Modeling Imatinib-Treated Chronic Myeloid Leukemia

Mid Year Presentation

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Introduction

CML – cancer of the blood

- 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

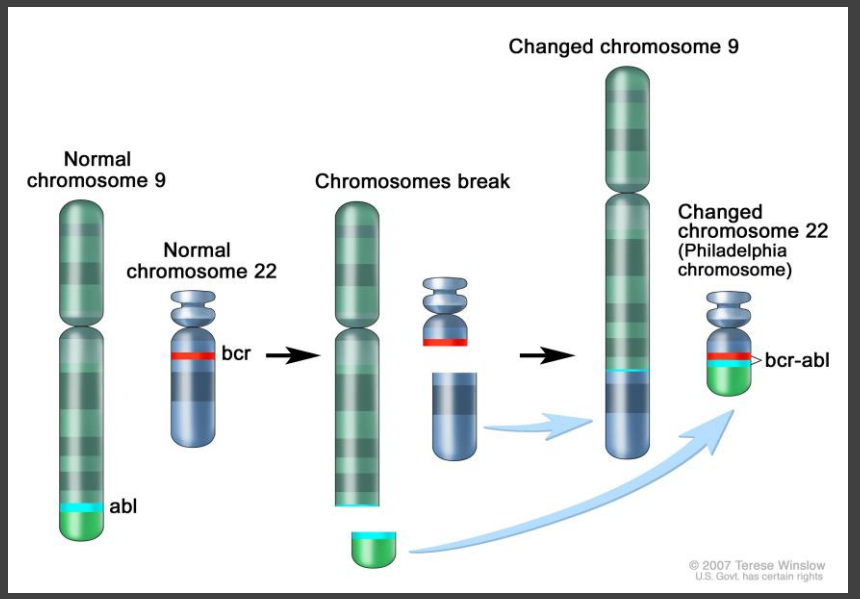


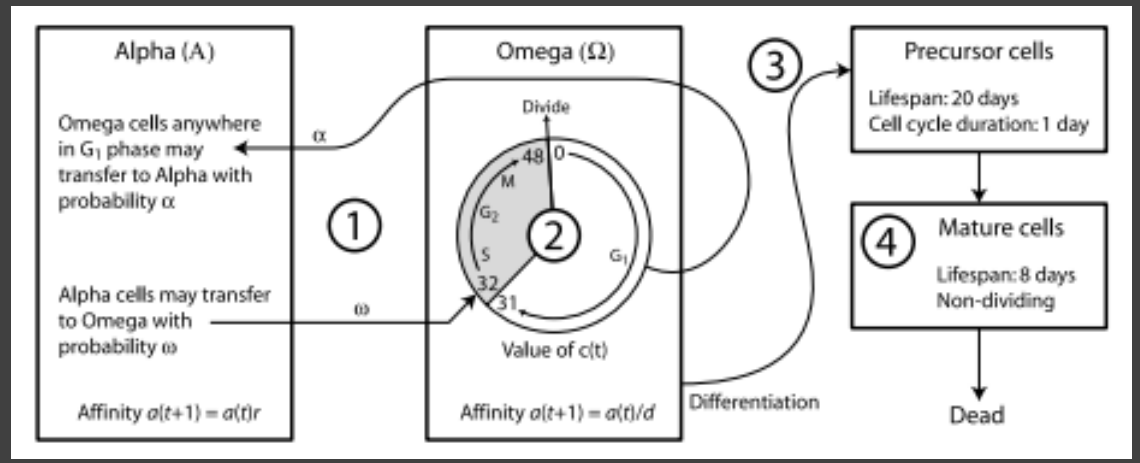
Figure: Chronic Myelogenous Leukemia Treatment. National Cancer Institute. 21 Sept. 2015. Web.

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

Assume fixed and known lifespans for Precursor and Mature cells

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

Project Goals

Mathematically model clinically observed phenomena of three non-interacting cell populations

- Nonleukemia cells (Ph^-)
- Leukemia cells (Ph^+)
- Imatinib-affected leukemia cells

Three model types based on cell state diagram

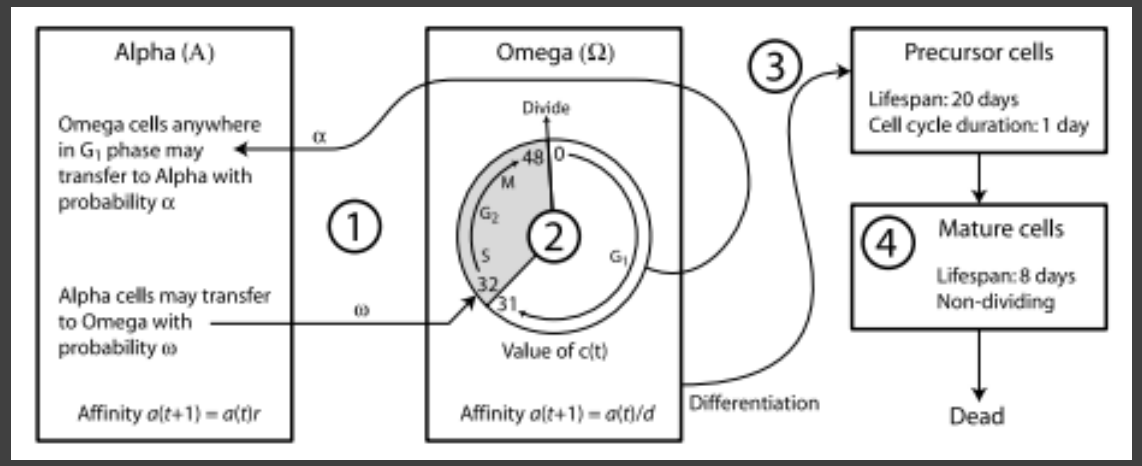
- Model 1: Agent Based Model (Roeder et al., 2006)
- Model 2: System of Difference Equations (Kim et al., 2008)
- Model 3: PDE (Kim et al., 2008)

Parameter values based on clinical data

Model 2: Kim et al., 2008

System of Deterministic Difference Equations

- Time, affinity and cell cycle discretized
- Transitions between A and Ω given by binomial distributions



$$A_k(t+1) = \begin{cases} (A_0(t) - B_0(t)) + (A_1(t) - B_1(t)) + (A_2(t) - B_2(t)), & k = 0, \\ (A_{k+2}(t) - B_{k+2}(t)) + \sum_{c=0}^{31} \Psi_{k,c}(t), & k = 1, \ldots, 125, \\ \sum_{c=0}^{31} \Psi_{k,c}(t), & k = 126, 127, \end{cases} \tag{2}$$

$$\Omega_{k,c}(t+1) = \begin{cases} B_0(t), & k = 0,\ c = 32, \\ 2\Omega_{k-1,48}(t), & k > 0,\ c = 0, \\ \Omega_{k-1,c-1}(t) - \Psi_{k-1,c-1}(t), & k > 0,\ c = 1, \ldots, 31, \\ (\Omega_{k-1,31}(t) - \Psi_{k-1,31}(t)) + B_k(t), & k > 0,\ c = 32, \\ \Omega_{k-1,c-1}(t), & k > 0,\ c = 33, \ldots, 48, \\ 0 & \text{otherwise.} \end{cases} \tag{3}$$

$$P_j(t+1) = \begin{cases} \sum_{c=0}^{48} \Omega_{124,c}(t) - \sum_{c=0}^{31} \Psi_{124,c}(t), & j = 0, \\ 2P_{j-1}(t), & j = 24, 48, 72, \ldots, 456, \\ P_{j-1}(t), & \text{otherwise,} \end{cases} \tag{4}$$

$$M_j(t+1) = \begin{cases} 2P_{479}(t), & j = 0, \\ M_{j-1}(t), & \text{otherwise,} \end{cases} \tag{5}$$

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

Modeling CML Genesis and Treatment

Healthy cells (Ph^-)

- Equations same as original
- Transition probabilities governed by sigmoidal functions $f_{\alpha/\omega}$ with corresponding Ph^- parameters

Leukemic cells (Ph^+)

- Equations for A, P and M compartments remain the same as the original
- During treatment, Ω cells may become Imatinib affected or die at each time step
  - $\Omega_{k,c}^{+/R}(t) = \Omega_{k,c}^{+}(t) - \Omega_{k,c}^{+/I}(t)$
- Transition probabilities governed by sigmoidal functions $f_{\alpha/\omega}$ with corresponding Ph^+ parameters

Affected cells ($Ph^{+/A}$)

- Equations for A, P and M compartments remain the same as the original
- Ω cells may undergo apoptosis at each time step
- Transition probabilities governed by sigmoidal functions $f_{\alpha/\omega}$ with corresponding $Ph^{+/A}$ parameters

Implementation and Simulation

Implemented in Matlab. Vectorized difference equations for efficiency.

Initialize Ph^- population: $\Omega_{0,32}(0) = 1$
For t = 1: Steady State
- Update Ph^- population

Initialize Ph^+ population: $\Omega_{0,32}(0) = 1$
For t = 1: Genesis
- Update Ph^- population
- Update Ph^+ population

For t = 1: Treatment
- Update Ph^- population
- Update Ph^+ population
- Update $Ph^{+/A}$ population

Results: Steady State Profile

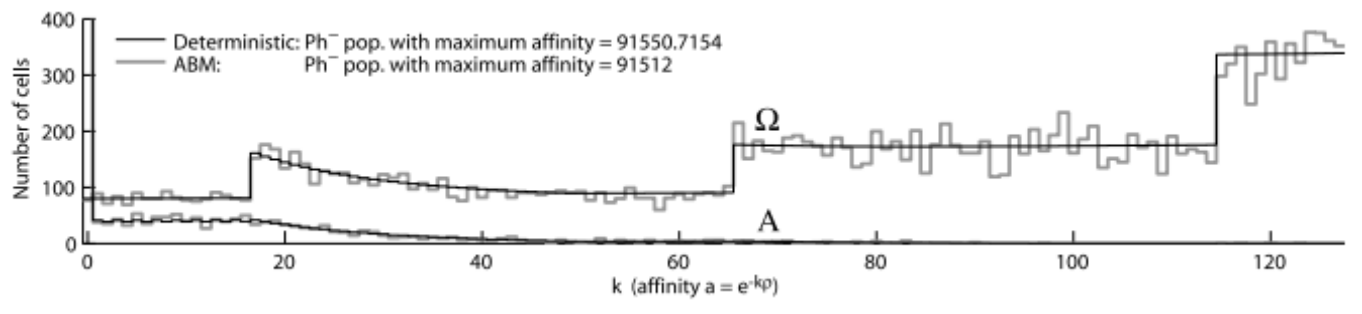
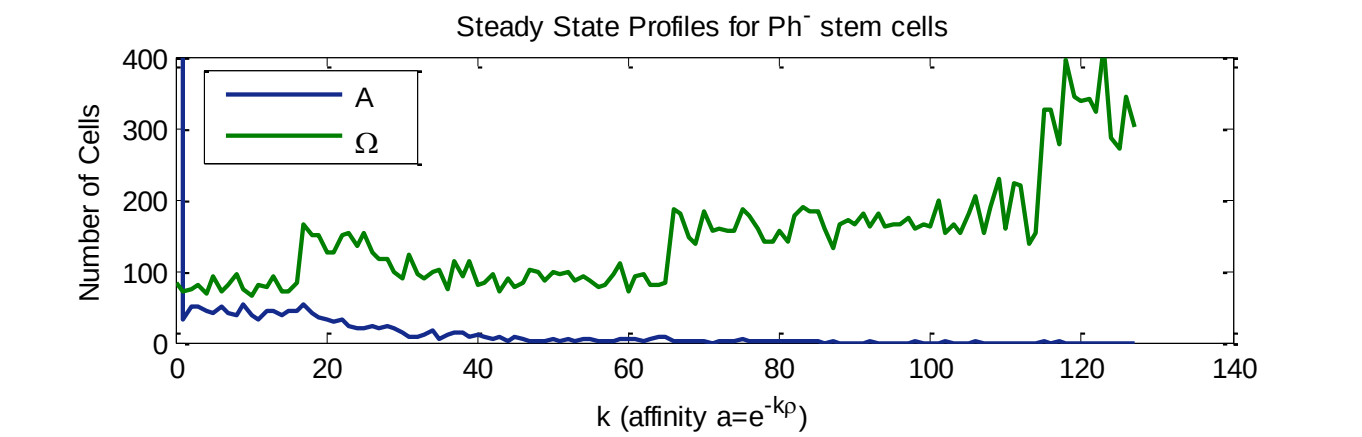


Figure: Kim et al. in Bull. Math. Biol. 70(3), 728-744 2008



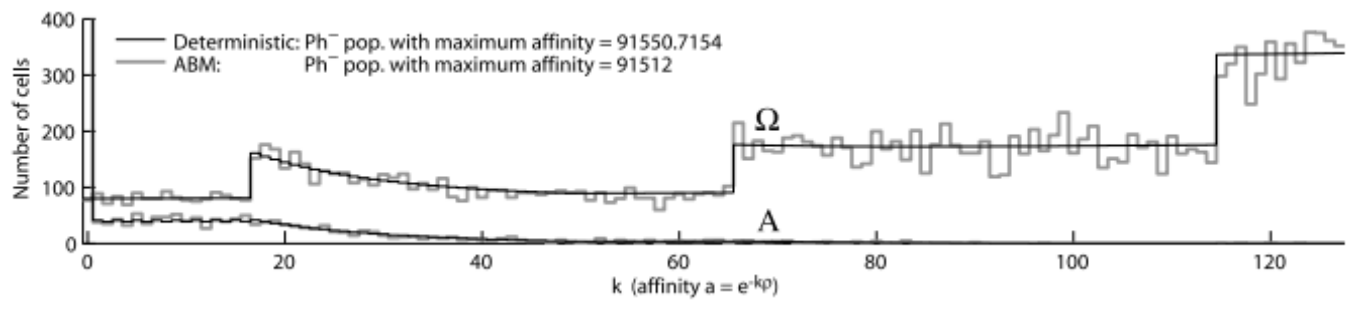
Simulation of healthy cell population for 1 year

Number of cells that transfer between stem cell compartments at time t given by:

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

$$\Psi_{k,c}(t) \sim Bin\left(\Omega_{k,c}(t), \alpha\left(\mathrm{A}(t), e^{-k\rho}\right)\right) \qquad c = 0,..31$$

Results: Steady State Profile



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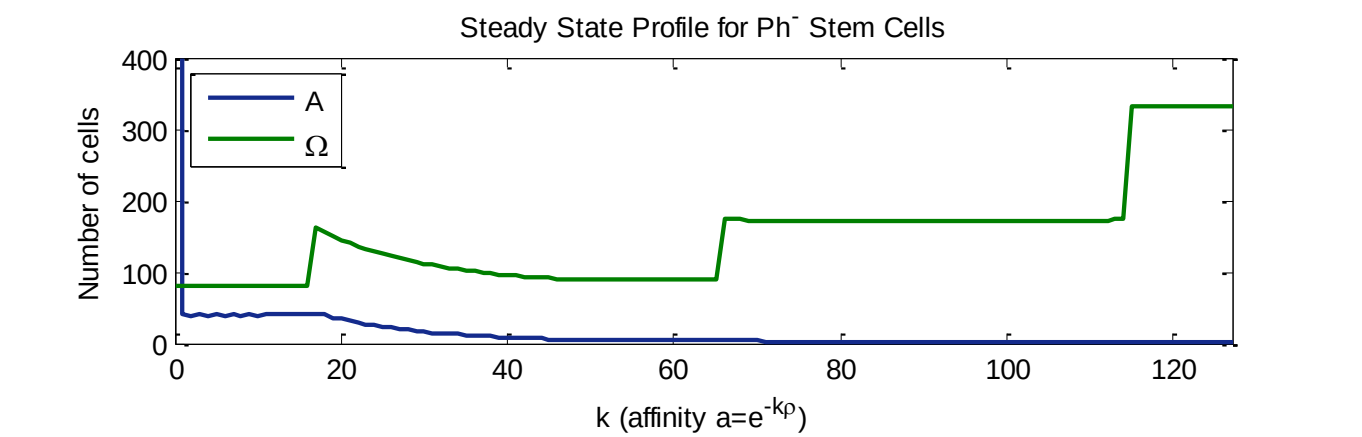


Simulation of healthy cell population for 1 year

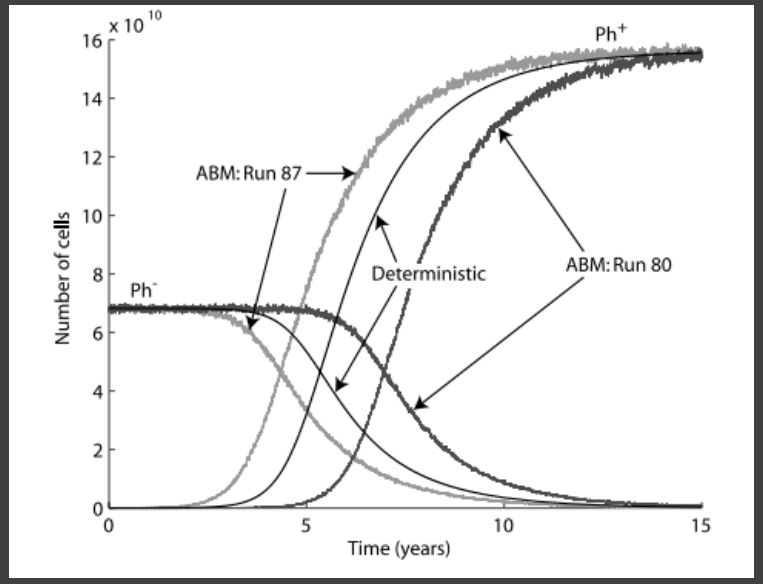
Mean of binomial random variable used to smooth curves

$$B_k(t) = \mathrm{A}_k(t) * \omega\left(\Omega(t), e^{-k\rho}\right)$$

$$\Psi_{k,c}(t) = \Omega_{k,c}(t) * \alpha\left(\mathrm{A}(t), e^{-k\rho}\right)$$

Results: CML Genesis

Mature cell progression for Ph^- and Ph^+ populations over 15 year span.



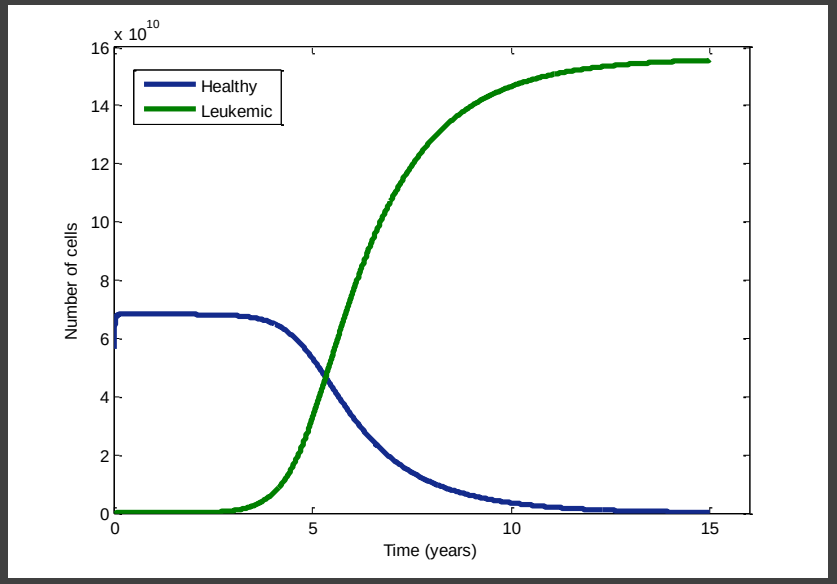
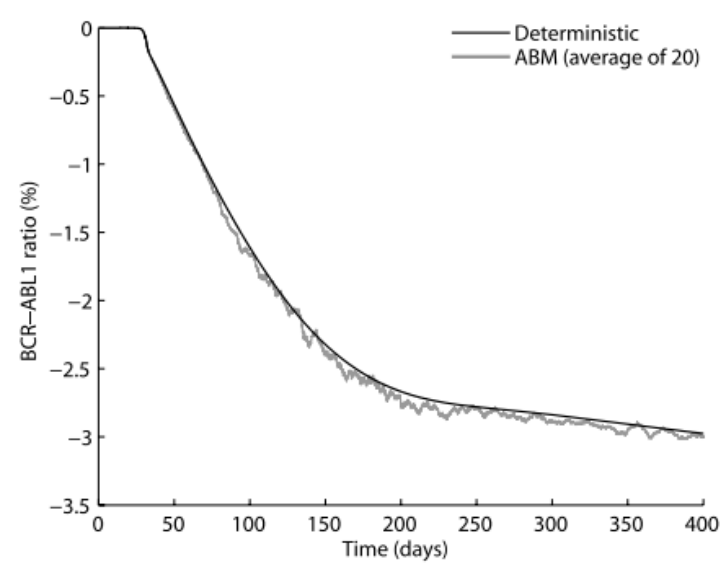


Figure: Kim et al. in Bull. Math. Biol. 70(3), 728-744 2008

Results: Treatment

BCR-ABL1 Ratio for duration of treatment (400 days)

$$BCR - ABL\ Ratio = \frac{Mature\ Ph^{+}cells}{Mature\ Ph^{+}cells + 2 * Mature\ Ph^{-}cells}$$



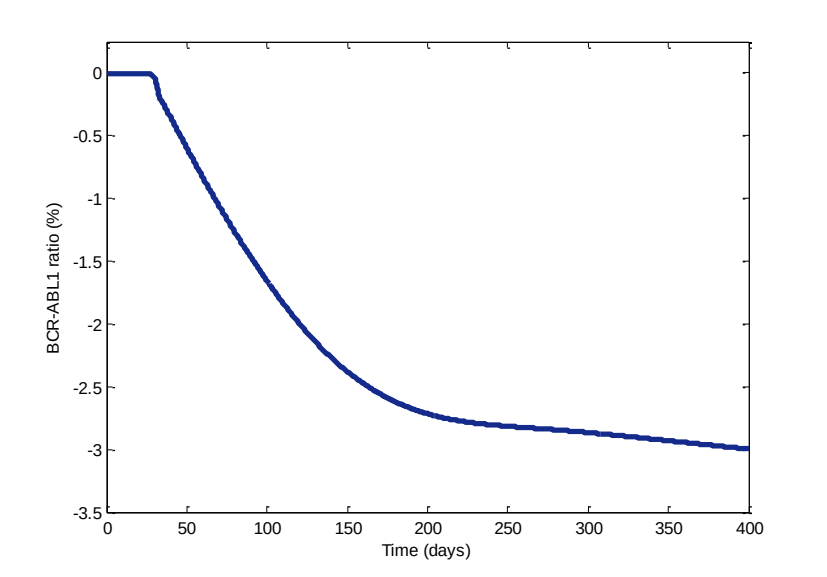


Figure: Kim et al. in Bull. Math. Biol. 70(3), 728-744 2008

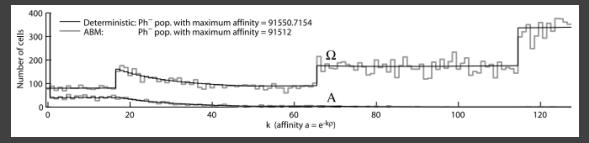
Model 1: Roeder et al., 2006

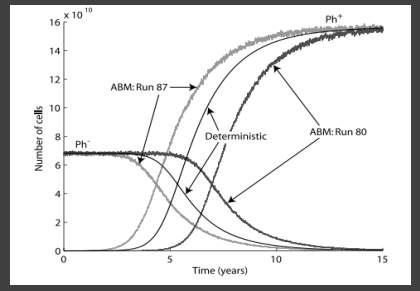
Single cell-based stochastic model

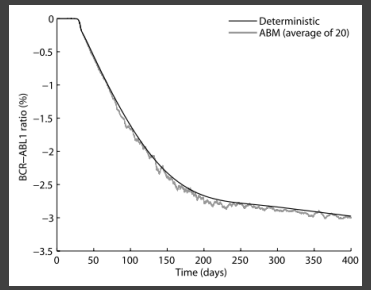
Complexity based on number of agents

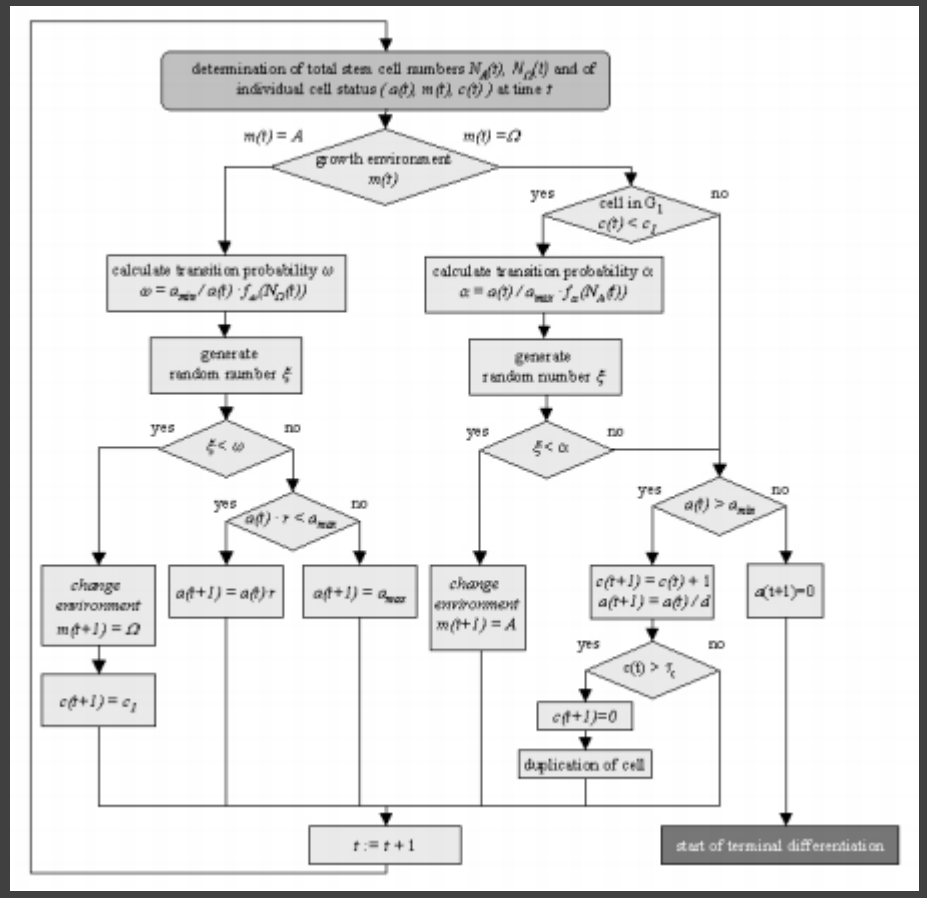
- ~10^5 cells
- Down-scaled to 1/10 of realistic values

Validate using figures from Kim et al., 2008









Model 3: Kim et al., 2008

Transform model into a system of first order hyperbolic PDEs

- Consider the cell state system as a function of three internal clocks
  - Real time (t)
  - Affinity (a)
  - Cell cycle (c)
- Each cell state can be represented as a function of 1-3 of these variables

Numerical Simulation

- Explicit solvers
- Upwinding
- Composite trapezoidal rule
- First order time discretization

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

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

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

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

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

Project Schedule

Phase 1

- Implement difference equation model
- Improve efficiency and validate

Phase 2: End of December

- Implement ABM
- Improve efficiency and validate

Phase 3: January – mid February

- Implement basic PDE method and validate on simple test problem

Phase 4: mid February – April

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

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.

Thank you

Questions?