The Role of the Immune Response in CML

Doron Levy

Department of Mathematics
Center for Scientific Computation and Mathematical Modeling
University of Maryland, College Park

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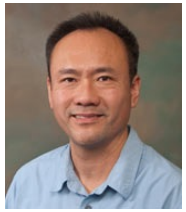
Joint work with

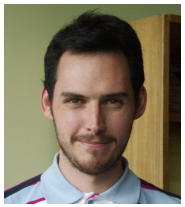
- Peter Lee, MD
  City of Hope



- Frank Nicolini, MD
  Lyon

- Peter Kim
  Sydney

- Thomas Lepoutre
  Lyon



- Cristian Tomasetti
  Johns Hopkins

- Geoff Clapp
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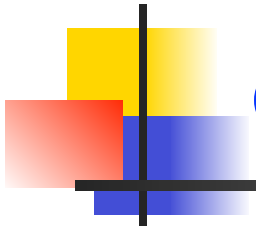


Outline

- Chronic Myelogenous Leukemia
- Modeling the role of the immune response
- Relapse: drug resistance and cancer stem cells
- Revisiting the role of the immune system

Leukemia

- **Normal state:**

  Stem cells turn into mature cells

- **Leukemia:**

  A malignant transformation of a stem cell or a progenitor cell
  - Myeloid or Lymphocytic
  - Acute or Chronic

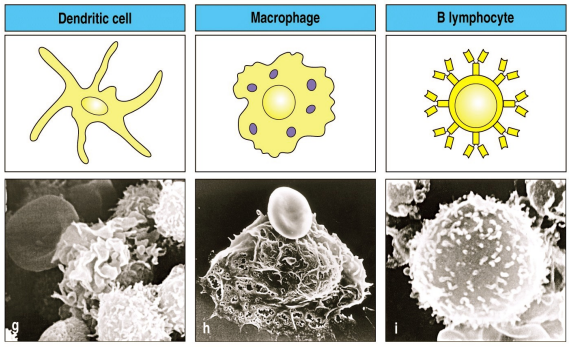


Figure 1-22 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

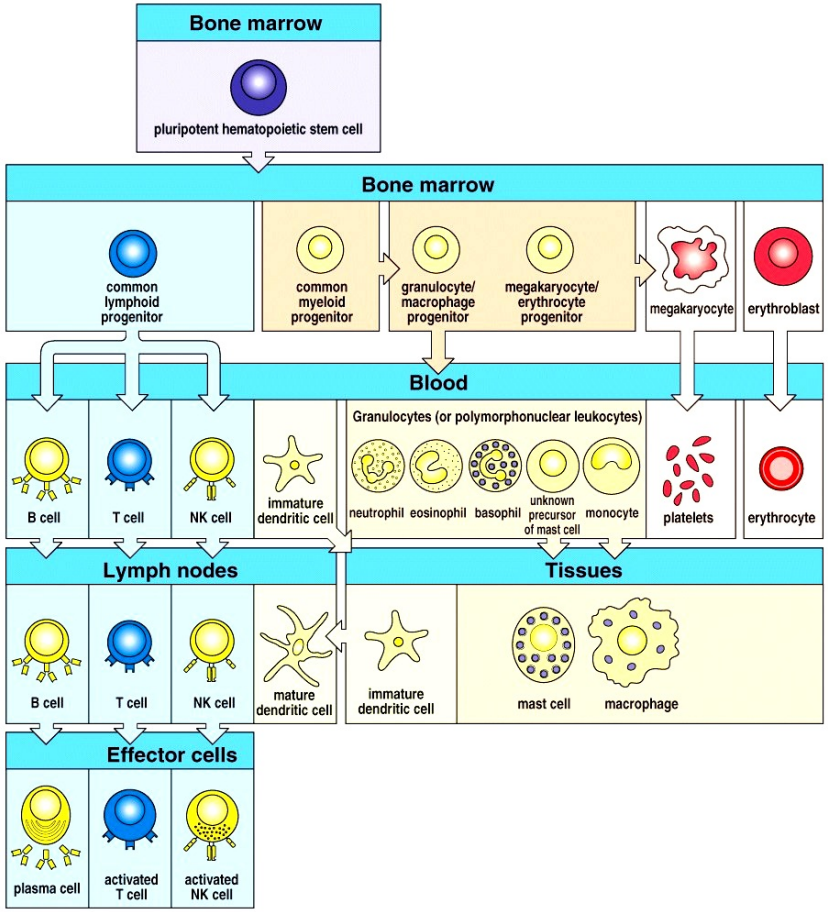
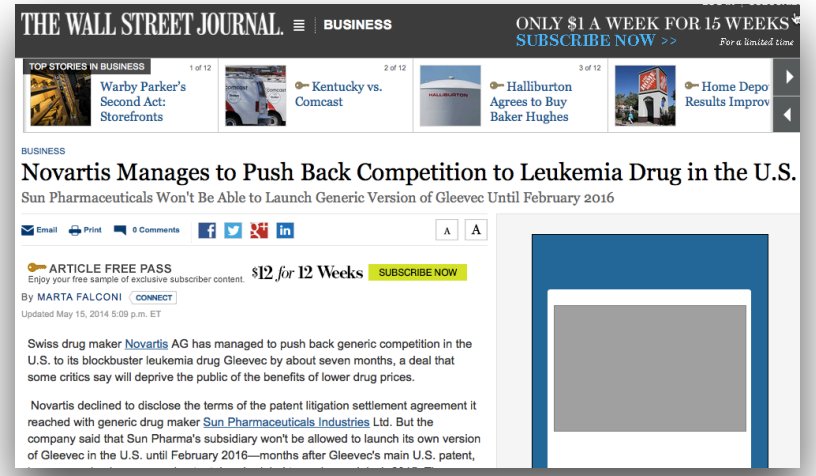


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

CML

- Philadelphia chromosome
  - Translocation (9;22)
  - Oncogenic BCR-ABL gene fusion
  - The ABL gene expresses a tyrosine kinase. Growth mechanisms
  - Easy to diagnose
  - Drug targeting this genetic defect (tyrosine kinase inhibitor)



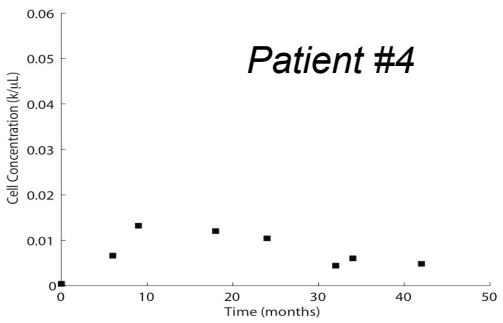
- Imatinib (Gleevec)
  - Molecular targeted therapy
  - $30K/yr ('01) – $98K/yr ('13)

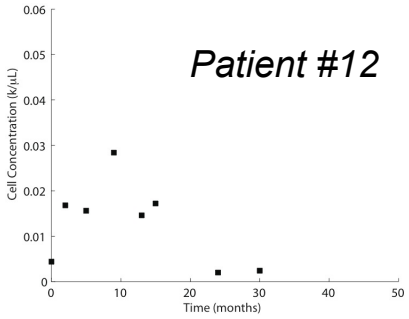
Motivation

1. Stop Imatinib

2. Combination immunotherapy + chemotherapy

Studying the immune response

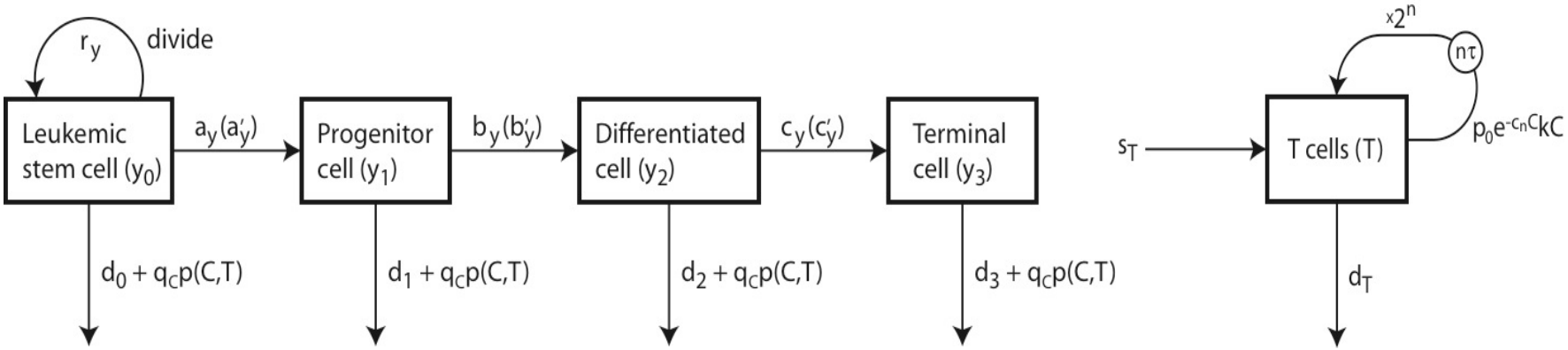




- Shown: the specific anti-leukemia immune response
  - Different patients, Imatinib, 50 months, each dot = one blood test
- A different immune response for each patient. However:
  - At the beginning of the treatment: no immune response
  - Peak: around 6-12 months (after starting the drug treatment)
  - Later: waning immune response

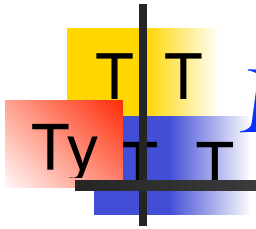
Question: What is the relation between the dynamics of the cancer, the drug, and the immune response?

A mathematical model (Kim, Lee, Levy 2008)



- Ingredients:
  - Leukemia cells: stem cells, …, fully functional cells
  - Mutations
  - Drug (Imatinib)
  - Anti leukemia immune response
- Michor *et al.* (Nature '05) + immune response

Cronkite and Vincent (69), Rubinow (69), Rubinow & Lebowitz (75), Fokas, Keller, and Clarkson (91), Mackey et al (99,...), Neiman (00), Moore & Li (04), Michor et al (05), Komarova & Woodarz (05).



Michor's model + immune response

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

- Cells without mutations

$$\dot{z}_0 = [r_z - d_0]z_0 - q_c p(C,T)z_0$$
$$\dot{z}_1 = a_z z_0 + d_1 z_1 - q_c p(C,T)z_1$$
$$\dot{z}_2 = b_z z_1 + d_2 z_2 - q_c p(C,T)z_2$$
$$\dot{z}_3 = c_z z_2 + d_3 z_3 - q_c p(C,T)z_3$$

- Cells with mutations

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

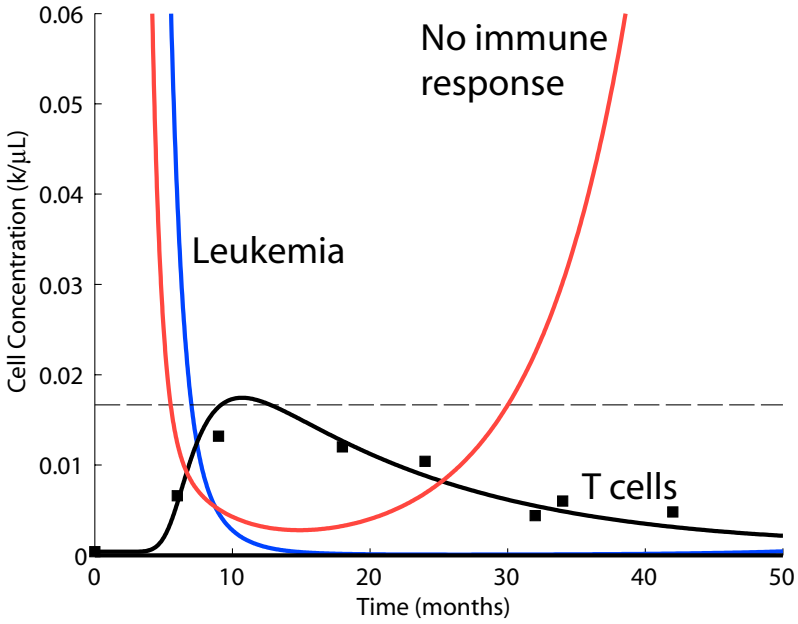
- Anti-Cancer T cells

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

Accounting for the immune response

- Dots: data from a patient
- Dashed line: remission

- Results of mathematical simulations
  - 50 months
  - Cancer load without an immune response
  - Cancer load with an immune response
  - The immune response



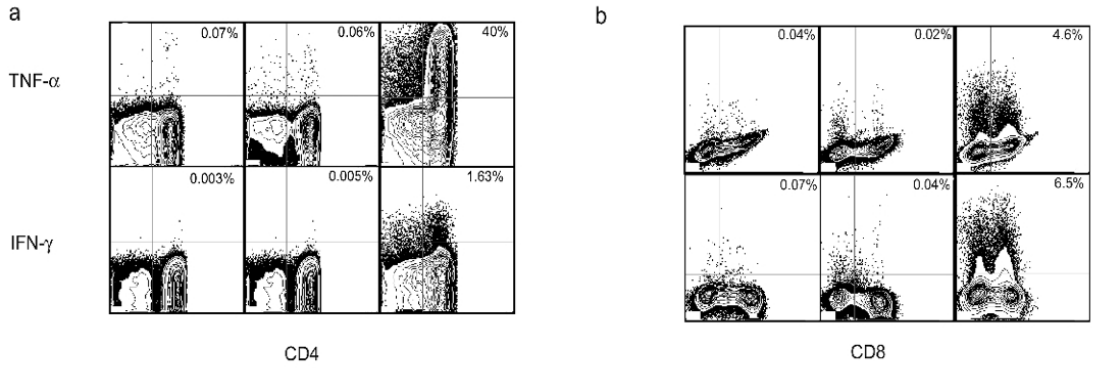
Biological conclusion from the math

Conclusion: remission is the result of a complex interaction between cancer, imatinib, and the immune response

Questions: Why does the immune response not cure the disease? Can we do something to cure it?

Idea: augment the immune response

Stimulating the immune response

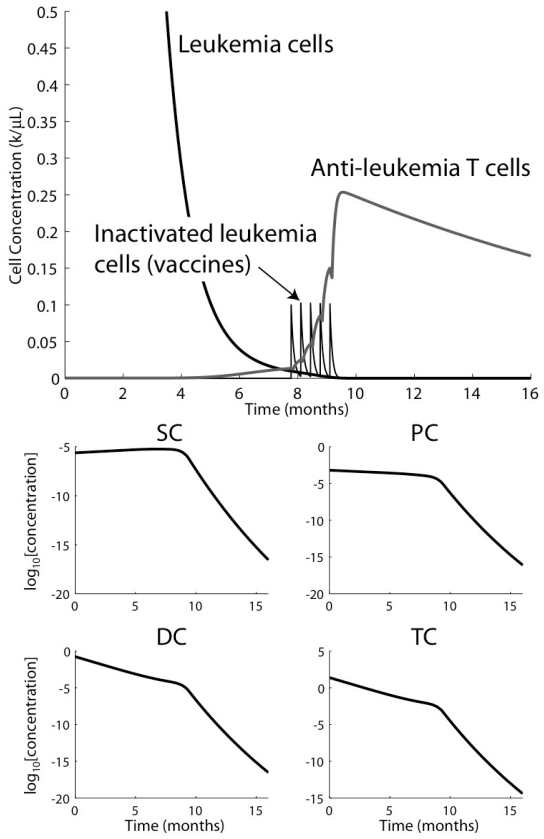


- Experimental design:
  - Irradiate the blood of the patient from when the disease was diagnosed
  - Mix it with blood taken from the patient at a later time point
  - Measure the anti-leukemia immune response

- Result:
  - Works *in vitro*. Leads to the notion of "Cancer vaccines"

Cancer Vaccines: a mathematical design

- ★ A vaccination plan
- ★ Solving an optimization problem:
  - Dosage
  - Timing
- ★ Individual planning: based on the immune response of each patient

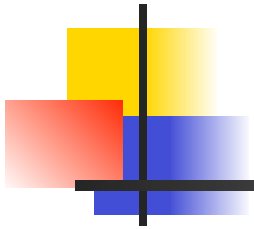


- Inactivated leukemia cells

$$\dot{V} = -d_V V - q_c p(C,T)V + s_V(t)$$

- Anti-Cancer T cells

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

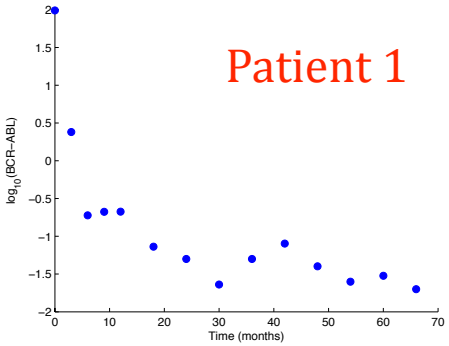


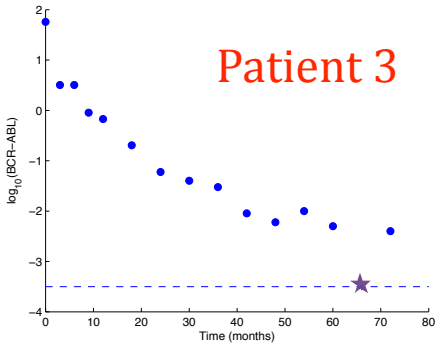
Interesting & Nice!

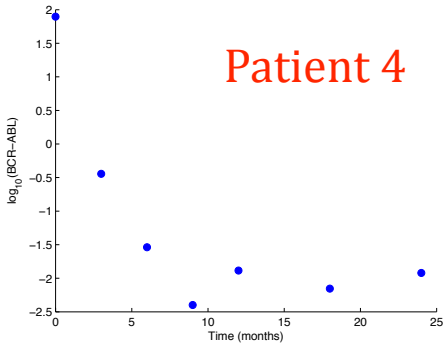
But –

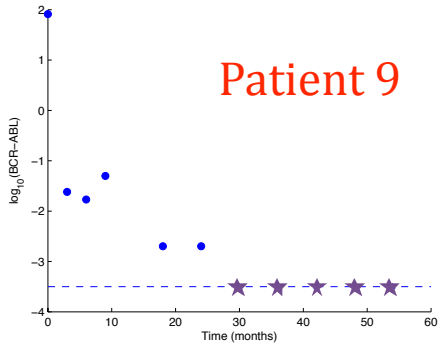
Is that what patients data really looks like?

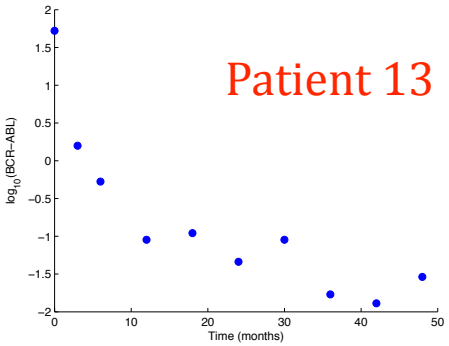
BCR-ABL Ratio (CML patients data from Lyon)

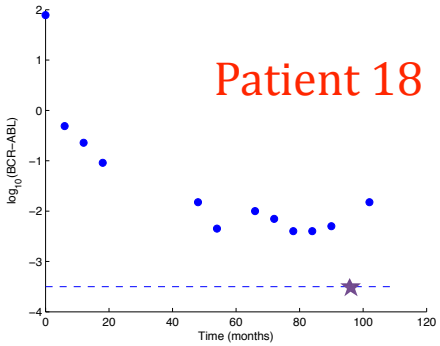












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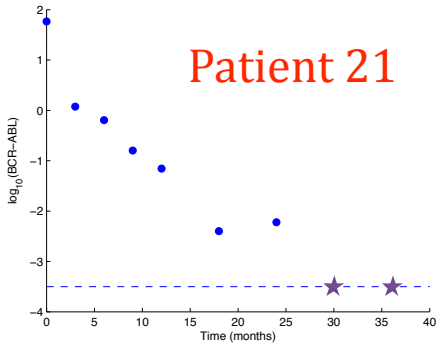
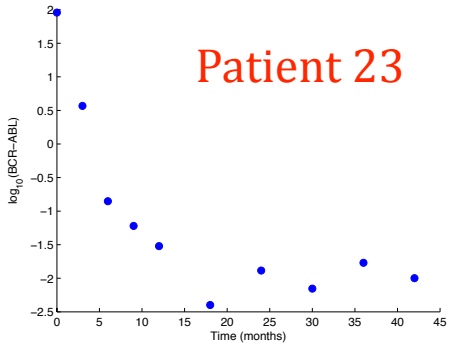
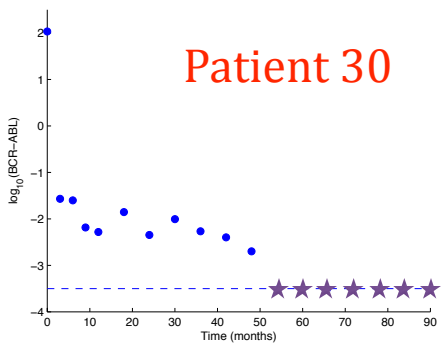
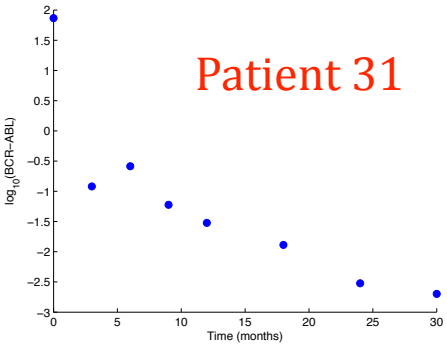
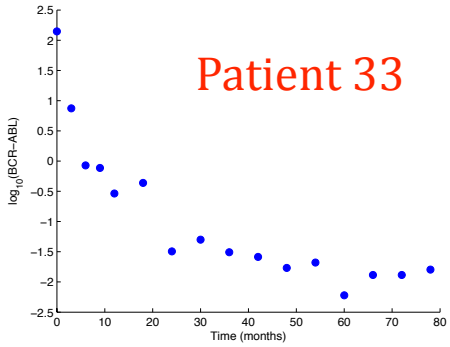
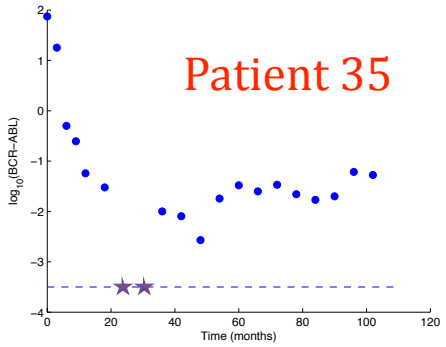


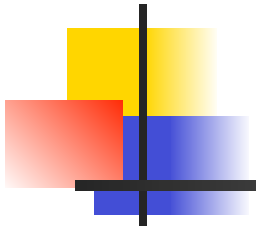












We see:

Relapse

Remission (cure??, oscillations)

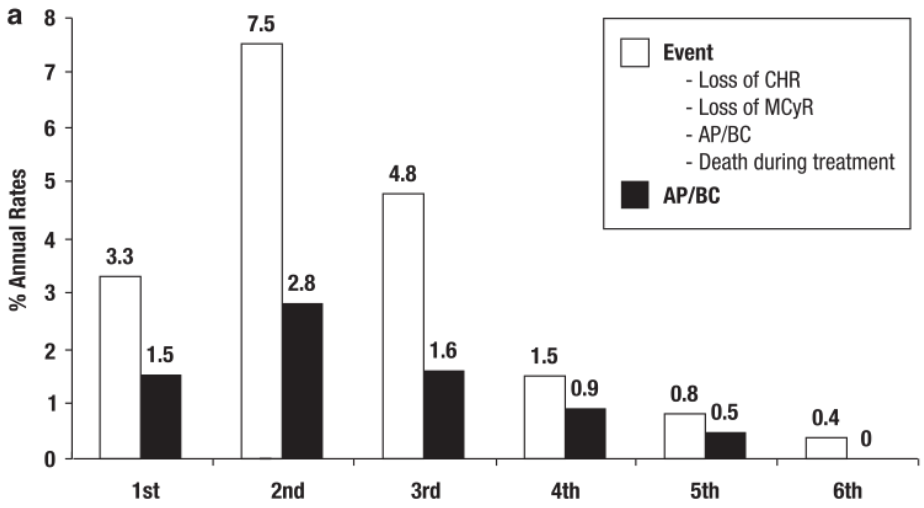
Mathematical models of drug resistance in cancer (Tomasetti + DL, PNAS 2010)

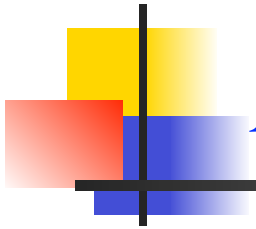
Studying the relapse:

A Tale in 3 Acts

CML: studying drug resistance

"Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia", *Hochhaus et al. (Leukemia 2009)*





Act I

On the probability of developing drug resistance by the time a tumor is diagnosed

Mathematical models of drug resistance in cancer

- Goldie & Coleman; Iwasa, Nowak, & Michor; Komarova; Roeder; ...
- **Iwasa, Novak, & Michor (Genetics, 2006):**
  - The probability of developing resistance by the time a tumor is diagnosed:

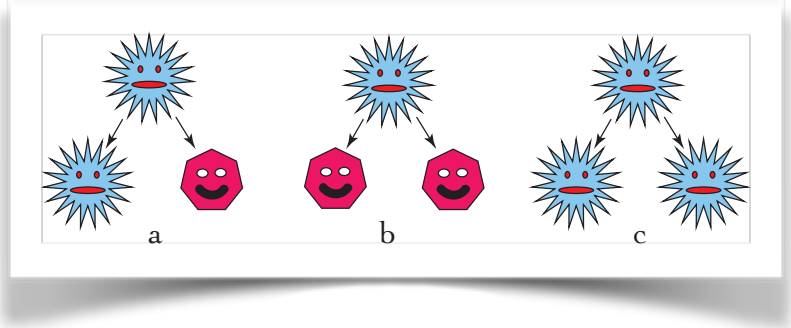
$$P = 1 - \exp\left(-\frac{MuL}{D} \ln \frac{L}{L-D}\right)$$

    - L & D = birth & death rates; u = mutation rate
    - M = total number of cancer cells (!)

- **Actual values:** $M = 10^9, \quad u \geq 10^{-8}$
  - The probability of developing resistance by the time a tumor is diagnosed is greater than 0.9999
  - Resistance must always be present in large numbers

Cancer Stem Cells

- **Leads to the Stem-Cell Hypothesis**
  - Cancer cells (just like healthy cells) are not all alike
  - The tumor population is heterogeneous
  - Stem cells have the ability of self-renewal. They are very long lived.
  - **From the point of view of drug resistance – it is the long lived cells we should care about**

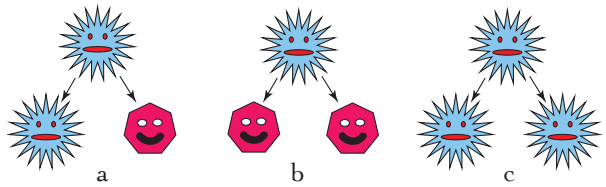


- **Division of stem cells:**
  - Asymmetric division prob = a
  - Symmetric differentiation prob = b
  - Symmetric renewal prob = $c = 1-a-b$

Drug resistance & cancer stem cells

- **Modified Question**: What is the probability that at the time of detection there are cancer stem cells that developed resistance to the drug?
- **Answer (Tomasetti+DL):** Extension of the Iwasa *et al.* result

$$P_R = 1 - \exp\left(-uM\left(\frac{1-\frac{a}{2}-b}{1-a-b}\right)\right)$$

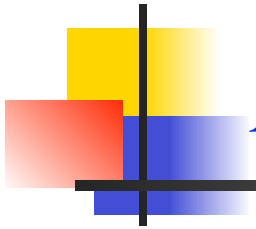


or (for nonzero D):

$$P_R = 1 - \exp\left(-uM\left(\frac{1-\frac{a}{2}-b}{1-a-b}\right)\frac{1}{C}\ln\left(\frac{1}{1-C}\right)\right)$$

$$C = \frac{D+Lb}{L(1-a-b)}$$

M=CSCs, u=mutation rate, $De^{3}L$=birth&death rates

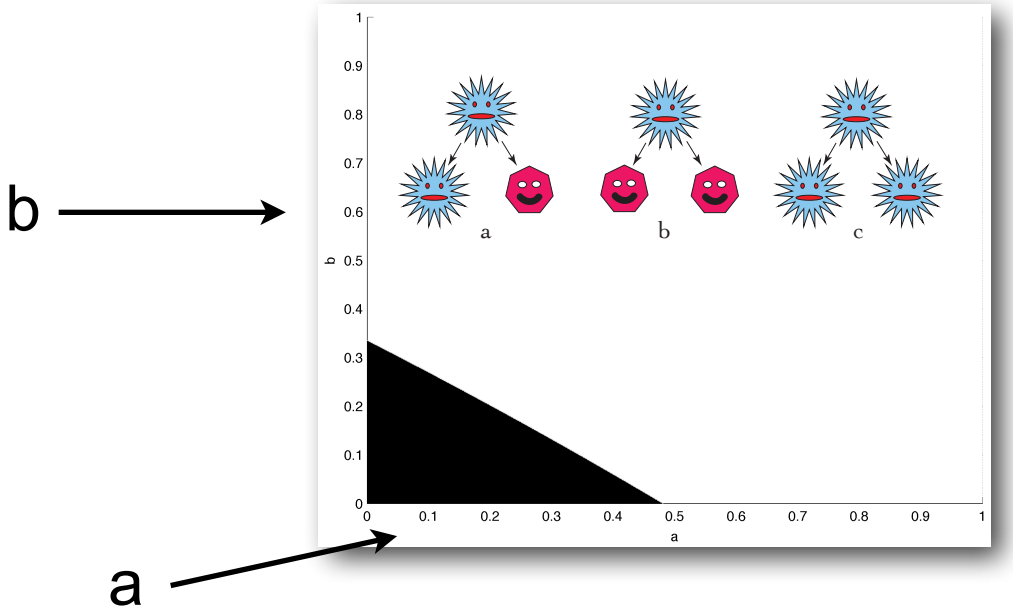


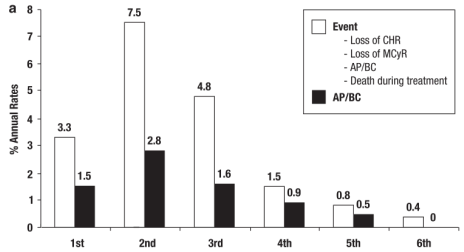
Act II

On symmetric vs. asymmetric differentiation

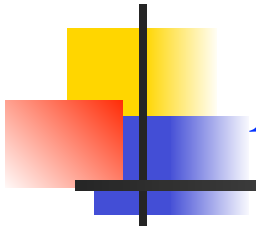
Question: What is the probability of developing resistance by the time of detection?

- The range of *a* and *b* for which $P_R < 0.15$.





Cancer Stem Cells must shift towards an increased symmetric renewal



Act III

What does it mean?

Why do relapses stop?

Hypothesis: relapses are related to the drug response

- Two points of view in the literature:
  - Cancer Stem Cells are the only sub-population that is resistant to the drug (Michor & Novak)
  - Cancer Stem Cells are sensitive to the drug but shift rapidly between active and dormant states (Roeder)

Our hypothesis: Cancer Stem Cells must be affected by the drug. The drug keeps the CSCs in a dormant state

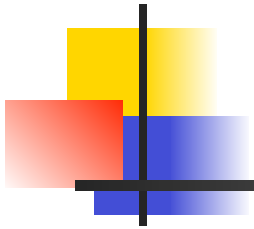
- Explains:
  - Why there is an immediate relapse when stopping Imatinib
  - Eventual relapse when there are pre-treatment drug-resistant CSCs
  - No further relapses after 5-6 years

When did the resistance develop?

- If resistance developed, it must have happened by the time of detection
- **The results of the the mathematical calculation:**
  - On average, resistance must have developed in the 3-4 months prior to detection

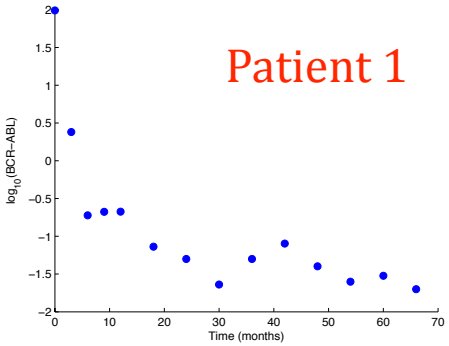
Finalé – Clinical consequences:

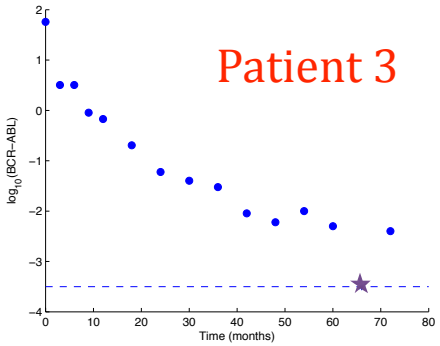
- **Early detection of CML will increase the chances of survival.**
- **Patients should be treated immediately.**

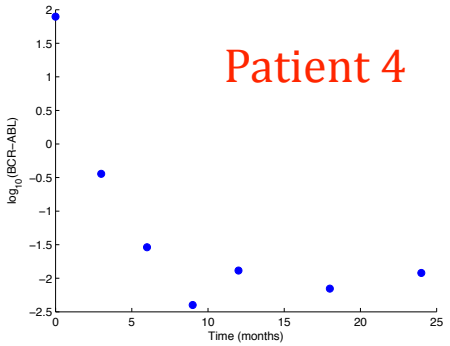


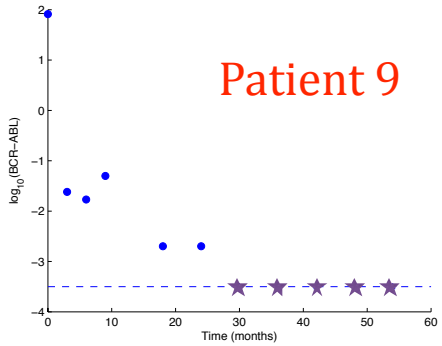
Revisiting the role of the immune response

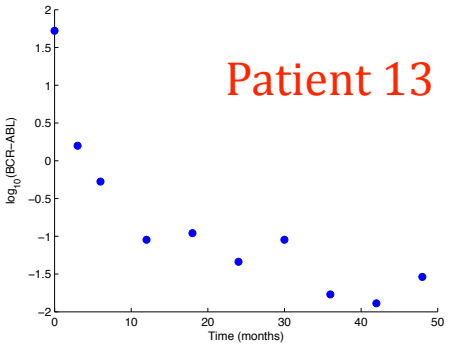
BCR-ABL Ratio (Patients data from Lyon)

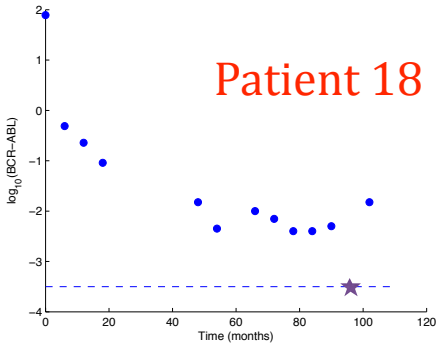




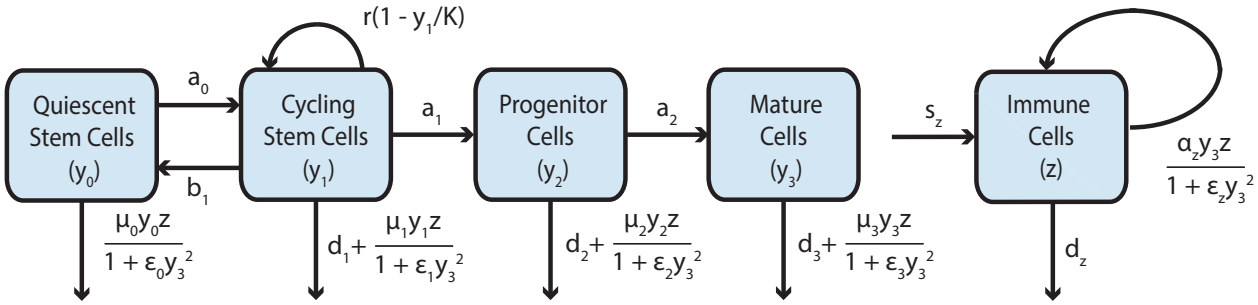








Modeling CML + immune system



$$\dot{y}_0 = b_1 y_1 - a_0 y_0 - \frac{\mu_0 y_0 z}{1 + \epsilon_0 y_3^2}$$

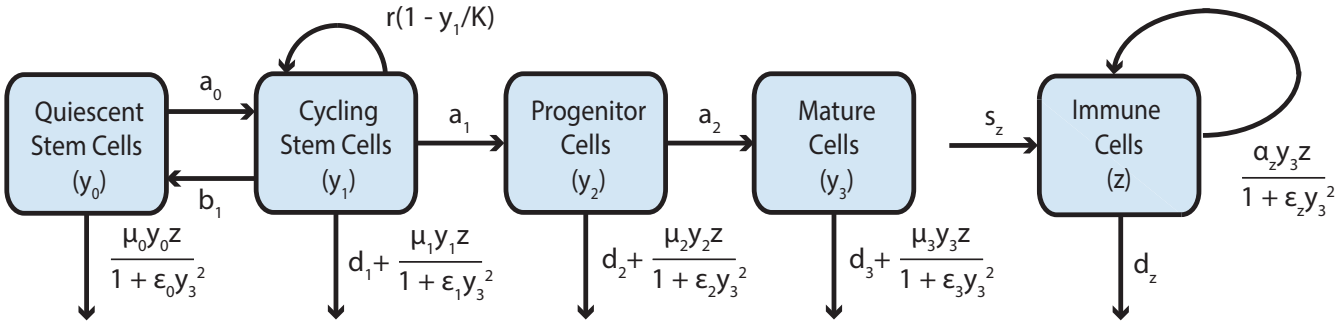
$$\dot{y}_1 = a_0 y_0 - b_1 y_1 + r y_1 (1 - \frac{y_1}{K}) - d_1 y_1 - \frac{\mu_1 y_1 z}{1 + \epsilon_1 y_3^2}$$

$$\dot{y}_2 = a_1 y_1 - d_2 y_2 - \frac{\mu_2 y_2 z}{1 + \epsilon_2 y_3^2}$$

$$\dot{y}_3 = a_2 y_2 - d_3 y_3 - \frac{\mu_3 y_3 z}{1 + \epsilon_3 y_3^2}$$

$$\dot{z} = s_z - d_z z + \alpha_z \frac{y_3 z}{1 + \epsilon_z y_3^2}$$

Modeling CML + immune system

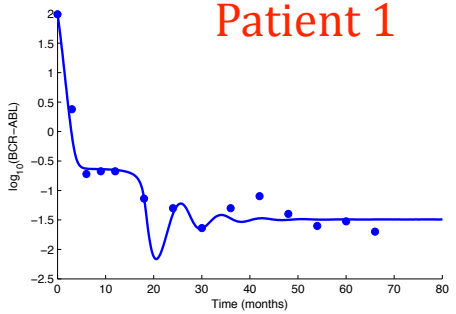


- IM affects a_1 and a_2
- Patient specific parameters: immune parameters, a_1, a_2
- Latin hypercube sampling is applied with cost function

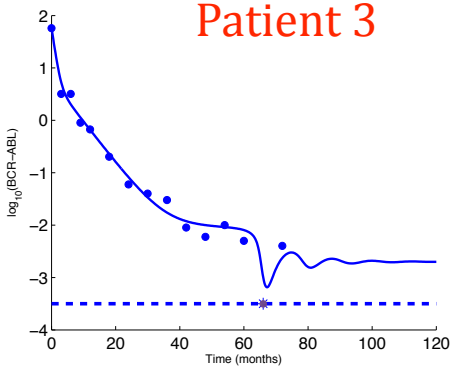
$$\sum_{i=0}^{k} (\log(r_e(t(i))) - \log(r_0(t(i))))^2$$

Fitting patients data

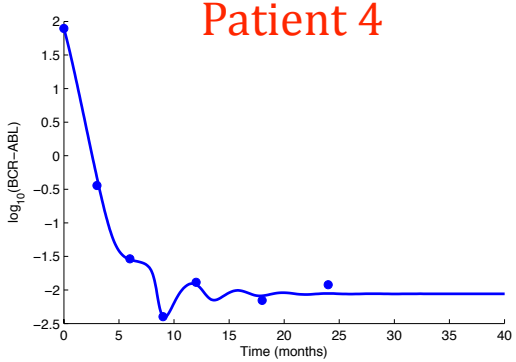
Patient 1



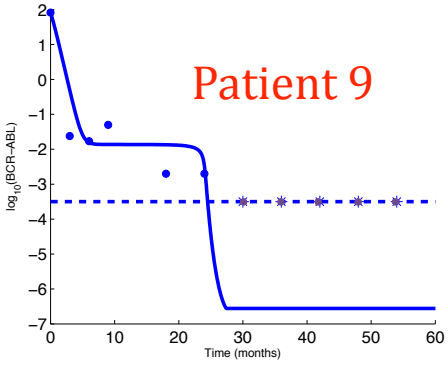
Patient 3



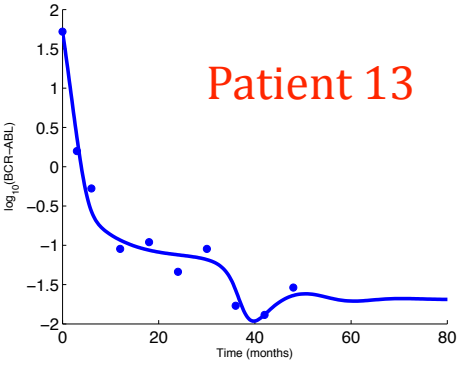
Patient 4



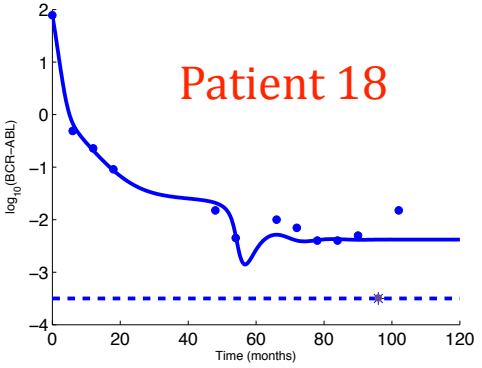
Patient 9



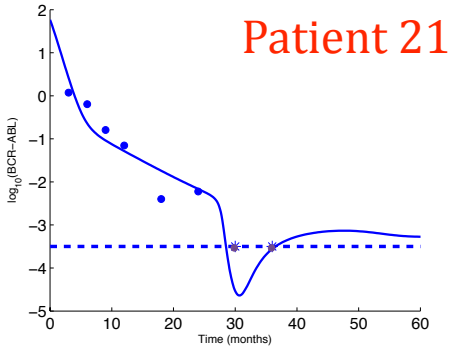
Patient 13

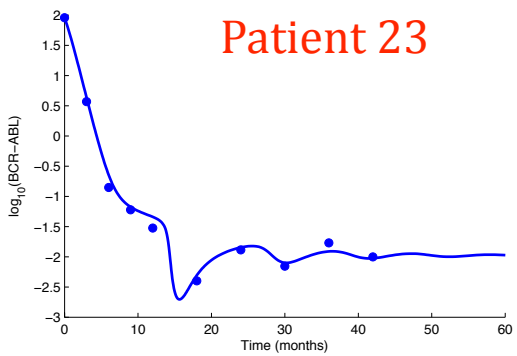


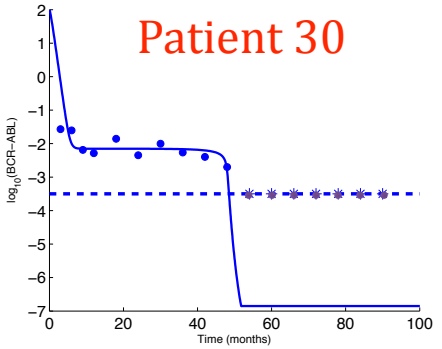
Patient 18

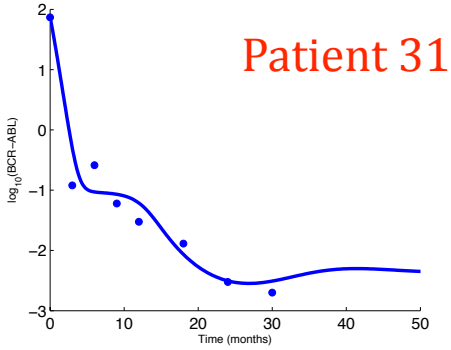


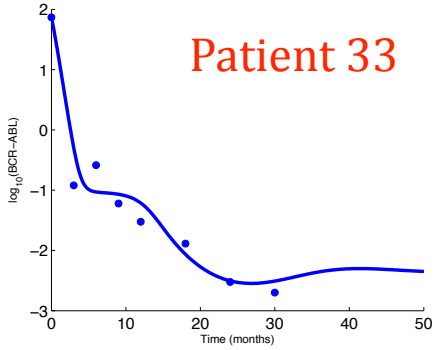
Fitting patients data

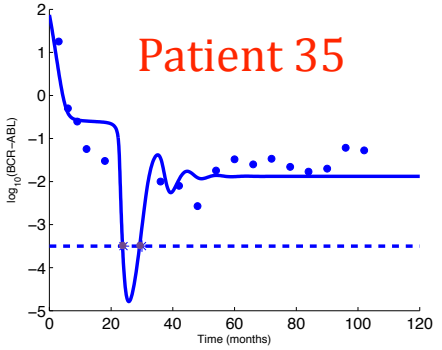












Resistance and drug delivery (w. Clap & Sontag)

- Assuming: a small resistance clone at diagnosis
- Resistance cancer population differs from the sensitive one by its growth rate and carrying capacity
- Sensitive and resistant cells compete
- Treatment has a stronger effect on the sensitive population: smaller growth rate and carrying capacity
- Interactions between the immune system and cancer is independent of the cancer's sensitivity to the drug

Resistant clone

$$\dot{y}_0 = b_1 y_1 - a_0 y_0 - \frac{\mu_0 y_0 z}{1 + \epsilon_0 (y_2 + x_2)^2}$$

$$\dot{y}_1 = a_0 y_0 - b_1 y_1 + r y_1 (1 - \frac{y_1 + x_1}{K_x}) - d_1 y_1 - \frac{\mu_1 y_1 z}{1 + \epsilon_1 (y_2 + x_2)^2}$$

$$\dot{y}_2 = a_{1y} y_1 - d_2 y_2 - \frac{\mu_2 y_2 z}{1 + \epsilon_2 (y_2 + x_2)^2}$$

$$\dot{x}_0 = b_1 x_1 - a_0 x_0 - \frac{\mu_0 x_0 z}{1 + \epsilon_0 (y_2 + x_2)^2}$$

$$\dot{x}_1 = a_0 x_0 - b_1 x_1 + r x_1 (1 - \frac{y_1 + x_1}{K_y}) - d_1 x_1 - \frac{\mu_1 x_1 z}{1 + \epsilon_1 (y_2 + x_2)^2}$$

$$\dot{x}_2 = a_{1x} x_1 - d_2 x_2 - \frac{\mu_2 x_2 z}{1 + \epsilon_2 (y_2 + x_2)^2}$$

$$\dot{z} = s_z - d_z z + \alpha_z \frac{(y_2 + x_2) z}{1 + \epsilon_z (y_2 + x_2)^2}$$

Effect of TKI on resistant & sensitive clones

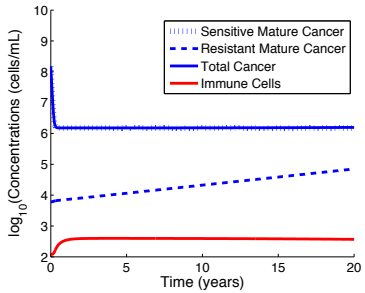
- Before, therapy:

$$K_y = K_x = K$$
$$a_{1y} = a_{1x} = A$$

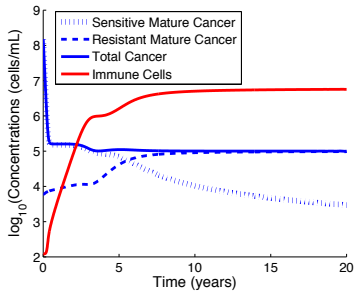
- During therapy:

$$K_y = K/inh_0$$
$$K_x = K$$
$$a_{1y} = A/inh_1$$
$$a_{1x} = A$$

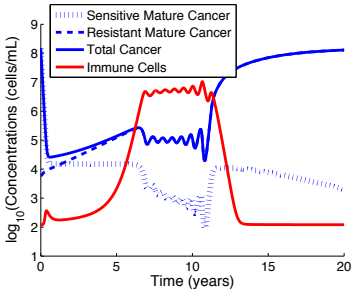
Low Dose: $inh_0 = 1.04$, $inh_1 = 100/1.04$



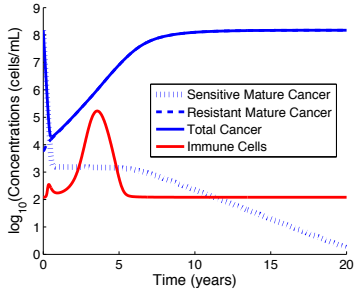
Moderate Dose: $inh_0 = 1.08$, $inh_1 = 1000/1.08$



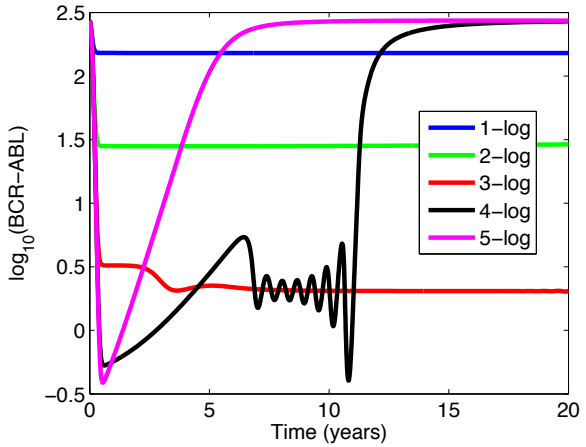
Higher Dose: $inh_0 = 1.16$, $inh_1 = 10000/1.16$



Highest Dose: $inh_0 = 1.32$, $inh_1 = 100000/1.32$



Varying dose in response to drug resistance



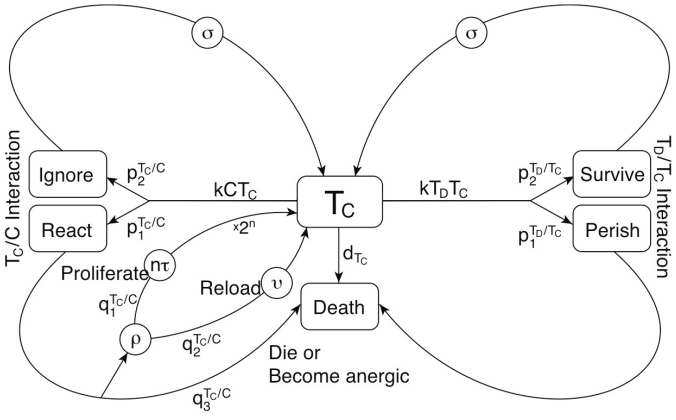
- Low doses only eliminate a small portion of the sensitive cancer load
- High doses eliminate the sensitive cells rapidly, making room for the resistant clone to expand
- At 3-log and 4-log doses, relapse is delayed significantly

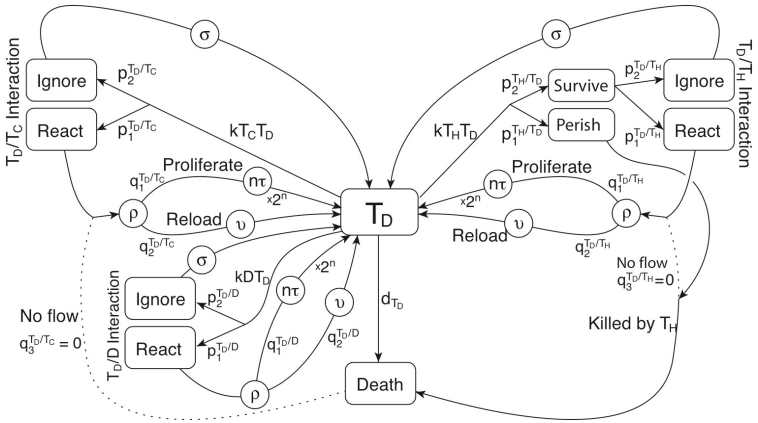
Conclusion

- **Medical Applications:**
  - Quantitative approach
  - A complex biological setup – the tip of the iceberg
  - Future directions: (i) stop imatinib; (ii) immunotherapy + drug therapy combination

- **Math:**
  - New challenges
  - New math
  - Can potentially be useful

Modeling a transplant (DeConde, Kim, Lee, DL - JTB)





- Mini-transplants
- Clinically used but only for tough patients
- Conclusion of mathematical/medical study: use for all patients
- Adjust the amount of chemo to the individual patient - quantitatively!

Stopping imatinib (simulation)

- Stopping Imatinib treatment after one year
- The disease relapses within months
- The mathematical simulation agrees with the medical experiments