

2012 Activity Report of the Regional Research Programme on Hadrontherapy for the ETOILE Center

G. Alphonse, D. Ardail, E. Armandy, M. Bajard, J. Balosso, M.-H. Baron, P. Battiston-Montagne, G. Bertrand, M. Beuve, Marie-Claude Biston, et al.

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2012 Activity Report

of the Regional Research Programme on Hadrontherapy for the ETOILE Center

June 15, 2013













Partners of PRRH



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International journals with reviewing committee		15	7	11	15	41	16	15		120
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Journals without classification					1					1
International conferences with reviewing committee	2		5	1	16	6	21	18		69
International conferences without reviewing committee			1			1				2
National conferences with reviewing committee		1	7		3	19		4		34
National conferences without reviewing committee			1			1				2
Invited conferences	3				6	9				18
Conferences without classification								1		1
PhD / HdR	1/0	1/0			8/1	8/0	6/3	2/1		26/5
Posters					15	30	5		2	52
ETOILE internal notes						3	1		3	7
Workshops without proceedings		1	1	2	1					5
Workshops without proceedings					1		1		2	4
Patents					1	1				2
Publications without classification			1		1					2
Book chapters						3	1			4
Oral communications	4	1			8	8		1		22
Total	10	26	26	14	78	139	54	43	7	**397**

Table 1: Statistics of the bibliographic database [2007, 2013].

Part I

Introduction

2012 a successful year and a period of changes

2012 is the penultimate year of financial support by the CPER 2007-2013 for ETOILE's research program, sustained by the PRRH at the University Claude Bernard. As with each edition we make the annual review of the research in this group, so active for over 12 years now.

Over the difficulties in the decision-making process for the implementation of the ETOILE Center, towards which all our efforts are focussed, some "themes" (*work packages*) were strengthened, others have progressed, or have been dropped. This is the case of the eighth theme (technological developments), centered around the technology for rotative beam distribution heads (gantries) and, after being synchronized with the developments of ULICE's WP6, remained so by ceasing its activities, coinciding also with the retirement of its historic leader at IPNL, Marcel Bajard. Topic number 5 ("In silico simulations") has suffered the departure of its leader, Benjamin Ribba, although the work has still been provided by Branka Bernard, a former postdoctoral fellow in Lyon Sud, and now back home in Croatia, still in contract with UCBL for the ULICE project.

Aside from these two issues (and the fact that the theme "Medico-economical simulations" is now directly linked to the first one ("Medical Project"), the rest of the teams are growing, as evidenced by the publication statistics at the beginning of this report. This is obviously due to the financial support of our always faithful regional institutions, but also to the synergy that the previous years, the European projects, the arrival of the PRIMES LabEx, and the national France Hadron infrastructure have managed to impulse.

The Rhone-Alpes hadron team, which naturally includes the researchers of LPC at Clermont, should also see its influence result in a strong presence in France Hadron's regional node, which is being organized. The future of this regional research is not yet fully guaranteed, especially in the still uncertain context of ETOILE, but the tracks are beginning to emerge to allow past and present efforts translate into a long future that we all want to see established.

Each of the researchers in PRRH is aware that 2013 will be (and already is) the year of great challenge : for ETOILE, for the PRRH, for hadron therapy in France, for French hadrontherapy in Europe (after the opening and beginning of treatments in the German [HIT Heidelberg, Marburg], Italian [CNAO, Pavia] and Austrian [MedAustron, Wien Neuerstadt]) centers. Let us meet again in early 2014 for a comprehensive review of the past and a perspective for the future ...

Pr. J. Remillieux & Pr. J-M. Moreau
University Claude Bernard Lyon 1
ETOILE's Scientific Management (PRRH)
Villeurbanne, June 15, 2013.

Part II

Reports [in English]

Chapter 1

Medical project

Scientific coordinator

- Prof. Jacques Balosso, radiotherapist, PUPH, (CHU de Grenoble),

Institutions & laboratories involved

- GCS ETOILE
- Université Claude Bernard (UCBL)
- Hospices Civils de Lyon (HCL)
- Université Joseph Fourier (UJF) / CHU de Grenoble
- Centre Léon Bérard (CRLCC de Lyon)
- Institut Lucien Neuwirth (ex Institut de Cancérologie de la Loire, Saint-Étienne)
- Centre Alexis Vautrin (Nancy)
- Université Jean Moulin Lyon III
- Centre François Baclesse (Caen)
- CHU de Besançon
- Institut Claudius Regaud (CRLCC de Toulouse)

General organization, full- or part-time researchers with institutional links

Set up of national and european network[‡]

- Prof. Jacques Balosso, radiotherapist, PUPH, (CHU de Grenoble),
- Dr. Guillaume Vogin, radiotherapist (Assistant Département de radiothérapie, Centre Alexis Vautrin, Nancy et CHR Metz-Thionville),

Evaluation in hadrontherapy:

- Clinical trials:
  - Main Investigator: Dr. Pascal Pommier, radiotherapist, (Centre de lutte contre le cancer Léon Bérard,Lyon).

[‡]Professor Jean Louis Habrand (Radiotherapist oncologist specializing in pediatrics, Head of the radiation department, Centre François Baclesse, Caen) may also be cited for his contribution.

    - Dr Marie-Hélène Baron, radiotherapist (PH, CHU de Besançon).
  - Epidemiological and geographical studies:
    - Project manager: Stéphanie Patin, epidemiologist, coordinator of the OMéRRIC network (GCS ETOILE),
    - Yohan Fayet, PhD – Health geograph (Université Jean Moulin Lyon III),
    - Isabelle Ray-Coquard, MD, PhD, medical oncologist (Centre Léon Bérard),
    - Dr. Françoise Ducimetiere, Scientific Coordinator of the Medical Evaluation of Sarcomas (EMS – Centre Léon Bérard)
  - Medico-economical evaluation:
    - Christell Ganne, (Pôle d'Information Médicale Evaluation Recherche des Hospices Civils de Lyon)
    - Dr Yi Hu, MD, methodologist (UCBL, UMR5558, département de pharmacologie clinique).

Biological study: Pr Claire Rodriguez-Lafrasse, UF Oncologie Moléculaire et Transfert - Centre de Biologie Sud, Centre Hospitalier Lyon-Sud 69495 Pierre Bénite

Medical literature study:

- Coordinator: Dr. Yi Hu, médecin, methodologist (UCBL, UMR5558, département de pharmacologie clinique).
- Dr Anne Laprie, Radiotherapist, specialized center (Institut Claudius Regaud, Toulouse).

Other scientifc and medical consultants:

- Laurence Vial, medical physicist, (Institut Lucien Neuwirth, St Etienne).
- Marie-Claude Biston, medical physicists, (Centre Léon Bérard).

1.1 Overall 2012 assessment

1.1.1 Context

2012 was the time to start preparing for the end of several funding programmes, which allowed the emergence of the hadrontherapy discipline at the local level (CPER 2007-2013) and at the European level (the ULICE project: September 2009-August 2013), and to prepare the ground for the organizations that will follow, in particular in the framework of the investment scheme initiated by the French Government (« Investissements d'Avenir »).

As for the medical aspects, the National Infrastructure project, France HADRON, was validated in 2012, with a strong recommendation for clinical research, and the ULICE program will end with the set-up of an organization and coordination group for clinical research in Hadrontherapy at the European level. In this regard, the so-called franco-german ETOILE-HIT prospective and comparative study is a model.

1.1.2 Organization of the French and European networks

France Hadron

To enable the consolidation of all the medical, scientific and technical forces in hadron therapy in France, the actors in this area, mainly located in major universities and national research institutions (CNRS, CEA, INSERM, IRSN) decided to join their forces to present the *France Hadron* project in response to the "National Infrastructure for Biology and Health[1]" call for projects. The scientific project includes four work packages (WP). The ETOILE center is the

[1] Link toward Investissements d'Avenir.

leader of WP1 and coordinator of the whole project. The objective is to develop knowledge of emphEvidence-Based Medicine in the field of particle therapy by proton therapy and carbon therapy, in relation to the most advanced techniques of photon therapy (X and gamma rays). WP1 participates as a whole to meet the second cancer plan (Plan Cancer 2009-2013).

Project evolution for 2012 this infrastructure was authorized to sign contracts with the National Agency for Research (ANR) on April 16, 2012. In the months that followed, proposals of financial use have been pooled to be included in the file that was prepared at the end of 2012, to be submitted to the ANR in January 2013.

Coordination of the construction of the European clinical research infrastructure in hadrontherapy

The ETOILE Center takes part in the coordination of the construction of the evaluation methodology in the ULICE program (Union of LIght Ions Centres in Europe). It is mainly concerned with phase III clinical studies in the hope of comparing Carbone therapy with the more advanced treatments in radiotherapy. The methodologies will be adapted to the specific constraints of hadrontherapy: 1) the necessary multicentric activities at an international level, 2) the need for common databases and for powerful and secure data exchange tools, 3) the need for an international, multidisciplinary, and detailed case analysis to include in clinical studies, 4) the low incidences of patients and the necessary time hindsight for the comparison of survival quantification and of the economical efficiency.

Project evolution for 2012 the methodology, tools and regulatory solutions developed for the construction of the Phase III clinical trials, the above-mentioned ETOILE-HIT PHRC, serve to define and to test practical aspects to take into account in the framework of European cooperation.

1.1.3 Evaluation in hadron therapy

Clinical study

The PHRC ETOILE-HIT project consists in a randomized prospective and comparative carbon ion radiotherapy study based on patients with localized, non resectable (or in R2 resection) and radioresistant cancers: the axial skeleton chordomas (skull excluded), adenoid cystic carcinoma of the head and neck sarcomas, with a comparison between the results of carbon therapy (performed abroad, at the HIT center in Germany) and alternative radiotherapeutic modalities (in France). The funding of this project was accepted by INCa through the 2011 PHRC (Hospital Clinical Research Program). This study aggregate 33 teams (university hospitals or anti-cancer centers, plus the HIT Center), and its promotion is ensured by Hospices Civils de Lyon (HCL).

Project evolution for 2012: the protocol has been fully defined, regulatory barriers identified and solutions proposed. The HIT center is involved. The documents are ready to be submitted to the CPP (Comité de Protection des Personnes) and the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) early 2013. Parallel evolution of this project is presented and analyzed in the framework of WP2 to ULICE in connection with the Austrian collaborators (MedAustron Project) in charge of this WP with us. It will be the first international multicenter carbon therapy study. The study should include its first patient in the second half of 2013.

Epidemiological and geographical study

Study of the socio-epidemiological factors in the hadrontherapy care pathways for Rhône-Alpes area sarcoma affected patients Funding for this project was provided by INCA in response to the call for projects "Free research projects in Humanities and Social Sciences, Epidemiology and Public Health 2012". The objective of the EMS-ETOILE study is to investigate the epidemiological factors of access to care and their impact on survival, for patients affected

with sarcoma who will be eligible for hadrontherapy treatment in the Rhône-Alpes Region. Thus the health care pathways, the role of social and geographical inequalities, will be demonstrated in the treatment of patients. This study will be performed on an exhaustive cohort of patients initiated in 2005 in the Rhône-Alpes area.

Project evolution for 2012: the study started and runs as expected in the general agenda of the project. A second selection of the patients was performed in the EMS database. Indeed, some patients present in the first cohort were removed because they had not been strictly enough selected about their clinical condition during the first selection. This approach increased the relevance of the representative population for Hadrontherapy. A list of 10 socio-economic variables was established and these are the subject of a specific collection in paper medical records of patients included in the study to answer its epidemiological aspects. An approach to geographic indicators is underway. Thus, three broad categories of territorial quality have been explored: life area, social space and resources space.

Medico-economical studies

a. The medico-economical study on the cost of ACC (adenoid cystic carcinoma). This study was launched in late 2010 with 31 diagnosed patients. In 2012, 90 patients diagnosed between late 2011 and early 2001 were added (including 18 patients of the Centre Hospitalier Lyon Sud, 55 of the Centre Léon Bérard (with one consulting both centres), and 18 of the CHU of Saint-Etienne) to form a total cohort of 121 patients. The average age of patients was 54.5 years, the ratio F/M is 72:49 (1.46:1). Clinical data have already been identified. We will continue this study in 2013 with cases of the Croix Rousse Hospital and presumably of the Hospital in Clermont-Ferrand, in function of the total number of patients included. Access to economic data is being negotiated with the CPAM of patients.

b. The medico-economical study from the ancillary study to the PHRC ETOILE–HIT study. The aim is to inform public deciders in the allocation of resources. Two perspectives will be considered: that of the fund bringer (health insurance) and that of society. The main objective of the study is to compare, according to two dimensions of costs and results, two radiotherapy-based strategies (carbon therapy compared to conventional therapy) for selected indications. A cost-effective analysis will allow a survival measurement. A second cost-effectiveness analysis will be performed with a measurement result expressed in terms of recurrences avoided. In further analysis, a cost-benefit study will be conducted to assess the duration of life gained, quality-adjusted life year (QALY), between the carbon therapy strategy and the strategy without carbon ions. This study is funded through the PHRC-hadron budgets and is managed by the Medical Information Sector and Evaluation Research of the Hospices Civils de Lyon in connection with the CNAMTS.

Project evolution: this study will start when the PHRC ETOILE-HIT study includes its first patient.

1.1.4 Medical literature analysis

Monographs

To learn more about rare cancers that represent the main indications for Hadrontherapy which will be recruited at ETOILE Center opening, we decided to gather as monographs all relevant information, useful to clinicians on these tumors. The diseases in question are: adenoid cystic carcinomas, chordomas, chondrosarcomas of the axial skeleton, tumors of the paranasal sinuses, adenocarcinoma of the head and neck mucosal melanomas, desmoid tumors, pelvic recurrences of rectum cancer, aggressive forms of meningiomas and pituitary carcinomas (very rare form of pituitary tumor in contrast to adenomas). Different aspects are covered: epidemiology, histopathology, carcinogenesis, symptoms, diagnosis, clinical manifestations and natural history, treatment, treatment efficacy, toxicity, prognostic factors... Manuscripts for the following pathologies are finalized:

adenoid cystic carcinomas, melanomas mucosal chordomas, chondrosarcomas of the axial skeleton, desmoid tumors, pelvic recurrences of rectal cancer and aggressive forms of meningiomas.

Keeping up to date and scientific veille monitoring

Throughout the acquisition process, data are updated if necessary. In 2012 we updated the data upon sarcomas and brain tumors in children. This topic resulted in a manuscript being finalized.

1.1.5 Communications

The methodology of the EpiHadron study "Epidemiological study of the incidence of cancers eligible for proton or carbon ions therapy" was presented in an oral communication during the Fifth International Congress of Epidemiology ADELF EPITER held in Brussels from 12 to 14 September 2012.

1.2 References for the chapter

[BCR+12] G. Buiret, P. Céruse, A. Ramade, C. Carrie, and P. Pommier. Acinic cell carcinoma of the parotid gland with skull base invasion: case study, managed by exclusive external 3d radiation therapy. *European Annals of Otorhinolaryngology, Head and Neck Disease*, 129(2):111–114, April 2012.

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[PMP+12] P. Pommier, M. Morelle, L. Perrier, R. De Crevoisier, A. Laplanche, P. Dudouet, MA. Mahé, B. Chauvet, TD. Nguyen, G. Créhange, A. Zawadi, O. Chapet, I. Latorzeff, A. Bossi, V. Beckendorf, E. Touboul, X. Muracciole, JM. Bachaud, S. Supiot, and J-L. Lagrange. Prospective economic evaluation of image-guided radiation therapy for prostate cancer in the framework of the national programme for innovative and costly therapies assessment. *Cancer Radiotherapy*, 16(5-6):444–451, September 2012.

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[TVT+12] J. Thariat, PO. Védrine, S. Temam, AM. Ali, D. Orbach, G. Odin, M. Makeieff, R. Nicollas, M. Penicaud, B. Toussaint, S. Vergez, A. Laprie, M. Rives, K. Montagne, N. Teissier, and L. Castillo. The role of radiation therapy in pediatric mucoepidermoid carcinomas of the salivary glands. *J. Pediatry*, 6, November 2012.

Chapter 2

Medico-economical simulations

Scientific coordinators

- Dr. Pascal Pommier (HDR, Centre Léon Bérard)

2.1 Overall 2011 assessment

This year again, the research in this theme are very closely linked to the "Programme de Recherche Hospitalier de Recherche Clinique" (PHRC) 2011 and hence to the medical project. All the 2012 actions in the medico-economical theme are described in the previous chapter.

Chapter 3

In silico modeling of therapeutic effects

Scientific coordinators

- Benjamin Ribba (CR, INRIA, NUMED team)
- Branka Cajavec-Bernard (ULICE project, Split, Croatie/UCBL)

Institutions & laboratories involved

- INRIA
- UCBL
- Split Polytechnic, Croatie

3.1 Overall 2012 assessment

This year again, Branka Cajavec-Bernard has been involved in the ULICE project (WP3: "Biologically-based expert system for individualised patient allocation"). In the collaboration with University of Dresden, group lead by Prof. Wolfgang Enghardt, software is being developed for the comparison of photon- and proton-based treatment plans. Exchange of treatment plans between proton and photon treatment facilities, and upload of photon-based treatment plans, has been resolved. With the availability of clinical data, we plan to use this technical basis to include biologically related models for treatment planning. This common project was discussed at the joint meeting of PARTNER, ENLIGHT, and ULICE Annual Meeting, September 14-16, 2012, at the CNAO Center, Pavia, Italy.

The manuscript with developed mathematical model that successfully describes low-grade glioma (LGG) tumor size evolution and predicts tumor response in patients treated with chemotherapy and radiotherapy, was published [**?**]. In the future, this model might be used to predict treatment efficacy in LGG patients and could constitute a rational tool to conceive more effective chemotherapy schedules.

Aware of the gap that needs to be bridged between clinical research and the complementing methodologies developed in computational cancer research groups, we are creating COMPLEMENT a Clinicians Computational Cancer Models Guide and Database. For a particular tumor type, COMPLEMENT gives information on available models, questions that can be tested by that model, input data needed to test that question, and a contact for associated research groups. Cancer clinical trials complemented with computational cancer models may contribute to the design of rational, tailored treatments. Computational models developed along a clinical trial present a

necessary step towards virtual clinical trials and a decision on the benefit of a particular treatment modality for an individual patient. To address this need, we are developing COMPLEMENT also as a guide for clinicians on how a clinical trial tailored computational model is created and implemented.

Chapter 4

Basic physical measures and on-line control

Scientific coordinators

- Denis Dauvergne (DR CNRS – IPNLyon)
- Gérard Montarou (DR CNRS – LPC-Clermont)

Institutions & laboratories involved

- IPNL, CNRS/IN2P3 and Université Lyon 1
- CREATIS, INSA et CNRS and INSERM and Lyon 1 University
- LPC-Clermont, CNRS/IN2P3 and Clermont University

Full-time researchers with institutional links

- IPNL : M. Dahoumane (IR CNRS), D. Dauvergne (DR CNRS), J. Krimmer (CR-CDD CNRS), C. Ray (MdC UCBL), E. Testa (MdC UCBL), H. Mathez (IR CNRS), Y. Zoccaratto (IR CNRS)

  + M. De Rydt (post-doc), G. Dedes (post-doc Envision) S. Deng (Th 2012), J.-L. Ley (Th 2015)M. Pinto (Th 2014), V. Reithinger (Th 2014), M-H. Richard (Th 2012), A. L. Pequegnot (M2)
- CREATIS : N. Freud (MdC INSA), J.M. Létang (MdC INSA), V. Maxim (MdC INSA), R. Prost (Pr INSA)
- LPC-Clermont : G. Montarou (DR CNRS), P. Force (Pr Clermont Université), N. Pauna (MdC Clermont Université), F. Martin (Pr Clermont Université), B. Joly (IR CDD), D. Lambert (IR CNRS), PE. Vert (IR CNRS), G. Blanchard (IR CNRS), L. Royer (IR CNRS), C. Insa (IR CNRS), B. Boutin (T UBP)

  + L. Lestand (Th 2012), O. Bouhadida (Th 2013)

4.1 Main objectives

4.1.1 General issues

Online monitoring and quality control of ion therapy is a crucial issue due to the ballistic precision and – for carbon – the large biologic efficiency of ions at the end of their range in matter (at the

Bragg peak). Indeed, a small deviation from the planned dose is the consequence of a possible patient mispositioning or uncertainties in the patient morphology (e.g. anatomy evolution during the treatment), or uncertainties in the determination of the stoechiometric composition, that is deduced from X-ray CT.

Unlike photons, incident ions are stopped inside the body, and techniques based on the observation of secondary particles – induced by nuclear fragmentation – are needed. The objectives of the present research field are the following:

- by means of simulations, feasibility experiments at large accelerator facilities and/or ion therapy centres, and through research and development programs, we intend to elaborate innovative techniques to monitor online the dose delivered to the patient. These techniques are based on the detection of secondary radiations: beta+ annihilation, prompt gamma photons, and light charged particles. The final quality control system could involve several of these modalities. In addition, prospective studies were undertaken to assess the clinical advantages of proton radiography over X-ray radiography, in terms of accuracy in density identification and absolute dose delivered during the examination.

- We contribute to the acquisition and the compilation of basic physical data for nuclear fragmentation. The objective is twofold:

  i to test and validate the physical models used for the treatment planning systems, and

  ii to obtain the required accuracy in the prediction of secondary radiation imaging.

4.1.2 Context

This research is undertaken in multiple frames of various scales, which shows the importance of improving the quality of ion-therapy treatments:

- The Programme Régional de Recherche en Hadronthérapie, supported by the Région Rhône Alpes and the Grand Lyon (CPER 2007 – 2013);

- At a larger regional scale (Cancéropôle CLARA: Lyon, Grenoble, St Étienne, Clermont-Ferrand), a Labex project, PRIMES (Physique, Rayonnement, Imagerie Médicale et Simulations), was selected (Investissements d'Avenir 2011) andas started in March 2012. Three workpackages over five are related to the research for ion therapy (WP1: innovative imaging for radiotherapy, WP3: Radiobiology, WP5 : simulation and modelling for imaging and therapy);

- The Research Groupement GDR MI2B, driven by the National Research Center CNRS (IN2P3), is leading a federative program "Instrumentation and Nuclear Methods against Cancer"; this GDR was reconducted for the period 2012-2015;

- The national research program in ion-therapy (PNRH) was reactivated in 2011 through the Infrastructure program for Biology and Health France-HADRON (Investissements d'Avenir 2011), that was approved for the period 2012-2020. This program aims at coordinating the research driven by the various clinical and research centers in France.

- The European network ENLIGHT++, a federative network that involves the various European centers, coordinates the collective response to research calls launched by the European Community. Online imaging of the dose during ion therapy is one of the major axes developed within this collaboration between clinical centers and research laboratories (project ENVISION 2009-2013). The educational part is also well represented (PARTNER and ENTERVISION Marie-Curie ITN programmes).

4.2 Overall 2011 assessment

4.2.1 Prompt-gamma SPECT imaging

We demonstrated, during a first experiment in 2007 at GANIL (Caen), that the emission profile of prompt gamma rays as a function of the target depth can be measured by means of a detection system with limited shielding. Thanks to the time of flight technique, it is possible to discern the arrival time of photons and massive particles emitted under ion impact on a phantom target. This emission profile is correlated to the range of the primary ions, and thus allows one to localize the Bragg peak. Moreover, the counting rates obtained are encouraging in view of a system for on-line and real-time monitoring of the dose.

This modality of on-line control was the object of a patent registration with PCT extension. Within the frameworks of a project ANR (Gamhadron) grouping together the IPNL, CREATIS, the CEA / LIST and the LPC-Clermont, and the European project ENVISION (driven by the ENLIGHT++ network), we develop a system of SPECT imaging which includes the following studies: one R&D on a collimated gamma camera, another one on a Compton camera, a simulation work for modelling prompt gamma emission, a R&D for a beam hodoscope, and a tomographic reconstruction task for the Compton camera.

Collimated gamma camera

Since 2007, new series of measurements at GANIL, GSI, Essen and HIT-Heidelberg, allowed us to confirm the suitability of prompt gamma rays detection with time-of-flight discrimination. We have shown that the correlation between the primary ion range and the gamma profile is kept at higher energies (for 15-20 cm ion ranges). Fast neutrons cannot be used to measure the dose profile, and therefore constitute a major background. Time-of-flight (TOF) selection is used in order to eliminate them and enhance signal-to-background ratio. Moreover, we have shown that the target composition and size do have an influence on the gamma count rate, but this does not prevent SPECT imaging from being efficient for dose monitoring. The time structure of the beam is not an obstacle, provided a beam fast-monitor is used to get a beam tagging for time-of-flight measurements.

LYSO scintillating detectors have been specially designed for the detection of high energy gamma rays through a multi-slit collimator. Their typical dimensions are 5 cm long (thick) $\times$ 5 cm high $\times$ 5 mm width, allowing good efficiency for the transmitted photons, and a minimum sensitivity to the background of neutrons and scattered gamma rays. This provides a significant improvement of the signal to background ratio, compared to the large volume detector used initially. Using an optimized detection setup under design-study, the Bragg peak position can be visualized with an accuracy of about 3 mm within the first pencil beam spot of a proton patient treatment, as illustrated on Figure 4.1.

For carbon ion therapy, the yield of prompt gamma is smaller, and control at the energy slice scale (some tens of spots) is foreseen with a reasonable size camera. Thanks to combined experiments at Essen (collaboration with IBA) and HIT in 2012, we could compare prompt gamma profiles for proton and carbon beams of the same range in matter. Gamma yield profiles have been measured in the protontherapy center of Essen with a proton beam of 160 MeV, in collaboration with the IBA research group. Figure 4.2 shows the results obtained with and without TOF selection (note that a time window of 5 ns was used, which is not as severe a selection as one would use in an optimized setup, therefore the background reduction is not maximum). This figure shows that TOF improves in any case the signal to background ratio, and, for carbon ions, it is mandatory to extract an information correlated to the ion range.

Yields correspond to energy deposition larger than 1 MeV with a time-of-flight selection of prompt-gamma rays (green line) and without time-of-flight selection (red line).

Further measurements were performed at GSI (cave A) in August 2012, in order to evaluate the realistic background for various shielding and collimation systems. These data will be used for the design of an optimized collimation system.

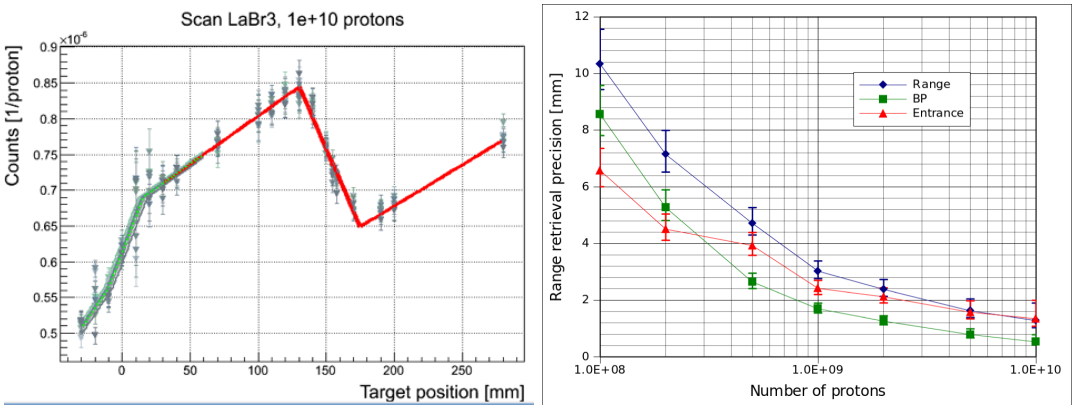


Figure 4.1: Prompt gamma resolution study on proton range, for 160 MeV protons incident on a 30 cm long, 15 cm diameter, cylindric PMMA target. Measurements are obtained with a LYSO scintillator (40 mm x 3 mm entrance surface and 50 mm thickness) placed behind a tungsten alloy collimator with a thickness of 10 cm and a single slit of 2 mm. Left: analytical fit of the measured scans, each point corresponding to 10^{10} incident protons. Right, determination, for sub-data sets of reduced statistics, of the rms dispersion of the prompt-gamma rise at target entrance, falloff at Bragg peak and their difference (range), as a function of the incident proton number.

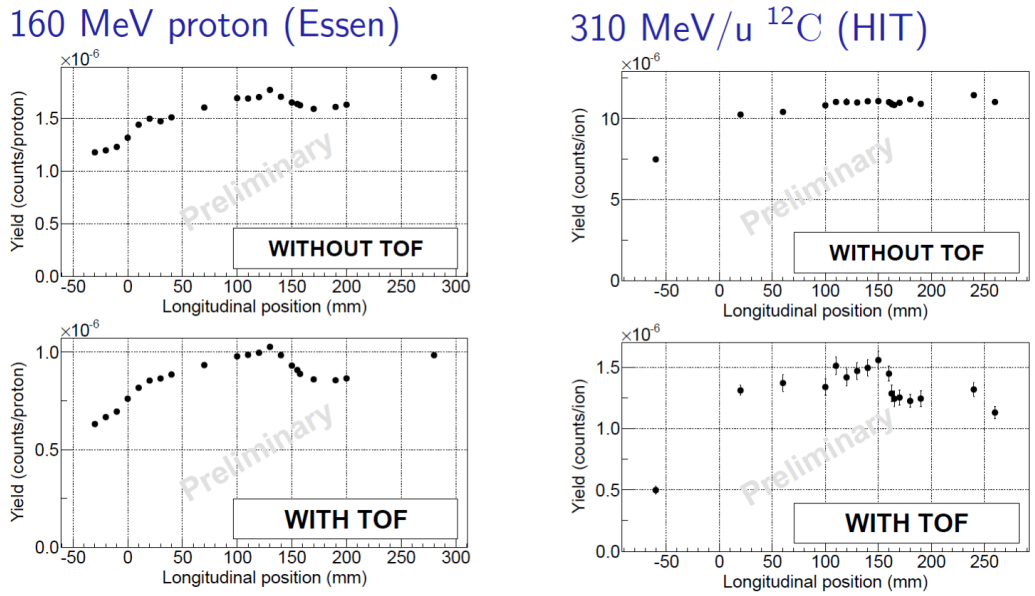


Figure 4.2: Prompt gamma profiles obtained with 160 MeV proton beam in a PMMA target, and with 310 MeV/u carbon ions at HIT, with the same detection setup, with and without time-of-flight selection (refer to text).

Compton camera

For single photon emission computed tomography (SPECT), a Compton camera has the advantage of a much greater efficiency than a classical collimated gamma-camera, since no mechanical collimation is needed. Thus the efficiency can be improved in principle by several orders of magnitude. The aim of the Gamhadron ANR project (2009-2013) is the design and setup of a time-of-flight Compton camera for online prompt-gamma monitoring of ion-therapy. This topic is also supported by the Envision project (WP3).

Simulations and detector design Design studies have been undertaken at IPNL and CREATIS to assess the performances of such a device, in terms of efficiency and spatial resolution. This is the subject of the thesis work of Marie Hélène Richard, co-directed by CREATIS and IPNL.

Two concepts have been followed. A first one concerns a double Compton-scattering camera, made of two thick (1 cm) silicon scatterer detectors and an absorber scintillator. The advantage of two scattering events is that there is no need for measuring the full energy of the residual photon in the absorber detector. It has nevertheless a limited efficiency, comparable to the collimated camera efficiency [RCD+11]. A second design dealt with a single Compton-scattering camera, made of a stack of about ten thin (2 mm) silicon scatter detectors and one absorber. This second system has a much better efficiency (about one order of magnitude), since only one Compton scattering and the absorption of the residual photon in the absorber are required. In this case, the spatial resolution is only slightly degraded; the point-spread function has an 8 mm FWHM [RRC+11].

After the adoption of the single Compton scattering system, our studies concentrated on the choice of the absorber scintillator material. As illustrated in Figure 4.3, our simulations show that, according to a realistic prompt gamma energy spectrum, a heavy scintillator like LYSO provides the best performances for the Compton camera, in terms of efficiency and spatial resolution [RDD+11]. BGO appears also as a good candidate, despite poorer energy and timing resolutions, since the most important property is the spatial resolution. The latter depends mostly on the photoabsorption probability, i.e on the effective atomic number of the material.

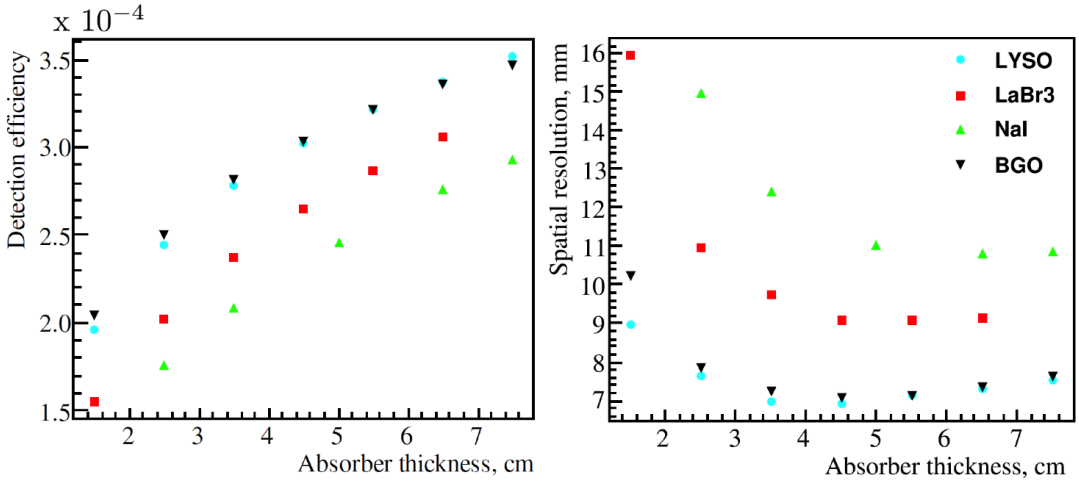
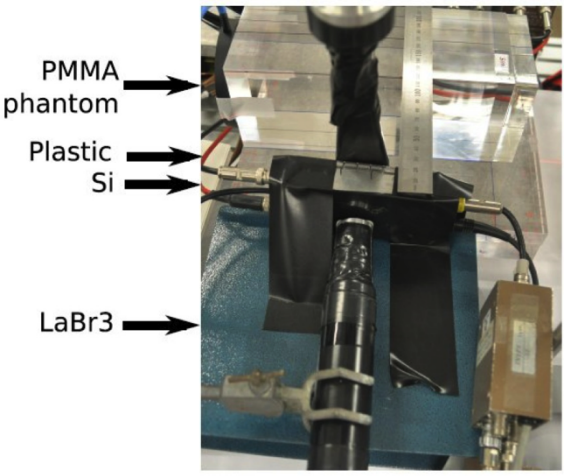


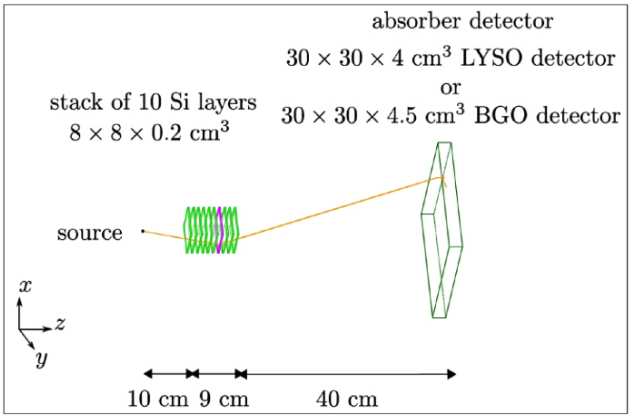
Figure 4.3: Simulation of a Compton camera performance according to the nature and thickness of the absorber scintillator [RDD+11].

A simulation experiment was performed at HIT-Heidelberg, where a reduced size Compton camera prototype was used: a 12 × 12 mm^2 area, 2 mm thick silicon detector was used as scatter detector, and a 2.5 cm diameter, 5 cm thick cylindrical LaBr3 scintillator served as absorber (see figure 4.4-a). Carbon and proton beams were sent onto a 25 cm thick PMMA target. The aim of

this experiment was to measure single and coincidence count rates in a realistic beam environment, and to extrapolate such count rates for the real size Compton camera shown in Figure 4.4-b.



(a)



(b)

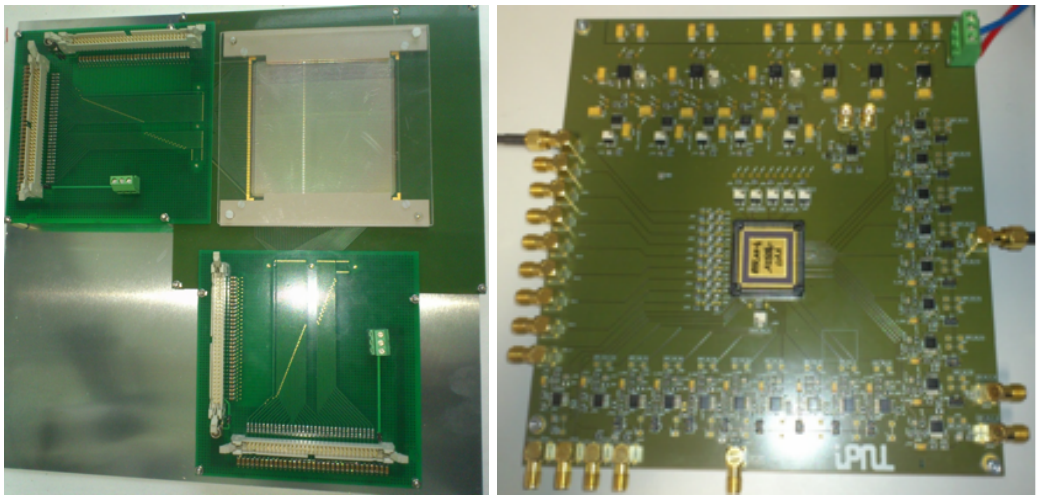
Figure 4.4: (a): Compton-camera-like setup at HIT-Heidelberg. (b): designed setup of the Compton camera for online control of the ion range during therapy.

The extrapolation was made by means of GEANT4 simulations. The expected count rates of the Compton camera presented in Figure **??**-b are reported in Table **??**. The conclusions are that high counting rates, especially for proton beams, may be a crucial issue, in particular for the absorber detector. Therefore, segmentation of this detector will be necessary in order to keep the camera efficiency acceptable.

	Proton beam	Carbon beam
Typical beam intensity (Hz)	10^{10}	10^{8}
First Si detector count rate (Hz)	4×10^{6}	1×10^{6}
Absorber count rate (Hz)	2.5×10^{7}	3×10^{6}
Coincidence 10 Si – Absorber rate (Hz)	3×10^{5}	8×10^{4}

Table 4.1: iSimulated count rates in clinical conditions for the Compton camera schematized in Figure 4.4-b, according to measured count rates at HIT.

Detector developments The above design studies allowed us to define the characteristics of the silicon detectors. Following previous measurements with reduced size detectors, real size detectors with 2 mm thickness, double-sided strip (1.4 mm pitch), and 96 × 96 mmi^2 active area are now under test at the IPNL laboratory (see figure 4.5). The integrated front-end electronics has been developed at the IPNL electronics lab [DDK$^+$12]. Figure 4.5 also shows the first version of the ASIC on its test board. The next version, with 16 channels and improved performances, is expected by Spring 2013. The energy resolution of these detectors is a key factor for the spatial resolution of the Compton camera.



(a) (b)

Figure 4.5: Left: final size double sided silicon strip detector on test board for leakage current measurements. Right: readout ASIC for silicon detector on test board.

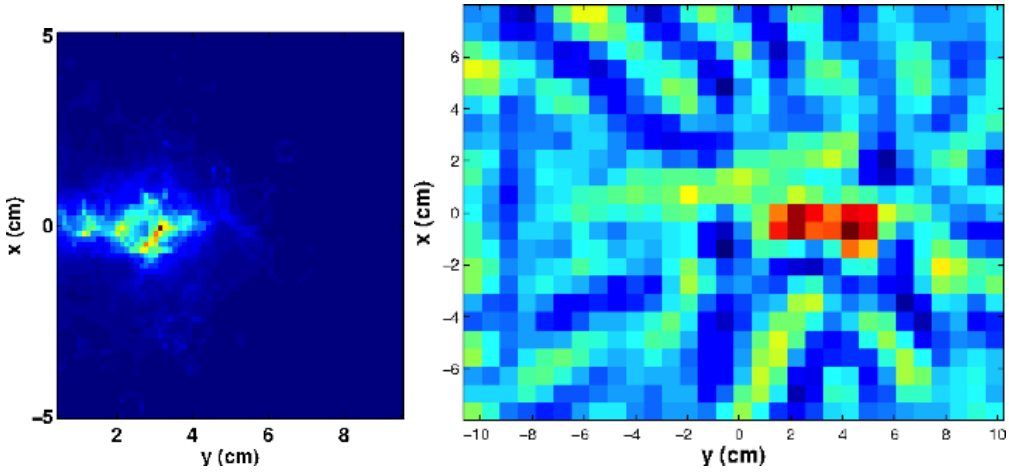
A data acquisition system, with high data flux and processing capability, is under development at LPC-Clermont-Ferrand (micro-TCA acquisition system).

Image reconstruction List-Mode Maximum Likelihood Expectation Maximization (LM-MLEM) algorithms use to be employed for Compton camera image reconstruction. As already known for nuclear medicine applications, they are able to faithfully reflect the physical processes taking place during emission and detection, at the expense of sometimes considerable computational burden [FZMP10]. The most costly and difficult to implement step is the computation of the system matrix. For instance, for n detected events and N^3 voxels in the image, the complexity of the standard algorithm is $O(nN^3)$. During his PhD thesis at CREATIS, supported by the European project ENVISION, Xavier Lojacono proposed a new calculation method [LMP11]. The method provides a better precision when the camera has ideal detection properties and has the complexity $O(nN^2)$. An extension aiming to account for measurement uncertainties was recently developed and shown at the IMAGIV colloquium in Lyon [LHP$^+$12]. The presentation also included some of the results from the Master thesis of Estelle Hilaire and Rohit Prasad (2012, CREATIS).

Simultaneously, fast analytic reconstruction methods are investigated. Following ideas from [MFP09], where a first analytic method capable to directly reconstruct images from standard geometries was developed, a filtered backprojection algorithm leading to practical computer implementation was proposed in [LMZ$^+$11]. Recent advances were presented in 2012 at the XIème Colloque Franco-Roumain de Mathématiques Appliquées in Bucarest [Max12], and should be pursued with a Master thesis supported by the Labex PRIMES.

In a collaborative work between CREATIS and IPNL, presented at the IEEE NSS-MIC conference [LRR$^+$11] and submitted for publication at IEEE-TNS, the imaging properties of the

simulated prototype described in section 4.2.1 were evaluated. The Point Spread Function and the ability to detect the position of a point source in images reconstructed with both iterative and analytic methods were analyzed. Iterative methods show to be well adapted for low statistics, hadrontherapy-type applications, whereas analytic methods are both fast and precise as soon as sufficient data are available [LRT+13].



(a) (b)

Figure 4.6: Reconstructed image of the gamma emission on the beam path. A PMMA phantom of 15x20x15 cm^3 and a Compton camera of 8 cm side for the scatterers, centered at $(x, y) = (0\text{ cm}, 5\text{ cm})$ were simulated at IPNL. The geometry of the camera is shown in figure 4.4. The position of the Bragg peak is supposed to be at $y = 5$ cm. Left: LM-MLEM image with 10 iterations and 7×10^3 detected events. Right: analytic reconstruction from 19×10^3 detected events. Note the high activity close to the end of the beam range and the absence of emission beyond the position of the Bragg peak. The color scale is in arbitrary units.

4.2.2 In-line beta+ imaging

Imaging of the beta+ activity is one of the three modalities envisaged for online control of ion-therapy with secondary radiations. One can observe a correlation of the deposited dose and the distribution of beta+ activity emitters that exhibits a falloff at the distal edge of the Bragg peak. The spatial distribution of positron emitters is to some extent correlated with the range of the ion.

It is possible to measure the spatial distribution of positron emitters during irradiation (in-beam PET), keeping the patient in the treatment room (in-room PET) or outside the treatment room (off-line PET). Off-line PET measurements with a clinical PET is disturbed by the metabolic washout. This tends to relocate the spatial distribution of radionuclides. The research activity of the LPC concerns development of in-beam PET-like detection system for the estimation of the positron emitting nuclear fragments induced by the incoming beam. The foreseen solution relies on four axes:

- the use of fast and luminous scintillators, like LYSO or LSO;
- fast response photosensors, like multichannel plates PMT (MCP-PMT);
- a fast sampling electronics, allowing, by numerical reconstruction with optimum filtering, to reconstruct both the timing and the amplitude of each signal, with a common reference clock.

- the use of a fast DAQ system using microTCA technology

The contribution to the European project ENVISION (WP2) and to the PRRH consists in developing a generic fast-acquisition electronics for PET and SPECT (prompt gammas). This work is undertaken in the frame of a collaboration between IN2P3 laboratories (LPC-Clermont, IPNL, IPHC, CPPM) and supported by the GDR MI2B.

Experimental beta+ activity measurement

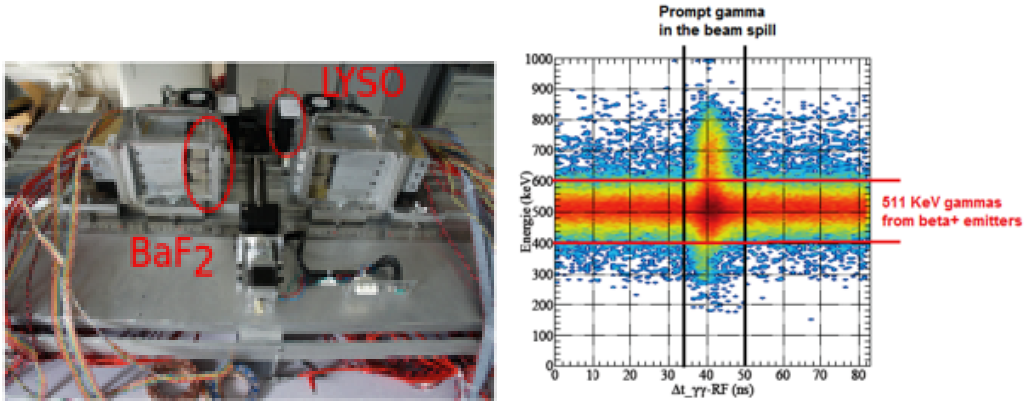
Measurements performed during irradiation (in-beam PET) are strongly affected by the presence of other secondary particles, like prompt gamma emission, that yields a high rate of random false coincidence, depending on the beam time structure.

These prompt gammas are correlated to the beam spill, unlike gammas induced by positron annihilation, which are uniformly distributed over time. In fact, random coincidences considering PET acquisition could be rejected using some conditions integrated into the trigger process. The research activity of the LPC concerns developments of in-beam PET like system for the estimation of the positron emitting nuclear fragments induced by the incoming beam.

We check the advantages and the constraints of the on-line measurements of the yield and the spatial distribution of positron emitters during hadrontherapy. These are based on some experimental results with different characteristics of incident beams (proton and carbon).

The first experiments performed at GANIL in Caen (France) demonstrated that in-beam PET acquisition could reasonably be achieved depending on specific beam configuration. GANIL accelerator is a cyclotron with a radio frequency (RF) of around 12 MHz (83 ns period) and a beam intensity of 10^8 carbon ions per second. Our experiments used two simple detectors operated in coincidence during irradiation of a PMMA target by a 75 A.MeV $^{13}C^{6+}$ beam.

Several detector devices were used: LYSO matrix coupled to Avalanche Photo-Diodes and BaF2 / LaBr3 blocks (see Figure 4.7-a). For each triggered event, the analogue waveforms of the two coincident detectors are sampled via custom-made electronic modules. Time mark and energy of the signal are extracted off-line through waveform samples analysis. In case of this specific beam time structure on can easily distinguish prompt radiation from delayed beta+ decay as shown on the 2D energy-time diagram like on Figure 4.7-b below.



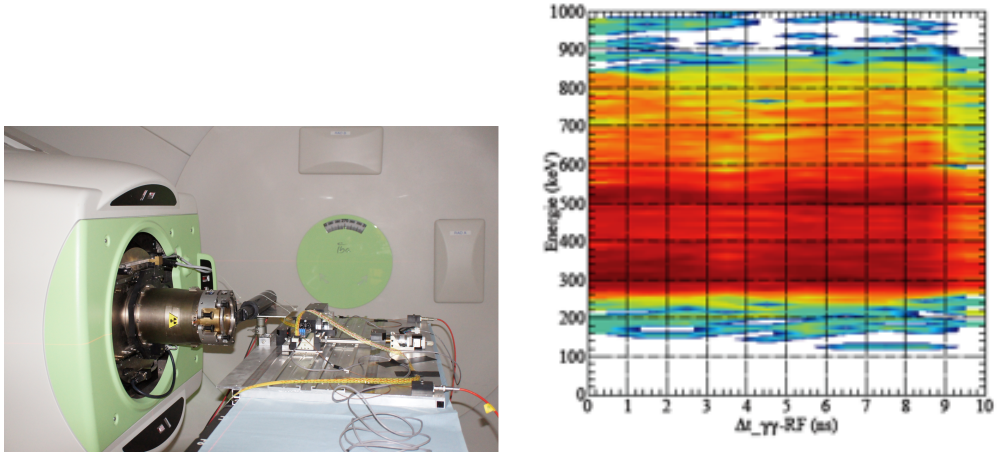
(a) (b)

Figure 4.7: (a) Experimental setup at GANIL, with small acceptance LYSO and BaF2 detectors. (b) Energy *vs* Time distribution of coincidence events between the two detector heads. The beam pulse is 1 ns in length, with a period of 80 ns.

Conclusion on the possibility of a PET acquisition between the ion bursts is quite different in case of an increase of the duty cycle. An experiment performed at Curie Institute for protontherapy

facility in Orsay (ICPO) demonstrated that, for continuous proton beams, one needs to improve the on-line rejection method of the false coincidence using more elaborate trigger. ICPO accelerator is a cyclotron with a radio frequency (RF) of around 10^6 MHz (9.4 ns period). Two simple detectors operate in coincidence during irradiation of a PMMA target by the 86 MeV proton beam.

Figure 4.8 shows that when adjusting the beam intensity to get on average 3 protons at each beam spill (4 Gy/min at the gantry nozzle), it is quite impossible to distinguish prompt radiation from delayed beta+ decay as shown on the 2D energy-time diagram like on Figure 4.8-b.



(a) (b)

Figure 4.8: (a) Experimental setup at ICPO, with small acceptance LYSO detectors. (b) Energy *vs* Time distribution of coincidence events between the two detector heads. The beam pulse is 1 ns in length, with a period of 9.4 ns.

Simulation work, including the time structure of the beam to study the feasibility of PET acquisition during the irradiation, showed that one needs to improve the on-line rejection method of the false coincidences. Thus one has to fully use the potentiality of the fast read-out electronics to design more elaborate trigger of the event acquisition. This study is part of Loïc Lestand's PhD at LPC-Clermont [Les12].

beta+ activity simulation

Geant4 simulations have been performed in order to first assess the accuracy of some hadronic models to reproduce experimental data. Two different kinds of data have been considered: beta+ emitting isotopes and prompt γ-ray production rates.

Beta+ emitting isotope yields as a function of depth were measured for 214, 260 and 337 AMeV ^{12}C beam interacting with a PMMA target ([Fiedler-2006], [Priegnitz-2008], [Priegnitz-2012][1]). Figure 4.9 presents the comparison between experimental and simulated profiles. Each profile was normalised to the total integrated area so only profile shapes are compared. Simulated profiles are in reasonably good agreement with experimental ones. This is especially true concerning the peak-to-plateau ratio which is well reproduced. In conclusion, the production rates and spatial

[1] F Fiedler, P Crespo, K Parodi, M Sellesk and W Enghardt, 2006, The feasibility of in-beam PET for therapeutic beams of 3He *IEEE Trans. Nucl. Sci.* **53**, pp 2252–59.
M Priegnitz, F Fiedler, D Kunath, K Laube, K Parodi, F Sommerer and W Enghardt, 2008, A Novel Approach for predicting the Positron Emitter Distributions Produced during Therapeutic Ion Irradiation, *IEEE NSS Conf. Record*, pp 4516–19.
M Priegnitz, F Fiedler, D Kunath, K Laube and W Enghardt, 2012, An experiment-based approach for predicting positron emitter distributions produced during therapeutic ion irradiation, *IEEE Trans. Nucl. Sci.*, **59**, pp 77–87.

distribution of beta+-emitting isotopes induced by carbon beam interacting with PMMA target are well reproduced by simulations using Geant4 toolkit version 9.4.

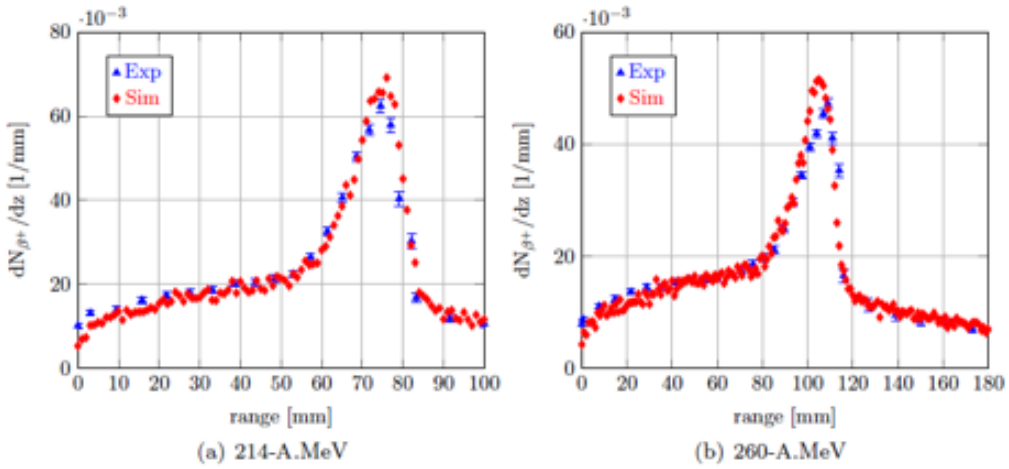


Figure 4.9: Experimental *versus* simulations: beta+-emitting isotopes depth profiles induced in a PMMA target by a 214 AMeV carbon beam (a), 260 AMeV carbon beam (b). Fiedler *et al* (2006), Priegnitz *et al* (2008, 2012)).

On the other hand prompt γ yield evaluation is important to estimate random false coincidence. By tuning the tolerance factor of the photon evaporation model available in Geant4, we adjust prompt γ-ray production rates until a very good agreement is reached with existing experimental data.

Nevertheless, the results obtained are in a sufficiently good agreement, in order to design a dedicated in-beam PET QA device. In other words, we are able to investigate, given simulated counting rates, the feasibility of in-beam QA.This study is part of Loïc Lestand's PhD at LPC-Clermont [Les12] and was published [[LMFP12].

TOF in-beam development

One way to improve the spatial resolution of beta+ activity reconstruction (in beam PET) by means of time-of-flight selection of the two photons in coincidence should allow a considerable gain in the data processing time to reconstruct an image. This would also reduce reconstruction artefacts associated to the necessary limited size of an in-line PET for ion-therapy and provide a much better image quality for a same counting statistics. The objective of this research and development program, undertaken by the LPC-Clermont and IPNL Lyon laboratories, in collaboration with IPHC Strasbourg and CPPM Marseille (IN2P3), is to achieve on the mid-term a detection system with a time resolution of 200 ps, which corresponds to a spatial resolution of 3 cm, i.e. the typical size of a tumour.

The achievement of a TOF-PET with 200-300 ps resolution will reinforce the relevance of such an imaging modality for online ion-therapy monitoring. In particular, the faster the timing resolution, the shorter the reconstruction times.

To achieve this goal developments will mainly focus on the use of micro channel plate based photodetectors. First, Photonis and Hamamatsu multichannel MCPPMT will be used to check what will be the ultimate TOF resolution accessible using such photodetectors.

The INCA Physique-Cancer project BETATRAC has been approved in 2011, in collaboration between LPC Clermont and IPHC-Strasbourg to achieve these first studies and prepare the use of large area MCP PMT under development in the LAPD collaboration at Chicago University. First prototype of large area MCP-PMTs (8 in $\times$ 8 in) that presents a good time resolution, at



Figure 4.10: Response of 3 of the 16 channels of a Hamamatsu MCPPMT exposed directly to a fast optical pulse (yellow pulse). This led pulse is 20 ns in length.

relatively low cost will be available in 2013. LPC Clermont and IPHC Strasbourg collaborate with LAPD collaboration to use this detector in TOF PET-like medical imaging.

4.2.3 Proton interaction vertex imaging

During carbon ion irradiations, the proton emission yields are quite high, and protons are directed forward. This opens the way to a new imaging modality, in particular by means of interaction vertex reconstruction (IVI), in which proton tracks are identified by several position sensitive telescopes. A resolution of the order of the millimetre for vertex positioning is expected. Previous preliminary measurements performed at GSI and GANIL allowed us to compare the measured charged particle yields and the predictions by Geant4. The thesis of Pierre Henriquet (supported by the PRRH 2008-2010) has demonstrated the ability of proton vertex imaging for online control of carbon ion therapy [Hen11]. This feasibility study has been carried out with Geant4 simulations to evaluate two detection techniques: a first one with double-proton detection by means of two forward-located trackers, and a second one with single-proton detection, in coincidence with the incoming carbon ion detected by means of a beam hodoscope. The first conclusion of this study is that the single-proton detection appears the most promising with detection efficiency ten times larger than the one of double-proton detection. Parameter influences have been considered with head-like phantom (Figure 4.11-a). Figure 4.11-b shows reconstructed-vertex distributions in this phantom for various ion beam energies (from 150 to 300 MeV/u). The smooth lines correspond to fits with complementary error function which provides the position of the inflection point. As expected, the shorter the ion range, the lower the reconstructed-vertex yields due to proton attenuation in the target. There is a clear correlation between the ion range and the inflection-point position of the vertex-distribution edge determined with fits of complementary error function (Figure 4.11-c). This correlation is not strictly linear so that a calibration procedure is required to set the function between the ion range and the inflection point position. Nevertheless the distance between the four points of Figure 4.11-b and a linear fit does not exceed 10 mm which tends to show that this calibration is not a critical issue to achieve millimetric precision. Moreover the precision on the inflection point position determined by a complementary function fit has been evaluated as a function of the incident ion amount: with the detection setup of Figure 4.11-a, this precision is 5 mm (FWHM) with a number of incident ions close to 10^5 which corresponds to the mean number of incident ions per raster position during a regular treatment of head-tumor.

In September 2011 we performed the first IVI measurements at GANIL, using CMOS-pixel silicon detectors for secondary proton tracking, and a beam hodoscope to track the incident carbon ion beam. A new experiment at higher ion energy took place in December 2011 at HIT – Heidelberg

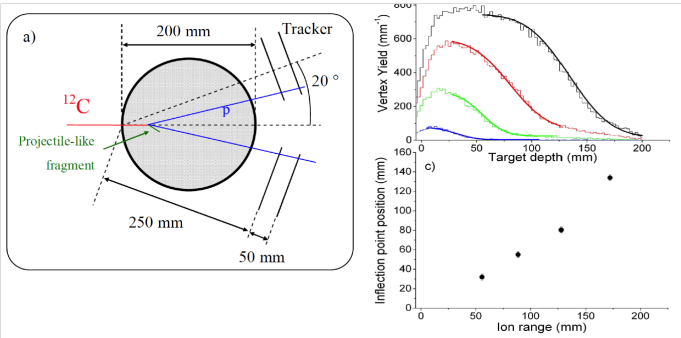


Figure 4.11: (a) Diagram of the spherical head phantom simulation: a hollow bone-equivalent sphere in which cortical tissue-equivalent material is located. The sphere diameter and thickness are 200 and 3 mm, respectively. (b) IVI reconstructed vertex distributions in the head phantom (diameter of 20 cm) for various ion beam energies (300, 250, 200 and 150 MeV/u). The smooth lines correspond to fits with complementary error function. (c) Inflection point position (determined from fits) as a function of ion range. Number of incident ions per simulation: 10^6 (from [HTC+12]).

in the frame of the ULICE transnational access to infrastructure program. A third experimental test dedicated to IVI was made in August 2012. Figure 4.12 shows the experimental setup at HIT, with a beam hodoscope, a PMMA target block, and the 4-plane CMOS tracking detectors (2 × 2 cm^2) located after the target, at an angle of 10°.

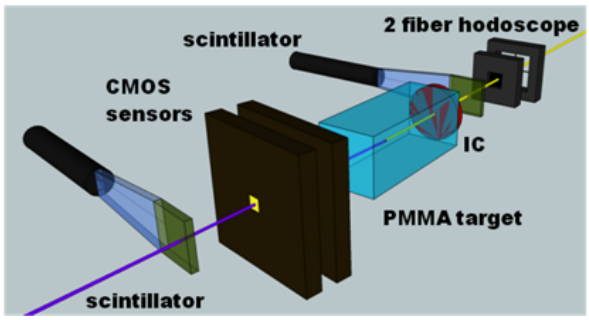


Figure 4.12: Sketch of the experimental setup for IVI imaging. The carbon ion beam is incident on the top right (refer to text).

For the first time we could observe that the longitudinal profiles of proton vertices are correlated to the carbon ion ranges in a homogenous phantom target. Figure **??** illustrates this correlation, for ion ranges varying from 155 to 245 mm in PMMA.

Simulations were undertaken during the Master internship of Anne-Laure Pequegnot at IPNL, and these simulations allowed to reproduce the shape of the experimental profile in the fall-off region. The influence of heterogeneities located along the ion path was studied. The influence of such heterogeneities close to the Bragg peak could not be pointed out.

The INCA Physique-Cancer project QAPIVI was approved in 2011, in collaboration between IPNL, CREATIS, IPHC-Strasbourg to develop a IVI prototype. This detector development is the thesis subject of Valérian Reithinger at IPNL (2011-2014).

Meanwhile we are collaborating with the TERA group in the framework of the ENVISION (WP3) project. This group has developed such a charged particle telescope using GEM tracking detectors. Common tests at carbon ion accelerator facilities are foreseen.

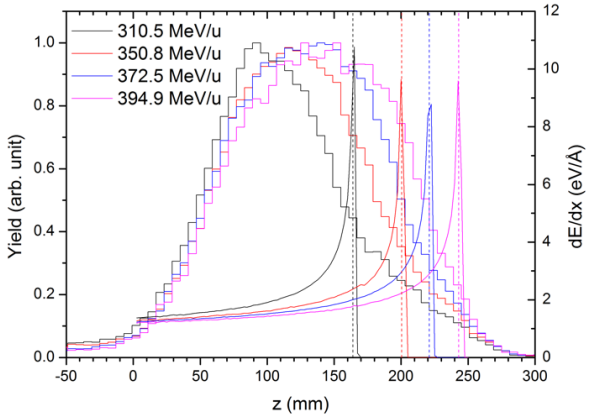


Figure 4.13: Measured longitudinal distributions of reconstructed proton interaction vertices, for various incident energies of the carbon ion beam. The calculated primary ion dose distribution profiles are also shown.

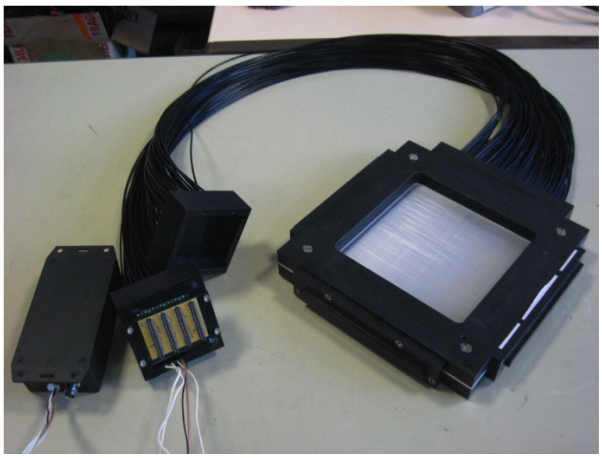
4.2.4 Beam hodoscope for time of flight

The time-of-flight measurement is required for prompt secondary radiation imaging, as illustrated above. To this purpose, an incident-ion beam tagging system is needed, whatever the time structure of the beam is. For ions issued from a synchrotron, the instant of impact of the incident projectile is randomly distributed. For protons accelerated by cyclotrons, the passive or active energy scanning systems will vary the phase between the HF pulse and the arrival time of beam pulses in the patient body.

We have been developing a beam hodoscope made of two (horizontal and vertical) planes of square scintillating fibers, read-out by a multi-anode photomultiplier. A first prototype was tested at GANIL at the end 2009. The quite encouraging results have shown that the time resolution of such a detector is about 500 ps (FWHM), and their resistance to ion irradiation damage allows one to use such fibers with fluences of the order of 5×10^{12} ions/cm^2. This corresponds to several weeks of clinical conditions utilization.

Since then we have built a larger prototype with 128×128 mm^2 active area (see Figure 4.14-a). A PhD thesis was defended in 2012 at IPNL (Shiming Deng, co-financed by ANR and the PRRH for the period 2009-2012) [Den12] to design and build the integrated electronic readout of the hodoscope. A first chip, made of current conveyor with charge preamplifier and discriminator (see figure 4.14-b), has been tested in laboratory and under beam conditions. A second ASIC chip designed by S. Deng has been submitted in 2012, integrating the Time to Digital Converter via a delay-locked-loop. S. Deng has published an article and made several presentations in international conferences about this electronic chip [DMDL11, DMD$^+$12, DDL$^+$12].

Beam tests at CAL-Nice in 2011, 2012, and at the Orsay Tandem in 2012, allowed us to evaluate the response of the ASIC chip, and to measure the count rate capability of the Hamamatsu H8500 multi-anode photomultiplier. The latter is limited to 10^7 counts/s, which implies to use several photomultipliers, in order to share the signals from adjacent fibers on different devices [DRDD$^+$12]. Another type of photomultiplier, based on large area micro-channel plates (MCP-PMTs), was also tested, but these tests did not present this kind of photomultiplier as a valuable alternative to PMTs.



(a)



(b)

Figure 4.14: (a) scintillating fibers hodoscope, made of two planes of 128 adjacent square scintillating fibers (1 mm size), and optically connected to a 64-channel flat panel Photomultiplier. (b) PMT connected to a test board containing the ASIC chip developed at IPNL.

4.2.5 Nuclear physical data and models

Nuclear fragmentation experiments

Two experimental programs, aiming at carbon ion fragmentation measurements in targets of relevance for ion therapy, were undertaken.

- At the national level, a collaboration with LPC-Caen, IPN-Lyon, IPHC-Strasbourg, GANIL and CEA-Saclay is supported by the GDR MI2B. It concerns mainly the measurement of nuclear fragmentation cross sections of carbon ions at energies less than 100 MeV/u. Such cross sections are not well known. A first experiment took place at GANIL in June 2008, where light fragments emitted from plastic (PMMA) targets of various thicknesses were detected and identified at different angles by means of telescopes. The results published in 2011 [BLB+11] exhibited noticeable discrepancies with Geant4 predictions. This motivated a second experiment, to perform systematic measurements with thin targets, that was performed in 2011 at GANIL. The data have been submitted for publication.

- At the European level, INFN physicists (supported by CNAO), in collaboration with GSI, the CEA-Saclay, and the above French collaboration, have initiated the FIRST program for fragmentation of light ions at energies between 100 and 400 MeV/u at GSI (Darmstadt). This experiment was performed in July 2011.

In the long term, a program of systematic measurements with a dedicated setup at the Archade research center will be implemented. This will contribute to provide inputs to physical data bases, in order to constraint the theoretical models used for the estimation of the dose deposited by secondary fragments. This is of particular interest for the present purpose of controlling online the dose by nuclear imaging.

Secondary radiation for imaging

The experimental feasibility studies on prompt radiation imaging are combined with Geant4 simulations which, in a first step, provide direct comparison with theoretical models, and, in a second step, will help for designing an optimized detection setup. First studies with Geant4 9.1 have shown that this Geant4 version overestimated the overall prompt gamma yields by more than an order of magnitude [LFCD+10]. Interactions with Geant4 developers have led to improvements in the last version of Geant4 (9.4, December 2010), and further tuning of the QMD model provides a reduced disagreement by only 20% between simulations and data (see figure 4.15). A comparison with other simulation packages like FLUKA (in collaboration with HIT-Heidelberg) and MCNPX (in collaboration with the industrial partner IBA) was undertaken, in the framework of the European ENVISION project (WP6), for which a post-doc (George Dedes) was recruited by UCBL.

As a further step, we investigate improvements to the aforementioned Geant4 theoretical models, in order to achieve the desired prediction accuracy required in the context of development and optimization of simultaneous prompt gamma and secondary proton imaging devices. This is part of the thesis of Marco Pinto (2011-2014), recruited with a Marie-Curie fellowship under joint supervision of IPNL and CREATIS (ENTERVISION program).

4.3 Perspectives for 2013 and beyond

Prototypes construction

In the next two years we will complete the technological developments of the collimated gamma camera and the Compton camera, in order to deliver the first prompt-gamma imaging prototype in 2013. Both cameras will be used with a dedicated beam hodoscope for TOF and a fast data acquisition system.

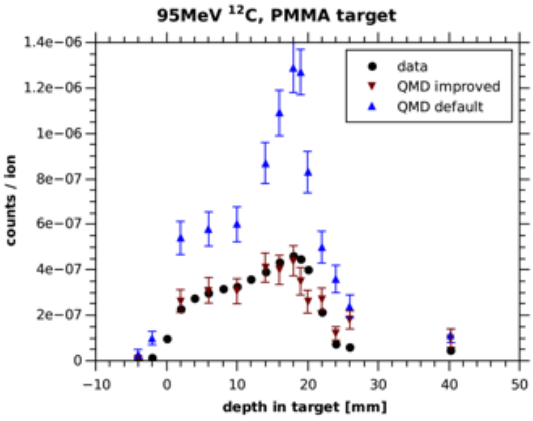


Figure 4.15: comparison between the prompt gamma profile measured at GANIL and simulations using various models in Geant 4 [DDDR$^+$12].

In particular, an optimised collimator will be developed in order to get the best compromise between the field of view (and thus the detection efficiency), and the spatial resolution.

All the detector prototypes will be made available for the ETOILE therapy center.

We will also study the potential of the Compton camera for clinical and pre-clinical imaging. Indeed, this new kind of camera, specially designed for high energy gamma rays, may open the way to the imaging of new isotopes, and/or to measurements at high statistics or low doses. This work is part of Jean-Luc Ley's PhD (2012-2015), co-supervised by CREATIS and IPNL, and supported by the Labex PRIMES.

For beta+ activity reconstruction, before using MCP-PMTs detectors to build a large acceptance detector DPGA, a preliminary configuration using a large number of simple channels using crystal (LYSO) and simple PMT will be available in 2013. This Large Area Pixelised Detector will be used first to test a high frequency sampling front-end electronic, as well as the MicroTCA acquisition system, on a large scale. This detector will be used also to test on proton beam (CP Orsay and Centre Antoine Lacassagne Nice) and Carbon (at HIT Heidelberg through ULICE network) to check innovative protocol for dose control and monitoring with beta+ production.

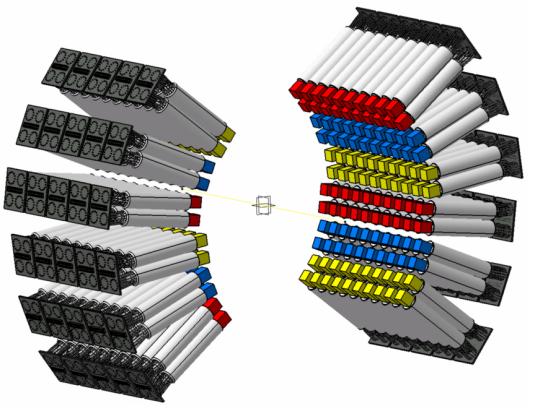


Figure 4.16: Schematic view of the Large Aera Pixelised Detector that will be use first to test on a large scale a high frequency sampling front-end electronic, as well as MicroTCA acquisition system.

4.3.1 Proton CT

A new research activity has recently emerged: proton radiography, in connection with ion-therapy. Indeed, radiographic image guidance is used both at the treatment planning stage and immediately before the treatment fraction as a quality assurance tool. However, X-rays present several shortcomings, notably:

i at the treatment planning stage, the mandatory conversion from Hounsfield numbers to proton stopping powers leads to ∼3% or more uncertainties in proton range and

ii X-ray digital radiographs and/or cone beam CT (CBCT), used to ensure correct patient positioning, suffer from artifacts and poor contrast in some anatomical regions, making it difficult to see the tumor and/or distinguish critical organs.

Proton radiography presents potential advantages as compared to conventional X-ray CT. Indeed, as each proton projectile is detected after the traversal of the patient, the information carried (residual energy, direction) may be used for imaging purpose.

Therefore, proton imaging based on the tracking of individual protons is thought to have the potential to improve treatment planning as well as in-room image guidance, with imaging doses equal to- or lower than the dose from kV x-ray CBCT. One of the main expected outcomes of proton imaging is a substantial reduction of range uncertainties in proton and carbon ion beam treatment. Improved verification of the patient positioning will also significantly reduce the risk of non-conformal dose delivery.

In the frame of the French GDR MI2B, we propose to design and develop a proton radiography and computed tomography demonstrator, together with suitable reconstruction algorithms based on the realistic modeling of the proton interactions. The goal is to go beyond the current international state of the art, both in hardware and software aspects: millimeter accuracy in range resolution and high counting- and data acquisition-rate capabilities (greater than 10^6 counts/s) seem to be under reach, making it possible to acquire high-quality radiographs in a matter of seconds, thus minimizing its cost.

The Physics-Cancer ProTom project, lead by CREATIS, was approved for a one year duration in 2011, in collaboration between CREATIS, IPNL, LPC-Caen and IPHC-Strasbourg, in order to assess the imaging potential by means of simulations. This project, lead by IPNL, involves IPNL, CREATIS, IPHC-Strasbourg and the Centre Antoine Lacassagne (Nice). A group project, in which IPNL and CREATIS are present, has been initiated within the GDR MI2B in 2012. This activity should be also one of the federative activities of the PRIMES Labex.

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Chapter 5

Radiobiological effects of carbon ions

General organization for this theme

Axis 1

Lyon Sud: EMR 3738, équipe 4 - Laboratoire de Radiobiologie Cellulaire et Moléculaire, Faculté de Médecine, Lyon Sud.
Scientific manager: C. Rodriguez-Lafrasse (PU-PH, UCBL/HDR, HDR)
Team members:

- D. Ardail (MCU-PH, UCBL/HCL, HDR)
- D. Poncet (MCU-PH, UCBL/HCL)
- G. Alphonse (Chargée d'étude HCL)
- N. Magné (PH radiothérapeute, ICL)
- S. Ferrandon (Doc UCBL)
- G. Bertrand (Doc PRRH/UCBL)
- C. Moncharmont (Doc ICL)
- M. Gilormini (Doc UCBL)
- E. Armandy (TCH UCBL)
- C. Malesys (TCH UCBL)
- P. Battiston-Montagne (ATCH UCBL)
- C. Gagnon (secrétariat, ATCH UCBL).

While in previous years we had access to the beam during three periods of time per year at GANIL and two at GSI, this number was drastically reduced in 2012. Due to the restructuring of the sites, only two beam-times were obtained at GANIL in 2012 and none at GSI. The time period attributed to biological experiments is too short and does not allow developing research in radiobiology only devoted to the cellular response to carbon ions. For this reason, the senior researchers and students have an equal share in the number of hours of carbon beam and the rest of the year answer their question with photon irradiation (320 KeV X-ray irradiator CERVO platform).

Axis 2

IPN Lyon, UCBL: scientific coordinator : M. Beuve (PR UCBL, HDR)
Team members:

- M. Bajard (IR IPNL, CNRS/IN2P3)
- L. Chollier (PhD IPNL, CNRS/IN2P3 - PRRH)

- J. Constanzo (PhD IPNL, UCBL)
- M. Cunha (PhD IPNL, CNRS/IN2P3)
- D. Dauvergne (DR IPNL, CNRS/IN2P3)
- M. Fallavier (CR IPNL, CNRS/IN2P3)
- N. Pauna (MCU, LPC Clermont, Clermont Université)
- C. Ray (MCU HDR IPNL, UCBL)
- E. Testa (MCU IPNL, UCBL)

LPC Clermont-Ferrand: scientific coordinator G. Montarou (DR IN2P3)
Team members:

- D. Dabli (IE CNRS)
- F. Chandez (IR CNRS)
- M. Gautier (Ph-D. CNRS)

The physicists take part in all the experiments at GANIL.

A good knowledge of the physio-chemical and biological events triggered in reponse to carbon therapy, and thier comparison to the results obtined with photon therapy, used as the reference technique, is mandatory for a reliable and secured transfer toward the clinic. This objective may be reached thanks to a multi-disciplinary approach gathering researchers with a unique expertise in physics, chemistry, biology, simulation and radiotherapy.

The objective of this theme are:

- to eludicate and quantify the molecular events triggered by carbon ions in the tumoral and sound tissues using various models (cellular, pre-clinical, and for patients) et various scales of time (from femtosecond to a few years);
- to predict the response to tumoral and sound tissues for both types of radiation;
- to improve ou develop new models for treatment planning, and to enrich them with biological parameters.

5.1 Axis 1 : Cellular and molecular response of tumors to carbon ion and photon irradiation (comparison with photons)

5.1.1 Overall 2012 assessment

The tumor and healthy cell responses to ionizing radiation depend on the balance between the mechanisms (mainly oxidative stress) leading to cell death and those of protection against Reactive Oxygen Species (ROS) and DNA repair. If the non-repaired DNA double strand breaks have been considered for a long time as the sole determining factor of radiation-induced cell death, for several years our group has contributed to the demonstration that plasma membrane and mitochondria are also compartments significantly involved in the cell death process. Two tumor models were used in this study:

- Head and Neck Squamous Cell carcinoma (HNSCC), including six cell lines with different radiosensitivity and p53 status ;
- Glioblastoma, including 12 cell lines with different radiosensitivity, p53 and MGMT status.

Both types of tumors have a bad prognosis and generally escape cancer treatment including conventional radiotherapy. They are thus a potential elective indication of carbon hadrontherapy.

HNSCC model

Implication of cancer stem cells in radioresistance It is now well-established that heavy ion radiotherapy can offer some potential benefit over conventional radiotherapy. The advantage of this new method of treatment lies in the physical and biological properties of carbon ions. We initiated studies on the mechanisms of cell death in two p53-mutated HNSCC cell lines with opposite radiosensitivity following carbon ion and X-ray exposure [BAM$^+$08], since recent clinical trials have shown that local treatment of HNSCC by carbon hadrontherapy was much less efficient than that of other radioresistant cancers.

We first showed that carbon ion irradiation does not modify the type of death involved, but amplifies it. In the radiosensitive SCC61 cell line, an early ceramide-dependent apoptotic cell death occurred after irradiation [AMBM$^+$12]. In contrast, the radioresistant SQ20B cells underwent G_2/M arrest associated with Chk1 activation and Cdc2 phosphorylation. Furthermore, 5 days after carbon ion irradiation, SQ20B cells bypassed the G_2/M arrest and underwent mitotic catastrophe [MAC$^+$09]. Although a majority of SQ20B cells go beyond mitotic catastrophe by a ceramide-dependent apoptosis mechanism, a subpopulation of cells was able to escape and continued to proliferate.

Recently, the involvement of Cancer Stem Cells (CSCs) has been demonstrated in solid tumors recurrences following conventional irradiation. We have then investigated whether CSCs might be the subpopulation of SQ20B cells resistant to carbon ion irradiation.

We first demonstrated that a subset of SQ20B cells presents different markers of CSCs such as CD44 expression, Hoechst efflux, ALDH over-activation and spheroid formation. We then separated a SQ20B/SP/ALDH+/CD44+ (CD44+) subpopulation as putative HNSCC cancer stem cells. The radiation response of this subpopulation of cancer cells that are likely to be critical for success or failure of cancer therapy was then studied. The CD44+ cells were more resistant to photon as well as carbon ion irradiation than the non-cancer stem cells. After the analysis of cell cycle we demonstrated that the lack of apoptosis induction, due to an extend G_2/M phase arrest induced by carbon ion irradiation, was responsible for this radioresistance. Moreover, we also showed that the resistance of CSCs may result from exacerbated self-renewal and proliferative capacities. Among the different pathways of self-renewal, Bmi-1 appeared to be involved and the high proliferative capacity of CSCs was related to a high aldehyde deshydrogenase (ALDH) activity. We then attempted to modulate these different processes to sensitize CSCs to photon or carbon ion irradiation.

Since irradiated CSCs do not undergo early apoptosis because of a transient arrest in G_2/M followed by mitotic catastrophe, treatment of CSCs with the inhibitor of the G_2/M arrest UCN-01 triggered early apoptosis thus leading to radiosensitisation after photon and carbon ion exposure. Concerning the self-renewal pathway, inhibition of Bmi-1 with artesunate significantly enhanced sensitivity to high and low LET radiation by triggering apoptotic cell death. Finally, inhibition of ALDH using all-trans retinoic acid induced differentiation of CSCs associated with a significant decrease in cell survival after either carbon ion or photon irradiation.

The combination of ATRA and UCN-01 treatment with irradiation drastically decreased the survival fraction at 2 Gy (SF2) of SQ20B-CSCs from 0.85 after photon irradiation to 0.38. Furthermore, SF2 decreased from 0.45 in response to carbon ions to 0.21 when associated with ATRA and UCN-01 [BMB$^+$13, BMB$^+$12, BMBM$^+$12].

In conclusion, whatever the pharmacological strategies used, an important radiosensitisation of CSCs was obtained. Adjuvant treatments targeting either the inhibition of survival/self-renewal pathways or the triggering of apoptosis should improve the results for patients treated with radio- or hadron- therapy.

Role of antioxidant defenses (glutathione) – Strategy of radiosensitization We previously reported that intracellular glutathione (GSH) levels correlate with a high level of radioresistance in HNSCC cell lines. This high endogenous GSH content was shown to be involved in the inhibition of the early triggering of pro-apoptotic signals generated at the plasma membrane level [BHA$^+$07]. We therefore designed a transient GSH depleting strategy before irradiation us-

ing 2 pharmacological compounds (DMF + BSO) in order to reverse the resistance of tumour cells to irradiation. This experimental approach was found to be effective in HNSCC stem- as well as non-stem cells thus suggesting that this treatment could reduce local recurrence of cancer after irradiation. Moreover, we further evaluated in vivo the potential radiosensitising effect of DMF + BSO on nude mice bearing SQ20B tumors. Our data show a real efficacy in radiosensitization since a decrease of 95% in the mean tumor volume was measured without apparent toxicity [BHM$^+$11]. Furthermore, carbon ions did not modify the nature of the signaling pathway involved after treatment but had a strong influence on the intensity (more pronounced effect) and the kinetics (earlier effect) of the biological response. Using this adjuvant strategy, we started experiments in collaboration with S. Sauvaigo (LAN – CEA, Grenoble) in order to demonstrate that GSH is able to directly regulate the DNA repair (single strand break) enzymes.

Effect of redox status on DNA damage, repair and chromosomal aberrations The balance between oxidative stress and anti-oxidant defenses such as glutathione (GSH) or N-acetylcysteine (NAC) influence the nature of DNA damage, repair and chromosome aberrations. The GSH depletion strategy developed in the laboratory as well as the addition of NAC (powerful antioxidant) can be used as tools to modulate the nature, amount or repair of DNA damage.

The study of radiation-induced lesions and their repair kinetics on SCC61 and SQ20B cell lines displaying opposite radiosensitivity showed that depletion of endogenous glutathione potentiates the effect of radiation on DNA, causing an increase in the number of lesions (double strand breaks, single strand breaks and oxidation of bases) following exposure to photons and an increase in the complexity of the lesions (lesions located on multiple sites and more deleterious to the cells) after irradiation with carbon ions. This effect was reversible by the addition of NAC, suggesting the involvement of oxidative stress or ROS in the generation of such damage. Moreover our results demonstrated the involvement of an indirect effect of photon and also carbon ion radiation, on a more local scale, in the generation of DNA damage [HBM$^+$12]. Further studies were conducted on Cal27 cell line exposed to carbon ions of different LET (33.6 and 100 keV/μm corresponding to the plateau and the Bragg peak entry, respectively). The kinetics of repair of double strand breaks (detected by γH_2AX immunoassay) showed a slower rate of repair and a higher number of residual breaks for cells exposed to carbon ions of 100 keV/μm, suggesting an increase in the complexity of lesions with TEL. GSH depletion increased the number of initial lesions measured for each TEL, increased the slowdown of repair and the number of unrepaired breaks. Glutathione depletion amplified the involvement of the indirect effect in the generation of complex lesions on a local scale regardless of the LET of the radiation.

Mis- or non-repaired DNA lesions may lead to the formation of potentially transmissible aberrations in the surviving cells and thus to the adaptation of cancer cells, which are considered to be a risk of local recurrence. The cytome assay allowed the identification of the loss of chromosome or chromatid as a specific biological signature of carbon ions. Moreover, our analysis showed that is the increase in the complexity of the lesions, but not their number, which could limit the transmission of aberrations to the cancer cell progeny [HBM$^+$12].

Prediction of tumor response to carbon ion irradiation

a. **Histone H2AX phosphorylation as a predictor biomarker of radiosensitivity** Analysis of the kinetics of appearance and disappearance of DSB after exposure to photons or carbon ions, provides evidence of protection capacities and repair of cancer cells, in relation to the intrinsic radiasensitivity of each line. The analysis of five HNSCC cell lines displaying gradual radioresistance highlights the importance of such relationships. Following exposure to photons or carbon ions, the rate of repair of these lesions, as well as the amount of residual unrepaired damage are correlated with cellular radiosensitivity; the most resistant cell lines rapidly repairing breaks. Measurements of the accumulation of unrepaired lesions after exposure to 1, 2, 5 and 10 Gy of photons or carbon ions show a linear relationship with the D10 estimated from the clonogenic survival of each line. A statistical analysis is being

conducted to evaluate the potential relationship between accumulation of these lesions and the RBE of radiation.

b. **Role of Nrf2 as a predictor biomarker of radiosensitivity** Given the major role played by the endogenous redox status of cancer cells in response to irradiation, we evaluated the predictive importance of the transcription factor Nrf2 in tumor resistance to radiotherapy. This factor is kept inactive in the cytosol via a protein, Keap1. In response to stress, dissociation of the Keap1-Nrf2 complex causes the translocation of the latter in the nucleus. This transcription factor, over-expressed in many cancers (including HNSCC) activates many genes involved in cellular response to various stresses, particularly those involved in cellular mechanisms of protection against oxidative stress. Having measured the basal expression of Nrf2 and Keap1 by RT-PCR and Western blot in a collection of 7 HNSCC cell lines of gradual radiosensitivity, we have developed the optimal conditions for the use of these markers by immunohistochemistry. Collaboration with the INCA platform of Strasbourg was initiated in order to validate the predictive potential of these two markers on tumor sections of human biopsies obtained from patients clearly identified clinically.

Glioblastoma model

Glioblastoma (GBM) is a primary brain tumor with very poor prognosis. Despite the treatment involving surgery, chemotherapy and radiotherapy, local recurrence is inevitable and patient survival rarely exceeds fifteen months. With its good ballistic and high RBE, hadrontherapy with carbon ions is a promising technique for radiation treatment of this type of tumor. As very few centers exist in the world, the amount of clinical studies is limited. Nevertheless, the first phase I/II clinical trial on 32 GBM patients has combined X-ray radiotherapy (50 Gy/25 fractions), concomitant chemotherapy (ACNU), and carbon ion hadrontherapy (8 fractions). Patients were assigned to three carbon ion dose groups: a low-dose group (16.8 GyE), an intermediate-dose group (16.4 to 24.8 GyE in 10% incremental steps), and a high-dose group (24.8 GyE). This trial has shown improved efficiency in terms of overall survival (7, 19, and 26 months) and disease-free survival (4, 7, and 15 months) in a manner dependent on the total carbon ion dose delivered, without major side effects[1]. Two other clinical trials are currently realised in order to evaluate carbon ion boost efficiency in GBM treatment (ICT01165671 and NCT01166308). These trials do not use biological markers to include patients, but in the future, patient selection will be necessary, owing to the cost of irradiation, technical constraints, and limited access to facilities.

Characterization of the cellular and molecular response of glioblastoma cell lines We previously initiated studies to understand the response to photon or carbon ion irradiation of 10 human glioma cell lines of gradual radiosensitivity in order to determine whether the p53 or MGMT status, the lack of production of ceramide, cell cycle arrest or the type of death, could be considered as factors predicting radioresistance. Further experiments have been carried out this year to complete the study. We confirmed that whatever the cell lines studied and their p53 status, photon or carbon ion irradiation induced a G_2/M phase arrest followed by mitotic catastrophe leading finally to a ceramide-dependent apoptotic cell death. Determination of the RBE at 10% survival gives data varying from 1.5 to 2.9 [AHH$^+$12]. A statistical study was performed in order to define a predictive factor that could improve treatment planning for particle therapy. The spearman statistic test was used to compare the data obtained during the experiments. A correlation was found between the SF2-photon and the SF2-Carbon (R^2=0.94, p = 0.0002), demonstrating that cell lines resistant to photons are also resistant to carbon ions. The ratio between percentage of cells in G_2/M phase after irradiation with 10 Gy photons and percentage of control cells was calculated and a significant correlation was found between this ratio and the SF2

[1] J.E. Mizoe, H. Tsujii, A. Hasegawa, T. Yanagi, R. Takagi, T. Kamada, H. Tsuji, K. Takakura ; Organizing Committee of the Central Nervous System Tumor Working Group. Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas : combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007:69(2):390-396.

or the D10 of carbon ions. We may then postulate that, using a mathematical model, these results could predict sensitivity to carbon ion irradiation (SF2 or D10) from the G_2/M phase arrest after irradiation by photons. Another positive correlation was found between the induction of mitotic catastrophe (quantified by the number of polyploid cells, observed in fluorescent microscopy) following photon irradiation and the RBE. These results will enable the treatment of patients to be personalized by developing new mathematical models and ultimately improve the planning of treatment.

Telomeric status and cellular response to carbon ions, towards the identification of a predictive biomarker Long telomeres and high telomerase activity (TA) have been widely associated with photon radioresistance in other cancers. Moreover, telomere protection, function, and length also depend on the shelterin protein complex (TRF1, TRF2, TPP1, POT1, TIN2, hRAP1). We thus decided to evaluate an enlarged telomeric status (telomere length (TL), telomerase catalytic subunit (hTERT), and the shelterin component expression level) as a potential radioresistance biomarker *in vitro* using cellular models and *ex vivo* using patient tumor biopsies. In addition, nothing was known about the role of telomeres in carbon ion response. We thus evaluated telomeric status after both types of irradiation. We have shown [FSC+13] a significant correlation between TL and the basal POT1 expression level and photon radioresistance *in vitro*, and a significant increase in the survival of patients with long telomeres or a high POT1 level *in vivo*. POT1 expression was predictive of patient response irrespective of the telomere length. Strikingly, these correlations were lost *in vitro* when considering carbon irradiation. We thus propose to assess POT1 expression level and TL on patient tumor biopsies to identify radioresistant patients who could benefit from carbon hadrontherapy.

5.1.2 Scientific objectives for 2013

HNSCC model

Metastatic capacity of Cancer Stem Cells We have previously demonstrated that CSCs are good candidates to explain the recurrence of cancers, in particular through their radioresistance. However, another explanation could be the strong migratory and invasive capacity of these cells. Indeed, it has recently been shown that photon irradiation is capable of promoting migration of pancreatic cancer- and glioblastoma cells. Hence our project will try to determine the effect of ionizing radiation (photons and carbon ions) on migration and invasion of stem- and non-stem HNSCC cells. The role of chemotherapy molecules traditionally used in the treatment of head and neck cancer (Erbitux and Cisplatin) will also be considered.

Role of antioxidant defenses (glutathione) - Strategy of radiosensitization In order to develop and characterize new adjuvant therapies to irradiation, we investigated the BCl-2 protein family as a potential target for radiosensitization since mitochondria serve as a hub for responses to cellular stresses. As Bcl-2 proteins were recently demonstrated to be involved in the transport of GSH from the cytosol to the mitochondria, we make the assumption that inhibiting the BcL-2 family should result in the generation of massive intra-mitochondrial stress, thereby favoring the triggering of apoptosis. This project will be performed in collaboration with W. Rachidi (LAN – CEA – Grenoble) and P. Vernet (Clermont Ferrand).

Predictive biomarker to the response of radiotherapy

a. **Keap 1 expression**
Given the *in vitro* results on the correlation between the SF2 of the HNSCC cell lines and the expression of Keap1 at the protein level, our goal will be to validate the role of this protein as a predictor of response to both conventional radiotherapy and hadrontherapy by an immunohistochemical approach using a collection of HNSCC tumor biopsies (Collaboration with INCA platform, Strasbourg).

b. **Tumor protein markers**
This project is an ancillary radiobiological study associated with the "Medical assessment and economic prospective randomized carbon ion radiotherapy for inoperable sarcomas and adenoid cystic carcinomas tumors" hospital programme (PHRC) for which clinical hadrontherapy results are better documented. The primary objective is to assess the positive predictive value of the failure of a treatment strategy (photon-or carbon-therapy) from the study of the selective expression of a panel of tumor protein markers (Bcl2/Bcl-XL, hsp27, survivin, p53, Ki67, COX2) in a prospective cohort of 250 patients. This project will develop a recruitment of patients for 3 years and provide an a posteriori indication of efficiency of radiotherapy and decision support for the therapeutic orientation. Advanced statistical analysis will determine if the selected markers enable the identification of patients resistant to conventional photon radiation therapy and for which carbon-therapy or an alternative treatment is necessary.

Glioblastoma model

Telomeric status and cellular response to irradiation Shorter telomeres and high telomerase activity are associated with shorter overall survival in glioblastoma patients. Our first objective was to determine if the telomeric status (telomere size, telomerase activity (hTERT), telomeric protein expression and localization) can predict the tumor response to photon and carbon ion irradiation. We established three stable cell lines expressing different levels of telomerase and demonstrating increasing telomere size. Thanks to this model we confirmed a correlation between increasing telomere size and higher radioresistance. This has been confirmed in a panel of 10 glioblastoma cell lines. However cell response to carbon ions seems not to be closely linked to the telomeric status in these two models. We have to confirm this result and understand the telomeric molecular events induced by both carbon ion and photon irradiation at the origin of this potential difference.

We have shown that telomeric status plays no preponderant role in cell response to carbon ions, while it is a determinant factor for cell response to photons. This discrepancy between the effects of carbon ions and photons was unexpected. As both types of irradiation produce major DNA damage and the same type of cell death, the role of telomere damage in cell death under the two conditions should be the same. However, two differences between carbon ion and photon irradiation could explain this observation:

i The most quantitatively important effect of photon irradiation is the immediate production of a high level of ROS, whereas the effect of carbon ion irradiation is not considered to involve ROS[2](which is why it is indicated for hypoxic tumor treatment). It is known that guanine-rich (T2AG3 repeats) telomeric sequences are especially sensitive to oxidative stress and produce more 8-oxoguanine and DNA breaks[3] than other genomic sequences. Telomeres should thus be a preferential target of photon irradiation within the genome and should play a leading role in the cell response to photon exposure.

ii Carbon ions mainly act by producing DNA lesion clusters that are very difficult to repair. LMDS are produced along the track of the beam and there is no reason for telomeres to be damaged more than the other sequences in the nuclear genome and their damage should not disproportionately affect the final cell response, as they represent only a small fraction of the genome. Moreover, LMDS are mostly lethal for cells. Thus, there is no reason for the cell response to carbon ions to be telomere-dependent.

To validate our hypothesis, we will evaluate the amount of telomeric damage in response to carbon ion and photon irradiation in a glioblastoma cell line. We will thus check if the initial telomeric damage is more extensive after photon irradiation than after carbon irradiation. Next we will compare the effect of telomere length on the frequency of telomeric damage in both kinds

[2]Nakano T., et al. (2006) Clin. Cancer Res., 12 (7 Pt 1):2185-2190.
[3]Du G.,(2011) Radiation research 176 (6):706-715.

of irradiation. Telomeric damage will be analyzed by confocal microscopy assessment of 53BP1 (DNA damage response protein) and TRF1 (telomeric protein) co-localization. Experiments with anti-oxydant could also be performed to evaluate the role of ROS in telomere-driven cell death in both types of irradiation.

5.2 Axis 2: Instruments, Methods and Modeling for radiobiology

The acquisition of radiobiological data and knowledge relies on the development of innovative instruments and methods:

1. To irradiate biological cells and rodents with a high level of efficiency and quality;
2. To imagine and measure relevant biological parameters;
3. To measure, store and analyze these data.

The resulting knowledge and better understanding will allow improvement of the treatments by hadrontherapy.

However the ultimate optimization requires the incorporation of these data into biophysics models to be implemented into the systems of treatment planning (TPS). In addition to this synthesizing role, biophysics modeling has to contribute to the understanding of the early stage following the impact of ionizing particles. This is particularly crucial for hadrontherapy since, the biological efficiency of high-LET ions is due to the spatial distribution of primary physical and chemical events at nano and microscopic scale.

5.2.1 Overall 2012 assessment

Oxidative stress and anti-oxidant defences: studies by physico-chemical simulations

Tumor response to ionizing radiation depends on the level of cell oxygenation. In conventional radiotherapy, a reduction in tumor vascularisation leads to radioresistance. Fortunately this effect is reduced in response to carbon irradiation and, as a benefit, hypoxic tissues are less radioresistant with carbon irradiation. Understanding this specific response would help to include oxygen effect in the biophysics models that are used for treatment planning and then to optimize hadrontherapy treatment in cases of hypoxic tumors. Among the different scenarios that are proposed in the literature, an increased production in superoxide anion O_2- and perhydroxyl radical HO_2 could explain the increased sensitivity of tissues to hadrontherapy. Chemically, both radicals are indirectly toxic. Biologically, it has been shown that a large quantity of these radicals can trigger cell death by necrosis or apoptosis.

We adapted our simulation model, dedicated to the simulation of the radical production by water radiolysis, to quantify the production of these reactive oxygen species (ROS) in various conditions of oxygenation. We also introduced a concentration of glutathione, which is known to influence the oxygen effect, and observed that the production of O_2/HO_2 radicals in water mimicked the variation of the oxygen effect with the LET and the partial pressure of oxygen. These results were published in [Col09, CGRLB11] and were presented as invited talks in two international conferences [BCGRL10, BCRLG11]. A detailed article describing the mechanisms of production of O_2-/HO_2 has been submitted for publication to the Radiation Research Journal.

Besides, we have converted these observations into a method to take into account the oxygen effect in 'any' hadrontherapy TPS for an adjustment of the irradiation parameters in the situation for which regions of hypoxia are suspected to increase the radioresistance of patient tumours.

We have written a patent, which is still in the submission process, with the support of Lyon Science Transfer.

The main objective of the work performed in Clermont-Ferrand in the mid-term will be to correlate observable events characterizing early biological events resulting from energy deposition

of ionizing radiations in cells. Physico-chemical models should be used to connect the effects of radiations with some biological observables. In particular we wish to correlate not only the energy deposition during irradiation in the different sub-volumes of the cell with these biological observables but also the produced radiolytic species such as free-radical distributions, ($OH^\bullet$, $H^\bullet \bullet$,e_{aq}), in a voxellised model of cell, focusing on the mitochondrial network.

Towards the new model Nanox of cell inactivation for treatment planning

Modelling the biological response of cells to carbon ion irradiations is required to take advantage of the radiobiological efficiency of hadrontherapy. The procedure used in the Japanese centres has yielded good results in hadrontherapy. However, this approach requires a large amount of experimental data, which reduces the possibilities of optimization according to the type of tumour, the irradiated healthy tissues and the patient's sensitivity.

Alternatively Scholz et al.[4] have proposed the Local Effects Model (LEM). After determining the parameters of this model from experimental data obtained with radiations of low LET, this model aims at predicting the fraction of inactivated cells depending on the ion nature, energy and irradiation dose. This model is used for the treatments performed in Germany. However, We showed that, to get correct predictions, the value of an important parameter should be fitted using a set of data obtained with high LET radiations [BAM$^+$08]. Moreover the comparison of the LEM predictions[5] with experimental data [BAM$^+$08] showed interesting results, but highlighted significant discrepancies that leaded the authors to improve the LEM[6] [Elsasser 2007.2008]. Our studies have shown that, beyond simple improvements, a radical reformulation of the LEM principles was required [BCD$^+$09, Beu09, Beu10]. We showed in particular that:

- the hypothesis of non-local effects should be considered in predictive models,
- the method of inserting experimental data obtained in response to X-ray radiation inconsistently mixes two scales of description: the scale of DNA damage and the scale of the macroscopic dose delivered by the accelerator,
- the LEM prediction of the shoulders in cell-survival curves as a function of dose arises from an artefact,
- the stochastic effects of the radiation had to be considered

Presently while the German group keeps on improving the LEM, the Japanese teams are moving toward other biophysical models and in particular to the models of microdosimetry (Microdosimetry Kinetic Model MKM[7]). We have undertaken an experimental evaluation of the MK model and compared its predictions to the LEM ones for the SQ20B SCC61 cell lines [Dab10]. We found that the relevance in the predictions of these models were comparable. However a great advantage of the MKM is its consistence with the stochastic nature of the ionizing radiations. Finally, for both models, improvements are required to reduce the discrepancies between predictions and experimental data. An article is in preparation.

Alternatively, we are developing a new model, Nanox, based on micro and nano-dosimetry, which:

- is consistent with the stochastic effects of radiations,
- encompasses the advantages of the existing models

[4]Scholz, M., A. M. Kellerer, W. Kraft-Weyrather, and G. Kraft. Computation of cell survival in heavy ion beams for therapy : the model and its approximation. Radiat. Environ. Biophys 36:59–66.1997

[5]Cluster Effects within the Local Effect Model. T. Elsasser and M. Scholz Rad. Res. 167, 319–329 (2007).

[6]Accuracy of the local effect model for the prediction of biologic effects of carbon ion beams in vitro and in vivo. T. Elsässer, M. Krämer, and M. Scholz.. Int. J. Radiat. Oncol. Biol. Phys 71:866–872 (2008).

[7]Sato, Y. Kase, R. Watanabe, K. Niita, and L. Sihver, Radiation Research 171:1, 107-117 (2009).
A statistical theory of cell killing by radiation of varying linear energy transfer "R.B Hawkins, Radiation research 140, 366-374 (1994)

- integrates physico-chemical effects, i.e. oxidative stress.

A first version of this model and its associated software have been developed during the PhD thesis of Laurie Chollier [Cho12]. This work is continued through the PhD thesis of Micaela Cunha.

We have already:

- derived the basic postulates,
- achieved a first version of the codes,
- applied this model to the cell line V79 and obtain very encouraging but sill preliminary results (see figure 5.1).

Since we are preparing a patent, this work was not presented, except for the preliminary results during the invited talk at the international conference MMND IPCT in Australia [BCT12].

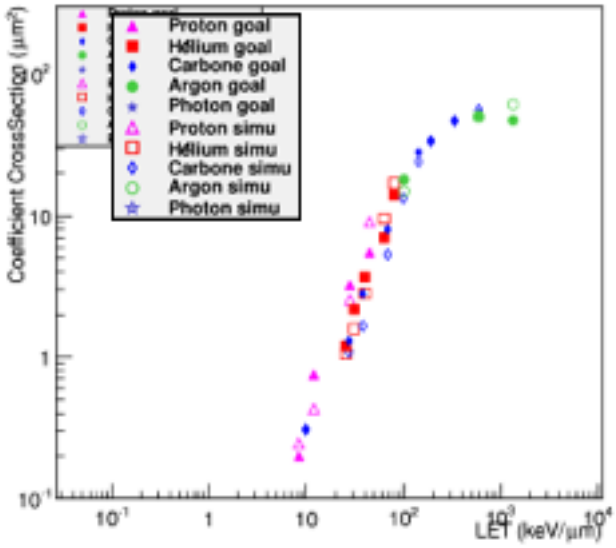


Figure 5.1: Cell Inactivation cross-section versus LET for various ion beam irradiating V79 cells. Comparison of the Nanox predictions (simu) to experimental data (goal).

From in-vitro to in-vivo In the framework of collaborative work with the Centre of Particle Therapy in Marburg and the University of Essen, we have undertaken a program to parametrize and evaluate biophysical models with clinical data. This project is the objective of Marie-Anne Chanrion's PhD (2014). Until now, we have studied the sensitivity of TCP (Tumour Control Probability) to the parameters of the LEM model. This work was presented as a poster at the PTCOG 2012 conference in Korea [CLW+12].

Methods for radiobiological data acquisition, processing and analysis Some radiobiological observables require more and more complex techniques for their acquisitions, processing and analysis. The use of immunofluorescence techniques to mark the nuclear DNA damage is one of the most common examples now. DNA damages induced by ionizing radiations produce fluorescent foci corresponding to the recruitment of certain proteins or by specific modifications such as phosphorylation of histones (eg γH_2AX foci). These foci could be analyzed using immunofluorescent confocal microsocopy. Determining the spatial distribution of these foci in the

nucleus, for different radiation qualities and their correlations with the initial energy deposition requires the establishment of technical analysis in images obtained with confocal immunofluorecent microscopes.

We have defined an automatic algorithm for non-parametric image processing and automatic foci identification using the ImageJ software. Early work on small batches of 2D images, realized at LPC [CM10] or IPNL [Wan10] showed that this type of application could be relatively efficient. Nevertheless, obtaining statistically significant results involves the acquisition of a large number of images by platforms and automated microscopy using confocal microscopy. Hence, the next goal is to apply this type of treatments on a large number of images.

Development of irradiation platforms

1. The Radiograaff plaform
   Because carbon beams are hardly available for radiobiology, we have considered the potential of the Van de Graaff accelerator at IPNL. This accelerator can produce mono-kinetic beams of protons with energy ranging from 1 to 3.75 MeV. According to the literature, the RBE (at 10% of survival) is about 1.5-1.8 for the reference V79 cell line irradiated by protons with energy lower than 3.5 MeV. Performing experiments with such a beam will be interesting for hadrontherapy. We are therefore developing the RADIOGRAAFF platform to provide radiobiologists with a beam of high-RBE protons and a control of the absolute and relative dose with a dose rate of 2 to 10 Gy/min. This platform will compensate for the current lack of beam time and will provide a complementary beam (medium energy) to the future ETOILE/research platform (high-energy).

   Although the accelerator can produce a beam of protons in air, some developments were necessary. Indeed with an energy of a few MeV, a proton's range is very short (< 200 micrometers), and the standard protocols of dosimetry and radiobiology would not be directly applicable. Moreover, the standard flux of protons is very high because the accelerator was designed for experiments in physics.

   The development of this platform is the purpose of the Julie Constanzo's PhD track (ending in 2013). Up to now, we have:

   - reduced the beam intensity to the desired levels,
   - enlarged the beam to get a uniform irradiation with an accuracy of $\pm$ 2% (better than the requested 5%),
   - developed a system to control the irradiation based on photomultipliers and scintillating optical fibers with a control in fluence under 5%,
   - developed a robotized sample holder,
   - developed a cave to encapsulate the sample holder in order to protect the samples from biological contamination and to ensure a thermal control,
   - designed some adapted "Petr" boxes.

   The Radiograaff platform will include a room ("bio room") with biological equipments, temperature and air control, laminar flow cabinet, computers... to prepare and manage biological samples before and after irradiations. The work on walls, floor and plumbing are achieved. Part of the equipment is already bought.

   Although the biological protocols and the Petri boxes still need to be improved, we have already obtained encouraging results. The platform, its dosimetry evaluation and the preliminary results on SQ2OB and SCC61 lines have been presented at the 39th European Radiation Research in Italy.

2. The Pavirma plaftform
   An irradiation platform combining in the same installation: an X-ray irradiator (320 kV X-ray tube) and a low-energy (2.5 MeV)-neutron generator, is under way on the campus of the

Clermont University. This cellular radiation-dedicated facility will produce low- and higha-LET radiations. The installation of the first phase of this device (X-ray irradiation and biology laboratory) was initiated in December 2011 and is now fully available for irradiation since January 2012.

5.2.2 Perspectives for 2013 and beyond

Studies by simulations of the physico-chemical processes

We plan to:

- Evaluate our method for prediction of the oxygen effect by facing the results to a large set of in-vitro experiments and also clinical data,
- Publish the method and the results,
- Contact private company for the exploitation of the patent if accepted.

We also plan to write an article gathering theoretical and experimental results on glutathione.

In parallel, we wish to undertake a medium-term program of quantum-based modeling to improve the accuracy of the physico-chemical processes descriptions, in particular regarding the recent experiments of femtolysis that give access to extremely short time. This programme has started within a national collaboration by the funding of the nanobiodose project.

Models of cell inactivation for treatment planning

From in-vitro to in-vivo Because a detailed set of clinical data for carbon therapy is not available yet for prostate in the perspective of developing TCP models for its treatment by hadrontherapy, we are developing a method to extrapolate the experience of neutrotherapy at an international level to carbon therapy. A collaborative work with the team of Prof. J. Gueulette, a radiobiologist from Bruxelles, has started. This project is one of the goals of Marie-Anne Chanrion's PhD (ending in 2014).

Development of the Nanox model We propose to pursue the development of the Nanox model of cell inactivation, by confirming and improving the Nanox predictions for V79 cell line, rewriting the code for an easier transfer to the industry, protecting it by a patent, providing a set of parameters for various tumour cell lines, incorporating the Nanox predictions into the international Geant4 simulation platform for an efficient promotion and to attract private companies.

Application of the Microdosimetric Kinetic Model It is now generally accepted that the linear energy transfer (LET) may not be the best quantity to express the relative biological effectiveness (RBE) when measuring cell survival during irradiation of cells to different types of heavy charged particles. Indeed, a variation with the type of particles, but with the same LET, was clearly observed for several experimental measurements of RBE.

A great number of studies, performed on clinical lines in Japan and Germany, show that the use of the formalism of microdosimetry, in particular variables such as lineal energy (y) was better suited than the linear energy transfer (LET) for the use and application of the MKM model.

The MKM model was improved by Kase et al.[8] (in terms of the saturation correction for expressing the decrease of RBE owing to the overkill effect). In the improved model, the cell-survival fraction for any type of radiations may be expressed as a function of only one parameter: the saturation-corrected dose-mean lineal energy in domains, referred as to $y*$ in the ICRU 36[9].

[8] Kase Y., Kanematsu N., Kanai T., Matsufuji N.Biophysical calculation of cell survival probabilities using amorphous track structure models for heavy-ion irradiation. Phys. Med. Biol. 2008; 53:37-59

[9] International Commission on Radiation Units and Measurements. Microdosimetry. Bethesda, MD: ICRU; 1986. ICRU Report 36.

However, the use of siumation-calculated lineal-energy distributions, requires experimental validation. The spectra of microdosimetric lineal energy could be measured with a Tissue-Equivalent Proportional Counter (TEPC). A TEPC is a gaseous detector that consists of a tissue equivalent (TE) plastic sphere situated in a hollow aluminium shell. This may be understood by simulating tissue-equivalent spherical volumes down to diameters of 1 micron or under. This effective diameter may be made smaller or larger by variation of the gas pressure. The instrument is generally used to accumulate a pulse-height spectrum proportional to the energy deposited in the sensitive volume. This spectrum may then be transformed into a distribution of lineal energy with the aid of computer processing. The microdosimetric experimental spectra could be measured for different radiation quality (photon, proton, helium, carbon ions), on a large range of LET. As an example Y. Kase et al.[10] measured the microdosimetric spectra for high-energy beams of photons and proton, helium, carbon, neon, silicon and iron ions (with a LET that ranges between 0.5 and 880 keV/μm), with a spherical walled tissue-equivalent proportional counter at various depths in plastic phantoms, simulating a diameter of 1 μm.

We plan to assemble a full microdosimetric set-up, using a reliable $\frac{1}{2}$" TEPC (from Far West company) that will be used as a reference set-up to facilitate inter-comparisons of results with other groups. This reference $\frac{1}{2}$" TEPC will be implemented on the Pavirma regional platform irradiation. The reference $\frac{1}{2}$ inch TEPC will be used also on proton beams (ICPO Orsay and Medycic Nice) or carbon ion beams (GANIL). The counter will be situated at the treatment position, in front of the therapeutic beam, inserted in slab geometry phantoms composed of different thicknesses of bone, lung, liver and water equivalent materials .

The main limitation of the reference $\frac{1}{2}$" TEPC is that we could access only to equivalent cellular volume between 500 nm and 1 μm. The only solution to access to smaller equivalent volumes (100 nm) is to build a mini TEPC. There is no such commercial product currently. After getting sufficient experience with the Far West TEPC, we plan to build, in the long term, such a mini TEPC following the designs based on the work of Burmeister et al.[11]. The use of this mini TEPC should provide access to distributions of microscopic linear energy in volumes corresponding to components of the cell smaller than the nucleus.

Effect of dose rate on cell survival During a treatment with an active system, the deepest part of the tumor will be irradiated in less than one second. Other parts of the tumor and most of the normal tissues will be irradiated within minutes. Changing the irradiation period from 15 s to 20 min may induce changes in the radiosensitivity – due, for instance, to the response of the cells (repair of DNA damage...). The effect of dose rate has been scarcely evaluated with ions of high LET and we propose to quantify it. We are studying this dose-rate effect by measuring the cell survival curves of our two HNSCC cell lines after carbon and argon ion irradiations with a dose rate ranging from 0.4 Gy/min to 10 Gy/min. We have performed all the irradiations and will develop statistical tools to analyze the results.

Effect of dose on DNA mitochondrial (ADNmt) It is now clearly assumed that although damage to nuclear DNA is a well identified cause of carcinogenesis, the possible links between cancer and mtDNA mutations begin to be analyzed. Indeed, mtDNA alterations have been observed in many cases of cancer and some of these mutations may increase the aggressiveness of the tumor as it has been shown in some cases of prostate cancer. These mtDNA mutations may be linked to other malfunctions during replication of these genomes, induced for instance by the presence of reactive oxygen species (ROS) produced during the operation of the respiratory chain, but also by an "ineffective" system of mtDNA repair. Recent insight into prostate cancer shows that the mitochondrial DNA of human prostate-cancer cells were riddled with mutations.

[10] Kase Y., Kanai T.,Matsumoto Y., Furusawa Y., Okamoto H., Asaba T., Sakama M. and Shinoda H., Microdosimetric measurements and estimation of human cell survival for heavy-ion beams, Radiation Research, 166, 629–38, 2006.

[11] Burmeister J., Kota C., Maughan R.L. and Waker A.J, Characterization of miniature tissue-equivalent proportional counters for neutron radiotherapy applications, Phys. Med. Biol., 47, 1633-1645, 2002.

So we will focus on the effect of irradiation on three different tumor cell lines: HeLa cells (adenocarcinoma), LNCaP (carcinoma) and PC3 (adenocarcinoma). But this study could be extended to other cell lines in the framework of a Lyon-Clermont collaboration.

Development of irradiation platforms

The Radiograaff platform We need to develop one or several biological protocols to irradiate cells at the Radiograaff platform since the present protocol works for some cell lines but not for others. We will also terinate the room dedicated to the preparation of the biological samples. Then the platform will be evaluated either by the production and the publication of experimental results and by making it visible and available to external teams, as for instance the partners of the PRIMES LabEx and the FranceHadron national infrastructures of Excellence.

The Pavirma platform The Pavirma platform combines two irradiation systems in the same facility at the campus of Clermont University: an X-ray irradiator (X-ray tube 320 KV for low-LET irradiation) and a low-energy neutron generator (2.5 MeV for high-LET irradiation), which are under way to irradiate cells. The first phase of this dedicated facility (X-ray irradiator and a biology laboratory) is complete. Inter-comparison measurements were performed with equivalent irradiators at Lyon University and the Curie Institute in Orsay. The second phase (neutron generator) should be finalized by the end 2013. Although the first phase was implemented in an existing building, the final platform will consist of a new building including two bunkers for irradiation and several rooms for biological preparations.

Platforms Radiograaff, Pavirma, and the X irradiator at the Lyon-Sud Medicine faculty will be included into a national network of irradiation platforms, comprising either X irradiators or other types of radiation modality (proton beams of various energies and intensity, light ions). The network will develop common protocols and radiation dosimetry.

Methods of acquisition, processing and analysis of radiobiology data

The measurements of the biological observables rely on the use of the latest techniques in confocal immunofluorescence microscopy. The number, the size, the light intensity and the spatial distribution of foci may change depending on the nature and energy of radiations. To get significant statistical results, one needs to have a large number of microscopy images, i.e., a large amount of data that should be processed in an automatic way. Up to date, ImageJ is one of the most used open source software for image processing in biology and medicine for treatment and analysis of images acquired by microscopy. It allows viewing, editing, processing and analyzing most of the existing file formats. ImageJ also offers a large number of algorithms for image analysis.

We have already some experience in using ImageJ to process H_2AX foci distribution in 2D immunofluorescence microscopy. We plan to extend this methodology to 3D images from immunofluorescence microscopy. However, when using confocal microscopy, the amount of data (images) increases a lot. The LPC group started to test a prototype of Client/Server toolkit for the storage and the distribution of microscopic images. This Client/Server software is based on the open-source software OMERO (OME Remote Objects), which provides collaborative methods in medical and radiobiological imaging to store, provide and analyze large collections of experimental data (cellular microscopy images). The OMERO server is an application that provides to client applications access through the web to share databases. The users (OMERO Client) may therefore remotely manage the data stored on the OMERO server. Client applications could be directly connected to microscopy platforms so that data storage could be processed automatically during image acquisition.

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Chapter 6

Simulation of the dose deposition for treatment planning

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6.1 Main objectives of the research theme

Treatment planning relies on simulation tools making it possible to predict dose deposition in the irradiated tissues. Simulation techniques have been successfully developed and widely used for several decades in the case of photon or proton irradiations of organs at rest. However, more research is still needed in the more complex cases, notably in the ion beam therapy field, when moving organs (*e.g.* lung) are irradiated with intensity-modulated scanned pencil beams. Moreover, a specific feature of ion beam therapy is the possibility of performing in-beam treatment monitoring, using PET imaging (already available) and prompt radiation imaging (on-going research). A

treatment planning system should therefore include the simulation of the emission of secondary particles (positrons, prompt gamma-rays, charged fragments), used as input data for imaging. In all of these simulations, temporal aspects have to be carefully taken into account (interplay effects between the beam and organs dynamics, management of coincidences in detectors, etc.). As in any complex simulation problem, two opposing characteristics are sought: physical realism and speed. In the field of radiation-matter interactions, simulation approaches may be divided into two main classes:

1. deterministic methods which are fast but not realistic enough for complex treatment plans;
2. Monte-Carlo methods which are very realistic but still far too slow for routine clinical application.

Our interdisciplinary research group consists of medical physicists (CLB), physicists with expertise in radiation-matter interactions and simulation techniques (IPNL, CREATIS), as well as computer scientists and experts in signal processing (CREATIS). Our objective is to devise and develop simulation tools making it possible to describe, in a realistic and fast way, the irradiation of a patient with light ion beams, considering dose deposition in tissues as well as the emission of secondary particles and their subsequent interactions in imaging detectors for treatment control (potentially in real time). Our developments are mostly carried out in the framework of the Monte-Carlo code Geant4 and within the OpenGATE community. Our research work is structured into three main topics, as described below.

6.1.1 Simulation realism

Physical models All relevant physical phenomena taking place during ion beam irradiation must be taken into account in Monte-Carlo simulations. One essential aspect, giving rise to intense research effort at the international level, is the modeling of nuclear fragmentation processes leading to the emission of neutrons, charged fragments, prompt gammas, and to the production of positron emitters. As a general rule, all simulation developments must be validated against existing or forthcoming experimental data. We take part in several collaborations aiming at gathering experimental data of interest in ion beam therapy (fragmentation cross sections, prompt gamma yields, beam characteristics, dose profiles, etc.), notably in the framework of the French network Modeling and Instrumentation for Biomedical Imaging (GdR MI2B) and of the European ENLIGHT++ network (FP7 ENVISION and ENTERVISION projects).

Medical realism The patient's anatomical complexity, including moving organs, must be described accurately in simulations. Medical data, such as CT scans, 4D CT and subsequent segmented images are used as input data for simulations. Moreover, predicting the irradiation biological effectiveness calls for specific algorithms taking into account radiation quality (particle spectrum with associated energy and LET distributions) and biological tissue characteristics. These aspects will rely on the results of the radiobiology and moving organs working groups.

6.1.2 Acceleration of simulations

Massively parallel computing Distributing calculations on a large number of computing nodes is a very effective way of accelerating simulations. Local clusters as well as computing grids may be used. Another actively investigated option is the recourse to GPU (graphics processing units). Recent developments in general-purpose GPU have lead to dramatically reduced reconstruction times in CT for instance. Such advances will make it possible to accelerate MC simulations considerably in the next few years.

Hybrid simulation approach Combining Monte-Carlo and deterministic calculations has already proven a fruitful approach for simulating multiple photon scattering in X-ray imaging and synchrotron radiation therapy. We investigate the use of hybrid algorithms fro variance reduction

in Monte-Carlo to accelerate the simulation of secondary particle emission or dose deposition in ion beam therapy. Such a hybrid approach is also under study for accelerating the simulation of in-beam emission tomography experiments for treatment monitoring.

6.1.3 Inverse planning strategies

In intensity-modulated particle therapy (*e.g.* pencil beam scanning modality), not only does treatment planning require an efficient and accurate dose calculation engine, but it also makes it necessary to optimize the many irradiation parameters, such as beam directions, Bragg peak positions and fluence values (a treatment fraction typically involves thousands of beamlets). To pave the way towards new strategies of irradiation ballistics, we investigate several optimization approaches, among which gradient techniques combined to genetic algorithms, as well as simulated annealing.

6.2 Overall 2012 assessment

Recent and ongoing activities carried out by our group are listed below with mention of the corresponding publications.

6.2.1 Simulation realism

- In the framework of the FP7 ENVISION project, work has been done to assess and improve the physical models of interest for on-line monitoring of ion beam therapy [BB11]. We have focused on the nuclear fragmentation processes leading to the emission of secondary particles, in particular prompt gamma-rays. Several parameters have been identified in the available models (notably the QMD model), which can be tuned to better reproduce experimental measurements [DDDR$^+$12].

- Active scanning delivery systems take full advantage of ion beams to best conform to the tumor and to spare surrounding healthy tissues; however, it is also a challenging technique for quality assurance. In this perspective, we upgraded the GATE/GEANT4 Monte Carlo platform in order to recalculate the treatment planning system (TPS) dose distributions for active scanning systems [GBF$^+$12]. A method that allows evaluating the TPS dose distributions with the GATE Monte Carlo platform has been developed and applied to the XiO TPS (Elekta), for the IBA proton pencil beam scanning (PBS) system. In homogeneous media, a satisfactory agreement was generally obtained between XiO and GATE. The maximum stopping power difference of 3% occurred in a human tissue of 0.9 g·cm^{-3} density and led to a significant range shift. Comparisons in heterogeneous configurations pointed out the limits of the TPS dose calculation accuracy and the superiority of Monte Carlo simulations. The new capabilities of the platform were applied to a prostate treatment plan and dose differences between both dose engines were analyzed in detail.

- The GATE package was also used to perform Monte Carlo hadrontherapy simulations of a cancer treatment combined with the complete description of an associated positron emission tomography (PET) imaging device for dose monitoring [JFS13]. This study demonstrated that the GATE platform has the capability to perform realistic simulations in the field of hadrontherapy, combining both dose and imaging systems. We defined the simulation configuration as a carbon ion pencil beam scanning of a thorax CT phantom together with a complete PET imaging system. We analysed the impact of dose delivery on PET image quality and found a difference of 20% on the PET estimation falloff between doses of 10 Gy and 1 Gy. This study shows that GATE, implemented on a computing system with a large number of CPUs (> 1000), has the potential to be used for quantitative evaluation of imaging protocols for radiation monitoring.

- Online dose monitoring in protontherapy is currently being investigated with prompt-gamma (PG) devices. PG emission was shown to be correlated with dose deposition. This relationship is to a large extent unknown under real conditions. We propose [GGD+12, GTL+12] a machine learning approach based on simulations to create optimized treatment-specific classifiers that detect discrepancies between planned and delivered dose. Simulations were performed with the Monte Carlo platform Gate/Geant4 for a spot-scanning protontherapy treatment and a PG camera prototype currently under investigation. The method first builds a learning set of perturbed situations corresponding to a range of patient translations. This set is then used to train a combined classifier using distal falloff and registered correlation measures. Classifier performances were evaluated using receiver operating characteristic (ROC) curves and maximum associated specificity and sensitivity. A leave-one-out study showed that it is possible to detect discrepancies of 5 mm with specificity and sensitivity of 85% whereas using only distal falloff leads to 77% on the same data set. The proposed method could help to evaluate performance and to optimize the design of PG monitoring devices.

- We have developed a filtered-backprojection reconstruction (FBP) algorithm for proton computed tomography (pCT) that takes advantage of the estimation of the most likely path of protons. Improvement in the spatial resolution has been observed on Monte Carlo simulations compared to existing straight-line approximations. The improvement in spatial resolution combined with the practicality of FBP algorithms compared to iterative reconstruction algorithms makes this new algorithm a candidate of choice for clinical pCT [RDF+13]. From preliminary studies, we have shown that the electron density can be reconstructed to within 2.5% for a 3 mGy imaging dose [DRD+12].

6.2.2 Acceleration of simulations

- Hybrid algorithms have been implemented in GATE for fast simulation of the dose absorbed by the patient during kV x-ray irradiations (cone beam CT, stereotactic synchrotron radiation therapy ...). The track length estimator approach is now available in GATE 6.2 [MBL+12]. A hybrid simulation scheme is also under development for fast simulation of CBCT projections with accurate description of the scatter contribution. This work was funded for 1 year (2010-2011) by the PRRH and additional funding (2012-2013) has been obtained in a collaboration with the Catholic Louvain University and IBA company. Our final objective is to improve the image quality of cone beam CT (quantitative imaging), without increasing the dose to the patient.

- Following the GateLab [GCPG+11] project, we introduced an end-to-end framework for efficient computing and merging of Monte Carlo simulations on heterogeneous distributed systems [CPGFdS+13]. Simulations are parallelized using a dynamic load-balancing approach and multiple parallel mergers. Checkpointing is used to improve reliability and to enable incremental results merging from partial results. A model was proposed to analyze the behavior of the proposed framework and help tune its parameters. Experimental results obtained on a production grid infrastructure showed that the model fits the real makespan with a relative error of maximum 10%, that using multiple parallel mergers reduces the makespan by 40% on average, that checkpointing enables the completion of very long simulations and that it can be used without penalizing the makespan.

- Within the FP7 Envision project, we develop a Geant4 software module to accelerate the simulation of prompt-gamma emission. This module, based on the track length estimator approach, will substantially speedup the simulation of prompt-gamma imaging for online monitoring of proton therapy treatments.

6.3 Perspectives for 2013 . . . or beyond

The simulation of dose deposition and of online treatment monitoring in ion beam therapy is in a very active phase of development with an increasing number of ongoing or forthcoming projects. Our objectives are ambitious and must be considered in a long term perspective. The main tasks for 2013 are the following:

- The work already carried out within the FP7 ENVISION project to improve the QMD model will be prolonged within the FP7 ENTERVISION project (M. Pinto's PhD thesis). The work will first focus on the tuning of the nuclear fragmentation processes to reproduce experimental measurements of prompt secondary radiation in proton therapy.
- A longer-term perspective is to devise a quality assurance methodology making it possible to (i) plan the expected prompt-gamma depth-profile (which will require developing semi-analytical fast algorithms) and associated camera response (in active beam delivery mode, on a spot by spot basis) and (ii) determine criteria for deciding whether the profiles measured online are within acceptable limits, with a certain level of confidence. We also plan to work on the relationship between the dose and prompt-gamma profiles. The same kind of methodology will be investigated for other types of secondary particles (*e.g.* protons) as well.
- A project devoted to cone beam CT imaging for proton therapy quality assurance has recently started, in collaboration with the Université Catholique de Louvain (UCL) and the IBA company. In this framework, we propose original reconstruction algorithms including a hybrid (Monte Carlo – deterministic) simulation stage, the aim of which is to reduce the artifacts and to provide quantitatively more accurate images, without increasing the dose to the patient.
- In order to go a step further towards translating proton CT to clinic, further studies are needed to propose design guidelines for a proton CT prototype, with a particular focus on the identification of the basic detector requirements (in terms of energy and spatial resolutions) and on the quantification of uncertainties in the proton range with a pCT-based treatment planning system.

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Chapter 7

Moving organs and tumors

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7.1 Axis 1: image-guided radiotherapy

7.1.1 Overall 2012 assessment

Improving deformation registration of thorax CT with lung masks Deformable registration generally relies on the assumption that the sought spatial transformation is smooth. Yet, breathing motion involves sliding of the lung with respect to the chest wall, causing a discontinuity in the motion field, and the smoothness assumption may lead to poor matching accuracy. In response, alternative registration methods have been proposed, several of which rely on prior segmentations. In [VBR+12] we propose an original method to extract automatically a specific segmentation, called a motion mask, from a CT image of the thorax.

The motion mask discriminates moving regions from less moving ones, conveniently allowing simultaneous estimation of their motion, while providing an interface where sliding occurs. The

sought segmentation is subanatomical and based on physiological considerations, rather than organ boundaries. We therefore first extract clear anatomical features from the image, with respect to which the mask is defined. Level sets are then used to obtain smooth surfaces interpolating these features. The resulting procedure comes down to a monitored level set segmentation of binary label images.

The method was applied to sixteen inhale-exhale image pairs. Registration using the motion mask resulted in higher matching accuracy for all patients, and the improvement was statistically significant. Registration performance was comparable to that obtained using lung masks when considering the entire lung region, but the use of motion masks led to significantly better matching near the diaphragm and mediastinum, for the bony anatomy and for the trachea. The use of the masks was shown to facilitate the registration, allowing to reduce the complexity of the spatial transformation considerably, while maintaining matching accuracy.

Thorax surface registration

In the framework of the European ULICE project and in collaboration with the groupe led by G. Baroni, at Politecnico di Milano, we investigated thoracic surface registration. Indeed, real-time optical surface imaging systems, such as VisionRT, offer a non-invasive way to monitor intra-fraction motion of a patient's thorax surface during radiotherapy treatments. Due to lack of point correspondence in dynamic surface acquisition, such systems cannot currently provide 3D motion tracking at specific surface landmarks, as available in optical technologies based on passive markers.

In [SFR+12], we propose to apply deformable mesh registration to extract surface point trajectories from marker-free optical imaging, thus yielding multi-dimensional breathing traces. The investigated approach is based on a non-rigid extension of the iterative closest point algorithm, using a locally affine regularization. The accuracy in tracking breathing motion was quantified in a group of healthy volunteers, by pair-wise registering the thoraco-abdominal surfaces acquired at three different respiratory phases using a clinically available optical system.

The motion tracking accuracy proved to be maximal in the abdominal region, where breathing motion mostly occurs, with average errors of 1.09 mm. The results demonstrate the feasibility of recovering multi-dimensional breathing motion from markerless optical surface acquisitions by using the implemented deformable registration algorithm. The approach can potentially improve respiratory motion management in radiation therapy, including motion artefact reduction or tumour motion compensation by means of internal/external correlation models.

Usefulness of abdominal compression In [BAR+12], we aim to determine the usefulness of abdominal compression in lung stereotactic body radiation therapy (SBRT) depending on lobe tumor location. For that, 27 non-small cell lung cancer patients were immobilized in the "Stereotactic Body Frame" (Elekta). Eighteen tumors were located in an upper lobe, one in the middle lobe and nine in a lower lobe (one patient had two lesions). All patients underwent two four-dimensional computed tomography (4DCT) scans, with and without abdominal compression. Three-dimensional tumor motion amplitude was determined using manual landmark annotation. We also determined the internal target volume (ITV) and the influence of abdominal compression on lung dose-volume histograms.

We obtained the following results: the mean reduction of tumor motion amplitude was 3.5 mm ($p = 0.009$) for lower lobe tumors and 0.8 mm ($p = 0.026$) for upper/middle lobe locations. Compression increased tumor motion in 5 cases. Mean ITV reduction was 3.6 cm^3 ($p = 0.039$) for lower lobe and 0.2 cm^3 ($p = 0.048$) for upper/middle lobe lesions. Dosimetric gain of the compression for lung sparing was not clinically relevant.

As a conclusion: the most significant impact of abdominal compression was obtained in patients with lower lobe tumors. However, minor or negative effects of compression were reported for other patients and lung sparing was not substantially improved. At our institute, patients with upper or middle lobe lesions are now systematically treated without compression and the usefulness of compression for lower lobe tumors is evaluated on an individual basis.

Lymph node stations

Other researches have been undertaken by our team in the field of lung tumor, in particular dedicated to the definition of lymph nodes stations in thoracic CT [LPB+13, PLCS12, SCR+12]. These researches were performed in collaboration with the group of Rod Lynch, MD, Geelong, Australia.

7.1.2 Perspectives

Several research efforts are ongoing. First, considering that sliding motion is a challenge for deformable image registration because it leads to discontinuities in the sought deformation, we aim to build a method to handle sliding motion using multiple B-spline transforms. Second, we investigated Proton CT (pCT) which has the potential to accurately measure the electron density map of tissues at low doses. However, the spatial resolution is prohibitive if the curved paths of protons in matter is not accounted for. We propose to account for an estimate of the most likely path of protons in a filtered backprojection (FBP) reconstruction algorithm.

7.2 Axis 2 : biomechanical and geometrical modelling

7.2.1 Overall 2012 assessment

Model for the respiratory movement

When the tumor is located on a moving organ, the main difficulty is to target it during treatment. This incertainty on the position makes indispensable the setting up of a strategy allowing the prediction of tumoral movement. Indeed this allows to guide the ion beam so it follows the tumoral movements. furthermore, the treatment by hadrontherapy alos requires access to a precise description of the density of all the organs traversed by the beam, since the position of maximum deposition of the the energy transported by the ions (Bragg peak) depends on it. Unfortunately, the breathing movement is complex and its prediction is fairly difficult – in particular, breathing is governed by the independant action of the rib cage muscles and of the diaphragm.

The known techniques based on imaging, such as the Cone-beam ou elastic registration, attempt to predict the position of the pulmonary tumors. These methods assume that the movements of the respiratory system are reproducible over time. Other techniques based on the use of two X ray cameras (cyberknife, the tracking method implemented at the carbon ion facility of Heidelberg [HIT]) may allow the prediction of the tumor position when its segmentation and automatic delineation is possible in real time. However, such methods are invasive, if not hazardous, and do not llow to compute the evolution of nearby organs, an information indispensable to determine the Bragg peak position. Thus, deducing the tumor movement from the sole use of sequences of images seems unsufficient. A solution to this fact may be to develop a biomechanical model of the respiratory system including the variability fo the respiratory movement. To be precise enough, this solution must include models for the rib cage, the diaphragm and the lungs. It is just as important for such a model to be monitored through parameters measured externally (3D sensors, spirometer, etc.), in order to preserve a non-invasive character and to correlateinternal movements with external movements of the thorax and abdomen, but also the air flow exchanges. The changes in mechanical properties of the mediums entered by the beam must also be modelled in order to satisfy the requirements of hadrontherapy. Finally, the complete simulation fo the respiratory dynamics induces the simulation of the diaphragm. In previous work we have developed a biomechanical model for the lungs and throax. However, the diaphragm represents one the major muscles in the action of breathing, the physiology and movements of which are very complex.

In 2011, we have developed a customized biomechanical model of the diaphragm structure based on data provided by CT scan images (Fig. 7.1). This biomechanical model leans upon an heterogeneous model (tendons and muscles) allowing elastic behaviour based on experimental data. The results of the model show a good fit with experimental data. The zones of largest

error are located in the sections of the thorax that are in contact with the ribs. A more complex model (heterogeneous and hybrid) of mechanical deformation based on hyper-elastic behaviour is being integrated, to take the presence of other elements (ribs, lung movement, heart beats) into account. The movements and deformations are computed by a method based on finite elements. The realistic model for the organ tissues is intended to help understand the effects of moving organs on the distribution of dose, as well as the response of normal issues as they move during treatment. Finite elements provide a better insight on the mechanical behaviour of organs and their response, due to the fact that they are based on material properties, the complex organ geometry and the anatomical limiting conditions.

Our biomechanical model for the respiratory system allows:

- to take the non reproductibility of the system into account;
- to adapt the model to the geometrical and physical information of the patients;
- its monitoring through external sensors during treatment.

Furthermore, this method should allow to compensate the differences between biomechanical parameters from one patient to the other.

Dose deposition

Complementarily to this research, a study on control imaging during irradiation is being made in collaboration with the CAS-PHABIO team at IPNL (Institut de Physique Nucléaire de Lyon, UMR 5822), in the framework of the ENVISION project (European ENLIGHT++ network).

In fact, accurate 4D dosimetry calculations are essential for treatement planning verification and evaluation. They require temporal information about the tumor position, size and shape, as well as information regarding the tissue density variation along the beam path during treatment. Several deformable image registration (DIR) algorithms are described in the literature[1] to investigate respiratory liver motion effects on 4D treatment planning for scanned proton therapy. Techniques based on image registration are particularly challenging in the case of the liver, due to low-contrast CT data, especially if no contrast enhancing agents are applied. Moreover, they can induce important deviations in patient dose calculation during treatment due to the non reproductibility of the breathing cycles. Velec et al[2] use a biomechanical model-based method for multi-organ registration of the abdomen between two extreme phases of the respiratory cycle, in order to study the impact of respiratory-induced organ motion on dose calculation during liver stereotactic body radiotherapy. They used CT images at the inhale and exhale stages to calculate two dose distribution matrices for liver cancer treatment planning. Further on, they used linear interpolation to modulate the dose distribution at intermediate breathing states. Unfortunately, this approximation does not take into account density variations and assumes that dose values vary in a linear way from one respiratory position to another. Moreover, the intermediate phases are not reproductible from one respiratory cycle to another.

Consequently we developped an alternative patient-specific biomechanical-based model for 4D dosimetry calculations during hadrontherapy simulations. As opposed to classical voxelized models, where the necessary information is distributed over a rigid structured grid of voxels, we represent the human anatomy with the use of a deformable grid of tetrahedra where the mass density is

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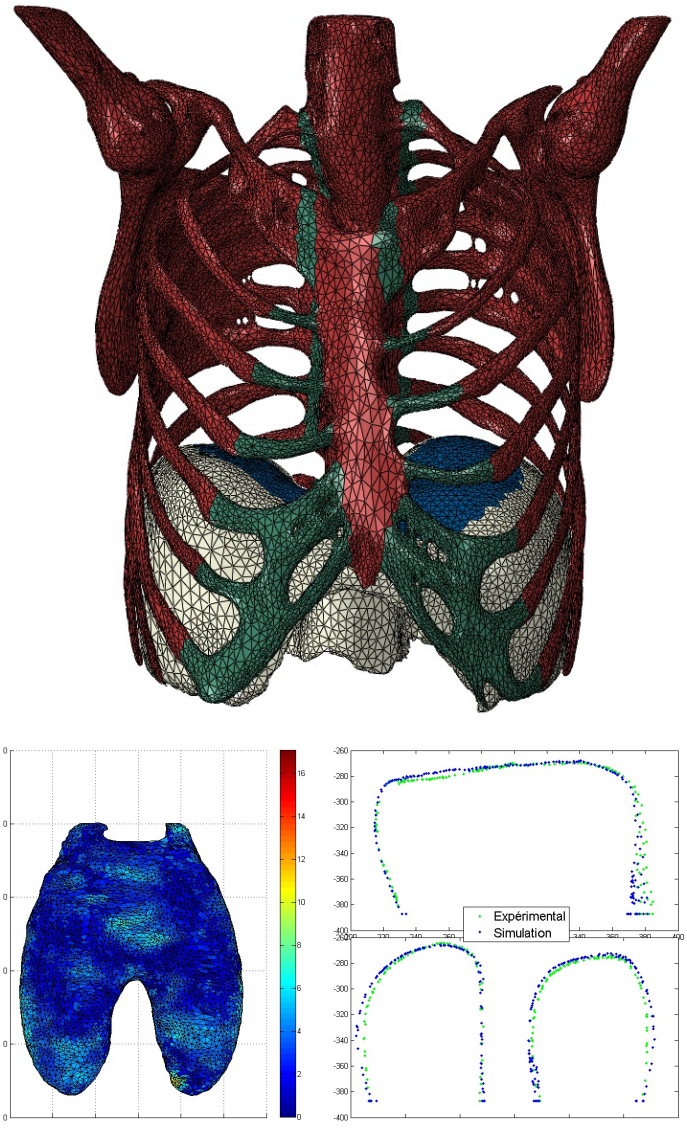


Figure 7.1: Simulations of the ribcage and diagphram in the biomechanical model.

distributed to the vertices of the grid. In this way, we can simulate at the same time and within the same geometry, organ motion and mass density variations required for dose calculations, without having to perform voxel tissue tracking. Using finite element analysis, deformations are described by mesh vertex displacements, tissue tracking being implicit. Our method generates intermediate density maps without using linear interpolation to approximate dose at intermediate breathing states. The deposited energy is then accumulated over each deformable tetrahedral element during treatment simulation and thus including internal motion when calculating dose distribution inside the tumors and surrounding organs.

This research resulted in four publications over 2012-2013 ([LSB+13, MAB+12, MAB+13a, MAB+13b].

Correlating internal (tumor, organs) and external movements In parallel to the research described above, and within the same team (SAARA, from the LIRIS laboratory), another research has been ongoing for several years, with the objective to estimate the displacements of a given tumor under the influence of the breathing mechanism. After preliminary studies over the first half of 2000-2010, a new PhD student joigned the team, for a Master's degree subject involving the definition and implementation of an easily reproducible protocole to measure external movements, and design algorithms to reconstruct the internal movements that it induced. The first measurements of this inside-outside correlation between the movements observed with cameras and the data obtained with a spyrometer and also using ultrasonic acquisitions in mode M and B, during the same sequence, were achieved in 2011 [FJZM11]. Thanks to other research efforts with another student in Chile using signal treatment and innovating techniques [CHJ+12], we are now trying to analyze the diaphragm movements in order to help drive the biomechanical model described above for human respiration, with the long term intent to predict the displacements of moving organs and tumors in function of synchronized external acquisition.

Our research also involves a PhD thesis to be defended at the beginning of 2014, with support from the 2007-2013 CPER in the framework of ETOILE, by Xavier Faure. The aim of this research is to model and simulate in a realistic way the organs inside the human body from physiological, anatomical characteristics, or data from multi-modal acquisition. In the long run, the model should allow to obtain in real time all the information required by algorithms in the aptative treatment modules (such as those for cancer treatments). Real time may only be achieved through the optimization and parallelization of the simulation algorithms used in this domain. To reach this goal, X. Faure focuses on modeling soft tissue using mass-tensors, an innovative technique and an alternative to finite elements. He has developed the algorithms allowing to simulate linear deformations and also deformations that are not linear in geometry [FZJM12b, FZJM12a]. The extension and generalization to hyper-elastic models (non-linear for mecanics) is underway. The GPU parallalization of these algorithms has been developed for the SOFA platform, with an implicit integration method.

Treatment room control

The statistics published in 2010 by the French Board for Nuclear Security (ASN, http://www.asn.fr) show that, in France, over the total amount of incidents reported during radiotherapy treatments, 10% involved an error in the identification of the patient (or of the treatment that he/she was supposed to be administered) and 67% were related to patient positionning. Ths proves the utmost importance of developing new and efficient methods to improve control during treatment as much as possible.

The SAARA team at LIRIS has undertaken the supervision of a CIFRE PhD with an industrial partner (DOSISoft, Cachan, a French leader in the development of treatment planning systems). This work, initiated in october 2008, ended in November 2011 with the defense of M. Portela-Sotelo [PS11]. The research was centered on using video cameras to follow the movements of staff, patients and equiments in a treatment room, using a precise geometrical model et techniques to recognize movements on the filmed images. This research, which was co-supervised with two radiophysicists at the Léon Béard Center (C. Ginestet and P. Dupuis), was not funded by the

CPER, but is included in the framework of the ETOILE project. It is accompanied by a certain degree of confidentiality for industrial property reasons. However, it was possible to publish several papers describing the methodology in major conferences or journals [PSDM11a, PSDM11b, PSDM$^+$12, PSDP$^+$12].

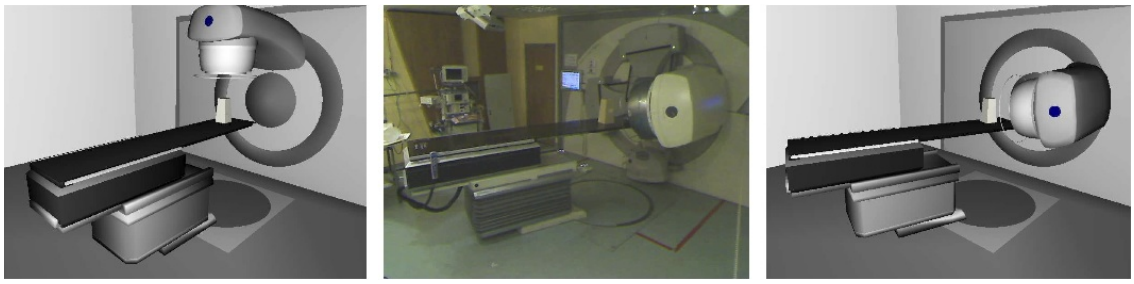


Figure 7.2: Movement detection in the treatment room. On the left image, virtual representation of the room using the model; all its elements occupy a predefined, fixed rest position. Center: image produced by one of the two cameras in the room at a given instant, inducing a random position of the couch and irradiation arm. Right: superimposition, over the filmed image, of the virtual model "registered" on the filmed positions of the various elements in the left image (augmented reality). The differences in colour, distance, pixel, object-feature, texture, computed for each frame of the filmed sequence, between the virtual and real images allow the registration, and then the detection and analysis of movement.

7.2.2 Perspectives

We developed a patient-specific multiphysics model that integrates the geometry of organs, displacement fields for the internal movements, the density and nature of biological tissues, the energy deposited by ionizing rays. We wish to progress towards a global multi-physics and multi-scale model of virtual human, merging the macroscopic (organ level) and microscopic (cellular level) scales representations. Work in the latter area is already planned.

The developments will indeed continue in the multiple framework of PRRH (until end 2013), the PRIMES Labex that was accepted in 2012, France Hadron (Infrastructures Biotechnologie pour la Santé, also accepted in 2012) and ENVISION (2010-2014). The research on video surveillance of the treatment room is on stand-by.

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Chapter 8

Technological developments

Scientific coordinators

- Marcel Bajard (IR, CNRS)

Institutions & laboratories involved

- IPNL, CNRS/IN2P3 and Université Lyon 1

Full-time researchers with institutional links

- Marcel Bajard (IR, CNRS)

8.1 Overall 2012 assessment

The researches of this group ended with the termination of ULICE's workpackage number 6 (gantries for carbon ion facilities) this year, and the retirement of Marcel Bajard who led the group at IPNL.

Part III

Cumulated bibliographical references for 2007-2013

Chapter 1

ETOILE Project

1.1 International conferences with reviewing committee

2011

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2007

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2009

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2008

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2007

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2008

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2008

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Chapter 2

Medical project

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2012

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2008

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Chapter 3

Medico-economical simulations

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2012

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2010

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2010

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[3] A. Shtiliyanova, F. Feschet, P. Pommier, and JY. Boire. Modeling: a tool for evaluation of innovative therapies. Cape Town, South Africa, 2010. Medinfo 2010 Congress. (submitted).

[4] Y. Jacquemin, E. Marcon, and P. Pommier. A pattern-based approach resolution of radiotherapy scheduling. In *18th World Congress of the International Federation of Automatic Control (IFAC) 2011*, page Submitted, Milano, Italy, 2010.

[5] Y. Jacquemin, E. Marcon, and P. Pommier. Towards an improved resolution of radiotherapy scheduling. Venise, Italie, February 2010. IEEE Workshop on Health Care Management.

3.4 International conferences without reviewing committee

2007

[1] L. Perrier, P. Pommier, M-O. Carrère, and P. Sylvestre Baron. Assessing the generalisability of cost evaluation results using the euclidean metric and principal component analysis: lesson from a high cost innovation in oncology. In *Value in Health Wiley*, volume 10, Dublin, Irlande, october 2007. 10th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research, Value in Health.

3.5 National conferences with reviewing committee

2009

[1] L. Trilling and Y. Jacquemin. Le lean dans la santé. Annecy, October 2009. Journées du GDR MACS.

[2] A. Shtiliyanova, F. Feschet, and P. Pommier. Outil d'évaluation médico-économique des thérapeutiques innovantes. Lyon, October 2009. Symposium Sciences Humaines et Oncologies abstract/poster ;; CLARA.

[3] Y. Jacquemin, E. Marcon, and P. Pommier. Towards an improved resolution of radiotherapy scheduling. Leuven, Belgique, July 2009. ORAHS.

[4] Y. Jacquemin, E. Marcon, and P. Pommier. Amélioration de la planification en radiothérapie. Saint Etienne, November 2009. Journée IFRESIS.

[5] Y. Jacquemin, E. Marcon, and P. Pommier. La planification en radiothérapie. Lyon, October 2009. Symposium Sciences Humaines et Oncologies abstract/poster ; CLARA.

2008

[1] P. Pommier and N. Geoges. Protons et ions carbones. les particules de l'avenir ? Eurocancer. Paris, 2008.

2007

[1] P. Pommier, N. Gueye, C. Buron, and S. Meyroneinc. Modélisation du coût de l'innovation thérapeutique pour l'aide à la décision. application à la radiothérapie par ions carbone (projet etoile). *Systèmes d'information et santé*, (10: 217-31), 2007.

3.6 National conferences without reviewing committee

2007

[1] L. Perrier, P. Pommier, M-O. Carrère, and P. Sylvestre Baron. Les évaluations de coûts en santé sont-elles transférables ? mesures et application à une innovation très coûteuse en cancérologie. In *Université Catholique, Lille, France*. 29ème Journées des Economistes Français de la Santé, december 2007.

3.7 Workshops without proceedings

2010

[1] Y. Jacquemin, B. Pellet, E. Marcon, and H. Collela Fleury. Outil d'aide à la décision de planification de traitement en hadronthérapie. In *GISEH*, Clermont-Ferrand, France, 2010.

3.8 Publications without classification

2009

[1] S. Oga. Déterminants du recrutement des patients pour les techniques innovantes en radiothérapie : enquête dans les centres de soins universitaires. master degree work, 2009.

Chapter 4

In silico modelling

4.1 International journals with reviewing committee

2011

[1] B. Ribba, E Watkin, M. Tod, P. Girard, E. Grenier, B. You, E. Giraudo, and G. Freyer. A model of vascular tumour growth in mice combining longitudinal tumour size data with histological biomarkers. *Eur. J. Cancer*, 47(3):479–90, February 2011.

2009

[1] B. Ribba, B. You, M. Tod, P. Girard, B. Tranchand, V. Trillet-Lenoir, and G. Freyer. Chemotherapy may be delivered upon an integrated view of tumor dynamics. *IET Syst Biol*, 2009.

[2] F. Billy, B. Ribba, O. Saut, H. Morre-Throuillet, T. Colin, D. Cresch, J-P. Boissel, E. Grenier, and J. P. Flandrois. A pharmacologically-based multiscale mathematical model of angiogenesis and its use in investigating the efficacy of a new cancer treatment strategy. *J Theor Biol (in press)*, 2009.

2008

[1] B. You, P. Perrin, G. Freyer, B. Tranchand, B. Ribba, E. HÖnin, A. Ruffion, V. Trillet-Lenoir, and P. Girard. A new approach : "psa clearance" predicts biochemical relapse risk of patients with prostate cancer in the first month following radical prostatectomy. *Fundam Clin Pharmacol*, 2008.

[2] B. You, P. Perrin, G. Freyer, A. Ruffion, B. Tranchand, E. HÖnin, P. Paparel, B. Ribba, M. Devonec, C. Flandry, C. Fournel, M. Tod, and P. Girard. Advantages of prostate-specific antigen (psa) clearance model over simple psa half-life computation to describe psa decrease after prostate adenomectomy. *Clin Biochem*, 2008.

[3] B. You, B. Tranchand, P. Girard, C. Falandry, B. Ribba, S. Chabaud, P. J. Souquet, I. Cout-Fortune, V. Trillet-Lenoir, M. Tod, and G. Freyer. Etoposide pharmacokinetics and survival in small cell lung cancer patients : results of a multicentre study. *Lung Cancer*, 2008.

[4] B. Tranchand, C. Falandry, B. You, P. Girard, B. Ribba, M. Tod, and G. Freyer. Pharmacology of anticancer drugs in the elderly : tools for dose adjustment. *Bull Cancer*, 2008.

[5] F. Bekkal-Brikci, J. Clairambault, B. Ribba, and B. Perthame. An age-and-cyclin-structured cell population model with proliferation and quiescence for healthy and tumoral tissues. *J Math Biol*, 2008.

2007

[1] Y. Kogan, B. Ribba, K. Marron, N. Dahan, V. Vainstein, and Z. Agur. Intensified doxorubicinbased regimen efficacy in residual non-hodgkin's lymphoma disease : Towards a computationally supported treatment improvement. *Mathematical Modelling of Natural Phenomena*, 2007.

[2] M-A. Dronne, E. Grenier, T. Dumont, M. Hommel, and J-P. Boissel. Role of astrocytes in grey matter during stroke: A modelling approach. *Brain Res.*, 1138, 2007.

[3] J-P. Boissel, B. Ribba, E. Grenier, G. Chapuisat, and M-A. Dronne. Progress in biophysics and molecular biology. *Modelling methodology in physiopathology*, 2007.

4.2 International conferences with reviewing committee

2007

[1] J-P. Boissel, M. Cucherat, P. Nony, S. Chabaud, F. Gueyffier, J-M. Wright, M. Lièvre, and A. Leizorovicz. New insights on the relation between untreated and treated outcomes for a given therapy. *Journal of Clinical Epidemiology*, 61(3), november 2007.

4.3 Workshops without proceedings

2008

[1] B. Ribba, B. You, P. Girard, B. Tranchand, V. Trillet-Lenoir, and G. Freyer. Mathematical modeling of cancer: a fulcrum from fundamental to clinical research. *Bulletin du Cancer*, (95), 2008.

[2] F. Billy, O. Saut, H. Morre-Throuillet, T. Colin, D. Bresch, B. Ribba, and E. Grenier. Multiscale mathematical model of tumoral angiogenesis and application of the efficiency of anti-angiogenic treatments. *Bulletin du Cancer*, (95), 2008.

Chapter 5

Basic physical measures and on-line control

5.1 International journals with reviewing committee

2013

[1] X. Lojacono, M. H. Richard, E. Testa, C. Ray, N. Freud, J.M. Létang, D. Dauvergne, V. Maxim, and R. Prost. Image reconstruction for compton camera applied to 3d prompt-gamma imaging in ion beam therapy. *IEEE Trans Nucl Sci*, submitted, 2013.

2012

[1] L. Lestand, G. Montarou, P. Force, and N. Pauna. In-beam quality assurance using induced beta + activity in hadrontherapy: a preliminary physical requirements study using geant4. *Physics in Medicine and Biology*, 57:6497–6518, 2012.

[2] P. Henriquet, E. Testa, M. Chevallier, D. Dauvergne, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, C. Ray, M. H. Richard, and F. Sauli. Interaction vertex imaging (ivi) for carbon ion therapy monitoring: a feasibility study. *Physics in Medicine and Biology*, 57:4655–4669, 2012.

[3] S Deng, H Mathez, D. Dauvergne, Y Zoccaratto, and GN. Lu. Front-end multi-channel pmt-associated readout chip for hodoscope application. *Nuclear Instruments and Methods in Physics Research A*, 2012.

2011

[1] F. Roellinghoff, M. H. Richard, M. Chevallier, J Constanzo, D. Dauvergne, N. Freud, P. Henriquet, F. Le Foulher, J.M. Létang, G. Montarou, C. Ray, E. Testa, M. Testa, and A. H. Walenta. Design of a compton camera for 3d prompt-γ imaging during ion beam therapy. *NIMA*, 648:S20–S23, 2011.

[2] M. H. Richard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, F. Le Foulher, J.M. Létang, G. Montarou, C. Ray, F. Roellinghoff, E. Testa, M. Testa, and A. H. Walenta. Design guidelines for a double scattering compton camera for prompt-gamma imaging during ion beam therapy: A monte carlo simulation study. *IEEE Trans. Nucl. Sci.*, 58(1):87–94, February 2011.

[3] B. Braunn, M. Labalme, G. Ban, M. Chevallier, J. Colin, D. Cussol, D. Dauvergne, JM. Fontbonne, F. Haas, A. Guertin, D. Lebhertz, F. Le Foulher, C. Pautard, C. Ray, M. Rousseau, M. D. Salsac, L. Stuttge, E. Testa, and M. Testa. Nuclear reaction measurements of 95mev/u

12c interactions on pmma for hadrontherapy. *Nuclear Instruments and Methods in Physics Research Section B*, 269(22):2676–2684, 2011.

2010

[1] M. Testa, M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, S. Karkar, F. Le Foulher, J.M. Létang, R. Plescak, C. Ray, M. H. Richard, D. Schardt, and E. Testa. Real-time monitoring of the bragg-peak position in ion therapy by means of single photon detection. *Radiation and Environmental Biophysics*, 49(3):337–343, March 2010.

[2] M. Frandes, A. Zoglauer, V. Maxim, and R. Prost. A tracking compton-scattering imaging system for hadron therapy monitoring. *IEEE Transaction in Nuclear Sciences*, 57(1):144–150, 2010.

2009

[1] V. Maxim, M. Frandes, and R. Prost. Analytical inversion of the compton transform using the full set of available projections. *Inverse Problems*, 25(9):1–31, 2009.

2008

[1] E. Testa, M. Bajard, M. Chevallier, D. Dauvergne, F. Le Foulher, N. Freud, J.M. Létang, J.-C. Poizat, C. Ray, and M. Testa. Monitoring the bragg peak location of 73 mev/u carbon ions by means of prompt gamma-ray measurements. *Applied Physics Letters 93, 093506*, 2008.

2007

[1] M. Taverne, M. Boutemeur, A. Buthod, L. Guigues, P. Henriquet, J. Lollierou, M-C. Ricol, R. Rosset-Lanchet, M. Roubin, R. Saidi, D. Sappey-Marinier, and E. Testa. Detector characterization for an inline pet scanner in hadrontherapy. *Nuclear Instruments and Methods in Physics Research A*, 571, February 2007. Provided by the SAO/NASA Astrophysics Data System.

[2] S. A. Pistrui-Maximean, N. Freud, J.M. Létang, A. H. Walenta, A. Koch, G. Montarou, and D. Babot. Simulation study of the role played by intensifying or support layers in scintillation screens. *IEEE Transactions on Nuclear Science*, 54(3), 2007.

[3] S. A. Pistrui-Maximean, J.M. Létang, N. Freud, A. Koch, A. H. Walenta, G. Montarou, and D. Babot. Measurement and monte carlo modeling of the spatial response of scintillation screens. *Nuclear Instruments and Methods in Physics Research A*, 581(3), 2007.

[4] M. Boutemeur and al. Requirements towards real time quality control in hadrontherapy. *Nucl. Inst. and Method.*, december 2007.

5.2 International journals without reviewing committee

2009

[1] M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, S. Karkar, F. Le Foulher, J.M. Létang, R. Plescak, C. Ray, D. Schardt, E. Testa, and M. Testa. Prompt gamma profile induced by carbon ions in water in view of real time ion therapy monitoring. GSI annual scientific report 2008, 2009.

5.3 Journals without classification

2009

[1] F. Le Foulher, M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, S. Karkar, J.M. Létang, R. Plescak, C. Ray, D. Schardt, E. Testa, and M. Testa. Monte carlo simulations of prompt-gamma emission during carbon ion irradiation. *IEEE Trans. Nucl. Sci. (to appear)*, 2009.

5.4 International conferences with reviewing committee

2012

[1] E. Testa, D. Dauvergne, M. De Rydt, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, M. Pinto, C. Ray, and V. Reithinger. Online monitoring of the dose during ion therapy by means of prompt secondary radiations. In *Conference Swift Heavy Ions in Matter, Kyoto, 24-27 octobre 2012*, October 2012.

[2] E. Testa, L. Balleyguier, J. Baudot, S. Brons, L. Caponetto, M. Dahoumane, D. Dauvergne, S Deng, R. Della-Negra, M. De Rydt, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, H Mathez, K. Parodi, M. Pinto, C. Ray, M. H. Richard, V. Reithinger, I. Rinaldi, F. Roellinghoff, M. Winter, and Y Zoccaratto. Real-time online monitoring of the ion range by means of prompt secondary radiations. In *Nuclear Science Symposium and Medical Imaging Conference*. IEEE, 2012.

[3] F. Roellinghoff, A. Benilov, D. Dauvergne, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, D. Prieels, C. Ray, M. H. Richard, J. Smeets, F. Stichelbaut, and E. Testa. Real-time proton beam range monitoring by means of prompt-gamma detection with a collimated camera. In *ICTR-PHE, International Conference on Translational Research in Radio-Oncology and Physics for Health in Europe*. CERN, February 2012.

[4] V. Reithinger, C. Ray, J. Baudot, S. Brons, D. Dauvergne, M. De Rydt, G. Dedes, P. Henriquet, J. Krimmer, K. Parodi, I. Rinaldi, E. Testa, and M. Winter. Proton interaction vertex imaging with silicon-pixel cmos telescopes for carbon therapy quality control. In *Nuclear Science Symposium and Medical Imaging Conference, IEEE, 2012*, October 2012.

[5] M. De Rydt, S Deng, D. Dauvergne, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, GN. Lu, H Mathez, K. Parodi, M. Pinto, C. Ray, V. Reithinger, M. H. Richard, I. Rinaldi, F. Roellinghoff, E. Testa, and Y Zoccaratto. Real-time monitoring during ion therapy: Development and evaluation of a beam hodoscope and its dedicated electronics. In *Nuclear Science Symposium and Medical Imaging Conference*. IEEE, 2012.

[6] G. Dedes, D. Dauvergne, M. De Rydt, N. Freud, J. Krimmer, J.M. Létang, M. Pinto, C. Ray, and E. Testa. Monte carlo nuclear models evaluation and improvements for real-time prompt gamma-ray monitoring in proton and carbon therapy. In *Nuclear Science Symposium and Medical Imaging Conference*. IEEE, 2012.

[7] G. Dedes, D. Dauvergne, M. De Rydt, N. Freud, J. Krimmer, J.M. Létang, M. Pinto, C. Ray, M. H. Richard, F. Roellinghoff, and E. Testa. Real-time prompt gamma ray monitoring for proton and carbon therapy: Monte carlo nuclear models evaluation and improvements. In *International Conference on Translational Research in Radio-Oncology – Physics for Health in Europe*, February 2012.

2011

[1] E. Testa, M. Bajard, M. Chevallier, D. Dauvergne, G. Dedes, P. Henriquet, J. Krimmer, C. Ray, N. Freud, J.M. Létang, R. Plescak, and D. Schardt. Interaction vertex imaging (ivi): a new method of real-time control imaging for carbon ion therapy. In *50th International PTCOG meeting (Particle Therapy Co-Operative Group)*, May 2011.

[2] X. Lojacono, V. Maxim, A. Zoglauer, F. Peyrin, and R. Prost. A filtered backprojection reconstruction algorithm for compton camera. In *Proceedings of the International conference Fully3D 2011, Postdam*, pages 96–99, January 2011.

2010

[1] P. Henriquet, M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, S. Iliescu, S. Karkar, F. Le Foulher, J.M. Létang, C. Ray, F. Sauli, D. Schardt, E. Testa, and M. Testa. Charged particle imaging for real-time control during ion therapy. International workshop Physics For health in Europe, CERN, January 2010, January 2010.

2009

[1] E. Testa, M. Bajard, M. Chevallier, D. Dauvergne, F. Le Foulher, N. Freud, J.M. Létang, J.-C. Poizat, C. Ray, and M. Testa. Dose profile monitoring with carbon ions by means of prompt-gamma measurements. *Nuclear Instruments and Methods in Physics Research B*, 267, 2009. available online at http://hal.archives-ouvertes.fr/hal-00283936/fr/.

[2] M. H. Richard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, F. Le Foulher, J.M. Létang, G. Montarou, C. Ray, F. Roellinghoff, E. Testa, M. Testa, and A. H. Walenta. Design study of a compton camera for prompt γ imaging during ion beam therapy. In *IEEE Nuclear Science Symposium, Medical Imaging Conference*, October 2009.

[3] B. Braunn, M. Labalme, G. Ban, J. Colin, D. Cussol, JM. Fontbonne, F. R. Lecolley, C. Portard, F. Haas, D. Lebhertz, M Rousseau, L. Stuttge, M. Chevallier, D. Dauvergne, F. Le Foulher, C. Ray, E. Testa, M. Testa, and M. D. Salsac. 12c nuclear reaction measurements for hadrontherapy. In *12th International Conference on Nuclear Reaction Mechanisms*, pages 531–538, June 2009.

[4] M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, S. Karkar, F. Le Foulher, J.M. Létang, R. Plescak, C. Ray, D. Schardt, E. Testa, and M. Testa. Prompt-gamma-ray monitoring during carbon ion therapy: comparison between measurements and geant4 simulations. In *First International Conference on Advancements in Nuclear Instrumentation, Measurement Methods and their Applications (ANIMMA)*, june 2009.

2008

[1] E. Testa, M. Bajard, M. Chevallier, D. Dauvergne, F. Le Foulher, N. Freud, J.M. Létang, C. Ray, and M. Testa. Detection of prompt gamma rays to monitor hadrontherapy. In *IEEE Nuclear Science Symposium, Medical Imaging Conference*, October 2008.

[2] N. Freud, M. Bajard, M. Chevallier, D. Dauvergne, F. Le Foulher, J.M. Létang, C. Ray, E. Testa, and M. Testa. Monitoring the bragg peak location by means of prompt-gamma measurements. In *European Science Foundation Exploratory Workshop "Advanced Instrumentation for Cancer Diagnosis and Treatment", Oxford, UK, 23-26 Sept.*, 2008.

5.5 National conferences with reviewing committee

2013

[1] E. Hilaire, C. Robert, X. Lojacono, C. Lartizien, I. Buvat, and V. Maxim. Imagerie caméra compton en protonthérapie : simulations gate et reconstruction d'images. page submitted. XXIVe Colloque GRETSI - Traitement du Signal et des Images (GRETSI'13), September 2013.

2012

[1] X. Lojacono, E. Hilaire, R. Prasad, V. Maxim, and R. Prost. Algorithmes lm-mlem pour la reconstruction d'images pour caméra compton. In *Nouvelles méthodologies en imagerie du vivant (IMAGIV)*, pages 9385–9385, December 2012.

2009

[1] N. Freud, M. Chevallier, D. Dauvergne, P. Henriquet, F. Le Foulher, S. Karkar, J.M. Létang, G. Montarou, C. Ray, M. H. Richard, E. Testa, M. Testa, and A. H. Walenta. Nouvelles méthodes d'imagerie en ligne pour le contrôle de l'irradiation en hadronthérapie. In *48èmes Journées Scientifiques de la Société Française de Physique Médicale : Innovations et bénéfices thérapeutiques : quelles limites ? Montauban, 3-5 juin 2009*, 2009. Exposé invité.

5.6 Invited conferences

2012

[1] V. Maxim. Reconstruction tomographique pour l'imagerie spect avec une caméra compton. In *XIème Colloque Franco-Roumain de Mathématiques Appliquées*, pages 74–74, August 2012.

2011

[1] E. Testa, D. Dauvergne, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, V. Maxim, G. Montarou, C. Ray, M. H. Richard, and F. Roellinghoff. Imaging system for qa: present status and future prospects. In *Proceedings of NIRS-ETOILE 2nd Joint Symposium on Carbon Ion Therapy*, volume NIRS-M-243, pages 134–142, November 2011. Invited talk at the NIRS-ETOILE 2nd Joint Symposium, Lyon, November 25-27, 2011.

[2] J.M. Létang. Real-time monitoring of ion ranges. In *2nd Workshop on Hadron Beam Therapy of Cancer*, May 2011. Invited talk.

[3] D. Dauvergne. Online control of the dose during ion-therapy by means of prompt radiations, April 2011. exposé invité, 3rd Workshop of the DFM/ISEC, Coimbra, Portugal, April 27, 2011.

[4] D. Dauvergne. Contrôle en ligne de l'hadronthérapie. In *Rencontre MELUSYN - ETOILE, Lyon, 8 février 2011*, February 2011. exposé invité.

2009

[1] D. Dauvergne, M. Battaglia, G. Montarou, and M. Testa. New methods of real-time control imaging for ion therapy. In H. Tsujii and J. Balosso, editors, *NIRS-ETOILE Joint Symposium 2009 on Carbon Ion Therapy*, volume NIRS - M - 218„ 2009. Available online at http://hal.in2p3.fr/in2p3-00363382/fr/.

5.7 PhD / HdR

2012

[1] M. H. Richard. *Design Study of a Compton Camera for Prompt-Gamma Imaging during Ion Therapy.* PhD thesis, Université Claude Bernard Lyon 1, September 2012.

[2] L. Lestand. *Etude de la mesure en ligne de l'activité beta+ induite lors des traitements d'hadronthérapie, en vue de leur contrôle balistique.* Thesis, Université de Clermont, September 2012.

[3] S Deng. *Etude de conception d'ASICs de lecture et d'étiquetage en temps associés à des photomultiplicateurs pour un hodoscope de faisceau en hadronthérapie.* Thesis, Université Claude Bernard Lyon 1, November 2012.

2011

[1] P. Henriquet. *Etude de l'émission de particules chargées secondaires dans l'optique d'un monitorage faisceau et de la dosimétrie en ligne en hadronthérapie.* Thèse, Université Lyon 1, July 2011.

2010

[1] M. Testa. *Physical measurements for ion range verification in charged particle therapy.* PhD thesis, Université Lyon 1 Institut de Physique Nucléaire de Lyon, 2010.

[2] F. Le Foulher. *Simulations Monte Carlo et mesures de l'émission de gamma prompts appliquées au contrôle en ligne en hadronthérapie.* PhD thesis, Ecole doctorale PHAST, October 2010.

[3] M. Frandes. *Gamma-ray detection and Compton camera image reconstruction with application to hadron therapy.* PhD thesis, Ecole Doctorale Electronique, Electrotechnique, atomatique de Lyon, September 2010.

2009

[1] C. Ray. *Canalisation d'ions lourds dans les solides et applications à l'hadronthérapie.* HDR, IPNL-Lyon1, December 2009. Mémoire pour l'obtention de l'habilitation à diriger des recherches, no d'ordre : 47-2009.

2008

[1] M-C. Ricol. *Contribution à l'étude des processus nucléaires intervenant en hadronthérapie et de leur impact à la délocalisation du dépôt de dose.* PhD thesis, Université Lyon 1, november 2008.

5.8 Posters

2012

[1] E. Testa, L. Balleyguier, J. Baudot, S. Brons, L. Caponetto, M. Dahoumane, D. Dauvergne, R. Della-Negra, S Deng, M. De Rydt, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, H Mathez, K. Parodi, M. Pinto, C. Ray, M. H. Richard, V. Reithinger, I. Rinaldi, F. Roellinghoff, M. Winter, and Y Zoccaratto. Real-time monitoring of the ion range by means of prompt-secondary radiation. In *Nouvelles Méthodologies en imagerie du vivant, Lyon, 11-13 décembre 2012*, page 9585, December 2012.

2011

[1] M. H. Richard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, J. Krimmer, J.M. Létang, C. Ray, F. Roellinghoff, E. Testa, and A. H. Walenta. Design guidelines for a compton camera for prompt-gamma imaging during ion beam therapy. poster at the International conference NDIP, Lyon, 4-7 July, 2011, July 2011.

[2] M. H. Richard, D. Dauvergne, M. Dahoumane, M. De Rydt, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, X. Lojacono, V. Maxim, G. Montarou, C. Ray, F. Roellinghoff, E. Testa, and A. H. Walenta. Design of a compton camera for hadrontherapy on-line control using geant4. In *IEEE-NSS-MIC conference records*, October 2011. IEEE NSS MIC conference, Valencia, 23-29 October 2011.

[3] X. Lojacono, V. Maxim, and R. Prost. Calcul de la matrice des probabilités de transfert en imagerie compton 3d. In *Proceedings of GRETSI*, pages 1–4, 2011.

[4] X. Lojacono, M. H. Richard, C. Ray, D. Dauvergne, E. Testa, N. Freud, J.M. Létang, V. Maxim, and R. Prost. Image reconstruction for compton camera applied to 3d prompt gamma imaging during ion beam therapy. In *IEEE-NSS-MIC conference records*, October 2011. Conference records IEEE-NSS-MIC, Valencia, 23-29 October, 2011.

[5] S Deng, H Mathez, D. Dauvergne, and GN. Lu. 16-channel readout ASIC for a hodoscope. In *Conference Internationale NDIP, Lyon, 4-7 Juillet 2011*, 2011. Conference Internationale NDIP, Lyon, 4-7 Juillet 2011.

2010

[1] M. Testa, M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, S. Karkar, F. Le Foulher, J.M. Létang, R. Plescak, C. Ray, M. H. Richard, F. Roellinghoff, D. Schardt, and E. Testa. Real time monitoring of the bragg-peak position in ion therapy by means of single photon detection. International workshop Physics for Health in Europe, CERN, 2-4 Février 2010, February 2010.

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2008

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5.9 Workshops without proceedings

2007

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2011

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2009

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2012

[1] D. Dauvergne, W. Enghardt, A. Müller, and J. Smeets. Compilation of gamma-ray yield data. ENVISION report D3.1, Février 2012., February 2012.

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2012

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Chapter 6

Radiobiological effects of carbon ions

6.1 International journals with reviewing committee

2013

[1] W. Rima, Sancey L, M.-T. Aloy, E. Armandy, GB. Alcantara, Epicier T, Malchère A, Joly-Pottuz L, P. Mowat, F. Lux, O. Tillement, Burdin B, Rivoire A, Boulé C, Anselme-Bertrand I, Pourchez J, Cottier M, S. Roux, C. Rodriguez-Lafrasse, and P. Perriat. Internalization pathways into cancer cells of gadolinium-based radiosensitizing nanoparticles. *Biomaterials.*, 34(1):181–195, January 2013.

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2012

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2011

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6.2 International journals without reviewing committee

2009

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6.3 National journals with reviewing committee

2012

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6.4 International conferences with reviewing committee

2011

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2010

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[2] S Ferrandon, P. Saultier, P. Battiston-Montagne, C. Malesys, M. Beuve, A. Colliaux, C. Rodriguez-Lafrasse, and D. Poncet. Determination of the telomeric status as a radiotherapy response predictive in glioma. 2010.

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6.5 International conferences without reviewing committee

2007

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6.6 National conferences with reviewing committee

2011

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[1] C. Rodriguez-Lafrasse, M. Maalouf, G. Alphonse, P. Battiston-Montagne, M. Beuve, A. Colliaux, M. Bajard, C. Fournier, and G. Taucher-Scholz. Echappement tumoral en réponse à l'irradiation par photons et ions carbone des carcinomes épidermoïdes de la tête et du cou. 9ème Colloque International de Radiobiologie Fondamentale et Appliquée (SIRLAF), ANNECY (France), September 2009.

[2] D. Poncet, P. Saultier, S Ferrandon, and C. Rodriguez-Lafrasse. Radiorésistance des glioblastomes et statut télomérique. 9ème Colloque International de Radiobiologie Fondamentale et Appliquée (SIRLAF), ANNECY (France), September 2009.

[3] M. Hanot, C. Malesys, A. Boivin, C. Colin, T. Douki, N. Foray, D. Ardail, and C. Rodriguez-Lafrasse. Radiosensibilisation par modulation du statut redox intracellulaire : caractérisation des lésions et des processus de réparation de l'adn impliqués en réponse à l'irradiation par rayons x et ions carbone. 9ème Colloque International de Radiobiologie Fondamentale et Appliquée (SIRLAF), ANNECY (France), September 2009.

[4] E. Hadchity, M.-T. Aloy, C Paulin, E. Armandy, A.P. Arrigo, A. Sabri, C. Diaz-Latoud, and C. Rodriguez-Lafrasse. Protéine de choc thermique hsp27 : un rôle majeur dans la tumorigénicité et la radiorésistance des carcinomes épidermoïdes orl. 9ème Colloque International de Radiobiologie Fondamentale et Appliquée (SIRLAF), ANNECY (France), September 2009.

[5] D. Dabli, G. Montarou, M. Beuve, and C. Rodriguez-Lafrasse. Application de la microdosimétrie pour le calcul de la survie cellulaire pour des cellules irradiées avec des particules à haut tel. 9ème Colloque International de Radiobiologie Fondamentale et Appliquée (SIRLAF), ANNECY (France), September 2009.

[6] A. Boivin, C. Malesys, M. Maalouf, C. Colin, O. Chapet, C. Rodriguez-Lafrasse, and D. Ardail. Sensibilisation aux rayonnements ionisants de cellules de carcinomes orl par déplétion transitoire en glutathion. 9ème Colloque International de Radiobiologie Fondamentale et Appliquée (SIRLAF), ANNECY (France), September 2009.

[7] G. Alphonse, NH Hau, S Ferrandon, P. Battiston-Montagne, D. Poncet, and C. Rodriguez-Lafrasse. Caractérisation de la réponse cellulaire et moléculaire de lignées de gliomes humains irradiées par des photons ou des ions carbone. 11éme CIRFA, September 2009.

2007

[1] C. Rodriguez-Lafrasse. Les systèmes oxydant/anti-oxydant, pro/anti-apoptotique : deux déterminants essentiels de la réponse tumorale à l'irradiation. 8ème Colloque International Radiobiologie Fondamentale Appliquée, La Londe les Maures, France, september 2007.

[2] M. Maalouf, G. Alphonse, P. Battiston-Montagne, M. Beuve, A. Colliaux, A. Demeyer, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Caractérisation des processus de mort activés en réponse à l'irradiation par ions carbone de carcinomes épidermoïdes tête et cou. 8ème Colloque International de Radiobiologie Fondamentale et Appliquée. La Londe Les Maures, (SIRLAF), september 2007.

[3] D. Ardail, M. Maalouf, E. Armandy, and C. Rodriguez-Lafrasse. Libération du céramide en réponse à l'irradiation : un mécanisme complexe et séquentiel. 8ème Colloque International de Radiobiologie Fondamentale et Appliquée, La Londe les Maures, France, september 2007.

6.7 National conferences without reviewing committee

2011

[1] C. Rodriguez-Lafrasse, M. Hanot, A. Boivin, C. Malesys, and D. Ardail. Signature spécifique de la réponse aux ions carbone ? MELUSYNE, 2011.

6.8 Invited conferences

2012

[1] M. Beuve, L. Chollier, and E. Testa. Toward the nanox model. MMND and IPCT Workshop, Wollongong 6-9 Dec, 2012, (Australia), November 2012.

2011

[1] M. Beuve, A. Colliaux, C. Rodriguez-Lafrasse, and B. Gervais. O2 and glutathione effects on water radiolysis by fast ions. 1ST NANO-IBCT CONFERENCE 2011, October 2011.

2010

[1] M. Beuve, A. Colliaux, B. Gervais, and C. Rodriguez-Lafrasse. Simulation of ho2/o2- production by water radiolysis: influence of various parameters. COST Chemistry CM0603 Free Radicals in Chemical Biology - MELUSYN Joint Meeting, March 2010.

[2] M. Beuve and E. Testa. Hadronthérapie : vers une dosimétrie clinique. Saint-François, Guadeloupe, December 2010. Journées de réflexion CNRS/IN2P3 des applications sociétales de la physique nucléaire : energie et santé.

[3] M. Beuve. Modélisation des effets radiobiologiques : échelles d'espace et de temps. Journée thématique MELUSYN - SOLEIL, January 2010.

2009

[1] C. Rodriguez-Lafrasse. Molecular mechanisms of tumor cell radioresistance in head and neck squamous cell carcinomas. In H. Tsujii and J. Balosso, editors, *NIRS-ETOILE Joint Symposium 2009 on Carbon Ion Therapy*, volume NIRS-M-218, 2009.

[2] *Modeling of RBE: Difficulties and Needs for a New Model.* In H. Tsujii and J. Balosso, editors, NIRS-ETOILE Joint Symposium on Carbon Ion Therapy, january 2009.

2008

[1] M. Beuve. Statistical effects of dose deposition in track-structure modelling of radiobiology efficiency. 7th International Symposium on Swift Heavy Ions in Matter (SHIM 2008), June 2008.

2007

[1] M. Beuve, A. Colliaux, D. Dabli, G. Montarou, and E. Testa. Modèles microdosimétriques et modèles de trace. 8ème Colloque International de Radiobiologie Fondamentale et Appliquée, La Londe les Maures, France, september 2007.

6.9 PhD / HdR

2013

[1] S Ferrandon. *Evaluation du statut télomérique : vers une thérapeutique personnalisée du glioblastome. Application à l'hadronthérapie par ions carbone.* PhD thesis, EDISS, January 2013.

2012

[1] L. Chollier. *Modélisation biophysique de l'interaction des ions de hautes énergies avec la matière vivante : application au traitement des tumeurs par hadronthérapie.* PhD thesis, UCBL, Villeurbanne, October 2012.

2011

[1] A. Boivin. *Implication du Statut Redox et de sa modulation dans la réponse tumorale à l'irradiation.* PhD thesis, EDISS, UCBL, July 2011.

2010

[1] D. Dabli. *Utilisation d'un modèle microdosimétrique cinétique (MKM) pour l'interprétation d'irradiations cellulaires dans le cadre de l'hadronthérapie: Application de simulations Monte-Carlo.* PhD thesis, Université Blaise Pascal - Clermont-Ferrand II, Université Blaise Pascal - Clermont-Ferrand II, February 2010.

2009

[1] M. Maalouf. *Mort cellulaire et mécanismes de résistance des carcinomes épidermoïdes de la tête et du cou en réponse à l'irradiation par ions carbone ou photons.* PhD thesis, EDISS, September 2009.

[2] E. Hadchity. *Developpement d'une stratégie de radiosensibilisation par inhibition de l'expression de la protéine de choc thermique hsp27 dans un modéle celluliare pré-clinique de carcinome épidermoïde de la tête et du cou.* PhD thesis, EDISS, 2009.

[3] A. Colliaux. *Implication de l'oxygène et des anti-oxydants dans le processus de radiolyse de l'eau induit par l'irradiation aux ions de haute énergie : simulations numériques pour la radiobiologie.* PhD thesis, Université Claude Bernard Lyon 1, December 2009.

2007

[1] C. Bionda. *Implication des microdomaines rafts de la membrane plasmique dans la résistance aux radiations ionisantes d'un modéle celluliare de carcinome epidermoïde de la tête et du cou.* PhD thesis, EDISS, december 2007.

6.10 Posters

2012

[1] I Miladi, M.-T. Aloy, A. Berniard, E. Armandy, P. Mowat, M. Benchaib, N. Magné, E. Noirault, C. Billotey, P. Perriat, F. Lux, O. Tillement, C. Rodriguez-Lafrasse, and M. Janier. Gadolinium based nanoparticules as radiosensitizing agents for radioresistant head and neck tumours. 7éme journéees Scientifique CLARA, Lyon, March 2012.

[2] I Miladi, M.-T. Aloy, A. Berniard, E. Armandy, P. Mowat, M. Benchaib, N. Magné, E. Noirault, C. Billotey, P. Perriat, F. Lux, O. Tillement, C. Rodriguez-Lafrasse, and M. Janier. Gadolinium based nanoparticules as radiosensitizing agents for radioresistant head and neck tumours. World Molecular Imaging Congress, September 2012.

[3] M. Hanot-Roy, A. Boivin, C. Malesys, D. Ardail, and C. Rodriguez-Lafrasse. Trancient glutathion depletion sensitize hnscc stem and non-stem cells to both photon and carbon irradiation and decreases carbon ion induced genomic instability. 7éme Journées Scientifique du Cancéropole CLARA, Lyon, March 2012.

[4] S Ferrandon, P. Saultier, J. Carras, P. Battiston-Montagne, G. Alphonse, M. Beuve, C. Malleval, J. Honnorat, T. Slatter, N. Hung, J. Royds, C. Rodriguez-Lafrasse, and D. Poncet. Telomere profiling: toward glioblastoma personalized medicine. Telomeres and the DDR meeting, October 2012.

[5] S Ferrandon, P. Saultier, P. Battiston-Montagne, M. Beuve, G. Alphonse, NH Hau, C. Rodriguez-Lafrasse, and D. Poncet. Evaluation du statut télomérique comme biomarqueur prédictif de réponse à la radiothérapie de lignées de glioblastome : orientation vers l'hadronthérapie. 6ème journée scientifique du cancéropole PACA, February 2012.

[6] S Ferrandon, P. Saultier, P. Battiston-Montagne, M. Beuve, G. Alphonse, NH Hau, C. Rodriguez-Lafrasse, and D. Poncet. Evaluation du statut télomérique comme biomarqueur prédictif de réponse à la radiothérapie de lignées de glioblastome : orientation vers l'hadronthérapie. 7ème journées scientifiques du Cancéropole Lyon Rhône-Alpes Auvergne, 2012.

[7] J Constanzo, M fallavier, G. Alphonse, C. Bernard, P. Battiston-Montagne, C. Rodriguez-Lafrasse, D. Dauvergne, and M. Beuve. Radiograaff, a proton irradiation facility for radiobiological studies at a 4mv van de graaff accelerator. 39th European Radiation Research (ERR2012) 15-19 oct., Vietri sul Mare (Italia), 2012, 2012.

[8] M-A. Chanrion, U. Lejen, A. Wittig, L. Zink, R. Engenhart-Cabillic, M. Beuve, and W. Sauerwein. Influence of the local effect model parameters on the biologically weighted dose for prostate cancer. 51st Annual Meeting of Particle Therapy Co-Operative Group (PTCOG51) Goyang (Korea), May 2012.

[9] G Bertrand, M. Maalouf, A. Boivin, P. Battiston-Montagne, M. Beuve, G. Alphonse, and C. Rodriguez-Lafrasse. Molecular mechanisms of tumor cell radioresistance in head and neck squamous cell carcinomas. 7ème journées scientifiques du Cancéropole Lyon Rhône-Alpes Auvergne, March 2012.

[10] G. Alphonse, NH Hau, P. Heudel, P. Battiston-Montagne, D. Poncet, S Ferrandon, M. Beuve, and C. Rodriguez-Lafrasse. Predictive markers of intrinsic radiosensitivity in human glioma cell lines irradiated with photon or carbon ions. 7ème journées scientifiques du Cancéropole Lyon Rhône-Alpes Auvergne, 2012.

2011

[1] M. Hanot, A. Boivin, C. Malesys, D. Ardail, and C. Rodriguez-Lafrasse. Transient glutathione depletion sensitizes hnscc stem and non-stem cells to both photon and carbon irradiation and decreases carbon ion induced genomic instability. NIRS-ETOILE, 2011.

[2] S Ferrandon, P. Battiston-Montagne, P. Saultier, M. Beuve, G. Alphonse, C. Rodriguez-Lafrasse, and D. Poncet. Telomeric status and radioresistance in glioma : a predictive biomarker for steering patient to hadrontherapy,. NIRS-ETOILE, 2011.

[3] S Ferrandon, P. Battiston-Montagne, P. Saultier, M. Beuve, G. Alphonse, NH Hau, C. Rodriguez-Lafrasse, and D. Poncet. Telomeric status and radioresistance in glioma : a predictive biomarker for steering patient to hadrontherapy. pages POS12–03. 14th International Congres of Radiation Research, 2011.

[4] G Bertrand, M. Maalouf, A. Boivin, P. Battiston-Montagne, M. Beuve, G. Alphonse, and C. Rodriguez-Lafrasse. Molecular mechanisms of tumor cell radioresistance in head and neck squamous cell carcinomas. NIRS-ETOILE, 2011.

[5] G. Alphonse, NH Hau, P. Heudel, P. Battiston-Montagne, S Ferrandon, M. Beuve, and C. Rodriguez-Lafrasse. Predictive markers of intrinsic radiosensitivity in human glioma cell lines irradiated with photon or carbon ions. NIRS-ETOILE, 2011.

2009

[1] M. Maalouf, G. Alphonse, P. Battiston-Montagne, M. Beuve, A. Colliaux, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Implication des cellules souches cancéreuses dans la radio-résistance des carcinomes epidermoïdes tête et cou (hnscc). 4ème journée du Cancéropôle Lyon Auvergne Rhône-Alpes, march 2009.

[2] M. Maalouf, G. Alphonse, P. Battiston-Montagne, M. Beuve, A. Colliaux, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Potential role of cancer stem cells in the resistance of head and neck squamous cell carcinoma to high and low let radiation. 11th International Wolfsberg Meeting 2009 on Molecular Radiation Biology / Oncology, june 2009.

[3] A. Boivin, C. Malesys, O. Chapet, C. Rodriguez-Lafrasse, and D. Ardail. Une nouvelle stratégie de radiosensibilisation tumorale par amplification du stress oxydant après déplétion transitoire du glutathion cellulaire. 4ème journée du Cancéropôle Lyon Auvergne Rhône-Alpes, Archamps, France, 2009, 2009.

[4] A. Boivin, C. Malesys, O. Chapet, C. Rodriguez-Lafrasse, and D. Ardail. The increase of oxidative stress after transient glutathione depletion and irradiation triggers apoptosis in head and neck squamous cell carcinoma. 8th Winter Research Conferences Oxidative DNA Damage: From Chemical Aspects to Biological Consequences, 2009.

2008

[1] M. Maalouf, G. Alphonse, P. Battiston-Montagne, M. Beuve, A. Colliaux, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Processus de mort cellulaire differentiellement activés dans deux modèles cellulaires de hnscc en réponse à l'irradiation (carbone et photons). 3ème journées scientifiques du cancéropôle Lyon Auvergne Rhône-Alpes (CLARA)-Lyon, march 2008.

[2] M. Maalouf, G. Alphonse, P. Battiston-Montagne, M. Beuve, A. Colliaux, A. Demeyer, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Different mechanisms of cell

death in radiosensitive and radioresistant p53 mutated head and neck squamous cell carcinomas exposed to carbon ions and x-rays. 36th Annual Meeting of the European Radiation Research Society, Tours, France, september 2008.

[3] A. Boivin, C. Malesys, O. Chapet, D. Ardail, and C. Rodriguez-Lafrasse. Radiosensibilisation d'un modèle de carcinome épidermoïde tête et cou (hnscc) par déplétion transitoire en glutathion intracellulaire. 3ème journées scientifiques du canceropole Lyon Auvergne Rhône-Alpes (CLARA)-Lyon, march 2008.

[4] A. Boivin, C. Malesys, O. Chapet, C. Rodriguez-Lafrasse, and D. Ardail. Transient glutathione depletion before irradiation triggers apoptosis in head and neck cell carcinoma. 36th Annual Meeting of the European Radiation Research Society Tours, France, september 2008.

2007

[1] M. Maalouf, G. Alphonse, M. Beuve, G. Taucher-Scholz, C. Fournier, and C. Rodriguez-Lafrasse. Characterization of cell death induced by high let irradiation in head and neck squamous cell carcinomas : implications for future clinical application in hadrontherapy. 11th Workshop on Heavy Charged Particles in Biology and Medicine, Heidelberg, september 2007.

[2] M. Maalouf, G. Alphonse, M. Beuve, P. Battiston-Montagne, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Characterization of cell death induced by high let irradiation in head and neck squamous cell carcinomas : implications for future clinical application in hadrontherapy. 2nd symposium Novel targeting drugs and Radiotherapy from the bench to clinic.13th International Congress of Radiation Research - San Francisco, july 2007.

[3] M. Maalouf, G. Alphonse, M. Beuve, P. Battiston-Montagne, M. Bajard, C. Fournier, G. Taucher-Scholz, and C. Rodriguez-Lafrasse. Different cell death pathways for radio-sensitive and radio-resistant head and neck squamous carcinomas cells exposed to high and low let radiation : Implications for future clinical application in hadrontherapy. 2nd symposium Novel targeting drugs and Radiotherapy from the bench to clinic, Toulouse, june 2007.

[4] M. Maalouf, G. Alphonse, M. Beuve, G. Taucher-Scholz, C. Fournier, and C. Rodriguez-Lafrasse. Caractérisation des processus de mort cellulaire activés en réponse a l'irradiation par ions carbone de lignées tumorales humaines. 2ème journée du Cancéropôle Lyon Auvergne Rhône-Alpes, Grenoble France, march 2007.

[5] M. Hollmark, M. Beuve, M. R. Edgren, T. Elsaesser, P. Kundrat, A.E. Meijer, C. Rodriguez-Lafrasse, M. Scholz, M.P.R. Waligorski, and I. Gudowska. A comparison of radiobiological models for light ion therapy. 11th Workshop of Heavy Charged Particles in Biology and Medicine – Heidelberg, september 2007.

[6] M. Beuve, G. Alphonse, M. Maalouf, A. Colliaux, P. Battiston-Montagne, P. Jalade, M. Bajard, and C. Rodriguez-Lafrasse. Hadronthérapie : Modélisation et mesure des effets biologiques des ions légers. Journées Scientifiques du Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA), Grenoble, march 2007.

[7] D. Ardail, C. Bionda, P. Battiston-Montagne, and C. Rodriguez-Lafrasse. Involvement of raft microdomains in the resistance of human carcinoma cells to irradiation. 2nd symposium : Novel Targeting Drugs and Radiotherapy. From the bench to the clinic, Toulouse, France, 2007.

6.11 ETOILE internal notes

2010

[1] G. Wannous. Automated counting of gamma-h2ax foci to evaluate the dna double strand breaks sites generated by ionizing radiation. Technical report, IPNL, January 2010.

[2] F. Chandez and G. Montarou. Analyse avec le logiciel imagej d'un lot d'images en microscopie par immunofluorecence de cellules de fibroblastes irradiées en x à l'esrf. Technical Report PCCF RI 1004, LPC Clermont, July 2010.

2007

[1] A. Joubert and N. Foray. Premiers resultats de radiobiologie sur amande-cadarache. Technical report, Rapport Interne IRSN, 2007.

6.12 Patents

2008

[1] C. Rodriguez-Lafrasse and E. Hadchity. Treatment of squamous cell carcinoma with hsp27 abtisense oligonucleotides and radiotherapy. Brevet University of British Columbia n° 60 / 893 086, 2008.

6.13 Book chapters

2008

[1] N. Foray, V. Favaudon, and J. M. Cosset. *RADIOTHERAPIE ONCOLOGIQUE, Enjeux et concepts nouveaux en radiobiologie*. Montrouge, john libbey eurotex edition, 2008.

[2] N. Foray and J. Balosso. *RADIATION CHEMISTRY : From basics to applications in material and life sciences*, chapter Advances i. EDP Sciences, Les Ulis, 2008.

[3] V. Favaudon and N. Foray. *RADIOBIOLOGIE*, chapter Effets Cel. Hermann, 2008. nouvelle édition, revue et augmentée.

6.14 Oral communications

2012

[1] D. Poncet, S Ferrandon, P. Saultier, J. Carras, P. Battiston-Montagne, G. Alphonse, M. Beuve, C. Malleval, J. Honnorat, and C. Rodriguez-Lafrasse. Statut télomérique : vers un traitement personnalisé du glioblastome. ANPMCB, September 2012.

[2] S Ferrandon, P. Saultier, J. Carras, P. Battiston-Montagne, G. Alphonse, M. Beuve, C. Malleval, J. Honnorat, T. Slatter, N. Hung, J. Royds, C. Rodriguez-Lafrasse, and D. Poncet. Telomere profiling: toward glioblastoma personalized medicine. The 10th International Symposium on Chromosomal Aberrations (ISCA10), October 2012.

[3] S Ferrandon, P. Saultier, J. Carras, P. Battiston-Montagne, G. Alphonse, M. Beuve, C. Malleval, J. Honnorat, T. Slatter, N. Hung, J. Royds, C. Rodriguez-Lafrasse, and D. Poncet. Telomere profiling: Toward glioblastoma personalized medicine. 39ème European Radiation Research (ERR2012) du 15 au 19 octobre 2012, October 2012.

[4] G Bertrand, M. Maalouf, P. Battiston-Montagne, M. Beuve, C. Fournier, D. Ardail, N. Magné, G. Alphonse, and C. Rodriguez-Lafrasse. Overcoming the resistance of head and neck squamous cell carcinoma to photon and carbon ion irradiation by targeting cancer stem cells. Vietri sul Mare (Italie), 2012.

2011

[1] M. Hanot, C. Malesys, D. Ardail, and C. Rodriguez-Lafrasse. Glutathion et radioresistance: Les effets biologique differentiels en radiotherapie conventionelle et hadrontherapie. 10éme Colloque International de Radiobiologie Fondamentale et Appliquée, 2011.

[2] S Ferrandon, P. Saultier, P. Battiston-Montagne, M. Beuve, C. Rodriguez-Lafrasse, and D. Poncet. Longeurs des télépmères et expression de la télomérase: Marqueurs predictifs pour l'orientation des patients atteints de glioblastome vers l'hadrontherapie. 10éme Colloque International de Radiobiologie Fondamentale et Appliquée, 2011.

[3] M. Beuve, M-A. Chanrion, U. Lejen, A. Wittig, L. Zink, F. Ammazzalorso, and W. Sauerwein. The need of clinical endpoint to feed rbe models. 2nd NIRS-ETOILE Joint Symposium on Carbon Ion Therapy, November 2011.

[4] G. Alphonse, P. Battiston-Montagne, NH Hau, P. Heudel, S Ferrandon, D. Poncet, and C. Rodriguez-Lafrasse. Predictive markers of intrinsic radiosensitivity in human glioma cell lines irradiated with photon or carbon ions. 14th International Congress of Radiation Research, September 2011.

Chapter 7

Simulations for treatment planning

7.1 International journals with reviewing committee

2013

[1] S. Rit, G. Dedes, N. Freud, D. Sarrut, and J.M. Létang. Filtered backprojection proton ct reconstruction along most likely paths. *Medical Physics*, 40(3), March 2013.

[2] S. Jan, T. Frisson, and D. Sarrut. Gate simulation of 12c hadrontherapy treatment combined with a pet imaging system for dose monitoring : A feasibility study. *IEEE Trans. Nucl. Sci.*, In press:1–8, 2013.

[3] S. Camarasu-Pop, T. Glatard, R. Ferreira da Silva, P. Gueth, D. Sarrut, and H. Benoit-Cattin. Monte-carlo simulation on heterogeneous distributed systems: a computing framework with parallel merging and checkpointing strategies. *Future Generation Computer Systems*, 29(3):728–738, 03/2013 2013.

2012

[1] P. Wils, J.M. Létang, and J. P. Bruandet. Secondary radiations in cbct: a simulation study. *Journal of Electronic Imaging*, 21(2), April 2012.

[2] L. Grevillot, D. Bertrand, F. Fessy, N. Freud, and D. Sarrut. Gate as a geant4-based monte carlo platform for the evaluation of proton pencil beam scanning treatment plans. *Physics in Medicine and Biology*, 57(13), 06/2012 2012.

2011

[1] S. Jan, D. Benoit, E. Becheva, T. Carlier, F. Cassol, P. Descourt, T. Frisson, L. Grevillot, L. Guigues, L. Maigne, C. Morel, Y. Perrot, N. Rehfeld, D. Sarrut, D. R. Schaart, S. Stute, U. Pietrzyk, D. Visvikis, N. Zahra, and I. Buvat. Gate v6: a major enhancement of the gate simulation platform enabling modelling of ct and radiotherapy. *Phys. Med. Biol.*, 56(4):881–901, 2011.

[2] L. Grevillot, D. Bertrand, F. Dessy, N. Freud, and D. Sarrut. A monte carlo pencil beam scanning model for proton treatment plan simulation using gate/geant4. *Phys. Med. Biol.*, 56:5203–5219, 2011.

[3] L. Grevillot, T. Frisson, N. Zahra, J. Badel, and D. Sarrut. Simulation of a 6 mv elekta precise linac photon beam with gate : a feasibility study. *Phys Med Biol*, 56(4), 2011.

2010

[1] F. Le Foulher, M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, S. Karkar, J.M. Létang, L. Lestand, R. Plescak, C. Ray, D. Schardt, E. Testa, and M. Testa. Monte carlo simulations of prompt-gamma emission during carbon ion irradiation. *IEEE Trans. Nucl. Sci.*, 57(5):2768 – 2772, October 2010.

[2] L. Grevillot, T. Frisson, N. Zahra, D. Bertrand, F. Stichelbaut, N. Freud, and D. Sarrut. Optimization of geant4 settings for proton pencil beam scanning simulations using gate. *Nucl. Instr. Meth. Phys. Res. B*, 268:3295–3305, 2010.

[3] S. Camarasu-Pop, T. Glatard, J. T. Moscicki, H. Benoit-Cattin, and D. Sarrut. Dynamic partitioning of gate monte-carlo simulations on egee. *Journal of Grid Computing*, 8(2):241–259, March 2010.

2009

[1] F. Smekens, N. Freud, J.M. Létang, J.F. Adam, C. Ferrero, H. Elleaume, A. Bravin, F. Estève, and D. Babot. Simulation of dose deposition in stereotactic synchrotron radiation therapy: a fast approach combining monte carlo and deterministic algorithms. *Physics in Medicine and Biology*, 54:4671–4685, 2009.

[2] T. Frisson, N. Zahra, P. Lautesse, and D. Sarrut. Monte-carlo based prediction of radiochromic film response for hadrontherapy dosimetry. *Nuclear Instruments and Methods in Physics Research Section A*, 2009.

2008

[1] D. Sarrut and L. Guigues. Region-oriented ct image representation for reducing computing time of monte carlo simulations. *Medical Physics*, 35(4), 2008.

[2] A. Peterzol, J.M. Létang, and D. Babot. A beam stop based correction procedure for high spatial frequency scatter in industrial cone-beam x-ray ct. *Nuclear Instruments and Methods in Physics Research B*, 266, 2008.

[3] N. Freud, J.M. Létang, C. Mary, C. Boudou, C. Ferrero, H. Elleaume, A. Bravin, F. Estève, and D. Babot. A hybrid approach for fast simulation of dose deposition in stereotactic synchrotron radiotherapy. *IEEE Transactions on Nuclear Science*, 55(3), 2008.

7.2 International conferences with reviewing committee

2012

[1] F. Roellinghoff, A. Benilov, D. Dauvergne, G. Dedes, N. Freud, J. Krimmer, J.M. Létang, M. Pinto, D. Prieels, C. Ray, M. H. Richard, J. Smeets, F. Stichelbaut, and E. Testa. proton beam range monitoring by prompt gamma detection: Experimental results for two types of camera. In *51st annual meeting of the Particle Therapy Co-Operative Group*, 2012.

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2011

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2007

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[3] N. Freud, J.M. Létang, C. Mary, C. Boudou, C. Ferrero, H. Elleaume, A. Bravin, F. Estève, and D. Babot. Fast dose calculation for stereotactic synchrotron radiotherapy. Lyon, France, august 2007. the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society.

7.3 PhD / HdR

2011

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[2] M. Vidal. *Evolution des modèles de calcul pour le logiciel de planification de la dose en Protonthérapie.* PhD thesis, INSA Lyon, ED EEA, September 2011.

[3] F. Smekens. *Planification inverse de la dose en hadronthérapie : prise en compte de la qualité du rayonnement pour une optimisation de la dose biologique.* PhD thesis, INSA Lyon, ED EEA, December 2011.

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2010

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2009

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[2] G. Bouilhol. *L'expérience des traitements modernes du cancer du poumon en radiothérapie peut-elle être appliquée à l'hadronthérapie ?* PhD thesis, CREATIS/INSA Lyon, October 2009.

2008

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[2] J.M. Létang. *Contribution à l'imagerie et à la dosimétrie des rayonnements ionisants : traitement du signal et simulation en physique de transport de particules*. HDR, UCBL / INSA Lyon, November 2008. Mémoire pour l'obtention de l'habilitation à diriger des recherches, no d'ordrer : 2008 009.

7.4 Posters

2011

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2009

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[3] C. Le Loirec, N. Freud, J.M. Létang, and D. Babot. Investigation of a fast hybrid simulation approach for dose calculations in hadrontherapy. In *Workshop on Hadron Beam Therapy of Cancer, Erice, Sicily, Italy, April 24 – May 1*, 2009.

2008

[1] J.M. Létang, N. Freud, F. Smekens, C. Boudou, C. Ferrero, H. Elleaume, A. Bravin, F. Estève, and D. Babot. Fast simulation of dose deposition in stereotactic synchrotron radiotherapy (ssrt). In *New prospects for brain tumour radiotherapy: Synchrotron light and Microbeam radiation Therapy, SYRAD*, june 2008.

7.5 ETOILE internal notes

2011

[1] I. Buvat and G. Battistoni. Envision wp6 report n°1. Technical report, 2011.

7.6 Workshops without proceedings

2011

[1] F. Baldacci, F. Delaire, N. Freud, and J.M. Létang. Accelerated dose calculations using the track length estimator. In *OpenGATE Technical Meeting*, November 2011.

7.7 Book chapters

2011

[1] S. Camarasu-Pop, T. Glatard, H. Benoit-Cattin, and D. Sarrut. *Enabling Grids for GATE Monte-Carlo Radiation Therapy Simulations with the GATE-Lab*, chapter 3. IntechOpen, 2011.

Chapter 8

Moving organs

8.1 International journals with reviewing committee

2013

[1] R. Lynch, G. Pitson, D. Ball, L. Claude, and D. Sarrut. Computed tomographic atlas for the new international lymph node map for lung cancer: A radiation oncologist perspective. *Practical Radiation Oncology*, 3, 2013.

2012

[1] J. Vandemeulebroucke, O. Bernard, S. Rit, J. Kybic, P. Clarysse, and D. Sarrut. Automated segmentation of a motion mask to preserve sliding motion in deformable registration of thoracic ct. *Med Phys*, 39(2):1006–1015, 02/2012 2012.

[2] J. Schaerer, A. Fassi, M. Riboldi, P. Cerveri, G. Baroni, and D. Sarrut. Multi-dimensional respiratory motion tracking from markerless optical surface imaging based on deformable mesh registration. *Physics in Medicine and Biology*, 57(2):357–373, 01/2012 2012.

[3] M. Portela Sotelo, E. Desserée, JM. Moreau, B. Shariat, and M. Beuve. 3d model-based multiple-object video tracking for treatment room supervision. *IEEE Transactions on Biomedical Engineering*, 59(2), 2012. (à paraître).

[4] G. Pitson, R. Lynch, L. Claude, and D. Sarrut. A critique of the iaslc lymph node map: a radiation oncology perspective. *Journal of Thoracic Oncology*, 7(3):478–480, 03/2012 2012.

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2011

[1] J. Vandemeulebroucke, S. Rit, J. Kybic, P. Clarysse, and D. Sarrut. Spatio-temporal motion estimation for respiratory-correlated imaging of the lungs. *Medical Physics*, 38(1), 2011.

[2] M. Portela Sotelo, E. Desserée, and JM. Moreau. Multiple object video tracking for the radiotherapy treatment room supervision : focussing on the model. Springer, June 2011.

[3] K. Murphy, B. van Ginneken, et al., J. Vandemeulebroucke, S. Rit, D. Sarrut, and JPW Pluim. Evaluation of registration methods on thoracic ct: The empire10 challenge. *IEEE Trans Med Imaging*, 30(11):1901–20, 2011.

2010

[1] D. Sarrut and J. Vandemeulebroucke. Fast and low memory b-splines image interpolation. *Computer Methods and Programs in Biomedicine*, 99(2):172–178, 2010.

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[1] J. Vandemeulebroucke, J. Kybic, P. Clarysse, and D. Sarrut. Respiratory motion estimation from cone-beam projections using a prior model. In *Medical Image Computing and Computer-Assisted Intervention (MICCAI'09)*, Springer LNCS, September 2009.

[2] S. Rit, D. Sarrut, and L. Desbat. Comparison of analytic and algebraic methods for motion-compensated cone-beam ct reconstruction of the thorax. *IEEE Transactions on Medical Imaging*, 28(10):1513–1526, October 2009.

2008

[1] Z. Wu, E. Rietzel, V. Boldea, D. Sarrut, and G. Sharp. Evaluation of deformable registration of patient lung 4dct with sub-anatomical region segmentations. *Medical Physics*, 35(2), 2008.

[2] V. Boldea, G. Sharp, S. Jiang, and D. Sarrut. 4d-ct lung motion estimation with deformable registration: quantification of motion nonlinearity and hysteresis. *Medical Physics*, 35(3), 2008.

2007

[1] D. Sarrut, B. Delhay, PF. Villard, V. Boldea, M. Beuve, and P. Clarysse. A comparison framework for breathing motion estimation methods from 4d imaging. *IEEE Transactions on Medical Imaging*, 26(12), 2007.

8.2 National journals with reviewing committee

2011

[1] M. Ayadi, G. Bouilhol, L. Imbert, C. Ginestet, and D. Sarrut. Scan acquisition parameter optimization for the treatment of moving tumors in radiotherapy. *Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique*, 15(2), 2011.

8.3 International conferences with reviewing committee

2013

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[3] H. Ladjal, J. Saadé, M. Beuve, J. Azencot, JM. Moreau, and B. Shariat. 3d biomechanical modeling of the human diaphragm based on ct scan images. In *World Congress on Medical Physics and Biomedical Engineering 2012*, volume 39, pages 2188–2191. www.springerlink.com, May 2013.

2012

[1] D. Sarrut, L. Claude, S. Rit, R. Pinho, G. Pitson, and R. Lynch. Investigating mediastinal lymph node stations segmentation on thoracic ct following experts guidelines. In *MICCAI, Proceedings of the First International Workshop on Image-Guidance and Multimodal Dose Planning in Radiation Therapy*, Nice, France, 2012.

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[3] X. Faure, F. Zara, F. Jaillet, and JM. Moreau. Implicit tensor-mass solver on the gpu. In *ACM/Eurographics Symposium on Computer Animation*. ACM, 2012.

[4] X. Faure, F. Zara, F. Jaillet, and JM. Moreau. An implicit tensor-mass solver on the gpu for soft bodies simulation. In *Eurographics Workshop on Virtual Reality Interaction and Physical Simulation*, pages 1–10, July 2012.

2010

[1] J. Saadé, AL. Didier, PF. Villard, R. Buttin, JM. Moreau, M. Beuve, and B. Shariat. A preliminary study for a biomechanical model of the respiratory system. In *Engineering and Computational Sciences for Medical Imaging in Oncology - VISAPP 2010*, pages 509–515, 2010.

2009

[1] Louise Greses-Besset, J. Vandemeulebroucke, P. Clarysse, and D. Sarrut. Respiratory motion tracking from different viewing angles during lung cancer treatment in radiotherapy. In *IEEE MIC/NSS conference*, October 2009.

[2] AL. Didier, PF. Villard, J. Saadé, JM. Moreau, M. Beuve, and B. Shariat. A chest wall model based on rib kinematics. In *6th International Conference on Biomedical Visualization*, Pompeu Fabra University, Barcelona, Spain, 2009. MediViz09, IEEE.

[3] V. Baudet, M. Beuve, F. Jaillet, B. Shariat, and F. Zara. Integrating tensile parameters in hexahedral mass-spring system for simulation. In *International Conference on Computer Graphics, Visualization and Computer Vision'2009 - WSCG'2009*, February 2009.

2008

[1] J. Vandemeulebroucke, P. Clarysse, J. Kybic, and D. Sarrut. Estimating respiratory motion from cone-beam projections. In Medical Image Computing and Computer-Assisted Intervention MICCAI'2008, The First International Workshop on Pulmonary Image Analysis, 2008. New York.

[2] P. Seroul and D. Sarrut. Vv: a viewer for the evaluation of 4d image registration. *The Insight Journal*, 2008.

2007

[1] S. Rit, D. Sarrut, and S. Miguet. Gated cone-beam CT imaging of the thorax: a reconstruction study. In *SPIE Medical Imaging*, volume 6510, San Diego, California, USA, February 2007.

[2] S. Rit, C. Ginestet, and D. Sarrut. Comparison of gated and dynamic cone-beam ct reconstruction methods. In *International Conference on the Use of Computers in Radiation Therapy (ICCR)*, Toronto, Canada, June 2007.

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8.4 National conferences with reviewing committee

2012

[1] J. Saadé, H. Ladjal, B. Shariat, M. Beuve, and J. Azencot. Modélisation biomécanique du diaphragme humain : du ct-4d au modèle du mouvement. In *RFIA*, 2012.

2011

[1] M. Portela Sotelo, E. Desserée, and JM. Moreau. Suivi 3d multi-objets basé modèle par vidéo pour la surveillance de salles de traitement. In *ORASIS 2011*, June 2011.

[2] X. Faure, F. Jaillet, F. Zara, and JM. Moreau. Acquisition multi-modale en temps réel pour le suivi du mouvement respiratoire. In *ORASIS 2011*, June 2011.

2007

[1] AL. Didier, PF. Villard, M. Beuve, and B. Shariat. Mechanical role of pleura on lung motion during breathing. In *XXXIIème Congrès Annuel de la SOCIÉTÉ DE BIOMÉCANIQUE*, August 2007.

8.5 Conferences without classification

2012

[1] L. Causa, C. M. Held, F. Jaillet, R. Chamorro, M. Garrido, C. Algarín, and P. Peirano. Automated detection of sleep breathing patterns in children. In *International Paediatric Sleep Association Congress 2012*, December 2012.

8.6 PhD / HdR

2011

[1] M. Portela Sotelo. *Videosurveillance d'une salle de traitement en radiothérapie.* PhD thesis, Univ. de Lyon, UCBL/LIRIS, Lyon, December 2011. PhD.

2009

[1] AL. Didier. *Simulation du Mouvement Pulmonaire pour l'amélioration des traitements par radiothérapie.* PhD thesis, Université Lyon1, march 2009.

2007

[1] M. Beuve. *Modélisation de l'intéraction des ions de haute énergie avec la matière inerte, la matière vivante et la matière en mouvement*. HDR, LIRIS-Lyon1, December 2007. Mémoire pour l'obtention de l'habilitation à diriger des recherches.

8.7 Oral communications

2012

[1] M. Portela Sotelo, P. Dupuis, A. Pereira, E. Desserée, JM. Moreau, C. Ginestet, and H. Kafrouni. Event and scenario recognition in a video surveillance system for radiotherapy treatments. Barcelone, May 2012. ESTRO 31.

Chapter 9

Technological developments

9.1 Posters

2009

[1] T. Peaucelle, T. Dupasquier, R. Fillol, G. Hadinger, G. Bruny, C. Montano, S. Eden, S. Feil, H. Abdoul-Carime, B. Farizon, and M. Bajard. Diam, a biomolecular cluster irradiation system. Particle Accelerator Conference, Vancouver (Canada) and Société Française de Physique Division "Accélérateurs", Roscoff (France), may 2009.

2008

[1] M. Bajard and F. Kircher. Rotative gantry for dose distribution in hadronthrapy. European Particle Accelerator Conference, Genova (Italy), july 2008.

9.2 ETOILE internal notes

2011

[1] M. Bajard. La radioprotection du patient, 2011.

2008

[1] M. Bajard, C. Berriaud, B. Bru, M. Carty, P. Daniel-Thomas, R Ferdinand, JM. Gheller, F. Kircher, JM. Lagniel, C. Pes, J. Rochat, J. Balosso, PY. Chaffard, A. Daël, M. Jacquemet, P. Lavocat, and P. Rebourgeard. Rapport de synthèse de la pré-étude d'une gantry rotative supraconductrice pour hadronthérapie par ions carbone. Technical report, CEA, Centre Etoile, Ganil, IPN Lyon, CHU Grenoble , ETIC, 2008.

2007

[1] M. Bajard and ETOILE. Annexe technique à la convention pour l'étude d'une gantry supraconductrice pour ions carbone. Rapport interne ETOILE, November 2007.

9.3 Workshops without proceedings

2007

[1] M. Bajard and ETOILE. Synchrotrons ffag pour la physique. Workshop FFAG. Grenoble, may 2007.

[2] M. Bajard. Les systèmes rotatifs de distribution de la dose en hadronthérapie. Congrès de la Société Française de Physique. Division des accélérateurs, Roscoff, october 2007.



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