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Activity Report 2018

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 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

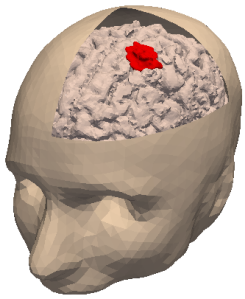

Figure 1. 3D numerical simulation of a meningioma. The tumor is shown in red.

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

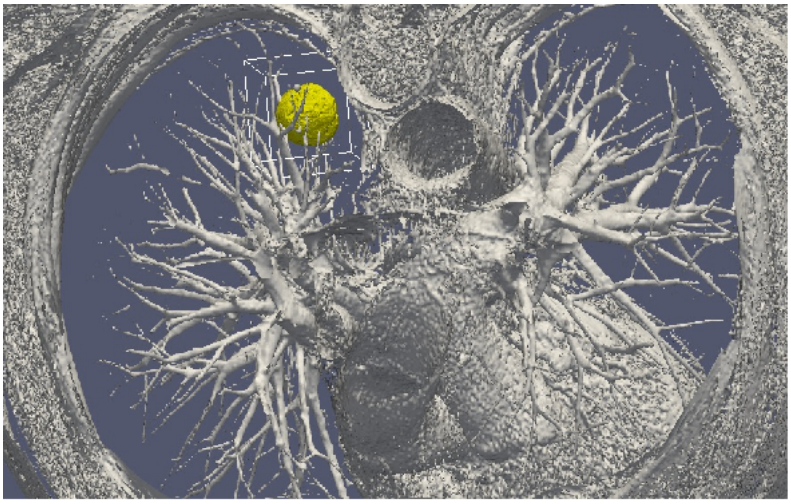

Figure 2. 3D numerical simulation of a lung tumor. The tumor is shown in yellow.

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.

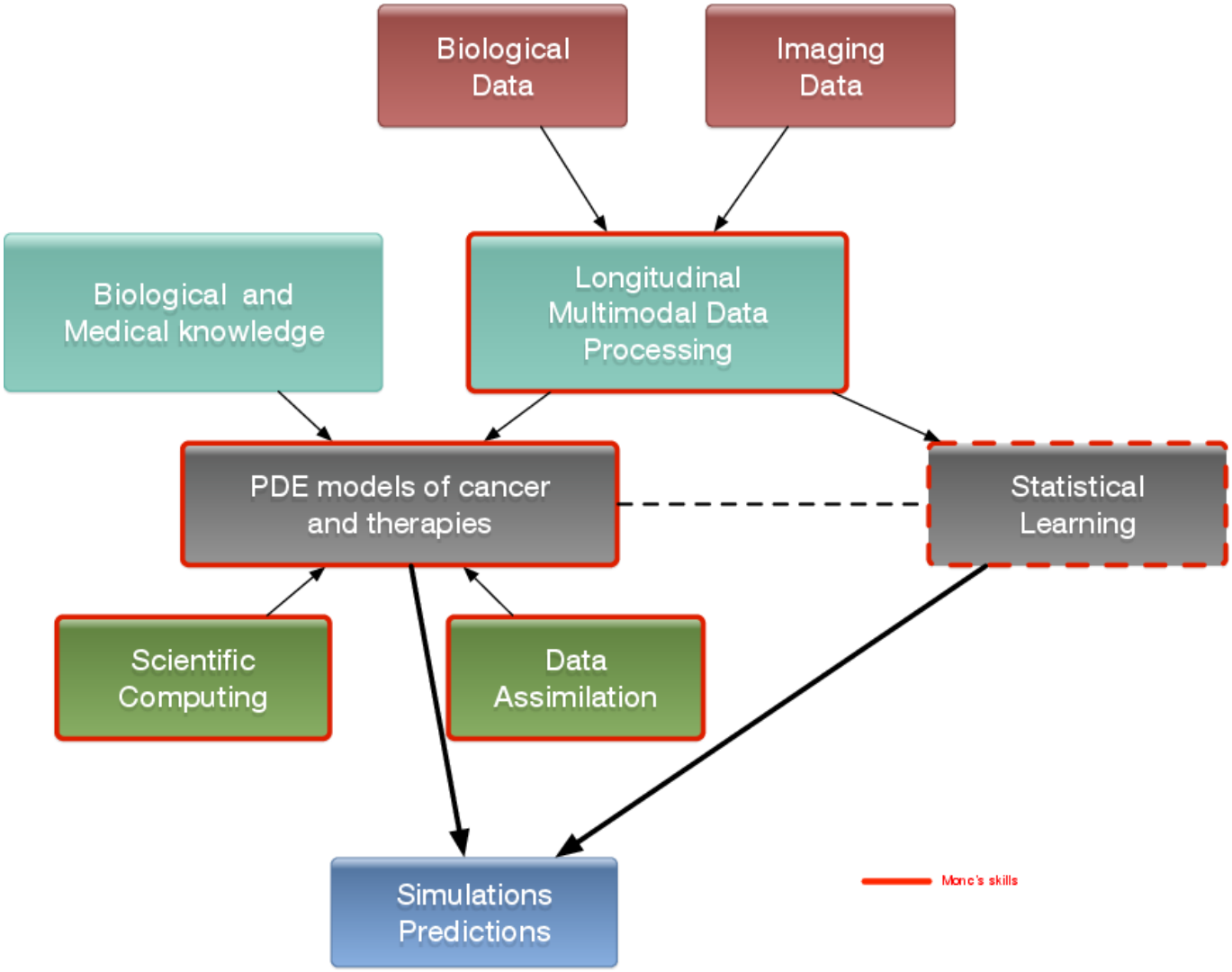

Figure 3. General strategy of the team to build meaningful models in oncology.

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.

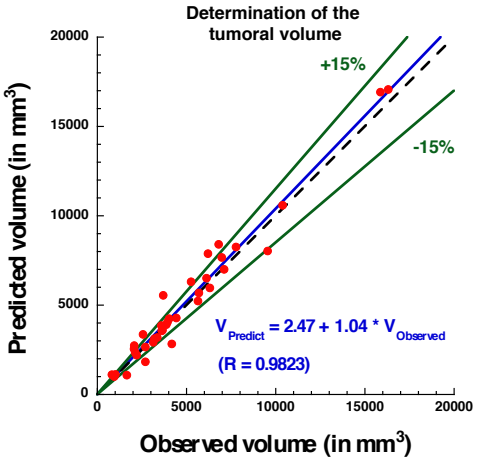

Figure 4. Plot showing the accuracy of our prediction on meningioma volume. Each point corresponds to a patient whose two first exams were used to calibrate our model. A patient-specific prediction was made with this calibrated model and compared with the actual volume as measured on a third time by 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. Experimental research in oncology

We use mathematical modeling as a tool to assist biological cancer research in testing mechanistic hypotheses and pharmacological research. More specifically, our applications include:

- 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,
- Rational and personalized dosing and scheduling of anti-cancer drugs in monotherapy or in combination,
- Mathematical modeling of intra-tumor drug transport to optimize the design of nanoparticules

5. Highlights of the Year

5.1. Highlights of the Year

- S. Benzekry was nominated expert within the scientific board of the national multi-thematic institute (ITMO) Cancer of the French alliance for health sciences (AVIESAN).
- In collaboration with the experimental team of the SMARTc unit of the Center of Cancer Research of Marseille (CRCM), we published the results of a four-years long study for optimizing the sequence and schedule of antiangiogenic-cytotoxics combinations in the treatment of non-small cell lung cancer [7]. With the objective to determine an optimal interval between the administration of the two types of drugs (currently administered concomitantly in the clinic), we validated a research strategy that consisted in three steps: 1) Initial experiments, 2) Calibration and refinement of a mathematical model adapted to the data and 3) experimental validation of the predictions of the calibrated model (superiority of a 3 days time interval).

6. New Software and Platforms

6.1. Nenuphar

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

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

- Partners: CNRS - INP Bordeaux - Université Bordeaux 1
- Contact: Olivier Saut
- URL: https://team.inria.fr/monc/software/

6.2. papriK

KEYWORDS: Medical imaging - DICOM - Image registration - Image segmentation - 2D - 3D - Image analysis - Image processing - Medical applications - Radiomics
SCIENTIFIC DESCRIPTION: PapriK is the team toolkit devoted to processing and analyzing medical images. It currently wraps VTK and ITK and contains our own algorithms as well : - images input/output (including DICOM) - filtering, rescaling, resampling - segmentation/registration - radiomics computation: histogram, texture, shape
NEWS OF THE YEAR: - add python3 support - work on registration - simplify the library - fix bugs

- Participants: Cynthia Perier, Olivier Saut and Erwan Le Masson
- Partners: Institut Bergonié - Université de Bordeaux
- Contact: Cynthia Perier
- Publications: T2-based MRI Delta-Radiomics Improve Response Prediction in Soft-Tissue Sarcomas Treated by Neoadjuvant Chemotherapy - Pre-treatment magnetic resonance-based texture features as potential imaging biomarkers for predicting event free survival in anal cancer treated by chemoradiotherapy
- URL: https://team.inria.fr/monc/software/

6.3. NENUCORE

KEYWORDS: Image segmentation - Biomedical imaging - Image processing - Real-time rendering
SCIENTIFIC DESCRIPTION: Standalone application for visualization, manipulation and segmentation of 2D and 3D images. The software has been developed for application to medical imaging. The visualization is done in real time and the segmentation can be manual or semi-automatic. The software contains a database including medical images of patients, the segmentation data of these images as well as the associated meta-data.

- Participants: Benjamin Taton, Boris Raymond, Jean Mercat and Vivien Pianet
- Contact: Boris Raymond

6.4. metamats_burden

KEYWORDS: Metastasis - Cancer - Data assimilation - Regression - Biostatistics - Mechanistic modeling - Simulation
SCIENTIFIC DESCRIPTION: This Matlab software is a minimal code for fitting simultaneously primary tumor growth and metastatic burden data using nonlinear mixed-effects modeling.
FUNCTIONAL DESCRIPTION: Set of functions for calibration of models of metastatic burden and primary tumor growth to empirical population data

NEWS OF THE YEAR: Submission to the French agency of software protection (APP). Inclusion of a new model for pre-operative anti-angiogenic treatment. Validation of the previous models on large databases (400+ animals)

- Participants: Sébastien Benzekry and Chiara Nicolo
- Partner: Roswell Park Comprehensive Cancer Center
- Contact: Sébastien Benzekry
- Publications: Modeling Spontaneous Metastasis following Surgery: An In Vivo-In Silico Approach - Computational Modelling of Metastasis Development in Renal Cell Carcinoma
- URL: http://metamats.bordeaux.inria.fr/

6.5. metamats_core

KEYWORDS: Metastasis - Cancer - Mechanistic modeling - Simulation - Modeling
SCIENTIFIC DESCRIPTION: This code is devoted to the simulation of partial differential equation (PDE) based models for the time development of a population of secondary tumors (metastases).
FUNCTIONAL DESCRIPTION: Metamats_core simulates a partial differential equation (PDE)-based model for the time development of a population of secondary tumors (metastases).
NEWS OF THE YEAR: Submission to the French agency of software protection (APP)

- Participant: Sébastien Benzekry
- Contact: Sébastien Benzekry
- Publications: Modeling Spontaneous Metastasis following Surgery: An In Vivo-In Silico Approach - Passing to the limit 2D-1D in a model for metastatic growth - Mathematical analysis of a two-dimensional population model of metastatic growth including angiogenesis - Modeling the impact of anticancer agents on metastatic spreading - Global Dormancy of Metastases due to Systemic Inhibition of Angiogenesis
- URL: http://benzekry.perso.math.cnrs.fr/

6.6. IRENA

Numerical Assessment of IRreversible Electroporation ablation
KEYWORDS: Cancer - Numerical electroporation
SCIENTIFIC DESCRIPTION: The C++ software IRENA developed by O. Gallinato and C. Poignard within the Inria team Monc enable sto compute the static electric field distribution in the clinical configuration of IRE ablation of liver tumors. The code is based on the finite volume method on Cartesian grid. The needles and the liver boundary are determined as the zero of a level-set function. Close to the boundaries, the first and second order derivatives are computed with the standard Ghost Fluid Method. The equivalent conductivities at half points are computed thanks to harmonic mean (additivity law of resistivity). In order to maintain a reasonable computation time, the refinement is low enough (1 mm3 grid voxels). As the mesh does not pick up the very fine needles, the Dirichlet conditions imposed on the active parts of the electrodes and the Neumann conditions imposed on the insulated parts are changed into Robin conditions on the first layer of points around the needles, thanks to a second order development. This results in a numerical scheme, which is computationally efficient and accurate enough.
FUNCTIONAL DESCRIPTION: Digital simulation tool for the assessment of irreversible electroporation clinical process

- Authors: Olivier Gallinato and Clair Poignard
- Contact: Clair Poignard

6.7. metamats_size

Fitting longitudinal data of size and number of metastases using mechanistic models

KEYWORDS: Cancer - Mechanistic modeling - Metastasis - Regression - Simulation - Data assimilation
SCIENTIFIC DESCRIPTION: This software fits models of metastatic development to longitudinal data of metastatic sizes and provides simulation and visualization tools for metastatic modeling.
NEWS OF THE YEAR: Establishment of a first clean and minimal version. Validation of the software on clinical data of brain metastases from non-small cell lung cancer. Submission to the French agency of software protection (APP).

- Participants: Sébastien Benzekry and Mariia Bilous
- Partners: Centre de Recherches en Cancérologie de Marseille - Institut Bergonié - Assistance Publique - Hôpitaux de Marseille
- Contact: Sébastien Benzekry
- Publication: Computational modeling reveals dynamics of brain metastasis in non-small cell lung cancer and provides a tool for personalized therapy
- URL: http://metamats.bordeaux.inria.fr/

6.8. Carcinom

Computer-Assisted Research about Cancer growth and INsights on Oncological Mechanisms
KEYWORDS: Cancer - Regression - Tumor growth
SCIENTIFIC DESCRIPTION: This software is primarily designed to perform a modeling analysis of tumor growth kinetics. Given a data set of longitudinal measurements of tumor size in a population, it fits multiple models of tumor growth (either user-defined or selected from a library of classical models), computes goodness-of-fit statistical metrics, identifies the parameters of the models and estimates associated standard errors. Fits of the data can be performed either individual per individual or using a population approach (nonlinear mixed-effects).
FUNCTIONAL DESCRIPTION: Software for modeling and fitting tumor growth kinetics. Given a data set of longitudinal measurements of tumor size in a population, it fits multiple models of tumor growth (either user-defined or selected from a library of classical models), computes goodness-of-fit statistical metrics, identifies the parameters of the models and estimates associated standard errors. Fits of the data can be performed either on an individual basis or using a population approach (nonlinear mixed-effects).

Graphical and statistical tools of use when analyzing growth curves are also included.
NEWS OF THE YEAR: Submission to the French agency of software protection (APP). Development of a python module for interaction with Monolix.

- Participants: Simon Evain, Vivien Pianet and Cristina Vaghi
- Partner: Roswell Park Comprehensive Cancer Center
- Contact: Sébastien Benzekry
- Publication: Classical Mathematical Models for Description and Forecast of Experimental Tumor Growth
- URL: https://team.inria.fr/monc/software/

6.9. Platforms

6.9.1. Transport Equation Solver v1

Submission to the French agency of software protection of the software "Transport Equation Solver v1".

Ce logiciel répond aux besoins liés à l'analyse fonctionnelle de la vascularisation d'un organe par imagerie dynamique et en particulier il concerne l'analyse de la vascularisation placentaire qui est destinée au diagnostic d'anomalies d'invasion placentaire par échographie dynamique de contraste. De manière plus précise, ce logiciel permet, à partir d'un modèle physique d'écoulement des fluides, d'estimer et de quantifier le transport du produit de contraste injecté lors d'une imagerie par échographie dynamique de contraste.

7. New Results

7.1. Mathematical Modeling of the Proliferation Gradient in MultiCellular Tumor Spheroids

Authors: *Thomas Michel*, J. Fehrenbach, V. Lobjois, J. Laurent, A. Gomes, *Thierry Colin, Clair Poignard*. Paper published in the Journal of Theoretical Biology. https://hal.inria.fr/hal-01883189

MultiCellular Tumor Spheroids are 3D cell cultures that can accurately reproduce the behavior of solid tumors. It has been experimentally observed that large spheroids exhibit a decreasing gradient of proliferation from the periphery to the center of these multicellular 3D models: the proportion of proliferating cells is higher in the periphery while the non-proliferating quiescent cells increase in depth. In this paper, we propose to investigate the key mechanisms involved in the establishment of this gradient with a Partial Differential Equations model that mimics the experimental setup of growing spheroids under different nutrients supply conditions. The model consists of mass balance equations on the two cell populations observed in the data: the proliferating cells and the quiescent cells. The spherical symmetry is used to rewrite the model in radial and relative coordinates. Thanks to a rigorous data postprocessing the model is then fit and compared quantitatively with the experimental quantification of the percentage of proliferating cells from EdU immunodetection on 2D spheroid cryosection images. The results of this calibration show that the proliferation gradient observed in spheroids can be quantitatively reproduced by our model.

7.2. Viscoelastic modeling of the fusion of multicellular tumor spheroids in growth phase

Authors: *Guillaume Dechristé*, Jérôme Fehrenbach, Elena Griseti, Valérie Lobjois, *Clair Poignard*. Paper published in the Journal of Theoretical Biology. https://hal.inria.fr/hal-01786027

Background. Since several decades, the experiments have highlighted the analogy of fusing cell aggregates with liquid droplets. The physical macroscopic models have been derived under incompressible assumptions. The aim of this paper is to provide a 3D model of growing spheroids, which is more relevant regarding embryo cell aggregates or tumor cell spheroids. Methods. We extend the past approach to a compressible 3D framework in order to account for the tumor spheroid growth. We exhibit the crucial importance of the effective surface tension, and of the inner pressure of the spheroid to describe precisely the fusion. The experimental data were obtained on spheroids of colon carcinoma human cells (HCT116 cell line). After 3 or 6 days of culture, two identical spheroids were transferred in one well and their fusion was monitored by live videomicroscopy acquisition each 2hours during 72h. From these images the neck radius and the diameter of the assembly of the fusing spheroids are extracted. Results. The numerical model is fitted with the experiments. It is worth noting that the time evolution of both neck radius and spheroid diameter are quantitatively obtained. The interesting feature lies in the fact that such measurements characterise the macroscopic rheological properties of the tumor spheroids. Conclusions. The experimental determination of the kinetics of neck radius and overall diameter during spheroids fusion characterises the rheological properties of the spheroids. The consistency of the model is shown by fitting the model with two different experiments, enhancing the importance of both surface tension and cell proliferation. General Significance. The paper sheds new light on the macroscopic rheological properties of tumor spheroids. It emphasizes the role of the surface tension and the inner pressure in the fusion of growing spheroid. Under geometrical assumptions, the model reduces to a 2–parameter differential equation fit with experimental measurements. The 3–D partial differential system makes it possible to study the fusion of spheroids in non-symmetrical or more general frameworks.

7.3. Mathematical analysis and 2-scale convergence of a heterogeneous microscopic bidomain model

Authors: *Annabelle Collin*, Sébastien Imperiale. Paper published in Mathematical Models and Methods in Applied Sciences. https://hal.inria.fr/hal-01759914

The aim of this paper is to provide a complete mathematical analysis of the periodic homogenization procedure that leads to the macroscopic bidomain model in cardiac elec-trophysiology. We consider space-dependent and tensorial electric conductivities as well as space-dependent physiological and phenomenological non-linear ionic models. We provide the nondimensionalization of the bidomain equations and derive uniform estimates of the solutions. The homogenization procedure is done using 2-scale convergence theory which enables us to study the behavior of the non-linear ionic models in the homogenization process.

7.4. Pre-treatment magnetic resonance-based texture features as potential imaging biomarkers for predicting event free survival in anal cancer treated by chemoradiotherapy

Authors: Arnaud Hocquelet, Thibaut Auriac, *Cynthia Perier*, Clarisse Dromain, Marie Meyer, Jean-Baptiste Pinaquy, Alban Denys, Hervé Trillaud, *Baudouin Denis de Senneville*, Véronique Vendrely. Paper published in European Radiology. https://hal.archives-ouvertes.fr/hal-01962472

AIM: To assess regular MRI findings and tumour texture features on pre-CRT imaging as potential predictive factors of event-free survival (disease progression or death) after chemoradiotherapy (CRT) for anal squamous cell carcinoma (ASCC) without metastasis.
MATERIALS AND METHODS: We retrospectively included 28 patients treated by CRT for pathologically proven ASCC with a pre-CRT MRI. Texture analysis was carried out with axial T2W images by delineating a 3D region of interest around the entire tumour volume. First-order analysis by quantification of the histogram was carried out. Second-order statistical texture features were derived from the calculation of the grey-level co-occurrence matrix using a distance of 1 (d1), 2 (d2) and 5 (d5) pixels. Prognostic factors were assessed by Cox regression and performance of the model by the Harrell C-index.
RESULTS: Eight tumour progressions led to six tumour-specific deaths. After adjusting for age, gender and tumour grade, skewness (HR = 0.131, 95% CI = 0-0.447, p = 0.005) and cluster shade_d1 (HR = 0.601, 95% CI = 0-0.861, p = 0.027) were associated with event occurrence. The corresponding Harrell C-indices were 0.846, 95% CI = 0.697-0.993, and 0.851, 95% CI = 0.708-0.994.
CONCLUSION: ASCC MR texture analysis provides prognostic factors of event occurrence and requires additional studies to assess its potential in an "individual dose" strategy for ASCC chemoradiation therapy.
KEY POINTS: MR texture features help to identify tumours with high progression risk. Texture feature maps help to identify intra-tumoral heterogeneity. Texture features are a better prognostic factor than regular MR findings.
KEYWORDS: Anal squamous cell carcinoma; Definitive chemoradiotherapy; Imaging biomarkers; Magnetic resonance imaging; Texture analysis

7.5. T2-based MRI Delta-radiomics improve response prediction in soft-tissue sarcomas treated by neoadjuvant chemotherapy

Authors: *Amandine Crombé, MS Cynthia Périer*, Michèle Kind, *Baudouin Denis De Senneville*, François Le Loarer, Antoine Italiano, Xavier Buy, *Olivier Saut*. Paper published in the Journal of Magnetic Resonance Imaging. https://hal.inria.fr/hal-01929807

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 relies 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: Sixty-five 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 two chemotherapy cycles.

Field Strength/Sequence: Pre- and postcontrast enhanced T1-weighted imaging (T1-WI), turbo spin echo T2-WI at 1.5 T.
Assessment: A threshold of $< 10\%$ viable cells on surgical specimens 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 voxel-sizes 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 crossvalidation (training and validation) on 50 patients ("training cohort") and was validated on 15 other patients ("test cohort").
Results: Sixteen patients were good-HR. Neither RECIST status (P = 0.112) nor semantic radiological variables were associated with response (range of P-values: 0.134–0.490) 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 three features: Δ_Histogram_Entropy, Δ_Elongation, Δ_Surrounding_Edema, which provided: area under the curve the receiver operating characteristic = 0.86, accuracy = 88.1%, sensitivity = 94.1%, and 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 Conclusion: A T2-based Delta-radiomics approach might improve early response assessment in STS patients with a limited number of features.

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

Authors: Diane-Charlotte Imbs, Raouf El Cheikh, Arnaud Boyer, Joseph Ciccolini, Celine Mascaux, Bruno Lacarelle, Fabrice Barlesi, Dominique Barbolosi, *Sébastien Benzekry*. Paper published in Clinical Pharmacology and Therapeutics: Pharmacometrics and Systems Pharmacology. https://hal.inria.fr/hal-01624423v2

Concomitant administration of bevacizumab and pemetrexed-cisplatin is a common treatment for advanced non-squamous 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 using. First, experiments demonstrated improved efficacy when using sequential versus concomitant scheduling of bevacizumab and chemotherapy. Using 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 (70 vs. 74 days). Alternate sequencing of 8 days failed in achieving 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.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

Research contract between the pharmaceutical company Roche and the MONC team.

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: 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)

9.1.1.2. 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)

9.1.1.3. 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.

9.1.1.4. 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)
- 116.64k€

9.1.2. 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€.

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. European Initiatives

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

9.3. International Initiatives

9.3.1. Inria International Labs

Inria@SiliconValley

Associate Team involved in the International Lab:

9.3.1.1. Num4SEP

Title: Numerics for Spherical Electroporation

International Partner (Institution - Laboratory - Researcher):

University of California, Santa Barbara (United States) - Department of 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.

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

9.3.2.1. 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.

9.3.3. Other international initiatives

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

9.3.4. Informal International Partners

- Collaboration with Jonathan Mochel at the Department of Biomedical Sciences of Iowa State University (Ames, Iowa, USA). Development of mechanistic pharmacokinetics/pharmacodynamics models for comparative oncology (i.e. translational oncology across species integrating veterinary medicine). Sebastien Benzekry is Affiliate Assistant Professor at Iowa State University.
- Collaboration between Sebastien Benzekry and the laboratory of Yuval Shaked at the Rappaport Faculty of Medicine of the Technion (Israel Institute of Technology, Haifa, Israel). Our joint work deals with validating mathematical models of host-mediated resistance mechanisms to anti-cancer therapies.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

June 2018: Visit of John Ebos (Roswell Park Cancer Institute, Buffalo, USA) in the context of the METAMATS Inria Associate team.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. General Chair, Scientific Chair

C. Poignard was one of the chair of the CEMRACS 2018 about “Numerical and mathematical modeling for biological and medical applications: deterministic, probabilistic and statistical descriptions"

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

S. Benzekry was in the Scientific Committee of the “Third MB2 conference (Mathematical Biology Modeling days of Besançon)" held in June 2018 in Besançon, France.

10.1.2.2. Reviewer

B. Denis de Senneville was a reviewer for the IEEE International Symposium on Biomedical Imaging (ISBI) held in April 2018 in Washington DC, 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 “Discrete and Continuous Dynamical Systems-S"

10.1.3.2. Reviewer - Reviewing Activities

- S. Benzekry served as a reviewer for PLoS Computational Biology, Medical Image Analysis, Cancer Chemotherapy and Pharmacology, Oncotarget and Applicandae Mathematica.
- B. Denis de Senneville served as a reviewer for IEEE Transactions on Medical Imaging, Physics in Medicine and Biology and Journal of Medical Imaging.
- O. Saut served as a reviewer for PLOS One and Computational and Applied Mathematics.

10.1.4. Invited Talks

- S. Benzekry: Jan 2018, Conference on Statistics and Health, Toulouse, France

- S. Benzekry: Feb 2018, CMM-Fields-Inria Workshop on Mathematics for Medicine, Toronto, Canada
- S. Benzekry: Jun 2018, 3rd Mathematical Biology Modelling Days, Besançon, France
- O. Saut: Computational Systems Biology of Cancer, Institut Curie, France
- S. Benzekry: Jun 2018, Mathematical perspectives in the biology and therapeutics of cancer, Marseille, France
- C. Poignard: Jul. 2018, Mathematical perspectives in the biology and therapeutics of cancer, Marseille, France
- S. Benzekry: Jul 2018, Annual Workshop on Mathematics in Medicine, Wolfgang Pauli Institute, Vienna, Austria
- C. Poignard: Aug. 2018, The XIVth Franco-Romanian Conference in Applied Mathematics, Bordeaux, France
- O. Saut: Sep 2018, Virtual Physiological Human Conference (VPH), Zaragoza, Spain
- B. Denis de Senneville: Oct. 2018, Partial Differential Equations for Social and Biological Events, Osaka, Japan
- C. Poignard: Oct. 2018, Partial Differential Equations for Social and Biological Events, Osaka, Japan
- S. Benzekry: Nov 2018, Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy, Oaxaca, Mexico

10.1.5. Leadership within the Scientific Community

- S. Benzekry was nominated expert within the scientific board of the national multi-thematic institute (ITMO) Cancer of the French alliance for health sciences (AVIESAN).

10.1.6. Scientific Expertise

- B. Denis de Senneville was a grant reviewer for the Swiss National Science Fundation.
- B. Denis de Senneville was in the selection committee for an Assistant Professor position in Bordeaux University.
- C. Poignard was in the Inria CRCN National selection committee

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Licence : S. Benzekry, Ordinary Differential Equations, 20h, L3, INP Bordeaux, France

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

Licence : B. Denis de Senneville, Probability and Statistics, 30h, 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

Doctorat: S. Benzekry, Computational modeling in medicine, 6h, Université de Bordeaux, France

10.2.2. Supervision

PhD : T. Kritter, *Utilisation de données cliniques pour la construction de modèles en oncologie*, Université de Bordeaux, 01/10/2018, under the supervision of Olivier Saut et de Clair Poignard

PhD in progress : C. Nicolò, *Mathematical modeling of systemic aspects of cancer and cancer therapy*, 2016 - 2019, under the supervision of S. Benzekry and O. Saut

PhD in progress: S. Corridore, *Mathematical Model for Electroporation*, 2016 - 2019, under the supervision of A. Collin, C. Poignard.

PhD in progress: C. Perier, *Combining texture analysis and modeling for evaluation of therapies and clinical outcome*, under the supervision of B. Denis de Senneville and O. Saut, 2016 - 2019.

PhD in progress: A. Crombé, *Beyond radiomics for soft-tissue sarcoma*, 2017-2020, under the supervision of O. Saut.

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

10.2.3. Juries

- S. Benzekry: Committee member of the PhD thesis of A. Rodallec (Aix-Marseille University)
- A. Collin: Committee member of the PhD thesis of T. Kritter (Bordeaux University)
- B. Denis de Senneville: Committee member of the PhD thesis of C. Zachiu
- C. Poignard: Reviewer of the PhD thesis of A. Auvray (Ecole Centrale de Lyon)
- C. Poignard: Committee member of the PhD thesis of T. Kritter (Bordeaux University)
- O. Saut : Committee member of the Phd thesis of J-E Bibault (Univ. Sorbonne Paris Cité).
- O. Saut : Committee member of the PhD thesis of Alexis Arnaud (Grenoble Alpes University).

10.3. Popularization

10.3.1. Internal or external Inria responsibilities

- S. Benzekry is a member of the local Inria commission of informatical tools users (CUMI)
- C. Poignard is an elected member of Inria's national evaluation committee.

10.3.2. Interventions

- O. Saut: Fête de la Science, Cap Science, Bordeaux.

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

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[10] F. RAMAN, E. SCRIBNER, O. SAUT, C. WENGER, T. COLIN, H. M. FATHALLAH-SHAYKH. *Computational Trials: Unraveling Motility Phenotypes, Progression Patterns, and Treatment Options for Glioblastoma Multiforme*, in "PLoS ONE", January 2016, vol. 11, n^{o} 1 [*DOI :* 10.1371/JOURNAL.PONE.0146617], https://hal.inria.fr/hal-01396271

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Articles in International Peer-Reviewed Journals

[11] A. ANDREYCHENKO, B. DENIS DE SENNEVILLE, R. NAVEST, R. TIJSSEN, J. LAGENDIJK, A. VAN DEN BERG. *Respiratory motion model based on the noise covariance matrix of a receive array*, in "Magnetic Resonance in Medicine", March 2018, vol. 79, n^{o} 3, pp. 1730-1735, https://hal.archives-ouvertes.fr/hal-01962483

[12] P. BOUR, V. OZENNE, F. MARQUET, B. DENIS DE SENNEVILLE, E. DUMONT, B. QUESSON. *Real-time 3D ultrasound based motion tracking for the treatment of mobile organs with MR-guided high-intensity focused ultrasound*, in "International Journal of Hyperthermia", April 2018, vol. 34, n^{o} 8, pp. 1225-1235, https://hal.archives-ouvertes.fr/hal-01962473

[13] T. COLIN, G. DECHRISTÉ, J. FEHRENBACH, L. GUILLAUME, V. LOBJOIS, C. POIGNARD. *Experimental estimation of stored stress within spherical microtissues: What can and cannot be inferred from cutting experiments*, in "Journal of Mathematical Biology", 2018, vol. 77, n^{o} 4, https://hal.inria.fr/hal-01782340

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[27] S. BENZEKRY. *Mathematical Modeling of Tumor-Tumor Distant Interactions Supports a Systemic Control of Tumor Growth*, in "3rd Mathematical Biology Modeling days of Besançon", Besançon, France, June 2018, https://hal.inria.fr/hal-01969102

[28] S. BENZEKRY. *Mechanistic modeling of metastasis: cancer at the organism scale*, in "Mathematical Models in Cancer", Vienna, Austria, July 2018, https://hal.inria.fr/hal-01969104

[29] S. BENZEKRY. *Optimization of sequential administration of bevacizumab plus cytotoxics in non-small cell lung cancer by combining in vivo experiments and mathematical modeling*, in "Mathematical perspectives in the biology and therapeutics of cancer", Marseille, France, July 2018, https://hal.inria.fr/hal-01969142

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[33] V. OZENNE, P. BOUR, B. DENIS DE SENNEVILLE, M. DELCEY, W. BEN HASSEN, A. VAUSSY, S. RAINER, B. QUESSON. *3D ultrasound based motion tracking combined with rapid multislice MR-thermometry for MR guided HIFU on mobile organs*, in "International Society of Magnetic Resonance in Medicine", Paris, France, June 2018, https://hal.archives-ouvertes.fr/hal-01963275

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