Proposal of BIRS workshop: Mathematical challenges in the analysis of continuum models for cancer growth, evolution and therapy

Tomás Alarcón Jean Clairambault Thomas Hillen

September 29, 2016

Abstract

In the past five years or so, cancer modelling has been approached by innovative mathematical methods of continuous dynamical systems, structured in spatial and in phenotypical variables, representing heterogeneous populations of cells. Stimulated by unexpected failures of medical treatments (in particular due to drug-induced drug resistance) that most often consider targets at the single cell level, these recent methods take tumour dynamics at the cell population level into account, which is the most relevant level to tackle questions about tumour growth. Such models of tumour dynamics address problems arising from intra-tumour spatial and phenotypical heterogeneity, from tumour-stroma symbiosis and from evolutionary mechanisms used by the tumour cell population to escape therapeutic control.

These models take the form of systems of non-linear and non-local partial differential equations (PDEs) and the asymptotic analysis of such models raises numerous mathematical questions. Some of these questions have been solved nd theorems have been obtained in simplified settings, leaving however many other questions open, that will be debated in the workshop.

Furthermore, methods of optimisation and optimal control applied to continuous models of cel popultions with targets representing pharmacological or radiological effects on healthy and tumour proliferation are also under development.

The objectives of this workshop are thus to confront new methods of mathematical modelling and optimal control with the most recent conceptions about evolution and cancer, to design new theoretical therapeutic strategies, aiming at reducing cancer to a mild, chronic disease.

We will structure the proposed 5-day workshop according to dedicated work groups and interventions of both outstanding international speakers and younger promising researchers following five main themes.

Overview of the workshop

(i) Non-local models for cancer evolution. Local and non-local PDE models for heterogeneous species distributions, evolution and tissue metabolism, number and phenotypes, local biochemical/biophysical constraints, genotypes, mutations, phenotype drift due to environmental pressure and selection.

(ii) Phenotypical and spatial heterogeneity. PDE models in heterogeneous domains. Intratumour spatial and phenotypic heterogeneity in the tumour ecosystem: multiscale methods, homogenisation methods, tissue structure, collagen fibres, blood vessels, also interactions with healthy cells, stromal cells, immune cells, etc.

(iii) Therapeutics of cancer. Optimal control methods on continuous models of tissue dynamics. Theoretical optimisation of treatment of physiologically related targets to take into account unwanted toxic side effects in healthy cells and resistance in cancer cells, tuning drug scheduling, radiation treatment, combination of therapies by existing treatments (pharmacological, radiological, immunological) or new ones.

(iv) Cancer as atavism. This novel viewpoint on cancer starts from the observation that human cancer cells bear all the mechanisms in their genome that have been used by their ancestors, from the first unicellular organisms, to adapt to the extremely hostile environmental conditions that prevailed in the first eons of planet Earth. These genes have been silenced in the process of evolution towards complex and coherent multicellularity in softer developmental conditions. In this "atavistic" theory, cancer arises as a reverse evolution of localised cell populationss to function selfishly as in hostile environments. It calls for the design of innovative mathematical methods to integrate (paleo)genomics data to challenge the so-called 'atavistic theory of cancer'. The models need to account for the mechanisms of the major transition steps that control coherence in multicellular organisms ('tinkered' constructs of the great evolution, according to F. Jacob, Science 1977) and that can be affected by gene mutations or mis-adaptations to external stress - without mutations - that entrain local dysregulations in tissue proliferation and eventually result in cancer.

(v) Philosophy of science. We will discuss the mathematical challenges of items (i)-(iv) with some of the best specialists of the concerned fields, in theory and in applications. In particular, to enlarge the workshop discussions with points of view from non-mathematicians, especially about evolutionary perspectives, we will also invite representatives from physics, genetics, paleobiology, epistemology and philosophy of science. We aim to find external enlightenment in exploring better practice in mathematical modelling for questions related to cancer.

Focus Areas

(i) Non-local models for cancer evolution

This theme has emerged as a major new field in cancer biology, with high hopes of discovering new ways of treating cancer patients that hitherto escape therapeutic success. However, in first modelling steps, only probabilistic methods, compartmental ODE models and individual-based models had been proposed to address these issues. Recently, adapting methods from mathematical ecology, structured PDE models, accounting for relevant variability in heterogeneous cell populations by continuous phenotype variables, have given rise to mathematical models of continuous cell population dynamics of a new type. In particular, non-genetic variability in cell populations, that is increasingly recognised as a determinant factor of heterogeneity and resistance to treatments of cancer, is naturally taken into account in such models. They take the form of non-local and non-linear birth-jump processes, as introduced recently in Hillen et al. 2015. These models generalise reaction-diffusion models as they allow for non-local description of spatial spread. They are particularly well suited to describe population dynamics over a phenotypical landscape as determined by mutation, selection and evolution. First results on the positivity, uniqueness, existence and asymptotic behaviour of solutions have been published recently by Lorz et al. 2013, 2015, Lorenzi et al. 2015, 2016, Chisholm et al. 2015. However, a rigorous solution theory for birth-jump models is still missing. The involved integral operators are often compact Hilbert-Schmidt operators and consequently, the generated semigroups do not regularise. Since it is known that asymptotic limits have the form of delta-singularities in phenotype space (Barles and Perthame 2008, Mirrahimi et al. 2011, 2014, 2015), a solution theory needs to include measure-valued solutions. First attempts for such a theory have been developed by Carrillo 2011 and Hillen 2010 and it is one focus of this meeting to exchange ideas about a measure-valued theory for non-local PDEs. A close analysis of the genetic composition and gene expression in cancers gives us some insight about the genetic and nongenetic (epigenetic) variability. In some cases, genetic changes are rather small, possibly only because of underexpression of the genes without mutation, and homogenisation and scaling methods can be considered. Homogenisation methods are well developed for reaction-diffusion equations as well as for physical applications. However, these methods are only beginning to be used in biological modelling and it is another emphasis of this workshop to exchange ideas about homogenisation and scaling limits in the context of cancer evolution.

(ii) Phenotypical and spatial heterogeneity

In many cancers we observe that the genetic and non-genetic phenotypic composition of the tissue is dependent on the spatial structure of the tumour. Cancer stem cells, for example, are found in very specific metabolic

environments, dependent on oxygen and nutrient availability. Highly invasive mesenchymal cancer cells are often responsible for local malignant extensions, presenting a different phenotype from the one of the tumour mass. A detailed combination of phenotype and spatial structure is a real modelling challenge and the mathematical description of this process is just beginning. It is a goal of this workshop to discuss ideas about the combination of phenotype and space and to identify promising theoretical approaches. The idea of a birth-jump process (Hillen 2015) would have to be extended to include both, phenotype and space (as in Lorz et al. BMB 2015). Clearly, these new methods will lead to new mathematical challenges. Representing heterogeneity in tumours and in particular inside the cancer cell populations that constitute their bulk, but also as related to cross-talks between the cancer cell population and its supporting stroma, is a challenge that has recently been tackled numerically by various teams dealing with cancer modelling (see e.g., Robertson-Tessi et al. Cancer Research 2015). Epigenetic regulation, a form of regulation of gene expression, is a major contributor to non-genetic heterogeneity and features prominently between those mechanisms contributing to the development of resistance to therapeutics. Epigenetic modifications are heritable and as such they provide a mechanism upon which Darwinian evolution can operate, even against a homogeneous genetic background (Dawson and Kouzarides Cell 2012). Furthermore, epigenetic regulatory mechanisms that are crucial in normal development and homeostasis have recently been found to be subverted in cancer cell populations to reprogram normal cells to exhibit cancer stem cell-like properties (Munoz et al. Molecular Oncology 2012). In view of its role in cancer, the enzymes underlying epigenetic regulation have become an object of interest as therapeutic targets. Numerous mathematical challenges arise from such models: How can we use methods of asymptotic analysis applied to phenotype-structured models of adaptive dynamics to make predictions? How important are transient behaviours? How can we integrate molecular mechanisms in continuous mathematical models at the cell population level? How can we use theoretical homogenisation methods to integrate models at the tissue level? As regards intercellular communications, what models of the reaction-advection-diffusion type (or other) should be used and how should different time scales be taken into account? On a more practical note, what type of imaging techniques and experimental settings should be used to identify and validate theoretical models? We will invite participants to discuss these and related issues during the workshop.

(iii) Therapeutics of cancer

There have been great therapeutic achievements in oncology in recent years; however, many cancers still escape the efforts of clinical teams to eradicate them. Can we take new physiological knowledge about heterogeneity and evolution in tumours mentioned above, to develop appropriate continuous models? Can we design optimal control methods, representing theoretically optimised (combined) treatments, with the aim to apply them in the clinic? Can we propose winning strategies to contain tumours, in particular by reducing them to dormancy, reducing cancer to a clinically acceptable chronic disease? In this respect, one of the biggest challenges for modellers is to design a consistent representation of the immune response in the context of anticancer drug therapy, and also in the context of pure immunotherapy such as by oncolytic viruses or by chimeric antigen receptor (CAR) T-cells. The resulting models will take the form of complex networks of partial or ordinary differential equations. New methods are currently being developed to analyse the network structure of these models and to understand their functions (R. Albert). Furthermore, optimisation of the aforementioned treatments produces a huge new challenge. Standard optimisation methods are often no longer able to produce efficient solutions and new optimisation methods need to be developed. Methods of optimal control relying on combined theoretical treatment functions have successfully been applied to systems of ODEs representing tumour growth (Hahnfeldt), yielding exact solutions (Ledzewicz and Schättler), and they are currently being applied to phenotypically structured systems of PDEs to circumvent the emergence of drug resistance in tumours. We will focus our exchanges about cancer therapeutics on challenges in optimal control methods tackling the two main pitfalls of cancer therapeutics: failure through severe side effects in healthy tissues and the emergence of resistance to treatment in tumours (Lorz et al. 2013, 2015).

Another question that calls for optimal control methods arises in the context of radiation treatment versus potential side effects. The *tumour control probability* (TCP) describes the probability that a tumour is eradicated by a given treatment, while the *normal tissue complication probability* (NTCP) denotes the probability of side effects. Mathematically, these objects are related to the *extinction probability*, which describes the probability that a certain species goes extinct. Kendall 1998 developed a birth-death framework for the extinction

probability, which since has been developed as TCP (Zaider, Minerbo 2001) and NTCP (Stocks 2016). There are various mathematical models for the TCP, which are based on stochastic processes and their corresponding PDE descriptions, such as the Poisson process, birth-death processes (Zaider, Minerbo, Stavrev, Hillen), and branching processes (Hanin, Lutscher). First studies have shown that these TCP models are powerful tools in the prediction of treatment success (Gong, Stavrev), however, further studies of their qualitative properties and further data analysis is needed. During the proposed meeting we will invite experts in treatment modelling to exchange ideas, and to help to focus on the most pertinent mathematical and medical questions.

(iv) Cancer as atavism: an innovative perspective on cancer

Closely related to the field of evolution in cancer, this point of view considers cancer as a reverse evolution towards coarse, localised, forms of multicellularity that lack coherence at the level of the organism. This view is not new (L. Israel JTB 1996), but it has recently been popularised and documented from paleontology data by physicists (P. Davies and C. Lineweaver Phys Biol 2011), oncologists (M. Vincent Bioessays 2011, 2014, 2016), and challenged by biological experiments (A. Wu et al PNAS 2015, H. Chen et al. Nature Comm. 2015). Indeed, our tinkered organisms (F. Jacob Science 1977) hold strong as a rule, as long as we are healthy; however, at times, tinkering finds its limits when destabilising micro-environmental conditions lead to breaching the dike of tissue coherence at the level of the organism. Focusing on the flaws and strengths of these constructs of coherence, that are related to the genes that constitute our 'multicellularity genetic toolkit' (Davies and Lineweaver Phys Biol 2011) and on the metabolic conditions that weaken or reinforce them, should help us to propose new model-based therapeutic means in oncology. In particular, we will address the question of distinguishing between 'hot' and 'cold' genes (A. Wu et al. PNAS 2015); the former allowing species to evolve by mutations whereas the latter are conserved by evolution to face acute life-threatening events at the species level. We propose to design models of adaptive dynamics for cell populations structured in phenotypes, including 'cold' genes that allow for survival in (suddenly) hostile conditions (as in the model by Chisholm et al. Cancer Research 2015), and 'hot' genes representing opportunities to adapt and proliferate. Furthermore, knowing that cancer means local breaches in the normal coherent multicellularity, is it possible to design mathematical models to assess this atavistic theory, to qualify coherence as a phenotype common to all cells in a given organism (a signature of the 'self': likely linked to immune surveillance)? Can models of adaptive dynamics and analysis of instability-driven continuous branching mechanisms be apprehended to cancer atavism? We invite all participants to engage in this new and exciting theory.

(v) Philosophy of science viewpoint

Philosophers of science have been active in the field of mathematical modelling of biology and systems biology for quite some time. Pioneers in mathematical theories of evolution, such as John Maynard Smith, have a strong impact to interdisciplinary studies that may be questioned from the point of view of philosophy of science; in this respect, the atavistic theory of cancer is a remarkable motivation to think outside the box. Recently also, studies in the philosophy of systems biology have emerged (I. Brigandt, S. Green); other crucial questions such as the biological status of stem cells are debated (L. Laplane), and have important consequences for their representation in mathematical models of evolution. We will invite speakers and representatives from this field to shine a different colour onto our understanding of mathematical modelling of cancer.

Structure of the meeting

Since the mathematical challenges, that are discussed in this meeting, come from cancer modelling, we envision an interdisciplinary approach to this conference. We will invite some clinical experts, and also physicists, geneticists, paleobiologists and philosophers of science, to give overview talks on cancer and evolutionary biology of cancer. As the core of our topic is about mathematical challenges, we will invite leading mathematicians to set the stage for a mathematical discussion. Given the high number of (mainly) mathematicians working in the field of cancer modelling (see a list below, *names of female participants in italics*) who have positively answered at short notice our request about willingness to participate, we can reasonably assume that this proposed event will have a strong impact in the community, all the more so as it deals with pioneering, not routine, views on cancer

modelling. We will allow plenty of time for detailed discussions on the mathematical topics presented as well as on their relevance to cancer. The participants will include leading researchers as well as young researchers, postdocs and graduate students and we strive for a strong representation of female colleagues. Given that 2018 is the year of mathematical biology in Europe, with events starting in April 2018, an optimal time for this North American meeting, be it hosted in Banff or in Oaxaca, will be one week between January and March 2018.

Agreed participants

Senior researchers:

Tomás Alarcón, ICREA, Barcelona
Luis Almeida, CNRS & UPMC, Paris
Alexander Anderson, Moffitt, Tampa
Helen Byrne, Wolfson Centre for Math Biology, Oxford
Mark Chaplain, U St Andrews
Jean Clairambault, INRIA & UPMC, Paris
Marcello Delitala, Politecnico di Torino
Marie Doumic, INRIA & UPMC, Paris
Philip Hahnfeldt, Cancer Systems Biology, Tufts U
Thomas Hillen, U Alberta, Edmonton
Lynn Hlatky, Cancer Systems Biology, Tufts U
Marek Kimmel, Rice U
Yang Kuang, Arizona State U
Urszula Łędżewicz, South Illinois U
Doron Levy, U Maryland at College Park
John Lowengrub, U California Irvine
Anna Marciniak-Czochra, U Heidelberg
John Nagy, Arizona State U
Benoît Perthame, UPMC, Paris
Vered Rom-Kedar, Weizmann Institute, Rehovot
Siv Sivaloganathan, Fields Institute,Toronto
Jack Tuszynski, U Alberta, Edmonton

Confirmed young researchers:

Mathilde Badoual, U Paris Diderot
Sébastien Benzekry, INRIA, Bordeaux
Ingo Brigandt, U Alberta, Edmonton
Juan Calvo, U Granada
Guillemette Chapuisat, U Aix-Marseille
Rebecca Chisholm, U Sydney
Silvia Cuadrado, U Barcelona
Amina Eladdadi, St Rose College, New York
Heiko Enderling, Moffitt, Tampa
Hermann Frieboes, U Louisville
Jana Gevertz, The College of New Jersey
Trevor Graham, Barts Cancer Institute, London
Sara Green, Copenhagen U
Haralampos Hatzikirou, Braunschweig U
Alexandra Jilkine, Notre Dame U
Peter Kim, U Sydney
Thomas Lepoutre, INRIA, Lyon
Tommaso Lorenzi, U St Andrews
Alexander Lorz, UPMC, Paris
Alicia Martínez-González, UCLM, Ciudad Real
Sepideh Mirrahimi, CNRS, Toulouse
Monika Piotrowska, U Warsaw
Katarzyna Rejniak, Moffitt, Tampa
Delphine Salort, UPMC, Paris
Olivier Saut, CNRS, Bordeaux
Nikolaos Sfakianakis, U Mainz
Angélique Stephanou, CNRS, Grenoble
Min Tang, Jiaotong U, Shanghai