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Project-Team MONC

Mathematical modeling for Oncology

IN COLLABORATION WITH: Institut de Mathématiques de Bordeaux (IMB)

RESEARCH CENTER
Bordeaux - Sud-Ouest

THEME
Modeling and Control for Life Sciences

Table of contents

Project-Team MONC

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Keywords:

Computer Science and Digital Science:

A6.1. - Mathematical Modeling
A6.1.1. - Continuous Modeling (PDE, ODE)
A6.1.4. - Multiscale modeling
A6.2.1. - Numerical analysis of PDE and ODE
A6.2.4. - Statistical methods
A6.2.6. - Optimization
A6.2.7. - High performance computing
A6.3.1. - Inverse problems
A6.3.2. - Data assimilation
A6.3.3. - Data processing
A6.3.4. - Model reduction

Other Research Topics and Application Domains:

B1.1.9. - Bioinformatics
B1.1.10. - Mathematical biology
B1.1.11. - Systems biology
B2.2.3. - Cancer
B2.4.2. - Drug resistance
B2.6.1. - Brain imaging
B2.6.3. - Biological Imaging

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2. Overall Objectives

2.1. Objectives

The MONC project-team aims at developing new mathematical models built on partial differential equations and statistical methods and based on precise biological and medical knowledge. 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 through quantitative numerical tools. We develop patient-specific approaches (mainly based on medical images) as well as population-type approaches in order to take advantage of large 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, recently, 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 techniques 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 or scales: physiological, molecular and cellular.

In the meantime, the understanding of the biological mechanisms of tumor growth, including the influence of the micro-environment, has greatly increased and medical doctors now have access to 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 in the clinical imaging routine like CT scans, MRIs and PET scans. We therefore want to offer 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 evolution of the pathology at subsequent times and the response to therapies. More precisely, our goal is to help clinicians answer the following questions thanks to our numerical tools:

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 accuracy and efficacy 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. The main purpose of our project is to create new mathematical models and new paradigms for data assimilation that are adapted to the biological nature of the disease and to the amount of multi-modal data available.

2.2. General strategy

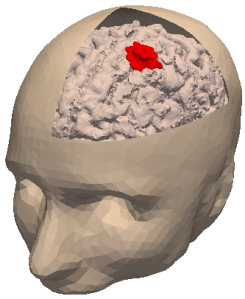

Figure 1. 3D numerical simulation of a meningioma. The tumor is shown in red.

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

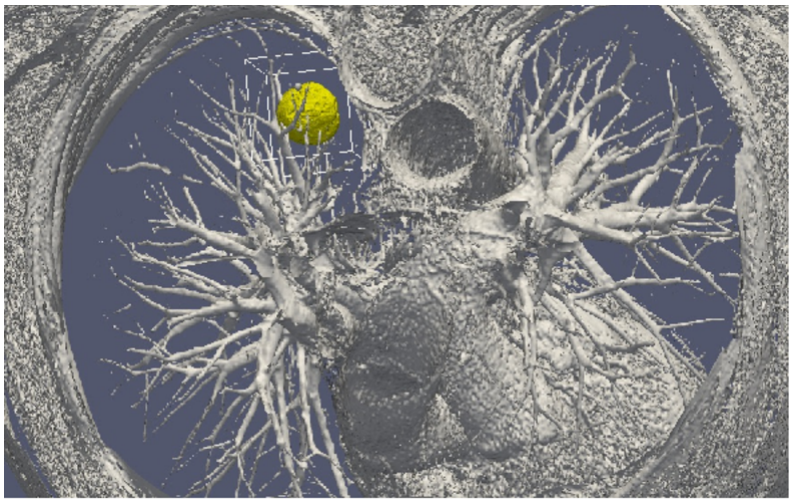

Figure 2. 3D numerical simulation of a lung tumor. The tumor is shown in yellow.

are targeted by new drugs. We emphasize that for this purpose, close interactions with biologists are crucial. Lots of works devoted to modeling at the cellular level are available in the literature. However, in order to be able to use these models in a clinical context, the tumor is also to be described at the tissue level. The *in vitro* mechanical characterization of tumor tissues has been widely studied. Yet 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 evolution of the disease. Data may also be obtained from analyses of blood samples or biopsies. A close collaboration with clinicians is required for selecting the specific cases to focus on, the understanding of the key points and data, the classification of the grades of the tumors, the understanding of the treatment,...In the preclinical context, data may for instance 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.
  - *Data processing:* Besides selection of representative cases by our collaborators, most of the time, data has to be processed before being used in our models. We develop novel methods for semi-automatic segmentations (they are implemented in SegmentIt), non-rigid registration and extraction of image texture information.
- Stage 3: *Adaptation of the model to data.* The model has to be adapted to data: it is useless to have a model taking many biological features of the disease into account if it cannot be reliably parameterized with available data. For example, very detailed descriptions of the angiogenesis process found in the literature cannot be used, as they have too much parameters to determine for the information available. 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: 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.* Because of data complexity - for example multimodal, longitudinal medical imaging - 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.
  - *Personalized models:* Currently, most of the inverse problems developed in the team are solved using a gradient method coupled with some MCMC type algorithm. We are now trying to use more efficient methods as Kalman type filters or so-called Luenberger filter (nudging). Using sequential methods could also simplify 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.
  - *Statistical learning:* In some clinical cases, there is no longitudinal data available to build a mathematical model describing the evolution of the disease. In these cases (*e.g.* in our collaboration with Humanitas Research Hospital), we use machine learning techniques to correlate clinical and imaging features with clinical outcome of patients (radiomics). When longitudinal data and a sufficient number of patients are available, we combine this approach and mathematical modeling by adding the personalized model parameters for each patient as features in the statistical algorithm. Our goal is then to have a better description of the evolution of the disease over time (as compared to only taking temporal variations of features into account). We also plan to use statistical algorithms to build reduced-order models, more efficient to run or calibrate than the original models.

– *Data assimilation of gene expression.* "Omics" data become more and more important in oncology and we aim at developing our models using this information as well. For example, in our work on GIST, we have taken the effect of a Ckit mutation on resistance to treatment into account. 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 and prediction*. 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.

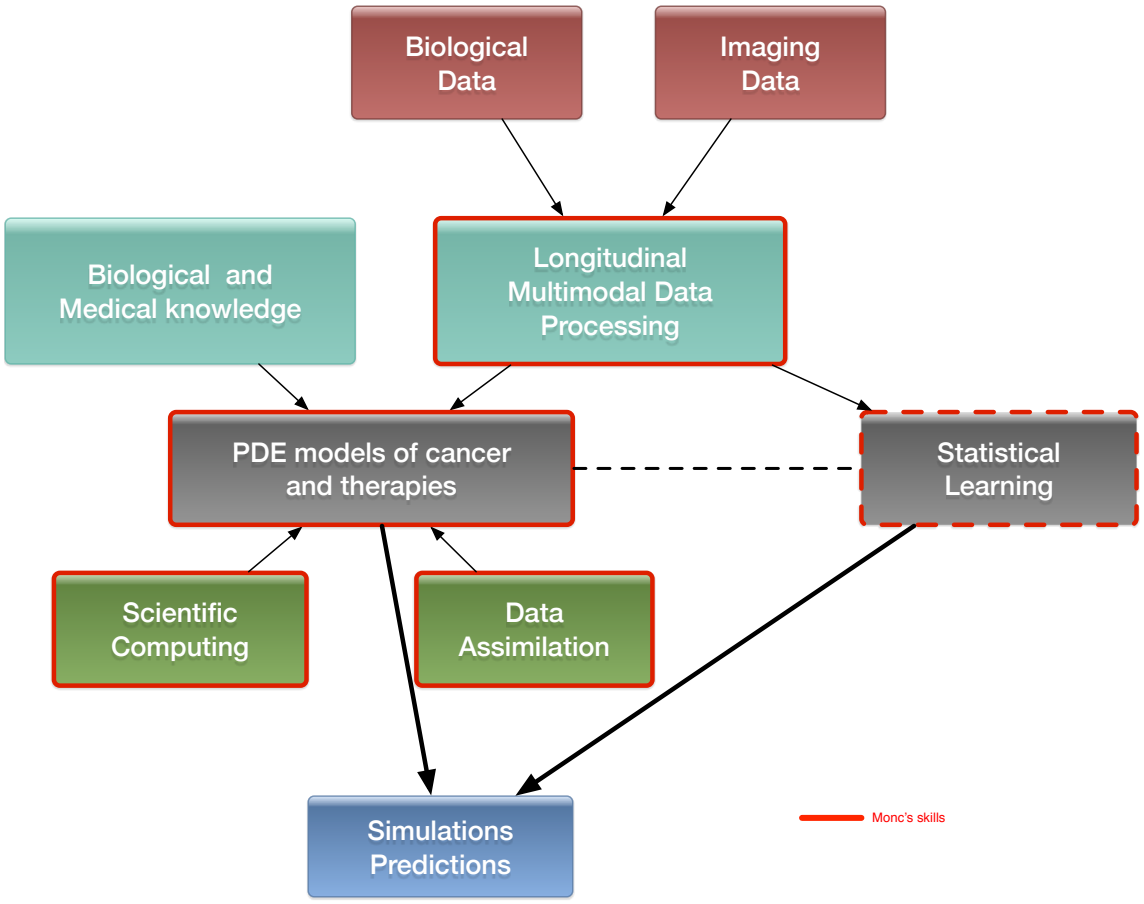

Figure 3. General strategy of the team to build meaningful models in oncology.

3. Research Program

3.1. Introduction

We are working in the context of data-driven medicine against cancer. We aim at coupling mathematical models with data to address relevant challenges for biologists and clinicians in order for instance to improve our understanding in cancer biology and pharmacology, assist the development of novel therapeutic approaches or develop personalized decision-helping tools for monitoring the disease and evaluating therapies.

More precisely, our research on mathematical oncology is three-fold:

- Axis 1: Tumor modeling for patient-specific simulations: *Clinical monitoring. Numerical markers from imaging data. Radiomics*.
- Axis 2: Bio-physical modeling for personalized therapies: *Electroporation from cells to tissue. Radiotherapy*.
- Axis 3: Quantitative cancer modeling for biological and preclinical studies: *Biological mechanisms. Metastatic dissemination. Pharmacometrics*.

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 offer a valuable insight on the disease to the clinicians in order to improve the decision process. This would be particularly useful in the cases of relapses or for metastatic diseases.

The second axis aims at modeling 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 may not be 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 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 monitor 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 glioma). A reliable patient-specific model of tumor evolution with or without therapy may have different uses:

- Case without treatment: the evaluation of the growth of the tumor would offer 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 plan the intervention. For slowly growing tumors, 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 prediction, this might mean that some events have occurred at the biological level. For instance, it could be the rise of an aggressive phenotype or 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 outcome 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 coupling deterministic and stochastic 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 ODE. or a PDE that describes the evolution of the growth rate as a combination of sigmoid 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 glioma 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 achieved 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.

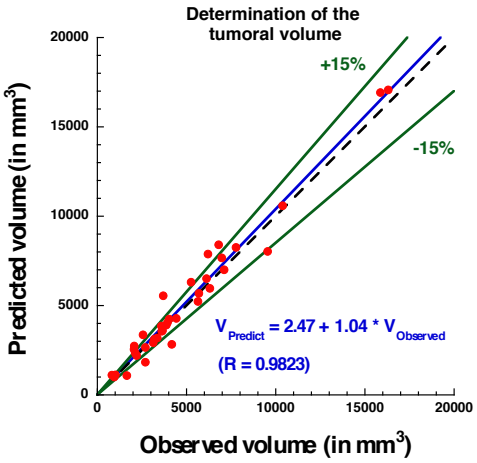

Figure 4. Plot showing the accuracy of our prediction on meningioma volume. Each point corresponds to a patient whose two first exams were used to calibrate our model. A patient-specific prediction was made with this calibrated model and compared with the actual volume as measured on a third time by clinicians. A perfect prediction would be on the black dashed line. Medical data was obtained from Prof. Loiseau, CHU Pellegrin.

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

In this axis, we investigate locoregional therapies such as radiotherapy, irreversible electroporation. Electroporation consists in increasing the membrane permeability of cells by the delivery of high voltage pulses. This non-thermal phenomenon can be transient (reversible) or irreversible (IRE). 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 focus on two particular approaches: some aspects of radiotherapies and electro-chemotherapy. This choice is motivated partly by pragmatic reasons: we already have collaborations with physicians on these therapies. Other treatments could be probably treated with the same approach, 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 healthy tissues. 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 was 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 collaborations with Institut Bergonié and CHU Bordeaux on different cancers (head and neck, pancreas). The response is evaluated from image markers (*e.g.* using texture information) or with a mathematical model developed in Axis 1. 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 for a few decades but it is still not well understood, therefore our interest is two fold:

  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...), one 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.

- Radiofrequency ablation. In a collaboration with Hopital Haut Leveque, CHU Bordeaux we are trying to determine the efficacy and risk of relapse of hepatocellular carcinoma treated by radiofrequency ablation. For this matter we are using geometrical measurements on images (margins of the RFA, distance to the boundary of the organ) as well as texture information to statistically evaluate the clinical outcome of patients.
- Intensity focused ultrasound. In collaboration with Utrecht Medical center, we aim at tackling several challenges in clinical applications of IFU: target tracking, dose delivery...

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 exploit 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 technical challenge that we need to overcome 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 feedback 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. Tumor growth monitoring and therapeutic evaluation

Each type of cancer is different and requires an adequate model. More specifically, we are currently working on the following diseases:

- Glioma (brain tumors) of various grades,
- Metastases to the lung, liver and brain from various organs,
- Soft-tissue sarcoma,
- Kidney cancer and its metastases,
- EGFR-mutated lung cancer.

In this context our application domains are

- Image-driven patient-specific simulations of tumor growth and treatments,
- Parameter estimation and data assimilation of medical images.

4.2. Biophysical therapies

- Modeling of electrochemotherapy on biological and clinical scales.
- Evaluation of radiotherapy and radiofrequency ablation.

4.3. In-vitro and animals experimentations in oncology

- 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

The team published in medical journals with strong impact factors like Cancer Research (*Mathematical modeling of tumor-tumor distant interactions supports a systemic anti-proliferative control of tumor growth* by S. Benzekry, *et al* for instance).

A new promising collaboration has started with the group of Yuval Shaked (double ERC laureate) at the Technion Israel Institute of Technology and first joint publication *Dose- and time-dependence of the host-mediated response to paclitaxel therapy: a mathematical modeling approach* by Benguigui *et al* will appear in Oncotarget, 2017.

Sébastien Benzekry received of the title of Assistant Associate Professor in the Department of Medical Biosciences of Iowa State University, reinforcing a starting collaboration with Jonathan Mochel about PK/PD modeling for comparative oncology.

Two former members of the team (Thierry Colin and Vivien Pianet) were hired by Sophia Genetics (http://www.sophiagenetics.com) to build its new imaging department and developed works initiated in Monc.

6. New Results

6.1. Mathematical modeling of tumor-tumor distant interactions supports a systemic control of tumor growth

Authors: *Sébastien Benzekry*, Clare Lamont, Dominique Barbolosi, Lynn Hlatky, Philip Hahnfeldt. Paper published in Cancer Research, https://hal.inria.fr/hal-01566947.

Interactions between different tumors within the same organism have major clinical implications, especially in the context of surgery and metastatic disease. Three main explanatory theories (competition, angiogenesis inhibition and proliferation inhibition) have been proposed but precise determinants of the phenomenon remain poorly understood. Here we formalized these theories into mathematical models and performed biological experiments to test them with empirical data. In syngeneic mice bearing two simultaneously implanted tumors, growth of only one of the tumors was significantly suppressed (61% size reduction at day 15, $p<0.05$). The competition model had to be rejected while the angiogenesis inhibition and proliferation inhibition models were able to describe the data. Additional models including a theory based on distant cytotoxic log-kill effects were unable to fit the data. The proliferation inhibition model was identifiable and minimal (4 parameters), and its descriptive power was validated against the data, including consistency in predictions of single tumor growth when no secondary tumor was present. This theory may also shed new light on single cancer growth insofar as it offers a biologically translatable picture of how local and global action may combine to control local tumor growth, and in particular, the role of tumor-tumor inhibition. This model offers a depiction of concomitant resistance that provides an improved theoretical basis for tumor growth control and may also find utility in therapeutic planning to avoid post-surgery metastatic acceleration. Major findings In mice bearing two tumors implanted simultaneously, tumor growth was suppressed in one of the two tumors. Three theories of this phenomenon were advanced and assessed against the data. As formalized, a model of competition for nutrients was not able to explain the growth behavior as well as indirect, angiogenesis-regulated inhibition or a third model based on direct systemic inhibition. This last model offers a depiction of concomitant resistance that provides an improved theoretical basis for tumor growth control and may also find utility in therapeutic planning to avoid post-surgery metastatic acceleration.

6.2. Precision of manual two-dimensional segmentations of lung and liver metastases and its impact on tumour response assessment using RECIST 1.1

Authors: *François Cornelis*, *Marie Martin*, *Olivier Saut*, Xavier Buy, *Michèle Kind*, Jean Palussiere, *Thierry Colin*. Paper published in European Radiology Experimental, https://hal.inria.fr/hal-01634849.

Response evaluation criteria in solid tumours (RECIST) has significant limitations in terms of variability and reproducibility, which may not be independent. The aim of the study was to evaluate the precision of manual bi-dimensional segmentation of lung, liver metastases, and to quantify the uncertainty in tumour response assessment. Methods: A total of 520 segmentations of metastases from six livers and seven lungs were independently performed by ten physicians and ten scientists on CT images, reflecting the variability encountered in clinical practice. Operators manually contoured the tumours, firstly independently according to the RECIST and secondly on a preselected slice. Diameters and areas were extracted from the segmentations. Mean standard deviations were used to build regression models and 95% confidence intervals (95% CI) were calculated for each tumor size and for limits of progressive disease (PD) and partial response (PR) derived from RECIST 1.1. Results: Thirteen aberrant segmentations (2.5%) were observed without significant differences between the physicians and scientists; only the mean area of liver tumours ($p = 0.034$) and mean diameter of lung tumours ($p = 0.021$) differed significantly. No difference was observed between the methods. Inter-observer agreement was excellent (intra-class correlation >0.90) for all variables. In liver, overlaps of the 95% CI with the 95% CI of limits of PD or PR were observed for diameters above 22.7 and 37.9 mm, respectively. An overlap of 95% CIs was systematically observed for area. No overlaps were observed in lung. Conclusions:

Although the experience of readers might not affect the precision of segmentation in lung and liver, the results of manual segmentation performed for tumor response assessment remain uncertain for large liver metastases.

6.3. Dose- and time-dependence of the host-mediated response to paclitaxel therapy: a mathematical modeling approach

Authors: Madeleine Benguigui, Dror Alishekevitz, Michael Timaner, Dvir Shechter, Ziv Raviv, *Sebastien Benzekry*, Yuval Shaked. Paper published in OncoTarget, https://hal.inria.fr/hal-01672568.

It has recently been suggested that pro-tumorigenic host-mediated processes induced in response to chemotherapy counteract the anti-tumor activity of therapy, and thereby decrease net therapeutic outcome. Here we use experimental data to formulate a mathematical model describing the host response to different doses of paclitaxel (PTX) chemotherapy as well as the duration of the response. Three previously described host-mediated effects are used as readouts for the host response to therapy. These include the levels of circulating endothelial progenitor cells in peripheral blood and the effect of plasma derived from PTX-treated mice on migratory and invasive properties of tumor cells in vitro. A first set of mathematical models, based on basic principles of pharmacokinetics/pharmacodynamics, did not appropriately describe the dose-dependence and duration of the host response regarding the effects on invasion. We therefore provide an alternative mathematical model with a dose-dependent threshold, instead of a concentration-dependent one, that describes better the data. This model is integrated into a global model defining all three host-mediated effects. It not only precisely describes the data, but also correctly predicts host-mediated effects at different doses as well as the duration of the host response. This mathematical model may serve as a tool to predict the host response to chemotherapy in cancer patients, and therefore may be used to design chemotherapy regimens with improved therapeutic outcome by minimizing host mediated effects.

6.4. Tumor growth model of ductal carcinoma: from in situ phase to stroma invasion

Authors: *Olivier Gallinato, Thierry Colin, Olivier Saut, Clair Poignard* Paper published in Journal of Theoretical Biology, https://hal.inria.fr/hal-01598837.

This paper aims at modeling breast cancer transition from the in situ stage –when the tumor is confined to the duct– to the invasive phase. Such a transition occurs thanks to the degradation of the duct membrane under the action of specific enzymes so-called matrix metallo-proteinases (MMPs). The model consists of advection–reaction equations that hold in the duct and in the surrounding tissue, in order to describe the proliferation and the necrosis of the cancer cells in each subdomain. The divergence of the velocity is given by the increase of the cell densities. Darcy law is imposed in order to close the system. The key-point of the modeling lies in the description of the transmission conditions across the duct. Nonlinear Kedem-Katchalsky transmission conditions across the membrane describe the discontinuity of the pressure as a linear function of the flux. These transmission conditions make it possible to describe the transition from the in situ stage to the invasive phase at the macroscopic level. More precisely, the membrane permeability increases with respect to the local concentration of MMPs. The cancer cells are no more confined to the duct and the tumor invades the surrounding tissue. The model is enriched by the description of nutrients concentration, tumor necrosis factors, and MMPs production. The mathematical model is implemented in a 3D C ++-code, which is based on well-adapted finite difference schemes on Cartesian grid. The membrane interface is described by a level-set, and the transmission conditions are precisely approached at the second order thanks to well-suited sharp stencils. Our continuous approach provides new significant insights in the macroscopic modeling of the breast cancer phase transition, due to the membrane degradation by MMP enzymes.

6.5. Superconvergent second order Cartesian method for solving free boundary problem for invadopodia formation

Authors: Olivier Gallinato, Clair Poignard. Paper published in Journal of Computational Physics, https://hal.inria.fr/hal-01483484.

In this paper, we present a superconvergent second order Cartesian method to solve a free boundary problem with two harmonic phases coupled through the moving interface. The model recently proposed by the authors and colleagues describes the formation of cell protrusions. The moving interface is described by a level set function and is advected at the velocity given by the gradient of the inner phase. The finite differences method proposed in this paper consists of a new stabilized ghost fluid method and second order discretizations for the Laplace operator with the boundary conditions (Dirichlet, Neumann or Robin conditions). Interestingly, the method to solve the harmonic subproblems is superconvergent on two levels, in the sense that the first and second order derivatives of the numerical solutions are obtained with the second order of accuracy, similarly to the solution itself. We exhibit numerical criteria on the data accuracy to get such properties and numerical simulations corroborate these criteria. In addition to these properties, we propose an appropriate extension of the velocity of the level-set to avoid any loss of consistency, and to obtain the second order of accuracy of the complete free boundary problem. Interestingly, we highlight the transmission of the superconvergent properties for the static subproblems and their preservation by the dynamical scheme. Our method is also well suited for quasistatic Hele-Shaw-like or Muskat-like problems.

6.6. A Voronoi Interface approach to cell aggregate electropermeabilization

Authors: Arthur Guittet, *Clair Poignard*, Frederic Gibou.

In this work, a Voronoi Interface approach to the study of cell electropermeabilization is presented. We consider the nonlinear electropermeabilization model of Poignard et al., which takes into account the jump in the voltage potential across cells' membrane. The jump condition is imposed in a sharp manner, using the Voronoi Interface Method of Guittet et al., while adaptive Quad-/Oc-tree grids are employed to automatically refine near the cells boundary for increased accuracy. Numerical results are provided to illustrate the accuracy of the methods. We also carry out simulations in three spatial dimensions to investigate the influence of shadowing and of the cells shape on the degree of permeabilization.

6.7. Revisiting bevacizumab + cytotoxics scheduling using mathematical modeling: proof of concept study in experimental non-small cell lung carcinoma

Authors: D.C. Imbs, R. El Cheikh, A. Boyer, J. Ciccolini, C. Mascaux, B. Lacarelle, F. Barlesi, D. Barbolosi and *S. Benzekry*. Paper published in CPT Pharmacometrics Syst Pharmacol, https://hal.inria.fr/hal-01624423.

Concomitant administration of bevacizumab and pemetrexed-cisplatin is a common treatment for advanced nonsquamous non-small cell lung cancer (NSCLC). Vascular normalization following bevacizumab administration may transiently enhance drug delivery, suggesting improved efficacy with sequential administration. To investigate optimal scheduling, we conducted a study in NSCLC-bearing mice. First, experiments demonstrated improved efficacy when using sequential vs. concomitant scheduling of bevacizumab and chemotherapy. Combining this data with a mathematical model of tumor growth under therapy accounting for the normalization effect, we predicted an optimal delay of 2.8 days between bevacizumab and chemotherapy. This prediction was confirmed experimentally, with reduced tumor growth of 38% as compared to concomitant scheduling, and prolonged survival (74 vs. 70 days). Alternate sequencing of 8 days failed in achieving a similar increase in efficacy, thus emphasizing the utility of modeling support to identify optimal scheduling. The model could also be a useful tool in the clinic to personally tailor regimen sequences.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

- Research contract between Roche and Monc team.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. Plan Cancer

8.1.1.1. NUMEP

Plan Cancer NUMEP: 2016–2019. Numerics for Clinical Electroporation Funding: 460 kE Partners: Inria Team MONC, Institut de Pharmacologie de Toulouse, CHU J. Verdier de Bondy Duration: Octobre 2016—Septembre 2019 Project leader: C. Poignard Co-PI: M-P. Rols (IPBS), O. Séror (CHU J. Verdier)

8.1.1.2. Dynamo

Plan Cancer DYNAMO: 2015–2018. Dynamical Models for Tissue Electroporation Funding: 370 kE Partners: Laboratoire Ampère, Lab. Vectorology and Anticancerous Therapies (IGR), Inria Team MONC Duration: Octobre 2015—Septembre 2018 Project leader: R. Scorretti (Laboratoire Ampère) Co-PI: L.M. Mir (IGR), C. Poignard (Inria Team MONC)

8.1.1.3. Moglimaging

- Project acronym - Moglimaging: Modeling of Glioblastoma treatment-induced resistance and heterogeneity by multi-modal imaging.
- Partners -
- Duration - from Nov. 2016 to Nov 2019.
- Coordinator - E. Cohen-Jonathan Moyal, Institut Universitaire du Cancer Toulouse / Local coordinator - O. Saut.
- Team participants - S. Benzekry, A. Collin, C. Poignard, O. Saut.

8.1.1.4. MIMOSA

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

8.1.2. Systems Biology of Renal Carcinoma using a Mouse RCC model

- Title: Plan Cancer Systems Biology of Renal Carcinoma using a Mouse RCC model
- Partners : LAMC, INSERM-Univ. Bordeaux.
- Team participants: O. Saut, S. Benzekry (co-PI)
- 116.64k€

8.1.3. Transnation call: INCA/ARC

- Title: Minimally and non-invasive methods for early detection and/or progression of cancer
- Acronym: TRANSCAN
- Team participants: A. Collin, C. Poignard, O. Saut (local PI)
- Total funds: 1M150, Monc's share 275k€.

8.1.4. Competitivity Clusters

- Labex TRAIL (http://trail.labex.u-bordeaux.fr): MOD Project Consolidation. 1 2-years post-doc position (100k€), led by A. Collin, 1 PhD funding (100k€) led by O. Saut.

8.2. European Initiatives

MONC is partner of the European Lab EBAM devoted to electroporation. C.Poignard is member of the steering committee.

8.3. International Initiatives

MONC is partner of the Japanese Core-to-Core project « Establishing networks in mathematical medicine » coordinated by T. Suzuki (Osaka University) with Vanderbilt Univ, and St Andrews Univ. Local PIs are V. Quaranta (Vanderbilt), M. Chaplain (St Andrews) and C.Poignard (MONC).

8.3.1. Inria Associate Teams Not Involved in an Inria International Labs

8.3.1.1. METAMATS

Title: Modeling ExperimenTAl MetAsTasiS

International Partner (Institution - Laboratory - Researcher):

Roswell Park Cancer Institute (United States) - Department of Cancer Genetics Department of Medicine Department of Pharmacology and Therapeutics (Graduate Program) - John Ebos

Start year: 2017

See also: http://metamats.bordeaux.inria.fr/

The aim of the METAMATS associate team is to bring together a cancer biology experimental laboratory led by John ML Ebos (Roswell Park Cancer Institute) and the inria MONC team composed of applied mathematicians. The Ebos laboratory is specialized in the study of anti-cancer therapeutics (in particular, novel biologically targeted therapeutics such as anti-angiogenics and immunotherapies) on the development of metastases and produces unique, hard-to-obtain data sets on this process' dynamics. The MONC team is specialized in mathematical models in oncology, with a dedicated axis about modeling support and methodological development for analysis of data from preclinical studies. In particular, the work of S. Benzekry puts emphasis on proposing, studying and validating mathematical models of metastatic development under the action of various therapeutic modalities. Indeed, metastatic expansion remains the main challenge in the treatment of cancer and integrative studies combining experiments, mathematical models and clinical data have the potential to yield predictive computational tools of help to assist both the design of clinical trials and clinical oncologists in therapeutic decisions such as the control of the toxicity/efficacy balance or the optimal combination of treatment modalities.

8.3.1.2. Num4SEP

Title: Numerics for Spherical Electroporation

International Partner (Institution - Laboratory - Researcher):

University of California, Santa Barbara (United States) - ___Mechanical Engineering___ - Frederic Gibou

Start year: 2017

See also: http://num4sep.bordeaux.inria.fr/

Electroporation-based therapies (EPTs) consist in applying high voltage short pulses to cells in order to create defects in the plasma membrane. They provide interesting alternatives to standard ablative techniques, for instance for deep seated badly located tumors. However their use is still limited due to a lack of knowledge of tissue electroporation. The goal of the associate team is to focus on the multiscale numerical modeling of spheroid electroporation, in order to provide new insights in electroporation at the mesoscopic scales (spheroids provide interesting tumor-like biological models). Benefiting from the expertise of F. Gibou's team in HPC for multiphysics, and the expertise of the team MONC in tumor growth and cell electroporation modeling, the goal of the associate team Num4SEP is to obtain accurate and efficient numerical tools for the quantitative evaluation of the EPTs at the mesoscopic scale.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Selection

9.1.1.1. Member of the Conference Program Committees

- Sébastien Benzekry: Membre du comité scientifique des *Mathematical Biology Modeling days of Besançon*, MB^2 (http://mb2.univ-fcomte.fr/index.html).
- Clair Poignard: Inria at Silicon Valley BIS'2017 at Berkeley. Session on level-set methods, parallel computing and uncertainty quantifications. (Chairs: C. Poignard F. Gibou).
- Clair Poignard: Organisation of the Theoretical Physics Day at the University of Bordeaux.

9.1.2. Journal

9.1.2.1. Member of the Editorial Boards

- Sébastien Benzekry: Invited editor of a special issue of the journal Complexity : "Mathematical Oncology: Unveiling Biological Complexity Using Mathematical Methods"
- Clair Poignard: Member of the editorial committee of DCDS-S.

9.1.2.2. Reviewer - Reviewing Activities

- Sébastien Benzekry: Bull Math Biol, Computational and Applied Mathematics.
- Clair Poignard: Radiology, Bioelectrochemistry, Math. Medi Biol, J. Sci Comp., M2AN, JMPA, ESAIM Proc.
- Olivier Saut : PLOS One, Nature Comm, Medical Image Analysis.

9.1.3. Invited Talks

- Sébastien Benzekry: December 2017, Seminar at the Rappaport Faculty of Medicine of the Technion Israel Institute of Technology (invitation by Yuval Shaked). Contributions in Mathematical Oncology: When Theory Meets Reality. Haifa, Israel. http://www.rappaport.org.il/Rappaport/Templates/ShowPage.asp?DBID=&TMID=10000&FID=78
- Sébastien Benzekry: December 2017, Mathematical methods and modeling of biophysical phenomena. Mathematical modeling and prediction of metastasis. Rio de Janeiro, Brazil. https://impa.br/eventos-do-impa/eventos-2017/mathematical-methods-and-modeling-of-biophysical-phenomena/
- Sébastien Benzekry: September 2017, Première session du GDR MAMOVI. Mathematical Modeling and Prediction of Clinical Brain Metastases in Non-Small Cell Lung Cancer. Lyon, France http://gdr-mamovi.math.cnrs.fr/spip/spip.php?article12
- Sébastien Benzekry: June 2017, XXV Congreso de ecuaciones diferenciales y aplicaciones / XV congreso de matematica aplicada, Optimization of the timing of sequential administration of bevacizumab plus cytotoxics in non-small cell lung cancer by a mathematical model. Cartagena, Spain. http://www.cedya2017.org/
- Sébastien Benzekry: May 2017, Laboratoire d'Analyse Topologie et Probabilites, Institut de Mathematiques de Marseille. Mathematical Oncology: Theory Meets Reality. Marseille, France.
- Clair Poignard: Conference in honor of the 60th Birthday of Y. Maday. Electroporation modeling, from cell to tissue.
- Olibier Galinato: Sept. 2017, Journées Françaises de Radiologie, Numerical Workflow for Clinical IRE Ablation, Paris, France.

9.1.4. Scientific Expertise

- Sébastien Benzekry: Reviewer for the Foundation for Polish Science (TEAM programme), European funds Smart Growth
- Clair Poignard: Member of the evaluation committee of the call of the Plan Cancer «Physique pour le Cancer »
- Olivier Saut: O. Saut is an expert for the French Ministry of Research (for various programs including PHC and EGIDE programs).
- Olivier Saut: reviewer for IDEX Université Grenoble Alpes projects.

9.1.5. Research Administration

- Clair Poignard: Member of the Inria evaluation committee.
- Clair Poignard: PI of the Plan Cancer projects NUMEP (2016–2019), and DYNAMO (2015–2018).
- Olivier Saut: member of the steering committee of Labex TRAIL (Translational Imaging) http://trail.labex.u-bordeaux.fr.
- Olivier Saut: member of the steering committee of ITMO consortium HTE (on tumor heterogeneity) and coordinator of work package Model and Data.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence: S. Benzekry, Analyse numérique, 24h ETD, L3, Bordeaux INP, France

Licence : A. Collin, TD EDO, 48h, niveau L3, INP Bordeaux, France.

Master : A. Collin, TP C++, 96h, niveau M1, INP Bordeaux, France.

Master : A. Collin, Cours de maillage, 36h, niveau M2, INP Bordeaux, France.

Master : A. Collin, Encadrement de projets, 30h, niveaux M1, M2, INP Bordeaux, France.

Licence : C. Poignard, Undergraduate teaching in Numerical and Applied Mathematics (L3, M1) 80heqTD: IPB, ENSAM.

9.2.2. Supervision

- HdR: S. Benzekry, *Contributions in Mathematical Oncology: When Theory Meets Reality*, Université de Bordeaux, 13 Novembre 2017.
- PhD: Manon Deville, *Mathematical Modeling of enhanced drug delivery by mean of Electroporation or Enzymatic treatment*, University of Bordeaux (cotutelle with R. Natalini, Univerity of Rome Tor Vergata), 22 Novembre 2017, Clair Poignard.
- PhD: Agathe Peretti, *Quantification de l'hétérogénéité tumorale à partir de l'imagerie médicale. Application à la classification de tumeurs rénales*, Université de Bordeaux, 20 décembre 2017, Thierry Colin, Olivier Saut.
- PhD in progress: C. Nicolò, *Mathematical modeling of systemic aspects of cancer and cancer therapy*, 12/2016, S. Benzekry and O. Saut.
- PhD in progress: T. Kritter, *Primary tumors modeling with a view to the gliomas and adenocarcinomas study*, Sep 2015, C. Poignard and O. Saut
- PhD in progress: S. Corridore, *Mathematical Model for Electroporation*, A. Collin, C. Poignard.
- PhD in progress: C. Perier, 2016-2019, B. Denis de Senneville and O. Saut, *Combining texture analysis and modeling for evaluation therapies and clinical outcome*.
- PhD in progress: A. Crombé, 2017-2020, O. Saut, *Beyond radiomics for soft-tissue sarcoma*.
- PhD in progress: C. Vaghi, *Improving intra-tumor drug distribution of anti-cancer nanoparticles by data-informed mathematical modeling* (beginning November 1rst 2017), S. Benzekry, R. Fanciullino and C. Poignard.

9.2.3. Juries

- Sébastien Benzekry: Committee member of the PhD thesis of K. El Alaoui Lasmaili, Université de Lorraine (mention Sciences de la Vie et de la Santé), 4 Avril 2017.
- Clair Poignard: reviewer of the PhD thesis of A. Barlukova (Université Aix-Marseille),
- Clair Poignard: reviewer of the PhD thesis of K. Van Nguyen (Ecole Polytechnique X)
- Clair Poignard: Committee member of the PhD thesis of T. Wintz: Super-resolution in wave imaging. (ENS Paris)
- Clair Poignard: Committee member of the PhD thesis of Z. Wenlong: Forward and Inverse Problems Under Uncertainty (ENS Paris).
- Olivier Saut: reviewer of the PhD thesis of Guila Fabrini. (Paris VI - Univ. Genova, Italy).
- Olivier Saut: reviewer of the PhD thesis of Clément Chesseboeuf. (Univ. Poitiers).

9.3. Popularization

- Sébastien Benzekry: Interview pour le journal « Sciences et Avenir ».
- A. Collin : Printemps de la mixité (une présentation sur le calcul scientifique devant 2 classes de première), Institut Mathématiques de Bordeaux, 04/04/17, https://www.u-bordeaux.fr/Actualites/De-l-universite/Le-Printemps-de-la-mixite.
- A. Collin: Filles & Maths (table ronde avec des lycéennes autour des études mathématiques et des applications des mathématiques), Université de Bordeaux, 05/06/2017, https://math-interactions.u-bordeaux.fr/Centres-de-ressources/IREM/Actions/Journee-Filles-et-Maths.
- A. Collin: Fête de la Science, Inria Bordeaux, 10/10/2017.
- A. Collin: Nuit des chercheurs, Cap Sciences, Bordeaux.
- A. Collin: Cinéma Sciences (discussion avec le public sur les mathématiques après la projection du film "Les figures de l'ombre"), Cinéma de Mérignac 18/05/2017.
- O. Saut: Les Entretiens de l'Excellence 2017 http://www.lesentretiens.org/.
- O. Saut: Table ronde "Comment l'innovation transforme les métiers de la santé", Journées Nationales de l'Innovation en Santé, 27-29 janvier 2017, cité des Sciences et de l'Industrie / webradio Cnrs.

10. Bibliography

Major publications by the team in recent years

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[3] S. BENZEKRY, A. TRACZ, M. MASTRI, R. CORBELLI, D. BARBOLOSI, J. M. L. EBOS. *Modeling Spontaneous Metastasis following Surgery: An In Vivo-In Silico Approach*, in "Cancer Research", February 2016, vol. 76, n^{o} 3, pp. 535 - 547 [*DOI :* 10.1158/0008-5472.CAN-15-1389], https://hal.inria.fr/hal-01222046

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