Leukaemia, Imatinib, and the Immune Response

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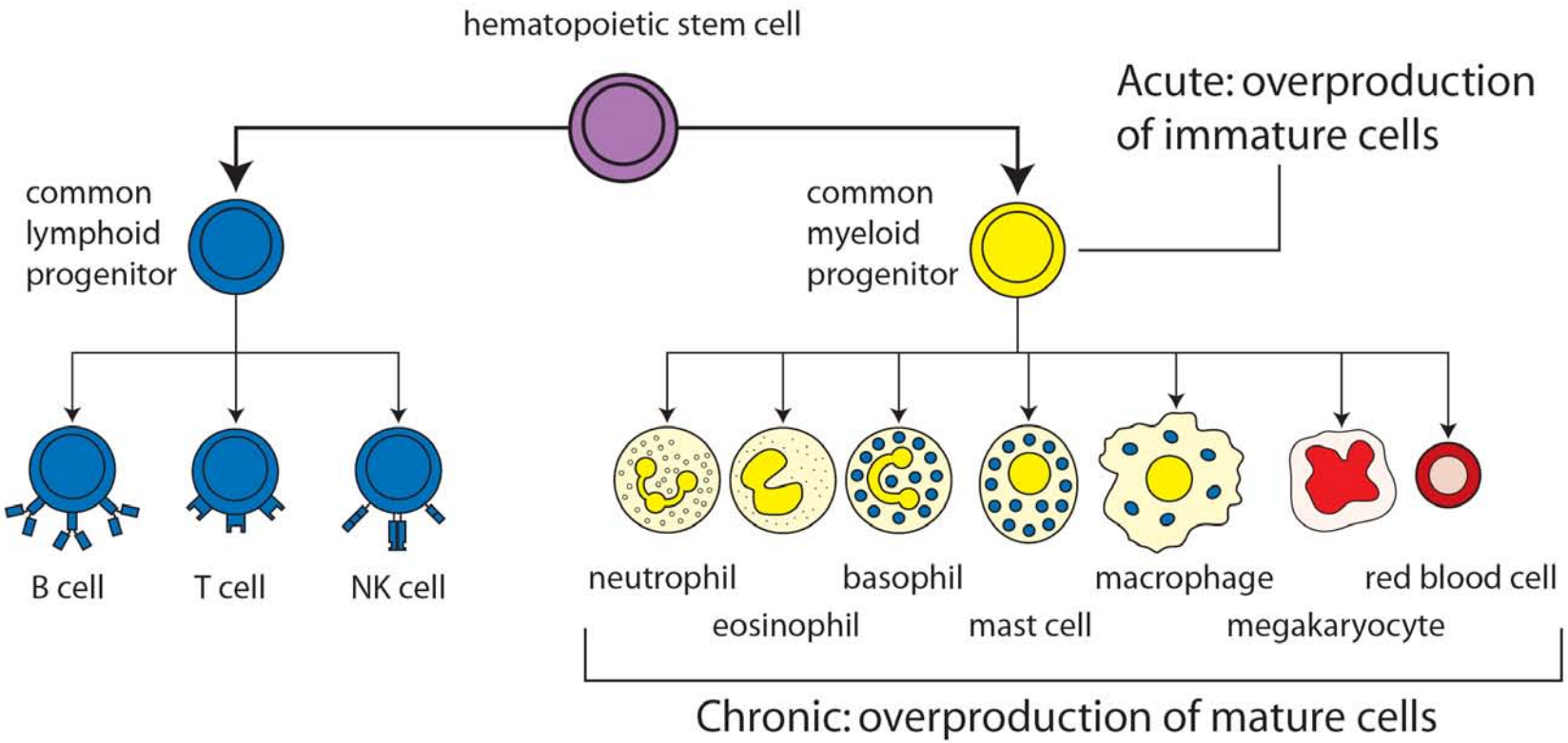
Leukaemia



Lymphocytic leukemia

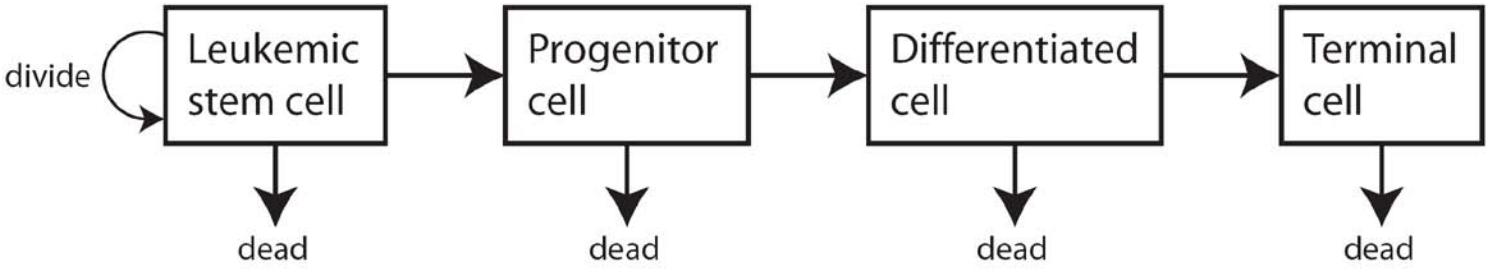
Myelogenous leukemia

Standard treatments

- **Chemotherapy**
  - targets proliferating cells
- **Bone marrow transplant**
  - chemotherapy + radiation + transplant
- **Gene-specific therapy** (imatinib)
  - turns off corrupted control system

CML, Imatinib, & T cell response

- Starting point: Michor et al. (*Nature* '05)
  - **Four stage** cell differentiation
  - Imatinib hinders cell differentiation



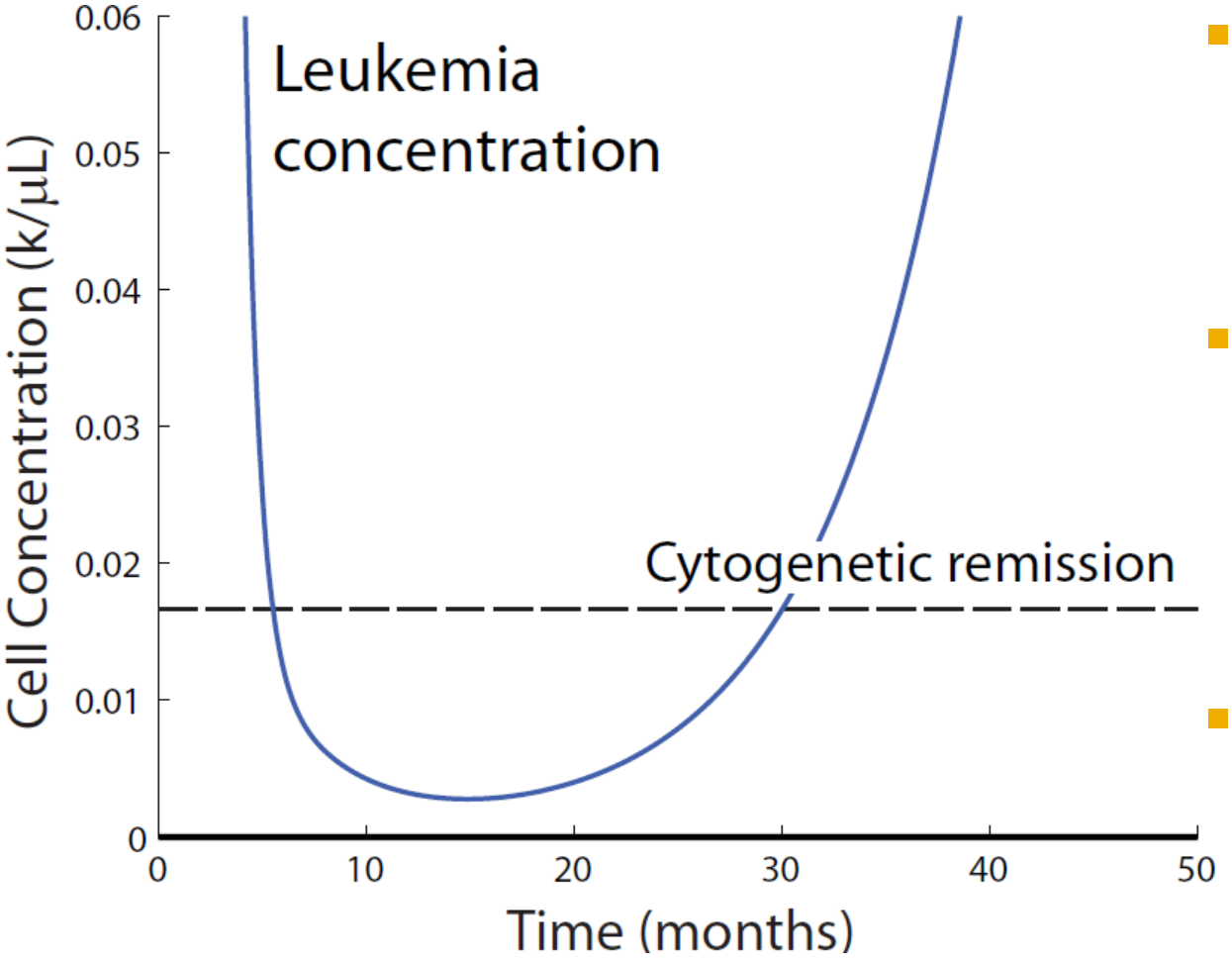
$$\dot{y}_0 = [r_y(1-u) - d_0]y_0 \xrightarrow{\text{mutation}} \dot{z}_0 = [r_z - d_0]z_0 + r_y y_0 u$$

$$\dot{y}_1 = a_y y_0 - d_1 y_1 \qquad \dot{z}_1 = a_z z_0 - d_1 z_1$$

$$\dot{y}_2 = b_y y_1 - d_2 y_2 \qquad \dot{z}_2 = b_z z_1 - d_2 z_2$$

$$\dot{y}_3 = c_y y_2 - d_3 y_3 \qquad \dot{z}_3 = c_z z_2 - d_3 z_3$$

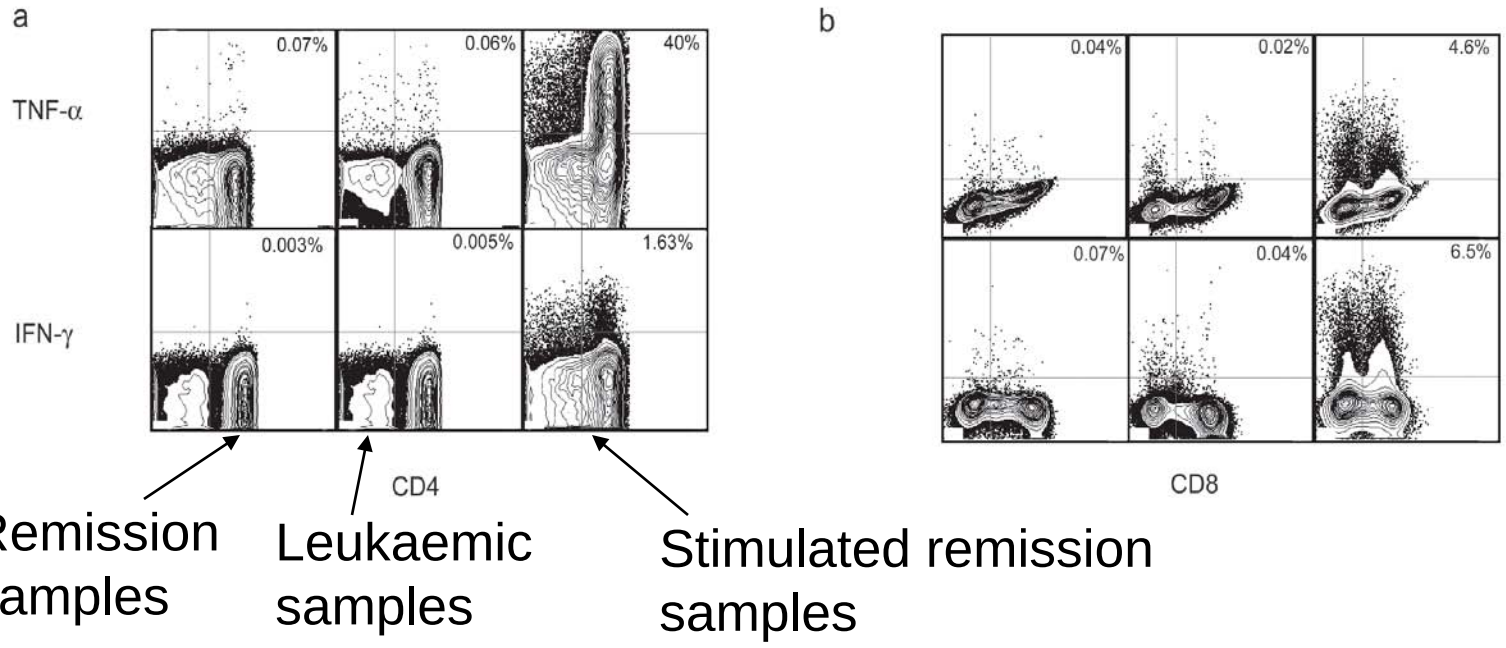
Early relapse is inevitable
(even without resistance mutations)



- Michor model: Predicts relapse after about 3 years.
- Clinical data: Most patients **don't relapse** for several years.
- **What sustains remission?**

Experiments (Chen et al. *Blood* 2008)

- **14** patients treated with imatinib
- All attained cytogenetic remission (complete/major)
- **9** of **14** showed an anti-leukaemia T cell response



Incorporate immune response

- Account for death from T cells

$$\dot{y}_0 = [r_y(1-u) - d_0]y_0 - q_c p(C,T)y_0$$
$$\dot{y}_1 = a_y y_0 - d_1 y_1 - q_c p(C,T)y_1$$
$$\dot{y}_2 = b_y y_1 - d_2 y_2 - q_c p(C,T)y_2$$
$$\dot{y}_3 = c_y y_2 - d_3 y_3 - q_c p(C,T)y_3$$

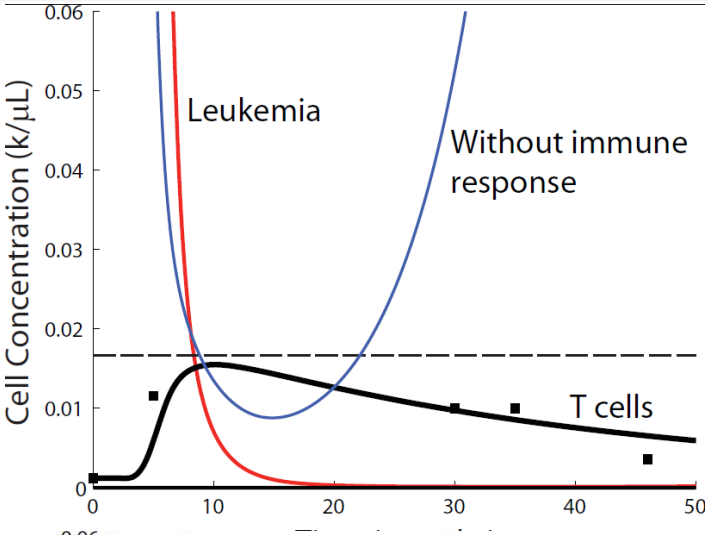
- Anti-leukaemiaT cells

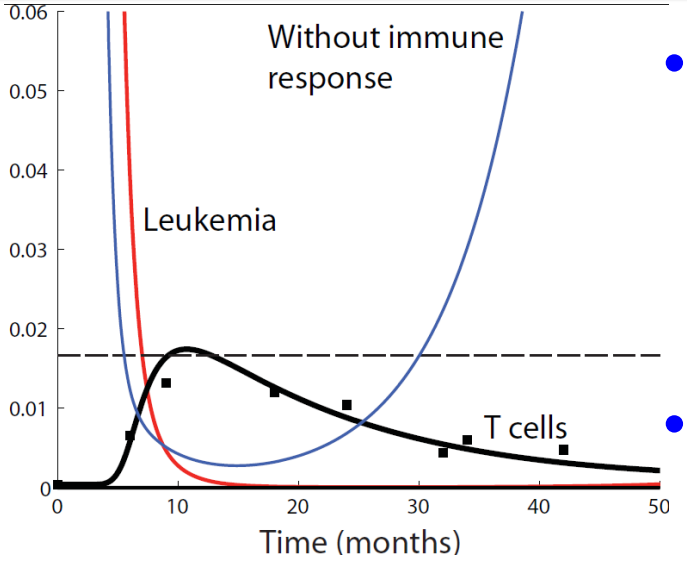
$$\dot{T} = s_t - d_t T - p(C,T)C + 2^n q_T p(C_{n\tau}, T_{n\tau})C_{n\tau}$$

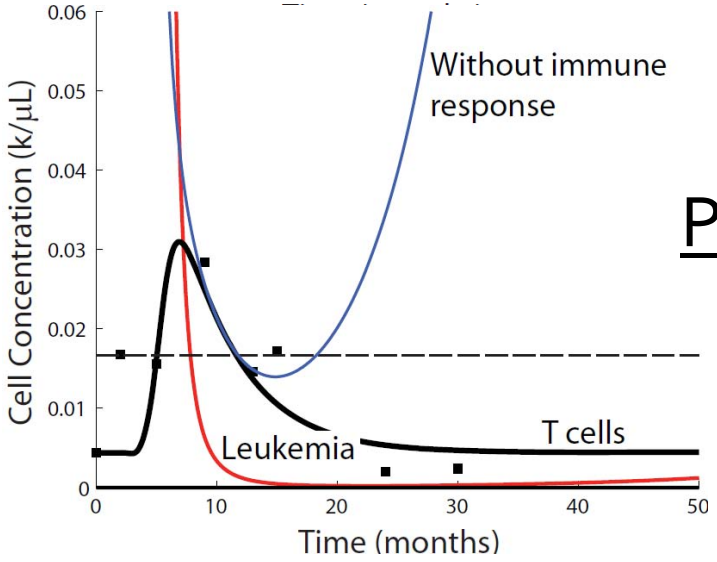
- Immune downregulation, total cancer population, time-delay term

$$p(C,T) = p_0 e^{-c_n C} kT, \quad C = \sum (y_i + z_i), \quad C_{n\tau} = C(t - n\tau)$$

Results for 3 patients







- Leukemia: With and without immune response
- Dashed line: cytogenetic remission

Possible interpretation: Sustained remission is due to **imatinib** & the **immune response**.

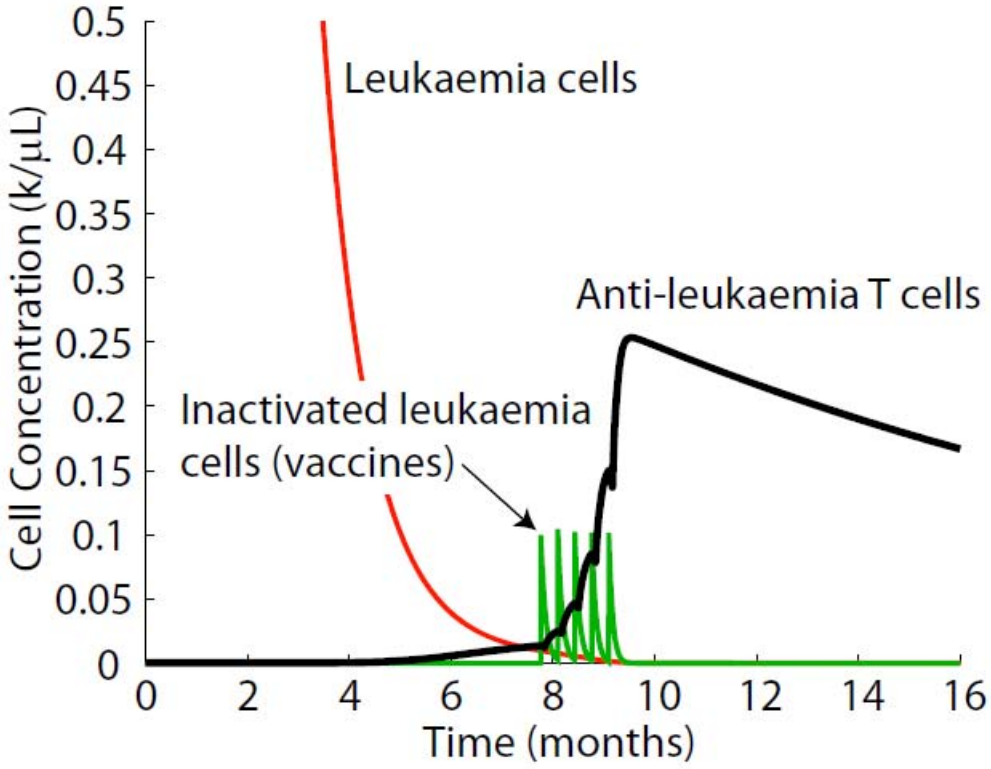
Cancer vaccines

(Goal: expand existing immune response)

- Introduce cryopreserved (frozen) leukaemia cells
  - Same stimulatory properties as leukaemia cells
  - Do not contribute to immune downregulation
  - Decay quickly (1/2 life of 3 days)

- For a given vaccine dosage
  - Optimize **timing** of first vaccine
  - Optimize **pacing** of successive vaccines

Example vaccination schedule



5 doses of $6x10^8$ cells on days 233, 243, 253, 263, 273.

Log_{10} [Min cancer load] = -10.5 (less than ½ cell remains)

Summary & Next step

- Old Starting point: Michor et al. (*Nature* '05)
  - ODE model
  - Add immune response
  - Kim, Lee, Levy, "Dynamics and potential impact of the immune response to CML", *PLoS Comput Biol*
- New Starting point: Roeder et al. (*Nat Med* '06)
  - Agent-based model
  - Goal: Add immune response

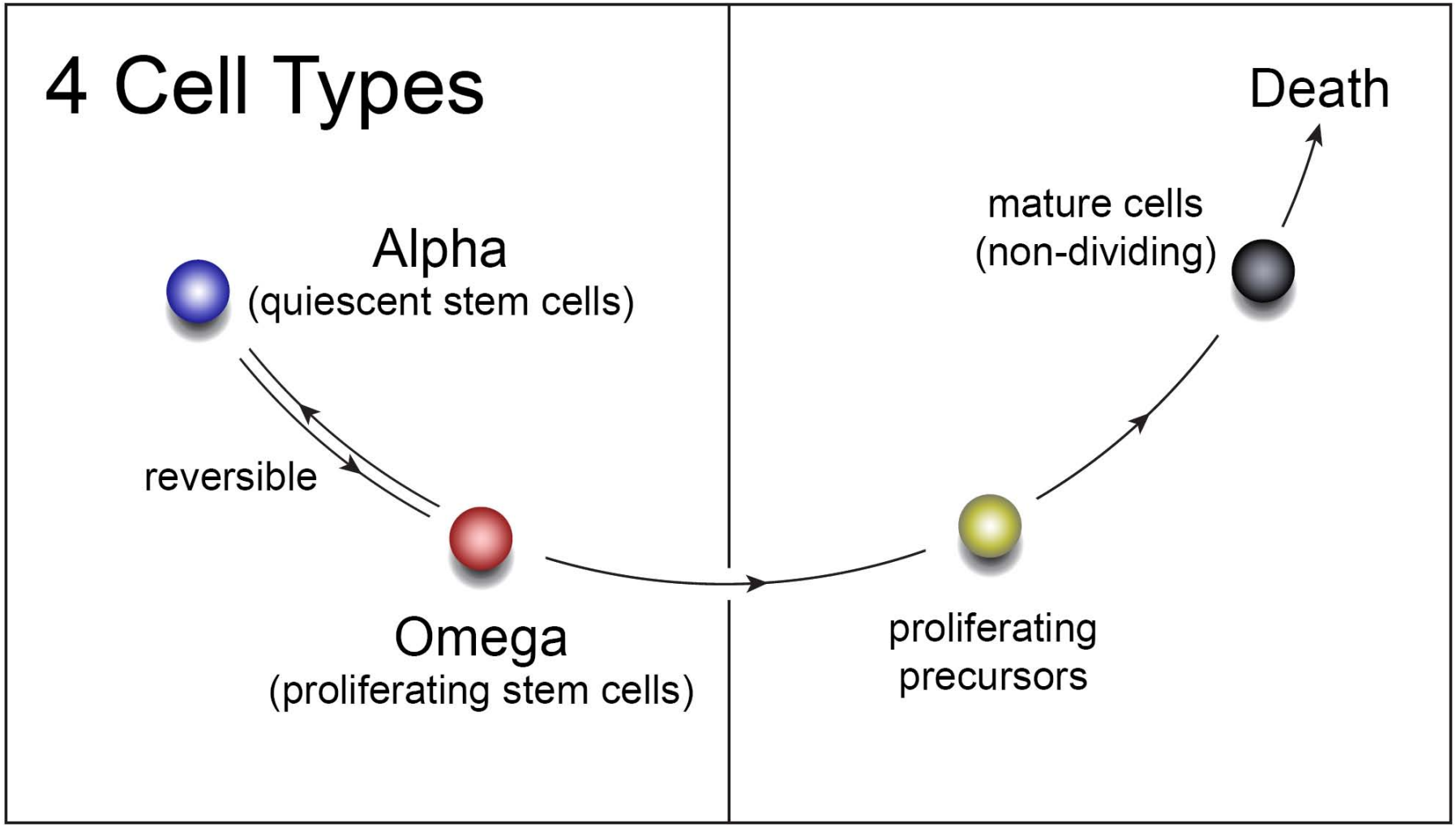
Agent-based model (ABM)

- Cells = **agents**
- Agents are **leukaemic** or **normal**

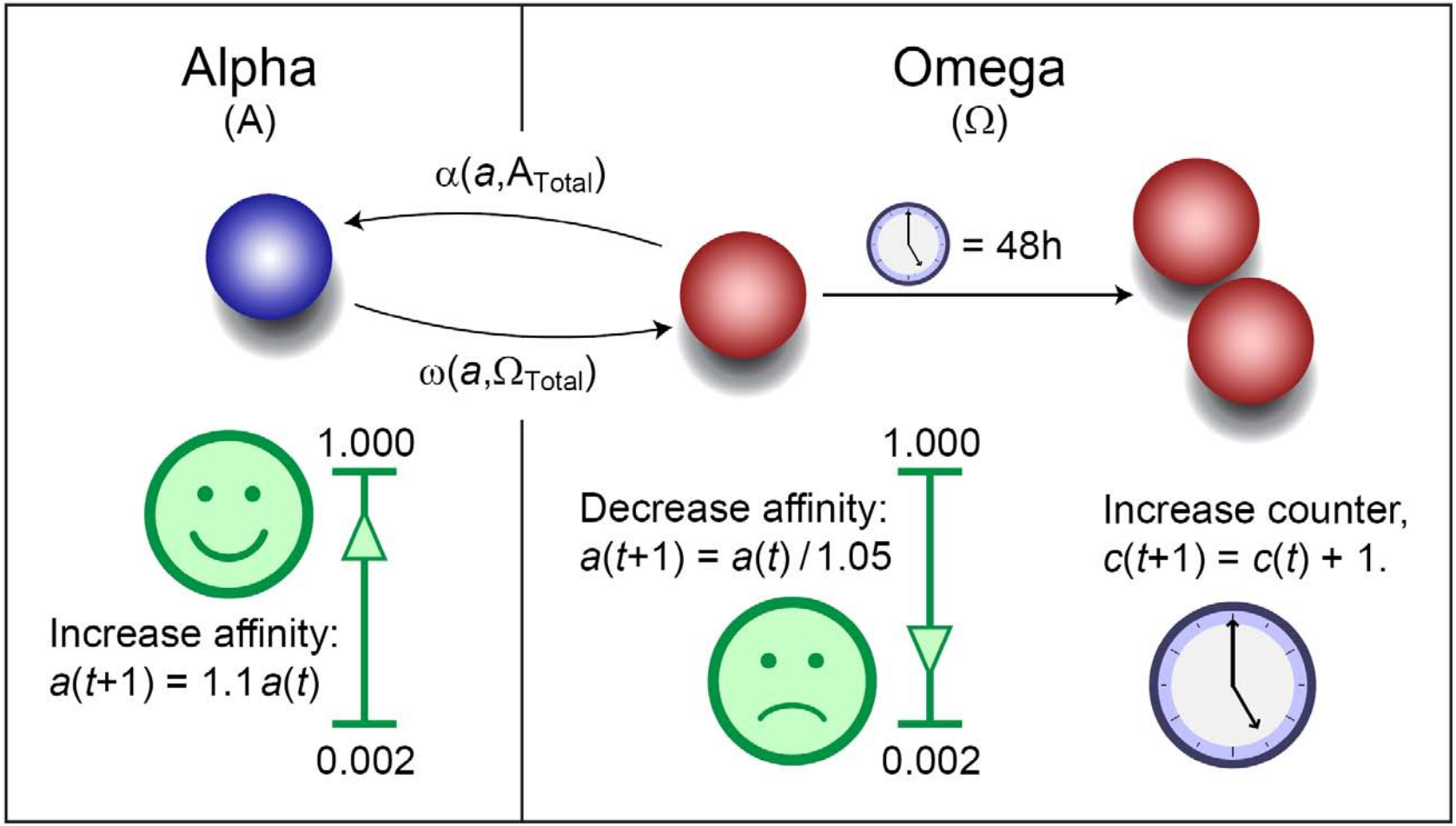
- Two **state variables** per agent
  - Affinity to stem cell niche (0.002 to 1)

  - Time Counter for cell cycle (48 hours)

Cell differentiation



Stem cells (dormant/proliferating)



Time step: 1 hour

ABM attributes

- Accounts for **individual diversity**
- **Probabilistic** transitions

- Computationally demanding
  - Number of cells ~ **100,000**
    - **1/10** of realistic value
  - **7** hours per simulation

Imatinib dynamics

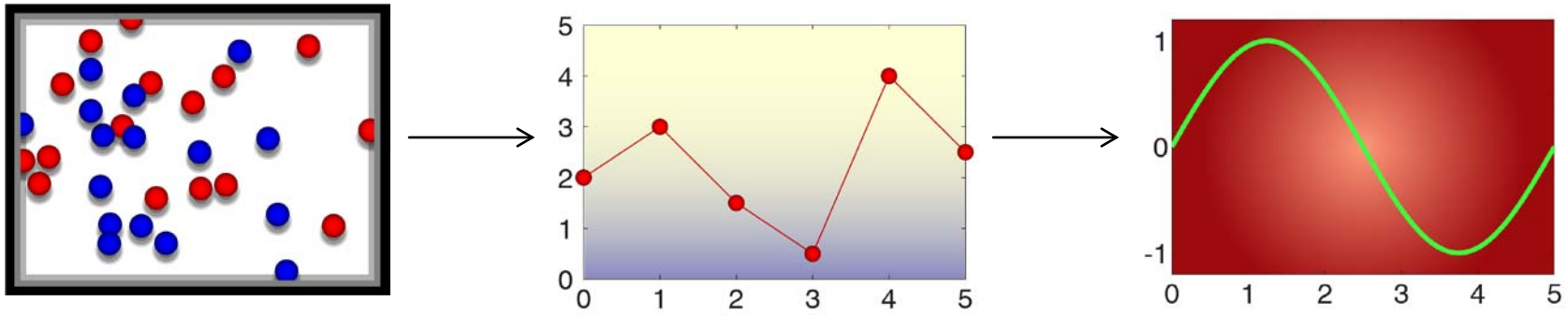
- Leukaemic cells turnover faster than normal
  - Enter proliferating state very frequently
- Imatinib decreases stem cell **turnover rates**
  - Reduced rate of entering proliferating state

- Sustained leukaemia remission
- Leukaemia **not eliminated**
- Eventual **relapse**

Incorporate T cell response

- Goal
  - Take Roeder model & add T cell response
- Difficulty
  - Agent-based model is time-consuming
    - 7 hours per simulation
    - 20 simulations to obtain average behavior
- First step: simplify agent-based model

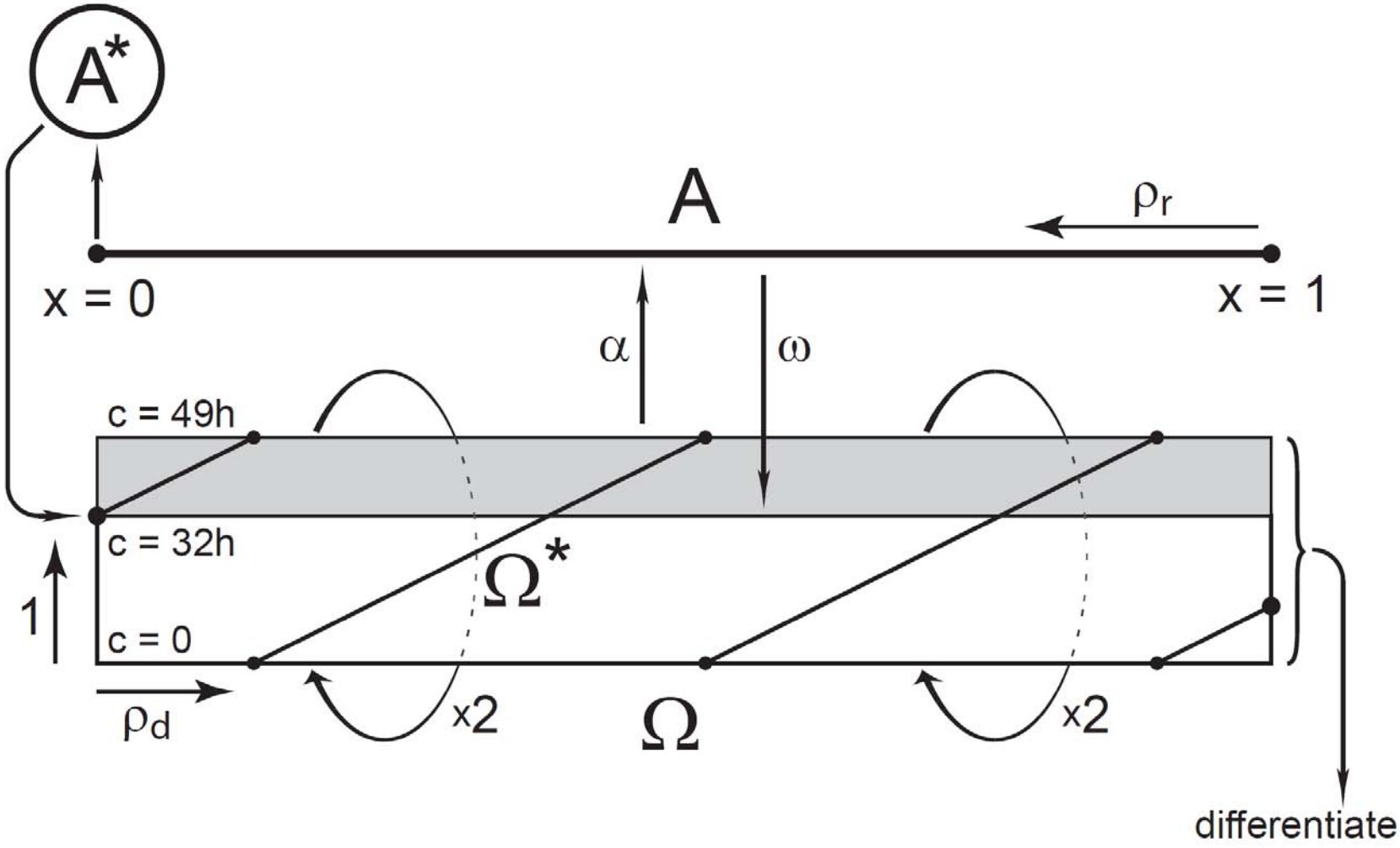
Simplify agent-based model



Agent-based model

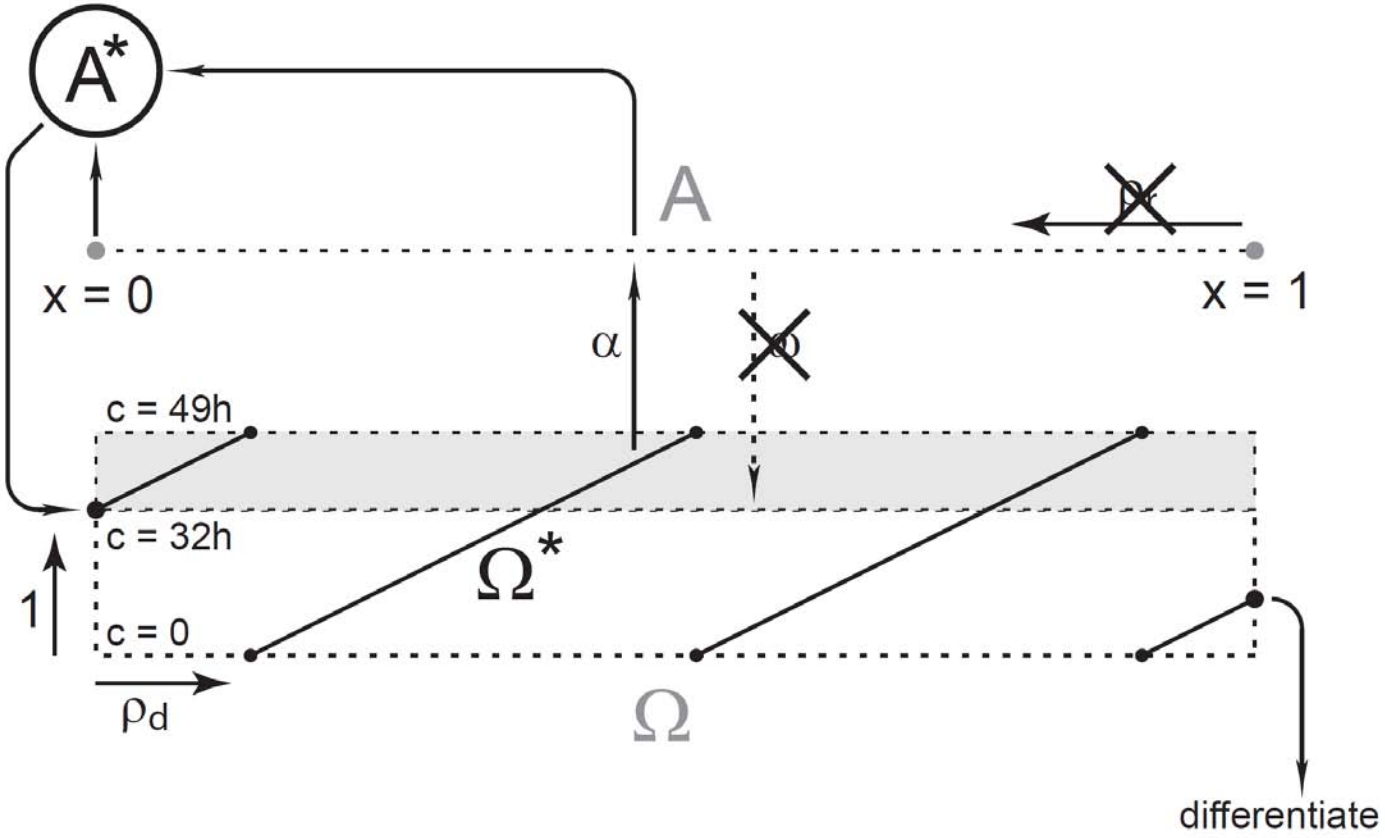
Partial differential equation model

Partial differential equation model



Approximation (Doumic et al. 2009)

Only keep $A^*(t)$ and $\Omega^*(t,x)$

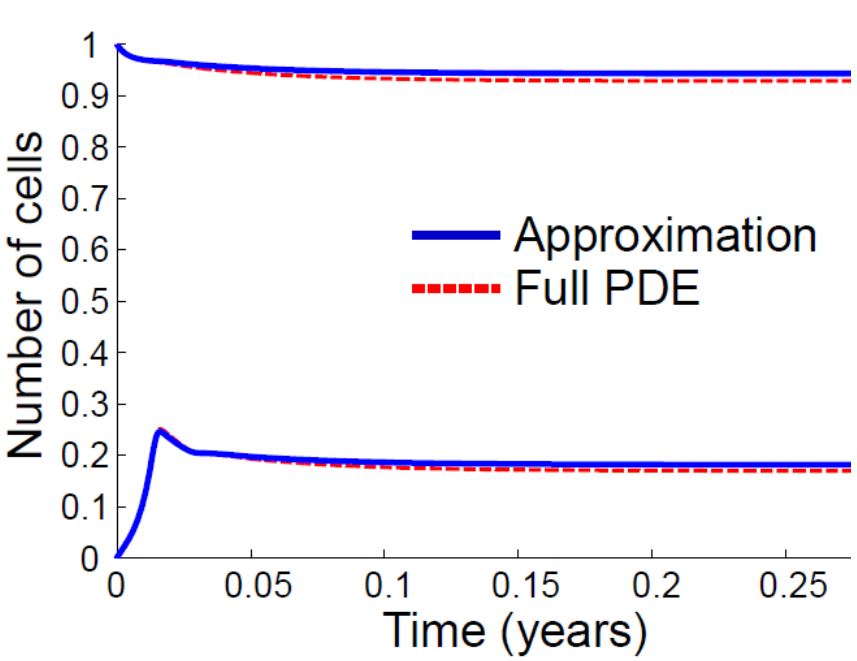


Full PDE vs Approximation

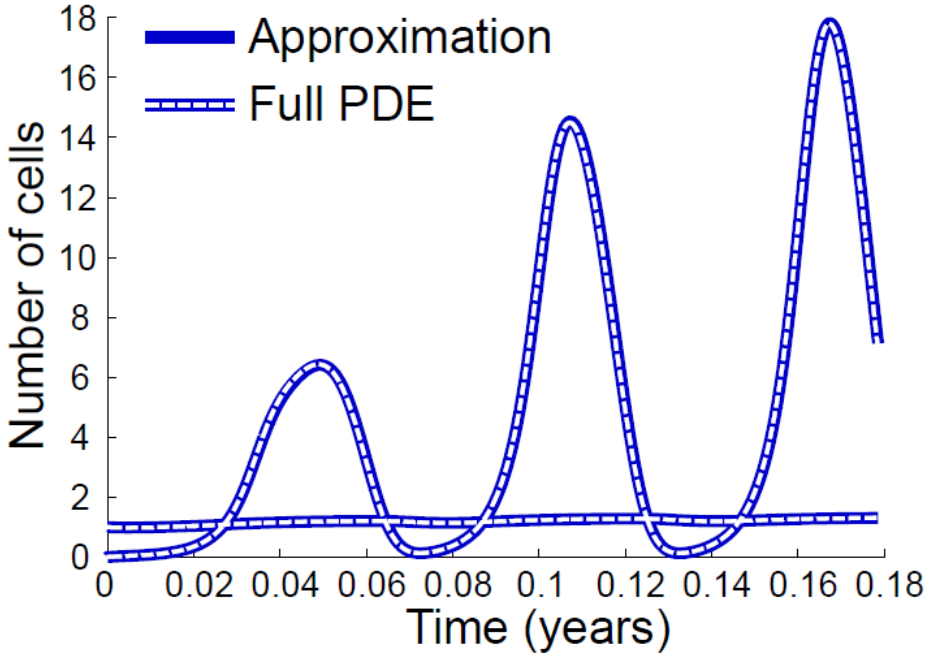
Comparing approach to steady states:

Solutions are nearly identical

Moderate rate of differentiation



Low rate of differentiation



Incorporate T cell response

- Account for T cell-induced death
  - Add $-q_c p(C,T)U$ to every equation for U_t or $U_t + \rho U_x$ for all variables U

- Anti-leukemia T cells

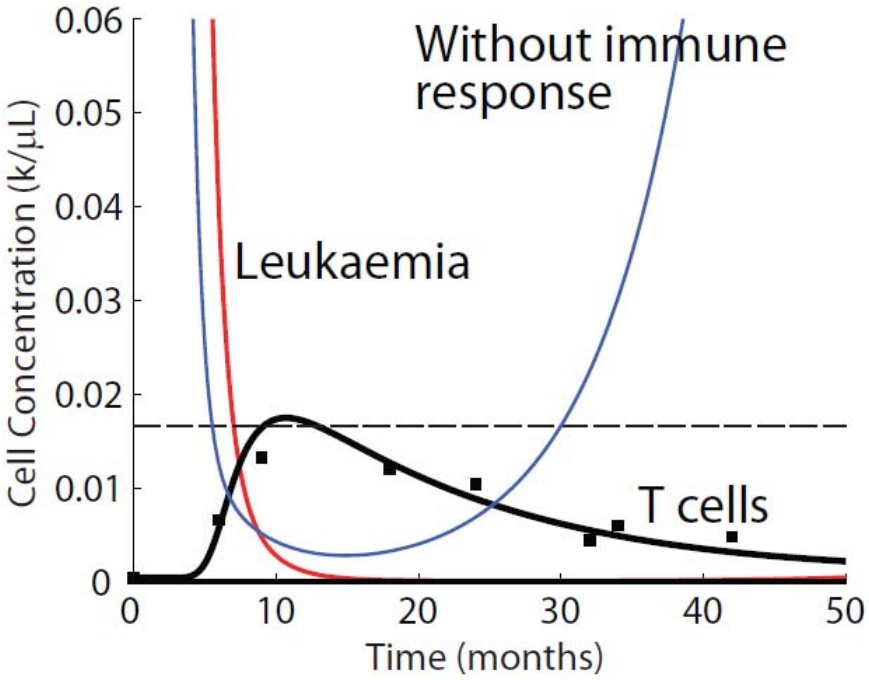
$$\dot{T} = s_t - d_t T - p(C,T)C + 2^n q_T p(C_{n\tau}, T_{n\tau}) C_{n\tau}$$

- Immune downregulation, total cancer population,

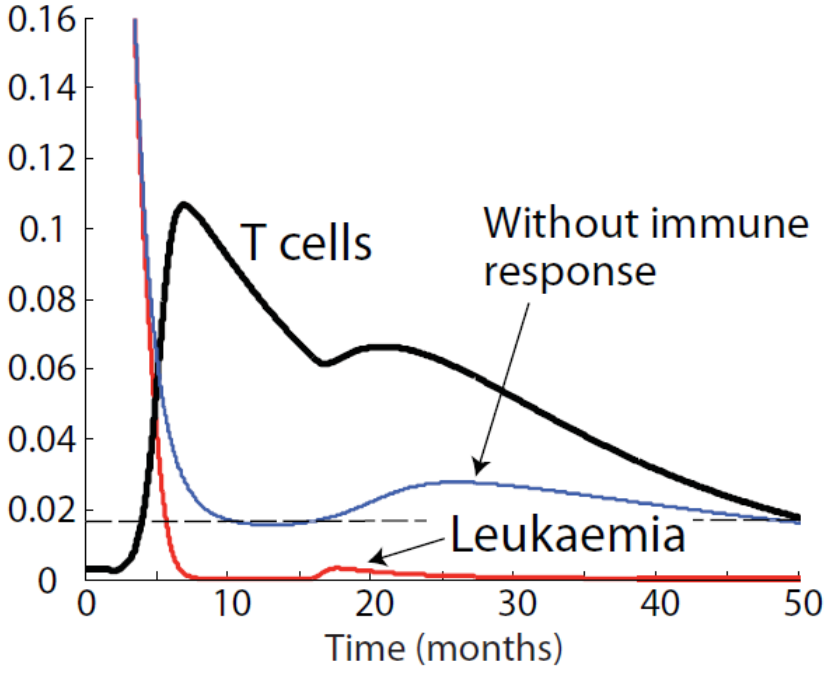
$$p(C,T) = p_0 e^{-c_n C} kT, \quad C = \sum (y_i + z_i), \quad C_{n\tau} = C(t - n\tau)$$

Examples with and without T cells

Michor model

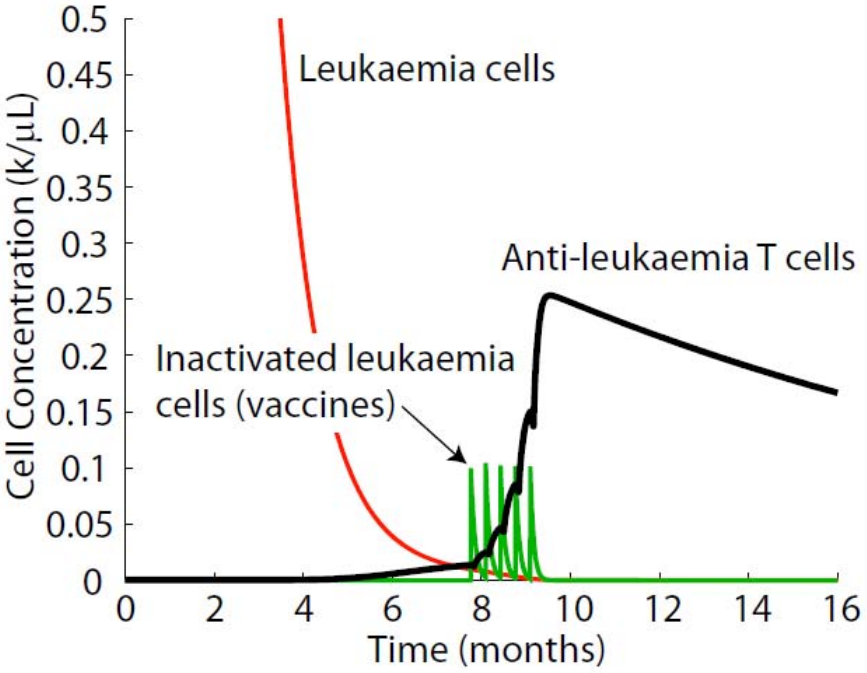


Roeder model

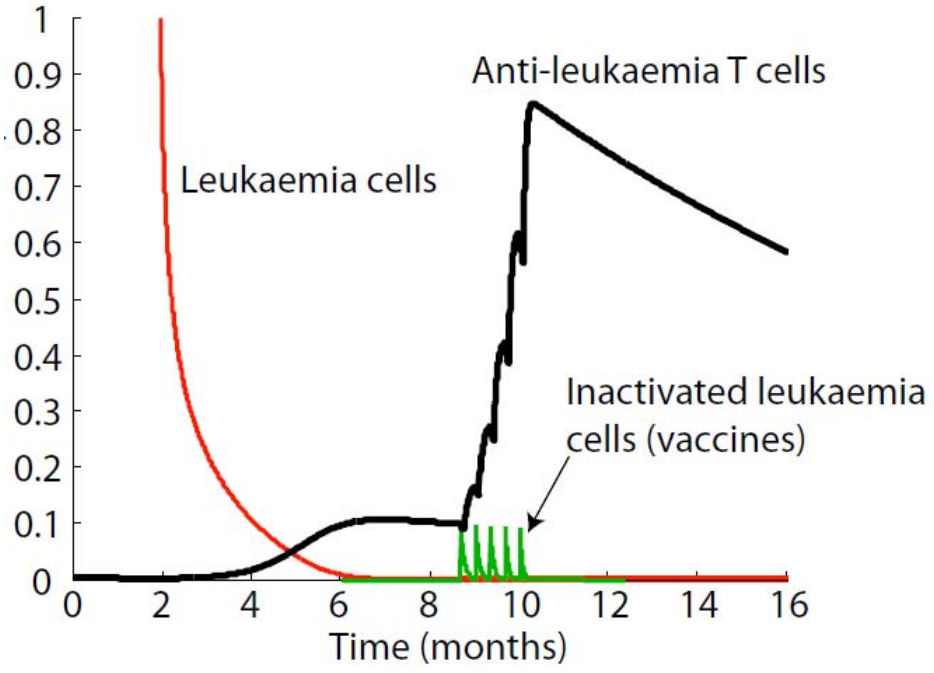


Example vaccination schedule

Michor model



Roeder model



5 doses of $6x10^8$ cells on days 233, 243, 253, 263, 273.

Log_{10} [Min cancer load] = -10.5 for **BOTH** models.

Compare two models

- Michor model (without immune response)
  - Fast remission, but early relapse
    - even without resistance mutations
- Roeder model (without immune response)
  - Slower remission, but sustained

- With immune response
  - Both models act more similarly

Open questions

- Does the immune response contribute to sustained remission?
- If so, can the anti-leukemia immune response be amplified? How effectively?

PDE model

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

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

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

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

PDE boundary conditions

$$A(x_{\max}, t) = 0.$$

$$\Omega(x, 0, t) = 2\Omega(x, 49, t).$$

$$\Omega\left(x, 32^{+}, t\right) = \Omega(x, 32^{-}, t) + \omega\left(\overline{\Omega}, e^{-x}\right) A,$$

$$\Omega^{*}(x_{\min}, t) = \frac{\omega(\overline{\Omega}, e^{-x_{\min}})}{\rho_d} A^{*}.$$

Approximation

$$\frac{dA^*}{dt} + \omega(x=0,\overline{\Omega})A^* = \int_0^1 \alpha(A^*,x)\Omega^*(t,x)\mathbf{1}_{x\in X_b}dx,$$

$$\frac{\partial\Omega^*}{\partial t} + \rho_d\frac{\partial\Omega^*}{\partial x} = -\alpha(x,A^*)\Omega^*\mathbf{1}_{x\in X_b}, \quad 0 \le x < 1,$$

$$\Omega^*(x=0,t) = \frac{\omega(x=0,\overline{\Omega})}{\rho_d}A^*,$$

$$\Omega^*(x=x_k^+,t) = 2\Omega^*(x=x_k^-,t), \qquad x_k < 1.$$