Mathematical Models of Chronic Myeloid Leukemia
Ph.D. Candidacy Prospectus, Applied Mathematics and Scientific Computation

1 Motivation

Chronic myeloid leukemia (CML) is a myeloproliferative disorder caused by the formation of the Philadelphia chromosome, which produces the BCR-ABL gene that codes for a constitutively active tyrosine kinase. The development of first (imatinib (IM)) and second generation (dasatinib, nilotinib) tyrosine kinase inhibitors (TKIs) has significantly improved patient outlook, sending a majority of patients into remission [4]. Still, several open questions about the dynamics of CML and TKIs remain. Mathematical modeling has been successfully applied to studying the effects of TKIs, combination therapies, and drug resistance. In the following, we will focus on applications of an ordinary differential equations (ODEs) and an agent-based model (ABM) to the study of CML.

2 Mathematical Models of CML

2.1 The Michor Model

In the model of Michor et al. [2], hematopoietic cells are divided into four categories based on their maturity: stem cells (x_0), progenitors (x_1), differentiated cells (x_2), and terminally differentiated cells (x_3). Leukemic cells are assumed to differentiate through the same stages, represented by y_0, y_1, y_2, and y_3. The mathematical model for these populations is given by

$$\dot{x}_0 = \left(\frac{r_x}{1 + p_x(x_0 + y_0)} - d_0\right)x_0, \tag{1a}$$
$$\dot{x}_1 = a_x x_0 - d_1 x_1, \tag{1b}$$
$$\dot{x}_2 = b_x x_1 - d_2 x_2, \tag{1c}$$
$$\dot{x}_3 = c_x x_2 - d_3 x_3, \tag{1d}$$
$$\dot{y}_0 = \left(\frac{r_y}{1 + p_y(x_0 + y_0)} - d_0\right)y_0, \tag{2a}$$
$$\dot{y}_1 = a_y y_0 - d_1 y_1, \tag{2b}$$
$$\dot{y}_2 = b_y y_1 - d_2 y_2, \tag{2c}$$
$$\dot{y}_3 = c_y y_2 - d_3 y_3. \tag{2d}$$

In Equations (1a) and (2a), r is the division rate, and p is the sensitivity of the stem cell population to crowding. The x_0+y_0 in the denominators incorporates competition between the healthy and leukemic stem cell populations. In Equations (1b)-(1d) and (2b)-(2d), a, b, and c are the differentiation rates of stem cells, progenitors, and differentiated cells. The parameters d_0, d_1, d_2, and d_3 are the death rates of stem cells, progenitors, differentiated cells, and terminally differentiated cells. The healthy and leukemic populations are assumed to differ in their division rates, sensitivity to crowding, and differentiation rates.

Treatment with TKIs is represented in the model by decreases in a_y and b_y. In order to compare their simulations of therapy to clinical data, the following formula is used to approximate the BCR-ABL ratio, a measurement used to evaluate a patient's progress during therapy.

$$\text{BCR-ABL ratio} = \frac{100\alpha y_3}{2x_3 + y_3}. \tag{3}$$

The BCR-ABL ratio is the ratio of the expression of BCR-ABL in the blood to the expression of a control gene, either BCR or ABL. Most cells in the blood are assumed to be terminally differentiated, so the contributions of the other compartments are ignored in the calculation. Each leukemic cell has one copy of BCR-ABL and one copy of the control gene, while each healthy cell has two copies of the control gene. This ratio is multiplied by an adjustment factor α to address the differing levels of

expression of the two genes, and by 100 in order to represent a percentage when $\alpha = 1$, and otherwise a value between 0 to 100α.

2.2 The Roeder Model

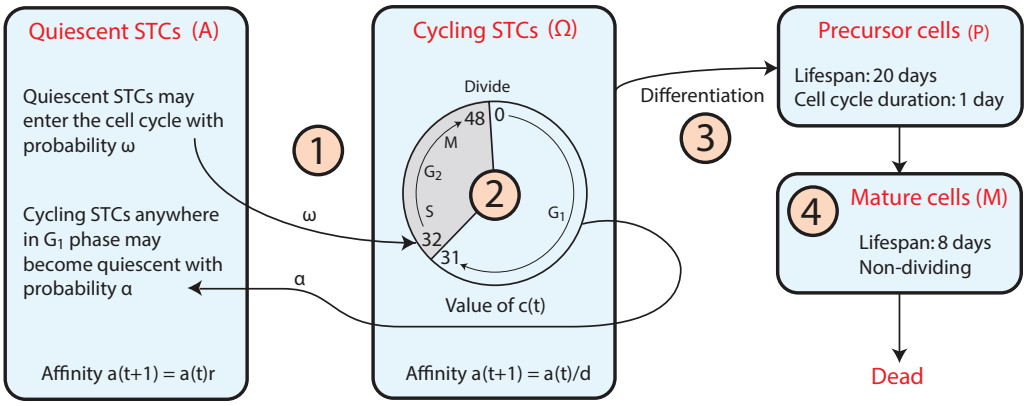

Figure 1: A state diagram for the Roeder model.

The ABM proposed by Roeder et al. [3], shown in Figure 1, divides hematopoietic cells into stem cells (STC), precursors (P), and mature cells (M). Stem cells are either quiescent, denoted by A, or cycling, denoted by Ω. Each individual stem cell is characterized by an affinity $a(t) \in [a_{min}, a_{max}]$, which determines the cell's tendency to be quiescent or cycle. At each time step, a quiescent stem cell will enter the cell cycle with probability ω, and an uncommitted cycling stem cell will become quiescent with probability α, where

$$\omega(\Omega(t), a(t)) = \frac{a_{min}}{a(t)} f_\omega(\Omega(t)), \tag{4}$$

$$\alpha(A(t), a(t)) = \frac{a(t)}{a_{max}} f_\alpha(A(t)). \tag{5}$$

Here, $\Omega(t)$ and $A(t)$ are the total number of cycling and quiescent stem cells. The functions f_ω and f_α are decreasing sigmoidal functions such that the probability of a cell transitioning into either compartment decreases as that compartment becomes larger. Individual cells with affinity close to a_{max} will tend to be quiescent, while those with affinity close to a_{min} will tend to cycle. If a quiescent stem cell remains quiescent, then its affinity will increase by a factor of r. If a cycling stem cell continues to cycle, its affinity will decrease by a factor of d. Thus, cells that remain in A or Ω during a time step become more likely to remain there in the future.

Cycling stem cells are also characterized by a counter $c(t)$ that marks their place in the cell cycle. Quiescent cells enter the cell cycle at hour 32, which marks the beginning of the S, G2, and M stages, during which a cell is committed to division. At hour 48, a cycling stem cell divides into two daughter cells, which enter the G1 phase of the cell cycle and have their counters reset to zero. During G1, cycling cells become uncommitted to division, transitioning to quiescence at a rate $\alpha(A(t), a(t))$.

A cycling cell whose affinity falls below a_{min} will differentiate into a precursor cell. Precursors divide once per day for twenty days. On their final division, each precursor cell differentiates into a mature cell, which lives for an additional eight days before dying.

Both healthy and leukemic cells are assumed to follow this hierarchy. Leukemic stem cells are assumed to transition between quiescence and cycling at much higher rates, and the probability of entering the cell cycle $\omega(\Omega(t), a(t))$ is only slightly affected by $\Omega(t)$. TKI therapy results in the killing of cycling leukemic stem cells at a rate of r_{deg}. Additionally, cycling stem cells become IM-affected

at a rate r_{inh}, which results in a decrease in the probability of a leukemic cell entering the cell cycle. As in [2], Equation (3) is used to approximate the simulated patient's BCR-ABL ratio.

3 Applications

3.1 Dynamics of TKI Therapy

Based on data collected from CML patients during their first year of therapy, Michor et al. [2] find that IM therapy often leads to a biphasic exponential decline in BCR-ABL ratio. The slope of the first decline indicates the death rate of differentiated cells, and the second slope represents the death rate of the progenitor compartment. Because IM is assumed to have no effect on leukemic stem cells in their model, this population continues to expand during therapy. As a result, their model predicts a relapse within about three years of therapy in all patients, independent of drug resistance or intolerance. Thus, their initial modeling results can be representative of at most the first few years of therapy.

In [10], patient data over several years of therapy with IM and nilotinib is used to evaluate the effects of TKIs on the stem cell population. For both drugs, long-term therapy results in a triphasic decline in BCR-ABL ratio. The first two slopes correspond to the slopes of the biphasic decline in [2], while the third slope represents an effect on an immature leukemic population. In most cases, the third slope is negative, but in some patients, it is zero or positive. Based on their results, it is hypothesized that long-term TKI therapy may affect the immature leukemic population, possibly including stem cells.

The research community remains divided about the effect of TKIs on leukemic stem cells, with arguments both in support of [3, 10] and against [2] such an effect. It may be that TKIs target certain subsets of the stem cell population. In the Roeder model [3], IM acts directly on cycling stem cells, while quiescent stem cells escape the drug. Determining the true effect of TKIs on stem cells has significant implications about the limitations of TKI therapy. If TKIs prove incapable of targeting stem cells, then an alternative approach may be necessary to eliminate the residual cancer burden. If TKIs affect cycling stem cells only, then a combination of TKIs and cell cycle inducers may be appropriate [3].

In [2], [3], and [10], a monotonic decline in the cancer population is predicted. However, long-term patient data often shows oscillations or periods in which the BCR-ABL ratios seem to level off temporarily and then decline further. Although these fluctuations may be partially due to measurement error or stochastic effects, they may also suggest a separate mechanism, such as the immune system, that is not included in either the Michor model or the Roeder model. Explaining the nonmonotonic behavior of some patients remains a challenge in CML modeling.

3.2 The Role of the Immune System

It is known that the immune system is capable of recognizing and mounting an attack against many types of cancer cells [8]. Immunotherapy is a promising complement to classical cancer therapies, and much research has been dedicated to boosting the immune response to allow it to fight cancer. With a better understanding of the immune response to CML, it may become possible to develop vaccines that aid in prevention and therapy.

In order to elucidate the role of the immune system during TKI therapy, Kim et al. [1] incorporate the immune response into the Michor model [2]. They propose the following system of delay differential equations representing the four cancer compartments (y_0, y_1, y_2, y_3) in [2] plus T cells

(T).

$$\dot{y}_0 = (r_y - d_0)y_0 - q_C p(C,T)y_0, \tag{6a}$$
$$\dot{y}_1 = a_y y_0 - d_1 y_1 - q_C p(C,T)y_1, \tag{6b}$$
$$\dot{y}_2 = b_y y_1 - d_2 y_2 - q_C p(C,T)y_2, \tag{6c}$$
$$\dot{y}_3 = c_y y_2 - d_3 y_3 - q_C p(C,T)y_3, \tag{6d}$$
$$\dot{T} = s_T - d_T T - p(C,T)C + 2^n p(C_{n\tau}, T_{n\tau}) q_T C_{n\tau}, \tag{6e}$$

where,

$$C = \sum_{i=0}^{3} y_i, \qquad C_{n\tau} = C(t - n\tau),$$
$$p(C,T) = p_0 e^{-c_n C} kT, \qquad T_{n\tau} = T(t - n\tau).$$

Excluding the last term, Equations (6a)-(6d) are the same as Equations (2a)-(2d), except that stem cells are assumed to divide at a constant rate r_y. The last term, $q_C p_0 e^{-c_n C} kT y_i$ in all four equations represents the immune response. The rate of interaction between T and y_i is given by kTy_i, where k is the kinetic coefficient. During an interaction, the T cell will engage the cancer cell with probability p_0, and the reaction will result in death of the cancer cell with probability q_C. The exponential $e^{-c_n C}$ represents inhibition of the immune system by the cancer population, where c_n is the rate of exponential decay of the immune response.

In Equation (6e), s_T is the constant source term, and d_T is the natural death rate of T cells. The third term is the rate at which T cells engage cancer cells and commit to n rounds of division. The fourth term represents the increase in the T cell population due to successful divisions. The resulting 2^n cells are reintroduced into the T cell population at a time $n\tau$ after engagement, to account for the time τ required to complete each of the n divisions. The parameter q_T is the probability that the T cell survives this encounter.

Modeling results and experimental data in [1] suggest that the immune response may play a significant role in maintaining patients in remission during TKI therapy. An optimal load zone is defined, which is the range of cancer loads that will stimulate a strong immune response. A small cancer load will be undetectable by immune cells. On the other hand, a large cancer population will overwhelm and suppress the immune system. TKI therapy may drive the cancer population below the optimal load zone, limiting the long-term effects of the immune system. Carefully-timed vaccines may help to maintain the immune response and potentially drive the cancer population to zero. The authors propose personalized vaccine schedules, where the timing and dosages of the vaccines are determined from individual patient data, as a potential complement to TKI therapy.

3.3 Stopping Imatinib

The Stop Imatinib (STIM) [7] trial sought to determine whether patients in sustained remission could be safely taken off IM. It was found that 61% of patients relapsed, mostly within the first six months of treatment cessation. Interestingly, the rest of the patients remained in treatment-free remission for the duration of the two-year trial. Although treatment-free remission may indicate elimination of the cancer burden in some patients, many patients continued to show low levels of BCR-ABL expression in their blood. This result suggests that another mechanism, such as the immune system, prevents the residual cancer population from expanding and taking over the blood.

Several research groups have sought to better understand the disparate outcomes of the STIM trial. Tang et al. [9] used parametrizations of the Michor model based on pre- and post-therapy data, to characterize the cancer populations before and after treatment. Their modeling results

indicate that cancer has much slower growth kinetics after therapy. They hypothesize that TKIs exert a selective pressure on the cancer population, resulting in different subsets of the heterogeneous population surviving. Differences in the composition of the surviving cancer populations may partially explain why only a subset of patients remains in remission after stopping treatment.

In [5], the Roeder model [3] is used to determine which CML patients can achieve a treatment-free remission. Individual patient data is used to determine r_{deg} and f_ω. The parametrized model is then used to simulate the outcome of cessation of treatment. In 15% of patients, the model predicts that TKI therapy will eliminate all cancer cells. Additionally, 31% of patients are predicted to achieve a treatment-free remission that lasts at least two years.

Despite these contributions, determining which patients should stop TKI therapy remains an open question. Several factors, including the kinetics of the cancer population's decline and the duration of remission, are currently being investigated. Moreover, the fact that only a fraction of patients in the STIM trial remain in remission after cessation motivates the question of how therapy can be improved to increase this success rate. Combination with other drugs [2, 3] and immunotherapy [1] has been proposed to further shrink the residual cancer population and possibly allow patients to stop TKIs.

3.4 Resistance to TKIs

Resistance to TKIs remains a major challenge in the treatment of CML [4]. Because of limitations in our ability to detect resistant cells at diagnosis, mathematical models offer a valuable tool for calculating the probability that a patient harbors resistant cells. The likelihood of resistance can inform the choice of initial therapy, for instance whether to use a single drug or a combination.

Resistance is incorporated into the Michor model [2] by allowing dividing cancer stem cells to mutate at a constant rate u into a drug-resistant cancer population z. Using a continuous-time branching process, the probability of resistance at diagnosis is determined to be

$$P = 1 - exp(-uy_0(0)s), \tag{7}$$

where $s = \frac{a_y - d_0}{d_0}$. The constants a_y and d_0 are the parameters in Equations (2a) and (2b), and $y_0(0)$ is the initial cancer stem cell load. Assuming that a later detection time is associated with a larger value of $y_0(0)$, diagnosis in the late stages of CML implies a higher probability of resistance.

Leder et al. [6] seek to characterize the composition of resistant cell populations at diagnosis, which is very difficult to observe experimentally. Using experimental data on the reproductive rates of leukemic cells with specific mutations, the probability and size of the resistant clone is computed as a function of mutation. It is found that a patient is expected to have at most one resistant clone at diagnosis. The resistant clone will likely have developed in the most recent stages of CML genesis, a result that emphasizes the importance of early detection. All mutant clones, regardless of growth rates, are approximately equally likely to occur. However, the more aggressive clones, when they exist, will be larger on average than their less aggressive counterparts. These findings are used to evaluate the benefits of combination therapies in patients diagnosed in early or late stages of CML. The authors recommend that patients with advanced CML receive a combination of at least two TKIs, while early CML can probably be treated effectively with a single TKI.

4 Future Direction

Despite the recent improvements in our understanding and treatment of CML, many open questions remain about the dynamics of cancer genesis and therapy. It remains to be determined which cancer

subpopulations are protected from the effects of TKIs and how combination therapies can be applied to attack the residual cancer burden. Elucidating the role of the immune system may allow us to enhance the body's natural defenses against CML. It is our goal to construct a mathematical model that is closely tied to the known biology of CML. Once the model is validated using patient data, it offers a valuable tool for testing hypotheses about treatment scheduling and combination therapies. Moreover, by applying the model to individual patient data, we may construct patient-specific therapies that will hopefully improve the percentage of patients who can be safely taken off TKIs.

Primary Material

[1] Kim, P. et al. Dynamics and potential impact of the immune response to chronic myelogenous leukemia. *PLoS Comput. Biol.*, **4**(6), e1000095, 2008.

[2] Michor, F. et al. Dynamics of chronic myeloid leukemia. *Nature*, **435**(7046): 1267–1270, 2005.

[3] Roeder, I. et al. Dynamic modeling of imatinib-treated chronic myeloid leukemia: Functional insights and clinical implications. *Nature Med.*, **12**(10): 1181–1184, 2006.

Secondary Material

[4] An, X. et al. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: A review. *Leukemia Research*, **34**: 1255-1268, 2010.

[5] Horn, M. et al. Model-based decision rules reduce the risk of molecular relapse after cessation of tyrosine kinase inhibitor therapy in chronic myeloid leukemia. *Blood*, **121**: 378-384, 2013.

[6] Leder, K. et al. Fitness conferred by BCR-ABL kinase domain mutations determines the risk of pre-existing resistance in chronic myeloid leukemia. *PLoS ONE*, **6**(11), e27682, 2011.

[7] Mahon, F. et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet. Oncol.*, **11**: 1029–1035, 2010.

[8] Murphy, K. *Janeway's Immunobiology*. Garland Science, Taylor & Francis Group, New York, pages 682–697, 2012.

[9] Tang, M. et al. Selection pressure exerted by imatinib therapy leads to disparate outcomes of imatinib discontinuation trials. *Haematologica*, **97**(10): 1553–1561, 2012.

[10] Tang, M. et al. Dynamics of chronic myeloid leukemia response to long-term targeted therapy reveal treatment effects on leukemic stem cells. *Blood*, **118**(6): 1622-1631, 2011.

Primary Mathematical Content

- AMSC 670 - Ordinary Differential Equations I. Linearization and stability, dependence on parameters and initial conditions.
- AMSC 671 - Ordinary Differential Equations II. Stability theory, bifurcation theory.
- AMSC 666 - Numerical Analysis I. Interpolation and approximation, numerical optimization, implementation of these algorithms in MATLAB.
- AMSC 667 - Numerical Analysis II. Numerical solutions to IVPs, numerical methods for eigenvalue problems.

Application Area

- BIOE 601 - Biomolecular and Cellular Rate Processes. Mathematical modeling of the dynamics of biological systems, enzymatic reactions.
- BIOL 704 - Cell Biology from a Biophysical Perspective. Mechanisms of cell biology.