# Modeling Imatinib-Treated Chronic Myelogenous Leukemia

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## Abstract

Chronic Myelogenous Leukemia (CML) is a blood cancer affecting approximately 1 in 100,000 people. While there are many different treatments for controlling CML, there is currently no cure. Recently, many mathematical models have been developed to explore disease genesis and the effects of various therapies with the hope of improving or discovering new therapeutic strategies. It is the goal of this project to study three such models: an agent-based model, a system of difference equations, and a system of partial differential equations. Implementation and successful validation for the difference equation model has been completed. This report includes the details of this progress.

# 1 Introduction

Chronic Myelogenous Leukemia (CML) is a type of blood cancer resulting in the overproduction of white blood cells. Approximately 20% of all leukemia cases are CML. CML can be characterized by a genetic mutation in hematopoietic stem cells in which a translocation between chromosomes 9 and 22 occurs. During this translocation, fusion of the bcr-abl gene occurs on chromosome 22 to form what is known as the Philadelphia (Ph) chromosome, a detectable characteristic in 90% of all CML patients. Fusion of this gene results in increased tyrosine kinase activity contributing to uncontrolled stem cell growth and survival, and ultimately cancer.

There are currently many types of treatment available to CML patients. Of particular interest is a form of targeted therapy involving the drug Imatinib. Imatinib is a tyrosine kinase inhibitor that specifically targets $Ph^+$ cells and binds to the bcr-abl enzyme. This drug controls the population of cancer cells in two ways: by preventing proliferation of mutated cells and increasing apoptosis or cellular suicide. Although quite effective as a control, Imatinib is not a cure for CML.

In the past decade, there has been much interest in the use of mathematical models to gain further insight into the dynamics of CML genesis and explore the effects of treatment. This project will consider three such models, each biologically based on the same cell differentiation process as described by Roeder *et al*. This process consists of three stages of cell differentiation: stem cells, precursors and mature cells. Additionally, stem cells are categorized as either non-proliferating ($A$) or proliferating cells ($\Omega$). Movement between compartments is as follows (fig. 1).

Each stem cell may be characterized by its cellular affinity, a quantity based on cell age and state. Cells in $A$ increase their affinity over time until the maximum affinity is reached. They transfer from $A$ to $\Omega$ with probability $\omega$ determined by affinity and the total number of proliferating cells. In $\Omega$, stem cells proliferate by completing the 48 hour cell cycle. The cell cycle consists of four necessary phases for cell growth and division. These stages in order are $G_1$, S, $G_2$, and M. Cells enter $\Omega$ from $A$ at hour 32 of the cell cycle, the beginning of the S phase during which DNA synthesis occurs. At hour 48, the cell divides into two daughter cells that each begin the cycle in the $G_1$ growth phase. Transitions from $\Omega$ to $A$ occur during the $G_1$ phase with probability $\alpha$. Cell affinity decreases over time in $\Omega$ until the minimum affinity is attained.

Stem cells with minimum affinity differentiate into precursor cells. These cells divide once every 24 hours for 20 days, at which point they become mature cells. Cells live in the mature stage for 8 days before dying.

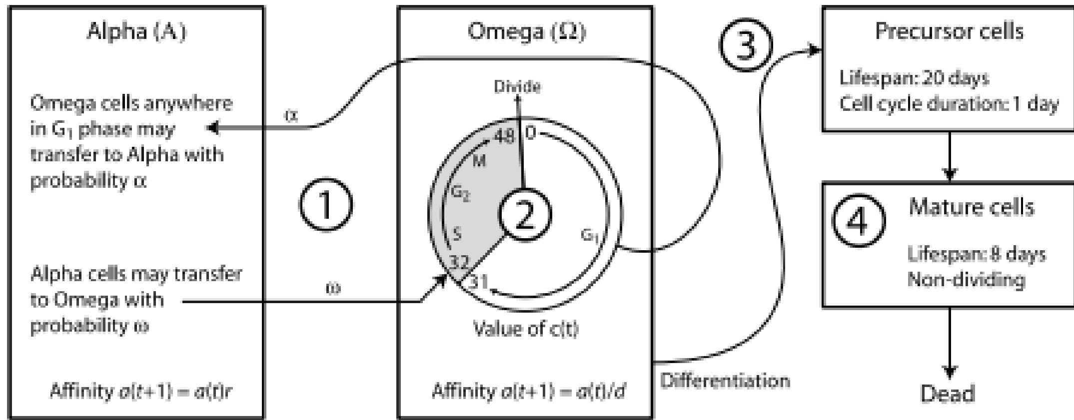


**Figure 1:** A cell state diagram as proposed by Roeder *et al*. Figure from [2].

The biology described here is a simplification of the cell maturation process and makes a few assumptions. Firstly, the differentiation process has been reduced to three stages of maturation. Second, transition probabilities between stem cell compartments are assumed to be based on affinity, an internal quantity for each stem cell that varies in time within an interval [$a_{min}$, $a_{max}$]. Affinity is a notion whose existence was postulated by Roeder [1] and is not directly associated with any known biological mechanism specific to the hematopoietic system. Furthermore, the time spent in each stage is deterministic. It is assumed that these lifespans are known and fixed.

As stated in the project proposal, three models will be implemented, validated and tested upon completion of this project. Model 1 is an agent based model (ABM) for describing CML genesis as described by Roeder *et al*. Model 2 is a reformulation of Model 1 as a system of discretized difference equations [2]. Lastly, in Model 3 a system of PDEs will be used to simulate CML and its treatment [3]. All three algorithms are based upon the same underlying biological model (fig. 1) and use the same parameter values as given by Roeder. Because it is the least complex of the three models, Model 2 has been completed first and is the focus of this mid-year report.

# 2 Approach

Model 2 formulates the cell state diagram as a system of discretized difference equations. Rather than simulating each cell individually as the ABM model does, this system groups cells by their common characteristics i.e., cell state compartment, affinity level, cell cycle position. The progression of CML is simulated by tracking the number of cells in each group. This approach reduces computational complexity and allows for simulation of realistic cell numbers.

In order to devise the difference equations, the state space must be discretized. Time is already discretized in the ABM; cell positions are updated at fixed time steps of one hour. Affinity is discretized by setting $a(t) = e^{-k\rho}$ where $\rho = 0.0488$ and $0 \leq k \leq 127$ is an integer. The affinity of each cell can now be characterized discretely by the value of $k$ where $\log\big(a(t)\big) = -k\rho$.

## 2.1 The Difference Equations

The stem cell populations are represented by the following difference equations with $k$ representing cell affinity and $c$ representing position in the cell cycle:

$$\mathrm{A}_k(t+1) = \begin{cases} \big(\mathrm{A}_0(t) - \mathrm{B}_0(t)\big) + \big(\mathrm{A}_1(t) - \mathrm{B}_1(t)\big) + \big(\mathrm{A}_2(t) - \mathrm{B}_2(t)\big), & k = 0 \\ \big(\mathrm{A}_{k+2}(t) - \mathrm{B}_{k+2}(t)\big) + \sum_{c=0}^{31} \Psi_{k,c}(t), & k = 1, \dots, 125 \\ \sum_{c=0}^{31} \Psi_{k,c}(t), & k = 126, 127 \end{cases} \tag{1}$$

$$\Omega_{k,c}(t+1) = \begin{cases} \mathrm{B}_0(t), & k = 0, c = 32 \\ 2\Omega_{k-1,48}(t), & k > 0, c = 0 \\ \Omega_{k-1,c-1}(t) - \Psi_{k-1,c-1}(t), & k > 0, c = 1, \dots, 31 \\ \big(\Omega_{k-1,31}(t) - \Psi_{k-1,31}(t)\big) + \mathrm{B}_k(t), & k > 0, c = 32 \\ \Omega_{k-1,c-1}(t), & k > 0, c = 33, \dots, 48 \\ 0 & otherwise \end{cases} \tag{2}$$

Transitions between the $\mathrm{A}_k$ and $\Omega_{k,c}$ compartments are determined by the binomial random variables $\mathrm{B}_k$ and $\Psi_{k,c}$ which have the following distributions:

$$\mathrm{B}_k(t) \sim Bin\Big(\mathrm{A}_k(t), \omega(\Omega(t), e^{-k\rho})\Big)$$

$$\Psi_{k,c}(t) \sim Bin\Big(\Omega_{k,c}(t), \alpha(\mathrm{A}(t), e^{-k\rho})\Big), \quad c = 0, \dots, 31$$

Here $\Omega(t) = \sum_{k,c} \Omega_{k,c}(t)$ and $\mathrm{A}(t) = \sum_k \mathrm{A}_k(t)$ denote the total number of proliferating and resting cells respectively. The transition probabilities $\omega$ and $\alpha$ are given by:

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

$$\alpha\big(\mathrm{A}(t), a(t)\big) = \frac{a(t)}{a_{max}} f_\alpha\big(\mathrm{A}(t)\big)$$

where $f_{\alpha/\omega}$ are sigmoidal functions given by equation (B.1) in the appendix .

The differentiated cells are represented in a similar fashion. The equations for precursors are denoted by $P_j(t)$ where $j = 0, \dots, 479$ is the number of hours a cell has spent in this compartment, up to 20 days. Similarly mature cells are denoted by $M_j(t)$ where $j = 0, \dots, 191$ is the number of hours spent as a mature cell, up to 8 days.

$$P_j(t+1) = \begin{cases} \sum_{c=0}^{48} \Omega_{127,c}(t) - \sum_{c=0}^{31} \Psi_{127,c}(t), & j = 0 \\ 2P_{j-1}(t), & j = 24, 48, 72, \dots, 456 \\ P_{j-1}(t), & otherwise \end{cases} \tag{3}$$

$$M_j(t+1) = \begin{cases} 2P_{479}(t), & j = 0 \\ M_{j-1}(t), & otherwise \end{cases} \quad (4)$$

These equations directly reflect the rules of cell differentiation as presented in the cell state diagram (fig. 1). The first line of (3) represents proliferating cells that have attained minimum affinity and differentiate into precursors. Precursors divide every 24 hours, producing two daughter cells, as represented by line two. Line three denotes an increase in age, which is necessary to track the time spent as a precursor before maturing. The first line of (4) signifies the number of precursors that undergo one final division before entering the mature state. Similar to the final line of (3), the second line of (4) tracks the age of mature cells before they die.

## 2.2 Modeling CML and Imatinib Treatment

Three non-interacting cell populations will be simulated to mathematically model clinically observed phenomena. These populations are healthy cells ($Ph^-$), leukemic cells ($Ph^+$) and Imatinib-affected cells ($Ph^{+/A}$). Equations (1) to (4) as written were used to simulate $Ph^-$ cells. Alterations to equation (2) and new parameter values were used to represent $Ph^+$ and $Ph^{+/A}$ cells.

$Ph^+$ cells uncontrollably proliferate, therefore the transition rates between A and Ω differ from those of $Ph^-$ cells. The transition functions $f_{\alpha/\omega}$ are updated with new parameter values that correspond to this behavior. This is the only update necessary to simulate CML genesis. Equations (1) – (4) remain unchanged.

A slight alteration to equation (2) for $Ph^+$ Ω cells is made when treatment simulation begins; equations (1), (3) and (4) are as previously stated. When Imatinib is introduced, proliferating stem cells become Imatinib affected with probability $r_{inh}$ and undergo apoptosis with probability $r_{deg}$ at each time step. The number of proliferating $Ph^+$ stem cells infected at time $t$ is given by $\Omega^{+/I}(t) \sim Bin(\Omega^+_{k,c}(t), r_{inh})$. The number of proliferating stem cells that die at time $t$ is given by $\Omega^{+/D}(t) \sim Bin(\Omega^+_{k,c}(t), r_{deg})$. These cells are removed from the $Ph^+$ cell population at the beginning of each time step before any other transition occurs. To accomplish this, $\Omega^{+/R}_{k,c}(t)$ is substituted into the right hand side of (2), where $\Omega^{+/R}_{k,c}(t) = \Omega^+_{k,c}(t) - \Omega^{+/I}_{k,c}(t) - \Omega^{+/D}_{k,c}(t)$ is the number of cycling $Ph^+$ stem cells remaining unaffected for the next time step. The overall structure of the equations remains unchanged.

The $Ph^{+/A}$ cell population differs from $Ph^-$ cells in two ways. First, since Imatinib inhibits the ability of these cells to proliferate, transition functions $f_{\alpha/\omega}$ will be updated with corresponding parameter values. Second, affected proliferating stem cells, $\Omega^{+/A}$ undergo apoptosis at each time step according to a binomial distribution with probability $r_{deg}$. These cells are removed at the beginning of each time step and infected cells are added, before regular transitions occur. In terms of the equations, $\Omega^{+/A,R}(t)$ is substituted into the right hand side of (2) where $\Omega^{+/A,R}(t) = \Omega^{+/A}_{k,c}(t) - \Omega^{+/A,D}_{k,c}(t) + \Omega^{+/I}_{k,c}(t)$. This new quantity is used to calculate $\Omega^{+/A}_{k,c}(t+1)$. Again, equations (1), (3) and (4) and the overall structure of (2) remain unchanged for $Ph^{+/A}$ population.

# 3 Implementation

The difference equations were vectorized to achieve efficient simulation. A and B are represented as column vectors, where the $k^{th}$ entry contains the number of cells with an affinity level of $k$. $\Omega$ and $\Psi$ cells are dependent on both affinity and cell cycle. These cells are tracked by a matrix whose $(k, c)$ entry contains the number of cells with affinity $k$, at position $c$ in the cell cycle. $P$ and $M$ are structured as column vectors whose $j^{th}$ entry contains the number of cells of age $j$ in the respective compartment.

The complete simulation for this project involves three steps: steady state, CML genesis, and treatment. For the first step, a single healthy cell is simulated by looping over time until a steady mature cell count is reached. The model is initialized by setting $\Omega_{0,32}^{-}(0) = 1$. Although the results are not dependent on the initial condition, choosing a cycling stem cell with maximum affinity at hour 32 of the cell cycle guarantees that the system will have two cycling stem cells 17 time steps later when the cell completes mitosis. Steady state is reached at one year when there are approximately $6.58 \times 10^{10}$ mature Ph$^-$ cells. Runtime for reaching steady state is approximately two seconds. The steady state profile for Ph$^-$ cells is used as the starting value for Ph$^-$ cells when CML genesis begins. The Ph$^+$ population is initialized by setting $\Omega_{0,32}^{+}(0) = 1$. The duration of CML genesis is 15 years, which in approximately 69 seconds of runtime. Lastly, treatment is simulated using the Ph$^-$ and Ph$^+$ population values from CML genesis as starting values. The Ph$^{+/A}$ initial population will be set during the first time step to be $\Omega_{k,c}^{+/A}(0) = \Omega_{k,c}^{+/I}(0)$. Treatment was simulated for 400 days, corresponding to a runtime of approximately 8 seconds.

Model 2 was implemented in Matlab R2014a. Simulations were run on an ASUS Notebook with a 2.4 GHz Intel Core i5 processor and 8 GB of RAM.

# 4 Validation

Validation of the difference equation model was achieved by recreating the figures presented in Kim *et al*. The results of simulation were overlaid onto the figures from [2] to determine if the figure was accurately recovered. Initially, Matlab's *binornd(N,P)* function was used to calculate $B_k(t)$ and $\Psi_{k,c}(t)$. This produced the results seen in figure 2. It can be seen that the desired dynamics are present, namely an accumulation of A cells at $k = 0$ which then tapers to zero around $k = 60$. To achieve smooth curves that exactly replicate the desired figure, all binomial distributions were replaced with their respective expected values.

Validation of this model's steady state is shown in Figure 3. The steady state profile of nonleukemic stem cells for the difference equations is achieved by plotting $A_k(t_s)$ and $\sum_c \Omega_{k,c}(t_s)$ versus affinity level $k$, where $t_s$ is the steady state time. The blue and red curves produced during simulation closely match the curves from [2]. Slight variations can be seen at the jumps in $\Omega$ that occur near $k = 15, 65, 115$. Overall, this simulation is considered successful.

Figure 4 depicts the number of mature leukemic ($M^+(t) = \sum_s M_s^+(t)$) and nonleukemic cells ($M^-(t) = \sum_s M_s^-(t)$) versus time. As expected, simulation of Ph$^-$ cells begin at a steady

state value of approximately $6.58 \times 10^{10}$ cells and begin to decrease to zero just before five years. Beginning at the same time point, the $Ph^{+}$ population begins to sharply increase until it approaches a cell count of $16 \times 10^{10}$ cells. This is consistent with the original model and therefore successfully validates CML genesis for this model.

Lastly, the treatment stage of simulation was validated using the BCR-ABL1 ratio. This ratio provides a measure of the ratio of leukemic cells to healthy cells. It is calculated using the formula given in Roeder *et al.*:

$$BCR-ABL1\ ratio = \frac{\#\ mature\ Ph^{+} cells}{\#\ mature\ Ph^{+} cells + 2 * \#\ mature\ Ph^{-}\ cells}.$$

The number of mature $Ph^{+}$ cells used here is the total number of leukemic cells, both affected and unaffected. The biphasic decline in the BCR-ABL1 ratio that can be seen in blue (fig. 5) is consistent with the original figure from [2].

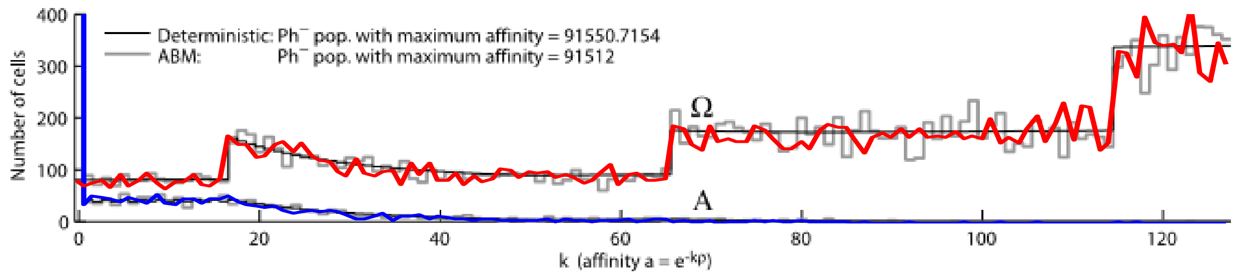


**Figure 2:** Steady state profile for nonleukemic stem cells achieved by ABM and difference equation method. Both resting and proliferating stem cell populations are shown. The original figure from [2] shown in gray, is overlaid with the results from this project. The blue line shows the number of resting stem cells while red plots the number of cycling stem cells. Binomial distribution used for $B_k$ and $\Psi_{k,c}$.

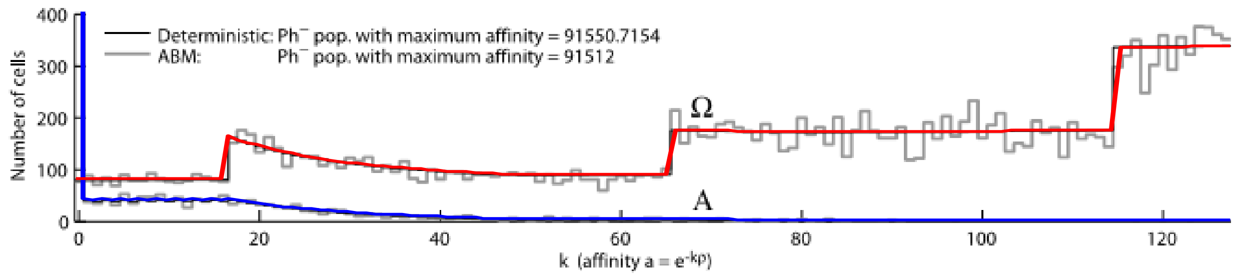


**Figure 3:** Steady state profile for nonleukemic stem cells achieved by ABM and difference equation method. Both resting and proliferating stem cell populations are shown. The original figure from [2] shown in gray, is overlaid with the results from this project. The blue line shows the number of resting stem cells while red plots the number of cycling stem cells. Expected value for $B_k$ and $\Psi_{k,c}$ used instead of binomial distributions.

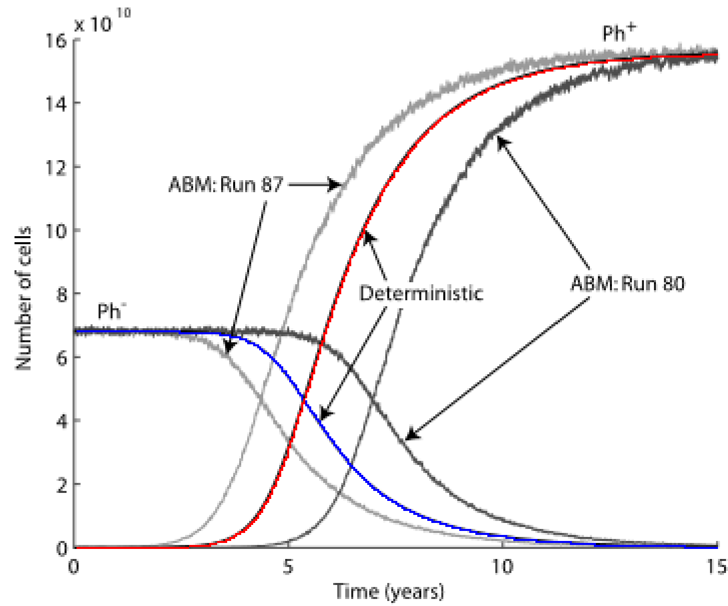


**Figure 4:** Simulation of CML genesis. Dynamics of both leukemic ($Ph^+$) and nonleukemic ($Ph^-$) cells are shown by plotting the number of mature cells in each population versus time. The original figure from [2] shown in gray is overlaid with the results from this project. $Ph^-$ cells are plotted in blue. $Ph^+$ cells are plotted in red.

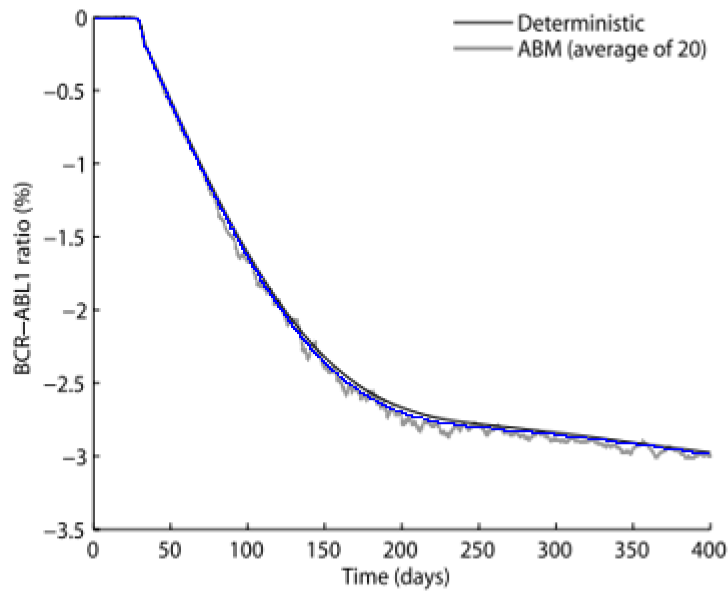


**Figure 5:** BCR-ABL1 ratio during Imatinib treatment. The original figure from [2] shown in gray is overlaid with the results from this project in blue.

# 5 Conclusion

Implementation and successful validation have been completed for Model 2, the system of difference equations. The next step towards completion of this project is to implement and validate the original ABM model, Model 1. To do so, the difference equations in a sense will be decompartmentalized to represent each cell transitioning independently of all other cells. Validations will be achieved by overlaying simulation results on to the figures from [2]. The results should mirror those seen in figures 3, 4 and 5. Because of the stochastic nature of this model, each run could produce slightly different results. However, the general characteristics for steady state, CML genesis and BCR-ABL ratio should still be present in each run.

After completion of the ABM model, work on the third and final component will begin. The PDE model, Model 3, restructures the original model into a continuous problem that can be expressed as a function of three internal clocks. The PDEs will be solved numerically and the results again should produce similar figures, which will be overlaid on the corresponding figures from [3]. The details for each of these models can be found in the project proposal.

## Appendix A: Project schedule

The project is divided into four phases:

*Phase 1: Complete*

- Implement difference equation model
- Improve efficiency and validate

*Phase 2: December*

- Implement ABM
- Improve efficiency and validate

*Phase 3: January – mid-February*

- Implement basic PDE method
- Validate on simple test problem

*Phase 4: mid-February – April*

- Apply basic method to CML - Imatinib biology and validate
- Test models with clinical data
- Draw conclusions

## Appendix B: Parameter estimates

The sigmoidal transition functions given by Roeder *et al*. take the form

$$f_{\alpha/\omega}\big(\mathrm{A}/\Omega(t)\big) = \frac{1}{\nu_1 + \nu_2 \exp\left(\dfrac{\nu_3 \mathrm{A}/\Omega(t)}{\widetilde{N}_{\mathrm{A}/\Omega}}\right)} + \nu_4 \tag{B.1}$$

where

$$\nu_1 = \frac{h_1 h_3 - h_2^2}{h_1 + h_3 - 2h_2},$$
$$\nu_2 = h_1 - \nu_1,$$
$$\nu_3 = \ln\left(\frac{h_3 - \nu_1}{\nu_2}\right),$$
$$\nu_4 = f_{\frac{\alpha}{\omega}}(\infty),$$

and

$$h_1 = \frac{1}{f_{\alpha/\omega}(0) - f_{\alpha/\omega}(\infty)},$$
$$h_2 = \frac{1}{f_{\alpha/\omega}\left(\frac{\tilde{N}_\mathrm{A}}{2}\right) - f_{\alpha/\omega}(\infty)},$$
$$h_3 = \frac{1}{f_{\alpha/\omega}(\tilde{N}_\mathrm{A}) - f_{\alpha/\omega}(\infty)}.$$

The parameter values for $f_{\alpha/\omega}(*)$ for each cell type are as given by Roeder *et al.* and can be found in the Table 1 with all other parameter values.

**Table 1** Parameters

| Parameter | Description | $Ph^-$ | $Ph^+$/Imatinib-affected |
|---|---|---|---|
| $a_{min}$ | Min value of affinity a | 0.002 | 0.002 |
| $a_{max}$ | Max value of affinity a | 1.0 | 1.0 |
| $f_\alpha(0)$ | Transition characteristic for $f_\alpha$ | 0.5 | 1.0 |
| $f_\alpha(\tilde{N}_A/2)$ | Transition characteristic for $f_\alpha$ | 0.45 | 0.9 |
| $f_\alpha(\tilde{N}_A)$ | Transition characteristic for $f_\alpha$ | 0.05 | 0.058 |
| $f_\alpha(\infty)$ | Transition characteristic for $f_\alpha$ | 0.0 | 0.0 |
| $\tilde{N}_A$ | Scaling factor for $f_\alpha$ | $10^5$ | $10^5$ |
| $f_\omega(0)$ | Transition characteristic for $f_\omega$ | 0.5 | 1.0/0.0500 |
| $f_\omega(\tilde{N}_\Omega/2)$ | Transition characteristic for $f_\omega$ | 0.3 | 0.99/0.0499 |
| $f_\omega(\tilde{N}_\Omega)$ | Transition characteristic for $f_\omega$ | 0.1 | 0.98/0.0498 |
| $f_\omega(\infty)$ | Transition characteristic for $f_\omega$ | 0.0 | 0.96/0.0496 |
| $\tilde{N}_\Omega$ | Scaling factor for $f_\omega$ | $10^5$ | $10^5$ |
| $r_{inh}$ | Inhibition intensity | | 0.050 |
| $r_{deg}$ | Degredation internsity | | 0.033 |

# References

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[4] National Cancer Institute: PDQ® Chronic Myelogenous Leukemia Treatment. Bethesda, MD: National Cancer Institute. Date last modified 9/21/2015. Available at: http://www.cancer.gov/types/leukemia/patient/cml-treatment-pdq.