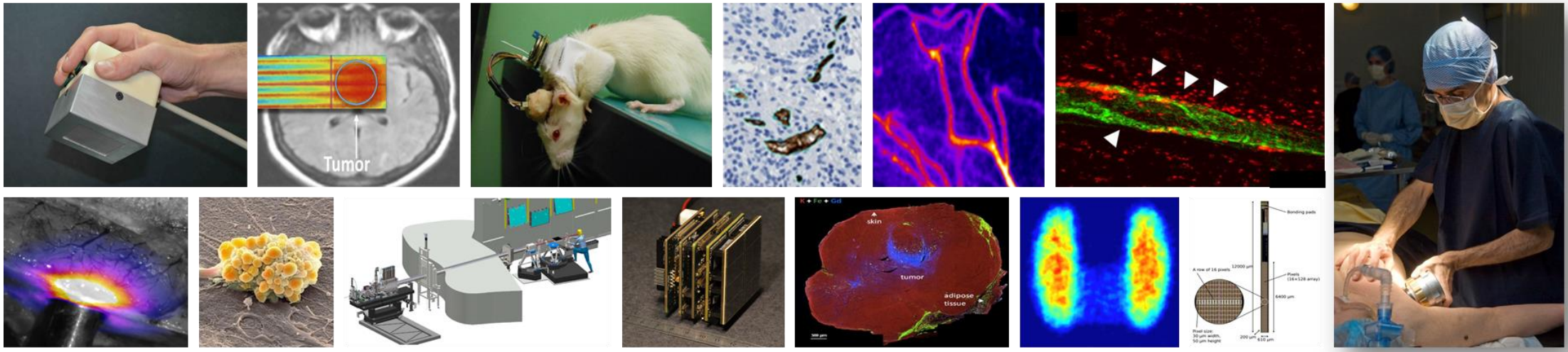
Health pole
IJCLab



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Health physics pole: our global approach

Detector R&D

Accelerator

Optics

Nuclear physics

Particle physics

Theory

Data science

PHYSICS ↔ LIFE SCIENCES

Neurosciences

Biology

oncology

Radiobiology

Medicine

Imaging

Therapy

Scientific challenges : Propose novel instrumental, methodological and theoretical approaches to improve exploration and understanding of living organisms and to strengthen the diagnosis and treatment of diseases

Research activities around 3 main themes : Biomedical imaging, Radiotherapy and Modeling

outline

I. Main goals in imaging, radiotherapy and modeling
II. Global view of the pole
III. Some project examples

Biomedical Imaging: main challenges

Towards a precision medicine, we must:

promote an early diagnosis

deliver targeted, customized, and reactive therapy: planification, interventional techniques, therapeutic follow up

accelerate the development of novel diagnostic or therapeutic molecules (theranostic agents)

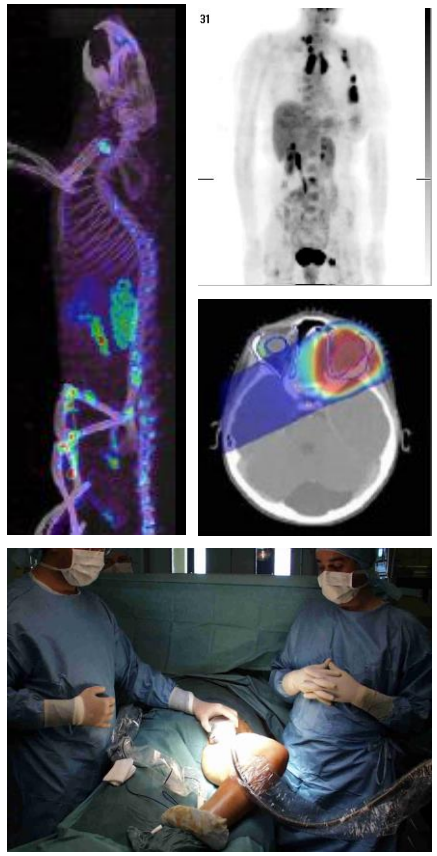
➥ develop multi-parametric quantitative molecular imaging

propose a dynamic multi-modal imaging with high resolution and high sensitivity

extend the spectrum of applications (cardio, neuro, pediatrics, neonatal, prenatal, ...)

increase accessibility to patients (miniaturization, portability, cost reduction, ...)

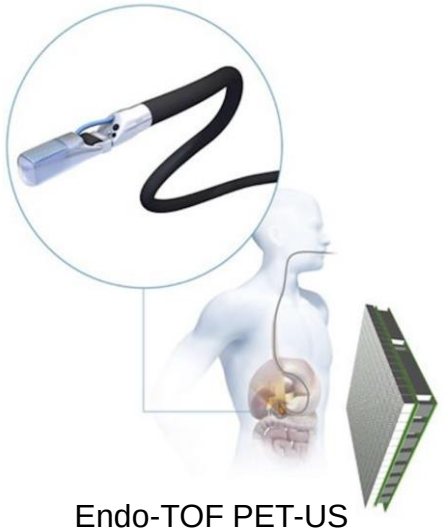
Reduce the dose associated with molecular imaging protocols



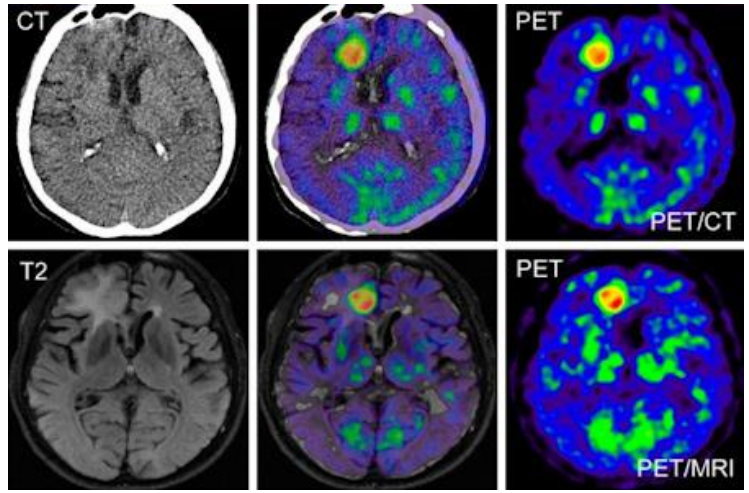
Biomedical imaging: technological challenges

- Introduce new technological approaches to increase the sensitivity of molecular imaging techniques by at least one order of magnitude: time-of-flight PET with high temporal resolution, whole-body PET, 3-gamma imaging, etc.
- Strengthen the coupling of imaging techniques by developing highly integrated or hybrid multimodal systems coupled with advanced signal processing and image analysis protocols (PET/CT/MRI/US...)
- Develop dedicated imaging systems strongly linked to the clinical purpose (organ, application)

TEP-mammo
(Onconvision)



Endo-TOF PET-US



Imagerie multi-modale (PET-CT et PET-IRM)

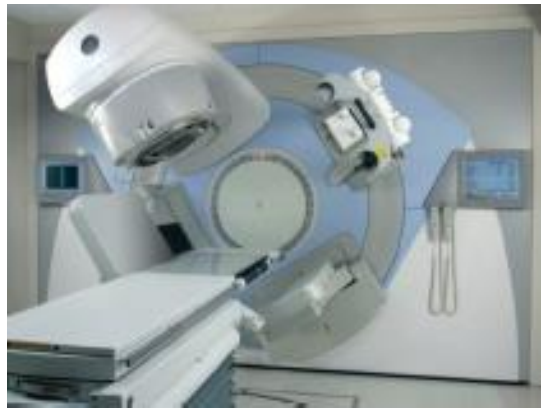
Radiotherapy: main challenges

Conventional Radiotherapy

Particles: X-rays 6-25 MV (every tumors), electrons 3-18 MeV (surface tumors)

Machines: clinical electron accelerators with multileaf collimator and embedded imaging systems

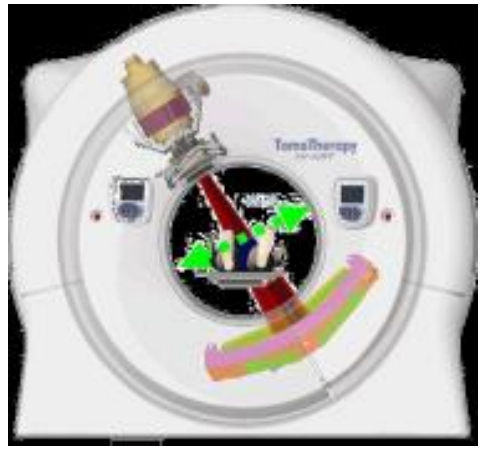
- Time fractionation: 2 Gy/session, 5 session/week
- Dose: 40-70 Gy
- Dose rate: 30-70 mGy/s
- Field sizes: 2 - 40 cm^2



Limits:

The toxicity to healthy tissue limits the dose

In particular for very radioresistant, bulky and diffuse cancers (glioblastomas), or non-localized tumors (multiple metastasis)



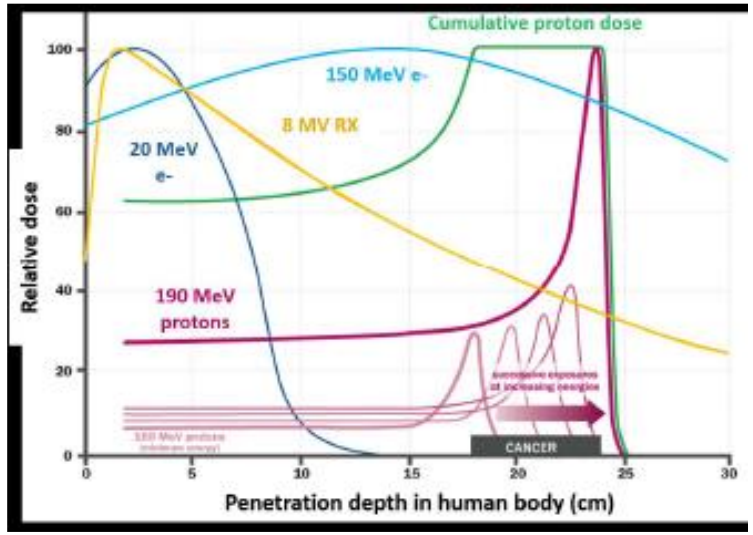
→ Objectives: large doses in tumor, low doses in healthy tissues

Radiotherapy: main challenges

How to improve the treatment?

Induce a more efficient tumoral irradiation
- Particle: hadrontherapy (p, α, ^{12}C, ions)
- Targeted radiotherapy: BNCT, nanoparticles, radionuclides…

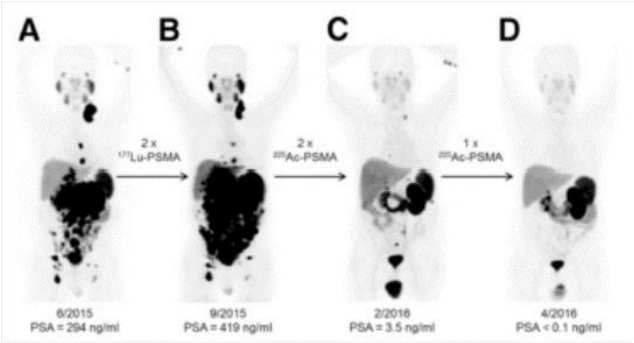
Preserve the healthy tissues
- Particle/energy: hadrontherapy, very high-energy electrons (VHEE)
- Dose delivery mode: spatial fractionation of dose (beam size < mm), “FLASH” irradiation (very high dose rate)



→ Play on physical parameters to induce a different biological effect

Main challenges

Create new modalities of dose delivery in external or internal radiotherapy (various type of rays, spatial and temporal fractionation of the dose, development of radiosensitive enhancers)
Perform radiobiological characterization of the new sources of irradiation



Develop methods to optimize dose delivery, for improved treatment planning and on-line control
- Dedicated instrumental developments (diversity of accelerators or radiation sources)
- models and simulations to meet clinical requirements in terms of accuracy and speed of execution.

Modeling of biological systems

➪ Revolutions in biotechnology and information technology have produced enormous amounts of data, at different scales (from molecules to cell populations to organs) and in interaction with its environnement and other systems.

But : it is difficult to analyze, interpret and connect these data.

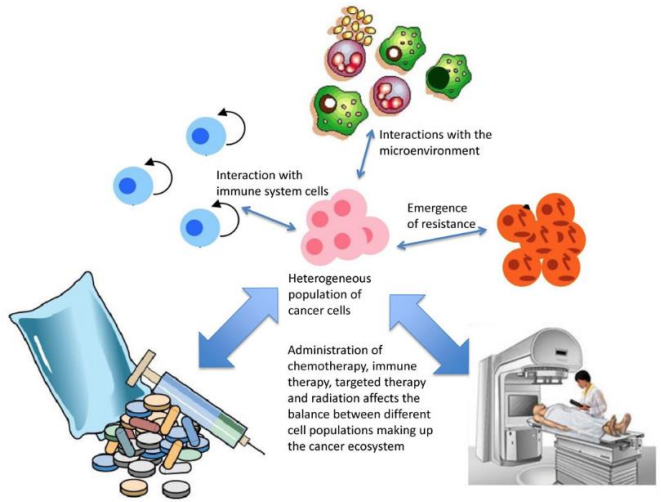
➪ Modeling can help to:

- interpret the data
- connect data from different scales.
- generate hypotheses and suggests experiments.
- predict the evolution of the tumor, with and without treatment
- identify optimum treatment strategies

A tumor = a complex system: different protagonists at each scale

Example of the cellular level:

- heterogeneous cell population of a tumor,
- interaction with the microenvironment and immune system
- responses to different kinds of treatments.



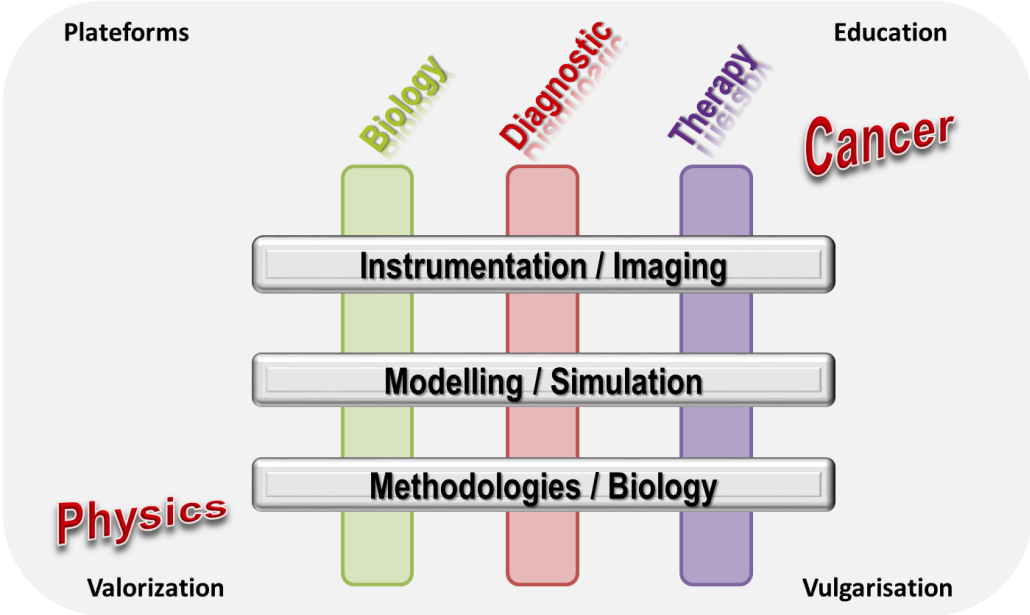
Outline

II. Global view of the pole

Health pole: scientific perimeter

Our project is mainly focused on oncology needs with a specific domain dedicated to brain tumors

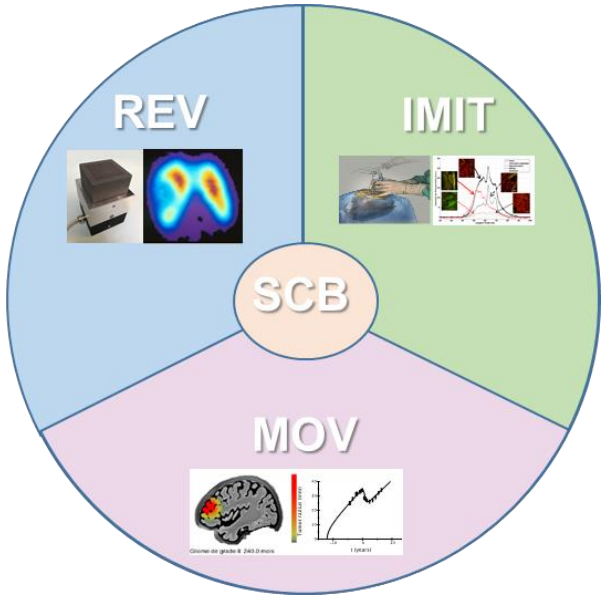
Perimeter centered on physics and cancer interfaces



Organization: 3 teams supported by a biological department

16 research scientists
10 PhD and post-doc students

Health pole components



3 scientific teams + a technical department

➜ *REV: Radiation et Vivant (radiation and living)*
➜ *IMIT: Instrumentation multimodale et Imagerie Tissulaire (multimodal instrumentation and tissue imaging)*
➜ *MOV: Modélisation du Vivant (Modeling the living)*
➜ *SCB : Service commun de Biologie (experimental biology department)*

Expertise skills

➜ *Instrumentation (isotopic, biophotonic)*
➜ *Nuclear physics (isotope production)*
➜ *Simulation (Geant 4, GATE)*
➜ *theoretical physics (statistical physics)*
➜ *biology (animal experimentation, histology, cell bio.)*

2 targeted areas

➜ *Clinical: Oncology (brain, peripheral organs)*
➜ *Biology: Cell interaction and morphology, Radiobiology and Neurosciences*

REV team: Radiation et Vivant

CO Bacri (DR CNRS), Y. Charon (Pr UP), M-A Duval (MCF U Evry), C. Guardiola (PD CNRS), L. Ménard (MCF UP), O. Seksek (CR CNRS), M-A Verdier (MCF UP)

Aims : Development of new instrumental and methodological approaches dedicated to external and internal radiotherapy and to the study of radiation effects on living from the cell to the tissue scale

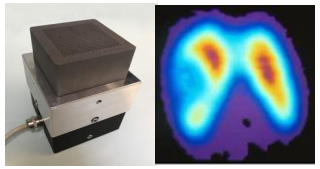
THEMES

- ✓ Strengthen the control of the dose deposited in internal and external radiotherapy by developing new instrumental and methodological approaches
- ✓ Strengthen the effectiveness of treatment methods in molecular radiotherapy (internal vectorized) through the production of new radionuclides and the implementation of more precise individualized dosimetry protocols
- ✓ To better understand the effects of radiation on living organisms from the cellular to the tissue level by developing new experimental and methodological approaches

TECHNICAL SKILLS

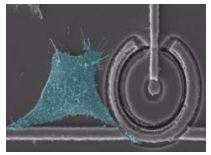
- ✓ Nuclear instrumentation /detector, dosimetry, microtechnology
- ✓ Monte Carlo simulation (for the conception and validation)
- ✓ Nuclear physics, isotopic separation (electromagnétic)
- ✓ Molecular imaging
- ✓ Cell biology, biochemistry, animal trials, optical imaging (videomicroscopy, epifluorescence),

HIGHLIGHTS



THIDOS: first gamma camera prototype dedicated to vectorized therapy (follow-up of thyrroid treatment)

Isotope production and Separation for medical use (PRISM)



IBTOOLS: Dosimeter at cell scale based on Si cylindrical 3D structures.

COLLABORATIONS (main)

- Hôpital Toulouse, IRSN
- ARRONAX, ILL
- Institut Curie
- CMB Barcelone

PUBLICATION

IEEE TNS, PMB, NIM A, Med Phys,

RAYONNEMENT

- Resp. axe Santé Labex P2IO 'Physique des deux infinis et ses origines'
- Resp. axe Imagerie GDR 'Modélisation et Instrumentation pour l'Imagerie Biomédicale

IMIT team: Instrumentation Multimodale et Imagerie Tissulaire

D. Abi Haidar (MCF UP), P. Laniece (DR CNRS), C. Rimbault (CR, CNRS)

Aims : Development of optical and radioisotipic probes for the characterization of brain tissue in physiological and pathological conditions

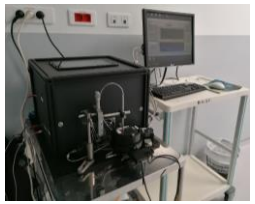
THEMES

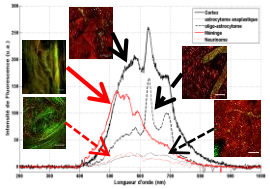
- ✓ Miniaturized instrumental developments dedicated to surgical assistance and analysis of brain mechanisms.
- ✓ Multimodal tissue imaging in neuroscience and oncology
- ✓ Preclinic Imaging for the study on awake and freely moving animal (behavioral neuroimaging)

TECHNICAL SKILLS

- ✓ Optical and nuclear instrumentation
- ✓ non linear optics, endomicroscopy, imaging of the fluorescence life time, spectroscopy
- ✓ Molecular imaging
- ✓ analysis of tissue data
- ✓ pharmacokinetics

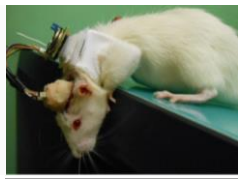
HIGHLIGHTS





IMOP: multimodal fibered endomicroscope and clinic analys of brain tumors

MAPSSIC: brain radioisotopic wireless probe dedicated to behavioral neuroimaging performed on awake small animal



COLLABORATIONS (main)

- Hôpitaux Sainte-Anne et Tenon
- University of Florida
- CPPM Marseille, IPHC Strasbourg
- CRNL Lyon et NeuroPSI Saclay
- CERMEP Lyon

PUBLICATION

Scientific reports, IEEE TNS, Optic letters, …

RAYONNEMENT

- GDR Physique de la cellule aux tissus
- GDR MI2B

MOV team: Modélisation du Vivant

M. Badoual (Pr UP), C. Deroulers (MCF UP), B. Grammaticos (DRem CNRS), R. Mastrippolito (MCF UPSaclay), A. Ramani (DRem CNRS)

Aims : To develop non-linear physics models based on clinical and biological data and to adapt them for the prediction and treatment of brain tumors

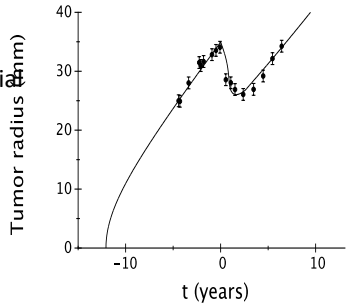
THEMES

- ✓ Clinical modelling: Modelling of tumors growth on low grade gliomas based on biopsies and clinical imaging, modelling of treatment effects
- ✓ Biological modelling: Modelling of cell migration and proliferation; modelling of colonies of bacteria
- ✓ Correlation between the cellular scale (biology) and tissue scale (medicine and imaging).

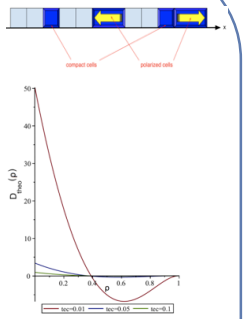
TECHNICAL SKILLS

- ✓ Biophysics Modelling and mathématics
- ✓ numerical Simulations (cell automates, numerical solving of equations)
- ✓ Analytical calculation
- ✓ Data Analysis (biological and clinical data)
- ✓ Big data Analysis of large files issued from the numerization of histological slides

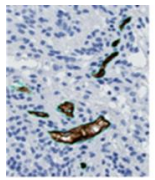
Modelling of the RT effect on low grade gliomas, based on partial differential equations with an automatic adjustment method delivered to adjust the data to clinical data.



discrete model of cell migration where a cell is compact (non-polarized) or extended (polarized); the passage to the hydrodynamic limit has highlighted areas of parameters where the diffusion coefficient is negative, indicating the formation of aggregates.



Imaging Analysis: software development for the segmentation and measurement of large images (tissue, blood vessels, cells,…) -> Application: the correlation between the density of blood vessels and MRI signal (with a specific sequence) was used to propose a new diagnostic process at Necker Hospital (Paris).



COLLABORATIONS (main)

- Hôpitaux Sainte-Anne, Lariboisière, Necker, Saint-Louis
- Université de Tokyo (dynamic Systems)

PUBLICATION

Physical Biology, Physical Review E, NeuroOncology
Solitons, Chaos and Fractals (dynamic Systems)

RAYONNEMENT

- GDR Physique de la cellule aux tissus
- GDR STIC Santé

III. Some project examples

applications in internal radiotherapy

- Internal targeted radionuclide therapy accounts for more than 10% of treatments by radiotherapy

- Nuclear medicine is expanding rapidly from diagnosis + therapy to the theranostic

→ stimulates the development of physical approaches to strengthen the use of targeted therapy (amount of suitable molecules and follow up of the treatment)

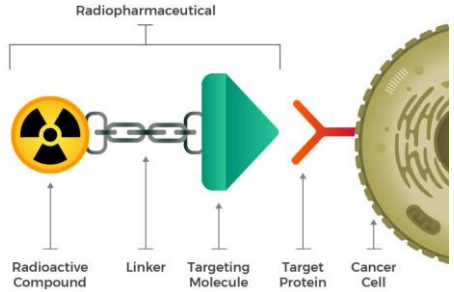
Many radioisotopes of medical interest (imaging and internal vectorized therapy) cannot be used because we do not know how to produce them with sufficient purity (chemical and isotopical) and in large quantities

→ need to develop new way of production to increase the choice radioisotopes for personalized medicine.

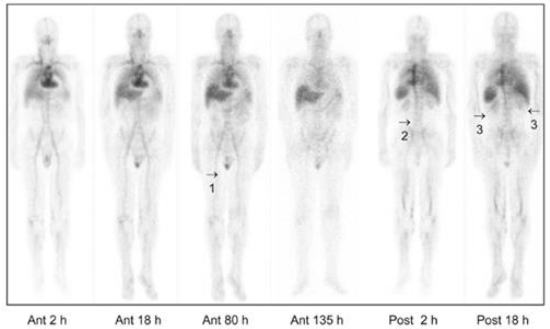
Patient-specific dosimetry of tumors and organs-at-risk (liver, kidney, ...) is image-based and relies on the quantification of radiopharmaceutical uptake as a function of time

Performances and availability of conventional gamma cameras are not suited for accurate quantification of the absorbed doses

→ need of Individualised patient dosimetry to optimize the follow up of the therapy



new radio-pharmaceuticals (peptides, antibodies, etc.) combined with new alpha emitting radio-isotopes (149Tb, 211At, 225Ac, 213Bi …) or beta (177Lu, 67Cu, 47Sc, 212Pb, …).



Ambulatory imaging for dose control in internal radiotherapy (THIDOS)

CONTEXT

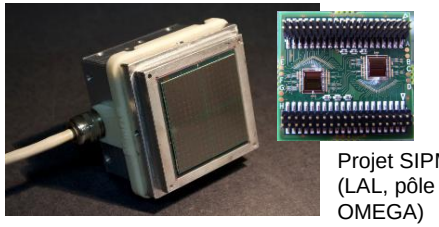
- Internal vectorized radiotherapy in full expansion (new more specific vectors and innovative alpha or beta emitting radionuclides)
- Accurate and personalized dosimetry essential to optimize the treatment (increase the dose in the tumor while preserving the organs at risk)

OBJECTIVES

- Develop a mobile gamma imaging system specifically dedicated to the measurement of the biodistribution and kinetics of the radiotracer at the bedside
- Evaluate the interest of the portable gamma camera for different radionucleide therapy protocols (thyroid/131I, bone metastases/223Ra)

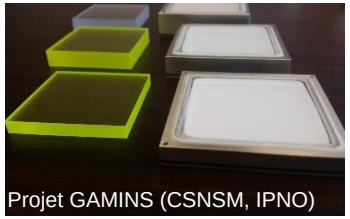
MATERIAL & METHODS

Optimization of the scintillator/photodetector interface



Projet SIPMED (LAL, pôle OMEGA)

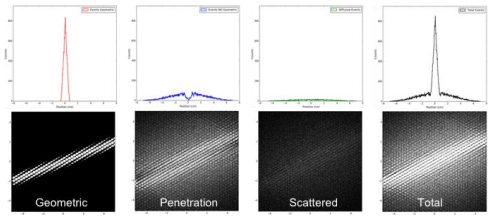
SiPMs array and miniaturized electronic readout board

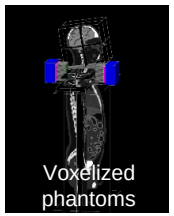


inorganic Scintillators (GaGG, CeBr3, LaBr(Ce), LYSO, LFS)

Optimization of the high-energy collimator design by Monte Carlo simulation (Gate)

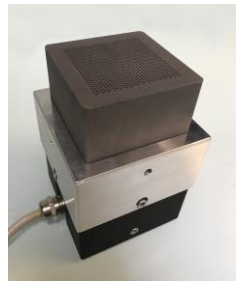
Transmission images of a source line (131I) according to the nature of the detected events



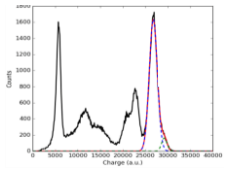


RESULTATS

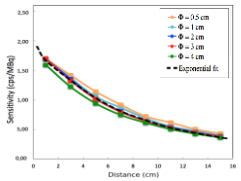
- First prototype of the ambulatory camera (5x5 cm2)
- **First evaluation of the quantification ability in a realistic clinical situation (IRSN, Hôpital Béclère)**



$CeBr_3$ + tungsten Collimator (3D print)



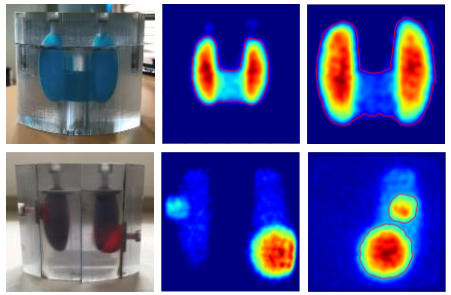
sub-millimetric Spatial resolution and distorsion
Energy resolution < 8% @356 keV



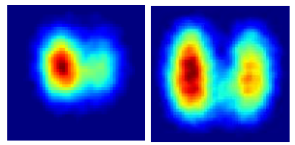
Camera calibration
Sensitivity ~1.1 cps/MBq @ 5 cm

Thyrroïd phantoms

MoTi camera
Lateral and anterior views



Activity Recovery Coefficient > 96 % in thyrroïd and nodules



Siemens Symbia T2
(SR of 13.4 mm @ 10 cm)

Support financier

Plan Cancer (AAP Physicancer, INSERM, 296 k€, 2019-2022) et AP-IN2P3

PRISM - Isotope Production and Separation for the Medical applications

CONTEXT

- Many radioisotopes of medical interest (imaging and internal vectorized therapy) cannot be used because we do not know how to produce them with **sufficient purity** (chemical and isotopical) and in **large quantities**.
- Needs for a better personalization of treatments

→ **theranostic approach**:
1 element, several isotopes
⇩
same biodistribution
and
same pharmacokinetic properties

^{155}Tb:
SPECT imaging, Auger therapy

^{152}Tb: TEP imaging

^{161}Tb: β^- therapy

^{149}Tb: α therapy

OBJECTIVES
(emerging project)

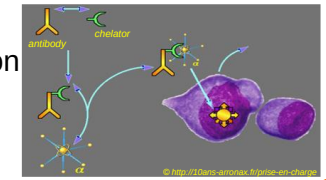
Proof of concept

R&D to determine the accurate production parameters - Proof of feasibility

$$^{nat}Gd \xrightarrow{\text{Sidonie}} {}^{155}Gd \xrightarrow{\text{ARRONAX}} (p,n)^{155}\boldsymbol{Tb}$$

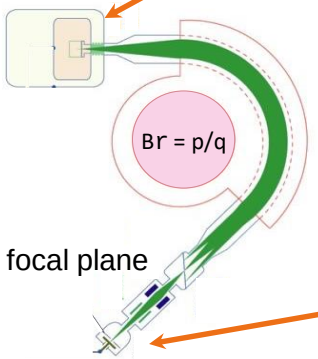
- ^{155}Gd target production: parameters optimization (source, transmission, purity, currents, ...)
- find the optimal E_p : cross section measurement at different incident energies

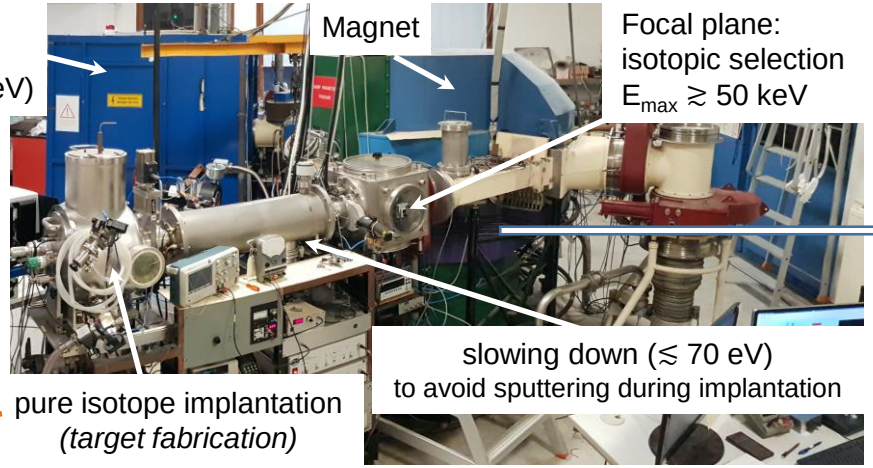
Investigate new chelator for Tb vectorization
synthetize functionalized chelator for a low temperature chelation (to improve stability in vivo)
- physico-chemical studies and bioconjugaison of functionalized chelator



Electromagnetic mass separation with SIDONIE

Bernas-Nier
Ion source
(extraction: 40 keV)





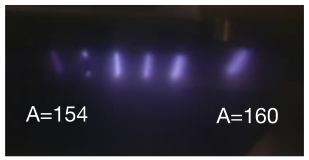
Focal plane:
isotopic selection
$E_{max} \gtrsim 50$ keV

slowing down ($\lesssim 70$ eV)
to avoid sputtering during implantation

pure isotope implantation
(target fabrication)

FIRST RESULTS

Measured isotopic purity at the focal plane of SIDONIE: $9.6 \pm 80\ 10^{-5} < {}^{157}Gd / {}^{158}Gd < 4.7 \pm 0.5\ 10^{-4}$

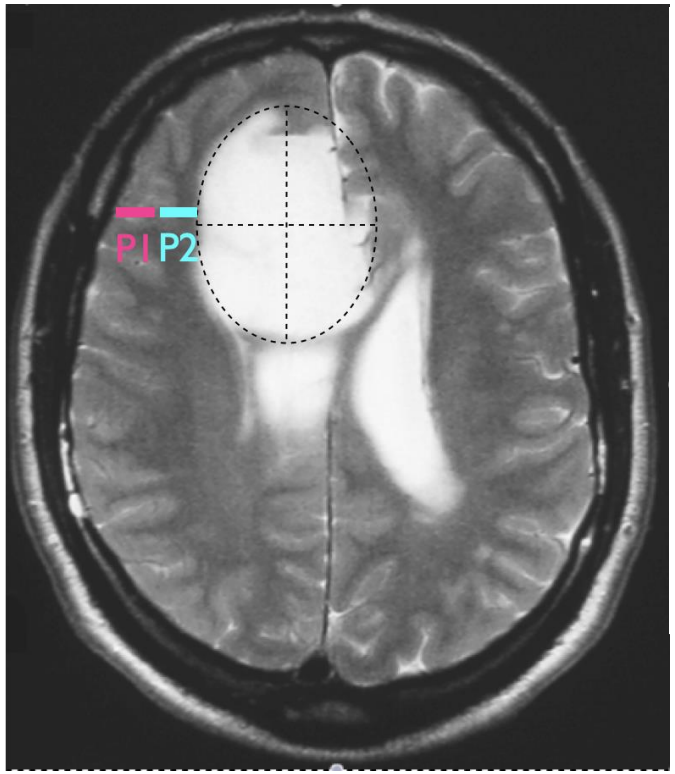


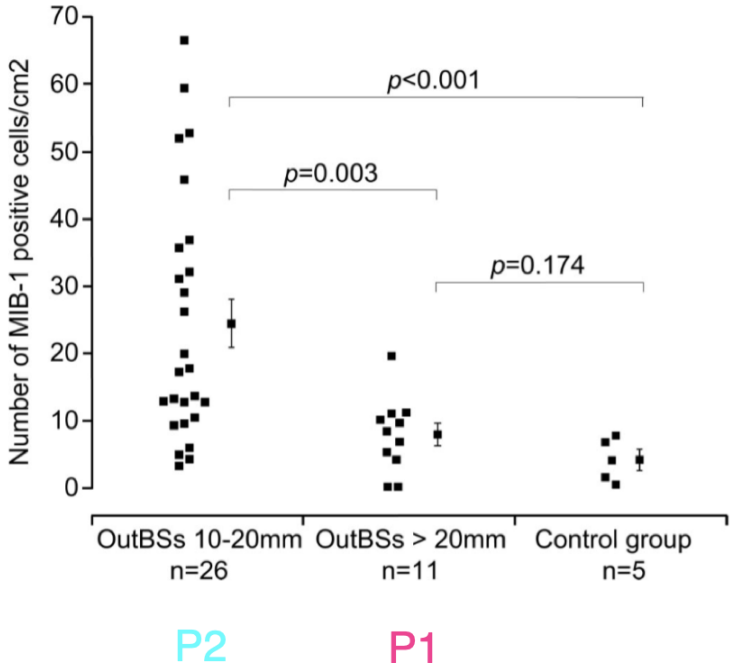
Gd isotopes at the focal plan

Target production
^{155}Gd (3.10^{18} at/cm^2)

Gliomas are rare tumors, but this pathology **cannot be cured.** Why?

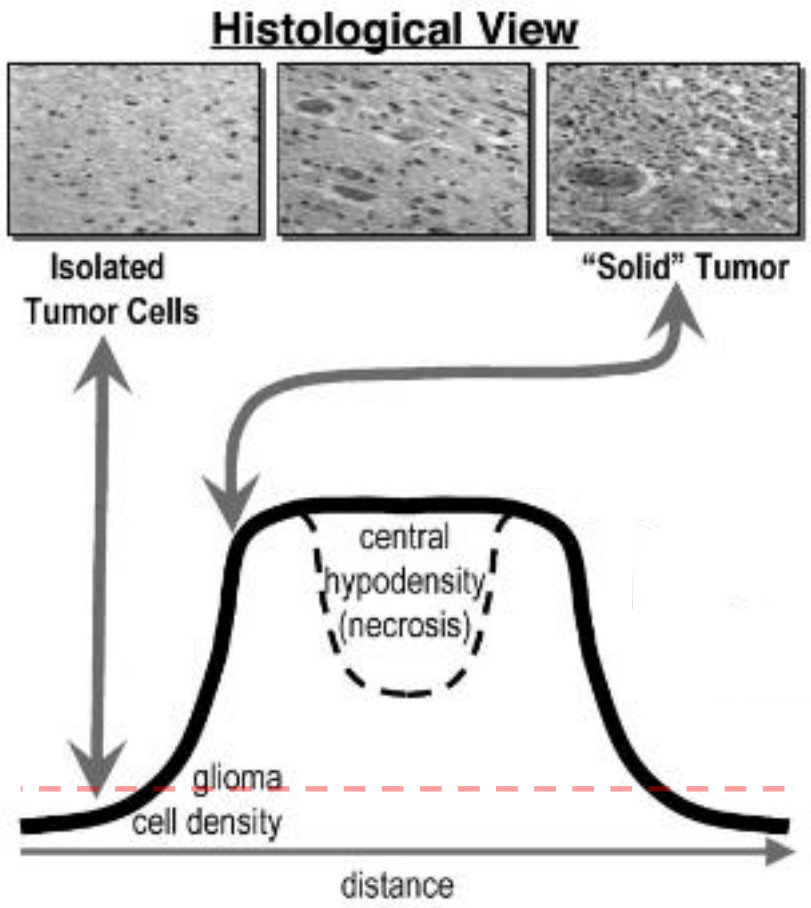
Proliferating tumor cells can be find **beyond** the limits of the MRI signal.





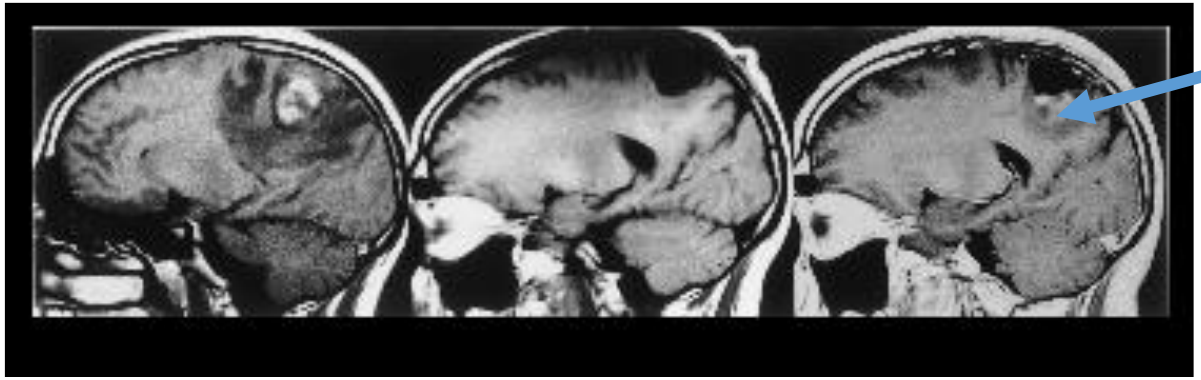
Pallud J, et al (2010) Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities, Neurology, **74**, 1724

Isolated and migrating tumor cells can be found beyond the MRI detection threshold and **are not removed by surgery.**



Harpold HL, Alvord EC Jr, Swanson KR., 2007, The evolution of mathematical modeling of glioma proliferation and invasion, J Neuropathol Exp Neurol. 2007 Jan;66(1):1-9.

Tumor cells migrate and invade surrounding normal tissues.
This migration decreases the efficiency of treatments such as surgery: tumor cells are left behind, leading to recurrence.



Systematic recurrence at the border of the cavity left by surgery, even after treatments (here, six months after surgery)

Giese A et al, (2003) Cost of migration: invasion of malignant gliomas and implications for treatment, *J Clin Oncol*, **8**, 1624-36

The surgery needs to be as extensive as possible:
-Analysis of the resected pieces during surgery
-Analysis of the borders of the cavity, in order to detect invaded tissues

⇨ IMOP: optical analysis of tissue, **during the surgery** (real-time analysis contrry to classical histology)

⇨ Another approach to understand and predict the tumor evolution: modeling

Multimodal optical endomicroscopy for *in vivo* diagnosis of brain tumors: IMOP

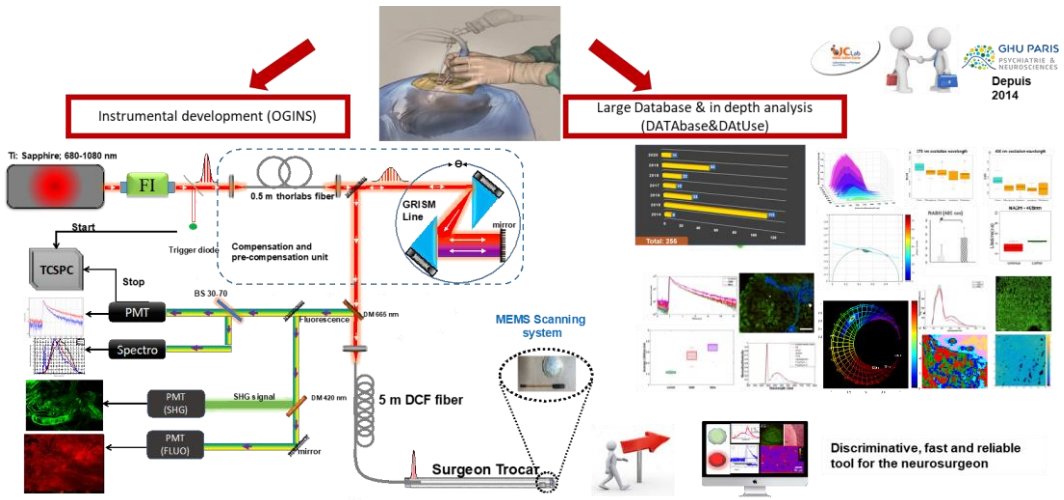
CONTEXT

The major challenge of any neurosurgical oncological intervention is the precise definition of the limits of the excision, which responds to the optimization of the onco-functional balance. The identification of brain tumor infiltration is not possible today under operative conditions and requires the development of a powerful and reliable imaging tool.

OBJECTIVES

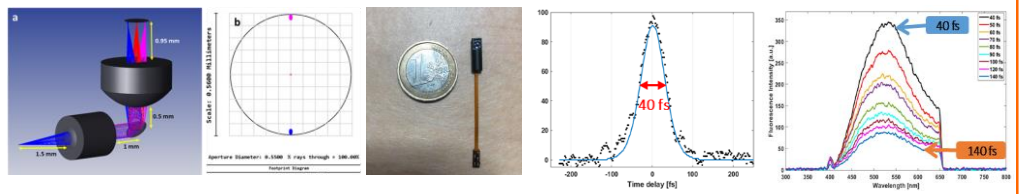
To improve the quality of the surgical procedure using a rapid optical method with sub-cellular resolution by developing a non-linear multimodal endomicroscope to assist in the immediate diagnosis and delineation of the edges of infiltrating tumors in real time during the surgical procedure.

MATERIAL & METHODS

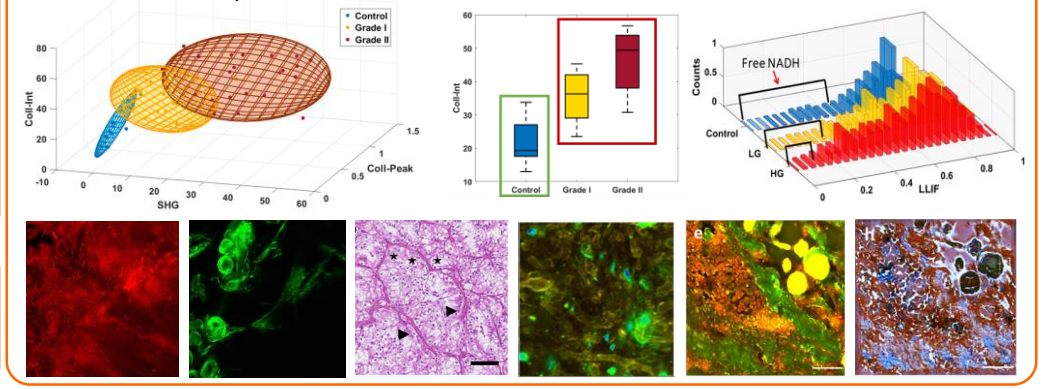


RESULTS

- Development of a miniature imaging probe based on a MEMS scanning system



- A multimodal and multiscale tissue database (from deep ultraviolet to near infrared) to discriminate tissue cancerization.



Financial Support

- AP Plan Cancer (projets MEMBO, MEVO, IMOP): 640 keuros
- Mission pour l'interdisciplinarité "l'instrumentation aux limites"- CNRS: 58 keuros

Modeling the effect of RT on low-grade gliomas (MOV team)

CONTEXT

Gliomas are incurable tumors despite treatment. This aggressiveness is due in particular to the heterogeneity of the tumors and to the migration of cells from the center of the tumor.

⇒ Necessary to develop new approaches such as modeling:

- Testing tumor growth scenarios using simple models, predict the future evolution of tumors, with and without treatment
- Link micro/macro between biology and medicine

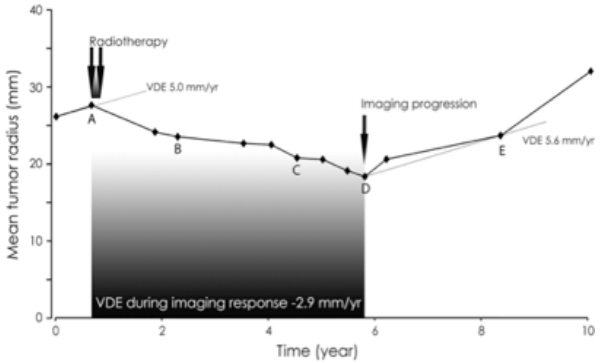
EXAMPLES OF QUESTIONS

- Prediction of patient age at tumor onset using modeling.
- **Modeling of the effect of standard RT on low-grade gliomas and prediction of regrowth time**
- Modeling the effect of pregnancy on the dynamics of low-grade gliomas
- Modeling the origin of gliomas
- Modeling of anaplastic transformation (low-grade / high-grade transition)

OBJECTIVES OF THE LOW-GRADE GLIOMA RT PROJECT

The radius of the tumor decreases during a long time **after** the end of the treatment by RT (see fig):

- How can we explain the delay of regrowth?
- The delay is very different from a patient to another patient: why? Is it possible to predict the duration of the delay at the beginning of RT (knowing only the dynamics of the tumor **before** RT)?



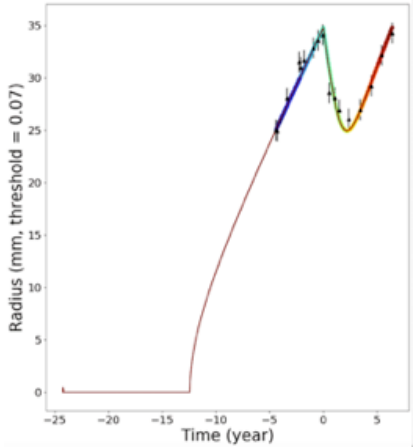
Badoual M, et al (2014) An oedema-based model for diffuse low-grade gliomas: application to clinical cases under radiotherapy, Cell Prolif, 47, 369

MATERIAL & METHODS

- Data collection and analysis (clinical data, biological data)
- Mathematical modeling
- Numerical simulations: partial differential equations, agent-based models…

RESULTS

- A simple model based a on partial differential equation (reaction-diffusion equation), with 4 parameters
- An automatic stochastic method to fit clinical data (CMAES).
- Very good agreement fit/data for the 49 patients
- Predictions ?

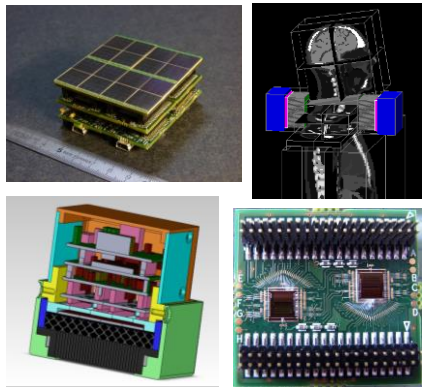


Adenis et al, Modelling radiotherapy for low-grade gliomas: how to choose the best model ? , in preparation

Health pole: global approach of the project

Integrated Approach : from upstream R&D to the biomedical validation

Physical Development



IJClab expertise: nuclear and optical instrumentation, electronics, modeling and simulation
R&D IN2P3 et industrial collaborations

Definition, design and conception of systems or models

Biomedical Validation

Clinical and biological collaboration network

Thanks for your attention