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Understanding Drug Resistance in Breast Cancer with Mathematical Oncology

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Abstract

Chemotherapy is mainstay of treatment for the majority of patients with breast cancer, but results in only 26% of patients with distant metastasis living 5 years past treatment in the United States, largely due to drug resistance. The complexity of drug resistance calls for an integrated approach of mathematical modeling and experimental investigation to develop quantitative tools that reveal insights into drug resistance mechanisms, predict chemotherapy efficacy, and identify novel treatment approaches. This paper reviews recent modeling work for understanding cancer drug resistance through the use of computer simulations of molecular signaling networks and cancerous tissues, with a particular focus on breast cancer. These mathematical models are developed by drawing on current advances in molecular biology, physical characterization of tumors, and emerging drug delivery methods (e.g., nanotherapeutics). We focus our discussion on representative modeling works that have provided quantitative insight into chemotherapy resistance in breast cancer and how drug resistance can be overcome or minimized to optimize chemotherapy treatment. We also discuss future directions of mathematical modeling in understanding drug resistance.

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Conflict of Interest

Terisse Brocato, Prashant Dogra, Eugene J. Koay, Armin Day, Yao-Li Chuang, Zhihui Wang, and Vittorio Cristini declare no conflict of interest.

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Keywords

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Introduction

Breast cancer continues to be a major cause of death in women in the United States and globally [1]. The lethality of this disease is related to its robust ability to resist anticancer therapies [2]. Drug resistance, either acquired or intrinsic, is believed to cause 90% of all chemotherapy failures, and the 5-year survival rate for metastatic breast cancer in United States is only 26% [3, 4]. Multiple biological factors are believed to cause drug resistance, including genetic alteration, bypass mechanisms, altered effectors in DNA repair, pathway independent acquired resistance, pH alterations, and up-regulation of efflux pumps in cellular membranes [4–6]. Another very important, but less-discussed reason that operates at a higher scale of organization is the existence of physical barriers that limit diffusive and convective drug transport in the required lethal drug concentrations to the regions of interest. The presence of dense extracellular matrix and interstitial hypertension in the tumor microenvironment and hostile conditions, marked by hypoxia and hyperacidity, affect drug penetration and drug efficacy respectively [7–9].

Mathematical modeling has been widely used as a method complementary to experimental investigations to provide insight into cancer initiation, progression, and invasion in the past several decades [10, 11]. Its importance is increasingly recognized for its capability to interpret and integrate the massive amount of data that experimental biologists are currently producing, especially in the era of data-intensive cancer research [12]. Modeling approaches can be briefly divided into three categories: discrete, continuum, and hybrid, i.e., the combination of both (the reader can refer to [11, 13–17] for recent excellent reviews). Discrete models explicitly represent individual cells (or part of a cell or a cluster of cells) in space and time, and then track and update their states and interactions according to pre-defined computational rules derived from experimental data. In contrast, continuum models represent the tumor as a continuous mass rather than as discrete components, and give information about the overall tumor morphological behavior while neglecting the influences of individual cells. By drawing on the strengths of both continuum and discrete descriptions, hybrid modeling provides a more complete description of the tumor and its microenvironment, hence having been accepted as the more desirable choice. Regardless of the modeling technique used, computational oncologists should note that the development of a successful cancer model is a long-term, integrative, and iterative process, where available experimental data are used to guide the model design and to validate the model.

Significant progress has been made in mathematical modeling of cancer drug resistance to understand how biological and physical factors of the tumor influence therapeutic outcomes. Mathematical models have applications that range from describing drug delivery, predicting cell kill from cytotoxic therapies, and anticipating tumor growth, among many others [18]. The ability to predict tumor-related outcomes aids the interpretation of experimental data

and generation of specific biological/medical hypotheses. In this review, we will discuss the progress that has been made in mathematically describing fundamental processes in signaling networks and the tumor microenvironment, highlighting how the physical sciences can contribute to our understanding and treatment of breast cancer and other tumors.

Molecular Level Modeling

Overexpression of efflux pumps

Molecular level alterations and mutations can promote tumor formation and cellular drug resistance [13], which can cause hypersensitivity and overexpression of receptors, promoting tumor cell proliferation. For example, P-glycoprotein overexpression effectively lowers the intracellular concentration of chemotherapy, enabling cellular resistance to toxic drugs. Atari *et al.* [19] studied drug resistance mechanisms of topotecan in breast cancer based on efflux pumps and drug resistance proteins. The primary efflux pump modeled, breast cancer resistance protein (BCRP), is known to be expressed in high concentrations in membranes of resistant tumor cells. A quasi-steady nonlinear drug kinetic model was developed in this study with consideration of a single cell's compartments, comprising the matrix, extracellular region, cell membrane, cytoplasm, and nucleus. This model demonstrates that topotecan resistance can be predicted from BCRP expression in the various compartments, which could aid the design of optimal dosing regimens.

P-glycoprotein transfer between cells

Cell-to-cell transfer of P-glycoprotein from resistant cells to sensitive cells not currently expressing P-glycoprotein is observed in cancer drug resistance [20]. Pasquier *et al.* studied the role of P-glycoprotein expression in MCF-7 breast cancer cells using time-dependent mathematical model based on a continuum population density function [3]. The model investigated and quantified how the overall drug resistance was affected by rates of cell proliferation and death, P-glycoprotein induction and degradation, and P-glycoprotein transfer between cells. Their simulation results showed that the transfer of P-glycoprotein between breast cancer cells confers the multidrug resistance phenotype to cells not expressing P-glycoprotein.

HER2 induced drug resistance

Breast cancer drug resistance of HER2 (human epidermal growth factor receptor; also known as ErbB2) targeting agents, including monoclonal antibodies for HER2-positive breast cancer, pertuzumab and trastuzumab, and/or a tyrosine kinase inhibitor, lapatinib, have been well studied [21–23]. Overexpression of HER2, found in 20–30% of breast cancers [24], has a negative prognosis for survival [25]. Faratian *et al.* used a systems biology approach to formulate a kinetic model that is predictive of resistance in response to receptor tyrosine kinase inhibitors. They found that the expression level of PTEN (a tumor suppressor protein) is the only significant predictor of survival by treatment with trastuzumab [21]. Kirouac *et al.* used a multiscale network-based pharmacokinetic and pharmacodynamics model to determine the best combination treatment for HER2-amplified breast cancer cells which resulted in the combination of trastuzumab, lapatinib, and an ErbB3 inhibitor, MM-111 being the most effective of the combinations tested [22].

Application of this model in a clinical setting will determine the best mixture of various chemotherapy drugs to minimize resistance in HER2-positive breast cancer. Niepel *et al.* developed a mathematical model based on partial least-squares regression method to determine ligands that predict the response to treatment. Heregulin and ErbB3 were found to be good predictors of drug response. Clinically this model can be used to determine biomarkers of drug sensitivity and resistance [23]. Vera *et al.* also created a kinetic model which determined chemoresistance based on genetic signatures of transcription factors E2F1 (positive regulation of proapoptotic genes) and miR-205 (repression of antiapoptotic genes) [26]. Results of this model demonstrate that genetic signatures can predict chemoresistance, helping to stratify patients for risk of therapy failure.

The effect of the cell cycle on chemotherapy

The cell cycle was found to play an important role in expression of P-glycoprotein and drug resistance. Roe-Dale *et al.* [27] determined that breast cancer patients given sequential drug treatment of doxorubicin (DOX) followed by CMF (cyclophosphamid, methotrexate, and 5-fluoruracil) was more successful in reducing drug resistance than patients given alternating amounts of CMF and DOX in cycles. Chemotherapy drugs are found to be toxic in a cell-stage dependent manner, with DOX being more effective in the beginning and late portions of the cell cycle, and the CMF drugs being most effective in the beginning of the cell cycle. Specifically in [27], modeling of the cell cycle and its effect on multidrug resistance through the use of successful sequential drug treatment compares four ordinary differential equation models (for drug treatment, cell cycle, drug resistance, and a combination of cell cycle and drug resistance, respectively) to determine importance of cell cycle and resistance on cell kill. The models included drug treatment model, cell cycle model, resistance model, and cell cycle and resistance model. The cell cycle and resistance model accounted for (1) cell cycle stage based on amount of DNA in a cell in a given stage and (2) cell cycle and accumulation of drug sensitivity due to P-glycoprotein. Their simulation results were consistent with patient and experimental data, with cellular drug resistance having a bigger impact than cell cycle stage.

Tissue-Scale Modeling

Overview: Biophysical barriers to drug delivery and therapeutic resistance

Solid tumors (including breast cancer) are either drug resistant at initiation of chemotherapy, or become resistant with the progression of therapy, arguably due to selection pressure induced by cytotoxic agents on surviving cells [28]. As discussed in the previous section, the molecular principles of drug resistance play an important role in making cancerous cells refractory to treatment. Before these molecular/cellular mechanisms come into picture, two very critical aspects contribute to therapeutic resistance: drug delivery across the tumor, and the physiology of the tumor microenvironment [9].

The tumor microenvironment can be divided into three components: (1) cancer cells, (2) interstitium, which consists of stromal cells (fibroblasts and inflammatory cells) and the extracellular matrix (ECM), and (3) tumor microvasculature [29]. This environment is hostile to normal cells and is characterized by hypoxia, hypoglycemia, ATP depletion,

acidosis, denser than normal ECM, and elevated interstitial fluid pressure (IFP) compared to normal tissue [9, 30]. This biochemical environment affects cellular behavior and drug chemistry, enabling tumor cells to survive chemotherapy. The microenvironment also poses a direct barrier to drug delivery. After a drug reaches the tumor microvasculature, extravasation from the microvasculature is the first challenge to overcome to enter the tumor interstitium [31]. Subsequently, drug molecules must penetrate through the abnormal tumor interstitium, cross the individual cancer cell membranes and eventually reach their sub-cellular targets. The transit from within the microvasculature to the inside of a cell is accompanied by biophysical and biochemical barriers of the microenvironment, and molecular barriers of cancer cells. Thus, the tumor microenvironment confers drug resistance in two ways, biochemical gradients and biophysical barriers [7–9, 28].

As a tumor grows in its vascular growth phase in a confined volume, it faces two kinds of solid stress: external stress and residual stress, applied by surrounding normal tissue and by the growing tumor, respectively. This stress is of the order of 1.3–13.0 kPa, sufficient enough for causing the collapse of blood and lymph microvessels. Vascular collapse of lymphatics leads to poor extracellular fluid drainage, while collapse of blood microvessels has implications for poor drug delivery and transport of oxygen, nutrients, etc. [32, 33]. As indicated previously, tumor vasculature is drastically abnormal compared to healthy tissues. The “leaky” nature of tumor vasculature has been exploited in the passive targeting of drugs [34], but a downside of this leakiness is the development of interstitial hypertension. Due to vascular hyperpermeability and poor lymphatic drainage, particularly at the center of the tumor, excess fluid accumulates in the interstitium, elevating the IFP. IFP equilibrates with microvascular pressure which nullifies the pressure gradient required for extravasation of drug molecules on account of convection with the outgoing fluid. Thus, elevated IFP is a formidable barrier to convective transport, limiting the drug molecules from exiting the vascular compartment [35, 36], and tends to exert an isotropic fluid-phase stress that also has direct implications for vascular collapse [32, 37].

Following extravasation, the penetration through tumor interstitium occurs primarily via drug gradient-driven passive diffusion, and to some extent through convection. Usually, IFP tends to diminish pressure gradients on account of its fairly uniform elevation across the tumor, thus diffusion remains the major determinant of interstitial migration of drug molecules [36]. However, diffusion of molecules through the interstitium to reach tumor cells at a distance from blood vessels is met by immense physicochemical resistance which tends to hamper drug distribution [7, 8, 38]. Diffusion barriers within the interstitium occur on account of factors, such as cellular adhesion, dense packing of tumor cells, composition of ECM, solid and fluid stress, and large distances between vessels [39]. The physicochemical properties of drugs, such as size and charge also affect their passage through the interstitium on account of their electrostatic, hydrodynamic, and steric interactions with the ECM [40].

Clinical trials assessing drug delivery and transport

Several trials have analyzed drug delivery in patients to variable degrees of sophistication to understand the factors that influenced how much drug reached the target. For example,

gemcitabine delivery was measured for patients with squamous cell cancers of the head and neck [41], but factors related to delivery were not assessed in this trial. The main goal of delivery measurement was to determine whether specific doses of gemcitabine were sufficient for detectable delivery. The transport-related changes after antiangiogenic therapy have also been assessed, supporting the hypothesis of vascular normalization [42]. In a study conducted in breast cancer patients treated with doxorubicin, it was seen that drug did not reach all parts of the tumor tissue, and gradients were established with more drug in the periphery of the tumor than its center. This effect was more pronounced in tumors with dense packing of cancer cells [43]. The effects of paclitaxel and doxorubicin on interstitial fluid pressure and oxygenation were measured in a trial of neoadjuvant chemotherapy for patients with breast cancer, showing that paclitaxel improved the transport properties of the tumors while doxorubicin did not. This provides rationale to optimize the sequence of chemotherapies [42]. In another study done on mouse models of various solid tumors, similar trends of exponential decrease in doxorubicin concentration with increasing distance from nearby blood vessels were observed [44]. These studies demonstrate non-uniformity of drug distribution across the tumor and indicate potential involvement of biophysical barriers in thwarting chemotherapy.

We recently published a first-in-kind clinical trial of intraoperative gemcitabine infusion for patients with resectable pancreatic cancer [45]. The objectives were to measure the incorporation of gemcitabine into the DNA of tumor cells and understand the factors that influence delivery. We used semi-quantitative scoring of the pathology to assess stromal score and the staining levels of the cellular transporter of gemcitabine, hENT1 [46], which may be associated with outcome in pancreatic cancer. We also developed a mathematical model to describe the changes in density during routine contrast-enhanced computed tomography (CT) imaging of patients with pancreatic cancer. We discovered that gemcitabine delivery to the cellular DNA could be described by multi-scale transport phenomena, as characterized by both the stromal score and hENT1 levels. Furthermore, the CT-derived transport properties also correlated with the drug delivery. We extended our CT transport analysis to 110 patients who received protocol-based neoadjuvant gemcitabine-radiation for resectable pancreatic cancer, and found that the pre-therapy CT-derived transport properties correlated with pathological response and survival. Thus, transport properties of pancreatic cancer describe the delivery of, response to, and survival after gemcitabine-based therapies.

Extending these methods to patients with breast cancer would help identify the major biophysical barriers to drug delivery. Such efforts could aid the design of new therapeutic strategies that overcome these physical impediments. If combined with mathematical oncology approaches, these clinical trials could provide a mechanistic understanding of drug delivery for each patient. We will highlight some of these mathematical models.

Vascular supply of drugs

A mathematical model by Sinek *et al.* [47] accounted for the morphologic and vascular heterogeneity of tumors, and predicted the effectiveness of anticancer agents. The model employed a multiscale tumor growth and angiogenesis simulator [48] based on an adaptive

finite element mesh by Cristini *et al.* [49] for simulating tumor growth and response to chemotherapy administration. Simulation results showed that tumor microenvironmental factors relevant to drug, oxygen, and nutrient distribution led to variations in tumor response to chemotherapy, implicating this variable drug delivery as a cause of therapeutic resistance. This model can potentially serve as a tool for predicting *in vivo* pharmacokinetics of anticancer agents.

Baish *et al.* [50] developed a mathematical model using fluorescent vascular images to determine the effect of architectural, physiological and branching irregularities of tumor vasculature on the delivery of therapeutic agents and nutrients. By calculating $\delta_{\max}$ (maximum distance from the nearest blood vessel) and λ (a measure of shape of voids between vessels) from vascular images, the authors showed that the model predicted the amount of “material” (e.g., nutrients and therapeutic drugs) and the time required for the material to reach its destination. The model predicted diffusion in irregularly shaped domains and evaluated the efficacy of therapeutic agents that induce “vascular normalization” [51]. This mathematical model accounted for the existence of diffusion barriers pertinent to irregular vasculature and can be used to quantify the effect of such impediments on drug delivery. Thurber *et al.* [52] also developed a model using *in vivo* images of drug distribution around tumor vasculature from murine tumor models. Their model predicted drug distribution profiles along the vasculature with intermittent blood flow. This model may be used as an assessing tool for predicting conditions where tumors may not receive therapeutic amounts of administered drug in clinical practice, and thus might be inclined to resistance.

Transvascular extravasation of drugs

Stapleton *et al.* [53] modeled convective drug transport across tumor microvasculature and tumor interstitium to study the transport of liposomal drug delivery that implements the enhanced permeation and retention (EPR) effect by accounting for transvascular and interstitial fluid dynamics [54]. The model provided a theoretical framework for predicting intra-tumor and inter-subject variations in liposomal accumulation due to variations in EPR based on microenvironmental physiological factors. Wu *et al.* [55] extended a previously developed vascular tumor growth model [56] by incorporating IFP and interstitial fluid flow (IFF), lymphatic drainage, and vascular leakage. The model revealed the effects of elevated IFP on drug, nutrient and oxygen extravasation, and tumor growth, as it indicated that interstitial pressure caused microvascular collapse and influenced tumor growth through nutrient and oxygen deprivation.

The extravasation of molecules tends to be affected by steric, hydrodynamic and electrostatic interactions between molecules and pores of leaky vessels. Stylianopoulos *et al.* [57] studied interactions between nanoparticles and negatively-charged pores to predict the existence of an optimum value of surface charge density. The model was applied to various sizes of nanoparticles and found that for every nanoparticle size, there is a value of surface charge density above which electrostatic forces become dominant and leads to a steep increase in transvascular flux. Such a mathematical model would play a critical role in guiding the design of nanotherapeutic formulations for anticancer drug delivery.

Drug diffusion through tumor interstitium

Stylianopoulos *et al.* [58, 59] modeled the tumor interstitium to predict the effects of repulsive electrostatic interactions and fiber network orientation on the diffusion of charged drug molecules through the matrix. Their model predictions suggested that electrostatic interactions between fibers and drug molecules/nanoparticles tended to slow down diffusion. This prediction explained the observation that neutral particles diffuse faster in comparison to charged particles. Simulating fiber network orientation with varying degrees of fiber alignment, their analysis demonstrated that the overall diffusion coefficient was not affected by network orientation; however, diffusion anisotropy was predicted as a result of structural anisotropy. Diffusion anisotropy becomes even more significant with increasing degree of fiber alignment, particle size, and fiber volume fraction.

As an extension to a three-dimensional multispecies nonlinear tumor growth model by Wise *et al.* [60], Frieboes *et al.* [61] developed a model based on *in vitro* spheroids and monolayers of breast cancer cells that incorporates the biophysical barriers for drug and nutrient diffusion and provides a quantitative relationship between tumor phenotype and its response to chemotherapy. The model simulates impeded diffusion of drug, oxygen and nutrients, and correlates it to poor response to chemotherapy on account of both poor drug delivery and lack of nutrients required for cellular proliferation. The model can be instrumental for clinical use in predicting the effect of chemotherapy on a tumor of known phenotype. Das *et al.* [62] also modeled the three-dimensional aspects of the tumor microenvironment in the context of the diffusion of interferon- γ through the tumor interstitium. The mathematical model predicted the limited success of immunotherapy in breast cancer on account of the diffusion barriers.

Recently, Pascal *et al.* [63] developed a mathematical model based on the physical laws of diffusion to predict the fractional tumor killed due to chemotherapy. The important parameters in the model were volume fraction occupied by tumor blood vessels and their average diameter, as measured from histopathology. Drug delivery to cells and subsequent tumor cell kill were assumed to be mediated by these microenvironmental properties. The model predicted tumor cell kill in colorectal liver metastases and glioblastoma, using patient-specific histopathology data (Fig. 1). Thus, it can be used to develop individualized treatment strategies that account for the amount, frequency, and delivery platform of drugs and other cytotoxic therapies.

Biochemical gradients within tumor microenvironment

For cancer cells to remain alive and actively dividing, it is critical that their metabolic requirements be met. When the metabolic load supersedes the supply of oxygen and nutrients, hypoxic tumor cells tend to induce angiogenesis to maintain a constant supply of oxygen and nutrient rich blood. Despite neovascularization, there is a continual gap between demand and supply; aggressive tumors might have high microvascular density but still have significant hypoxia and acidosis due to inadequate perfusion [64]. Due to aberrations in the vessel wall integrity, tumor blood tends to become hyperviscous. As a result of solid and fluid stress within the tumor, vascular collapse can occlude the flow of blood, leading to high resistance to blood flow and thus insufficient perfusion.

The distribution of tumor vasculature within the tumor is heterogeneous, creating anisotropy in perfusion in terms of both space and time. As a result of heterogeneity of blood perfusion, drug does not reach uniformly to all parts of the tumor leading to a population of cancer cells being untouched, or only moderately touched by the cytotoxic agent. Tumor tissue tends to develop gradients of oxygen level, pH, glucose, ATP and rates of cancer cell proliferation across the tumor. A direct implication of hypoxia is G₁/S-phase cell cycle arrest [65]. Due to low extracellular pH, weakly basic drugs tend to get protonated and exhibit lower cellular uptake [66, 67]. Eventually these biochemical gradients result in reduced sensitivity to cell cycle specific cytotoxic agents [68]. In extension to a mathematical model [69] that predicted the extent and location of quiescent cells in multicellular spheroids, Venkatasubramanian *et al.* [70] incorporated cell cycle progression, nutrient and drug transport limitations, and pharmacodynamics and pharmacokinetics to predict the effect of tumor microenvironmental heterogeneity and hostility on drug cytotoxicity. Their simulation results suggest a therapeutic strategy: optimizing molecular weights of drug molecules to reach an optimum diffusion coefficient that is neither too small to be cleared from blood before effective penetration, nor too large to limit effective drug retention.

Overcoming physical barriers with nanotherapeutics

Current standard therapies for breast cancer are efficacious to a limited extent [62]. Nanotherapies may confer advantages over conventional drugs in overcoming therapeutic resistance. Possible advantages include delivering higher concentrations of drug, promoting greater drug uptake by tumor cells, overwhelming drug efflux pumps, accumulating drug in tumor vasculature, and causing less toxic effects on the patient [71, 72]. Silica nanovectors with doxorubicin were able to overcome therapeutic resistance and outperform traditional therapies against hepatocellular carcinoma *in vitro* because of their ability to carry much higher concentrations of drug. This promoted a higher amount of overall drug uptake and greater overall cell kill [73]. Nanoparticles (NPs) also use far less drug overall, allowing for the potential to deliver larger quantities of NPs or even higher concentrations with still fewer negative cytotoxic effects [74]. A study done with osteosarcoma found that NPs loaded with doxorubicin were more effective because they had higher levels of accumulation in solid tumors and they were able to deliver drug to the nucleus of the tumor cells [75]. This accumulation may be attributed to longer circulation times due to their small size and specific surface ligands. These small NPs can specifically target tumor endothelium with low or high affinity, enabling them to distribute throughout the tumor, or accumulate at the inlet depending on which is desired in a specific treatment [71, 72]. Many researchers also contribute NPs effectiveness to its ability to circumvent therapeutic resistance efflux pumps such as P-glycoprotein, preventing drug loss from tumor cells [73, 75].

Conclusions

Mathematical models of drug resistance are summarized in Table 1. These efforts have produced encouraging results in understanding cancer drug resistance, as seen in other research areas such as identification of novel therapeutic targets [76–78], development of alternative therapeutic strategies [79], and prediction of surgical volume and tumor size [80].

Eventually, these data-driven models could help improve patient outcomes and reduce costs of cancer treatment. However, the results reported to date based on mathematical methods have not been sufficiently accurate or particularly helpful for clinical use. Here, we discuss some directions in applying this type of integrated experimental and systems modeling approach in understanding drug resistance in cancer.

Multiscale modeling

Cancer results from multiple genetic, epigenetic, and environmental factors in a developmental context across a number of biological scales in time and space [10]. Hence, understanding cancer drug resistance mechanisms by mathematical modeling should not be limited to any specific biological scale, whether it is at the molecular level (gene, protein, or signaling network) or higher, such as a tissue or organ level. By integrating data from multiple levels of biological complexity, modeling tumor resistance to chemotherapy drugs across different scales can potentially be more powerful in guiding the development of new treatment strategies. In this perspective, by taking into account important oncological characteristics such as individual and collective cellular activities, tumor heterogeneity, and the changing heterogeneous microenvironment, a multiscale model of drug resistance may provide a new means of predicting the overall tumor drug resistance behavior in responding to changes that occur on any biological scale. This research has not yet been fully explored in the field. It is also noteworthy that the development of a successful cancer model of drug resistance is a long-term process, and that available experimental data should be used to guide the model design and to verify and validate model results.

Translational clinical trials

Understanding drug resistance through the use of mathematical modeling will help in tailoring medical care to each patient. Carefully designed clinical trials that specifically integrate a mathematical oncology component are needed to achieve this goal. Currently, radiological and pathological data are not fully utilized in most clinical trials for correlative studies. We have shown how both sources of data can reveal critical insights into the physical mechanisms of drug delivery and cytotoxicity [45, 63]. These individualized approaches using physics can complement efforts to personalize treatment based on biological factors specific to an individual (genes, proteins, environment) [81], which has been the major focus of correlative studies of most clinical trials. As we move toward an era of integrated, personalized cancer care, it will be imperative to combine biological and physical sciences to circumvent drug resistance mechanisms in the effort to cure cancer.

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Figure 1.

Results of fitting the model [63] to patient data by a regression analysis. Fraction of tumor killed f_{kill} and thickness of dead tumor regions r_k were measured in 49 histopathological sections of colorectal cancer metastatic to liver after chemotherapy. Quadratic least-square fit (dashed curve; $R^2 = 0.92$) and least-square fit (red curve; $R^2 = 0.94$) of the model are shown. Biologically realistic parameter values obtained from the fit are shown in the inset table. BVF: blood volume fraction; r_b : blood vessel radius; and L : diffusion penetration

distance. This analysis demonstrates that the model agrees with the distribution of the patient data. Adapted with permission from [63].

Table 1

Summary of mathematical models addressing drug resistance in cancer at different scales.

Phenomenon	Source	Major finding	Clinical relevance
Overexpression of efflux pumps	Atari <i>et al.</i> [19]	<i>In vitro</i> topotecan resistance can be determined by aldehyde dehydrogenase concentration and expression of the efflux pump, BCRP	Provides framework for <i>in vivo</i> studies to predict topotecan resistance for breast cancer based on parameters measured
P-glycoprotein transfer between cells	Pasquier <i>et al.</i> [3]	P-glycoprotein transfers between cells to confer resistance to cells not expressing the efflux pump	Predicts population of resistant cells and framework for how resistance spreads in breast cancer
HER2-induced drug resistance	Faratian <i>et al.</i> [21]	Tumor suppressor protein (PTEN) is only significant predictor of resistance in patients	Predicts survival of treatment for HER2 positive breast cancer
	Kirouac <i>et al.</i> [22]	Combination of drugs is required to be most effective against resistance	Predicts optimal drug combinations necessary to overcome resistance in HER2 positive breast cancer
	Niepel <i>et al.</i> [23]	Heregulin and ErbB3 concentrations are good predictors of cell sensitivity to anti-HER2 drugs	Predicts biomarkers that can be used in clinical setting to determine drug sensitivity and resistance
	Vera <i>et al.</i> [26]	Chemoresistance determined by genetic signature of E2F1, MiR-205, and the genes they target	Predicts resistance caused by genetics
The effect of cell cycle on chemotherapy	Roe-Dale <i>et al.</i> [27]	A model considering both cell cycle and cellular drug resistance was most consistent with patient chemotherapy outcomes, sequential drug treatment was found to be the most effective chemotherapy compared to alternating drugs	Predicts that sequential ordering of drugs in chemotherapy will be more effective than alternating between drugs
Vascular supply of drug	Sinek <i>et al.</i> [47]	Microenvironmental factors relevant to drug, oxygen, and nutrient distribution lead to variations in tumor response to chemotherapy	Predicts <i>in vivo</i> pharmacokinetics and efficacy of some anticancer agents
	Baish <i>et al.</i> [50]	Architectural and physiological irregularities of tumor vasculature affect drug and nutrient delivery to tumors	Predicts efficacy of vasculature normalizing agents
	Thurber <i>et al.</i> [52]	At current clinical doses, virtually all cells in a human tumor (> 99% including cancer and non-cancer cells) should attain therapeutic drug concentrations	Predicts clinical conditions when sub-therapeutic concentrations of drug is achieved
Transvascular extravasation	Stapleton <i>et al.</i> [53]	Variations in inter-subject heterogeneity of liposomes are related to heterogeneity of peak interstitial fluid pressure.	Predicts intra-tumoral and intersubject variations in liposomal accumulation due to variations in EPR based on microenvironmental physiological factors
	Stylianopoulos <i>et al.</i> [57]	Cationic nanoparticles have superior transvascular flux into solid tumors	Guides the design of nanotherapeutic formulations
	Wu <i>et al.</i> [55]	Elevated interstitial hydraulic conductivity combined with poor lymphatic function leads to plateau profiles of IFP	Develops strategies of targeting tumor cells based on the cues in the interstitial fluid

Phenomenon	Source	Major finding	Clinical relevance
Interstitial penetration	Pascal <i>et al.</i> [63]	Biophysical mediators of therapeutic resistance and the diffusion penetration limit of drug molecules governs relative success and failure of chemotherapy	Develops individualized chemotherapy regimen, by using histopathological measurements of blood volume fractions of patient tumors
	Das <i>et al.</i> [62]	Success of immunotherapy in breast cancer limited on account of the existent diffusion barriers	Discusses potential way of overcoming the diffusion barriers to improve therapy response and prevent resistance
	Stylianopoulos <i>et al.</i> [58, 59]	Electrostatic interactions between fibers and drug molecules/nanoparticles tend to slow down diffusion when the fiber size is comparable to Debye length; diffusion anisotropy occurs as a result of fiber structural anisotropy	Guides the design of nanoparticles for effective diffusion migration through interstitium
	Frieboes <i>et al.</i> [61]	Quantifies diffusion barrier effect	Predicts the effects of chemotherapy on a tumor of known phenotype
Cellular proliferation, biochemical gradients	Venkatasubramanian <i>et al.</i> [70]	There exists an optimum value of drug diffusion coefficient, neither too high, nor too low	Makes suggestions for improving therapeutic efficacy of anticancer agents by optimizing molecular weights of drug molecules to reach an optimum diffusion coefficient