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2019-2023: cinco años de experiencia investigadora en terapia de protones en el centro de Protonterapia Quironsalud

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En la presentación se describirán las líneas de investigación en protonterapia seguidas en el Centro Quirónsalud desde su puesta en marcha hasta la actualidad, además de dar una visión general de la actividad investigadora presente y de las líneas futuras a desarrollar en el centro.

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A Deep Learning Approach to Proton Range Reconstruction from PET Activity Measurements

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Proton therapy is a radiation treatment that targets tumoral cancers more precisely than conventional radiotherapy. This is because most of the dose is deposited near the end of the proton range at the Bragg Peak. However, different factors such as gas regions in the body, patient movement, or short-term physiological changes can produce deviations in the dose deposition. In turn, this may lead to tumor undertreatment or damage to crucial organs. Therefore, it is crucial that these deviations are detected in a proton therapy treatment.

Among other methods, it is possible to use positron emission tomography (PET) to estimate the dose from the generated positron emission activity that the proton beams induce. To this end, a recent work from our group proposed using a precomputed patient-specific and treatment-specific Dose-Activity Dictionary (DAD). With this DAD, the positron activity measured using a PET scanner immediately after the treatment could be translated into a dose distribution. This method searches for the linear combination of cases that best reproduces the observed activities. However, the performance depends significantly on how the considered case is similar to the simulated ones.

In this work, we propose a model based on a 3D U-Net architecture that accurately predicts the deposited dose from the activity induced by new, non-simulated proton beams. The U-Net can do this by capturing the high- and low-level features relating activity to dose at different tissues and proton beam spot depths. This model consists of three encoder and decoder layers and is trained on 948 simulated activity-dose pairs from the DAD. The training is completed in 20 minutes using an NVIDIA V100 GPU, which is sufficiently fast considering that it would be trained on data from a CT scan obtained a day before the treatment.

Preliminary results show a similar relative error distribution with respect to the previous work, as well as range deviations under a millimeter. Moreover, no signs of overfitting have been observed. Other recent methods, such as diffusion models and vision transformers, are being studied to further

improve our model. This would increase the robustness of this approach, which shows promising capabilities for proton range verification.

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A novel stochastic model towards personalized dosimetry for transarterial radioembolization

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Background and purpose: Transarterial radioembolization (TARE) procedures treat liver tumors by injecting radioactive microspheres into the hepatic artery. Currently, there is a critical need to optimize TARE towards personalized dosimetry. This is crucial to transition TARE to a first-line treatment for unresectable liver tumors. To this aim, we present a novel MIcrosphere DOSimetry (MIDOS) stochastic model to estimate the activity delivered in three compartments: the tumor(s), normal liver, and lung.

Methods: MIDOS incorporates adult male/female liver computational phantoms with the hepatic arterial, hepatic portal venous, and hepatic venous vascular trees. Tumors can be placed in both models at user discretion. The perfusion of microspheres follows cluster patterns, and a Markov Chain approach was applied to microsphere navigation, with the terminal location of microspheres determined to be in either normal hepatic parenchyma, hepatic tumor, or lung. A tumor uptake model was implemented to determine if microspheres get lodged in the tumor, and a probability was included in determining the shunt of microspheres to the lung. A sensitivity analysis of the model parameters was performed, and radiation segmentectomy/lobectomy procedures were simulated over a wide range of activity perfused. Then, the impact of using different microspheres, i.e., 90Y (SIR-Sphere®), 90Y (TheraSphere®) and166Ho (QuiremSphere®), on the tumor-to-normal ratio (TNR) and lung shunt fraction (LSF) was analyzed.

Results: Highly vascularized tumors translated into increased TNR. Treatment results (TNR and LSF) were significantly more variable for microspheres with high particle load. In our scenarios with 1.5 GBq perfusion, TNR was maximum for TheraSphere® at calibration time in segmentectomy/lobar technique, for SIR-Sphere® at 1-3 days post-calibration, and regarding QuiremSphere® at 3 days post-calibration.

Conclusion: This novel approach is a decisive step towards developing a personalized dosimetry framework for TARE. MIDOS assists in making clinical decisions in TARE treatment planning by assessing various delivery parameters and simulating different tumor uptakes. MIDOS offers evaluation of treatment outcomes, such as TNR and LSF, and quantitative scenario-specific decisions. Future steps include translating the activity-compartment map into dose distributions, accounting for patient-specific vasculature models in normal liver and tumor.

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An Ionizing Radiation Acoustics Imaging (iRAI) system for dose monitoring in FLASH proton therapy

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Recently, the use of ultra-high dose rates (FLASH) in radiation treatments has emerged as a new promising modality, where a pulsated ultra-high dose rate (>40 Gy/s) is delivered in comparison to conventional radiation therapy (~0.05 Gy/s). FLASH radiotherapy has demonstrated an unprecedented ability to reduce healthy tissue toxicity while maintaining tumor control, as shown in several in vivo preclinical [1-6] and early clinical [7] studies performed mostly with electron beams. However, these studies have also revealed the associated risks FLASH-RT may have for clinical implementation without proper real-time "image-pulse" guidance to mitigate discrepancies between planned and delivered dose. The clinical translation of this technique is limited by the lack of proper dosimetric methods that can accurately measure, in real-time, the dose distribution in deep tissues as expected from modern proton to ensure its safe delivery in such high-risk mode [8,9].
On the other hand, FLASH radiotherapy using protons is expected to be the de facto therapy for deep-seated tumors and pediatric tumors, because it can combine FLASH tissue sparing with the spatial advantages of protons to shape the dose (Bragg peak) [10-12]. However, its associated higher risks with respect to conventional proton therapy without proper real-time "image-pulse" guidance results in barely a few preclinical studies [6,7] of the FLASH effect, and just one clinical study that has recently announced the completion of accrual for symptomatic bone metastases [13]. Therefore, there is an urgent need that demand investigating the unknown physical requirements (e.g., dose/pulse, dose/s, pulse width, beam size, etc.) of the proton beam to produce tumor control while sparing healthy tissues [14].
This work aims to overcome these two challenges by leveraging the concept of ionizing radiation acoustic dosimetry, where acoustic waves are generated following the absorption of pulsated high energy radiation. In this work, an ionizing radiation-induced acoustic imaging (iRAI) system has been developed to achieve real-time pulse-by-pulse 3D dose monitoring using FLASH dose rates with proton beams. Furthermore, the combination of iRAI with an ultrasound imaging system will facilitate the mapping of dose on anatomical structures [15,16].
This dual system has been tested at the Massachusetts General Hospital (USA) in tissue-mimicking phantoms. A description of the system and preliminary results will be presented. In addition, future work combining proton FLASH dosimetry and its correlation to tissue damage/toxicity response will be discussed to achieve a better understanding of the physical requirements to produce the FLASH effect during proton delivery.

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Aprendizaje deportivo asistido por sensores inerciales e inteligencia artificial

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Los sistemas de reconocimiento de la actividad humana (HAR) suelen utilizar datos inerciales recogidos con acelerómetros para modelar actividades de locomoción sencillas (correr, andar, subir y bajar escaleras, etc.). Es decir: el objetivo de los sistemas HAR es clasificar qué tipo de movimiento ha realizado el usuario. Sin embargo, estos desplazamientos pueden ser más complejos. Tal es el caso de la práctica de una actividad física, donde el deportista necesita aprender, siguiendo un enfoque de repetición psicomotriz, a dominar la ejecución de los desplazamientos implicados. En estos casos lo que interesa ahora es conocer si la ejecución del ejercicio o práctica es correcta o no.

En este trabajo de investigación nos preguntamos, por tanto, si los sistemas HAR pueden utilizarse también para modelar el nivel de pericia de una persona durante el aprendizaje de habilidades psicomotoras y deportivas. Para abordar esta cuestión, hemos seleccionado el dominio de las artes marciales, ya que la correcta ejecución de este tipo de disciplinas deportivas (sobre todo en el caso de la disciplina marcial japonesa del Aikido) depende en gran medida del aprovechamiento de las leyes y conceptos relacionados con la dinámica y la cinemática (movimiento circular, conservación de los momento de inercia y angular, torque, etc.). El otro arte marcial estudiado es el Kempo americano. En el caso del Aikido, se ha evaluado y medido varios movimientos de casi 200 practicantes de unos 20 dojos repartidos por toda la geografía española.

Nuestros resultados sugieren que transformar los datos inerciales brutos usando diferentes sistemas de representación (coordenadas esféricas, cilíndricas, etc.) puede ser significativo para ajustar el rendimiento psicomotor del usuario y permitir, por ejemplo, distinguir entre practicantes expertos y no expertos en las mencionadas artes marciales. Además de los sistemas de coordenadas mencionados, también se usaron cuaterniones. Estos números hipercomplejos, aunque típicamente empleados en robótica, juegos de ordenador y navegación aeroespacial, permiten representar y operar con orientaciones y rotaciones en el espacio tridimensional de manera más elegante y eficiente (reducción de dimensiones).

Para inferir el nivel de rendimiento de los participante, se han utilizado y comparado dos alternativas modernas en el ámbito del aprendizaje-máquina. La primera de ellas está basada en la extracción de características de series de tiempo. La otra en una red neuronal convolucional aleatoria.

Aunque nuestra investigación se ha centrado en el ámbito de las artes marciales y la Física deportiva, la metodología seguida sería perfectamente trasladable a otros ámbitos relacionados con otras áreas de la Física aplicada a la Salud (p.e., rehabilitación, entrenamiento personal, etc.).

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Building a low-field dental MRI scanner

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Magnetic Resonance Imaging (MRI) of hard tissues is challenging due to the short lifetime and low strength of their resonance signals, due to strong spin-spin couplings and proton escarcity. Thus, the impact of MRI on some dental applications continues to be minor compared to X-rays techniques [1]. However, the latter employ ionizing radiation and only detect hard tissues.

MRI pulse sequences, such as Zero Echo Time, have demonstrated their potential for dental imaging [2], but they typically rely on extremely expensive hardware. A clinically viable MR-based solution must be competitive also in terms of cost, which imposes the use of weak magnetic fields (B0<0.3T). However, the signal-to-noise ratio of the signal scales as SNR α B07/4, so the quality of low-field reconstructions can be compromised unless every step of the process is exquisitely optimized.

Our group has been pearheading this challengue, reporting the first 3D MRI images of ex vivo tooth samples featuring soft and hard tissues simultaneously at sub-Tesla magnets [3]. This achievement was reached in a home-made, pre-medical MRI scanner (Fig. 1) with Zero Echo Time sequences. We have also reported on caries diagnosis, enamel demineralization or fast tooth thresholding (Fig. 2). Moreover, to accelerate image acquisitions, we have developed, patented and succesfully tested a slice-seletion method with Zero Echo Time [4].

The next step is to translate this proof of concept to a system compatible with clinical life, which poses major physical and engineering challengues. The compromise between system weight and achieving a size large enough for human anatomy means magnetic fields can be strongly inhomogeneous in the región of interest, mandating advanced reconstruction strategies that incorporate spatial knowledge of the magnetic field. Presently, our team has finished building of the first dental, low cost MRI scanner reported until now (Fig. 3). In this work, we present the system and the first images of phantoms and ex vivo dental pieces (Fig. 4), a milestone in the road towards clinical application.

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Bunker Shielding Monte Carlo Simulation for the HUMV Proton Therapy Facility

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The Spanish Nuclear Safety Council (CSN) demands a Radiation Protection (RP) study for the commissioning and operating authorization of the BeamPro 250 cyclotron at Valdecilla Hospital (HUMV). In response, the Physics Institute of Cantabria (IFCA) has developed a Geant4-based simulation tool called BUNSHI. Given the machine's geometry and anticipated annual workload, this tool accurately estimates specific shielding conditions and Radiation Protection occupational zones, aligning with international safety standards and legal requirements. This paper showcases the application of the BUNSHI code to the future Proton Therapy facility at Valdecilla Hospital.

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Characterization of novel silicon microdosimeter using the IBIC technique

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Proton therapy is one of the radiotherapy options currently available, which has significant advantages over conventional photon therapy. In order to assess the beam dose delivered to the patients at the cellular level during the hadrontherapy treatments, the Instituto de Microelectrónica de Barcelona (IMB-CNM) has designed and manufactured a new generation of silicon microdosimeters. The microdetectors are cylinder-shaped with a size comparable to that of human cell nuclei (20 μm-thick, 26 μm-diameter). These sensors have been characterized at the microbeam line of the Centro Nacional de Aceleradores (CNA) using the Ion Beam Induced Charge (IBIC) technique with a 1.17 MeV focused proton beam.

Taking advantage of the fact that our system allows the acquisition of data in "event-by-event" format (List mode), a program has been developed to obtain energy spectra from any part of the detector and for any desired dose range. By means of a model proposed in a previous work [1], based on the shape of the energy spectrum to evaluate the radial dependence of the Charge Collection Efficiency (CCE), the evolution of the CCE as a function of proton fluence has been studied for proton fluences up to $1.7 \times 10^{12} p \cdot cm^{-2}$ (~ 16 kGy).

The pristine microdosimeter presents a nearly perfect CCE profile, showing 100% CCE from the center to a radius of 10 microns, and dropping sharply to zero as the edge of the detector is approached. Moreover, the active volume of the sensor is ≈ 95%. This behaviour has been observed up to doses about two orders of magnitude higher than those used in a clinical protontherapy treatment (~ 50 Gy), which indicates that the lifetime of these sensors is long enough for this application. For higher doses the transport properties of the microdosimeters show a progressive degradation, with the CCE drop being more pronounced at the edge of the detector, probably due to the presence of a lower electric field in this area, and propagating towards the center as the proton fluence increases.

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Design of an X-ray irradiator with FLASH dose-rate capabilities for preclinical research

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Introduction
The practice of radiation oncology has undergone a substantial improvement in all the stages of the radiotherapy process. However, the progress in our understanding of radiobiological processes has fallen behind. Take for instance FLASH therapy, whose underlying biological mechanisms still remain unknown [1]. An improvement of the accuracy, availability, and reproducibility of radiobiology experiments at both conventional and FLASH conditions, would greatly help to fill this gap. X-ray irradiators for preclinical research are becoming increasingly popular in cancer research and specially in radiobiology experiments, representing an alternative to traditional gamma irradiators with several advantages, such as their relative low cost, ease of use, smaller certification/authorization burden, and good control of dose rate [2]. Therefore, a FLASH capable X-ray irradiator would be of interest [3,4].
Materials and methods
In this work, we propose a new concept of small animal X-ray irradiator based on a conventional imaging X-ray tube for preclinical research [5]. We assessed its feasibility to deliver FLASH dose rates. Our design puts the imaging X-ray tube into a shielded cabinet, which makes the system affordable and suitable to use without disruption in existing laboratories and with minimum regulatory burden. Two conventional 150 kVp X-ray tubes were characterized with Gafchromic films for dose rates and dose uniformity. Monte Carlo simulations were also performed to model the irradiator, and the efficiencies of the tube and dose rates (with and without additional filtration) were calculated and compared with measurements. The feasibility of achieving ultra-high dose rates was determined from the rating charts provided by the manufacturer and measurements.
Results
The small animal irradiator proposed in this work was able to deliver conventional dose rate irradiation (0.5-1 Gy/min) at 150 kVp at 20 cm distance with minimum amount of filtration. FLASH irradiations (a 10 Gy dose delivered at >40 Gy/s) were also possible at the maximum capabilities of the tubes by placing the samples at the closest distances from the sources.
Conclusion
An irradiator based on a standard imaging X-ray tube with FLASH dose-rates capabilities for preclinical research is feasible. A prototype has already been built by SEDECAL Molecular Imaging, one of the largest manufacturers of X-ray portable imaging systems worldwide.

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Estimación de la dosis biológica en el fraccionamiento espacial de haces de iones pesados.

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El fraccionamiento espacial de la dosis en radioterapia utilizado desde los inicios de la práctica clínica, sobre todo como tratamiento paliativo, está ganando protagonismo en la investigación de nuevas técnicas terapéuticas. Aprovechando las instalaciones de investigación de los grandes aceleradores, se comenzó a probar una variante de microhaces de fotones, encontrando resultados muy significativos en la preservación del tejido sano y posibilitando aumentar la dosis en el sitio tumoral.

En la actualidad se continúa investigando esta técnica, llevándola a instalaciones de producción de fotones de forma convencional [1], a los aceleradores de electrones de muy alta energía [2] y a partículas que muestran una distribución de dosis más favorable en profundidad como resultado del pico de Bragg, protones y iones. [3]

Este trabajo evalúa el fraccionamiento espacial con haces de carbono y neón, utilizando el código de simulación Monte Carlo GATE (Geant4) para obtener las distribuciones espaciales óptimas de estos dos iones. Se estudia, la dosis física, la transferencia lineal de energía y se propone un modelo basado en la respuesta biológica del tejido para estimar la dosis biológica.

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Estudios preliminares del efecto radiosensibilizador de nanopartículas de oro para hadronterapia

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El uso de la nanotecnología ha revolucionado el mundo de la medicina y está cambiando la forma en que se combaten y se tratan varias enfermedades. Se utilizan nano-sensores para diagnóstico, nanopartículas para administrar medicamentos o nano-dispositivos para regenerar tejido dañado. Desde hace más de una década también se estudia el uso combinado de nano-partículas y radiaciones en terapias contra el cáncer para aumentar la eficacia de estos tratamientos.

Las nanopartículas metálicas de alto número atómico han demostrado experimentalmente ser potenciales radiosensibilizadores tumorales. Las células tumorales se cargan previamente con estas nanopartículas, mejorando los efectos radiobiológicos de la radiación aplicada. Esta técnica podría dar lugar a una reducción de la duración de los tratamientos y de la dosis depositada en los tejidos sanos. Este efecto se ha observado en experimentos radiobiológicos in-vitro e in-vivo tanto con rayos-X, haces de electrones y haces de protones.

Estudios de simulación concluyen que el mecanismo físico detrás de la mejora de la dosis con rayos-X se basa en un aumento de los fotoelectrones, electrones Auger y rayos-X de fluorescencia. Esta radiación secundaria generada de corto alcance provoca un aumento de la dosis local en las células tumorales. Sin embargo, los mecanismos físicos detrás de la mejora de la dosis inducida por nanopartículas con haces de protones y electrones parecen ser controvertidos y dependientes de la distribución de dosis con una resolución de unos pocos nanómetros, de la geometría del problema y de procesos químicos y biológicos. Para protones la información disponible es mucho menor que para fotones, y en general es difícil comparar los resultados encontrados en la bibliografía debido a que las características de las nanopartículas y las condiciones de haz utilizadas son muy diferentes entre los distintos estudios. Por ello, se necesitan experimentos sistemáticos en función de algunas de las variables involucradas en el problema (características de las nanopartículas, concentraciones...) que nos permitan por un lado entender mejor los mecanismos que potencialmente inducen una mejora de la eficiencia de la radiación a nivel físico, químico y biológico, y por otro lado definir unos parámetros óptimos para la aplicación de esta tecnología. Así como, evaluar la eficiencia de la tecnología en casos concretos dónde su uso puede ser más beneficioso como por ejemplo en tratamientos de cáncer de cerebro y próstata.

En este trabajo presentamos estudios de puesta a punto para abordar el efecto radiosensibilizador de nanopartículas de oro, así como resultados preliminares obtenidos en un primer experimento radiobiológico realizado en la línea de radiobiología del ciclotrón del Centro Nacional de Aceleradores de Sevilla con protones.

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Experiencia investigadora, asistencial y docente en la instalación de protonterapia de la Clínica Universidad de Navarra

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En 2020, tras concluir el comisionado de la instalación de protonterapia, la CUN empezó los tratamientos clínicos de pacientes, dentro de un proyecto asistencial, investigador y docente. En esta charla se discuten algunos aspectos relacionados con la investigación en física médica que tienen interés por su aplicación clínica, involucrando aspectos de procesado de imagen médica, cálculo de la dosis absorbida mediante Monte Carlo, y modelos de eficacia biológica de la dosis depositada por haces de protones. Asimismo se mencionarán aspectos docentes y de actividad asistencial.

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Experimental tests of the scanner prototype for imaging with protons developed at IEM-CSIC

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Proton therapy requires precise knowledge of the patient's anatomy to guarantee an accurate dose delivery [1]. X-ray computed tomography (CT) images are used nowadays to calculate the relative stopping power (RSP) needed for proton therapy treatment planning [2]. Recent studies indicate that tomographic imaging using protons has the potential to provide a more accurate and direct measurement of RSP with a significantly lower radiation dose than X-rays [3].
The proton CT (pCT) scanner prototype developed at IEM-CSIC is composed of a tracking system of two double-sided silicon strip detectors, and the CEPA4 detector as the residual energy detector. Our pCT scanner prototype was tested at the Cyclotron Centre Bronowice (CCB) facility in Krakow,

Poland during three experimental campaigns conducted in 2021 and 2022. Radiographs were generated from pixelated detectors. Volumetric phantoms composed of matrices made of PMMA with inserts of air, ethanol, water, Delrin, Teflon, and aluminum were imaged. The radiographs displayed great fidelity with respect to the shapes of the studied samples. The spatial resolution of this proton imaging scanner prototype is better than 2 mm and the MTF-10%=0.3 line pairs per mm [4]. We are currently engaged in the data analysis of new samples for the study of radiographs and tomography scans using proton beams with energies up to 200 MeV.
At this conference, we will present preliminary findings, including the imaging capabilities of our prototype, showcasing its potential applications for the future of medical imaging detectors.

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First experimental hybrid Compton-PET imaging for ion-range monitoring in hadron therapy

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Hadron Therapy has advantages with respect to conventional radiotherapy because of the maximization of the dose at the Bragg peak. As a drawback, and because of different systematic uncertainty sources, a quasi-real time monitoring for ion-range verification is required to reduce safety margins and thus enhance its potential benefits. Two of the most promising methodologies for in-room real-time monitoring are positron-emission tomography (PET) and prompt-gamma imaging (PGI). The PGI technique is well suited for real-time monitoring due to the prompt-nature of the emitted radiation [Ler22], whereas PET imaging can provide tomographic and functional information relevant to study physiological processes and tumor response.
We have implemented a hybrid imaging monitoring based on the combination of both PGI and PET within the same system [Bal22], thus exploiting the advantages of both techniques. This is accomplished by means of an array of Compton cameras in a twofold front-to-front configuration operating in synchronous mode.
In this contribution I will present a summary of a proof-of-concept experiment performed at CNA-Sevilla and first results from the HIT-Heidelberg facility, where clinical conditions were used to validate the hybrid technique with protons, alpha and C ion beams.

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First experimental microdosimetry 2D-maps in proton therapy

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Around 40 % of people surviving cancer do so because of radiotherapy. For improving this statistic, treatments based on hadron radiotherapy (HT) are allowing a better protection of the organs at risk by conforming the dose around the tumor target [1]. Nevertheless, some toxicities have recently been reported, being hypothesized that they can be due to the fact that hadrons deliver higher linear energy transfer (LET) that may generate collateral damages. Additionally, there is a rising interest in the medical-physics community in placing the enhanced LET of the beam within the tumour or removing it from the most sensitive normal structures around [2]. Thus, the experimental assessment of LET with high resolution would be a powerful tool to achieve optimized treatments. However, there are no radiation sensors capable of measuring the LET 2D-maps during treatments due to the technology complexity associated.

To face this challenge, we have created novel silicon 3D-cylindrical microdetectors (25 μm diameter, 20 μm depth, and 200 μm pitch) specifically designed for this purpose [3-5]. In particular, the present work shows four new multi-array configurations of these sensors (microdosimeters), first of its kind, enable of quantifying the LET 2D-maps in clinical conditions and covering a wide range of resolutions, namely: (i) a 11×11 array covering a 2 mm×2 mm radiation sensitive area [2] and (ii) a linear array of 3 × 3 microdetectors with a total surface of 0.4 mm×12 cm [3] (Fig. 1); (iii) a 5×25 pixel configuration covering an area of 1.9 cm × 0.1 cm and (iv) a 1×10 strip layout of 5.1 cm × 0.1 cm [4] (Fig. 2). To the best of our knowledge, these are the largest radiation sensitive surface covered with microdosimeters by now.

These systems have been tested in the the Accélérateur Linéaire et Tandem à Orsay facility (ALTO, France) by irradiating them with monoenergetic proton beams from 6 to 20 MeV at clinical-equivalent fluence rates to verify their potential application in the medical physics field (Figure 3). Likewise, we have irradiated some of these sensors in the the Orsay Proton Therapy Centre (CPO, France) with clinical fluence rates (~ 108 cm-2·s-1). The microdosimetry 2D-maps were obtained with a spatial resolution of 200 μm, the highest achieved so far at different positions of the Bragg curve by using a water-equivalent phantom (Figure 4) [5]. We will show the results of both sets of experiments. All the experimental results were crosschecked with Monte Carlo simulations and also compared to literature results (Figure 5).

We have demonstrated for first time that we may obtain microdosimetry distributions in two dimensions, which would be very useful for clinical conditions, e.g., close to organs-at-risk where we may have heterogeneous LET distributions, distal edges, for further voxel-by-voxel optimization treatments, etc. They can be used clinically as microdosimeters for measuring the LET distributions and, thus contributing to the optimization of HT treatments.

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First in-vitro proton FLASH irradiation with a clinical synchrocyclotron on healthy and cancerous lung cell lines

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Purpose
FLASH radiotherapy (RT) is a promising technique in radiotherapy, where ultra-high dose rates (>40 Gy/s) have demonstrated, in *in-vitro* and animal studies, a protective effect on healthy tissues, while maintaining isoefficacy with conventional (CONV) RT in treating tumors. We performed several biological essays with proton beams at FLASH vs CONV dose rates, using healthy lung fibroblasts and lung cancer cells to study potential biological mechanisms that could be at the root of the FLASH effect.

Materials and methods
Healthy lung fibroblasts (IMR90) and lung adenocarcinoma cells (A549) were cultured in DMEM supplemented with 10% FBS under standard culturing conditions. Before irradiation, 9.6M cells were collected and pellet in eppendorf vials and irradiated with proton beams at the IBA proteusOne in Quironsalud.
FLASH irradiations (>800 Gy/s average dose rate, dose range 0-12 Gy) with a 230-MeV beam were performed at the synchrocyclotron room of the facility using a portable 3D-printed system to degrade the beam and position the samples. CONV rate irradiations (<0.2 Gy/s, dose range 0-16 Gy) were performed in the treatment room using a SOBP (depth 2 cm, modulation 1 cm).
In-vitro clonogenic study (A549) and viability assay (IMR90) were performed by seeding 300 irradiated cells. 7 days later, cells were fixed, stained with crystal violet and number of colonies/viable cells quantified. Data was analyzed with the linear quadratic model. Irradiation-induced cell cycle arrest was studied via flow cytometry 48h post-radiation. Dose-dependent expression of p21 protein (associated with cell cycle arrest) was studied via immunofluorescence (IF) on irradiated cells fixed and permeabilized 48h after irradiation.

Results
Preliminary analysis of the results suggests little to no differential biological effects related with dose rate. Clonogenic assays for the A549 cells and viability study for the IMR90 cells showed no differential dose-rate effect in the biological response (Fig. 1). Cell cycle analysis via flow cytometry and IF showed G1 arrest rates and p21 induction probability both increase with dose for healthy and tumor cells, with no significant dose-rate dependence observed (Fig. 2).

Conclusions
The irradiation system, designed and fabricated in-house, made FLASH irradiation of biological samples possible in a clinical proton therapy center without any hardware or software system modifications. Equivalent biological results were obtained in an *in-vitro* study at normoxic conditions between conventional and FLASH dose rate protons for both healthy fibroblasts and lung cancer cells.

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IA, radiomics, y radiogenomics

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IMAS: a total-body PET with TOF and DOI capabilities

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Total-Body Positron Emission Tomography (TB-PET) technology and designs have become very popular in recent years. The advantages of these systems are many, pinpointing the high sensitivity achieved by their long axial FOV and eventually TOF, and the capabilities to simultaneously study the kinetics of multiple organs. Most of TB-PET designs and implementations are based on LYSO crystal pixels without DOI. In this work we present a TB-PET system based on semi-monolithic crystals and, therefore, simultaneously enabling TOF and depth of interaction capabilities. Furthermore, the design named IMAS, makes use of a reduction of signals without compromising performance. We carried out exhaustive simulation studies of the system geometry, based on 5 rings of 10 cm in the axial direction each, and gaps of about 5 cm, with a total axial length of 71.4 cm. These studies confirm the good performance of the system in terms of spatial resolution, sensitivity and other relevant parameters. Moreover, the system has been constructed and installed at the largest hospital in our region, La Fe. Very preliminary experimental tests, already predict a homogeneous spatial resolution below 4 mm in the whole FOV. The system sensitivity is 7.6% with a source at the CFOV. The detectors reached a TOF of about 350 ps. We aim to report a full characterization of the scanner during the conference.

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Imaging Ac-225 with MACACO III Compton camera

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The IRIS group at IFIC is testing a Compton camera for the visualization of the radiopharmaceutical in the patients body in targeted radionuclide therapy (TRT) assessment.

The prototye, MACACO III, is composed of three LaBr3 monolithic scintillator crystals coupled to SiPMs arrays, and it employs the ASIC VATA64HDR16 driven by the AliVATA data acquisition board for the readout. To enhance the system's efficiency an enlarged second detector configuration has also been developed by combining four crystals per plane.

Initial successful tests were conducted in collaboration with La Fe Hospital (Valencia) to image phantoms filled with FDG and 131I-NaI, as well as thyroid cancer patients. Within the ICOR project (ASFAE/2022/019) the evaluation of the system has now been extended to include alpha emitters. Simulation studies have indicated the potential for imaging Ac-225 and a measurement campaign has been carried out at the Léon Bérard Centre (Lyon). Preliminary images of a phantom filled with Ac-225 have been obtained.

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Improved breast models for whole-body numerical phantoms

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Simulations of acquisitions in medical imaging techniques such as SPECT, PET, CT, Ultrasound, etc. is a fundamental tool in medical physics research. One of the important aspects of the simulation

procedure is the use of the most realistic numerical models of the human body possible. In this regard, it is very helpful for these models to be segmentated in tissues and organs so that specific physical properties can be accurately inserted in the phantoms. The principal limitation for many applications is the availability of a large set of those detailed models.

One of the most commonly used numerical human phantoms, is the XCAT phantom simulator, developed by Duke university researchers. The anatomy in XCAT is defined using non-uniform rational b-splines (NURBS) and includes thousands of defined structures as well as parameterized models for the beating heart and respiratory motions. Its capacity to generate dynamic images allows the simulation of different medical images techniques that would not be possible with static models. In XCAT users can define numerous parameters to create normal and abnormal anatomical and motion variation, with specific properties and geometries. This flexibility makes it ideal for creating a large database of models for use in simulations. However the XCAT models are severely lacking in certain areas of the body, such as the breasts. Real breasts are composed of ducts, adipose tissue, lobules, etc. whereas the XCAT models do not show any internal structures.

On the other hand, the VICTRE package is a software developed as part of the Virtual Imaging Clinical Trials for Regulatory Evaluation (VICTRE) project of the Food and Drug Administration (FDA) in the USA. The VICTRE tools enable creating realistic breast phantoms and provide a complete simulated imaging chain for mammography and digital breast tomosynthesis, and it is an accessible tool. It allows modeling breast with different sizes and different proportion of fat and fibroglandular tissues.

In this work, we took advantage of the advanced image coregistration techniques provided by the SimpleITK python library to incorporate the VICTRE breast models into the full body XCAT phantom. We were able to generate female full body phantoms with realistic breast models (Fig. 1) which could be used for numerical simulations in the torso area. Some of these simulations include cardiac ultrasonography and positron emission mammography. The properties of the phantoms, and their capabilities will be described, as well as some metrics of the performance of the corregistration procedure.

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Introducing AMBER (Agent-based Modeling of Biophysical Evolution after Radiotherapy): a computational model for tumor response to radiation

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The efficacy of radiation therapy in oncological treatment depends on multiple interrelated physical, chemical, and biological effects. Agent-based computational models have emerged as invaluable tools for elucidating these intricate interactions, although existing models predominantly rely on absorbed dose as the sole metric for predicting tumor response. Mechanistic models that incorporate tumor microenvironmental factors into the biological response to radiation are therefore necessary.

To address this gap, we introduce AMBER (Agent-based Modeling of Biophysical Evolution after Radiotherapy), a novel hybrid computational framework that synergistically combines agent-based and continuum approaches within a voxelized geometry. AMBER is engineered to simulate four fundamental mechanisms governing tumor dynamics: (i) cellular proliferation and migration, (ii) microenvironmental oxygenation, (iii) angiogenic signaling, and (iv) cellular fate determination. Specifically, AMBER employs Gamma-distributed cellular division times within each voxel and diffusive migration to adjacent voxels. Oxygen distribution is calibrated through sub-voxel simulations based on vessel density and cellular crowding, represented by a Beta distribution. Angiogenesis is modeled as a directed random walk influenced by vascular endothelial growth factor (VEGF) gradients and

cellular crowding. Cellular vitality, a composite metric, is evaluated at each time step to categorize cells as either cycling, quiescent, or undergoing apoptosis/necrosis.

Radiation effects are incorporated using dose metrics obtained from the TOPAS Monte Carlo toolkit, with cell death modeled as a dose-dependent phenomenon following a log-normal time distribution. AMBER is thus uniquely positioned to simulate the impact of fractionated radiation doses on tumor dynamics, taking into account both microenvironmental and radiosensitivity variables. Preliminary results, depicted in Figure 1, demonstrate the capability of the model to simulate the effects of 6 MeV gamma irradiation over a five-day course on both cellular count and tumor volume.

AMBER is designed as a modular piece of code thought to be extended, facilitating the future integration of high-fidelity radiation bioeffect models such as TOPAS-nBio, as well as models elucidating DNA damage and repair mechanisms. This makes AMBER a versatile and comprehensive tool for advancing our understanding of the complex interplay between radiation therapy and tumor biology.

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Irradiation of cell samples with laser-generated X-rays and protons

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During recent years the relevance of dose rate, in addition to total dose, has been recognized to understand the response of biological systems to ionizing radiation. Particle sources based on ultra-intense laser-plasma interactions offer unique conditions to apply instantaneous dose rates orders of magnitude larger than classical accelerators. We present an ongoing research program on radiation effects of laser-generated X-rays and protons on living cells.
A stabilized X-ray source has been realised at the Laser Laboratory for Acceleration and Applications (L2A2, Santiago de Compostela). A 30 fs pulsed laser with 1 mJ beam energy at 1 kHz shot rate is focalized on a rotating copper plate. It generates a bremsstrahlung spectrum at low X-ray energies (up to some tens of keV). This source has been used to apply a total dose of 3-8 Gy to 36 monolayer cell cultures of a human adenocarcinoma (A549) which were prepared at the close-by Instituto de Investigación Sanitaria (IDIS). At 10 cm target distance the irradiation time per sample is about 30-120 s. The applied dose is measured with radiochromic film. In addition, an ionization chamber has been implemented for real-time control.
Our first experiment on biological effects of laser-accelerated protons has been recently run at Centro de Láseres Pulsados (CLPU, Salamanca). A three-axis controlled wheel, developed by IGFAE, has been applied for the precise positioning of 808 individual targets per vacuum cycle in the focal spot of the VEGA-3 laser (1 PW, 27 J at 1 Hz pulse rate). A magnetic energy selector, developed by i3M and previously tested at the 18 MeV cyclotron of Centro Nacional de Aceleradores (CNA, Sevilla),

has been implemented to obtain a quasi-monoenergetic proton beam which was conducted through a thin vacuum window. A total of 27 cell samples, prepared by Instituto de Biología Funcional y Genómica (IBFG), have been exposed to tens of nanosecond proton pulses accumulating total dose values between 3 and 8 Gy.
In addition to first results we will highlight the manyfold, technological and logistic challenges of the two experimental campaigns which, on the national level, have been the first combining laser-particle sources with biological sample manipulation. The aim of our research program is to compare the cellular effects of ultra-short, pulsed sources from high-power laser-plasma interactions with continuous beam facilities such as clinical linacs, proton therapy centers, or external accelerator beamlines.

The authors would like to thank the Spanish Center of Pulsed Lasers (CLPU) and the members of the Consortium (Central Government, Regional Government of Castilla y Léon and Universidad de Salamanca) for considering experiment 00562-0101 as a strategic proposal that develops new potentialities for CLPU and, therefore, finance the access to its facilities, as well as to acknowledge the results obtained with its petawatt laser t system (VEGA-3) and its scientific and technical assistance. Supported by the Government of Castilla y León under the project CLP263P20 “Transport and manipulation of particles in laser accelerators: New scenarios in flash radiotherapy (TYMPAL), co-financed with FEDER funds. i3M received funding by Generalitat Valenciana, ref. CIAICO/2022/008 and EDGJID/2021/204.

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Metasurface of capacitively-loaded split rings for field homogenization in a 7 T MRI birdcage coil

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This work is part of an interdisciplinary research that joins the area of electromagnetic metamaterials and the area of magnetic resonance imaging for medical imaging. Ultra-high field magnetic resonance imaging systems provide an increased signal-to-noise ratio and resolution in comparison with high field systems, and the only drawback of ultra-high field systems is the inherent inhomogeneity of the radiofrequency excitation field. The transmit field B1+ in a 7 T birdcage coil is inherently inhomogeneous due to the effects of wavelengths on tissue. In the literature, there are several approaches addressing the issue of homogenizing this field. This work investigates the homogenization of this field through metasurfaces that consist of a two-dimensional planar array of capacitively loaded conducting rings. Electromagnetic simulations are carried out with the software CST Studio Suite for a 7 T birdcage loaded with metasurfaces to validate the proof-of-concept. The metasurfaces are placed in the intermediate space between the head model and the birdcage on either side of the head. The periodical structure of this type of metasurface supports magnetoinductive waves because of the mutual inductive coupling existing between the elements of the array. The analysis takes advantage of this coupling and exploits the excitation of a standing magnetoinductive wave across the arrays, which creates a strong local field that contributes to homogenize the field of the birdcage. The presence of the arrays does not detune the birdcage, so that they can be used with commercial birdcages that operate both to transmit and to receive. The figures show screenshots of the implementation in CST of the model under study and the results of the simulation for the transmit field B1+ in the absence and in the presence of the metasurfaces.

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Microdosimetric Kinetic Modeling and Clonogenic Data in Clinical RBE Assessment

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To evaluate the impact of various radiation types on biological damage, the Relative Biological Effectiveness (RBE) is defined as the ratio of doses required to produce a given biological response (endpoint) between the radiation source under study and a reference radiation type, typically photons. To potentially account for this in clinical practice, phenomenological and mechanistic models have been proposed to determine the RBE in particle therapy, such as the Microdosimetric Kinetic Model (MKM). The MKM introduces the concept of "domain" linked to the maximum distance over which sublethal lesions can interact, leading to lethal lesions and cell death. The size of the cell nucleus is also relevant to characterize how many lethal and sublethal lesions can be induced by radiation and at what point a lethal lesion is warranted from a given radiation.

Clonogenic experiments are important for this purpose because they determine the percentage of cells that keep their mitotic viability after exposure to ionizing radiation. The Particle Irradiation Database Ensemble (PIDE), developed at the GSI Helmholtz Center (Germany), is a database that provides data on irradiation conditions, the ion used, cell line information, and the parameters of the linear-quadratic model (LQ) for different clonogenic experiments. By analyzing these data derived from experimental campaigns with protons, alpha particles, or carbon ions, two key quantities of the MKM can be obtained: the statistical distribution of domain radius values and the cell nucleus radius. These parameters are used by the MKM to obtain the linear parameter (α) of the LQ model for a given radiation type.

In this work, survival curves obtained from clonogenic assays were employed to determine the values of cell-specific parameters mentioned above in a systematic way. This determination represents an approach to include further information on the cell line-specific radiosensitivity. Our results showed large variability among different cell lines [1], illustrating the importance of intrinsic response to radiation of different biological systems when determining RBE. The considerable deviations among groups and experiments raise the question of how valuable RBE models based on clonogenic assays are for the clinics. Also, the significant number of nuances to be considered in these models and the lack of connection with realistic biological processes in the clinical response to radiation contribute to challenging the translatability of clonogenic survival data in the clinic.

It is likely that a significant portion of the reported variability in PIDE comes from the fact that multiple institutions and laboratories carried out these experiments in different experimental conditions. Hence, standardized methods to perform clonogenic assays for different particles and energies, especially clinical ones, may help to decrease the variability observed in experimental results, leading to a better RBE assessment for clinical practice.

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Monte Carlo simulation of the water equivalent ratio for therapeutical proton beams in cortical bone

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The use of energetic ions in radiotherapy, including protons, has several advantages when compared with conventional treatments. The great targeting precision of ion beams comes from their reduced angular scattering, as well as the fact that they deposit the main part of their energy at the end of their trajectories, giving place to the depth-dose curve known as the Bragg peak. These facts make

protons optimal particles to treat deep-seated tumors while minimizing the damage on the surrounding healthy tissues. In addition, physics is essential in the task of understanding not only the cellular damaging processes, but also the fundamental aspects involved in the energy deposition by primary ion beams in biologically relevant materials[1].
This work shows the simulated Bragg curves for swift proton beams, for different energies characteristic of protontherapy, interacting with biologically relevant materials such as liquid water[2] and cortical bone[3], with the aim of determining the relevant quantity known as water equivalent ratio (WER). The depth-dose distributions are obtained with the simulation code SEICS (Simulation of Energetic Ions and Clusters through Solids), which has been developed by our research group. This code considers the energy loss due to inelastic collisions, as well as elastic collisions, the fragmentation nuclear reactions, and the projectile electron capture and loss processes. It uses accurate stopping powers and energy-loss straggling values obtained from a detailed description of the electronic excitation spectrum of the condensed-phase targets, accounted for by the MELF-GOS (Mermin Energy-Loss Function–Generalized Oscillator Strengths) method[2].
Simulations for relevant energies in protontherapy (of tens and hundreds of MeV) are compared with reference simulations and experimental data for both Bragg curves and WER values (Figs. 1 and 2, respectively) for liquid water and solid cortical bone, showing a good agreement.
This work underlines the relevance of Monte Carlo simulations for analyzing the proton beams depth-dose distributions for the development and improvement of protontherapy treatments.

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Monte Carlo simulations for in vitro radiopharmaceutical experiments using the TOPAS toolkit

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Radiopharmaceutical therapy (RPT) is a novel modality of oncology treatments that uses radiolabeled agents affine to biomolecules overexpressed in tumor cell environments. RPT has the potential to improve outcomes for oncologic patients with distant metastases compared to external radiation therapies. This is due to its ability to target specifically cancerous cells while sparing healthy cells. In vitro radiopharmaceutical experiments are crucial because they provide a controlled environment to examine the interactions between radiolabeled compounds and biological systems.

Our research group has developed a computational extension to the TOPAS Monte Carlo toolkit to model irradiation experiments involving in vitro cell adherent layers. We have built a new geometry for monolayer cells, assumed as identical cylinders in a regular layout. Also, our tool simulates the time evolution of radioactive decay, particularizing results in time steps for the entire decay chain of a given radionuclide. Thus, the extension recreates the temporal evolution of irradiation conditions by specifying the radionuclide, the initial activity, the number of time steps to be simulated, and the duration of the experiment.

Typically, in vitro experiments exploring the effects of RPT have three separate processes of relevance: the injection of the radionuclide into the culture medium, the binding process of the radiopharmaceutical to a receptor on cell membranes, and the internalization process into the cell

cytoplasm. Our simulations are correspondingly divided into three static stages: (i) when the radiopharmaceuticals are diluted in the medium, for which we consider a uniform distribution of sources; (ii) a second stage when the culture is washed out and the medium replaced but no internalization has taken place yet, for which radioactive emissions happen from cell membranes; and (iii) a final stage with only internalized radioactivity. With this approach, the simulation provides dose and dose rate evolution along the experiment.

Radiopharmaceutical in vitro experiments with pancreatic ductal adenocarcinoma (PDAC) cell lines, published by Kasten et al. [1] have been recreated. In their work, they set the duration of the first stage enabling binding processes to 2 hours, the second stage, which involves the internalization process to 48 h, and during the third stage, the cell culture was irradiating with sources along the cytoplasm for 12 days. The curve of the dose rate averaged over all cell nuclei is shown in the figure attached.

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Neural Network-Based Localization of Photon Interactions in Monolithic Scintillators.

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Compton camera imaging is currently under active investigation in the field of medical physics, with researchers exploring its potential for various applications. The IRIS group at IFIC-Valencia has assembled the MACACO III Compton camera prototype, equipped with three detector planes housing LaBr3 crystals coupled to silicon photomultiplier arrays. This technology aims to accurately determine the distribution of incoming photons. Thus, it necessitates image reconstruction algorithms that rely on the precise positions of photon interactions within the crystals. Previous studies have explored machine learning algorithms and analytical methods to calculate those interaction coordinates. In this work, we focused on the application of a convolutional neural network model, trained with simulated data. The main aim was to predict photon interaction positions within a monolithic scintillator crystal. The training dataset was generated through simulations conducted in Gate v8.0, utilizing a LaBr3 crystal coupled to a silicon photomultiplier array. These simulations captured the light collected by the photomultiplier array pixels for both model training and testing. The convolutional neural network model architecture was adapted from the well-known model VGG16. FWHM, Euclidean distance and Mean Absolute Error were used to assess the model's accuracy. After achieving an effective model for predicting x and y coordinates, its application was extended to estimate the depth of interaction. A comparison with earlier studies highlights the reliable performance of the model in both 2D and 3D research. The CNN model was compared to a state-of-the-art analytical method developed in the IRIS group. The CNN model predictions were found to be promising for accurately localizing photon interactions within a scintillator crystal.

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New opto-electro-mechanical sensor for 2D-dosimetry

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A precise determination of the dose locally delivered is of interest in multiple fields. In the case of radiotherapy, the measurement of the radiation dose ensures that the prescribed dose is properly delivered to the patient at the targeted location. Radiochromic films (RCFs) are currently the gold–standard (passive) detectors for the measurement of dose distribution in radiology and radiotherapy. However, they are passive dosimeters, i.e., there is a considerable delay between irradiation and corresponding readout, and the subsequent evaluation of the dose delivered. In this context, the time-delay of the radiochromic films makes them an unfeasible tool for real-time daily dose evaluation. In response to these issues, we have proposed a new device based on a 2D-sensor that consists of a matrix of micro-opto-electro-mechanical (MOEM) elements [1] by using potential values of the system output as dose transducer. It consists of an optical sensor with light emitting diodes (LEDs) and an array of light-dependent resistors (LDRs) integrated in a fully tailored mechanical and electrical system including an in-house data analysis software and a graphical user-interface. A patent was filled in March 2021 [2]. Thanks to the high electronic versatility of our MOEM system, we may extend its scalable configuration to reach multiple sensitive spots, i.e. having high spatial resolution and covering large radiation areas, which is crucial for monitoring the dose.

The proposal is a new system based on a 5 × 10 matrix of photodetectors controlled by both in-house electronic circuit and graphical user interface (Figure 1). We present the first tests performed in an X-ray machine and 137Cs source with that array by using Gafchromic EBT3 films. We obtained similar results than with a standard method (e.g. flat-bed scanner). Results were compared with Monte Carlo simulations and very good agreement was found. Likewise, we have verified the proper performance of the MOEM sensor in a low-energy proton beamline at CNA (Seville). The outcomes demonstrate the viability of employing this technique for additional dose map assessment.

To the best of our knowledge, this is the first matrix of MOEMs as an active 2D sensing system for fast radiochromic film analysis. Further developments are ongoing to develop a portable dosimetry tool delivering dose maps in real time.

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Novel silicon carbide dosimeters for FLASH therapy

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The main challenge in radiotherapy is to deposit a high enough (curative) dose in the tumor while risk organs remain at tolerable doses. Nevertheless, delivering higher doses are limited by radiation-induced toxicities in the healthy tissues surrounding tumor. A promising approach that is facing this issue is the FLASH therapy [2], which delivers ultra-high dose-rate (UHDR) (≥40Gy/s), i.e., several orders of magnitude faster than the applied dose in traditional RT (~0.05Gy/s) [1]. It points to reduce toxicities in the healthy tissue surrounding the tumor while facilitate a better tumor response, reducing the treatment time and therefore the organ motion-related issues. Thus, the FLASH effect substantially can widen the therapeutic window of radiotherapy and overcome the dose-limiting radiation toxicity, opening a new paradigm in RT treatments. However, enabling the clinical implementation of FLASH RT is very challenging and current dosimeter systems renders obsolete most of the available dosimetry equipment [2].

The implementation of FLASH therapy requires accurate real-time dosimetry. Novel Silicon carbide p-n diode dosimeters have been designed and fabricated at the IMB-CNM-CSIC, and characterized in an ultra-high pulse dose rate electron beam. They were fabricated in 3 μm epitaxial 4H-SiC. Their characterization was performed in PTB's ultra-high pulse dose rate reference electron beam.

The linearity of the diode response was investigated up to doses per pulse (DPP) of 11 Gy and pulse durations ranging from 3 to 0.6 μs (Figure 1). The diode response was independent both of DPP and of pulse dose rate up to at least 11 Gy per pulse and 6 MGy/s, respectively, with tolerable deviation for relative dosimetry (<5%).

Percentage depth dose measurements were performed in ultra-high dose per pulse conditions. When measuring the percentage depth dose under UHDR conditions, with DPP values of 11.6 Gy per pulse for 2.9 μs at the maximum of the curve, the SiC diode performed comparably well to the reference flashDiamond (Figure 2).
The sensitivity reduction after 100 kGy accumulated dose was <2% of 20 MeV electrons. A diamond prototype detector (flashDiamond) and Alanine measurements were used for reference dosimetry.

The results of this study demonstrate for the first time the suitability of silicon carbide diodes for relative dosimetry in ultra-high dose rate pulsed electron beams up to a DPP of 11 Gy per pulse [3]. Currently we are developing 3D configurations for both FLASH therapy and advanced microdosimetry.

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Off-line Total Absorption Spectroscopy of 76Br and 152Tb for their medical interest

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Radionuclides are widely applied in different medical techniques for treatment and diagnosis. The success of the treatments and imaging, as well as dose minimisation to healthy tissue depend, among other things, on the decay characteristics of the radionuclide in use. This includes the different particles and radiation emitted, the emission energies and the emission probabilities. These are essential for the calculation of the dose administered to the patient in medical imaging or treatment with radioisotopes.

A recent work by Nichols [1], shows a list of radionuclides of actual or potential use in medicine and with deficiencies in their decay data provided. In some of the listed decays the author has explicitly specified the need for a Total Absorption Spectroscopy (TAS) measurement. Among them, 152Tb, and 76Br are used in PET/SPECT and are recommended for a TAS measurement. In particular, 152Tb is a PET isotope that works as theranostic pair of 149Tb, 161Tb and 177Lu used for therapy with labeled PSMA-617 (prostate cancer) or DOTATOC (neuroendocrine cancer).

In this contribution we will present the TAS measurement of 76Br and 152Tb, carried out recently at CERN-ISOLDE and whose decay properties were not well established before.

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PenG4: Integration of the PENELOPE physics models and class-II transport algorithm in Geant4 simulations

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Introduction
The Fortran Monte Carlo code PENELOPE is widely used in radiation therapy physics as it implements the most reliable interaction models of electron, positron and gamma currently available for general purpose radiation transport codes. The transport of charged particles is modeled with a class-II algorithm in which "hard" interactions are sampled from the relevant restricted differential cross sections. In this work, we describe and validate the PenG4 package, a full translation of all PENELOPE physics subroutines, including interaction models and class-II transport algorithm, to C++ classes adapted to the specific structure of the Geant4 Monte Carlo toolkit.

Design of C++ classes and coupling to Geant4
The translation of the Fortran code PENELOPE includes all the interaction models and class-II transport mechanics implemented in PENELOPE for electrons, positrons and gammas travelling in arbitrary materials. In order to use the class-II transport algorithm without interfering with the native algorithm of Geant4, dedicated "PENELOPE-like" particles classes were derived from *G4ParticleDefinition* base class. All the PENELOPE physics models are registered as a unique Geant4 process with a wrapper class called *PenEMProcess*. The code covers the scenario of converting a normal Geant4 particle into a PENELOPE-like particle if its energy falls below an energy threshold set by the user, being 1 GeV the upper limit; this is implemented by a "single-body decay" process called *PenPartConvertProcess*. If a particle becomes a PENELOPE-like particle, it is tracked as such until the end of its trajectory. A physics list constructor called PenelopeEMPhysics is responsible of the appropriate process registration and energy threshold definition for the conversion into a PENELOPE-like particle. Moreover, the materials used in the geometry model must be registered as PENELOPE materials to load all the properties calculated in PENELOPE from its own material database and set the PENELOPE transport parameters.

Validation
PenG4 has been verified with adaptations of examples included in the PENELOPE public distribution and in the Geant4 toolkit. We covered various cases of a pencil beam impinging on a cylindrical geometry, composed by one or more different materials, as shown in [1]. We also verified dose-point kernel (DPK) curves against reference calculations carried out with Geant4 and EGSnrc. Calculations carried out with PenG4 agreed with those obtained with PENELOPE within statistical uncertainties.

Conclusions
With the aim of incorporating all the functionalities and reliability of PENELOPE code into a Geant4 application, we translated the PENELOPE physics and class-II tracking subroutines to C++ classes so that they can be used as an additional physics list constructor. The PenG4 package, including code examples, is currently available at https://gitlab.com/miancortes/PenG4 and has been tested since Geant4 version 10.6 to the most recent one.

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Portable MRI indoors, outdoors, at home and for major sporting events

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Magnetic resonance imaging (MRI) is an essential tool for the diagnosis and treatment of numerous health conditions. However, its use is limited to a small fraction of potential patients due to its high cost and lack of portability. Low-field (< 0.3 T), cheap and light MRI systems are now starting to become a valuable complement to standard MRI [1]. At the MRILab we have developed an extremity LF-MRI scanner based on a yokeless Halbach magnet of 72 mT, inspired on a previous system by LUMC [2]. We have mounted the complete system on a wheeled structure of width 70 cm, with an overall weight ≈ 250 kg and component cost < 50 k€. The scanner runs from a standard wall power outlet. The control electronics is based on MaRCoS, an open-source, high-performance Magnetic Resonance Control System [3,4], which we are currently working on adapting to clinical practice.

As a first result, we have demonstrated the true portability of the system and benchmarked its performance in various relevant scenarios, having acquired images of a volunteer's knee in different locations. These include: (a) an MRI physics laboratory; (b) in open air, powered from a small fuel-based generator; and (c) at the volunteer's home, (Fig. 1). Despite small differences in SNR value (Fig. 1 right), the main anatomical features and different tissues remain clearly identifiable across all acquisitions, demonstrating the system portability with the world-first MR images of patients inside their house [5].

Secondly, we studied the potential MR value of this system for use in major sporting events, specifically in the Motorcycle Grand Prix held in the Ricardo Tormo Racing Circuit in Valencia (Spain) between November 3rd and 6th, 2022 [6]. The system was transported in a small truck, installed in the main surgery room of the circuit medical facilities, and operational around 30 minutes after arrival. Our results demonstrate that LF-MRI scans can provide valuable information in the diagnosis and monitoring of injuries in sporting events. The highlight is we were able to detect a traumatic arthritis in a wrist that went otherwise unnoticed by the MotoGP medical staff (Fig. 2).

In conclusion, we have operated in scenarios where high-field MRI is unlikely to play a role but where a low-field system can lead to improved medical attention. Arguably, this can be extrapolated to numerous other environments and diverse circumstances.

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Positron Range Correction in PET with Neural Networks

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Positron range (PR) is one of the most important sources of resolution degradation in Positron Emission Tomography (PET). Despite that, most PET reconstruction software do not provide a specific

accurate PR correction (PRC) for radionuclides with large PR such as 68Ga (including only a PRC for 18F in water), which impacts the accuracy of the studies. We recently developed Deep-PRC, a fast and accurate PRC based on a Convolutional Neural Network (CNN), as a post-processing step for reconstructed PET images. In this work, we introduce Deep-PRC as a useful tool for the PET community.

Deep-PRC is based on the CNN U-NET architecture. It was trained with a large number of 68Ga and 18F PET/CT images obtained from realistic Monte Carlo (MC) simulations from an adapted version of penEasy. As PR is a local effect, 3D patches from the input volumes were used as training elements. The results obtained with the trained Deep-PRC were compared against a standard Richardson-Lucy (R-L) deconvolution algorithm using an isotropic gaussian kernel as a model of the PR blurring. Trained Deep-PRC models can be generated for each isotope and PET scanner and stored as HDF5 files. These models can be applied to correct PR effects in PET/CT studies using, as input, the reconstructed 3D PET and CT images in the most common medical imaging formats.

We present results for 68Ga simulated acquisitions for the preclinical Inveon PET/CT scanner. The initial 68Ga images and the PR-corrected ones obtained by Deep-PRC and the Richardson-Lucy method, were compared against the 18F ones (used as a reference). The Full-Width-At-Half-Maximum (FWHM) of a small hot region was used to evaluate the differences in the spatial resolution in each case, while the noise was evaluated on a uniform region. Qualitatively, there is a clear improvement in the image quality with the use of 3D patches for the training. Models for other radionuclides with large PR, such as 124I, are being developed, as well as an extensive application to preclinical and clinical studies.

Deep-PRC provides a fast and accurate PRC method to recover the resolution loss present in PET studies with radionuclides such as 68Ga that emit positrons with large PR. A stand-alone application can apply the pretrained models to reconstructed PET/CT images to improve their accuracy without compromising the image quality.

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Proton Irradiation might trigger preferentially Homologous Recombination-driven DNA repair

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A fine control of DNA metabolism is needed in order to ensure genomic stability, which is compromised in cancer cells. Proton Beam Therapy (PBT) is considered the most precise and less invasive form of radiation therapy available nowadays for cancer treatment and it is particularly important for paediatric cases involving brain tumours. However, the detailed biological response triggered by PBT remains to be elucidated. We are trying to explore in detail the cellular response to the irradiation with protons in Human cell lines. Indeed, we have already started working with cell cultures irradiated with proton beams. The irradiations were performed at CNA making use of the 3 MV Tandem Accelerator and the 18 MeV Cyclotron which have provided proton beams up to 4 MeV and 18 MeV, respectively. In both cases the beamline was optimized to ensure the irradiation of cell cultures with an accurate and homogeneous dose. Indeed, we have a very preliminary yet highly interesting observation that might indicate that the DSBs produced by protons might be channelled preferentially through the homologous recombination pathway.

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Prototipo de sistema de dispersión pasiva para irradiación FLASH

de muestras biológicas en la sala de sincrociclotrón de una instalación clínica

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Objetivo:
El descubrimiento del efecto FLASH, o el aumento potencial de la ventana terapéutica de la radioterapia de alta tasa, ha traído consigo la necesidad de desarrollar instalaciones donde poder llevar a cabo experimentos a tasas suficientemente altas (>40Gy/s). Dado que en una instalación de protonterapia clínica, como el IBA proteusOne de Quironsalud, no es posible alcanzar tasas FLASH en sala de tratamiento sin una modificación sustancial del sistema, presentamos un diseño prototipo para irradiar muestras biológicas pequeñas con tasas FLASH, aprovechando un espacio existente de 4 cm a la salida del sincrociclotrón y antes del degradador de energía (Fig 1a).

Metodología:
Tras un primer estudio con películas radiocrómicas (RC) en el que se determinó la óptica del haz en el punto de interés, se desarrolló un colimador de plomo optimizado mediante simulación Monte Carlo. Adicionalmente, se diseñó un dispositivo de posicionamiento (holder) por impresión 3D para el colimador y las muestras biológicas, en este caso, esferas de células contenidas en tubos Eppendorf de 0.5 ml (Fig 1b). El sistema permite una instalación rápida y con precisión <1mm, minimizando la exposición de los experimentadores debida a la activación de la sala. El sistema completo (holder + degradador) se probó en irradiaciones sucesivas (0-12 Gy) a 230 MeV para determinar, mediante medidas con RC, las características dosimétricas del campo de radiación en muestra, así como su repetibilidad. El sistema fue utilizado también para realizar la primera irradiación de muestras biológicas en la instalación a tasa FLASH.

Resultados:
A pesar de mínimas variaciones en la óptica del haz entre irradiaciones consecutivas, el campo en muestra presenta una adecuada repetibilidad (Fig 2a), y un tamaño suficiente (68 mm2) para garantizar la cobertura total de dos muestras biológicas simultáneamente (Fig 2b). El campo presentó una tasa de dosis promedio de >800 Gy/s y una homogeneidad del 25%. La dosis ambiental recibida por los experimentadores fue inferior a 6 μSv.

Conclusiones:
Este sistema prototipo ha demostrado ser capaz de ampliar significativamente el campo de irradiación, posibilitando la irradiación FLASH de muestras biológicas en equipos clínicos de protonterapia sin necesidad de alteraciones en el sistema. Esto sienta las bases para una investigación detallada y eficiente de los efectos biológicos inducidos por la técnica FLASH en un entorno clínico.

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Radioisotope production using a high-repetition-rate, laser-based proton source

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In recent years, there has been a growing interest in laser-driven ion accelerators as a potential alternative to conventional accelerators for certain applications [1], mainly because of their smaller footprint and cost-effectiveness. A particularly promising application is the production of radionuclides of interest for medical imaging and therapy, via nuclear reactions such as ^{11}B(p,n)^{11}C [1,2,3]. Typically, the production of these radionuclides is centralised at large cyclotrons, which reduces the number of facilities required, but limits the range of usable radionuclides to those with longer lifetimes [2]. For this reason, laser-driven accelerators could be an interesting option for in-situ generation of short-lived isotopes [2], such as ^{11}C, which is valuable for PET medical imaging but currently restricted in use due to its short lifetime ($t_{1/2}$= 20.36 min).

However, techniques such as PET imaging require activities in the range of 10 – 30 MBq for pre-clinical, and between 200 MBq and 1 GBq for clinical imaging, above those that can be produced in a single irradiation by ion beams driven by commercial laser systems, but potentially achievable by the continuous irradiation of an activation sample. For this purpose, a rotating wheel developed in-house at L2A2 allowing for multi-Hz operation [4]. A modified version of this target, allocating up to 808 shots, has been successfully deployed at a recent experiment at CLPU (Spain), where protons with energy in excess of 12 MeV were obtained, using 200 fs pulses with energies of up to 30 J focused down to 18 μm of spot size. The accelerated protons were used to produce ^{11}C in a proof-of-principle experiment. This was achieved via the aforementioned ^{11}B(p,n)^{11}C nuclear reaction by placing a boron disk close to the interaction point. A diagnostic based on the use of two CsI detectors operating in coincidence was developed to measure in-vacuum the activity generated in the sample. A total activity above 230 kBq was measured from a burst of only 20 shots at 0.1 Hz, giving activities greater than 12 kBq/shot. These results indicate that pre-clinical activities are already achievable under the current conditions with extended irradiation times. Furthermore, in order to reach higher activities, additional developments towards a system capable of producing thousands of shots at 10 Hz will be presented.

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Study of epitaxial graphene contacts for Silicon Carbide radiation dosimetry and detection

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Silicon Carbide (SiC) is a radiation hard wide bandgap semiconductor, which makes it an interesting alternative for radiation detection applications such as radiotherapy instrumentation. Reducing the amount of metal over the active can positively affect the accuracy of the measurement.

The first SiC diodes with epitaxial graphene contacts were produced at IMB-CNM for radiation detection. These detector prototypes have been characterised by means of a pulsed laser transient current measurement and a radioactive alpha source, showcasing the charge collection properties. These measurements have been followed by a characterisation by means of a Linac at the University of Santiago de Compostela. These show a percent-level dose rate linearity of the prototypes, which is promising for future iterations for the medical application.

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Termografía e Imágenes de perfusión de Láser Doppler para la caracterización de la dermatitis por radiación y la calidad de vida del paciente.

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Introducción: La dermatitis (DR) es una de las manifestaciones del efecto de la radiación sobre la piel. Su evaluación se realiza mediante puntuaciones subjetivas, siguiendo la escala RTOG (Radiation Therapy Oncology Group). Estas evaluaciones se ven comprometidas por variaciones intra e Interevaluador [1,2].
La termografía infrarroja (TI) y las imágenes de perfusión de láser Doppler (LDPI) son dos técnicas, no lesivas e invasivas, que han sido propuestas en la literatura para medir cuantitativamente la DR. La TI permite obtener la temperatura superficial de la piel y LDPI evaluar la perfusión tisular producto del flujo sanguíneo microvascular.
Por otro lado, la DR también es valorable a partir de cuestionarios como el del Índice de Calidad de Vida Dermatológico (DLQI) [4] que miden el impacto de las enfermedades de la piel en la calidad de vida y permite clasificar, según la puntuación obtenida, el efecto sobre la vida del paciente (1. Sin efecto alguno; 2. Leve efecto; 3. Efecto moderado; 4. Efecto muy importante; 5: Efecto extremadamente importante).

Objetivo: Encontrar variables cuantificadoras del daño tisular y buscar su correlación con las determinaciones más subjetivas utilizadas en clínica (RTOG y DLQI).

Material y método: Se administró IMRT a 35 pacientes (39 – 81 años), en toda la mama tratada, con una dosis total de 40,05 Gy suministrada en 15 sesiones (2,67Gy /fracción). A cada paciente se le realizó un registro termográfico y de perfusión en tres momentos del tratamiento, antes de iniciar (Basal), al finalizar la 5ª sesión y al finalizar la RT. Los registros se realizaron en ambas mamas, siendo la mama no tratada tomada como control. Se determinó el índice termográfico (DT) como la diferencia de temperatura entre las dos mamas, y el índice de microcirculación (IMC) como diferencia relativa entre la perfusión de ambas mamas. Las pacientes realizaron el cuestionario DLQI antes y al finalizar la RT. Los valores considerados corresponden a la diferencia entre las puntuaciones en los dos momentos del estudio.

Resultados: La figura 1 muestra, a título de ejemplo, las imágenes correspondientes a las imágenes termográficas y de vascularización en dos momentos del estudio, basal y al finalizar la RT, mostrando el cambio de ambos parámetros, temperatura y vascularización a lo largo del estudio.

La figura 2 muestra la relación entre las dos variables cuantificadoras DT e IMC y la figura 3 los valores de estas variables y los de RTOG de los pacientes.
Por último, la figura 4 muestra la relación ente los índices estudiados y la valoración de sensación de los pacientes según el cuestionario DLQI

Discusión y conclusiones: Se observa una buena correlación entre los dos índices determinados tanto en general como diferenciando para los diferentes valores de RTOG, así como con los valores de DLQI.

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The LINrem project: neutron dosimetry and radiation protection in particle therapy facilities

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Neutrons are a highly penetrating type of radiation that can contribute significantly to the total absorbed dose in the human body. As a result, the monitoring of neutron dose rates is crucial to asses the risk of harm to workers, patients, and the public. Commercial portable neutron detectors, also known as ambient neutron dosimeters, are typically used for this purpose. However, there are concerns about the reliability of these detectors, particularly in modern facilities that produce radiation fields with high-energy contributions (E>20MeV) or complex time structures (pulsed or quasi-pulsed neutron fields). This issue is especially relevant in medical facilities, such as proton therapy centers, where high-energy neutrons of up to 250 MeV are produced as secondary stray radiation. Furthermore, the International Commission on Radiation Units and Measurements (ICRU) recently recommended alternative definitions for operational quantities currently used for radiation protection. The new operational quantity has a direct impact on the performance of neutron dosimeters for energies lower than 100 eV and higher than 50 MeV. The LINrem project aims to provide solutions that meet the new requirements for energy sensitivity and time resolution in neutron dosimetry, in particular, focusing on applications for medical facilities. In this work, we review the technical challenges for active and time-resolved neutron dosimetry in particle therapy. We also present the status of the LINrem project, including validation of prototypes and our latest experimental results in proton therapy. Finally, we discuss the future of the LINrem project and the impact of the new ICRU recommendation for radioprotection in proton therapy centers.

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The challenge of multidisciplinarity in proton therapy

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Desde que en la década de los 40 Robert Wilson propuso, de forma teórica, los beneficios de la terapia con protones para el tratamiento del cáncer, el número de centros que usan este tipo de terapia y el de pacientes tratados ha ido creciendo de forma imparable, principalmente en los últimos quince años.

No obstante, las implicaciones clínicas, biológicas, dosimétricas y de liberación del tratamiento demuestran que la protonterapia no es un tema exclusivo de los físicos nucleares experimentales, ni de los físicos médicos, ni siquiera de los oncólogos radioterápicos.

Por el contrario, los máximos beneficios que pueden alcanzarse con esta terapia sólo pueden alcanzarse mediante el concurso adecuado de todas las ramas de la ciencia implicadas.

En esta exposición se enumeran algunos aspectos en los que la Física puede aportar una contribución muy significativa orientada a la optimización del tratamiento del cáncer mediante la terapia con protones.

Asímismo se expone el estado actual de la protonterapia en España y su evolución prevista para los próximos años.

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Tomografía por Emisión de Positrones Registrada con Ultrasonidos para la obtención de imágenes moleculares, anatómicas y funcionales

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En las últimas décadas hemos presenciado un amplio despliegue de sistemas de imagen in vivo que buscan brindar una visión multiparamétrica del tejido que responda a la gran complejidad biológica que caracteriza a varias de sus enfermedades más complejas. Cuando se habla de imagen in vivo multimodal, una pregunta que se plantea con frecuencia es si la adquisición simultánea de información biológica con un instrumento híbrido tiene realmente alguna ventaja sobre la adquisición secuencial de información similar con instrumentos distintos. Esta pregunta es legítima, ya que el coste de construir instrumentos híbridos para la simultaneidad no es despreciable. Sin embargo, una situación obvia en la que la simultaneidad marca la diferencia sobre la secuencialidad es la co-localización, en el tiempo y en el espacio, del flujo sanguíneo y el metabolismo. Ambos aspectos están estrechamente vinculados en todos los órganos: la sangre transporta hacia los tejidos vivos nutrientes, células y diversos efectores, inhibidores y elementos reguladores, y elimina los productos del metabolismo tisular. Los diferentes tejidos controlan su perfusión atrayendo, abriendo o cerrando vasos, y envían señales a otros órganos a través de la red vascular. La pérdida o apropiación indebida de este vínculo estrechamente regulado desempeña un papel fundamental en el desarrollo de tumores y en los trastornos isquémicos. Por lo tanto, cabe esperar un mayor progreso y comprensión de los nuevos métodos de imagen que exploran in vivo las interacciones entre estas características principales del tejido. Sin embargo, lograr una cartografía precisa y simultánea de la vascularización y el metabolismo en las mismas coordenadas espaciales en un organismo vivo es una tarea de enormes proporciones. En la mayoría de los casos, estos mapas se obtienen utilizando distintas modalidades de imagen en momentos diferentes y, por lo tanto, en un estado fisiológico diferente (temperatura, frecuencia cardiaca, anestesia, etc.), por lo que el registro conjunto a posteriori supone un enorme

reto. Para dar respuesta a ello, el grupo de Imágenes In vivo del Centro de Investigación Cardiovascular de París (Francia), asociado con otras instituciones como el grupo de Física para la Medicina de Paris, el Grupo de Física Nuclear de la Universidad Complutense de Madrid, entre otros, ha desarrollado un instrumento híbrido preclínico denominado PETRUS: Tomografía por Emisión de Positrones Registrada con Ultrasonidos. PETRUS ofrece una combinación ideal de imágenes para la lectura del metabolismo mediante 2'-deoxi- 2'[18F]fluoro-D-glucosa (FDG) PET, y la microvascularización mediante Doppler Ultrarrápido, de forma simultánea, no invasiva y directamente en el mismo sistema de coordenadas espaciales. En esta charla abordaré aspectos sobre la construcción de este nuevo instrumento, sus características, los primeros resultados de imagen en roedores obtenidos con este prototipo preclínico y su traslación al ámbito clínico.

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Updates on G4-Med, a Geant4 benchmarking for bio-medical physics applications: regression tests and computing performance

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Introduction
Geant4 is a Monte Carlo toolkit widely used in bio-medical applications. As such, validation and performance monitoring focused on physics quantities relevant to this domain are of crucial need for the community. To respond to these needs, we developed *G4-Med*, a fully automated benchmarking tool and regression testing suite of Geant4 for relevant use cases in the bio-medical field. The first benchmark against reference data was carried out for version 10.5, as described in [1], from which recommendations on physics lists were proposed according to each use case.

Materials & Methods
G4-Med includes 20 testing cases, covering from basic physical quantities (attenuation coefficients, stopping powers, cross sections, dose point kernels, etc.) to tests of more realistic set-ups typical of medical physics applications (hadron therapy, brachytherapy, external electron beam therapy, mammography, etc). The latest tests incorporated, not covered in [1], aim at the validation of Geant4-DNA physics, and of fragment production for hadrontherapy and *in-vivo* PET, respectively. Each test runs with various reference physics lists to cover all relevant electromagnetic and hadronic physics interaction models. The tests were integrated in the *geant-val* platform [2] and have been executed for Geant4 development tags and public releases, including the latest public version 11.1. The calculations are compared to reference data for validation, and to previous Geant4 versions for regression testing. Further, execution times measured with various physics lists have been compared for version 11.1. Physics lists used as reference were *G4EmStandardPhysics_option3* (*"emstd_opt3"*) and *G4EmDNAPhysics_option2* (*"emdna_opt2"*), which are the fastest ones for condensed-history and track-structure simulations, respectively.

Results
As for electromagnetic physics, the EPICS2017 dataset was added. In the electromagnetic tests, in general, results remained stable across versions, showing *"emstd_opt3"*, *"emstd_opt4"*, *"emlivermore"* and *"empenelope"* similar accuracy when compared to experimental measurements. A significant improvement was obtained in the *Brachytherapy* test, where a better agreement against experimental data was observed with version 11.1, when calculating the dose at larger distances from an I-125 source. All the EM physics lists under study showed a computing performance between 1.5 and 2 times slower than the *"emstd_opt3"*. As for hadronic physics, charge-changing cross sections improved in Geant4 version 11.1. For the case of ion Bragg peak curves, versions 10.5 and 11.1 gave similar results. In the case of the carbon fragmentation tests, the results showed an improvement of version 11.1 against 10.5 in terms of angular distribution of the emitted light fragments. More results of the *G4-Med* regression testing can be accessed and downloaded from *geant-val* web site [2].

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Updating the GOS for ionisation and excitation of liquid water: new proton impact cross section dataset relevant for Geant4-DNA

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The processes involved in the passage of radiation through matter is of great interest in medical radiation physics among other areas. Monte Carlo codes are widely used in research fields such as micro/nanodosimetry and computational radiobiology, which demand an accurate modelling of the interaction cross sections in liquid water and other materials of interest. In Geant4-DNA, the physical processes are simulated together with the radiation-induced physico-chemistry and chemistry processes for water radiolysis at sub-cellular scale, all of which contributes to the later damage caused to DNA. At present, no cross sections for the interaction of ions in liquid water have been experimentally determined. Up to our knowledge, the only data available are for the impact of ions in water vapour and these are scarce. Because of this, great efforts have been made to model interactions of radiation with liquid water.

In particular, the extension of the ionisation and excitation models for proton above 100 MeV was performed by the authors of this work [1], using the Relativistic Plane Wave Born Approximation (RPWBA) [2]. This theory separates the contribution to the DDCS of the projectile and the medium, being the last one represented by the generalized oscillator strength (GOS). The latter plays a key role on the determination of the cross section. For a condensed medium, its computation by means of first quantum principles become unfeasible because it is necessary to deal with a many-particle system. Fortunately, the GOS can be computed from the dielectric function (DF) of the medium. The implemented cross section datasets were computed used a GOS model for liquid water based on ideas developed in previous works [3,4].

Here, a new extended optical-data GOS based on Drude functions is presented and used to characterize the most recent available data for the liquid water DF [4], which has not been done previously. This update allows to compute a new dataset of cross sections, which is in good agreement with the experimental data available in water vapour as a reference. Furthermore, the stopping power computed with this model for relativistic proton energies are in excellent agreement with the ICRU report 90 within 1%, validating the dataset also for the higher energy regime.

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