HORIZON 2020

RESEARCH INFRASTRUCTURES

H2020-INFRAIA-2014-2015

INFRAIA-1-2014-2015 INTEGRATING AND OPENING EXISTING NATIONAL AND REGIONAL RESEARCH INFRASTRUCTURES OF EUROPEAN INTEREST

ENSAR2

EUROPEAN NUCLEAR SCIENCE AND APPLICATION RESEARCH 2

GRANT AGREEMENT NUMBER: 654002

DELIVERABLE D5.1 - SPECIFIC NEEDS AND PROPOSED SOLUTIONS OF NUCLEAR TOOLS FOR MEDICINE

Version: 4.0
Author: G. Magrin, P.G. Thirolf
Date: 30.10.2016

PROJECT AND DELIVERABLE INFORMATION SHEET

ENSAR2 Project Ref. №	654002
Project Title	European Nuclear Science and Application Research 2
Project Web Site	http://www.ensarfp7.eu/
Deliverable ID	D5.1
Deliverable Nature	Report
Deliverable Level*	PU
Contractual Date of Delivery	30.11.2016
Actual Date of Delivery	30.11.2016
EC Project Officer	B. Fabianek

* The dissemination level are indicated as follows: PU – Public, PP – Restricted to other participants (including the Commission Services), RE – Restricted to a group specified by the consortium (including the Commission Services). CO – Confidential, only for members of the consortium (including the Commission Services).

DOCUMENT CONTROL SHEET

Document	Title: Specific needs and proposed solutions of nuclear tools for medicine	
	ID: D5.1	
	Version 1.0	
	Available at: http://www.ensarfp7.eu/	
	Software Tool: Microsoft Office Word 2007	
	File: ENSAR2_Deliverable_5.1	
Authorship	Written by:	G. Magrin, P.G. Thirolf
	Contributors:	NA5 MediNet WP Conveners/Participants
	Reviewed by:	S. Brandenburg
	Approved by:	

DOCUMENT STATUS SHEET

Version	Date	Status	Comments
V1.1	11.10.2016	For internal review	Introduction
V1.2	12.10.2016	For internal review	Introd. to Sect. 1
V1.3	18.10.2016	For internal review	T1, WP1-5 included References, Glossary
V2.0	23.10.2016	For internal review	T2 included
V2.1	25.10.2016	For internal review	Revision Sect. 1.1
V2.2	29.10.2016	For internal review	Executive Summary, part 1, ext. Sect. 1.1
V2.3	31.10.2016	For internal review	Final revisions T2
V3.0	29.11.2016	after internal review	General revision
V4.0	30.11.2016	Final Version subm. to EC Participant Portal	Submitted

Document Keywords

Keywords	Particle therapy, medical imaging, radiation detectors, radiation quality, clinical effects

Disclaimer

This deliverable has been prepared by Work Package 5 (MediNet – Network: Nuclear Physics for Medicine) of the Project in accordance with the Consortium Agreement and the Grant Agreement n°654002. It solely reflects the opinion of the parties to such agreements on a collective basis in the context of the Project and to the extent foreseen in such agreements.

Copyright notices

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF ACRONYMS AND ABBREVIATIONS

ADC	Analog-to-digital converter
ALICE	A large hadron collider experiment: acronym of an experiment located at CERN
APD	Avalanche photo diode
APSS	Protonterapia, Agenzia Provinciale per I Servizi Sanitari (Trento/Italy)
ATCA	Advanced Telecom Computing Architecture
ATLAS	A Toroidal LHC ApparatuS : acronym for large collider detector at the LHC ring
BGO	Bismuth germanate (Bi4Ge3O12): scintillation detector crystal material
CERN	Centre Europeen de Recherche Nucleaire

CFD	Constant fraction discriminator: analog electronics module
CMOS	Complementary metal oxide semiconductor
CMS	Compact muon solenoid : acronym for large collider detector at the LHC ring
CNAO	Centro Nazionale di Adroterapia Oncologica (Pavia/Italy)
CPPM	Centre de Physique des Particules de Marseille
CRT	Coincidence resolving time
CsI	Cesium iodide: scintillation detector crystal material
CT	Computed Tomography is a medical imaging technique using a large series of two-dimensional X-ray images.
D	Absorbed dose is a measure of the energy deposited per unit mass of medium by ionising radiation, and so has the unit Gy.
DAQ	Data acquisition
DCR	Dark count rate
DoPET	Name of a planar PET prototype detector system at the CNAO therapy center (Pavia/Italy)
DRS4	Domino ring sampler (version 4)
dSiPM	Digital silicon photomultiplier
ELBE	Electron Linac for beams with high Brilliance and low Emittance, Dresden, Germany
ENLIGHT	The European Network for LIGht ion Hadron Therapy
eV	Practical unit for energy used in atomic and nuclear physics (e.g. for particle beam energy): 1 eV = 1.6x 10^{-19} J
FDG	Fluorodeoxyglucose is a radiopharmaceutical used in PET imaging.
fMRI	functional Magnetic Resonance Imaging is a type of specialised MRI scan measuring the hemodynamic response (change in blood flow) related to neural activity.
FPGA	Field programmable gate array
GAGG(Ce)	$Gd_3Al_2Ga_3\ O_{12}$ (Cerium doped): scintillation detector crystal material
GHz	1 billion Hertz (oscillations per second)
GSI	Gesellschaft für SchwerIonenforschung – Centre for Heavy Ion Research located at Darmstadt, Germany
GSO	Gadolinium oxyortho silicate: scintillation detector crystal material
Gy	Gray is the name of the special unit of absorbed dose of ionising radiation, i. e. the absorption of one joule of ionising radiation by one kilogram of matter. 1Gy = 1 J/kg = 1 m^2/s^2
HIMAC	Heavy Ion Medical ACcelerator located at the National Institute of Radiological Sciences in Chiba, Japan.
HIT	Heidelberger Ionenstrahl-Therapiezentrum – Heidelberg Ion-Beam Therapy Centre located at the Heidelberg University Hospital, Germany.
HZDR	Helmholtz-Zentrum Dresden Rossendorf
IBA	Ion Beam Applications SA (manufacturer of medical accelerators and accessories)
ICRP	International Commission on Radiological Protection is an advisory body providing recommendations and guidance on radiation protection.
ICRU	International Commission on Radiation Units and Measurements is a standardisation body set up in 1925 by the International Congress of Radiology.
IFIC	Instituto de Fisica Corpuscular (Valencia/Spain)
IFJ-PAN	Instytut Fizyki Jądrowej, Polish Academy of Sciences (Krakow/Poland)

IMRT	Intensity-Modulated Radiation Therapy is an advanced type of high-precision radiation therapy technique.
INFN	Istituto Nazionale di Fisica Nucleare, Italy
INSIDE	INnovative Solutions for In-beam DosimEtry in Hadrontherapy, a project born from the collaboration of a number of Italian Universities and INFN
IPNL	Institut de Physique Nucleaire de Lyon (Lyon/France)
JLU	Justus-Liebig-Universität (Giessen/Germany)
J-PET	Collaboration at the Institute of Physics of the Jagiellonian University (Warsaw) dedicated to R&D on novel TOF-PET scanner technologies
KVI-CART	Kernfysisch Versneller Instituut- Center for Advanced Radiation Technology (Groningen/Netherlands)
LaBr3(Ce)	Lantanum bromide (doped with Cerium): scintillation detector crystal material
LAPPD	Large Area Picosecond Photodetector (collaboration targeting large-area, fast photon detectors)
LEM	Local Effect Model used for the treatment planning system for ion therapy TRiP at GSI and HIT, Germany.
LET	Linear Energy Transfer is a measure of the energy transferred to material as an ionising particle travels through it.
LHC	Large Hadron Collider : high-energy ring accelerator at CERN
LIP	Laboratory of Instrumentation and Experimental Particle Physics (Coimbra/Portugal)
LMU	Ludwig-Maximilians-Universität (München/Germany)
LNL	INFN Laboratori Nazionali di Legnaro, Legnaro National Laboratories (Legnaro/Italy)
LNS	INFN Laboratori Nazionali del Sud, South National Laboratories (Catania/Italy)
LPC	Laboratoire de Physique Corpusculaire (Clermont-Ferrand/France)
LPSC	Laboratoire de Physique Subatomique et de Cosmologie (Grenoble/France)
LSO	Lutetium Orthosilicate: scintillation detector crystal material
LYSO	Lutetium Yttrium Orthosilicate: scintillation detector crystal material
MC	Monte Carlo (computational simulation method)
MCP	Microchannel plate
MedAustron	EBG MedAustron, Ion-Beam Therapy Center (Wiener Neustadt/Austria)
MEMS	Micro-electromechanical systems
MRI	Magnetic Resonance Imaging is a medical imaging technique using a powerful magnetic field and radiowaves of around 40 MHz.
MRI-FLAIR	Magnetic Resonance Imaging FLuid Attenuated Inversion Recovery is a pulse sequence (inversion recovery technique that nulls fluids) used in MRI.
MTCA	Micro Telecom Computing Architecture
NaI	Sodium iodide: scintillation detector crystal material
NINO	Name of an application-specific integrated circuit (ASIC) chip developed at CERN (Geneva) for electron and photon detection in medical imaging
NIRS	National Institute of Radiological Sciences located at Chiba, Japan
NuPECC	Nuclear Physics European Cooperation Committee
OAR	Organ At Risk or critical normal structures are tissues, which if irradiated could suffer significant morbidity, and thus might influence the treatment planning and/or the dose prescription.
OER	Oxygen Enhancement Ratio in radiobiology refers to the enhancement of therapeutic

	or detrimental effect of ionising radiation due to the presence of oxygen.
OncoRay	Center for Radiation Research in Oncology (Dresden/Germany)
PET	Positron Emission Tomography is a medical imaging technique using pairs of gamma rays emitted indirectly by a positron-emitting radionuclide.
PET-CT	Positron Emission Tomography and Computed Tomography is a medical imaging device which combines in a single gantry system both a PET and a CT.
PIN	Semiconductor diode with the structure: p-type intrinsic n-type
PMMA	Polymethyl methacrylate
PMT	Photomultiplier tube
PTCOG	Particle Therapy Co-Operative Group, https://www.ptcog.ch/
RBE	Relative Biological Effectiveness is defined as the ratio of a dose of a reference radiation quality to the dose of the test radiation quality required to cause the same biological level of effect, all other conditions being the same.
RF	Radiofrequency (accelerator property, ca. 100 MHz for typical medical cyclotron accelerators)
SiPM	Silicon photomultiplier
SOPB	Spread-Out Bragg peak is an overlap of several pristine Bragg peaks at staggered depths.
SPAD	Single photon avalanche photo diode
SPECT	Single-Photon Emission Computed Tomography
TDC	Time-to-digital converter
TOF	Time of flight
TOF-PET	Time-of-Flight Positron Emission Tomography
TPS	Treatment Planning System used in radiation therapy for planning the doses in the tumour and the surrounding healthy tissue (critical organs).
TU Delft	Technical University of Delft (The Netherlands)
TV	Treated Volume is the volume of tissue that receives at least the dose specified by the radiation oncologist in charge of the patient and considered as appropriate to achieve the goal of the treatment within the bounds of acceptable complications.
UCM	Universidad Complutense de Madrid (Madrid/Spain)
UICC	International Union Against Cancer is a non-governmental organisation dedicated exclusively to the global control of cancer.
UNIBAS	Basel University, (Basel/Switzerland)
U Milan	University of Milan (Italy)
U Pisa	University of Pisa (Italy)
U Rome	University of Rome “La Sapienza” (Rome/Italy)
UW	University of Warsaw (Warsaw/Poland)
VINS-UB	Vinca Institute of Nuclear Sciences, University of Belgrade (Belgrade/Serbia)
keV,MeV, TeV, ps	Prefix letters together with a unit denote an abbreviated order of magnitude: keV(kilo-eV): 10^3 eV, MeV (Mega eV): 10^6 eV, TeV (Tera eV): 10^{12} eV, ps (pico second): 10^{-12} s

EXECUTIVE SUMMARY

The MediNet Networking Activity of the ENSAR2 initiative brings together leading European experts in the field of medical physics research, working on cancer therapy with particle (or photon) beams or developing detector technologies to improve the quality of this treatment modality and its auxiliary diagnostics. This document presents an overview of requirements and currently pursued strategies concerning technologies developed in the context of nuclear physics for application in medicine. While most nuclear physics phenomena or technologies are not part of our daily experience, there is a variety of related techniques and applications, such as those in medicine, which have considerable impact on society. Application of ionizing radiation in medicine have benefitted from progress in the nuclear physics that in turn is strongly connected to development of accelerator and detector technology and information technology. Following an introduction, the document is organized in two main sections, reflecting the two pillars of the MediNet networking initiative: The first section presents needs, challenges and possible solutions in the intensively studied field of radiation detector development for imaging applications in assistance of radiation therapy. Particle therapy, via the specific stopping behaviour of charged particles in matter (here: tissue), where the dominant fraction of the delivered dose is confined in the so-called Bragg peak at the very end of the particle trajectory, provides the possibility of a well-localized dose deposition. However, this favorable property cannot be fully exploited in clinical practice at present, since the actual position of the Bragg peak in the patient's tissue is not known precisely enough and safety margins have to be applied, which in part compromise the benefit of this treatment modality. Therefore it is a central goal of presently pursued detector developments to provide an in-vivo beam range monitoring system that will allow for improving the precision of particle therapy dose delivery.

Signatures that can be exploited comprise secondary radiation from the interaction of the therapeutical beam with the tissue, either photons (sect. 1.1) or charged particles (sect. 1.2). The need for improved therapeutical precision also calls for improved detection technologies, comprising novel scintillation detectors and their applications (sect. 1.3), new photosensors (sect. 1.4) and optimized signal processing and data acquisition electronics (sect. 1.5). All of these fields of research are addressed in the MediNet networking activity of ENSAR2. These developments naturally will also foster medical imaging in neighboring medical fields like nuclear medicine.

The second section of this document focus on another challenge of particle therapy which concerns the assessment of the clinical effects based on the physical characteristics of the radiation: different radiations types, such as photons, protons, or ions, produce different impacts on the biological tissue for a fixed amount of energy. Also the effectiveness depends on the energy of the specific radiation type. The fundamental concept of radiation quality is defined, as well as its specifications via linear energy transfer, LET, and lineal energy. The first application of the radiation quality is to correct the readings of the detectors used in ion-beam therapy (2.1). The relative biological effectiveness, RBE, is described to correlate the assessment of radiation quality to the effects produced by the radiation to a specific biological target (2.2). The use of mean values of LET and lineal energy is inadequate to therapy application (2.2.1). Spectra of LET and lineal energy can qualitatively describe the radiation quality but are not directly usable for the quantitative assessments needed by the treatment planning systems, TPS, and further experimental and computational investigations are necessary (2.2.2). The results could be instrumental to the progress of the painting techniques of treatment (2.2.3). In the specific field of proton therapy, the developed radiation quality tools (instruments and computations) can help resolving a discrepancy between the biological data collected in vitro and the clinical data and have an important impact on therapy technique (2.3).

INTRODUCTION

A long and fruitful history brings together Medicine and Nuclear Physics, in a process that started at least 120 years ago. Some of the most famous and prolific physicists of the beginning of the past century have their names linked also to medical applications: among others Röntgen – the X-rays were applied in diagnostic and therapy shortly after his discovery— the Sklodowska-Curie couple – Marie applied her studies on radiation for instance to build the first mobile X-ray unit in a truck used during World War I— Lawrence – Ernest, physicist, invented the cyclotron in the early 1930's and in 1935 John, his medical doctor brother, join him to investigate the potentialities to apply the radioisotopes produced and the new particle beams to diagnostic and therapy. These are probably the most well-known examples of collaboration between to the apparently distant sciences. Nevertheless, the connection between nuclear physics and medicine never stopped in all these years and it is still strong today, developing in two directions, the improvement of the consolidated physics tools to meet specific medical needs and a constant look at new physics advances and discoveries to explore their relevance for medical applications. The two fields of applications are still the same of the early years, treatment and diagnostics, and the physics competences involved are *accelerator technologies*, *radiation detection*, and *computational and simulation* tools.

Accelerators. National and international research communities as well as private companies are focusing today on accelerator technologies. These groups are engaged in producing novel systems that have the flexibility of moving the beam direction around the patient to guide the radiation to the tumor target from the optimum angles. The challenge is to conform the radiation dose to the tumor, while sparing as much as possible the surrounding healthy tissue. In the case of ion beams, a big effort is also put in studying machines based on novel acceleration concepts. It is becoming more and more important to improve access to ion-beam therapy for a large population, which means containing the costs and reducing the overall size of the centers, in order to be able to optimize their distribution in the territory. In this effort, many European institutes and collaborations, also financed by the European Union, play an important role, but, as they do not fit in the framework of the specific activity performed by MediNet, we refer for additional information to specific publications as, for instance, the NuPECC monography published in 2014[1].

According to the statistics of the Particle Therapy Co-Operative Group (PTCOG)[2] , 70 proton and carbon ion therapy centers were operational worldwide as of September 2016 (22 of them in Europe), while another 38 accelerator facilities are under construction (14 in Europe). The map of active proton and carbon ion therapy centers worldwide, as of 2014, is shown in Fig. 1. Typically these facilities are equipped with compact commercial accelerators: cyclotrons (fixed magnetic field and constant energy, quasi-continuous beam) or synchrotrons (ramping magnetic field, pulsed beam). These clinical therapy facilities require large investment costs (from about 30 MEUR for a single-room proton facility up to more than 200 MEUR for a facility using carbon therapy with a synchrotron accelerator. Given these numbers, the development of more compact, lower-cost accelerator systems is highly desirable to lower the cost gap between particle and conventional photon-based radiotherapy.

[1] Nuclear Physics European Collaboration Committee (NuPECC), Nuclear Physics for Medicine, European Science Foundation (ESF), April 2014, ISBN: 978-2-36873-008-9

[2] Particle Therapy Co-Operative Group (PTCOG), webpage http://www.ptcog.ch

Both particle therapy equipment manufacturers and research institutions are targeting this goal, either by optimizing conventional accelerator technologies or by exploring completely new accelerator concepts [1].

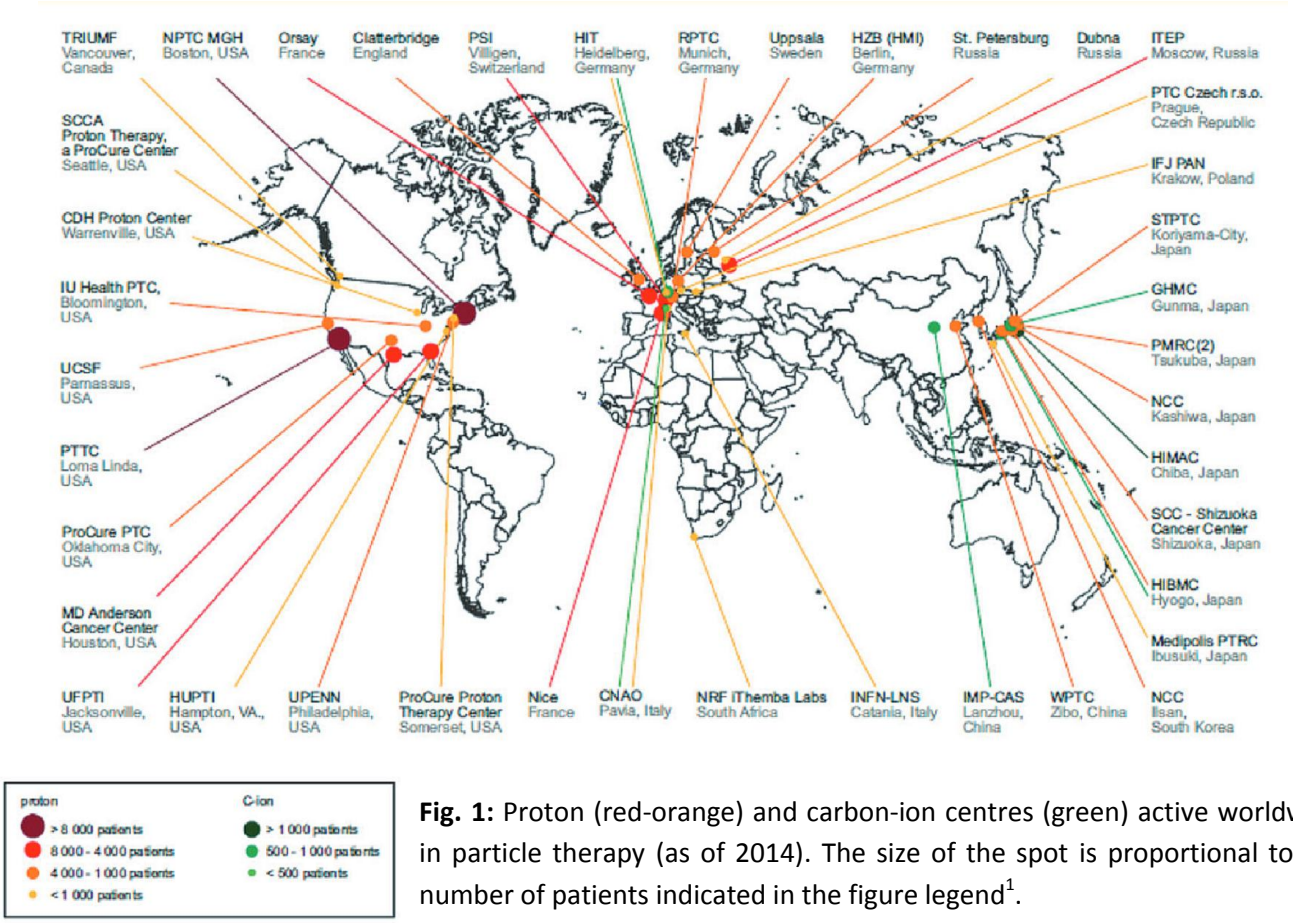

Fig. 1: Proton (red-orange) and carbon-ion centres (green) active worldwide in particle therapy (as of 2014). The size of the spot is proportional to the number of patients indicated in the figure legend[1].

Radiation detection. Basing on the daily interaction with the specialists who perform radiation therapy, the groups of MediNet are focusing on issues concerning the detection and the assessment of the radiation for conventional radiotherapy facilities as well as for ion-beam based therapy facilities. The novel therapeutic techniques bring in new challenges to the detection techniques. A typical example is given by the ion beams that are used in the recently developed facilities, the so-called “pencil beams”, which are scanned in three dimensions across the tumors. Their characteristic is a precise penetration and an increasing biological effectiveness at the end of their path, which are very favorable conditions if the tumor is located close to an organ for which the radiation should be completely avoided or if a deep seated tumor should be treated. Nevertheless, these advantages are preserved only if the radiation depth is constantly verified during the treatment, despite the different densities and atomic compositions of the tissues traversed and despite the involuntary internal movements. A new set of detection tools needs to be produced for that purpose, based on tight exchanges between the medical staff as final users and the physicists as providers.

Simulation tools. The use of the Monte Carlo simulations and other computational instruments developed within the physics community using nuclear physics information is an indispensable tool in any development linked to radiation and even more for optimizing the equipment and for the interpretation of the results. Today any development of medical apparatus involving radiation constantly need Monte Carlo analysis and these

computational tools complement all phases of the development, the project, the prototyping, the analysis of the data, the study of the safety, until they become medical products.

Special emphasis is put in Section 1 of this document on detectors for photon detection, detectors for charged particle detection, novel scintillators and applications, new photosensors, and data acquisition electronics.

Section 2 is dedicated to the “radiation quality”, which is the characteristic of the radiation strongly linked to its biological effectiveness. Improving the description of the radiation quality allows foreseeing the efficacy of the radiation in killing the tumor cells and on sparing the healthy tissue unavoidably irradiated.

SECTION 1: NEEDS AND CONCEPTS FOR MEDICAL IMAGING IN RADIATION THERAPY

The interplay between nuclear physics tools serving medical needs has since many decades been extremely fruitful especially in the field of medical imaging. Detector technologies initially developed in basic nuclear physics research quickly were translated into the realm of medical physics. Combining those with knowledge gained on radioactive isotopes has led to the invention of powerful imaging techniques like single photon emission tomography (SPECT) or positron emission tomography (PET). The combination of PET with X-ray computed tomography (CT) promoted PET as the dominant tool in oncology: "PET/CT is a technical evolution that has led to a medical revolution"[3]. Nowadays SPECT and PET imaging techniques are entering a new era, where technological improvements will play an increasingly important role. As an example for SPECT, dedicated cardiac imagers already make full advantage of solid-state detectors. Time-of-flight PET and the combination with MRI (magnetic resonance imaging) will continue to challenge researchers: "PET/MRI is a medical evolution based on a technical revolution"[4]. The development of silicon-based photosensors, which are insensitive to magnetic fields, has made truly integrated systems possible. These systems allow simultaneous PET and MRI without quality loss in either imaging modality. Because of the need for topical focusing the activities of the MediNet NA concentrate on the field of radiotherapy, in particular with charged ion beams. The spectacular progress of molecular imaging, i.e. the visualization of cellular function and the follow-up of the molecular processes in living organisms without perturbing them can only be mentioned here. The multiple and numerous potentialities of this field are applicable to the diagnosis of diseases such as cancer, neurological and cardiovascular diseases. This technique also contributes to improving the treatment of these disorders by optimizing the pre-clinical and clinical tests of new medication. They are also expected to have a major economic impact due to earlier and more accurate diagnosis. Nowadays, quality control in hadron therapy, i.e. tumor treatment by charged particle beams, exploiting the well-localized dose deposition of particle beams based on their finite range in tissue (Bragg peak) emerges as a central field of application for various radiation detection techniques. In clinical practice, significant uncertainties of the proton (or ion) beam stopping range remain and the exact position of the beam range is not known with the desired accuracy, enforcing safety margins that could be relaxed with better knowledge on the particle beam stopping range. While pre-treatment dosimetric quality controls and cross calculations are already commonly used in current clinical practice, in-vivo verification methods would represent an optimum solution for full exploitation of the advantages offered by the ion beam. Positron emission tomography (PET) is currently the only clinically applied method for in-vivo range verification during or shortly after irradiation, and its potential benefit for ion tumor therapy has been proven. Further treatment verification methods based on the detection of secondary nuclear reaction products are prompt gamma imaging and charged particle imaging, which are currently under investigation. Another promising imaging tool in particle therapy is ion radiography and tomography, which is intended to be primarily used for position verification and treatment planning, but also can serve as a range verification method.

In all of these fields MediNet participant groups are acting at the forefront of research and development and the following paragraphs present the ongoing activities pursued by MediNet participant groups along the organization of the Task 1 of the Networking Activity in 5 topical Working Groups. In the following, each of the Working Groups present medical physics-related needs for nuclear-physics based tools in radiation detection, the related challenges and solution approaches in the research areas of photon and charged particle detectors, novel

[3] Comment of Johannes Czernin from UCLA, at the 2003 annual DGN (German Society of Nuclear Medicine) meeting, quoted in Ref. 4.

[4] T. Beyer, Journal of Nuclear Medicine 48, 331 (2007)

scintillator materials and their application together with novel photosensors optimizing their readout, together with the field of high-performance signal processing and data acquisition electronics, which is crucial for the application of all detector types.

1.1 Detectors for photon detection

(WG1, Convener: Denis Dauvergne (LPSC/IPNL); participants: TU Delft, GSI, JLU, KVI-CART, LIP, LMU, IPNL, LPC, LPSC, OncoRay, UCM, INFN Pisa, INFN Rome)

Imaging of the particle range during hadron therapy relies on the observation of secondary radiation following nuclear reactions. The observation of gamma rays uses two different techniques: PET imaging, following the decay of radioactive nuclei, and prompt-gamma imaging, which is more closely related to the nuclear reactions. Both kinds of detection systems present specific challenges:

- PET imaging consists in detecting the decay of radioactive nuclei such as ^{11}C or ^{15}O, that are formed during inelastic collisions of the impinging therapeutic particle beam with tissue. These nuclei have a spatial distribution that is correlated with the primary ion range; typical decay times are of the order of 10^2 seconds (Enghardt et al., 2004; Kraan et al., 2015, Parodi, n.d.; Sportelli et al., 2014). Therefore, in order to realize the most efficient imaging of the beta+ decays in-beam imaging devices are required, possibly recording data online during beam pauses (Piliero et al., 2015). (Piliero et al., 2015) in order to increase statistics while minimizing metabolic washout, and, in addition, permitting imaging of short lifetime isotopes like ^{12}N. This is favoured with low duty cycle accelerators.For such purpose, detectors need to be fast and need a high efficiency for 511 keV photons. The first property is required for in-beam Time-of-Flight PET, which is seen as a main achievement to be accomplished, in order to reduce the high background level and considerably shorten the reconstruction time (e.g. by realizing a CRT of 100 ps which reduces the LOR to 1.5 cm segments). So far, timing below 100 ps has not been reached in real size prototypes, and this remains a challenge (van Dam et al., 2013). High efficiency PET detection relies on two properties. The first one is purely geometrical: one has to maximize the coincidence detection efficiency, and therefore the solid angle of the camera. Thus, in-beam PET has to fulfill a compromise between the need for a full size PET scanner ring and the requirements for beam and patient rotations. The second property is based on the quality of the detectors: a high photoelectric efficiency is requested for millimetric photon interaction positioning.

- Prompt-gamma imaging consists in detecting the gamma decays of excited nuclei, which are emitted in a very short time after inelastic beam particle collisions (less than 1 ps). Prompt-gamma spectra depend on the nuclear species, and range typically between 100 keV – 10 MeV. Mainly high energy gamma rays – above 1 MeV – have a large probability to escape the patient without scattering, and thus carry the information about the primary ion range. Various strategies for prompt-gamma detection are currently being followed: passively collimated cameras are designed to image the Bragg peak of protons; an IBA-prototype with knife-edge collimation is presently at an advanced stage of clinical tests (Priegnitz et al., 2016; Richter et al., 2016). Multi-collimated cameras are expected to reach similar properties (sensitivity and resolution), but, in addition, they have the potential of covering the full particle range, and of an adjustable spatial resolution, which may be a valuable asset in the case of heterogeneous target composition (Biegun et al., 2012; Lin et al., n.d.; Roellinghoff et al., 2014; Smeets et al., 2016). Besides hardware collimated cameras, electronically collimated Compton cameras (exploiting the Compton scattering kinematics to reconstruct the photon origin) may be seen as the next generation devices for range imaging, with enhanced efficiencies and 3D-imaging capabilities (Hueso-González et al., 2014; Krimmer et al., 2015; Polf et al., 2015; Solevi et al., 2016; Thirolf et al., 2016). Alternatives of direct range imaging are proposed

with prompt-gamma spectroscopy and prompt-gamma timing. The first one relies on the complex inter-dependence of specific gamma lines, beam energy and target composition. The idea is that, with a single detector pointing at a given position of a proton beam path (through a collimator), the yields of the various gamma rays are a unique function of beam energy and target composition, and thus of the residual range (Joost M. Verburg, 2014; Verburg et al., 2015). Prompt-gamma timing measures the shape of the prompt-gamma time profile, and it was shown that, without collimation, but with an excellent timing resolution, the transient time of the protons in matter (thus their range) can be estimated with millimetric precision within a very short time, of the order of a second (Hueso-González et al., 2015).

Both prompt-gamma spectroscopy and prompt-gamma timing make use of time-of-flight (TOF) in order to properly detect photons emitted from the patient, and to reject background. It has been shown that also for range imaging devices (collimated or Compton cameras), TOF can be used to improve the contrast-to-background ratio. For prompt-gamma imaging of particle beams (protons, carbon ions), TOF is needed to extract the prompt-gamma signal from the large background caused by neutrons and secondary heavy particles (Testa et al., 2008).

The question of TOF is closely related to the problematics of the (pulsed) beam time structure, and part of the next challenges will consist in finding adapted solutions for each type of accelerator: synchrotrons, synchro-cyclotrons and cyclotrons, and each type of beam (ion species, intensity). In some cases, external monitoring devices are needed to measure precisely the impact of each ion – or each bunch of ion – on the patient, since the accelerator RF is not necessarily synchronized to this very moment (Dauvergne et al., 2014).

In a novel approach for the well-established PET technology, the J-PET collaboration is developing a PET scanner device based on axially arranged strips of plastic scintillators (Moskal et al., 2015; Moskal et al., 2016), which will enable two- and three-photon imaging (Gajos, A. et al.,2016; Kaminska, D. et al., 2016) . At present a full scale PET scanner with 50 cm axial field-of-view has been constructed and as a next step a prototype will be built, in which the plastic scintillators will be read out by SiPM photomultipliers. Also, forthcoming strategies may combine different modalities in order to optimize the information. The INSIDE project at the Italian CNAO therapy facility includes simultaneous PET and secondary particles detection (and prompt-γ-ray detection in a less efficient way) (Piliero et al., 2015). PET devices, with appropriate triggering systems, could be used also for single-photon computed tomography (SPECT) during beam delivery. The reciprocal is also valid for SPECT devices (Thirolf et al., 2014). However, systematic studies of the assets of such combinations are still missing, and important simulation work is needed beforehand. In this context, it is obvious that exchange and interplay between the various European institutions contributing to the MediNet initiative will push forward the state of the art in this domain.

1.2 Detectors for charged particle detection

(WG2, Convener: Vincenzo Patera (U Rome); participants: IFIC, TU Delft, JLU, KVI-CART, LIP, IPNL, LPC, OncoRay, INFN/U Rome)

The second main group of secondary reaction products generated from therapeutic particle beams in tissue are charged particles. In case of tumor treatment with carbon ion beams, the beam range monitoring technique based on the emitted photons is even more challenging than in proton therapy, because the γ-ray flux is reduced due to the lower number of primary beam particles needed to release the same dose to the tumor, and due to the severe background of neutrons. However, among the several kinds of radiation produced by the interaction of a particle therapy beam within the patient, there is also a sizeable component of charged particles.

The therapeutic beam can experience several inelastic nuclear collisions in the patient and that may result in partial fragmentation or complete disintegration of both projectile and target nuclei. In the case of carbon beams, the fragmentation of projectile (beam) nuclei produces more and higher-energy secondary fragments with respect to proton beams, with kinetic energies that may exceed a hundred MeV, mostly emitted in the forward direction (Dudouet et al. 2014, De Napoli et al. 2012). Protons and neutrons are the most abundant components, with wide angular and energy distributions. Since the produced fragments have different charge, energy and direction than the primary beam, they are a source of unwanted dose deposition outside the target tissue that must be taken into account in the treatment planning system. On the other hand, the penetrating proton component often escapes from the patient and can be detected with high efficiency by means of a tracking detector (Agodi et al. 2012, Gwosh et al 2013). This feature can be exploited for range monitoring in case of an active pencil-beam scanning treatment, using the Interaction Vertex Imaging technique (Henriquet et al. 2012), namely the reconstruction of the proton emission point as the point of minimum approach between the detected proton trajectory and the known direction of the treatment pencil beam.

A resolution of the order of millimeters on the geometrical parameters of the emission shape, and in turn of the Bragg peak, can be achieved only by the collection of large amounts of statistics. Two different approaches are suggested for this aim from a practical point of view: i) large size tracking detectors (like drift chambers or scintillating fiber trackers) placed at large angles with respect to the beam, ii) small size silicon devices that collect the copious flux of protons at low angles. There is no clear advantage of one solution, since the first devices can back-track the proton perpendicular to the beam line in a favorable geometry, if the finite transverse size of the pencil beam is taken into account, while the second solution could be easier to be accommodated in a clinical treatment room.
This charge-based monitoring is a promising, but not yet mature, technique, in particular the calibration of the correlation between the emission profile and the Bragg-peak position asks for further investigation. A minimal possible approach could be the comparison between the computed profile (via Monte-Carlo simulation codes) and the detected one, as already implemented for the correlation of the induced PET activity with the beam range.
Within the MediNet collaboration, the group of the University of Rome “La Sapienza” is actively working in the framework of the INSIDE collaboration on a pre-clinical, multi-modal range monitor prototype for carbon beam treatment (Marafini et al.2015), developed in cooperation with the CNAO therapeutic centre in Pavia. The test and calibration of the charged-based section of the INSIDE detector system are foreseen in 2017.

Apart from the detection of secondary charged particles, the detection of the primary beam is requested in some features: time-of-flight for prompt-gamma detection (Krimmer et al., 2015), transverse position identification of the primary beam in secondary particle vertex reconstruction (Henriquet et al., 2012), ion trajectory reconstruction in particle radiography. Depending on the beam time-structure, the detection at very high rates (100 MHz) is quite challenging, both for the detectors (Gallin-Martel et al., 2016) that need to be fast and radiation-hard, and for the associated electronics (Deng et al., 2013). Sect. 1.5 will recur to these issues and present possible approaches to overcome them.

1.3 Novel scintillators and their applications

(WG3, Convener : Jose Udias (UCM) ; participants: TU Delft, GSI, JLU, LIP, LMU, LPC, OncoRay, UCM, INFN/U Pisa, INFN/U Rome)

Inorganic scintillation detectors, where an energetic impinging photon is converted in an optical transparent crystal into a multitude of visible or near-UV photons which are then registered in a photosensor, are the

workhorses of photon-based medical imaging. The quest for better scintillation detector materials with higher stopping power and higher light yield (that enable good energy and time resolution), as well as shorter signal rise time to optimize the time resolution, is a research activity, where state of the art experiments in nuclear physics and developments in nuclear medicine detectors complement each other. Medical imaging via Positron Emission Tomography (PET) and Single Photon-Emission Computed Tomography (SPECT), however, adds another important prerequisite, which is the related price tag. Further, in PET the shortest possible decay time is sought for, to allow for high counting rates, usually much higher than in nuclear experiments or in SPECT, while the potential presence of intrinsic radioactivity in the scintillator crystal (occurring for some commonly used detector materials) is not a serious concern. Very low intrinsic radioactivity is, however, a strong prerequisite for SPECT imaging, since here one has to deal with only moderate count rates. In PET and SPECT most scanners are based on inorganic scintillators. BGO and later GSO were used for PET, while NaI or CsI crystals have been used for SPECT for many years since the beginning of nuclear imaging. The last decade, however, has seen the introduction of new inorganic scintillators. LSO and LYSO are the best choice for PET scanners as a much superior choice compared to BGO or GSO in terms of energy and time resolution, and they are a must for time-of-flight PET scanners. $LaBr_3$(Ce) is increasingly being introduced for SPECT, in order to benefit from its much better energy resolution. And more recently, a bunch of new inorganic scintillators are being introduced. GAGG(Ce) crystals are now widely available in large quantities and for a competitive price, with an advantage in energy resolution compared to LYSO and LSO scintillators, and essentially without intrinsic radioactivity (Sanchez-Tembleque et al. 2015). They are getting closer to the energy resolution of $LaBr_3$, at a lower price and with higher stopping power, but their time resolution properties lag behind the ones of LYSO or GSO. With organic scintillators, we eventually expect to reach, at least in theory, 100 ps coincidence resolving times (CRT) (Fraile et al. 2011). While 100 ps CRT will certainly improve the quality of nuclear imaging, it will not likely introduce a revolution in the way nuclear imaging is done. To reduce the CRT more significantly, one must seek for a different approach. Plastic scintillators and scintillator fibers, which would provide a very short decay time, suffer from low stopping power and insufficient optical photon yield. However, novel methods, developed in the last few years, allow for increasing the thickness of the plastic detector and at the same time the determination of the depth of the interaction of the registered gamma photon. In addition, they are inexpensive and can be easily arranged in many different shapes. This might make it possible to compensate the reduction of detector efficiency by an increase of the acceptance. However, even with the improved TOF capability, the small ratio of photopeak-to-Compton interaction probabilities for these materials poses a tremendous challenge for image reconstruction.

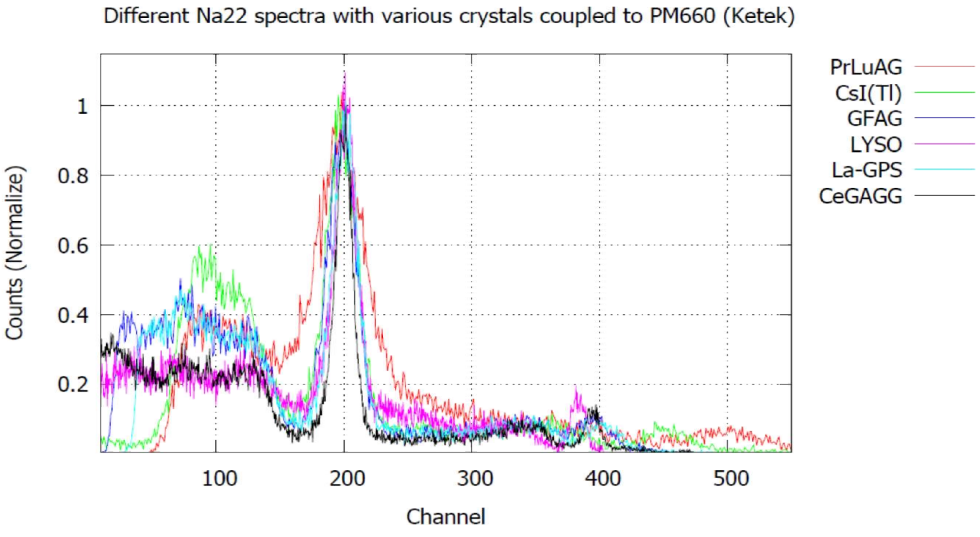

Fig. 2: New scintillators coupled to a SiPM readout system and exposed to a ^{22}Na source (Fraile et al. 2011).

A further technological development has been in a very preliminary stage for many years and finally seems to begin to become a viable way of improving the

performance of inorganic scintillators: Inorganic scintillators that consist of an incorporation of *Photonic* crystals (i.e. a periodic optical nanostructure that affects the motion of photons in much the same way that ionic lattices affect electrons in solids), which may allow for full control of the refraction index on one side of the scintillator. With scintillators engineered with a photonic crystal pattern, the light collection at the interface between the scintillator and the photodetector would be improved (Knapitsch et al. 2014) and this may finally allow for breaking current limits in the performance of medical imaging devices.

Many of the groups in MediNET have strong activities in scintillator development and testing, both motivated by interests in nuclear physics experiments and nuclear imaging. MediNET will foster the complementarity between these two aspects.

1.4 New photosensors

(WG4, Convener: Dennis Schaart (TU Delft); participants: IFIC, TU Delft, GSI, LIP, LPC, UCM)

The readout of the tiny light signals created in scintillators upon the absorption of ionising radiation requires highly sensitive photodetectors. In high-end applications, such as in advanced detectors for radiation therapy, photosensors with single-photon detection capability are needed. The ideal photosensor for such applications would have unit quantum efficiency, unlimited dynamic range, and the capability to perfectly determine the position and time of arrival of each scintillation photon.

Historically, the first device capable of detecting single optical photons is the photomultiplier (PMT), developed about 80 years ago. A PMT relies on photoelectric conversion and subsequent electron multiplication in vacuum to generate a measurable electronic signal. PMTs still are widely used, in spite of their volume, weight, poor functioning in magnetic field, limited quantum efficiency, and moderate time resolution. Various types of PMTs exist, including position-sensitive multi-anode PMTs and microchannel-plate PMTs (MCP-PMT), which can offer position information and relatively high time resolution.

The development of large-area MCP-PMT photodetectors by the LAPPD Collaboration (LAPPD) with time resolutions of picoseconds (10^{-12} s) and sub-millimeter space resolutions would open new opportunities in time-of-flight positron emission tomography (TOF-PET).
The LAPPD design is based on an MCP consisting of a 20×20 cm^2 (8 in.×8 in.) capillary glass plate with 20-µm20-µm pores (Incom), functionalized with resistive and emissive layers using atomic layer deposition (Incom) and (D.R. Beaulieu et *al.* 2011).
This method allows separately optimizing the three functions performed by a conventionally constructed MCP: providing the pore structure, a resistive layer for current supply, and the secondary emitting layer. In addition, the micro-pore substrates are a hard glass, providing a more chemically stable platform and improved mechanical strength. Pre-industrial prototypes of such large area MCP-PMT are now in progress and will be tested in an in-beam PET demonstrator in the Nice proton therapy center in the framework of the France Hadron project.

Recent research efforts in PMT technology include the development of more compact devices through microelectromechanical system (MEMS) fabrication techniques. These techniques may enable new approaches such as the development of PMTs based on stacked transmission dynodes, with potentially superior position and time resolution (van der Graaf et al 2013).

Currently, much research effort is being put into the development of semiconductor photosensors with single-photon detection capability. Compared to PMTs, solid-state single-photon sensors are much more compact, are much less sensitive to magnetic fields, and have the potential to offer better quantum efficiency, position resolution, and time resolution.

Whereas the use of solid-state photosensors such as PIN diodes and avalanche photodiodes (APDs) in scintillation detectors has been explored, a particularly interesting new class of devices are silicon photomultipliers (SiPMs) (Antich *et al* 1997, Bondarenko *et al* 2000, Britvitch *et al* 2007, Golovin and Saveliev 2004, Herbert *et al* 2007, Lewellen 2008, McElroy *et al* 2007, Musienko *et al* 2007, Renker 2007, Yamamoto *et al* 2007). SiPMs allow the detection and counting of single photons in weak light pulses by means of discrete and localized conversion/amplification processes. To achieve this, the sensitive area is subdivided into an array of avalanche regions operated in the Geiger-regime. Each of these single photon avalanche photodiodes (SPADs) is a highly non-linear device, in fact a binary switch, that is capable of detecting the absorption of one or more photons, but incapable of resolving the actual photon number. Nevertheless, the integration of a large number of parallel-connected SPADs in a SiPM allows counting the number of photons in a low-level light pulse, provided that the incident photons are distributed randomly over the sensor area.

SiPMs can be fabricated using CMOS technology, offering the possibility of low cost when made in large quantities. They have gains in the order of ~10^6 and fast response. Whereas the performance of SiPMs has improved dramatically during the last decade, their inherent properties continue to impose challenges, such as reducing the dark count rate (DCR), increasing the fill factor, enhancing the dynamic range that is limited by saturation effects (van Dam et al 2010), and improving the timing properties (Seifert et al 2012).

The implementation of SPADs in CMOS opens up the possibility of using them as digital switches that quickly switch from one logic state to the other upon the detection of a photon. The local integration of each SPAD with logic circuitry in so-called digital SiPMs (dSiPMs) enables the use of active quench and recharge techniques as well as the implementation of functionality to mask noisy SPADs. Another advantage is that the breakdown of a SPAD in a dSiPM is detected by sensing local voltage changes. This makes the sensor response faster and less sensitive to gain fluctuations, which can be exploited to achieve more accurate timing, better sensor uniformity, and lower sensitivity to temperature drifts. Furthermore, digital signal processing circuits can be integrated in a dSiPMs, such as a time-to-digital converter (TDC) circuitry for determining the total photon count (Schaart et al 2016).

Digital SiPMs can have excellent low-level light sensing properties and represent a new paradigm in low-level light sensing technology. Their digital operation makes them true photon counting devices. As a consequence, their operation can be fully understood in statistical terms only. The fact that the single-photon time resolution (SPTR) of a dSiPM to first order approximation is independent of its sensitive area is just one example of such a new paradigm, which can be exploited to improve the time resolution of scintillation detectors in novel ways (van Dam et al., 2013). As another example, the ability of dSiPMs to provide spatio-temporal information on the incident photon fluence with high granularity in each dimension enables novel approaches to extract information from the measured data (Meijlink et al., 2011, Mandai et al., 2013, Fischer et al., 2015, Tabacchini et al., 2015). Whereas a number of papers proposing quantitative models of the properties and operation of dSiPMs have been published (Fishburn and Charbon, 2010, Seifert et al., 2012a, van Dam et al., 2012, Tabacchini et al., 2014, Therrien et al., 2014, Mandai et al., 2014, Venialgo et al., 2015), the theory of these devices is still under development.

It seems likely that SiPMs and dSiPMs only represent the first steps into the new field of large-area, solid-state photon counting devices. In line with recent developments in many other domains, it would not seem implausible that the trend towards fully digital and highly integrated detection, acquisition, and processing of (optical) information carriers will also continue in the field of biomedical imaging equipment. Besides spatial and time information, future sensors might even be able to provide data on, e.g., the energy (wavelength) and/or polarization of the photons detected, which would open up many new paths for exploration.

1.5 Data acquisition electronics

(WG5, Convener: Gerard Montarou (LPC); participants: IFIC, GSI, JLU, IPNL, LPC, LPSC, UCM, INFN/U Pisa)

The recent developments in detector systems for medical applications, whether in the field of imaging or for the development of more specific systems for particle therapy monitoring, evolves to the combined use of various particle detection modalities. In the development of new tools for molecular imaging, Positron Emission Tomography (PET) is most often now combined with X-ray Computed Tomography (PET/CT) and aims to be combined with Magnetic Resonance (PET/MR).

For hadron therapy monitoring systems, recent projects aim to detect all the particles escaping the patient: 511 keV annihilation photons, "prompt" photons, secondary charged particles (mainly protons). The project INSIDE (INnovative Solutions for In-beam DosimEtry in Hadrontherapy) to be installed in a treatment room of the CNAO centre in Pavia is the most representative example of such evolution (M. Marafini *et al.* 2015).

The Antoine Lacassagne Centre in Nice will help in the framework of the French research project 'France Hadron' , to study equivalent multimodal systems for proton therapy, combining all imaging and monitoring modalities, including proton-CT.

In this variegated detector landscape, one important deliverable of the different projects is the development of a multi-purpose data acquisition system (DAQ) suitable for different medical imaging set-ups.

Such a combined set-up involves the use of a large number of electronics channels, whatever the detector used. Especially the device around the patient must be sensitive enough not to increase treatment time and be able to reach an "real time" control system.

When the detection efficiency becomes high, the next important question that has to be faced is dead-time. The actual efficiency for a given detector material is dominated by the product of the dead time (i.e. the time when the data acquisition system is internally busy with data processing and thus unable to accept further events) and the front surface area of the detector (W. Moses *et al.* 1994, R.R. Raylman *et al.,* 2008).

Although it is difficult to quantify dead-time losses, state-of-the-art electronics have been demonstrated to require dead-time management in clinical imaging even for limited-angle sampling systems (R.R. Raylman *et al.* 2008a, L. MacDonald *et al.* 2009).

Dead-time correction procedures have been proposed in the past (M. Daube-Witherspoon and R. Carson 1991); they are typically based on the combination of paralysable and nonparalysable models[5], but involve a series of empirical parameters, which are affected by measurement and fitting errors. Conversely, detector modularization has already been addressed as the most practical solution for reducing dead time (W. Moses *et al.* 1994, R. Raylman *et al.* 2008), although it requires some degree of electronics parallelization.

Based on previous experiences with the first dedicated in-beam DoPET system (Vecchio *et al* 2009), the INSIDE collaboration developed a new in-beam PET device with wider detectors and modularized acquisition for better counting performances (Sportelli *et al.* 2011).

[5] A detector, or detection system, can be characterized by a paralysable or non-paralysable behavior (W.R. Leo, 1994). In a non-paralysable detector, an event happening during the dead time is simply lost, so that with an increasing event rate the detector will reach a saturation rate equal to the inverse of the dead time. In a paralysable detector, an event happening during the dead time will not just be missed, but will restart the dead time, so that with increasing rate the detector will reach a saturation point where it will be incapable of recording any event at all.

The coincidence detection is likely to be the most sophisticated stage of the PET acquisition system and the one to which is dedicated the most expensive and cutting edge hardware. This is particularly true when the number of detectors increases, the tight timing constraints being harder to meet.

In the last decade, digital electronics has turned more and more into a serious competitor, if notr replacement, of more conventional analog electronics. Field-programmable gate arrays (FPGAs) have been successfully adopted in both coincidence gating and time digitizing (TDC) processing approaches. This provided higher levels of flexibility, and the possibility of implementing fully functional systems on a single chip. Such an approach simplifies sensibly the design and reduces costs. However, the finite resources and pin-out of the device may limit the maximum achievable number of controlled detectors. So, as an example, the DAQ architecture chosen for the in-beam PET of the INSIDE set-up is a modularized FPGA-based acquisition electronics that provides state-of-the-art performances with a low-cost approach for multichannel coincidence processing (G. Sportelli et *al.* 2011, G. Sportelli et *al.* 2014).

The currently existing electronics dedicated to precise time measurements (below 100-ps range) was up to now mainly based on the use of constant fraction discriminators (CFD) associated with Time to Digital Converters (TDC). The ultrafast front-end preamplifier-discriminator chip called NINO that has been developed for use in the ALICE time-of-flight detector is one of the most representative developments using this method (F. Anghinolfi *et al.* 2004).

Another approach consists in labelling each detected particle with a finely calculated timestamp, synchronous with a commonly distributed clock. Coincidences are thus resolved by computing differences in real time or off line. These alternative methods based on digital treatment of the analogue sampled and then digitized detector signal have been developed in the France Hadron project. Such methods permit achieving a timing resolution far better than the sampling frequency.

Digitization systems have followed the progress of commercial ADCs, but the latter have prohibitory drawbacks, such as their huge output data rate and power consumption. Conversely, high speed analog memories now offer sampling rates far above 1GHz at low cost and with very low power consumption, especially if the number of channels is large (E. Delagnes et *al.*2006, G. Varner et *al.* 2008). The 'Domino Ring Sampler' (DRS4) is one of such high speed waveform sampling chips (S. Ritt et *al.* 2010).

Sampling the analog signals of the photodetectors requires being able to deal with large amounts of data. Such a constraint has been already solved for LHC experiments. Originally developed for the telecommunication industry, the MicroTCA (MTCA) and AdvancedTCA (ATCA) modular electronics standards have been selected as the platform for many of the on-going and planned upgrades of the off-detector trigger and data-acquisition systems of the ATLAS and CMS experiments at the LHC at CERN.

A data acquisition system for medical imaging applications is now developed at the Centre de Physique des Particules de Marseille (CPPM), it provides high performance, generic data acquisition and processing capabilities. The mezzanine boards work flawlessly, and the firmware is finished, tested and working. This firmware is intended to serve as a framework for detector developers, providing all the necessary tools to implement a full-featured DAQ without dealing with the board's complexity, but by just writing the specific application code needed. Compatibility at a physics level has been verified with different read-out boards, while firmware-level compatibility is ongoing (C. Abellan et *al*. 2014).

SECTION 2: RADIATION QUALITY AND CLINICAL EFFECTS

(participants: APSS, ENLIGHT, GSI, IFJ-PAN, INFN LNL and LNS, LPC, MedAustron, U Milan, UCM, UNIBAS, UW, VINS-UB)

Before entering into a discussion on why further studies are needed on radiation quality and on what are the proposed nuclear physics tools, it is appropriate to describe what *radiation quality* is and what it is useful for. The radiation quality is used to represent the radiation focusing on the way the energy is delivered to the medium: for ions the energy is densely released and concentrated along the track of the particle, for photons the energy is more sparsely distributed. These characteristics, linked to the biological effectiveness, change drastically with the radiation type. The highest changes are for ions heavier than protons at low energies, but significant changes are evident also in low-energy protons.

Since these characteristics are the same for all particles of a certain species and energy, we can give the general definition of the radiation quality stating that it is *the type and energy spectrum of each radiation type in a specific point*. Though this definition is very simple in its expression, its use is very problematic. For instance, to describe the radiation quality in a small volume of a tumor treated with carbon ions, we should be able to collect the energy spectra of carbon ions, those of each of the ions species resulting from the fragmentation of the primary carbon beam, as well as the spectra of the neutrons and the gamma rays crossing that volume. These measures are extremely challenging and practically unfeasible. The usual ways in which the radiation quality is specified is via linear energy transfer (LET) values, or via microdosimetry quantities. The verb “specify” was used the first time 60 years ago by Harald Rossi, when he described his newly invented microdosimeter (Rossi, 1959) and it remains today when LET of microdosimetric quantities are used to “specify the radiation quality” (ICRU 1986).

LET spectra and lineal energy spectra (not be confused with the energy spectra mentioned above) represent the distribution of energy exchanged when a charged particle of the beam traverses a small distance in the medium. Although not coincident, LET and lineal energy spectra have strong analogies. LET spectra are generally the result of Monte Carlo simulations and computations, while microdosimetry spectra are collected experimentally, using a detector with (simulated) size of the order of one micrometer, from this deriving their name.

In the most common way, a single number, the mean value of LET or the mean value of the lineal energy, is used to specify the radiation quality: this simplifies the description of an irradiated field, but also omits important information. For the ions used in radiation therapy the frequency-mean lineal energy (calculated from the microdosimetric spectrum) is, with a good approximation, coincident to the frequency-mean LET (calculated from the LET spectrum).

There are two ways to evaluate the mean from the LET and the lineal energy spectra obtaining distinct values: the dose mean value and the frequency mean value. We are not describing in these pages the details of the two evaluations and we refer the reader to specific publications (ICRU 1970).

2.1 Radiation quality and detectors

The reading of the detectors used in clinical practice depends on the radiation quality. Several gas-based and solid-state radiation detectors are used before the treatment to verify that the dose and the conformity of the irradiation to the planned treatment, to perform quality assurance tests on the shape and energy of the beam, and to monitor the delivery of the beam to the tumor. Appropriate correction functions should be used to adapt the detector readings to the radiation quality at the measuring point.

2.2 Radiation quality in clinics

One concept represents the link between the radiation quality and therapy, the relative biological effectiveness, RBE. This is a dimensionless quantity, which estimates how two radiations of different qualities require different doses to produce the same biological effect. Let us consider an example: a certain ion beam is more efficient than cobalt-60 photon beams in producing cell killing, because it needs only 1/3 of the dose of the photon beam to produce the same effect. This is shown saying that the RBE of that ion beam is 3. RBE depends on the radiation quality, on the dose, and on other conditions of the target and the radiation described in details in (IAEA-ICRU 2008). To avoid confusion, each time the RBE is cited the most representative conditions should be reported, in particular indicating the specific biological effect considered and the dose at which it is calculated.

In passively spread ion-beam therapy systems, the clinical RBE has a fundamental importance and it is used directly in the evaluation of the treatment planning as a multiplication factor for the dose (Petrovic et al., 2010). In actively-scanned ion-beam therapy, the clinical effectiveness is the result of a complex computation performed by the treatment planning systems on the components of the radiation (primary particles and fragments) in specific points.

2.2.1 Mean LET values and mean lineal energy values

In today's ion-beam therapy, the estimation of the radiation quality via mean values of the LET is not sufficient. Different ion species with the same LET show different RBE values, and thus the LET is not a unique descriptor of radiation quality (Friedrich et al., 2013).

Three-dimensional maps of LET and lineal energy mean values might be helpful to estimate the general trends concerning biological effect distributions, but are not suitable for a sufficiently accurate quantitative prediction of the biological/clinical effects.

2.2.2 Spectra of LET and spectra of lineal energy

LET spectra and lineal energy spectra would help to resolve ambiguities that arise between mean LETs and RBEs. For instance, the biological effectiveness of a monoenergetic ion beam with a given LET is expected to be different from a mixed field having the same dose mean LET value, but a broad distribution of individual LET values. On the other hand, these spectra are insufficient to completely resolve differences in radiation quality and therefore cannot be used for the quantitative predictions, at least as long as they do not resolve the differences in track structure that lead to the different effectiveness of different ion species at the same LET.

The complementary work of microdosimetry experiments and Monte Carlo simulations is instrumental in determining how well a spectrum of lineal energy is able to define a complex radiation distinguishing all ion species and energies. A series of experiments should be carried out, exploring different treatment conditions including different primary irradiation energies, fragmentation processes, and target compositions. The comparison of the experimental and simulation data will allow for the estimation of the uncertainty in assessing radiation quality from lineal energy spectra.

2.2.3 "Painting" techniques

In actively scanned beams, the precise assessment of the two parameters, dose and radiation quality, allows optimizing the outcomes of the treatment, adapting the two quantities to the characteristics of the tumour and the healthy surrounding tissue. These three-dimensional assessments of physical quantities coupled to the corresponding three-dimensional assessments of the clinical effectiveness can optimize the treatment: The so-called "painting" techniques allow the creation of treatment plans, which biologically spare the organs at risk and, at the same time, boost specific areas in the tumor with extra harm.

2.3 Radiation quality and protons

Several in-vitro studies show a significantly enhanced RBE value at the end of the proton path. It is frequently claimed that this enhancement in general is not seen in the clinics and the most important consequence is that treatment planning systems of protons ignore radiation quality changes. Therefore, it needs to be elucidated how this serious discrepancy between the in-vitro results and the clinical results can be explained and to identify the situations where the increased RBE might appear.

The task is complex and it requires assessing the clinical effectiveness using tumour parameters and side effects reported by the physicians during and after the treatment, or deducted from sophisticate analysis based on retrospective studies (Giantsoudi, 2016).

One possibility could be offered by the modern imaging techniques that allow the acquisition of detailed three dimensional physiological maps and anatomical structures in-vivo and non-invasively. Those data could be used to evaluate the clinical effectiveness, together with the unwanted side effects, directly on patients and during radiation treatment. Moreover, such approach has the advantage to elucidate the effects of radiation treatment with adjuvant therapy (i.e. the use for the same patient of an additional therapy associated to the radiation therapy) as the administration of chemo-toxic drugs, which is strongly affected by tumor physiology and is patient-dependent. This approach is not limited to proton therapy but it can be applied to other ions.

It is important to mention here the microdosimetric measurements performed in the 62 MeV therapeutic proton beam in Nice. The RBE values (accounting for early effects in mouse crypt cells at a dose of 8 Gy) were assessed with the use of a weighting function, previously computed by comparing microdosimetric and radiobiological measurements. The results (De Nardo, 2004) clearly show that the microdosimetric RBE assessment fits very well the radiobiological RBE values at different penetrations. This weighting function cannot be directly extended to other types of beams as carbon-ion beams. Dedicated experiments can be designed to extract appropriate weighting functions for other ions and for specific biological effects, and to assess the uncertainty linked to the contribution of the fragments of the carbon in the spectra along the path.

The INFN-LNS group together with VINS-UB developed a Geant4 application completely dedicated to the simulation of a proton passive beam line for ocular melanoma treatment. The application is now part of the Geant4 suite. It contains a specific class to calculate 3D averaged and specific LET distributions (Romano et al., 2014). At the moment the application is being updated and a module for the RBE calculation, based on the LEM module, will soon be released. In the next two years, the main aim of the work will be the identification and understanding of the contribution of target fragmentation (under proton irradiation) to the LET and RBE three dimensional distributions. Different hadronic models, already available in Geant4, will be introduced and their effect on the calculated distribution will be studied. In-vivo and in-vitro verification will be carried out, at INFN-LNS Laboratory jointly with VINS-UB. This activity will be part of two different projects that will be funded by INFN in the period 2016-2019: the Move-IT project (that will be focused on the radiobiological modelling and verification of target fragmentation and hypoxic effects in proton treatment planning systems); and the FOOT project whose main aim will be the design of a specific experimental campaign dedicated to the quantification of the target fragmentation. Data from FOOT will be used for the Monte Carlo hadronic models verification and they will hence have a strict connection with Move-IT and with the Geant4 activity.

CONCLUSION

Cooperative strategies in the MediNet NA, targeting the needs for nuclear physics tools for medicine, in particular in the field of radiation detection for particle therapy, will be based on the concentrated expertise gathered in the MediNet participant groups that will allow, on the radiation-detector oriented side, for combined experiments and joint measurement campaigns in order to allow for comparative studies of complementary (or alternative) detector approaches. The network can also play a role in coordinating experimental efforts, which could be helpful to (i) avoid duplicate work, (ii) have an easier/fairer comparison of different detector systems by (a) agreeing on common experimental protocols, (b) possibly agreeing to test different systems at the same time in one location, (c) generally enabling progress in a more efficient way.

For example, comparative tests of Compton imaging systems based on different scatter-absorber detector solutions in complementary environments and conditions are foreseen to be pursued in some of the participating groups (OncoRay, IPNL, IFIC, LMU). Corresponding campaigns could involve timing tests at the ELBE Bremsstrahlung beam, imaging tests with “point” sources of monoenergetic gammas (Tandetron accelerator at HDR Dresden-Rossendorf), gamma rays with a continuous energy distribution (ELBE Bremsstrahlung), or gammas with an energy distribution as produced by monoenergetic proton beams at the energy threshold for medically relevant nuclear reactions (Tandem accelerator in Garching), Imaging tests under realistic therapy conditions (AGOR at KVI-CART, proton therapy facility at OncoRay). In the context of such comparative measurements, it would be useful to define “reference scenarios” and to establish corresponding “reference setups” for comparing various aspects of the performance of detectors components (scatter detector modules, absorber detector modules) or complete imaging systems (Compton cameras, imaging setups with passive collimation).

Such ‘reference setups’ could be jointly agreed upon for comparative studies, such as (i) for imaging in the laboratory, e.g. a ^{60}Co point source of a given (minimum) activity, given distance to the camera front face, given measuring time normalized to the source activity; (ii) a reference setup for timing measurements (^{60}Co source, ELBE beam); (iii) reference setup for detector characterization and/or imaging with monoenergetic gammas at the HZDR Tandetron – given minimum distance, given integrated beam charge; (iv) reference setup for therapy conditions in the OncoRay experimental cave: given minimum distance, given beam current, beam spot size, and integrated beam charge. Additional detector developments could be considered that complement the “established” methods of prompt-gamma imaging, addressing specific questions relevant for medical applications. Examples are (i) beam hodoscopes, addressing the topics of (a) low-cost solutions for pencil beam monitoring, (b) count-rate limits for single-particle tracking and (c) detector and data acquisition concepts for extremely high rates. A second line of research could be (ii) detectors for proton or ion CT, where relevant questions to be solved comprise (a) the best (lowest-cost) solution for tracking, (b) the best (lowest-cost) solution for measuring the residual particle energy or water-equivalent range.

When it comes to assess the (therapeutical) radiation quality and its clinical effectiveness, in ion beam therapy microdosimeters are an important tool that can be used in different phases of the treatment for improving the description of the radiation quality. The needs are challenging, since treatment planning requires the full information on particle species and energies for the whole irradiated volume, the tumor and the healthy tissue surrounding it. The microdosimetric spectra are instrumental in this process, although they cannot directly provide the complete description of the radiation quality. The collection of microdosimetric data on the ion-beam therapy has started and more regular tests are planned. A comprehensive collection of data and the analysis via Monte Carlo simulation and other computational tools will allow assessing the level of accuracy of the microdosimeters in assessing radiation quality. The investigation should focus not exclusively on carbon-ion beams, but should also consider proton beams.

In order to be effective for the therapy, the radiation quality information must be paired to the information on the clinical effectiveness. The direct translation of radiobiological data on cell cultures to clinical effectiveness is critical, as described by Paganetti in the case of proton therapy (Paganetti, 2014). It is essential to explore other ways of assessing the clinical effectiveness as the use of modern imaging techniques directly on patient during the treatment.

The success of the developments depends on the possibility of creating new tools, experimental and computational, but primarily depends on the ability of collaborating with the specialists of the ion-beam therapy clinics on key issues as assessing the feasibility, improving the compatibility with the clinical environment, and reducing invasiveness and discomfort to the patients.

Therefore, the MediNet NA partner groups will work in cooperative efforts, both broad in their goals and focused to the needs of subsequent translation into clinical routine, to propose adequate solutions and concepts for the outlined specific needs in radiation therapy.

REFERENCES AND APPLICABLE DOCUMENTS

Abellan C. et al., “A micro-TCA Data Acquisition System and its application for Hadrontherapy Monitoring using a Compton Camera”, In Radiation Oncology. ICTR-PHE Conference. Geneva, p. S1-S2, (2014)

Agodi C. , Battistoni G. , Bellini F. , Cirrone G.A.P. , Collamati F., Cuttone G. et al., Charged particle’s flux measurement from PMMA irradiated by 80 MeV/u carbon ion beam, Phys. Med. Biol. 57, 5667 (2012).

Anghinolfi F., Jarron P., Krummenacher F., Usenko E., and Williams M.C.S. ,” NINO: An Ultrafast Low-Power Front-End Amplifier Discriminator for the Time-of-Flight Detector in the ALICE Experiment”, IEEE Transaction on Nuclear Science, 51, (5), pp. 1974—1978, (2004)

Anticha P P, Tsyganova E N, Malakhovc N A, Sadygovc Z Y, 1997 Avalanche photo diode with local negative feedback sensitive to UV, blue and green light, Nucl. Instr. Methods Phys. Res. A 389 491-498.

Beaulieu D.R et al., “Plastic microchannel plates with nano-engineered films“, Nucl Inst Methods A 633, S59-S61 (2011).

Biegun, A.K., Seravalli, E., Lopes, P.C., Rinaldi, I., Pinto, M., Oxley, D.C., Dendooven, P., Verhaegen, F., Parodi, K., Crespo, P., Schaart, D.R., 2012. Time-of-flight neutron rejection to improve prompt gamma imaging for proton range verification: a simulation study. Phys. Med. Biol. 57, 6429. doi:10.1088/0031-9155/57/20/6429

Bondarenko G et al 2000, Limited Geiger-mode microcell silicon photodiode: new results Nucl. Instr. Methods Phys. Res. A 442 187-192

Britvitch I, Johnson I, Renker D, Stoykov A and Lorenz E 2007 Characterization of Geiger-mode avalanche photodiodes for medical imaging applications Nucl. Instrum. Methods Phys. Res. A 571 308-311

Dam, H.T. van, Borghi, G., Seifert, S., Schaart, D.R., 2013. Sub-200 ps CRT in monolithic scintillator PET detectors using digital SiPM arrays and maximum likelihood interaction time estimation. Phys. Med. Biol. 58, 3243. doi:10.1088/0031-9155/58/10/3243

Daube-Witherspoon M. and Carson R. , “Unified dead time correction model for PET,” IEEE Trans. Med. Imag., 10, (3), pp. 267–275, (1991)

Dauvergne, D., Krimmer, J., Maxim, V., Solevi, P., 2014. Report on the influence of a beam monitor system on the ibSPECT performances (No. ENVISION Report D3.6).

De Napoli M, Agodi C, Battistoni G, Blancato AA, Cirrone GA, Cuttone G et al., Carbon fragmentation measurements and validation of the Geant4 nuclear reaction models for hadrontherapy. Phys. Med. Biol. 57, (2012) 7651.

De Nardo L., CesariV. , Iborra N., Conte V., Colautti P., Herault J., Tornielli G., Chauvel P., Microdosimetric Assessment of Nice Therapeutic Proton Beam Biological Quality, Physica Medica · Vol. XX, N. 2 (2004) 71-77

Delagnes E., Degerli Y., Goret P., Nayman P., Toussenel F., and Vincent P., "SAM: A new GHz sampling ASIC for the H.E.S.S.-II front-end electronics", Nucl. Instrum. Meth. A, 567, pp. 21-26, (2006)

Deng, S., Dauvergne, D., Lu, G.-N., Mathez, H., Zoccarato, Y., 2013. Very fast front end ASIC associated with multi-anode PMTs for a scintillating-fibre beam hodoscope. J. Instrum. 8, C01047–C01047. doi:10.1088/1748-0221/8/01/C01047

Dudouet J, Cussol D, Durand D, Labalme M. Benchmarking Geant4 nuclear models for hadron therapy with 95 MeV/nucleon carbon ions. Phys. Rev. C 89 (2014) 54616–7.

Enghardt, W., Crespo, P., Fiedler, F., Hinz, R., Parodi, K., Pawelke, J., Pönisch, F., 2004. Charged hadron tumour therapy monitoring by means of PET. Nucl. Instrum. Meth.. A 525, 284–288. doi:10.1016/j.nima.2004.03.128

Fischer, P., et al. (2015), 'SPAD array chips with full frame readout for crystal characterization', 4th Conference on PET/MR and SPECT/MR (PSMR2015) (EJNMMI Physics, 2; La Biodola, Isola d’Elba, Italy), 1.

Fishburn, Matthew W. and Charbon, Edoardo (2010), 'System Tradeoffs in Gamma-Ray Detection Utilizing SPAD Arrays and Scintillators', IEEE Transactions on Nuclear Science, 57 (5), 2549-57.

Fraile L.M. et al., “Fast timing study of a CeBr 3 crystal: Time resolution below 120 ps at 60 Co energies”, Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, V701 (2011), 235-242.

Friedrich T., Durante M., Scholz M., Particle species dependence of cell survival RBE: Evident and not negligible, Acta Oncologica, 2013; 52: 589–603

Gajos, A. et al, Nucl. Inst. and Meth. A 819 (2016) 54-59, Trilateration-based reconstruction of ortho-positronium decays into three photons with the J-PET detector.

Gallin-Martel, M.-L., Bes, A., Boukhémiri, A., Bosson, G., Collot, J., Dauvergne, D., Fontana, M., Gallin-Martel, L., Gorecki, A., Hostachy, J.-Y., Krimmer, J., Lacoste, A., Morse, J., Muraz, J.-F., Rarbi, F.E., Salomé, M., Testa, E., Yamouni, M., 2016. Large Area Polycrystalline Diamond Detectors for Online Hadron Therapy Beam Tagging Applications, in: Conference Abstract. Presented at the IEEE-NSS-MIC, Strasbourg, France.

Giantsoudi D., Sethi R.V., Yeap B.Y., Eaton B.R., Ebb D.H., Caruso P.A., Rapalino O., Chen Y.L., Adams J.A., Yock T.I., Tarbell N.J., Paganetti H., MacDonald S.S., Incidence of CNS Injury for a Cohort of 111 Patients Treated With Proton Therapy for Medulloblastoma: LET and RBE Associations for Areas of Injury, Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):287-96

Golovin V and Saveliev V 2004 Novel type of avalanche photodetector with Geiger mode operation Nucl. Instr. Methods Phys. Res. A 518 560-564

Gwosch K, B Hartmann, J Jakubek, C Granja, P Soukup, O Jäkel and M Martišíková Non-invasive monitoring of therapeutic carbon ion beams in a homogeneous phantom by tracking of secondary ions, Phys. Med. Biol. 58 (2013) 3755.

Henriquet P, Testa E, Chevallier M, Dauvergne D, Dedes D, N Freudet et al., Interaction vertex imaging (IVI) for carbon ion therapy monitoring: a feasibility study. Phys. Med. Biol. 57 (2012) 4655.

Henriquet, P., Testa, E., Chevallier, M., Dauvergne, D., Dedes, G., Freud, N., Krimmer, J., Létang, J.M., Ray, C., Richard, M.-H., Sauli, F., 2012. Interaction vertex imaging (IVI) for carbon ion therapy monitoring: a feasibility study. Phys. Med. Biol. 57, 4655–4669. doi:10.1088/0031-9155/57/14/4655

Herbert D J, Moehrs S, D'Ascenzo N, Belcari N, Del Guerra A, Morsani F and Saveliev V 2007 The silicon photomultiplier for application to high-resolution positron emission tomography Nucl. Instrum. Methods Phys. Res. A 573 84-87

Hueso-González, F., Enghardt, W., Fiedler, F., Golnik, C., Janssens, G., Petzoldt, J., Prieels, D., Priegnitz, M., Römer, K.E., Smeets, J., Stappen, F.V., Wagner, A., Pausch, G., 2015. First test of the prompt gamma ray timing method with heterogeneous targets at a clinical proton therapy facility. Phys. Med. Biol. 60, 6247. doi:10.1088/0031-9155/60/16/6247

Hueso-González, F., Golnik, C., Berthel, M., Dreyer, A., Enghardt, W., Fiedler, F., Heidel, K., Kormoll, T., Rohling, H., Schöne, S., Schwengner, R., Wagner, A., Pausch, G., 2014. Test of Compton camera components for prompt gamma imaging at the ELBE bremsstrahlung beam. J. Instrum. 9, P05002. doi:10.1088/1748-0221/9/05/P05002

IAEA-ICRU, International Atomic Energy Agency and International Commission on Radiation Units and Measurements , Relative Biological Effectiveness in Ion Beam Therapy, Technical Reports Series No. 461, Jointly sponsored by the IAEA and ICRU, Vienna 2008,

ICRU, International Commission on Radiation Units and Measurements, Linear Energy Transfer, ICRU report 16, Washingtond D.C. 20008, USA, 1970

ICRU, International Commission on Radiation Units and Measurements, The Quality Factor in Radiation Protection, ICRU report 40, Woodmont Avenue, Bethesda, Maryland, 20814, USA, 1986

InCom; The glass capillary substrates are produced by Incom Inc., Charlton, MA. See〈http://www.incomusa.com/〉

Kaminska, D. et al., Eur. Phys. J. C 76 (2016) 445, A feasibility study of ortho-positronium decays measurement with the J-PET scanner based on plastic scintillators.

Knapitsch A., Lecoq P., "Review on photonic crystal coatings for scintillators", International Journal of Modern Physics A 29 (2014), DOI: 10.1142/S0217751X14300701.

Kraan, A.C., 2015. Range Verification Methods in Particle Therapy: Underlying Physics and Monte Carlo Modeling. Front. Oncol. 5. doi:10.3389/fonc.2015.00150

Krimmer, J., Ley, J.-L., Abellan, C., Cachemiche, J.-P., Caponetto, L., Chen, X., Dahoumane, M., Dauvergne, D., Freud, N., Joly, B., Lambert, D., Lestand, L., Létang, J.M., Magne, M., Mathez, H., Maxim, V., Montarou, G., Morel, C., Pinto, M., Ray, C., Reithinger, V., Testa, E., Zoccarato, Y., 2015. Development of a Compton camera for medical applications based on silicon strip and scintillation detectors. Nucl. Instrum. Methods Phys. Res. Sect. Accel. Spectrometers Detect. Assoc. Equip., New Developments in Photodetection NDIP14 787, 98–101. doi:10.1016/j.nima.2014.11.042

Krimmer, J., Ley, J.-L., Abellan, C., Cachemiche, J.-P., Caponetto, L., Chen, X., Dahoumane, M., Dauvergne, D., Freud, N., Joly, B., Lambert, D., Lestand, L., Létang, J.M., Magne, M., Mathez, H., Maxim, V., Montarou, G., Morel, C., Pinto, M., Ray, C., Reithinger, V., Testa, E., Zoccarato, Y., 2015. Development of a Compton camera for medical applications based on silicon strip and scintillation detectors. Nucl. Instrum. Methods Phys. Res. Sect. Accel. Spectrometers Detect. Assoc. Equip., New Developments in Photodetection NDIP14 787, 98–101. doi:10.1016/j.nima.2014.11.042

LAPPD : The Original LAPPD Institutions Include ANL, Arradiance Inc., The University of Chicago, Fermilab, the University of Hawaii, Muons, Inc, SLAC, SSL/UCB, and Synkera Corporation.

Leo W. R. (1994). Techniques for Nuclear and Particle Physics Experiments. Springer. pp. 122–127. ISBN 3-540-57280-5.

Lewellen T K 2008 Recent developments in PET detector technology Phys. Med. Biol. 53 R287-R317

Lin, H.-H., Chang, H.-T., Chao, T.-C., Chuang, K.-S., A comparison of two prompt gamma imaging techniques with collimator-based cameras for range verification in proton therapy. Radiat. Phys. Chem. doi:10.1016/j.radphyschem.2016.04.020

MacDonald L. et al., "Clinical imaging characteristics of the positron emission mammography camera: PEM flex solo II," J. Nucl. Med., vol. 50, (10), pp. 1666–1666, (2009).

Mandai, S., E. Venialgo and E. Charbon (2014). "Timing optimization utilizing order statistics and multichannel digital silicon photomultipliers." Optics Letters 39(3): 552-554.

Mandai, S., Venialgo, E., and Charbon, E. (2013), 'Energy estimation technique utilizing timing information for TOF-PET application', 2013 IEEE Nuclear Science Symposium and Medical Imaging Conference (2013 NSS/MIC). Seoul, South Korea. 27 Oct.-2 Nov. 2013.

Marafini M, Attili A, Battistoni G, Belcar N., Bisogni MG, Camarlinghi N et al., The INSIDE Project: Innovative Solutions for In-Beam Dosimetry in Hadrontherapy. Acta Physica Polonica A127 (2015) 1465.

Marafini M. et al., The INSIDE Project: Innovative Solutions for In-Beam Dosimetry in Hadrontherapy for the CNAO treatment produced by the beam, Acta Physica Polonica A, Vol.127, No. 5, pp. 1465–1467, (2015)

McElroy D P, Saveliev V, Reznik A and Rowlands L A 2007, Evaluation of silicon photomultipliers: a promising new detector for MR compatible PET Nucl. Instrum. Meth. A 571, 106-109

Meijlink, J. R., et al. (2011), 'First Measurement of Scintillation Photon Arrival Statistics Using a High-Granularity Solid-State Photosensor Enabling Time-Stamping of up to 20,480 Single Photons', 2011 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2254-57.

Minot Michael J. et al., Pilot Production & commercialization of LAPPDTM, Nucl Inst Method A 787, 78-84, (2015)

Moses W. et al., "PET detector modules based on novel detector technologies," Nucl. Instrum. Meth. A, 353, (1–3), pp. 189–194, (1994).

Moses W. et al., "PET detector modules based on novel detector technologies",Nucl. Instrum. Meth. A, vol. 353, (1–3), pp. 189–194, (1994).

Moskal, P. et al., Nucl. Inst. and Meth. A 775 (2015) 54-62, A novel method for the line-of-response and time-of-flight reconstruction in TOF-PET detectors based on a library of synchronized model signals.

Moskal, P. et al., Phys. Med. Biol. 61 (2016) 2025-2047, Time resolution of the plastic scintillator strips with matrix photomultiplier readout for J-PET tomograph.

Musienko Y, Auffray E, Lecoq P, Reucroft S, Swain J and Trummer J 2007 Study of multi-pixel Geiger-mode avalanche photodiodes as a read-out for PET Nucl. Instrum. Methods Phys. Res. A 571 362-365

Nuclear Physics European Collaboration Committee (NuPECC), Nuclear Physics for Medicine, European Science Foundation (ESF), April 2014, ISBN: 978-2-36873-008-9

Paganetti H., Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer, Phys. Med. Biol. 59 (2014) R419–R472

Parodi, K., n.d. On- and off-line monitoring of ion beam treatment. Nucl. Instrum. Methods Phys. Res. Sect. Accel. Spectrometers Detect. Assoc. Equip. doi:10.1016/j.nima.2015.06.056

Petrović I., Ristić-Fira A., Todorovic D., Korićanac L., Valastro L., Cirrone P., Cuttone G., Response of a radio-resistant human melanoma cell line along the proton spread-out Bragg peak. International Journal of Radiation Biology, 2010, 86(9): 742-751.

Piersanti L, Bellini F, Bini F, Collamati F, De Lucia E, Durante M et al. Measurement of charged particle yields from PMMA irradiated by a 220 MeV/u 12C beam. Phys. Med. Biol. 59 (2014) 1857.

Piliero, M.A., Bisogni, M.G., Cerello, P., Del Guerra, A., Fiorina, E., Liu, B., Morrocchi, M., Pennazio, F., Pirrone, G., Wheadon, R., 2015. Performance of a fast acquisition system for in-beam PET monitoring tested with clinical proton beams. Nucl. Instrum. Methods Phys. Res. Sect. Accel. Spectrometers Detect. Assoc. Equip. 804, 163–166. doi:10.1016/j.nima.2015.09.034

Polf, J.C., Avery, S., Mackin, D.S., Beddar, S., 2015. Imaging of prompt gamma rays emitted during delivery of clinical proton beams with a Compton camera: feasibility studies for range verification. Phys. Med. Biol. 60, 7085. doi:10.1088/0031-9155/60/18/7085

Priegnitz, M., Helmbrecht, S., Janssens, G., Perali, I., Smeets, J., Stappen, F.V., Sterpin, E., Fiedler, F., 2016. Detection of mixed-range proton pencil beams with a prompt gamma slit camera. Phys. Med. Biol. 61, 855. doi:10.1088/0031-9155/61/2/855

Raylman R. et al., “Quantification of radiotracer uptake with a dedicated breast PET imaging system,” Med. Phys., 35, (11), pp. 4989–4989, (2008).

Raylman R.R. et al., “Quantification of radiotracer uptake with a dedicated breast PET imaging system,” Med. Phys., 35, (11), pp. 4989–4989, (2008).

Raylman R.R. et al., “The positron emission mammography/tomography breast imaging and biopsy system (PEM/PET),” Phys. Med. Biol., 53, (3), pp. 637–653, (2008a).

Renker D 2007 New trends in photodetectors Nucl. Instrum. Methods Phys. Res. A 71 1-6

Richter, C., Pausch, G., Barczyk, S., Priegnitz, M., Keitz, I., Thiele, J., Smeets, J., Stappen, F.V., Bombelli, L., Fiorini, C., Hotoiu, L., Perali, I., Prieels, D., Enghardt, W., Baumann, M., 2016. First clinical application of a prompt gamma based in vivo proton range verification system. Radiother. Oncol. 118, 232–237. doi:10.1016/j.radonc.2016.01.004

Ritt S., Dinapoli R., and Hartmann U., "Application of the DRS chip for fast waveform digitizing", 623, pp. 486-488, (2010)

Roellinghoff, F., Benilov, A., Dauvergne, D., Dedes, G., Freud, N., Janssens, G., Krimmer, J., Létang, J.M., Pinto, M., Prieels, D., Ray, C., Smeets, J., Stichelbaut, F., Testa, E., 2014. Real-time proton beam range monitoring by means of prompt-gamma detection with a collimated camera. Phys. Med. Biol. 59, 1327–1338.

Romano F. , Cirrone G.A.P., Cuttone G., Di Rosa F., Mazzaglia S.E., Petrovic I., Ristic Fira A., Varisano A., A Monte Carlo study for the calculation of the average linear energy transfer (LET) distributions for a clinical proton beam line and a radiobiological carbon ion beam line. Physics in Medicine and Biology, 2014, 59: 2863-2882.

Rossi H.H., Specification of Radiation Quality, Radiat. Res. 10, 522 (1959).

Sanchez-Tembleque V. et al., “Evaluation of New Inorganic Scintillators for High Performance ToF PET Applications”, 2015 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), Conference Record.

Schaart, D.R., Charbon E., Frach T., Schulz V., “Advances in Digital SiPMs and their Application in Biomedical Imaging,” Nuclear Instruments and Methods in Physics Research A 809, 31-52, 2016.

Seifert S., van Dam H.T., Vinke R., Dendooven P., Löhner H., Beekman F.J., and Schaart D.R., “A Comprehensive Model to Predict the Timing Resolution of SiPM-Based Scintillation Detectors: Theory and Experimental Validation,” IEEE Transactions on Nuclear Science 59, 190-204, 2012.

Seifert, S., van Dam, H. T., and Schaart, D. R. (2012), 'The lower bound on the timing resolution of scintillation detectors', Phys Med Biol, 57 (7), 1797-814.

Smeets, J., Roellinghoff, F., Janssens, G., Perali, I., Celani, A., Fiorini, C., Freud, N., Testa, E., Prieels, D., 2016. Experimental Comparison of Knife-Edge and Multi-Parallel Slit Collimators for Prompt Gamma Imaging of Proton Pencil Beams. Front. Oncol. 6. doi:10.3389/fonc.2016.00156

Solevi, P., Muñoz, E., Solaz, C., Trovato, M., Dendooven, P., Gillam, J.E., Carlos Lacasta, Oliver, J.F., Rafecas, M., Torres-Espallardo, I., Llosá, G., 2016. Performance of MACACO Compton telescope for ion-beam therapy monitoring: first test with proton beams. Phys. Med. Biol. 61, 5149. doi:10.1088/0031-9155/61/14/5149

Sportelli G., Belcari N., Camarlinghi N., Cirrone G.A. P., Cuttone G., Ferretti S., Kraan A., Ortuno J.E., Romano F., Santos A., Straub K., Tramontana A., Del Guerra A., and RossoV. , First full-beam PET acquisitions in proton therapy with a modular dual-head dedicated system, Phys. Med. Biol., 59, pp. 43–60, (2014)

Sportelli G., Belcari N., Guerra P., Santos A., Low-resource synchronous coincidence processor for positron emission tomography, Nucl. Instrum. Meth. A 648, pp. S199–S201, (2011)

Sportelli, G., Belcari, N., Camarlinghi, N., Cirrone, G. a. P., Cuttone, G., Ferretti, S., Kraan, A., Ortuño, J.E., Romano, F., Santos, A., Straub, K., Tramontana, A., Guerra, A.D., Rosso, V., 2014. First full-beam PET acquisitions in proton therapy with a modular dual-head dedicated system. Phys. Med. Biol. 59, 43. doi:10.1088/0031-9155/59/1/43

SportelliG., Belcari N., Guerra P., Spinella F., Franchi G., Attanasi F., Moehrs S., Rosso V., Santos A., and Del Guerra A., Reprogrammable Acquisition Architecture for Dedicated Positron Emission Tomography, IEEE Transaction on Nuclear Science, 58, (3), pp. 695, (2011)

Tabacchini, V., Borghi, G., and Schaart, D. R. (2015), 'Time-based position estimation in monolithic scintillator detectors', Physics in Medicine and Biology, 60 (14), 5513-25.

Tabacchini, V., et al. (2014), 'Probabilities of triggering and validation in a digital silicon photomultiplier', Journal of Instrumentation, 9.

Testa, E., Bajard, M., Chevallier, M., Dauvergne, D., Le Foulher, F., Freud, N., Létang, J.-M., Poizat, J.-C., Ray, C., Testa, M., 2008. Monitoring the Bragg peak location of 73 MeV/u carbon ions by means of prompt γ-ray measurements. Appl. Phys. Lett. 93, 93506. doi:10.1063/1.2975841

Therrien, A. C., et al. (2014), 'Modeling of Single Photon Avalanche Diode Array Detectors for PET Applications', IEEE Transactions on Nuclear Science, 61 (1), 14-22.

Thirolf, P.G., Aldawood, S., Böhmer, M., Bortfeldt, J., Castelhano, I., Dedes, G., Fiedler, F., Gernhäuser, R., Golnik, C., Helmbrecht, S., Hueso-González, F., Kolff, H. v.d., Kormoll, T., Lang, C., Liprandi, S., Lutter, R., Marinšek, T., Maier, L., Pausch, G., Petzoldt, J., Römer, K., Schaart, D., Parodi, K., 2016. A Compton camera prototype for prompt gamma medical imaging. EPJ Web Conf. 117, 5005. doi:10.1051/epjconf/201611705005

Thirolf, P.G., Lang, C., Aldawood, S., v.d. Kolff, H.G., Maier, L., Schaart, D.R., Parodi, K., 2014. Development of a Compton Camera for Online Range Monitoring of Laser-Accelerated Proton Beams via Prompt-Gamma Detection. EPJ Web Conf. 66, 11036. doi:10.1051/epjconf/20146611036

van Dam H.T., Seifert S., Vinke R., Dendooven P., Löhner H., Beekman F.J., and Schaart D.R., "A comprehensive model of the response of silicon photomultipliers," IEEE Transactions on Nuclear Science 57, 2254-2266, 2010.

van Dam, H. T., et al. (2013), 'Sub-200 ps CRT in monolithic scintillator PET detectors using digital SiPM arrays and maximum likelihood interaction time estimation', Physics in Medicine and Biology, 58 (10), 3243-57.

van Dam, H. T., Seifert, S., and Schaart, D. R. (2012), 'The statistical distribution of the number of counted scintillation photons in digital silicon photomultipliers: model and validation', Phys. Med. Biol., 57 (15), 4885-903.

van der Graaf H., Bakker M., Chan H.W., Charbon E., Santagata F., Sarroc P. and Schaart D.R., "The Tipsy single soft photon detector and the Trixy ultrafast tracking detector," Journal of Instrumentation 8, C01036, 2013.

Varner G., Ruckman L., and Wong A., "The first version buffered large analog bandwidth (BLAB1) ASIC for high luminosity collider and extensive radio neutrino detectors", Nucl. Instrum. Meth. A, 591, pp. 534-545, (2008)

Vecchio S. , Attanasi F. , Belcari N., Camarda M., Cirrone G.A.P., Cuttone G., Di Rosa F., Lanconelli N., Moehrs S., Rosso V., Russo G., and Del Guerra A., A PET Prototype for "In-Beam" Monitoring of Proton Therapy , IEEE Transactions on Nuclear Science, 56, (1), pp. 51-56, (2009)

Venialgo, E., et al. (2015), 'Time estimation with multichannel digital silicon photomultipliers', Phys Med Biol, 60 (6), 2435-52.

Verburg, J.M., Seco, J., 2014. Proton range verification through prompt gamma-ray spectroscopy. Phys. Med. Biol. 59, 7089–7106. doi:10.1088/0031-9155/59/23/7089

Verburg, J.M., Testa, M., Seco, J., 2015. Range verification of passively scattered proton beams using prompt gamma-ray detection. Phys. Med. Biol. 60, 1019. doi:10.1088/0031-9155/60/3/1019

Yamamoto K, Yamamura K, Sato K, Ota T, Suzuki H and Ohsuka S 2007 Development of multi-pixel photon counter (MPPC) 2007 IEEE Nucl. Sci. Symp. Conf. Record 1094-1097