PET monitoring of proton therapy: an overview

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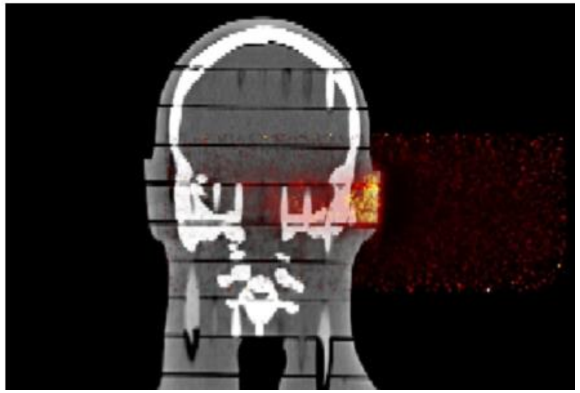
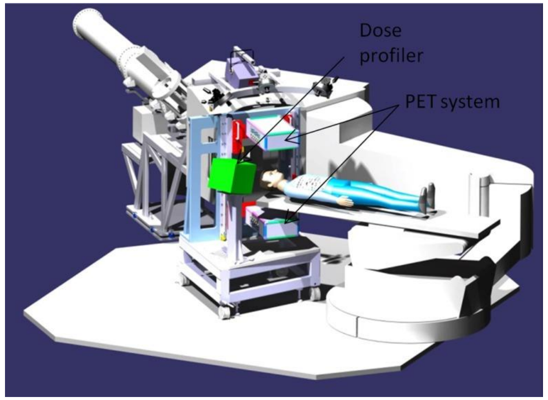




Outline

Basic notions

- Particle therapy and radiotherapy
- Range uncertainties

Treatment monitoring

- About secondary radiation
- PET cameras as monitoring system

Applications

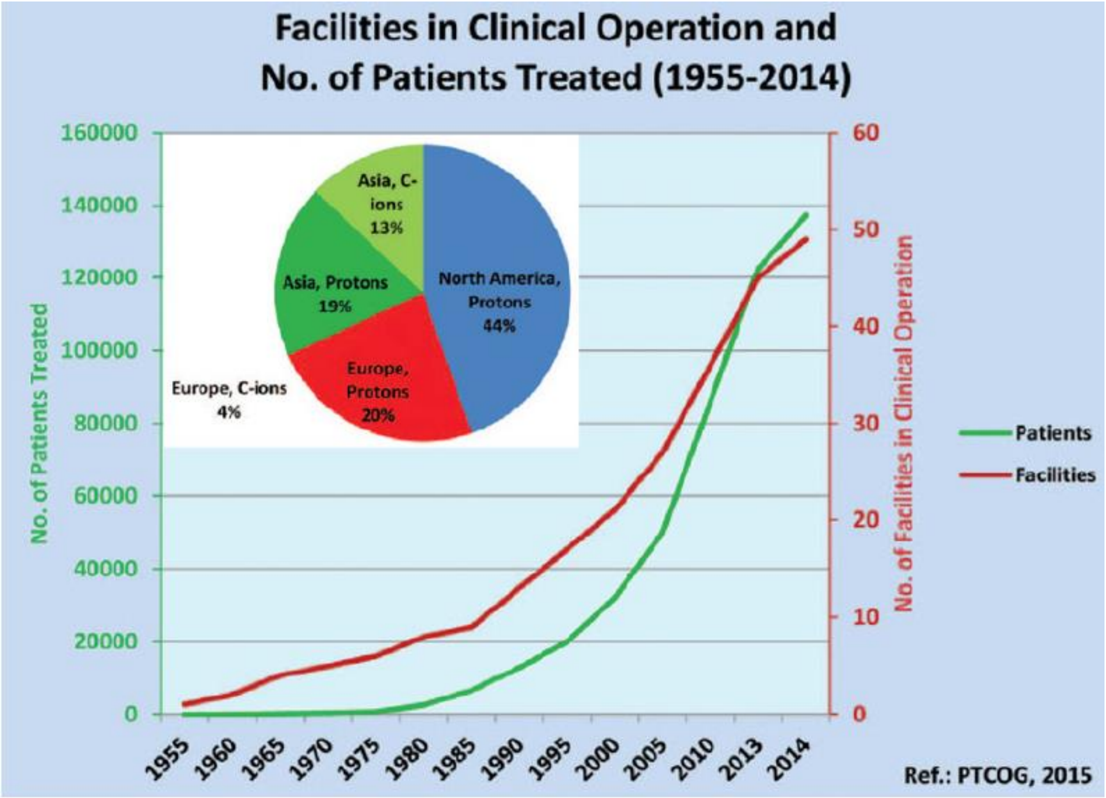
- The INSIDE project
- Conclusions

Hadrontherapy

BASIC NOTIONS

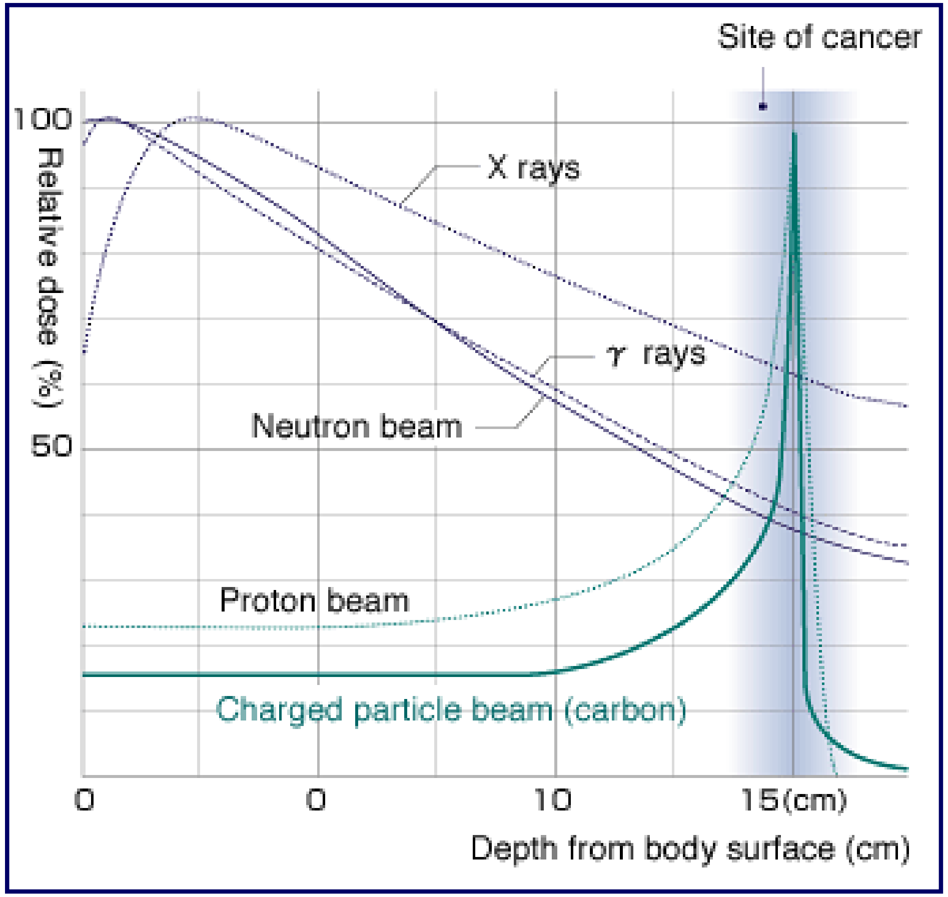
Standards of cancer therapy

- Combination of:
  - Surgery
  - Chemotherapy
  - Radiotherapy
- Only 0.8% of radiotherapy involves particles…
- …but charts show that number of patients is increasing!



Hadrontherapy

- Involves the use of hadronic beams to deliver energy to tissues:
- Main advantage: deposited energy shows a steep peak at the end of range, known as Bragg peak
  - Better depth-dose distribution compared to radiotherapy
  - Reduction of side effects
- Downside:
  - X-rays are a cheaper solution!
  - Range uncertainties



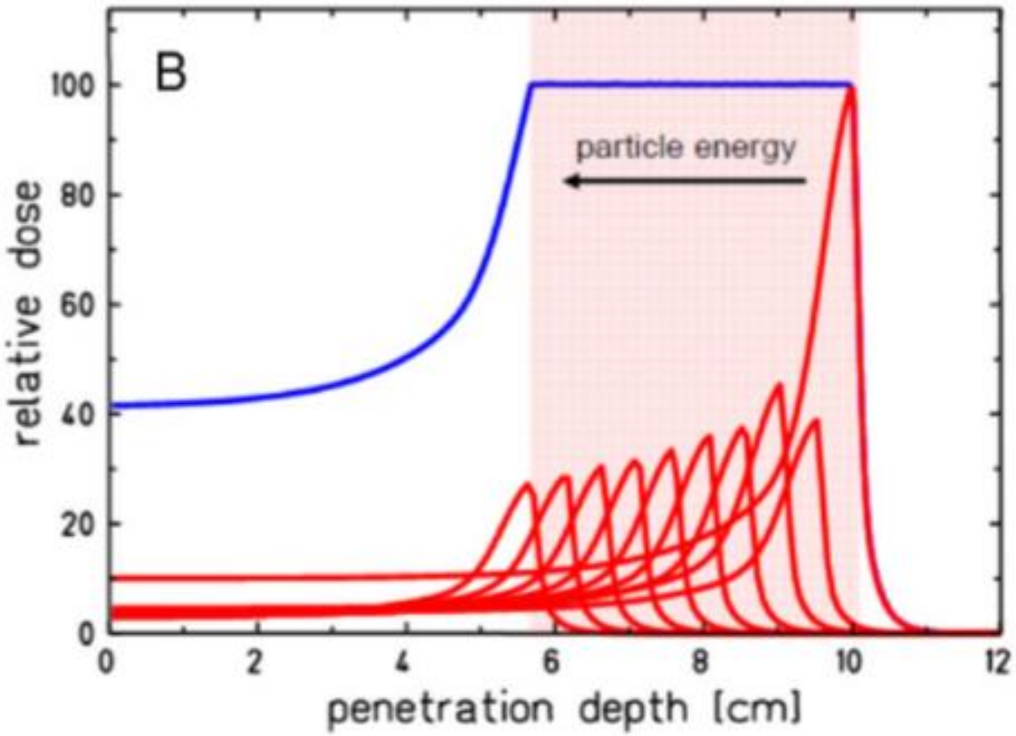
Passive scattering vs Active scanning

- Passive scattering:
  - Narrow beam broadened using:
  - Apertures for lateral conformation,
  - Range compensators that yield the Spread-Out Bragg Peak (SOBP)
  - Complex and patient -specific machinery required

- Active scanning:
  - Narrow, mono-energic pencil beam scanned across the target via two magnets
  - Planning is easier
  - Yields a greater target dose conformity

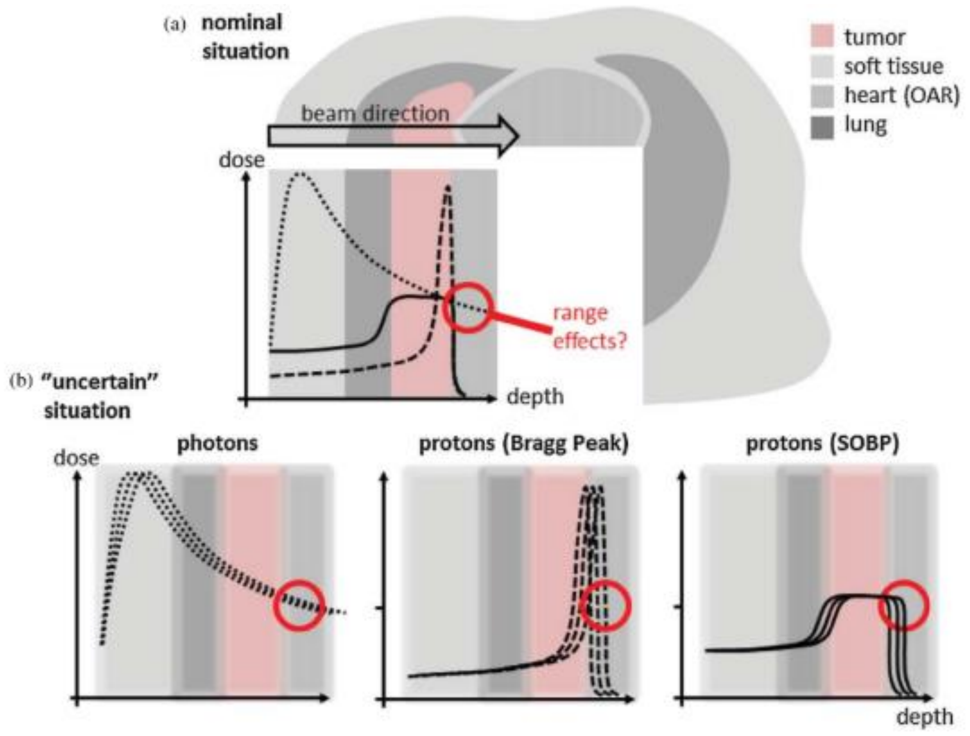
Spread-Out Bragg Peak

- The Bragg peak must be extended to cover all the tumour
- Different pristine beams with different intensity are overlapped (red lines)
- The resulting dose (blue line) is known as Spread Out Bragg Peak (SOBP)



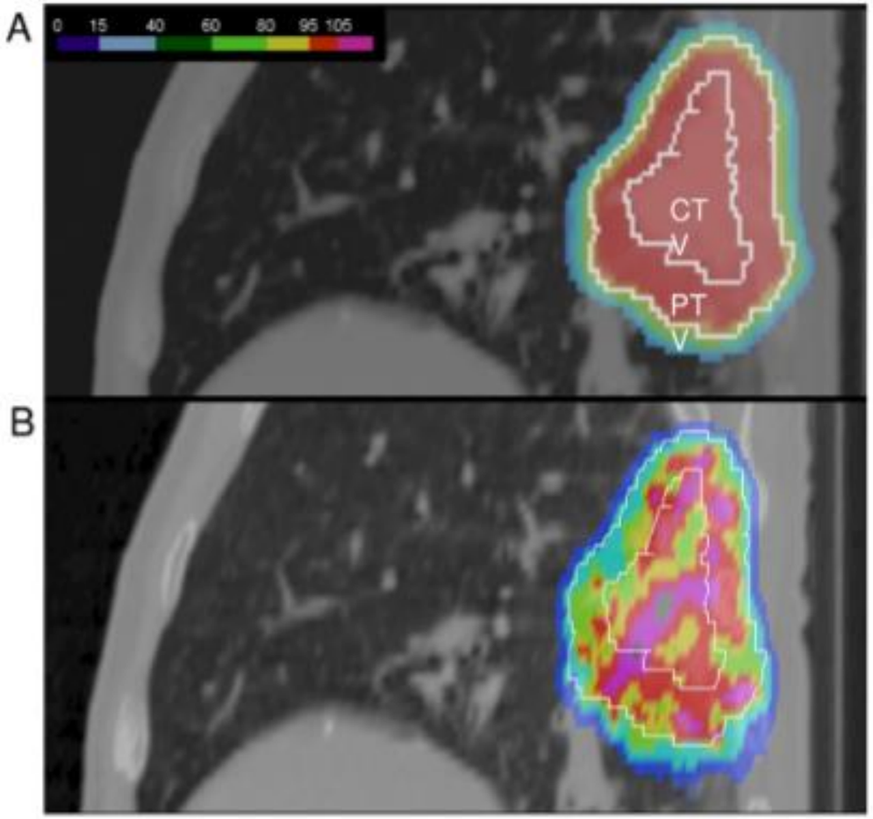
Range uncertainties

- General uncertainties:
  - Beam reproducibility
  - Positioning of patient and tumour variation
  - Compensator design
- Dose-dependent uncertainties
  - Biology: relative biological effect
  - Imaging and calibration?
- No analytical approach available
- Monte Carlo simulations are performed in order to study adequate treatment plans



Uncertainties: organ motion

- In active scanning, organ motion jeopardises the dose distribution:
- Upper figure:
  Planning requires uniform dose the clinical target volume (CTV) and in the Planning Therapy Volume (PTV)
- Lower figure:
  Non-uniform dose due to organ motion!



Treatment monitoring

SECONDARY RADIATION

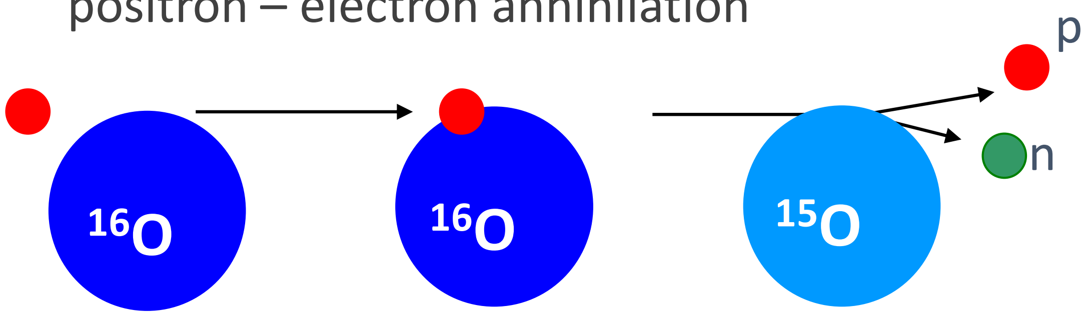
Monitoring proton therapy

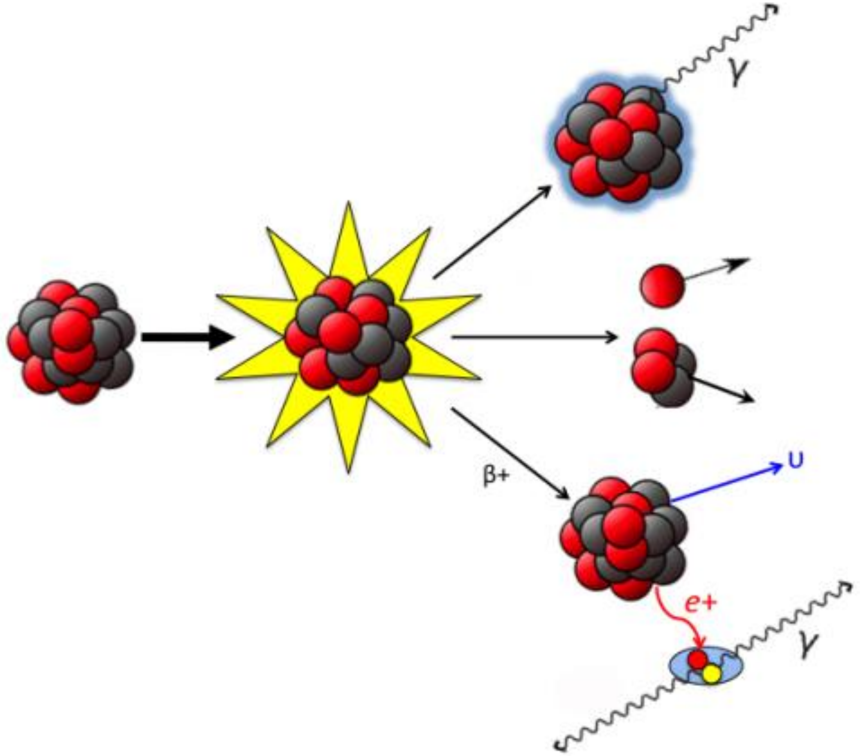
- Previous examples show the importance of monitoring
- Exploit the properties of charged particle therapy:
  - Secondary radiation such as photons and charged particles
- Three different methods:
  - PET (Positron Emission Tomography) – positron emitting nuclei can be created when ion beams travel through matter
  - Prompt gamma radiation – some nuclear de-exicitations lead to photon creation
  - Charged particles detection – charged particles can be detected

Secondary radiation

- Kinetic energy is transferred from the beam to the target, leading to several processes
  - Nuclear de-excitation
  - Nucleon loss, leads to
    - Charged particle emisson
    - β+ decay

- PET focuses on β+ decay and consequent positron – electron annihilation





β+ decay and PET imaging

$$G(A,Z) \rightarrow F(A,Z-1)$$

$$p \rightarrow n + e^{+} + \nu_e$$

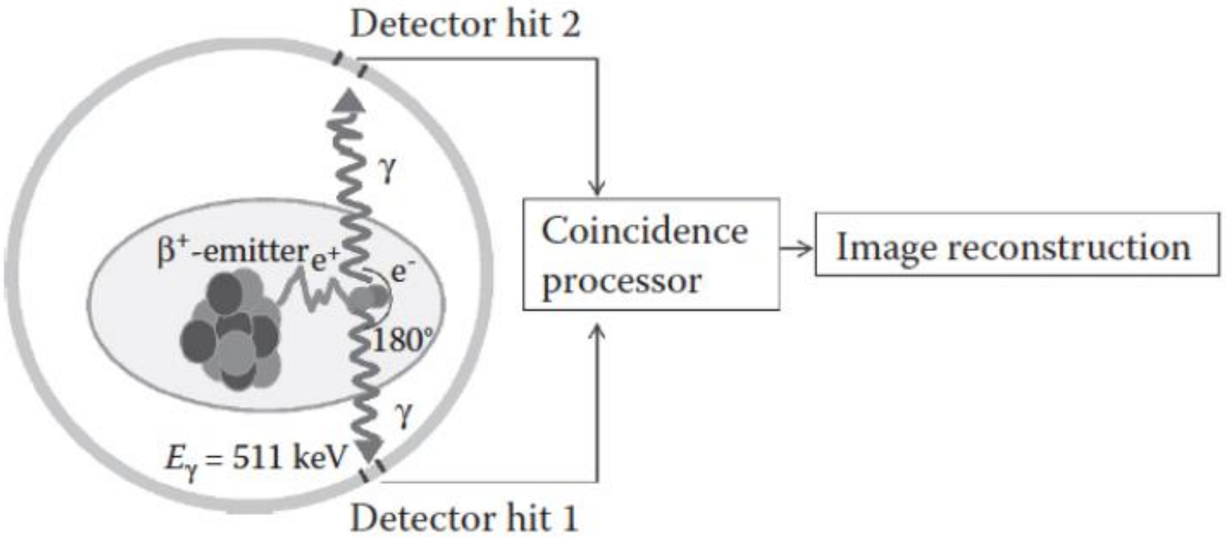
The isotopes most commonly found in biological systems are 15O and 11C:

$T_{15\text{-}O}$=121.8 s $T_{11\text{-}C}$=1222.8 s

Positron emission is followed by annihilation with an electron:

$$e^{+} + e^{-} \rightarrow 2\gamma$$

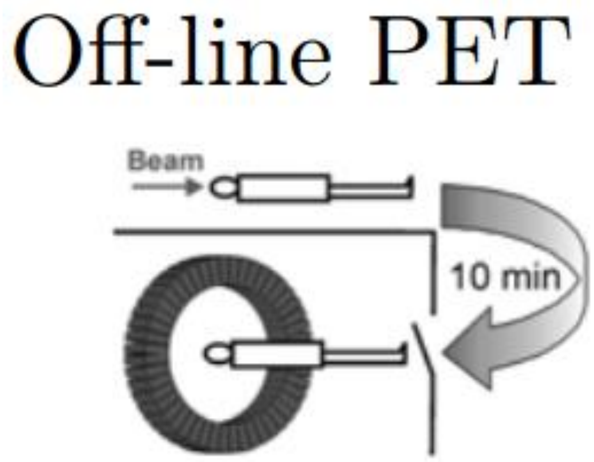
The energy of each photon created in the annihilation is equal to the rest energy: 511 keV



Off-line PET

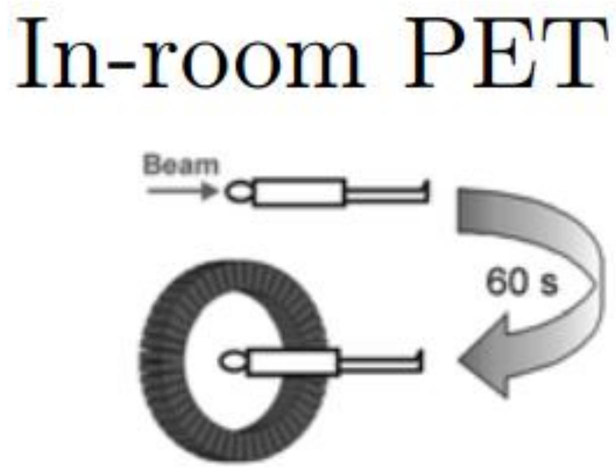
- Measurements are carried out after ion irradiation
- The patient is moved to a conventional PET scanner
- Activation induced by irradiation is compared with a Monte Carlo simulation

- Influence on treatment plan:
  - 25-40 mins extra time
  - Activity is influenced by decay of emitters and metabolic processes
  - Low costs



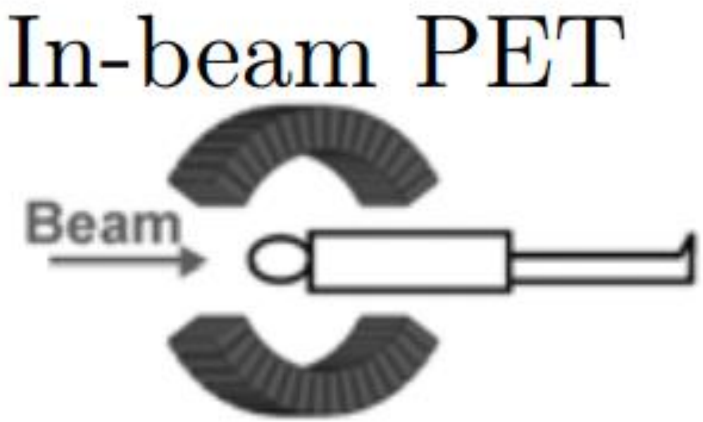
In-room PET

- A PET scanner can be positioned in the same room where treatment takes place
- Reduction of time delays: 4 mins per radiation
- Activity is moderately influenced by the decay of emitters
- Moderate cost



In-beam PET

- Delays in treatment plans are reduced to 40 sec per radiation
- Measurement is more relevant than off-line and in-room pet:
  - Better correlation between distribution of the measured activity and the deposited dose
- High costs compared to previous methods
- Cyclotron machines produce continuous beams
- Sychrotron machines deliver beams during short phases, known as *spill*, followed by a pause (*interspill*)

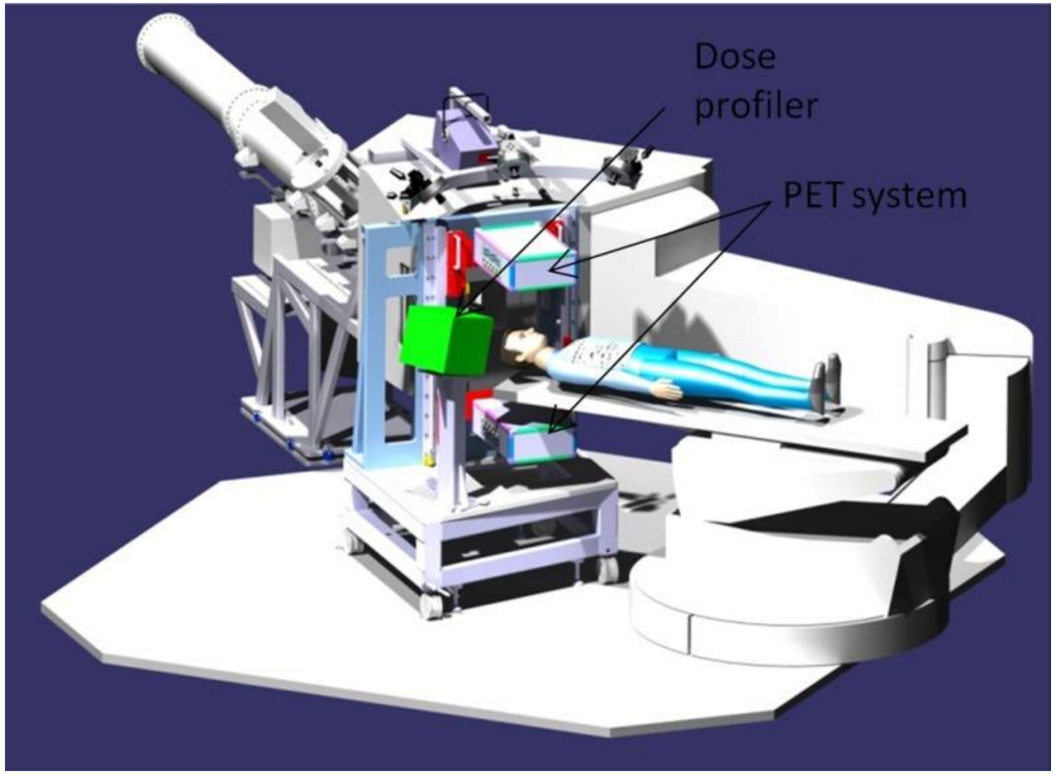


INSIDE project

SOME RESULTS

INSIDE project: Innovative Solutions for In-beam DosimEtry in hadrontherapy

- INSIDE project is an example of on-line verification
- Bimodal system
  - β+ activity
  - Charged particle tracking
- Active delivery system, the target is subdivided in isorange slices
- Beam energies: 74-135 MeV
- Doses 1-2 Gy



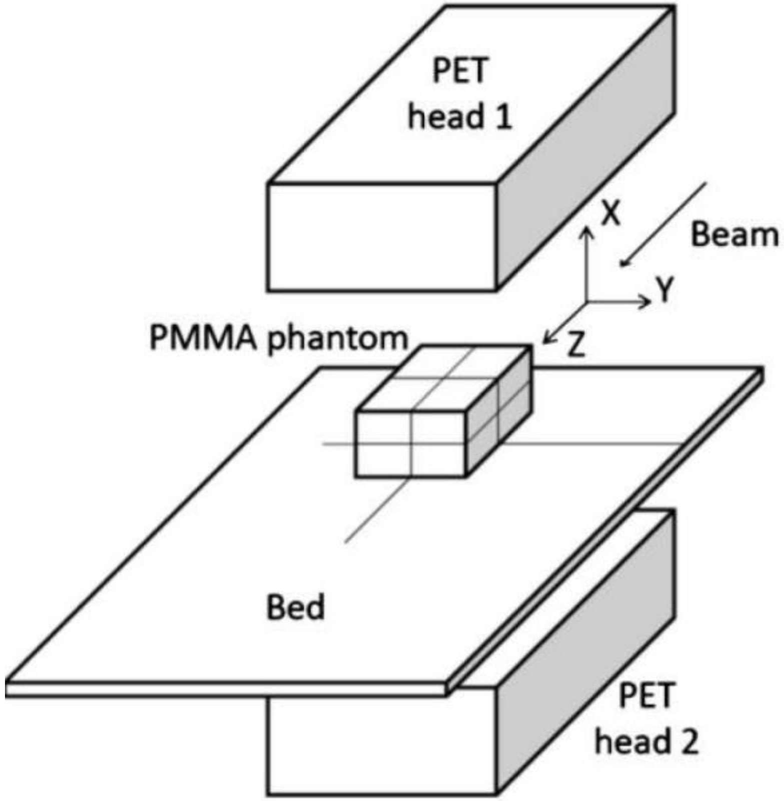
Ref: Bisogni et al. «Inside in-beam positron emission tomography system for particle range monitoring in hadrontherapy.» *Journal of Medical Imaging* 4.1 (2017): 011005-011005

Methodology

- Installed at CNAO in Pavia, several tests performed:
  - Homogeneus and inhomogeneous PMMA block – phantoms (5 × 5 × 14 cm^3)
  - Anthropomorfic phantom with tissue equivalent to skeletal components
- Range assessment was based on the comparison between the expected PET image and the one measured by the detection system
- For the INSIDE project, a Monte Carlo code based on FLUKA predicted the induced β+ activity, the production of prompt photons and charged particles
- Physical processes other than β+ isotopes production were not taken into account

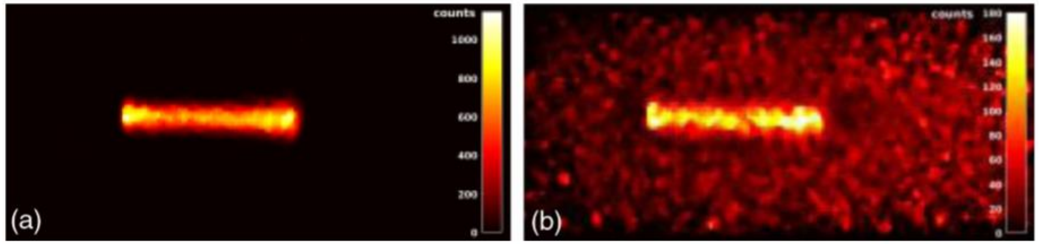
PMMA phantoms: experimental set-up

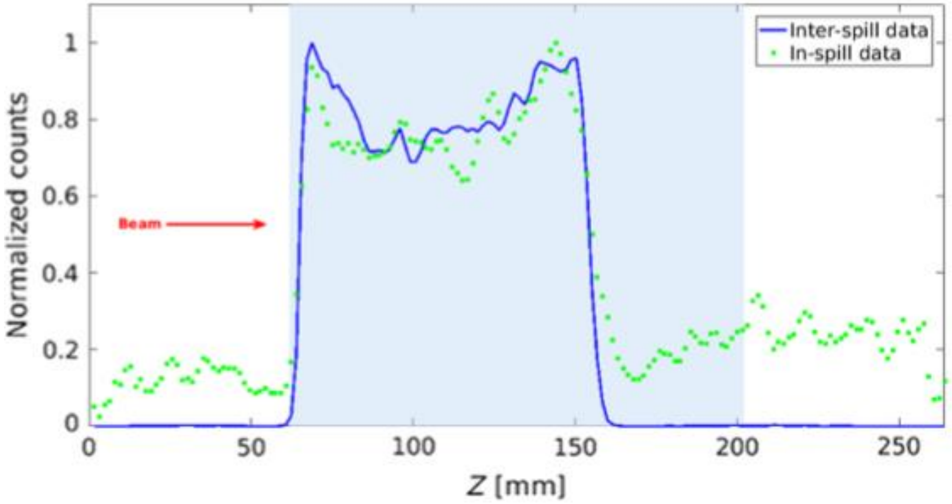
- Comparison of in-spill and interspill data beams (In-spill: 17 s, interspill 68 s)
- Comparison of differences between phantom A and B (A: 519 s, B: 485 s)



Inter-spill VS in-spill

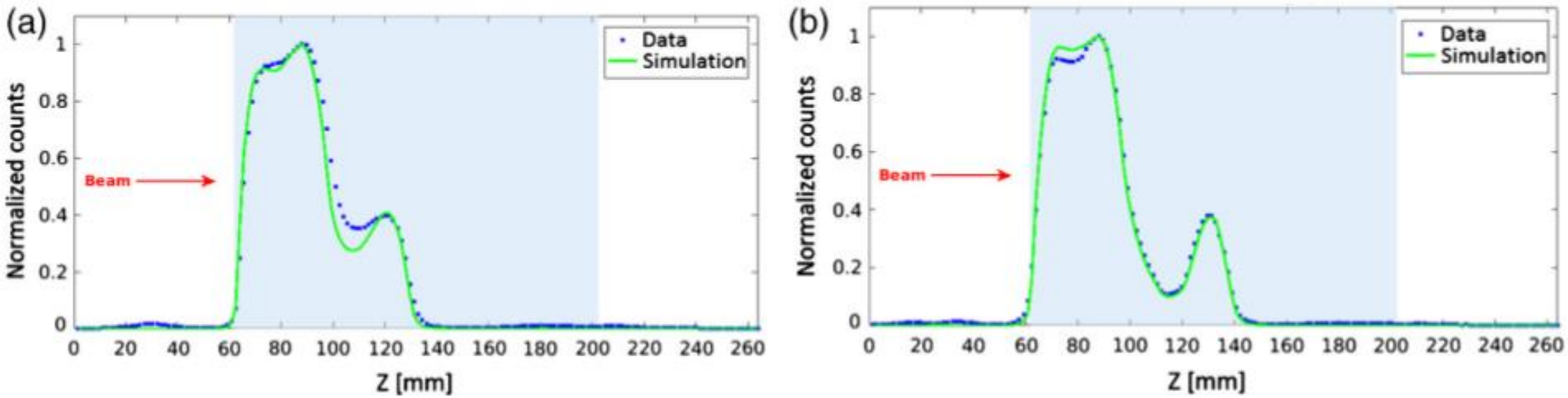
- In-spill PET (b) shows higher noise:
  - Reduced acquisition time
  - High background noise due to induced radiation
  - Proximal rise and distal fall-off edges are in good agreement
- The agreement is promising for reducing inter-spill time, confirmed by sigmoidal fit of activity





PMMA Phantom A and B

- Comparison of experimental and simulated data from the two phantoms (a) and (b) (without and with air cavities)
- Exposition time A: 519 s, B: 485 s, only inter-spill and after treatment data
- A fit with a sigmoidal function shows good agreement (within 1 mm) between simulations and measurements



Conclusions

- The popularity of hadrontherapy is constantly increasing, due to better dose conformity compared to traditional radiotherapy
- The knowledge of the expected activity distribution and the experimental distribution can be used to validate treatment sessions
- Monitoring is pursued through different mechanisms: the INSIDE project focuses on in-beam PET monitoring:
  - Real time reconstruction
  - Good agreement between simulations and measurements
  - Tests on patients is taking place now!
- Treatment of moving organs is not yet possible

Main references

[1] Paganetti, H. and Bortfeld, T. (2005), Proton Beam Radiotherapy – The State of the Art, *New Technologies in Radiation Oncology*, Medical Radiology Series

[2] Knopf, A-C and Lomax, A. (2013), In vivo proton range verification: a review, *Physics in Medicine and Biology* 58(15):R131-60

[3] Amaldi, U. (2015), History of Hadrontherapy, *Modern Physics Letters A*, 30(17), 1540018

[4] Bisogni et al. (2017), INSIDE in-beam positron emission tomography system for particle range monitoring in hadrontherapy, *J. Med. Imaging*, 4(1), 011005

[5] www.ptcog.ch - Particle Therapy Co-Operative Group website

Appendices

EXTRA SLIDES

Proton acceleration: cyclotron and synchrothon

CYCLOTRON

- Dipole magnets produce two regions of uniform magnetic field
- Between the two dipoles, an oscillating electric field accelerates the particles
- Particles gain energy and cover a larger arc each time they pass through the gap
- Mono-energic beams are produced

SYNCHROTRON

- Particles move on the same radius as they accelerate thanks to electromagnetic resonant cavities around the ring
- The strength of the magnetic field must be varied in accordance to particle energy
- A synchrotron allows beam extraction for any energy

Physics of proton therapy

- The energy loss of protons within matter is described by the stopping power: $S(E) = \frac{1}{\rho}\frac{\partial E}{\partial z}$
- Bethe-Block formula

$$S(E) = 0.307\frac{Z}{A}\frac{1}{\beta^2}\left(\frac{1}{2}\ln\frac{2m_e c^2\gamma^2\beta^2 T_{max}}{I^2} - \beta^2\right)$$

- Proportional to $\frac{1}{v^2}$: as the proton beam slows down within matter, the stopping power increases

Proton scattering

- Deflection through Coulomb interactions with electrons. This effect can be ignored due to the mass difference.
- Coulomb interaction with atomic nuclei, effect known as multiple Coulomb scattering
- Inelastic collisions with nuclei, in which protons are lost from the beam and nuclei composition is changed

Detection modules of INSIDE PET device

- The PET detector is based on solid state photodetector (SiPM), coupled to lutetium fine silicate (LFS) pixelated scintillating crystals
- SiPM: solid state photodetectors made of arrays of avalanche photodiodes (ADP). They are faster than photomulplier tubes.
- Detection module:
  - 16x16 3x3x20 mm^3 LFS crystals, couplet to SiPMs
  - 10 detection modules are disposed in a 5x2 array
  - A single PET head contains 2560 detector channels
- The channels are processed by front end electronics (FE) and DAQ system based on field programmable gate array (FPGA)

Test on anthropomorfic phantom

- Activation map generated in the phantom by a proton beam shaped following a real treatment plan with proton energies ranging from 74 to 134 MeV
- Aim of the test: provide a proof of the system functionality in clinical conditions
- PET images have been acquired and reconstructed within the irradiation session in a set-up reproducing a clinical treatment.