

Parallel Session
Cancer V

MATHEMATICAL MODELING OF BLOOD CANCER EVOLUTION

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Keywords: Blood cancer evolution, Inflammation, Mathematical modeling, Feedback signals, Clinical data.

We develop and investigate a mathematical model of the blood cancer type Philadelphia-negative myeloproliferative neoplasms (MPNs) [1]. The MPNs have a low incidence but a prevalence as lung cancer, since most MPN patients live with their MPNs for decades although with an increased morbidity burden due to a high risk of thrombosis and an increased propensity to develop autoimmune and chronic inflammatory diseases. Chronic inflammation is today considered to be a highly important pathogenetic factor for the development of MPNs – both as a trigger and a driver of clonal evolution. Several years prior to the typical MPN-diagnosis the patients also have an increased risk of cardiovascular, autoimmune and inflammatory diseases. During the last decade major breakthroughs have occurred in the understanding of the pathogenesis of the MPNs, the most important being the identification of the somatic clonal markers – JAK2, MPL and CALR.

We develop and investigate a mathematical model of the MPN dynamics coupling the time evolution of healthy and cancerous stem cells and mature cells and the innate immune response including inflammatory load. Due to several feedback signals e.g. stem cell niche interaction, and cytokine feedback on the stem cell dynamics, the governing differential equations are nonlinear. Parameters are estimated from the literature and from clinical data.

Due to a time scale separation of the governing equations, we then investigate a new reduced model with only two dynamic variables and four algebraic equations which approximate the original model very well. Results of the reduced models comprise 1) Formulation of identifiable, new parameters being combinations of the original parameters of the problem. 2) Dynamical variables accessible in typical, clinical measurements. 3) The reduction to two dimensions allows for a complete mathematical investigation of steady states and their stability. We provide conditions for a globally stable healthy state, MPN state or coexisting state with low number of cancerous cells. An approximate, closed form solution is derived. The results are compared to clinical data and implications for treatment strategies are discussed.

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**INVESTIGATION OF REASONS FOR TRANSIENT
ALLEVIATION OF TUMOR HYPOXIA DURING
ANTIANGIOGENIC THERAPY**

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Keywords: Tumor growth, Antiangiogenic therapy, Radiotherapy, Normalization window, Warburg effect.

Angiogenesis, i.e. the process of new blood vessels formation, has been marked as one of the major hallmarks of cancer [1]. Excessive production of angiogenic factors by tumor cells, most important of which is vascular endothelial growth factor (VEGF), leads to formation of chaotic microvasculature networks with abnormal structure of capillaries. Anti-VEGF therapy, as well as other types of antiangiogenic therapy, results in so-called maturation of capillaries, i.e., brings them to physiologically normal state, and ceases formation of new capillaries, that ultimately results in significant decrease of nutrients inflow to the tumor. However, in several experiments on certain mouse tumor models is has been demonstrated, that antiangiogenic treatment can lead to transient improvement in oxygen levels inside the tumor during first days of its administration [2, 3]. This discovery is of great medical importance, since it provides an opportunity to increase the effectiveness of consequent radiotherapy, which depends on concentration of oxygen as main radiosensitizer. In works on the topic, this phenomenon has been explained by transiently enhanced tumor perfusion, caused by result of capillaries maturation, and leading to increase in oxygen inflow into the tumor. However, changes in tumor perfusion haven't been always directly measured in relevant works, moreover, antiangiogenic therapy has been demonstrated to have ambiguous effect on tumor perfusion both in mouse tumor models and in clinics [4, 5]. Herein, we suggest that transient alleviation of tumor hypoxia may manifest itself even under unchanged tumor blood flow, being caused by the decrease in tumor oxygen consumption rate due to the reduction of tumor proliferation level, caused by nutrient shortage in result of antiangiogenic treatment.

We illustrate our hypothesis via the means of mathematical modeling. The model in use is a spatially-distributed model of reaction-diffusion-convection type. One of its prominent features is simultaneous account of two basic nutrients, i.e., glucose and oxygen, with detailed consideration of their inflow and consumption, which is crucial for the phenomenon

under study. We investigate the influence of the model parameters on oxygen dynamics inside the tumor while neglecting blood flow alterations in result of capillaries maturation; we demonstrate that transient improvement of tumor oxygenation takes place in a wide range of physiologically justified values of parameters; also we identify the main factors that determine oxygen dynamics during antiangiogenic therapy. The obtained results provide the basis for further search for optimization of combined antiangiogenic and radiotherapy.

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**PREDICTING OBSERVED PATIENT RESPONSES TO A
SHORT-PEPTIDE CANCER VACCINE VIA CLINICAL
TRIAL SIMULATIONS**

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Keywords: Immunology, Oncology, T-cell, Vaccination, Virtual clinical trial.

In this talk, I will present a simulation of the clinical trial, IMA901, a cancer vaccination study in which 9 ‘short’ peptides highly expressed by renal cell carcinomas (RCC) were injected into the dermis of patients with RCC. In the real trial, it was found that most patients produced immune responses to only one or none of these peptides, and that no patient responded to more than three. Considering the differences between patients, we hypothesise that these results are determined by the amount of administered peptide delivered by specialised innate immune cells (dendritic cells) in lymph nodes, the number of interacting adaptive immune cells (T-lymphocytes) in the lymph nodes, and the timescales involved.

We developed a mechanistic agent-based model of immune activation in the lymph node that quantifies the trade-off between these variables. Two simulated types of immune cells perform an off-lattice random walk until they interact, whereupon there is a chance of immune activation. One of the cell types presents peptides that its receptors bound to in the dermis. I will show that when immune activation depends on the amount of presented peptide, the critical variable that determines immune activation following short-peptide vaccination is the off-rate of each distinct peptide from this cell type’s receptors. Clinical trial simulations based on this model successfully capture the range of observed IMA901 patient outcomes. I will use the biological/clinical insights derived from these simulations to suggest alterations to the clinical trial design that may have yielded enhanced patient response.

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INVESTIGATION OF METASTATIC CELL DOMINANCE PHENOMENON VIA MODELING OF TUMOR PROGRESSION

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Keywords: Tumor progression, Cell population dynamics, Age-structured model, Epithelial–mesenchymal transition, Metastatic cell dominance.

The classical approach in mathematical modeling of tumor growth and therapy regards tumor as a monoclonal population of cells, all of which have the same characteristics. This approach does not allow to correctly consider tumor progression, which severely limits its potential, since mutations due to genome instability is one of the general features of cancer [1]. This deficiency has led to emergence of more complicated models of tumor growth in which tumor cell population is structured by the parameter of age, which changes in time and quantitatively determines the features of cell behavior [2, 3].

We introduce a novel approach of tumor progression modeling, wherein cell aging is not considered, however, mutations of tumor cells are accounted for explicitly by the fact that division of a single cell results in birth of two new cells, which characteristics with a certain probability differ from that of a parent cell. We introduce a spatially-distributed model of tumor growth and progression in tissue, which relies on the abovementioned approach. We investigate the progression of initially monoclonal tumor, considering alterations of two cell characteristics, i.e., motility and proliferation rate, with mutations leading to simultaneous changes of opposite sign in values of parameters of daughter cells. Numerical simulations demonstrate that the outcome of tumor progression depends on the initial values of motility and proliferation rate. Under sufficiently low values for initial motility the tumor evolves towards increase in proliferation rate, i.e., the average proliferation rate of the colony increases. Under high initial motility the tumor ultimately becomes more motile, i.e., average motility of the colony increases, which corresponds to epithelial–mesenchymal transition, which is considered to be the necessary step for initiation of metastasis in cancer progression. We investigate the influence of different properties, including the rate of angiogenesis and administration of antitumor therapy, on the direction and speed of tumor progression.

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