Parameter estimation and mathematical modeling for the quantitative description of therapy failure due to drug resistance in gastrointestinal stromal tumor metastasis to the liver

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In this work we develop a general mathematical model and devise a practical identifiability approach for gastrointestinal stromal tumor (GIST) metastasis to the liver, with the aim of quantitatively describing therapy failure due to drug resistance. To this end, we have modeled metastatic growth and therapy failure produced by resistance to two standard treatments based on tyrosine kinase inhibitors (Imatinib and Sunitinib) that have been observed clinically in patients with GIST metastasis to the liver. The parameter identification problem is difficult to solve, since there are no general results on this issue for models based on ordinary differential equations (ODE) like the ones studied here. We propose a general modeling framework based on ODE for GIST metastatic growth and therapy failure due to drug resistance and analyzed five different model variants, using medical image observations (CT scans) from patients that exhibit drug resistance. The associated parameter estimation problem was solved using the Nelder-Mead simplex algorithm, by adding a regularization term to the objective function to address model instability, and assessing the agreement of either an absolute or proportional error in the objective function. We compared the goodness of fit to data for the proposed model variants, as well as evaluated both error forms in order to improve parameter estimation results. From the model variants analyzed, we identified the one that provides the best fit to all the available patient data sets, as well as the best assumption in computing the objective function (absolute or proportional error). This is the first work that reports mathematical models capable of capturing and quantitatively describing therapy failure due to drug resistance based on clinical images in a patient-specific manner.