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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

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2. Overall Objectives

2.1. Objectives

The MONC project-team aims at developing new mathematical models from partial differential equations and statistical methods and based on biological and medical knowledge. Our goal is ultimately to be able to help clinicians and/or biologists to better understand, predict or control the evolution of the disease and possibly evaluate the therapeutic response, in a clinical context or for pre-clinical studies. We develop patient-specific approaches (mainly based on medical images) as well as population-type approaches in order to take advantage of large databases.

In vivo modeling of tumors is limited by the amount of information available. 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 evolution, assess tumor status as well as anatomical or functional details. Using different techniques from biology or imaging - 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. Medical doctors now have access to a wide spectrum of therapies (surgery, mini-invasive techniques, radiotherapies, chemotherapies, targeted therapies, immunotherapies...).

Our project aims at helping oncologists in their followup of patients via the development of novel quantitative methods for evaluation cancer progression. 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 evolution 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?

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 dire need of integrating biological knowledge into mathematical models based on clinical or experimental data. A major purpose of our project is also 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

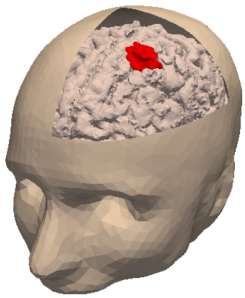

Figure 1. 3D numerical simulation of a meningioma. The tumor is shown in red.

Our general strategy may be described with the following sequence:

- 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

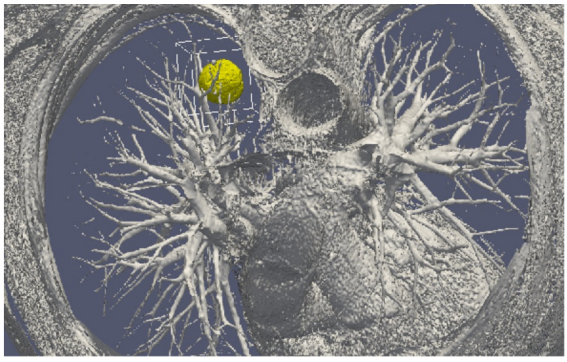

Figure 2. 3D numerical simulation of a lung tumor. The tumor is shown in yellow.

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. We need *longitudinal* data in time in order to be able to understand or describe the evolution of the disease. Data may also be obtained from analyses of blood samples, biopsies or other quantitative biomarkers. 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 (implemented in SegmentIt) as well as supervized approaches (machine learning or deep learning) for segmentation, non-rigid registration and extraction of image texture information (radiomics, deep learning).
- Stage 3: *Adaptation of the model to data.* The model has to be adapted to data: it is useless to have a model considering many biological features of the disease 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 and scarcity - 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 on low grade gliomas or Institut Bergonié on soft-tissue sarcoma), 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 as in delta-radiomics approaches). 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: *Patient-specific Simulation and prediction, Stratification*. Once the mechanistic models have been parametrized, they can be used to run patient-specific simulations and predictions. The statistical models offer new stratifications of patients (*i.t.* an algorithm that tells from images and clinical information wheter a patient with soft-tissue sarcoma is more likely to be a good or bad responder to neoadjuvant chemotherapy). Building robust algorithms (*e.g.* that can be deployed over multiple clinical centers) also requires working on quantifying uncertainties.

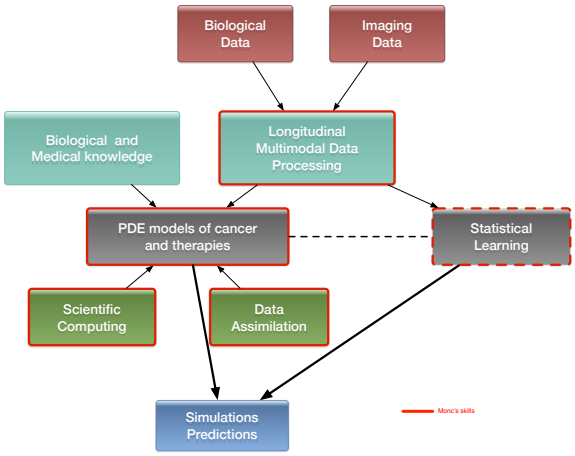

Figure 3. General strategy of the team to build meaningful models in oncology.

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, clinical 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 electroporation, but also radiotherapy, thermo-ablations, radio-frequency ablations or electroporation that play a crucial role for a local treatment of the disease if possible limiting the metastatic dissemination, which is precisely the clinical context where the techniques of axis 1 will be applied.

The third axis 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 may 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.

The scientific challenge is therefore as follows: given the history of the patient, the nature of the primitive tumor, its histopathology, knowing the treatments that patients have undergone, 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 images 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.

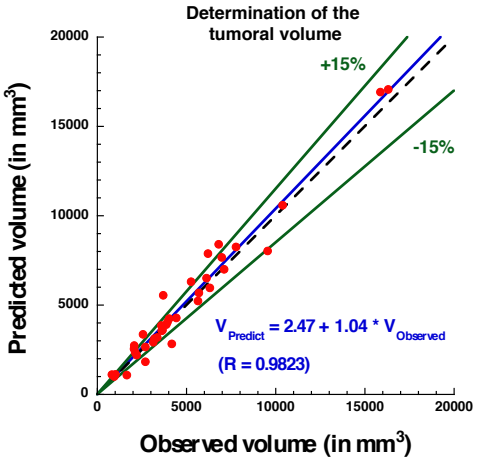

Figure 4. Plot showing the accuracy of our prediction on meningioma volume. Each point corresponds to a patient whose two first exams were used to calibrate our model. A patient-specific prediction was made with this calibrated model and compared with the actual volume as measured on a third time by 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 markers (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,
- non small cell lung carcinoma.

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.
- Machine and deep learning methods for delineating the lesions and stratifying patients according to their responses to treatment or risks of relapse.

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

- 2 abstracts accepted as oral communications at the PAGE meeting (main international conference in population modeling) (C. Nicolò and S. Benzekry)

5.1.1. Awards

- Floriane Gildel is French Young Talent 2019 - L'Oréal-UNESCO for Women in Science.

6. New Software and Platforms

6.1. August

Antibody Drug Uptake Simulator

KEYWORD: Mechanistic modeling

FUNCTIONAL DESCRIPTION: Numerical code to compute the uptake of an antibody drug at the scale of an histopathology blade. The computation domain (reconstructed from segmented images) is completely meshed and sub-divided accross computational nodes to distribute the load efficiently. The model (based on reaction-diffusion equations) is then solved in parallel using a domain decomposition method. C ++

- Contact: Olivier Saut

7. New Results

7.1. Machine learning and mechanistic modeling for prediction of metastatic relapse in early-stage breast cancer

Authors: *C. Nicolò; C. Périer*; M. Prague; C. Bellera; G. MacGrogan; *O.Saut; S. Benzekry*. Accepted for publication in the Journal of Clinical Oncology: Clinical Cancer Informatics.

Purpose: For patients with early-stage breast cancer, prediction of the risk of metastatic relapse is of crucial importance. Existing predictive models rely on agnostic survival analysis statistical tools (e.g. Cox regression). Here we define and evaluate the predictive ability of a mechanistic model for the time to metastatic relapse.

Methods: The data consisted of 642 patients with 21 clinicopathological variables. A mechanistic model was developed on the basis of two intrinsic mechanisms of metastatic progression: growth (parameter α) and dissemination (parameter μ). Population statistical distributions of the parameters were inferred using mixed-effects modeling. A random survival forest analysis was used to select a minimal set of 5 covariates with best predictive power. These were further considered to individually predict the model parameters, by using a backward selection approach. Predictive performances were compared to classical Cox regression and machine learning algorithms.

Results: The mechanistic model was able to accurately fit the data. Covariate analysis revealed statistically significant association of Ki67 expression with α (p=0.001) and EGFR with μ (p=0.009). Achieving a c-index of 0.65 (0.60-0.71), the model had similar predictive performance as the random survival forest (c-index 0.66-0.69) and Cox regression (c-index 0.62 - 0.67), as well as machine learning classification algorithms.

Conclusion: By providing informative estimates of the invisible metastatic burden at the time of diagnosis and forward simulations of metastatic growth, the proposed model could be used as a personalized prediction tool of help for routine management of breast cancer patients.

7.2. Numerical workflow for clinical electroporation ablation

Authors: *Olivier Gallinato*, *Baudouin Denis de Senneville*, Olivier Seror, *Clair Poignard*. Published in Physics in Medicine and Biology. https://hal.inria.fr/hal-02063020/file/paperIRE_workflow_R3.pdf.

The paper describes a numerical workflow, based on the “real-life” clinical workflow ofirreversible electroporation (IRE) performed for the treatment of deep-seated liver tumors. Thanksto a combination of numerical modeling, image registration algorithm and clinical data, our numerical workflow enables to provide the distribution of the electric field as effectively delivered by theclinical IRE procedure. As a proof of concept, we show on a specific clinical case of IRE ablation ofliver tumor that clinical data could be advantageously combined to numerical simulations in a nearfuture , in order to give to the interventional radiologists information on the effective IRE ablation.We also corroborate the simulated treated region with the post-treatment MRI performed 3 days after treatment.

7.3. A reduced Gompertz model for predicting tumor age using a population approach

Authors: *C. Vaghi*, A. Rodallec, R. Fanciullino, J. Ciccolini, J. Mochel, M. Mastri, *C. Poignard*, J. ML Ebos, *S. Benzekry*. Accepted for publication in PLoS Computational Biology. https://www.biorxiv.org/content/10.1101/670869v2

Tumor growth curves are classically modeled by means of ordinary differential equations. In analyzing the Gompertz model several studies have reported a striking correlation between the two parameters of the model, which could be used to reduce the dimensionality and improve predictive power.

We analyzed tumor growth kinetics within the statistical framework of nonlinear mixed-effects (population approach). This allowed the simultaneous modeling of tumor dynamics and inter-animal variability. Experimental data comprised three animal models of breast and lung cancers, with 833 measurements in 94 animals. Candidate models of tumor growth included the exponential, logistic and Gompertz. The exponential and – more notably – logistic models failed to describe the experimental data whereas the Gompertz model generated very good fits. The previously reported population-level correlation between the Gompertz parameters was further confirmed in our analysis ($R^2 > 0.92$ in all groups). Combining this structural correlation with rigorous population parameter estimation, we propose a reduced Gompertz function consisting of a single individual parameter (and one population parameter). Leveraging the population approach using Bayesian inference, we estimated times of tumor initiation using three late measurement timepoints. The reduced Gompertz model was found to exhibit the best results, with drastic improvements when using Bayesian inference as compared to likelihood maximization alone, for both accuracy and precision. Specifically, mean accuracy was 12.2% versus 78% and mean precision was 15.6 days versus 210 days, for the breast cancer cell line.

These results offer promising clinical perspectives for the personalized prediction of tumor age from limited data at diagnosis. In turn, such predictions could be helpful for assessing the extent of invisible metastasis at the time of diagnosis.

The code and the data used in our analysis are available at https://github.com/cristinavaghi/plumky.

7.4. T2-based MRI Delta-Radiomics Improve Response Prediction in Soft-Tissue Sarcomas Treated by Neoadjuvant Chemotherapy

Authors: *Amandine Crombé*, *Cynthia Perier*, Michèle Kind, *Baudouin Denis de Senneville*, Francois Le Loarer, Antoine Italiano, Xavier Buy, *Olivier Saut*. Published in Journal of Magnetic Reasonance Imaging https://hal.inria.fr/hal-01929807v2

Background: Standard of care for patients with high-grade soft-tissue sarcoma (STS) are being redefined since neoadjuvant chemotherapy (NAC) has demonstrated a positive effect on patients' outcome. Yet, response evaluation in clinical trials still remains on RECIST criteria.

Purpose: To investigate the added value of a Delta-radiomics approach for early response prediction in patients with STS undergoing NAC Study type: Retrospective Population: 65 adult patients with newly-diagnosed, locally-advanced, histologically proven high-grade STS of trunk and extremities. All were treated by anthracycline-based NAC followed by surgery and had available MRI at baseline and after 2 cycles. Field strength/Sequence: Pre- and post-contrast enhanced T1-weighted imaging (T1-WI), turbo spin echo T2-WI at 1.5T.

Assessment: A threshold of <10% viable cells on surgical specimen defined good response (Good-HR). Two senior radiologists performed a semantic analysis of the MRI. After 3D manual segmentation of tumors at baseline and early evaluation, and standardization of voxelsizes and intensities, absolute changes in 33 texture and shape features were calculated. Statistical tests: Classification models based on logistic regression, support vector machine, k-nearest neighbors and random forests were elaborated using cross-validation (training and validation) on 50 patients ('training cohort') and was validated on 15 other patients ('test cohort').

Results: 16 patients were good-HR. Neither RECIST status, nor semantic radiological variables were associated with response except an edema decrease (p=0.003) although 14 shape and texture features were (range of p-values: 0.002-0.037). On the training cohort, the highest diagnostic performances were obtained with random forests built on 3 features, which provided: AUROC=0.86, accuracy=88.1%, sensitivity=94.1%, specificity=66.3%. On the test cohort, this model provided an accuracy of 74.6% but 3/5 good-HR were systematically ill-classified.

Data conclusions: A T2-based Delta-Radiomics approach can improve early response prediction in STS patients with a limited number of features.

7.5. Quantitative mathematical modeling of clinical brain metastasis dynamics in non-small cell lung cancer

Authors: *M. Bilous*, C. Serdjebi, A. Boyer, P. Tomasini, *C. Pouypoudat*, D. Barbolosi, F. Barlesi, F. Chomy, *S. Benzekry*. Published in Scientific Reports. https://hal.inria.fr/hal-01928442v2

Brain metastases (BMs) are associated with poor prognosis in non-small cell lung cancer (NSCLC), but are only visible when large enough. Therapeutic decisions such as whole brain radiation therapy would benefit from patient-specific predictions of radiologically undetectable BMs. Here, we propose a mathematical modeling approach and use it to analyze clinical data of BM from NSCLC. Primary tumor growth was best described by a gompertzian model for the pre-diagnosis history, followed by a tumor growth inhibition model during treatment. Growth parameters were estimated only from the size at diagnosis and histology, but predicted plausible individual estimates of the tumor age (2.1–5.3 years). Multiple metastatic models were further assessed from fitting either literature data of BM probability (n = 183 patients) or longitudinal measurements of visible BMs in two patients. Among the tested models, the one featuring dormancy was best able to describe the data. It predicted latency phases of 4.4–5.7 months and onset of BMs 14–19 months before diagnosis. This quantitative model paves the way for a computational tool of potential help during therapeutic management.

7.6. Optimizing 4D abdominal MRI: Image denoisingusing an iterative back-projection approach

Authors: *B Denis de Senneville*, C R Cardiet, A J Trotier, E J Ribot, L Lafitte, L Facq, S Miraux. Published in Physics in Medicine and Biology. https://hal.archives-ouvertes.fr/hal-02367839/file/2019_4D_reconstruction_revision2_final.pdf

4D-MRI is a promising tool for organ exploration, target delineationand treatmentplanning. Intra-scan motion artifacts may be greatly reduced by increasing the imagingframe rate. However, poor signal-to-noise ratios (SNR) are observed when increasingspatial and/or frame number per physiological cycle, in particular inthe abdomen.In the current work, the proposed 4D-MRI method favored spatial resolution, framenumber, isotropic voxels and large field-of-view (FOV) during MR-acquisition. Theconsequential SNR penalty in the reconstructed data is addressed retrospectively usingan iterative back-projection (IBP) algorithm. Practically, after computing individualspatial 3D deformations present in the images using a deformable image registration(DIR) algorithm, each 3D image is individually enhanced by fusing several successiveframes in its local temporal neighborood, these latter being likely tocover commonindependent informations. A tuning parameter allows one to freely readjust the balancebetween temporal resolution and precision of the 4D-MRI.The benefit of the method was quantitatively evaluated on the thorax of 6 miceunder free breathing using a clinically acceptable duration. Improved 4D cardiacimaging was also shown in the heart of 1 mice. Obtained results are comparedto theoretical expectations and discussed. The proposed implementation is easilyparallelizable and optimized 4D-MRI could thereby be obtained with a clinicallyacceptable duration.

7.7. Optimal Scheduling of Bevacizumab and Pemetrexed/cisplatin Dosing in Non-Small Cell Lung Cancer

Authors: Benjamin Schneider, Arnaud Boyer, Joseph Ciccolini, Fabrice Barlési, Kenneth Wang, *Sébastien Benzekry**, Jonathan Mochel*. * = co-senior authors. Published in CPT: Pharmacometrics and Systems Pharmacology. https://hal.inria.fr/hal-02109335

Bevacizumab-pemetrexed/cisplatin (BEV-PEM/CIS) is a first line therapeutic for advanced non-squamous non-small cell lung cancer (NSCLC). Bevacizumab potentiates PEM/CIS cytotoxicity by inducing transient tumor vasculature normalization. BE V- PEM/CIS has a narrow therapeutic window. Therefore, it is an attractive target for administration schedule optimization. The present study leverages our previous work on BEV-PEM/CIS pharmacodynamic modeling in NSCLC-bearing mice to estimate the optimal gap in the scheduling of sequential BEV-PEM/CIS. We predicted the optimal gap in BEV-PEM/CIS dosing to be 2.0 days

in mice and 1.2 days in humans. Our simulationssuggest that the efficacy loss in scheduling BEV-PEM/CIS at too great of a gap is much less than the efficacy loss in scheduling BEV-PEM/CIS at too short of a gap.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

- Research contract between Roche and the MONC team.
- Collaboration contract with Sophia Genetics in the context of the Pimiento project.

8.2. Bilateral Grants with Industry

Pimiento project from MSDAvenir (http://www.msdavenir.fr/) through Inria Foundation.

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. Plan Cancer

9.1.1.1. NUMEP

Plan Cancer NUMEP: 2016–2019. Numerics for Clinical Electroporation

Funding: 460 kE.

Partners: 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)

9.1.1.2. Moglimaging

Project acronym - Moglimaging: Modeling of Glioblastoma treatment-induced resistance and heterogeneity by multi-modal imaging.

Partners - Inria Monc, IUCT, Institut Pasteur, Univ. Grenoble, INSERM, Inria Mamba.

Duration - from Nov. 2016 to May 2020.

Coordinator - E. Cohen-Jonathan Moyal, Institut Universitaire du Cancer Toulouse / Local coordinator - O. Saut.

Team participants - S. Benzekry, A. Collin, C. Poignard, O. Saut.

9.1.1.3. Systems Biology of Renal Carcinoma

Title: Plan Cancer Systems Biology of Renal Carcinoma using a Mouse RCC model

Partners : LAMC, INSERM-Univ. Bordeaux.

Duration - June 2018 to June 2021

Team participants: O. Saut, S. Benzekry (co-PI)

Funding: 116.64k€

9.1.1.4. QUANTIC

Plan Cancer QUANTIC: 2020–2022. QUANTitative modeling combined to statistical learning to understand and predict resistance to Immune-checkpoint inhibition in non-small cell lung Cancer.

Funding: 338 k€

Partners: Inria Team MONC, SMARTc (Centre de Recherche sur le Cancer de Marseille, Inserm, CNRS), Assistance Publique Hôpitaux de Marseille

Duration: Décembre 2019 — Décembre 2022

Project leader: S. Benzekry

Co-PI: D. Barbolosi (SMARTc), F. Barlési (AP-HM)

9.1.2. Transnation call: INCA/ARC

Title: Minimally and non-invasive methods for early detection and/or progression of low grade glioma

Partners: Inria Monc, Inria SISTM, INSERM, Humanitas Research Hostital, Univ. Bergen

Acronym: Glioma PRD

Team participants: A. Collin, C. Poignard, O. Saut (local PI)

Total funds: 1M150, Monc's share 275k€.

9.1.3. 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.

9.2. International Initiatives

9.2.1. Inria International Labs

Inria@SiliconValley
Associate Team involved in the International Lab:

9.2.1.1. Num4SEP

Title: Numerics for Spherical Electroporation

International Partner (Institution - Laboratory - Researcher):

University of California, Santa Barbara (United States) 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.

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

9.2.2.1. 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.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events: Organisation

10.1.1.1. General Chair, Scientific Chair

- C. Poignard: Organization of the Core-to-Core meeting March 21st-22nd at Bordeaux. This is the annual meeting of the JSPS Consortium « Establishing networks in mathematical medicine », which gathers Osaka University (Suzuki's lab), Vanderbilt University (Quaranta's lab), St Andrews Univ. (Chaplain's lab), and Inria Bordeaux team MONC.

10.1.2. Scientific Events: Selection

10.1.2.1. Reviewer

S. Benzekry served as a reviewer for the IEEE Control Systems Society Conference and for the International Symposium on Mathematical and Computational Oncology (Lake Tahoe, NV, USA).

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

- S. Benzekry is a member of the Editorial Board of "Mathematical Biosciences and Engineering"
- C. Poignard is a member of the editorial board of DCDS-S.

10.1.3.2. Reviewer - Reviewing Activities

- S. Benzekry served as a reviewer for Nature Communications, Cancer Research, Clinical Pharmacology and Therapeutics, Scientific Reports and ESAIM: Proc.
- A. Collin: Reviewer for Plos One.
- C. Etchegaray: ESAIM: Mathematical Modelling and Numerical Analysis, Royal Society Open Sciences.
- O. Saut: Mathematical Modelling of Natural Phenomena, PLOS One, Journal of Theoretical Biology, EBioMedicine, Nature Communications, Medical Image Analysis.

10.1.4. Invited Talks

- S. Benzekry: May 2019, RITS conference (Recherche en Imagerie et Technologies pour la Sante) of the French Society of Biomedical Engineering (SFGBM), Tours, France.
- S. Benzekry: May 2019, Seminaire phases I en oncologie, Marseille, France. Old concept, new name? l'intelligence artificielle en oncologie.
- S. Benzekry: May 2019, Masterclass Mathematiques appliquees CEPS Mathematiques Des Sciences du Vivant, CIRM, Marseille, France.
- S. Benzekry: May 2019, NCI Mathematical Oncology Meeting, Portland, USA.
- S. Benzekry: May 2019, Biomedicum Helsinki Seminar (Invitation by Sampsa Hautaniemi), Faculty of Medicine, Helsinki, Finland.
- S. Benzekry: June 2019, Seminar in the Novartis pharmacometrics department. Basel, Switwerland. Artificial intelligence and machine learning in oncology: myths and reality.
- S. Benzekry: July 2019, International Society of Pharmacometrics (ISoP) workshop. Paris, France.
- C. Etchegaray: Equadiff conference, Leiden.
- O. Saut: July 2019, Mathematical models in Biology and Medicine, Vienna, Austria.

10.1.5. Scientific Expertise

- S. Benzekry is expert within the scientific board of the national multi-thematic institute (ITMO) Cancer of the French alliance for health sciences (AVIESAN).
- A. Collin, Steering Committee Axe 5, Cancéropole Grand Sud Ouest
- C. Poignard: Member of the INCA committee on pediatric cancer data structuration
- C. Poignard: Member of the GAMNI prize committee.
- O. Saut: expert in the "Single Cell" call at ITMO Cancer / Plan Cancer.
- O. Saut: expert for the French Ministry of Research (for various programs including PHC and EGIDE programs).
- O. Saut: reviewer for SIRIC CURAMUS projects.

10.1.6. Research Administration

- S. Benzekry is a member of the local Inria commission of informatical tools users (CUMI)
- Annabelle Collin, member of "conseil de Laboratoire", Institut Mathématique de Bordeaux.
- Annabelle Collin, "chargée de mission parité", Institut Mathématique de Bordeaux.
- Annabelle Collin, member of "commission ADT", Inria Bordeaux Sud-Ouest.
- Annabelle Collin, "chargée de mission Développement Durable et Responsabilité Sociétale", ENSEIRB-MATMECA.
- Annabelle Collin, elected member of "comité de centre", Inria Bordeaux Sud-Ouest.
- C. Poignard is a member of the Inria Evaluation Committee
- Clair Poignard, member of "conseil scientifique", Institut Mathématique de Bordeaux.
- Olivier Saut: member of the steering committee of ITMO consortium HTE (on tumor heterogeneity) and coordinator of work package Model and Data.
- Olivier Saut: member of the steering committee of Labex TRAIL (Translational Imaging) http://trail.labex.u-bordeaux.fr.
- Olivier Saut: in charge of "Interdisciplinarité" at Institut de Mathématiques du CNRS http://www.cnrs.fr/insmi.
- Olivier Saut: member of the steering committee of the MITI at CNRS http://www.cnrs.fr/mi.
- Olivier Saut: member of the steering committee of the Oncosphere Project https://siric-brio.com/oncosphere/.

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Master : S. Benzekry, Cours "Modélisation de la croissance tumorale", 3h, niveau M2, Université de Tours, France.

Master : S. Benzekry, Cours "Mathematical tools for pharmacometrics", 10h, niveau M2, Aix-Marseille Université, France.

Master : S. Benzekry, TP "Introduction to Monolix", 2 x 3h, EUR "Modeling Life Sciences" (Université de Bordeaux) and DESU “Pharmacokinetics modeling" (Aix-Marseille Université), France.

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

Master: A. Collin, Mesh theory, 36h, niveau M2, INP Bordeaux, France.

Master: A. Collin, Machine Learning, niveau M2, INP Bordeaux, France.

PHD: A. Collin, Modeling Life Science Module, Digital Public Health, Graduate Program.

Licence : C. Poignard, Undergraduate teaching in Numerical and Applied Mathematics, 80h, L3-M1, INP Bordeaux, ENSAM, France.

Master: O. Saut, Mathematical modeling in Oncology, 2h, niveau M2, Univ. Bordeaux, France.

10.2.2. Supervision

PhD: C. Nicolò, *Mathematical modeling of systemic aspects of cancer and cancer therapy*, 2016 - 2019, supervision S. Benzekry and O. Saut. Defended October 14th, 2019.

PhD in progress: C. Vaghi, Improving intra-tumor drug distribution of anti-cancer nanoparticles by data-informed mathematical modeling, Nov 2017 - Nov 2020, supervision S. Benzekry and C. Poignard.

PhD in progress: Sergio Corridore, 2016-..., supervision A. Collin and C. Poignard

PhD in progress: Pedro Jaramillo-Aguayo, 2019-..., supervision A. Collin and C. Poignard

PhD: C. Perier, *Analyse quantitative des données de routine clinique pour le pronostic précoce en oncologie*, 2016-2019, supervision B. Denis de Senneville and O. Saut. Defended November 14th, 2019.

PhD in progress: A. Crombé, 2017-..., supervision O. Saut

10.2.3. Juries

- S. Benzekry: Reviewer of the PhD thesis of E. Kozlowska (University of Helsinki, Finland)
- S. Benzekry: Reviewer of the PhD thesis of A. Alvarez-Arenas Alcami (Universidad de Castilla La Mancha, Ciudad Real, Spain)
- S. Benzekry: Reviewer of the PhD thesis of A-S Giaccobi (Université Picardie Jules Verne)
- S. Benzekry: Reviewer of the PhD thesis of J Goya-Outi (Paris Saclay University)
- A. Collin, Phd defense committee, Antoine Gérard, Inria Bordeaux Sud-Ouest, Modèles numériques personnalisés de la fibrillation auriculaire, 10 juillet 2019
- A. Collin, Phd defense committee, Thibaut Hirschler, INSA Lyon, IsoGeometric Modeling for the Optimal Design of Aerostructures, 13 nov. 2019
- A. Collin, Jury member, agrégation de Mathématiques
- O. Saut: Reviewer of the HdR thesis of A. Decoene, Univ. Paris Sud, France.
- O. Saut: Reviewer of the PhD thesis of A. Perrillat-Mercerot, Univ. Poitiers, France.
- O. Saut: PhD defense committee, A. Hocquelet, Univ. Bordeaux, France
- O. Saut: PhD defense committee, G. Birindelli, Univ. Bordeaux, France

10.3. Popularization

10.3.1. Internal or external Inria responsibilities

10.3.2. Interventions

- A. Collin, intervention "midi-rencontre sur les femmes dans les sciences", association TousEn-Sciences
- A. Collin, intervention "place de la femme dans les métiers scientifiques", Robot makers' days
- C. Etchegaray: Fête de la science.
- O. Saut: Journée Scientifique Institut Bergonié.

10.3.3. Internal action

- O. Saut: Café des Sciences.

11. Bibliography

Major publications by the team in recent years

[1] S. BENZEKRY, C. LAMONT, D. BARBOLOSI, L. HLATKY, P. HAHNFELDT. *Mathematical modeling of tumor-tumor distant interactions supports a systemic control of tumor growth*, in "Cancer Research", 2017 [*DOI :* 10.1158/0008-5472.CAN-17-0564], https://hal.inria.fr/hal-01566947

[2] S. BENZEKRY, C. LAMONT, A. BEHESHTI, A. TRACZ, J. M. EBOS, L. HALTKY, P. HAHNFELDT. *Classical Mathematical Models for Description and Forecast of Experimental Tumor Growth*, in "PLoS Computational Biology", August 2014, vol. 10, n^{o} 8, e1003800 p. [*DOI :* 10.1371/JOURNAL.PCBI.1003800], https://hal.inria.fr/hal-00922553

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