Special Session 8: Biomathematics and cancer modelling

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It is nowadays well admitted that tumor growth is a very complex process, involving different phenomena occurring at various scales of the organism. From a modeling point of view, there are three scales of particular interest: the subcellular scale, the cellular scale and the macroscopic scale. To develop multi-scale mathematical models requires the use of a wide variety of theoretical tools to perform both qualitative and quantitative predictions. The objective of this session is to give the opportunity to young researchers to present innovative mathematical models of cancer growth.

An age-cyclin structured cell population model with proliferation and quiescence

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We present a nonlinear model of the dynamics of a cell population divided in a proliferative and quiescent compartments. It is structured by the cell age inside the proliferative phase, and the amount of cyclinD/(CDK4 or 6) complexes. Cells can pass from one compartment to the other, following transition rules which differ according to the tissue state, healthy or tumoral. The asymptotic behaviour of solutions of the nonlinear model is investigated in two cases, exhibiting tissue homeostasis or exponential growth. The model allows for fast numerical solution which ensure the theoretical predictions.

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A multiscale mathematical model of 5-fluorouracil activity on metastatic colorectal cancer

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We developed a multiscale mathematical model of 5-fluorouracil (5FU) activity in order to explain and if possible improve poor clinical results observed in metastatic colorectal cancer patients.

On the basis of recommendations for 5FU use, we modelled its efficacy by taking into account two different observation levels. At a molecular level, we focused on 5FU effect on DNA synthesis while, at a tissue level, the model integrates the consequence of DNA damage on metastasis growth through cell cycle regulation. Haematotoxicity is modelled by focusing on the temporal evolution of white blood cell count expressed as a function of 5FU plasma concentration.

Simulation results may help comparing different 5FU-based protocols in terms of efficacy and provide relevant information about the optimal association with other drugs such as oxaliplatin to improve clinical outcomes.

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Continuum Models for Cell Movement in Network Tissues

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From recent experimental studies, much has been learned about cell movement in tissues. Cells that move through tissues (like cancer metastases, or leukocytes) interact with the tissue matrix as well as with other cells, involving many different biological and physical processes in a complicated way. We choose the framework of transport equations to derive a continuum model. We describe our most general transport model for cell movement in tissues, including drag forces, chemotactic forces, cell-ECM interactions, contact guidance from network fibres and cell-cell interactions. We derive the system of moment equations for mass and momentum and apply a moment closure technique to derive a continuum model for mesenchymal motion including taxis.

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The Keller-Segel system for chemotaxis: existence and long time behavior of solutions

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The Keller-Segel system describes the motion of a biological population under the chemotaxis process. This system has been intensively studied in the last thirty years. However, the problem of the critical space for the initial density population giving rise to global solutions of the system is not yet entirely understood. We study the Keller-Segel system on the whole space when the chemoattractant concentration is described by a parabolic equation. We prove that the critical spaces for the initial bacteria density and the chemical gradient are respectively : $L^a(\mathbb{R}^d)$, $a > d/2$ and $L^d(\mathbb{R}^d)$. In these spaces, we prove that small initial data give rise to global solutions that vanish as the heat equation for large times and that exhibit a regularizing effect of hypercontractivity type.

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Cell response to a shear flow in a microchannel

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Cell adhesion in blood vessels and capillaries is a key step in a lot of biological phenomena such as those related to the immune response or cancer proliferation. Cancer cells or leukocytes interact and adhere to the endothelial wall, under specific flow conditions. Here, we present a tentative model to take into account the effect of the flow field, the cell-wall adhesion properties and the cell membrane rigidity on its deformability. The cell is confined in a 2D channel and subjected to a flow field (Q). It is adhering to the wall with a defined density of receptor-ligand bonds (N). The cell membrane is modelled as an elastic sheet with a given elasticity (E). The cell contact area (A) and cell shape are allowed to vary. Assuming a known flow field, the equations for membrane deformation are solved until an equilibrium is found, assuming the receptor-ligand bond density satisfies a biochemical equation [Dong et al., 1999]. This allows us to study the cell shape, the cell contact area, and the time evolution of receptor-ligand bonds. Also information about rolling velocity and critical flow rate for cell detachment can be obtained. Such results are compared qualitatively with the available experimental data.

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Long period oscillations in chronic myelogenous leukemia

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We propose a two age-structured partial differential equations model of blood cells production, that reduces to a system of two nonlinear differential equations with distributed time delay corresponding to the cell cycle duration. We investigate the existence of a Hopf bifurcation that would lead to the existence of periodic solutions about a positive equilibrium, and we show the existence of long period oscillations that can be related to some oscillations observed with the periodic form of chronic myelogenous leukemia, when the Hill coefficient of the cell cycle regulation function is finite. The study maybe helpful in understanding the connection between the relatively short cell cycle durations and the relatively long periods of peripheral cell oscillations in some periodic hematological diseases.

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A Topology Game for Tumoral anti-angiogenesis

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Angiogenesis is the biological process by which networks of blood vessels are initiated and proliferate towards a mature vasculature. At the early development and growth, angiogenesis is necessary to go from the embryonic vasculogenesis into a complete and mature blood system. It is also an important factor of wound healing and tissue repairing. Unfortunately, angiogenesis is also a fundamental step in the growth of cancer tumours and in the tumoral metastasis. Recently, oncologists have suggested that the use of inhibitors of angiogenesis, an approach generically termed anti-angiogenesis, could prove effective in cancer treatment. In the present work, we consider anti-angiogenesis as a mathematical game between two players : activators of angiogenesis, willing to develop an efficient feeding network of blood vessels, and inhibitors, with a specific action on the tumour vasculature. We use a porous media model and criteria like as the pressure drop as approximation to the complex angiogenesis phenomenon. The strategies are angiogenic factors and inhibitor densities, so that we are in a topology design context. We define a static Nash game, for which we address the question of existence of an equilibrium. Numerical results illustrate how -theoretical- tumors develop multiple channels as an optimal response to optimal distribution of inhibitors.

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Blow-up estimates for some chemotaxis model

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It is well known that, for a large enough initial data, the solution to usual chemotaxis models blow up in finite time. This talk presents a way to estimate the rate of blow-up, using energy and energy dissipation. This is important in order to get stability estimates up to the blow-up time.

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Effect of Internal Viscosity on Brownian Dynamics of DNA Molecules in Shear Flow

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The results of Brownian dynamics simulations of a single DNA molecule in shear flow are presented taking into account the effect of internal viscosity. The DNA molecule is modeled as a bead-spring chain and the springs between two adjacent beads are assumed finitely extensible nonlinear elastic (FENE). A force balance on the chain leads to a stochastic differential equation governing the movement of each bead. The Euler method is applied to the solution of the model and the results for some differently disposed internal viscosities are discussed. The extensions for different values of strains are analyzed and comparison with the available experimental results is made to estimate the contribution of the effect.

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Dynamic and control of cell population : age structured model

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We address the following question: Can one sustain, on the basis of mathematical models, that for cancer cells, the loss of control by circadian rhythm favours a faster population growth? This question, which comes from the observation that tumour growth in mice is enhanced by experimental disruption of the circadian rhythm, may be tackled by mathematical modelling of the cell cycle. For this purpose we consider an age-structured population model with control of death (apoptosis) rates and phase transitions, and two eigenvalues: one for periodic control coefficients (via a variant of Floquet theory in infinite dimension) and one for constant coefficients (taken as the time average of the periodic case).

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A simplified model of TCA cycle

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Mitochondria play an important role in energetic metabolism in producing a large part of cellular ATP. A central role in this metabolism is played by TCA cycle (also called Krebs cycle). TCA cycle has been extensively modelized since the pioneer work of Garfinkel. Contrary to previous works our aim is to derive a simple set of differential equations able to reasonably simulate the main features of this metabolic pathway in different tissues and in different situations. We present a simplified model of TCA cycle with differential equations using the recognized fact that TCA cycle can be split into two mini cycles of enzymatic reactions. The modelling of the ATP production in the mitochondria also requires a minimal model of the enzymes of the respiratory chain. Our way to create such a system is described precisely. Under some assumptions, we prove the existence of a unique non negative solution and of a steady state. Numerical simulations are presented : it allows the simulation of normal and pathological functioning with in this latter case accumulation of metabolites as observed in some cases of mitochondrial diseases. It can also exhibit oscillations, which could be at the basis of physiological pulsatory mechanisms.

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Contribution to the study of periodic chronic myelogenous leukemia

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Leukemia is a progressive, malignant disease of the blood-forming organs, characterized by uncontrolled proliferation of immature and abnormal white blood cells in the bone marrow, the blood, the spleen, and the liver.

It is classified clinically on the basis of the character of the disease (chronic or acute), the type of cells involved (myeloid, lymphoid, or monocytic), and the increase or lack of increase in the number of abnormal cells in the blood (leukemic or aleukemic). In this presentation we focus our attention on chronic myelogenous (or myeloid) leukemia (CML) and more specifically on its periodic form (PCML). We propose different cell cycle models of pluripotential stem cells to understand the origin of the long period oscillations of blood cell levels observed in PCML. We show the existence of long periods when the hill coefficient of the cell cycle regulation function is infinite. Then, we claim that it is possible to prove a similar result in the most general case where the hill coefficient is finite.

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Mathematical modelling of apotosis

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Programmed cell death or apoptosis is a highly conserved pathway, which is functional in all higher organisms. This mechanism eliminates deficient cells without damaging neighbouring tissue cells and is therefore recommended for tissue maintenance. However, deregulation of apoptotic signalling plays an essential role in various diseases, and insufficient apoptosis leads to cancer. Most of the molecular mechanisms of the apoptosis have been elucidated during the last years. However, in spite of an always-increasing number of works on the subject, there is not any experimental approach to know all the modifications of the molecular concentrations, occurring in the apoptotic process. Then, mathematical modelling become essential tools to understand the global behaviour of this pathway. Within this context, the goal of this work is to model, the different critical steps in the apoptosis signalling pathways, specifically in the initiation of the Fas mediated cell death signalling and in the role of mitochondria. Indeed, the understanding of these aspects is crucial for the development of cancer treatment strategies. In both cases, the cascade of the kinetic reactions involves a large number of enzymes. For these reasons, we have chosen to use a system of ordinary differential equations to describe the pathways.

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Computional modeling of avascular tumor growth

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We present a multiscale model of avascular tumor growth. This model takes the cell-cycle into account and several environmental conditions which could affect tumor growth (namely hypoxia, overcrowding). For this matter, we describe the evolution of the proliferative and quiescent phases through several PDEs. The environment appears as a source term and as boundary conditions in these equations. To model hypoxia, we also have to compute the evolution of the oxygen distribution through a diffusion equation. Furthermore, through a level-set formulation, this model can render the mechanical effects of an elastic membrane surrounding the cancer cells. The hydrodynamic variables (fluid velocity and pressure) are obtained as solution of a Stokes equations. The elastic force due to the membrane we have just mentionned appears as a source term in these equations (and is vanishing outside the smoothed interface). We will also present the numerical methods used to discretize this model in three dimensions. With these numerical schemes, we will finally show various numerical experiments highlighting the accuracy of the model.

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