Understanding Tumor Heterogeneity and Plasticity Through the Lens of Cancer Stem Cell Model and Mathematical Modeling

Waddington's epigenetic landscape quantified with quasi-potential

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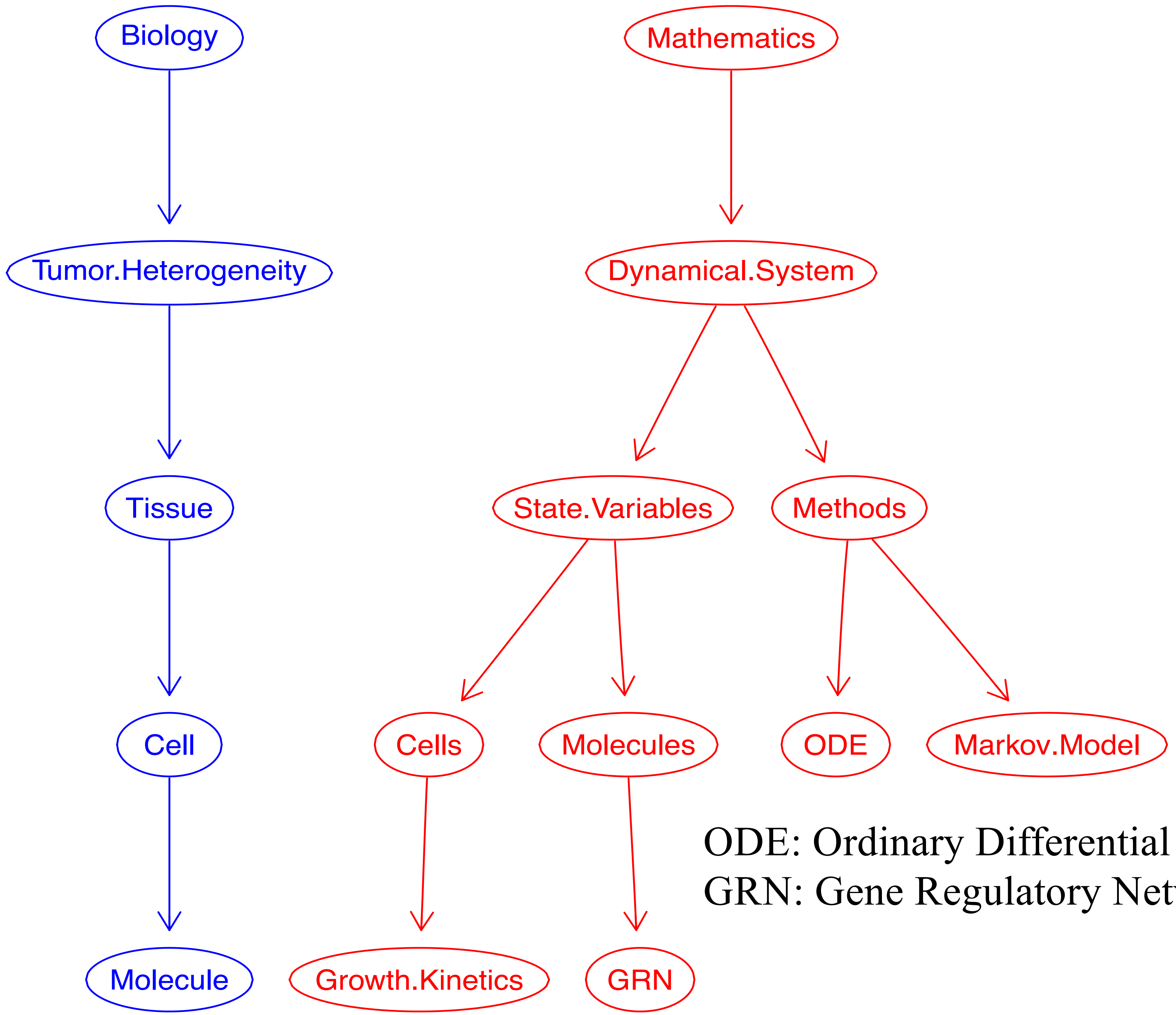
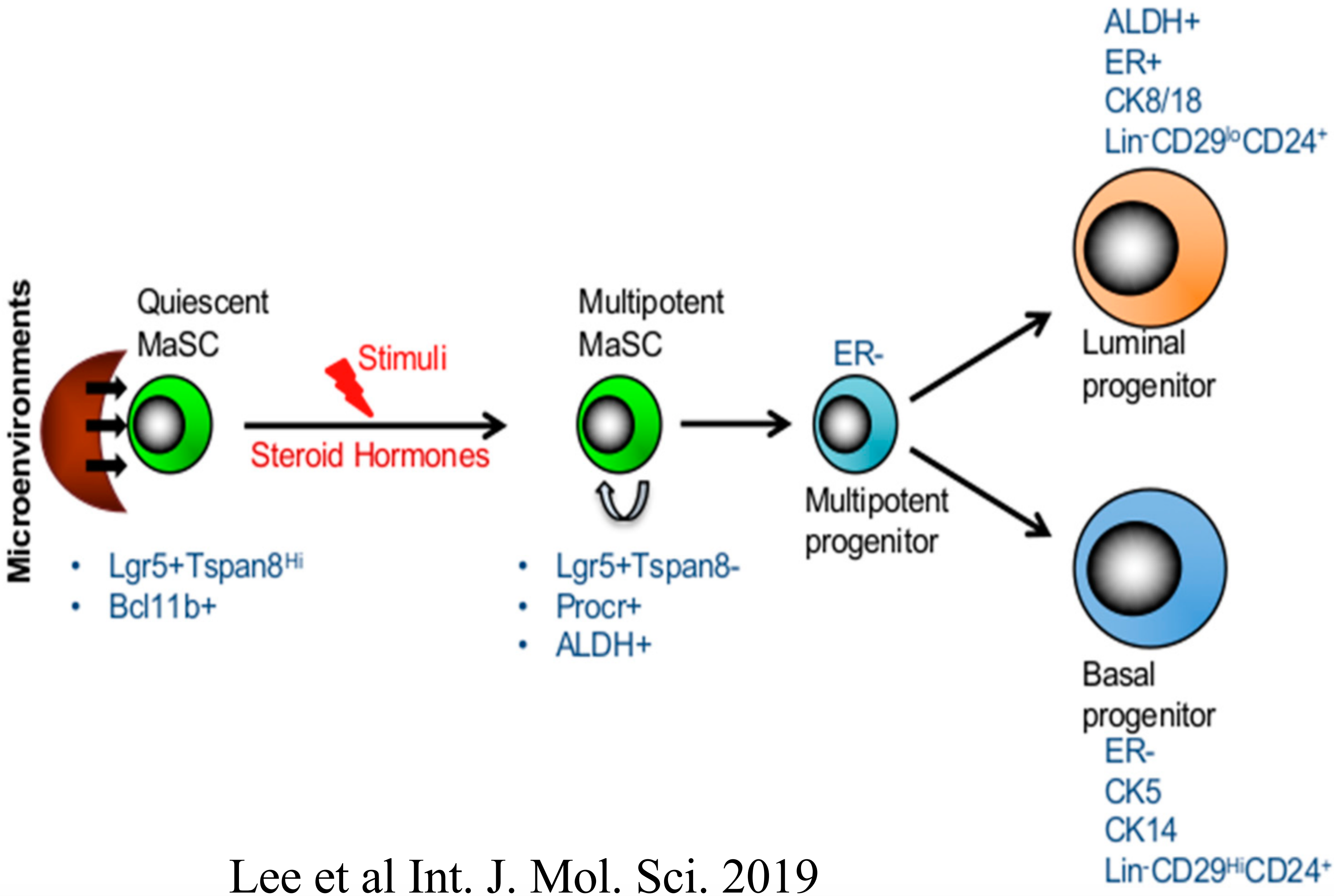
Understanding Biology with Mathematical Modeling



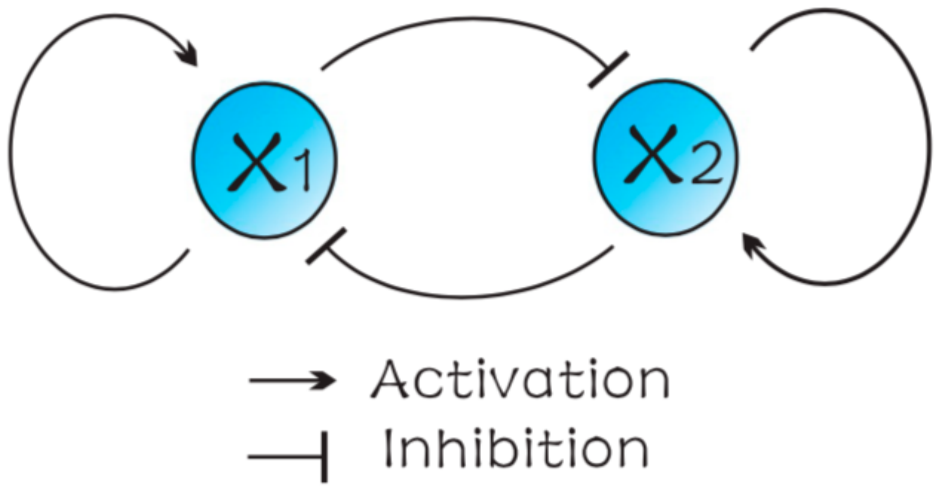
ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

Mammary Stem Cell Model



Lee et al Int. J. Mol. Sci. 2019

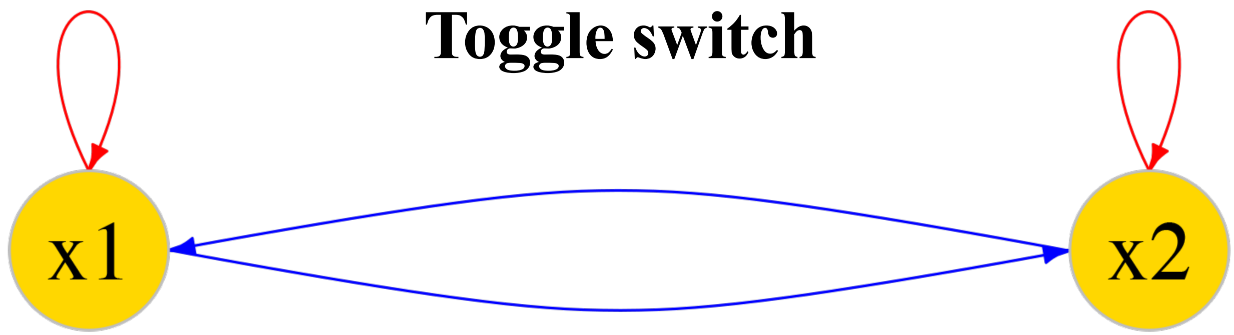
Toggle Switch
Gene Regulatory Network (GRN)



Gardner et al Nature 2000, 403:339 Wang et al PNAS 2011, 108:8257

Differential Equation Model of Gene Regulatory Network (GRN)

Toggle switch



$$\frac{dx_1}{dt} = \boxed{\frac{a_1 x_1^n}{S^n + x_1^n}} + \boxed{\frac{b_1 S^n}{S^n + x_2^n}} - k_1 x_1$$

$$\frac{dx_2}{dt} = \boxed{\frac{a_2 x_2^n}{S^n + x_2^n}} + \boxed{\frac{b_2 S^n}{S^n + x_1^n}} - k_2 x_2$$

b_1 and b_2 are weights for mutual inhibition

a_1 and a_2 are weights for auto-activation

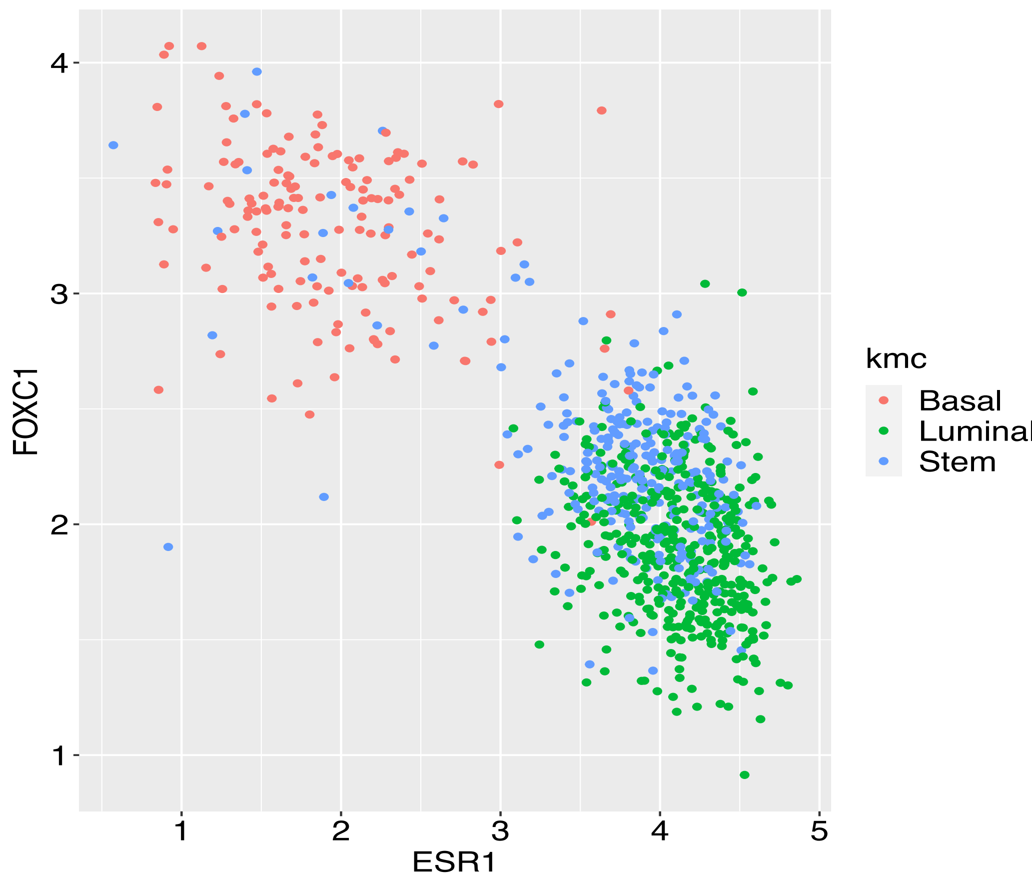
k_1 and k_2 are weights for degradation

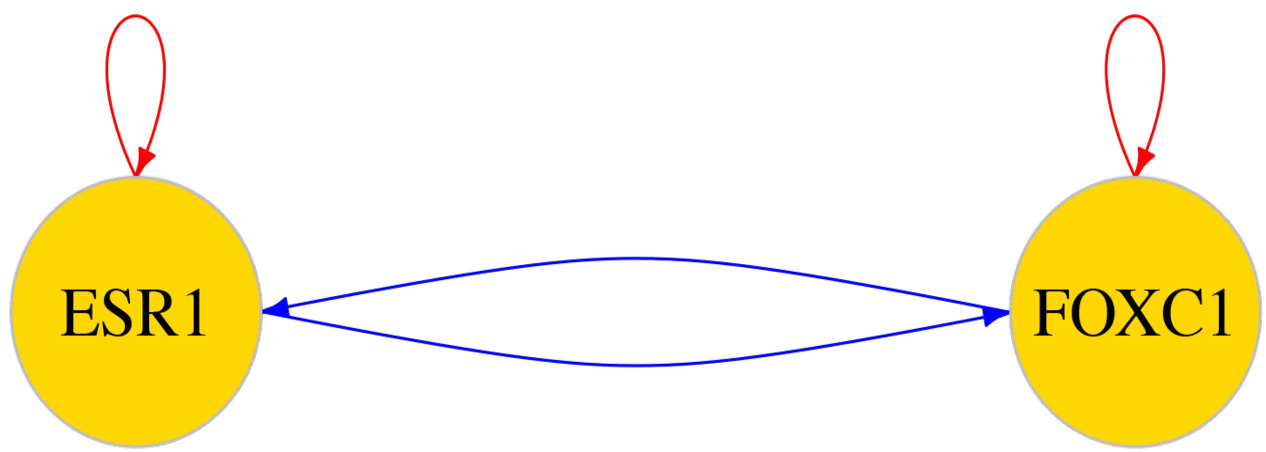
n is Hill Coefficient

S is threshold of Hill function

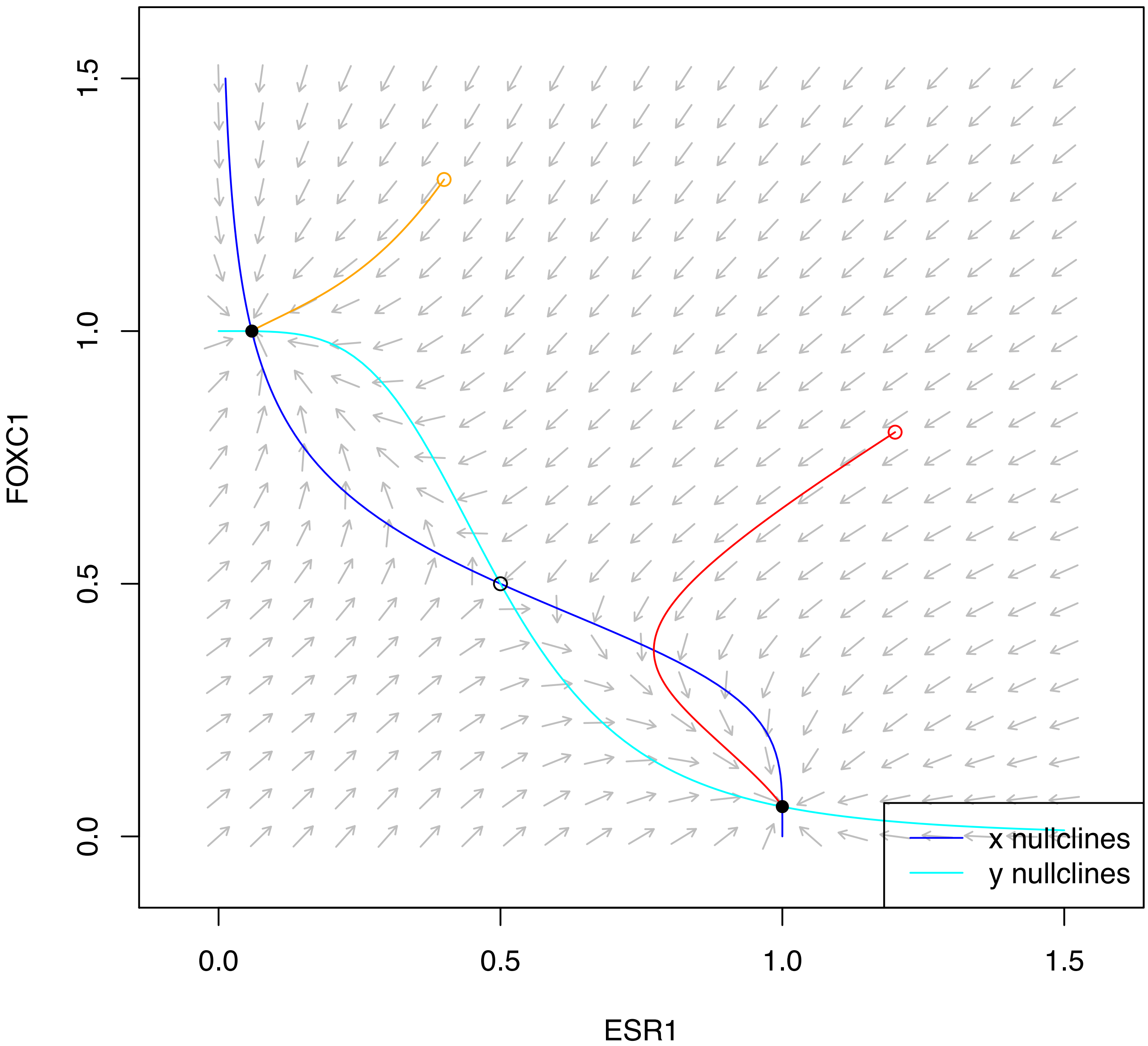
Wang et al PNAS, 2011;108:8257–8262

GRN of Luminal and Basal States



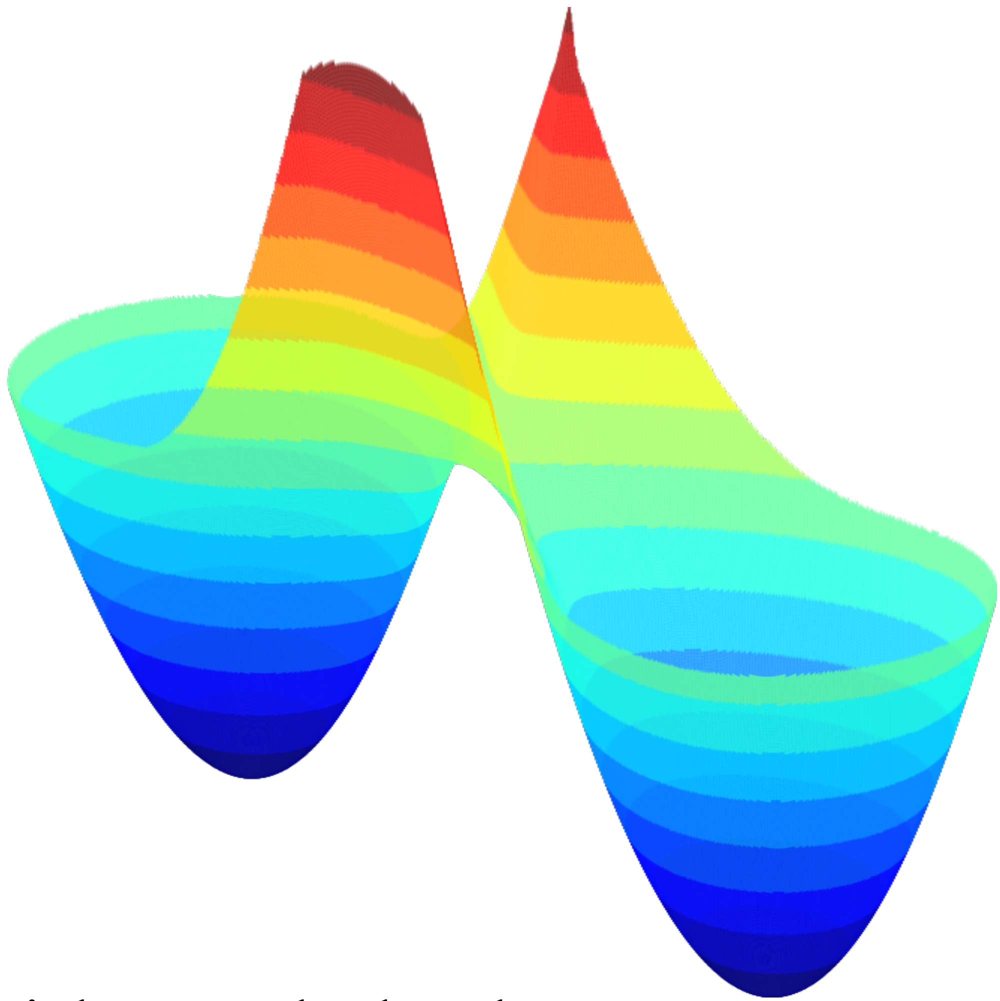


Flow Diagram of Toggle Switch GRN



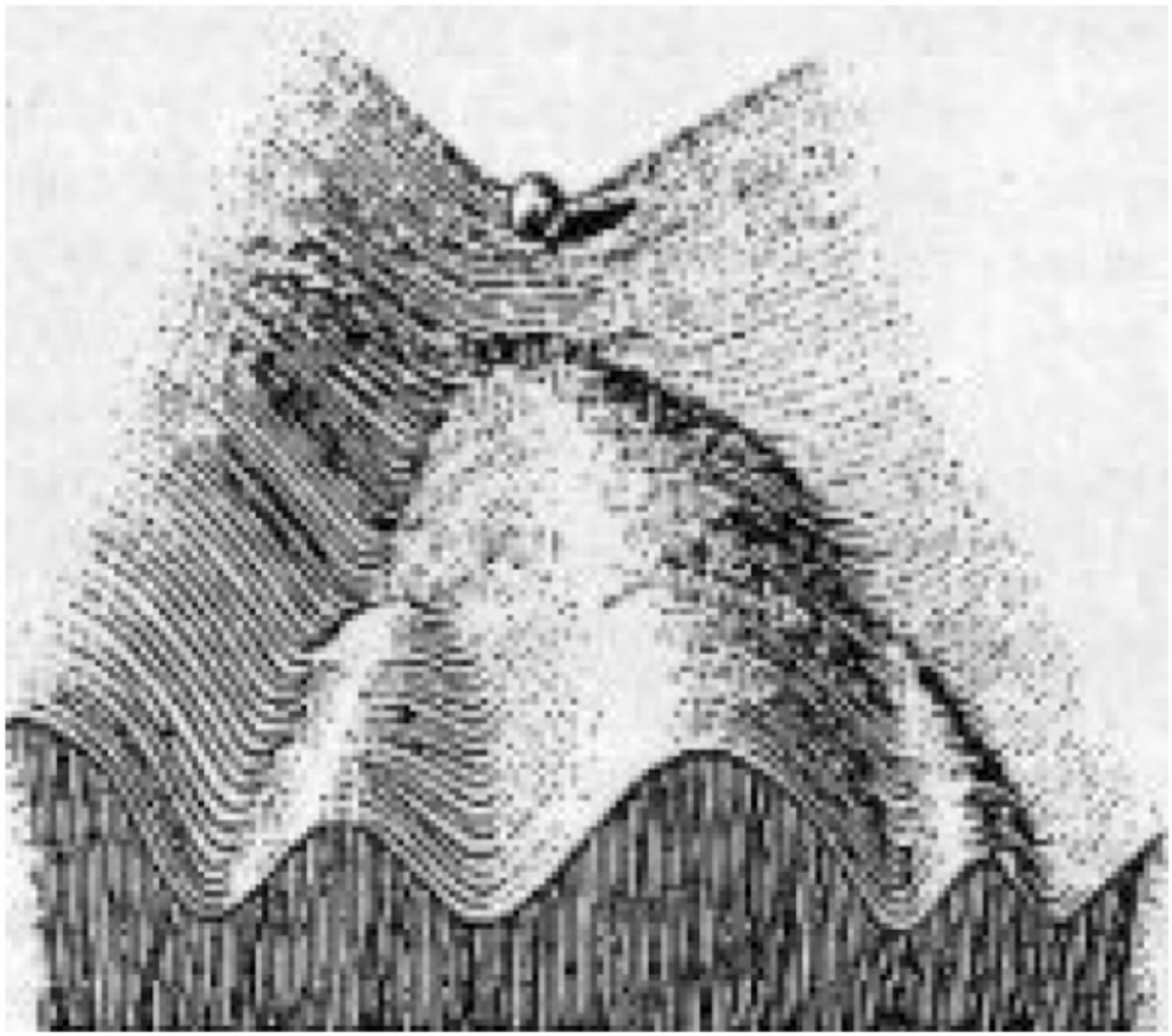
a1=a2	**0**
b1=b2	1
k1=k2	1
n	4
S	0.5

Quasi-Potential of GRN

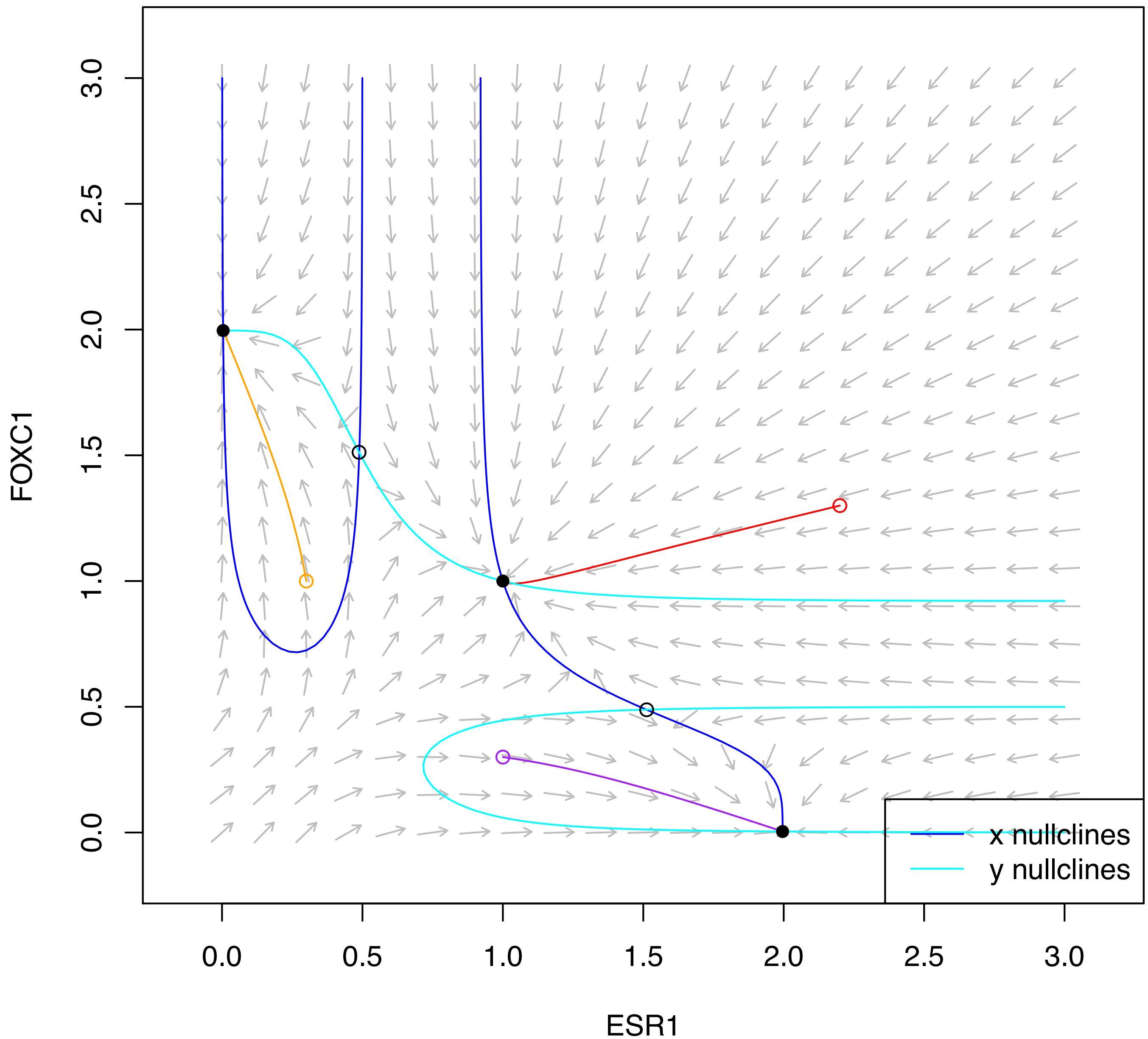


Quasi-potential was calculated
with R package QPot

Waddington's Epigenetic Landscape

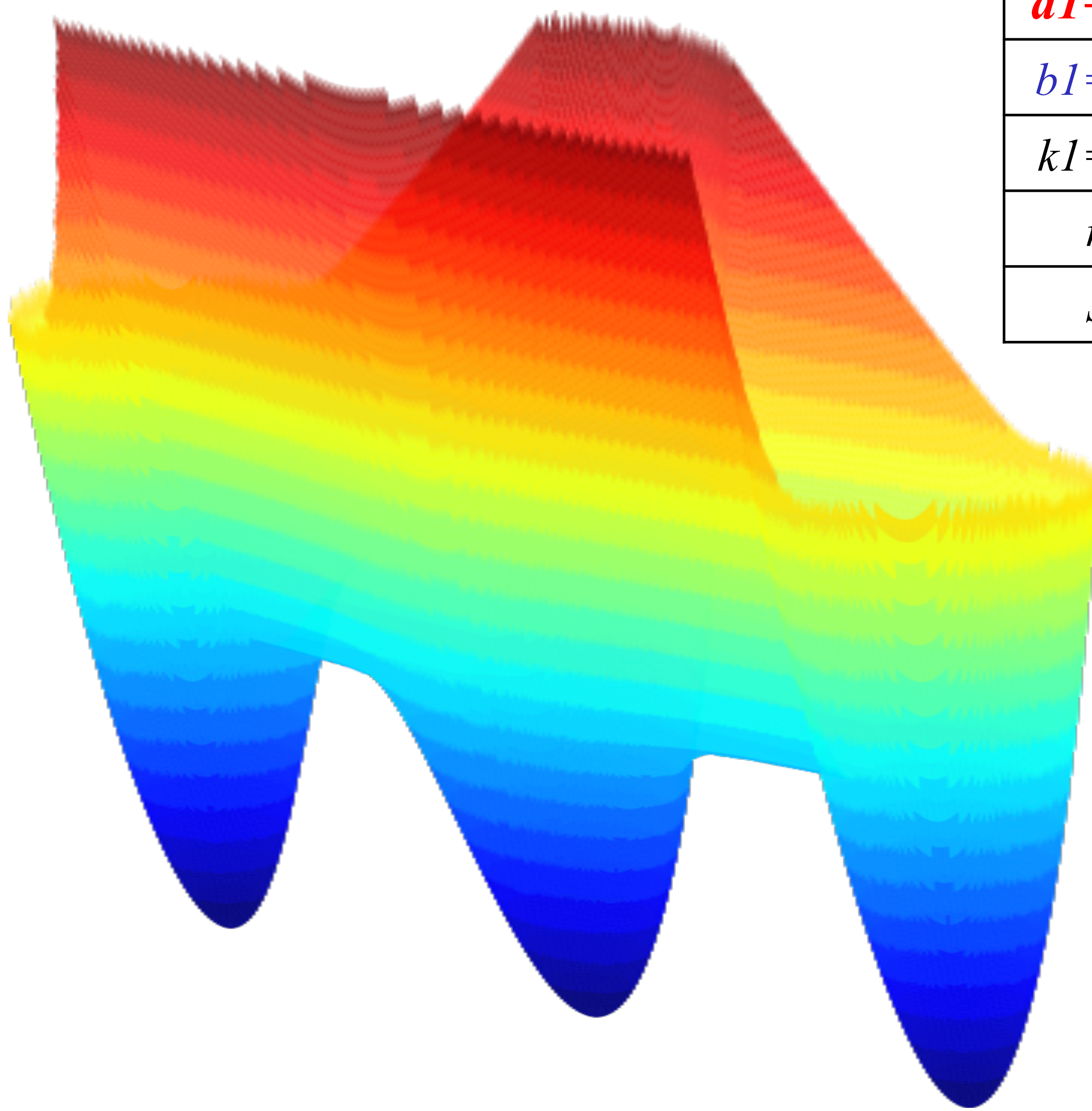


Toggle Switch GRN with Auto-Activation

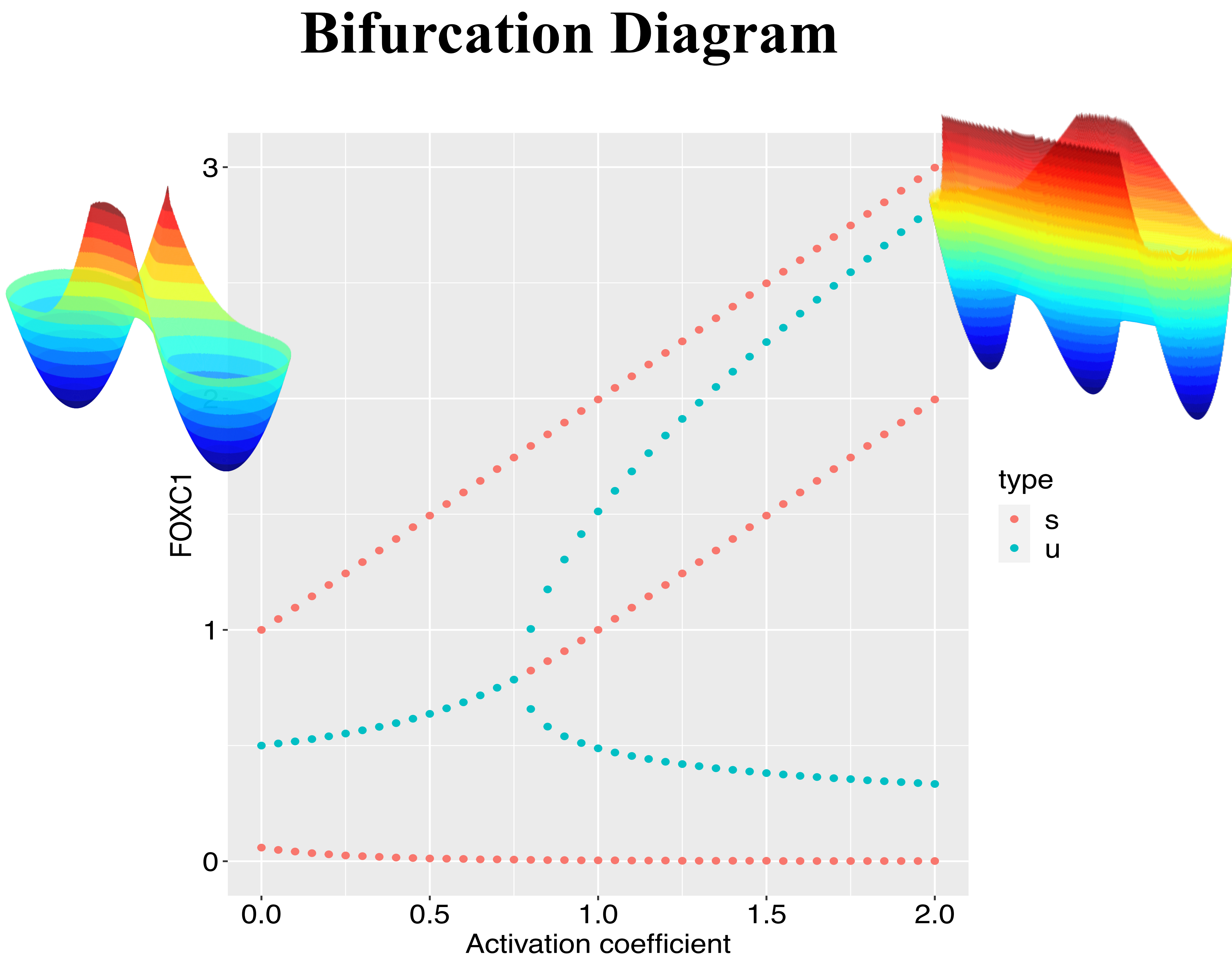


a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Quasi-Potential of GRN

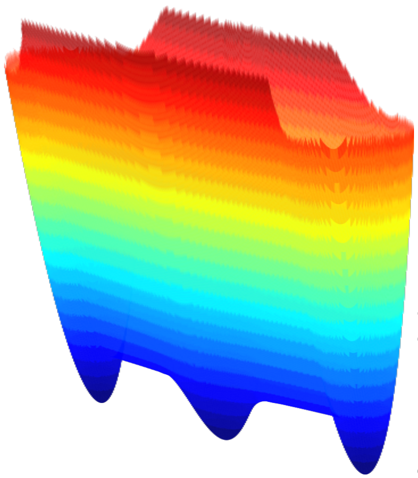


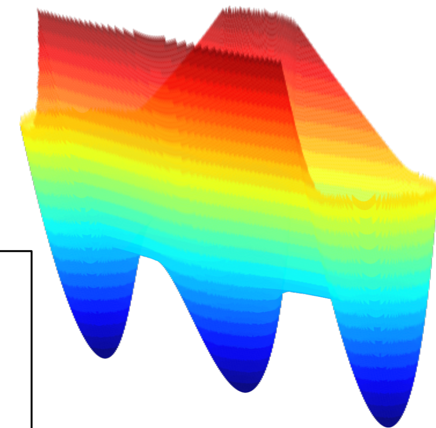
a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

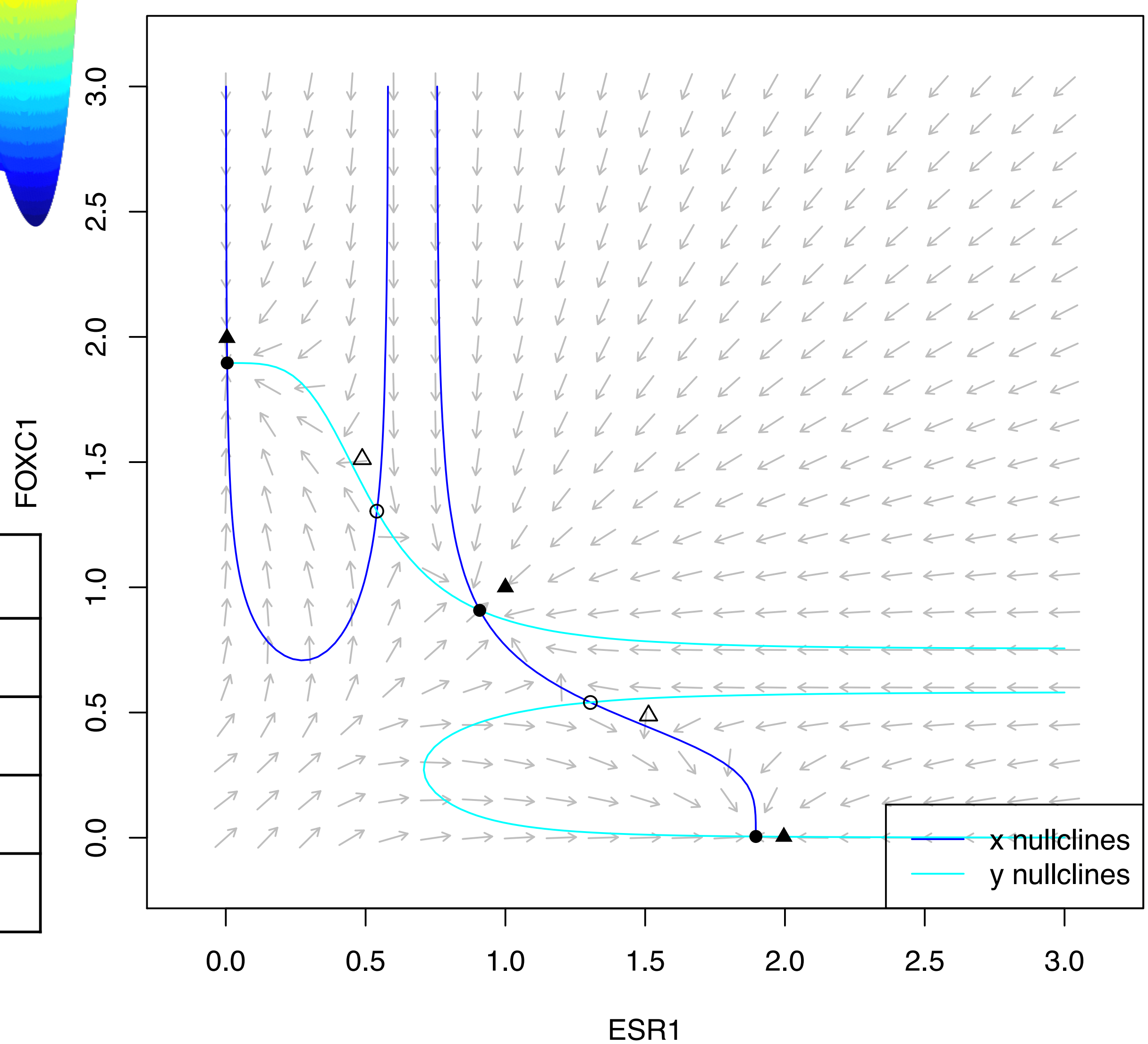


Bifurcation Diagram
FOXC1
Activation coefficient
0
1
2
3
0.0
0.5
1.0
1.5
2.0
type
s
u

Effect of Activation Coefficient on GRN



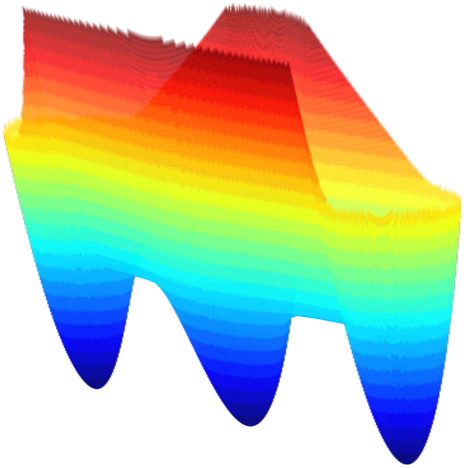




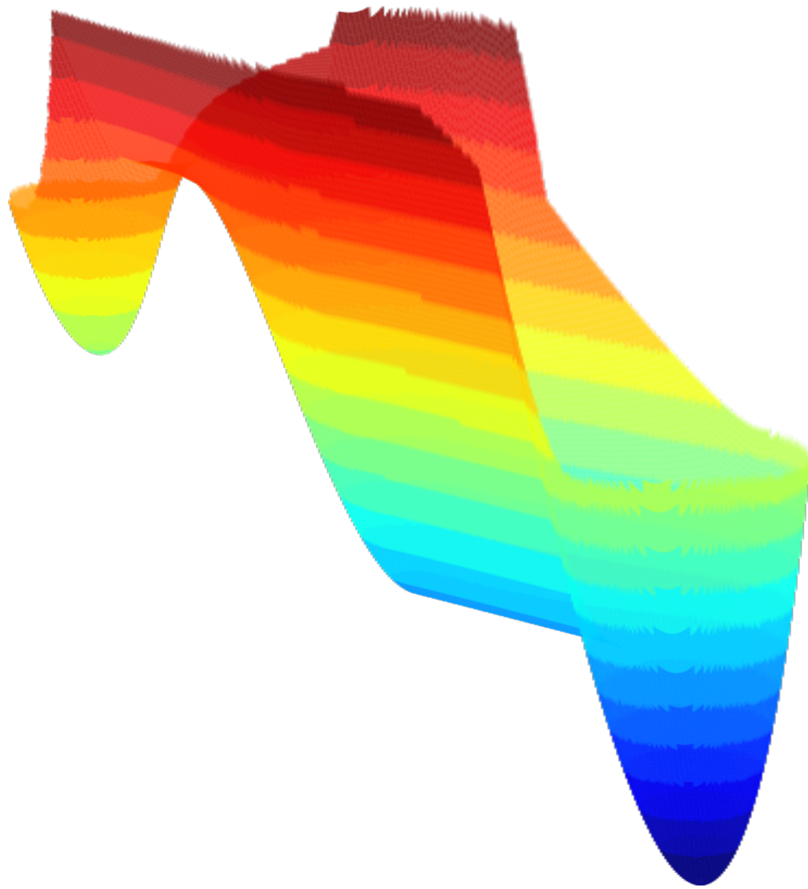
$a1=a2$	0.9
$b1=b2$	1
$k1=k2$	1
n	4
S	0.5

$a1=a2$	1
$b1=b2$	1
$k1=k2$	1
n	4
S	0.5

Quasi-Potential of GRN

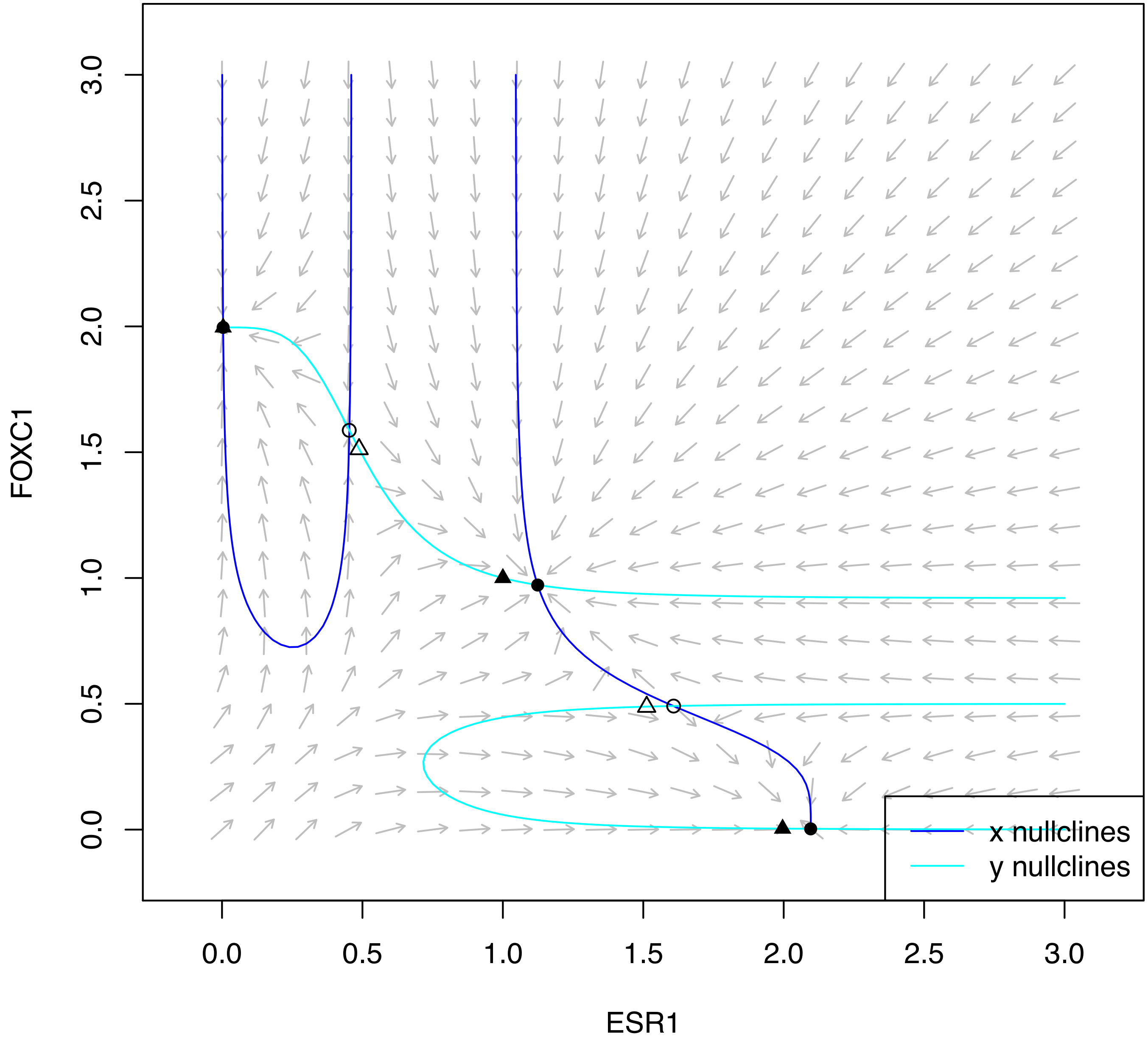


a1=a2	1
b1=b2	1
k1=k2	1
n	4
S	0.5



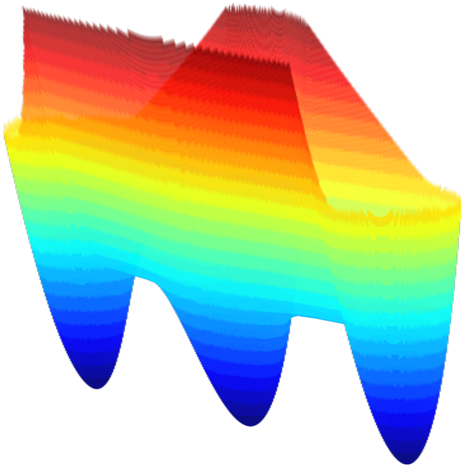
a1	1.1
a2	1
b1=b2	1
k1=k2	1
n	4
S	0.5

Flow Diagram of GRN with Auto-Activation

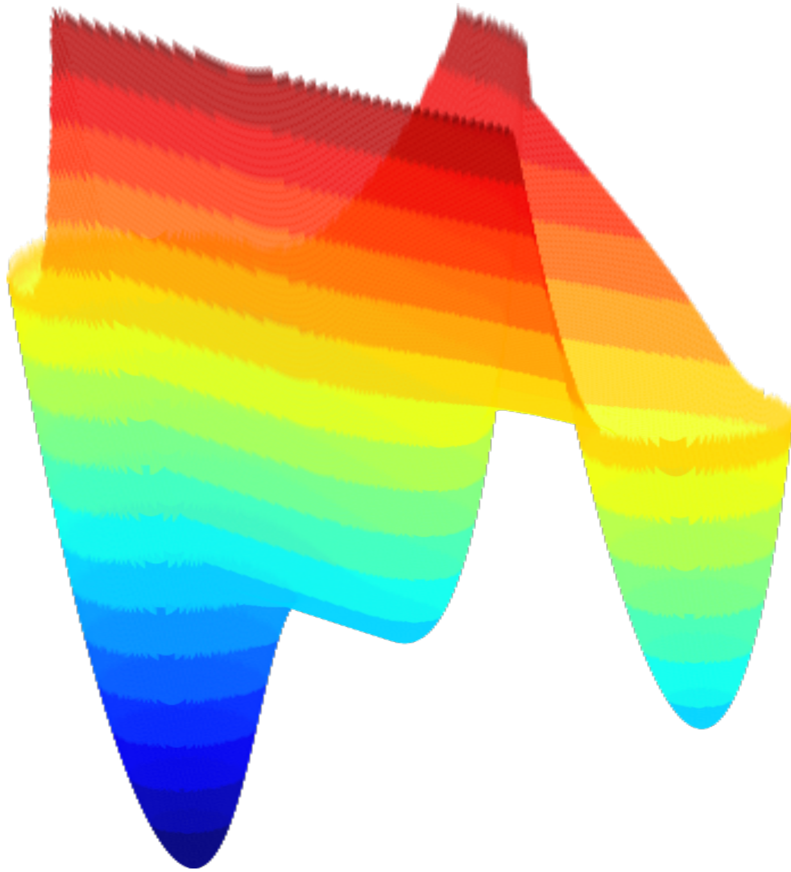


a1	**1.1**
a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Quasi-Potential of GRN

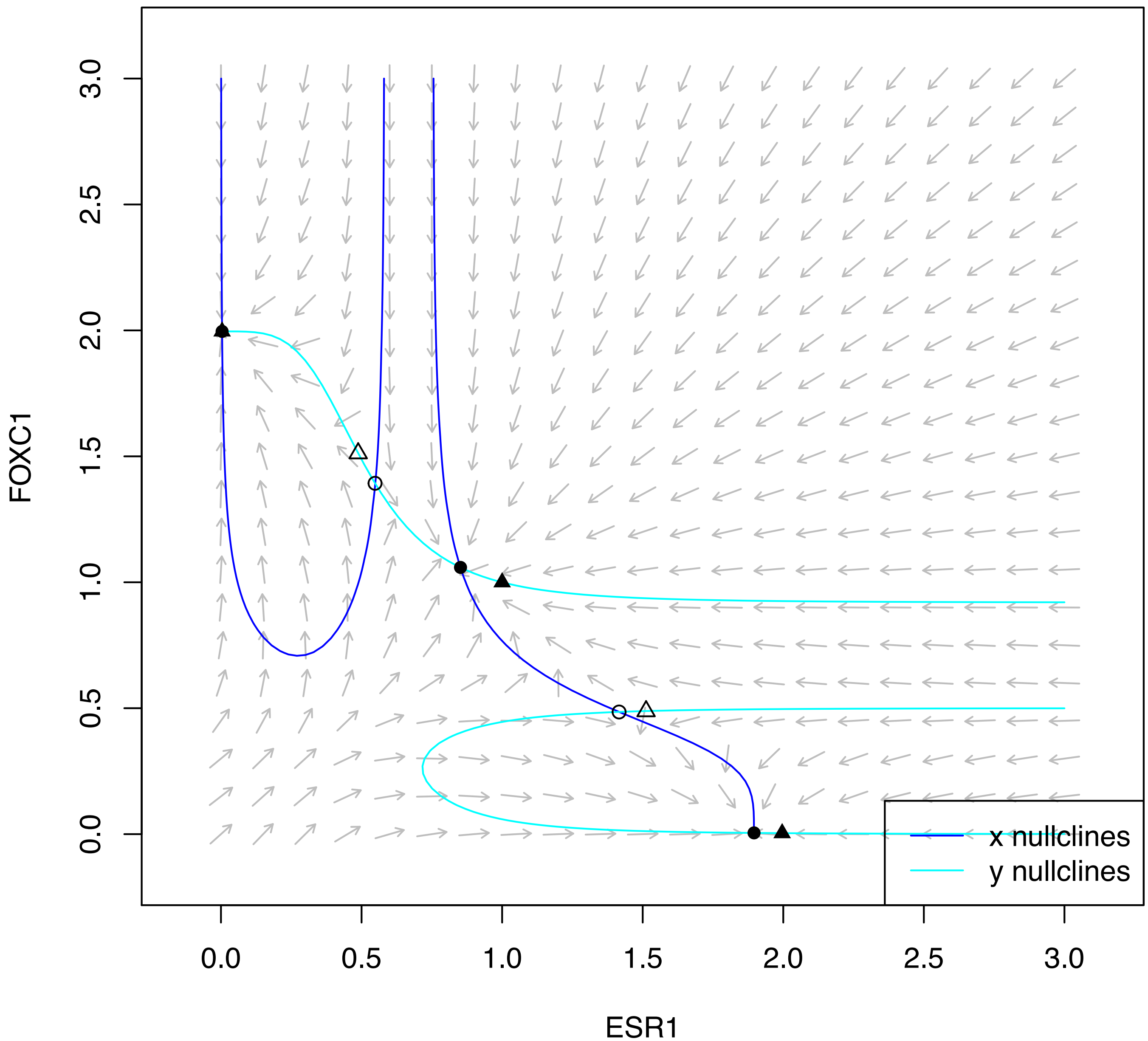


a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5



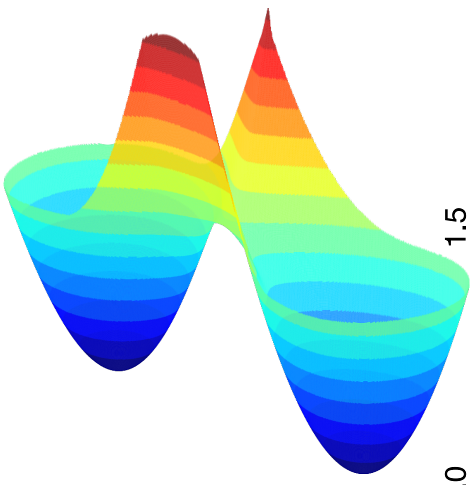
a1	**0.9**
a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Flow Diagram of GRN with Auto-Activation

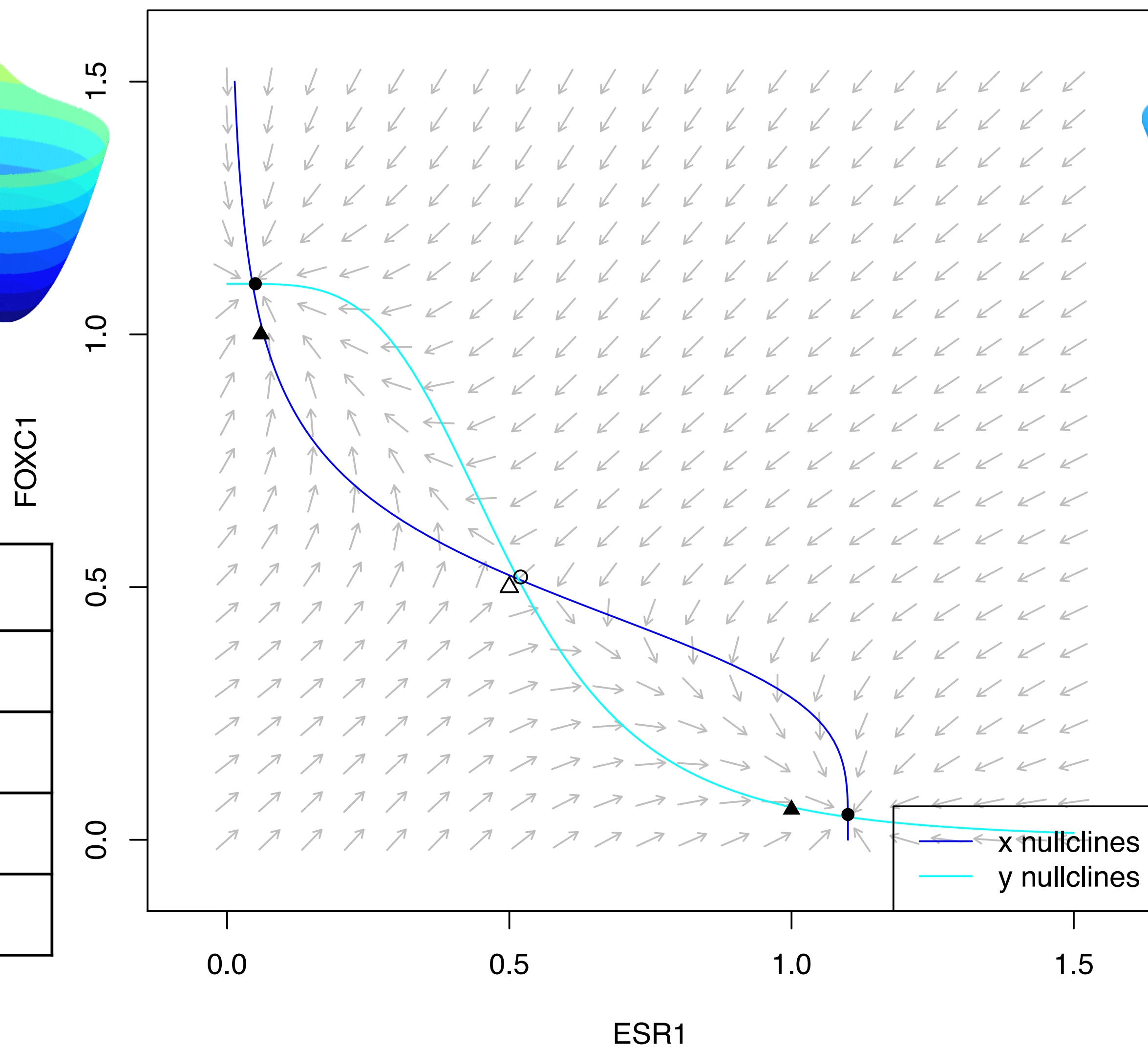


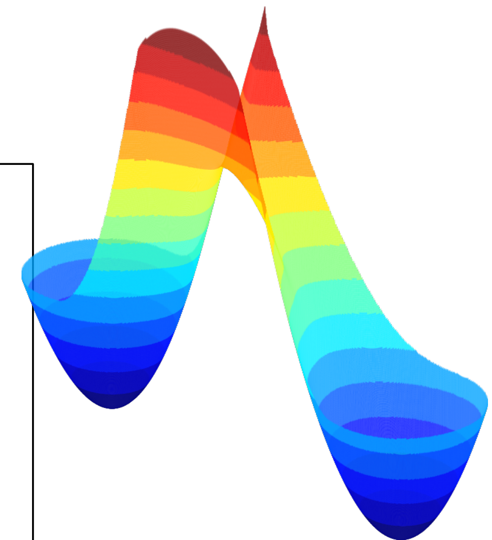
a1	**0.9**
a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Effect of Inhibition Coefficient on GRN



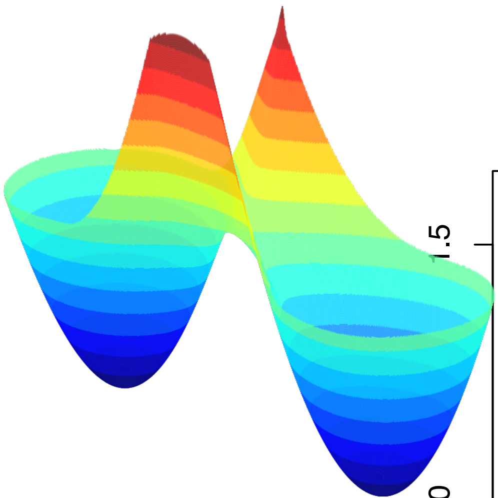
a1=a2	**0**
b1=b2	1
k1=k2	1
n	4
S	0.5

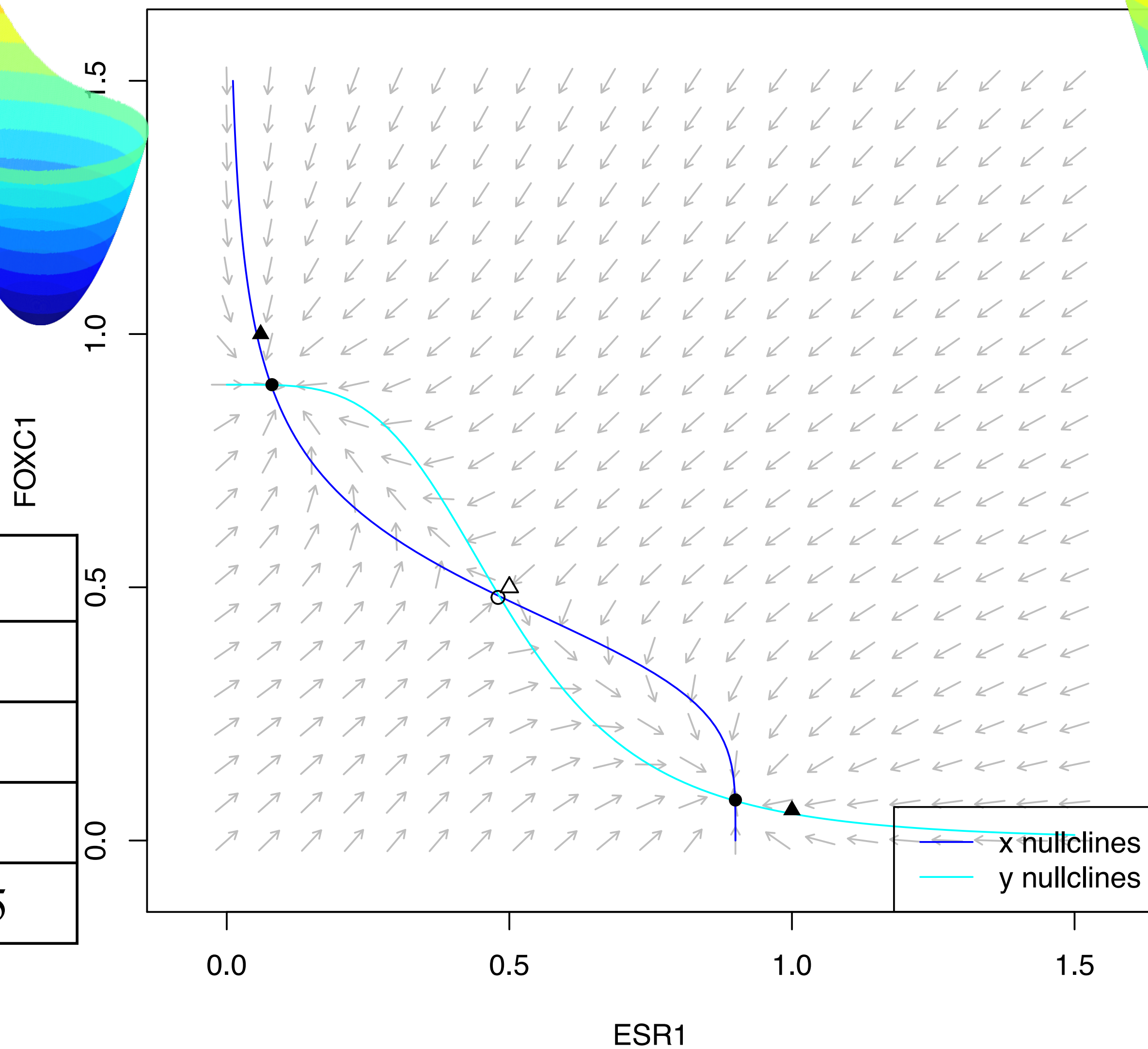


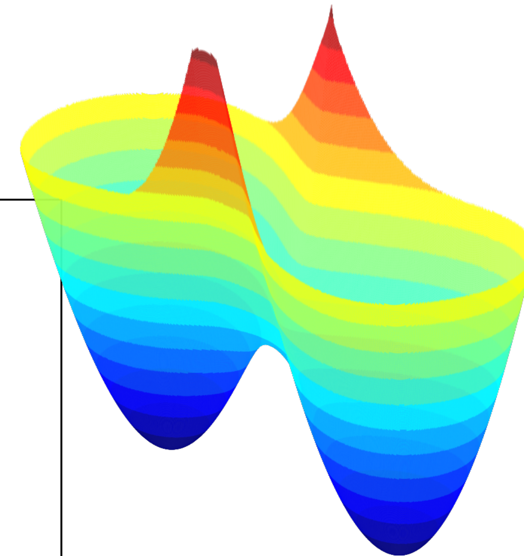


a1=a2	**0**
b1=b2	1.1
k1=k2	1
n	4
S	0.5

Effect of Inhibition Coefficient on GRN



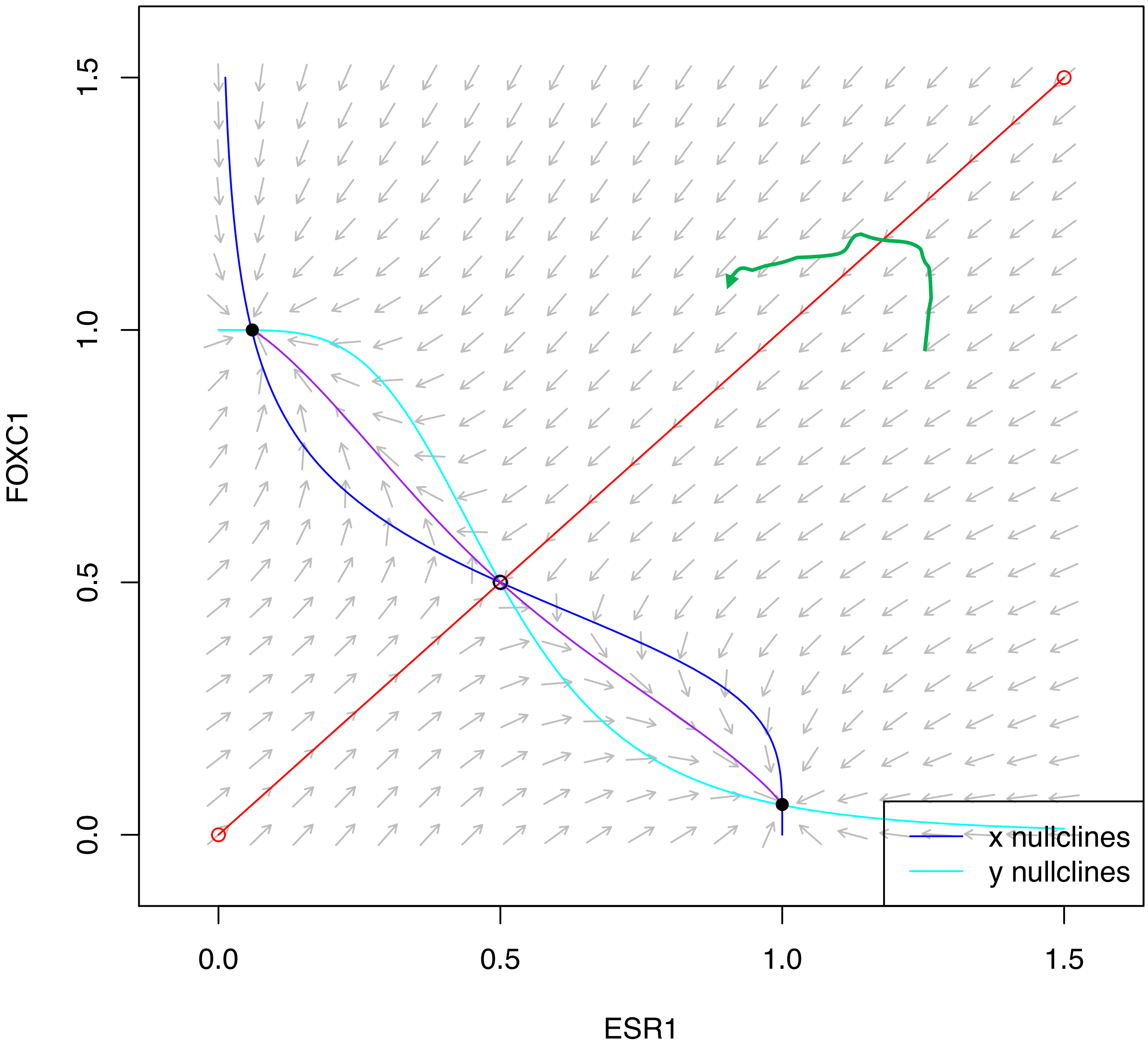




a1=a2	**0**
b1=b2	1
k1=k2	1
n	4
S	0.5

a1=a2	**0**
b1=b2	0.9
k1=k2	1
n	4
S	0.5

Two Regions Separated by Eigen Vector



a1=a2	**0**
b1=b2	1
k1=k2	1
n	4
S	0.5

$$J = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}$$

Jacobian matrix

Stochastic Differential Equation (DE) Model

$$\frac{dx_1}{dt} = \frac{a_1 x_1^n}{S^n + x_1^n} + \frac{b_1 S^n}{S^n + x_2^n} - k_1 x_1$$

$$\frac{dx_2}{dt} = \frac{a_2 x_2^n}{S^n + x_2^n} + \frac{b_2 S^n}{S^n + x_1^n} - k_2 x_2$$

$$d\mathbf{X} = f(\mathbf{X})\, dt$$ Deterministic DE

$$d\mathbf{X} = f(\mathbf{X})\, dt + \sigma\, d\mathbf{W}$$ Stochastic DE

Wiener process

$$dX = -U'(X)\, dt + \sigma\, dW$$ *U* is quasi-potential

Nolting et al Ecology 2016;97:850-864

Stochastic Differential Equation (DE) Model

$$dX = -U'(X)\,dt + \sigma\,dW$$

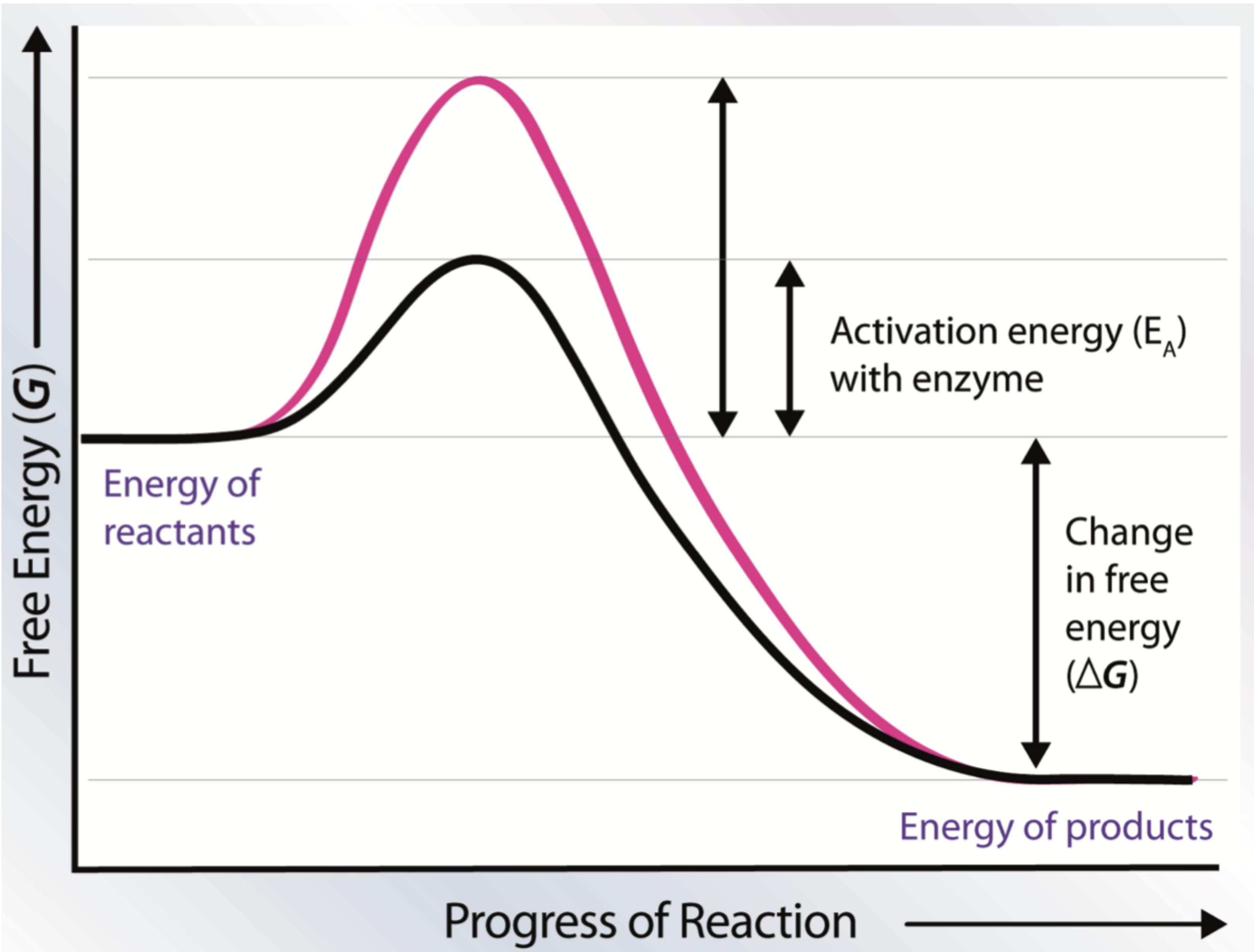
Fokker-Planck equation

$$\frac{\partial p(x,t)}{\partial t} = \frac{\partial}{\partial x}\left(U'(x)p(x,t)\right) + \frac{\sigma^2}{2}\frac{\partial^2 p(x,t)}{\partial x^2}$$

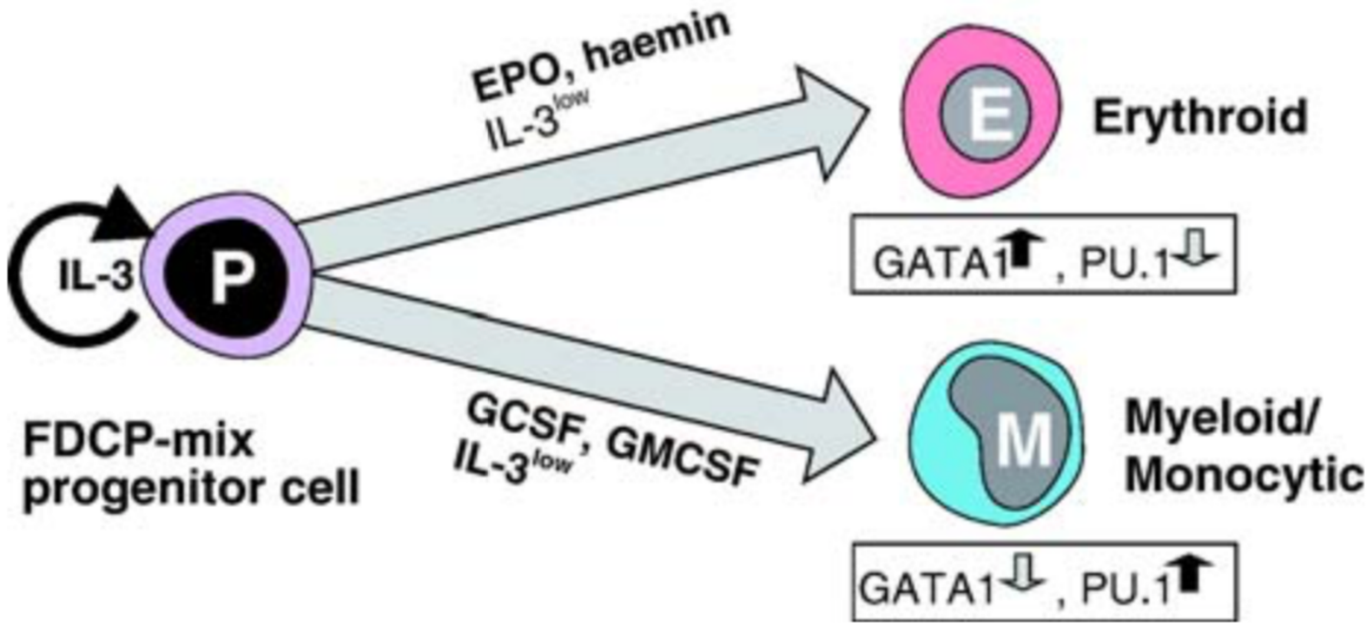
$$p_s(x) = \frac{1}{Z}\exp\left(-\frac{2U(x)}{\sigma^2}\right)$$

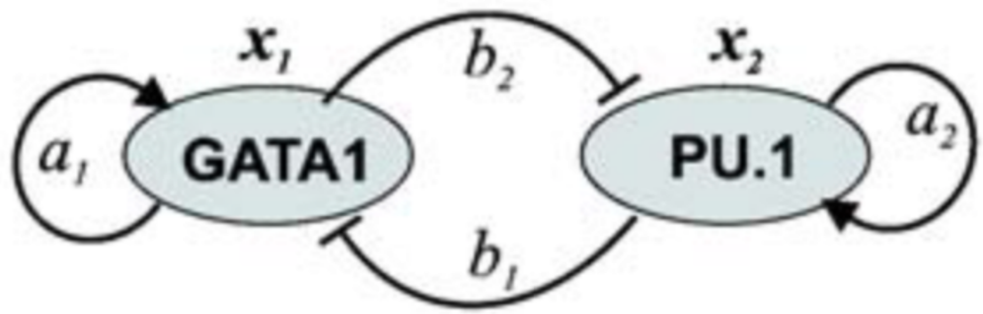
$p_s(x)$ is steady state probability
Z is normalization factor

Chemical Reaction Kinetics



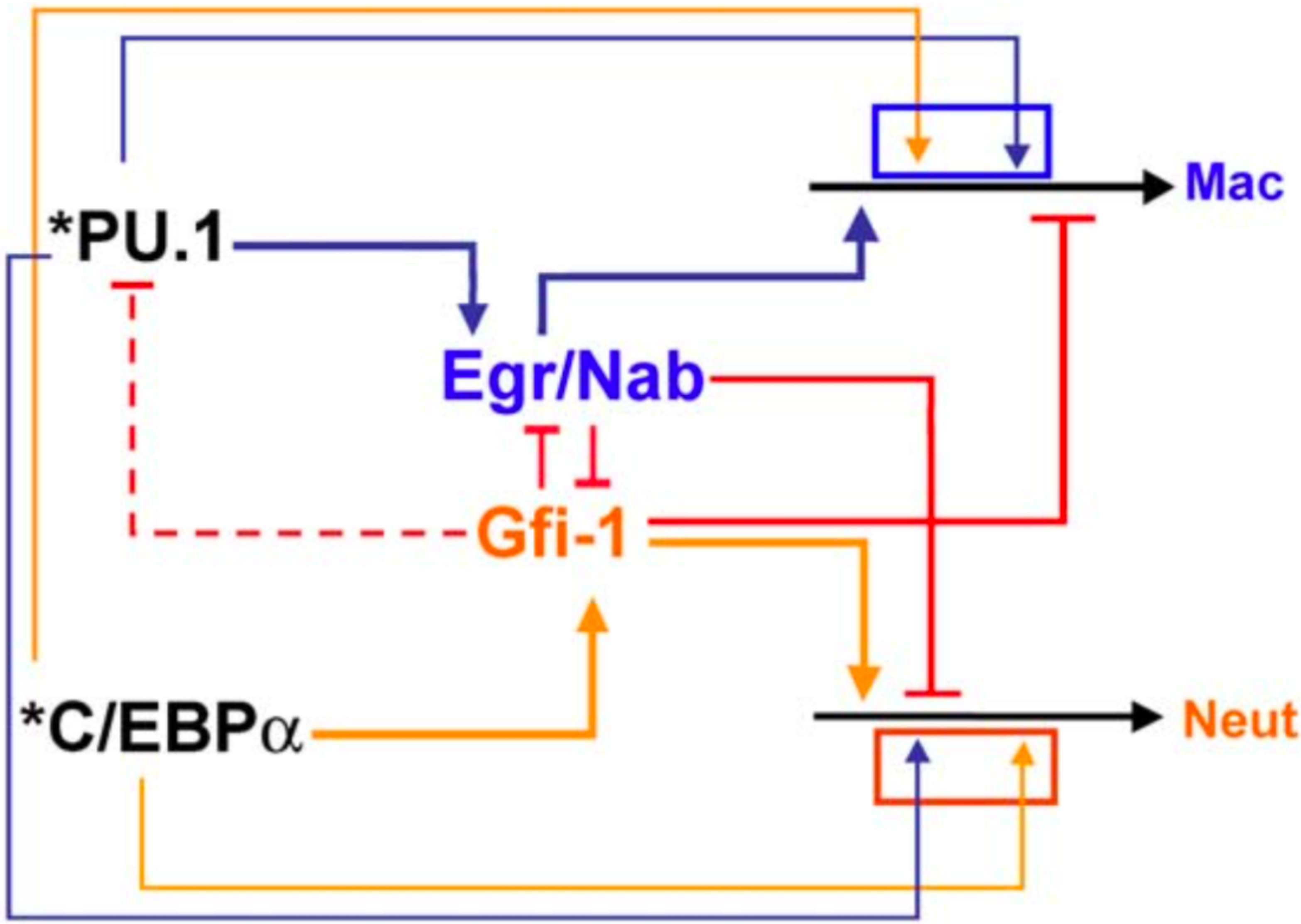
GRN of Hematopoietic Cell Fate Decision





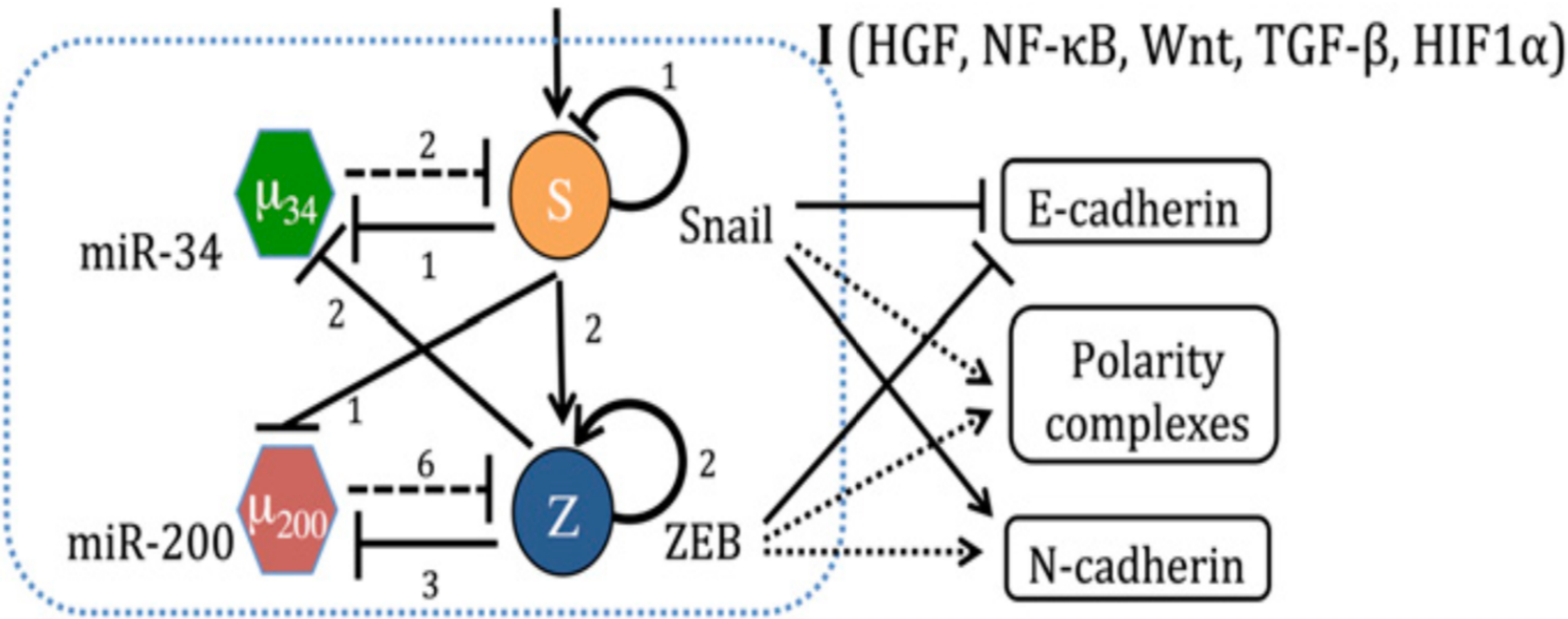
Huang et al 2007, Developmental Biology 305:695

GRN of Hematopoietic Cell Fate Decision



Laslo et al 2006, Cell 126:755

GRN of EMT Mediated by microRNA



Lu et al PNAS 2013, 110:18144

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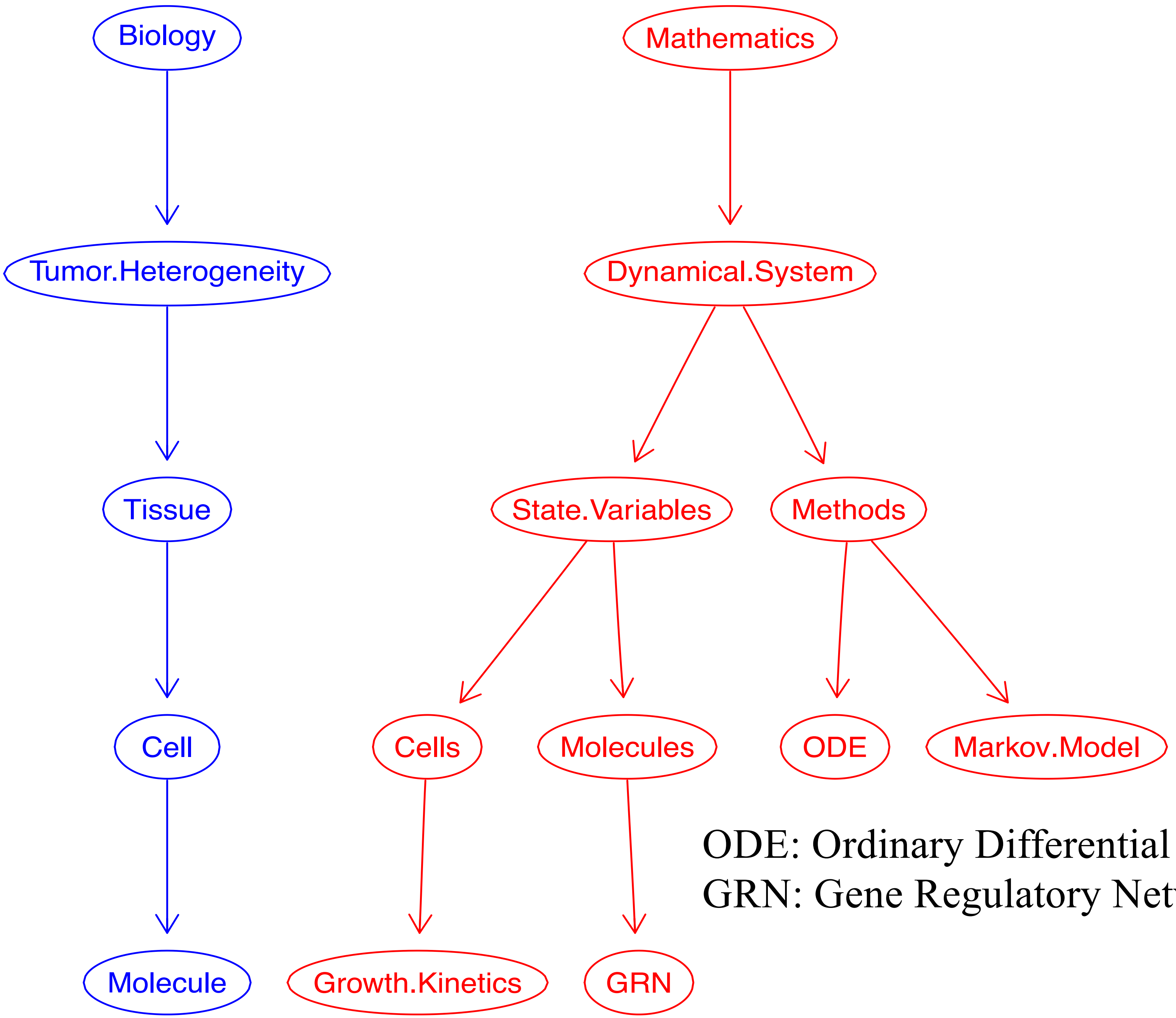

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GRN: Gene Regulatory Network