Thursday, July 26th, 14:00 **Room: C8.2.10**

MINISYMPOSIUM

TOPICS ON DRUG RESISTANCE IN CANCER

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Minisymposium Keywords: Cancer, Cell population dynamics, Therapy, Drug resistance, Optimal control

Drug resistance in cancer cell populations is still a major pitfall of most anticancer chemotherapies in the clinic. Eliciting the dynamics of its emergence and evolution (reversible or not, epigenetic stress response or established mutation, with tumour bet hedging or not) has been in recent years the object of many biological observations in cell cultures and mathematical models to understand and predict them. Stepping from them, methods of optimal control have been proposed to help designing innovating therapeutic strategies in oncology. We present such aspects of mathematical modelling, analysis and control that take into account these biological observations, ultimately aiming at optimising cancer treatments in the clinic.

Minisymposium: Topics on drug resistance in cancer

GROWTH SPEED OF HETEROGENEOUS TUMOURS : A COMPETITION-DIFFUSION SPREADING RESULT

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Keywords: Tumour heterogeneity, Cell population dynamics, Co-evolution, Competition-diffusion.

The presence inside a single tumour of different phenotypes can be a source of treatment failure. We propose a model of competition-diffusion of two tumoral cells species, invading empty space while competing for space and nutrients. We show that the global behaviour of the tumour depends on the Fisher-KPP speeds of each species alone. A consequence of this is that reducing the proliferating rate of the dominating species can favour the emergence of the second species outside of competition, thus maintaining the tumour growth rate constant.

Minisymposium: Topics on drug resistance in cancer

ECOLOGICAL CONTEXT OF COEVOLUTIONARY DYNAMICS BETWEEN CANCER AND THERAPEUTIC INTERVENTION

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Keywords: Intratumour heterogeneity, Tumour progression, Clonal evolution, Phenotypic switching, Evolving therapeutic strategies.

Many contemporary ideas about the nature of cancer are deeply connected with its evolutionary nature at the somatic level [1]. Notwithstanding their stylised and conceptual level, the evolutionary attributes become an integral part of the mathematical models of cancer as well as the models of therapeutic interventions [2] with potentially high adaptive power [3]. Our contribution provides an overview of possible evolutionary-based anticancer therapeutic strategies. Nonlinear multidimensional filtering [4], feedback-generated therapies that define various therapeutic intervention targets in combination with the terms describing phenotypic switching dynamics [5] and competitive inter-clonal processes have been involved into proposed conceptual model based on the systems of ordinary differential equations. Preliminary simulations reveal an interesting issue of the time variability of an adaptive therapeutic treatment [3] that induces a tumor-modifying microenvironment allowing the evolutionary advantage of a phenotypic switching mechanism [6]. The main findings based on the simulations deal with the issues concerning evolutionary time scales, progression of cancer and phenotypic heterogeneity.

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Minisymposium: Topics on drug resistance in cancer

ANTI-CANCER THERAPY: BLAZING THE TRAIL WITH MELANOMA

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Keywords: Cancer therapeutics, Drug resistance, Melanoma, Targeted therapy, Immunotherapy.

Interfering with the intrinsic oncogenesis and the tumor microenvironment in order to eliminate cancer cells was one of the most attractive and exciting goals in oncology. After decades of deceived efforts and disappointing clinical trials, this long lasting objective was finally reached in 2011 with patients suffering from metastatic melanoma, which is one of the most challenging situations in oncology. These innovative treatments, based on the blockade of oncogenic signaling and physiological brake of the immune system, was the first specimen of a new generation of drugs involved in two main therapeutic fields, including targeted therapy and immunotherapy. Along with these new concepts, re-evaluations of assessing the efficacy of the drugs, managing the new challenges of drug resistance are emerging and leading to a global revolution of the field of cancer treatment.

Minisymposium: Topics on drug resistance in cancer

MATHEMATICAL MODELLING OF EMERGENT GENE EXPRESSION

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Keywords: Phenotype selection, Antibiotherapy, Cancer chemotherapy, Multi-scale modelling, Drug resistance.

A number of recent studies have shown that natural selection occurs not only on genes (on genetic variation), but also at the level of gene expression (on heritable phenotypic variation). Emergent gene expression can be defined as the selective upregulation of expression of a fitness conferring gene when a cell population is placed in a stressful environment. For example, if cancer cells are exposed to chemotherapy and it is known that a certain gene product (such as that of MDR1) is required for increased cell division, low expression will slow down division, giving time for expression levels to build up stochastically, reinforcing the presence of high-expressing cells. Feedbacks between gene expression levels, metabolic and cell division rates therefore drive expression higher than expected from hard-wired network regulation alone. Fit epigenetic states with upregulated antibiotic resistance genes or certain oncogenes are thus actively selected, in the absence of hard-wired molecular signalling or genetic variation. In this talk I will present a multiscale mathematical model of the cell that links stochastic gene expression to cell growth and partitioning/dilution. I will then go on to present the minimal ingredients required for emergent gene expression to take place as well as discussing applications to antibiotic resistance and chemotherapeutic resistance and strategies for overcoming these resistance mechanisms.

References

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