Theoretical physics activity for health at IN2P3

The theoretical physics activity in health is currently based on the Modélisation du Vivant team (IJCLab, Orsay) and the theory part of the PRISME team (IPN, Lyon).

The activity of these two teams combines mathematical modeling, statistical physics, numerical simulations, Monte-Carlo simulations, data and image analysis. The objective of this activity is to get a better understanding of cancer development without and with treatment such as radiotherapy, by developing models bridging temporal and spatial scales (from molecules to tissues via cells).

Team Modélisation du Vivant, IJCLab, Orsay

Presentation

The invasivity of gliomas makes them incurable and despite technical progress over the past twenty years, the life expectancy of patients has barely improved. Modeling is an original approach, which, by integrating in a formal framework the main phenomena occurring at different scales (in particular the cell's scale in biology and the tissue's scale in medicine) in the tumor evolution, makes it possible to better understand and predict the evolution of these tumors. In addition, biology offers, by its intrinsically out-of-equilibrium character, original and challenging problems of theoretical physics. The team's work includes a part of data production and analysis (image analysis, for example) and a part of model design and confrontation to the data. In addition, we cultivate our expertise in integrable discrete dynamical systems and out-of-equilibrium statistical physics.

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

The themes of research of this team are the following:

- 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

Modeling of clinical and biological data of gliomas

This theme consists in developing 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), and establish a link between tumor growth studied at the micro scale (biology) and at the macro scale (medicine).

We are working on modeling the tumor evolution with and without radiotherapy, with a simple model, from clinical data, started during Léo Adenis' thesis (2017-2020).

A short-term objective is to predict the effectiveness of RT for a new patient, before the end of treatment. This aspect of prediction is of course more important for the clinician than being able to fit a model to data. The objective is to be able to classify patients, as quickly as possible, into fast or slow responders (slow responders being those for which the effect of RT lasts for years, with a tumor radius continuously decreasing, before re-growth). This classification would make it possible to adapt the follow-up of these patients and the frequency of MRI examinations.

In the longer term, other clinical data modeling projects will be addressed:

- Adjustment of clinical data from pregnant patients with gliomas, using the same model as above.

- Effect of chemotherapy on low-grade gliomas.
- Modeling of anaplastic transformation (transformation of a low-grade glioma into a high-grade glioma).

We are also studying the collective effects occurring between populations of irradiated and non-irradiated cells, from an experimental (in vitro) and modeling point of view. This project is in its early stages of development and it is the experimental aspect that has been initiated so far.

Highlight:

We have developed a model based on a cellular automaton to reproduce the dynamics of a population of precursor cells in the brain. We have shown that these cells manage to keep a constant density at the scale of the population, even if individual cells proliferate, die and move. The mean field approximation was calculated for a simplified model and by studying the stability of the fixed points, we could explain the existence of damped oscillations in the system.

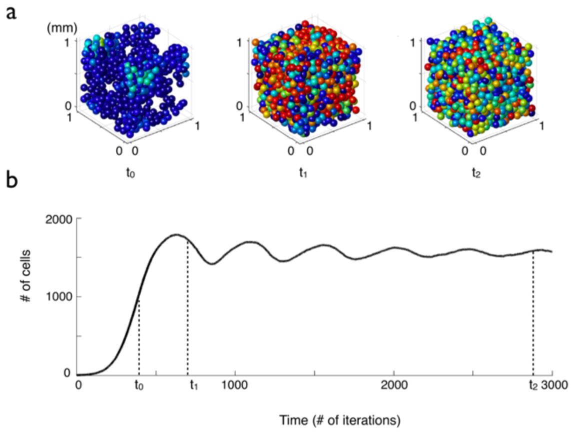

Fig1: Evolution of the cell density versus time for cells. Cells trigger a countdown when they are in contact with two other cells an die at the end.

From: *Dufour A, Gontran E, Deroulers C, Varlet P, Pallud J, Grammaticos B, Badoual M., Modeling the dynamics of oligodendrocyte precursor cells and the genesis of gliomas (2018) PLoS Comput Biol. 2018 Mar 28;14(3):e1005977.*

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).

In particular, in the context of collective cell migration that appear in cancer, we studied a discrete model of cell migration where cells can polarize and/or extend. We computed the hydrodynamic limit in mean field, and corrections to the mean field approximation. This problem was initiated in the PhD work of Enzo Fabiani (2016-2019), then continued with the postdoctoral fellowship of Gilberto Nakamura (2019-2021).

Many aspects remain to be studied: for example, it has been shown that when the concentration of cells is high enough and the rate of depolarization is low, the cells, initially uniformly distributed, form aggregates, even if there is no adhesion between cells. This phase transition and the dynamics of the aggregates remain to be studied precisely.

A longer-term objective is to take into account the heterogeneous and reactive migration substrate (the brain tissue).

Highlight:

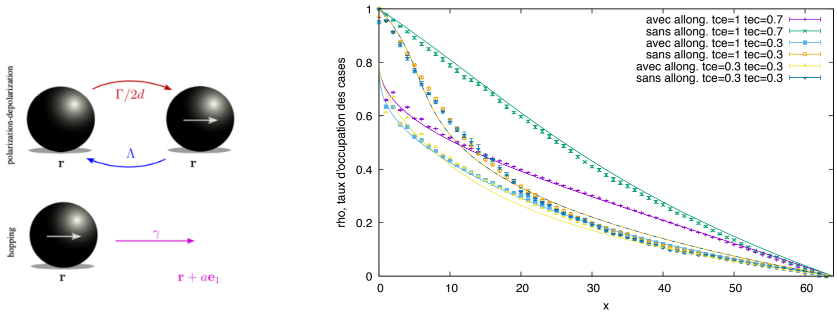

Fig2: Discrete model of cell polarization (left) and comparison between simulations and non linear diffusion coefficients calculated in the mean filed approximation.
From*: Nakamura G, Badoual M, Fabiani E, Deroulers C, dispersal and organization of polarized cells: non-linear and cluster formation without adhesion, submitted to Journal of Statistical Mechanics: Theory and Experiments*

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.

National Collaborations

Laboratoire TIMC (Grenoble), hôpitaux Sainte-Anne, Necker, Saint-Louis, Institut Gustave Roussy, Institut Curie.

International Collaborations

Tokyo University, University of Castilla-La Mancha Spain.

Publications (last 5 years):
33 publications (all themes)

Michael Beuve's group, PRISME team, IPN Lyon.

Presentation

The PRISME team is made up of physicists, biochemists, biologists and radiotherapists who have a multidisciplinary approach that aims to quantify, understand and predict the effect of ionizing radiation on living things from processes induced at extremely short times (attoseconds) at small scales (atomic nucleus) to long-term consequences (years) at the patient level, in the context of innovative radiotherapies, whether it be hadrontherapy or therapies using radioactive elements emitting ions or nanoparticles.
A research axis of this team (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. One of their important achievement is the multiscale model NanOx based on a fully stochastic theory of radiation and used to model the effect of hadrontherapy (CLINANOX, a former Physique Cancer grant, to improve NanOx by combining it with Geant4).

Human ressources

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

Links with experimentalists

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

Research projects

Cross-section activity and Monte-Carlo simulation

In collaboration with in particular the University of Rosario in Argentina and the CIMAP laboratory in Caen, we are working on the calculation of cross sections of interaction between gaseous matter and condensed matter ions as well as of electron interaction with this matter and use these cross sections to improve Monte-Carlo simulations of physical and chemical processes.

Modeling biological dose activity

(PICTURE : a Physique Cancer grant that has been accepted recently ; the objective is to predict the biological dose in the context BNCT by combining NanOx et G4DNA and by taking into account cellular geometries obtained by microscopy)

This modeling consists in predicting the rates of cell survival in response to irradiation. This is an approach inspired by statistical physics, since the cell response is a space-averaged response of irradiation patterns represented by traces of energy deposition and free radical production. This approach was first developed within the framework of the prediction of the biological dose for hadrontherapy. But recently, as part of a collaboration with the LPSC in Grenoble, we are currently expanding its development for applications related to BNCT. In addition, as part of a collaboration with the LPC of Clermont-Ferrand, we are developing an actor under GATE to calculate the biological dose from the GEANT4 tool.
Insight :

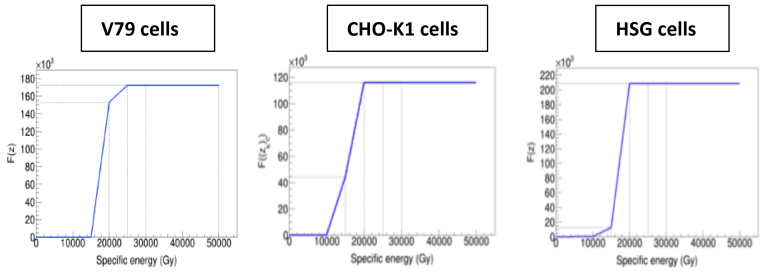

Fig3 : Construction of the function of lethal events from a complete family of polynomial functions: applications to 3 cell lines.
From: Monini C, Cunha M, Chollier L, Testa E, Beuve M, Determination of the Effective Local Lethal Function for the NanOx Model (2020), Rad.Res., 193,,331-340.

4D dose modeling

As part of a long-standing collaboration with the LIRIS computer lab, we are working on the development of biomechanical models of the respiratory system to perform 3D dose calculations over time, via multiphysics tetrahedral meshes.

Modeling of tumor control:

Modeling of the probability of tumor control using a fish-type approach in the context of hadrontherapy treatments. For information, we are also doing 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 conditions. We also have activities linked to RADIOGRAAFF.

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.

National Collaborations

In Lyon : ENS, LIRIS, CREATIS

In France : LPC Clermont, LPSC, CIMAP, Subatech/Arronax and IJCLab (starting)

International Collaborations

University of Rosario (Argentina), INFN de Legnaro (Italie) + and the partners of the european network EURADOS

Publications (last 5 years):
25 publications

The Master project MOVI (Modélisation du Vivant), that has now disappeared, 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 (both of the teams presented here belonged to that Master Projet, but there were several other teams). Indeed, one major issue for the coming year 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 etc).