"Present Challenges of mathematics in oncology and biology of cancer: modelling and mathematical analysis"

CIRM Marseille, France

December 7-11, 2015

Organizing committee

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Ursula Ledzewicz (Southern Illinois University Edwardsville, USA)
Christophe Meille (Novartis, Bale, SWITZERLAND)

December 7, 2015

Chapter 1

Timetable

Monday	Tuesday	Wednesday	Thursday	Friday
9h00-9h15 Welcome	9h00-10h00 Hartung Niklas	9h00-10h00 Benzékry Sébastien	9h00-10h00 Letellier Christophe	9h00-10h00 Meunier Nicolas
9h15-10h15 Perthame Benoit	10h00-11h00 Colin Thierry	10h00-10h30 Ballester Pedro	10h00-10h30 Bogdanska Magdalena	10h00-11h00 Stéphanou Angélique
10h15-10h30 Coffee break	**11h00-11h15 Coffee break**	**10h30-10h45 Coffee break**	**10h30-10h45 Coffee break**	**11h00-11h15 Coffee break**
10h30-11h30 Bonnet Catherine	11h15-12h15 Muracciole Xavier	10h45-11h45 Pasquier Eddy	10h45-11h45 Pisco Angela	11h15-12h15 Marciniak-Czochra Anna
11h30-12h00 Ledzewicz Urszula		11h45-12h15 Lepoutre Thomas	11h45-12h15 Pichard Teddy	12h15-12h30 Closure
12h00-12h30 Rashkov Peter				
12h30 Lunch	**12h30 Lunch**	**12h30 Lunch**	**12h30 Lunch**	**12h30 Lunch**
14h30-15h30 Tuszynski Jack	14h30-15h30 André Nicolas		14h30-15h00 Ballesta Annabelle	
15h30-16h00 Honoré Stéphane	15h30-16h30 Taieb David		15h00-15h30 Folguera Nuria	
16h00-16h30 White Diana	16h30-17h00 Coffee break		15h30-16h00 Konstorum Anna	
16h30-17h00 Coffee break	17h00-17h30 Serre Raphaël		16h00-16h30 Coffee break	
17h00-18h00 Natalini Roberto			16h30-17h00 Srimaneekarn Natchalee	
			17h00-17h30 Summer Ilysa	
	18h00-21h00 Poster session - Cocktail party In Annexe		17h30-18h00 Helal Mohammed	
19h30 Dinner		**19h30 Dinner**	**19h30 Gala Dinner**	

Poster session

- ALVAREZ-ARENAS Arturo
- BARATCHART Etienne
- BARLUKOVA Ayuna
- BESSE Apollos
- BERMENT Perrine
- BENZEKRY Sébastien
- BUTTENSCHOEN Andreas
- CARRERE Cécile
- HADDAD Ghassen
- HARTUNG Niklas
- HENARES MOLINA Araceli
- KAROLAK Aleksandra
- MICHEL Thomas
- POUCHOL Camille
- TESSON Rmi
- TREVISAN Dario

Monday December 7th

9h00-9h15 **Welcome Session**

9h15-10h15 **Benoît Perthame** (Laboratoire J.-L. Lions, Université P. et M. Curie, INRIA-Rocquencourt, France)
Models of living tissues and free boundary asymptotics

10h15-10h30 **Coffee Break**

10h30-11h30 **Catherine Bonnet** (Inria Saclay, L2S Centrale-Supelec, Gif-sur-Yvette, France)
Modeling hematopoietic cell population dynamics for Acute Myeloid Leukemia with perspectives in control

11h30-12h00 **Urszula Ledzewicz** (Southern Illinois University Edwardsville, USA and Technical University of Lodz, Poland)
Mathematical Modeling of Tumor Microenvironment and Metronomic Chemotherapy: Optimal Control Approach

12h00-12h30 **Rashkov Peter** (University of Exeter, UK)
Emergence of drug resistance in cancer from the perspective of ecological competition

12h30 -13h30 **LUNCH**

14h30-15h30 **Jack Tuczynski** (Department of Physics and Department of Oncology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada)
Mathematical Measures of Network Complexity for Cancer Signaling Networks

15h30-16h00 **Stéphane Honoré** (Center for Research in Oncobiology and Oncopharmacology, Aix-Marseille University)
Microtubule dynamic instability: implication in oncopharmacology and modeling

16h00-16h30 **Diana White** (Institut de Mathématiques de Marseille, Aix-Marseille University)
Modelling the Dynamics of Microtubules in the Presence of End Binding Proteins and Microtubule Targeting Agents

16h30-17h00 **Coffee Break**

17h00-18h00 **Roberto Natalini** (Istituto per le Applicazioni del Calcolo "M. Picone", Consiglio Nazionale delle Ricerche, Rome, Italy)
Mathematical models of the transportation of anti-tumoral genetic vaccines

19h30 **DINNER**

Tuesday December 8th

9h00-10h00 **Niklas Hartung** (Dept. of Clinical Pharmacy and Biochemistry, Freie Universität Berlin, Germany)
Mathematical modeling of tumor growth and metastatic spreading: Validation in tumor-bearing mice

10h00-11h00 **Thierry Colin** (INRIA Bordeaux, France)
Nenuphar: a software for the evaluation of the aggressiveness of a tumor

11h00-11h15 **Coffee Break**

11h15-12h15 **Xavier Murracciole** (Hopital de la Timone, Marseille)
Mathematical modeling of the kinetics of PSA method for early detection of prostate cancer

12h30 -13h30 **LUNCH**

14h30-15h30 **Nicolas André** (Hopital de la Timone Enfants, Aix-Marseille University)
From metronomic to chaotic therapy

15h30-16h30 **David Tayeb** (Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University)
^{18}*F-FDG in paraganglioma imaging*

16h30-17h00 **Coffee Break**

17h00-17h30 **Raphaël Serre** (Multidisciplinary Oncology and Therapeutic Innovations, Assistance Publique Hôpitaux de Marseille)
Metronomic chemotherapy in human lung cancer: mathematical modeling for an optimal schedule

18h00-21h00 **Poster Session in Annexe**
Cocktail Party

Posters session

Arturo Álvarez-Arenas (Universidad de Cadiz, Spain)
Transfer of resistance between cancer cell subpopulations: From biological data to mathematical models and back

Etienne Baratchart (Inria Bordeaux, France)
Data-driven modelling of metastatic initiation and tumour-tumour spatial interactions

Ayuna Barlukova (I2M, Aix-Marseille University)
Modeling of dynamic instability of MTs with aging and impact of drugs

Perrine Berment (Bordeaux University, France)
A mathematical model for colorectal tumors using fonctional imaging

Apollos Besse (INRIA Rhône Alpes, Lyon, France)
Mathematical study of long-term treatment effects on Chronic Myeloid Leukemia

Andreas Buttenschon (Alberta University, Edmonton, Canada)
A space-jump derivation for non-local models of cell-cell adhesion

C. Carrère (I2M, Aix-Marseille University)
Optimal treatment for an heterogeneous in vitro tumor composed of resistant and sensitive cells

Ghassen Haddad (Lab. de modélisation mathématique et numérique, Tunis)
Optimization of cancer treatment, application to bladder cancer

Niklas Hartung (Freie Universität Berlin, Germany)
Mathematical modeling of tumor kinetics in metastatic melanoma treated with B-RAF inhibitors

Araceli Henares (Facultad de Ciencias, Universidad de Granada, Spain)
Protracted metronomic therapies to target low-grade glioma malignant transformation

Aleksandra Karolak (Moffitt Cancer Center and Research Institute, Tampa, United States)
Using computational modeling to quantify targeted agent binding and internalization in pancreatic cancers

Thomas Michel (INRIA Bordeaux, France)
A mathematical model for Multicellular Tumor Spheroids: the impact of nutrient on proliferative cells

Camille Pouchol (Université Pierre et Marie Curie, Paris, France)
Some phenotype-structured integro-differential models, asymptotic analysis and optimal control

Rémi Tesson (I2M, Aix-Marseille University)
A model for cell migration involving microtubules

Dario Trevisan (University a degli Studi di Pisa, Italy)
A particle systems approach to cell-cell interaction

Wednesday December 9th

9h00-10h00 **Sébatstien Benzékry** (INRIA Bordeaux France)
Modeling spontaneous metastasis following surgery and tumor-tumor interactions: an in vivo-in silico approach

10h00-10h30 **Pedro Ballester** (Cancer Research Center of Marseille, Marseille)
Unearthing new genomic markers of drug response by improved measurement of discriminative power

10h30-10h45 **Coffee Break**

10h45-11h45 **Eddy Pasquier** (Center of Research in Oncology and oncopharmacology, Aix-Marseille University)
Next-generation drug repositioning in oncology: deciphering resistance mechanisms and discovering novel therapeutic targets by functional pharmacology

11h45-12h15 **Thomas Lepoutre** (INRIA Lyon, France)
Implication of the autologous immune response in the treatment response for chronic myeloid leukemia

12h30 -13h30 **LUNCH**

13h30 **Departure for MUCEM**
with Ayuna BARLUKOVA and Cécile CARRERE

13h45 **Departure for calanques**
with Rémi TESSON and Diana WHITE

19h30 **DINNER**

Thursday December 10th

9h00-10h00 **Christophe Letellier** (CORIA-Normandie Universit, INSA Rouen , France)
How the dynamics between cell populations affects tumor growth

10h00-10h30 **Magdalena Bogdańska** (University of Warsaw, Poland and Universidad de Castilla-La Mancha, Spain)
A mathematical model of low grade gliomas treated with temozolomide and its therapeutical implications

10h30-10h45 **Coffee Break**

10h45-11h45 **Angela Pisco** (Kings College London, Centre for Stem Cells and Regenerative Medicine, Guys Hospital, London, UK)
Non-genetic cancer cell plasticity

11h45-12h15 **Teddy Pichard** (CELIA, Bordeaux University / MathCCES, RWTH Aachen University)
Moment models for radiotherapy dose simulation

12h30 -13h30 **LUNCH**

14h30-15h00 **Annabelle Ballesta** (Systems Biology Centre, University of Warwick, UK)
A multi-scale systems pharmacology approach for anticancer therapy personalisation

15h00-15h30 **Núria Folguera-Blasco** (Centre de Recerca Matematica, Barcelona, Spain)
Mathematical modelling of oncometabolic reprogramming of somatic cells

15h30-16h00 **Anna Konstorum** (Center for Quantitative Medicine, University of Connecticut Health Center; Farmington, CT, USA)
Feedback regulation in a cancer stem cell model can cause an Allee effect

16h00-16h30 **Coffee Break**

16h30-17h00 **Natchalee Srimaneekarn** (University of Southampton, UK)
Statistical classification for diagnosis of cirrhosis patients

17h00-17h30 **Ilyssa Summer** (Applied Mathematics for the Life and Social Sciences, Arizona State University, USA)
Mathematical Model for Virotherapy and Immunotherapy Combinations towards Cancer

17h30-17h30 **Mohammed Hellal** (Laboratory of Biomathematics, Djillali Liabes University, Algeria)
Mathematical model of chronic myeloid leukemi

19h30 **DINNER**

Friday December 11th

9h00-10h00 **Nicolas Meunier** (University Paris Descartes, France)
A minimal model for cell migration

10h00-11h00 **Angélique Stéphanou** (Laboratoire TIMC-IMAG (DyCTiM), Grenoble, France)
An integrated computational approach for the design of patient-specific virtual tumours

11h00-11h15 **Coffee Break**

11h15-12h15 **Anna Marciniak-Czochra** (Heidelberg University, Germany)
Structured population models of clonal selection and evolution of resistance in acute leukemias

12h15-12h30 **Closure session**

12h30 -13h30 **LUNCH**

Chapter 2

Abstracts

2.1 Plenary talks

Nicolas André

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From metronomic to chaotic therapy

TBA

Sébastien Benzekry

INRIA team MONC, Bordeaux France

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Modeling spontaneous metastasis following surgery and tumor-tumor interactions: an in vivo-in silico approach

The post-surgical development of metastases (secondary tumors spread from a primary one) represents the major cause of death from a cancer disease. Mathematical models may have the potential to further assist in estimating metastatic risk, particularly when paired with in vivo tumor data that faithfully represent all stages of disease progression.

In this talk I will first describe a modeling approach that uses data from clinically relevant mouse models of spontaneous metastasis developing after surgical removal of orthotopically implanted primary tumors. Both presurgical (primary tumor) and postsurgical (metastatic) growth was quantified using bioluminescence. The model was able to fit and predict pre-/post-surgical data at the level of the individual as well as the population. Importantly, our approach also enabled retrospective analysis of clinical data describing the probability of metastatic relapse as a function of primary tumor size, where inter-individual variability was quantified by a key parameter of intrinsic metastatic potential. Critically, our analysis identified a highly nonlinear relationship between primary tumor size and postsurgical survival, suggesting possible threshold limits for the utility of tumor size as a predictor of metastatic recurrence.

In the second part of my talk, I will focus on some very intriguing phenomenon concerning systemic interactions between tumors within the organisms, termed "concomitant resistance", by which, in the presence of two tumors, one inhibits the growth of the other. This has important clinical consequences as it can lead to post-surgery metastatic acceleration. Based on experimental data involving the simultaneous growth of two tumor implants, we will test biological theories underlying this process and establish a biologically relevant and minimally parameterized mathematical model.

These findings represent a novel use of clinically relevant models to assess the impact of surgery on metastatic potential and may guide optimal timing of treatments in neoadjuvant (presurgical) and adjuvant (postsurgical) settings to maximize patient benefit.

Catherine Bonnet

Inria Saclay-Ile-de-France and L2S CentraleSupélec, Gif-sur-Yvette, France

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Modeling hematopoietic cell population dynamics for Acute Myeloid Leukemia with perspectives in control.

Acute Myeloid Leukemia (AML) is a rare disease whose treatment relies on heavy chemotherapy. With the ultimate goal to optimize polychemotherapies delivered in the case of AMLs which present a high level of FLt-3 duplication, we design deterministic mathematical models (inspired from a discrete-maturity model introduced by M. Adimy, F. Crauste and A. El Abdllaoui in 2008) with a limited number of variables and parameters chosen according to specific goals : the representation of bone marrow cell population dynamics, healthy or leukemic, and of the functional effects of the drugs used on the fate of cell populations.

Our models take into account the fast self-renewal observed in AML cells, which present a high level of FLt-3 duplication (Flt-3 ITD, enhancing uncontrolled proliferation) as well as blockade of differentiation. We focus here on stability analysis of these models, showing how they may predict evolution of AML under treatment.

Thierry Colin

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Nenuphar: a software for the evaluation of the aggressiveness of a tumor.

A huge number of mathematical/numerical models of tumor growth are available in the literature. Most of them aim at integrating an increasing amount of biological/medical knowledges. These models are able to account at least qualitatively for several complex phenomenas (angiogenesis, influence of particular molecular pathway, effects of targeted therapies, ...). They could be useful for clinical applications in order to help to understand the evolution of the disease or the response to the treatment in a personalized clinical context. The challenge is therefore to be able to obtain a parametrization of the models with the available data. If we restrict ourself to a clinical context the information is scarce. It consists mainly in the nature of the cancer that is known thanks to biological exams (blood samples, biopsies) and also to imaging data (CT-scans, MRI, PET-scans). The model has therefore to be designed according to the nature of the cancer, its localization but also according to the available imaging data. The images will give information on the volume, but also on the shape and the metabolism of the tumor (thanks to functional imaging technics like perfusion MRI or CT-scans). Moreover, for a particular patient, we often have several successive exams at different times. We therefore have to solve a complex inverse problem in order to be able to give a forecast of the progression of the disease or of the answer to a treatment. In this talk, I will present two examples of such inverse problems. concerning lung metastases and meningiomas. The challenge is to be able to give some forecast of the evolution of the disease for patients that have no treatment in order to help to understand what could be the best moment for starting some therapy.

Niklas Hartung

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Mathematical modeling of tumor growth and metastatic spreading: Validation in tumor-bearing mice

Defining tumor stage at diagnosis is a pivotal point for clinical decisions regarding patient treatment strategies. In this respect, early detection of occult metastasis invisible to current imaging methods would have a major impact on best care and long-term survival. Mathematical models that describe metastatic spreading might estimate the risk of metastasis when no clinical evidence is available. In this study, we adapted a top-down model to make such estimates. The model was constituted by a transport equation describing metastatic growth and endowed with a boundary condition for metastatic emission. Model predictions were compared to experimental results from orthotopic breast tumor xenograft experiments conducted in Nod/Scid gamma mice. Primary tumor growth, metastatic spread and growth were monitored by 3D bioluminescence tomography. A tailored computational approach allowed the use of Monolix software for mixed-effects modeling with a partial differential equation model.

Primary tumor growth was described best by Bertalanffy, West and Gompertz models which involve an initial exponential growth phase. All other tested models were rejected. The best metastatic model involved two parameters describing metastatic spreading and growth, respectively. Visual Predictive Check, analysis of residuals and a bootstrap study validated the model. Coefficients of determination were $R^2 = 0.94$ for primary tumor growth and $R^2 = 0.57$ for metastatic growth. The data-based model development revealed several biologically significant findings. First, information on both growth and spreading can be obtained from measures of total metastatic burden. Second, the postulated link between primary tumor size and emission rate is validated. Finally, fast growing peritoneal metastases can only be described by such a complex partial differential equation model and not by ordinary differential equation models. This work advances efforts to predict metastatic spreading during the earliest stages of cancer.

Christophe Letellier[1] joint work with Louise Viger[1], Clement Draghi[1], Fabrice Denis[1,2]

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How the dynamics between cell populations affects tumor growth

Describing tumor growth is a key issue in oncology for correctly understanding the underlying mechanisms leading to deleterious cancers. In order to take into account the micro-environment in tumor growth, we used a model describing at the tissue level the interactions between host (non malignant), effector immune and tumor cells to simulate the evolution of cancer [1,2,3]. We investigated how the evolution of the tumor diameter is related to the dynamics (periodic or chaotic oscillations, stable singular points) underlying the interactions between the different populations of cells in proliferative sites. Dynamically speaking, it is also shown that a chaotic regime at the tumor site scale (roughly 10-3 mm3 in our simulations) leads to a more resistive micro-environment (thus providing a stronger barrier against the tumor growth) at the tissue scale (greater than 1 mm3) [4,5].

References [1] L. G. De Pillis, A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, Journal of Theoretical Medicine, 3, 79-100, 2001. [2] C. Letellier, F. Denis & L. Aguirre, What can be learned from a simple cancer model?, Journal of Theoretical Biology, 322, 7-16, 2013. [3] L. Viger, F. Denis, M. Rosalie & C. Letellier, A cancer model for the angiogenic switch, Journal of Theoretical Biology, 360, 21-33, 2014. [4] L. Viger, Approche dterministe des dynamiques de cancers : Vers une individualisation des pronostics dvolution des cancers, Ph.D. Thesis, Rouen University, November 27, 2015. [5] L. Viger, F. Denis, C. Draghi, T. Mnard & C. Letellier, Spatial avascular growth of tumor in a homogeneous environment, submitted.

Anna Marciniak-Czochra

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Structured population models of clonal selection and evolution of resistance in acute leukemias.

Motivated by clonal selection observed in acute myeloid leukemia (AML), we propose mathematical models describing evolution of a multiclonal and hierarchical cell population. The models in a form of partial and integro-differential equations are applied to study the role of self-renewal properties and growth kinetics during disease development and relapse. Effects of different time and space scales are investigated. It is shown how resulting nonlinear and nonlocal terms may lead to a selection process and ultimately to therapy resistance. The results are compared to AML patient data. Model based interpretation of clinical data allows to assess parameters that cannot be measured directly. This might have clinical implications for future treatment and follow-up strategies.

Nicolas Meunier[1] joint work with C. Etchegaray[2], M. Piel[3], R. Voituriez[4]

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A minimal model for cell 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.

Xavier Muracciole joint work with N. Branger[1], X. Muraciolle[2], C. Bastide[1], S. Garcia[1], S. Giusano[1], E. Lechevallier[3], D. Rossi[1], D. Barbolosi[4]

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Mathematical modeling of the kinetics of PSA method for early detection of prostate cancer

Objectives
Our goal is to improve the empirical interpretation of PSA assays by a more rigorous mathematical approach by developing a simple and robust modeling based on the kinetics of PSA. The goal is to better predict the presence of prostate cancer, the risk of clinical progression and help in the decision to perform PBP (prostatic biopsies).
Material and Methods Based on differential equations, two models (Benin and malignant) taking into account, prostate volume, and PSA kinetics of 3 successive assays were developed. In each respective model, a doubling time (TD) and a volume of the normal prostate (or BPH Benign Prostatic Hypertrophia) (VB) or cancer (VT) will be estimated in order to fit the best points of the PSA on the curve versus time. From the proposed values of VB and VT with the respective TD, clinically valid model is retained.
Results
The model was used to classify a learning cohort of 10 patients either in the Benign model (BPH and indolent cancer) and either in malignant model (significant cancer) and was very satisfactorily. In a cohort of patients who underwent radical prostatectomy, the correlation between the average estimated by malignant VT model (2.04 mL) and the calculated transverse serial sections of prostaticpathological block (1.80mL) was excellent ($r = 0.95$). This correlation was observed regardless if the importance of the VT.
Conclusion
Tthese very encouraging preliminary results need to be validated in a larger cohort of patients. A prospective study of early detection of prostate cancer using this modeling will evaluate the contribution of this approach in terms of sensitivity and specificity.

Roberto Natalini joint work with Maria Grazia Notarangelo and Emanuela Signori

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Mathematical models of the transportation of anti-tumoral genetic vaccines

Anti-tumoral genetic vaccines are a new and promising approach for the prevention and/or treatment of cancer. Viral and non-viral vectors are used to vehiculate deliver DNA sequences of tumour-associated or tumor-specific antigens that can be expressed into the nucleus of muscle cells, so activating an adequate immune response against cancer. In the last few years, intramuscular gene transfer by non viral-vectors such as plasmid DNA, is receiving considerable attention for due to its safety, simplicity and low cost of production. Neverthless, compared with viral vectors, DNA plasmids show a low transfection efficiency and a poor transgenic expression. Therefore, strategies to improve DNA uptake into the nuclei of cells for its expression are required.

It is well known that the microtubule network and the importin play important roles in the intracellular trafficking. The mechanisms regulating this process need to be elucidated, since they have a significant role in gene delivery. Here, we propose a new methodological approach based on the coupling of biology assays and predictive mathematical models to clarify the mechanisms of the DNA transport and uptake into cells. The space-time mathematical model takes into account the diffusion of plasmids in a cell, their active transport along the microtubules, and their interaction with importin and Ran cycle. Through numerical simulations, we can reproduce some experimental studies reported in the literature and discuss some transport mechanisms that could be improved to obtain a higher gene expression from the DNA vaccines.

Eddy Pasquier[1,2,3]

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Next-generation drug repositioning in oncology: deciphering resistance mechanisms and discovering novel therapeutic targets by functional pharmacology

Intrinsic and acquired drug resistance remains the main therapeutic challenge in modern oncology. We have recently developed an innovative methodology that combines drug repositioning, bioinformatics and functional genomics in order to discover new ways to overcome resistance mechanisms. First, high-throughput technology is used to screen $> 3,700$ already approved drugs and pharmacologically active molecules to identify hit compounds that can increase the efficacy of chemotherapy or targeted therapy against cancer cells. Secondly, bioinformatic tools are applied to list all the known target genes of the hit compounds. A custom siRNA library is then designed and screened to individually silence the expression of the target genes and determine which ones play a critical role in cancer cell proliferation and response to therapy. This leads to the identification of key signalling pathways involved in drug resistance, which can be specifically targeted by hit compounds in order to increase the efficacy of current treatments. We have successfully applied this methodology to two aggressive forms of cancer: neuroblastoma, an embryonal tumour of the peripheral nervous system affecting infants and young children; and glioblastoma multiforme, a very aggressive form of brain tumour affecting both adults and children. This led to the discovery of novel, actionable therapeutic targets whose patho-physiological role is currently being investigated and which could be rapidly translated into the clinic to improve patient outcome once validated. This cost- and time-effective methodology can be applied to virtually any form of refractory cancer and potentially to patient-derived tumour cells to develop personalized therapeutic strategies.

Benoît Perthame

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Models of living tissues and free boundary asymptotics

Tissue growth, as in solid tumors, can be described at a number of different scales from the indivudual cell to the organ. For a large number of cells, the 'fluid mechanical' approach has been advocated recently by many authors in mathematics, physics and biomecanics. Several levels of mathematical descriptions are commonly used, including elastic or visco-elastic effects, nutrients, active movement, surrounding tissue, vasculature remodeling and several other features.

We will focuss on the links between two types of mathematical models. The 'compressible' description is at he cell population density level and a more macroscopic, description is based on a free boundary problem close to the classical Hele-Shaw equation. Asymptotic analysis is a tool to derive these Hele-Shaw free boundary problems from cell density systems in the stiff pressure limit. This modeling also opens other questions as circumstances in which instabilities develop and questions on the regularity of the interface between heathy and cancerous tissues.

This presentation follows collaborations with F. Quiros and J.-L. Vazquez (Universidad Autonoma Madrid), M. Tang (SJTU), N. Vauchelet (LJLL), A. Mellet (College Park), A. Lorz (LJLL) and T. Lorenzi (St Andrews).

Angela Pisco[1,2] joint work with Joseph Zhou[2], Sui Huang[2]

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Non-genetic cancer cell plasticity

Therapy resistance and tumour relapse after drug therapy are commonly explained by Darwinian selection of pre-existing drug-resistant, often stem-like cancer cells resulting from random mutations. However, the ubiquitous nongenetic heterogeneity and plasticity of tumour cell phenotype raises the question: are mutations really necessary and sufficient to promote cell phenotype changes during tumour progression? Tumorigenesis is a dynamic biological process that involves distinct cancer cell subpopulations proliferating at different rates and interconverting between them. Cancer therapy inevitably spares some cancer cells, even in the absence of resistant mutants. Accumulating observations suggest that the non-killed, residual tumour cells actively acquire a new phenotype simply by exploiting their developmental potential. These surviving cells are stressed by the cytotoxic treatment, and owing to phenotype plasticity, exhibit a variety of responses. By entering such stem-like, stress-response states, the surviving cells strengthen their capacity to cope with future noxious agents. Considering nongenetic cell state dynamics and the relative ease with which surviving but stressed cells can be tipped into latent attractors of the gene regulatory network provides a foundation for exploring new therapeutic approaches that seek not only to kill cancer cells but also to avoid promoting resistance and relapse that are inherently linked to the attempts to kill them.

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An integrated computational approach for the design of patient-specific virtual tumours

The design of a patient-specific virtual tumour is an important step towards personalized medicine since the virtual tumour can be used to define the most adapted and efficient treatment protocol. However this requires to capture the description of many key events of tumour development, including angiogenesis, matrix remodelling, hypoxia, cell heterogeneity that will all influence the tumour growth kinetics and degree of tumour invasiveness. To that end, an integrated hybrid and multiscale approach has been developed based on data acquired on a preclinical mouse model as a proof of concept. Fluorescence imaging is exploited to build case-specific virtual tumours and to validate their spatiotemporal evolution. The validity of the model will be discussed as well as its potential to identify the best therapeutic strategy for each individual tumour case.

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^{18}*F-FDG in paraganglioma imaging*

Since the development of radioiodinated meta-iodobenzylguanidine (MIBG) over 30 years ago, nuclear imaging has had a central role in managing patients with paraganglioma (PGL), aiding in the diagnosis and staging of this rare but, for many patients, devastating disease. Based on these characteristics, nuclear imaging provides a means of linking imaging phenotype to genotype and can be considered a member of the multi-omics approach. For example, an intense 2-fluoro-2-deoxy-D-glucose (18F-fluorodeoxyglucose, 18F-FDG) uptake by a PGL is mostly associated with mutations involving one of the genes encoding the succinate dehydrogenase (SDH) complex. Conversely, a low uptake can often rule out a classic SDH deficiency linked to SDH mutations. The uptake of 18F-FDG is often characterised by calculating the standardised uptake value (SUV) from late static imaging. Despite high tumor SUV values observed in PGLs (especially SDH tumors), proliferation indices are very low. These discrepancies might be related to high proportion of unmetabolised 18 F-FDG components in the tumor. We propose a method that enables to calculate different 18 F-FDG kinetic parameters based on a new mathematical approach that integrates a measurement error model. The estimations of these new kinetic parameters are more accurate for in vivo metabolic assessment of PGLs at the molecular level.

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Mathematical Measures of Network Complexity for Cancer Signaling Networks

The 5-year survival for patients after diagnosis/treatment is strongly dependent on tumor type. Prostate cancer patients have a ¿99% chance of survival past 5-years since diagnosis, while pancreatic patients have ¡6% chance of survival past 5-years. Since each cancer type has its own molecular signaling network, we asked if there are signatures embedded in these networks that inform us as to the 5-year survival. In other words, are there statistical metrics of the network that correlate with survival? And further, if there are, can such signatures provide clues to selecting new therapeutic targets? From the KEGG Cancer Pathway database we computed several conventional and some less conventional network statistics. In particular we found a high correlation (R2 = 0.7) between degree-entropy and 5-year survival based on the SEER database. This correlation suggests that cancers that have a more complex molecular pathway are more refractory than those with less complex molecular pathway. We also found potential new targets by computing the betweenness a statistical metric of the centrality of a node for the molecular networks. We have also investigated algebraic and topological indices for network complexity for protein-protein interaction networks of 11 human cancers. We have found evidence that greater network complexity is associated with lower five year survival probabilities. Moreover, we identify several protein families (PIK, ITG, AKT) that are repeated motives in many of the cancer pathways. Our results can aide in the identification of promising targets for anti-cancer drugs.

2.2 Oral communications

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A multi-scale systems pharmacology approach for anticancer therapy personalisation

Anticancer chemotherapy personalisation requires to reliably account for molecular pathways of patients response to drug administration. In a context where clinical molecular data is usually minimally available in individual patients, multi-scale physiologically-based modelling appears as an adapted solution to describe underlying gene and protein networks ultimately responsible for treatment antitumor efficacy and side effects. Basing mathematical models on physiology allows the use of in vitro studies to design whole-body preclinical rodent models, to be further scaled to patient population data. The resulting human model, that describes an average cancer patient, may then be used in global parameter sensitivity analyses to generate specific predictions on relevant circadian biomarkers. Partial re-calibration of the population human model for a given cancer patient according to individual biomarker recordings, patients genetic background and therapeutic history further allow for chemotherapy personalisation. The patient-specific models then appeal for clinical validation, thus initiating a novel trial design, where each individual patient receives personalised drug combinations/scheduling computed via mathematical models, informed with a continuous flow of multidimensional information obtained and tele-transmitted from patients. The models we are designing mainly represent the intracellular protein networks together with the pharmacokinetics-pharmacodynamics (PK-PD) of drugs of interest in the main relevant organs. While PK quantifies the transport and metabolism of the drug and its metabolites that are driving exposure concentration over time, PD quantifies drug interactions with cellular targets and subsequent cytotoxicity. I will present how this approach was undertaken for personalising i) chronotherapy against digestive cancers with a particular focus on the anticancer drug irinotecan [1-3] and ii) temozolomide-based combination therapy against brain tumors [4].

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Pedro Ballester joint work with Cuong Dang, Antonio Peon

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Unearthing new genomic markers of drug response by improved measurement of discriminative power

The screening of selected drugs against a large panel of molecularly-profiled cancer cell lines constitutes a valuable community resource for biomarker discovery. A prominent example is that by Garnett et al.1, who released data from testing 130 drugs against a panel of 637 cell lines and used them to search f or those gene mutations providing the best discrimination between sensitive and resistant cell lines to each drug. Based on the p-values from a MANOVA statistical test, 387 of the 8203 drug-gene associations were found to be significant and thus potentially suitable as genomic markers of drug response. Here we directly measured the discriminative power of each of these drug-gene associations by posing each association as a binary classification problem (this was enabled by the introduction of a meaningful criterion to determine the sensitivity threshold). Thus, we calculated the Matthews Correlation Coefficient2 (MCC) of each association and compare the resulting MCCs with the corresponding p-values. The analysis showed that there are highly significant drug-gene associations with no discriminative power (e.g. mutated-FLT3 sensitising cancer cells to the experimental drug GW441756 with p-valueMANOVA $\sim$ 10-10 but a MCC=0.05), which therefore are not useful as markers of drug response. More importantly, we could rescue drug-gene associations that were rejected by the MANOVA test, but actually have substantially more discriminative power than significant gene associations for the same drug (e.g. EWS_FLI1 translocation sensitising cancer cells to the drug Mitomycin-C with p-value$_{MANOVA}$ $\sim$ 10-2 but a MCC=0.27). Overall, it was found that only a few drug-gene associations offer high discrimination power (however markers providing much lower discrimination are still a more effective way to assign drugs to tumours than not using any biomarker). Lastly, a χ^2 statistical test was also carried out for each association in order to evaluate how likely was the corresponding classification of cells to arise by chance (p-value$_{\chi^2}$). MCC and log(p-value$_{\chi^2}$) were observed to have a Spearman correlation of 0.99, with associations with MCC>0.19 being always significant according to the χ^2 test.

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Magdalena Bogdańska[1,2] joint work with M. Bodnar[1] , M.J. Piotrowska[2], J. Belmonte-Beitia[2] , M. Murek[3] , P. Schucht[3] , J. Beck[3] , V.M. Pérez-García[2]

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A mathematical model of low grade gliomas treated with temozolomide and its therapeutical implications

Low grade gliomas (LGGs) are primary brain tumours which evolve very slowly, however inevitably causing death. Due to many controversies in the treatment of LGGs, we aim to use a mathematical framework to answer questions of the tumour assessment and the choice of the therapy. We propose a simple mathematical model of LGG growth and its response to chemotherapy (temozolomide, TMZ) which allows to describe the tumour evolution in real patients. Results agrees with data of patients diagnosed with LGGs and treated with TMZ at Bern University Hospital. The model predicts, and our clinical data confirms, that the speed of response to chemotherapy as well as change in tumour volume are related to both proliferative potency of tumour and its resistance to therapy. Moreover, we provide estimated formulae for time of tumour response to therapy and decrease in tumour volume, which can be used as a measure of LGG aggressiveness. Thus, we propose a new tool to find the best personalised therapies. Finally, we suggest chemotherapy fractionation scheme that might be therapeutically useful to predict the tumour growth and further prognosis.

Núria Folguera-Blasco[1,2] joint work with Javier Menéndez [3,4] and Tomás Alarcón[1,2]

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Mathematical modelling of oncometabolic reprogramming of somatic cells

In our work, we aim to model the minimal gene regulatory netwok which allows differentiated cells to reprogram into pluripotent cells. This network consists of three pluripotency genes- the three Yamanaka factors: Oct4, Sox2 and Klf4- and two generic lineage-specific genes (LSGs). The main difference between our model and models previously built is the introduction of epigenetic regulation (ER) of the LSGs, which will enable to account for the effects of metabolism in the reprogramming process[1]. More precisely, ER will be expressed by the acetylation and methylation levels of the LSGs. Acetylation and methylation, as well as deacetylation and demethylation, are assumed to be mediated by some enzymes such as the hystone demethylases (HDMs)[2]. These enzymes are the responsi- ble for the coupling of the differentiation/reprogramming system and the metabolism. Both asymptotic and numerical methods have been used to study our model for metabolic reprogramming. In the numerical case, Gillespie's stochastic simulation algorithm[3] has been used, whilst for studying the deterministic system, a separation of time-scales together with a quasi- steady state approximation (QSSA) have been applied. We conclude that metabolic transformations normally associated to cancer interfere with the epigenetic regulation of lineage-specific genes, thus enhancing the efficiency of the reprogramming of somatic cells by induction of the Yamanaka factors.

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Helal Mohamed[1] joint work with Adimy Mostafa, Lakmeche Abdelkader, Pujo-Menjouet Laurent

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Mathematical model of chronic myeloid leukemi

A model describing the dynamic of chronic myeloid leukemia is studied. By analyzing the corresponding characteristic equations, the local stability of trivial and nontrivial equilibria are discussed. By establishing appropriate Lyapunov functions, we prove the global stability of the positive constant equilibrium solutions. The mathematical form of the system we shall investigate satisfies

$$\begin{aligned}
\dot{x_0} &= (\beta - a_x - \beta_0 x_0 - \lambda(x_1 + y_1 + z_1))x_0;\\
\dot{x_1} &= a_x x_0 - d_1 x_1;\\
\dot{y_0} &= (\gamma - a_y - \gamma_0 y_0 - \lambda(x_1 + \alpha[y_1 + z_1]))y_0 - r y_0;\\
\dot{y_1} &= a_y y_0 - d_2 y_1;\\
\dot{z_0} &= (\gamma - a_z - \gamma_0 z_0 - \lambda(x_1 + \alpha[y_1 + z_1]))z_0 + r y_0;\\
\dot{z_1} &= a_z z_0 - d_3 z_1;
\end{aligned}$$

The population of interest is divided into three compartments coming from dictated by the epidemiological stages; normal cells, sensitive leukemic cells and resistant leukemic cells. We assume that normal (resp. leukemic) cells differentiate through two stages of their life cycle, beginning with leukemic stem cells which produce. Table 1 list the definitions and symbols of populations used in our model.

symbol	definition
x_0	normal stem cells
x_1	normal progenitor cells
y_0	leukemic sensitive stem cells
y_1	leukemic sensitive progenitor cells
z_0	leukemic resistant stem cells
z_1	leukemic resistant progenitor cells

Symbols and definitions of populations.

Stéphane Honoré[1] joint work with A. Barlukova[2], C. Gomez[2], F. Hubert[2], M. Petit[1], S. Oddoux[1], D. White[2]

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Microtubule dynamic instability: implication in oncopharmacology and modeling

MTs are governed by an intrinsic property called microtubule dynamic instability. The GTP cap model proposes that the GDP-tubulin core of MT is stabilized at the plus end by a layer of GTP-tubulin subunits that may act to maintain association between protofilaments. When this cap is stochastically lost, the protofilaments peel outward and the MT rapidly depolymerizes. Although both MT ends can either grow or shorten, the changes in length at the plus end are much greater than at the minus end. In cells, MT dynamics are regulated both spatially and temporally in cells by an impressive number of binding proteins. EB1, a Microtubule plus-end tracking protein (+TIPs) play an essential role in regulating microtubule dynamics and in conferring molecular recognition of the microtubule end which is crucial for many microtubule functions. Microtubule dynamics is an essential and indispensable property of microtubules. Requirement of dynamic MT is evident most notably during assembly of bipolar spindle and segregation of duplicated chromosomes in mitosis. During interphase, MT dynamics is also essential for maintaining cell shape and for controlling cell polarity and migration.

MT dynamics is the target for a large and chemically diverse group of molecules called MTDs. The effectiveness of MTDs has been validated by the successful use of several Vinca alkaloids and taxanes for the treatment of a wide variety of human cancers. MTDs exert their inhibitory effects on cancer cell proliferation primarily by blocking mitosis, which requires a finely regulated control of MT dynamics. MTDs are therefore referred as anti-mitotic drugs. At cytotoxic concentrations, MTDs potently suppress MT dynamics. This occurs through several ways, depending on cell types, on the tubulin binding site (i.e. colchicine, Vinca alkaloid or paclitaxel binding site) but also on molecules. However, we noticed that low and non-cytotoxic concentrations that impair cell migration have opposite effects on MT dynamic instability. Indeed, they increased it. Such paradoxal effects were associated with an inhibition of EB1 decoration time at microtubule plus end suggesting an effect on the GTP cap hydrolysis rate. Moreover, in vitro experiments demonstrate that EB proteins sensitize and modify the effect of MTDs on MT dynamics, being responsible for increased MT catastrophes. Observation of the effect of Drugs on EB1 decoration of the MT end allowed us to propose (1) a new model for tubulin- GTP hydrolysis at the microtubule end which is vectorial, delayed, and age dependant and (2) new concept of how the MTDs affect microtubule dynamics. Such concepts are the basis for mathematical modelling by our interdisciplinary group.

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Feedback regulation in a cancer stem cell model can cause an Allee effect

The exact mechanisms of spontaneous tumor remission or complete response to treatment are phenomena in cancer biology and oncology that are not completely understood. We use a concept from ecology, the Allee effect, to help explain tumor extinction in a model of tumor growth that incorporates feedback regulation of stem cell dynamics, which occurs in many tumor types where certain signaling molecules, such as Wnts, are upregulated. Due to feedback and the Allee effect, a tumor may become extinct spontaneously or after therapy even when the entire tumor has not been eradicated by the end of therapy. We quantify the Allee effect using an Allee Index that approximates the area of the basin of attraction for tumor extinction. We show that effectiveness of combination therapy in cancer treatment may occur due to the increased probability that the system will be in the Allee region after combination treatment vs. monotherapy. We identify therapies that can attenuate stem cell self-renewal, alter the Allee region and increase its size. We also show that decreased response of tumor cells to growth inhibitors can reduce the size of the Allee region and increase stem cell densities, which may help to explain why this phenomenon is a hallmark of cancer.

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Mathematical Modeling of Tumor Microenvironment and Metronomic Chemotherapy: Optimal Control Approach

In this talk, a minimally parameterized model that includes the main aspects of the tumor microenvironment (the cancerous cells, the tumor vasculature and tumor immune system interactions) will be described and analyzed under metronomic chemotherapy. The mathematical equations combine a model for anti-angiogenic signaling by Hahnfeldt et al with a classical model for tumor-immune system interactions by Stepanova and incorporate a single-input control that represents cytotoxic, anti-angiogenic and pro-immune action of low dose chemotherapy. The analysis of the model as a dynamical system with constant controls shows that it inherits all the geometric characteristics of the model for tumor-immune system interactions including multi-stability with what can be considered benign and malignant region of attractions. The connection between saddle-node bifurcations and immune-surveillance will be discussed. More generally, the model is then considered as an optimal control problem with controls that are allowed to vary in time. The properties of the underlying dynamical system give good insights into the construction of an objective functional that rather than purely minimizing the cancerous cells focusses more on an attainable maintenance strategy to control the tumor. Partial results about the form of the optimal protocols which relate to the metronomic chemotherapy as a biologically optimal dose BOD will be presented.

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Implication of the autologous immune response in the treatment response for chronic myeloid leukemia

We introduce a new model that takes into account a possible role of the immune response in the response to Tyrosine Kinase Inhibitors (TKI). The immune response would be submitted to an immunosuppression mechanism that lead to oscillations. Oscillations in the data could therefore be the trace of this response. This has potential consequences for the understanding of treatment cessation. We test our model on patients data.

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Moment models for radiotherapy dose simulation

Radiotherapy dose computation requires the study of particles trans- port (for photontherapy photons and electrons) through human body. Solving numerically the kinetic equations modeling this transport is com- putationally requires higher computational power than normally available in medical centers. As an alternative, we study the angular moment mod- els, which have lower computational costs. However the moments equa- tions require a closure. We propose an approximation of the entropic closure for the first two models in the hierachy (i.e. M_1 and M_2 models), as it provides several desirable properties (hyperbolicity, entropy, models correctly beams). Numerical test cases shows that M_2 model provides results in aggreement with the kinetic ones, while M_1 model is inaccurate in some cases.

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Emergence of drug resistance in cancer from the perspective of ecological competition

A major obstacle in the chemotherapeutical cure of cancer is the emergence of drug-resistant cell clones inside the tumour, an event which ultimately leads to tumour relapse and poor patient prognosis. The mechanisms behind acquiring drug resistance in cancers are still poorly understood. A recent experimental study (Obenauf et al, Nature, 2015) reports how targeted therapy of mixed tumours (consisting of both drug-sensitive and drug-resistant clones) leads to an accelerated expansion of the volume of resistant clones compared to the control group of no therapy. The authors hypothesise that this expansion results from a stress response of the drug-sensitive clones, which release signalling macromolecules into the tumour microenvironment that support and stimulate the expansion of the drug-resistant clones. I propose a mathematical model based on ecological competition to demonstrate that accelerated growth of the drug-resistant clones under targeted therapy can occur independently of any additional signalling. The model predicts that reduced environmental competition due to targeted therapy can significantly accelerate the volume expansion of drug-resistant clones originating from a mixed tumour. This happens also when the drug-resistant clones are at a proliferative disadvantage compared to the sensitive clones. The model is based on a reaction-diffusion system with a nonlinear diffusion term. Travelling wave solutions of the model are studied analytically and numerically.

Raphaël Serre joint work with D. Barbolosi[2], X. Elharrar[1,2], J. Ciccolini[2], C. Meille[5], C. Faivre[2], B. Lacarelle[2], N. André[2,4] and F. Barlesi[1,2,3]

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Metronomic chemotherapy in human lung cancer: mathematical modeling for an optimal schedule

Body: Introduction: Improving the efficacy/toxicity balance of anticancer therapy is still challenging, especially in metastatic Non Small Cell Lung Cancer (NSCLC) patients. Metronomic oral Vinorelbine is known to have an activity in NSCLC, but all the studies published thus far were based upon a variety of empirical and suboptimal schedules, with inconsistent results.
Objective: To determine an optimized Vinorelbine metronomic schedule, using advanced mathematical modeling.
Methods: We transposed into mathematical language pharmacokinetics (PK) and pharmacodynamics (PD) efficacy and toxicities issues of oral vinorelbine. All the parameters were calibrated using previous data from preclinical and clinical trials with metronomic vinorelbine. To identify the schedule which achieves higher efficacy on tumor with acceptable tolerance, multiple metronomic modalities have been tested by simulation, using our PK/PD model and Monolix software.
Results: This study describes the development of our mathematical model and its consistency when simulating previously published data. In addition, mathematical modeling showed by simulation that a new metronomic protocol could lead to a better safety and efficacy profile. Whereas most of the trials with oral metronomic vinorelbine used a D1, D3, D5 schedule with a fixed dose of 50 mg, our mathematical model suggested an alternative D1, D2 and D4 innovative schedule with a dynamic intake of 60, 30 and 60 mg, respectively.
Conclusions: Mathematical modeling provides an opportunity to improve efficacy of metronomic regimen. A phase I trial will begin this year to prospectively confirm and to validate clinically this new metronomic protocol in NSCLC patients. Close Window

Srimaneekarn Natchalee joint work with Wei Liu

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Statistical classification for diagnosis of cirrhosis patients

To classify a patient in term of whether he or she has a disease, based on some diagnostic measurements, is an important problem of statistical classification. Four classification methods for classification into two classes have been studied. They are logistic regression, classification tree, Bayes decision theory and the new confidence set method. The new method constructs a confidence set for the true class for a new patient by inverting the acceptance sets. The advantage of this method is that the probability of correct classification is not less than 1-alpha. The methods are illustrated specifically with the well known Iris data and applied to a data set for classifying patients as normal or having cirrhosis based on some measurements on blood samples. The total misclassification error and sensitivity (true positive rate) are used for comparing the methods.

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Mathematical Model for Virotherapy and Immunotherapy Combinations towards Cancer

Oncolytic viruses are a form of cancer treatment used to target tumor cells without harming healthy cells. These viruses have been engineered to specifically infect and kill cancer cells. Immunotherapy boosts the body's natural defenses towards cancer. This combination is shown through a deterministic system of nonlinear differential equations, for gaining insight into the viral and immunological cancer interactions. Key simulation results will be discussed.

Diana White joint work with S. Honoré, F. Hubert

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Modelling the Dynamics of Microtubules in the Presence of End Binding Proteins and Microtubule Targeting Agents

Understanding how microtubule (MT) targeting agents (MTAs) alter MT dynamics has been studied both experimentally and theoretically. It has been well established that MTAs exert their cytotoxic affect on MTs by suppressing MT dynamic instability. However, at low non-cytotoxic levels, more interesting dynamics have been observed, such as an increase in MT dynamic instability. Also, it has recently been discovered that the EB family of tip tracking proteins sensitize the affect of MTAs on MT dynamics *in vitro* [1] and *in vivo* [1,2].

Here, we develop a novel modelling approach, based on the work of Hinow *et al.* [3], to accurately describe MT dynamics. In particular, we develop an integro-partial differential equation model that accurately describes MT dynamic instability. Further, we show numerical simulations of our model that illustrate the action of EBs and MTAs on MT dynamics. To our knowledge, no such model has been developed. Our goal is to not only describe the action of MTAs (at high and low doses) on MTs, but to also understand how the EB proteins work to sensitize the MTA affect on MT dynamic instability.

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2.3 Poster session

Arturo Álvarez-Arenas[3] joint work with María Rosa Durán[1], Ana Podoloski-Renic[2], Jelena Dinic[2], Juan Belmonte-Beitia[3], Milica Pesic[2], Gabriel F.Calvo[3], Víctor M. Pérez-García[3]

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Transfer of resistance between cancer cell subpopulations: From biological data to mathematical models and back

Resistance to chemotherapy is a major cause for the cancer treatment failure [1-2]. The processes of resistance induction and selection of resistant cells cells (due to the overexpression of membrane transporter P-glycoprotein) are well documented in the literature and a number of mathematical models have been developed [3-5]. However, the processes of resistant characteristics transfer with a phenotype change in sensitive cell subpopulations are less known and have received little attention in the mathematical literature.
In this talk I will discuss the potential of mathematical models to describe the process of resistance transfer of in mixtures of resistant and sensitive tumor cell populations based on two different biological hypotheses: (i) P-glycoprotein transfer through direct contact and (ii) through microvesicles released to the culture medium. I will discuss discrete models using ordinary differential equations and continuous models using PDEs as well as test the models validity with experimental data.

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Etienne Baratchart[1] joint work with Sébastien Benzekry[1], Andreas Bikfalvi[2], Thierry Colin[1], Lin Cooley[2], Emeline Ribot[3], Olivier Saut[1], Wilfried Souleyreau[2]

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Data-driven modelling of metastatic initiation and tumour-tumour spatial interactions

The biology of the metastatic colonization process remains a poorly understood phenomenon. To improve our knowledge of its dynamics, we conducted a modelling study based on multi-modal data from an orthotopic murine experimental system of metastatic renal cell carcinoma. The stan- dard theory of metastatic colonization usually assumes that secondary tumours, once established at a distant site, grow independently from each other and from the primary tumour. Using a math- ematical model that translates this assumption into equations, we challenged this theory against our data that included: 1) dynamics of primary tumour cells in the kidney and metastatic cells in the lungs, retrieved by green uorescent protein tracking, and 2) magnetic resonance images (MRI) informing on the number and size of macroscopic lesions. Critically, when calibrated on the growth of the primary tumour and total metastatic burden, the predicted size distributions were not in agreement with the MRI observations. Moreover, tumour expansion only based on proliferation was not able to explain the volume increase of the metastatic lesions. These findings strongly suggested rejection of the standard theory, demonstrating that the time development of the size distribution of metastases could not be explained by independent growth of metastatic foci. This led us to investigate the effect of spatial interactions between merging metastatic tumours on the dynamics of the global metastatic burden. We derived a mathematical model of spatial tumour growth, confronted it with experimental data of single metastatic tumour growth, and used it to provide insights on the dynamics of multiple tumours growing in close vicinity. Together, our results have implications for theories of the metastatic process and suggest that global dynamics of metastasis development is dependent on spatial interactions between metastatic lesions.

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Modeling of dynamic instability of MTs with aging and impact of drugs

Microtubules (MTs) are long tube polymers of tubulin, found throughout the cytoplasm. They are characterized by dynamic instabilities involved in a number of cellular processes, including cell division and migration. Microtubule-targeted drugs induce perturbation in their instabilities making them attractive for anti-cancer therapies. Recent studies as [1] show that MTs age might play a crucial role in the effects of microtubule targeted drugs on MT instabilities. The aim of this work is to improve modeling of MT instability by introducing phenomenon of aging of MTs. We propose a new deterministic mathematical model inspired by the work of P. Hinow et al. [2] to simulate the behavior of a MT population with presence of stabilizing and destabilizing drugs. The model couples transport equations with ordinary differential equations (ODE) with nonlocal terms endowed with suitable boundary conditions for both catastrophe and rescue. The mathematical model takes into account results of biological observations provided by the pharmacologist of our interdisciplinary research group [3]. New model allows us to demonstrate the pharmacological action of some anti-microtubule drugs on MT population through their influence on MT aging and, thus, on MT instabilities. Numerical results are in a good agreement with biological observations. *The program is funded thanks to the support of the A*MIDEX project (ANR-11-IDEX-0001-02) funded by the Investissements dAvenir French Government program, managed by the French National Research Agency (ANR) and the support of Plan Cancer 2014, INSERM.*

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Modeling spontaneous metastasis following surgery: an in vivo-in silico approach

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

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A mathematical model for colorectal tumors using fonctional imaging

Colorectal cancer is one of the most common cancer in France. Hence, there is an important mediacl need for modeling the growth of this tumors. We use a spacial model including angiogenesis and a response to radiotherapy. The originality of this model is to include fonctional imaging. Our first model is based on partial diffrential equation to predict the evolution of colorectal tumors ans the evolution of the associate PET-scan. An asymptotic analysis of this first model gave us a simplified model witch is easier to calibrate. Brest team : "Imagerie multi-modalit quantitative pour le diagnostic et la thrapie" give us a sequence of medical images of PET-scan which are segmented by them. So we include this observable data and the other medical imaging to estimate patient specific parameters, witch permetted to have a better optimization between the predicted and observed images of the tumors.

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Mathematical study of long-term treatment effects on Chronic Myeloid Leukemia.

We present and analyze a simplified version of a partial differential equation (PDE) model for chronic myeloid leukemia (CML).
This model describes the proliferation and differentiation of leukemic stem cells. We mathematically show a nonmonotonic dependence of the speed of convergence to healthy steady state with respect to treatment dose, Therefore, while optimal asymptotic dosage might not be the best one at short time scales, our results raise interesting perspectives in terms of strategies for achieving and maintaining long-term remission.

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A space-jump derivation for non-local models of cell-cell adhesion

Cellular adhesions are one of the fundamental biological interactions between cells and their surroundings. However, the continuum modelling of cellular adhesions has remained mathematically challenging. In 2006 Armstrong et. al. proposed a mathematical model in the form of an integro-partial differential equation. This model was successful at replicating Steinberg's cell sorting experiments and since has been used in models of cancer invasion and morphogenesis. In this poster we derive models of cell-cell adhesion from an underlying stochastic random walk. Through this derivation we are able to include micro biological properties in the model. It is shown that a particular choice of these properties yields the original Armstrong model.

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Optimal treatment for an heterogeneous in vitro tumor composed of resistant and sensitive cells

We propose to present a mathematical model of heterogeneous tumor growth based on experiments by M. Carr. This model is a competition ODE model and takes into account tumor cells sensitive or resistant to chemotherapy. The originality of the model relies in the control of the resistant cells by the sensitive cells when the chemotherapy only acts on the sensitive cells. First we prove that this simple model is able to simulate various situations that M. Carr has experimented in vitro. Specially metronomic (i.e. low-dose) chemotherapies are more efficient than the classical Maximum Tolerated Dose treatment. This confirms the hypothesis of M. Carr that metronomic therapy take better account of the complex relations of sensitive and resistant cells. Second, we study optimal treatments to control the global size of the tumor. Such optimal control problems can lead to singular controls of the tumor size. These mathematical results have to be confirmed by in vitro experiments, but this work will help in understanding the mode of action of metronomic chemotherapy and thus in calibrating them.

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Optimization of cancer treatment, application to bladder cancer

This research is within the scope of personalized medicine, one of the challenges of tomorrow's medicine. This is taken into account before prescribing treatment, the patient's biological profile and the molecular features of the disease (cancer in our case). The goal of the subject is to better understand the role of interactions patient / tumor / treatment to develop a decision support tool for doctors so that they can simulate and monitor the effect of treatment before administration . Thus this project will allow the oncologist to have a systemic approach by enabling the prescription of a controlled, optimized and personalized treatment, which takes account of all the biological factors.

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Mathematical modeling of tumor kinetics in metastatic melanoma treated with B-RAF inhibitors

The development of targeted agents such as B-RAF inhibitors has revolutionised the treatment of metastatic melanoma, increasing patient survival considerably. Resistances to B-RAF inh may develop, which are difficult to monitor due to high inter-patient and inter-metastasis heterogeneity. Based on the hypothesis that resistance is expressing in the disease phenotype, our objective is to assess whether monitoring of metastatic kinetics before or after the treatment is indicative about resistance and survival. Here, we present a retrospective study of a series of 37 patients under BRAF-inhibitor that did not receive any other new active molecules. The volume of all metastases (573 in total) was measured on all available CT scans before, during, and after B-RAF inhibitor treatment. Longitudinal data on the metastases and patient survival data are analysed jointly within the framework of mixed-effects modelling using NONMEM software.

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Protracted metronomic therapies to target low-grade glioma malignant transformation

Grade II gliomas are slowly growing primary brain tumours that mostly affect young patients and become fatalonly several years after diagnosis. Current clinical management includes surgery as first line treatment. Cytotoxic therapies such as radiotherapy or chemotherapy are used initially only for patients with bad prognosis. Therapies such as radiotherapy are administrated following the maximum dose in minimum time principle(Maximum Tolerated Dose, or MTD paradigm). This is basically the same schedule as for high grade brain tumours in spite of their growth being much faster. A series of previous studies has developed a model describing the basic features of grade II glioma progression and response to radiotherapy [1]. The model includes the time dynamics of two cellular compartments (active tumor cells and lethally damaged tumor cells). The fraction of tumour cells damaged by a radiation dose is estimated by the linear-quadratic model. The model describes most of the well-known clinical facts of grade II glioma response to radiotherapy [2]. Then maintaining one day (Monday to Friday) distance between doses, that if the toxicity is to be preserved, the most effective dose fractionation is that of the standard scheme [3]. However, the model predicts that there is a much more effective (protracted) fractionation scheme in which the doses of 1.8 Gy are spaced by a distance that can be estimated to be a fraction of the tumour potential doubling time and radiosensitivity, typically of the order of 1-2 months, the potential survival gain being of the order of years [4].

In this work, we have studied the optimal strategy when both the dose per fraction and the time spacing between fractions are left free under three different restrictions: (a) same toxicity (biological effect on the healthy tissue) as the standard fractionation, (b) same total dose as the standard fractionation and (c) both restrictions. Typically, the best scheme is a combination of protraction with metronomic therapies, lowering the dose per fractions to levels below 1 Gy [5].

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Using computational modeling to quantify targeted agent binding and internalization in pancreatic cancers.

The pancreatic adenocarcinoma is one of the most deadly cancers with only 6% overall 5-year survival rate. Since the current therapies fail to provide successful results, the improvement of techniques for early detection, predicting of treatment efficacy and monitoring of tumor spread during and after surgical procedures remain under focused research. Recently, our group reported the toll-like receptor 2 (TLR2) to be a bona fide cell-surface marker for targeting pancreatic cancer. Development of an intravital fluorescence microscopy method allowed for the real time in vivo imaging of the TLR2L conjugated to near-infrared fluorescent dye, Cyanine 5 (TLR2L-Cy5) and its penetration through the tissue of pancreatic adenocarcinoma tumor xenografts in mice with endogenous expression of TLR2. In order to quantify the space- and time-dependent dynamics of TLR2L we combined intravital dorsal window chamber experiments with computational modeling of TLR2L-Cy5 diffusion and internalization following intravenous administration. Our studies led to quantification of the TLR2L-Cy5 intratumoral transport including agent extravasation, diffusion and intracellular accumulation in relation to tumor tissue structure and vascular architecture. The performed computational simulations allowed for detailed continuous in time assessment of the targeted imaging agent penetration on the cell-to-tissue level. The calibrated in silico model revealed the time-dependent dynamics of TLR2L-Cy5 agent binding, internalization and intracellular distribution. This integrated approach can be used in the future for the development of other targeted imaging and therapeutic agents, for other solid tumors, and for optimizing the administration schedules and time points for data collection from individual human tumor xenografts in order to improve treatment efficacy.

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A mathematical model for Multicellular Tumor Spheroids: the impact of nutrient on proliferative cells

In this study we work on in vitro data on MultiCellular tumor Spheroids. MultiCellular Tumor Spheroids can accurately reproduce the behavior of 3D solid tumors, they are used to understand dynamics of tumor growth and to evaluate new cancer drugs. The integration of EdU marker during cell division gives the distribution of proliferative cells inside the spheroid [1]. Our aim is to describe the impact of the external concentration of nutrients on the growth of a spheroid and the distribution of proliferative cells. We provide a partial differential equations model on cell densities. We consider two kinds of cells, proliferative cells and quiescent cells. The model consists in mass balance equations on cells densities and is similar to [2]. For the nutrient concentration we consider a diffusion equation. Radial symmetry leads to a simpler model and makes computations faster for the identification of the parameter of the model. We present the results of this parameter identification on several sets of data.

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Some phenotype-structured integro-differential models, asymptotic analysis and optimal control

We consider integro-differential models for which the structuring variable is a continuous phenotype. Such models are known to lead to concentration of populations on one or several phenotypes. The first model is designed to study the mutualistic interaction between cancer cells and adipocytes in breast cancer. Biological evidence indeed suggests that the interaction results in a greater proliferation of cancer cells and a change of phenotype in both populations: cancer cells become more motile as they undergo the epithelial-to-mesenchymal transition, and adipocytes change size and other characteristics to become what is now commonly called Cancer Associated Adipocytes (CAAs). The cancer population is thus structured by a phenotype representing motility, the adipocyte population by a phenotype representing how much the cell has become a CAA. We analyze the model and prove that some asymptotic properties known for a single equation can be extended to a system. The second model aims at investigating optimal therapeutical strategies combining cytotoxic and cytostatic drugs. The difficulty comes from the usual pitfalls of such treatments: resistance to the therapy of the cells must be avoided, and toxicity to healthy cells must be taken into account. Two populations of healthy and cancer cells, both structured by a phenotype representing resistance to the drugs, are thus considered. The optimal control problem consists of minimizing the number of tumorous cells after some fixed time T, with constraints on the number of healthy cells as well as their proportion with respect to the total number of cells. We fully describe the best administration strategy obtained when T is large, together with simulations to illustrate this mathematical result.

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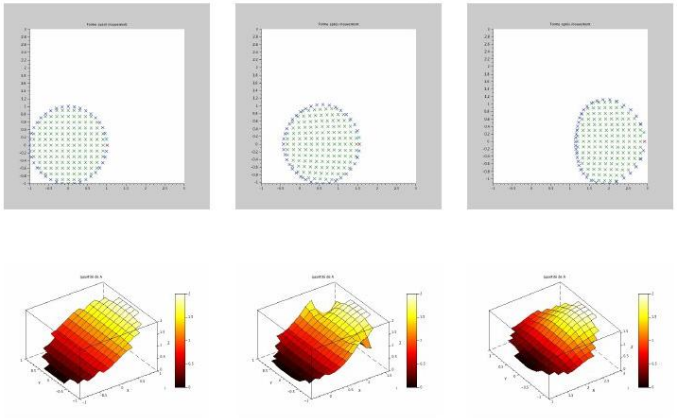
A model for cell migration involving microtubules

Angiogenesis and metastasis are two phases of cancer development that mainly involved cell migration. It has been shown that drugs, like anti-microtubule drugs, can disturb cell migration and are used as targeted anticancer therapies. As cell migration is a complex biological process, the aim of this work is to propose a mathematical model that describe the migration of a single cell in order to better understand the implication of microtubules in this process. We first follow a model proposed by [1] that describes the motion and the deformation of the cell's membrane using Stokes equations. This model take into account the effect of a protrusive force, which represents the action of some biochemical signal generated by the cell. This biochemical signal is then determined using reaction-diffusion equations.



The novelty of our model is to introduce also a contractile force based on another biochemical signal. We choose the concentration of Rac and Rho protein as biochemical agent respectively for protrusive force and contractile force. Then we add the action of microtubules, which is to modulate the action of Rac and Rho protein inside the cell and thus protusive and contractile force.

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A particle systems approach to cell-cell interaction

We investigate micro-to-macroscopic derivations of existing models for cancer-cell movement and interaction, including cell-cell adhesion, e.g. [1, 2]. We focus on stochastic models of repulsion and attraction of particles, with mean-field, moderate [4, 3] or strong interactions [6, 5]. Numerical results will be included.

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