SSSC
Brown Bag Lunch Seminar

Schedule:

ccrod.cancer.gov/confluence/display/CCRSSSCArchive/Home

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

Cancer Stem Cell Model and Evolutionary Dynamics

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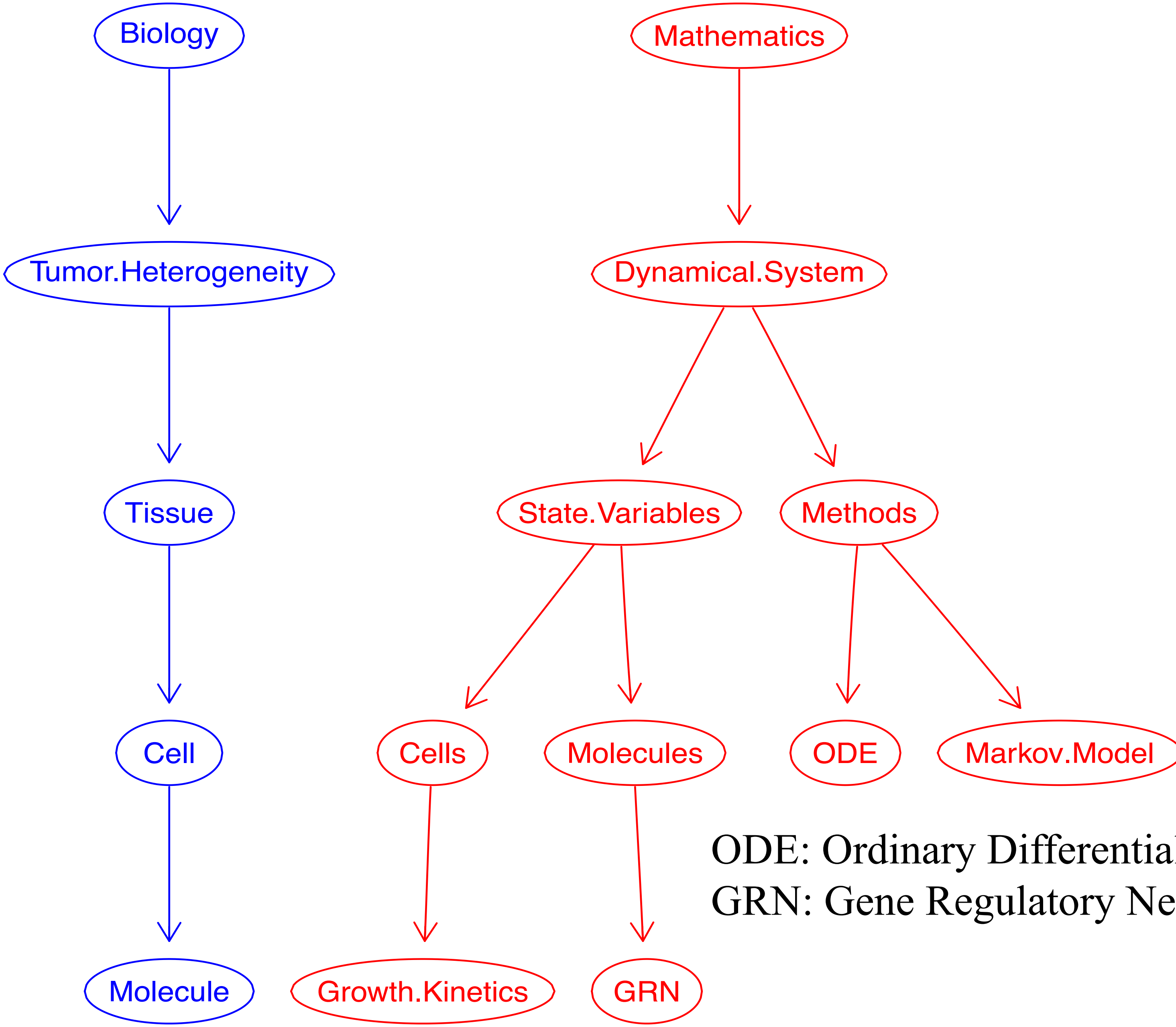
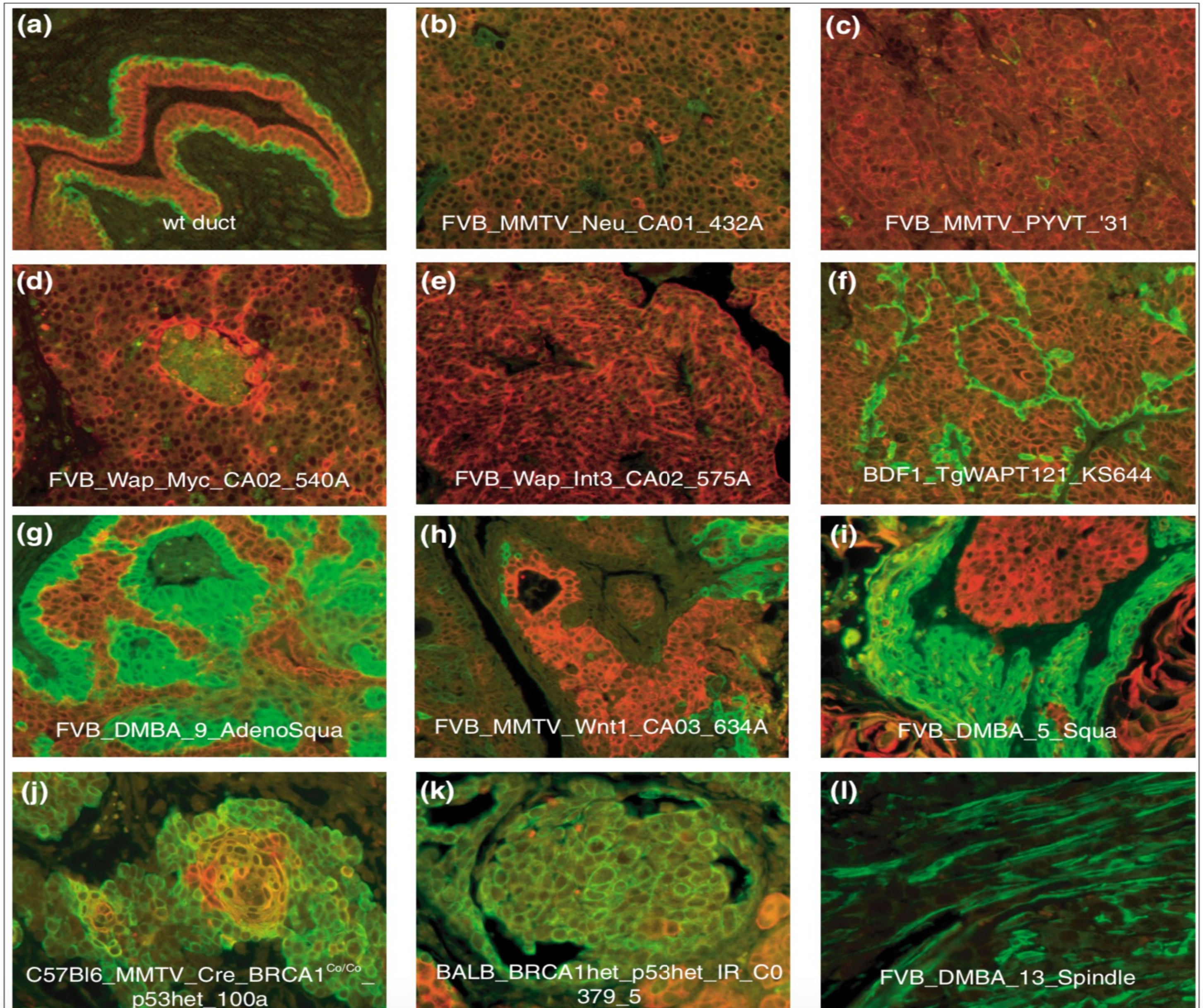
April 12, 2021

Understanding Biology with Mathematical Modeling



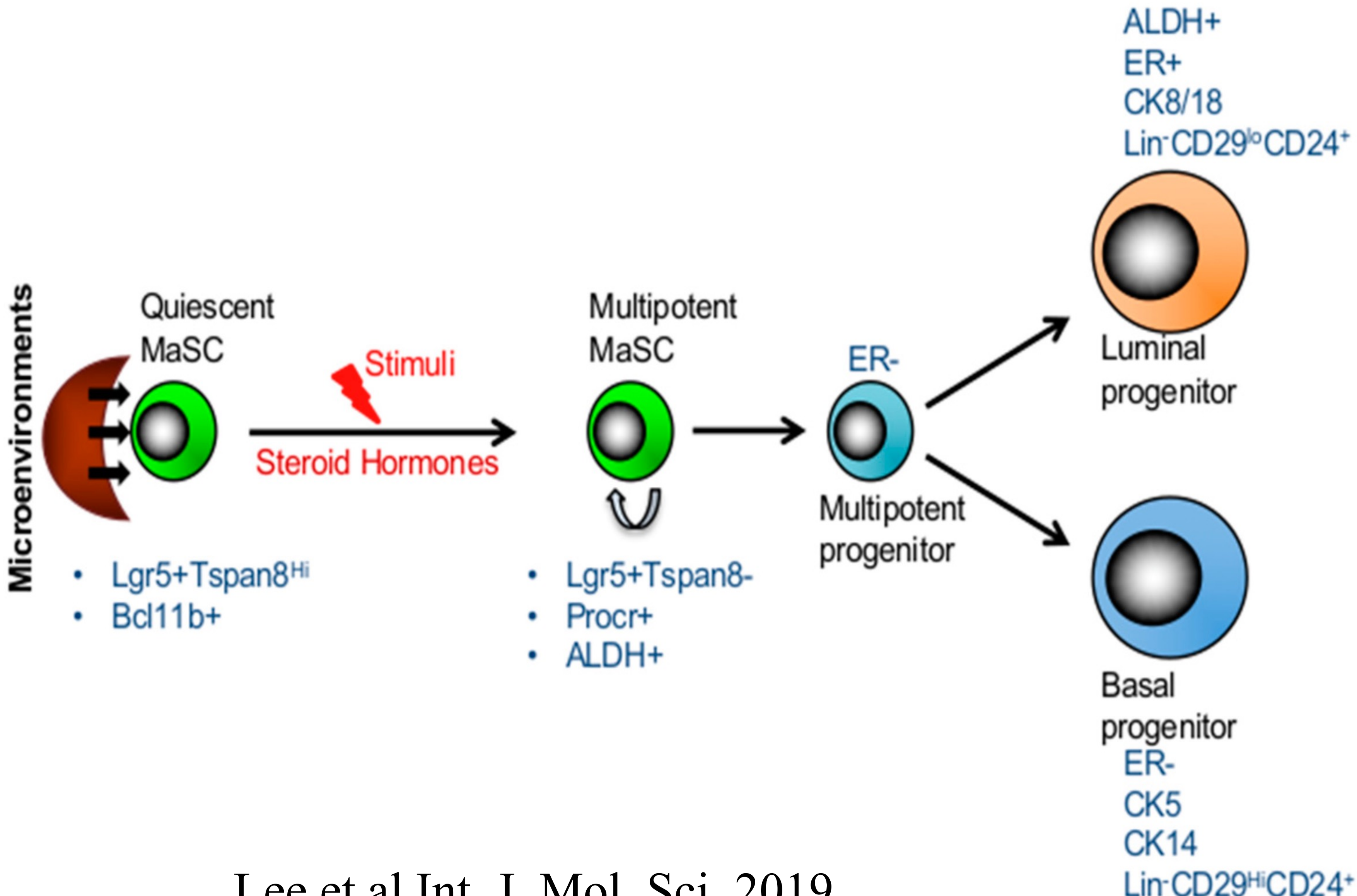
ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

Heterogeneity of Mouse Mammary Tumors



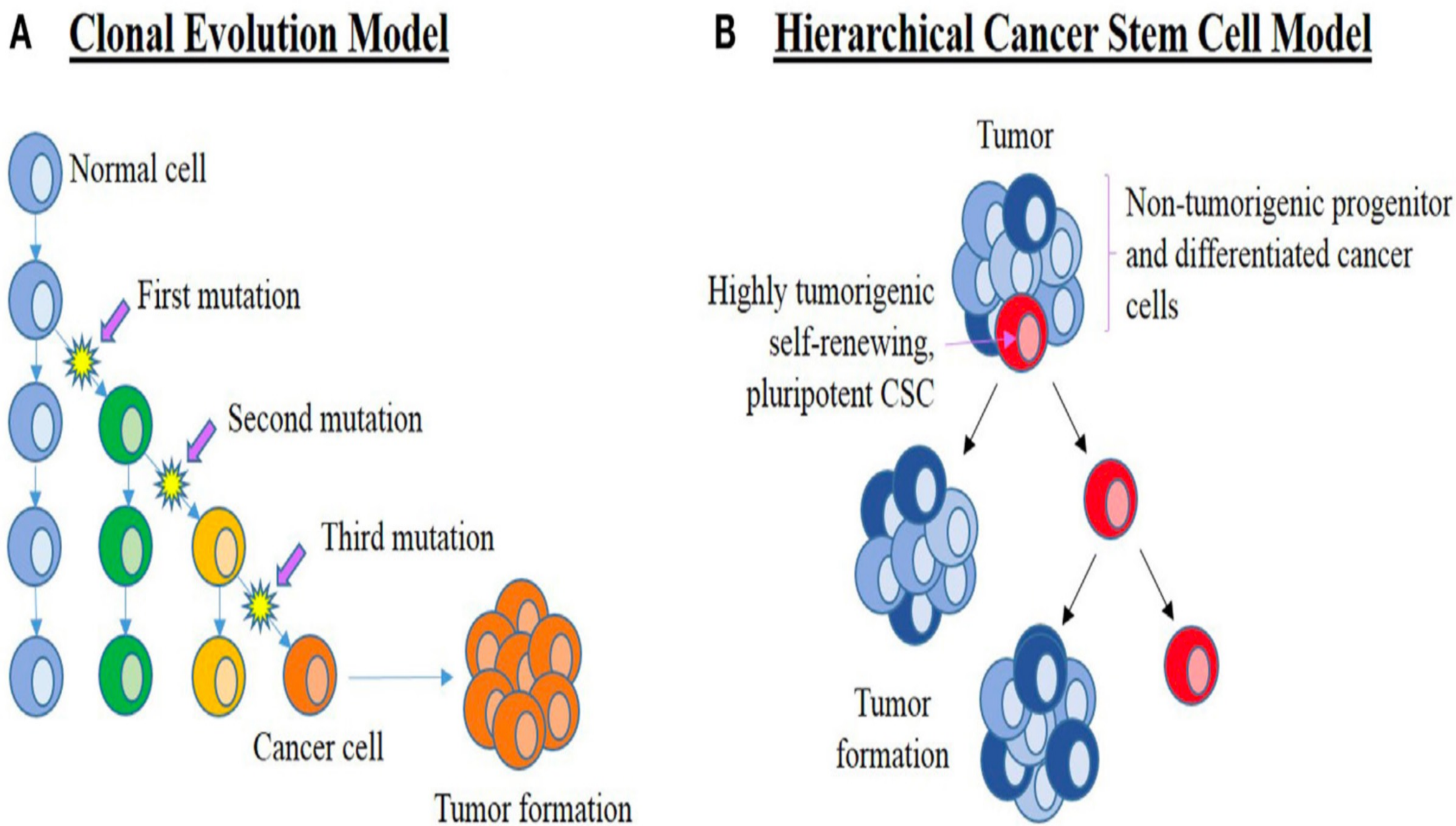
Keratins 8/18 Keratin 5 Herschkowitz, …, Perou Genome Biology 2007

Mammary Stem Cell Model



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

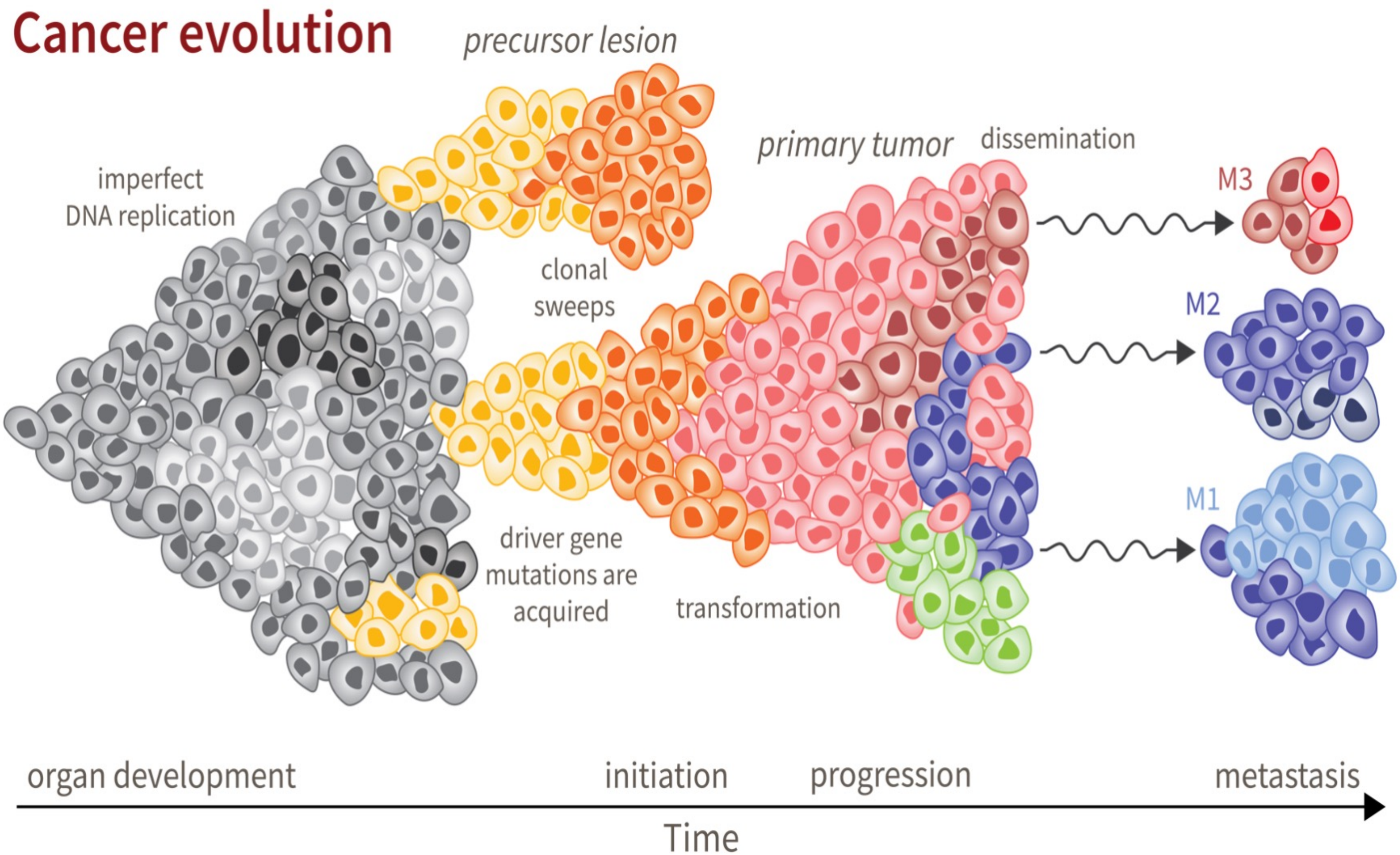
Carcinogenesis Models



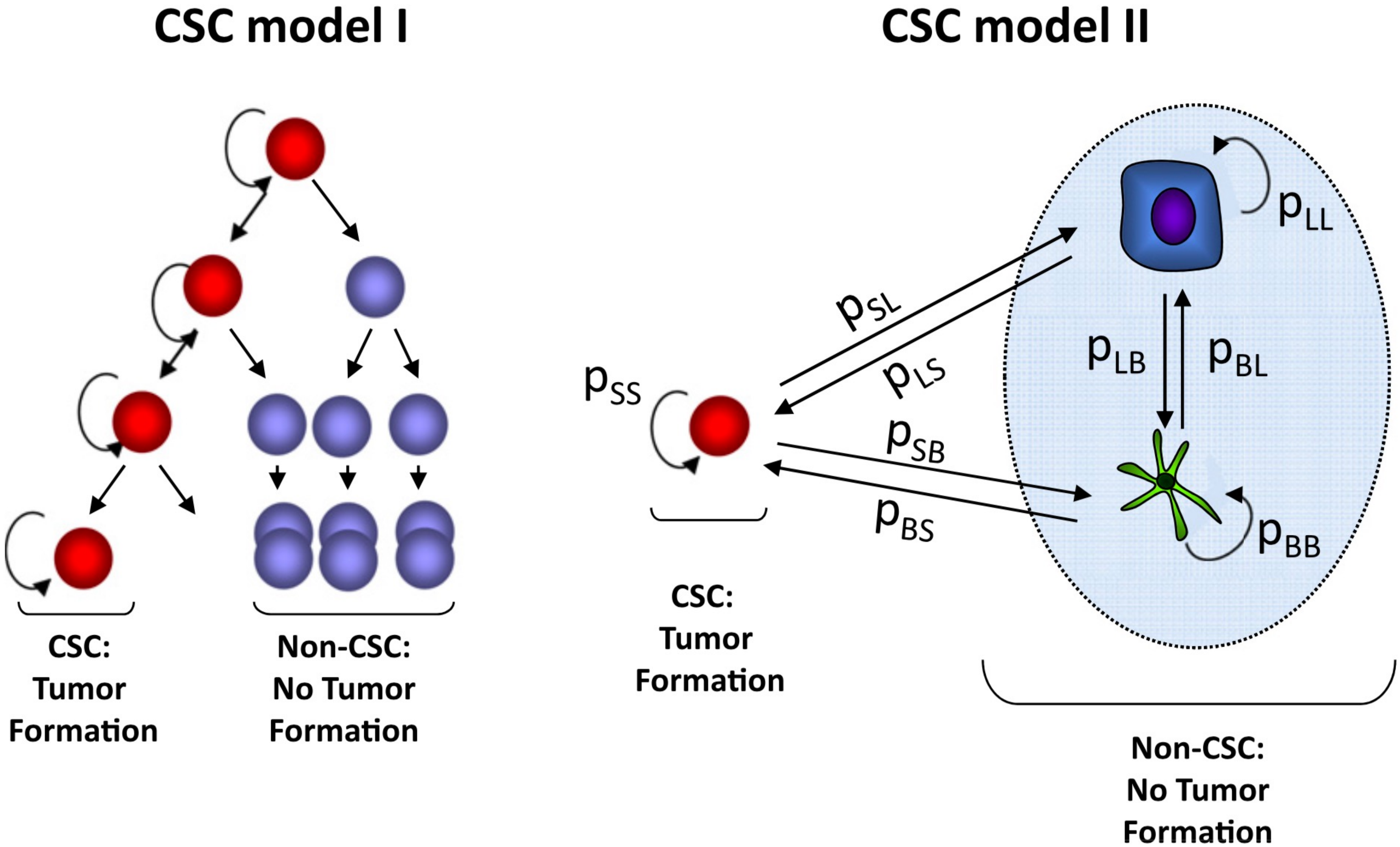
Genetic

Non-genetic

Cancer Evolution Model

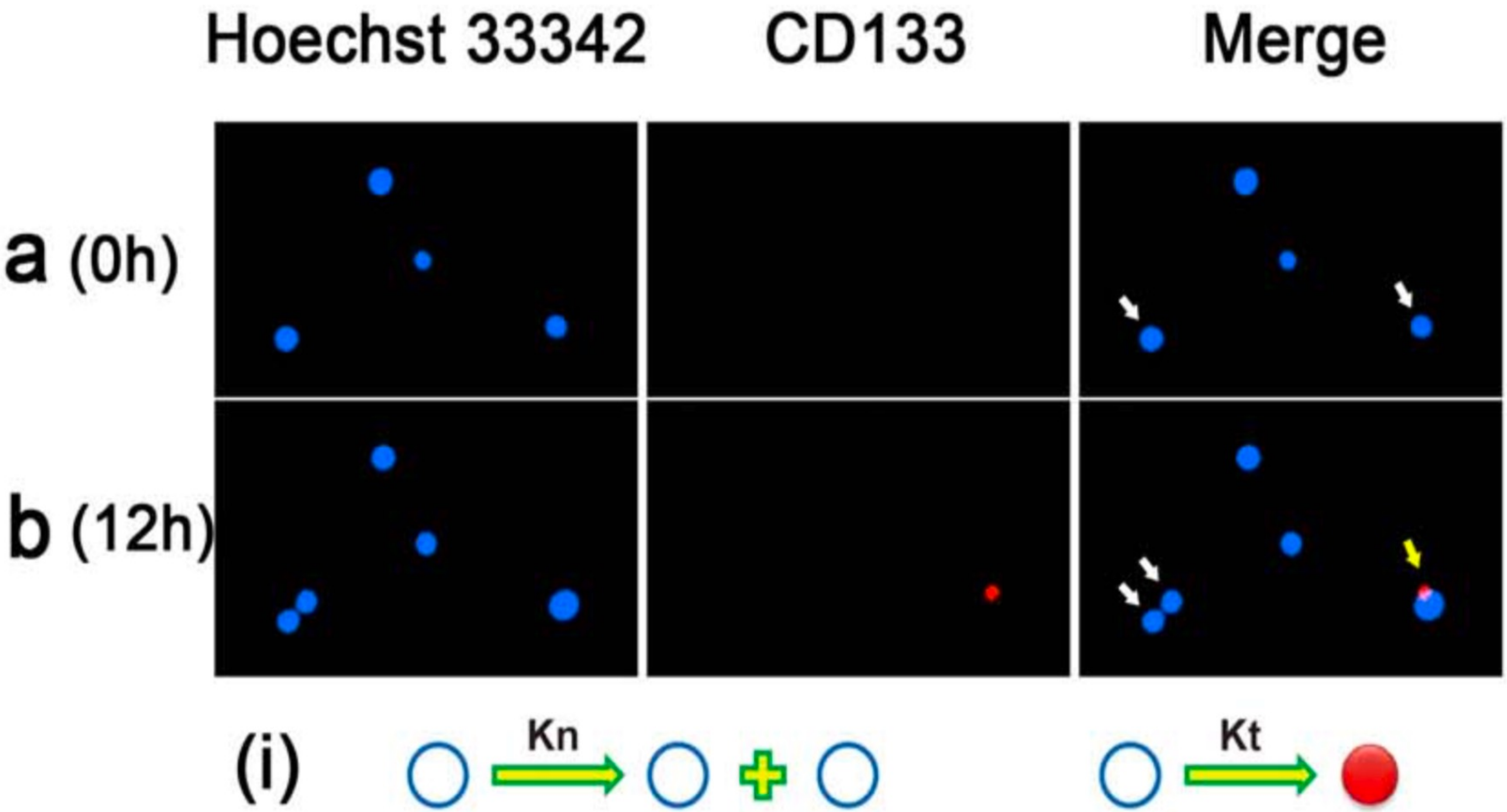


Cancer Stem Cell Model



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

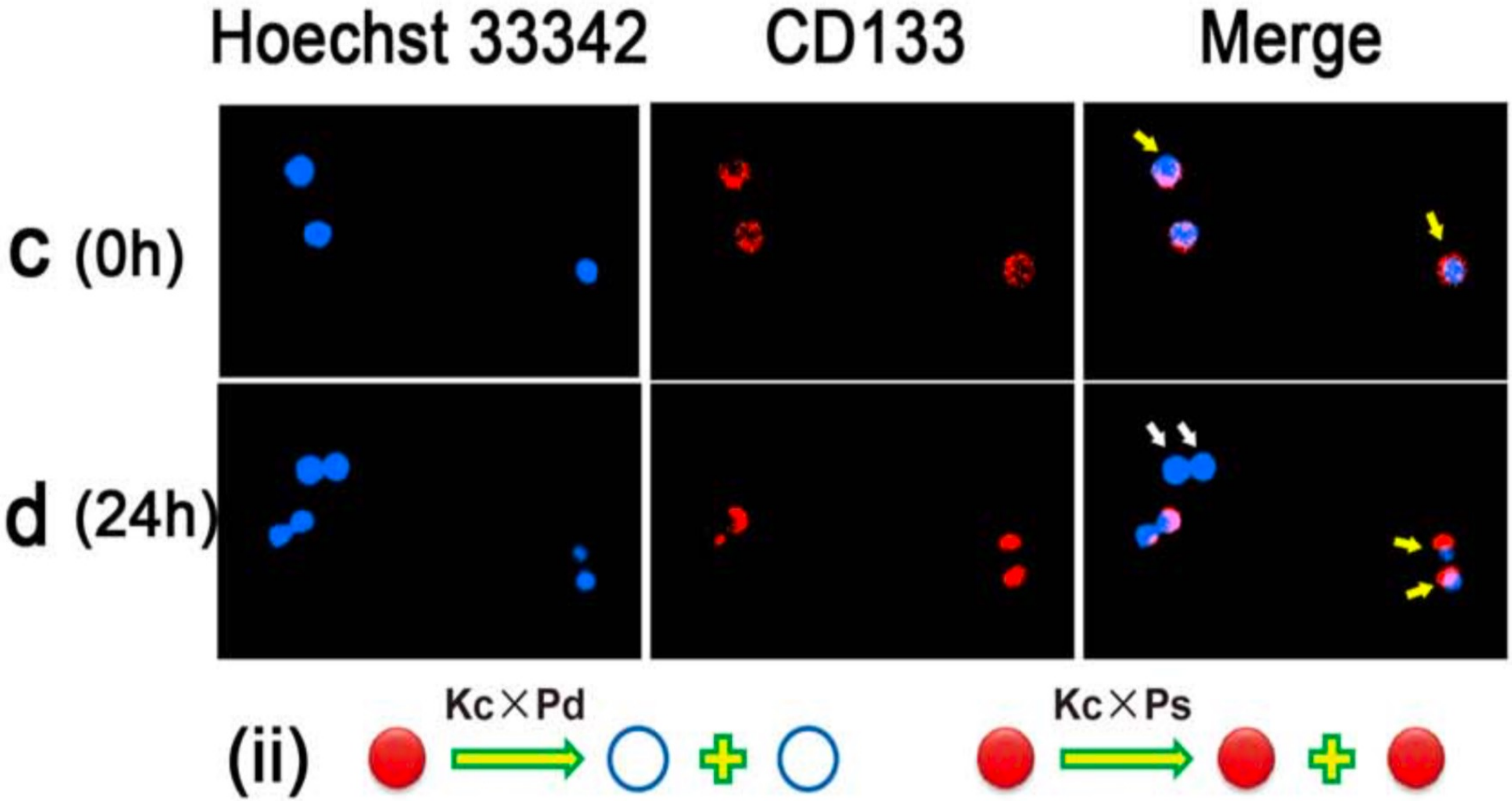
Cancer Stem Cell Dynamics



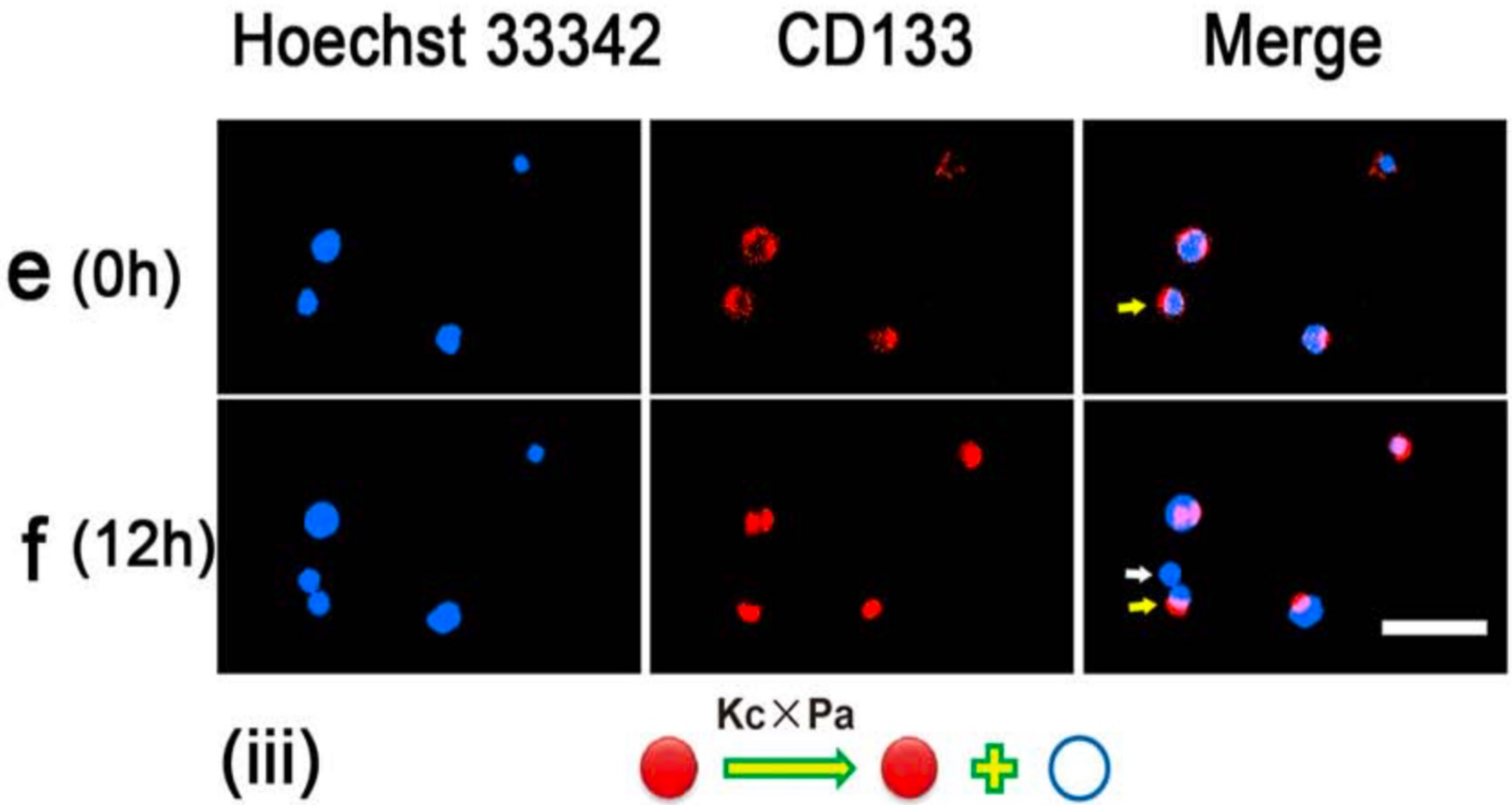
SW620 human colon cells

Wang et al. PLoS One 2014 Jan 9;9(1):e84654

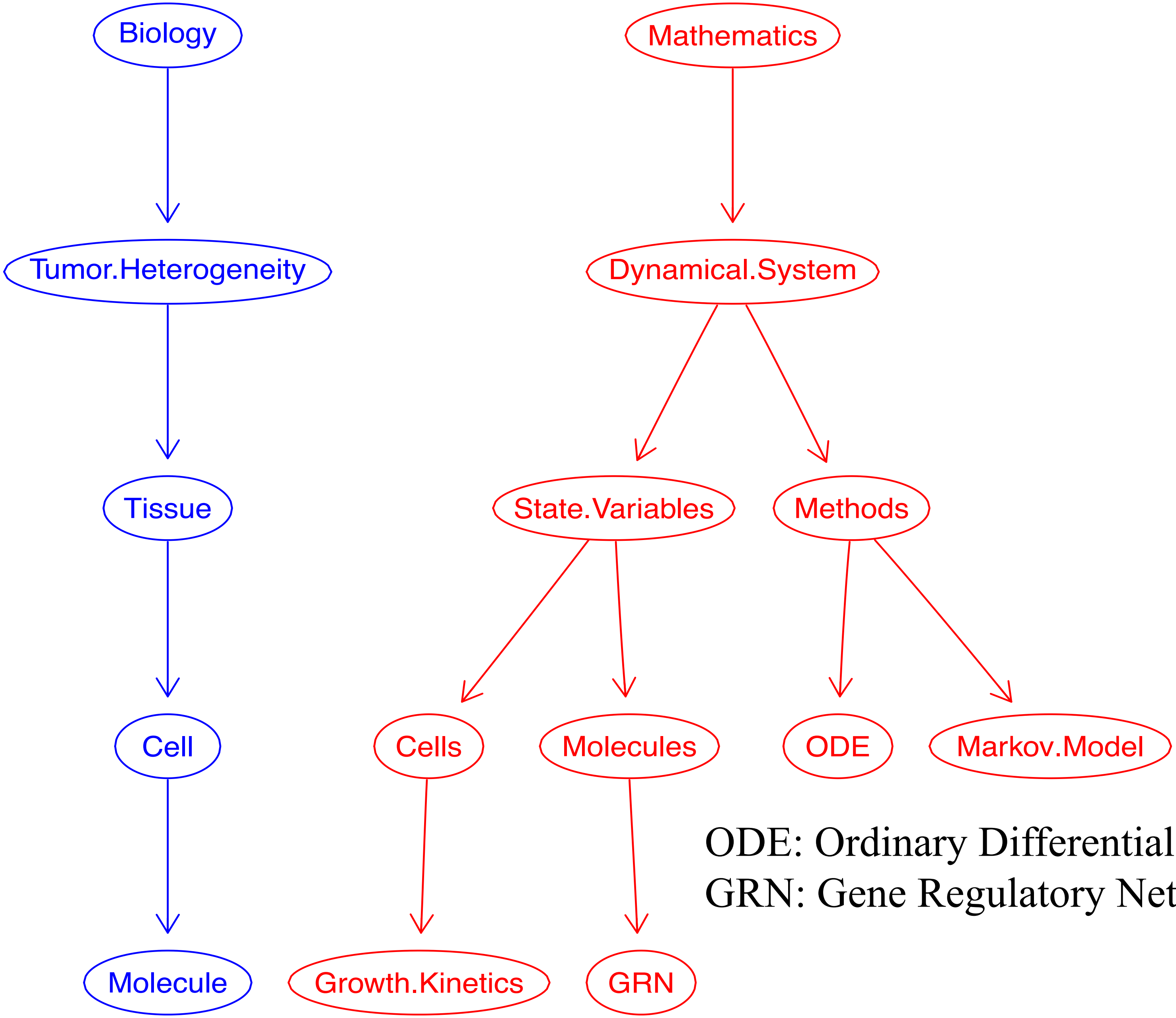
Cancer Stem Cell Dynamics



Cancer Stem Cell Dynamics



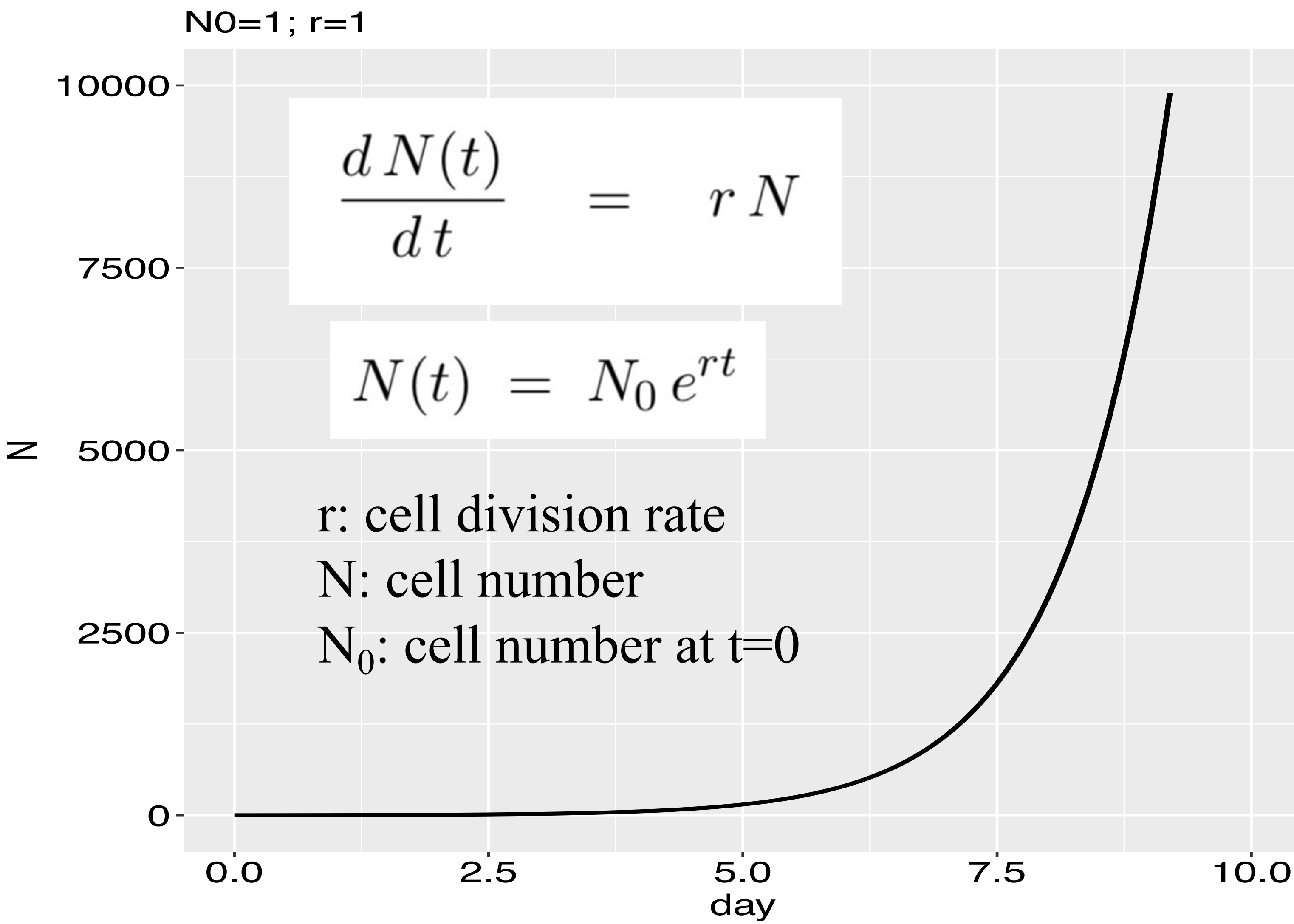
Understanding Biology with Mathematical Modeling



ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

Evolutionary Dynamics

Ordinary Differential Equation (ODE) for **exponential growth**



$$\frac{d\,N(t)}{d\,t} = r\,N$$

$$N(t) = N_0\,e^{rt}$$

r: cell division rate

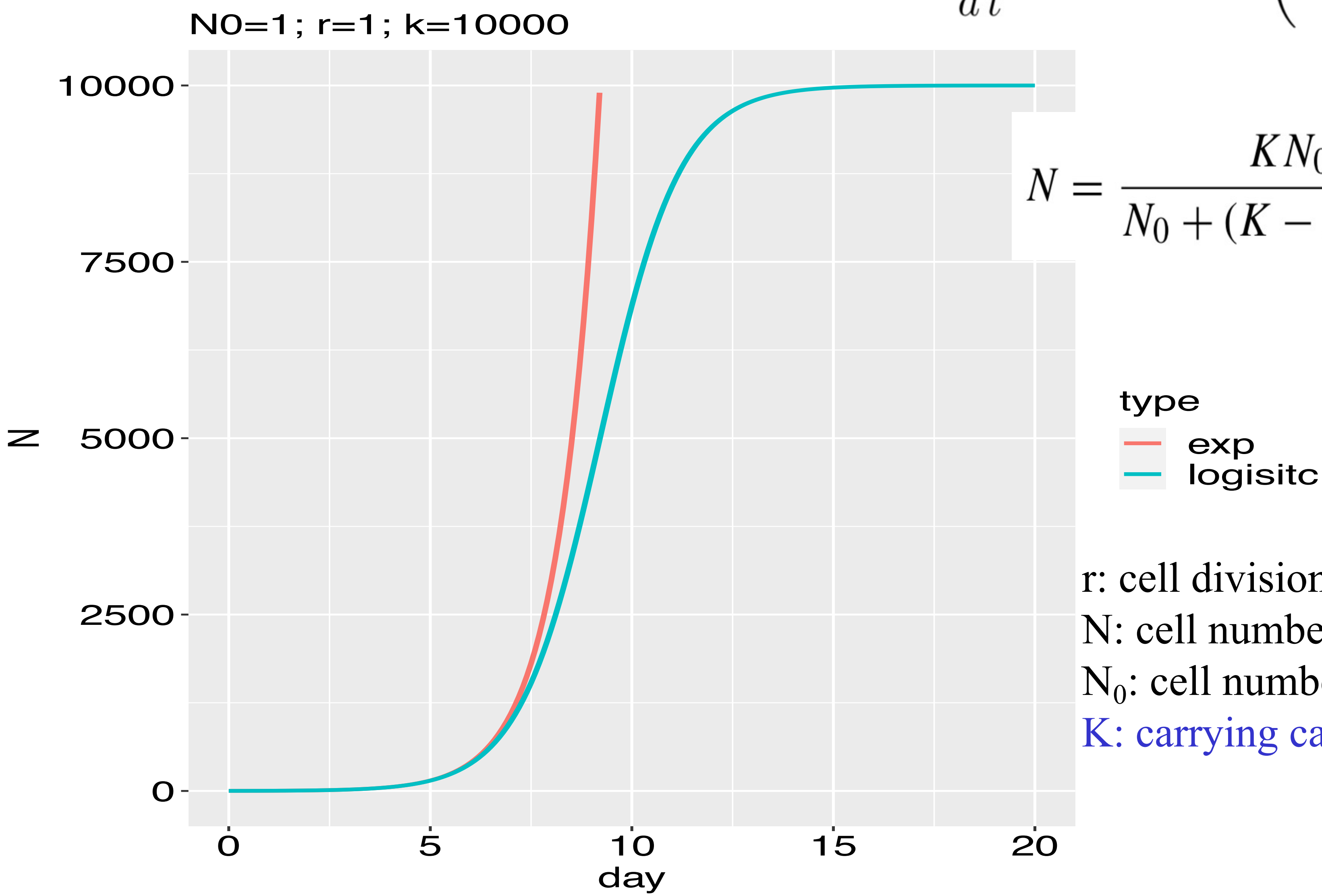
N: cell number

N_0: cell number at t=0

Evolutionary Dynamics

Ordinary Differential Equation (ODE)
for **logistic growth**

$$\frac{dN(t)}{dt} = rN\left(1 - \frac{N}{K}\right)$$



$$N = \frac{KN_0}{N_0 + (K - N_0)e^{-rt}}$$

r: cell division rate
N: cell number
N_0: cell number at t=0
K: carrying capacity

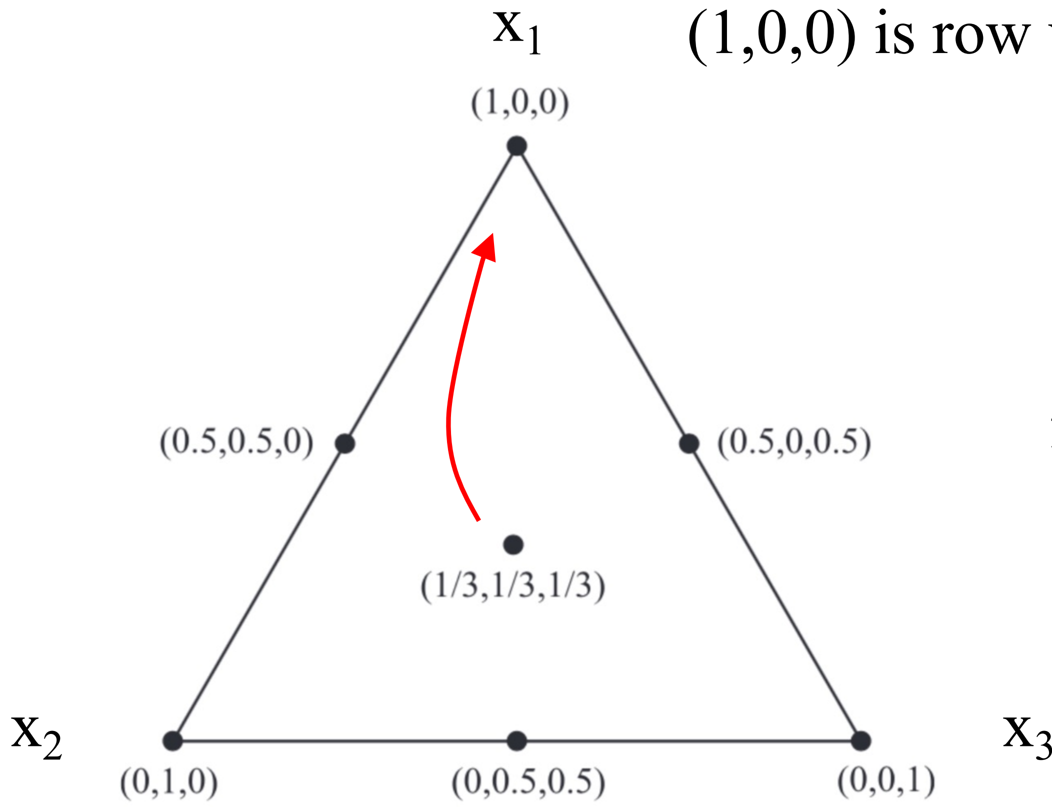
Evolutionary Dynamics

Ordinary Differential Equation (ODE)
for exponential growth of three cell types

x_i: frequency of cell type i

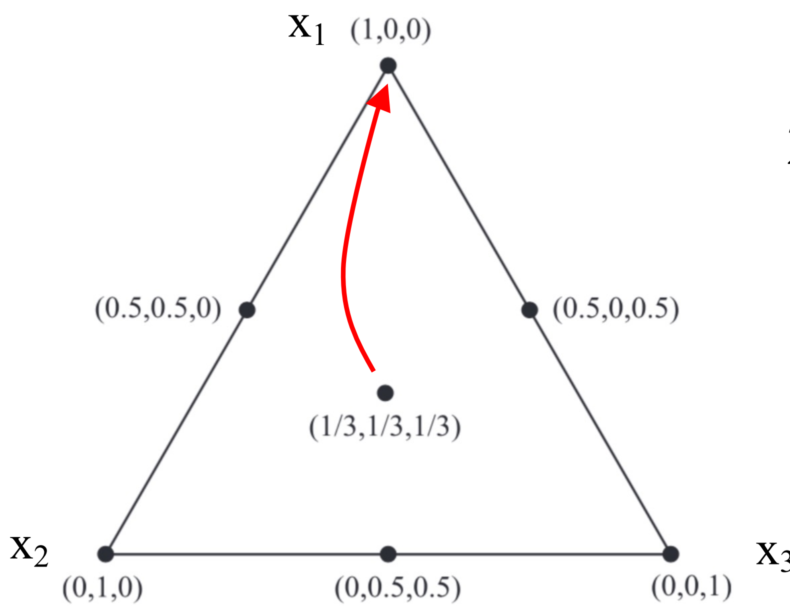
2-simplex
$x_i >= 0$
$\Sigma x_i = 1$

(1,0,0) is row vector of x



$f_1 > f_2 > f_3$

Evolutionary Dynamics



$f_1 > f_2 > f_3$

2-simplex

$x_i >= 0$

$\Sigma\, x_i = 1$

$$\dot{x}_i = x_i[f_i(x) - \phi]$$

x_i: frequency of species i

$f_i(x)$: fitness of species i

ϕ: average fitness

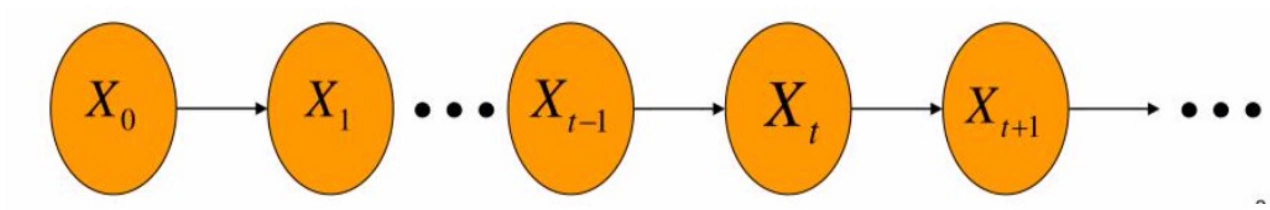
x_i increases if $f_i(x) > \phi$

Darwinian selection: survival of the fittest

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



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

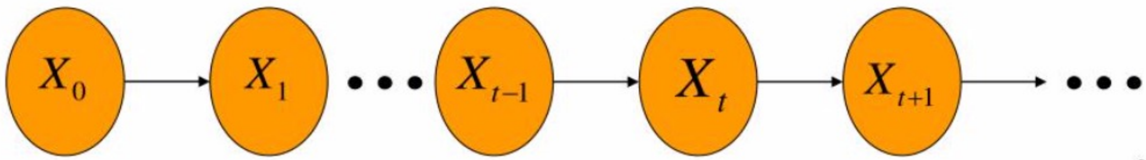
transition probability matrix

$p_{ij} >= 0$

$\Sigma_j \, p_{ij} = 1$

R package markovchain

Markov Process for Cancer Stem Model



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

$x = (x_1, x_2, \ldots, x_n)$

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

Assuming fitness is the same for all x_i

$$x^t P_{n1} = x_1 p_{11} + x_2 p_{21} + \ldots + x_n p_{n1} = x_1^{t+1}$$

$$x^t P_{n2} = x_1 p_{12} + x_2 p_{22} + \ldots + x_n p_{n2} = x_2^{t+1}$$

$$x^t P_{nn} = x_1 p_{1n} + x_2 p_{2n} + \ldots + x_n p_{nn} = x_n^{t+1}$$

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

x^* is the left eigen vector of matrix P

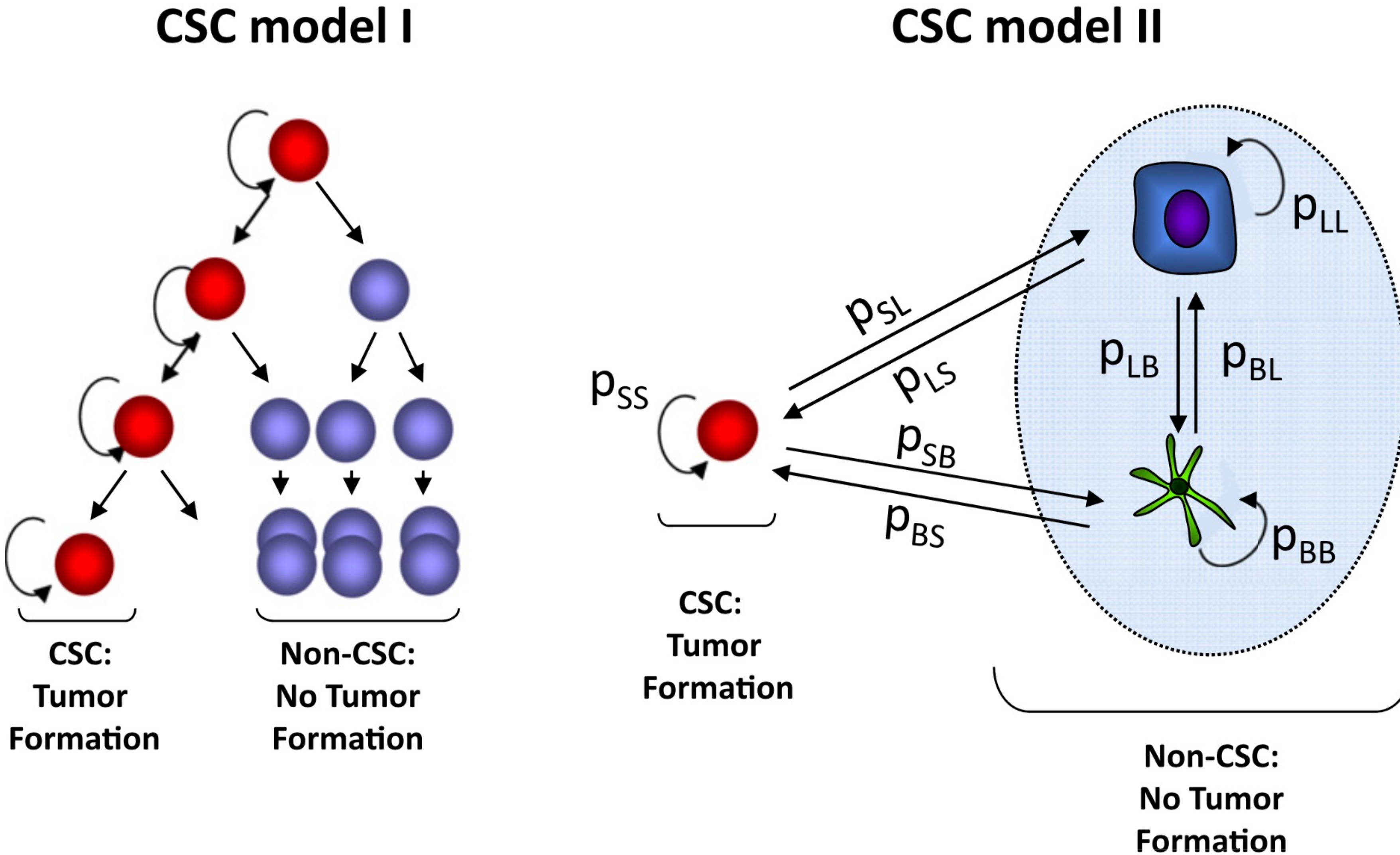
Its eigen value is 1, which is the largest eigen value

Markov Model of Dynamical System

- Stem cells and non-stem cells
- Epithelial-to-mesenchymal transition (EMT)
- Epigenetic states
- Gene expression and isoforms
- Protein expression and post-translational modifications

$$P = \begin{bmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ & \cdots & \cdots & \\ p_{n1} & p_{n2} & \cdots & p_{nn} \end{bmatrix} \qquad \boldsymbol{x} = \begin{bmatrix} x_1 \\ x_2 \\ \\ \\ x_n \end{bmatrix}$$

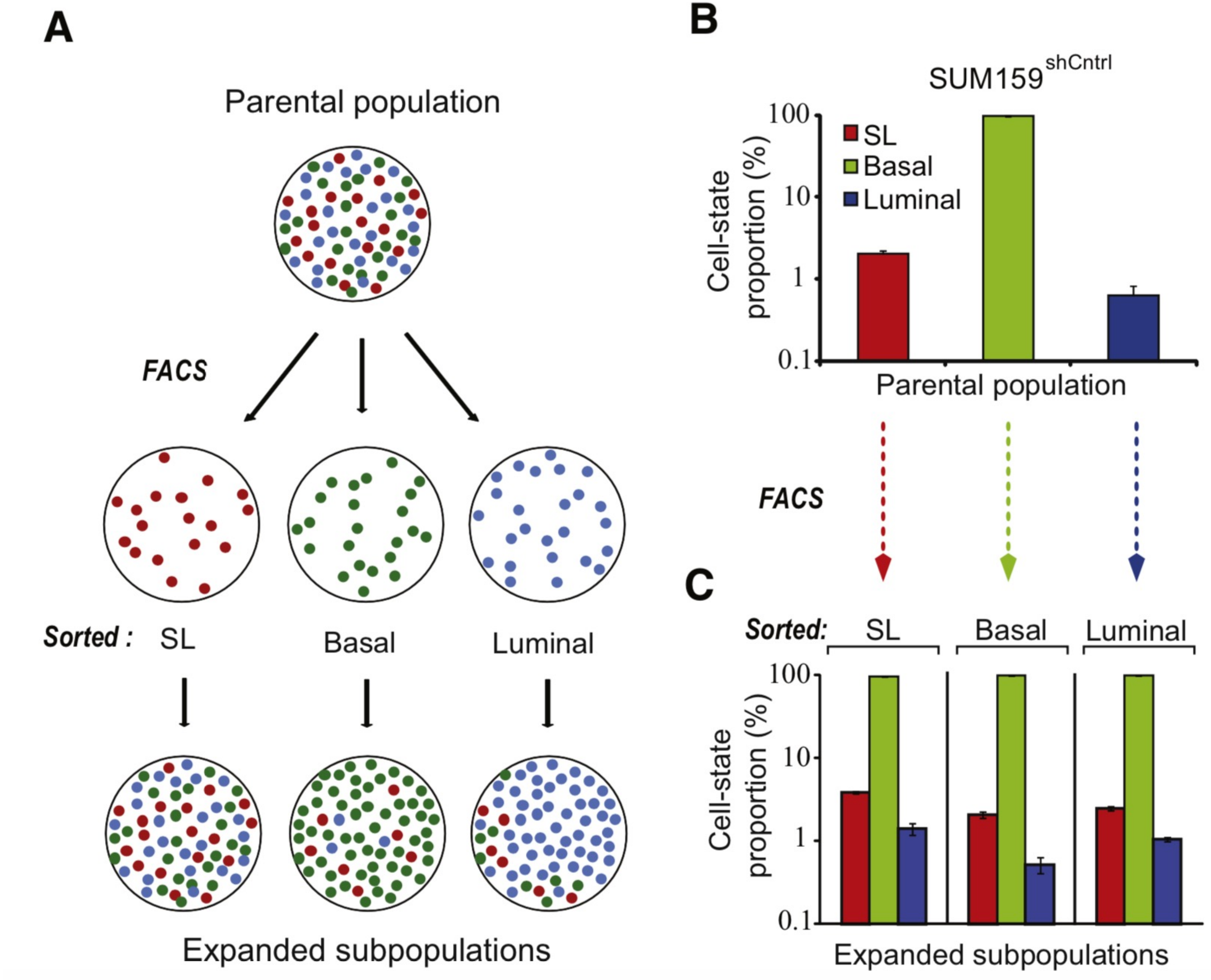
Cancer Stem Cell Model



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

Conversion Between Cancer Stem Cell and Non-stem Cells

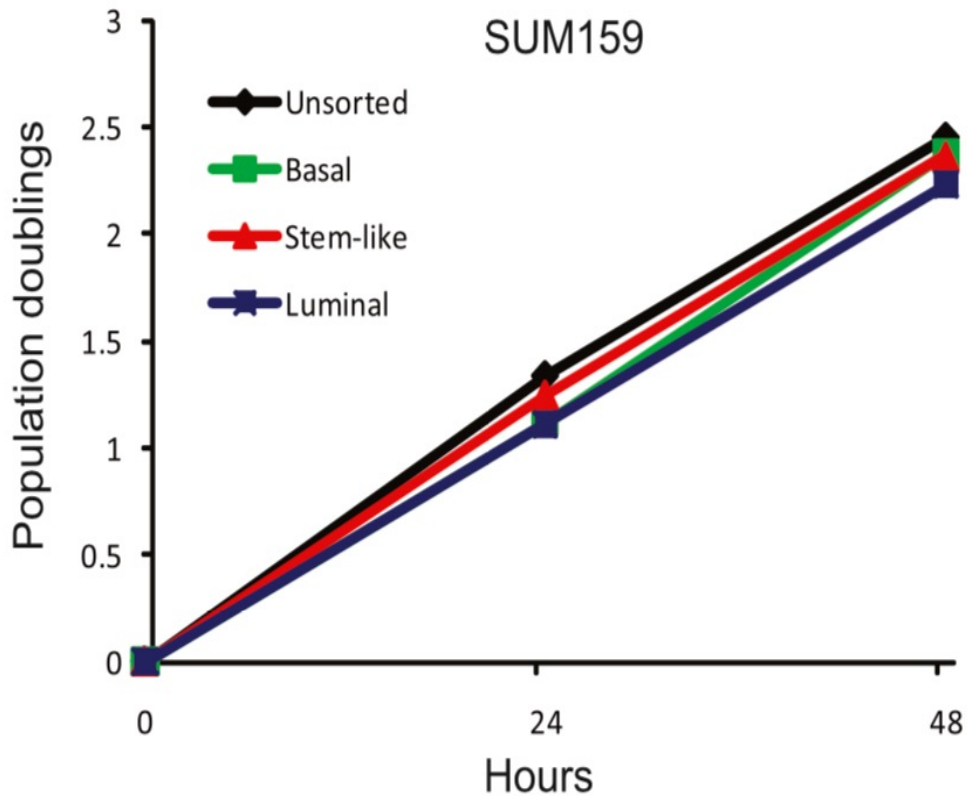
SL: stem-like



6 days

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

Subtypes Have Similar Growth Rate



Conversion Between Cancer Stem Cell and Non-stem Cells

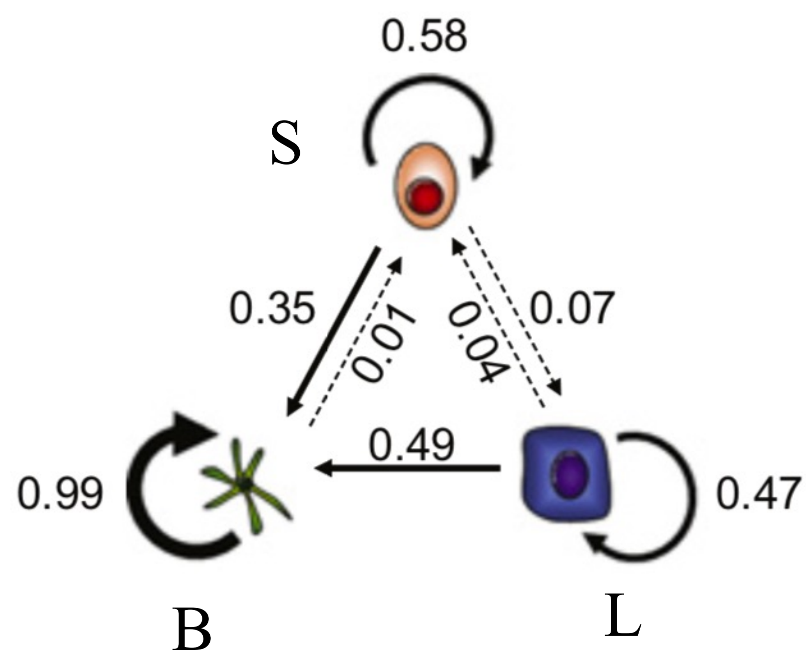
$$
\begin{array}{cc}
 & \begin{array}{ccc} S & B & L \end{array} \\
X^0 = & \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}
\end{array}
$$

growth rates are the same
P is fixed

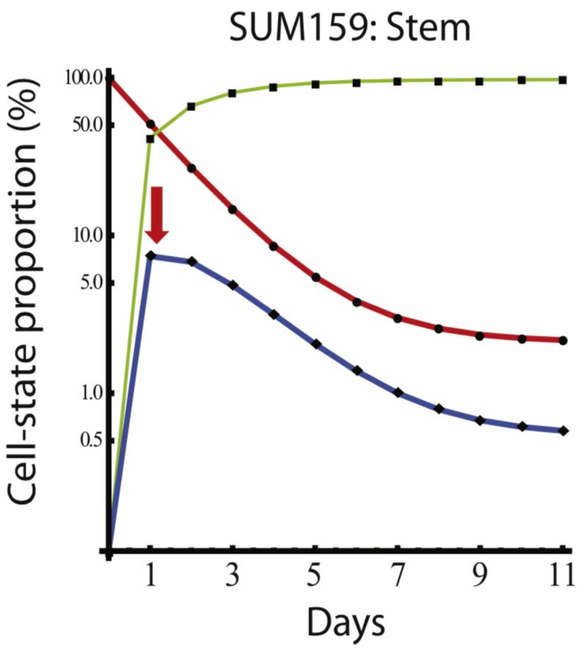
$$X^t = X^0 P^{\wedge t}$$

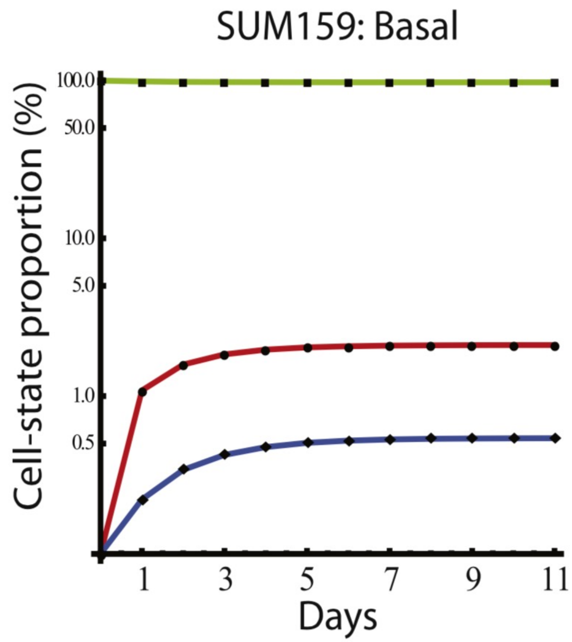
	S	B	L
S	**0.58**	**0.35**	**0.07**
B	**0.01**	**0.99**	**0**
L	**0.04**	**0.49**	**0.47**

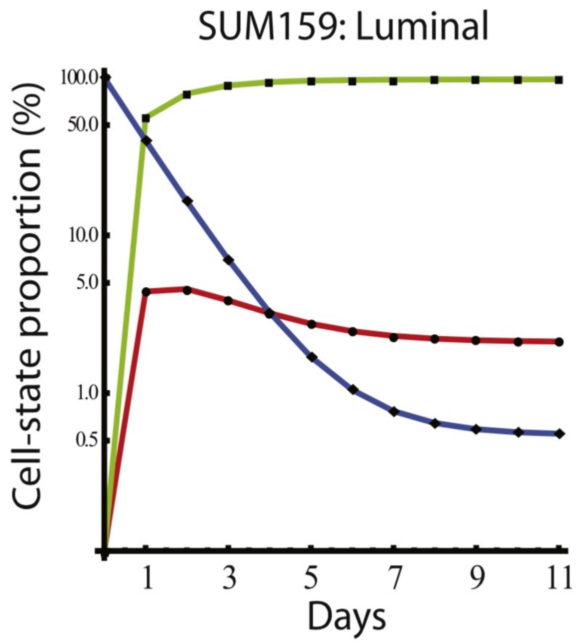
transition probability matrix

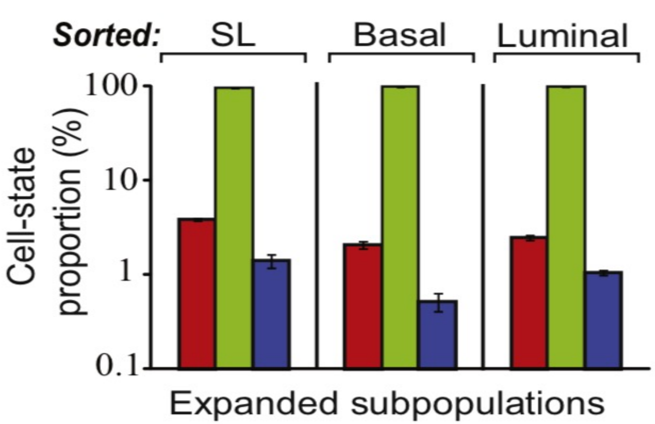


Different Kinetics of Markov Model



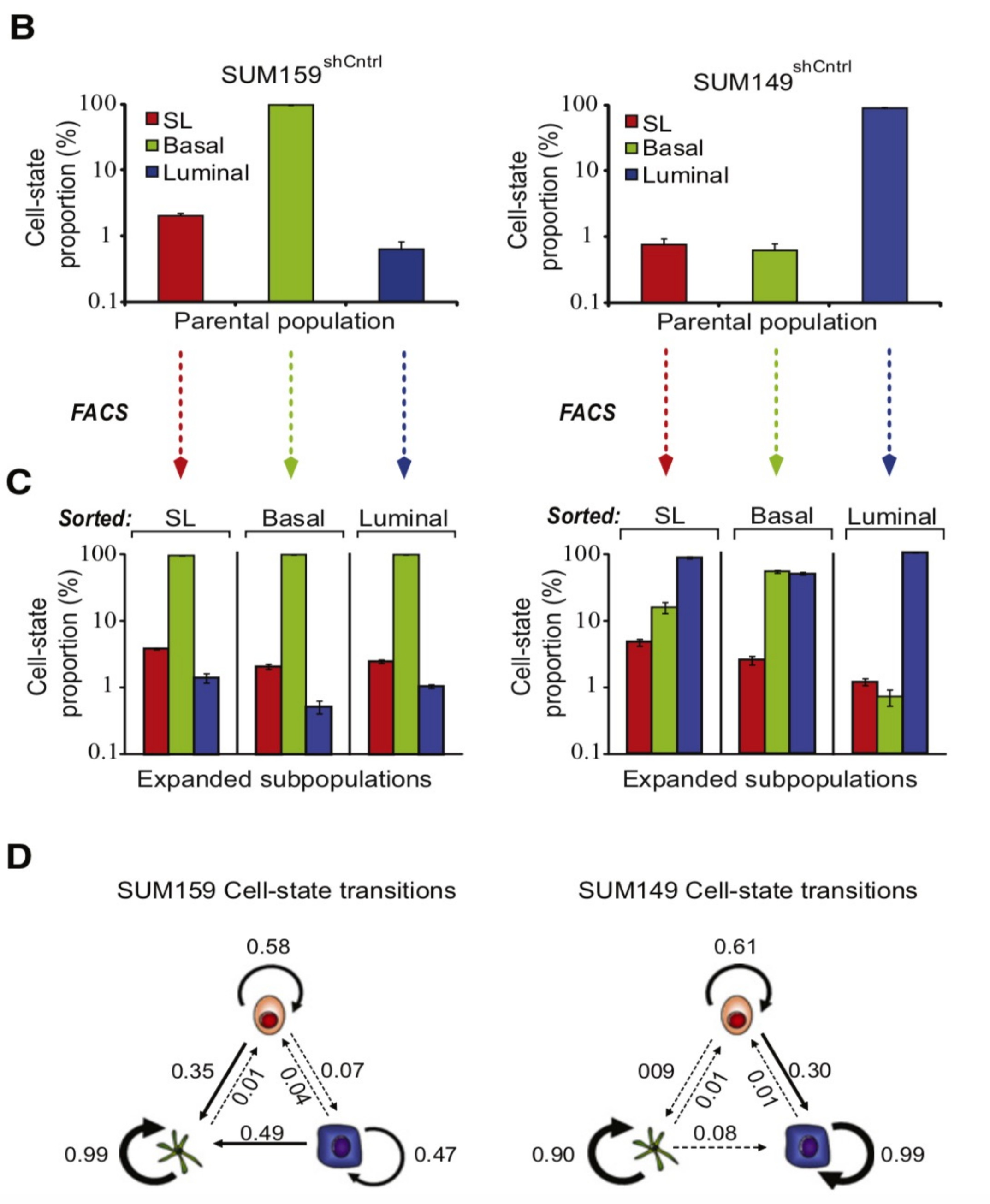




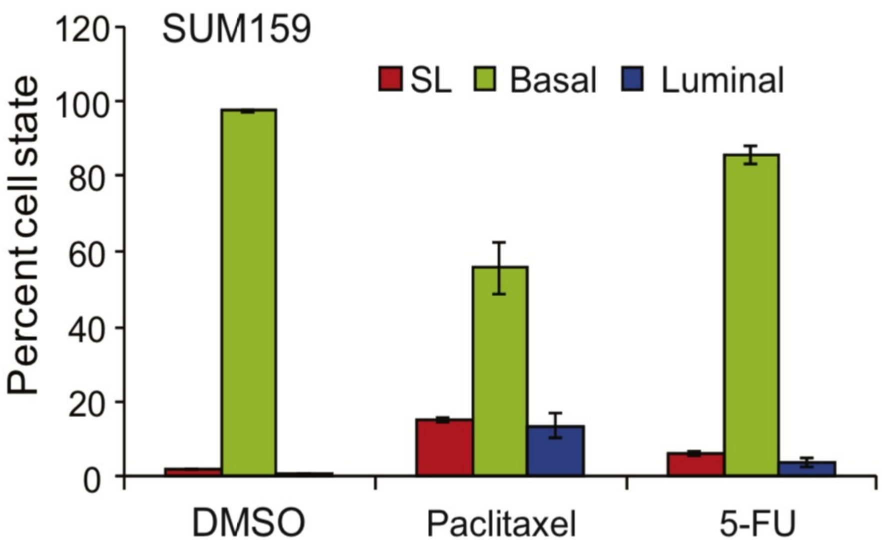


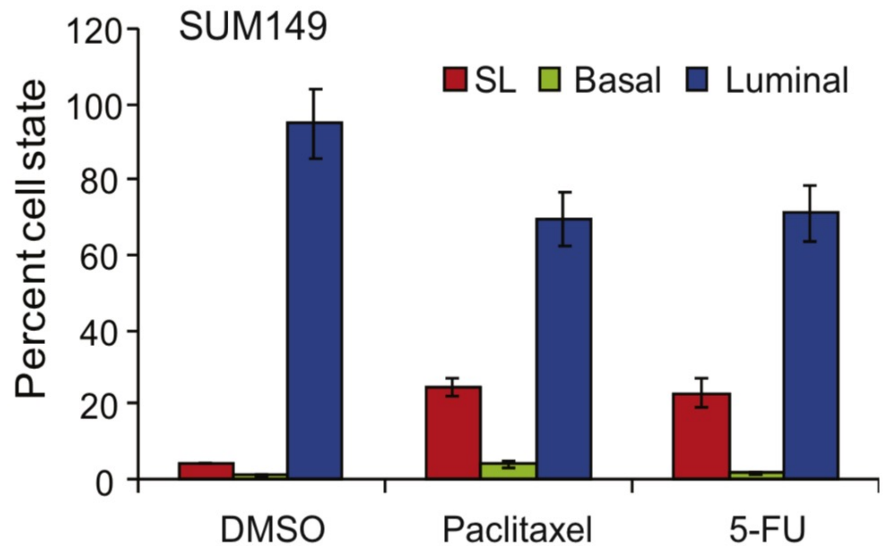
6 days

Different Cellular Distribution of Basal and Luminal Cell Types



Cellular State Distribution Affected by Chemotherapy Treatment

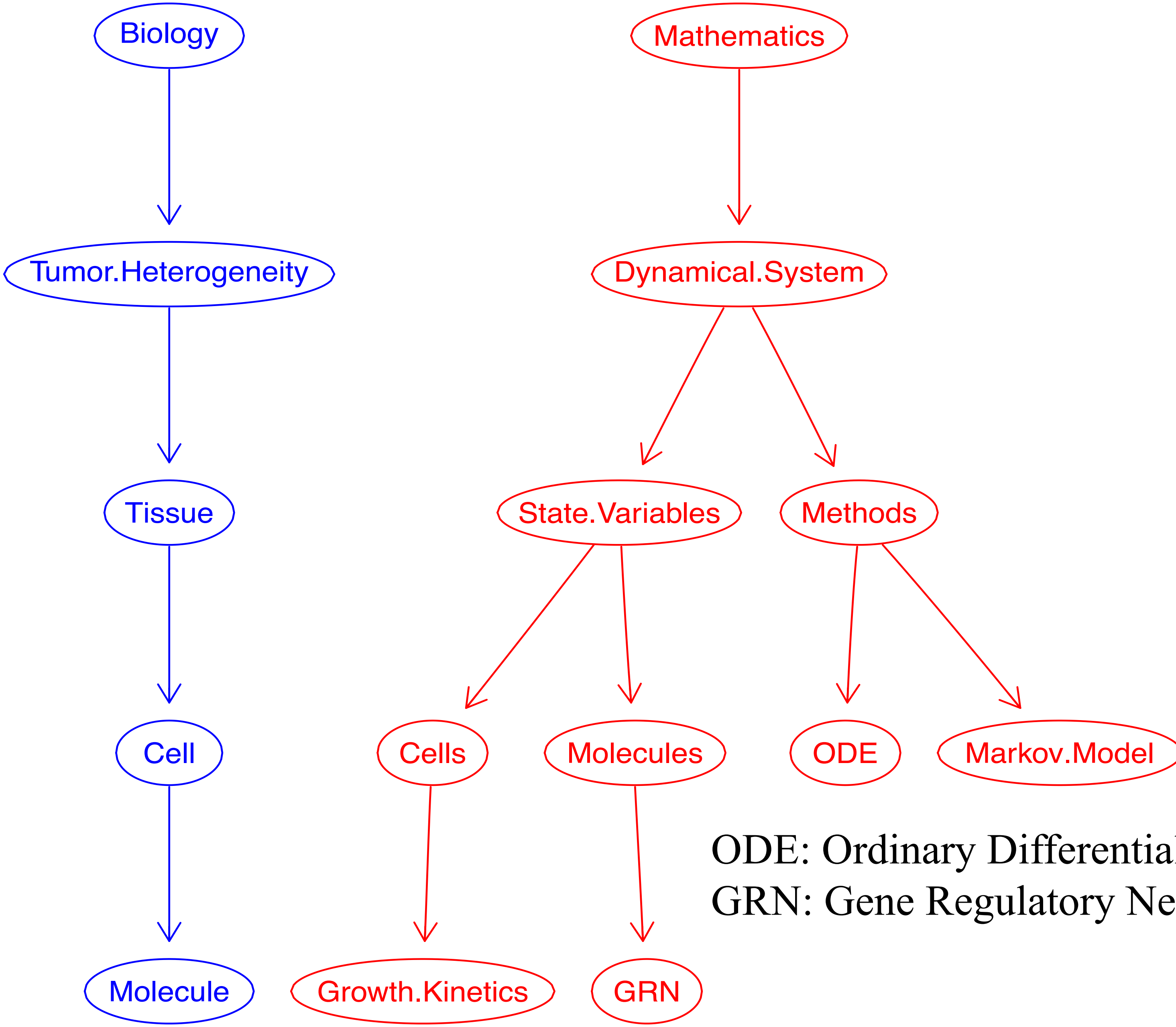




$$x^* = x^* DP$$

D is diagonal matrix of drug resistance
x* is the left eigen vector of matrix product of DP
with the largest eigen value

Understanding Biology with Mathematical Modeling



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