

# Hybrid Compton-PET imaging for ion-range monitoring in hadron-therapy



J. Balibrea-Correa, C. Domingo-Pardo, I. Ladarescu, J. Lerendegui-Marco, I. Ladarescu, A. Tarifeño-Saldivia

IFIC (CSIC-UV)

C. Guerrero, M.C. Jimenez, J.M. Quesada, T. Rodriguez-González

University of Seville / Centro Nacional de Aceleradores

V. Babiano-Suarez, F. Calviño, M. Pallás

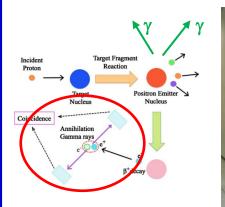
UPC-Barcelona

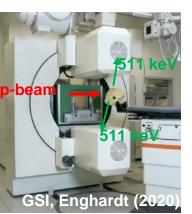
Thanks to the Organizing committee Antonio Fernández Prieto Dolores Cortina Gil Iris García Rivas José Benlliure Anaya Pablo Cabanelas Eiras Pablo Vázquez Regueiro

César Domingo-Pardo, IGFAE Workshop Proton-Therapy, Santiago de Compostela, May 2023

## PET monitoring, pros & cons

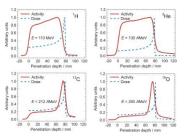
## Prompt-Gamma Imaging, pros & cons



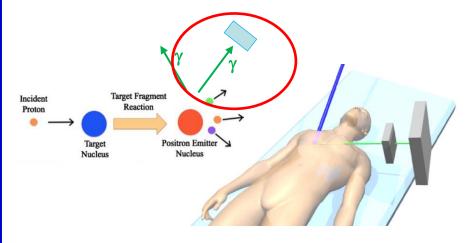


- → Range verification via PET (Llacer, 1979)
- Delayed (biological washout, organ motion...)
- Not directly coinciding with the Bragg peak
- Low counting statistics (10 Bq/ml) → Low efficiency
- Sensitive to tissue stoichiometry and mass density
- Functional character: physiological processes and tumour RF
- Excellent sensitivity (1.3 mm, 50ms, 10<sup>8</sup>p) and tomographic functionality (KVI-Group, Siemens PET heads, <sup>12</sup>N, <sup>13</sup>O, b+ 10ms Ozoemelam 2020)

#### Dresden, Enghardt (2020)



Prev. Talks by: Laura Moliner (I3M), Antoni Rucinski (CCB), A. Espinosa, C. Guerrero (USe)

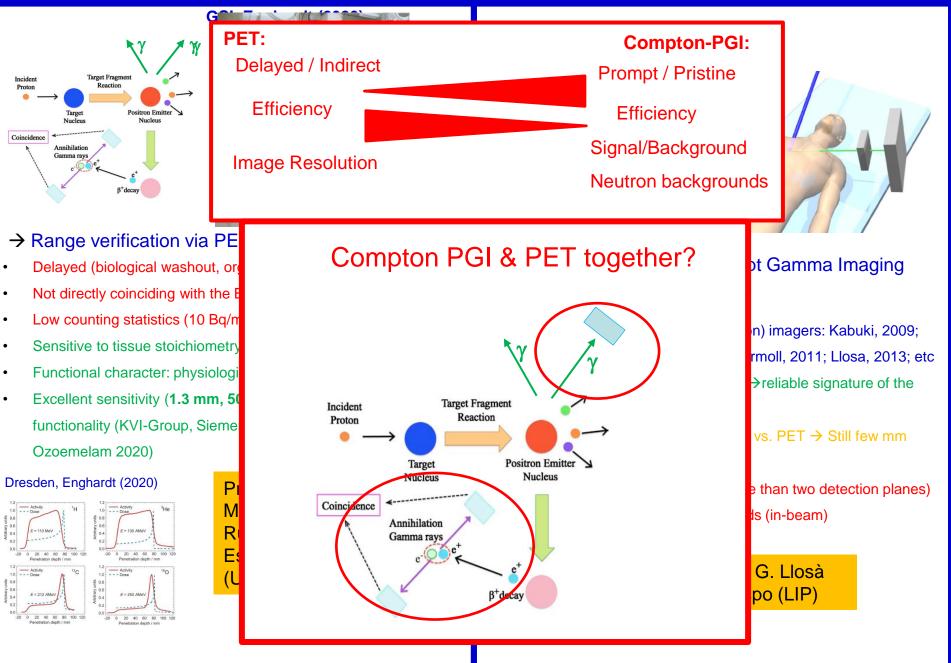


- → Range verification via Prompt Gamma Imaging (Stichelbault&Jongen, 2003)
- Most advanced electronic (Compton) imagers: Kabuki, 2009;
   Richard, 2012; Peterson, 2010; Kormoll, 2011; Llosa, 2013; etc
- High g-ray yield at the Bragg peak→reliable signature of the ion-range
- Limited intrinsic imaging resolution vs. PET → Still few mm range-shift feasible
- Low efficiency (particularly for more than two detection planes)
- Large neutron-induced backgrounds (in-beam)

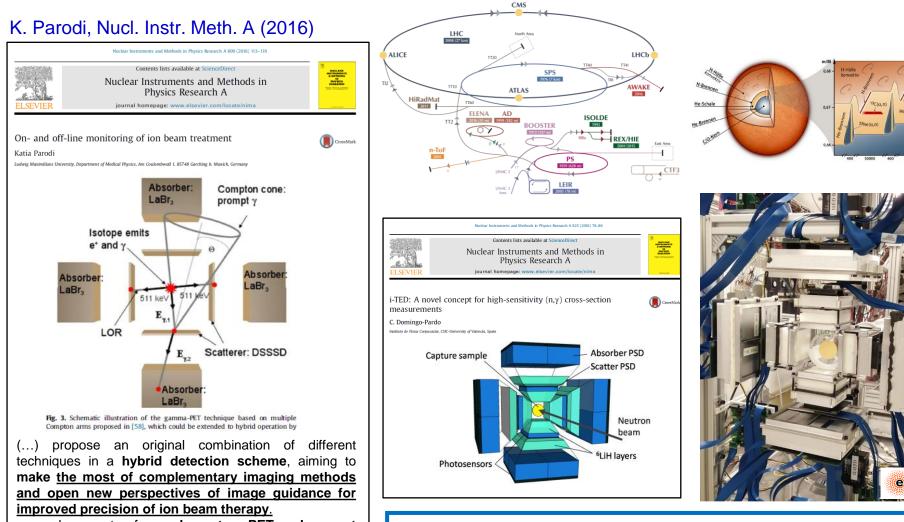
Prev. Talks by G. Llosà (IFIC), P. Crespo (LIP)

## PET monitoring, pros & cons

## Prompt-Gamma Imaging, pros & cons



## Hadron therapy: concept of hybrid Compton-PET imaging for ion-range verification



...novel concepts of complementary PET and prompt gamma imaging in a so called hybrid detection scheme. As already observed in [58], a possible solution would be a combination of multiple Compton camera arms offering sufficient solid angle over- age and using opposite single detector layers to serve as Compton camera scatterers or PET coincidence identifiers, complemented by additional absorbers for Compton imaging or total energy check in PET operation (Fig. 3). ...
High detection efficiency (500 cm<sup>2</sup> PSDs) → Online real-time range verification
Low sensitivity to n-induced backgrounds (LaCl<sub>3</sub>, <sup>6</sup>LiPE) → Improved S/B-ratio
Good performance in the g-ray energy range up to 5-6 MeV (thick crystals)
Compact & lightweight (TOFPET-ASICs) → Compatible with clinical environment

#### HYMNS ERC-CoG https://cordis.europa.eu/project/id/681740

## Hadron therapy: concept of hybrid Compton-PET imaging for ion-range verification

## K. Parodi, Nucl. Instr. Meth. A (2016)

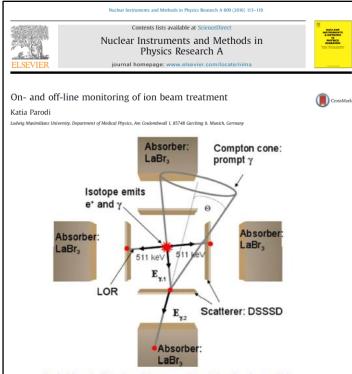
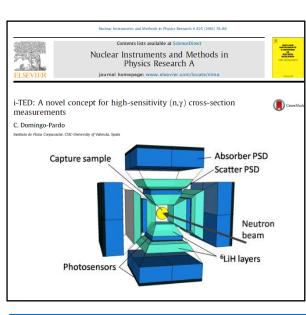
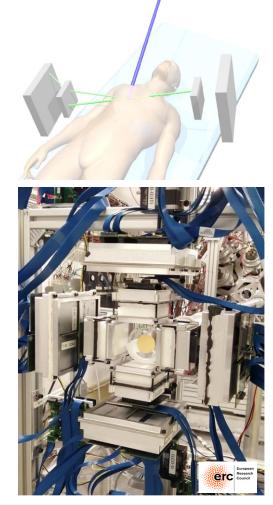


Fig. 3. Schematic illustration of the gamma-PET technique based on multiple Compton arms proposed in [58], which could be extended to hybrid operation by

(...) propose an original combination of different techniques in a hybrid detection scheme, aiming to make the most of complementary imaging methods and open new perspectives of image guidance for improved precision of ion beam therapy.

...novel concepts of **complementary PET and prompt gamma imaging** in a so called hybrid detection scheme. As already observed in [58], a possible solution would be a combination of multiple Compton camera arms offering sufficient solid angle over- age and using opposite single detector layers to serve as Compton camera scatterers or PET coincidence identifiers, complemented by additional absorbers for Compton imaging or total energy check in PET operation (Fig. 3). ... Applicable to ionrange monitoring in proton-therapy?





- High detection efficiency (500 cm<sup>2</sup> PSDs)  $\rightarrow$  Online real-time range verification
- Low sensitivity to n-induced backgrounds (LaCl<sub>3</sub>, <sup>6</sup>LiPE) → Improved S/B-ratio
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## Hadron therapy: concept of hybrid Compton-PET imaging for ion-range verification

#### J.Krimmer' Review on PGI, 2018:



#### 2.3. Specificity of PG imaging

Table 2 presents the specificities of PG cameras for hadrontherapy with respect to conventional medical imaging. It is clear from these specificities that dedicated cameras are needed, with special features like high energy detection capability and count rate capability, and data acquisition systems that have to be adapted to the beam time structure.

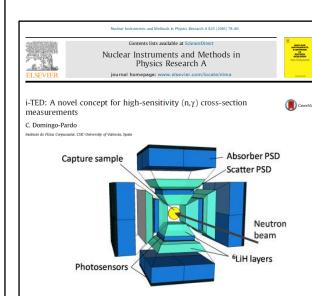
For the particular objective of the precision for the falloff determination in the 1D-profile, the background plays a major role. Indeed, if we describe the falloff features in terms of contrast C, falloff width FW and background level B, it has been shown that the falloff retrieval precision FRP is determined by the following equation for homogeneous targets [32]:

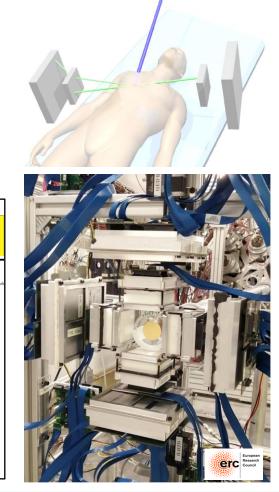
$$FRP = \frac{\sqrt{B}}{C} = \frac{1}{\sqrt{N}} \tag{1}$$

where N is the number of incident ions. A striking result is that the falloff width has no influence on the *FRP*. This means that the priority when optimizing camera designs is the detection efficiency and the background rejection (shielding, TOF,...).

As we will see in Section 4, detection efficiencies of PG cameras – ranging from  $10^{-5}$  (collimated cameras) to  $10^{-4}$  (Compton cameras) – will lead to relatively low numbers of detected PG at spot level for pencil beam scanning systems.

Applicable to ionrange monitoring in proton-therapy?





- High detection efficiency (500 cm<sup>2</sup> PSDs) → Online real-time range verification
- Low sensitivity to n-induced backgrounds (LaCl<sub>3</sub>, <sup>6</sup>LiPE) → Improved S/B-ratio
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#### HYMNS ERC-CoG https://cordis.europa.eu/project/id/681740



Time (s)

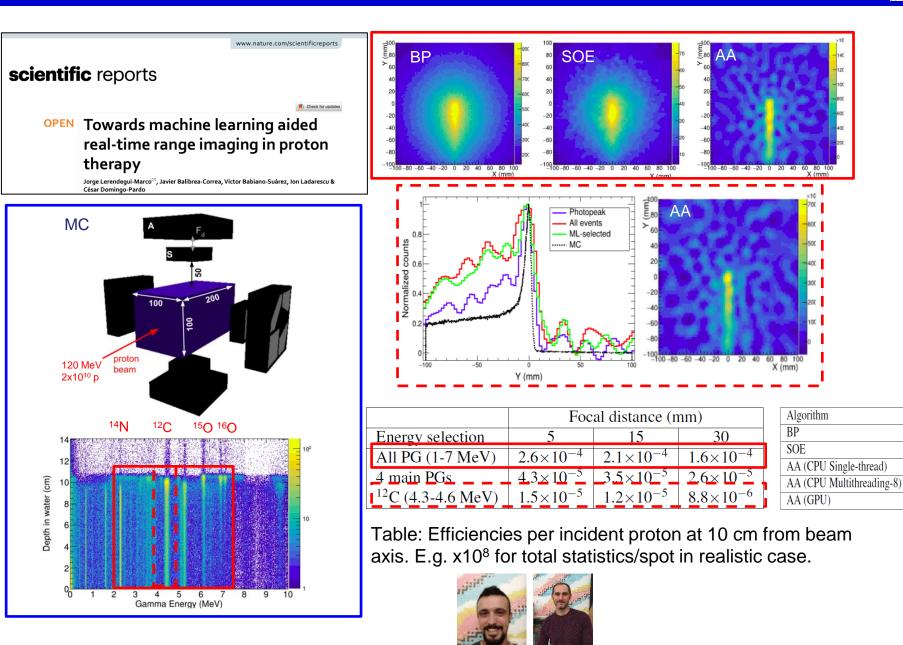
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14

1821

260

15

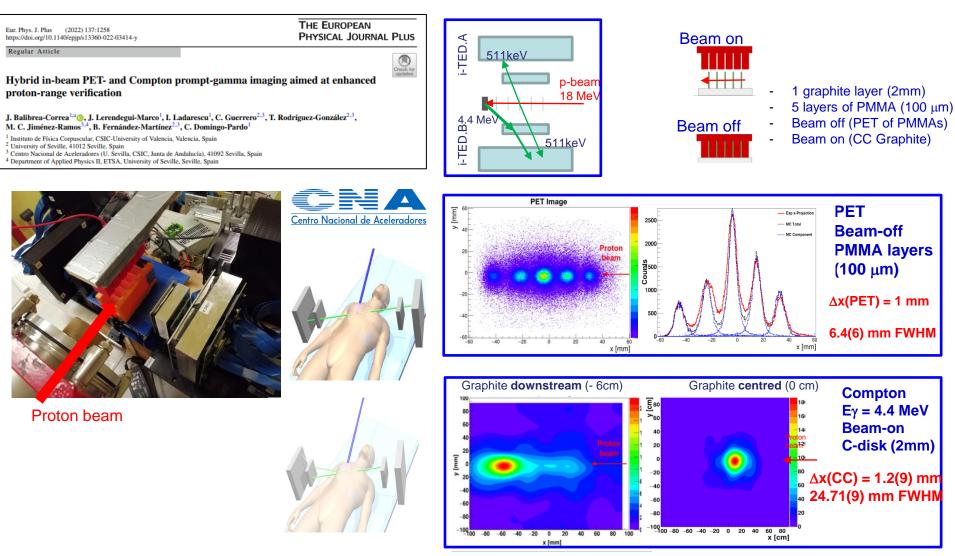


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## Hybrid Compton-PET imaging: first Proof-of-Concept measurements at CNA-Seville

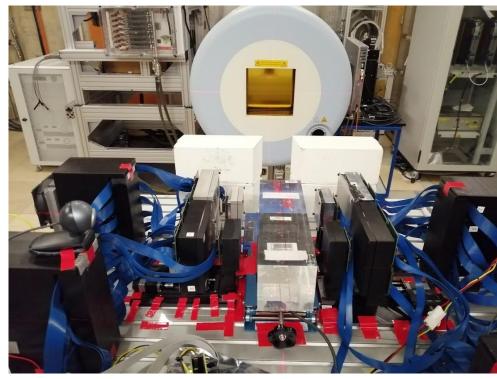




→ First experimental demonstration of in-room hybrid Compton-PET concept with proton beams

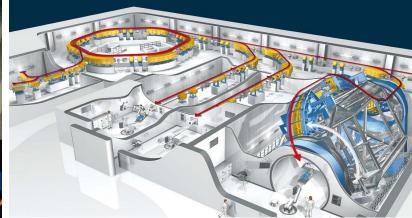
J. Balibrea-Correa et al., Eur. Phys. Jour. Plus 137 (2022).

## First hybrid Compton-PET imaging with i-TED in clinical conditions at HIT Heidelberg

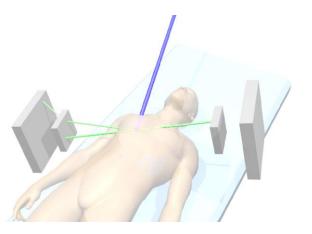


Heidelberg Hadrontherapy Center

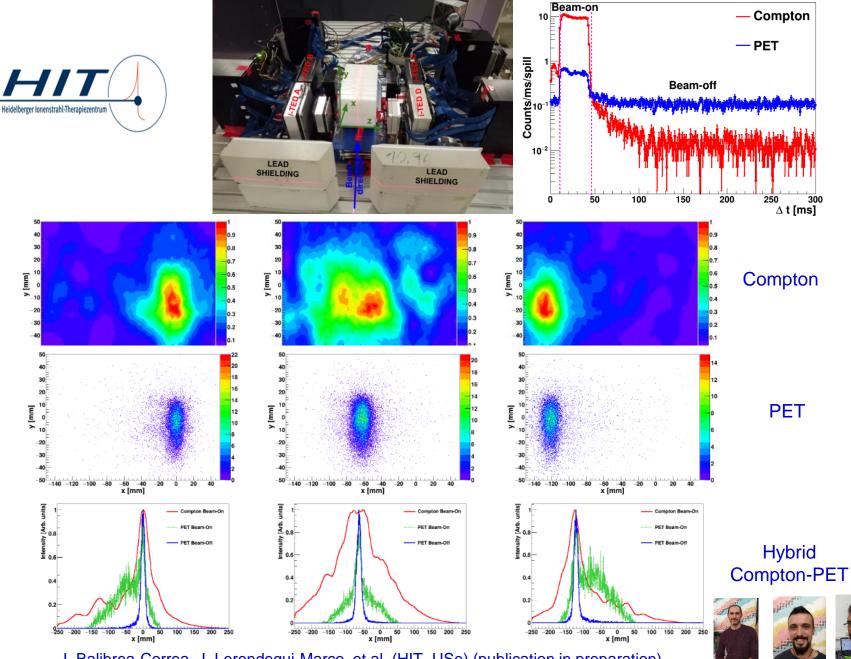




- → Clinical proton-beam energy (50-200 MeV)
- → Clinical proton-intensity (2x10<sup>9</sup> p/point)



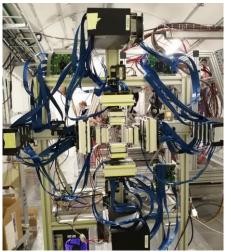
## First hybrid Compton-PET imaging with i-TED in clinical conditions at HIT Heidelberg



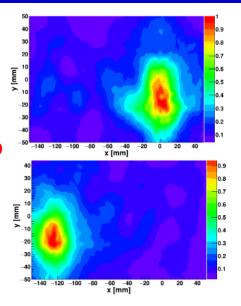
J. Balibrea-Correa, J. Lerendegui-Marco, et al. (HIT, USe) (publication in preparation)

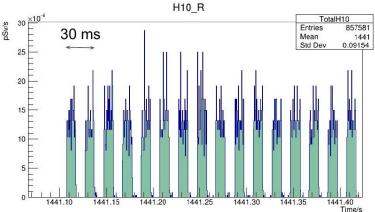
# Next steps: Hybrid Compton-PET and "multimessenger" approach: combining gamma-rays and neutrons MCIN-PDC2021-12536-C21

### 4x i-TED CCs in cross-config:









Prev. Talk by A. Tarifeño "Neutron dosimetry in particle therapy facilities: status of the LINrem project"

- Next measurements planned at Quironsalud, Madrid in july 2023,
- Future access to an
  experimental protontherapy room, like the one
  foreseen at Santiago dC,
  would be an excellent
  opportunity!

## **ICPO**

Collimator: Brass collimator 65mm thickness and 55 mm circular aperture Phantom: 34×40×35 cm<sup>3</sup> water phantom Clinical dose: 3.5 Gy at the entrance of the phantom Energies: 100, 150 and 200 MeV Time structure: spots 10 ms width, 10 ms beam-off (approx)

## **Summary & Outlook**

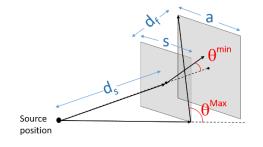
- We have developed an array of four Compton cameras optimized for high detection sensitivity and low neutron-induced backgrounds, whith potential applications in ion-range monitoring for proton-therapy treatments
- MC Simulations [Lerendegui22], as well as previous review studies (Krimmer'18) show the relevance of large efficiency and low neutron backgrounds to aim for real-time ion-range monitoring
- First proof-of-concept measurements for the hybrid Compton-PET approach [Parodi2016] have been carried out with two CCs in front-to-front configuration at the CNA cyclotron using 18 MeV proton beam, delivering excellent results for both PET and Compton imaging [Balibrea23]
- Measurements have been made with four CCs in front-to-front configuration at HIT Heidelberg, using p-, He- and C-beams at clinical energies and intensities. Data analysis is in progress and preliminary results are quite satisfactory.
- Next steps involve new measurements (in plan at Quironsalud in july 2023 at Madrid), thereby aiming at four CCs in cross-configuration and time-synchronization with <sup>3</sup>He-based neutron dosimeters (LINrem) for exploring the interplay between primary and secondary dose
  - A dedicated experimental proton-therapy room at Santiago de Compostela would be highly beneficial for future R+D+I works and developments!!!

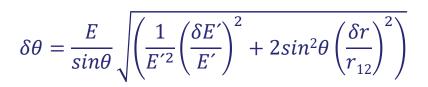




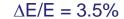
# **Backup slides**

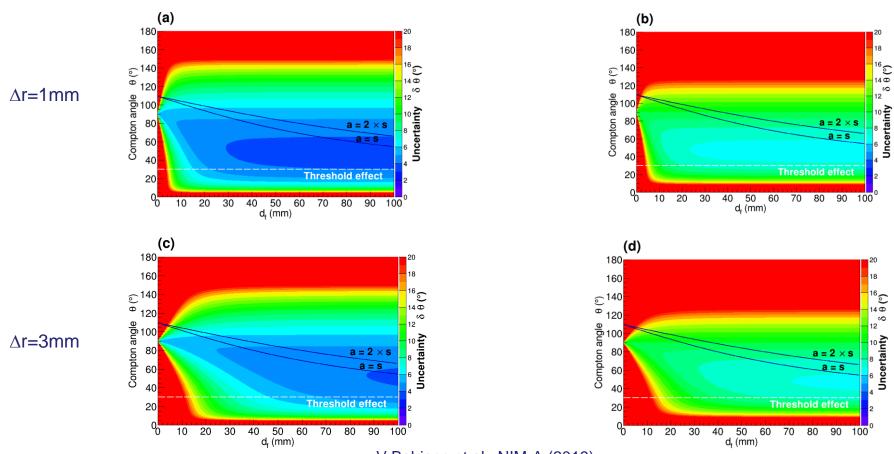
## i-TED requirements for $(n,\gamma)$ experiments with enhanced S/B-ratio





 $\Delta E/E = 6.5\%$ 

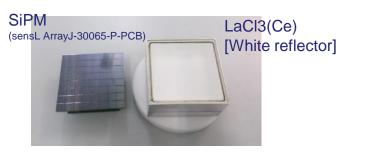




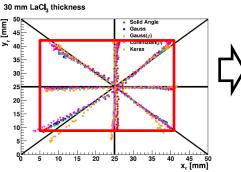
V.Babiano et al., NIM-A (2019)

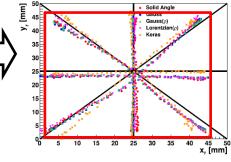






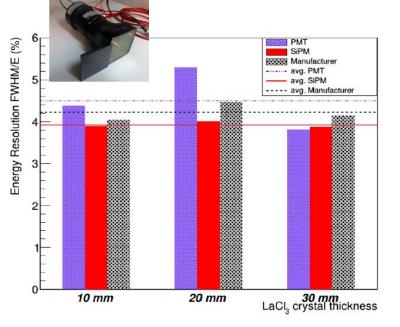
<∆E/E> = 4.5% @ 662keV

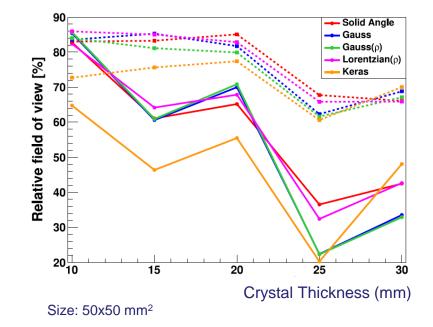




30 mm LaCl<sub>3</sub> thickness

#### Support Vector Machine (linear kernel) Python sklearn-learn

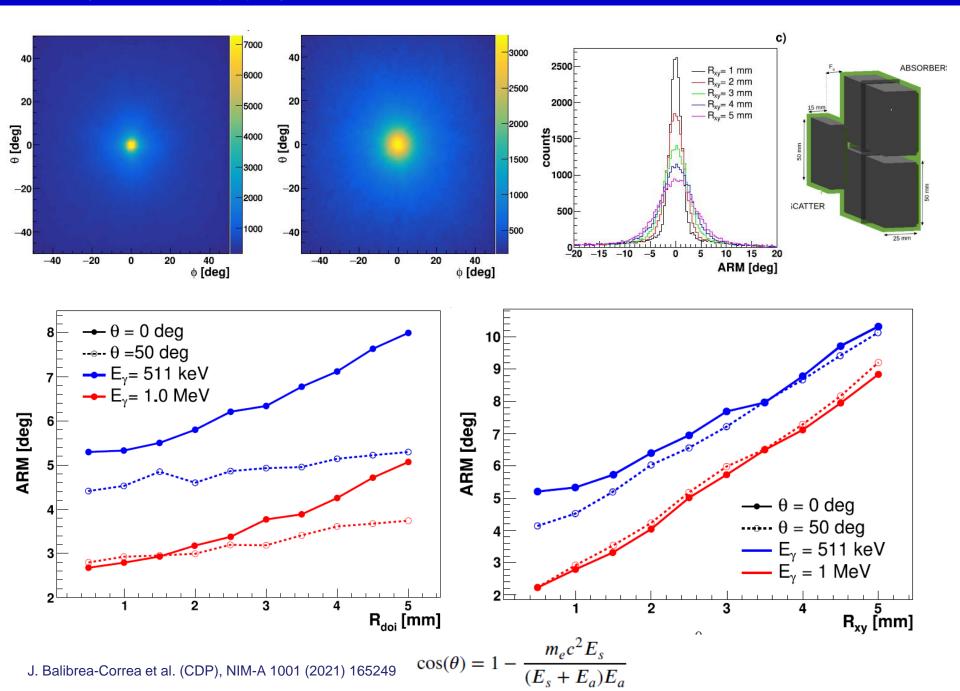






## P. Olleros et al., JINST 13-P03014 (2018) P.Olleros, TFM@HYMNS, Avail. https://hymnserc.ific.uv.es

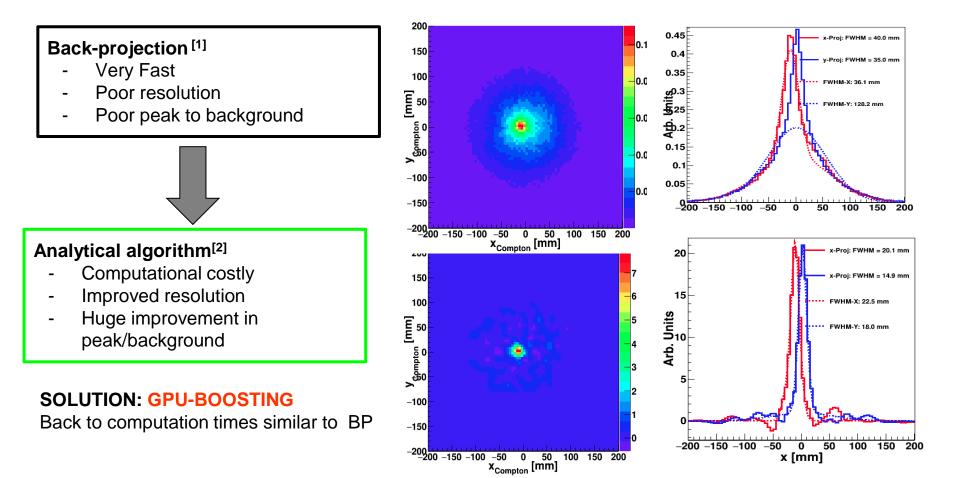
#### i-TED requirements for $(n,\gamma)$ experiments with enhanced S/B-ratio







## Na-22 source, 1274 keV peak, i-TED @ 100 mm



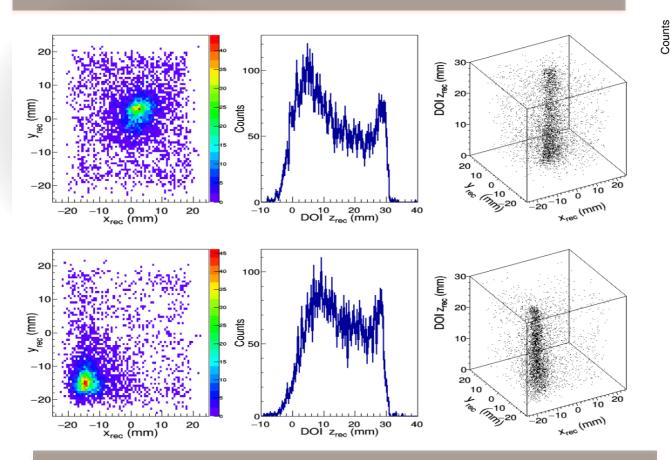
 $ARM(BP) = 11^{\circ} \rightarrow ARM(AA) = 5^{\circ}$ 

[1] Wilderman, S. J., et al. DOI:10.1109/NSSMIC.1998.773871 (1998) [2] Tomitani et al., DOI: 10.1088/0031-9155/47/12/309 (2002)

## i-TED: intrinsic position resolution $\Delta r$ FWHM / DOI

reconstructed Dol coordinates for the central scan position

# Dol





450

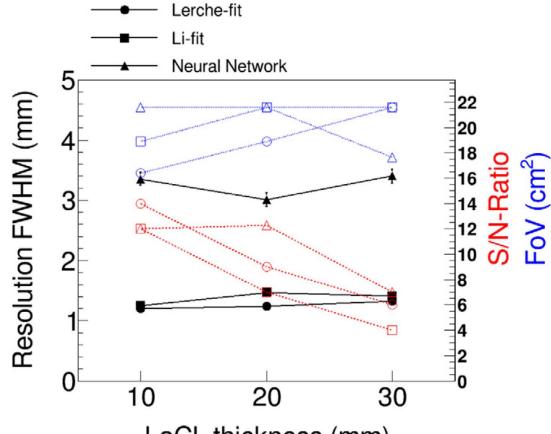
400 350 300 250 200 150 100 50 -10 -5 5 10 15 20 25 30 35 40 n Dol z<sub>rec</sub> (mm) The measured values for Aw at half maximum

The measured values for Aw at half maximum (already calibrated) are compared against MC calculated Dols and true or ideal simulated Dol values.

reconstructed Dol coordinates for a peripheral scan position

V.Babiano et al, NIM-A 931 (2019)

## i-TED: intrinsic position resolution $\Delta r$ FWHM / SUMMARY & COMPARISON



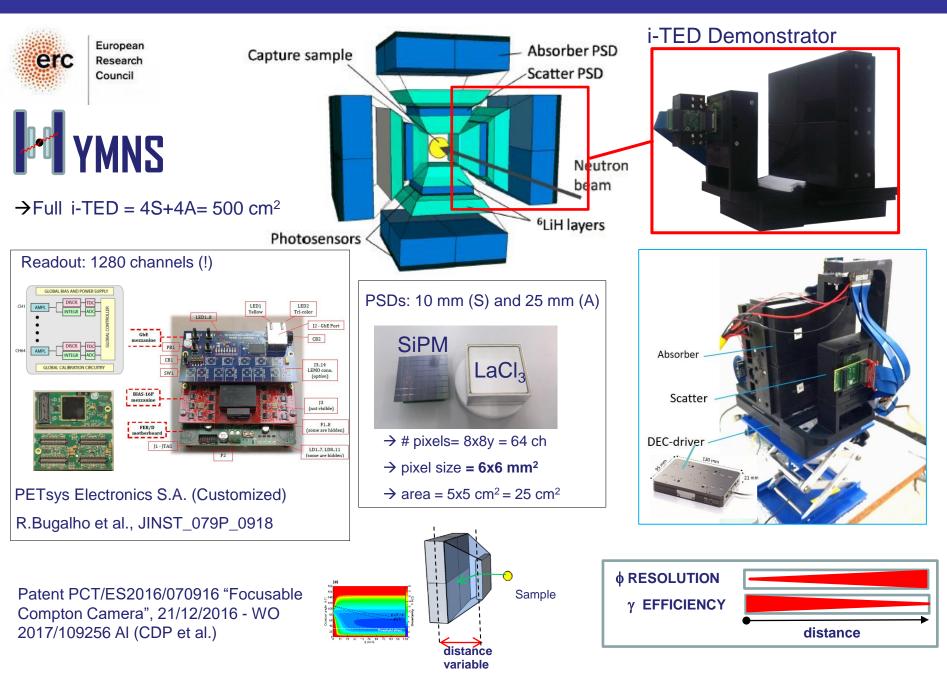
LaCl<sub>3</sub> thickness (mm)

Model	Crystal size (mm <sup>3</sup> )	Resolution (FWHM) <sub>x,y</sub> (mm)	RMS $r_{rec} - r_{true}$ (mm)	FoV (cm <sup>2</sup> )	S/N-ratio
Lerche	$\begin{array}{c} 50 \times 50 \times 10 \\ 50 \times 50 \times 20^{a} \\ 50 \times 50 \times 30^{a} \end{array}$	1.20(15) 1.24(10) 1.32(20)	0.84(19) 0.69(8) 0.86(13)	15.2 18.9 21.6	14(3) 9(2) 6(2)
Li	$50 \times 50 \times 10$ $50 \times 50 \times 20^{a}$ $50 \times 50 \times 30^{a}$	1.24(10) 1.46(12) 1.43(12)	0.86(23) 0.67(4) 0.88(16)	18.9 21.6 21.6	12(5) 7(3) 4(2)

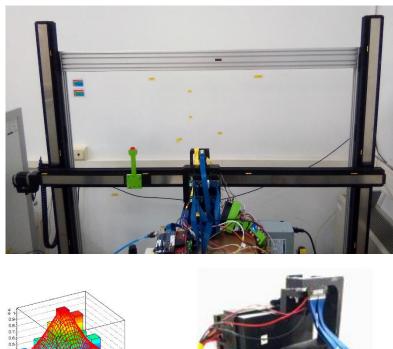
Crystal size (mm <sup>3</sup> )	Resolution $\langle PWHM \rangle_{(x,y)}$ (mm)	$\frac{r_{rec}}{r_{rec}} - r_{true}$ (mm)	FoV (cm <sup>2</sup> )	S/N-ratio
$50 \times 50 \times 10$	3.35(11)	0.86(7)	21.6	12.0(2)
$50 \times 50 \times 20$	3.01(11)	0.83(6)	21.6	12.3(4)
50  imes 50  imes 30	3.4(11)	0.94(16)	17.6	7.0(4)

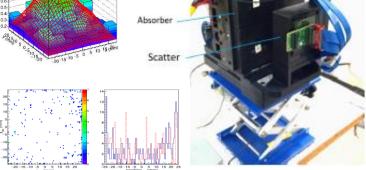
V.Babiano et al, NIM-A 931 (2019)

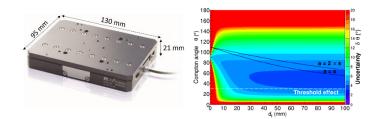
## HYMNS: High sensitivitY Measurements of key stellar Nucleo-Synthesis reactions



## i-TED Total Energy Detector with $\gamma$ -ray imaging capability







### Back-projection Compton test:

200

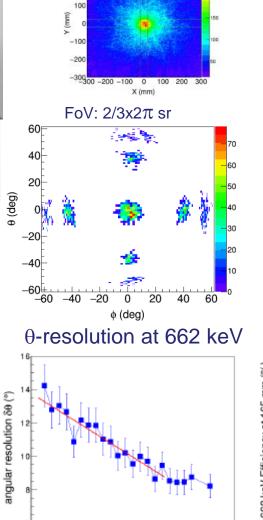
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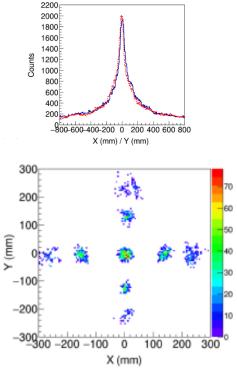
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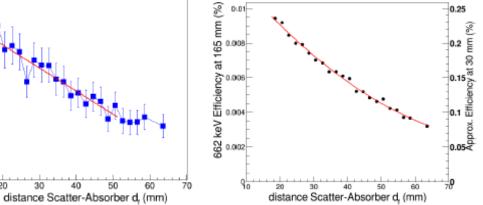
50

60





## Efficiency at 662 keV



V.Babiano et al., NIM-A (in review, 2019)



 $10^{3}$ 

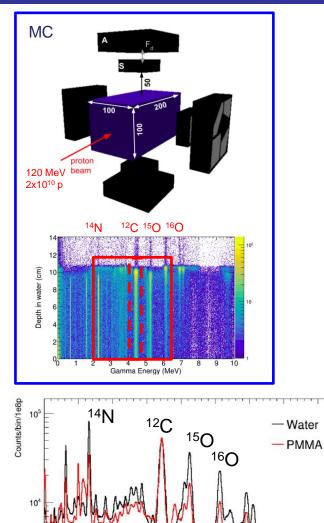
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3

4

## i-TED applied to Hadron Therapy: A MC viewpoint





Target	$\gamma$ energy (MeV)	Assignments	Other data
<sup>16</sup> O	1.89	<sup>16</sup> O( <i>p</i> , <i>pp</i> γ <sub>1.89</sub> ) <sup>15</sup> N	
	2.0	$^{16}O(p, x\gamma_{2.04})$ $^{15}O$	
		$^{16}O(p, x\gamma_{2.00})$ $^{11}C$	
	2.31	${}^{16}O(p, x\gamma_{2.31}) {}^{14}N$	(Foley et al 1962)
			(Lang et al 1987)
	2.8	${}^{16}O(p, p'\gamma_{2.74}) {}^{16}O$	(Lang et al 1987)
		${}^{16}\mathrm{O}(p, x\gamma_{2.79}) {}^{14}\mathrm{N}$	(Kiener et al 1998)
		$^{16}O(p, x\gamma_{2.80})$ $^{11}C$	
		$^{16}O(p, x\gamma_{2.87})$ $^{10}B$	
	3.68	$^{16}O(p, x\gamma_{3.68})$ $^{13}C$	
	4.44	$^{16}O(p, x\gamma_{4.44})$ $^{12}C$	(Foley et al 1962)
		4,7,1,	(Lang et al 1987)
			(Belhout et al 2007)
	5.2	$^{16}O(p, x\gamma_{5.24})$ <sup>15</sup> O	(Foley <i>et al</i> 1962)
		<sup>16</sup> O( <i>p</i> , <i>pp</i> γ <sub>5.27</sub> ) <sup>15</sup> N	(Lang et al 1987)
		$^{16}O(p, x\gamma_{5.18})$ <sup>15</sup> O	(Belhout et al 2007)
		$^{16}O(p, pp\gamma_{5.30})$ $^{15}N$	
	6.1	${}^{16}O(p, p'\gamma_{6.13}) {}^{16}O$	(Foley et al 1962)
		$^{16}O(p, x\gamma_{6.18})$ $^{15}O$	(Narayanaswamy et al 1981)
		4, 10,105	(Lang et al 1987)
			(Kiener et al 1998)
			(Belhout et al 2007)
	6.32	${}^{16}O(p, x\gamma_{6.32}) {}^{15}N$	
	7.0	${}^{16}O(p, p'\gamma_{6.92}) {}^{16}O$	(Foley et al 1962)
		${}^{16}\mathrm{O}(p, p'\gamma_{7.12}) {}^{16}\mathrm{O}$	(Kiener et al 1998)
<sup>12</sup> C	2.0	${}^{12}C(p, x\gamma_{2,00}) {}^{11}C$	(Clegg <i>et al</i> 1961)
			(Lang et al 1987)
	2.1	<sup>12</sup> C( <i>p</i> , <i>pp</i> γ <sub>2.12</sub> ) <sup>11</sup> B	(Lang et al 1987)
		$^{12}C(p, x\gamma_{2.15})$ $^{10}B$	
	2.8	${}^{12}C(p, x\gamma_{2.80}) {}^{11}C$	
		${}^{12}C(p, x\gamma_{2.87}) {}^{10}B$	
	4.44	${}^{12}C(p, p'\gamma_{4,44}) {}^{12}C$	(Clegg et al 1961)
		4 / 1 /	

5

6

8 9 10 γ-ray energy [MeV])

J.M. Verburg, J.Seco, Phys. Med. Biol (2014)

 ${}^{12}C(p, x\gamma_{4.80}) {}^{11}C$ 

4.80

(Lang et al 1987)

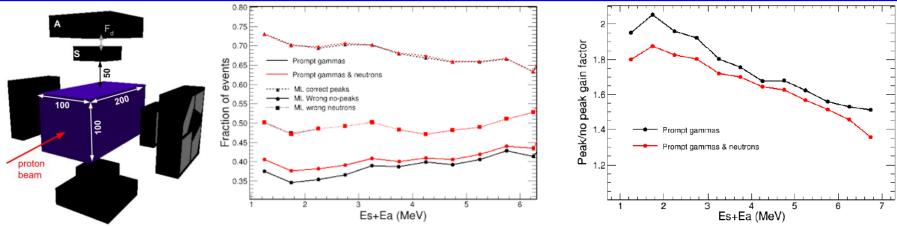
(Kiener et al 1998)

(Belhout et al 2007)

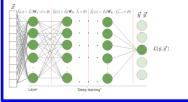


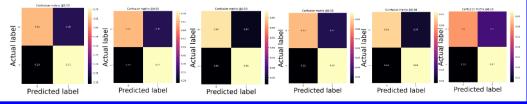


- High detection efficiency, high CR-capability → Real time
- Low sensitivity to n-induced backgrounds → Improved S/B-ratio
- Good E- and spatial resolution → Few mm accuracy
- Suitable performance in the gamma-ray energy range up to 5-6 MeV
- Compact & lightweight → Compatible with clinical environment



- →Best ML algorithms Boosted Decision Trees (XGBoost) and ANN (Tensorflow), out of kNN, Logistic Regression, SVM, Gaussian Naive Bayes, RandomForest, AdaBoost and Quadratic Discriminant Analysis
- Trained with 5x10<sup>10</sup> γ-rays in 200keV-7MeV Energy range, using r1(x1,y1,z1), r2(x2,y2,z2), E1, E2, Compton angle, KN-formula
- →Classifier Output: 0 (Non FEE) or 1 (FEE)
- →Accuracy between 65% (6MeV) and 73% (1MeV), Confussion: 35-40% of Non FEE predicted as FEE.
- →S/N ratio enhanced between 1.5 and 2.1
- →Capable of rejecting 50% of neutron events (neutron sensitivity)





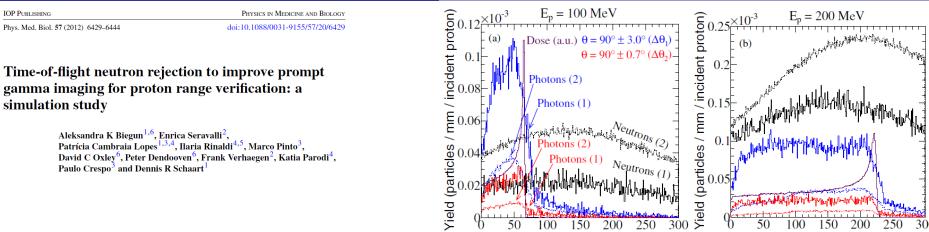
J. Lerendegui, J. Balibrea, et al. (CDP), Nat. Scientific Reports, 2021



IOP PUBLISHING

### Neutrons in HT: the role of a CC optimized for low neutron sensitivity





50

100

50

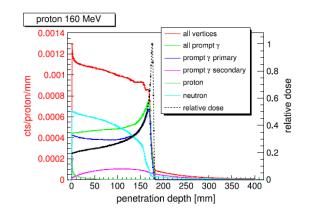
z (mm)

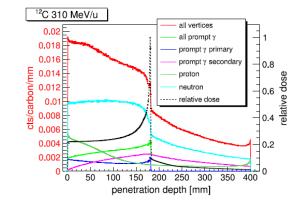
200

250

300

#### J. Krimmer et al. NIM-A (2018)





50

100

150z (mm)

200

250

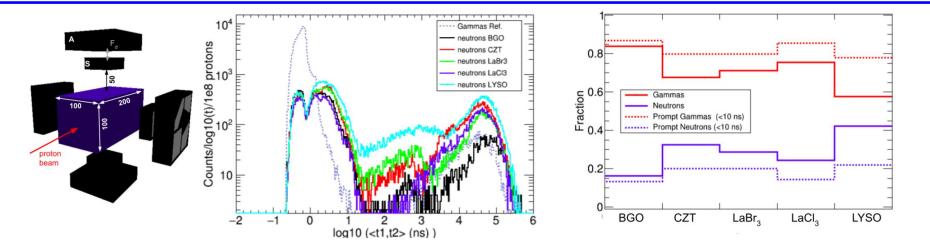
300

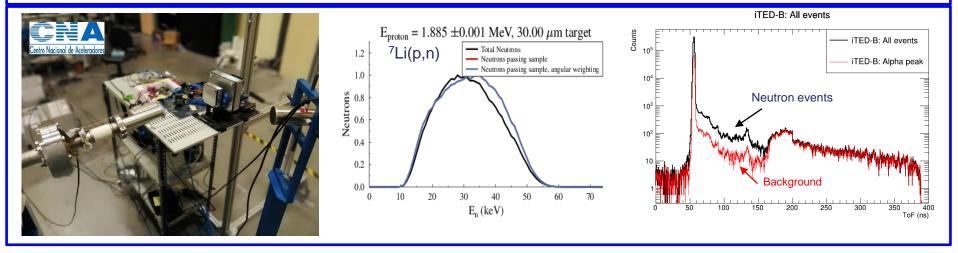
Fig. 1. Emission vertices of secondaries with energies larger than 1 MeV emerging from a water target (cylinder with 15 cm diameter, 40 cm length) irradiated by a 160 MeV proton beam.

Fig. 2. Same as Fig. 1, for 310 MeV/u carbon ion beam.

## i-TED applied to HT: A MC constrasted with neutron measurements at CNA-Seville

- High detection efficiency, high CR-capability → Real time
- Low sensitivity to n-induced backgrounds → Improved S/B-ratio
- Good E- and spatial resolution → Few mm accuracy
- Suitable performance in the gamma-ray energy range up to 5-6 MeV
- Compact & lightweight  $\rightarrow$  Compatible with clinical environment









#### 2.3. Specificity of PG imaging

Table 2 presents the specificities of PG cameras for hadrontherapy with respect to conventional medical imaging. It is clear from these specificities that dedicated cameras are needed, with special features like high energy detection capability and count rate capability, and data acquisition systems that have to be adapted to the beam time structure.

For the particular objective of the precision for the falloff determination in the 1D-profile, the background plays a major role. Indeed, if we describe the falloff features in terms of contrast C, falloff width FW and background level B, it has been shown that the falloff retrieval precision FRP is determined by the following equation for homogeneous targets [32]:

$$FRP = \frac{\sqrt{B}}{C} = \frac{1}{\sqrt{N}} \tag{1}$$

where N is the number of incident ions. A striking result is that the falloff width has no influence on the *FRP*. This means that the priority when optimizing camera designs is the detection efficiency and the background rejection (shielding, TOF,...).

As we will see in Section 4, detection efficiencies of PG cameras – ranging from  $10^{-5}$  (collimated cameras) to  $10^{-4}$  (Compton cameras) – will lead to relatively low numbers of detected PG at spot level for pencil beam scanning systems.

Precision for the falloff determination in 1D profile C = contrast FW = Falloff width B = Background level

# **Falloff Retrieval Precision:** EPD = $B^{1/2}/C = 1/N^{1/2}$

 $FRP = B^{1/2}/C = 1/N^{1/2}$ 

[→ Falloff width has no impact → (non Bragg-peak PGs and broad e+ distributions (PET) are ok)]

Key aspects of CC for PGI in HT:

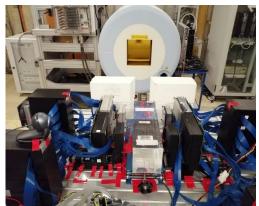
- $\rightarrow$  Efficiency ( $\rightarrow$  i-TED array 4 CCs of large S.A.)
- → Background rejection (→ i-TED low Neutron Sensitivity)

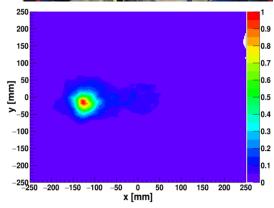
## Simultaneous Compton and PET imaging with i-TED in-situ in clinical conditions at HIT Heidelberg



#### **Heidelberg Hadrontherapy Center**

#### Compton 4x i-TED





Compton & PET 4x i-TED



