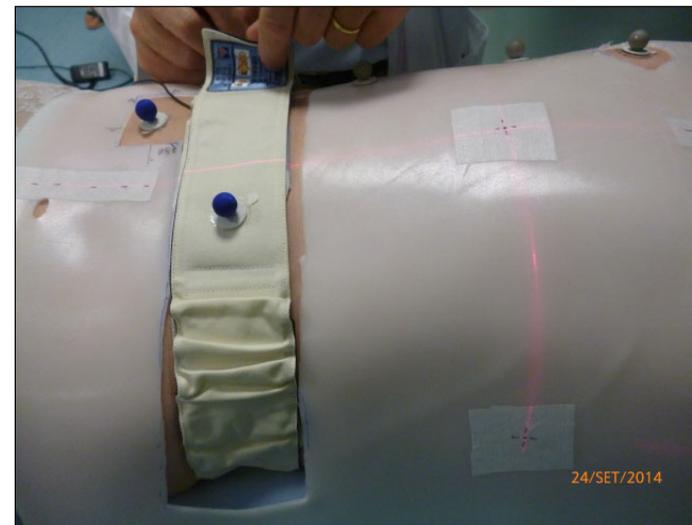
- Many research activities on technical, preclinical and translational subjects
- Typical research subjects carried out at CNAO are aimed at improving treatment
 - Improving the understanding of biological mechanisms
 - Improving the knowledge of basic physical processes
 - Improving the technical performance of the accelerator system
 - Improving the technical performance of the dose delivery
 - Providing new types of radiation (new weapons to the clinician)
 - ...
- Collaborations with many institutions

DDS improvement and development

Gating + rescanning



- Resp. motion reduction (down to 5 mm) using thermo-plastic mask or pneumatic compression belt
- Multiple beams (2-3) and multi-fractionation
- Gating (ref. phase: end-exhale; ANZAI system or OTS) plus rescanning (N=5)



DDS developments

A new version has been developed in collaboration with GSI.

Multi-phase treatments can be delivered.

For moving organs multiple treatments are build to treat the target in different positions.

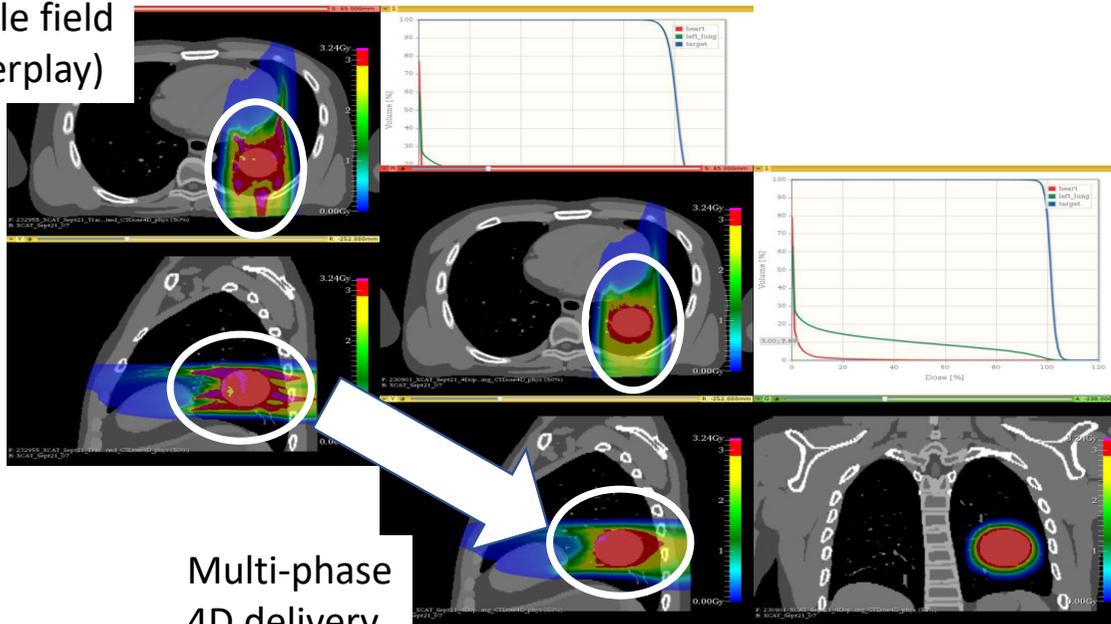
DDS switches between plan in real-time avoiding time waste as in gated modality.

Additional x and y tracking is implemented.

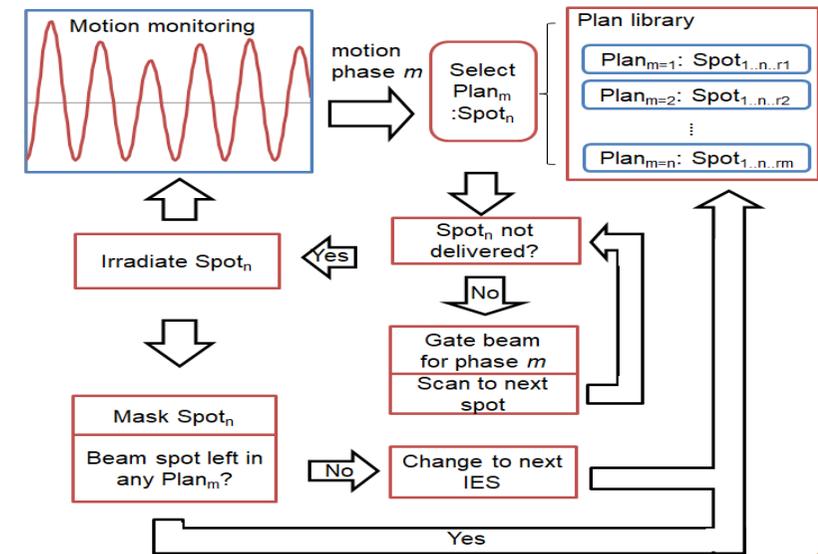
Energy layers scan kept (synchrotron).

Faster field switch for multienergy extraction.

Single field
(interplay)

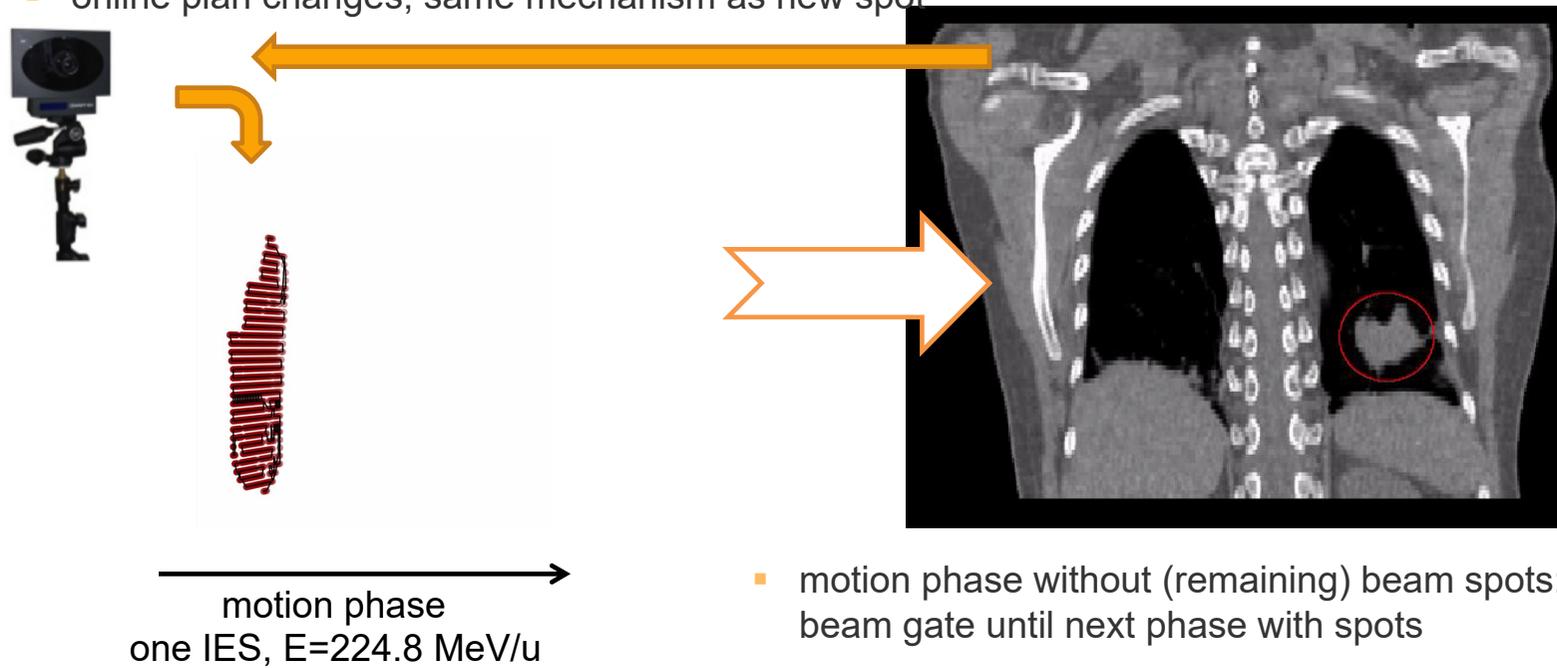


Multi-phase
4D delivery



Motion-synchronized plan libraries

- online plan changes, same mechanism as new spot

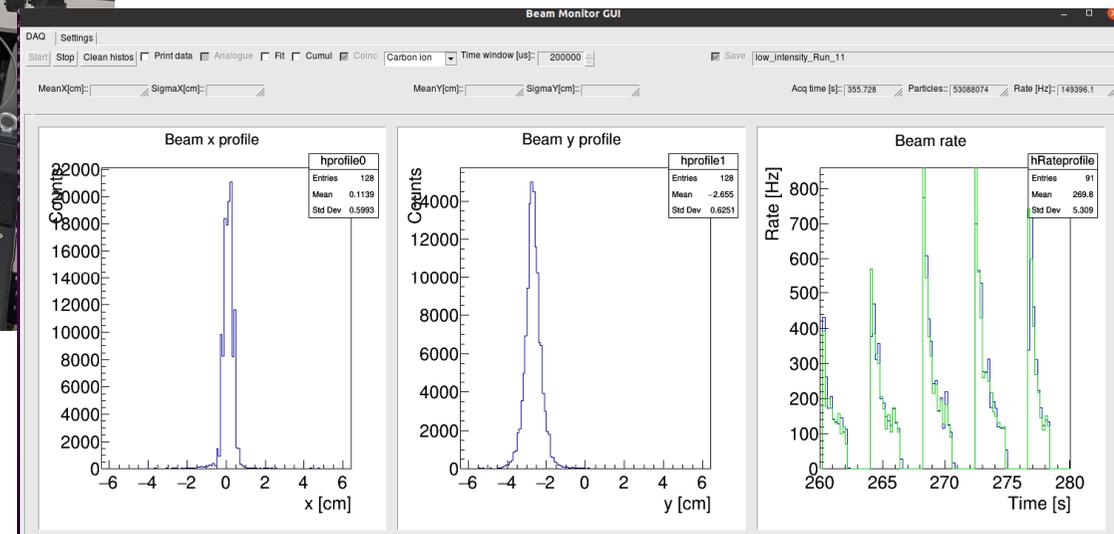


Courtesy of C. Graeff

Low intensity Monitor for XPR (LENTO)



- LENTO (Low intEnsiTy beam moNiTOR) is a scintillating fiber-based detector designed to monitor beam intensity and position in the experimental room @ CNAO. Two orthogonally oriented fiber planes read-out by SiPMs are used to count the incoming particles as a function of the transversal coordinates (x,y) . The whole active area of the detector is 12.8x12.8 cm².
- Next step is including it in the DDS

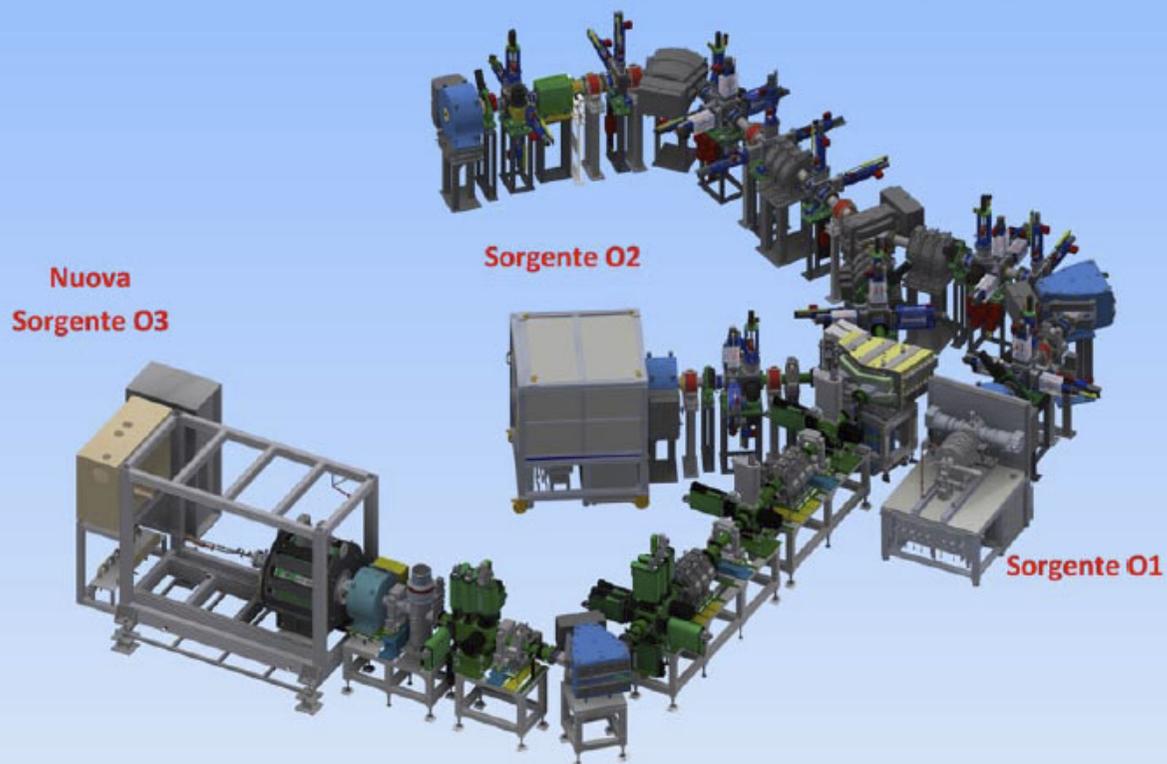


Accelerator improvements

New source

Aisha 2 at CNAO – He, Li, O, Fe

Aisha 1 in INFN LNS



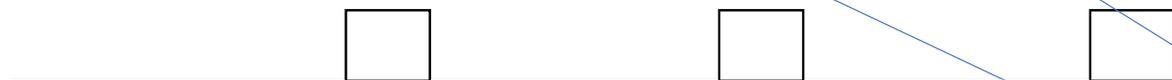
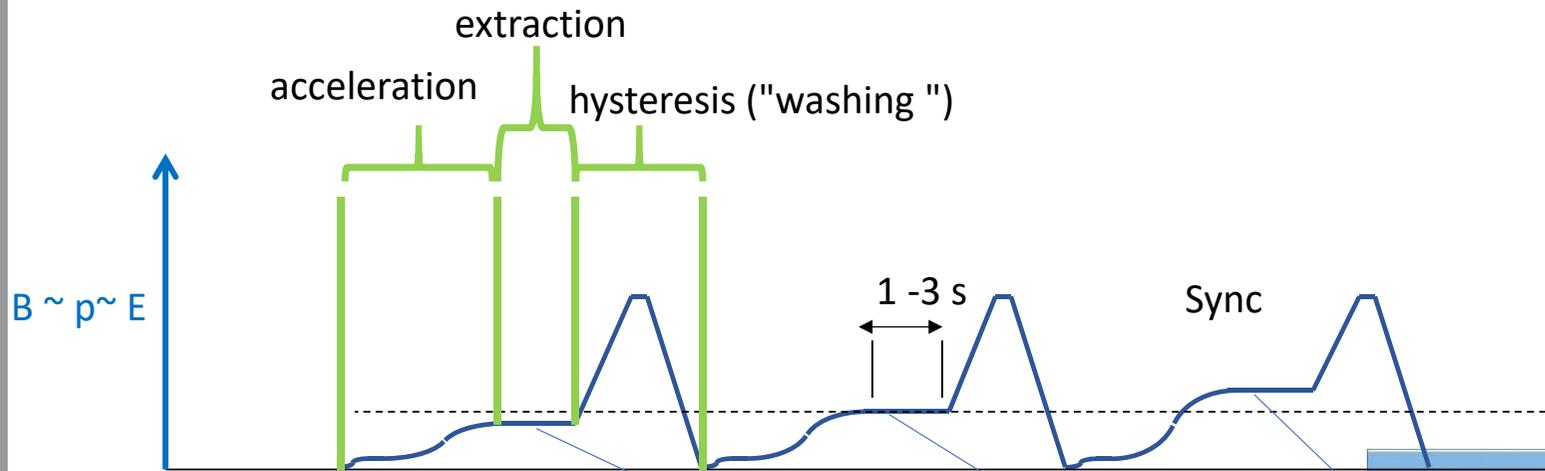
Charge state	Beam intensity [eμA]	$\epsilon_{rms,norm}$ [$\pi \cdot mm \cdot mrad$]
$^{16}\text{O}^{6+}$	1400	0.2198
$^{16}\text{O}^{6+}$	225	0.115
$^{16}\text{O}^{7+}$	350	0.247
$^{12}\text{C}^{4+}$	650	0.272
$^{12}\text{C}^{4+}$	150	0.222
$^{12}\text{C}^{5+}$	165	---
$^{40}\text{Ar}^{11+}$	155	0.201
$^{40}\text{Ar}^{12+}$	140	0.201
He^{2+}	5400	0.418
He^{2+}	700	0.245

Courtesy of L. Celona

2025-02-15 helium beam to treatment room



Treatment execution



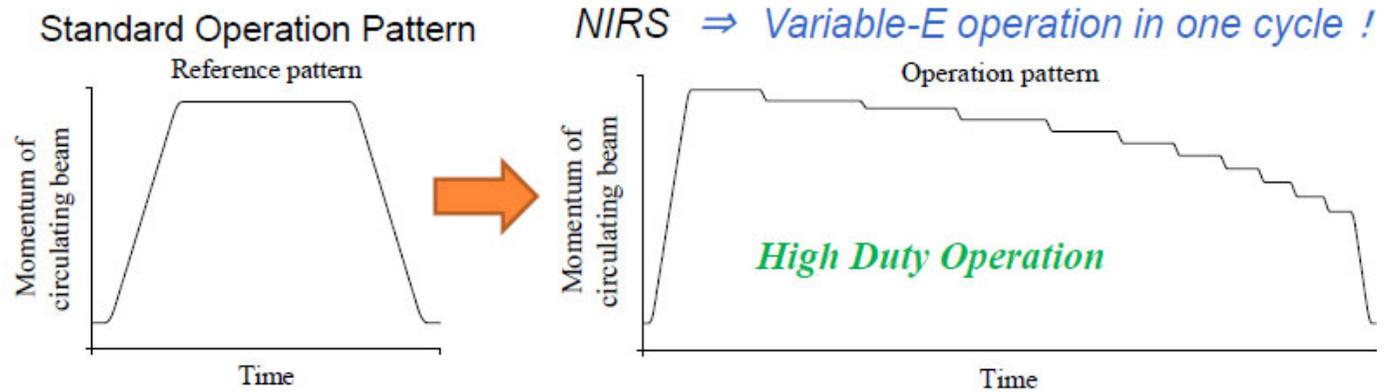
This block details the scanning system and radiation control:

- Scanning System:** Includes Scanning Magnets, Wire Chambers, and Ionization Chambers.
- Monitor System:** Displays a cross-section of the irradiated tumor volume.
- Radiation Control:** Shows a grid of elements, with treated elements highlighted in green.
- Target Volume:** A 3D model of a patient's head showing the target area.
- Example:** A graph of Relative Dose vs. Depth showing the Bragg peak for different particles and energies.

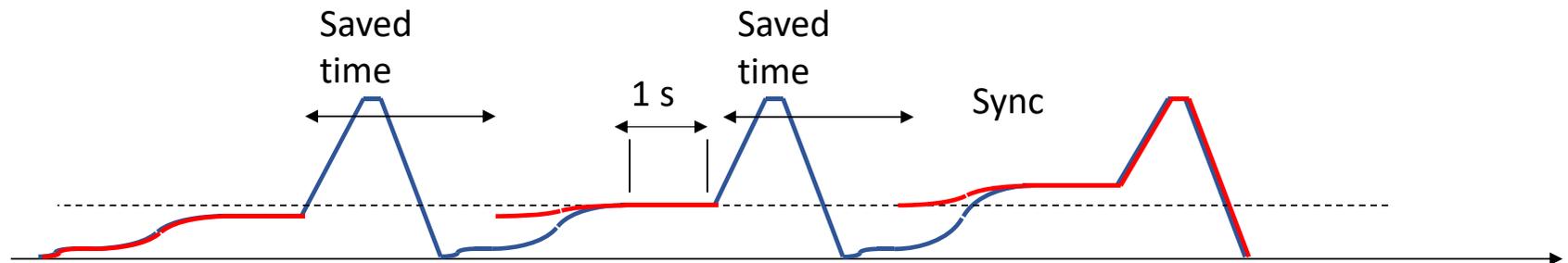
Depth	Particle	Energy
5 cm	Proton	80 MeV
150 MeV/u	Carbon	150 MeV/u
25 cm	Proton	195 MeV
380 MeV/u	Carbon	380 MeV/u

Treatment execution with Multi Energy Extraction

Use remaining beam after slice completion

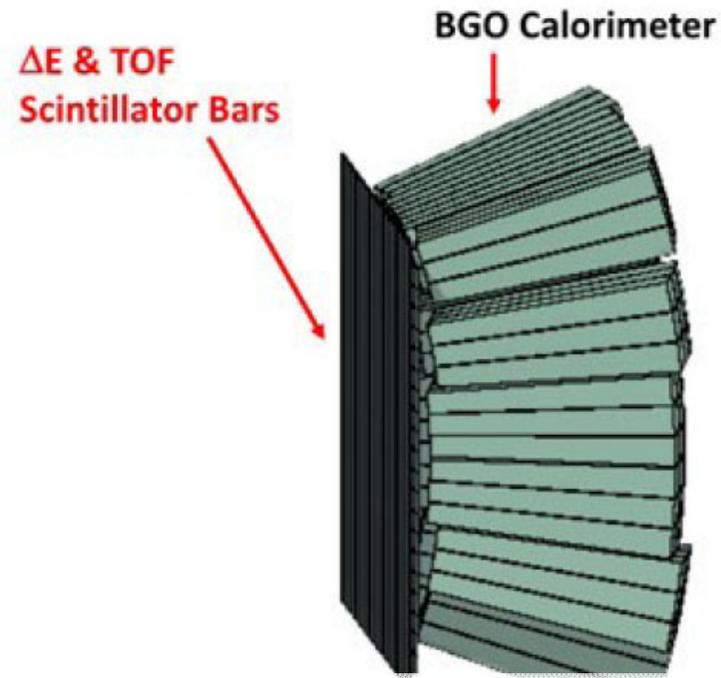
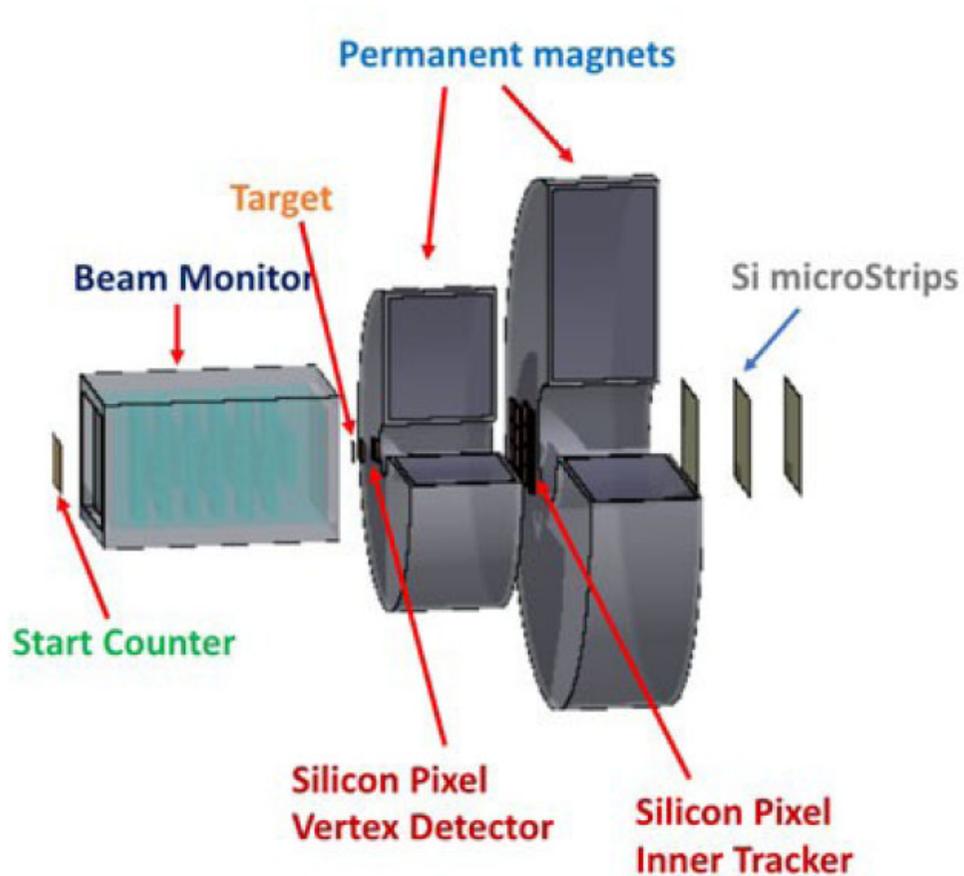


(Courtesy K. Noda – CAS Medical)



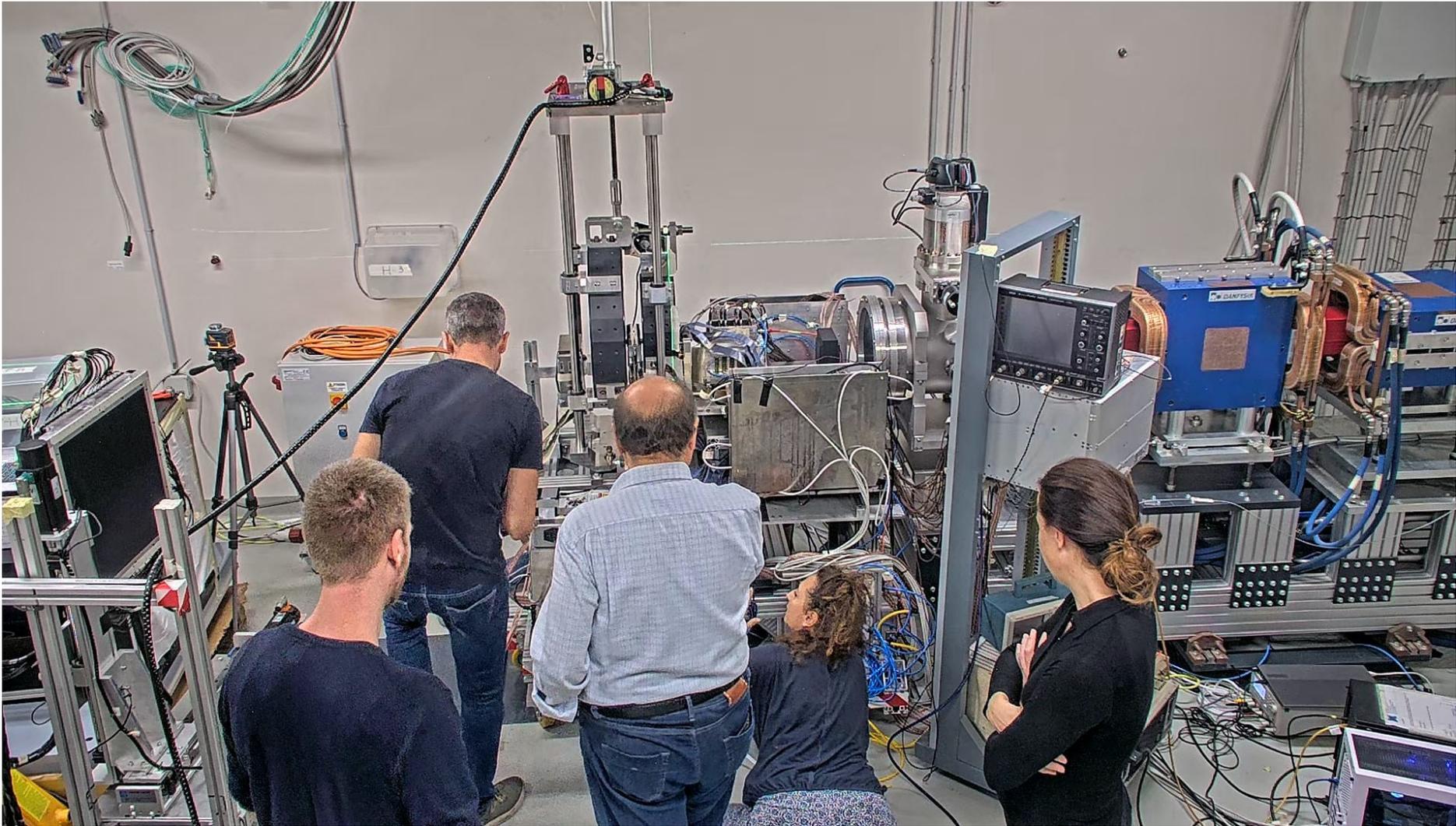
Long(ish) experiments possible

FOOT: FragmentatiOn Of Target



Measurement of the differential cross sections as a function of energy and direction of the produced fragments in the nuclear interaction between a ion beam (proton, helium, carbon, oxygen) and different targets containing hydrogen, carbon or oxygen.

Hadrontherapy and optimization of spaceships shielding .



...and many R&D subjects like

Space research (detectors)

Space research (radiobio)

Dosimetry, microdosimetry, nanodosimetry

Channelling in crystals

Detector/beam diagnostics development

Radiobiology (many different subjects)

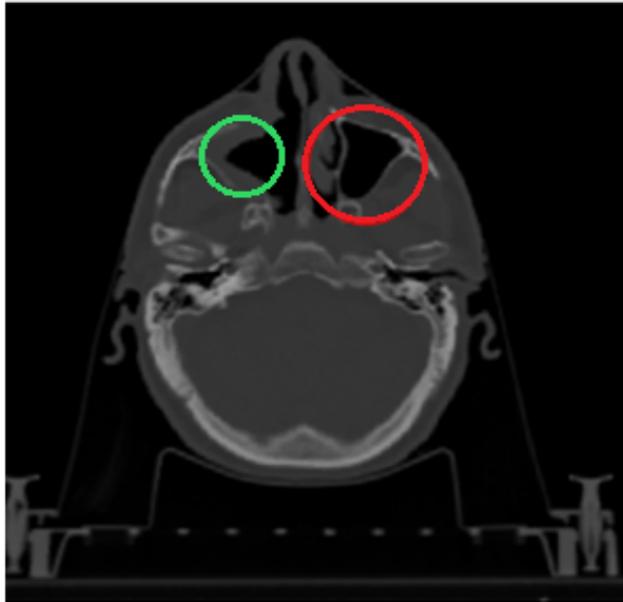
...

And

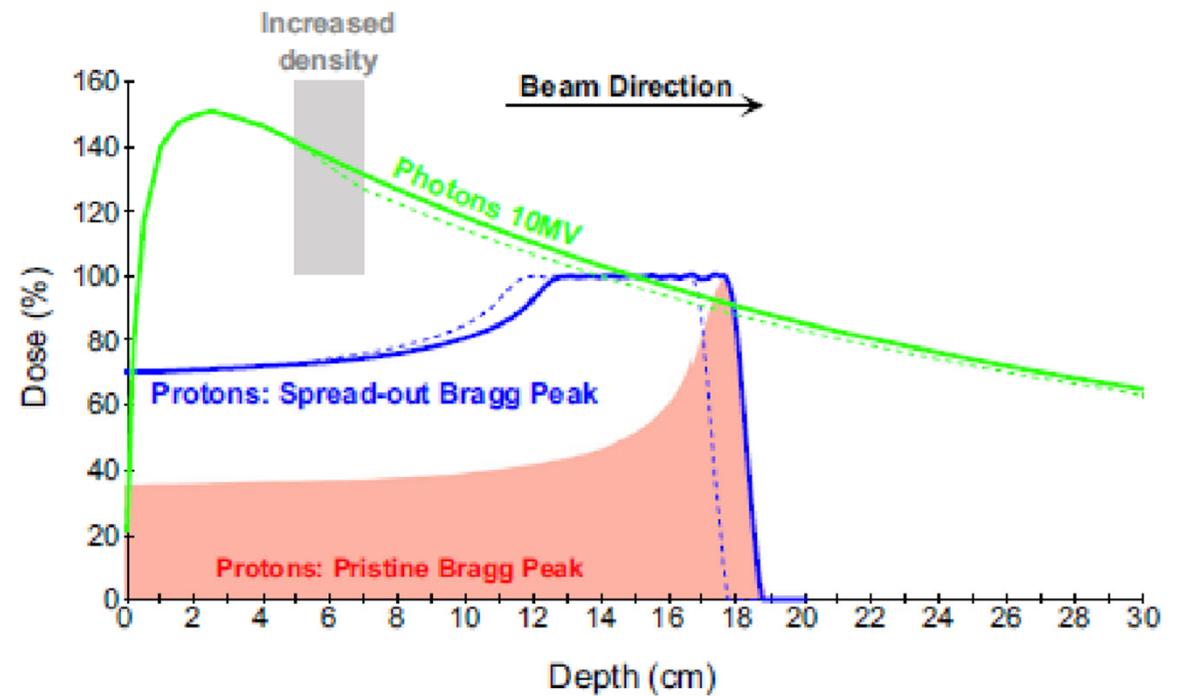
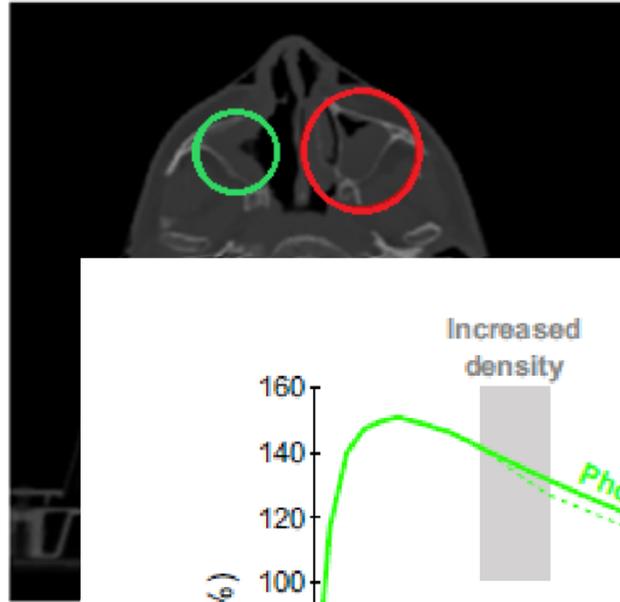
Range verification

Why we want range verification

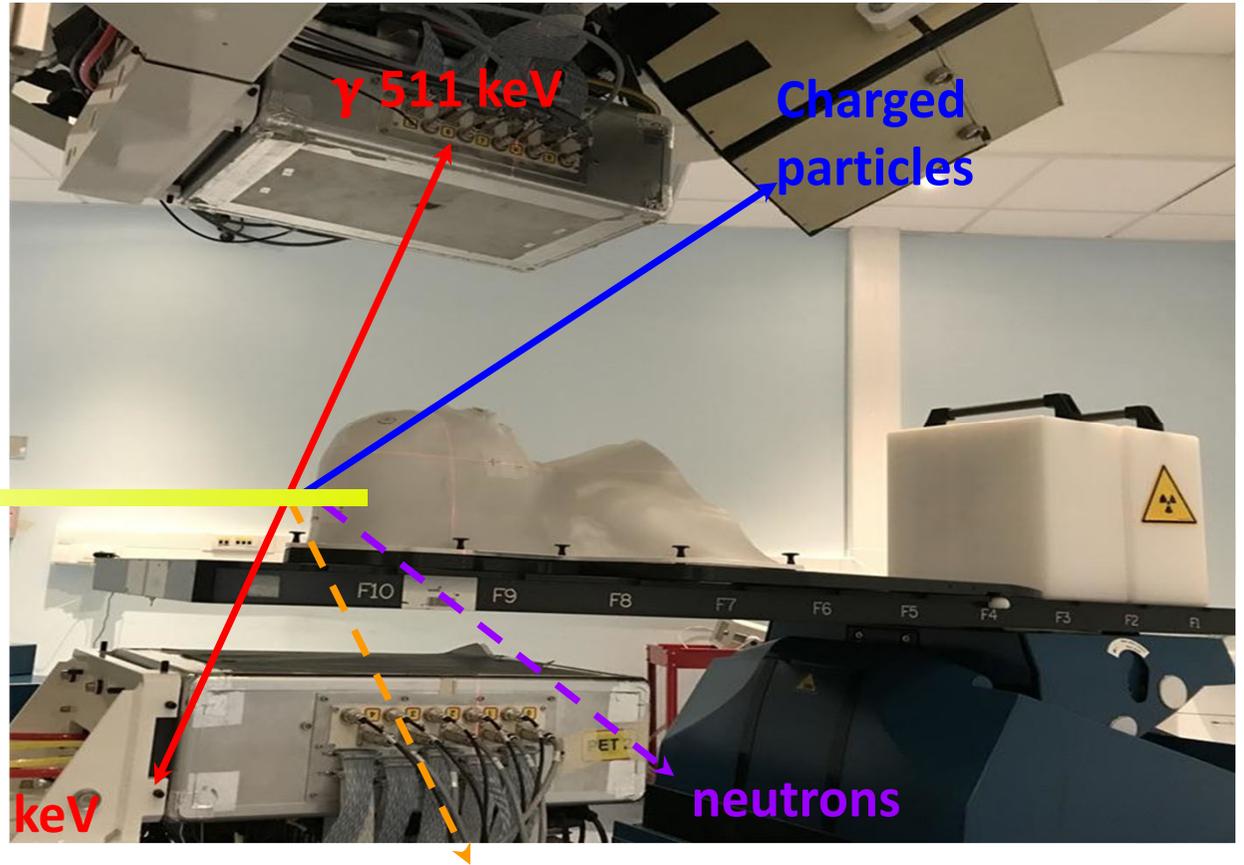
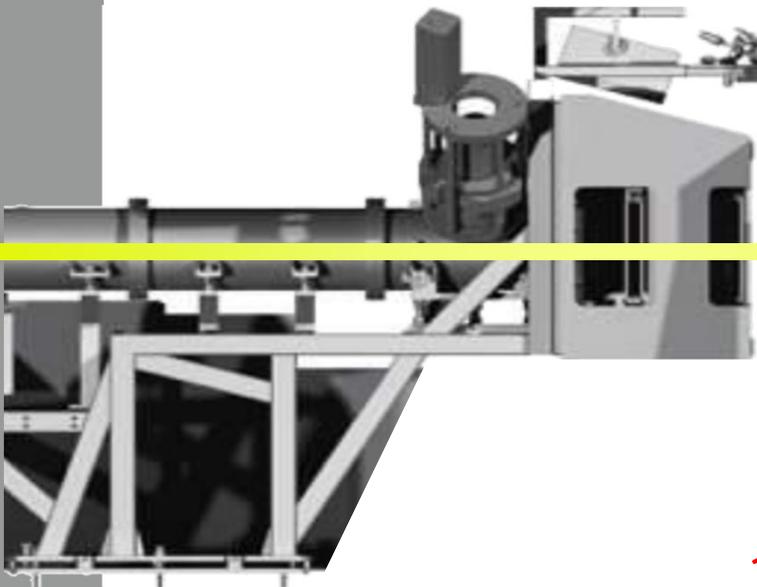
CT INIZIALE



CT RIVALUTAZIONE



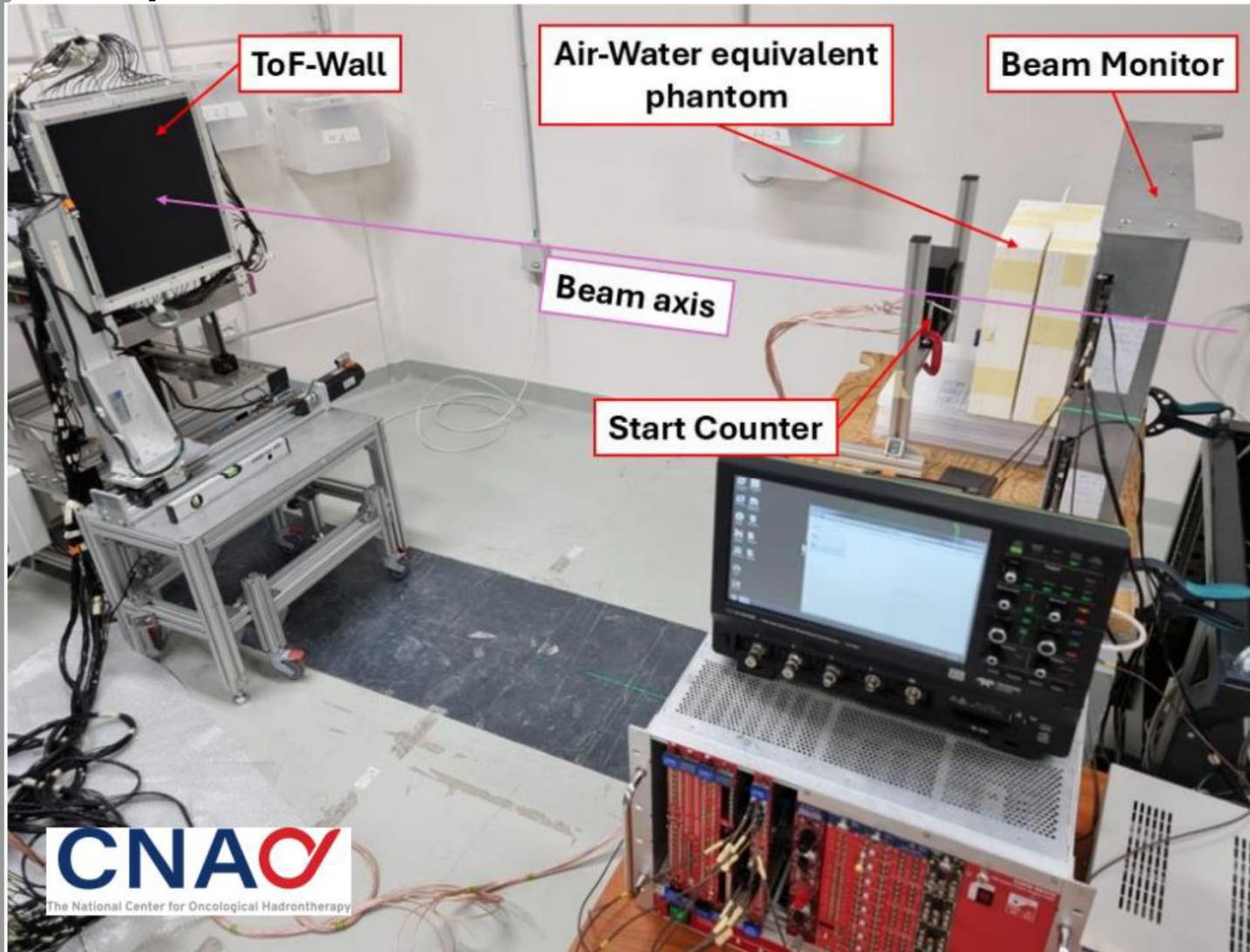
Range verification with PET



SEE TALK IN THIS WORKSHOP



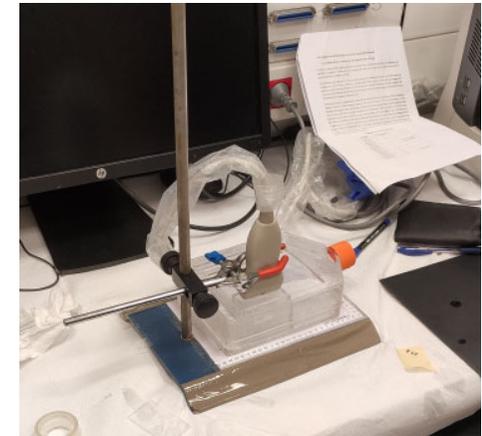
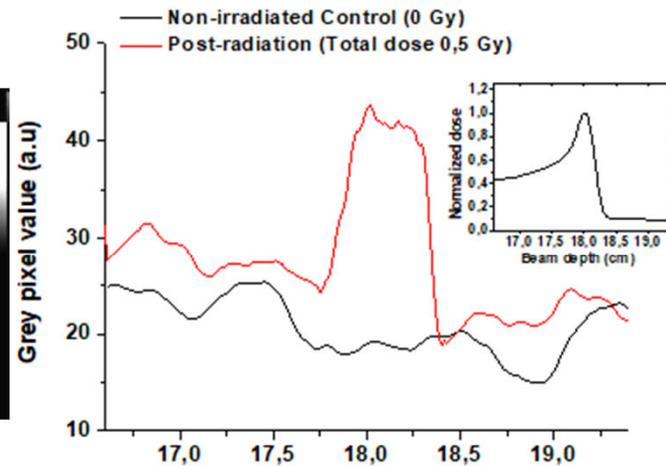
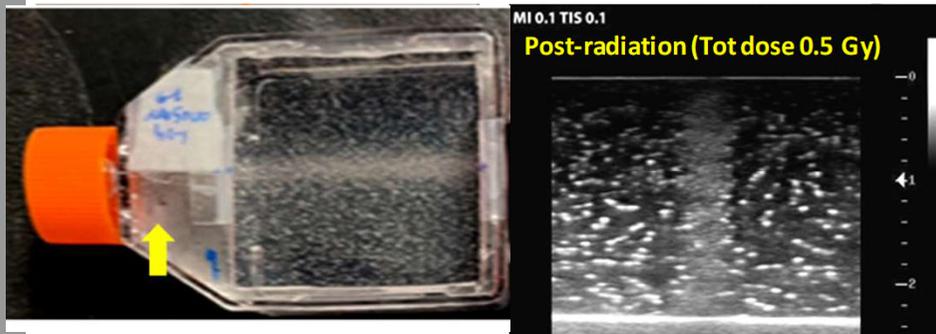
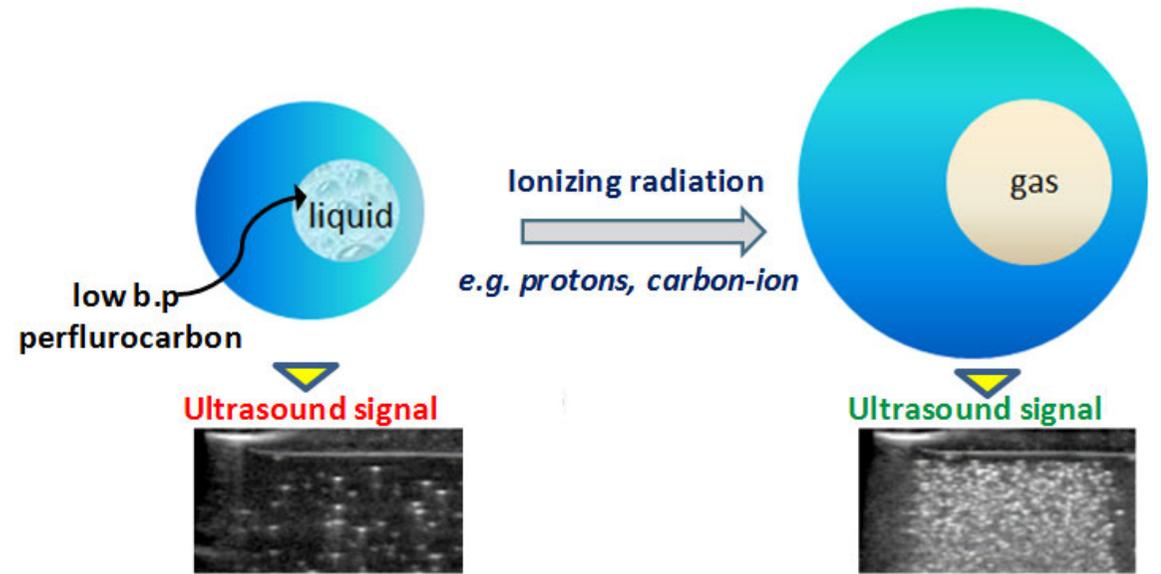
ToFpRad



SEE TALK IN THIS WORKSHOP

grant PRIN: PROGETTI DI RICERCA DI
RILEVANTE INTERESSE NAZIONALE - Bando 2022
"TOFpRad: Time Of
Flight Proton RADIography with plastic scintillators"
grant nr.
202293MEL9, CUP I53D23000970001.

Nanodroplets



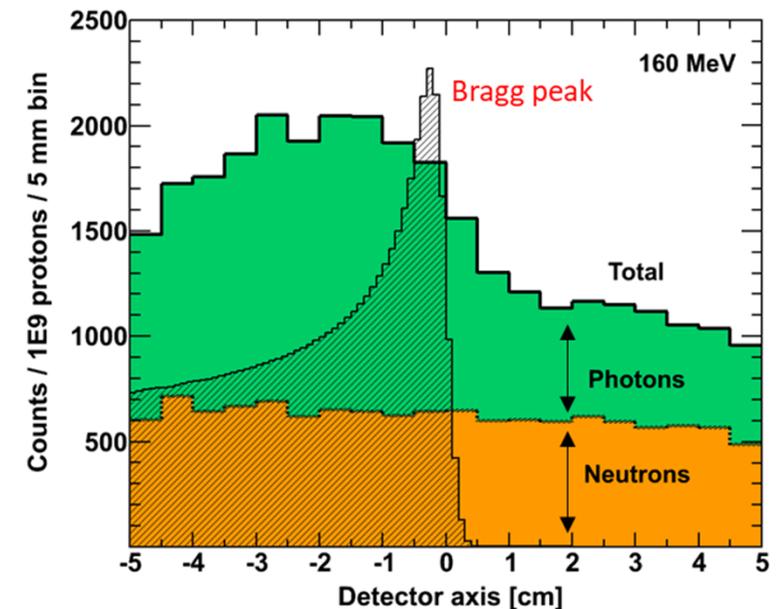
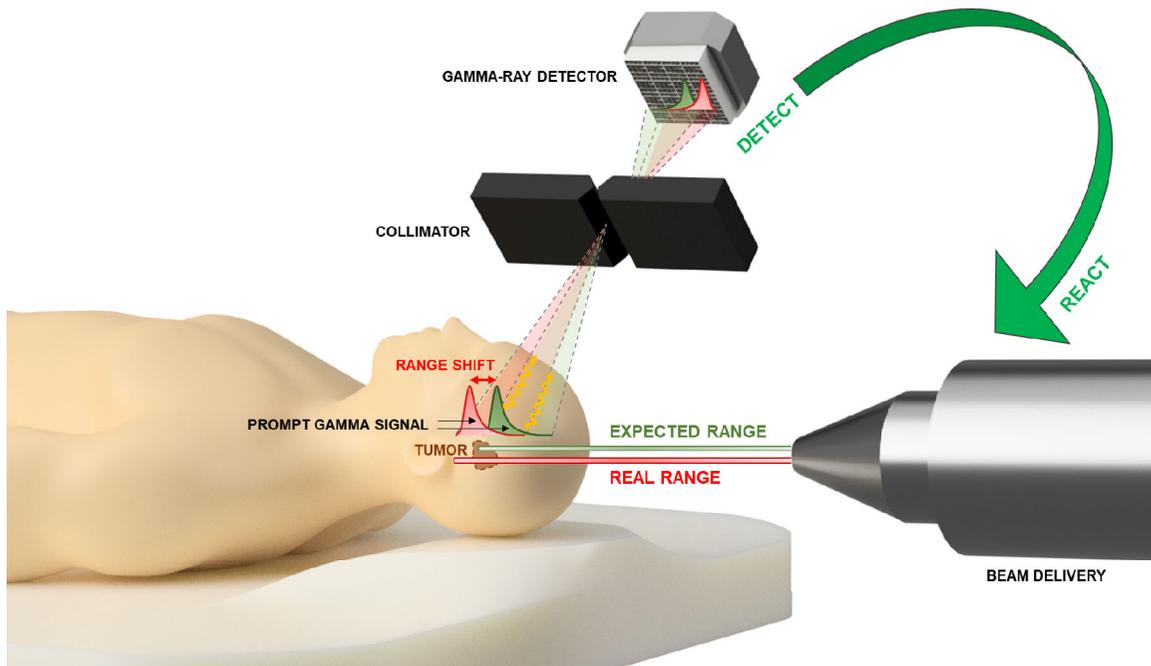
Dipartimento di Scienze e Tecnologie Chimiche,
 Università degli Studi di Roma Tor Vergata
 INFN sez. Roma Tor Vergata



Toumia, Y., Pullia, M., Domenici, F. et al. "Ultrasound-assisted carbon ion dosimetry and range measurement using injectable polymer-shelled phase-change nanodroplets: in vitro study". *Sci Rep* 12, 8012 (2022).
<https://doi.org/10.1038/s41598-022-11524-x>

Prompt gamma imaging

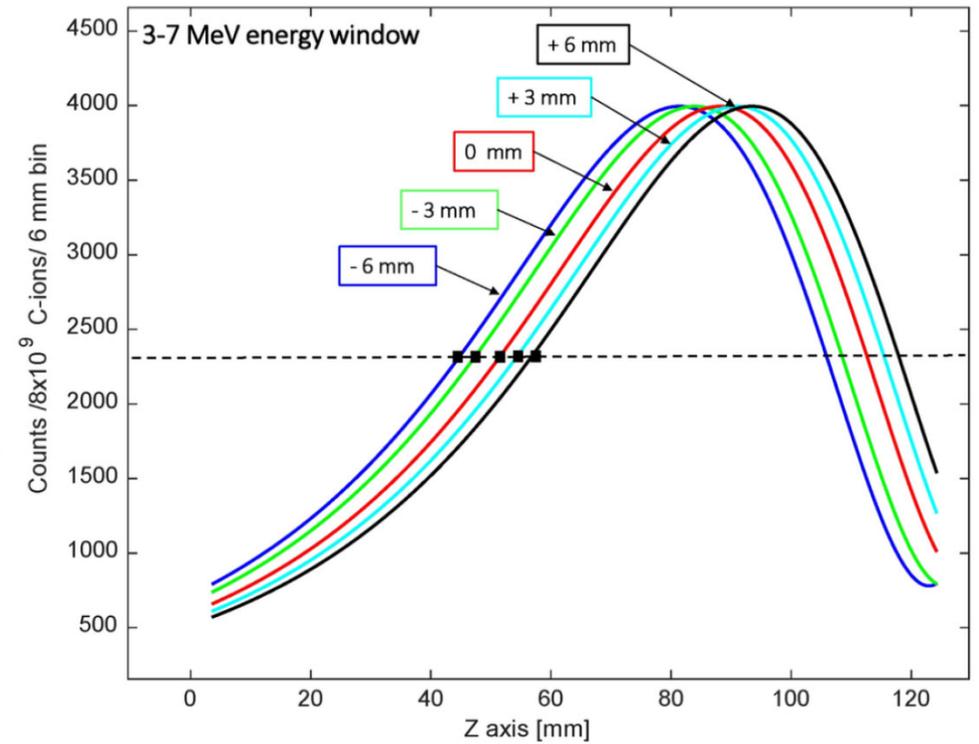
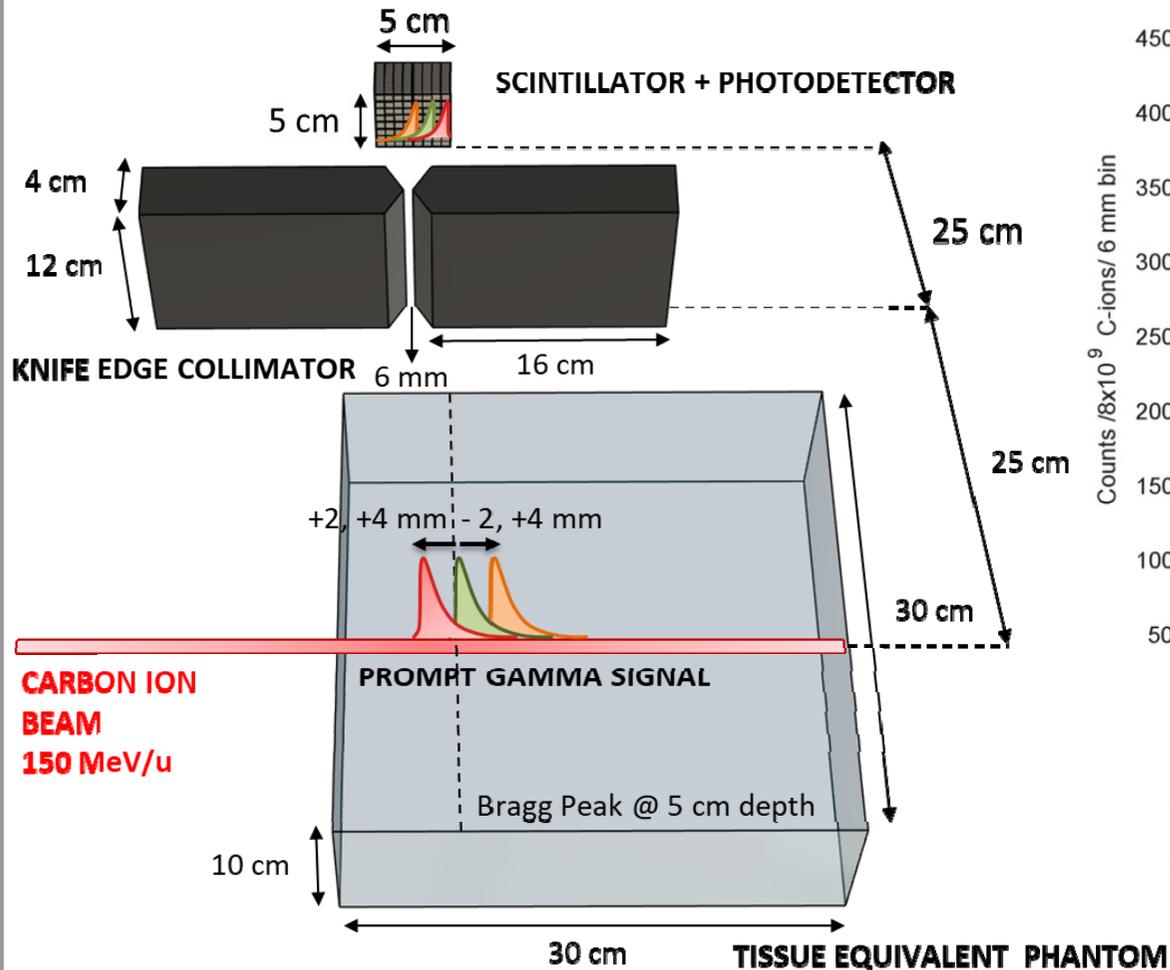
REALPATH - A Real-Time Range Verification System for Hadron Therapy



Goal of **REALPATH** is to develop an instrument capable to carry out a **real-time verification** of the highly-localized **irradiation range** in the patient during hadrontherapy treatments. This feature will allow to verify the correspondence with the treatment plan and to avoid the irradiation of organs at risk. The instrument is based on the measurement of **prompt-gamma rays**, with an **industrial-oriented approach** based on innovative sensors, electronics and Artificial Intelligence algorithms.

Courtesy of C. Fiorini

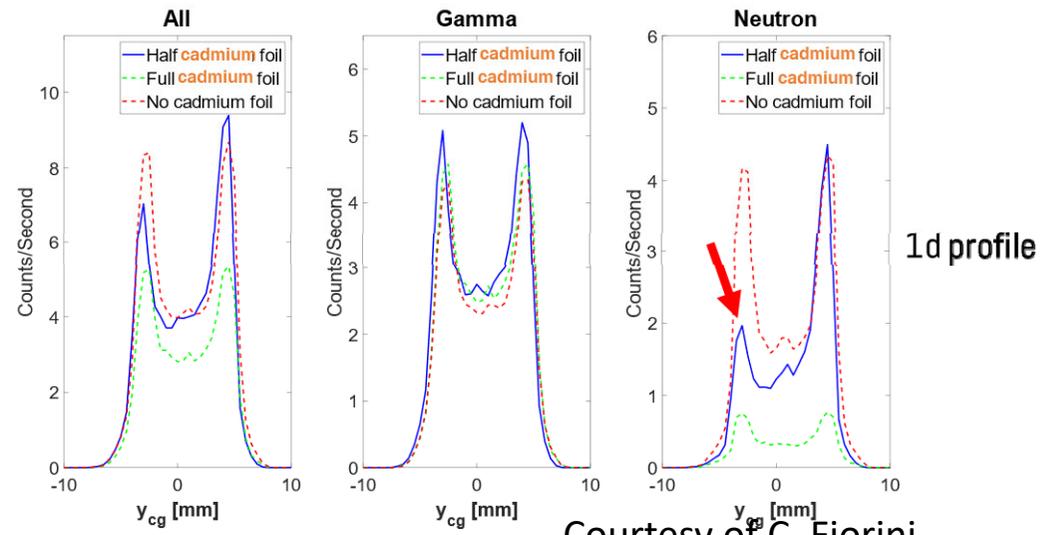
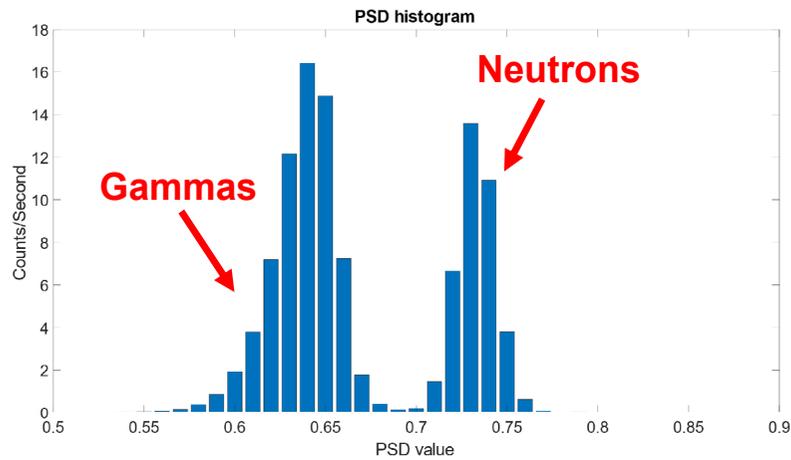
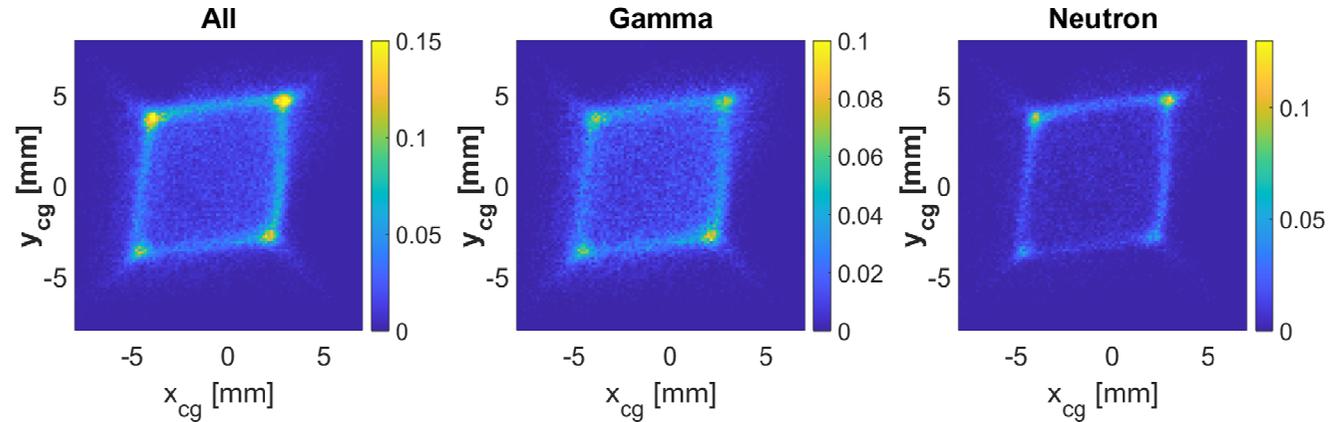
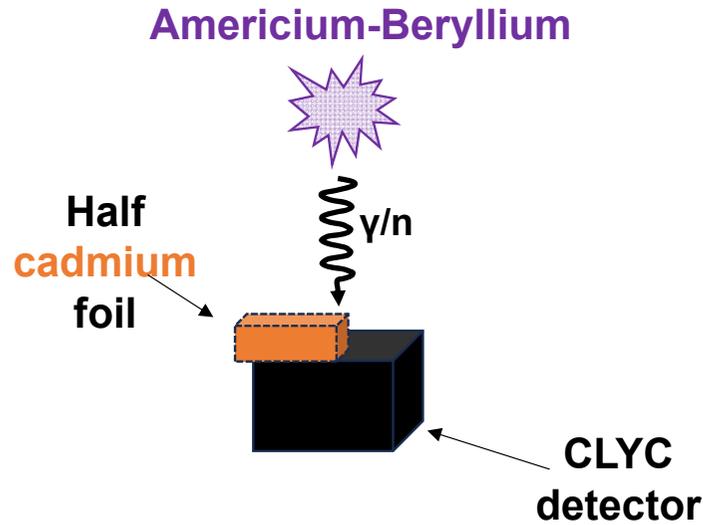
First Prompt Gamma Imaging with C-ions



(A.B. Idrissi, *et al.* First experimental verification of prompt gamma imaging with carbon ion irradiation. *Sci Rep* **14**, 25750 (2024))

Courtesy of C. Fiorini

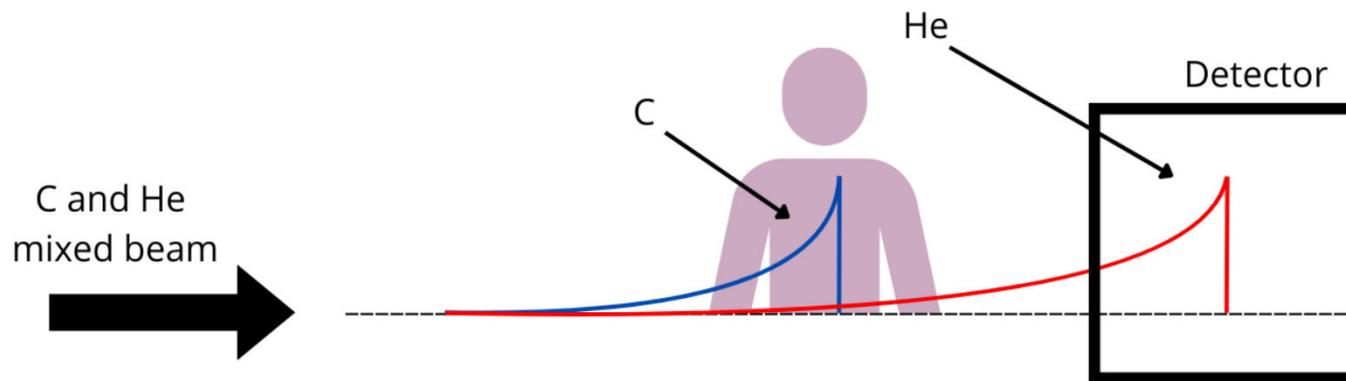
PSD-resolved gamma-ray position-sensitive detector



Courtesy of C. Fiorini

HeCheck: range verification with mixed beams

HeCheck



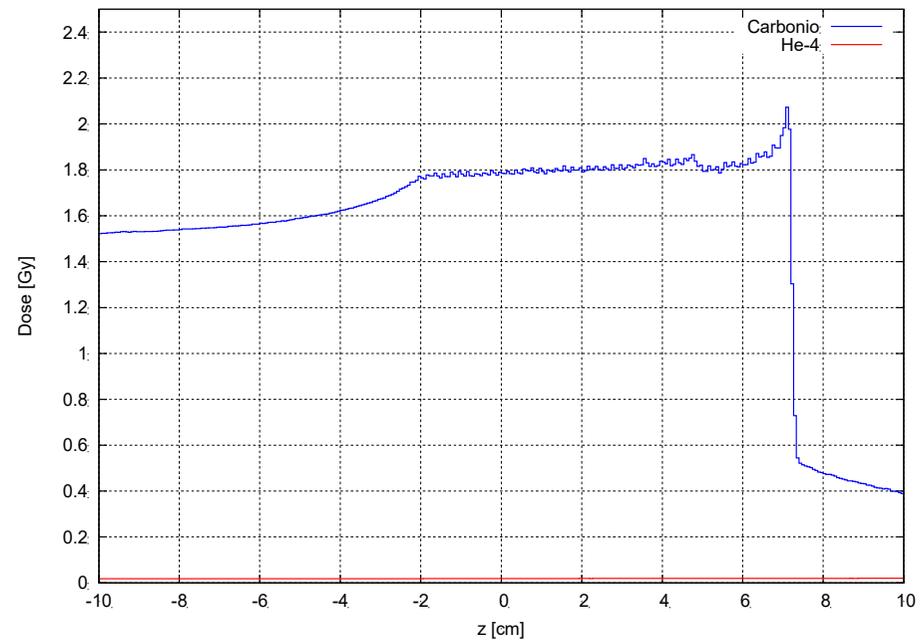
Proof of principle

He 10% in number wrt C

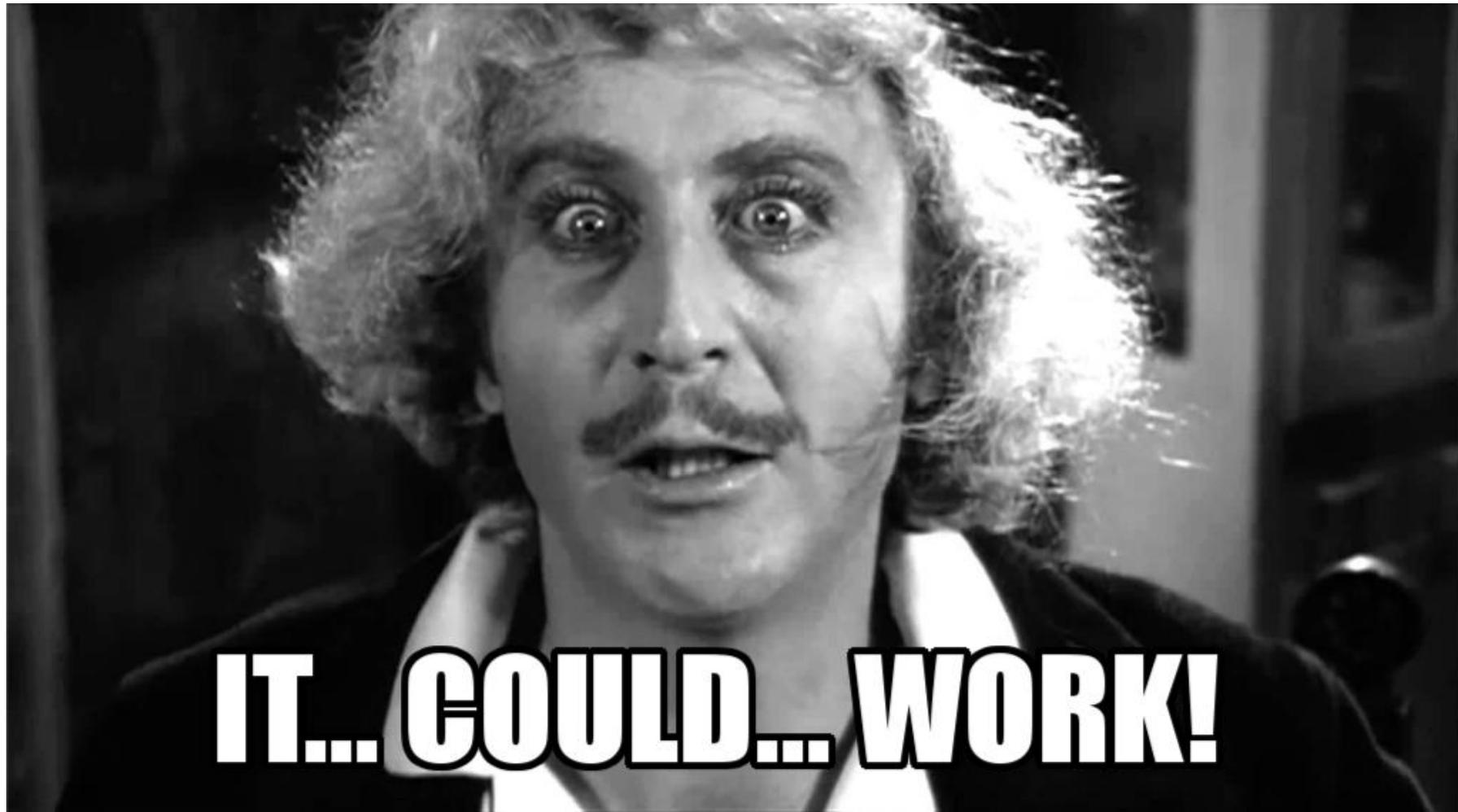
1% in dose

Mazucconi et al, Mixed particle beam for simultaneous treatment and online range verification in carbon ion therapy: Proof-of-concept study

<https://doi.org/10.1002/mp.13219>



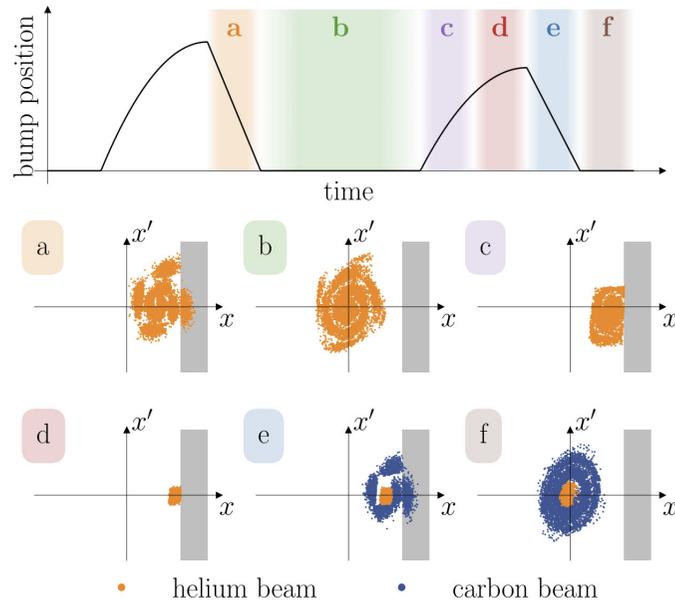
Is it really possible?



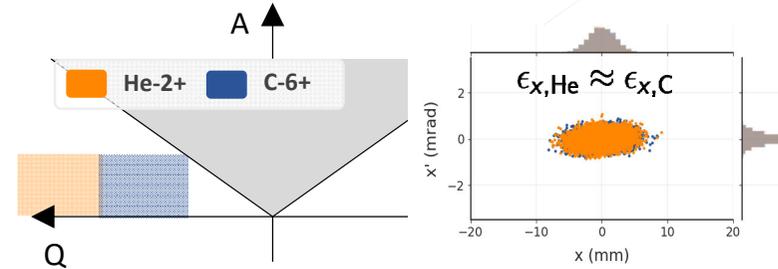


${}^4\text{He}^{1+} + {}^{12}\text{C}^{3+} \rightarrow$ cannot be accelerated in LINAC

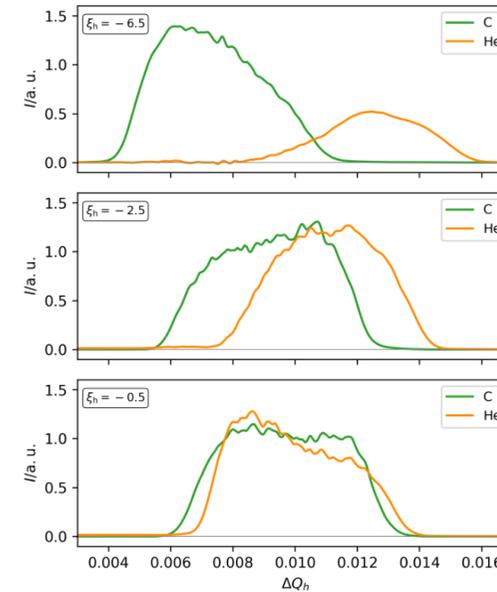
${}^4\text{He}^{2+} + {}^{12}\text{C}^{6+} \rightarrow$ insufficient ${}^{12}\text{C}^{6+}$ yield



Courtesy of M. Kausel



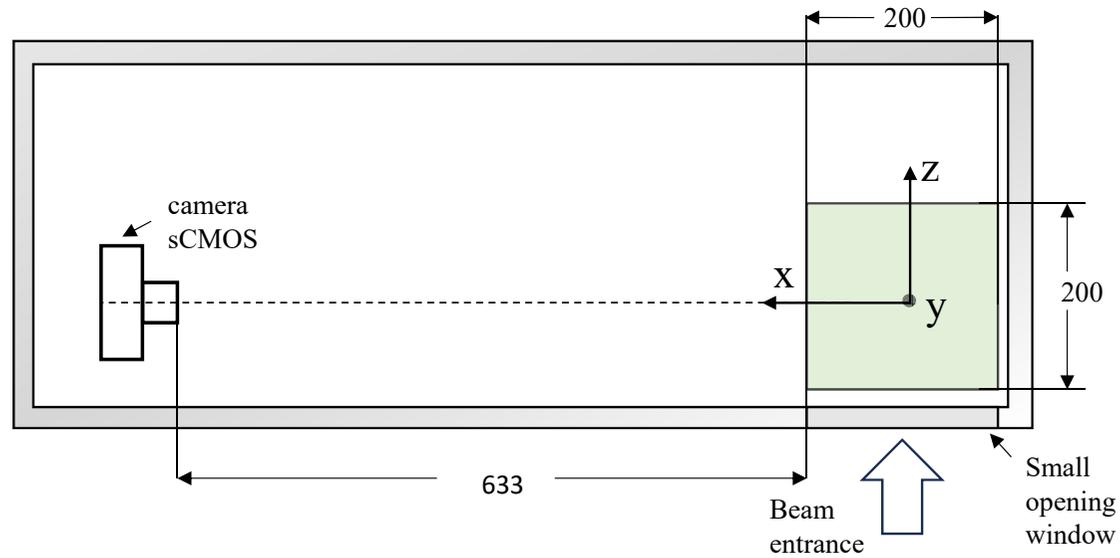
Schematic illustration. Proportions not to scale



Single ion source: He and C with similar initial horiz. emittances

Courtesy of A. Pastushenko

First setup



Camera sCMOS

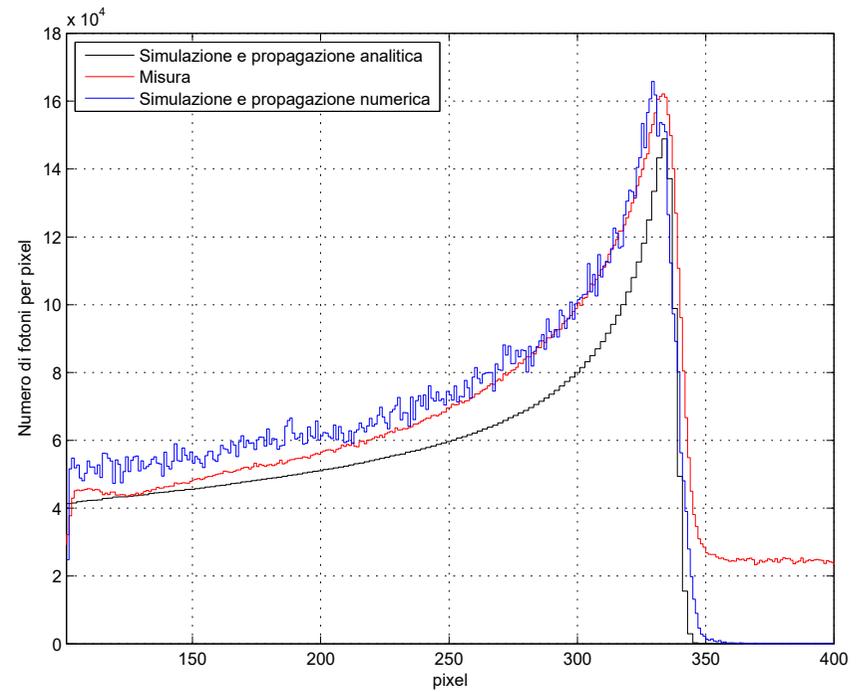
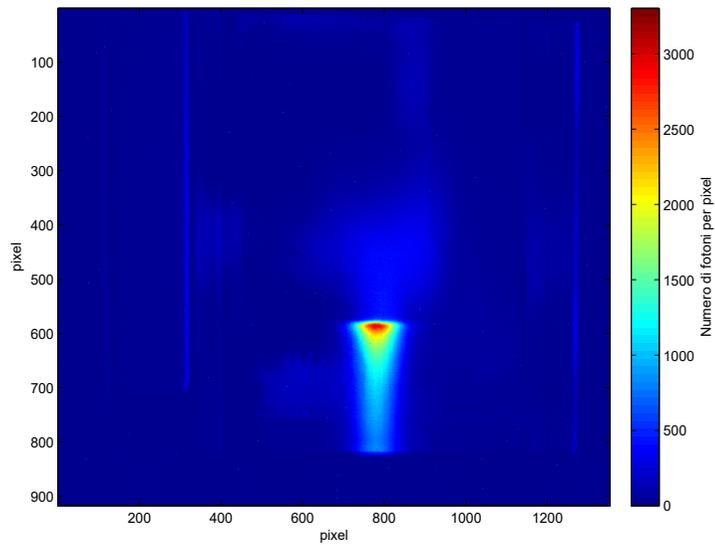
Marca e modello camera	SBIG STL-11000M
Dimensioni sensore	4008×2672 pixel, 36 × 24.7 mm
Dimensione pixel	9×9 μm
Full well capacity	50000 e ⁻
Corrente di buio	1.5 e ⁻ /pixel/s a 0 °C
Convertitore A/D	16 bit
Elettroni per unità digitale	0.8 e ⁻ /ADU
Rumore di lettura	11 e ⁻ RMS
Raffreddamento	Termoelettrico a due stadi (ΔT= -50 °C)
Marca e modello obiettivo	Nikkor 85 mm f/1.4

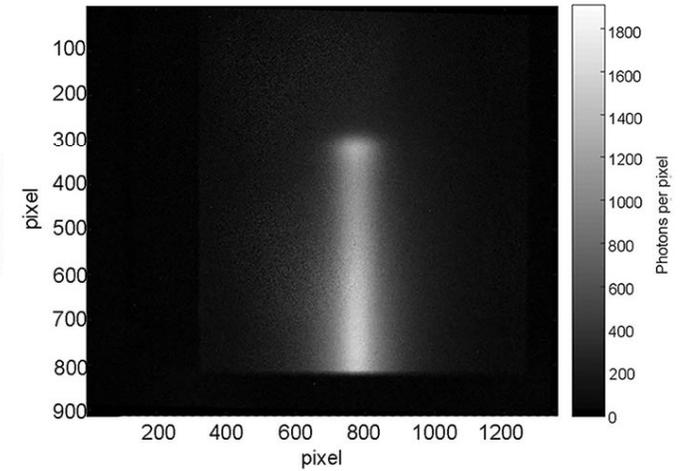
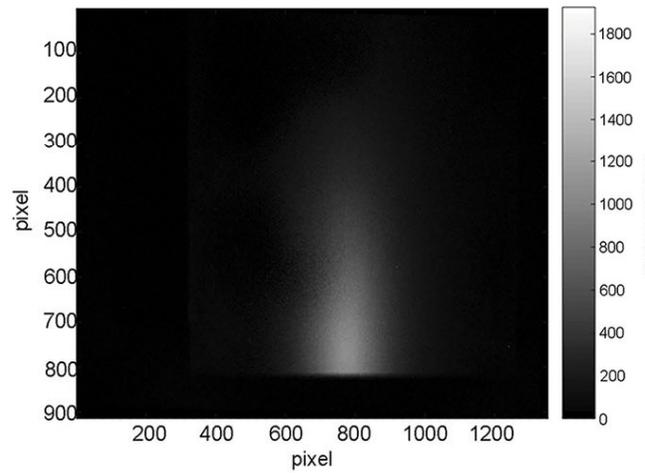
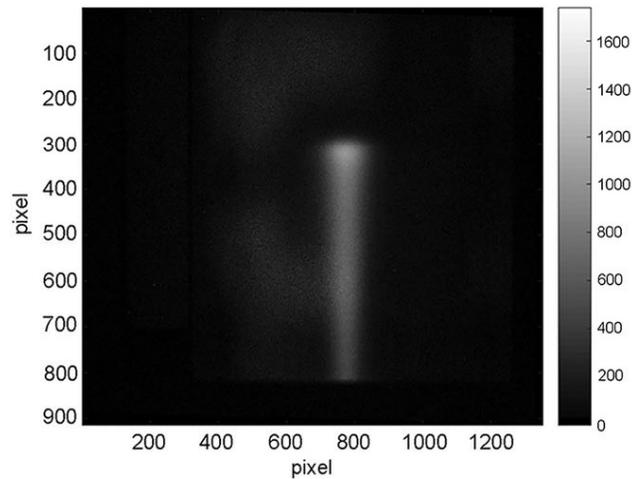
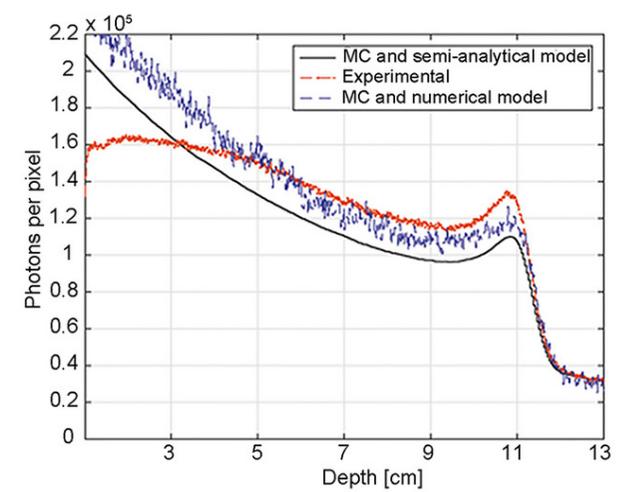
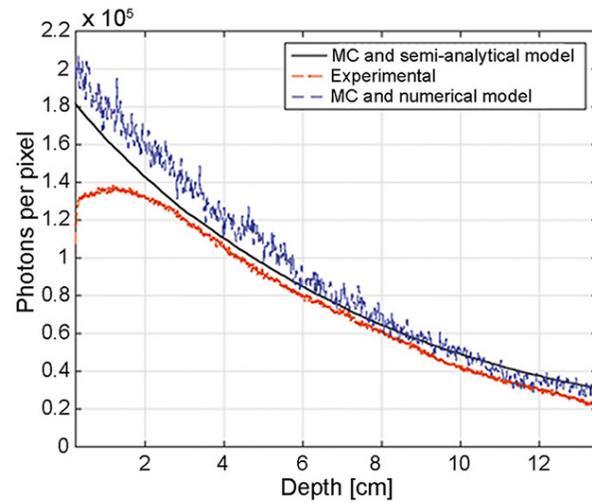
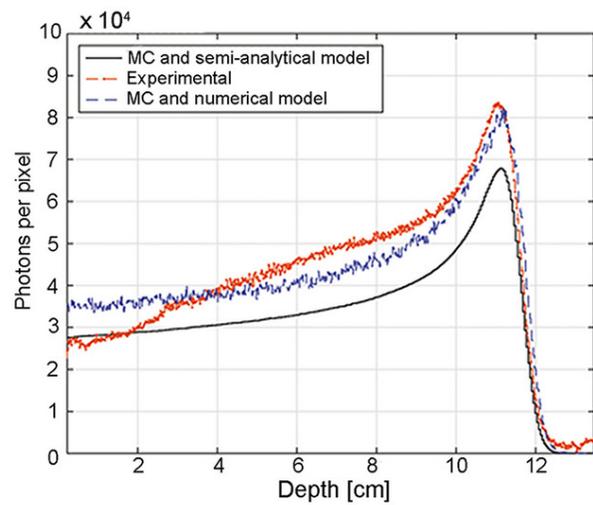
Scintillatore

Producer and Model	Saint Gobain Crystals BC-408 Plastic Scintillator
Dimensions [cm]	20×20×20
Light yield [% Antracene]	64
Emission wavelength [nm]	425
Main component decay constant [ns]	2.1
Attenuation length [cm]	380
Refraction index	1.58
Density [g/cm ³]	1.032
H:C ratio	1.104

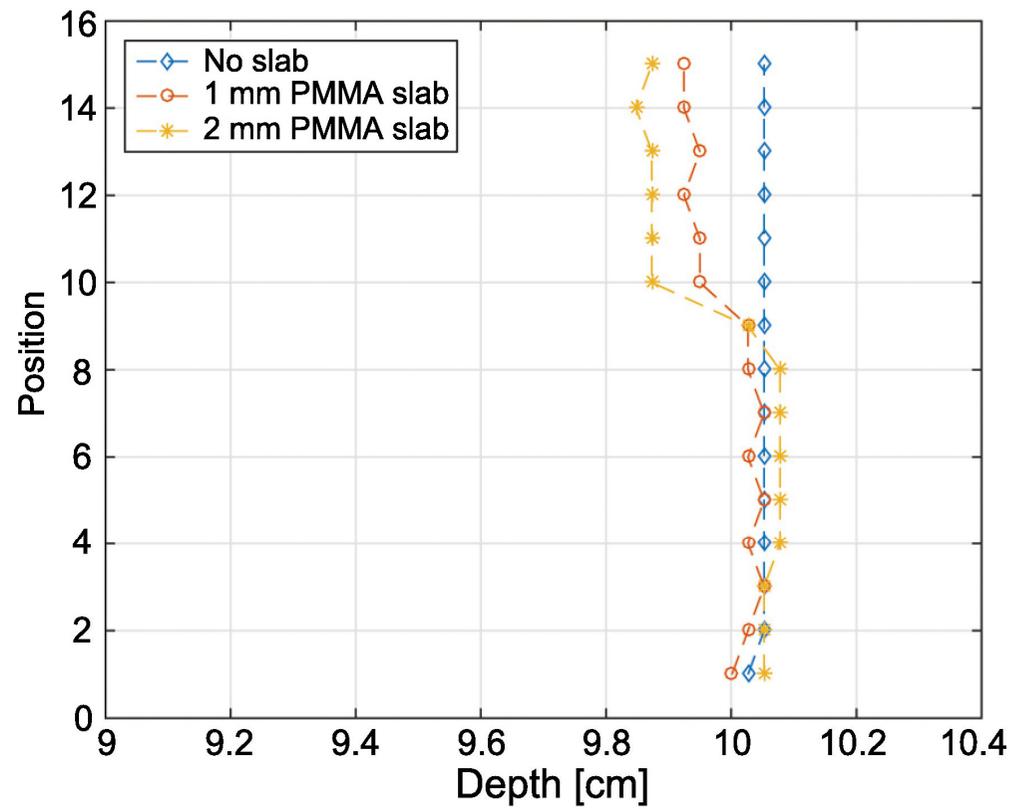
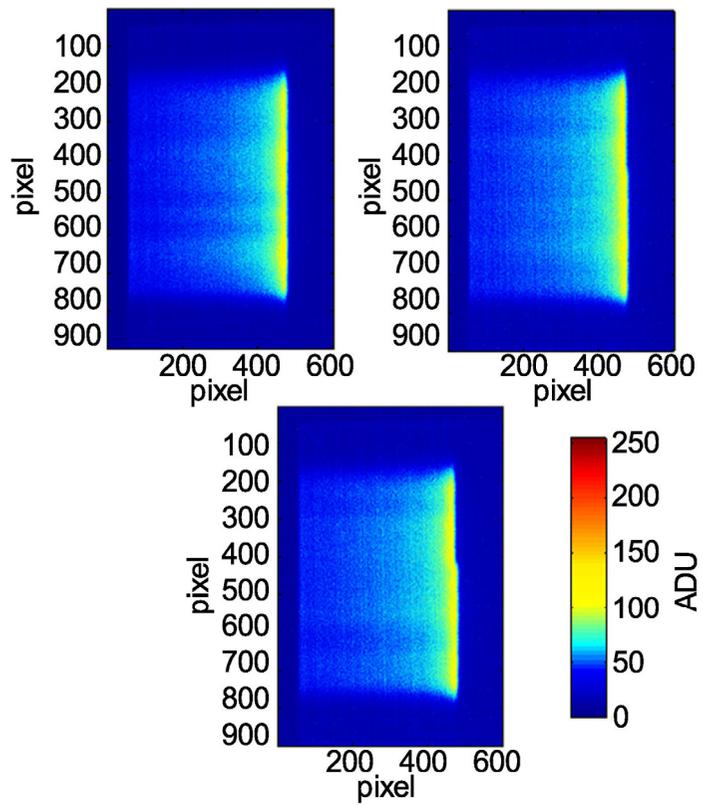
Simulation and measurement

81 MeV protons
(5×10^5 primaries)

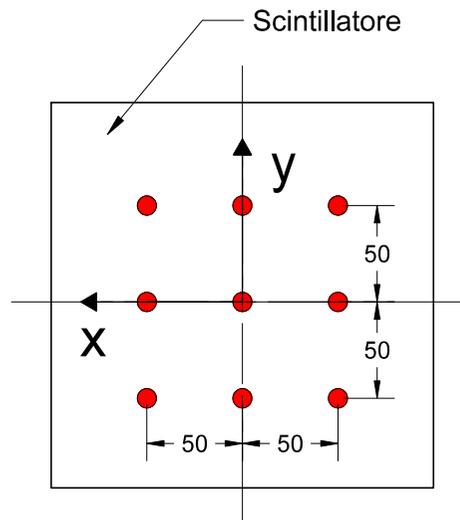




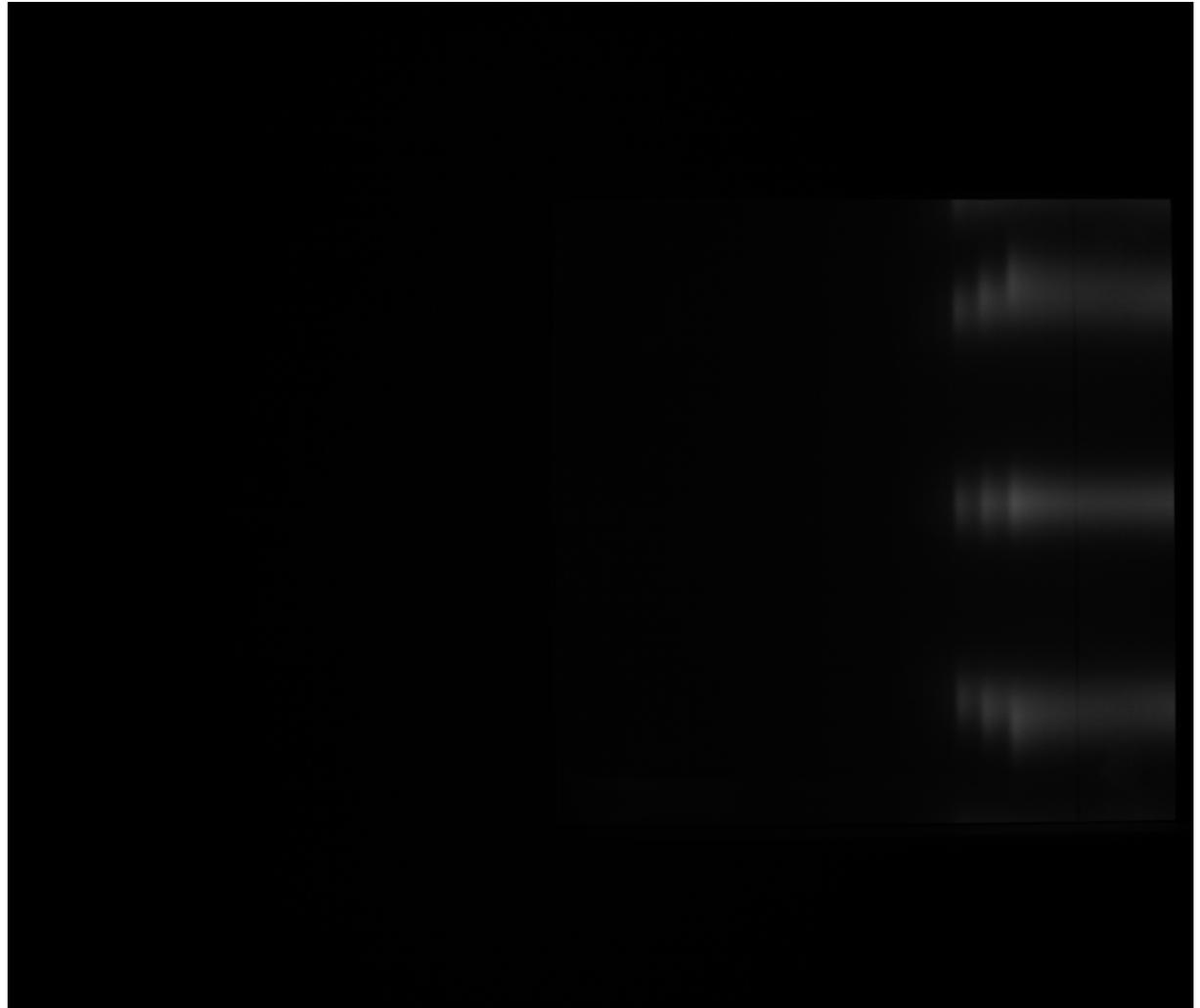
Comparison between simulated and measured photons per pixel for a 226.9 MeV proton beam and a 226.5 MeV/u carbon beam. Protons are 10% in number with respect to carbon ions. The image shows the comparison for only protons (up-left), carbon fragments (up-center), and the superimposed image (up-right). Bottom: 2D acquired images converted in photons per pixel. Target 20 cm thickness



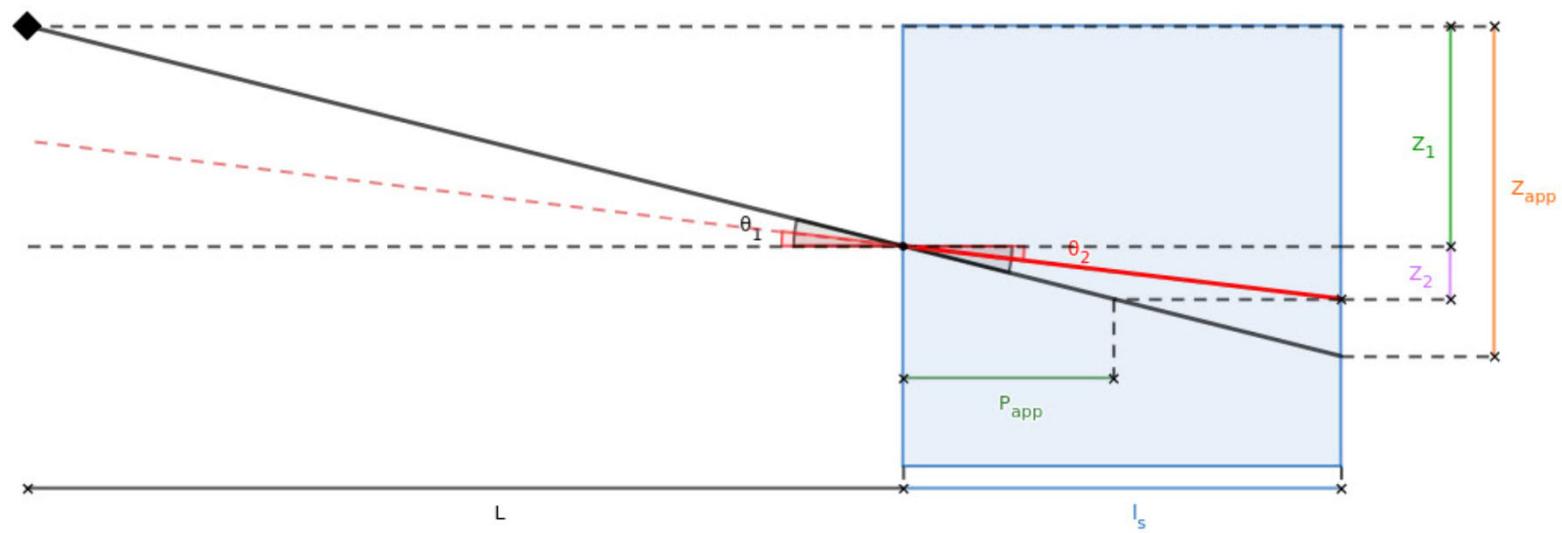
Optical effects



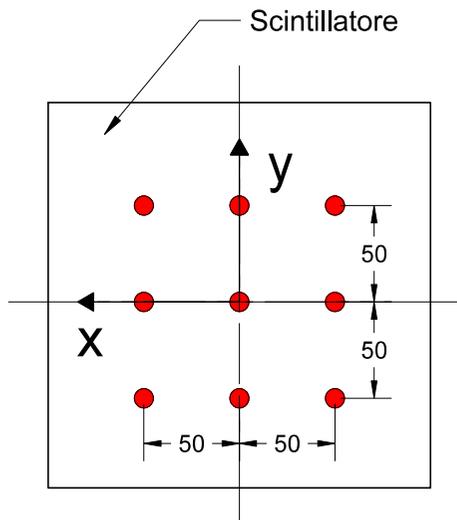
Perspective
Refraction
Reflection



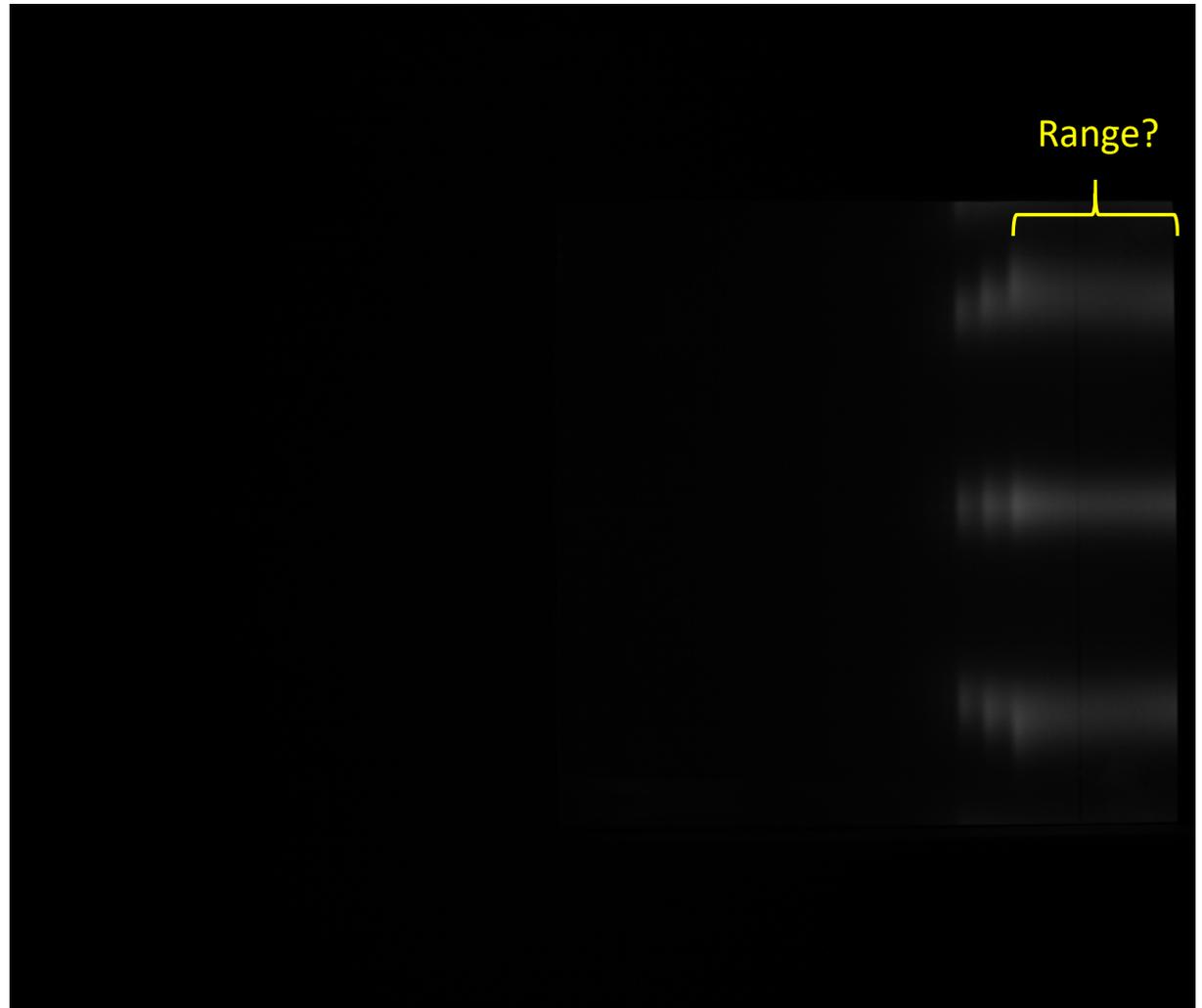
Camera



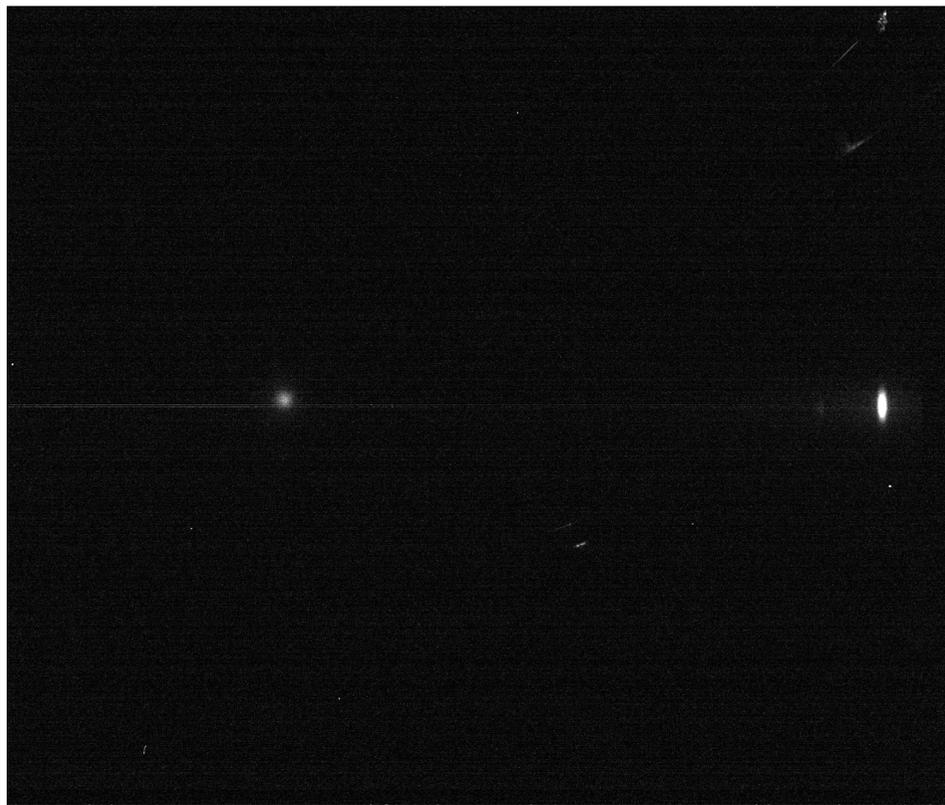
Optical effects



Perspective
Refraction
Reflection



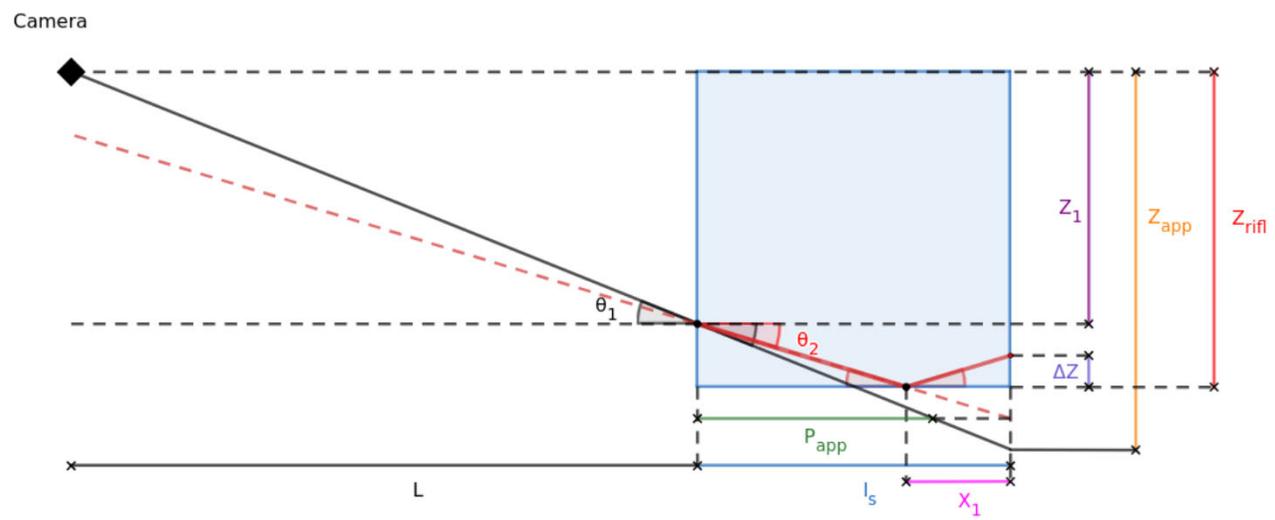
Reflection on scintillator face



C 54 mm with 50 mm RW3



C 60 mm with 50 mm RW3



1. Perspective correction (depends on x)

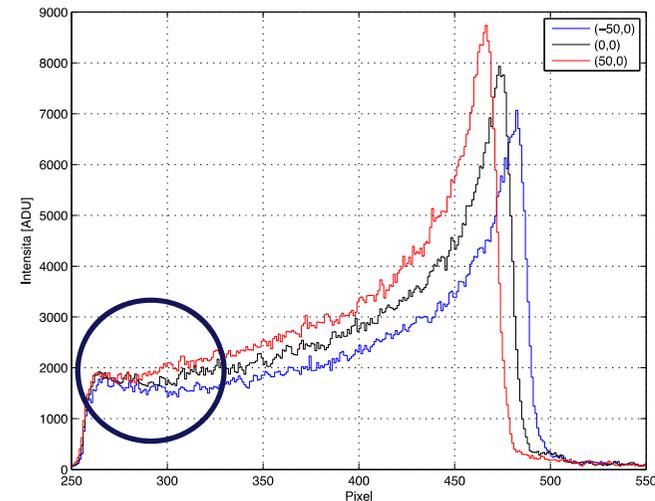
$$K(x) = \frac{K_{x=100} - K_{x=-100}}{L_s} \left(x - \frac{L_s}{2} \right) + K_{x=100}$$

- $K_{x=100}=0.236$ mm/pixel
- $K_{x=-100}=0.296$ mm/pixel
- $L_s=20$ cm (scintillator length)

2. refraction

$$x_{apparente} = \frac{L_s}{2} - \left(\frac{L_s}{2} - x_{reale} \right) \frac{n_{aria}}{n_{scintillatore}}$$

3. Light reflected on the inner face

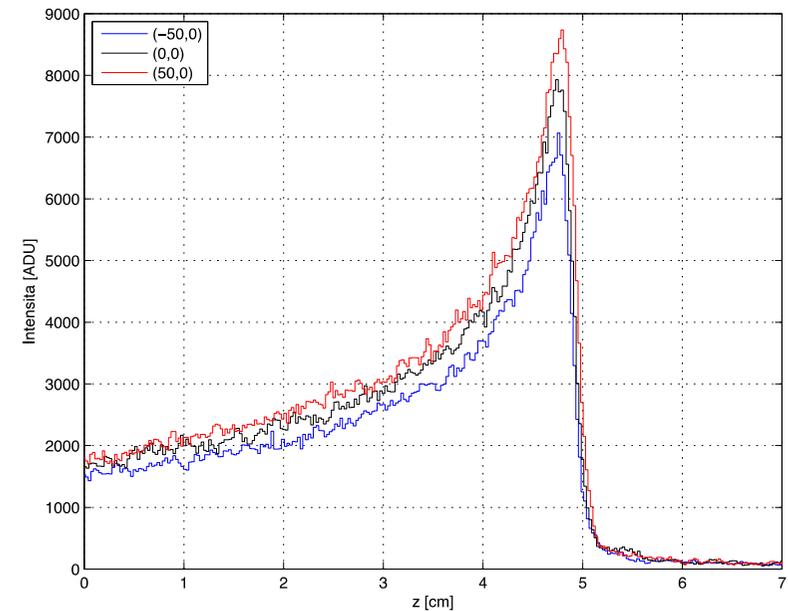


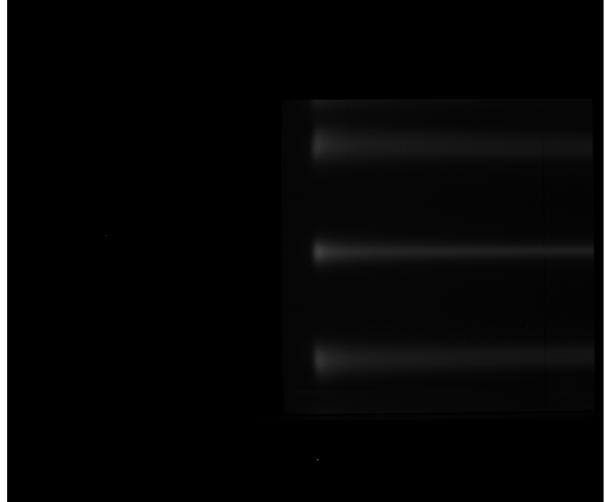
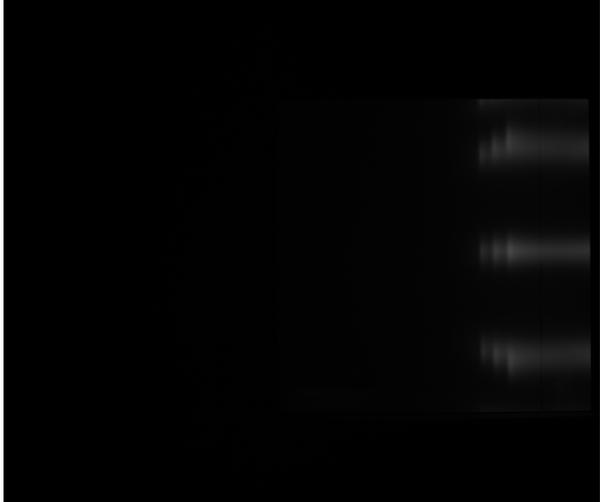
After correction

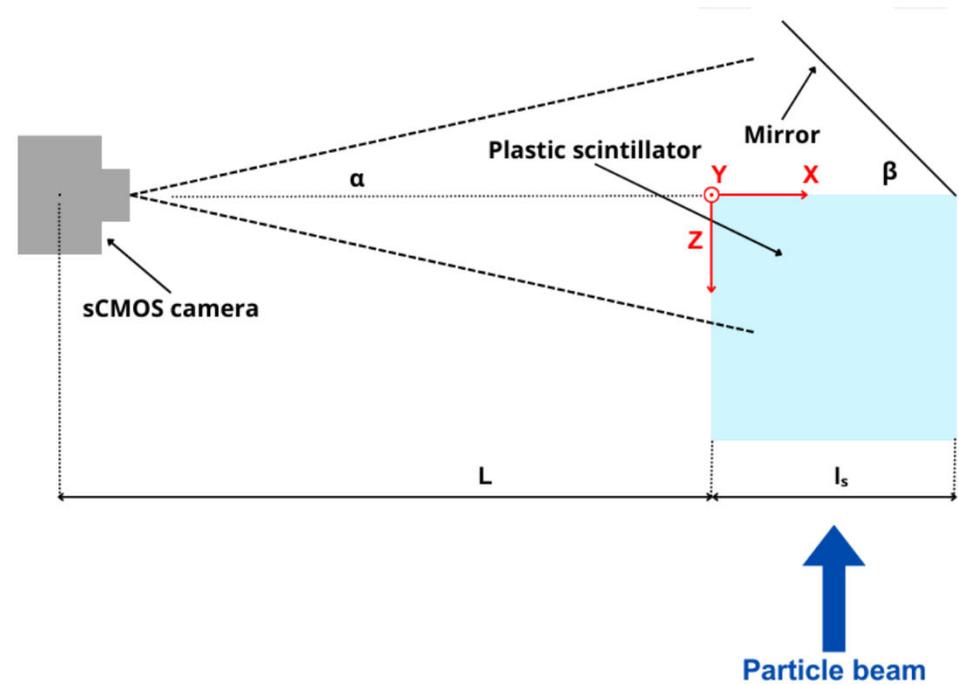
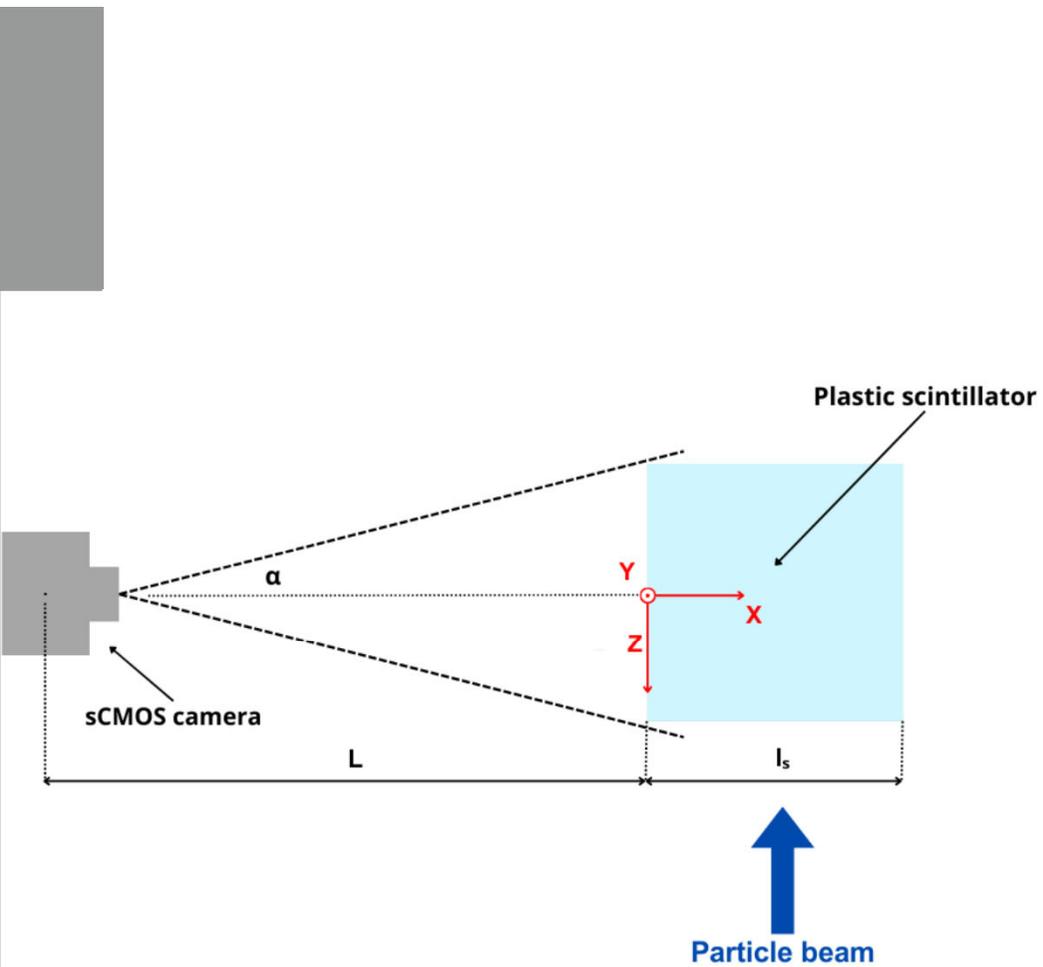
x [mm]	y [mm]	Range prima della correzione [mm]	Range dopo la correzione [mm]
-50	50	54.542	49.417
-50	0	54.542	49.417
-50	-50	54.306	49.151
0	50	52.889	49.333
0	0	52.889	49.333
0	-50	52.889	49.333
50	50	51.236	49.389
50	0	51.000	49.143
50	-50	51.000	49.143

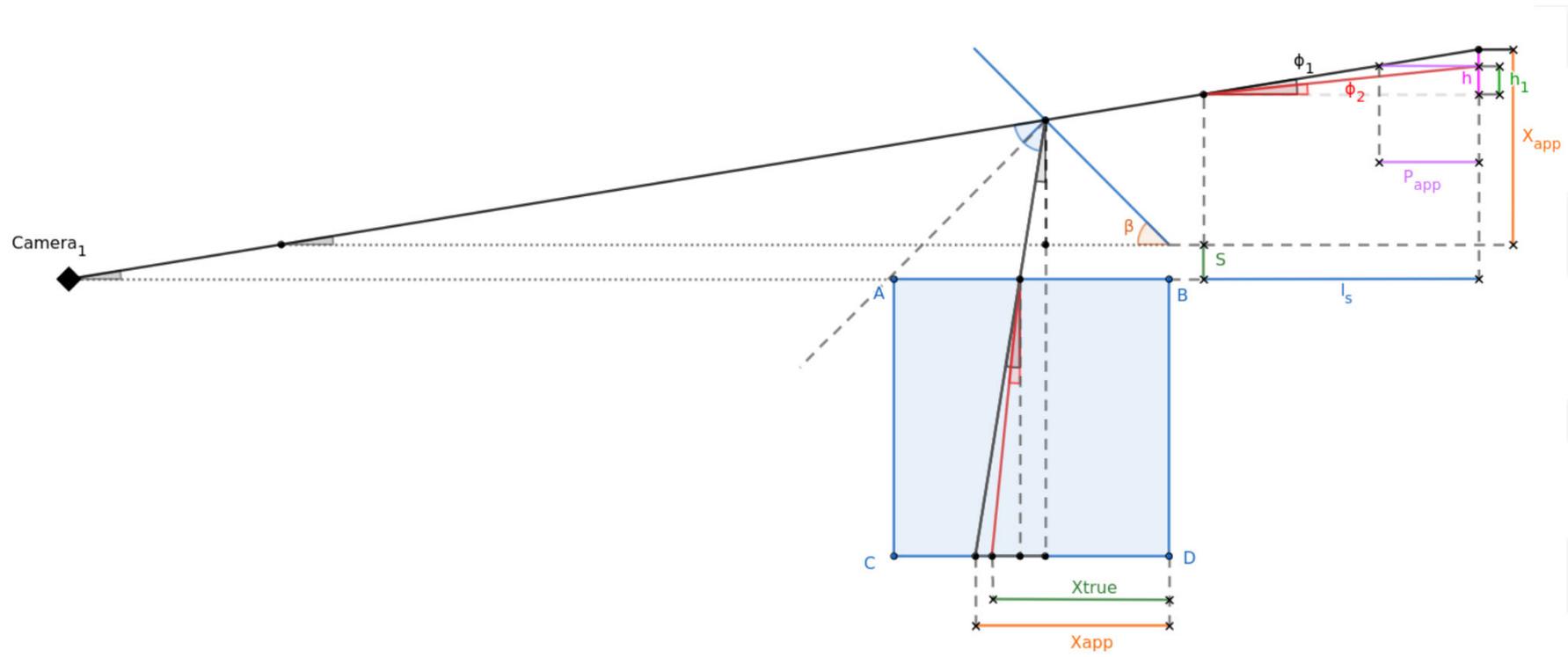
Range misurati:

- 9 punti, protoni da 81 MeV i range sono nell'intervallo (2σ): **49.295 ± 0.234 mm**
- 9 punti, protoni da 118.2 MeV i range sono nell'intervallo (2σ): **99.469 ± 0.304 mm**

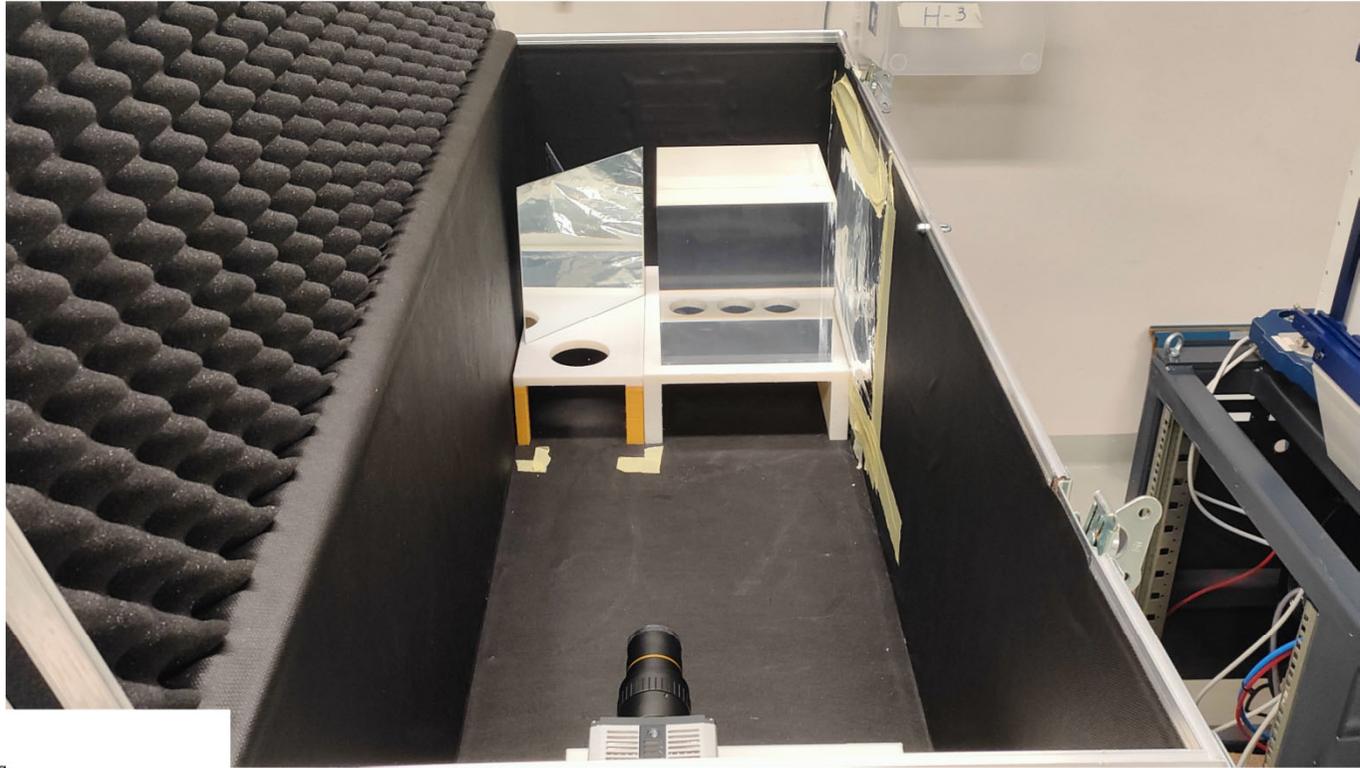






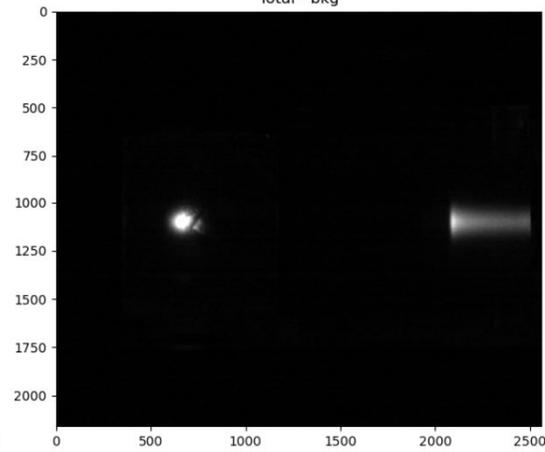
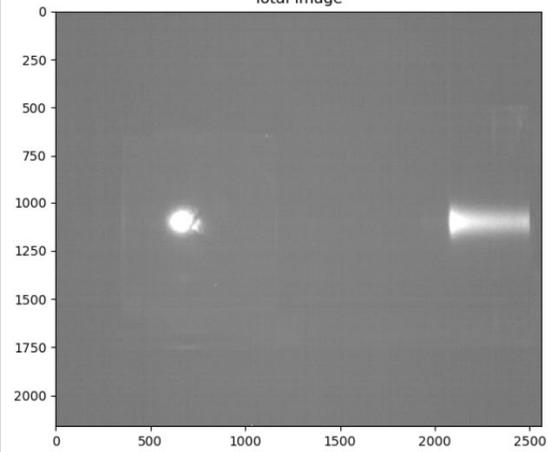


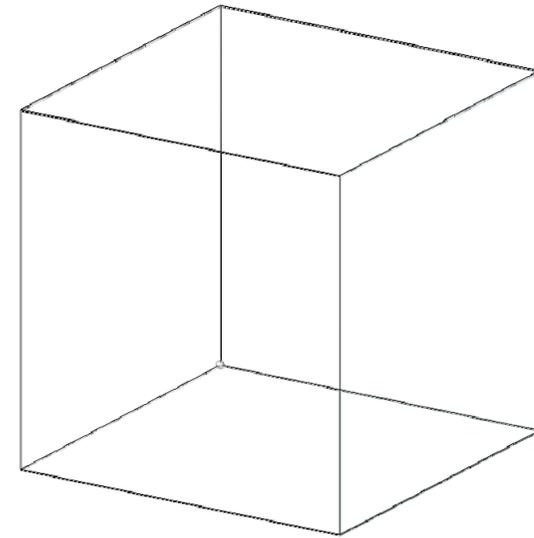
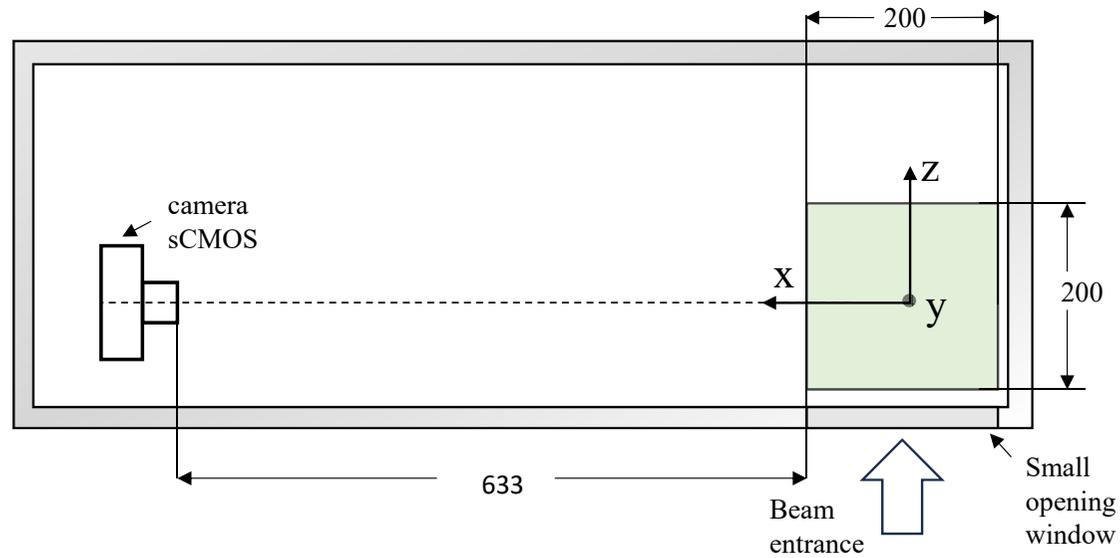
Present setup



Total image

Total - bkg





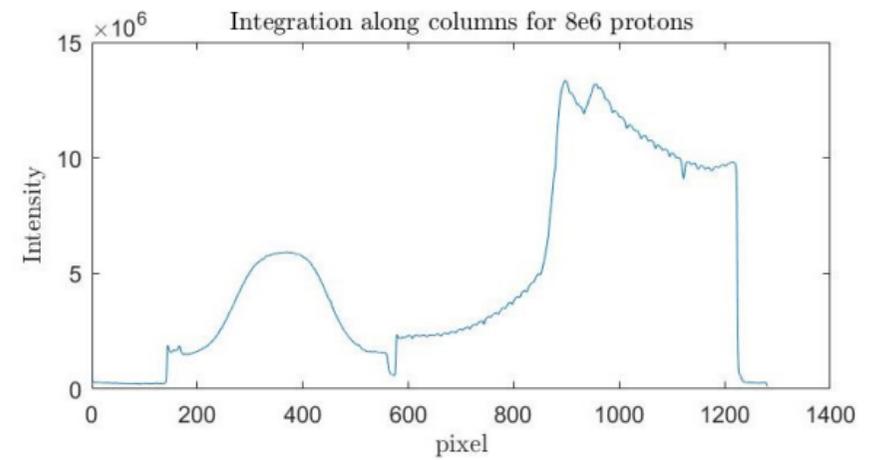
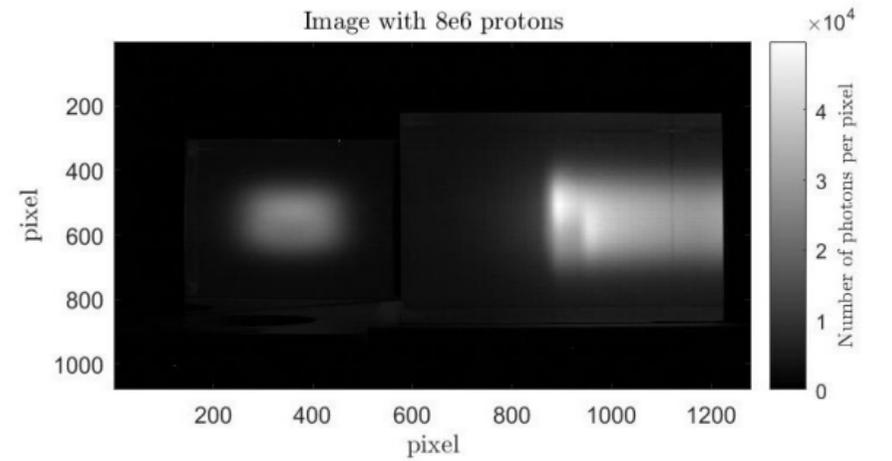
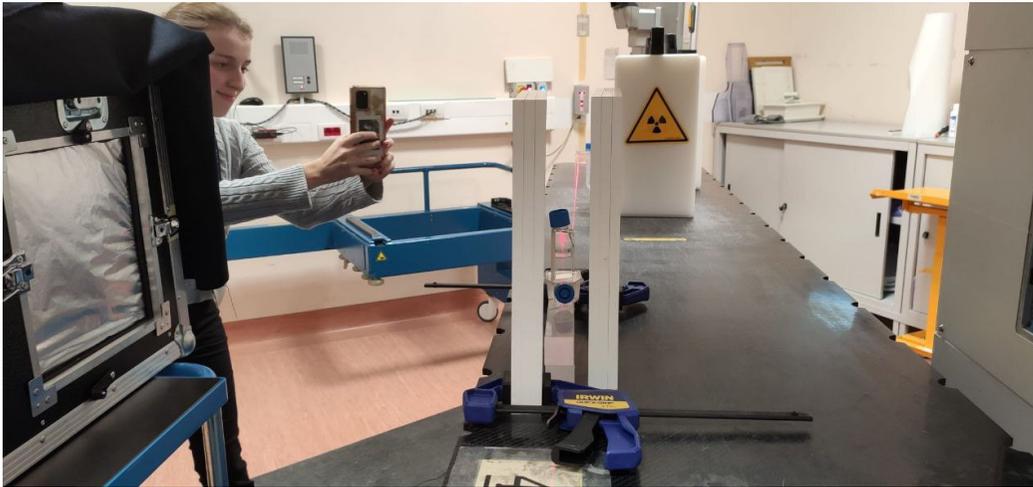
Camera sCMOS

Producer and Model	Andor Zyla 5.5 sCMOS
Sensor dimensions	2560×2160 pixel, 16.6 mm × 14 mm
Pixel size (W×H)	6.5 μm × 6.5 μm
Full well capacity	30000 e ⁻
Dark current	0.1 e ⁻ /pixel/s at 0 °C
A/D converter	Dual amplifier stage: 16-bit and 12-bit
Electrons per digital unit	0.45 e ⁻ /ADU
Read-out noise	2.5 e ⁻ RMS
Cooling	Thermoelectrical
Producer and Model of the lens	Azure photonics 2520MX5M

Scintillator

Producer and Model	Saint Gobain Crystals BC-408 Plastic Scintillator
Dimensions [cm]	20×20×20
Light yield [% Anthracene]	64
Emission wavelength [nm]	425
Main component decay constant [ns]	2.1
Attenuation length [cm]	380
Refraction index	1.58
Density [g/cm ³]	1.032
H:C ratio	1.104

Not always a single spot



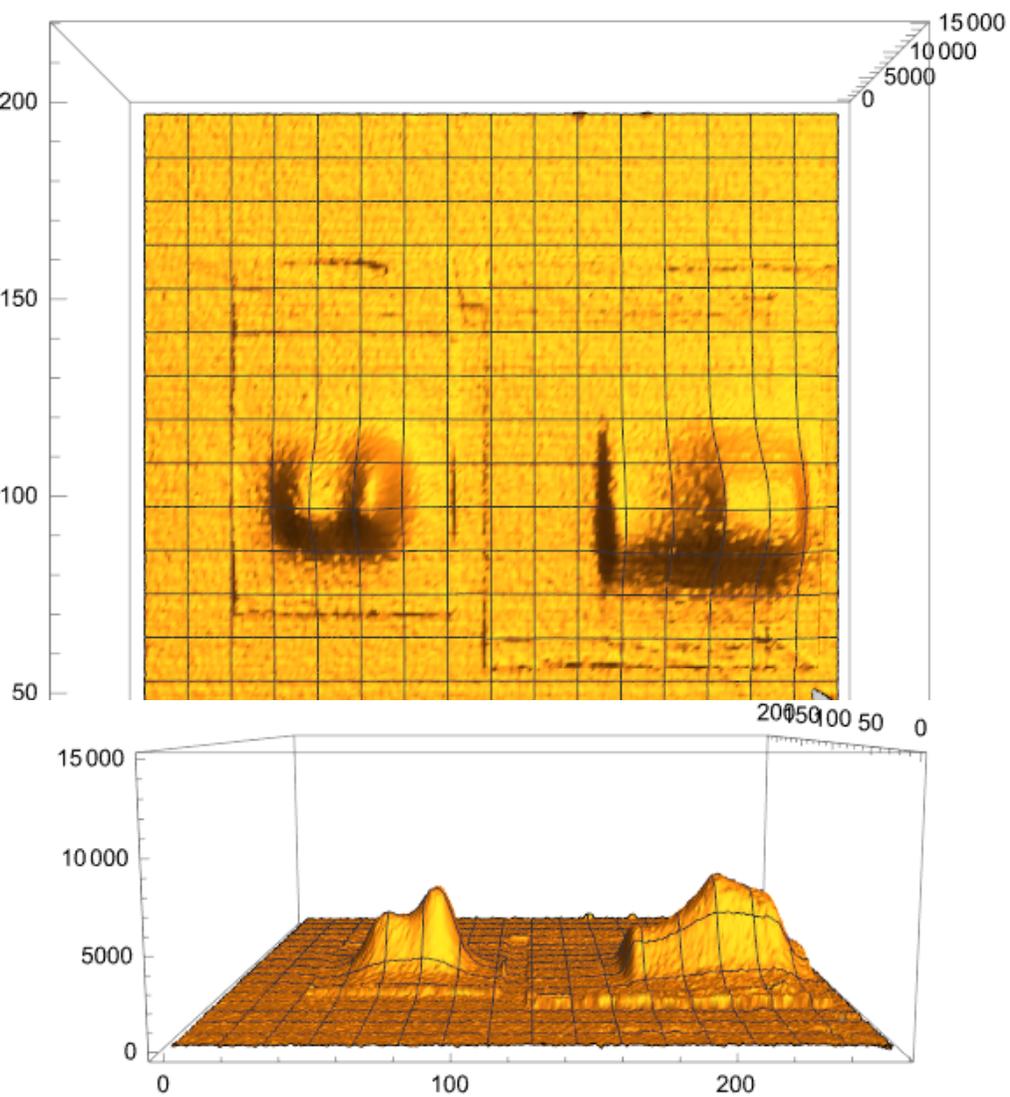
May 2025 – GSI beamtime



May 2025 – GSI



He #9, 5E6 C/spot



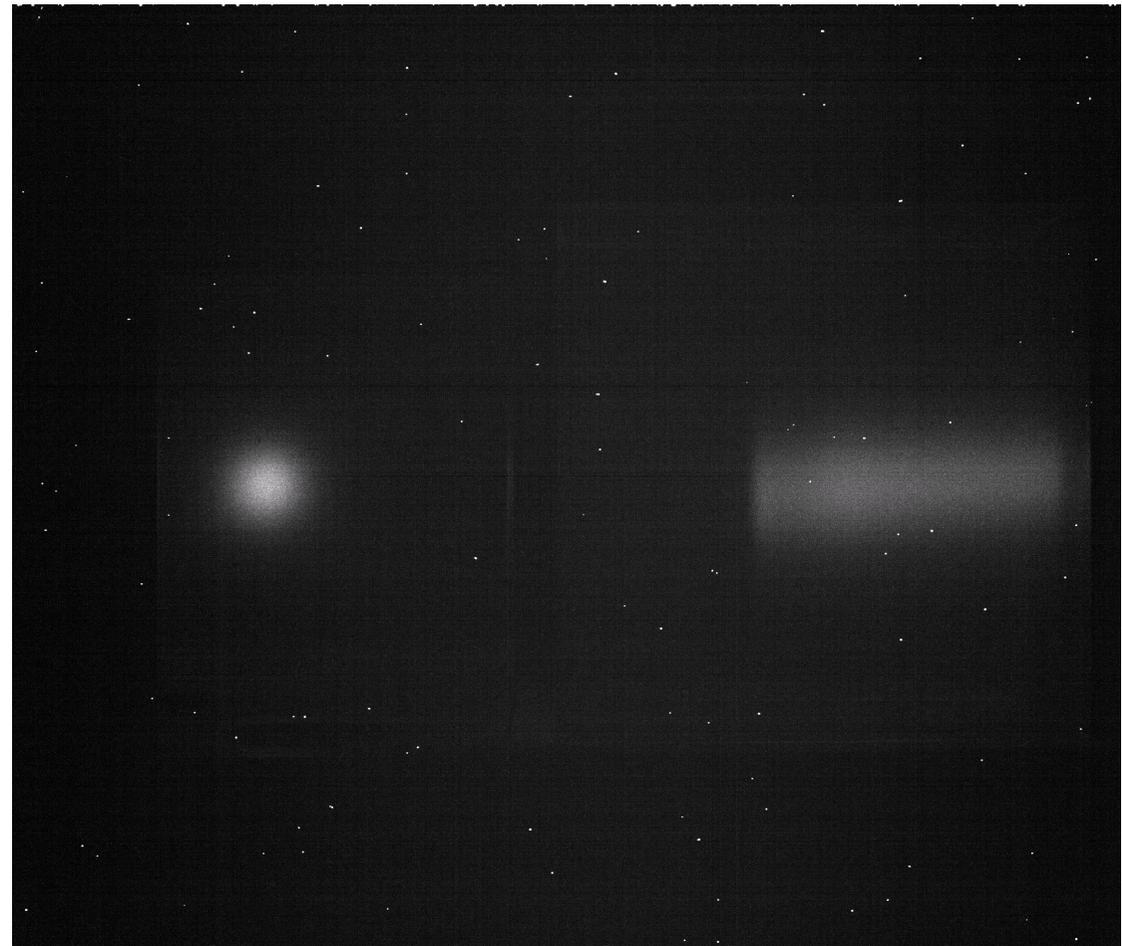
260 MeV/u

Scan 70x45 mm (spot interval 2mm)

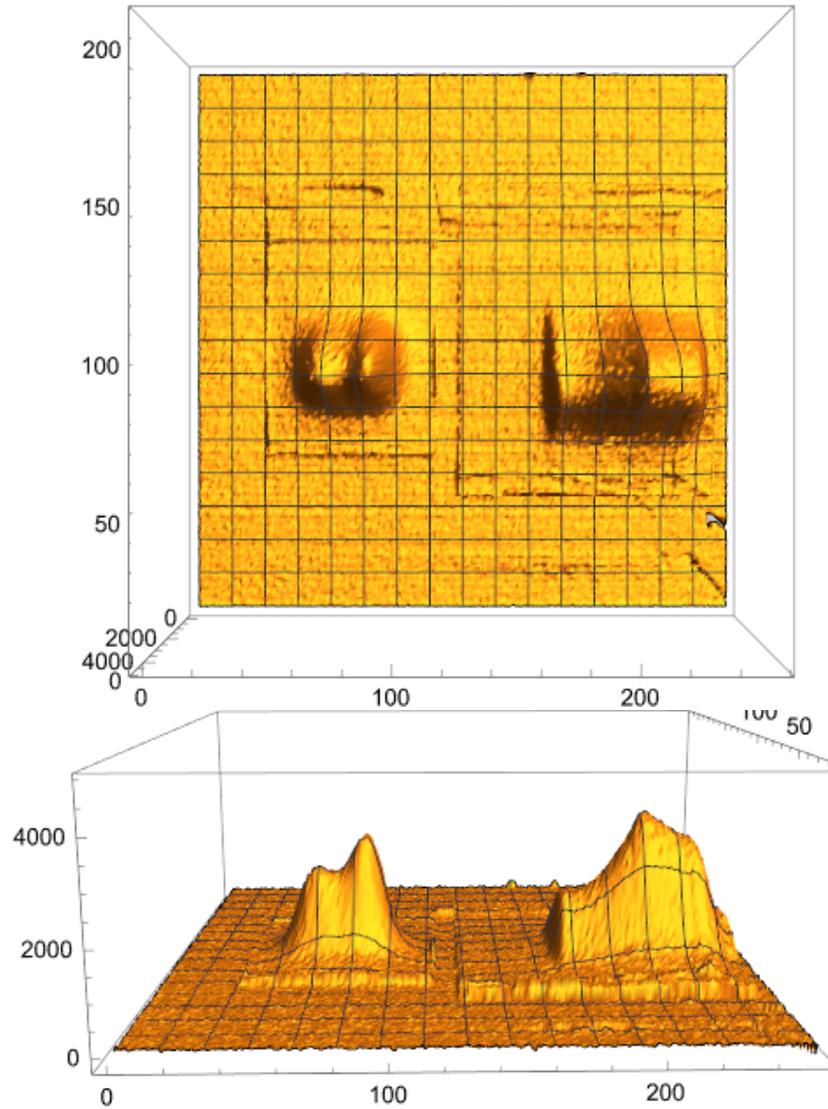
Ratio C/He 1:1

5 10^6 C x spot (thus about $4.5 \cdot 10^6$ C + $4.5 \cdot 10^6$ He)

Sphere + London detector: Carbon is stopped, only He



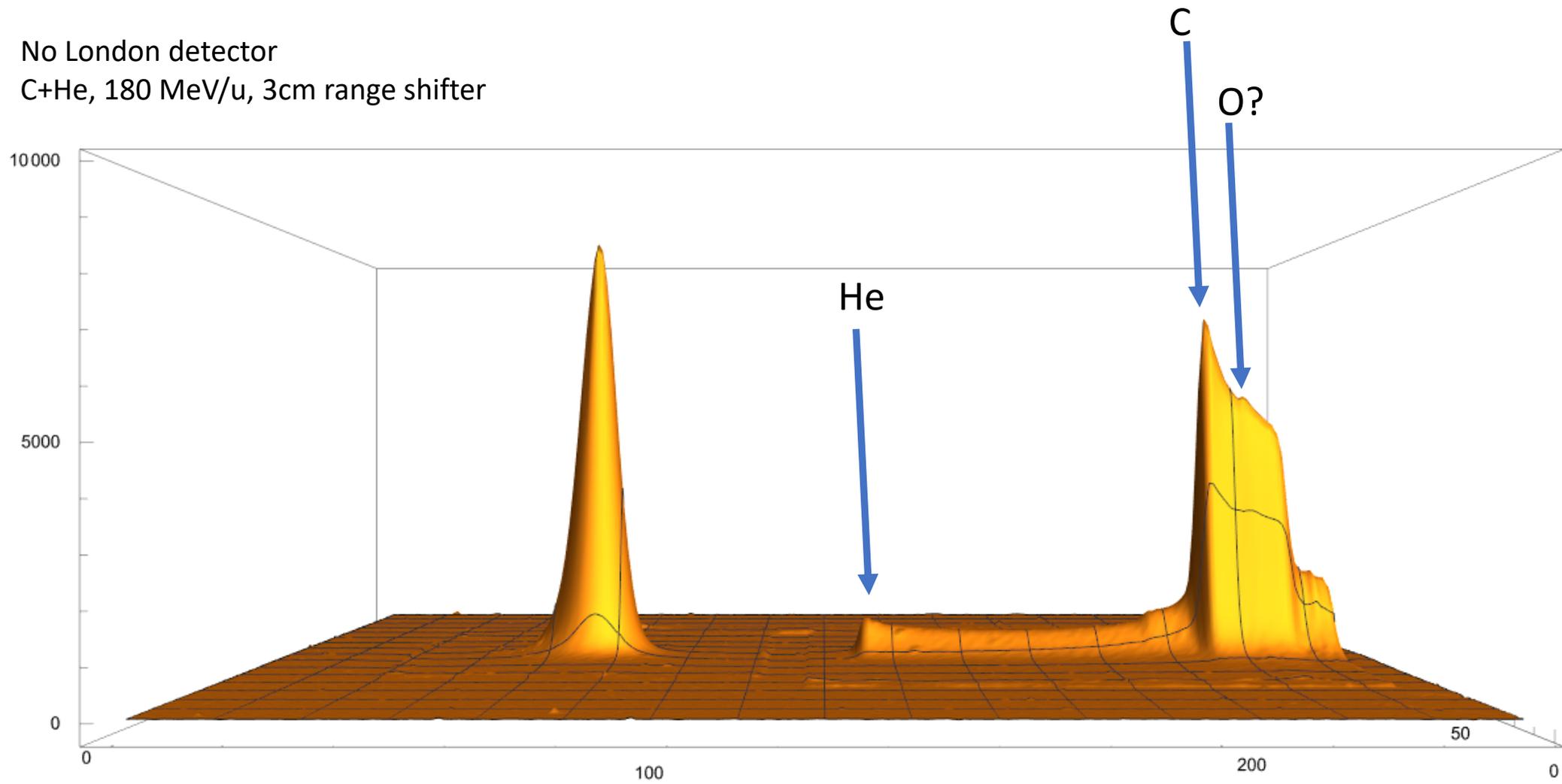
He#10, 2E6 C/spot



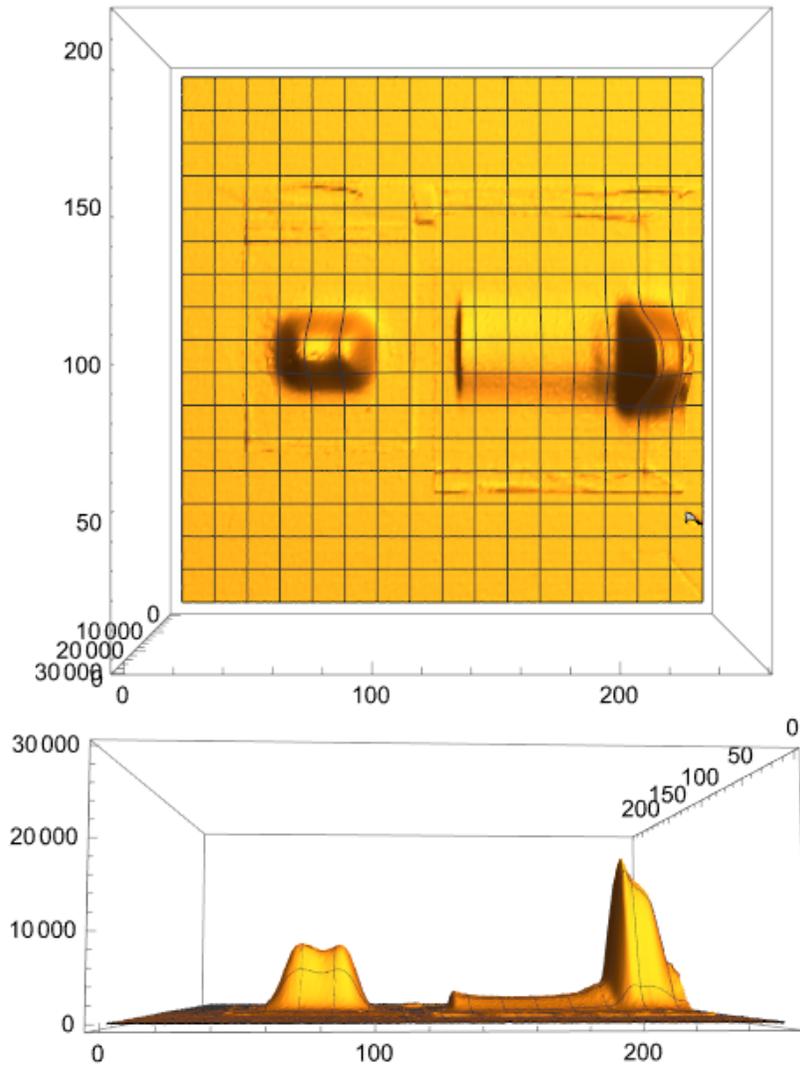
C+He#17 + 3cm range shifter

No London detector

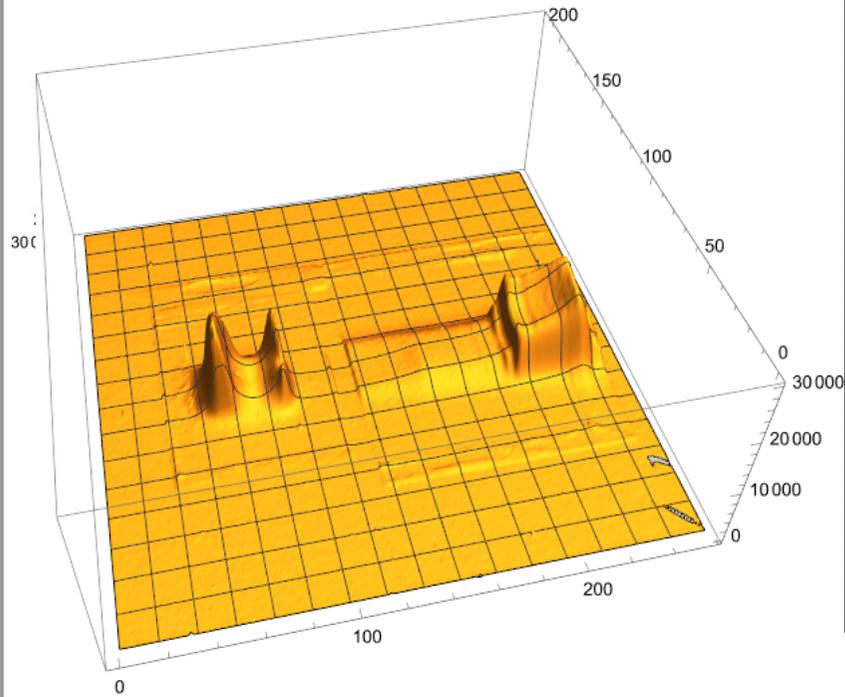
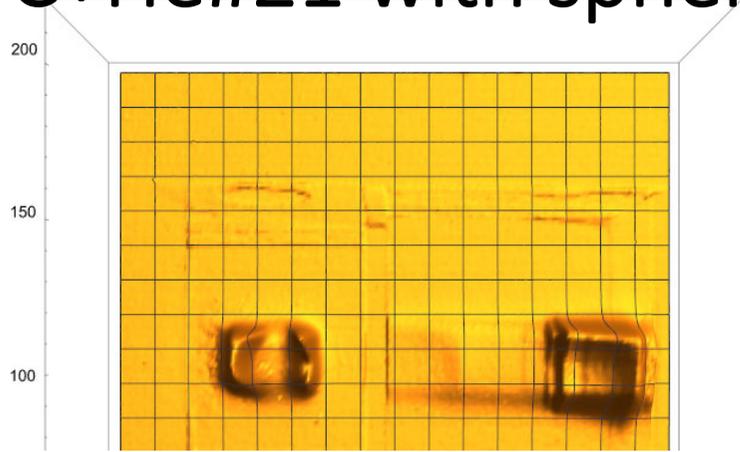
C+He, 180 MeV/u, 3cm range shifter



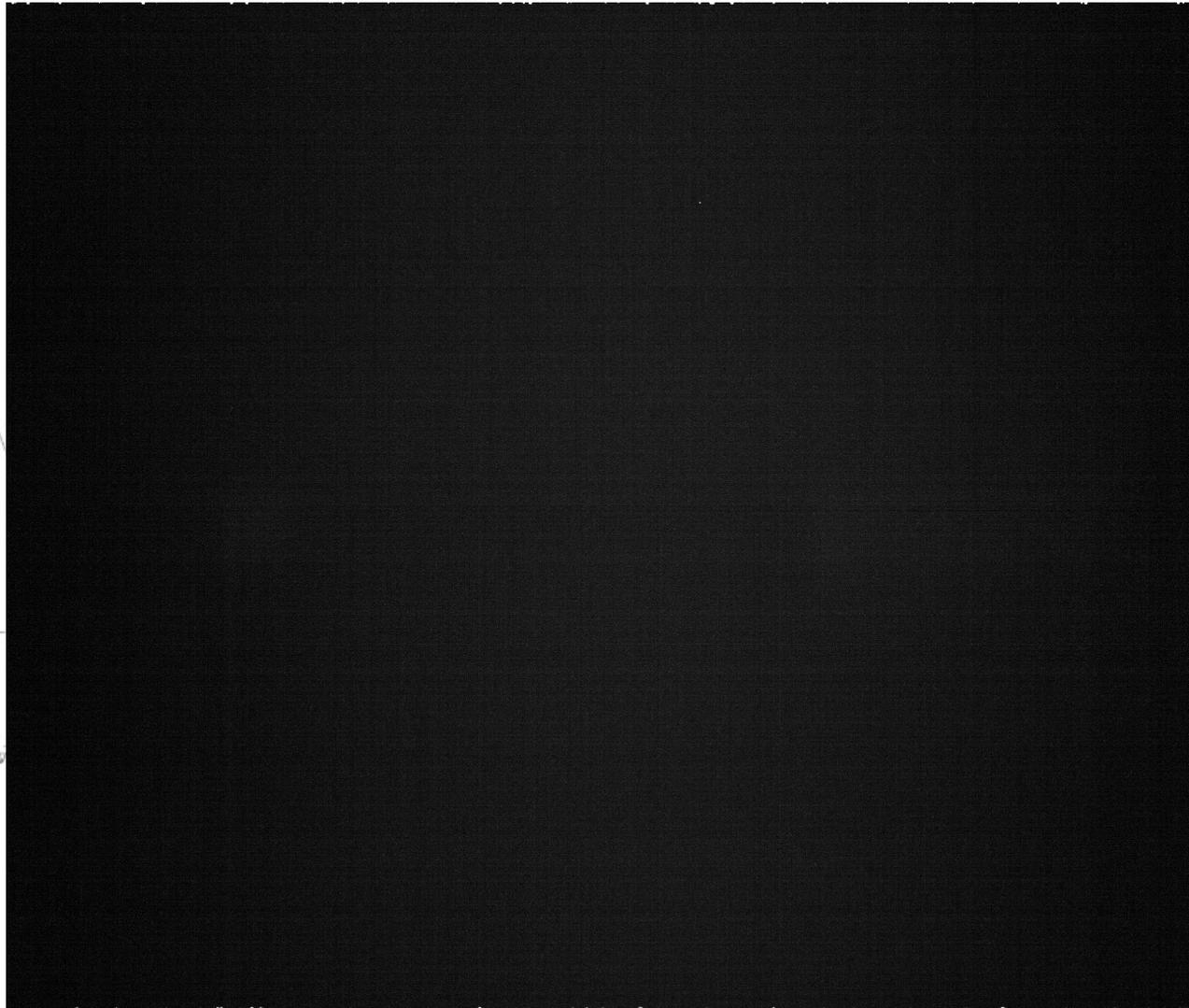
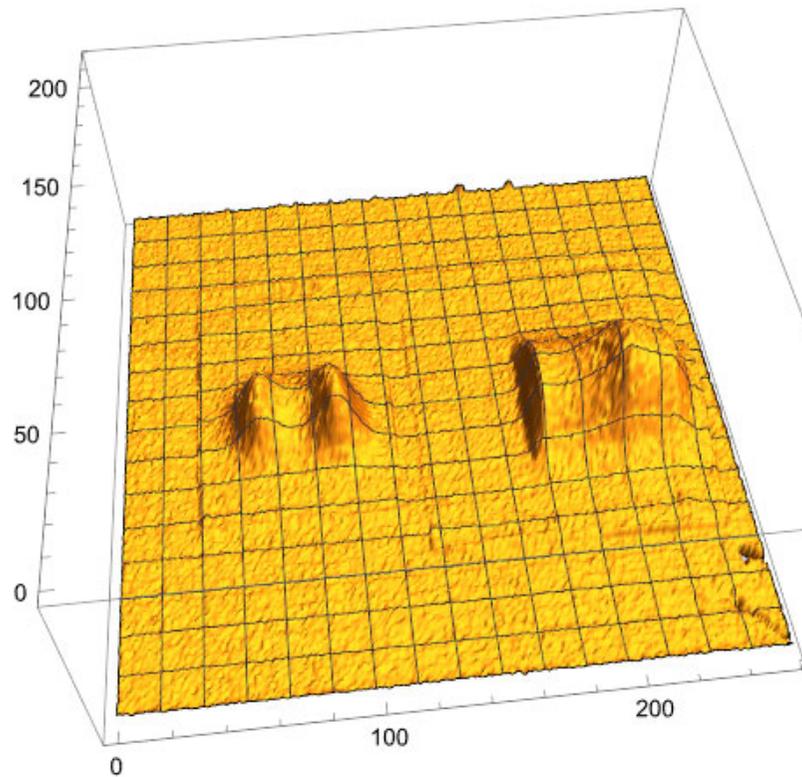
C+He#19 + 3cm range shifter - scan



C+He#21 with sphere, no range shifter



He#22 with sphere, 10 cm range shifter (no C)



He#22 with sphere displaced, 10 cm range shifter (no C)

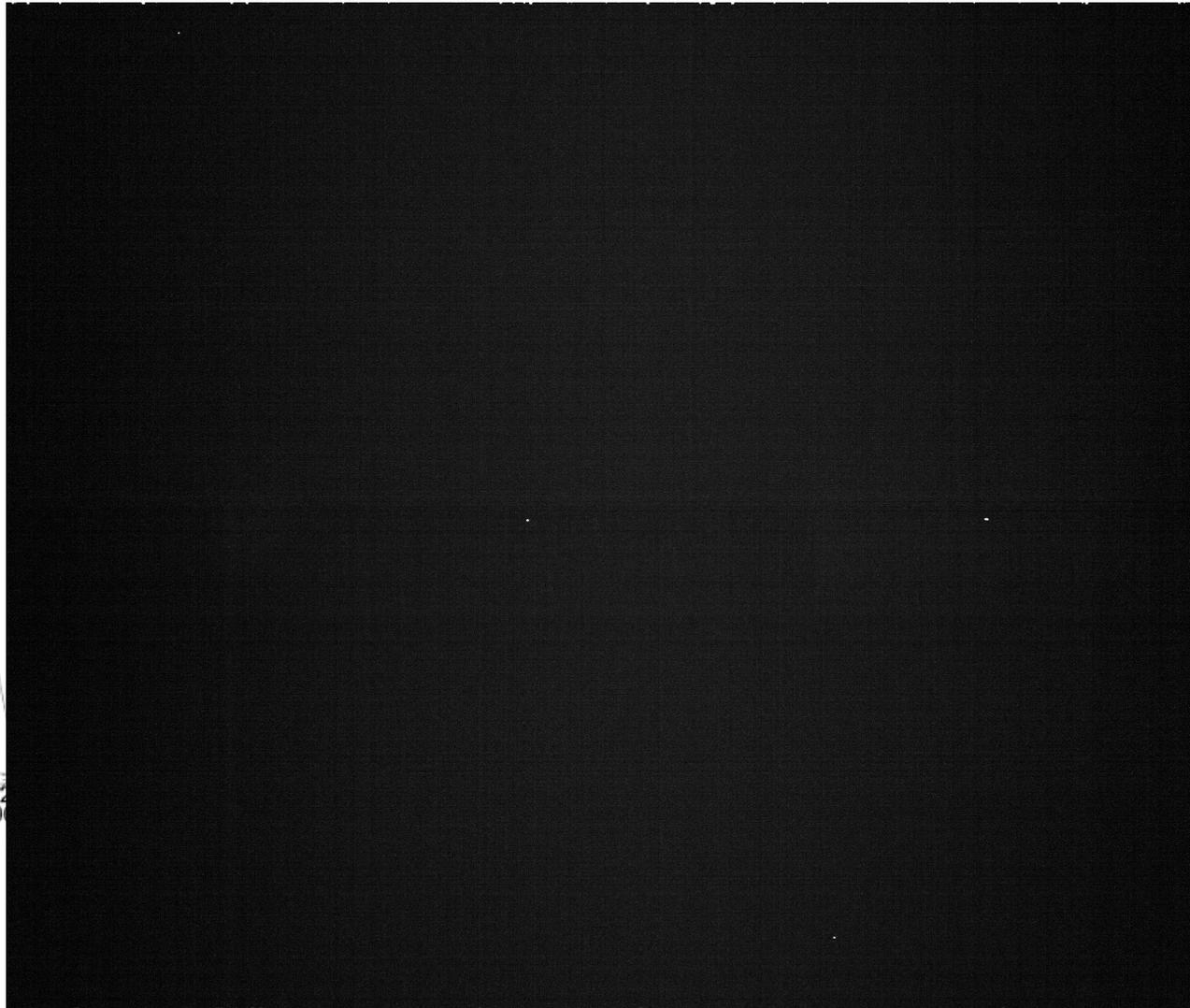
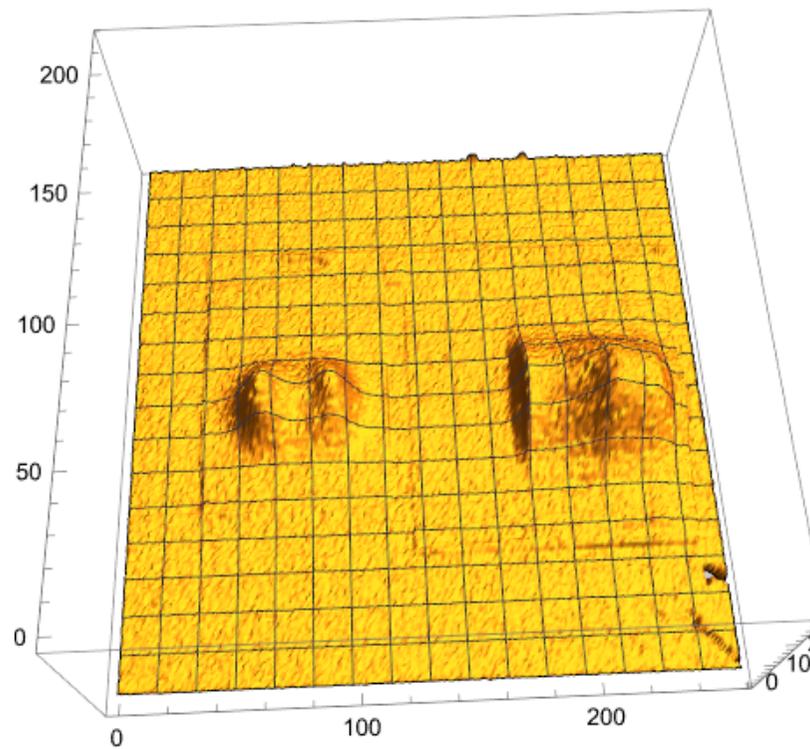
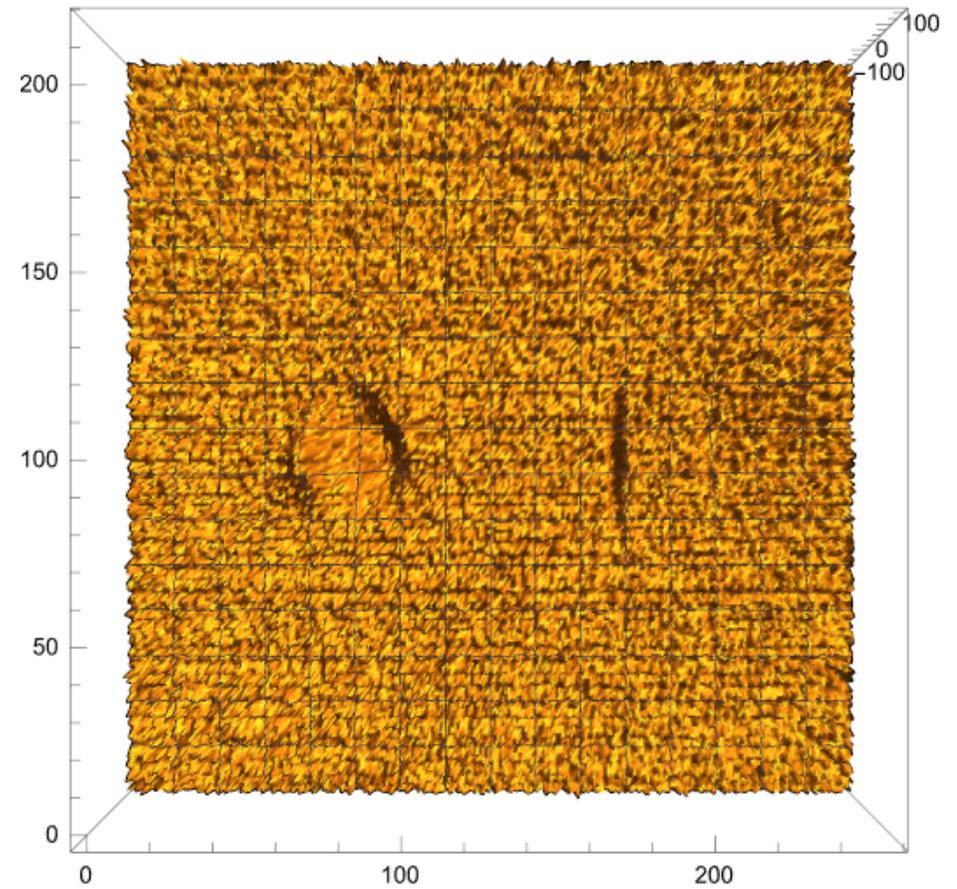
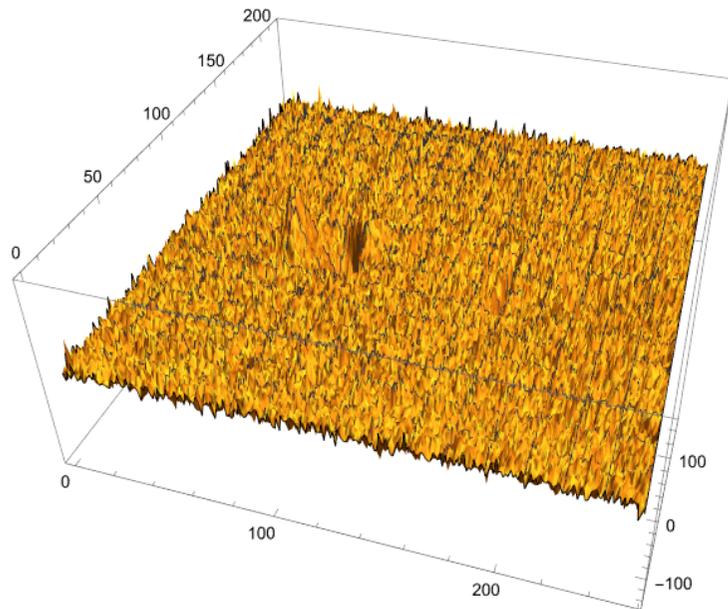
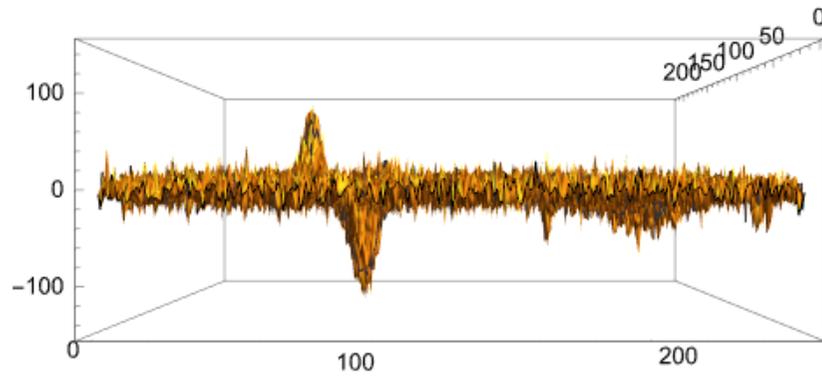
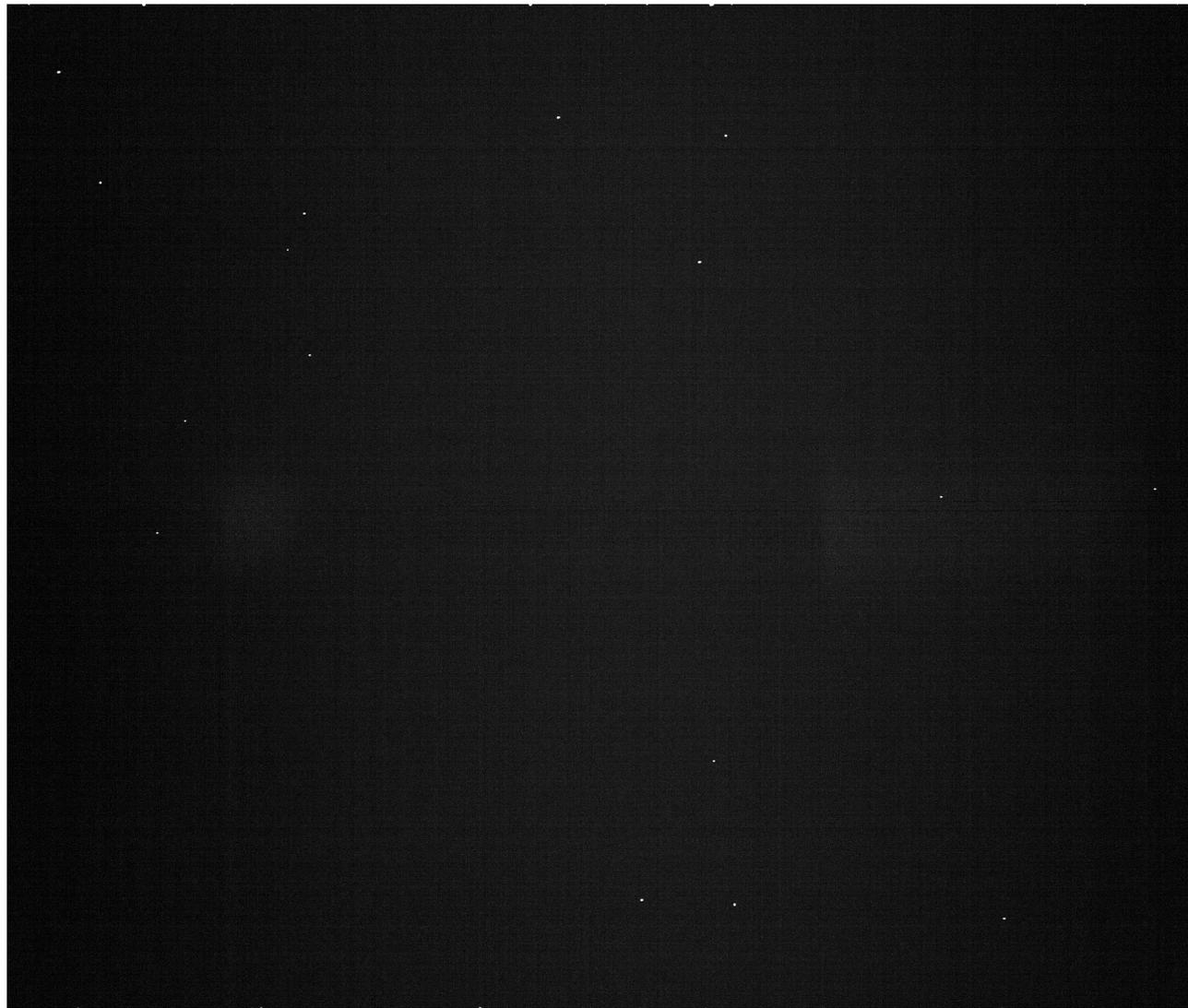
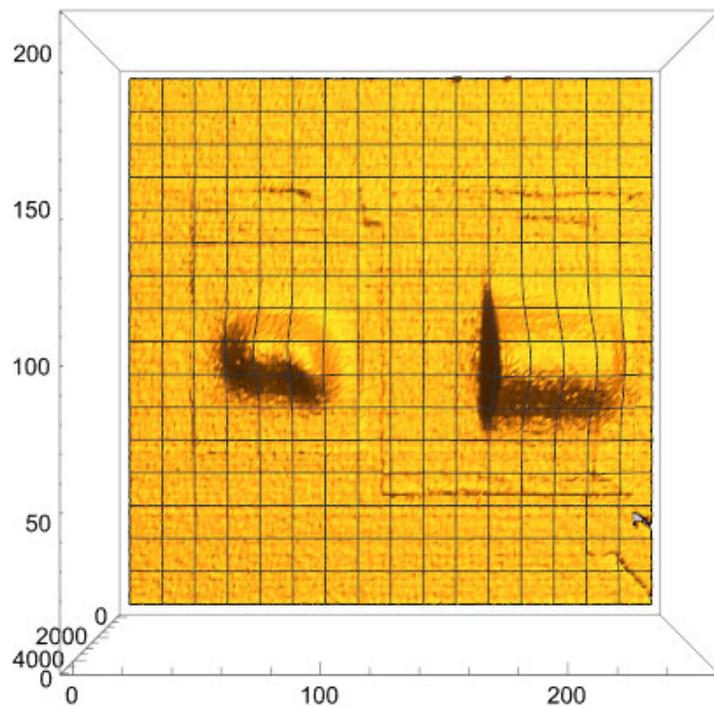


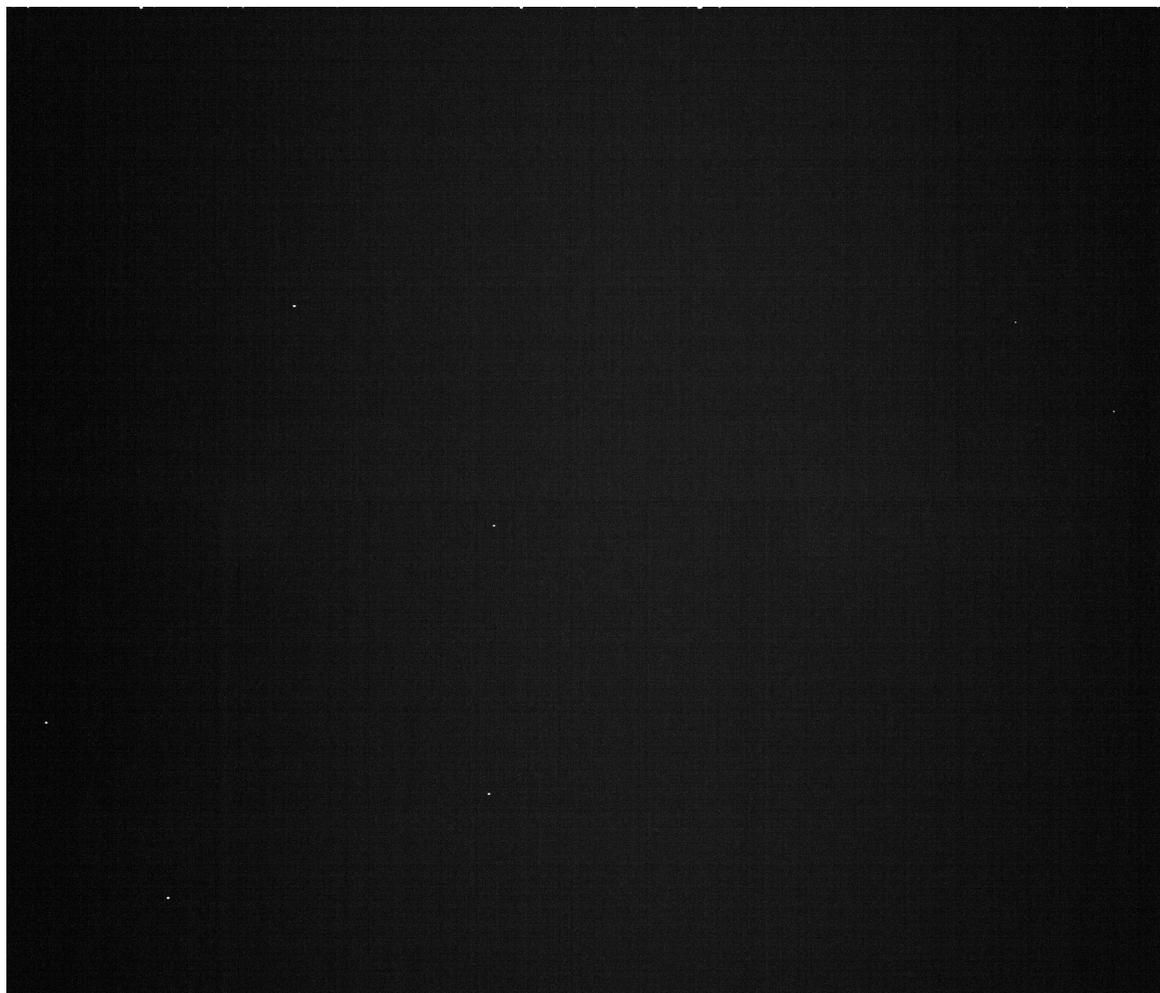
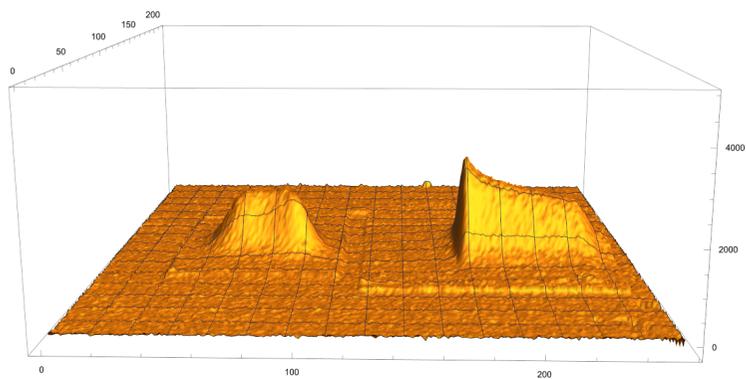
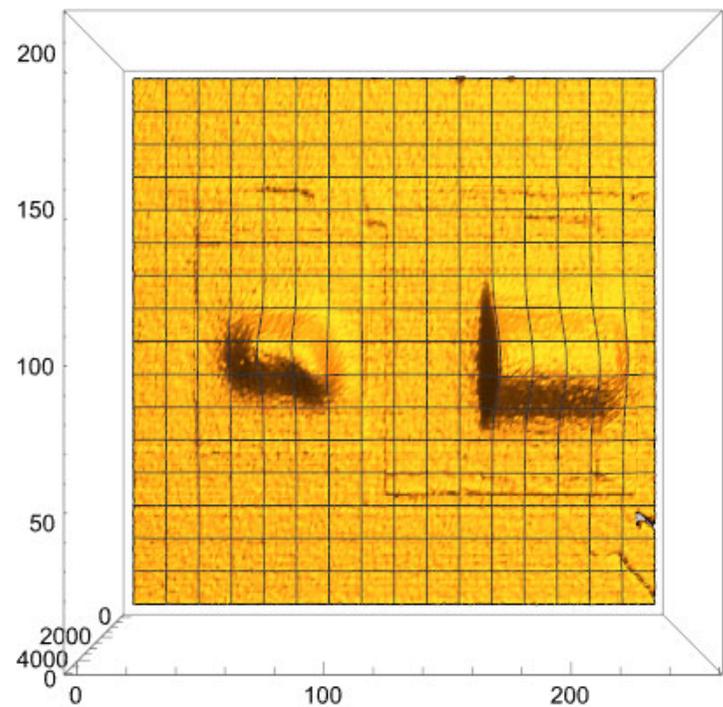
Image difference



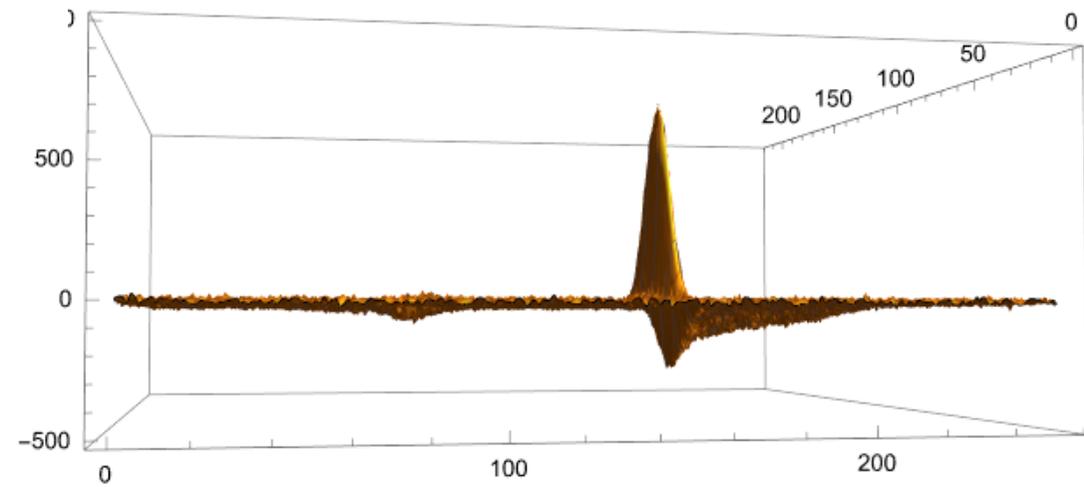
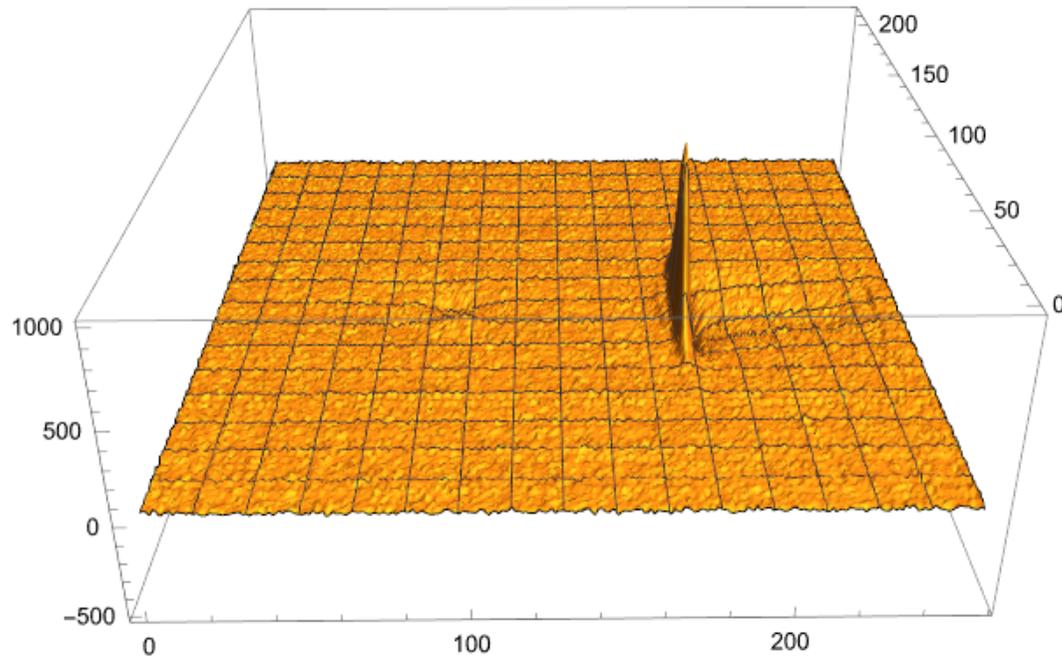
He#27, range shifter 10.4 cm



He#30, range shifter 10 cm



Difference Image



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Simone Savazzi

And certainly others that I forgot but
to whom I am grateful

“If you think research is expensive, try disease!”

Mary Lasker

