Research topics @ IJCLab associated with the CNRS research fellow position (n°04/09)

Context

The main challenge of radiotherapy is to succeed in depositing, in an individualized way, a curative dose in the target structure (tumor or organ) while ensuring that the surrounding healthy tissues are irradiated as little as possible and always below the tolerance threshold in order to preserve their integrity. This optimization of treatments requires first of all a better understanding of the different mechanisms involved during irradiation, from biochemical effects at the cell level to collective effects at the tissue level. The improvement of the biological efficiency and ballistics of beams for external radiotherapy (proton, light and heavy ions, high energy electrons) or the development of novel radiopharmaceuticals for internal radiotherapy (alpha emitters, theranostic agents) are also central issues, as well as the control of treatment delivery (beam metrology, on-line control of the delivered dose), the implementation of new modes of dose delivery (spatial modulation of the dose rate, very high dose rates, nanoparticles, vectorization for internal radiotherapy ...) and the optimization of individualized treatment planning systems (improving physical and biological input data, simulation). The research activities of the Radiation and Living (REV) team, composed of 8 researchers and teacher-researchers, are part of this thematic context and aim at developing new experimental and methodological approaches in order to better understand the effects of ionizing radiation on living organisms, to improve the control of the dose deposited in external and internal radiotherapy and to enhance the efficiency of treatment methods in molecular radiotherapy through the production of new radionuclides and development of original bioconjugates with innovative chelators to better target the tissues to be treated or imaged. The various research projects are focused on three main areas:

1) **Study of the effect of ionizing radiation from the cellular to the tissue level**
2) **Multi-scale dosimetry for monitoring internal and external radiotherapy**
3) **Development of new radionuclides and associated ligands for biomedical applications**

The CNRS research fellow position opened in 2026 focuses primarily on thematics 2 and 3 (https://gestionoffres.dsi.cnrs.fr/fo/offres/detail-fr.php?&offre_id=18). These two thematics are closely linked since they both are related with internal radiotherapy, for which a precise evaluation of the deposited and absorbed dose per organ is a crucial point. The dosimetry project (thematic 2) aims to develop different tools in order to quantify the deposited activities into organs. The third thematic aims, for its part, to propose a proof of concept for the production of radiopharmaceuticals, as alternative to existing methods that are ineffective for certain radionuclides.

1) Study of the effect of ionizing radiation from the cellular to the tissue level

In order to improve radiotherapy, innovative approaches, such as the use of heavier ions [1] (e.g., ^{4}He, ^{12}C, ^{16}O), are being investigated. These ions offer higher linear energy transfer (LET) than protons, resulting in more double-strand breaks in DNA and greater efficacy against radioresistant tumours. However, the high cost and complexity of ion therapy facilities have limited their widespread adoption. Compact accelerators and additional radiobiological research are needed to fully exploit the potential of heavy ions.

In this context, the BioALTO project [2] aims to develop a new irradiation platform at the ALTO facility (IJCLab, Orsay), dedicated to preclinical research in hadron therapy. Complementing other French radiobiological irradiation platforms for hadron therapy, BioALTO will enable studies to be conducted on the relative biological effectiveness (RBE) for all ions of interest for future treatments. RBE, which compares the biological effect of ion doses to that of photon doses, depends on the type of particle, the LET and the type of cell. BioALTO will guarantee precise irradiation conditions

(homogeneity, dose control, repeatability) and will develop tools such as microdosimeters [3] to measure LET at the cellular level, in partnership with international teams (Barcelona Microelectronics Centre IMB CNM, and the Polish IFJ PAN laboratory/CCB radiotherapy center). The platform will include an upgraded beamline, an in vitro irradiation station and a dedicated space for the preparation of biological samples. The development of the irradiation line also involves the development and integration of new dosimetry and beam monitoring tools, in partnership with several IN2P3 laboratories (IP2I, LPSC, SUBATECH, LLR) and the RESPLANDIR network of national platforms. Funded by the Île-de-France region, the project benefits from a strong regional radiobiology network, notably through collaborations with leading institutions such as Gustave Roussy (specialising in radiotherapy), ISMO (specialising in nanoparticle-enhanced treatments [4]) and the Institut Curie (a pioneer in very high-dose FLASH therapy [5]). The future capabilities of the BioALTO platform and its network position BioALTO as a hub for advancing research in hadron therapy.

2) Multi-scale dosimetry for monitoring internal radiotherapy

In parallel with the development of increasingly specific radiopharmaceuticals, one of the main challenges in the use of molecular radiotherapy (MRT), and especially targeted alpha therapy (TAT), is the individual determination of absorbed doses to organs-at-risk and target regions, which relies primarily on the accurate quantification of the radiopharmaceutical biokinetics [6,7]. At present and despite its obvious interest, dosimetry-based treatment personalization is rare, with most therapies relying on fixed activity protocols [8]. Current limitations are primarily due to the fact that most clinical gamma-cameras used to image the distribution of radionuclides from their gamma emissions are based on the Anger's principle, which relies on the mechanical collimation of incident gamma rays, that is no longer effective when their energy is above 300 keV (131-I, 90-Y, 177-Lu, 225-Ac, 227-Th, 213-Bi, 211-As, 212-Pb, ...) [9]. TAT also poses unique imaging challenges due to the administered activity, which is typically more than two orders of magnitude lower than dose used for beta-emitting radionuclides (around 100 kBq/kg against 1 MBq/kg for 225-Ac and 177-Lu therapies, respectively), which places severe constraints on detection sensitivity. From a dosimetric point of view, another issue is the assessment of migration to non-target organs of daughter radionuclides after the bond between the radionuclide and the ligand has broken, which is a limiting factor with alpha-emitting radioisotopes. This requires the development of systems capable of imaging multiple isotopes. More generally, the availability of the camera and the possibility of using it at the patient's bedside opens up the possibility of obtaining accurate temporal sampling of the biokinetics of the tracer before (patient-specific treatment planning) and after treatment administration, which is a key parameter for quantifying absorbed doses. For high demand applications, such as those using 225Ac-PSMA-617-Targeted alpha therapy, there is therfore a growing need for advanced imaging and dosimetry solutions. In that context, our objective is to propose new instrumental and methodological approaches aiming to strengthen the control of the dose released during MRT by reducing the uncertainties related to dose calculation.

Status report on current projects

The first approach was focused on the treatment of benign and malign thyroid diseases with 131-I (365 keV). The project was carried out in collaboration with IRSN and Institut Claudius Régaud and was funded by the Cancer Plan (AAP Physicancer, INSERM, 2019-2023). A high spatial resolution mobile gamma camera specifically designed to improve the quantitative assessment of 131-I biokinetics in the thyroid and organs at risk before and after treatment administration was first developed (fig. 1). The first prototype of the camera was commissioned in November 2021. All the objectives in terms of spatial and energy resolution, image quality and compactness have been achieved. Pre-clinical studies based on precise calibration of the camera and measurements on 3D thyroid phantoms have demonstrated its ability to quantify activity with a high degree of accuracy (maximum bias of less than 5%, even for small radioactive sources). These very promising results are due both to the very high

spatial resolution of the camera compared with conventional devices (4-6 mm versus 1.5 cm @ 365 keV), and to the implementation of accurate and robust quantification methods (segmentation of the source image, correction for the partial volume effect and scattering). The first clinical evaluation of the mobile camera involving 20 patients with benign thyroid diseases was completed in March 2025. Results are currently being analyzed. A detailed assessment of the sources of uncertainty in the quantification process was also carried out using Monte Carlo simulation. The second axis of the project focused on the reliability and quality of dosimetric calculations through the implementation of innovative error propagation methods based on a Bayesian network to estimate dose uncertainties. This method will soon be evaluated using clinical data acquired by the mobile camera. The whole project was carried out as part of three doctoral theses [10-12] and resulted in 3 papers in peer-reviewed scientific journals [13-15].

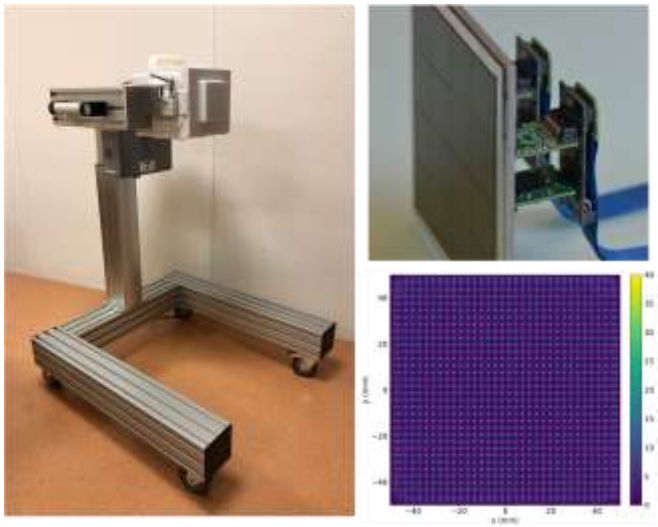

Figure 1: The mobile gamma-camera for estimation of absorbed dose in molecular radiotherapy (left); photodetection module consisting of a silicon photomultiplier array and reading electronics (top right); Intrinsic spatial performance of the camera (133-Ba, 356 keV) [Bossis 2023]

Perspectives

Beyond setting up an extended clinical protocol of the mobile gamma camera for the treatment of thyroid diseases (differentiated thyroid cancers and benign thyroid diseases), the next steps involve adapting this camera to dose-based treatment planning for thyroid diseases using 123-I (Cochin Institute collaboration), and opening up its use to clinical applications using medium-energy gamma emitters, such as 177-Lu-PMSA for prostate cancer treatment (200 keV, CHUV-Lausanne collaboration).

In the long term, we have just initiated a collaboration with South Korea to develop a Compton camera dedicated to dosimetric monitoring with high-energy gamma rays for targeted alpha therapy. This development will rely on AI-based reconstruction methods. Indeed, while our initial studies showed that it is possible to push the limits of current detection technologies in order to significantly improve the performance of standard gamma cameras in the medium energy range, other detection must be implemented when the energy of the gamma ray is above 400 keV. One possible solution is to rely on the principle of Compton imaging, which is based on reconstructing the paths of incident gamma rays using Compton kinematics using two detectors—a scatterer (detector where incident gamma rays undergo Compton scattering) and an absorber (detector where the scattered photon is absorbed). Unlike collimation-based imaging, where high-energy photons often penetrate the collimator and reduce image quality, Compton cameras provide superior sensitivity at higher photon energies, but suffer from limited spatial resolution due to uncertainties in interaction position and scattering angle mainly constrained by the energy resolution of the detector acting as a diffuser, they

typically require precise event-by-event processing and are computationally intensive. While Compton cameras are employed from a long time in a wide range of applications to locate sources of gamma radiation [16], their use in nuclear medicine, and in particular in targeted radiotherapy, is much more limited due to their specific constraints [17]. This mainly involves imaging of near-field sources with high sensitivity and spatial resolution (of the order of a few millimeters) in order to improve the quantification of heterogeneous activity distributions, and thus the accuracy of dosimetry on a macroscopic scale. The challenge is even greater for 225-Ac, because its gamma emissions are in an energy range that is too high for standard gamma camera but relatively low for Compton imaging (218-keV emission from Fr-221 and 440-keV emission from Bi-213, two daughters of Ac-225). To meet these stringent requirements and cover the entire energy range of gamma emission from the main radionuclides of therapeutic interest (from 200 keV to 2.7 Mev, for 177-Lu and 212-Pb, respectively), it is therefore necessary to push back the limits of current standard gamma cameras as we already done, implement Compton imaging and optimize data reconstruction methods using AI methods, which can help reduce the constraints on the detector.

The main objective of our new project is to propose a versatile and high-performance mobile gamma camera capable of imaging medium- and high-energy gamma emissions to monitor the absorbed dose during different targeted therapy protocols before and after treatment administration. Two complementary research axes will be investigated. The first one will be focused on the development of a new gamma detection module combining both Anger detection and Compton imaging principles in order to take advantage of the complementarity of the two methods for imaging gamma radiations above 200 keV. The second axis involves the development of new AI-based reconstruction methods to improve the performance of Compton imaging. This axis will evaluate and combine different complementary approaches including the reconstruction of the position of gamma interaction in the detectors, the reconstruction of the Compton cones and the image reconstruction of the source localization.

A key originality of our project is to propose **a hybrid detector design combining the best of Anger detection and Compton imaging** in order to achieve high performance in terms of sensitivity and spatial resolution across a wide range of gamma energies. Building on the IJClab laboratory's previous experience in the field of high spatial resolution gamma imaging, a continuous inorganic scintillator read by a SiPM array will be used both as a detector for conventional gamma imaging and the absorber for Compton imaging. By combining this detector with a modular head consisting of a 3D-printed tungsten collimator or a scatterer, it will be possible to adapt the detection mode to the incident gamma energy in a range from 200 to 2 MeV in order to optimize performance. Different detector technologies, including silicon detector and inorganic scintillator, will be investigated. The developed detection module will serve as a building block for a future mobile clinical camera dedicated to near-field quantitative imaging of radiopharmaceutical biokinetics at the patient's bedside. The evolution towards a clinical system could be achieved by increasing the field of view of a single basic module or by using a small number modules distributed around the patient to improve the reconstruction of tomographic information.

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3) Development of new radionuclides and associated ligands for biomedical applications: the PRALINE project

The PRALINE project (Production of Radionuclides and Ligands for Dosimetry and Nuclear Imaging) aims to improve the effectiveness and personalisation of molecular radiotherapy treatments through various complementary areas of research, from the development of new methods for producing radionuclides using a precursor with high isotopic purity to their complexation with biological tracers, and the design of new imaging approaches for dosimetry.In this context, the development of new radiopharmaceuticals is sometimes hampered by the difficulty of producing

radionuclides in sufficient quantity and purity, and of synthesising bifunctional ligands compatible with a wider range of biological vectors. Our initial studies focused on terbium (Tb), an interesting element that offers four clinically relevant radioisotopes with complementary physical decay characteristics: ^{149}Tb ($T_{1/2}$ = 4.12 h, α therapy), ^{152}Tb ($T_{1/2}$ = 17.5 h, PET), ^{155}Tb ($T_{1/2}$ = 5.32 days, SPECT and Auger therapy) and ^{161}Tb ($T_{1/2}$ = 6.9 days, β^- therapy and possibly Auger therapy). Another interesting theranostic pair is ^{43}Sc ($T_{1/2}$ = 3.9 h, PET) and ^{47}Sc ($T_{1/2}$ = 3.3 days, β^- therapy). The main aim of the PRALINE project is to develop a 'proof of concept' for an alternative production route for radiopharmaceuticals for isotopes that are difficult to obtain using conventional methods.

Status report on current projects

Since 2022, our initial research has focused on methodological issues relating to the production of radionuclides (^{155}Tb in our case) and their biodistribution via a biological vector. Several complementary aspects of this topic have been studied: optimising the production of ^{155}Tb with a purity compatible with large-scale clinical use, and quantifying 'acceptable' levels of contamination by studying their adverse effects on patients.

With regard to production, the excitation function of the ^{155}Gd(p,n)^{xxx}Tb reaction in the 7-25 MeV range was studied using the SIDONIE isotope separator at IJCLab [18].To achieve this, the separator had to be upgraded to improve the machine's reliability. After separating the different isotopes present in the ion source at the focal plane, the isotope of interest, ^{155}Gd, is selected using slits and then slowed down to allow it to be deposited at less than 150 eV on a graphite substrate. This slowing down is necessary to avoid 'sputtering' in the target, i.e. the removal of atoms present on the substrate during deposition. This device has made it possible to obtain ^{155}Gd targets with purities better than 99.9%.

Based on these measurements, it was possible to determine the optimal proton energy for the production of ^{155}Tb and to show that ^{154}Tb and ^{156}Tb are the main contaminants to be avoided for clinical use. Thus, the minimum purity required for ^{155}Gd targets for the production of ^{155}Tb for medical purposes could be determined. This work formed the basis of M. Bouteculet's PhD thesis [19-21].
To complete this work, a second PhD thesis is currently underway to study in order to determine the impact of ^{155}Tb pollution on the quality of SPECT images that can be produced. This simulation work is based on the construction of a digital twin of an existing pre-clinical camera. Two experiments carried out on a phantom with ^{155}Tb and a mixture of ^{155}Tb+^{156}Tb then enabled simulations to characterise and quantify the undesirable effects on SPECT tomographic images. This made it possible to determine a maximum threshold for ^{156}Tb pollution in regards of the cameras shielding and collimation.

The second challenge addressed by the project is to develop and characterise specific bifunctional terbium chelators, which were previously unavailable, that are compatible with the use of monoclonal antibodies as biological vectors. The specificity of this type of vector (generally proteins) stems from the fact that they are very sensitive to temperature and must therefore be able to chelate (i.e. form a stable complex with the radionuclide) at room temperature, which is not usually the case. Several candidates have been synthesised and characterised. The study of their in vitro and in vivo stability, as well as their chemical and radiological toxicity, has enabled several to be selected and tested with ^{161}Tb to measure their biodistribution in xenografted mice. Part of this work was carried out in a thesis supervised at IJCLab and defended at the end of 2025 [22].

Perspectives

The first medium-term objective is to complete the studies conducted on ^{155}Tb, in particular through dosimetry studies, in order to obtain further information on the possible content of contaminants produced. This will ensure that potential contaminants do not expose patients to an unnecessarily high additional dose. To this end, the biodistribution kinetics of a ^{156}Tb-contaminated-^{155}Tb-labelled radiopharmaceutical in a mice phantom will be simulated allowing to evalaute the dose in each organ. Next, it will be important to evaluate the added value of ^{155}Tb for imaging by comparing its use with other isotopes already in use, such as for instance ^{68}Ga. To this end, it will be interesting to use ^{161}Tb

as a partner for therapy, since its chemistry and therefore its kinetic distribution properties are identical.

Once proof of concept for the methodology has been established, it will be interesting to use it for other Tb isotopes, such as ^{152}Tb and ^{149}Tb. To achieve this, it will be important to equip the SIDONIE separator with diagnostics to improve the quality of the beams obtained and thus optimise beam time by collecting all the separated isotopes that are not slowed down directly at the focal plane. A collection box system has been designed for this purpose and is expected to be tested in the first half of 2026. The system will then be validated by measuring the collection yield and the precise isotopic composition of what has been collected. It will then be necessary to finalise the manufacture of targets from the isotopes collected.

Beyond similar studies conducted on Tb, ^{43}Sc and ^{44}Sc will also be studied. Both are PET emitters with an additionnal prompt γ of respectively 372 keV and 1157 keV. 3-γ imaging of these isotopes will also be therefore explored with dedicated instrumental approaches. This modality would significantly improve the resolution of the images obtained by measuring the coincidence of the β+ decay (PET image) and γ decay (SPECT image) of ^{44}Sc. This would make diagnostics more accurate and open up an additional avenue for better personalising the treatment of certain cancers.

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