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Computational models of blood diseases

A review of mathematical models for leukemia and lymphoma

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Recently, there has been significant activity in the mathematical community, aimed at developing quantitative tools for studying leukemia and lymphoma. Mathematical models have been applied to evaluate existing therapies and to suggest novel therapies. This article reviews the recent contributions of mathematical modeling to leukemia and lymphoma research. These developments suggest that mathematical modeling has great potential in this field. Collaboration between mathematicians, clinicians, and experimentalists can significantly improve leukemia and lymphoma therapy.

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Introduction

According to the Leukemia and Lymphoma Society, in the United States, over one million people are living with leukemia or lymphoma [1]. In 2013, the incidence rates of these two classes of disease were 12.8 and 22.5 per 100,000, respectively. Thanks to advances in both diagnosis and treatment (see, for instance, [2–4]), patient outlook has significantly improved over the last few decades [1]. However, many questions about treatment remain unresolved, including optimal timing and dosage schedules, the benefits of combination therapies, and methods of preventing drug resistance and treatment failure. Mathematical models are a powerful research tool that can be applied to understanding leukemia and lymphoma. They can identify mechanisms that control the progression of the disease, or motivate and guide future experimental and clinical designs. Ultimately, the combination of mathematical models, experiments, and clinical trials can lead to significant improvements in the treatment of leukemia and lymphoma.

Hematopoiesis

Mathematical models of hematopoiesis provide a framework for mathematicians to study cancer genesis and treatment strategies. Hematopoiesis can be modeled as a system of discrete maturity stages starting with hematopoietic stem cells (HSCs) and ending with mature blood cells. Within each stage, a balance between self-renewal and differentiation must be achieved. When a cell divides, each daughter cell remains in its current compartment with a certain probability, referred to as the renewal fraction, or differentiates and enters the next stage. This complex and well-regulated process produces more than 10^{11} cells per day in order to maintain the equilibrium levels of cells in the erythroid, lymphocyte and myelocyte lines.

Despite the complexity of hematopoiesis, several simple ordinary differential equation (ODE) models have provided insight into the process. Michor *et al.* [5] divide blood cells into four categories based on maturity – stem, progenitor, differentiated and terminally differentiated – and represent each by a linear ODE. Healthy cells and cancer cells are assumed to both progress through these differentiation stages, differing only in their rates of differentiation and their ability to compete for resources.

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Marciniak-Czochra *et al.* [6] also model hematopoiesis with a system of ODEs but incorporate feedback inhibition via cytokines. It is known that environmental signals, such as granulocyte colony-stimulating factor (G-CSF) [7] and erythropoietin [8], play a significant role in regulating hematopoiesis [9]. In order to explore these regulatory mechanisms and, specifically, their role in the rapid recovery of the mature blood cell population following chemotherapy [10], the authors in [6] implement feedback inhibition from mature cells that affects proliferation rates and/or renewal fractions of the less mature compartments. This feedback is assumed to take the form of a single cytokine, such as G-CSF. When the population of mature blood cells is large, the cytokine is consumed by these cells. When the population of mature blood cells declines, the cytokine becomes more abundant, and its presence triggers an increase in proliferation, an increase in renewal fraction, or both. Numerical simulations suggest that regulation of renewal fractions alone leads to a more rapid regeneration of the mature blood cells than does regulation of proliferation rates alone, although combining the two leads to slightly faster recovery [6]. This model has also been applied to studying the dynamics of leukemogenesis [11].

By incorporating time delays or accounting for spatial or age heterogeneity, more complex models have been constructed in order to better capture the biology of the system. Time delays have been added to account for events such as cell divisions (for instance [12,13]) and the interactions between cancer and immune cells (for instance [14]). In [13], Adimy and Crauste present three delay differential equation (DDE) models of cycling and quiescent HSCs, with constant, distributed and state-dependent delays. These delays represent the time to complete one cell division. The system with distributed delays is derived from an age-structured partial differential equation (PDE) in [12]. All three models have been applied to studying periodic hematological diseases, which are characterized by oscillations in various blood cell populations. It is concluded that although all three models produce periodic solutions, the nature of the oscillations depends on the type of delay [13].

To explore oscillations that occur in multiple cell lines simultaneously, Colijn and Mackey [15] combine constant DDEs representing HSCs, leukocytes, erythrocytes and platelets. This model includes more biological detail than those mentioned earlier, in that it replaces the generic mature cell compartment with three different cell lines. The model is later applied to cyclical neutropenia and G-CSF therapy [16].

In general, deterministic ODE and DDE models, like the ones presented so far, can serve as good approximations of the average behavior of a system when the populations are large. However, when considering small cell populations, stochasticity plays a key role in the emerging dynamics. In [17], larger populations of mature cells are represented by ODEs, while a stochastic model is used for the smaller populations of less mature cells. Using a bivariate Markov process and its deterministic approximation, Chrobak *et al.* [18] model the competition between healthy and precursor T-cell lymphoma cells, for a survival stimulus. Cancer T cells are assumed to be more competitive and able to accept a wider variety of stimuli. Simulations show that healthy T cells with more specific receptors survive longer than healthy T cells with less specific receptors, while cancer T cells, despite their lack of specificity, are able to out-compete normal cells. To study drug resistance, branching processes [19,20] and birth-death processes [21,22] with mutations have been applied to calculate mutation probabilities and sizes of mutant clones at the time of cancer diagnosis. Stochastic models are especially useful when considering cancer genesis and resistance mutations, as both processes start from a single cell.

In contrast to the previous population-based models, the agent-based model (ABM) of Roeder *et al.* [23] treats each individual cell as an autonomous agent. The model considers quiescent and cycling stem cells, progenitors, and mature cells. Each stem cell is characterized by an affinity variable, which represents its tendency to either cycle or remain quiescent. Though ABMs retain valuable information about individual cells and their interactions, they are very computationally demanding, and simulations involving a realistic number of cells may not be feasible. To address this limitation, Kim *et al.* reduces the ABM of [23] to systems of difference equations [24], while Roeder *et al.* and Kim *et al.* reduce the model to a system of PDEs [25,26]. Although some detail is lost in these reductions, both systems can be used to quickly capture quantities of interest, such as the steady state distribution of stem cells, with a realistic number of cells, as computation time does not depend on the total number of cells.

Once these models have been parameterized and validated using experimental and clinical data, they serve as useful tools for studying cancer treatment and drug resistance. The models mentioned above have been applied to several diseases within the leukemia and lymphoma families, including chronic myeloid leukemia (CML) [5,17,23,26–29], acute myeloid leukemia (AML) [12], T-cell lymphoma [18] and periodic hematological diseases [13,15,16,30].

Treatment

One of the main goals of mathematical modeling of cancer is to improve treatment, either by optimizing the way existing therapies are being administered, or by motivating novel therapies. The optimal timing and dosage schedule remains an open question for many drugs used to treat leukemia and lymphoma [2–4]. Figure 1 illustrates several timing and dosage schedules, for single- and multiple-drug therapies. Mathematical models have been utilized to investigate treatment strategies, by considering, for instance, impulse versus continuous doses [29] as well as the number of drugs to be used and their order [20,22,23]. Using sensitivity analysis and

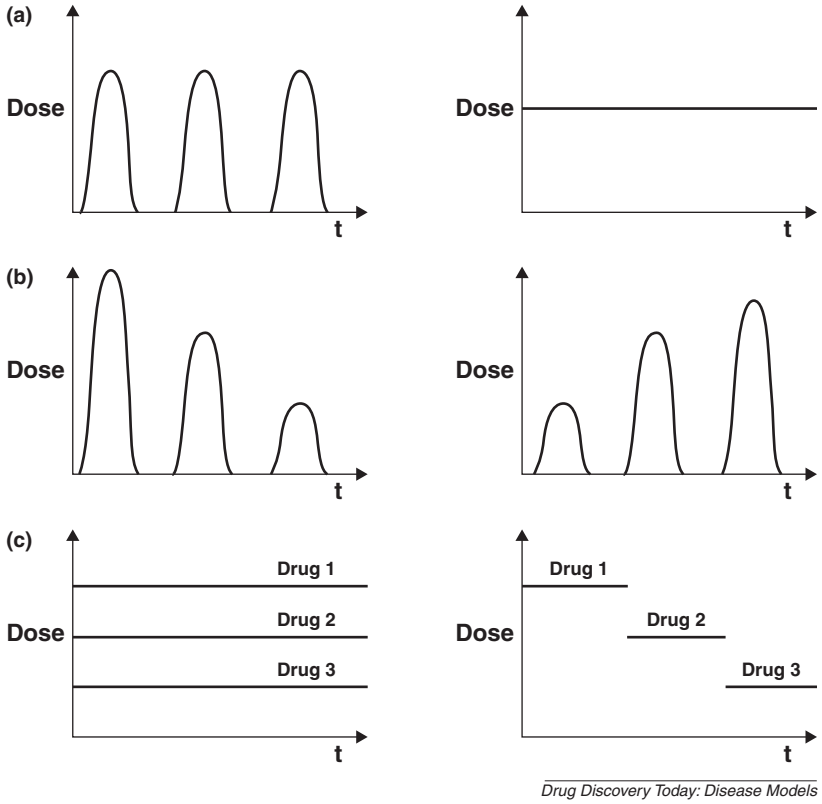

Figure 1. Timing and dosage scheduling remains an open question for many drugs used to treat leukemia and lymphoma. **(a)** For single-drug therapy, the drug can be administered in impulses or continuously. **(b)** Dosage can also vary over time, for instance by steadily decreasing or increasing the pulses. **(c)** When considering multiple-drug therapies, the number of drugs and their order must be determined. Moreover, these drugs can either be administered simultaneously or sequentially.

numerical simulation, the dependence of a treatment outcome on specific model parameters can be determined. Mathematical models can be applied to interpret experimental or clinical data, or to evaluate a treatment strategy before it is tested in an experimental or clinical setting.

Models of a single cell are useful for studying intracellular drug accumulation and concentrations of substances involved in cell fate decisions. In [31], intracellular and extracellular concentrations of methotrexate (MTX), a treatment for acute lymphoblastic leukemia (ALL), are modeled. *In vivo* measurements indicate that levels of intracellular MTX are greater in leukemia B cells than in T cells. Simulations show that increasing the dose can only partially compensate for the lower levels of intracellular MTX in T cells. It is hypothesized that extending the infusion time would lead to greater MTX accumulations in leukemia T cells and may enhance the effectiveness of the therapy [31]. A follow-up study [32] that compares infusion times of four and twenty-four hours, in a clinical trial and with an extended MTX model that includes the drug's effects on the folate pathway, supports this hypothesis.

Alarcon *et al.* [33] take a similar modeling approach to attempt to understand the factors that determine the fate of lymphoma B cells during antibody treatment. Treatment of lymphoma B cells with a specific antibody causes either apoptosis or quiescence. In order to determine how to induce apoptosis in these B cells, an ODE model of intracellular substances involved in cell fate decisions is developed. The modeling results suggest that Myc plays a crucial role in cell fate decision of lymphoma B cells during antibody therapy.

A significant amount of attention has been given to modeling the treatment of CML. Although tyrosine kinase inhibitors (TKIs) have greatly improved patient outlook [2], it remains to be determined whether TKIs alone can cure at least some patients. Several groups have argued in support of [17,23] and against [5,27] imatinib's ability to cure patients. Even in patients whose cancer has remained in remission for several years, a small number of leukemic cells may persist. In the Stop Imatinib trial [34], patients in long-term remission were taken off imatinib in order to determine whether they were cured. While 60% of patients relapsed within the first six months, 40% remained in remission for the duration of the two-year trial. It remains to be determined whether these patients were cured or whether the immune system or another mechanism was containing the remaining cancer cells. Using the ABM discussed in [23], Horn *et al.* use individual patient data to predict whether a patient would relapse if they stopped imatinib treatment [30]. Their model predicts that 14% of patients will be cured within 15 years and that 31% will remain in

remission two years after being taken off treatment. The result motivates the question of how TKIs can be improved, to speed up cancer eradication and to increase the fraction of patients who can be safely taken off treatment.

Combination therapy is a promising approach that may enhance the effects of TKIs and other drugs used to treat leukemia and lymphoma. Glauche *et al.* [29] consider the combination of TKIs and interferon-alpha (IFN-α), using the model described in [23]. They found that continuous TKI administration coupled with pulsed IFN-α is the most effective combination with the fewest side-effects. In [14], Kim *et al.* introduce a DDE model of CML and the immune response of T cells. Experimental and modeling results suggest that the immune system may play a significant role in keeping CML patients in remission during imatinib treatment [35]. An optimal load zone for leukemic cells that maximizes the anti-leukemia immune response is defined. During treatment, the cancer cell population generally falls below the optimal load zone and is thus able to evade the immune system. Carefully-timed vaccines are proposed in order to maintain a strong immune response throughout treatment [14].

Drug resistance

Drug resistance remains a major challenge in leukemia and lymphoma therapy. Mathematical models can be used to assess a patient's risk of relapse upon diagnosis and to identify strategies that minimize the probability of treatment failure.

In [28], Tang *et al.* seek to understand the contrasting outcomes of the Stop Imatinib trial [34]. By parameterizing their model [5] using patient data before and after imatinib treatment, it is found that cancer has significantly slower growth kinetics after treatment than before treatment. This result suggests that selection pressures during treatment lead to different subsets of the heterogeneous cancer population surviving, which in part explains the different patient outcomes of the trial [28].

Panetta *et al.* [36] conduct an experiment in which ALL T cells, of varying drug resistance, are treated with mercaptopurine (MP), and cell cycle distributions and apoptosis rates are measured. Using this data, they construct a mathematical model of the cell cycle and apoptosis during MP treatment. The model divides cells into normally cycling cells; cells that are cycling with thioguanine nucleotides (TGNs), a byproduct of MP, incorporated in their DNA and RNA; apoptotic cells and necrotic cells. Interestingly, the model parameterization suggests that the rate of TGN incorporation is greater in resistant cells than in sensitive cells. However, this difference is overcome by the higher rates of entry into apoptosis found for the sensitive cell line compared to the resistant lines. This result suggests that although the drug is able to incorporate itself into the cancer cells' DNA, resistance is explained by an inability of resistant cells to detect damaged TGN-incorporated DNA [36].

Using branching processes [19,20] and birth-death processes with mutations [21,22], several groups have sought to quantify the probability of resistance and the size and diversity of resistant clones, at the time of diagnosis. In both types of models, cancer initiates from a single cell, with a birth rate, death rate, and a small probability of mutation per division. Mutations can lead to several different resistance clones, each with its own growth kinetics. The time of diagnosis is estimated by the time at which the cancer population reaches a certain size. Using both simulation and analysis techniques, the aforementioned quantities can be determined.

Tomasetti and Levy [19] construct a model of cancer stem cells in which the cells may divide in one of three ways. A stem cell may divide into two stem cells (symmetric renewal), differentiate into two progenitor cells (symmetric differentiation), or divide asymmetrically into one stem cell and one progenitor cell. By incorporating data on the relapse rate of patients that are treated with imatinib [37], it is concluded that cancer stem cells tend to symmetrically renew, as opposed to their healthy counterparts that predominantly divide asymmetrically [19]. In a later paper [38], Tomasetti argues that, based on modeling results [19] and clinical data [34], imatinib affects leukemic stem cells the same way it affects all leukemic cells, by decreasing their proliferation rates.

Leder *et al.* [20] and Komarova *et al.* [21,22] use their models to determine when combination therapy can be administered to minimize the chance of resistance mutations. In [20], the authors calculate that if a patient is diagnosed at an early stage of cancer, then there is only a 12% chance of having a resistance mutation. However, when diagnosed at a late stage, the risk increases, and multiple mutations become possible [20]. Their modeling results demonstrate the importance of early detection and also suggest that combination therapy is advantageous when the cancer is detected at a late stage. Komarova and Wodarz [21] create a mathematical framework to study resistance to targeted therapies. It is found that the combination of three drugs should prevent resistance in the treatment of CML. Komarova *et al.* [22] later consider specific resistance mutations to TKI treatment of CML. They evaluate the effectiveness of combinations of imatinib, dasatinib and nilotinib. Most of the known resistance point mutations confer resistance to only one of the three, but the T315I mutation causes resistance to all three [2]. It is concluded that two-drug combination therapies can increase the probability of treatment success, but adding a third drug does not lead to further improvements [22].

Conclusion

Mathematical modeling is a valuable tool with great potential in leukemia and lymphoma research. Mathematical models

have already been applied to many aspects of these diseases. The development and validation of these models requires experimental and clinical data, and therefore the availability of this data to the research community is of central importance. Access to this data represents a crucial step toward achieving more active collaboration between mathematicians, clinicians and experimentalists. A research environment in which ideas and data are shared across disciplines will lead to more rapid discoveries that will improve our ability to treat leukemia and lymphoma.

Conflict of interest

The authors have no conflict of interest to declare

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