Interdisciplinary Symposium on Signals & Systems fc Medical Application

Program and abstracts of ISSSMA workshop on Modeling and analysis of cancer cell dynamics

Session 2.1: Cancer modelling with new insight on therapeutics
June 3rd, 11:00-12:30, room 201. Chair: M. Adimy

Pierre Hirsch - *St Antoine Hospital, Paris, (France)*

Acute myeloid leukaemia: clinical and biological aspects. What clinicians can expect from mathematics?

Acute myeloid leukaemia (AML) is a cancer developed from hematopoietic stem cells, and leads to normal bone marrow failure. Since 1960s, treatments are based on chemotherapy (association of cytosine arabinoside and anthracyclines) and bone marrow transplantation. However, in nearly 50 % of cases, these treatments are not efficient enough to cure the patients. This can lead to primary resistance or to relapse. Mechanisms of this chemo-resistance are partially known. For example ABC-proteins expression can lead to drug-efflux from the cancer cells and to direct resistance to cytotoxic drugs, or bone marrow micro-environment can protect leukaemia iniating cells from chemotherapy.
Moreover, these last 20 years, many molecular abnormalities associated to leukaemo-genesis have been described. Basically the association of only two molecular events is sufficient to lead to AML: the first event leads to an increase in proliferation by activation of tyrosine kinases pathway, and the second one to a blockade of cell maturation mainly by mutation of transcriptions factors. The better understanding of molecular mechanisms of leukaemo-genesis has led to the development of targeted therapy, including inhibitors of tyrosine kinases. These last treatments are still in early development phases, and are barely used in association of other treatments.
The development of mathematical models of normal and leukaemic haematopoiesis, including proliferation and differentiation variables could be very helpful for clinicians, in order to better understand mechanisms of bone marrow failure associated with leukaemia development, and to guide new treatments administration. From these models, strategies of drug administration, and optimal timing to obtain the best efficacy and to limit toxicity could be developed. Mathematics could be a way to overcome clinical resistance to standard treatments.

Doron Levy - *University of Maryland (USA)*

Mathematical models for tumor-immune interactions and their applications

In this talk we will describe our recent mathematical models of the interaction between the immune system and cancer focusing on two specific components: TGF-beta and B7-H1. TGF-beta is an immunoregulatory protein that contributes to inadequate antitumor immune response in cancer patients. The surface protein B7-H1 is found on carcinomas of the lung, ovary, colon and melanomas but not on most normal tissues. We develop mathematical models in order to gain insight on into the cooperative interaction between anti- TGF-beta and vaccine treatment, and to gain insights on the mechanisms that control the interaction between cytotoxic T cells and tumor cells. This is a joint work with Amanda Galante, Shelby Wilson, and Koji Tamada.

Peter Kim - *University of Sydney (Australia)*

A mathematical model of oncolytic virotherapy

Oncolytic virotherapy is new strategy for cancer treatment that relies on injecting tumors with genetically-engineered viruses that selectively infect and kill tumor cells and release immunostimulatory signals that recruit a concurrent anti-tumor immune response. Recent experiments with engineered oncolytic adenovirus have caused substantial reduction in growth rates of tumors in mice; however, the tumors always eventually relapse. By fitting time series data to mathematical models, we attempt to elucidate the underlying cancer-virus and cancer-immune dynamics to clarify the strengths and limitations of oncolytic virotherapy and suggest improved methods of treatment.

Session 2.2: Modelling of Acute Myeloid Leukemia

June 3rd, 16:30-18:00, room 201. Chair: C. Bonnet

Mostafa Adimy - *Inria Grenoble/Rhone-Alpes (France)*

Discrete maturity-structured model of cell differentiation with application to acute myelogenous leukemia

We propose and analyze a mathematical model of hematopoietic stem cell dynamics that takes into account a finite number of stages in blood production, characterized 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). The resulting model is a system of age-structured partial differential equations that reduces to a system of delay differential equations, with several distributed delays. We investigate the existence of positive and axial steady states for this system, and we obtain conditions for their stability. Numerically, we concentrate on the influence of variations in differentiation coefficients on the behavior of the system. In particular, we focus on applications to acute myelogenous leukemia, a cancer of white cells characterized by a quick proliferation of immature cells that invade the circulating blood. We show that a blocking of differentiation at an early stage of immature cell development can result in the over-expression of very immature cells, with respect to the mature cell population.

Anna Marciniak-Czochra - *University of Heidelberg (Germany)*

Mathematical modeling of stem cells-initiated cancer development

Self-renewal is a constitutive property of stem cell behavior. Testing the cancer stem cell hypothesis requires investigation of the impact of self-renewal on cancer expansion. To understand better this impact, we propose a mathematical multi-compartment model describing time dynamics of healthy and cancer cells. The model includes two nonlinear feedback mechanisms regulating stem- and progenitor cell proliferation and differentiation. Our study reveals different scenarios of possible cancer initiation and provides qualitative hints to possible treatment strategies.

The proposed model is applied to myelodysplasia (MDS) which is an important example of a malignant disease with hypothetical stem cell origin. In agreement with experiments, we further assume that expansion of dysplastic cells impairs self-renewal potential of bone marrow cells and that cell proliferation is enhanced if mature cell counts decrease. Numerical and theoretical results indicate that this scenario is sufficient for expansion and maintenance of myelodysplastic cells, even in case of slow malignant cell proliferation. Model simulations are compatible with observed changes in bone marrow cellularity and onset of peripheral manifestations during human life span. The obtained results stress the importance of self-renewal in cancer dynamics and allow to conclude that slowly proliferating cancer cells are in principle able to explain clinical dynamics and observations such as treatment resistance.

Hitay Ozbay - *Bilkent University (Turkey)*

A System Theoretic Analysis of Cell Dynamics in AML

In this presentation a mathematical model of cell dynamics in acute myelogenous leukemia (AML) will be considered. The model consists of several sub-systems involving distributed delays and static nonlinearities in the form of Hill functions. Equilibrium points of this nonlinear system are determined, and conditions under which these equilibrium points are locally (or globally) stable are derived. Results are illustrated with time domain simulations.

Session 2.3: Cell cycle and clock modelling for cancer 1

June 4th, 10:30-12:00, room 201. Chair: F. Lévi

Claude Gérard and A. Goldbeter - *ULB Brussels, (Belgium)*

The cell cycle and the circadian clock: Dynamics of two coupled cellular rhythms

This presentation will focus on the dynamics of the cell cycle and its entrainment by the circadian clock. We will first discuss a detailed computational model for the network of cyclin-dependent kinases (Cdks) that controls the dynamics of the mammalian cell cycle. The model contains four Cdk modules regulated by phosphorylation-dephosphorylation, association with Cdk inhibitors, and cyclin synthesis or degradation. Growth factors trigger the transition from a quiescent, stable steady state to self-sustained oscillations in the Cdk network. These oscillations correspond to the repetitive, transient activation of cyclin D/Cdk4-6 in G1, cyclin E/Cdk2 at the G1/S transition, cyclin A/Cdk2 in S and at the S/G2 transition, and cyclin B/Cdk1 at the G2/M transition. The model accounts for major properties of the mammalian cell cycle such as continuous cell cycling in the presence of suprathreshold amounts of growth factor, control of cell cycle progression by the balance between antagonistic effects of the tumor suppressor pRB and the transcription factor E2F, existence of a restriction point in G1, and endoreplication. The model for the mammalian cell cycle shows how the regulatory structure of the Cdk network results in its temporal self-organization, leading to the repetitive, sequential activation of the four Cdk modules that brings about the orderly progression through the cell cycle phases. We then will show that the coupling of the cell cycle to the circadian clock can lead to synchronization of these two major cellular rhythms. Entrainment of the cell cycle by the circadian clock may occur through several modes of coupling based on the circadian control of cell cycle proteins such as cyclin E, kinase Wee1, and the Cdk inhibitor p21.

Jean Clairambault – *INRIA & LJLL-UPMC (France)*

Theoretical drug delivery optimisation using physiologically structured cell population models

With the aim to optimise combinations of anticancer drugs, I will present models of proliferating cell dynamics coupled via external control targets, representing different drug effects, with pharmacological models of a few number of drugs that are of classical use in the clinic of cancers.

Cell population dynamic models are either systems of age-structured PDEs for the division cycle in cell populations or integro-differential equations structured in a continuous phenotype representing evolution towards drug resistance. Pharmacological models are ODEs describing the fate of drugs in living organisms.

Numerical optimisation algorithms used to design optimal combined drug delivery schedules in cell populations or at the whole body level, under toxicity or drug resistance constraints, will then be sketched."

François Fages - *INRIA (France)*

A bidirectionnal coupled model of the cell cycle and the circadian clock

It has been observed that the circadian clock has an effect on the cell cycle, and at the molecular level, that the clock genes regulate the synthesis of Wee1, an inhibitor of the maturation promotion factor necessary to mitosis. Models of the cell cycle and the circadian clock coupled through Wee1 exhibit time gating for mitosis and cell cycle period doubling phenomena. In this talk, we consider a reverse effect of the cell cycle on the circadian clock, through the inhibition of synthesis during mitosis. We present a bidirectional coupled model fitted on C5Sys project data and its predictions concerning the possible perturbations of both cycles.

Session 2.4: Cell cycle and clock modelling for cancer 2

June 4th, 15:30-17:00, room 201. Chair: F. Fages

Franck Delaunay - *IBV, Univ. Nice (France)*

Visualizing the circadian and cell cycle oscillators

For many years, the analysis of highly dynamic biological processes such as the circadian clock and the cell cycle have relied on biochemical techniques, endpoint measurements in fixed cells, bulk analysis of cell populations and chemical or physical synchronization methods. Fluorescent biosensors have now become an approach of choice in cell biology to study such processes because when coupled with time lapse video cell imaging they can produce high resolution time series at the single cell level in long term experiments. The application of this technology to the analysis of cell cycle and circadian clock dynamics in individual cells, in combination with dedicated cell tracking and data processing tools will be presented and discussed.

Filippo Tamanini - *Erasmus University Medical Center (NL)*

Changes in clock performance of fibroblasts upon contact with breast cancer cells

The molecular clock is a cell autonomous mechanism driving 24 hours oscillations in gene expression. Although cell communication through gap junction and electrical activity is an important aspect of circadian synchronization between SCN neurons, this mechanism is not present in peripheral cells. In fact, single cell imaging has demonstrated that the clock of fibroblasts is independent from period and/or phase of neighboring cells.
In this study we asked whether there is clock communication between breast cancer cells and fibroblasts. For that we first studied the circadian performance of a set of 18 human breast cancer cell lines and identified two cell lines with unusually long (MM453, 30h) and short (MM231, 20h) periods. By culturing those cancer cells in physical contact with mouse NIH3T3 fibroblasts (23h) and human primary fibroblasts (25h) expressing a Per2-Luciferase reporter we observed changes in phase and period of their oscillations that were dependent on the clock characteristic of the co-cultured cancer cells. Next we performed single cell imaging of NIH3T3 cells expressing the clock reporter RevErb-VENUS in presence or absence of MM453, and observed a cancer-dependent lengthening of period as well as unexpected clock synchronization of fibroblasts in contact with cancer cells.
Translated in vivo, our data suggest that breast cancer cells may induce alteration of circadian homeostasis of normal tissues, and in turn this may interfere with the development and/or spreading of the cancer cells.

Ali Mohammad-Djafari – *CNRS-L2S (France)*

Multicomponent and multivariate data analysis and processing in cancer biology

To understand the cancer, biologists and physicists study the cells in different experiences: individual in vitro, cells population in vitro and in vivo in small animals and finally in humans. For these studies, they measure many data: genes expressions, proteins, hormones, temperature, activity level, etc. There are great number of variables, time series, signals, images, videos, etc. All these data are in general multi components and multi variates. We have then to analyze them, to model them and to extract knowledge from them.

In terms of data and signal processing, between the main questions to answer, we have:

- *What is the intrinsic dimension of the data? This needs methods related to Dimensionality Reduction (DR).*
- *What are the main factors? This needs methods related to Factor Analysis (FA), Principal Components Analysis (PCA) and Independent Components Analysis (ICA).*
- *What are the main factors to be able to discriminant some labeled data? This needs methods related to Discriminant Analysis (DA).*
- *What are the minimum number of variables needed to keep to extract the same amount of information from the data? This needs methods related to variables selection methods. We may mention some of them such as Sparse FA, Sparse PCA, Sparse LDA.*
- *Can we cluster or classify those data? (Unsupervised and Supervised classification).*
- *Can we measure the dependencies between variables and show a graph of these dependencies? This needs the criteria to measure the dependencies between variables such as Pearson, Spearman correlations or Kendhal tau or more generally Copulas and the graph theory and graph similarity measures.*

In this talk, I will present some of these methods and some of the results we obtained and discuss the limitations of the present methods and what we need to do next.