Parallel Session

Cancer II

MODELING THE INFLUENCE OF COMPRESSIVE STRESSES ON THE EFFICACY OF ANTICANCER TREATMENTS

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Keywords: Mathematical Modeling, Tumor Spheroids, Mechanical Compression, Growth Inhibition, Drug Response.

Drug resistance is still one of the major causes of poor therapy outcomes in cancer. Chemotherapy agents are generally designed to target cells that are rapidly dividing, acting on specific cellular pathways that regulate cell replication. However, in many cancers there exists a low-proliferating cell population that can elude the action of these drugs, contributing significantly to treatment resistance. Notably, recent investigations have proposed that compressive stresses may act on solid tumors by hindering cell proliferation. Indeed, these mechanical stresses have been shown to induce growth inhibition by a mechanotransduction pathway that controls cell entrance in the replication stage. At the moment, only a few studies have investigated the influence of mechanical compression on the therapeutic efficacy of cancer treatments. In this work [1], we develop an existing mathematical model, based on porous media mechanics, which is able to account for the presence of mechanical stresses in solid avascular tumors. We introduce governing equations for the transport and uptake of a chemotherapeutic agent, which is assumed to target cell proliferation. Model equations are adapted for tumor spheroids, and the interactions between compressive stresses and drug action is investigated. Interestingly, we find that the variation in tumor spheroid volume, caused by the presence of a drug that targets cell proliferation, is significantly influenced by the compressive stress levels in the cell aggregate. Our results suggest that mechanical compression in the tumor may compromise the efficacy of proliferation-targeting chemotherapeutic agents. Indeed, a therapy dose that is effective in reducing the tumor volume in stress-free conditions may not perform equally well in a mechanically compressed environment.

References

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STRUCTURE AND DYNAMICS OF A GENE REGULATORY NETWORK DRIVING HEPATOCELLULAR CARCINOMA

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Keywords: Mathematical Modelling, Gene Regulatory Network, Principal Components Analysis, Hepatocellular Carcinoma.

Hepatocellular carcinomas show distinct gene expression profile and response to therapy in different patients. Therefore, design of efficient therapeutic strategies requires understanding of the function of tumor-promoting genes in individual tumors, and faithfull prediction of the therapeutic response of the molecular network in which the tumor promoting genes exert their function. Here, we identify a gene regulatory network (GRN) which drives development of HCC. The activity of the network correlates with vital prognosis of HCC patients, with proliferation and embryonic markers and was found to be specific to gastrointestinal cancers. Based on data from the The Cancer Genome Atlas and transfection experiments, we generated and calibrated a quantitative mathematical model which allows to theoretically predict the impact of one GRN component on the expression of all the others. We then compared the impact on the GRN of pharmacological inhibition of a network component in cultured HCC cell lines with the model's predictions of a pharmacological inhibition. The experimental data faithfully recapitulated the model predictions. We conclude that the mathematical model, which is made available via two user-friendly applications deployed on a web platform, can be used as a tool to predict the impact of therapeutic agents targeting the GRN.

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MULTISCALE MODELLING OF CANCER GROWTH AND SPREAD: A MULTISCALE MOVING BOUNDARY APPROACH

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Keywords: Cancer modelling, Reaction-diffusion-taxis PDEs, Moving boundary, Multiscale methods, Front checking techniques.

Recognized as one of the hallmarks of cancer, cancer cell invasion into tissue is a complex process that plays a key role in the growth and spread of cancer, culminating in metastatic spread (secondary cancers). One common aspect of all cancer progression is the secretion of matrix degrading enzymes (MDEs) by the cancer cells that modify or destroy the surrounding tissue or extracellular matrix (ECM) and support local cancer cell invasion. In conjunction with MDE activities, increased cancer cell motility due to changes in cell-adhesion properties further exacerbates the invasion. Transmembrane calcium-dependent adhesion molecules (cadherins) interact with intra-cellular proteins, such as β-catenin and give rise to adhesion junctions. Of particular importance in cancer invasion are the dynamics between the calcium-sensing receptor distribution and the calcium ions (Ca2+) from the ECM. In addition to cell-cell adhesion, the binding of various ECM ligands to cell-surface receptors (integrins) enables cell- matrix adhesion. Thus, processes occurring at a molecular (micro) scale give rise to processes occurring at the tissue (macro) scale, via processes taking place at the cellular (meso) scale. The interplay between micro-, meso- and macro-scale processes involved in cancer cell invasion are still not fully understood. This talk will address recent advancements in multiscale modelling of cell-cell adhesion inside the tumour in conjunction with the activity of various proteolytic processes occurring along the invasive edge of the tumour. Finally, we will present computational simulations of the resulting multiscale moving boundary model and discuss a number of important fundamental properties that follow.

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PERSONALIZED CANCER TREATMENT SIMULATION: A MULTI-SCALE MODEL INFORMED BY MULTI-SOURCE CLINICAL DATA

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Keywords: Multi-scale modelling, Cellular automata, Birth-death processes, Partial Differential Equations, Ordinary Differential Equations.

The usefulness of multi-scale models to disentangle complex cancer processes such as treatment response has been widely acknowledged. However, a major barrier for multi-scale models to predict the outcomes of therapeutic regimens in a particular patient lies in their initialization and parameterization in order to reflect individual cancer characteristics accurately. In this study we use multi-source routinely acquired measurements on a single breast tumor, including histopathology, magnetic resonance imaging, and molecular profiling to personalize a complex multi-scale model of breast cancer treated with chemotherapeutic and anti-angiogenic agents. We model the dynamics of drugs in the tissue (pharmacokinetics) and the corresponding effects on their targets (pharmacodynamics). We implemented a computer programme that simulates cross-sections of tumors under a randomised 12-week therapy regime and demonstrated how the model was able to reproduce and explain the treatment outcome of patients from a clinical trial for both responders and non-responders. Our model-driven approach for the integration of multi-source clinical data helps to identify the most relevant tumor features differentiating treatment outcomes in each patient. Furthermore, it can be used to suggest alternative regimes for non-responders with improved outcomes, as we show by scenario simulations.

Acknowledgements: The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7-PEOPLE-2013-COFUND) under grant agreement n° 609020 - Scientia Fellows.

RADIOTHERAPY AND CHEMOTHERAPY CHANGE VESSEL TREE GEOMETRY AND METASTATIC SPREAD

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Keywords: Computer simulation, Blood vessels, Cisplatin chemotherapy, Hypofractionated radiotherapy, Metastasis formation.

Growth and spreading behaviour of tumours and metastases are still subject of intensive research regarding the most effective treatment intervention in individual cases. It is difficult to evaluate experimental data regarding different treatment strategies and its individual characteristics for their clinical relevance. Our collaboration developed a computer model which allows a quantitative comparison of effects of treatment interventions with clinical and experimental data.

The computer model is based on a discrete event simulation protocol. Analytical functions describe the growth of primary tumour and distant metastases, a rate function models the intravasation events of the primary tumour and its metastases. Events describe the behaviour of the emitted malignant cells until the formation of new metastases.

We analysed data from experiments with untreated groups of mice from human small cell lung cancer lines OH-1 and extracted information about the growing and spreading behaviour. On this basis we modelled experimental data from groups of mice, which were treated with chemotherapy and radiation therapy. Our results reveal that the fractal dimension of the primary tumor vasculature changes during treatment. That indicates that the therapy affects the blood vessels' geometry. We corroborated that finding by a quantitative histological analysis showing that the blood vessel density is depleted during treatment [1].

References

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Parallel Session

Cancer II

EVOLUTION OF COMPETING DIVERSITIES: TUMOR VS. IMMUNE

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Keywords: Immunology, Cancer, Antigenicity, Evolution.

T-cells, part of the human adaptive immune system, have T-cell receptors that recognize antigens (i.e. short amino acid sequences) presented by cells. Each T-cell clone responds to a different antigen, and therefore the T-cell repertoire is highly diverse. To prevent auto-immunity, this repertoire undergoes strong negative selection against 'self' antigens during T-cell development, leading to a skewed diversity that primarily responds to 'foreign' antigens (e.g. viral). Proto-tumor cells initially start out presenting only 'self' antigens typical of their cell-type of origin, since they arise from normal tissue cells. However, oncogenic mutations will cause the antigenic profile of a tumor cell to emerge from the protective shadow of self-antigen privilege. This exposure can occur through production of mutated antigens that appear 'foreign', or by over-production of self-antigens to a level at which they foment an auto-immune response. The accumulation and diversification of oncogenic strategies (i.e. acquisition of beneficial 'drivers') is therefore subject to increased exposure to immune attack, particularly in early-stage tumors where broad immunosuppressive strategies have not had time to develop. Here, we use a mathematical model to study how different aspects of tumor progression (cell turnover rate, radial growth rate, mutation rate, vascular density, and tissue density) stimulate different immune responses. These lead to either complete tumor eradication by the immune system, or immunologic escape and tumor growth. In the tumors that do escape, different patterns of heterogeneity emerge (e.g. big bang vs. clonal sweep vs. highly diverse). Additionally, a diversity of T-cell memory is developed over time, which has implications for the viability of future oncogenic alterations.