MINISYMPOSIUM

HEMATOPOIESIS AND ITS DISEASES

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The human hematopoietic system produces more than 10^{11} blood cells per day. Despite the tremendous production rate and significant maturation delays in the system, hematopoiesis proceeds flawlessly for nearly all individuals over many decades, implying the existence of finely tuned control mechanisms and feedback loops. Most of these processes occur in the bone marrow where direct real time observation is difficult, and consequently there has been a long history of mathematical modelling of hematopoiesis [1].

Because hematopoiesis is so well regulated usually, it is necessary to consider the system away from homeostasis to gain insight into the control mechanisms. This occurs in diseases such as leukemia and cyclic neutropenia, and in subjects undergoing chemotherapy. These scenarios are particularly interesting to model because mathematical insights may have clinical implications.

In this minisymposium four mathematical models of hematopoiesis will be presented. The first three focus on the production of blood cells and the dynamics of the hematopoietic production system in three different but related scenarios. In the first talk the production of neutrophils and its disruption by chemotherapeutic agents is modelled. The second talk presents a detailed mathematical study of the dynamics of a hematopoietic stem cell (HSC) model, while in the third talk the clonal selection of HSCs in acute leukemia is modelled.

In modelling the production of hematopoietic cells, it is important not to lose sight of the function of the mature cells including to carry oxygen and fight infection. These functions are typically tied to cell production by feedback loops, such as in erythropoiesis where hypoxia stimulates the production of erythropoietin which in turn stimulates the production of more red blood cells. Whereas production of cells can be considered to take place in the 'bone marrow' without further consideration for spatial issues, when white blood cells fight infection or platelets cause clotting, these processes occur in some localised tissue and spatial effects become important. The final talk of this session will present such a model for the role of platelets in blood coagulation.

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MODELLING GRANULOPOIESIS WITH STATE-DEPENDENT DELAYS

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Keywords: Granulopoiesis, State-dependent delay differential equations, Neutropenia, Granulocyte Colony-Stimulating Factor.

The production of white blood cells is modelled from hematopoietic stem cells (HSCs) through to circulating neutrophils [2]. Granulocyte Colony-Stimulating Factor (G-CSF) is the main cytokine that regulates this process. A physiologically realistic model of G-CSF kinetics is included which incorporates the binding and internalisation G-CSF at receptors on mature neutrophils. G-CSF is used to regulate the differentiation rate of HSCs, the proliferation rate during mitosis, the maturation time, and the rate at which mature neutrophils are released into circulation from the bone marrow. The variable maturation time results in a model for granulopoiesis as a system of state-dependent delay differential equations. We discuss the application of this model to study subjects undergoing chemotherapy or suffering from cyclical neutropenia.

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AGE-STRUCTURED AND DELAY DIFFERENTIAL-DIFFERENCE MODEL OF HEMATOPOIETIC STEM CELL DYNAMICS

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Keywords: Age-structured partial differential equations, Delay differential-difference system, Stability switch, Hopf bifurcation, Hematopoietic stem cells.

We investigate a mathematical model of hematopoietic stem cell dynamics. We take two cell populations into account, quiescent and proliferating one, and we note the difference between dividing cells that enter directly to the quiescent phase and dividing cells that return to the proliferating phase to divide again. The resulting mathematical model is a system of two age-structured partial differential equations. By integrating this system over age and using the characteristics method, we reduce it to a delay differential-difference system, and we investigate the existence and stability of the steady states. We give sufficient conditions for boundedness and unboundedness properties for the solutions of this system. By constructing a Lyapunov function, the trivial steady state, describing cell's dying out, is proven to be globally asymptotically stable when it is the only equilibrium. The stability analysis of the unique positive steady state, the most biologically meaningful one, and the existence of a Hopf bifurcation allow the determination of a stability area, which is related to a delay-dependent characteristic equation. Numerical simulations illustrate our results on the asymptotic behavior of the steady states and show very rich dynamics of this model. This study may be helpful in understanding the uncontrolled proliferation of blood cells in some hematological disorders.

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CLONAL EVOLUTION AND EMERGENCE OF RESISTANCE IN ACUTE LEUKEMIAS: INSIGHTS FROM MATHEMATICAL MODELING

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Keywords: Acute leukemias, Clonal evolution, Mathematical modeling, Integro-differential equations, Selection and mutation.

Motivated by clonal selection observed in acute leukemias, we propose a range of mathematical models describing evolution of a multiclonal and hierarchical cell population. The models in form of differential and integro-differential equations are applied to study the role of self-renewal properties, growth kinetics and regulatory feedbacks during disease development and relapse. Effects of different time and space scales are investigated. It is shown how resulting nonlinear and nonlocal terms may lead to a selection process and ultimately to therapy resistance. Model results imply that enhanced self-renewal of cancer stem cells may be the key mechanism in the clonal selection process, while heterogeneity in the progenitor cell population does not play such a role in cancer evolution. The models allow also to study how mutation rates and phenotypic changes induced by mutations influence the genetic interdependence of the leukemic clones. The latter class of models is compared to clonal hierarchies reconstructed from patients' data using a novel algorithm. The results help to understand which phenotypes may be present at different times over the course of disease and how treatment affects the clonal evolution of the disease. Model-based interpretation of clinical data allows estimating parameters that cannot be measured directly. This may have clinical implications for future treatment and follow-up strategies.

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MODELING AND SIMULATIONS OF THE BLOOD COAGULATION PROCESS

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Keywords: Cell-based model, Coagulation cascade, Platelets, Blood slip velocity, Reaction-advection-diffusion equations.

Blood coagulation is an extremely complex biological process in which blood forms clots (thrombus) to prevent bleeding; it is followed by their dissolution and the subsequent repair of the injured tissue. The process involves different interactions between the plasma, the vessel wall and platelets with a huge impact of the flowing blood on the thrombus growth regularization.

Recent developments of the phenomenological cell-based models will be explained to demonstrate the current shift from the classical cascade/waterfall models and a short survey of available mathematical concepts used to describe the blood coagulation process at various spatial scales will be referred.

A mathematical model and some numerical results for thrombus growth will be presented in this talk. The cascade of biochemical reactions interacting with the platelets, resulting in a fibrin-platelets clot production and the additional blood flow influence on thrombus development will be discussed. This reduced model consists of a system of 13 nonlinear convection-reaction-diffusion equations, describing the cascade of biochemical reactions, coupled with a non-Newtonian model for the blood flow. The model includes slip velocity at the vessel wall and the consequent supply of activated platelets in the clot region.

The model captures disorders affecting the blood clotting system and provoking different abnormalities, such as thrombosis or bleeding. Numerical simulations related to clotting diseases will be shown.

References

[1] L. Pujo-Menjouet. (2016). *Blood Cell Dynamics: Half of a Century of Modelling*, Math. Model. Nat. Phenom. 11, 92–115.

[2] M. Craig, A.R. Humphries, and M.C. Mackey. (2016). *A mathematical model of granulopoiesis incorporating the negative feedback dynamics and kinetics of G-CSF/neutrophil binding and internalisation*, Bull. Math. Biol. 78, 2304–2357.