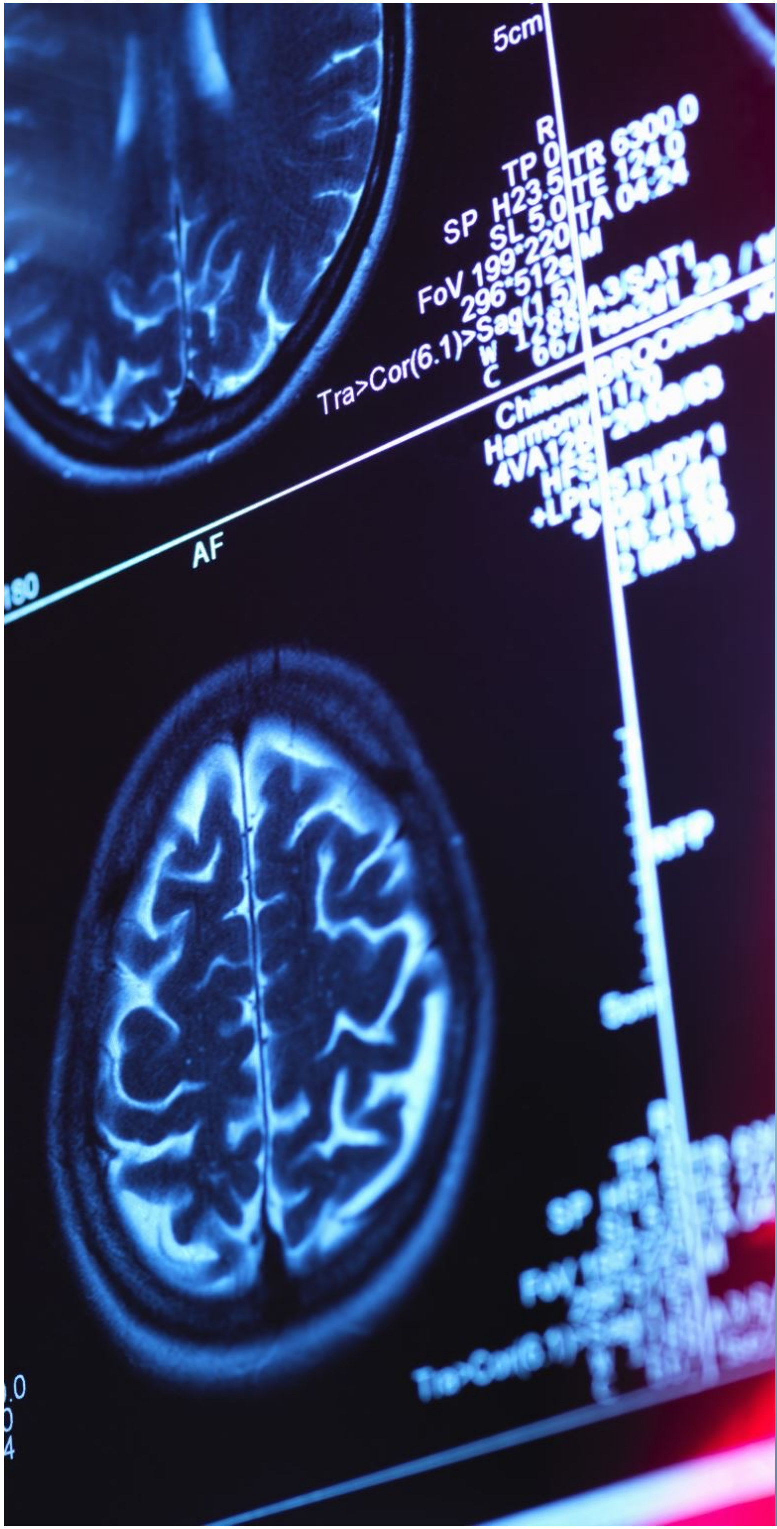
LE ATTIVITÀ IN FISICA MEDICA DELL'INFN E DEL PROGETTO QUASIMODO

PROF. SABINA SONIA TANGARO

PROF. ROBERTO BELLOTTI

UNIBA &INFN-BA

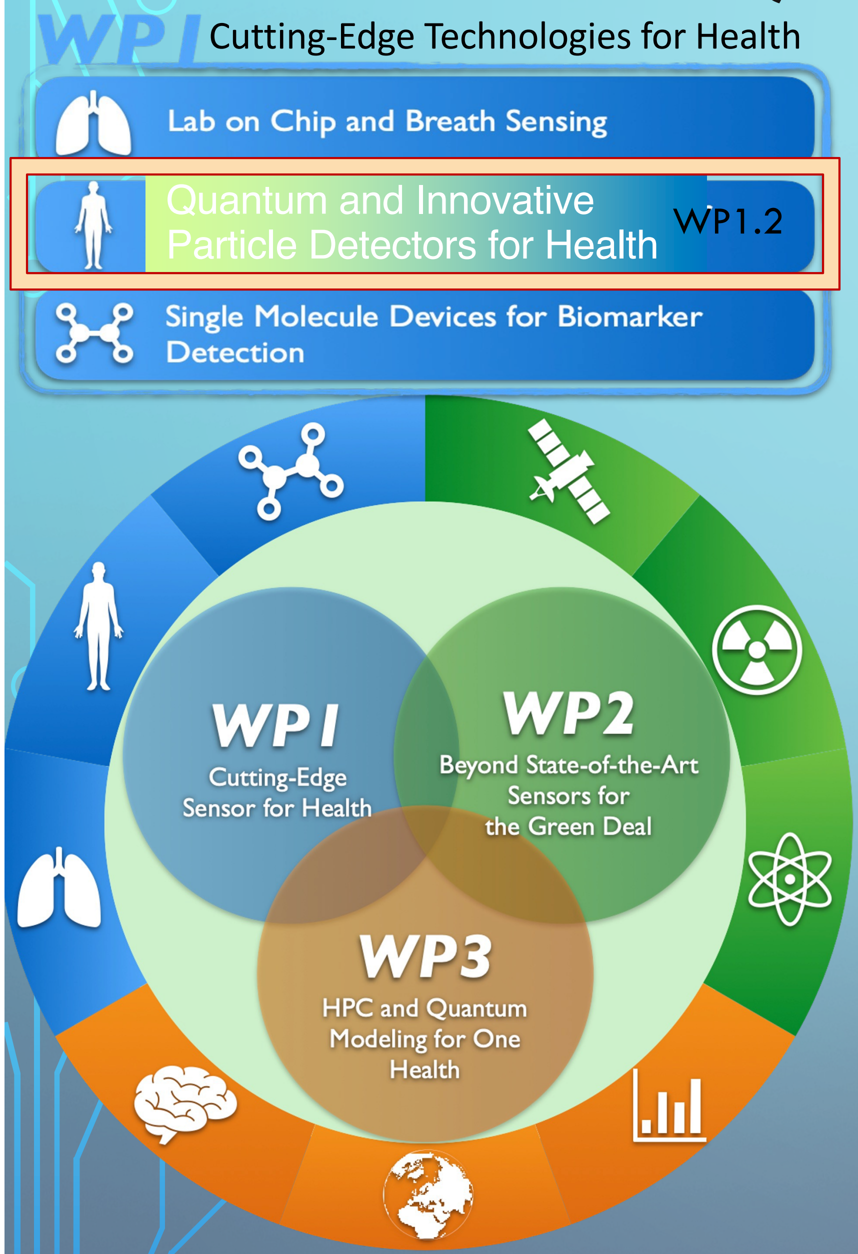


SUMMARY

- Detectors for
  - Radio-guided surgery,
  - hadrontherapy
  - BNCT
  - pCT
  - Theranostics

- Interdisciplinary
  - Reconstruction algorithm
  - Computing
  - AI for health

QUASIMODO



Scope of WP 1.2 is twofold:

- development of pioneering particle detectors and their application to health
    1. Compton Camera exploiting a "Pixel Chamber"
    2. Fast Scintillating Heterostructures for TOF-PET

- support and promote cooperation among several other ongoing activities in this *excellent* department
    - this first workshop is indeed an example

COMPTON CAMERA FOR HADRONTHERAPY

Hadrontherapy provides a unique benefit for cancer therapy, allowing for dose escalation to the tumor and a reduction of exposure for the surrounding healthy tissues

In vivo beam monitoring of the Bragg peak is essential to guarantee the treatment effect of hadrontherapy.

Compton Cameras do not yet allow an on-line monitoring of the treatment, which requires high-resolution imaging of direct gamma sources to be performed over a time of a few seconds.

The main limitation is the large number of gammas required to determine the source with sufficient precision.

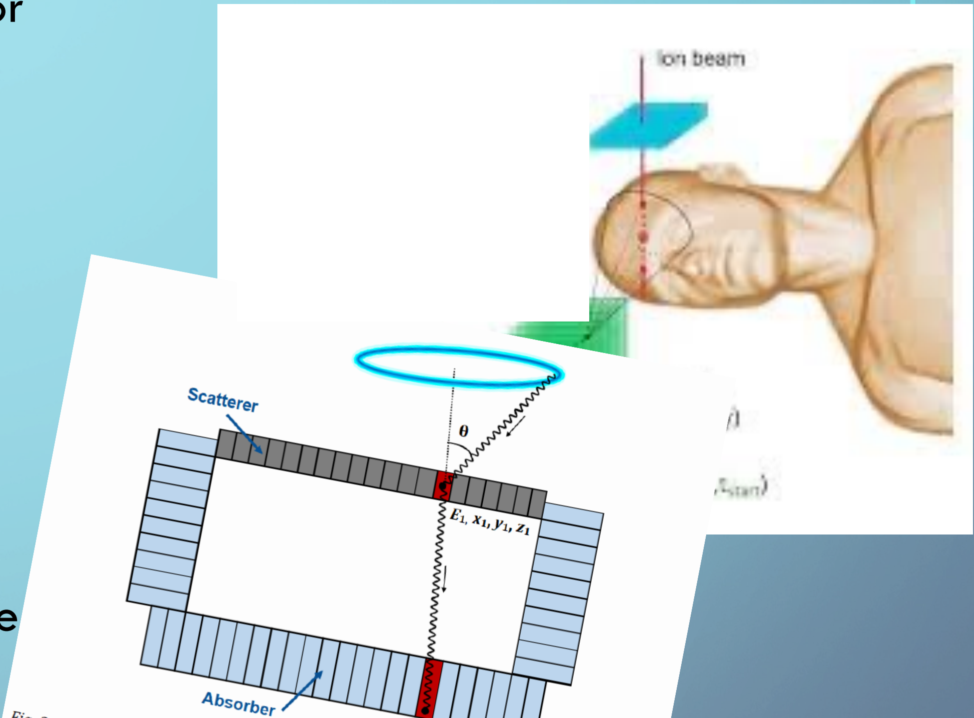


Fig. 3 - General design of a standard Compton camera. A typical Compton interaction, and the kinematic information that can be measured, are highlighted.

COMPTON CAMERA BASED ON PIXEL CHAMBER

The Pixel Chamber would offer the extraordinary possibility to also reconstruct the direction of the emitted electron

With this additional piece of information, the original direction can be already constrained using a single photon

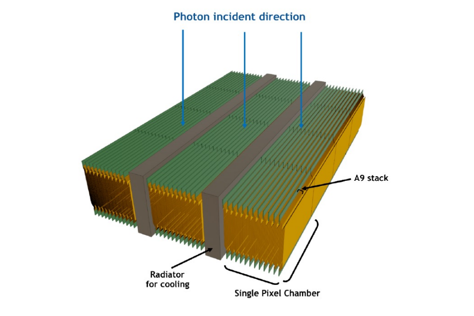


Fig. 14 - Assembly of multiple Pixel Chambers to obtain a wide-surface radiator (note: only a part is shown)

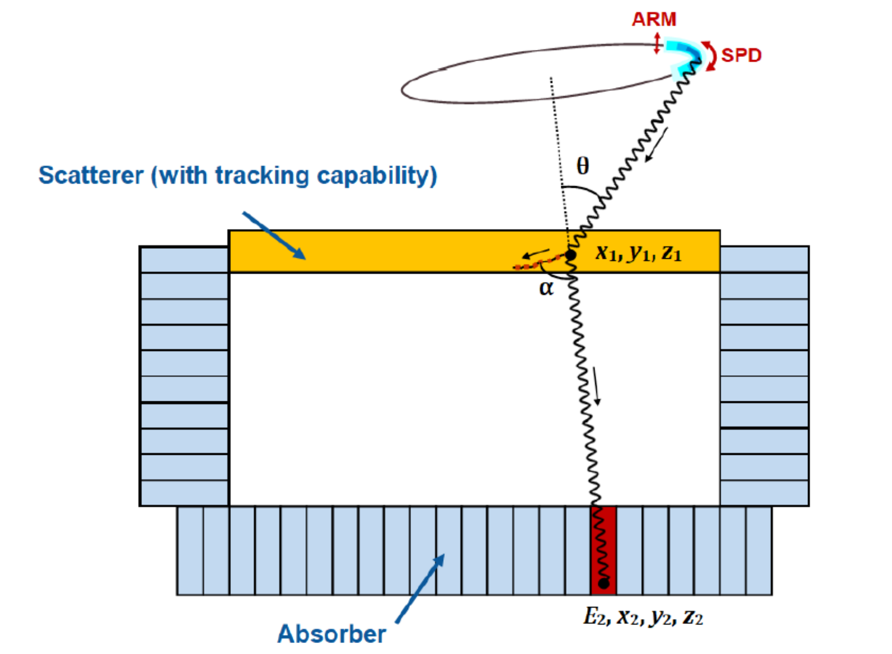


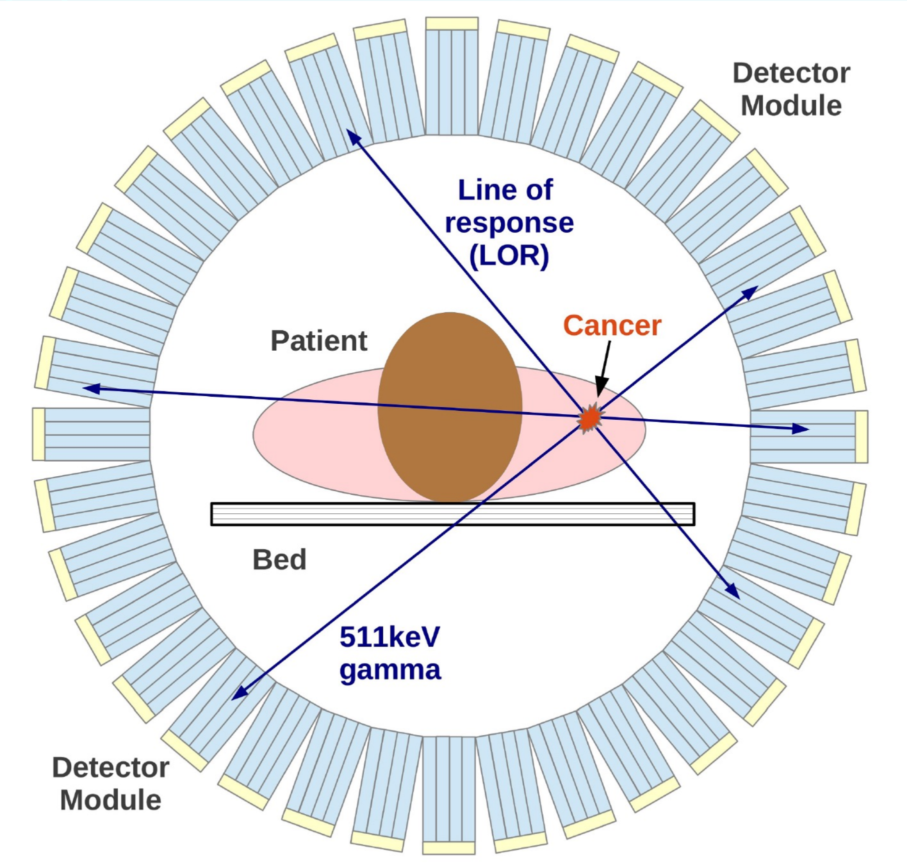
Fig.4 - General design of a standard Compton camera with electron tracking, with definition of SPD and ARM parameters of merit. A typical Compton interaction, and the kinematic information that can be measured, are highlighted.

PRIN2022 project "A pioneering Compton Camera for hadrontherapy with a 3D silicon Pixel Chamber" - Three units: UniCa F. Fionda (PI); INFN Bari F. Colamaria; Poliba G.Bruno

In this project the Pixel chamber is mostly based on the ALPIDE chips used for the ITS2 of the ALICE experiment

DIAGNOSTICS: FAST SCINTILLATING HETEROSTRUCTURES FOR TOF-PET

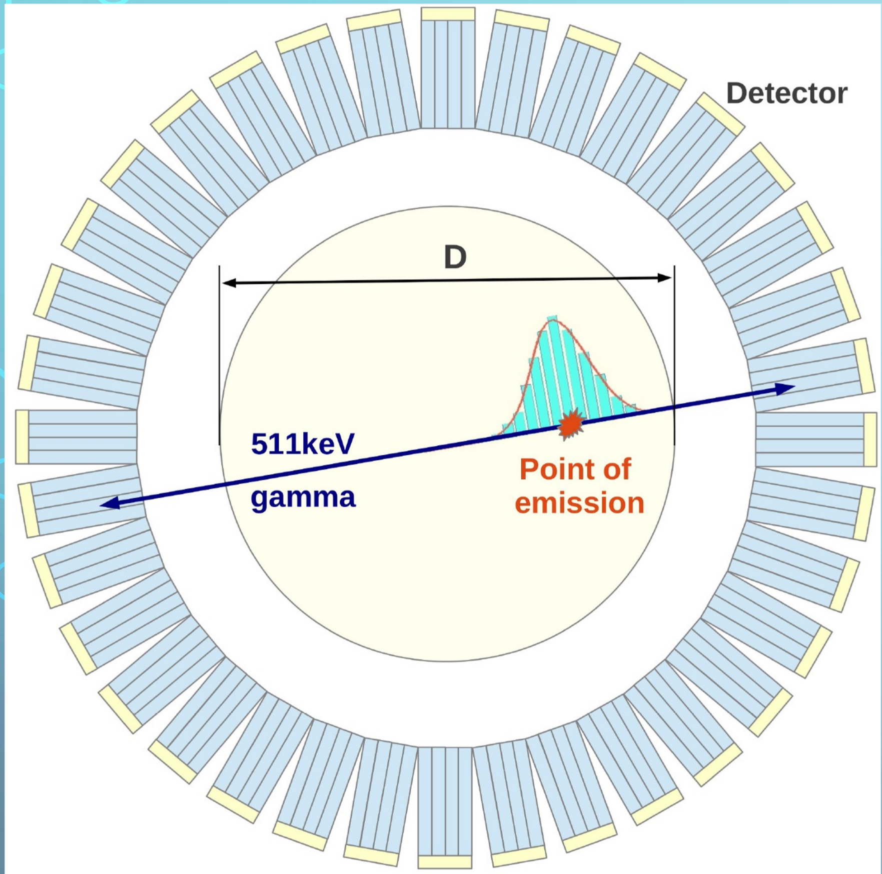
FLASH Radiotherapy with hIgh Dose-rate particle beAms



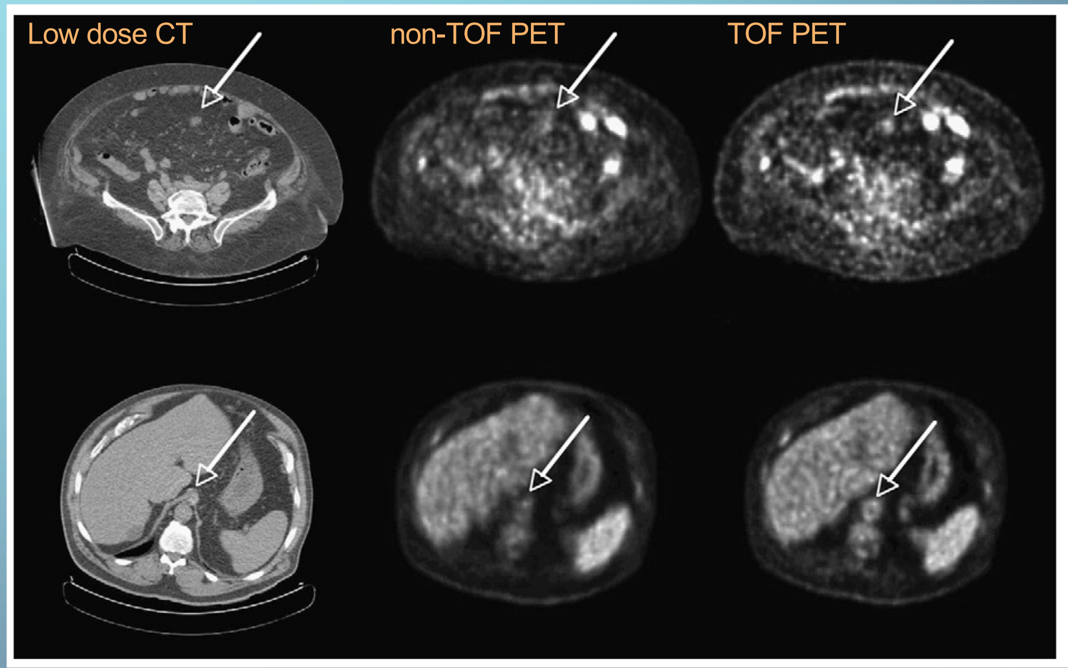
- Distribution of biomarkers labelled with a radioactive isotope which undergoes β^+-decay
- Emitted e^+ annihilates in the tissue producing two collinear 511 keV gammas ($e^+ e^- \rightarrow 2\gamma$)
- Detect such energetic photons in coincidence via scintillating crystals:
  - high gamma attenuation, light yield, probability of photoelectric effects and fast decay time
  - LYSO (Lutetium Oxyorthosilicate) shows the best compromise

- scintillator detector:
  - People: R. Radogna, A. Colaleo, V. Cellamare, P. Verwilligen, A. Pellecchia, F. Simone, R. Venditti, A. Stamerra, L. Longo
  - In collaboration with University College London
  - Sigla INFN FRIDA
- MRPC detector:
  - People: D. Ramos, G. Iaselli, G. Pugliese

TIME OF FLIGHT PET

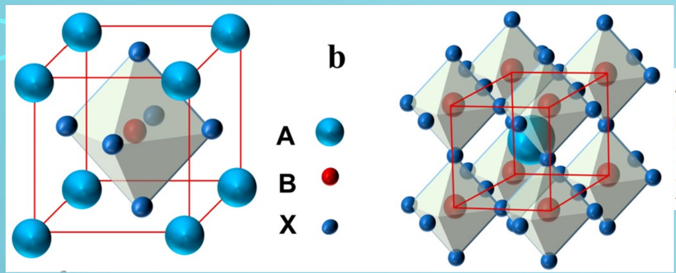


The image quality (SNR) can be drastically improved by using time of flight (TOF) information to estimate the emission position.

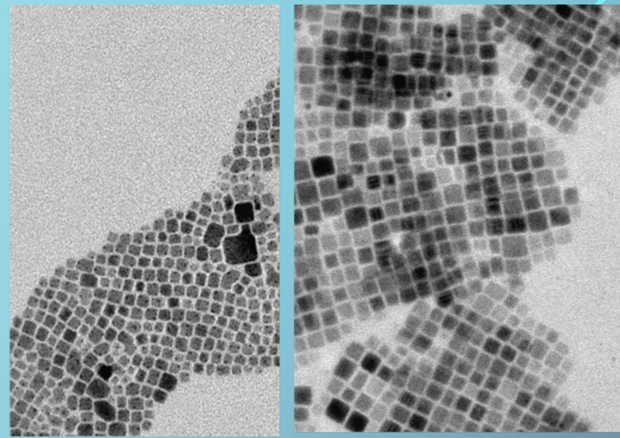


FAST TIME SCINTILLATING NANOCRYSTALS

Typical perovskite chemical formula ABX_3

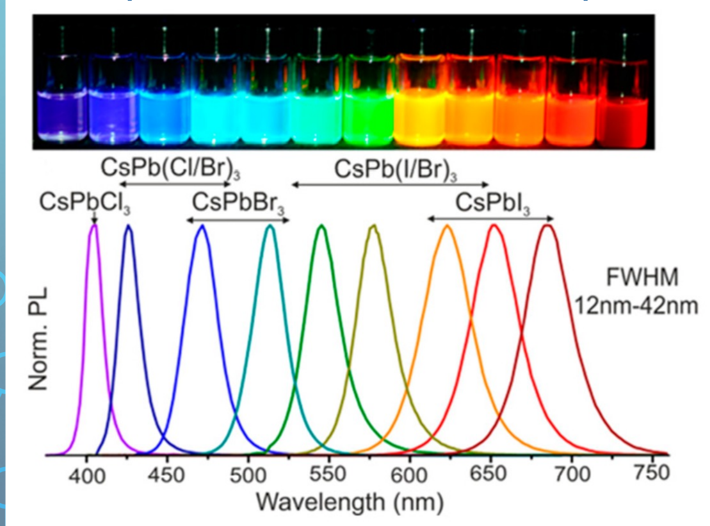


A: cation, organic (i.e. $CH_3NH_3^+$, $CH(NH_2)_2^+$) or inorganic (i.e. Cs^+, Rb^+)
B: metal cation (i.e. Pb^{2+}, Sn^{2+}, Ge^{2+})
X: halogen anion (i.e. F^-, Cl^-, Br^-, I^-)



Fanizza et al. Nano Research 2019, 12(5): 1155–1166

Emission spectrum of lead halide perovskites

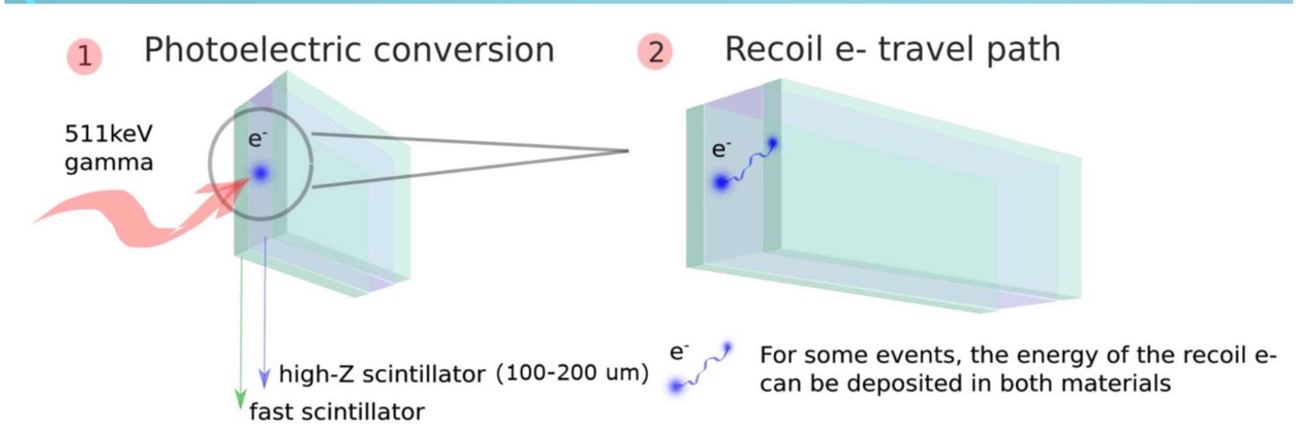


- Perovskite Material ABX_3: large stopping power; high mobility lifetime product; fast response (~ns); large bulk resistance, low cost.
- High photoluminescence quantum yields ;
- Tunable band-gap with composition
- Possibility to synthesize 3D nano-dots, nano-wire and nano-plates
- Their nano-scale sizes impose several limitations in terms of energy deposition per platelet.

HETEROSTRUCTURED SCINTILLATORS FOR FAST TIMING

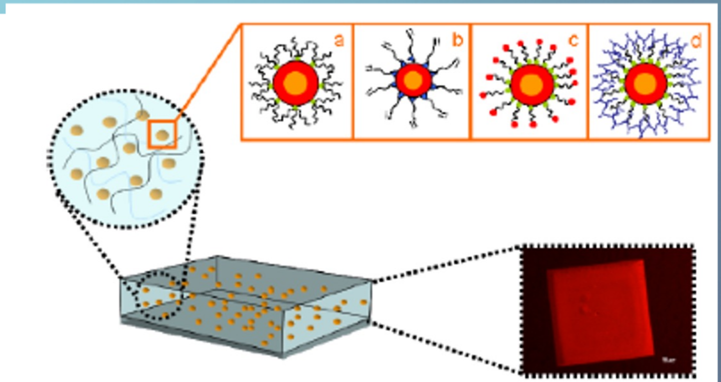
Hybrid structures in which high-Z inorganic scintillator is combined with scintillating nano-crystals (NC) for time tagging.

Alternating layers of a high-Z and a fast NC



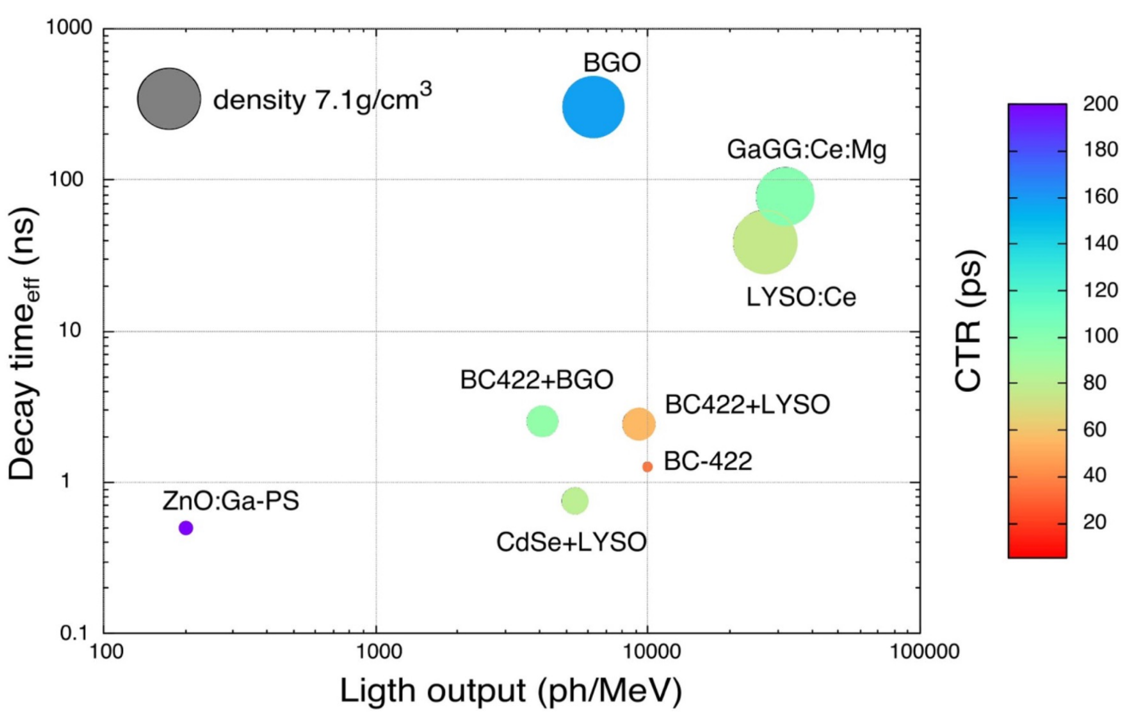
P. Lecoq et al 2020 Phys. Med. Biol. 65 21RM01

Perovskite-polymer 3D composite



Striccoli et al Materials **2010**, 3, 1316-1352

STATE OF THE ART



ONGOING R&D

- ultra-fast scintillators for medical applications and HEP (Crystal Clear Collaboration)
- doped plastic scintillators (AidaInnova)

Despite the low light output, the timing obtained is at the level of state-of-the-art inorganic scintillators, leaving a **rather large room for optimization.**

P. Lecoq et al 2020 Phys. Med. Biol. 65 21RM01

PEROVSKITES NCS SYNTHESIS AND DEPOSITION

Synthesis and Characterization

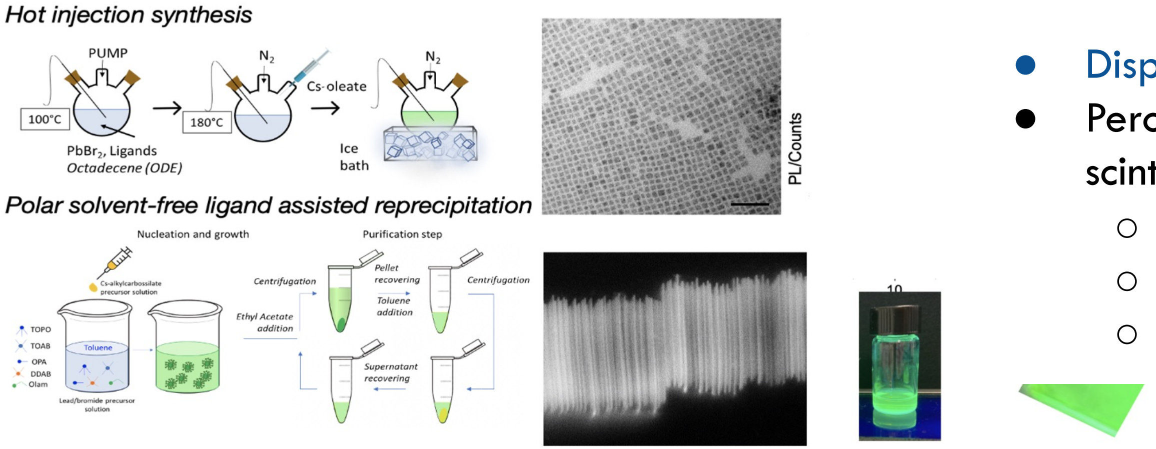


Fig. 2: Scheme of the synthetic approaches for the preparation of colloidal perovskite NCs with tuneable size and shape. TEM (scalebar 50 nm) and SEM-FEG characterization of the perovskites. Time decay recombination of nanocomposites with PMMA and PS host matrices and structure of the PVK NCs. Picture under UV light of colloidal NC solution and film.

Heterostructures Fabrication

- Dispersion into polymeric host matrix
- Perovskite NCs solid-state films depositions for scintillator device fabrications:
  - Drop-casting (CNR)
  - Spin coating (CNR)
  - Laser Ablation (INFN-Le and UniLe)

QUASIMODO

- Collaboration: CNR-Bari (perovskites synthesis and deposition).
- Facilities dedicated to these activities are foreseen within this project. We are building the setup to characterize the time performance of the scintillator using pulsed X-rays.

PRIN-PNRR:

- Our group has been granted funds for the project “**Development of Ultra-fast Perovskites ScinTillAtoR for TOF-PET** (UPSTART)” Collaboration: CNR-Bari (perovskites synthesis and deposition), INFN-Lecce (deposition using laser ablation)

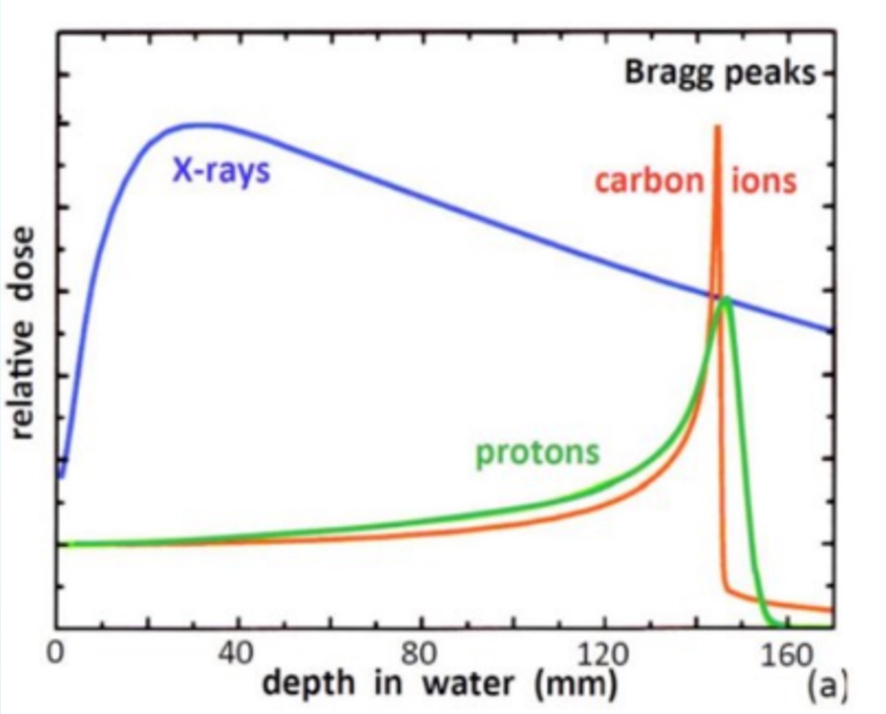
SHINE:

- Existing INFN-project “**Plastic Scintillators Phantom via additive manufacturing techniques**” (Responsible Anna Paola Caricato INFN-Lecce)
- Perovskite-polymer nanocomposite and polysiloxanes-based resin for 3D-printable scintillators.
- Collaboration: INFN-Lecce, LNFN-LNS, TIFPA

THE PROTON THERAPY (DOSIMETRY)

- Radiotherapy: **use of ionizing radiation to damage cancer cells preserving as much as possible healthy tissues**
- Dose: energy absorbed per unit target mass [Gy]
- Charged particles deposit dose in a narrow region, named "Bragg peak".
- Range uncertainties are important.

Depth-dose distribution for X-rays, protons and carbon ions



BEAM QUALITY ASSURANCE (QA) IN PBT

Each proton therapy centre has a rich program of Quality Assurance (QA) controls necessary to ensure a safe treatment to the patient.

QA checks are:

- Daily
- Monthly
- Annually

Daily checks include the measurement of beam parameters such as the proton beam range, spot size, spot position and dose.

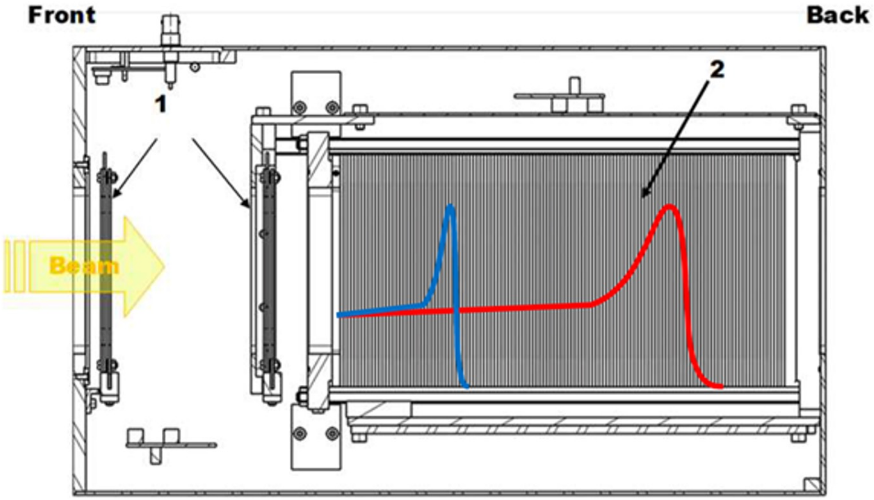
→

Daily beam QA checks are time-consuming operations (~44 min/day/treatment room).

BEAM DAILY QA STATUS OF ART

Commercially available devices are:

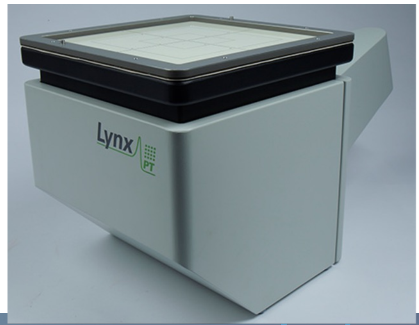
- IBA Giraffe detector for the Bragg peak measurement in a one single proton beam shot. It suitable for pencil beams.
- IBA Lynx detector for beam spot characterization



(Main) Disadvantages:

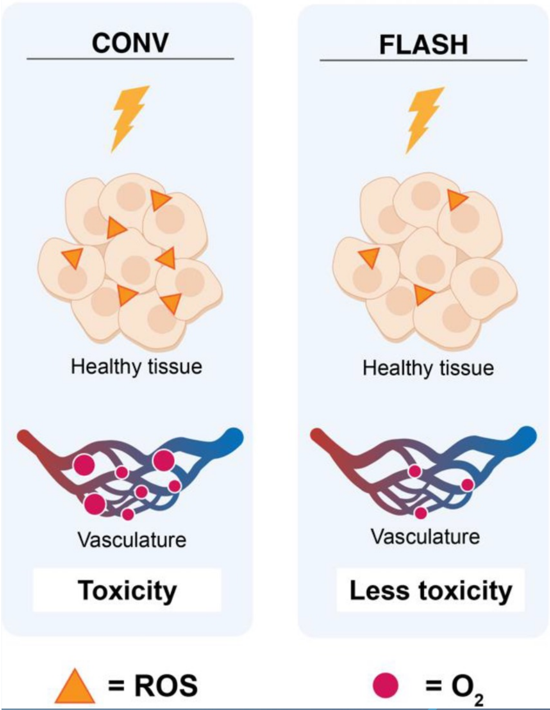
Fast acquisition time but long setup time

No device exists to make simultaneous measurements of different beam parameters



FAST DOSE DELIVERY: THE FLASH RADIOTHERAPY

- FLASH radiotherapy: new radiation delivery technique at ultra-high dose rate (>40 Gy/s) using short-duration pulses.
- FLASH effect: **reduces the trauma to normal tissue around the tumour**, whilst equalling the anti-tumour effect of conventional dose rate radiotherapy.
- Commercial Dosimetric Detectors:
  - Radiochromic films and Alanine (passive detectors, no online measurements)
  - Scintillators (dose rate independent)
  - Ionization Chambers (dose rate dependent)
- No Dosimetric protocol available for FLASH
- None of the existing QA device is scalable at FLASH rate.



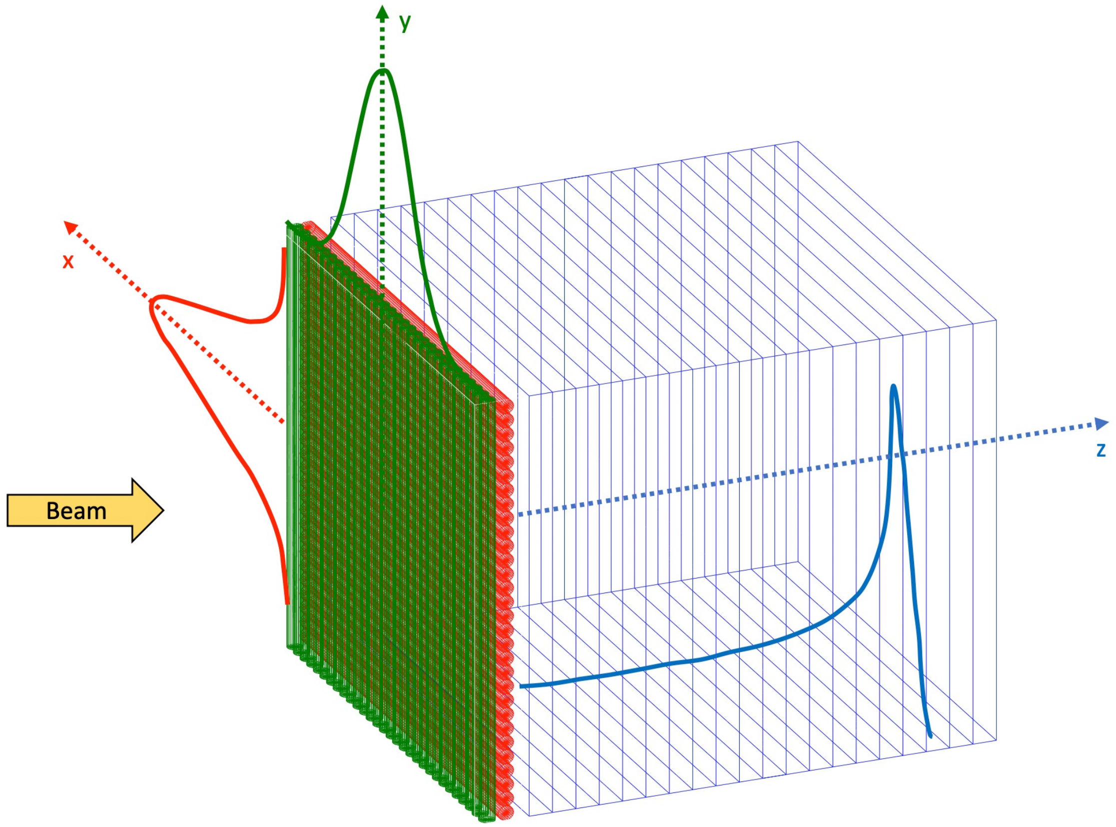
SCINTILLATOR-BASED DETECTOR FOR CLINICAL PROTON BEAM QA

INFN BARI

UCL

FLASH Radiotherapy with hIgh Dose-rate particle beAms

Integrated system for range, spot position and size reconstructed with single beam delivery.



RANGE MODULE

- stack of plastic scintillator sheets
- reconstruction of the depth-dose beam profile

BEAM TRACKER

- 2x1D scintillating fibre arrays
- Reconstruction of the transverse beam profiles at the entrance of the detector

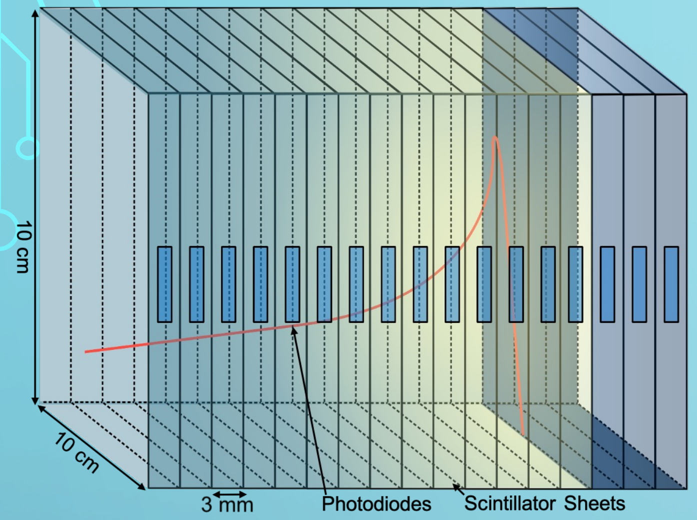
Key benefits:

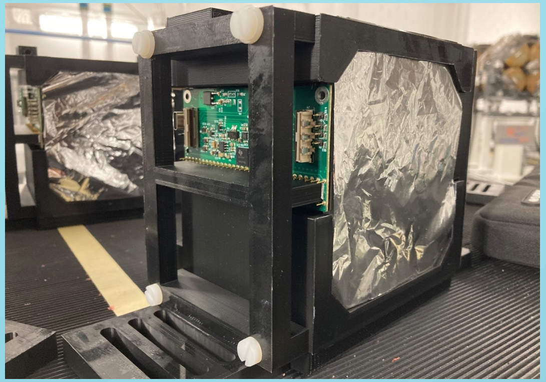
Plastic scintillator inexpensive and water-equivalent.

Easy detector setup and no optical artefacts.

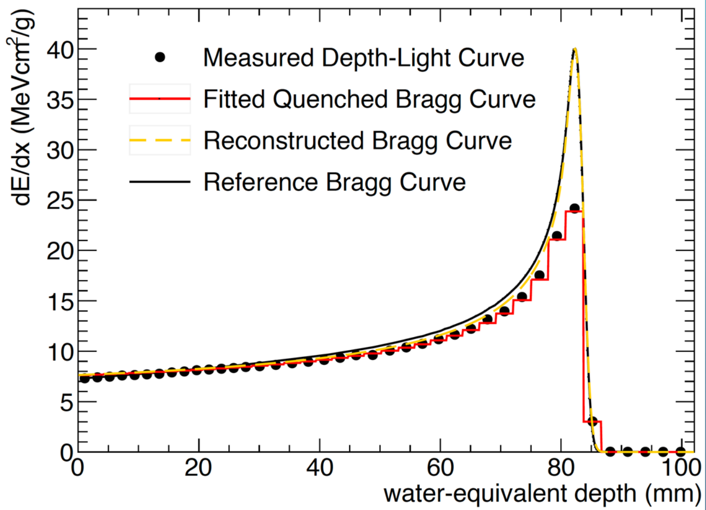
Light output dose-rate independent.

RANGE VERIFICATION





Beam E = 106.2 MeV



- Series of optically isolated polystyrene scintillator sheets of size: 10 cm×10 cm×3 mm.
- Photodiodes coupled to fast, modular ADC electronics read light levels at over 5 kHz.
- Measure depth-*light* curve & reconstruct Bragg depth-*dose* curve to measure proton range.
- Promising preliminary results at FLASH currents (tested at The Christie, Manchester and UMCG PARTREC, Groningen)

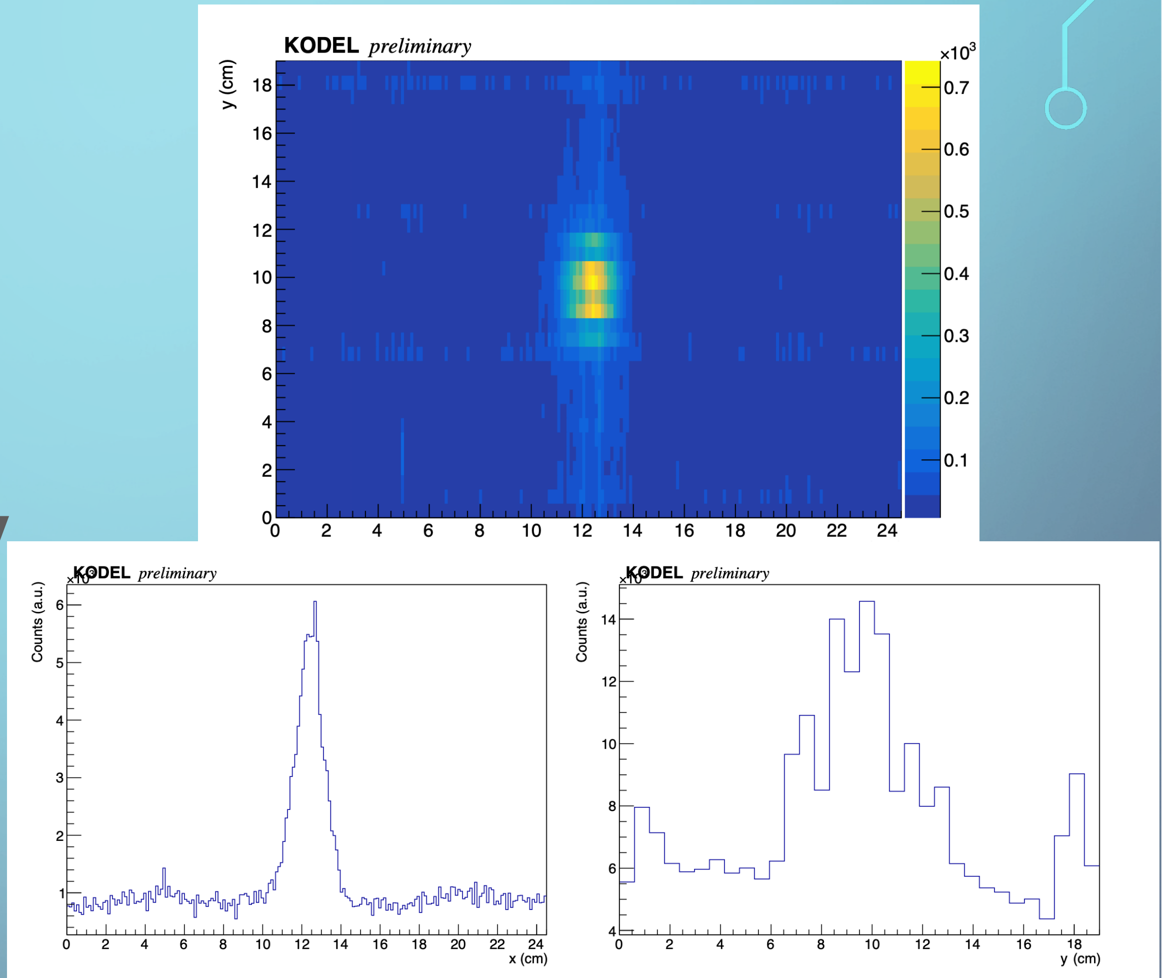
GAMMA SOURCE SCAN

MRPC prototype covered with 2 cm thick lead bricks
1D collimator 1-cm pitch made of twenty 5 x 5 x 100 mm^3 tungsten bars

4.74 GBq Cs-137 gamma source detector 30 cm apart

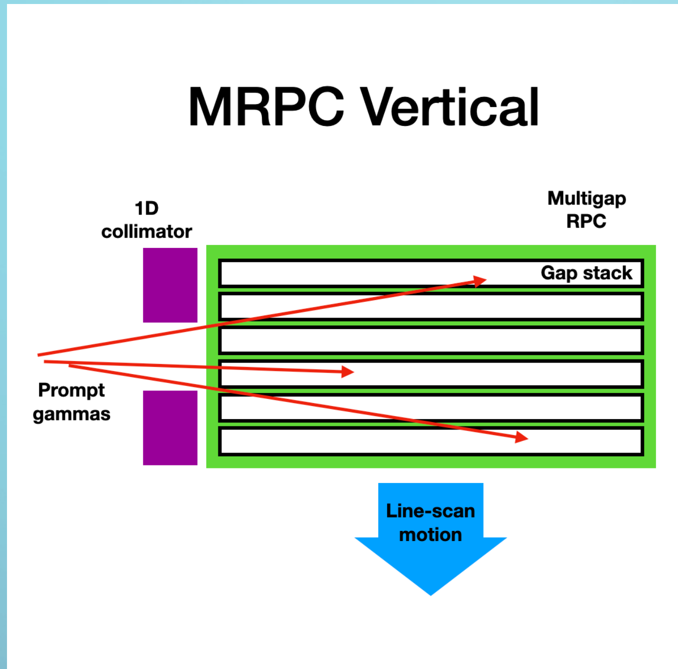
8

100 s with a lineal velocity of 0.64 cm/s



Blurred effect → small angle Compton scatterings in the collimator
System quite far

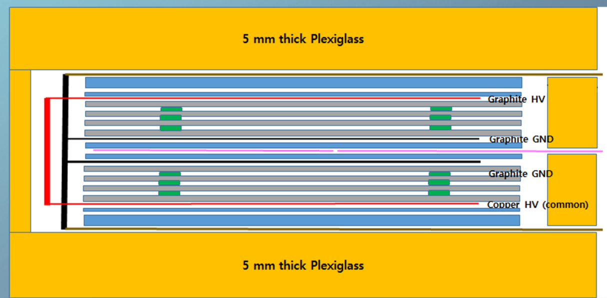
MRPC LINE-SCAN MEASUREMENTS BEAM MONITORING IN HADRON THERAPY



Multigap RPC prototype built based on MC simulations

2-triplets

500 um thickness,
550 um soda-lime glass electrodes
300 x 192 mm^2 layers -> vertical mode



Multigap RPC in Vertical configuration to increase the active volume for gamma detection

Ph.D. thesis of D. Ramos "Development of RPC-type gas detectors for beam monitoring in medical application"

SPOC - SPect for Online boron dose verification in bnCt (Boron Neutron Capture Therapy)

G. Pugliese (RL), G. Bruno, G. Iaselli, D. Ramos Lopez,
N. Ferrara
on behalf of SPOC collaboration

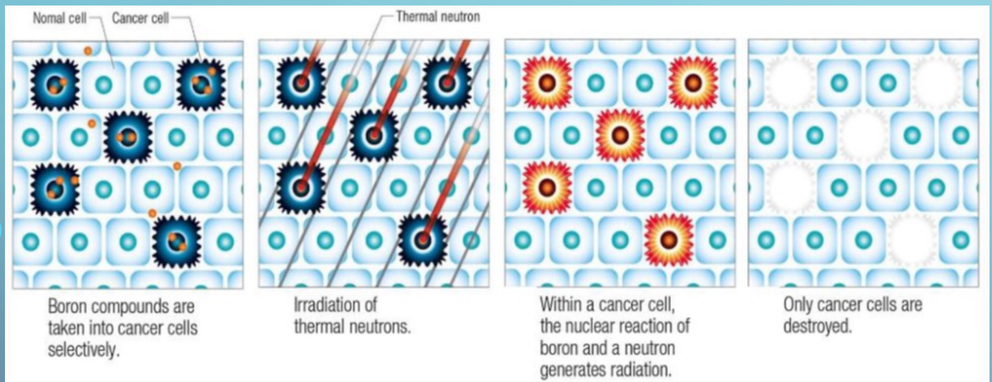
Sezione INFN e Politecnico di Bari

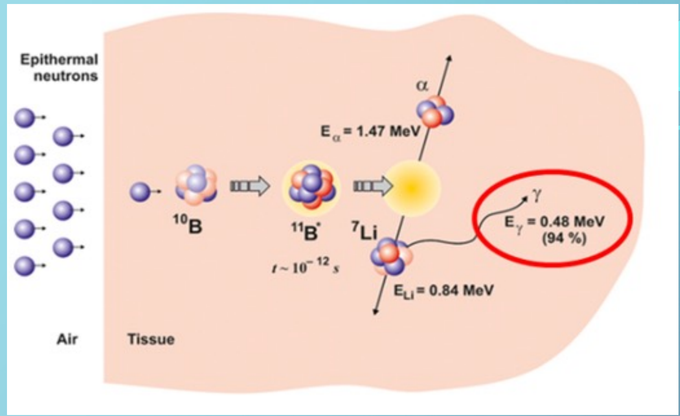
Email: gabriella.pugliese@ba.infn.it

Working Principle and Worldwide Diffusion of Boron Neutron Capture Therapy (BNCT)

BNCT is a targeted hadrontherapy technique:

- Tumor cells are loaded with ^{10}B-enriched molecules and then irradiated with thermal neutrons
- Neutron undergo to capture reaction with boron-10: $^{10}B(n,alpha)^{7}Li$
- Energetic charged particles released by reaction produce damage to the tumour cells.





- ➢ In recent years BNCT has re-gained significant attention and investments thanks to the development of accelerator-based BNCT (AB-BNCT) facilities [1].

Italian projects:

- CNAO
- Anthem @ Caserta

[1] Advances in Boron Neutron Capture Therapy. in Non-serial Publications. Vienna: INTERNATIONAL ATOMIC ENERGY AGENCY, 2023. [Online]. Available: https://www.iaea.org/publications/15339/advances-in-boron-neutron-capture-therapy

The Dosimetry Issue in Boron Neutron Capture Therapy (BNCT)

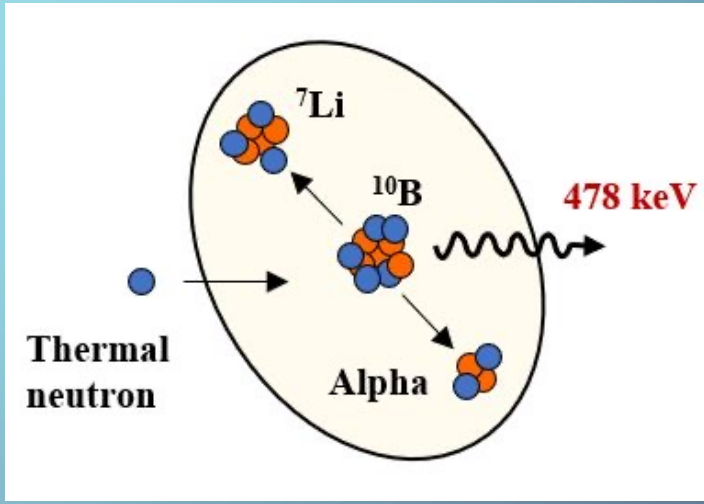
Delivered dose is currently estimated offline using:

- Direct/indirect measurements of Boron concentration in tissues (ICPS, PET)
- Neutron flux in treatment room
- Monte Carlo calculations

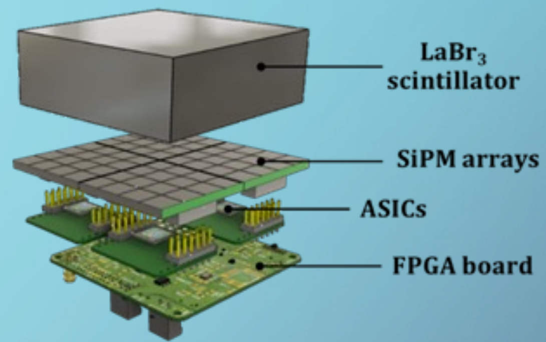
Possible alternative method: online SPECT imaging of 478-keV gamma rays emitted by ^{7}Li produced in capture reaction (personalized dosimetry).

SPECT main specifications:

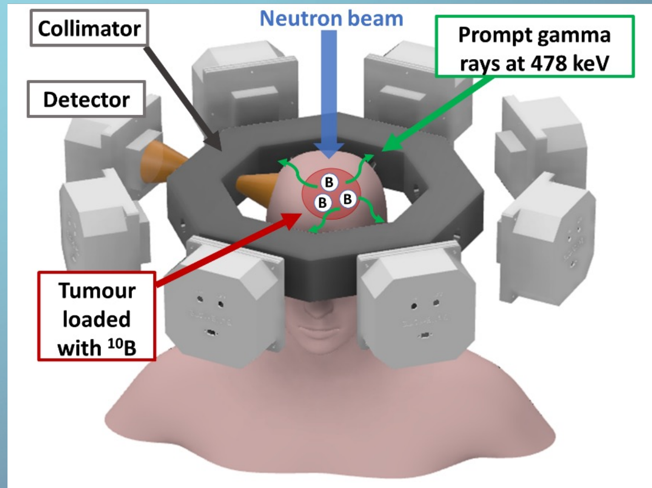
- Good efficiency and energy resolution at 478keV (to separate it from 511keV annihilation photons)
- Spatial resolution: 5-10mm (limited by the collimator)
- Possibly, extended efficiency up to 2.2MeV (H-capture) for neutron flux estimation



SPOC - SPect for Online boron dose verification in bnCt
Aims of the Project



PROJECT GOAL: design a dedicated SPECT system for BNCT dose verification, build the first prototype (few modules), and test it with realistic irradiation conditions.



Proposed SPECT system:

- Detector: gamma camera based on LaBr3(Ce+Sr) square crystal + SiPMs
- Channel edge pinhole collimator
- Optimized detector shielding to avoid detector activation
- Unconventional scanner geometry due to constraints given by fixed neutron beam
- Modified image reconstruction algorithms to account for specific system geometry

SPOC - SPect for Online boron dose verification in bnCt
INFN funds & Synergies

Funds: The 3 years project is funded by INFN for about 96k Euro

Synergies: The project will take profit of the synergy with the PRIN – PNRR project with the tittle “Development of a SPECT (Single Photon Emission Computed Tomography) detector prototype for dose measurements in BNCT (Boron Neutron Capture Therapy) . Duration of the project: two year (2024 – 2025) .
Collaboration: Politecnico di Milano (PI), Univeristà di Pavia, Politecnico di Bari
Bari Member: G. Pugliese (RU), G. Iaselli, D. Ramos
Funded for about 270k Euro

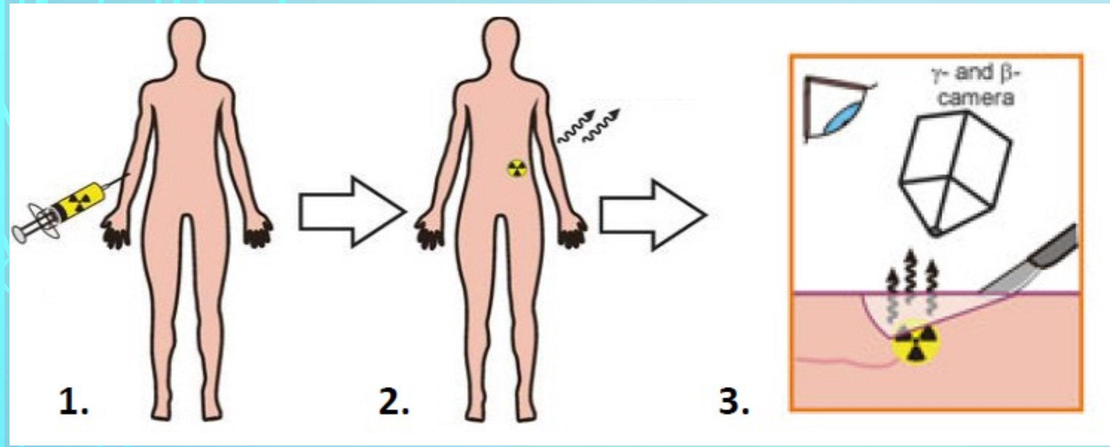
RIPARTI - Feasibility study for the development of advanced techniques in neutron beam radiotherapy

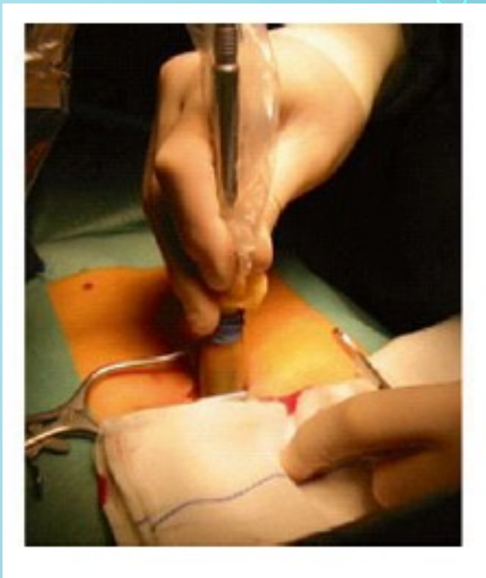
Bari task ⇆ synergy with ITEL Linearbeam s.r.l. facility for protontherapy

1 post-doctoral position

General goal: Feasibility study to become a protontherapy facility into Accelerator-based BNCT facility by introduction of a target system: Beam Shaping Assembly (BSA)

Radio-Guided Surgery: *a potential application in oncology*





How does it work?

1. **Before operation:** administration of specific **pharmaceutical linked to a radio-nuclide** (radio-tracer)
2. The pharmaceutical is **preferentially absorbed by tumors** rather than healthy tissues
3. With an **intra-operative probe** capable of **detecting emitted radiation**, the surgeon can verify the correct tumor resection and presence of residuals **during the operation**

Crucial to ensure a complete surgical resection of all tumoral masses

people: F. Colamaria and other INFN colleagues, L. Magaletti, D. Creanza, D. Colella, G.Bruno

An exploratory study was conducted (INFN SIDERAS project) with thin silicon detectors
→ encouraging results

A new project founded for the call Prin2022_pnrr

Radio-Guided Surgery: *a potential application in oncology*

Different kind of radio-tracers for different kind of RGS

<u>γ-emitting radio-tracers</u> (e.g. ^{99}Tc-m)
used in combination with gamma-probes or cameras for scintigraphy

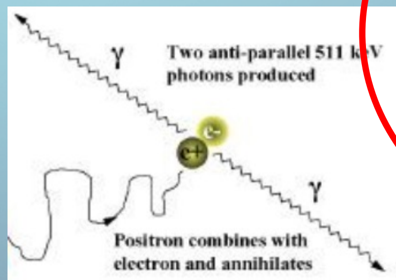
- **γ-radiation highly penetrating!** (140 keV γ ~ 8 cm in body)
  - **high-level of background** γ due to uptake of radio-tracer from far and healthy tissues.
  - not well suited for imaging and for tumors requiring precise spatial delineation (e.g. brain, abdominal and pediatric tumors)

<u>β emitting radio-tracers</u>

- **much shorter range** (1 MeV e ~ **5** mm in body)
- high-spatial resolution for clear delineation of radioactive tissue

❑ **<u>β^--emitting radio-tracers</u>** <u>(e.g. ^{90}Y-DOTATOC)</u>

- promising, but still limited clinical applicability



❑ **<u>β^+-emitting radio-tracers</u>** <u>(e.g. ^{18}F-FDG)</u>

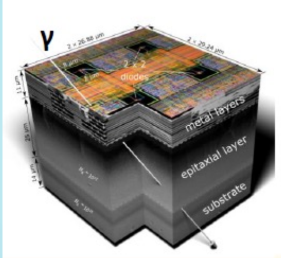
- wider clinical applicability
- can be used with well-known protocols (PET)

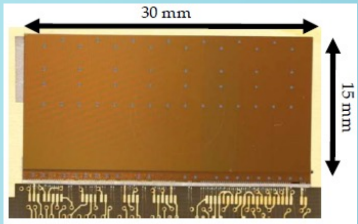
but applicability is limited by annihilation photon background! ($e^+e^- \rightarrow \gamma\gamma$)

- typically requires probes implementing background subtraction techniques..

Radio-Guided Surgery: *a potential application in oncology*

The ALPIDE chip matches all requirements for a usage as RGS probe, in association with both and β^+ and β^- radiotracers:





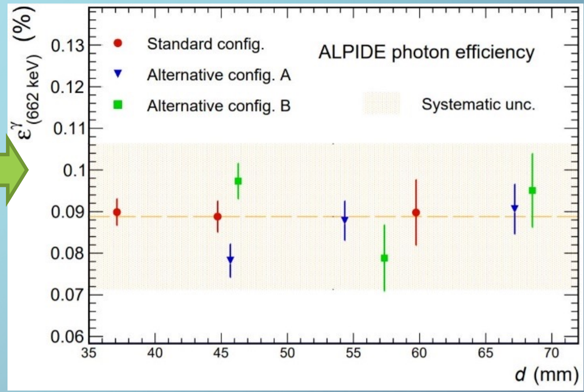
Specific RGS needs

- High charged particle efficiency
- Low noise and fake-hits rate
- Very low sensitivity to photon radiation (for usage w/ β^+ radiotracers)
- High spatial resolution
- Possibility of imaging
- Portability and compactness
- Low power consumption
- Safety of usage

ALPIDE features

- ✓ ε_{ch} > 99% also at lower p_T values
- ✓ Fake hit rate of 10^{-5} pixel^{-1} event^{-1}
- ✓ Due to small tickness, ε_γ(662 KeV) < 0.1%
- ✓ Pixel size ≈27 x 29 µm^2 → spatial resolution much smaller than request, O(0.1 mm)
- ✓ Capable of 2D imaging with appropriate readout and data processing
- ✓ Chip is small, no explicit request for attached electronics readout/processing system
- ✓ Only 40 nW/pixel
- ✓ No reverse bias or high voltage required

Potentially, excellent capabilities!



ALPIDE Efficiency for 662 KeV photon reconstruction

Measurement performed within the SIDERAS project

Study of the photon rejection of the ALPIDE pixel detector for medical applications

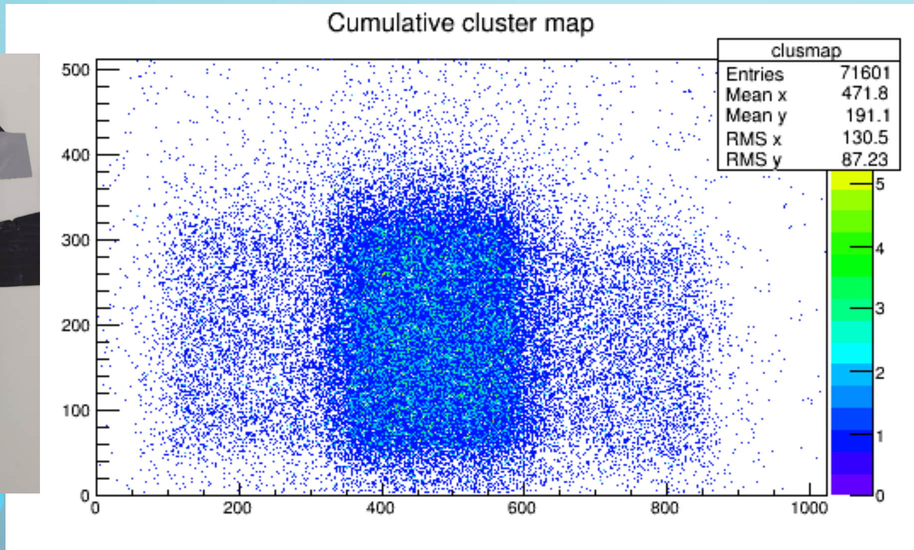
F. Colamaria[1], G. Trombetta[1], G. E. Bruno[1,2], G. De Robertis[1], V. Manzari[1], A. Mazzone[1,3], C. Pastore[1]
[1]*Istituto Nazionale di Fisica Nucleare, Sezione di Bari, Italy*
[2]*Politecnico di Bari, Italy*
[3]*Consiglio Nazionale delle Ricerche, Bari, Italy*

978-1-7281-0557-4/19/$31.00 ©2019 IEEE

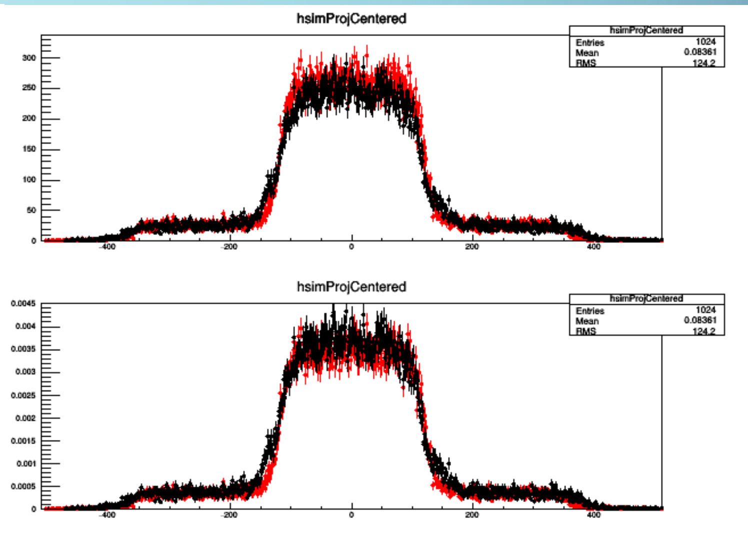
Feasibility studies

After demostrating the excellent photon rejection, we have performed various feasibility studies of the ALPIDE used as a sensitive device, in association with positron-emitting radiotracer (18F-FDG):

- Performance studies with ALPIDE + radiotracer drops / sponges soaked with radiotracers @ ITEL in Ruvo di Puglia



ALPIDE hitmap for a 180 s acquisition of a 7x7x1 mm^3 sponge (representing a tumoral mass) placed between two 7x7x1 mm^3 sponges (representing healthy tissues), both irradiated with typical 18F-FDG radiotracer concentrations

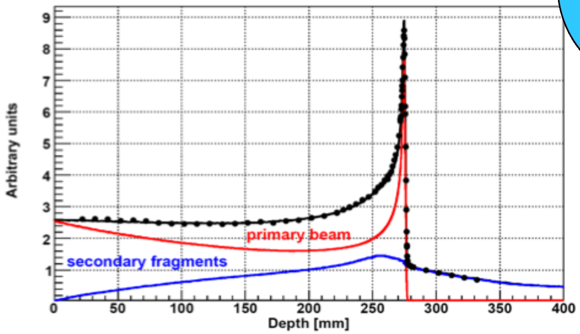


Comparison of the x-axis profile of the recorded hitmap (black) with a GEANT4-simulated hitmap (red), before and after the normalisation to the same number of total counts (top and bottom, respectively)

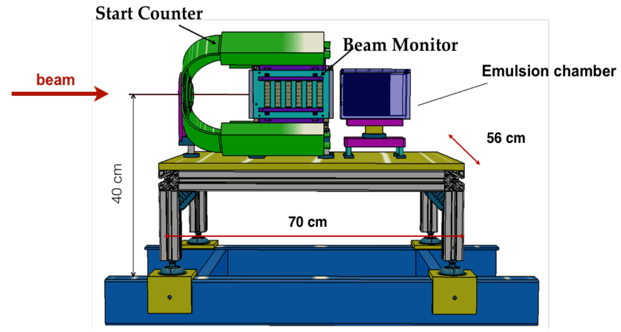
G. Galati

FOOT: measure the impact of Nuclear Interaction in Particle Therapy

- Charge Particle Therapy efficiency currently limited by the lack of knowledge of the nuclear fragmentation cross sections in body tissues
- The FOOT (FragmentatiOn Of Target) experiment aims at measuring nuclear fragmentation cross sections to develop more precise Treatment Planning Systems for proton and ion therapy
- Produced fragments ≤100 μm: inverse kinematic to measure fragmentation cross section
- 2 complementary *table-top* setups: nuclear emulsions spectrometer to measure Z≤3 + electronic setup to measure Z≥3



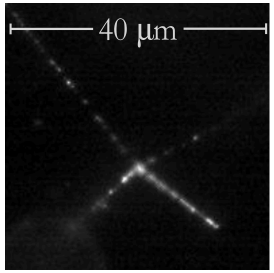
Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008



NUCLEAR EMULSIONS SPECTROMETER SETUP

NEW: **PRIN "DAMON: Direct meAsureMent of target fragmentatiON"**

- direct measurement of target fragments produced by a proton beam using Nano Imaging Trackers emulsions and optical microscopes overcoming the diffraction limits



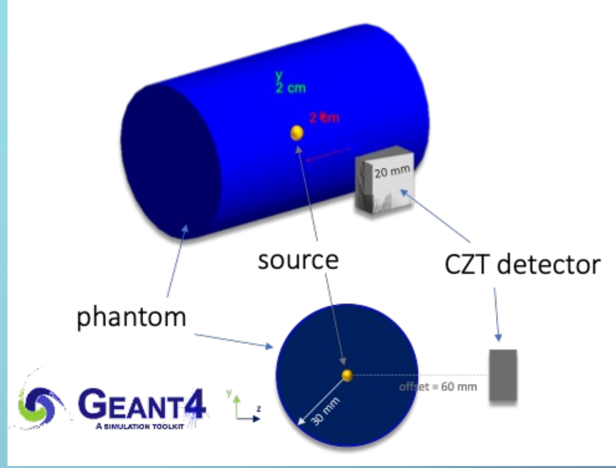
IMAGING METHODS FOR BNCT

People: D. Ramos, G. Iaselli, G. Pugliese, T. Maggipinto, A. Monaco, etc…

General goal: Develop an alternative method for a possible imaging protocol based on the measurement of the prompt gamma-ray of 478 keV with a **CZT Compton camera type detector**.

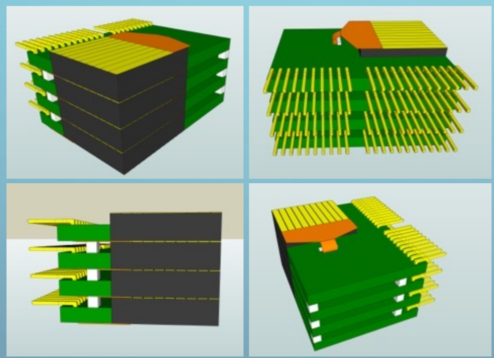
- Monte Carlo methods to simulate a **Compton image** data-set within a BNCT approach.
- Reconstruct the normalized simulated distributions using three methods: the classic **Maximum Likelihood Expectation Maximization (MLEM)** iterative method, a method based on **image processing operations**, and **Convolutional Neural Networks (CNN)** approach.

Monte Carlo set-up



3D CZT detector

CZT single unit: **20x20x5 mm^3**,
planar transversal field (PTF),
orthogonal drift strip electrodes



Room-temperature gamma-ray spectroscopic
Sub-millimetre spatial resolution and excellent energy resolution (**<1% FWHM at 661.7 keV)**
3D positioning

Tumor segmentation evaluation

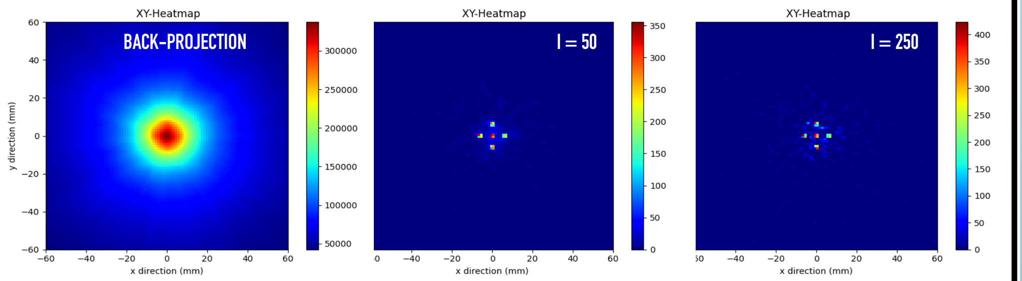
$$\text{Accuracy} = \frac{TP}{TP+FP} \qquad \text{Sensitivity} = \frac{TP}{TP+FN}$$

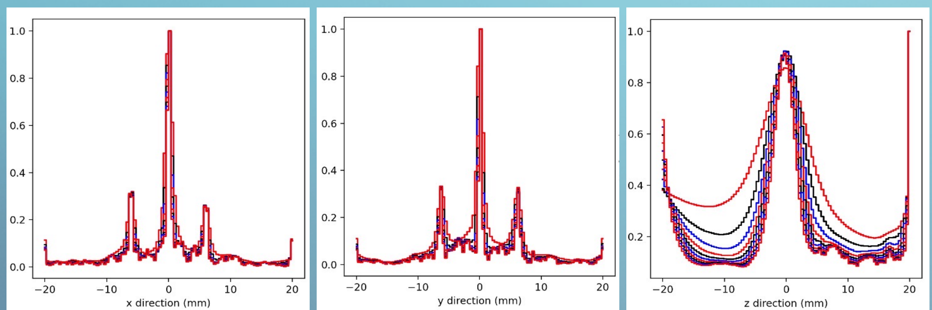
DOSE MONITORING

Maximum Likelihood Expectation Maximisation (MLEM)

$$\lambda_j^n = \frac{\lambda_j^{n-1}}{s_j} \sum_{i=1}^{N} \frac{t_{ij}}{\sum_k t_{ik} \lambda_k^{n-1}}$$

On Air phantom





tumor monitoring

Erosion and dilation filters to back-projection image

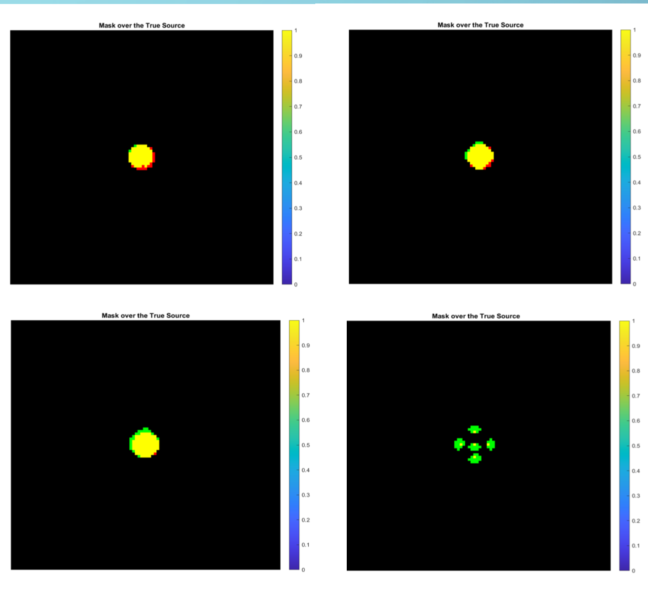
Morphological filters

Spheric source on Air

Spheric source on Tissue (T/N=2)

Spheric source on Tissue (T/N=5)

5 point-like source on Air



	Accuracy	Sensitivity
case 1	97.0%	82.0%
case 2	79.0%	98.0%
case 3	90.0%	91.0%
case 4	8.0%	100%

Human supervised method -> known a-priori the Boron distribution

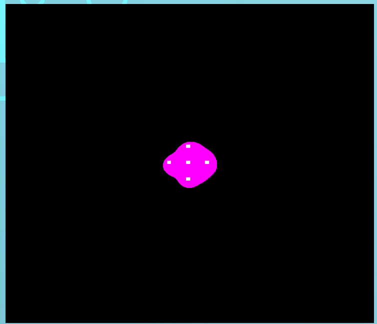
Convolutional Neural Network tumor monitoring

Data augmentation + Transfer Learning

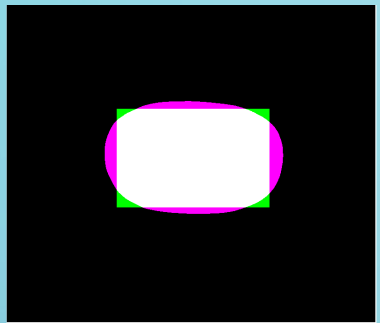
ResNet50(ImageNet)

Property	Value
Layers	206×1 Layer
Connections	227×2 table
InputNames	1×1 cell
OutputNames	1×1 cell

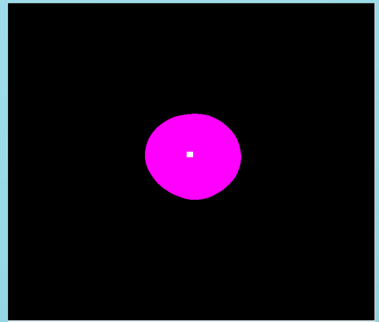
5 point-like on air



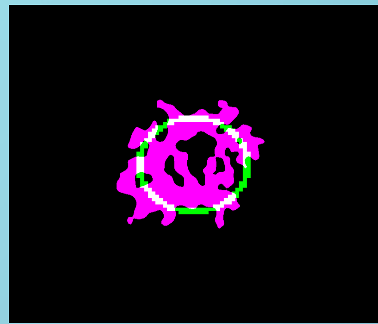
Cubic on air



Point-like on air

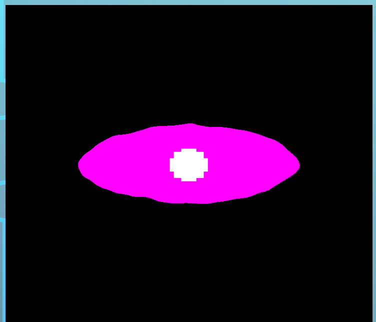


Ring on tissue

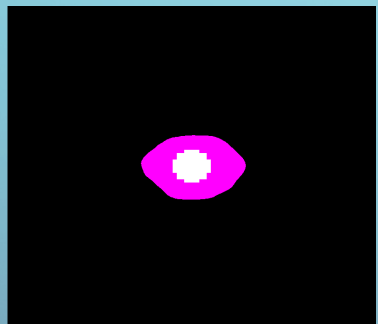


- Ground truth
- Source segmented
- Overlap

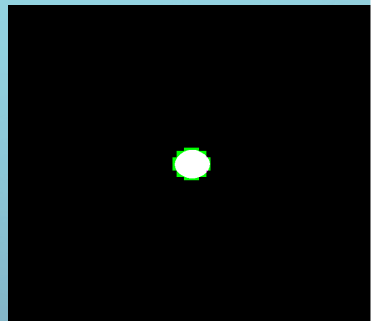
T/N = 2



T/N = 5



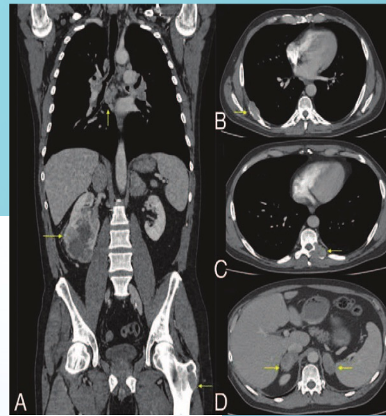
Spheric on air



	Accuracy	Sensitivity
5 point-like on tissue	3.81%	100%
Cubic on air	86.09%	96.27%
point-like on air	0.55%	100%
Ring on tissue	13.46%	59.20%
Spheric $T/N = 2$	4.83%	100%
Spheric $T/N = 5$	3.81%	100%
Spheric on air	99.73%	77.99%

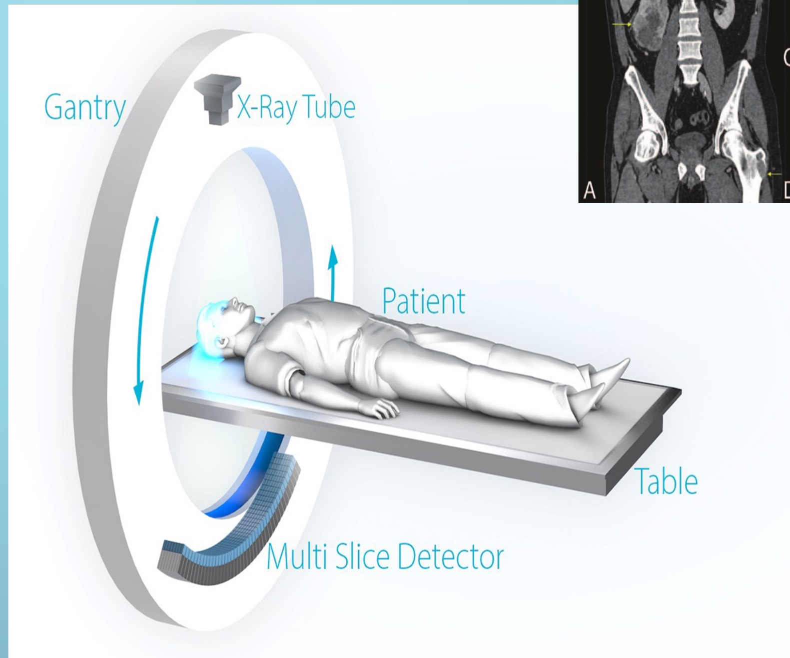
TOMOGRAFIA COMPUTERIZZATA (COMPUTED TOMOGRAPHY, CT)

La tomografia computerizzata è una tecnica diagnostica per immagini che consente di esaminare ogni parte del corpo per la prevenzione, diagnosi e studio dei tumori e di numerose altre patologie.



Le CT sono oggi eseguite con la tecnica convenzionale che utilizza raggi X.

Gli esami CT rappresentano circa il 10% degli esami radiologici eseguiti annualmente. Essi **sono responsabili di circa la metà della dose radiante complessiva erogata alla popolazione**.



Interested people: A.G. Torres, F. Barile, D. Colella, G.B.

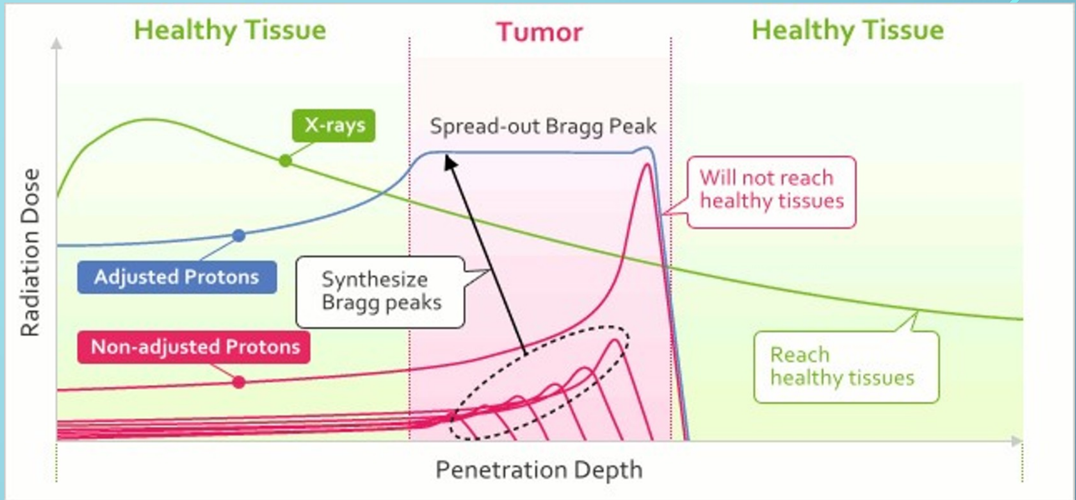
Project RiParti with LinearBeam s.r.l. (spinoff di Itel Telecomunicazioni) with title "Studio di fattibilità di un sistema di tomografia computerizzata che utilizzi un fascio di protoni"

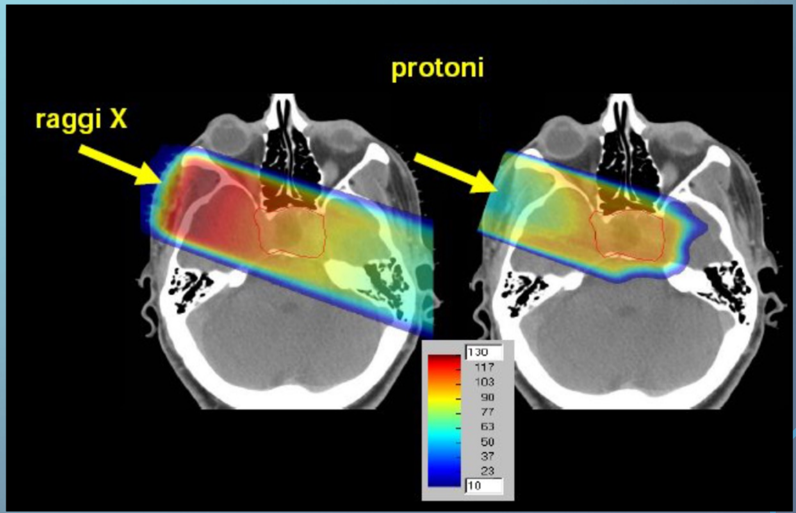
MOTIVAZIONE DELLA ATTIVITÀ

Lo sviluppo di un sistema per CT che utilizzi un fascio di protoni anziché la tecnica convenzionale coi raggi X ridurrebbe in maniera significativa la dose associata all'esame diagnostico.

Il fascio di protoni deve essere portato ad una maggiore energia di quella usata per il trattamento, perché i protoni devono solo perdere una piccola frazione della loro energia nel corpo del paziente, senza che si giunga al picco di Bragg, e fuoriuscire dal paziente per essere misurati.

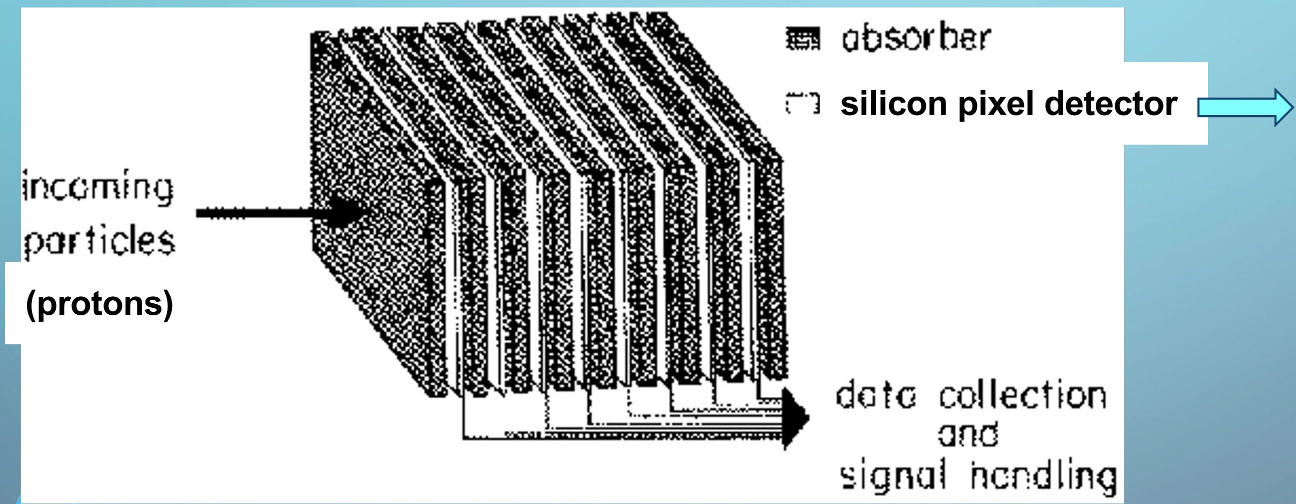
Dalla misura della perdita di energia dei protoni nei tessuti si può realizzare la tomografia protonica.

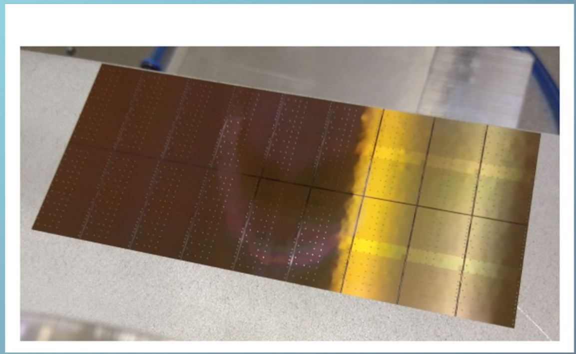




DESCRIZIONE DELLA ATTIVITÀ

Studio di fattibilità di un sistema di rivelazione per la tomografia protonica, basato su innovativi rivelatori a pixel di silicio di grandi dimensioni intervallati con assorbitori disposti a sandwich, per realizzare un cosiddetto "calorimetro" ibrido ad alta segmentazione.



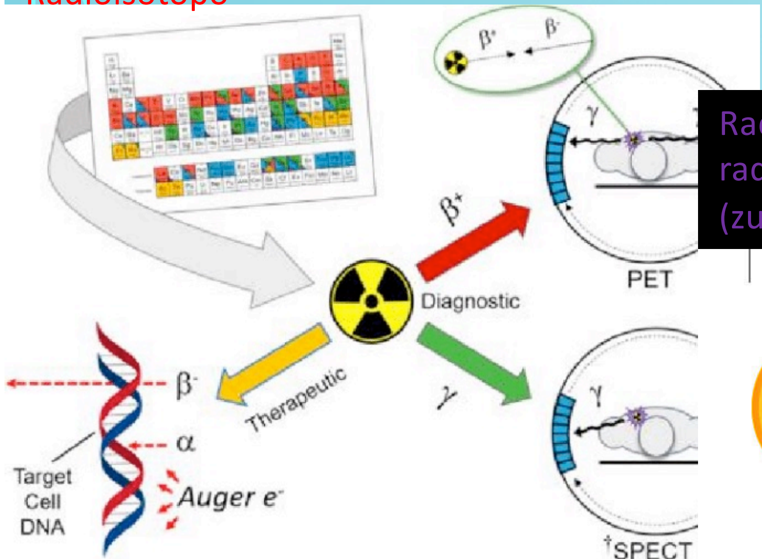


Prototipo di un rivelatore a pixel di silicio di dimensioni 138 mm × 60.1 mm e spessore di 40 micrometri.

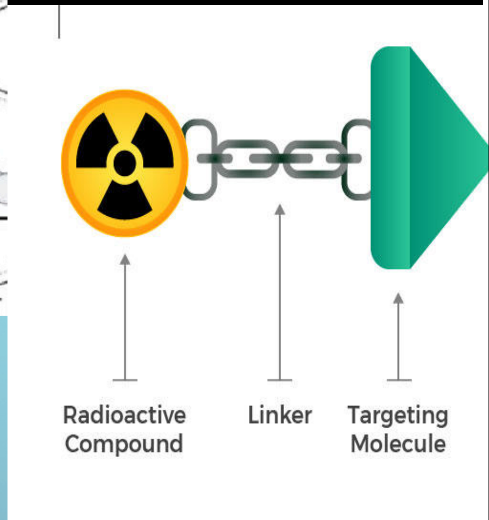
RADIOISOTOPI TERANOSTICI

Un radiofarmaco teranostico rappresenta un approccio combinatorio di diagnosi (mediante imaging) e terapia della malattia, che mira a trattamenti terapeutici più tempestivi e a migliorare la cura del paziente.

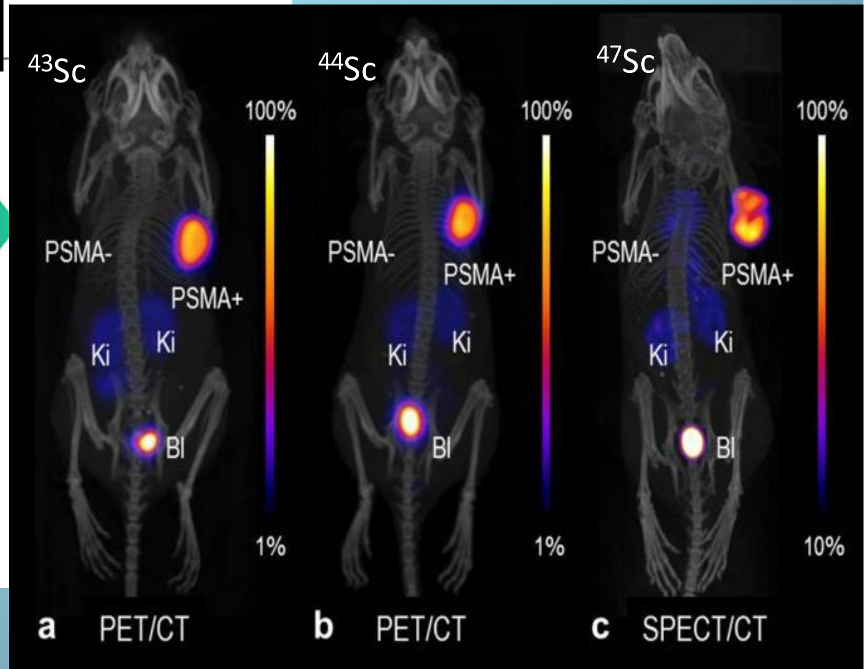
Radioisotopo



Radiofarmarco: radioisotopo + carrier (zucchero, p tc)



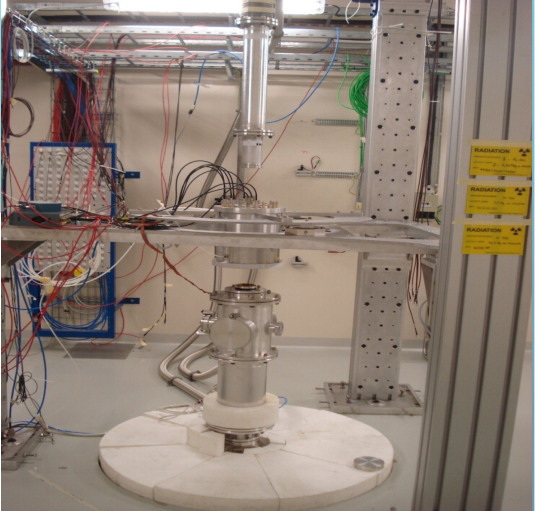
Esempi di Imaging: PET e SPECT

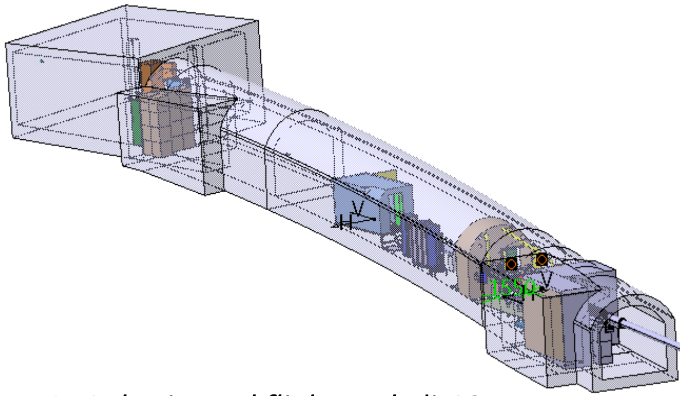


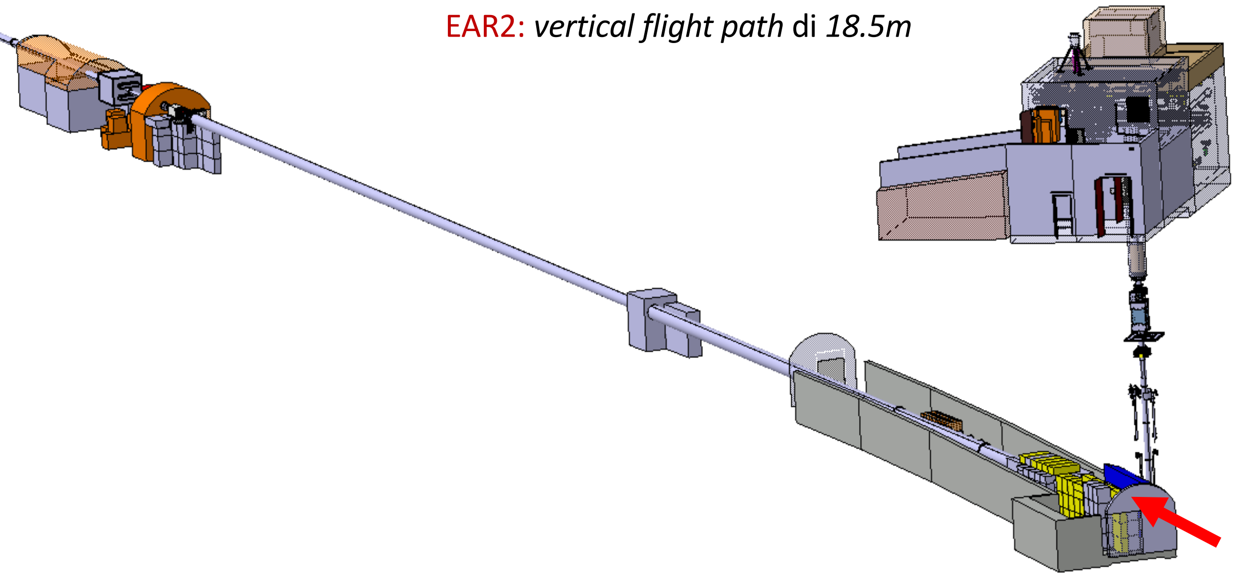
Interested people: <u>M. Mastromarco</u>, N. Colonna and other INFN colleagues

Mario Mastromarco is *RTDA at* Dipartimento di Fisica, UniBa, working on the REFIN project "**Produzione di Radioisotopi per la Teranostica con Fasci di Neutroni e Protoni**"

N_TOF FACILITY @ CER

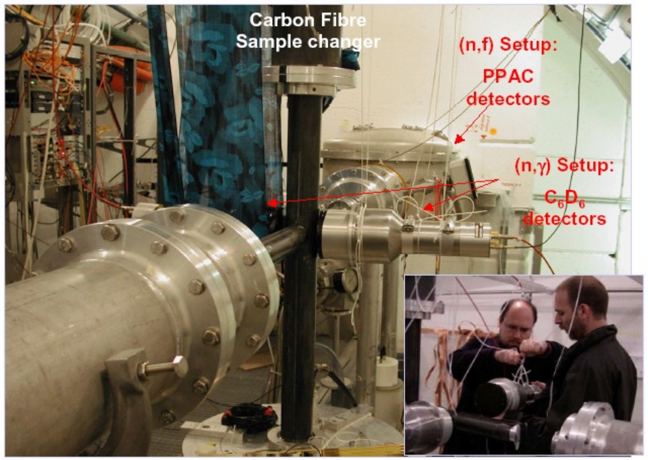






EAR2: *vertical flight path* di *18.5m*

EAR1: *horizontal flight path* di *185m*

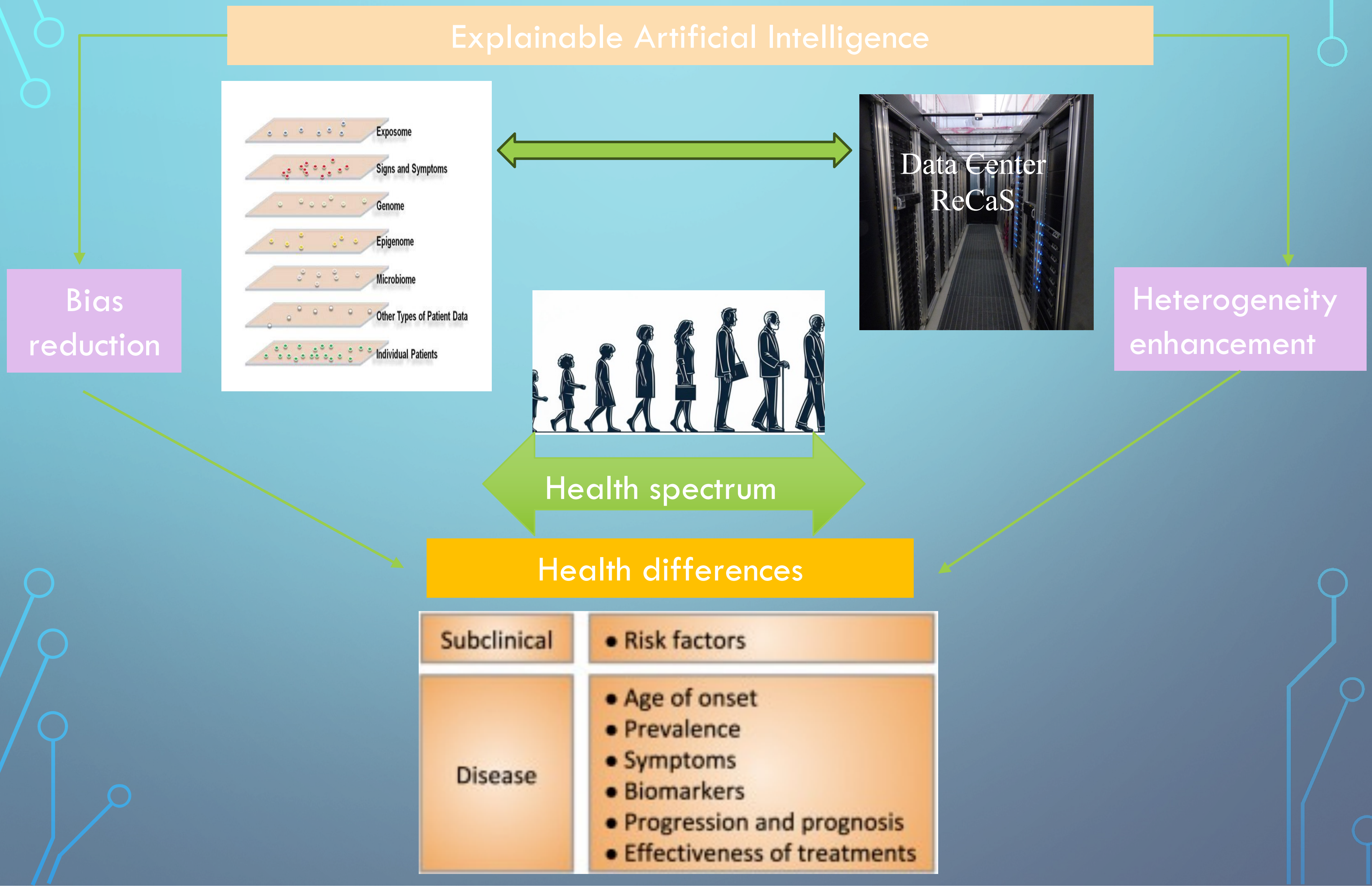


PROGETTI CALCOLO IN AMBITO HEALTH – BARI

PROGETTI PNRR

- Spoke8 - ICSC - Development of a Processing Pipeline for Medical Images and Omics Data in Patients with Pancreatic Cancer
- DARE
  - Già presentato in INFN-LS
- ITINERIS
  - Progetto sulla Biodiversità: INFN-Bari si occupa di fornire risorse di Calcolo e Servizio Cloud evoluti per supportare la comunità nazionale e internazionale che lavora nell'ambito del monitoraggio della biodiversità
- UNIBA come ReCaS-Bari partecipa ad altri progetti:
  - Centro Nazionale 3 (Omics)
  - ElixirXNextGenIT
    - Infrastruttura di ricerca per la realizzazione di una piattaforma nazionale di sequenziamento, analisi e gestione dati.
    - ReCaS-Bari fornisce risorse e tecnologie cloud

EXPLAINABLE ARTIFICIAL INTELLIGENCE FOR HEALTH APPLICATIONS



Public large-scale validation studies

Segmentation and classification results can be exploited to design computer aided detection systems.

The lack of an unbiased comparison among different studies has motivated in recent years a number of international challenges have been promoted to compare algorithms and methodologies within a common framework.

Conclusions

we are just at the beginning…

PROGETTI EU

- EuroScienceGateway:
  - START: 01/09/2022 || END 31/08/2025
  - Obiettivo:
    - Accessible e-Infrastructure resources for European scientists to enable pioneering data-driven research across scientific domains.
    - Support the varieties of analysis types and diverse usage patterns through efficient and smart job distribution to appropriate and sustainable infrastructures.
    - The application of FAIR principles to workflows and adoption of FAIR Digital Objects to stimulate reusable and reproducible research and enable the EOSC Interoperability Framework.
    - Adoption of the EuroScienceGateway by researchers in diverse scientific disciplines.
  - EuroScienceGateway will leverage a distributed computing network across 13 European countries, accessible via 6 national, user-friendly web portals, facilitating access to compute and storage infrastructures across Europe as well as to data, tools, workflows and services that can be customized to suit researchers' needs. At the heart of the proposal workflows will integrate with the EOSC-Core. Adoption, development and implementation of technologies to interoperate across services, will allow researchers to produce high-quality FAIR data, available to all in EOSC. Communities across disciplines -- Life Sciences, Climate and Biodiversity, Astrophysics, Materials science -- will demonstrate the bridge from EOSC's technical services to scientific analysis.

Further detail …

SPOC - SPect for Online boron dose verification in bnCt
Collaboration, Project Organization – Milestones

Collaboration: 3 INFN Units Bari – Pavia – Milano (PI)

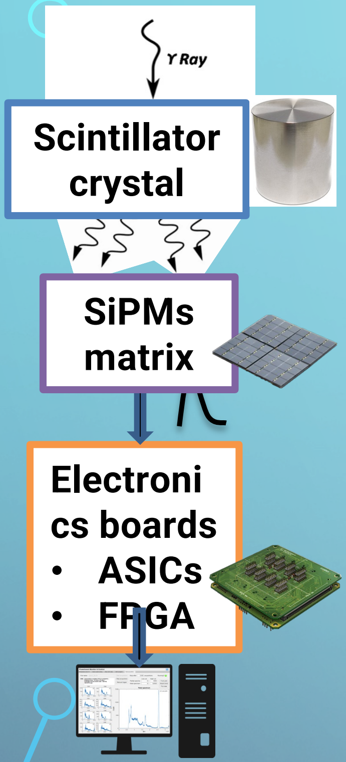
Project Organization: 4 Work Packages and 2 Milestones for each WP

- **WP1**: Simulations of irradiation neutron fields and of gamma and neutron fluxes on the detector. Study of shielding. Study of overall SPECT configuration (Polimi-Energia)
- **WP2**: Development of the gamma-ray detector, electronics, collimation system and algorithms for the gamma-ray position reconstruction. Development of the SPECT prototype. (Polimi-DEIB)
- **WP3**: BNCT dedicated tomographic reconstruction. (Bari)
- **WP4**: Beam tests at nuclear reactor and with accelerator-based sources. (Pavia)

Month:	1-3	3-6	7-9	10-12	13-15	16-18	19-21	21-24	25-27	28-30	31-33	34-36
WP1				M1		M5		M6				
WP2				M2						M8		
WP3				M3				M7				
WP4				M4								M9

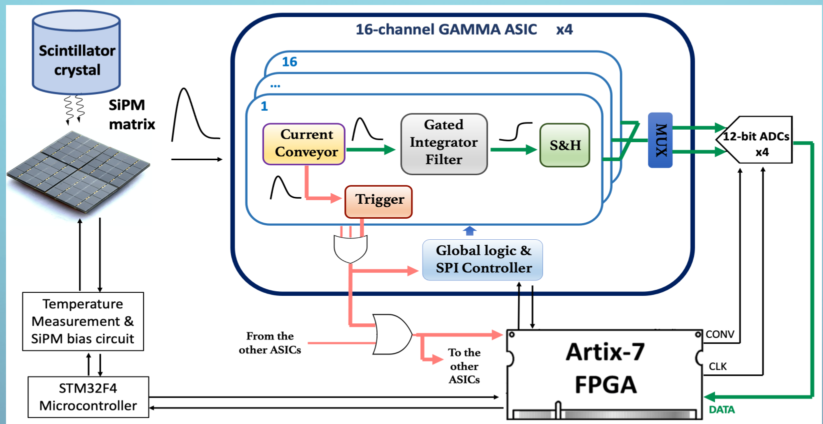
2024 2025 2026

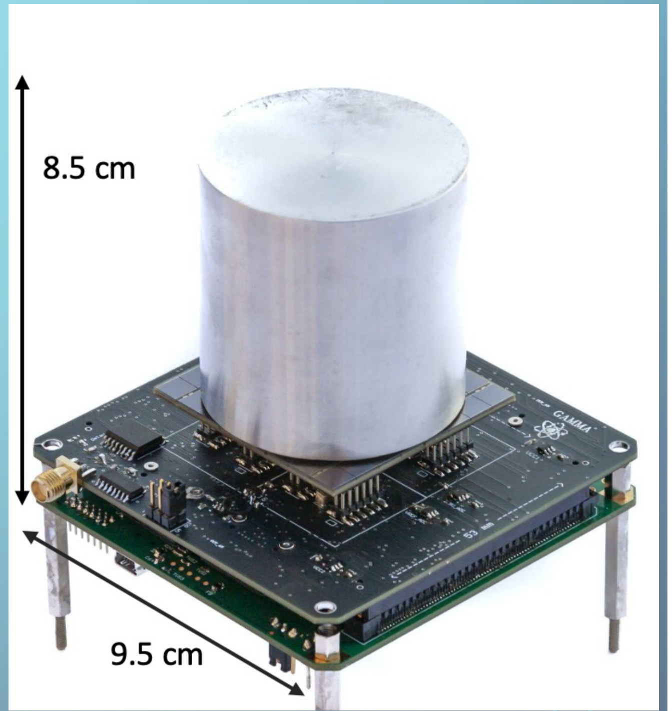
The V0 Detector Prototype



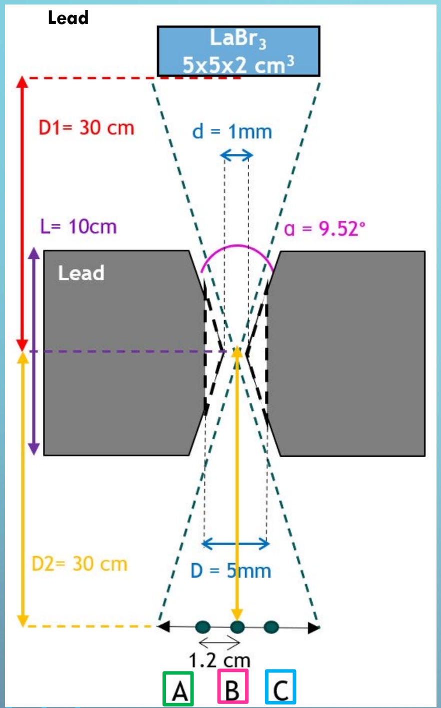
Gamma-ray detection module:

- 2" cylindrical LaBr3(Ce+Sr) scintillator crystal
- 4 arrays of 4x4 SiPMs
- 4 custom 16-channels GAMMA readout ASICs
- Data acquisition is managed by an FPGA.



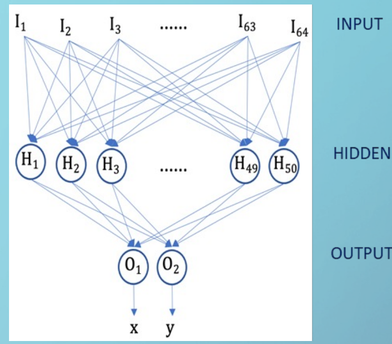


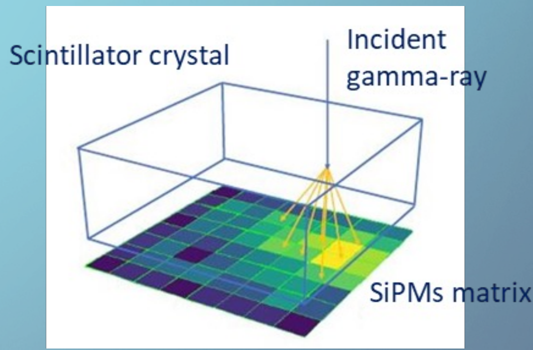
Preliminary Results
MC Simulations of Square Gamma Camera



Preliminary MC simulations performed to estimate imaging capabilities of a Gamma camera based on square LaBr3:

- Channel edge pinhole collimator used for image acquisition
- Position estimation in the crystal performed with artificial neural networks (input: SiPM signals / output: x-y coordinates)
- Training of the network performed by scanning the crystal surface in 320 positions with a 1mm-collimated ^{137}Cs source (662 keV)
- The ANN is able to reconstruct the position of a 137Cs source in measurements acquired with the pinhole collimator with a spatial resolution of 3.25 mm





Overview of previous/ongoing projects
RIPARTI - Feasibility study for the development of advanced techniques in neutron beam radiotherapy

Bari task ⇆ synergy with ITEL Linearbeam s.r.l. facility for protontherapy

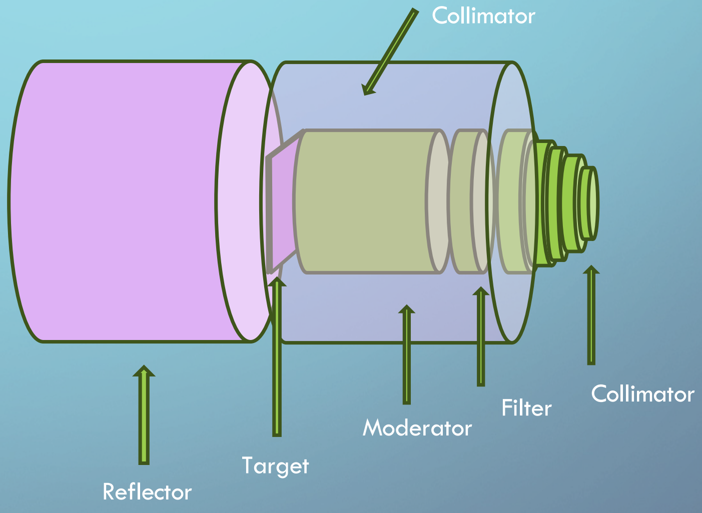
1 post-doctoral position

General goal: Feasibility study to become a protontherapy facility into Accelerator-based BNCT facility by introduction of a target system: Beam Shaping Assembly (BSA)

- Proposed target materials: **Lithium** and **Beryllium** → highest cross section for the reacctions p(^{9}Be,^{9}B)n and p(^{7}Li,^{7}Be)n, respectively.
- **Function:** Thermalize and moderate neutrons

Preliminary BSA layout

1. Moderator: AlF_3 , Al , MgF_2 , CaF_2, polyethylene
2. Filter: ^{7}LiF
3. Collimator: Pb, polyethylene
4. Reflector: Pb



Overview of previous/ongoing projects
SPOKE 8 - Development of a Processing Pipeline for Medical Images and Omics Data in Patients with Pancreatic Cancer

Objectives

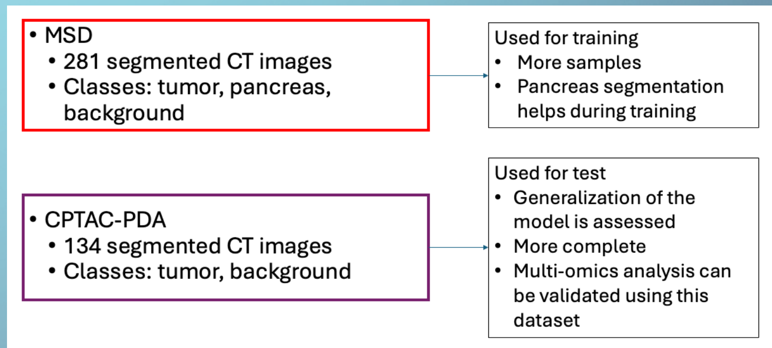
Image analysis for the study of neoplasms of internal organs with particular attention to pancreas neoplasms.
Extraction of data useful for the treatment of patients and to establish correlations with clinical data and genome.

Tools

Radiological images (before and after surgery), digitized biopsies, ultrasound, clinical picture, genomic sequencing.

Two main public datasets available as pipeline workflow input data

- Medical Segmentation Decathlon - Task07_Pancreas
- CPTAC-PDA



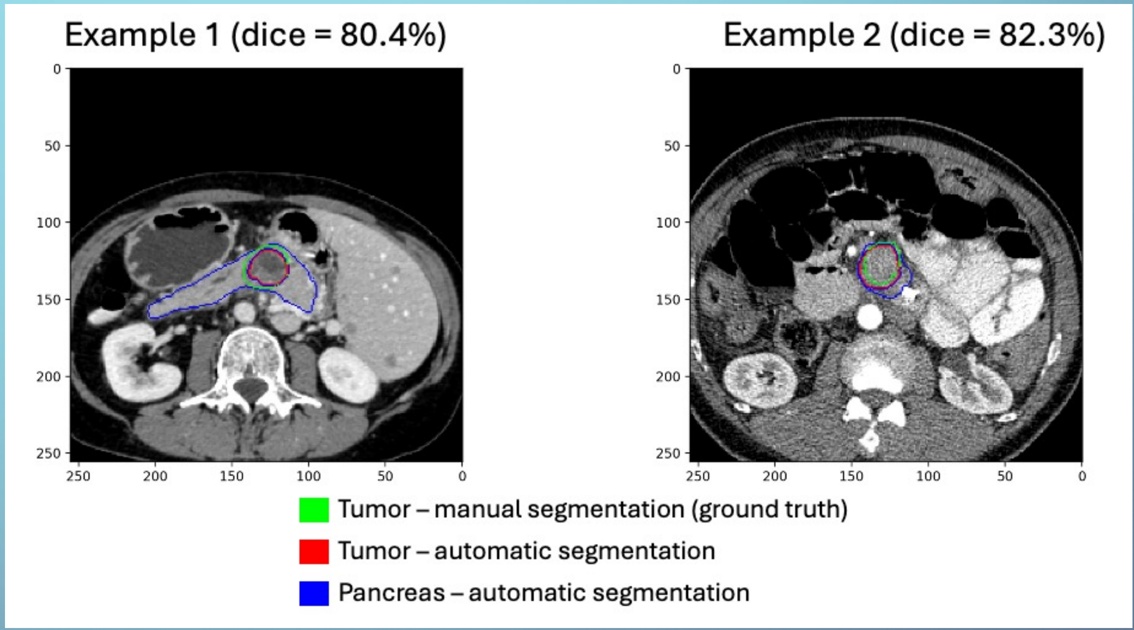
Overview of previous/ongoing projects SPOKE 8 - Development of a Processing Pipeline for Medical Images and Omics Data in Patients with Pancreatic Cancer

Preliminary results from segmentation models

Mean dice score for the tumor class

	MSD validation set	Full CPTAC-PDA
SRSNet_v05 (ours)	37.5%	42.1%
nnU-Net (3d model)	53.1%	46.7%

examples from CPTAC-PDA



FUNDED PROJECTS / INFN-COLLABORATIONS

FLASH Radiotherapy with hIgh Dose-rate particle beAms

FUTURE PLANS

- Main challenges will be mechanical and DAQ integration of range module and beam tracker.
- Test the integrated system with clinical and FLASH beams.

COLLABORAZIONI SCIENTIFICHE

- Elixir-IT
  - Una collaborazione fra 29 fra enti pubblici e università italiane con l'obiettivo di supportare la ricerca nel settore delle scienze della vita
- Lifewatch
  - Una collaborazione fra 35 fra enti pubblici e università italiane che hanno l'obiettivo di creare una infrastruttura per la ricerca sulla biodiversità e gli ecosistemi.

CERTIFICAZIONE ISO DATA CENTER

- Si sta lavorando ad una certificazione multi-sito (CNAF, Bari e CT) di una infrastruttura di Cloud computing evoluta per gestire servizi e data biomedicali e alte comunità con dati critici
- Per la prima volta si punta a servizi più evoluti che il solo IaaS

New scope

Coprogettazione, sviluppo e manutenzione di soluzioni software di DataCloud per il settore della ricerca.

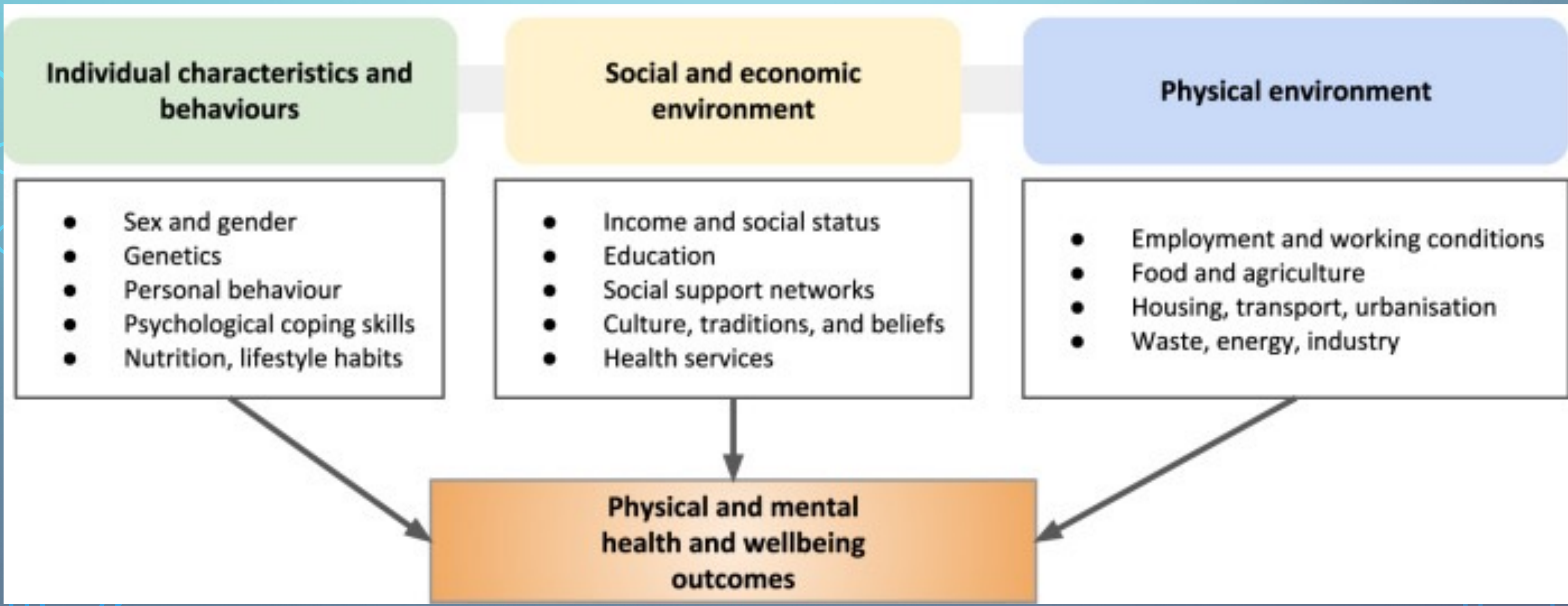
Erogazione di servizi di DataCloud IaaS, SaaS e PaaS in community deployment model.

Artificial intelligence for Medicine in digital age

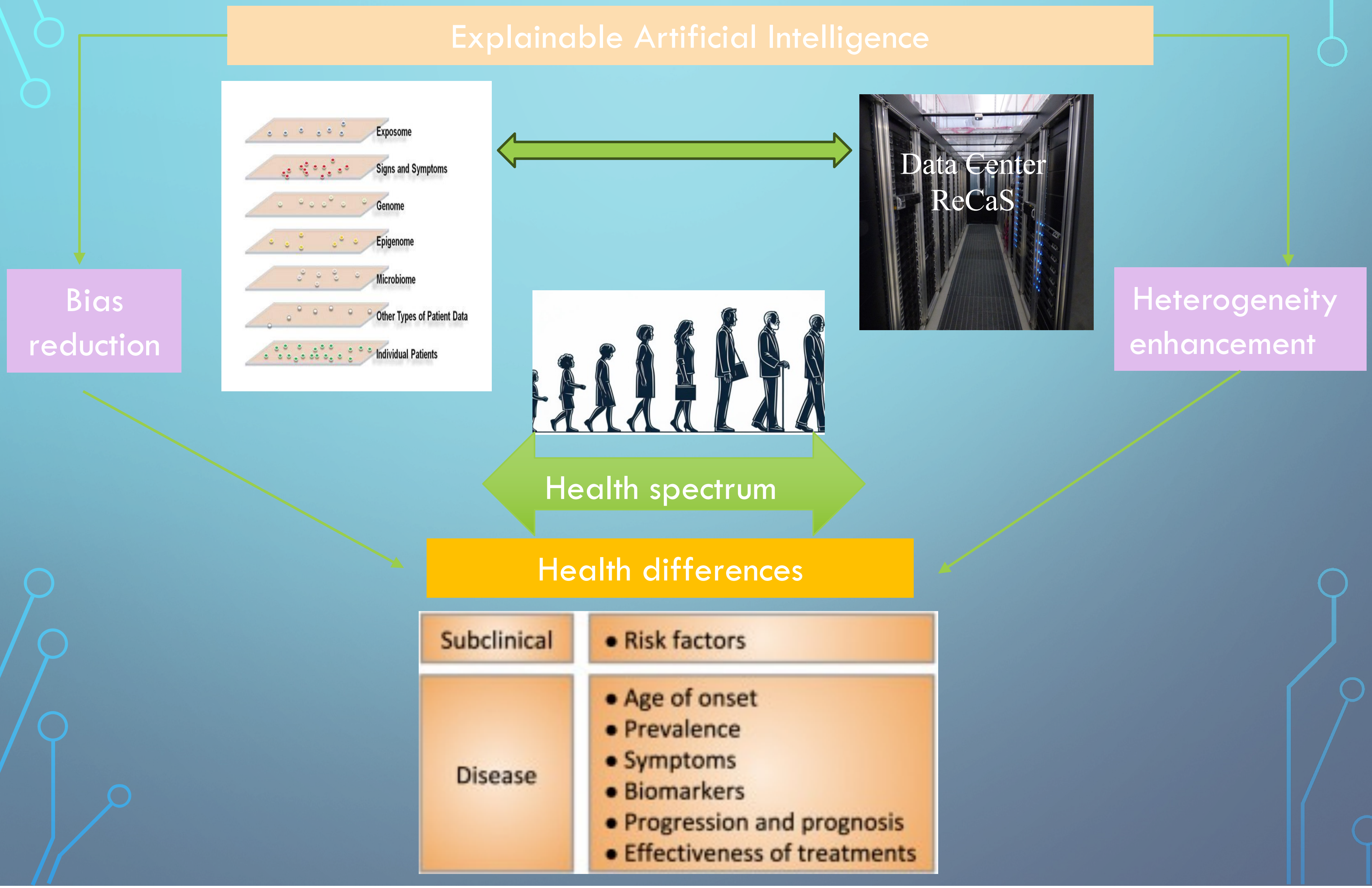
S. Tangaro, R. Bellotti, D. Diacono, A. Monaco, N. Amoroso, L. Bellantuono, M. Larocca, E. Pantaleo, …

DETERMINANTS OF PHYSICAL AND MENTAL HEALTH

Explainable Artificial Intelligence

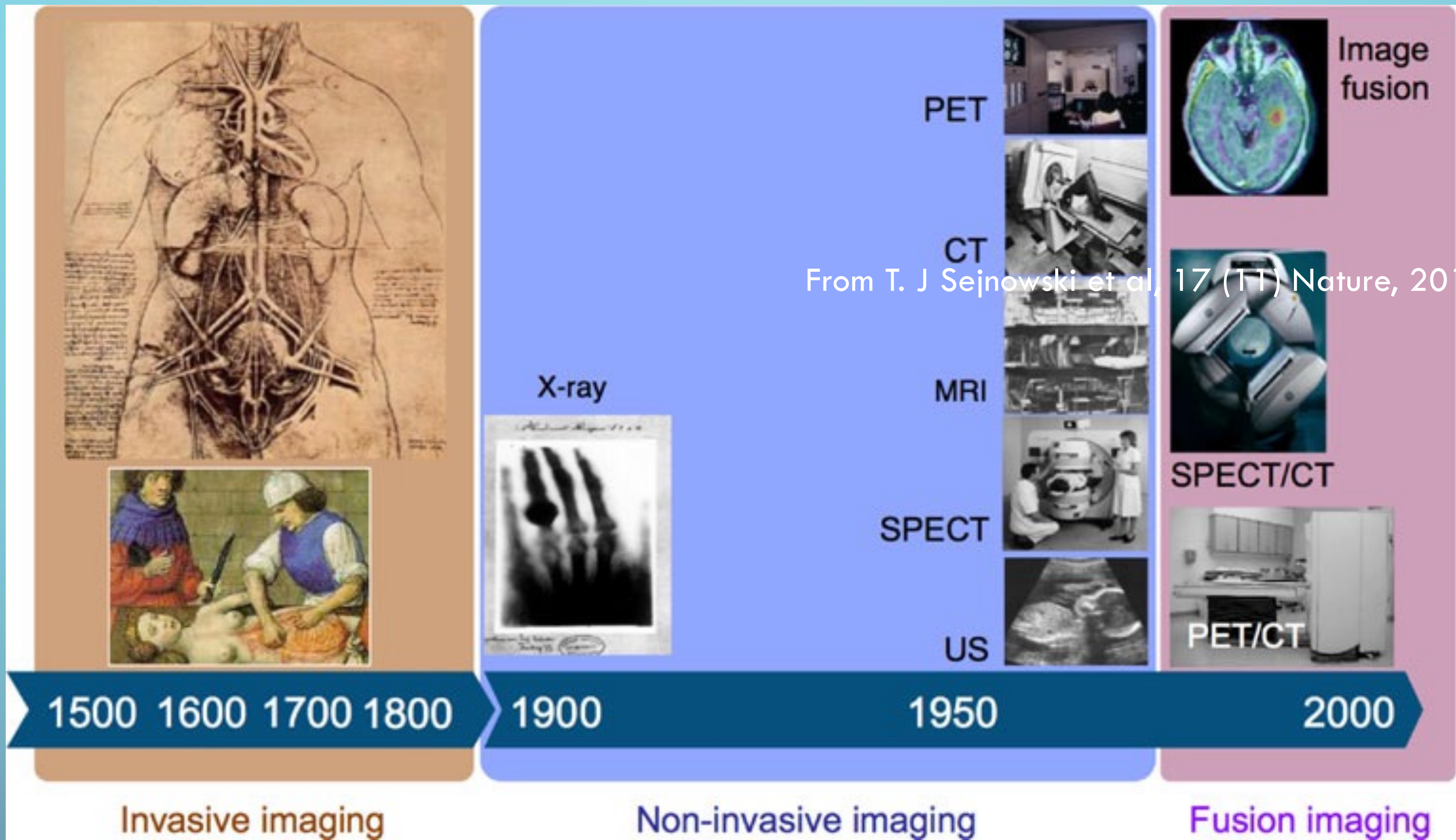


EXPLAINABLE ARTIFICIAL INTELLIGENCE FOR HEALTH APPLICATIONS



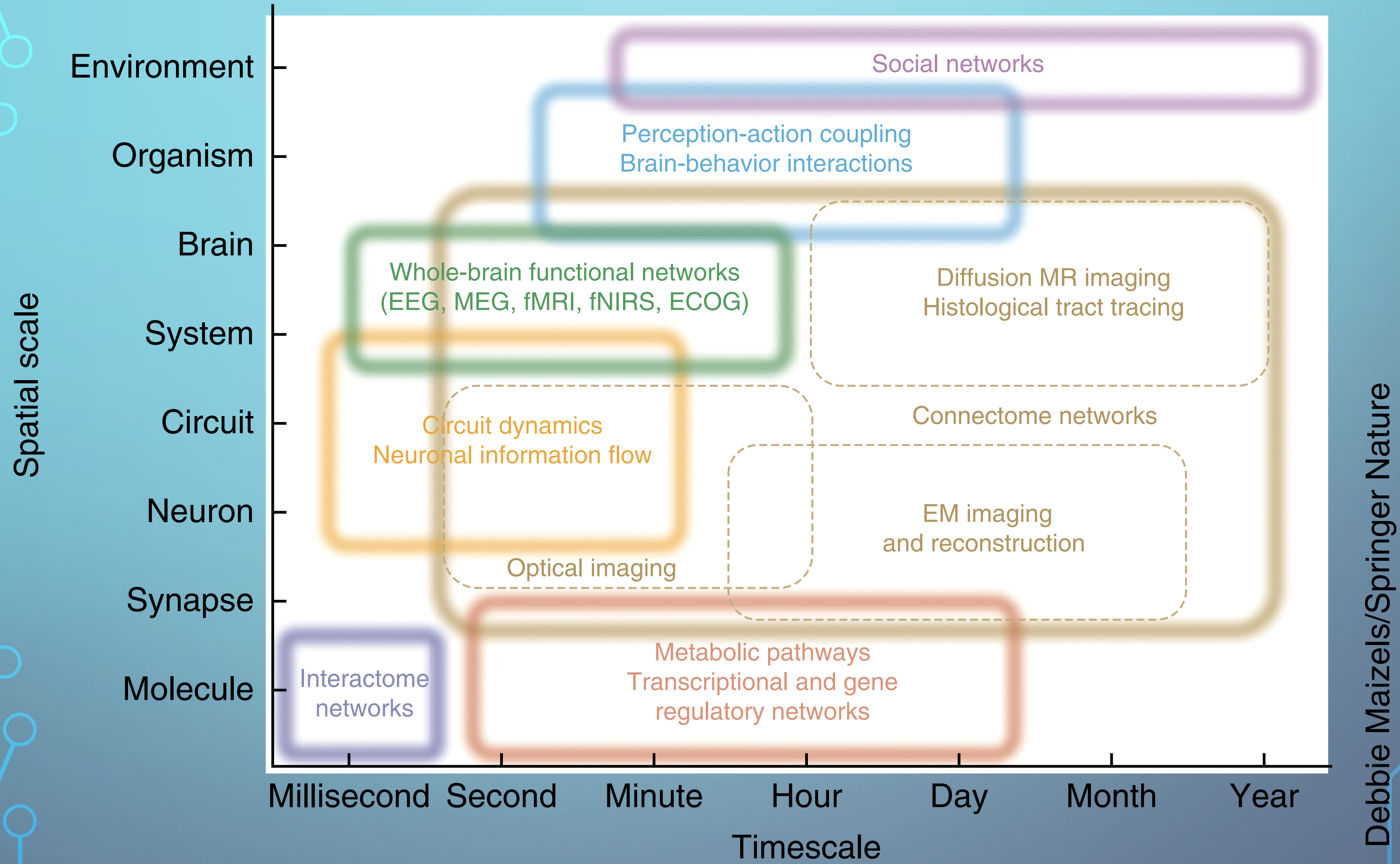
IMAGING ADVANCES

from T. Beyer et al., Insights Imaging (2011)



From T. J Sejnowski et al, 17 (11) Nature, 2014

NETWORK NEUROSCIENCE



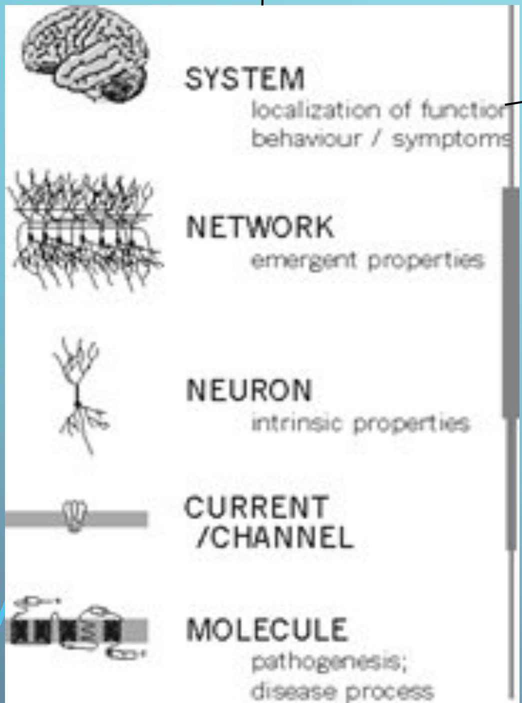
Danielle S Bassett & Olaf Sporns, 20 (3) Nature 2017

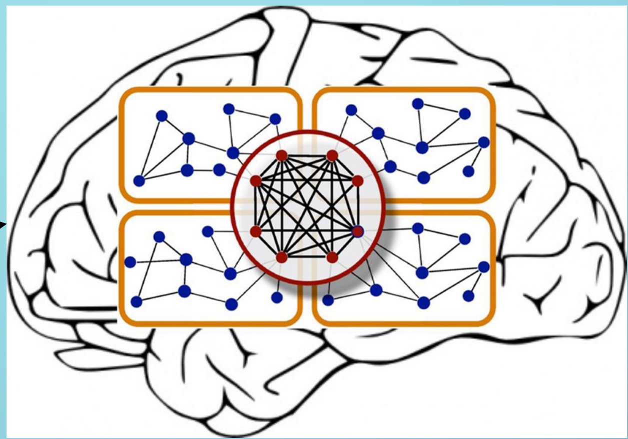
ARTIFICIAL INTELLIGENCE

- **Machine learning** (supervised or unsupervised)
    - **Data mining** (used also for Natural Language Process and Images classification)
        - Classification trees (for classifying/predicting discrete outcomes, e.g. bad/good)
        - Regression trees (for continuous outcomes, e.g. cost forecasting)
        - Belief networks (learning of probabilistic models)
        - Support vectors machines (learning of mathematical models)
        - Neural networks (learning of mathematical models)
          » **Deep learning**
        - Conditional random fields
        - Reinforcement learning
    - **Process mining**
        - temporal pattern discovery
- **Complex Network and emergent behaviour** (physiological phenomena result from a complex series of interactions that occur hierarchically)
    - Dynamic interactions
    - Emergence

THE BRAIN AS A COMPLEX SYSTEM

Large – scale observations: neuroimaging/electrophysiological recordings





Complexity and emergent behaviour: cognitive and physiological phenomena result from a complex series of interactions that occur hierarchically.

- Many components
- Dynamic interactions
- Emergence

next_AIM - Artificial Intelligence in Medicine: *next steps*

INFN-CSN5

Project coordinator:
A. Retico, Pisa

13 Research Units:
- Bari (S. Tangaro)
- Bologna (D. Remondini)
- Cagliari (P. Oliva)
- Catania (M. Marrale)
- Ferrara (G. Paternò)
- Firenze (C. Talamonti)
- Genova (A. Chincarini)
- Lab. Naz. Sud (G. Russo)
- Milano (C. Lenardi)
- Napoli (G. Mettivier)
- Pavia (A. Lascialfari)
- Padova (A. Zucchetta)
- Pisa (M.E. Fantacci)

https://www.pi.infn.it/aim/

AIM [2019-2021]
next_AIM [2022-2024]

WP1 — Challenge I: no-so-big data

Strategies for efficient learning with limited data samples.

Evaluation of robustness and reliability of trained models.

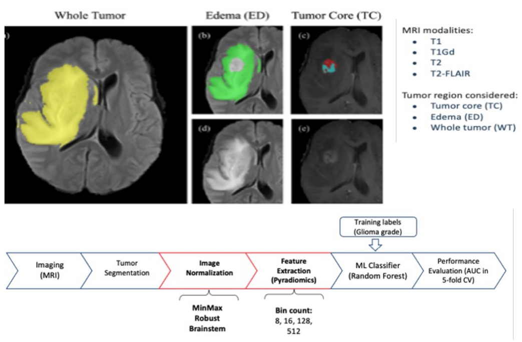
WP2 — Challenge II: explainable AI (XAI)

Make AI results understandable to humans.

Which image/data features are relevant to make a decision?

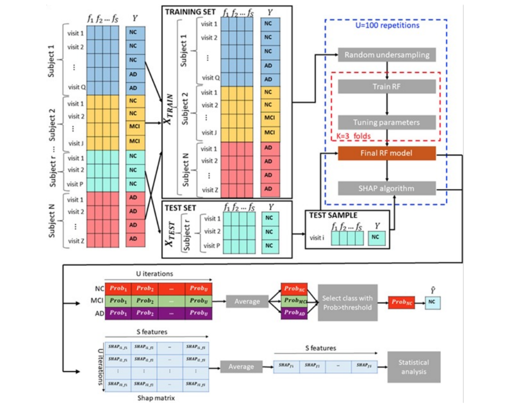
WP3 — Applications to real-world data samples include ….

Evaluation of the robustness of radiomic features in multiparametric MRI and its impact on predictive value of AI models



Ubaldi L, Saponaro S, Giuliano A, Talamonti C, **Retico A**. Deriving quantitative information from multiparametric MRI via Radiomics… *Phys Medica* 2023;107:102538 https://doi.org/10.1016/j.ejmp.2023.102538.

Robust implementation of explainable AI methods



Lombardi A, Diacono D, Amoroso N, Biecek P, Monaco A, Bellantuono L, … **Tangaro S,** Bellotti R. A robust framework to investigate the reliability and stability of explainable artificial intelligence …. *Brain Informatics* 2022; 9:17. https://doi.org/10.1186/s40708-022-00165-5.

WP4 — Computing resources and SW repository organization

ReCaS, IBiSCo, INFN-Cloud + local HW resources

WP5 — Exploitation of research results and communication

conferences, publications and outreach, collaboration with aifm

Long-standing collaboration with Italian centers (hospitals and IRCCS) and with international consortia for data sharing

ASSOCIAZIONE ITALIANA di FISICA MEDICA e SANITARIA
La Fisica al servizio della salute

POS 2

RN: P. Oliva

TELE-NEURART | Rete Nazionale Pediatrica per il tele-monitoraggio e la tele-riabilitazione dei disturbi e delle disabilità del neurosviluppo tramite l'individuazione e l'analisi di biomarker digitali, identificati tramite intelligenza artificiale

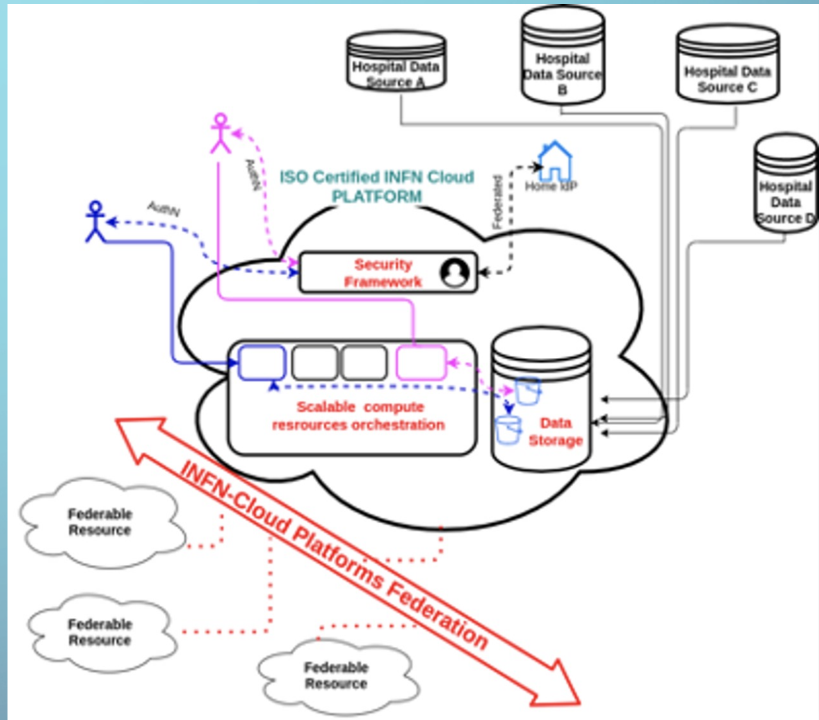
Design of a dedicated platform for medical data analysis with AI

The joint effort by the **Medical Physics and High Energy Physics communities** led to the design of a dedicated computing infrastructure which can link Clinical, Medical Research and Technical Research Centers.

The INFN-cloud based computing infrastructure is:

- **especially suited for training AI models**
- equipped with **secure storage and communication** systems (ISO/IEC 27001 27017 27018)
- **compliant with data protection regulation (GDPR)**

It would be able to accelerate the **development and extensive validation of AI-based solutions for Medical Imaging**.



[Retico A, Avanzo M, Boccali T, Bonacorsi D, Botta F, Cuttone G, et al. Enhancing the impact of Artificial Intelligence in Medicine: A joint AIFM-INFN Italian initiative for a dedicated cloud-based computing infrastructure. Phys Medica 2021;91:140–50. https://doi.org/10.1016/j.ejmp.2021.10.005.]

POS 3 - GENESIS ATI

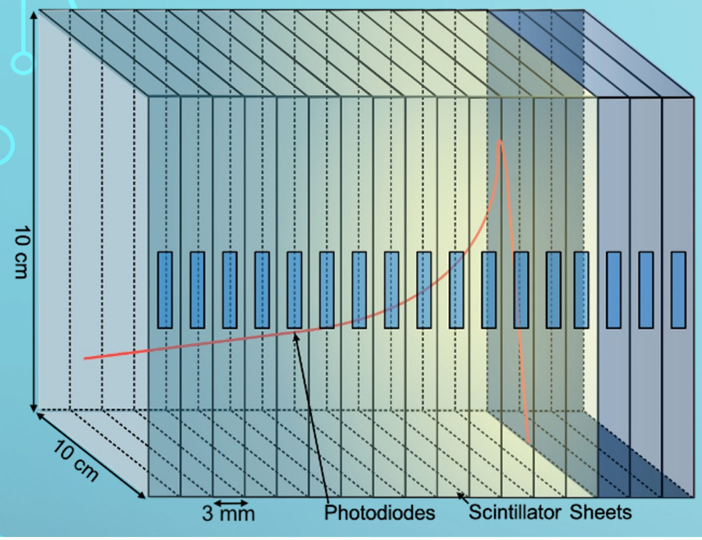
Studio degli eventi GENEtici alla baSe della CarcInogeneSi in aree ad Alto Tasso di Inquinamento per tipologia produttiva

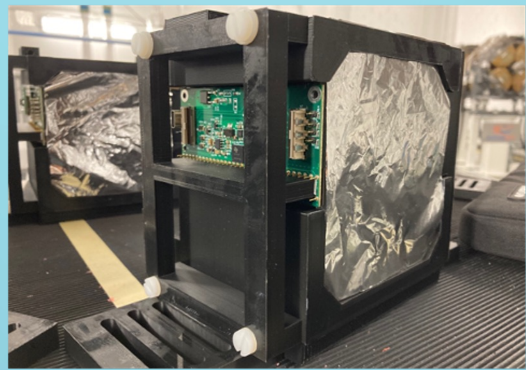
Obiettivo del progetto

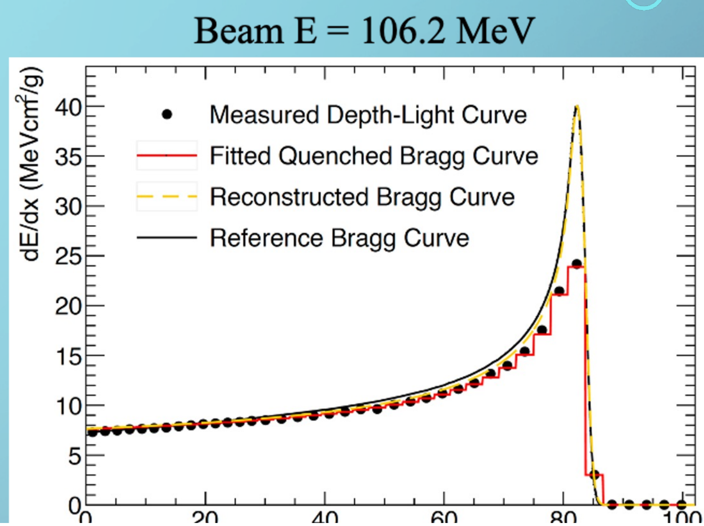
Obiettivo del progetto è mettere in relazione i dati ambientali forniti da ARPA Sicilia, relativi alla presenza di sostanze chimiche e alla loro concentrazione in acque superficiali e profonde, con i dati clinici di pazienti oncologici, già presenti nel Registro Tumori gestito dall'ASP di Ragusa; oltre all'analisi retrospettiva dei dati già presenti nel database di ARPA Sicilia e nel Registro Tumori, il progetto prevede l'attivazione di studi clinici condotti dall'Università di Palermo e dallo IOR con il coinvolgimento di soggetti residenti a zone a rischio alto e basso, con lo scopo di creare un setting predittivo di potenziali malattie tumorali correlate o comunque condizionate dalla presenza di agenti ambientali inquinanti.

BACKUP

RANGE MODULE







•Series of optically isolated polystyrene scintillator sheets of size: 10 cm×10 cm × 3 mm.

•Photodiodes coupled to fast, modular ADC electronics read light levels at over 5 kHz.

•Measure depth-*light* curve to reconstruct Bragg depth-*dose* and proton range with accuracy < 0.5mm.

•Modular design: one detector module (32 sheets, 96 mm total depth) can test pencil beam energies between 70–130 MeV. Possibility to daisy chain to cover the full clinical energy range.

•Real-time range reconstruction: 6 kHz data-rate, 40 Hz range fitting.

SCALING TO FLASH

- Dose-rate for FLASH estimated around 40 Gy/s.
    - Estimated delivery time of 100 ms
    - Corresponds to a current of 600 nA to the patient.
- Due to the nanosecond decay time of the plastic scintillator and the large dynamic range of the detector, range measurements are also possible at FLASH dose rates.
    - scintillation light output scales linearly with dose-*rate*.
- Clinical beam performed at UCLH in 2022 has 300 nA cyclotron current.
    - Approx. 1% transmission ratio to treatment room.
    - Expect 600/(300*1%) = 200 factor increase in light.


Range QA measurements for FLASH proton therapy using the Quality Assurance Range Calorimeter

Saad Shaikh[1], Sonia Escribano-Rodriguez[1], Raffaella Radogna[2], Connor Godden[1], Matthew Warren[1], Derek Attree[1], Ruben Saakyan[1], Samuel Manger[34], Nicholas Henthorn[34], John-William Warmenhoven[34], Michael Taylor[34], Karen Kirkby[34], Marc-Jan van Goethem[5], Alexander Gerbershagen[5], Simon Jolly[1]
[1]Department of Physics and Astronomy, University College London, London, UK
[2]Department of Physics, University of Bari, Bari, Italy
[3]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
[4]The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[5]PARTREC, UMCG, University of Groningen, The Netherlands
E-mail: saad.shaikh@ucl.ac.uk

Abstract. The purpose of this work was to demonstrate the design and performance of a full-sized clinical prototype of the Quality Assurance Range Calorimeter (QuARC): a segmented large-volume scintillator-based detector for fast, accurate proton range quality assurance (QA) measurements. The detector used 128 scintillator sheets of size 105 × 105 × 3 mm arranged into 4 modules of 32 sheets, where each sheet was directly coupled to a photodiode. Fast analogue-to-digital conversion facilitated measurement of scintillator sheet light output to 20-bit precision at 6 kHz, with a dynamic range of up to 350 pC. Proton range measurements with the full-size detector were performed at The Christie at clinical (approx. 1 nA nozzle current) dose-rates, where the range accuracy of the QuARC was found to be within 0.4 mm of facility reference across the full clinical energy range. The QuARC was successfully able to perform range measurements of the 245 MeV beam at FLASH dose-rate (approx. 50 nA nozzle current), where the fitted range agreed with the clinical current measurement to 0.3 mm. Follow-up measurements with 2 detector modules at UMCG PARTREC investigated the linearity of the scintillator light output with beam current, which found non-linearity effects of up to 25% between beam energies of 60-150 MeV. Several convoluted variables are discussed as possible causes to this effect as well as improvements to the detector design for future experiments.

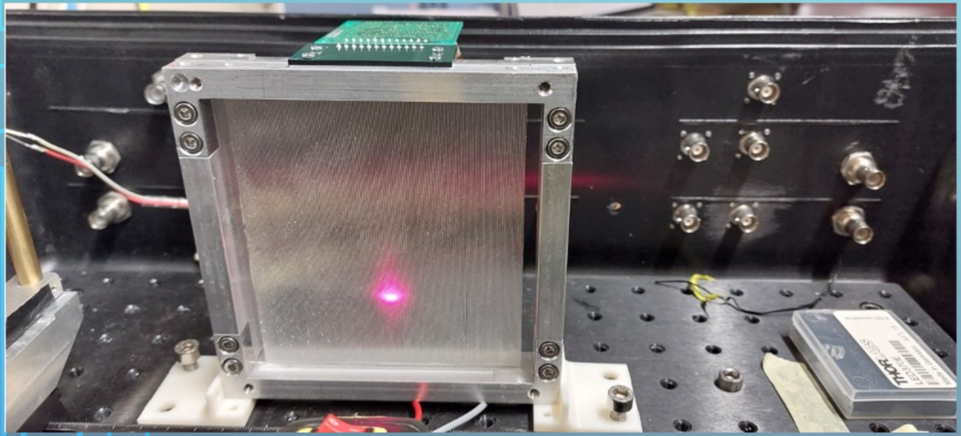
proton therapy, plastic scintillator, FLASH, quality assurance

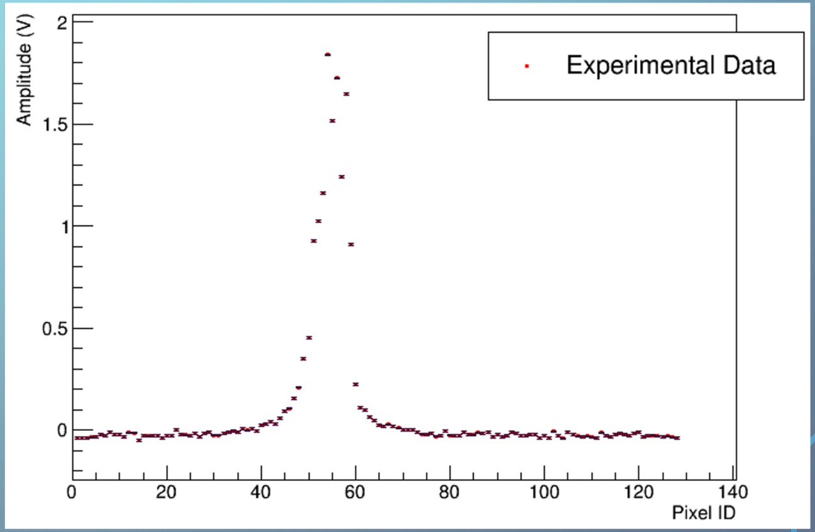
Submitted to: *Phys. Med. Biol.*

BEAM TRACKER

The potential for an integrated QA solution for FLASH PBT

- First detector prototype now produced in 2023 and under test @INFN-Bari
- 10 cm x 10 cm arrays made of BCF-60 plastic scintillating fibers by the Saint-Gobain, 0.50 mm diameter.
- emission peak at 530 nm.





SPOC - SPect for Online boron dose verification in bnCt
Project Organization – Milestones

Milestones:
M1 (12m): Simulations of irradiation fields as well as signal and background on the detector.
M2 (12m): First prototype of the detector ready, including subcomponents for the detector procured (scintillator, SiPMs, ASICs) and DAQ system.
M3 (12m): First release of the Tomography reconstruction algorithm. ← Bari
M4 (12m): Characterization of neutron beam at UNIPV LENA PGNAA facility using neutron activation measurements and Bayesian unfolding methods.
M5 (18m): Conclusion of shieldings studies and procurement.

Milestones:
M6 (24m): Simulations of the optimized scanner geometry.
M7 (24m): Tomography reconstruction algorithms ready. ← Bari
M8 (30m): Development of further detector modules (up to 4 additional modules) concluded. Construction of SPECT prototype system concluded.
M9 (36m): Results from beam tests of the prototype in accelerator-based neutron sources. Final release of the BNCT-specific reconstruction algorithm.

Preliminary Results
Publications

Pubblicazioni:

1- D, Dayron, G. Pugliese, G. Iaselli, N. Amoroso, C. Gong, V. Pascali, S. Altieri, and N. Protti. 2023. "Study of Alternative Imaging Methods for In Vivo Boron Neutron Capture Therapy» Cancers 15, no. 14: 3582.
DOI: https://doi.org/10.3390/cancers15143582

2- D. Ramos on behalf of G. M. I. Pugliese, G. Iaselli, N. Protti, S. Altieri, C. Gong. 2023. “Monte Carlo study of 3D image reconstruction for boron dose distribution in BNCT with CZT-based Compton camera” IL NUOVO CIMENTO 46 C (2023) 73. DOI: 10.1393/ncc/i2023-23073-2

Overview of previous/ongoing projects
ENTER_BNCT

Bari task: Imaging methods for BNCT ⇆ synergy with University and INFN of Pavia

General goal: Develop an alternative method for a possible imaging protocol based on the measurement of the prompt gamma-ray of 478 keV with a **CZT Compton camera type detector**.

- Monte Carlo methods to simulate a **Compton image** data-set within a BNCT approach.
- Reconstruct the normalized simulated distributions using three methods: the classic **Maximum Likelihood Expectation Maximization (MLEM)** iterative method, a method based on **image processing operations**, and **Convolutional Neural Networks (CNN)** approach.

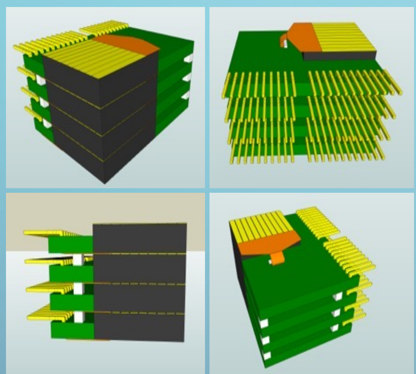
3D CZT detector

CZT single unit: 20x20x5 mm^3, planar transversal field (PTF), orthogonal drift strip electrodes

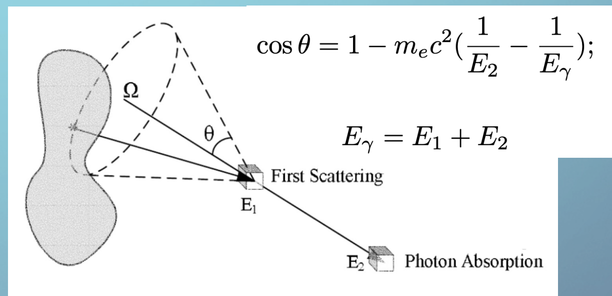
Room-temperature gamma-ray spectroscopic

Sub-millimetre spatial resolution and excellent energy resolution (<1% FWHM at 661.7 keV)

3D positioning



Compton camera principle



Reconstruction evaluation

$$\text{Accuracy} = \frac{TP}{TP+FP}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

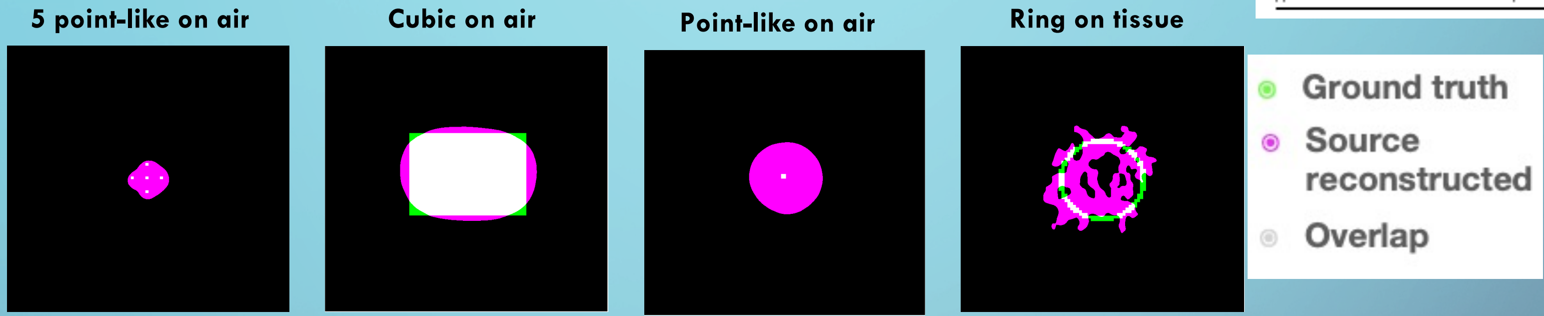
Overview of previous/ongoing projects
ENTER_BNCT

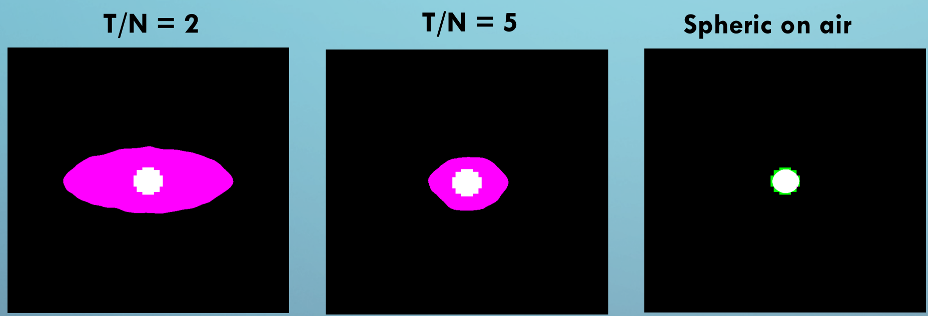
Data augmentation + Trasfer Learning

ResNet50 model

CNN layout

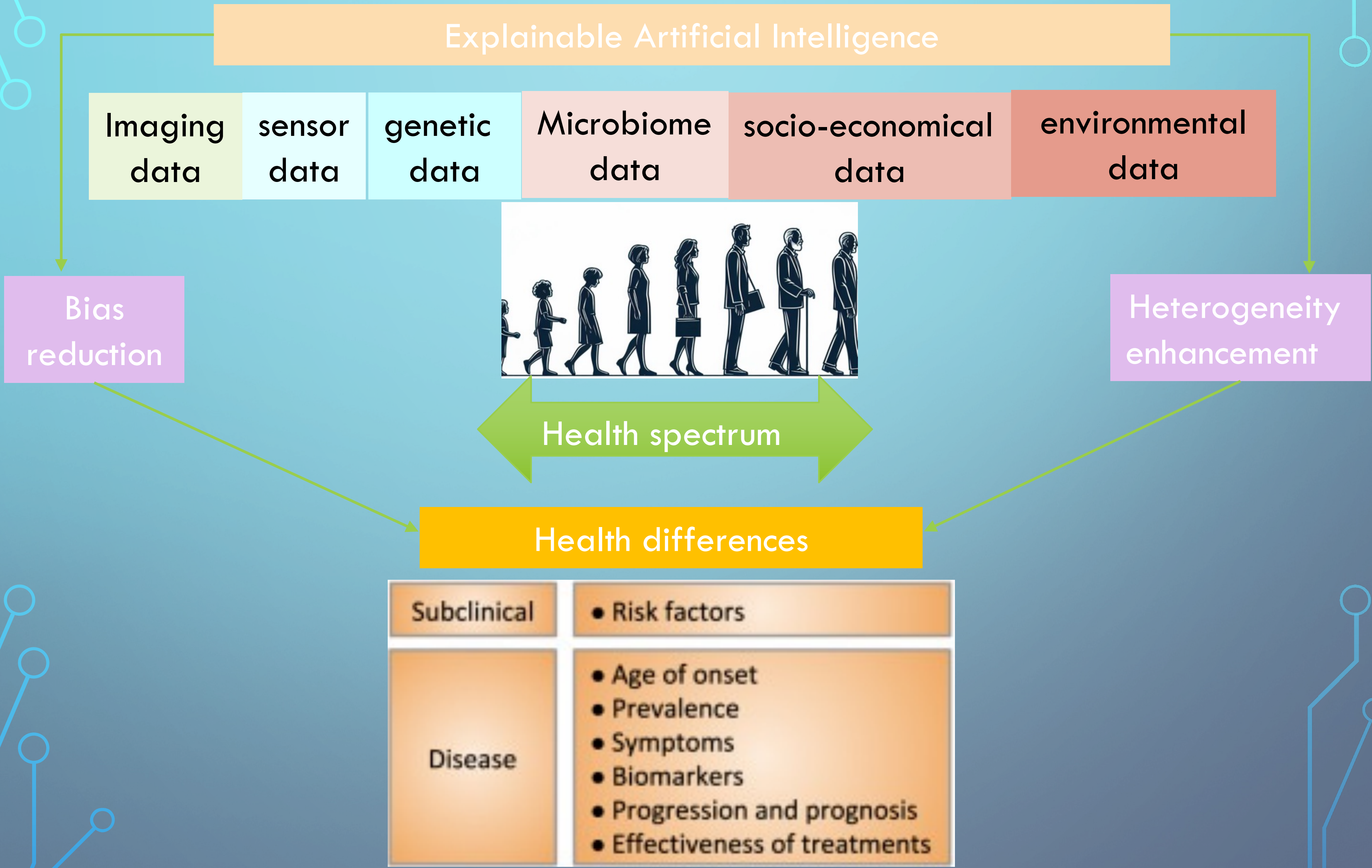
Property	Value
Layers	206 × 1 Layer
Connections	227 × 2 table
InputNames	1 × 1 cell
OutputNames	1 × 1 cell





	Accuracy	Sensitivity
5 point-like on tissue	3.81%	100%
Cubic on air	86.09%	96.27%
point-like on air	0.55%	100%
Ring on tissue	13.46%	59.20%
Spheric $T/N = 2$	4.83%	100%
Spheric $T/N = 5$	3.81%	100%
Spheric on air	99.73%	77.99%

EXPLAINABLE ARTIFICIAL INTELLIGENCE FOR HEALTH APPLICATIONS



A GENERAL APPROACH FOR MEDICAL BIG DATA ANALYTICS