Theoretical physics activity for health at IN2P3

IN2P3 scientific counsel, June 29th 2021

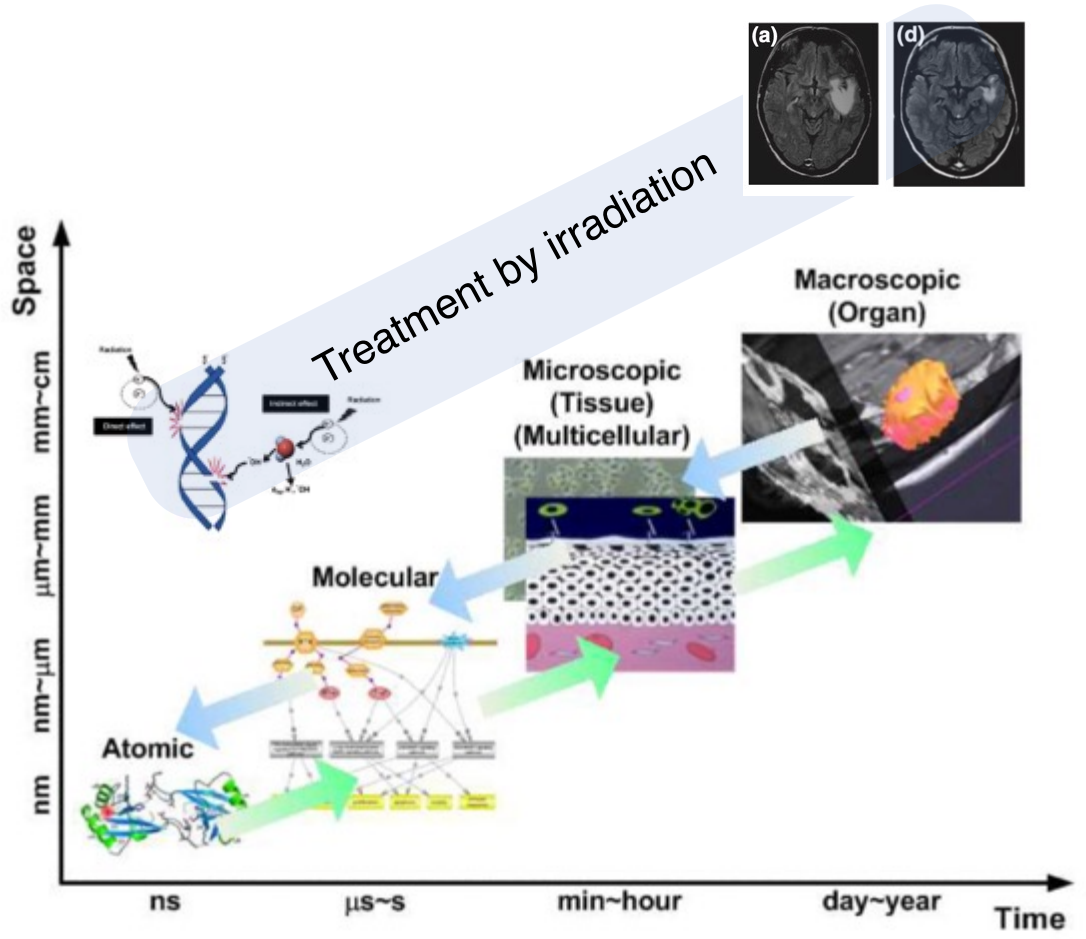
Introduction

A biological system such as a tumor is characterized by different time and space scales: ⇨ Very complex system !

⇨ Revolutions in biotechnology and information technology : 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.

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



Deisboeck TS et al (2011), Multiscale cancer modeling, Annu Rev Biomed Eng, 13, 127-55.

Team Modélisation du Vivant, IJCLab, Orsay

Human ressources

2 assistant professors, 1 professor, 2 emeritus, 1 postdoctoral fellow, and two former PhD student (2017-2020 and 2016-2019)

Links with experimentalists

Data that are used come from literature or are produced by the biologists of the Pôle Santé (IJCLab).

Research themes

- Integrability of discrete dynamical systems (not health-related so not developed here)
- Modeling of clinical and biological data of gliomas
- Statistical physics of out-of-equilibrium complex systems
- Big data approach to brain tissue samples

Publications (last 5 years):

33 publications (all themes)

Collaborations:

National: IJCLab (pôle théorie), Laboratoire TIMC (Grenoble), hôpitaux Sainte-Anne, Necker, Saint-Louis, Institut Gustave Roussy, Institut Curie.
International: Tokyo University, University of Castilla-La Mancha Spain
Responsabilité pôle GDR MI2B
Organisations de conférences, workshops, conférences invitées…

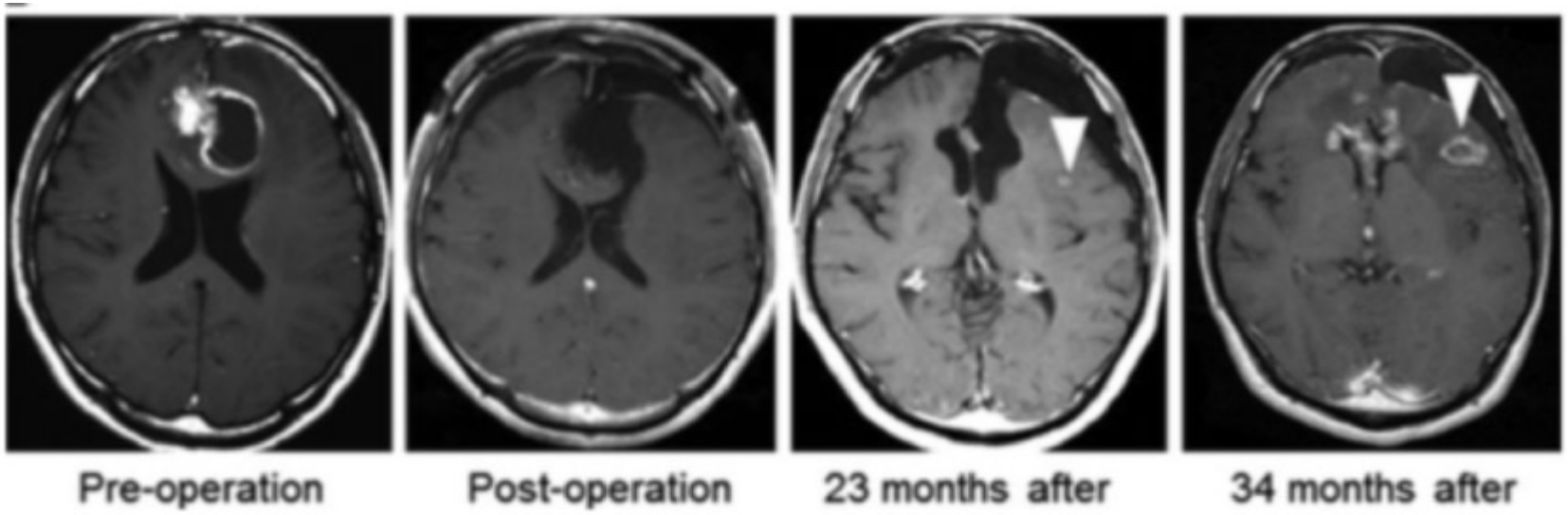
Funding:

Institut Systèmes complexes, Gefluc, MITI CNRS

Team Modélisation du Vivant, IJCLab, Orsay

Gliomas: a unifying problematic for the team

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, even after treatments, at the margin of the operative field

Shibahara, I et al (2015), Neuro Oncol., 17, 136-144.

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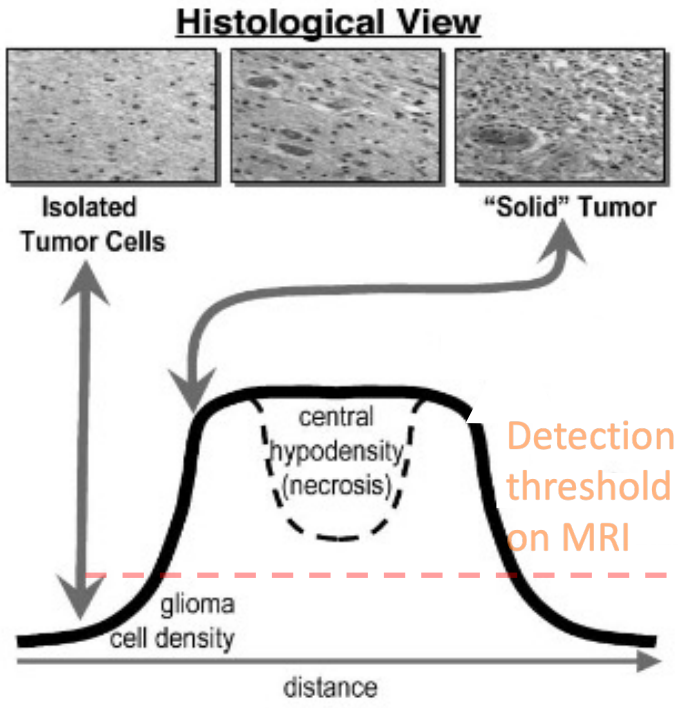
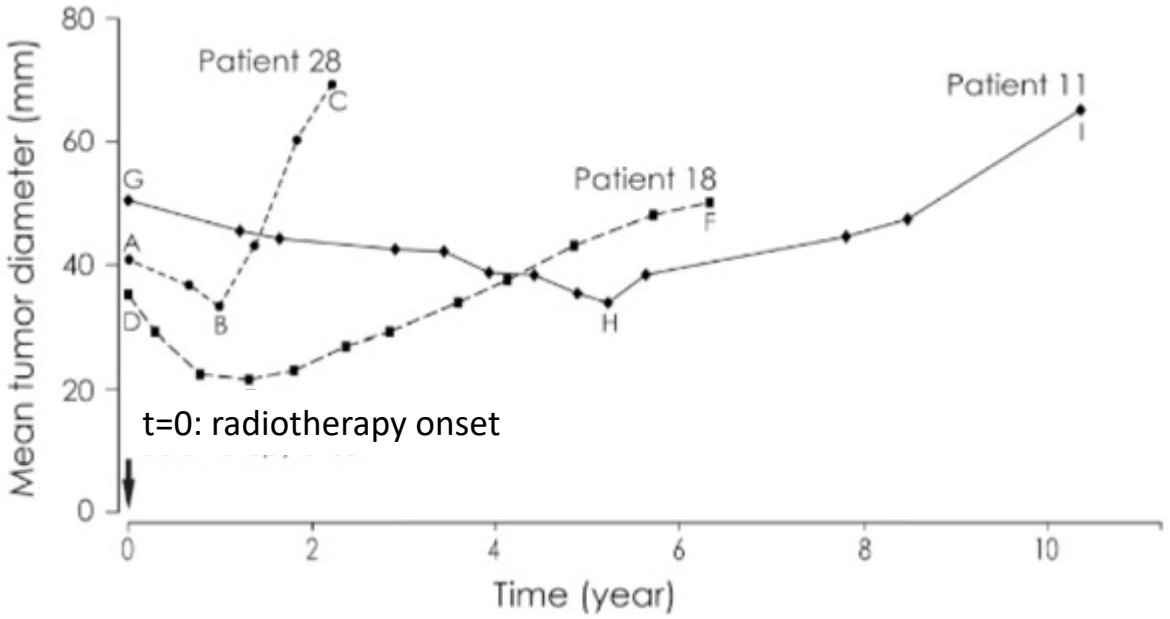


Isolated and migrating tumor cells can be found beyond the MRI detection threshold and are not removed by surgery.

Harpold HL, Alvord EC Jr, Swanson KR., 2007, J Neuropathol Exp Neurol. 2007 Jan;66(1):1-9.

Temporal evolution of tumor diameter after radiotherapy



After treatments such as radiotherapy, the tumor always recurs.

Pallud J, Llitjos JF, Dhermain F, Varlet P, Dezamis E, Devaux B et al (2012) Dynamic imaging response following radiation therapy predicts long-term outcomes for diffuse low-grade gliomas, Neuro Oncol, 14, 496–505

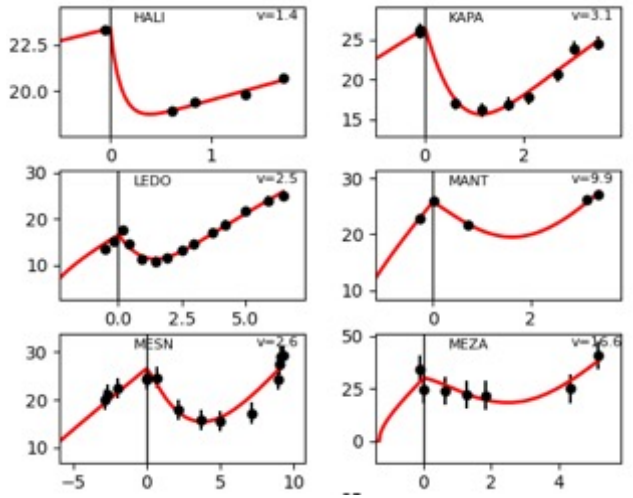
Team Modélisation du Vivant, IJCLab, Orsay: research themes

Modeling of clinical and biological data of gliomas

Development of simple models (with PDE, agent-based models, ...), with a number of parameters limited to a minimum, and comparing them with clinical and/or biological data, in order to

- test tumor growth scenarios
- predict the future evolution of tumors
- study and predict the effect of treatments on tumors, such as radiotherapy (RT),
- establish a link between tumor growth studied at the micro scale (biology) and at the macro scale (medicine).

Highlight 1: Modeling the effect of radiotherapy on low-grade gliomas



$$\frac{\partial \rho(\vec{r},t)}{\partial t} = D\Delta\rho(\vec{r},t) + [\kappa - \kappa_D(t)]\rho(\vec{r},t)(1-\rho(\vec{r},t))$$

with $\kappa_D(t) = \kappa_d e^{-(t-t_r)/\tau}$ for $t > t_r$ and $\kappa_D = 0$ for $t < t_r$

ρ: cell density
κ: proliferation coefficient
κ_D: death coefficient
D: diffusion coefficient

⇨ automatic fitting of the 4 (+1) parameters for 43 patients

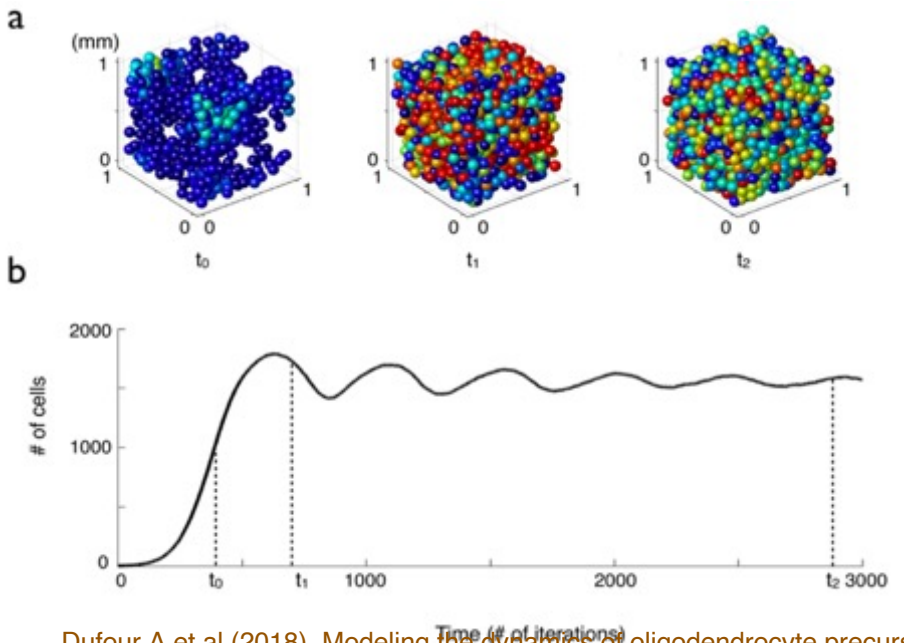
Adenis L et al, Radiotherapy effects for low grade gliomas: confronting theory to clinical data, in preparation

Team Modélisation du Vivant, IJCLab, Orsay: research themes

Modeling of clinical and biological data of gliomas

Highlight 2: An agent-based model to model the onset of gliomas in a population of normal precursor cells

Evolution of the cell density versus time for cells. Cells trigger a countdown when they are in contact with two other cells an die at the end.

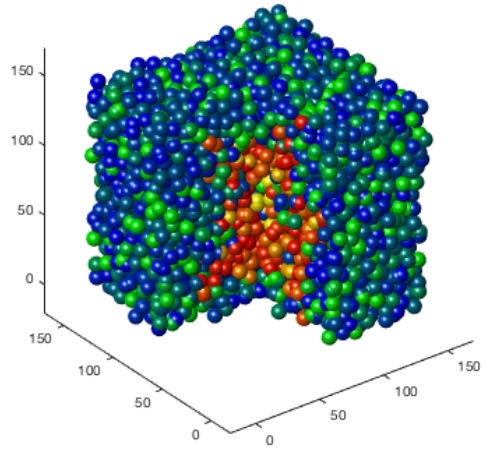


$$w' = \lambda w(1-w) - \tilde{w}\tilde{c}$$

$$c' = \lambda w(1-w) - wc$$

with $\tilde{w} = w(t-\tau)$.

w: density of occupied sites
c: density of occupied sites with a started countdown
λ: proliferation rate
τ: initial value of the countdown



Introduction of a highly proliferating cells to model the onset of a glioma

Dufour A et al (2018), Modeling the dynamics of oligodendrocyte precursor cells and the genesis of gliomas (2018) PLoS Comput Biol. 2018 Mar 28;14(3):e1005977.

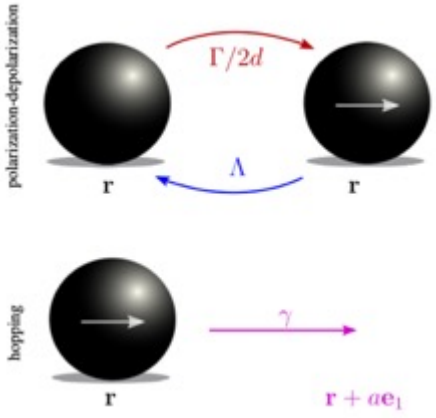
Team Modélisation du Vivant, IJCLab, Orsay: research themes

Statistical physics of out-of-equilibrium complex systems

This theme consists in studying (with analytical tools and Monte-Carlo simulations) the collective behaviors of assemblies of cells, based on simple rules of cell movement and interactions between cells and using statistical physics tools (active matter).

Highlight : A model for cell migration with polarization

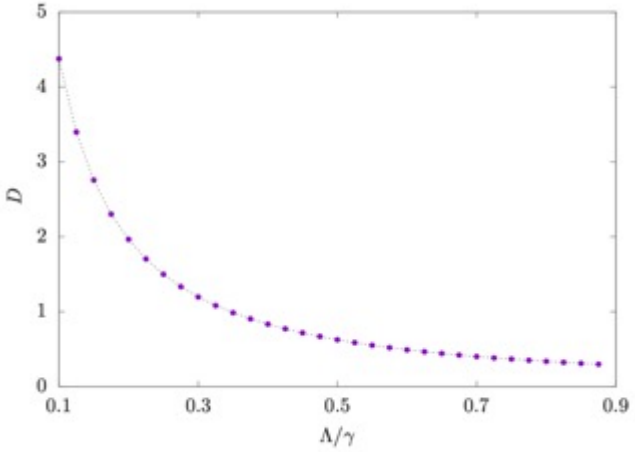
Cells can move, polarize and depolarize



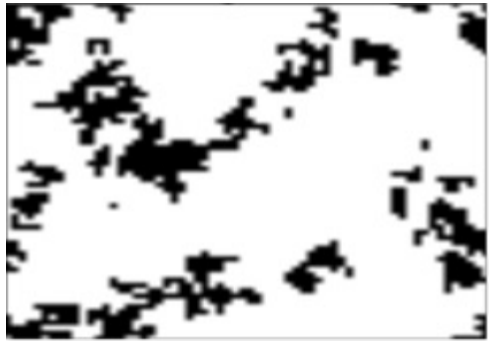
Mean field approximation

$$D_{\text{eff}} = \frac{\gamma a^2}{2d}\left(\frac{\Gamma}{\Gamma+\Lambda}\right)\left[1+\frac{2\gamma}{\Lambda}(1-\rho)(1-2\rho)\right]$$

ρ: cell density
γ: displacement rate
Λ: depolarization rate
Γ: polarization rate



One cell



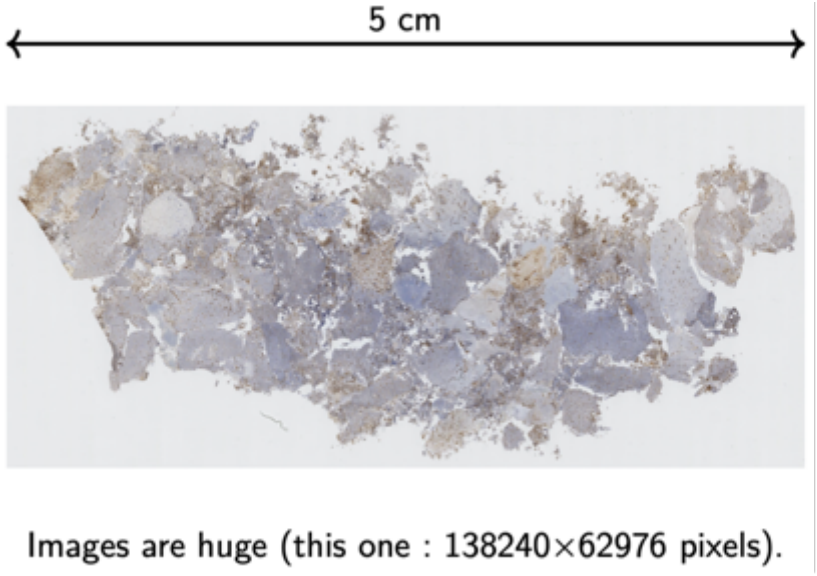
Many cells
Clusters form

G. Nakamura, M. Badoual, E. Fabiani, and C. Deroulers, Dispersal and organization of polarized cells: non-linear diffusion and cluster formation without adhesion., submitted

Team Modélisation du Vivant, IJCLab, Orsay: research themes

Big data approach to brain tissue samples.

This theme consists in data analysis, with the middle-term aim of fueling predictive mathematical models, of images obtained by scanning histology slides (10^9 pixels per image). This implies developing software (with industrial application or publication) for handling and analyzing large image files resulting from the digitization of histological slides.



Images are huge (this one : 138240×62976 pixels).

Deroulers C et al (2016) Automatic quantification of the microvascular density on whole slide images, applied to paediatric brain tumours, *Diagnostic Pathology*, **2**, 209

Michael Beuve's group in the PRISME Team

Human ressources

1 professor, 1 assistant professor, 1 postdoctoral fellow, 1PhD student, 1 M2 student

Research themes

Michael Beuve's group focuses on the development of multiscale models and simulations to describe and predict the physical, chemical and biological processes induced by irradiation.

- Cross-section activity and Monte-Carlo simulation
- Modeling biological dose activity
- 4D dose modeling
- Modeling of tumor control

Links with experimentalists

Data that are used come from litterature or are produced by the PRISME team (GANIL, Arronax, Legnaro et Radiograaff)

Collaborations

National: in Lyon (ENS, LIRIS, CREATIS), LPC Clermont, LPSC, CIMAP, Subatech/Arronax and IJCLab (starting)
International: University of Rosario (Argentina), INFN de Legnaro (Italie) + and the partners of the european network EURADOS
Responsabilité pôle GDR MI2B
Organisations workshops, conférences invitées…

Publications (last 5 years):

25 publications

Funding:

INCA Pysique Cancer, Labex PRIMES

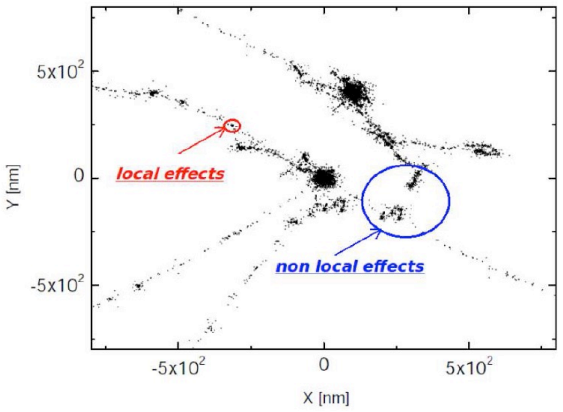
Michael Beuve's group in the PRISME Team

Modeling biological dose activity

This modeling consists in predicting the rates of cell survival in response to irradiation. Cell response = space-averaged response of irradiation patterns represented by traces of energy deposition and free radical production.
For hadrontherapy = Nanox
Project: application to BNCT (PICTURE : Physique Cancer grant)

Highlight: Nanox

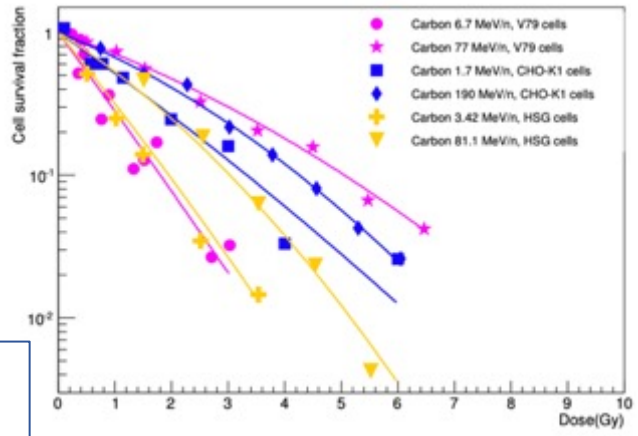
From the tracks of ions...



…cell survival probability in terms of the average over all configurations of radiation impacts is calculated...

$$\overline{S(D)} = \sum_{K=0}^{K=\infty} P(K,D) \cdot \langle {}^{cK}S \rangle_{cK}$$

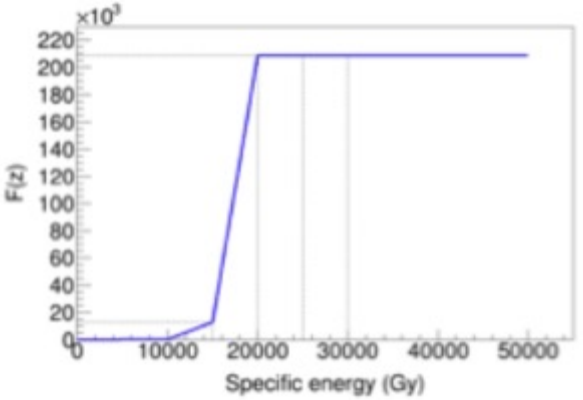
S(D): mean cell survival probability
D: dose
P(K,D): probability to have K impact with a dose D
$\langle {}^{cK}S \rangle_{cK}$: the mean survival probability over all the configurations cK



…and the model is compared to experimental results with cells

… an effective lethal function F is derived…

$$ {}^{cK}S_{\mathrm{L}} = \prod_{k=1}^{K} \exp\left(-\left\langle F\left({}^{c_i,c_k}z\right)\right\rangle_{c_i}\right)$$



$^{ci,ck}z$: energy in the local target i with configuration ci (i.e. position and orientation) after one radiation impact with configuration ck

Monini C et al (2020), Rad.Res., 193,,331-340.

Michael Beuve's group in the PRISME Team

4D dose modeling

Development of biomechanical models of the respiratory system to perform 3D dose calculations over time, via multiphysics tetrahedral meshes (collaboration with the LIRIS computer science lab).

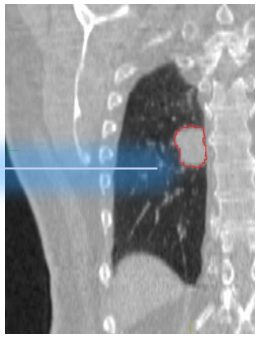
Highlight: Modeling organs in motion

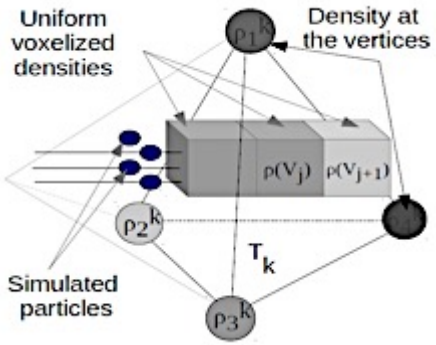
Respiration⟹motion ⟹ difficult to target the tumor during radiotherapy treatment

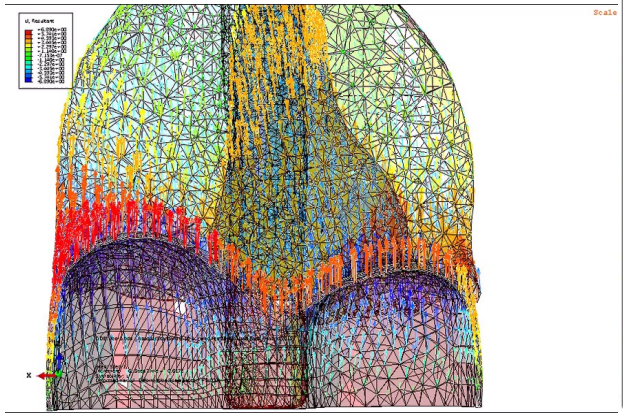
Tetrahedral mesh, with a model that takes into account the density of the tissues and of the tumor, the conditions at the borders, the displacements, other physiological parameters…

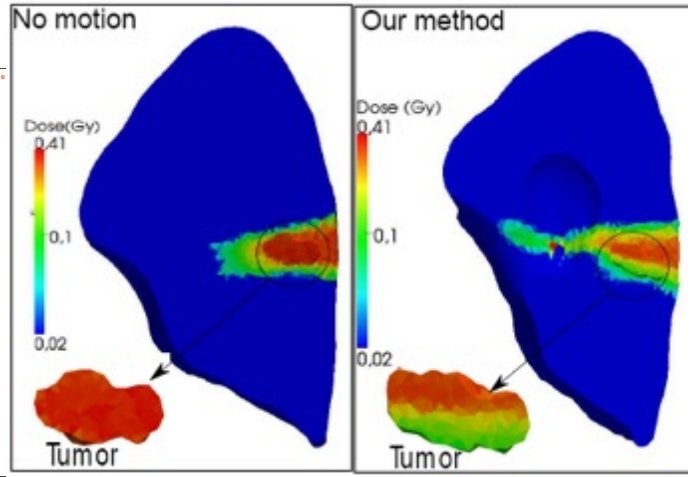
⟹ prediction of the displacement of the tumor (a mm precision), optimization of the treatment

Faisceau









Michael Beuve's group in the PRISME Team

Cross-section activity and Monte-Carlo simulation

Calculation of cross sections of interaction between gaseous matter and condensed matter ions as well as of electron interaction with this matter to improve Monte-Carlo simulations of physical and chemical processes.

Modeling of tumor control:

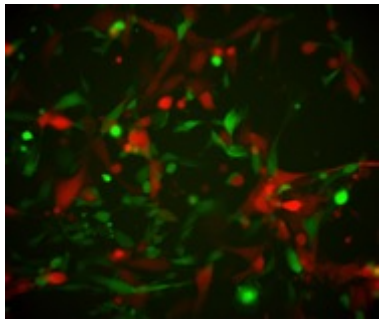
Monte-Carlo simulations as part of the development of irradiation means for radiobiology, in collaboration with Arronax Subatech in particular for the performance of experiments under SOBP (spread-out Bragg peak, alpha irradiation) conditions. We also have activities linked to RADIOGRAAFF (amedium energy proton irradiation plateform).

Collaboration between the two teams

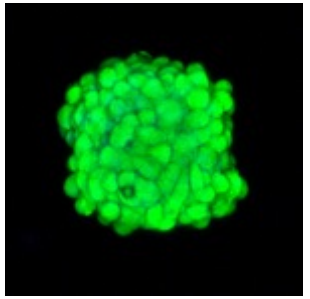
The Master project MOVI (Modélisation du Vivant) was a good way to federate the modeling and the theoretical aspects in order to model the effect of irradiation on the living matter at all scales.

One major challenge for the coming years will be to develop multiscale models combining the effects of radiation at a molecular/cellular level to biophysical models of tumor growth (at the tissue scale) taking into account:

- mechanical constraints
- cellular heterogeneity
- cell metabolism
- microenvironment etc…



Interactions between a cell population irradiated (red) and not irradiated (green)



A spheroid

⟹The two teams involved in the activities of theoretical physics for health are starting a new project consisting in developing a mesoscopic scale model for the response to irradiation (hadrontherapy) of tumors, in the context of the new MRI-Linac facility in Lyon.