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Precision Medicine with Imprecise Therapy: Computational Modeling for Chemotherapy in Breast Cancer[1]

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Abstract

Medical oncology is in need of a mathematical modeling toolkit that can leverage clinically-available measurements to optimize treatment selection and schedules for patients. Just as the therapeutic choice has been optimized to match tumor genetics, the delivery of those therapeutics should be optimized based on patient-specific pharmacokinetic/pharmacodynamic properties. Under the current approach to treatment response planning and assessment, there does not exist an efficient method to consolidate biomarker changes into a holistic understanding of treatment response. While the majority of research on chemotherapies focus on cellular and genetic mechanisms of resistance, there are numerous patient-specific and tumor-specific measures that contribute to treatment response. New approaches that consolidate multimodal information into actionable data are needed. Mathematical modeling offers a solution to this problem. In this perspective, we first focus on the particular case of breast cancer to highlight how mathematical models have shaped the current approaches to treatment. Then we compare chemotherapy to radiation therapy. Finally, we identify opportunities to improve chemotherapy treatments using the model of radiation therapy. We posit that mathematical models can improve the application of anticancer therapeutics in the era of precision medicine. By highlighting a number of historical examples of the contributions of mathematical models to cancer therapy, we hope that this contribution serves to engage investigators who may not have previously considered how mathematical modeling can provide real insights into breast cancer therapy.

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Introduction

On May 25, 1961, President Kennedy proposed to Congress that the United States should commit itself to "landing a man on the moon and returning him safely to earth" by the end of the decade. Similarly, on December 23, 1971 President Nixon signed into law the National Cancer Act and stated it was time for the concentrated effort that resulted in the lunar landings to be turned towards conquering cancer. Of course, Neil Armstrong first set foot on the lunar surface

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on July 20, 1969, yet 46 years after Nixon's announcement we have made only modest advances in controlling this disease. This is particularly striking with the renewed lunar-centric announcement of the Cancer Moonshot Initiative by former President Obama in his 2016 State of the Union. A fundamental difference between the planetary and cancer moonshots is that the basic mathematics for gravity were known for nearly three centuries at the time of Kennedy's speech, while we still do not have a mathematical description of cancer that allows us to compute the spatiotemporal evolution of an individual patient's tumor. In the current state of oncology, we are tasked with getting to the moon without knowing $F = ma$.

Precision medicine is the concept of incorporating patient-specific variability into prevention and treatment strategies [1]. The advent of precision medicine has brought significant advances to oncology. The majority of these efforts have focused on the use of genetics to classify and pharmaceutically target cancers [2]. This approach has led to a paradigm in which tumor genotypes are matched to appropriate treatments [3,4]. For example, the addition of trastuzumab, a monoclonal antibody targeting the human epidermal receptor 2 (HER2) protein, to chemotherapeutic regimens in breast cancer patients with HER2-positive disease has resulted in improved disease-free and overall survival [5]. While the current genetic-centric approach to cancer therapy has great merit in appropriately selecting therapies and identifying new pharmaceutical targets, it can frequently overlook a host of patient-specific measures that influence response to therapy. For example, the microenvironment of the tumor alters response [6], delivery of therapy to tumors is variable as tumor perfusion is limited [7,8], and patient-specific pharmacokinetic properties vary [9,10]. Intratumor heterogeneity, at the genetic and epigenetic levels, complicates the use of gene-centric precision medicine approaches. In some tumors, a single dominant clone may be identified [11,12] and that clone may be targetable by therapy; however, neutral evolution and vast clonal diversity are more common scenarios [13–15]. For example, a single hepatocellular carcinoma may include more than 100 million different coding region mutations, including multiple sets of potential 'driver' mutations [16]. Further, the schedule on which therapy is given may significantly alter response [17–19]. These issues may be partly responsible for the high attrition rates of proposed cancer therapeutics [20].

The goal of precision medicine is to tailor therapeutic strategies to each patient's specific biology. More specifically, we define the goal of precision medicine to be the use of the optimal dose of the optimal therapy on the optimal schedule for each patient. Under this interpretation, there is an opportunity to expand precision oncology beyond the tumor-genotype-driven selection of therapy. To achieve this goal, new hypotheses related to optimal dosing and scheduling are needed. Whereas the hypotheses in genetic studies often compare tumor volume changes to a static genetic marker, dosing and scheduling require temporally-resolved hypotheses and concomitant treatment response measures. In particular, such hypotheses would need to specify *quantitatively* how the tumor microenvironment and/or patient pharmacokinetics influence response to therapy in order to adapt therapeutic approaches to measured responses. Fortunately, the tools to probe cancer from the genetic to tumor scales have rapidly matured over the past decade. While more time is needed to fully understand and contextualize the micro-, meso-, and macro-scale data coming online, several groups have demonstrated the utility of new technologies. For example, advances in imaging technologies, such as diffusion weighted magnetic resonance imaging (DW-MRI) and dynamic contrast enhanced MRI (DCE-MRI), have led to the discovery of clinically-relevant biomarkers that are predictive of response [21]. We (and others [22–24]) believe that mathematical modeling holds the potential to synthesize available biomarkers to test new hypotheses. These models will not only improve our ability to treat cancer, but it will also allow precision cancer care to enter the dosing and scheduling domains.

A goal of mathematical modeling is to abstract the key features of a physical system to succinctly describe its behavior in a series of mathematical equations. In this way, the system can be simulated *in silico* to further understand system behavior, generate hypotheses, and guide experimental design. When experimental data is available, model predictions can be compared to those data. The model can then be iteratively refined to account for data-prediction mismatches. Models can also identify high-yield experiments in cases where an exhaustive investigation of experimental conditions is infeasible [25]. Traditionally, cancer models are built off of first order biological and physical principles, such as evolution [26] and diffusion [27]. Part of the recent excitement about applications of mathematical models to cancer is the discovery of higher-order, emergent properties that any one model component does not possess [28]. For example, cancer models have been constructed to investigate the role of tumor cell-matrix interactions in shaping tumor geometry and in enhancing selective pressures [29]. Fundamentally, models built from these first principles are designed to discover new biological behaviors and principles, identify new hypotheses for further investigation, and predict the behavior of cancer systems to perturbations. These models are tuned with any available data and simulated to discover system properties [24]. However, the majority of these models are not structured to leverage currently-available clinical data to make patient-specific predictions [30]. Often, these complex mechanism-based models have been limited to *in silico* exploration, and their utility in generating patient-specific predictions remains to be investigated. Medical oncology is in need of a mathematical, mechanism-based modeling framework to leverage all available clinical information, spanning from tumor genetic to tumor imaging data, to make impactful changes on patient management [31]. In this way, models can be used to make specific and measurable predictions of the response of an individual patient to an individualized therapeutic regimen. While these models may not explicitly consider all scales of biological interactions, they may be of practical utility by consolidating clinically-available data sources into a coherent understanding of tumor growth and treatment response.

The interaction of matter is governed by weak nuclear, strong nuclear, gravitational, and electromagnetic forces just as the behavior of cells is governed by genetics and genetic expression. However, for macroscopic objects traveling at speeds much less than the speed of light, $F = ma$ is an excellent approximation of the movement of those objects. While the understanding of fundamental physical laws is still being advanced, a complete understanding is not necessary to leverage classical mechanical models to engineer mechanical tools (such as a rocket to lift astronauts to the moon). There is an opportunity in oncology to develop an analogous "classical oncology" toolkit. We posit that a complete understanding of cancer is not necessary to create tools that leverage clinical data to improve the treatment of cancer. This toolkit will likely consist of "simple" models that approximate the behavior and treatment response of tumors. Fortunately, the tools to make analogous force measurements in cancer already exist.

This perspective will highlight the utility of modeling and discuss opportunities for modeling in breast cancer treatment. Our target