Inference and dynamical modeling of regulatory networks controlling hematopoiesis

JOSÉ TELES

The Second q-bio Summer School and Conference

LANL – 23 July 2008

OUTLINE

I. INTRODUCTION

II. (BROAD) PROJECT DESCRIPTION

III. CURRENT WORK

IV. IMMEDIATE PROSPECTS

PhD @ Lund

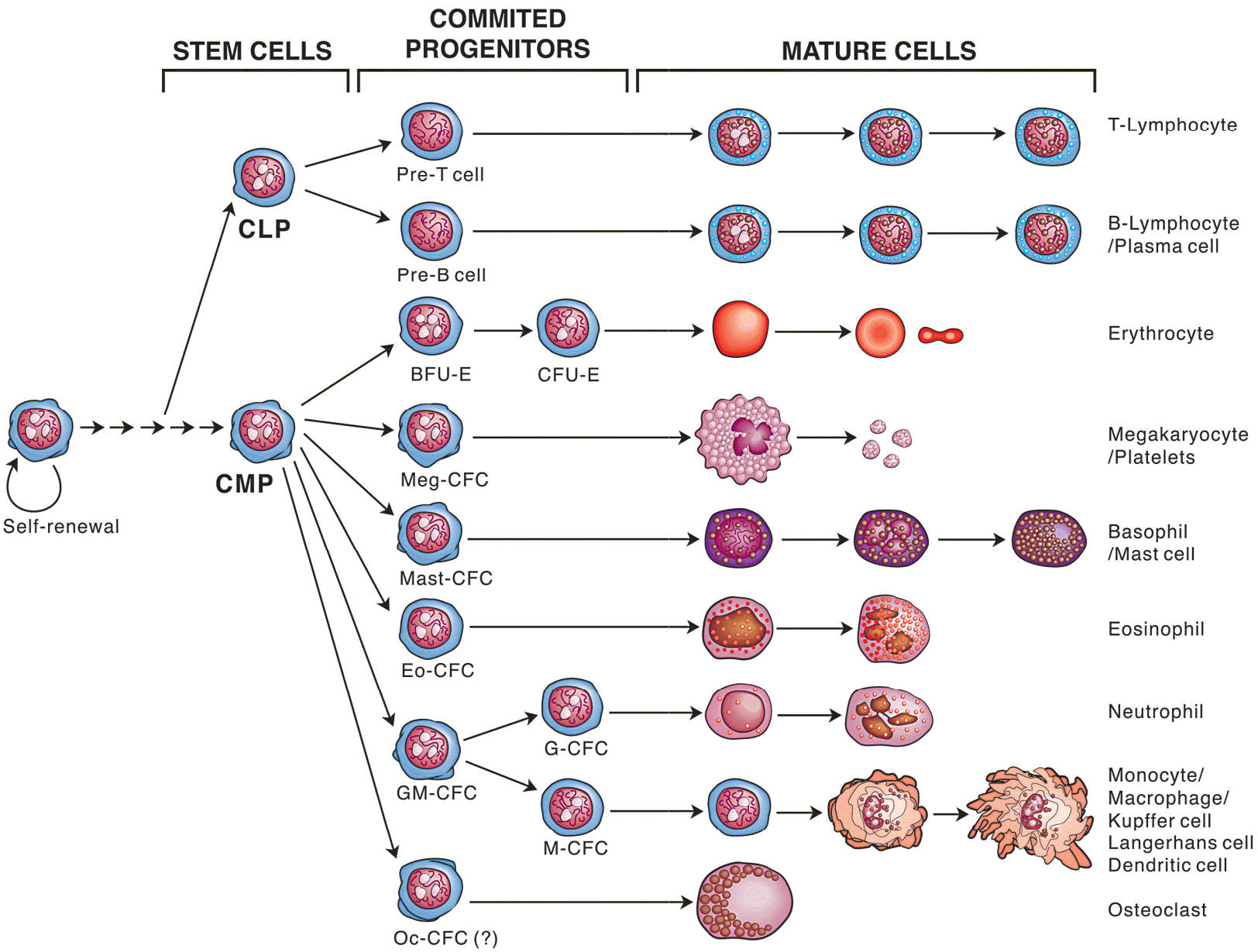
CARSTEN PETERSON

PhD @ Lund

Computational Biology &
Biological Physics

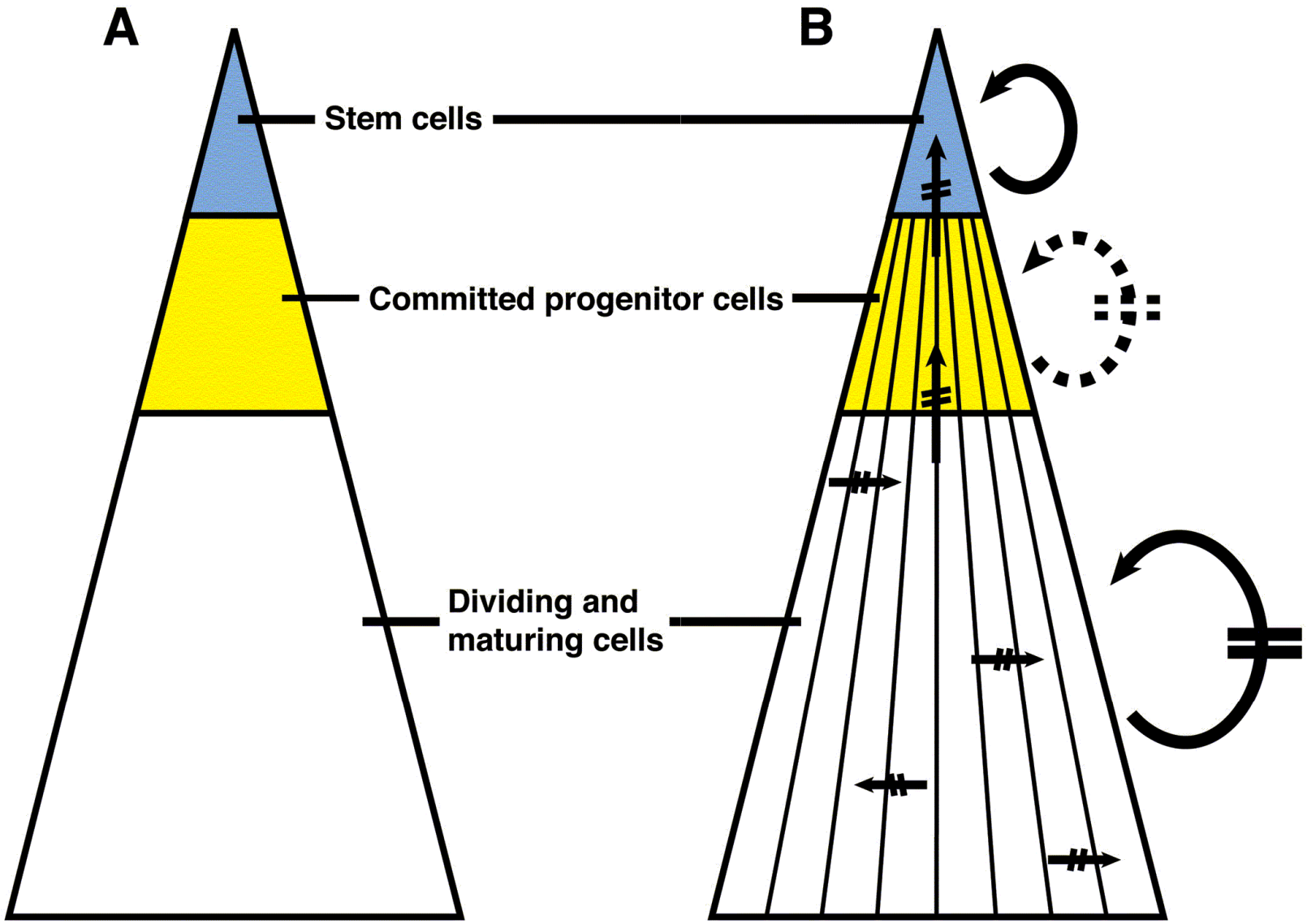
LUND UNIVERSITY

Hematopoiesis



Metcalf D. Blood Lines (2006)

Hematopoiesis: general principles



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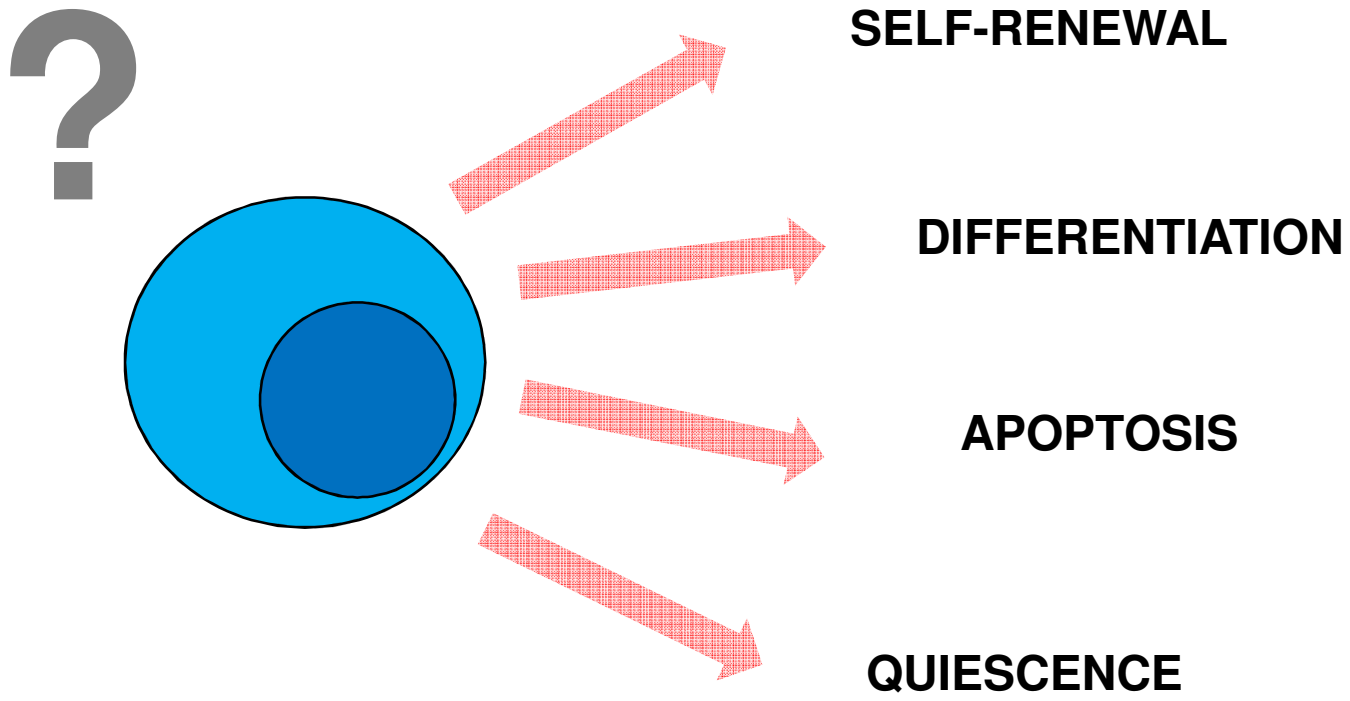
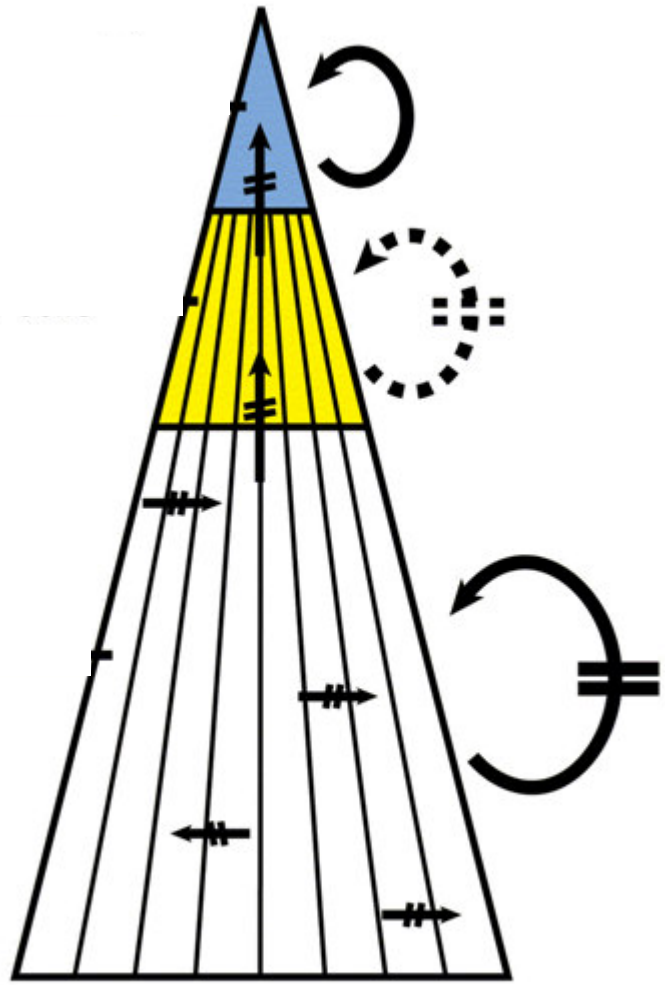
Cell fate decisions



Main questions

ORGANIZATIONAL PRINCIPLES OF GENE EXPRESSION REGULATION

“STEMNESS”



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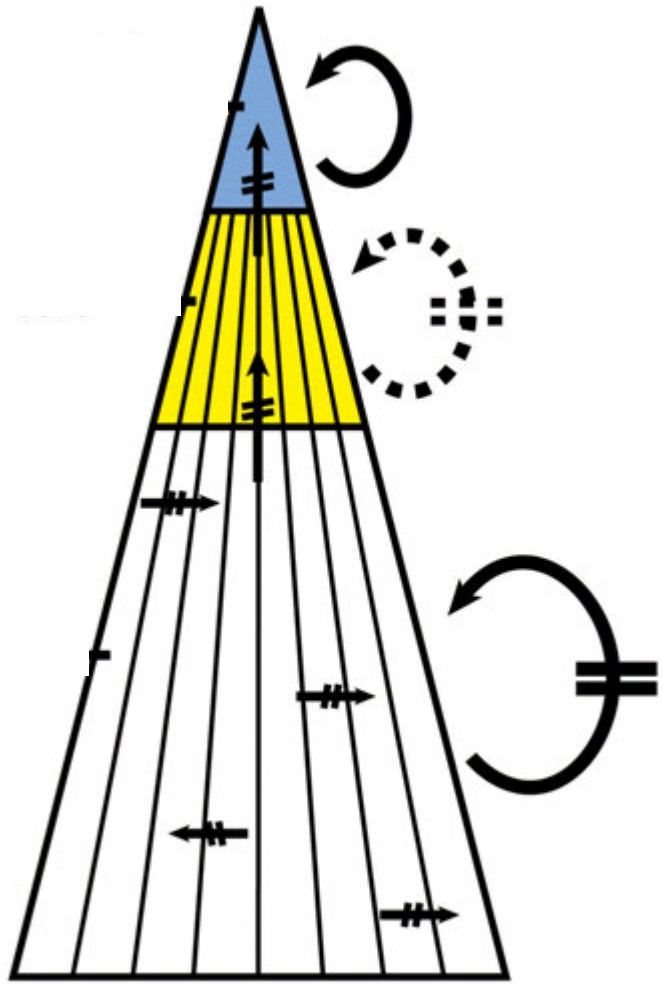

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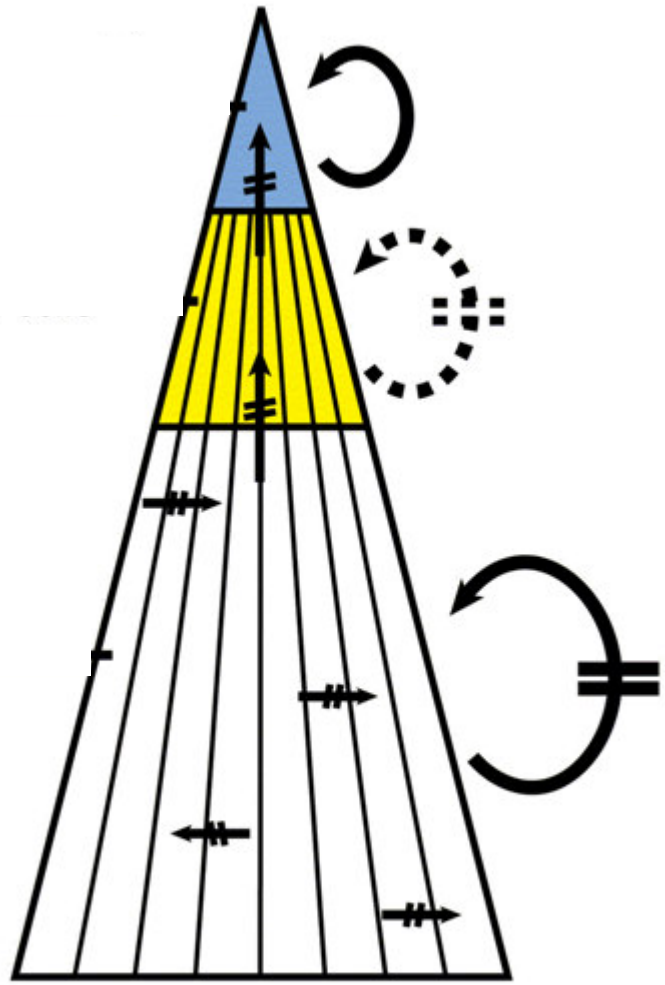

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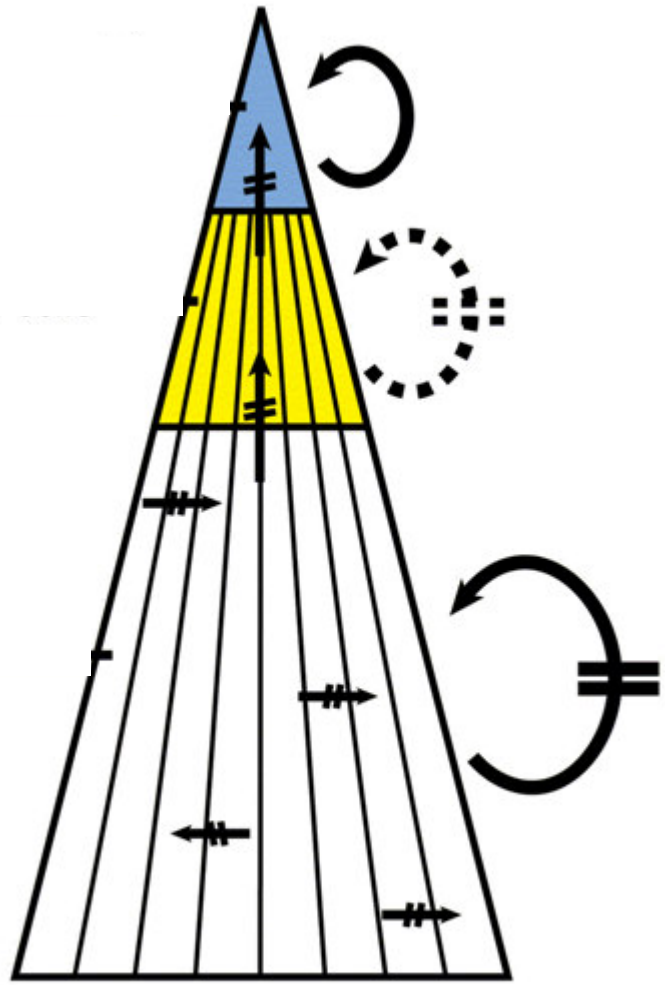

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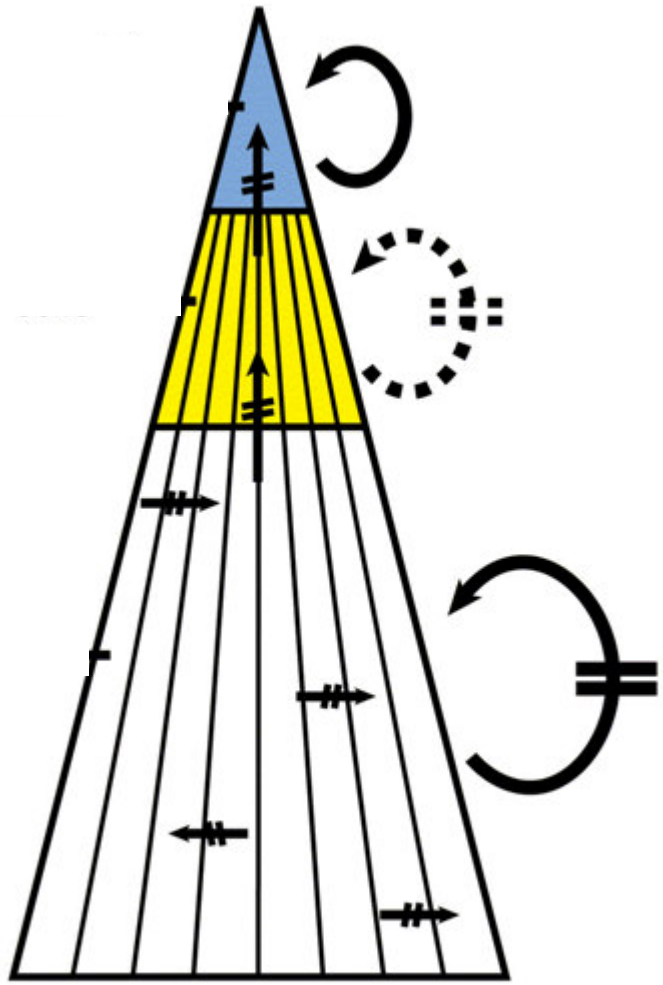

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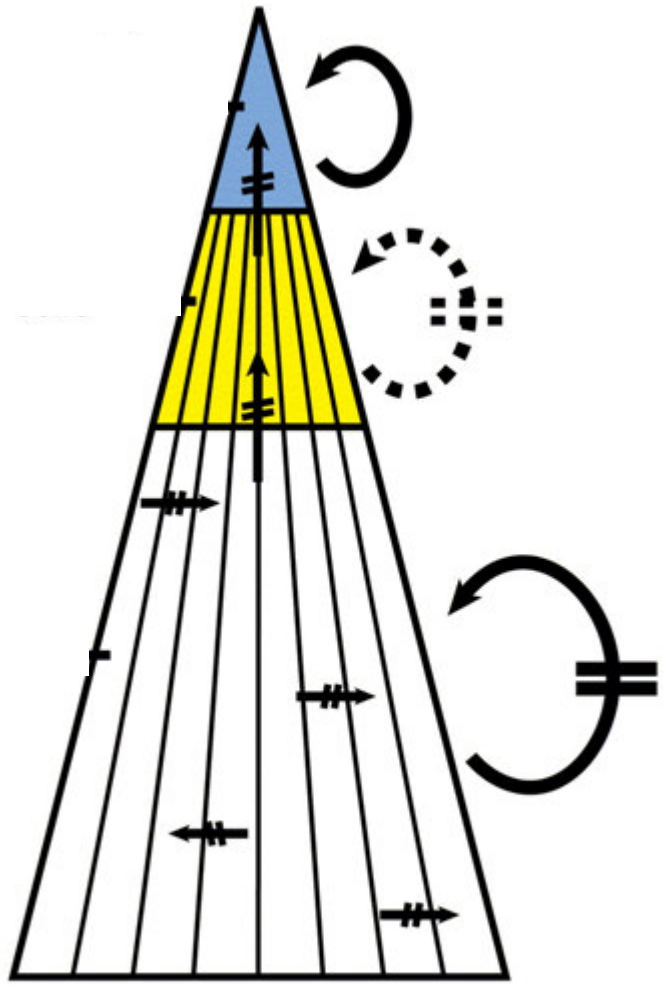
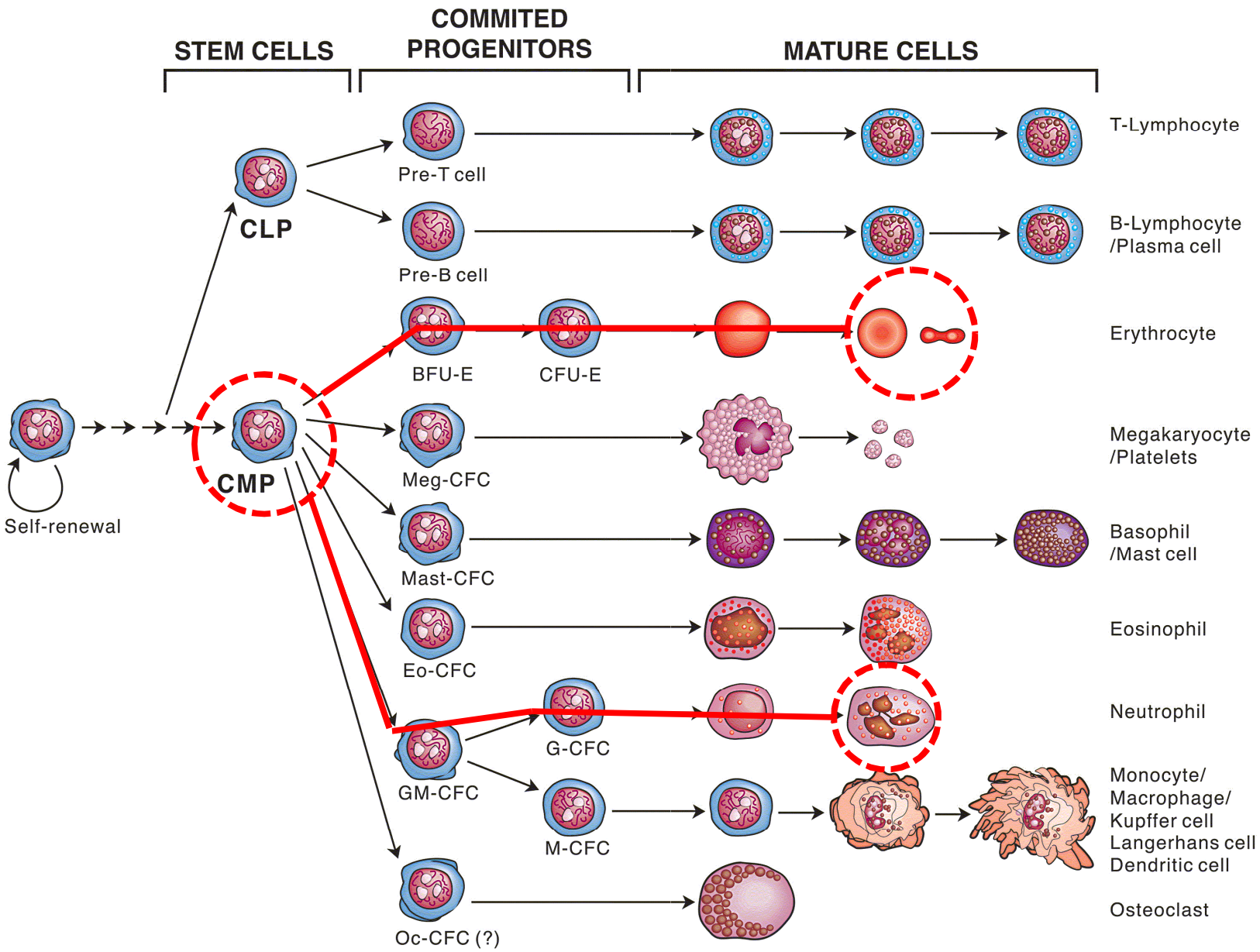
CELL EXPANSION



Metcalf D. Blood Lines (2006)

Gene expression in hematopoiesis



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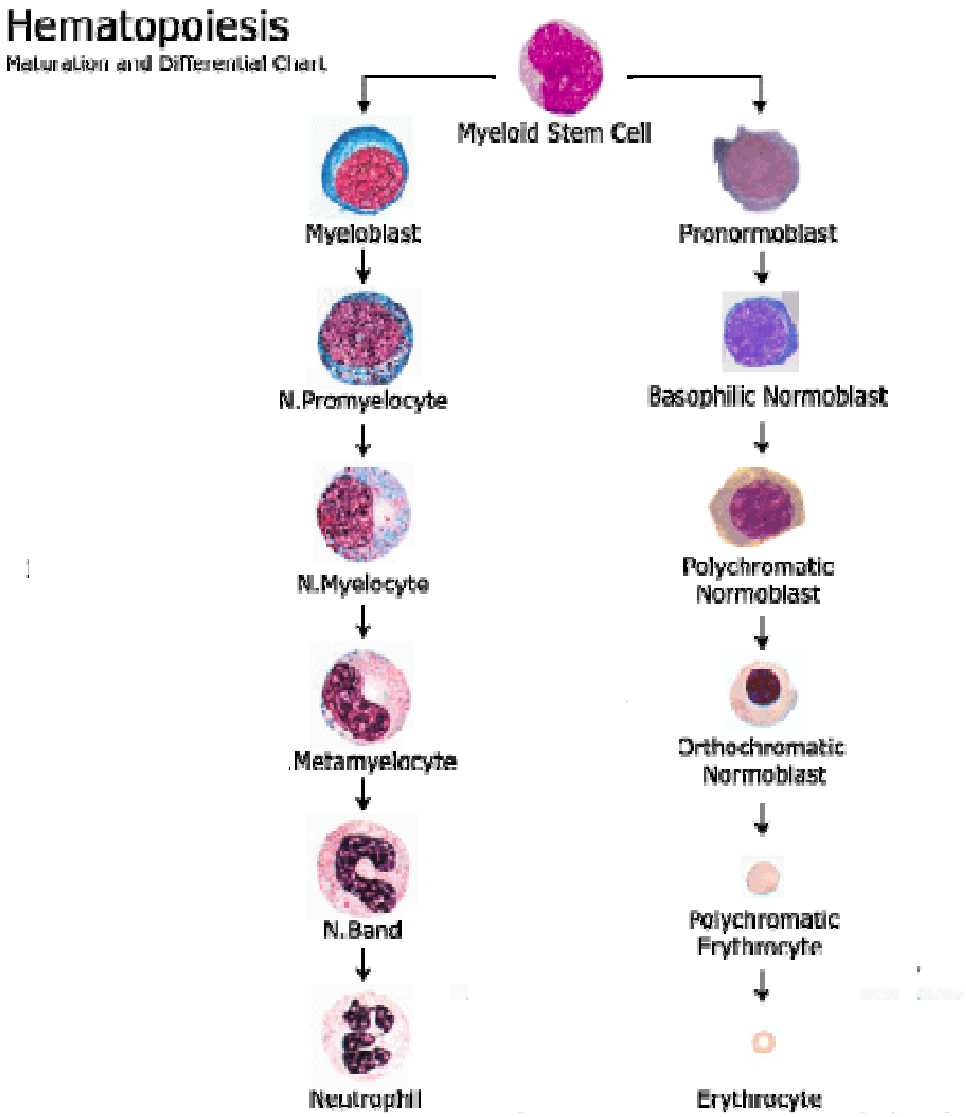
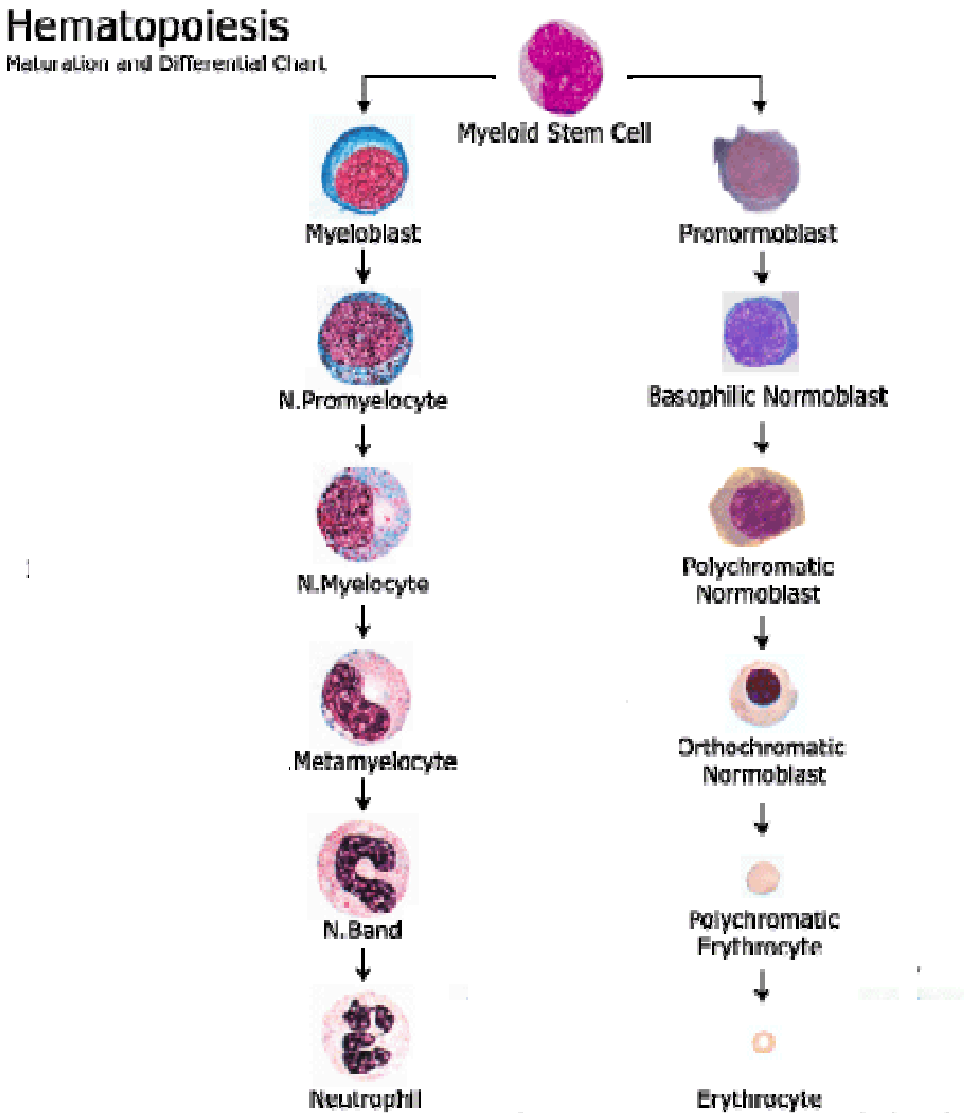


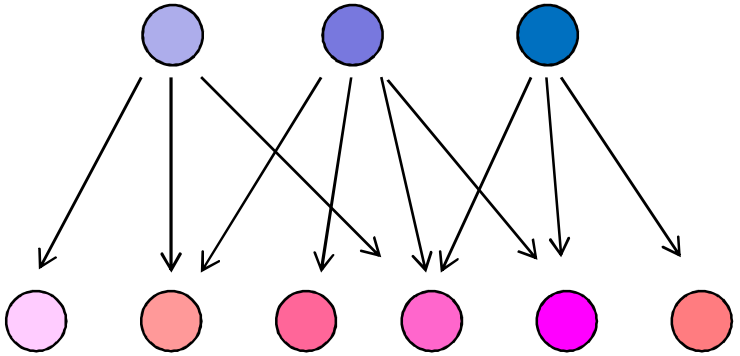
MASTER REGULATORS

- Cell lineages representing discrete “genetic programs” mutually exclusive and intrinsically robust.

- Transcription factors act in intricate circuits of gene regulation, specifying the stable lineage-specific transcriptome.

Gene expression in hematopoiesis





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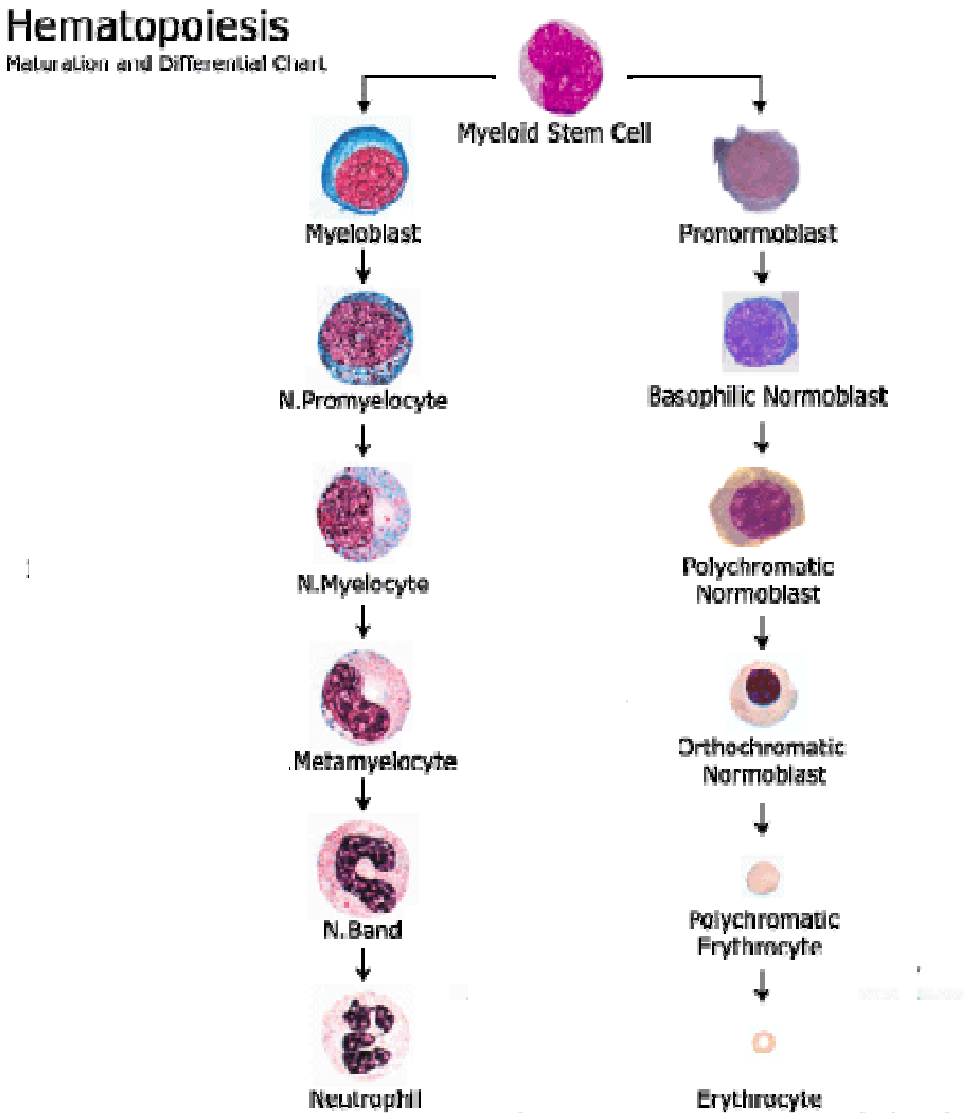

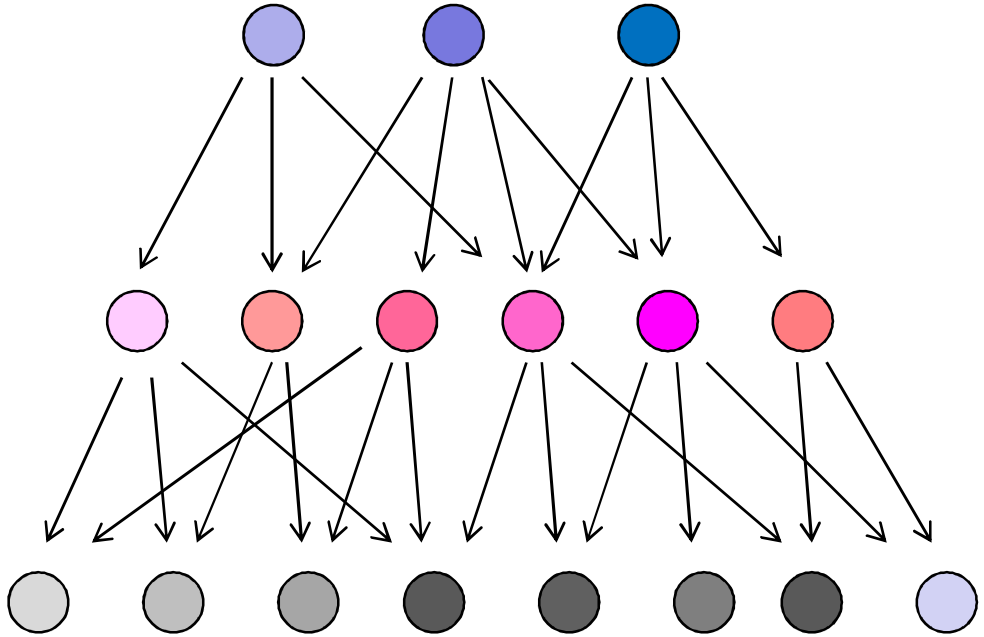

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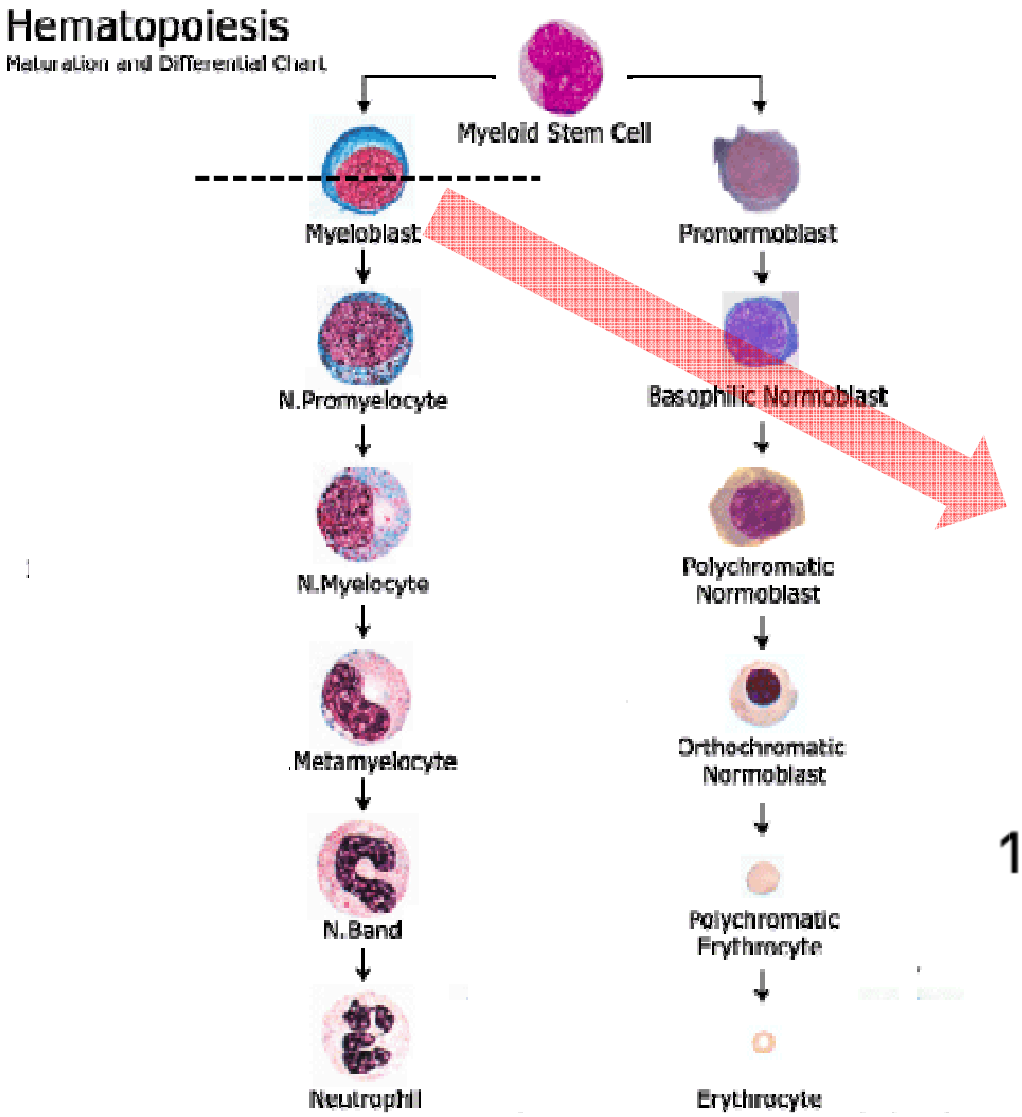


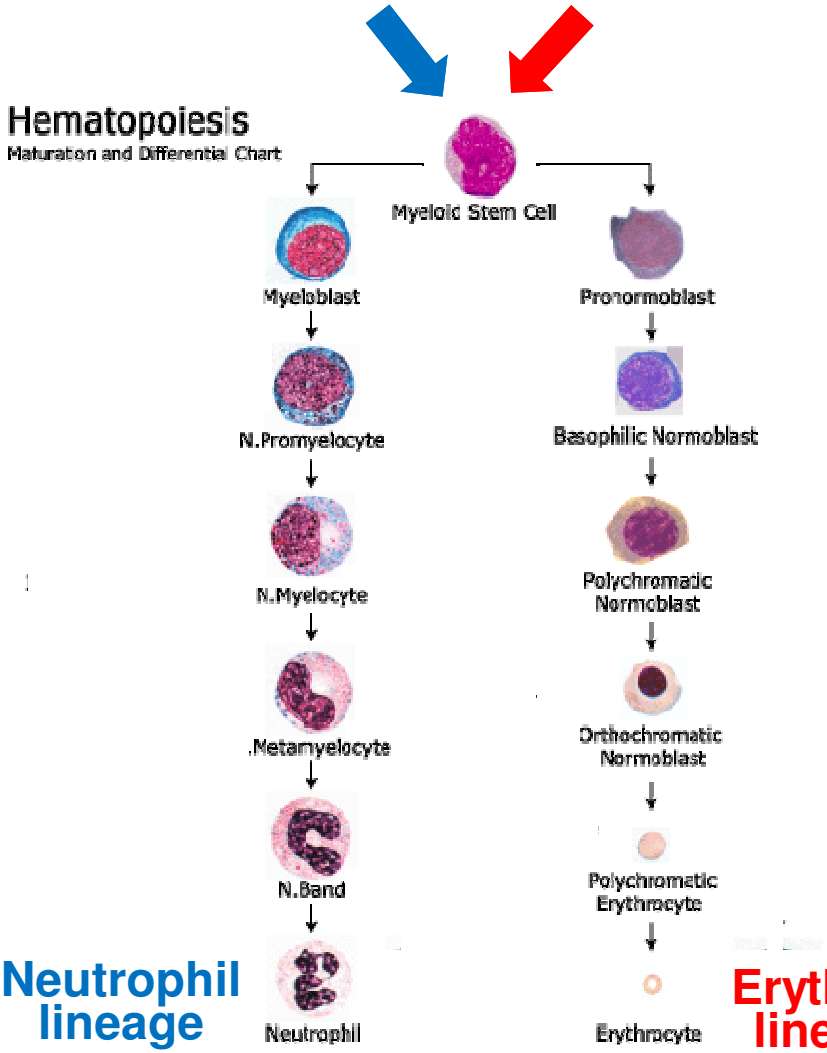
Gene expression signatures

Experimental setup

FDCPmix cells (murine)

GCSF, GMCSF, IL-3 low

EPO, haemin, IL-3 low



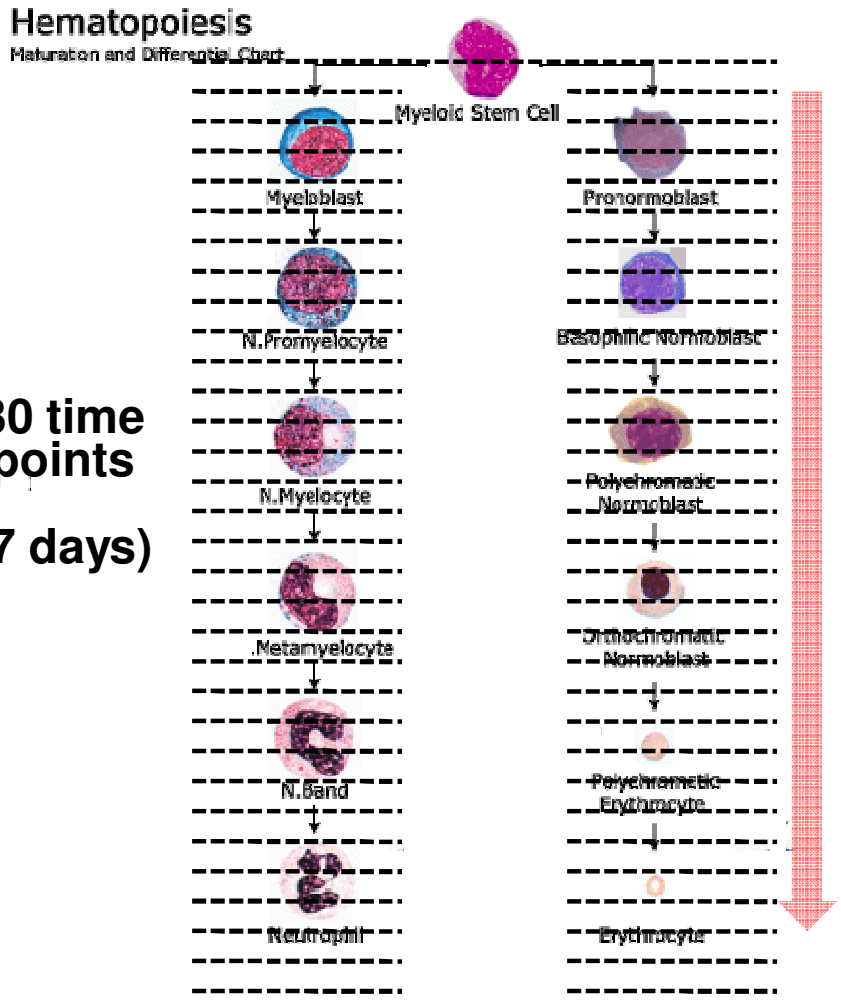
Neutrophil lineage

Erythroid lineage

The Weatherall Institute of Molecular Medicine

Tariq Enver

Experimental setup



30 time points

(7 days)

24-36 hrs

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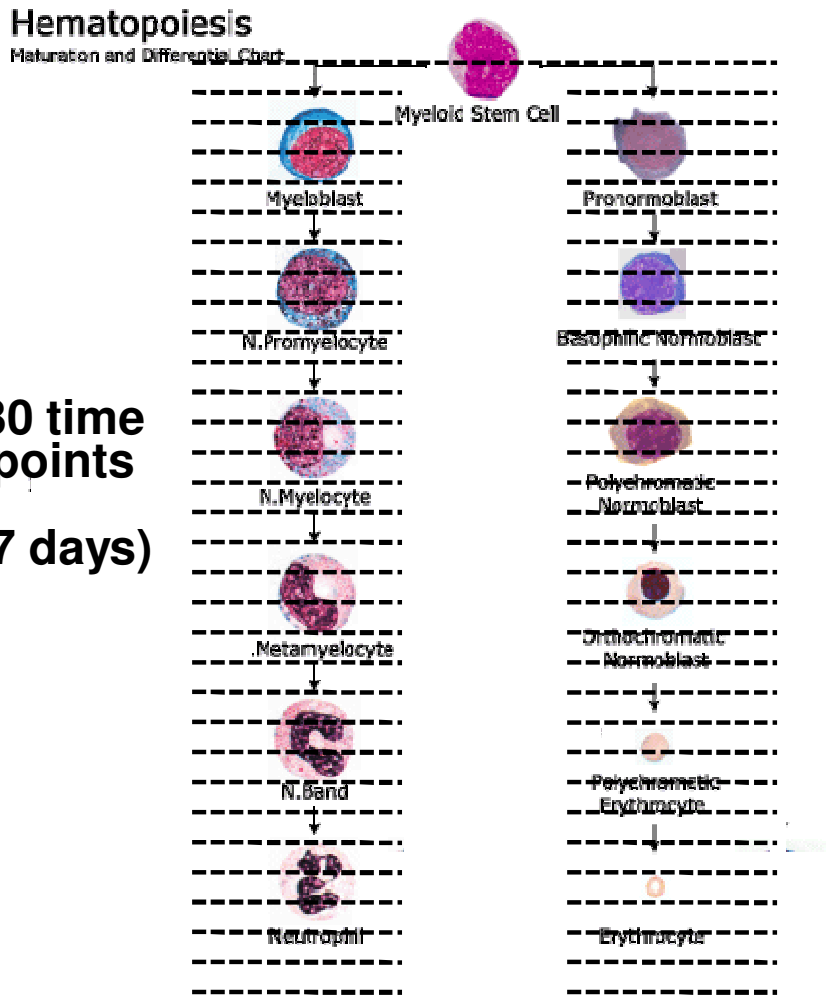


30 time points

(7 days)

a) Microarray data:

- (N): 3600 diff exp genes (265 TFs)
- (E): 4500 diff exp genes (354 TFs)

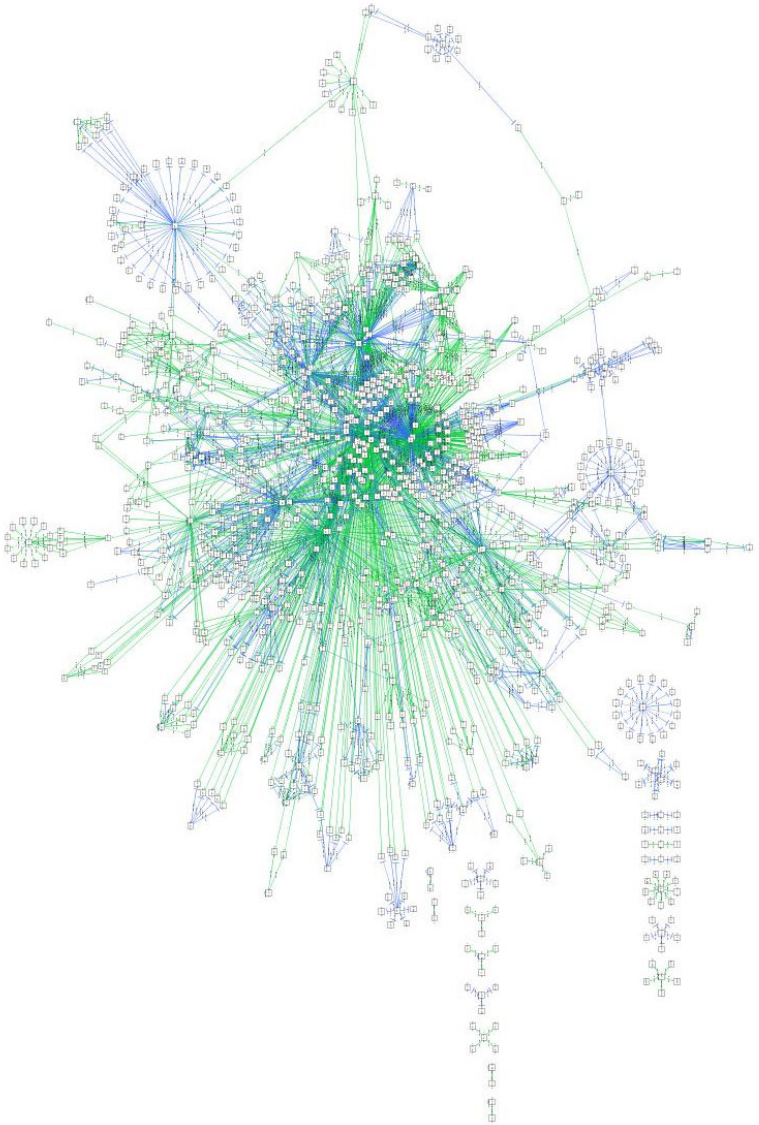
b) ChIP-on-chip data:

- Key TFs (Gata1, Gata2, Pu.1, Fog-1)

c) Cell population counts (<u>7 time points</u>):

- Blasts (progenitor)
- Immature erythroid
- Immature neutrophils
- Macrophages
- Megakaryocytes

Transcriptional network inference



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Transcriptional network inference

Probabilistic graphical models

(Friedman N, 2004)

Dynamic Bayesian Networks

(Perrin BE et al, 2003)

Probabilistic Boolean Networks

(Shmulevich I et al, 2002)

Mutual Information Based

(Basso et al, 2005)

Microarray + ChIP analysis

(Ernst et al, 2007)

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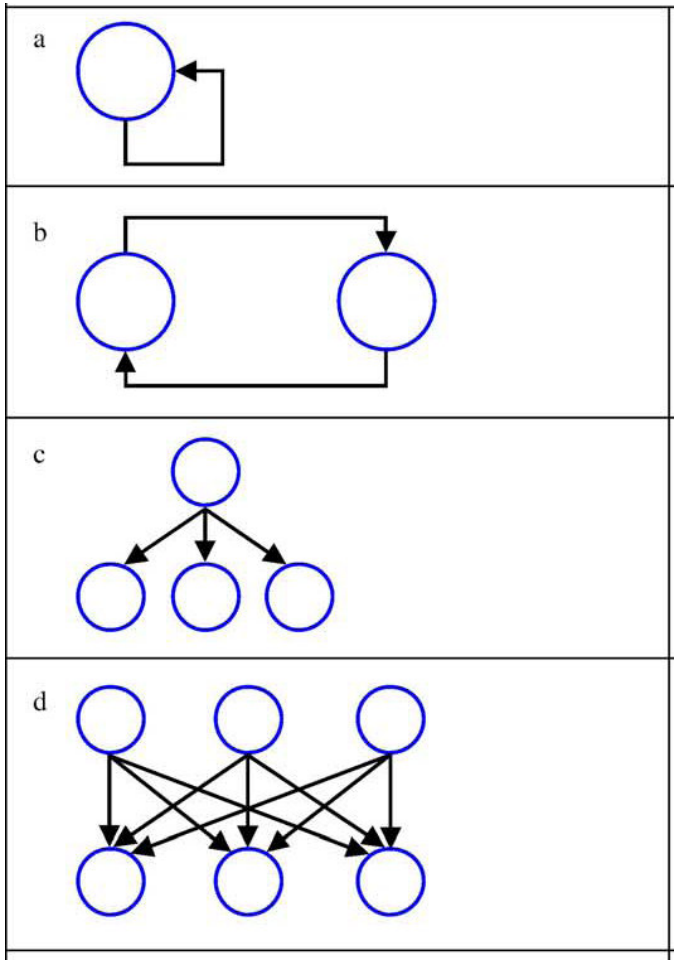
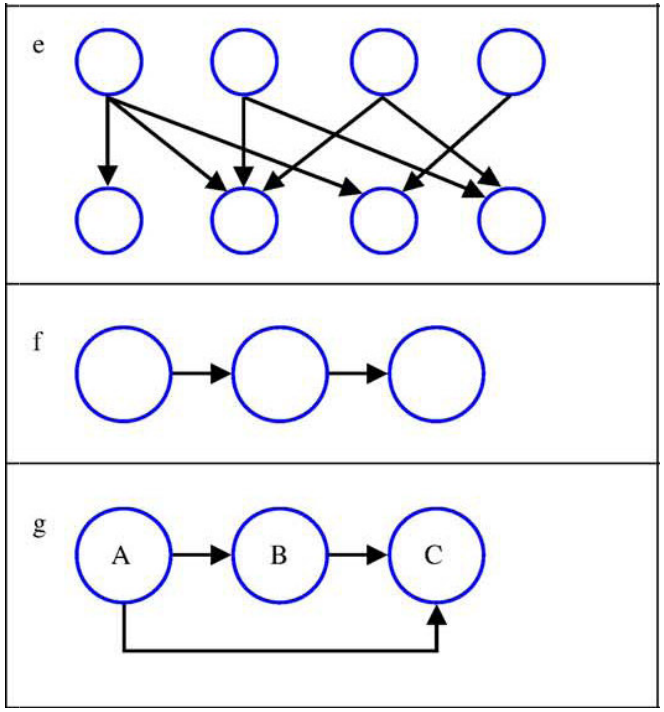
Structural motifs





Swiers et al. Developmental Biology (2006)

Dynamical features of hematopoiesis

- Stable atractors of gene circuits represent states of differentiation. *(Cinquin & Demongeot, 2005)*

- The discrete transitions in bistable biochemical systems underlie cell fate decision or differentiation *(Laslo et al, 2006)*

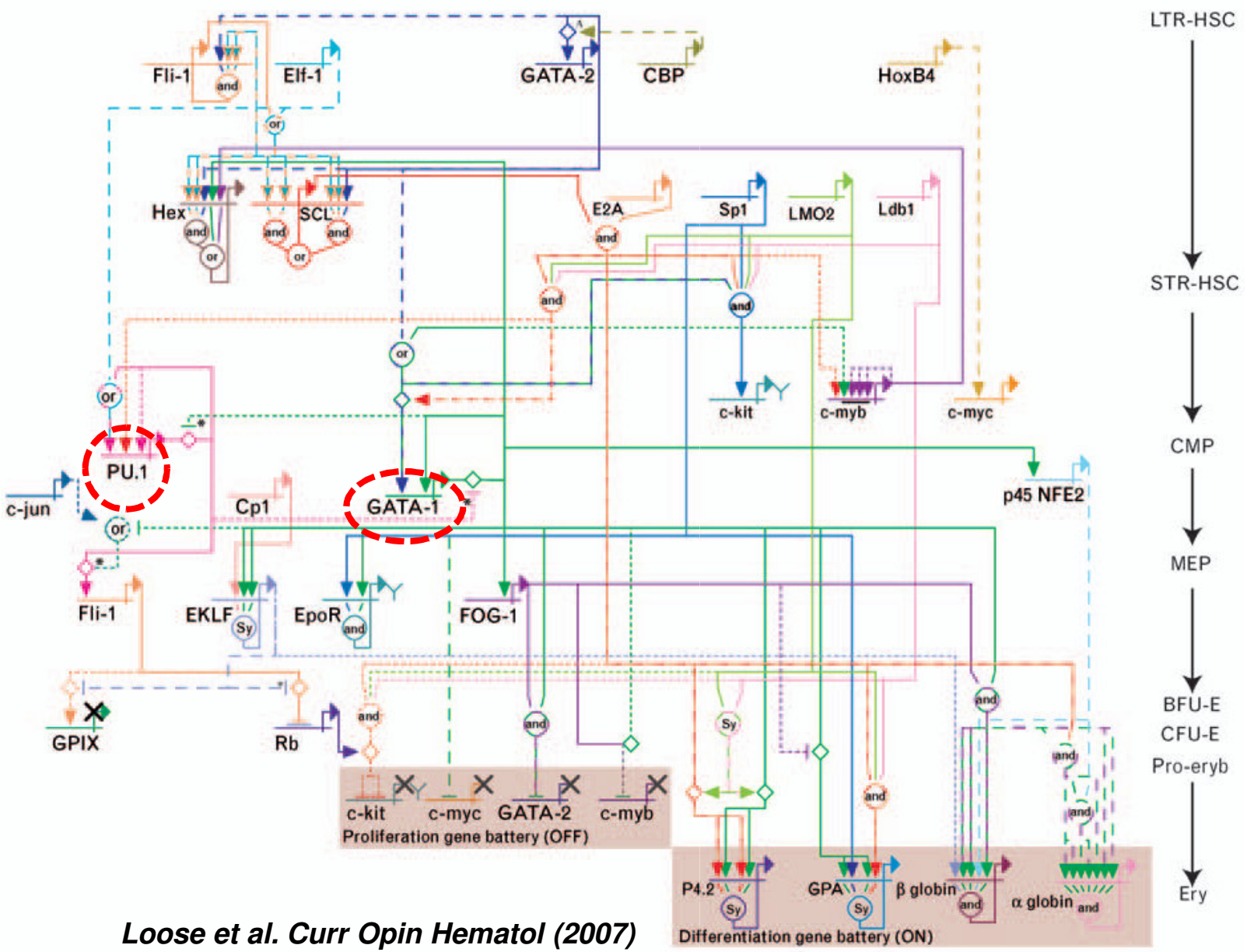
- Control by external regulatory signals (Enver et al, 1998):

  a) Stochastic ("selective") cell fate control: cell fates constitute preexisting programs adopted by the cell in a chance fashion. External signals act as survival/growth factors.

  b) Deterministic ("instructive") cell fate control: external signals impose the program by activating/repressing sets of genes via signal transduction cascades.

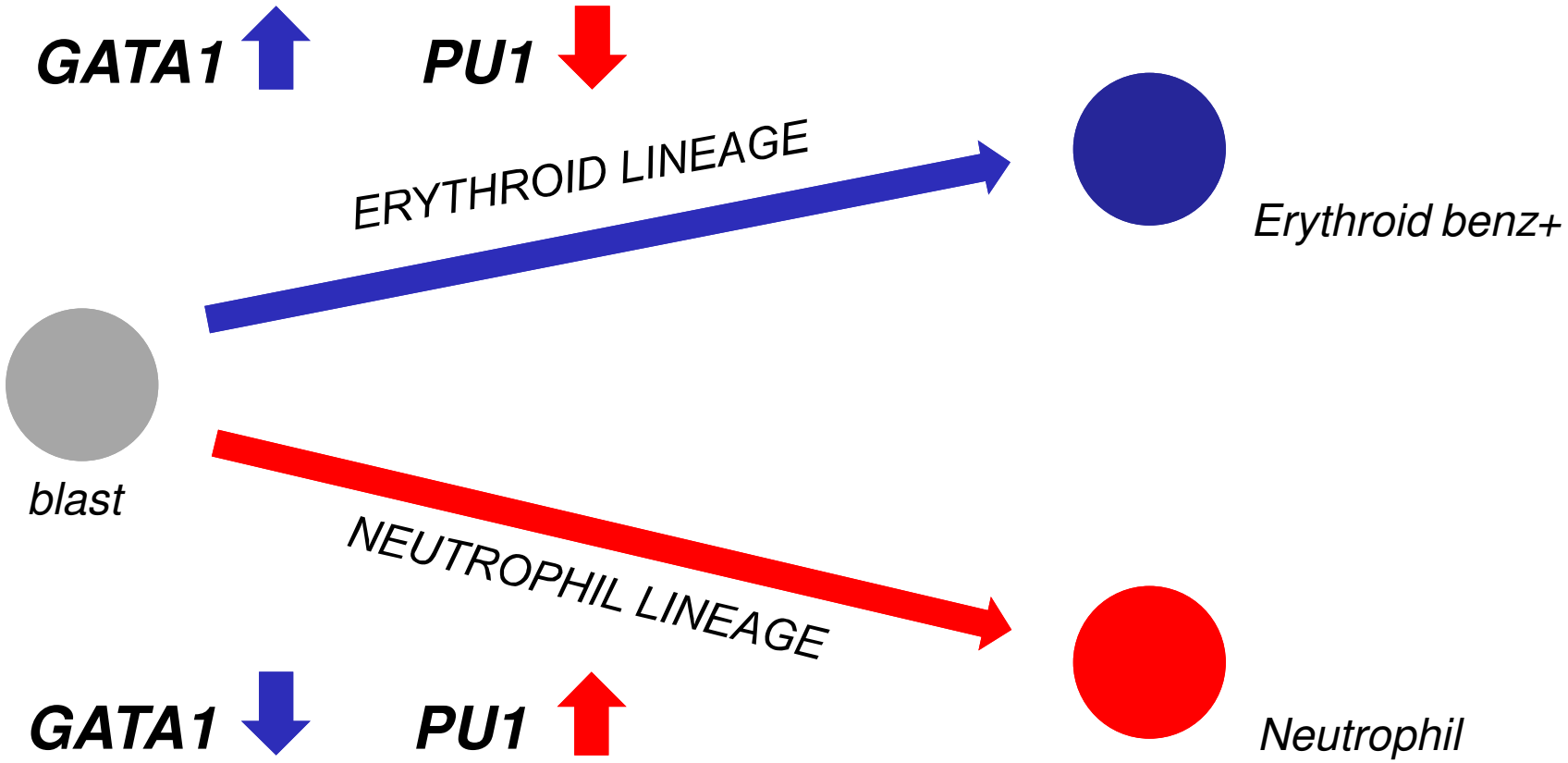
Hematopoiesis as a case-study for genetic control of lineage specification

Dynamical modeling



Loose et al. Curr Opin Hematol (2007)

Dynamical modeling: the PU.1 / Gata1 switch



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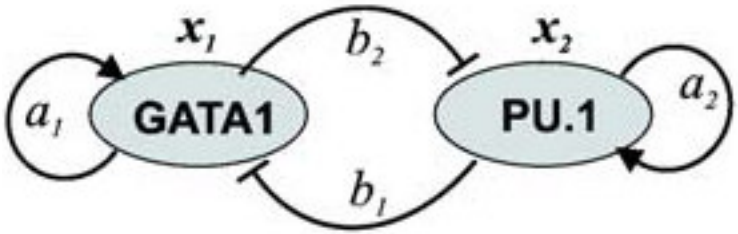

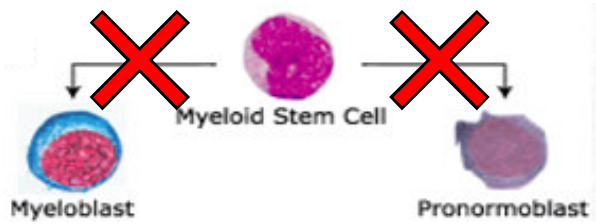

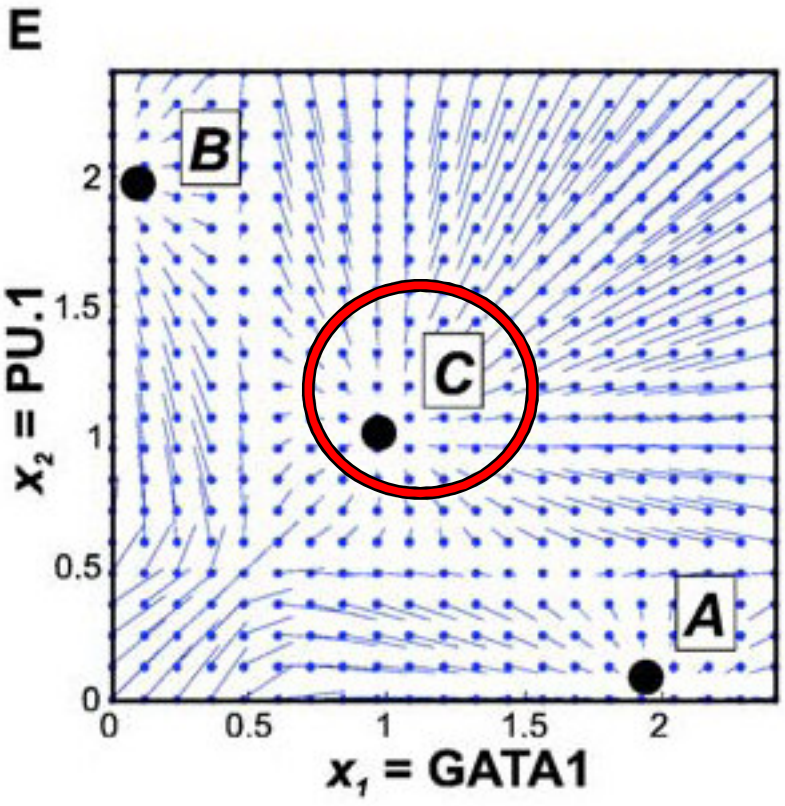

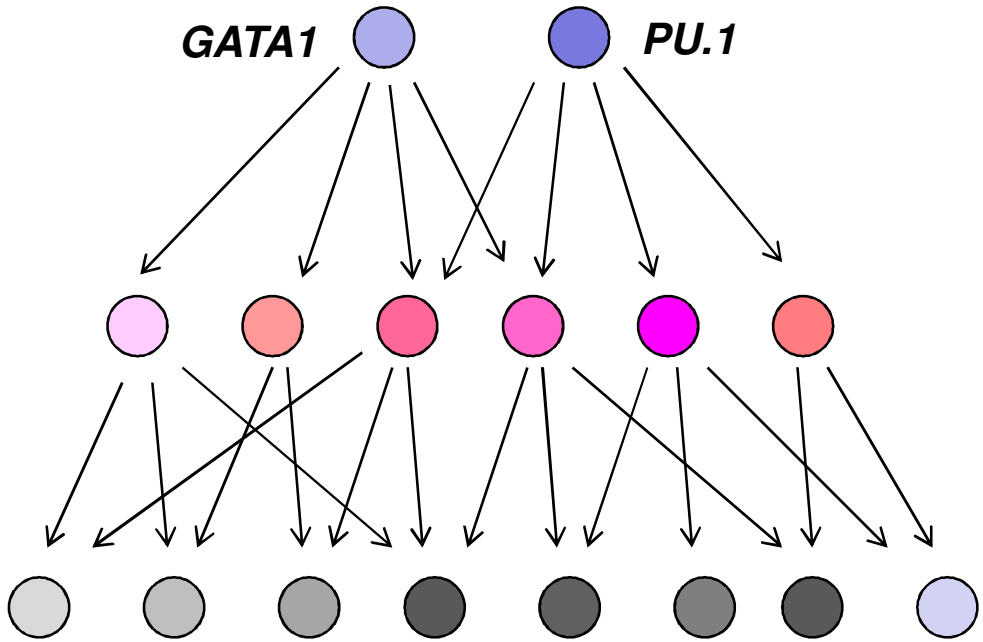

Huang et al. Developmental Biology (2007)

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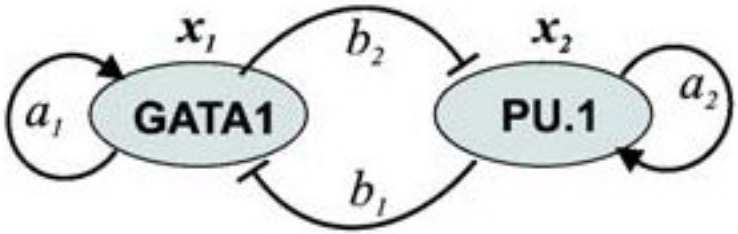

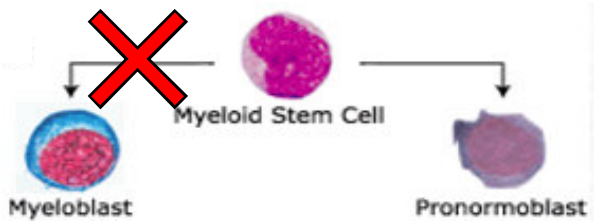

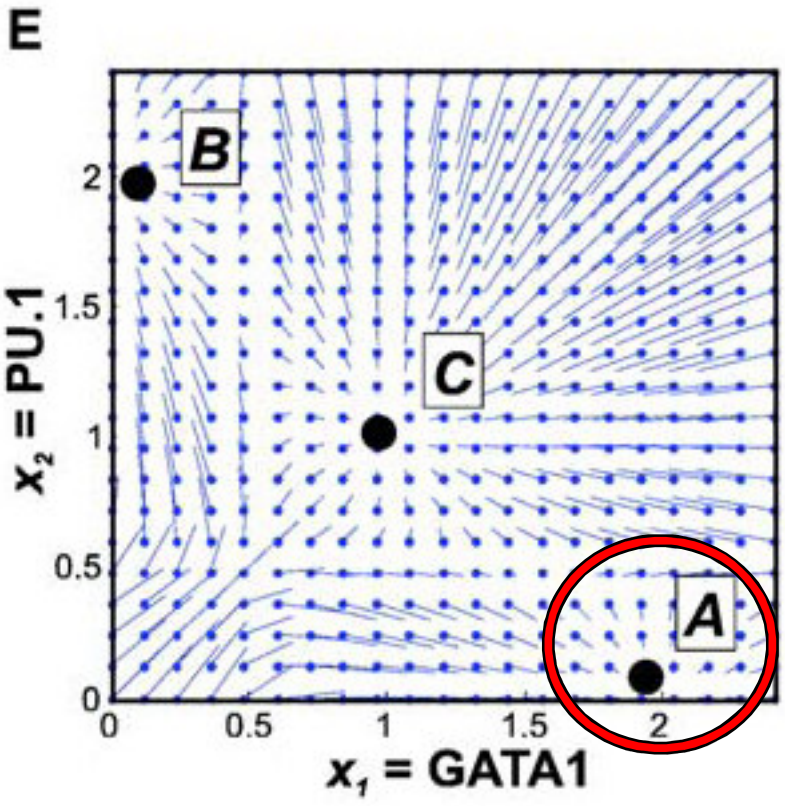

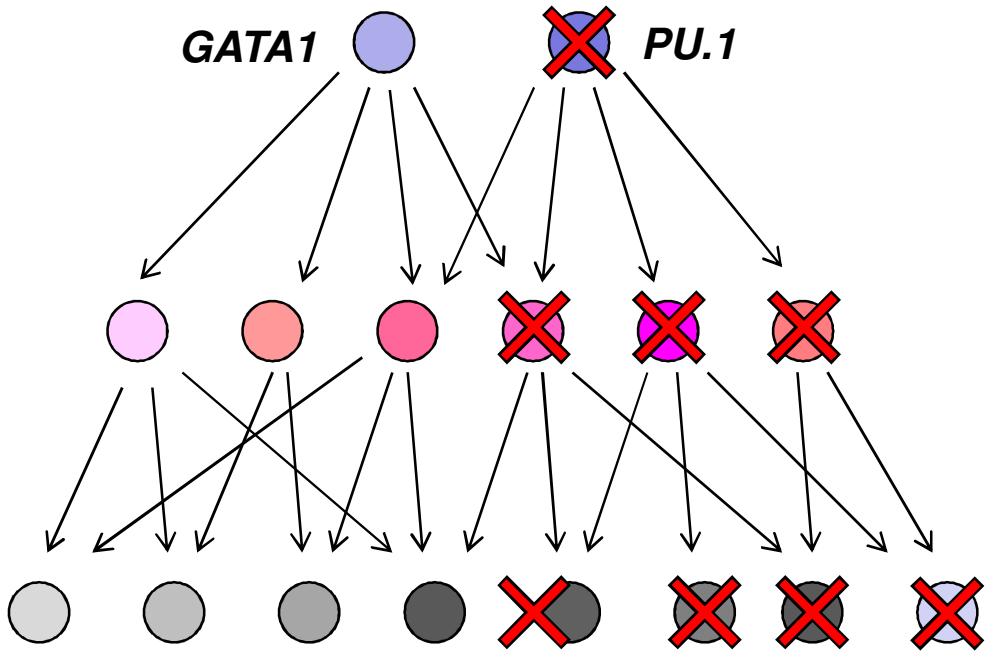

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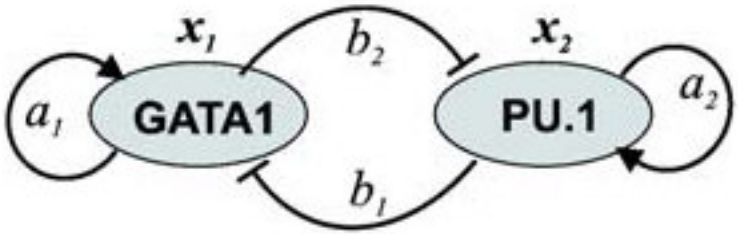

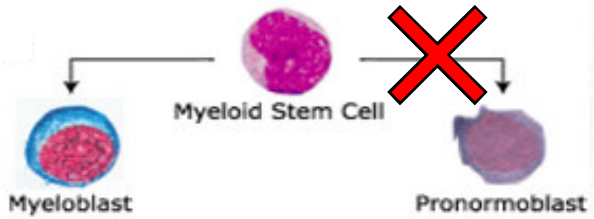

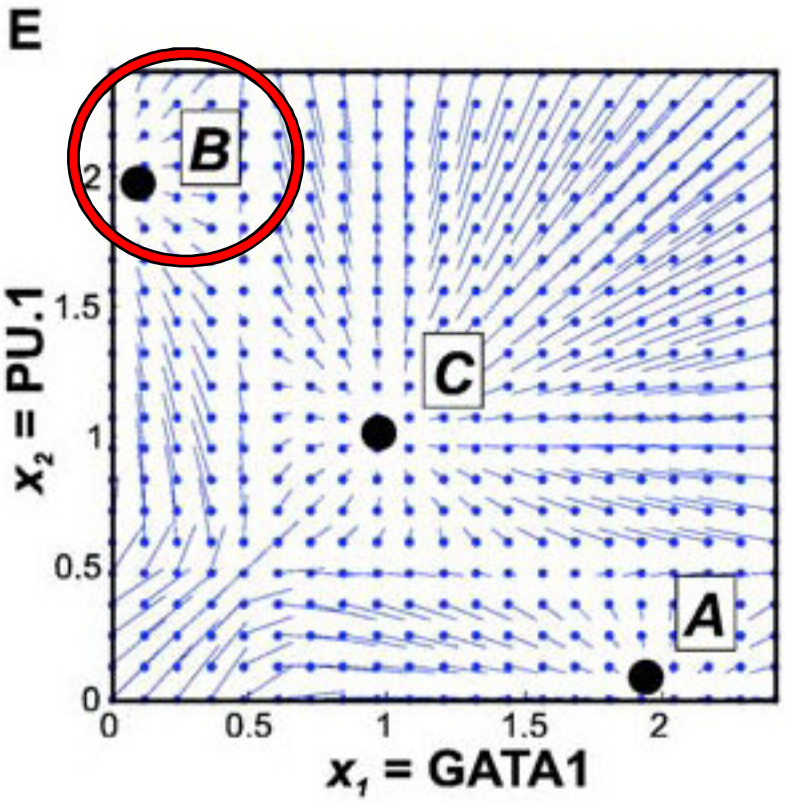

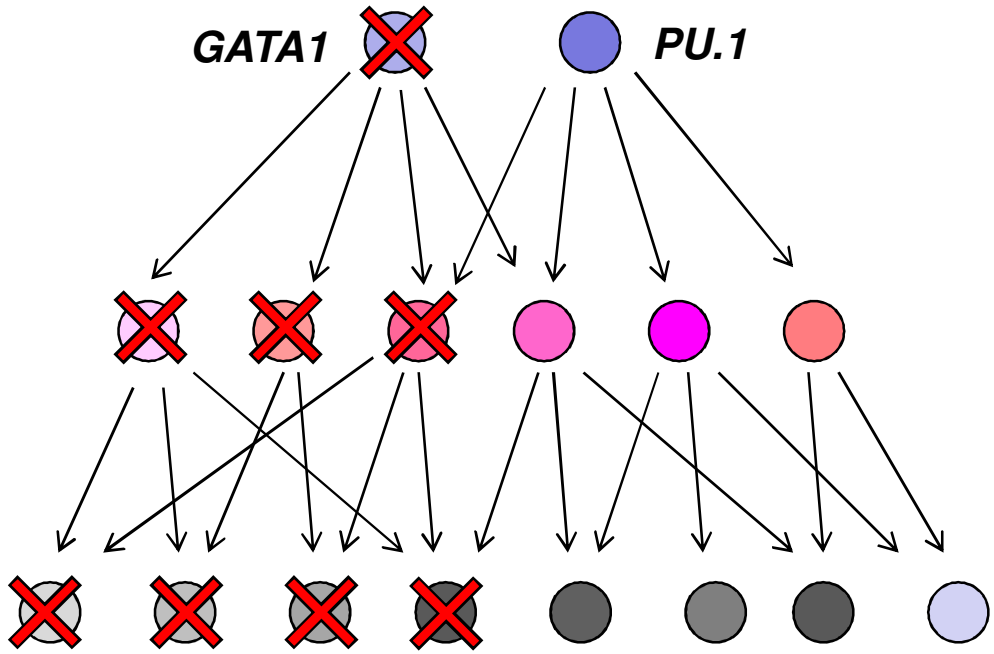

Huang et al. Developmental Biology (2007)

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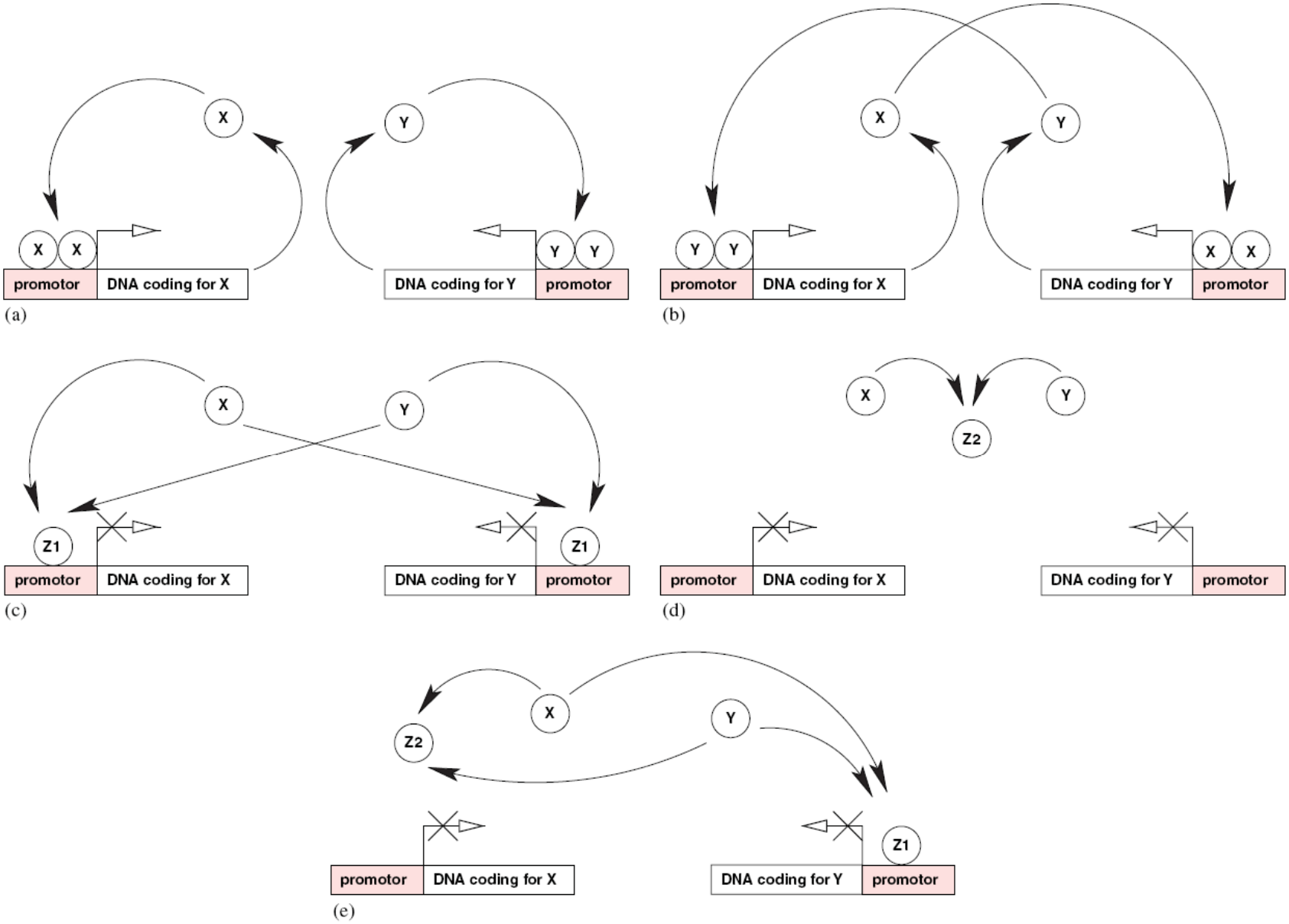
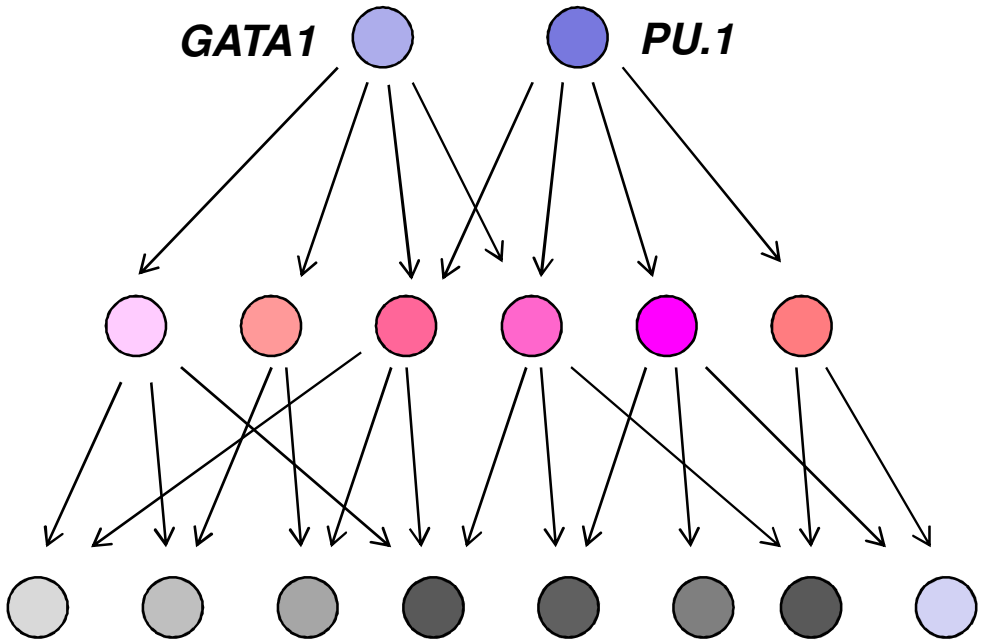
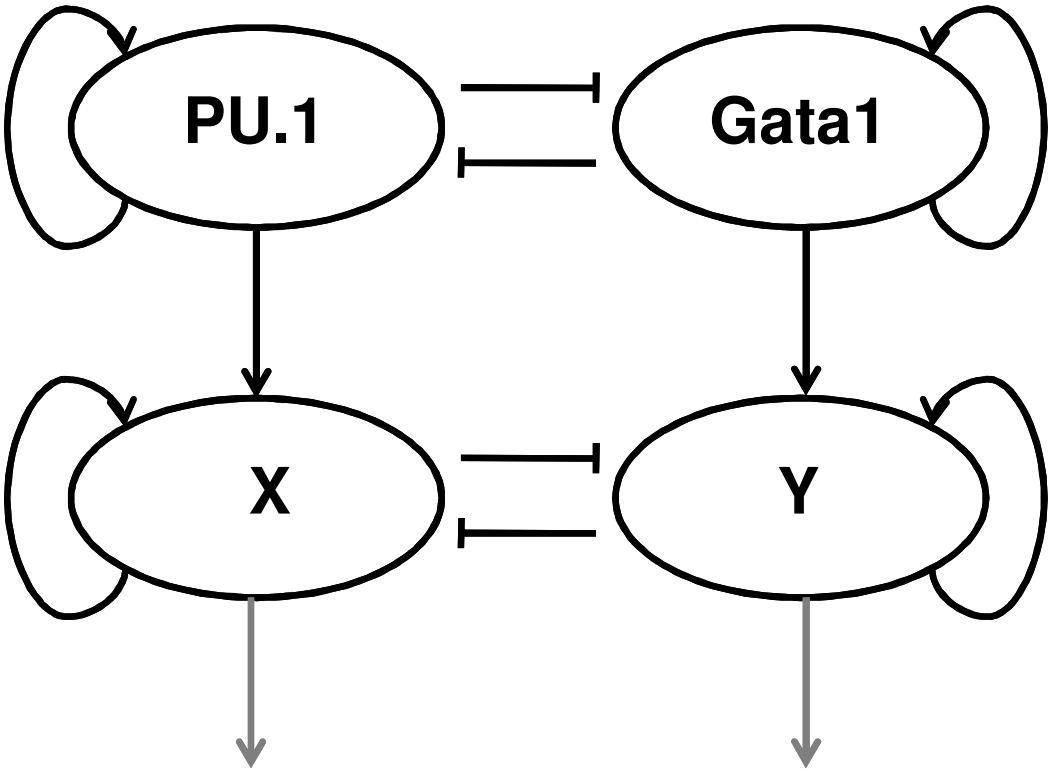


Roeder et al. J Theor Biol (2006)

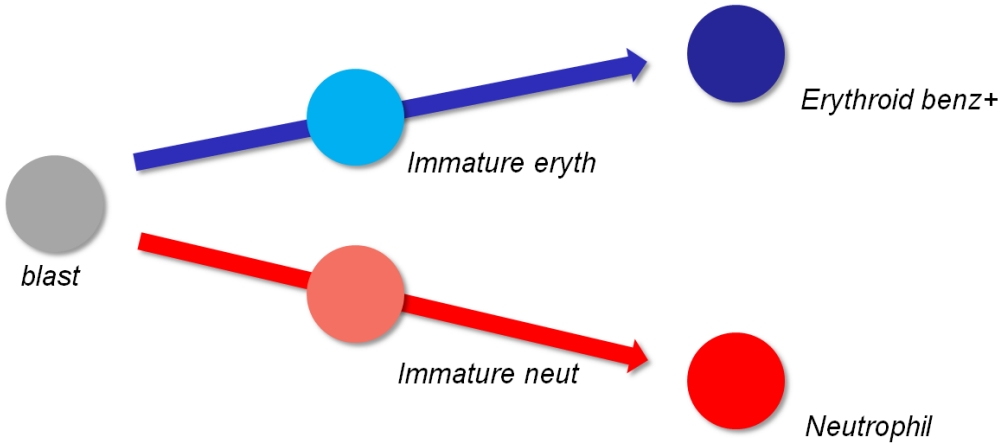
Dynamical modeling: extending the PU.1 / Gata1 switch

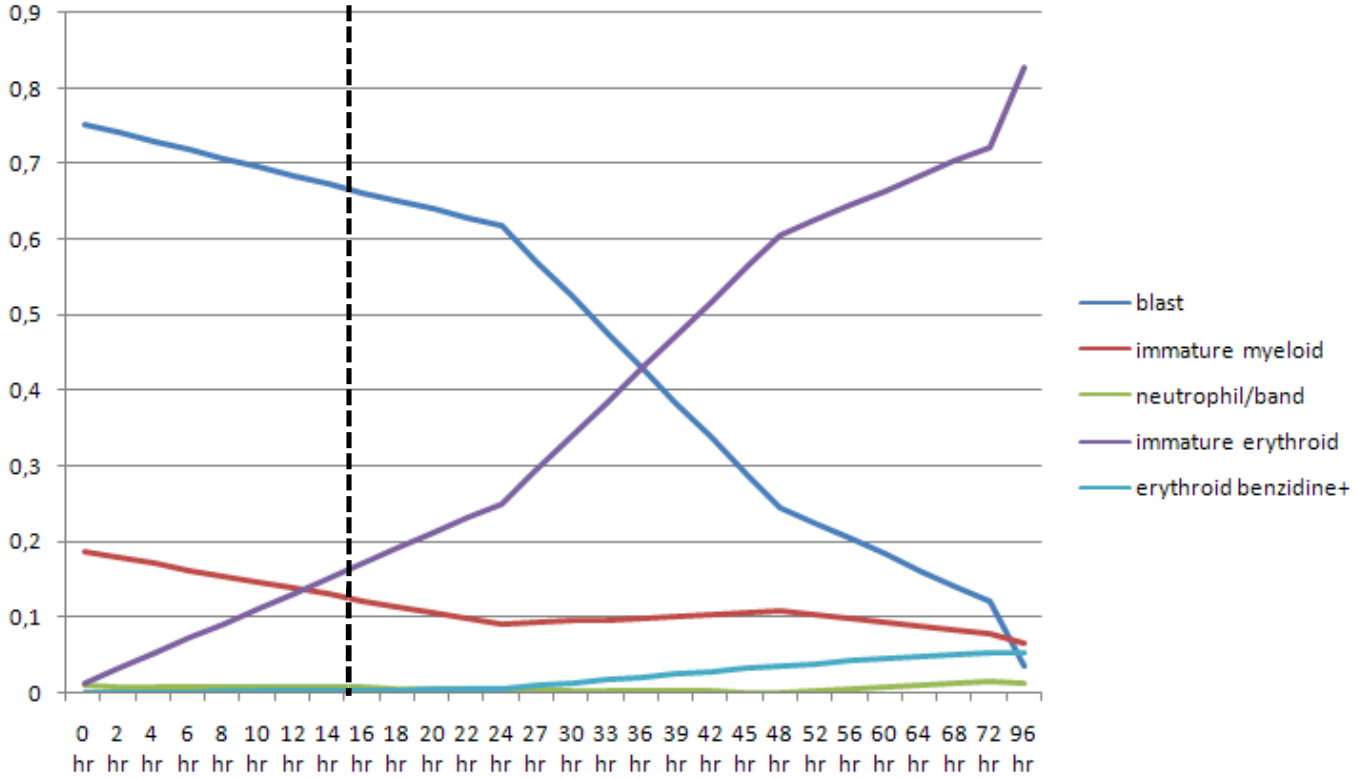




Current work

a) In silico microdissection of microarray data





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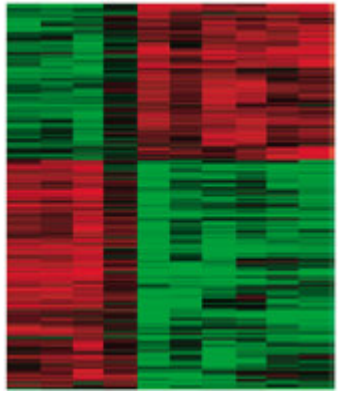
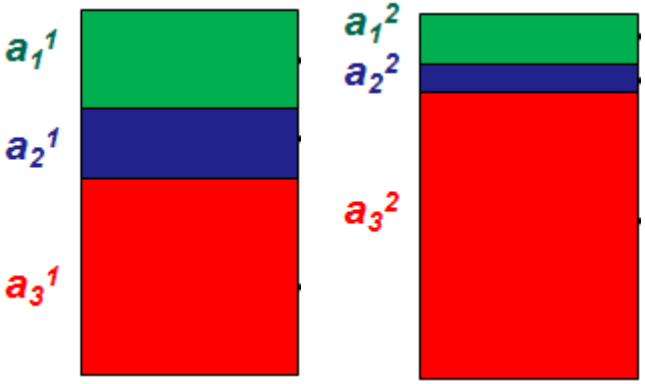
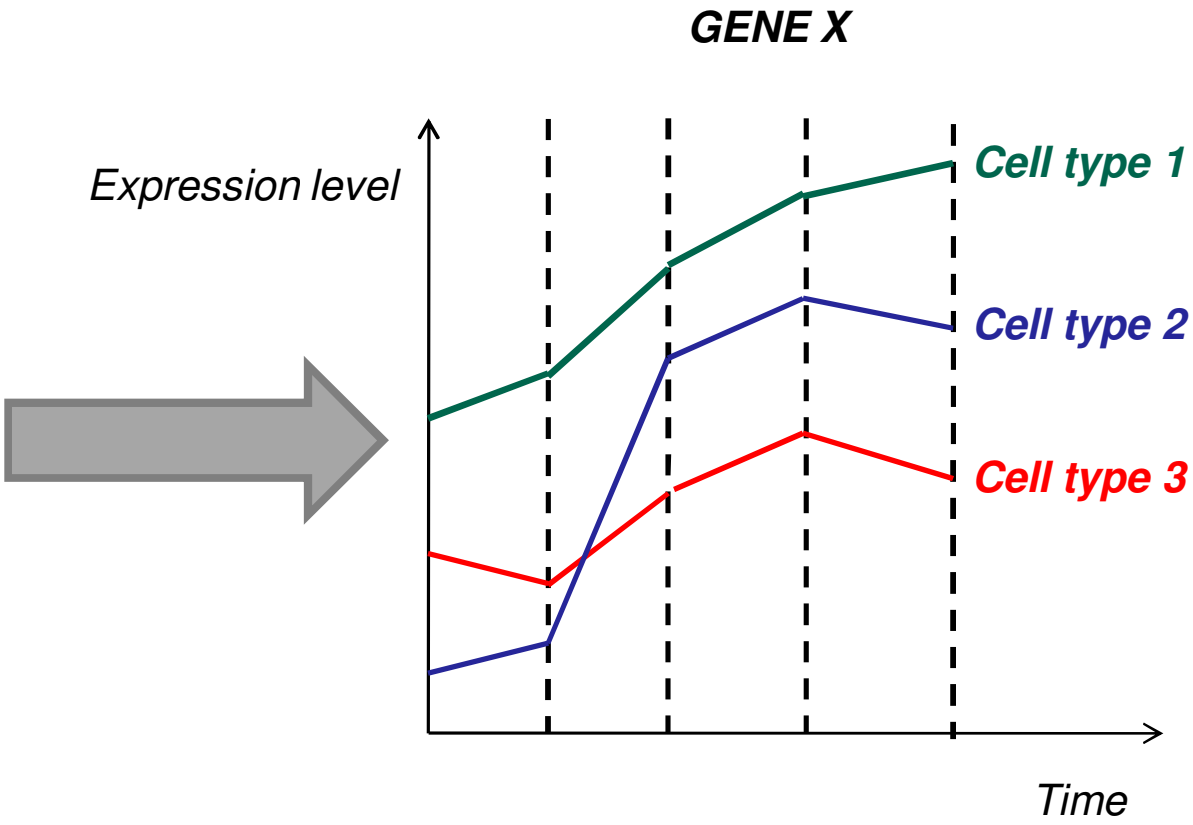


Raw expression data



Cell type fraction measurements

TO:



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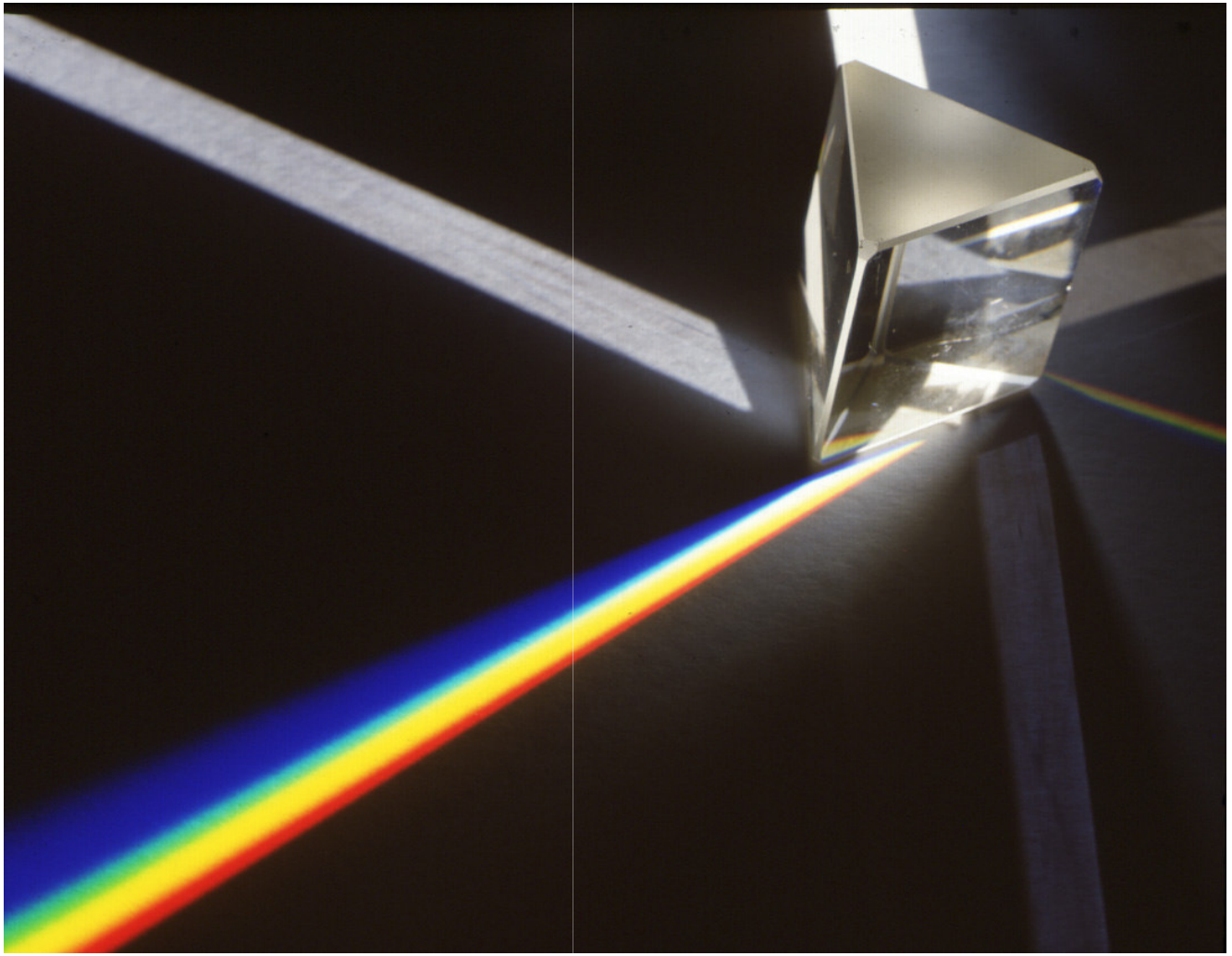
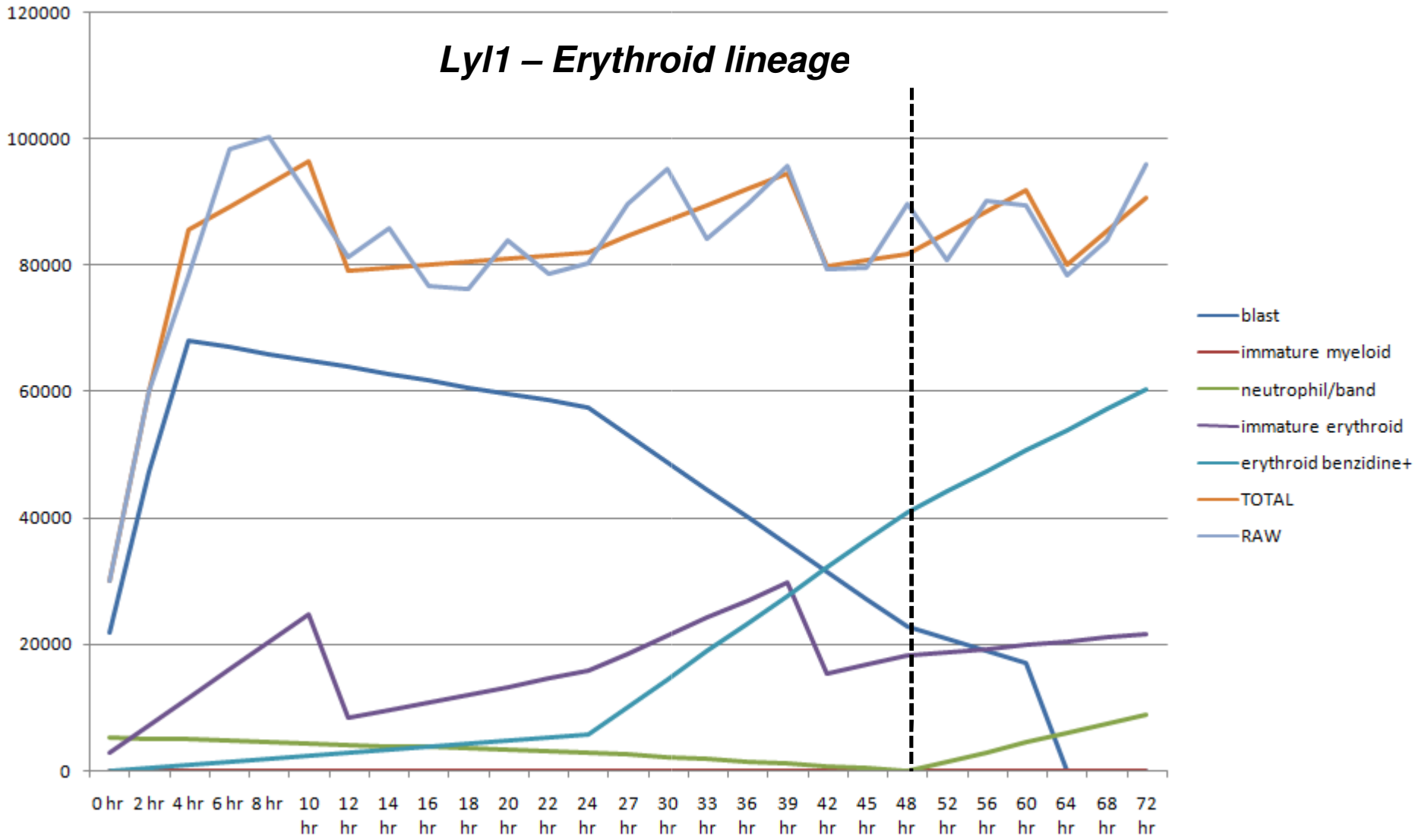


Current work

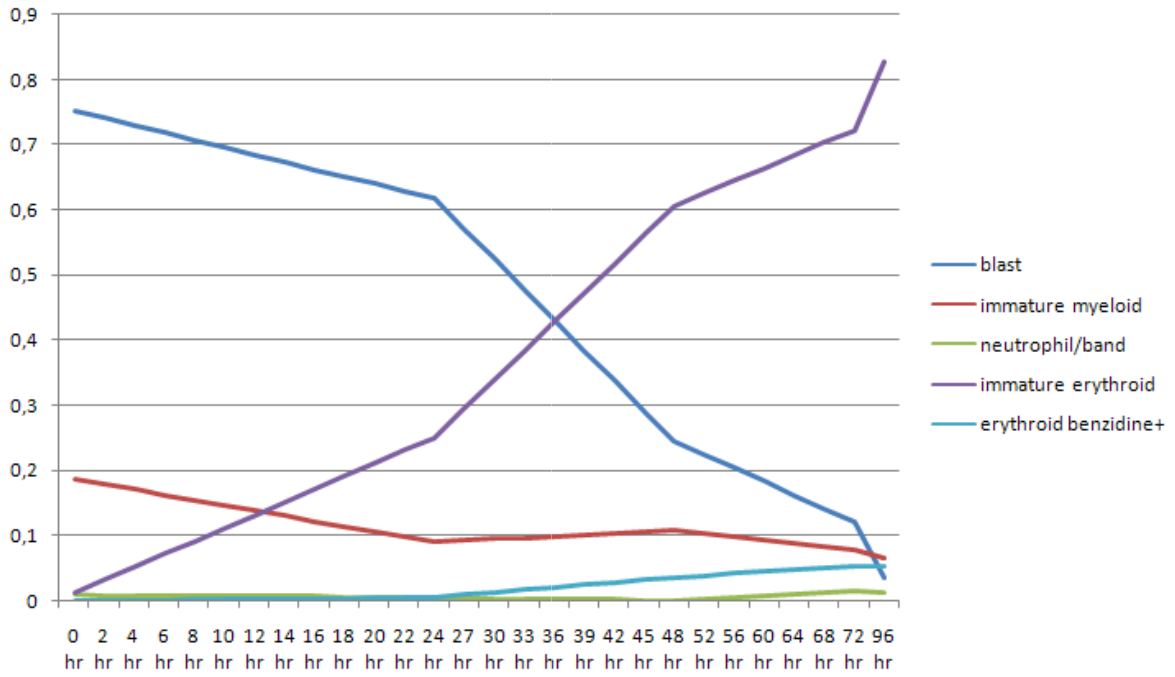
a) In silico microdissection of microarray data

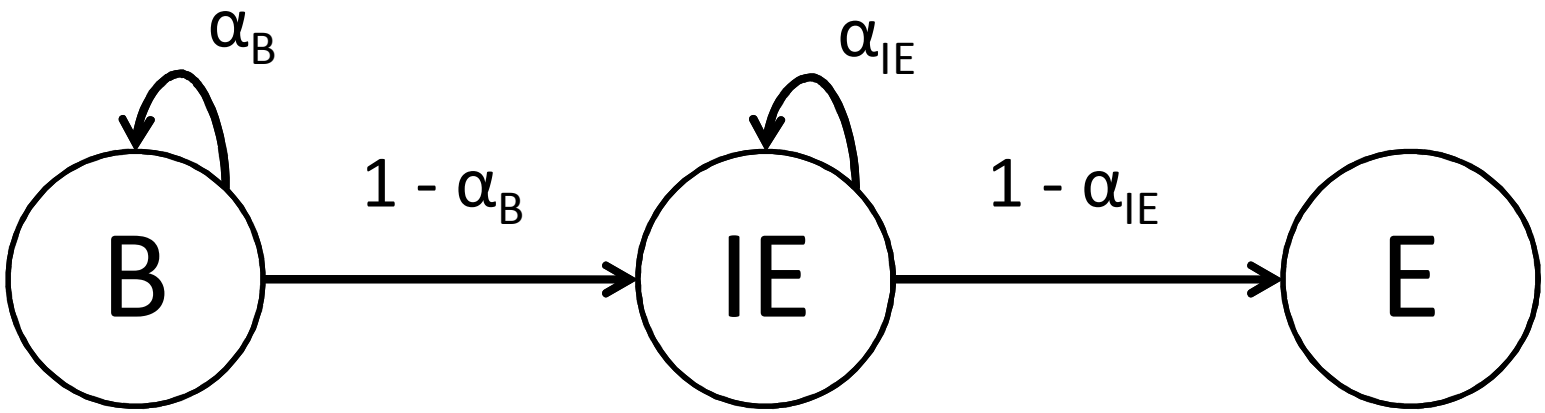
OPTIMIZATION PROBLEM: ***Standard least squares solution as the linear estimate for each one of the cell type-specific gene expression levels***



Current work

b) Cell population models





Future work

a) In silico microdissection of microarray data

b) Cell population models

c) Dynamical modeling (Pu.1 / Gata1 ?)

d) Network inference

Acknowledgements

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