

A C

Elementary particles and Medical Applications

Basic concept:

<u>"Inject"</u> radiactive material or particles inside the patient

If the particle interacts inside the patient

Radiotherapy: RT, Radio Methabolic Therapy, Brachitherapy, Hadrotherapy, Flash Therapy

Nuclear decays of interest

<u>Gamma rays</u>: escape patient, interact outside it extracting electrons

> **beta+ decays**: positrons s annihilate with eand produce 2 photons that escape patient and interact outside

<u>Beta- decays</u>: electrons do not escape patient

Ś

<u>Alpha decays:</u> like electrons but even shorter path



Accelerators: the Cyclotron

Used for protons/ions

- 10-30 MeV for radio-isotopes production
- up to 200 MeV per radiotherapy







Accelerators: the syncrotrons



Vacuum Pipe Accelerate protons/carbon-ions for therapy (up to Ejection 4800 MeV)





Artificial Intelligence

Different Levels of Data Analysis in Particle Physics







Diagnostics

- Two major categories:
 - Morphologic: sensitive only to densities
 - Radiography
 - · TAC
 - ultrasound, ...
 - Functional: sensitive to organ functionalities
 - PET
 - · SPECT

Diagnostics: Tomography

- Generic mathematical tool from 1D → 2D
- CT with X-rays is most renown

Diagnostics: SPECT

Single Photon Emission Computerized Tomography

- Inject radionuclide (typically ⁹⁹Tc but also ¹³¹I)
- Decays with single photon
- Detection ~50cm from source with anger camera

Gamma decays

Diagnostics: PET

Positron Emission Tomography

- Inject radionuclide (¹⁸F in FDG, FET, 11C in methionine, choline)
- β + decay
- Detect the two gammas in coincidence outside patient

Beta+ decays

Radio-guided surgery

- Administer, before operation to patient (either systemically or locally) a drug which:
 - the tumor takes up significantly more than the healthy tissue.
 - is linked to a radio-nuclide that emits particles via nuclear decay
- Wait for the drug to diffuse to the margins of the tumor
- Start operation
 - Remove the bulk of the tumor
 - Verify with a probe that detects the emitted particles the presence of:
 - Residuals
 - Infected lymph nodes

Beta decays

Radioguided surgery

Three approaches

- Gamma: well established, e.g. sentinel lymph-node
- Beta+: based on the dual probe approach
- Beta-: future fronteer

127 px Value: 25.03 nm Y -0.46 mm Z -153.40 mr

robe

A CHANGE IN PARADIGM

- Use of β⁻ tracers (electrons):
 pros
 - Detect electrons that travels
 ~100 times less than γ
 - Tracers with ⁹⁰Y can be used (already used for Molecular RT)
 - No background from gamma

17

- Shorter time to have a response
 - » Smaller administered activity
- Smaller and more versatile detector
- Very reduced effect of nearby healthy tissues

Reduced dose to medical staff

EXTEND RGS TO MORE CLINICAL CASES E. Solfaroli Camillocci et al, Sci. Repts. 4,4401 (2014)

radiomethabolic/ Brachitherapy

- Inject/ position radionuclide (e.g. 1311)
- Beta- decays
- Electrons release energy in tumor locally

Available theses

diagnostics

A C

Radio Guided Surgery

Probe Prototype

Compact, easy to handle, local measurement

Simple technology:

- scintillating crystal
- Light sensor (SiPM)

Most stringent constraints:

- Mechanics
- electrical safety
- sterilization

Ongoing R&D:

- Detector improvements to lower energy threshold
- Laparoscopic application (adjustment in size, multiple reading for information from the side)

Fig: Probe in ex-vivo tests on meningioma

RESEARCH PATH

Radioguided Surgery with β - decays

- Development and tests of a detector for low energy electrons
 - Multichannel device with imaging capabilities
 - Low energy sensitivity
- Data analysis and MC simulation of clinical cases
- Application to different radionuclides

Thesis topics contacts

F. Collamati (francesco.collamati@roma1.infn.it)

R. Faccini(riccardo.faccini@roma1.infn.it)

Both SW (simulation, image reconstruction) and HW activities (detector assembly and experiment robotics)

Dosimetry in Target Radio Therapy

- TRT: Injection of radio-tracer that links preferentially with tumor → beta- radiation for therapy
- Need to certify acquired dose on patientby-patient basis

Development of sensors (evolution of the probe)

MC simulation/data analysis → proof of principle

Thesis topics contacts

- F. Collamati (francesco.collamati@roma1.infn.it)
- R. Faccini(riccardo.faccini@roma1.infn.it)

We have an R&D work on innovative plastic scintillators in collaboration with the LEOS group (Chemistry) of SBAI.

Organic Scintillators with hi-Z

After a long R&D work with many samples we select 4 new fluorophores that show promising performances in terms of light spectrum, transparency and time response.

We performed test with cosmics^{*}, protons and carbon ions beams. The most recent results have been obtained with cosmic rays at SBAI.

Readout system:

- PMT H10721-20
 - rise time (from datasheet) 0.57 ps
 - guantum efficiency impacts on the final light output (QE peak at 400nm)

Samples	Primary Dopant	Wavelength emission	Light Output* % EJ232	Rise-Time [ns]	Width [ns]	Time Resolution [ps]	
	%	[nm]	systematic and statistics error 10%				
EJ-232	-	370	100	2	9	123	
EJ-204	-	408	200	2.5	11	211	
2N	14%	405	110	2	12	81	
2Т	14%	-	240	3	18	97	
1N	14%	415	155	3	17	102	
2B	14%	420	160	2.5	14	110	

=> Thesis on the scintillator characterisation and development

TOPS: Fast timing plastic scintillators

=> Thesis on the scintillator characterisation and prototypes realisation (measurement with FOOT experiment)

Thesis topics contacts M. Marafini (Michela.Marafini@roma1.infn.it)

Nuclear Medicine: Portable β/γ Imaging System

10

60

20

Ready for measurement

Compact, flexible gamma camera-like device based on independent channel electronics and dedicated imaging of β (or γ) radionuclides in small animal preclinical studies. Challenging image reconstruction of Bremsstrahlung radiation

Activities: development of the image processing algorithms for beta emitters; characterization and measurement campaigns; validation of the simulation twin model toward quantitative imaging; investigation of new imaging modalities.

E. Cisbani (evaristo.cisbani@roma1.infn.it)

Nuclear Medicine: Limited Angle Tomography

Scintimammographic device for early detection of breast cancer based on dual-asymmetric gamma sensors. Study of new acquisition modality for improved tumor detection and 3-dimensional localization

Activities: evaluation of Silicon Photomultiplier sensor

performances; development of a dedicated 3-dimensional image reconstruction;

montecarlo simulations and data analysis

Thesis topics contacts E. Cisbani (<u>evaristo.cisbani@roma1.infn.it</u>)

Application of Au-NPs in medicine

Plasmonic-NPs, thanks to a physical phenomenon called Localized Plasmonic Resonance (LPR), hehave as nano-sized sources of heat.

Plasmonic Photo-Thermal Therapy (PPTT) is a drug-free cancer therapy utilized for producing a photothermal damage of tumors cells without damaging the surrounding healthy tissue.

A suitable laser radiation induces a localized heating εm (a)

The 1/r dependence of $\Delta T(r)$ outside the sphere leads to an infinite amount of thermal energy stored in the surrounding medium.

Au-NPs! why?

Completely biocompatible

Easy surface functionalization

In-vivo detection of photo-heated and radio labelled gold nanoparticles via MR (magnetic resonance) thermometry and PET (positron emission tomography) technique

MR thermometry image (left) shows the temperature distribution under a resonant laser illumination of a cancer tissue (right)

For more details on available thesis topics

Prof. Roberto Pani (roberto.pani@uniroma1.it)

In collaboration with: Center for Biophotonics/Latina (nanoparticles and optics);

Policlinico Umberto I (PET detector technology); S.M.Goretti/Latina (PET imaging)

PET imaging of radio labeled AuNPs

From conventional to Hadrotherapy

A

Radiotherapy

- Goal:
 - Deliver energy on tumor cells in order to break them in an irreparable way

🗩 Mean:

- passage of particles through matter

Conventional radiotherapy

Large release of energy outside tumor

Hadrontherapy

Comparison ¹²C vs IMRT

Better confinement of energy release

More effectiveness in killing cells

The FLASH effect

Recently (starting from 2015, exploding from 2019) the 'fractionation' paradigm has been questioned.

Before: dose has to be delivered in several fractions, and slowly as the 'healty' tissue has better healing capabilities and can recover in a better way → 60 Gy treatments are currently delivered in 30 fractions of 2 Gy that can last more than 1 month!

- Now: the FLASH revolution overturns that idea. A better sparing can be achieved if high doses and ultra high dose rates (3 orders of magnitude larger wrt conventional irradiation!) are used. Instead of going with 0.1 Gy/s one goes 100 Gy/s!
- Mechanism is yet to be understood... but.. It works!

Accelerators

Required proton/Carbon energy

Proton Kinetic Energy between 100-250 MeV Carbon Kinetic Energy between 200-400 MeV/u

Present of hadrotherapy

USA - 9 centres Japon - 8 centres Allemagne - 5 centres France - 2 centres Italie - 1 centre Suisse - 1 centre Taïwan - 1 centre Chine - 1 centre Corée du Sud - 1 centre

Chine - 1 Corée du

HT: accelerators

- Cyclotrons: past, mostly for low energy applications (e.g. ocular tumors)→ today up to 250 MeV/u
- Syncrotrons: present → cover also carbon-therapy
- Future applications: CYCLINACS, proton LINACS, ...

HT: Monitoring the dose

 Why is so crucial to monitor the dose in hadrontherapy ? Is like firing with machine gun or using a precision rifle..

Effect of density changes in the target volume

Measuring the dose

Based on nuclear reactions between the projectile and the patient

Available theses

Radiotherapy

AFE

Fragmentation in particle therapy

- Projectile fragmentation: production of fragments with higher range and different direction vrt the primary ions
- **<u>Target fragmentation</u>**: production of short range, low energy, high RBE fragments

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

Target fragmentation in proton therapy: gives contribution also outside the tumor region!

Relative Dose

Thesis topics contacts

V. Patera (vincenzo.patera@roma1.infn.it)

A. Sarti (alessio.sarti@roma1.infn.it)

MONDO

In Particle Therapy (PT) the beam interacts with the patient producing secondary particles. Secondary neutrons can release **additional dose** also far away from the volume under treatment. The incidence (also years after the treatment) of SMNs (**Secondary Malignant Neoplasm**) impacts directly on the quality and life expectation of the patient.

The FLASH implementation demands ultra high dose rates and a minimum dose per fraction: PT treatments can hardly satisfy such requirements: therapy with electrons, instead looks very promising!

A new R&D era for accelerators (high intensities are needed!), beam monitors and dosimeters (UHDR cannot be addressed with standard Ionization Chambers), and treatment planning tools is just started..

FRIDA [Flash Radiotherapy with hIgh Dose-rate particle beAms, <u>https://web.infn.it/FRIDA</u>] is an INFN project that will address all the different challenges in the field..

In roma three main items: accelerator development [not covered here], beam monitoring, treatment planning!

Monitors for UHDR

At ultra high dose rates, beams can induce fluorescence in air that could be exploited to measure the beam intensity.

A prototype detector has been built (just to demonstrate the possibility to exploit the effect) and has been tested against an e- beam at FLASH intensities..

arobid

FRIDA aim is to explore what Very High Energy Electrons can do (VHEE), for the treatment of deep seated tumors...

Prostate, Head &neck have been alread studied. Promising preliminary results have been already obtained... Other districts can be explored (Pancreatic cancer... Lungs..)

Es: trattamento di un meningioma con protoni, RT convenzionale e VHEE. Nervi Ottic Chiatma Il trattamento prevede ~60 Gy di dose, ed è effettuato in presenza di organi Jan Ott Post Occhi a rischio in estrema prossimità (nervi ottici, chiasma, tronco encefalico..) Bionco

Organo		Protoni	Fotoni	VHEE
PTV	$V_{35\%} = V_{100\%} = V_{105\%} =$	100% 90.62% 0.01%	100% 81.60% 0.01%	99.44% 67.41% 1.16%
Nervi Ottici	Dmax	53.52 GyRBE	54.36 GyRBE	55.61 GyRBE
Chiasma	Dmax	53.60 GyRBE	54.19 GyRBE	54.59 GyRBE
Vie Ottiche Posteriori	Dmax	53.81 GyRBE	54.30 GyRBE	55.13 GyRBE
Occhi	Dmax	2.82 GyRBE	12.62 GyRBE	4.76 GyRBE
Tronco Encefalico	Dmax	54.26 GyRBE	53.61 GyRBE	54.73 GyRBE
Arterie Carotidi	Vintit	0.03%	9.17%	0.19%

Protoni

VHEE

Protontherapy: Dose Monitors for p-LinAc

TOP-IMPLART facility: proton Linear Accelerator for cancer therapy under development @ENEA-Frascati

Main activities:

2D segmented ionization chamber prototype in Micro-Pattern Gaseous technology for the simultaneous x/y beam profile monitor

- R&D on alternative sensors (e.g. Micro Megas) for very high beam intensity monitor
- Readout electronics upgrade and related software
- Test and calibration campaigns
- Radiobiology irradiation studies

Thesis topics contacts E. Cisbani (<u>evaristo.cisbani@roma1.infn.it</u>)

meses w istituto super

Protontherapy: Low Energy Proton Vertical Line

- Peculiar facility for radiobiological and other irradiation experiments
- part of TOP-IMPLART LINAC
- Essential to define optimal delivery protocols of the unique p-LINAC beam

Main activities:

- Characterization of fluence monitors and dosimeters based on Silicon, naked Diamond and LiF detectors
- Inter-calibration campaigns
- Data analysis and optimization of working conditions

Thesis topics contacts E. Cisbani (<u>evaristo.cisbani@roma1.infn.it</u>)

Available theses

Accelerators

ALE

Thesis with Sapienza SBAI group

Thesis topics contact L. Palumbo (luigi.palumbo@uniroma1.it)

Title: Compact cryogenic electron source for advanced radiation sources

A new generation of particle sources is foreseen in order to provide beams of unprecedented six-dimensional brightness which can be employed to drive novel radiation sources, such as FELs and Compton sources. Radio-frequency photo-injectors operated at cryogenic temperatures are capable to achieve very high accelerating fields which enhance the peak brightness of the electron beam reducing its emittance. The design of such advanced devices is a challenging task which demands strong efforts, either technologically and for a successful control of the dynamics of the ultra-bright beam itself. (esperimento: INFN-ARYA)

Title: Plasma accelerators for novel radiation sources

Plasma based accelerator can profit off an extremely high accelerating field, order of magnitude higher than conventional accelerators. Experimental studies have been performed to produce ultra-short driver and witness beams with excellent transverse properties, starting from the optimization of beam generation device (laser on photocathodes) and then finely tuning the following linear accelerator to produce a high brightness beam at entrance of the plasma cell. Among others, the main activities concern simulation studies for the optimization of plasma density profile, experimental studies for the beam transport optimization, design and construction of an ultra-compact beam position monitor, executive design of Cherenkov effect based beam diagnostics as well as studies on graphene-copper photocathodes. (esperimento: INFN-SL_Comb2Fel)

Title: Medical electron accelerators for Flash Therapy

The Radiation Therapy (RT) is nowadays one of the most common methodology to treat cancer cells. The most important requirement is to destroy the cancer cells and to minimize the damage of the healthy cells as well as any side effect. In this scenario, an innovative technique has been proposed and already tested: the FLASH Therapy, which uses short pulses of electrons at very high dose rates. It foresees millisecond pulses of radiation (beam on time < 100-500ms) delivered at a high dose-rate (>40-100 Gy/s), over 2000 times faster and more than 1000 more intense than conventional RT. These bursts of radiation are less harmful to healthy tissues but just as efficient as conventional dose rate radiation to inhibit cancer growth. We will work on the implementation of this methodology based on an electrons linear accelerator. (esperimento INFN-ARYA)

Title: Compact linear electron accelerators for sterilization

The use of ionizing radiation is a well-established approach for the sterilization of industrial and medical devices. In order to be achieved, bursts of high doses are required (few kGy). High intensity pulses of electron and X-ray beams, which destroy the DNA of bacteria and other pathogens, are able to deliver the required dose in a short amount of time (few seconds) for the sterilization process. Nowadays, RF accelerators and in particular linacs (linear accelerators) are important devices used for such purpose. Nevertheless, most linacs work in S-band are bulky and expensive machines that often are not suitable for small facilities. In this scenario, there is a need for the development of a novel design of an ultra-compact linac that can be proposed as a viable solution for the production of high pulsed beam currents (up to few mA) and medium-low energies (below 9 MeV). The choice of the operation RF frequency range, such as C-band, will need to be explored with RF and beam dynamics optimization procedure. Moreover, up-to-date fabrication techniques will be investigated in order to obtain the design of an ultra-compact and low-cost linac that can be installed also in small facilities.

Artificial Intelligence in Medicine

A

AI Applied to Medical Imaging

OR

Aim: help the clinician to take clinical decision based on images (CT, MRI, PET..)

Various **tasks**:

- segmentation of lesion (e.g. tumor)
- tumor staging and re-staging
- prognosis
- evaluation of response to therapy

The image can be directly input to a **Neural Network** that learns a specific task

Radiomic pipeline

=> compute mathematical quantities (features) from the images and then use a AI algorithms to learn the task ...

Image Acquisition & Tumor Segmentation

PyRadiomics Toolbox

Data Analysis & Correlation Studies

Available theses

Artificial Intelligence in Medicine

ALE

ATTRACT- AI based Radiogenomics in Colon Tumors

Funded AIRC project in collaboration with Policlinico Umberto I (2021-2025)

Goal: develop a radiogenomic signature that characterize colon tumor =

Radiomic & Machine learning techniques applied to colon CT and genomic data

Steps:

- tumor segmentation with artificial network from CT
- radiomic feature extraction and reduction
- radiogenomic model

300 retrospectiveannotated cases200 prospective annotatedcases for external validation

Thesis topics contact S.Giagu (stefano.giagu.uniroma1.it) C.Voena (<u>cecilia.voena@uniroma1.it</u>)

MUCCA- AI Explainability of Medical Imaging

Funded by CHIST-ERA (EU) call "Explainable Artificial Intelligence"

Goal: develop explainable AI algorithms in different fields (Physics Applied to Medicine, High Energy Physics, Physics Applied to Neuroscience)

Explainable AI models for the brain lesion segmentation in publicly available MRI dataset (Unet2D, Resnet 3D)

Thesis topics contact S.Giagu (stefano.giagu.uniroma1.it) C.Voena (<u>cecilia.voena@uniroma1.it</u>)

CORONA – Prognostic Algorithm for COVID-19

The goal of the project is to make real-time predictions of the patient respiratory **condition** and functional response at few days using an **AI algorithm** on the basis of:

initial CT

Arterial Blood Gas (ABG) analysis

Time series prediction

biomechanical simulations

Can be a support to ventilatory management

Collaborative research agreement between INFN, Sapienza, and Medlea srls

Thesis topics contact S.Giagu (stefano.giagu.uniroma1.it) C.Voena (cecilia.voena@uniroma1.it)

^{12}C at 259.5 MeV/u

GEANT4

Emulate a low energy nuclear interaction model with Deep Learning

http://www.roma1.infn.it/exp/gen

- Nuclear reaction models are of utmost importance for MC simulation in hadrontherapy
- Geant4 is one of the most used tools to develop MC simulation also in this domani (also through a dedicated program, TOPAS)
- It's models fail to simulate nuclear reactions below 100 MeV/u
- We interfaced a model developed by theoreticians but it's far too slow
- It's possible to use Deep Learning generative algorithms (such as VAE and GAN) to emulate the model
- We published a paper with preliminary results but it has to be optimised and finalised
- Several tasks could become a thesis

Thesis topics contact C. Mancini Terracciano (carlo.mancini.terracciano@roma1.infn.it)

- A. Ciardiello et al. Phys. Med. 73 (2020). doi: 10.1016/j.ejmp.2020.04.005. arXiv: 2004.0496
- C. Mancini-Terracciano et al. Phys. Med. 67 (2019), doi: 10.1016/j.ejmp.2019.10.026.

The Neptune project

Goal: enhancement of proton therapy effectiveness using nuclear reactions

Technique: administration of borated and fluorinated compounds, that accumulate in tumor, to patients before irradiation

 $p + {}^{11}B \longrightarrow 3$ alpha (up to 4 MeV)

 $p + {}^{19}F \longrightarrow {}^{16}O + alpha (up to 13 MeV)$

development of ¹⁹F-MRI imaging

Improving ¹⁹F-MRI

¹⁹F-MRI currently limited from low SNR ratio

Different strategies:

- improve raw signal processing
- => Software Defined Radio technology

¹H-MRI + ¹⁹F-MRI

P. Porcari, S. Capuani, E. D'Amore *et al.* 2008 *Phys. Med.* Biol.

- Deep learning based image analysis

f

fully convolutional Architecture

Thesis topics contact C.Voena (<u>cecilia.voena@roma1.infn.it</u>)

