Modeling Imatinib-Treated Chronic Myeloid Leukemia

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Introduction

Chronic Myeloid Leukemia (CML)

- Cancer of the blood—white blood cells
- Genetic mutation in hematopoietic stem cells – Philadelphia Chromosome (Ph)
- Increase tyrosine kinase activity allows for uncontrolled stem cell growth

Treatment –

- Imatinib: tyrosine kinase inhibitor
- Controls population of mutated cells in two ways
- Not effective as a cure

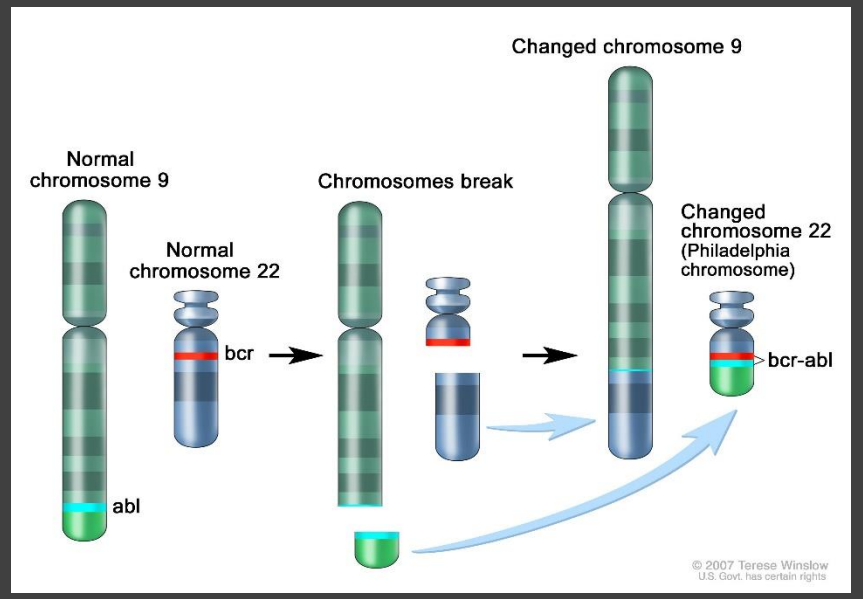


Figure: Chronic Myelogenous Leukemia Treatment. National Cancer Institute. 21 Sept. 2015. Web.

Project Goals

Mathematically model clinically observed phenomena of three non-interacting cell populations to simulate CML genesis and Imatinib treatment

- Nonleukemia cells (Ph^-)
- Leukemia cells (Ph^+)
- Imatinib-affected leukemia cells ($Ph^{+/A}$)

Three model types based on cell state diagram

- Model 1: Agent Based Model (Roeder et al., 2006)
- Model 2: System of Difference Equations (Kim et al., 2008)
- Model 3: PDE (Kim et al., 2008)

How do these models compare?

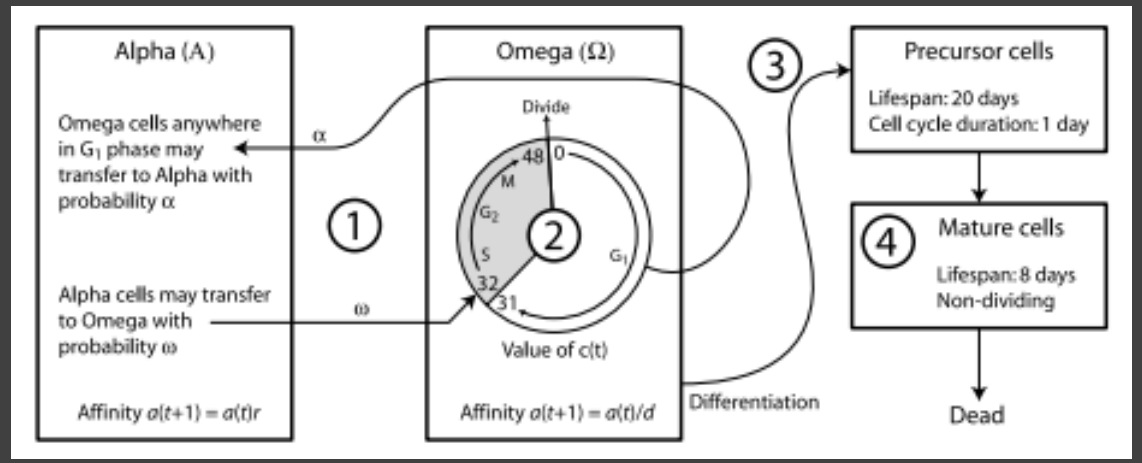
What do they tell us about CML and the effects of Imatinib?

Cell State Diagram (Roeder et al., 2006)

Stem cells
- Non-proliferating (A)
- Proliferating (Ω)

Precursor cells

Mature cells



Circulation between A and Ω based on cellular affinity
- High affinity: likely to stay in/switch to A
- Low affinity: likely to stay in/switch to Ω

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

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

Figures: Kim et al. in Bull. Math. Biol. 70(3), 728-744 2008

Review of Completed Models

Generate a steady state population of healthy cells

Introduce a single leukemic cell and simulate cancer growth

Start treatment by simulating the effects of Imatinib on leukemic cells

Model 1: Agent Based Model

Cells simulated individually

Stochastic

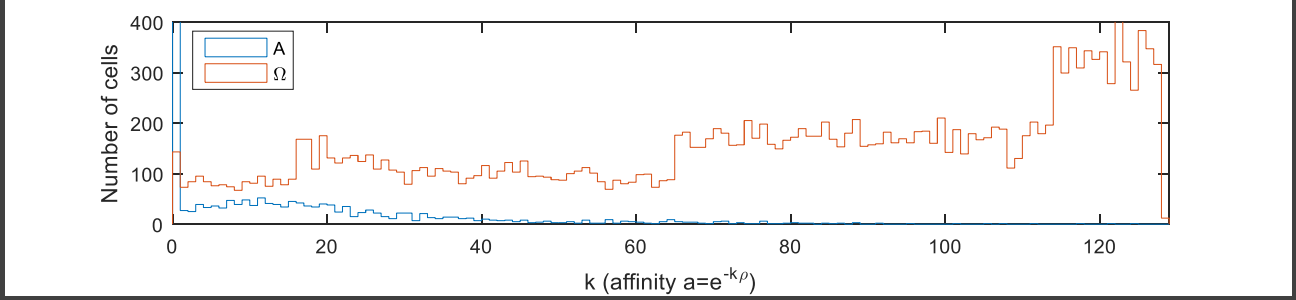
Discrete, time steps of 1 hour

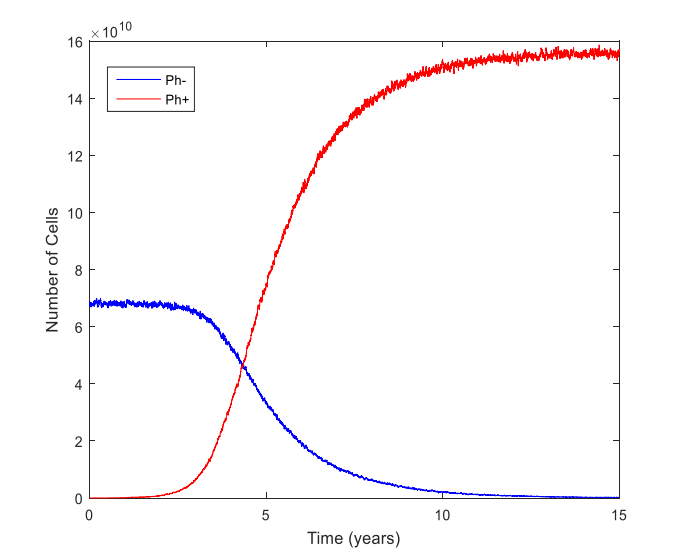
Model 2: System of Difference Equations

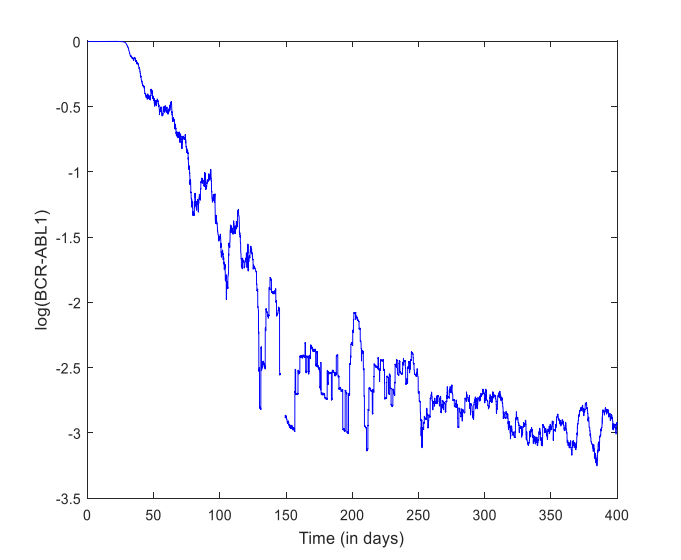
Cells grouped by common characteristics

Discrete, time steps of 1 hour

Model 1: ABM (Roeder et al., 2006)







Top:

- Simulation of healthy cell population for 2 years

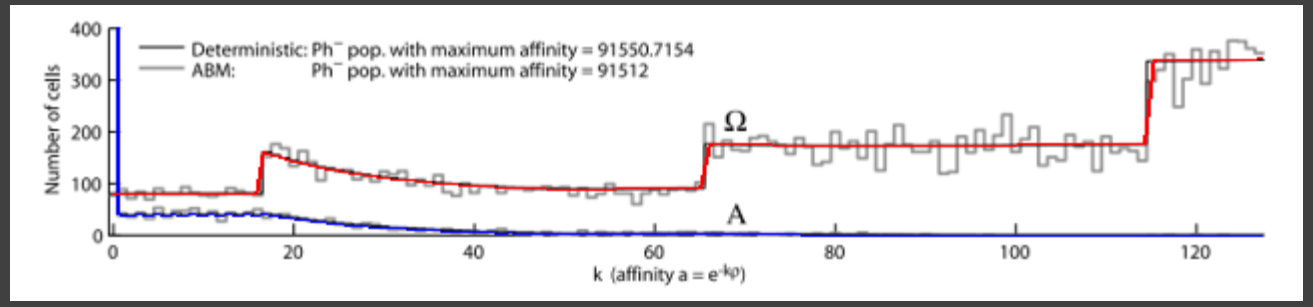
Left:

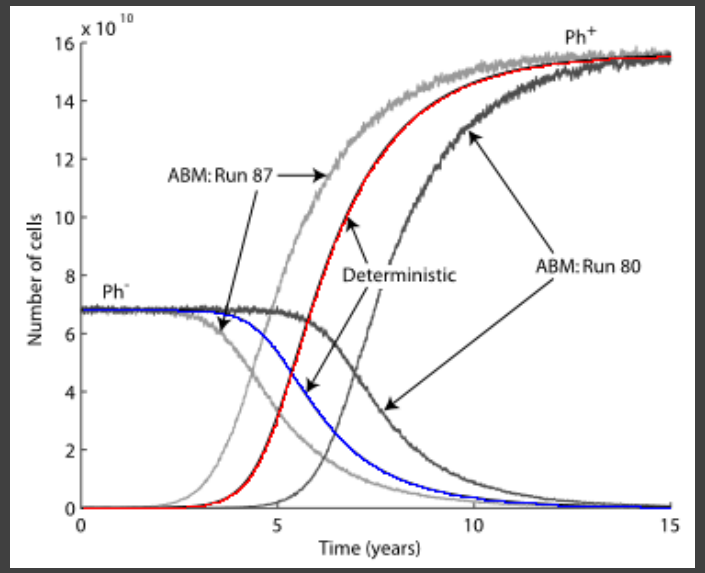
- CML genesis over 15 years
- Ph^+ cells in red, Ph^- in blue

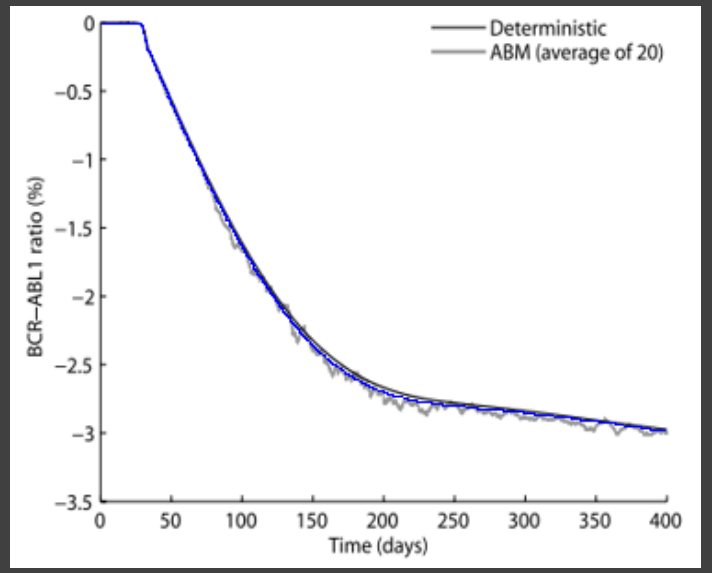
Right:

- BCR-ABL1 ratio calculated during treatment (400 days)
- Biphasic decline

Model 2: Difference Equations (Kim et al., 2008)







Top:

- Simulation of healthy cell population for 1 year

Left:

- CML genesis over 15 years
- Ph^+ cells in red, Ph^- in blue

Right:

- BCR-ABL1 ratio calculated during treatment (400 days)
- Biphasic decline

Model 3: PDE (Kim et al., 2008)

Transform model into a system of first order hyperbolic PDEs

- Consider the cell state system as a function of multiple internal clocks
  - Real time (t)
  - Affinity ($x = -\log(a)$)
  - Cell cycle (c)
  - Cell Age (s)
- Each cell state can be represented as a function of 1-3 of these variables

$$\frac{\partial A}{\partial t} - \rho_r \frac{\partial A}{\partial x} = -\omega\left(\overline{\Omega}, e^{-x}\right)A + \alpha\left(\overline{A}, e^{-x}\right)\int_0^{32} \Omega(x, c, t)\, dc + \begin{cases} 0, & x \in X_a, \\ \alpha(\overline{A}, e^{-x})\Omega^*, & x \in X_b, \end{cases}$$

$$\frac{\partial \Omega}{\partial t} + \rho_d \frac{\partial \Omega}{\partial x} + \frac{\partial \Omega}{\partial c} = \begin{cases} -\alpha(\overline{A}, e^{-x})\Omega, & \text{for } c \in (0, 32], \\ 0, & \text{for } c \in (32, 49]. \end{cases}$$

$$\frac{dA^*}{dt} = \rho_r A(x_{\min}, t) - \omega\left(\overline{\Omega}, e^{-x_{\min}}\right)A^*.$$

$$\frac{\partial \Omega^*}{\partial t} + \rho_d \frac{\partial \Omega^*}{\partial x} = \begin{cases} 0, & x \in X_a, \\ -\alpha(\overline{A}, e^{-x})\Omega^*, & x \in X_b. \end{cases}$$

$$\frac{\partial P}{\partial t} + \frac{\partial P}{\partial s} = 0, \quad s \in [0, 480).$$

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial s} = 0, \quad s \in [0, 192),$$

Figures: Kim et al. in Bull. Math. Biol. 70(3), 1994-2016 2008

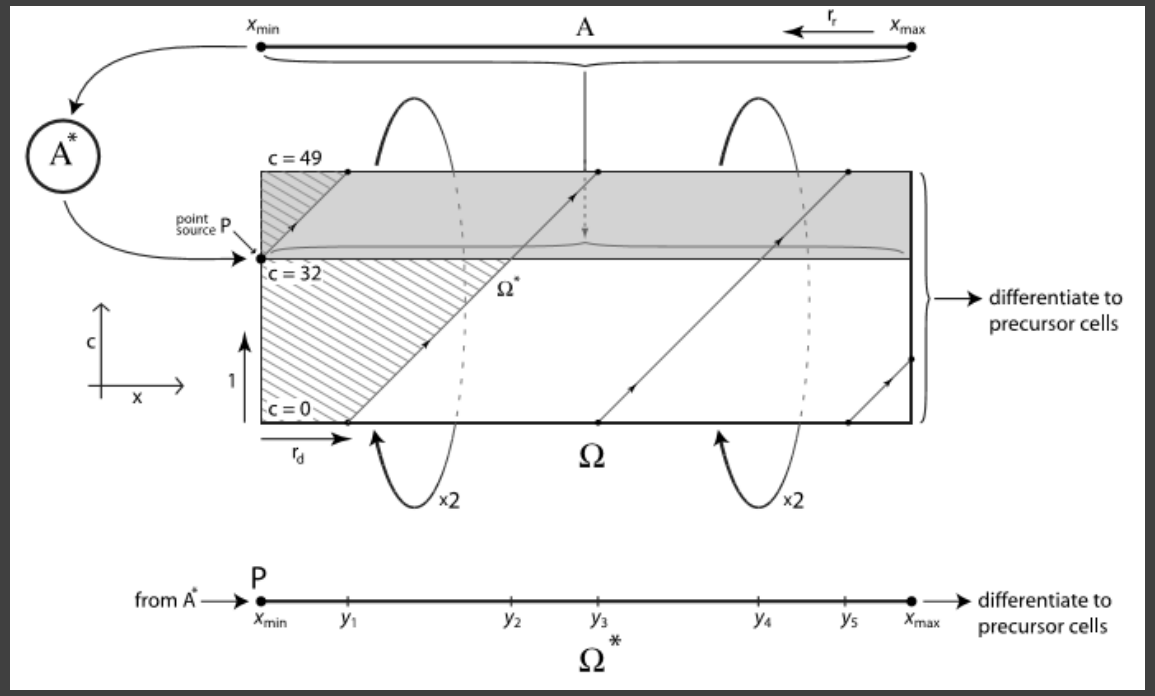
Numerical Simulations

Discretization:

- A stem cell domain:$[x_{min}, x_{max}] \times \mathbb{R}_0^+$
- A* stem cell domain: $\mathbb{R}_0^+$
- Ω stem cell domain:$[x_{min}, x_{max}] \times [0, 49) \times \mathbb{R}_0^+$
- Ω* stem cell domain:$[x_{min}, x_{max}] \times \mathbb{R}_0^+$
- Equally spaced meshes:
  - $\Delta x = \frac{x_{max} - x_{min}}{J}$
  - $\Delta c = \frac{49}{K}$

Boundary Conditions:

- $\widetilde{\mathrm{A}}_{J,n+1} = 0$
- $\widetilde{\Omega}_{0,k,n} = 0 \quad \forall k, n$
- $\widetilde{\Omega}_{j,0,n+1} = 2\widetilde{\Omega}_{j,K,n}$
- $\widetilde{\Omega}_{j,\overline{k^+},n+1} = \widetilde{\Omega}_{j,\overline{k^-},n+1} + \omega\left(\widehat{\Omega}_n, e^{-x_j}\right)\widetilde{\mathrm{A}}_{j,n+1}$
- $\widetilde{\Omega}^*_{0,n+1} = \frac{\omega\left(\widehat{\Omega}_n, e^{-x_0}\right)}{\rho_d}\widetilde{\mathrm{A}}^*_n$
- $\widetilde{\Omega}^*_{j^+,n+1} = 2\widetilde{\Omega}^*_{j^-,n+1}$



Figures: Kim et al. in Bull. Math. Biol. 70(3), 1994-2016 2008

Numerical Simulations

Discretization:

- Precursor cell domain: $[0, 480] \times \mathbb{R}_0^+$
- Mature cell domain: $[0, 192] \times \mathbb{R}_0^+$
- Equally spaced meshes: $\Delta s = 1/w$

First Order Upwind Scheme:

- $\tilde{P}_{i,n+1} = \tilde{P}_{i,n} - \lambda_s(\tilde{P}_{i,n} - \tilde{P}_{i-1,n}) \qquad i = 1, \dots, \mathrm{I_p}$
- $\widetilde{M}_{i,n+1} = \widetilde{M}_{i,n} - \lambda_s(\widetilde{M}_{i,n} - \widetilde{M}_{i-1,n}) \qquad i = 1, \dots, I_m$

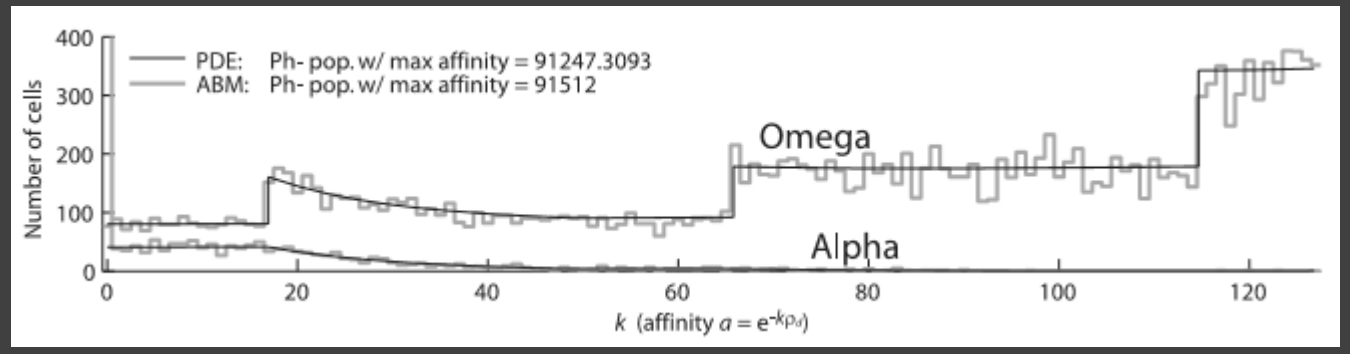
Boundary Conditions:

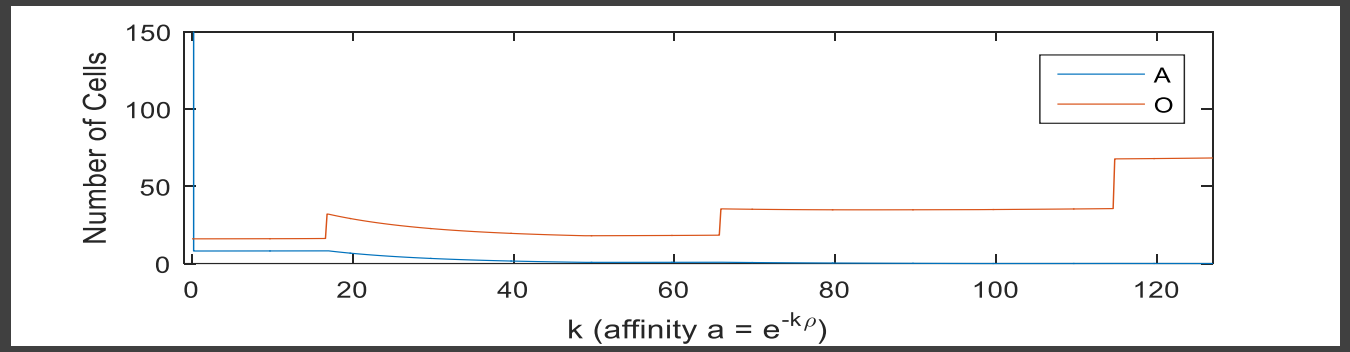
$\tilde{P}_{0,n} = \rho_d(\mathcal{T}_c(\widetilde{\Omega}_{J,-,n}) + \widetilde{\Omega}^*_{J,n})$

- $\tilde{P}_{vw^+,n} = 2\tilde{P}_{vw^-,n} \qquad for\ v = 24, 48, 72, \dots, 456$

$\widetilde{M}_{0,n} = 2\tilde{P}_{480,n}$

Model 3: PDE—Steady State Profile





Top:

- Validation image
- PDE vs Agent Based Model

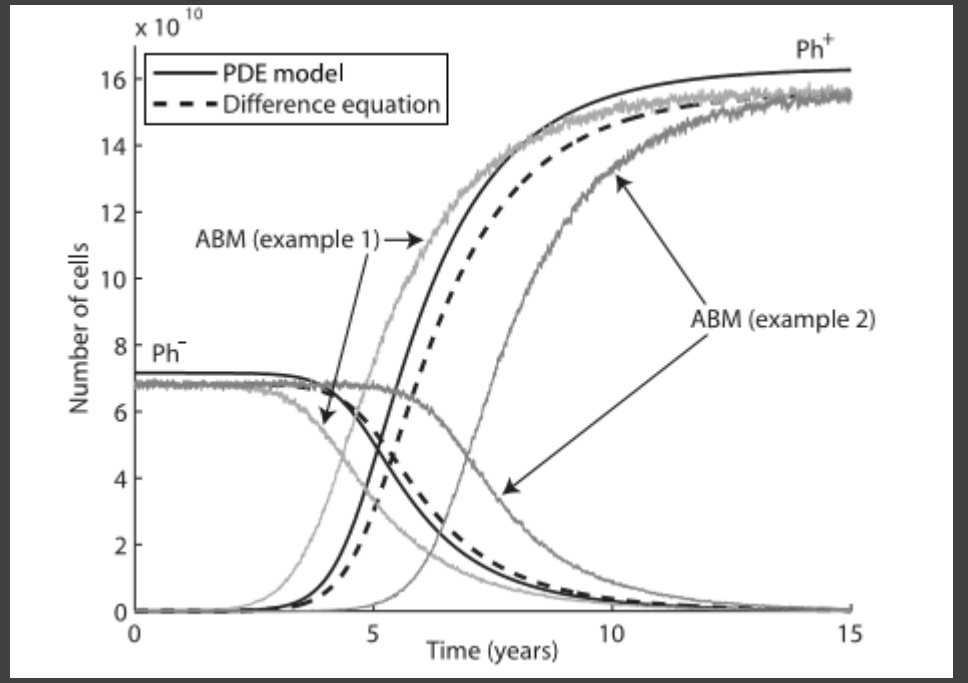
Bottom:

- Simulation of healthy cell population for 1 year.
- Cells with max affinity: 91,314

Model 3: PDE—CML Genesis

Mature Ph^- and mature Ph^+ cells simulated over 15 years

- Same general behavior as Model 1 and 2
- Overestimates number of Ph^+ cells at steady state

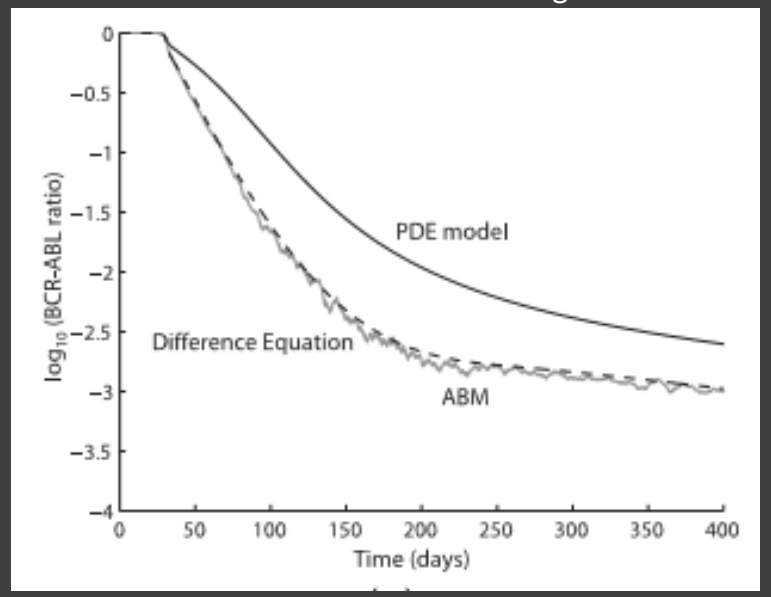


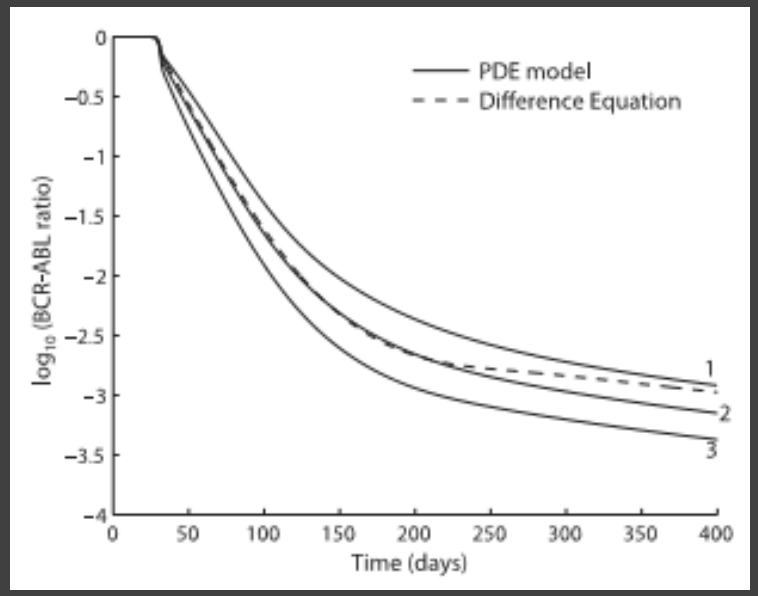
Figures: Kim et al. in Bull. Math. Biol. 70(3), 1994-2016 2008

Model 3: PDE—Imatinib Treatment

BCR—ABL Ratio during simulation of Treatment (400 days)

- Left: Project results (tba)
- Center: Validation image.
- Right: Treatment simulation with variation of r_{inh} and r_{deg} parameters





Figures: Kim et al. in Bull. Math. Biol. 70(3), 1994-2016 2008

Implementation

Implementation Hardware

- Asus Laptop with 8 GB RAM

Implementation Language

- Matlab R2015b

Parameter values from Roeder et al., 2006

Model Complexity and Comparison

Average Run Time	Model 1: ABM	Model 2: Difference Equations	Model 3: PDE
Steady State (2 years)	44.4919 s	2.5857 s	8.93 min (dt=0.1)
CML genesis (15 years)	14.06 min	45.606 s	31.33 min (dt=0.5)
Treatment (400 days)	38.5801 s	5.4113 s	TBA (dt=0.45)

Original paper average run times for CML genesis

- 6 hours 22 mins (Agent Based Model)
- 4 mins 32 secs (Difference Equations)
- ~ 2 hours (PDE)

Model 1—ABM complexity based on number of agents, i.e. number of stem cells (~10^6)

Model 2—Difference Equations computation of 10^5 simpler equations

Model 3—PDE computation of several more complex equations

Testing

Questions to answer:

- What are the transition rates between A and Ω?
- How long does disease genesis take?
- Does Model 1 always predict CML genesis?
- What is the relationship between Model 1 and Model 2?
- With treatment, does a steady state occur? What does it look like?
- Drug administration – when, how often?

Duration of CML Genesis

Calculate average time to reach three different thresholds

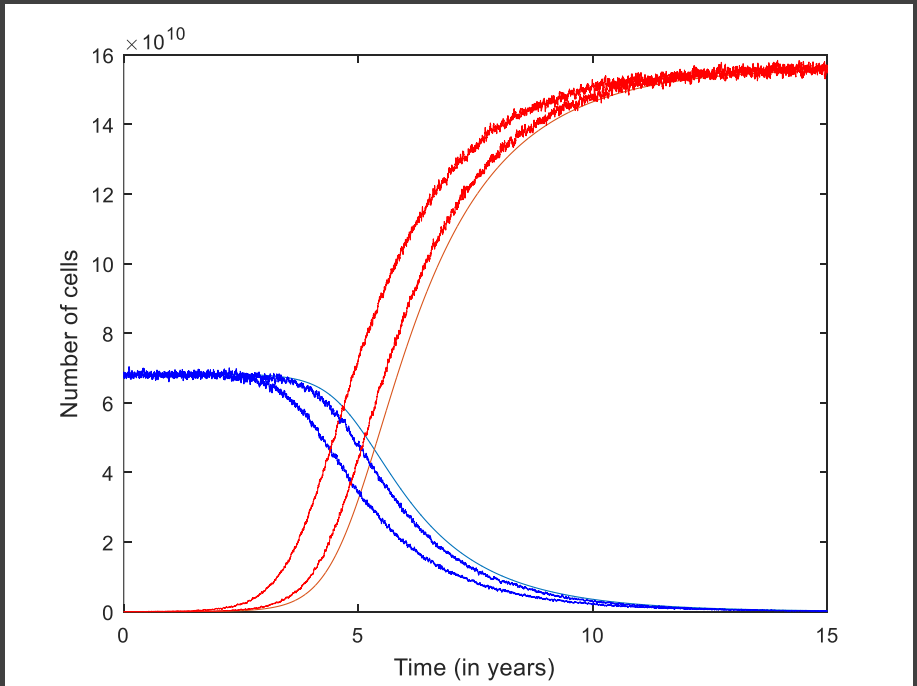
- $BCR - ABL\ Ratio = \frac{Mature\ Ph^{+} cells}{Mature\ Ph^{+} cells + 2 * Mature\ Ph^{-} cells}$
- Thresholds tested: BCR – ABL Ratio = 20%, 50%, 99%

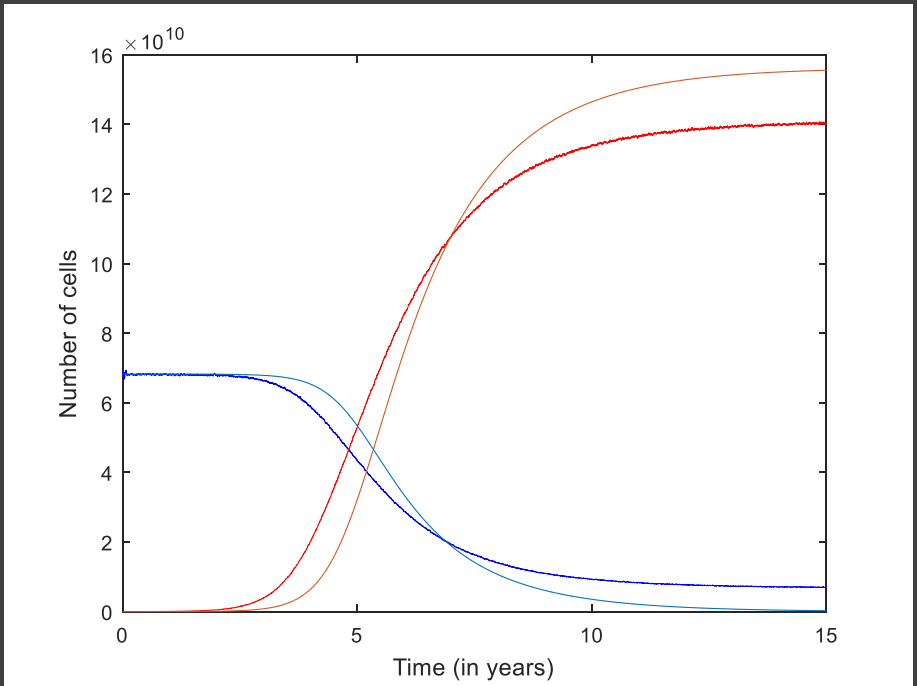
	Model 1: ABM	Model 2: Difference Equations	Model 3: PDE
20% Threshold	3.8289 years	4.8825 years	
50% Threshold	4.7506 years	5.90 years	
99% Threshold	10.8669 years	12.884 years	

Comparison of Discrete Models

CML Genesis

- Left: Two single runs of Model 1—Agent Based versus Model 2—Difference Equations
- Right: Average of 20 Model 1 simulations in comparison to Model 2 simulation

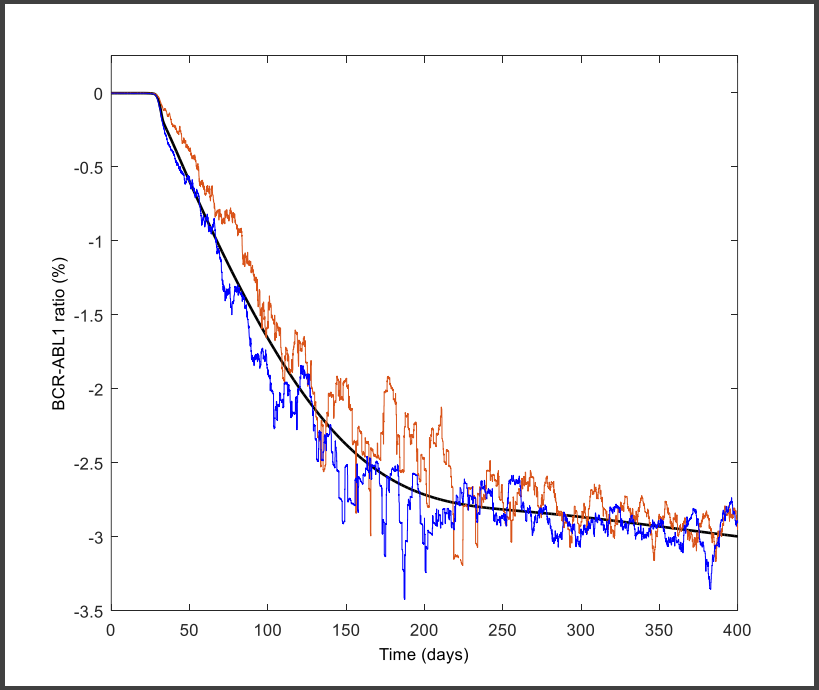


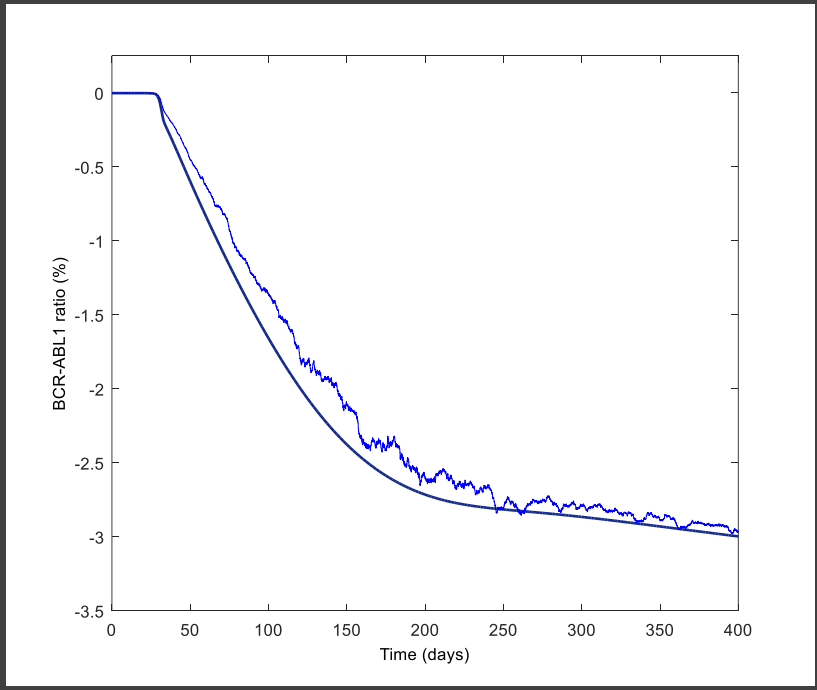


Comparison of Discrete Models

Effects of Imatinib Treatment

- Left: Two single runs of Model 1 versus Model 2
- Right: Average of 20 Model 1 simulations in comparison to Model 2 simulation



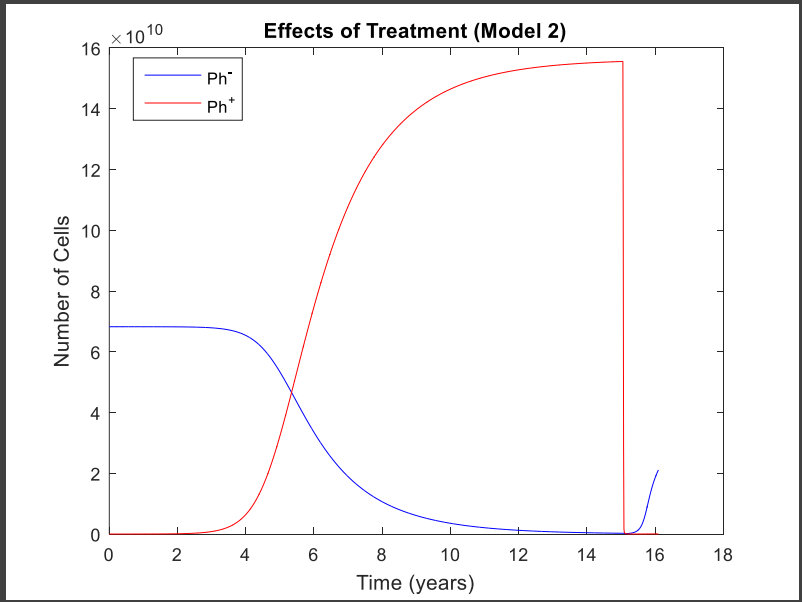


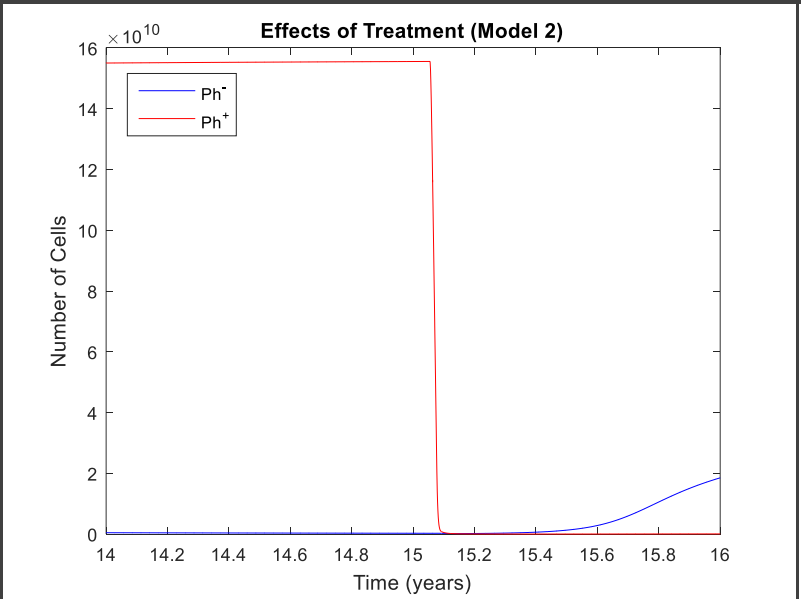
Effects of Imatinib Treatment

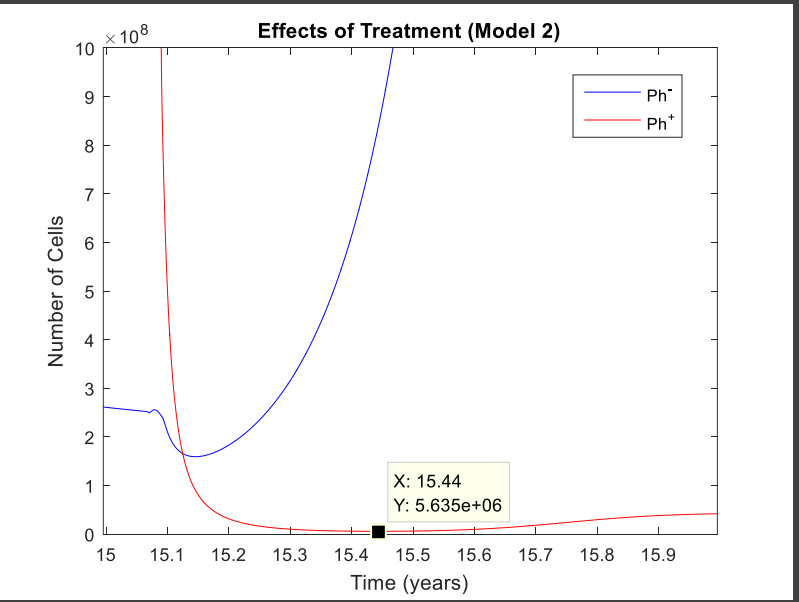
Mature cell populations plotted over ~16 years – Treatment starts at year 15

Number of Ph^+ cells drops drastically in about one tenth of a year

Ph^- grows rapidly



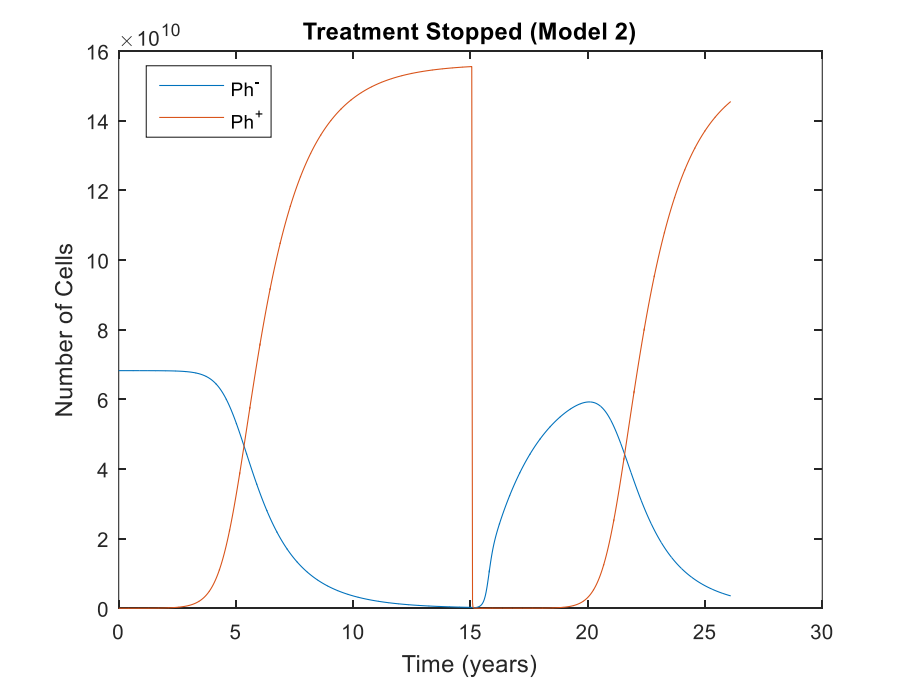


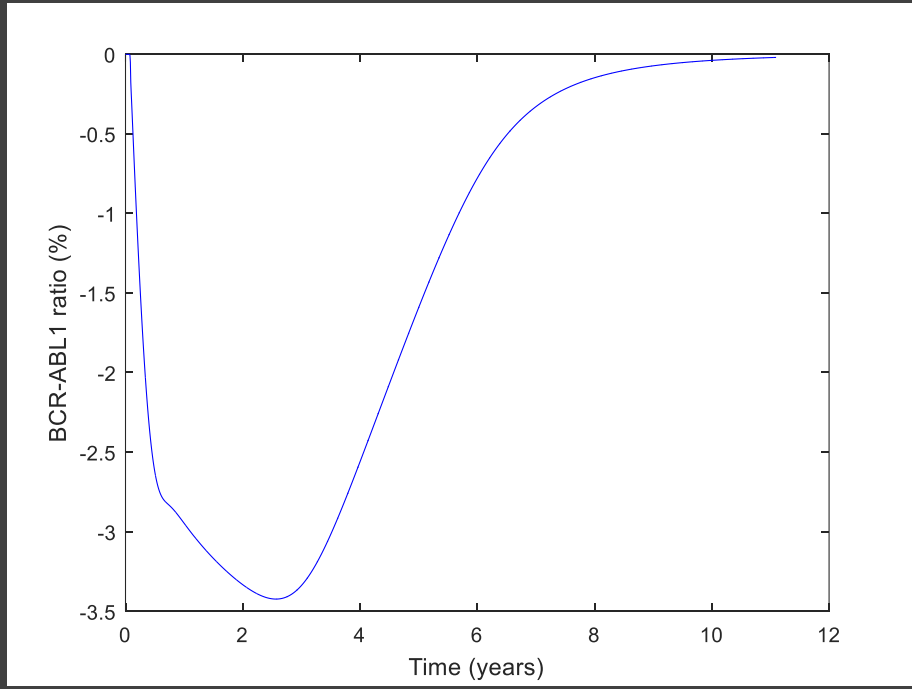


Post Treatment

The model predicts a recurrence of CML once treatment stops

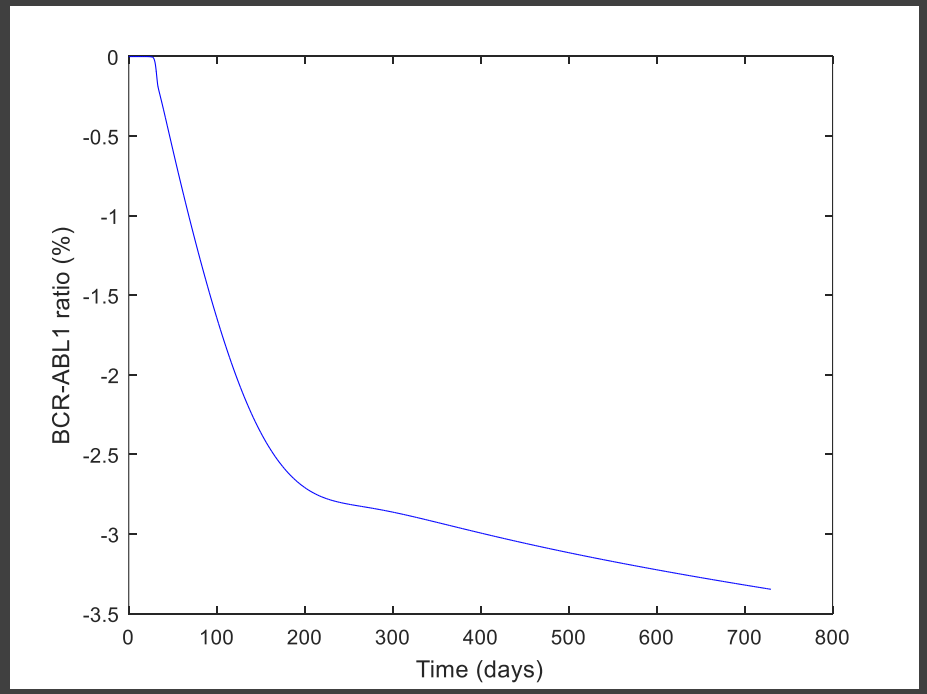
- Left: Mature cell populations during CML genesis (15 years), followed by 400 days of treatment and 10 years post treatment
- Right: BCR—ABL Ratio during and post treatment

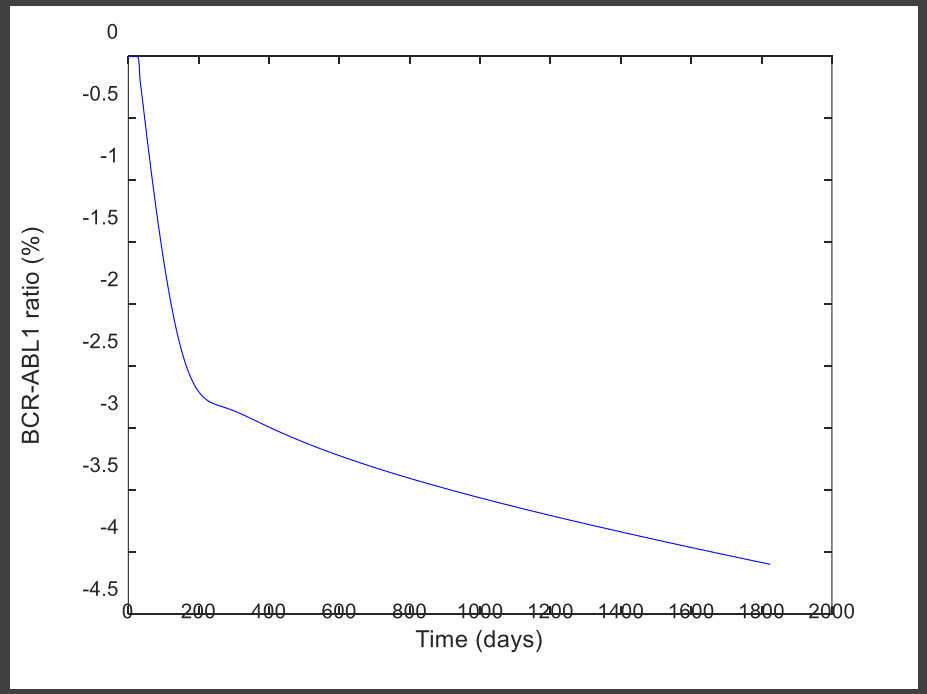




Extended Treatment

Simulations over longer periods of time (2 and 5 years respectively) suggest that CML cells will eventually die out





Final Thoughts

Model 1—ABM:

- Realistically simulates cells individually
- Not the most efficient
- Does not allow for realistic stem cell population sizes

Model 2—Difference Equations:

- Most efficient, but perhaps least realistic

Model 3—PDE:

- Continuous time model correlates better to real life cell growth development
- Explore parameter sensitivity (step sizes, r_{inh}, r_{deg}, etc.)

Further improvements:

- Allow for variation in fixed parameters (cell lifespans, cell cycle clock duration, cellular division, etc)
- Address discrepancies in outcome of treatment

Project Schedule

Phase 1: October—Early December

- Implement difference equation model
- Improve efficiency and validate

Phase 2: January—Early March

- Implement ABM
- Improve efficiency and validate

Phase 3: March—Early April

- Implement basic PDE method and validate on simple test problem

Phase 4: April—May

- Apply basic method to CML - Imatinib biology and validate
- Testing and Model Comparison

References

Roeder, I., Horn, M., Glauche, I., Hochhaus, A., Mueller, M.C., Loeffler, M., 2006. Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications. Nature Medicine. 12(10): pp. 1181-1184

Kim, P.S., Lee P.P., and Levy*, D.,* 2008. Modeling imatinib-treated chronic myelogenous leukemia: reducing the complexity of agent-based models. Bulletin of Mathematical Biology. 70(3): pp. 728-744.

Kim, P.S., Lee P.P., and Levy*, D.,* 2008. A PDE model for imatinib-treated chronic myelogenous leukemia. Bulletin of Mathematical Biology. 70: pp. 1994-2016.