

Dynamics of gene regulatory circuits

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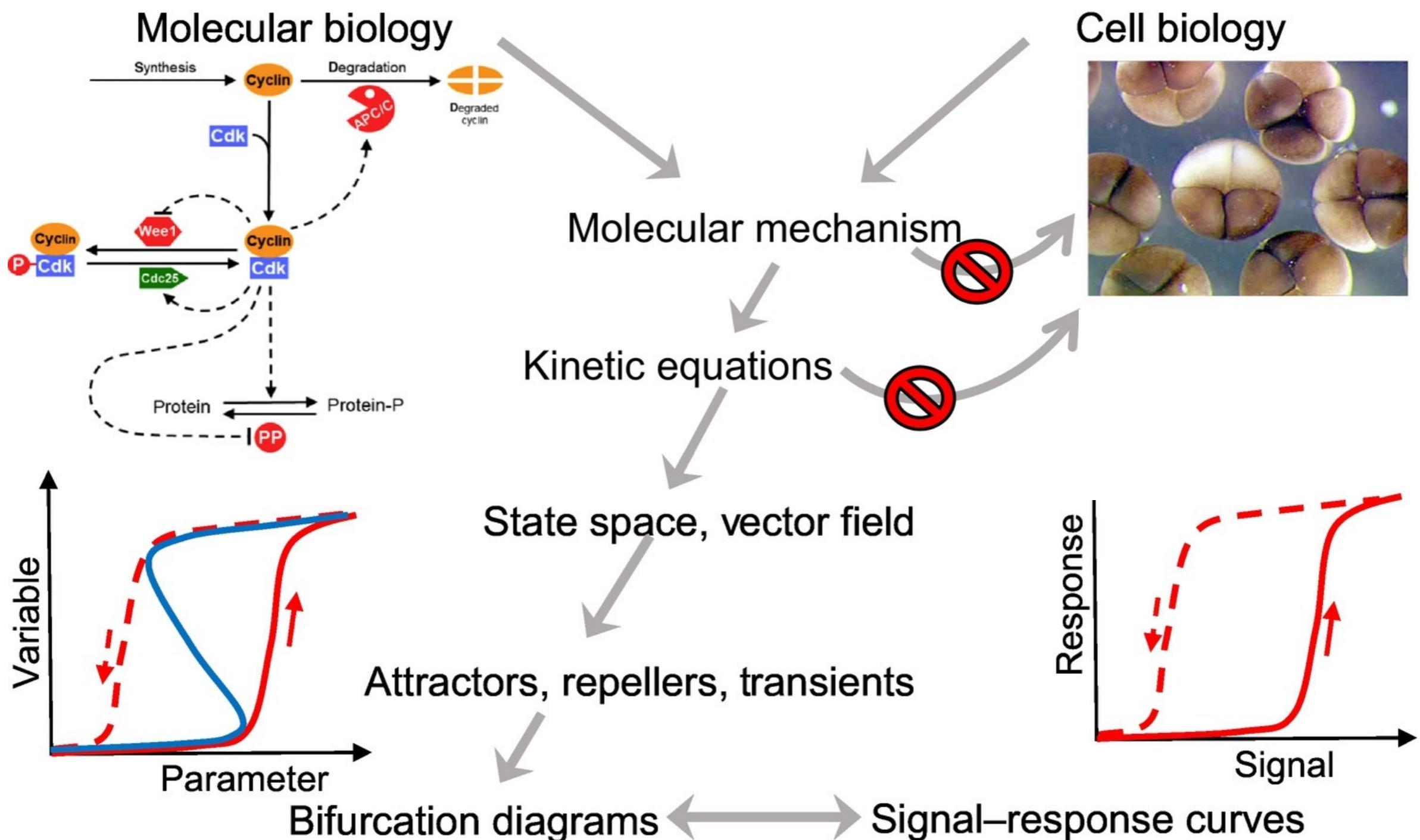
Dynamics of gene regulatory circuits

1. Gene circuit dynamics
2. Dissecting a genetic circuit
3. Noise in genetic circuits

The challenges of systems biology

- Molecular interactions are:
 - ▶ usually nonlinear
 - ▶ highly abundant
 - ▶ strongly dynamic

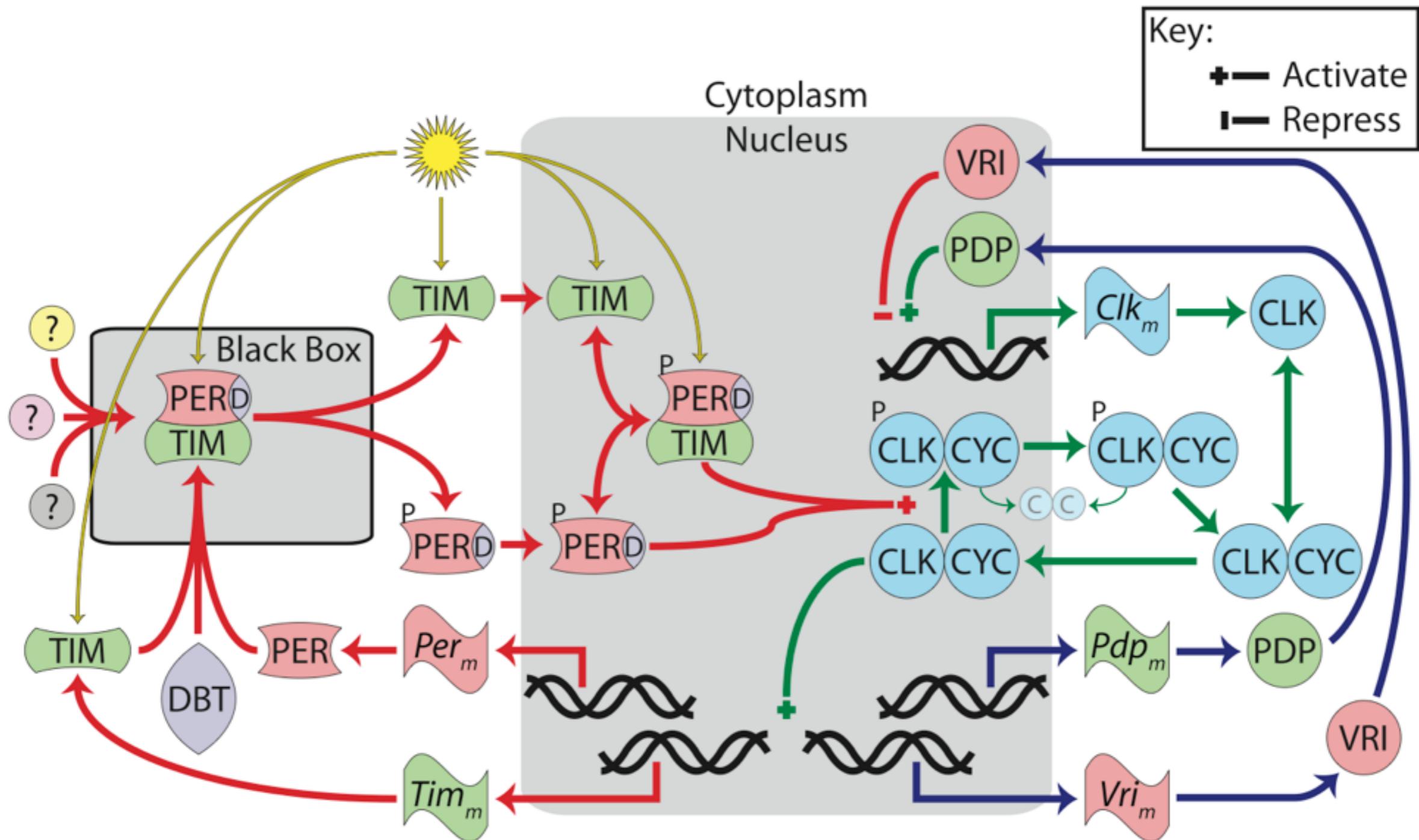
A dynamical paradigm for molecular cell biology



Trends in Cell Biology

Tyson and Novak, "A dynamical paradigm for molecular cell biology"
Trends in Cell Biology, vol. 30, p. 504 (2020)

Gene regulatory networks are large

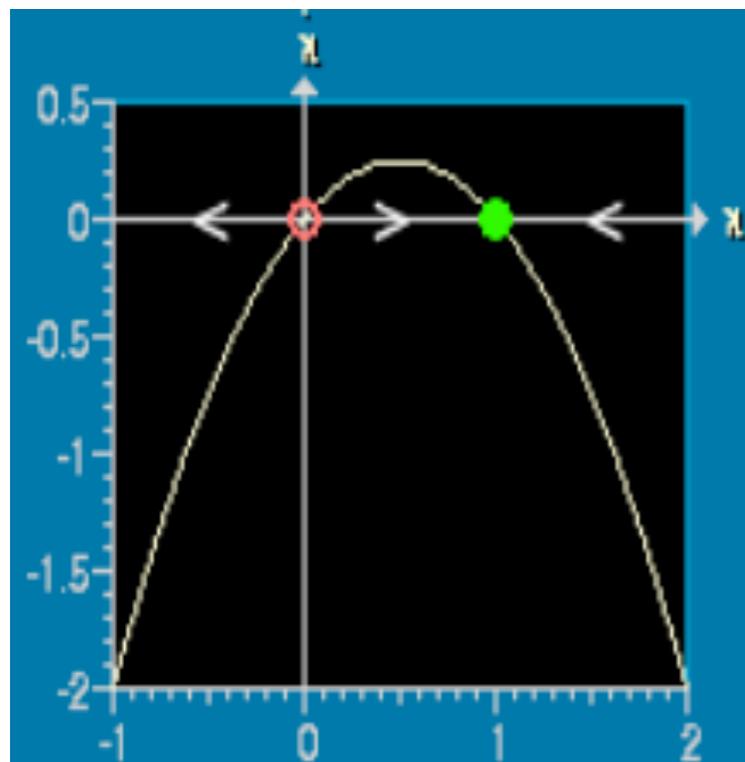


Model for circadian oscillations in *Drosophila*

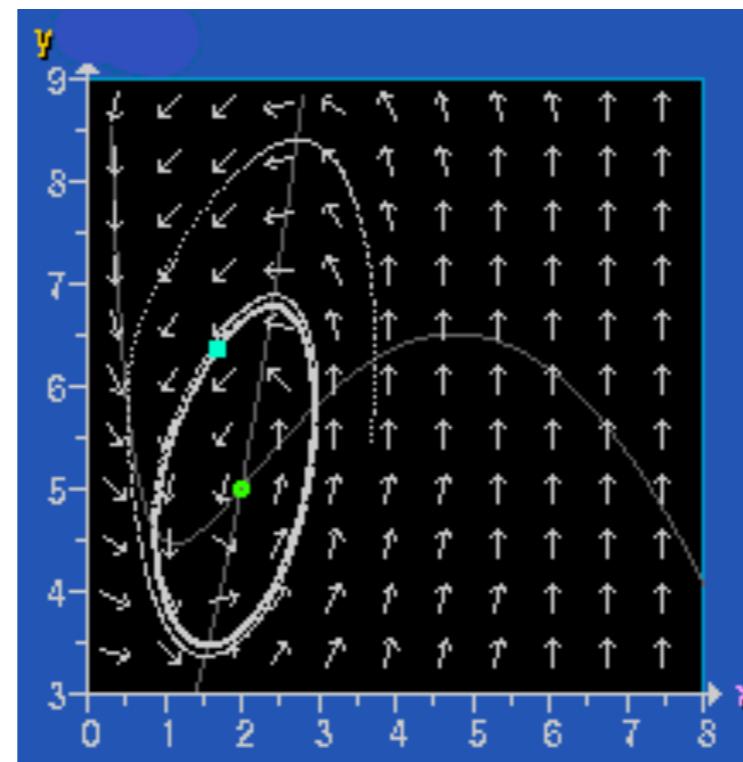
Kuczenski, Hong, JGO and Kelvin, PLOS Comp. Biol. 3, e154 (2007)

Requirements for dynamical behavior:

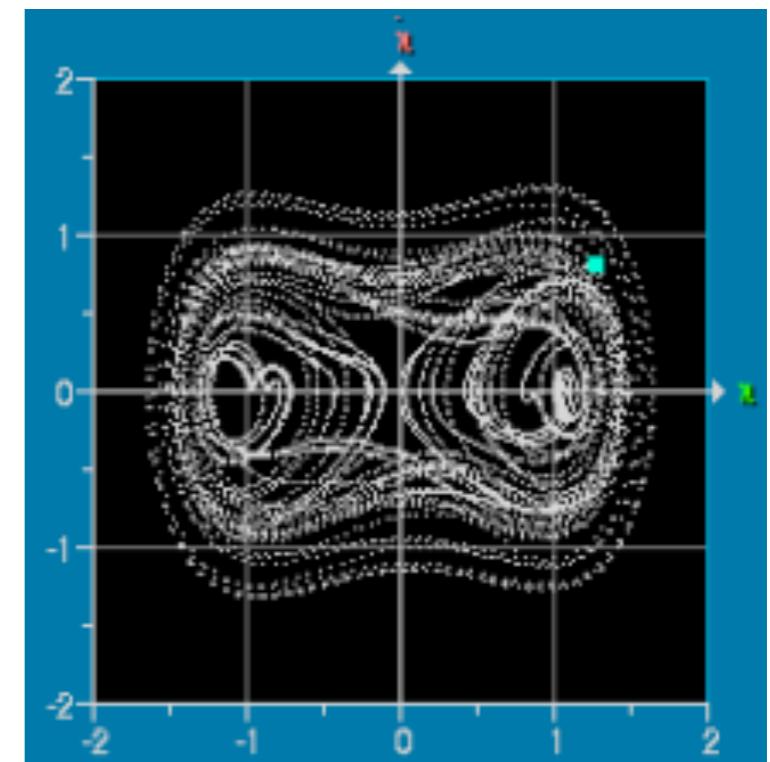
- 1 degree of freedom \rightarrow monotonic growth/decay
- 2 degrees of freedom \rightarrow oscillations
- 3 degrees of freedom \rightarrow chaos



$d = 1$

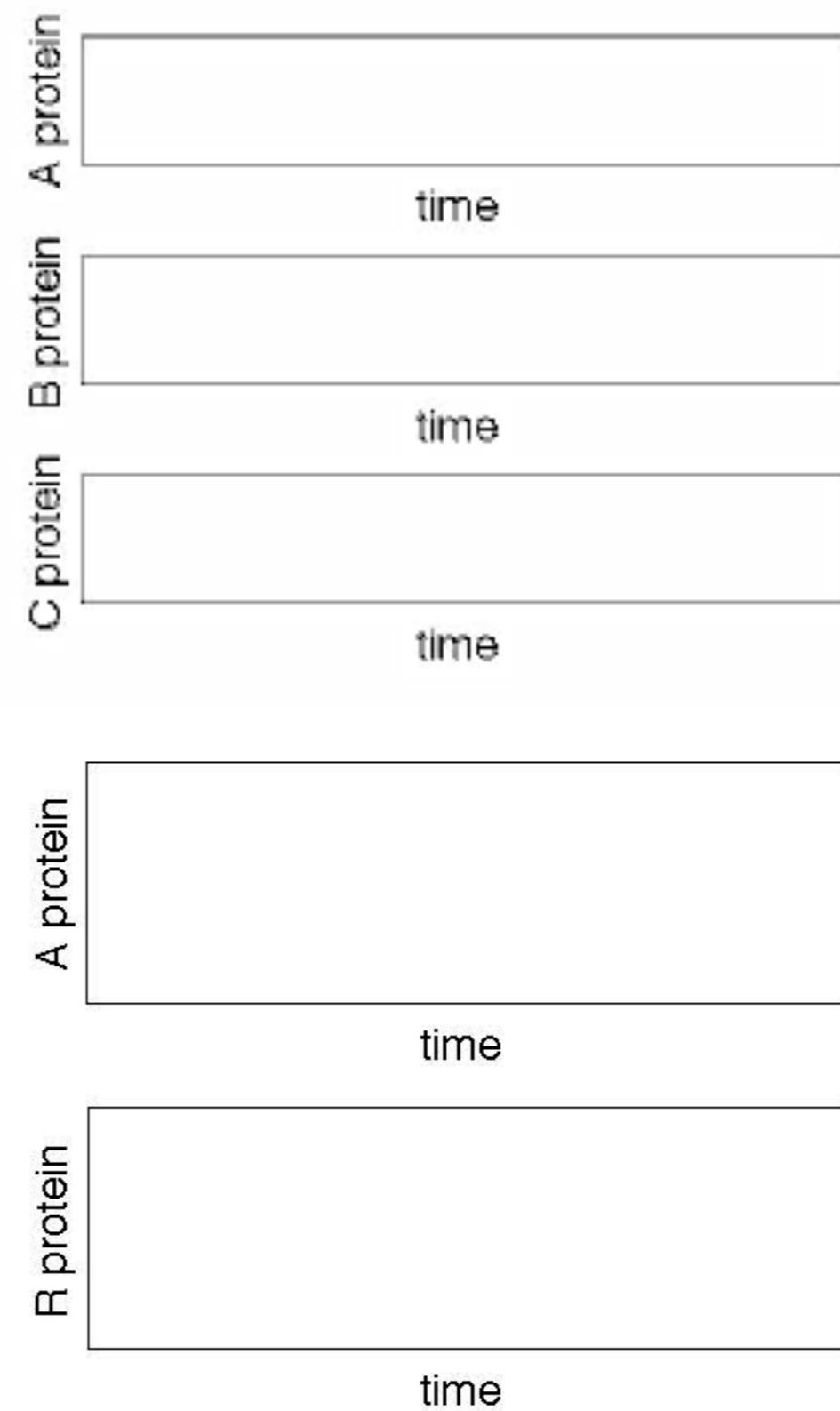
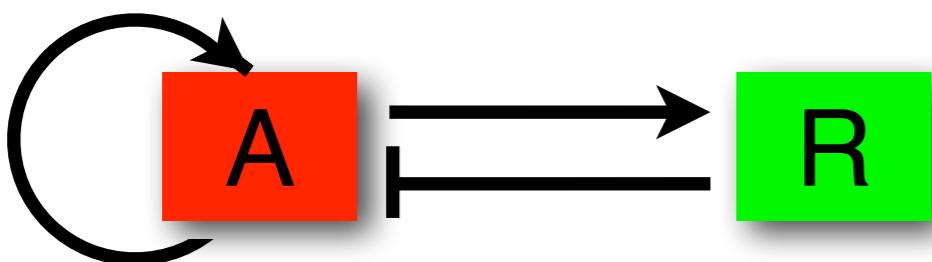
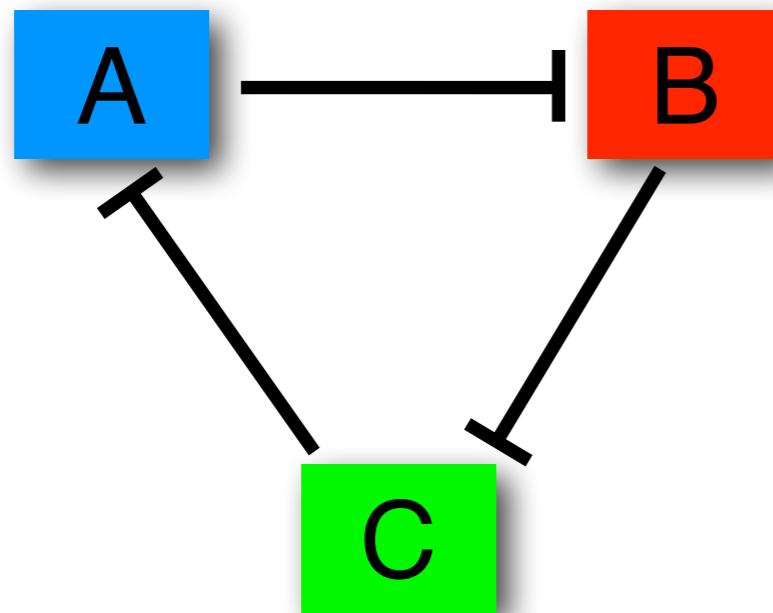


$d = 2$

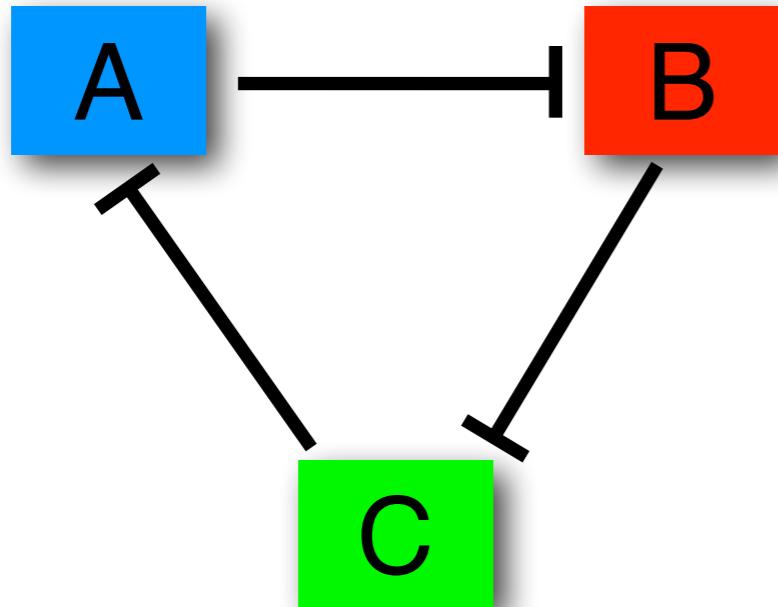


$d = 3$

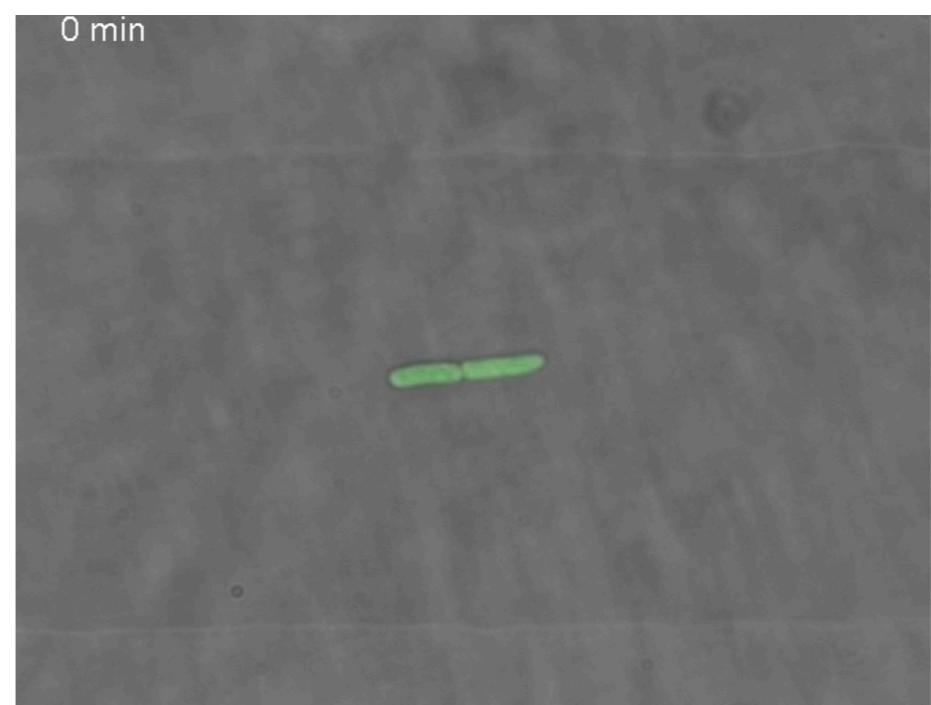
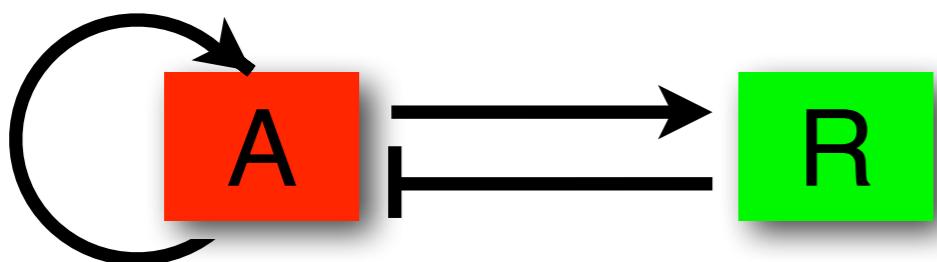
Synthetic oscillators



Synthetic oscillators



Elowitz and Leibler, *Nature* **403**, 335 (2000)

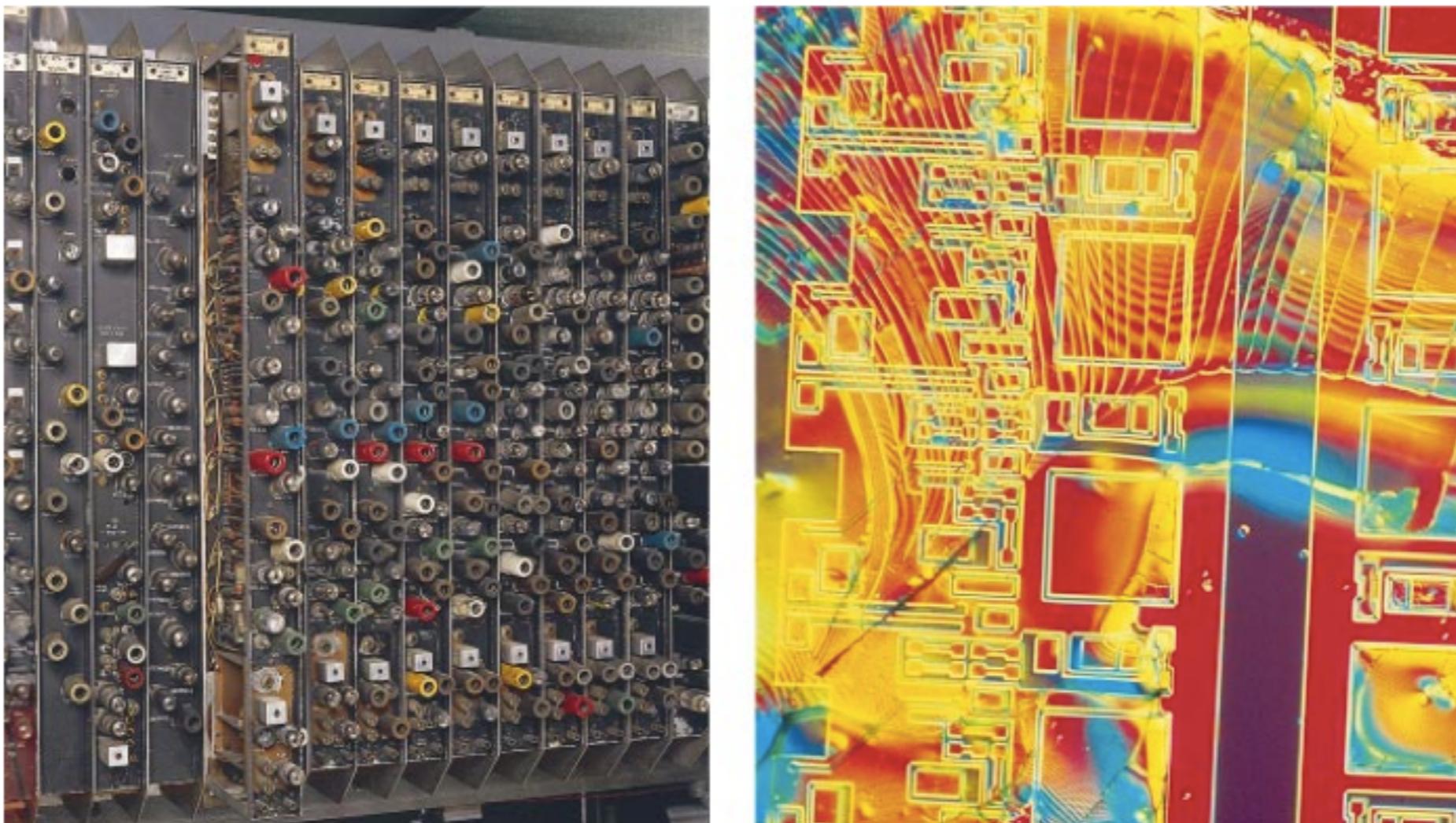


Stricker et al, *Nature* **456**, 516 (2008)

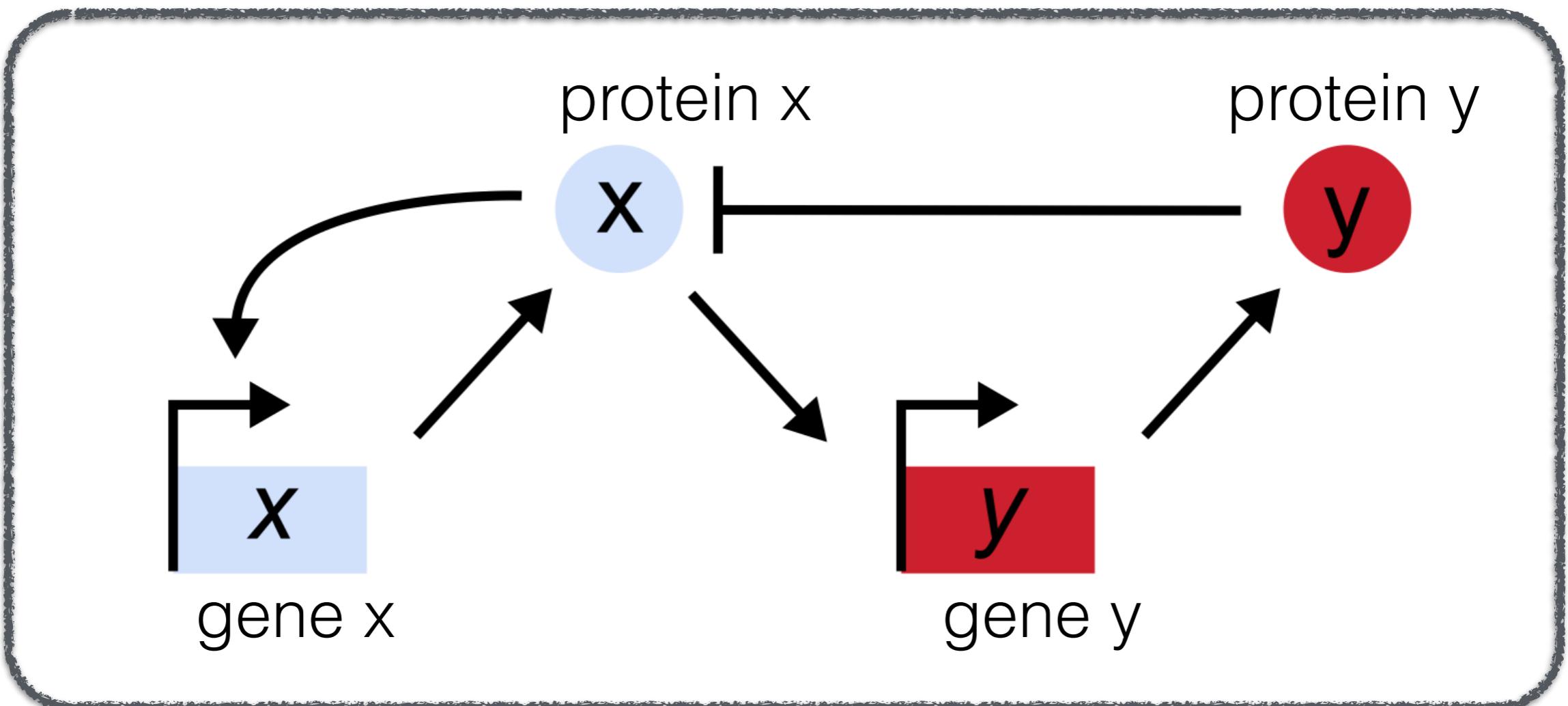
From molecular to modular cell biology

Leland H. Hartwell, John J. Hopfield, Stanislas Leibler and Andrew W. Murray

Cellular functions, such as signal transmission, are carried out by 'modules' made up of many species of interacting molecules. Understanding how modules work has depended on combining phenomenological analysis with molecular studies. General principles that govern the structure and behaviour of modules may be discovered with help from synthetic sciences such as engineering and computer science, from stronger interactions between experiment and theory in cell biology, and from an appreciation of evolutionary constraints.



Gene circuits

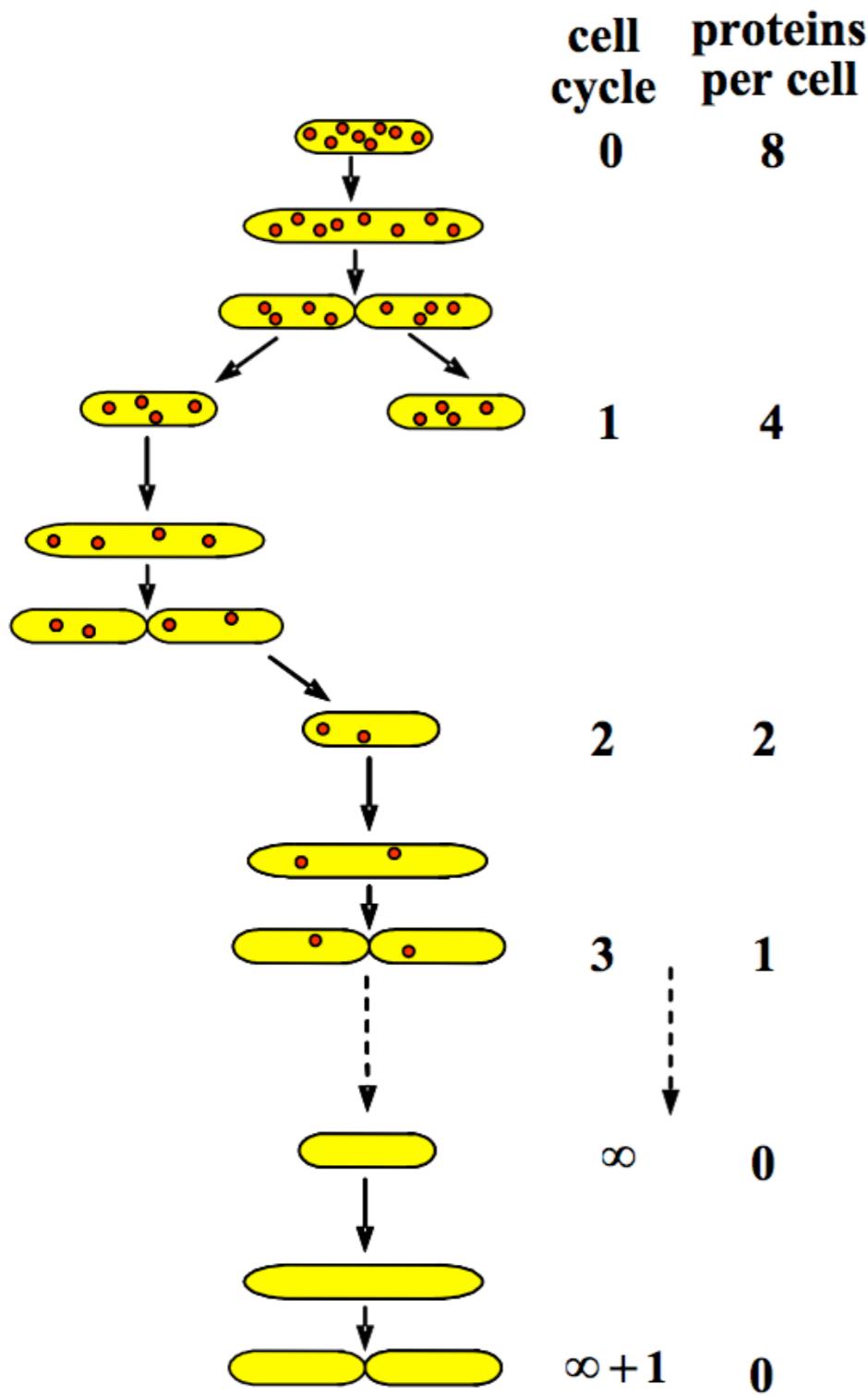


→ activation

→ repression

Modeling gene regulation

Modeling cell growth and protein dilution



- $N(t)$: number of cells in the population

$$\frac{dN}{dt} = \alpha N \implies N(t) = N_0 e^{\alpha t}$$

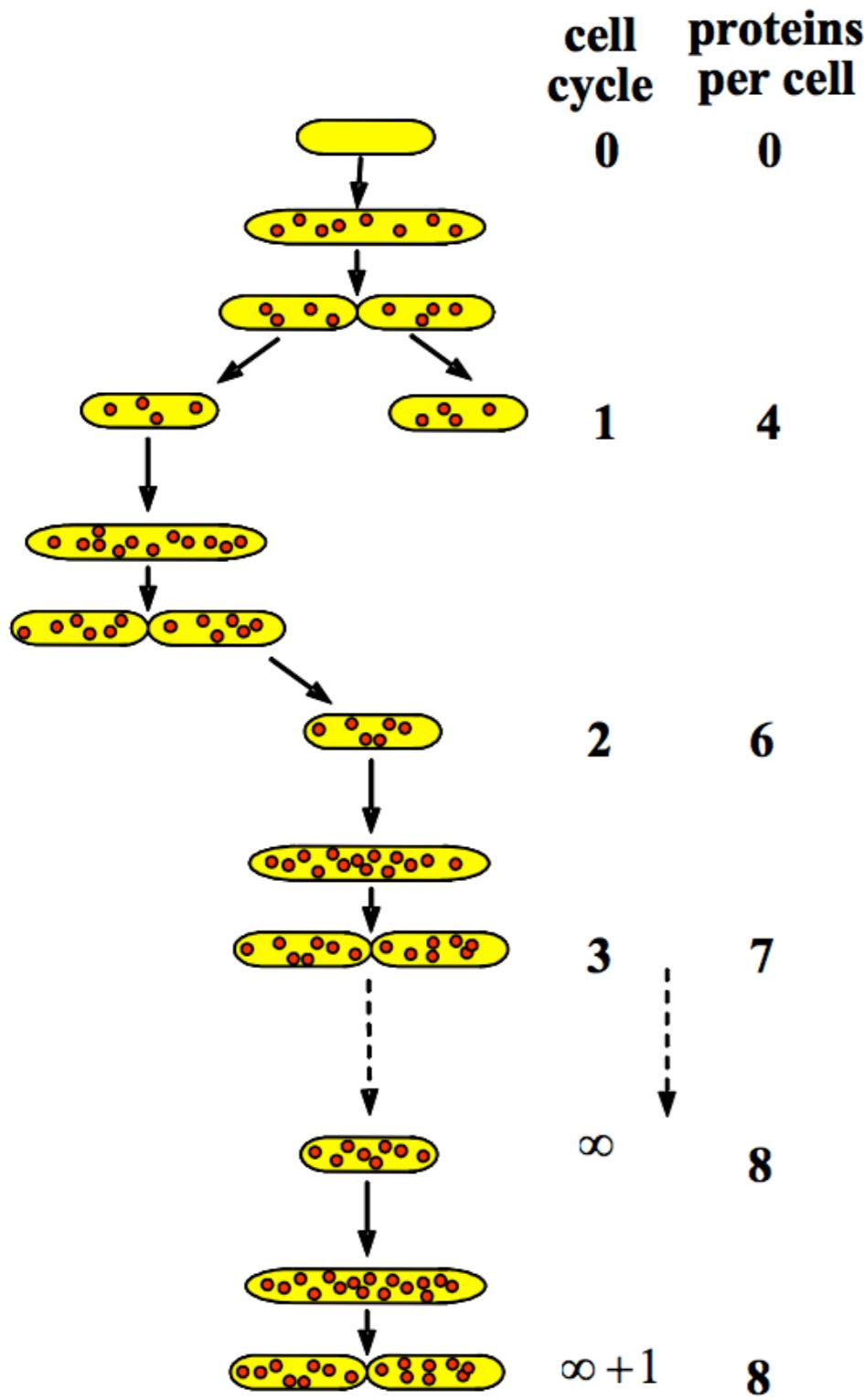
- $x(t)$: protein concentration

$$x(t) \equiv \frac{X_0}{N(t)} = \frac{X_0}{N_0} e^{-\alpha t} \implies \frac{dx}{dt} = -\alpha x$$

$$\alpha = \frac{\ln 2}{\tau} \quad (\tau: \text{cell cycle time})$$

[Nitzan Rosenfeld, “A math primer for the perplexed gene-expression-ist”]

Modeling constitutive protein production



Production rate A vs dilution rate a

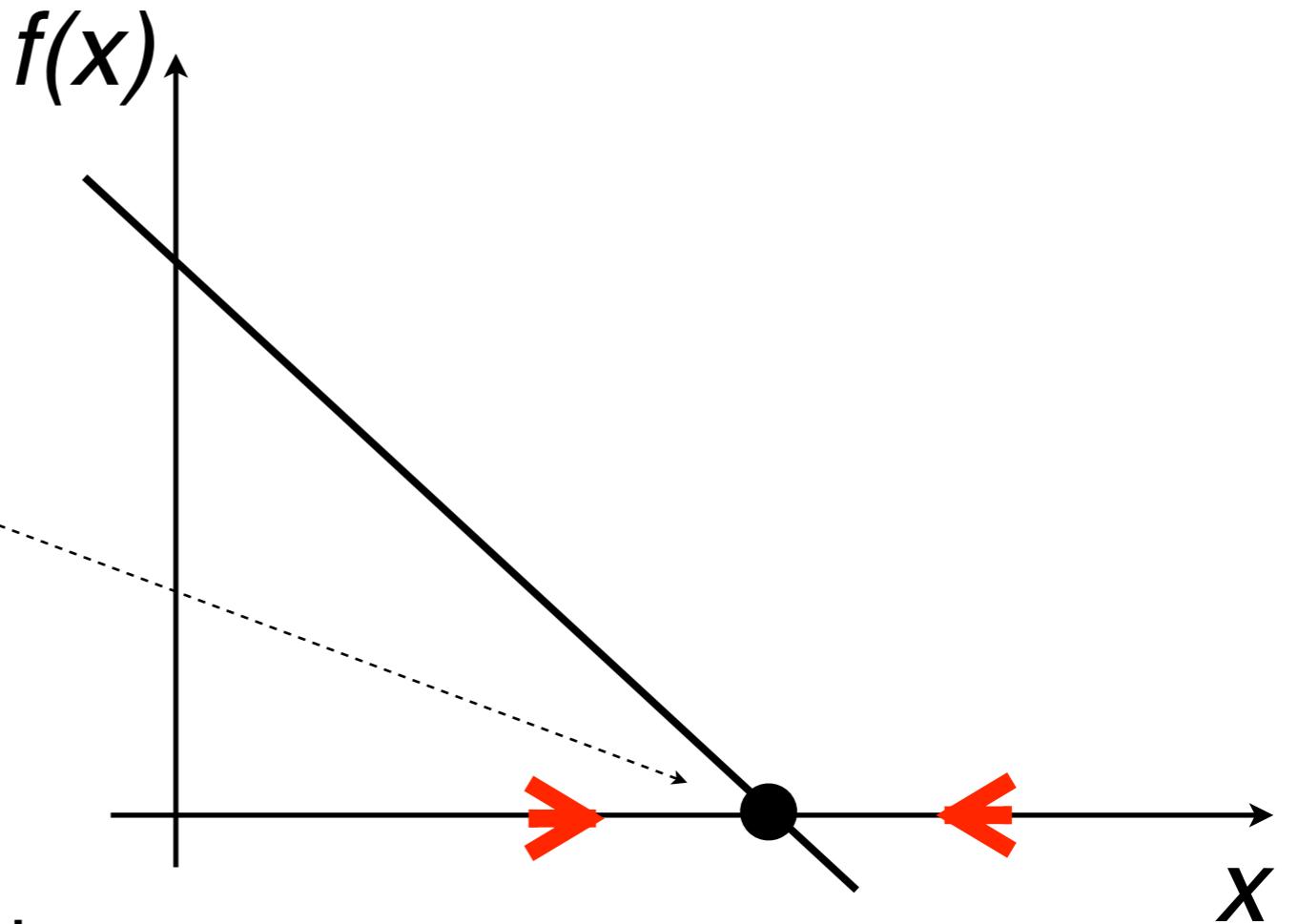
$$\frac{dx}{dt} = A - \alpha x$$

[Nitzan Rosenfeld, “A math primer for the perplexed gene-expression-ist”]

Phase line

$$\frac{dx}{dt} = f(x) = A - \alpha x$$

$f(x^*) = 0$ fixed point

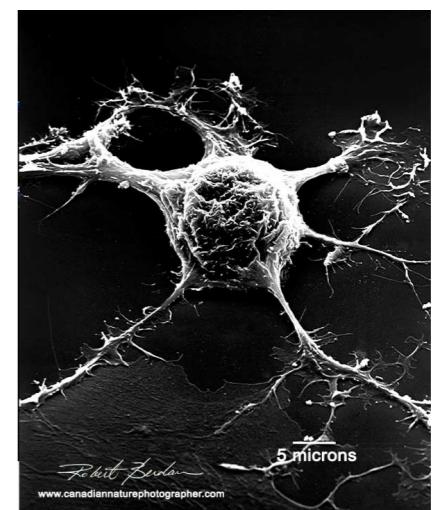
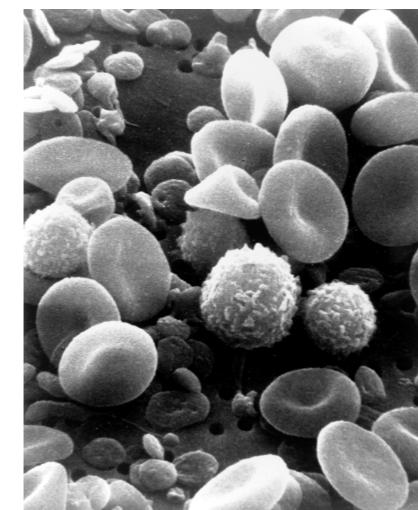
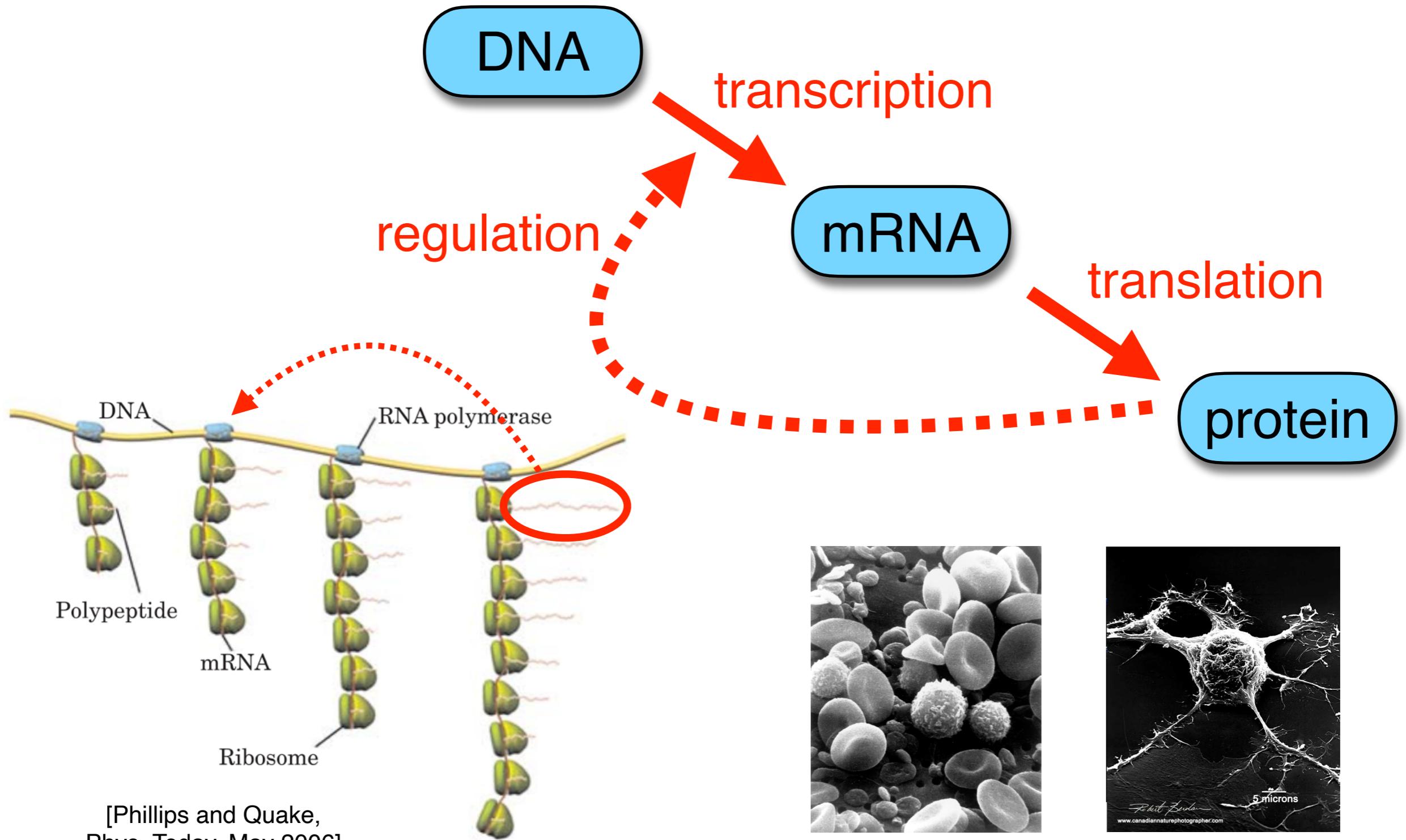


- Stability of the fixed point:

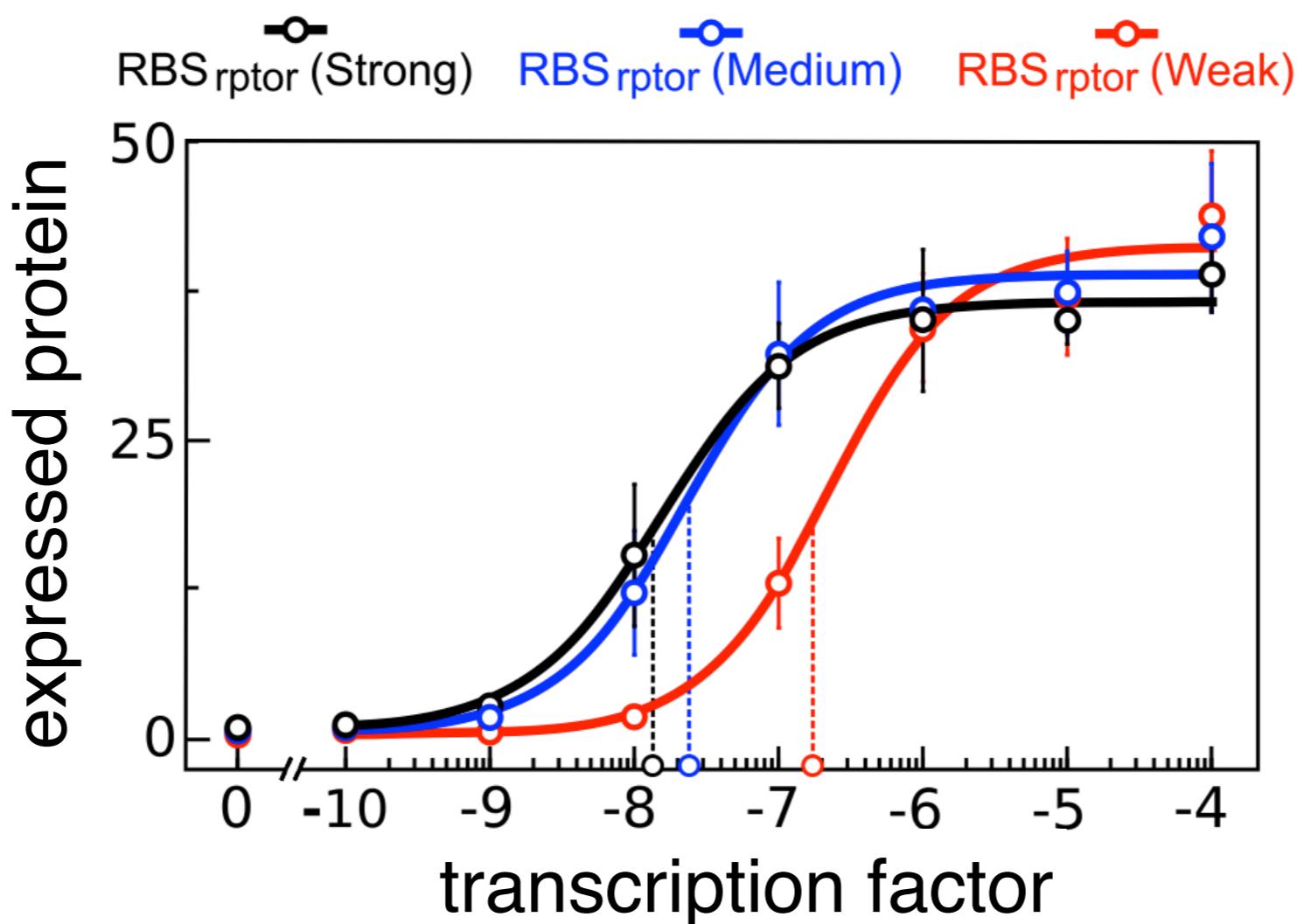
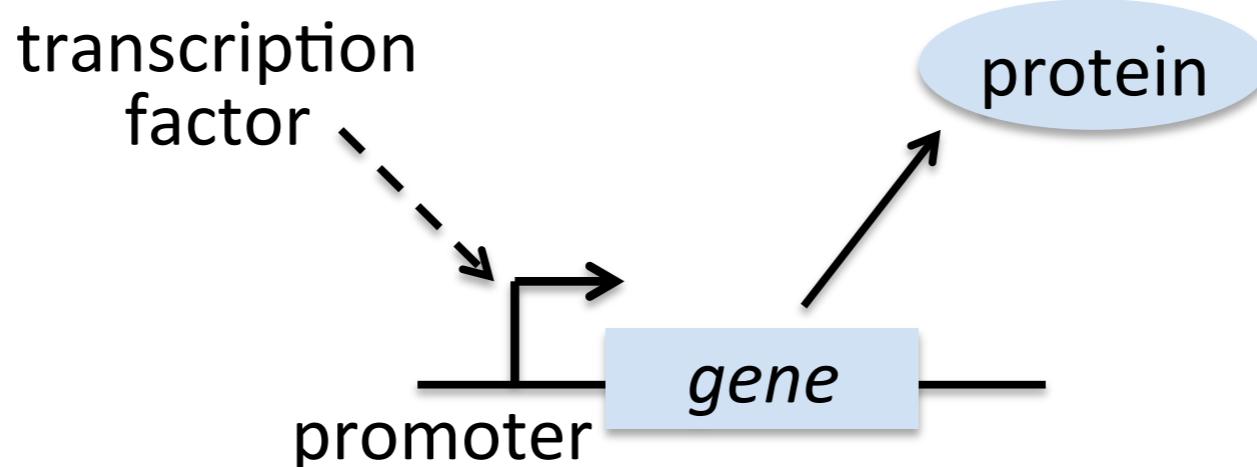
$$f'(x^*) < 0 \implies x^* \text{ stable}$$

$$f'(x^*) > 0 \implies x^* \text{ unstable}$$

Gene expression is usually regulated by transcription factors

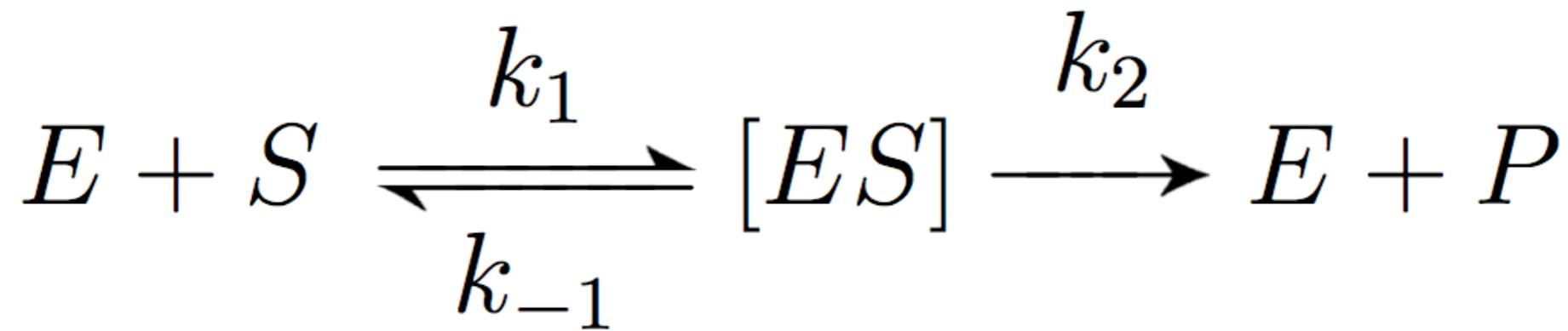


Gene expression is usually regulated by transcription factors



Carbonell-Ballester et al,
Nucleic Acid Res, 2014

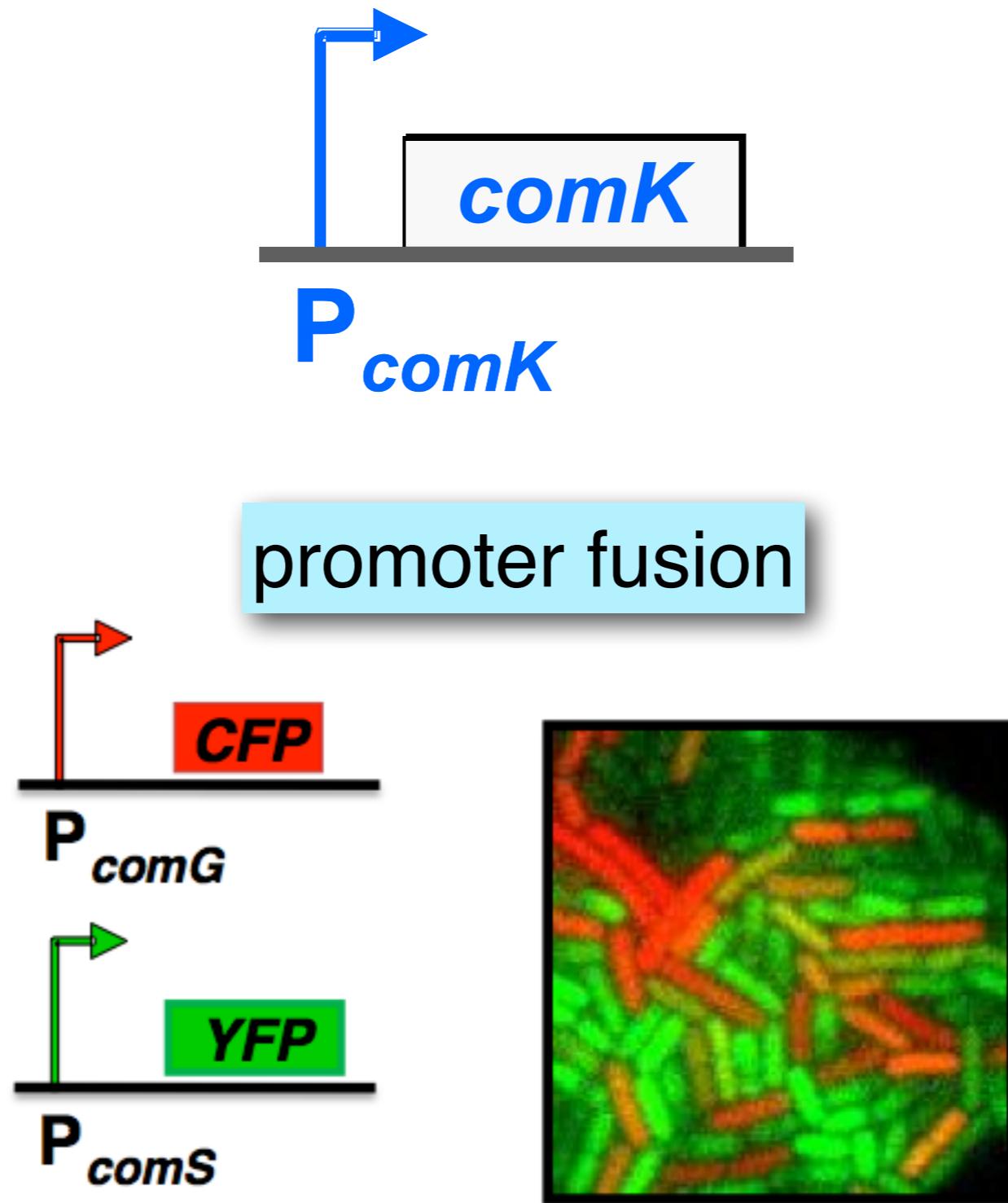
Basic regulation: Michaelis-Menten kinetics



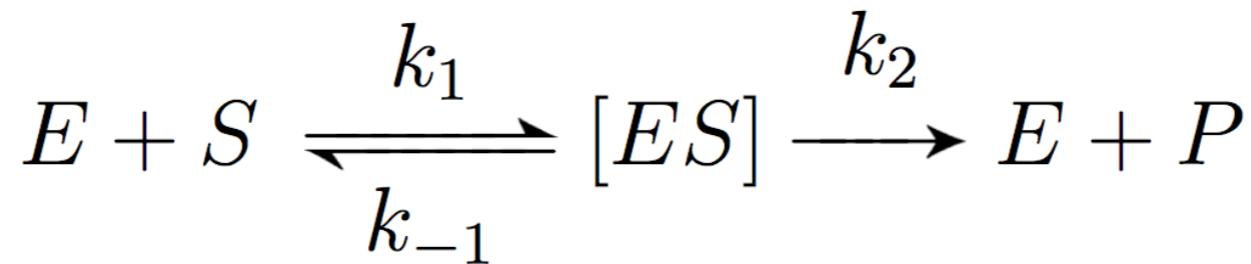
- **Enzymatic** regulation:
 - ◆ E: enzyme
 - ◆ S: substrate
 - ◆ P: product

- **Transcriptional** regulation:
 - ◆ E: DNA promoter
 - ◆ S: transcription factor
 - ◆ P: mRNA

The promoter: experiments



Transcriptional activation



- Evolution equation for the complex $[ES]$:

$$\frac{d[ES]}{dt} = k_1 ES - (k_{-1} + k_2)[ES]$$

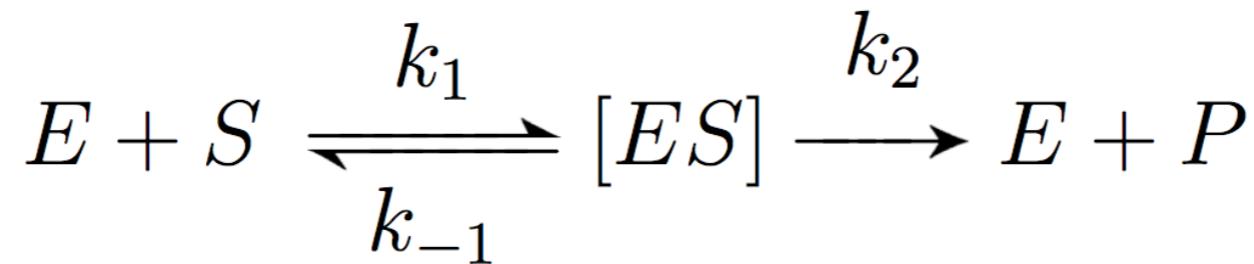
- Conservation equation for E :

$$E + [ES] = E_T \implies \frac{d[ES]}{dt} = k_1 S E_T - (k_{-1} + k_2 + k_1 S)[ES]$$

- Quasi-steady-state approximation:

$$\frac{d[ES]}{dt} = 0 \implies [ES] = \frac{k_1 S E_T}{k_{-1} + k_2 + k_1 S} = E_T \frac{S}{K_m + S}$$

Transcriptional activation

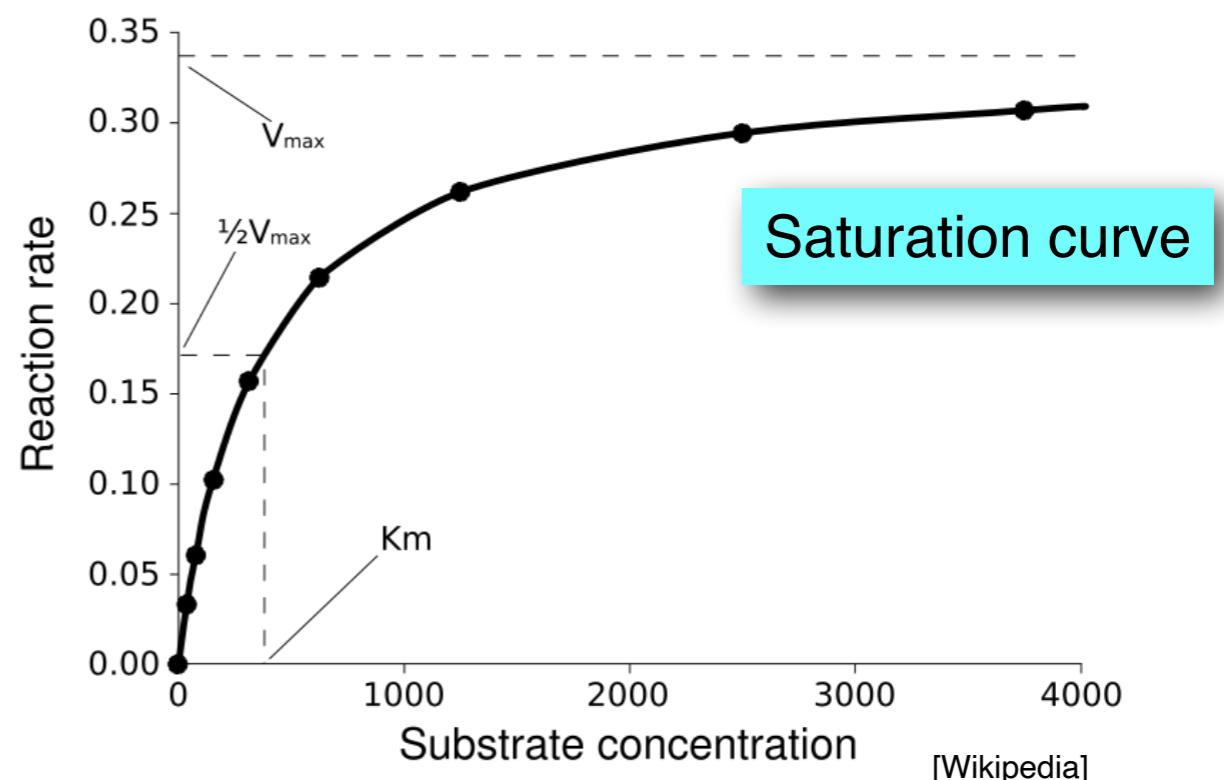


- Michaelis-Menten regulation equation:

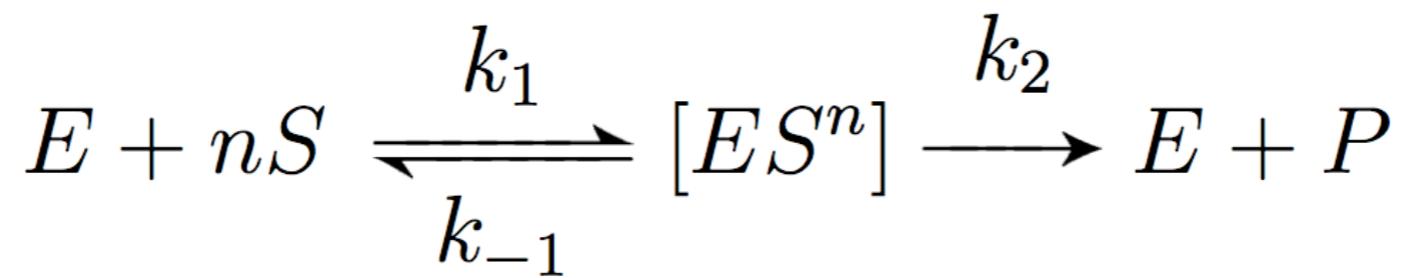
$$\frac{dP}{dt} = k_2[ES] = k_2 E_T \frac{S}{K_m + S} = \boxed{\frac{\beta S}{K_m + S}}$$

- Michaelis constant (half-maximal effective concentration, EC50):

$$K_m = \frac{k_{-1} + k_2}{k_1}$$



Cooperativity in transcriptional activation

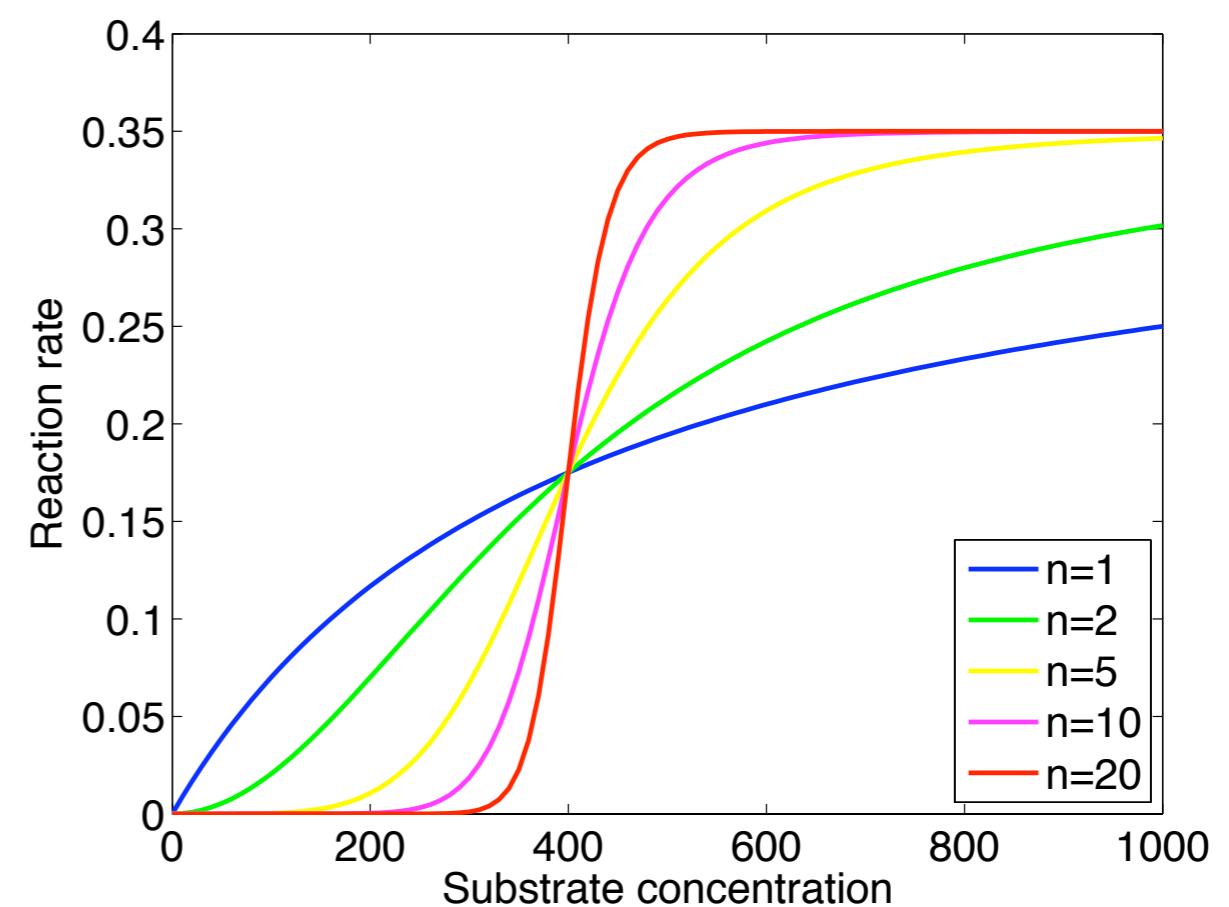


$$\frac{dP}{dt} = \frac{\beta S^n}{K_m^n + S^n}$$

Hill function

n : Hill coefficient

$$K_m = \left(\frac{k_{-1} + k_2}{k_1} \right)^{1/n}$$



Transcriptional repression



- Evolution equation for the complex $[ES]$:

$$\frac{dE}{dt} = k_{-1}[ES] - k_1 ES$$

- Conservation equation for E :

$$E + [ES] = E_T \implies \frac{dE}{dt} = k_{-1}E_T - (k_{-1} + k_1S)E$$

- Quasi-steady-state approximation:

$$\frac{dE}{dt} = 0 \implies E = \frac{k_{-1}E_T}{k_{-1} + k_1S} = E_T \frac{1}{1 + S/K_m}$$

Transcriptional repression

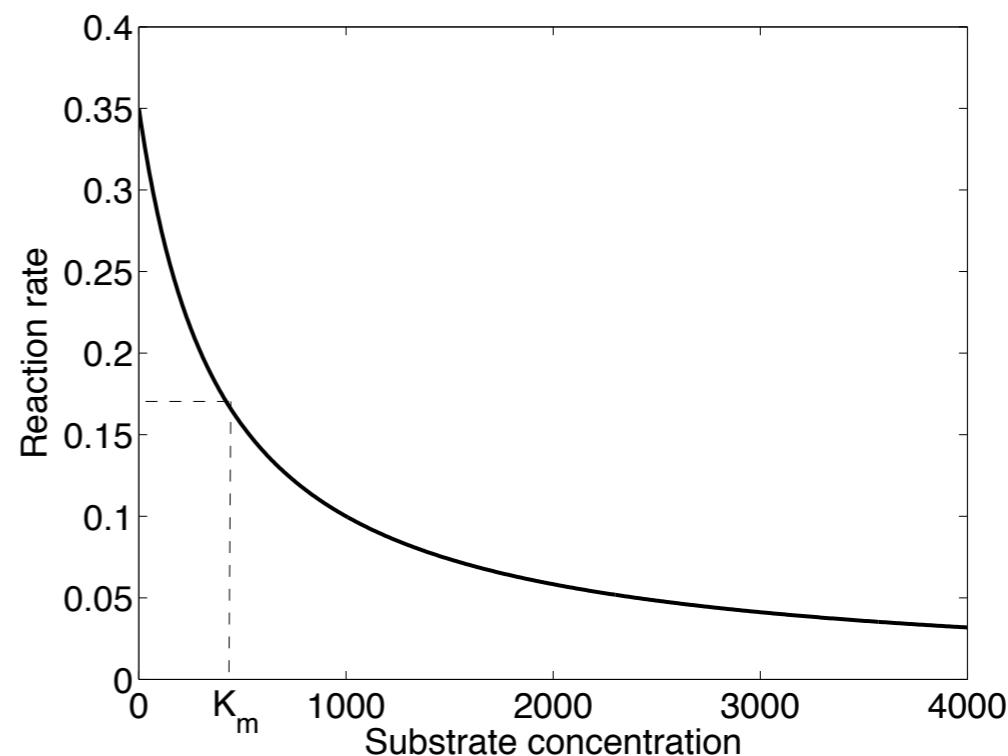


- Michaelis-Menten regulation equation:

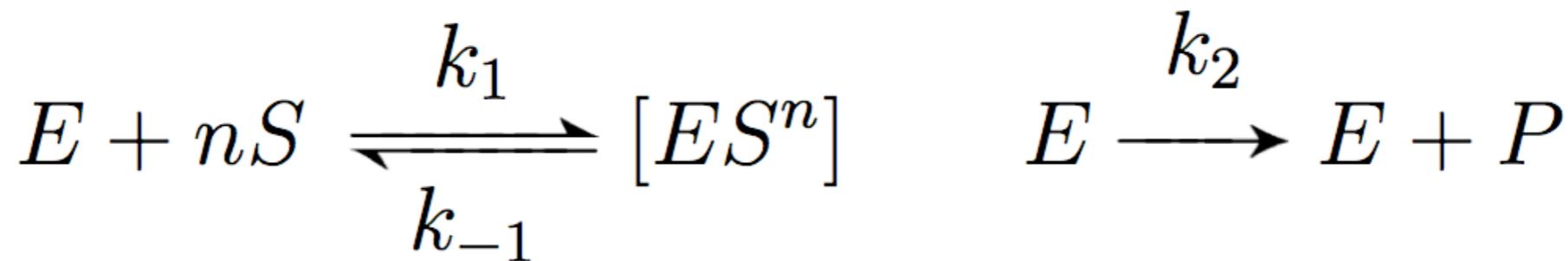
$$\boxed{\frac{dP}{dt} = \frac{\beta}{1 + S/K_m}}$$

- Michaelis constant (half-maximal inhibitor concentration, IC₅₀):

$$K_m = \frac{k_{-1}}{k_1}$$



Cooperativity in transcriptional repression

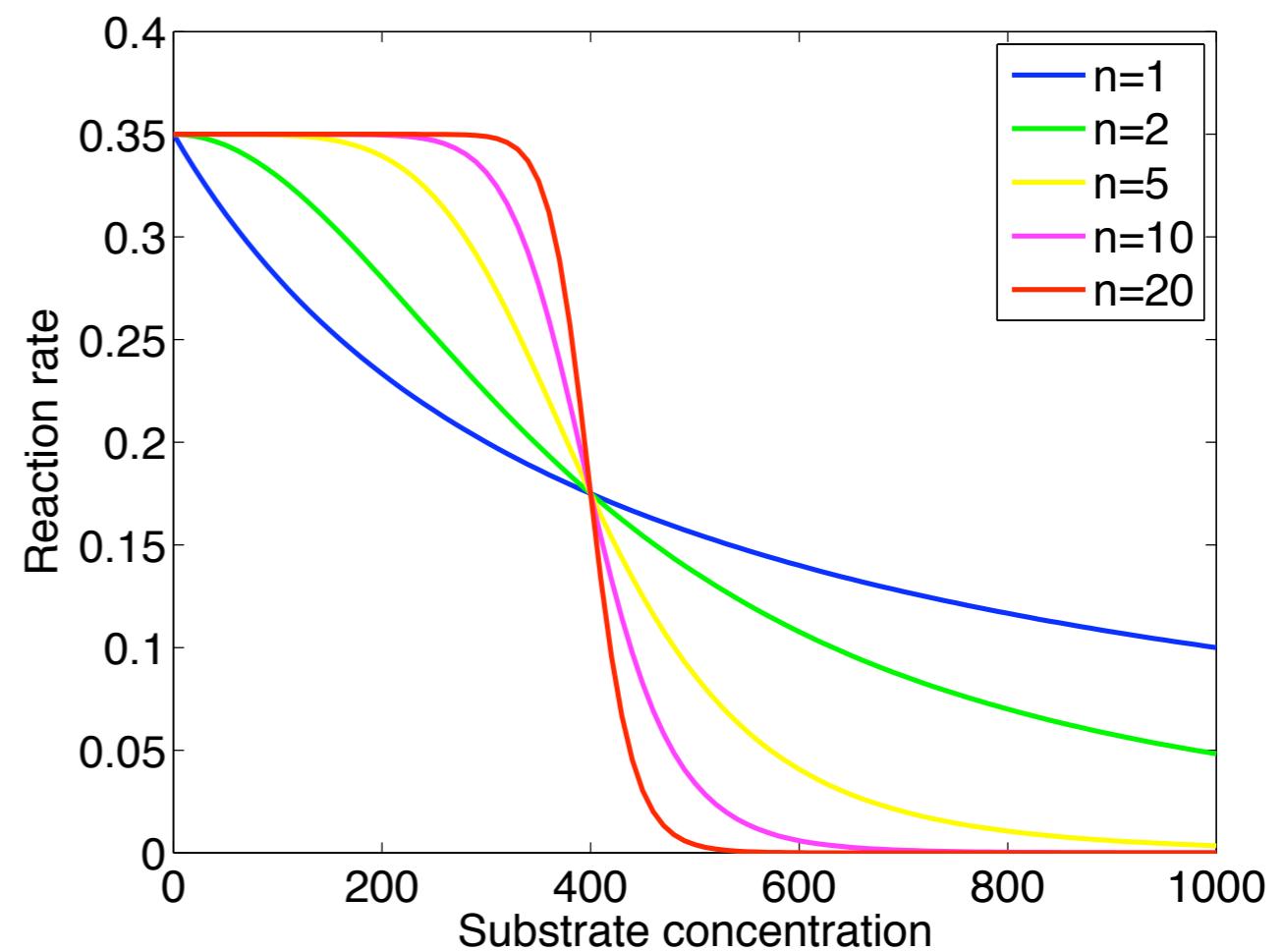


$$\frac{dP}{dt} = \frac{\beta}{1 + (S/K_m)^n}$$

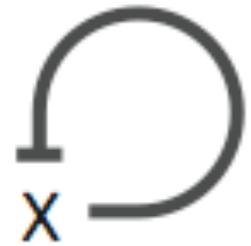
Hill function

n : Hill coefficient

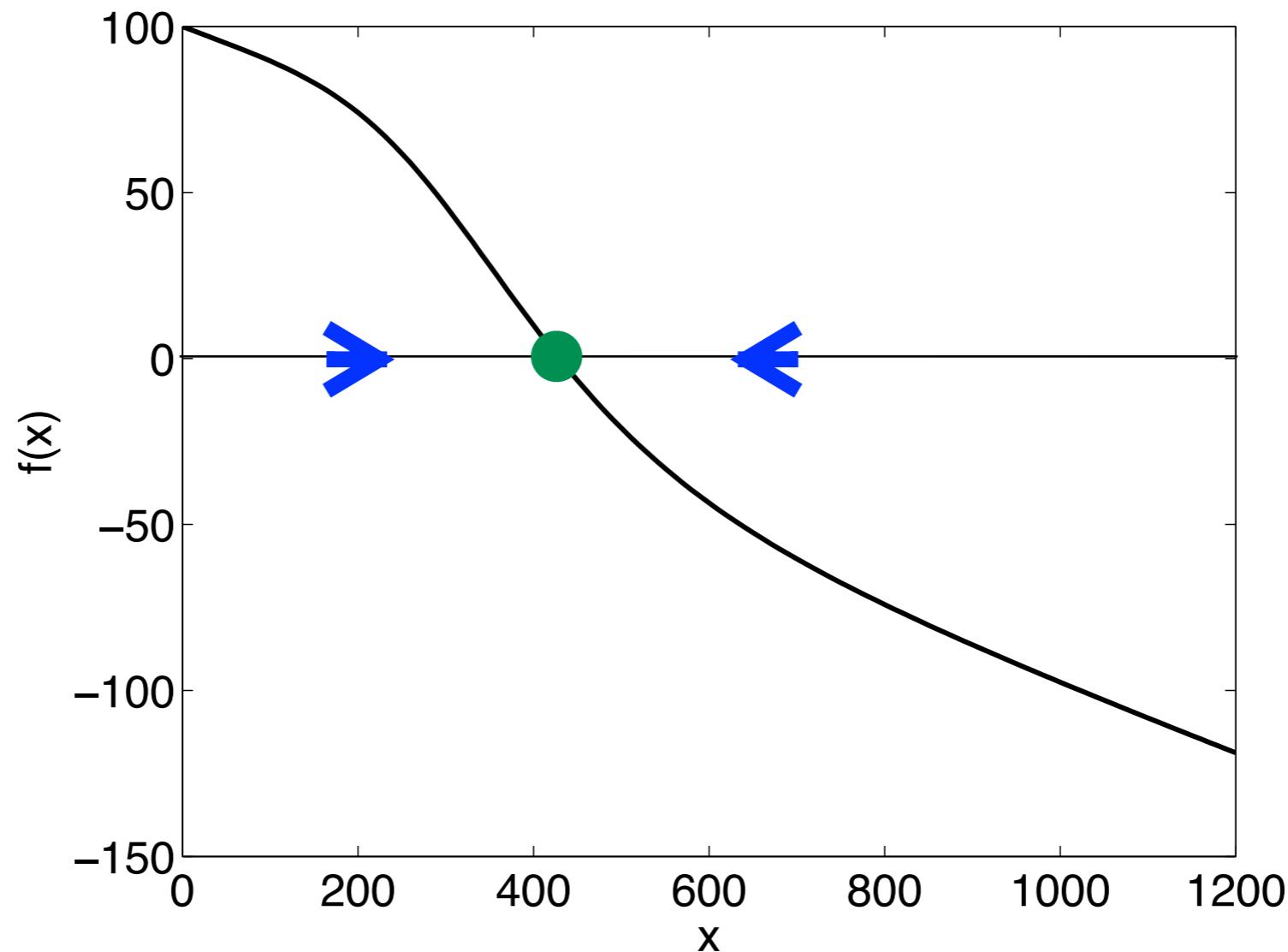
$$K_m = \left(\frac{k_{-1}}{k_1} \right)^{1/n}$$



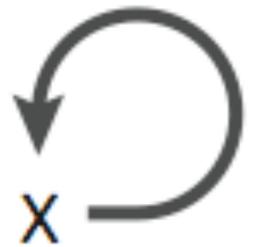
Negative feedback provides homeostasis



$$\frac{dx}{dt} = \frac{\beta}{1 + (x/K_m)^n} - \gamma x \equiv f(x)$$



Positive feedback provides a bistable switch



$$\frac{dx}{dt} = \frac{\beta x^n}{K_m^n + x^n} - \gamma x \equiv f(x)$$

