Target Audience Those interested in 1) predicting breast cancer response, and 2) mathematical modeling of tumor growth.

Purpose There is currently a paucity of reliable techniques for predicting the response of breast tumors to neoadjuvant chemotherapy. One promising approach to address this need is to integrate quantitative imaging data into physically realistic biomathematical models of tumor growth. The goal of this effort is to employ quantitative MRI data acquired early in the course of therapy to initialize and guide a mechanistic model to predict eventual tumor status at the completion of neoadjuvant chemotherapy.

Methods MRI was performed on eight breast cancer patients using a 3T Achieva MR (Philips, Best, Netherlands) scanner. Anatomical T_1-weighted, DCE-, and DW-MRI data were acquired prior to beginning NAC, after one cycle of NAC, and at the conclusion of 8-12 cycles (depending on patient regimen) of NAC. All images for each patient were longitudinally co-registered to the final time point using an adaptive basis algorithm with a tumor volume preserving constraint[1]. DCE-MRI data sets at each time point were used to define a tumor ROI by comparing the averages of the baseline pre-contrast images and the enhanced post-contrast images. Voxels exhibiting ≥100% signal intensity increase after contrast infusion were used to define tumor voxels. The diffusion data for the tumor voxels was transformed to estimate tumor cell number as previously described[2]. The coupled set of PDE's governing the model are shown in Eqs. (1)-(3) and describe the cell number as the sum of random cell diffusion and logistic growth. The cell diffusion term is coupled to surrounding tissue stiffness through von Mises stress, and mechanical equilibrium governs the evolution of an expansive force as determined by changes in cell number. Figure 1 outlines the approach for generating and comparing model predictions at the final time point to clinical observations.

Results As shown in Figures 1 and 2, the model predictions of tumor cellularity at the final time point of NAC agree well with the observed cellularity, with the mechanical coupling model exhibiting greater accuracy. Average prediction errors

$$\frac{\partial N_{TC}(\bar{x},t)}{\partial t} = \nabla \cdot \left(D\nabla N_{TC}(\bar{x},t) \right) + k(\bar{x},t)N_{TC}(\bar{x},t)\left(1 - \frac{N_{TC}(\bar{x},t)}{\theta} \right) \quad (1)$$

$$D = D_0 e^{-\gamma \sigma_{vm}(\bar{x},t)} \quad (2)$$

$$\nabla \cdot \sigma + \lambda \nabla N_{TC}(\bar{x},t) = 0 \quad (3)$$

were 5.4×10^6 +/- 4.7×10^6 and 10.3×10^6 +/- 5.9×10^6 for the mechanics coupled and non-mechanics coupled models, respectively.

Discussion We present a mechanically constrained modeling approach that integrates quantitative *in vivo* imaging data and biomathematical models of tumor growth to predict response based on early measurements during therapy. We use the optimized parameters fit between the initial and post one cycle time points to project the model forward in time and compare the model prediction to experimental data for tumor cell number at the final time point. The results indicate that the incorporation of mechanics within the biomathematical model enhances the accuracy and specificity of the model.

Conclusion Incorporating tissue mechanical properties into the reaction-diffusion equation provides excellent agreement with clinical observations and suggests that an imaging-based modeling approach to the prediction of tumor response may provide valuable early feedback during the course of NAC.

References 1. Li, X., et al., Magn Reson Imaging. 2009;27(9):1258-1270. 2. Anderson, A.W., et al., Magn Reson Imaging. 2000;18(6):689-695.
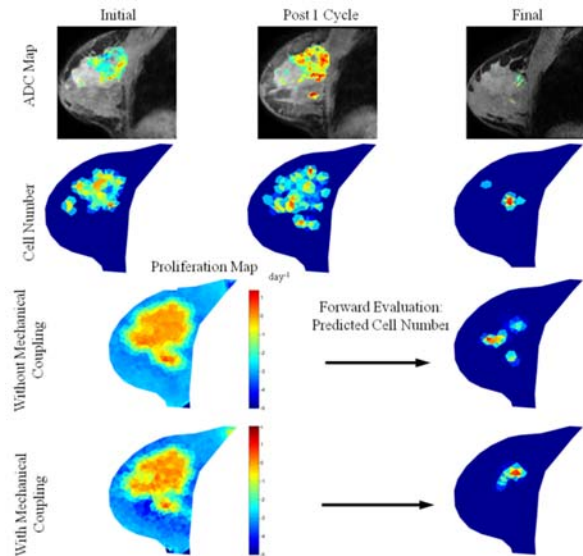
Figure 1. ADC maps are converted to cell number and the models are used to optimize parameters between the initial and post 1 cycle time points and projected forward to the final time point.
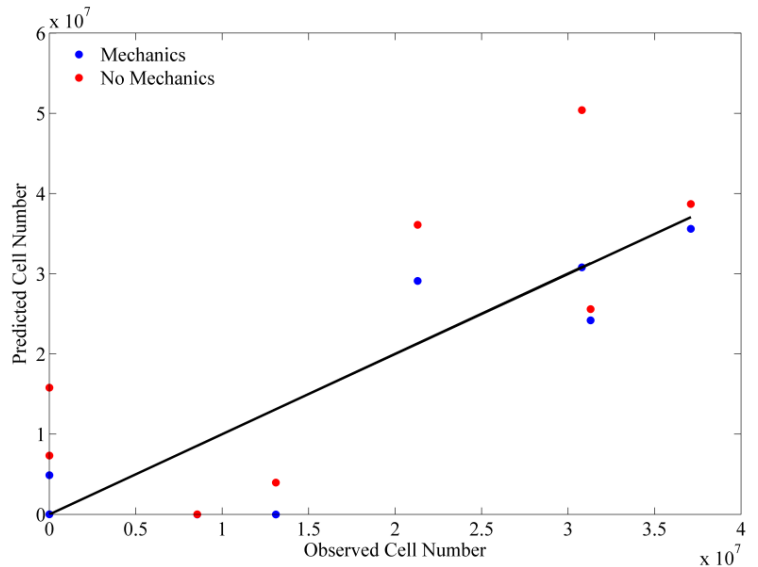

Figure 2. Model predicted cell number vs. observed cell number at the final time point for the mechanics coupled (blue) and non-mechanics coupled (red) models. Black line indicates line of unity.