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Three-dimensional image-based mechanical modeling for predicting the response of breast cancer to neoadjuvant therapy

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Highlights

- Medical imaging data can be used to inform mathematical models of tumor growth.
- Models may assist therapeutic intervention for breast cancer therapeutic response.
- We present a volumetric extension of our data driven mathematical model predictions.
- Inclusion of additional volumetric patient-specific data enhances model predictions.

Abstract

The use of quantitative medical imaging data to initialize and constrain mechanistic mathematical models of tumor growth has demonstrated a compelling strategy for predicting therapeutic response. More specifically, we have demonstrated a data-driven framework for prediction of residual tumor burden following neoadjuvant therapy in breast cancer that uses a biophysical mathematical model combining reaction–diffusion growth/therapy dynamics and biomechanical effects driven by early time point imaging data. Whereas early work had been based on a limited dimensionality reduction (two-dimensional planar modeling analysis) to simplify the numerical implementation, in this work, we extend our framework to a fully volumetric, three-dimensional biophysical mathematical modeling approach in which parameter estimates are generated by an inverse problem based on the adjoint state method for numerical efficiency. In an *in silico* performance study, we show accurate parameter estimation with error less than 3% as compared to ground truth. We apply the approach to patient data from a patient with pathological complete response and a patient with residual tumor burden and demonstrate technical feasibility and predictive potential with direct comparisons between imaging data observation and model predictions of tumor cellularity and volume. Comparisons to our previous two-dimensional modeling framework reflect enhanced model prediction of residual tumor burden through the inclusion of additional imaging slices of patient-specific data.
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1. Introduction

There is considerable interest in the use of computational methods to study and model the growth and behavioral dynamics of cancer [1,2]. With the significant advancement of imaging methodologies [3], efforts have begun to incorporate imaging data into macroscopic models of tumor cell growth in order to include elements of patient specificity into these modeling efforts [4,5]. We [6,7] and others [8,9] have shown the significant potential of using computational methods in a patient-specific and predictive framework to forecast [10] the response of tumors to therapy. This application is particularly compelling as it offers the opportunity for biologically-inspired computational methodologies to direct therapeutic interventions. In particular, predictive modeling strategies are potentially of great clinical significance in the setting of neoadjuvant therapy (NAT; i.e., therapy before surgery) of breast cancer.

In the neoadjuvant setting, breast cancer patients receive therapy to reduce tumor burden to a size more amenable to surgery. Furthermore, patients whose primary breast tumor responds to NAT are more likely to respond systemically, while a lack of response in the primary tumor makes systemic response unlikely. Importantly, patients who have no residual tumor burden (i.e., a pathological complete response, pCR) at the conclusion of NAT have increased survival; conversely, patients who have residual disease at the conclusion of NAT are at increased risk of early recurrence and death [11,12]. If it could be definitively determined – early in the course of NAT – that a particular therapeutic regimen is unlikely to achieve a pCR, the treating physician could discontinue the ineffective (and potentially toxic) treatment and substitute an alternative regimen. With the numerous options for NAT that have become available, development of a method to predict response early in the course of therapy is a highly relevant clinical objective. Unfortunately, conventional, tissue-based biomarkers of response require invasive biopsy with concomitant pain and morbidity as well as sampling errors due to tumor heterogeneity. Standard tumor size-based methods of evaluating response may lag behind biological response and are therefore not well-suited for predicting eventual response [13–15]. Moreover, size-based techniques may underestimate early efficacy for targeted agents exhibiting predominantly cytostatic rather than cytotoxic effects [14–16]. Accurate model prediction strategies would offer the chance to intervene in the case of prediction of failed therapy and potentially allow for a switch to a more effective regimen. To address this problem, we have recently been focused on models of tumor growth and response to therapy that incorporate important biological aspects of the cancer cell niche, such as coupling with the mechanical nature of the extracellular matrix.

Recent evidence has identified an increasingly important role for the supportive extracellular matrix stroma and demonstrated that surrounding tissue mechanics is active in shaping the growth and response of tumors [17–23]. For example, mechanical aspects of the extracellular matrix, such as tissue density and stiffness, have been linked to cancer cell proliferation and motility [24–28], with strong correlations to the aggressiveness of particular tumors. Extracellular matrix stiffness has been shown to act in a mechanoinhibitory role, whereby increased mechanical stiffness limits the expansion (proliferation and migration) in a cancer cell invasiveness-dependent manner [29–31]. These mechanobiology discoveries have motivated efforts to incorporate mechanical coupling into predictive modeling frameworks to enhance biological specificity [6,7,9,32–39]. In previous work [6,7,40], we introduced and tested the hypothesis that interactions between cancer and tissue mechanics at the macroscopic level could be described by a coupled reactive–diffusive mechanics system, where tumor cells grow and diffuse in space depending on their mechanical environment. While there is considerable data on the use of mathematical modeling to describe tumor growth and response to therapy, previous approaches are often not of the form that can be easily applied to clinical data to generate testable predictions in individual patients. Therefore, rather than use our modeling framework to simulate tumor growth *de novo*, we leverage the rich non-invasive imaging data available to construct and test patient-specific models [5–7]. Thus, we developed a mathematical approach to integrate quantitative *in vivo* imaging data into biophysical mathematical models of tumor growth in order to predict eventual response based on measurements performed before and early in the course of NAT. More specifically, we modified the reaction–diffusion model of tumor growth to include mechanical coupling to the surrounding tissue stiffness, creating a mechanically-restricted cell diffusion model. The combination of quantitative, medical imaging data to initialize and guide a mechanistic understanding provided by mathematical models has demonstrated a compelling strategy for these complex evaluations. In particular, we have previously shown that model predictions of tumor cellularity are correlated with data observations and predictive of eventual response to therapy [6,7].

In this work, we make an important step forward by extending our work to a full three-dimensional representation of the biophysics. In past work, our strategies had been limited to two-dimensional planar assumptions, i.e. we only assessed the imaging slice at the center of the tumor and assumed a plane strain approximation, implying a thick body

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