In the name of the most high

Introduction to Bioinformatics

Differentiation

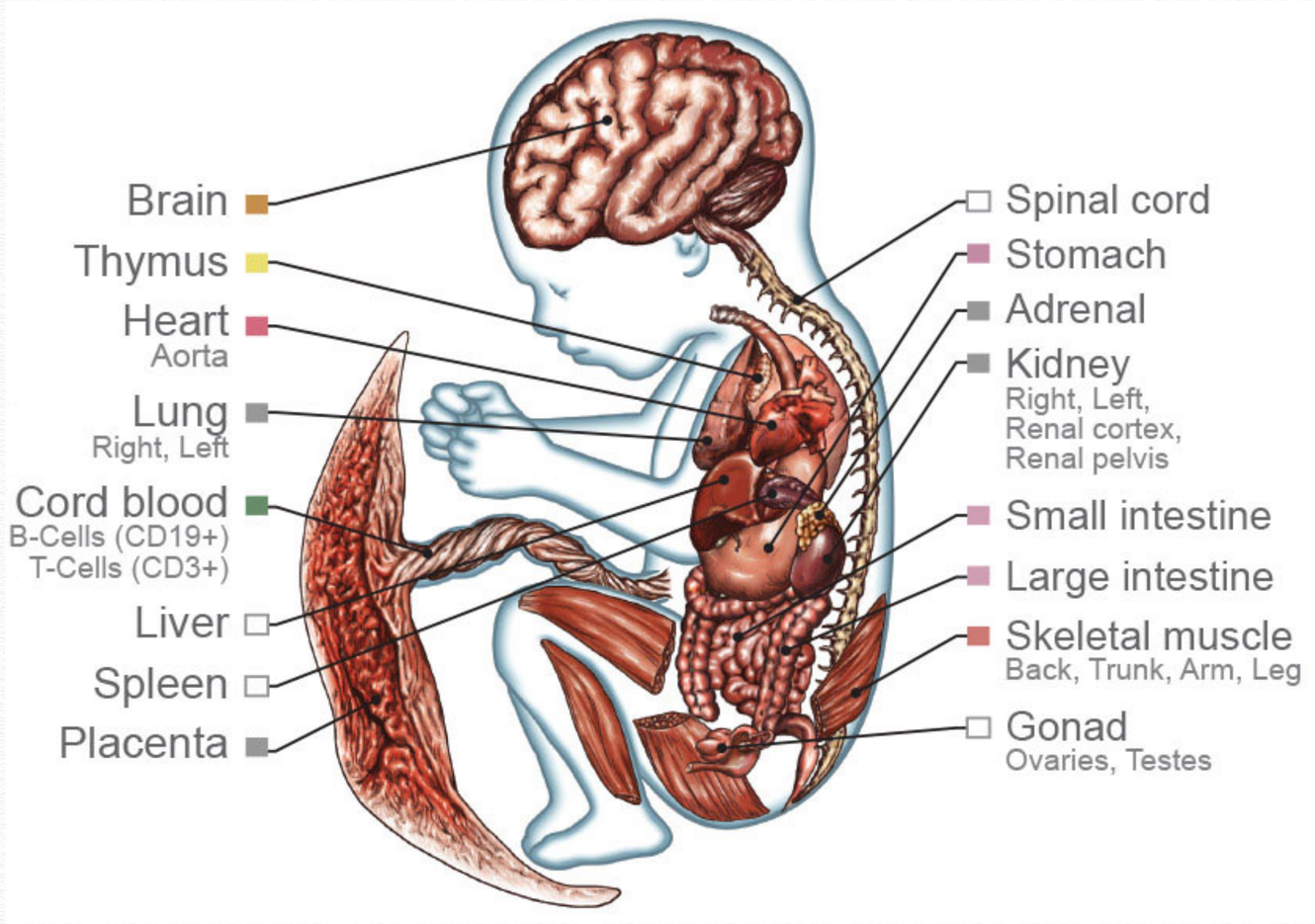
Ali Sharifi-Zarchi
Department of Computer Engineering, Sharif University of Technology

The Secret of Cellular Diversity

Biological Diversity

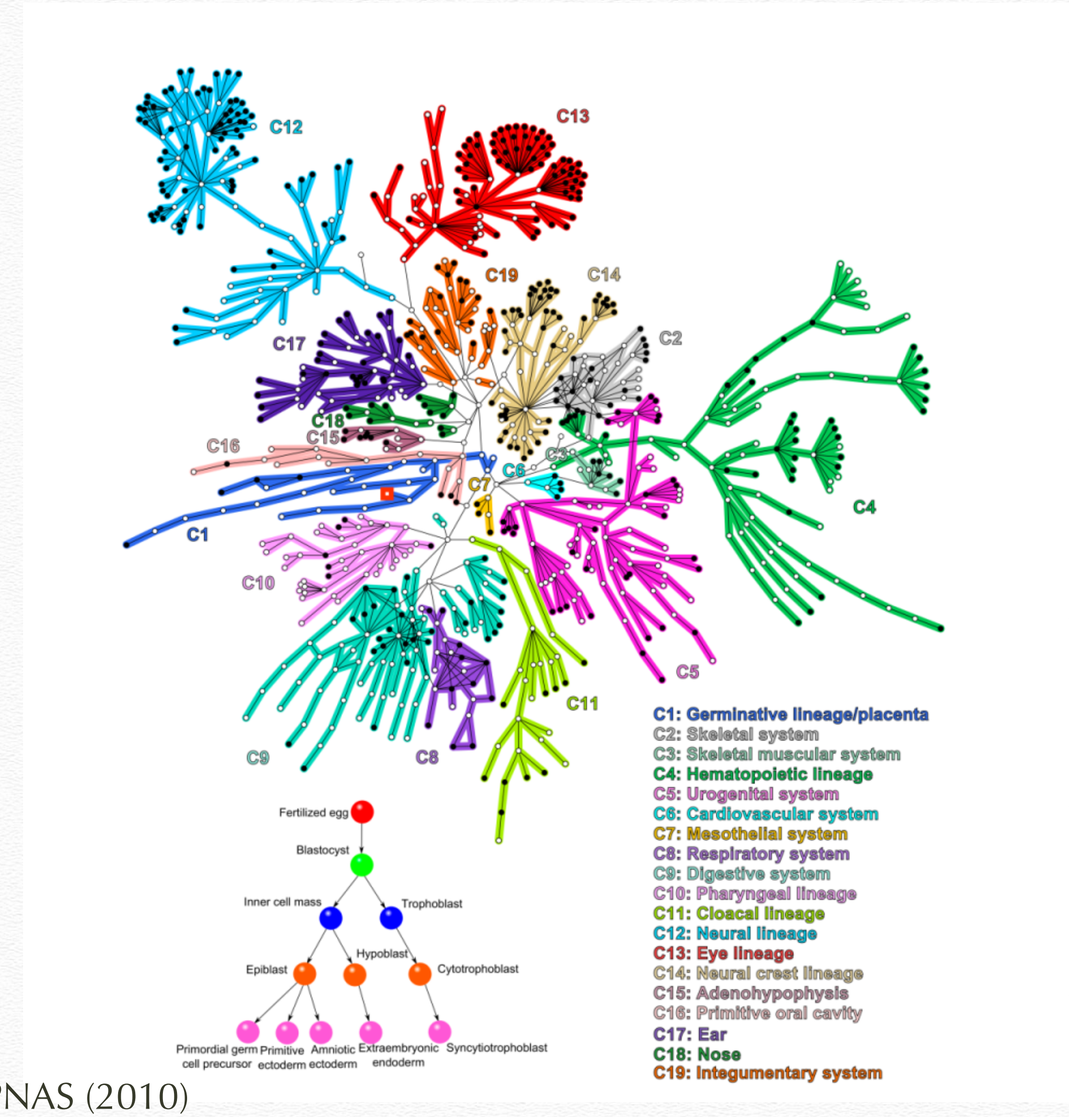
http://www.greenrooftechnology.com/biodiversity

Diversity in Our Body



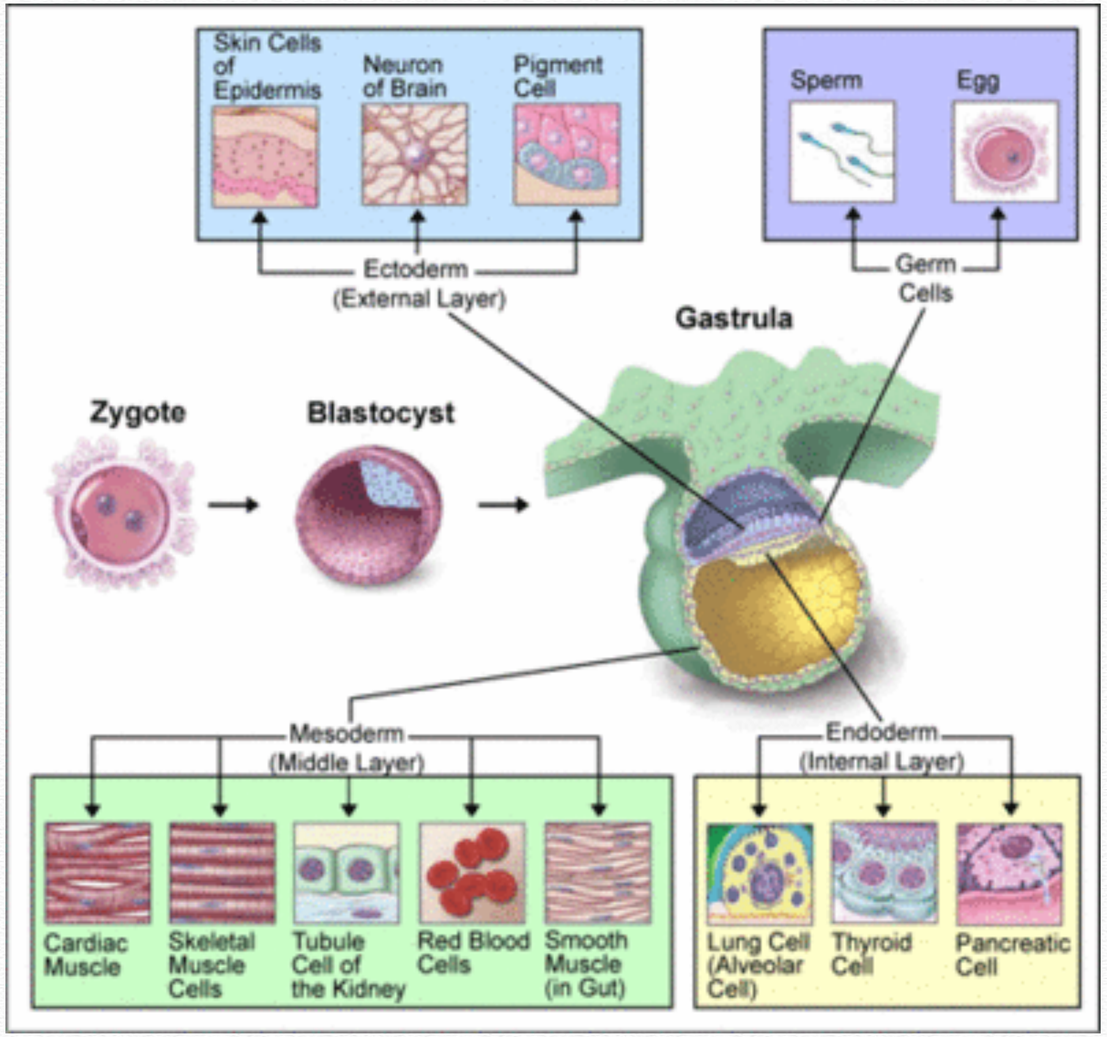
http://www.nih.gov/news/health/feb2015/images/niehs-18_xl.jpg

Differentiation Network

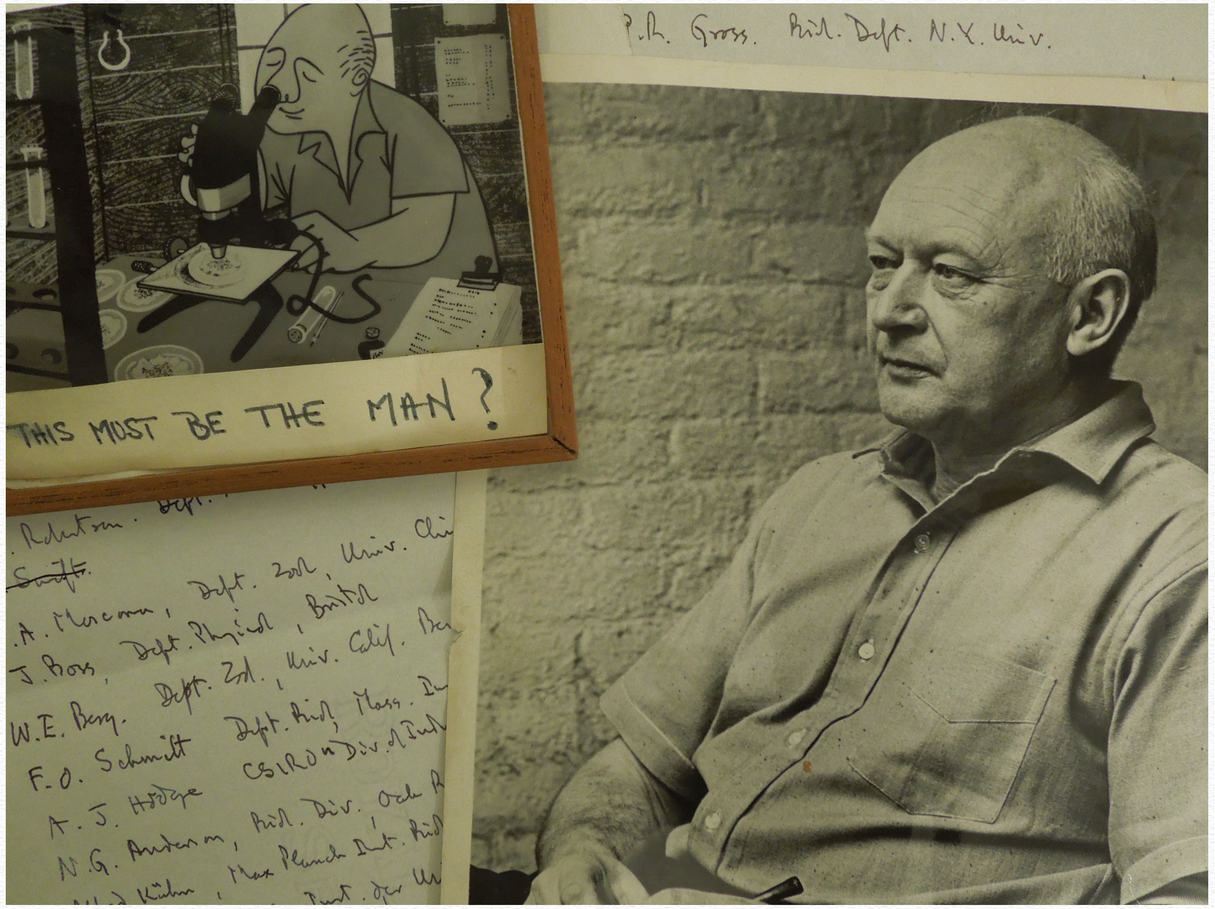


Galvão, V., et.al. PNAS (2010)

Human Development

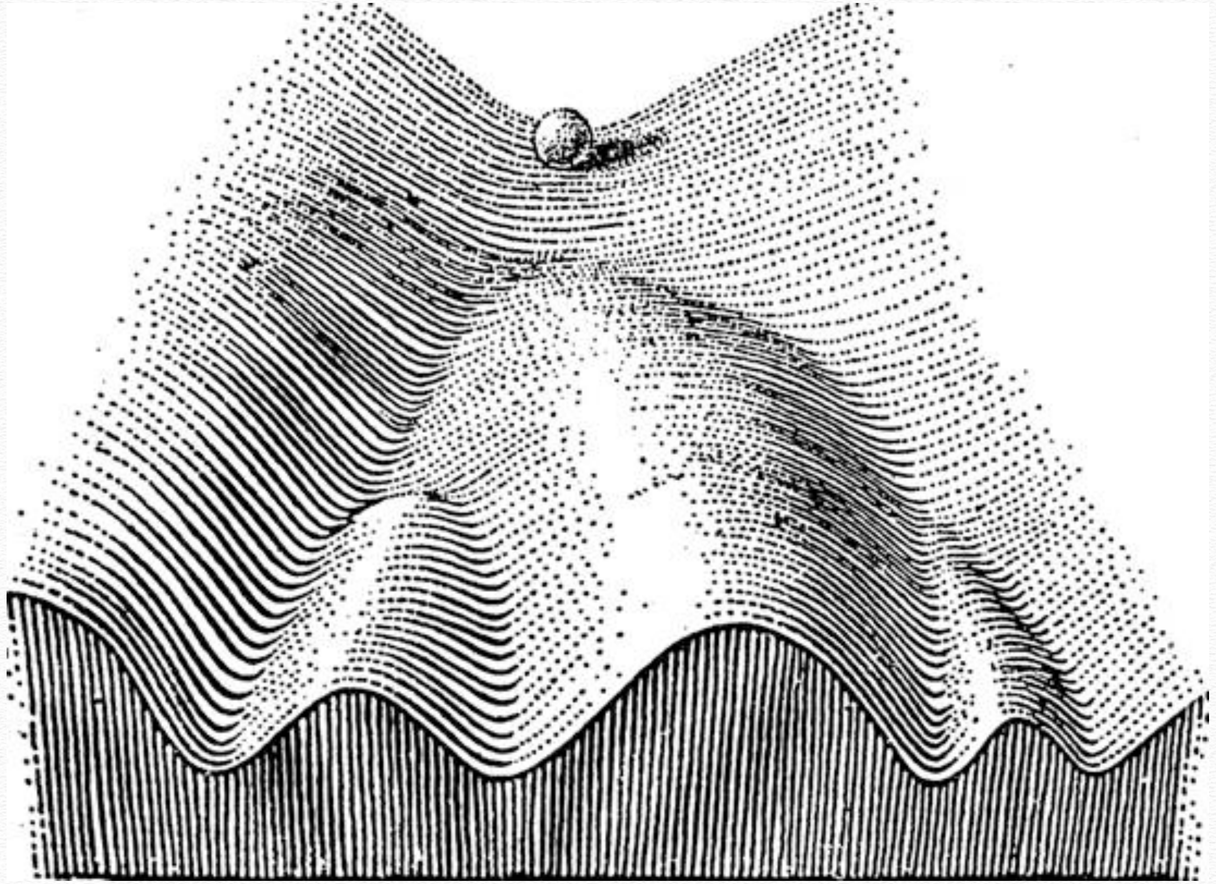


Conrad H. Waddington



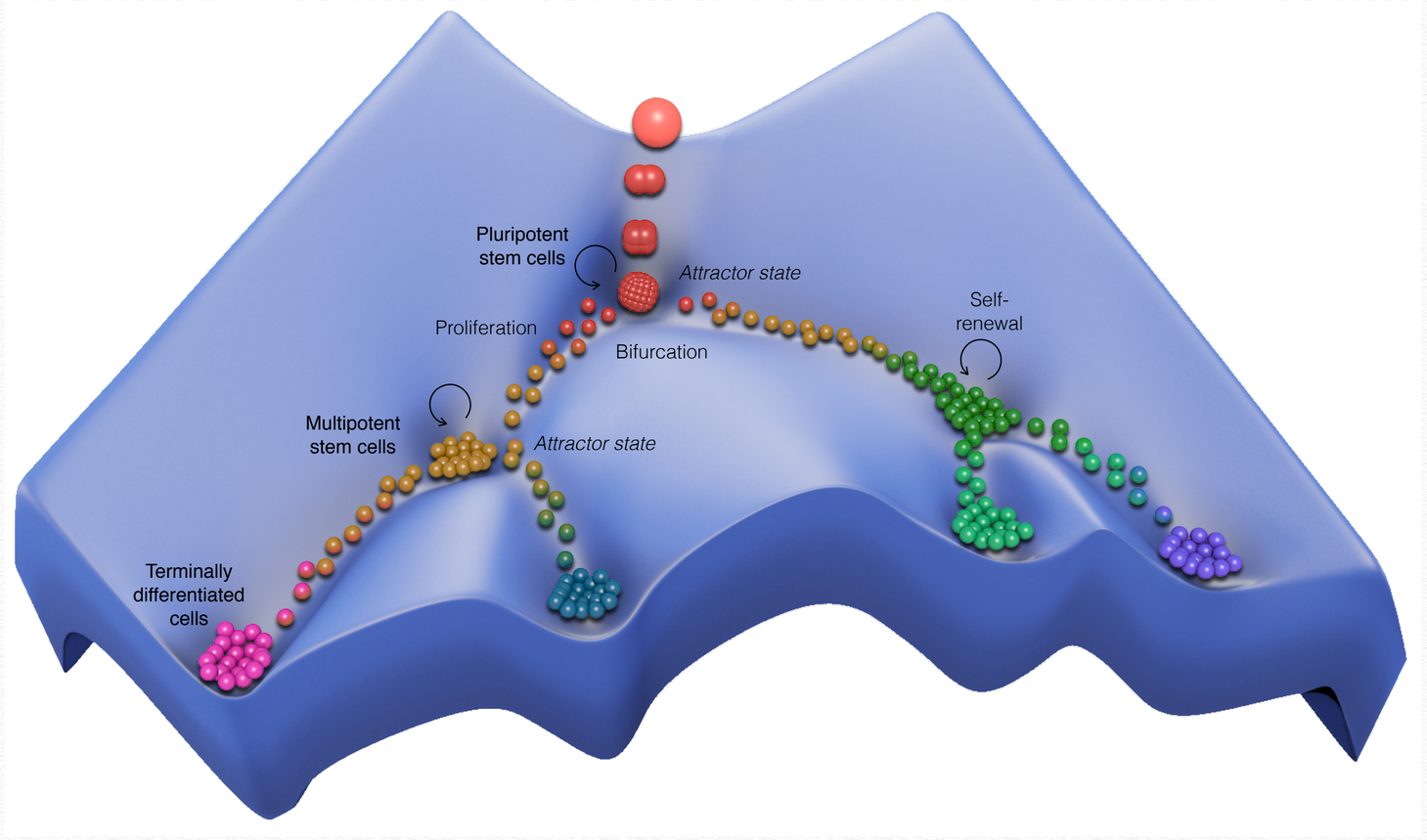
http://libraryblogs.is.ed.ac.uk/towardsdolly/2012/09/28/wad-conrad-hal-waddington-1905-1975

Epigenetic Landscape



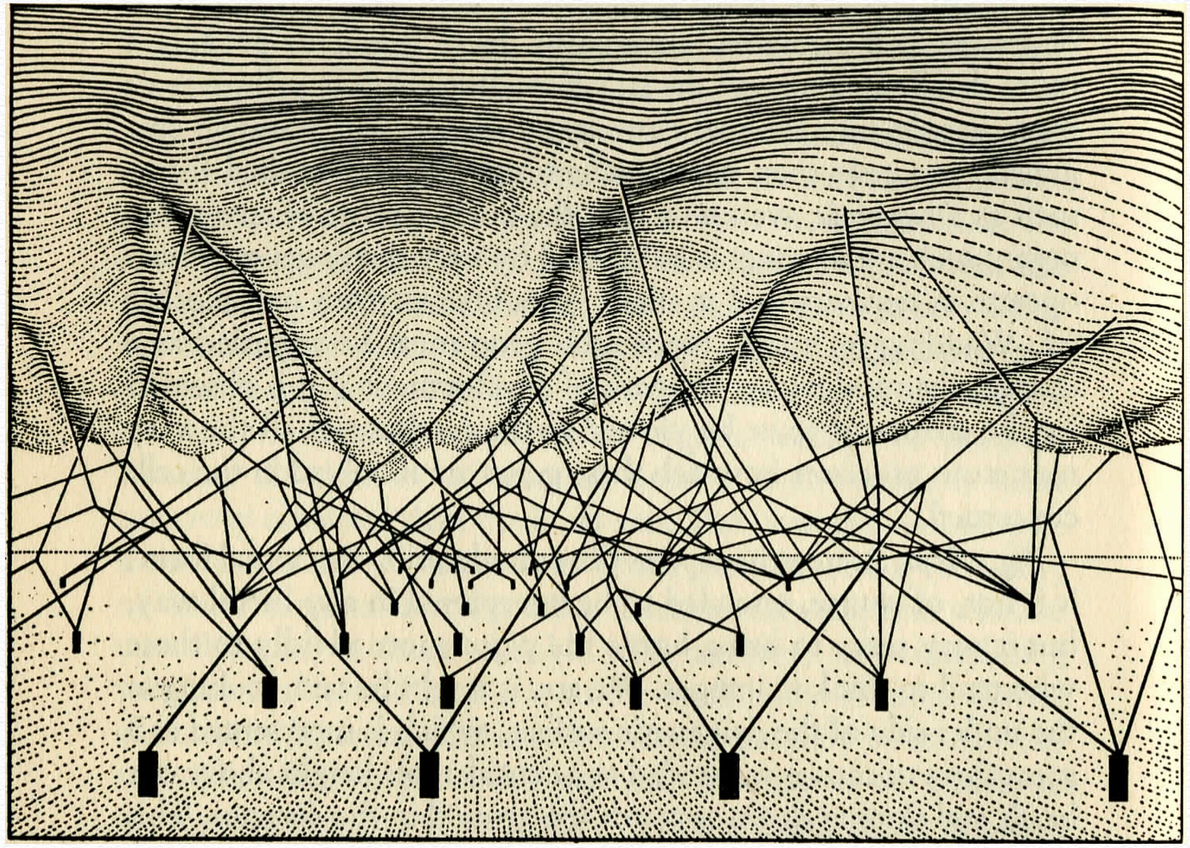
Waddington, C H. The Strategy of the Genes. London: George Allen & Unwin, 1957.

Epigenetic Landscape



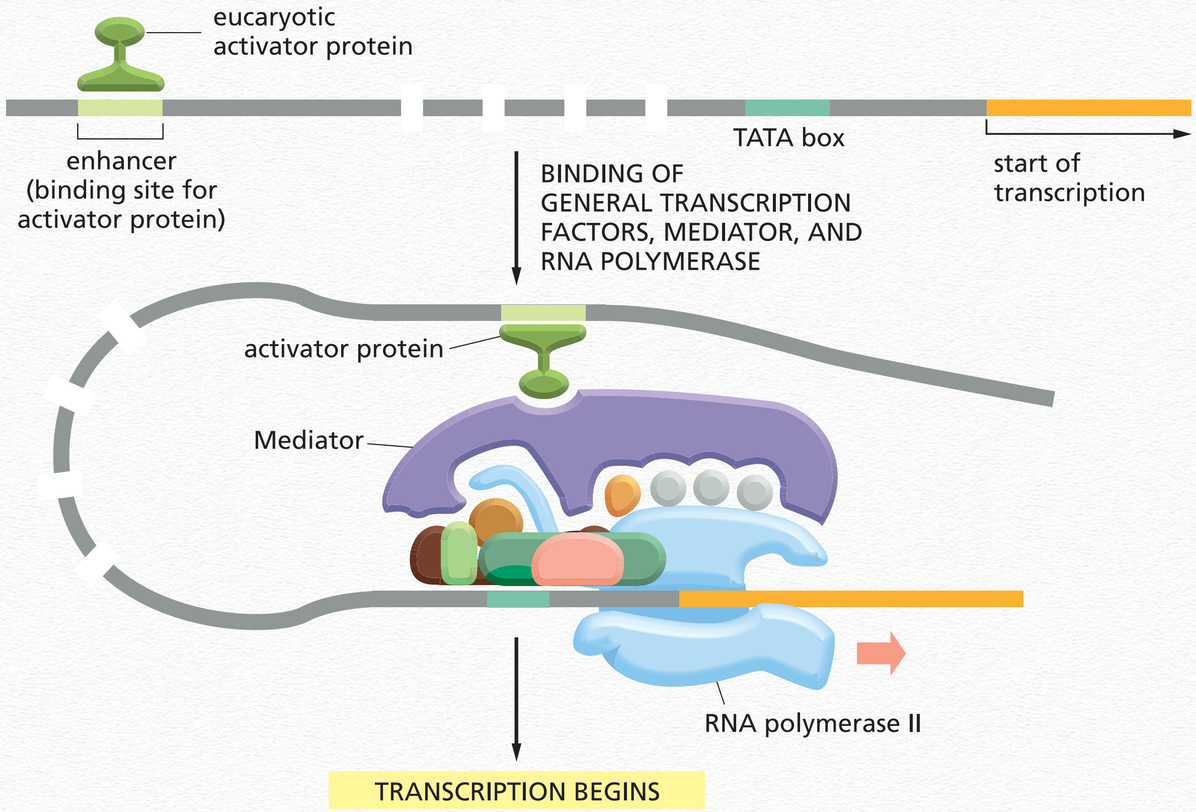
Courtesy of Ms. Razieh Karamzadeh, Royan Institute for Stem Cell Biology & Technology

The Landscape Backstage



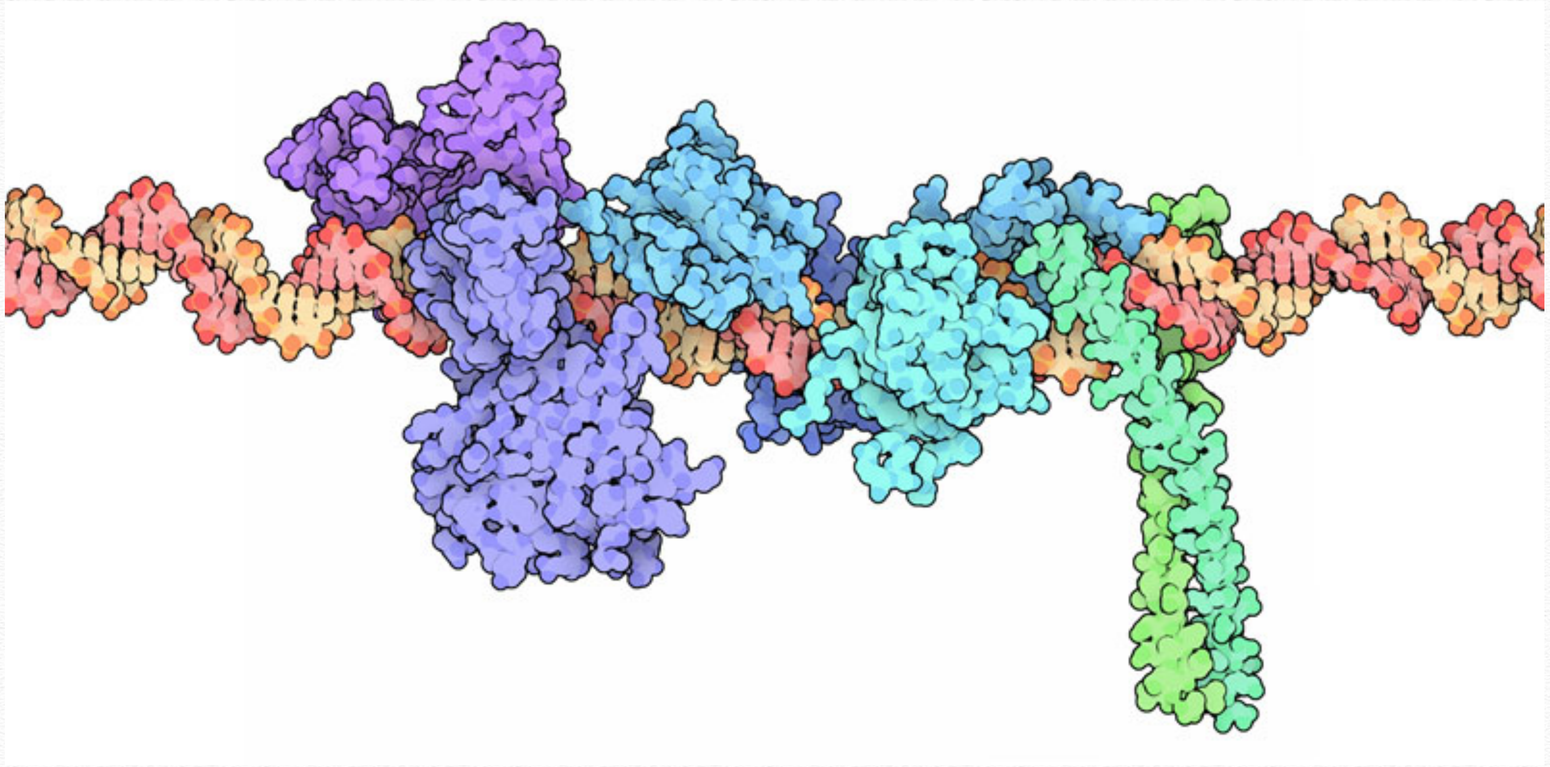
Waddington, C H. The Strategy of the Genes. London: George Allen & Unwin, 1957.

How do Genes Interact?



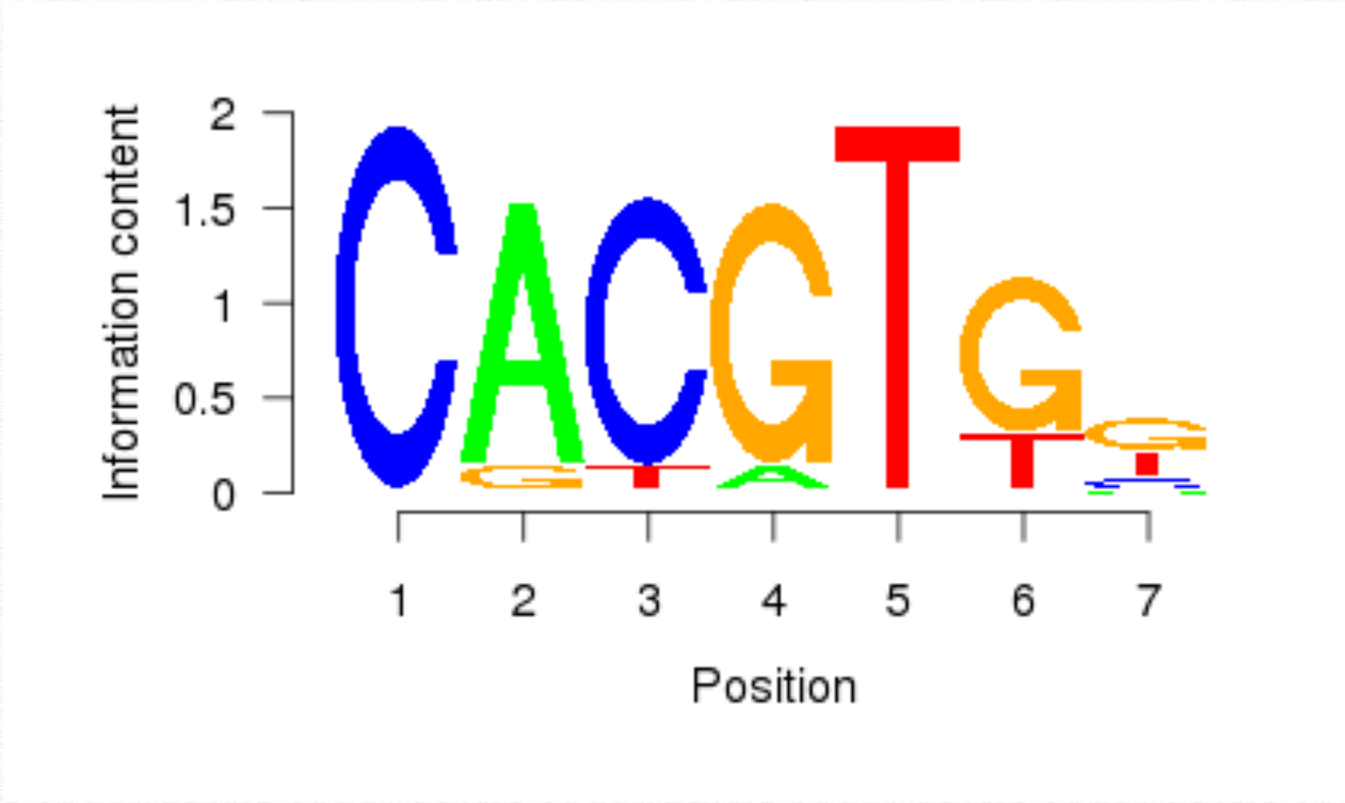
Alberts B., et al., Essential Cell Biology, 3rd Edition

Transcription Factor Bound to Enhancer

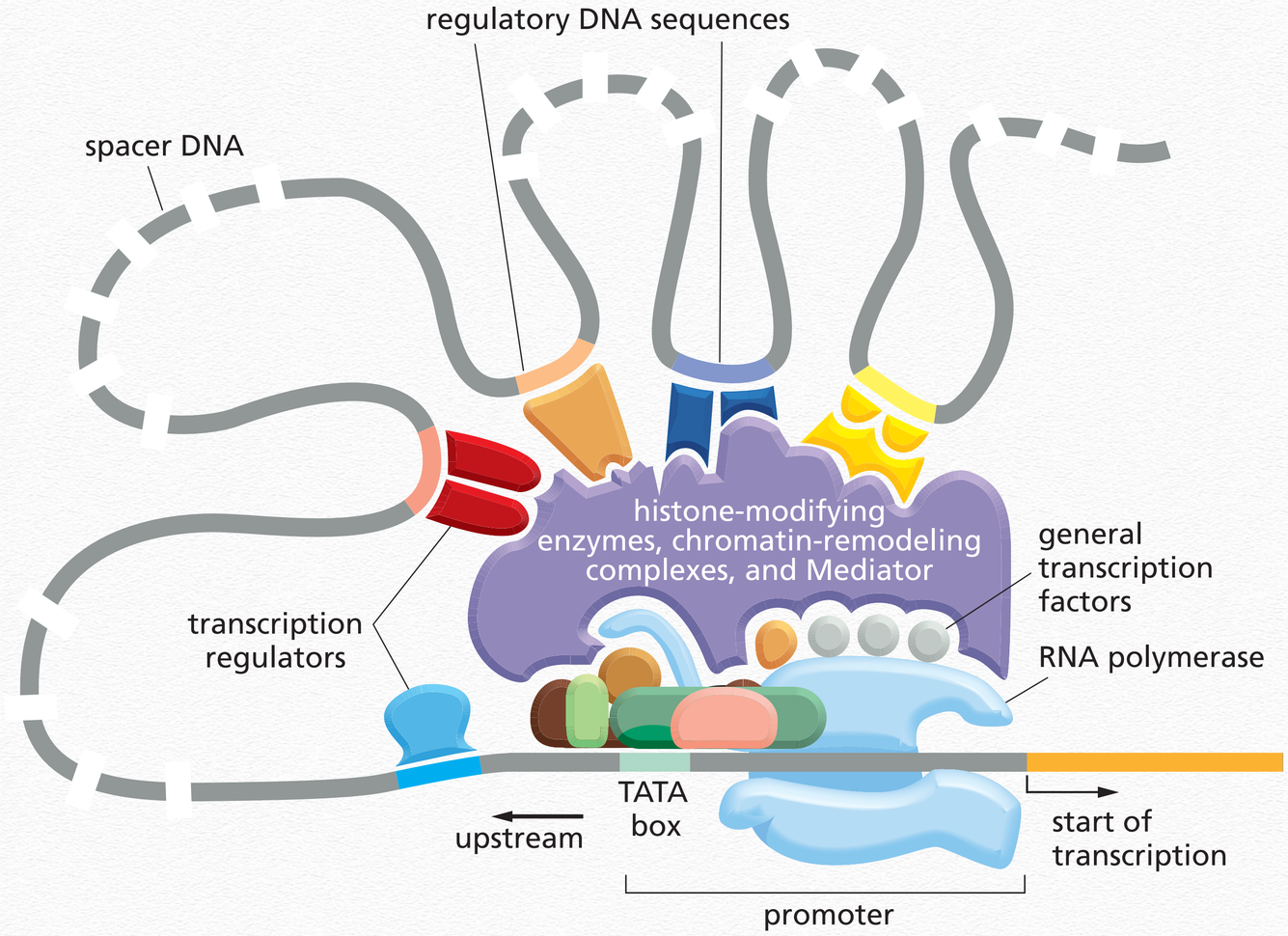


http://www.rcsb.org/pdb/101/motm.do?momID=122

Motifs

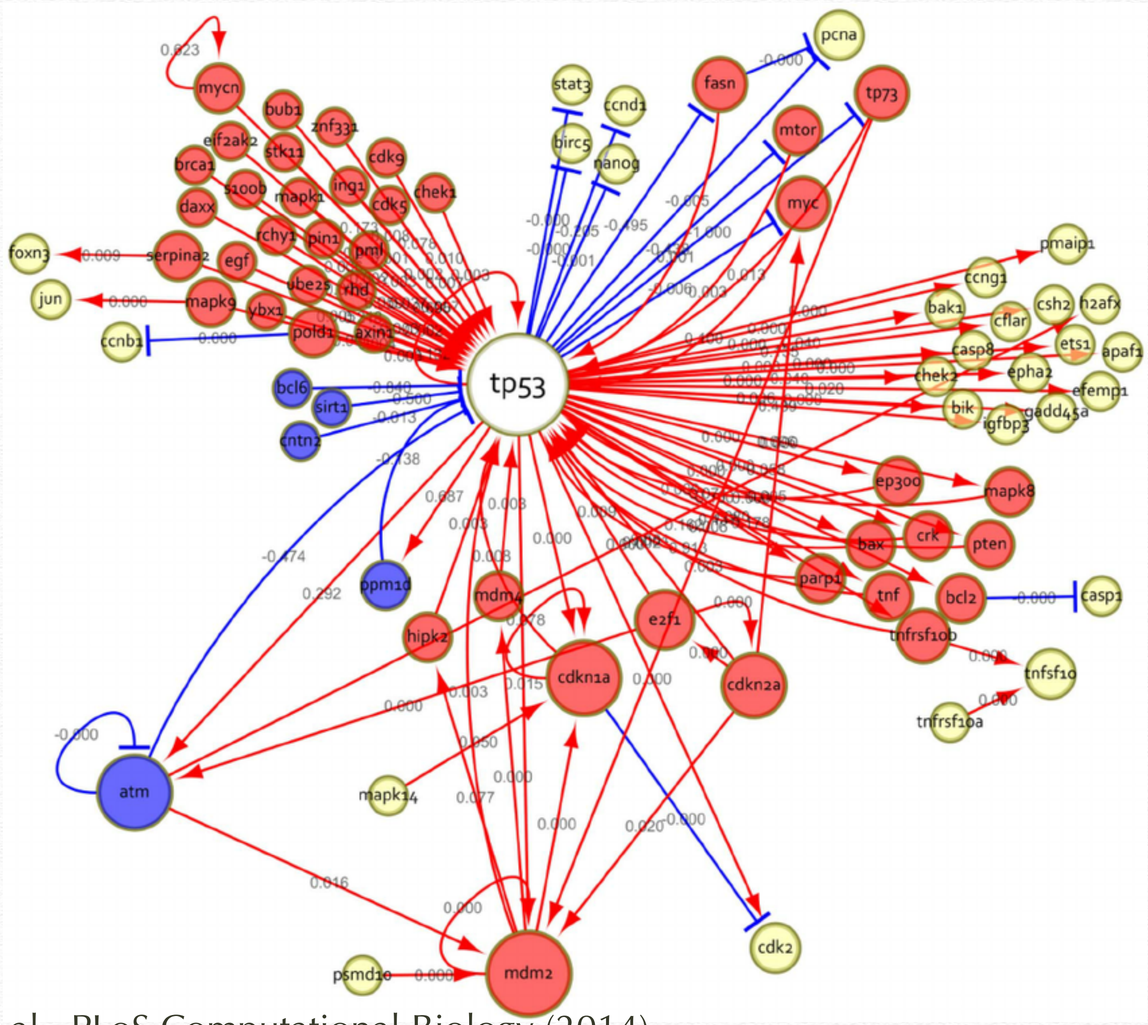


Can be More Complicated

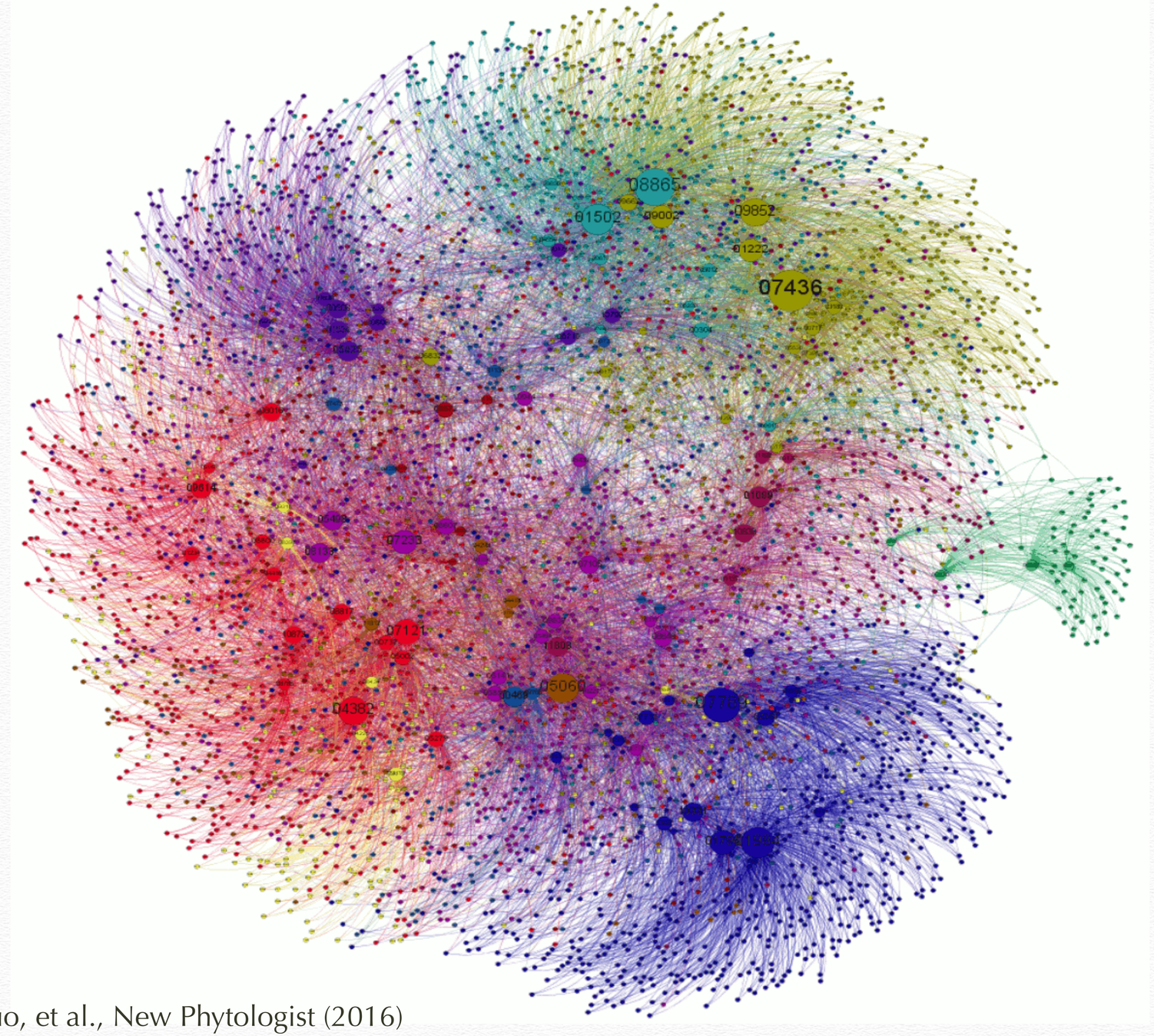


Alberts B., et al., Essential Cell Biology, 3rd Edition

Gene Regulatory Networks (GRN)

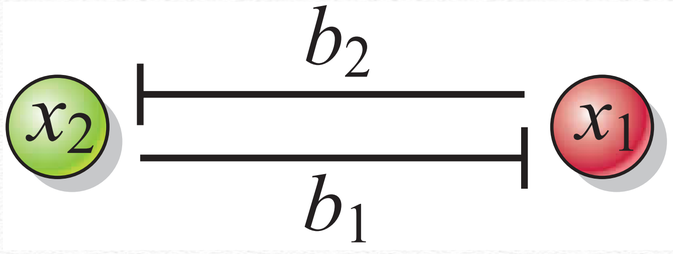


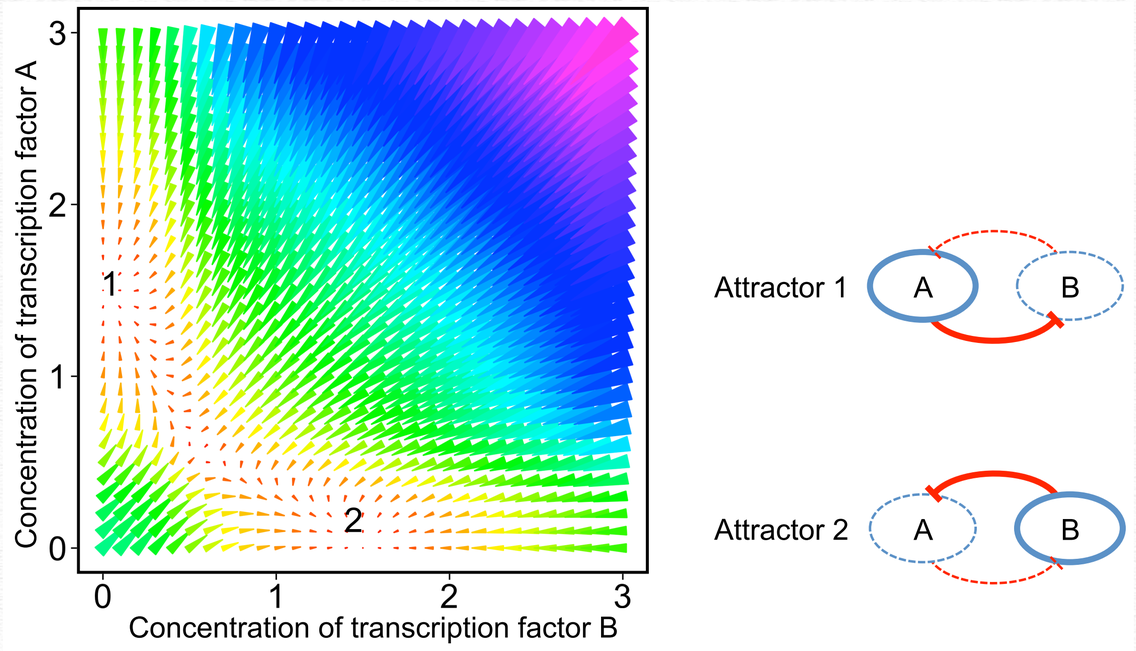
Guocai Chen, et al., PLoS Computational Biology (2014)



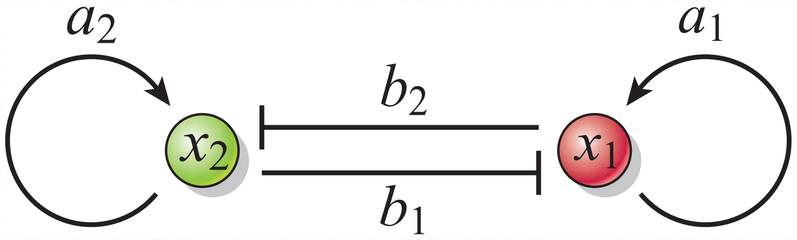
Li Guo, et al., New Phytologist (2016)

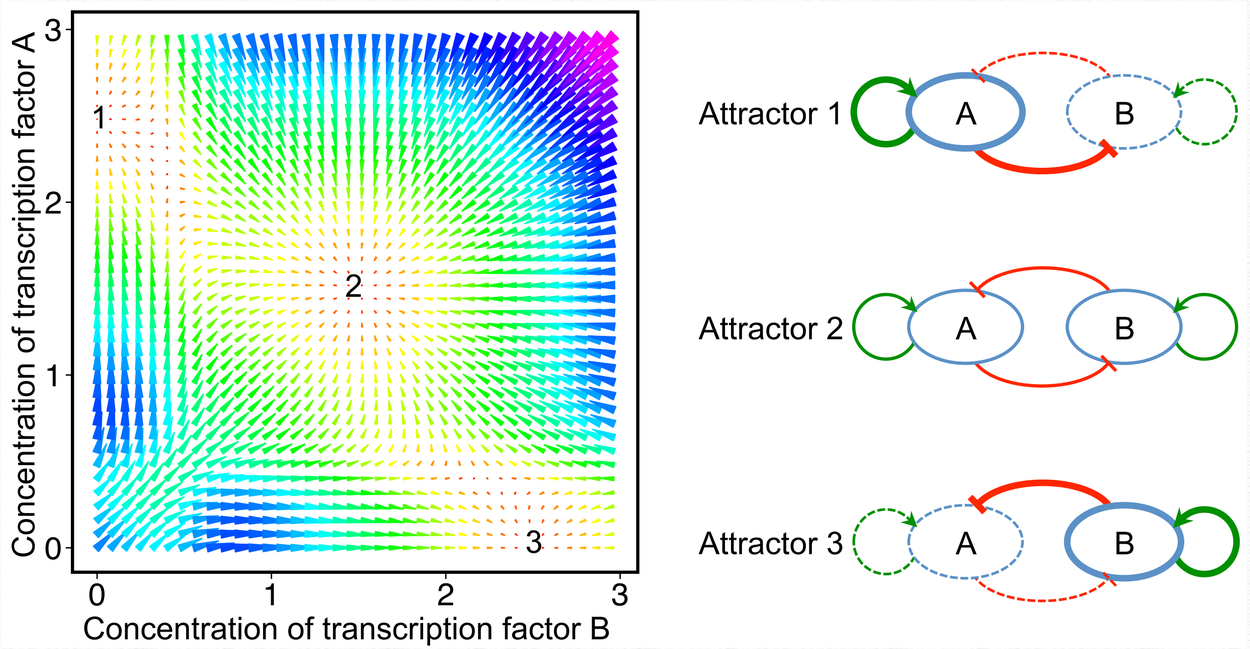
Bistable Switch



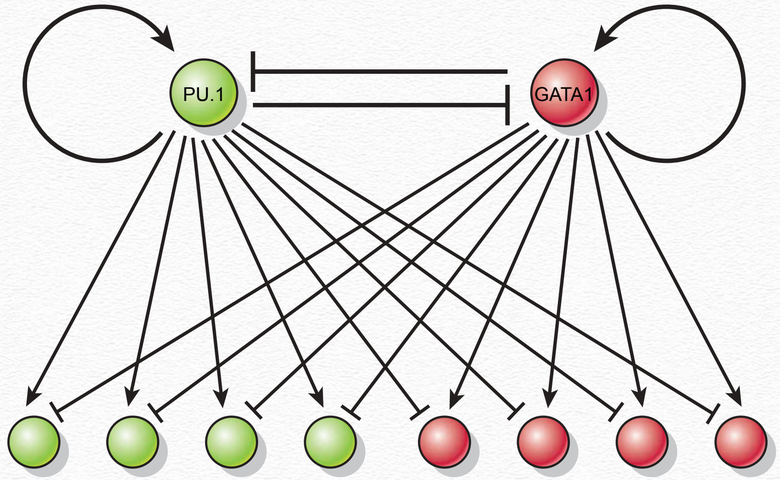


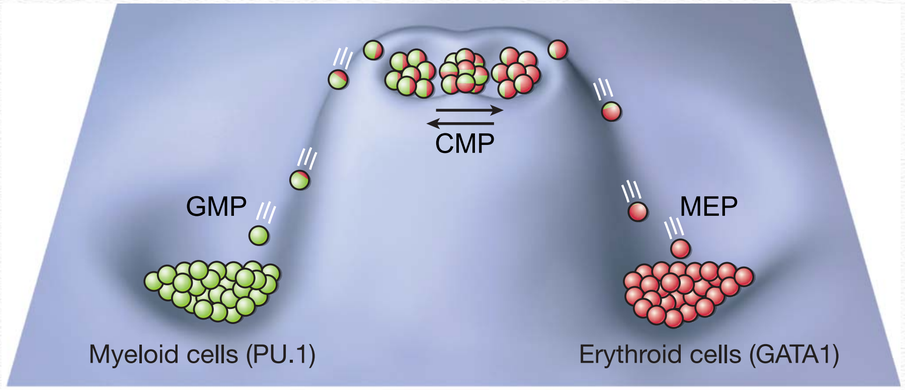
Tristable Switch





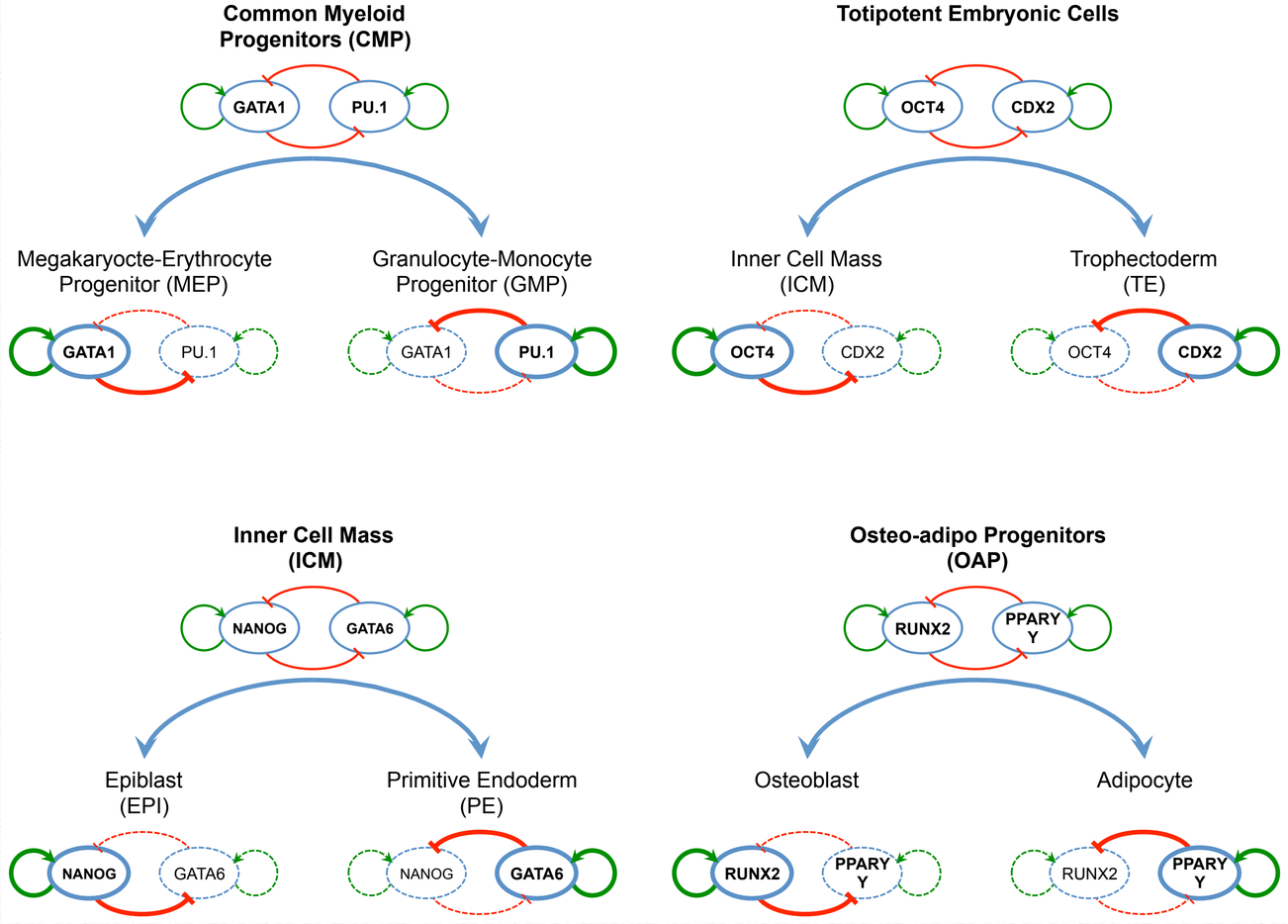
Lineage Bifurcation





Graf, Thomas and Enver, Tariq. Nature, 462(7273):587– 594 (2009).

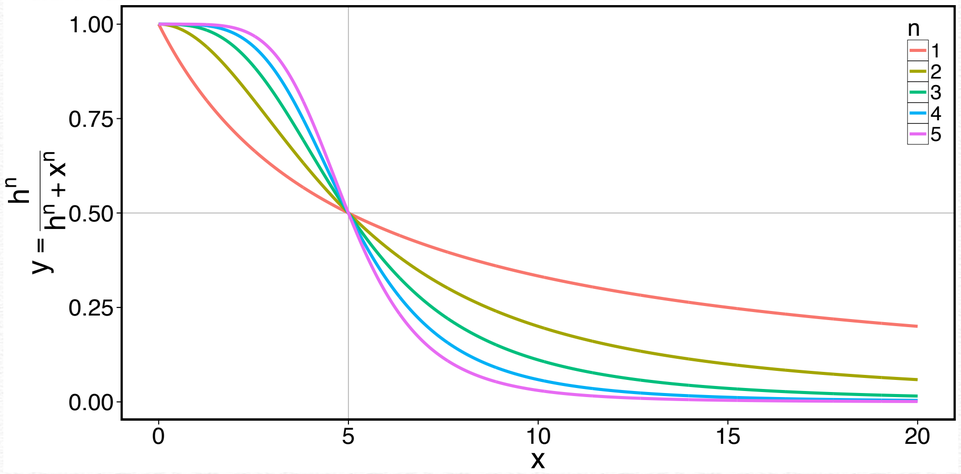
Human Development



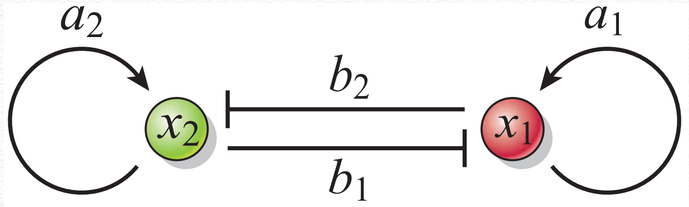
How to Model a Switch?

Mutual Inhibition

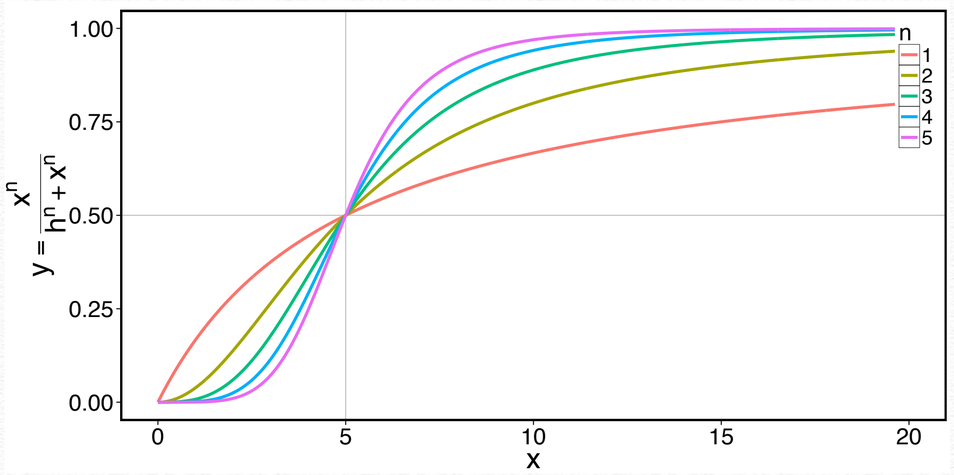
$$y = \frac{h^n}{h^n + x^n}$$



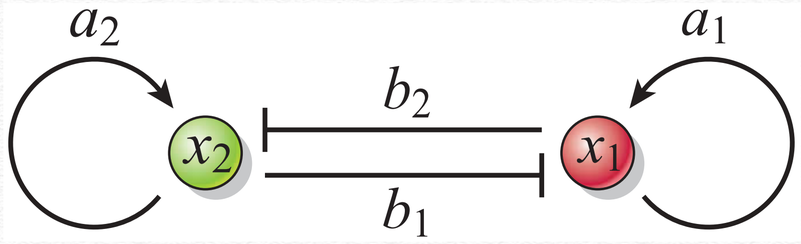
Self Activation



$$y = \frac{h^n}{h^n + x^n} \rightarrow y = \frac{x^n}{h^n + x^n}$$



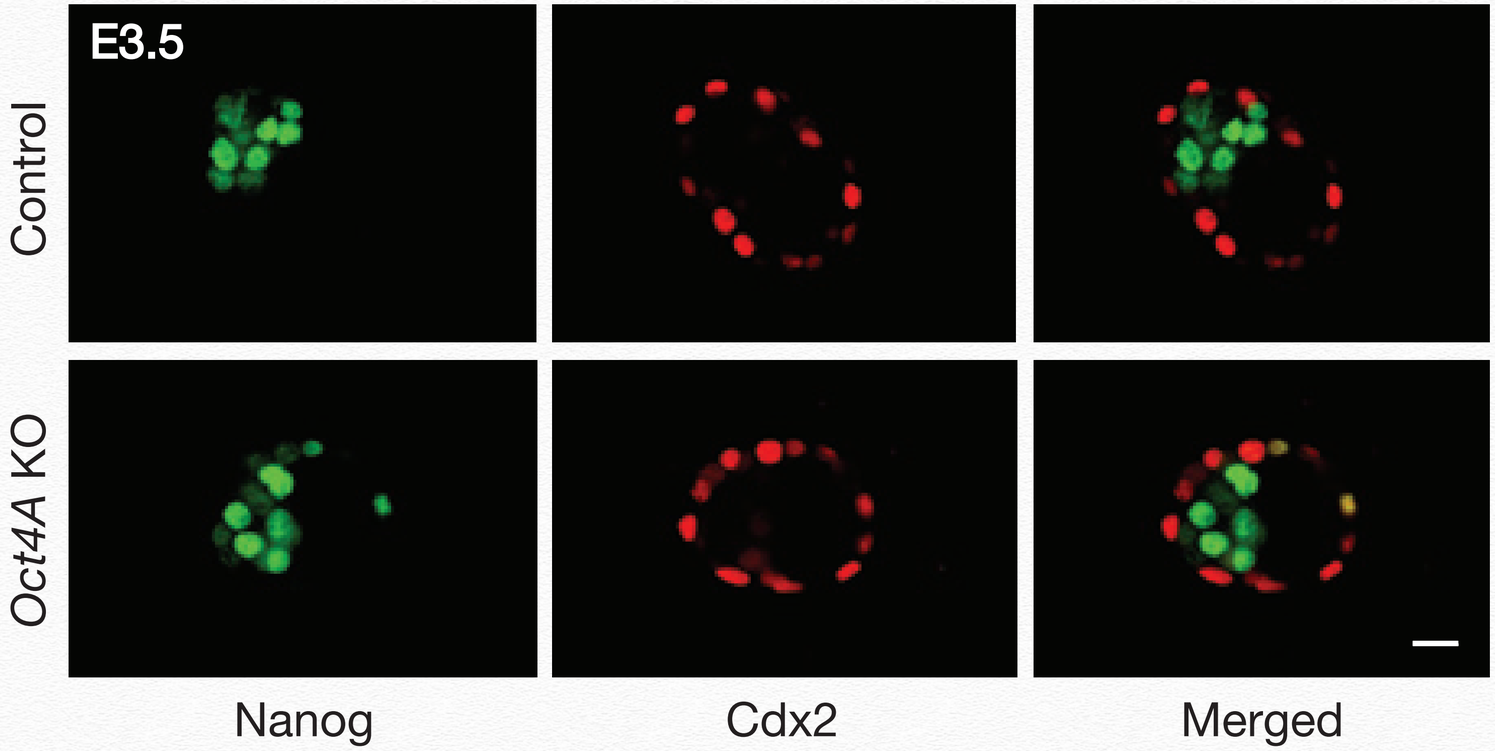
Ordinary Differential Equations (ODEs)



$$\frac{dx_1}{d_t} = a_1 \frac{x_1^n}{h^n + x_1^n} + b_1 \frac{h^n}{h^n + x_2^n} - cx_1$$

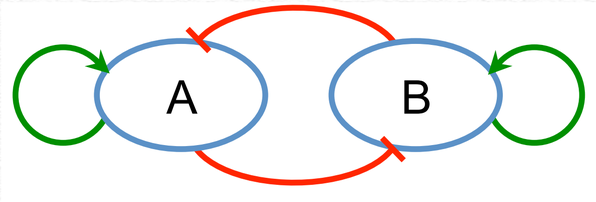
$$\frac{dx_2}{d_t} = a_2 \frac{x_2^n}{h^n + x_2^n} + b_2 \frac{h^n}{h^n + x_1^n} - cx_2$$

Controversy



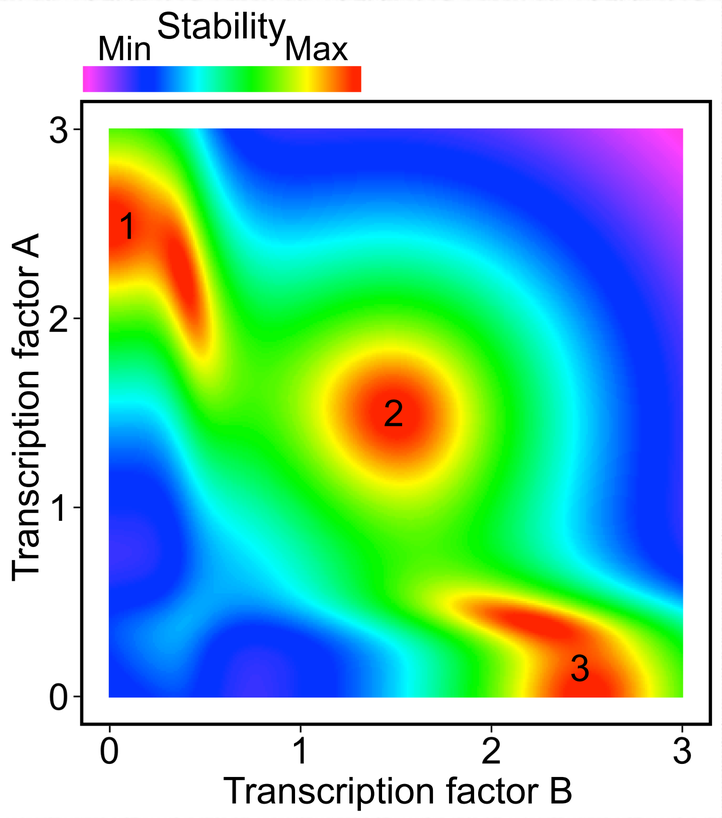
Wu, G., et al. Nature Cell Biology, 15(9), 1089–1097 (2013).

Two-Factor Circuit

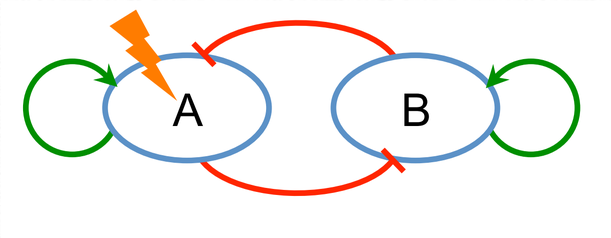


$$\frac{dx_1}{d_t} = a_1 \frac{x_1^n}{h^n + x_1^n} + b_1 \frac{h^n}{h^n + x_2^n} - cx_1$$

$$\frac{dx_2}{d_t} = a_2 \frac{x_2^n}{h^n + x_2^n} + b_2 \frac{h^n}{h^n + x_1^n} - cx_2$$

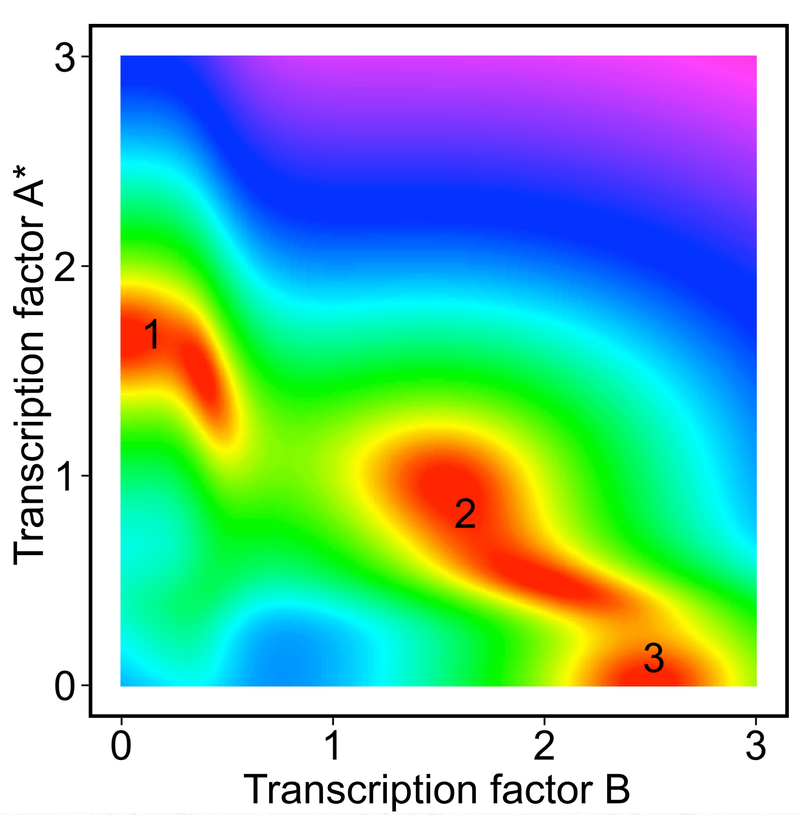


Perturbation

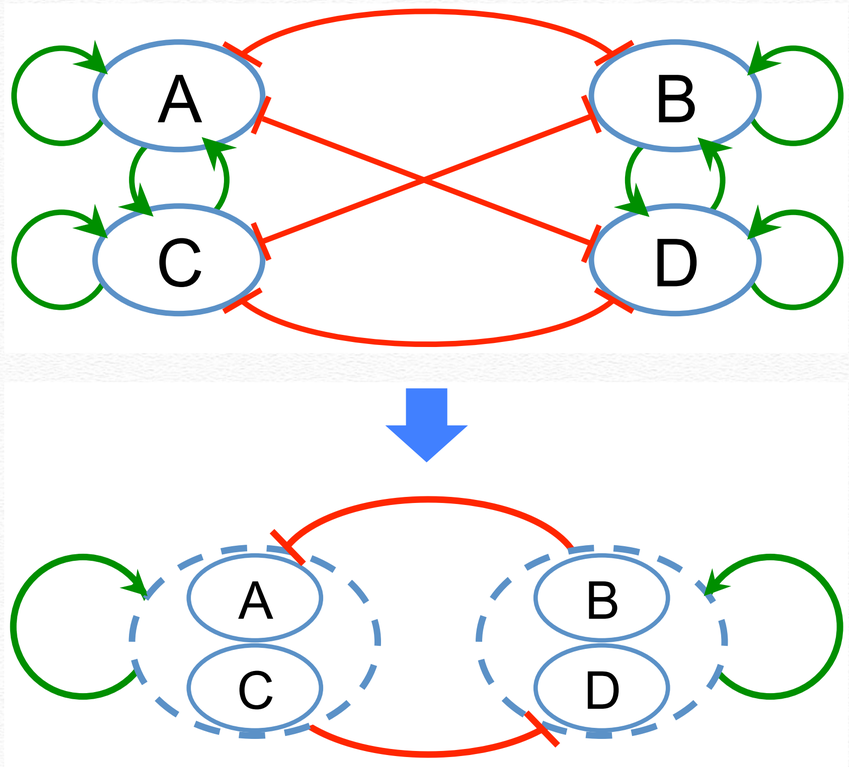


$$\frac{dx_1}{d_t} = a_1 \frac{x_1^n}{h^n + x_1^n} + b_1 \frac{h^n}{h^n + x_2^n} - c^* x_1$$

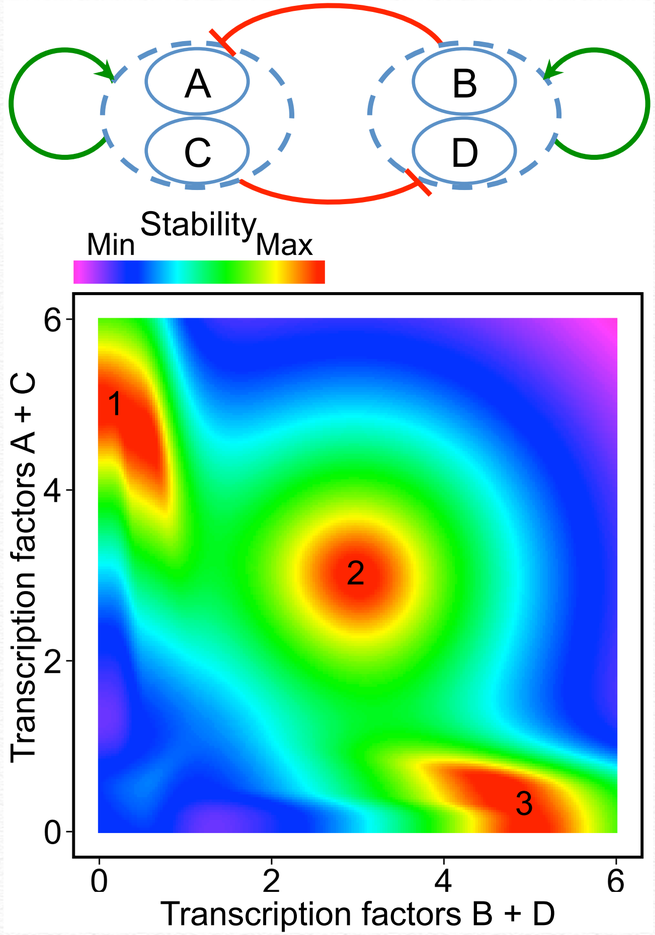
$$\frac{dx_2}{d_t} = a_2 \frac{x_2^n}{h^n + x_2^n} + b_2 \frac{h^n}{h^n + x_1^n} - c x_2$$

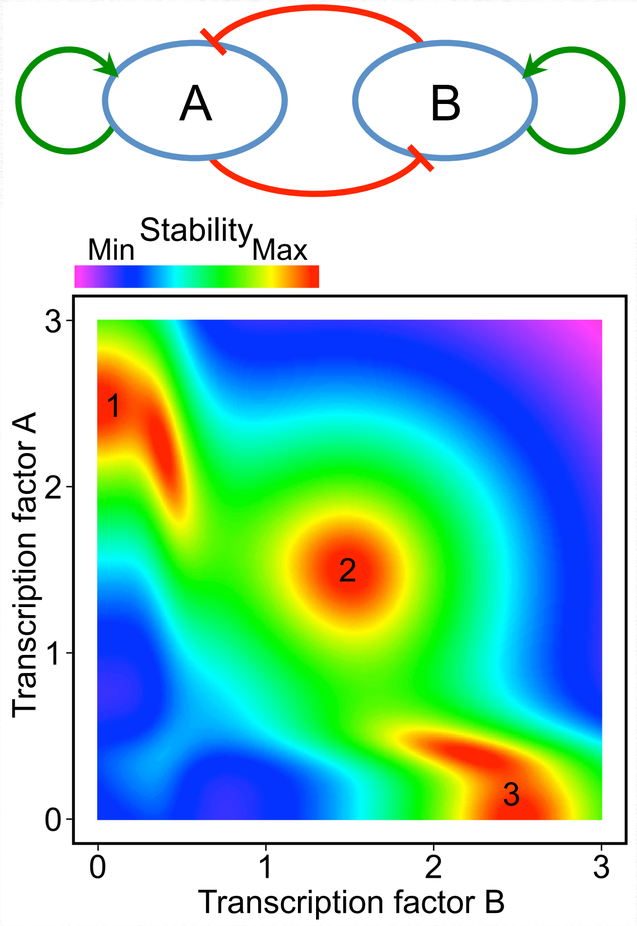


Two-Cluster Circuit

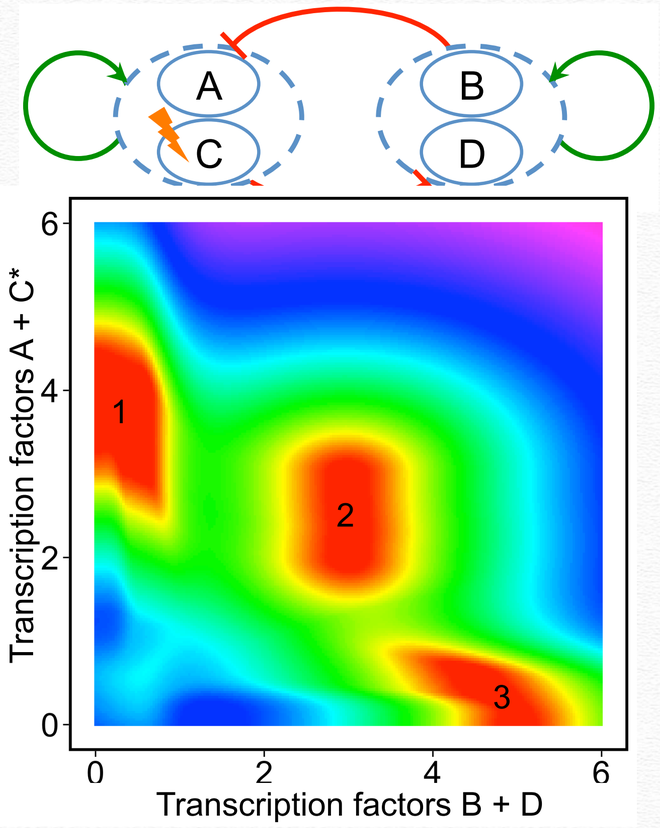


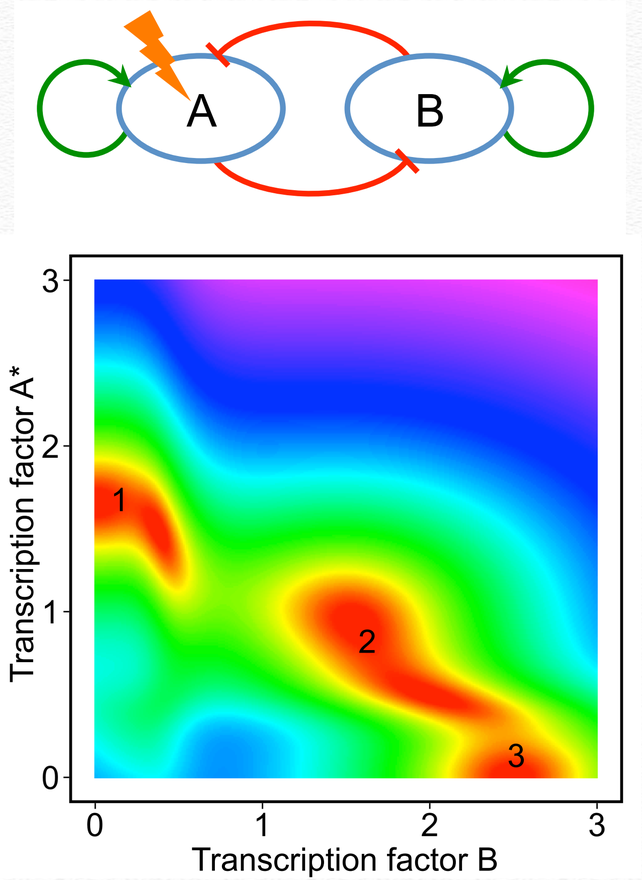
Two-Cluster Attractors



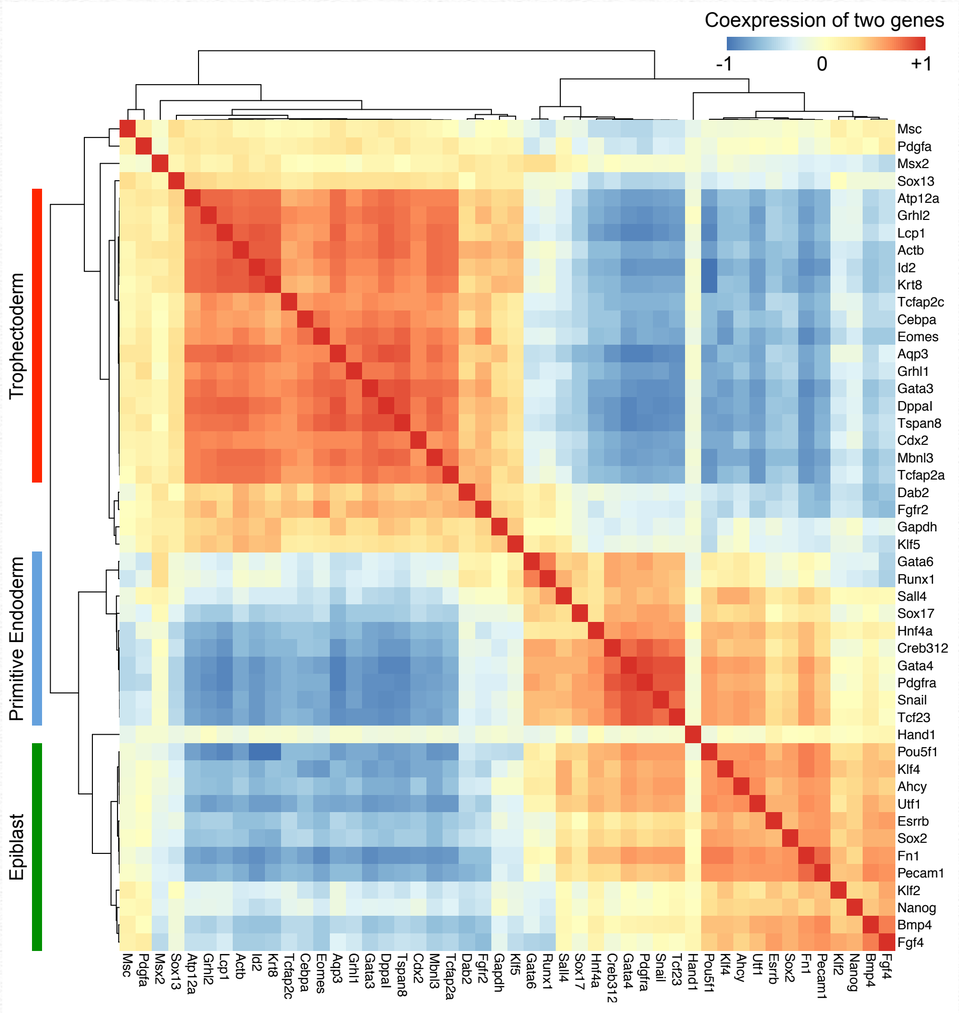


Robustness Comparison

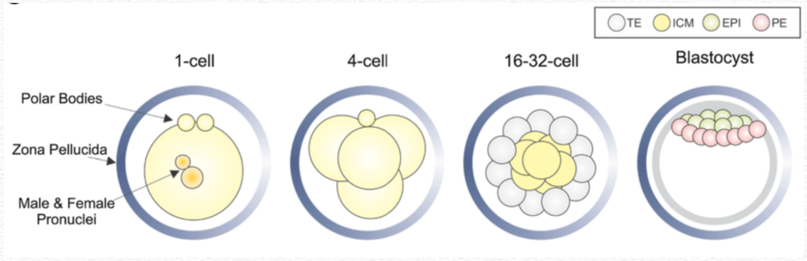


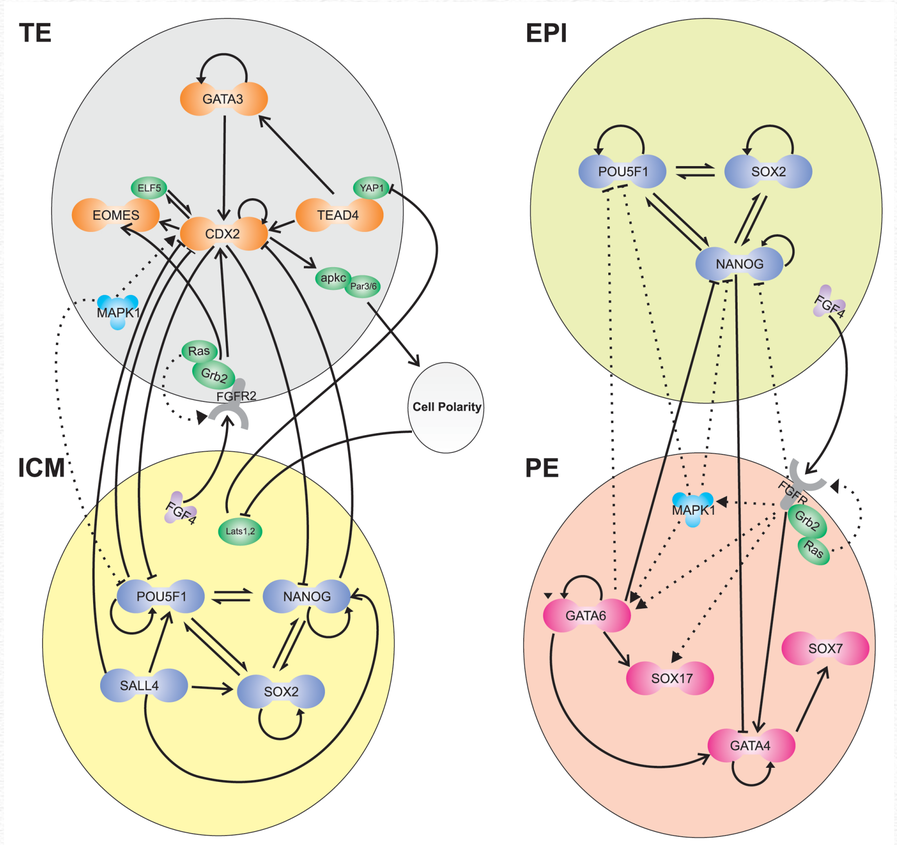


Clusters

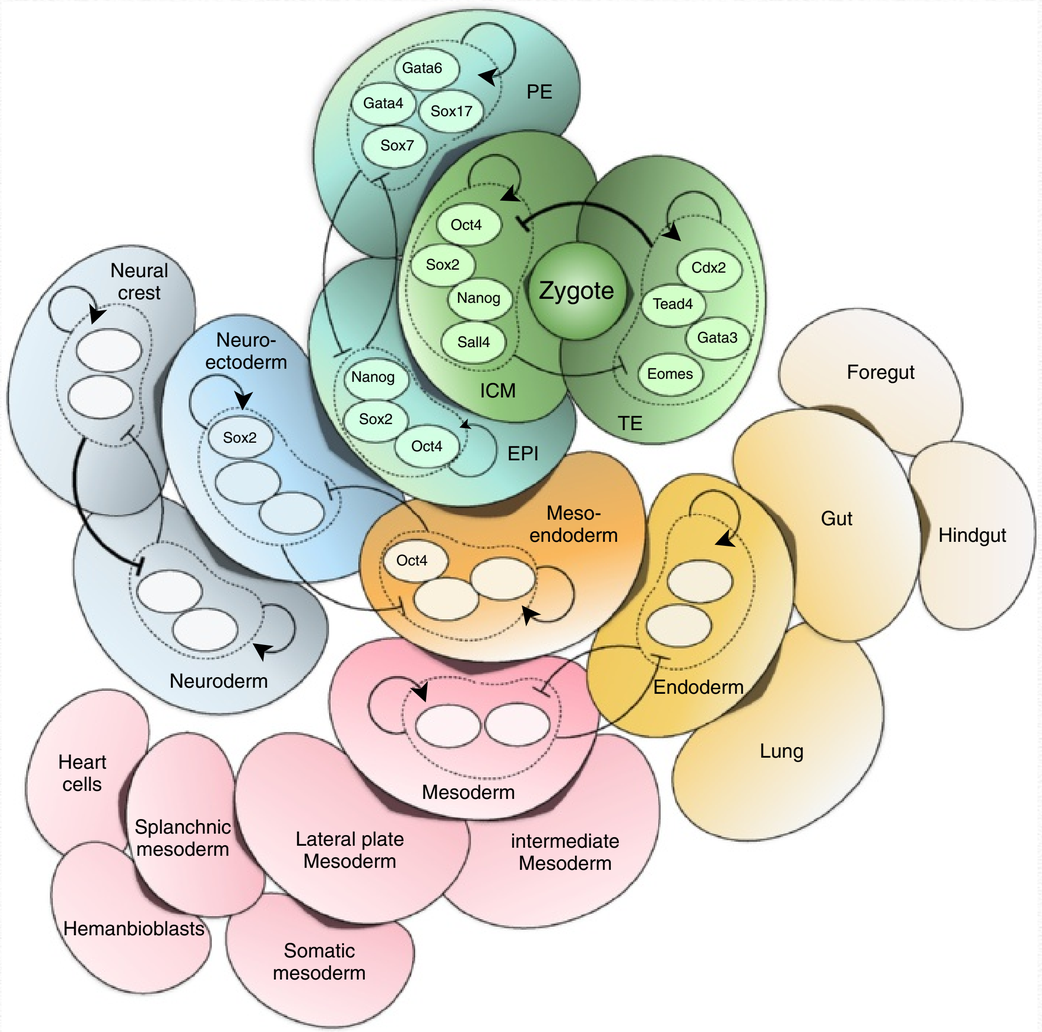

Coexpression of two genes
-1
0
+1
Trophectoderm
Primitive Endoderm
Epiblast
Msc
Pdgfa
Msx2
Sox13
Atp12a
Grhl2
Lcp1
Actb
Id2
Krt8
Tcfap2c
Cebpa
Eomes
Aqp3
Grhl1
Gata3
Dppal
Tspan8
Cdx2
Mbnl3
Tcfap2a
Dab2
Fgfr2
Gapdh
Klf5
Gata6
Runx1
Sall4
Sox17
Hnf4a
Creb312
Gata4
Pdgfra
Snail
Tcf23
Hand1
Pou5f1
Klf4
Ahcy
Utf1
Esrrb
Sox2
Fn1
Pecam1
Klf2
Nanog
Bmp4
Fgf4

Clusters


TE
ICM
EPI
PE
1-cell
4-cell
16-32-cell
Blastocyst
Polar Bodies
Zona Pellucida
Male & Female Pronuclei


TE
GATA3
ELF5
YAP1
EOMES
CDX2
TEAD4
apkc
Par3/6
MAPK1
Ras
Grb2
FGFR2
Cell Polarity
ICM
FGF4
Lats1,2
POU5F1
NANOG
SALL4
SOX2
EPI
POU5F1
SOX2
NANOG
FGF4
PE
MAPK1
FGFR
Grb2
Ras
GATA6
SOX7
SOX17
GATA4

Two-Cluster Model



Sharifi-Zarchi *et al. BMC Systems Biology* (2015) 9:23
DOI 10.1186/s12918-015-0169-8

BMC
Systems Biology

RESEARCH ARTICLE Open Access

Increased robustness of early embryogenesis through collective decision-making by key transcription factors

Ali Sharifi-Zarchi[1,2,11], Mehdi Totonchi[2,3], Keynoush Khaloughi[2], Razieh Karamzadeh[2,4], Marcos J. Araúzo-Bravo[5,6,7], Hossein Baharvand[2], Ruzbeh Tusserkani[8], Hamid Pezeshk[9,10], Hamidreza Chitsaz[11] and Mehdi Sadeghi[10,12*]