CARDIOVASCULAR SYSTEM DIAGNOSTICS: MATHEMATICAL MODELING OF PULSE-WAVE PROPAGATION IN THE ARTERIAL TREE

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Each heartbeat generates a pulse (pressure) wave that propagates in the arterial tree. Several parameters (biomarkers) derived from the pulse aortic waveform are currently used in the clinic to assess the state of cardiovascular system. The aim of the proposed PhD project is to dissect the information contained in the pressure waveform using a mathematical model of pulse wave propagation in order to propose new, more accurate biomarkers. The model should consider elasticity of vessels and describe the changes of the blood flow and pressure throughout the entire arterial tree as a function of time. We assume that the model will be expressed as a multiple systems of partial and ordinary differential equations coupled at the branching points of the arterial tree. The model will be calibrated with clinical data from pulse wave measurements at different points of the arterial system and other hemodynamic parameters. The Laboratory of Mathematical Modeling of Physiological Processes is equipped with a device for non-invasive assessment of arterial stiffness and central pressure containing an applanation tonometer (SphygmoCor, AtCor Medical) and an impedance cardiograph (PhysioFlow). Those devices allow for assessment of many parameters such as: pulse wave velocity, aortic pressure, augmented pressure, augmentation index, subendocardial viability ratio, ejection time, stroke volume, cardiac output, systemic vascular resistance, etc. The use of mathematical modeling for the analysis of parameters describing the cardiovascular system will provide detailed information on the propagation of the pulse wave and factors that affect its characteristics. The analysis of clinical data of groups of patients with various diseases will hopefully allow for better diagnosis and optimization of therapy. An example of the application of mathematical wave modeling to the analysis of medical data can be found in the paper by Poleszczuk et al. "Subject-specific pulse wave propagation modeling: towards enhancement of cardiovascular assessment methods" (access from www.plosone.org).

SYNERGY OF RADIATION AND IMMUNE SYSTEM: MATHEMATICAL MODELS TO ENHANCE CURRENT TREATMENT PROTOCOLS FOR METASTATIC CANCER PATIENTS

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Animal studies and clinical trials identified a synergy of irradiation and immunotherapy. This synergy stems from the fact that radiation induces cell stress and immunogenic cell death, thereby exposing a wealth of previously hidden tumor-associated antigens, stress proteins and danger associated molecular patterns (HSPs, DAMPs), which are endogenous immune adjuvants that can initiate and stimulate an immune response. What is the most important, local immune system stimulation is propagated systematically through the lymphatic system making other metastatic sites also susceptible to this new wave of locally-induced immune attack. Thus, immunotherapy can be more efficient after irradiation and it boosts radiation-induced immune system stimulation. There are, however, many clinically important questions about radiation-immune system synergy that remain unanswered: 1) irradiation of which metastatic lesion would result in the best overall response; 2) what is the optimal radiation dose to stimulate the biggest immune response; 3) which immunotherapy synergizes with radiation the most. The goal of the proposed PhD project is to develop a quantitative mathematical framework that predicts systemic response of metastatic tumors to focal radiotherapy – either alone or in combination with immunotherapy – that can be further used to provide at least partial answers to the abovestated questions. It is assumed that the framework will be expressed in terms of ordinary differential equations describing temporal evolution of various cellular populations, i.e. cancer cells and various types of immune cells. The framework will be calibrated with clinical/experimental data using appropriate optimization methods. An example of modeling systemic immune-mediated response after focal irradiation can be found in the paper by Poleszczuk et al. “Abscopal Benefits of Localized Radiotherapy Depend on Activated T-cell Trafficking and Distribution between Metastatic Lesions” (access from http://cancerres.aacrjournals.org).

TUMOR-IMMUNE SYSTEM INTERACTIONS MODELING ON A SINGLE CELL LEVEL

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Steady accumulation of genetic mutations by cancer cells leads to the creation of new tumor-specific antigens that can be recognized and attacked by the immune system. There are, however, several mechanisms in which cancer cells can become resistant to the immune system attack. Without a doubt, introducing immunotherapies based on checkpoint inhibitors which aim at overcoming those resistance mechanisms was a major breakthrough in the war against cancer. For some patients tumor responses to anti-PD-1/PD-L1 or anti-CTLA4 therapies are spectacular and last long after the therapy is withdrawn. Interestingly, disease regression can occur even after an initial phase of tumor growth during the therapy. However, despite spectacular successes, therapies based on checkpoint inhibitors still suffer from relatively low response rates and it is not completely clear what is the most prominent mechanism through which those immunotherapies achieve sometimes such an amazing efficacy. The goal of the proposed PhD project is to develop a detailed computational/mathematical model that describes tumor-immune system interactions on a single cell level and use its predictions to explain how immunotherapies, especially immune checkpoint inhibitors, lead to complete responses in some of the patients. An additional goal of the project would be to use developed framework to look for new therapeutic targets in the tumor-immune system axis. It is assumed that the developed model will be written as an agent-based model with cancer cells and various immune cells considered as a distinct type of agents. The model should be coupled with partial differential equations describing concentrations of various important substances in the tumor microenvironment. An example of tumor-immune system modelling using agent-based model can be found in the paper by Kather, Poleszczuk, et al. “In Silico Modeling of Immunotherapy and Stroma-Targeting Therapies in Human Colorectal Cancer” (access from http://cancerres.aacrjournals.org).