Appel à projet « Projets P2I 2023 »

Titre du projet /Title of the project: dosimetry at BioALTO

Acronyme /Acronym: dosiBioALTO

Durée du projet : 24 months

Responsable du projet :

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Unité : Pôle Physique des Accélérateurs, IJCLab UMR9012

Autres unités associées :

Unité : Pôle Physique Santé, IJCLab UMR9012
Contact projet au sein de l'unité : philippe.laniece@IJClab.in2p3.fr

Visa du directeur de l'unité du porteur et, le cas-échéant, par le ou les directeurs des unités associées au projets :

Pôle Physique des Accélérateurs, IJCLab: Walid Kaabi

Pôle Physique Santé, IJCLab: : Philippe Laniece

Thématique (compatible avec la stratégie de P2I) :

Accélérateurs et Santé

Budget prévisionnel :

Nature	Description brève / Brief description	Montant demandé / Grant request	Autres financements / Other source of funding
Equipment	Data acquisition electronics	15 000 €	
Equipment	Ionization chamber + Calibration + Electrometer	11 500 €	
Equipment	Vacuum parts and mechanical components	8 500 €	
Equipment	Faraday cup and electrometer	5 000 €	
TOTAL		**40 000 €**	

Résumé de la proposition / Abstract

The project BioALTO at IJCLab has the goal of setting up RadioGraaff, an irradiation platform originally located at IP2I, Lyon, that allows radiobiological studies, at ALTO, IJCLab, and its subsequent adaptation to be able to deliver a large variety of heavy ion beams. Furthermore, we envision to open this installation to external users by developing a radiobiology platform which can be of great interest to the preclinical hadron therapy. In the project proposed here named dosiBioALTO, we propose to develop a dosimetry system based on 3D cylindrical silicon microdosimeters in order to perform beam diagnostics to ensure the strict beam quality requirements of radiobiological experiments, and provide linear energy transfer maps of interest to study the relative biological effectiveness of ionizing radiation.

Contexte scientifique / Scientific context

The ongoing BioALTO project at IJCLab, Orsay, aims to develop a new irradiation beamline at the Accélerateur Linéaire et Tandem à Orsay (ALTO) facility dedicated to radiobiological studies and detector characterization for hadron therapy applications. The tandem accelerator provides stable ion beams of most of the elements in the periodic table, of which protons, alpha particles, carbon and oxygen ions are of interest to the hadron therapy community. ALTOs' ion beams need to be modified to be compatible with the beam quality requirements of radiobiological experiments. To accomplish this, we envision the installation of the RadioGraaff apparatus [1], which was previously located at the Van de Graaff accelerator of the Institut de Physique des 2 Infinis de Lyon, at ALTO and its adaptation to the energy and ions delivered at this facility

This project is organized in three phases that span several years and different stages of development. The first phase is dedicated to the integration of RadioGraaff in the beamline at ALTO, the upgrade of the dosimetry system and the validation of the beam quality specifications. Phase II comprises the biological irradiations that are included in the PICTURE project (IP2I, Lyon and LPSC, Grenoble) - dedicated to the improvement of biological dose prediction of innovative radiotherapies involving low-energy ions, namely Targeted alpha therapy (TAT) and boron neutron capture therapy (BNCT) using adapted simulation codes and the biophysical model NanOx; and the MODERATO (Pôle Physique Santé, IJCLab) project, which has the goal of obtaining quantifiable data on the effects of different modalities of ionizing radiation on experimental models of cell population growth of progressive complexity: from in vitro 2D cell cultures to Organs-on-Chips, which will then be used in the mathematical modelling and prediction of the effects of radiation on tumour growth. Finally, in Phase III we propose the development of a radiobiology platform so that external users can perform radiobiological experiments, or characterize their detectors, at ALTO using the BioALTO setup. This platform will equip the Île-de-France region with a unique radiobiology platform which will be of high interest to the preclinical hadron therapy research community of the region, particularly the research groups working on radiobiology within the Paris-Saclay perimeter. Indeed, this community has existed for several years taking advantage of the rich multidisciplinary environment of the laboratories present within this perimeter, and of the existing radiotherapy treatment centers such as the Gustave Roussy Institute (IGR) or the proton therapy center of Orsay (CPO). This community was formalized within the framework of a strategic research initiative of the University of Paris-Saclay - iNanoTheRad.

Besides the large variety of available ion beams, the BioALTO platform will distinguish itself by providing the possibility to study experimentally the relative biological effectiveness (RBE) of the hadron in question. Indeed, one way to evaluate the effects of different modalities of ionizing radiation is to study the RBE [2], which is defined as the ratio of the reference photon dose to the hadron dose necessary to cause the same biological effect. The RBE depends, among others, on the ionizing particle, the energy loss per unit length by a charged particle (linear energy, LET) and the cell type parametrized by α and β coefficients which characterize the cell line response to a specific irradiation. For ion beams, the cell response is driven

by the α coefficient. Figure 1 illustrates the variation of α coefficient values as a function of LET for V79 cells and we can notice that this coefficient rapidly increases with LET before a fall-off corresponding to the "over-killing" phenomenon (in the case of "heavy ions").

The α and β parameters can be experimentally obtained through clonogenic cell survival assays, while the LET information relies on the precise quantification of the lineal energy transfer, *y*, which is defined as the ratio between the deposited energy by a single event into a given microscopic volume and the corresponding mean chord length of that irradiated volume. The evaluation of *y* and of the microdosimetric dose distribution, *d(y),* is only possible with detectors such as microdosimeters [5] which allow the measurement of (micro)dosimetric quantities at scales comparable to the size of the cell.

The study of RBE is especially important for the clinical community as, for example, in proton therapy a fixed RBE of 1.1 is applied in treatment plans to account for the higher biological effectiveness of protons over photons. However, the RBE is expected to vary within the irradiated volume and, in particular, to increase at the distal part of the tumor and surrounding healthy tissues, which correspond to regions of higher LET due to the presence of low-energy protons. This effect has been proposed to explain the observed toxicities following hardon therapy treatment. Moreover, in carbon ion therapy the nuclear fragmentation of carbon ions leads to a more complex distribution of LET and RBE in patients. Alternative planning strategies based on variable LET and RBE-weighted dose distributions have been put forward [6] to reduce normal tissue toxicity but are hindered by, among others, the lack of tools to measure the LET and RBE.

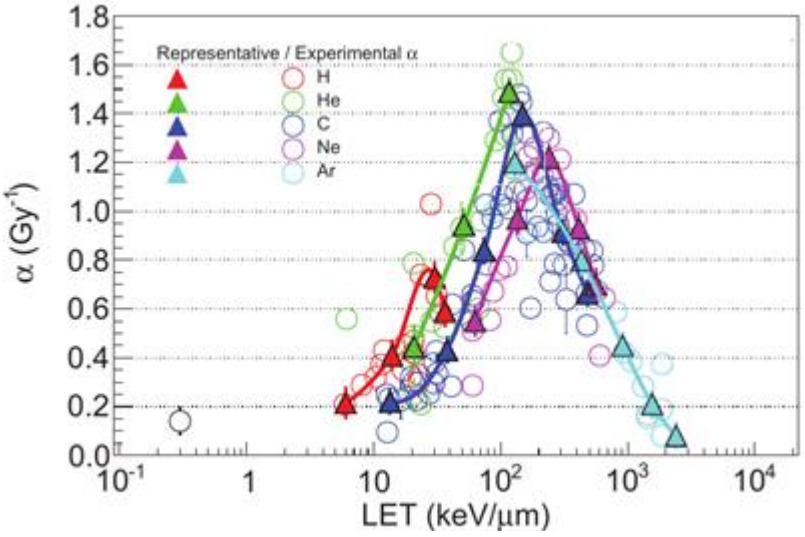

Figure 1. Values of α coefficients from cell survival curves of V79 cells. The empty circles correspond to values extracted from the PIDE project database [3] and the full symbols to those chosen as representative of the experimental data. For photons, the single point shown matches the α coefficient reported in [4], i.e. 0.112 Gy^{-1}, for an LET of 0.3 keV/µm.

References:

[1] J. Constanzo *et al.*, Nuclear Instruments and Methods in Physics Research B 334 (2014) 52–58. doi: 10.1016/j.nimb.2014.05.005

[2] A. McNamara *et al.*, Phys Med Biol. 2015 November 7; 60(21): 8399–8416. doi:10.1088/0031-9155/60/21/8399

[3] T. Friedrich et al. 2012, Radiation Research Vol. 178, No. 5, pp. 385-394. doi: 10.1667/RR2964.1

[4] N. Tilly et al. Int J Radiat Biol. 1999;75:233–43. doi: 10.1080/095530099140690

[5] A.B. Rosenfeld *et al.*, Nuclear Instruments and Methods in Physics Research A 809 (2016) 156–170. doi: 10.1016/j.nima.2015.08.059

[6] C. Hahn et al., Acta Oncologica, 61:2, 206-214, doi: 10.1080/0284186X.2021.1992007

Proposition / Proposal

Exposé du projet scientifique et technique (6000 caractères maximum)**:**

The RadioGraaff setup was originally installed at the 4 MV Van de Graaff accelerator of IP2I Lyon and has two systems consisting of a scattering foil and a collimator which are used to produce a large beam (diameter of ~ 2 cm) with +/- 2% homogeneity. It contains several beam diagnostics such as a Faraday cup, luminescent materials, cameras, and a dose monitoring system. The setup was designed to perform cell irradiation experiments with precise and homogeneous irradiation dose over the full cell sample with a monoenergetic proton beam of 3.5 MeV and a nominal dose rate of 2 Gy/min, while being maintained at constant temperature and atmosphere adapted to living cells.

At ALTO we envision to perform irradiations not only with protons, but also with alpha particles, carbon ions and other heavier ions, and take advantage of the larger energies that the tandem accelerator is capable of providing. For this reason, the beam-modifying elements of RadioGraaff, i.e., scatterers and collimators, need to be adapted to fulfil the constraints of radiobiological experiments (energy, energy spread, fluence, beam divergence and alignment) for each beam type and energy to be used, but also to be as robust as possible against possible beam variations. Additional beam diagnostic equipment will be installed to aid the alignment of the beam and to perform precise dosimetry, and extra vacuum elements such as a pump with the associated instrumentation will be required. In addition, the mechanical robustness of the RadioGraaff line will be improved to reduce the risk of damage and to ensure the stability and reproducibility of the geometrical alignment.

The goal of BioALTO is to equip ALTO with an irradiation setup capable of performing radiobiological experiments. Indeed, these experiments, which consist in the irradiation of *in vitro* samples and posterior processing and analysis in a biology laboratory, rely on strict beam time calendars as well as precise and reproducible irradiation conditions such as irradiation time, homogeneity, dose and dose-rate. Accordingly, for each requested irradiation condition a dosimetry protocol will be put in place and a campaign of dosimetric measurements is necessary in order to tune the transport of ALTO's beam and verify that it conforms to the required radiation quality. The beam characterization will be performed using diagnostic equipment such as a Faraday cup to measure the beam current, calibrated radiochromic films to evaluate the absolute dose and the radiation field homogeneity, an ionization chamber for dose measurements and a silicon microdosimeter system that provides maps of beam intensity and LET. Guardiola et al. [1] have developed such a system based on microdetector arrays with well-

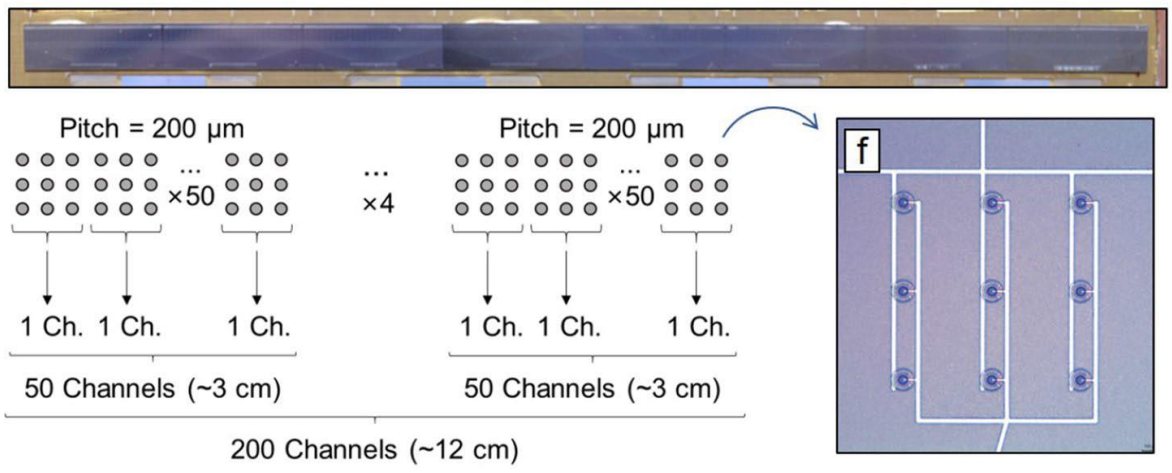

Figure 2. Photograph of the eight pad-type arrays stacked laterally covering a 12 cm length. Sketch of the pad-type array. Optical image of one of the 3 × 3 cells [5].

delimited sensor volumes that reproduce the shapes and microscopic sizes of mammalian cells of few micrometers of diameter and have shown that they can be used not only for microdosimetry measurements, but also for beam monitoring with high spatial resolution. This system has the potential to be a great asset to this platform by allowing the correlation of biological endpoints with the obtained LET maps in the same irradiation conditions as of the *in vitro* samples, and in that way estimate the respective RBE. No other platform in France has this capability.

The microdosimetry system that we propose to use is based on a 3D cylindrical architecture silicon microdosimeters, in which the energy dynamic range is adapted to heavy ions and the back-scattering contribution is reduced. These devices have already shown a good performance in microdosimetry at both carbon therapy [2], low energy proton facilities [3] and in clinical proton therapy conditions [4]. The system consists of multi-arrays of 3D microdosimeters (with 20 µm thickness and 25 µm diameter) organized in a strip configuration (see Figure 2), and assembled into adapted readout electronics with in-house codes enabling in situ data analysis and visualization. This system proposed for the BioALTO platform covers a total area of 0.4 mm × 12 cm. The readout electronics consists of two printed circuit boards: a daughterboard that contains the read-out chips and the arrays of 3D microdetectors (a different PCB for each system), and a motherboard (the same for both systems) that includes the data-acquisition (DAQ) system. We envision to acquire such as system by establishing a collaboration with the National Center of Microelectronics (IMB-CNM, CSIC), Spain.

The DAQ system that we envision to purchase through this project consists of a multichannel readout electronics which communicates with the computer via Ethernet controls the acquisition, receives the data, handles the trigger and the data monitoring, and it requires just one small power supply for functioning, making it portable. On-line analysis can be performed after the irradiation in order to obtain the energy spectra and the microdosimetry maps with a resolution of 600 µm (see Figure 3 and 4). The data analysis software and its graphical user interface (GUI) will be integrated in the BioALTO user-interface

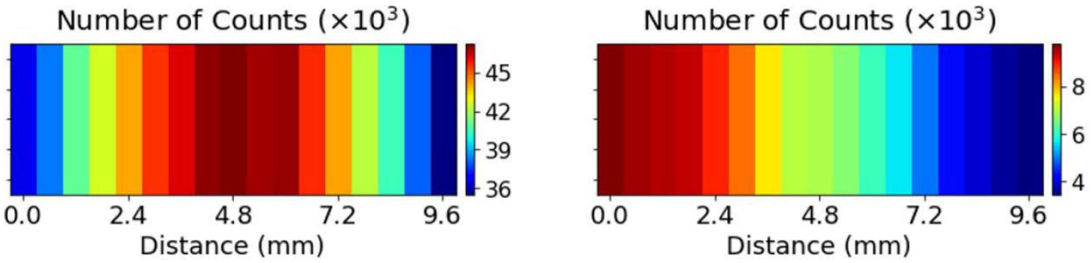

Figure 3. Number of counts measured with 6 MeV (left) and 18 MeV (right) proton beams.

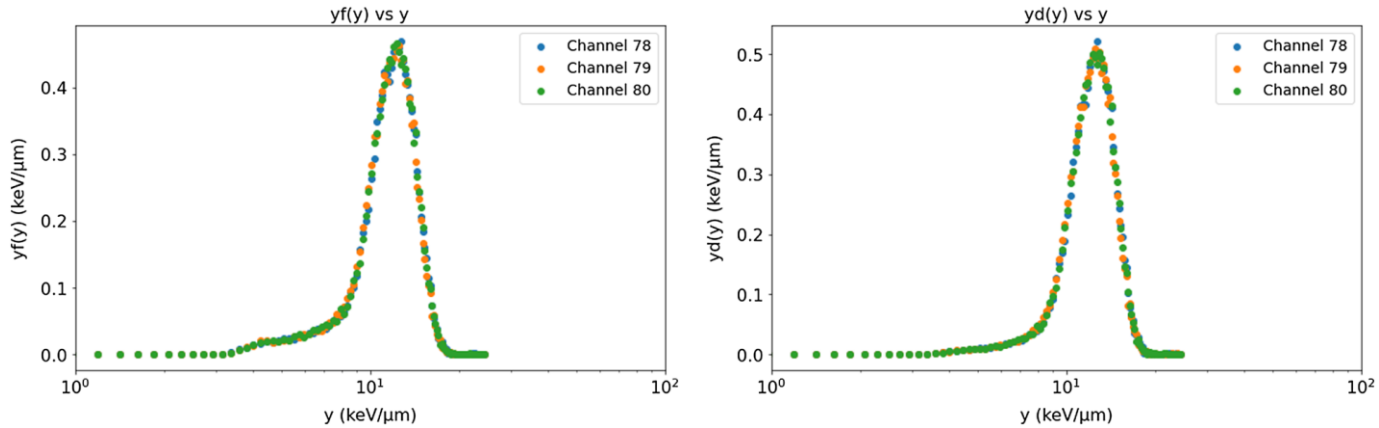

Figure 4. Lineal energy and absorbed dose distributions, f(y) and d(y), obtained in silicon with three different 3 × 3 cells (each color in the graphs corresponds to one of the three cells) of the pad-type system under 8 MeV.

software. Furthermore, Monte Carlo (MC) simulations that reproduce the irradiation configuration and sensor geometries will be performed crosscheck the experimental pulse-height spectra. To test and characterize the microdetectors, measurements will be carried out using an alpha source and ion beams at different energies in collaboration with ARRONAX, Nantes, and also compared to respective Monte Carlo simulations.

References:

[1] C. Guardiola *et al.*, Appl. Phys. Lett. (2015) 107, 023505. doi: 10.1063/1.4926962
[2] J. Prieto-Pena *et al.*, IEEE Trans Nucl Sci (2019) 66:1840–7. doi:10.1109/tns.2019.2921453
[3] C. Guardiola *et al.*, Phys Med Biol (2021) 66:114001. doi:10.1088/1361-6560/abf811
[4] D. Bachiller-Perea *et al.*, Front. (2022) Phys. 10:958648. doi:10.3389/fphy.2022.958648
[5] D. Bachiller-Perea *et al.*, Sci Rep (2022) 12, 12240. doi:10.1038/s41598-022-14940-1

Organisation et plan de travail du projet (succinct pour les petits projets) (chronogramme/diagramme de Gantt - 1000 caractères maximum) :

Tasks	2023		2024			2025	
	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Fabrication of microdosimetry detector array.	■						
Purchase of data acquisition electronics.	■						
Simulation of microdosimeter response in BioALTO beams.	■	■	■	■			
Development of acquisition software.	■	■					
Tests and calibration of microdosimeter with source and at Arronax, Nantes.		■					
Test and calibration of microdosimeter at BioALTO.		■					
Radiobiology experiments at BioALTO.		■	■	■	■	■	■
Publication of results.				■	■	■	■
BioALTO platform development.						■	■

Synergie éventuelle entre les laboratoires (complémentarité des actions, intérêt pour les différents partenaires - 500 caractères maximum) :

The recent foundation of IJCLab offers the potential to successfully carry out the proposed project. The Pôle Physique Santé, IJCLab provides the experience in biology and microdosimetry and will be in charge of the development and testing of the microdosimeter. The Pôle Physique des Accélérateurs, IJCLab is in charge of the development of the BioALTO radiobiology irradiation platform, the beam characterization and dosimetry, and the irradiations to test and then employ the microdosimeter detector in radiobiology studies.

Composition et expertise des équipes (tableau avec FTE - 1000 caractères maximum) :

Name	Institute	Position/Expertise	FTE
Amélia Maia Leite	Pôle Physique des Accélérateurs, IJCLab	Ingénieur Recherche/ Radiotherapy & dosimetry	0.6
Philippe Laniece	Pôle Physique Santé, IJCLab	Directeur de Recherche	0.2
Yuwei Zhu	Pôle Physique Santé, IJCLab	Postdoc/Instrumentation & simulation	0.6
Olivier Seksek	Pôle physique Santé, IJClab	CRCN	0.2
MCF (recrutement au 01/10/23)	Pôle physique Santé, IJClab	MCF UPCité	0.3
Consuelo Guardiola	National Centre of Microelectronics (IMB-CNM, Barcelona, Spain)	Researcher/ Expert in microdosimetry	0.2

Besoin d'utilisation des plateformes (si pertinent) : *Les responsables de plateforme devront être consultés ; un avis leur sera demandé. A noter qu'il est possible de demander des améliorations des plateformes existantes. Les propositions concernant les plateformes P2I seront privilégiées.*

The RadioGraaff setup in the ALTO platform in the context of the BioALTO project.

Financement

Justification de la demande, Indiquez, si applicable, les autres sources de financement obtenues ou demandées.

The BioALTO project is strongly supported by IJCLab, which has allocated 39 800 € of funding. 30 000 € has been requested to IP2I, Lyon, which is a partner laboratory of the BioALTO project. The radiobiology part of this project is financed by the PICTURE project with 39 800 € (Physicancer INSERM). The dosiBioALTO project here described aims to upgrade the dosimetry system of the RadioGraaff setup and represents a contribution of 40 000 € out of the total cost of the project of 149 600 €.