Sensitivity Analysis of a Multi-scale Tumor Growth Model Parameterized with in vivo Imaging Data

Matthew T. McKenna, Stephanie L. Barnes, David A. Hormuth II, Jared A. Weis, Michael I. Miga, Thomas E. Yankeelov

Abstract

Recent advances in imaging techniques have provided clinicians with copious amounts of data on the molecular, cellular, and physiological characteristics of tumors. For example, diffusion weighted MRI (DW-MRI) can provide an estimate of the cell density of a tumor. Dynamic 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) data can estimate regional glucose consumption. We have developed a multi-scale model that integrates these complimentary, noninvasive measures into patient-specific predictions of tumor behavior. Our model consists of a system of coupled partial differential equations (PDEs) parameterized by values drawn from PET-MRI data. In this study, we perform a sensitivity analysis to determine the influence of each parameter over its physiologic range on the predictive ability of the model. For this analysis, we borrow methods from systems biology: the extended Fourier amplitude sensitivity test and a Latin hypercube sampling-based approach. These approaches intelligently sample the entirety of the input space to choose parameter sets for simulations. We calculate how the variance of the simulation outputs can be apportioned to each input parameter and how each input parameter correlates with the outputs. For these simulations, we initialize the system with dynamic FDG-PET and DW-MRI data from a murine glioma model. The range for each parameter is defined from a literature search. We represent the model output with the concordance correlation coefficient, comparing each experimental simulation to a ground truth simulation. This ground truth is defined using the mean value for each parameter. Preliminary results have revealed the influence of select parameters on the spatial distribution of tumor cell development and the predicted number of tumor cells. The sensitivity analysis will: 1) identify model parameters that can be eliminated, and 2) inform the design of future experiments in regard to the type and precision of imaging data required to invert the PDE system to estimate patient-specific model parameters. This will then allow the model to be projected forward in time to make experimentally testable hypotheses. The results of the sensitivity analysis will help guide the development of a patient-specific model that will allow for better prediction of tumor progression for the individual patient and provide insight into the underlying biology.