Multiscale and multistages mathematical models of stem cell systems and their malignancies

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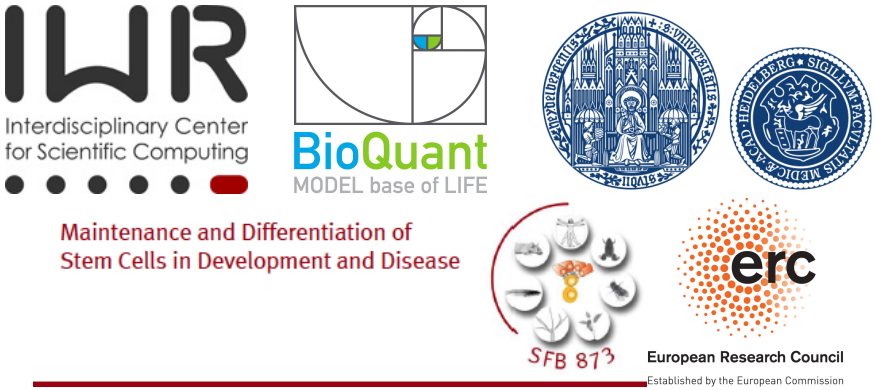


August 25, 2014

Interdisciplinary collaboration and models of blood production system

- Collaboration with Anthony Ho and Natalia Baran (Department of Medicine V, Univ. Heidelberg, Collaborative Research Center (SFB) "Maintenance and Differentiation of Stem Cells in Development and Disease") and Wolfgang Wagner (University of Aachen, WIN Kolleg "How old are stem cells?")
- Models of hematopoiesis and leukemia: with Thomas Stiehl (Heidelberg Univ.)
- Models of continuous cell differentiation: with Marie Doumic, Benoit Perthame (Univ. P. et M. Curie and INRIA Equipe BANG) and Jorge Zubelli (IMPA)
- Models of clonal evolution: with Jan-Erik Stecher (Heidelberg Univ.) and Piotr Gwiazda (Warsaw Univ.)

Outline

- Stem Cells and Blood Production System: Biological background and aims of mathematical modelling
- Models with discrete and continuous structure
  - Multi-compartment models of healthy hematopoiesis
  - Structured population model of continuous cell differentiation
  - Models of stem-cells initiated cancer growth
  - Multi-compartment and structured population models of clonal evolution in acute leukemias
- Clinical applications

Stem cells

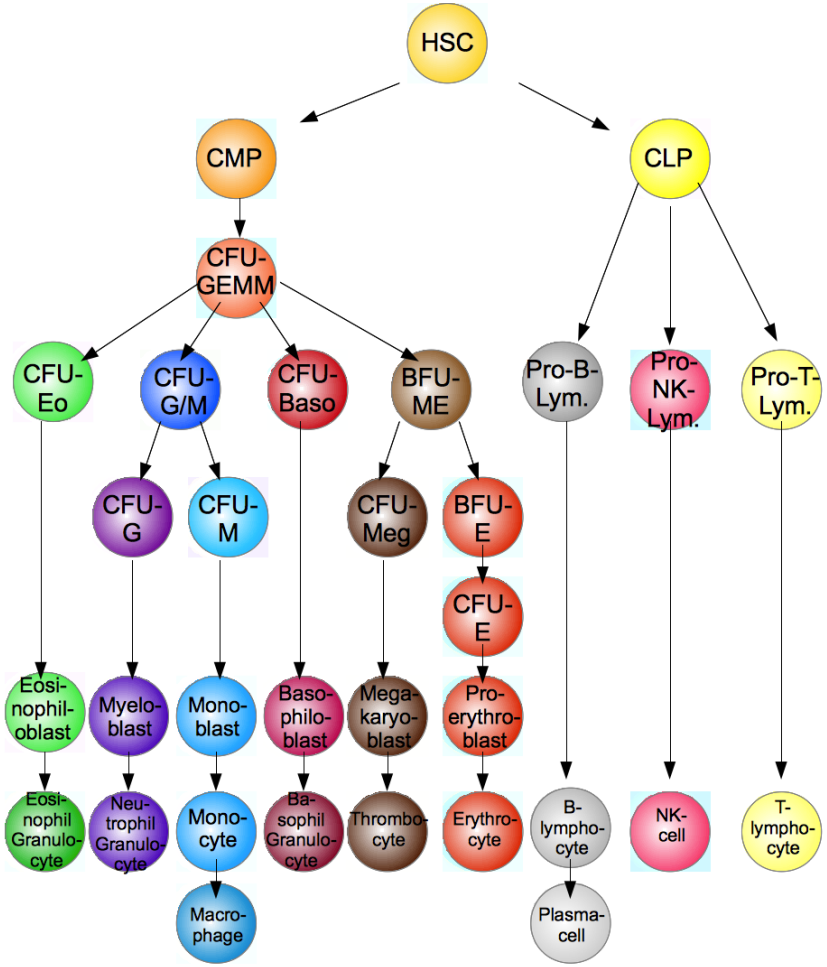
"Definition"

- functionally undifferentiated
- able to proliferate
- give rise to a large number of more differentiated progenitor cells
- maintain their population by dividing to undifferentiated cells
- heterogeneous in respect to morphological and biochemical properties

Role of adult stem cells

- Populations of adult stem cells can be found in lots of different tissues (epidermis, blood, liver, intenstinal crypts, neural tissue, ...)
- Adult stem cells govern regeneration processes
- Stem cells are found to play an important role in cancerogenesis (cancer stem cells)

Our example: Blood cell production system

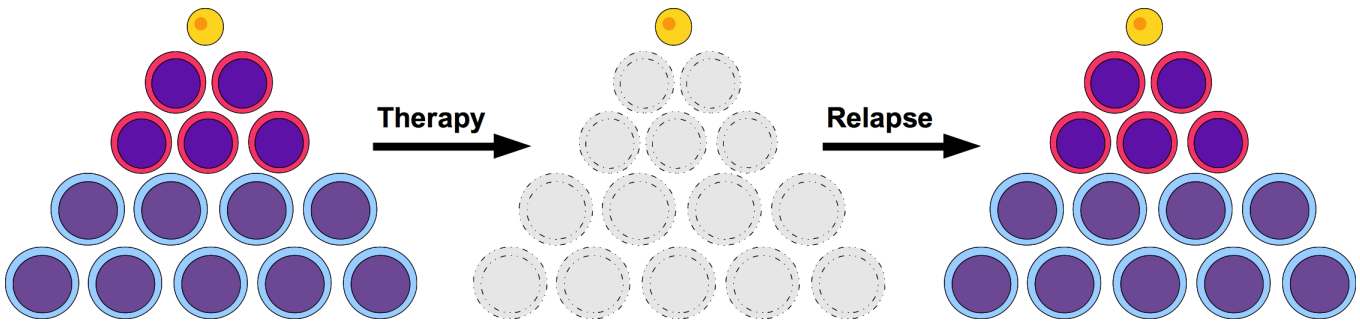


- The Hematopoietic Stem Cell gives rise to all types of mature blood cells.
- Production of mature blood cells is a stepwise process: Cell pass through a sequence of different maturation stages.
- Cell properties are regulated by different signals.

Adapted from Blau, Brazelton, Weimann, Cell 105, 2001 and Benninghoff, Drenckhahn, 17 ed, 2008

Stem cell initiated cancer

There exists evidence that some cancers originate from cells with stem cell like properties (e.g. Bonnet et al, Nat Med 1997).



Definition of Leukemia

Leukemia is characterized by an increase of aberrant cells (blasts) in bone marrow

Challenge: Multiscale character of the process

- Hematopoietic Stem Cells (HSC) are situated in red bone marrow
- Biochemical and biomechanical regulatory mechanisms
- Cell migration (eg. chemotaxis)

Models of hematopoiesis

Choice of the model depends on the questions we want to address.

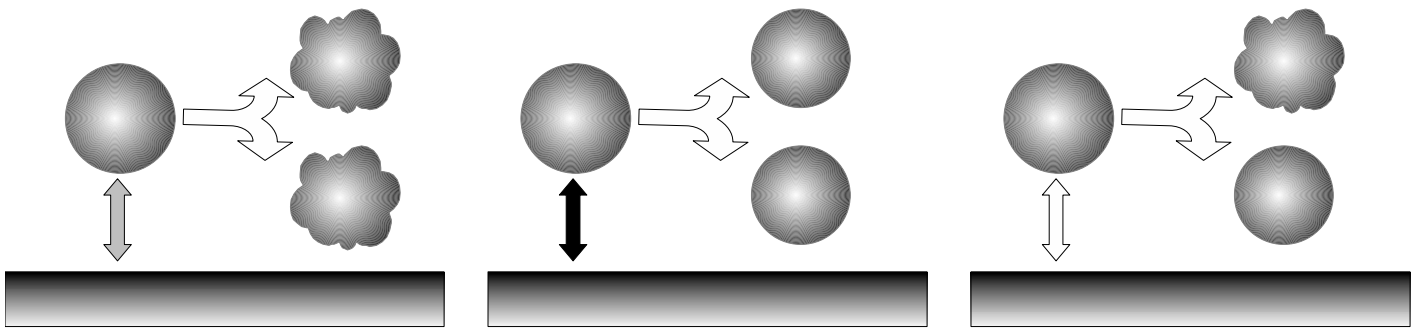
- Quiescence, proliferation and replicative senescence
- Modelling of cell cycle (or simplifications)
- Nonlinearities to regulate the system
  - Feedback-loops
  - Competition for space (eg. stem cells niches)
- Differentiation (maturation): discrete or continuous process?
- $\longrightarrow$ IBM or PDE/ODE/DDE/SDE models

Partial overview of existing models of blood production system

- Michor, Dingli, Pacheco, Traulsen et al: Linear models to describe exponential growth of cancer cells populations.
- Loeffler and Roeder et al:
  - Stochastic transition of stem cells between proliferation and quiescence.
  - Linear transition between stem cells and mature cells.
- Kim, Perthame, Doumic: Reduction of Roeder's model to differential equations with the same behaviour.
- Mackey, Adimy, Crauste et al: Models with delay to describe possible oscillations.
- Tomasetti, Levy, Kimmel: Branching processes and evolution of leukemia
- ...

Our aim: to understand better cell differentiation and the regulation process

- Symmetric vs. asymmetric cell divisions
- Dynamically regulated cell properties
- Nonlinear feedback and signalling molecules

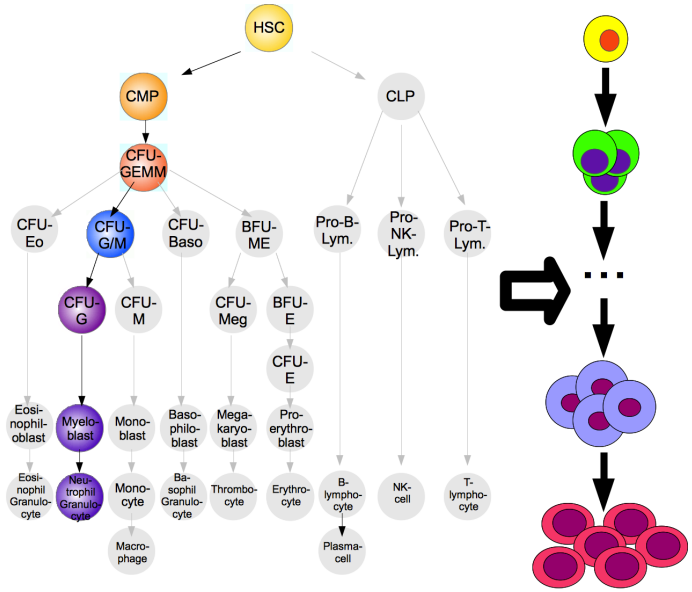


Ho and Wagner, Curr. Opin. Hematol., 2007.

Multi-compartment models of cell differentiation: healthy hematopoiesis

Model assumptions

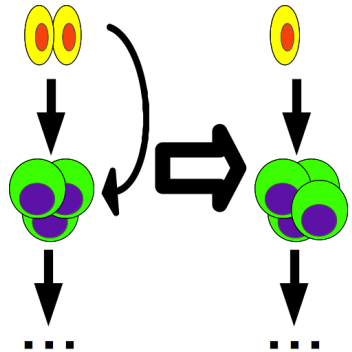
We consider only one cell lineage



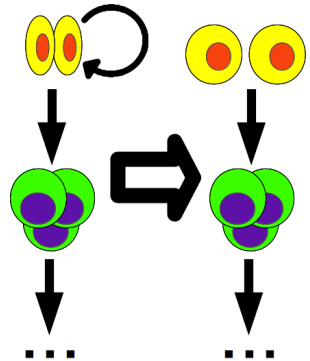
Cells can die

Cells can divide

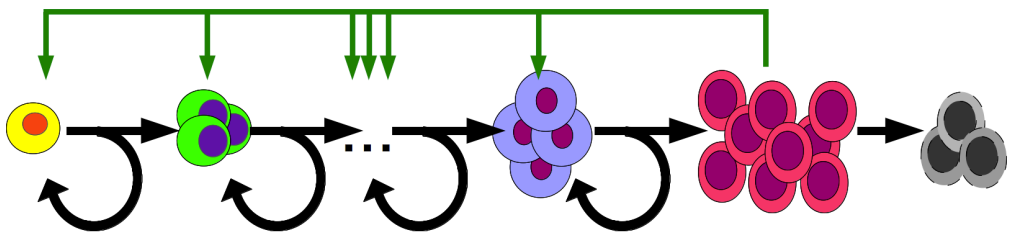
Cells differentiate



Cells self-renew

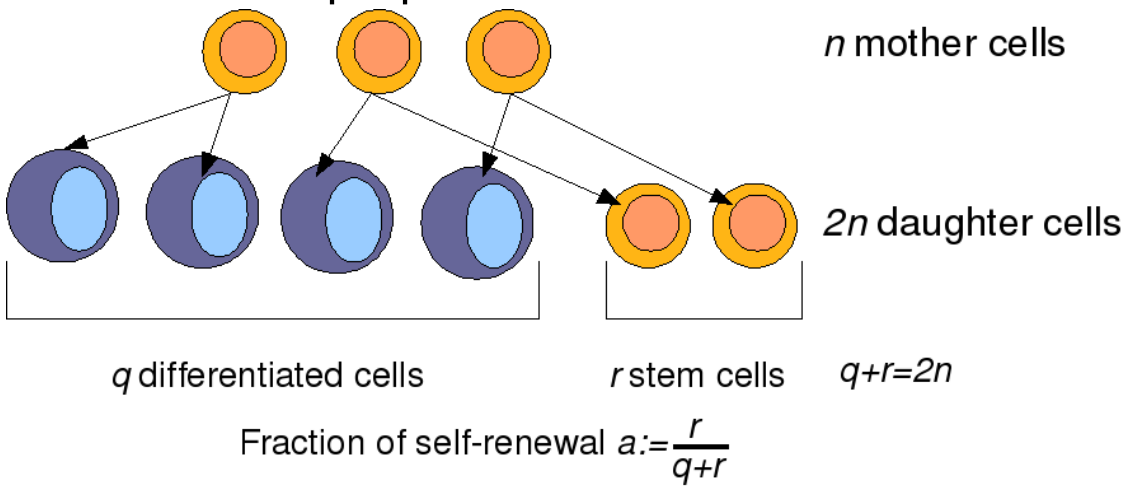


- Signalling molecules influence behaviour of unmature cells.
- Signal concentration depends on mature cell counts.
- Mature cells do not divide



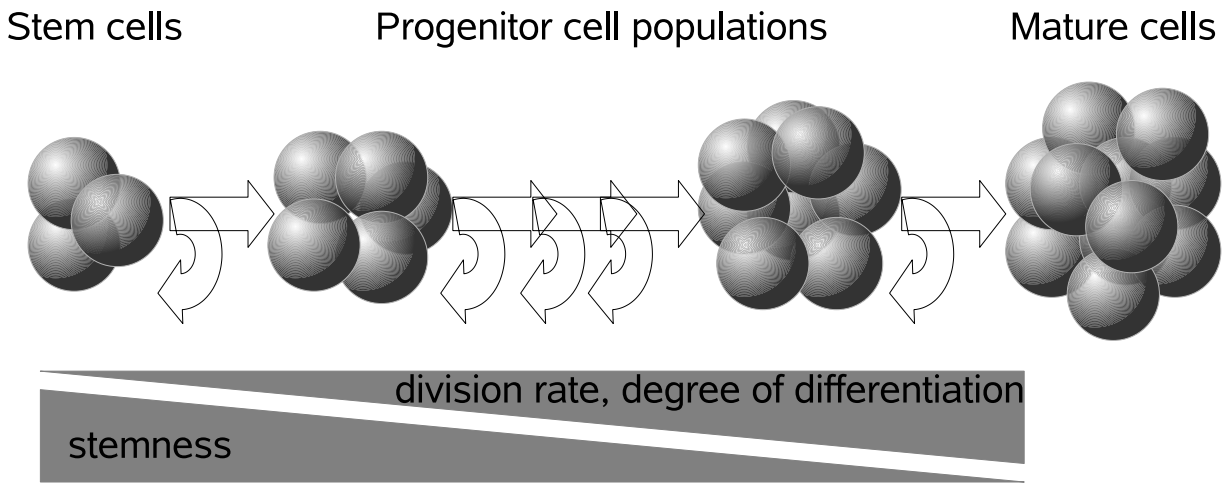
Key parameters

- Proliferation rate describes how often a given cell divides
- Fraction of self-renewal describes which fraction of daughter cells has the same properties as the mother cells



- Death rate describes which fraction of a given cell population dies per unit of time

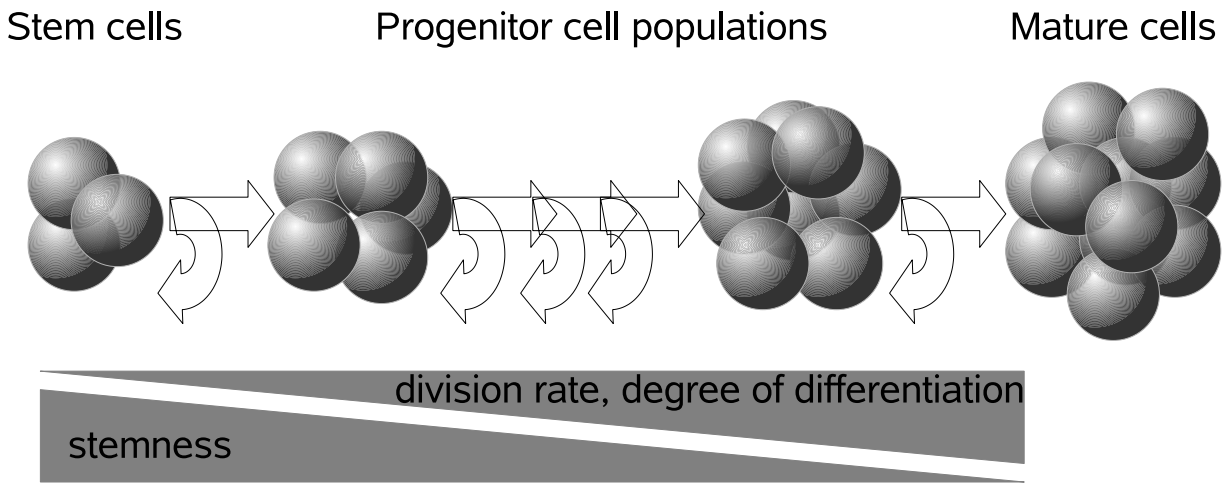
Multi-compartment model: discrete structure



$$
\begin{aligned}
\frac{du_1}{dt} &= p_1(u_1, s) - g_1(u_1, s) - d_1 u_1, \\
\frac{du_i}{dt} &= g_{i-1}(u_{i-1}, s) + p_i(u_i, s) - g_i(u_i, s) - d_i u_i, \\
\frac{du_n}{dt} &= g_{n-1}(u_{n-1}, s) - d_n(u_n, s).
\end{aligned}
$$

Marciniak-Czochra, Stiehl, Jäger, Ho, Wagner, SC Dev 18, 2009

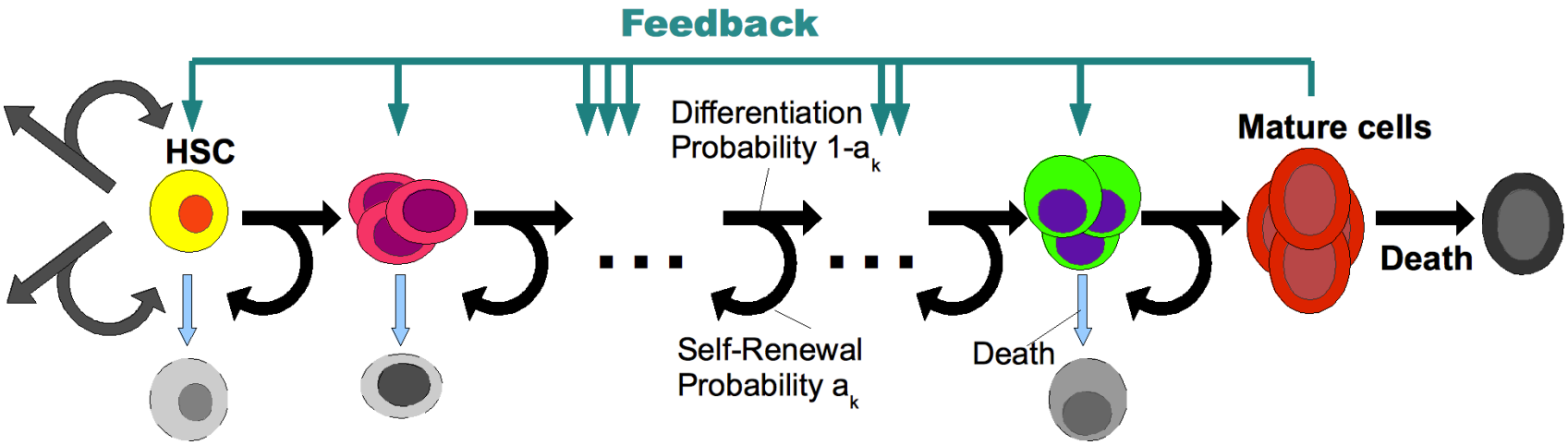
Multi-compartment model: discrete structure



$$
\begin{aligned}
\frac{du_1}{dt} &= 2p_1 a_1 u_1 - p_1 u_1 - d_1 u_1, \\
\frac{du_i}{dt} &= (2a_i - 1)p_i u_i + 2(1 - a_{i-1})p_{i-1} u_{i-1} - d_i u_i, \\
\frac{du_n}{dt} &= 2(1 - a_{n-1})p_{n-1} u_{n-1} - d_n u_n.
\end{aligned}
$$

Marciniak-Czochra, Stiehl, Jäger, Ho, Wagner, SC Dev 18, 2009

Model of feedback



Dynamics of signalling molecules (cytokines)

$$\frac{dS(t)}{dt} = \alpha - \mu S(t) - \beta u_n(t) S(t)$$

Quasi steady state approximation (Tikhonov Theorem)

$$s(t) = \frac{1}{1 + k u_n(t)} \in [0, 1],$$

where $s(t) := \frac{\mu}{\alpha} S(t)$ and $k := \frac{\beta}{\mu}$.

Assumptions on cytokines

Regulation modes

- All regulated cell properties depend linearly on the cytokine concentration

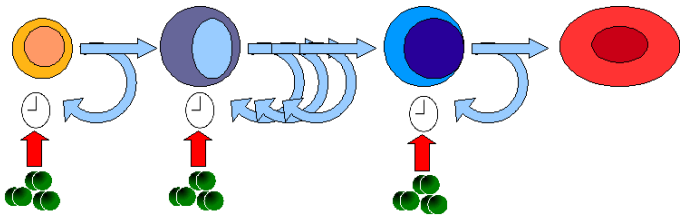
1. Regulation of proliferation: $p_i(s(t)) := p_i s(t) = \frac{p_{i,max}}{1+k u_n(t)}$
2. Regulation of self renewal versus differentiation
   $a_i(s(t)) := a_i s(t) = \frac{a_{i,max}}{1+k u_n(t)}$

Three models are considered

	Proliferation Rate	**Fraction of Self-Renewal**
Model 1	cytokine-dependent	constant
Model 2	constant	cytokine-dependent
Model 3	cytokine-dependent	cytokine-dependent

Model 1

constant self-renewal
regulated proliferation



$$\frac{du_1}{dt} = (2a_1 - 1)p_{1,max}su_1 - d_1u_1$$

$$\cdots$$

$$\frac{du_i}{dt} = (2a_i - 1)p_{i,max}su_i + 2(1 - a_{i-1})p_{i-1,max}su_{i-1} - d_iu_i$$

$$\cdots$$

$$\frac{du_n}{dt} = 2(1 - a_{n-1})p_{n-1,max}su_{n-1} - d_nu_n$$

$$s = \frac{1}{(1 + ku_n)}$$

u_i - cell density

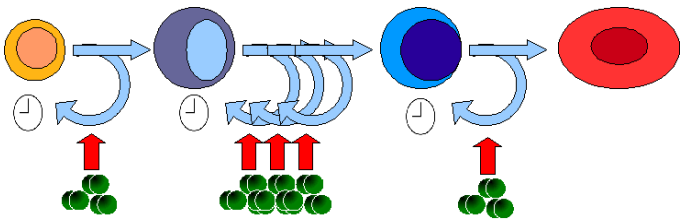
a_i - fraction of self-renewal

$p_{i,max}$ - maximal proliferation rate

d_i - death rate

Model 2

regulated self-renewal
constant proliferation



$$\frac{du_1}{dt} = (2a_{1,max}s - 1)p_1 u_1 - d_1 u_1$$

$$\cdots$$

$$\frac{du_i}{dt} = (2a_{i,max}s - 1)p_i u_i + 2(1 - a_{i-1,max}s)p_{i-1} u_{i-1} - d_i u_i$$

$$\cdots$$

$$\frac{du_n}{dt} = 2(1 - a_{n-1,max}s)p_{n-1} u_{n-1} - d_n u_n$$

$$s = \frac{1}{(1 + ku_n)}$$

u_i - cell density

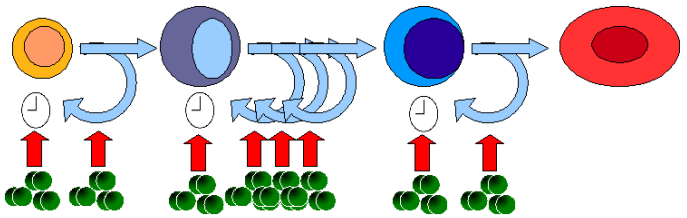
$a_{i,max}$ - max. fraction of self renewal

a_i - fraction of self-renewal

d_i - death rate

Model 3

regulated self-renewal
regulated proliferation



$$\frac{du_1}{dt} = (2a_{1,max}s - 1)p_{1,max}su_1 - d_1u_1$$

$$\cdots$$

$$\frac{du_i}{dt} = (2a_{i,max}s - 1)p_{i,max}su_i + 2(1 - a_{i-1,max}s)p_{i-1,max}su_{i-1} - d_iu_i$$

$$\cdots$$

$$\frac{du_n}{dt} = 2(1 - a_{n-1,max}s)p_{n-1,max}su_{n-1} - d_nu_n$$

$$s = \frac{1}{(1 + ku_n)}$$

u_i - cell density

$a_{i,max}$ - max. fraction of self renewal

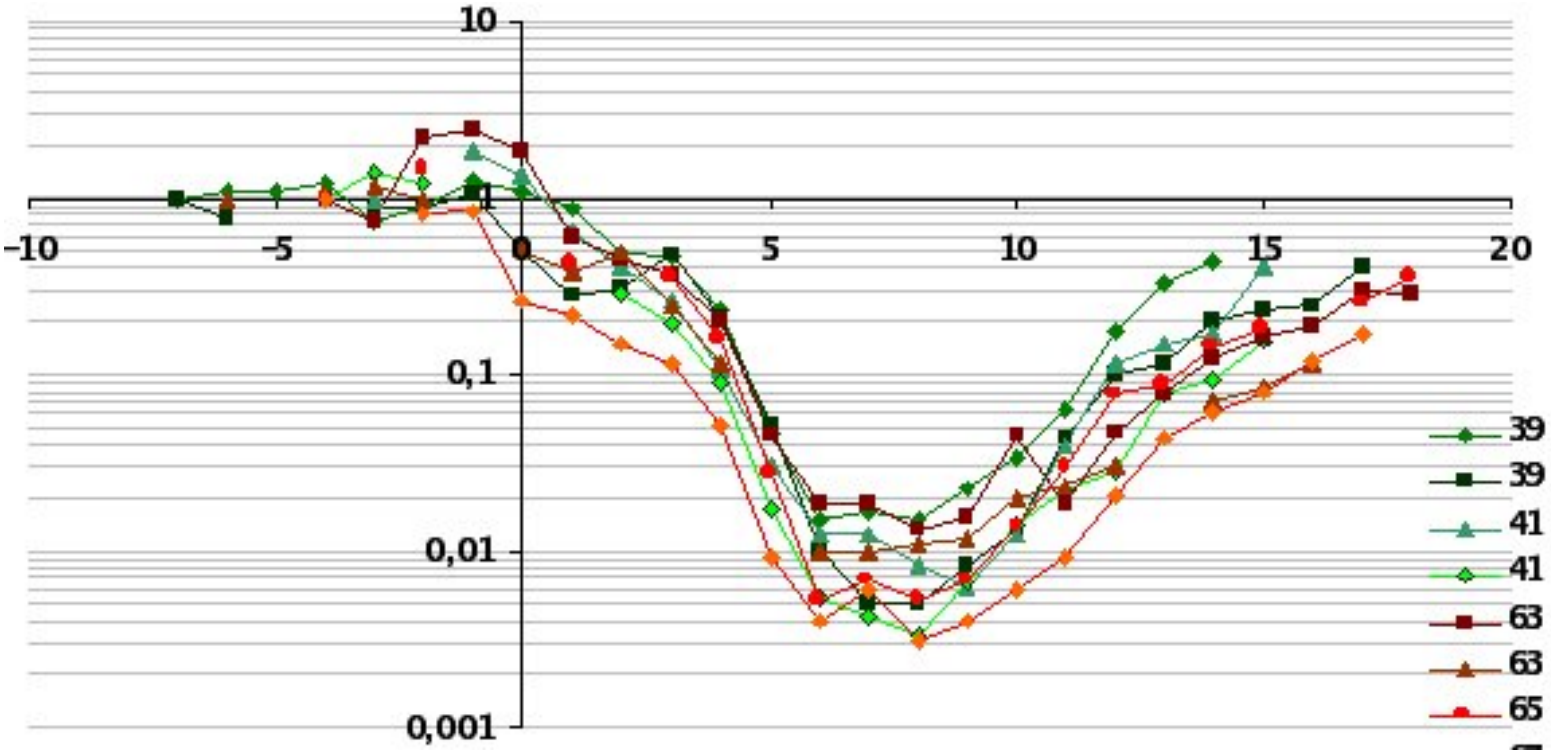
d_i - death rate

a_i - fraction of self-renewal

$p_{i,max}$ - max. prolif rate

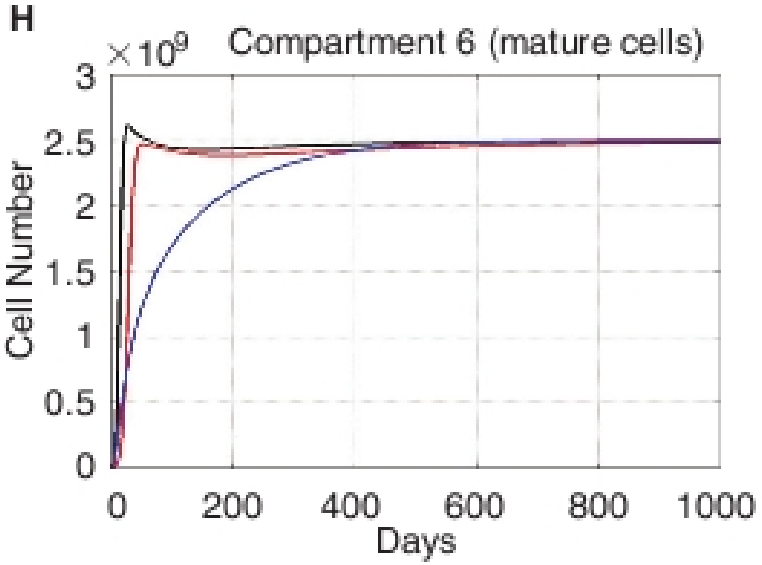
Medical application: Hematopoietic reconstitution

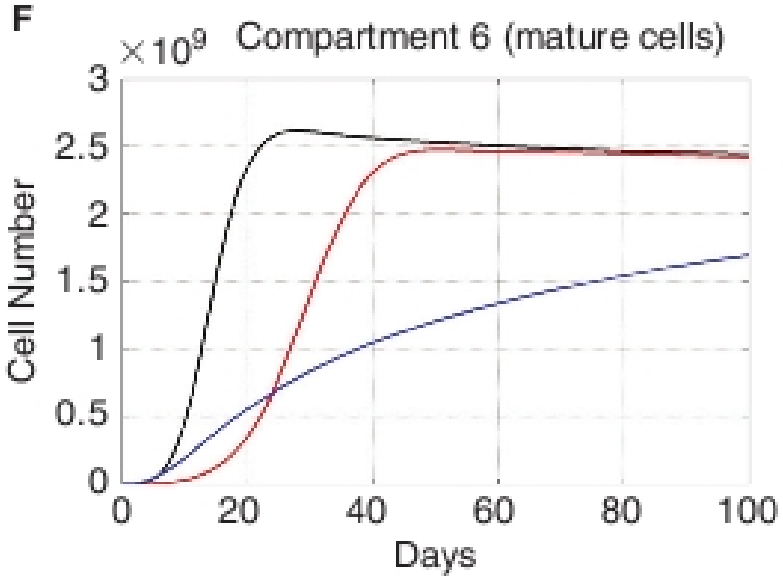
- Stress conditions (chemotherapy)
- Bone marrow transplantation (CD34+ cells)
- Blood regeneration



Numerical results

- Regulation of self-renewal fractions is the most effective mechanism of hematopoietic reconstitution





Model calibration

Available data

- Initial conditions
- Proliferation rates in a steady state
- Steady state population sizes
- Clearance of leukocytes from blood stream

Initial conditions

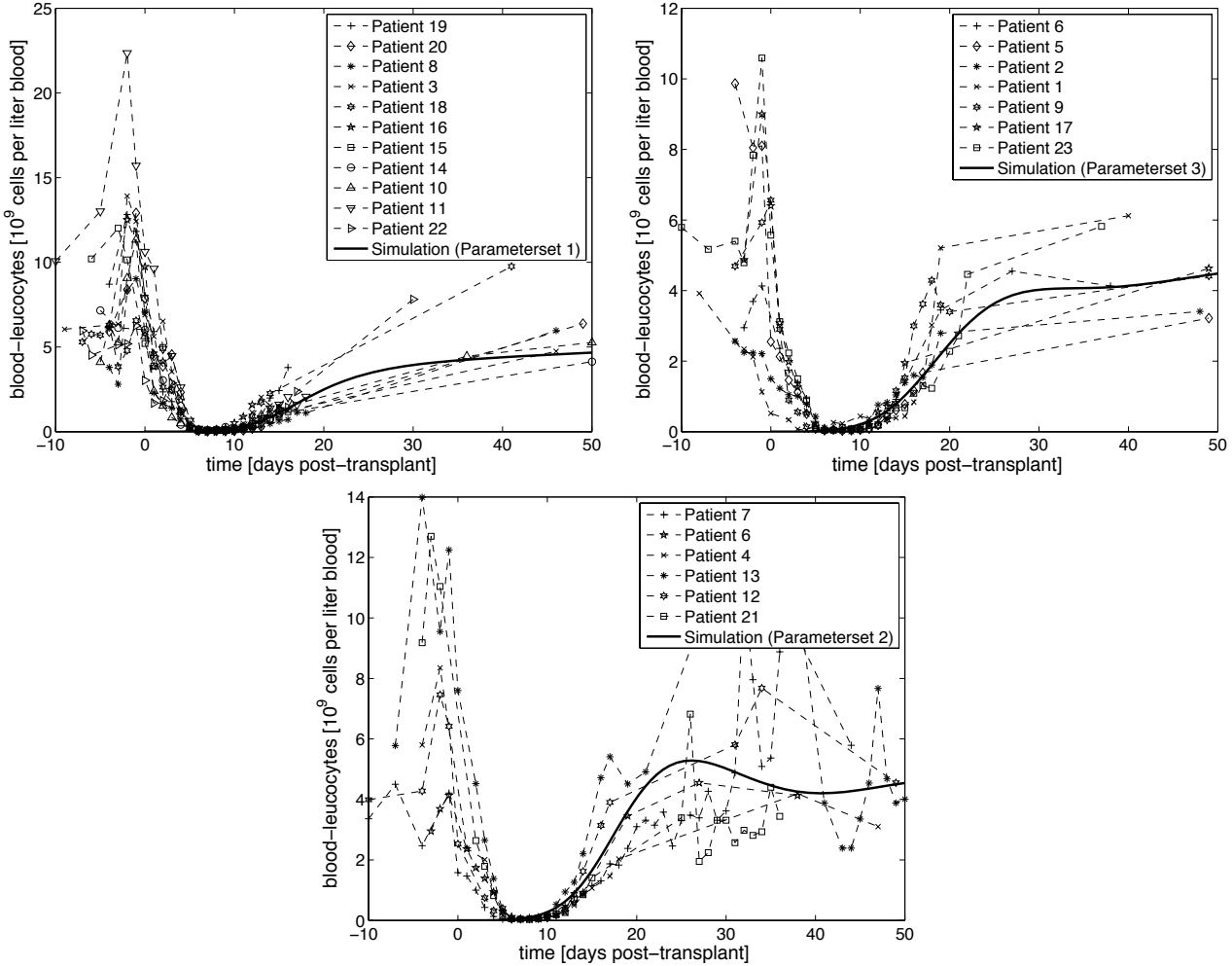
Cell Type	number of transplanted cells per kg body weight
prim HSC [1]	$\approx 3 \cdot 10^3$
LTC-IC	$\approx 36 \cdot 10^3$
CFU-GM	$\approx 155 \cdot 10^3$
CFU-G	$\approx 54 \cdot 10^4$
Myeloblast	0
Promyelocyte	0
Myelocyte	0
Mature neutrophil	0

Parameter sets

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
a_1	0.5	$a_{1,max}$	0.77	p_1	$2.15 \cdot 10^{-3} \frac{1}{\text{day}}$	$p_{1,max}$	$7.6 \cdot 10^{-3} \frac{1}{\text{day}}$
a_2	0.4993	$a_{2,max}$	0.7689	p_2	$11.21 \cdot 10^{-3} \frac{1}{\text{day}}$	$p_{2,max}$	$39.6 \cdot 10^{-3} \frac{1}{\text{day}}$
a_3	0.4779	$a_{3,max}$	0.7359	p_3	$5.66 \cdot 10^{-2} \frac{1}{\text{day}}$	$p_{3,max}$	$0.2 \frac{1}{\text{day}}$
a_4	0.4986	$a_{4,max}$	0.7678	p_4	$0.1586 \frac{1}{\text{day}}$	$p_{4,max}$	$0.56 \frac{1}{\text{day}}$
a_5	0.1	$a_{5,max}$	0.154	p_5	$0.32 \frac{1}{\text{day}}$	$p_{5,max}$	$0.32 \frac{1}{\text{day}}$
a_6	0.0714	$a_{6,max}$	0.11	p_6	$0.7 \frac{1}{\text{day}}$	$p_{6,max}$	$0.7 \frac{1}{\text{day}}$
a_7	0.3929	$a_{7,max}$	0.605	p_7	$1 \frac{1}{\text{day}}$	$p_{7,max}$	$1 \frac{1}{\text{day}}$

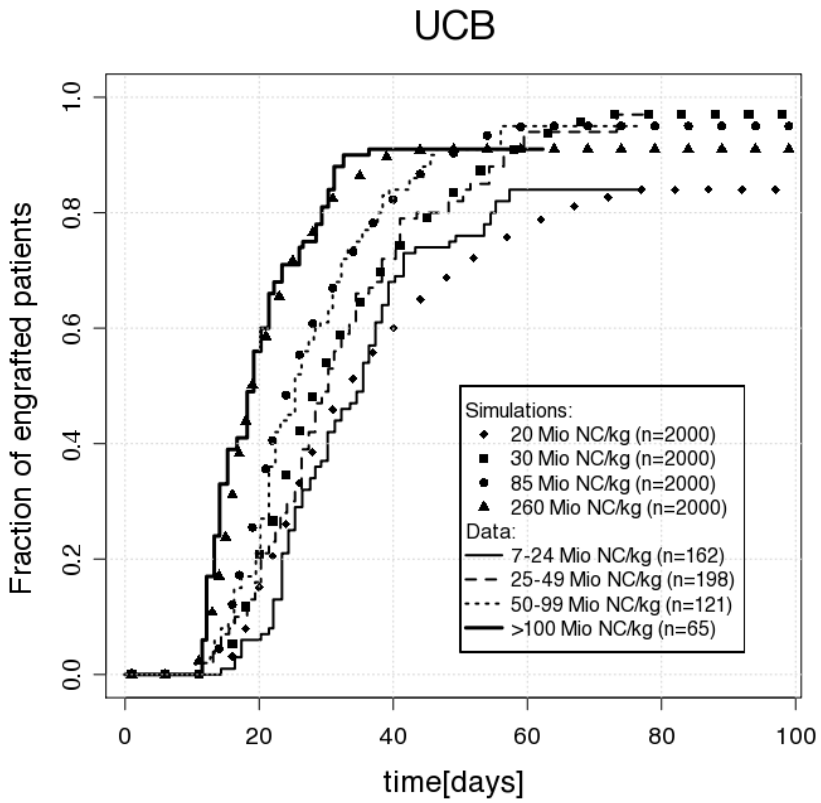
Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
a_1	0.5	$a_{1,max}$	0.77	p_1	$2.15 \cdot 10^{-3} \frac{1}{\text{day}}$	$p_{1,max}$	$7.6 \cdot 10^{-3} \frac{1}{\text{day}}$
a_2	0.4994	$a_{2,max}$	0.769	p_2	$11.21 \cdot 10^{-3} \frac{1}{\text{day}}$	$p_{2,max}$	$39.6 \cdot 10^{-3} \frac{1}{\text{day}}$
a_3	0.4743	$a_{3,max}$	0.7304	p_3	$5.66 \cdot 10^{-2} \frac{1}{\text{day}}$	$p_{3,max}$	$0.2 \frac{1}{\text{day}}$
a_4	0.4982	$a_{4,max}$	0.7673	p_4	$0.1586 \frac{1}{\text{day}}$	$p_{4,max}$	$0.56 \frac{1}{\text{day}}$
a_5	0.4286	$a_{5,max}$	0.66	p_5	$0.32 \frac{1}{\text{day}}$	$p_{5,max}$	$0.32 \frac{1}{\text{day}}$
a_6	0.0714	$a_{6,max}$	0.11	p_6	$0.7 \frac{1}{\text{day}}$	$p_{6,max}$	$0.7 \frac{1}{\text{day}}$
a_7	0.0357	$a_{7,max}$	0.055	p_7	$1 \frac{1}{\text{day}}$	$p_{7,max}$	$1 \frac{1}{\text{day}}$

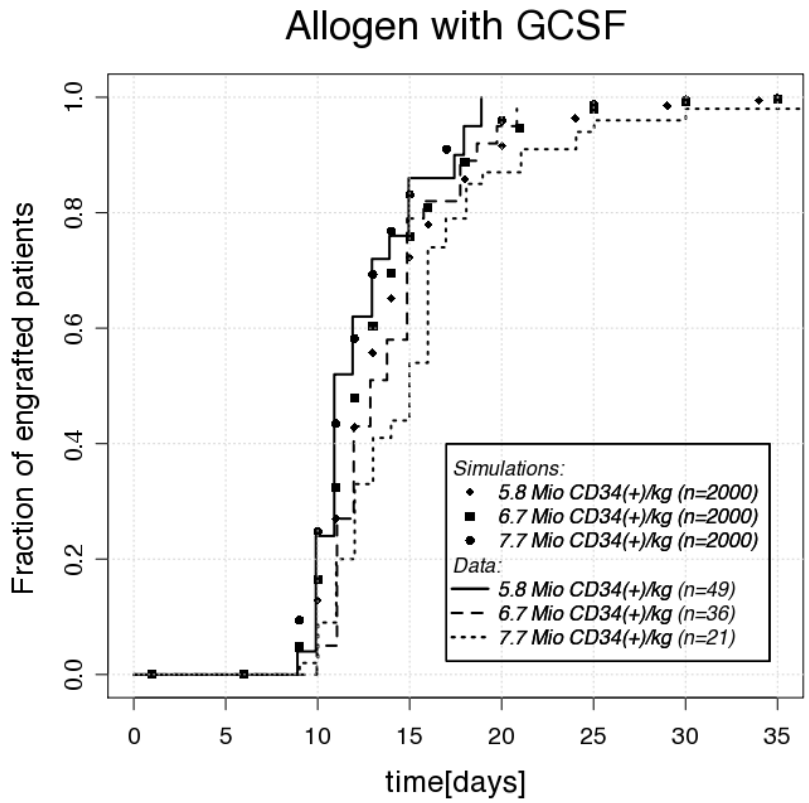
Model validation: Comparison to patients data



Stiehl, Ho, Marciniak-Czochra, Bone Marrow Transplantation 49, 2014

Comparison to Clinical Trial Data Data





Stiehl, Ho, Marciniak-Czochra, Bone Marrow Transplantation 49, 2014

Model analysis

- Trivial steady state - unstable (unless it is the only equilibrium)
- Semi-trivial steady state: $(0, ..0, \bar{u}_k, .., \bar{u}_n)$ - linearly unstable iff there exists a steady state with more positive components
- Unique positive steady state: $(\bar{u}_1, .., \bar{u}_n)$ - globally stable ?
  - Global stability for the 2-compartment model

$$L(u_1(t), u_2(t)) := \frac{1}{p_1 G(\bar{u}_2)} L_{21}(t, u_1(t), u_2(t)) + \frac{1}{d_2} L_{22}(t, u_1(t), u_2(t))$$

with $G(\xi) = 2(1 - a_1/(1 + ku_2))$ and

$$L_{21}(t, u_1, u_2) := \frac{u_1}{\bar{u}_1} - 1 - \ln \frac{u_1}{\bar{u}_1},$$

$$L_{22}(t, u_1, u_2) := \frac{u_2}{\bar{u}_2} - 1 - \frac{1}{\bar{u}_2} \int_{\bar{u}_2}^{u_2} \frac{G(\bar{u}_2)}{G(\xi)} d\xi.$$

- Hopf bifuraction and oscillations in the 3-compartment model.

Stiehl and Marciniak-Czochra, Math. Comp. Models., 2010

Nakata, Getto, M-C and Alarcon, J. Biol. Dynamics, 2012 Getto, M-C, Nakata and dM Vivanco, Math. Biosciences, 2013

Biological interpretation of analytical constraints

(1) $(2a_{1,max} - 1)p_1 > d_1$

$\Leftrightarrow \quad \exists s \in (0,1) \text{ s. t. } (2a_{1,max}s - 1)p_1 > d_1$

$\Leftrightarrow \quad \exists s \in (0,1) \text{ s. t. } \frac{dc_1}{dt} > 0$

Interpretation: There exist signal levels s. t. the death rate is not larger than the reproduction rate

Special case:

If $d_1 = 0$: (1) $\Leftrightarrow a_{1,max} > \frac{1}{2}$

Interpretation: Self-renewal of stem cells has to be greater than differentiation

Biological interpretation of analytical constraints

Signal intensity of self-maintenance

The signal intensity that is needed to maintain the size of population i without cell influx from downstream compartments is needed (i.e., $(2a_{i,max}s_i - 1)p_i c_i - d_i c_i = 0$)

$$(2)\quad 2a_{1,max}p_1(d_i + p_i) - 2a_{i,max}p_i(d_1 + p_1) > 0, \text{ for } i = 2, \ldots, n-1$$

$$\Leftrightarrow \qquad s_1 < s_i \text{ for } i = 2, \ldots, n-1$$

Interpretation: The stem cell population needs less cytokine molecules to maintain its size than all other cell populations without cell influx from downstream compartments.

Special case:

If $d_1 = \cdots = d_{n-1} = 0$: $(2) \Leftrightarrow \; a_{1,max} > a_{i,max}$

Biological synthesis

"Stem-Cell-Theorem"

In the given models the stem cell population can be characterised by the following properties:

(1) For some cytokine levels the death rate is smaller than the reproduction rate

(2) The signal intensity (cytokine level) needed for maintenance of the population size is smaller than that of all other cell populations.

Remark

The signal intensity of self-maintenance is defined on the level of a whole *(sub)population* and not on the level of single cells. It takes therefore heterogeneity of stem and progenitor cell populations into account.

What did we learn from the discrete models?

Conclusions

- Regulation of a self-renewal coefficients is a key factor during hematopoietic recovery after bone marrow transplantation
- The proposed model is able to explain observed heterogeneity of clinical outcomes and gives an idea how recovery depends on the transplant size
- Stem cell behaviour might be a property of a whole cell population

Questions and ideas

- In how far is "stemness" a cellular property and in how far is it the result of an interplay of cells and their environment?
- Is "stemness" a kind of program that could be executed in a great number of cells under suitable conditions?
- Is the self-renewal potential important in cancer development?

Models of continuous differentiation

Continuous maturation

Differentiation process

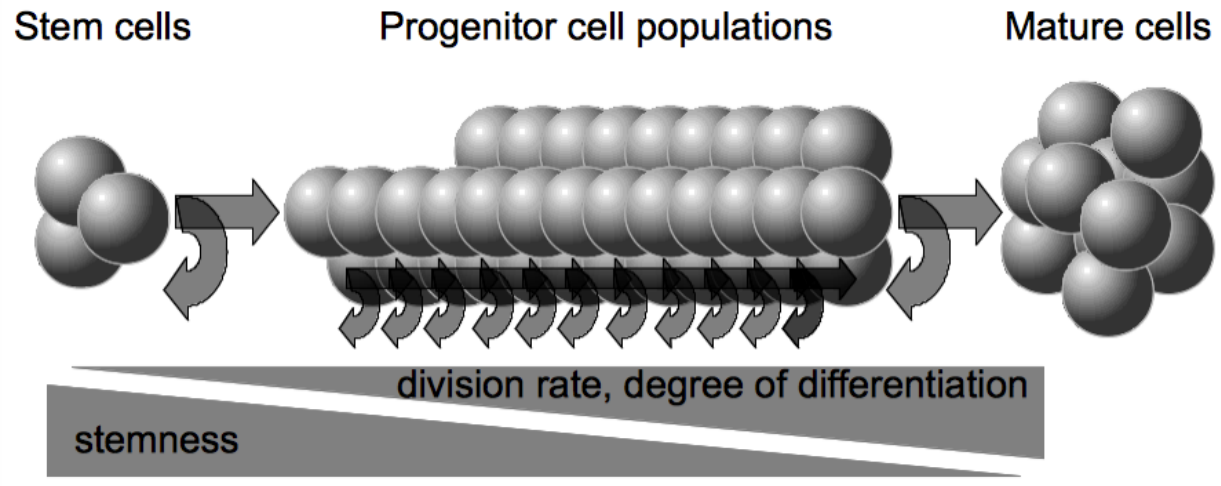
- There are indications that the differentiation process involves transitions which are continuous, along with discrete ones
- Cells may undergo continuous transformations between divisions
- Stage of differentiation may be quantified by the level of some proteins

Do we need different models?

- Continuous maturation structure may lead to the new effects in the dynamics

Structured population model: continuous structure

We consider a continuous structure variable describing the differentiation stage of a cell.



$$\partial_t u(x,t) + \partial_x [g(x, v(t)) u(x,t)] \quad = \quad p(x) u(x,t)$$

Doumic, M-C, Perthame, Zubelli, SIAM J Appl Math 71, 2011

Structured population model

Stem cells

$$\frac{d}{dt}w(t) \quad = \quad \alpha(v(t))w(t)$$

Mature cells

$$\frac{d}{dt}v(t) \quad = \quad g(x^*, v(t))u(x^*, t) - \mu v(t),$$

Progenitor cells - structured by a maturity level $x \in [0, x^*]$

$$\begin{aligned} \partial_t u(x,t) + \partial_x[g(x, v(t))u(x,t)] &= p(x)u(x,t), \\ g(0,t)u(0,t) &= g_w(t)w(t) \end{aligned}$$

Assumptions: $p_w = p(0)$ and $a_w = a(0)$.

Discrete vs continuous model

- Question: Can we obtain the continuous model from the discrete one?

$$
\begin{aligned}
\frac{du_1}{dt} &= p_1(u_1, s) - g_1(u_1, s) - d_1 u_1, \\
\frac{du_i}{dt} &= g_{i-1}(u_{i-1}, s) + p_i(u_i, s) - g_i(u_i, s) - d_i u_i, \\
\frac{du_n}{dt} &= g_{n-1}(u_{n-1}, s) - d_n(u_n, s).
\end{aligned}
$$

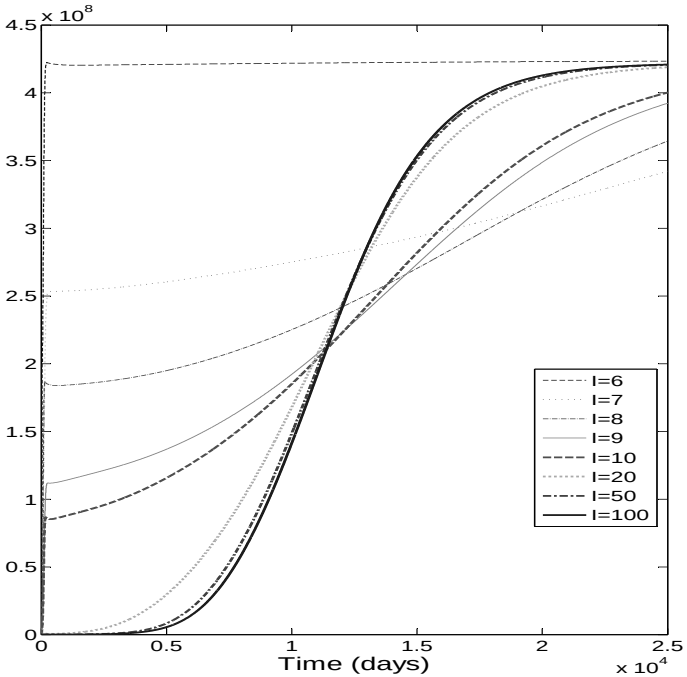
- Answer: No. Only if we assume that differentiation is independent on proliferation

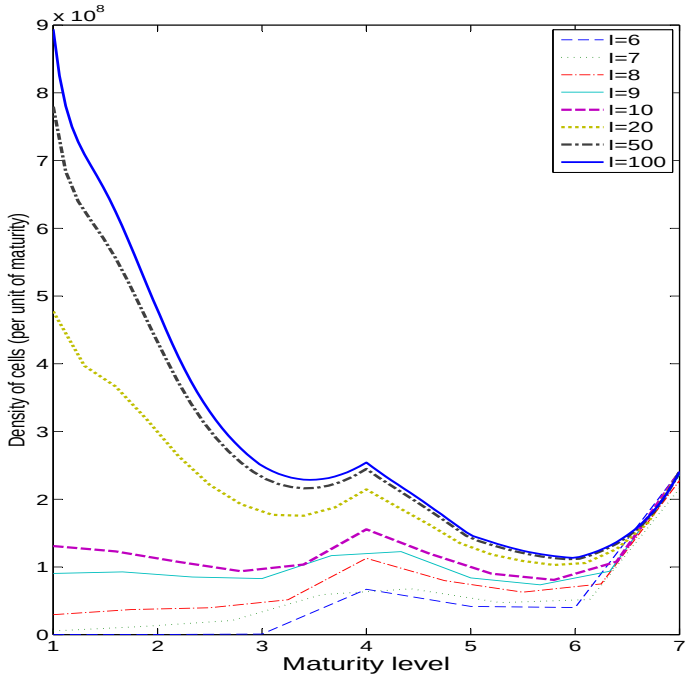
Discrete vs continuous model

Corrective term

Decorrelation between differentiation and proliferation is needed, else due to orders of magnitude in the limit equation the transport appears as a first order corrective term and we obtain

$$\partial_t u(x,t) + \varepsilon \partial_x [g(x,s)u(x,t)] = p(x,s)u(x,t)$$





Model analysis - Stationary solutions

- Solutions $(\bar{w}, \bar{u}, \bar{v})$ of the system

$$\begin{aligned} \alpha(\bar{v})\bar{w} &= 0, \\ \frac{d}{dx}[\bar{g}(x)\bar{u}(x)] &= p(x)\bar{u}(x), \\ \bar{u}(0) &= \bar{w}, \\ \bar{g}(x^*)\bar{u}(x^*) - \mu\bar{v} &= 0, \end{aligned}$$

  where $\bar{g}(x) := g(x, \bar{v})$.

- There exists a positive steady state iff $\alpha(0) > 0$ ($a_w > 1/2$). In this case, it is unique.

- Similar condition as in the discrete model, but here no semi-trivial steady states.

Model analysis - Extinction and persistence

Theorem

$\alpha(0) < 0 \longrightarrow$ *extinction at exponential rate,*
$\alpha(0) > 0 \longrightarrow$ *solutions bounded away from zero*

Proof of extinction using entropy

$\gamma w(t) + \int_0^{x^*} e^{-\beta x} u(x,t)dx + e^{-\beta x^*} v$, with $\gamma, \beta > 0$.

Proof of positivity using

$$\frac{dw}{dt} \geq \alpha\left(M_4 w^\gamma\right) w$$

Remark

A similar alternative is found in many other nonlinear structured models (Doumic, Kim, Perthame for CML, Calvez, Lenuzza et al. for prion equations, Bekkal, Brikci, Clairambault, Perthame for cell cycle)

Linearised system and eigenvalue problem

- Characteristic equation in the most general case

$$\Lambda + \mu - \frac{dg}{dv}(x^*, \bar{v})\bar{u}(x^*) =$$

$$= \left(p_w^2 \frac{d\alpha}{dv}(\bar{v}) \frac{\bar{w}}{\Lambda} + \int_0^{x^*} f(s) e^{\int_0^s \frac{\Lambda}{g(\sigma,\bar{v})} d\sigma} ds \right) e^{-\int_0^{x^*} \frac{\Lambda - p(s)}{g(s,\bar{v})} ds}$$

with $f(x) e^{\int_0^x \frac{p(s)}{g(s,\bar{v})} ds} = -\partial_x [\frac{dg}{dv}(x, \bar{v})\bar{u}(x)]$

Simplest case: no feedback on the maturation process $g(x, v) = g(x)$

- Characteristic equation

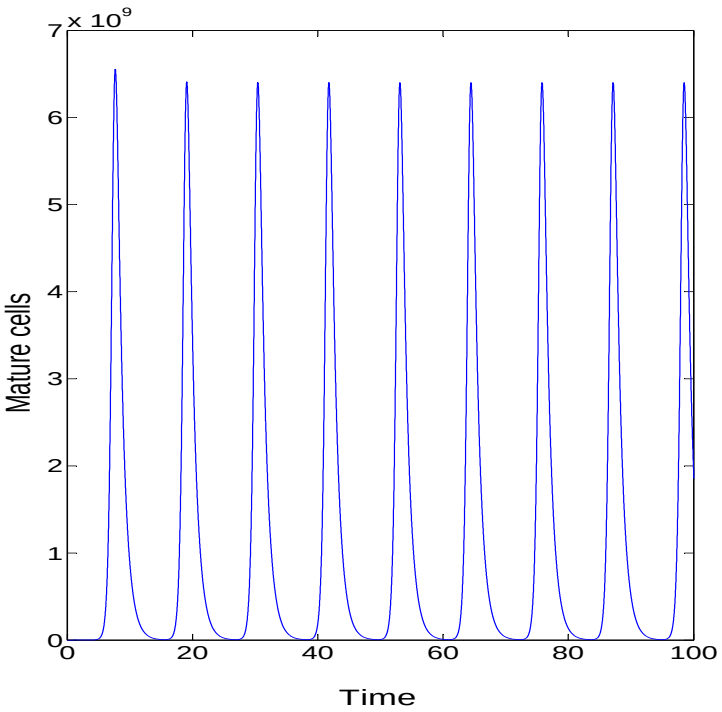
$$\lambda^2 + \mu\lambda = \mu\bar{v}\frac{d\alpha}{dv}(\bar{v})e^{-\tau\lambda}, \qquad \tau = \int_0^{x^*} \frac{1}{g(s)}ds > 0$$

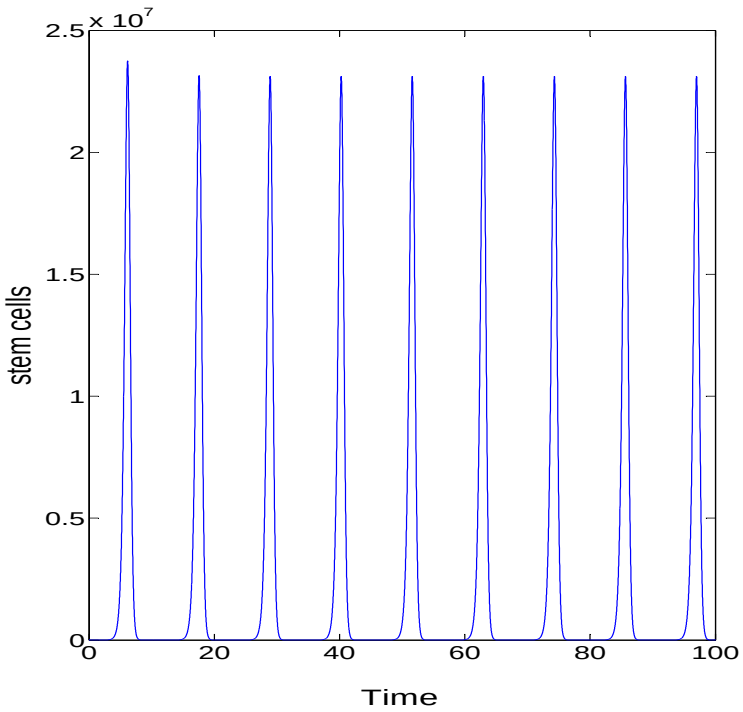
Proposition

Assume that $\alpha(0) > 0$, and g is independent of v. Then,
(i) for $1 < \tau\bar{v}\,|\frac{d\alpha}{dv}(\bar{v})| < \frac{\pi}{2}$, the system undergoes a Hopf bifurcation for a single value $\mu_0 > 0$ of the parameter μ. Therefore the steady state can be either locally stable or unstable.
(ii) Further bifurcations also occur for $\tau\bar{v}\,|\frac{d\alpha}{dv}(\bar{v})| > 2k\pi + \frac{\pi}{2}$ and $k \geq 1$ for at least one value $\mu_k > 0$.

Proof by looking for purely imaginary solutions, which are the places where a bifurcation can occur.

Numerical simulations of the unstable case I





Case motivated by the discrete model

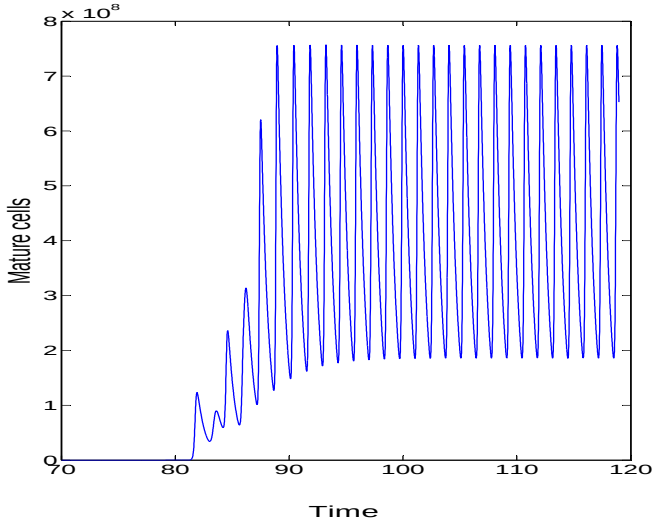
- Case of $\alpha(v) = p_w(\frac{2a_w}{1+kv} - 1)$ and g independent of x

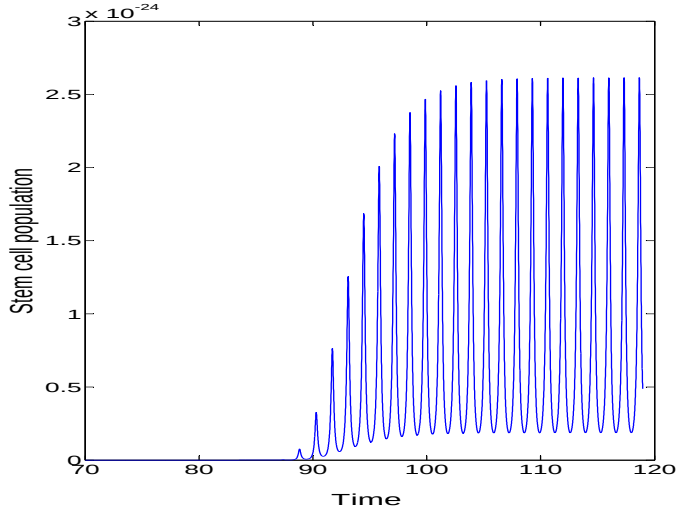
Theorem

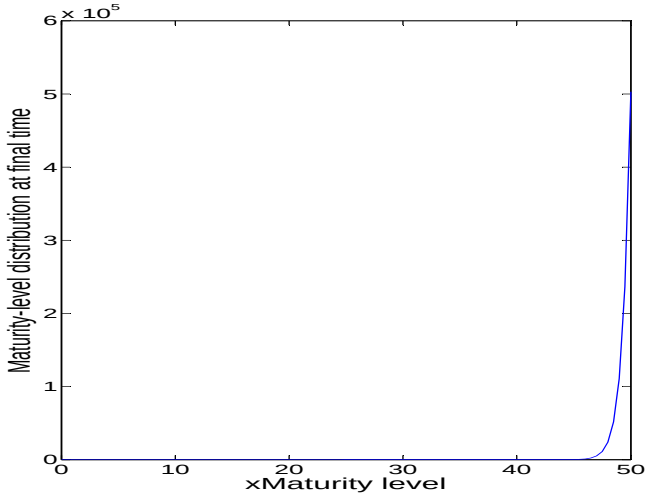
Let $a_w > \frac{1}{2}$, and $(\bar{u}, \bar{v}, \bar{w})$ the unique steady state solution. If the maturation rate $g(x, v)$ is independent of the maturity of the cell x and if the proliferation rate p is constant, then the steady state $(\bar{u}, \bar{v}, \bar{w})$ is locally linearly stable. For a non-decreasing proliferation rate, instability may appear.

Proof using the same ideas, but longer calculations.

Numerical simulations of the unstable case II







Comparison of the models

Discrete differentiation model

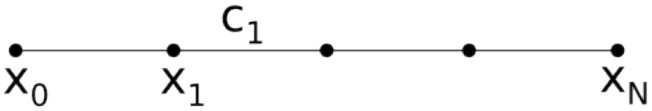
- Trivial steady state - unstable (unless it is the only equilibrium)
- Semi-trivial steady state: $(0, ..0, \bar{u}_k, .., \bar{u}_n)$ - linearly unstable iff there exists a steady state with more positive components
- Unique positive steady state: $(\bar{u}_1, .., \bar{u}_n)$ - globally stable

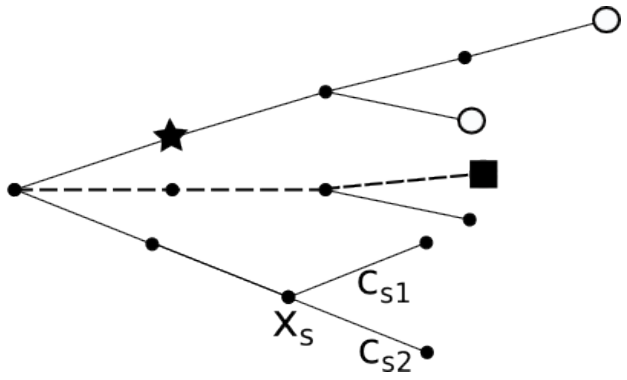
Continuous differentiation model

- There exists a unique positive steady state.
- Similar conditions as in the discrete model, but here no semi-trivial steady states.
- The structure of steady states as in 2-compartment models
- Hopf bifurcation and oscillations possible (as in 3 (and more) - compartment models)

Discrete vs continuous model $\longrightarrow$ challenges

- Unexpected: different structure of steady states.
- It is important to understand the nature of differentiation process (gene expression or epigenetics changes?)
- To include effects of semi-extinction of populations in the structured population approach, it is necessary to allow for the non-Lipschitz velocity function function g and lack of the uniqueness (multistability and hysteresis in the intracellular regulation?)
- Structured population model with measure-transmission conditions (in a spaces of positive Radon measures) can account for both discrete and continuous effects.





Gwiazda, Jamroz and Marciniak-Czochra, SIAM Math Anal, 2012

Stem cells-initiated cancer development

Extension of the model to the case of cancer

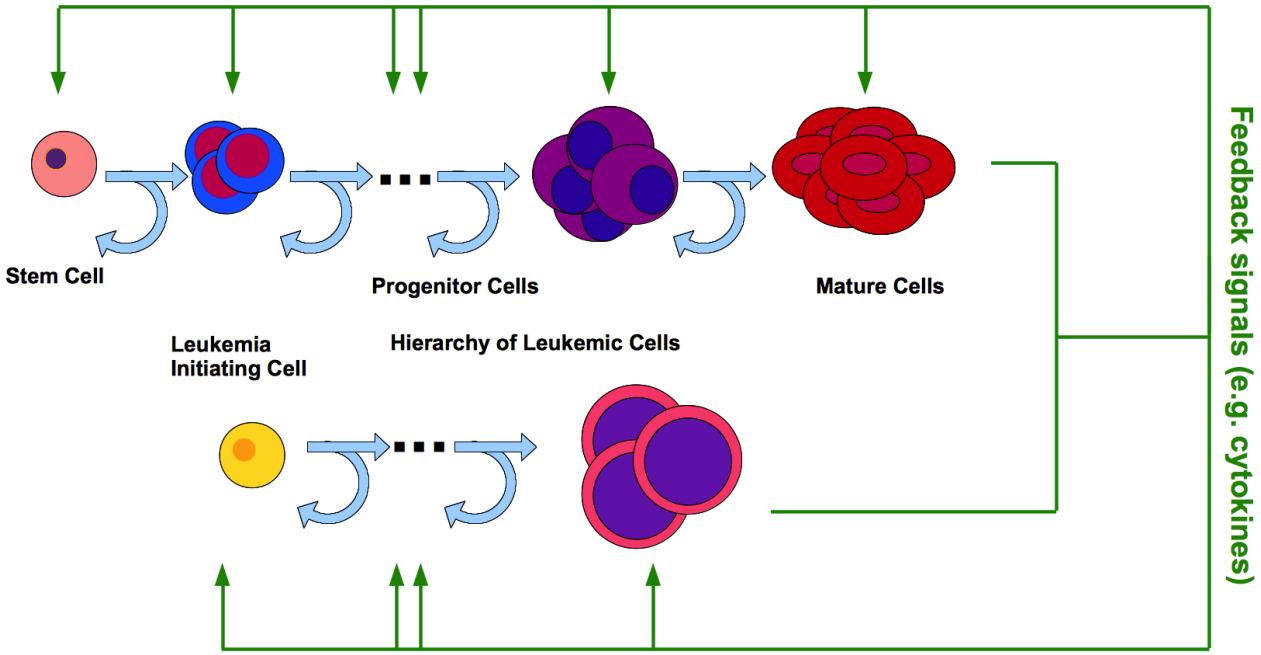
Questions

- What are crucial properties of leukemia initiating cells (LIC) enabling them to establish a leukemic cell population?
- What distinguishes LIC from HSC?
- How do properties of LIC influence treatment response?

Model of leukemia

- We include a leukemic cell line in the model of hematopoiesis
- We do not model the process of mutation.
- We investigate what happens to a (small) population of leukemic cells appearing at time $t = 0$ in the healthy equilibrium.

Model of leukemia



How to model competition between healthy and cancer cells?

- Leukemic cells are sensitive to cytokines of healthy hematopoiesis.
- Cells compete for spatial or environmental resources.

Model of leukemic and healthy cell lines

$$
\begin{aligned}
\frac{d}{dt} l_1 &= (2a_1^l s - 1) p_1^l l_1 - d_1^l l_1 \\
\frac{d}{dt} l_2 &= (2a_2^l s - 1) p_2^l l_2 + 2(1 - a_1^l s) p_1^l l_1 - l_2 d_2^l \\
\dots & \quad \dots \\
\frac{d}{dt} l_{m-1} &= (2a_{m-1}^l s - 1) p_{m-1}^l l_{m-1} + 2(1 - a_{m-2}^l s) p_{m-2}^l l_{m-2} - l_{m-1} d_{m-1}^l \\
\frac{d}{dt} l_m &= 2(1 - a_{m-1}^l s) p_{m-1}^l l_{m-1} - l_m d_m^l
\end{aligned}
$$

$$
\begin{aligned}
\frac{d}{dt} c_1 &= (2a_1^c s - 1) p_1^c c_1 - d_1^c c_1 \\
\frac{d}{dt} c_2 &= (2a_2^c s - 1) p_2^c c_2 + 2(1 - a_1^c s) p_1^c c_1 - c_2 d_2^c \\
\dots & \quad \dots \\
\frac{d}{dt} c_{n-1} &= (2a_{n-1}^c s - 1) p_{n-1}^c c_{n-1} + 2(1 - a_{n-2}^c s) p_{n-2}^c c_{n-2} - c_{n-1} d_{n-1}^c \\
\frac{d}{dt} c_n &= 2(1 - a_{n-1}^c s) p_{n-1}^c c_{n-1} - c_n d_n^c
\end{aligned}
$$

$$
s = \frac{1}{1 + k^c c_n + k^l l_m}
$$

l_i: Leukemic cell line, parameters a_i^l, p_i^l, d_i^l,

c_i: Healthy cell line, parameters: a_i^c, p_i^c, d_i^c,

s: Feedback signal, parameters k^c, k^l

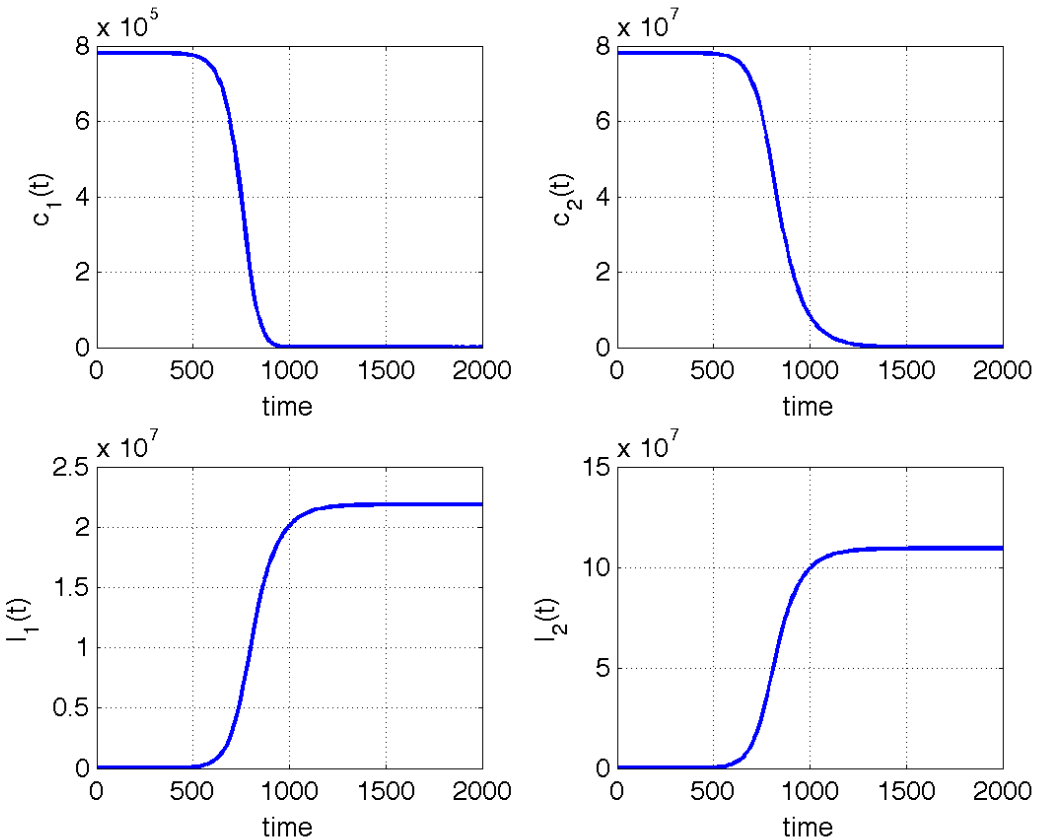
Stiehl and Marciniak-Czochra, Math. Mod. Nat. Phenomena, 2012

Establishment of leukemia: Stability analysis

Question:

What properties are necessary that a small clone of LSC is able to expand?

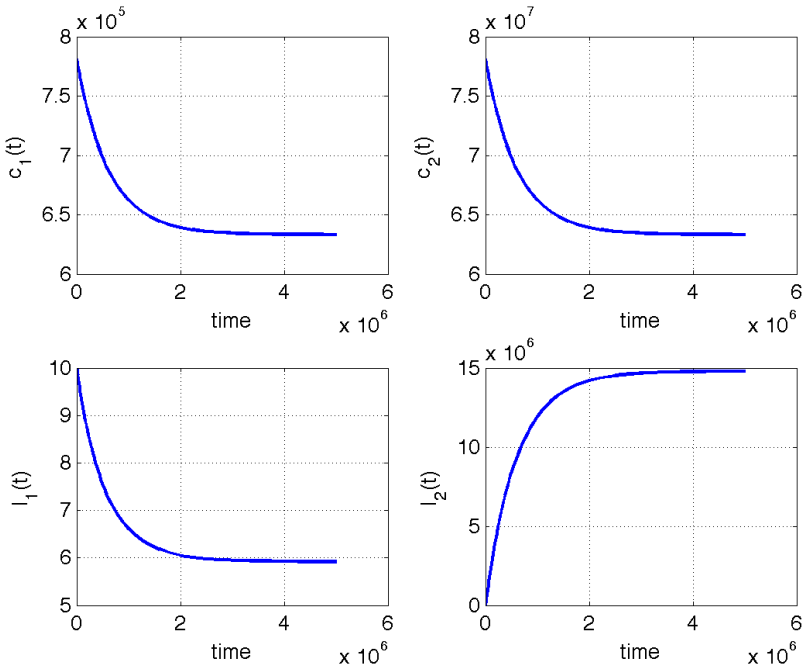
$n = m = 2$

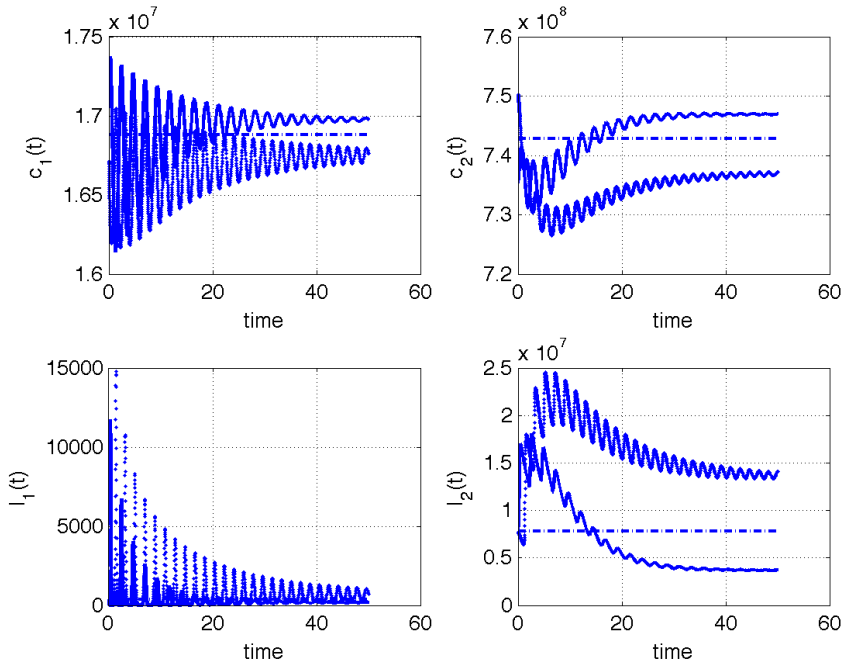


Coexistence of healthy and cancer cell populations

Examples:

- Myelodysplasia, monoclonal gammopathia of unknown significance (MGUS), preleukemic states, chronic phases





Different scenarios of leukemia establishment

- Linearised stability analysis.
- Change of one cell property out of a_1, p_1, d_1 may lead to establishement of leukemia, but with different dynamics.

Example 1

$a_1^l = a_1^c$, $p_1^l > p_1^c$, $d_1^l = d_1^c \neq 0$

Interpretation:

1. Enhanced proliferation in leukemia cells due to mutations (e.g. Burkitt-Lymphoma)
2. Inhibition of proliferation in healthy cells by leukemic cells

Example 2

$a_1^l = a_1^c$, $p_1^l = p_1^c$, $d_1^l < d_1^c$

Interpretation:

1. Reduced apoptosis in leukemia cells due to mutations (e.g. B-CLL)
2. Induction of apoptosis in healthy cells by leukemic cells (e.g. myelodysplastic syndromes)

The role of self-renewal potential

- Enhanced self-renewal is always sufficient to induce leukemia even if the other cell properties are the same as in HSC

Example 3 (the case not understood before)

$a_1^l > a_1^c$, $p_1^l = p_1^c$, $d_1^l = d_1^c$

Interpretation:

1. Enhanced self-renewal in leukemia cells due to mutations (partial or total differentiation block, e.g. acute promyelocytic leukemia)
2. Inhibition of self-renewal in healthy cells by leukemic cells

Implications of the model analysis

- The case $a_1^l = a_1^c$, $p_1^l > p_1^c$, $d_1^l = d_1^c = 0$ always leads to existence of multiple steady states where leukemic and healthy cells coexist
- This is not necessarily the case if $a_1^l > a_1^c$, $p_1^l = p_1^c$, $d_1^l = d_1^c$.
- Since mixed steady states may cause less severe symptoms, changes in differentiation behaviour may be more severe than increased proliferation.
- Even if leukemic cells divide slower than hematopoietic cells, establishment of a leukemic population is possible.
- It may lead to a reduced /absent efficacy of chemotherapy.
- Slow dividing LSC need large self-renewal to establish. The disease establishes slow, but may be resistant to the classical chemotherapy.

Models of clonal evolution in acute leukemias

Clonal evolution (AML)

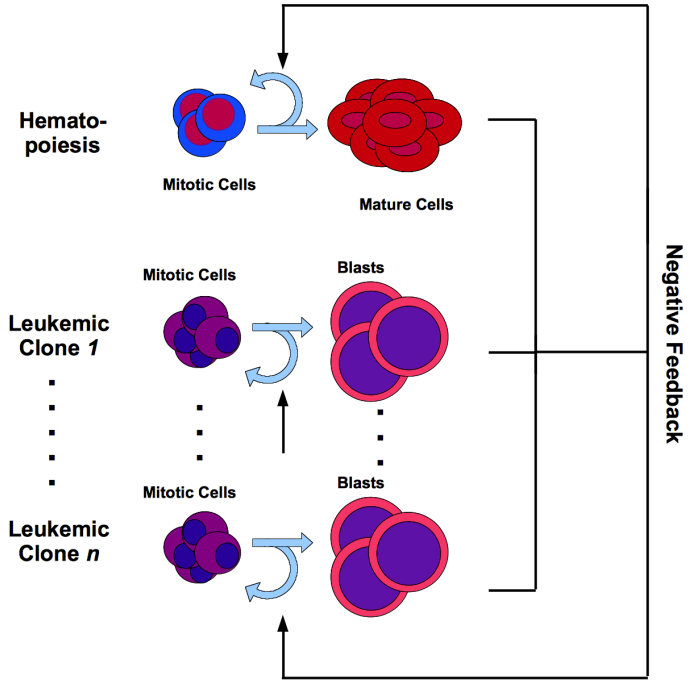
Recent Experimental Findings

- Deep sequencing techniques allow to study the clonality and clonal evolution patterns in leukemias (Ding et al, Nature 2012)
- Primary manifestation as well as relapses involve only few clones
- 2 major evolution patterns have been defined:
  1. Repeating clones
  2. Related but different subclones.

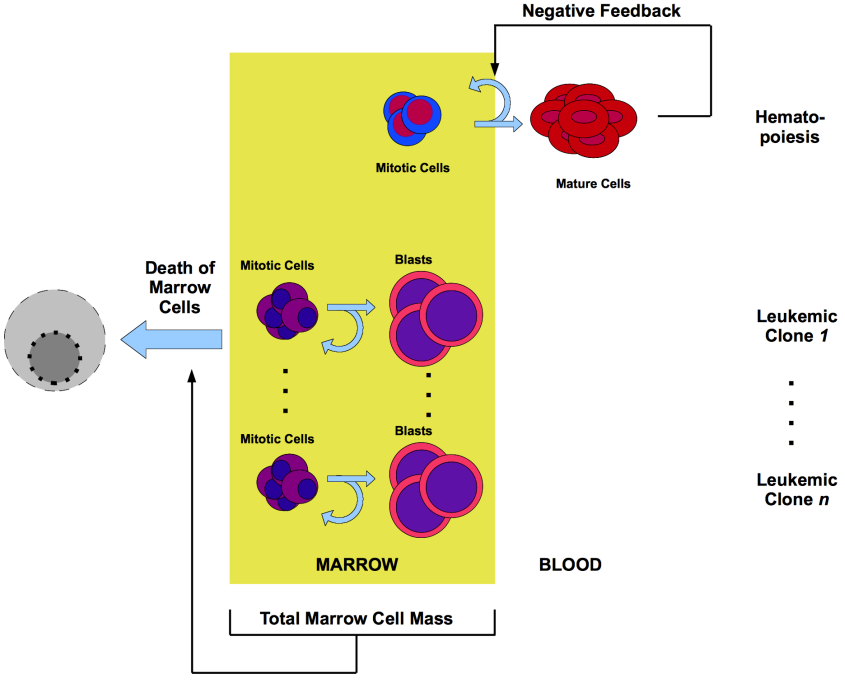
Open Questions

- Why is the number of observed clones relatively small?
- Which properties allow (sub-)clones to survive to generate relapses?
- What could be clinical implications of the sequencing studies?

Multi-clonal models



Competition for surviving factors

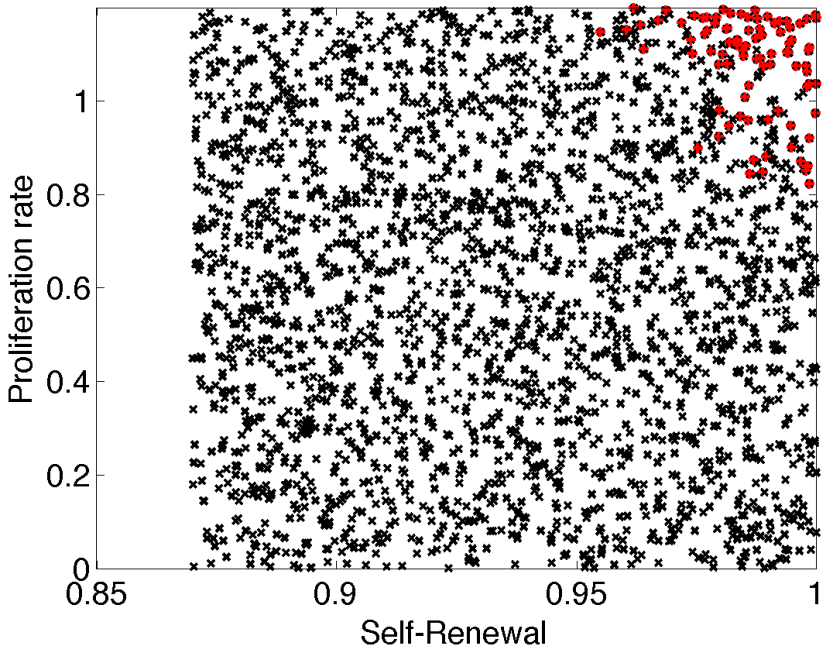


Competition for space

- Initially m clones with varying cell properties
- We do not model mutations
- Results independent of the choice of plausible regulation

Stiehl, Baran, Ho and Marciniak-Czochra, JRS Interface, 2014

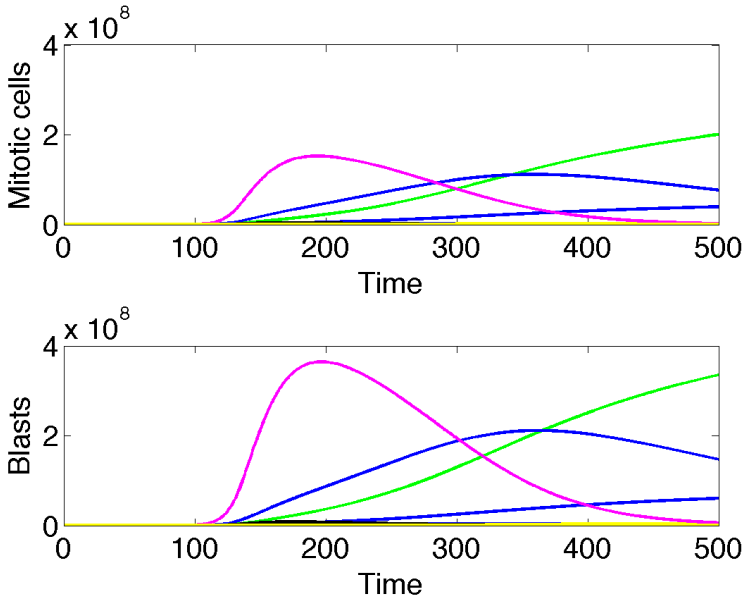
Characteristics at diagnosis



- **Simulation:** Evolution of 50 different clones in 50 patients
- **Conclusion:** Cells at primary manifestation have high proliferation and high self-renewal

Number of clones contributing to cell mass

Independently of the number of clones present at time 0, the number of clones significantly contributing is rarely higher than 5.



- **Conclusion:** Clonal selection is a dynamic property reducing the number of relevantly contributing leukemic clones
- Mathematical analysis shows a selection process even if the number of initial clones tends to ∞

Structured population model of clonal evolution

Model structured by a self-renewal potential

$$\begin{aligned}
\partial_t u_1(t,x) &= \left(\frac{2a(x)}{1+K\rho_2(t)} - 1\right) p u_1(t,x), \\
\partial_t u_2(t,x) &= 2\left(1 - \frac{a(x)}{1+K\rho_2(t)}\right) p u_1(t,x) - d u_2(t,x),
\end{aligned}$$

where $\rho_i(t) = \int_\Omega u_i(t,x)dx, \quad i = 1,2$

- Assumptions: p, d and K are positive constants
- $a \in C(\overline{\Omega})$ with $\frac{1}{2} < a < 1$

Main result: Clonal selection

Theorem

(i) *Both u_1 and u_2 converge to measures with support contained in the set*

$$\Omega_a = \arg\max_{x\in\overline{\Omega}} a(x) = \left\{ \bar{x} \in \overline{\Omega} \,\middle|\, a(\bar{x}) = \max_{x\in\overline{\Omega}} a(x) \right\}$$

as t tends to infinity.

(ii) *If Ω_a consists of a single point $\bar{x}$, then the solution converges to a stationary measure (Dirac measure multiplied by a positive constant) concentrated in $\bar{x}$.*

(iii) *If Ω_a is a set with positive measure, then the solutions converges to a discontinuous bounded function.*

We present main steps of the proof.

1. Boundedness and positivity of masses.

Lemma

Both ρ_1 and ρ_2 are uniformly bounded and strictly positive.

Proof.

- Showing uniform boundedness of $U(t,x) = \frac{u_1(t,x)}{u_2(t,x)}$, we obtain

$$\int_\Omega u_1(t,x)dx \leq M_1 \int_\Omega u_2(t,x)dx = M_1\rho_2(t)$$

- and using it to estimate the first equation, we obtain boundedness of masses.
- Boundedness of ρ_2 allows to show positivity of ρ_1 by showing uniform boundedness of $\frac{\rho_2}{\rho_1^\gamma}$ for some $0 < \gamma < 1$ (and hence also of ρ_2).

2. Exponential extinction of solutions in $x \notin \Omega_a$

Lemma

Let $x_1, x_2 \in \Omega$ such that $a(x_1) - a(x_2) < 0$. Then,

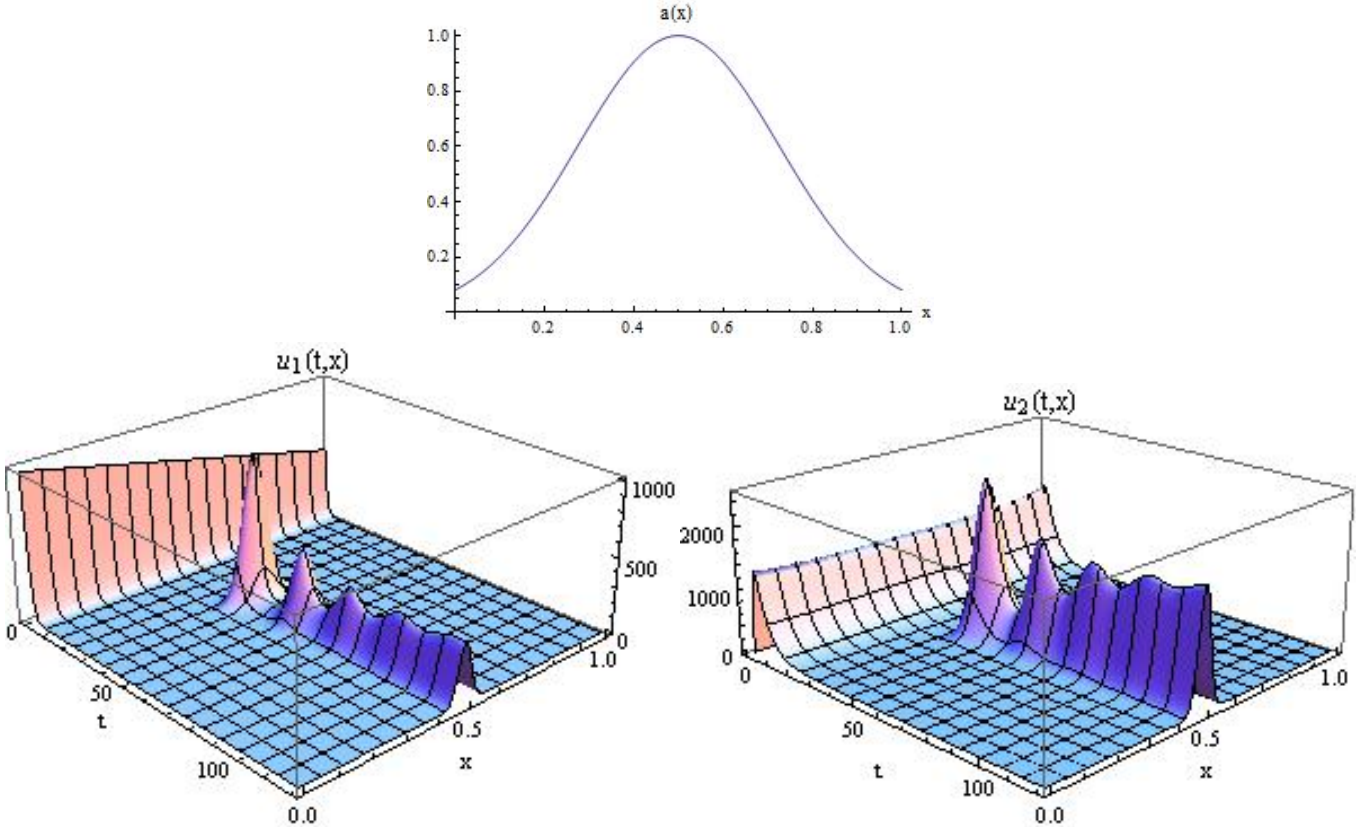
$$\frac{u_1(t,x_1)}{u_1(t,x_2)} = \frac{u_1^0(x_1)}{u_1^0(x_2)} e^{p\frac{2\left(a(x_1)-a(x_2)\right)}{1+KM_3}t} \overset{t\to\infty}{\longrightarrow} 0.$$

- **Proof.** Choosing two points $x_1, x_2 \in \Omega$ such that $a(x_1) - a(x_2) < 0$, and calculating

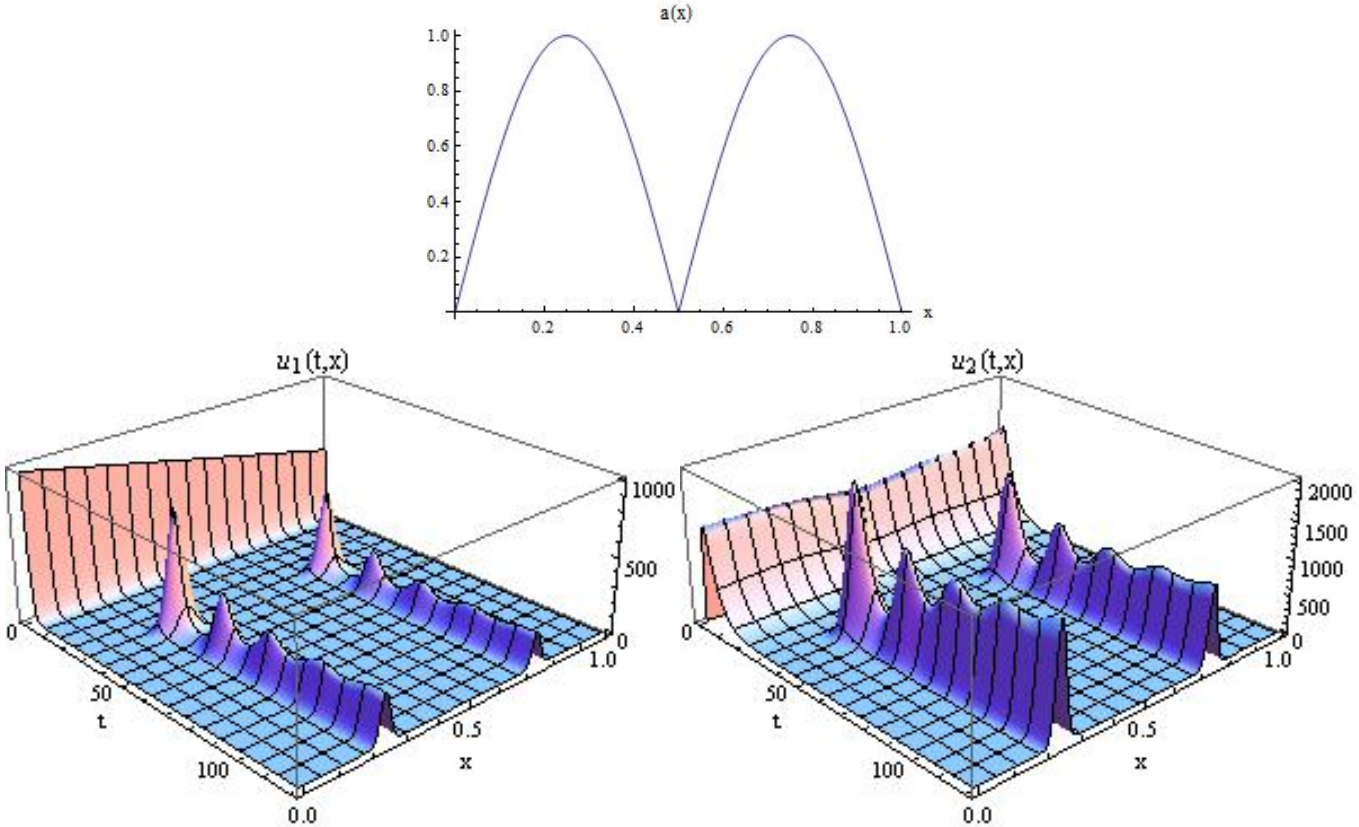
$$\partial_t \frac{u_1(t,x_1)}{u_1(t,x_2)} = p\frac{u_1(t,x_1)}{u_1(t,x_2)}\left(2\frac{a(x_1)-a(x_2)}{1+\rho_2(t)}\right).$$

- The Lemma implies that the solution decays exponentially to zero in all points x except those with maximal value of $a(x)$.
- Strict positivity of masses excludes extinction of the solution
- Together with boundedness of mass, it leads to the conclusion that the model solutions converge to Dirac measures localised in points corresponding to the maximum of function a.

Simulations of a single clone selection



Simulations of multiple clones selection



Stationary solutions

- Masses $(\bar{\rho}_1, \bar{\rho}_2)$ given by

$$\begin{aligned} \bar{\rho}_2 &= \frac{2 \max a - 1}{K}, \\ \bar{\rho}_1 &= \frac{d\bar{\rho}_2}{p} \end{aligned}$$

- Infinitely many steady states explaining coexistence of several clones with sizes dependent on initial data
- Proof of the stability is based on the Lyapunov function for the discrete model and the following comparison result,

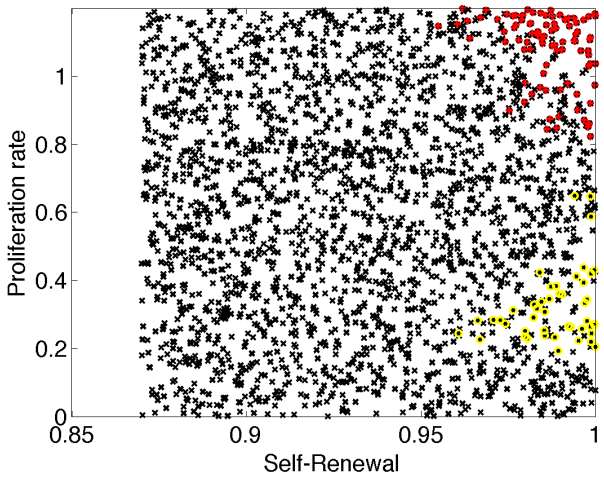
Lemma

Let u be a solution of $\frac{du}{dt} = F(u)$ with a globally stable stationary solution $\bar{u}$ and let $V(u)$ be a Lyapunov function for this equation with compact level sets and the minimum δ achieved at the stationary solution $\bar{u}$. If $\tilde{u}$ is a solution of $\frac{d\tilde{u}}{dt} = F(\tilde{u}) + f$, where $f \in L^1(\mathbb{R}^+)$, then $\tilde{u} \to \bar{u}$ for $t \to \infty$.

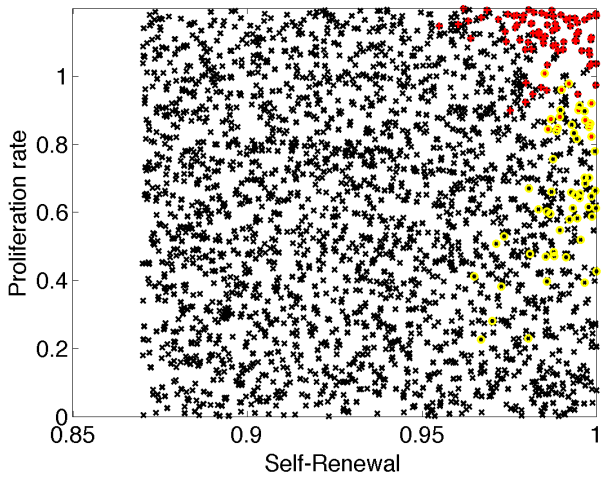
Application to therapy and cancer relapse

Cellular Properties at Relapse

Strong Chemotherapy



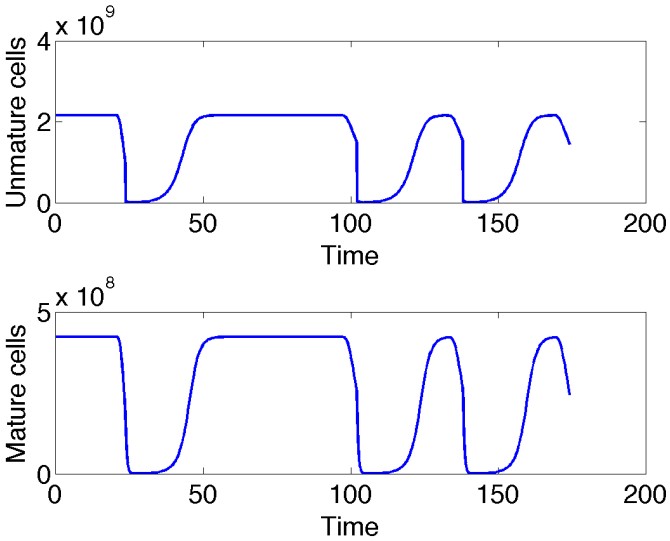
Weak Chemotherapy



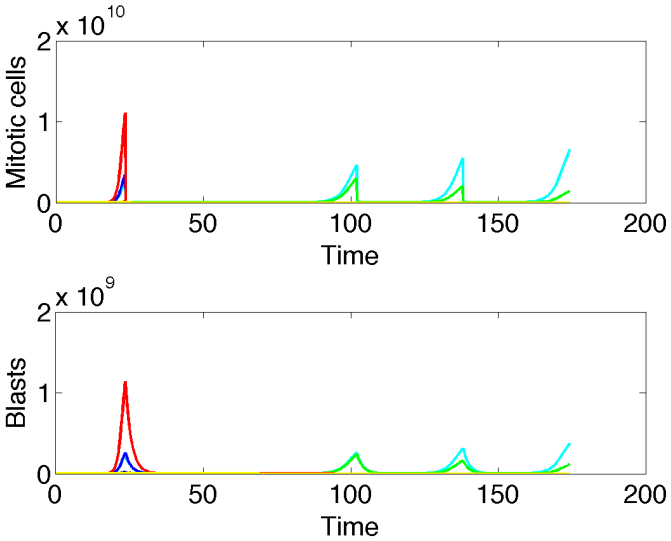
- (Sub-)clones already present at diagnosis but not contributing to cell mass can survive therapy and trigger relapse
- Chemotherapy influences cell properties at relapse
- Chemotherapy selects for slowly proliferating cells with high self-renewal

Iterated Therapy

Healthy

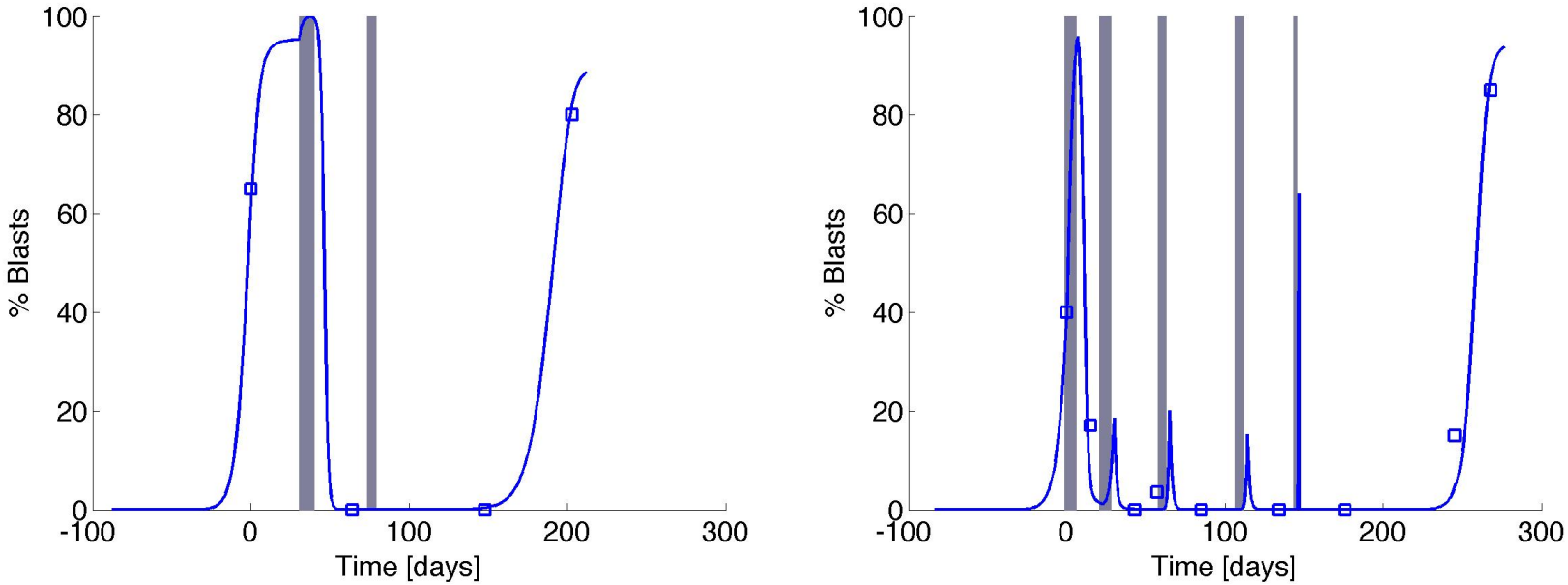


Leukemic



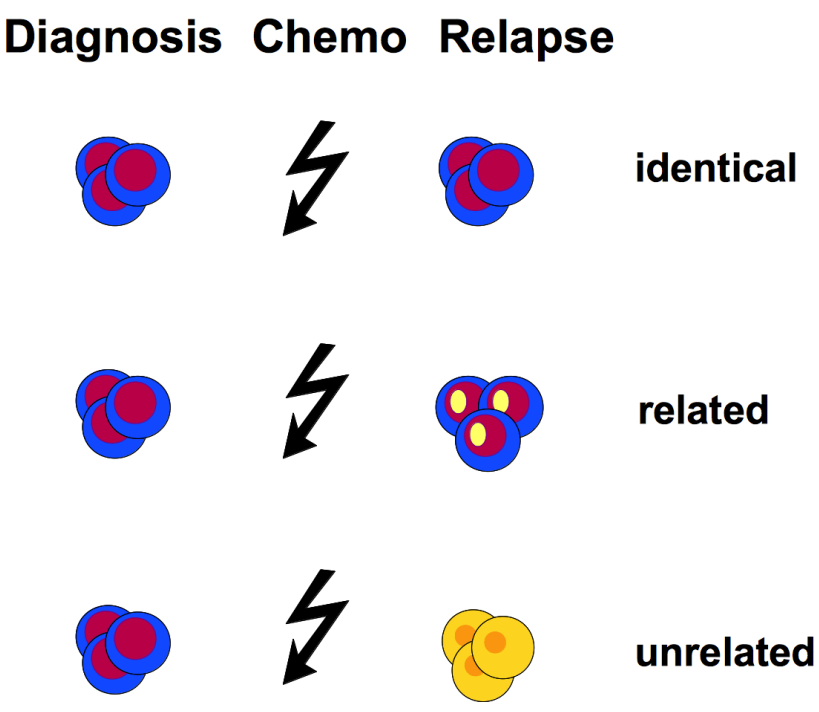
- Identical treatment of primary manifestation and relapse may be insufficient
- Different relapses may be triggered by the same clones
- High self-renewal and low proliferation leads to a high resistance to chemotherapy

Comparison to Data



Fit of the Model to blast dynamics of two patients.

Clinical Implications



Possible Conclusions

$\Rightarrow$ Insufficient therapy (low dose, resistance, slow proliferation)

$\Rightarrow$ Probable properties: high self-renewal, slow proliferation

$\Rightarrow$ No conclusions possible

To think of:

- How to attack slowly proliferating cells ?
- How to reduce self-renewal (enhance asymmetric cell divisions)?

Perspectives

What do we need?

- Data of the processes; given in different time points; for different subpopulations, distinguishing between normal and cancer cells.
- Better understanding of the process of cell differentiation.

Mathematical challenges

- Models of multiscale processes; including heterogeneity of cell cycle and cell clones
- Parameter estimation
- Stochasticity
- Coupling space and structure
- Stability of new models

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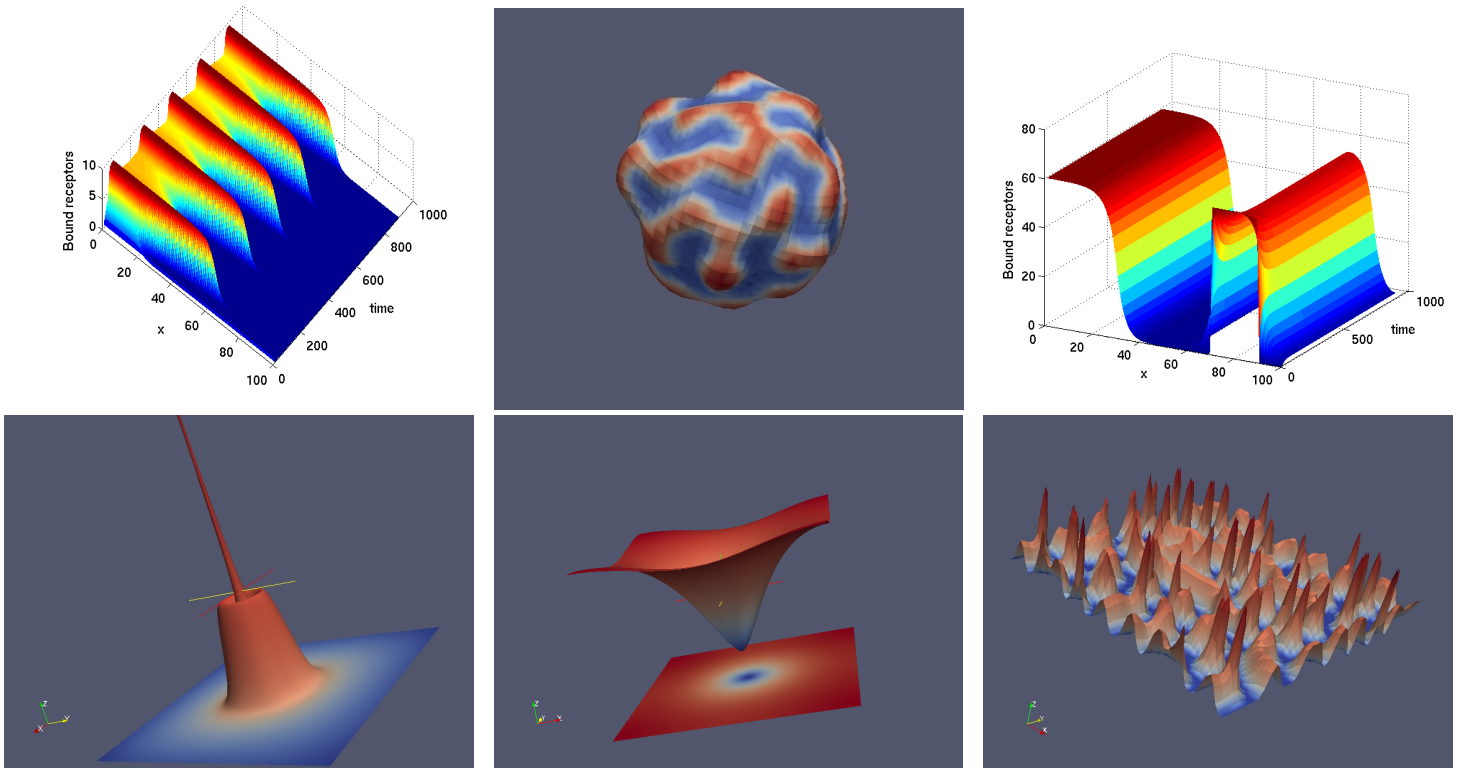
Bound receptors
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200
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Bound receptors
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time
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Thank you!