Sub-Nanosecond Timing for In-Beam PET in hadrontherapy

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1. In-beam Positron Emission Tomography for treatment verification in hadrontherapy
   - Hadrontherapy
   - Real-time monitoring of ion ballistic
   - Interest of Time-Of-Flight PET

2. Technological factors determinig time resolution
   - Detection process
   - Experimental set-up
   - Comparison of scintillators
   - Comparison of timing algorithms

Introduction

- Hadrontherapy is raising interest for the treatment of certain tumors.
- Need for treatment verification systems.
- Positron Emission Tomography is a promising technique for this application.
- Instrumentation development is required to adapt the technique.
- Time Of Flight (TOF): a key point for performance, and a technological challenge.

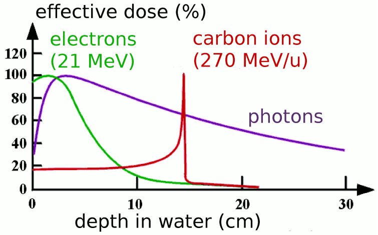
1. In-beam PET for treatment verification in hadrontherapy

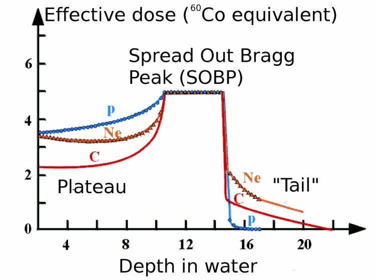
A technique for inoperable and radioresistant tumors

Localized (58%)	surgery only	22%
	radiotherapy only	12%
	surgery and radiotherapy	6%
	inoperable and radioresistant	**18%**
Metastatic (42%)	chemotherapy	5%
	palliative treatment	37%

- Cancer: 2nd cause of death in the West.
- $\approx$ 18% of localized tumors are both:
  - Inoperable, close to organs at risk.
  - Radioresistant for conventional radiotherapy.
- Hadrontherapy is suited for those tumors because of the properties of ion-matter interaction.

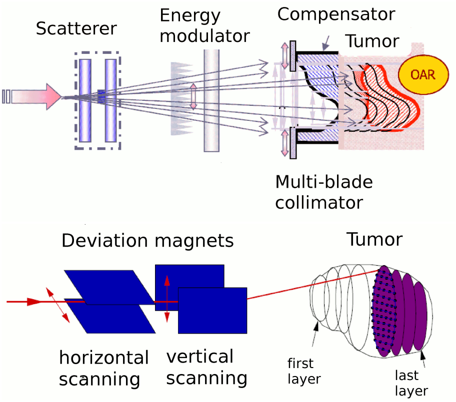
Ionisation properties and biological effect





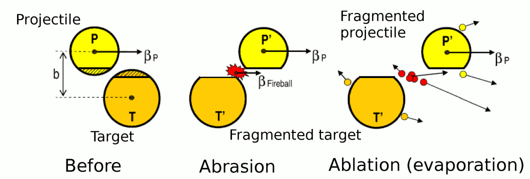
- Dose distribution:
  - Photons, electrons: dose decreases with depth.
  - Ions: maximum at Bragg peak.
- Dense ionisation in the trajectory $\Rightarrow$ high biological efficiency.
- During a treatment, the energy is modulated $\Rightarrow$ Spread-Out Bragg Peak (SOBP).
- Effective dose profile for several ions:
  - Dose (SOBP) > dose (entrance plateau).
  - Tail: radioactive fragments.
  - Carbon: adapted to hadrontherapy.

Operation



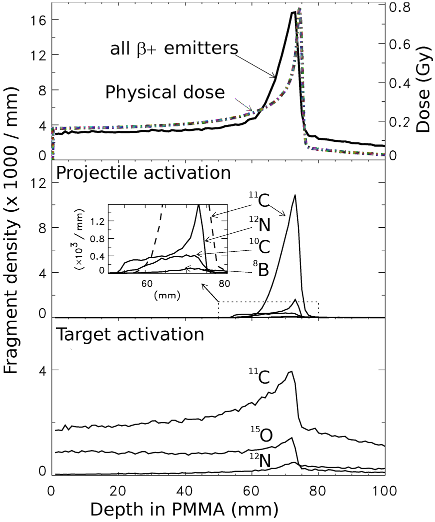
- Passive shaping:
  - Lateral scattering.
  - Energy dispersion.
  - Compensator: modulates energy.
- Active shaping:
  - Magnetic deviation: lateral scanning ($x - y$).
  - Energy modulation: depth scanning layer by layer.

Nuclear fragmentation



- Collisions ions - nuclei of the bio. medium $\Rightarrow$ fragmentation ($\approx$ 50% of C ions at 300 MeV/u).
- $\Rightarrow$ Prompt and slow activity.
- Abrasion-ablation model:
  - Collision with impact parameter *b*.
  - Abrasion: formation of a “fireball”, target and projectile fragments.
  - Ablation (ou evaporation): de-excitation, emission of n, p, γ.
  - Radioactive nuclei produced.
- Dispersion of dose after Bragg peak.
- Possibility to detect γ or β^+ activity $\Rightarrow$ PET.

Detecting β^+ activity to control the ion ballistic



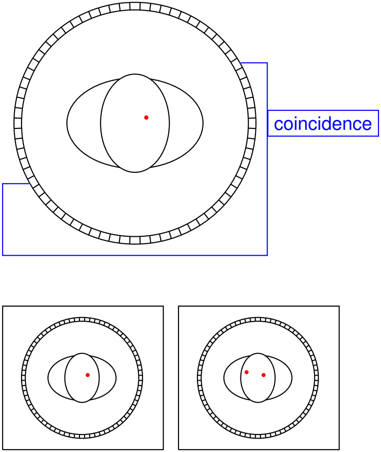
P. Crespo 2005, PosGen simulation.

- Fragmentation $\Rightarrow$ β^+ nuclei,
  - Projectile fragments: activity concentrated at the end of the traject.
  - Target fragments: spread the activity.
  - ^{11}C predominant (T=20 min).

radionuclide	half-life
^{11}C	20.4 min
^{15}O	2 min
^{12}N	11 ms
^{10}C	19.3 s
^{8}B	770 ms

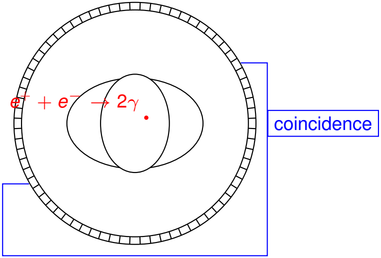
- Activity correlated with dose, maximal at Bragg peak.
- $\Rightarrow$ *In-beam PET*.

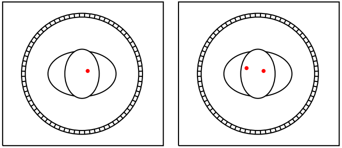
PET principle



- β^+ annihilation: two 511 keV γ photons emitted back to back $\approx 180°$.
- Coincidence detection (if $|t_1 - t_2|$ < time window).
- Recording of a line of response (LOR).
- Parasitic events:
  - Scattered pairs (30-40% of annihilation pairs).
  - Random pairs, high rate for in-beam PET (nuclear γ).

PET principle





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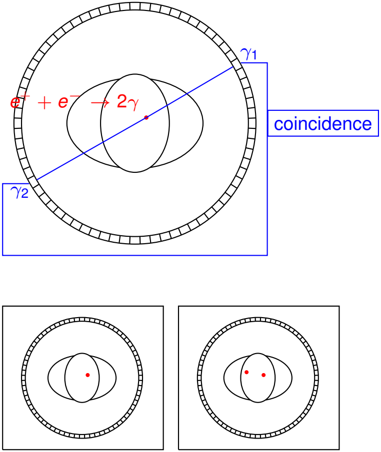

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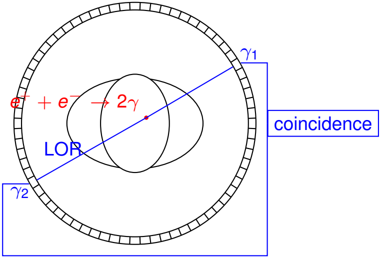

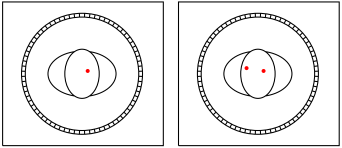

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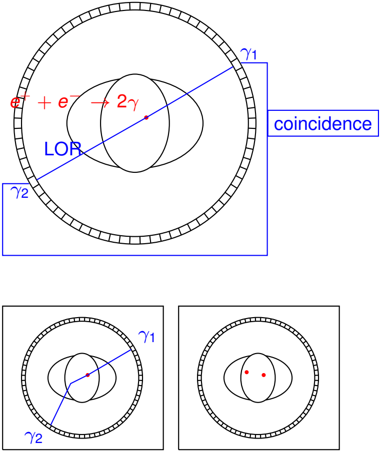

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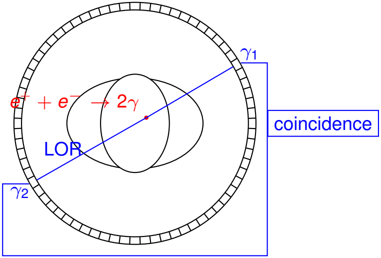

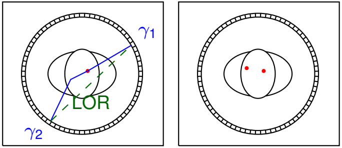

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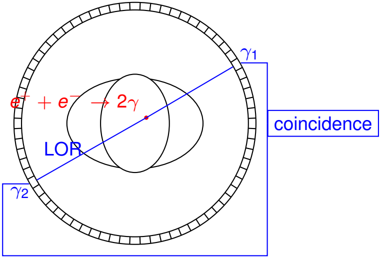

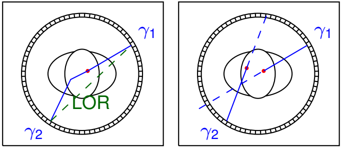

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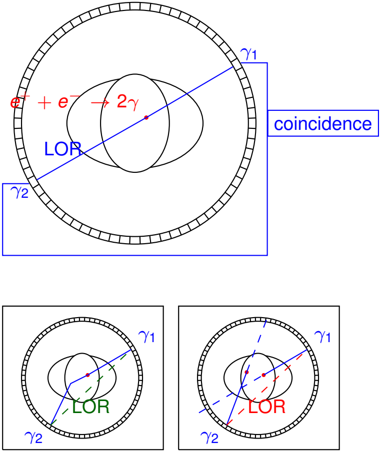

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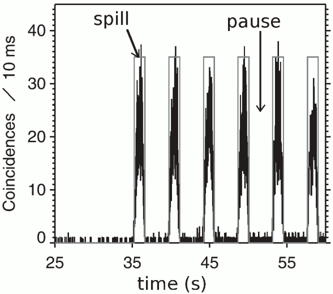
Experience on in-beam PET at GSI, Darmstadt



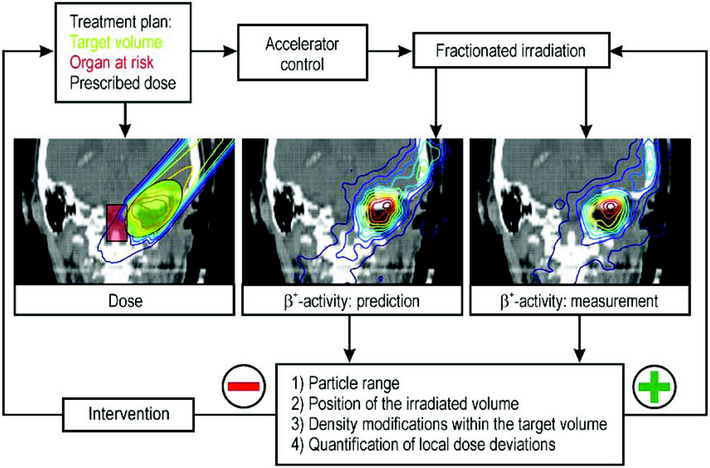
Example: BASTEI (GSI)

- Two blocks from a commercial camera (ECAT EXACT, CTI).
- System modified to stamp the events:
  - Beam on (1500 cps) ⇒ noise.
  - Beam off (200 cps) ⇒ reconstruction.
- Verification after the irradiation.

Necessary developments

- Geometry (sensitivity, artefacts).
- Rejection of randoms, beam on.
- “Real-time” verification (<session).

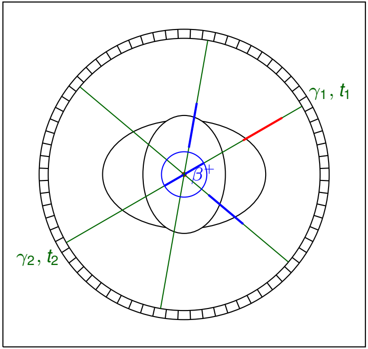
Treatment verification process at GSI

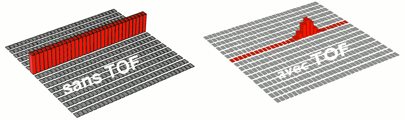


In-beam PET: a challenge

- Limits of BASTEI-like systems
  - Low β^+ activity
    - Clinical PET, radiotracer: 10-100 kBq cm^{-3}.
    - In-beam PET: 200 Bq Gy^{-1} cm^{-3} $\Rightarrow$ a few kBq cm^{-3}.
  - β^+ activity is rapidly “washed out” by metabolism ($\approx$4 min) $\Rightarrow$ “in-beam” acquisition necessary.
  - In hadrontherapy, the nb. of irradiation fractions tends to 1 $\Rightarrow$ verification must be done during one fraction.
  - Hight parasitic activity (γ, neutrons, p, e$^-$).
  - The new beams are continuous, i.e. without “macro” pause $\Rightarrow$ the acquisition must be synchronized with beam at ns time scale to reject parasitic prompt particles ($\approx$ 1 ns after fragmentation).
- Benefits of Time-of-Flight:
  - Better exploitation of the low statistics,
  - Better rejection of parasitic particles.

Time of Flight: principle and benefit

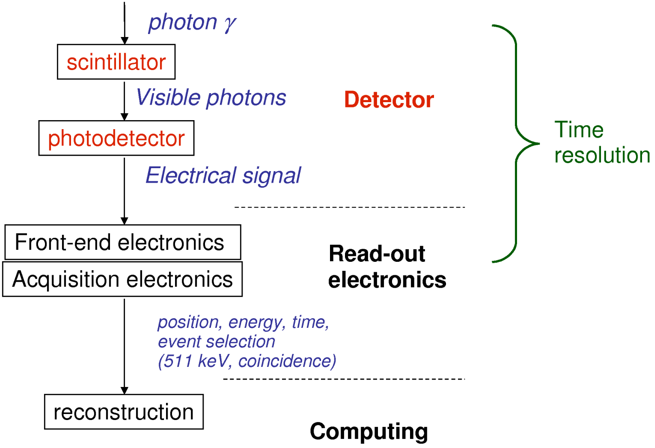




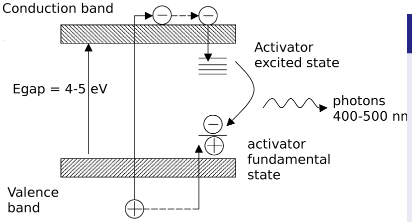
- $t_1 - t_2 \Rightarrow$ localization along the LOR
  - Time resolution Δt,
  - Localization $\Delta x = c/2\,\Delta t$,
  - Example 500 ps $\longrightarrow$ 7.5 cm.
- Better rejection of randoms.
- Better image quality by reducing the coupling btw. voxels:
  - Smaller statistical noise (factor $D/\Delta x$),
    - Example: whole body PET,
    - $\Delta x = 7.5$ cm, $D = 40$ cm,
    - $\Rightarrow$ Improvement factor $F = 5$.
  - Reconstruction: faster convergence.
- Time of flight is the industrial state of the art of recent clinical PET systems.

2. Technological factors determinig time resolution

Detection process



Inorganic scintillators for PET



Scintillation mechanism

- Photoelectric or Compton interaction.
- Secondary ionisations in cascade.
- Excitation of luminescent centres.
- Radiative de-excitation 400-500 nm, decay time=some 10 ns.
- Random emission times $\Rightarrow$ statistical limit to time resolution.

Candidate materials

name	attenuation length at 511 keV (mm)	PE fraction (%)	light yield (ph/keV)	decay time (ns)
LSO	11.4	32	30	40
LYSO	12		32	41
LPS	14.1	29	20	30
LuAP	10.5	30	11	18(90%)
$LaBr_3$ (h)	22.3	13.1	70	16
$LaCl_3$ (h)	28.0	14.7	46	25(65%)
LuI_3 (h)	18.2	28	95	24(60%)

drawbacks (h):

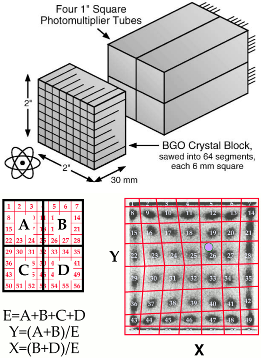
hygroscopic

advantages

Photodetectors: today

Photomultiplier tubes (PMT)

- Only photodetectors used in clinical PET until now.
- Advantages: fast, high gain.
- Drawbacks: dimensions ⇒ block detector with position "decoding".



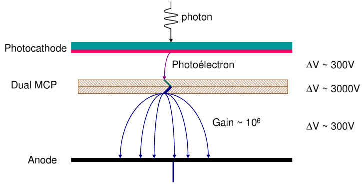
Detector block

- Light sharing btw. 4 PMT,
- Position reconstructed from charge ratios,
- Light loss and propagation path limit time resolution.

Compact photodetectors

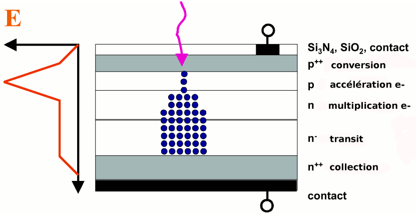
Micro-Channel Plate Photo Multiplier Tubes (MCPPMT)

- \+ High gain (10^5-10^6),
- \+ Very fast response,
- \- Cost of commercially available models,
- \- Aging.



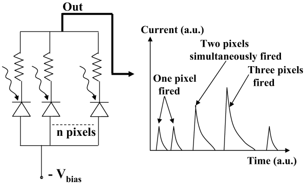
Avalanche Photo-Diode(APD)

- \+ High quantum efficiency (70-80%),
- \+ Low cost,
- \- Noise,
- \- Low gain (50-200).

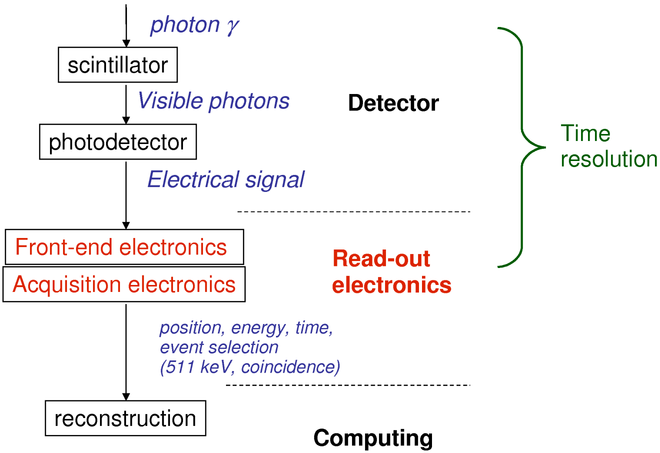


Geiger-mode APD matrices (SiPM)

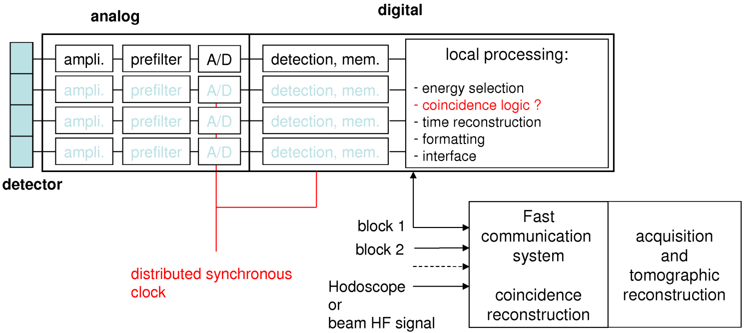
- \+ High gain (10^5-10^6),
- \+ Fast response,
- \- Noise,
- \- Stability T° and V_{pol}.



Signal read-out



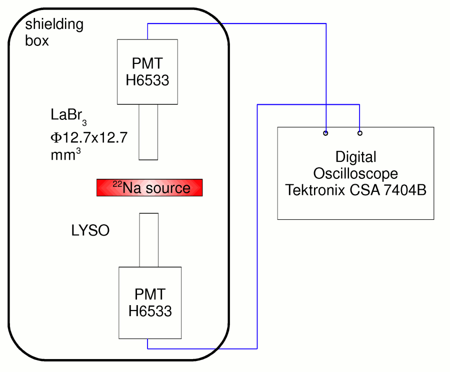
Digital front-end concept

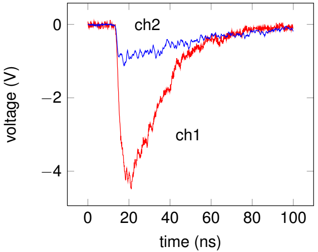


Avantages compared to analog circuits

- Generic scheme,
- Reconfigurable,
- Versatile,
- Stability: baseline shift correction,
- Piled-up events can be handled.

Two detectors in coïncidence

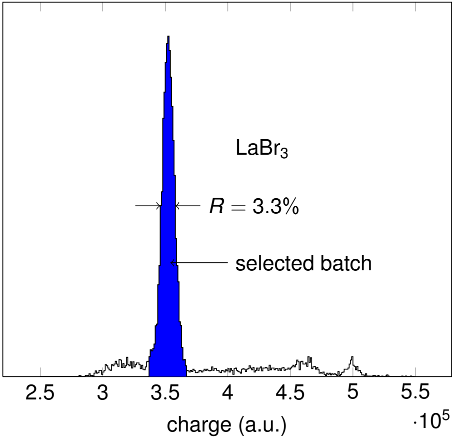




- Channel 1: "fast", reference channel, $LaBr_3$ (16 ns, 63 ph/keV).
- Channel 2: "test channel", here LYSO (41 ns, 32 ph/keV).

- Fast PMTs (rise $\approx$ 700 ps).
- Oscilloscope Bandwidth=4 GHz, Sampling Rate=10 GSps.
- Algorithm $\Rightarrow$ event energy and time.

Data Processing



- Event selection on energy ($\pm 2.5\sigma$).

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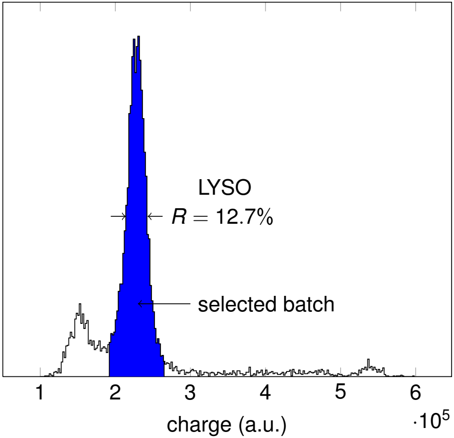

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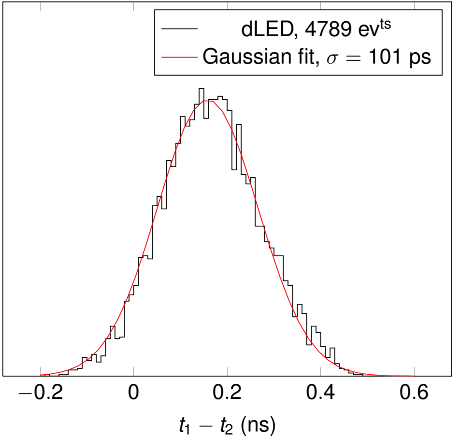


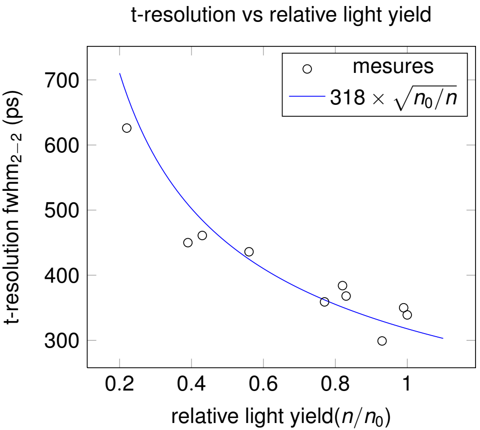
- Event selection on energy ($\pm 2.5\sigma$).
- First measurement: $LaBr_3$ on both channels, $\text{fwhm}_{1-1} = 237\ ps$.
- Second measurement: $LaBr_3$ on ch1, LYSO on ch2, fit gives fwhm_{1-2}.
- Meaningful figure: coincidence resolution for 2 detectors like ch2 $\text{fwhm}_{2-2} = \sqrt{2 \times \text{fwhm}_{1-2} - \text{fwhm}_{1-1}}$.

Crystal shape and reflector

- Test channel 2: LYSO crystal of different shapes and surface state.
- In each case, we measure:
  - Time resolution,
  - Peak of amplitude distribution $\propto$ nb of photoelectrons n,
  - Light yield is normalised by the best configuration, n_0.
- Time resolution is normalised by $\sqrt{n_0/n}$.

dimensions		reflector	relative nb. of	t-resolution fwhm$_{2-2}$ (ps)	
length (mm)	coupled area (mm^2)		phe$^-$ n/n_0	measured	normalized $\times\sqrt{n/n_0}$
4	4×22	white painting	1	339	339
4	4×22	none	0.82	384	348
4	4×22	black paint.	0.22	626	292
22	4×4	white paint.	0.43	461	304
22	4×4	none	0.56	436	328
22	4×4	Teflon tape	0.77	359	315
22	4×4	aluminum sheet	0.39	450	283
22	5×5	Teflon	0.83	368	336
2	2 × 10	white paint.	0.93	299	288
10	10 × 10	white paint.	0.99	350	348

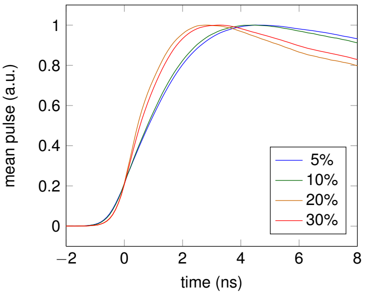
Correlation between light yield and time resolution



- Relation in $1/\sqrt{n}$ confirmed.
- No extra effect of light propagation time in long crystals.

Comparison of $LaBr_3$ crystals with increasing cerium concentration

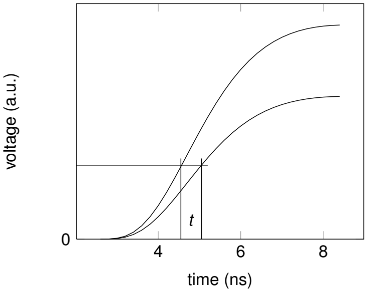
% Ce	relative nb. of phe$^-$	t-res. fwhm$_{2-2}$ (ps)	
		measured	normalized $\times\sqrt{n/n_0}$
5	1	255	255
10	1.11	236	249
20	1.30	160	182
30	0.62	194	152



- Rise time decreases with increasing Ce concentration.
- Light yield changes must be corrected for.
- Normalized t-resolution is improved.
- Problem: high Ce concentration makes the crystal brittle.

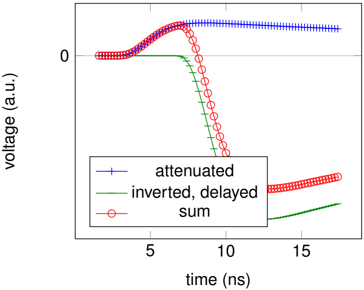
Timing algorithms

Leading Edge Discriminator (LED)



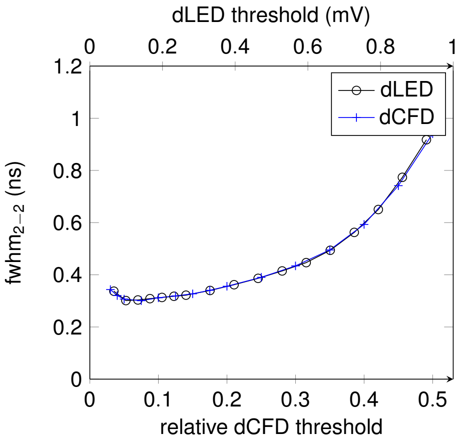
- Search the time when signal crosses threshold.
- Fine time by interpolation.
- Sensitive to amplitude fluctuation.

Constant Fraction Discriminator (CFD)



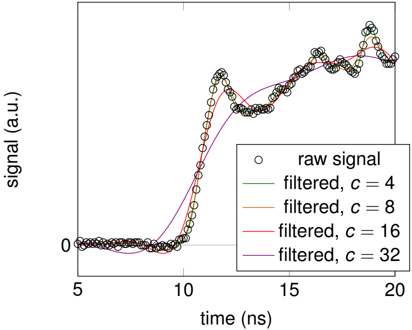
- Search the time when bipolar signal crosses ground level.
- Insensitive to amplitude fluctuation.

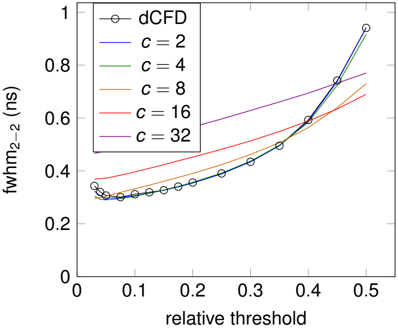
Results



- Results very similar with dLED / dCFD.
- Cause: amplitude fluctuation $\ll$ shape fluctuation.
- Optimal threshold $\approx$ 6-8%.
- Time reconstructed by least squares fit of the pulse with a reference shape: $\mathrm{fwhm}_{2-2} = 552$ ps.
- The time information is carried by the initial part of the rising edge (first photoelectrons).

Effect of low-pass filtering

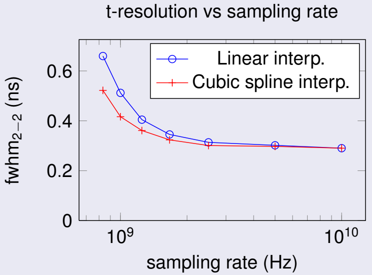




- Optimal low-pass filtering $c \approx 5$: little improvement.
- Results degrade if frequency cut (3dB) < 1GHz.

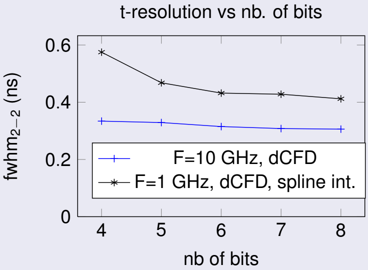
Effect of sampling rate and ADC resolution

Sampling rate



- Signal is downsampled at freq. F/n.
- Strong dependence at $F < 1.5$ GSps.
- Little improvement beyond.
- Curve interpolation useful when $F \approx 1$ GSps.

ADC Resolution



- 5 bits are enough.
- 4 bits at $F = 10$ GSps.

Conclusions

- In-beam TOF PET $\Rightarrow$ instrumentation challenge.
- Time resolution is limited fundamentally by the scintillation process:
  - Light yield and time constants are crucial.
  - The information is carried by the first photoelectrons.
  - T-resol. $\propto 1/\sqrt{n}$ (nb. of phe$^-$) $\Rightarrow$ a gain is possible on light collection efficiency and photodetector quantum efficiency.
- MCPPMT development is promising for PET: large area, fine position reconstruction, high gain and fast response.
- The recent developments in fast sampling electronics make possible a TOF PET system with digital signal readout.
- Simple and performant algorithm proposed: low-pass filter and constant fraction discriminator, with ajusted parameters.

Perspectives

- In-beam measurements at GANIL ion cyclotron, Caen, France (first experiment done, analysis soon):
  - Count rates ?
  - β^+ emitter production rate ?
  - Possibility to discriminate β^+ and prompt γ events ?
  - Specifications for a dedicated electronics ?
- Collaborations involving Clermont-Ferrand:
  - National scale: GdR MI2B / WP9 *Contrôle de dose en ligne* (in-beam dose monitoring).
  - 7th European Framework Prog. / ENVISION *European NoVel Imaging Systems for ION therapy*.
  - Large Area PhotoDetector (LAPD) project, use of Micro-Channel Plate PMTs.

Thank you for attention