ICRAMCS 2026
THE EIGHTH EDITION OF THE INTERNATIONAL CONFERENCE ON RESEARCH IN APPLIED MATHEMATICS AND COMPUTER SCIENCE
April 23-24-25, 2026 | Marrakech, Morocco

Vascular-Coupled Modeling of Treatment Resistance in Tyrosine Kinase Inhibitor Therapy: Parameter Estimation and Phase-Dependent Sensitivity Analysis

Communication Info

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Keywords:
(1) Tumor heterogeneity
(2) Drug resistance
(3) Parameter estimation
(4) Sensitivity analysis

Abstract

Acquired resistance to tyrosine kinase inhibitors (TKIs) remains the primary obstacle to long-term disease control in targeted cancer therapy, yet whether resistance emerges gradually through clonal selection or abruptly via mutation acquisition remains unclear. We develop a four-dimensional ordinary differential equation model coupling drug-sensitive and drug-resistant tumor populations with dynamic vascular support and explicit TKI pharmacokinetics. Mathematical analysis establishes solution positivity and uniform boundedness, characterizes all equilibrium states, and determines local stability conditions via Jacobian eigenvalue analysis, revealing threshold relationships between drug efficacy and evolutionary outcomes.

We perform systematic parameter estimation using differential evolution on longitudinal tumor mass data from a gastrointestinal stromal tumor patient treated with imatinib. Models assuming continuous effective drug pressure fail systematically, with best fit achieving only coefficient of determination R-squared equals 0.721, unable to reproduce the observed 24-fold tumor mass increase during relapse. In striking contrast, incorporating a sigmoid resistance modulation function—where cytotoxicity progressively vanishes due to mutant clonal expansion near day 683—yields near-perfect agreement with R-squared equals 0.999, accurately capturing all three clinical phases. The estimated transition rate implies a rapid 10–90 percent clonal takeover within approximately 2.5 days, providing quantitative evidence that explosive relapse reflects abrupt mutation acquisition rather than gradual selection.

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