Pharmacokinetics-Pharmacodynamics Modeling of TKIs Action during Tumorigenesis

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Abstract

The epidermal growth factor (EGF) receptor cascade plays a crucial role in the survival and proliferation of tumor cells. Tyrosine kinase inhibitors (TKIs) are a class of drugs that inhibit epidermal growth factor receptors (EGFRs), thereby preventing downstream signal transduction. We used a previously developed 3D model [1] where cells are considered as discrete objects that move, grow, divide or die by apoptosis and their fate is regulated by the activation of transcription factors following the transduction of the EGFR cascade. In this study, we explore the role of TKIs on tumor growth by extending the 3D model with the introduction of the FDA approved TKIs, like erlotinib and gefitinib. The model describes EGF and TKIs as individual objects that move according to Brownian dynamics and react with EGFR. This work captures the competition of TKIs with EGFs for binding to EGFRs. We simulate tissue-level concentrations of TKI drugs by applying their specific pharmacokinetic models, and integrate their effects on EGFRs in our 3D simulations. Experiments are conducted to observe the effects of TKIs on tumor growth at different levels of EGF and EGFR overexpression. The long-term goal is to provide insights into the mechanisms of TKIs and to generate testable hypotheses for experiments aimed at identifying factors that affect the efficacy profile of these drugs.

References:

[1] Bouchnita, Anass, Stefan Hellander, and Andreas Hellander. "A 3D multiscale model to explore the role of EGFR overexpression in tumourigenesis." *Bulletin of mathematical biology* 81 (2019): 2323-2344.