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Investigating the role of tumor tissue architecture in chemotherapy: from tumor histopathology to drug efficacy

Part of the minisymposium "Data-driven modeling in Mathematical Oncology" organized by Dr. Banu Baydil

Abstract:
Poor penetration of the tumor tissue by drug particles contributes to low efficacy of therapeutic compounds, and, in many cases, results in the failure of the Phase II clinical trials, even if the therapeutic compounds were successful in laboratory experiments. This may be attributed, at least partially, to the fact that experimental models do not recreate the process of drug penetration into the tumor tissue in a way it takes place in the patient body. We developed a computational model of drug penetration that operates on the microscopic tissue scale and recreates various physico-chemical conditions of the tumors. This model integrates histopathology images of various tumor tissues, and includes explicitly defined tissue morphology that is comprised of individual and/or stromal cells surrounded by the interstitial space filled with the fluid that impacts drug transport. We investigated the dynamics of a class of drugs activated in regions characterized by either low oxygen or high acid levels, and showed that they may lead to shifting of the tissue metabolic profile. Our computational results showed that there is a non-linear relation between tissue permeability, its cellular density and penetration of drug molecules due to the convective interstitial transport. Moreover, we demonstrated that heterogeneity in tissue composition, such as irregular cell configurations, might solely be responsible for the emergence of tissue zones that are not exposed to drugs in concentrations sufficient to provide therapeutic action.