Improving Cancer Treatment via Mathematical Modeling: Surmounting the Challenges Is Worth the Effort

Franziska Michor[1,2,*] and Kathryn Beal[3,*]
[1]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
[3]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
*Correspondence: michor@jimmy.harvard.edu (F.M.), bealk@mskcc.org (K.B.)
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Drug delivery schedules are key factors in the efficacy of cancer therapies, and mathematical modeling of population dynamics and treatment responses can be applied to identify better drug administration regimes as well as provide mechanistic insights. To capitalize on the promise of this approach, the cancer field must meet the challenges of moving this type of work into clinics.

Cancer research and oncology has entered a new era of targeted therapy (Sawyers, 2004) and patient-tailored therapeutic intervention (Shrager and Tenenbaum, 2014), but resistance (Gottesman et al., 2002; Holohan et al., 2013) and tumor heterogeneity (Anderson et al., 2011; Burrell et al., 2013; Ding et al., 2012; Gerlinger et al., 2012; Landau et al., 2013) have been a barrier for realizing the clinical impact of these discoveries. This barrier is, in essence, a quantitative population genetics problem—the need to quantitatively describe heterogeneous tumor cell populations and their dynamics over time and during treatment. Using such mathematical descriptions, it is then possible to evaluate which drugs, combinations, and schedules are best for a given patient. For instance, if drugs are administered at sufficiently low doses, no drug holidays are necessary to limit the side effects and reduce patient toxicity; however, if drugs are administered at more concentrated doses, which may lead to higher cell kill, then rest periods are needed to limit side effects. Such drug holidays can lead to an exponential rebound of the tumor cell population and hence pose a significant risk for the emergence of resistance. It is unclear, a priori, which of these two example strategies are going to be more effective in reducing tumor burden and preventing the emergence or outgrowth of a resistant tumor subclone. In order to answer this question, several clinical studies have been performed to identify optimum dosing frequencies (Hryniuk, 2001; Lake and Hudis, 2004). However, it is both unethical and too time consuming to test all possible dosing schedules in pre-clinical or clinical studies, and therefore only limited clinical experimentation can be performed.

Mathematical modeling of the treatment response of heterogeneous cell populations represents an attractive avenue toward narrowing the set of possibilities that should be tested in pre-clinical models and in the clinical setting (Figure 1). Mathematical modeling can, in principle, be used to systematically search through the millions of possible dose administration strategies (each determined by a unique dose-time profile) and combination schedules (each determined by a combination of different drugs administered at different dose-time profiles) to identify the schedules that maximally extend patient survival. Indeed, a

significant amount of research effort has been devoted to developing mathematical models that identify the most effective chemotherapeutic administration regimens using optimization and control techniques (Coldman and Murray, 2000; Costa et al., 1992, 1995; Katouli and Komarova, 2011; Kimmel and Swierniak, 2006; Ledzewicz and Schattler, 2009; Martin et al., 1992; Martin and Teo, 1993; Murray and Coldman, 2003). These models are in general aimed at rapidly minimizing the total tumor burden. However, long-term patient survival depends not only on quickly decimating the total number of tumor cells, but also on controlling drug-resistant subpopulations within the tumor. The simultaneous achievement of these two goals is complicated by the fact that they are often accomplished by exerting opposing evolutionary selection pressures. Furthermore, both long-term toxicity and dose-limiting side effects must be avoided.

Below, we will highlight several examples of promising, modeling-based findings, some of which represent the few that have been or will soon be tested clinically. We will then discuss the challenges that the field must meet to enable more extensive clinical testing of mathematically discovered treatment modalities. In a landmark study, Norton and Simon (Norton and Simon, 1977) observed that clinical experience was at odds with a fundamental concept that had been instrumental in designing dose schedules for the treatment of human cancer: that small tumors were more sensitive to cytotoxic therapy than larger tumors of the same histology. The underlying assumption was that smaller tumors have a large fraction of actively dividing cells. However, Norton and Simon observed that, in many cases, the low-dose low-concentration schedules used for smaller tumors were inferior to more high-concentration, dose-dense protocols that were a relatively novel approach at that time. To understand this observation, they probed the relationship between tumor size and sensitivity to therapy by inspecting growth curves of tumors exposed to anti-cancer agents. They found that most untreated malignancies can be described using a Gompertzian growth law, which predicts an S-shaped growth curve. According to this law, the growth rate
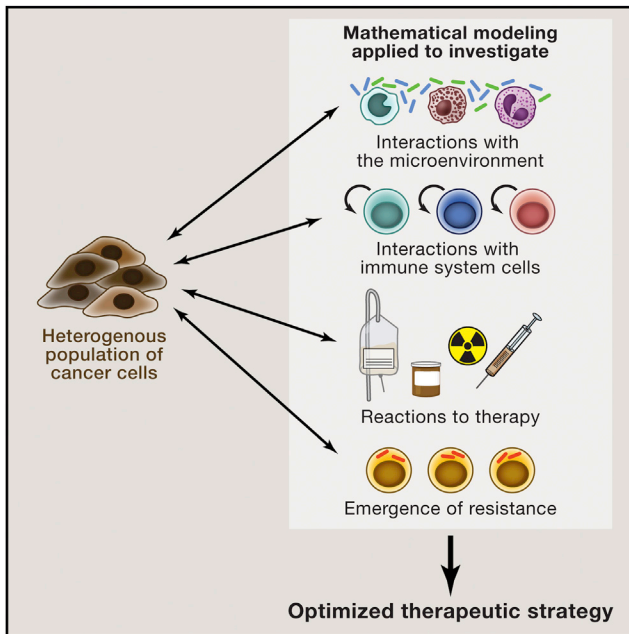
Figure 1. Exploring Complex Dependencies in Cancer Biology with Mathematical Modeling

The complexity of cancer includes not only the heterogeneous cell population of a tumor, but also its interaction with the microenvironment and immune system and responses to different kinds of treatments. Mathematical modeling of the impact of these factors on tumor cell population dynamics facilitates the generation testable hypotheses regarding the evolution of resistance and identifying prospectively optimum treatment strategies designed to maximize the chance of a cure.

of tumor cells is smallest for both very small and very large tumors but is maximum at the inflection point. Their resulting mathematical model led to the conclusion that a dose schedule capable of dramatically depleting a tumor of intermediate size may not be sufficient to cure a small tumor. They thus suggested more intense schedules, higher doses, and prolonged therapy. The authors later set out to validate their predictions in a large randomized clinical trial (Citron et al., 2003) of axillary node-positive breast cancer. They found, as predicted, that dose-dense schedules significantly increased disease-free survival and overall survival. Their approach thus became the first mathematical model providing clinically validated predictions.

The model by Norton and Simon was based on the observation that treatment efficacy can drop if insufficient drug is administered at a time when the tumor is kinetically less sensitive to treatment. This "kinetic resistance" is unlike acquired resistance due to genetic and/or epigenetic events that prevent the drug from entering the cell, binding to its target, or other mechanisms. This "biochemical" type of resistance was first mathematically addressed by Goldie and Colman, who developed a mathematical model relating the probability of drug sensitivity of a tumor to the rate at which cells accumulate changes that enable them to become resistant to therapy (Goldie and Coldman, 1979). The model assumed that there is a certain probability per cancer cell division that a resistance-causing (epi)genetic change arises. By calculating the probability of resistance and the expected number of resistant cells, the authors found not only that an increase in the mutation rate increases the probability of a resistant phenotype emerging, but also that the probability of there being at least one resistant cell will increase dramatically during a very short interval in the biological history of the tumor. The clinical recommendation based on these results was that therapy be initiated as quickly as possible to maximize the probability of a cure. This approach was later also predicted to maximize patient survival due to the emergence of more lethal cancer states such as metastases (Haeno et al., 2012).

A subsequent extension of this mathematical model considered two types of resistant cells, each insensitive to a different chemotherapeutic agent (Goldie et al., 1982). The goal of the model was to take both types of resistance into account and identify treatment schedules that would maximize the chance of a cure by preventing the emergence of doubly resistant cells. Using a computer program to simulate the development of such doubly resistant cells, the authors predicted that alternating the treatment regimen of the two drugs at every cycle would be the most effective strategy to prevent resistance. This prediction became known as the Goldie-Coldman hypothesis. A clinical trial in Italy tested this hypothesis in women with resectable mammary carcinoma and more than three positive axillary lymph nodes (Bonadonna et al., 1995). The patients were randomized into two treatment arms, either receiving treatments sequentially or in an alternating fashion. The primary endpoints were relapse free, and overall survival and the median duration of follow-up was 9 years. The trial results demonstrated significantly longer survival, both progression free and overall, for patients who received the sequential regimen as compared to the alternating regimen. A subsequent phase II study also evaluated the efficacy of alternating and sequential regimens of docetaxel and doxorubicin as first-line chemotherapy for metastatic breast cancer (Paridaens et al., 2003). The alternating and sequential groups achieved similar objective tumor response rates and median duration of response, but medial survival times were significantly shorter in the alternating than the sequential group. Furthermore, patients receiving sequential therapy were more likely to complete the planned eight chemotherapy cycles and had a lower incidence of side effects.

These trial results suggest that, at least in those clinical settings, the Goldie-Coldman hypothesis did not hold. However, the possibility remains that the hypothesis might lead to better survival times in other cancer types and/or treatment approaches (such as chemotherapy and radiation therapy). Indeed, several studies have investigated the outcome of radiation therapy followed by chemotherapy versus chemotherapy concomitant with radiation therapy. For example, in non-metastatic breast cancer, both radiation and chemotherapy are often used as adjuvant treatment following surgery. A randomized study performed in the 1990s comparing the sequencing options (of radiation versus chemotherapy first) showed a reduction in the rate of distant metastases in the group that received chemotherapy first (Recht et al., 1996). However, those results were later updated (Bellon et al., 2005) and shown to be non-significant and were then disputed in a meta-analysis of three well-documented randomized trials designed to study this question (Hickey et al., 2013). Thus, the findings regarding implementations of the

Goldman-Coldie hypothesis in the clinic remain mixed, and no clear validation of the hypothesis has been obtained so far. In fact, other recent approaches have suggested that it would be beneficial to administer combination treatment upfront to prevent the outgrowth of resistance (Bhang et al., 2015; Bozic et al., 2013; Glickman and Sawyers, 2012).

To determine whether modeling approaches could be applied to specific resistance mechanisms to individual drugs, we developed a mathematical model of non-small cell lung cancer cell response to treatment with the epidermal growth factor receptor (EGFR) inhibitor erlotinib (Chmielecki et al., 2011) in which resistance was considered to arise predominantly due to a second-site EGFR mutation (Pao et al., 2005), T790M, which emerges with a low probability during each sensitive cell division. The model, similar to the approach by Goldie and Coldman, was based on a stochastic branching process in which erlotinib-sensitive cells proliferate and die according to rates determined in a patient-derived cell line. Resistant cells then also proliferate and die according to rates determined in cells isogenic to the sensitive line apart from the T790M mutation. These in vitro cell culture experiments demonstrated that resistant cells had a fitness lower than sensitive cells in the absence of treatment, a finding explaining the low frequencies of pre-existing T790M-positive clones in patients (Chmielecki et al., 2011). The mathematical model was then used to search through the space of all clinically tolerated erlotinib schedules to identify the one that would significantly delay the emergence of T970M-driven resistance. Unlike the FDA-approved schedule of 150 mg per day, the optimum consisted of administering a low dose of 50 mg per day together with twice weekly high-dose pulses at the clinically determined maximally tolerated dose; the clinical study testing this hypothesis was initiated at Memorial Sloan-Kettering in 2013 (http://clinicaltrials.gov/show/NCT01967095). Preliminary results show that this schedule is well tolerated and might reduce the rate of progression in patients with brain metastases (H.A. Yu et al., 2015, ASCO, poster).

Although only these three population-based modeling approaches have so far led to clinical implementation, several other frameworks have been developed that might soon be tested in the clinic. These include a mathematical model suggesting the use of an adaptive therapeutic approach that changes in response to the variability in both space and time of the tumor microenvironment, cell phenotype, and response to treatment (Gatenby et al., 2009) and a model investigating alternative radiation schedules in primary glioblastoma (Leder et al., 2014). Another recent approach incorporates genetic heterogeneity in the context of selecting optimum combination strategies (Zhao et al., 2014). Other groups have used evolutionary game theory to investigate optimal combination therapies (Basanta et al., 2012) or have used patient-derived data on tumor stem cell turnover to identify prognostic factors (Stiehl et al., 2015).

These studies serve as examples of quantitative descriptions of heterogeneous cell populations responding to treatment. The potential of this approach is obvious—it enables us to systematically investigate hypotheses and test alternative options for treatment. While mathematical models and pre-clinical studies of optimized treatment schedules are encouraging, limitations of the approach are also plentiful, as illustrated by the

lack of resolution regarding the efficacy of alternating versus sequential treatments discussed above. The predictive utility of a model parameterized using a particular pre-clinical model depends on the accuracy not only of the mathematical model, but also the in vitro or in vivo model vis a vis the human cancer that it models, as well as the biological assumptions and quality of the data. The ability of the modeling predictions to be verified or falsified—not just in a model system, but eventually in a clinical study—is the essential test. In addition, knowledge is evolving: more complex aspects of tumor biology are emerging and need to be incorporated into quantitative modeling approaches. These include single-cell genetic and epigenetic heterogeneity (Van Loo and Voet, 2014) and interactions between cancer cells and the immune system (Sharma et al., 2011) as well as the microenvironment. The analysis of datasets that comprehensively and quantitatively capture such features may require novel mathematical approaches and simulation tools that, for instance, can take advantage of today's most powerful supercomputers.

Importantly, translation of these concepts and ideal models into a clinical setting presents both logistical and patient-specific challenges related to the tumor micro-environment. It is always difficult to translate a result from a cell line or animal model into a human clinical study; while there are logistical concerns related to administering any type of cancer-related treatment, we will discuss the complexities of treating brain tumor patients with radiation as a specific example. The first challenge regarding scheduling altered or "optimized" scheduled radiation, for instance, as proposed in Leder et al. (2014), reflects the process of treating patients at a specific time each day. There are staffing concerns with respect to hours of operation and coordination of scheduling multiple patients throughout the day on each linear accelerator. There is also the potential of treatment- or tumor-related toxicity that may fluctuate daily and may affect whether or not patients can tolerate treatment at very specific time(s) each day. Most patients are also fatigued and may have neurologic symptoms related to their brain tumors or treatment, which makes it difficult to adhere to a complicated or specific timing schedule. With careful patient selection and consideration of scheduling constraints, though, these challenges may be overcome. The observation of variable tumor volume among patients reflects the fact that there is great variability among patients with the extent of their brain tumor resection related to the location of their tumors in different regions of the brain and the original extent of the tumor. A patient who has a gross total resection with only microscopic residual disease may have a very different response to an altered or optimized treatment schedule than a patient who has a large, relatively intact tumor. The potential variability of tumor volume between brain tumor patients is much greater than in the breast cancer studies referred to above. This variability could certainly affect the outcome of an optimized radiation schedule clinical trial.

Other challenges are related to variability in the tumor microenvironment that may be the result of molecular differences among patients' tumors or even more simply the wide range of medications, or chemotherapy, that brain tumor patients often require as part of the management of their brain tumors. These medications may alter the cancer cells' sensitivity to radiation

or may change the vascular environment and thus indirectly affect sensitivity to radiation. Even if a study were designed that controlled for the use of common medications for brain tumor patients, such as corticosteroids, antiepileptics, or temozolomide, the requirements of some medications are likely to change during the course of radiation, or patients may discontinue some medications in the midst of their course of radiation due to toxicity. There are innumerable possibilities of drug combinations during radiation therapy for brain tumors that could both positively and negatively impact the effect of radiation. The exact schedule of those standard adjuvant chemotherapies, or perhaps investigational immunotherapies, may also alter the radiosensitivity, or clonal expansion, possibilities at any given moment. A fully optimized model would need to incorporate those possible influences as well.

Despite these challenges in designing and effectively executing a clinical trial to test treatment regimes derived from mathematical modeling and preclinical data, the endeavor should be pursued. The results with the current standard treatment are suboptimal, with a median survival of only 15 months for patients with primary glioblastoma, the most common type of malignant brain tumor. However, following surgery, radiation remains the most effective therapy for glioblastoma, and thus optimizing the effect of radiation remains an attractive option. Historically there have been many studies of various schedules of radiation for glioblastomas, including dose escalation, but the results from all are disappointing to date (Brada et al., 1999; Horiot et al., 1988; W.J. Curran et al., 1996, Proc. Am. Soc. Clin. Oncology, abstract). Notably, none of these studies have been based upon a mathematically optimized schedule. A hypothesis worth testing is that a clinical trial of a mathematically optimized radiation schedule could yield an improved result and could identify altered radiation scheduling as an opportunity for improved outcomes in other types of brain tumors or other cancer types.

Despite the logistical, tumor-, and patient-specific challenges listed above, a trial of an optimized radiation schedule is an achievable goal with careful patient selection, patient management, and support from all of the stakeholders, including clinicians, scientists, and the patients and their families. The glioblastoma mouse model study comparing a standard schedule to an optimized schedule (Leder et al., 2014) proves the concept that an altered radiation schedule can affect survival. This theory must be tested in humans with glioblastoma, as these patients need every opportunity possible to improve their outcome.

Despite the operational, biological, and mathematical obstacles that need to be overcome for successful implementation of a mathematically predicted treatment strategy in the clinic, we strongly believe that surmounting these challenges is worth the effort. The Norton-Simon hypothesis was the first demonstration that a mathematically derived schedule might be clinically superior, but many recent and forthcoming approaches hold great promise, and we have high expectations that rational quantitative investigations might contribute to new hope for cancer patients.

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