Time-Of-Flight based PG detection for particle therapy

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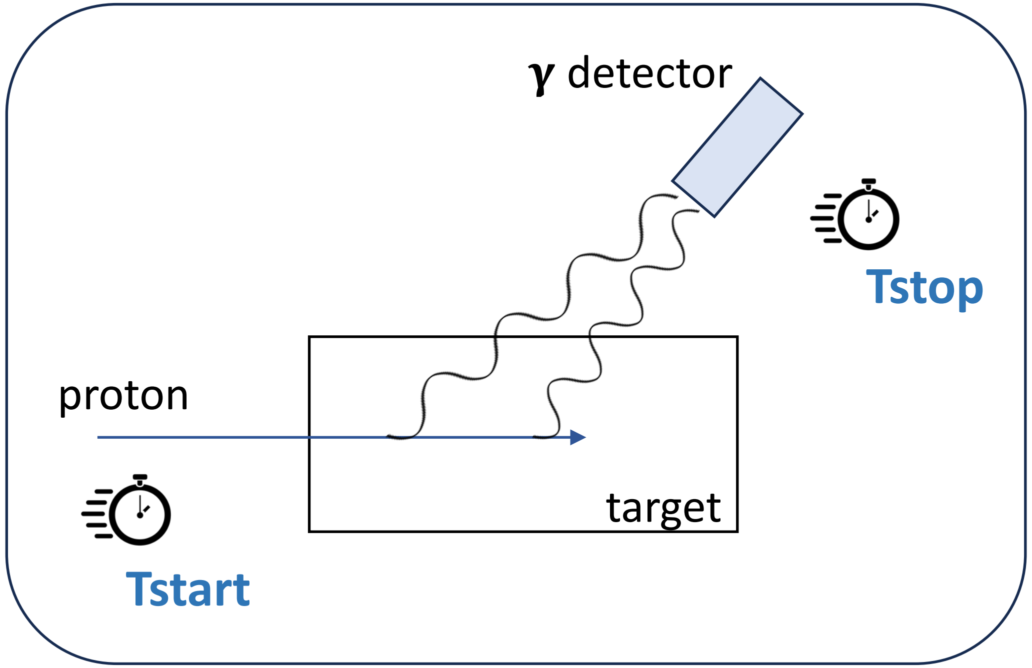
Prompt Gamma Timing (PGT)



Golnik et al. Phys. Med. Biol. 59 (2014) 5399

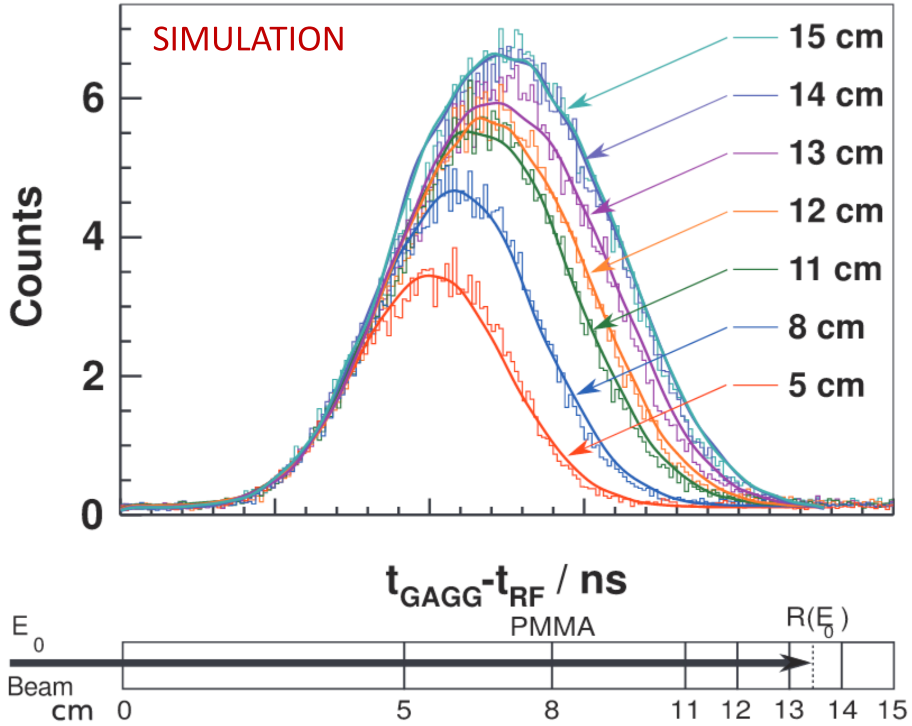


Figure 9. Comparison of experimental (histograms) and modeled time profiles (solid lines) of a PMMA target varied in thickness. All experimental curves are normalized to one incident gigaproton (10^9 protons). The experimental PGT spectra energy ROI is *All*4440 (3.2 MeV–4.6 MeV). The modeled PGT spectra are based on the *simG*4 profile for g_x. The absolute time offset of the modeled data was set to fit the mean for 5 cm PMMA thickness. The experimental detector setup (figure 7) was taken into account to incorporate the influence of the prompt γ-ray time of flight on the spectral shape. The modeled system time resolution is $\sigma_\Sigma = 450$ ps (9).

Indirect measurement of proton range from the distribution characteristics of:

TOF = Tstop – Tstart

- Mean value
- Sigma
- Others (*Marcatili et al Phys. Med. Biol. 65 (2020) 245033; Jacquet et al. Phys. Med. Biol. 66 (2021) 135003; Schellhammer et al. (2022) Front. Phys. 10:932950.*)

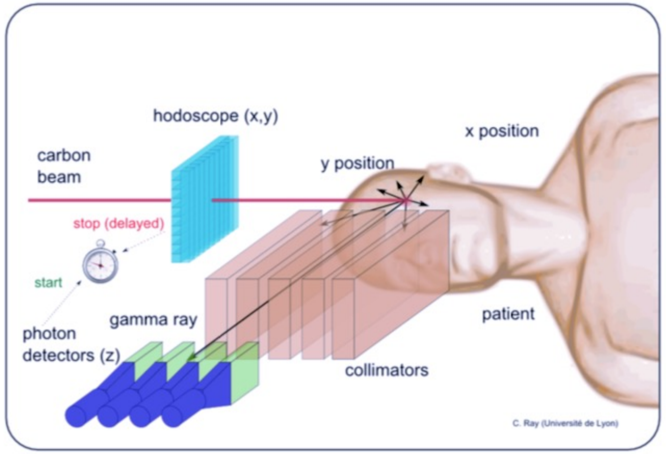
Advantages : no need for collimation

Gamma camera

Det. Efficiency :

$\epsilon \sim 10^{-5}$

Physical collimator

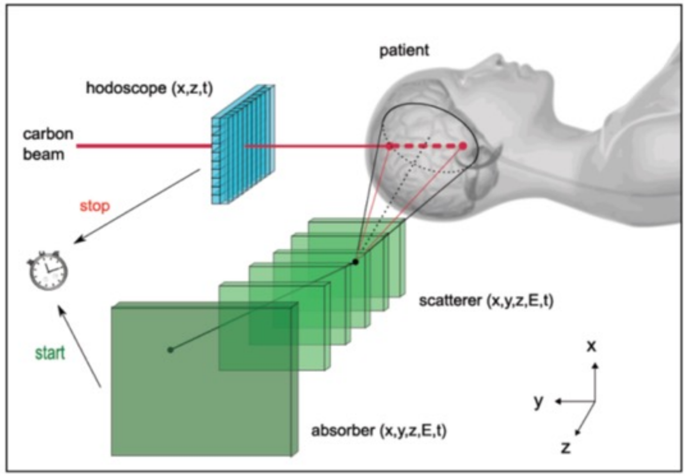


Compton camera

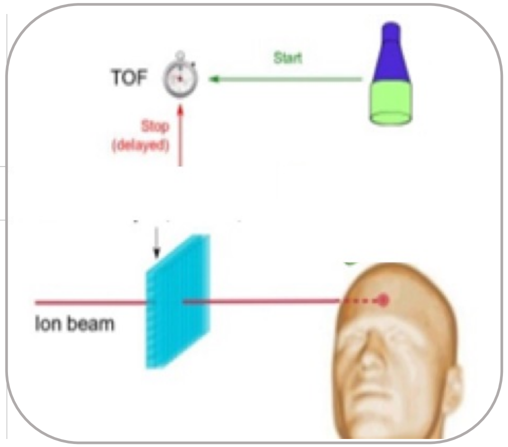
Det. Efficiency :

$\epsilon \sim 10^{-5} \div 10^{-4}$

Electronic collimation



Prompt Gamma Timing



$$\epsilon = \epsilon_\gamma \times \frac{S}{4\pi r^2}$$

e.g.

$\epsilon_\gamma \sim 0.2$; S = 4 cm^2 ; r = 20 cm

$\epsilon \sim 10^{-4}$ per detector module

<u>No collimation means:</u>

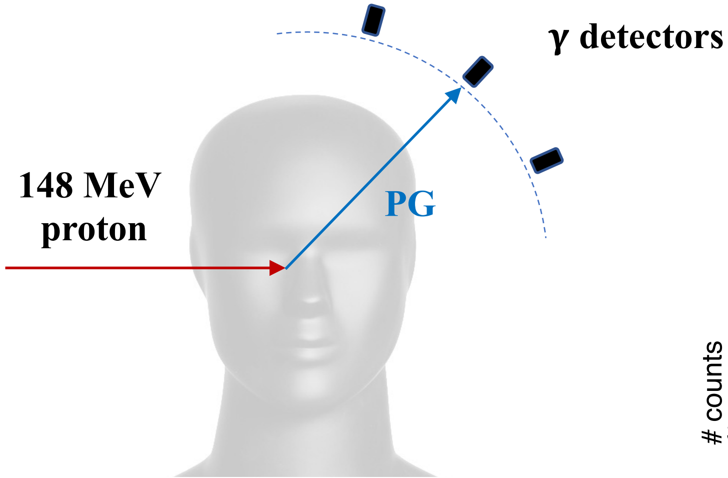
- Relatively high detection efficiency (easy to upgrade)
- Compact and light detection system
- Reduced amount of material to avoid secondary neutrons and PGs

=> Impact on Signal To Noise ratio

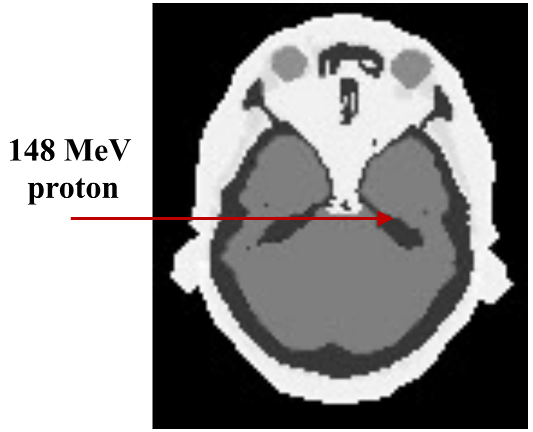
*Pictures from CLaRyS collaboration

Advantages: TOF neutron rejection

A practical example

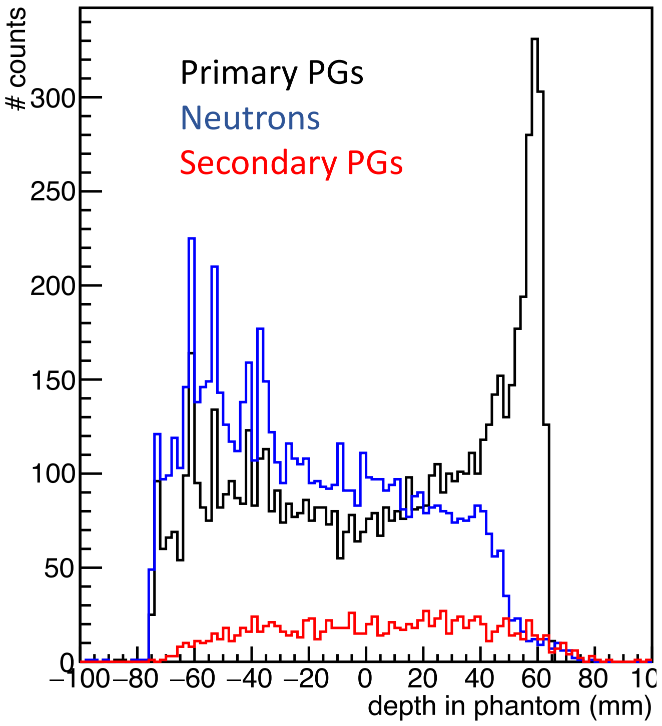


ICRP110 phantom

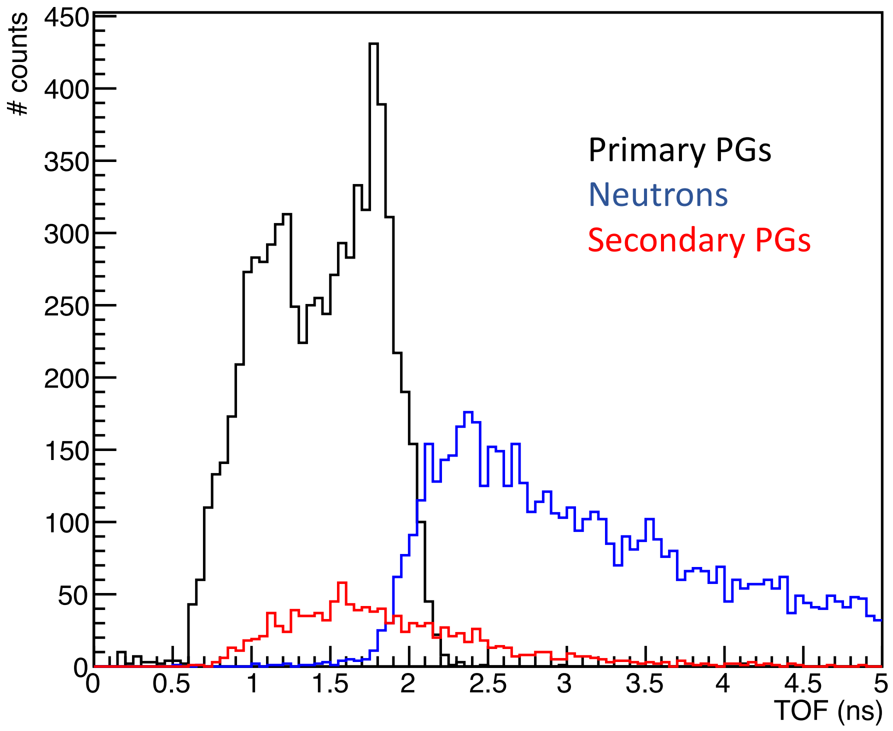


- 148 MeV protons impinging on a human head phantom (ICRP110)
- 30 perfect detectors surrounding the phantom (d=15 cm)
- Ecut = 3 MeV

Vertex distribution



TOF distribution: Tstop - Tstart



Advantages: TOF neutron rejection

From the literature…

AK Biegun et al. Phys. Med. Biol. 57 6429 (2012)

- **200 MeV protons on PMMA**
- Perfect detector

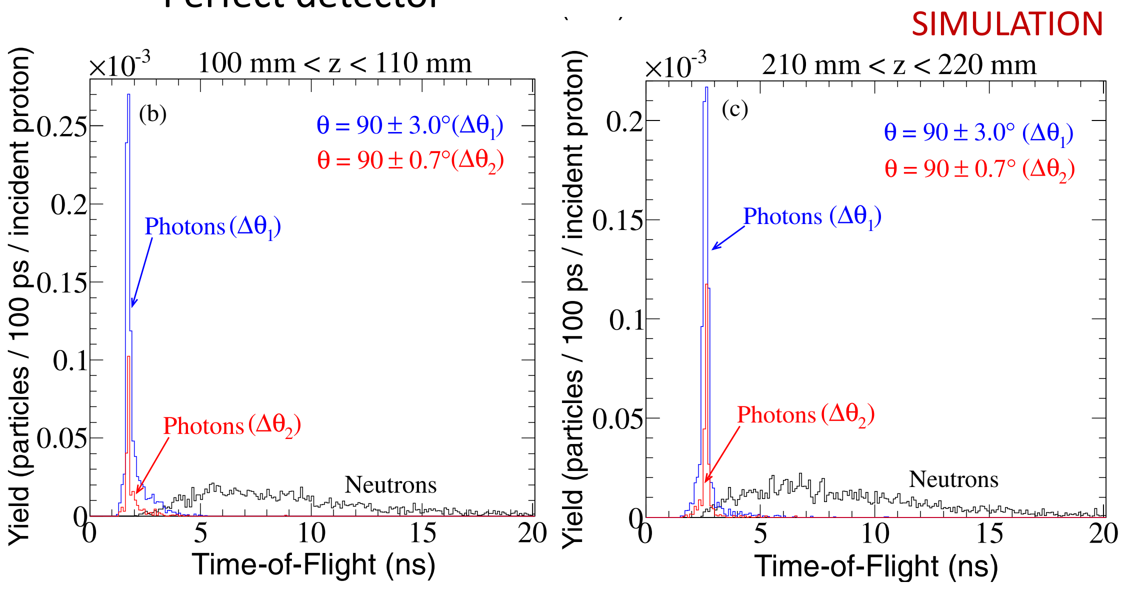
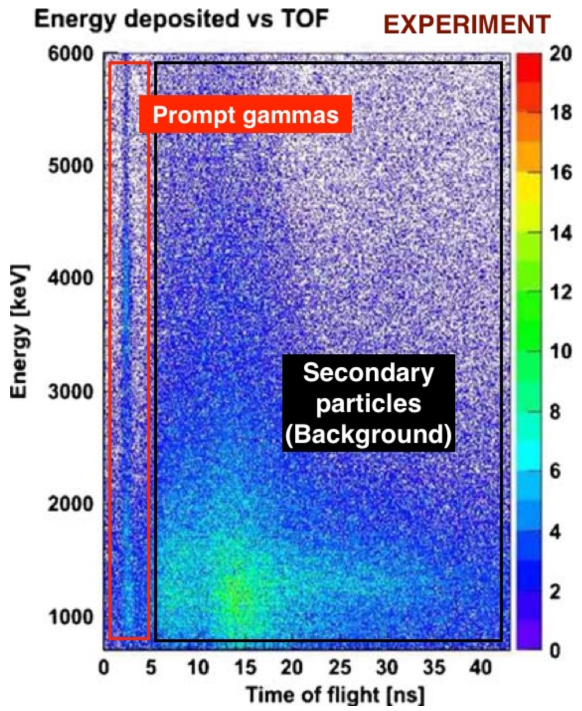


Figure 3. (a) Simulated depth–dose profile of 200 MeV protons in PMMA. Two examples of 10 mm wide regions along the proton beam path are indicated. (b), (c) The TOF spectra of the prompt gamma photons (blue and red) and neutrons (black) impinging onto the corresponding two detector regions (see also figure 1). Photon profiles are shown for the two angular collimation windows $\Delta\theta_1$ (blue) and $\Delta\theta_2$ (red). All results were simulated with Geant4.

E Testa et al. Radiat Environ Biophys ***49****, 337–343 (2010)*

- **95 MeV/u ^{12}C beam on PMMA**
- BaF_2 at d>50cm from target

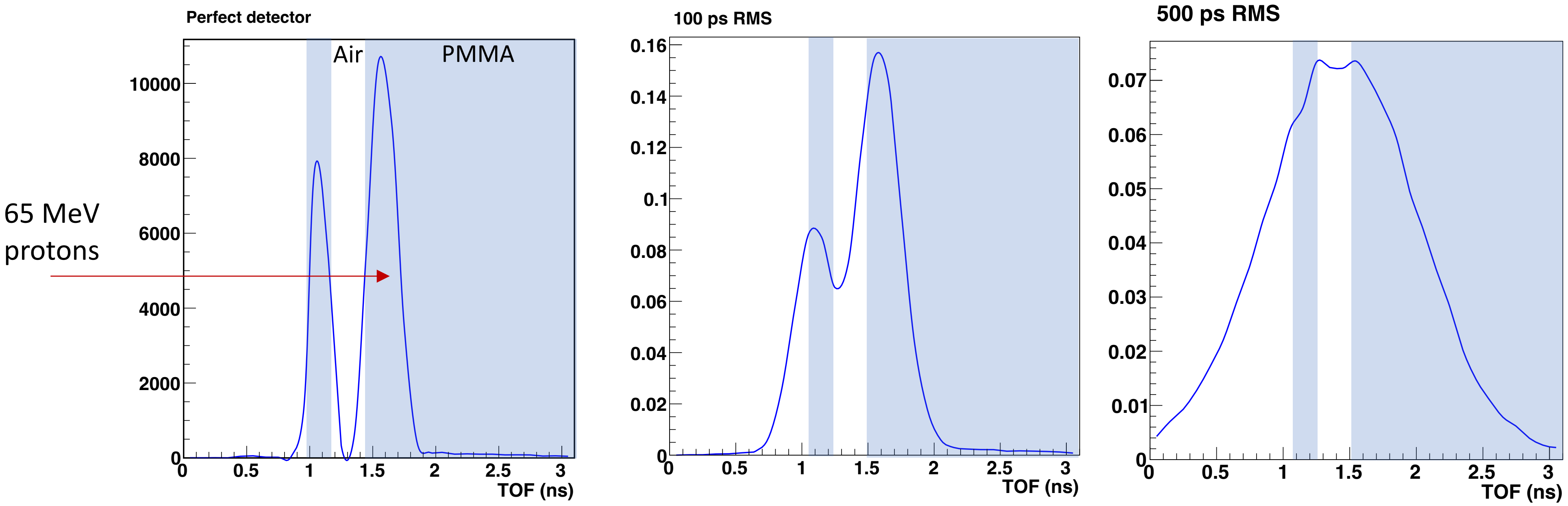


A TOF resolution of ~ 1 ns is enough to reject most neutrons

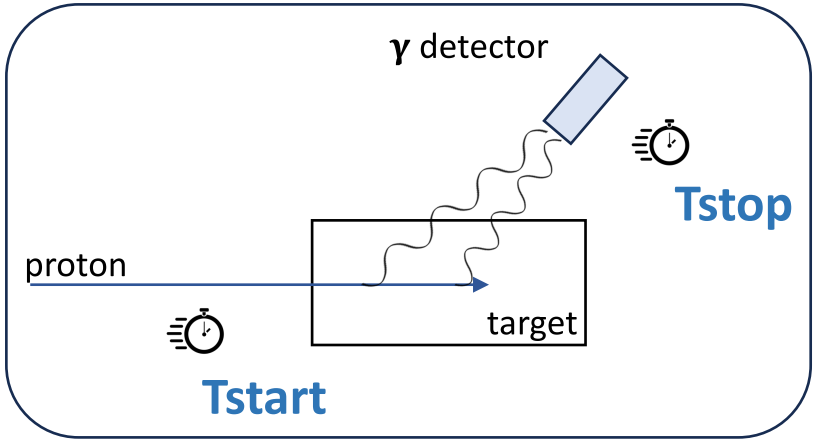
Technical challenges in PGT

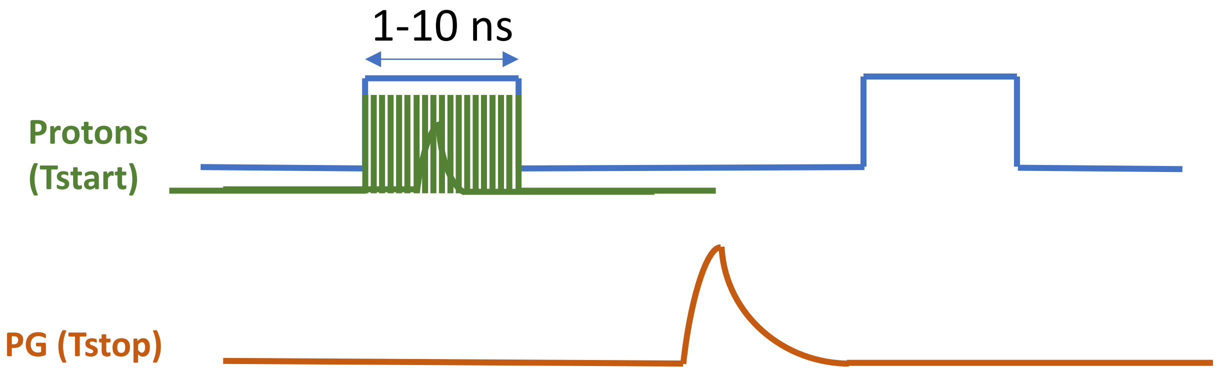
Time resolution

- Relevant parameters
- Beam temporal structure
- Reference Time
  - RF/phase synchronisation
  - Beam monitors



Parameters affecting time resolution in PGT





Temporal structures of main accelerators

		Synchrotron (CNAO, HIT)		Cyclotron (IBA, Varian)	Synchro-cyclotron (S2C2 IBA)
		^{12}C	Protons		
Typical intensity (ions/s)		10^7	10^9	10^{10}	10^{11}
Macro-structure	Period (s)	1 - 10		Ø	10^{-3}
Micro-structure	Bunch width (ns)	20 - 50		0.5 - 2	8
	Period (ns)	100 - 200		10	16
	Ions/bunch	2-5	200 - 500	200	10^5

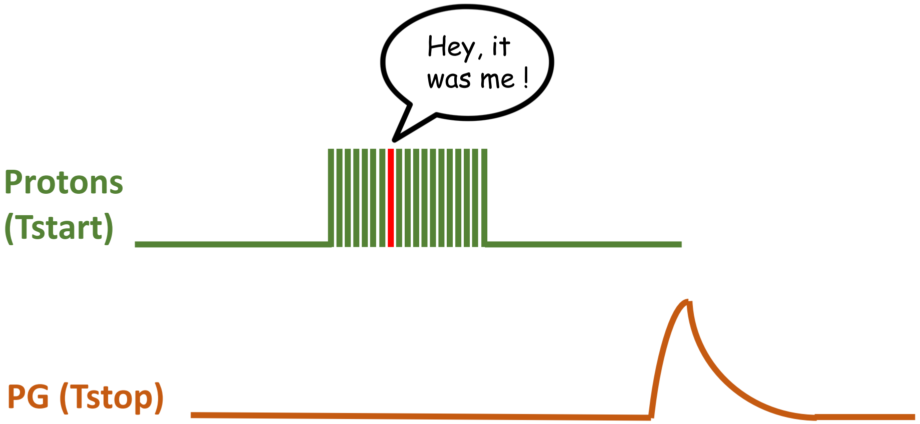
Source: CLaRys collaboration

1) Time resolution on reference time (Tstart)

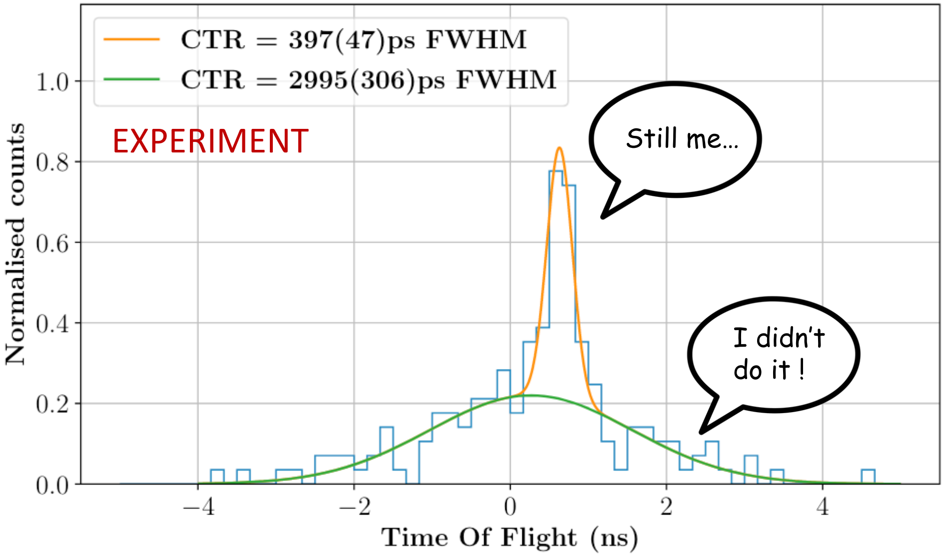
2) Time resolution of PG detector (Tstop)

3) Beam temporal structures

Time resolution: beam temporal structure



S2C2 synchro-cyclotron: 8 ns bunch width, 7 p/bunch, thin target

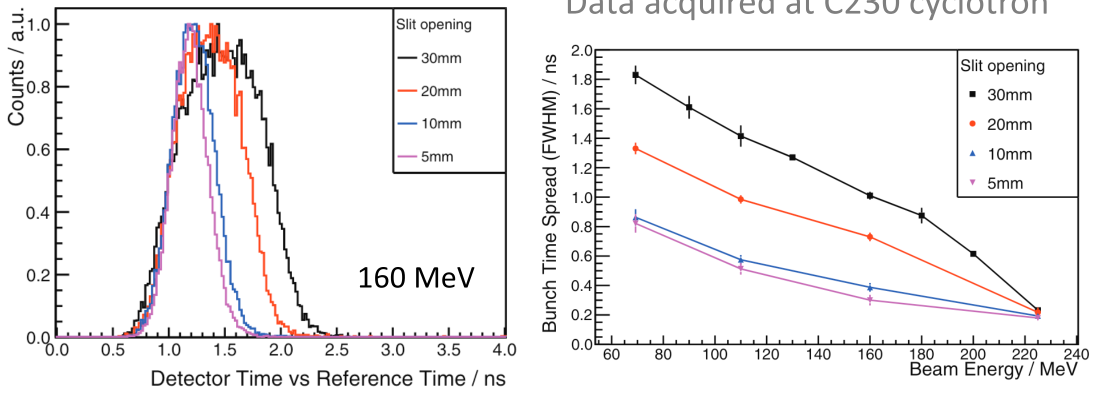


Jacquet et al. Scientific report (2023) 13:3609

Reduce bunch-width related time uncertainty

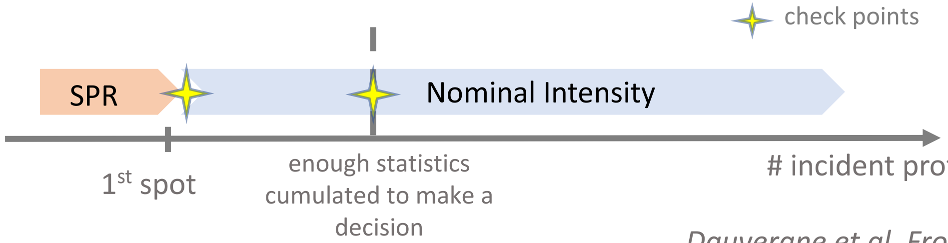
1) Play with accelerator settings

Data acquired at C230 cyclotron



Petzoldt et al, Phys. Med. Biol. 61 (2016) 2432

2) Lower the beam intensity to Single Proton Regime (SPR)



Dauvergne et al, Front. Phys. 8:567215 (2020)

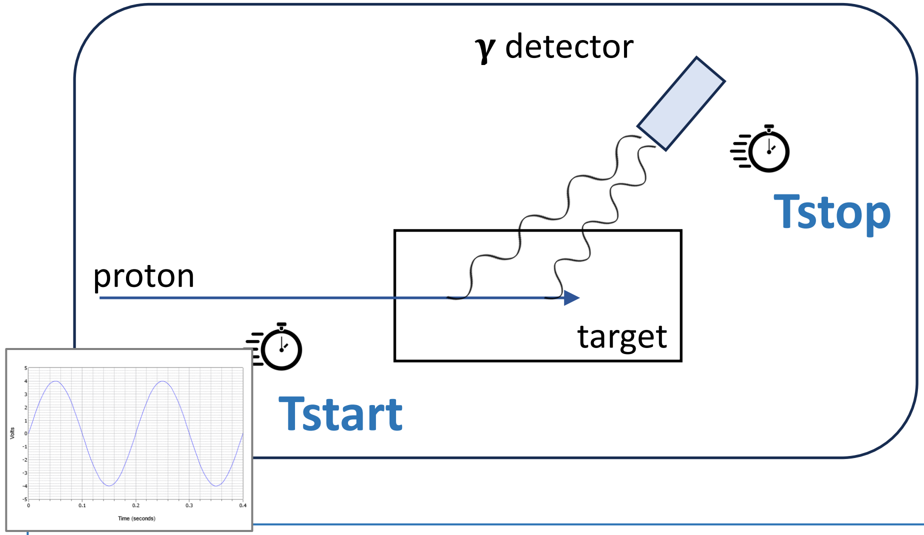
3) Build a ultra-fast monitor that can time-tag protons at clinical intensities

=> But still you need to find the right PG-proton couples !

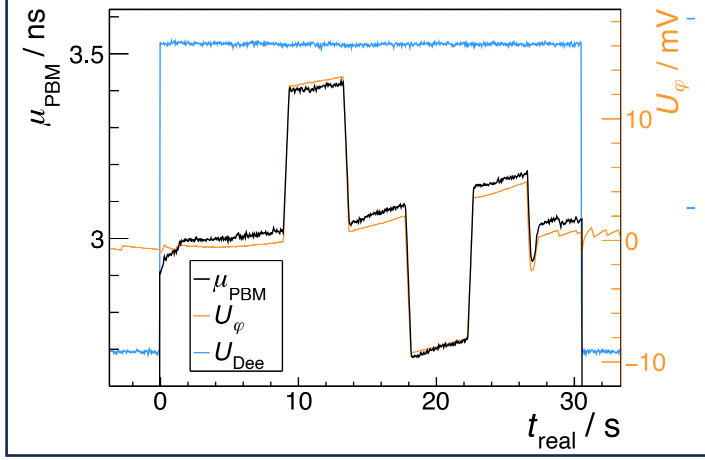
Time resolution: reference time Tstart

Synchronisation with accelerator signal

Kôgler M-20-05 IEEE NSS-MIC 2022, Oral contribution



Low Level RF phase Uφ

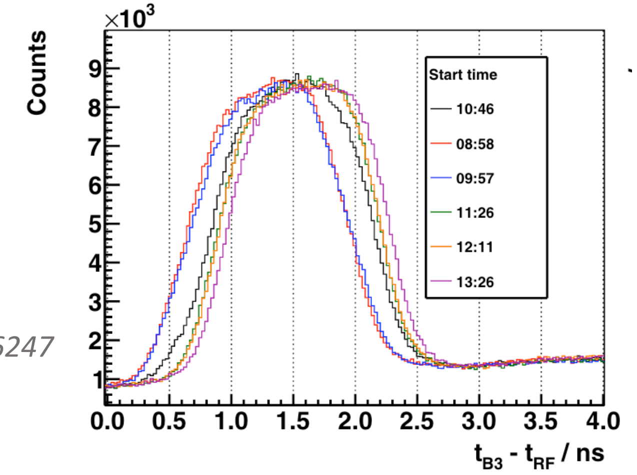


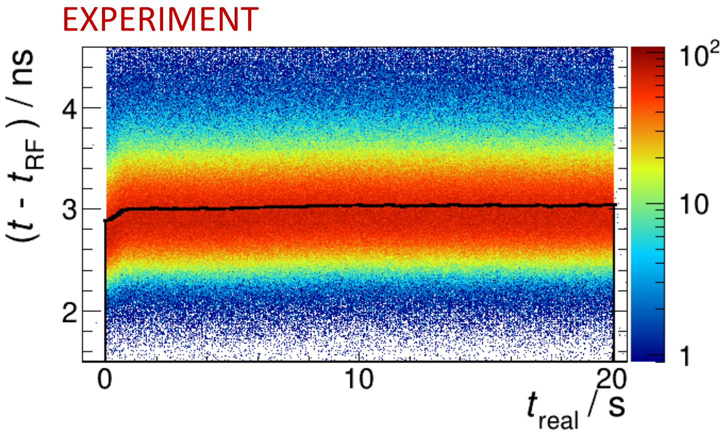
R.D. Werner, Master thesis 2021

Accelerator Radio-Frequency RF

Long-term phase drift (inter-layer)
Due to variation in cyclotron magnetic field/current

Hueso-Gonzàlez et al., Phys. Med. Biol. 60 (2015) 6247





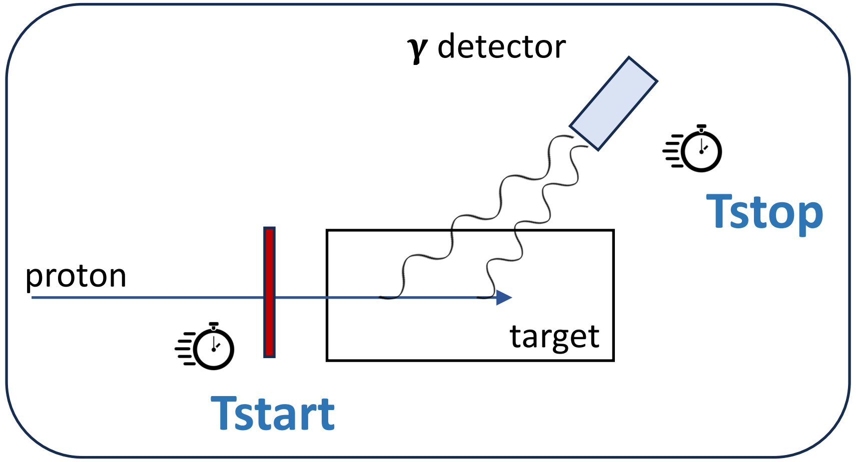
Short-term oscillation (intra-layer)
Due to voltage regulation between each energy layer.

- Only within first ~2 s
- Can be parametrised and corrected

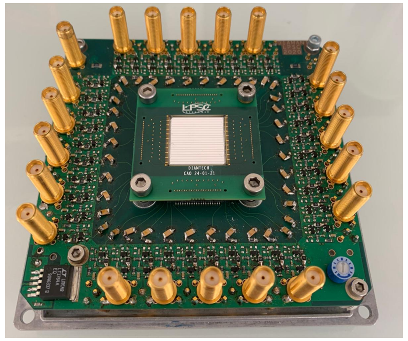
R.D. Werner, Master thesis 2021

Time resolution: reference time Tstart from Beam Monitor

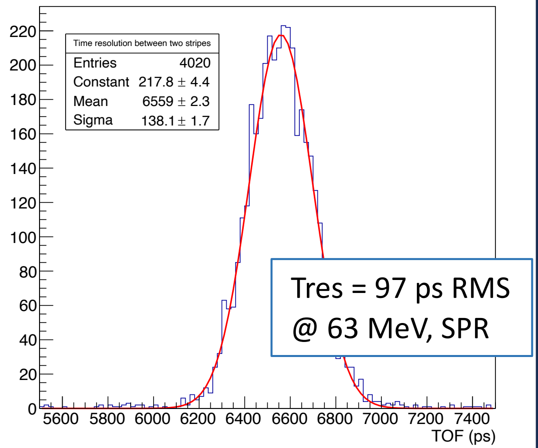
Diamond detector



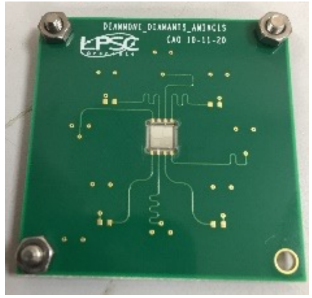
Stripped detector: 9 x 9 x 0.5 mm², 1 mm pitch



Clarys-UFT project

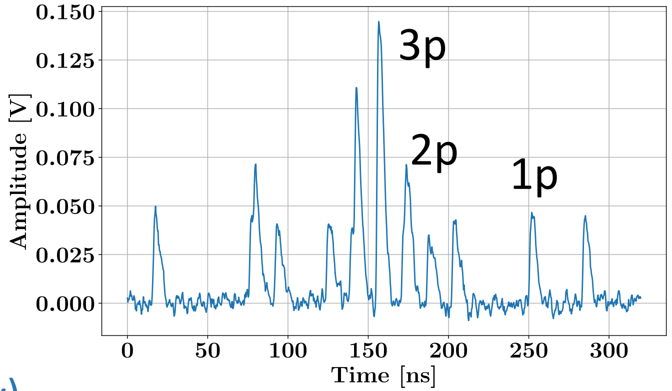


Single channel, single crystal diamond detector: 4.5 x 4.5 x 0.5 mm²



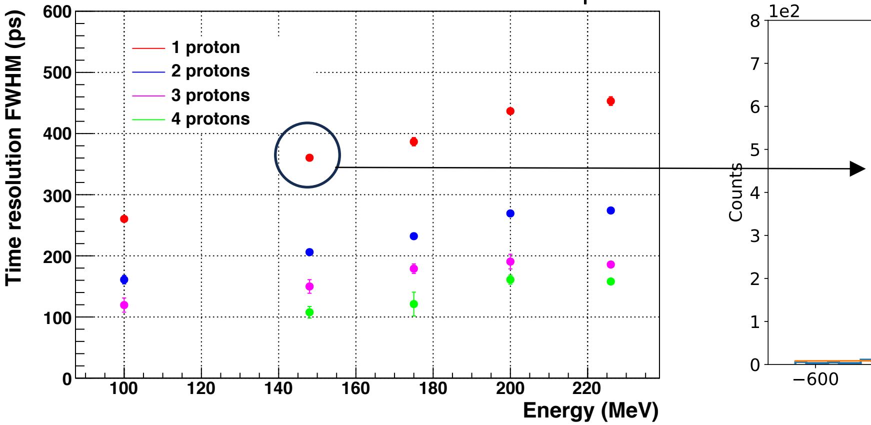
Beam size

Proton counting (at low intensity)

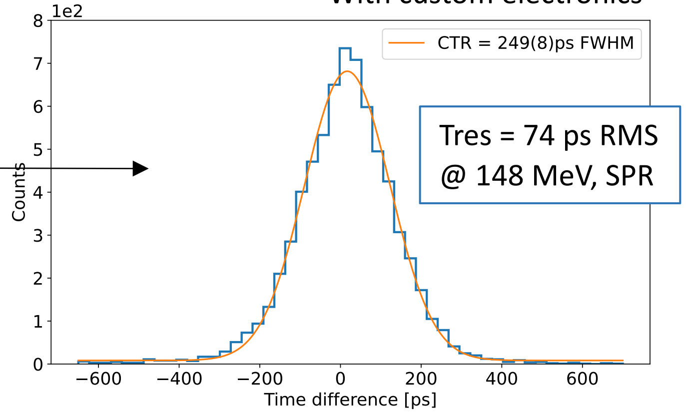


Time resolution (at low intensity)

With Cividec C2 amplifier



With custom electronics

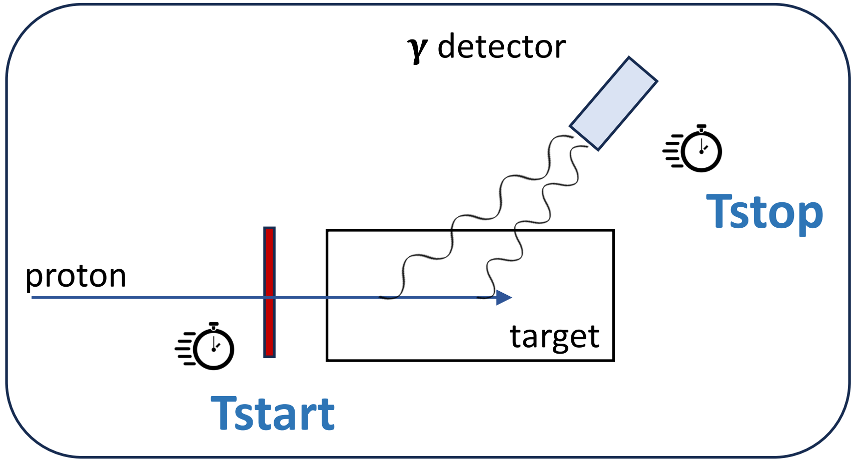


Time resolution, Rad-hard

Surface, thickness

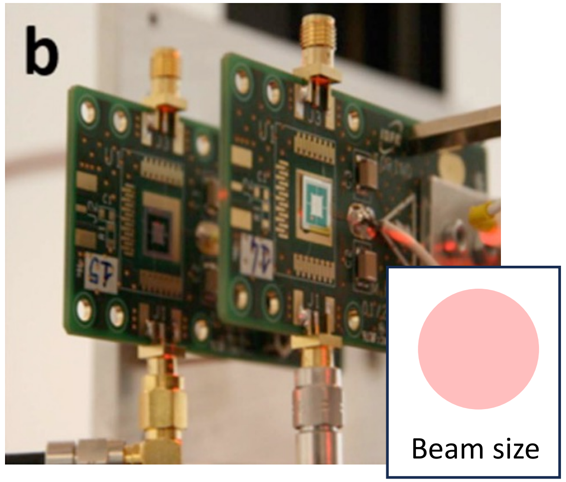
Time resolution: reference time Tstart from Beam Monitor

Ultra Fast Silicon Detectors

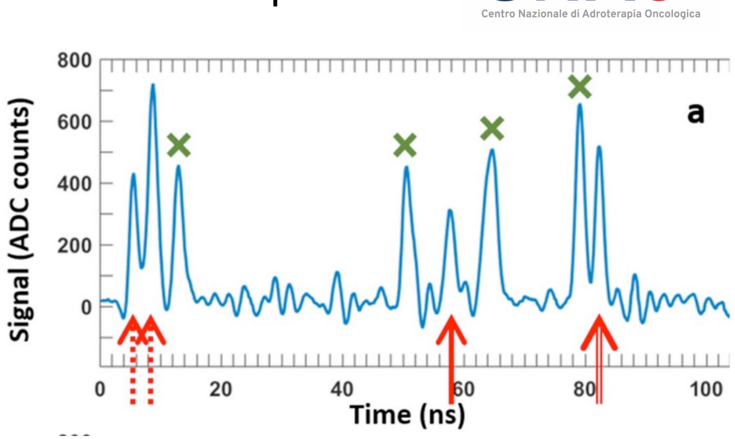


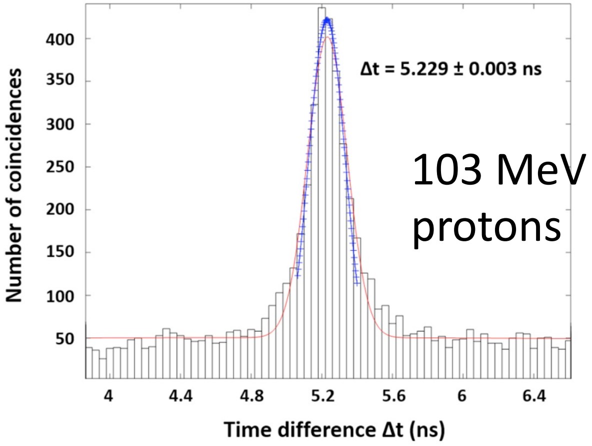
- 😀 Very narrow signals (~ 2 ns)
  => reduced pile-up
- 😀 Limited thickness
  => no beam perturbation
- 😀 Time resolution
  => down to 10 ps for other prototypes
- 😕 Detection surface
  => on-going developments

4 pads detector, 3x3 mm^2 each, 150 um thickness



228 MeV protons at CNAO



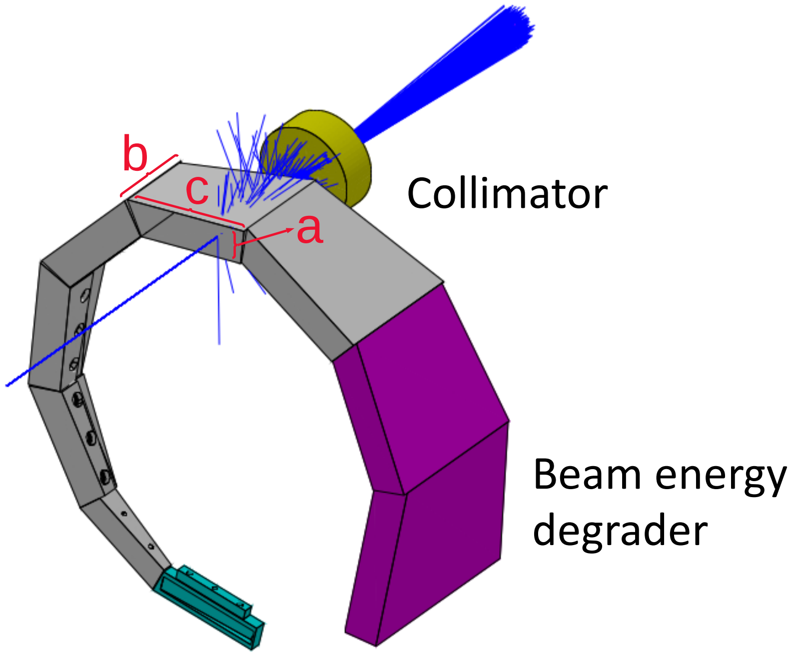


Tres = 75 - 115 ps RMS depending on beam energy

Vignati et al. Phys. Med. Biol. 65 (2020) 215030

Time resolution: reference time Tstart from Beam Monitor

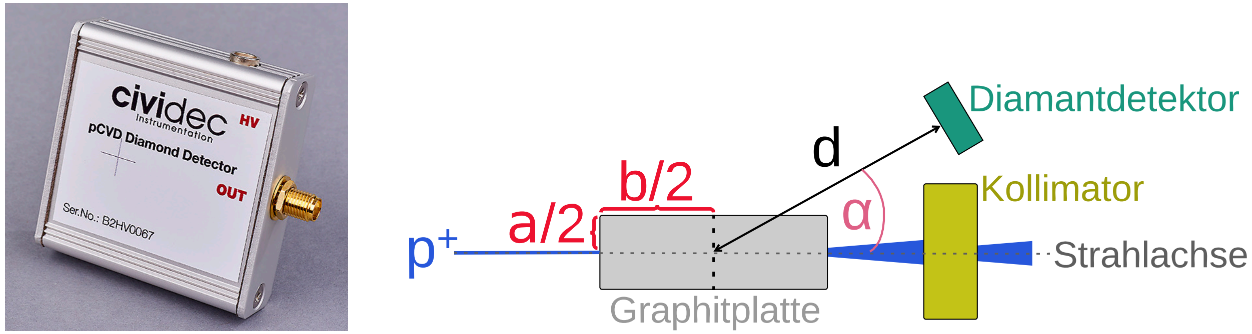
Off-axis diamond detector

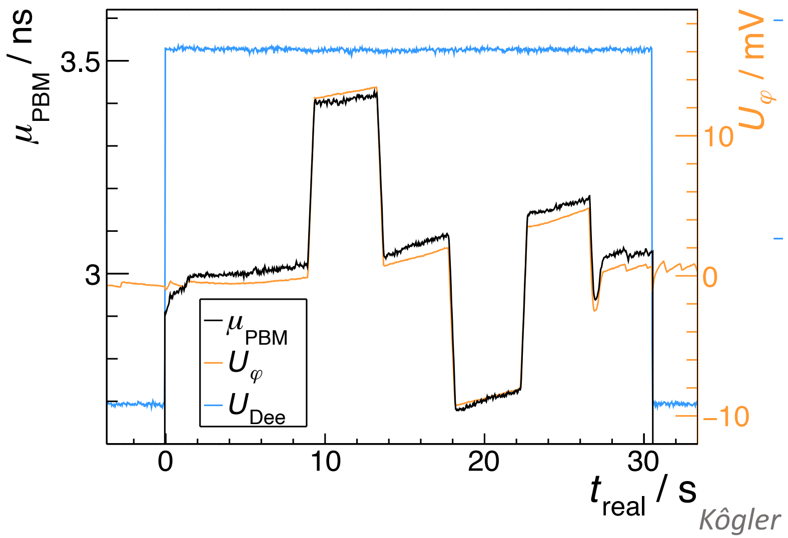


Tesse et al., J. Phys.: Conf. Ser. 1067, 092001 (2018)

- 😀 Time resolution
- 😀 Rad-hard
- 😀 High rate capabilities

Poly-crystalline diamond detector from Cividec: 10 x 10 x 0.5 mm²





Tres = 85 ps RMS
Achieved with minimum ionizing electrons

R.D. Werner, Master thesis 2021

Kôgler M-20-05 IEEE NSS-MIC 2022, Oral contribution

Technical challenges in PGT

Time resolution

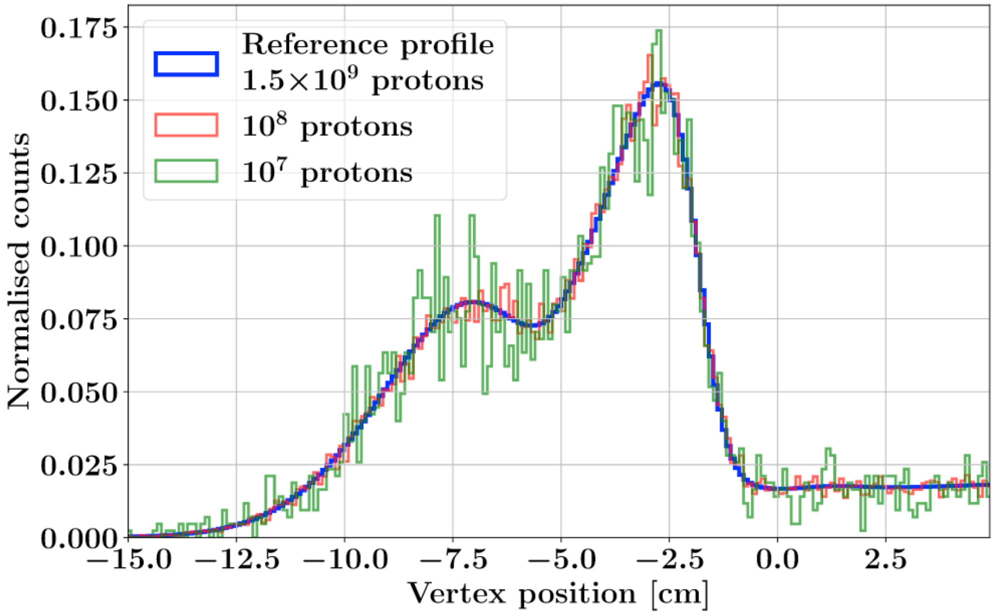
- Relevant parameters
- Beam temporal structure
- Reference Time
  - RF/phase synchronisation
  - Beam monitors

Sensitivity: towards real-time monitoring

- Proton statistics
- SNR and background
- Detector arrangement

Detector development for PGT

Reconstruction



Jacquet et al. Phys. Med. Biol. 66 (2021) 135003;

Sensitivity: SNR and background

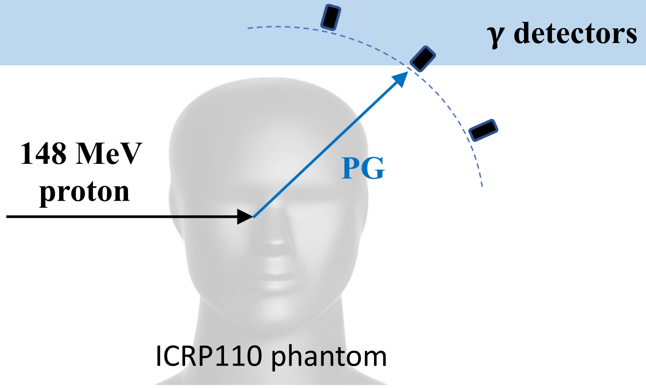
Goal: Real time monitoring

1) Detection efficiency
2) Detector pile-up
3) Background

} **SNR**

A practical example

- 148 MeV protons
- 30 perfect detectors
- Ecut = 3 MeV



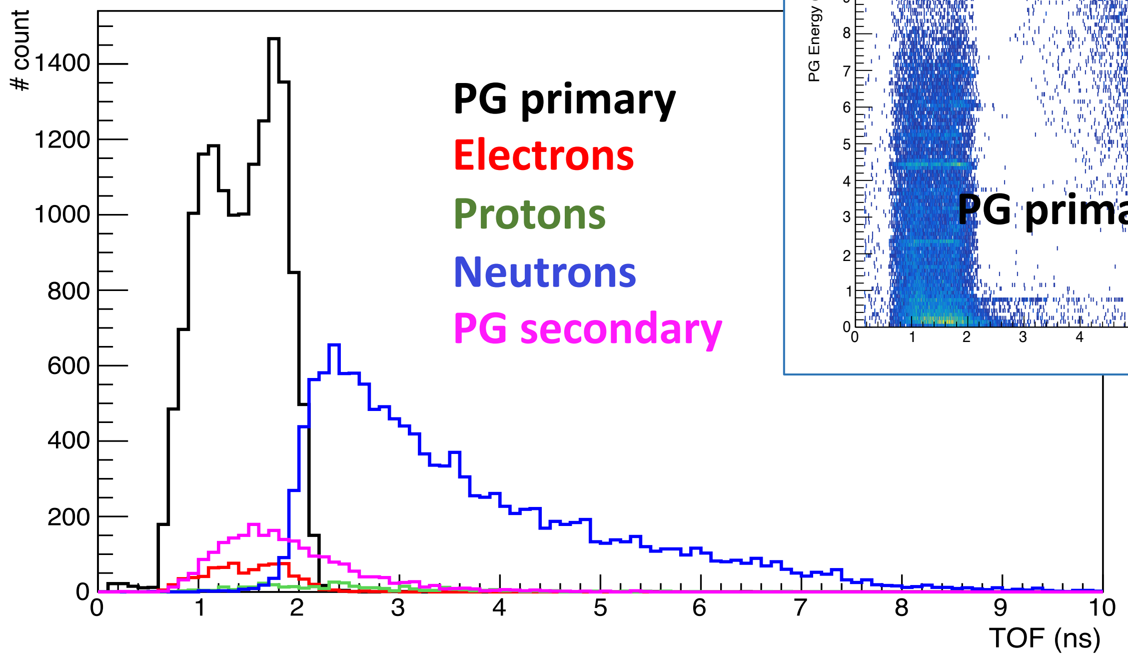
Background from target and detectors

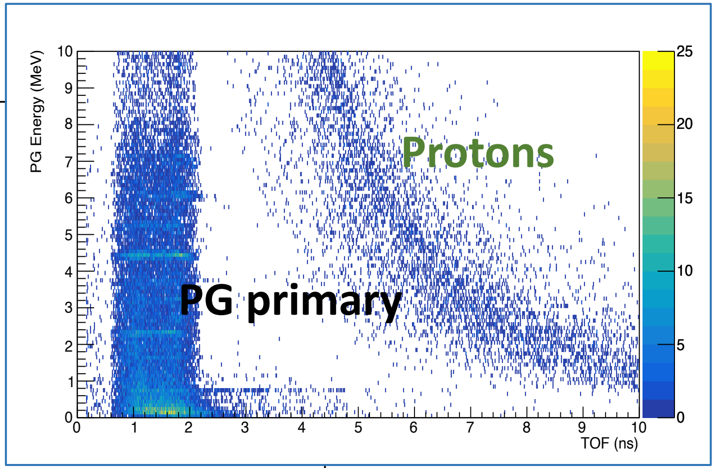
Electrons
Few, many are cut with acquisition threshold

Protons
Few, cut on the E vs TOF distribution

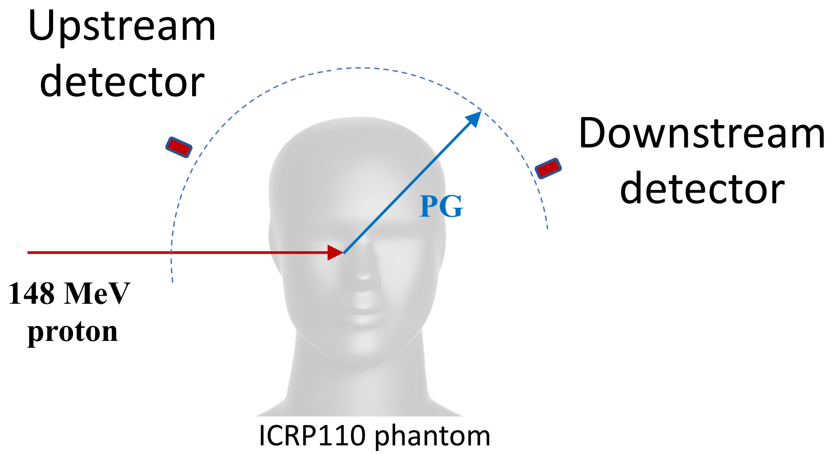
Neutron
TOF rejection does not work at PG profile fall-off
⇒ Affect proton range measurement

Secondary PGs
Same energy and timing of primary PGs.
=> Affect proton range measurement

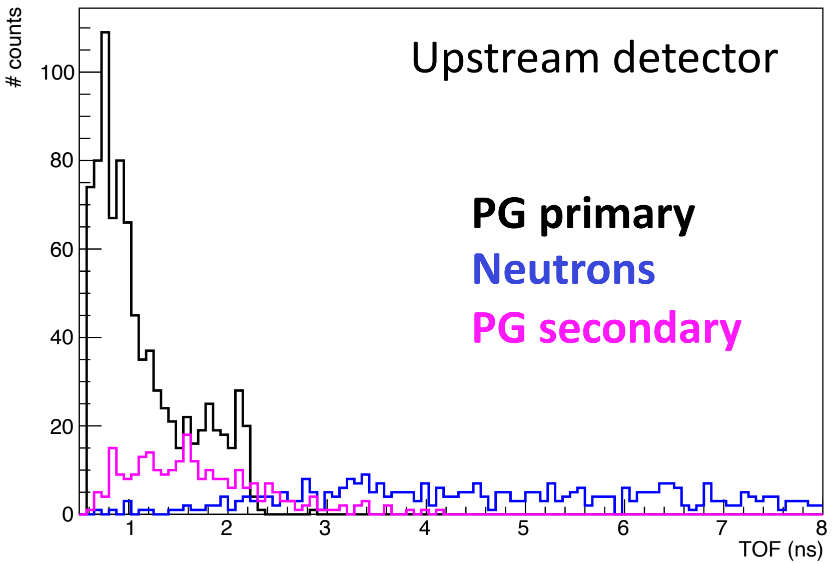


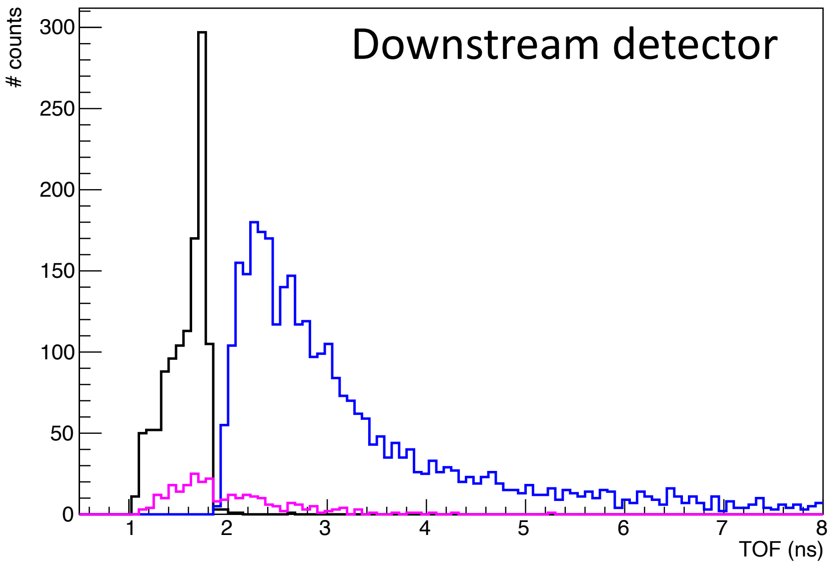


Sensitivity: Detector arrangement

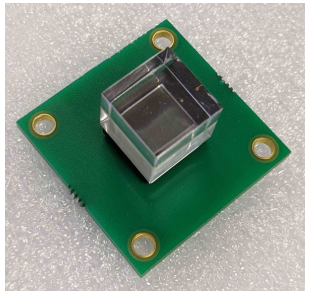


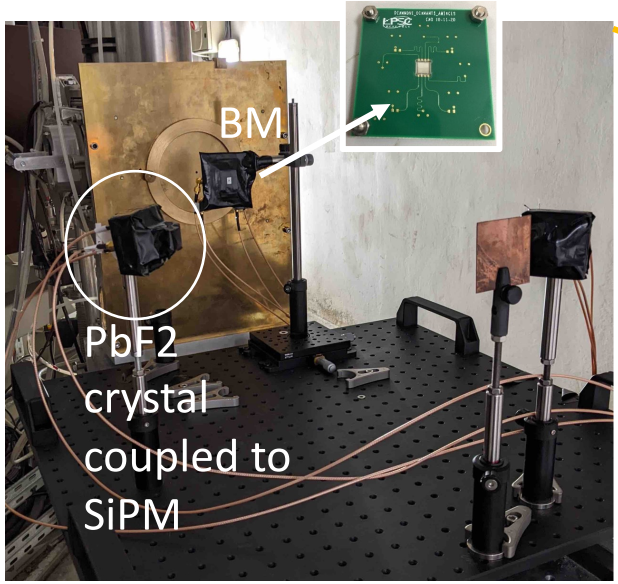
Placing the gamma detector upstream seems more advantageous for background reduction

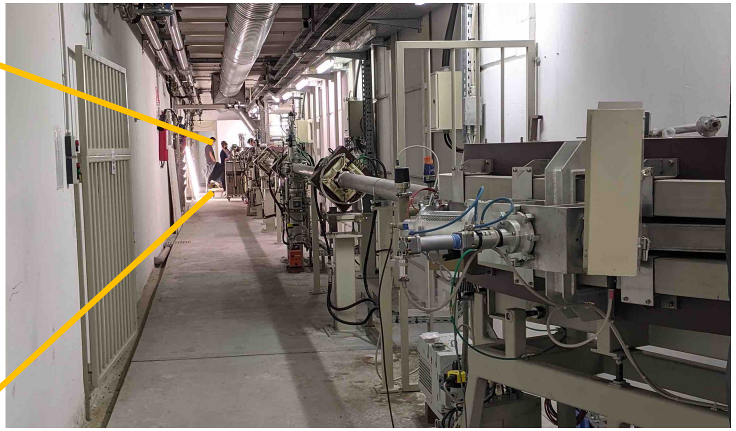


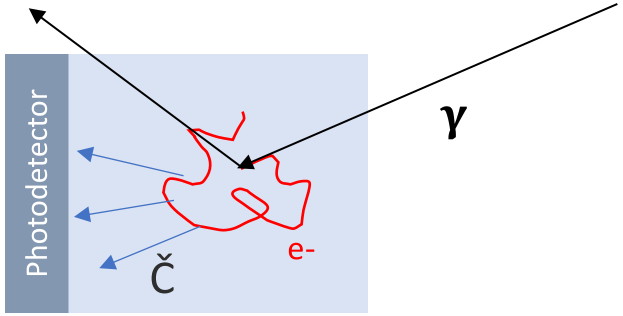


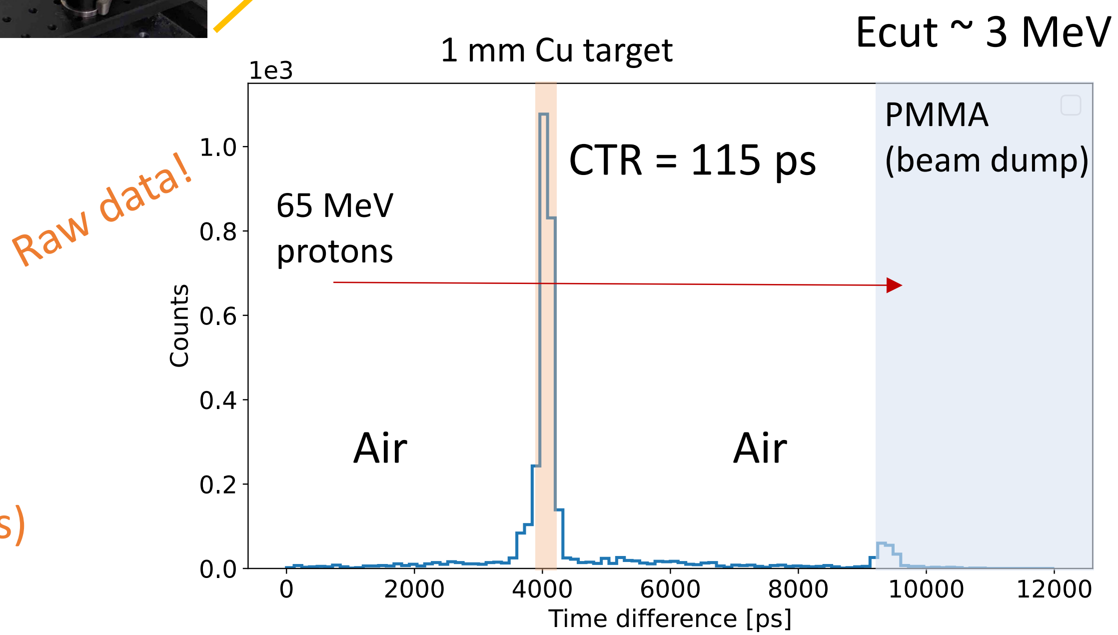
Sensitivity: the case for pure Cherenkov radiators











Cherenkov detectors

- short pulses (pile –up)
- high density (det. efficiency)
- very low sensitivity to background (threshold process)
- NO energy measurement !

Technical challenges in PGT

Time resolution

- Relevant parameters
- Beam temporal structure
- Reference Time
  - RF/phase synchronisation
  - Beam monitors

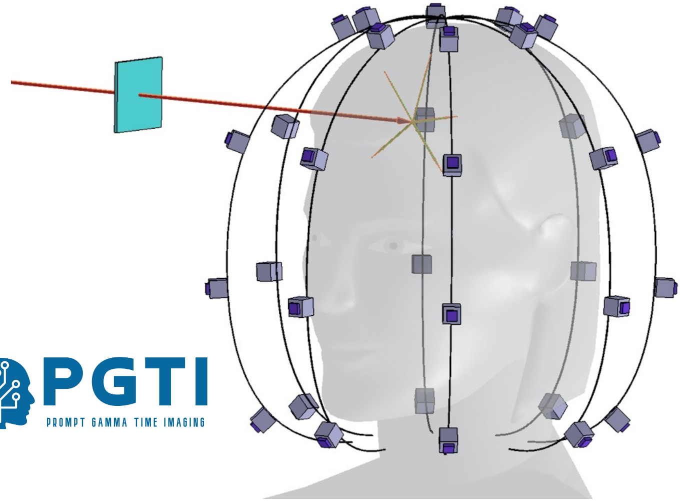
Sensitivity: towards real-time monitoring

- Proton statistics
- SNR and background
- Detector arrangement

Detector development for PGT

Reconstruction

Detectors: TIARA (Tof Imaging ARrAy)

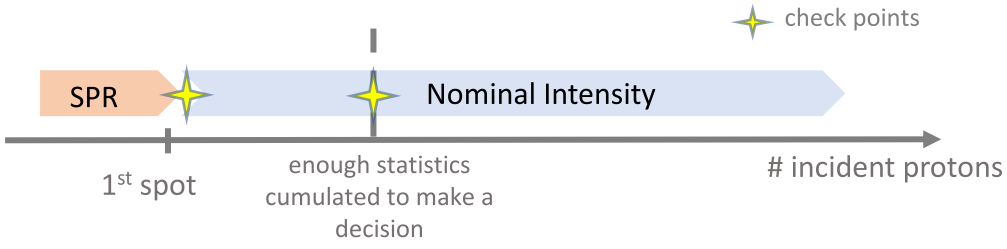


PGTI

PROMPT GAMMA TIME IMAGING

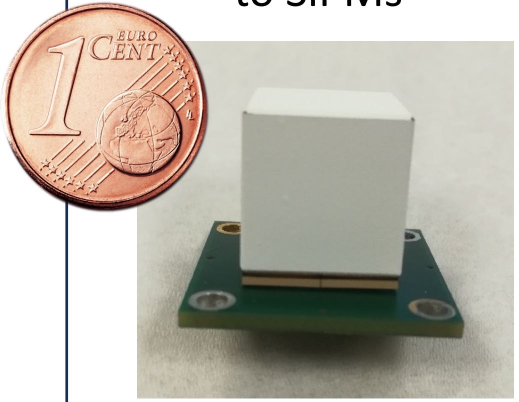
GOAL

- 30 γ detectors to achieve a uniform target coverage
- Detection efficiency ~0.5%
- Targeted coincidence time resolution ~100 ps RMS



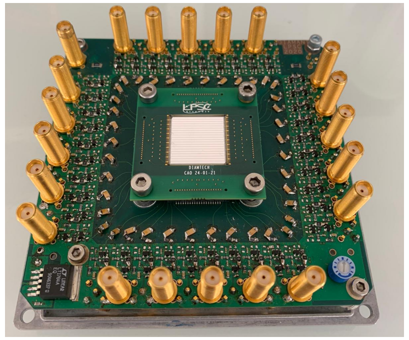
TIARA γ module

(1.5 cm)^3 PbF2 coupled to SiPMs



Beam monitor for SPR

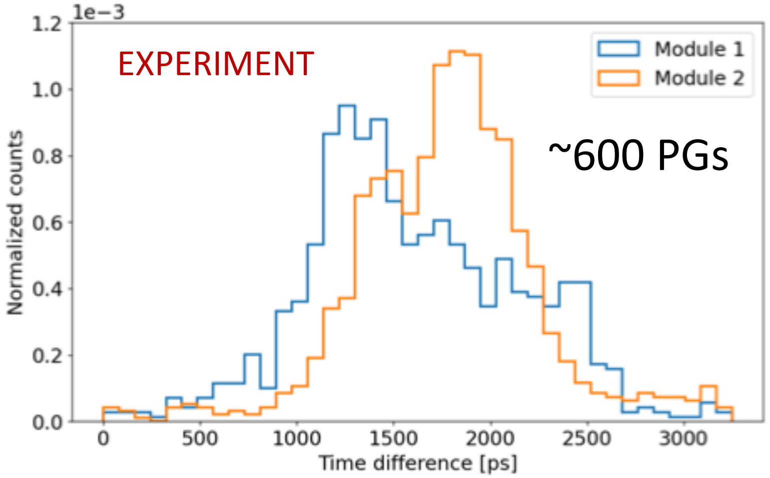
~ 1cm^2 single crystal diamond, 8x8 strips

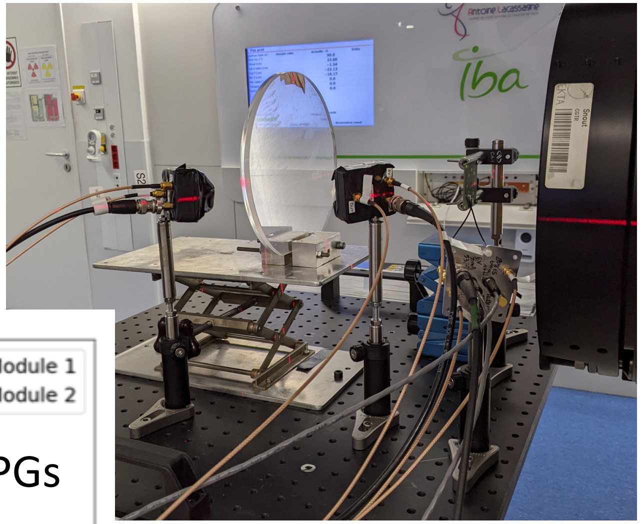


CURRENT DEVELOPMENT

CTR = **112 ps RMS**
at 148 MeV, in SPR

Large PMMA target



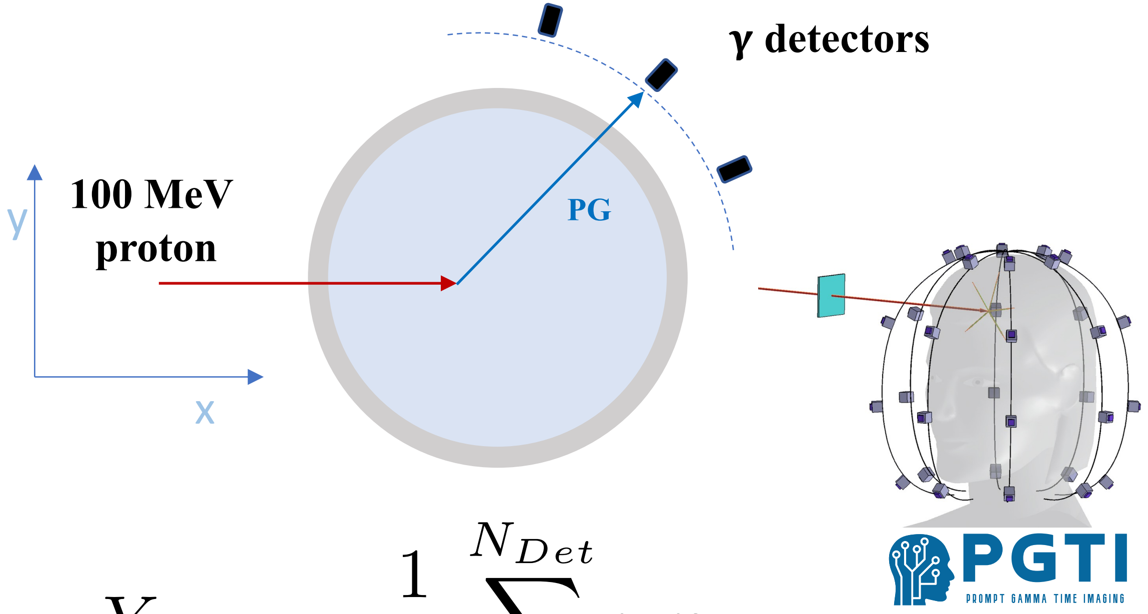


IBA, Proteus One

Uniform sensitivity all over the range

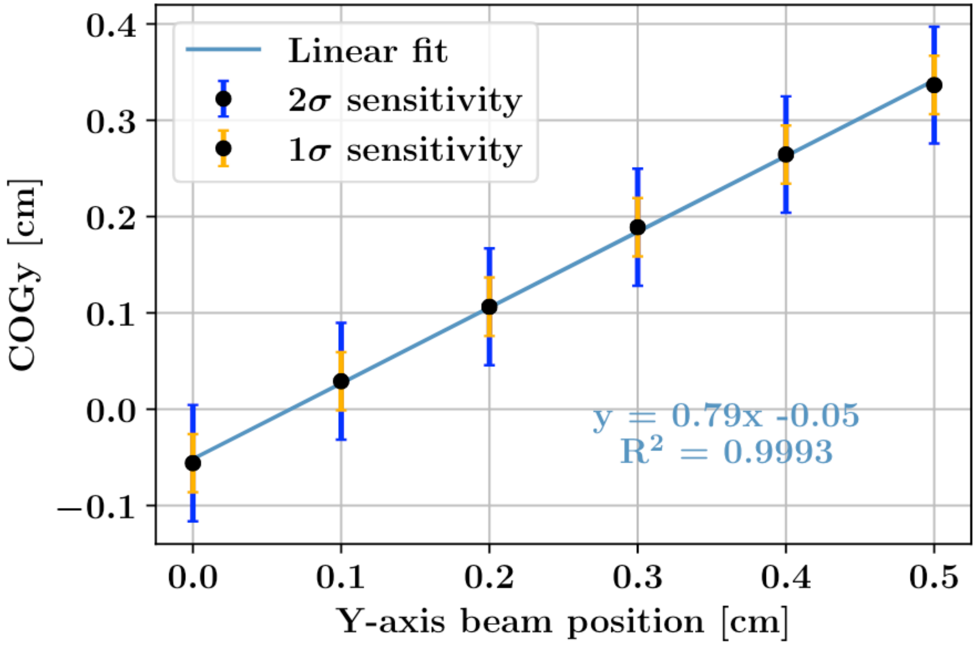
Detectors: TIARA (Tof Imaging ARrAy)

Jacquet et al. Phys. Med. Biol. 66 (2021) 135003;



$$Y_{COG} = \frac{1}{N}\sum_{i=1}^{N_{Det}} y_i n_i$$

N = total number of PG detected
N_i = number of PG detected in module $_i$
y_i = x coordinated of gamma detector



Possible to distinguish a lateral beam displacement of **2 mm at 2 sigma**

- **3D info:** multiple detectors allow a full angular coverage to measure deviations in any direction.
- Could be **compatible with IMPT**

Detectors: Oncoray

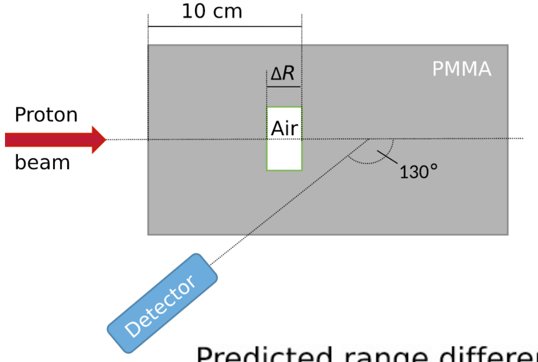
Fig. 1: Setup for PGT tests using six detection units, each consisting of a Ø 2” × 1” or Ø 2” × 2” $CeBr_3$ scintillation detector by Scionix and an ultrafast digital plug-on spectrometer U100 by Target Systemelektronik [9], in the treatment room of the proton therapy facility in Dresden (OncoRay/UPTD).

- 6 $CeBr_3$ modules
- Clinical ready

T. Werner et al., 2017 IEEE (NSS/MIC), Atlanta, GA, USA, 2017, pp. 1-5

Experiment with a single detection module

- 227 MeV protons
- 10 mm air cavity
- Ecut = 3 ÷ 5 MeV
- (~10^8 protons per spot) x 8
- Tstart = RF
- CTR – 225 ps



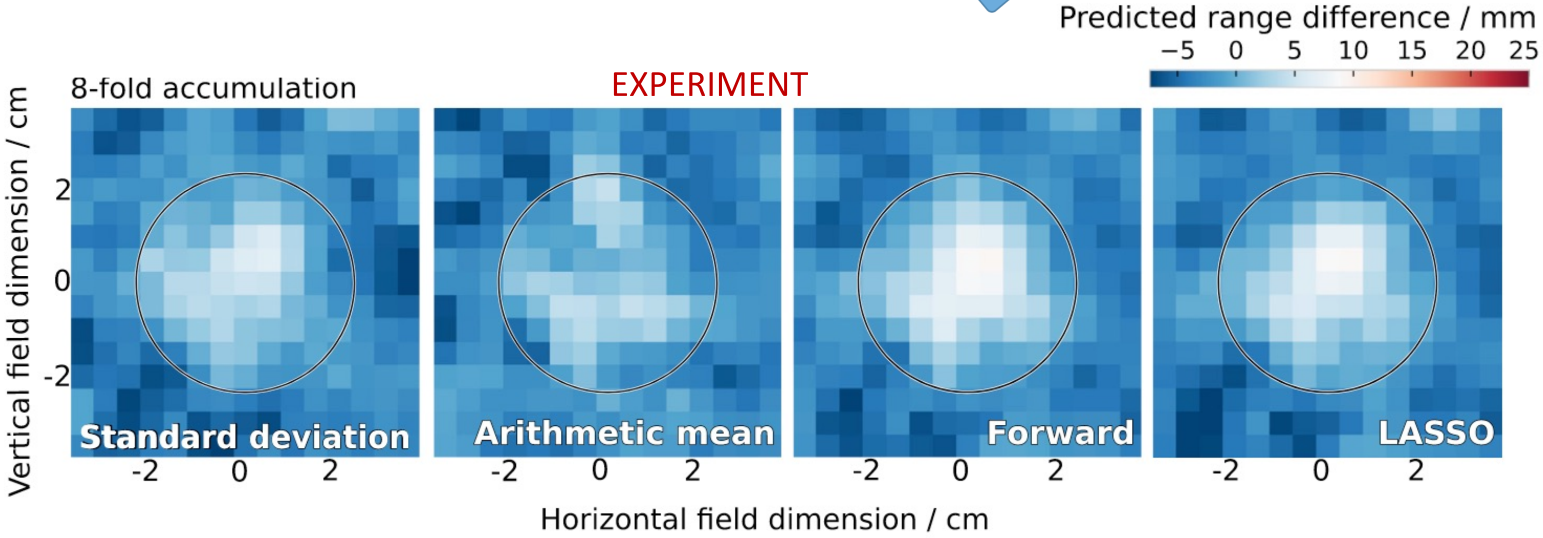


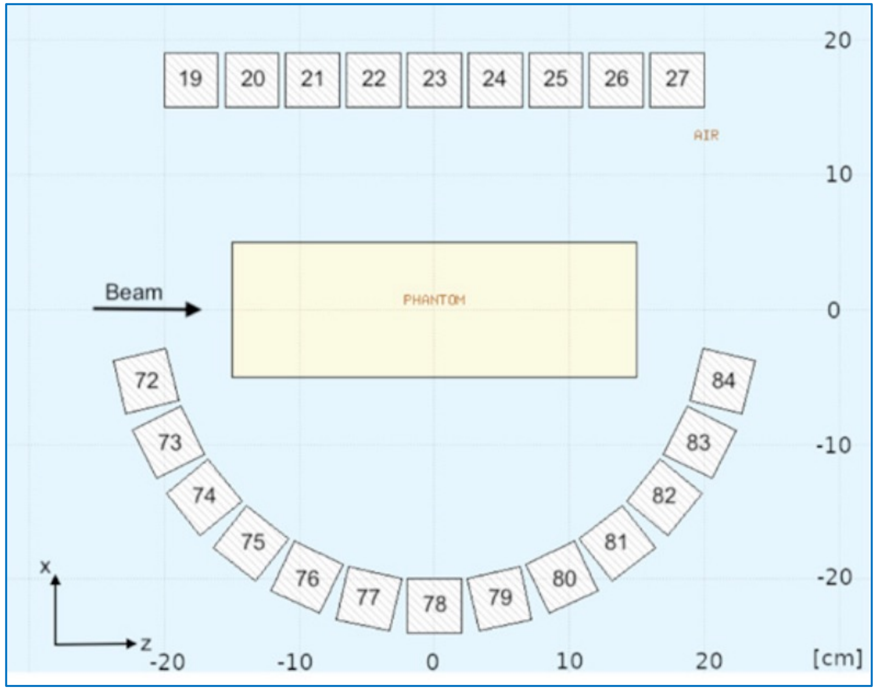
FIGURE 6

Range difference in the scanned treatment field of 227 MeV as reconstructed by the previously used methods (standard deviation, arithmetic mean) and the newly developed statistical models (forward and LASSO selection). The actual cavity thickness was 10 mm inside the circle. The colormap diverges from this actual cavity thickness in white to lower values in blue and higher values in red. The cavity was clearly detected by the new models.

Werner et al. Phys. Med. Biol. 64 (2019) 105023 (20pp)
Schellhammer et al. 2022 Front. Phys. 10:932950.

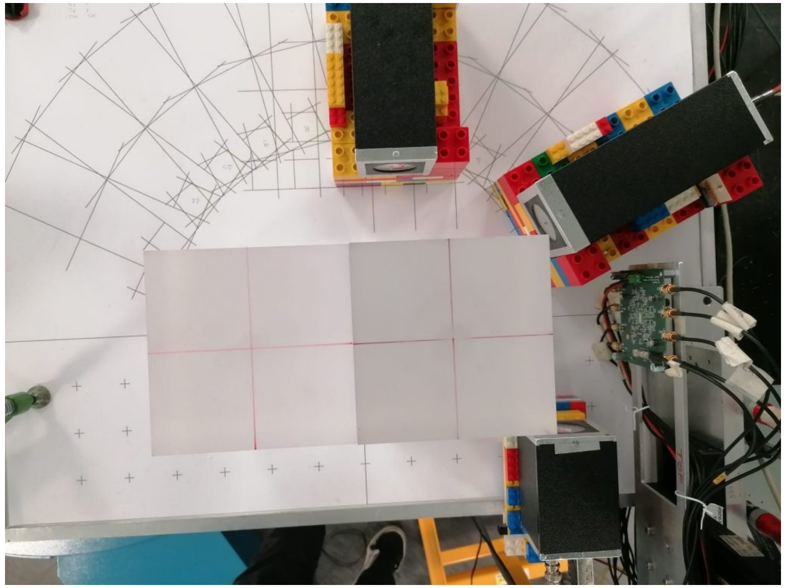
GOAL

- 110 detection modules
- Cylindric LaBr3:Ce 3.81 cm diameter, 3.81 cm height
- Readout by PMTs
- USFD beam monitor



CURRENT DEVELOPMENT

MERLINO detector



Module time resolution= 124 ps RMS @ 511 keV

Ferrero et al. JINST 2022 vol. 17 (11) C11031
https://www.to.infn.it/attivita-scientifica/ricerca-tecnologica/merlino/

Technical challenges in PGT

Time resolution

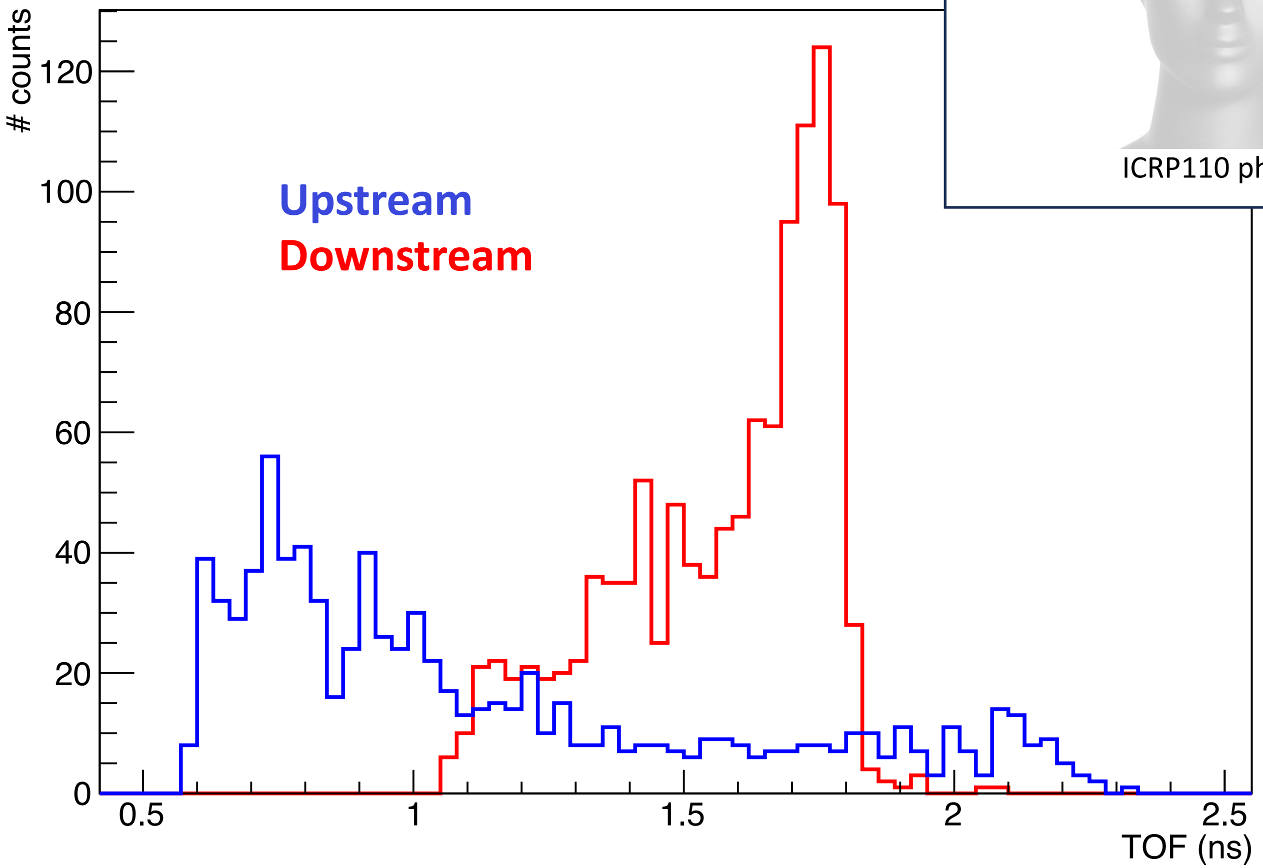
- Relevant parameters
- Beam temporal str
- Reference Time
  - RF/phase syn
  - Beam monitc

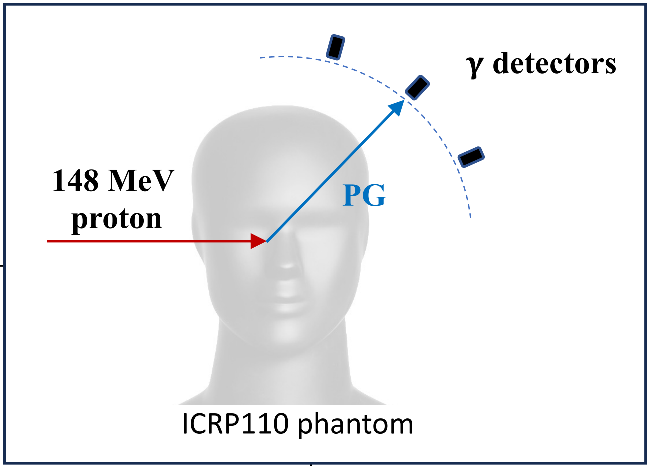
Sensitivity: towards real-tim

- Proton statistics
- SNR and backgrou
- Detector arrangem

Detector development for P

Reconstruction





Reconstruction: Prompt Gamma Time Imaging (PGTI) – v0

1) $TOF = T_{proton} + T_{PG} + T_{decay}$

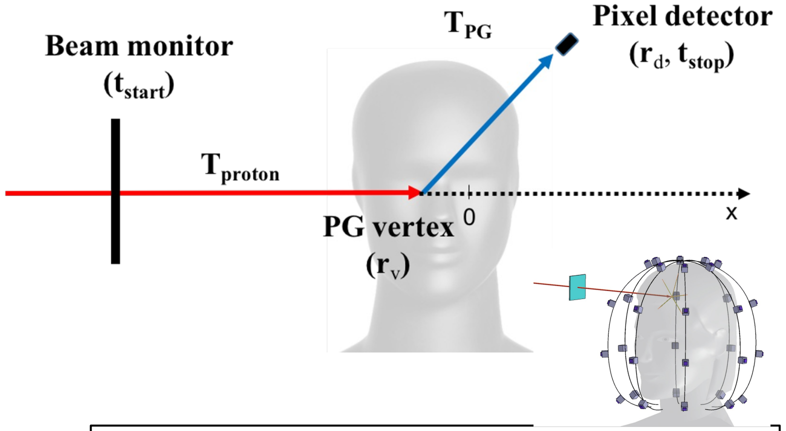
2) $TOF = \int_0^{\lambda} \frac{1}{v(s)} ds + \frac{1}{c}\sqrt{(x_\lambda - x_d)^2 + (y_\lambda - y_d)^2 + (z_\lambda - z_d)^2}$

λ = PG vertex

x_d, y_d, z_d = detector centroid coordinates

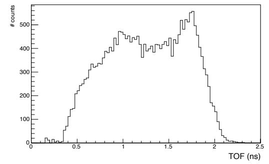
Hyp 0: $T_{decay} < 1ps$

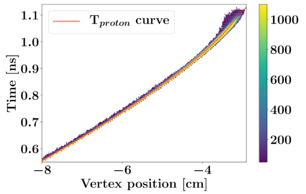
Hyp 1: Proton moves on a straight line and beam trajectory is known



3) $TOF = T_{proton}(\lambda, v) + T_{PG}(\lambda)$

- Experimental data
- Preliminary MC in TPS conditions
- Trivial function

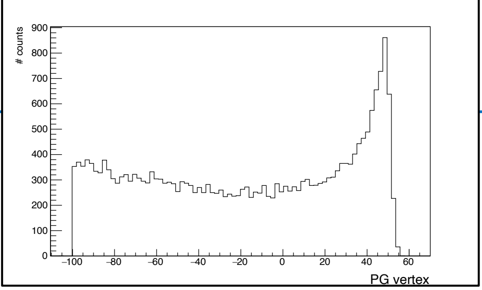




Hyp 2: T_{proton} is known from TPS

- MC simulation of proton time at different depths
- Geometry is the same of CT used for TPS
- Very fast convergence
- T_{proton} depends on anatomy

4) **Non-iterative binary search for zeros** to find PG vertex distribution (λ)



Input data

- Patient's CT scan to calculate T_{proton}
- Detectors' position (centroids)

Features

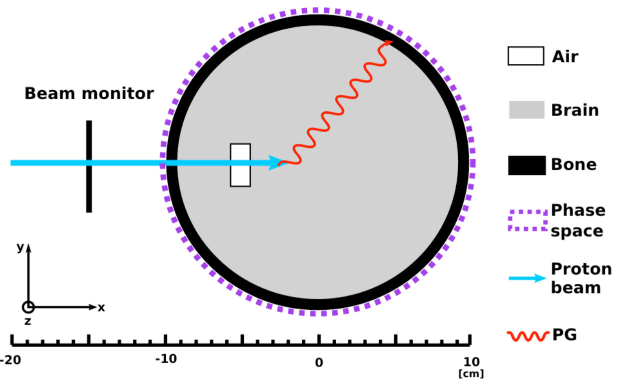
- Event-by-event reconstruction during acquisition
  => Real-time first spot probing
- DO NOT provide actual PG distribution in case of anatomical variation
- Sensitive enough to detect a variation from TPS

Jacquet et al. Phys. Med. Biol. 66 (2021) 135003;

Reconstruction: PGTI, MC validation

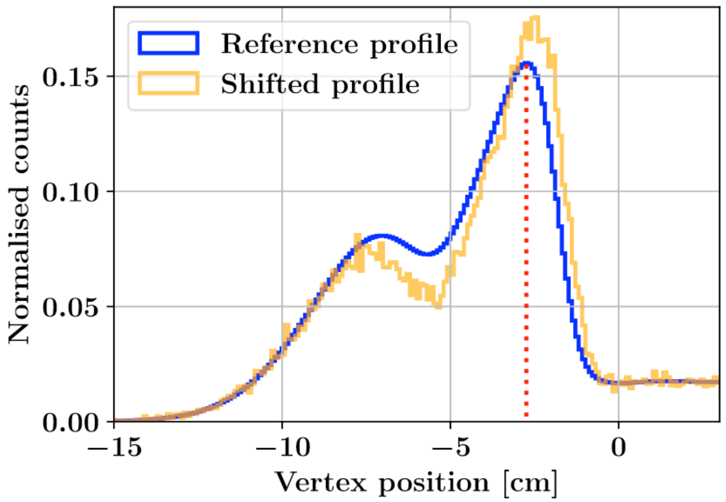
MC validation

- 100 MeV protons
- Air cavity of variable thickness
- 30 detection modules (1 cm^3)
- 0.6% overall detection efficiency

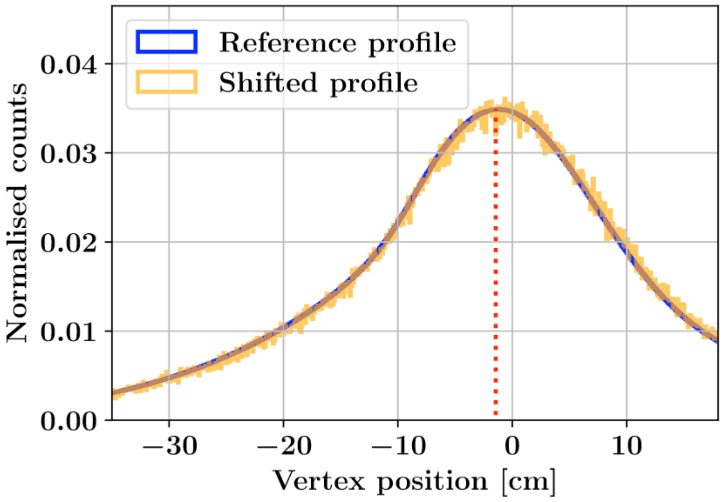


Sensitivity is a compromise between time resolution and proton statistics

SPR scenario: 10^8 protons, 100 ps rms



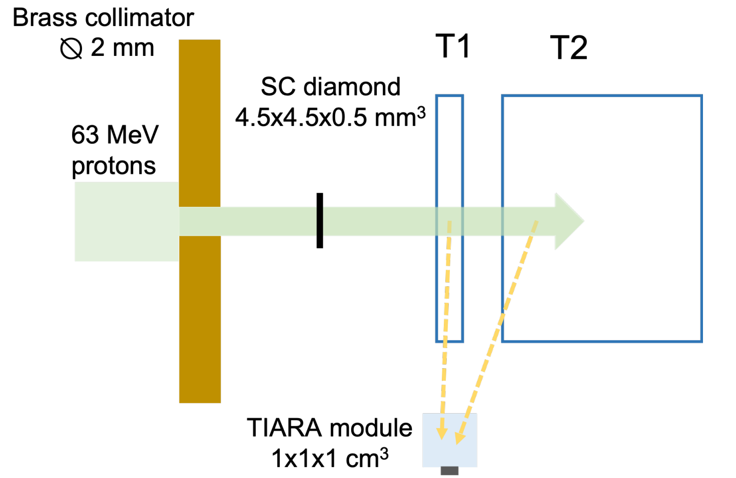
Nominal intensity: 10^9 protons, 1 ns rms



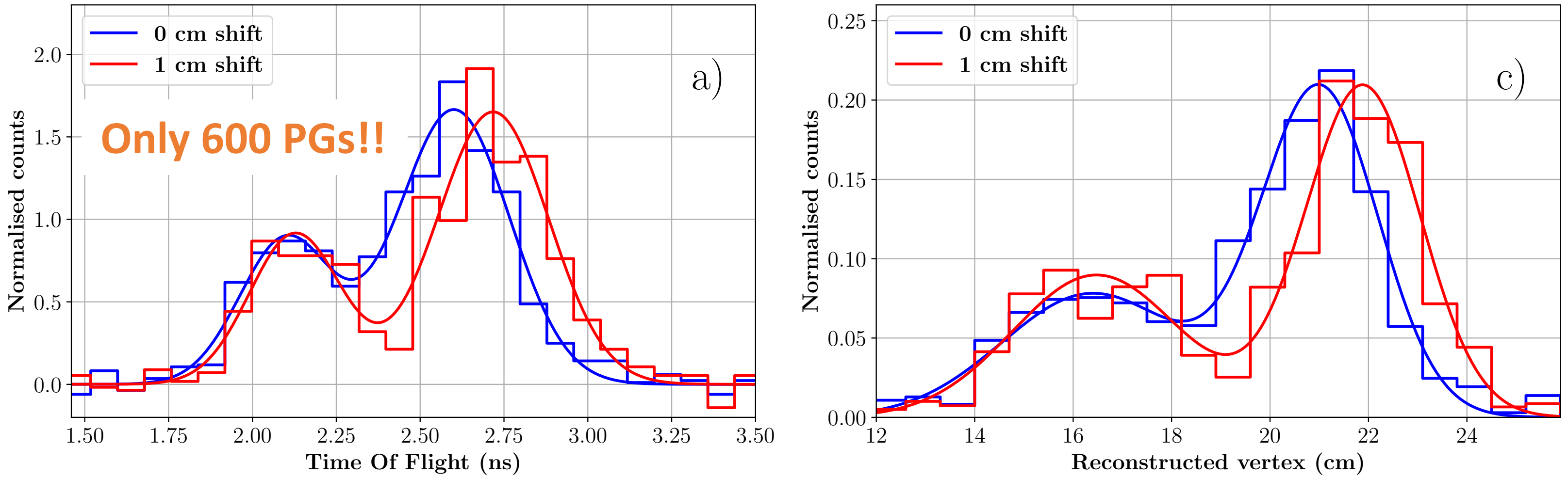
CTR (RMS)	# protons	# PG	Sensitivity at 1 σ	Sensitivity at 2 σ	Beam Intensity	Goal
100 ps	10^7	3×10^3	**2**	3	Single proton regime	Pre-treatment probing
100 ps	10^8	3×10^4	1	1		
1 ns	10^9	3×10^5	1	2	Nominal	On-line monitoring

Jacquet et al. Phys. Med. Biol. 66 (2021) 135003;

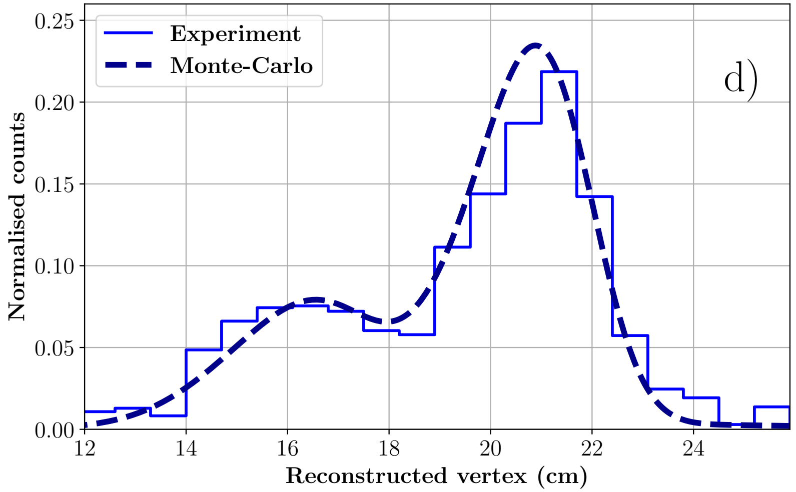
Reconstruction: PGTI, experimental validation



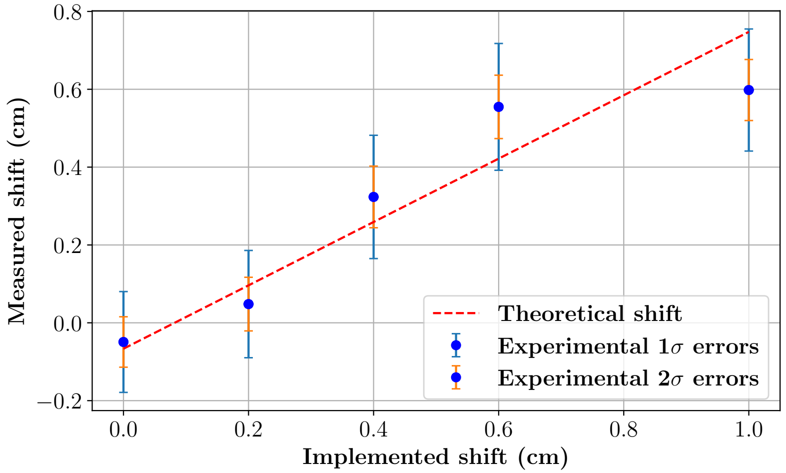
1) PG profiles from time to space domain



2) Comparison with reference conditions



2) Range shift sensitivity



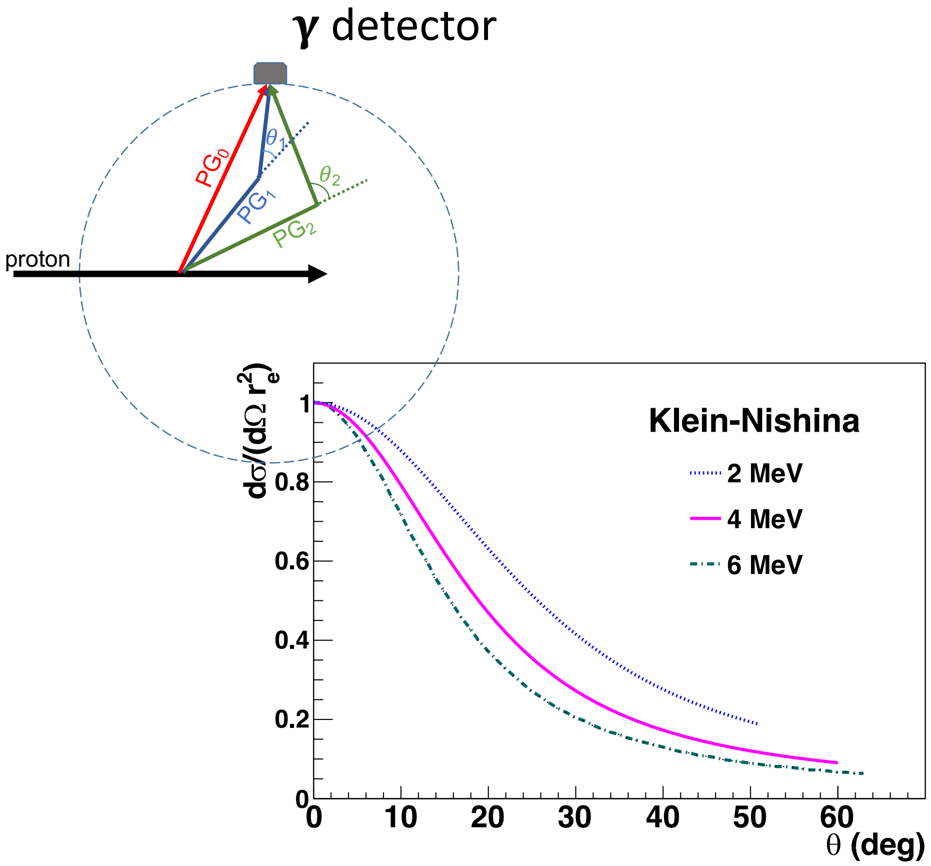
@ 63 MeV, SPR

- Can measure a proton range shift of **4 mm at 2 sigma**
- Better than anticipated by MC simulations

Jacquet et al. Scientific report (2023) 13:3609

Notes on reconstruction: low sensitivity to Compton scattering

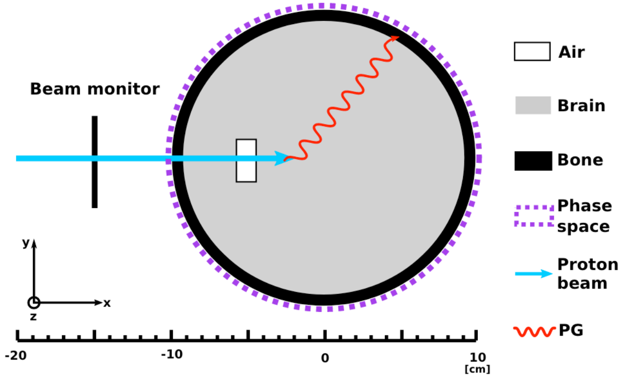
Theory…

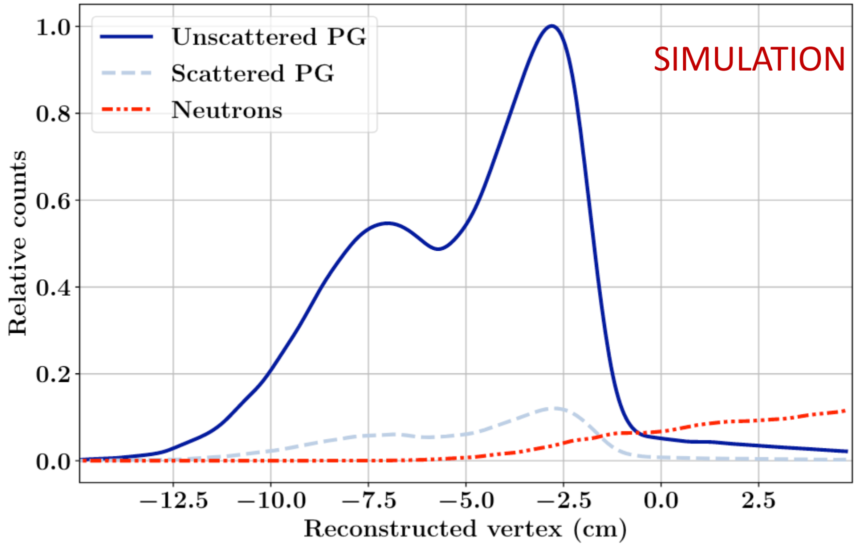


Forward scattering angles are more probable, especially at high energies.

… and a practical example

- 100 MeV protons impinging on a spherical head
- 30 perfect detectors surrounding the phantom (d=10 cm)





Few ps time delay, negligible for most PGT systems

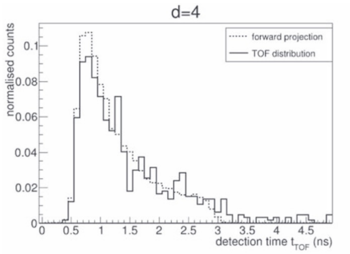
Reconstruction: Spatiotemporal Emission Reconstruction (SER-PGT)

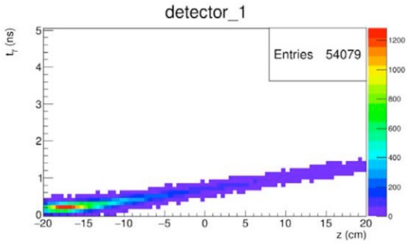
1) Hyp 0: $T_{decay} < 1ps$

2) Hyp 1: Proton moves on a straight line and beam trajectory is known

3) $TOF = t_p + t_\gamma$

Experimental data → t_p ; Preliminary MC → t_γ





Hyp 2: The system matrix H (and S) is known

- MC simulation of uniform PG distribution in vacuum
- Gives an a priori information of t**γ**(z)
- t**γ** depends on detector

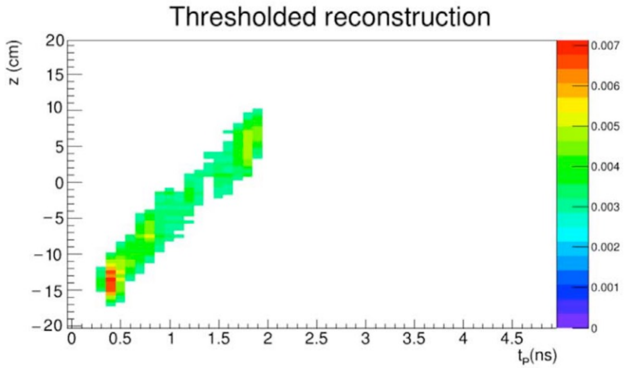
First iteration

4) **Maximum Likelihood Expectation Maximisation** to find $z(t_p)$

$$\hat{X}^{(k+1)} = \frac{\hat{X}^{(k)}}{S} H^T \frac{Y}{H\hat{X}^{(k)}},$$

k= iteration
Y = PGT distribution
X = $z(t_p)$ function (unknown)
H= detector response (system matrix)
S = detector sensitivity

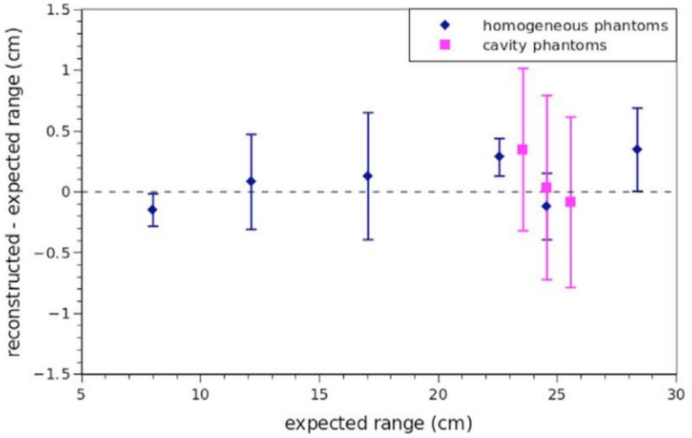
$$s_{jp} = \sum_d \sum_n h_{dnjp}.$$



Input data
- Full detector response

Features
- Provide actual T_{proton} distribution
- Proton range sensitivity with cavity phantom: 7 mm at 1 σ for 10^7 incident protons

PMMA target, 10^7 proton,



Pennazion et al. Phys. Med. Biol. 67 (2022) 065005

Reconstruction: SER-PGT

Bortfeld analytical approximation for Stopping Power

$$R_0 = \alpha E_0^p$$

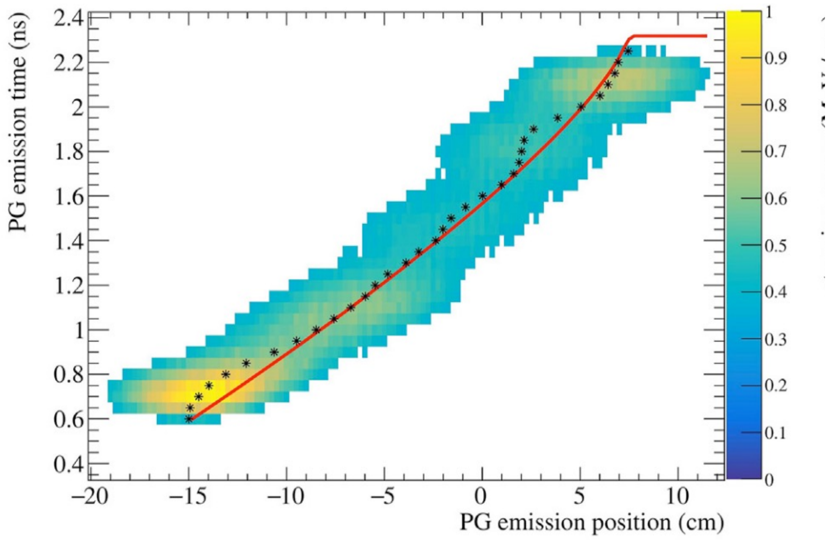
R_0 = particle range
E_0 = initial proton energy
z_0 = proton entry position

t_0 = proton entry time
p = proton energy dependent parameter
α = target material-dependent parameter

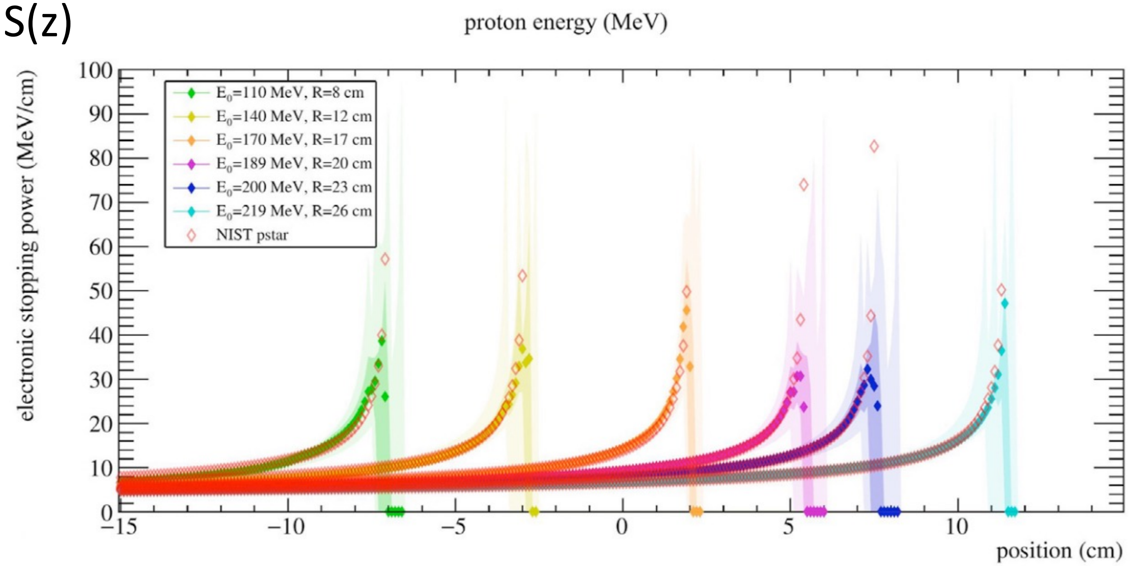
$$t(z) = \int_0^{z-z_0} \frac{\mathrm{d}\hat{z}'}{v(E(\hat{z}'))} + t_0, \quad \text{where } E(z) = \sqrt[p]{\frac{R_0 - z}{\alpha}},$$

$$S(z) = -\frac{\mathrm{d}E}{\mathrm{d}z} = \frac{1}{p\alpha^{1/p}}(R_0 - z)^{1/p-1},$$

Fit with t(z)



S(z)



Ferrero et al. (2022) Frontiers in Physics 10:971767.

<u>Range resolution ~ 0.3 cm when comparing to **NIST** data (Bethe-Bloch formula)</u>

Reconstruction: PGTI – v1, MC validation

MC MODEL (including all physics interactions)

Hypotheses

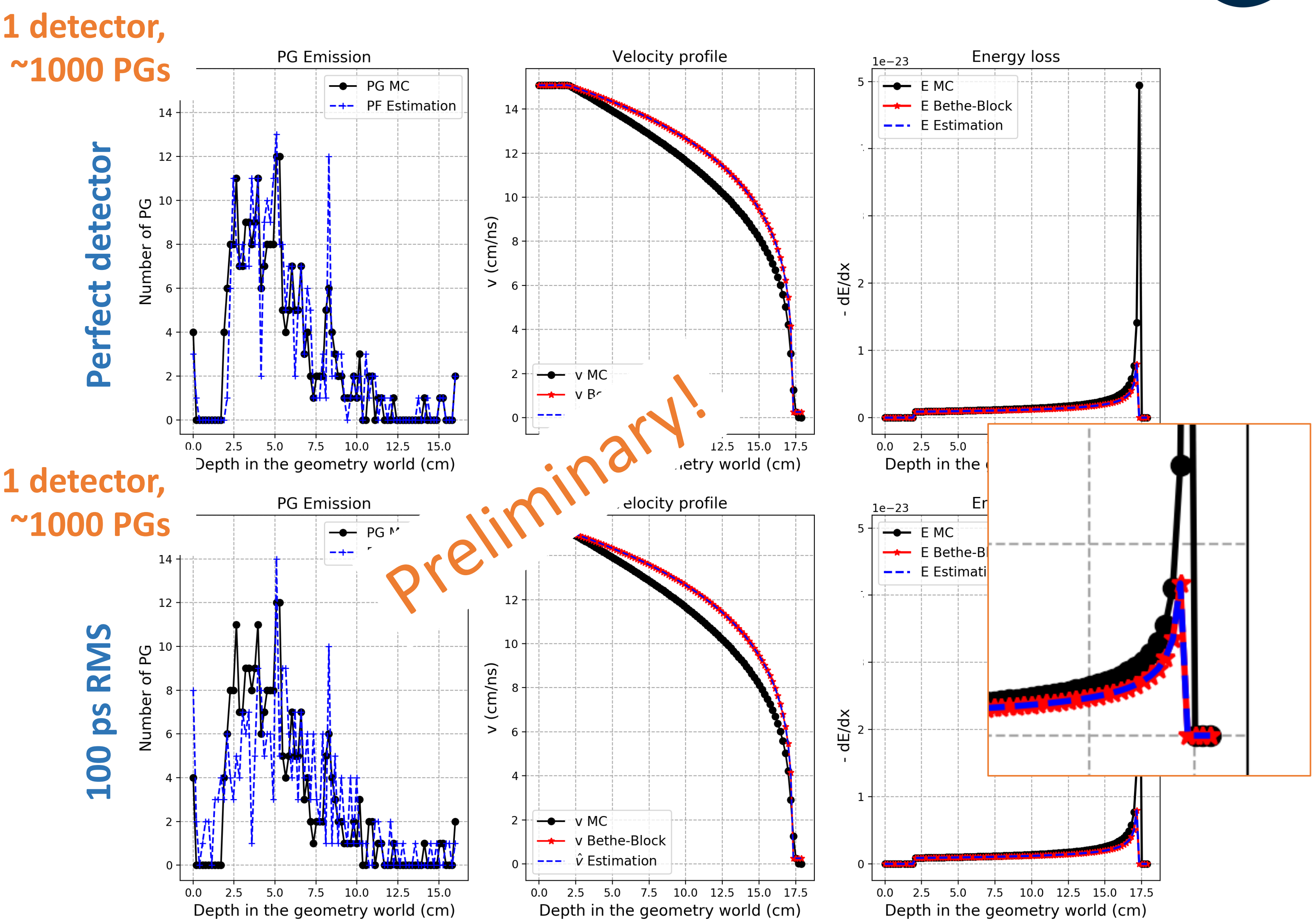
- Water sphere
- 148 MeV protons

Initial condition:

Constant proton velocity (v)

Perfect match with Bethe-Bloch theory but the algorithm should include proton scattering model to match MC data!

Courtesy of A. Cherni
To be submitted to PMB



Conclusions

- PGT technique is very promising for real-time applications
- Dedicated detection systems are being developed

  Beam monitors: Diamond detectors (in-axis or off-axis) and UFSD

  PG detection systems: Scintillator- and Cherenkov-based

- The community goes towards the use of multiple gamma detectors :
  - to increase sensitivity
  - to measure proton beam deviations in any direction
  - to achieve uniform sensitivity all over the range
- Need for dedicated reconstruction algorithms to merge data from different detectors
- The technique/detector performances ultimately depend on the time characteristics of the accelerator used

Acknowledgements

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PGTI collaboration

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CPPM Y. Boursier, A. Cherni, M. Dupont, A. Garnier, C. Morel

CAL D. Maneval, J. Hérault

We are hiring !!

Postdoc fellow (2-years)
Monte Carlo simulation and data reconstruction within the Prompt Gamma Time Imaging project
(to be opened after the summer break)

Contact: sara.marcatili@lpsc.in2p3.fr