Politecnico di Torino

Dipartimento di Scienze Matematiche "G. L. Lagrange"

DISMA Dipartimento di Scienze Matematiche G. L. Lagrange

ECCELLENZA 2018 • 2022

BioTOMath Conference

Mathematical Challenges in Biology and Medicine

September 6-9, 2022

Torino, Italy

Book of Abstracts

Programme

	TUESDAY 6	WEDNESDAY 7	THURSDAY 8	FRIDAY 9
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10.40-11.20	Painter	Weigelin	Goriely	Estrada-Rodriguez
11.20-12.00	Perez-Garcia	Bironzo	Musesti	Meunier
12.00-12.40	Ciarletta	Di Fiore	Cavalcanti	Ptashnyk
	LUNCH	LUNCH	LUNCH	LUNCH
14.00-14.40	Ribba	Engwer	Poignard	Almeida
14.40-15.20	Quarteroni	Bretti	Raimondi	Bardelli
15.20-16.00	Gallo	Gomez	Cappello	
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Evolution of cancer cell populations under cytotoxic therapy: insight from phenotype-structured models

Luís Almeida[1]

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Abstract

In this talk, phenotype-structured model of evolutionary dynamics in cancer cell populations exposed to the action of cytotoxic drugs will be considered. The models consist of nonlocal partial differential equations governing the evolution of cell population density functions. Analytical and numerical results summarising the behaviour of the solutions to the model equations will be presented and the biological insight generated by these results will be briefly discussed.

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Exploiting immune surveillance to target colorectal cancer evolution and mutability

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Abstract

The emergence of drug resistance limits the efficacy of targeted therapies in human tumors. Strategies to prevent or overcome resistance are essential to design the next generation of clinical trials. The prevalent view is that resistance is a fait accompli: when treatment is initiated, cancers already contain drug-resistant mutant cells. Notably, bacteria exposed to antibiotics transiently increase their mutation rates (adaptive mutability) thus improving chances of survival. We studied colorectal cancer (CRC) to assess whether tumour cells similarly exploit adaptive mutability to evade therapeutic pressure. We found that EGFR and BRAF inhibition activates stress-induced mutagenesis through downregulation of MMR and HR DNA repair effectors, and concomitant up-regulation of error-prone polymerases in drug-tolerant persister cells resulting in increased mutation rates. Overcoming drug resistance, therefore, means considering as a target not "only" individual oncogenes but also the evolving nature of human tumors. One possibility is to unleash the ability of the immune system to recognize mutations induced by therapy. We tested this possibility in syngeneic mouse models of CRC. Our findings indicate that inactivation of DNA repair mechanisms and manipulation of mutational loads can trigger immune surveillance and prolonged therapeutic responses.

Patient-derived organoids from oncogene-addicted non-small-cell lung cancer (NSCLC): from patients to the bench and back

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Abstract

Lung cancer is the first cause of cancer-related death worldwide [1]. The identification of subgroups of patients whose tumor depends on specific gene mutations (so called "oncogene addicted tumors") has paved the way for precision medicine approaches in thoracic oncology with targeted therapies [2,3]. However, despite the high efficacy of these agents, resistance inevitably occurs leading to cancer progression. The identification of mechanisms underlying such resistances and the development of specific drugs to tackle them is therefore an urgent medical need. However, due to the system complexity, not all patients treated with tailored approaches derive benefit. In this talk, the state of the art of resistance mechanisms to targeted agents in advanced oncogene-addicted NSCLC along with examples of therapeutic strategies in clinical development will be briefly discussed, followed by original data from our research group about the potential role of patient-derived organoids as avatar to explore therapeutic strategies to tackle such resistances.

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Mathematical models and simulations inspired by immunocompetent cancer-on-chip experiment

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Abstract

The present work is inspired by recent developments in laboratory experiments and by the availability of data within the framework of cancer-on-chip technology [1], an immune-oncology microfluidic chip aiming at studying the fundamental mechanisms of immunocompetent behavior to test and understand the complex mechanisms behind cell dynamics and the interaction between immune and tumor cells.

Here we present an overview on the mathematical models developed in this framework. First we introduce macroscopic modeling of COC experiment, with ad hoc transmission conditions for chip geometry and related estimation techniques for model parameters is proposed, describing long-range dynamics of immune cells driven by the chemical substances secreted by cancer cells in the chip environment [2,3].

A discrete-in-continuous hybrid approach [4] is also formulated as a PDE reaction–diffusion partial model for the evolution of the chemicals, coupled with an ODE particle model for cell motion, with simulations reproducing the dynamics in only on a small portion of the right chamber and not on the whole area observed in video footage of the laboratory experiment.

Finally, a rather general, easy to implement approach mathematical model based on cellular automata is proposed [5]. Such model is able to reproduce the main features of the observed COC experiments such as cell migration driven by a chemical stimulus, as well as possibly short- and long-range interactions between immune cells.

We found that the qualitative behavior of the solutions obtained by our simulation algorithms is comparable with the experimental observations. The validation of the proposed models with real data coming from laboratory experiments is a work in progress.

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Approaches to understanding tumour-immune interactions

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Abstract

While the presence of immune cells within solid tumours was initially viewed positively, as the host fighting to rid itself of a foreign body, we now know that the tumour can manipulate immune cells so that they promote, rather than inhibit, tumour growth. Immunotherapy aims to correct for this by boosting and/or restoring the normal function of the immune system. Immunotherapy has delivered some extremely promising results. However, the complexity of the tumour-immune interactions means that it can be difficult to understand why one patient responds well to immunotherapy while another does not. In this talk, we will show how mathematical, computational and topological methods can contribute to resolving this issue and present recent results which illustrate the complementary insight that different approaches can deliver.

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Extracellular matrix in multicellular aggregates acts as a pressure sensor controlling cell proliferation, motility and contractility

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Abstract

Biological tissues are inherently composite. They are made of cells, which are virtually impermeable and incompressible but deformable and active, and extracellular matrix, which is permeable to water and about a thousand times more compressible than cells. The whole is permeated by interstitial fluid, which is incompressible but flows according to the mechanical stress suffered or exerted by the tissue.

The rheological features of each of these three components are very different. Consequently, a composite tissue made of cells, extracellular matrix and fluid will exhibit emerging rheological properties that depend both on the structural arrangement and on the volumetric ratio of the three constituents.

In our work, we point the existence of a peculiar feedback between the cells and the extracellular matrix: cells read and react to the deformation of the extracellular matrix imposed by an external perturbation. In response to a gentle compression of the matrix, cells change their proliferation rate, their motility and their contractility.

In other words, the cells use the extracellular matrix as an external stress gauge and take advantage of its large compressibility to detect weak (but physiological) mechanical stimuli.

Mechanical regulation of migration by cell surface receptors

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Abstract

During migration, cells sense external physical cues, such as rigidity and geometry, and adjust to them by modifying their shape and adhesion mechanisms. Cell surface receptors, such as integrins at the cell-matrix adhesions and cadherins at the cell-cell junctions, regulate sensing and transduction of mechanical signals. In my presentation I will discuss our work on how local changes in receptor organization and binding strength affect the migration of single cells and cell collectives. I will also present how cells adjust their mechanical behavior in response to perturbations of receptor-mediated adhesion.

Advanced bioengineering methods for direct cell reprogramming in myocardial regeneration

Camilla Paoletti[1,2,3], Letizia Nicoletti[1,2,3], Elena Marcello[1,2,3], Giovanni Paolo Stola[1,2,3], Clara Mattu[1,2,3], Silvia Arpicco[4], Barbara Stella[4], Carla Divieto[5], Valeria Chiono[1,2,3]

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Abstract

Cardiovascular diseases are one of the leading causes of death worldwide. Particularly, myocardial infarction (MI) causes the irreversible loss of cardiomyocytes and the formation of dysfunctional fibrotic scar tissue, leading to heart failure [1]. To date, heart transplantation is the only available therapy for end-stage heart failure. Hence, extensive research is in progress to develop novel strategies for post-MI cardiac regeneration. Among them, the administration of microRNAs (miRNAs) has attracted interest as a promising new strategy to modulate gene expression and to potentially induce cardiac regeneration. In our previous research, Paoletti *et al*. demonstrated that transient transfection with four microRNA mimics (termed "miRcombo") using a commercial lipid transfection agent (DF) triggers direct reprogramming of human adult cardiac fibroblasts (AHCF) into induced cardiomyocytes (iCMs) *in vitro* [1]. However, *in vivo* administration of naked miRNAs is hindered by their degradation and poor cell internalization. Hence, safe and efficient nanocarriers for direct reprogramming of AHCFs into iCMs are demanded.

In our work, we demonstrated the key role of safe and efficient delivery systems for miRcombo and biomimetic culture conditions in enhancing direct reprogramming efficiency of AHCFs into iCMs.

New lipoplexes (LP) were designed showing higher miRNA encapsulation efficiency (~99%) and biocompatibility, and similar cell transfection efficiency respect to DF-based lipoplexes. AHCF transfection with LP/miRcombo vs DF/miRcombo increased *in vitro* direct reprogramming efficiency of AHCFs into iCMs. However, the *in vitro* direct reprogramming efficiency of DF/miRcombo-transfected cells strongly increased when they were cultured in 3D biomimetic hydrogels based on fibrin/cardiac extracellular matrix produced *in vitro* by cells [2]. Finally, AHCFs transfection with LP/miRcombo and their culture in a biomimetic hydrogel further enhanced direct reprogramming efficiency of AHCFs.

In parallel, we designed an alginate-based injectable hydrogel with double crosslinked network for controlled *in situ* release of miRcombo-loaded nanocarriers during *in vivo* application. As alginate presents limitations, such as low degradability *in vivo* and limited cell adhesion, it was blended with alginate dialdehyde (ADA) and

chemically-modified gelatin. Hydrogel composition was selected to ensure injectability, cell adhesion, biomimetic stiffness and proper stability in physiological conditions.

Modified LP/miRNAs nanocarriers were designed and patented keeping the same miRNA loading efficiency and biocompatibility as LP/miRNA nanocarriers, but showing superior stability and easy surface functionalization with ligands for receptor-mediated cell targeted release, as well as the ability to be encapsulated and released from the injectable hydrogel. *In vitro* direct reprogramming experiments from release media and *in vivo* tests in mouse model are in progress.

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Diffuse interface modeling for life sciences

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Abstract

In the first part, I will present a mathematical model, based on pre-clinical observations performed at Ospedale San Raffaele in Milan, of tumor evolution in presence of adoptive cellular therapy, a type of immunotherapy that enhances the immune system natural response by means of genetic manipulations of autologous T cells.

In the second part, I will present a diffuse interface model of wound healing that is validated against existing experimental results for wound closure in epithelial monolayers.

Modeling of organoid's invasion

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Abstract

The aim of the talk is to summarize the theoretical findings on the mechanics of invasion in the context of the mouse-derived cancer organoids developed in the project Mechanocontrol. With the Arroyo's group at UPC we formulated the hypothesis that invasion is the result of a bio-mechanical instability and selforganized pattern formation of the organoid-matrix system. This hypothesis has the potential to recapitulate the mechanical and biological requirements of invasion suggested by experiments, it is amenable to mathematical and computational modeling, and it may provide experimentally testable predictions.

The major genetic alterations in breast cancer converge on the disruption of asymmetric division in the stem cell compartment

Pier Paolo Di Fiore[1,2], Maria Grazia Filippone[1], Ivan Colaluca[1], Stefano Confalonieri[1], Elena Piretto[1], Luca Marchetti[3], Salvatore Pece[1,2], Daniela Tosoni[1]

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Abstract

In breast cancer (BC), the frequent activation of PKCs leads to aberrant phosphorylation of the tumor suppressor Numb, a cell fate determinant that by asymmetrically partitioning at the mitosis of the mammary stem cell impart different fates to its progeny. Aberrantly phosphorylated Numb fails to determine asymmetric cell division, resulting in expansion of the cancer stem cell compartment, associated with an aggressive disease course. We uncovered a circuitry linking the major genetic alterations present in breast cancer (ErbB2 overexpression, PI3K activation, PKC activation, Notch activation and p53 loss-of-function) to the dysregulation of Numb phosphorylation and to the skewing of the division of cancer stem cells from an asymmetric to a symmetric pattern of division. The circuitry relies a positive feedback loop between NUMB and p53 (involving miR-34a and PKCs) that sits downstream of ERBB2 and PIK3 and controls NUMB phosphorylation in physiology and in BC. A detailed molecular characterization of the circuitry will be presented, along with an initial bottom-up model that allows non-intuitive predictions of its behavior in mammary cancerogenesis.

Modelling collective cell movement: from Dictyostelium to cancer

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Abstract

Collective cell movement is a characteristic of tissue remodelling that underlies various processes in morphogenesis, wound repair and cancer invasion. In this talk, we review some continuum and hybrid models developed over the last few years to understand various biological aspects in morphogenesis and cancer invasion: from the interplay between cell movement, cell sorting, cell-type differentiation and proportioning in Dictysotelium discoideum, to the role of cell-cell and cell-ECM adhesion in cancer invasion, as well as the role of structure and directionality of ECM on the migration of cancer cells. We cover both single-scale and multi-scale models in 1D, 2D and 3D, while emphasising various issues related to the availability and use of data to parametrise such models.

Linking growth models and image data to estimating the extent of glioblastoma tumors

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Abstract

Glioblastoma Multiforme is a malignant brain tumor with poor prognosis. There have been numerous attempts to model the invasion of tumorous glioma cells via partial differential equations in the form of advection-diffusion-reaction equations. The patient-wise parametrization of these models, and their validation via experimental data has been found to be diffcult, as time sequence measurements are mostly missing. Also the clinical interest lies in the actual (invisible) tumor extent for a particular MRI/DTI scan and not in a predictive estimate.

Based on an instationary model with patient specific model parameters, derived from MRI/DTI scans, we propose a stationalized approach to estimate the extent of glioblastoma (GBM) invasion at the time measurement.

The underlying dynamics can be derived from an instationary GBM model, falling into the wide class of advection-diffusion-reaction equations. The stationalization is introduced via an analytic solution of the Fisher-KPP equation, the simplest model in the considered model class. We investigate the applicability in 1D and 2D, in the presence of inhomogeneous diffusion coefficients and on a real 3D DTI-dataset.

Motility switching and front-back synchronisation in polarized cells

Gissell Estrada-Rodriguez[1], Benoît Perthame[2]

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Abstract

The combination of protrusions and retractions in the movement of polarized cells leads to understand the effect of possible synchronisation between the two ends of the cells. This synchronisation, in turn, could lead to different dynamics such as normal and fractional diffusion. Departing from a stochastic single cell trajectory, where a "memory effect" induces persistent movement, we derive a kinetic-renewal system at the mesoscopic scale. We investigate various scenarios with different levels of complexity, where the two ends of the cell move either independently or with partial or full synchronisation.

Advanced methods for deciphering cardiovascular flows complexity

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Abstract

The study of cardiovascular flows is of great interest because of the role of blood flow mechanics in cardiovascular diseases, the single largest cause of death worldwide. Blood flow in arteries is highly four-dimensional, as a consequence of arterial anatomy and of the flow unsteadiness imparted by the heart pulsatility [1]. To allow for an effective and valuable understanding of complex blood flow patterns and of their physiological significance, methods capable of characterizing blood flow spatiotemporal complexity and organization have been developed in recent years.

These methods focused primarily on wall shear stress (WSS, i.e., the force per unit area exerted by the flowing blood on the endothelial cells lining the vessel lumen) to provide quantitative indicators of blood flow disturbances. In particular WSS having low magnitude and undergoing directional (oscillatory) changes along the cardiac cycle has been identified as a localizing factor of vascular disease [2]. However, the consideration of low and oscillatory WSS only may result in an oversimplification of the complex fluid dynamic environment establishing in the arterial system. To improve the current understanding of the association between local blood flow complexity and vascular disease, recent efforts on the analysis of the topological skeleton of the WSS vector field will be presented. In particular, the ability of WSS topological skeleton to reflect cardiovascular flow features like flow stagnation, separation and recirculation, known to be promoting factors for vascular disease [2], will be discussed. Moreover, evidence of a direct association between WSS topological skeleton features and markers of vascular disease will be provided.

A complete description of cardiovascular flows complexity should complement analyses based on WSS with a quantitative description of intravascular flow. To pursue the aim of characterizing the spatiotemporal evolution of intravascular flow patterns, a network-based approach for the quantification and interpretation of spatiotemporal flow coherence will be presented [3].

Finally, open questions on the clinical utility of the presented methods and on the inherent limitations to their *in silico* and *in vivo* application will be discussed.

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Inverting tumor angiogenesis with fluid flow and chemokine matrix-binding affinity

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Abstract

Angiogenesis, the growth of blood vessels from pre-existing ones, plays a key role in cancer progression. Cancerous tumors release pro-angiogenic growth factors into the extracellular matrix that promote vessel growth once they reach the pre-existing vasculature. The neovasculature provides nutrients to the tumor, usually accelerating its growth. Therefore, the understanding and control of angiogenesis are critical to combat cancer. Until very recently, the literature had systematically assumed that the interstitial flows unavoidably occurring in the extracellular matrix had little impact on angiogenesis. Surprisingly, recent experimental evidence has shown that even very mild flows like those likely occurring in the human body can significantly alter vascular growth patterns. However, the mechanisms whereby fluid flow alters angiogenesis remain unknown; and different experiments show opposite effects of fluid flow on angiogenesis. In this seminar, I will present our recent modeling work to investigate the influence of fluid flow in tumor angiogenesis. Our model demonstrates the key role of interstitial flow in angiogenesis and reconciles two seemingly contradicting experiments: one showing more prominent angiogenic growth against the flow and another other showing more prominent growth with the flow. The model suggests that fluid flow may be used to invert the direction of angiogenic growth when combined with the adequate isoform of the growth factors.

References

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Frequency slowing and hyperactivity in Alzheimer's disease

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Abstract

Alzheimer's disease is the most common cause of dementia and is linked to the spreading of pathological amyloid beta and tau proteins throughout the brain. Recent studies have highlighted stark differences in how amyloid beta and tau affect neurons at the cellular scale. On a larger scale, Alzheimer's patients are observed to undergo a period of early-stage neuronal hyperactivation followed by neurodegeneration and frequency-slowing of neuronal oscillations. In this talk, I model the spreading of both amyloid beta and tau across a human connectome and investigate how the neuronal dynamics are affected by disease progression. By including the effects of both amyloid beta and tau pathology, our model shows that AD-related frequency slowing, early-stage hyperactivation, and late-stage hypoactivation. By testing different hypotheses, we show that hyperactivation and frequency-slowing are not due to the topological interactions between different regions but are mostly the result of local neurotoxicity induced by amyloid beta and tau protein leading to an early increase in neuronal activity and a late decrease in excitatory neuronal activity.

This is joint work with Christoffer G. Alexandersen (Oxford), Willem de Haan and Christian Bick (VU Amsterdam).

Modelling collective cell movement in development and disease

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Abstract

Collective cell movement is a common process in biology, observed in normal development, wound healing, and disease. In this talk, I will discuss work we have done on two applications: (a) tumour cell invasion, where we use a partial differential equation model to suggest that cooperation between different cell phenotypes may facilitate cancer cell invasion [1]; (b) cranial neural crest cell migration, where we use a hybrid discrete-continuum model to suggest new biological hypotheses, which have subsequently been validated experimentally.

References

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Mathematical analysis and numerical simulations on models of cell motility

Nicolas Meunier[1]

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Abstract

In this talk, I will present a model to describe cell migration. Cell migration plays a key role in many physiological processes, such as embryogenesis, wound repair or metastasis formation. It is the result of a complex activity that involves different time and space scales. I will first detail the construction of the model and then present rigorous results and numerical simulations.

A mathematical description of the flow in a lymph node

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[3]*Dipartimento di Matematica e Fisica, Università Cattolica del Sacro Cuore, Brescia, Italy*

Abstract

The motion of the lymph has a very important role in the immune system and it is influenced by the porosity of the lymph nodes: more than its 90% takes the peripheral path without entering the lymphoid compartment. In this talk we show some mathematical models of a lymph node assumed to have a simplified geometry, where the sub-capsular sinus is a thin shell near the external wall of the lymph node and the core is a porous material describing the lymphoid compartment. We assume incompressibility and we use both Stokes equation and Darcy-Brinkman equation for the flow of the lymph. In some cases we find an explicit solution for the fully developed pulsatile flow in terms of special functions. A finite-element simulation is provided in the case of physiological parameters.

References

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The impact of phenotypic heterogeneity on chemotactic invasion and self-organisation

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Abstract

Standard mathematical models for chemotaxis assume homogeneity of a population, for example a group of cells in which the members display identical chemotactic ability, growth potential, nutrient uptake etc. Growing evidence, rather, suggests that the phenotypic traits within populations can vary considerably: strains of *E. coli* bacteria placed in maze-like configurations will form a clear population structuring, such that those with the strongest chemotactic motility infiltrate the deepest. Investing in any particular behaviour has an energy cost, however, and the sum expenditure must be balanced according to the energy influx: a trade-off results where, say, greater motility could mean less energy for growth, and vice versa. The extent to which trade-offs impact on population-level dynamics is therefore of manifest interest. In this talk I will discuss extensions to classic chemotaxis models that incorporate trade-offs, through their extension to include a phenotypically heterogeneous population. Using two classic case studies – the formation of chemotactic invasion waves and self-aggregation – I will explore how trade-offs impact on population-level behaviour, and the degree to which specific responses to the evolving environment alter structuring of the population.

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On the macroscopic growth laws of brain metastases: From the blackboard to the clinics

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Abstract

Tumor growth is the result of the interplay of complex biological processes between a huge amount of individual cells in a changing environment. Effective simple mathematical laws have been shown to describe accurately tumor growth in-vitro or in animal models with bounded-growth dynamics. However, results for human cancers in patients are scarce.

Brain metastases (BMs) are the most common intracranial tumor and a major complications of many cancers, with including lung, breast and colorectal cancers, melanoma or renal cell carcinomas.

20%-30% of cancer patients developing BMs in the course of their disease [1]. However, very few mathematical studies have addressed the many problems arising in the management and treatment of brain metastases.

We mined a dataset of 1131 brain metastases (BMs) with longitudinal imaging follow-up treated with radiosurgery (SRS) to find the growth laws of untreated BMs, relapsing treated BMs, and radiation necrosis (RN). Untreated BMs showed a sustained growth acceleration most likely related to an underlying evolutionary dynamics. Relapsing BMs growth was slower, most likely due to a reduction in tumor heterogeneity after SRS, which may limit the tumor evolutionary capabilities. RN lesions had significatively larger growth exponents than relapsing BMs, providing a way to differentiate them from true progressions. I will describe hybrid

approaches to the problem based on simple (ordinary differential equation) and more complex (discrete simulators) models together with clinical and imaging data. The results may help in solving a problem of clinical relevance, since the first condition may resolve spontaneously, not requiring further work-up while the second requires therapeutic actions [2].

We also studied in detail the definition of `relapse' itself, that is not trivial when based on observational data. We proved that the commonly accepted definition of BM relapse based on the so-called RANO criteria [3] leads to a late detection of the event that may result in treatment delays of several months, leading to a high probability of loss of control of the disease and patient's death.

In the talk I will describe other imaging biomarkers of BM aggressiveness inspired in previous results for primary brain tumors and discuss what might be the role of mathematical models in understanding the findings [4].

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Modelling across scales in development and disease

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Abstract

Most biological systems span multiple spatial and temporal scales. It is often the case that the experimental data is available at a coarse-grained level, while the process of interest operates at much finer scales. Mathematical modelling can help the understanding of how dynamical interactions at different scales filter through at the level of the observable data.

I will talk about two model systems, the developing brain and cancer, to show how data-driven modelling can describe the processes of interest and make testable predictions.

In the first example I will focus on neurogenesis in the mammalian cerebral cortex. Many factors influence how cortical neurogenesis differs between species, leading to brains of different shapes and sizes. In order to map the divergence of evolutionary trajectories resulting in such diversity, we must study and compare the developmental programmes in different species. Critically, to fully characterise neurogenesis in development, we are faced with the challenge of understanding the temporal changes in the cell division strategies of neural progenitor cells involved in the producing the required number of cortical neurons.

In the second example I will look at the emergence of environment-mediated drug resistance in molecularly targeted cancers. This type of resistance is the result of complex interactions between the cancer cells, the host tissue, and the drug. Using a mathematical and computational framework to bridge between experimental models and scales, we can separate intrinsic and extrinsic components of resistance. The ultimate goal is to design an intermittent treatment protocol able to control the emergence of resistance during drug administration, while limiting tumour regrowth during treatment holidays.

The power of these interdisciplinary efforts is to drive an understanding of what is known, and what is left to discover, planning onwards to systematically fill in the gaps. For both systems I will present some preliminary findings and highlight the current limitations in the interpretation of model predictions, identifying a specific need for experimental quantifications.

Electroporation for liver tumor ablation: from microscale modeling to clinical applications

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Abstract

Electropermeabilization (also called electroporation) is a significant increase in the electrical conductivity and permeability of the cell membrane that occurs when pulses of large amplitude (a few hundred volts per centimeter) are applied to the cells: due to the electric field, the cell membrane is permeabilized. If the pulse duration is sufficiently short (a few milliseconds or a few microseconds, depending on the pulse amplitude), the cell membrane reseals within several tens of minutes: reversible electroporation, preserves the cell viability and is used in electrochemotherapy to vectorize the drugs until the cell inside. If the pulses are too long, too numerous or if their amplitude is too high, the cell membrane is irreversibly destroyed and the cells are killed. Irreversible electroporation provides thus a novel non thermal and minimally invasive ablation therapy.

In this talk I will present some recent results from the Inria Team MONC on the mathematical modeling of electroporation at the cell scale and at the micro-tissue scales. I will also present some recent results of the impact of pulsed electric field on the growth of microtumors. In the last part of my talk, I will present a numerical strategy to help interventional radiologists in their practice of percutaneous liver tumor ablation by irreversible electroporation.

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Multiscale modelling, analysis, and simulation of intercellular signalling process

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Abstract

To understand development, growth and remodelling of biological tissues and organs, a better understanding of interactions between cells in a tissue is required. Essential parts of communications between cells, as well as cell responses to external and internal stimuli, are governed by intercellular signalling processes.

In this talk we consider multiscale modelling and analysis for cellular signalling processes on the level of a single cell. The dynamics of signalling molecules in the inter- and intra-cellular spaces and of cell membrane receptors are described by a coupled system of nonlinear bulk-surface partial differential equations. Using multiscale analysis techniques we derive macroscopic two-scale model for signalling processes defined on the tissue level. The two-scale numerical method is developed and implemented for simulations of the macroscopic bulk-surface problem.

Physics-based and data-driven mathematical models for the simulation of the heart function

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Abstract

This presentation focuses on machine learning (the computers' ability to learn based on training from large data sets) and computational science (the use of mathematical models originated from fundamental principles of physics) in solving mathematical problems of interest in real life. Similarities and differences, potentials and limitations are discussed, as well as the enormous possibilities offered by their synergistic use. The driving application will be the simulation of the cardiac function, in both physiological and pathological regimes.

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Mechanobiology of cancer progression

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Abstract

Invasive cancers are a leading cause of death worldwide, with almost ten million deaths per year caused by resistance to antitumor treatments. In breast cancer, aggressiveness correlates with fibrotic stiffening of the tumour. There is an urgent need to understand how the fibrotic microenvironment evolves, to design better targeted cancer therapies. Fibrotic stiffening is caused by fibroblasts secretion of a matrix with mechanical properties that stabilise the tumour vascular network. However, the hierarchy and stability of the tumour vascular network are not reproducible *in vitro*. To advance the field, we will develop a revolutionary platform able to recapitulate tumour fibrosis by exploiting the vascularisation of a living organism.

To achieve our goal, we will use human breast cancer cells adhering to 3D polymeric micro scaffolds to create arrays of tumour microenvironments. We will implant the arrays *in vivo* in the chorioallantoic membrane of an embryonated avian egg, to elicit a foreign-body fibrotic reaction. We will vary the micro scaffolds geometry to condition tumour infiltration by the host's vessels and cells. We will exploit fluorescent spatial beacons incorporated in the micro scaffolds[1] for multiphoton image correlation, to derive morphological and functional information of the regenerated fibrous matrix and vessels. We will predict mass transport of solutes and anticancer agents in the tumour microenvironments by multiphysics computational modelling. To validate the platform, we will quantify *in vivo* the dose-dependent efficacy and cancer specificity of therapeutic agents whose success is known to depend on the fibrotic stage of tumours.

This project combines mechanobiology to bioengineering, biomechanics, oncology, genetics, microtechnology, intravital imaging, biophysics and pharmacology to understand the progression mechanisms of the most incurable cancers. It will also provide an ethical and standardizable testing platform to boost the clinical translation of new therapeutic products in oncology. This project has received funding from the European Research Council under the European Union's Horizon Europe research and innovation program (G.A. 101053122 - BEACONSANDEGG).

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Examples of models and algorithms for therapeutic innovation

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Abstract

Developing new effective disease treatments is notoriously difficult and many historical examples point out the predominance of trial and errors, risk-taking and luck, as critical aspects of success stories. Meanwhile the continuous development of mathematical modeling approaches and its use in clinical pharmacology to better understand dose-response relationship offers significant possibilities to further rationalize therapeutic innovation.

Following a recent framework proposing that a launchable drug is a sweet spot between three dimensions: biology understanding, technology and clinical needs [1], we will showcase examples of models and algorithms sitting at the intersections between these dimensions.

At the intersection between biology understanding and technology, we will first discuss the application of a mathematical model capturing the biological understanding of peripheral and tissue pharmacokinetic/pharmacodynamic for the development of a new therapeutic antibody construct [2]. At the intersection between technology and clinical need, we will then discuss the application of reinforcement learning (RL) - an algorithmic technique mimicking the process of learning by animals and humans - for personalized dosing [3].

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Stress-free morphing by means of 3D target metric

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Abstract

We study the morphing of 3D solids within the framework of non-linear elasticity with large distortions. In this work, we explore the possibility of deforming elastic 3D bodies through distortions with the aim of proposing a blueprint for the characterization of compatible metric tensors to which there correspond a sought shape transformation, that is a 3D morphing towards a target shape having zero stress. Shape-morphing has been used as modeling tools to the study of biological growth [1], and the morphing of 2D bodies has been extensively studied in the recent decade, both from the theoretical point of view [2, 3], and from the point of view of morphing design [4].

We support that morphing through compatible distortions is a key strategy exploited by nature, enabling living organisms to perform vital tasks such as change shape, move, adapt to the environment [5]. Design of morphing is now at the core of many applications, and our work investigates about the possibility of designing stress-free morphing for 3D bodies, following [6, 7].

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Epithelial mechanobiology from the bottom up

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Abstract

Epithelial sheets form specialized 3D structures suited to their physiological roles, such as branched alveoli in the lungs, tubes in the kidney, and villi in the intestine. To generate and maintain these structures, epithelia must undergo complex 3D deformations across length and time scales. How epithelial shape arises from active stresses, viscoelasticity and luminal pressure remains poorly understood. I will present different approaches to study the mechanobiology of epithelial shape from the bottom up. I will discuss new technologies to design epithelia of arbitrary size and geometry and to subject them to controlled mechanical deformations in 3D. I will show that monolayers exhibit superelastic behavior when stretch is applied and that they readily buckle when tension is released. We use this phenomenology and a 3D vertex model to rationally direct spontaneous pattern formation, and hence engineer tissue folding. I will also present our recent advances to understand the mechanobiology of intestinal organoids. We map the three-dimensional cell-ECM and cell-cell forces in mouse intestinal organoids grown on soft hydrogels. We show that these organoids exhibit a non-monotonic stress distribution that defines mechanical and functional compartments. From these experiments we conclude that the stem cell compartment folds through apical constriction and that cells are pulled out of the crypt along a gradient of increasing tension, rather than pushed by a compressive stress downstream of mitotic pressure as previously assumed. This experimental and theoretical work unveils how patterned forces enable folding and collective migration in the intestinal crypt.

Uncovering electrodynamic design principles of living cells and a potential role of quantum interactions in cellular signal processing

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Abstract

The structure-function relationship is the basis of quantitative analysis of living organisms whose fundamental unit is a cell. Cellular structural and functional complexity is a challenge to our understanding of responses to various environmental changes affecting cells. Electrical and electromagnetic interactions with cells are particularly poorly understood. I will discuss recent experiments [1,2] performed in parallel with computational modelling [3] aimed to develop an integrated model of the cell as a bioelectric circuit. I will summarize key bio-electric properties of the cell as a whole and its major components, which will allow to reverse engineer the underlying bio-electrodynamic design principles. While much is known about the electric properties of cell membranes, explorations of the cytoskeleton, are still nebulous. Key cytoskeleton components, actin filaments and microtubules, play essential roles in cell motility, mitosis, cell differentiation, transport and signaling. Their elementary protein building blocks self-assemble into cell-spanning filaments, and are strongly affected by temperature, ionic concentrations, pH and other factors. These factors are involved in cellular structure formation and significantly affect cellular responses to electric and EM fields. My ultimate objective is to uncover an electrodynamic design blueprint for eukaryotic cells accounting for these factors, both generically and in comparison between normal and cancer cells [4]. While cancer cells exhibit major changes in their electro-chemical properties compared to normal cells, this property is yet to be substantially exploited for therapeutic applications, although some promising advances have recently been made and I'll discuss them in this talk. This work is intended to unveil a new paradigm for health and disease and enable new therapeutic interventions. Finally, in relation to the potential role of the cytoskeleton in quantum mechanisms of consciousness, I'll report some recent experimental and computational results obtained within the Templeton Foundation supported project I am coordinating.

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Multiscale microscopy to understand systemic immunotherapy response

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Abstract

Most of our textbook knowledge of immune cell behavior and function in live tissues during cancer immunotherapy is based on the reconstruction of dynamic events from static images. Only with the evolution of intravital microscopy in the last decades it became possible to directly monitor the dynamic interaction of immune and tumor cells within tissue niches [1]. Using multiphoton microscopy to monitor mouse melanome, we captured all functionally relevant steps of adoptive T cell transfer, including arrival of transferred CTL in the lesion, early effector function and induction of tolerance and CTL death. This approach allowed to identify a CTL crowd-based killing mechanism dependent on serial CTL-tumor cell interactions and the accumulation of sub-lethal hits to overcome melanoma cell resistance [2]. The cooperation between multiple CTL requires high local density of antigen-specific CTL and may thereby provide a "filter" which limits unintended tissue damage by miss-targeted CTL. Using higher harmonic generation microscopy [3], we further identified the tumor invasion niche as yet unappreciated tumor subregion with particular high CTL swarming, multi-hit activity and tumor cell eradication. In summary, we identified 'additive cytotoxicity' as novel mechanism which defines the efficacy of CTL effector function and can be exploited by targeted immunotherapy to increase both, single contact efficacy and cooperation of immune effector cells. In ongoing projects, we explore the correlation of cellular microscopy with mesoscopic and macroscopic imaging modalities. The multiscale data collection allows to translate mechanistic insights gained by microscopic imaging into clinically relevant information and generates new opportunities and challenges for modeling systemic immune responses.

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A mathematical model for guided cancer cell patterning in a collagen-based model

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Abstract

Metastatic tumor cell invasion into heterogenous interstitial tissues of network-, channel- or cleft-like architecture involves both cell adaptation to tissue geometry and matrix metalloproteinase (MMP)-mediated tissue remodeling. We developed collagen-based channel- and cleft-like assays in vitro, with the latter containing an interface between two lattices of defined density, and probed the impact of geometry on tumor cell invasion. A cellular automaton modelling approach predicted that, whereas migration into dense 3D matrix of randomly organized pores strongly requires collagenolysis, guidance cues facilitate cell patterning. Our experimental data showed that Inhibition of collagen degradation compromised migration into 3D collagen in dependence of density, whereas interface and track-guided migration remained effective, verifying the predictions of the mathematical model. In conclusion, interfaces but not dense 3D matrix support effective non-proteolytic migration, identifying linear guidance cues as a MMP-independent invasion niche.