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Incorporating drug delivery into an imaging-driven, mechanics-coupled reaction diffusion model for predicting the response of breast cancer to neoadjuvant chemotherapy: theory and preliminary clinical results

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Abstract

Clinical methods for assessing tumor response to therapy are largely rudimentary, monitoring only temporal changes in tumor size. Our goal is to predict the response of breast tumors to therapy using a mathematical model that utilizes magnetic resonance imaging (MRI) data obtained non-invasively from individual patients. We extended a previously established, mechanically coupled, reaction-diffusion model for predicting tumor response initialized with patient-specific diffusion weighted MRI (DW-MRI) data by including the effects of chemotherapy drug delivery, which is estimated using dynamic contrast-enhanced (DCE-) MRI data. The extended, drug incorporated, model is initialized using patient-specific DW-MRI and DCE-MRI data. Data sets from five breast cancer patients were used—obtained before, after one cycle, and at mid-point of neoadjuvant chemotherapy. The DCE-MRI data was used to estimate spatiotemporal variations in tumor perfusion with the extended Kety-Tofts model. The physiological parameters derived from DCE-MRI were used to model changes in delivery of therapy drugs within the tumor for incorporation in the extended model. We simulated the original model and the extended model in both 2D and 3D and compare the results for this five-patient cohort. Preliminary results show reductions in the error of model predicted tumor cellularity and size compared to the experimentally-measured results for the third MRI scan when therapy was incorporated. Comparing the two models for agreement between the predicted total cellularity and the calculated total cellularity (from the DW-

MRI data) reveals an increased concordance correlation coefficient from 0.81 to 0.98 for the 2D analysis and 0.85 to 0.99 for the 3D analysis ($p < 0.01$ for each) when the extended model was used in place of the original model. This study demonstrates the plausibility of using DCE-MRI data as a means to estimate drug delivery on a patient-specific basis in predictive models and represents a step toward the goal of achieving individualized prediction of tumor response to therapy.

Keywords

DCE-MRI; diffusion MRI; tumor; computational; mathematical modeling; drug delivery

1. Introduction

Neoadjuvant chemotherapy (NACT) is widely considered the standard-of-care for treatment of stage II–III, locally advanced breast cancer. NACT increases the success rate for breast conservation surgery by reducing tumor size and provides the opportunity to treat micrometastases in a naïve state. Furthermore, patients whose primary breast tumor responds positively to NACT are more likely to respond systemically, while a lack of response in the primary tumor makes systemic response unlikely. Importantly, patients who achieve a pathological complete response (pCR) in the neoadjuvant setting have increased recurrence-free survival; conversely, patients who have residual disease after NACT are at increased risk of early recurrence and death [1, 2]. If it could be definitively determined—early in the course of NACT—that a particular therapeutic regimen is unlikely to achieve a pCR, the oncologist could discontinue the ineffective (and potentially toxic) treatment and substitute an alternative treatment strategy. With numerous therapeutic options available, the importance of developing a method that predicts treatment response early in the neoadjuvant setting and enables therapy optimization is paramount to achieve the goal of individualized care of cancer patients.

Tissue-based biomarkers of response require an invasive biopsy with concomitant sampling limitations due to tumor heterogeneity. Standard tumor size-based methods of evaluating response, including conventional magnetic resonance imaging (MRI), are not well-suited for *early* prediction of treatment response because therapy-induced tumor size change generally lags behind biological response [3–5]. Additionally, this approach can only *assess* response—they cannot *predict* response because it only reports on changes that are temporally downstream from underlying molecular, cellular, and physiological changes; critically, the response evaluation criteria in solid tumors (i.e., RECIST, [6]) cannot be used to optimize or plan therapy. One reason for this is that the RECIST method does not account for changes in important tumor characteristics such as the quantity and distribution of tumor cells and vasculature. However, advanced quantitative imaging measurements from MRI or positron emission tomography (PET) can provide quantification of various tumor characteristics. For example, MRI and PET techniques can non-invasively assess tissue properties such as cellularity (diffusion-weighted MRI [7]), blood volume (dynamic susceptibility contrast MRI [8] or dynamic contrast-enhanced MRI [9], hypoxia (oxygen enhancing MRI [10] or

^{18}F -fluoromisonidazole PET [11]), and metabolism (^{18}F -fluorodeoxyglucose PET [12]) in 3D before, during, and following the conclusion of therapy.

We have proposed using non-invasive imaging measurements obtained on a patient-specific basis to initialize and calibrate *predictive* biophysical models of tumor growth and response [13]. Models written in terms of measureable or calibrated parameters could potentially be initialized with the pre-treatment tumor cellularity, calibrated with the follow-up scan, and then validated with the remaining scans; thus, providing a feasible framework to “forecast” individualized tumor growth and response. Furthermore, the ability to make repeatable, non-invasive, spatially discretized, quantitative measurements of tumor growth supports the development, testing, and refinement of mathematical models resulting in a more accurate description of tumor growth. Mathematical models have recently been developed that begin to address the limitations of current clinical measurements of tumor response [1, 14–17], and modeling strategies that are initialized and constrained by experimental data generate predictions that can be tested experimentally. An important end goal of such studies is to use mathematical modeling to rigorously investigate alternative therapies *in silico* to generate predictions that then can be used to systematically and to make testable hypotheses regarding optimal drug delivery.

Previously, a reaction-diffusion model coupled with logistic growth for breast cancer was shown to outperform RECIST measures for predicting tumor response to therapy when initialized with patient specific MRI data [1]. This original model utilized diffusion-weighted MRI (DW-MRI) data, which were used to estimate tumor cellularity as well as mechanical properties of breast tissue to initialize the model and calibrate parameters. The results of the biomechanical, data-driven approach were shown to be predictive of patient response at the conclusion of NACT. The goal of this study is to improve the predictive ability of this mathematical model by incorporating data characterizing the vascular features of each individual tumor, as well as their specific therapeutic regimen. More specifically, we utilize the parametric maps derived from dynamic contrast-enhanced MRI (DCE-MRI) data to obtain estimates of vascular characteristics related to blood flow and vessel permeability, which are then used in the model to estimate the delivery of drugs to each tumor voxel for the purpose of appraising the local proliferation and death rates.

2. Materials and Methods

2.1 Patient cohort

Quantitative MRI data (detailed below) was acquired in a cohort of five patients diagnosed with grade 2 to 3 invasive breast cancers and who were eligible for NACT as a component of their clinical care. The patient data was collected in an institutional review board-approved and HIPAA-compliant study where patients consented to participate in a longitudinal MRI study [2]. Table 1 summarizes the clinical features of these patients.

MRI data were acquired at four time points: at baseline (after diagnosis but before initiation of therapy), after at least one cycle of NACT, at a midpoint of NACT, and after the completion of NACT but prior to surgery. NACT regimens included cycles of adriamycin and cyclophosphamide approximately every 2 weeks for 4 cycles, followed by paclitaxel

every 1–2 weeks for 4 cycles. Three patients began treatment with paclitaxel before proceeding to adriamycin and cyclophosphamide, while the remaining two patients received therapy in the opposite order. For this study, only imaging data from the first three imaging sessions (i.e., pre-therapy, after one cycle of NACT, and at the midpoint of NACT—during the cycle interval before the change of the drug) is utilized; the first two time points are used to calibrate the mathematical models, which are then used to make a prediction for the third time point. The model prediction is compared to the third time point data to assess model performance.

2.2 MRI data acquisition

MRI was performed using a 3 T Siemens Tim Trio system with the body coil and a four-channel bilateral phased-array breast coil as the transmitter and receiver, respectively. Each MRI session began with pilot scans, axial T_2 -weighted MRI with fat-saturation, and axial T_1 -weighted without fat-saturation, before proceeding to DW-MRI and DCE-MRI acquisitions. The bilateral DW-MRI was acquired in the axial plane with a single-shot spin echo echo planar imaging sequence, with b -values of 0, 200 and 800 s/mm², and $TR/TE = 8000$ ms/77 ms, and 4 signal averages. The acquisition matrix was $192 \times 192 \times 32$ over a $320 \times 320 \times 160$ mm³ field of view. Then bilateral, full breast-coverage, axial DCE-MRI was acquired with a water-excitation only, gradient echo-based 3D TWIST (Time-resolved angiography With Stochastic Trajectories) sequence. DCE-MRI acquisition parameters were $TR/TE/\alpha = 6.2$ ms/2.9 ms/10°, with a parallel imaging acceleration factor of 2, and an acquisition matrix of 320×320 , slice thickness 1.4 mm with 30 to 34 cm field of view. The intravenous injection of Gd(HP-DO3A) [ProHance (Bracco Diagnostic Inc.), Princeton, New Jersey] was 0.1 mmol/kg at 2 mL/s delivered by a programmable power injector after the acquisition of two baseline image volumes, followed by a 20 mL saline flush. The acquisition time for the DCE-MRI was approximately 10 minutes with 14.6 s to 20.2 s temporal resolution, depending on the number of slices needed (112–120) in each image volume for full breast coverage.

2.3 MRI data analysis

For each patient, MR images acquired at each session were registered to a common image space *via* a non-rigid registration algorithm that uses the adaptive basis algorithm with a constraint that preserves the tumor volumes at each time point [3–5, 18]. Following registration, the DCE-MRI data was used to segment the tumor region of interest (ROI) at each time point (details provided in the Supplemental Material).

The apparent diffusion coefficient (ADC) values for individual voxels were calculated using the DW-MRI data in the usual fashion [19]. Then the ADC value for each voxel within the tumor was converted to an estimate for the number of tumor cells per voxel at a 3D position $\vec{x}$ and time t , $N_{TC}(\vec{x}, t)$, *via*:

$$N_{TC}(\vec{x}, t) = \theta \left(\frac{ADC_w - ADC(\vec{x}, t)}{ADC_w - ADC_{min}} \right), \quad (1)$$

where ADC_w is the ADC of free water ($3 \times 10^{-3} \text{mm}^2/\text{s}$) [20], $ADC(\bar{x}, t)$ is the ADC value for a specific voxel, and ADC_{min} is the minimum ADC value in a tumor voxel for the patient [16, 21]. The parameter θ is the carrying capacity for the likely density of tumor cells that can fit within a voxel—determined using an assumed spherical packing density of 0.7405 [22], a nominal tumor cell radius of 10 μm and the known voxel volume. We return to this transformation between ADC and cell number per voxel in the Discussion section.

2.4 Mathematical model

We have previously presented a mechanically coupled, reaction-diffusion (MC-RD) model, initialized with patient specific MRI data, developed to predict tumor response to therapy in breast cancer [1, 14, 15]. The MC-RD model consists of the following set of coupled, partial differential equations:

$$\frac{\partial N_{TC}(\bar{x}, t)}{\partial t} = \nabla \cdot (D \nabla N_{TC}(\bar{x}, t)) + k(\bar{x}) \left(1 - \frac{N_{TC}(\bar{x}, t)}{\theta} \right) N_{TC}(\bar{x}, t) \quad (2)$$

$$D(\bar{x}, t) = D_0 \exp(-\gamma \sigma_{vm}(\bar{x}, t)) \quad (3)$$

$$\nabla \cdot G \nabla \vec{u} + \nabla \frac{G}{1-2\nu} (\nabla \cdot \vec{u}) - \lambda \nabla N_{TC}(\bar{x}, t) = 0, \quad (4)$$

where $D(\bar{x}, t)$ is the diffusion coefficient, $k(\bar{x})$ a spatially resolved proliferation rate map for tumor cells, θ the carrying capacity for logistic growth, D_0 the tumor cell diffusion constant in the absence of stress (please note that D_0 is the diffusion value for the tumor cells and is not to be confused with the ADC , which is the apparent diffusion coefficient of water molecules), γ an empirical coupling constant for the von Mises stress, σ_{vm} , G the shear modulus, where $G = E/(2(1-\nu))$ for the Young's modulus (E) and Poisson's ratio (ν) material properties; $\vec{u}$ is the displacement due to tumor cell growth, and λ is another empirical coupling constant. Eq. (2) describes the spatiotemporal change in voxel tumor cell density due to the combined effects of tumor cell diffusion (first term on the right-hand side) and logistic growth (second term). The random diffusion (movement) of the tumor cells (D) is mechanically linked to the breast tissue's material properties using the von Mises stress ($\sigma_{vm}(\bar{x}, t)$ in Eq. (3)) and a linear elastic, isotropic equilibrium (Eq. (4)) dependent upon changes in tumor cell number. (The von Mises stress reflects the total experienced stress for a given section of tissue and is often used within failure criterion strategies in materials. Here, it is used to reflect the interaction between the growing tumor and its environment.) Therefore, when there is no stress, the diffusion coefficient is equal to D_0 . Briefly, this model describes tumor growth changes that can cause deformations in the surrounding healthy tissues (breast fibroglandular tissue and adipose tissue), potentially increasing stress and therefore reducing the outward expansion of tumor growth. While the MC-RD model was shown to outperform clinically used measures for predicting tumor response to therapy

[1], one of the fundamental limitations of this model is it assumes constant proliferation/death values throughout the course of NACT. Here the model is extended to include the temporal effects of drug delivery with the goal of improving the predictive ability of the system.

2.4.1 Incorporation of patient-specific therapeutic regimens—We use the extended Kety-Tofts model of DCE-MRI to return estimates of blood flow, vessel wall permeability, and tissue volume fractions on a voxel by voxel basis [23–26]. It is a two-compartment model that describes the temporal variations of the concentration of contrast agent between the tissue and blood plasma spaces:

$$C_{tissue}(t) = K^{trans} \int_0^t C_{plasma}(u) \cdot \exp\left(-\frac{K^{trans}}{v_e}(t-u)\right) du + v_p C_{plasma}(t), \quad (5)$$

where $C_{tissue}(t)$ and $C_{plasma}(t)$ are the concentrations of the contrast agent in the tissue and plasma, respectively, K^{trans} is the volume transfer constant from the plasma space to the tissue space, v_p is the volume fraction of the plasma space, and v_e is the volume fraction of the extravascular extracellular space (for more details, see [9]). Eq. (5) was fit to the DCE-MRI data from each voxel within the tumor by using a population averaged $C_{plasma}(t)$ [27] to estimate K^{trans} , v_p , and v_e on a voxel-by-voxel basis: $K^{trans}(\vec{x})$, $v_p(\vec{x})$, $v_e(\vec{x})$. Voxels for which Eq. (5) did not converge or converged to non-physical values (i.e., K^{trans} , v_p , $v_e < 0$, or v_p , $v_e > 1$) were set to zero.

With K^{trans} , v_e , and v_p assigned for each voxel, we then estimate the time course of drug in each tumor voxel, given the patient specific therapeutic regimen. More specifically, we use the measured population curves for drug concentration in the plasma for specific therapies [28–30], the individual dosing schedule for each patient, and a “new” version of Eq. (5); that is, the $C_{tissue}(t)$ and $C_{plasma}(t)$ time courses from Eq. (5) now represent those quantities for the administered drug, and not the contrast agent. Therefore, the concentration of drug in the tumor tissue is spatially nonuniform and temporally varying based on the individual patient’s NACT schedule. This effect is incorporated directly into Eq. (2) as an explicit death term.

$$\frac{\partial N_{TC}(\vec{x}, t)}{\partial t} = \nabla \cdot (D \nabla N_{TC}(\vec{x}, t)) + k(\vec{x}) \left(1 - \frac{N_{TC}(\vec{x}, t)}{\theta}\right) \overbrace{N(\vec{x}, t) - \alpha C_{tissue}^{drug}(\vec{x}, t) N_{TC}(\vec{x}, t)}^{\text{Drug Delivery}}, \quad (6)$$

where α is a globally fitted parameter describing the efficacy of the drug. The term $C_{tissue}^{drug}(\vec{x}, t)$ is the distribution of the drug in the tissue calculated using Eq. (5) where $C_{plasma}^{drug}(t)$ is defined as the concentration of drug in the plasma:

$$C_{tissue}^{drug}(\bar{x}, t) = K^{trans} \int_0^t \left(C_{plasma}^{drug}(u) \cdot \exp \left(-\frac{K^{trans}}{v_e}(t-u) \right) \right) du + v_p C_{plasma}^{drug}(\bar{x}, t). \quad (7)$$

We note that this approach implicitly assumes that the chemotherapy will extravasate into the tumor tissue in a manner similar to that of the gadolinium-based contrast agent. We return to this important point in the Discussion section. Below, we refer to this extended model as the drug incorporated MC-RD model (DI-MC-RD); see Table 2 for parameter descriptions, values, and units.

2.5 Method for integrating clinical data into the mathematical model

Fig. 1 shows a flow chart for data processing. For each patient, after the MRI data were registered to a common image space, the tumor ROIs were selected (panel a to b). The DCE-MRI data was analyzed with Eq. (5) yielding K^{trans} , v_e , and v_p parameter maps (panel c) that were subsequently used to calculate drug delivery maps for each time step according to the patient's individual therapy schedule using Eq. (7) (panel d to e). ADC values are converted to cell number *via* Eq. (1) (panels f to g). Fig 2 shows a graphical description of the model calibration process, see Fig. 2. The tumor cell density, tissue properties for mechanical coupling, and drug distribution maps derived from the pre-treatment scan (scan 1, panel a) is used to initialize the model and simulated forward to the time of the second scan (model simulation and calibration methods are described below in Numerical Methods section). In the calibration process, a comparison is made between the model's result for the spatially distributed tumor cell numbers and the "actual" tumor cell densities calculated from the DW-MRI data of the second scan (panels c to d). If the error between the tumor cell distributions is greater than the prescribed tolerance, the cycle repeats, simulating the model with updated parameter values, until the stopping criteria is met (panel b).

After calibration was complete, the model was reinitialized with the second scan's tumor cell numbers, drug dosing maps, tissue properties, and the optimized parameters from calibration. The model was then simulated forward in time to the third scan. The model's prediction was tested against tumor cell densities derived from the scan 3 data to determine the quality of the prediction (see Fig. 3).

2.6 Numerical methods

2.6.1 Simulation scheme and model calibration—All simulation codes and numerical calculations were written and executed in MATLAB (MathWorks, Natick, MA). Both the MC-RD (Eqs. (2)-(4)) and DI-MC-RD models (Eqs. (3), (4), (6)) were implemented in two dimensions (2D) and three dimensions (3D) and initialized using patient specific DW-MRI and DCE-MRI data. Model simulations in 2D were evaluated using the numerically stable Crank-Nicolson finite difference scheme, and in 3D using a fully explicit finite difference scheme (due to the computational cost of the Crank-Nicolson scheme in 3D) with $\Delta t = 0.25$ days with the mesh dimensions defined by the size of the MRI voxels. The size of the computational domain is set by a rectangle whose dimensions are determined by the size of the breast for each patient. To reduce computation time for all calibrations, the

voxel matrix within this designated rectangular domain was down sampled by a factor of two. A no flux boundary condition was prescribed at the boundary of the breast.

To calibrate model parameters, a Levenberg-Marquardt (LM) least squares non-linear optimization is used, where the sum of squared errors between the simulated tumor cell numbers from the model and the calculated tumor cell densities from the imaging data is minimized. The first two MRI scans were used to calibrate the model, and the parameters D_0 , $k(\vec{x})$, θ , and α are calibrated, where $k(\vec{x})$ is spatially distributed. (We note that in previous efforts [1, 14, 15], θ was assigned a global value based on the assumption of an average cell size of 10 μm). Other parameters such as the Young's modulus for fibroglandular and adipose tissues were assigned with literature values [31].

2.6.2 Specific notes on temporal dynamics—Note that in the newly proposed system (i.e., Eqs. (3), (4), (6), and (7)), there is a continuous development in time for the number of tumor cells, but the model is initialized with different spatial information given by the most recent MRI data for the patient. Specifically, for elapsed time between the first and second scans, the model simulation results were calculated using the information available from the patient's first scan, and for elapsed time after the second scan up to the third, the patient's second scan information was used to continue the simulation. It is also important to note that drug concentration in any given voxel is dynamic in time depending on the patient's dosing schedule (driving the evolution of the drug distribution maps), whereas calibrated proliferation maps and all global parameters were not varied throughout model simulations.

2.7 Statistical Analysis

Descriptive statistical analysis was performed for percent changes in tumor cellularity and size between scans.

To summarize the models' performances, the percent differences between the calculated cellularity and tumor size from the third scan data and the corresponding predicted values from the original MC-RD and the extended DI-MC-RD models, respectively, were calculated for each patient. To account for model performance differences in instances where the model predicts there will be tumor present and the MRI data indicates there is no tumor, the percent differences in cellularity and volume were calculated using all slices containing the tumor ROI. Additionally, the concordance correlation coefficient (CCC) was used in two ways. First, the CCC was computed between the total tumor cellularity predicted by the model and the total tumor cellularity calculated from the DW-MRI data across patients. The formula for CCC comparing N ordered pairs (x, y) is:

$$\text{CCC} = \frac{2 \cdot \text{CoV}(x, y)}{\text{Var}(x) + \text{Var}(y) + (\bar{x} - \bar{y})^2}, \quad (8)$$

where $\bar{x}$ is the mean and $\text{CoV}(x, y)$ and $\text{Var}(x)$ are the covariance of x and y and variance of x , respectively. We used the CCC to compare the total tumor cell number for each patient as predicted by the model to the total tumor cell number for each patient as calculated from the DW-MRI data; we refer to this comparison as CCC_t with $N = 5$ for the total number of

patients, y is the total tumor cell numbers for each patients from the model's prediction, and x is the total tumor cell number for all patients from the MRI data. Second, we used the CCC to evaluate agreement between the predicted spatial distribution of tumor cells and the calculated (from DW-MRI data) spatial distribution of tumor cells on a voxel-voxel basis for each patient; we refer to this comparison as CCC_s with N being the total number of voxels per patient, y is the tumor cell numbers for all the voxels from the model's prediction for a given patient, and x is the tumor cell number for all voxels from the corresponding patient's data. The median and range for the absolute percent differences between predicted and calculated values for scan 3 in cellularity and tumor size were reported. The median and range of the CCC_s values per patient were also computed.

To determine if simulation results between 2D and 3D models were significantly different, the percent differences between predicted and calculated results and CCC_s values were compared between the two models using the Wilcoxon rank sum test. For all calibrated parameters, the resulting distributions were assessed for normalcy using functions from MATLAB's statistical package for the Lilliefors test and Jarque-Bera test.

3. Results

3.1 Clinical data

Fig. 4 presents ADC and K^{trans} maps on a slice through the center of a tumor for a patient at all three time points. From the ADC values and tumor ROIs, tumor cell numbers per voxel and size of tumors was calculated. Note that smaller ADC values indicate higher cellularity, and, as the tumor shrank in time, areas with low ADC values became more isolated regions in the tumor. Also, K^{trans} values changed with the changing vasculature due to therapeutic effects. For this same patient, Fig. 5 presents an example of the calculated drug distributions in the tumor tissue at three different time points between scans 1 and 2 for a central slice—pre-drug administration, peak drug, and residual drug times. Table 3 summarizes the change in tumor cellularity and size for each patient between MRI exams. Note that for patient 3 the tumor first shrank from scan 1 to scan 2, but then regrows from scan 2 to scan 3. Also, for patient 4, the tumor cellularity and size changes from scan 2 to scan 3 are the smallest compared to the other patients (-12% and -10% where the medians for the cohort are -49% and -33% , respectively), but has the shortest time between scans 2 and 3 (22 days where the median for the cohort is 41).

3.2 Two-dimensional simulation studies

Three global variables and one locally defined variable were calibrated for the DI-MC-RD model for each patient in the cohort—none of the sets of calibrated parameter values were found to yield normal distributions. From the 2D calibrations of all five patients, the global parameter D_0 has a median value of 4.20×10^{-3} and range of 3.11×10^{-4} to $0.10 \text{ mm}^2/\text{day}$ across all tumor-containing slices of all patients. Similarly, for the global parameters θ and α , their values are 1.42×10^5 with a range of 9.93×10^4 to 2.47×10^5 cells and 2.16 with a range of 0.01 to $81.00/(\mu\text{M}\cdot\text{day})$, respectively. Proliferation rates across all tumor voxels have a median of -9.93×10^{-7} and a range of -43.77 to $26.15/\text{day}$.

Results in tumor cell densities from 2D simulations using both the MC-RD and DI-MC-RD models for a central tumor slice together with those observed from the patients' third scans are illustrated in Figure 6 for the whole cohort. Note the differences in tumor cell numbers between the simulation and patient data for patients 1, 2, and 5, and the differences in shape for patients 2 and 3 driven by the drug distribution. Several metrics (see Table 4) were used to determine if explicitly including the therapeutic regimen (*via* Eq. (6)) improved the predictive accuracy over the original model (Eq. (2)). Comparing the median percent differences (between simulated and calculated) across the cohort, the DI-MC-RD model exhibits less than half the error than the MC-RD for tumor cellularity (24% compared to 62%), and there is an 17% reduction in the percent differences for the size of tumor for DI-MC-RD compared to MC-RD, but neither of these percent differences are statistically significant.

The CCC_s also reports differences between the two models (MC-RD and DI-MC-RD) when comparing the predicted spatial distribution of tumor cells in each voxel to the calculated (from ADC data) spatial distributions of each voxel (Table 4), where the DI-MC-RD model has a larger CCC_s compared to the MC-RD for each patient in the cohort. Though the median CCC_s for the DI-MC-RD model is larger than the original model, it is not a significant difference (0.33 and 0.27, respectively). Note that for patient 3 the CCC_s is near zero for both models, and we remind the reader that this tumor shrunk from scan 1 to scan 2, but then regrew from scan 2 to scan 3—unlike the rest of the cohort. Additionally, the CCC_t analysis comparing the total cellularity predicted per patient by each model versus the calculated cellularity is illustrated in Fig. 7a, showing the CCC_t value increased from 0.81 to 0.96 ($p < 0.01$) by explicitly incorporating the individual patient's therapeutic regimen into the MC-RD model to generate the DI-MC-RD model.

3.3 Three-dimensional simulation results

Three global variables and one locally defined variable were calibrated for the DI-MC-RD model for each patient in the cohort—none of the calibrated parameter values were found to yield normal distributions. From the 3D calibrations of all five patients, parameter D_0 has a median value of 1.13×10^{-3} and a range of 1.00×10^{-3} to $0.01 \text{ mm}^2/\text{day}$; the parameter θ has a median value of 1.34×10^5 and a range of 1.19×10^5 to 1.56×10^5 cells; and α has a median value of 51.47 and a range of 18.13 to 485.15/($\mu\text{M} \cdot \text{day}$). Proliferation values across all tumor voxels have a median of -1.89 and a range of -37.43 to $28.52/\text{day}$.

Results in tumor cell number from 3D simulations using both the MC-RD and DI-MC-RD models for a central tumor slice together with those observed from the patients' third scans are illustrated in Figure 8 for the whole cohort. Note the differences in concentrations of cells for all patients—with more isolated areas of high cellularity for the MC-RD model—and the differences in shape for patients 3 and 4 driven by the drug distribution. Comparing the median percent differences across the cohort (Table 4), the DI-MC-RD model exhibits less than half the error than the MC-RD for tumor cellularity (27% compared to 71%, respectively), and there is only a 13% reduction in the percent differences for the size of tumor, but neither are statistically significant.

The CCC_s also reports differences between the two models (MC-RD and DI-MC-RD) when comparing the predicted spatial distribution of tumor cells in each voxel to the calculated spatial distributions of each voxel (Table 4). The DI-MC-RD model has a larger CCC_s compared to the MC-RD for each patient in the cohort. However, the median CCC_s is the same for both models (0.33). Again, note that for patient 3 the CCC_s is near zero for both models. Additionally, the CCC_t comparing the total cellularity predicted by each model versus the calculated cellularity is illustrated in Fig. 7b, showing the CCC_t value is increased from 0.85 to 0.99 ($p < 0.01$) by incorporating drug into the MC-RD model to generate the DI-MC-RD model.

3.4 Comparing results for 2D and 3D

Except for the case of Patient 3, the 3D analysis generated predictions for tumor size and cellularity that were closer to the calculated values compared to the 2D results (Table 4). However, with this cohort of only five patients, no significant difference in the percent differences (between predicted and calculated) in cellularity or tumor size was observed between the 2D and 3D analysis, using the two-sided Wilcoxon rank sum test ($p > 0.05$). For total predicted cell number, the CCC_t values for the models in 3D are larger than in 2D. However, the CCC_s values comparing the spatial distribution of tumor cells are not significantly different between the 2D and 3D analysis, but small changes in the tumor shape and cell densities are visible in the central slice results presented in Figures 6 and 8.

For the calibrated parameters, there are some distinctions between the 2D and 3D results. For the carrying capacity (θ), the ranges for the 2D versus 3D calibration values overlap. However, for the parameter D_θ , the fact that the median value for the 2D calibration is greater than that of the 3D calibration is likely due to the “movement” of tumor cells required for the 2D calibrations. That is, the 2D slice simulation is limited in that it cannot consider any potential shrinking (or growing) of the tumor in the z direction (i.e., data from slices above or below any given tumor slice are, of course, not included in the a 2D simulation in the x - y plane), so to match the shape of the tumor changing from scan 1 to scan 2, tumor cell diffusion tends to be greater in the 2D case. Similarly, the larger differences in α between the 2D and 3D calibrations (an order of magnitude in their medians) are likely due to the effect of drug being severe in the 2D case as cells cannot move in the z direction.

4. Discussion

Specific improvements were made to a reaction-diffusion model for tumor response by incorporating patient-specific therapy regimen, using DCE-MRI data kinetic modeling to estimate distribution of drugs in the tumor tissue. We compared the performances of the two models, the modified DI-MC-RD and the original MC-RD, for predicting tumor response at each patient’s third MRI scan using the observed, MRI measurement-based response results as the reference standards and four different measures: total tumor percent difference in cellularity, total tumor percent difference in size, CCC_s to assess the relationship between the predicted and calculated spatial distribution of tumor cells at the voxel level, and CCC_t to assess the relationship between the predicted and calculated total cellularity for the whole

tumor. For a cohort of five patients, on average the DI-MC-RD model outperformed the original MC-RD model on all measures in the 2D and 3D analysis. In 2D, the extended model outperformed the original model for each individual patient as well. The median of the percent difference in the total tumor cellularity between DI-MC-RD predicted and calculated values is less than half of those for the original MC-RD model in both 2D and 3D analysis. It is important to note that changes in cellularity was shown to be better than RECIST for prediction of breast cancer response to neoadjuvant chemotherapy in the previous study using the MC-RD model [1]. Additionally, the CCC_t for the total predicted cellularity versus the calculated cellularity improved from 0.81 to 0.96 in 2D and 0.85 to 0.99 in 3D ($p < 0.01$) when comparing the extended model with the original model. These preliminary results provide strong evidence in support of using DCE-MRI to estimate drug delivery and incorporating this information in the model [32–34].

There is an option to model with MRI data and simulate results in 2D or 3D. The spatial resolution of breast DCE-MRI data can vary substantially between data acquisition protocols used at different sites. It is debatable whether a 3D simulation in place of a 2D simulation is necessary due to the usually greater computational burden for the former. The data utilized in this study was acquired with nearly isotropic, high spatial resolution ($1.0 \text{ mm} \times 1.0 \text{ mm} \times 1.4 \text{ mm}$), while the previous modeling studies used images with relatively low spatial resolution with 5 mm slice thickness [1, 14, 15]. Therefore, this begs the question of whether there would be significant differences between 2D and 3D model predictions using the high-resolution data. While our model simulations in 3D generally gave predictions closer to the calculated values for tumor cellularity and size than the 2D results, the differences between the 2D and 3D analysis were not statistically significant. Further investigation with a large sample size may lead to findings of differences with statistical significance.

This work demonstrates the promise of incorporating imaging data into mathematical models to predict tumor growth and response to therapy. Recent work in this growing field of subject-calibrated mechanistic models shows strong potential of these models to be used for improved cancer care by accurately predicting tumor growth and response outcomes to radio- and chemo-therapies [31, 35–40]. Specifically, on breast cancer patient response to NACT, our study shows that a data driven extension of the MC-RD model to include the dynamics of NACT drugs, estimated using DCE-MRI data, can significantly improve the model's performance for prediction of tumor response. Furthermore, in previous investigations with 2D analysis, only the central slice of the tumor was considered [1, 14], whereas here we have assessed the predictive ability of both models for all MRI slices. Moreover, we assessed the models' ability to match the spatial distribution of tumor cells on a voxel-by-voxel basis, which was not previously measured. Perhaps most importantly, this work further illustrates the ability of a mathematical model in predicting tumor response compared to conventional methods using a cohort of patients with different types of breast cancer, therapies, and tumor responses—including a patient where the tumor regrew after initial response to therapy.

There are several limitations in this study. One limitation is the small sample size (a cohort of five patients); however, as an initial effort to determine if this model extension can improve the performance of the original MC-RD model, this data set does provide sufficient

evidence supporting the use of DCE-MRI data as means to incorporate patient specific drug regimens in the model to improve predictive performance. Another limitation is that the modeling approach assumes there is only one tumor cell phenotype, while it is well known that tumors are quite heterogeneous at all spatial and temporal scales. While the spatially defined proliferation map allows the model to better capture local behavior of the tumor cells, a simplifying assumption was made that all tumor cells respond similarly to drug therapy with the global α parameter in Eq. (6). It is important to note that assigning the delivery of drug in the DI-MC-RD model is only a first order approximation, not unlike other efforts that have incorporated drug therapy heterogeneously through tissue [34, 41–43]. Also, with respect to concentration maximums in the plasma, there can be a 10–30% variation between patients. If a patient's drug concentration in the plasma deviate from these population curves, this would affect the calibration of the model parameters. However, the tumor death due to the drug concentration parameter (α) provides a layer of flexibility in the model whereby the population averaged approximation of the drug in the plasma is modulated by this global parameter.

A limitation in our approach for estimating cellularity is that there is a level of ambiguity in the source of changes in ADC , as many other factors (cell membrane permeability [44], cell size, and tissue tortuosity [45]) in addition to cellularity can also effect the ADC . While there is abundant literature on the inverse relationship between the measured ADC and tumor cellularity [21, 46–49], the approach of appraising cellularity with ADC is, admittedly, an approximation, and future efforts are needed to investigate how to eliminate some of the ambiguity in the interpretation of ADC . Further, to assign the maximum number of the tumor cells that can fit within the voxel (i.e., the carrying capacity, θ) for each patient, we find the minimum ADC over all ADC values measured during the three patient scans. That minimum ADC value determines the carrying capacity, θ , which is then kept fixed for all three data sets. A more biologically based approach would be to allow the carrying capacity to evolve in time [50]; though this would, of course, lead to a more complex model requiring another model equation for θ .

A next step for improving the DI-MC-RD model, are the incorporation of drug diffusion within the tissue after it has been delivered, and a more complete characterization of the mechanisms by which a given therapeutic regimen induces cell death. We will also draw on our current efforts in modeling angiogenesis using MRI data [51, 52] to include evolving vasculature for drug delivery in the model to improve its ability to match the heterogeneity within the tumor.

However, in spite of the above limitations, it is important to note that we have developed a spatially and temporally resolved model of tumor growth and treatment response that can be calibrated almost entirely with data that can be obtained from individual patient in clinical settings. To the best of our knowledge, this study is the first attempt at using patient specific DCE-MRI data to estimate drug delivery, which is then explicitly used in a model system to predict tumor response to NACT. We posit that these are important and highly novel attributes of our tumor modeling philosophy [13, 53, 54].

5. Conclusion

We have developed a significant extension of previously published models [1, 14, 15] by incorporating patient-specific therapy regimen into a mechanics-coupled, reaction-diffusion model for predicting tumor response to treatment, using DW-MRI to estimate tumor cellularity and DCE-MRI to estimate drug delivery. Preliminary results from a cohort of five breast cancer patients show substantial reductions in the errors of the model predicted tumor cellularity and size in response to NACT when compared to the original model. This work demonstrates the plausibility of using DCE-MRI to characterize drug delivery for incorporation in the model system, and represents a step toward the goal of achieving patient-specific prediction of tumor response to NACT in breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Slices from all three scans (indicated by the triplicate images) from each patient must be pre-processed to extract ROIs, tumor cell numbers, tissue properties, and drug distribution maps. After the breast ROI is manually identified (panel a), DCE-MRI data from each scan is used to determine tumor ROIs from the levels of enhancement (please see section supplemental materials for details, panel b). Additionally, physiological parameters associated with vasculature are estimated from the EKT model and breast tissue properties (fibroglandular and adipose) are identified (panel c). Using the patient's individual therapeutic schedule (panel d) and the EKT model parameters, the distribution of drug throughout the tumor tissue for all time points is calculated (panel e). Tumor cell densities are calculated using the DW-MRI data (panel f), where ADC values are converted to the number of tumor cells per voxel within the defined tumor ROI (panel g). Dashed box (panels e and g) indicates the resulting processed data used for the calibration and prediction steps.

Figure 2.

For each patient, model parameters must be calibrated (panels a–d). Tumor cell numbers, tissue properties, and drug distribution maps from Scan 1 (panel a) are used to initialize the model along with a first guess for global parameters (i.e., D_0 , θ and α) and the spatially defined proliferation map, $k(\vec{x})$ (panel b). The model is then simulated forward in time to Scan 2 (panel c), where the model result for tumor cell density is compared to the calculated tumor cell number from the patient’s Scan 2 DW-MRI data (panel d). If the difference between the model simulated and the MRI data-derived tumor cell numbers is not minimized, using the Levenberg-Marquardt method, the parameters are updated (panel b), and the model is evaluated again (panel c). This process will repeat until the model simulation is a sufficient match to results derived from the actual patient data; then the parameters are considered optimized and stored for the prediction step. Dashed boxes indicate results generated from pre-processing (Fig. 1) of scan 1 (panel a) and scan 2 (panel d) data.

Figure 3.

For the prediction step (panels a–d), tumor cell numbers, tissue properties, and drug distribution (panel a) maps from scan 2 are used to initialize the model along with the optimized values for global parameters and the spatially defined proliferation map from calibration (panel b). The model is then simulated forward in time to scan 3 (panel c), where the model prediction for tumor cell densities is compared to the calculated tumor cell number from the patient's scan 3 (panel d). The concordance correlation coefficients (CCCs) across all voxel values and percent differences in cellularity and tumor size are calculated for each patient. Dashed boxes indicate data generated from the pre-processing of scan 2 (panel a) and scan 3 (panel d) data.

Figure 4.

Example ADC (top row) and K^{trans} (bottom row) maps for voxels within the tumor ROIs on a central slice for one patient (patient 1) for all three scans. Note that the smaller the ADC , the denser the tumor is (higher cellularity). As the tumor shrank in time, areas with low ADC values became more isolated regions in the tumor. K^{trans} values changed with the changing vasculature effected by chemotherapies.

Figure 5.

Example “snap shots” of a drug dosing schedule and drug distribution map changing in time for the central slice of patient 1 between scans 1 and 2. On the left, is an example curve of the concentration of drug in the plasma. Different time points are indicated by the vertical dashed lines and corresponding tissue maps from these time points are on the right. At time point (a), the patient has not yet received chemotherapy, time point (b) is just after the administration of the drug, and time point (c) is several days after therapy. The corresponding calculated drug distribution in the tissue for all three example time points (a–c) are on the right with the same labels, using the EKT model.

Figure 6.

Two-dimensional results for both the MC-RD (top row) and DI-MC-RD (bottom row) models of a central slice compared to the observed results for the patients' third scans (middle row) for all five patients. Note the differences in concentrations of cells and spatial distributions throughout the tumors—also differences in shape between MC-RD model and the DI-MC-RD model driven by the drug distribution.

Figure 7.

Plots of the model predicted tumor cell number with both the MC-RD and DI-MC-RD models versus the MRI estimated tumor cell density over the whole tumor for each patient: the two-dimensional (a) and three-dimensional (b) results. The dashed line is the line of unity. The CCC_t value is significantly larger for the DI-MC-RD model compared to the MC-RD model in both cases ($*p < 0.01$).

Figure 8.

Three-dimensional results for both the MC-RD (top row) and DI-MC-RD (bottom row) models of a central slice compared to the observed results for the patients' third scans (middle row) for all five patients. The differences between model predicted and calculated cell numbers and tumor shape are similar to those from the 2D analysis; but in 3D, there are generally lower cell densities overall but not statistically different.

Table 1

Clinicopathologic characteristics of the patient cohort.

Patient	Age (yr)	Tumor Type	Tumor Grade	Receptor Status (ER,PR,HER2)	Therapy
1	56	IDC	3	(-, -, -)	P → AC
2	39	IDC	3	(+, -, +)	P → AC
3	34	IDC	2	(+, +, -)	P → AC
4	75	ILC	2	(-, -, -)	AC → P
5	31	IDC	3	(-, +, -)	AC → P

IDC: invasive ductal carcinoma; ILC invasive lobular carcinoma; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2. P: Paclitaxel; AC: adriamycin + cyclophosphamide.

Table 2

Description of variables and parameters for the DI-MC-RD system (Eqs. (3), (4), and (6)) including assigned parameter values and specification of units—all assigned values in the DI-MC-RD system are the same as for the MC-RD system (Eqs. (2), (3), and (4)).

Variable	Description
$N_{TC}(\vec{x},t)$	Number of tumor cells in the voxel at position $\vec{x}$ at time t
D	Diffusion coefficient of tumor cells, where $D = D_0 \exp(-\gamma \sigma_{vm}(\vec{x},t))$ (mm ² /day)
σ_{svm}	von Mises stress (kPa)
$\vec{u}$	Displacement vector due to tumor cell growth (mm)
G	Shear modulus due to breast tissue properties, where $G = E(2(1-\nu))$ (kPa)
$C_{tissue}^{drug}(\vec{x},t)$	Concentration of drug in the tissue in the voxel at position $\vec{x}$ at time t (μM)

Parameter	Description	Value
D_0	Diffusion coefficient of tumor cells without stress	Calibrated, mm ² /day
γ	Mechanical coupling coefficient for stress	Assigned at 2.0×10^{-3} (1/kPa, [1,7])
ν	Poisson’s ratio	Assigned, 0.45 (dimensionless) [1,7]
E	Young’s modulus for adipose, fibroglandular, and tumor tissues	Assigned, 4 kPa, 2kPa, and 20 kPa, respectively [1,7]
λ	Coupling constant for displacement of tumor cells	Assigned as 2.5×10^{-3} (dimensionless) [1,7]
$k(\vec{x})$	Proliferation rate of tumor cells in the voxel at position $\vec{x}$	Calibrated, 1/day
θ	Carrying capacity of tumor cells per voxel	Calibrated, cells
α	Efficacy of the drug against tumor cells	Calibrated, 1/(μM·day)

Table 3

Time between scans for each patient and the percent changes in total tumor cellularity and size between scans.

Patient	Tumor Cellularity Percent Change		Tumor Size Percent Change		Time Between Scans (Days)	
	Scan 1 to Scan 2	Scan 2 to Scan 3	Scan 1 to Scan 2	Scan 2 to Scan 3	Scan 1 to Scan 2	Scan 2 to Scan 3
1	-66%	-32%	-61%	-33%	26	36
2	-62%	-49%	-40%	-51%	43	62
3	-95%	61%	-91%	67%	55	65
4	-52%	-12%	-40%	-10%	42	22
5	-23%	-49%	-24%	-34%	14	41
Median	-62%	-49%	-40%	-33%	42	41
Range	-95% to -23%	-49% to 61%	-91% to -24%	-51% to 67%	14 to 55	22 to 65

Percent differences in cellularity, size, and CCC_s for comparing tumor cell values predicted by each model to the calculated values at each patient's third scan for both 2D and 3D results. The average, median, and range of the percent differences in cellularity and tumor size, as well as those of CCC_s, are given for the cohort.

Table 4

Patient	Model	Total Tumor Percent Difference					
		Cellularity		Size		CCC _s	
		2D	3D	2D	3D	2D	3D
Median across cohort (using absolute values)	MC-RD	62%	71%	58%	43%	0.27	0.33
	DI-MC-RD	24%	27%	41%	30%	0.33	0.33
Range across cohort (using absolute values)	MC-RD	10 to 165%	6% to 138%	16% to 155%	4% to 86%	0.05 to 0.50	0.05 to 0.51
	DI-MC-RD	3% to 92%	8% to 60%	10% to 142%	10% to 54%	0.08 to 0.51	0.10 to 0.49
1	MC-RD	62%	51%	58%	43%	0.38	0.41
	DI-MC-RD	20%	8%	41%	22%	0.46	0.45
2	MC-RD	113%	85%	155%	86%	0.28	0.33
	DI-MC-RD	66%	42%	142%	51%	0.37	0.33
3	MC-RD	-43%	-71%	-31%	-52%	0.05	0.05
	DI-MC-RD	-24%	-27%	-11%	-53%	0.08	0.10
4	MC-RD	10%	6%	16%	4%	0.50	0.51
	DI-MC-RD	3%	-13%	10%	-10%	0.51	0.49
5	MC-RD	165%	139%	135%	37%	0.15	0.17
	DI-MC-RD	92%	60%	134%	30%	0.25	0.30