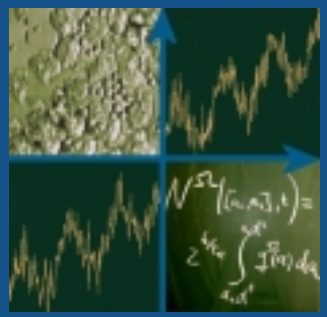

imise.

UNIVERSITÄT LEIPZIG

Project group:

DYNAmical MOdeling of tissue stem cell organization

Mathematical modeling of *imatinib* treatment in patients suffering from chronic myeloid leukemia

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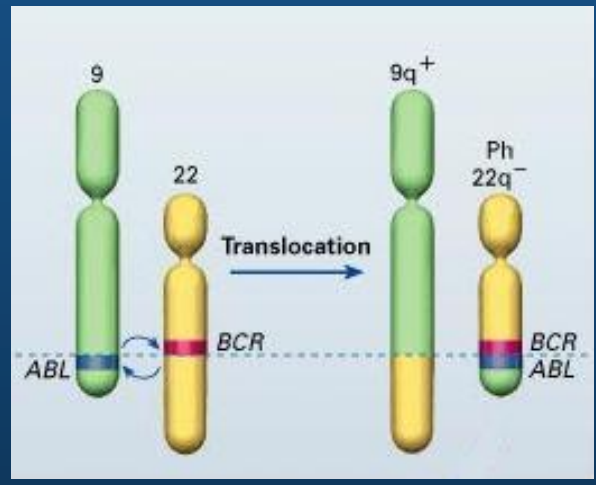
GMDS 2006, Leipzig, Germany

Chronic myeloid leukemia (CML)

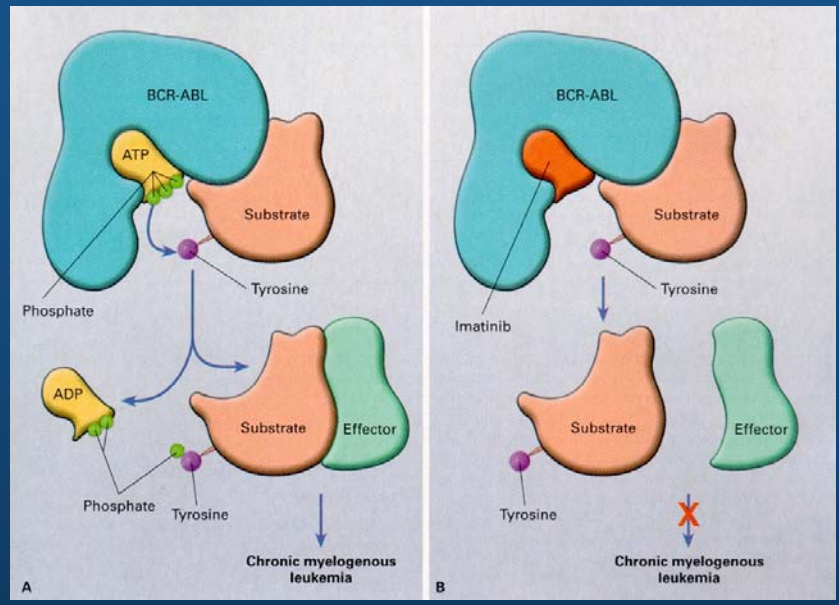
- **genetic aberration** in a hematopoietic stem cell (single mutation event)
- reciprocal **translocation** of chromosomes 9 and 22 ("**Philadelphia chromosome** [Ph]")
- fusion gene: **BCR-ABL**
- resulting oncoprotein: **p210$^{BCR-ABL}$**
- **constitutively activated tyrosine kinase** (leads to excessive expansion of malignant clone)



(Savage and Antman, NEJM, 2002)

Imatinib treatment

- molecularly targeted therapeutic approach
- *imatinib* **occupies kinase pocket** of BCR-ABL oncoprotein
- **blocking** of oncogenic **signaling pathways**



(Savage and Antman, NEJM, 2002)

Two main mechanisms of action:

- **inhibition of** excessive **proliferation** of leukemia cells
- **induction of apoptosis** selectively for malignant cells

Objective

Contribute to

- a **deeper understanding** of **functional mechanisms**

By means of

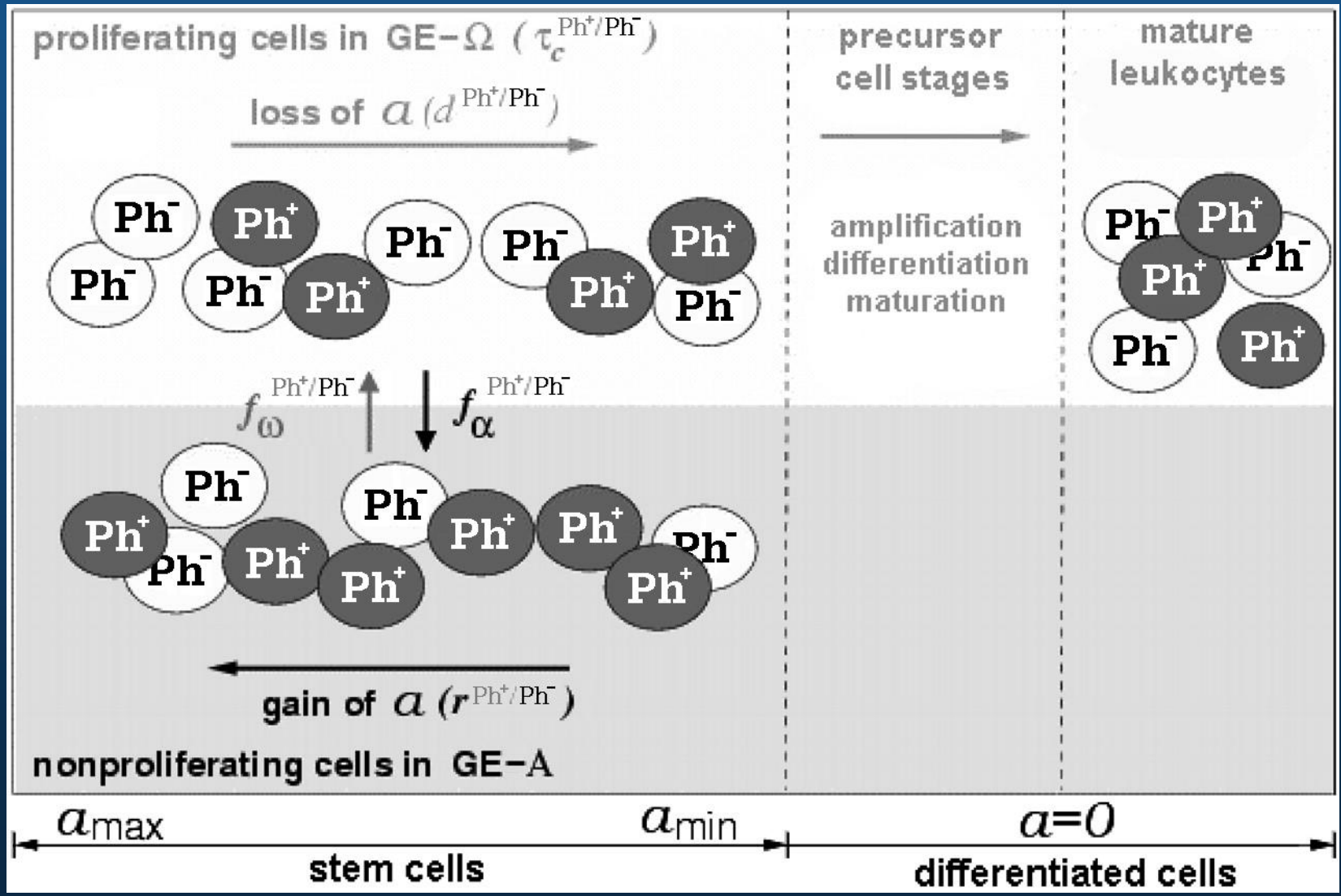
- **model analysis** of clonal competition between Ph^+ and Ph^- cells on the hematopoietic **stem cell level**

Utilizing a

- **mathematical stem cell model** (validated for animal data) (Roeder and Loeffler, Exp. Hematol., 2002)

➢ apply and adapt this model to the human situation

Model scheme



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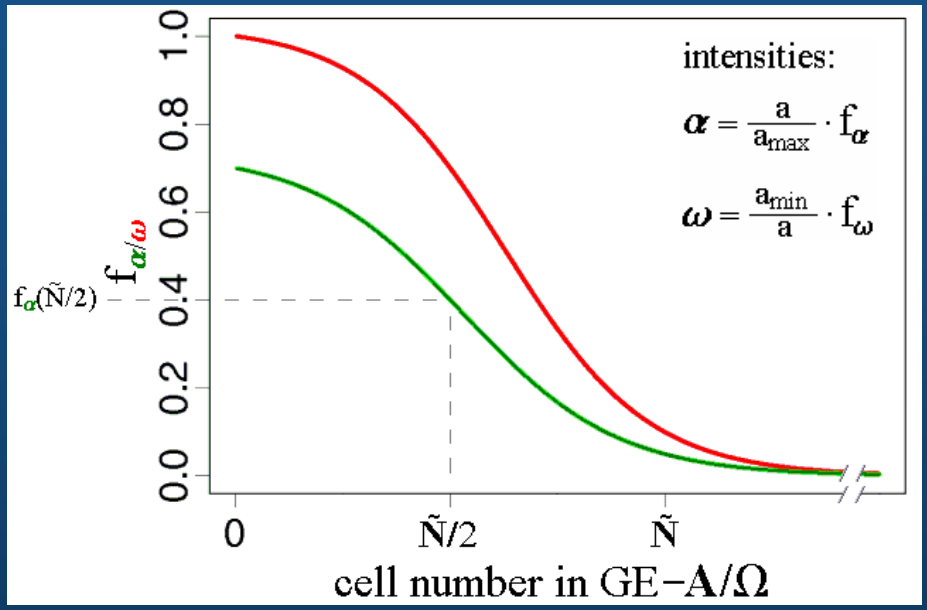
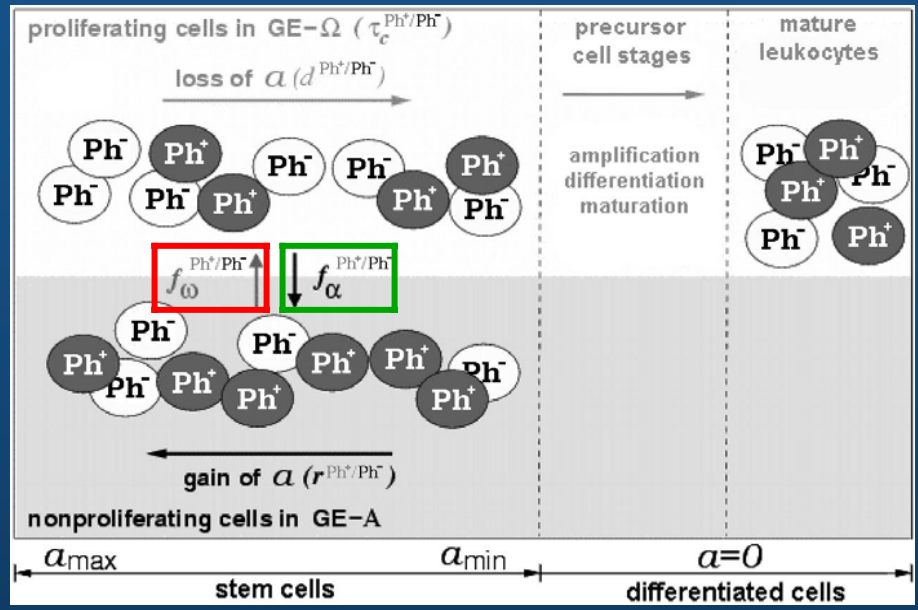
Transition functions





- each cell is described by $z(t) = (a(t), c(t), m(t))^T$
  $a \in [a_{min}, a_{max}]$, $0 \le c < \tau_c$, $m \in \{A,\Omega\}$
- **computer simulation** (synchronous update of all cells within each discrete time step)

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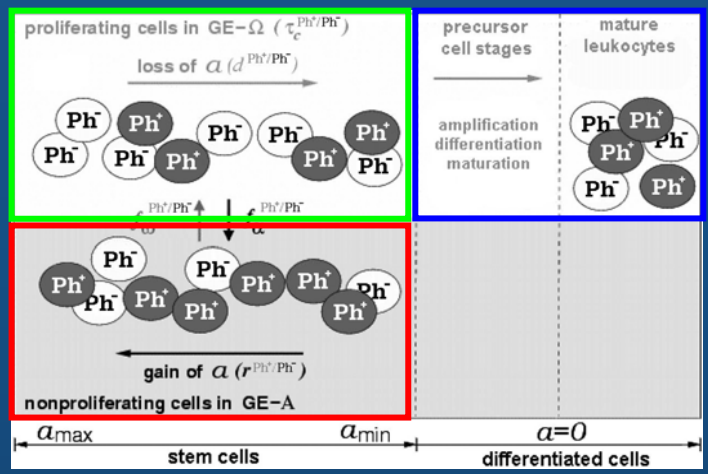
CML genesis: Qualitative criteria

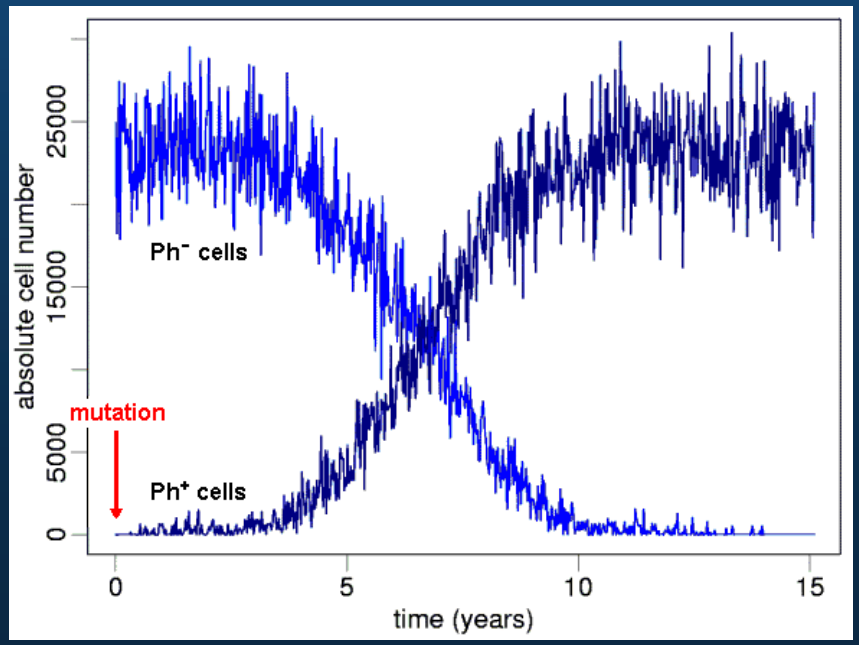
- **long latency time** (median 4-6 years) and **coexistence** of normal and malignant cells, starting from **a single cell mutation**
- eventual **overgrowth** of the system by the malignant clone (**suppression** of normal cells)
- highly **increased production of** Ph^+ leukocyte **progenitors** compared to normal progenitor cells
- **delayed Ph positivity** of quiescent stem cells

CML genesis: Scenario I

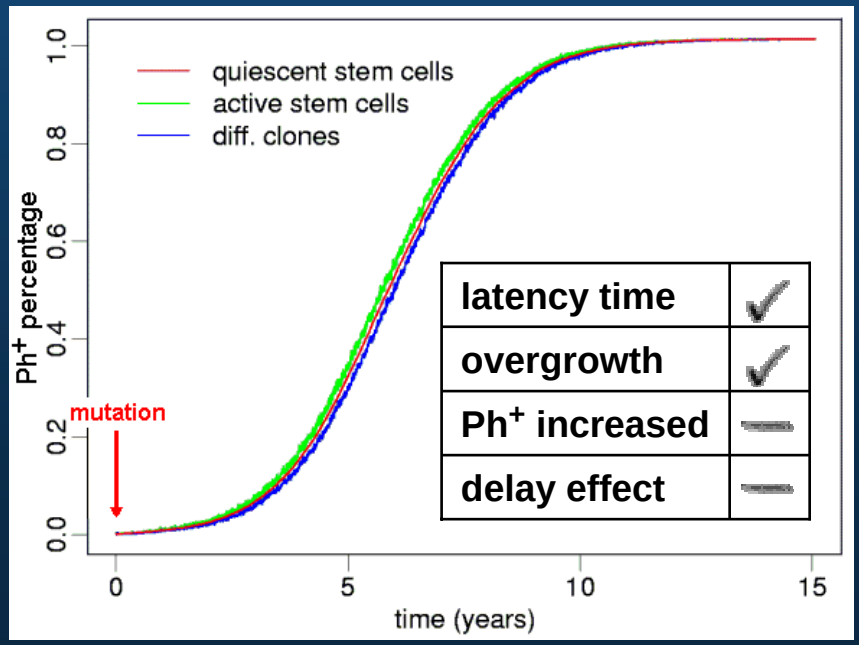
- small difference in parameter ***d***
  $d_{Ph^+} = 1.045 < d_{Ph^-} = 1.050$
- no differences in all other parameters
  $r = 1.1$, $\tau_c = 48h$, f_α, and f_ω



single simulation run



population statistic (n=100)



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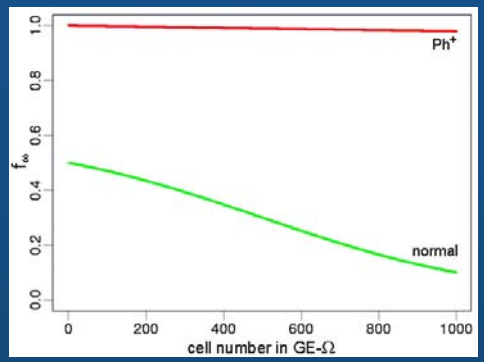
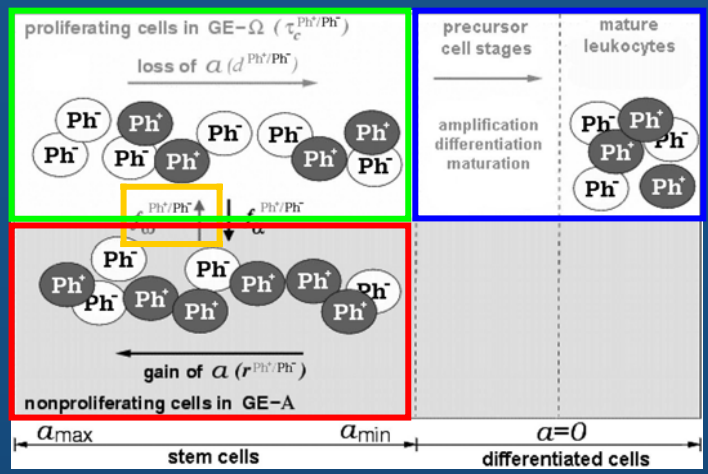
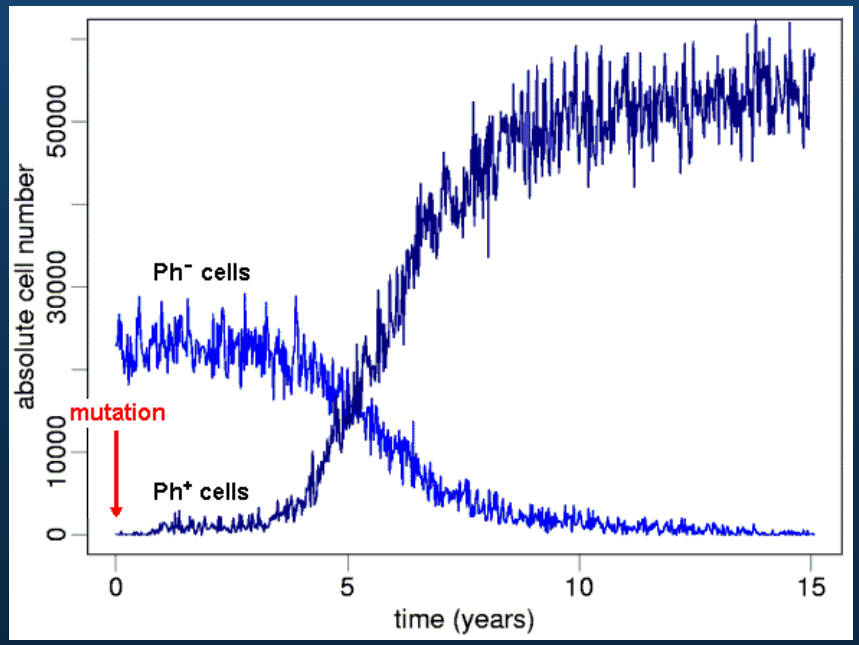
CML genesis: Scenario II

- additional change of transition function $\mathbf{f_\omega}$ of malignant cells
- no further changes

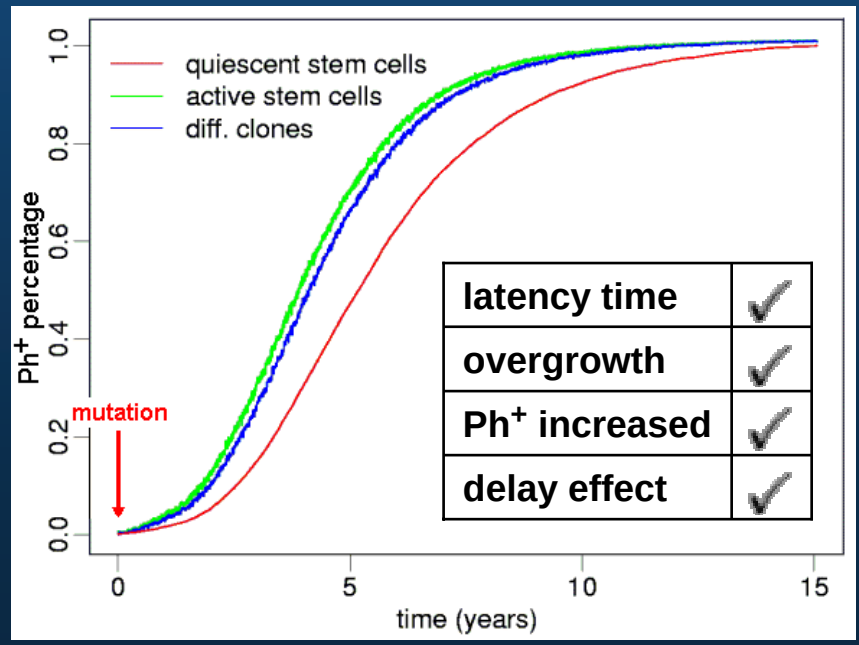




single simulation run



population statistic (n=100)



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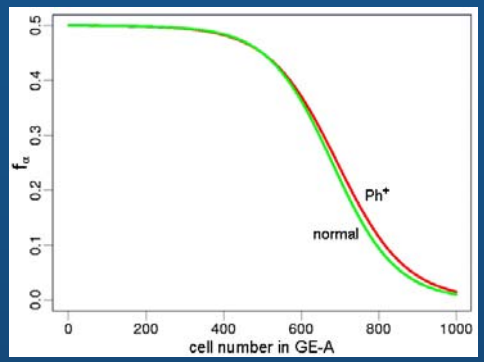
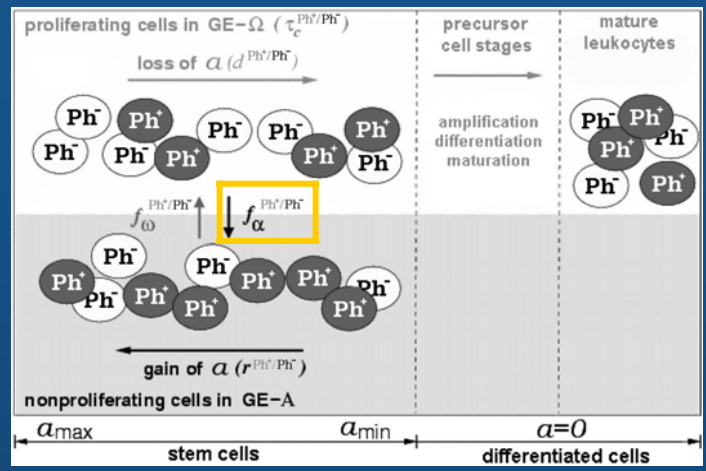
CML genesis: Scenario III

- slight difference in $\mathbf{f_\alpha}$
- $\mathbf{f_\omega}$ as in scenario II, but no change in ***d*** **(d = 1.05)**





➢ results qualitatively identical to scenario II

CML genesis: Scenario IV

- difference in $\boldsymbol{\tau_c}$**: 45*h*** (Ph^+) vs. **48*h*** (Ph^-)
- $\mathbf{f_\omega}$ as in scenario II, but no change in ***d***

➢ results qualitatively identical to scenario II

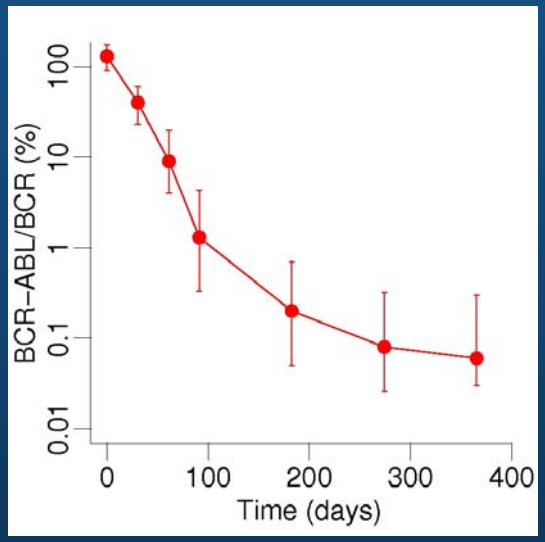
Question:

Can one discriminate these three qualitatively identical scenarios by applying treatment strategies?

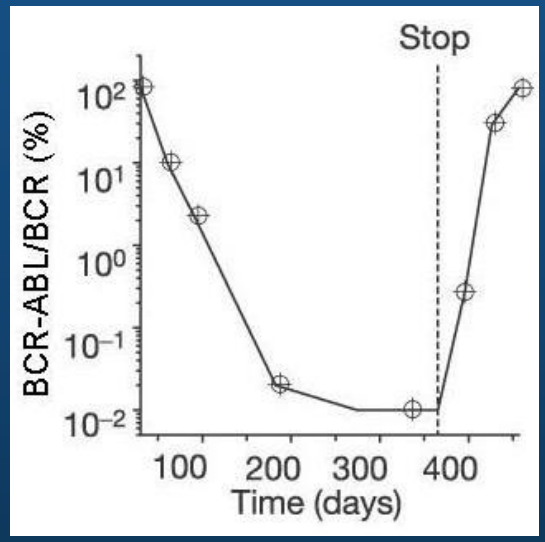
Clinical data on *imatinib* treatment

Quantitative PCR measurements in 68 patients

population median



single patient



(Michor et al., Nature, 2005)

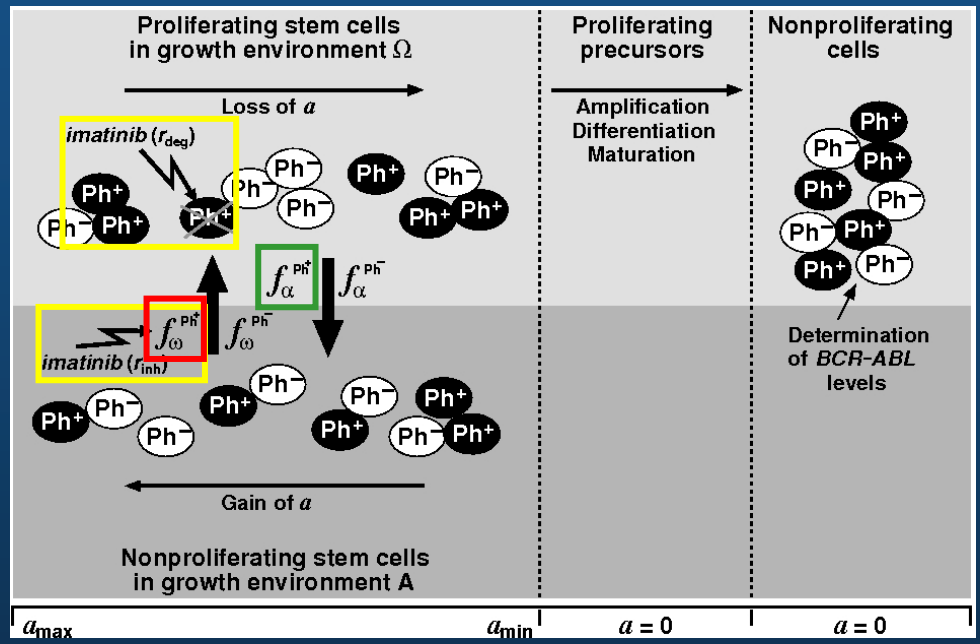
- Qualitative criteria:
  - **bi-phasic decline** of BCR-ABL transcript levels
  - **rapid relapse** of BCR-ABL transcripts after treatment stop

Imatinib treatment

Model assumptions:

Effects on Ph$^+$ cells:

- **proliferation inhibition** (inhibition intensity r_{inh})
- induction of **apoptosis** (degradation intensity r_{deg})



➢ only Scenario III meets qualitative criteria (parameter difference in $\mathbf{f_\alpha}$ and $\mathbf{f_\omega}$)

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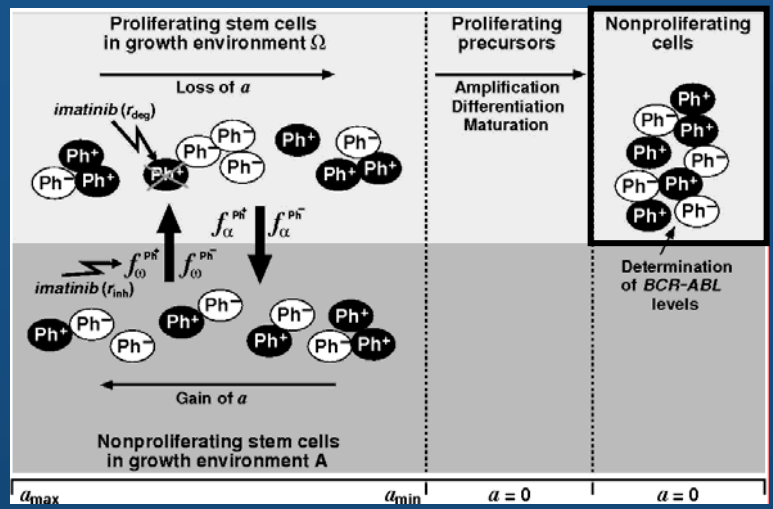
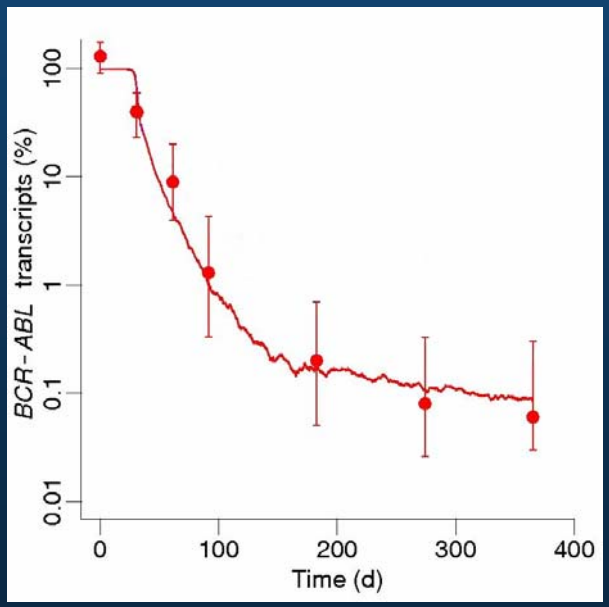
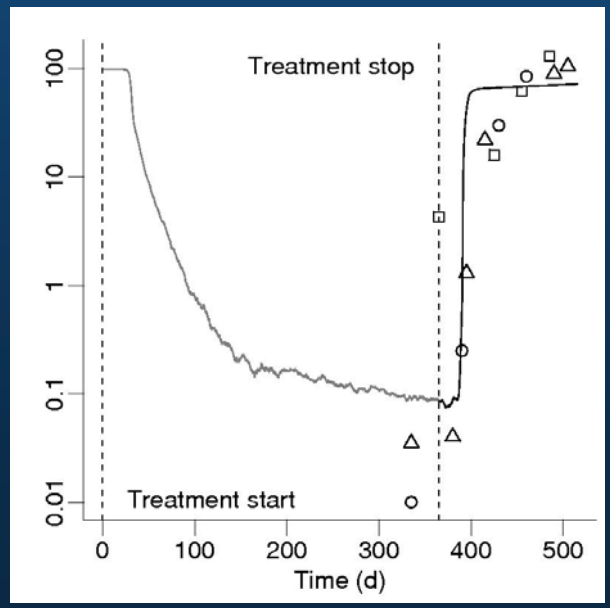
Imatinib treatment

- degradation intensity r_{deg}=0.033
  inhibition intensity r_{inh}=0.050
- **quiescent stem cells**
  responsible for rapid relapse







criteria list

bi-phasic	✓
rapid relapse	✓

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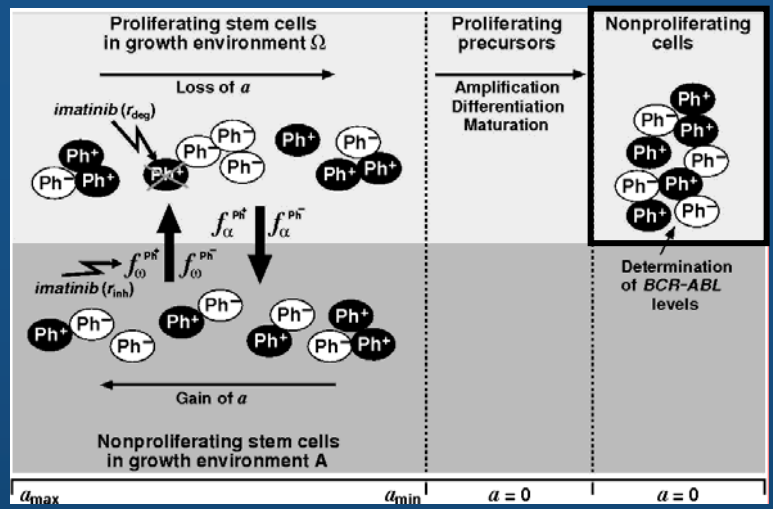
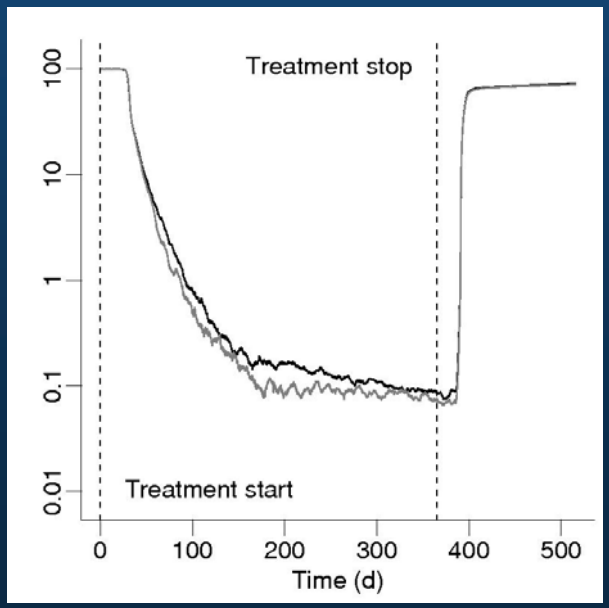
Model predictions

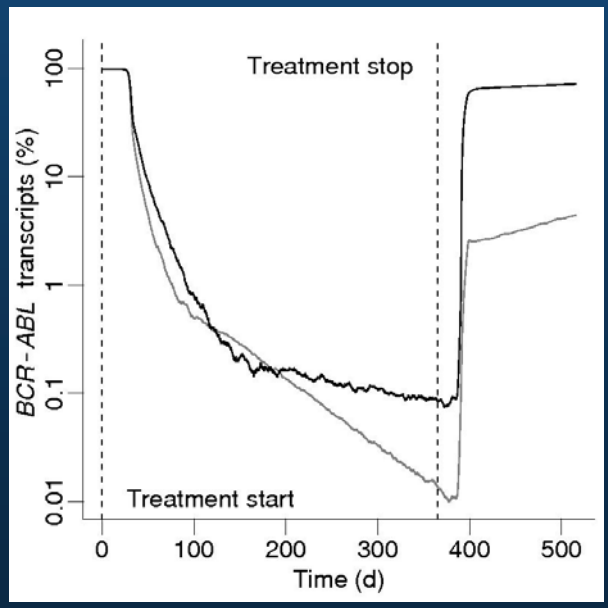
- additional cytotoxic therapy: **almost no** additional **benefit**
- **potential benefit** by additional **proliferation stimulation**



additional cytotoxicity



proliferation stimulation



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Conclusion / Outlook

The dynamic model

- is consistent with clinical data
  (BCR-ABL decline kinetics as well as rapid relapse)
- provides testable predictions on combination therapies

The model provides possible explanation for

- genesis of CML (e.g., long latency times)
- mechanisms of action of *imatinib* treatment

In the future,

- further model analyses (e.g., resistance mutations)
- clinical trials testing the generated predictions desirable
- more biological data on resistance mutations needed

Thank you!