

Lineage Commitment of Hematopoietic Stem Cells: An Agent-based Model

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Outline

- ① Biological background
 - ▶ stem cell definition
 - ▶ the hematopoietic system
 - ▶ the hematopoiesis control mechanisms
- ② How and why a model can be useful
- ③ An agent-based model
 - ▶ goal of the model
 - ▶ assumption of the model
 - ▶ description of the model
 - ▶ implementation of the model
- ④ Experiments and simulation results
- ⑤ Conclusion and future works



Motivations

Premises

- ① Utility of models for overcoming the biological experiments constraints
- ② Utility of multi-agent systems for modelling complex systems
- ③ Evidence of complex properties in the hematopoietic system (heterogeneity, hierarchy, non-linear dynamics...)

Consequence

- ① Adoption of multi-agent systems for modelling the hematopoietic system



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- 1 Biological Background
- 2 The Adoption of Models
- 3 An Agent-based Model for the Hematopoietic System
- 4 Simulation Results



Background – Stem Cells Biology (1/2)

Stem cells are able to

Self-renewal Go through numerous cycles of cell division while maintaining the undifferentiated state

Differentiation Produce a progeny of distinct cell types

Quiescence Remain in a state where they are not dividing

Apoptosis Activate the programmed cell's death

They are required where there is a need of

- Recovering the tissue after injury or disease
- Replacing the differentiated cells that naturally die (normal turnover)



Background – Stem Cells Biology (2/2)

The observed behaviour of stem cells seems to depend on multiple factors

- Stem cells are partially predetermined, *i.e.*, already committed to the generation of a specific class of terminally differentiated cells
- Stem cells fate is partially determined by stochastic events
- Stem cells dynamics are partially influenced by different environmental stimuli

→ it is not clear how the interplay between these factors is managed



The Hematopoietic System

The hematopoietic (*blood-forming*) system is involved in the production and maintenance of the blood cells

- Three main classes of differentiated cells with different functions

Erythrocytes transport of oxygen

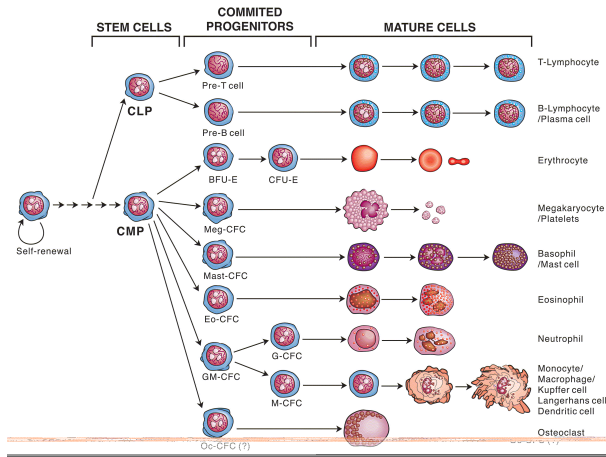
Leucocytes production of antibodies to fight infection

Platelets blood clotting

The hematopoietic stem cells are able to generate every lineage of the hematopoietic system



Hematopoietic Stem Cell Lineage Tree



<http://www.bloodlines.stemcells.com/chapters.html>



The Hematopoiesis Control Mechanisms

Interplay between the internal genetic processes and cell-to-cell interactions

Internal dynamics

- Signalling pathways
- Gene regulation network

Cell-to-cell interactions

- Mediated by cues spread out in the micro-environment
→ important role of the molecules diffusion
- Direct through cells' membrane proteins



Open Questions

- Is lineage differentiation determined by stochastic or by deterministic processes? Which are these processes?
- Is everything determined by the environment signals, or the cells are in some sense predetermined?
- How are the specific gene expression dynamics generated, and how are they controlled by cell-cell and cell-environment interactions?
- How do stem cells commit to a particular lineage?



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Need for Modelling and Simulating Techniques

- Experimental techniques are constrained
 - ▶ adult stem cells cannot be easily isolated
 - ▶ in-vivo experiments are often not allowed
 - ▶ each experiment alters the real system behaviour
 - ▶ in-vitro experiments cannot reproduce the exact environment present in the real system



Agent-based Model as Multi-level Model

The hematopoietic system's emergent behaviour depends on

- How the cells interact with their surrounding
- How each of them modifies its internal states and performs its autonomous activities

ABM provides methods to

Heterogeneity Model individual structures and behaviours of different entities of the biological system

Locality Model local interactions between biological entities

Environment Model the microenvironment structure and dynamics

Interaction Define biological entities – environment interactions

Hierarchy Capture the hierarchical organisation of the biological system, describing at least two levels

→ **Multi-level model**

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Goals of the Model

- ① To maintain the cellular population at a stationary level, in order to observe the oscillatory behaviour characteristic of the homeostatic state
- ② To observe the myeloid and lymphoid differentiation

...demonstrating the fundamental dependency between the intracellular dynamics and the extracellular ones



Assumptions of the Model

- Few cellular processes, assuming all the others as perfectly working
- Few molecular types
- Only two main stages of the lineage
 - ▶ stem
 - ▶ mature
- Only two branches of the lineage tree
 - ▶ myeloid
 - ▶ lymphoid



Description of the Model (1/6)

Cells as agents

Agent state

The agent's state is identified by a set of variables which represent the gene expression level:

- ① *SelfRen*
- ② *Diff*
- ③ *Adhesion*
- ④ *Apoptosis*
- ⑤ *Quiescence*

all with range $\mathbf{R}_0^1$

They are not *real genes* but *abstract genes* representative for the processes of interest



Description of the Model (2/6)

Cells as agents

Agent Behaviour

SENSE Investigation of the local environment composition

PLAN Update of the agent state as a consequence of

- 1 the stimuli from the environment

$$SelfRen(t + 1) = SelfRen(t) + k * [MolS]$$

- 2 some internal mechanisms

$$SelfRen(t + 1) = m * SelfRen(t)$$

k and m are model's parameters

ACT Identification of the next actions to perform, triggered by the values of the state variables when their maximum is reached.

Description of the Model (3/6)

Cells as agents

Agent Actions

- **Self-renewal** Entrance in the cell cycle for dividing
- **Myeloid differentiation** Differentiation into a myeloid mature cell
- **Lymphoid differentiation** Differentiation into a lymphoid mature cell
- **Apoptosis** Death
- **Molecules release** Filling the cell grid place into the maximum value
- **Movement** Random movement in one of the positions available in the eight around



Description of the Model (4/6)

Cell microenvironment as MAS environment

The environment collects the molecules

MolS Stimulating the self-renewal

Produced by stromal cells when there are not stem cells in the positions around

MolDm Stimulating the differentiation in the myeloid lineage

Produced by Myeloid mature cells when are dying

MolDI Stimulating the differentiation in the lymphoid lineage

Produced by Lymphoid mature cells when are dying

MolQ Stimulating the quiescence

Produced by stromal cells when a stem cell is in the positions around and by mature cells when they born

MolA Stimulating the apoptosis

Produced by every cell under specific circumstances –genetic mutations, virus infections, starvation...



Description of the Model (5/6)

Cell microenvironment as MAS environment

The environment regulates molecules diffusion

Updating the concentration value of the molecules in each position with the average value of that position and the eight around

The environment regulates molecules degradation

$$[Molx](t + 1) = [Molx](t) - d[Molx]$$

d is a model's parameter



Description of the Model (6/6)

Cell microenvironment as MAS environment

The environment defines the topology of the space as a grid

- Cells can occupy one position
- The same position can also be filled with a variety of molecules with a specific concentration



Implementation of the Model

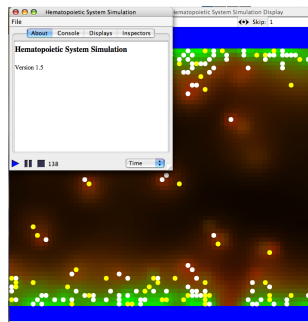
Using MASON (Java library for discrete-event multiagent simulation)

Simulation management

by a *scheduler* that collects the events that should occur and determines the exact time and order for their execution.

MAS environment implemented

by the Bone.java that contains two object of class DoubleGrid2D: one grid contains the cells, and the other all the molecules.



Agents as instances of

the Cell.java class that implements Steppable.java, which deals in MASON with the generation of the events.

Outline

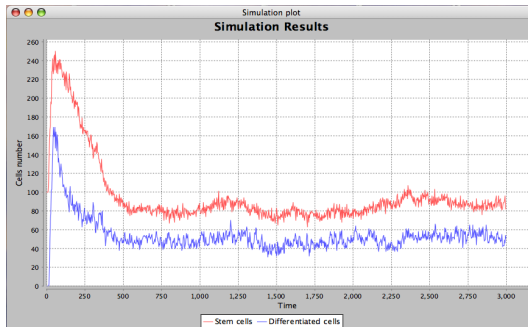
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Preliminary Experiment

- Initial condition
 - ▶ random number of stem cells, randomly collocated in the environment
 - ▶ constant number of stromal cells, at the boundary of the simulation environment
 - ▶ no molecules in the environment
 - ▶ $k = 1$ (no heterogeneity and stochasticity introduced)
- Once the simulation runs, stem cells begin to move and release molecules.



Preliminary Results After 3000 Steps of the Simulation



- Pure qualitative results
 - ▶ no possible comparisons with real data
- The cell number oscillates around a constant average value after a transition period
 - ▶ exact behaviour of the system under homeostatic conditions



Future Works

- ① Improve the model with
 - ▶ the differentiation in four different lineage
 - neutrophil, macrophage, erythroblast, megakaryocyte –
 - ▶ stochastic components
 - ▶ different environmental composition (different cultures)
 - ▶ agents heterogeneity
 - for investigating the interplay among pre-determination, stochastic phenomena and environmental effects
- ② Validate the model
 - ▶ against experimental evidence (see experimental data¹)
- ③ Comparison with the performances of existing models²

¹H. Takano, H. Ema, K. Sudo, and H. Nakauchi. Asymmetric division and lineage commitment at the level of hematopoietic stem cells: Inference from differentiation in daughter cell and granddaughter cell pairs. *The Journal of Experimental Medicine*, 199(3):295–302, 2004.

²I. Glauche, M. Cross, M. Loeffler, and I. Roeder. Lineage specification of hematopoietic stem cells: Mathematical modeling and biological implications. *Stem Cells*, 25(7):1791–1799, July 2007.



Conclusions

- Model
 - ▶ composed by elements with a biological meaning
 - ▶ designed for performing further experiments
 - ▶ designed for adding more biological behaviours
- Simulation
 - ▶ preliminary experiment
 - ▶ only qualitative results
- Significant future works



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