SAPIENZA UNIVERSITÀ DI ROMA

INFN

CENTRO RICERCHE ENRICO FERMI

16TH TOPICAL SEMINAR ON INNOVATIVE PARTICLE AND RADIATION DETECTORS (IPRD23)

Siena, 25 - 29 September 2023

Test beam results of a fluorescence-based monitor for ultra-high dose rates

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FLASH Radiotherapy with hIgh Dose-rate particle beAms

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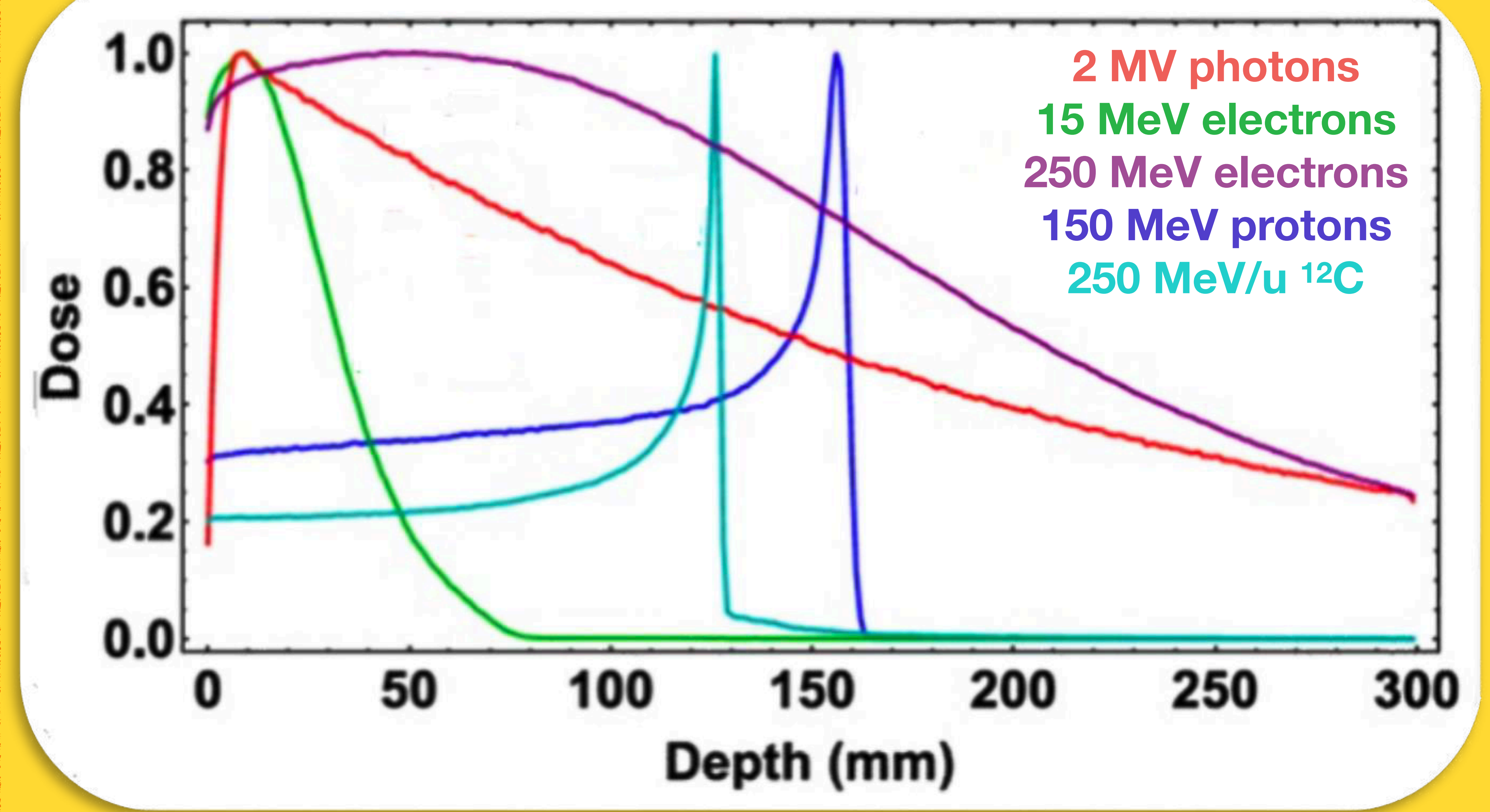
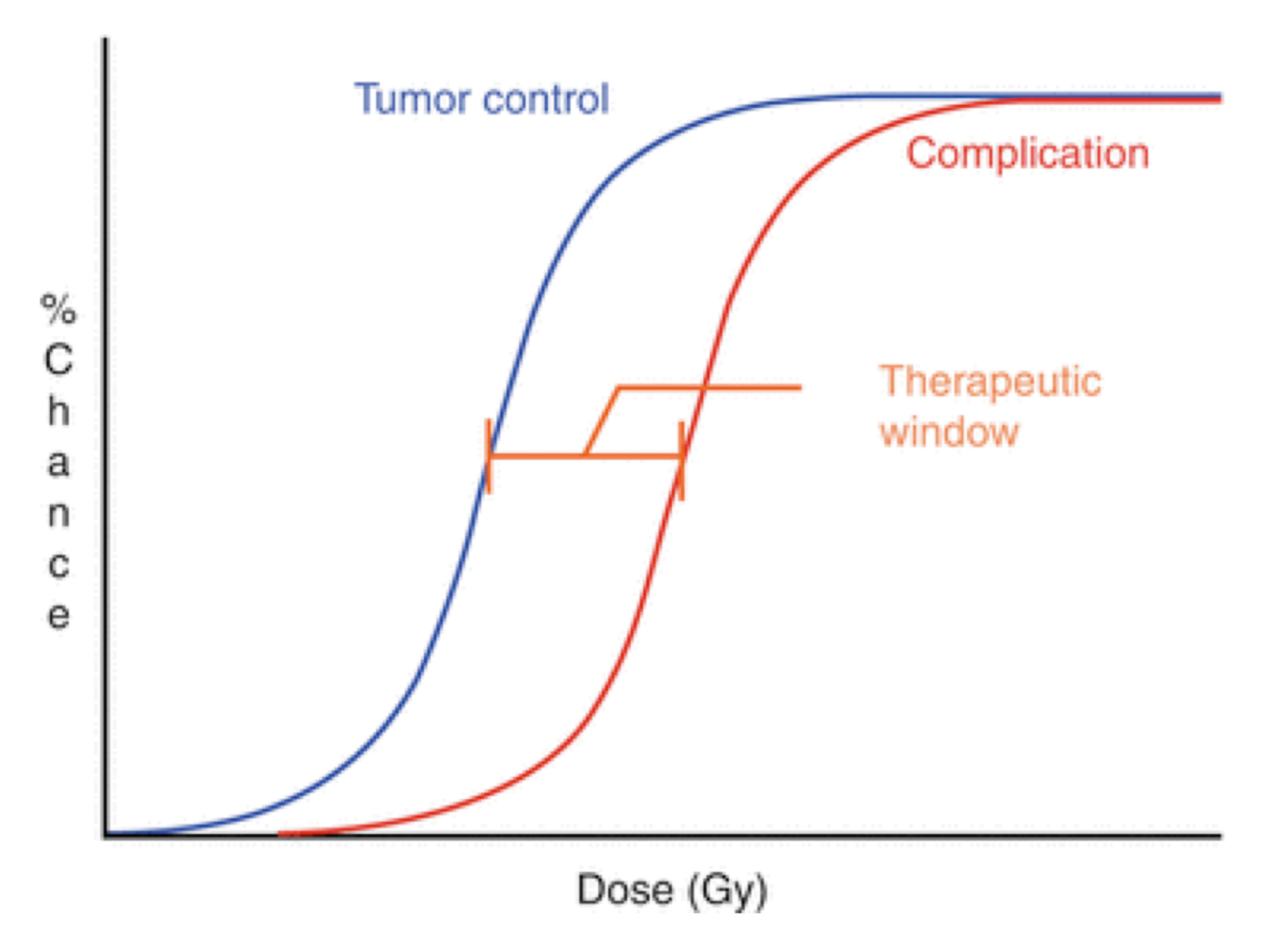
Radiotherapy

Goal: destroy tumors while saving the healthy tissue

- **Therapeutical beam** (electrons, photons, light ions) release energy inside the human tissues — **dose** — following an optimized **treatment plan**.





$$D = \frac{dE}{dm} \text{ [Gy]}$$

Dose: the amount of radiation we need to deliver during treatment (also as function of time).

$$LET = \frac{dE_L}{dx} \text{ [MeV/cm]}$$

Linear Energy Transfer: energy as a function of distance travelled inside the tissue… we can play with this.

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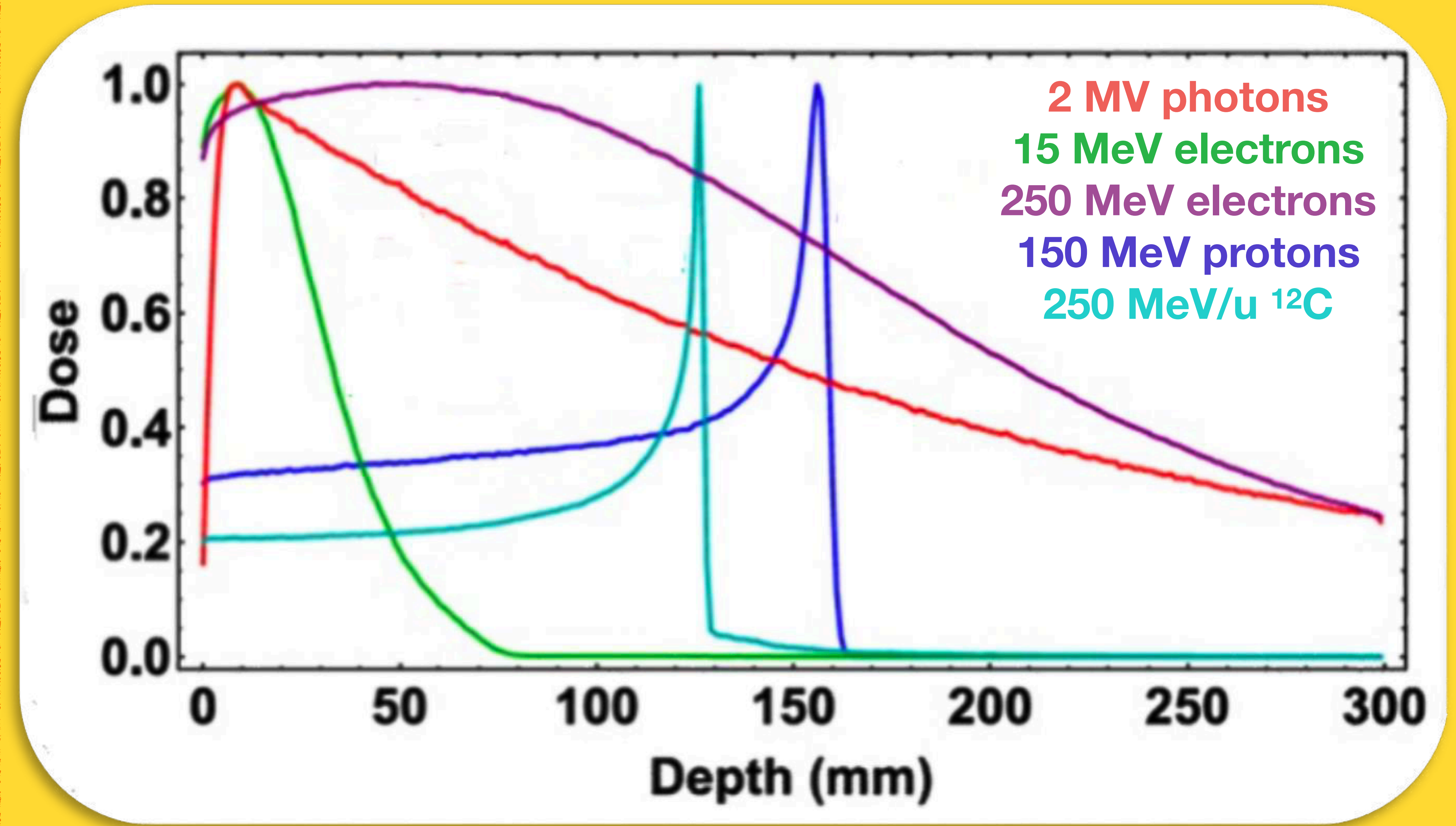

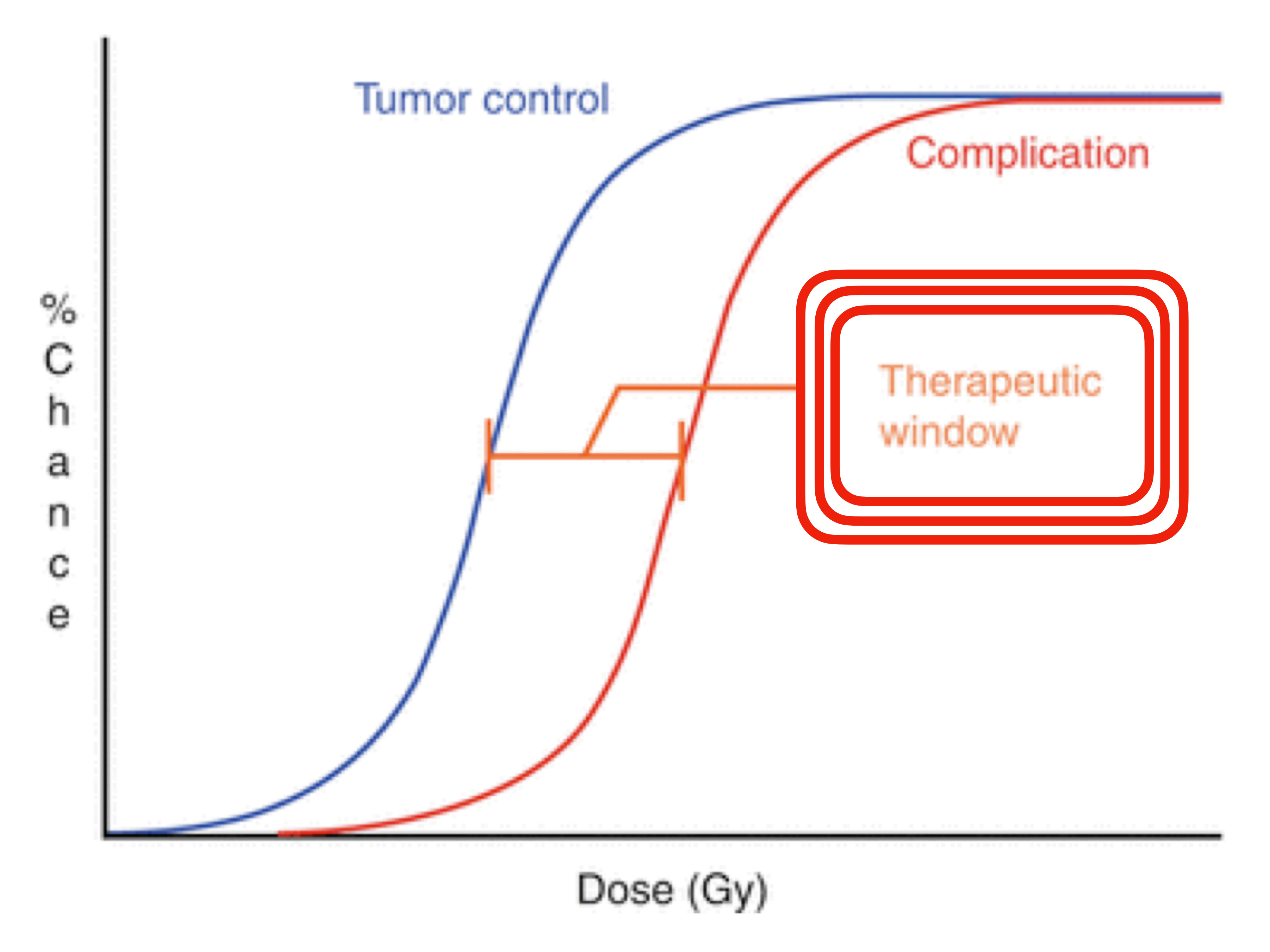

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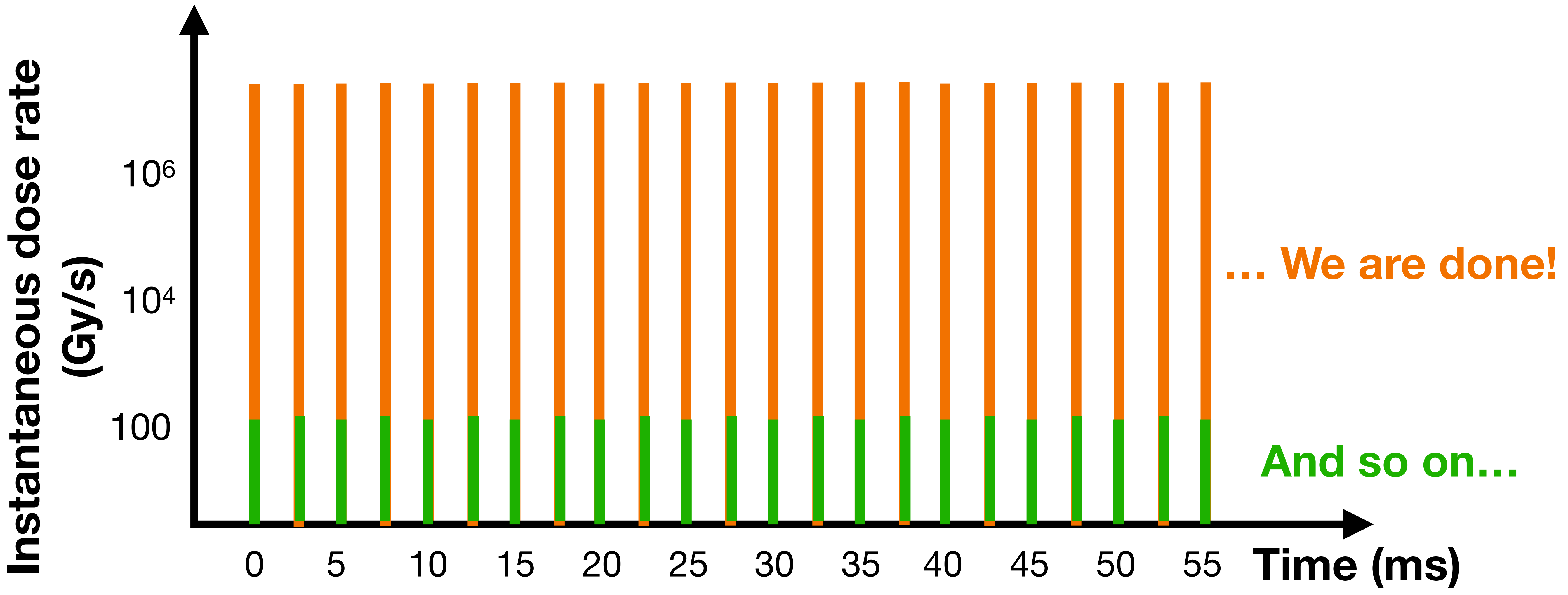
FLASH effect

- The usual way a radiotherapy treatment is delivered is through a **pulsed** structure. The total dose is delivered in tens of **fractions** (~2 Gy, ~minutes or hours), each made of a sequence of pulses (~1 μs) carrying a small amount of dose.
- Recently, a new approach has gained great attention, to the point of being considered the next paradigm in the future of RT.
- An increased radio-resistance — **reduced toxicity** — is observed **in normal tissues** when delivering a single irradiation at ***ULTRAHIGH*** dose rates in a very short time (keeping anti-tumor efficacy).
- This has been named **FLASH** effect. Its biological mechanisms are not yet understood, and there is a lot of investigation going on.
- New accelerators are entering commissioning and operation, new theories are emerging awaiting validation…

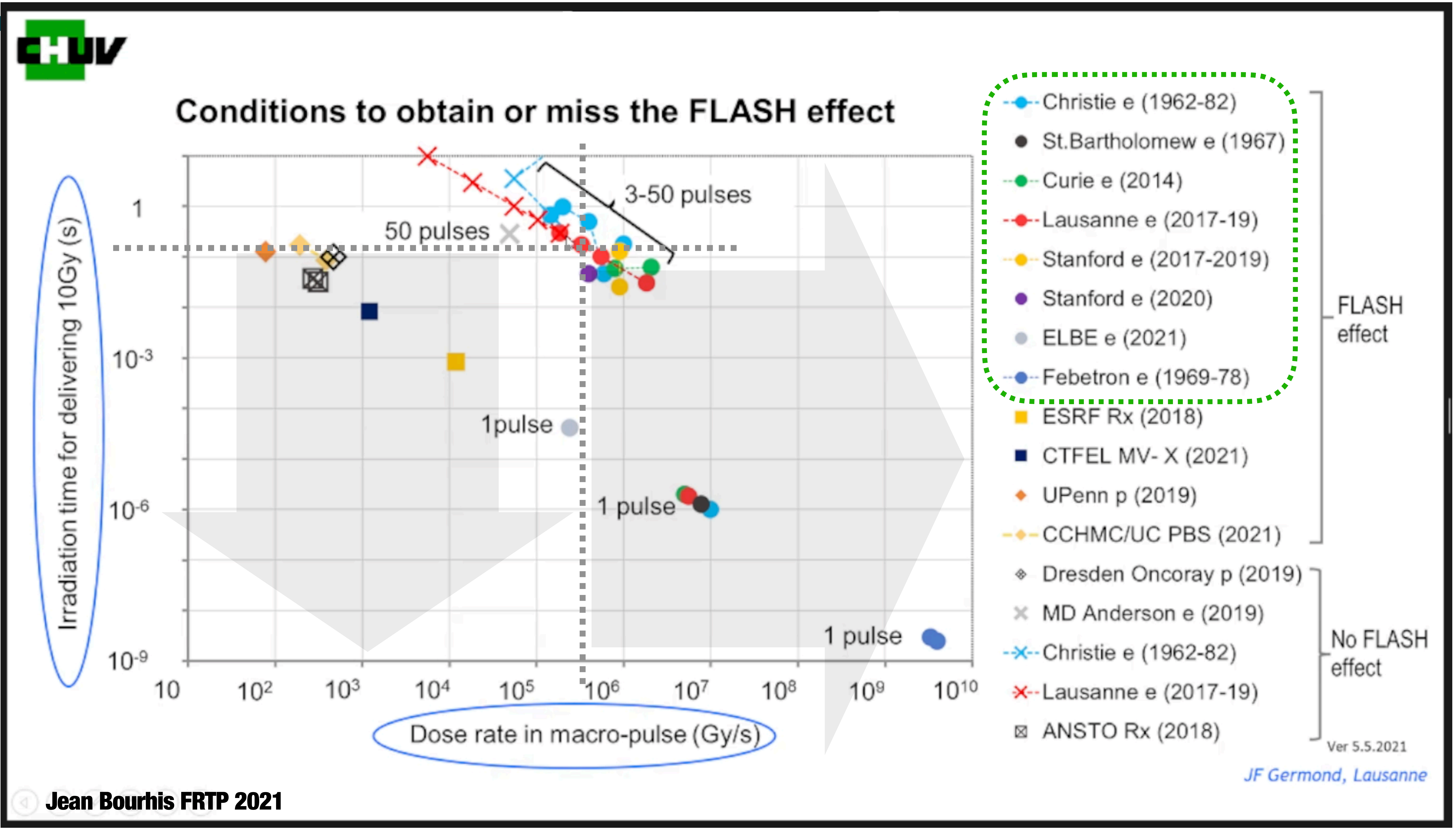
J. Wilson, et al., Ultra-high dose rate (FLASH) radiotherapy: Silver bullet or fool's gold?, Front. Oncol. 9:1563 (2020). doi:10.3389/fonc.2019.01563



Beam characteristics	CONV	FLASH
Dose per pulse	~ 0.4 mGy	> 1 Gy
Inst. dose rate (single pulse)	~ 100 Gy/s	> 10^6 Gy/s
Mean dose rate (single fraction)	~ 0.1 Gy/s	> 100 Gy/s
Total treatment time	~ days	< 100 ms

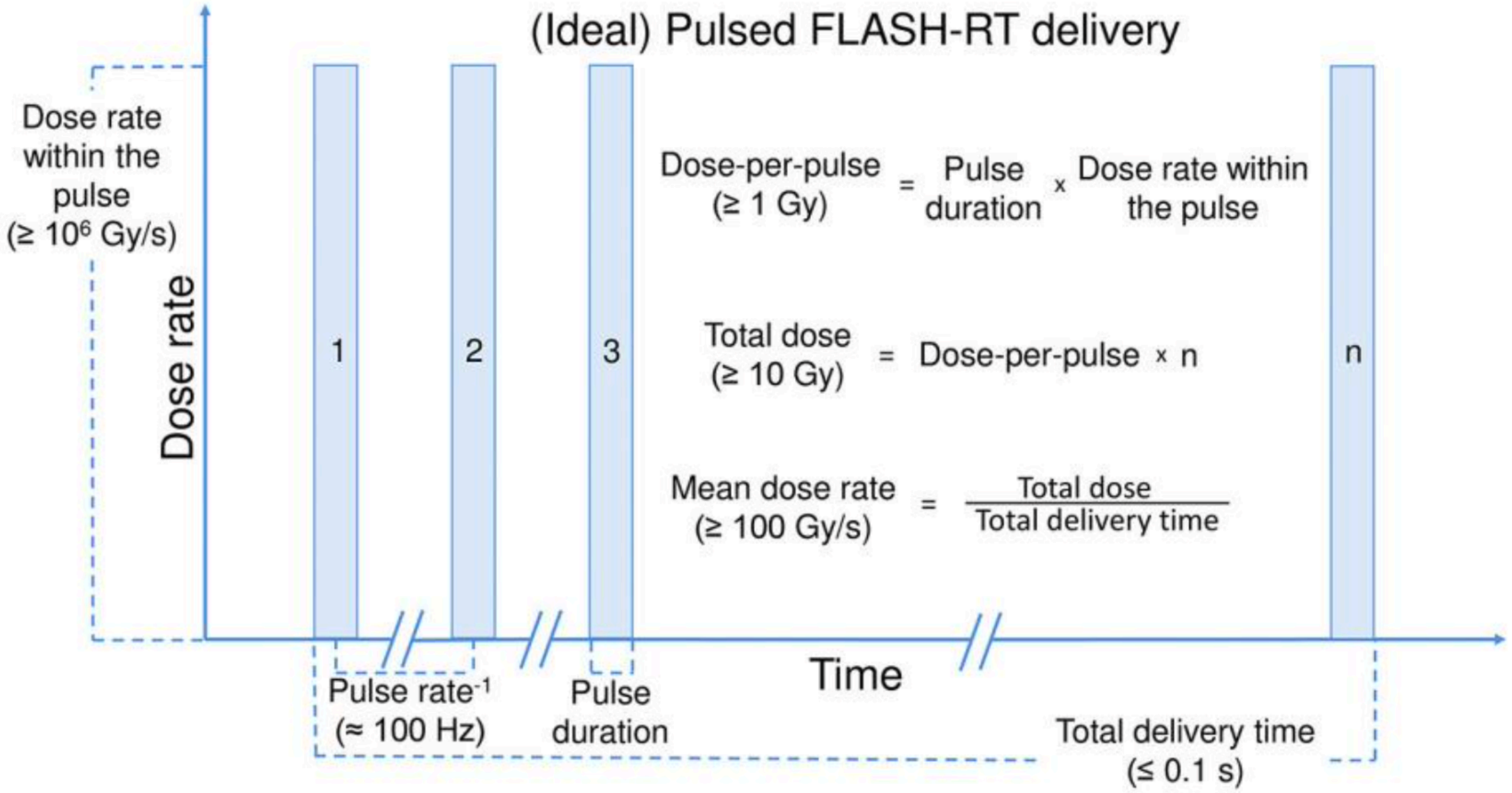
FLASH effect

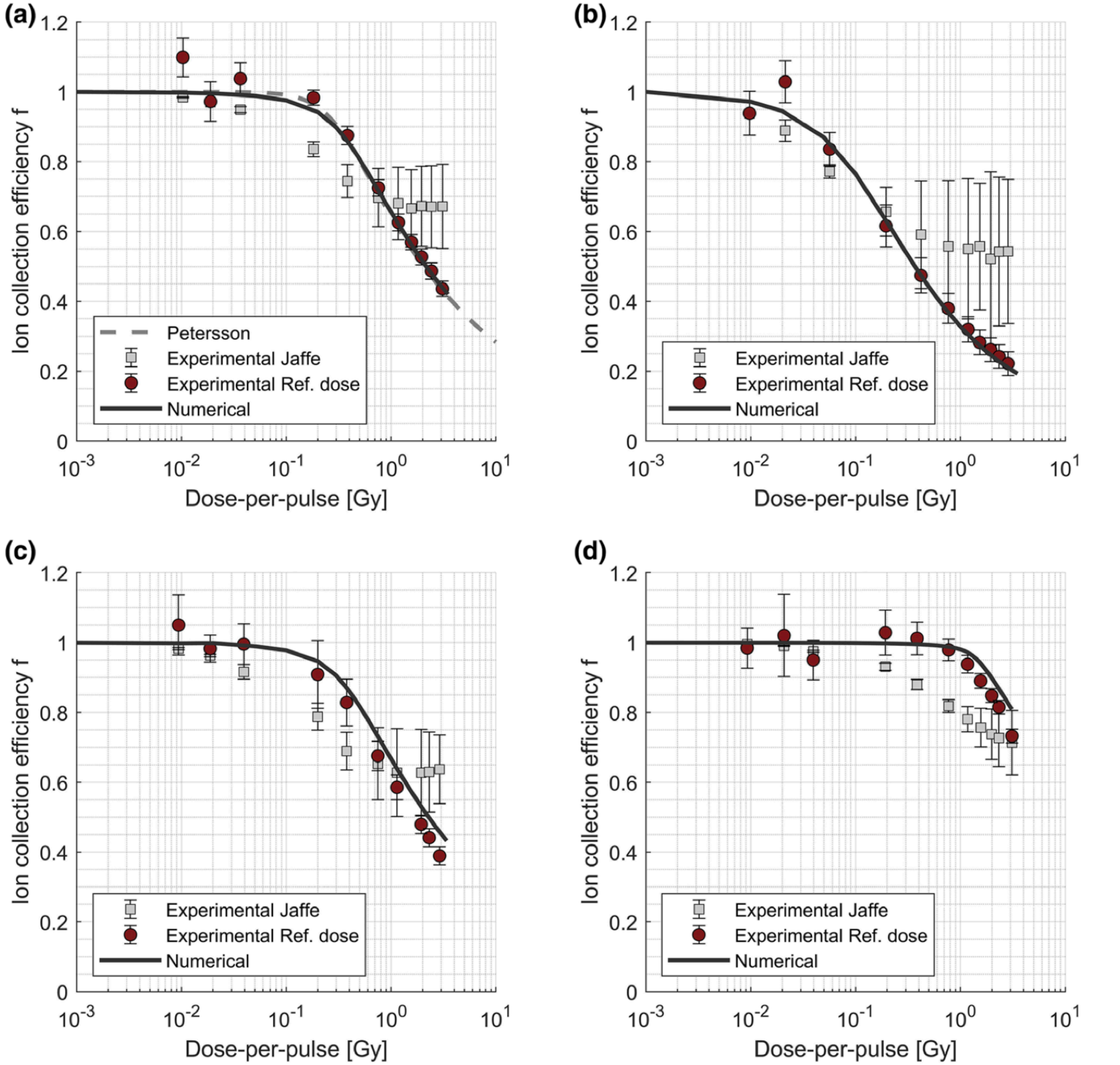
- Currently the experimental evidence points to the description of FLASH as a **threshold** effect. However, its characterization is complicated by many uncertainties:
  - **<u>In measurement strategies</u>**: it is difficult to evaluate quantitatively the sparing effect during *in vivo* evaluations;
  - **<u>In dose measurements:</u>** it is difficult to de-convolute the role played by the **<u>dose within each pulse</u>** and the **<u>time of irradiation</u>**.



FLASH effect

- Beam monitoring is a cornerstone of this research, that must provide the reliable assessment of the (sometimes extreme) beam parameters.
- Problem is, BM can be hardly operated in FLASH environment. ICs undergo substantial energy dependencies due to **volume recombination**.
- (There are attempts to characterize this saturation effect by introducing correction factors.)



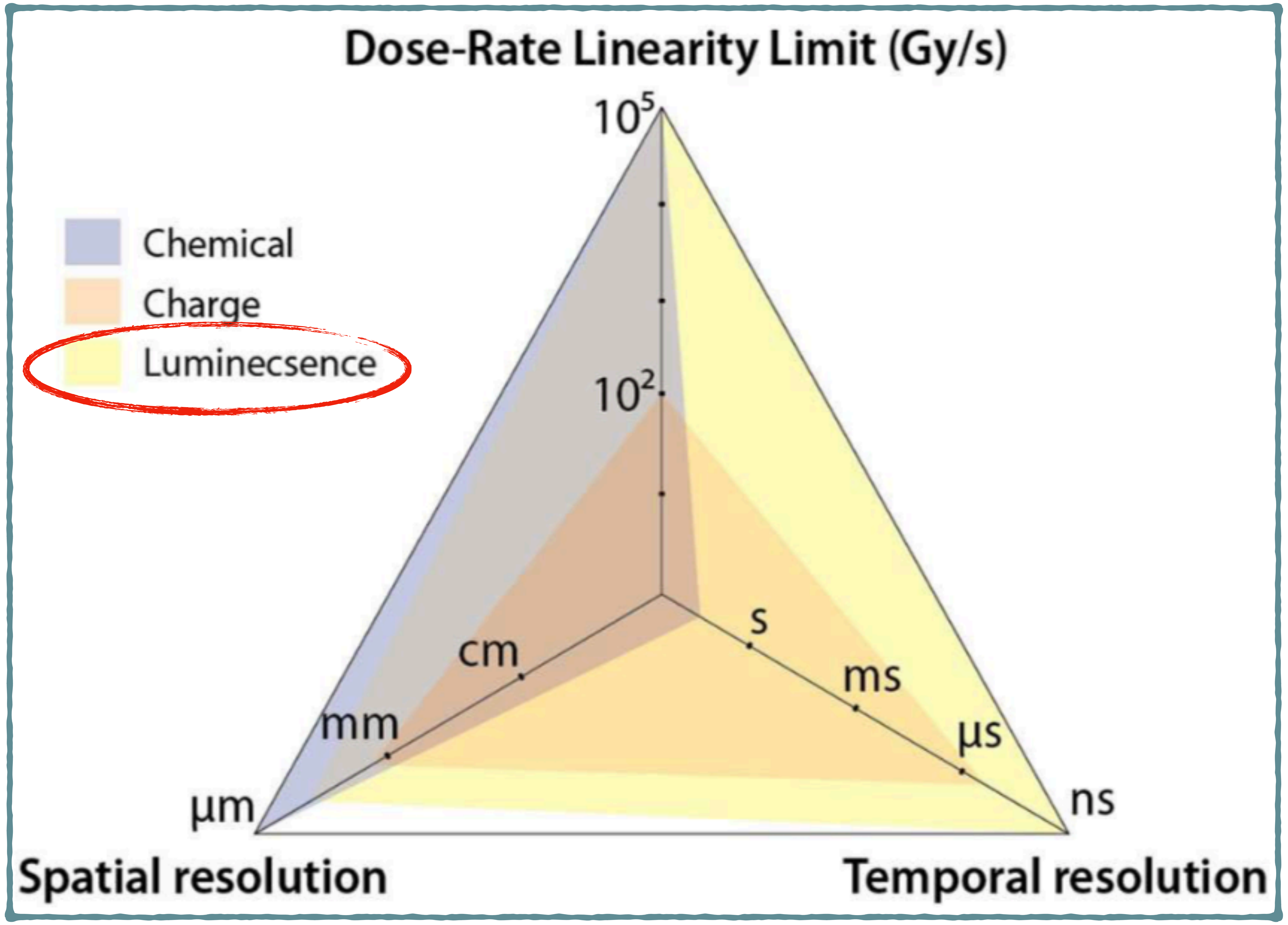


Ion collection efficiency for the ionization chambers with a polarizing voltage of 300 V. **(a)** Advanced Markus, **(b)** EWC2, **(c)** EWC1, **(d)** EWC05. doi: 10.1002/mp.14620

FLASH beam monitoring

- It is clear that we need *new monitoring devices*, essential to reach the degree of precision necessary to fully characterize the FLASH effect and determine its beneficial impact (both for pre-clinical studies and in the perspective of clinical implementation).

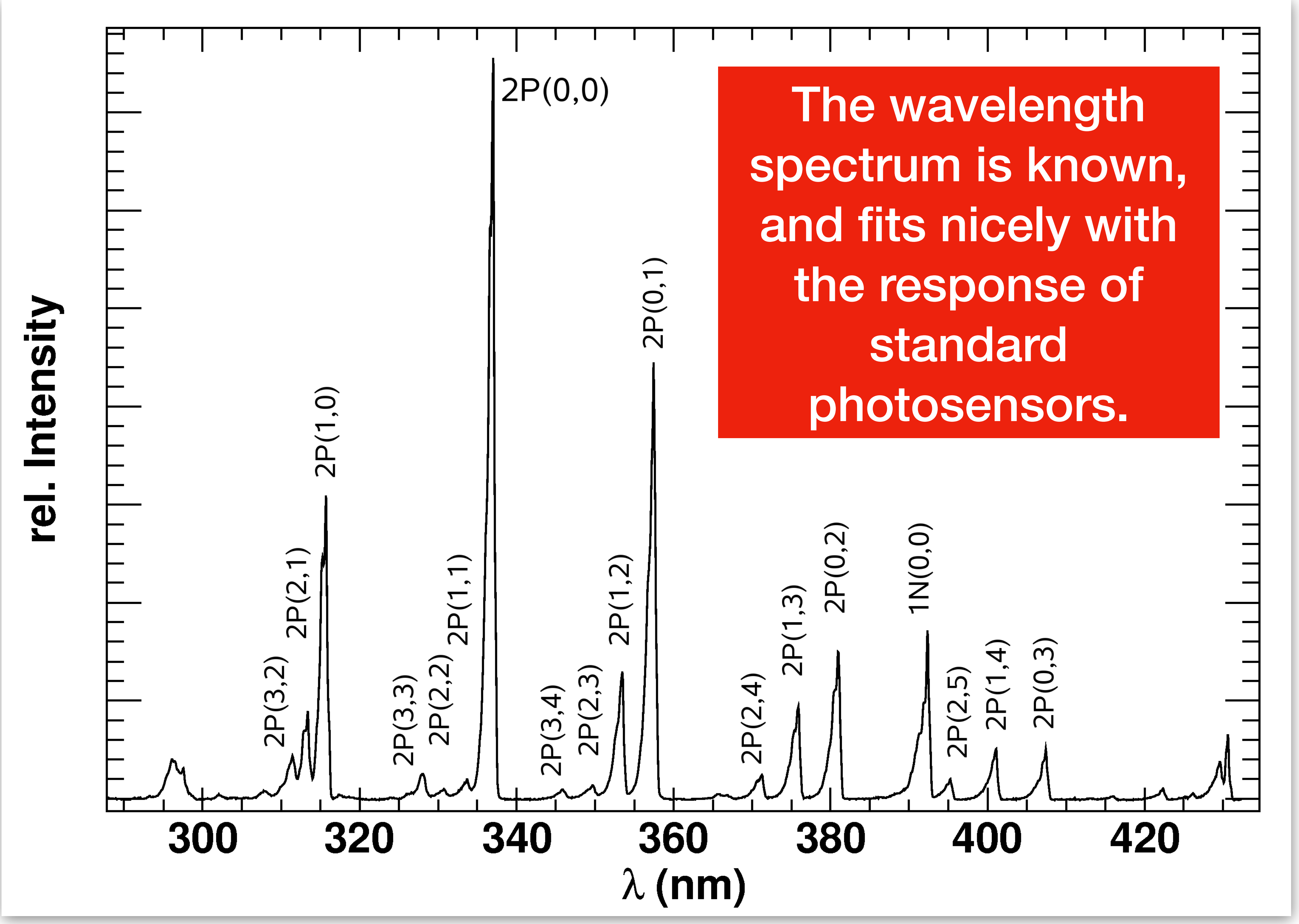
- Most importantly, monitor **the rate of impinging particles per pulse** (real-time, position by position), with:
  - ☆ Dose Rate Linearity (up to 10^6 Gy/s)
  - ☆ Spatial Resolution (~ mm)
  - ☆ Temporal Resolution (< 1μs)
  - ❏ **High beam transparency**
  - ❏ **Large response dynamic range**
  - ❏ **Reduced footprint**
  - ❏ **Large coverage area**
  - ❏ **Radiation hardness**

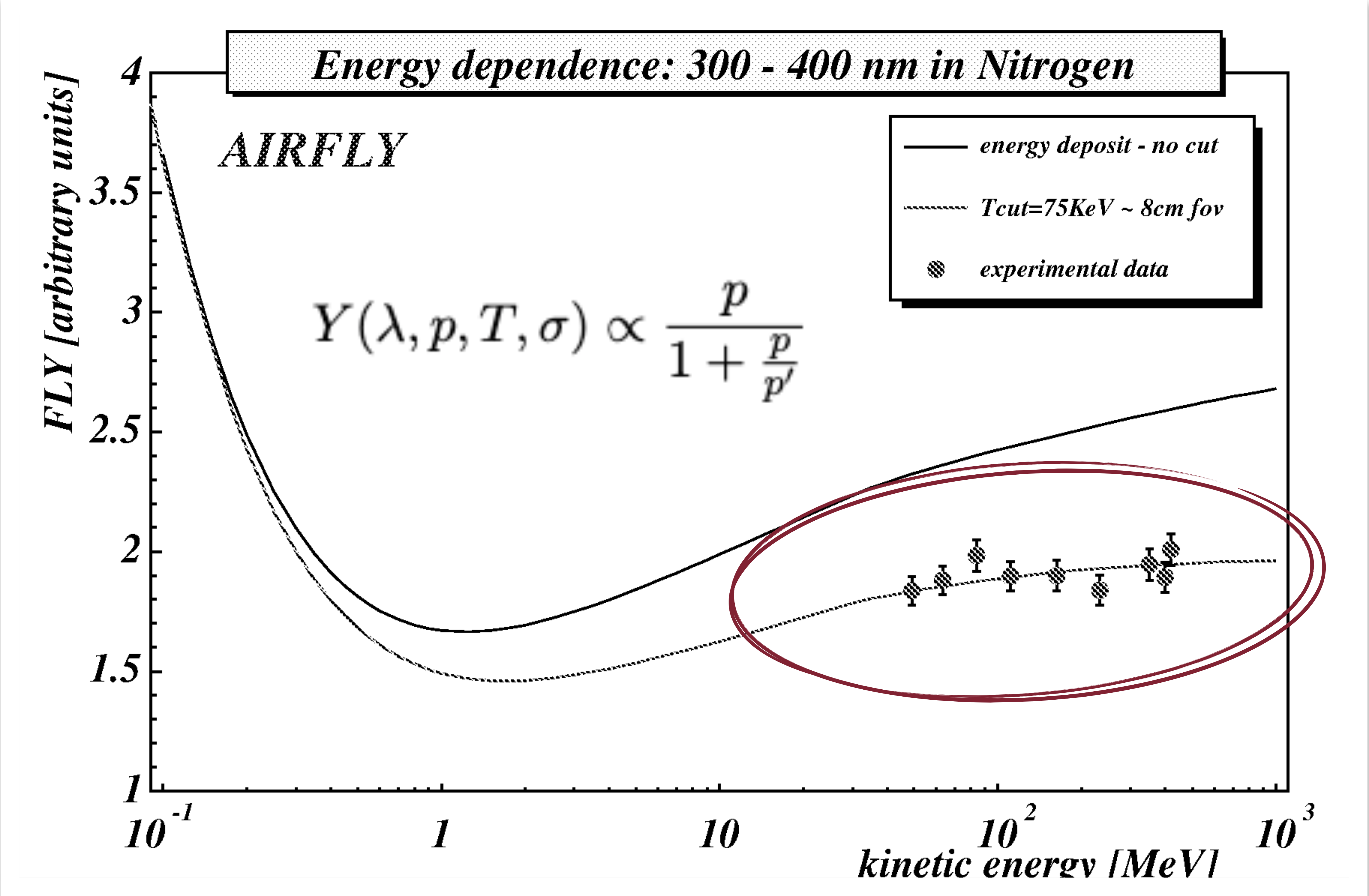


Ashraf MR et al, Dosimetry for FLASH Radiotherapy
doi: 10.3389/fphy.2020.00328

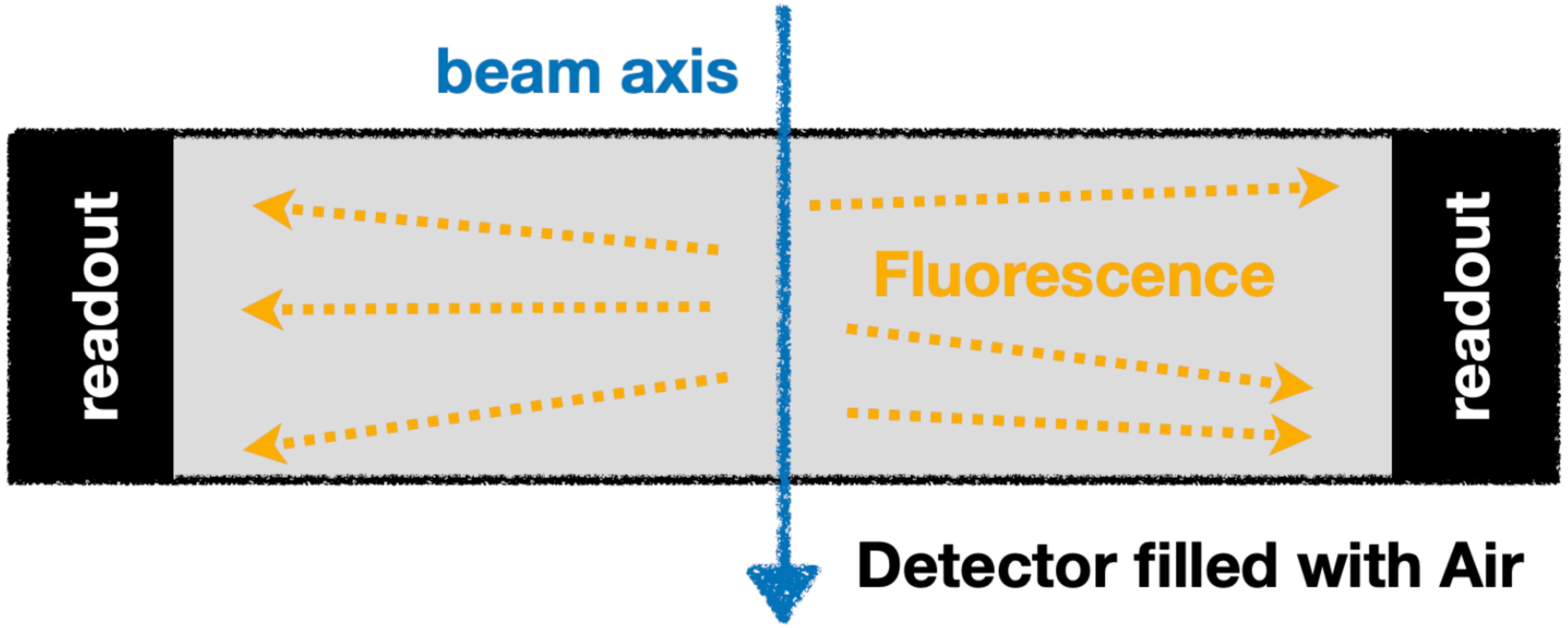
Fluorescence for FLASH BM

- According to data in literature, air fluorescence can do the job for us.
- In general, fluorescence is a form of luminescence. It is the emission of light from an excited atom or molecule, with a lifetime of the excited state around 10^{-8} s.
- In air, fluorescence occurs on the nitrogen molecule and it is excited via electron impact.





Fluorescence for FLASH BM



- Pressure and temperature dependencies, as well as the impact of different percentages of quenching elements, are present in literature, and can be accounted for with detector calibration.
- Above all else, the philosophy of using air as the active volume is to be as "invisible" to the beam as possible. The system should have minimal impact (the **empty box** approach).

- Conceptually, it would fit nicely with the ultra-high dose rate regime of FLASH-RT.
- Fluorescence is already used to detect extensive air showers in atmosphere. However, it has been rarely, if ever, exploited for medical BM purposes; it is thus a rather open field for research.

Photon emission	Isotropic (3D)
Excited state lifetime	10 ns
Fluorescence yield	$\propto dE/dx$ (~ 4 ph./m)
Signal-to-#e⁻ relation	**LINEAR**
Transparency wrt ref. cond.	100%
Shielding required	Minimal

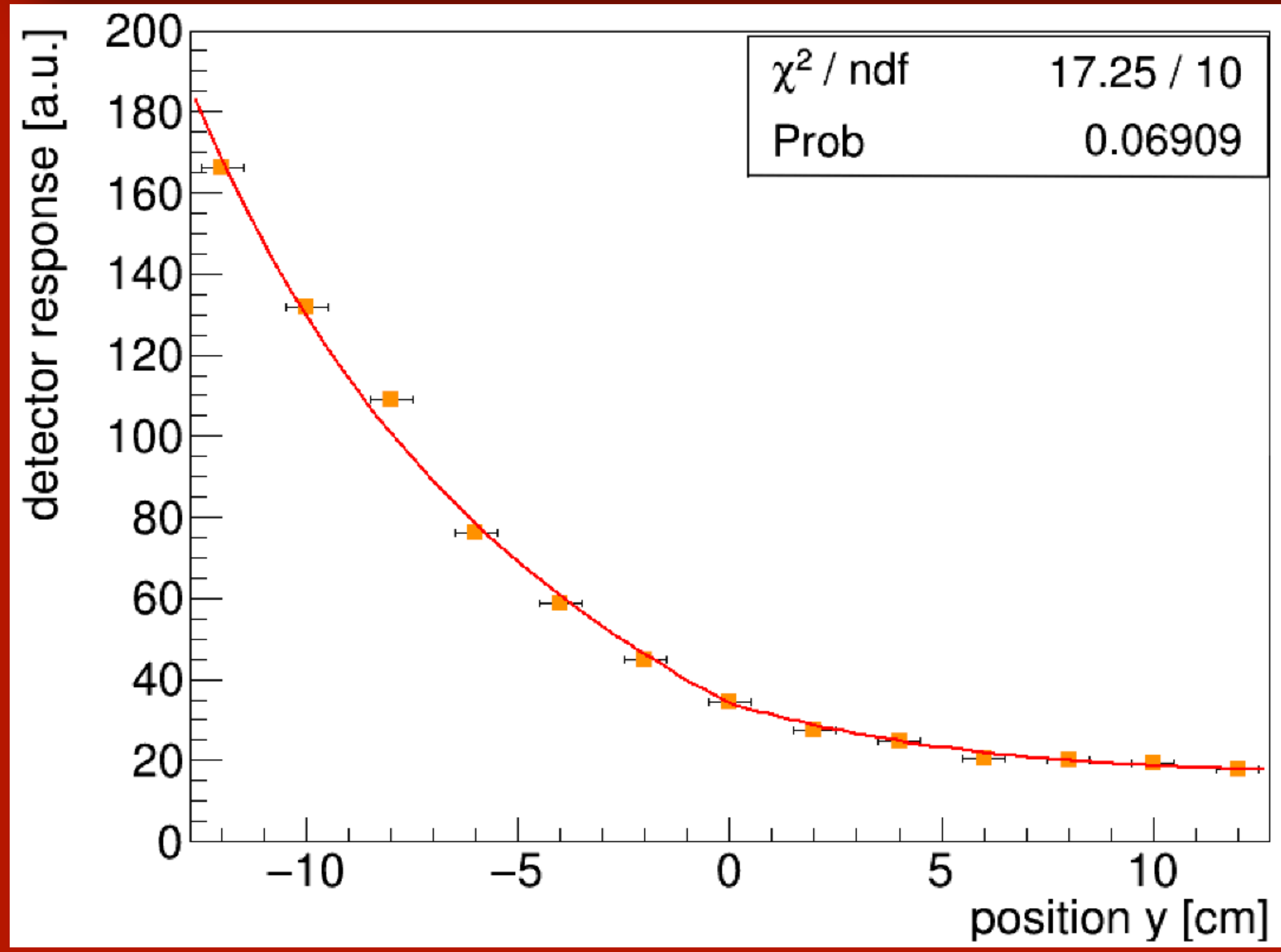
FlashDC

The first mandatory step is the validation of detection technique (linearity with the dose rate per pulse) with dedicated test beam at FLASH facilities.

FLASH beam monitoring

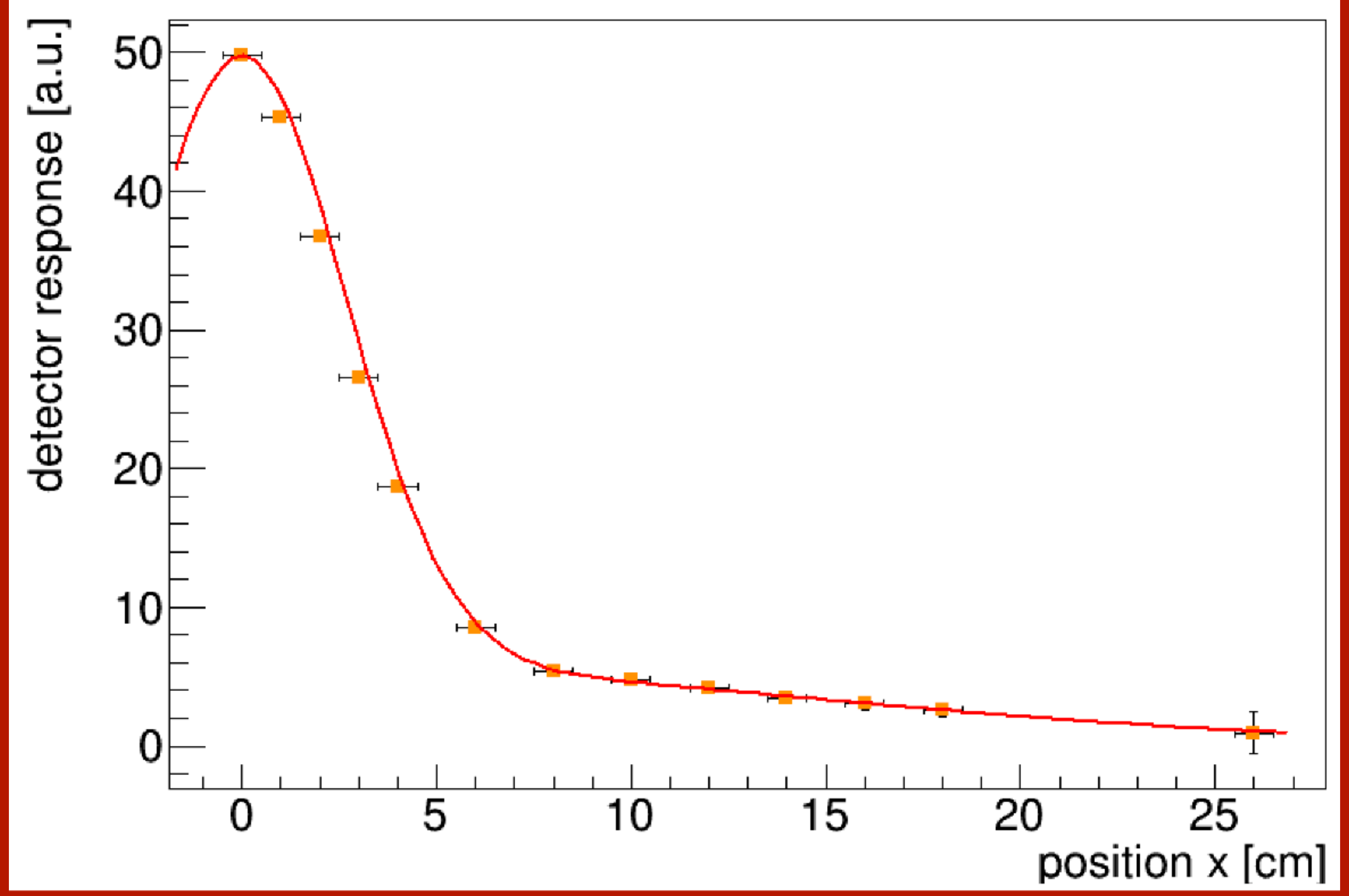
The signal is sensitive to the position with respect to the beam (shift, in/off beam)

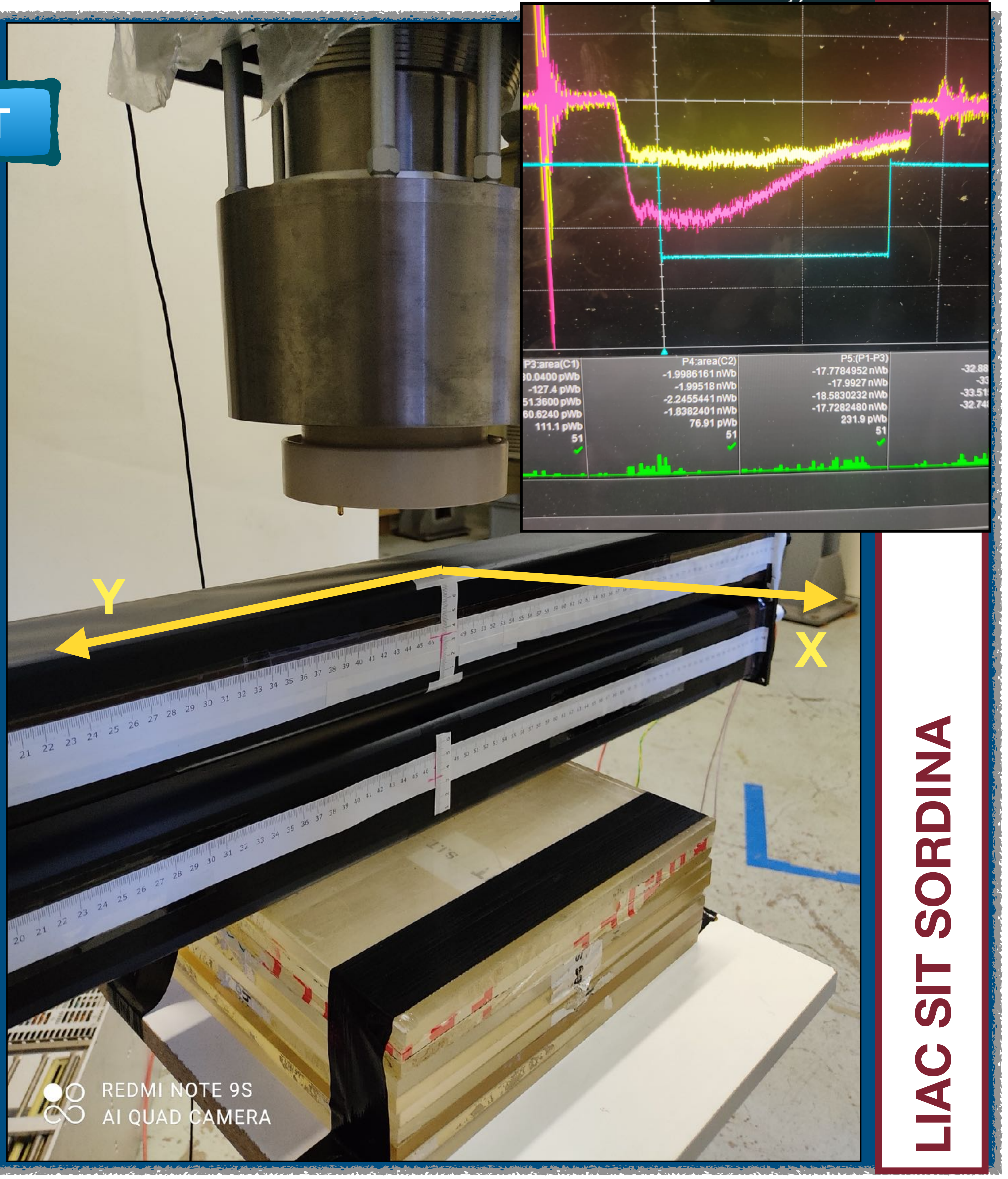
2020: SIT



- We verified the expected geometry dependencies of the detector response in different positions.
- Further indication that the signal is indeed due to the production of optical photons **inside** the active volume.

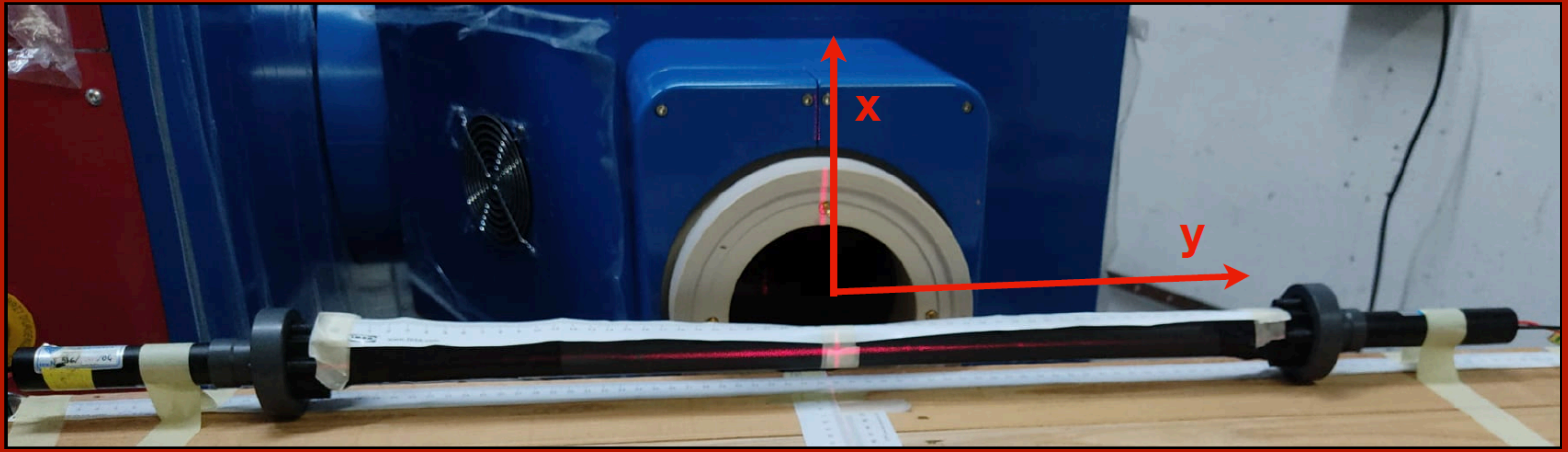
- Plot obtained gradually moving the detector off the beam to reconstruct the transverse shape.
- The in-beam/off-beam difference is observed.





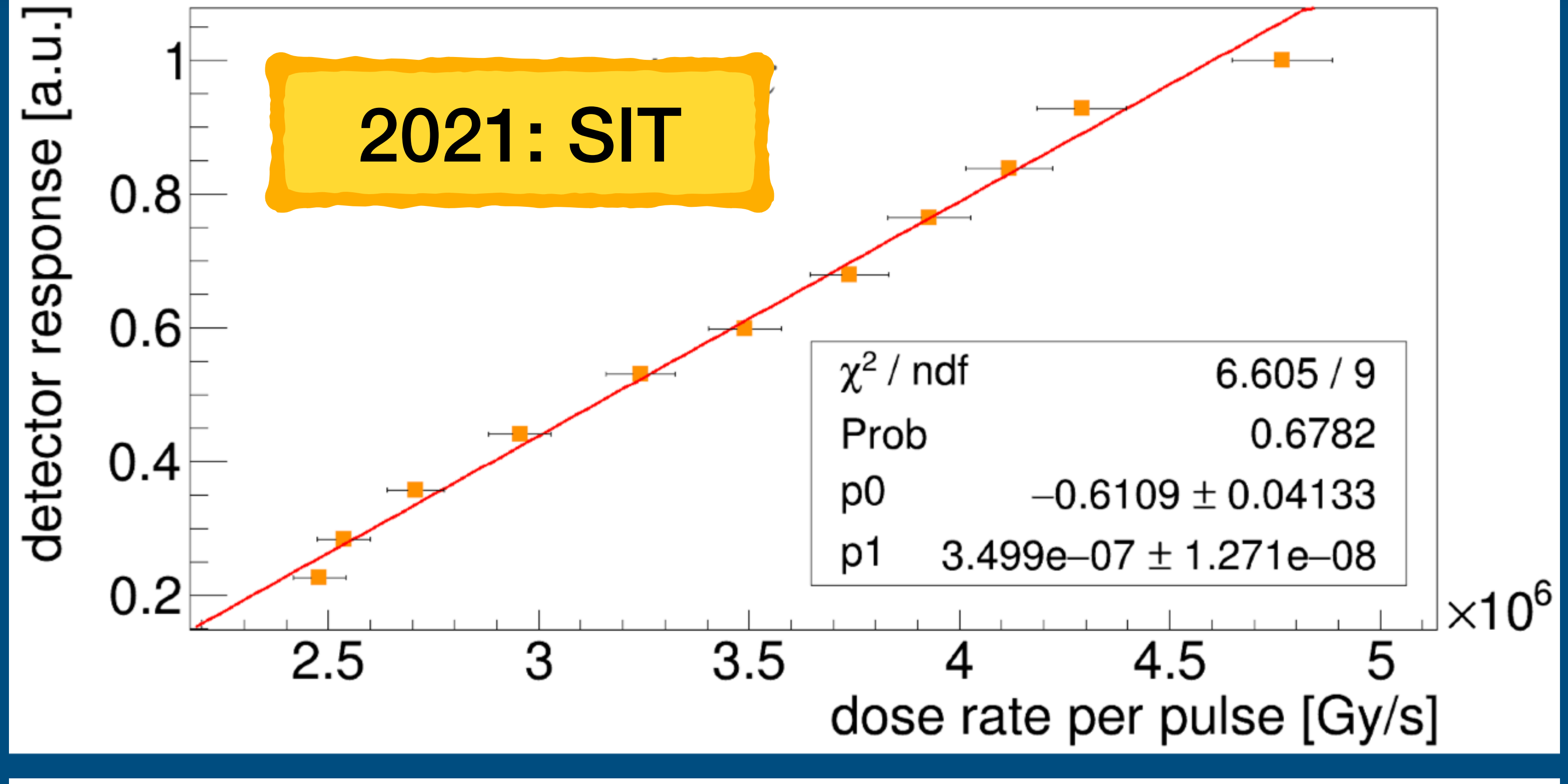
LIAC SIT SORDINA

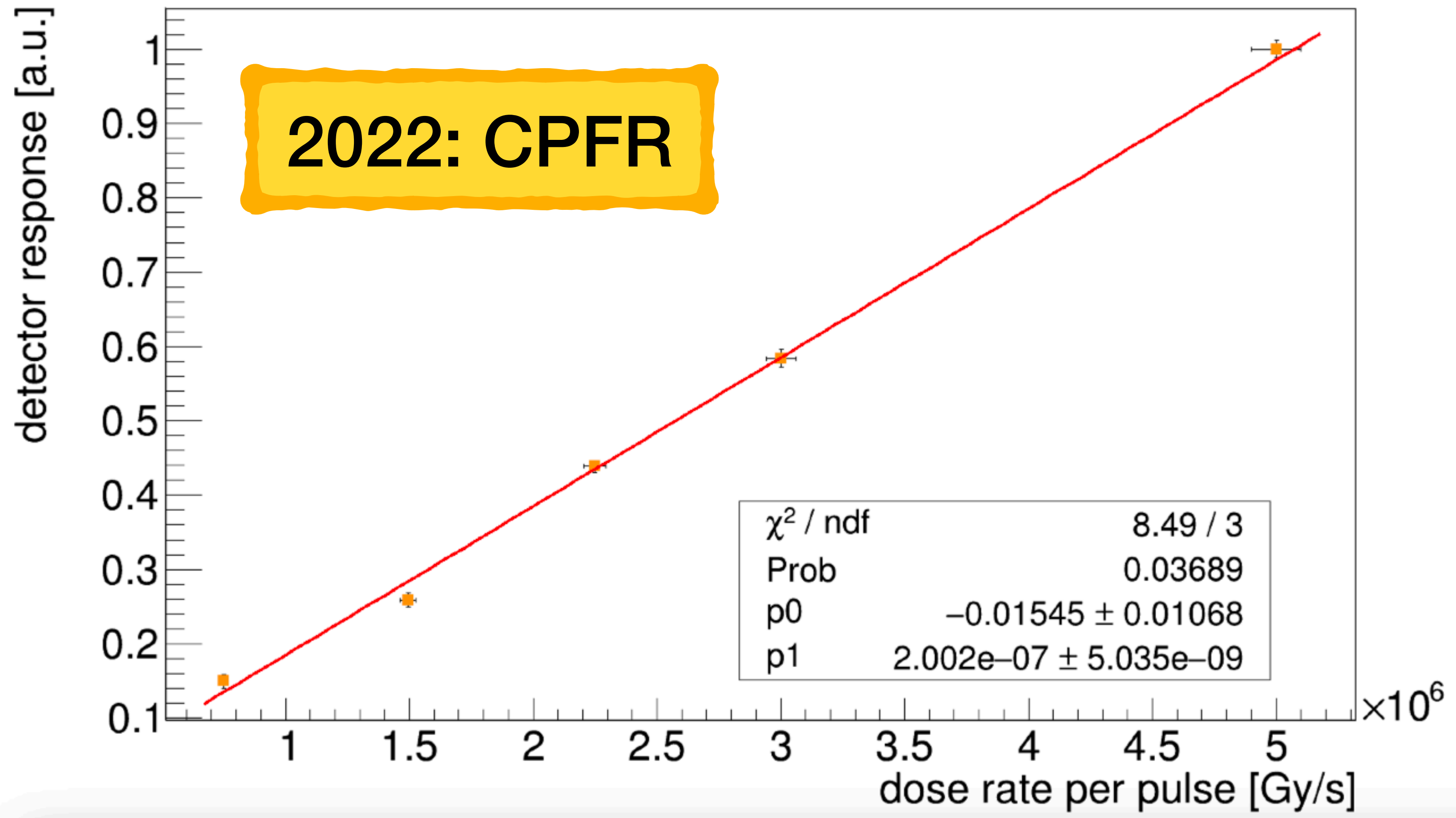
FLASH beam monitoring



- The machine available at Pisa is the first electron beam accelerator that can provide different beam currents => it is the best place to verify the detector linearity!
- However the background induced by the PVC box forced us to remove the material from the beam line.

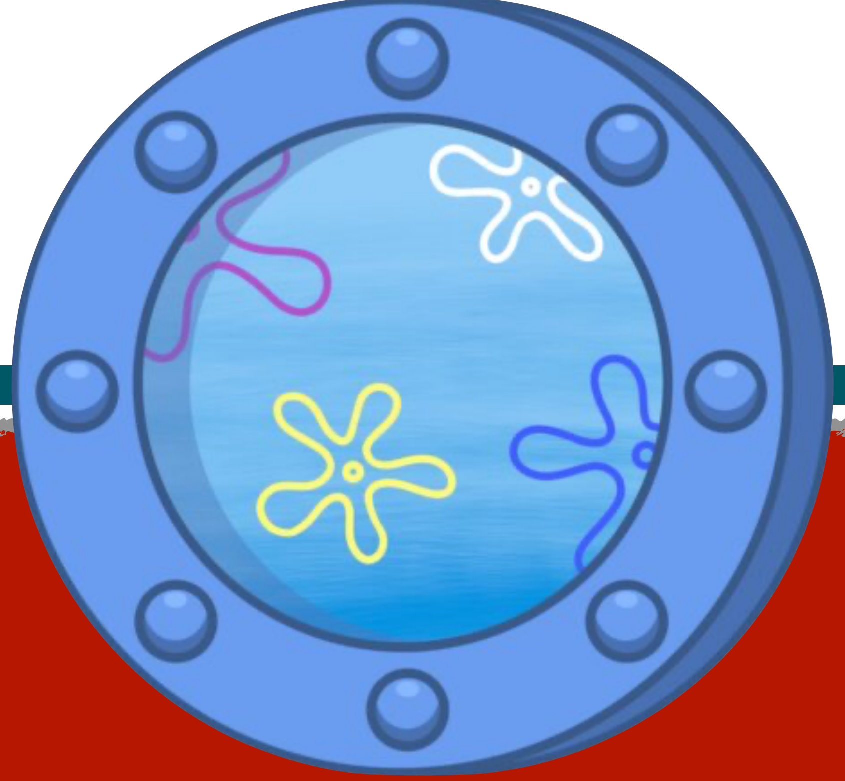
A linear response is observed over the full range of intensities explored.



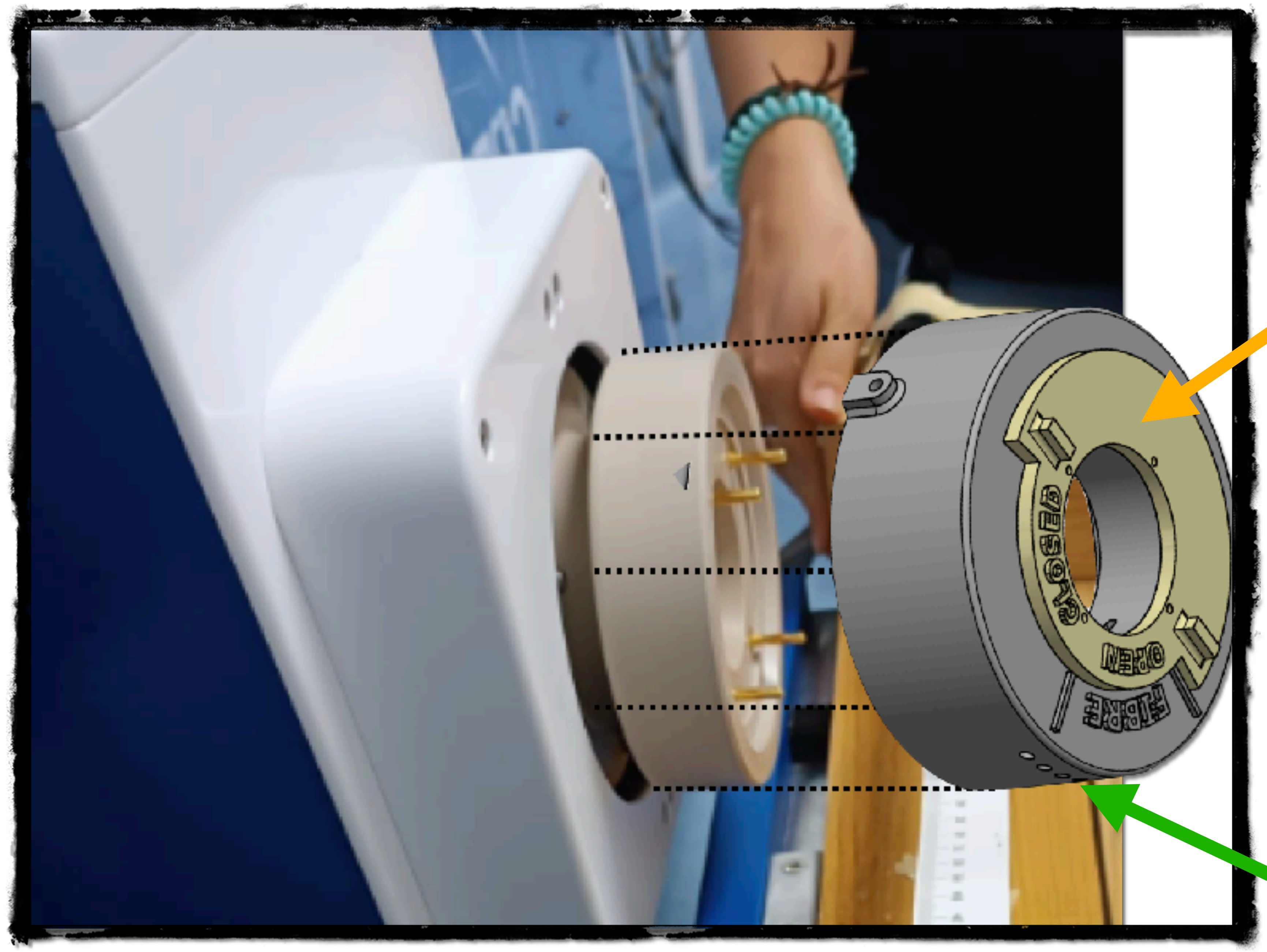


ElectronFlash: SIT SORDINA & CPFR PISA

FLASH beam monitoring

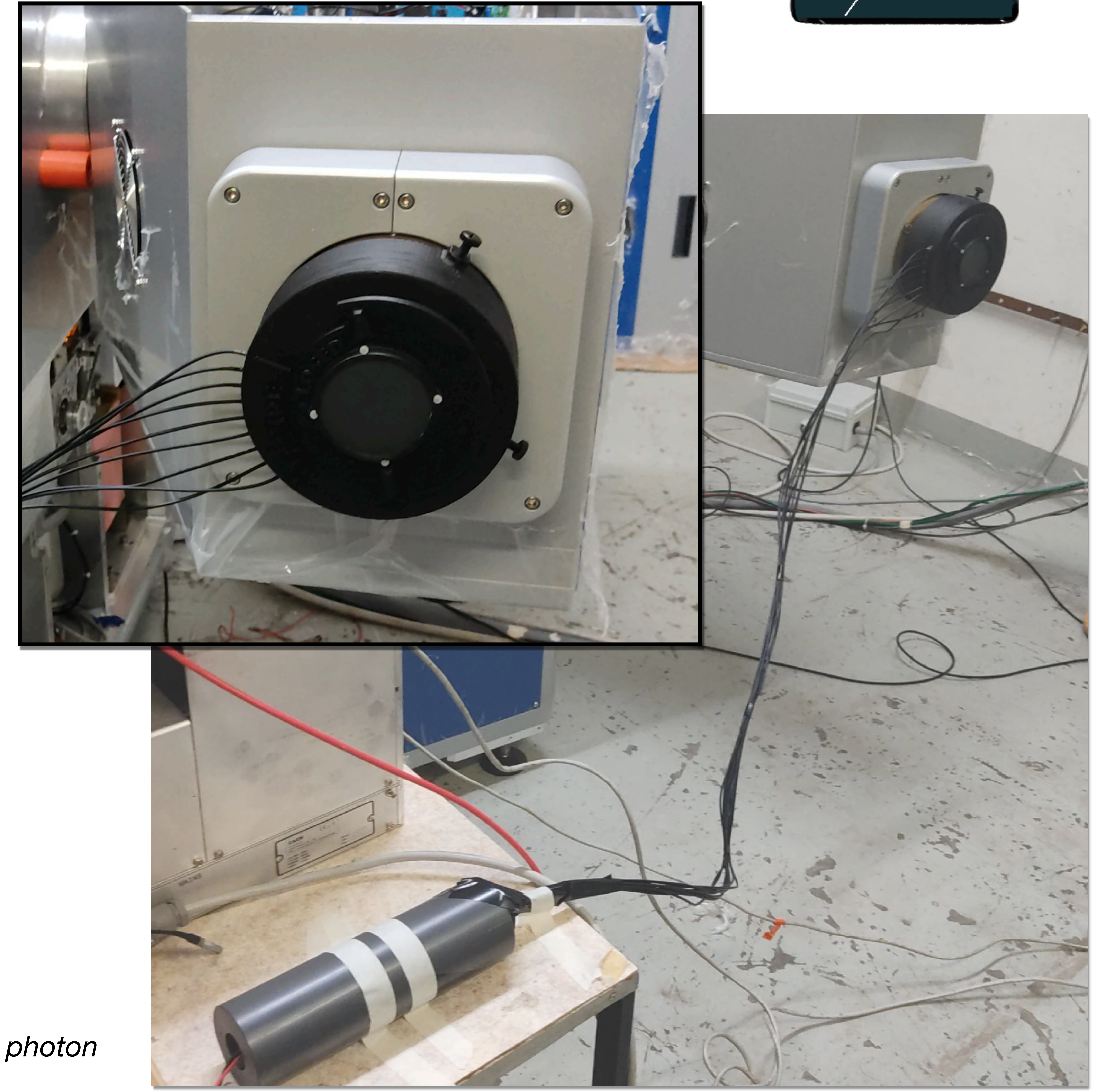


- Next step is to prove that the signal we see is actually fluorescence.
- We go from a tube to… a porthole.
- The active volume is the air immediately after the beam exit window, enclosed in this cylindrical case.
- A window on the external face can be closed and opened for background measurement.



FLASH beam monitoring

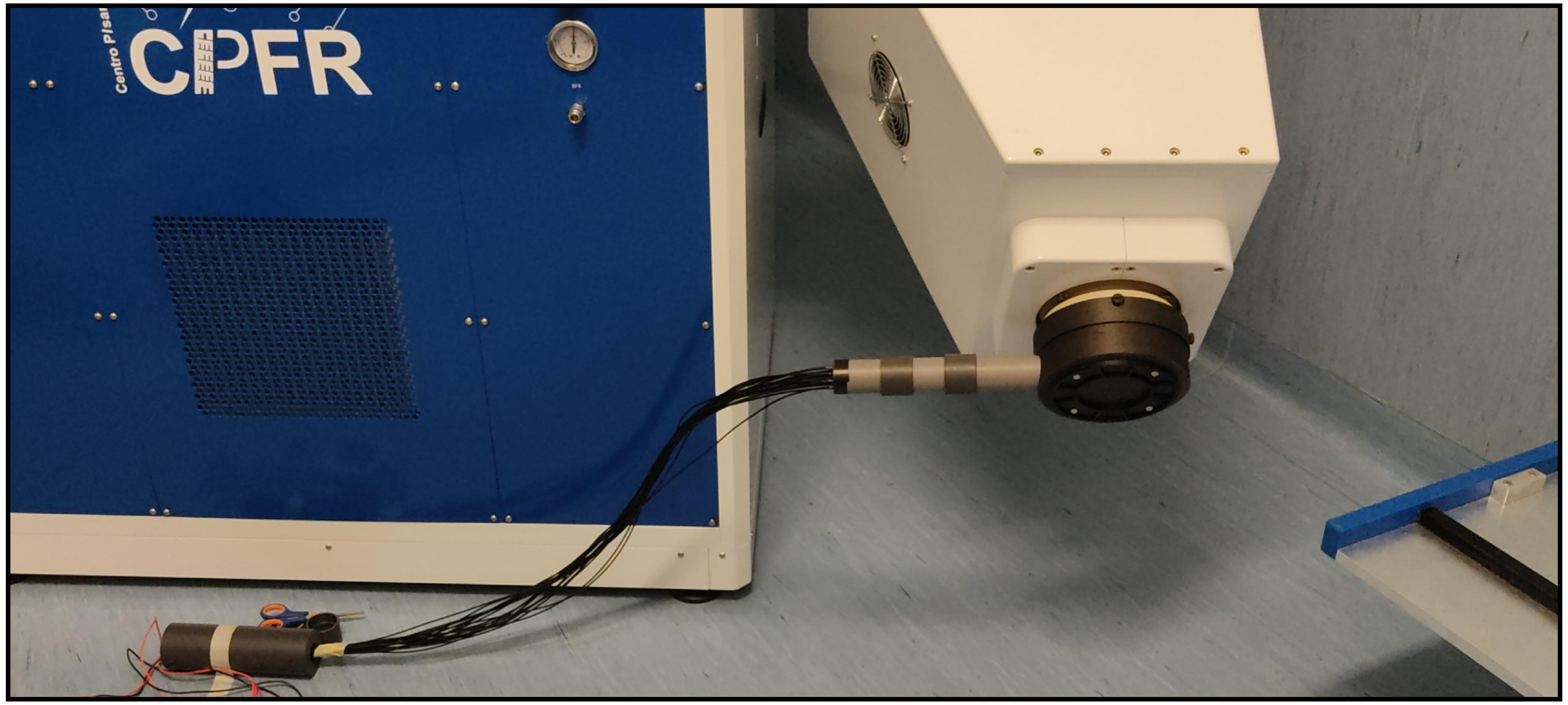
- In this configuration we the active volume is too close to the beam: we need to carry the signal away towards the PMTs.
- A new detector based on optical fibers could allow to drive and collect the fluorescence light far from the beam line.



- A preliminary measurement at SIT demonstrated that, even if we distance the light collection system from the beam, we are still not able to “switch off” the signal.
- **Cherenkov light** is produced inside the fibers [1]. The background is still too important.
- We need to further distance the system from the beam, carrying the light outside the room.

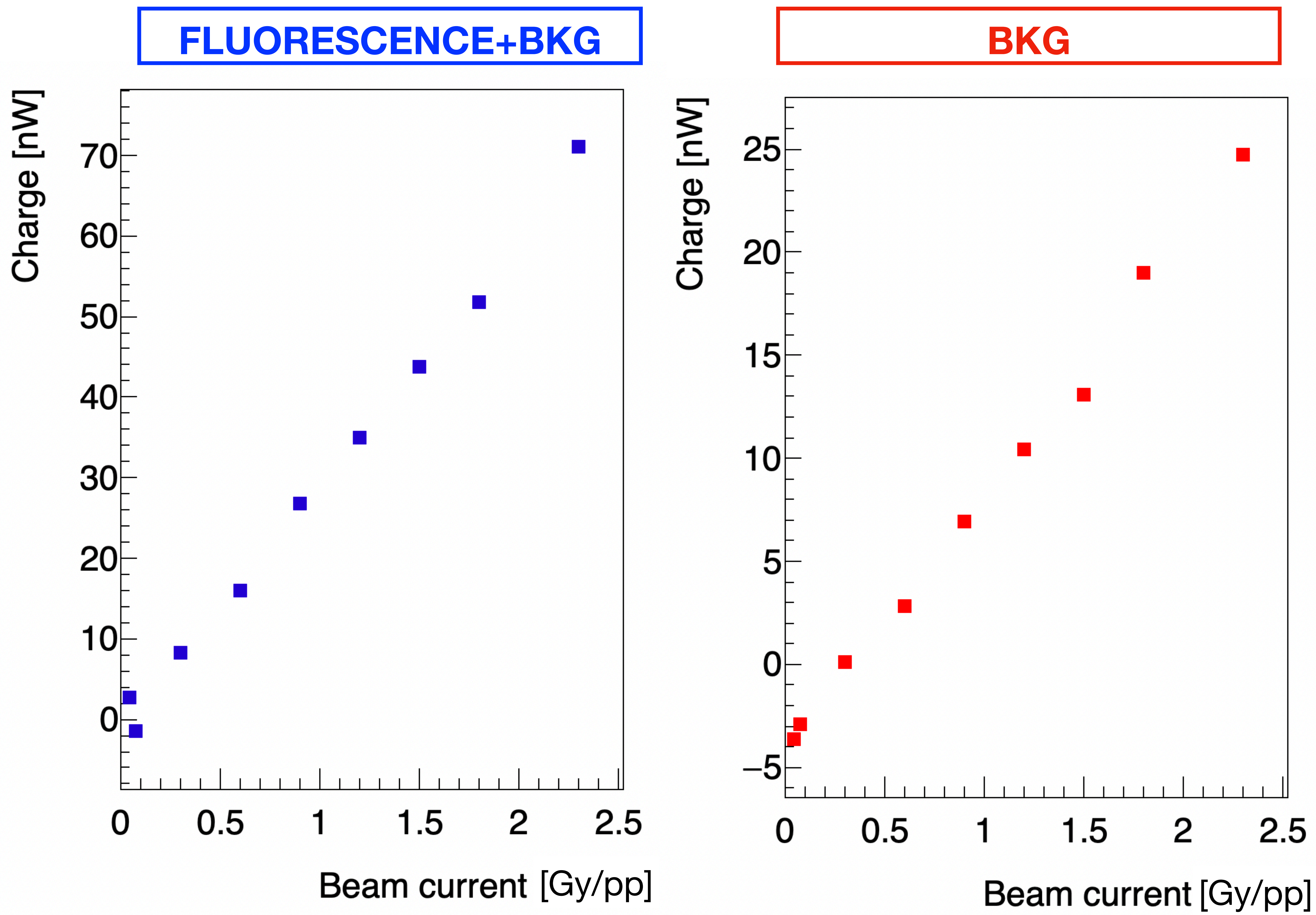
[1] Journal of Biomedical Optics, Vol. 18, Issue 2, 027001 (2013).
Kyoung Won Jang et al. *Application of Cerenkov radiation generated in plastic optical fibers for therapeutic photon beam dosimetry.* https://doi.org/10.1117/1.JBO.18.2.027001

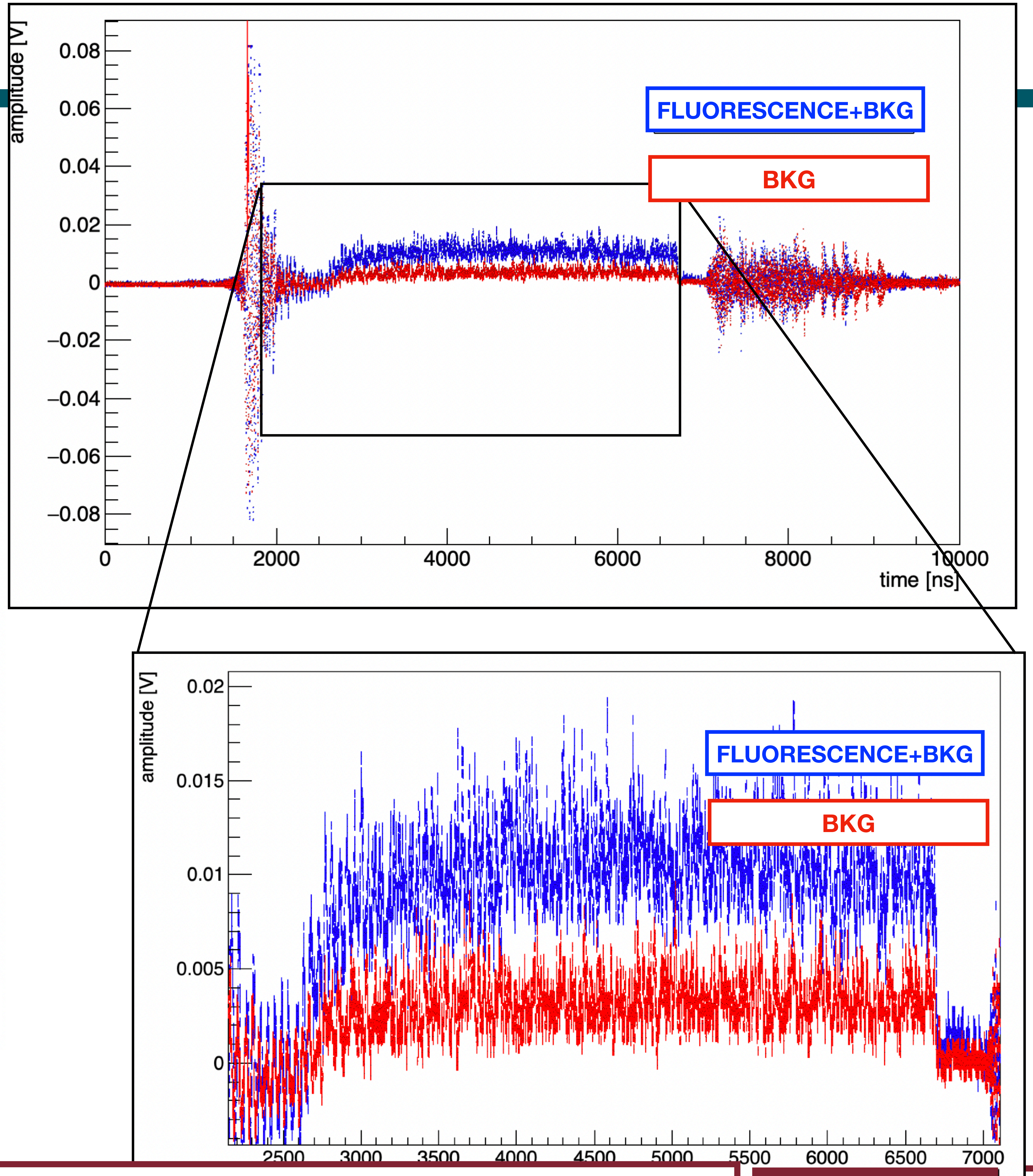
FLASH beam monitoring



- For our second round of testing at Pisa, we verified that, even at 2 m away from the machine, the fibers still produce background, so we remove them and put the PMT at 2 m from the beam exit window.
- The setup is, as usual, equipped with the possibility to measure also the background for each configuration and perform a background subtraction to evaluate the fluorescence contribution.

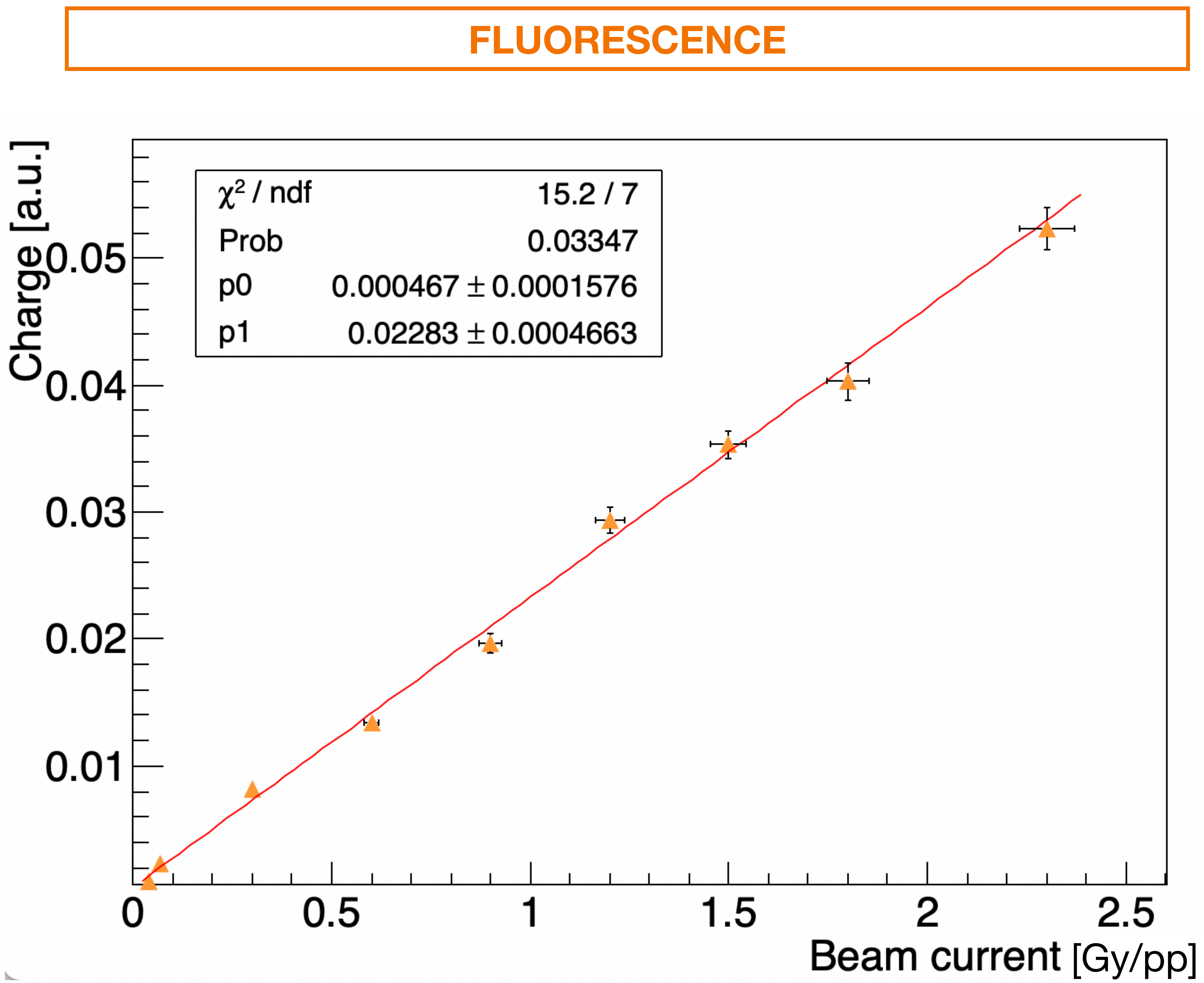
FLASH beam monitoring

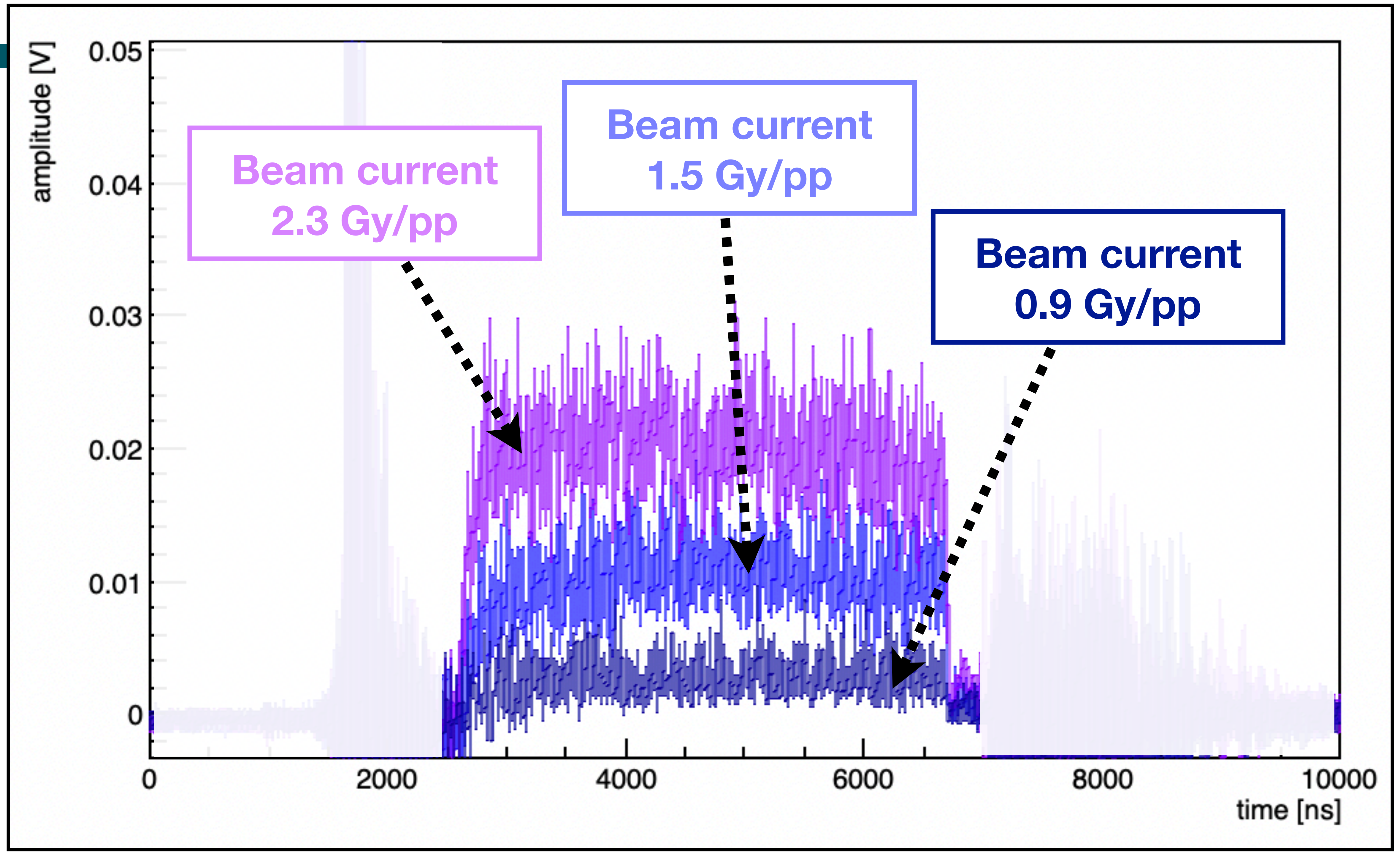




☑ S/N is still large… but this is due to the readout system.

FLASH beam monitoring





- ☑ Fluorescence signal linearity as a function of the beam current is confirmed!
- ☑ The statistics is very low… only 30 pulses have been acquired (for each current).

Conclusions

Thanks to:
Angelica De Gregorio, Valerio Di Domenico, Gaia Franciosini, Marco Garbini, Michela Marafini, Riccardo Mirabelli, Vincenzo Patera, Alessio Sarti, Angelo Schiavi, Adalberto Sciubba, Marco Toppi, Giacomo Traini

- ☑ Definitely strong evidence that fluorescence signal has the expected linearity as a function of the beam current.
- ☐ The background in the readout system (PMT) is not negligible also at very large distances (only behind the wall of the room is zero).
- ☐ With this setup we have background of about 30%.
- ☑ Fluorescence is huge (we saturate easily at high currents).
- ☐ We had to reduce the acceptance with a diaphragm… this feature is necessary to avoid saturation of the PMT at high currents.
- ☑ We have a detector that has no material at all on the beam line…

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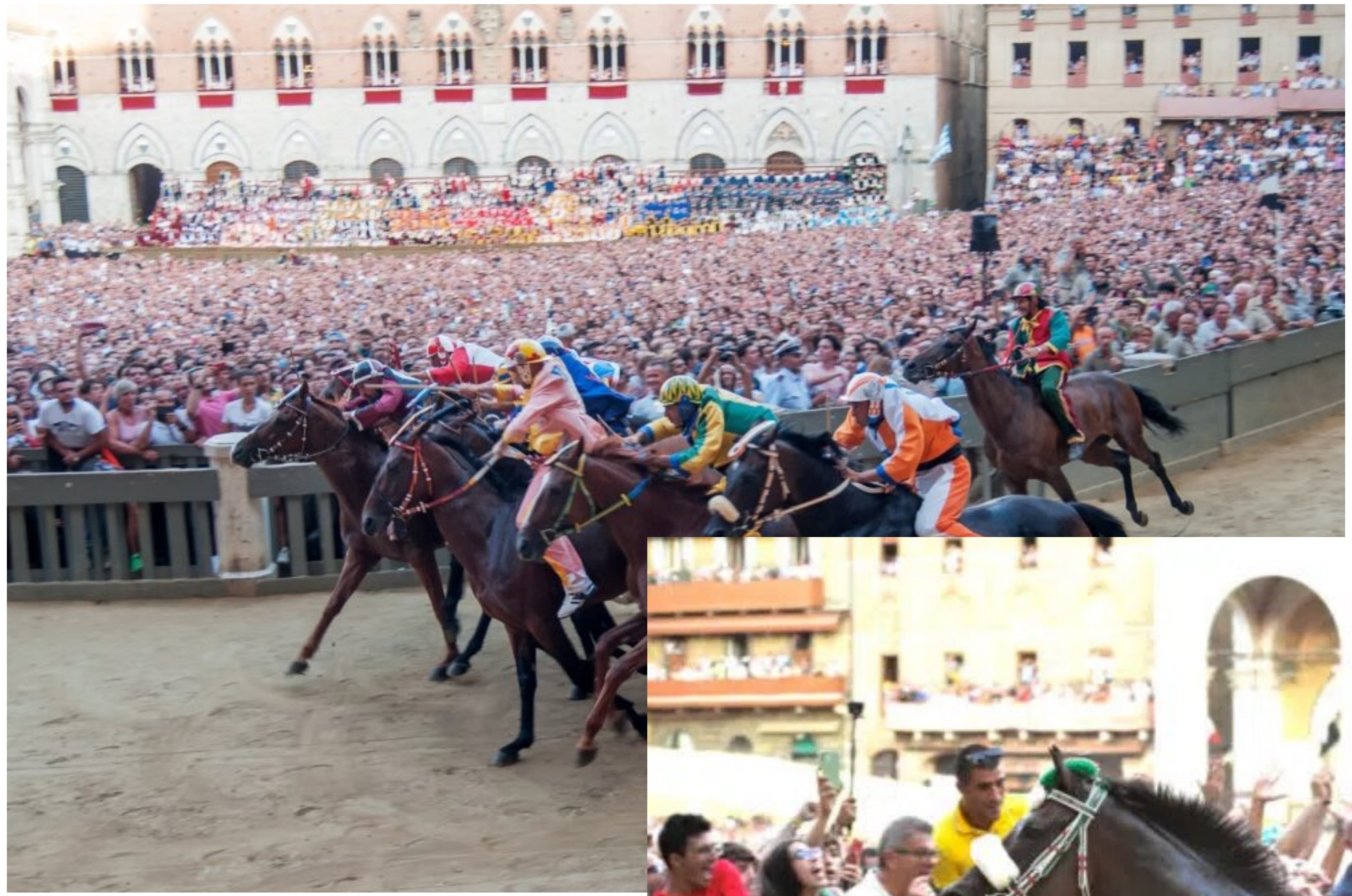
FLASH effect

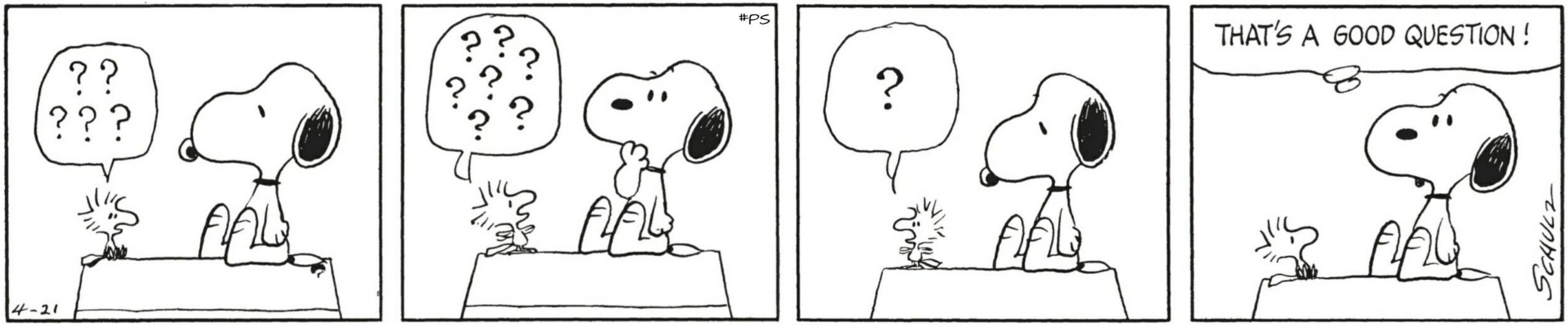
- If you come to Siena to see the Palio, you will enjoy 4 days with the big Medieval parade, musicians, flags, the entrance of the horses, the legendary “mossa”, the rivalries, alliances…

FLASH effect



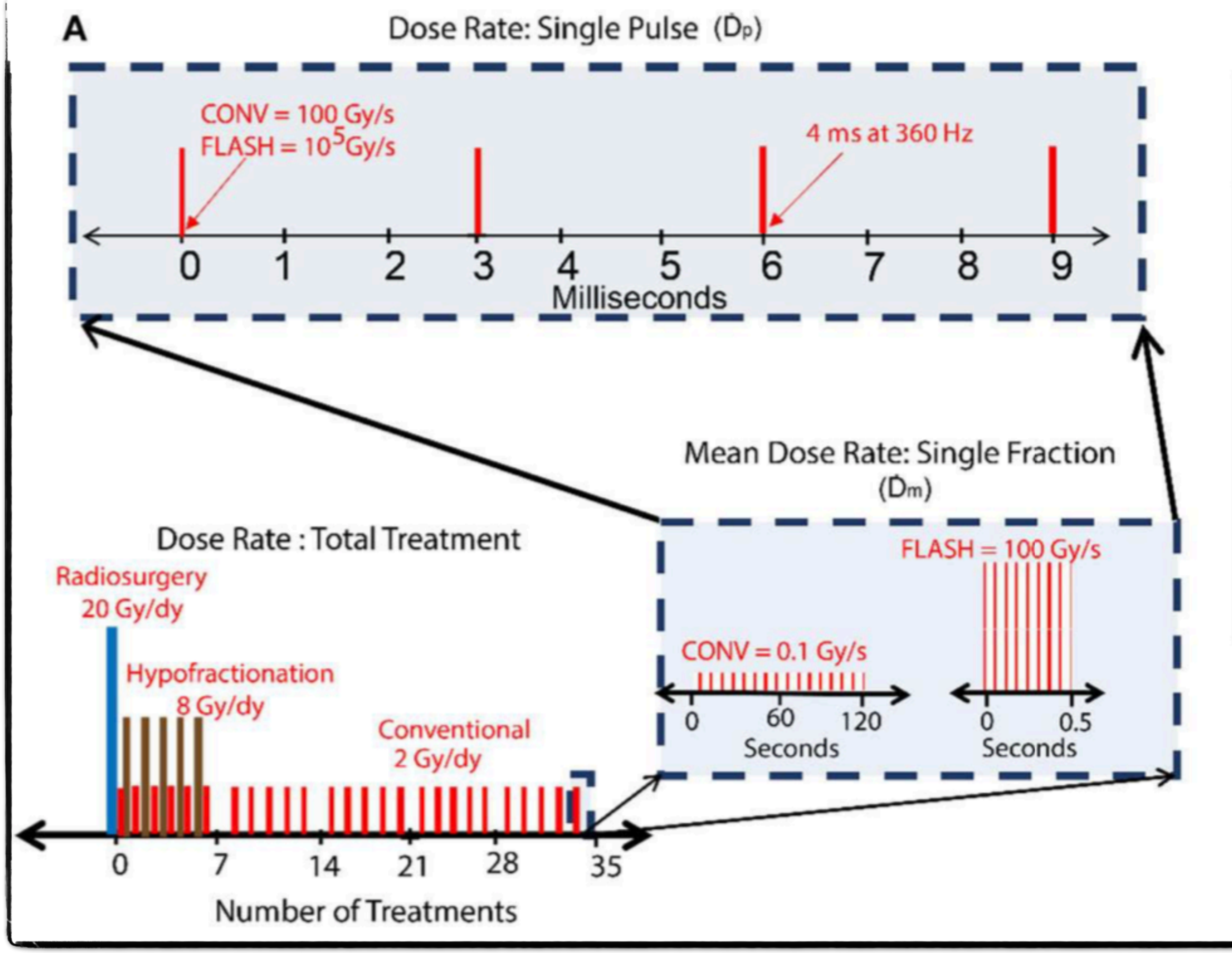
- If you come to Siena to see the Palio, you will enjoy 4 days with the big Medieval parade, musicians, flags, the entrance of the horses, the legendary “mossa”, the rivalries, alliances…
- And then the actual race… lasts for 1:30 minutes.
- The **FLASH-est** event in the world!

Thank you for your attention!



Backup

Ashraf MR, Rahman M, Zhang R, Williams BB, Gladstone DJ, Pogue BW and Bruza P (2020) Dosimetry for FLASH Radiotherapy: A Review of Tools and the Role of Radioluminescence and Cherenkov Emission. Front. Phys. 8:328. doi: 10.3389/fphy.2020.00328



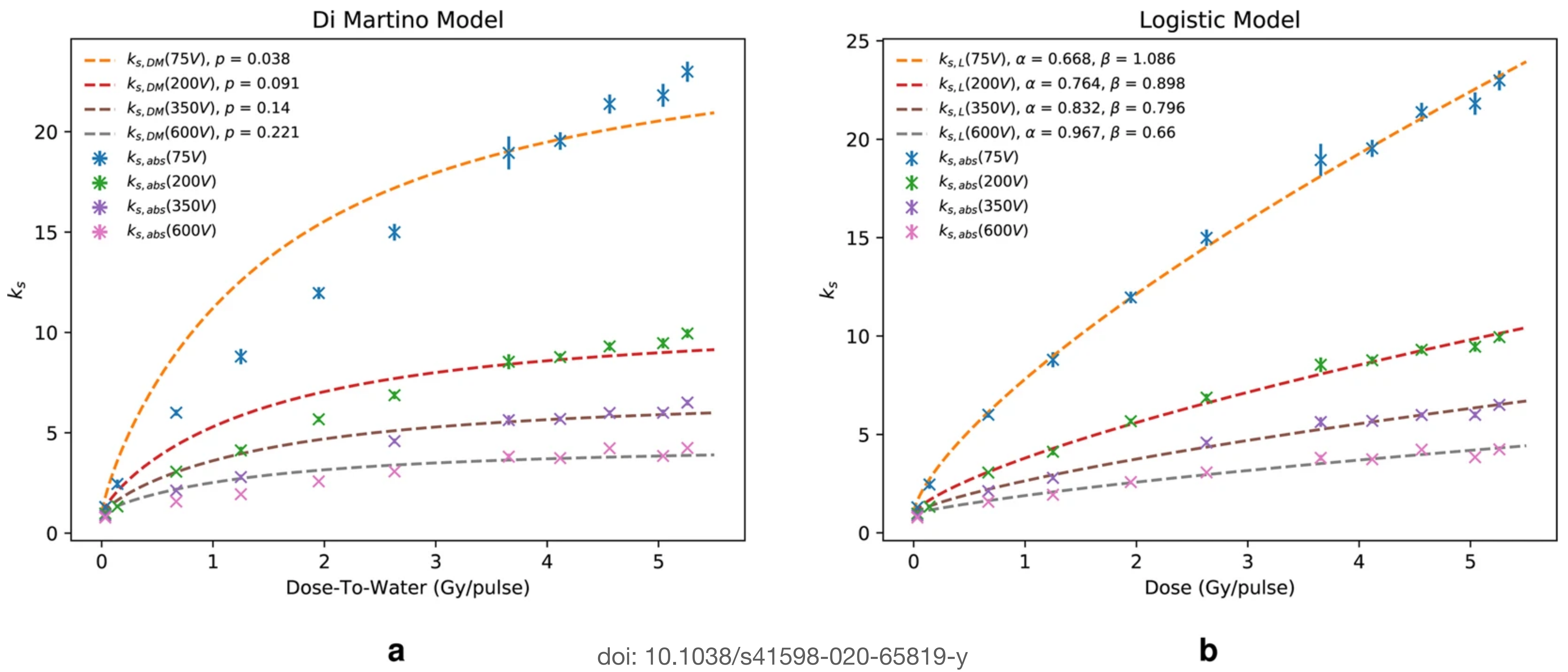
B

Beam Characteristics	CONV	FLASH
Dose Per Pulse D_p	~0.4 mGy	~1 Gy
Dose Rate: Single Pulse $\dot{D}_p$	~100 Gy/s	~10^5 Gy/s
Mean Dose Rate: Single Fraction $\dot{D}_m$	~0.1 Gy/s	~ 100 Gy/s
Total Treatment Time T	~days/minutes	< 500 ms

Backup

Response	Detectors	Measurement type	FLASH study	Instantaneous dose-rate/dose per pulse (D_p) dependence	Spatial resolution	Time-resolution	Energy dependence
Luminescence	TLD/OSLD	**1D,** 2D	e [15, 37, 71]	Independent (~10^9 Gy/s) [80, 137]	~ 1 mm	Passive	Tissue-equivalent
	Scintillators	1D, **2D**, 3D	p [13, 18]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ns	Tissue-equivalent
	Cherenkov	**1D**, 2D, 3D	e [29]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ps	Energy dependent
	FNTD	2D	NA	Independent (~10^8 Gy/s) [85]	~ 1 μm	Passive	Energy dependent
Charge	Ionization chambers	**1D**, **2D**	p [13, 18, 19] e [15, 37, 71] ph [16, 17]	Dependent on D_p [48, 52] (>1 Gy/pulse),	~3–5 mm	~ms	Energy dependence shows up > 2 MeV
	Diamonds	**1D**	p [18]	Dependent on D_p (>1 mGy/pulse) [49]	~ 1 mm	~μs	Tissue-equivalent
	Si diode	**1D**, 2D	NA	Dependent on D_p [54] (Independent ~0.2 Gy/s) [138]	~ 1 mm	~ms	Energy dependent
Chemical	Alanine pellets	**1D**	e [12, 15, 37, 139]	Independent (10^8 Gy/s) [69]	~ 5 mm	Passive	Tissue-equivalent
	Methyl viologen/fricke	**1D**	e [29, 48]	Depends on the decay rate and diffusion of radiation induced species	~ 2 mm	~ns	Tissue-equivalent
	Radiochromic film	**2D**	p [18, 19] e [10–12, 15, 30, 37, 71, 140] ph [16]	Independent (10^9 Gy/s) [70, 71]	~1 μm	Passive	Tissue-equivalent
	Gel dosimeters	3D	NA	Strong dependence below 0.001 Gy/s [141] and above 0.10 Gy/s [142]	~1 mm	Passive	Tissue-equivalent

Backup

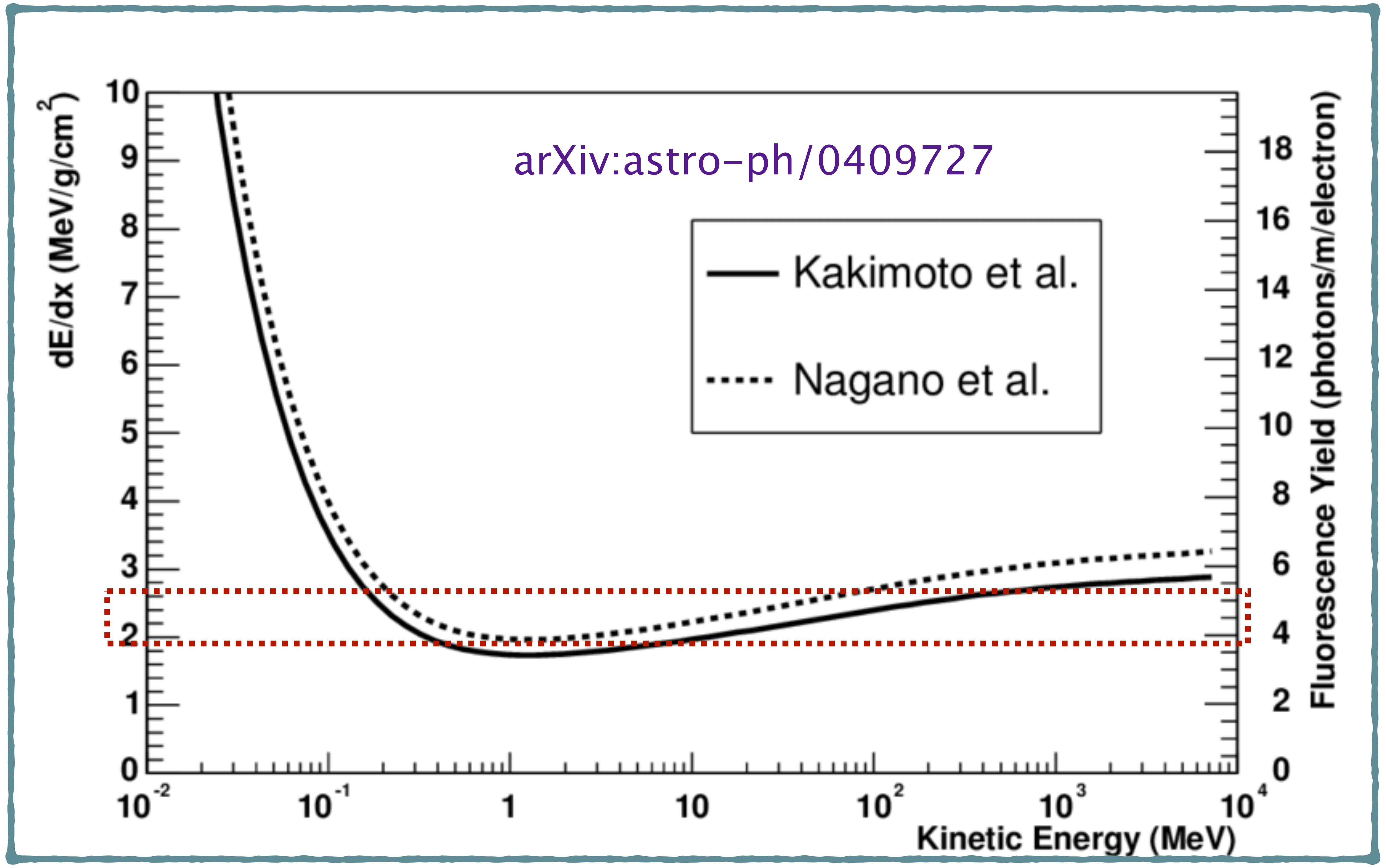


doi: 10.1038/s41598-020-65819-y

Backup

- How many photons we expect at typical IOeRT and VHEE energies?

E_K	ph./m (Fluor.)	ph./m (Ch.)
10 MeV	4 (@4π)	Under thr.
20 MeV	4 (@4π)	6 (@0.1°)
130 MeV	5 (@4π)	70 (@1.4°)



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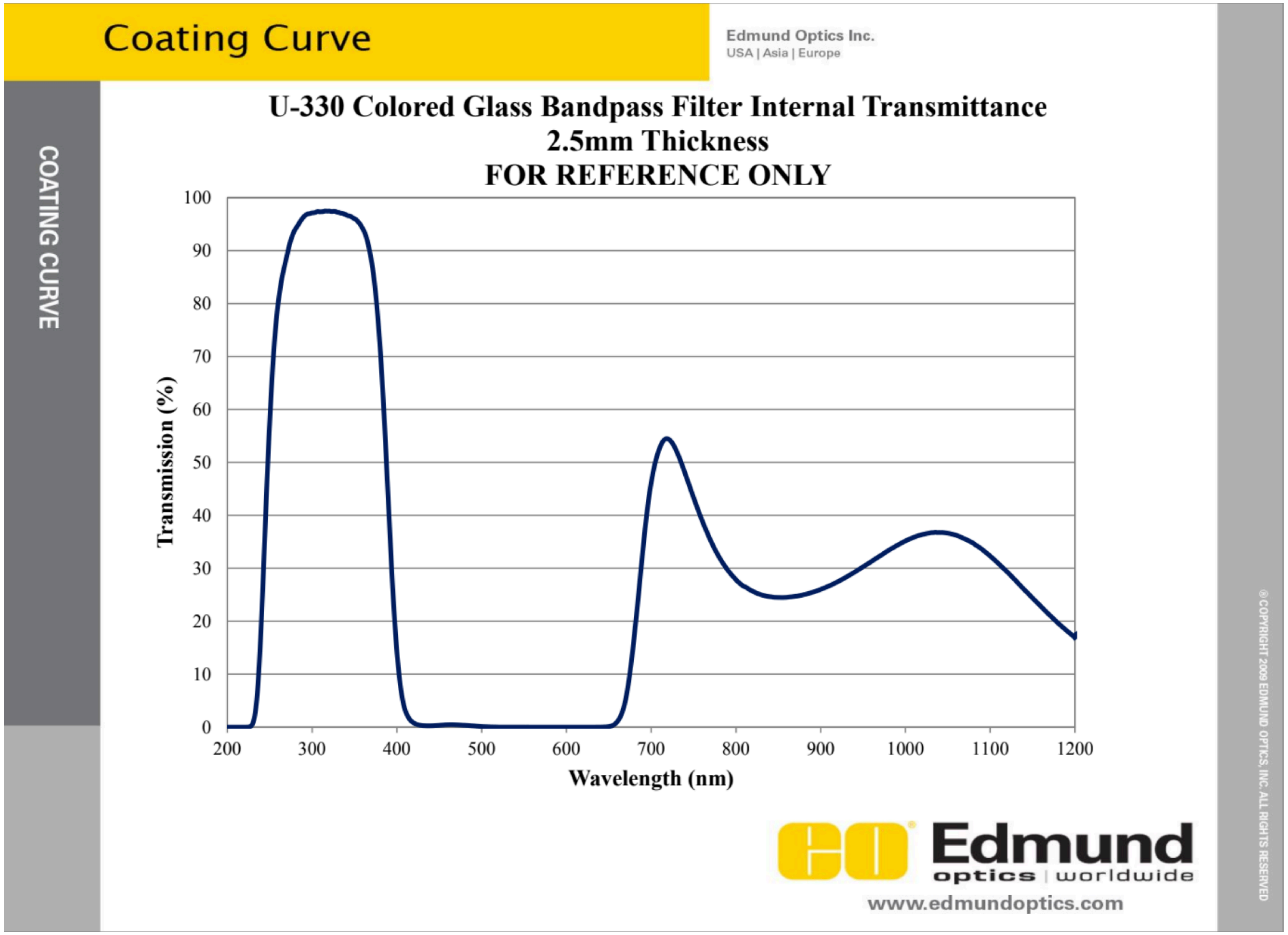

Coating Curve
Edmund Optics Inc.
USA | Asia | Europe
COATING CURVE
U-330 Colored Glass Bandpass Filter Internal Transmittance
2.5mm Thickness
FOR REFERENCE ONLY
Transmission (%)
Wavelength (nm)
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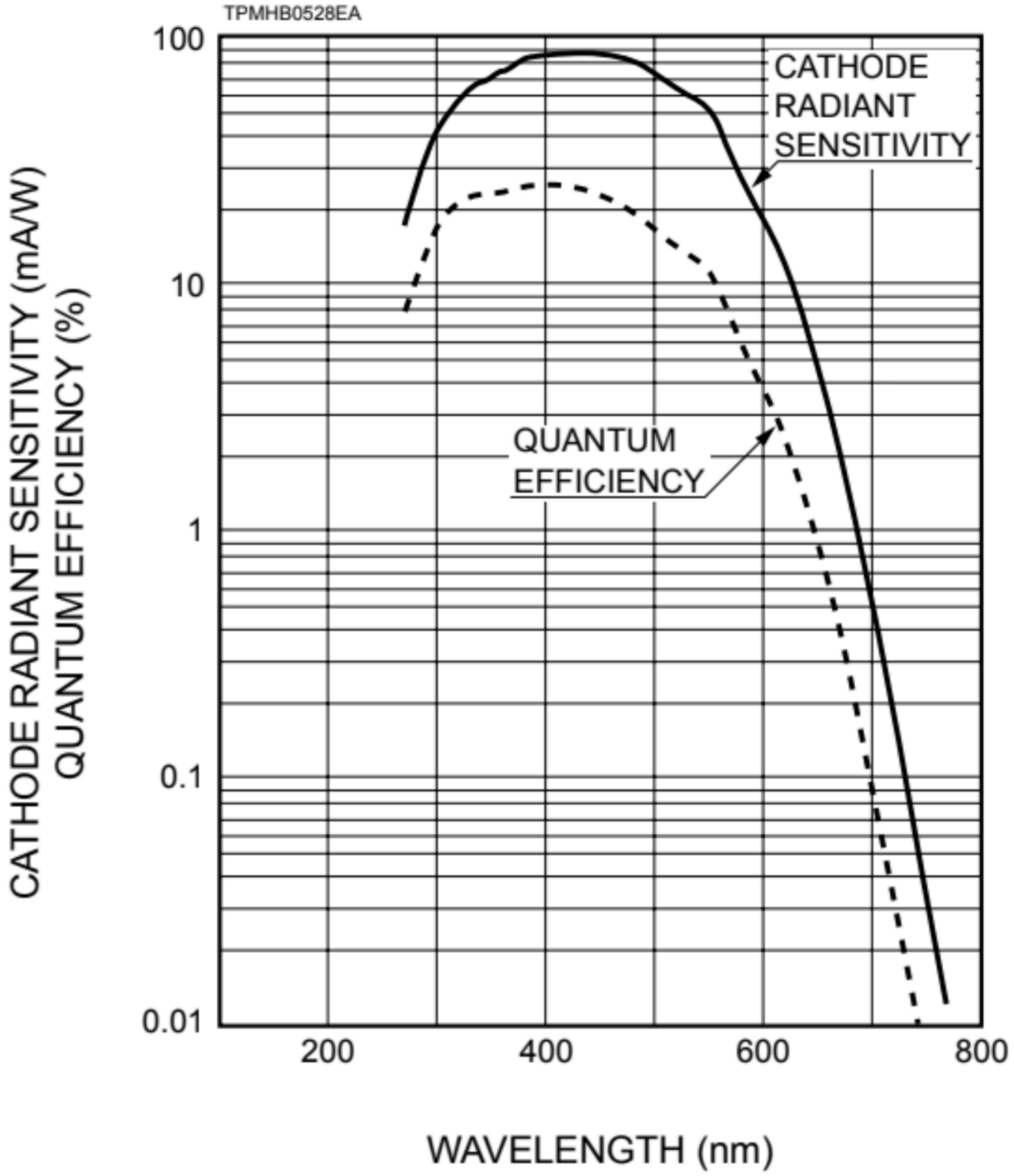

TPMHB0528EA
CATHODE RADIANT SENSITIVITY
QUANTUM EFFICIENCY
CATHODE RADIANT SENSITIVITY (mA/W)
QUANTUM EFFICIENCY (%)
WAVELENGTH (nm)

Backup

- A MC simulation has been developed to perform a model of the detection technique.
- It works well with the expected beam parameters (some of which are not present in the simulation, secondaries and uncertainties in the energy and angular divergence…)
- Introducing the measured parameters in this model we will continue with the optimization of the geometry.