Nov 8: **Eric Deeds**, University of California at Los Angeles
"The evolution of cellular individuality"

Nov 15: **Daniel Merkle**, University of Southern Denmark
"Graph rewriting and chemistry"

Nov 22: **Jean Krivine**, Paris Diderot
"From molecules to systems: the problem of knowledge representation in molecular biology"

Nov 29: **Eric Smith**, Earth Life Sciences Institute, Tokyo
“Easy and Hard in the Origin of Life"

Dec 6: **Massimiliano Esposito**, University of Luxembourg
"Thermodynamics of Open Chemical Reaction Networks: Theory and Applications"

Dec 13: **Yarden Katz**, Harvard Medical School
"Cells as cognitive creatures"

Jan 17: **Aleksandra Walczak**, ENS Paris
"Prediction in immune repertoires"

Jan 24: **Tommy Kirchhausen**, Harvard Medical School
"Imaging sub-cellular dynamics from molecules to multicellular organisms"

Previous Lectures

1. The Topology of the Possible
   (La représentation de l'information biologique)

2. Propagation of Genetic, Phenotypic, and Molecular information
   (Limites de la transmission de l'information biologique)

Mutation and (Simple) Darwinian Selection

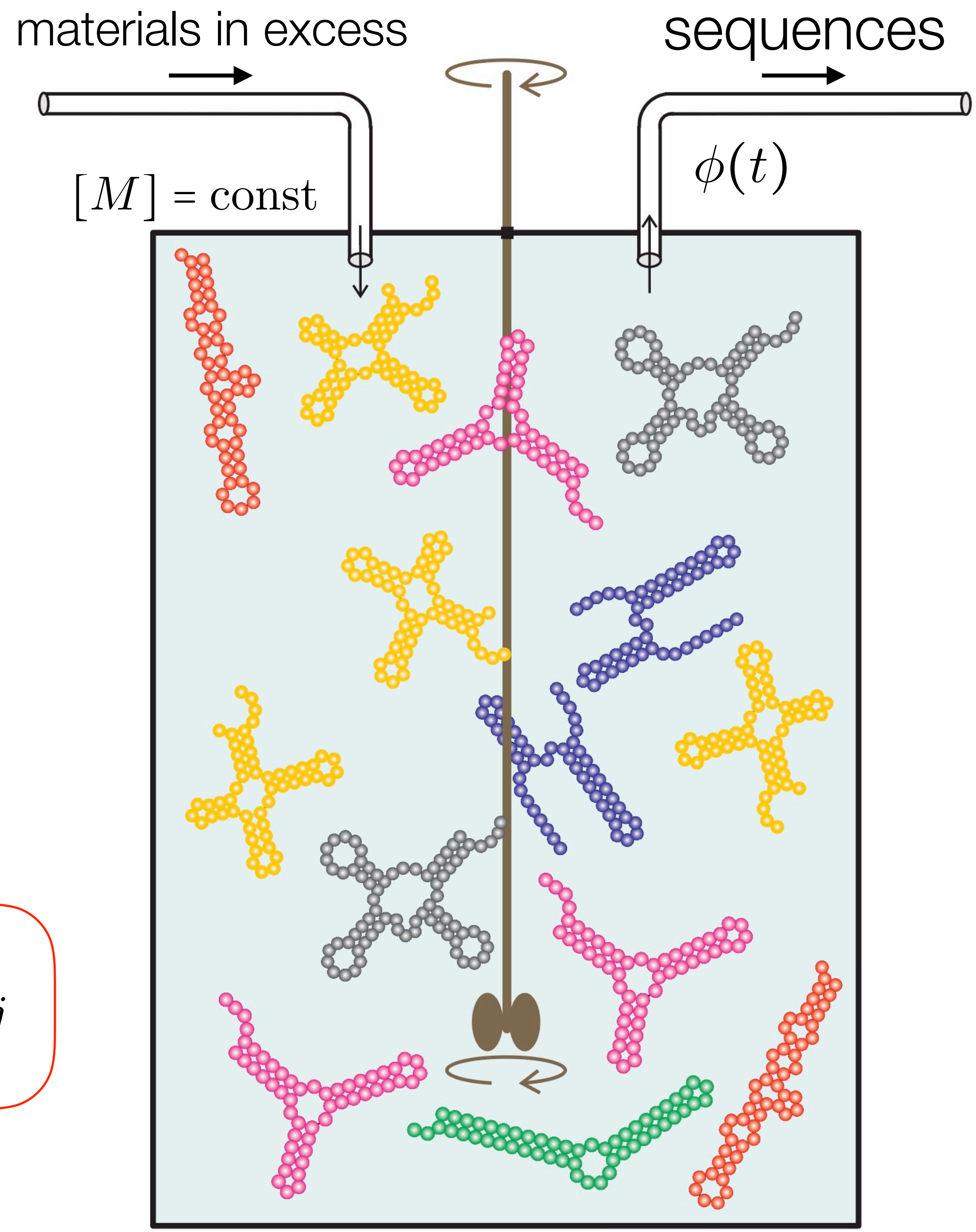
$$I_i \xrightarrow{Q_{ii} f_i} I_i + I_i$$

$$I_i \xrightarrow[Q_{ji} f_i]{} I_i + I_j \qquad j \neq i$$

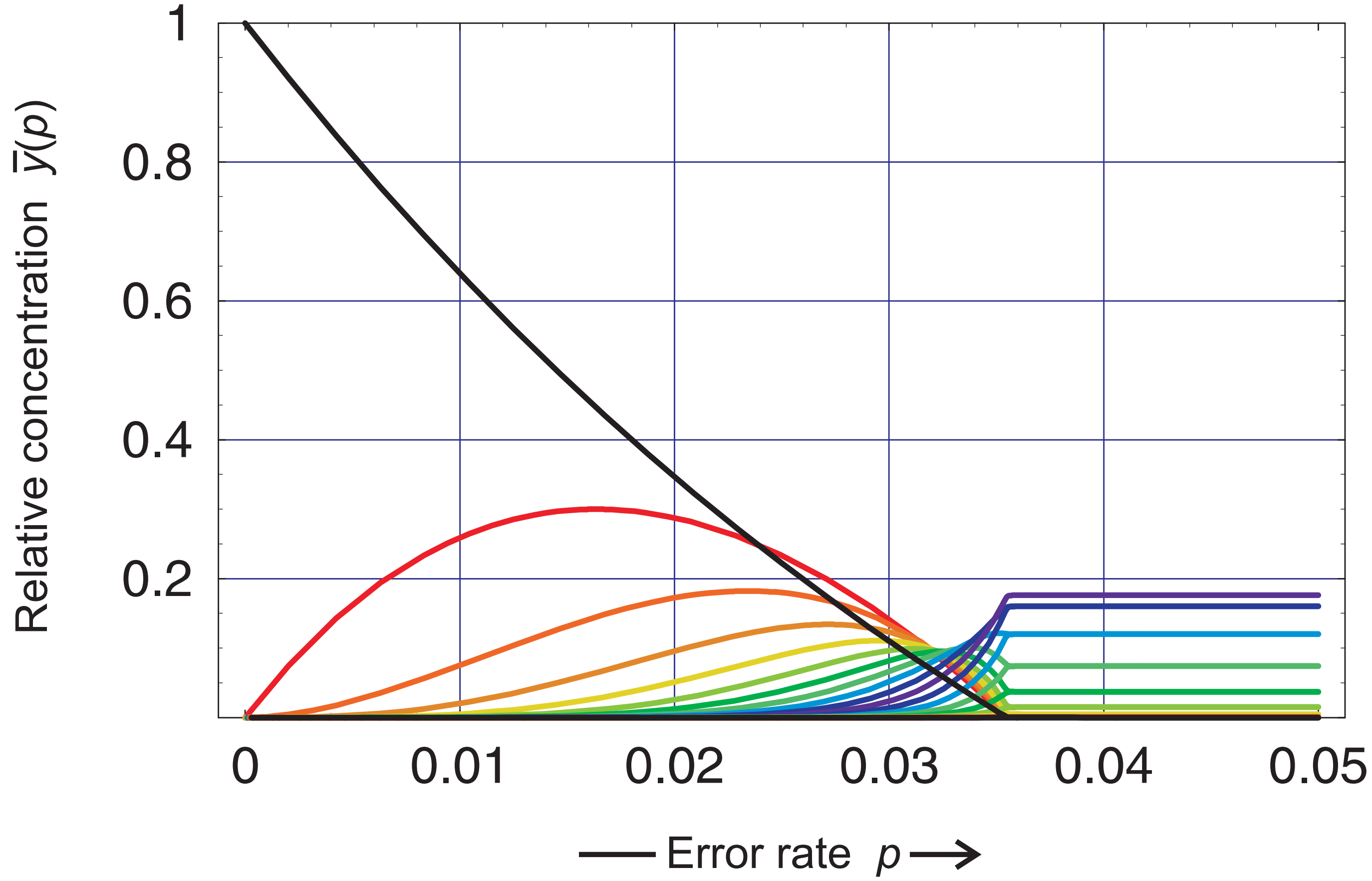
$$\dot{x}_i = \sum_{j=1}^{n} Q_{ij} f_j x_j - \overline{f(t)} x_i$$

with $\overline{f(t)} = \sum_{j=1}^{n} f_j x_j$

$$\dot{x}_i = \left(Q_{ii} f_i - \overline{f(t)} \right) x_i + \sum_{j \neq i}^{n} Q_{ij} f_j x_j$$



Error Thresholds

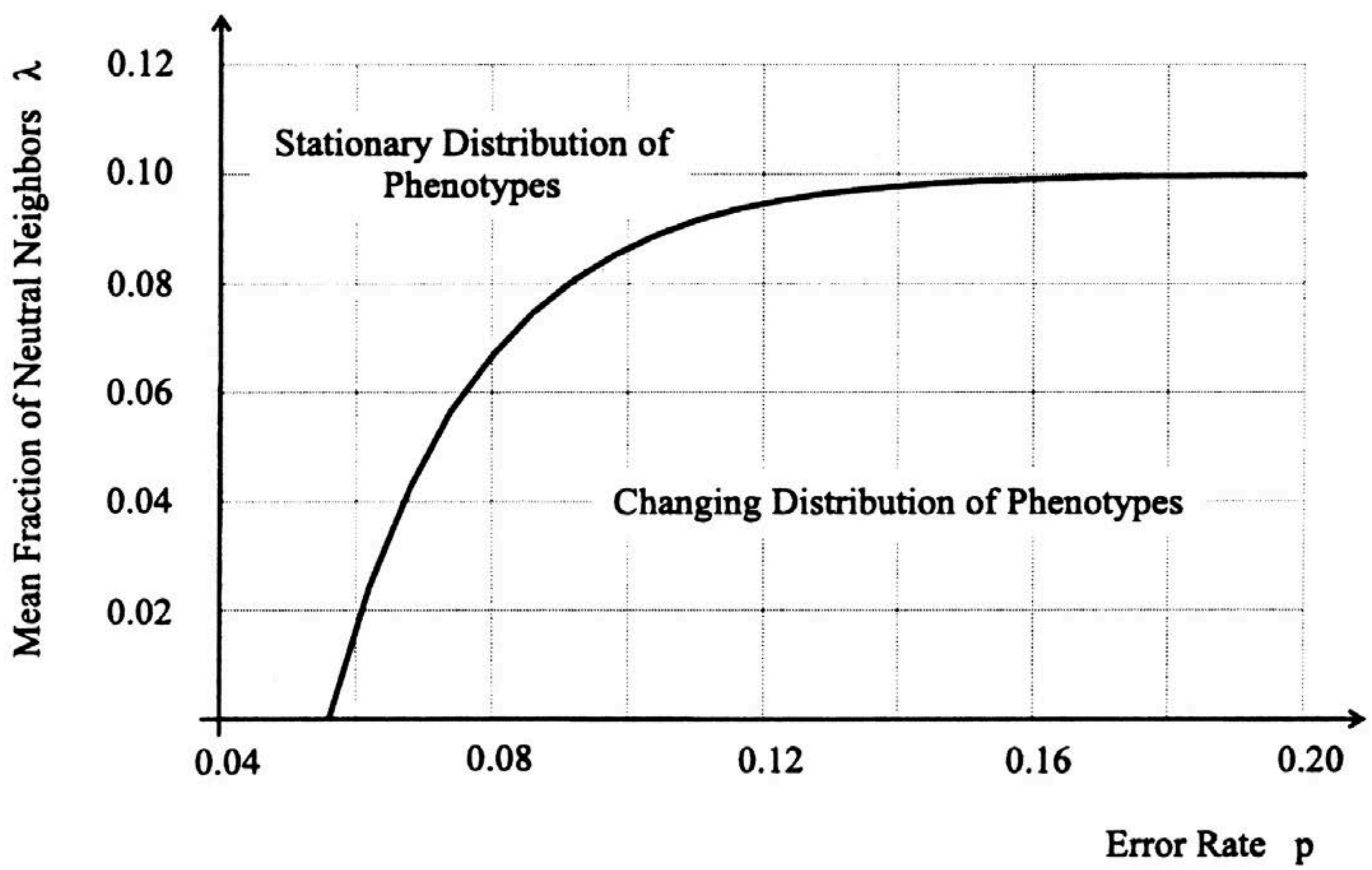


genotypic error threshold

$$p_c = 1 - \sigma_m^{-\frac{1}{l}} \approx \frac{\ln \sigma_m}{l}$$

sequence length

superiority of master sequence

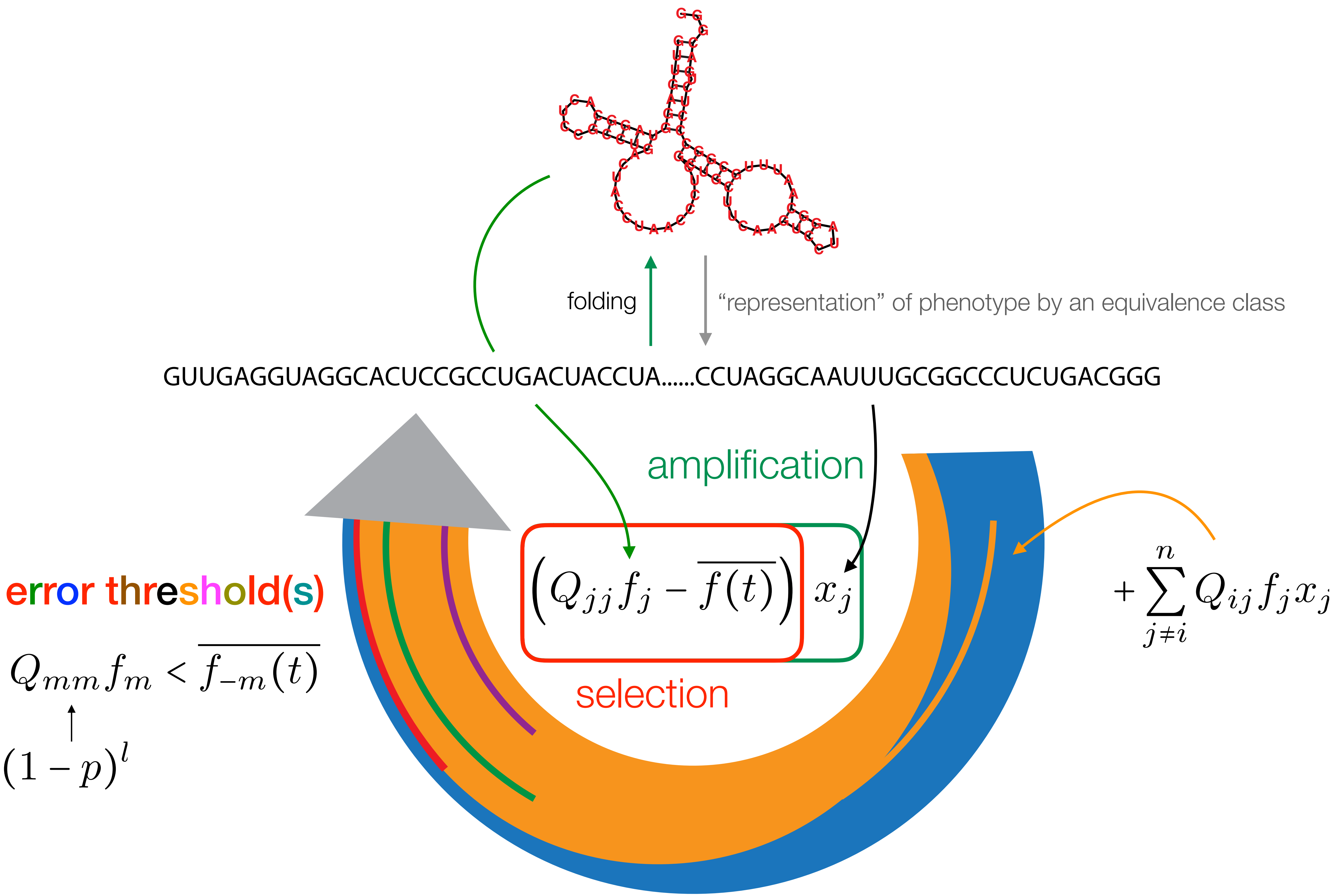


phenotypic error threshold

fraction of neutral mutants

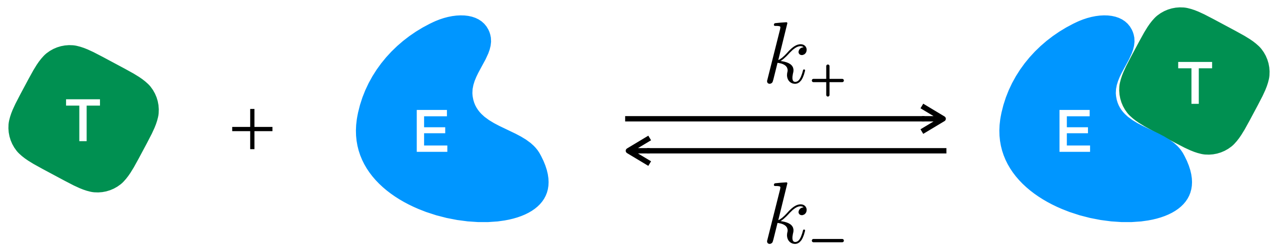
$$p_c = 1 - \left(\frac{1 - \lambda_m \sigma_m}{(1 - \lambda_m)\sigma_m} \right)^{1/l}$$

Putting it All Together



2. (part 2)
The Propagation of Genetic, Phenotypic, and Molecular information

Basics



$$\mathrm{T} + \mathrm{E} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{ET}$$

$$v_+ = k_+[E][T]$$

$$v_- = k_-[ET]$$

reaction velocity (flux)

$$v_+ = v_-$$

kinetic equilibrium

thermodynamic equilibrium

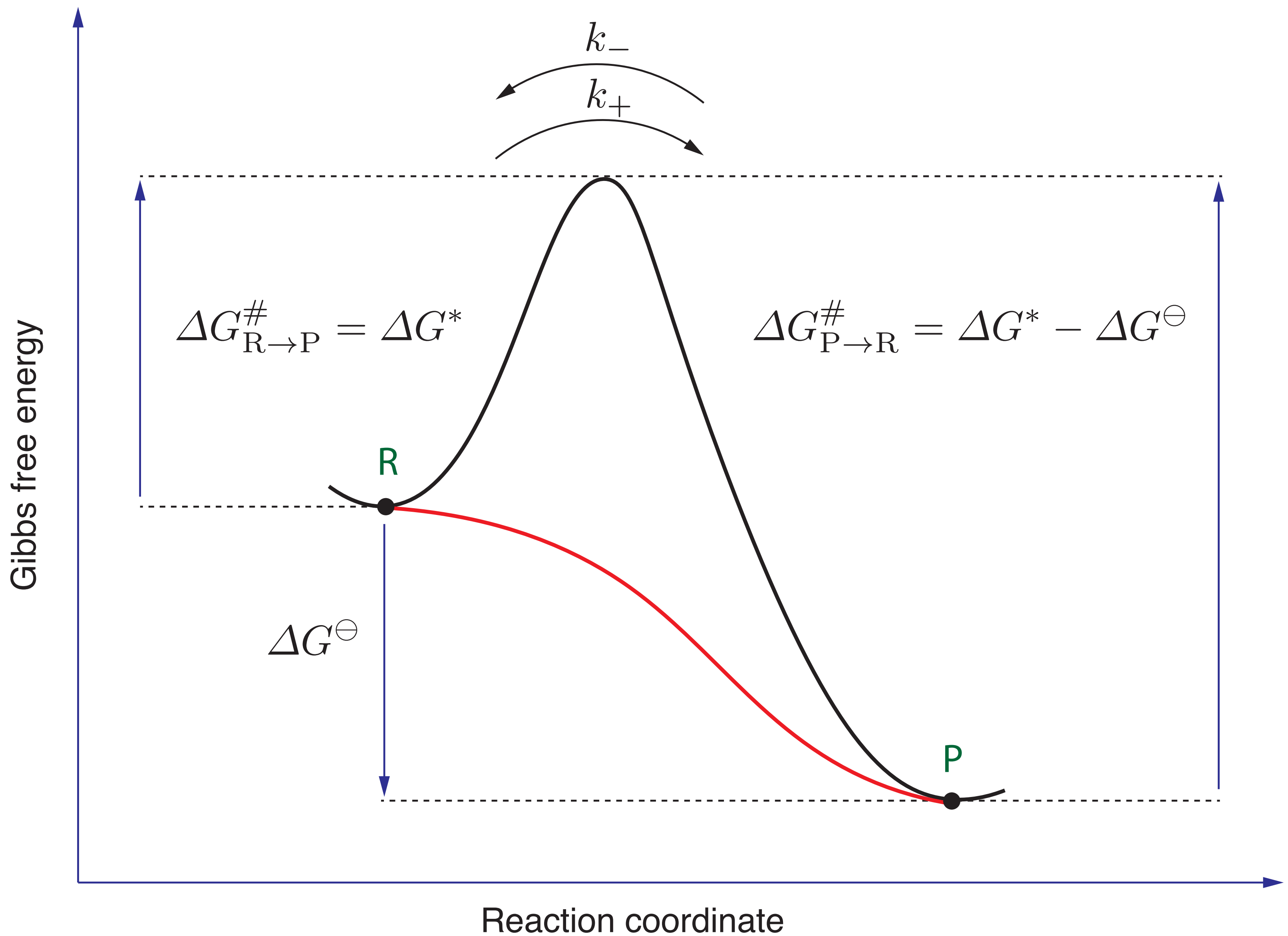
$$\Delta G = 0$$

$$\frac{k_+}{k_-} = \underbrace{\frac{[ET]_{eq}}{[E]_{eq}[T]_{eq}}}_{K} = \exp\left(-\frac{\Delta G^{\ominus}}{RT}\right)$$

equilibrium constant

connects energetics with kinetics

Basics



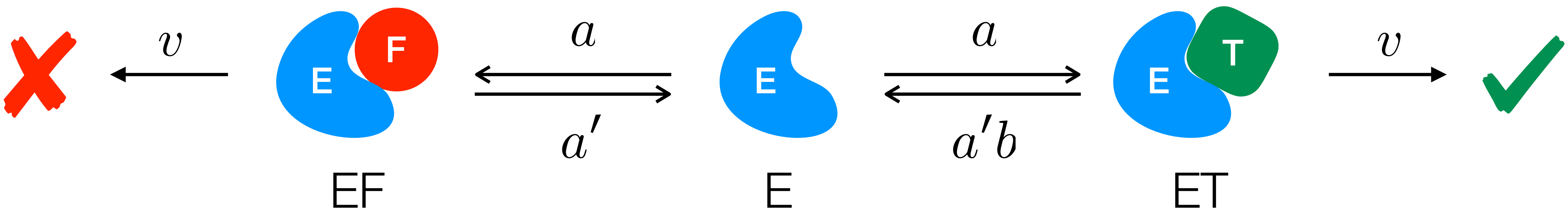
$$\mathrm{R} \rightleftharpoons \mathrm{P}$$

$$k = \omega \exp(-\Delta G^{\#}/RT)$$

$$k_+ = \omega \exp(-\Delta G^*/RT) = \omega'$$

$$k_- = \omega \exp(-\Delta G^*/RT) \exp(\Delta G^{\ominus}/RT) = \omega' \exp(\Delta G^{\ominus}/RT)$$

Kinetic Proofreading Problem



assume

$$a \equiv k_+[F] = k_+[T]$$

discriminating factor

$$b = \exp\left(-(\Delta G_F^\ominus - \Delta G_T^\ominus)\right) \stackrel{!}{=} \exp\left(-\Delta G_{FT}^\ominus\right)$$

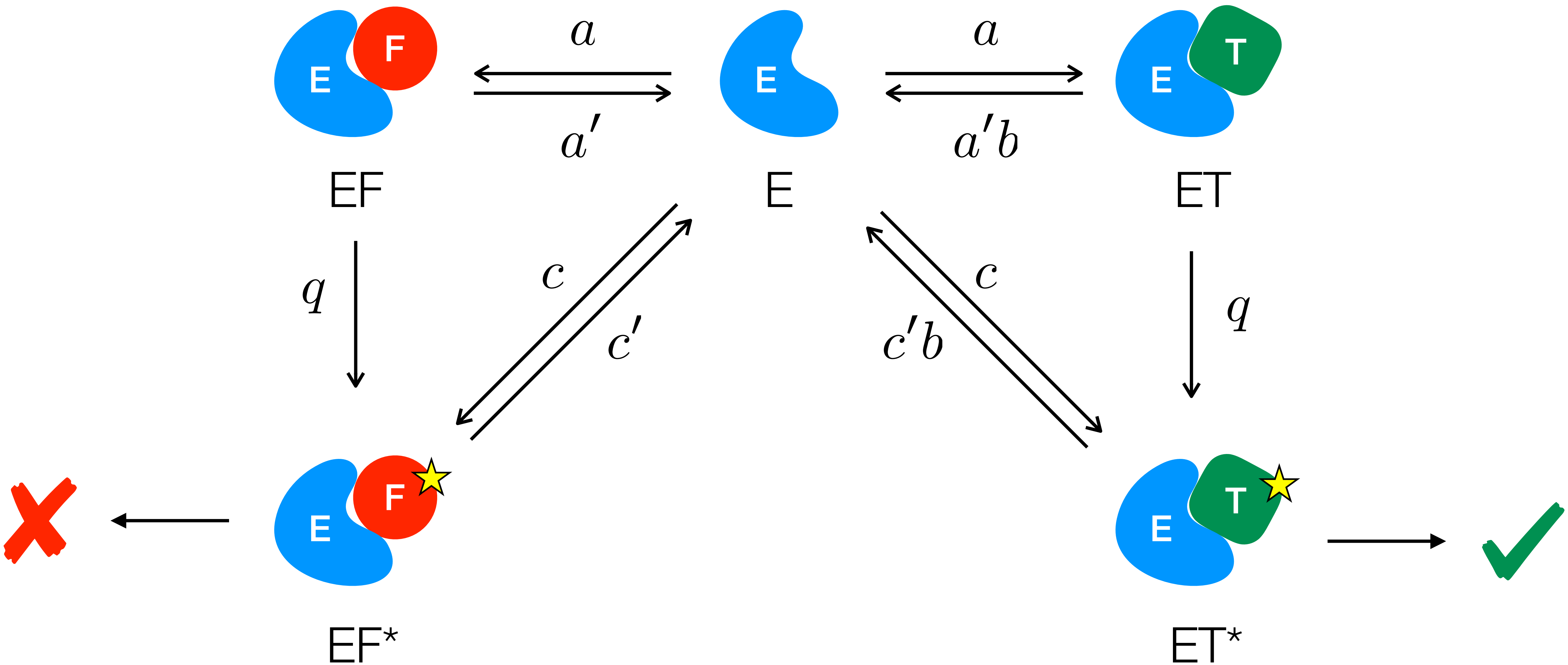
at steady-state

$$[ET] = \frac{a[E]}{a'b + v} \quad \text{and} \quad [EW] = \frac{a[E]}{a' + v}$$

error rate

$$\eta = \frac{v[EW]}{v[ET]} = \frac{[EW]}{[ET]} = \frac{a'b + v}{a' + v}$$

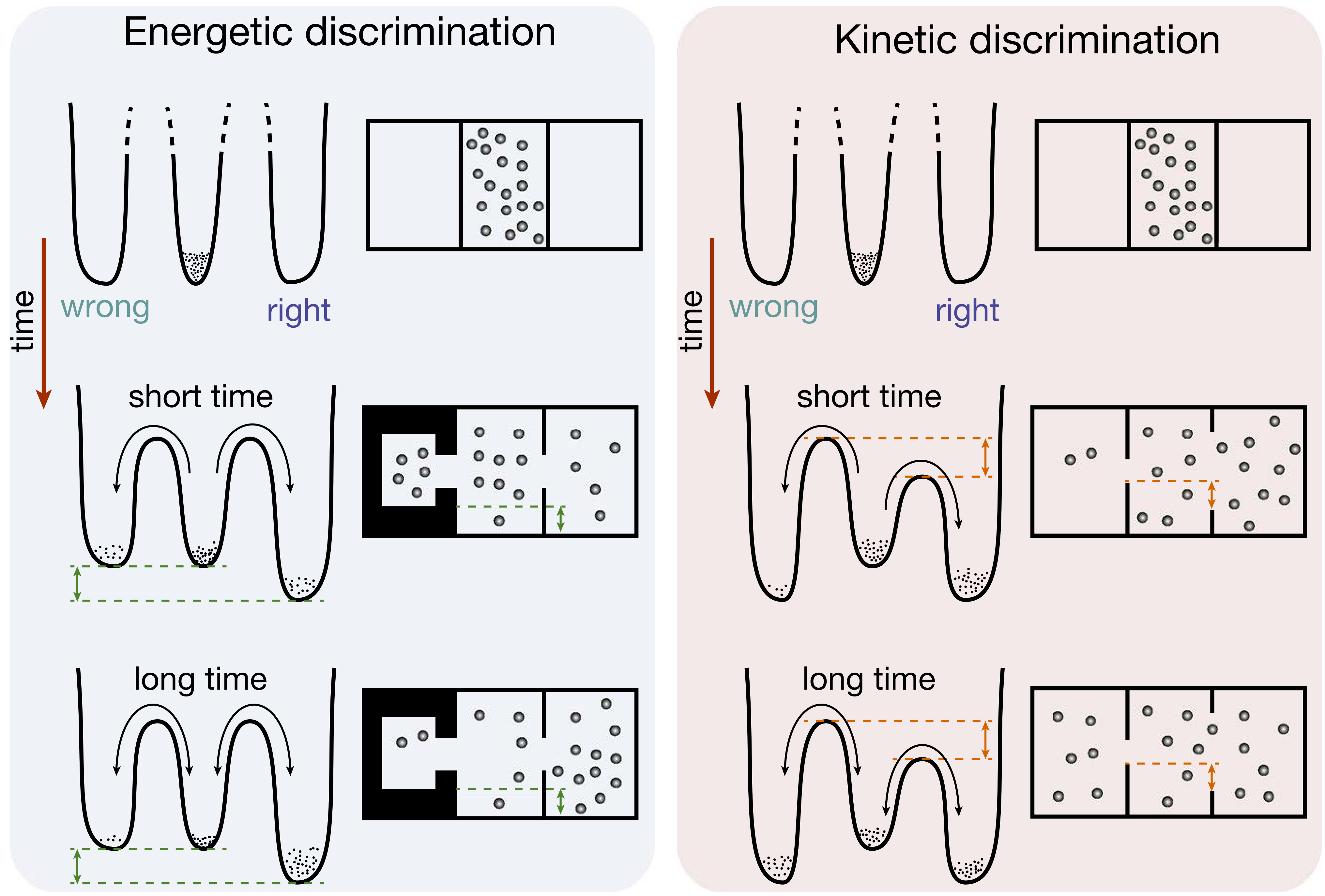
Kinetic Proofreading Scheme



$$\eta = \frac{[EF^*]}{[ET^*]} = \frac{b(a'b+q)(a'c+(a+c)q)}{(a'+q)(a'bc+(a+c)q)}$$

drawing after Jeremy Owen

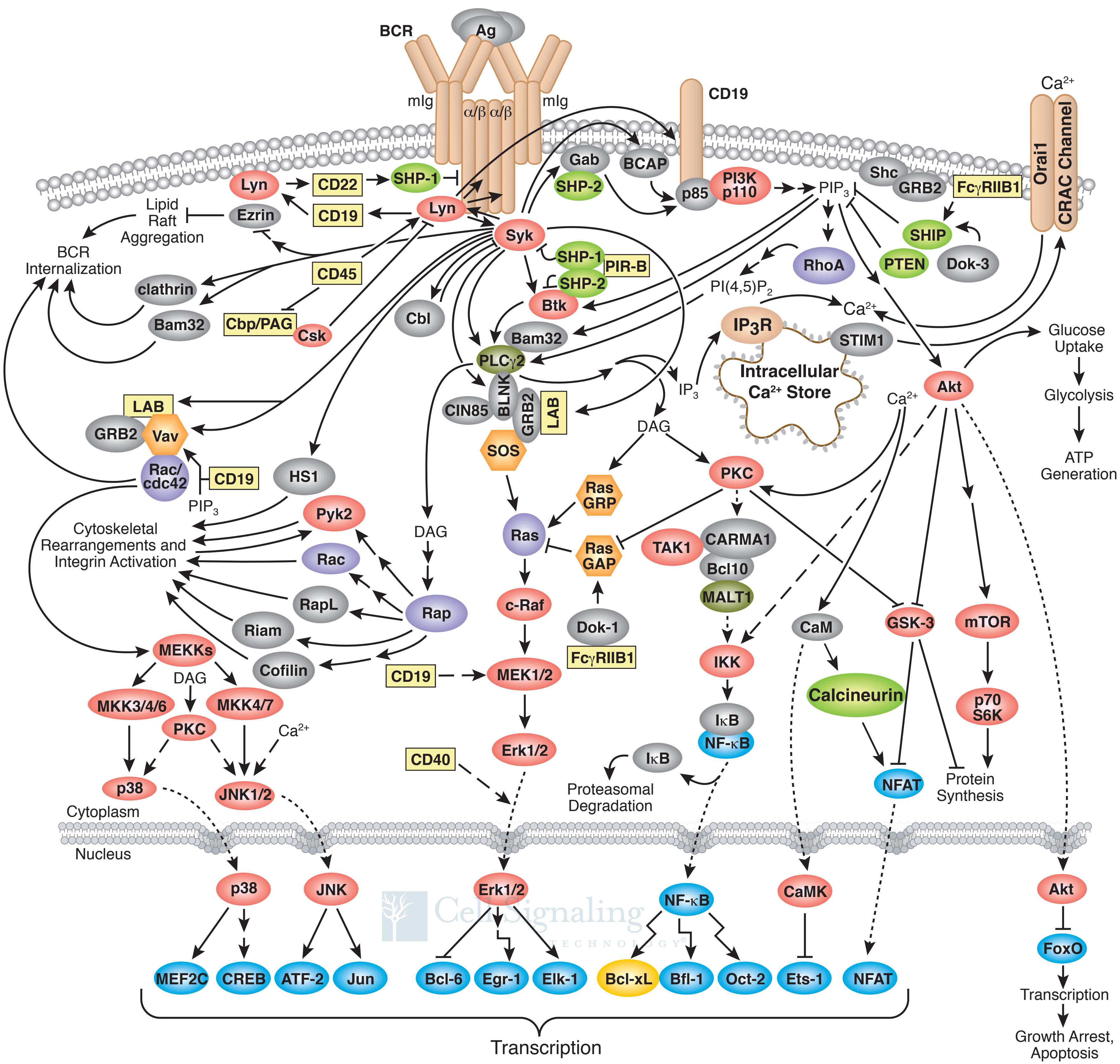
Proofreading Schemes



S. Pigolotti & P. Sartori. J Stat Phys (2016) 162:1167–1182

3.
Modeling cellular information processing

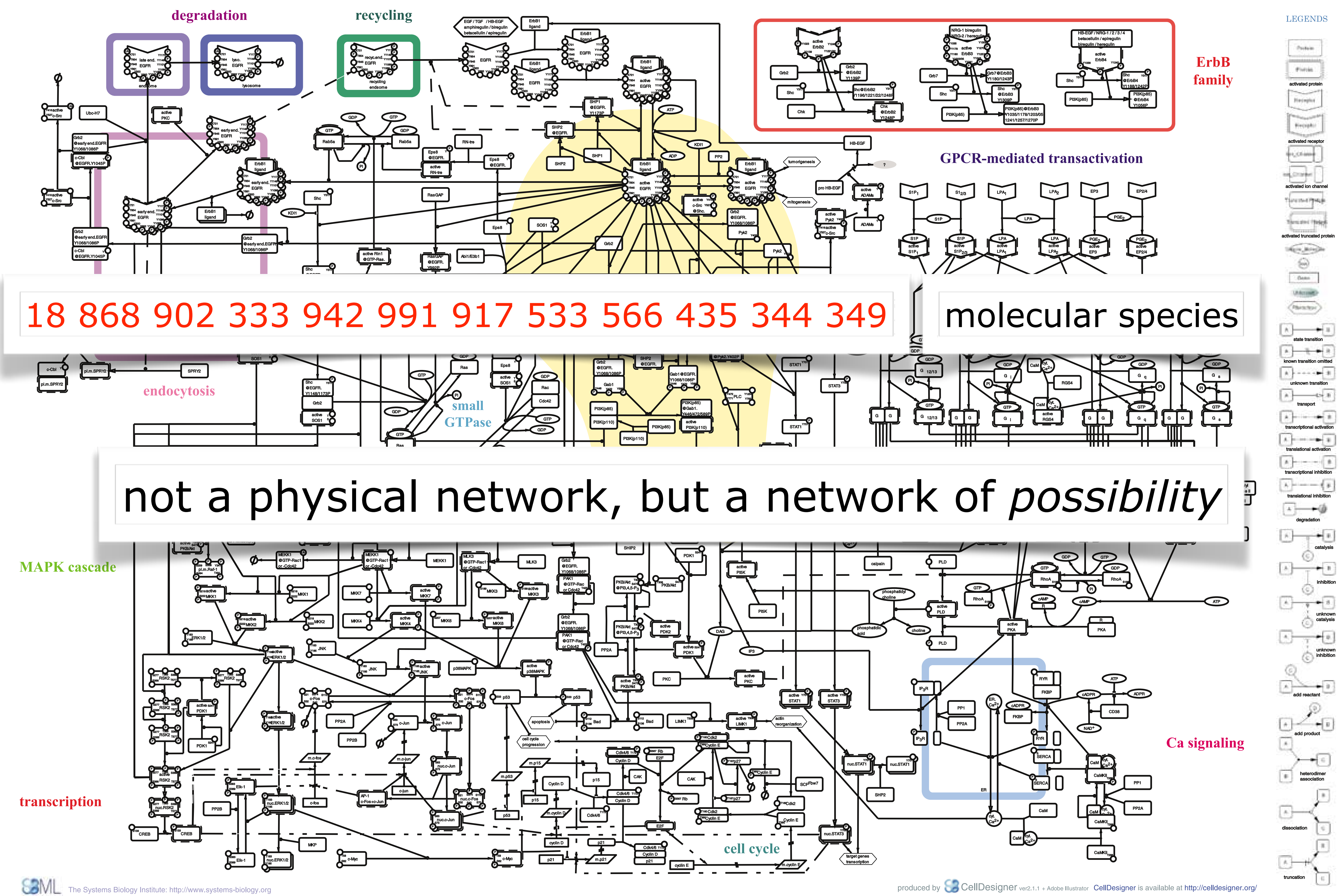
Signaling: A Circulatory System of Information



tasks:

cell fate,
division,
repair,
cell death,
motility,
morphology,
...

Signaling: A Circulatory System of Information



18 868 902 333 942 991 917 533 566 435 344 349

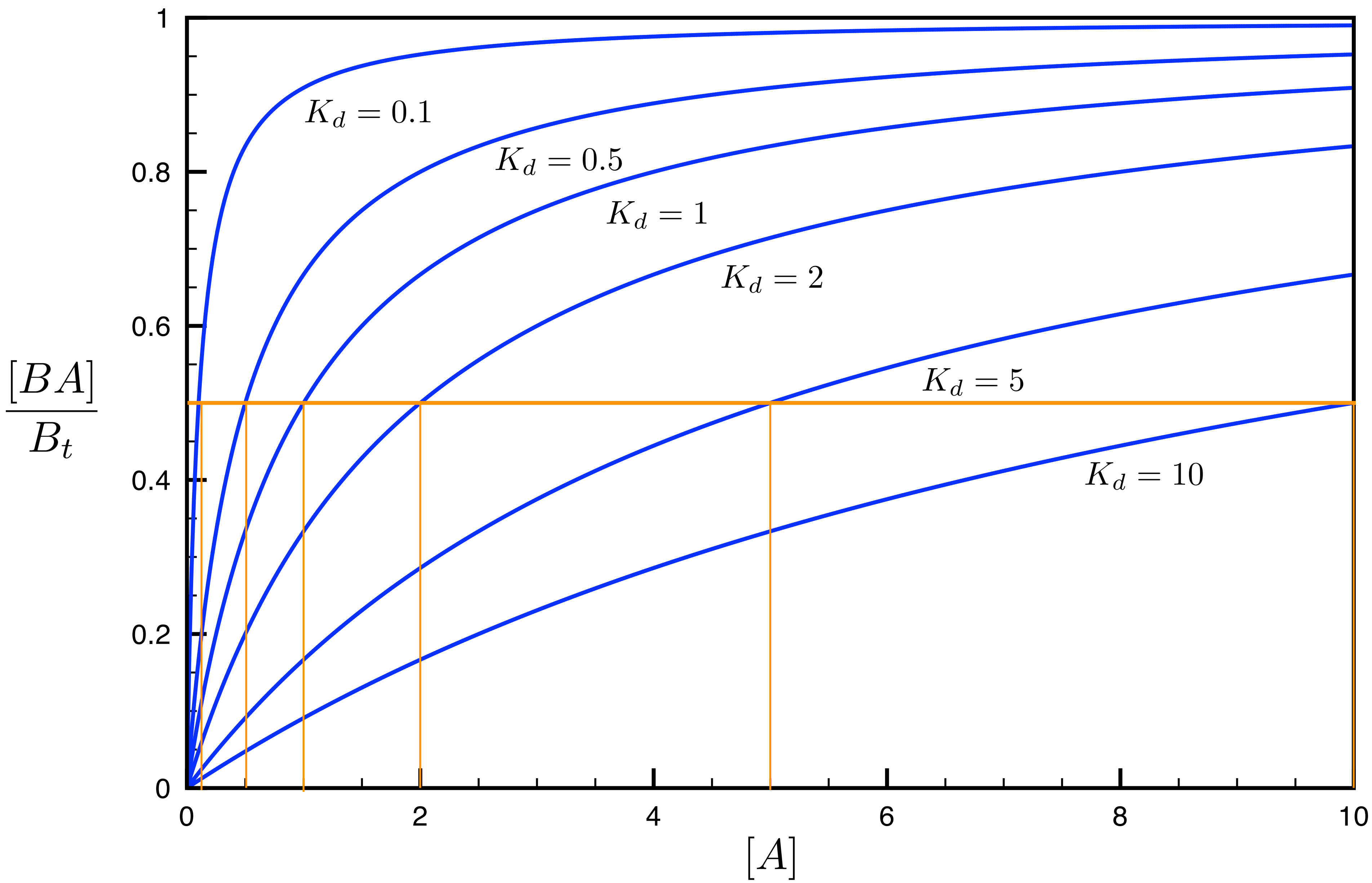
molecular species

not a physical network, but a network of *possibility*

Start with simplicity…

Binding

$$B + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BA$$



$$\frac{k_1}{k_{-1}} = K = \frac{[BA]}{[B][A]}$$

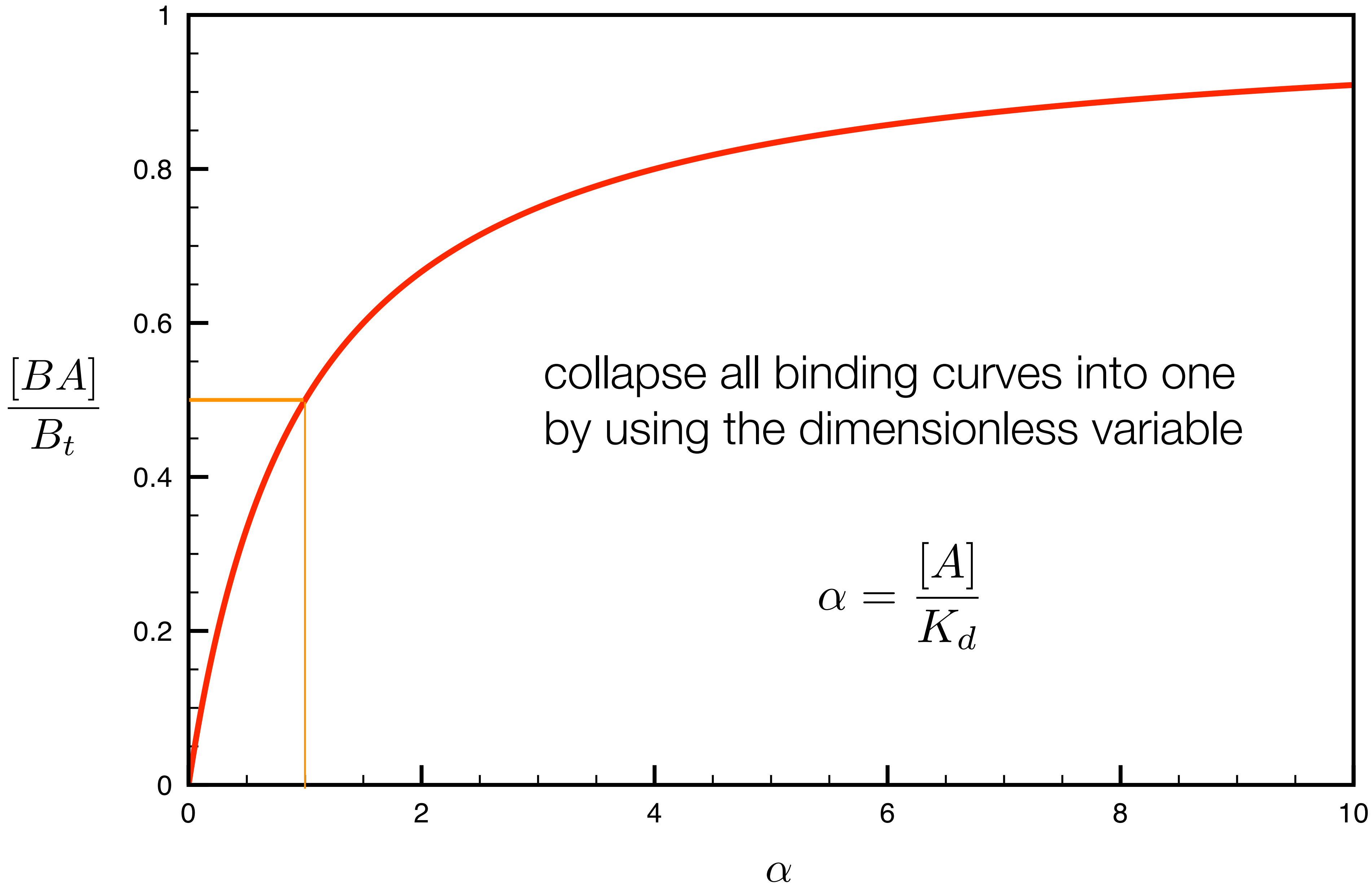
$$B_t = [B] + [BA]$$

$$\frac{[BA]}{B_t} = \frac{[A]}{[A] + K_d}$$

$$K_d = K^{-1}$$

Binding

$$B + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BA$$

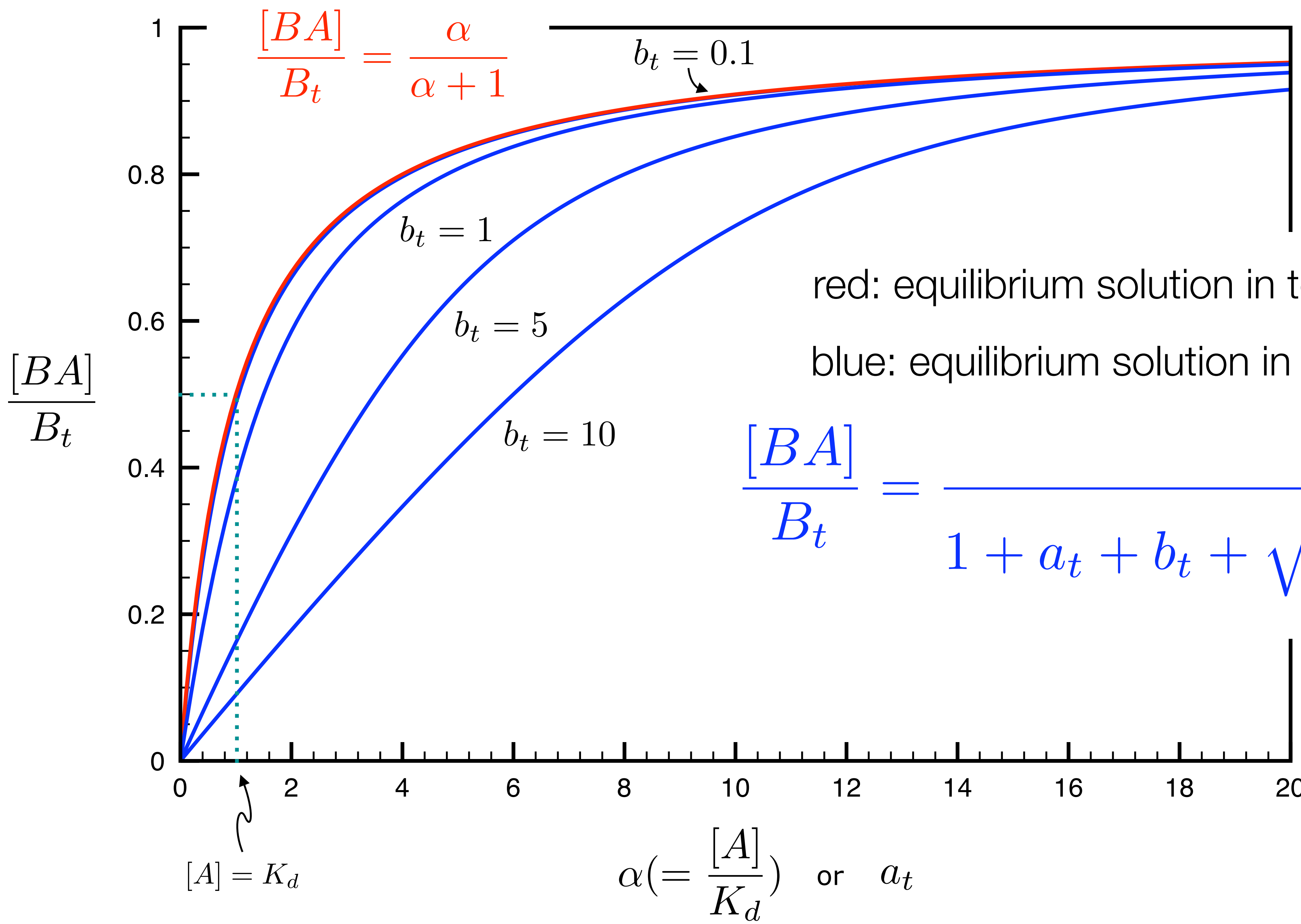


$$\frac{[BA]}{B_t} = \frac{[A]}{[A] + K_d}$$

$$\frac{[BA]}{B_t} = \frac{\alpha}{\alpha + 1}$$

Binding

$$B + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BA$$



red: equilibrium solution in terms of free A

blue: equilibrium solution in terms of known parameters

$$\frac{[BA]}{B_t} = \frac{2a_t}{1 + a_t + b_t + \sqrt{(1 - a_t + b_t)^2 + 4a_t}}$$

$$a_t = \frac{A_t}{K_d}$$

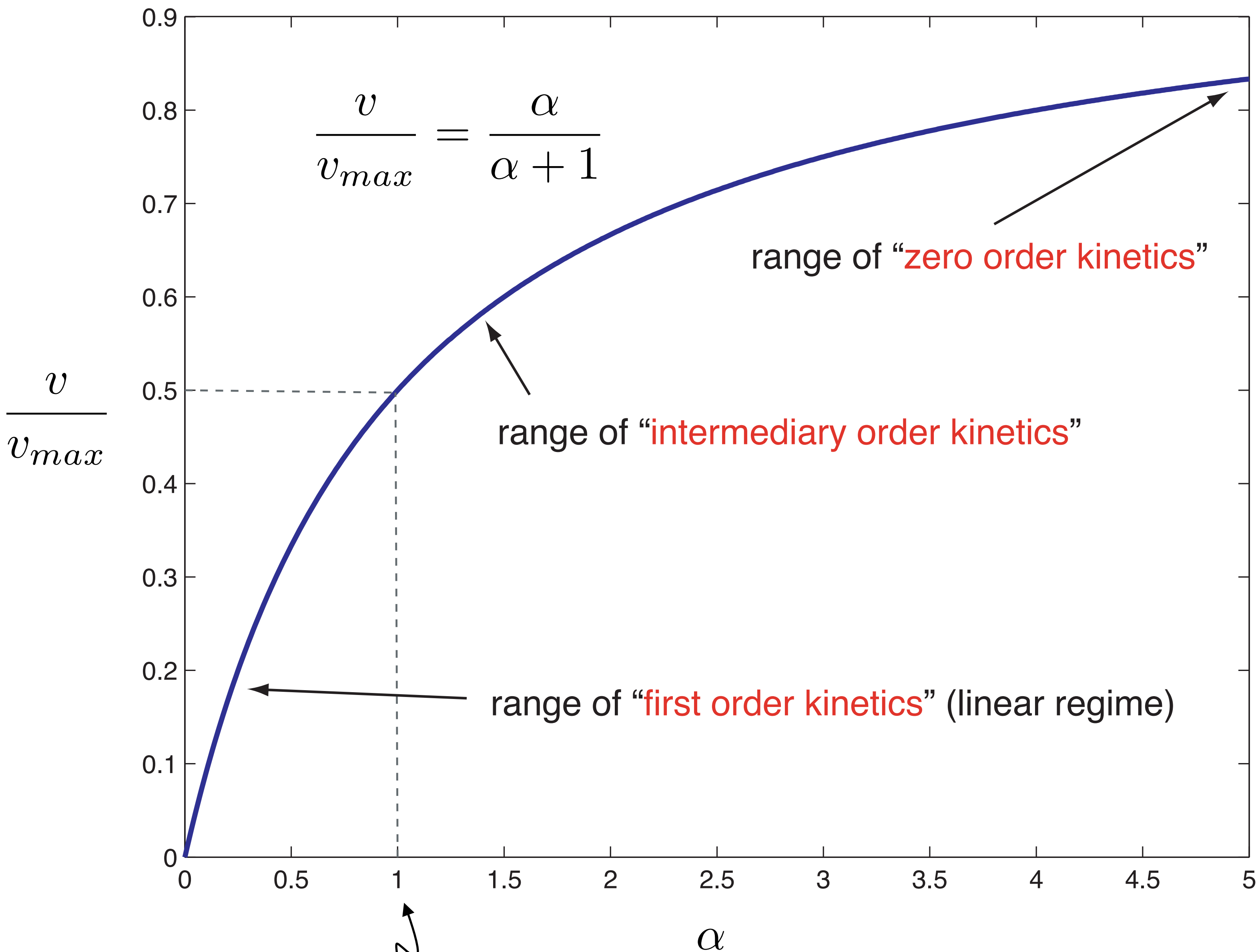
$$b_t = \frac{B_t}{K_d}$$

Binding Equilibria As "Prefixes"

$$B + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BA \xrightarrow{k_2} B + P$$

$$v \doteq \frac{dP}{dt} = k_2[BA] = k_2 B_t \frac{\alpha}{\alpha + 1}$$ when $A_t \gg B_t$

with $\alpha = \frac{[A]}{K_m}$

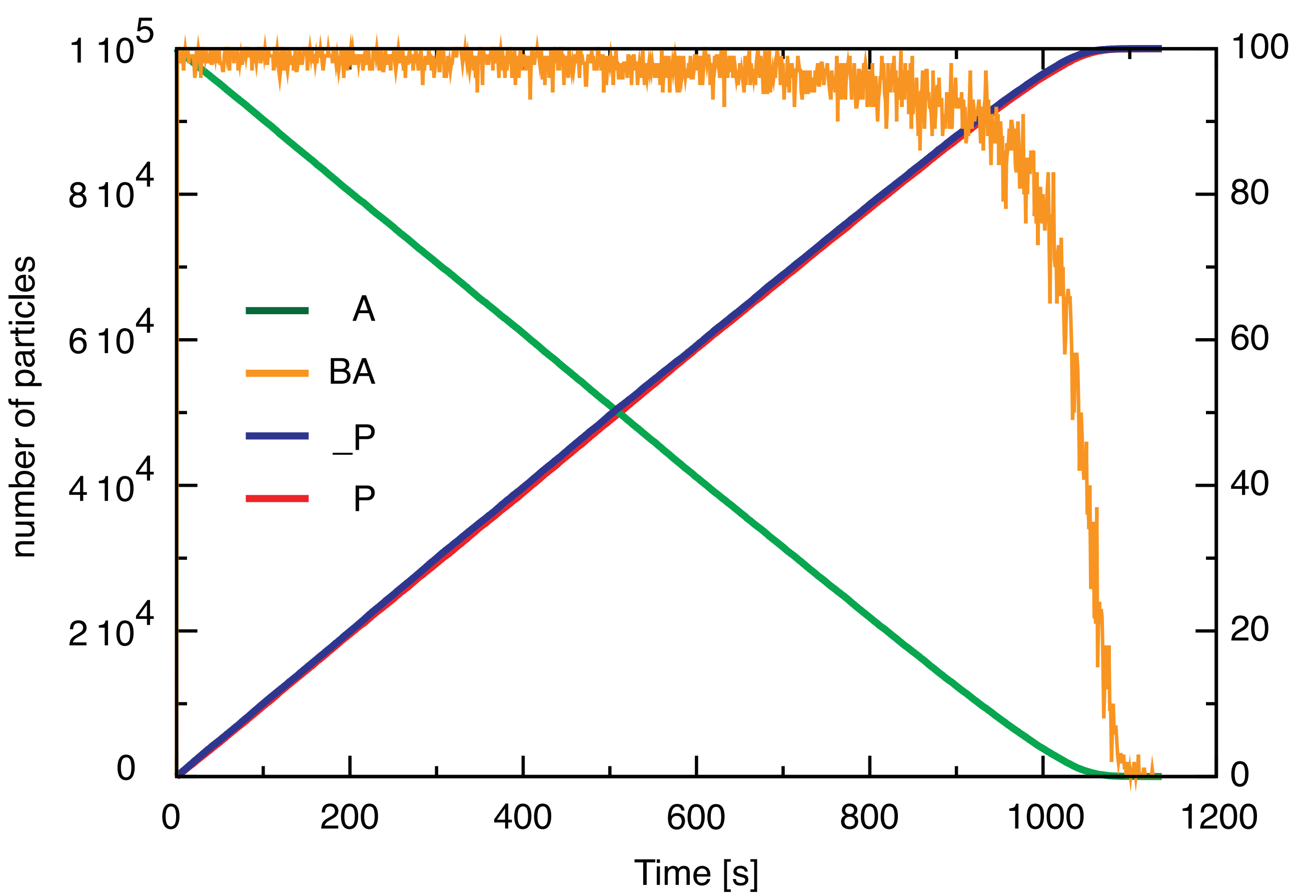


$$[A] = K_m = \frac{k_{-1} + k_2}{k_1}$$

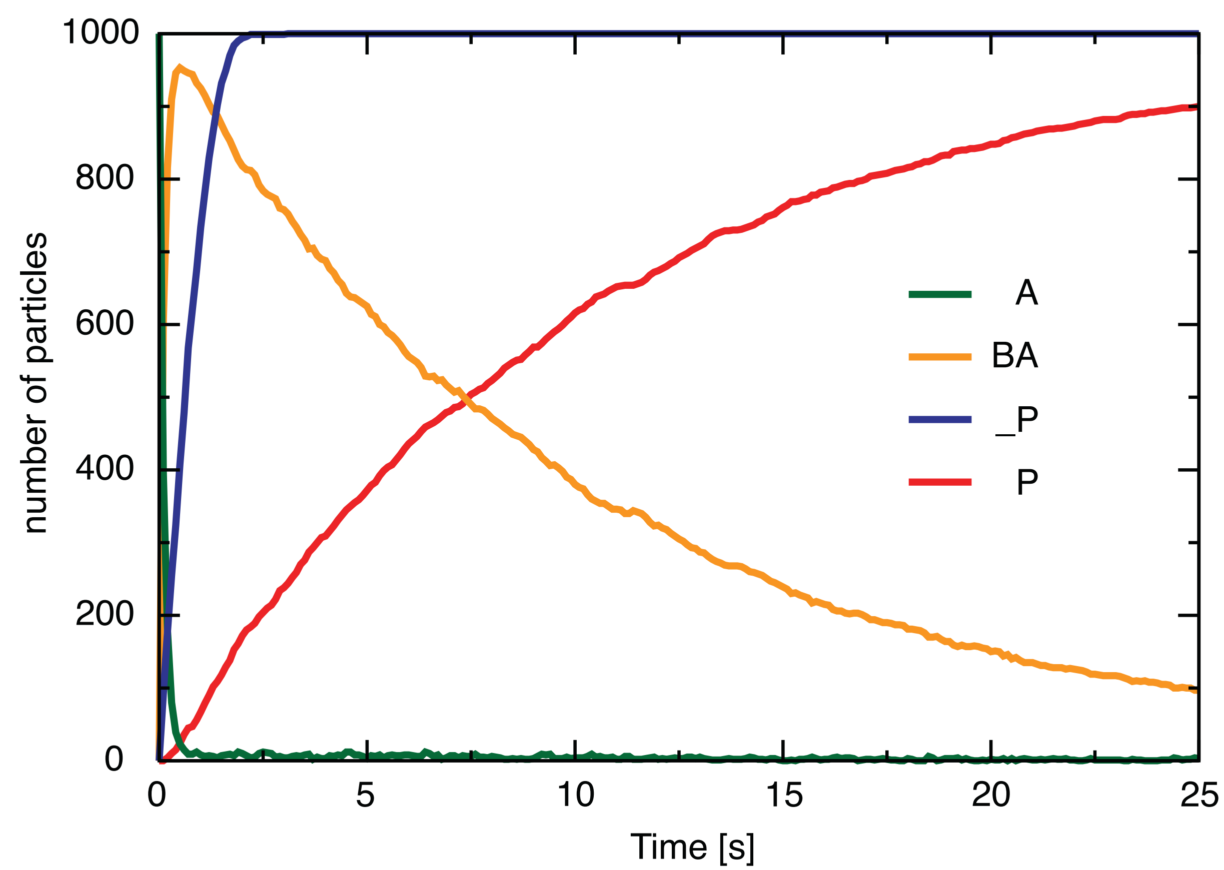
$k_1, k_{-1} >> k_2$	quasi-equilibrium of ES
$A_t \gg B_t$	quasi-steady state of ES
$A_t \gg K_m$	enzyme is saturated

Binding Equilibria As "Prefixes"

$$B + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BA \xrightarrow{k_2} B + P$$

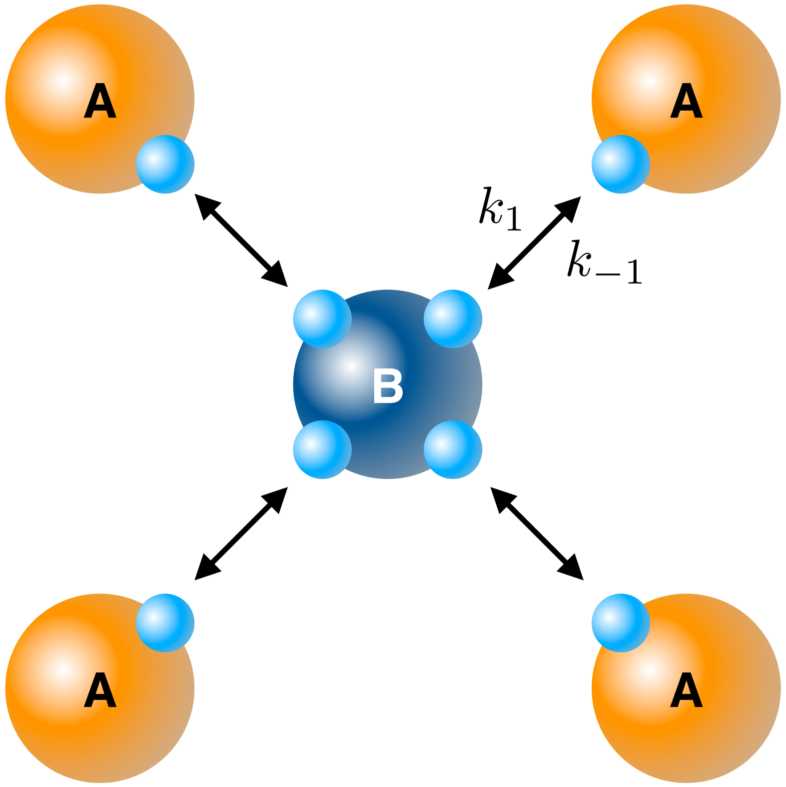


$A_t \gg B_t$ ✓



$A_t \gg B_t$ ✗

Multiple Binding Sites: Scaffolds

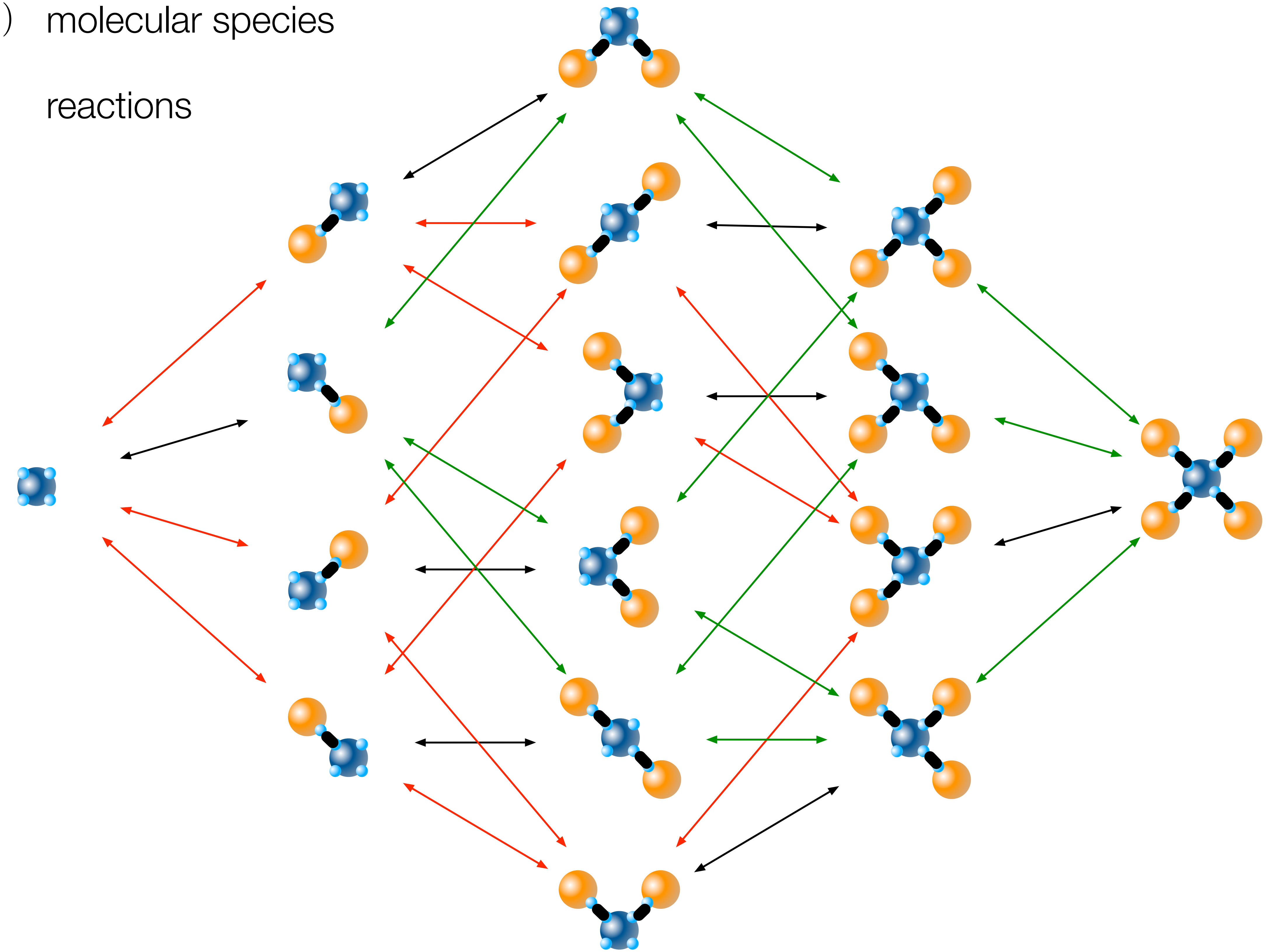


a scaffold protein with *n* binding partners

Combinatorial Reaction Network

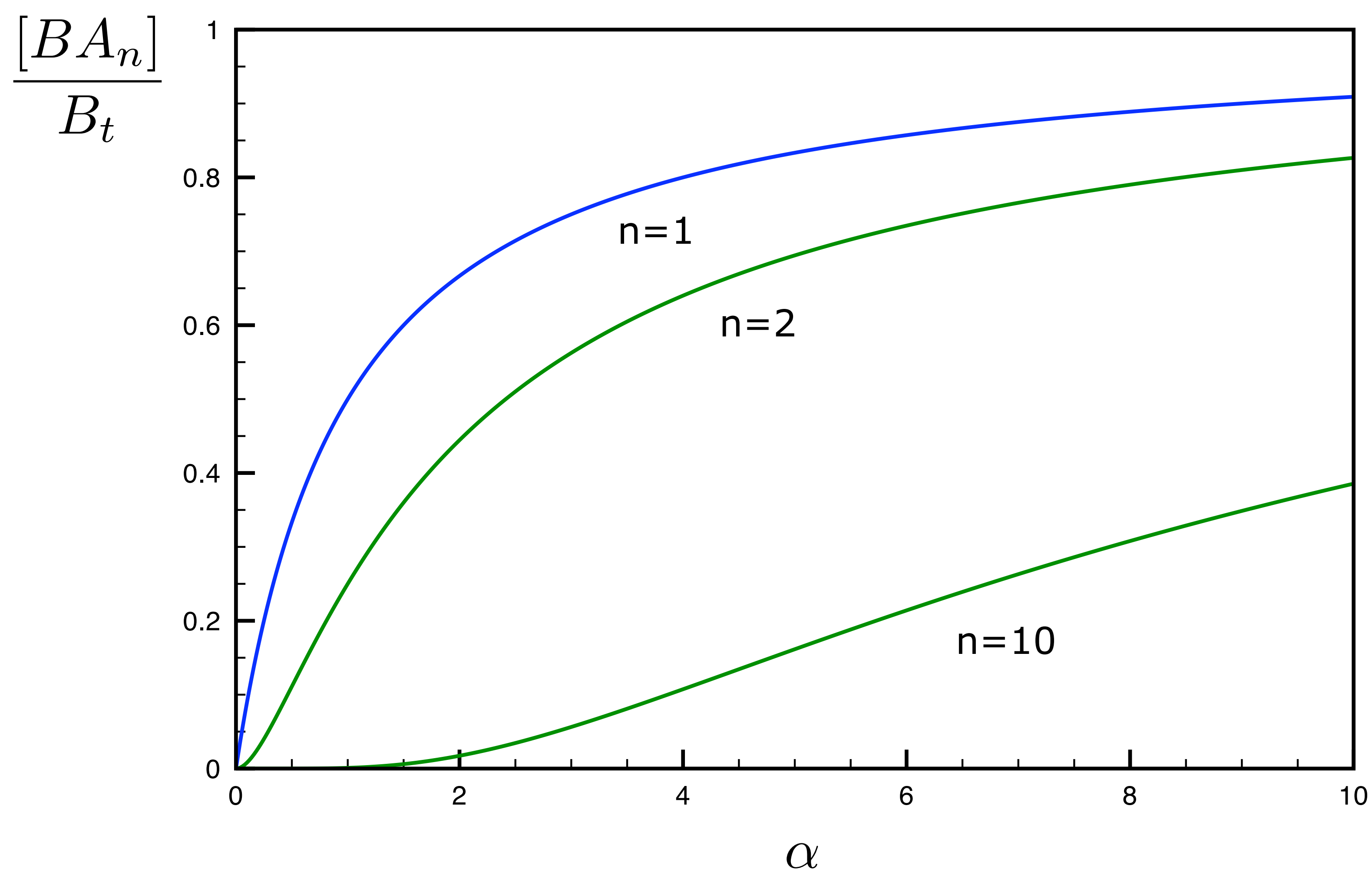
2^n $(+1)$ molecular species

$n2^{n-1}$ reactions



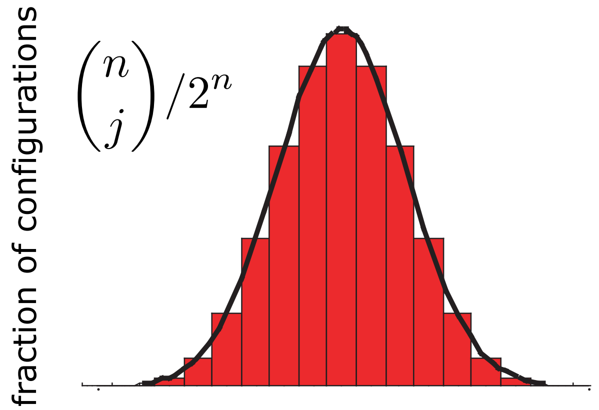
n binding sites (disordered)

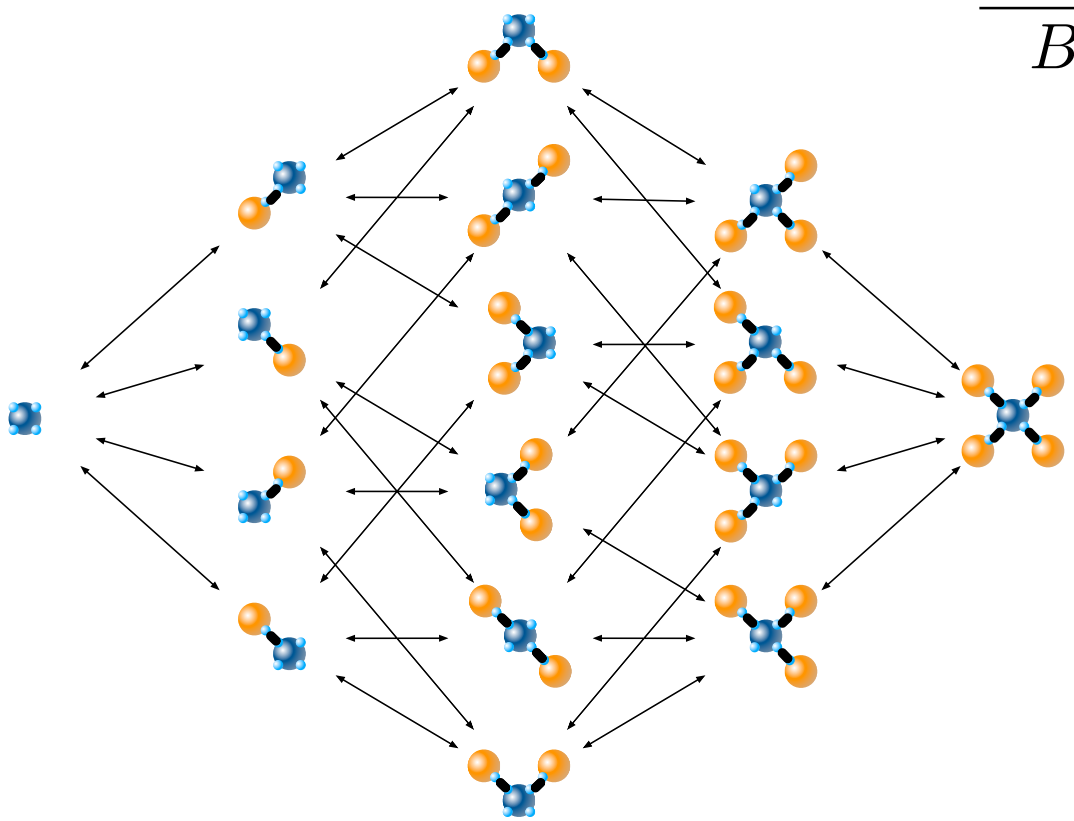
$$\frac{[BA_n]}{B_t} = \left(\frac{\alpha}{\alpha+1}\right)^n$$



$$\left(\frac{\alpha}{\alpha+1}\right)^n = \frac{1}{\left(1+\frac{1}{\alpha}\right)^n} \to 0$$

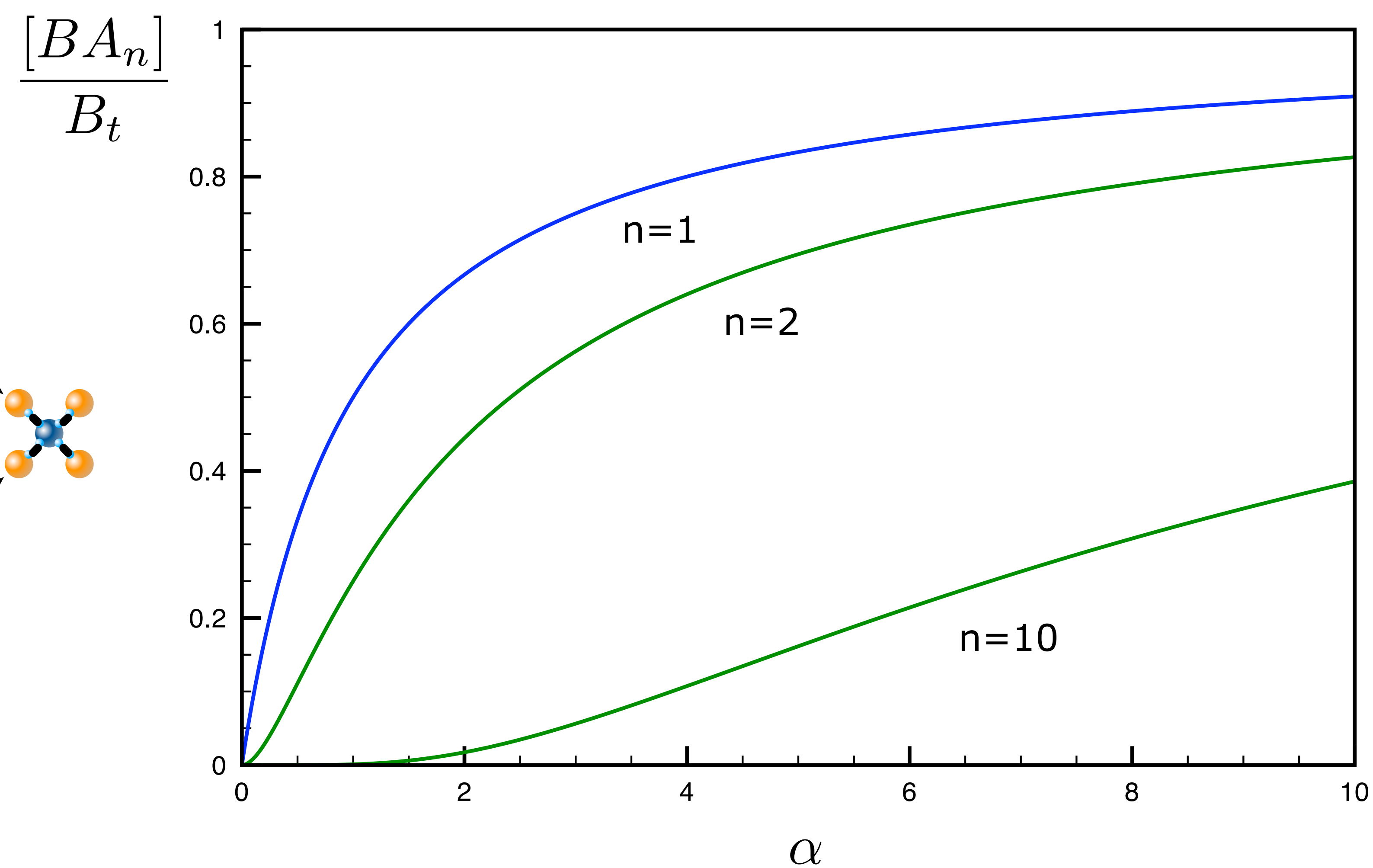
for any finite $\alpha \geq 0$ as $n \to \infty$



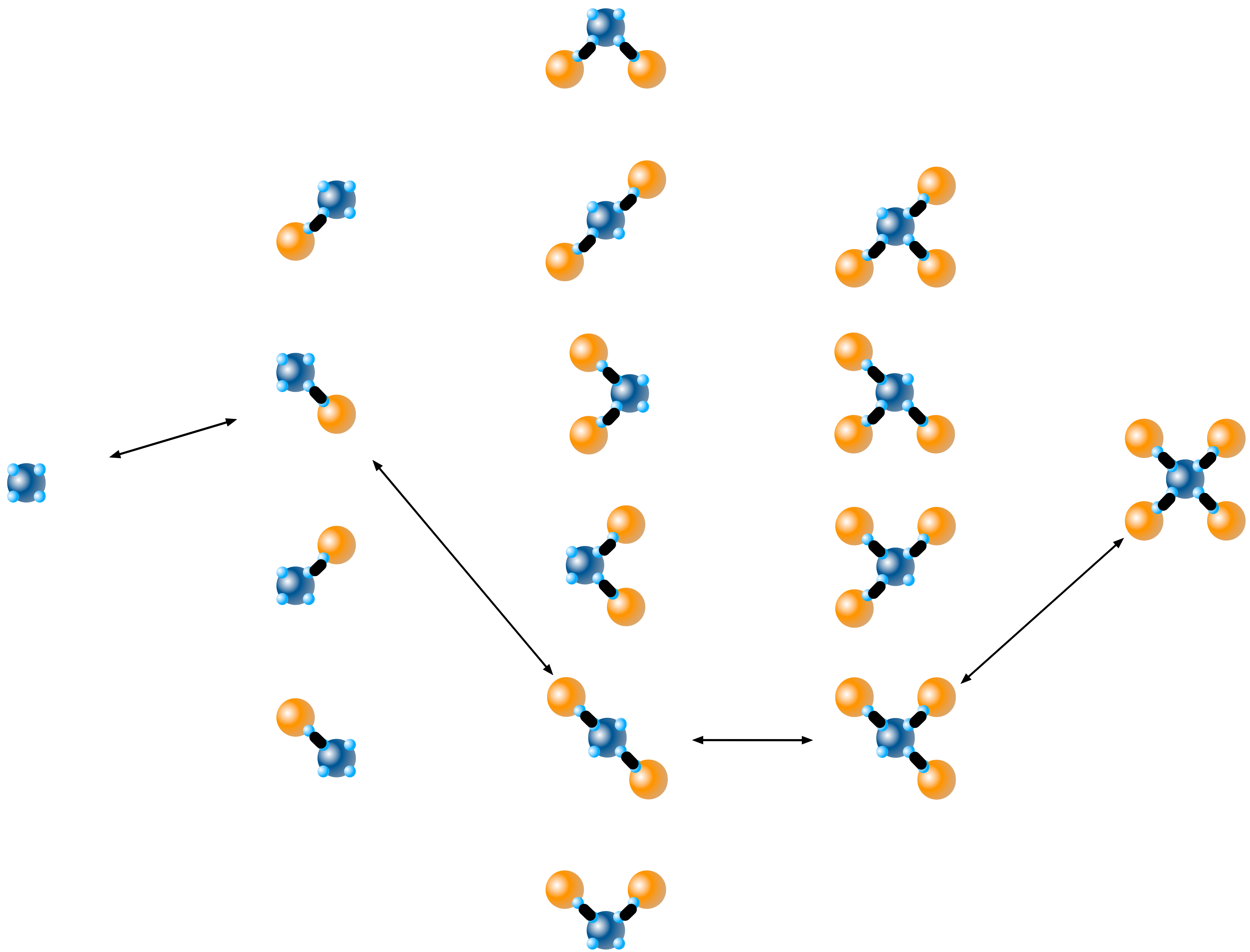


n binding sites (disordered)

$$\frac{[BA_n]}{B_t} = \left(\frac{\alpha}{\alpha+1}\right)^n$$



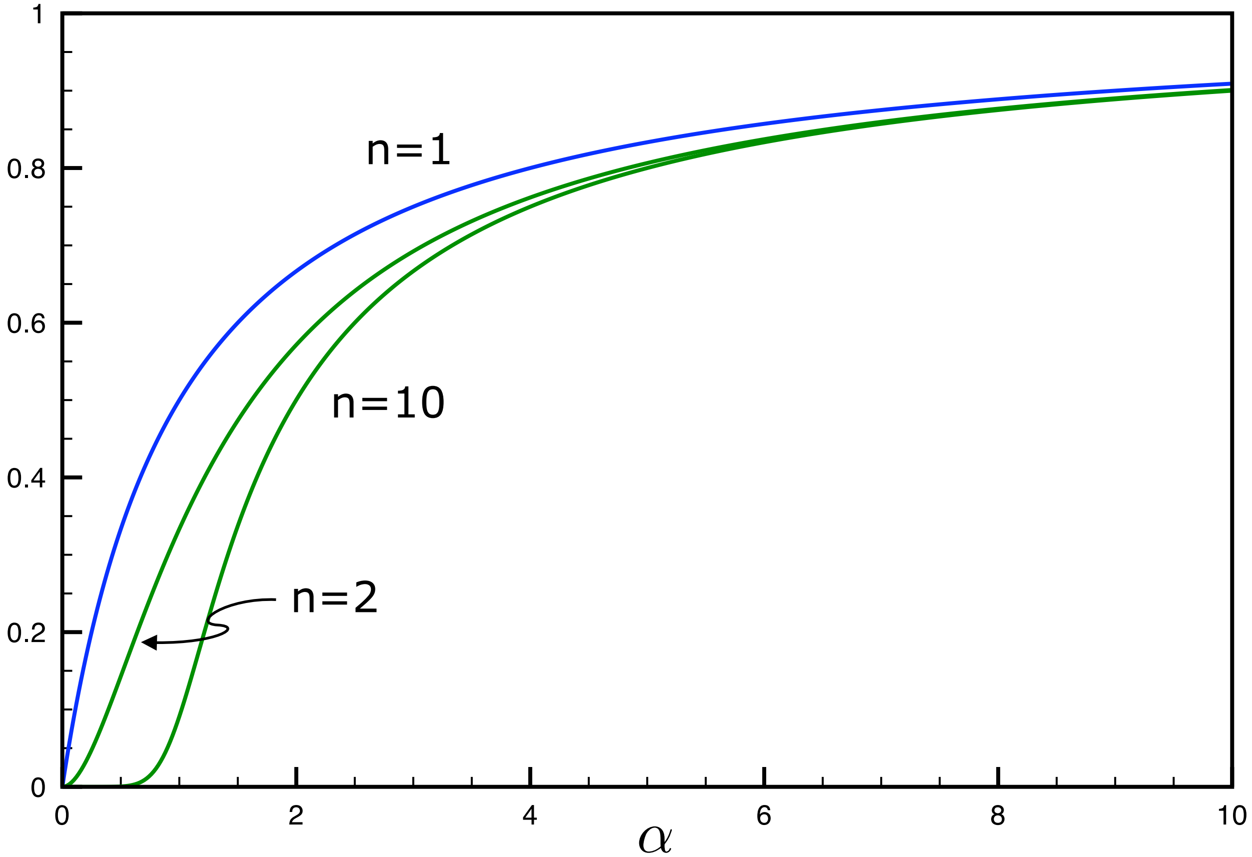
Sequential Binding



Sequential Binding & All-Or-None

sequential binding

$$\frac{[BA_n]}{B_t} = \frac{\alpha^n(1-\alpha)}{1-\alpha^{n+1}}$$

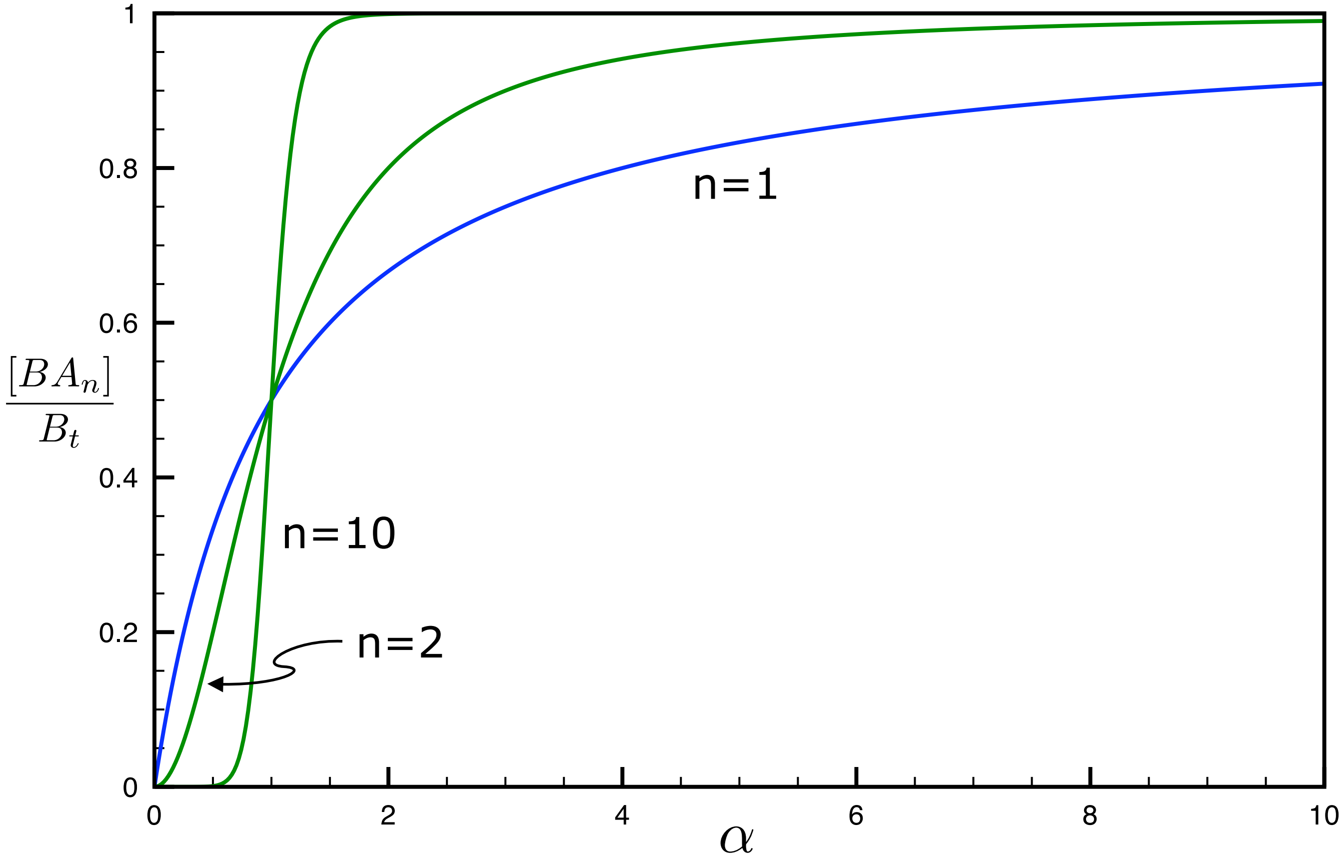


$$\frac{\alpha^n(1-\alpha)}{1-\alpha^{n+1}} \xrightarrow[n\to\infty]{} \begin{cases} 0 & \text{for } \alpha \leq 1, \\ (\alpha-1)/\alpha & \text{for } \alpha > 1 \end{cases}$$

a threshold for large n

all-or-none cooperativity (Hill)

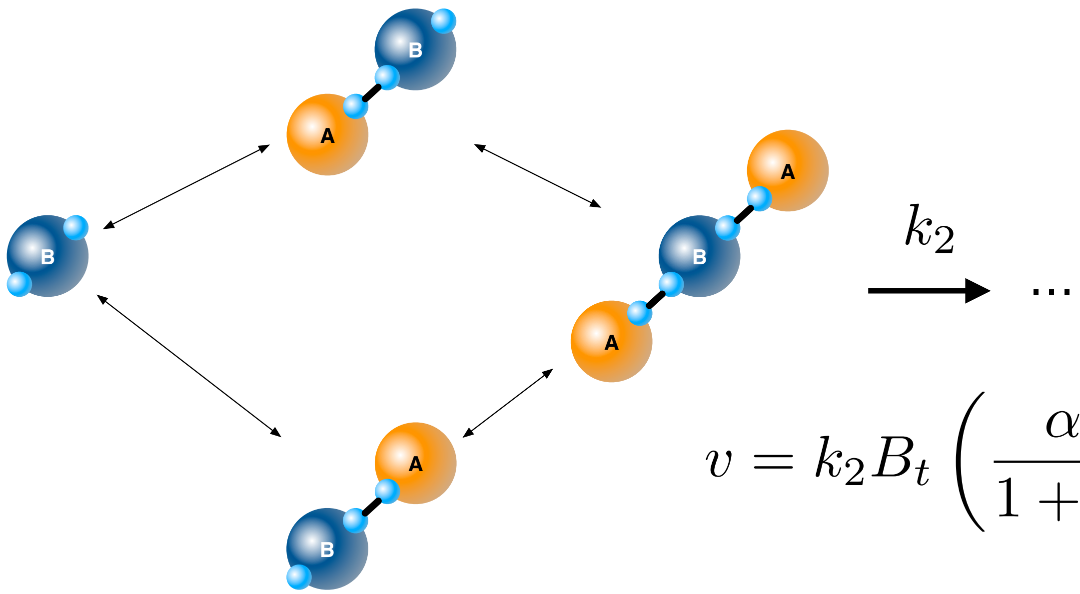
$$\frac{[BA_n]}{B_t} = \frac{\alpha^n}{1+\alpha^n}$$



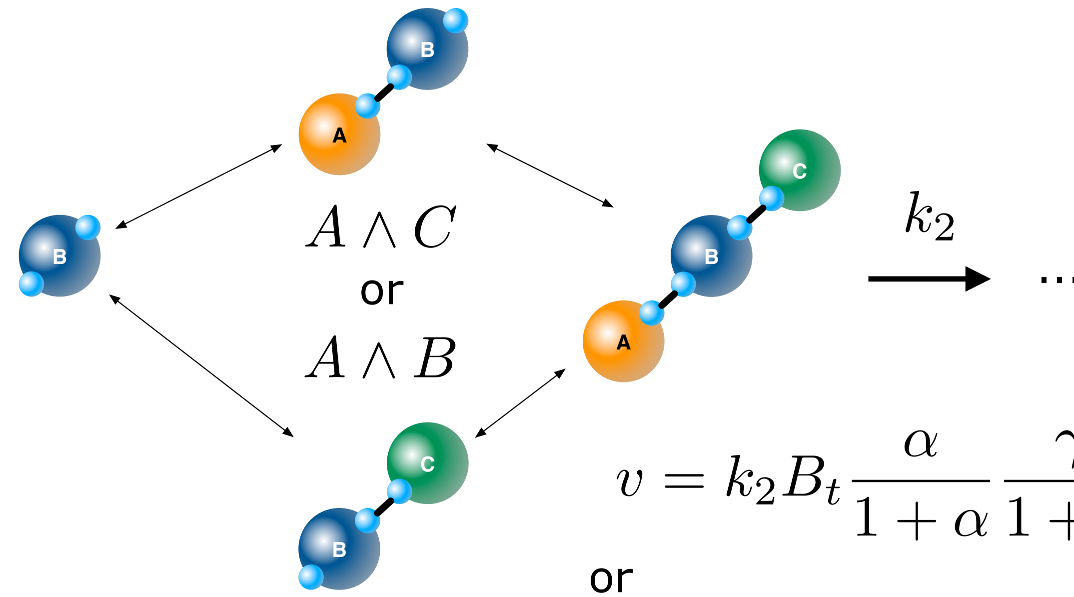
$$\frac{\alpha^n}{1+\alpha^n} \xrightarrow[n\to\infty]{} \begin{cases} 0 & \text{for } \alpha < 1, \\ 1 & \text{for } \alpha > 1 \end{cases}$$

a step-function for large n

Binding Logic



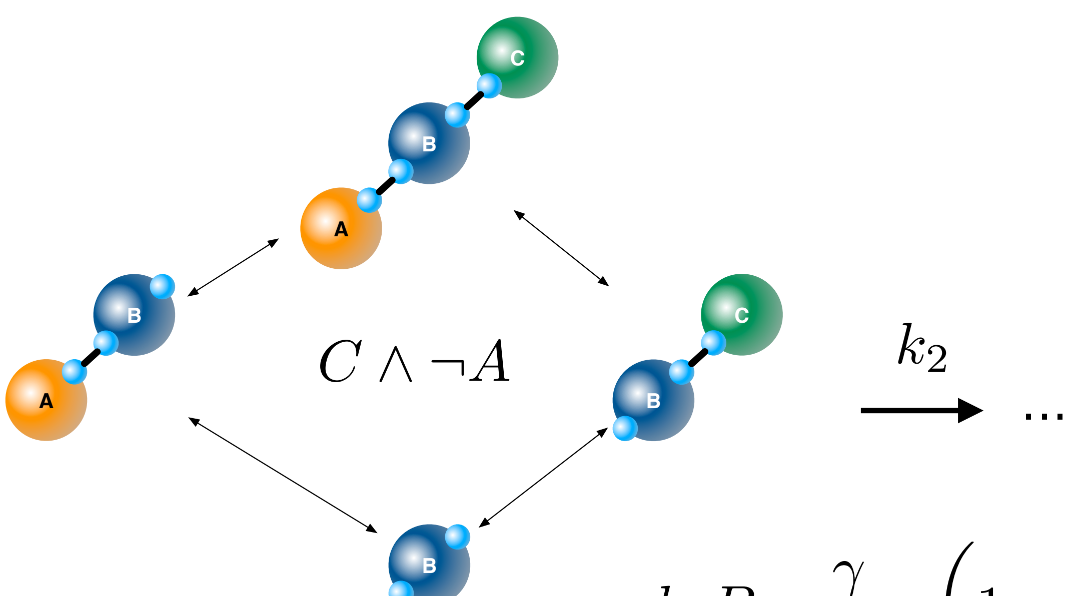
$$v = k_2 B_t \left(\frac{\alpha}{1+\alpha}\right)^2$$



$$v = k_2 B_t \frac{\alpha}{1+\alpha} \frac{\gamma}{1+\gamma}$$

or

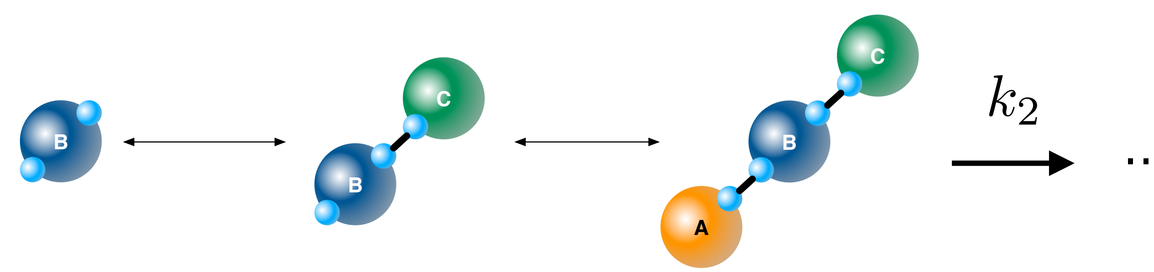
$$v = k_2 C_t \frac{\alpha\beta}{1+\beta+\alpha\beta}$$



$$v = k_2 B_t \frac{\gamma}{1+\gamma} \left(1 - \frac{\alpha}{1+\alpha}\right)$$

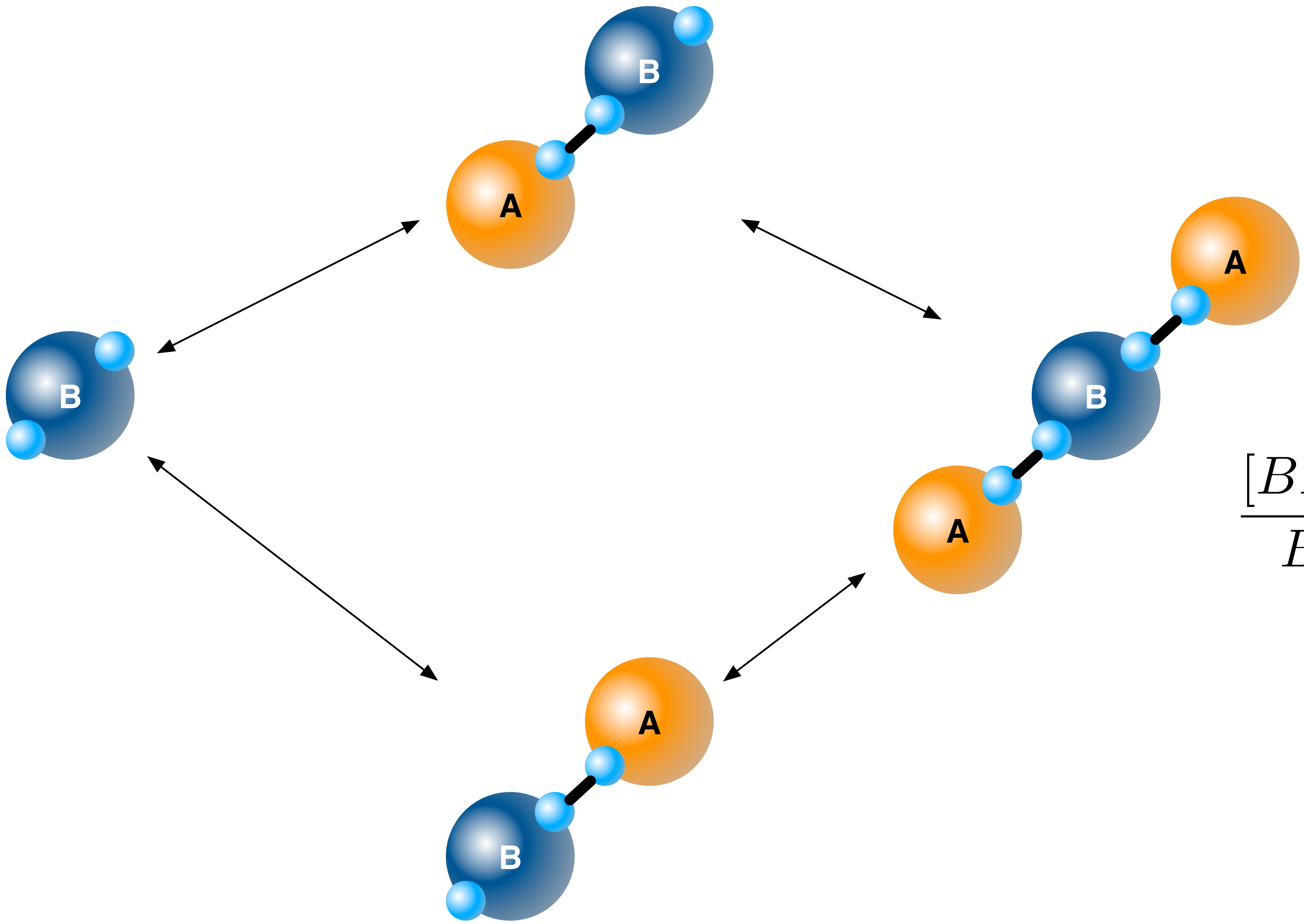
(this is non-competitive inhibition)

sequential: first BC, then ABC



$$v = k_2 C_t \frac{\alpha\beta}{1+\alpha\beta}$$

The B Side

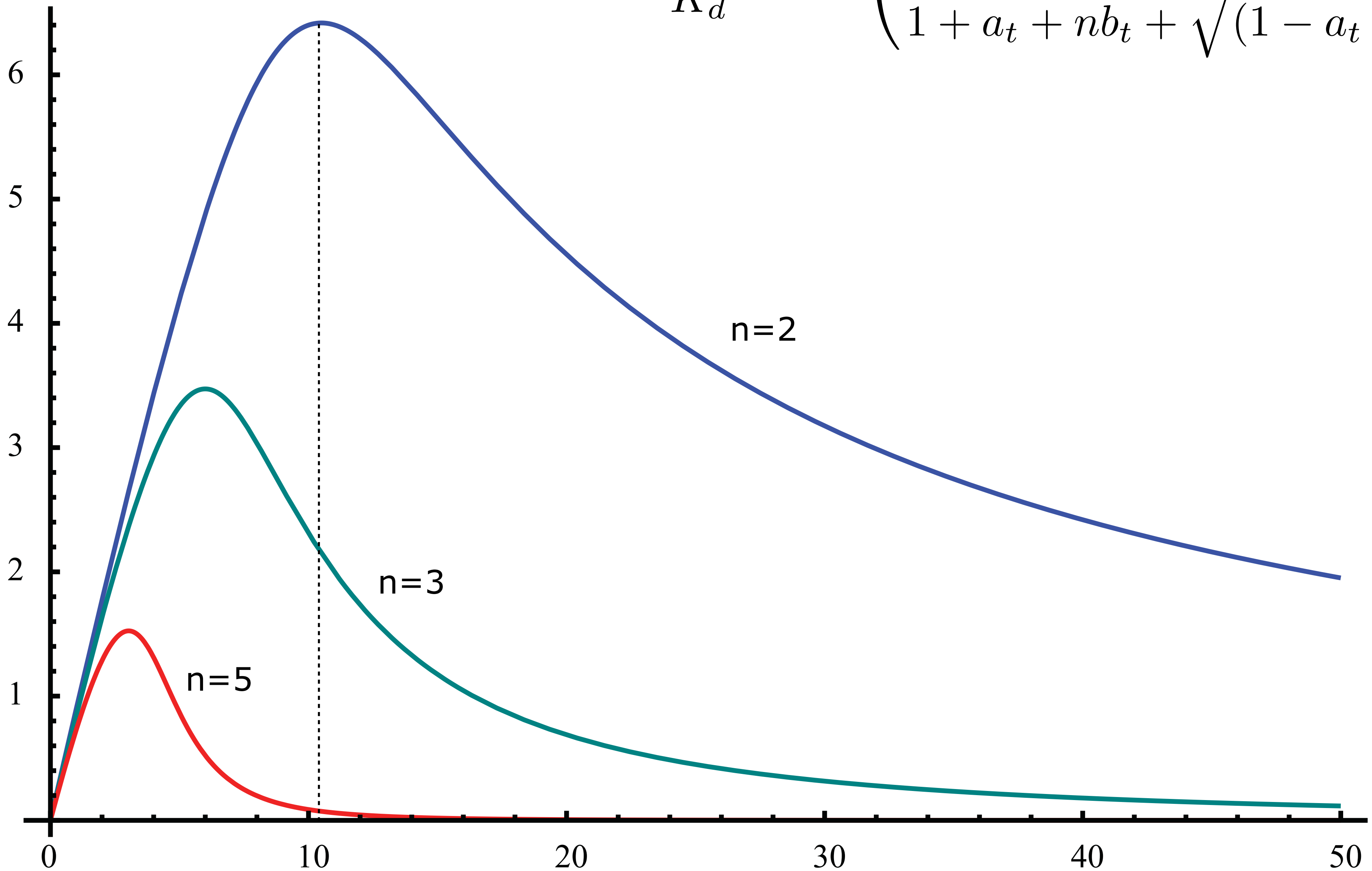


$$\frac{[BA_2]}{B_t} = \left(\frac{\alpha}{1+\alpha}\right)^2$$

Increase total B.   What happens?

The B Side

$$\frac{[BA_n]}{K_d} = b_t \left(\frac{2a_t}{1 + a_t + nb_t + \sqrt{(1 - a_t + nb_t)^2 + 4a_t}} \right)^n$$

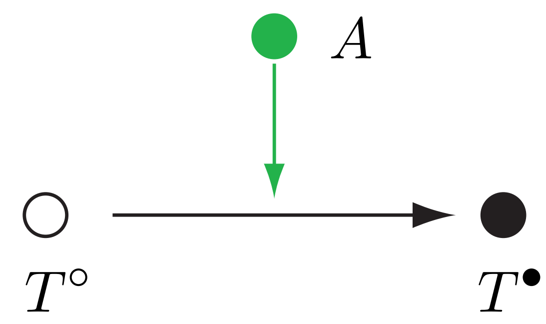


$\frac{[BA_n]}{K_d}$ vs. b_t

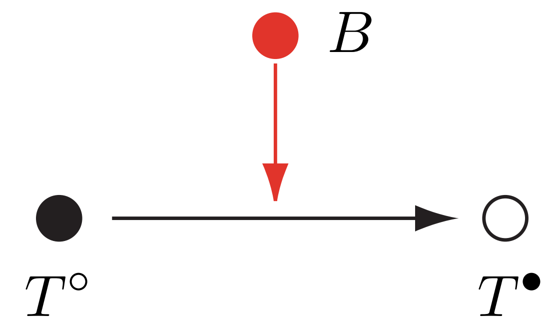
$$b_t = \frac{1}{2}(1 + a_t) \qquad (@\, n = 2)$$

A Do-Undo Loop

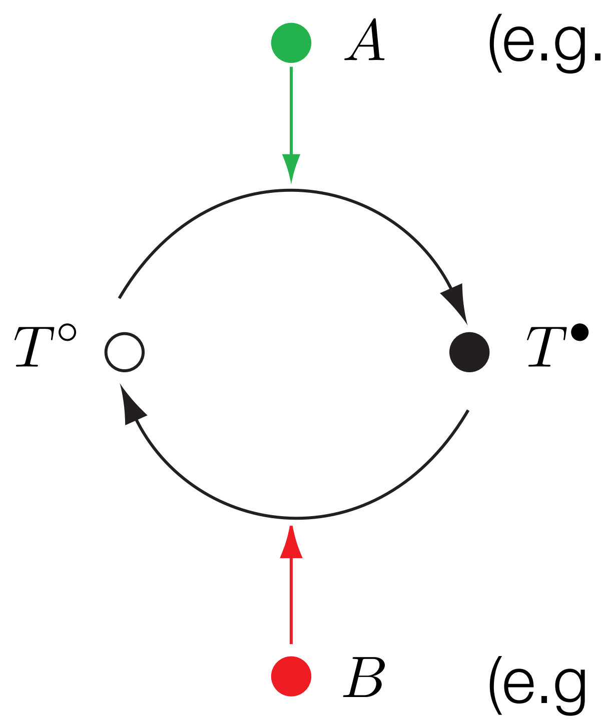
$$A + T^{\circ} \underset{k_{-1}^{A}}{\overset{k_1^{A}}{\rightleftharpoons}} AT^{\circ} \xrightarrow{k_2^{A}} A + T^{\bullet}$$



$$B + T^{\bullet} \underset{k_{-1}^{B}}{\overset{k_1^{B}}{\rightleftharpoons}} BT^{\bullet} \xrightarrow{k_2^{B}} B + T^{\circ}$$



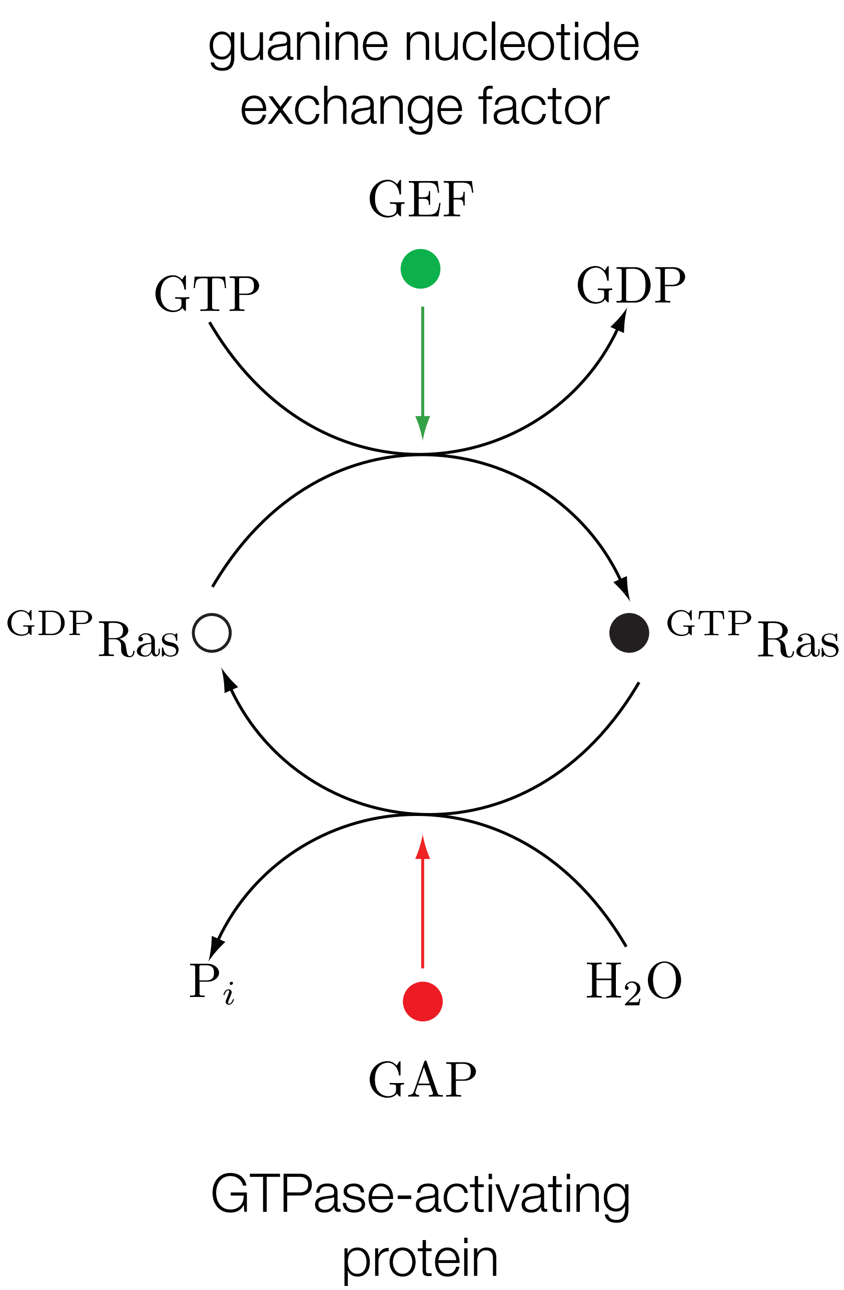
$$T = [T^{\circ}] + [T^{\bullet}]$$



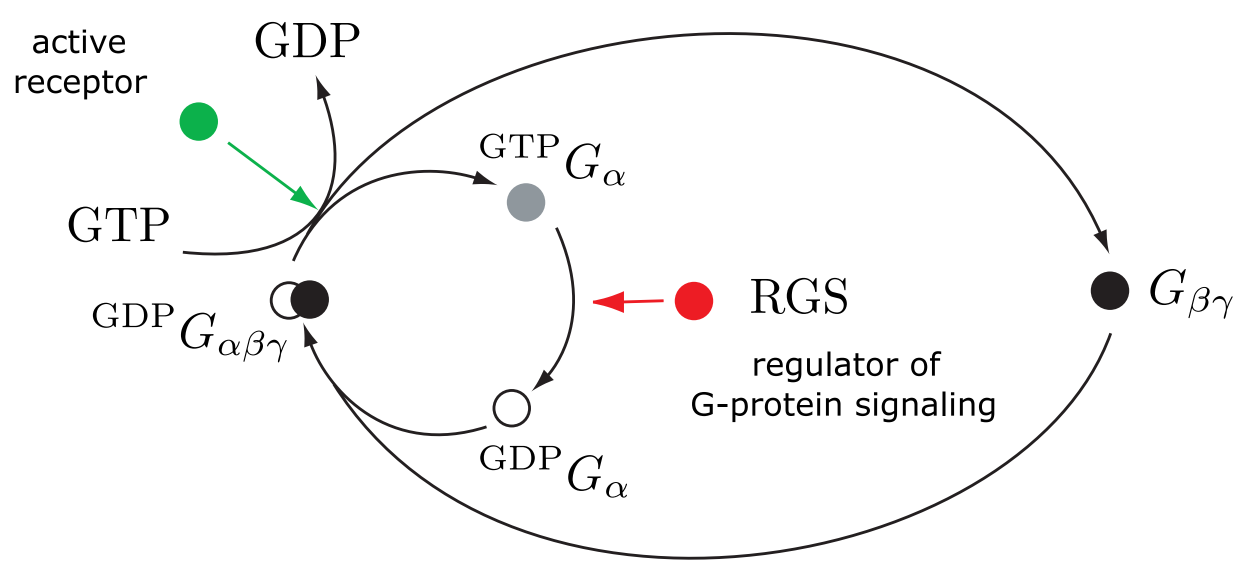
(e.g. a kinase)

(e.g a phosphatase)

$$\frac{d[T^{\bullet}]}{dt} = \frac{k_2^{A} A_t (T_t - [T^{\bullet}])}{K_m^{A} + T_t - [T^{\bullet}]} - \frac{k_2^{B} B_t [T^{\bullet}]}{K_m^{B} + [T^{\bullet}]}$$



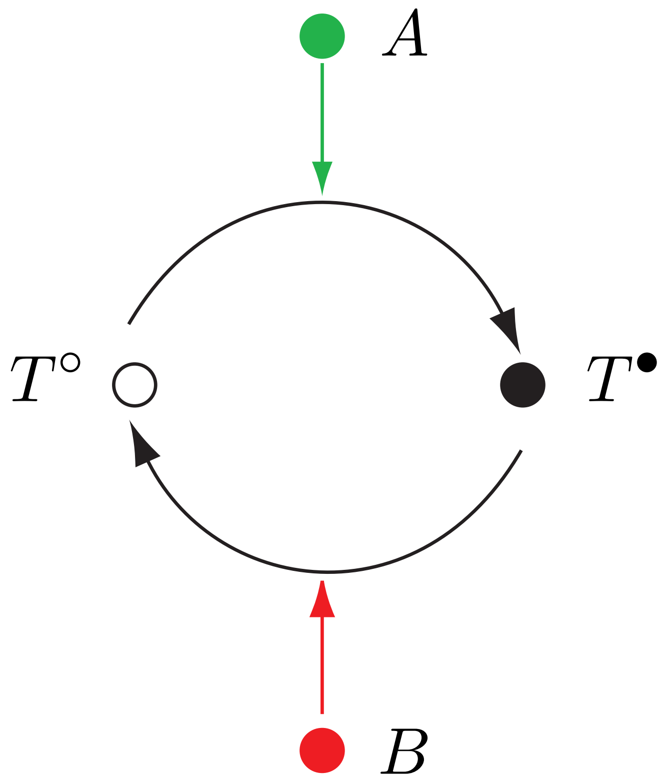
small G proteins



heterotrimeric G proteins

(a variety of combinations from 23 G_α, 6G_β, 12G_γ subunits)

A Do-Undo Loop



$$\frac{d[T^\bullet]}{dt} = \frac{k_2^A A_t (T - [T^\bullet])}{K_m^A + T - [T^\bullet]} - \frac{k_2^B B_t [T^\bullet]}{K_m^B + [T^\bullet]} \quad \text{with} \quad T = [T^\circ] + [T^\bullet]$$

$$\frac{\overline{[T^\bullet]}}{T} = \frac{2r}{1 + r + (K - r)t_B + \sqrt{(1 + r + (K - r)t_B)^2 - 4r(K - r)t_B}}$$

dimensionless

with $K = \dfrac{K_m^B}{K_m^A}$

$$t_B = \frac{T}{K_m^B}$$

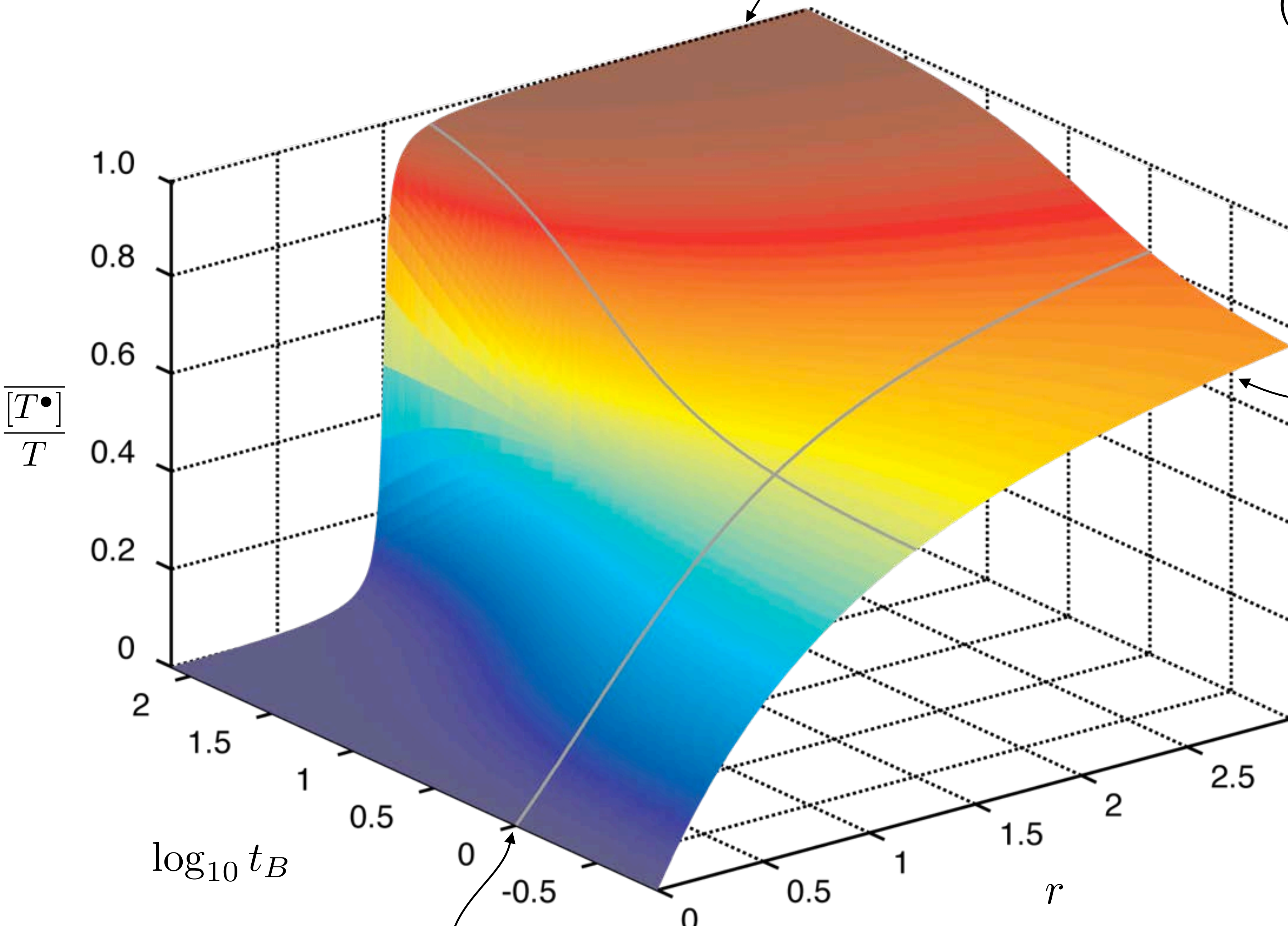
$$r = \frac{k_2^A a_t}{k_2^B b_t} \qquad a_t = \frac{A_t}{K_m^A} \qquad b_t = \frac{B_t}{K_m^B}$$

The Do-Undo Loop: An "Atom" Of Molecular Control

$$K = \frac{K_m^B}{K_m^A} = 1$$

steady-state solution of $\frac{d[T^\bullet]}{dt} \approx k_2^A A_t - k_2^B B_t$

(saturated regime)



steady-state solution of

$$\frac{d[T^\bullet]}{dt} = \frac{k_2^A A_t}{K_m^A}(T - [T^\bullet]) - \frac{k_2^B B_t}{K_m^B}[T^\bullet]$$

(linear regime)

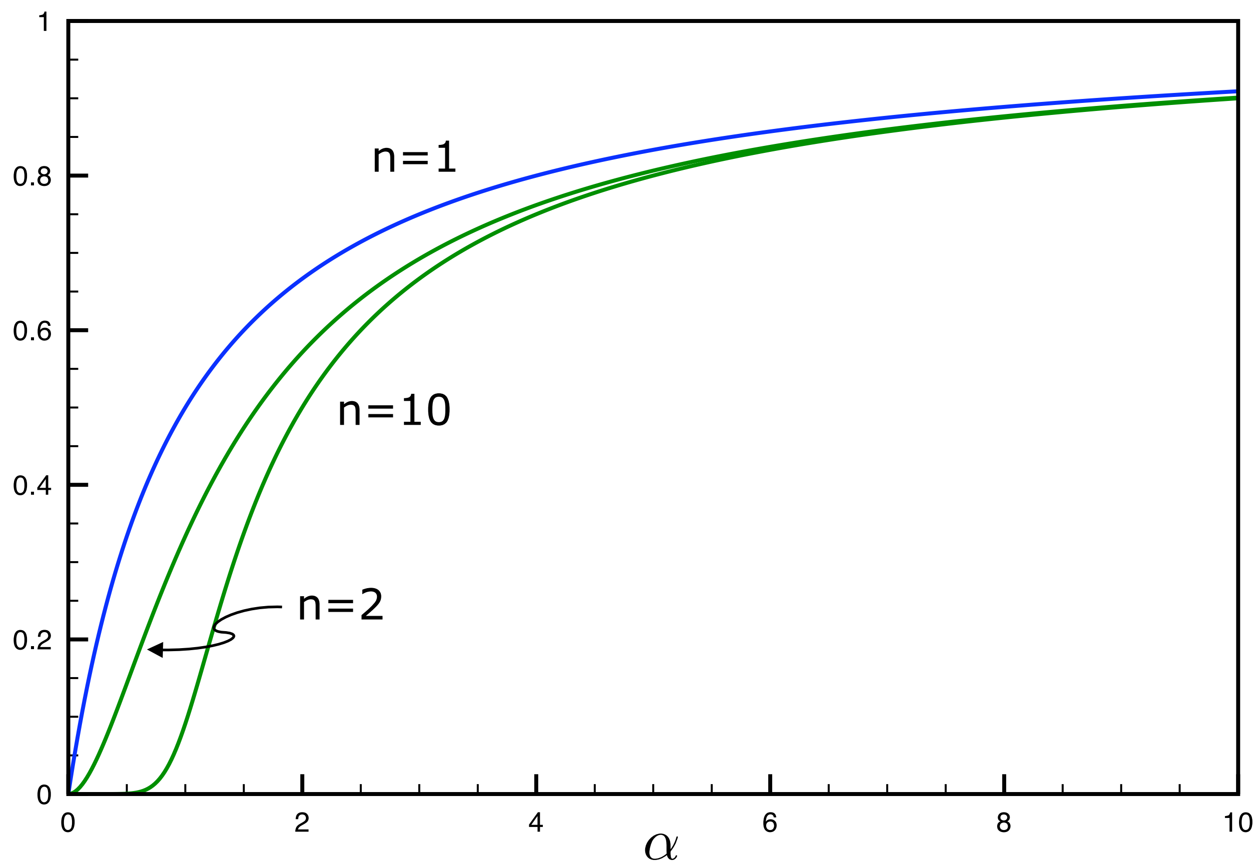
$$\frac{[T^\bullet]}{T} = \frac{r}{r+1}$$

$K_m^A = K_m^B = 0.74\ \mu M$

The Do-Undo Loop Chain

sequential binding

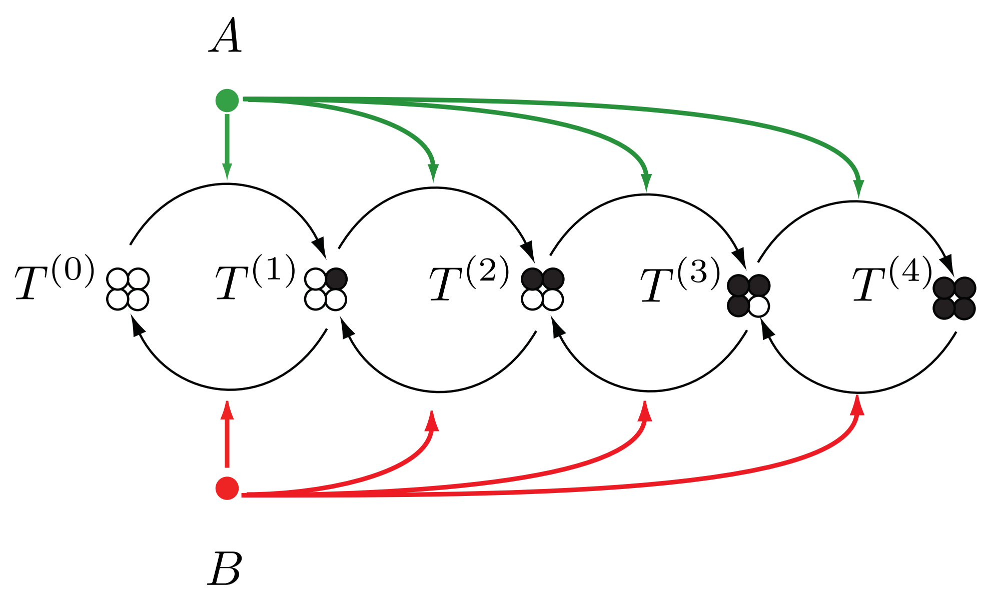
$$\frac{[BA_n]}{B_t} = \frac{\alpha^n(1-\alpha)}{1-\alpha^{n+1}}$$



$$\frac{\alpha^n(1-\alpha)}{1-\alpha^{n+1}} \xrightarrow[n\to\infty]{} \begin{cases} 0 & \text{for } \alpha \leq 1, \\ (\alpha-1)/\alpha & \text{for } \alpha > 1 \end{cases}$$

sequential phosphorylation w/ linear kinetics

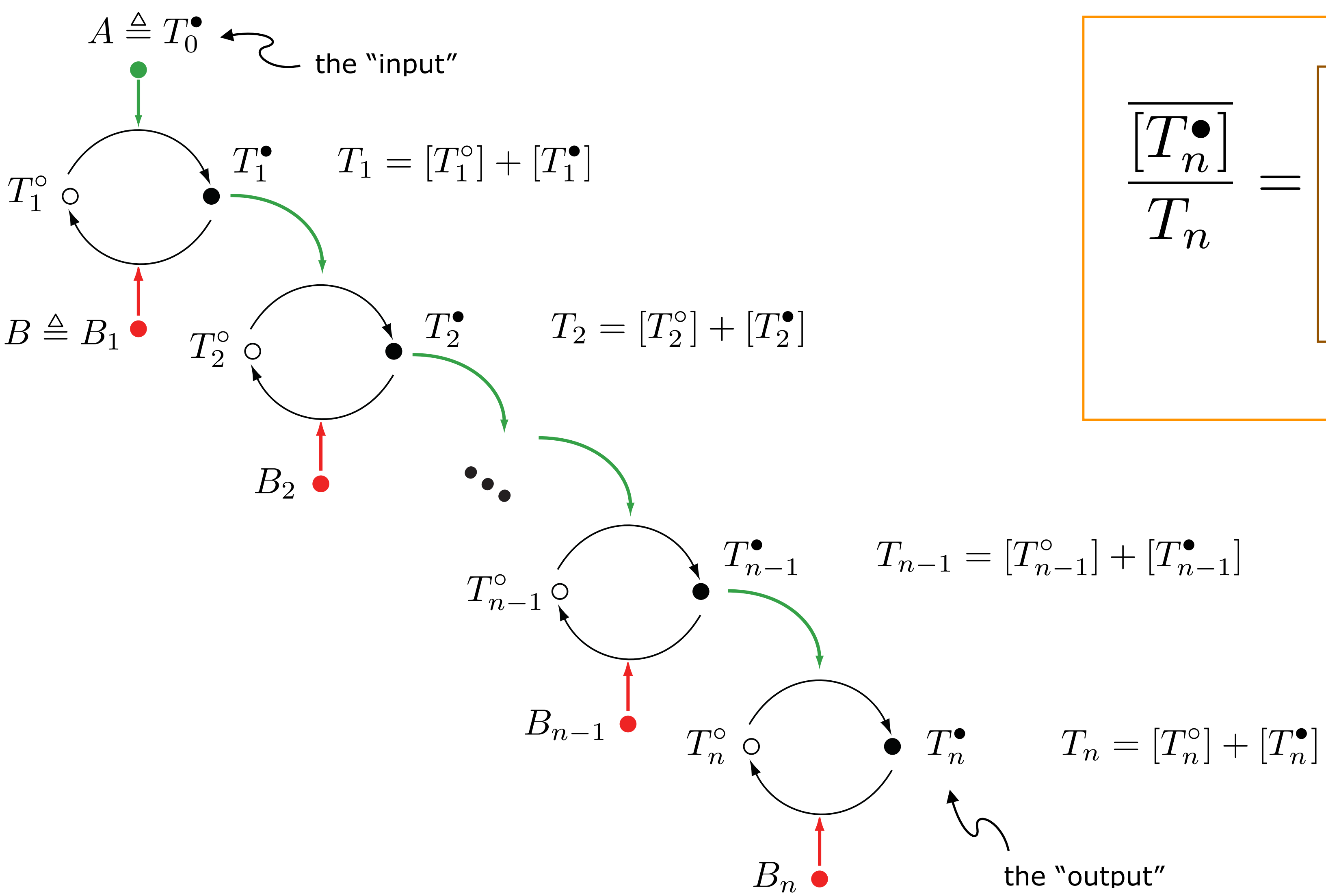
$$\frac{\overline{[T^{(n)}]}}{T} = \frac{r^n(1-r)}{1-r^{n+1}} \quad \text{with} \quad r = \frac{k_2^A a_t}{k_2^B b_t}$$



The Do-Undo Loop Cascade

$$r_i = \frac{k_2^A T_{i-1}}{k_2^B B_i} \quad \text{and} \quad r_i = r \quad i = 2, \ldots, n$$

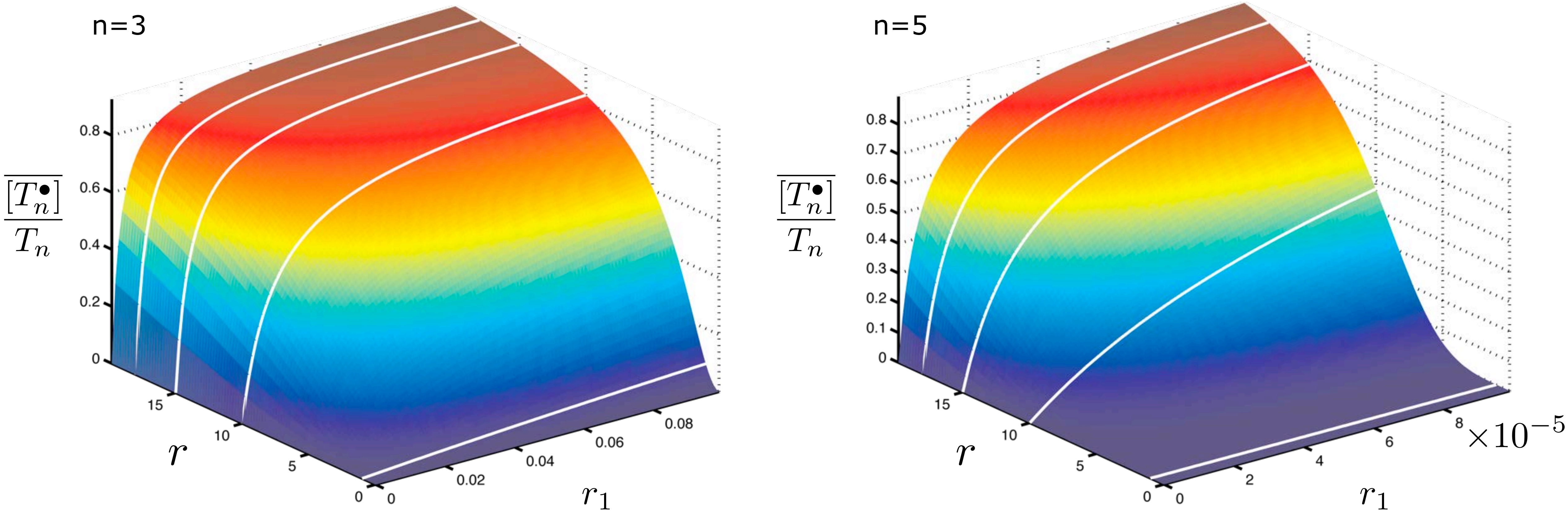
$$r_1 = \frac{k_2^A A}{k_2^B B} \quad \text{the input variable}$$



$$\frac{\overline{[T_n^\bullet]}}{T_n} = \frac{r_1}{r_1 + \dfrac{r-1}{r^n - 1}} \; \frac{r^{n-1}(r-1)}{r^n - 1}$$

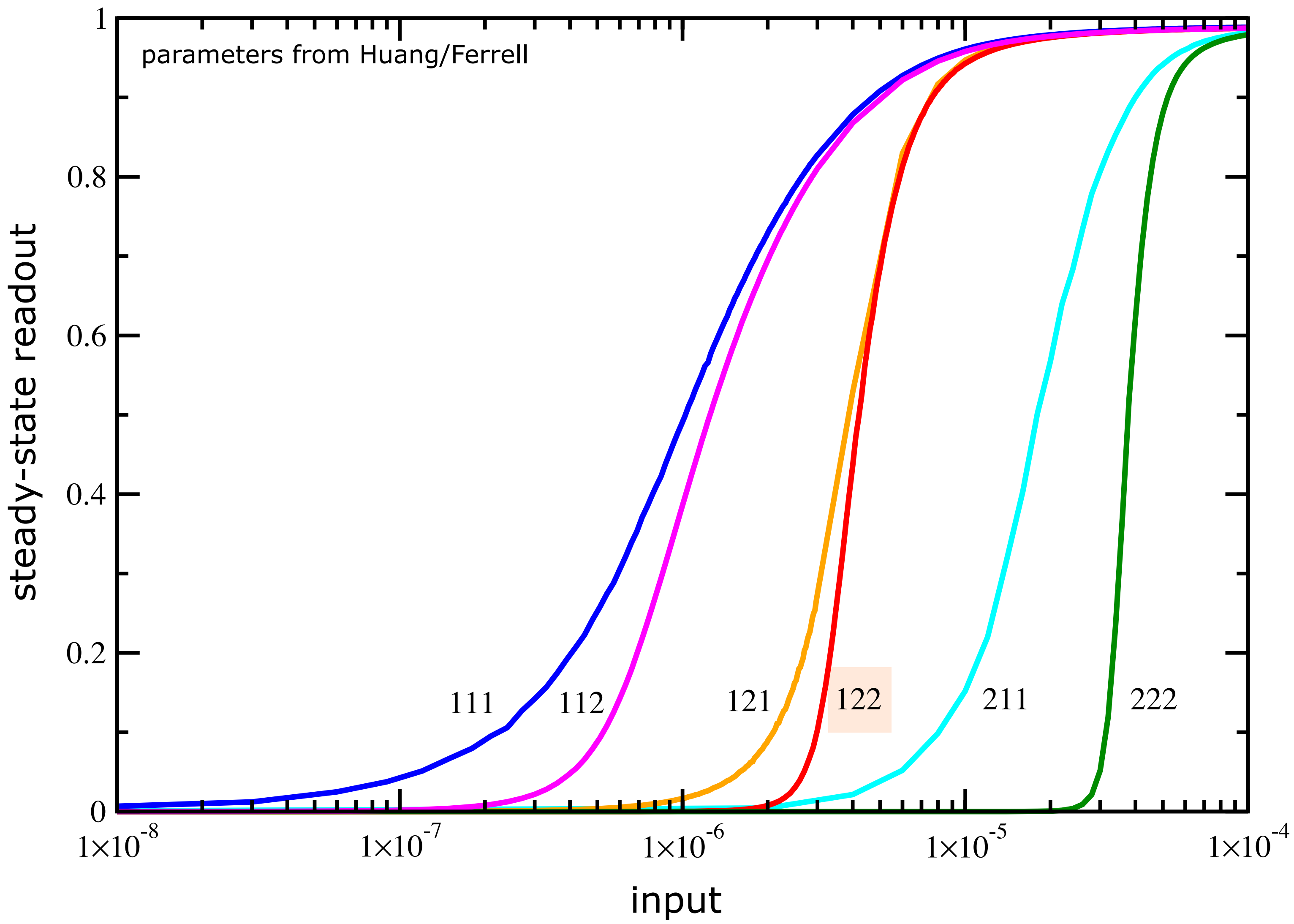
The Do-Undo Loop Cascade

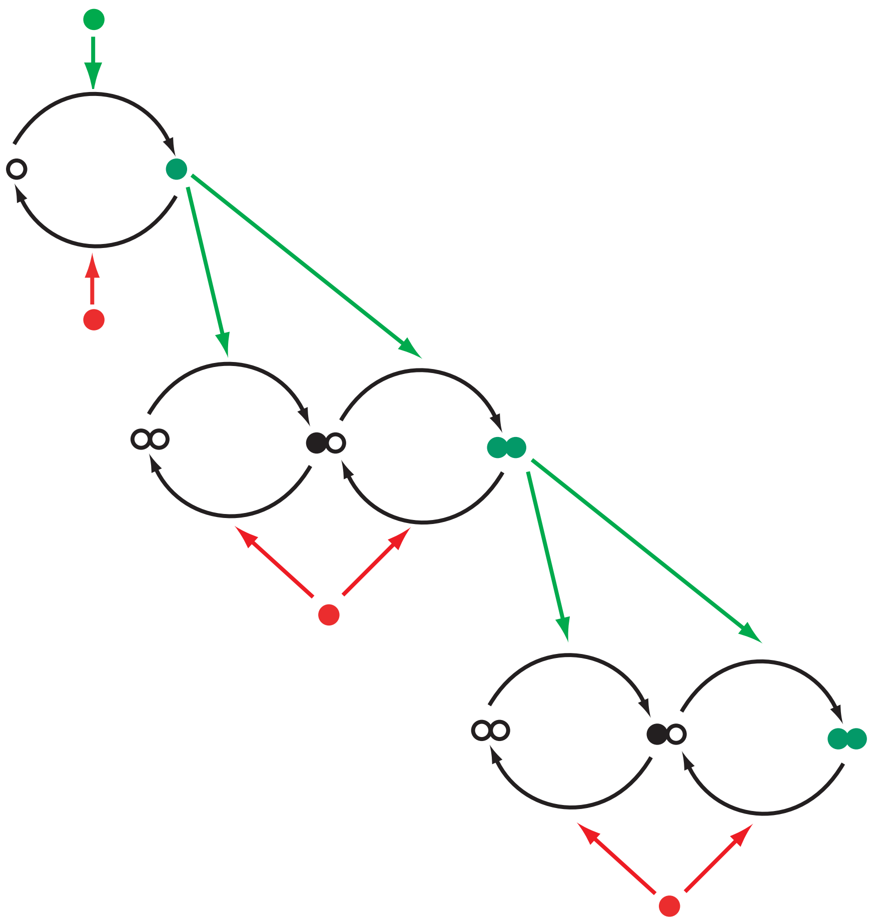
$$\frac{\overline{[T_n^\bullet]}}{T_n} = \frac{r_1}{r_1 + \frac{r-1}{r^n - 1}} \frac{r^{n-1}(r-1)}{r^n - 1}$$



notice the scale difference between n=3 and n=5

The Do-Undo Loop Cascade With "Depth" and "Width"

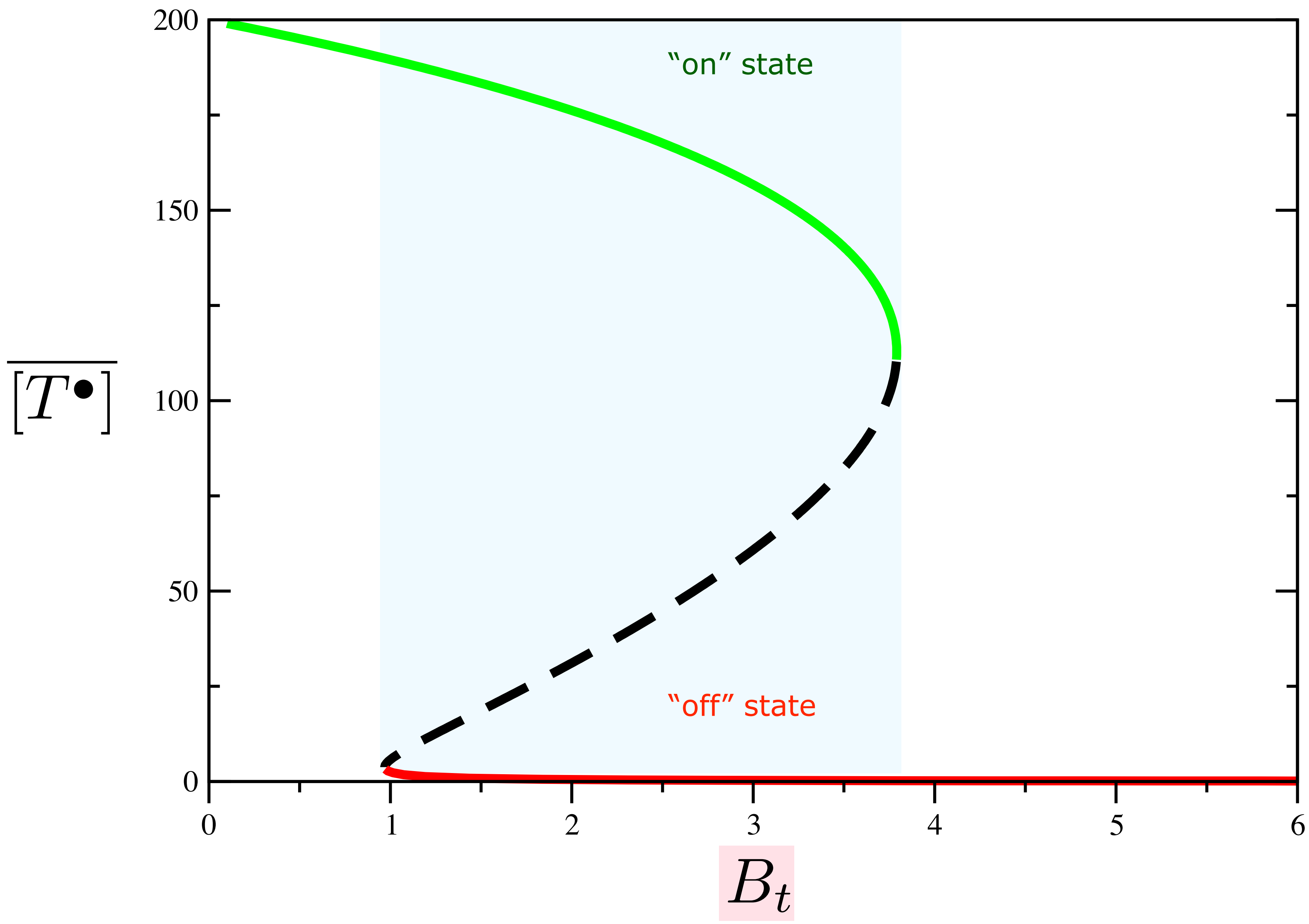


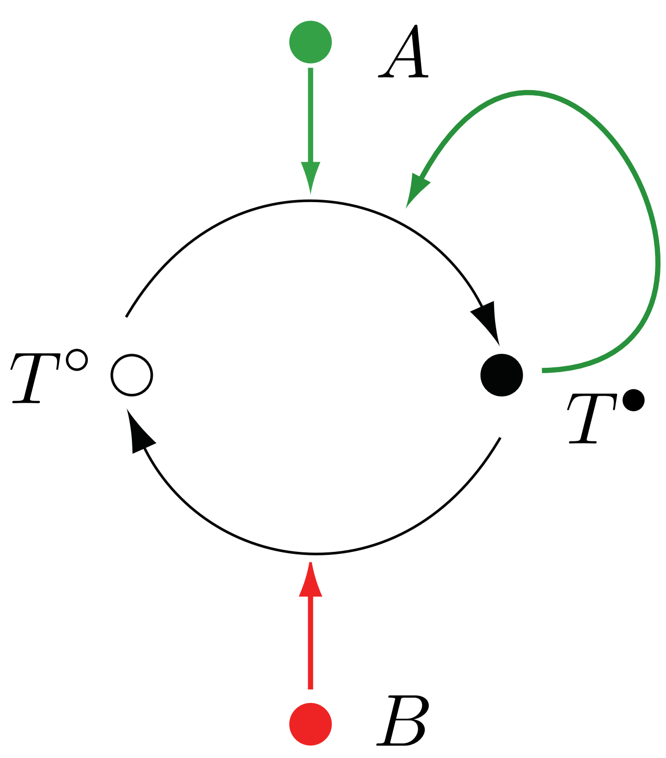


"122" cascade

The Do-Undo Loop With Feedback: Memory

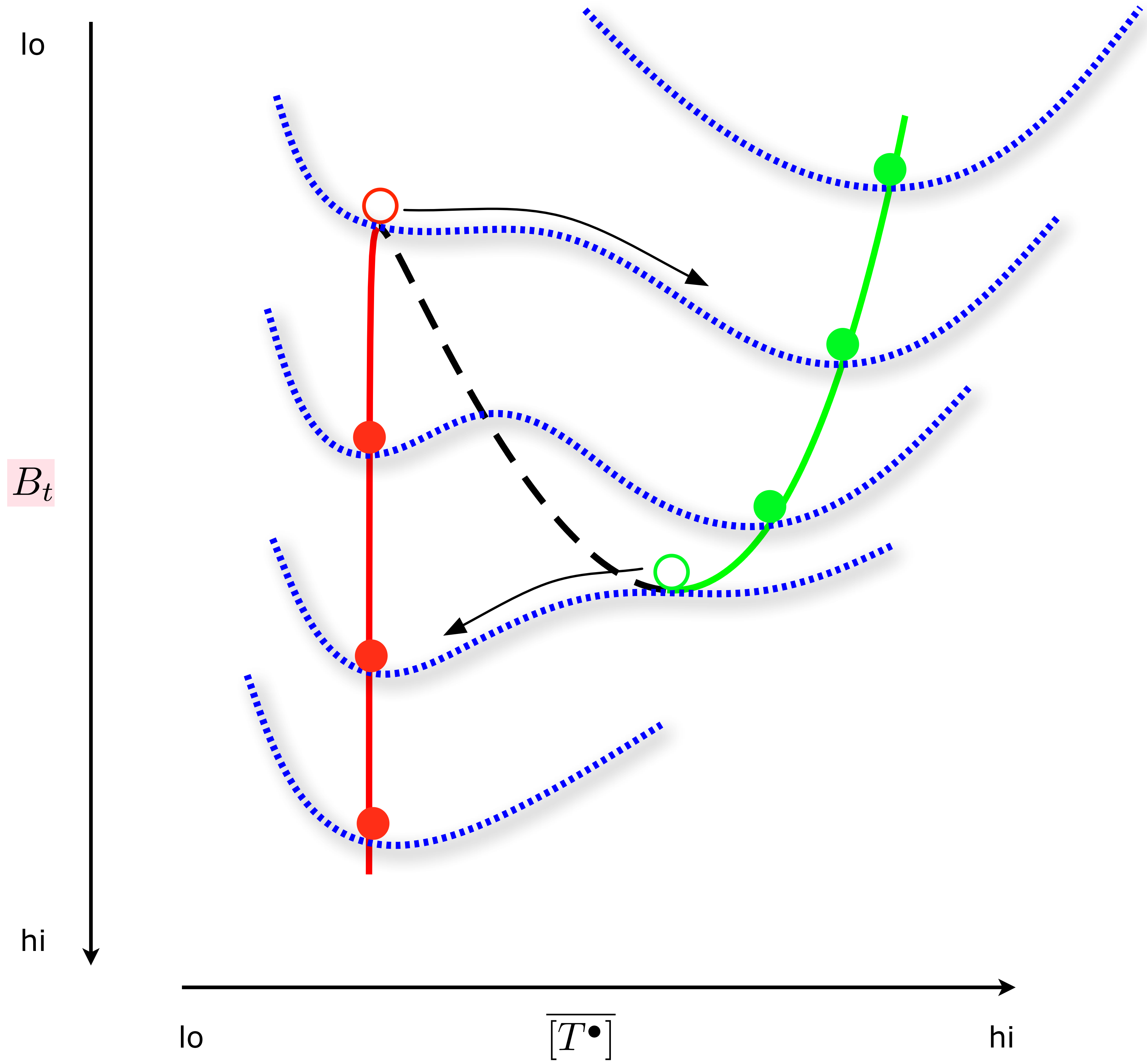
$$\frac{d[T^\bullet]}{dt} = \boxed{\frac{k_2^A A_t (T - [T^\bullet])}{K_m^A + T - [T^\bullet]} + \frac{k_2^T [T^\bullet](T - [T^\bullet])}{K_m^T + T - [T^\bullet]}} - \boxed{\frac{k_2^B B_t [T^\bullet]}{K_m^B + [T^\bullet]}}$$

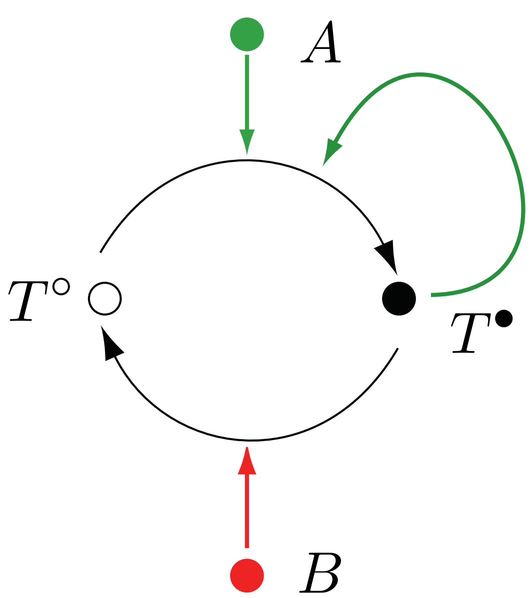


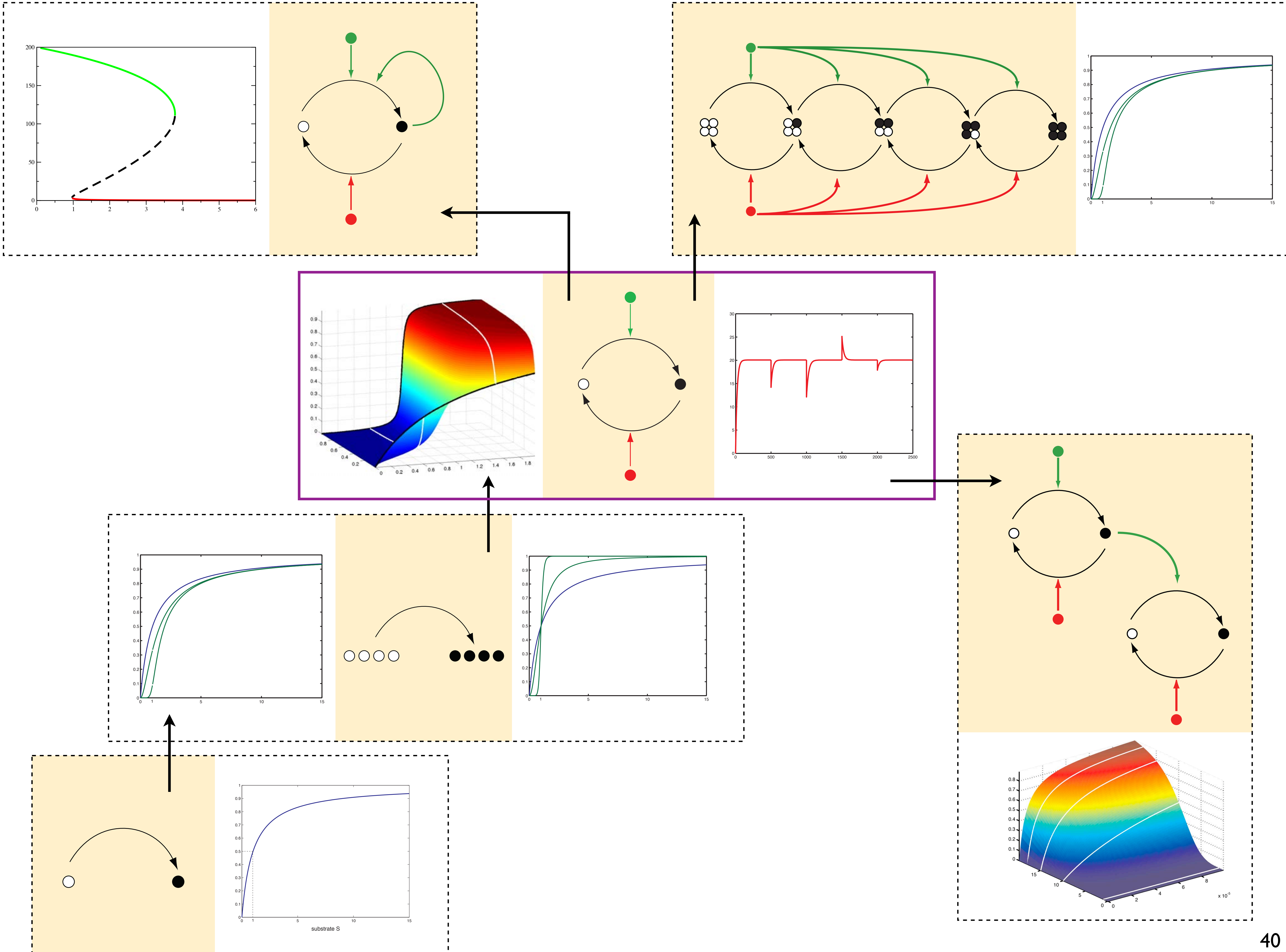


$E_a = 40$
$S = 200$
$K_m^{(a)} = 1100$
$K_m^{(s)} = 200$
$K_m^{(b)} = 11$
$k_2^{(a)} = 0.1$
$k_2^{(b)} = 10$
$k_2^{(s_1)} = 1$

Double-Well Analogy






substrate S