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

Network Motifs and Dynamics of Cellular States

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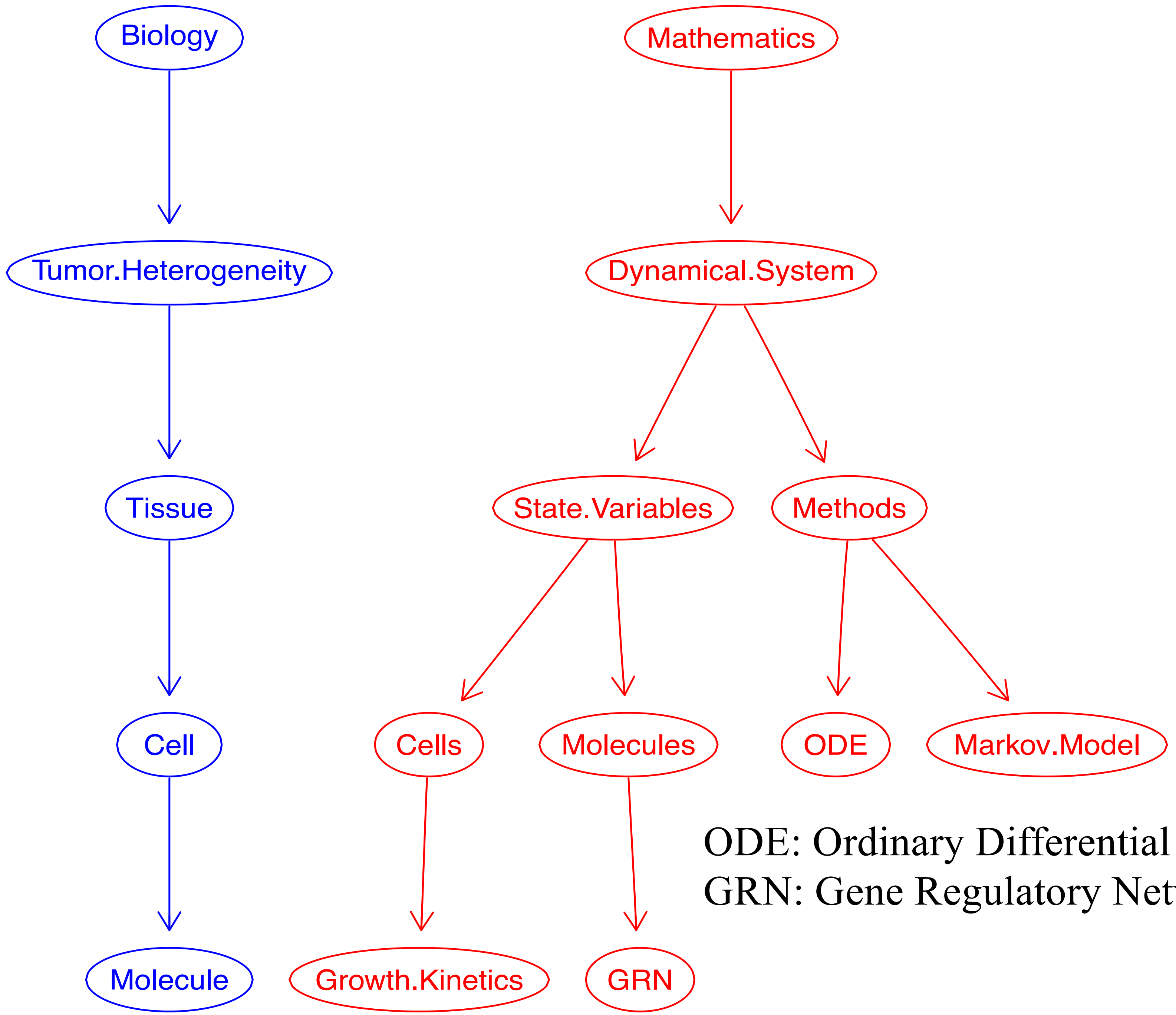
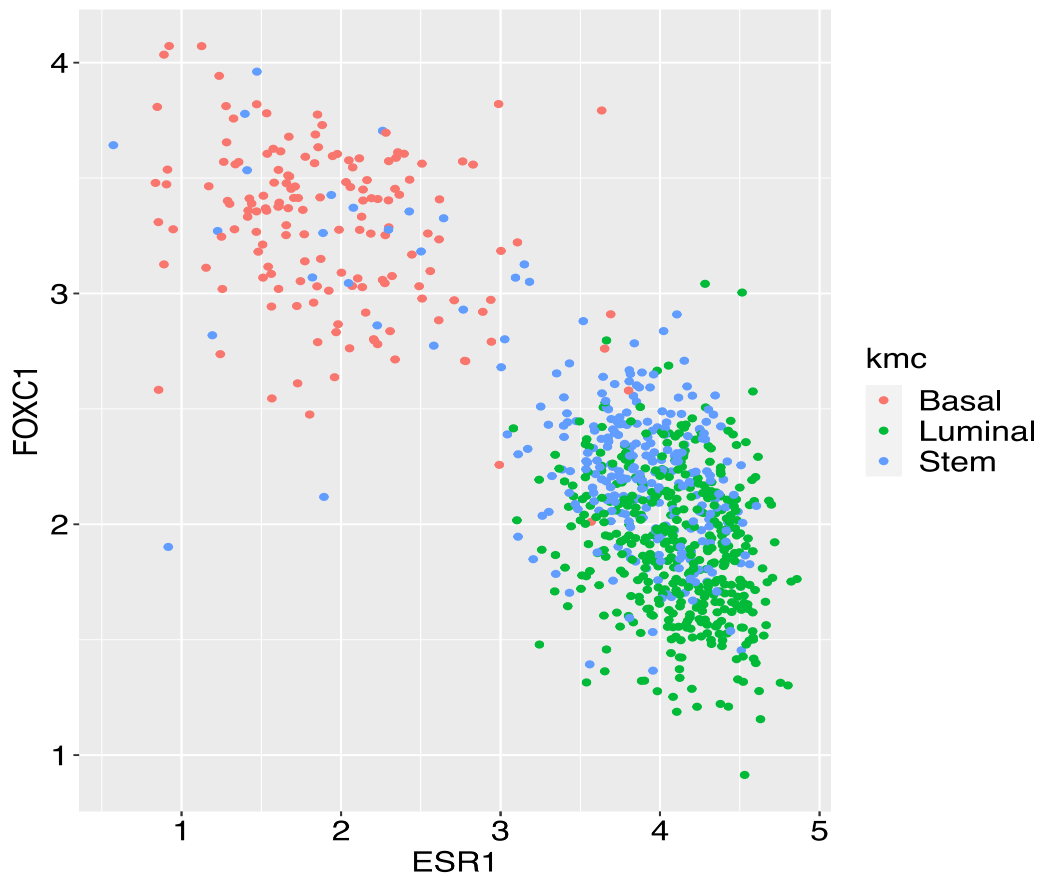
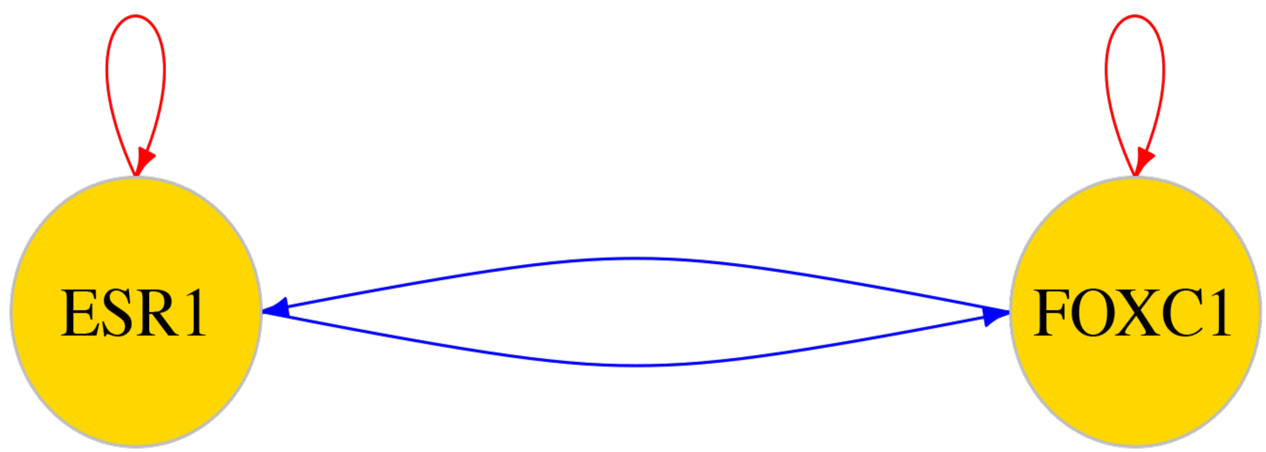
Understanding Biology with Mathematical Modeling



ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

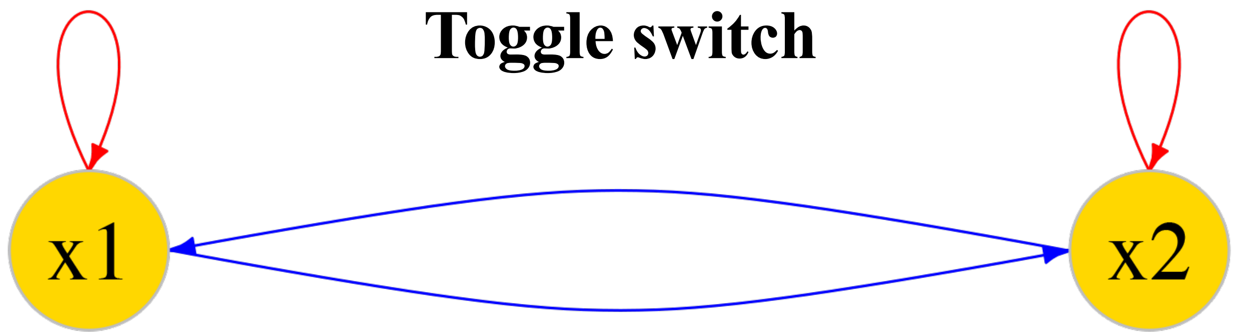
GRN of Luminal and Basal States





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

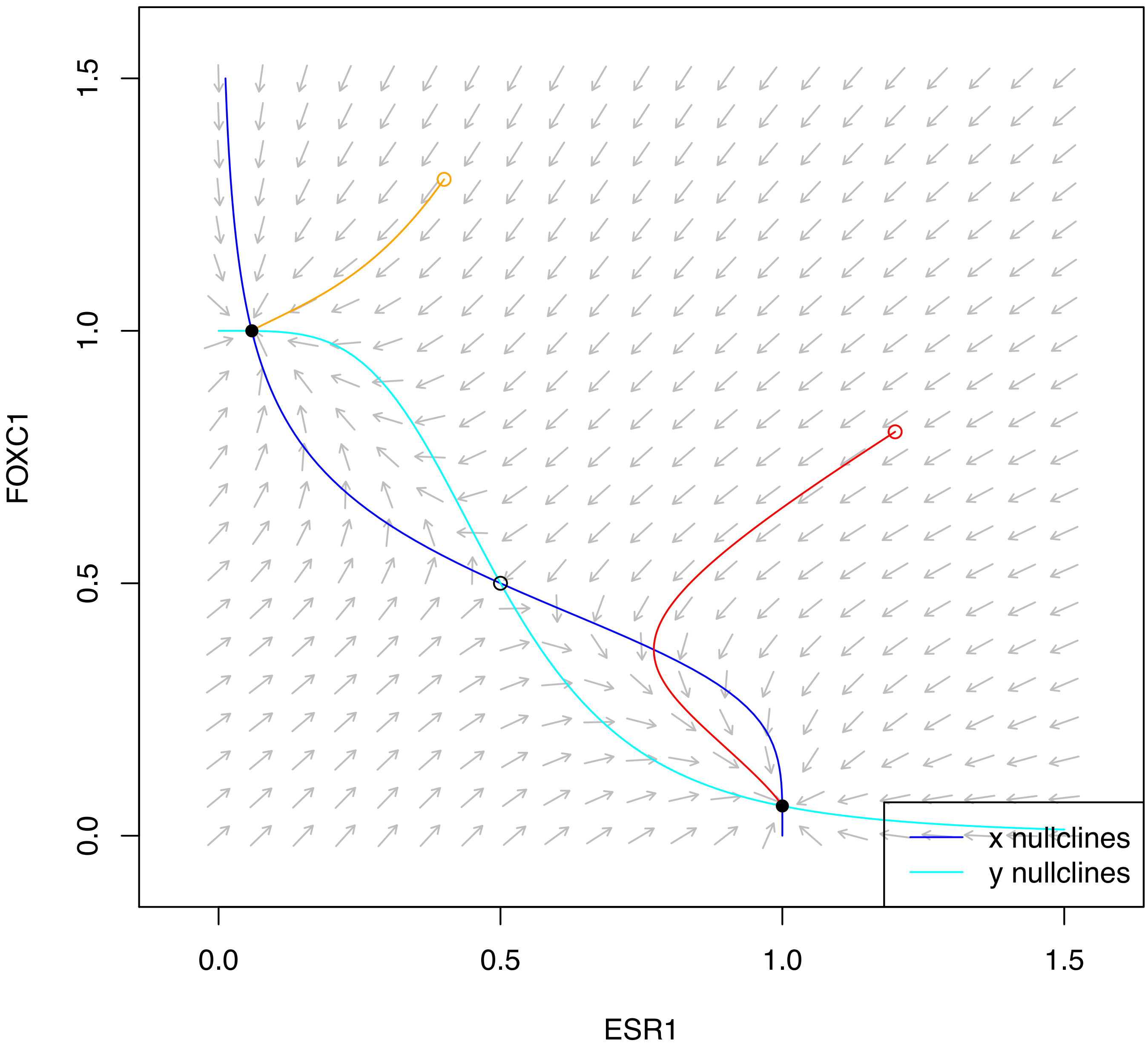
k_1 and k_2 are weights for degradation

n is Hill Coefficient

S is threshold of Hill function

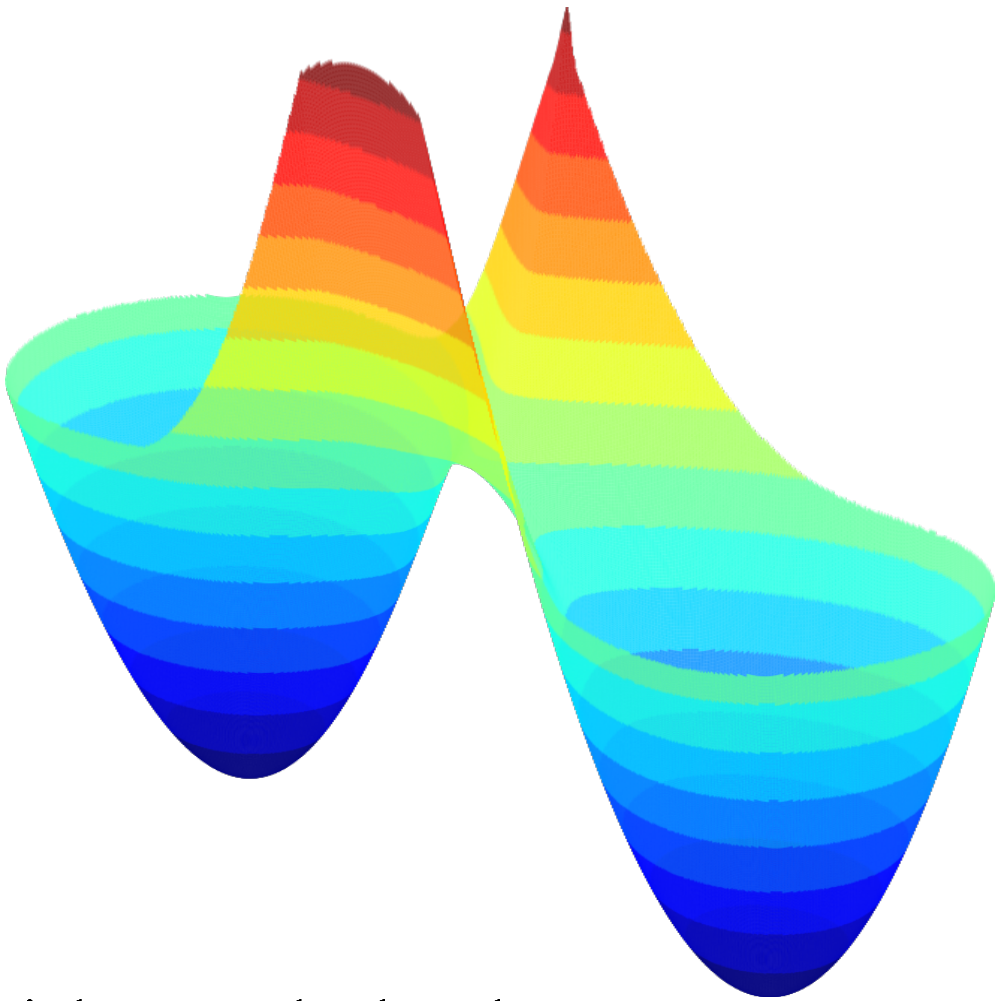
Wang et al PNAS, 2011;108:8257–8262

Flow Diagram of Toggle Switch GRN



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

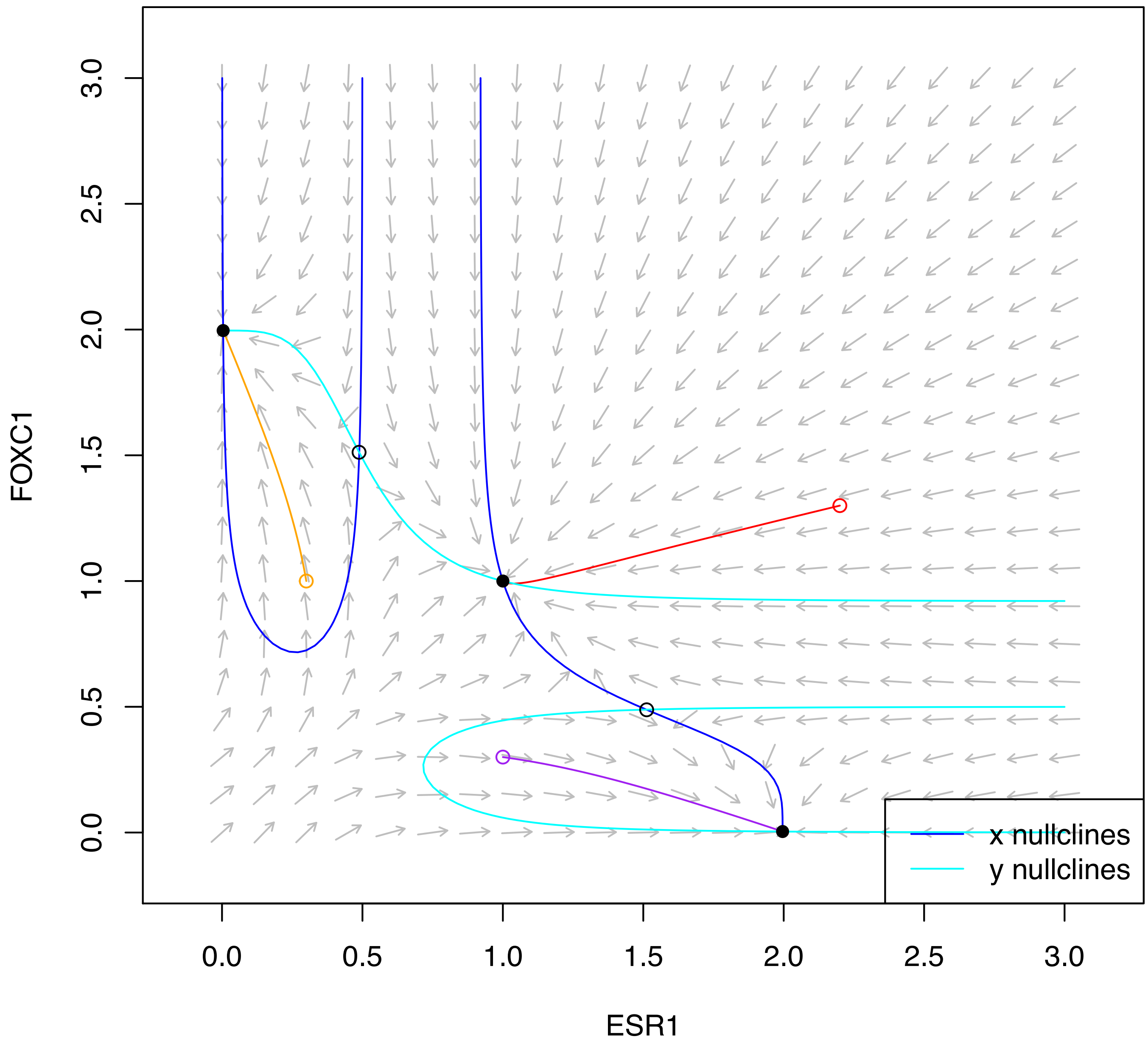
Quasi-Potential of GRN



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

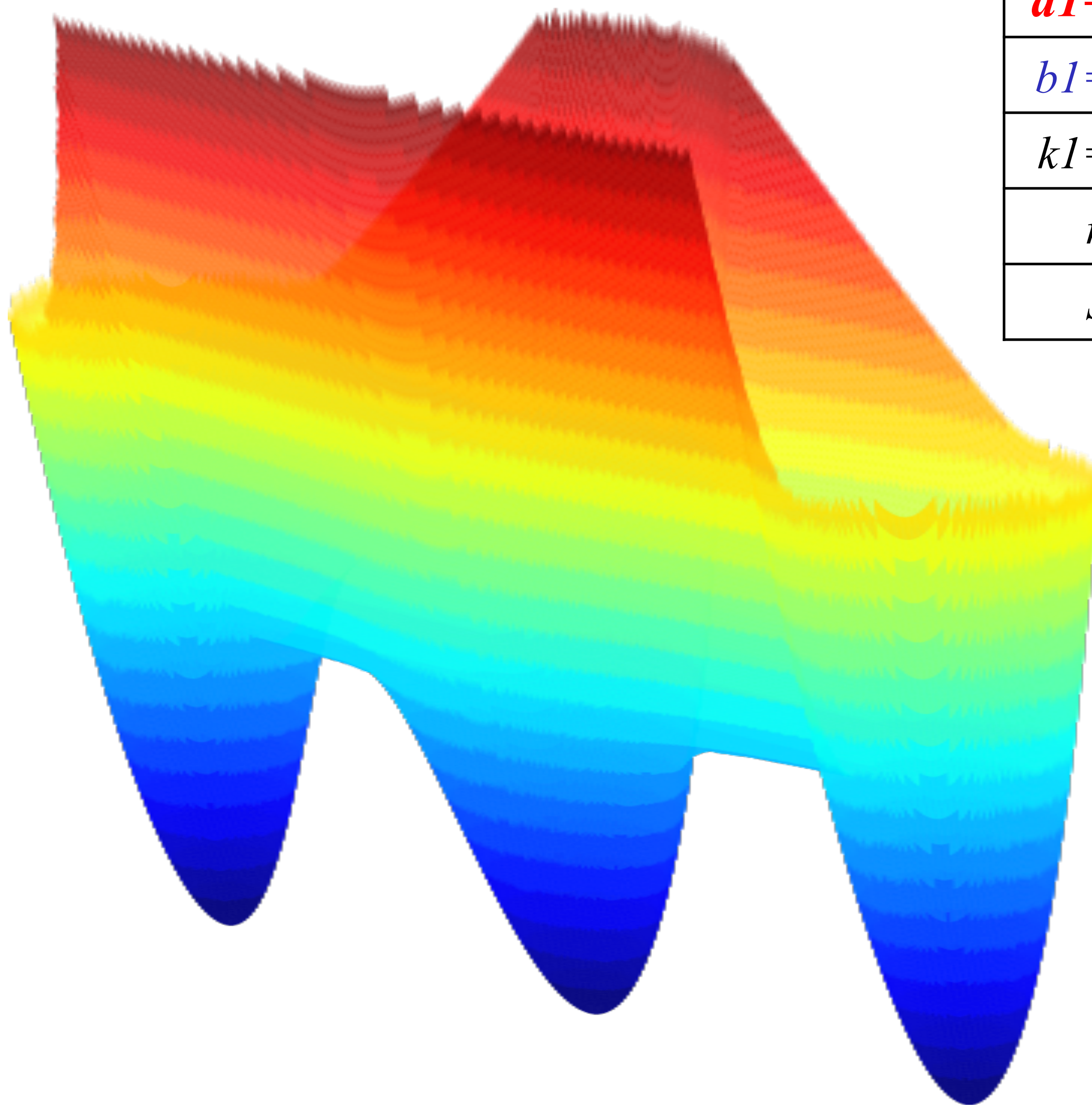
Quasi-potential was calculated
with R package QPot

Toggle Switch GRN with Auto-Activation



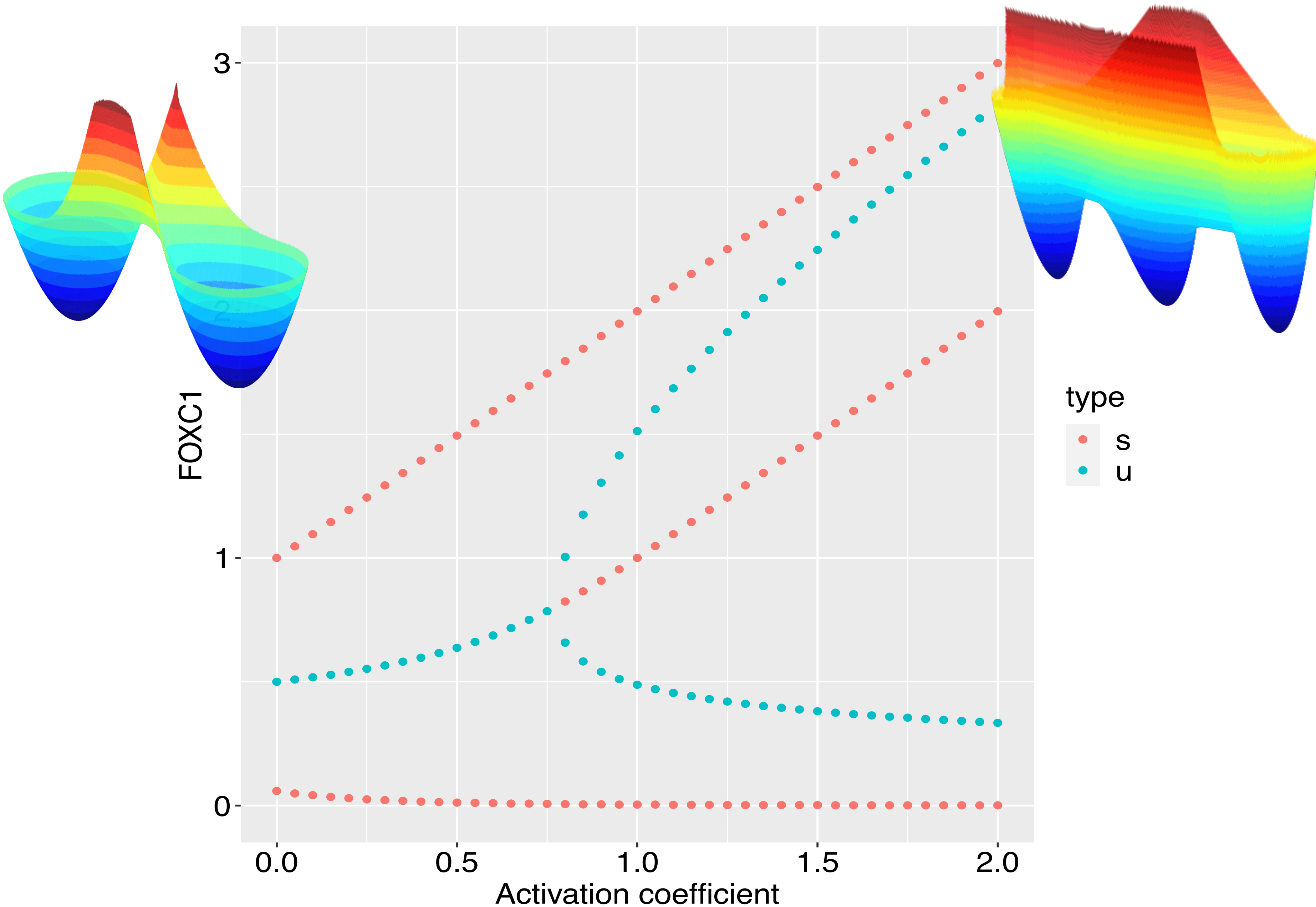
a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Quasi-Potential of GRN

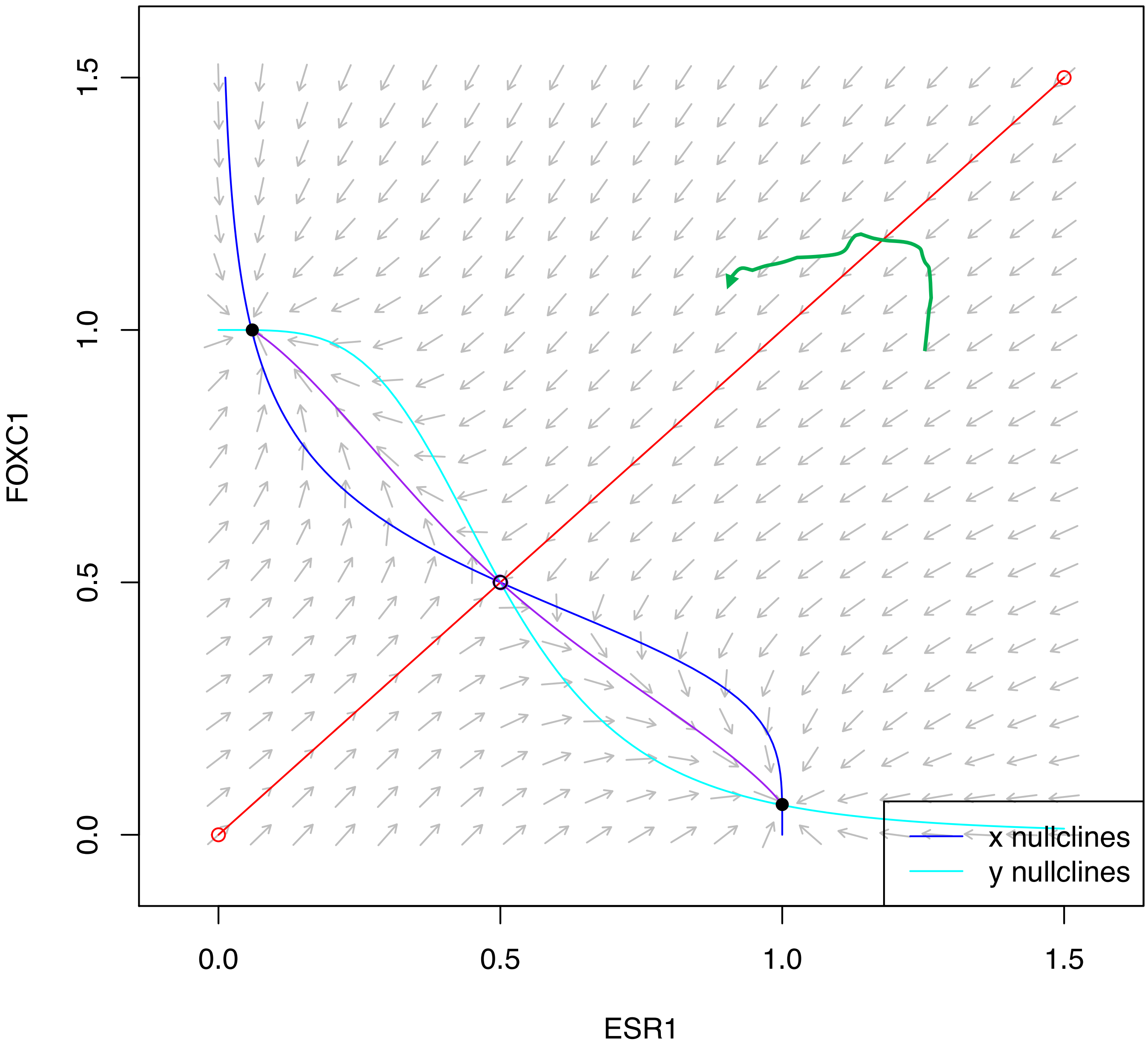


a1=a2	**1**
b1=b2	1
k1=k2	1
n	4
S	0.5

Bifurcation Diagram



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

Negative Feedback Motif of NF-κB Signaling Pathway

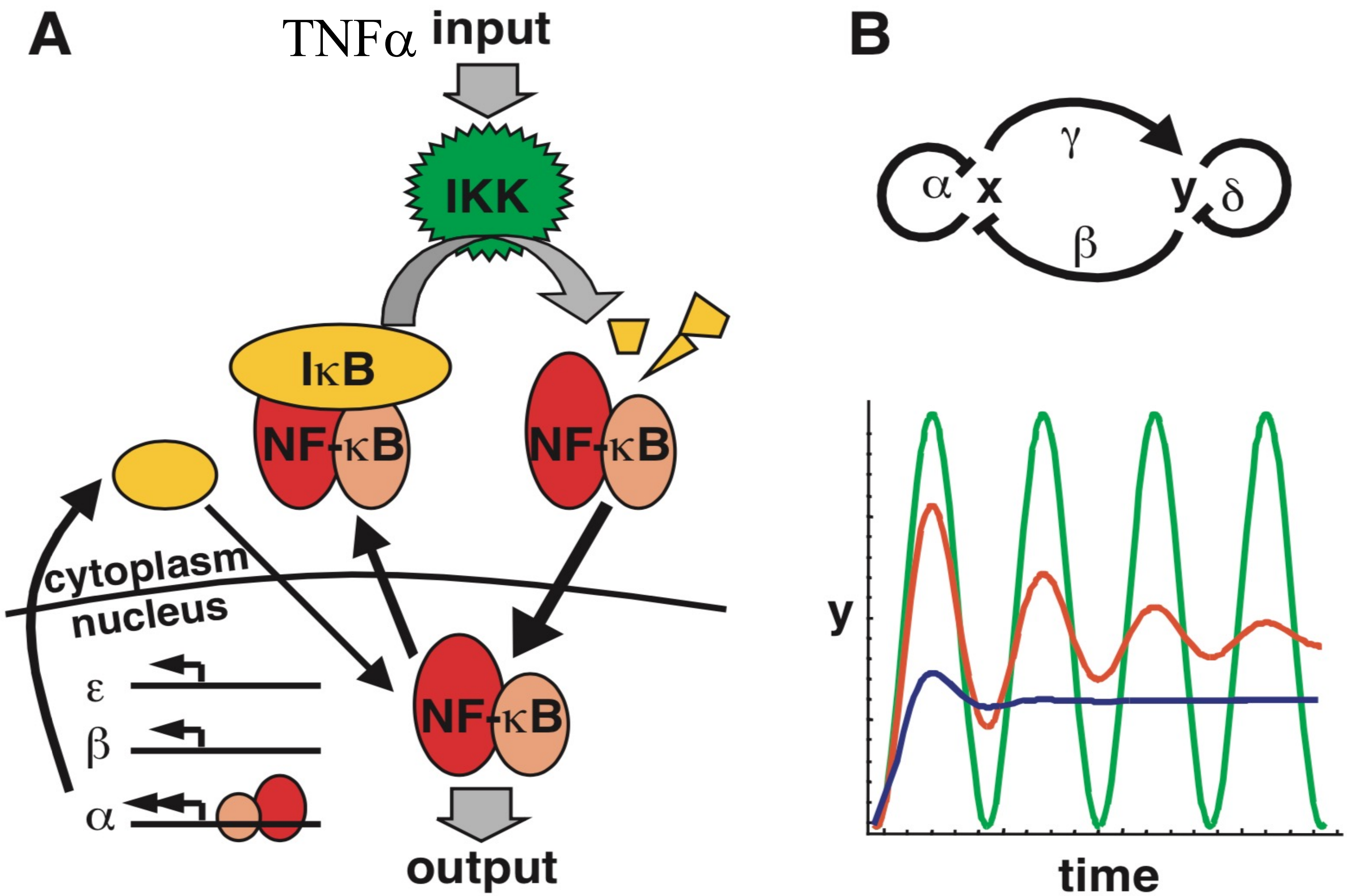


Figure 1

Hoffmann et al. Science 2002, 298:1241

Negative Feedback Motif of NF-κB Signaling Pathway

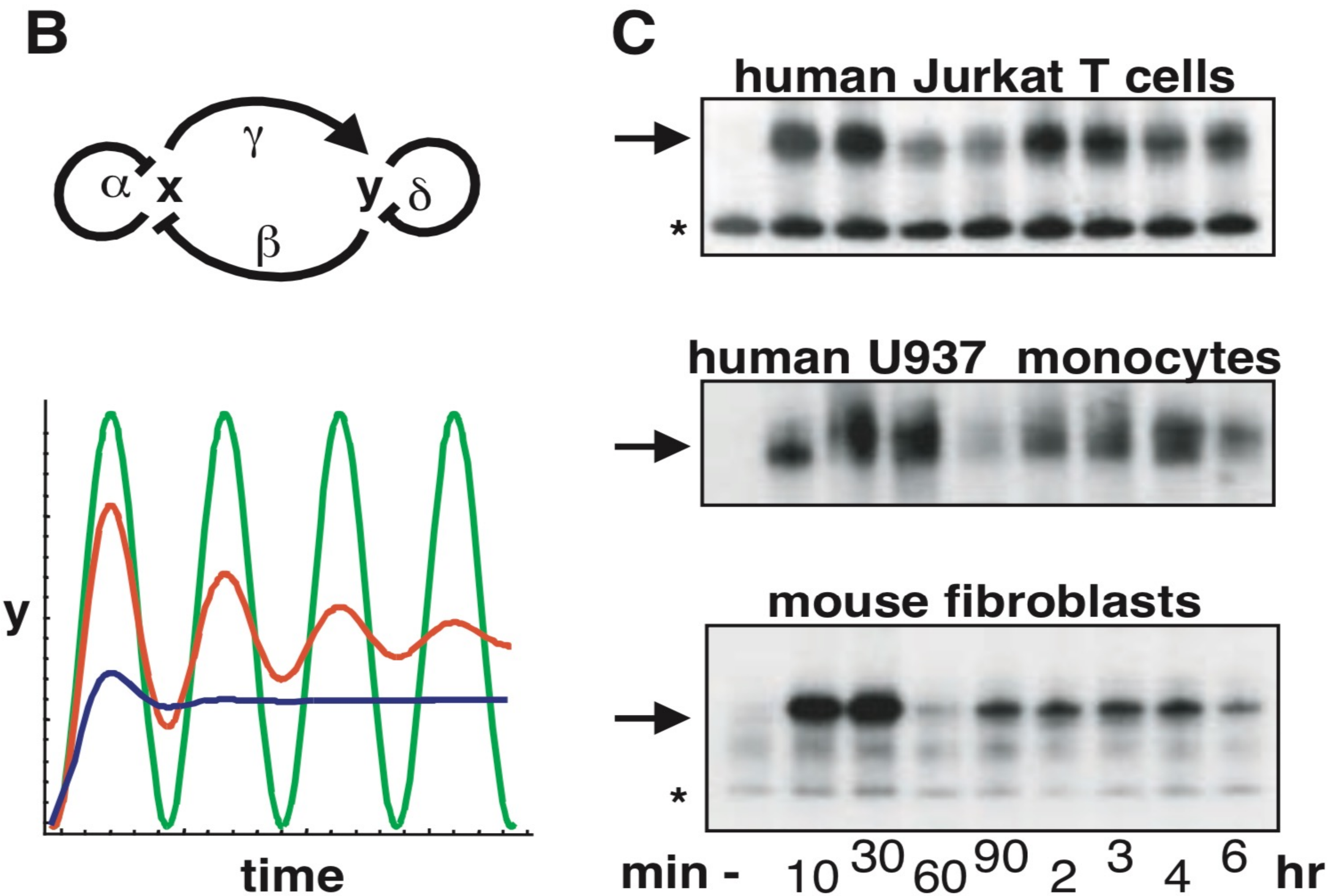


Figure 1

Hoffmann et al. Science 2002, 298:1241

Negative Feedback Motif of NF-κB Signaling Pathway

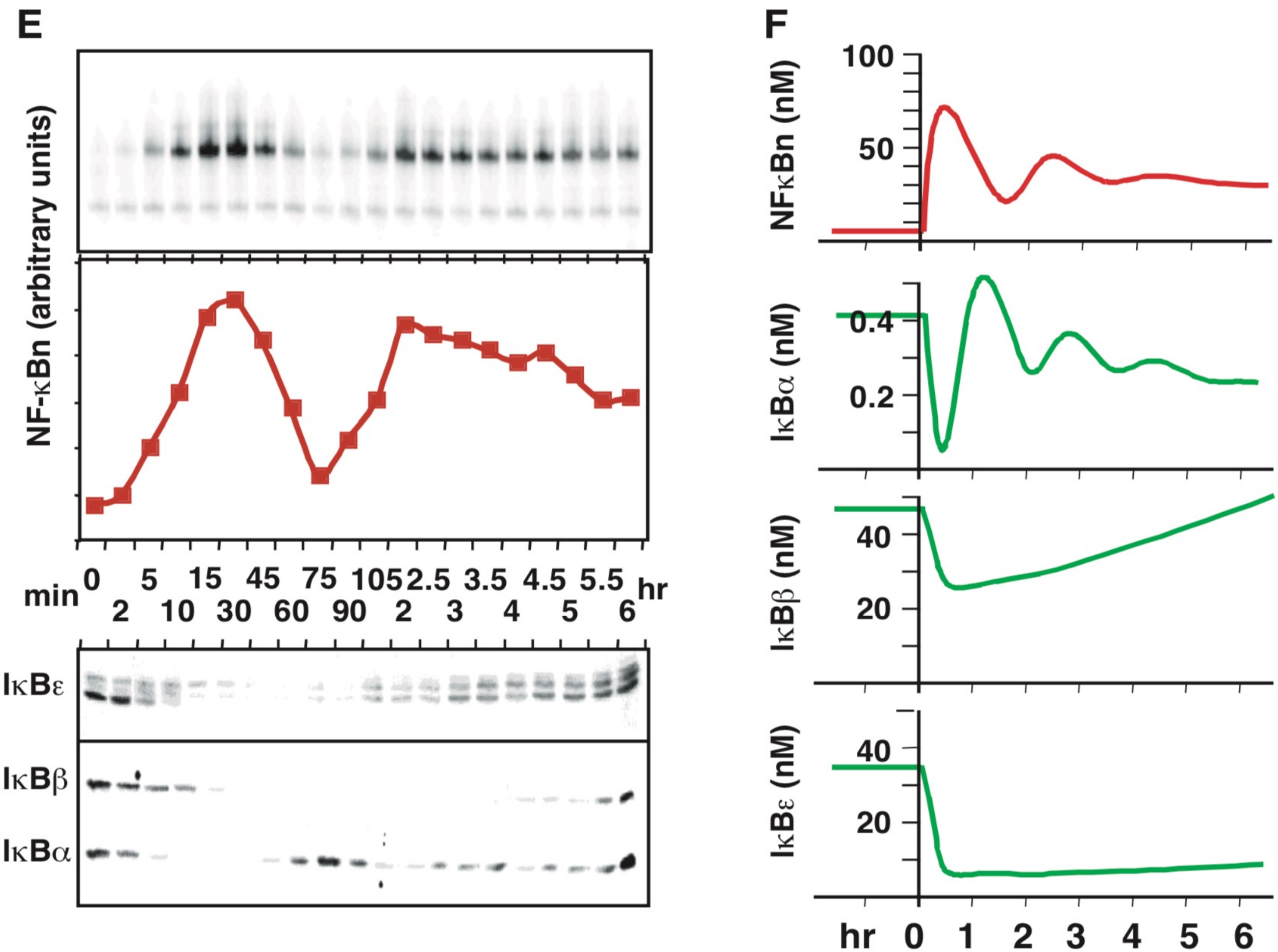


Figure 2 wild-type fibroblasts

IκBα Is Required For Oscillation of NF-κB Signal

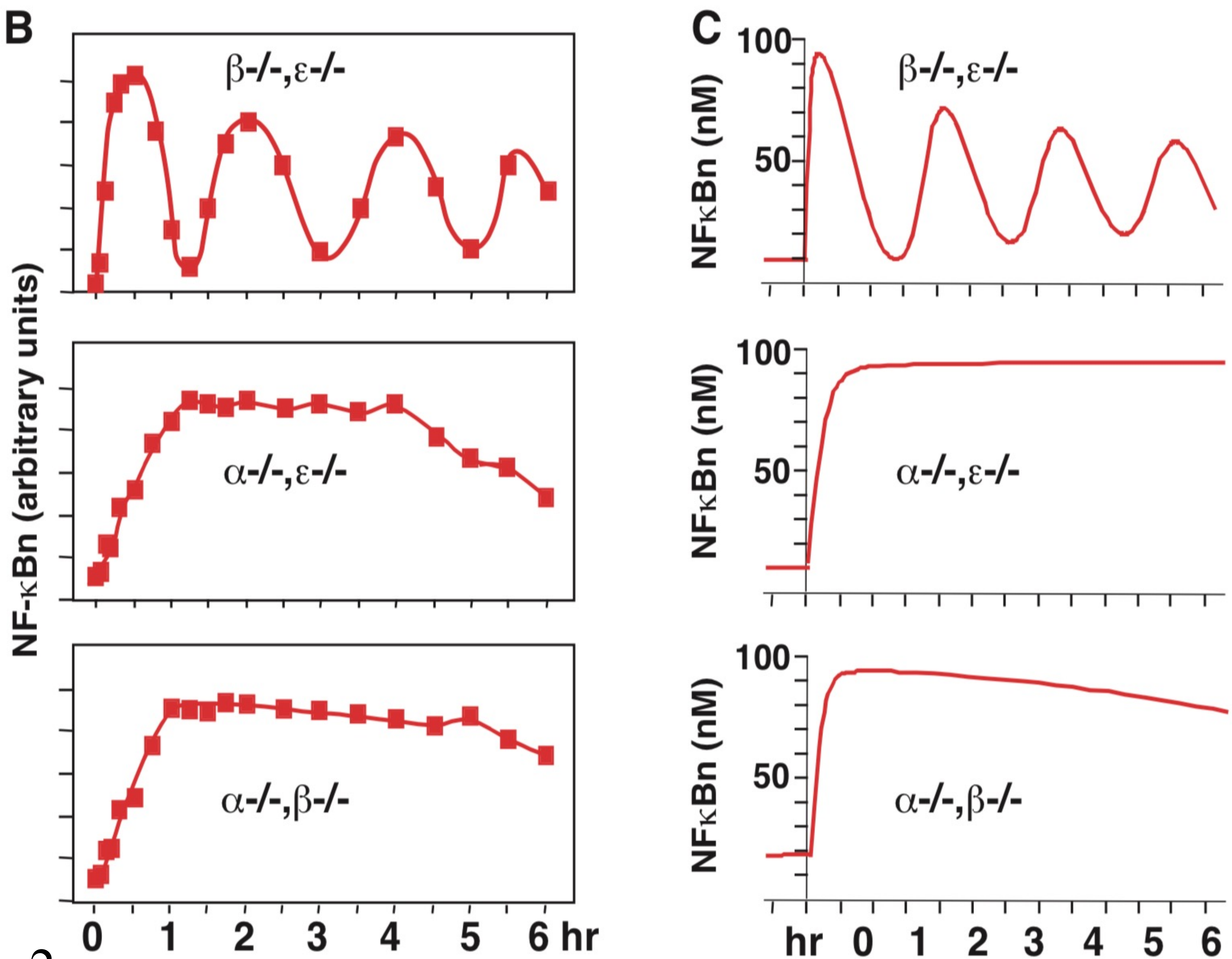
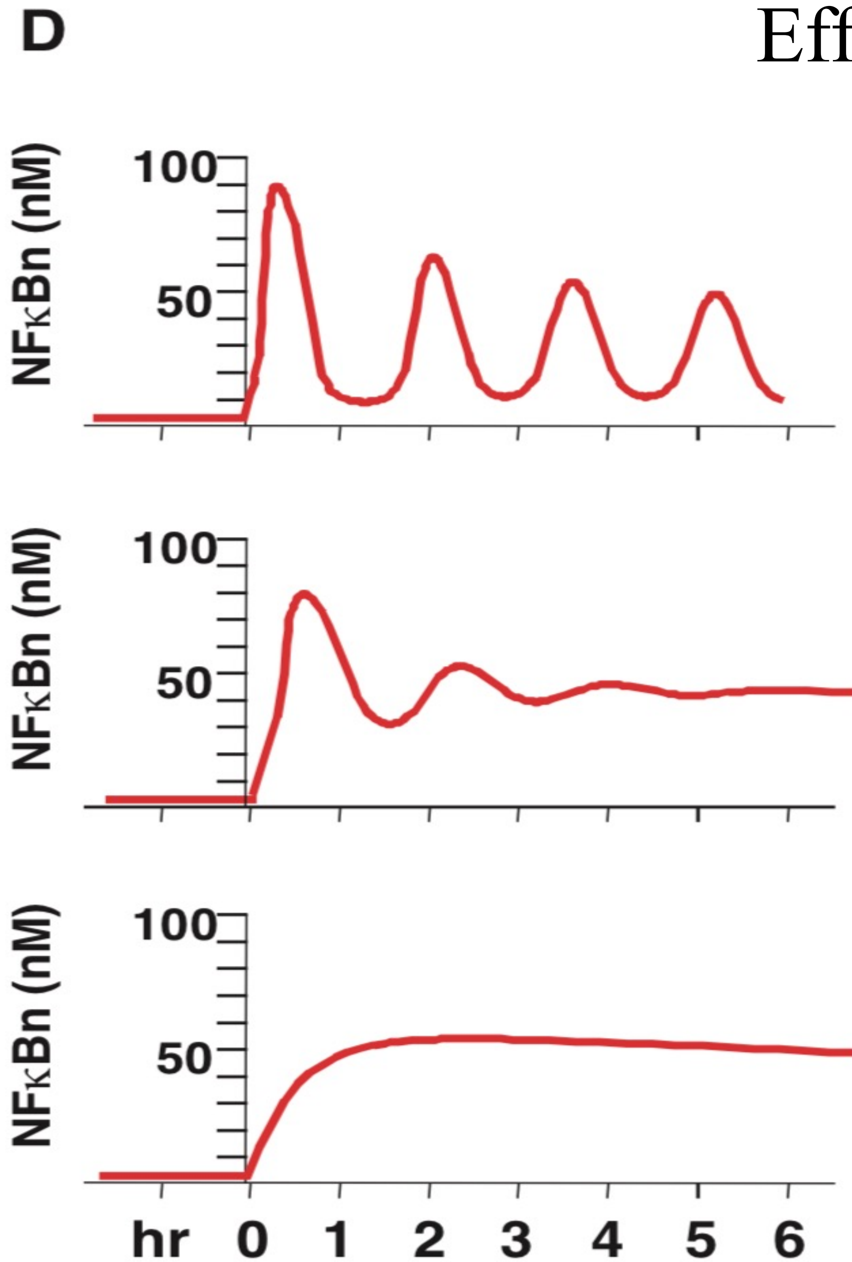


Figure 2

IκBβ/ε Causes Damped Oscillation of NF-κB Signal

Effect of IκBβ and IκBε



Reduced by 5-fold

Baseline in WT

Increased by 7-fold

Figure 2

NF-κB response to TNFα of various durations

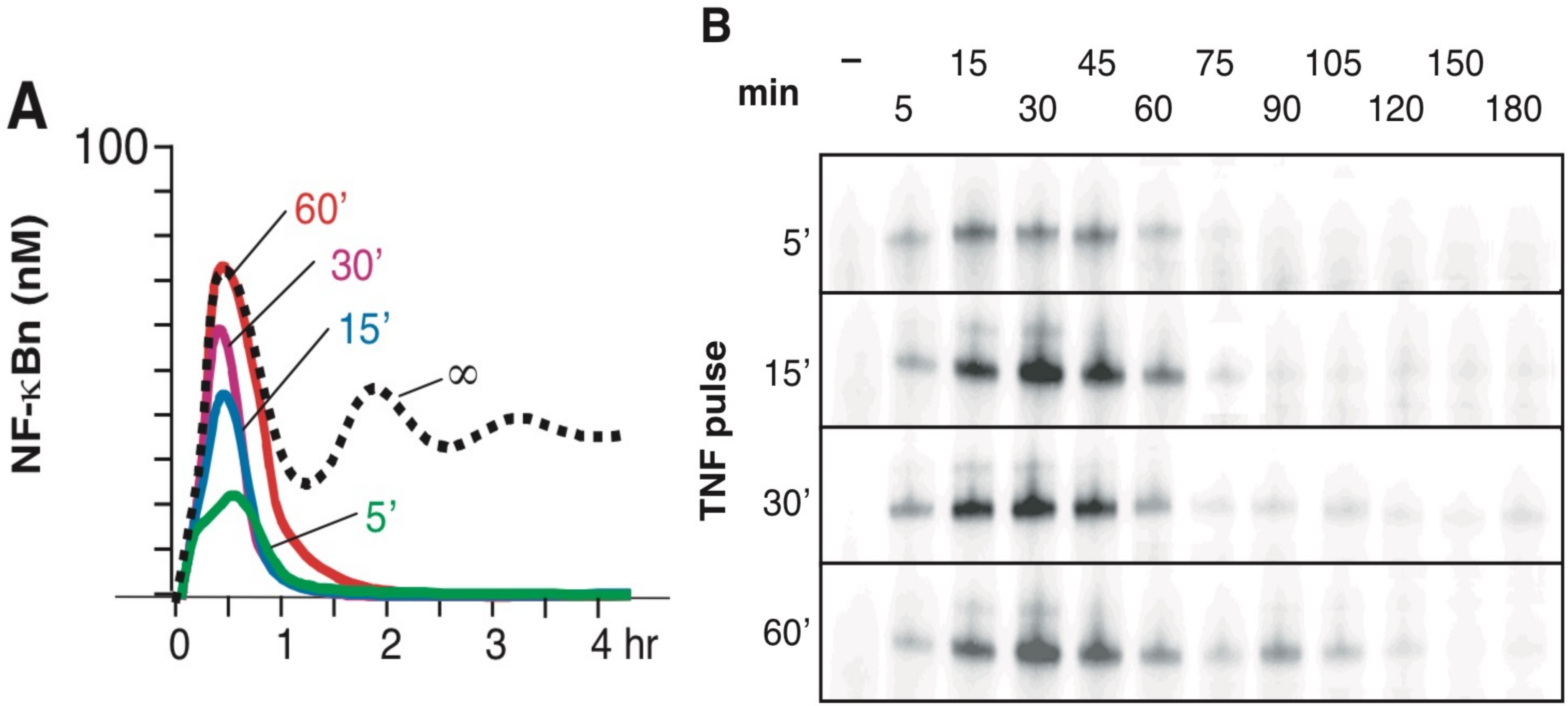
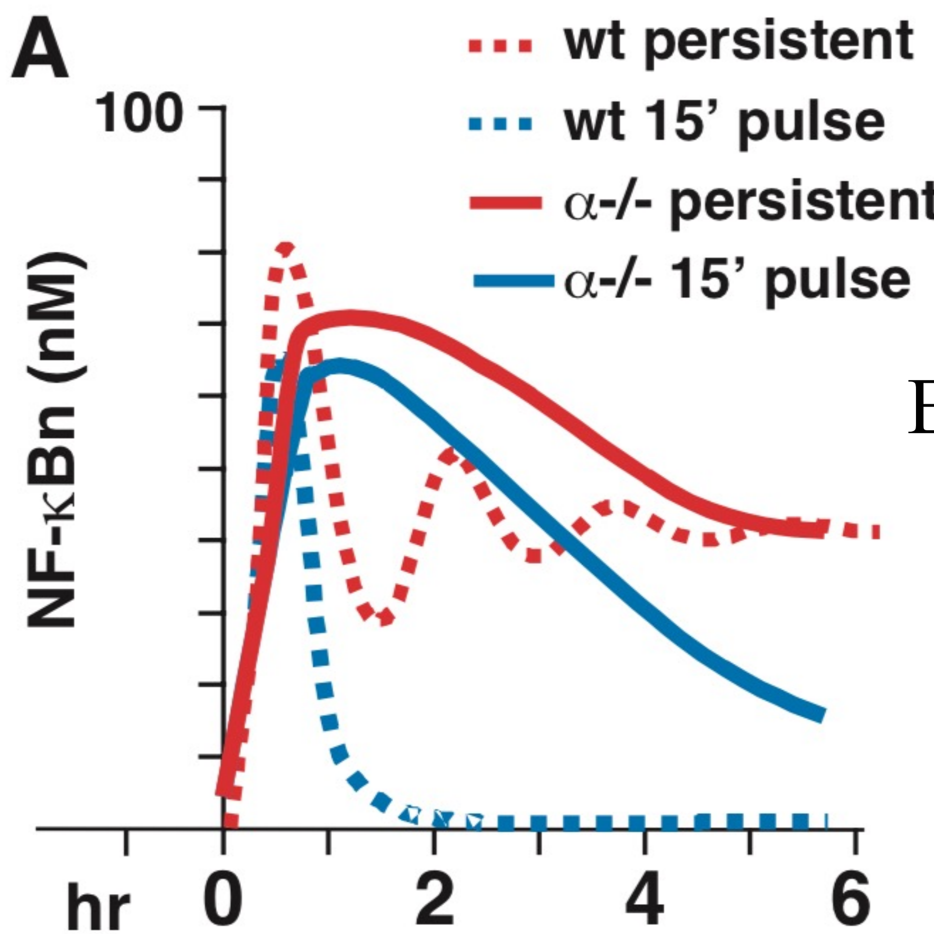


Figure 3

NF-κB Signal in WT Shows Bimodal Response

The Bimodal Response Requires IκBα



Effect of IκBα$^{-/-}$

Figure 4

RANTES Activation Requires Persistent TNFα Stimulation

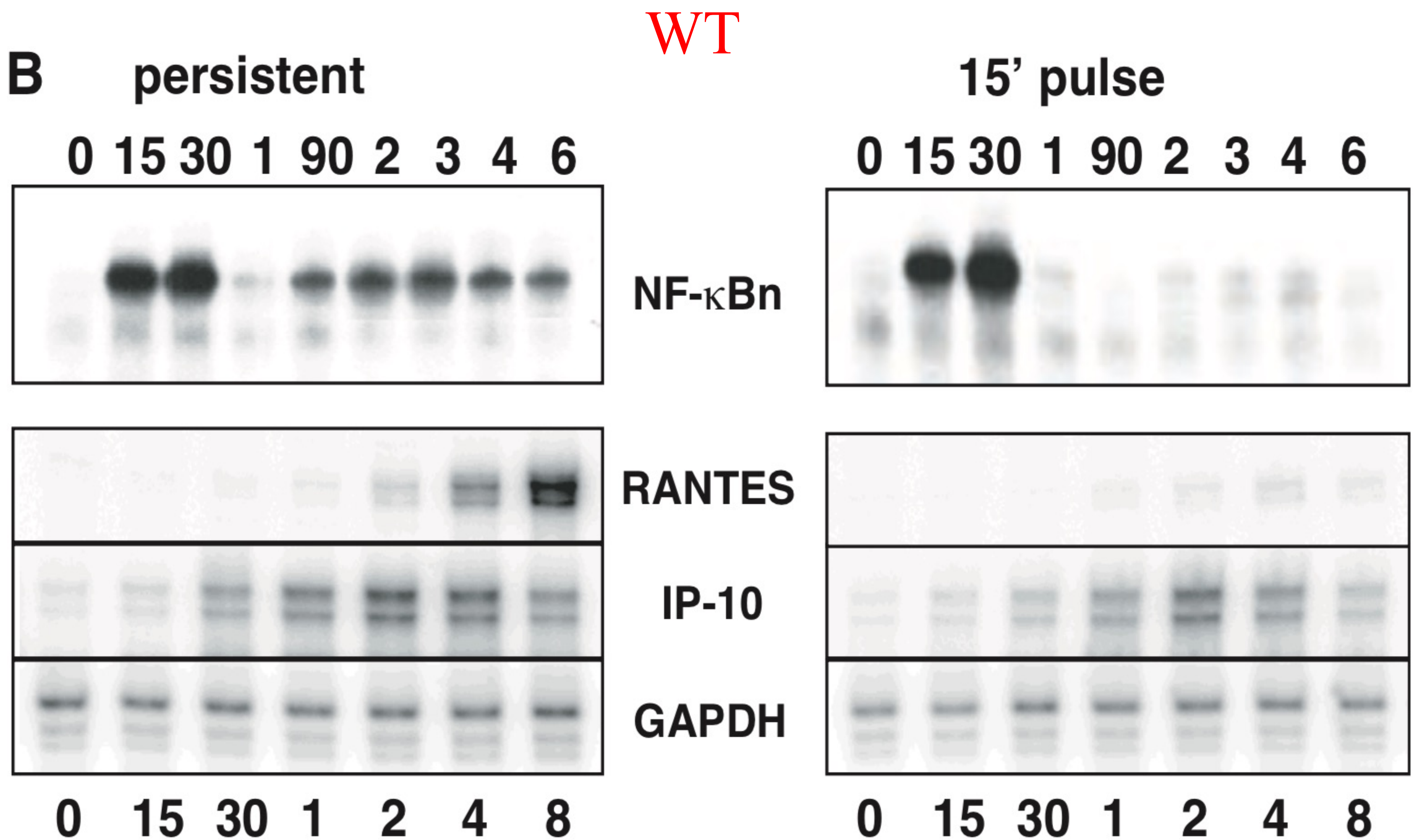


Figure 4

RANTES: CCL5
IP-10: CXCL10

RANTES Activation Requires Persistent TNFα Stimulation

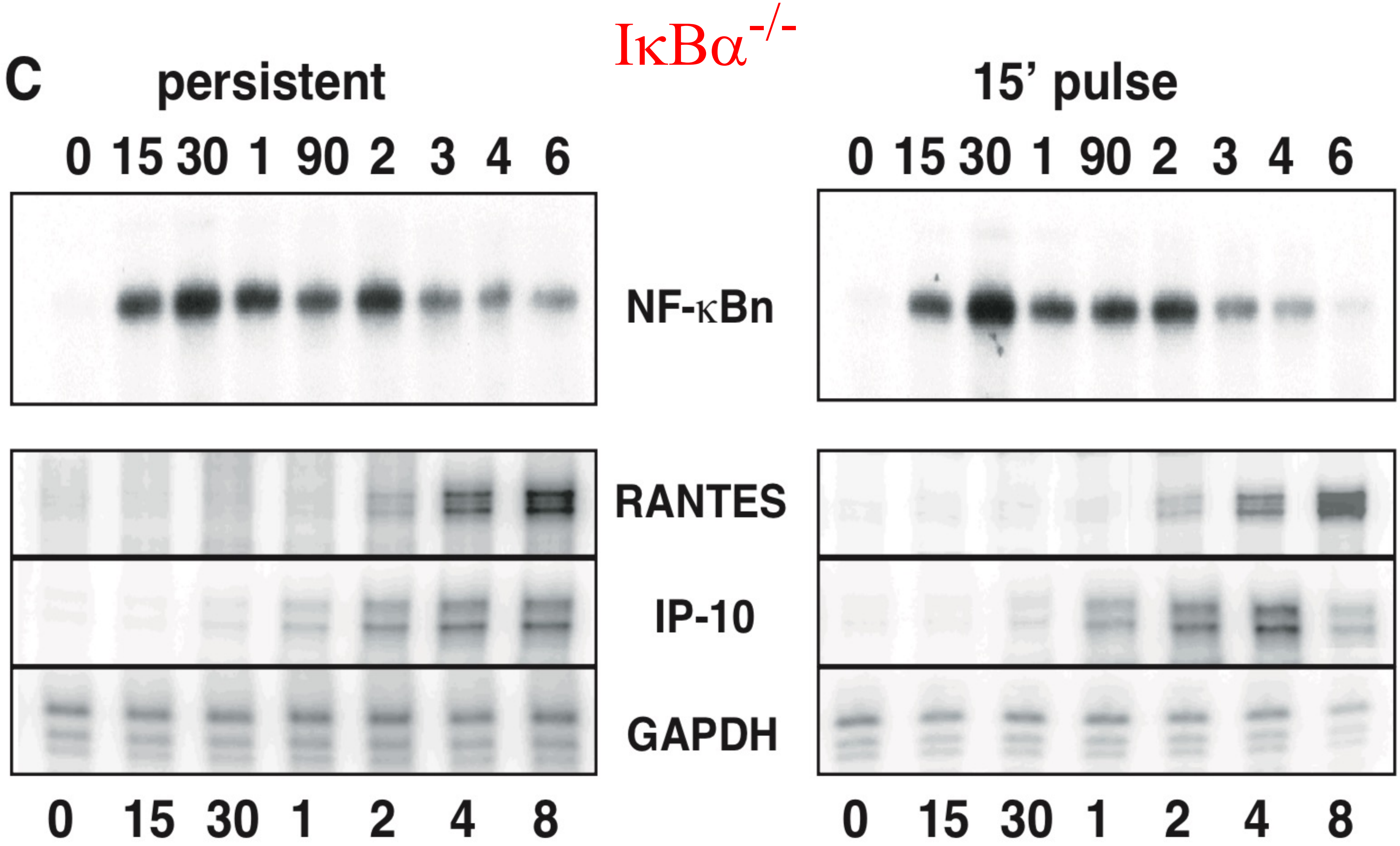


Figure 4

RANTES: CCL5
IP-10: CXCL10

Negative Feedback Motif of NF-κB Signaling Pathway

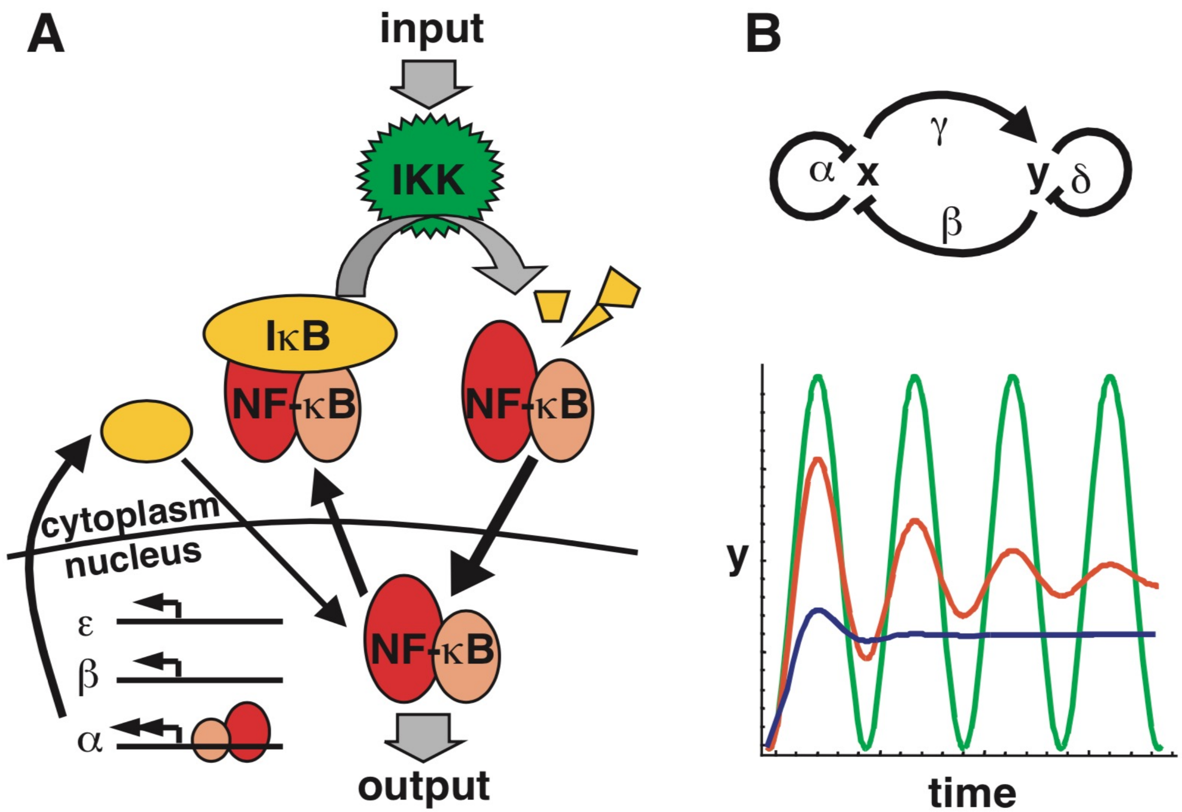


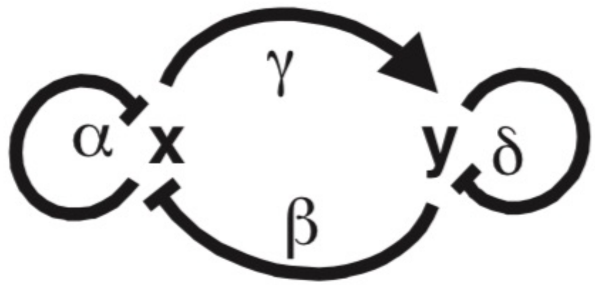
Figure 1

3 IκBα/β/ε interact with NF-κB

3 IκBα/β/ε interact with IKK

NF-κB translocation

Negative Feedback Motif of NF-κB Signaling Pathway



x: NF-κB
y: IκBα

$$\dot{x} = S - \alpha x - \beta y,$$
$$\dot{y} = \gamma x - \delta y,$$

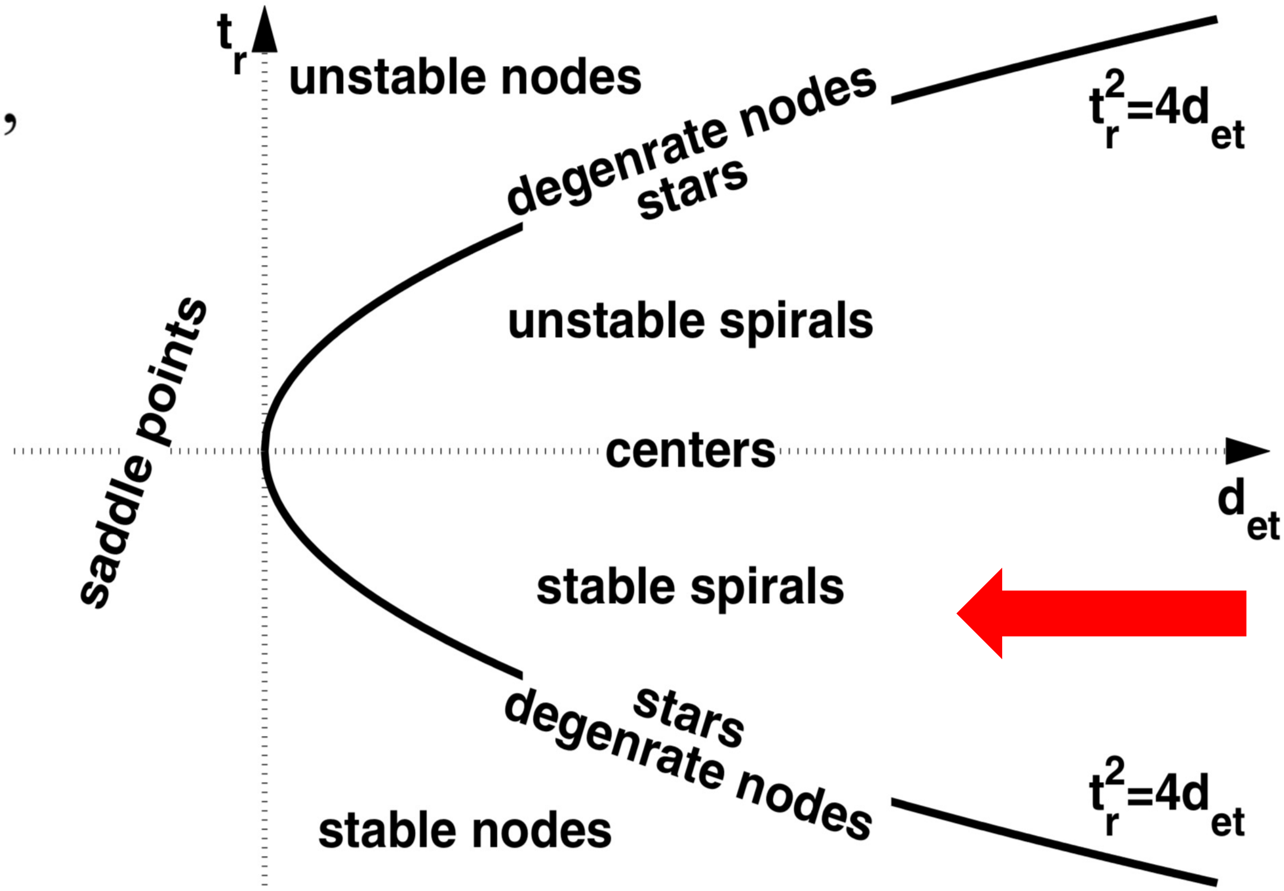
$$J = \begin{vmatrix} -\alpha & -\beta \\ \gamma & -\delta \end{vmatrix}$$

Classification of 2D ODE Linear Systems

$$\dot{x} = S - \alpha x - \beta y,$$
$$\dot{y} = \gamma x - \delta y,$$

$$J = \begin{vmatrix} -\alpha & -\beta \\ \gamma & -\delta \end{vmatrix}$$

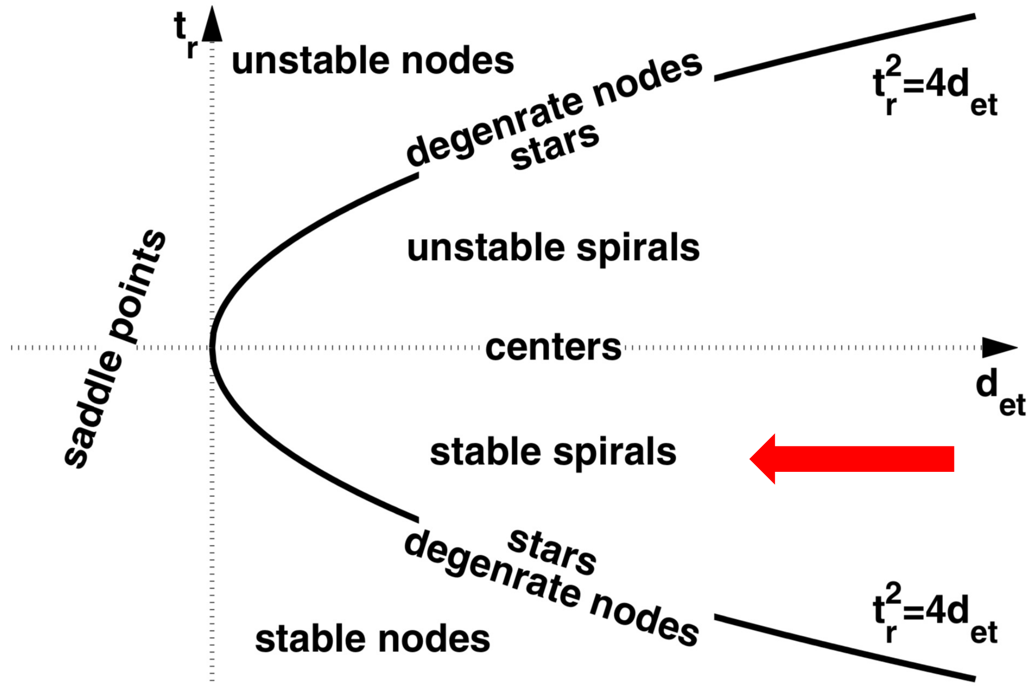
$$t_r = -(\alpha + \delta)$$
$$d_{et} = \alpha\delta + \beta\gamma$$

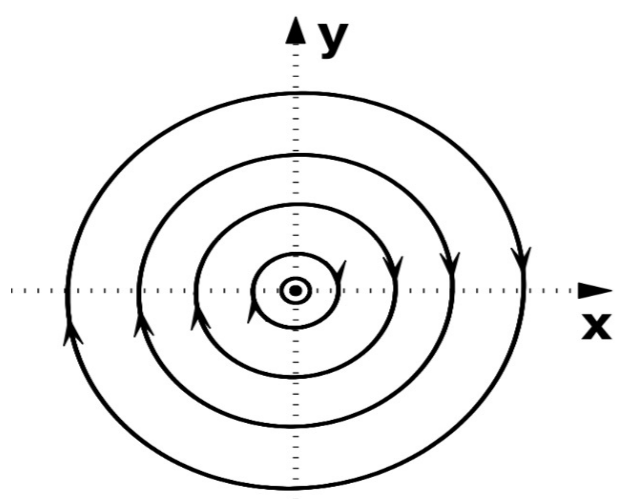


$$\lambda_{1,2} = \frac{1}{2}\{t_r \pm \sqrt{t_r^2 - 4\,d_{et}}\}$$

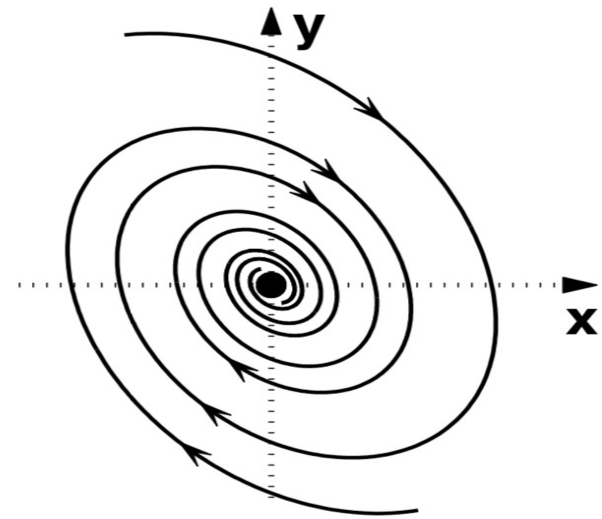
$$t_r = \lambda_1 + \lambda_2$$
$$d_{et} = \lambda_1 \lambda_2$$

Classification of 2D ODE Linear Systems



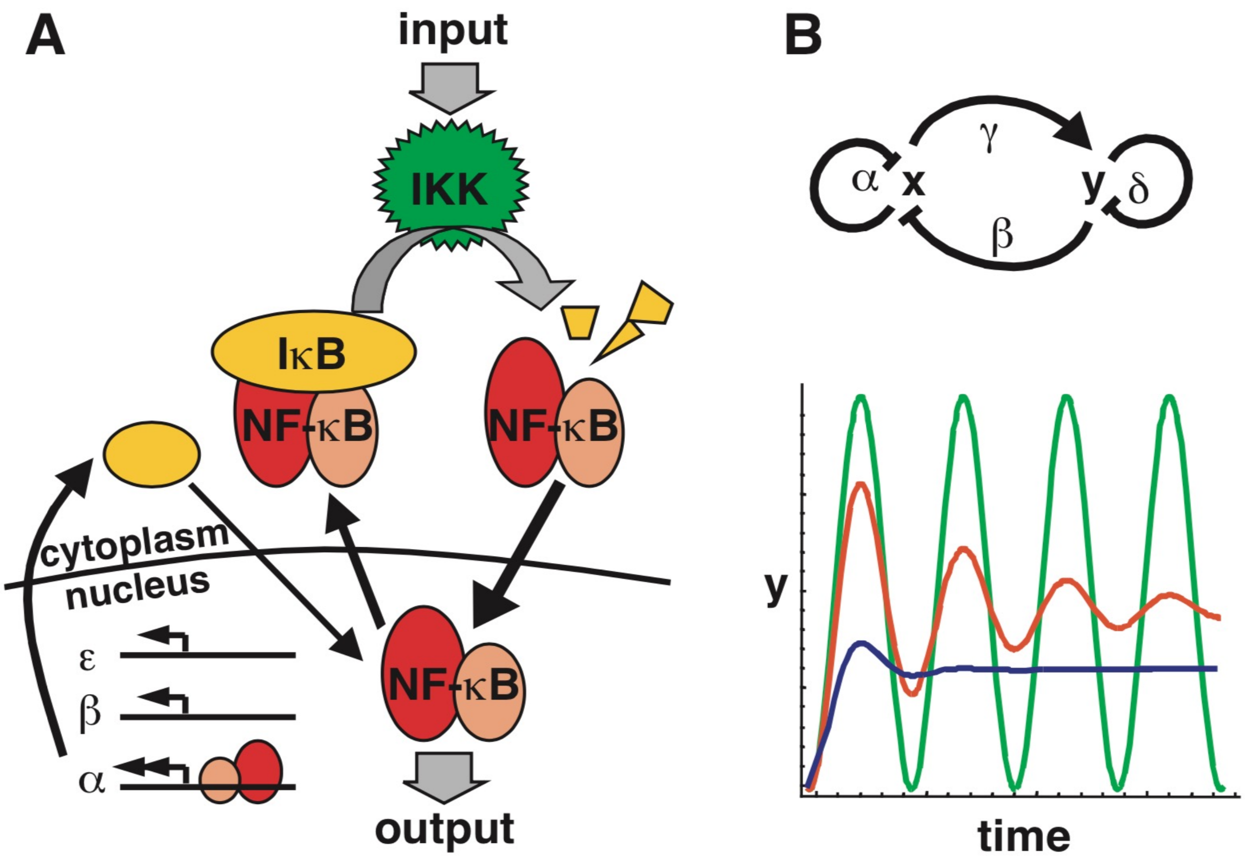


center



stable spiral

Negative Feedback Motif of NF-κB Signaling Pathway

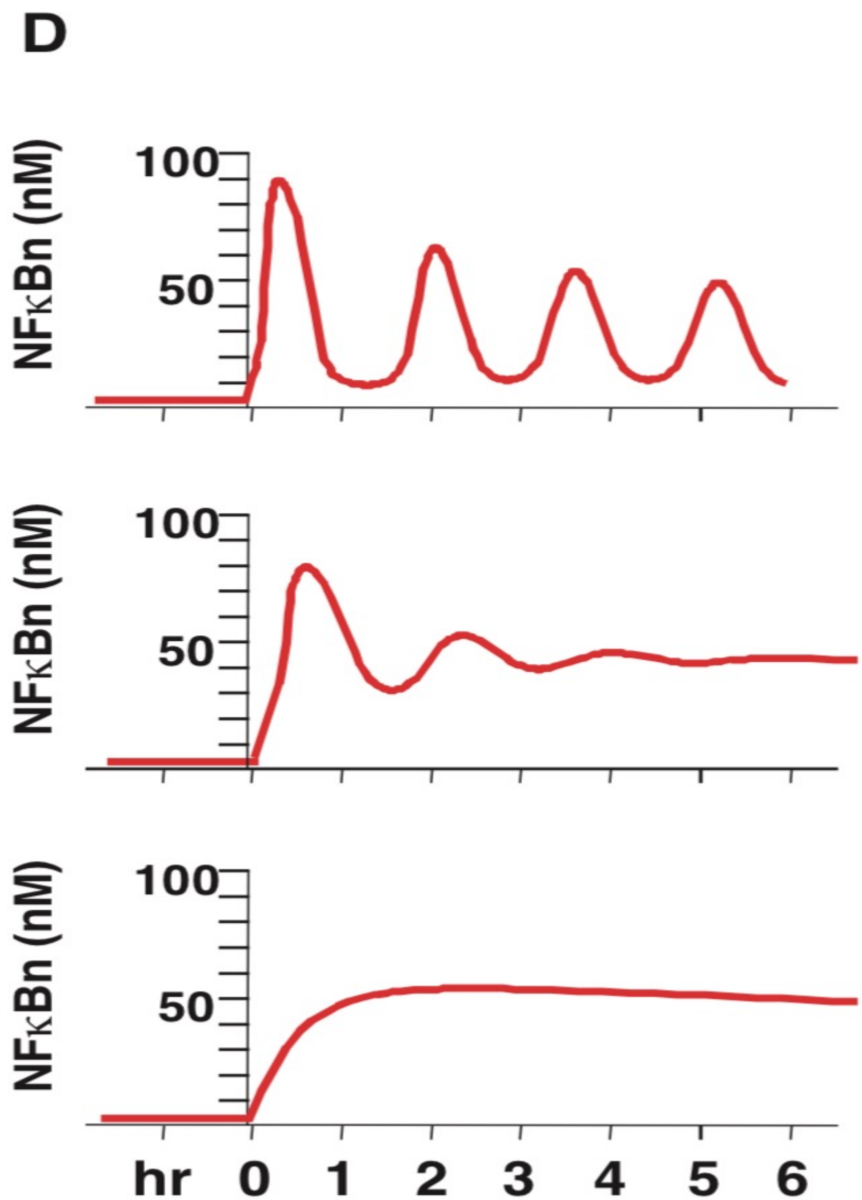


oscillation: center

damped oscillation: stable spiral

over-damped oscillation: stable spiral

Negative Feedback Motif of NF-κB Signaling Pathway



Effect of IκBβ and IκBε

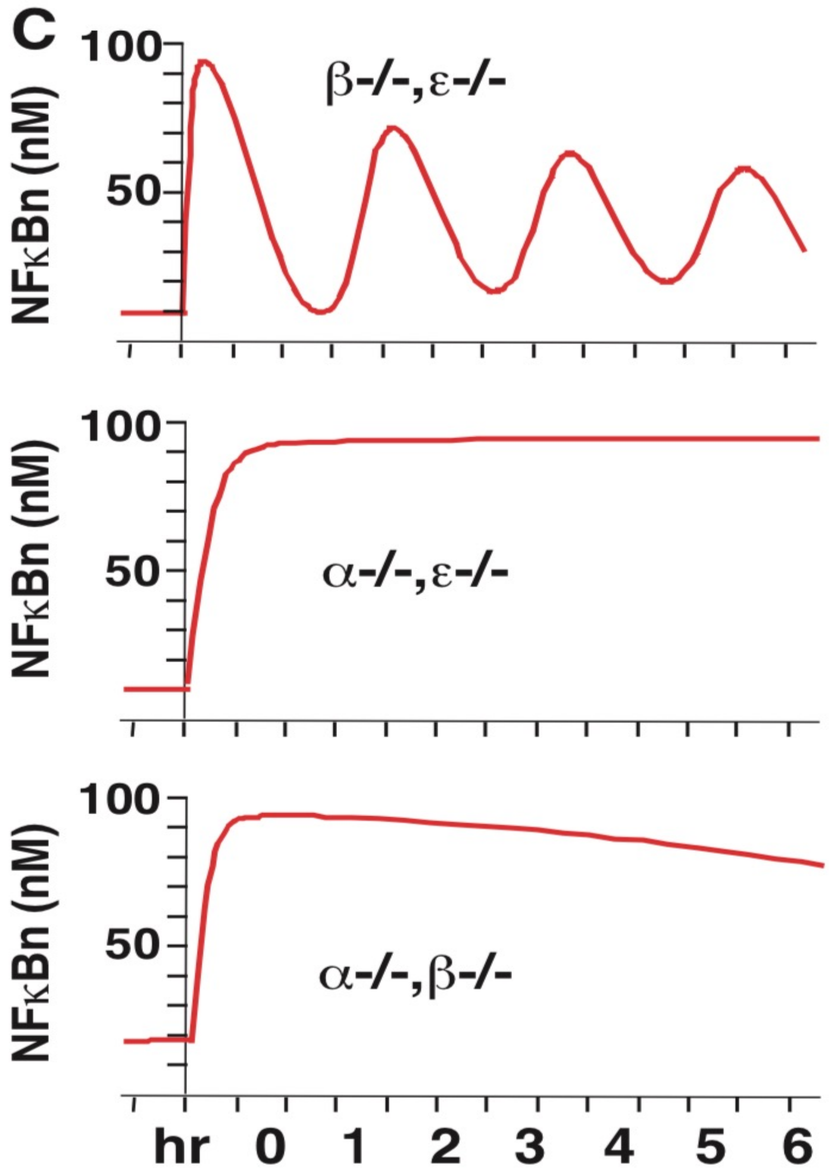
Reduced by 5-fold
slightly damped oscillation

Baseline in WT
damped oscillation

Increased by 7-fold
over-damped oscillation

Figure 2

Negative Feedback Motif of NF-κB Signaling Pathway



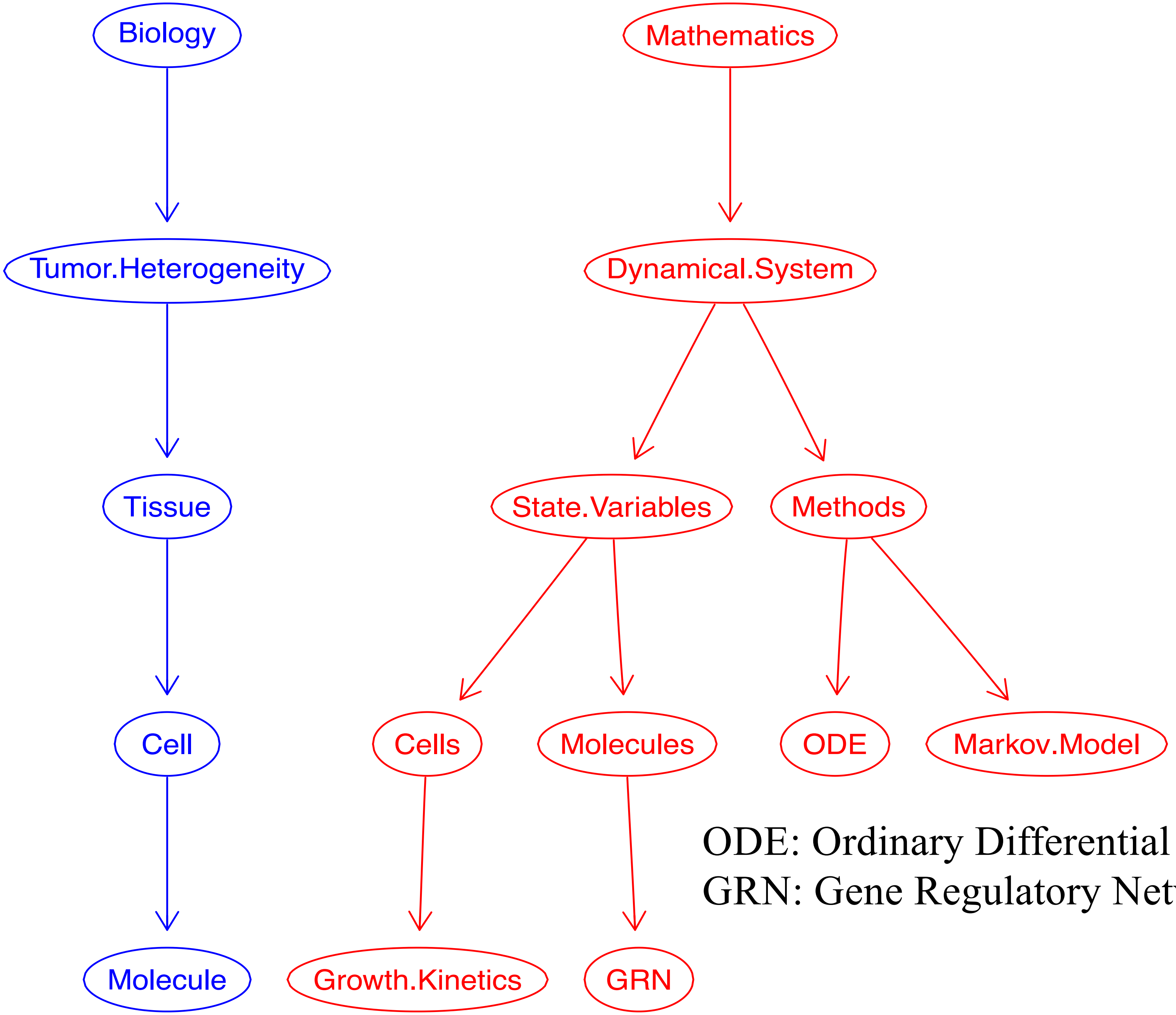
slightly damped oscillation

IκBα controls oscillation
no oscillation

IκBα controls oscillation
no oscillation

Figure 2

Understanding Biology with Mathematical Modeling



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GRN: Gene Regulatory Network