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

Cell Fate Decision Determined by Gene Regulatory Network (GRN)

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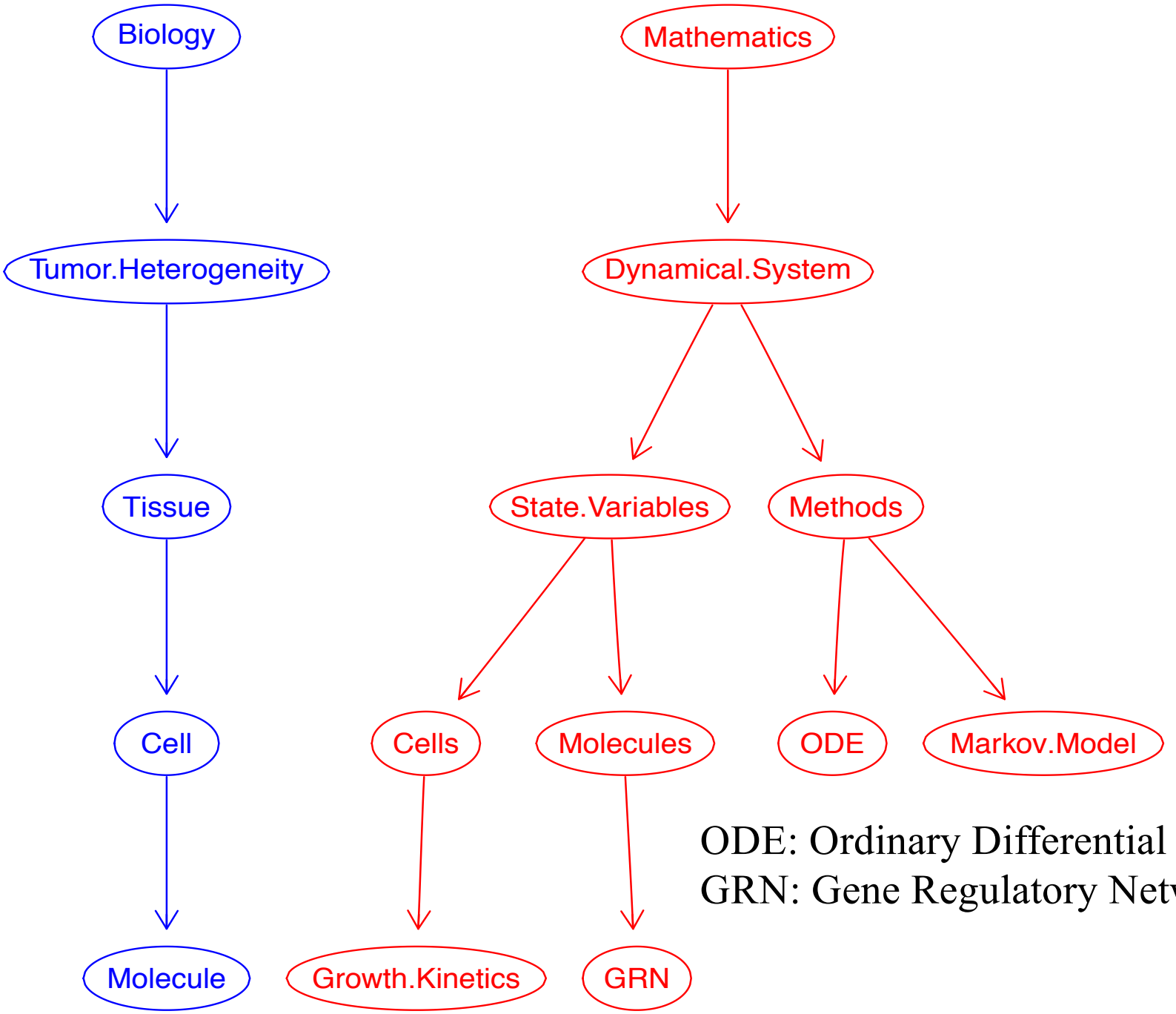
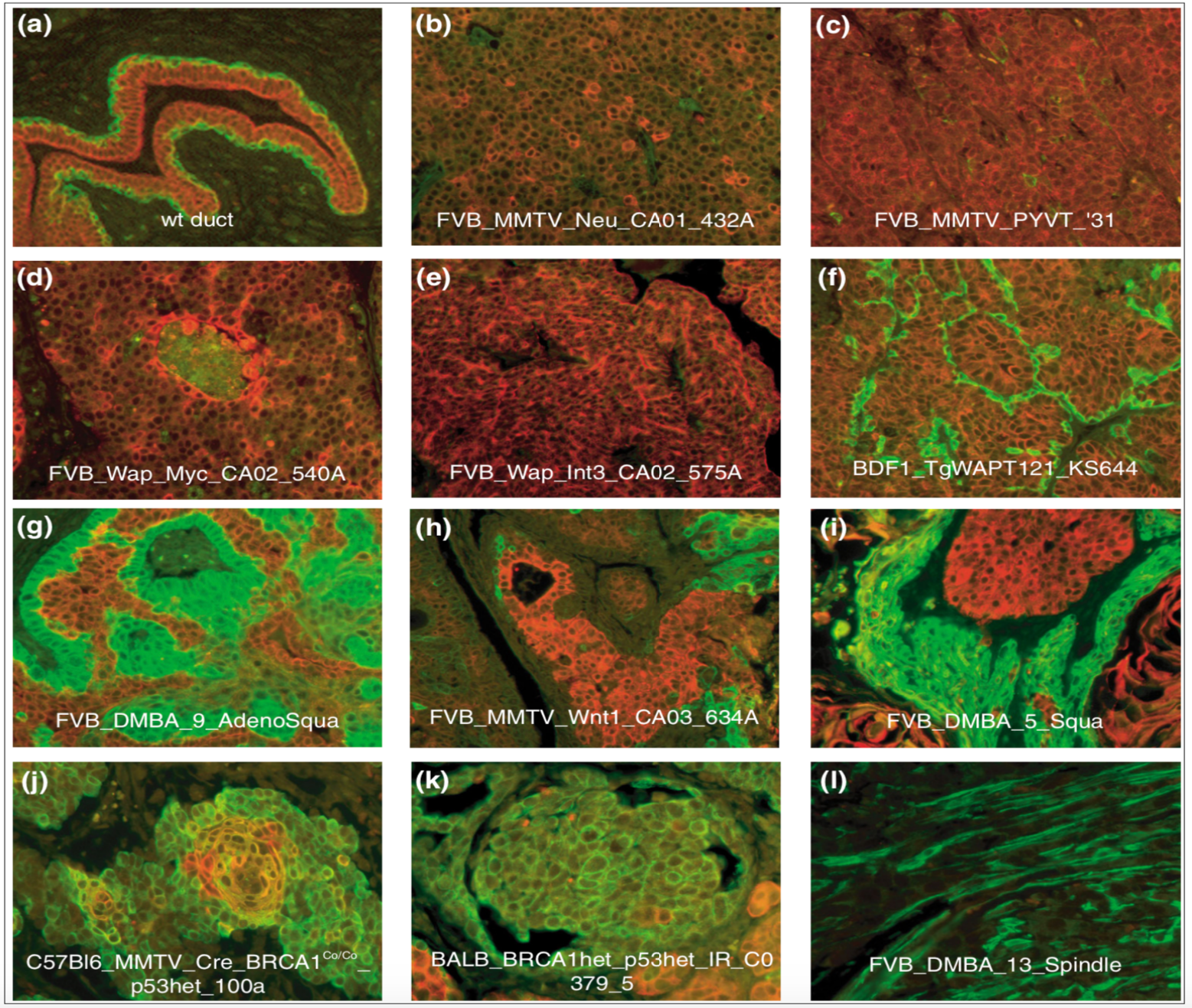
Understanding Biology with Mathematical Modeling



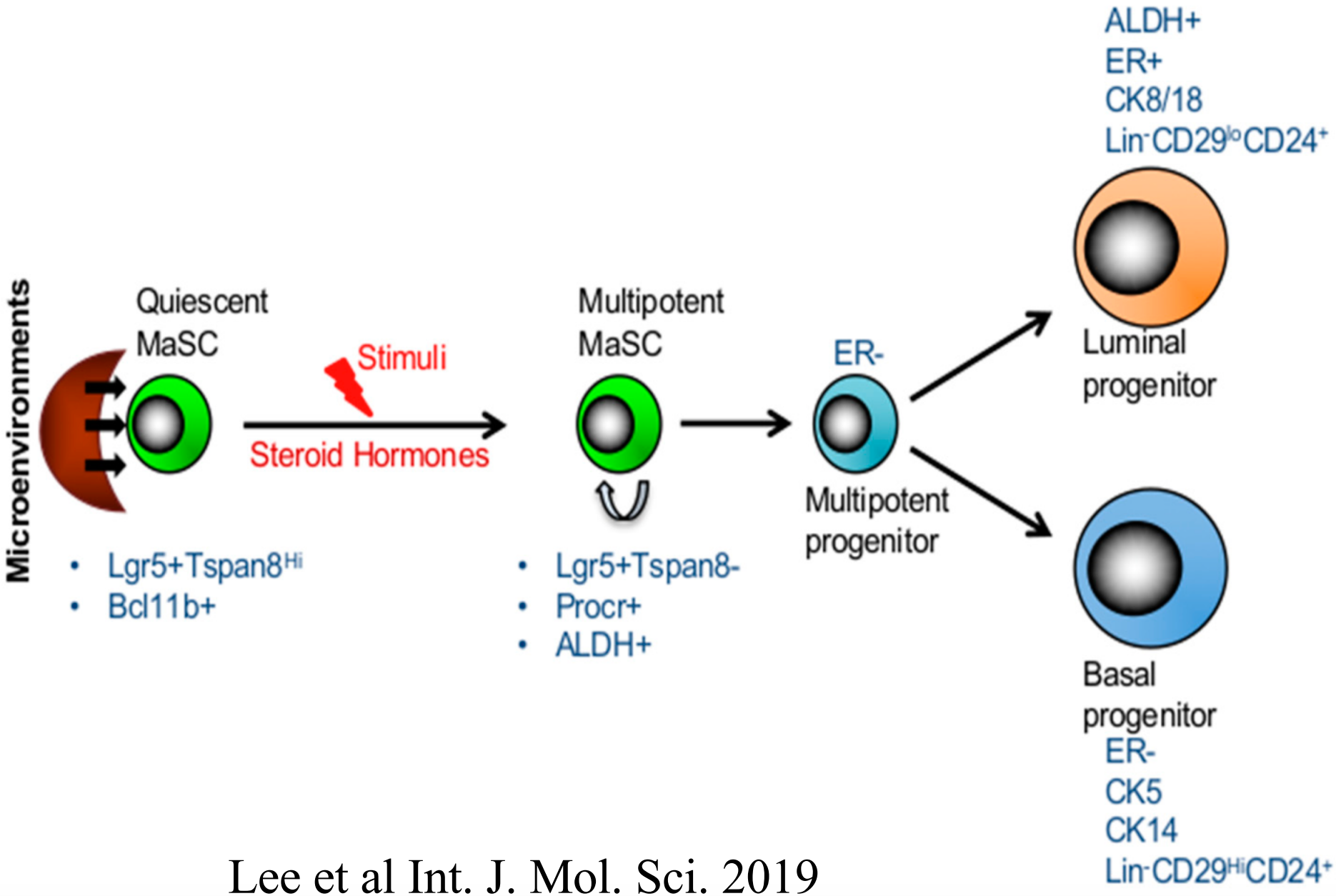
ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

Heterogeneity of Mouse Mammary Tumors



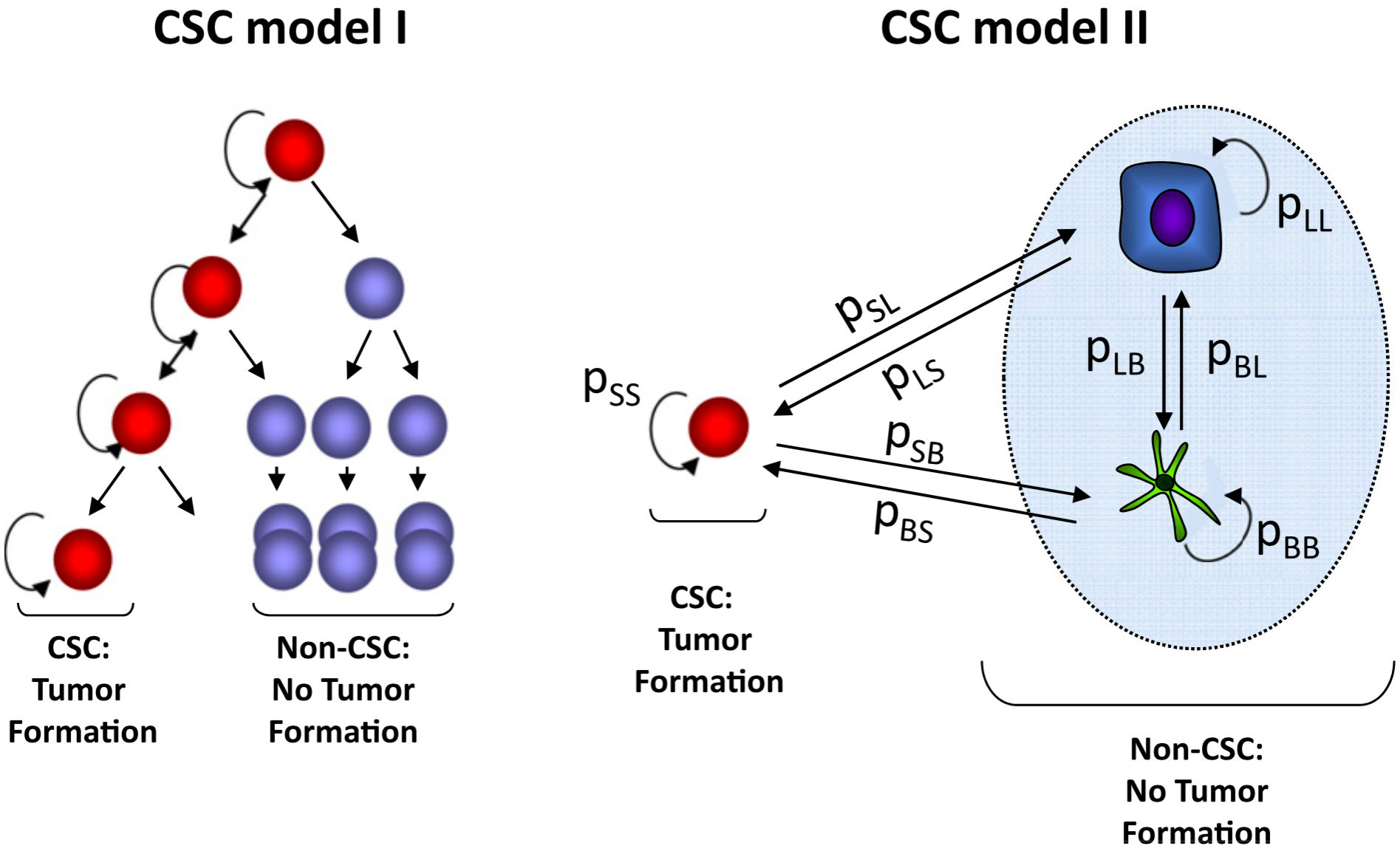
Keratins 8/18 Keratin 5 Herschkowitz, …, Perou Genome Biology 2007

Mammary Stem Cell Model



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

Cancer Stem Cell Model

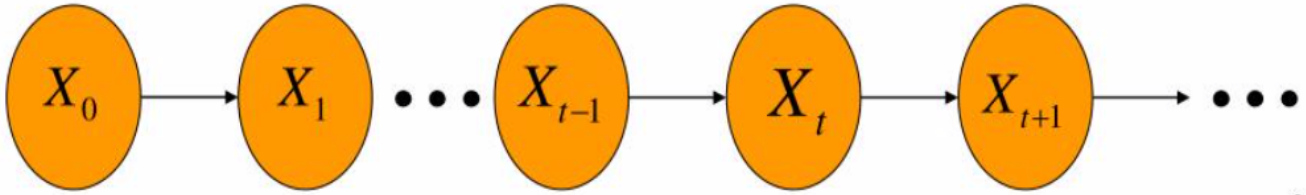


Gupta et al Cell 2011 Aug 19;146(4):633-44

Markov Process for Cancer Stem Model

$$\boldsymbol{x} = \begin{bmatrix} x_1 \\ x_2 \\ \\ \\ x_n \end{bmatrix}$$

x_i: frequency of cell type i



$$P = \begin{bmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ & \cdots & \cdots & \\ p_{n1} & p_{n2} & \cdots & p_{nn} \end{bmatrix}$$

transition probability matrix

$p_{ij} >= 0$

$\Sigma_j p_{ij} = 1$

$$x^{t+1} = x^t P_{nn}$$

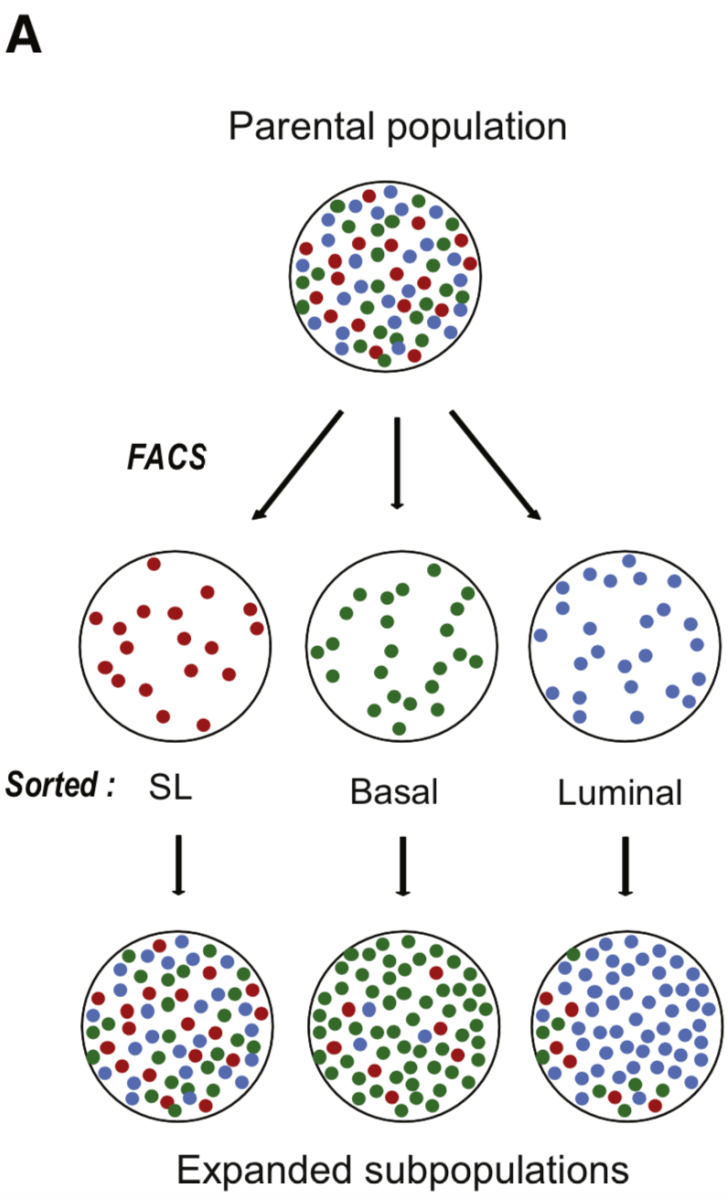
$$x^* = x^* P \qquad \text{at steady state}$$

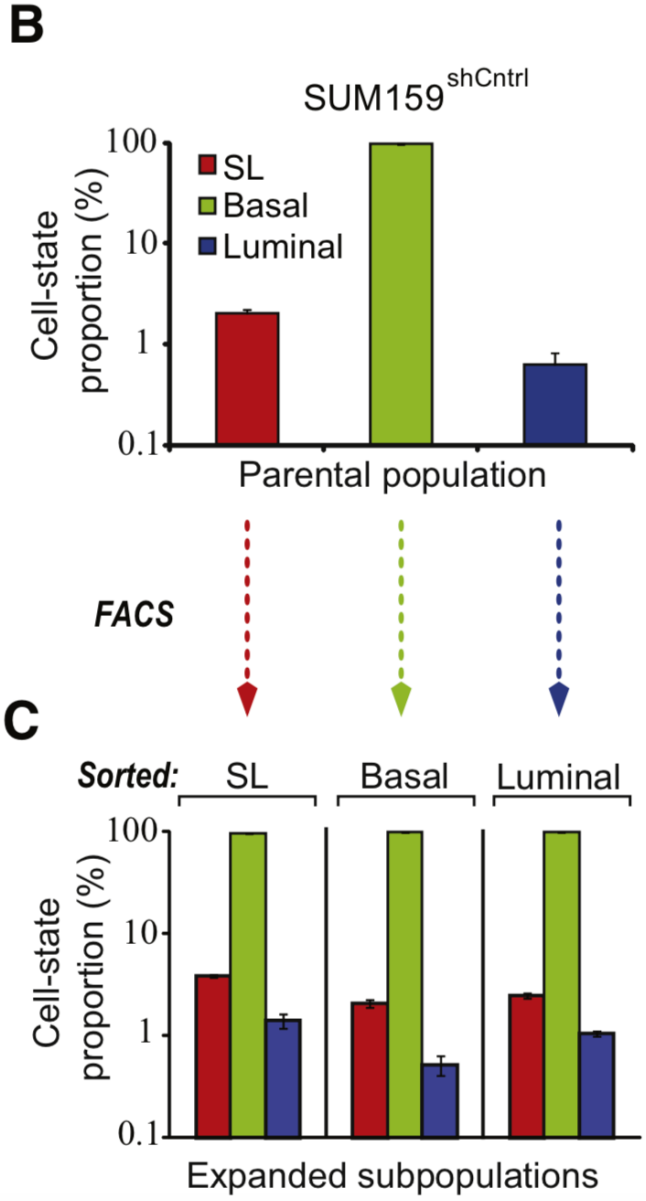
x^* is the left eigen vector of matrix P

Its eigen value is 1, which is the largest eigen value

Conversion Between Cancer Stem Cell and Non-stem Cells

SL: stem-like

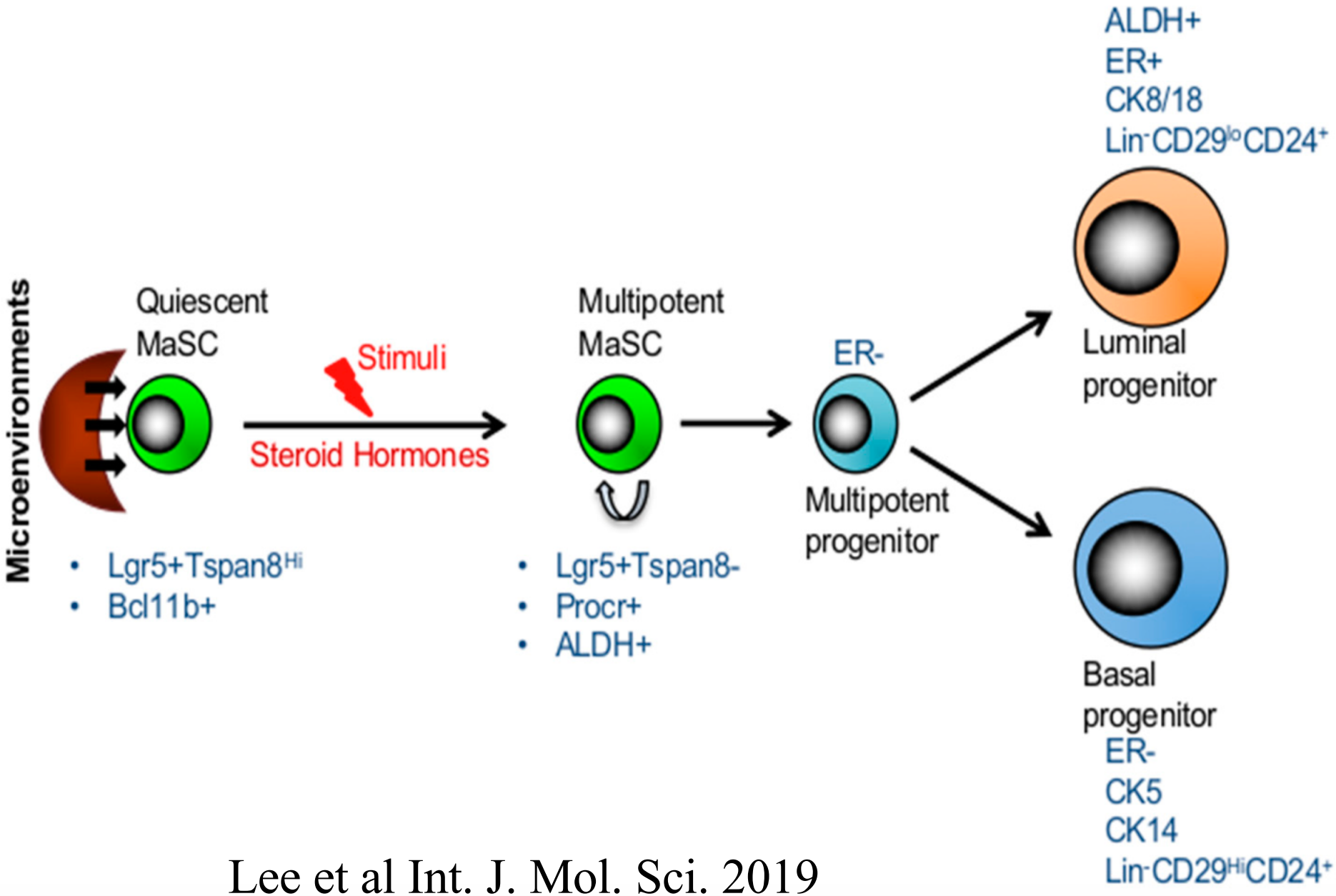




6 days

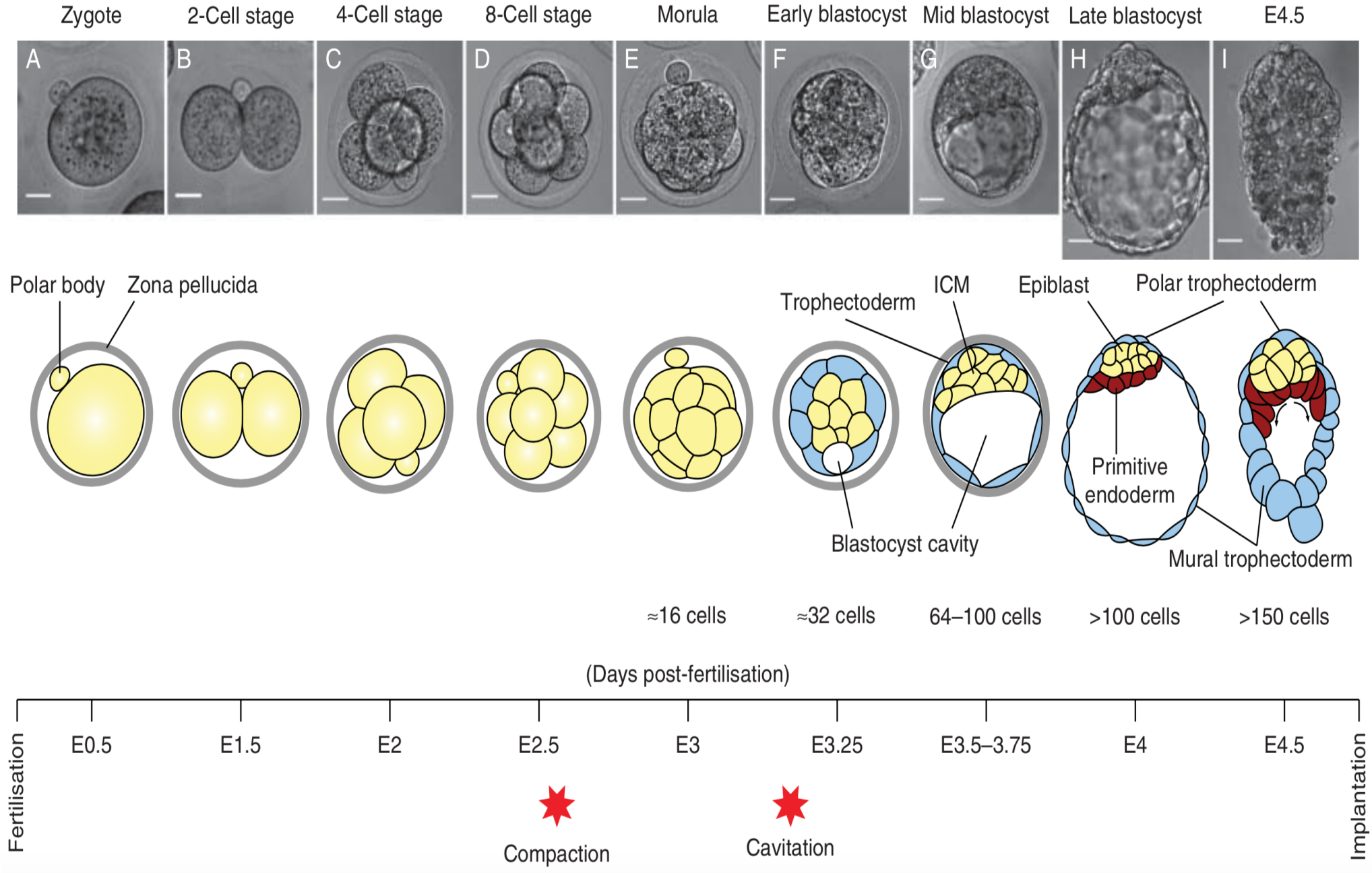
Gupta et al Cell 2011 Aug 19;146(4):633-44

Mammary Stem Cell Model



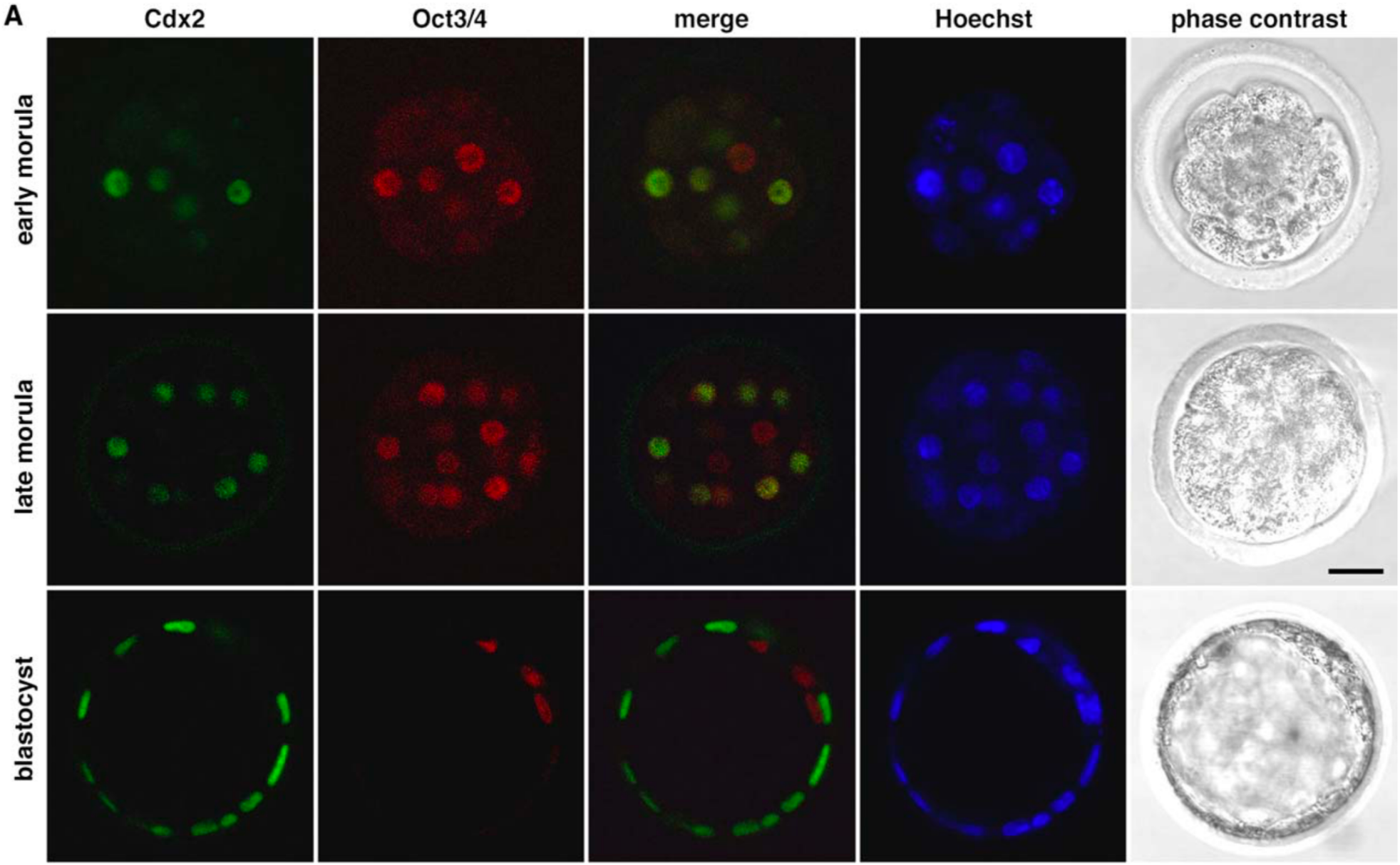
Lee et al Int. J. Mol. Sci. 2019

Mouse Embryo Developmental Stages



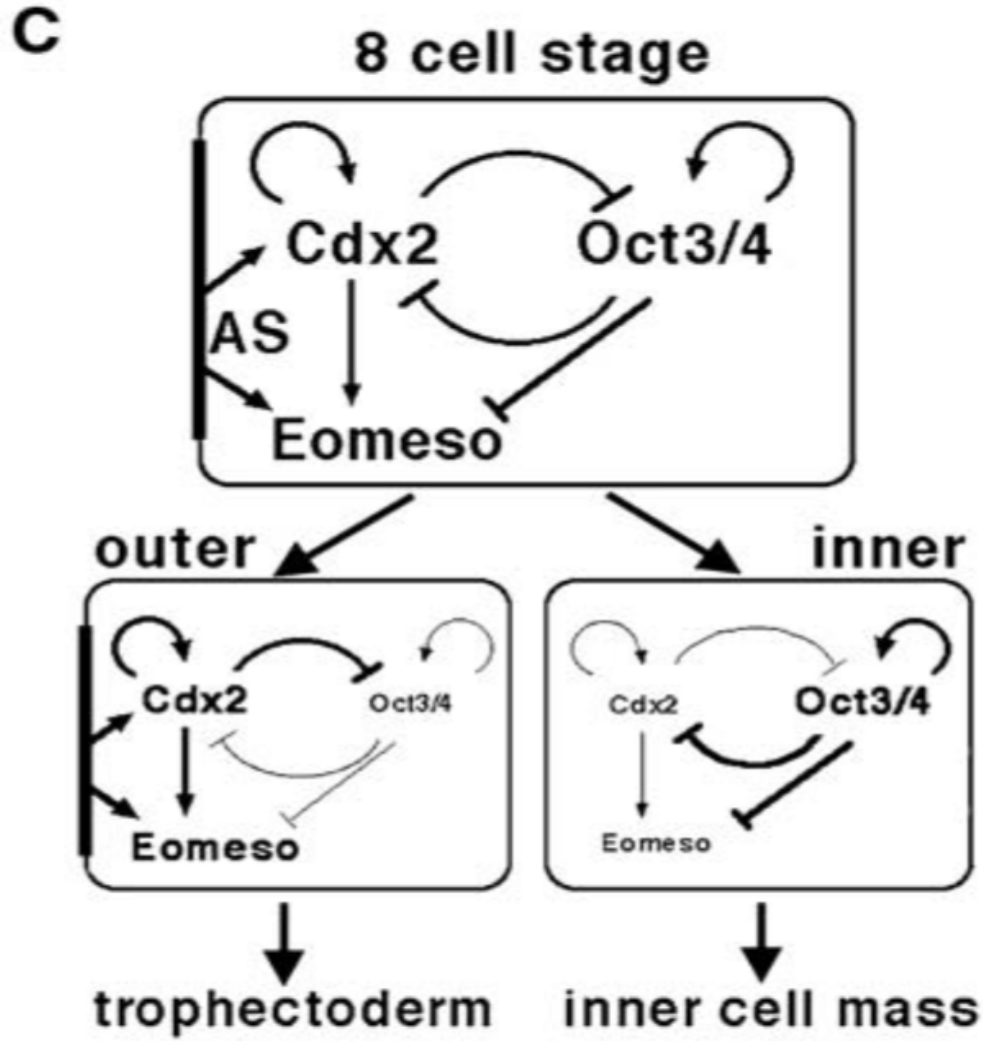
Saiz et al Reproduction 2013

Interaction Between Oct3/4 and Cdx2 Expression Determines Trophectoderm Differentiation



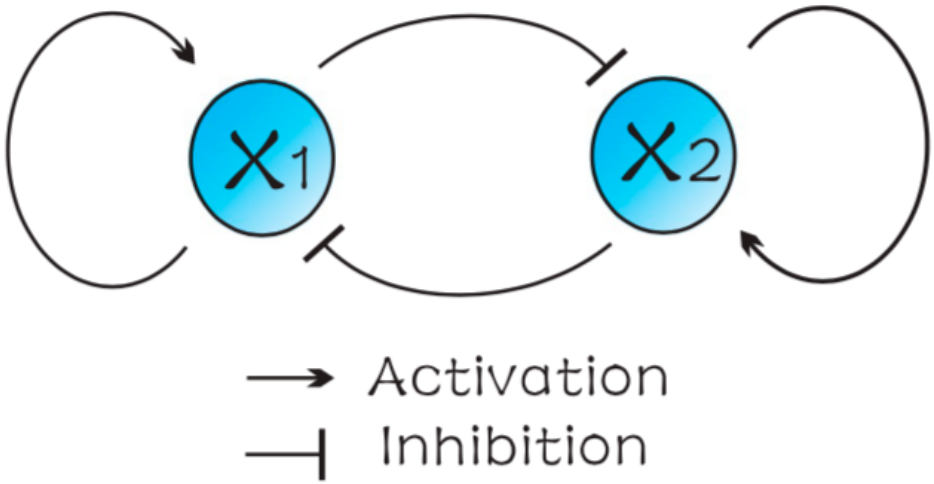
Niwa et al Cell 2005, 123:917

Gene Regulatory Network of Oct3/4 and Cdx2 Determines Trophectoderm vs. Inner Cell Mass (ICM) Lineage



Niwa et al Cell 2005, 123:917

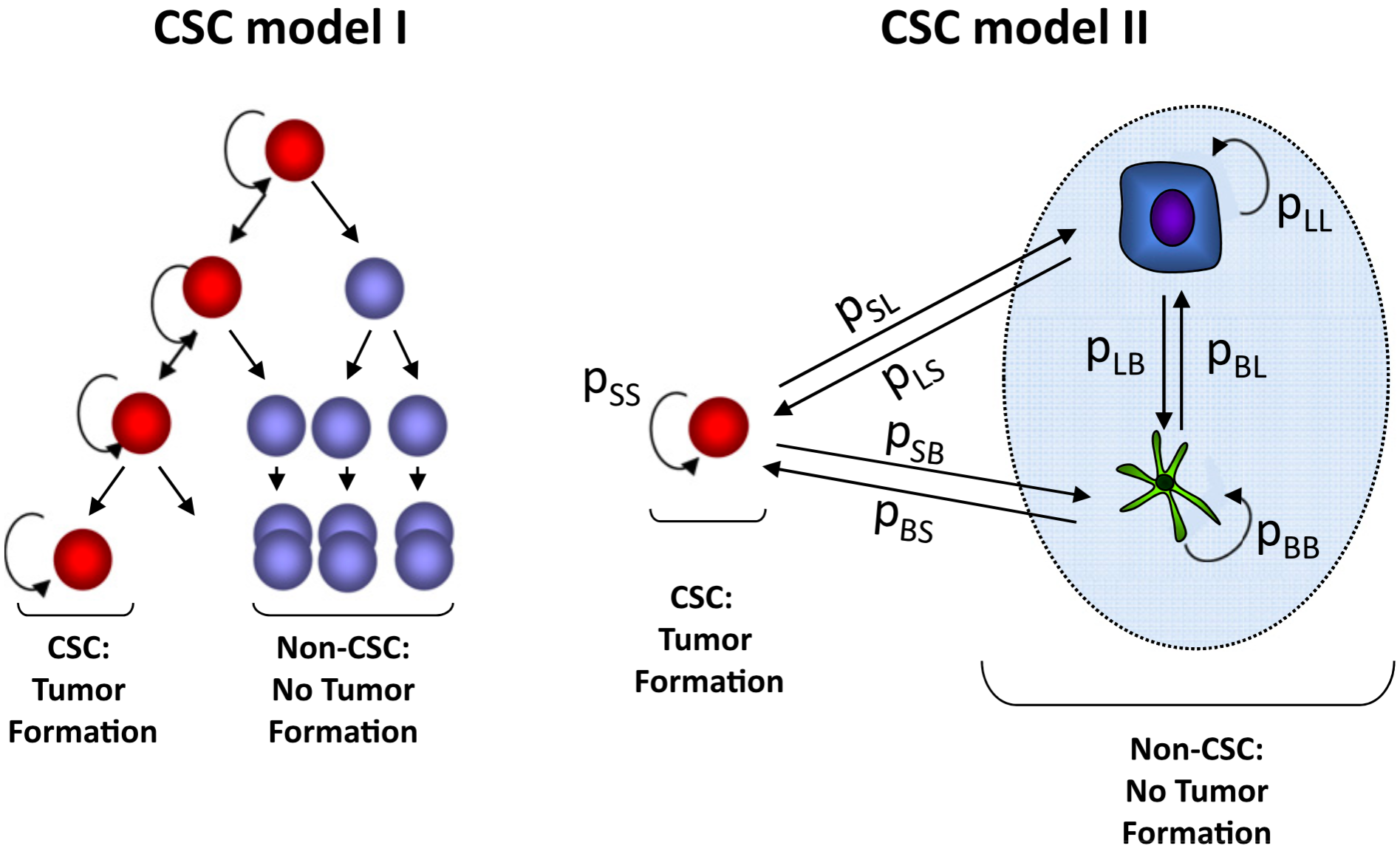
Toggle Switch
Gene Regulatory Network (GRN)



Gardner et al Nature 2000, 403:339

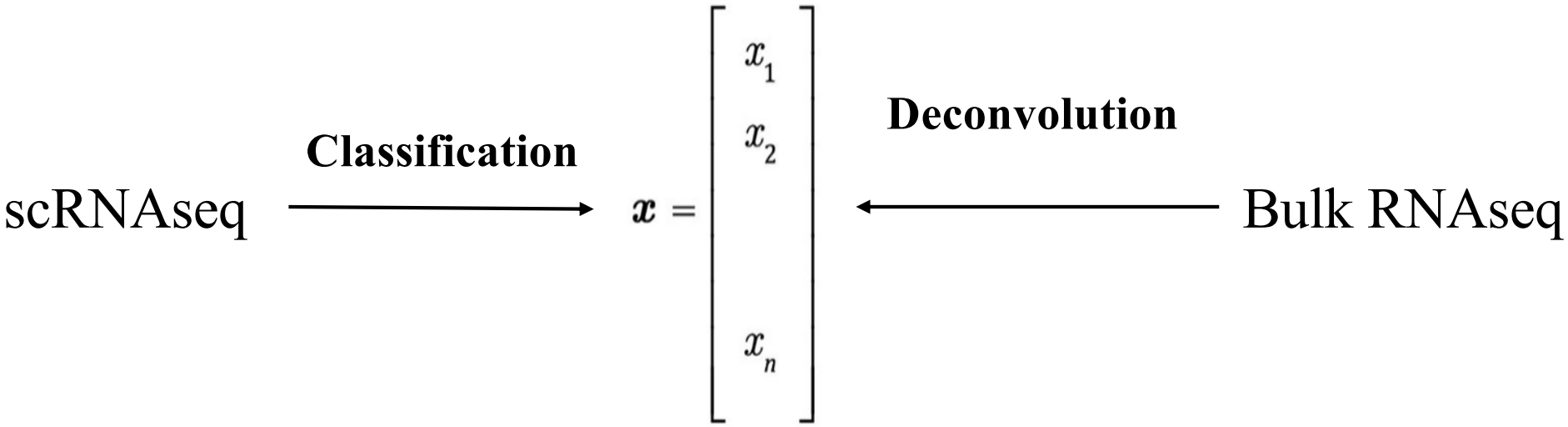
Wang et al PNAS 2011, 108:8257

Cancer Stem Cell Model



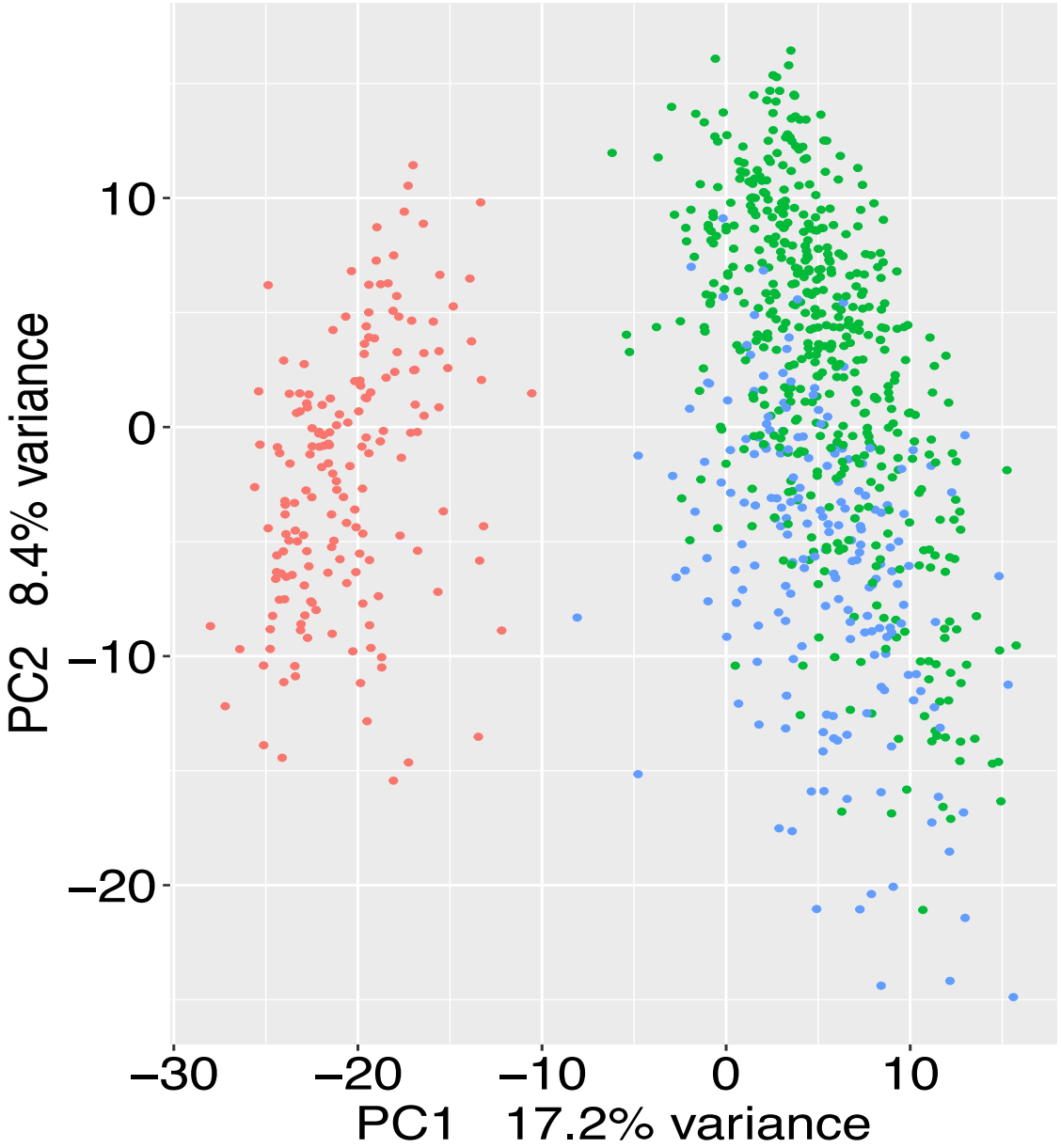
Gupta et al Cell 2011 Aug 19;146(4):633-44

Two Complementary Approaches to Study Tumor Heterogeneity



TCGA BRCA Pam50 subtypes

BRCA: breast cancer



Basal	173
LumA	500
LumB	193

Deconvolution of Bulk RNAseq Data

y: gene expression of a sample
n genes

$s_1 ... s_p$ are gene signature

$$\begin{bmatrix} y_1 & s_{11} & s_{12} & \cdots & s_{1p} \\ y_2 & s_{21} & s_{22} & \cdots & s_{2p} \\ . & & & & . \\ . & & & & . \\ y_n & s_{n1} & s_{n2} & \cdots & s_{np} \end{bmatrix}$$

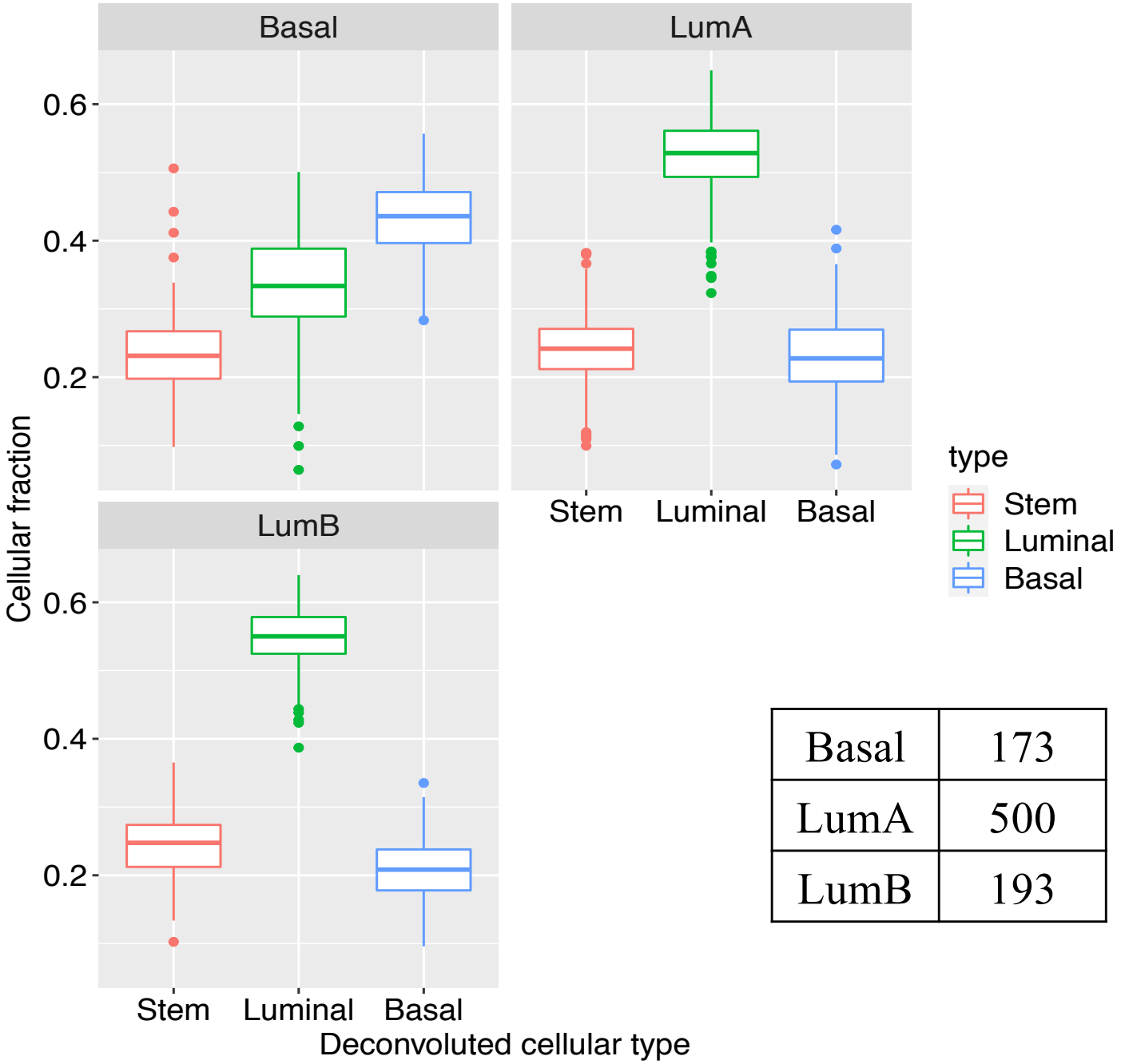
$$\min(|\mathbf{Sx} - \mathbf{y}|^2)$$

$$\Sigma x_i = 1$$

$$x_i >= 0 \ \& \ < 1$$

Deconvolution with mixture model
using R package DeconRNASeq

Deconvolution of TCGA BRCA Tumors



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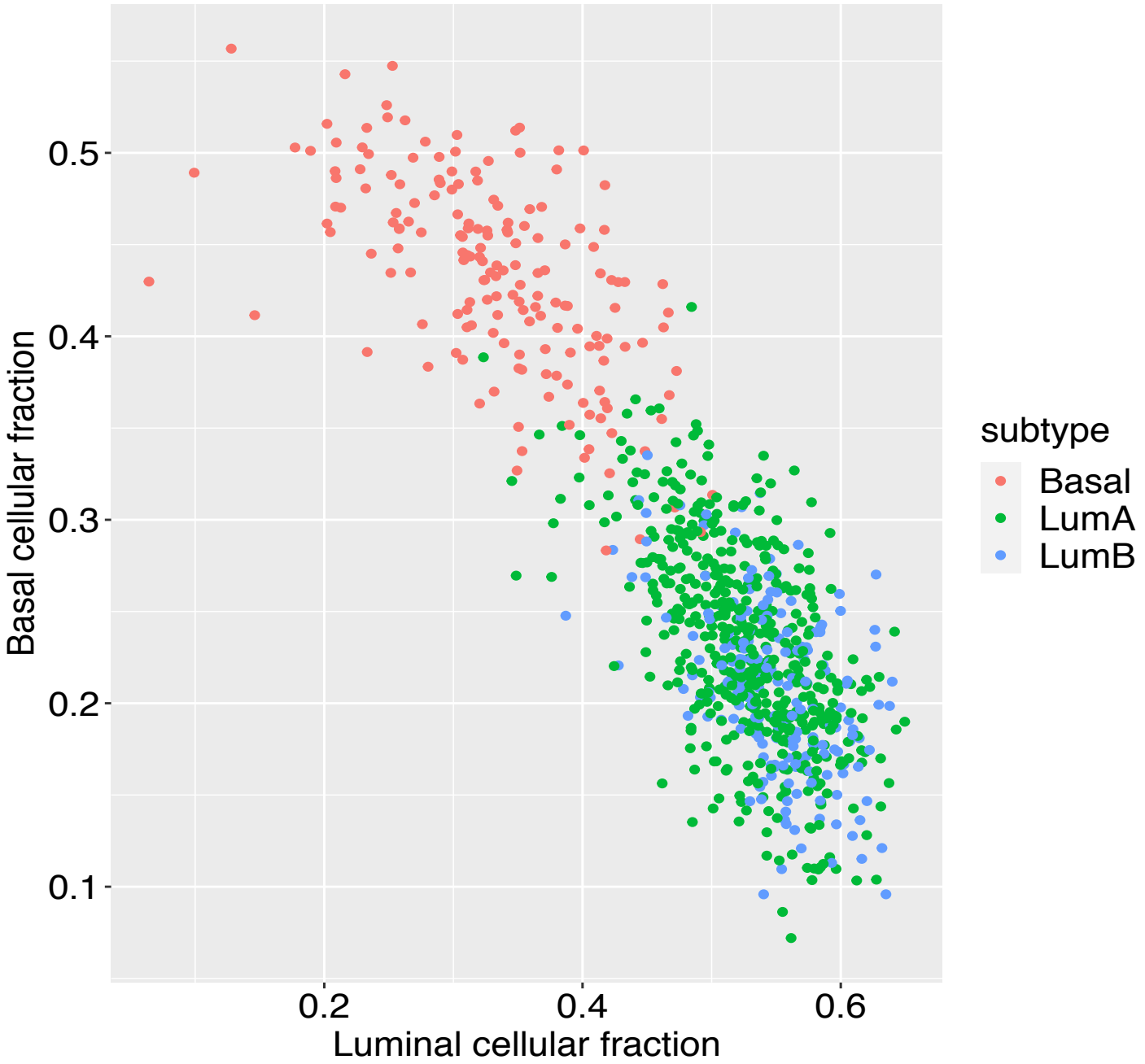
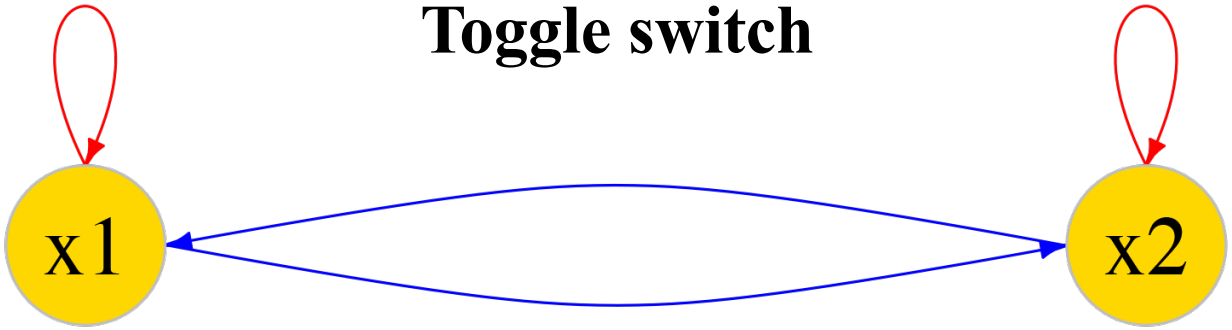
Deconvolution of TCGA BRAC Tumors



Differential Equation Model of Gene Regulatory Network (GRN)

Toggle switch



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

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

b_1 and b_2 are weights for mutual inhibition

a_1 and a_2 are weights for auto-activation

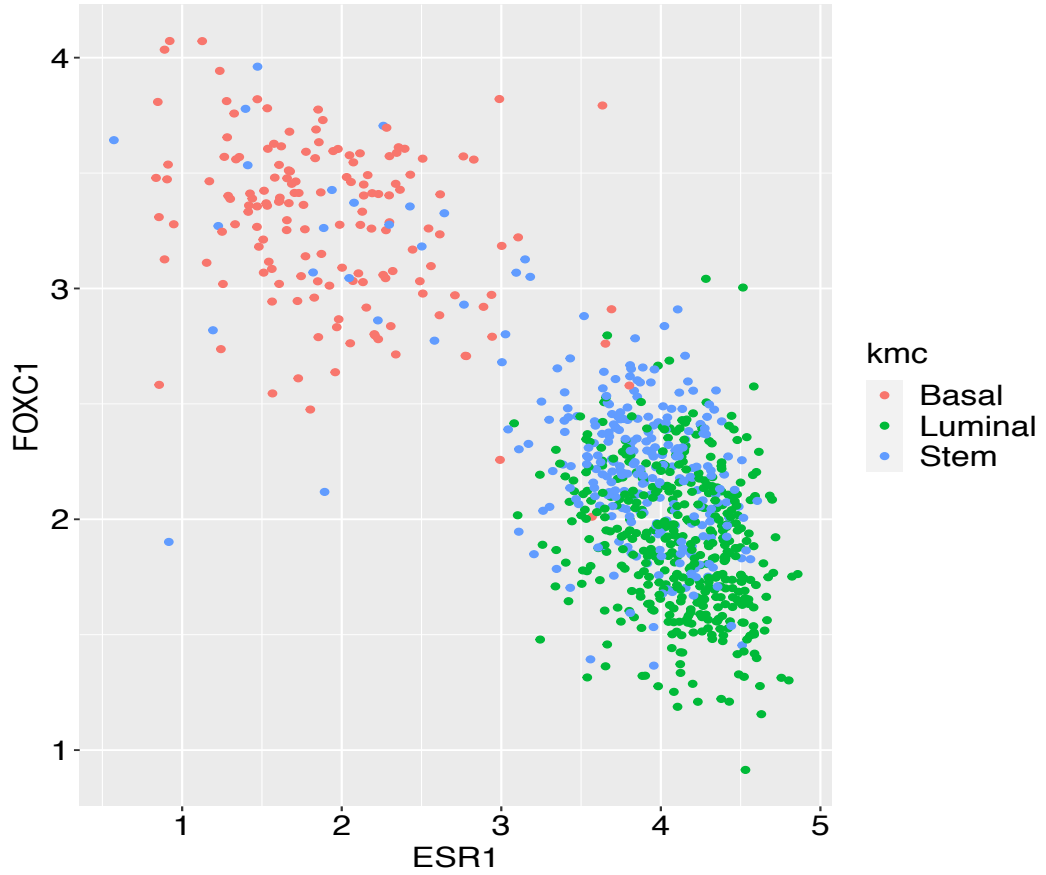
k_1 and k_2 are weights for degradation

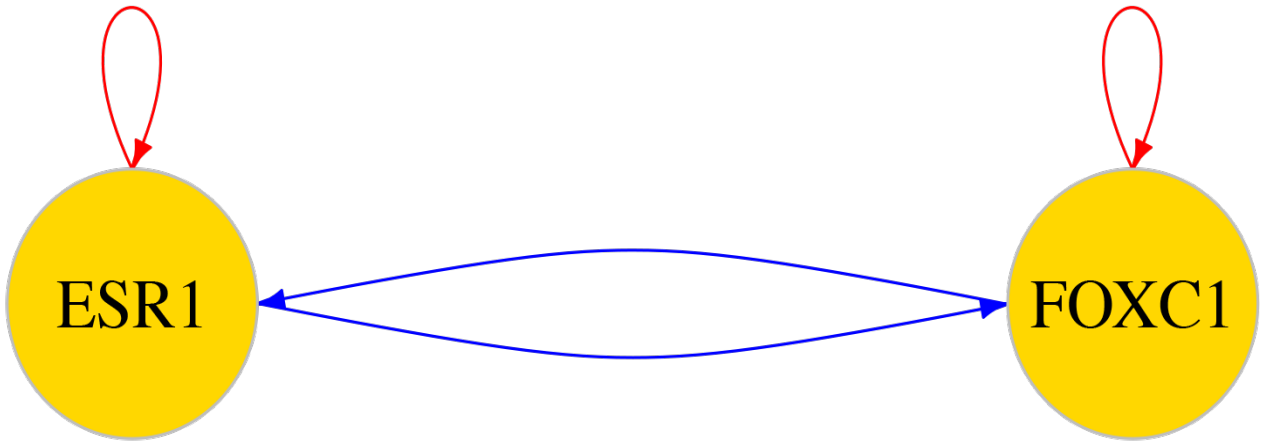
n is Hill Coefficient

S is threshold of Hill function

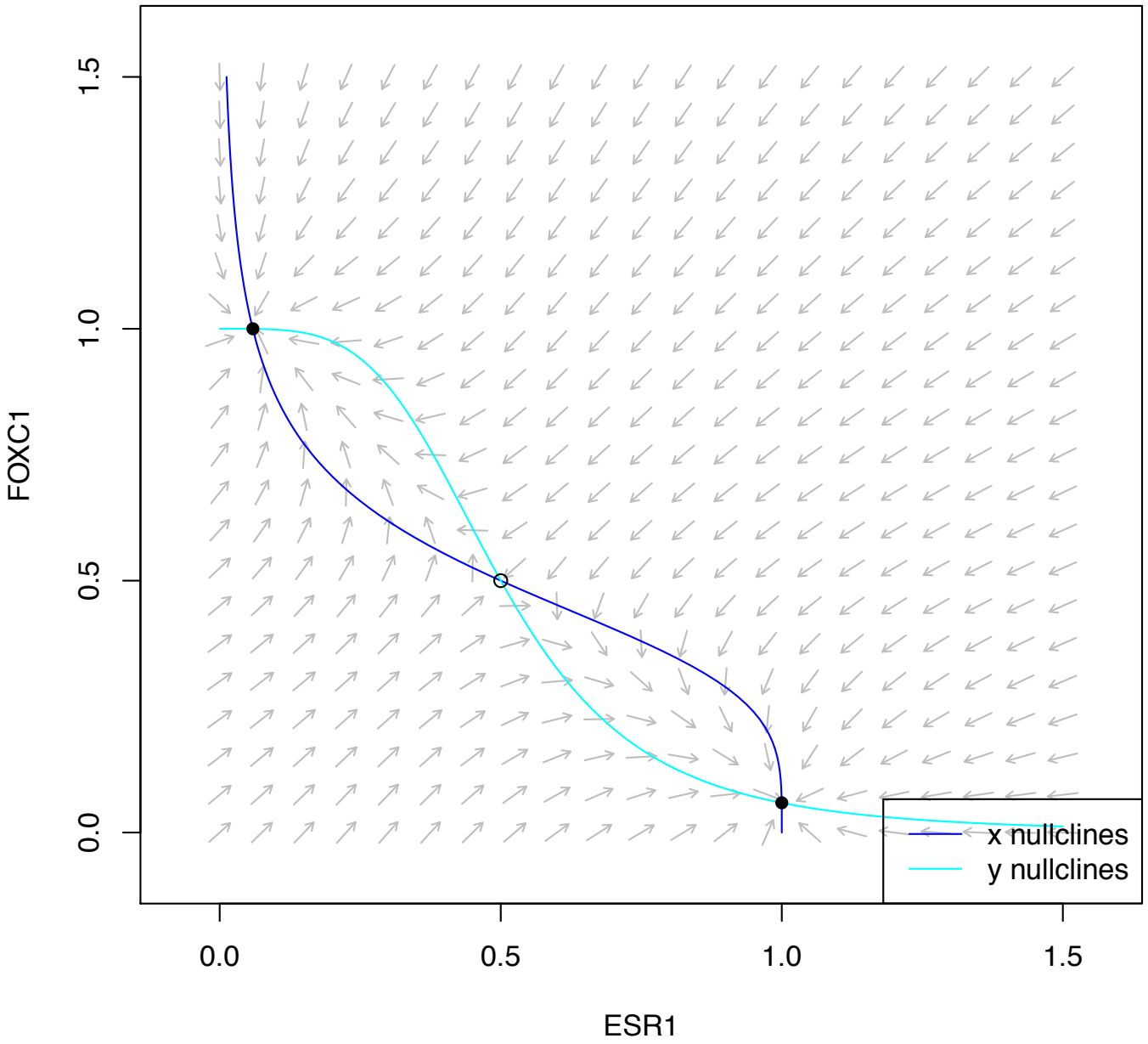
Wang et al PNAS, 2011;108:8257–8262

GRN of Luminal and Basal States



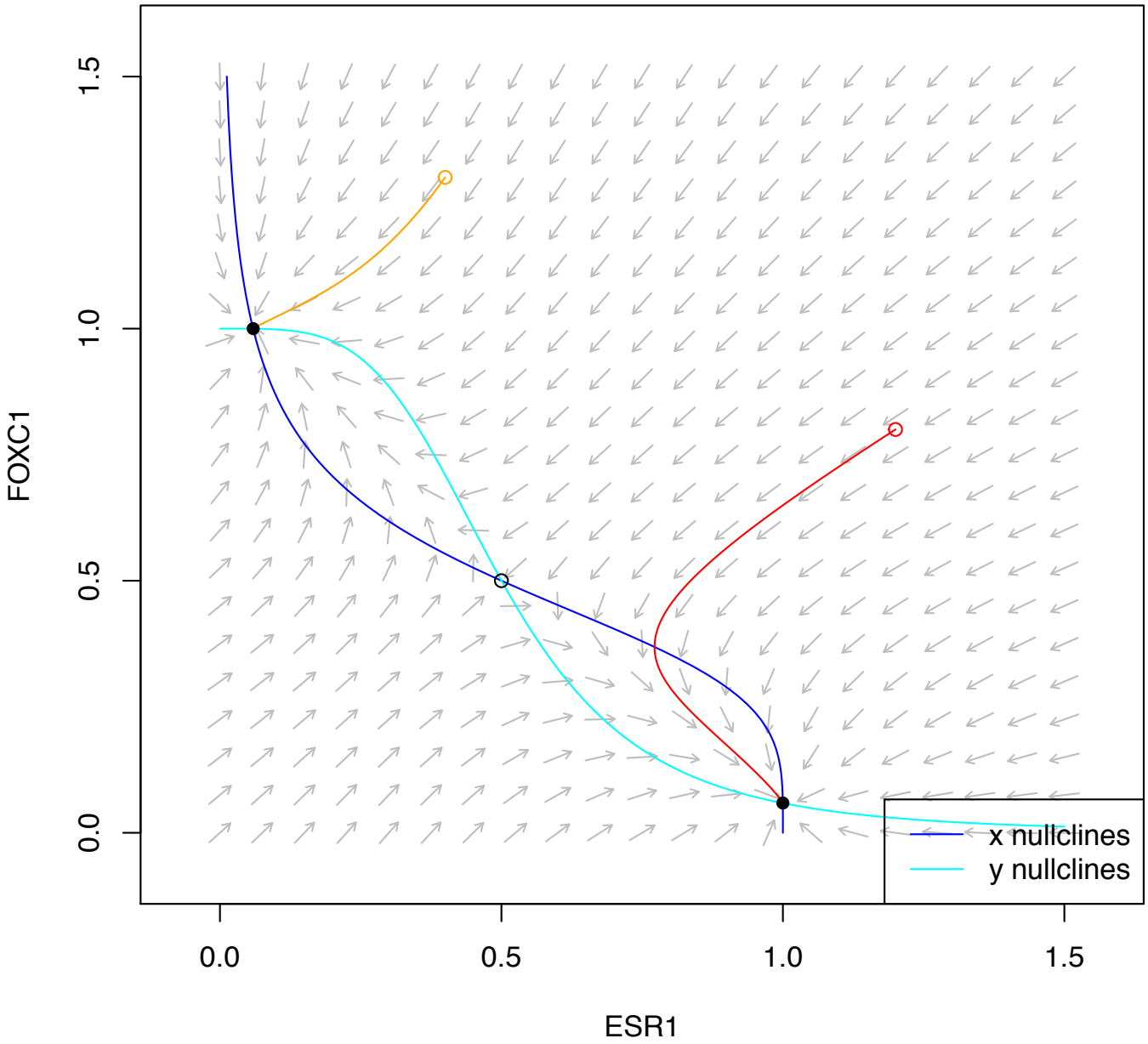


Flow Diagram of Toggle Switch GRN



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

Flow Diagram of Toggle Switch GRN



$a1=a2$	0
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n	4
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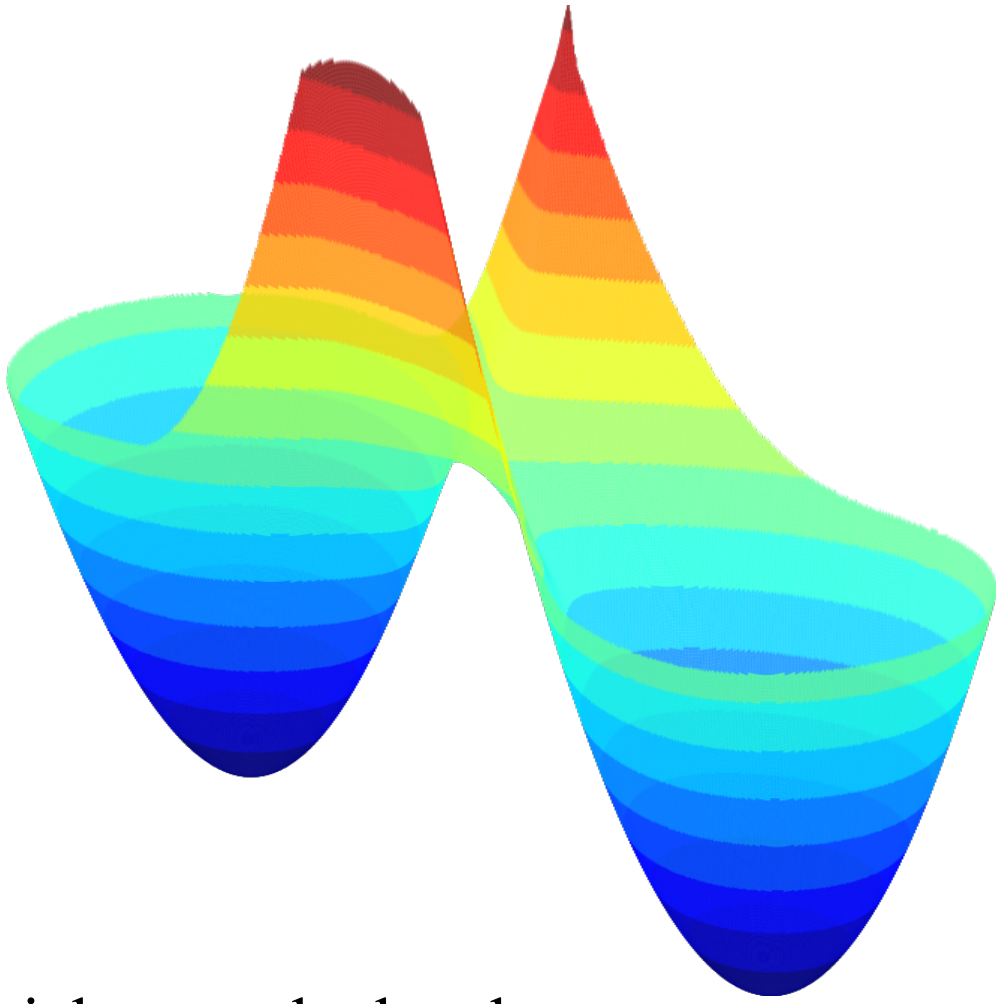
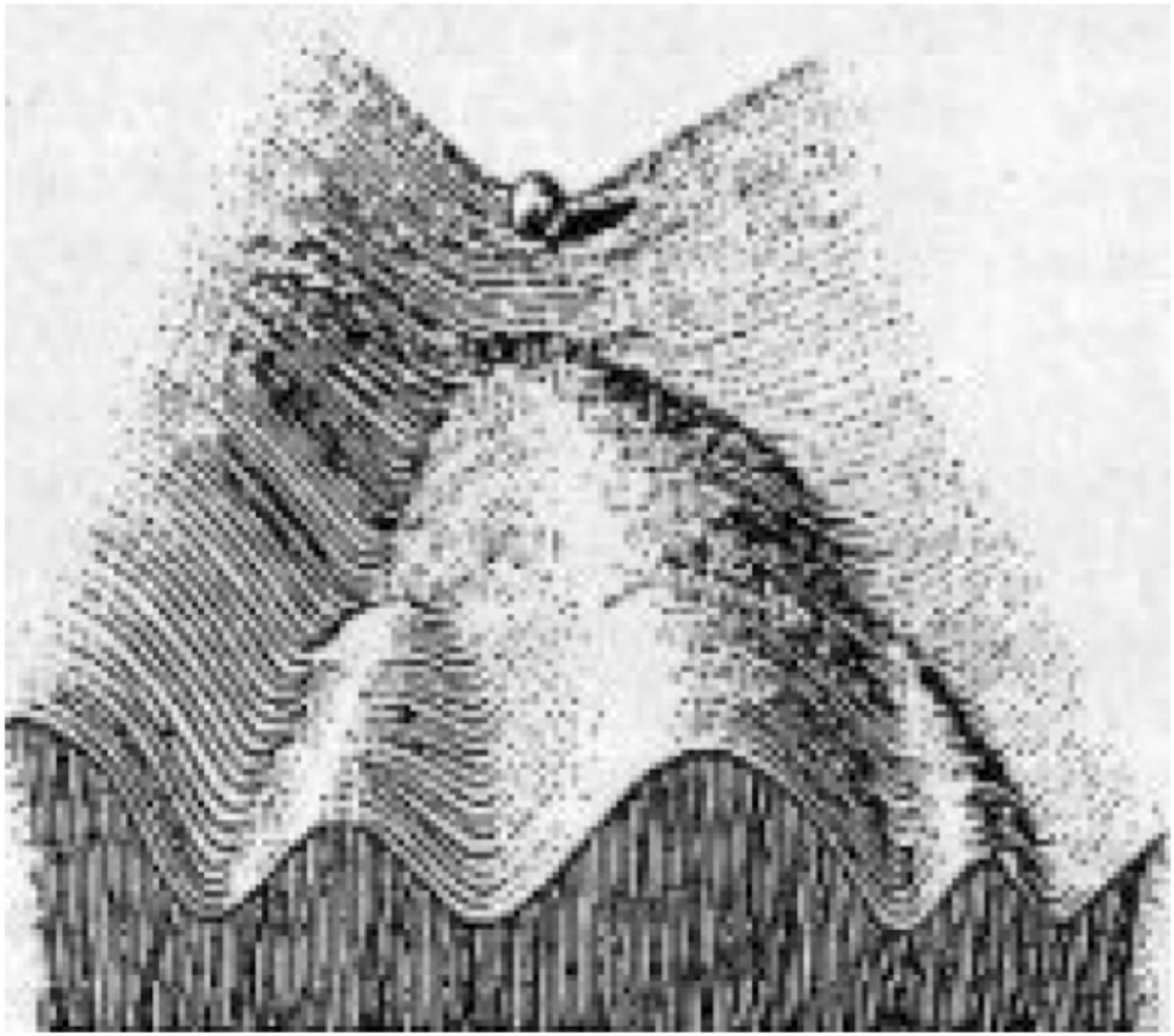
Quasi-Potential of GRN

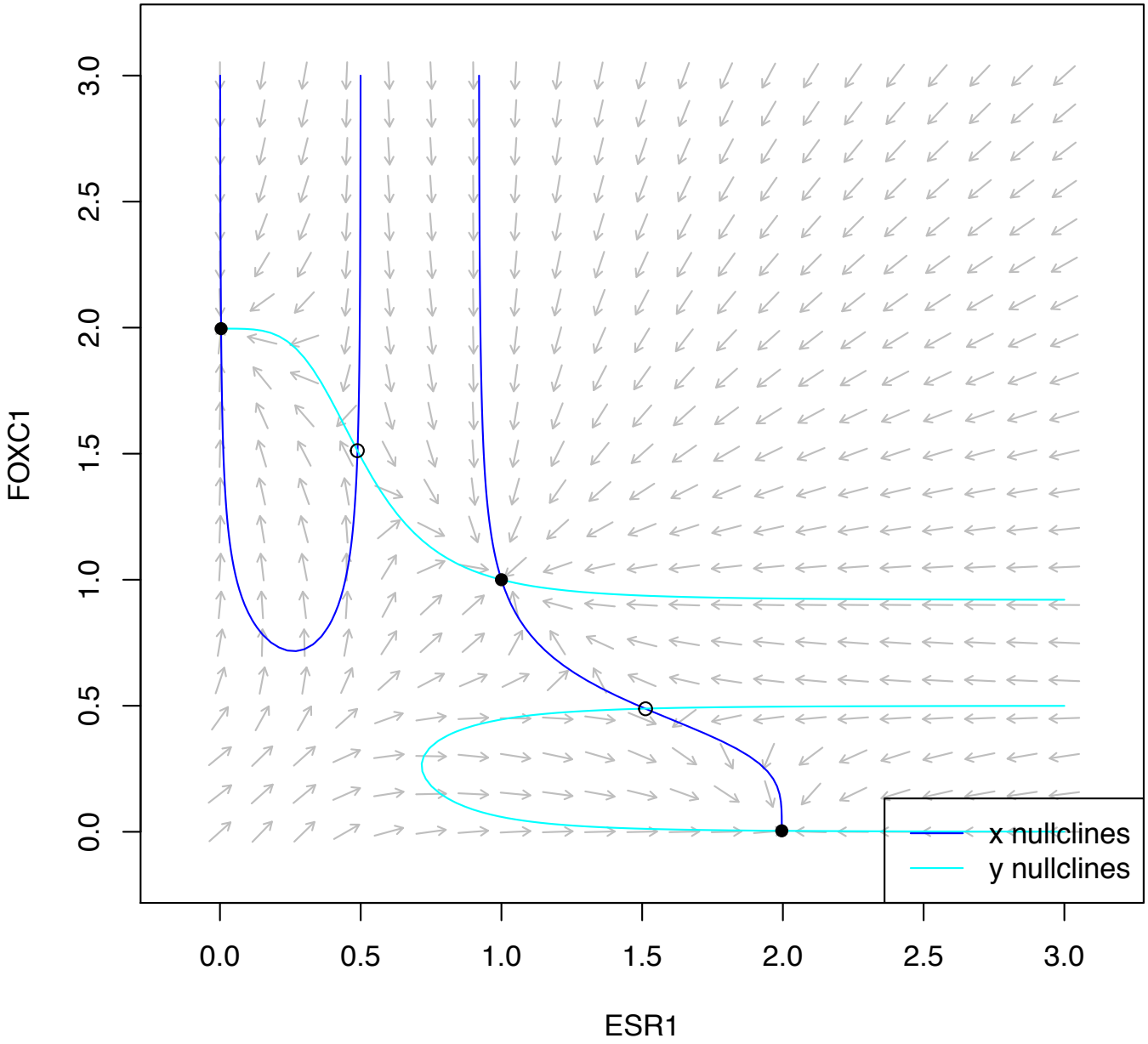


Quasi-potential was calculated
with R package QPot

Waddington's Epigenetic Landscape

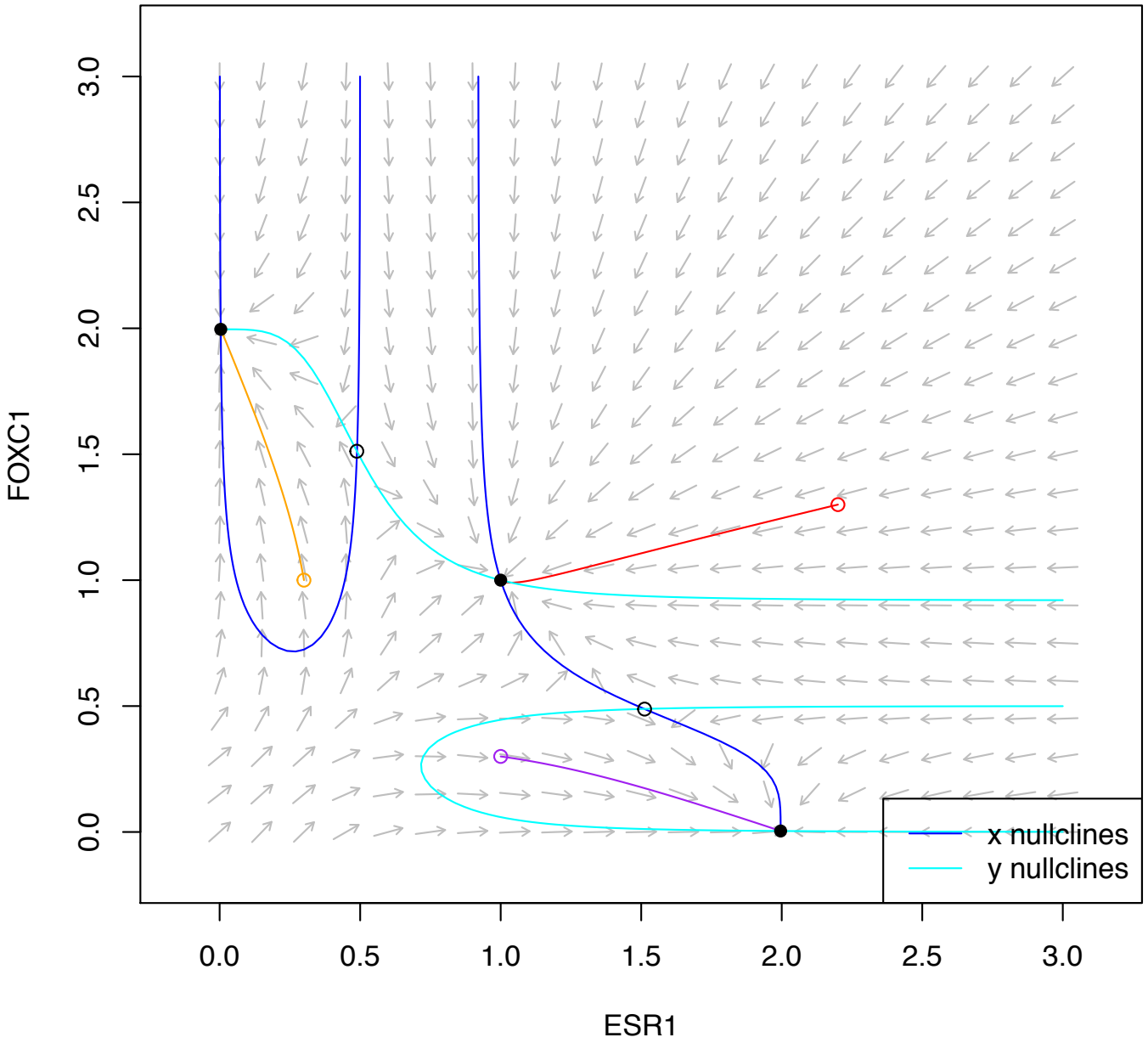


Toggle Switch GRN with Auto-Activation



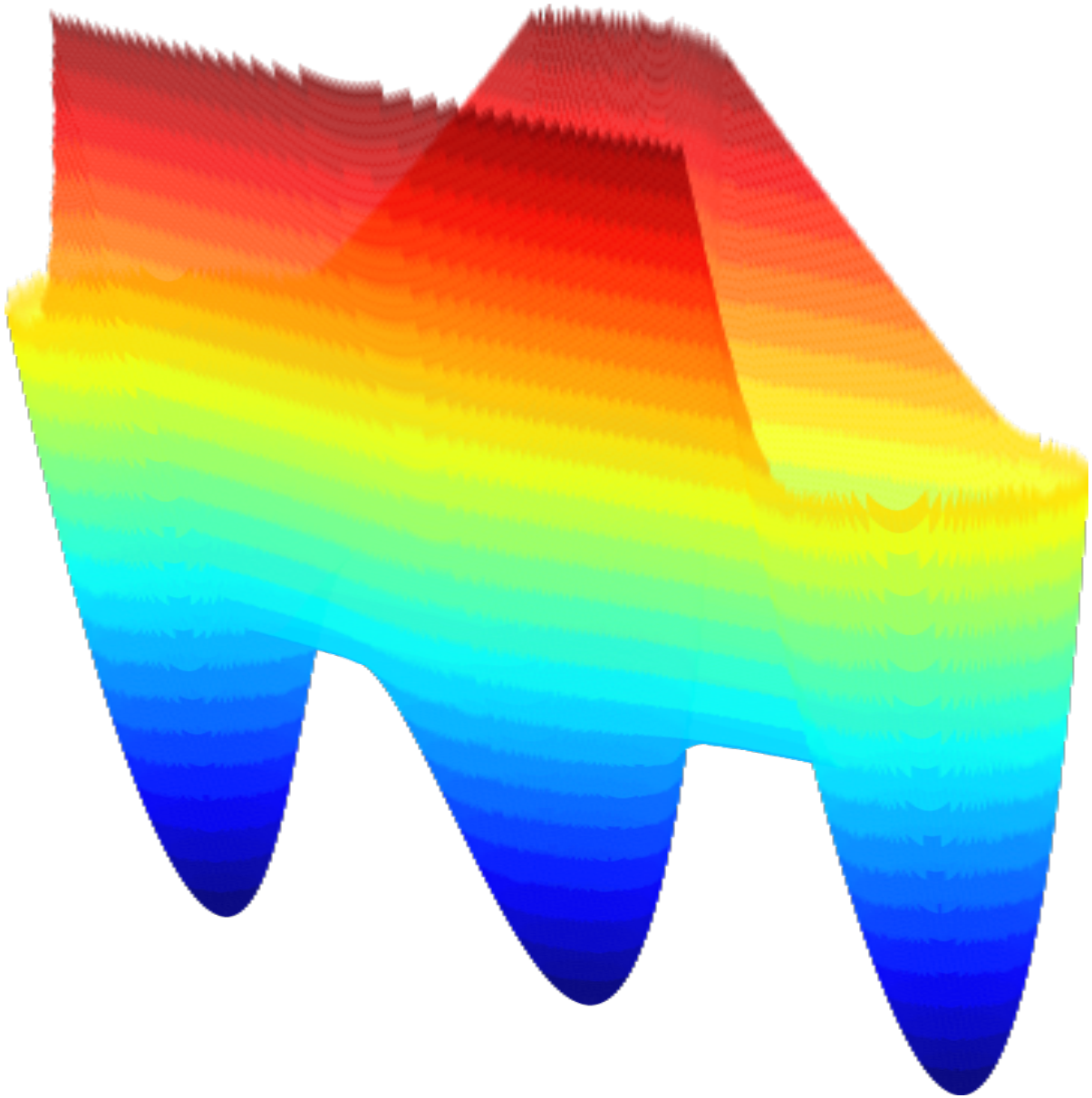
a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Toggle Switch GRN with Auto-Activation

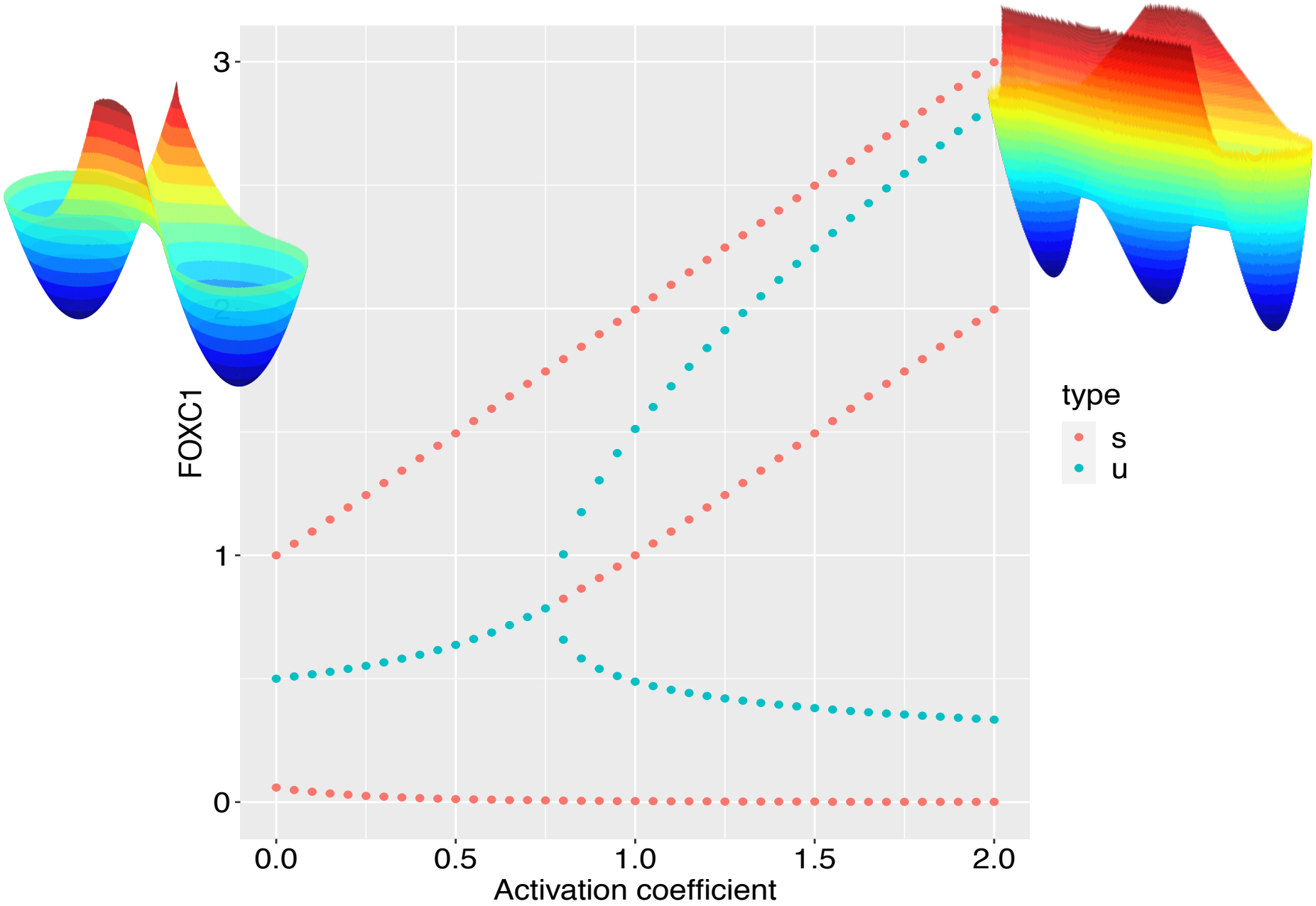


a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Quasi-Potential of GRN



Bifurcation diagram



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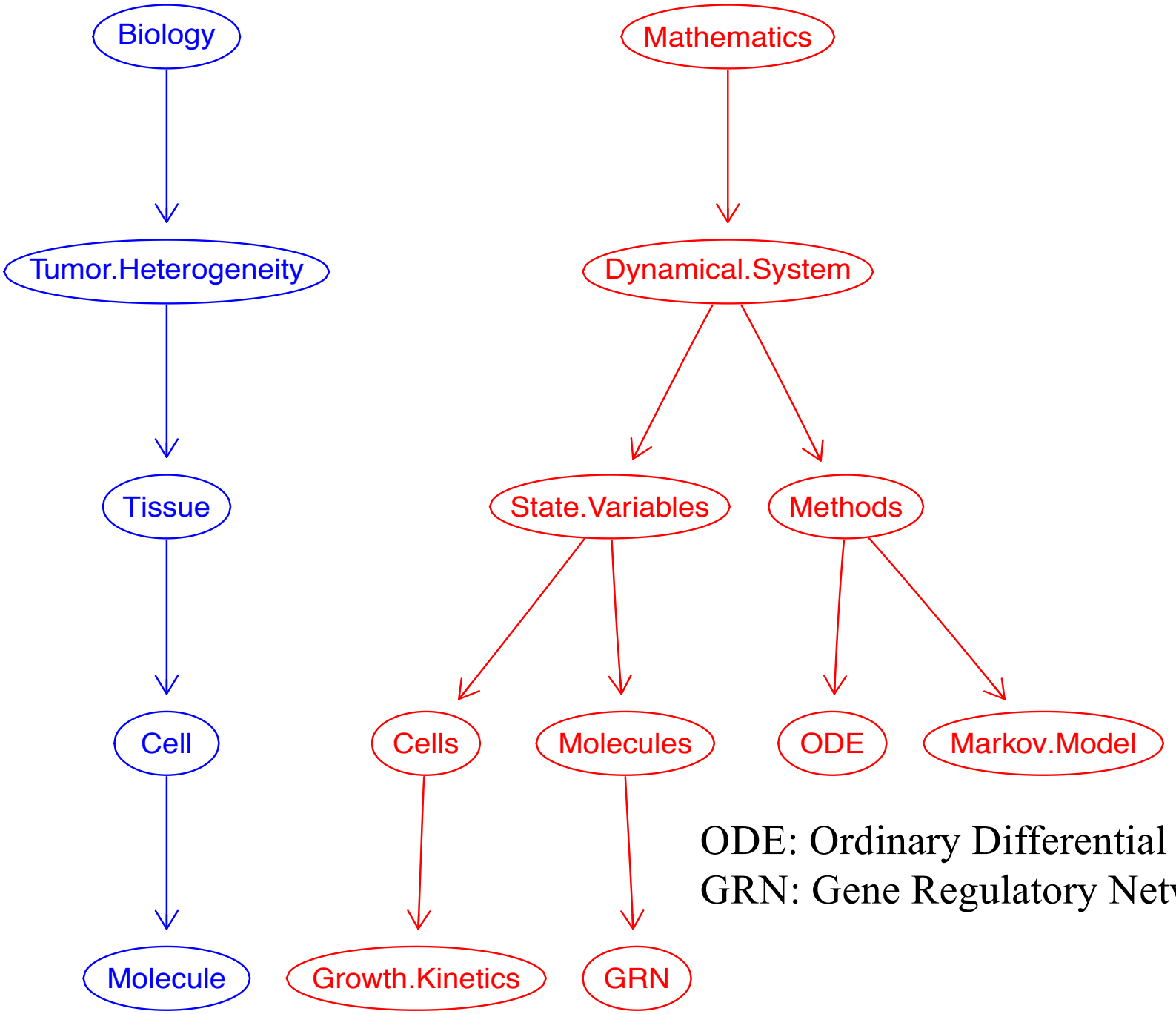

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