

Title: A Formalism for Detecting the Emergence of the Resistant Phenotype Using Quantitative Diffusion Weighted Magnetic Resonance Imaging

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Abstract:

We examine the potential for diffusion weighted magnetic resonance imaging (DWMRI) data coupled with a mathematical model of tumor evolution to identify the presence of drug resistant cells early in the course of drug therapy. We use a set of models based on logistic growth of a tumor containing both a sensitive and resistant cell fraction to generate simulated DWMRI data of the local tumor cell number as a function of time. Heterogeneous tumors containing a sensitive and resistant fraction initially decrease in total cell number then rebound. From this time course, we extract the tumor model growth parameters e.g., the drug induced proliferation rate of the cell fractions and the initial tumor composition. We find that accurate parameter estimation for a heterogeneous tumor requires tracking the cell population in a region to the minimal total cell number, frequently reached early in the course of therapy. For instance, using experimentally constrained cell growth rates, we find that the parameters describing a tumor containing a 10% resistant fraction can be accurately determined via 7 scans taken over 49 days. Incorporating spatial information into the parameter extraction improved the accuracy by an order of magnitude. By using statistical methods to compare the predictions of two possible models, we find serial noninvasive imaging can identify tumor resistance well before current standards. To the best of our knowledge, this represents the first effort to construct a formalism that employs clinically available, noninvasive imaging data to predict the emergence of the resistant phenotype.