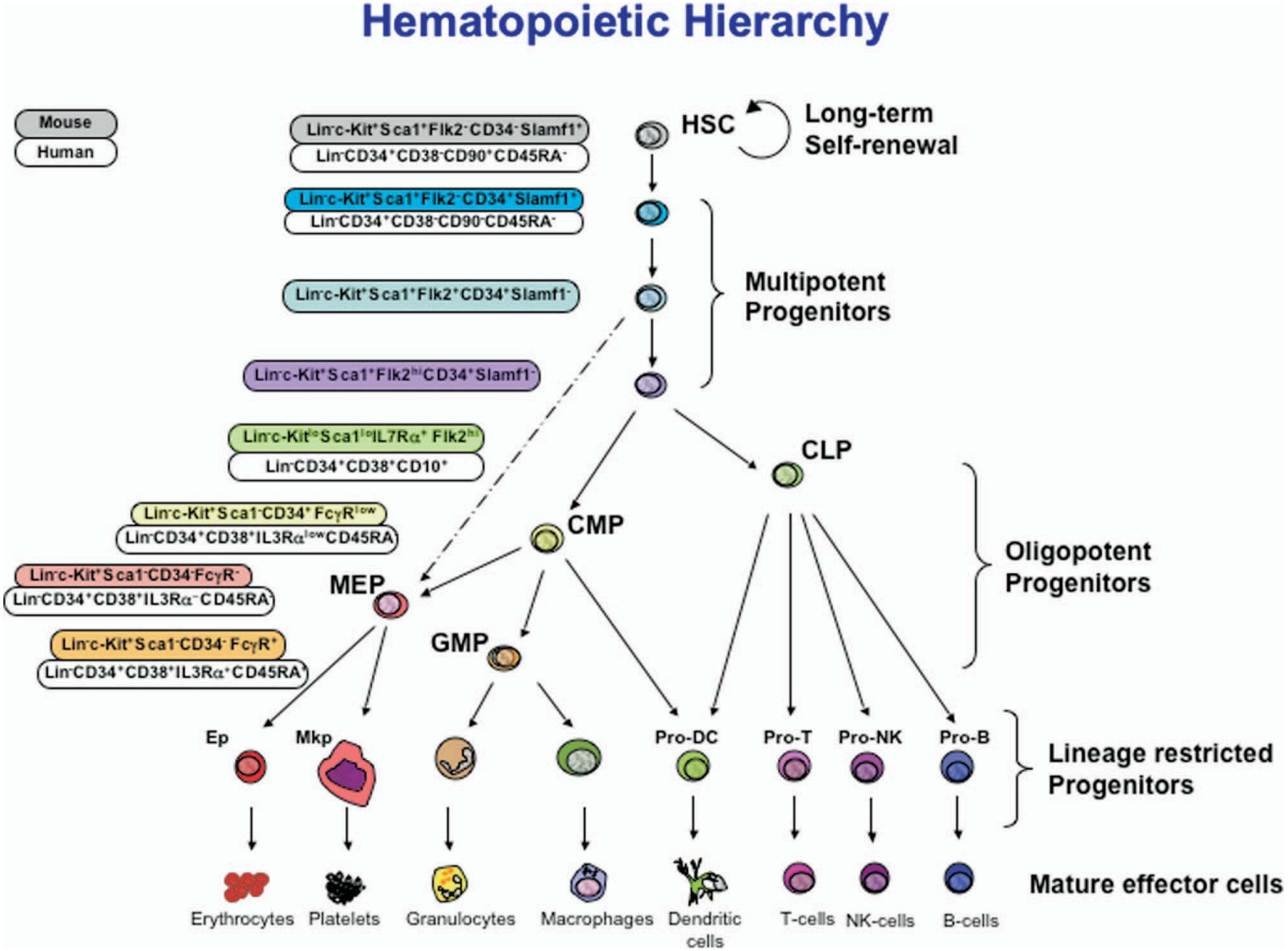
Cell Differentiation

Cristian Tomasetti

Cancer Dynamics RIT

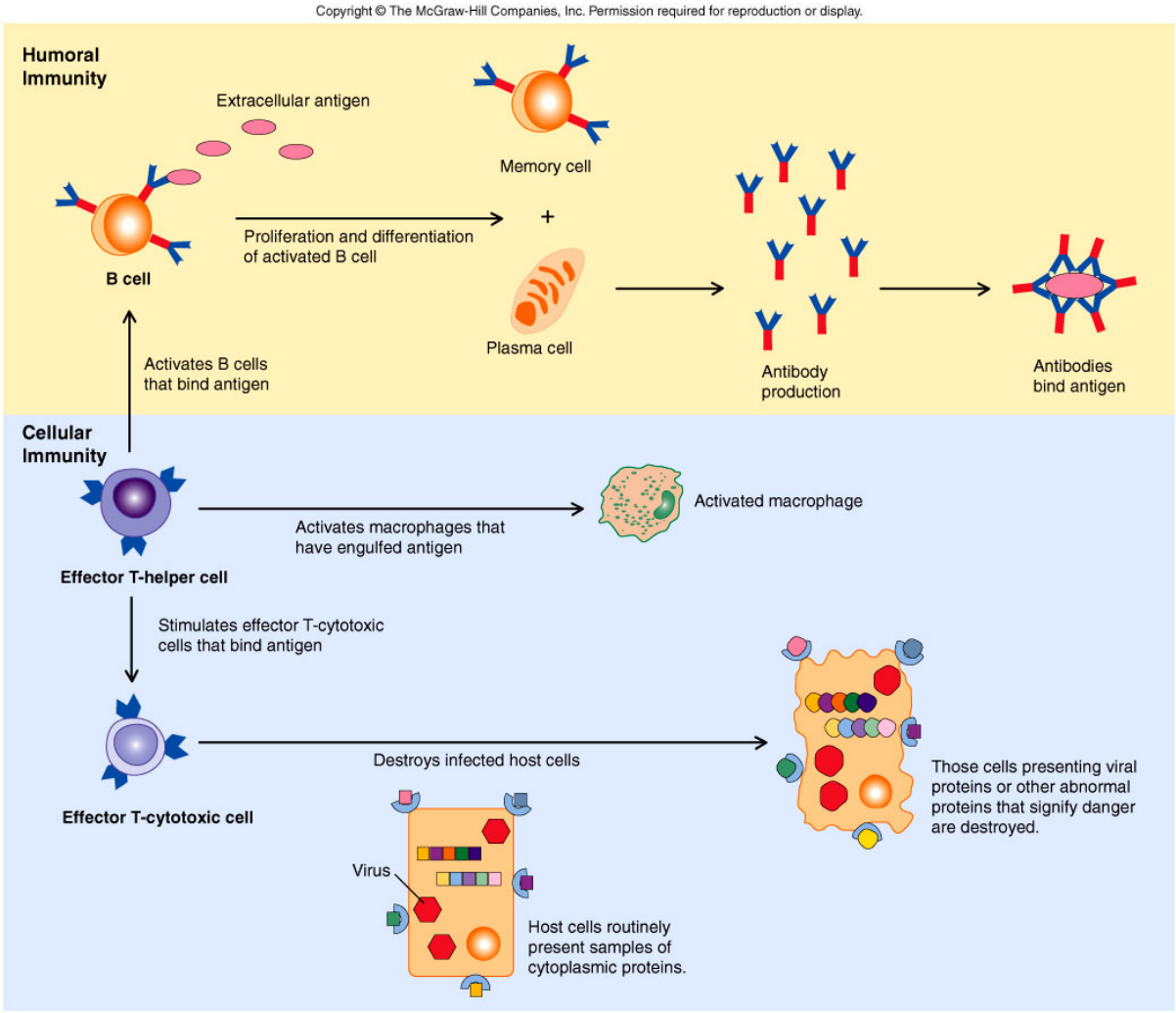
Friday October 30th, 2009

An Example of Differentiation



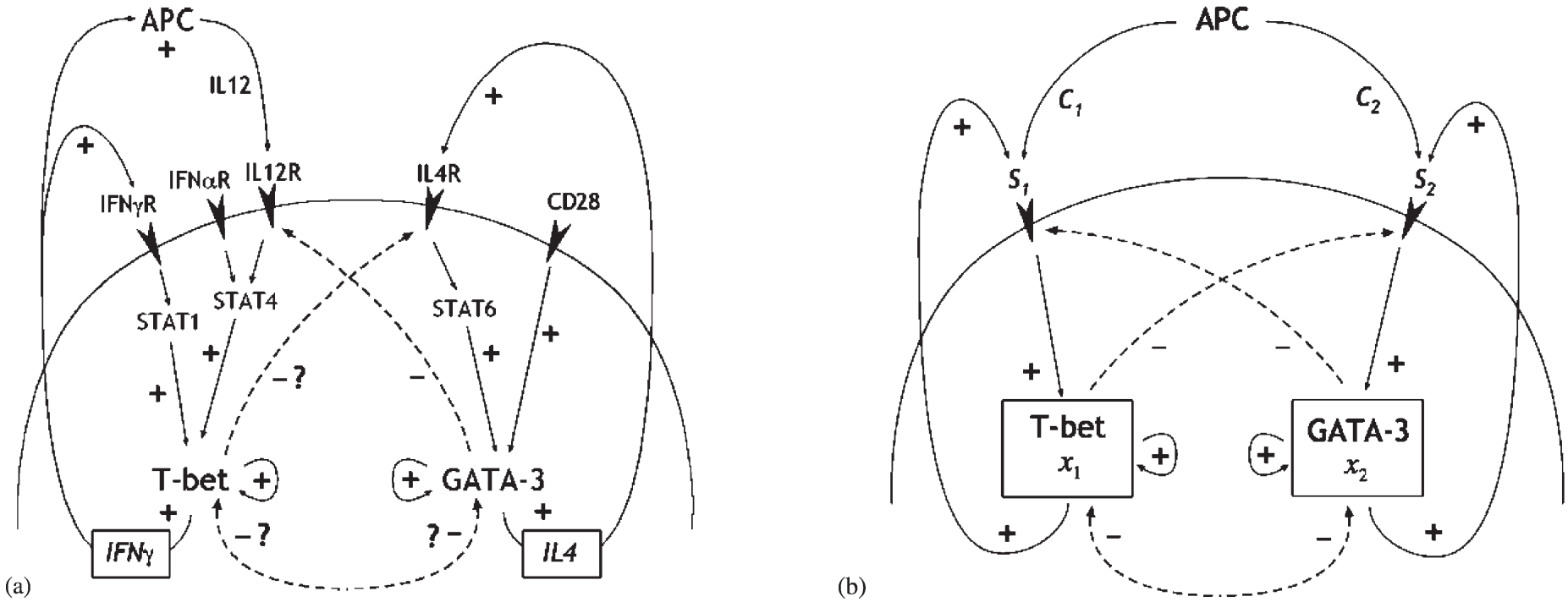
Yates - Callard - Stark
Journal of Theoretical Biology 2004

Humoral vs Cellular Immunity



Helper T cells (CD4+) differentiate either into Th1 (cellular immunity: production of IFNγ to combat intracellular pathogens) or Th2 (humoral immunity: production of cytokines IL-4, IL-5, IL-13 that activate B cells to produce antibodies against extracellular pathogens).

Network Diagram: a Binary Switch



Whether a precursor helper T cell becomes Th1 or Th2 depends on the strenght of polarizing signals (Il-12 and IFNγ for Th1 and Il-4 for Th2). There is cross-antagonism between the two transcription factors T-bet and GATA-3.

C_i = extrinsic signals (antigen on the surface of APCs).

S_i = cytokine external signaling (C_i plus signals dependent on the intracellular level of x_1 and x_2).

Equations for One Single Cell

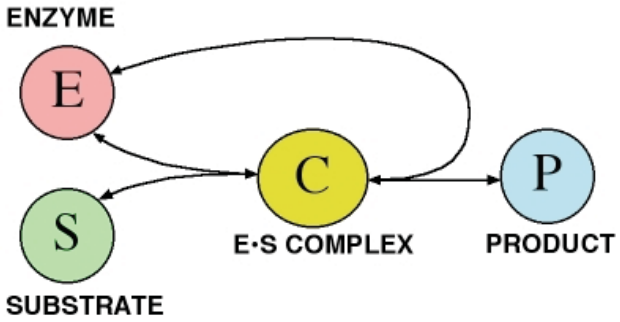
$$f_1 = \frac{\mathrm{d}x_1}{\mathrm{d}t} = -\mu x_1 + \left(\alpha_1 \frac{x_1^n}{\kappa_1^n + x_1^n} + \sigma_1 \frac{S_1}{\rho_1 + S_1}\right) \times \frac{1}{(1 + x_2/\gamma_2)} + \beta_1,$$

$$f_2 = \frac{\mathrm{d}x_2}{\mathrm{d}t} = -\mu x_2 + \left(\alpha_2 \frac{x_2^n}{\kappa_2^n + x_2^n} + \sigma_2 \frac{S_2}{\rho_2 + S_2}\right) \times \frac{1}{(1 + x_1/\gamma_1)} + \beta_2.$$

x_1 and x_2 are the intracellular concentrations of T-bet and Gata-3.
α and σ are maximum rates, n is the Hill exponent (sharpness of the autoactivation switch).
μ = decay rate constant. β = basal rate of protein synthesis.

Michaelis-Menten Kinetics

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$$

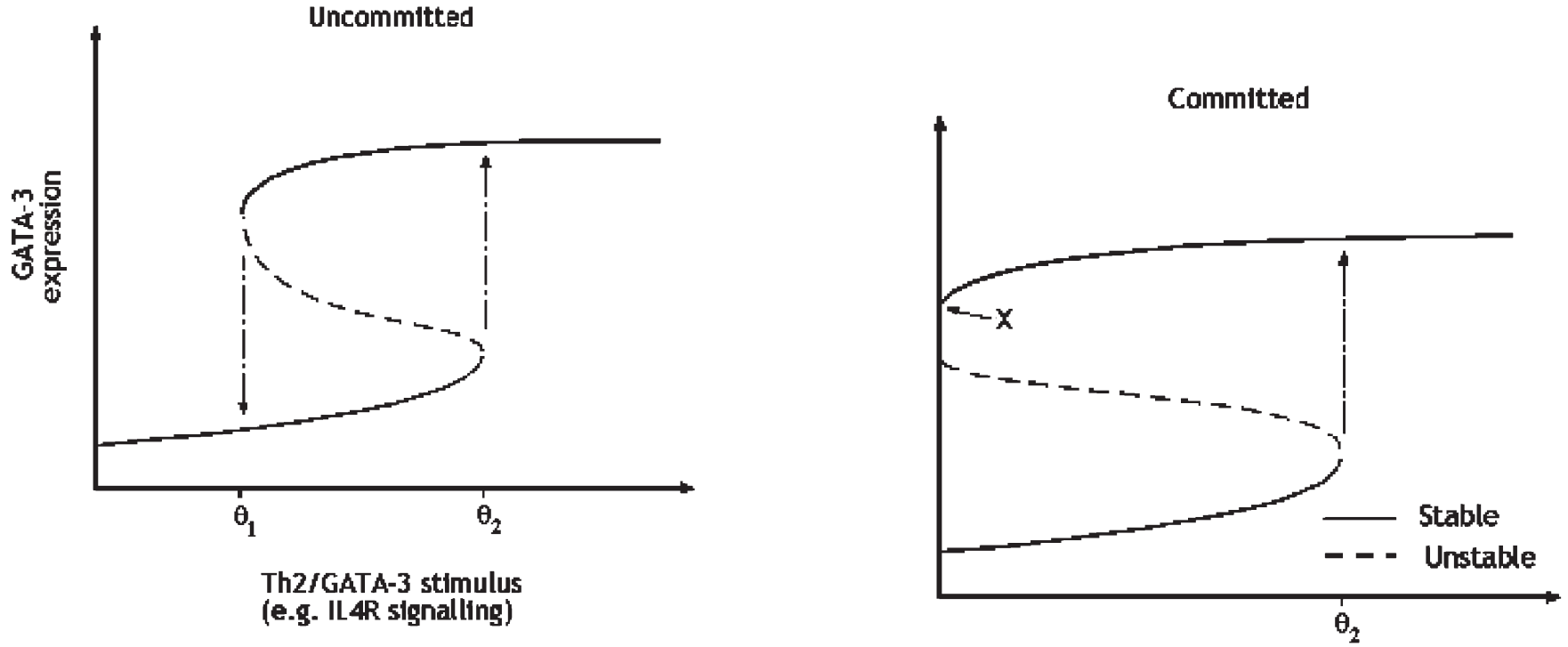


Assumptions: the total enzyme concentration and the concentration of the intermediate complex do not change over time (say the concentration of the substrate-bound enzyme ([ES]) changes much more slowly than those of the product ([P]) and substrate ([S])). Also, the enzymatic reaction is assumed to be irreversible, and the product does not bind to the enzyme.

$$V = -\frac{dS}{dt} = -\frac{V_{max} S}{K_m + S}$$

where $V_{max} = k_2 E_{Total}$ $K_m = \frac{k_{-1} + k_2}{k_1}$

Bistability and Cytokine Memory



a) Effect of increasing S_2 on a precursor Th0.
b) The curve shifts to the left when α is increased or μ is decreased (coupled to cell division?), and we obtain irreversible commitment, i.e. cytokine memory.

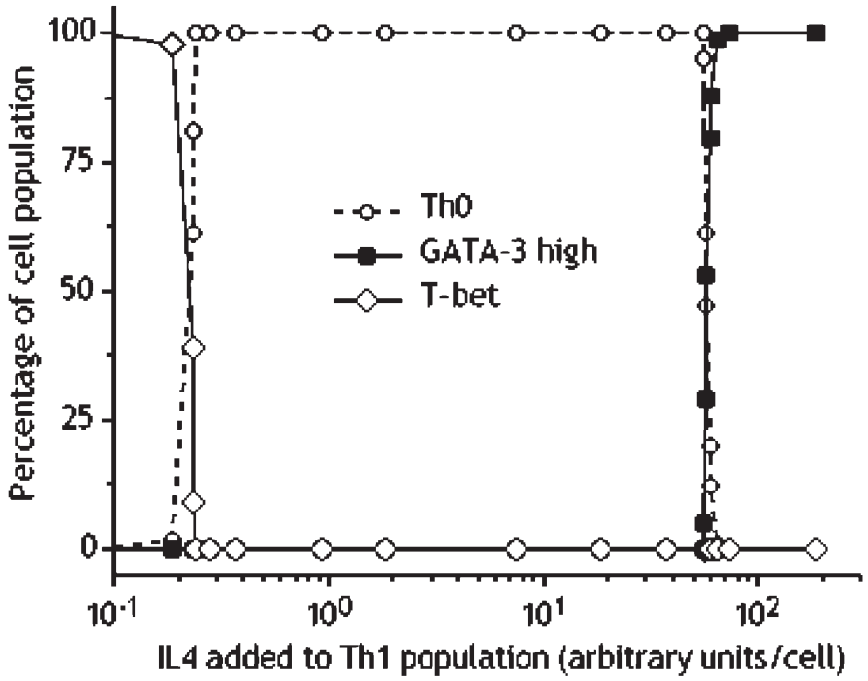
Equations for the Population Density $\phi(x_1, x_2, t)$

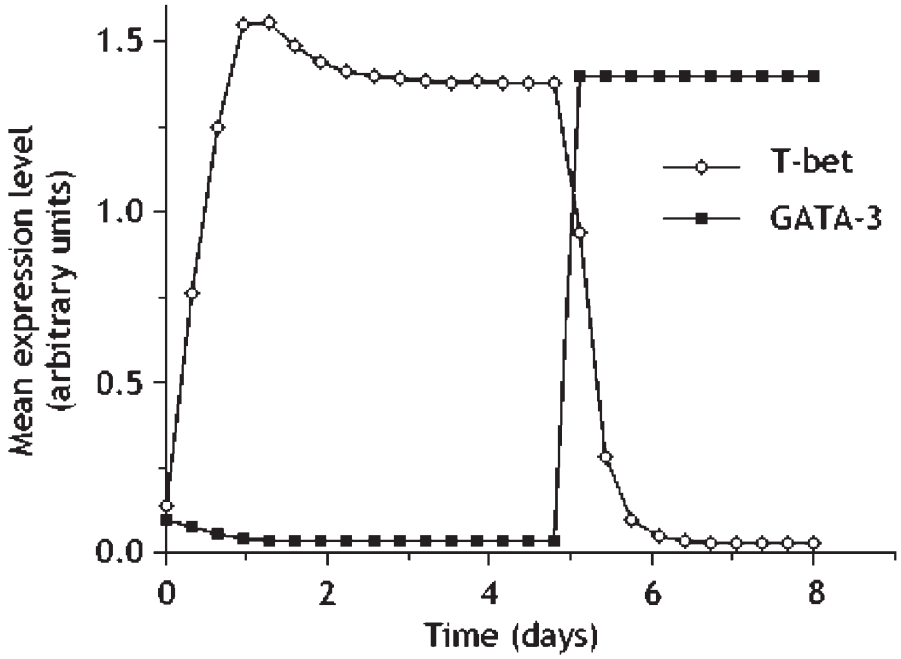
$$S_i = \frac{C_i(t) + \int x_i \phi \, \mathrm{d}x_1 \mathrm{d}x_2}{\int \phi \mathrm{d}x_1 \mathrm{d}x_2}, \quad i = 1, 2.$$

$$g\,\phi = \frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x_1}(f_1 \phi) + \frac{\partial}{\partial x_2}(f_2 \phi), \text{ where}$$
$$f_1 = \mathrm{d}x_1/\mathrm{d}t, \quad f_2 = \mathrm{d}x_2/\mathrm{d}t.$$

Recall that x_1 and x_2 are the intracellular concentrations of T-bet and Gata-3.
Extracellular cytokine signal S_i depends on the total level of the intracellular transcription factor x_i (each cell senses the population average) and on the extrinsic signal C_i.
$g =$ division rate (2 per day).
Then the time evolution of the population density is given by a conservation law (mass), solved by the method of characteristics.

Reversal and Retroviral Expression



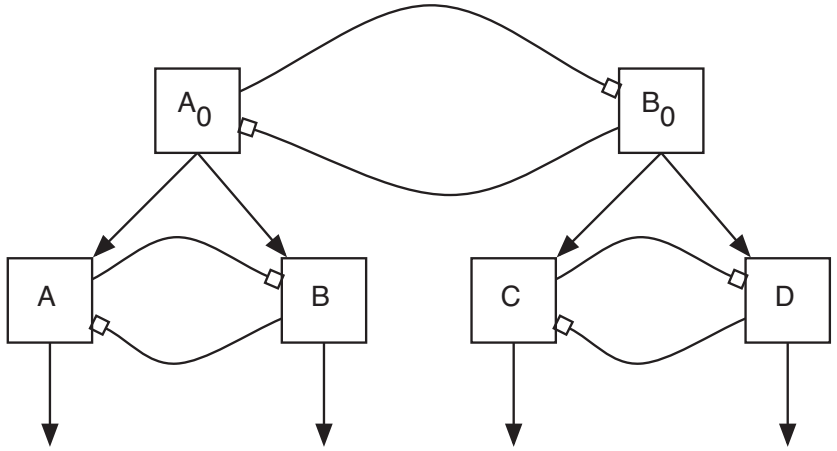


a) Effect of increasing C_2 on a Th1 population.
b) Retroviral expression causes a genuine switch, without passing through state Th0.
Retrovirus: An RNA virus (a virus composed not of DNA but of RNA). Retroviruses have an enzyme called reverse transcriptase that gives them the unique property of transcribing RNA (their RNA) into DNA. The retroviral DNA can then integrate into the chromosomal DNA of the host cell to be expressed there. The human immunodeficiency virus (HIV), the cause of AIDS, is a retrovirus.

Cinquin - Demongeot
Journal of Theoretical Biology 2005

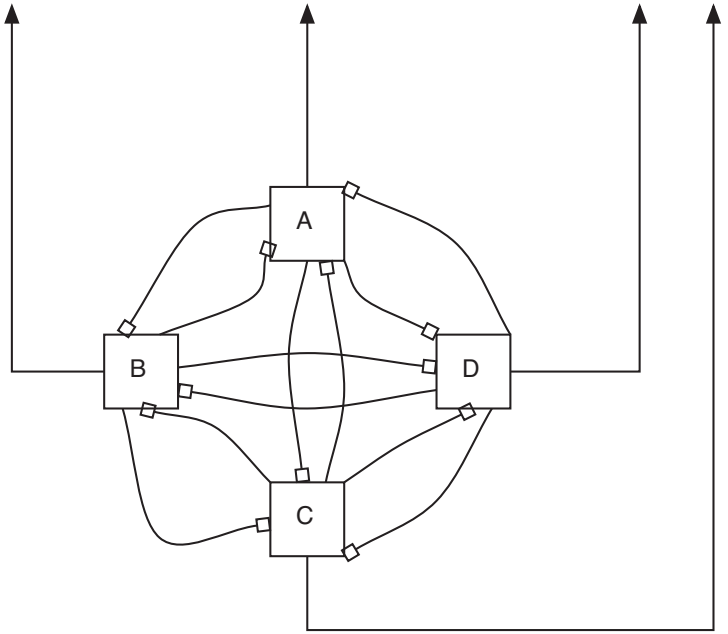
High Dimensional Differentiation Switches

a) Binary, hierarchic decisions model



Genes specific for cell-type

b) Simultaneous decision model



The Model

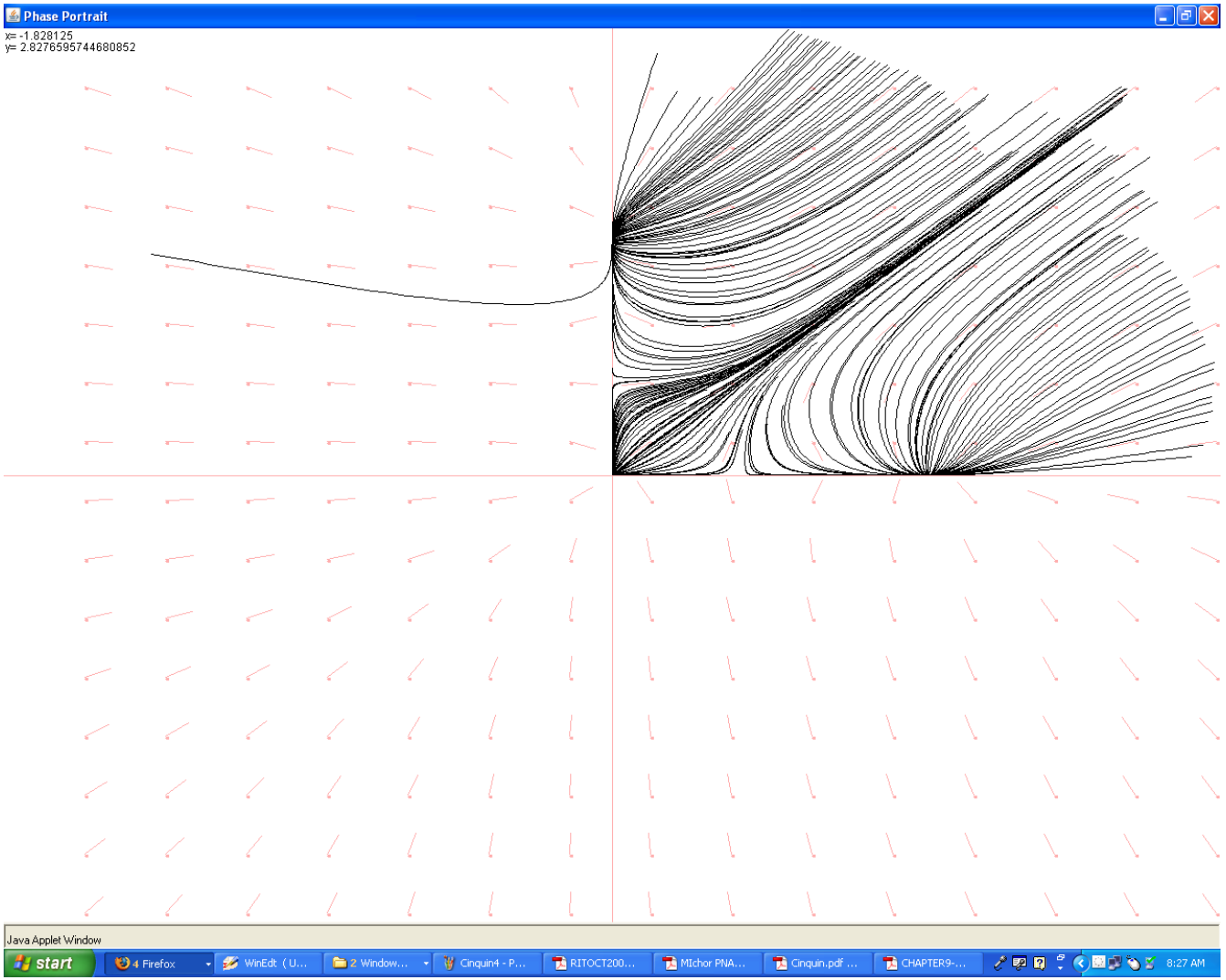
$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -x_1 + \frac{\sigma x_1^c}{1 + \Sigma_{i=1}^{n} x_i^{\mathrm{c}}} + \alpha$$

$$\cdots$$

$$\frac{\mathrm{d}x_n}{\mathrm{d}t} = -x_n + \frac{\sigma x_n^c}{1 + \Sigma_{i=1}^{n} x_i^{\mathrm{c}}} + \alpha$$

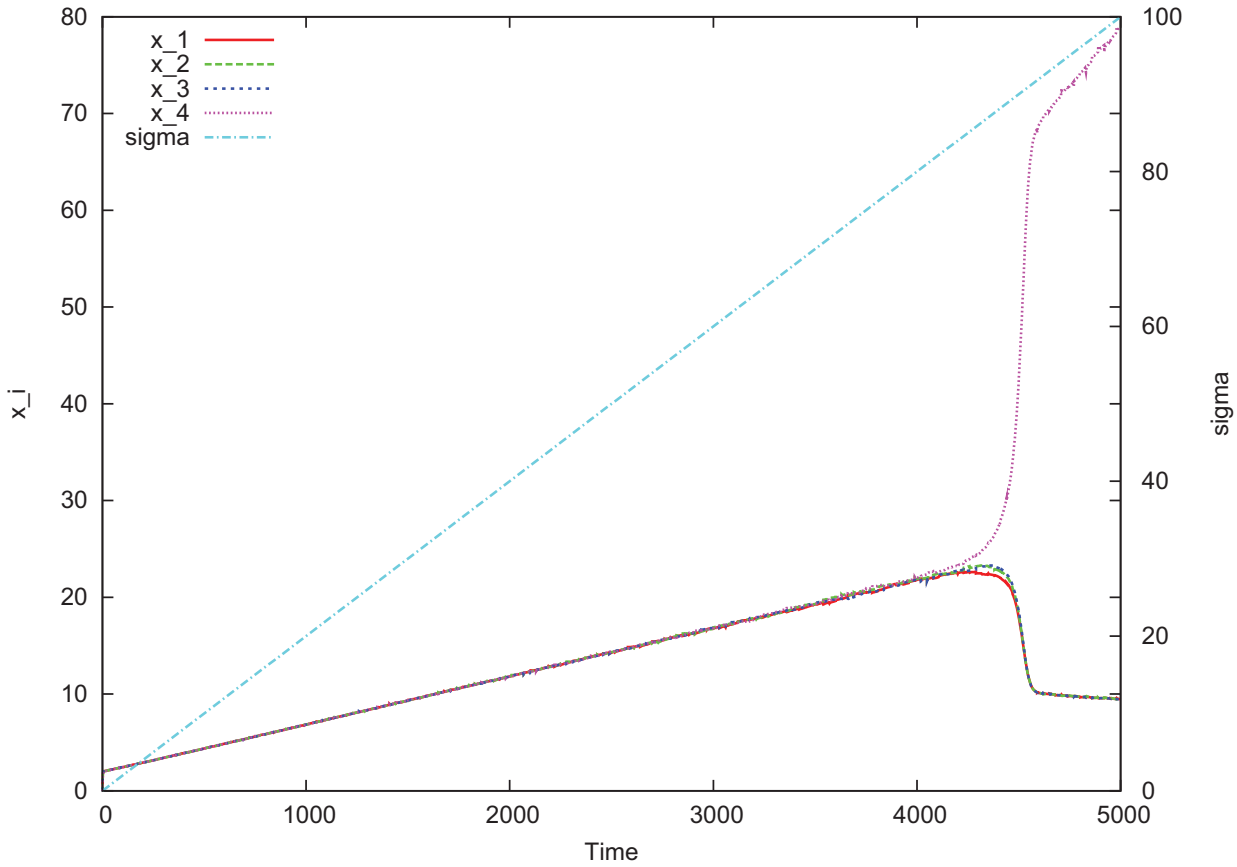
The model includes a first order degradation rate, a leak α, autoactivation and mutual inhibition.
x_i are the intracellular concentrations of transcription factor i.
c is the Hill exponent, i.e. the sharpness of the autoactivation switch.
σ is related to the strength of gene expression.
By increasing σ, the total number of steady states increases.

The Phase Portrait



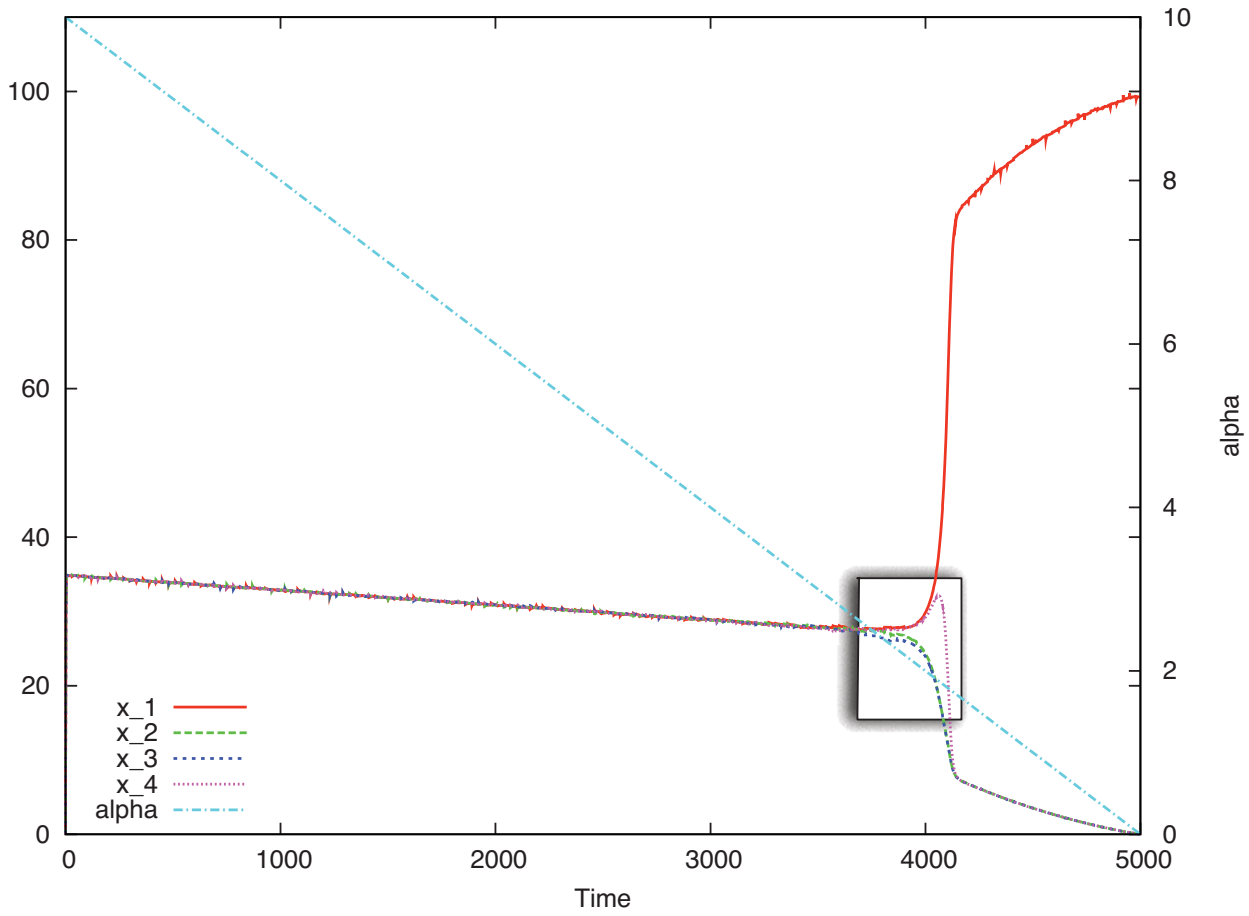
A precursor cell Th0 (the steady state at the origin) starts differentiating by increasing the levels of x_1 and x_2, and therefore decreasing the probability that the cell will keep its phenotype.
In the above figure, $\alpha = 0$, $c = 2$ and $\sigma = 2.2$.

Time Evolution Increasing σ



The 4 elements are initially coexpressed at an identical level, which increases with σ; when σ reaches a threshold level, one element is upregulated, and others are downregulated. Parameters in the simulation were $\sigma = 2$ and $c = 1.1$. Low, random noise was added to allow the system to escape the equilibrium as it became unstable.

Time Evolution Decreasing α



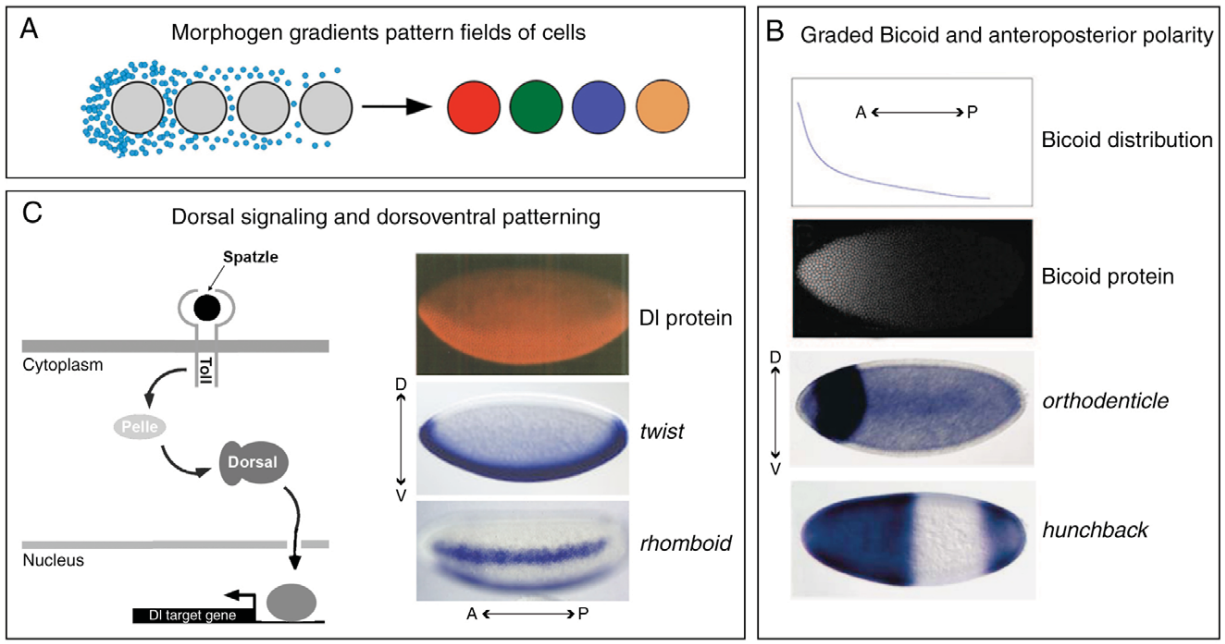
The 4 elements are initially coexpressed at identical levels (higher than the leak α because of autocatalysis); when the leak reaches a threshold level, one element is upregulated, and others are downregulated. Low, random noise was added to allow the system to escape the equilibrium as it became unstable. Parameters in the simulation were $\sigma = 100$ and $c = 1.1$.

Ashe - Briscoe
Development 2006

Morphogens: Signalling Gradients

- Cells receive positional information that instructs them to develop in specific ways, depending on their location within a tissue.
- Typically, in current models it is proposed that a signal (morphogen) produced from a defined localised source forms a concentration gradient as it spreads through surrounding tissue. The graded signal then acts directly on cells, in a concentration-dependent manner, to specify gene expression changes and cell fate selection.
- Examples: limb appendages and the nervous systems in vertebrates and Drosophila.

Morphogens: Signalling Gradients



a) Theoretical example.
b) Anterior-posterior polarity of the transcription factor Bicoid in Drosophila.
c) Dorsal-ventral polarity: the ligand Spatzle binds to the transmembrane receptor Toll which initiates the signal that activates the transcription factor Dl.