MINISYMPOSIUM

MATHEMATICAL MODELING OF LEUKEMIA AND MYELOPROLIFERATIVE NEOPLASMS

Organizer
Morten Andersen
Roskilde University
Denmark
moan@ruc.dk

Co-organizer
Thomas Stiehl
Heidelberg University
Germany
thomas.stiehl@iwr.uni-heidelberg.de

Leukemias and myeloproliferative neoplasms (MPN) are closely related diseases of the blood forming (hematopoietic) system. Major subtypes of both categories are stem cell driven disorders that result in excessive production of cells with healthy, dysplastic or cancerous phenotypes. This minisymposium aims to bring together clinicians and mathematical modelers investigating disease evolution of leukemias and MPN.

A complex network of regulatory feedbacks controls the response of the hematopoietic system to perturbations such as blood loss, immune reactions or chronic inflammation and it mediates the competition between healthy and mutated stem cell clones. The resulting dynamics is nonlinear, and a precise understanding of hematopoiesis and its diseases remains challenging. The focus of our minisymposium is to better understand the interplay of regulatory signals, multiclonal dynamics and treatment interventions in leukemias and myeloproliferative neoplasms.

The talks of this minisymposium cover a broad range of regulatory signals reaching from feedback mechanisms that stabilize physiological homeostasis to signalling in immune response and chronic inflammation. There is evidence that all of them contribute to pathogenesis and disease progression. Different mathematical approaches including dynamical systems, integro-differential equations, Markov chains and individual based models will be used to study how pathological and physiological feedbacks impact on clinically relevant phenomena such as mutant cell expansion, clonal evolution or treatment response.

There is a huge potential in applying mathematical modelling, dynamical systems techniques and parameter estimation procedures in order to understand fundamental disease mechanisms and develop treatment strategies. In combination with clinical or experimental data mathematical models provide a framework which allows rigorous understanding of the implications of multiple feedback loops on system dynamics and to discriminate between different hypotheses. Mathematical models can provide insight to how the course of the disease and the response to treatment may be altered by increased sensitivity of cell clones to feedback signals, escape from regulatory cues or constitutive activation of signaling pathways. In addition, a mathematical model based on physiological mechanisms can pinpoint which lacking experiments are the most crucial to perform in order to obtain data to estimate system parameters reliably.

Minisymposium: Mathematical modeling of leukemia and myeloproliferative neoplasms

MODELING FEEDBACK SIGNALS IN ACUTE LEUKEMIAS: BIOLOGICAL INSIGHTS AND CLINICAL APPLICATIONS

Thomas Stiehl

Thomas.Stiehl@iwr.uni-heidelberg.de

Institute of Applied Mathematics, Heidelberg University, Heidelberg, Germany

Joint work with Anna Marciniak-Czochra (Institute of Applied Mathematics, Heidelberg University, Heidelberg, Germany) and Anthony D. Ho (Department of Hematology and Oncology, Heidelberg University Hospital, Heidelberg, Germany)

Keywords: Mathematical modeling, Leukemia, Feedback signals, Stem cell, Cancer evolution.

The first part of this talk will give a biological overview of leukemias and myeloproliferative neoplasms. Open biological and medical questions will be summarized. It will be outlined how mathematical modeling can contribute to a better understanding of disease mechanisms and treatment approaches. The second part of the talk focuses on mathematical models of acute leukemias. Acute leukemias are characterized by malignant cell expansion in the bone marrow and out-competition of healthy blood cell formation (hematopoiesis). For a better understanding of this process it is crucial to take into account that hematopoiesis is regulated by a nonlinear network of feedback signals, so called cytokines. Biological experiments suggest that in some patients leukemic cells require stimulation by feedback-signals to expand (cytokine-dependent leukemia) whereas in other patients leukemic cells expand independently of feedback signals (cytokine-independent leukemia). The clinical impacts of this finding are not well understood. We establish a set of nonlinear multi-compartment models describing time evolution of healthy and leukemic cell populations in presence of different regulatory signals. On the basis of model analysis, computer simulations and patient data we investigate the following questions:

- How does the response of leukemic cells to regulatory signals impact on the course of the disease and the patient prognosis?
- Can mathematical models help to discriminate between patients with cytokine-dependent and cytokine-independent leukemia?
- How do patients with cytokine-dependent and cytokine-independent leukemic cells respond to treatment? Can we identify patients with a high risk of treatment failure?

Minisymposium: Mathematical modeling of leukemia and myeloproliferative neoplasms

HEMATOPOIETIC STEM CELL DYNAMICS AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

David Dingli

Dingli.David@mayo.edu

Division of Hematology and Department of Molecular Medicine, Mayo Clinic, Rochester, MN, USA

Joint work with Nathaniel Mon Père (Interuniversity Institute of Bioinformatics in Brussels ULB-VUB & MLG, Département d'Informatique, Université Libre de Bruxelles, Brussels, Belgium), Tom Lenaerts (Interuniversity Institute of Bioinformatics in Brussels ULB-VUB & MLG, Département d'Informatique, Université Libre de Bruxelles & AI lab, Computer Science Department, Vrije Universiteit Brussel, Brussels, Belgium) and Jorge M. Pacheco (Centro de Biologia Molecular e Ambiental, Universidade do Minho & Departamento de Matemática e Aplicaçōes, Universidade do Minho, Braga, Portugal & ATP-group, Porto Salvo, Portugal)

Keywords: Mathematical modeling, Hematopoietic stem cell, Paroxysmal nocturnal hemoglobinuria.

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell (HSC) disorder characterized by intravascular hemolysis and a high risk of thrombosis. Its origin has been traced to a somatic mutation in the PIG-A gene within HSC that interferes with the synthesis of glycosylphosphatidylinositol (GPI) which is an important anchor for membrane proteins. GPI deficiency leads to loss of significant reduction in the surface expression of many proteins including CD55 and CD59 that prevent complement activation and red cell destruction. However, to date the exact mechanism of how this mutant clone expands in size to contribute significantly to hematopoiesis remains under debate. One hypothesis posits the existence of a selective fitness advantage for PIG-A mutated cells due to an immune mediated attack against normal HSC, but the evidence supporting this hypothesis is inconclusive. An alternative (and simpler) explanation attributes clonal expansion to neutral drift, in which case selection neither favors nor inhibits expansion of PIG-A mutated HSC.

Methods: We studied the implications of the neutral drift model by numerically evolving a Markov chain for the probabilities of all possible outcomes, and investigated the possible occurrence and evolution, within this framework, of single and multiple independently arising mutant clones within the HSC pool.

Results: The predictions of the model agree well with the known incidence of the disease and the average age at diagnosis. Notwithstanding the slight difference in clonal expansion rates between our results and those reported in the literature, our model neatly reproduces the observed relative stability of clone size when averaging multiple cases. The probability of a patient harboring a second clone in the HSC pool was found to be extremely low ($\sim 10^{-8}$). Thus our results suggest that in clinical cases of PNH where two independent clones of mutant cells are observed, only one of those is likely to have originated in the HSC

pool. The probability of 'spontaneous' clonal elimination in the absence of therapy is also predicted. We compare our results with large observation studies available in the literature.

Conclusions: Our neutral drift model based on first principles can accurately predict many of the salient features relating to the natural history of an acquired HSC disorder – PNH. This is the first example in medicine where neutral drift may be used to explain the dynamics of an uncommon disorder.

Minisymposium: Mathematical modeling of leukemia and myeloproliferative neoplasms

THE CANCITIS MODEL: A COUPLED LEUKEMIC-INFLAMMATORY RESPONSE.

Johnny T. Ottesen

Johnny@ruc.dk

Department of Science and Environment, Roskilde University, DK

Joint work with Morten Andersen (Roskilde University), Rasmus K. Pedersen (Roskilde University), Zamra Sajid (Roskilde University), Johanne Gudmand-Hoeyer (Roskilde University), Lasse Kjær (Zealand University Hospital), Vibe Skov (Zealand University Hospital), Niels Pallisgaard (Zealand University Hospital), and Hans Carl Hasselbalch (Zealand University Hospital),

Keywords: Leukemia and MPN diseases, Inflammation, Mathematical modeling, Patient specific, Dynamical sytems.

Inflammation triggers and drives leukemia and the related Myeloproliferative Neoplasm (MPNs) diseases through the innate immune system while leukemia and MPNs stimulates the inflammatory responds of adaptive immune system fighting the malign cells of the diseases. Where the two-way coupling of tumorous cancer and the adaptive immune system has drawn some attention during the last decades and inspired to immuno- and gene-therapy, leukemia and MPNs have been left unnoticed with respect to such coupling until recently. Furthermore, the two-way coupling of leukemia and MPNs on one side and the innate immune system on the other side is by the large left unstudied, e.g. with respect to treatments and preventive measures. We pose a novel 6D mathematical model of the development of leukemia and MPNs taking these two-way couplings into account and show that geometric singular perturbation theory suggests a reduction to a reduced 2D model suitable for many purposes and analysis. The model is validated against human data. As a result it follows that the innate immune response is crucial in the development and treatment of leukemia and MPNs as it affects the numbers, the location, and the stability properties of the steady states in state space. Finally, the model is used to show superiority of treatment with Interferon-alpha 2 versus Hydroxyurea and that early treatment is preferable. These findings are in good agreement with human data from the clinic.

Minisymposium: Mathematical modeling of leukemia and myeloproliferative neoplasms

THE ROLE OF THE AUTOLOGOUS IMMUNE RESPONSE IN CHRONIC MYELOGENOUS LEUKEMIA

Doron Levy

dlevy@umd.edu

Department of Mathematics, University of Maryland, College Park, US

Keywords: Leukemia, Immune response, Mathematical modeling.

Imatinib and other tyrosine kinase inhibitors (TKI) have improved treatment of chronic myelogenous leukemia (CML); however, most patients are not cured. Deeper mechanistic understanding may improve TKI combination therapies to better control the residual leukemic cell population. In analyzing patients' data we found that many patients who otherwise responded well to imatinib therapy still showed variations in their BCR–ABL transcripts. In this talk we will present mathematical models that suggest that the autologous immune response may explain the observed oscillations in the BCR–ABL transcripts. Applications to immunotherapy will be discussed.