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

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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 and theorems have been obtained in simplified settings, leaving however many other questions open. Furthermore, methods of optimisation and optimal control applied to continuous models of cel populations with targets representing pharmacological or radiological effects on healthy and tumour proliferation are also under development.

The objectives of this workshop were 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.

Focus areas of the workshop

(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 homogenisation and scaling limits in the context of cancer evolution were discussed the workshop.

(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. At the workshop we discussed 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? Participants actively discussed these ideas 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).

(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, it is 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).

(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. Representatives from this field were able to shine a different colour onto our understanding of explanations of cancer through mathematical modelling.

Abstracts of participants

Mustafa Adimy, INRIA Lyon

Discrete maturity and differential-difference model of hematopoietic cell dynamics with applications to Acute Myelogenous Leukemia

Abstract: We investigate a mathematical model of hematopoietic stem cell dynamics. This model takes into account a finite number of stages in blood production, characterised by cell maturity levels, which enhance the difference, in the hematopoiesis process, between dividing cells that differentiate (by going to the next stage) and dividing cells that keep the same maturity level (by staying in the same stage). For each maturity level, we take two cell populations into account, quiescent and proliferating one, and we note the difference between dividing cells that enter directly to the quiescent phase and dividing cells that return to the proliferating phase to divide again. The resulting mathematical model is a system of nonlinear differential-difference equations. We start by studying the existence and positivity of the solutions. We then investigate the boundedness and unboundedness of the solutions of the system. We also discus the existence of steady states. Sufficient conditions for the global asymptotic stability of the trivial steady state as well as conditions for its instability are obtained. Numerical simulation is carried out to show that a blocking of the differentiation at some stage may lead to an over-expression of immature cells. Such situation corresponds to the observation in the case of Acute Myelogenous Leukemia.

Luis Enrique Ayala, MôLab, Ciudad Real, España

A mathematical model suggests novel standardized treatment protocols for grade II oligodendrogliomas with improved survival

Abstract: The use of mathematical models for personalization of cancer therapies and raising hypothesis of potential clinical impact is an emerging topic in the interface between mathematics and oncology. Here we put forward a mathematical model describing the response of low-grade (WHO

grade II) oligodendrogliomas (LGO) to temozolomide (TMZ). The model described accurately the longitudinal volumetric dynamics of tumor response to TMZ. Our initial test bench was a cohort of 11 LGO patients treated with TMZ with long-term radiological follow-up. After finding patient-specific parameters, different therapeutical strategies were tried computationally on the ?in-silico twins? of those patients. Chemotherapy schedules with larger-than-standard rest periods between consecutive cycles had either the same or better long-term efficacy than the standard 28-day cycles. These results were confirmed in a large virtual clinical trial including 2000 patients. Long-cycle schemes would also have reduced toxicity and defer the appearance of resistances. On the basis of those results, a combination scheme consisting of five induction TMZ cycles given monthly plus 12 maintenance cycles given every three months was found to provide substantial survival benefits for the in-silico twins of the 11 LGO patients (median 5.69 years, range: 0.67 to 68.45 years). Thus, the proposed alternative scheme could provide a basis for defining a standardized TMZ treatment for LGO patients with substantial survival benefits.

Mathilde Badoual, Laboratoire IMNC, CNRS, Univ Paris Saclay, Univ Paris-Sud
Modeling origin, natural evolution and response to radiotherapy of gliomas

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Abstract: Diffuse low-grade gliomas are slowly growing tumors. After tens of years, they transform inexorably into more aggressive forms, jeopardizing the patient?s life. Mathematical modeling could help clinicians to have a better understanding of the natural history of these tumors and their response to treatments. We present here different models of these tumors: the first one is discrete and describes the appearance of the first glioma cells and the genesis of a tumor. The second model is continuous and consists in a PDE that describes the evolution of the cell density. This model can describe the natural evolution of gliomas, their response to treatments such as radiotherapy and the changes in their dynamics in pregnant women. The discrete and the continuous models are designed to be close to the biological reality. The results are quantitatively compared with either biological data or clinical data, at the cellular level (histological samples) and at the tissue level (MRI scans).

Annabelle Ballesta, University of Warwick, UK
Towards personalisation of combination chemotherapy against brain tumors

Abstract: The quest for personalized anticancer treatment has fostered the development of new technologies enabling the measurement of multi-type data in individual patients. A critical current challenge lays in translating such individual datasets into personalized therapies. We here develop a multi-scale systems pharmacology approach to personalize multi-agent chemotherapies based on multi-type tumor data. The model disease is here glioblastoma (GBM), the most common and devastating primary brain tumor currently associated with a median overall survival below 18 months. The project focuses on temozolomide (TMZ), the cornerstone of GBM treatments, and its combination with targeted therapies. We have developed a framework of mechanistic ODE-based models representing TMZ pharmacokinetics-pharmacodynamics (PK-PD) in a heterogeneous cell population, and at the whole-body level in mice and in patients. The effect of pH on TMZ activation was studied as a potential therapeutic target as healthy and cancer cells regulate their intracellular pH differently.

The cellular PK-PD model was fitted to multi-type data obtained in GBM patient-derived cell lines and aims to design cell line-specific TMZ-based combination chemotherapies. Next, the cellular PK model was included into a hybrid tumour model to further investigate spatial effects and cell-to-cell variability (see Angélique Stéphanou's presentation). Such modeling framework would ultimately allow for the integration of both multi-omics and imaging tumor data to personalize GBM treatment.

Rachel Bearon, U Leeds

Music and mathematics interrogate brain tumour dissemination

Rachel Bearon, Marianne Scott, Violaine See, Emily Howard.

Abstract: Glioblastoma (GBM) is the most common malignant brain tumour and has an extremely poor prognosis. The invasion of tumour cells into normal brain tissue makes complete surgical removal impossible; GBM is also resistant to treatment with chemotherapy and radiotherapy. However it is not clear how cells move within the tumour, nor how they move in the surrounding brain tissue, nor how their behaviour is affected by drugs. Experimental studies of cell movement have traditionally been done on 2D plates; however this does not well represent the 3D tissue environment. Recently VS lab have established an experimental system which allows them to image live cells in 3D spheroid systems. For spheroid systems built on glioblastoma cell lines, they have been able to obtain a large data set of cell trajectories and investigate the effect of different chemotherapy treatments on cell motility. The trajectories can be analysed to calculate not only cell speed, but also the type of movement, e.g. how tortuous is the trajectory. Furthermore because of the 3D imaging facility, they can examine how these properties change with position in the spheroid, and also can examine how motility patterns are dependent on the local environment, for example, whether cells moving through regions of the spheroid that are densely populated behave differently to those moving through the external matrix gel. By tracking individual cells they also can examine the full range of population behaviours, and are able to identify, for example, fast outliers. Mathematical models of cell motility have been developed which link individual-level behaviour (e.g. speed, turning frequency) to population-level descriptors (drift, diffusion). This can be done using classical probability theory (e.g. deriving diffusion approximations from simple random walks can be a simple application of the central limit theorem), or using tools from classical continuum mechanics which have been developed to describe solid and fluid mechanics, e.g. partial differential equation conservation equations. There are active theoretical research questions being explored in this area, for example, when cell-cell interactions become important, or individual behaviour is density dependent. Furthermore, much mathematical theory is developed with very limited experimental data; the imaging data obtained in VS lab is a fantastic data set from which to build and then test models. EH has a long-term interest in Ada Lovelace's idea to create a Calculus of the Nervous System: a mathematical model for how the brain would give rise to thought, and nerves to feelings. After exploring this by initially composing an orchestral work "Calculus of the Nervous System" (Wien Modern Commission 2011, subsequently performed at BBC Proms 2012), treating the structure of the work as a 'neural network with its roots in strictly engineered time, pitch and rhythmic calculations using values derived from one source (an exponential equation and its derivative), subsequently muddled and reordered by chance processes', Howard then metaphorically put "Calculus of the Nervous System" under the microscope to create orchestral work "Axon" (a BBC Commission for BBC Philharmonic, 2013) where the compositional process is one of "passing musical material through an imagined axon". Most recently, Howard composed "Afference" (2014-15) for string quartet (short- listed for a British Composer Award 2016) where throughout she "uses the idea of the axon transferring an impulse to a synapse to inform the music?s trajectory, and the interplay of parts". The new proposed work will explore the brain in a different angle. It will

focus on how cancer cells in the brain have a resilient ability to migrate and infiltrate in different brain regions, making brain tumours very hard to cure.

Sébastien Benzekry, Inria team MONC, Institut de Mathématiques de Bordeaux
Mathematical Modeling and Prediction of Clinical Metastasis

Abstract: In the majority of cancers, secondary tumors (metastases) and associated complications are the main cause of death. To design the best therapy for a given patient, one of the major current challenge is to estimate, at diagnosis, the burden of invisible metastases and the future time of emergence of these, as well as their growth speed. In this talk, I will present the current state of our research efforts towards the establishment of a predictive computational tool for this aim. I will first shortly present the model used, which is based on a physiologically-structured partial differential equation for the time dynamics of the population of metastases, combined to a nonlinear mixed-effects model for statistical representation of the parameters distribution in the population. Then, I will show results about the descriptive power of the model on data from clinically relevant ortho-surgical animal models of metastasis (breast and kidney tumors). The main part of my talk will further be devoted to the translation of this modeling approach toward the clinical reality. Using clinical imaging data of brain metastasis from non-small cell lung cancer, several biological processes will be investigated to establish a minimal and biologically realistic model able to describe the data. Integration of this model into a biostatistical approach for individualized prediction of the model?s parameters from data only available at diagnosis will also be discussed. Together, these results represent a step forward towards the integration of mathematical modeling as a predictive tool for personalized medicine in oncology.

Ingo Brigandt, University of Alberta
Philosophy of science on modelling molecular systems: current debates and future agendas

Abstract: I will first present current philosophical discussions in the context of modelling and systems biology, but then also map out a future agenda for philosophers of science. Starting less than a decade ago, philosophical interest in systems biology was among other things a reaction to the hitherto dominant notion of mechanistic explanation. Mechanists maintained that only mechanistic (part-whole) explanations count as genuine explanations, sometimes deeming mathematical models to be non-explanatory. In response, other philosophers have pointed to systems biology to argue that mathematical models can be mechanistic ('dynamic mechanistic explanation') or that there are explanations in terms of mathematical features that are fully explanatory yet non-mechanistic (topological and structural explanation). My position is that philosophers' attempts to articulate an authoritative notion of '(non-)mechanistic explanation' is fruitless, and the agenda should instead be to investigate the diversity of explanations in systems biology. Indeed, going beyond the traditional topic of explanation, the future agenda for philosophy of science ought to be to examine modelling and other research strategies, including strategies for analyzing and representing large datasets and strategies for developing and analyzing mathematical models of complex systems. Some work by philosophers of biology have addressed strategies and investigative practice, but limited attention has been devoted to the modelling of cancer. In this latter context, what I view as in need of future philosophical attention are scientific strategies to deal with variability across systems (as a challenge to model validation), to deal with heterogeneity and robustness within systems (as a feature to be modeled), to deal with phenomena across different levels and scales, as well as strategies for coordinating across experimental, modelling, and clinical work.

Andreas Buttenschoen, UBC Vancouver, Canada

Non-Local Cell Adhesion Models: Derivation, Bifurcations, and Boundary Conditions

Abstract: In both normal tissue and disease states, cells interact with one another, and other tissue components using cellular adhesion proteins. These interactions are fundamental in determining tissue fates, and the outcomes of normal development, wound healing and cancer metastasis. Traditionally continuum models (PDEs) of tissues are based on purely local interactions. However, these models ignore important nonlocal effects in tissues, such as long-ranged adhesion forces between cells. For this reason, a mathematical description of cell adhesion had remained a challenge until 2006, when Armstrong et. al. proposed the use of an integro-partial differential equation (iPDE) model.

The initial success of the model was the replication of the cell-sorting experiments of Steinberg (1963). Since then this approach has proven popular in applications to embryogenesis (Armstrong et. al. 2009), zebrafish development (Painter et. al. 2015), and cancer modelling (e.g. Painter et. al. 2010, Domschke et. al. 2014, Bitsouni et. al. 2018). While popular, the mathematical properties of this non-local term are not yet well understood.

I will begin this talk by outlining, the first systematic derivation of non-local (iPDE) models for adhesive cell motion. The derivation relies on a framework that allows the inclusion of cell motility and the cell polarization vector in s stochastic space-jump process. The derivation's significance is that, it allows the inclusion of cell-level properties such as cell-size, cell protrusion length or adhesion molecule densities into account.

In the second part, I will present the results of our study of the steady-states of a non-local adhesion model on an interval with periodic boundary conditions. The significance of the steady-states is that these are observed in experiments (e.g. cell-sorting). Combining global bifurcation results pioneered by Rabinowitz, equivariant bifurcation theory, and the mathematical properties of the non-local term, we obtain a global bifurcation result for the branches of non-trivial solutions. Using the equation's symmetries the solutions of a branch are classified by the derivative?s number of zeros. We further show that the non-local operator's properties determine whether a sub or super-critical pitchfork bifurcation occurs.

Finally, I want to demonstrate how the equation's derivation from a stochastic random walk can be extended to derive different non-local adhesion operators describing cell-boundary adhesion interactions. The significance is that in the past, boundary conditions for non-local equations were avoided, because their construction is subtle. I will describe the three challenges we encountered, and their solutions.

At the end of the talk, I will discuss possible extensions of our work, to models of cancer and evolution.

Juan Calvo, Departamento de Matemática Aplicada, Universidad de Granada

Structured population models and tumor growth: stochastic and hybrid simulation procedures

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Abstract: A new way to tackle cancer modeling has been introduced during recent years by means of models describing heteroge- neous cell populations. Populations are tipically structured in spatial and/or phenotypical variables. New mathematical mod- els of continuous cell population dynamics

have been considered in the form of structured partial differential equations of reaction- diffusion type. Discrete counterparts have been also considered as a way to describe stochastic fluctuations linked with the struc- tural variables; those fluctuations may be central to an accurate description of invasive phenomena such as tumor growth. We present a set of multiscale population models along the previous lines (R. de la Cruz, P. Guerrero, J. Calvo, T. Alarcón, Journal of Computational Physics 2017). Discrete frameworks provide the most detailed description, however they are computationally ex- pensive. We use coarse-graining procedures to derive mean-field and hybrid deterministic-stochastic representations, together with computational simulation methods. Hybrid computational models provide a suitable balance between an accurate description and a reasonable simulation time. These representations enable us to assess the role of stochastic fluctuations at the leading edge of invasion fronts.

José Ariel Camacho Gutiérrez
Bone metastasis treatment modeling via optimal control

Abstract: Several treatments are used to deal with bone metastases formation, but they are palliative since the disease is considered incurable. Computational and mathematical models are used to understand the underlying mechanisms of how bone metastasis evolves. In this way, new therapies aiming to reduce or eliminate the metastatic burden in the bone tissue may be proposed. We present an optimal control approach to analyze some common treatments for bone metastasis. In particular, we focus on denosumab treatment, an anti-resorptive therapy, and radiotherapy treatment which has a cell killing action.

Juan Carlos Chimal Eguía, Polytechnical University of Mexico
Enhancing dendritic cell immunotherapy for melanoma using a simple mathematical model

Abstract: The immunotherapy using dendritic cells (DCs) against different varieties of cancer is an approach that has been previously explored which induces a specific immune response. This work presents a mathematical model of DCs immunotherapy for melanoma in mice based on work by Experimental Immunotherapy Laboratory of the Medicine Faculty in the Universidad Autonoma de Mexico (UNAM). The model is a five delay differential equation(DDEs) which represents a simplified view of the immunotherapy mechanisms. The mathematical model takes into account the interactions between tumor cells, dendritic cells, naive cytotoxic T lymphocytes cells (inactivated cytotoxic cells), effector cells (cytotoxic T activated cytotoxic cells) and transforming growth factor β cytokine (TGF-β). The model is validated comparing the computer simulation results with biological trial results of the immunotherapy developed by the research group of UNAM.

Kit Curtius, Barts Cancer Institute, London, UK
Spatial evolution of Barrett's esophagus: insights from molecular clocks and mechanistic modelling.

Abstract: There is great interest in the molecular characterisation of intestinal metaplasia, such as Barrett?s esophagus (BE), to understand the basic biology of metaplastic development from a tissue of origin. BE is asymptomatic, so it is not generally known how long a patient has lived with this precursor of esophageal adenocarcinoma (EAC) when initially diagnosed in the clinic. Since curative interventions carry patient risks and the annual risk of cancer progression is $< 1\%$, BE is usually left in the body but knowledge of BE tissue age may be advantageous in predicting a patient?s future risk of developing cancer. A recently published BE clock model uses patient-specific methylation data to

estimate BE onset times using Bayesian inference techniques, and thus obtain the biological age of BE tissue (Curtius et al. 2016). We find such epigenetic drift to be widely evident in BE tissue (Luebeck et al. 2017) and the corresponding tissue ages show large inter-individual heterogeneity in two patient populations (52 patients).
From a basic biological standpoint, we also do not fully understand mechanistically how the Barrett?s tissue forms in the human esophagus, and such information is critical to inform such biomarkers of risk based on biological tissue age. We analysed multi-region samples from 17 BE patients (including multiple phenotypes) to 1) measure the spatial heterogeneity in biological tissue age and 2) use these ages to calibrate mathematical models of the mechanisms for formation of the segment itself.
Mathematical challenges arise when attempting to combine such rich molecular data into mechanistic models of evolutionary processes at the cell level, which for BE can currently only be inferred from tissue biopsies or resections sampled in vivo with spatial and practical constraints. For example, there may be more than one plausible biological assumption in a model that can explain the patterns observed from cross-sectional data. Using the epigenetic clock to estimate tissue ages, the main questions we explored with simulations using an agent-based computational model were 1) What are the important biophysical assumptions needed to be capture evolution from a tissue of origin? 2) What are the timescales involved in both the growth of BE to a certain size? 3) Which mechanistic parameters (e.g., cellular birth and death rates) are found to be patient-specific and which evolutionary "rules" seem to be universal in the population?
Most importantly, we found that tissue must be regenerated nearer to the stomach, perhaps driven by wound healing caused by exposure to reflux, implying a gastric tissue of origin for the lesions observed in BE. Combining bioinformatics and mechanistic modelling allowed us to infer evolutionary processes that cannot be clinically observed and we believe there is great promise for the community to develop such novel hybrid methods to better understand multiscale cancer data.
References: Curtius K, Wong C, Hazelton WD, Kaz AM, Chak A, et al. (2016) A Molecular Clock Infers Heterogeneous Tissue Age Among Patients with Barrett's Esophagus. PLoS Comput Biol 12(5): e1004919
Luebeck EG, Curtius K, Hazelton WD, Made S, Yu M, et al. (2017) Identification of a key role of epigenetic drift in Barrett's esophagus and esophageal adenocarcinoma. J Clin Epigenet 9:113

Meghan Hall, University of Alberta
A DTI-based continuum mechanics computational model of glioma

Abstract: Glioblastoma is an aggressive form of glioma often having diffuse boundaries, making the definition of treatment area challenging. We aim to more precisely determine the location of tumor cells by using modern diffusion tensor imaging (DTI) data to advance current mathematical models. The brain is composed of white matter and grey matter, where glioma cells travel faster along white matter fibers faster than within grey matter. DTI is a magnetic resonance imaging (MRI)-based neuroimaging technique that locates white matter fibers and determines the rate of diffusion along these fibers. Previous uses of DTI data have increased the accuracy of glioma models in predicting tumor volume. Anisotropic diffusion tensors are a way of specifying that rate of glioma diffusion at each point in the brain and it has been shown that anisotropic models more accurately capture tumor volume. Our goal is to provide a more accurate model of tumor growth using a continuum mechanics approach to model the tumor and the forces acting on the tumor by the brain and skull. The tumor will be modeled as a viscoelastic body with anisotropic diffusion (i.e. white vs. grey matter) using DTI data to define diffusion tensors. Using a continuum mechanics approach treats the glioma as a continuous mass, allowing for the incorporation of more physical and mechanical aspects than previous models.

Thomas Hillen, University of Alberta
The Metastatic Reproduction Number

Abstract: The mathematical modelling of metastasis is a challenge. The occurrence of metastasis is basically random, hence the use of stochastic modelling seems appropriate. We introduce a stochastic process called branched random walk with settlement to derive equations for the expected number of particles, the variance, the furthest particle and the extinction probability. We are able to identify a parameter R_0, such that metastasis spread for $R_0 > 1$ and they die out for $R_0 < 1$. Hence we call R_0 the metastatic reproduction number. We compare this index to experimental outcomes in animal studies and we discuss its relevance for the treatment of metastasis. (Joint work with A. Rhodes and C. Frei).

Thomas Lepoutre
Impact of the immune system on chronic myeloid leukemia

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

Doron Levy, University of Maryland
Modeling the chemotherapy-induced selection of drug-resistant traits during tumor growth

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

A. Martínez-González, Mathematical Oncology Laboratory, Universidad de Castilla-La Mancha, Spain
Mathematical predictions for brain tumor response to novel therapies validated by in vivo and in vitro experiments

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Abstract: Glioblastoma (GBM) is the most frequent and lethal malignant brain tumor in adults due to its invasive capability and resistance to conventional therapies. GBM typically shows an heterogenous microenviron- ment including necrotic and hypoxic areas, abnormal vasculature and different tumor cell phenotypes. We will focus on mathematical models based on PDE that try to reproduce this complex system in order to understand it and better predict the tumor behaviour [1, 2]. In addition, we will discuss in-silico simu- lations based on a mathematical model for brain tumor response to the combination of antithrombotic, antioxidants and radiation therapies [3]. Our mathematical results predict a synergistic decrease in tumor volume when both, cytotoxic therapies and antioxidants were applied. In vitro and in vivo results have confirmed this benefit not only in terms of tumor reduction but also in terms of toxicity reduction. Com- bined mathematical simulations and on-chip validation of malignant cellular structures formation in GBM have confirmed their usability to better understand the tumor behaviour [4, 5]. Considering the promising results, a clinical trial is being designed.

José Héctor Morales Bárcenas
Modeling the dynamics of microenvironment of solid tumors

Abstract: For decades, elucidate the dynamics of the microenvironment of solid tumors has been considered a major research challenge. The fact is that different therapies have not succeeded to eliminate entirely cancer cells in tumors. This resistance feature to anticancer drugs is often attributed to genetic or even epigenetic causes. Another important, but less appreciated cause of this resistance -a possible manifestation of the former, is the geometrical and physical heterogeneity within the tumor microenvironment that leads to marked gradients in the rate of cell proliferation and to regions of hypoxia and acidity, all of which can influence the sensitivity of the tumor cells to drug treatment. There have been different approaches to overcome this resistance, mainly altering solid tumors' microenvironment, for instance, promoting angiogenesis to help the entrance of drugs. Radiation some times is not an option due to the hypoxia in the tumor deep tissue. On the other hand, these physical and geometrical factors have been identified to be responsible of the unsuccessful drug disperse in tumors in some specific time and spatial scales. In this direction, we present an update of our model of drug transport in solid tumors, that quantifies these factors in terms of space-dependent coefficients of the Fokker-Planck equation. The model follows experiments conducted in the Laboratory of Medical Physics and Molecular Imaging of the National Institute for Cancer (INCan) and the Institute of Physics (IFUNAM).

Ramón Plaza, Universidad Autónoma de Mexico
Diffusive limits of stochastic velocity jump processes for biological agents
Abstract: In this talk, some mathematical aspects related to mean field reaction-diffusion-chemotaxis systems that model the complex spatio-temporal dynamics of certain biological agents will be discussed. Special attention will be paid to the derivation of such systems as diffusive limits of stochastic velocity-jump processes. This justification is based on a microscopic description of the movement of individual cells whose changes in velocity (in both speed and orientation) are governed by a transport equation of Boltzmann type. For that purpose, the asymptotic method introduced by Hillen and

Othmer (2000, 2002) is applied, consisting of the computation of the leading order terms in a regular Hilbert expansion for the solution to the transport equation, under an appropriate parabolic scaling and a first order perturbation of the turning rate of Schnitzer type (1993). As an example, I will discuss a system with nonlinear degenerate cross diffusion and chemotactic terms which was proposed to model the aggregation patterns of the bacterium Bacillus subtilis. Although the former is used as a prototype, the method and results apply in more generality.

Guillermo Ramírez-Santiago, Instituto de Física y Matemáticas, Universidad Michoacana de San Nicolás de Hidalgo

Model for Breast Cancer Diversity and Heterogeneity

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Abstract: We analyzed a model of an avascular tumour growth that considers the basic biological principles of cell proliferation, motility, dead and genes mutations. We identified two sets of genes and a set of sixteen and six genes that are believed to play an important role in tumour growth. Gene mutations were modelled as a markovian process and mutation rate was assumed to depend on nutrient concentration. Thus, mutations dynamics was coupled to a set of reaction-diffussion equations that describe the transport of nutrients. Tumour malignancy was characterized by its fractal dimension and we measured genetic heterogeneity with the Shannon index. The results suggest that tumour malignancy and heterogeneity arise from a relatively small number of events that are driven by stochasticity and nutrients concentration. J.R.R.A. would like to acknowledge financial support from CONACyT-FORDECyT under Grant No. 265667. G.R.S. would like to acknowledge financial support from DGAPA- UNAM Grant No. IN108916. J.X.V.H. would like to acknowledge financial support from DGAPA-UNAM Grant No. IN110917.

Adam Rhodes, University of Alberta

Tumor-Educated Immune Cells Promote Metastatic Growth

Abstract: Metastasis -the spread of cancer from a primary to a distant secondary location - is implicated in over 90% of all cancer related deaths. Despite its importance in patient outcome, a full understanding of the metastatic process remains elusive, largely because of the difficulty in studying the phenomenon experimentally. Recent experimental evidence - including the discovery of the so-called 'pre-metastatic niche' - has suggested that metastasis may be a more precisely controlled process than previously thought. In particular, it has been suggested that a developing tumor may be able to corrupt, or 'educate', infiltrating immune cells and have them switch from cytotoxic to tumor-promoting roles. Such 'tumor educated' immune cells can then travel to distant sites and establish favorable conditions for the settlement and growth of circulating tumor cells. In order to investigate the consequences of tumor-mediated immune education on metastatic spread and growth, we have developed an ordinary differential equation model for tumor-immune dynamics in the metastatic context. The model is studied analytically and numerically, with an examination of the effects of tumor education of immune cells on metastatic dormancy and metastatic blow-up.

Erica Rutter, North Carolina State University
Estimating Intratumoral Heterogeneity from Spatiotemporal Data

Abstract: Glioblastoma Multiforme (GBM) is a malignant heterogenous cancer in the brain. We propose modeling GBM with heterogeneity in cell phenotypes using a random differential equation version of the reaction-diffusion equation, where the parameters describing diffusion (D) and proliferation (?) are random variables. We investigate the ability to perform the inverse problem to recover the probability distributions of D and ? solely from spatiotemporal data, for a variety of probability distribution functions. We test the ability to perform the inverse problem for noisy synthetic data. We then examine the predicted effect of treatment, specifically, chemotherapy, when assuming such a heterogeneous population and compare with predictions from a homogeneous cell population model.

Nikolaos Sfakianakis, Institute of Applied Mathematics, Heidelberg University Heidelberg
The FBLM-FEM: from cell-cell adhesion to the cluster ofells and cell monolayers
Abstract: The lamellipodium is a thin, sheet-like structure that is found in the propagating front of fast moving cells like fibroblasts, keratocytes, cancer cells, and more. It is a dense network of linear biopolymers of the protein actin, termed actin-filaments. These actin-filaments are highly dynamic structures that participate in a plethora of processes such as polymerization, nucleation, capping, fragmentation, and more. These processes are important for the structure and functionality of the lamellipodium and the motility of the cell. They are, to a large extent, affected by the extracellular environment; for example, the chemical landscape in which the cell of resides and the local composition and architecture of the Extracellular Matrix (ECM), lead to biased motility responses of the cell. When in proximity to each other, they develop cell-cell adhesion via specialized transmembrane proteins of the *cadherin* family. Collectively, they coagulate to clusters of cells that eventually merge to form cell monolayers. We model these phenomena using the Filament Based Lamellipodium Model (FBLM); an anisotropic, two-phase, two-dimensional, continuum model that describes the dynamics the lamellipodium at the level of actin-filaments and their interactions. The model distinguishes between two families (phases) of filaments and includes the interactions between them, as well as between the network of the filaments and the extracellular environment. The FBLM was first proposed in [1] and later extended in [2,4,5]. The FBLM is endowed with a problem specific Finite Element Method (FEM) that we have previously developed in [3]. In this talk we present the basic components of the FBLM and the FEM and focus on a series of simulations reproducing fundamental components of the motility of the cells, such us chemotaxis, haptotaxis, interaction with the environment [3, 4]. We also present our new findings with respect to cell-cell collision and adhesion, as well as the formation of clusters of cells and cell monolayers [5]. To confront the increased computational needs of the monolayer, we have developed a parallel version of our numerical method which we also address in this talk. Literature: [1] D. Oelz, C. Schmeiser. How do cells move? in Cell mechanics: from single scale-based models to multiscale modeling, Chapman and Hall, (2010).
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sion to cluster formation, (in review).

Senshi Shen

Acquisition by cancer cells of a plethora of resistance-conferring genetic alterations greatly limits the clinical utility of most anti- cancer drugs.

Abstract: Acquisition by cancer cells of a plethora of resistance-conferring genetic alterations greatly limits the clinical utility of most anti- cancer drugs. Therefore, there is a need to improve the effectiveness of treatment before mutational-acquired resistance prevails. Relapse is driven by a small subpopulation of residual or "drug-tolerant" cells, which are traditionally called "minimal residual disease" (MRD), that remain viable upon drug exposure. Recent in vitro findings have indicated that the emergence of these per- sisters is unlikely due to mutational mechanisms. A non-mutually exclusive scenario proposes that the drug-tolerant phenotype is transiently acquired by a small pro- portion of cancer cells through non-mutational mechanisms. To gain insights into the biology of MRD, we applied single-cell RNA sequencing to malignant melanoma BRAF mutated cells, and we identified a subpopulation of melanoma cells is tolerant to targeted therapy via metabolic reprogramming. Cancer cells were known to reprogram their metabolic profiles geared toward glycolysis, despite sufficient oxygen available to support oxidative phosphorylation (OXPHOS), a phenomenon known as the Warburg effect. We found that melanoma MRD can switch their metabolic program from glycolysis towards mitochondrial OXPHOS alimented by fatty acid oxidation (FAO), thereby renders the melanoma MRD highly sensitive to FAO inhibition in vitro and in mouse tumor models. This MRD-directed metabolic reprogramming suggests a more clever treatment combination regimen to fight against cancer resistance.

Angélique Stéphanou, CNRS Grenoble

On the interest of modelling spatiality of the pharmacokinetics of temozolomide, a drug against brain tumours; towards therapeutic optimization and innovations

Abstract: Pharmacokinetics-pharmacodynamics (PK-PD) models are standardly used to assess the availability and effects of a drug. However those models expressed with ordinary differential equations (ODEs) only describe the evolution of the drug concentration with time assuming that all cells receive the same amount and are targetted homogeneously in the same way. In a tumour case however, the cells states and the local cell environment - in terms of oxygenation and acidity - vary depending on the cells location in the tumour (periphery versus core). As a consequence it might prove useful to integrate spatiality in the models in order to get a more accurate evaluation of the drug uptake by the cells. In this presentation, we show how the effects of temozolomide - a pH-dependent drug directed against brain tumours - can be over-evaluated by the standard PK approach. The integration of the spatial component also shows how the healthy tissue might also be affected by the drug and gives a mean to evaluate collateral effects. The model is thus very helpful to highlight the weaknesses of this therapy and to suggest some new means to significantly improve it.

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