" Mathematical perspectives in the biology and therapeutics of cancer"

CIRM Marseille, France

July 9-13, 2018

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July 10, 2018

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For more details :

`https://mathscancer.sciencesconf.org`

Chapter 1

Timetable

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19H30 DINNER	19H15 DINNER	19H15 DINNER	19H30 DINNER	
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Poster session

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Mathematical modelling of the interaction between a tumor and the immune system

Stefano AVANZINI (University of Edinburgh, UK)
Cancer Recurrence Times from a Branching Process Model

Federica BUBBA (University Paris Sorbonne, FRANCE)
Density-dependent Keller-Segel models for cell culture pattern formation

David CHEEK (Edinburgh University, UK)
Mutation frequencies in a birth-death branching process

Martina CONTE (BCAM - Basque Center for Applied Mathematics, SPAIN)
Glioma Proliferation, Spread and Therapy: a Multiscale Approach

Chloé DOMINICI (IBDM, Aix-Marseille Université, FRANCE)
3D analysis of neuronal networks remodeling in pancreatic cancer

Clément DRAGHI (Institut Rafael, Levallois-Perret, FRANCE)
Towards an individualized spatial modeling for tumor growth

Antonio FERNÁNDEZ ROMERO (Universidad de Sevilla, SPAIN)
Glioblastoma evolution model in relation to vasculature

Karina GARCIA (Center of Molecular Immunology, Havana, CUBA)
Mathematical modeling of the evolution of heterogeneous tumors interacting with Effector and Regulatory T cells

Jérémy GUILLOT (IBDM, Aix-Marseille Université, FRANCE)
Role of sympathetic nervous system in pancreatic cancer development

Ghassen HADDAD (Institut Pasteur de Tunis, TUNISIA)
An optimal control model of a heterogeneous tumor treatment in the context of stem cell cancer

Sara HAMIS (Swansea University, UK)
Chemotherapeutic drug resistance in cancer: Insights from a multiscale in silico study

Roger HILL (University of Warwick, UK)
Optimizing circadian drug infusion schedules towards personalized cancer chronotherapy

Martin HOFFMANN (Fraunhofer ITEM, Regensburg, GERMANY)
Stochastic system identification without an a priori chosen kinetic model—exploring feasible cell regulation with piecewiselinear functions

Odelaisy LEÓN-TRIANA (University of Castilla-La Mancha, SPAIN)
Brain metastasis: Growth laws and imaging biomarkers

Maciej LESZCZYNSKI (Lodz University of Technology, POLAND)
On the Role of Pharmacometrics in Optimal Control of Models for Cancer Therapies

Michael NICHOLSON (University of Edinburg, UK)
Competing Paths in Growing Populations over Fitness Valleys

Ana OSOJNIK (University of Oxford, UK)
Systematic analysis of a bifurcating model of tumour-immune interactions

Julián PÉREZ-BETETA (Universidad de Castilla-La Mancha, SPAIN)
Quantifying the complexity of the spacing between surfaces: Applications to brain tumors.

Pirmin SCHLICKE (Technical University Munich, GERMANY)
An extended model for the growth and the size distribution of metastases including therapy methods

Laure TALARMAIN (University of Cambridge, UK) *Identifying drugging strategies using evolutionary principles in lymphoma mouse model*

1.2 Detailled planning

Monday July 9th

8h50-9h00 **Welcome Session**

9h00-09h50 **Avner FRIEDMAN** (Ohio State University, USA))
Combination therapy in cancer

9h50-10h15 **Christophe LETELLIER** (Université de Rouen, FRANCE)
Optimizing intermittent hormonotherapy after a prostatectomy by using individualized model

10h15-10h40 **Sara HAMIS** (Swansea University, UK)
Trojan-horse cancer drugs: An in silico investigation into hypoxia activated prodrugs

10h40-11h00 **Coffee Break**

11h00-11h25 **Annabelle BALLESTA** (University of Warwick, UK)
P-glycoprotein (Abcb1) expression and activity are sex-, feeding-, and circadian time-dependent, implications for mechanistic pharmacokinetics modeling.

11h25-12h15 **Tomás ALARCÓN** (Barcelona, SPAIN)
Heterogeneity in epigenetic regulatory systems: Epigenetic plasticity inaging and cancer

12h30 -13h30 **LUNCH**

14h00-14h50 **Victor M. PÉREZ-GARCÍA** (Universidad de castilla-La Mancha, SPAIN)
Morphological MRI-based features derived from biologically-inspired mathematical models predict glioblastoma survival

14h50-15h15 **Nicolas MEUNIER** (University Paris Descartes, FRANCE)
A minimal multi-scale approach for cell migration modelisation

15h15-15h40 **Rémi TESSON** (Aix-Marseille University , FRANCE)
Cell migration modeling of the impact of microtubules dynamics on cell migration

15h40-16h00 **Coffee Break**

16h00-16h25 **Mathilde BADOUAL** (CNRS, Paris, FRANCE)
Modeling the origin of gliomas

16h25-17h15 **Clair POIGNARD** (INRIA Sud-Ouest, FRANCE)
Numerical Workflow for Electroporation Ablation of Liver Tumors

19h30 **DINNER**

Tuesday July 10th

9h00-09h50 **Tommaso LORENZI** (University of St Andrews, UK)
Partial differential equation models of evolutionary and spatial dynamics of cancer cell populations

9h50-10h15 **Peter RASHKOV** (University of Sofia, BULGARIA)
Multistability and hormesis in the dual phosphorylation-dephosphorylation cycle

10h15-10h40 **Cecilia POLA** (Universidad de Cantabria, SPAIN)
Analysing Optimal Control Problems for the Gompertz Model in Chemotherapy

10h40-11h00 **Coffee Break**

11h00-11h25 **Clément DRAGHI** (Institut Rafael, Levallois-Perret, FRANCE)
MooveCare: a web-mediated follow-up based on weekly self-reported symptoms From chaos theory to clinical practices

11h25-12h15 **Doron LEVY** (University of Maryland, USA)
Modeling the chemotherapy-induced selection of drug-resistant traits during tumor growth

12h30 -13h30 **LUNCH**

14h00-14h50 **Marc WILLIAMS** (Barts cancer Institute, University of London, UK)
Quantifying evolution in human cancers with genomics

14h50-15h15 **Geneviève FOUREL** (ENS Lyon, FRANCE)
Why we should care about repeat sequences and not only genes, in cancer?

15h15 -19h30 **Visit of calanques or visit of Marseille**

19h00 **DINNER**

20h00-... Semi Final of FIFA world CUP

Wednesday July 11th

9h00-10h40 **- ITMO CANCER Symposium**

9h00-9h25 **Christine CHOMIENNE** (Director of ITMO Cancer Aviesan and Research and Innovation department INCA, Paris, FRANCE)
Where Math meets Cancer Research

9h25-9h50 **Pedro BALLESTER** (Centre de recherche en cancérologie de Marseille, FRANCE)
Precision and recall oncology: combining multiple gene alterations for improved identification of drug-sensitive tumours

9h50-10h15 **Sébastien BENZEKRY** (INRIA Sud Ouest, Bordeaux, FRANCE)
Optimization of sequential administration of bevacizumab plus cytotoxics in non-small cell lung cancer by combining in vivo experiments and mathematical modeling

10h15-10h40 **David TAIEB** (AP-HM, Aix-Marseille University, FRANCE)
Mathematical modeling of disease dynamics in SDHB- and SDHD-related paraganglioma: Further step in understanding hereditary tumor differences and future therapeutic strategies

10h40-11h05 **Patrick BREST** (Institute of Research on Cancer and Aging of Nice)
Role of tumor microenvironment in tumor progression

11h05-11h20 **Coffee Break**

11h20-12h30 **POSTER SESSION**

12h30 -13h30 **LUNCH**

14h00-14h50 **Mark VINCENT** (London Regional Cancer Centre, University of Western Ontario, CANADA)
A-Theory: Why atavism must now be taken seriously as an explanation for cancer

14h50-15h40 **Philip MAINI** (University of Oxford, UK)
Modelling tumour angiogenesis

15h40-16h00 **Coffee Break**

16h00-16h50 **Charles DUMONTET** (Centre de Recherche en Cancérologie de Lyon)
Resistance to anticancer agents : a multifactorial problem

19h00 **DINNER**

20h00-... Semi Final of FIFA world CUP

Thursday July 12th

9h00-09h50 **Marcello DELITALA** (Politecnico di torino, ITALY)
Combination therapies and drug resistance in heterogeneous tumoral populations

9h50-10h15 **Cécile CARRÉRE** (Sorbonne Université, FRANCE)
Dynamical programming of a chemotherapy preventing drug resistance for in vitro heterogeneous tumours

10h15-10h40 **Camille POUCHOL** (Sorbonne Université, FRANCE)
Efficient chemotherapy in spite of drug resistance: optimal strategy and robustness

10h40-11h00 **Coffee Break**

11h00-11h25 **Mihály KOLTAI** (Insitut Curie, Paris, FRANCE)
Mathematical modeling of drug resistance and sensitivity in colon cancer cell lines

11h25-12h15 **Thomas LEPOUTRE** (INRIA Rhône Alpes, FRANCE)
Impact of the immune system on chronic myeloid leukemia

12h30 -13h30 **LUNCH**

14h00-14h25 **Maria Pia SACCOMANI** (University of Padova, ITALY)
The relevance of identiability in model-based oncological studies. A new method to calculate all the possible parameter solutions of a tumor model.

14h25-14h50 **Magdalena E. STRAUSS** (University of Cambridge, UK)
Bayesian hierarchical context-dependent across-clustering for multi-omics pan-cancer data

14h50-15h15 **Juan CALVO** (Universidad de Granada, SPAIN)
Estimating compartment size for stochastic and hybrid simulations of structured populations

15h15-15h40 **Coffee Break**

19h30 **GALA DINNER**

Friday July 13th

9h00-09h50 **John EBOS** (Roswell Park Comprehensive Cancer Center, Buffalo, USA)
Modeling metastasis after tumor microenvironment inhibition: An in vivo/in silico approach

9h50-10h15 **Niklas KOLBE** (University of Mainz, GERMANY)
Modeling and simulation of EMT and tumor cell heterogeneity in cancer invasion

10h15-10h40 **Cristina VAGHI** (INRIA Sud-Ouest, FRANCE)
Improving the efficacy of antibody nanoconjugates in cancertherapy with mathematical modeling

10h40-11h00 **Coffee Break**

11h00-11h25 **Martin HOFFMANN** (University of Tübingen, Germany)
Genetic alterations driving metastatic colony formation are acquired outside of the primary tumour in melanoma

11h25-12h15 **Dominique BARBOLOSI** (Aix-Marseille University, FRANCE)
Is there again a place for the phenomenological models in medicine?

12h15-12h30 **Closure session**

12h30 -13h30 **LUNCH**

Chapter 2

Abstracts

2.1 Invited Speakers

1. ALARCON Tomas
2. BARBOLOSI Dominique
3. DELITALA Marcello
4. DUMONTET Charles
5. EBOS John
6. FRIEDMAN Avner
7. LEPOUTRE Thomas
8. LEVY Doron
9. LORENZI Tommaso
10. MAINI Philip
11. PÉREZ-GARCÍA Victor M.
12. POIGNARD Clair
13. TAVARE Simon
14. VINCENT Mark
15. WILLIAMS Marc

ALARCÓN Tomás

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Heterogeneity in epigenetic regulatory systems: Epigenetic plasticity in aging and cancer

Evidence is accumulating regarding the central role of the mechanisms controlling cell fate and phenotypic robustness in age-associated diseases, in particular cancer. Recent experimental results have revealed that aging affects both robustness of the (differentiated) phenotypes of somatic cells, which are more likely to revert to a pluripotent phenotype as the organism ages, and the ability of tissues to regenerate by locking progenitor cells in the pluripotent phenotype. Epigenetic regulation (ER) is one of the key mechanisms regulating cell phenotype. ER refers to a series of modifications of the cell's DNA. Such modifications can disrupt or allow expression of particular genes. Recent theoretical work and experimental evidence, has brought to bear the concept of *epigenetic plasticity*, particularly regarding the pathogenesis of cancer. Epigenetic plasticity refers to the emergence of overly restrictive or overly permissive chromatin states. In order to further explore these issues, we consider a system where a model of gene network which regulates the phenotypic switch between the differentiated and the pluripotent states. Each gene within this regulatory system is acted upon by epigenetic regulation which restricts/enables their expression capability, so that ER is crucial to tip the scale one way or the other. Beyond that, a key element in our model is heterogeneity in the epigenetic regulatory system. ER is carried out by means of covalent modifications of the histones which depend on enzymatic catalysis to occur. In this talk, we review recent work addressing the study of variability of the abundance of both HMEs and their corresponding co-factors on ER function leading to drastic changes in the systems that regulate cell fate.

BARBOLOSI Dominique

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Is there again a place for the phenomenological models in medicine?

It is usual to contrast phenomenological models with mechanistic models, however though the mechanistic models allow to tacking account a more great complexity, in practice clinical the data are poor and thus these models are often not adapted for the applications, mainly because it is not possible to estimate the parameters involved. In order to plaid in favour of the phenomenologicals models, we shall give fews examples in the field of the medecine which will show that, at each stage of the care of a patient (diagnostic, treatment, evaluation of the therapeutic response,...) of the simple mathematical models can be an useful tool to help the clinicians to realize a better precision medecine.

Marcello DELITALA

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Combination therapies and drug resistance in heterogeneous tumoral populations

How combination therapies can reduce the emergence of cancer resistance? Can we exploit intra-tumoral competition to modify the effectiveness of anti-cancer treatments?
Bearing these questions in mind, we present a mathematical model of cancer-immune competition under therapies. The model consists of a system of differential equations for the dynamics of two cancer clones and T-cells. Comparisons with experimental data and clinical protocols for non-small cell lung cancer have been performed.
In silico experiments confirm that the selection of proper infusion schedules plays a key role in the success of anti-cancer therapies. The outcomes of protocols of chemotherapy and immunotherapy (separately and in combination) differing in doses and timing of the treatments are analyzed.
In particular, we highlight how exploiting the competition between cancer populations seems to be an effective recipe to limit the insurgence of resistant populations. In some cases, combination of low doses therapies could yield a substantial control of the total tumor population without imposing a massive selective pressure that would suppress the sensitive clones leaving unchecked the clonal types resistant to therapies.

Bibliography

[1] E. Piretto, M. Delitala and M. Ferraro (2018). *Combination therapies and intra-tumoral competition: insights from mathematical modelling*, Journal of Theoretical Biology, 446, 149–159.
[2] E. Piretto, M. Delitala and M. Ferraro (2018). *How combination therapies shape drug resistance in heterogeneous tumoral populations*, Preprint.

DUMONTET Charles

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Resistance to anticancer agents : a multifactorial problem

Treatment of cancer has greatly diversified during the past decades. Initially limited to local therapy such as surgery and radiotherapy, the treatment of cancer patients then benefited from systemic therapies with anti-hormone approaches and cytotoxic chemotherapies. More recently the discovery of molecular characteristics of tumor cells has lead to the development of small molecule targeted therapies and to a first generation of tumor targeting immunotherapies. The latest and most promising breakthrough has consisted in the unleashing of the patient's immune system thanks to "immune checkpoint inhibitors" and the use of genetically modified immune cells. In spite of this large variety of therapeutic options there still remains a large number of patients whose disease will not respond to therapy. Resistance to therapy remains a major issue and is due to a large variety of mechanisms, some of which are shared by several therapies while some are highly specific of some treatments. A better understanding of these resistance mechanisms is essential both to optimize the use of existing compounds through the selection of patients most likely to benefit from certain therapies, and to contribute to the development of more potent agents and strategies.

EBOS John

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Modeling metastasis after tumor microenvironment inhibition: An in vivo/in silico approach

Cancer therapies targeting the tumor microenvironment include drugs that block angiogenesis (VEGF) and immunecheckpoints (PD-1/PD-L1) have been efficacious in treating metastatic disease. But determining how such agents, either alone or in combination, will work in earlier disease stages remain unclear and few preclinical models exist which can faithfully mimic progression as it occurs in patients. Work in my laboratory focuses on the use of surgical metastasis models (orthotropic tumor implantation followed by resection) to evaluate VEGF and PD-1 pathway inhibitor impact on disease progression after neoadjuvant (before surgery) and adjuvant (after surgery) treatments. In collaboration with Dr. Sebastien Benzekry (INRIA, Bordeaux), we have used mouse kidney, breast, and melanoma data to build mathematical models that i) may account for the impact of surgery and treatment on metastatic progression and, ii) establish potential biomarkers which may predict outcome. The goal of this work is to evaluate whether a combined in vivo/in silico model can provide a clinical guide for trial development of VEGF/PD-1 inhibitor use in the perioperative setting.

FRIEDMAN Avner

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Combination therapy in cancer

Most clinical trials for cancer therapy fail: 70In this talk I will consider combination therapy where one of the drugs is one of the recently FDA-approved checkpoint inhibitors, anti-PD-1, or anti-CTLA-4. I will show, for several choices of a second drug, that there are zones of antagonism in the combination therapy, e.g., an increase in the drug anti-PD-1 has the effect of increasing the cancer volume. Such zones of antagonism should be avoided in clinical trials. The mathematical models are represented by systems of PDEs and the tumor boundary is a "free boundary." This work is joint with Dr. Xiulan Lai.

LEPOUTRE Thomas[1] joint work with Bernard S., Besse A., Clapp G., Levy D., Nicolini FE

INRIA Rhônes Alpes, Lyon, FRANCE

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Impact of the immune system on chronic myeloid leukemia

Chronic myeloid leukemia is a blood cancer for which there exists a very efficient targeted therapy (Tyrosine Kinase Inhibitors). While this has revolutionnized the long term prognosis of treated patients, the next question is the possibility of stopping the treatment and thereby entering so called Treatment Free Remission (TFR). We present recent results on the mathematical modelling of chronic myeloid leukemia. Describing the interaction between chronic myeloid leukemia and autologous immune response, we propose an interpretation of treatment free remission as a stability property. The interpretation is then a control of the disease by the immune system rather than an eradication.

LEVY Doron

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Modeling the chemotherapy-induced selection of drug-resistant traits during tumor growth

The emergence of drug-resistance is a major challenge in chemotherapy. In this talk we will present our recent mathematical models for describing the dynamics of drug-resistance in solid tumors. Our models follow the dynamics of the tumor, assuming that the cancer cell population depends on a phenotype variable that corresponds to the resistance level to a cytotoxic drug. We incorporate the dynamics of nutrients and two different types of drugs: a cytotoxic drug, which directly impacts the death rate of the cancer cells, and a cytostatic drug that reduces the proliferation rate. Through analysis and simulations, we study the impact of spatial and phenotypic heterogeneity on the tumor growth under chemotherapy. We demonstrate that heterogeneous cancer cells may emerge due to the selection dynamics of the environment. Our models predict that under certain conditions, multiple resistant traits emerge at different locations within the tumor. We show that a higher dosage of the cytotoxic drug may delay a relapse, yet, when this happens, a more resistant trait emerges. Moreover, we estimate the expansion rate of the tumor boundary as well as the time of relapse, in terms of the resistance trait, the level of the nutrient, and the drug concentration. Finally, we propose an efficient drug schedule aiming at minimizing the growth rate of the most resistant trait. By combining the cytotoxic and cytostatic drugs, we demonstrate that the resistant cells can be eliminated.

LORENZI Tommaso

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Partial differential equation models of evolutionary and spatial dynamics of cancer cell populations

A growing body of research indicates that mathematical modelling can complement experimental cancer research by offering alternative means of interpreting experimental data and by enabling extrapolation beyond empirical observation. This talk deals with mathematical models formulated in terms of nonlinear partial differential equations which can be used to study evolutionary and spatial dynamics of cancer cell populations. I will present a number of results which illustrate how the analysis and numerical simulation of these equations can help to uncover fresh insights into the critical mechanisms which underpin tumour progression and the emergence of resistance to cytotoxic therapy.

MAINI Philip

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Modelling tumour angiogenesis

Tumour vascular is highly disordered and has been the subject of intense interest both clinically (anti-angiogenesis therapies) and theoretically (many models have been proposed). In this talk, I will review aspects of modelling tumour angiogenesis and how different modelling assumptions impact conclusions on oxygen delivery and, therefore, predictions on the possible effects of radiation treatments.

PÉREZ-GARCÍA Victor Manuel[1]

1 - Mathematical Oncology Laboratory (MôLAB), Universidad de Castilla-La Mancha, Spain.

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Brain gliomas: Survival prediction and therapy personalization using mathematics and imaging data

The study of gliomas has attracted strong attention from the mathematical community. Many different types of models describing the growth of gliomas and their response to therapies, mostly based on (systems of) partial differential equations, have been developed. In parallel, the imaging and computer science communities have tried to construct survival and response predictors based on features 'blindly' extracted from the images and analyzed via statistical and machine learning methods, the so-called 'radiomics'.
In this talk I will describe how to combine the best of both worlds to predict survival of high-grade gliomas with an unprecedented level of accuracy. I will also discuss how our approach can also be used for therapy personalization that can be (and is being) implemented in clinical practice. I will discuss also related problems on therapy optimization for low-grade gliomas.

POIGNARD Clair

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Numerical Workflow for Electroporation Ablation of Liver Tumors

Electroporation-based therapies (EPT) consist in applying high voltage short pulses to cells (typically several hundred volts per centimeter during about one hundred microseconds) in order to create defects in the plasma membrane. They provide interesting alternatives to standard ablative techniques, in particular for deep seated located tumors (near vital organs or important vessels). However their use and their evaluation are still controversial in clinics. We present here a clinical workflow combined with numerical studies dedicated to IRE ablation. The clinical data consist on the one hand of a pre-treatment CT-scan, a C-arm Cone Beam CT with the electrodes and the post-treatment MR performed 3days after the IRE. On the other hand, chronograms of the electric intensity measured during the treatments are available. This study focused on one specific patient paves the way of augmented reality tools to evaluate a priori the IRE ablation efficacy thanks to advanced medical registration tool and appropriate electroporation models.

VINCENT Mark

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A-Theory: Why atavism must now be taken seriously as an explanation for cancer

Atavism, the idea that cancer is a 'throwback', has recently been boosted by genomic phylostratigraphy, an approach to genetic analysis which enables evolutionary aging of particular genes. This has revealed that de-repression of unmutated, archaic unicellular genes are heavily involved in carcinogenesis. To allow this to happen, two other groups of genes (the very old 'caretakers', and much younger 'gatekeepers') must be mutated to dysfunctionality. Caretakers,required for genomic integrity, are pre-eukaryotic; whereas gatekeepers evolved later, with early metazoa. Disruption of caretakers results in loss of gatekeeper functionality, leading in turn to the derepression of the ancient unicellular program that actually constructs the malignant phenotype. Just before the recent publication of this phylostatigraphic data, theoretical considerations had led some authors to to a re-formulation of the atavism hypothesis (which itself is an old idea). This author started with the idea that cancer represents a bona fide but highly unusual form of speciation, which, unlike typical Darwinian gradualism, involved a discontinuous jump back into the kingdom of the unicellular protozoa. This line of thinking led to the positing of four key questions: where on the Tree of Life do cancer cells reside; why is the malignant phenotype always the same; why are the traits of the malignant phenotype the way they are; and could the switch to cancer ever subserve some biological function. To explain these phenomena, parsimony seems to favour re-emergence, rather than the invention of a totally new form of life. Furthermore, the stereotypy of the malignant phenotype, irrespective of considerable genomic heterogeneity, is more easily explicable in terms of common ancestry than convergent evolution, although there could well be some role for convergence. The very unusual collection of traits of the malignant phenotype can at least be partly explained by the original evolution of eukaryotes in the harsh geochemistry of the Proterozoic oceans. Finally, the recent and surprizing description of free-living planktonic leukemia cells from molluscs provides backing to the idea that biomass conversion, genomic re-scrambling and anatomic escape (ie the real 'Hallmarks of Cancer') could have subserved a survival purpose at some point in evolutionary history. Atavism (A-Theory) is not necessarily incompatible with somatic mutation theory ('Mtheory'); but M-theory by itself is no longer an adequate explanation of cancer. This leads to consideration of the therapeutic implications of both theories, and an attempt to provide a (recently published) unifying hypothesis: a General Theory of the Target.

WILLIAMS Marc

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Quantifying evolution in human cancers with genomics

High throughput genomics has shown that tumours across all cancer types are highly heterogeneous, to the point that each cell may potentially be genetically unique. In single samples of cancers that have been subjected to high depth sequencing this heterogeneity manifests itself as mutations at different variant allele frequencies (VAF), that is some mutations are present in a high proportion of cells in the tumour, others in lower proportions.

Using a mathematical model of tumour evolution together with Bayesian statistical inference we show how these VAF distributions encode the underlying evolutionary processes in tumour growth. This allows us to measure the mutation rate, the fitness advantage and the time of emergence of sub-populations which are selected for during tumour growth. We observed that such sub populations had strikingly high fitness advantages (¿20%) and emerged early (within the first 15 tumour doublings). Taken together, these measurements allow for predicting how the cancer genome is expected to change over time with potential important applications in rationalizing sampling and treatment strategies.

2.2 Wednesday ITMO symposium

1. BALLESTER Pedro
2. BENZEKRY Sébastien
3. BREST Patrick
4. CHOMIENNE Christine
5. TAEIB David

aviesan
alliance nationale
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Precision and recall oncology: combining multiple gene alterations for improved identification of drug-sensitive tumours

Cancer patients often respond differently to the same treatment. Precision oncology aims at predicting which treatments will be effective on a given patient. Such predictive biomarkers of drug response typically take the form of a particular somatic mutation. However, lessons from the past indicate that these single gene-drug response associations are rare and/or often fail to achieve a significant impact in clinic. In this context, Machine Learning (ML) is emerging as a particularly promising complementary approach to precision oncology. Our results show that combining multiple gene alterations of the tumours via ML often results in better discrimination than that provided by the corresponding single-gene marker. This approach also permits assessing which type of molecular profile is most predictive of tumour response depending on treatment and cancer type. Moreover, ML multi-gene predictors generally retrieve a much higher proportion of treatment-sensitive tumours (i.e. they have a higher recall) than the corresponding single-gene marker. The latter suggest that a higher proportion of patients could benefit from precision oncology by applying this ML methodology to existing clinical pharmacogenomics data sets.

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Optimization of sequential administration of bevacizumab plus cytotoxics in non-small cell lung cancer by combining in vivo experiments and mathematical modeling

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

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The tumor microenvironment, which consists of resident fibroblasts, endothelial cells, leukocytes and extracellular matrix, also contributes to the progression of cancer . Accumulating evidence has confirmed that tumor cells must recruit and reprogram the surrounding normal cells to serve as contributors to tumor progression. Tumor cells and the supporting normal cells form an organ-like structure and make concerted efforts for rapid proliferation, local invasion and metastases. Here, we showed that miRNA transfert from inflammatory immune cell to cancer cells contributed to EMT phenotype acquisition. Now, we would like to model the microenvironment signature by RNA transcriptome analysis given unique cell population pattern.

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Where Math meets Cancer Research

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Mathematical modeling of disease dynamics in SDHB- and SDHD-related paraganglioma: Further step in understanding hereditary tumor differences and future therapeutic strategies

Succinate dehydrogenase subunit B and D (SDHB and SDHD) mutations represent the most frequent cause of hereditary pheochromocytoma and paraganglioma (PPGL). Although truncation of the succinate dehydrogenase complex is thought to be the disease causing mechanism in both disorders, SDHB and SDHD patients exihibit different phenotypes. These phenotypic differences are currently unexplained by molecular genetics. The aim of this study is to compare disease dynamics in these two conditions via a Markov chain model based on 4 clinically-defined steady states. Our model corroborates at the population level phenotypic observations in SDHB and SDHD carriers and suggests potential explanations associated with the probabilities of disease maintenance and regression. In SDHB-related syndrome, PPGL maintenance seems to be reduced compared to SDHD (p=0.04 vs 0.95) due to higher probability of tumor cell regression in SDHB vs SDHD (p=0.87 vs 0.00). However, when SDHB-tumors give rise to metastases, metastatic cells are able to thrive with decreased probability of regression compared with SDHD counterparts (p=0.17 vs 0.89). By constrast, almost all SDHD patients develop PGL (mainly head and neck) that persist throughout their lifetime. However, compared to SDHB, maintenance of metastatic lesions seems to be less effective for SDHD (p=0.83 vs 0.11). These findings align with data suggesting that SDHD-related PPGL require less genetic events for tumor initiation and maintenance compared to those related to SDHB, but fail to initiate biology that promotes metastatic spread and metastatic cell survival in host tissues. By contrast, the higher number of genetic abnormalities required for tumor initiation and maintenance in SDHB PPGL result in a lower penetrance of PGL, but when cells give rise to metastases they are assumed to be better adapted to sustain survival. These proposed differences in disease progression dynamics between SDHB and SDHD diseases provide new cues for future exploration of SDHx PPGL behavior, offering considerations for future specific therapeutic and prevention strategies.

2.3 Oral communications

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2. BALLESTA annabelle
3. CALVO Juan
4. CARRÈRE Cécile
5. DENIS Fabrice
6. FOURREL Geneviève
7. HAMIS Sara
8. KOLBE Niklas
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10. LETELLIER Christophe
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Modeling the origin of gliomas

Oligodendrocyte precursor cells (OPCs) have remarkable properties: they represent the most abundant cycling cell population in the adult normal brain and they manage to achieve a uniform and constant density throughout the brain. This type of precursor is also strongly suspected to be the "cell-of-origin" of gliomas. Here, we present a model of the dynamics of OPCs, first in a normal tissue then in the pathological framework of glioma genesis. This model is based on a cellular automaton and its rules are similar to the ones that regulate the dynamics of real OPCs. Our automaton model consists in a collection of cells (modeled by spheres) that evolve according to a given set of rules. Each cell can participate in three different processes, at each iteration: proliferation, migration and differentiation/death.

We show that there exists a fair quantitative agreement between the simulated and experimental parameters, such as the cell velocity, the time taken to close a lesion, and the duration of the cell cycle.

We show that an increase in the proliferation coefficient is sufficient to trigger the growth of a tumor that has low-grade glioma features: an invasive behavior, a linear radial growth of the tumor with a corresponding constant growth velocity of less than 2 mm per year, as well a cell density at the center which exceeds the one in normal tissue by a factor of less than two. Our model thus represents a possible scenario of transformation of a normal tissue into a glioma.

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P-glycoprotein (Abcb1) expression and activity are sex-, feeding-, and circadian time-dependent, implications for mechanistic pharmacokinetics modeling.

P-glycoprotein (P-gp) is a main efflux transporter that mediates the detoxification of many anticancer drugs and other xenobiotics. Both P-gp expression and toxicities of P-gp substrates may largely vary according to the patient's sex, feeding status, and circadian timing system that rhythmically regulates the organism over 24h. A molecular understanding of inter- and intra-patient variations of P-gp activity would allow for optimizing drug exposure though personalized administration schedules. A systems pharmacology approach enabled us to simultaneously study the effect of sex, feeding status and circadian time on P-gp activity in the gastro-intestinal system of mice. Robust circadian changes in P-gp mRNA and protein levels were demonstrated in the ileum of mice of both sexes, with larger amplitudes and earlier phases in females as compared to males. In the colon, no circadian rhythm was found in P-gp mRNA amounts whereas protein levels only displayed time-dependent variations in females. Similarly, liver P-gp protein expression showed 24h-rhythm in females, but not in males. P-gp activity was assessed through multi-factorial PK studies of talinolol, a pure P-gp substrate. Statistically significant differences were found in plasma, ileum and liver talinolol PK profiles according to sex, feeding status and circadian timing. Physiologically-based modelling revealed that P-gp activity circadian mean was higher in males compared to females in both ileum and liver, for all feeding conditions. P-gp activity circadian amplitudes were consistently higher in females than in males. P-gp activity circadian maxima significantly varied with respect to sex by up to 10h.

Fasting increased P-gp activity in both liver and ileum of male mice, and only in ileum of females, and decreased P-gp activity circadian amplitudes. The mathematical model of P-gp circadian activity that was developed in the gastro-intestinal system provided parameter estimates according to sex and feeding status. It can further be incorporated into physiologically based PK models of any P-gp substrates for personalizing their circadian administration.

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Estimating compartment size for stochastic and hybrid simulations of structured populations

A new way to tackle cancer modeling has been introduced during recent years by means of models describing heterogeneous cell populations, structured in spatial and in phenotypical variables. New mathematical models of continuous cell population dynamics have been considered in the form of structured partial differential equations of reaction-diffusion type. Discrete counterparts have been also considered as a way to describe stochastic fluctuations linked with the structural variables; those fluctuations may be central to an accurate description of invasive phenomena such as tumor growth [1]. Hybrid deterministic-stochastic multiscale models could be considered as well; however, the computational implementation of these representations poses a number of problems. One important consideration when performing stochastic or hybrid simulations of a reaction-diffusion system concerns cell size choice. A criterion to ensure fast homogeneization of the reacting species within a voxel was proposed in [2]. We generalize this criterion to cellular population models structured by an age variable (time elapsed since last division), in order to provide an upper bound for the computational compartment size. These ideas can be arguably extended to more general structured population models.

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Dynamical programming of a chemotherapy preventing drug resistance for in vitro heterogeneous tumours

Resistance to chemotherapy is a major cause of treatment failure for tumours. Several observations currently suggest that it is often due to heterogeneity in the cancer cells, even in the initial tumour before beginning the treatment[1]. Taking into account this phenomenon is thus important in the conception of new treatment protocols. We base our study on an in vitro experiment done by M.Carré1. Two cancer ligneages are cocultivated in a Petri dish, and are subject to a treatment, one ligneage being sensitive to it and the other one resistant. Using the competition between the two ligneages, it is possible to reduce the tumour volume without letting the resistant population emerge. To propose better treatment schedules, we design based on previous work[2] an ODE model of these experiments, with uncertainties on some parameters. The objective we set is, given a certain threshold, to determine a treatment maintaining the tumour size below the threshold. If this objective cannot be attained, whether the tumour is initially too big or too resistant, we want to bring it to an admissible size as fast as possible. These two problems can be expressed mathematically in terms of controllability problems, which can be solved by the study of Hamilton Jacobi Bellman equations[3]. The numerical resolution of said equation is studied, and we present convergence results that allow the reconstruction of trajectories and treatment for an actual situation.

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MooveCare: a web-mediated follow-up based on weekly self-reported symptoms From chaos theory to clinical practices

Chaos theory was developed to improve the characterization of dynamics governed by nonlinear systems which are very sensitive to initial conditions and, consequently, produce behavior that are non-predictable at long term. Its use in oncology is recent and it can help in better understanding tumor dynamics. Interactions between tumor cells, host cells, immune cells and endothelial cells are described by competition models which may lead to chaotic dynamic. The observability theory, which allows determining the most relevant variable in such model to better assess dynamics, shows that host cells (that can be represented by patients symptoms and weight variation) is the variable providing the best observability of the tumor dynamics. We thus developed a clinical application to detect relapse of lung cancer that is based on the tumor environment as follows. To assess this environment, we developed a web-application (MooveCare) based on weekly self-reported symptoms which are transmitted automatically via the web. Internet access it thus required. An email alert was sent to the oncologist when some predefined clinical criteria were fulfilled. An imaging is thus triggered to assess the actual state of the tumor. A multi-institutional phase III randomized study to compare survival between i) our web-mediated follow-up (experimental arm) and ii) a clinical routine assessment with a CT-scan (every 3-6 months or at investigator's discretion - standard arm). High-risk lung cancer patients without progression after an initial treatment were included. Maintenance chemotherapy or TKI therapy were allowed. Early supportive cares were provided if adequate. Secondary outcomes were quality of life and performance status at relapse. 133 patients were randomized and 121 patients were included in the intent-to-treat analysis (96% stage III/IV). Median follow-up was 9 months. Median overall survival was 19 months versus 12 in favor of the experimental arm (p=0.0014 - hazard ratio equal to 0.325, 95% CI 0.157 to 0.672; p=0.0025) and the performance status at the first relapse was 0-1 for 76% of the patients in the experimental and 33% in standard arm (p¡0.001). The one-year survivals were 75% and 49% in the experimental and the standard arms, respectively (p=0.0025). The quality of life (QOL) was improved in the experimental arm. This trial showed a significant survival and QOL improvement with our web-mediated follow-up. This is thus an example of how the nonlinear dynamical systems theory can help physicians to develop new clinical practices.

In the daily practice, tumor response to therapy such as immunotherapy could be improved by the use of Moovecare. In a case report, we showed that a pseudo-progression of lung cancer to immunotherapy was detected by Moovcare. The progression of the tumor observed in the routine imaging was in clear contradiction with the improvements in patient's global status as assessed by the reduced score computed from patient self-reported symptoms. Immunotherapy was maintained and tumor regression was then confirmed by the imaging performed 2 months later. Self-reported symptoms with Moovcare may improve tumor response assessment under therapy and avoid inadequate interruption of an effective therapy.

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Why we should care about repeat sequences and not only genes, in cancer

- **Pathology - The nucleus of a cancer cell may look quite different from a normal, differentiated cell under a microscope**
  The nucleus of a cancer cell may look quite different from that of a normal, differentiated cell. Pathologists have been knowing this for long. Pathologists indeed count nucleoli on tumor slides, they assess chromatin texture and homogeneity and density. They estimate the size and shape of the nucleus and use this to decide upon a diagnostics. The nucleus is indeed globally reshaped in cancer. Cancer usually starts with one or a handfull of chromatin factors being altered, or a signal transduction pathway being abnormalously activated. In the end, every level of chromatin organization is concerned, as we have been learning over the past 20 years. Thus, cell transformation is a reprogramming process, that correates with a change in nuclear organization. Cancer epigenomics aims at characterizing these chromatin changes at every level of genome organization ranging from chromatin fibre assembly to nuclear compartments. Cancer epigenomics thus emerges as a molecular, modern anathomic pathology, a molecular microscope to decipher cancer reprogramming at its heart. Such a view further open new therapeutic avenues, and new EpiDrugs (that target chromatin enzymes) now enter medical practice on a regular basis.
- **The genome of a differentiated cell is largely repressed**
  A differentiated cell expresses only a minor part of its gene complement, and repressive mechanisms ensure that genes which are not supposed to be expressed are actually securely repressed. Such is the case for instance of genes involved in cell proliferation in the embryo, whose untimely expression could be at the origin of cancer. Repression can affect single genes, or affect more or less all genes within a chromatin domain. It is then called silencing and is enacted by a chromatin complex with a particular composition called repressive chromatin, or silent chromatin, or yet heterochromatin. At the genome scale, chromatin partitions into domains in the 200kb to 2Mb range, which are prone to either expression or repression, which exhibit a less or more compact chromatin, and are called domain types - A and - B, respectively. B-type domains tend to associate in the nucleus, forming the "B-compartment". Of note therefore, when a gene is activated upon stimulation or in the course of development, most often initial repression must be overcome before or at the same time as transcription factors genuinely activate transcription initiation.

- **Deciphering repression - The role of Repeat Sequences in genome organization and in cancer**
  Such repression has been largely overlooked. Indeed, far more attention has been brought upon activation by people studying gene regulation than upon repression, especially repression that extends over large domains. In the same vein, gene regulation studies during the past 40 years have delineated unique cis-regulatory sequences and cognate transcription factors, and repeat sequences have been thorougly "filtered out". It was assumed that repeat sequences have no role in gene regulation, and that "non-genic" sequences are a mere passive substrate onto which genes hold. I will explain how we deciphered the grammar of silent chromatin by making use of the uniquely simple heterochromatin of the yeast S.cerevisiae. Our dynamic framework for genome organization urges to a chromatin-domain centered vision of gene regulation, instead of a gene-centered vision which still prevails today. It further led us to fathom that repeat sequences are major players in organizing the genome of higher Eukaryotes, in particular in organizing the B-compartment. Accordingly, a Repeat- Sequence based epigenomics approach was developped and applied to cancer. I will explain why it should be considered as modern, molecular Anatomy Pathology Recent investigations in cancer now converge in pointing out repeat sequences in cell transformation, in surveillance mechanisms and escape thereof, and in cancer drug resistance. This new appreciation of the key role of repeat sequences in both physiological genome organization and in cancer is a real change in paradigm and should now be integrated in all approaches pertaining to cancer, namely : in diagnostics , in drug discovery, and in mathematical modeling.

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Trojan-horse cancer drugs: An in silico investigation into hypoxia-activated prodrugs

Hypoxic cancer cells in solid tumours express reduced sensitivity to anticancer treatments such as radiotherapy and some chemotherapeutic drugs. Thus hypoxia has an adverse effect on treatment delivery and significantly impacts clinical outcome. Consequently, multiple strategies to combat hypoxia have been explored. Hypoxia-Activated Prodrugs (HAPs) present a means to not only combat, but also exploit, hypoxia. HAPs are bioreductive prodrugs that reduce, and thus convert, to active cytotoxins upon reaching hypoxic regions. These drugs act as trojan horses, being harmless until they are converted in target areas.

Despite being conceptually promising, clinical trials of HAPs have produced mixed results. In order to closely study the appropriate conditions and optimal delivery of multimodality treatment regimes that involve HAPs, we have developed a three-dimensional *in silico* framework simulating tumour dynamics and treatment response. Our framework is based on a multiscale mathematical model, specifically a cellular automaton incorporating intracellular, extracellular and intercellular dynamics. Our results indicate that the successfulness of HAP-Radiation combination treatments depend on multiple factors including tumour oxygenation status and synergistic bystander responses in cells.

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Genetic alterations driving metastatic colony formation are acquired outside of the primary tumour in melanoma

In this contribution, we focus on the modelling and biostatistics aspects of our recent publication in [1] and additionally present unpublished results on the clonal evolution of melanoma cells in the sentinel lymph node. In [1], we find that lymphatic dissemination occurs early and that primary tumour samples and disseminated cancer cells (DCCs) are largely disparate. Our data show that typical driver changes, including BRAF mutation and gained or lost regions comprising genes like MET or CDKNA2, are acquired within the lymph node at the time of colony formation. Specifically, we identify the most likely acquisition site for each genomic alteration (i.e. primary tumour or lymph node) in DCCs according to an alteration risk model that well explains our data.

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Modeling and simulation of EMT and tumor cell heterogeneity in cancer invasion

Only small sub-populations within tumors possess the ability to metastasize. These consist of so-called cancer stem cells that differ in their differentiation state, their motility and their resilience to therapy from the bulk of the cancer cells. They transition from the common differentiated cancer cells via a de-differentiation program, termed Epithelial-Mesenchymal Transition, which takes place during the invasion of the extracellular matrix. The program is triggered by growth factors in the cancer micro-environment, and it significantly affects the invasion process.
In this contribution we consider a spatio-temporal PDE model combining a (microscopic) model of the transition between the two types of cancer cells based on interactions of cell receptors and growth factors with a (macroscopic) model of the invasion of the extracellular matrix by the cancer cell ensemble. We discuss the solvability of the model and present numerical experiments exhibiting the dynamics of both types of cancer cells.

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Mathematical modeling of drug resistance and sensitivity in colon cancer cell lines

In the framework of the European project 'COLOSYS – A systems approach to preventing drug resistance in colon cancer' (collaborators: Christine Sers (Charité), Lodewyk Wessels (NKI) and Martin Kuiper (NTNU)) we constructed mathematical models of drug resistance and combinatorial drug effects in KRAS/BRAF mutant colon cancer cell lines. We use background knowledge (mutations, prior knowledge on signaling networks) and perturbation experiments performed within the consortium to infer a logical model of drug resistance optimized with a global search method [1]. In addition, we built a minimal model based on ordinary differential equations to reproduce the interaction of KRAS signaling with DNA damage and repair. The study of network motifs showed that the presence of a negative feedback loop is needed to explain the resistance mechanism to monotherapy and the sensitivity to a double inhibition involving a DNA repair-associated protein and a MAPK cascade component [2].

A novel aspect of our approach is to couple mathematical modeling predicting drug effects with a targeted CRISPR screen and to use these results for model inference and validation. A selected colon cancer cell line (SW620) sensitive to both the single and (more strongly) the double inhibition will undergo targeted deletions in a screening experiment. Identifying the deletions that have the most pronounced positive or negative growth effect will be used to distinguish between the different resistance mechanisms suggested by the network motif analysis.

Our aim is two-fold. On the one hand, using an analysis of network motifs, we want to explore the possible mechanisms leading to drug resistance in KRAS mutant cell lines. On the other hand, we are developing a large-scale logical model to predict drug effects and ultimately suggest novel drug combinations that are more potent than the ones currently used. In terms of biological relevance our study analyzes in detail the understudied interaction of two crucial cellular functions, namely MAPK signaling and DNA-repair. This is a question with high clinical relevance due to the importance of KRAS mutations in colon cancer patients who develop drug resistance.

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Optimizing intermittent hormonotherapy after a prostatectomy by using individualized model

The prostate adenocarcinoma is the most frequent cancer affecting the eponym walnut- size gland in the male reproductive system. The tumor is graded according to the Gleason score based on a biopsy. For score less than 6, the tumor is not considered as a cancer. For a score equal to 6, the cancer has a very slow progression. Contrary to this, the prognostic is "dark" when the score is equal to 10, meaning that tumor cells are spreading very quickly. Prostate adenocarcinoma has at least two specificities. i) It is hormone-dependent and, consequently, hormonotherapy is a possible treatment. ii) The rate of PSA (prostate specific antigen, PSA) is a rather reliable marker of the evolution of the cancer. Since few years, hormonotherapy started to be provided by intermittences, to reduce cardio-vascular risks, delay the occurrence of hormone independent tumor cells and, as a result, increase the survival rate as well as the quality of life by reducing side effects. Today, durations of on- and off-treatment periods are still chosen in a rather random way; such an approach most likely explain why there is no clear benefit from the survival point of view when patients receive an intermittent treatment rather than continuous one. Consequently physicians clearly need helps to optimize these parameters for each of their patients. In order to do that, we started by developing a model for describing the interplay between the tumor micro-environment (host cells), hormone dependent and hormone independent tumor cells, and the rate of prostate specific androgens. The rate of PSA - the single variable easily measured in patients - is directly correlated to the number of tumor cells. Model parameters were identified using a genetic algorithm applied to PSA time series for a few patients, who initially received prostatectomy, and then treated by intermittent hormonotherapy (LHRH analogue and anti-androgen). It is thus shown that our model can accurately reproduce the collected PSA time series by free runs over few years. Model parameter values allow distinguishing different types of patient (age and Gleason score). It was possible to show that the microenvironment plays a significant role in the evolution of the cancer. We then showed that the long-term evolution of the cancer was affected by durations of on- and off-treatment periods.

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A minimal multi-scale approach for cell migration modelisation

This study aimed to develop a model to accurately predict cell crawling migration. Cell migration plays a key role in many physiological processes, such as embryogenesis, wound repair, or metastasis formation. Cell migration is the result of a complex activity. It involves many different time and space scales, which makes it difficult to understand. Our goal is to build a minimal model of cell trajectories, which includes the different scales involved in cell migration. We are interested in cell crawling for cells located on a 2D adhesive plane. A recent study [1] has highlighted a universal process through which the structures responsible for migration reinforce cell polarisation, which favours a ballistic displacement. This positive loop passes through a molecular marker, which is transported by the cell cytoskeleton. Its inhomogeneous distribution characterises a polarised state. In this talk I shall present a deterministic model for unicellular migration. In a first step, I shall describe our approach, which is inspired from [1], that allows describing the internal structures linked to migration as an active fluid. In this approach, the active character appears through boundary terms, which makes its original. Then, we shall see that the marker concentration obeys to a non-linear and non-local convection-diffusion equation, where the convection field corresponds to the fluid advection field. Finally, the marker distribution on the domain boundary exerts a feedback loop on the fluid. From the mathematical viewpoint, it is possible to study the 1D model [2]: global existence or apparition of a singularity in finite time, non-trivial steady states, long-time convergence. Some numerical simulations in 2D will be presented in rigid domain and also in deformable domain.

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POLA Cecilia joint work with Fernández Luis A.

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Analysing Optimal Control Problems for the Gompertz Model in Chemotherapy

In 1977, L. Norton and R. Simon [4] used the Gompertz ordinary differential equation to model the macroscopic growth of some cancer tumors. Moreover, they hypothesised that "chemotherapy results in a rate of regression in tumor volume that is proportional to the growth of an unperturbed tumor of that size". This hypothesis tried to overcome the clinical observations contradicting the previously assumed Skipper-Schabel-Wilcox (log-kill) hypothesis which claimed that the rate of regression was proportional to the tumor volume itself.
Despite the large amount of literature in this field, in most of the mathematical works the log-kill hypothesis continues to be assumed, and in very few cases the Norton-Simon hypothesis (see for example [3] for an exception). In our opinion there is not a completely rigourous and detailed study in this framework from the mathematical point of view that can be used for compative purposes. This is the aim of our work (see [1] and [2]). We study a collection of optimal control problems related with the cancer chemotherapy treatment under the log-kill hypothesis and the Norton-Simon hypothesis, varying the pharmacokinetics, the pharmacodynamics and the way in which the side effects are taken into account in the model (as constraints or through a penalty term). The influence of all these variants is analysed by obtaining explicit expressions for the corresponding optimal controls in terms of the parameters defining the optimal control problems. We have got some unexpected results that have not been reported in the literature, as far as we know.

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POUCHOL Camille[1,2] joint work with Clairambault Jean [2,1], Lorz Alexander [1,2,3], Olivier Antoine [1], Trélat Emmanuel [1]

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Efficient chemotherapy in spite of drug resistance: optimal strategy and robustness

This presentation aims at providing insights into answering the following question: how can one minimise the tumour load at the end of given therapeutic-window, while avoiding resistance and limiting damage to the healthy tissue? To address this problem, we consider an optimal control problem with a phenotype-structured PDE model for both the cancer and healthy cell populations. The phenotype variable is a continuous trait standing for the level of resistance of cells to chemotherapy. This type of model comes from adaptive dynamics, the branch of mathematical biology focusing on evolution. Numerical results for the optimal control problem show that a clear strategy emerges: the central idea is to first give low doses for a long time, in order for the tumour to be sensitive enough for a successful second phase with high doses. I will explain the modelling in detail, and will focus on the nu- merical approach to solve the problem. As a proof of robustness of the strategy, I will consider a slightly more general model with genetic instability. The optimal control problem is then significantly harder to solve and I will introduce a homotopy approach to still manage to compute the optimal strategy.

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Multistability and hormesis in the dual phosphorylation-dephosphorylation cycle

The dual phosphorylation-dephosphorylation cycle is a major building block in the mitogen-activated protein kinase (MAPK) pathway, whose deregulation is responsible for abnormal cell proliferation in cancers. Despite the apparent simplicity of the cycle, mathematical modelling demonstrates a range of dynamic behaviour is possible. The multistability property of the cycle results from the kinetic mechanism of two-site MAPK phosphorylation and dephosphorylation and so the MAPK cascade can serve as a bistable switch (Markevich, et al., *J Cell Biol*, 2004; Ortega et al., *FEBS J*, 2006).

Extending the model with a simple mechanism of kinase inhibition reveals the phenomenon of hormesis (an inverted U-shape dose response) in the cycle. This undesirable phenomenon has profound consequences for tumour therapy because low drug concentrations during drug clearance in the body may actually stimulate tumour growth. Despite a wide range of experimental observations on hormesis (Hall-Jackson et al., *Chem Biol*, 1999; Hatzivassiliou et al., *Nature* 2010; Heidorn et al., *Cell* 2010), the mechanistic understanding behind such paradoxical responses is incomplete. The proposed model (Rashkov et al., *PLoS Comput Biol*, 2016) shows that under certain conditions the steady state amount of the doubly phosphorylated MAPK in the cycle can substantially increase at low inhibitor doses compared to the base level. Therefore, the dose-response curve is upward sloping at low inhibitor doses and downward sloping at high inhibitor doses. The existence of hormesis in the model depends on the mechanism of inhibition and on the dissociation rates of the kinase-substrate-inhibitor complexes. Numerical simulations reveal that the magnitude of the maximum hormetic response compared to base level depends on the substrate-kinase ratio in a non-monotone way.

Putting the model into the perspective of the multistability of the dual phosphorylation-dephosphorylation cycle provides clues as to why hormesis and the possible mechanisms behind it may not be properly identified in pre-clinical population-level studies.

SACCOMANI Maria Pia joint work with THOMASETH Karl

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The relevance of identifiability in model-based oncological studies. A new method to calculate all the possible parameter solutions of a tumor model

studies. In this context, the most widely used models are nonlinear ODE models, whose identification is often difficult due to experimental limitations and/or mathematical ill-posedness. Given the increased model complexity required to describe the more and more available data, many of the models employed in oncological studies are locally or non identifiable, i.e. they have multiple or an infinite number of parameter solutions, however this problem is not always recognized. Typically these solutions are equivalently describing experimental data, but they are associated with different dynamic evolution of the not directly measurable variables. Such a situation is undesirable since mathematical models are principally used to predict unobservable quantities and time-varying phenomena. By starting from these observations, we focus on locally and non identifiable models, i.e. models with more than one parameter solutions equivalently describing the experimental data. This issue will become crucial also to increase the precision of the recently proposed treatments personalization methods. To guarantee goodness and reliability of the parameter estimation results, we propose a joint use of two different identifiability methodologies, namely "structural" and "practical" identifiability, which are traditionally regarded as disjoint because they are based, in turn, on differential algebraic manipulations and on numerical simulation of systems equations, respectively. For the first time, this joint implementation allows to know:

1. the number of parameter solutions, technically speaking the check of model "structural identifiability";
2. in case of a finite number of solutions and given a parameter estimate obtained with a whatever optimization procedure, the numerical values of all the remaining solutions equivalently describing the experimental data;
3. the analytic relations between the correlated parameters (just by inspection, one can know which are the redundant parameters of the model);
4. a ranking between parameters with respect to their capability to affect the output func- tion measured with statistical figures;
5. how to correctly define an equivalent identifiable model of reduced complexity.

Practically, this findings can constitute a rational and powerful tool for the oncologist to dis- entangle the various causes of non identifiability assessed with sensitivity-based approaches, and to provide practical suggestions on how to modify the model and/or the experiment.

In principle, the proposed methodology does not require experimental data and thus it can be viewed as a tool for addressing the "experiment design" problem. In particular, it may avoid waste of resources for doing uninformative experiments. In the model-based oncological studies literature, the identifiability issue is still neglected and collection of experimental data precedes the formulation of mathematical models, which is often carried out by trial and error by fitting different model structures to the acquired data. However, only if the model parameterization is unique, the numerical estimate of the unknown parameter provided by whatever optimization algorithm is correct and allows to arrive to reliable conclusions. If not, the parameter estimates that could still be obtained by numerical optimization algorithms would be unreliable and vary randomly depending for instance on the initialization of the algorithm. Our methodology is implementable by using a freely available differential algebra software which does not required specific mathematical expertise by the user, together with statistical packages. In conclusion, this paper aims to demonstrate that, in oncological studies, when a model is formulated and its parameters need to be estimated from available measurements, to check the uniqueness of the parameter solution is crucial. By neglecting all the solutions of a parameter (except that estimated with an optimization algorithm), the investigator can arrive to ambiguous conclusions. To show that the proposed methodology is an effective tool to discover the behavior of nonaccessible variables of clinical interest as well as for scheduling cancer therapy by guaranteeing the reliability of the results, we apply it to recently published complex oncological models.

STRAUSS Magdalena E. [1] joint work with REID John E. [1,2], WERNISCH Lorenz[1]

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Panomics: Bayesian hierarchical context-dependent across-clustering for multi-omics pan-cancer data

An integrative method for the clustering of biopsy samples based on pan-cancer data ideally allows both the integration of different contexts such as RNA expression, miRNA expression, methylation and others and a set-up in which the clustering structures for different cancer types are automatically informed by each other. This challenge is addressed by our proposed method, panomics, by combining a recent context-dependent approach to integrative clustering with hierarchical Dirichlet mixture modelling. Panomics allows the cluster structures for the different contexts to differ from each other, while there is an exchange of information between the cluster allocations for the different contexts via an additional level of global multi-omics clusters. We correct for the known heterogeneity due to cancer type by across-clustering. Across-clustering refers to the clustering of data centred to zero-mean for each variable for each cancer type individually. Set up in a Bayesian framework, panomics also models the uncertainty of the clustering structure. Our applications to multi-omics TCGA-data from several different cancer types reveal new insights into the similarities of subtype structures for different cancer types, and the heterogeneity of the clustering structures for different contexts, which necessitate a method able to integrate this heterogeneity while enabling an exchange of information between the different contexts.

TESSON Rémi joint work with DENICOLAI Emilie, HONORE Stéphane,HUBERT Florence

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Cell migration modeling of the impact of microtubules dynamics on cell migration

Angiogenesis and metastasis are the two main phasis of the development of cancer that involve cell migration in a critical way. The efficiency of drugs like antimicrotubules in the modification of the migratory behavior of cells has been established, which can lead to their use as targeted cancer therapies.
Our work focus on the mathematical modeling of the impact of microtubules on cell migration. The aim of this model is to better understand the action of microtubules on cell migration and to study the effect of antimicrotubules drugs on the migration.
We propose a 2D PDE model describing the deformation and displacement of the cell membrane, using a fluid description of the cell. The model is based on the work proposed initialy in [**?**] and which has been adapted to feat the context of microtubules action. The mechanical part of the model use a Level-set representation of the membrane which move at a velocity given by Stokes equations. A coupling between the mechanical part and the biochemical part is done through forces exerced on the membrane representing the protrusive and contractile behavior of the cell. The biochemical part describe the action of microtubules as activator of proteins of the RhoGTPase family. In this model, the polymerization of microtubules is responsible of the activation of Rac1 proteins which promote the protrusion of the cell whereas the depolymerization of microtubules is causing the activation of RhoA proteins which promote the contractility of the cell.
In our work we motivate the use of the DDFV framework for the numerical approximation of the equations of the model. We design some specific tools, mostly for transport equation and diffusion on a moving domain, in this framework.
The calibration of the model was made with data from the litterature but also with data provided by the team of Stéphane Honoré from the CRO2 of Marseille.
A study of the action of the vincristin at low dose on cell migration has been done. The comparison between the results of the model and data of the experiments offer a better understanding of the effect of the drug and lead to new biological and mathematical hypothesis on the mechanism of action of the molecule.

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VAGHI Cristina [1] joint work with Rodallec A.[2], Fanciullino R. [2], Ciccolini J. [2], Poignard C. [1], Benzekry S. [1]

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Improving the efficacy of antibody nanoconjugates in cancer therapy with mathematical modeling

One of the major challenges in anti-cancer chemotherapy is the very high toxicity associated with cytotoxic agents. To overcome this issue, nanoparticles conjugated with cancer cell specific antibodies are being developed to improve drug delivery to the tumor, while sparing healthy tissues. However, intra-tumor penetration of antibody nanoconjugates (ANCs) properties are not fully understood and could be improved. In a joint collaboration between pharmacologists and computational scientists, we aim at developing mathematical and numerical tools to optimize the efficacy of ANCs and to improve their biodistribution. Pharmacokinetics and pharmacodynamics modeling allows patient-specific therapy schedule, enhancing efficacy of the drug at the site of action while decreasing its toxicity. In a first step, from in vitro and in vivo data we modeled the dose-concentration-response relationships and subsequently predicted the in vivo effect of an additional dose range.

2.4 Poster session

1. ATSOU Kévin
2. AVANZINI Stefano
3. BUBBA Federica
4. CHEEK David
5. CONTE Martina
6. DRAGHI Clément
7. DOMINICI Chloé
8. FERNÁNDEZ ROMERO Antonio
9. GARCIA Karina
10. GUILLOT Jérémy
11. HAMIS Sara
12. HADDAD Ghassem
13. HILL Roger
14. HOFFMANN Martin
15. LEÓN-TRIANA Odalesi
16. LESZCZYNSKI Maciej
17. NICHOLSON Michael
18. OSOJNIK Ana
19. PEREZ-BETETA Julian
20. SCHLICKE Pirmin
21. TALARMAIN Laure

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Mathematical modelling of the interaction between a tumor and the immune system

Nowaday, Immunotherapy is an emerging approach to cancer treatment that seeks to enhance and stimulate a body's immune defenses, especially Cytotoxic T cells, to recognize, combat and potentially eliminate tumors. We develop a spatio-temporal and size-structured mathematical model to decribe the interactions beetween immune cells and tumors. Our model exhibits an uncontrolled tumor growth in absence of an immune response, and leads to asymptotic states with residual tumors and activated immune cells in presence of cytotoxic T cells (despite their strength or their Chemotaxis). The last behavior describes an immunosurveillance process (observed biologically) and a possibility of relapse. We also show that the oscillations, often observed in this dynamic, both at the biological level and in some models of ordinary differential equations (ODE) validated by biological experiments, depend more intrinsically on a certain spatial heterogeneity.

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Cancer Recurrence Times from a Branching Process Model

Despite improvements in treatment and therapy of primary tumours, disease recurrence is still a major cause of death for cancer-diagnosed patients. In particular, even when a primary cancer is successfully and completely resected, its ability to generate distant metastases often lead to tumour recurrence. Mathematically, the initiation and growth of metastases can be described through different generalizations of the famous Luria-Delbrück model. I first introduce one of these generalizations, which models the initiations of distant metastases as a non-homogeneous Poisson process and their growth as independent branching birth-death processes. The rate of metastases occurrences thus depends on the deterministic primary growth function n(t): I consider the cases of logistic and exponential functions, and highlight the main differences in the recurrence dynamics that these kinds of growth lead to. Within this framework I then discuss different features of the model, focussing in particular on the probability distribution of the time to cancer relapse. Finally, I compare some of the mathematical results provided by this model with real estimates collected from relevant clinical literature on colorectal cancer.

BUBBA Federica joint work with Perthame, Benoît, Pouchol, Camille

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Density-dependent Keller-Segel models for cell culture pattern formation

Chemotaxis, the movement of cells or organisms in response to chemical gradients, is a phenomenon that can be observed in many biological species, from bacteria to tumor cells. We collaborate with a team of cancer biologists at INSERM (Paris) that carried out three-dimensional biological experiments to understand the reciprocal interactions between breast cancer cells and adypocites. Their experiments show a collection of inhomogeneous spheroidal spots, i.e. spatially inhomogeneous aggregates of cells. Changing some important parameters, such us the initial number of cells or their invasiveness, several different patterns can be observed.
Our aim is to explore the possibility to replicate the patterning behaviors observed experimentally with two different variants of the original Keller-Segel system. Our models take into account volume effects that prevent overcrowding of cells, thus excluding blow-up of solutions and enabling a better understanding of the evolution in time of the solutions. Due to the presence of nonlinear terms, the models we study are mainly analytically untractable and thus suitable numerical methods are required. We propose a conservative, semi-implicit in time, finite difference scheme which maintains the nonnegativity of solutions, preserves the conservation of the total mass at the discrete level and the dissipation of the energy of the system at both the semi-discrete and discrete level. Extensive two-dimensional numerical simulations are compared to the experiments in terms of distribution of aggregate size.

CHEEK David joint work with Tibor Antal

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Mutation frequencies in a birth-death branching process

First we revisit a classic two-type branching process which describes cell proliferation and mutation: widespread application has been seen in cancer and microbial modelling. We prove limit theorems and exact results for the number of mutants, clone sizes, and mutation times. Then we extend the model to consider mutations at multiple sites on the genome. We characterise the site frequency spectrum for a large population size and small mutation rate. We recover a power-law distribution commonly observed in cancer genetic data.

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Glioma Proliferation, Spread and Therapy: a Multiscale Approach

The invasion of tumor cells into healthy tissue is a highly complex process involving several scales, from the microscopic to the macroscopic level. Furthermore, most of the events taking place on the various scales are still not completely understood. In this work we focus on glioma, a particular invasive brain tumor; owing to the peculiarities of the underlying nervous tissue geometry, it shows highly heterogeneous patterns and anisotropic diffusion. We analyze a multiscale model for the glioma migration and proliferation, taking into account a possible therapeutic approach, in the line of well-established approaches in this field [1, 2, 3]. Starting with the description of the subcellular level, we formulate the equation for the mesoscopic level and we derive the macroscopic partial differential equation for the glioma density function. After the model set up and the study of some mathematical properties of this macroscopic setting, we focus on the calibration of the parameters and the coefficient functions involved in the equations [4]. In particular, we first consider the fiber density function, comparing different possible choices in order to understand which approach could better describe the actual fiber density and orientation. Then, we analyze the Tumor Diffusion Tensor, deducing a realistic estimation of its coefficients from experimental data of glioma cells' migration in an aligned tissue. We ultimate the study with some numerical simulations, based on real data, that show the role of each modelled process in the evolution of the solution. Joint work with M. Groppi (University of Parma) and L. Preziosi (Politecnico di Torino).

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3D analysis of neuronal networks remodeling in pancreatic cancer

Cancers are biological systems in which tumor cells interact with a complex tumor microenvironment (TME). This TME plays a fundamental role in cancer progression and development and in the response to treatments. In recent years, a new component of TME has been highlighted: axonal projections of neurons from the peripheral nervous system (PNS). Various studies in humans and in animal models show that tumors are innervated and that different divisions of the PNS regulate tumor progression. TME of pancreatic ductal adenocarcinoma (PDAC) has unique features that partly explain why current therapeutic treatments targeting PDAC are not very effective. Here, we propose to describe the innervation of pancreatic tumors which is the starting point to better understand the importance of this TME component. The objectives were to visualize and analyze the 3D architecture of axonal networks innervating the healthy pancreas and their evolution at all stages (pre- cancerous and cancerous) of PDAC development, and study their interactions with other cells types of TME, focusing in particular on blood vessels (BV, known physiological targets of PNS axons). For this purpose, we used a technique of organ clearing combined with immunostainings (to describe sympathetic, parasympathetic neurons and BV) and light sheet microscopy imaging methods on pancreas from two genetically engineered murine models of PDAC. We observed an increased density of sympathetic and parasympathetic fibers in pre-malignant lesions of the pancreas. In PDAC, these fibers remained scattered. Interestingly, whereas in healthy tissues the sympathetic and parasympathetic axons were mainly associated with BV, they were mostly isolated in pre- malignant structures and PDAC. The 3D reconstruction of these networks allowed to define several quantitative values. Principal component analysis (PCA) was used to study the potential cluster of the individuals based on the 3D networks characteristics. PCA results indicated that healthy and symptomatic tissues could be separated by the characteristics of their 3D neuronal networks. Thus, analysis of the 3D structure of the projections could represent a predictive and prognostic value for the progression of pancreatic tumors. .

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Towards an individualized spatial modeling for tumor growth

The evolution of tumor growth is governed by interactions between different cell types present at the tumor site.1,2 Clinical observations reveal that such a growth can strongly differ from one patient to another for the same type of cancer. The way the body responds to tumor growth or treatment is specific to the patient. Indeed, the patient can present a specific symptomatology such as fatigue, anxiety, weight loss, some side effects related to treatment, or the appearance of para-neoplastic syndromes. All these phenomena result from interaction between different actors within the tumor site, thus leading to a unique tumor evolution. Understanding these interactions is therefore relevant for reproducing the tumor growth observed in a given patient. We started from the system of ordinary differential equations introduced by De Pillis and Radunskaya,3 describing a generic tumor growth without treatment. The specificity of this model is that it takes into account interactions between host cells, cytotoxic lymphocyte-type active immune cells, and tumor cells. We then enriched it to take into account different biological processes that influence tumor growth as the vascular tree, or some mechanical barriers as organ boundaries. We considered different types of host cells, pre-existing organ-specific vascularization and added quiescent states to tumor cells as well as anoxia necrosis and neo-angiogenesis. The model is developed for reproducing what is observed in routine imaging, that is, in a two-dimensional slice. Our simulations are thus compared to some clinical cases. For instance, we are able to explain the particular shape of a tumor (looking as a horseshoe) by the pre-existing vascular tree.

FERNÁNDEZ ROMERO Antonio joint work with Guillén Gonzálezy F. and Suárez Fernández A.

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Glioblastoma evolution model in relation to vasculature

Glioblastoma accounts for 15-17% of all primary brain tumors and is the most frequent (50-75%) of astrocytomas, type of cancer of the brain which originate in a particular kind of brain cells in the cerebrum called astrocytes, in which Glioblastoma is included. We will present and study a PDE-ODE modeling the behaviour of the Glioblastoma with respect to the vasculature present in the enviroment for some differents situations. Besides, the tumor is modeled by two type of elements, the live tumor cells and the necrosis, who is very common in this type of brain tumours.

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Mathematical modeling of the evolution of heterogeneous tumors interacting with Effector and Regulatory T cells.

We developed a mathematical model to study the evolution of an heterogeneous tumor, formed by different cellular clones, in interaction with the immune system. For this, we considered the existence of multiple T cells clones, including Effector and Regulatory T cells, that modulate tumor growth through the recognition with different affinities of tumor associated antigens. This model is based in a previous one that allowed us to study the role of immune response regulation, mediated by Regulatory T cells, in the growth of an homogeneous tumor. With this previous model, we were able to predict the existence of two alternative dynamic modes of an homogeneous tumor growth: a mode where tumors growth instead the expansion of Effector T cells out-competing Regulatory T cells (mode GR-); and an alternative mode where tumors growth due to the presence of Regulatory T cells inhibiting immune response (mode GR+). Both tumor classes were predicted to respond different to immunotherapies. Here, we extended this model to study the impact of tumor heterogeneity in cancer evolution. In particular, we determined how the appearance of heterogeneous tumor clones during evolution can modify the mode of tumor growth. We predict that tumors that begin to growth in mode GR-, do not reverse their growth mode with the appearance of new tumor clones. On the other hand, tumors that initially grow in mode GR+, can break the initial immune tolerance during their evolution and be rejected or change to grow in the other mode. We characterized the dynamical properties of individual tumor clones constituting the heterogeneous tumors during evolution. We obtain that during tumor growth, the model predicts the accumulation of clones with high growth capacity: high growth rate and less sensitive to effector immune action. Additionally, the emergence of clones of greater immunogenicity causes the rejection of existing clones; and on the other hand, with the accumulations of clones with low immunogenicity the coexistence of clones is allowed. Future work will be focused in studying the impact of the appearance of neoantigens during tumor evolution, recognized with different affinity by T cell clones. The final goal is to study the impact of tumor heterogeneity in the efficacy of tumor immunotherapies.

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Role of sympathetic nervous system in pancreatic cancer development

Despite significant improvement in cancer therapy, pancreatic cancer is still incurable. It is among the 5 deadliest cancers, and the number of cases is increasing continuously.

This research project studies on KIC model, a newly discovered population of tumoral microenvironment: the neuronal axons of peripheral nervous system (PNS). Our results show that there is a progressive and subtype specific remodeling of PNS fibers during PDAC progression. Their heterogeneity might explain their effects on pancreatic cancers progression.

The current idea is that tumoral progression depends on their innervation which suggests new therapeutic approaches in order to modify PNs activity. Thus, it is important to better understand the role of each PNS division functions and to test their pro or anti-tumoral activity.

My denervation experiments on sympathetic nervous system show a survival reduction and an increase of metastasis spreading, suggesting a protective effect on pancreatic tumor development. To conclude, the identification of cellular interactions between tumoral microenvironment cells and nerve fibers will lead us to a better understanding of the nerve fibers remodeling process and the mechanisms acting on tumor progression.

The plan, based on the literature and my preliminary results, proposes to study the bi-directional interactions between sympathetic fibers and tumor associated macrophages (TAM). Indeed my results present in denervation context an increase of CD163 TAM population in pre-tumorales lesions. This macrophage population is considered as a poor prognostic in pancreatic cancer patient, it is important to better understand the link between sympathetic nerve and these CD163 macrophages. These results would give us a base to develop new therapeutic tools.

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An optimal control model of a heterogeneous tumor treatment in the context of stem cell cancer

The heterogeneity of cancer cells introduces significant challenges in designing effective treatment strategies. Indeed, This difference between cancer cells is a very important trait for disease progression, metastases and resistance to treatment. Tumor growth is significantly impacted by this heterogeneous population whose primary cause is the presence of stem cancer cells that are epigenetically different. The aim of our work is to develop a decision support tool to simulate and monitor the effect of treatment prior to administration. Thus we propose a model based on the hypothesis that stem cells are the cause of cancer. We have drawn inspiration from the work of Jinzhi Lei [1], to construct a mathematical model describing the growth of a tumor taking into account the intra-tumor heterogeneity, and assuming that the growth of this tumor is regulated by a CSC niche. Moreover, we applied the principle of maximum Pontryaguin to identify treatment protocols that incorporate knowledge of heterogeneity to yield higher efficacy. These optimal therapy protocols are improvements to the standard protocols used today since they limit the toxic side effects of drugs, which are generally very important in the case of cancer especially when it is treated by chemotherapy.

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Chemotherapeutic drug resistance in cancer: Insights from a multiscale in silico study

Tumour recurrence post chemotherapy is an established clinical problem and cancers are often observed as increasingly drug resistant subsequent to chemotherapy treatments. In many cases it has been observed that cancer cells have the ability to posses, acquire and communicate drug resistant traits, enabling them to survive in the presence of chemotherapeutic drugs. The existence of drug resistant phenotypes in cancer cell populations significantly impacts the efficacy and successfulness of chemotherapy treatments.

Using an *in silico* framework, we investigate tumour dynamics and drug response in cancer cell populations hosting various types of drug resistant phenotypes. We include drug resistant cell traits derived from inheritance or mutations that are spontaneous, drug-induced or communicated via exosomes. The framework is based on a hybrid multiscale cellular automaton incorporating mechanistic partial differential equations, ordinary differential equations extracted from a regulatory molecular network, stochasticity and phenomenological rules formulated by observations from biological experiments and clinical observations.

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Optimizing circadian drug infusion schedules towards personalized cancer chronotherapy

Systems medicine methods are used to develop quantitative understanding of precision chrono-modulated delivery system and patient specific whole-body drug pharmacokinetics. Current profiles used for chrono-modulated delivery are shown to have unexpected time delays and delivery spikes due to equipment and drug concentration. This poster will show the consequences of the delay and delivery spike and present a new delivery profiles to negate these phenomena. Using the model of chronomodulated delivery, pharmacokinetic models are created for individual patients and used to investigate inter-patient variability of current gold standard colorectal cancer treatment FOLFIRNOX (Oxaliplatin, Irinotecan and 5-Fluorouracil).

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Stochastic system identification without an a priori chosen kinetic model—exploring feasible cell regulation with piecewiselinear functions

Kinetic models are at the heart of system identification. A priori chosen rate functions may, however, be unfitting or too restrictive for complex or previously unanticipated regulation. We applied general purpose piecewise linear functions for stochastic system identification in one dimension using published flow cytometry data on E.coli and report on identification results for equilibrium state and dynamic time series. In metabolic labelling experiments during yeast osmotic stress response, we find mRNA production and degradation to be strongly co-regulated. In addition, mRNA degradation appears overall uncorrelated with mRNA level. Comparison of different system identification approaches using semi-empirical synthetic data revealed the superiority of single-cell tracking for parameter identification. Generally, we find that even within restrictive error bounds for deviation from experimental data, the number of viable regulation types may be large. Indeed, distinct regulation can lead to similar expression behaviour over time. Our results demonstrate that molecule production and degradation rates may often differ from classical constant, linear or Michaelis–Menten type kinetics.

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LEÓN-TRIANA Odelaisy [1] joint work with Pérez-Beteta Juliab[1], Ortiz A. [2], Arana E.[3],Pérez-García V. M. [1]

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Brain metastasis: Growth laws and imaging biomarkers

Brain metastases (BMs) are cancer cells that spread to the brain from primary tumors in other organs. About 10The treatment of BM patients who have well-controlled extracranial disease and less than four lesions consists typically of high, localized doses of radiation (Stereotactic Radio Surgery –SRS) on the visible lesions and often whole brain radiotherapy to target potentially hidden BM. Very few studies have addressed the mathematical modeling of the macroscopic growth of BMs and their response to RT [3,4]. Up to now, no mathematical-model-based quantitative biomarkers have been found to help in prognosis estimation. We have developed an in-depth study of the dynamics and response to therapy using diagnosis and follow-up imaging data from a database of 200 BM patients treated with SRS obtained from different institutions participating in the METMATH (METastasis and MATHematics) retrospective study. Here we will discuss in detail the first results of the project. First, we will discuss what are the growth laws of untreatred BMs. Secondly, we will describe how simple few-compartment mathematical models are able to describe the response to SRS. Finally, we present several quantitative imaging biomarkers obtained from our mathematical models with prognostic and predictive value [5].

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On the Role of Pharmacometrics in Optimal Control of Models for Cancer Therapies

We consider optimal control problems for a general mathematical model for cancer therapy with a single agent. Depending on whether a pharmacokinetic model (PK) for the drug action is included in the dynamics or not, the control represents the dosage, respectively the concentration of the agent. The effect of the drug is modelled by either a log-kill or a saturating Hill-function (Michaelis-Menten) pharmacodynamic relation (PD). The objective is to administer an a priori given total amount of agents in an optimal way to achieve a minimum tumor volume/maximum tumor reduction.

In this talk, we discuss how the structure of optimal solutions changes depending on specific assumptions made about PK and PD models. For example, if PD is modelled by a Michaelis-Menten relation, then, and in agreement with an interpretation of the controls as concentrations, optimal controls are continuous functions of time that change between full or no dose segments with connecting pieces that take values in the interior of the control set. On the other hand, optimal controls may be discontinuous for a log-kill model in line with an interpretation of controls as dose rates.

We illustrate the changes in the structure of optimal protocols for a mathematical model of tumor anti-angiogenic treatment based on a model by Hahnfeldt et al. (Cancer Research, 1999). In this case, if PD is modelled by a Hill function, optimal controls are concatenations between full and partial dose segments and a final no dose segment when, because of after effects, still small tumor reductions occur. A typical optimal concatenation sequence consists of an initial full dose segment followed by one segment when the control lies in the interior of the control set and changes from maximum dose to zero and a final no-dose segment. Numerical illustrations are given and the results for this model are compared with the one where a log-kill pharmacodynamic model is used to model the control actions.

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Competing Paths in Growing Populations over Fitness Valleys

We consider cells in a growing population that can undergo birth, death and transitions. Transitions, which may affect the genotype or environment of the cells, result in new cellular types. Motivated by the measured fitness cost of resistance in bacteria and sensitive cells in contact with drugs, we focus on the setting where the initial cellular type has the highest reproductive ability. We answer two questions. Firstly, for a target type of interest, how long do we wait until a cell with that type exists. Secondly, what is the probability that a particular sequence of transitions led to the target type. Our answers contain simple, explicit formulas that can be used to gain biological insight.

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Systematic analysis of a bifurcating model of tumour-immune interactions

Due to cancer heterogeneity, outcomes of immunotherapy trials often show a separation of tumour responses into two groups; these are uncontrolled tumour growth vs tumour shrinkage or eradication. Our aim is to determine whether a mechanistic model of tumour-immune interactions with bifurcating switches or bistability between different tumour growth regimes can explain variability in responses observed experimentally.

We focus on a simple two-compartment model, describing interactions between tumour and activated immune cells, that was proposed by Kuznetsov et al.1 (1994), and is frequently encountered in modelling literature. As parameter values are varied the model exhibits tumour escape, dormancy, and eradication; in some parameter regions bistability between tumour escape and dormancy is observed.

This model is a quasi-steady-state approximation (QSSA) of a full five-compartment model that incorporates kinetics of inactivated immune cells, programmed-for-death tumour cells, and conjugates of activated immune and tumour cells, dissociation of which results either in tumour cell programmed death or immune cell inactivation. By reconsidering the model simplifying assumptions, we deduce existence of a small parameter in the full model, and observe a separation of timescales.

Using asymptotic methods, we deduce a two-compartment long-timescale model, which is different from the QSSA model, but has equivalent steady states. Numerical solutions of this asymptotically reduced model correspond with those of the full model. Further simulations and linear stability analysis of this model and the QSSA model reveal large differences in typical solution trajectories and the bifurcation structure between the two.

Our analysis suggests that the QSSA does not necessarily preserve model behaviour, and careful application of asymptotic methods is crucial for valid model simplifications. Understanding the behaviour of the asymptotically reduced model, which preserves the modelled mechanistic properties of tumour-immune interactions, will allow us to explore whether this model can explain the dichotomy in tumour responses observed in immunotherapy drug trials.

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Quantifying the complexity of the spacing between surfaces: Applications to brain tumors.

Measuring the properties of the region contained between two surfaces is of interest in different applications $[1-3]$. In our case, we are interested in quantifying the differences be- tween two surfaces related to a growth process. Thus, one of the surfaces S1 (internal) is enclosed in the other S2 (external) but there is no a priori mapping between the points of S1 and S2. Our specific goal is to describe tumor areas obtained from MRI images. Inner parts of the tumor are necrotic and active tumor areas appear as complex 3D rim-like structures. To characterize the space between the surfaces we have first generated a set of distances be- tween them and characterized this set using different measures, leading to a set of quantifiers of the rim shape complexity (RSC). We have quantified RSC for pretreatment postcontrast T1-weighted images of 311 glioblastomas, the most prevalent and malignant primary brain tumors called glioblastomas, that are the most malignant and prevalent brain tumors. The measures defined here extend previous subsets found to have prognostic and predictive value for this type of tumors [4, 5]. Some of the measures were found to be associated to the patient prognosis and tumor prop- erties [6]. Thus, the spatial complexity quantifiers defined here and obtained from medical images can be useful in oncology to classify tumors and to predict patient survival.

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An Extended Model for the Growth and Size Distribution of Metastases Including Therapy Methods

The observation and ability to form prognosis for the amount and sizes of possible metastases of a tumor is of high interest for oncologists. Mathematical models describing the seeding and growth of metastases are possibly of clinical use in optimizing individual therapy algorithms. I adapted the well-known von-Foerster equation used by Iwata, Kawasaki and Shigesada (2000) to describe metastases' dynamics when metastases are seeded at a cell size of exactly one. With redefined boundary conditions I was capable to reformulate the model to describe the seeding of metastasis of any size, also taking into account secondary metastases. As the model is defined in a continuous way, it can also be used to model a crossing of a T1N0M0 cancer towards an uprising metastatic disease. The model is illustrated numerically with the data given by Iwata et al. to examine the differences of both approaches. Further, some therapy dynamics are included into the model equations for being able to analyze clinical data.

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Identifying drugging strategies using evolutionary principles in lymphoma mouse model

The evolutionary process of mutation accumulation in cancer leads to the development of drug resistance and therapy failure. Insights into growth dynamics can lead to a better understanding of tumour growth and with that improved treatment strategies. To this end, we have developed rule-based models describing the evolution of sensitive and resistant subpopulations with Luria-Delbrück-like growth under different treatment regimes. With the addition of a carrying capacity that decreases tumour proliferation at later stage, we are able to recapitulate biological experiments depicting resistance emergence with a mouse model of tumour growth under daily drug administration or absence of treatment, though the inferred growth parameters appear to contradict in vitro experiments. We further find that this paradigm is not able to recapitulate growth in more complex treatment strategies. The addition of a competitive regrowth process is sufficient to reconcile growth curves and in vitro data. This competitive regrowth process suggests a counterintuitive response to removal of drug, where the substantially larger sensitive cell population is able to regrow faster than the resistant population despite their apparently similar relative fitnesses. Thanks to this competition, tumours may be temporarily stabilised by using reduced efficacy treatments.

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