Activity Report 2015

Team Monc

Modeling in Oncology

Inria teams are typically groups of researchers working on the definition of a common project, and objectives, with the goal to arrive at the creation of a project-team. Such project-teams may include other partners (universities or research institutions).

RESEARCH CENTER
Bordeaux - Sud-Ouest

THEME
Modeling and Control for Life Sciences

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Team Monc

Creation of the Team: 2015 January 01

Keywords:

Computer Science and Digital Science:

6. - Modeling, simulation and control
6.1.1. - Continuous Modeling (PDE, ODE)
6.3.1. - Inverse problems
6.3.2. - Data assimilation

Other Research Topics and Application Domains:

1.1.10. - Mathematical biology
1.4. - Pathologies
2.2.3. - Cancer

The team is issued from the MC2 team that started 10 years ago and most of the works have been initiated within MC2.

1. Members

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Sebastien Benzekry [Inria, Researcher]
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Thibaut Kritter [Univ. Bordeaux, from Sep 2015]
Guillaume Lefebvre [Univ. Bordeaux]
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Vivien Pianet [Univ. Bordeaux]
Taton Benjamin [Medical doctor, Univ. Bordeaux]

Visiting Scientist

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Maxime Prodhomme [Normale Sup Rennes, Internship, from Jun 2015 until Jul 2015]
Michael Leguèbe [Associate member]

2. Overall Objectives

2.1. Objectives

The MONC project-team aims at developing new mathematical models involving partial differential equations and statistical methods based on precise biological and medical knowledge in order to build numerical tools informed by on available quantitative data about cancer. The goal is ultimately to be able to help clinicians and/or biologists to better understand, predict or control tumor growth and possibly evaluate the therapeutic response, in a clinical context or for pre-clinical studies. We develop patient-specific approaches (mainly based on medical imaging) as well as population-type approaches in order to take advantage of large available databases. We claim that we can have a clinical impact that can change the way of handling certain pathologies.

In vivo modeling of tumors is limited by the amount of information obtainable. However, in the last few years, there have been dramatic increases in the scope and quality of patient-specific data from non-invasive imaging methods, so that several potentially valuable measurements are now available to quantitatively measure tumor growth, assess tumor status as well as anatomical or functional details. Using different methods such as CT scan, magnetic resonance imaging (MRI), or positron emission tomography (PET), it is now possible to evaluate and define tumor status at different levels: physiological, molecular and cellular.

In the meantime, the understanding of the biological mechanisms of tumor growth, including the influence of the micro-environment, has dramatically increased and the medical doctors now dispose of a wide spectrum of therapies (surgery, mini-invasive techniques, radiotherapies, chemotherapies, targeted therapies...).

Our project aims at supporting the decision process of oncologists in the definition of therapeutic protocols via quantitative methods. The idea is to build phenomenological mathematical models based on data obtained from medical imaging like CT scans, MRIs and PET scans. We therefore want to provide medical doctors patient-specific tumor growth models, which are able to evaluate – on the basis of previously collected data and within the limits of phenomenological models – the time dynamics of the pathology at subsequent times and the response to therapies. Our goal is to provide some numerical tools built to help answering the crucial questions for a clinician:

1. When is it necessary to start a treatment?
2. What is the best time to change a treatment?
3. When to stop a treatment?

In addition, we also intend to incorporate real-time model information for improving the precision and effectiveness of non invasive or micro-invasive tumor ablation techniques like acoustic hyperthermia, electroporation, radio-frequency, cryo-ablation and of course radiotherapies.

There is therefore a critical need of integrating biological knowledge into mathematical models based on clinical or experimental data in order to perform patient specific simulations. The main purpose of our project is to create new mathematical models and news paradigms for data assimilation that are adapted to the biological nature of the disease and to the amount of multi-modal data.

2.2. General strategy

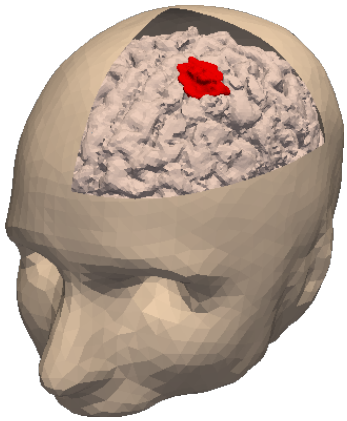

Figure 1. 3D numerical simulation of a meningioma tumor. The tumor is shown in red.

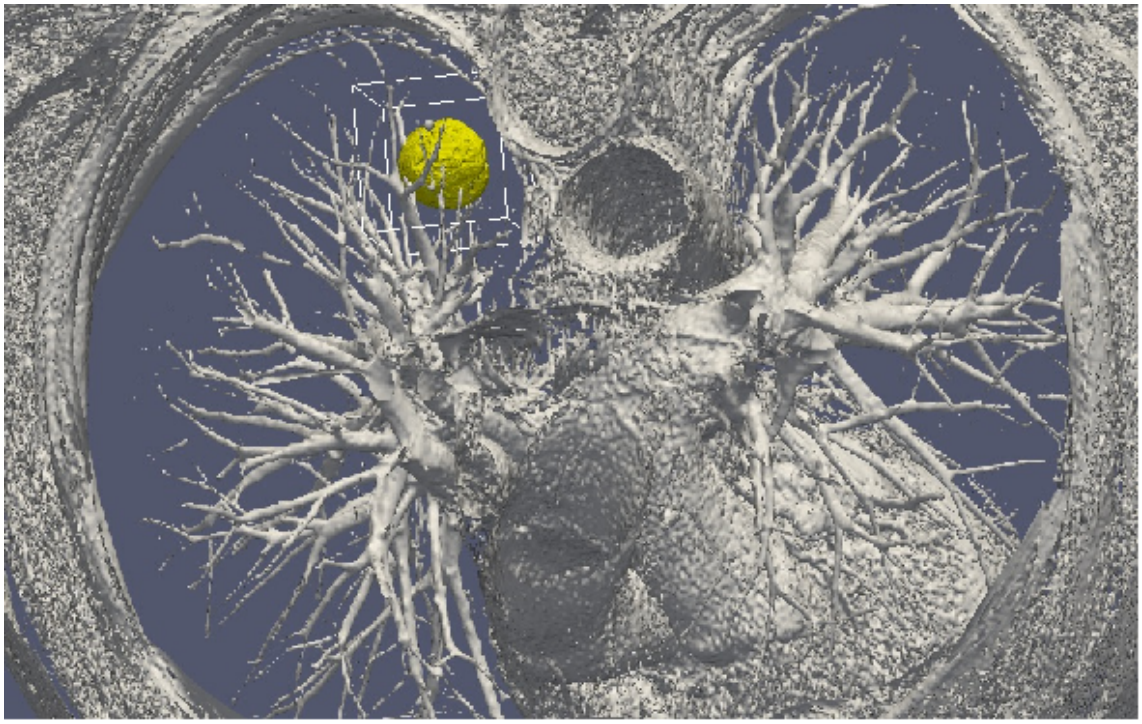

Figure 2. 3D numerical simulation of a lung tumor. The tumor is shown in yellow.

The general strategy consists of the interactions of several stages:

- Stage 1: Derivation of mechanistic models based on the biological knowledge and the available observations. The construction of such models relies on the up-to-date biological knowledge at the cellular level including description of the cell-cycle, interaction with the microenvironement (angiogenesis, interaction with the stroma). Such models also include a “macroscopic" description of specific molecular pathways that are known to have a critical role in carcinogenesis or that are targeted by new drugs. We emphasize that for this purpose, tight interactions with biologists are crucial. Lots of works devoted to the modeling at the cellular level are available in the literature. However, in order to be able to use these models in a clinical context, we also need to describe the tumor at the tissue level. The *in vitro* mechanical characterization of tumor tissues has been widely studied. However, no description that could be patient specific or even tumor specific is available. It is therefore necessary to build adapted phenomenological models, according to the biological and clinical reality.
- Stage 2: Data collection. In the clinical context, data may come from medical imaging (MRI, CT-Scan, PET scan) at different time points. It is also a crucial point: we need longitudinal data in time in order to be able to understand the time course of the disease. The data can also be obtained from the analysis of blood samples or biopsies. It is critical to have tight collaborations with clinicians for the selection of the specific cases to focus on, the understanding of the key points and of the key data, the classification of the grades of the tumors, the understanding of the treatment, ...In the preclinical context, data can be macroscopic measurements of the tumor volume for subcutaneous cases, green fluorescence protein (GFP) quantifications for total number of living cells, non-invasive bioluminescence signals or even imaging obtained with devices adapted to small animals.
- Stage 3: Adaptation of the model to the data. The model has to be adapted to the data: it is useless to have a model taking many biological features of the disease into account if it cannot be reliably parameterized with the data. For example, very detailed description of the angiogenesis process given in the literature cannot be used, even if one has data arising from perfusion MRIs. A pragmatic approach has to be developed for this purpose. On the other hand, one has to try to model any element that can be useful to exploit the image. Parameterizing must be performed carefully in order to achieve an optimal trade-off between the accuracy of the model, its complexity, identifiability and predictive power. Parameter estimation is a critical issue in mathematical biology, which we cannot avoid: if there are too many parameters, it will be impossible to estimate them but if the model is too simple, it will be too far from reality.
- Stage 4: Data assimilation. Due to the complexity of the data – for example multimodal, longitudinal medical imaging – the data assimilation is a major challenge. Such a process is a combination of methods for solving inverse problems and statistical methods including machine learning strategies. Presently, most of the inverse problems – developed in the team – are solved using a gradient method coupled with some Monte-Carlo type algorithm. More efficient methods could be used as for example the sequential methods, *i.e.* the Kalman type filters or the so-called Luenberger filter (nudging). Using the sequential methods can also simplify the Stage 3 because they can be used even with complex models. Of course, the strategy used by the team depends on the quantity and the quality of data. It is not the same if we have an homogeneous population of cases or if it is a very specific isolated case.
- Stage 4’: Data assimilation of gene expression. "Omics" data become more and more important in oncology and we aim at developing our models using the available information. For example, in our previous work on GIST, we have taken into account the cases with mutation on Ckit. However, it is still not clear how to use in general gene expression data in our macroscopic models, and particularly how to connect the genotype to the phenotype and the macroscopic growth. We expect to use statistical learning techniques on populations of patients in order to move towards this direction, but we emphasize that this task is very prospective and is a scientific challenge in itself.
- Stage 5: Simulation. Once the models have been parametrized, the simulation part can be done. We

also need to include a quantification of uncertainties and to produce 3D simulations that can be confronted to reality.

3. Research Program

3.1. Introduction

We address the problem of cancer modeling through 3 axis.

- Axis 1: Tumor modeling for patient-specific simulations.
- Axis 2: Bio-physical modeling for personalized therapies.
- Axis 3: Quantitative cancer modeling for biological and preclinical studies.

In the first axis, we aim at producing patient-specific simulations of the growth of a tumor or its response to treatment starting from a series of images. We hope to be able to give information to the clinicians in order to improve the decision process. It is mainly useful in the case of a relapse or for metastatic diseases.

The second axis aims at modeling the biophysical therapies like radiotherapies, but also thermo-ablations, radio-frequency ablations or electroporation that play a crucial role in the case of a relapse or for a metastatic disease, which is precisely the clinical context where the techniques of axis 1 will be applied.

The third axis, even if not directly linked to clinical perspectives, is essential since it is a way to better understand and model the biological reality of cancer growth and the (possibly complex) effects of therapeutic intervention. Modeling in this case also helps to interpret the experimental results and improve the accuracy of the models used in Axis 1. Technically speaking, some of the computing tools are similar to those of Axis 1.

3.2. Axis 1: Tumor modeling for patient-specific simulations

The gold standard treatment for most cancers is surgery. In the case where total resection of the tumor is possible, the patient often benefits from an adjuvant therapy (radiotherapy, chemotherapy, targeted therapy or a combination of them) in order to eliminate the potentially remaining cells that are not visible. In this case personalized modeling of tumor growth is useless and statistical modeling will be able to quantify the risk of relapse, the mean progression-free survival time...However if total resection is not possible or if metastases emerge from distant sites, clinicians will try to adopt a strategy in order to control the disease for as long as possible. A wide set of tools are available. Clinicians may treat the disease by physical interventions (radiofrequency ablation, cryoablation, radiotherapy, electroporation, focalized ultrasound,...) or chemical agents (chemotherapies, targeted therapies, antiangiogenic drugs, immunotherapies, hormonotherapies). One can also decide to follow the patient without any treatment (this is the case for slowly growing tumors like some metastases to the lung, some lymphomas or for some low grade gliomas). If we had a reliable patient specific model of tumor growth with or without treatment, it could have different uses for the patient follow-up.

- Case without treatment: the evaluation of the growth of the tumor would provide a useful indication for the time at which the tumor will reach a critical size. For example, radiofrequency ablation of pulmonary lesion is very efficient as long as the diameter of the lesion is smaller than 3 cm. Thus, the prediction can help the clinician for the planification of the intervention. For tumor with very slow growth, quantitative modeling can also help to decide at what time interval the patient has to undergo a CT-scan. CT-scans are irradiative exams and there is a challenge for decreasing their occurrence for each patient. It has also an economical impact. And if the disease evolution starts to differ from the forecast, this can mean that some events have occurred at the biological level. It can be the apparition of an agressive phenotype, cells that leave a dormancy state. This kind of events cannot be predicted, but some mismatch with respect to the prediction can be an indirect proof of their existence. It could be an indication for the clinician to start a treatment.

- Case with treatment: a model can help to understand and to quantify the final effect of a treatment using the early response. It can help for a redefinition of the treatment planning. Modeling can also help to anticipate the relapse by analyzing some functional aspects of the tumor. Again, a deviation with respect to reference curves can mean a lack of efficiency of the therapy or a relapse. Moreover, for a long time, the response to a treatment has been quantified by the RECIST criteria which consists in (roughly speaking) measuring the diameters of the largest tumor of the patient, as it is seen on a CT-scan. This criteria is still widely used and was quite efficient for chemotherapies and radiotherapies that induce a decrease of the size of the lesion. However, with the systematic use of targeted therapies and anti-angiogenic drugs that modify the physiology of the tumor, the size may remain unchanged even if the drug is efficient and deeply modifies the tumor behavior. One better way to estimate this effect could be to use functional imaging (Pet-scan, perfusion or diffusion MRI, ...), a model can then be used to exploit the data and to understand in what extent the therapy is efficient.
- Optimization: currently, we do not believe that we can optimize a particular treatment in terms of distribution of doses, number, planning with the model that we will develop in a medium term perspective. But it is an aspect that we keep in mind on a long term one.

The scientific challenge is therefore as follows: knowing the history of the patient, the nature of the primitive tumor, its histopathology, knowing the treatments that patients have undergone, knowing some biological facts on the tumor and having a sequence of images (CT-scan, MRI, PET or a mix of them), are we able to provide a numerical simulation of the extension of the tumor and of its metabolism that fits as best as possible with the data (CT-scans or functional data) and that is predictive in order to address the clinical cases described above?

Our approach relies on the elaboration of PDE models and their parametrization with the image by a coupling of gradient methods and Monte-Carlo type methods. The PDE models rely on the description of the dynamics of cell populations. The number of populations depends on the pathology. For example, for glioblastoma, one needs to use proliferative cells, invasive cells, quiescent cells as well as necrotic tissues to be able to reproduce realistic behaviors of the disease. In order to describe the relapse for hepatic metastases of gastro-intestinal stromal tumor (gist), one needs three cell populations: proliferative cells, healthy tissue and necrotic tissue. The law of proliferation is often coupled with a model for the angiogenesis. However such models of angiogenesis involve too many non measurable parameters to be used with real clinical data and therefore one has to use simplified or even simplistic versions. The law of proliferation often mimics the existence of an hypoxia threshold, it consists of an O.D.E. or a P.D.E that describes the evolution of the growth rate as a combination of sigmoidal functions of nutrients or roughly speaking oxygen concentration. Usually, several laws are available for a given pathology since at this level, there are no quantitative argument to choose a particular one. The velocity of the tumor growth differs depending on the nature of the tumor. For metastases, we will derive the velocity thanks to Darcy's law in order to express that the extension of the tumor is basically due to the increase of volume. This gives a sharp interface between the metastasis and the surrounding healthy tissues, as observed by anatomopathologists. For primitive tumors like gliomas or lung cancer, we use reaction-diffusion equations in order to describe the invasive aspects of such primitive tumors. The modeling of the drugs depends on the nature of the drug: for chemotherapies, a death term can be added into the equations of the population of cells, while antiangiogenic drugs have to be introduced in a angiogenic model. Resistance to treatment can be described either by several populations of cells or with non-constant growth or death rates. As said before, it is still currently difficult to model the changes of phenotype or mutations, we therefore propose to investigate this kind of phenomena by looking at deviations of the numerical simulations compared to the medical observations. The calibration of the model is done by using a series (at least 2) of images of the same patient and by minimizing a cost function. The cost function contains at least the difference between the volume of the tumor that is measured on the images with the computed one. It also contains elements on the geometry, on the necrosis and any information that can be obtained through the medical images. We will pay special attention to functional imaging (PET, perfusion and diffusion MRI). The inverse problem is solved using a gradient method coupled with some Monte-Carlo type algorithm. If a large number of similar cases is available, one can imagine to use statistical algorithms like random forests to use some non quantitative data like the gender, the age, the origin of the primitive tumor...for example for choosing the model for the

growth rate for a patient using this population knowledge (and then to fully adapt the model to the patient by calibrating this particular model on patient data) or for having a better initial estimation of the modeling parameters. We have obtained several preliminary results concerning lung metastases including treatments and for metastases to the liver.

3.3. Axis 2: Bio-physical modeling for personalized therapies

In this axis, we investigate locoregional therapies such as radiotherapy, irreversible electroporation. Electroporation consists of an increase of the membrane permeability of cells due to the delivery of high voltage pulses. This phenomenon can be transient (reversible) or irreversible. This is a non-thermal phenomenon. (IRE) or electro-chemotherapy – which is a combination of reversible electroporation with a cytotoxic drug – are essential tools for the treatment of a metastatic disease. Numerical modeling of these therapies is a clear scientific challenge. Clinical applications of the modeling are the main target, which thus drives the scientific approach, even though theoretical studies in order to improve the knowledge of the biological phenomena, in particular for electroporation, should also be addressed. However, this subject is quite wide and we will focus on two particular approaches: some aspects of radiotherapies and electro-chemotherapy. This choice is motivated by some pragmatic reasons: we already have collaborations with physicians on these therapies. Other treatments could be probably tackled in the same spirit, but we do not plan to work on this subject on a medium term.

- Radiotherapy (RT) is a common therapy for cancer. Typically, using a CT scan of the patient with the structures of interest (tumor, organs at risk) delineated, the clinicians optimize the dose delivery to treat the tumor while preserving the healthy tissue. The RT is then delivered every day using low resolution scans (CBCT) to position the beams. Under treatment the patient may lose weight and the tumor shrinks. These changes may affect the propagation of the beams and subsequently change the dose that is effectively delivered. It could be harmful for the patient especially if sensitive organs are concerned. In such cases, a replanification of the RT could be done to adjust the therapeutical protocol. Unfortunately, this process takes too much time to be performed routinely. The challenges faced by clinicians are numerous, we focus on two of them:
  - *Detecting the need of replanification:* we are using the positioning scans to evaluate the movement and deformation of the various structures of interest. Thus we can detect whether or not a structure has moved out of the safe margins (fixed by clinicians) and thus if a replanification may be necessary. In a retrospective study, our work can also be used to determine RT margins when there are no standard ones. A collaboration with the RT department of Institut Bergonié is underway on the treatment of retroperitoneal sarcoma and ENT tumors (head and neck cancers). A retrospective study was performed on 11 patients with retro-peritoneal sarcoma. The results have shown that the safety margins (on the RT) that clinicians are currently using are probably not large enough. The tool used in this study is being further developed by an engineer funded by Inria (Cynthia Périer, ADT Sesar). We used well validated methods from a level-set approach and segmentation / registration methods. The originality and difficulty lie in the fact that we are dealing with real data in a clinical setup. Clinicians have currently no way to perform complex measurements with their clinical tools. This prevents them from investigating the replanification. Our work and the tools developed pave the way for easier studies on evaluation of RT plans in collaboration with Institut Bergonié. *There was no modeling involved in this work that arose during discussions with our collaborators.* The main purpose of the team is to have meaningful outcomes of our research for clinicians, sometimes it implies leaving a bit our area of expertise.
  - *Evaluating RT efficacy and finding correlation between the radiological responses and the clinical outcome:* our goal is to help doctors to identify correlation between the response to RT (as seen on images) and the longer term clinical outcome of the patient. Typically, we aim at helping them to decide when to plan the next exam after the RT. For patients whose response has been linked to worse prognosis, this exam would have to be planned

earlier. This is the subject of a starting collaboration with Institut Bergonié. The response is evaluated from image markers (*e.g.* using texture information) or with a mathematical model (another collaboration is also ongoing with LATIM team in Brest on response of colorectal tumors to RT using PET scans). The other challenges are either out of reach or not in the domain of expertise of the team. Yet our works may tackle some important issues for adaptive radiotherapy.

- Both IRE and electrochemotherapy are anticancerous treatments based on the same phenomenon: the electroporation of cell membranes. This phenomenon is known since a few decades but it is still not well understood, therefore we address the modeling two different purposes:
  1. We want to use mathematical models in order to better understand the biological behavior and the effect of the treatment. We work in tight collaboration with biologists and bioeletromagneticians to derive precise models of cell and tissue electroporation, in the continuity of the research program of the Inria team-project MC2. These studies lead to complex non-linear mathematical models involving some parameters (as less as possible). Numerical methods to compute precisely such models and the calibration of the parameters with the experimental data are then addressed. Tight collaborations with the Vectorology and Anticancerous Therapies (VAT) of IGR at Villejuif, Laboratoire Ampère of Ecole Centrale Lyon and the Karlsruhe Institute of technology will continue, and we aim at developing new collaborations with Institute of Pharmacology and Structural Biology (IPBS) of Toulouse and the Laboratory of Molecular Pathology and Experimental Oncology (LMPEO) at CNR Rome, in order to understand differences of the electroporation of healthy cells and cancer cells in spheroids and tissues.
  2. This basic research aims at providing new understanding of electroporation, however it is necessary to address, particular questions raised by radio-oncologists that apply such treatments. One crucial question is "What pulse or what train of pulses should I apply to electroporate the tumor if the electrodes are located as given by the medical images"? Even if the real-time optimization of the placement of the electrodes for deep tumors may seem quite utopian since the clinicians face too many medical constraints that cannot be taken into account (like the position of some organs, arteries, nerves...), on can expect to produce real-time information of the validity of the placement done by the clinician. Indeed, once the placement is performed by the radiologists, medical images are usually used to visualize the localization of the electrodes. Using these medical data, a crucial goal is to provide a tool in order to compute in real-time and visualize the electric field and the electroporated region directly on theses medical images, to give the doctors a precise knowledge of the region affected by the electric field. In the long run, this research will benefit from the knowledge of the theoretical electroporation modeling, but it seems important to use the current knowledge of tissue electroporation – even quite rough –, in order to rapidly address the specific difficulty of such a goal (real-time computing of non-linear model, image segmentation and visualization). Tight collaborations with CHU Pellegrin at Bordeaux, and CHU J. Verdier at Bondy are crucial.

3.4. Axis 3: Quantitative cancer modeling for biological and preclinical studies

With the emergence and improvement of a plethora of experimental techniques, the molecular, cellular and tissue biology has operated a shift toward a more quantitative science, in particular in the domain of cancer biology. These quantitative assays generate a large amount of data that call for theoretical formalism in order to better understand and predict the complex phenomena involved. Indeed, due to the huge complexity underlying the development of a cancer disease that involves multiple scales (from the genetic, intra-cellular scale to the scale of the whole organism), and a large number of interacting physiological processes (see the so-called “hallmarks of cancer"), several questions are not fully understood. Among these, we want to focus on the most clinically relevant ones, such as the general laws governing tumor growth and the development of metastases

(secondary tumors, responsible of 90% of the deaths from a solid cancer). In this context, it is thus challenging to potentiate the diversity of the data available in experimental settings (such as *in vitro* tumor spheroids or *in vivo* mice experiments) in order to improve our understanding of the disease and its dynamics, which in turn lead to validation, refinement and better tuning of the macroscopic models used in the axes 1 and 2 for clinical applications.

In recent years, several new findings challenged the classical vision of the metastatic development biology, in particular by the discovery of organism-scale phenomena that are amenable to a dynamical description in terms of mathematical models based on differential equations. These include the angiogenesis-mediated distant inhibition of secondary tumors by a primary tumor the pre-metastatic niche or the self-seeding phenomenon Building a general, cancer type specific, comprehensive theory that would integrate these dynamical processes remains an open challenge. On the therapeutic side, recent studies demonstrated that some drugs (such as the Sunitinib), while having a positive effect on the primary tumor (reduction of the growth), could *accelerate* the growth of the metastases. Moreover, this effect was found to be scheduling-dependent. Designing better ways to use this drug in order to control these phenomena is another challenge. In the context of combination therapies, the question of the *sequence* of administration between the two drugs is also particularly relevant.

One of the recurrent technical challenge that we need to address when dealing with biological data is the presence of potentially very large inter-animal (or inter-individual) variability.

Starting from the available multi-modal data and relevant biological or therapeutic questions, our purpose is to develop adapted mathematical models (i.e., identifiable from the data) that recapitulate the existing knowledge and reduce it to its more fundamental components, with two main purposes:

1. to generate quantitative and empirically testable predictions that allow to assess biological hypotheses or
2. to investigate the therapeutic management of the disease and assist preclinical studies of anti-cancerous drug development.

We believe that the iterative loop between theoretical modeling and experimental studies can help to generate new knowledge and improve our predictive abilities for clinical diagnosis, prognosis, and therapeutic decision. Let us note that the first point is in direct link with the axes 1 and 2 of the team since it allows us to experimentally validate the models at the biological scale (*in vitro* and *in vivo* experiments) for further clinical applications.

More precisely, we first base ourselves on a thorough exploration of the biological literature of the biological phenomena we want to model: growth of tumor spheroids, *in vivo* tumor growth in mice, initiation and development of the metastases, effect of anti-cancerous drugs. Then we investigate, using basic statistical tools, the data we dispose, which can range from: spatial distribution of heterogeneous cell population within tumor spheroids, expression of cell makers (such as green fluorescent protein for cancer cells or specific antibodies for other cell types), bioluminescence, direct volume measurement or even intra-vital images obtained with specific imaging devices. According to the data type, we further build dedicated mathematical models that are based either on PDEs (when spatial data is available, or when time evolution of a structured density can be inferred from the data, for instance for a population of tumors) or ODEs (for scalar longitudinal data). These models are confronted to the data by two principal means:

1. when possible, experimental assays can give a direct measurement of some parameters (such as the proliferation rate or the migration speed) or
2. statistical tools to infer the parameters from observables of the model.

This last point is of particular relevance to tackle the problem of the large inter-animal variability and we use adapted statistical tools such as the mixed-effects modeling framework.

Once the models are shown able to describe the data and are properly calibrated, we use them to test or simulate biological hypotheses. Based on our simulations, we then aim at proposing to our biological collaborators new experiments to confirm or infirm newly generated hypotheses, or to test different administration protocols of the drugs. For instance, in a collaboration with the team of the professor Andreas Bikfalvi (Laboratoire

de l'Angiogénèse et du Micro-environnement des Cancers, Inserm, Bordeaux), based on confrontation of a mathematical model to multi-modal biological data (total number of cells in the primary and distant sites and MRI), we could demonstrate that the classical view of metastatic dissemination and development (one metastasis is born from one cell) was probably inaccurate, in mice grafted with metastatic kidney tumors. We then proposed that metastatic germs could merge or attract circulating cells. Experiments involving cells tagged with two different colors are currently performed in order to confirm or infirm this hypothesis.

Eventually, we use the large amount of temporal data generated in preclinical experiments for the effect of anti-cancerous drugs in order to design and validate mathematical formalisms translating the biological mechanisms of action of these drugs for application to clinical cases, in direct connection with the axis 1. We have a special focus on targeted therapies (designed to specifically attack the cancer cells while sparing the healthy tissue) such as the Sunitinib. This drug is indeed indicated as a first line treatment for metastatic renal cancer and we plan to conduct a translational study coupled between A. Bikfalvi's laboratory and medical doctors, F. Cornelis (radiologist) and A. Ravaud (head of the medical oncology department).

4. Application Domains

4.1. Introduction

We now present our contribution to these above challenges. We do an investigation of particular cancers:

- Gliomas (brain tumors),
- Meningioma,
- Colorectal cancers,
- Lung and liver metastasis,
- Breast cancer.

4.2. Axis 1: Tumor modeling for patient-specific simulations

- Patient-specific simulations
- Parameter estimations (with the help of low order models)

4.3. Axis 2: Bio-physical modeling for personalized therapies

- Modelling of electrochemotherapy

4.4. Axis 3: Quantitative cancer modeling for biological and preclinical studies

- Theoretical biology of the metastatic process: dynamics of a population of tumors in mutual interactions, dormancy, pre-metastatic and metastatic niche, quantification of metastatic potential and differential effects of anti-angiogenic therapies on primary tumor and metastases.
- Mathematical models for preclinical cancer research: description and prediction of tumor growth and metastatic development, effect of anti-cancerous therapies

5. Highlights of the Year

5.1. Highlights of the Year

Awards

Perrine Berment won the third price of *Ma thèse en 180 secondes* of the Aquitaine region.

6. New Software and Platforms

6.1. CADMOS

KEYWORDS: Health - Cancer - Partial differential equation - Cartesian grid

- Participants: Olivier Saut and Julien Jouganous
- Partners: Université de Bordeaux - CNRS - INP Bordeaux
- Contact: Olivier Saut

6.2. Carcinom (Computer-Assisted Research about Cancer growth and INsights on Oncological Mechanisms)

KEYWORDS: Cancer - Data modeling - Regression

- Participants: Sébastien Benzekry
- Contact: Sébastien Benzekry
- FUNCTIONAL DESCRIPTION A software for nonlinear regression of tumor growth and therapy models and statistical inference. This software is primarily designed to perform a modeling analysis of tumor growth kinetics. Given a data set of longitudinal measurements of tumor size in a population, it fits several models of tumor growth, computes several goodness-of-fit statistical metrics, identifies the parameters of the models and estimates the uncertainty associated to their determination. It provides several graphical and numerical outputs (in the form of LaTeX tables).

6.3. ELMO (Numerical Simulation of cell electroporation)

KEYWORDS: Bioinformatics - Biology - Numerical electroporation - Finite difference method in 2D-3D

- Participants: Clair Poignard and Michael Leguebe
- Partners: Université de Bordeaux - CNRS - INP Bordeaux
- Contact: Michael Leguebe
- URL: http://www.math.u-bordeaux1.fr/~mleguebe/phd_fr.html
- SCIENTIFIC DESCRIPTION 2D-3D code of finite difference method in C++ to compute the electroquasistatic field in a biological cell, with non-linear model of membrane conductance and lateral diffusion of lipids.
- FUNCTIONAL DESCRIPTION Compute the electroquasistatic field and the porated region of the cell membrane. The aim is to provide a user-friendly code for applied mathematicians and biophysicists.

6.4. Meta-poumon

KEYWORDS: Health - Evolution - Cancer - Medical imaging

- Participants: Olivier Saut, Thierry Colin, Marie Martin and Julien Jouganous
- Partners: Université de Bordeaux - CNRS - IPB
- Contact: Olivier Saut
- FUNCTIONAL DESCRIPTION The software evaluates the aggressiveness of pulmonary metastasis or response to treatment for predictive goal. To do this, we use a mathematical model based on a set of equations to nonlinear partial differential equations. This model is calibrated to the patient data using a longitudinal sequence of CT or MRI of the patient.

6.5. Nenuphar

KEYWORDS: Modeling - Oncologie - Cancer - Partial differential equation - Medical - Medical imaging

- Partners: CNRS - INP Bordeaux - Université Bordeaux 1
- Contact: Marie Martin
- FUNCTIONAL DESCRIPTION The goal of project is to evaluate the aggressiveness of a tumor or its response to therapy. For that purpose, we use a mathematical model based on a set of nonlinear partial differential equations. This model is calibrated on patient data using a longitudinal sequence of CT Scan or MRI of the patient. This approach has been validated on about 35 clinical cases of lung metastases from various primary tumors (kidney, bladder, thyroid). Using two initial images showing the targeted lesion, we recover the patient-specific parameters of the model. The evolution of the disease is then predicted by letting the model run for later times with these parameters.

6.6. SESAR (Monitor of the effect of RT on Retroperitoneal Sarcoma)

KEYWORDS: Segmentation - Health - DICOM - Cancer - Medical imaging

- Partner: Institut Bergonié
- Contact: Olivier Saut

6.7. SegmentIt

KEYWORDS: Health - Signal - Registration of 2D and 3D multimodal images - 3D - Image analysis - Image - Processing - Medical imaging

- Participants: Thierry Colin, Olivier Saut, Vivien Pianet, Agathe Peretti, Marie Martin, Sébastien Benzekry, Baudoin Denis De Senneville, Cynthia Perier, Benjamin Taton, Nicolas Grenier and Christian Combe
- Contact: Benjamin Taton
- FUNCTIONAL DESCRIPTION Image processing software for anatomical and functional data. Segmentation, registration and digital filtering. Assessement of the kidney perfusion and the kidney function (to be continued).

7. New Results

7.1. Axis 1: Tumor modeling for patient-specific simulations

7.1.1. Lung metastasis

Patient specific simulation of tumor growth, response to the treatment and relapse of a lung metastasis: a clinical case [10], [1]
Team participants: Thierry Colin, Julien Jouganous, François Cornelis (Hôpital Pellegrin), Olivier Saut
Other participant: Jean Palussière (Bergonié Institute)

In this work, a parametrization strategy based on reduced order methods is presented for tumor growth PDE models. This is applied to a new simple spatial model for lung metastasis including angiogenesis. The goal is to help clinicians monitoring tumors and eventually predicting its evolution or response to a particular kind of treatment. To illustrate the whole approach, a clinical case including the natural history of the lesion, the response to a chemotherapy and the relapse before a radiofrequency ablation is presented.

Nenuphar
Team participants: Thierry Colin, Julien Jouganous, Marie Martin, Olivier Saut

This work concerns the development of *Nenuphar* which is a software devoting to the evaluation and the surveillance of the tumor aggressiveness.

7.1.2. Take into account the drug resistance

Modeling and analysis of tumor heterogeneity during treatments resistance: GIST liver metastases case
Team participants: Thierry Colin, François Cornelis, Guillaume Lefebvre, Clair Poignard, Olivier Saut

This works deals with tumor heterogeneity analysis and modeling during treatments resistances. A patient-dependent PDEs model, that takes into account two kinds of treatments, is presented. It qualitatively and quantitatively reproduces the different stage during the tumor growth undergoing treatments. In order to overcome a numerical instability linked to the type of modeling, a new numerical scheme is built. Then, an image synthesis method is developed to enable a better comparison between the numerical results and the clinical data. Finally, a robust criteria that quantifies the tumor heterogeneity from the clinical data and from the synthesis images, is built.

Mathematical study and asymptotic analysis of a model for tumour drug resistance [19]
Team participants: Thierry Colin, Thomas Michel, Clair Poignard

In this work we study a partial differential equations model for tumour growth taking into account drug resistance. It is well known that angiogenesis, the process of creation of new blood vessels from existing ones, is induced by tumour cells to get the amount of nutrients and oxygen needed to continue their proliferation when the tumour has reached a critical size. Angiogenesis is therefore a target for therapy. The model we study takes into account two kinds of treatments: a cytotoxic treatment and a treatment which is both cytotoxic and anti-angiogenic. It is based on mass-balance equations on cells densities coupled with a diffusion equation for the nutrients and oxygen concentration. In a first part we prove that the model is well-posed if the initial tumour is compactly supported in the domain, which is the case for tumour metastases. The proof states that the tumour remains compactly supported in a finite time. In the model, we also consider the presence of a necrotic compartment composed of dead cells. Since some tumours can present necrosis while other do not, we want a model which can reproduce these two different cases. The second part of this work is devoted to an asymptotic analysis which proves that the absence of necrosis is the limit case of our model when the necrosis is immediately evacuated.

7.1.3. Motility phenotype

TMOD-03 * Motility controls growth and progression patterns of glioblastoma multiforme [13]
Team participants: Olivier Saut, Thierry Colin
Other participants: Hassan Fathallah, Elizabeth Scribner

Purpose: Glioblastoma multiforme (GBM) is a malignant brain tumor with poor prognosis and high morbidity due to its invasiveness. Hypoxia-driven motility (HM) and concentration-driven motility (CM) are two mechanisms of GBM invasion in the brain. The use of anti-angiogenic drugs has uncovered new progression patterns of GBM associated with significant differences in overall survival times. Here, we test the hypotheses that the types and rates of GBM motility predict its progression pattern and the patients' survival times. Methods: We applied a mathematical model of GBM growth and invasion in humans to simulate a clinical trial and study the effects of the rate and mechanism of motility on the patterns of progression and on survival times. Results: The motility phenotype appears to determine the progression pattern as well as the survival time of a patient treated by anti-angiogenesis. Highly-dispersive tumors are associated with the longest survival times (p , 0.001) and with progression by Expanding FLAIR. Moderately-Dispersive tumors are associated with short survival times and with progression by Expanding FLAIR + Necrosis. Tumors with HMare associated with the shortest survival times and with progression by Expanding Necrosis. The survival times of the latter are similar to non-responders. This investigation also uncovered the HM-CM principle: the aggressive HM-dependent phenotype surfaces only when the rate of CM is low in both untreated and bevacizumab-treated GBM. Conclusions: Finding that the motility phenotype is a fundamental property that controls progression and survival times, has biological, clinical and therapeutic implications.

7.2. Axis 2: Bio-physical modeling for personalized therapies

7.2.1. Electropermeabilization

Non-Linear Steady-State Electrical Current Modeling for the Electropermeabilization of Biological Tissue [8]
Team participants: Clair Poignard, Michael Leguebe
Other participants: Marie Breton, Lluis M. Mir (Vectorology and Anticancer Therapies), Francois Buret, Riccardo Scorretti, Damien Voyer, Laurent Krähenbühl (Ampère Laboratory (Lyon) participants), Ronan Perrussel (LAPLACE - Laboratoire Plasma et Conversion d'Energie, Toulouse)

We propose a non-linear steady-state model of irreversible electropermeabilization in a biological tissue. The non-linear problem is solved using a modified fixed point iteration. The unknown parameters are experimentally estimated from the observation of the necrosis on a potato tissue for different applied voltages. A variability study of the parameters involved in the model is performed.

A second-order Cartesian method for the simulation of electropermeabilization cell models [12]
Team participants: Clair Poignard, Michael Leguèbe
Other participant: Lizl Weynans (Memphis team, Inria)

In this work, we present a new finite differences method to simulate electropermeabilization models, like the model of Neu and Krassowska or the recent model of Kavian et al. These models are based on the evolution of the electric potential in a cell embedded in a conducting medium. The main feature lies in the transmission of the voltage potential across the cell membrane: the jump of the potential is proportional to the normal flux thanks to the well-known Kirchoff law. An adapted scheme is thus necessary to accurately simulate the voltage potential in the whole cell, notably at the membrane separating the cell from the outer medium. We present a second-order finite differences scheme in the spirit of the method introduced by Cisternino and Weynans for elliptic problems with immersed interfaces. This is a Cartesian grid method based on the accurate discretization of the fluxes at the interface, through the use of additional interface unknowns. The main novelty of our present work lies in the fact that the jump of the potential is proportional to the flux, and therefore is not explicitly known. The original use of interface unknowns makes it possible to discretize the transmission conditions with enough accuracy to obtain a second-order spatial convergence. We prove the second-order spatial convergence in the stationary linear one-dimensional case, and the first-order temporal convergence for the dynamical non-linear model in one dimension. We then perform numerical experiments in two dimensions that corroborate these results.

Cell membrane permeabilization by 12-ns electric pulses: Not a purely dielectric, but a charge-dependent phenomenon [15]
Team participants: Clair Poignard, Michael Leguèbe
Other participants: Aude Silve (KIT - Karlsruhe Institute of Technology), Isabelle Leray, Lluis M. Mir (Université Paris Sud)

Electric pulses of a few nanoseconds in duration can induce reversible permeabilization of cell membrane and cell death. Whether these effects are caused by ionic or purely dielectric phenomena is still discussed. We address this question by studying the impact of conductivity of the pulsing buffer on the effect of pulses of 12 ns and 3.2 MV/m on the DC-3F mammalian cell line. When pulses were applied in a high-conductivity medium (1.5 S/m), cells experienced both reversible electropermeabilization and cell death. On the contrary, no effect was observed in the low-conductivity medium (0.1 S/m). Possible artifacts due to differences in viscosity, temperature increase or electrochemical reactions were excluded. The influence of conductivity reported here suggests that charges still play a role, even for 12-ns pulses. All theoretical models agree with this experimental observation, since all suggest that only high-conductivity medium can induce a transmembrane voltage high enough to induce pore creation, in turn. However, most models fail to describe why pulse accumulation is experimentally required to observe biological effects. They mostly show no increase of permeabilization with accumulation of pulses. Currently, only one model properly describes pulse accumulation by modeling diffusion of the altered membrane regions.

7.2.2. Cell protrusion

Free boundary problem for cell protrusion formations: theoretical and numerical aspects [20]
Team participants: Olivier Gallinato, Clair Poignard
Other participants: Masahito Ohta (Tokyo University of Sciences), Takashi Suzuki (Osaka University)

In this work, we derive a free boundary problem for cell protrusion formation in which the cell membrane is precisely described thanks to a level-set function, whose motion is due to specific signalling pathways. The model consists in Laplace equation with Dirichlet condition inside the cell coupled to Laplace equation with Neumann condition in the outer domain. The motion of the interface is due the gradient of the inner quantity. We prove the well-posedness of our free boundary problem under a sign condition on the datum similarly to the Taylor criterion in water waves. We also propose an accurate numerical scheme to solve the problem and we exhibit the main biological features that can be accounted for by the model. Even though simplistic from the modeling point of view, we claim that this work provides the theoretical and numerical grounds for single cell migration modeling. In particular, specific chemical reactions that occurred at the cell membrane could be precisely described in forthcoming works.

7.3. Axis 3: Quantitative cancer modeling for biological and preclinical studies

7.3.1. Modelling of metastasis development

Computational Modelling of Metastasis Development in Renal Cell Carcinoma [2]
Team participants: Etienne Baratchart, Sébastien Benzekry, Thierry Colin, Olivier Saut
Other participants: Andreas Bikfalvi, Lindsay S. Cooley, Raphäel Pineau, Wilfried Souleyreau (LAMC - Laboratoire Angiogenèse et Micro-environnement des Cancers), Emeline J Ribot (RMSB - Résonance magnétique des systèmes biologiques)

To improve our understanding of the biology of the metastatic colonization process, we conducted a modelling study based on multi-modal data from an orthotopic murine experimental system of metastatic renal cell carcinoma. The standard theory of metastatic colonization usually assumes that secondary tumours, once established at a distant site, grow independently from each other and from the primary tumour. Using a mathematical model describing the metastatic population dynamics under this assumption, we challenged the theory against our data that included: 1) dynamics of primary tumour cells in the kidney and metastatic cells in the lungs, retrieved by green fluorescent protein tracking, and 2) magnetic resonance images (MRI) informing on the number and size of macroscopic lesions. While the model could fit the primary tumour and total metastatic burden, the predicted size distribution was not in agreement with the MRI observations. Moreover, the model was incompatible with the growth rates of individual metastatic tumours. To explain the observed metastatic patterns, we hypothesised that metastatic foci derived from one or a few cells could aggregate, resulting in a similar total mass but a smaller number of metastases. This was indeed observed in our data and led us to investigate the effect of spatial interactions on the dynamics of the global metastatic burden. We derived a novel mathematical model for spatial tumour growth, where the intra-tumour increase in pressure is responsible for the slowdown of the growth rate. The model could fit the growth of lung metastasis visualized by magnetic resonance imaging. As a non-trivial outcome from this analysis, the model predicted that the net growth of two neighbouring tumour lesions that enter in contact is considerably impaired (of $31\% \pm 1.5\%$, mean $\pm$ standard deviation), as compared to the growth of two independent tumours. Together, our results have implications for theories of metastatic development and suggest that global dynamics of metastasis development is dependent on spatial interactions between metastatic lesions.

Modeling spontaneous metastasis following surgery: an in vivo-in silico approach [6]
Team participant: Sebastien Benzekry
Other participants: Amanda Tracz, Michalis Mastri, Ryan Corbelli, Dominique Barbolosis, John Ebos (Buffalo University)

Rapid improvements in the detection and tracking of early-stage tumor progression aim to guide decisions regarding cancer treatments as well as predict metastatic recurrence in patients following surgery. Mathematical models may have the potential to further assist in estimating metastatic risk, particularly when paired with in vivo tumor data that faithfully represent all stages of disease progression. Herein we describe mathematical analysis that uses data from mouse models of spontaneous metastasis developing after surgical removal of orthotopically implanted primary tumors. Both presurgical (primary tumor) and postsurgical (metastatic) growth was quantified using bioluminescence and was then used to generate a mathematical formalism based on general laws of the disease (i.e. dissemination and growth). The model was able to fit and predict pre-/post-surgical data at the level of the individual as well as the population. Our approach also enabled retrospective analysis of clinical data describing the probability of metastatic relapse as a function of primary tumor size. In these data-based models, inter-individual variability was quantified by a key parameter of intrinsic metastatic potential. Critically, our analysis identified a highly nonlinear relationship between primary tumor size and postsurgical survival, suggesting possible threshold limits for the utility of tumor size as a predictor of metastatic recurrence. These findings represent a novel use of clinically relevant models to assess the impact of surgery on metastatic potential and may guide optimal timing of treatments in neoadjuvant (presurgical) and adjuvant (postsurgical) settings to maximize patient benefit.

Migration and orientation of endothelial cells on micropatterned polymers: A simple model based on classical mechanics [11]
Team participants: Thierry Colin, Clair Poignard, Olivier Saut
Other participants: Julie Joie, Marie-Christine Durrieu (IMB - Institut de Mathématiques de Bordeaux), Yifeng Lei (French Institute of Health and Medical Research, Paris)

Understanding the endothelial cell migration on micropatterned polymers, as well as the cell orientation is a critical issue in tissue engineering, since it is the preliminary step towards cell polarization and that possibly leads to the blood vessel formation. In this work, we derive a simple agent-based model to describe the migration and the orientation of endothelial cells seeded on bioactive micropatterned polymers. The aim of the modeling is to provide a simple model that corroborates quantitatively the experiments, without considering the complex phenomena inherent to cell migration. Our model is obtained thanks to a classical mechanics approach based on experimental observations. Even though its simplicity, it provides numerical results that are quantitatively in accordance with the experimental data, and thus our approach can be seen as a preliminary way towards a simple modeling of cell migration.

7.3.2. Tumor-host crosstalk

Host age is a systemic regulator of gene expression impacting cancer progression [3]
Team participant: Sebastien Benzekry
Other participants: Afshin Beheshti, Lili Ma, Philip Hahnfeldt, Lynn Hlatky (CCSB - Center of Cancer and Systems Biology), J. Tyson Mcdonald (University of Houston), Michael Peluso (Cancer Risk Factor Branch, Molecular Biology Laboratory)

Aging is the major determinant of cancer incidence, which, in turn, is likely dictated in large part by processes that influence the progression of early subclinical (occult) cancers. However, there is little understanding of how aging informs changes in aggregate host signaling that favor cancer progression. In this study, we provide direct evidence that aging can serve as an organizing axis to define cancer progression-modulating processes. As a model system to explore this concept, we employed adolescent (68 days), young adult (143 days), middle-aged (551 days), and old (736 days) C57BL/6 mice as syngeneic hosts for engraftment of Lewis lung cancer to identify signaling and functional processes varying with host age. Older hosts exhibited dysregulated angiogenesis, metabolism, and apoptosis, all of which are associated with cancer progression. TGFβ1, a central player in these systemic processes, was downregulated consistently in older hosts. Our findings directly supported the conclusion of a strong host age dependence in determining the host tumor control dynamic. Furthermore, our results offer initial mechanism-based insights into how aging modulates tumor progression in ways that may be actionable for therapy or prevention.

Capturing the Driving Role of Tumor-Host Crosstalk in a Dynamical Model of Tumor Growth [4]
Team participant: Sebastien Benzekry
Other participants: Afshin Beheshti, Philip Hahnfeldt, Lynn Hlatky (CCSB - Center of Cancer and Systems Biology)

In 1999, Hahnfeldt et al. proposed a mathematical model for tumor growth as dictated by reciprocal communications between tumor and its associated vasculature, introducing the idea that a tumor is supported by a dynamic, rather than a static, carrying capacity. In this original work, the carrying capacity was equated with the variable tumor vascular support resulting from the net effect of tumor-derived angiogenesis stimulators and inhibitors. This dynamic carrying capacity model was further abstracted and developed in our recent publication to depict the more general situation where there is an interaction between the tumor and its supportive host tissue; in that case, as a function of host aging. This allowed us to predict a range of host changes that may be occurring with age that impact tumor dynamics. More generally, the basic formalism described here can be (and has been), extended to the therapeutic context using additional optimization criteria. The model depends on three parameters: one for the tumor cell proliferation kinetics, one for the stimulation of the stromal support, and one for its inhibition, as well as two initial conditions. We describe here the numerical method to estimate these parameters from longitudinal tumor volume measurements.

7.3.3. Metronomic oncology

Metronomic Reloaded: Theoretical Models Bringing Chemotherapy into the Era of Precision Medicine [5]
Team participant: Sebastien Benzekry
Other participants: Eddy Pasquier, Dominique Barbolosi, Joseph Ciccolini, Nicolas André (CRO2 - Centre de recherches en oncologie biologique et oncopharmacologie), Bruno Lacarelle (Clinical Pharmacokinetics), Fabrice Barlési (Service d'Oncologie Multidisciplinaire et d'Innovations Thérapeutiques)

Oncology has benefited from an increasingly growing number of groundbreaking innovations over the last decade. Targeted therapies, biotherapies, and the most recent immunotherapies all contribute to increase the number of therapeutic options for cancer patients. Consequently, substantial improvements in clinical outcomes for some disease with dismal prognosis such as lung carcinoma or melanoma have been achieved. Of note, the latest innovations in targeted therapies or biotherapies do not preclude the use of standard cytotoxic agents, mostly used in combination. Importantly, and despite the rise of bioguided (a.k.a. precision) medicine, the administration of chemotherapeutic agents still relies on the maximum tolerated drug (MTD) paradigm, a concept inherited from theories conceptualized nearly half a century ago. Alternative dosing schedules such as metronomic regimens, based upon the repeated and regular administration of low doses of chemotherapeutic drugs, have emerged as possible strategies to improve response rates while reducing toxicities. The recent changes in paradigm in the way we theorize cancer biology and evolution, metastatic spreading and tumor ecology, alongside the recent advances in the field of immunotherapy, have considerably strengthened the interest for metronomic approaches. This work aims at reviewing the recent evolutions in the field of theoretical biology of cancer and computational oncology, with a focus on the consequences these changes have on the way we administer chemotherapy. In particular, a step towards developing adaptive dosing should help to further optimize the efficacy of metronomic therapy. There is a rising trend to establish personalized medicine in oncology. Developing extensive bio-guided strategies for decision-making in the choice of drugs to be administered is now a common practice at the bedside. Similarly, developing extensive model-guided strategies for decision-making in refining dosing and scheduling should be undertaken to achieve precision medicine in oncology.

7.3.4. Protein-protein interaction networks

Design principles for cancer therapy guided by changes in complexity of protein-protein interaction networks [7]
Team participant: Sebastien Benzekry
Other participants: Jack A Tuszynski (Alberta University), Edward Rietman, Giannoula Lakka Klement (Newman-Lakka Institute)

The ever-increasing expanse of online bioinformatics data is enabling new ways to, not only explore the visualization of these data, but also to apply novel mathematical methods to extract meaningful information for clinically relevant analysis of pathways and treatment decisions. One of the methods used for computing topological characteristics of a space at different spatial resolutions is persistent homology. This concept can also be applied to network theory, and more specifically to protein-protein interaction networks, where the number of rings in an individual cancer network represents a measure of complexity. Results: We observed a linear correlation of R = -0.55 between persistent homology and 5-year survival of patients with a variety of cancers. This relationship was used to predict the proteins within a protein-protein interaction network with the most impact on cancer progression. By re-computing the persistent homology after computationally removing an individual node (protein) from the protein-protein interaction network, we were able to evaluate whether such an inhibition would lead to improvement in patient survival. The power of this approach lied in its ability to identify the effects of inhibition of multiple proteins and in the ability to expose whether the effect of a single inhibition may be amplified by inhibition of other proteins. More importantly, we illustrate specific examples of persistent homology calculations, which correctly predict the survival benefit observed effects in clinical trials using inhibitors of the identified molecular target. Conclusions: We propose that computational approaches such as persistent homology may be used in the future for selection of molecular therapies in clinic. The technique uses a mathematical algorithm to evaluate the node (protein) whose inhibition has the highest potential to reduce network complexity. The greater the drop in persistent homology, the greater reduction in network complexity, and thus a larger potential for survival benefit. We hope that the use of advanced mathematics in medicine will provide timely information about the best drug combination for patients, and avoid the expense associated with an unsuccessful clinical trial, where drug(s) did not show a survival benefit.

7.4. Other new results

Superconvergent Cartesian Methods for Poisson type Equations in 2D–domains [21]
Team participants: Olivier Gallinato, Clair Poignard

In this work, we present three superconvergent Finite Difference methods on Cartesian grids for Poisson type equations with Dirichlet, Neumann or Robin conditions. Our methods are based on finite differences and high-order discretizations of the Laplace operator, to reach the superconvergence properties, in the sense that the first-order (and possibly the second-order) derivatives of the numerical solution are computed at the same order as the solution itself. We exhibit the numerical conditions that have to be fulfilled by the schemes to get such superconvergences and extensively illustrate our purpose by numerical simulations. We conclude by applying our method to a free boundary problem for cell protrusion formation recently proposed by the authors and colleagues. Note that quasistatic Stefan-like problem can be accurately solved by our methods.

Adaptive radiotherapy in routine: The radiation oncologist's point of view [14]
Team participant: Olivier Saut
Other participants: Bénédicte Henriques de Figueiredo, Adeline Petit, Paul Sargos, Guy Kantor, Claudia Pouypoudat, Christina Zacharatou, Mikael Antoine (Institut Bergonié, radiology department)

Adaptive radiotherapy is defined as all processes leading to the modification of a treatment plan on the basis of patient-specific variations observed during the course of a treatment. This concept is currently of particular relevance due to the development of onboard volumetric imaging systems, which allow for daily viewing of variations in both tumour and organs at risk in terms of position, shape or volume. However, its application in routine clinical practice is limited due to the demanding nature of the processes involved (re-delineation and replanning) and increased dependence on available human resources. Even if "online" strategies, based on deformable image registration (DIR) algorithms, could lead to a reduction in both work and calculation time, for the moment their use is limited to the research field due to uncertainties surrounding the validity of results gathered. Other strategies without DIR can be used as "offline" or "hybrid offline-online" strategies that seem to offer a compromise between time consumption and therapeutic gain for the patient.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. BIS-Japan Idex Université de Bordeaux

- Project acronym - BIS-Japan Idex
- Duration - 2015
- Coordinator - C. Poignard
- Abstract - The project proposes to gather the skills of the Japanese partner on cell migration modeling, molecular pathways in cancer and theoretical aspects of partial differential equations with the experience of the Bordeaux team MONC (Modeling in ONCology), which involves researchers from University of Bordeaux, IPB, CNRS and Inria, in cancer modeling. More particularly, the team MONC is invoved in the derivation of tumor growth models and of accurate finite volume numerical schemes to solve the partial differential equations in order to provide a deep multiscale knowledge of the tumor development at the cell scale. The overall aim of this project is to propose a comprehensive study of the metastatic processes at the cell scale, by highlithing the molecular pathways and the main chemical processes involved in cancer cell migration and division.

8.2. National Initiatives

8.2.1. Plan cancer DYNAMO

- Project acronym - Plan Cancer DYNAMO
- Partners - Lab Ampère-Lyon, Lab. Vectorologie et thérapies anticancéreuses- Villejuif and Equipe Inria MONC-Talence
- Duration - from sep. 2015 to sep 2018
- Coordinator - R. Scorretti, Lab. Ampère / Local coordinator - C. Poignard
- Team participants - C. Poignard
- Abstract - Electroporation (EPN) is a method which allows either killing the cells in a target region (tumors) by a nonthermal mechanism (irreversible EPN, or IRE) or allowing non permeant molecules (drugs, DNA) to penetrate the cells. EPN opens new perspectives for cancer treatment (electrochemotherapy, or ECT) and for gene therapy. In spite of its advantages, applications of EPN are still limited because of the scarcity of quantitative data concerning the reaction of tissues following electric pulses. Moreover, due to the lack of reliable tools for treatment planning, most clinical applications deal with superficial tumors in patients treated in more than 130 EU cancer centers using validated standard operating procedures. However the more difficult treatment of deep-seated tumors is still at the stage of academic research and a crucial challenge for forthcoming cancer therapies. This project aims at investigating how EPN can be effectively modeled, from the scale of cell up to the scale of tissue, and how molecular uptake holds and is enhanced by electric field delivery. To develop a dynamic model of tissue EPN, two approaches will be followed: one derived from the macroscopic scale (ad hoc tissue model) and the other from the microscopic scale using homogenization techniques. In order to enable accurate elaboration of the models, experiments will be carried out on raw potato tubers, HEK-293 (Human Embryonic Kidney) cell aggregates and on mice liver and muscle. The transport of molecules through the tissue, which is also a bottleneck, will be overcome thanks to a porous medium approach, which will provide qualitative and quantitative behaviour of the transport in the tissue.

8.2.2. Plan Cancer METASIS

- Project acronym - Plan Cancer METASIS

- Partner - Laboratory of Biology, Bordeaux University
- Duration - from 2013 to 2015
- Coordinator - A. Bikfalvi
- Team participants - S. Benzekry, Th. Colin, C. Poignard, O. Saut
- Title - Modeling the Interaction of the (Metastasis) Vascular/Tumor Niche Using a Systems Biology Approach

8.2.3. Plan Cancer MIMOSA

- Project acronym - Plan Cancer MIMOSA (Physique, Mathématiques et Sciences de l'ingénieur appliqués au Cancer)
- Partner - Laboratory of Biology, Bordeaux University
- Duration - from 2014 to 2017
- Coordinator - Th. Colin
- Team participants - S. Benzekry, Th. Colin, C. Poignard, O. Saut
- Title - Mathematical modeling for exploration of the impact of mechanical constraints on tumor growth

*8.2.4. A*Midex MARS*

- Project acronym - A*Midex MARS
- Partner - Service d'Oncologie Multidisciplinaire & Innovations Thérapeutiques, Hopitaux de Marseille
- Duration - from 2014 to 2016
- Coordinator - F. Barlesi
- Team participant - S. Benzekry
- Title - Modeling Anticancer Research & Simulation

8.2.5. PEPS CNRS

- Project acronym - PEPS Electroporation
- Partners - Lab Ampère-Lyon and Equipe Inria MONC-Talence
- Duration - June-Dec 2015
- Leader - D. Voyer, Lab. Ampère / Local leader - C. Poignard

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Informal International Partners

LIA EBAM

- Title - LIA EBAM
- Partners - University of Ljubljana, IPBS, Institut Gustave Roussy, XLim, Institute of Oncologie, Ljubljana and Equipe Inria MONC-Talence
- Duration - 2015-2019 (renewal)
- Leader - L.M. Mir / Local leader - C. Poignard

- The main aim of the LIA EBAM is to use an interdisciplinary approach, integrating biology, chemistry, physics, biophysics, mathematics, computational modelling and engineering, through the expertise of its members in order to 1- Enhance our understanding on the mechanisms of classical electropermeabilization and of the new nanopermeabilization (electropermea-bilization using nanosecond electric pulses), as well as on the mechanisms of transmembrane transport of molecules into electroporated cells and tissues on a microscopic and macroscopic scale. 2- Contribute to a better and safer implementation of the electropermeabilization-based applications, and to the development of new applications. 3- Develop new devices and new equipment for the nanopermeabilisation at cell and tissue levels. 4- Develop new approaches like treatment planning in existing applications, such as antitumor electrochemotherapy and in vivo gene transfer for therapeutic purposes. 5- Disseminate the knowledge and the applications in the scientific community and in the society, through publications, a one-week course (already implemented) co-directed by the LEA directors, internal and external training, and through other means that the LEA will develop and/or will apply for (to the EC programs for example). Partners participating in the project possess complementary knowledge and skills, which only if brought together will allow for successful accomplishments of the above objectives.

JSPS Core-to-Core Program on Establishing International Research Network of Mathematical Oncology

- Title - JSPS Core-to-Core Program on Establishing International Research Network of Mathematical Oncology
- Partners - Osaka University, Vanderbilt University, Dundee university and Equipe Inria MONC-Talence
- Duration - 2015-2019 (renewal)
- Leader - T. Suzuki, Osaka University / Local leader - C. Poignard
- Establishing International Research Network of Mathematical Oncology

Collaboration with John Ebos, Roswell Park Cancer Institute, Buffalo, NY, USA. Quantification of metastatic potential and differential effect of anti-angiogenenic therapies on primary tumor and metastasis, in a preclinical setting.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

- Tadeja Forjanic (PhD Student Ljubljana), 2 weeks in jan. 2015. *Tumor growth modeling after electroporation* (Local supervisor: C. Poignard)
- Ariff Admon (PhD Student Osaka University), 1month June 2015. *Free boundary problem for invadopodia*. (Local supervisor: C. Poignard)

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. Chair of conference program committees

- S. Benzekry: member of the scientific committee of the “Journées de modélisation BioMathématique de Besançon" (http://mb2.univ-fcomte.fr/).

9.1.2. Journal

9.1.2.1. Member of the editorial boards

- Th. Colin - SIAM News, Mathematical Biosciences and Engineering, SMAI Mathématiques et Applications

9.1.2.2. Reviewer - Reviewing activities

- S. Benzekry - biomathematical modeling journals: Journal of Theoretical Biology, Mathematical Biosciences, Bulletin of Mathematical Biology, Theoretical Biology and Medical Modeling, Mathematical Biosciences and Engineering, Journal of Biological Informatics, Journal of Biological Systems, ESAIM:Proc, Mathematics and Computers in Simulation; and medical/biological journals about cancer: Clinical Pharmacokinetics, BMC Cancer
- C. Poignard - SIAM Journal on Mathematical Analysis, IEEE Trans on Mag, J. Math. Biology, J. Theoretical Biology
- O. Saut - IEEE Trans. Med. Imaging, PLOS Computational Biology, Medical Image Analysis, Nature Comm.

9.1.3. Invited talks

- Th. Colin - Congrès de la société Francophone de Biologie Théorique (Poitiers, June 2015), Present challenges of mathematics in oncology and biology of cancer (CIRM, Dec 2015).

9.1.4. Leadership within the scientific community

- O. Saut is the head of the CNRS GDR 3471 Metice (http://metice.math.cnrs.fr).

9.1.5. Scientific expertise

- O. Saut is an export for the French Ministry of Research (PHC and EGIDE programs)

9.1.6. Research administration

- C. Poignard is elected member of the Inria evaluation committee.
- O. Saut is a member of the Steering Committee of Labex TRAIL (http://trail.labex.u-bordeaux.fr).

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence : T. Michel, *Travaux encadrés de recherche*, 41h, L3, ENSEIRB-Matmeca, France

Licence : T. Michel, *TD Probabilités/Statistiques*, 32h, L3, ENSEIRB-MATMECA, France

Licence : T. Michel, *Harmonisation Maths (cours-TD Séries, Intégrales)*, L3, ENSEIRB-MATMECA, France

Licence : C. Poignard, *TD Équations Différentielles Ordinaires*, 30h, L3, ENSEIRB-Matmeca, France

Licence : E. Baratchart, *Initiation au calcul scientifique*, 64h, L3, ENSCBP, France

Licence : O. Gallinato, *Méthodes numériques linéaires*, 64h, L3, Université de Bordeaux, France

Licence : G. Lefebvre, *Mathématiques pour les sciences de l'environnement*, 48h, L1, Université de Bordeaux, France

Licence : G. Lefebvre, *Mathématiques et représentation des phénomènes physiques*, 35h, L1, Université de Bordeaux, France

Licence : G. Lefebvre, *Fondamentaux pour les mathématiques et l'informatique*, 35h, L1, Université de Bordeaux, France

Licence : S. Benzekry, *Equations Différentielles*, 20h, L3, ENSEIRB-MATMECA, France

Licence : A. Collin, *TD Equations Différentielles*, 20h, L3, ENSEIRB-MATMECA, France

Master : C. Poignard, *Modélisation électromagnétique des cellules*, 36h, M2, Université Bordeaux, France

Master : C. Poignard, *CM-TD Analyse Numérique*, 50h, L3, Formation SC - ENSCPB, France

Master : O. Saut, *TD Analyse des Equations aux dérivées partielles*, 30h, M1, ENSEIRB-Matmeca, France

Master : A. Collin, *TD Analyse des Equations aux dérivées partielles*, 30h, M1, ENSEIRB-MATMECA, France

Master : O. Saut, *TP C++*, 44h, M1, ENSEIRB-Matmeca, France

Master : A. Collin, *TP C++*, 44h, M1, ENSEIRB-MATMECA, France

DAEU-B : P. Berment, *Mathématiques pour le DAEU-B*, 64h, DAEU-B, Université de Bordeaux, France

9.2.2. Supervision

PhD : J. Jouganous, Lung metastases growth modeling and simulation, Université de Bordeaux, 23rd Sep 2015

PhD : G. Lefebvre, Modeling and analysis of tumor heterogeneity during treatments resistance: case of GIST liver metastases, Université de Bordeaux, 3rd Dec 2015

PhD in progress : P. Berment, Mathematical modelling evaluating radiotherapy outcome for colorectal tumor with Pet Scan, Oct 2013, Thierry Colin and Olivier Saut

PhD in progress : E. Baratchart, Quantitative study of the dynamics and spatial aspects of metastatic development using mathematical models, Dec 2012, S. Benzekry, Th. Colin and O. Saut

PhD in progress : M. Deville, Modeling of electroporation and gene transfection across tissue. Theoretical and numerical aspects., Sep 2014, C. Poignard and R. Natalini (IAC, CNR Roma)

PhD in progress : O. Gallinato, Invasive process modeling of the tumor metastatic cells, Nov 2013, C. Poignard and T. Suzuki (Osaka University)

PhD in progress : T. Kritter, Primary tumors modelling with a view to the gliomas and adenocarcinomas study, Sep 2015, C. Poignard and O. Saut

PhD in progress : T. Michel, Analysis of mathematical growth tumor models, Sep 2013, C. Poignard and Th. Colin

PhD in progress : A. Perreti, Anti-angiogenic traitements modeling using medical imaging, Oct 2014, Th. Colin and O. Saut

9.2.3. Juries

- O. Saut was a reviewer of the PhD of Baptiste Bedessem "Influence des contraintes environnementales (mécaniques, stérique, hypoxique, acidité) sur la durée du cycle cellulaire dans un contexte tumoral Approche par la modélisation computationnelle et par l'expérimentation", Univ. Grenoble, Oct 2015.
- O. Saut was a reviewer of the PhD of Joris Costes "Développement de méthodes de résolution d'équations aux dérivées partielles : du schéma numérique à la simulation d'une installation industrielle", ENS Cachan, June 2015.

9.3. Popularization

- C. Poignard gave a lecture at IREM "Des décharges électriques contre le cancer" (April 2015)
- O. Saut is a regular speaker at Entretien de l'Excellence (http://www.lesentretiens.org)
- O. Gallinato gave a lecture at "la nuit des chercheurs" (Sep 2015)
- P. Berment is participating at a "Math en jean" project with the "collège Chambéry" of Villenave d'Ornon since December 2015
- A. Perreti and C. Perier represented Inria to the Aquitec forum (Jan 2015)

- S. Benzekry gave an interview to "radio campus" in June 2015 (http://www.c-yourmag.net/article/2015-06-03/il-modelise-levolution-des-tumeurs-avec-les-mathematiques-16763)

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] J. JOUGANOUS. *Lung metastases growth modeling and simulation* , Université de Bordeaux, September 2015, https://hal.inria.fr/tel-01245553

Articles in International Peer-Reviewed Journals

[2] E. BARATCHART, S. BENZEKRY, A. BIKFALVI, T. COLIN, L. S. COOLEY, R. PINEAU, E. J. RIBOT, O. SAUT, W. SOULEYREAU. *Computational Modelling of Metastasis Development in Renal Cell Carcinoma*, in "PLoS Computational Biology", November 2015, vol. 11, n^{o} 11 [*DOI :* 10.1371/JOURNAL.PCBI.1004626], https://hal.inria.fr/hal-01164834

[3] A. BEHESHTI, S. BENZEKRY, J. T. MCDONALD, L. MA, M. PELUSO, P. HAHNFELDT, L. HLATKY. *Host Age Is a Systemic Regulator of Gene Expression Impacting Cancer Progression*, in "Cancer Research", March 2015, vol. 75, n^{o} 6, 10 p. [*DOI :* 10.1158/0008-5472.CAN-14-1053], https://hal.inria.fr/hal-01132048

[4] S. BENZEKRY, A. BEHESHTI, P. HAHNFELDT, L. HLATKY. *Capturing the Driving Role of Tumor-Host Crosstalk in a Dynamical Model of Tumor Growth*, in "bio-protocol", November 2015, vol. 5, n^{o} 21, https://hal.inria.fr/hal-01222068

[5] S. BENZEKRY, E. PASQUIER, D. BARBOLOSI, B. LACARELLE, F. BARLÉSI, N. ANDRÉ, J. CICCOLINI. *Metronomic Reloaded: Theoretical Models Bringing Chemotherapy into the Era of Precision Medicine*, in "Seminars in Cancer Biology", 2015, 23 p. [*DOI :* 10.1016/J.SEMCANCER.2015.09.002], https://hal.inria.fr/hal-01195547

[6] S. BENZEKRY, A. TRACZ, M. MASTRI, R. CORBELLI, D. BARBOLOSI, J. M. EBOS. *Modeling spontaneous metastasis following surgery: an in vivo-in silico approach*, in "Cancer Research", October 2015 [*DOI :* 10.1158/0008-5472.CAN-15-1389], https://hal.inria.fr/hal-01222046

[7] S. BENZEKRY, J. A. TUSZYNSKI, E. A. RIETMAN, G. LAKKA KLEMENT. *Design principles for cancer therapy guided by changes in complexity of protein-protein interaction networks*, in "Biology Direct", 2015, 14 p. [*DOI :* 10.1186/S13062-015-0058-5], https://hal.inria.fr/hal-01158313

[8] M. BRETON, F. BURET, L. KRÄHENBÜHL, M. LEGUÈBE, L. M. MIR, R. PERRUSSEL, C. POIGNARD, R. SCORRETTI, D. VOYER. *Non-Linear Steady-State Electrical Current Modeling for the Electropermeabilization of Biological Tissue*, in "IEEE Transactions on Magnetics", March 2015, vol. 51, n^{o} 3, 7402104 p. [*DOI :* 10.1109/TMAG.2014.2351836], https://hal.archives-ouvertes.fr/hal-01153095

[9] J. CICCOLINI, S. BENZEKRY, B. LACARELLE, D. BARBOLOSI, F. BARLÉSI. *Improving efficacy of the combination between antiangiogenic and chemotherapy: Time for mathematical modeling support*, in "Proceedings of the National Academy of Sciences U S A", 2015, 1 p. [*DOI :* 10.1073/PNAS.1506689112], https://hal.inria.fr/hal-01168635

[10] T. COLIN, F. CORNELIS, J. JOUGANOUS, J. PALUSSIÈRE, O. SAUT. *Patient specific simulation of tumor growth, response to the treatment and relapse of a lung metastasis: a clinical case*, in "Journal of Computational Surgery", 2015, 18 p. [*DOI :* 10.1186/S40244-014-0014-1], https://hal.inria.fr/hal-01102586

[11] J. JOIE, Y. LEI, M.-C. DURRIEU, T. COLIN, C. POIGNARD, O. SAUT. *Migration and orientation of endothelial cells on micropatterned polymers: A simple model based on classical mechanics*, in "Discrete and Continuous Dynamical Systems - Series B", June 2015, vol. 20, n^{O} 4 [*DOI :* 10.3934/DCDSB.2015.20.1059], https://hal.inria.fr/hal-01203488

[12] M. LEGUÈBE, C. POIGNARD, L. WEYNANS. *A second-order Cartesian method for the simulation of electropermeabilization cell models*, in "Journal of Computational Physics", July 2015, vol. 292, 26 p. [*DOI :* 10.1016/J.JCP.2015.03.028], https://hal.inria.fr/hal-01158377

[13] O. SAUT, T. COLIN, H. FATHALLAH, E. SCRIBNER. *TMOD-03 * Motility controls growth and progression patterns of glioblastoma multiforme*, in "Neuro-Oncology", November 2015 [*DOI :* 10.1093/NEUONC/NOV237.03], https://hal.inria.fr/hal-01243554

[14] O. SAUT, B. HENRIQUES DE FIGUEIREDO, A. PETIT, P. SARGOS, G. KANTOR, C. POUYPOUDAT, C. ZACHARATOU, M. ANTOINE. *Adaptive radiotherapy in routine: The radiation oncologist's point of view*, in "Cancer Radiothérapie", October 2015, vol. 19, n^{O} 6 [*DOI :* 10.1016/J.CANRAD.2015.06.016], https://hal.inria.fr/hal-01243562

[15] A. SILVE, I. LERAY, M. LEGUÈBE, C. POIGNARD, L. M. MIR. *Cell membrane permeabilization by 12-ns electric pulses: Not a purely dielectric, but a charge-dependent phenomenon*, in "Bioelectrochemistry", December 2015, vol. 106, Part B, pp. 369–378 [*DOI :* 10.1016/J.BIOELECHEM.2015.06.002], https://hal.inria.fr/hal-01203284

International Conferences with Proceedings

[16] L. KRÄHENBÜHL, P. DULAR, V. PÉRON, R. PERRUSSEL, R. V. SABARIEGO, C. POIGNARD. *Efficient delta-parametrization of 2D Surface-Impedance solutions*, in "Compumag", Montréal, Canada, Proceedings of the 20th International Conference on the Computation of Electromagnetic Fields, June 2015, 442 p. , https://hal.archives-ouvertes.fr/hal-01174983

National Conferences with Proceedings

[17] L. KRÄHENBÜHL, P. DULAR, V. PÉRON, R. PERRUSSEL, R. SABARIEGO, C. POIGNARD. *Impédances de surface en 2D : comparaison de méthodes de paramétrisation en δ*, in "Numélec", Nantes, France, M. FÉLIACHI (editor), Actes de la 8ème Conférence Européenne sur les Méthodes Numériques en Electromagnétisme, Université de Nantes - IREENA, June 2015, https://hal.archives-ouvertes.fr/hal-01199546

Conferences without Proceedings

[18] S. BENZEKRY, J. M. EBOS. *On the growth and dissemination laws in a mathematical model of metastatic growth*, in "Workshop on Multiscale and Hybrid Modelling in Cell and Cell Population Biology", Paris, France, March 2015 [*DOI :* 10.1051/ITMCONF/20150500007], https://hal.inria.fr/hal-01222088

Research Reports

[19] T. COLIN, T. MICHEL, C. POIGNARD. *Mathematical study and asymptotic analysis of a model for tumour drug resistance*, Inria Bordeaux Sud-Ouest, October 2015, n° RR-8784, 23 p. , https://hal.inria.fr/hal-01211770

[20] O. GALLINATO, M. OHTA, C. POIGNARD, T. SUZUKI. *Free boundary problem for cell protrusion formations: theoretical and numerical aspects*, Inria ; Institut de Mathématiques de Bordeaux ; Université de Bordeaux ; Tokyo University of Science ; Osaka University, November 2015, n° RR-8810, 36 p. , https://hal.inria.fr/hal-01228013

[21] O. GALLINATO, C. POIGNARD. *Superconvergent Cartesian Methods for Poisson type Equations in 2D–domains*, Inria ; Institut de Mathématiques de Bordeaux ; Université de Bordeaux, November 2015, n° RR-8809, 33 p. , https://hal.inria.fr/hal-01228046

[22] L. KRÄHENBÜHL, V. PÉRON, R. PERRUSSEL, C. POIGNARD. *On the asymptotic expansion of the magnetic potential in eddy current problem: a practical use of asymptotics for numerical purposes*, Inria Bordeaux ; Inria, June 2015, n° RR-8749, https://hal.inria.fr/hal-01174009

Other Publications

[23] M. PROD'HOMME. *Etude de sensibilité de modèles de croissance tumorale sous contrôle angiogénique*, Inria Bordeaux Sud-Ouest, September 2015, https://hal.inria.fr/hal-01215779