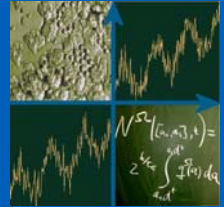# Quantitative lineage specification: mathematical modeling and biological implications

51. GMDS-Jahrestagung, Leipzig, 12. September 2006

Ingmar Glauche
Ronny Lorenz
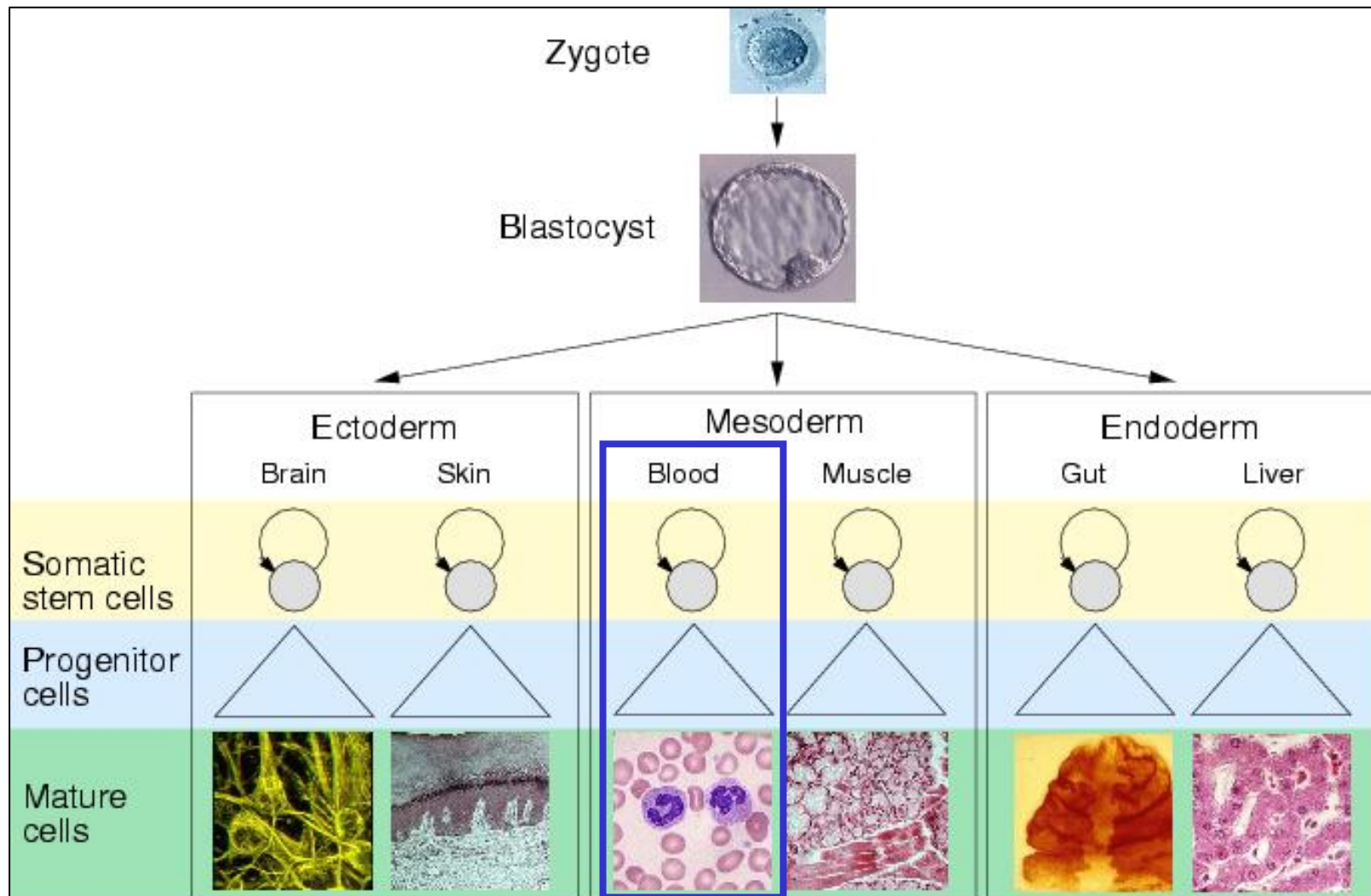**Markus Löffler**
Ingo Röder

DYNAmical MOdeling of Tissue Stem Cell Organization

imise.

Institut für Medizinische Informatik, Statistik und Epidemiologie
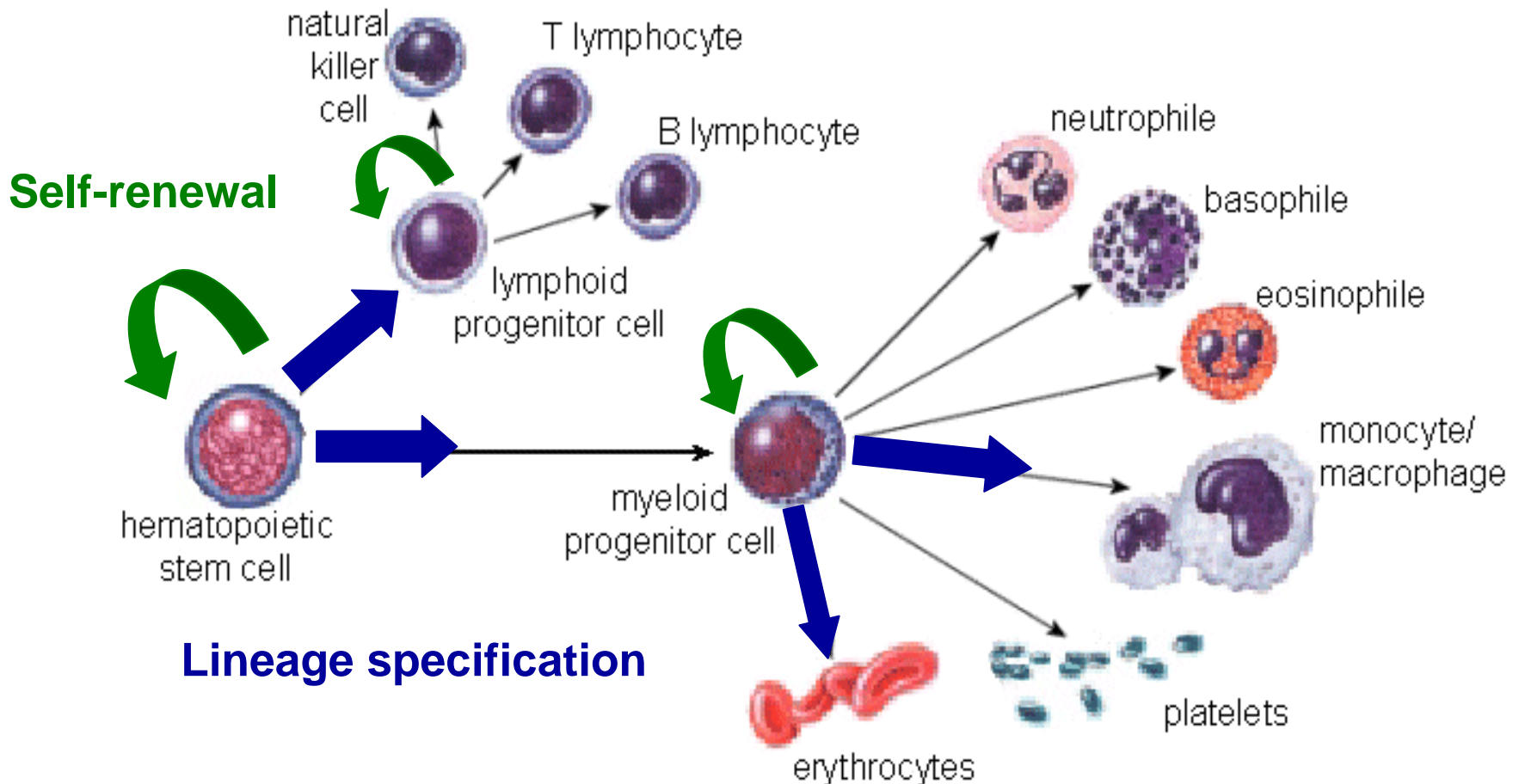
Tissue stem cell systems

after G. Wei, et al. (2000), Stem Cells, 18(6):409

The hematopoietic system
(Classical hierarchy structure)

Self-renewal

Lineage specification

after Kirschstein and Skirboll, 2001
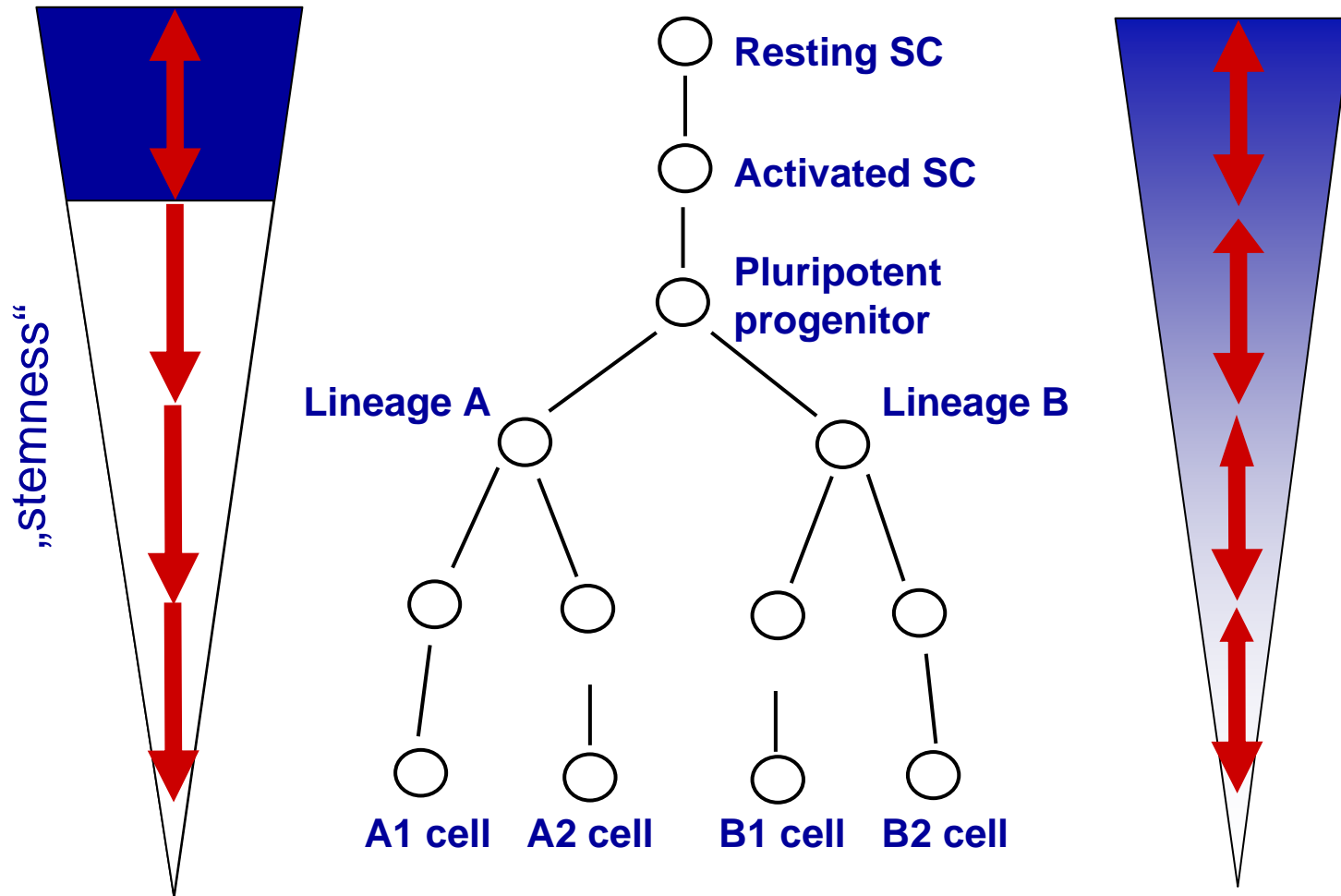
Observed Phenomena

- **Heterogeneity of stem cell populations**
  - Repopulating ability
  - Cycling activity
  - Phenotypic markers
  - Lineage development

- **Microenvironmental dependence**
  - Cytokine regulation
  - Stem cell / stroma interaction
  - Tissue (stem cell) plasticity

- **Clonal fluctuation / competition**
  - Fluctuating contribution of clones
  - Dis- and reappearance of clones
  - Fluctuations of individual clones size and lineage contribution

- **Flexibility / reversibility (within-tissue plasticity)**
  - Cycling status
  - Phenotype (e.g. adhesion molecules)
  - Lineage commitment

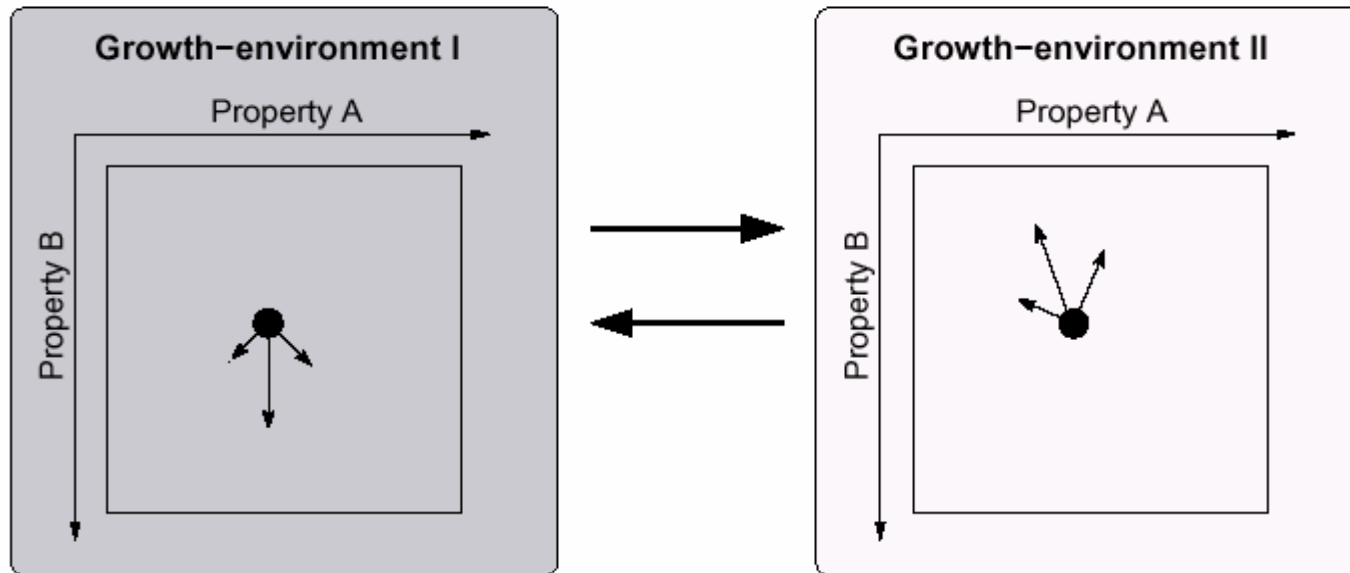# Changing the view on stem cell organization

Traditional concept based on unidirectional hierarchy

Continuum concept including reversible developments

„stemness"

Resting SC

Activated SC

Pluripotent progenitor

Lineage A

Lineage B

A1 cell   A2 cell   B1 cell   B2 cell

Plasticity concept of stem cell organisation
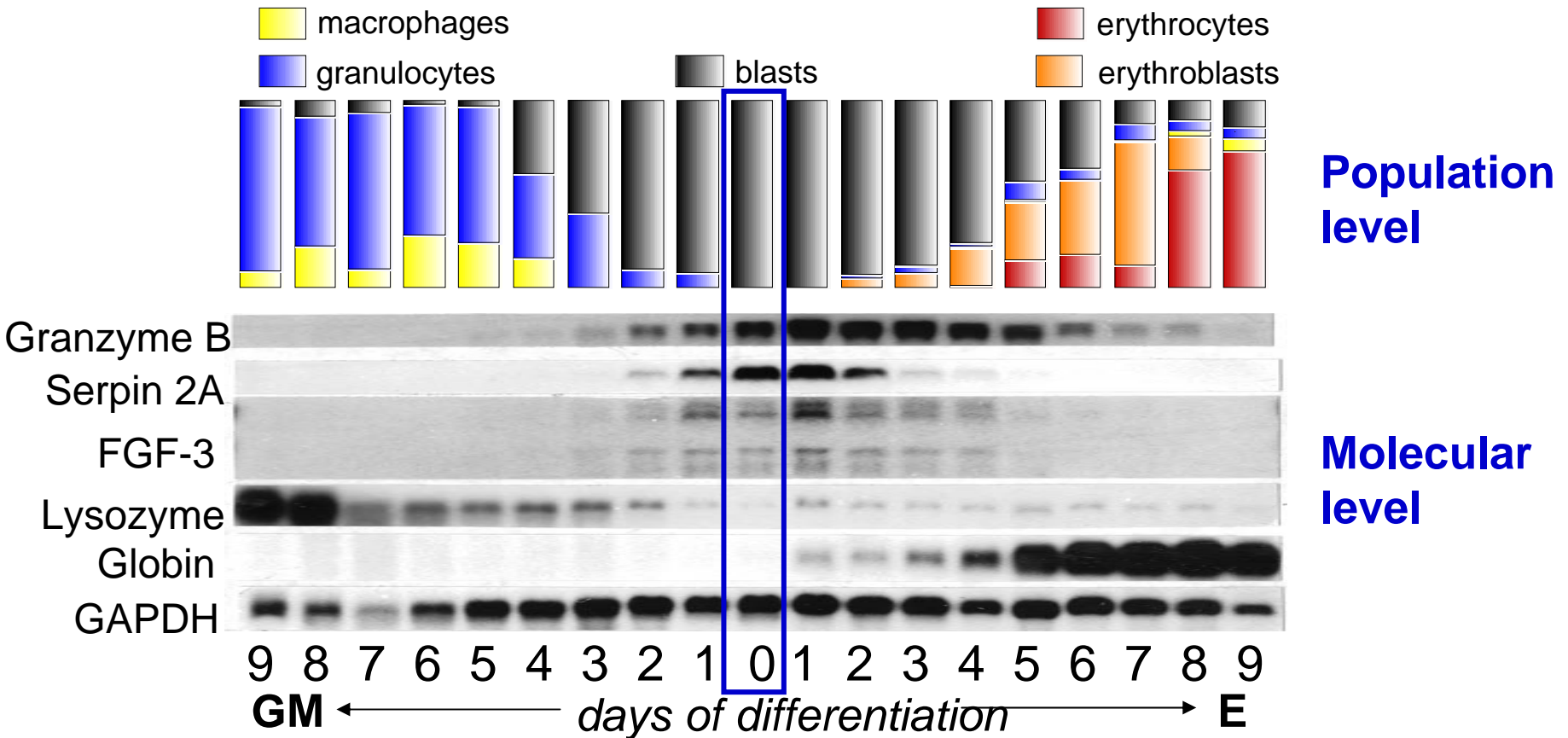The role of the microenvironment

quantitative model is successfully applied to describe self-renewal and differentiation of hematopoietic stem cells (Roeder and Loeffler, 2002)

Is lineage specification organized in a similar context?
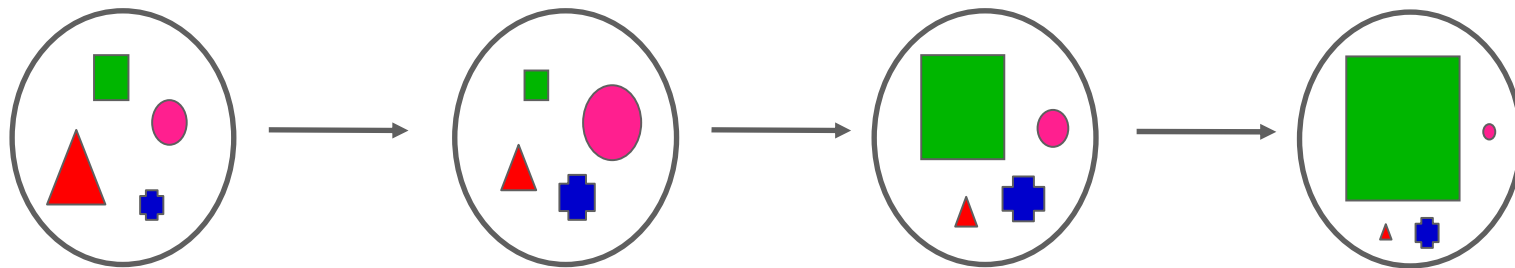
Phenomenology

FDCPmix cell differentiation in vitro

Gratefully provided by Michael Cross

Phenomenology
The simplified view

Priming:
Low level co-expression of potentially antagonistic factors

Differentiation:
Dominance of transcription factors that are specific for a particular lineage

Conceptual model of lineage specification

Central idea: Lineage specification as a competition process between mutually interacting components (lineage specific factors):

Assumptions:

• All transcription factors, that code for a common cell fate, are summarized into one generic lineage specific factor

• Complex interaction mechanisms are comprised into two antagonistic control regimes
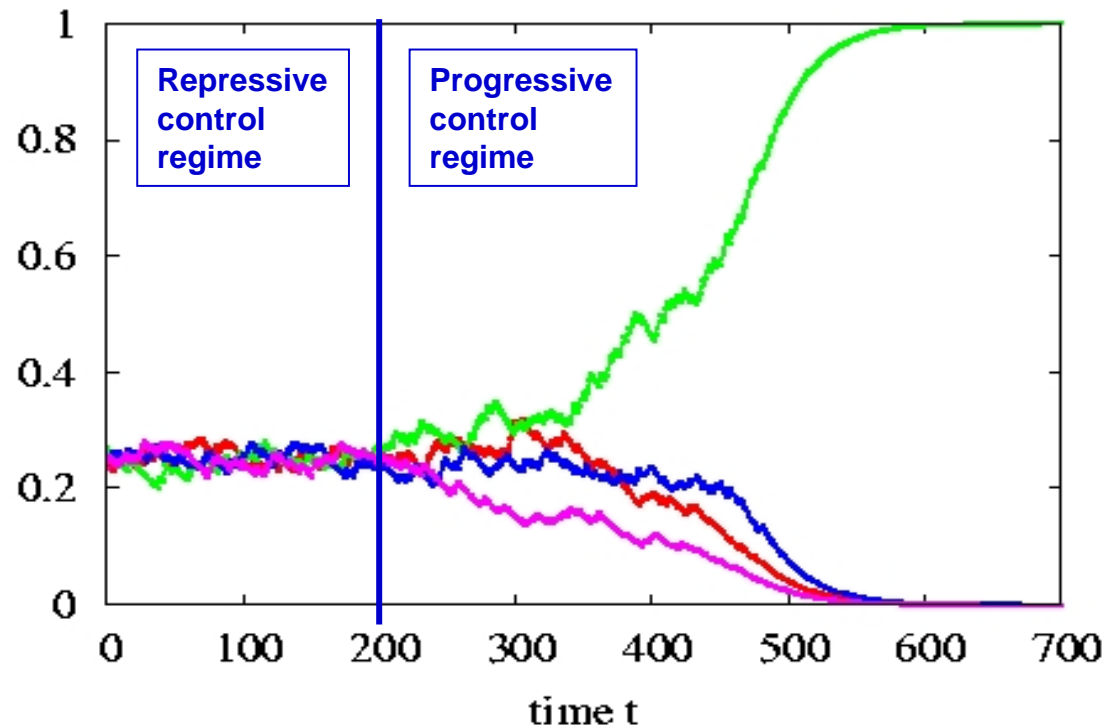
-> simplified picture of the intra-cellular dynamic

Conceptual model of lineage specification

Technical details - A stochastic decision process

- each cell is defined by an intrinsic set of factors $\mathbf{x}(t) = (x_1(t), x_2(t), \ldots)$ with $\sum_j x_j(t) = 1$

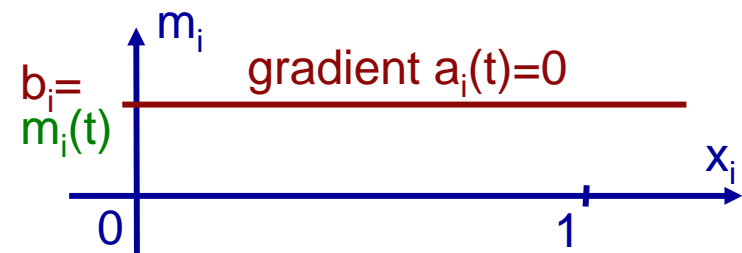- in each time step a lineage i is chosen randomly with a probability $p_i = x_i$

- x_i is updated as
$$x_i(t+1) = x_i(t)(1 + m_i(t))$$
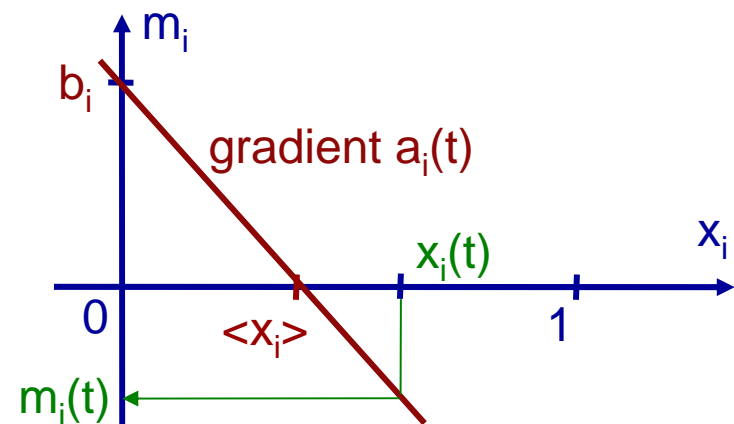
  with multiplier
$$m_i(x_i(t), t) = -a_i(t)x_i(t) + b_i$$

- $\mathbf{x}$ is normalized again according to $\sum_j x_j = 1$

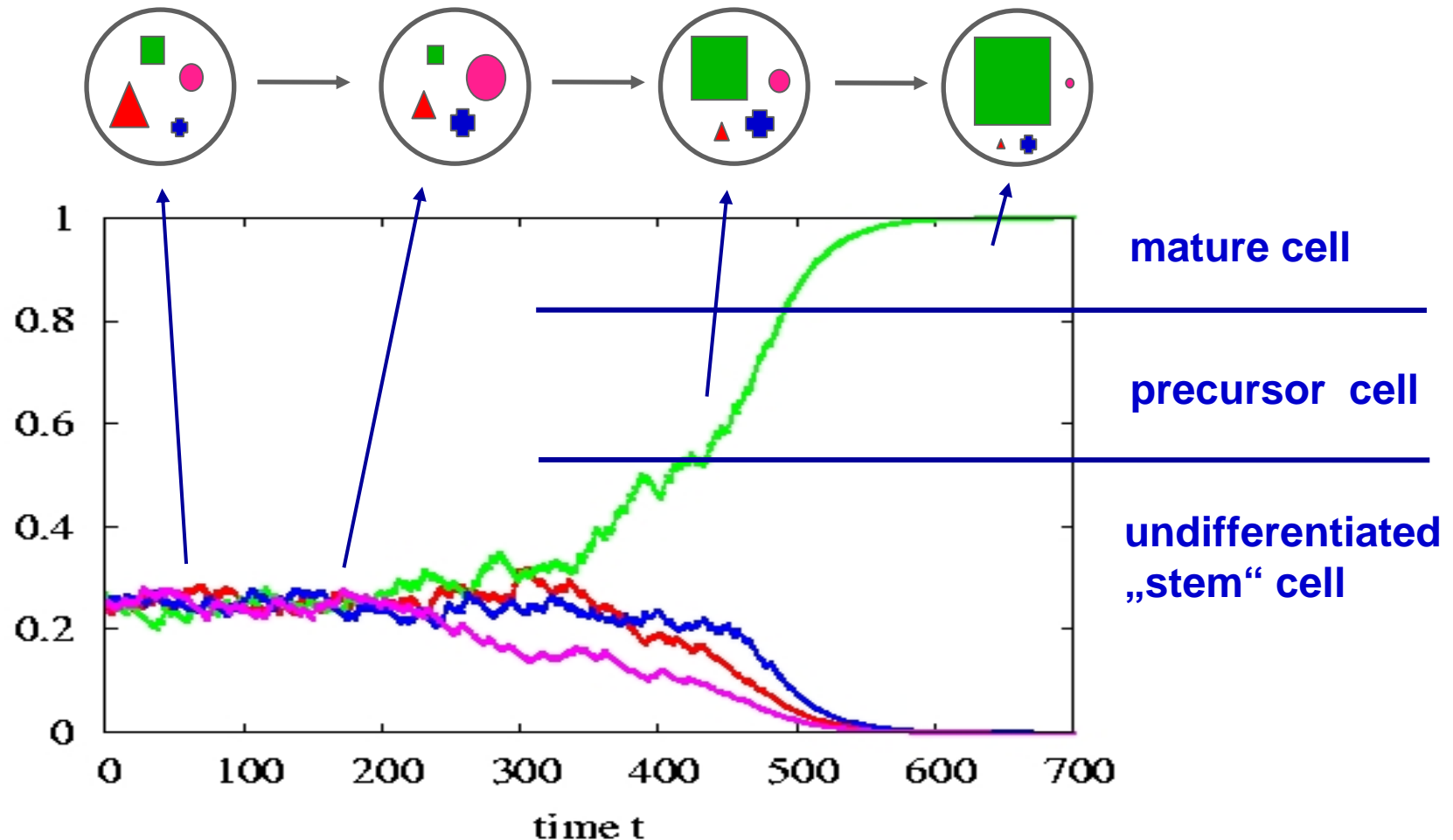**Progressive control regime**
promotes the chosen lineage

m_i

$b_i = m_i(t)$ gradient $a_i(t) = 0$

x_i

0   1

Repressive control regime
equalizes the system

m_i

b_i

gradient $a_i(t)$

$x_i(t)$

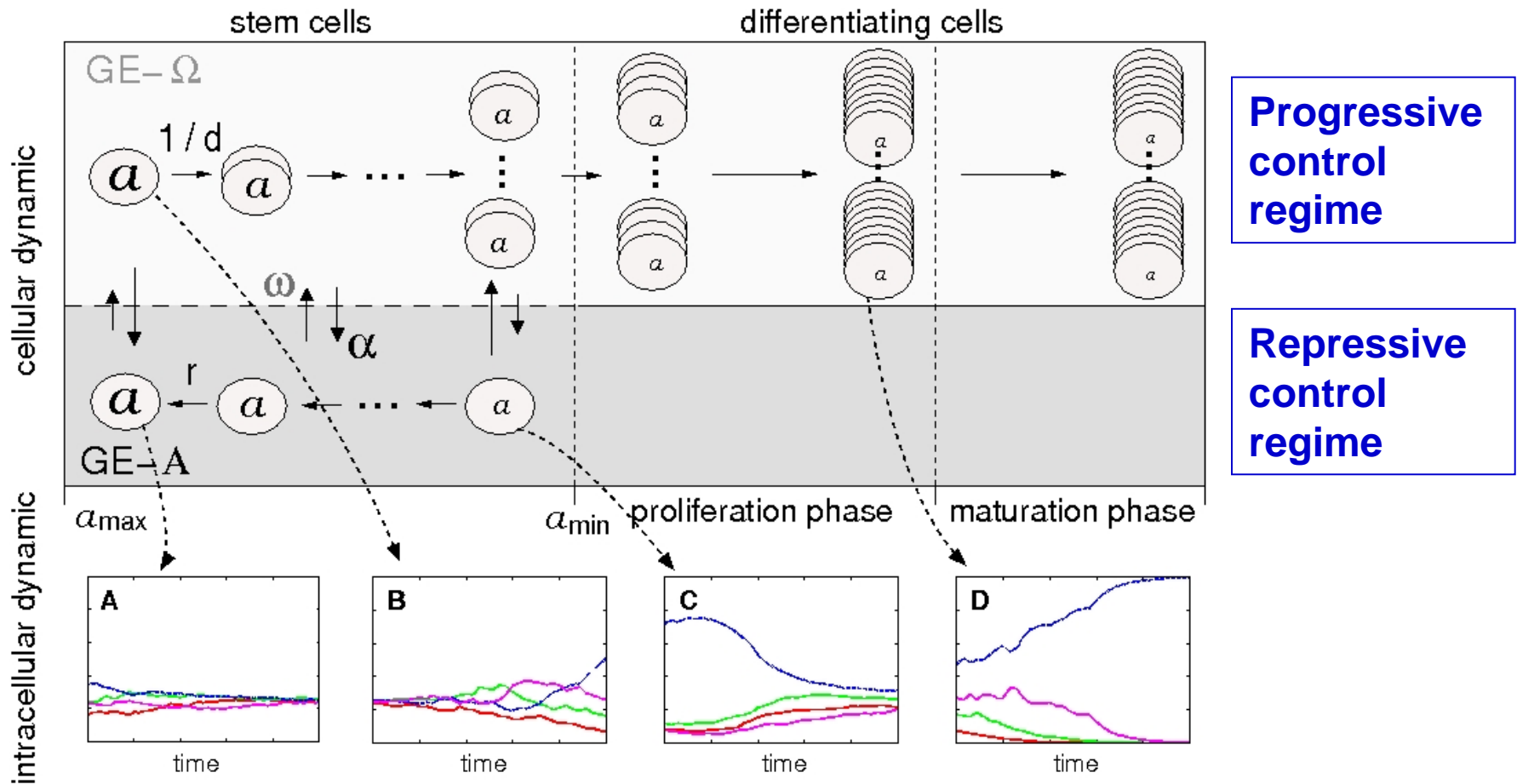x_i

0    $<x_i>$ 1

$m_i(t)$

Conceptual model of lineage specification

Mapping phenotypes

Conceptual model of lineage specification

Incorporation into the stem cell model (Roeder & Loeffler)

Progressive control regime
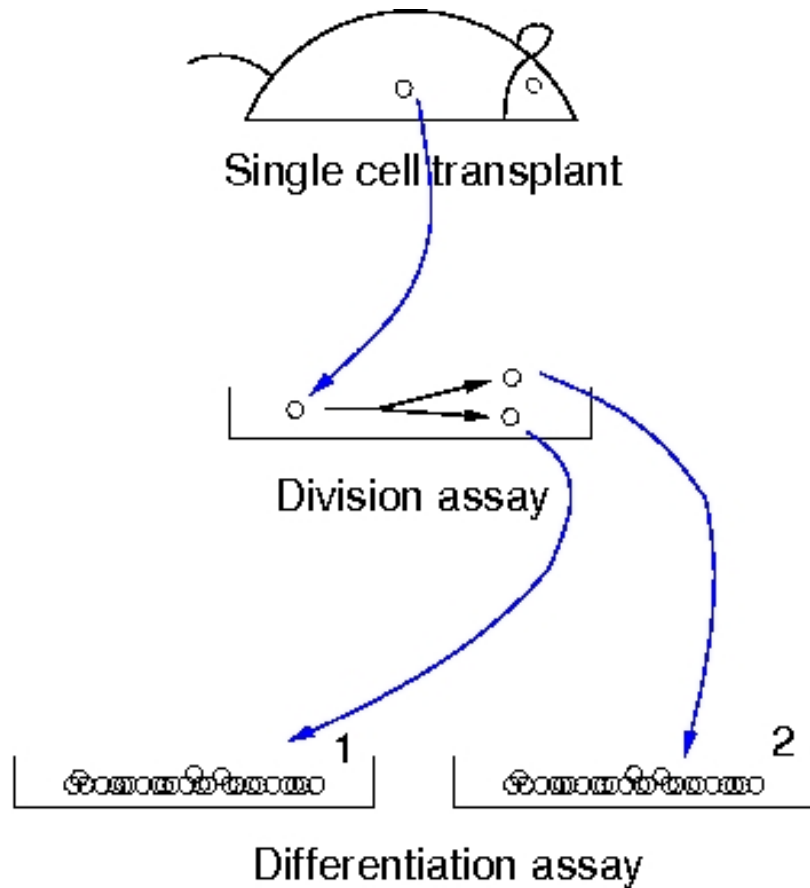
Repressive control regime
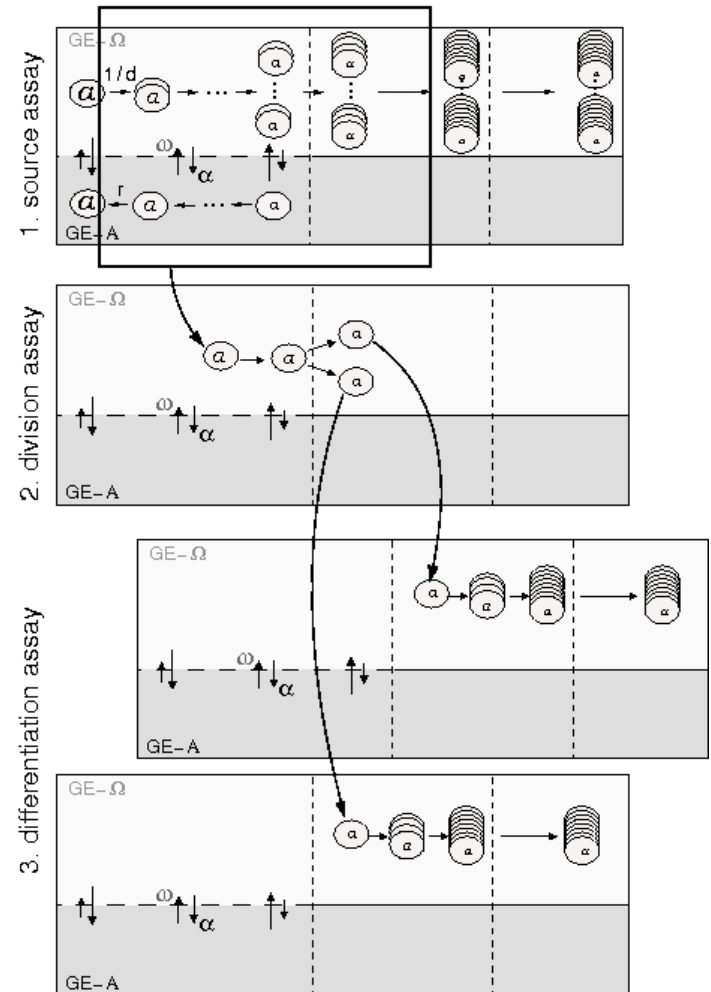
Reversibility as an emerging consequence

Single cell differentiation
Experiments with identical daughters

Experimental strategy suggested
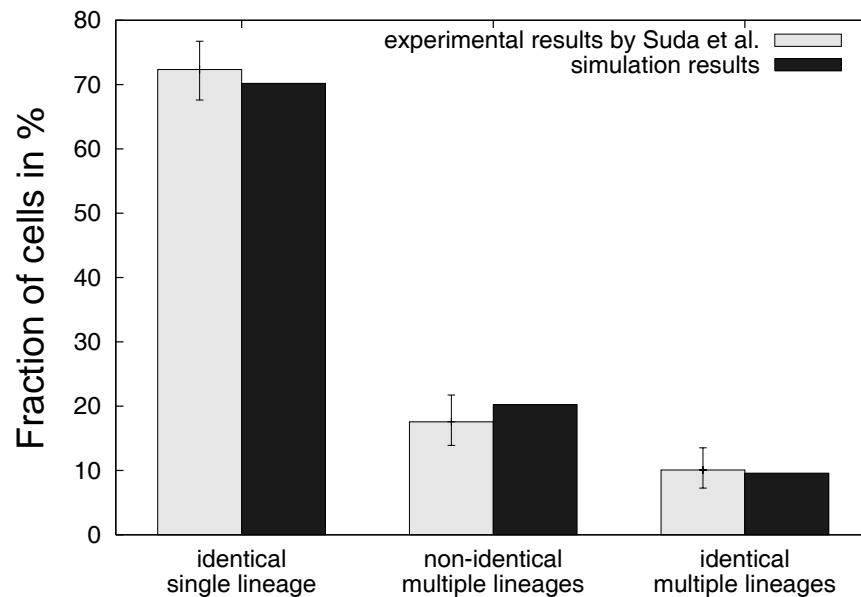by Suda et al., 1984

Simulation setup
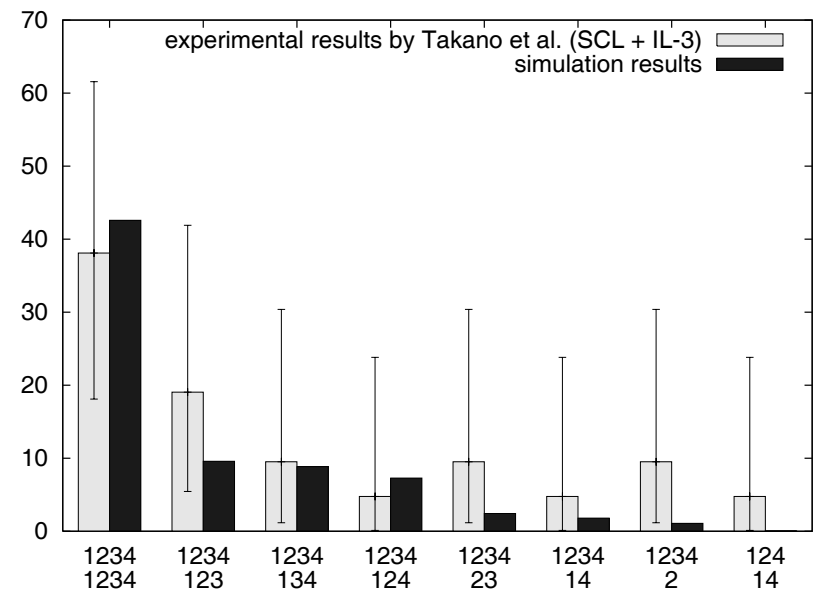
Single cell differentiation
Simulation results

Comparison of the experimental data with the simulation results
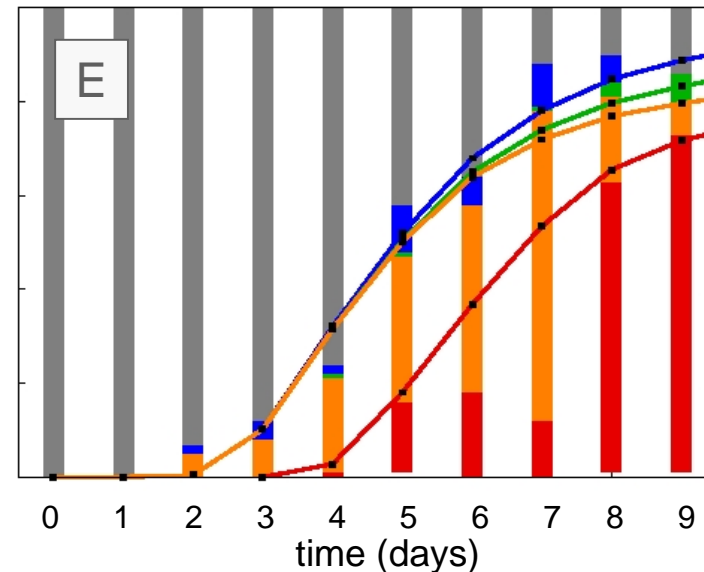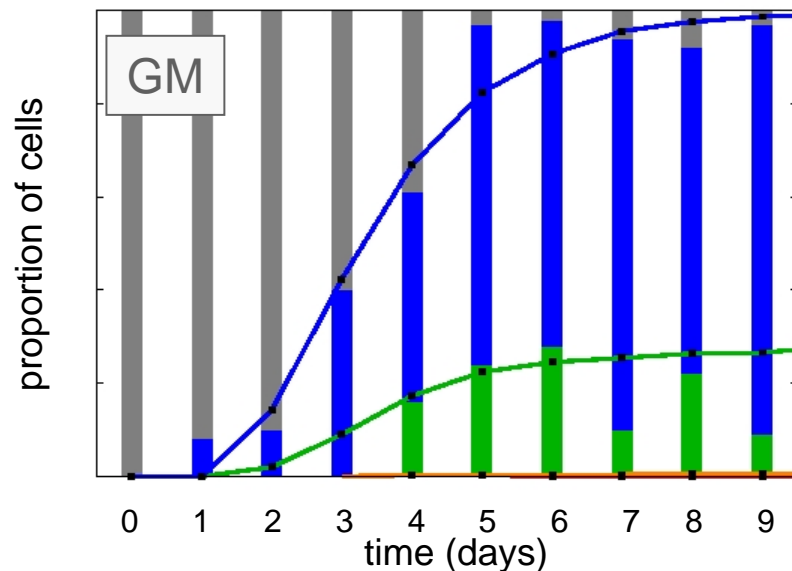
Suda et al., 1984

Takano et al., 2004

imise.

DYNAMO
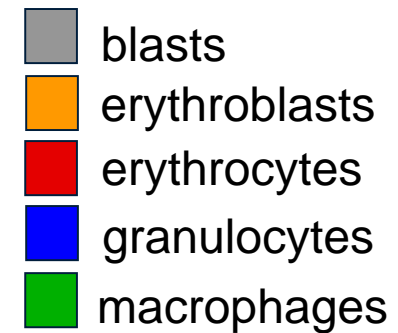
Cell population dynamics

Directed differentiation of FDCPmix cells

Tuning the lineage specific rewards m_i to account for the temporal development of the fraction of cells

Legend:
- blasts (grey)
- erythroblasts (orange)
- erythrocytes (red)
- granulocytes (blue)
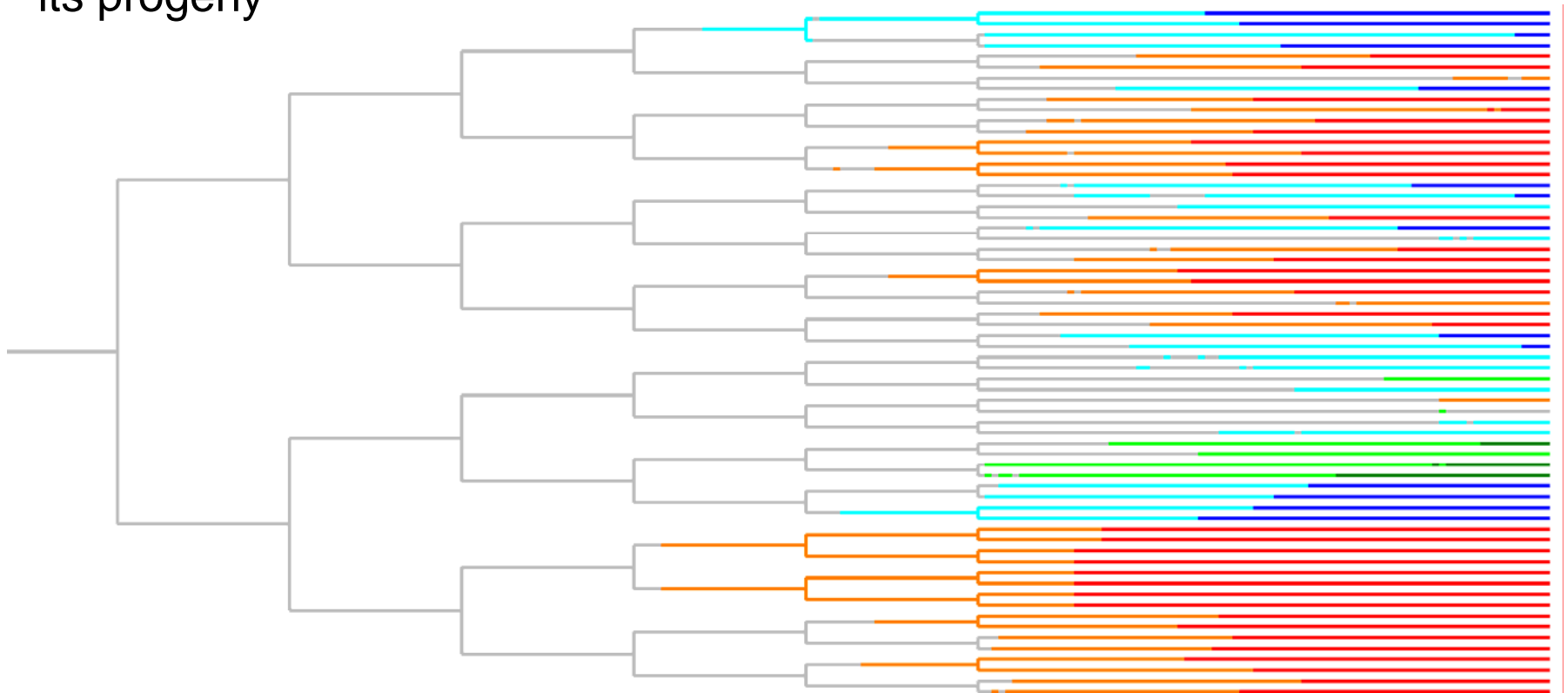- macrophages (green)

What happens after culture change?

Cellular genealogical trees

Tracking of single cell fates – an experimental challenge

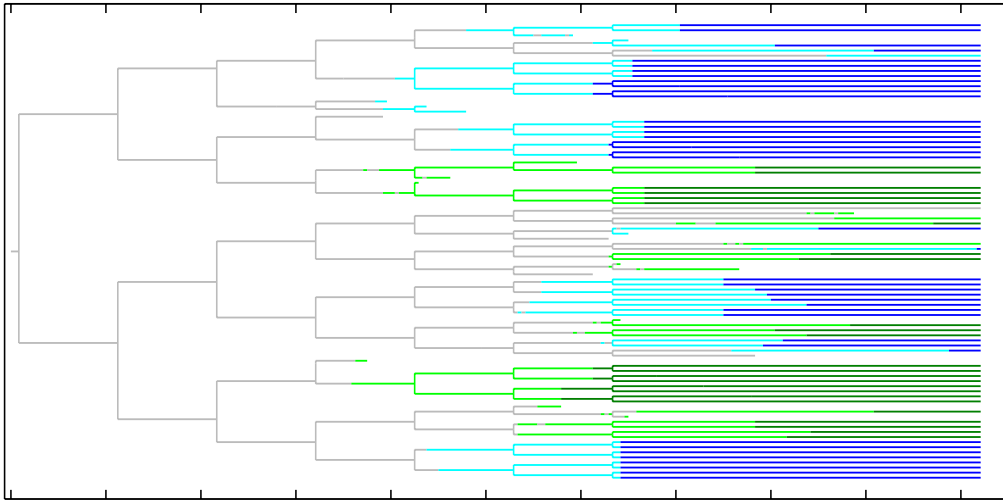Single cell based model allows the tracking of a single cell with all its progeny

Idea: comparison with experimental data can potentially reveal critical mechanisms of lineage specification
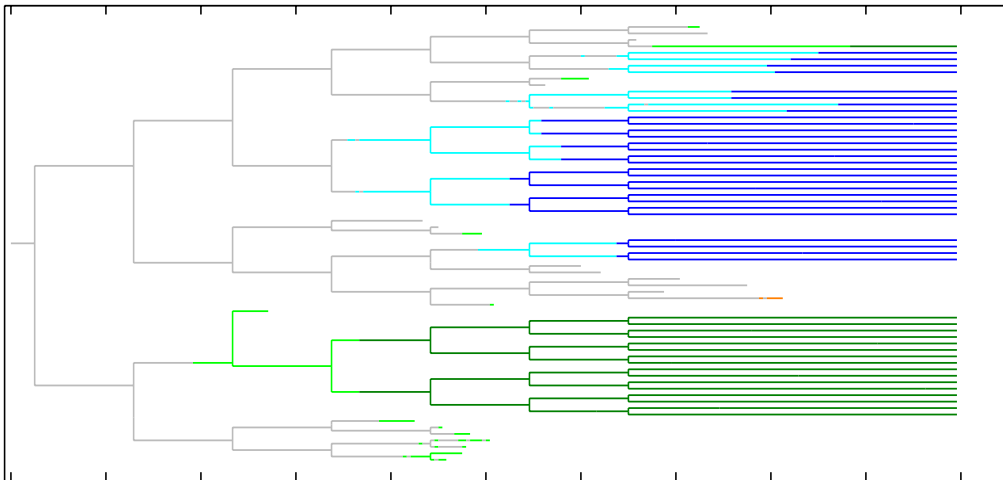
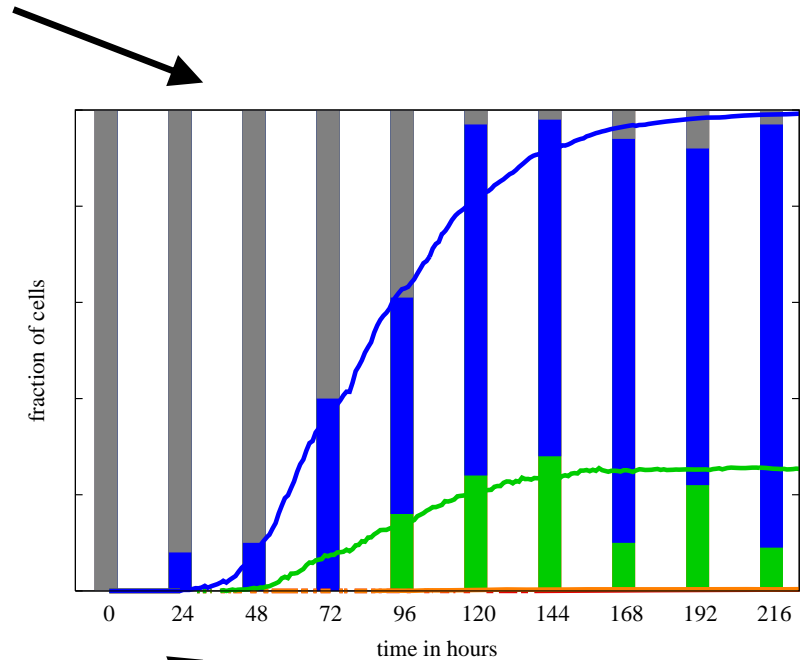# Cellular genealogical trees

Selection as a potential mechanism of lineage specification

Instructive: a biased stochastic decision process

Selective: lineage specific apoptosis

Cellular genealogical trees
Analysis

- **Direct topological comparison of two genealogical trees**
  - Evaluating distances in undirected trees
    - Cost functions need to reflect parameter of interest
    - Difficulties with heterogeneity within one ensemble of trees
    - Computationally extensive

- **Characterization of individual genealogical trees**
  - Specification of typical measures (cell cycle times, occurrence of apoptosis)
    - Measures designed for particular parameters
    - Ensemble averages
    - Analysis of the correlation structure
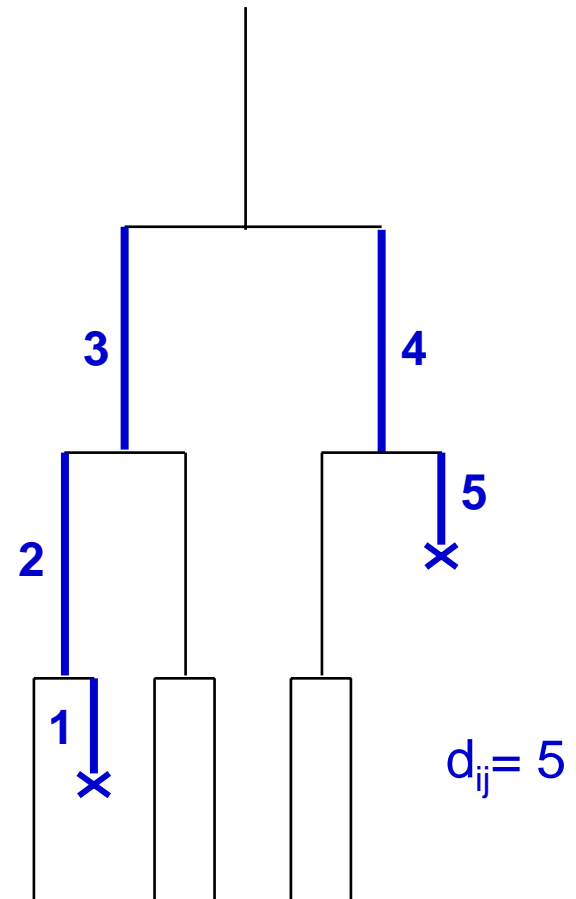
Cellular genealogical trees
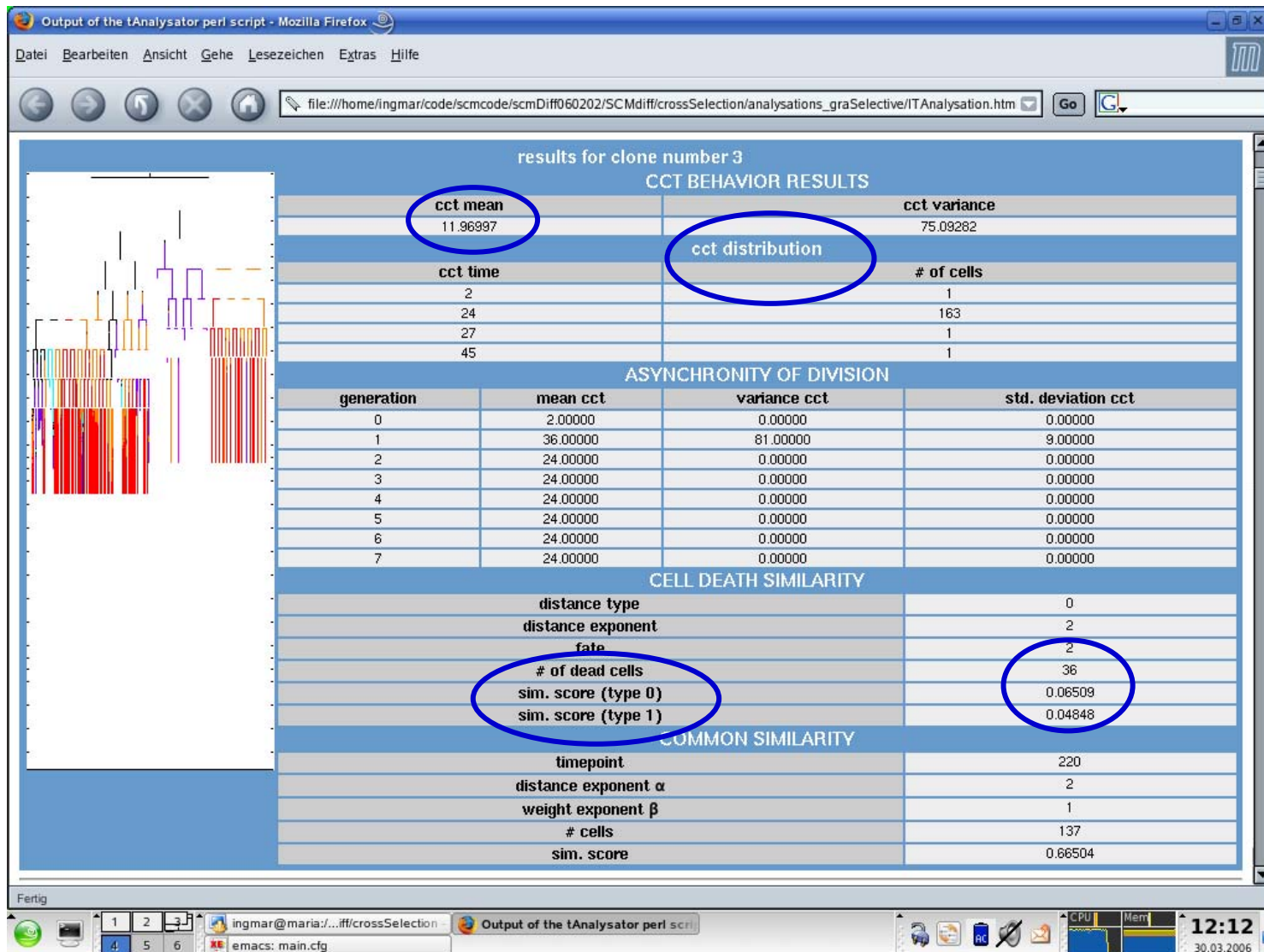## Correlation structure

Correlation measure

$$C = \frac{\sum_{i,j} D_{ij}^{\alpha} W_{ij}^{\beta}}{\sum_{i,j} D_{ij}^{\alpha}}$$

- distance measure $D_{ij} = 2/d_{ij}$ (with d_{ij} as hop distance)

- weight function W_{ij}

- distance coefficient α

- weight coefficient β

correlation of apoptosis events: $W_{ij} = D_{ij}$

$d_{ij} = 5$

Cellular genealogical trees

html output of the tAnalyzer script

Summary

• tissue stem cell organization as a self-organizing process: flexibility and heterogeneity as building principles

• quantitative understanding of lineage specification based on the idea of a competition process between different lineage specific factors

• phenomena to be addressed with the model

- lineage specification dynamics in the progeny of single cells

- lineage specification dynamics in cell populations

- single cell/clone tracking (structural analysis of the genealogical trees potentially reveals mechanisms of lineage determination)

- lineage specification as an instructive or a selective process

- developmental asymmetry

• To continue:

- analysis of cellular genealogical trees
- better understanding of the molecular dynamic of lineage specification

Thanks

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	University of Leipzig