Integrating multiple scales and imaging modalities to predict tumor response for individual patients and generate personalized therapy regimens

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BACKGROUND: We have previously established a 3D mechanically coupled, reaction-diffusion model at the tissue scale for predicting breast tumor response to neoadjuvant therapy (NAT), initialized with patient-specific, quantitative, magnetic resonance imaging (MRI) data. We have expanded this model to differentiate between the effects of different chemotherapies to generate personalized and, potentially, optimized regimens for individual patients. However, one limitation of the model is that it does not explicitly account for targeted therapies. Therefore, to extend this model further to include the effects of specific targeted therapies, we turn to multi-modality data. Specifically, we interlace MRI data and positron emission tomography (PET) data estimating the dynamics of targeted drugs. We propose that an imaging-based, multi-modal, mathematical-experimental approach bridging tissue and cellular scales can elucidate optimal strategies for combination therapy for breast cancer.

METHODS: First, the mathematical model incorporating the effects of individual chemotherapies is evaluated for its predictive ability across a cohort of 18 patients using MRI data collected early in the course of NAT. These results are compared within the cohort for patients that received chemotherapies to those who also received targeted therapies for human epidermal growth factor receptor 2 positive (HER2+) breast cancer tumors. Second, alternative therapy regimens are evaluated for a subset of patients for which the model's predictions are highly correlated with actual response. Third, the model is then expanded to account for antibody localization as estimated by ^{64}Cu-labeled trastuzumab PET data. We modify the model such that the proliferation of the tumor cells is dependent on the distribution of the targeted drugs where drug concentrations (trastuzumab and pertuzumab) are approximated using the ^{64}Cu PET data. We utilize data sets for two patients who were diagnosed with locally advanced HER2+ breast cancers and treated with the same NAT regimen but had very different clinical responses (a pathological complete response (pCR), and a non-pCR at the time of surgery) from a unique study where both quantitative MRI and PET data were acquired together (clinical trial NCT02827877).

RESULTS: The model's predictions of tumor response are significantly correlated to the measured tumor burden at the time of scan 3 ($r^2 > 0.88$, $p < 0.01$) for total cellularity, total volume, and longest axis ($N = 18$). However, the model performs more modestly for the subgroup of patients that received targeted therapies. Evaluating alternative dosing regimens, defined using the same total amount of drug each patient received during their standard regimen while varying dosages and frequency, the model predicted that individual patients could have achieved, on average, an additional 21% (0-46%) reduction in total cellularity. The optimal dosing regimens chosen by the model were predicted to significantly outperform standard regimens for tumor control ($p < 0.001$). For the model that does not incorporate the targeted therapy, it predicts that both tumors of the PET/MRI data set would regrow by the time of surgery. By incorporating HER2-targeted therapy, the model predicts opposite responses by the time of surgery between the two patients, in agreement with their actual clinical responses—for the pCR patient, the tumor shrinks, and for non-pCR patient, the tumor regrows.

CONCLUSIONS: These results suggest that the mathematical model can be predictive of tumor response by MRI in the clinical setting using data at the earliest times of therapy. With *in silico* studies, we illustrate how therapeutic regimens can be selected for individual patients for better tumor control, revealing that standard regimens may not be the most effective for every patient. We provide proof-of-concept results that MRI and PET data can be combined in a mathematical model to improve predictions of patient-specific tumor response to combination chemo- and HER2-directed therapy. These preliminary results are a first step to combining multiple modalities of clinically-relevant imaging data in a mathematical model for individualized predictions of therapy response.

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