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, IRIF, Université de Paris
"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 And Look-Ahead

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)

3. Modeling cellular information processing the classical way
   (Modélisation 'classique' du traitement de l'information cellulaire)

4. Modeling cellular information processing the rule-based way
   (Modélisation basé sur les règles; introduction)

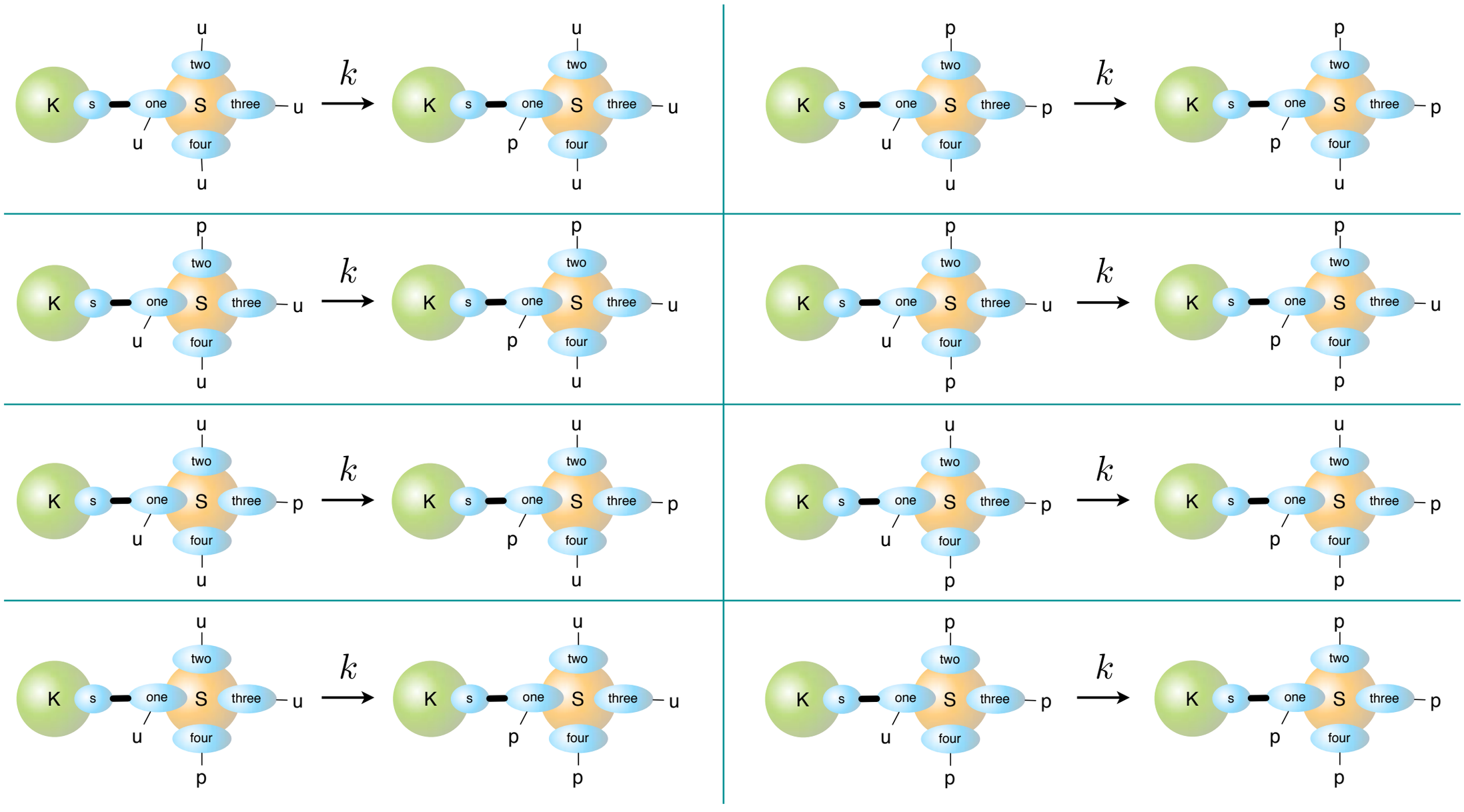
5. Examples of rule-based models
   (Modélisation basé sur les règles; examples)

6. Causality in rule-based dynamics
   (Causalité)

7. Combinatorial scaffolding
   (Echafaudage combinatoire)

8. Cellular learning?
   (Apprentissage cellulaire?)

Reactions Don't Leverage Independence



Basic CTMC Loop

stochastic rate constant

$$\gamma = \frac{k}{\mathcal{A}V^{n-1}} \quad \text{molecule}^{-1}s^{-1}$$

rules

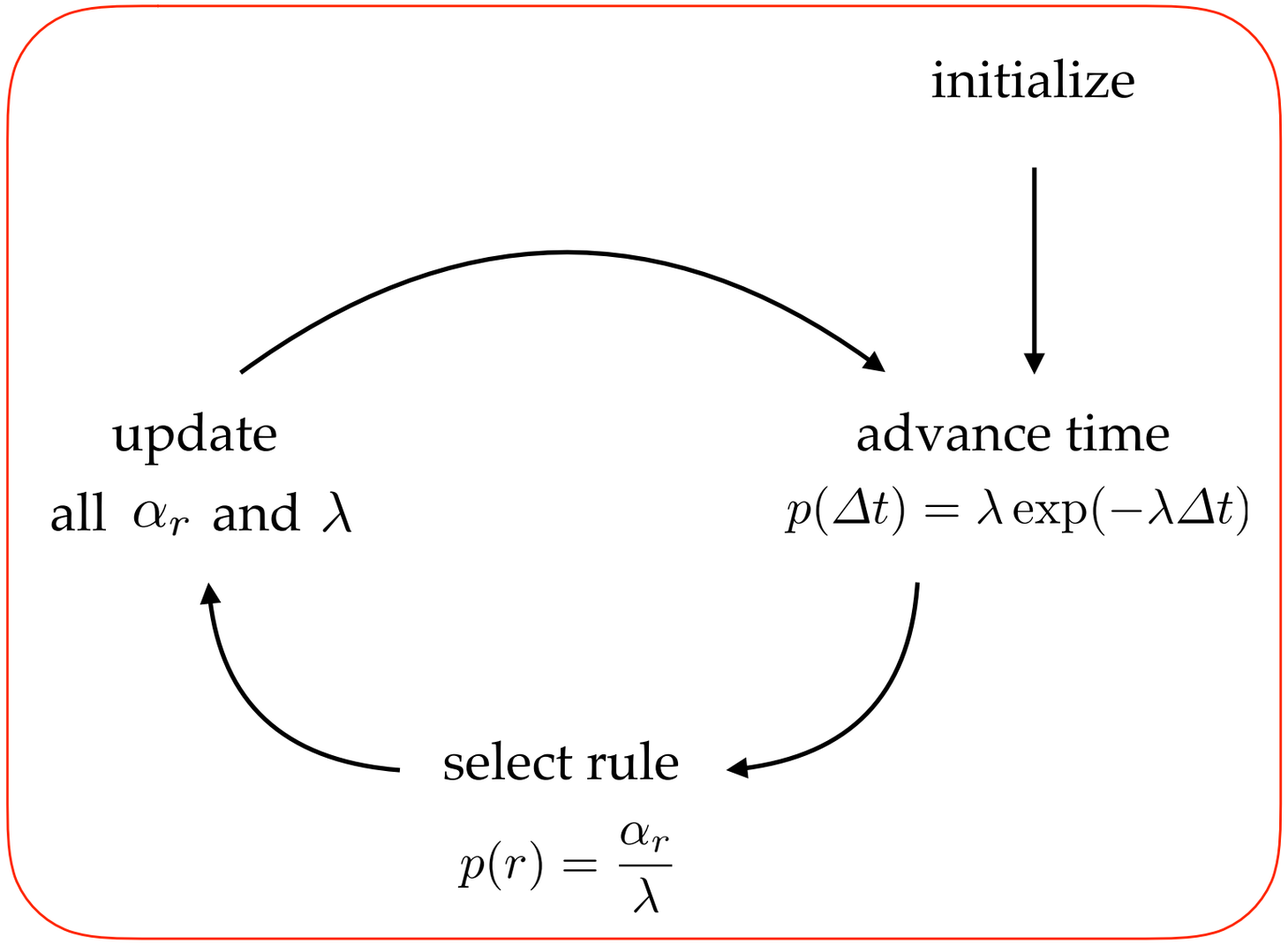
$$r: \quad \mathcal{L}_r \to \mathcal{R}_r \quad @\ \gamma_r$$

rule activities

$$\alpha_r = \gamma \cdot [\mathcal{L}_r; \mathcal{M}] \cdot \frac{1}{\#\ \text{auto}\ (\mathcal{L}_r \to \mathcal{R}_r)}$$

system activity

$$\lambda = \sum_s \alpha_s$$



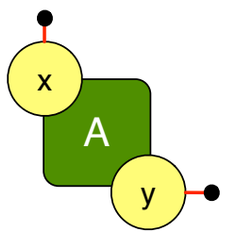
5.
Modeling with Kappa

Kappa: Patterns

the *interface* of A is a set, **not** a multi-set

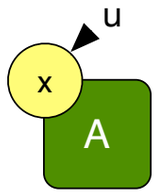
bond identifier (comes in pairs)

`A(x[.],y[.])`



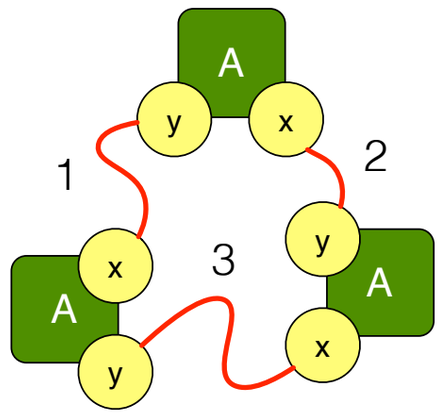
I

`A(x{u}[#]) = A(x{u})`



II

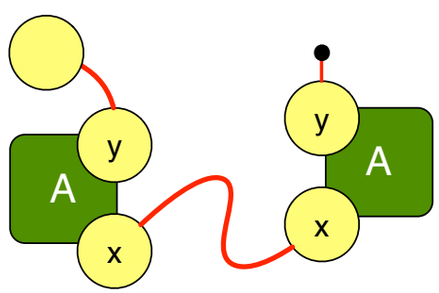
`A(x[1],y[3]), A(x[2],y[1]), A(x[3],y[2])`



III

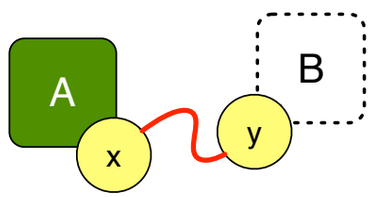
state identifier

`A(x[1],y[_]), A(x[1],y[.])`



IV

`A(x[y.B])`



V

Kappa: Patterns

- `A(x[.],z[.])`
- `A(x[.],z)`
- `A(loc{membrane},z{p}[0]),B(loc{cytosol},x[0])`
- `A(x{u}[#])`
- `A(x[1],y[3]),A(x[2],y[1]),A(x[3],y[2])`
- `A(x[1],y[_]),A(x[1],y[.])`
- `A(x[.],y[x.B])`

Kappa: Rules

```
'rule' A(x[.]), B(x[.]) -> A(x[1]), B(x[1]) @ 0.001
//      #1L      #2L        #1R      #2R
```

```
'error' A(x[.]), B(x[.]) -> C(x[1]), B(x[1]) @ 0.001
//          #1L      #2L        #1R      #2R
```

```
'indel' A(x[1]), B(x[1]), .   ->  A(x[1]), . , C(y[1]) @ 0.001
//       #1L      #2L     #3L      #1R    #2R   #3R
```

---

tokens

```
'hybrid rule a' S(x{u}[1]),K(y[1]) ->
                S(x{p}[1]),K(y[1])    | -1E-6 ATP, +1E-6 ADP @ 'k'
```

Kappa: Rule Examples

```
▶ 'asymmetric dimerization'
  A(x[.]), A(y[.]) -> A(x[1]), A(y[1]) @ 0.001
  'symmetric dimerization'
  A(x[.]), A(x[.]) -> A(x[1]), A(x[1]) @ 0.001

▶ 'conditional asymmetric dimerization'
  A(x[.]), A(y{p}[.]) -> A(x[1]), A(y{p}[1]) @ 0.001

▶ 'degrade'   A(x[1]), A(y{p}[1]) -> . , A(y{p}[.]) @ 0.001

▶ 'create'   A(x[.]), . -> A(x[1]), A(y{p}[1]) @ 0.001

▶ 'force1'     A(y{#}) -> A(y{p}) @ 0.001
  ⛔ 'nono1'   A(y)    -> A(y{p}) @ 0.001
  ⛔ 'nono2'   A()     -> A(y{p}) @ 0.001
  'force2'     A(y[#]), B(x[.]) -> A(y[1]), B(x[1]) @ 0.001
```

Kappa: Rule Examples

```
▶ 'side effect'          A(x[_])   -> A(x[.]) @ 0.001
  'also side effect'     A(x[y.B]) -> A(x[.]) @ 0.001

▶ 'many modifications at once'
  A(y{#}[1]),    .   , B(x[1],y[_]), C()  ->
  A(y{p}[7]), D(q[0]), B(x[0],y[7]),  .     @ 0.001

▶ ⛔ 'nonsense'                  A(x[.]) -> A(x[_]) @ 0.001
  ⛔ 'bidirectional nonsense'    A(x[#]) <-> A(x[_]) @ 0.001, 0.001
  ⛔ 'more nonsense'             A(x[#]) -> A(x[y.B]) @ 0.001
  ⛔ 'not allowed'               A(x{p}) -> A() @ 0.001

▶ 'reversible association'
  K(s[.]),S(e[.],x{u}) <-> K(s[1]),S(e[1],x{u}) @ 0.001, 0.1
  'phosphorylation'
  K(s[1]),S(e[1],x{u})  -> K(s[1]),S(e[1],x{p}) @ 0.1
  'dephospho'
  S(x{p}) -> S(x{u}) @ 0.001

▶ 'ambiguous molecularity'
  A(x[.]), A(y[.]) -> A(x[1]), A(y[1]) @ 0.001 {0.1}
```

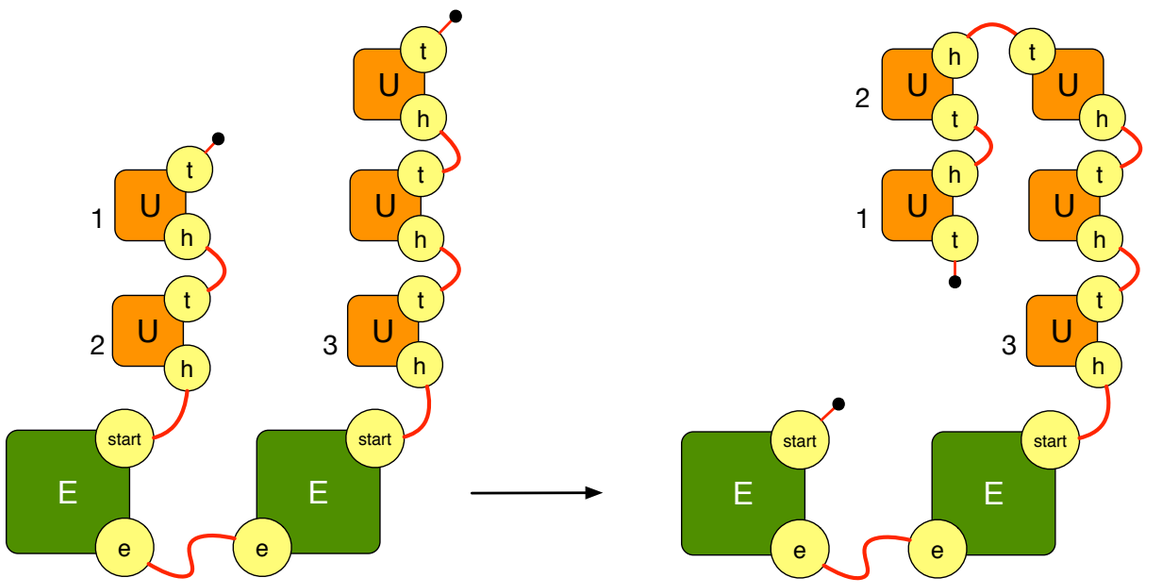
Kappa: Rules in "Edit Notation"

- `'asymmetric dimerization' A(x[./1]),A(y[./1]) @ 0.001`
- `'degrade' A(x[1])-, A(y{p}[1/.]) @ 0.001`
- `'create' A(x[./1]), A(y{p}[1])+ @ 0.001`
- `'many modifications at once'`
  `A(y{#/p}[1/7]), D(q[0])+, B(x[1/0],y[_/7]), C()-  @ 0.001`

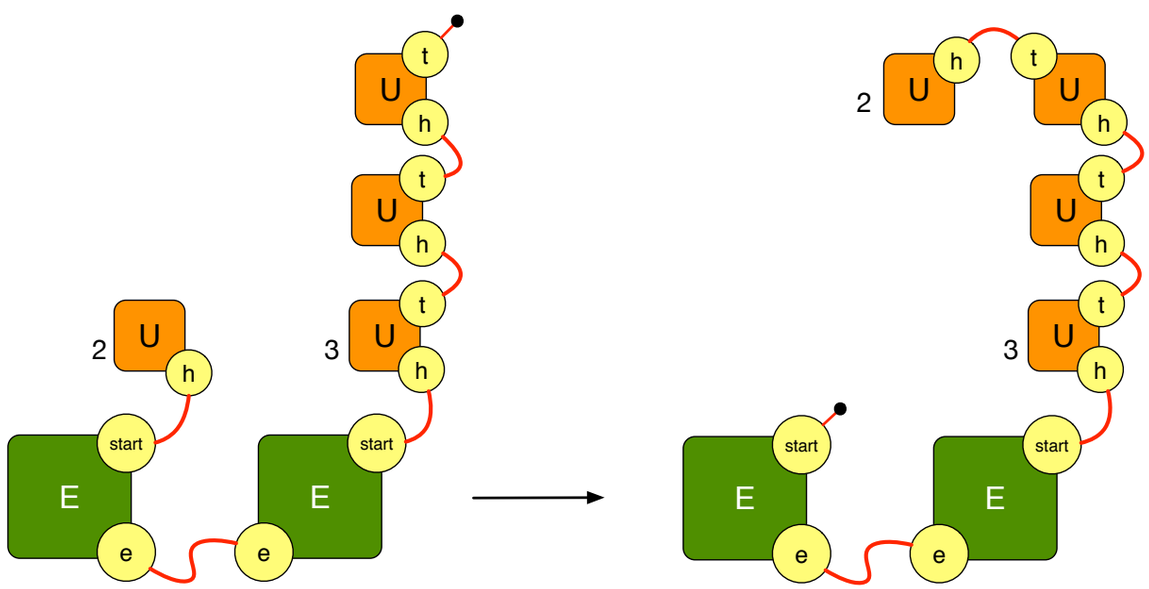
- `'dephospho' S(x{p/u}) @ 0.001`
- `'also side effect' A(x[y.B/.]) @ 0.001`
- `'ambiguous molecularity' A(x[./1]), A(y[./1]) @ 0.001 {0.1}`
- `'m+n minimalist'`
  `E(e[1],start[2/.],end[3/.]),U(h[2]),U(l[3/5]),`
  `E(e[1],start[6],end[5]),U(h[6]),U(l[5/.],t[./2]) @ 0.001`

Kappa: Concatenating Chains

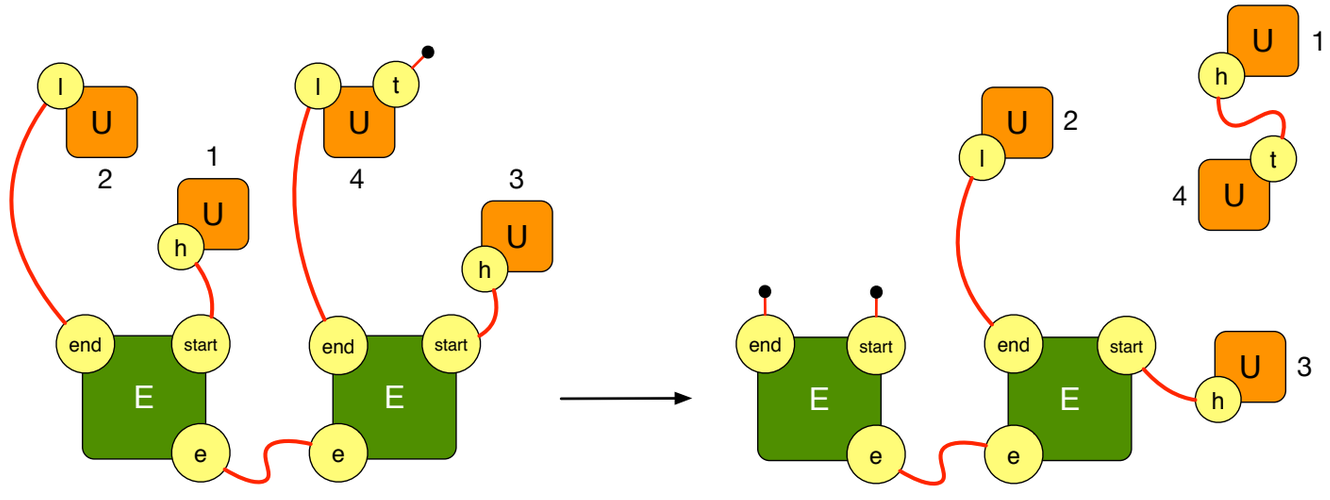
2+3



m+3



m+n (minimalist)



Kappa: Signature

the possible internal states of A at site z

```
%agent: A(x[a.B y.A]{u p}, y[x.A], z{z1 z2 z3})  // sig of A
```

the possible binding states of A at site x

a “binding stub”

Hello Biology

```
1  %agent: E(s[e.S])
2  %agent: S(e[s.E], x{u p})
3
4  %agent: _E(s)
5  %agent: _S(e, x{u p})
6
7  %var: 'k1'  0.001
8  %var: 'k_1' 0.1
9  %var: 'k2'  1
10
11 %var: 'Km' ('k_1'+'k2')/'k1'
12
13 E(s[.]), S(e[.],x{u}) <-> E(s[1]), S(e[1],x{u})  @ 'k1', 'k_1'
14 E(s[1]), S(e[1],x{u}) -> E(s[.]), S(e[.],x{p})   @ 'k2'
15
16 _E(s[.]), _S(e[.],x{u}) -> _E(s[.]), _S(e[.],x{p})
17 @ 'k2'/('Km'+|_S(e[.],x{u})|)
18
19 %init: 100     E(s[.])
20 %init: 100000  S(e[.], x{u})
21
22 %init: 100     _E(s[.])
23 %init: 100000  _S(e[.], x{u})
24
25 %obs: 'P'   |S(e[.],x{p})|
26 %obs: 'ES'  |E(s[1]), S(e[1],x{u})|
27 %obs: 'S'   |S(e[.], x{u})|
28
29 %obs: '_P'  |_S(e[.],x{p})|
```

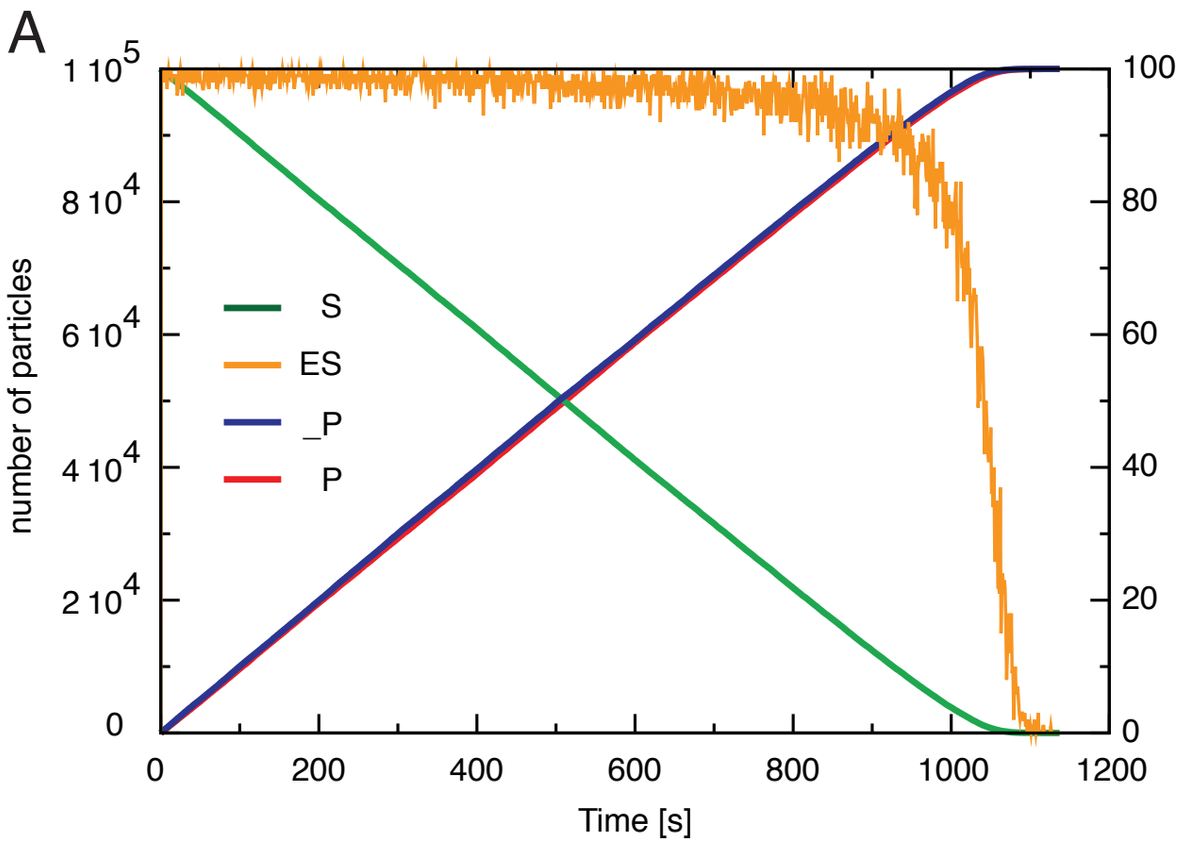
$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

$$[S] >> E_t$$

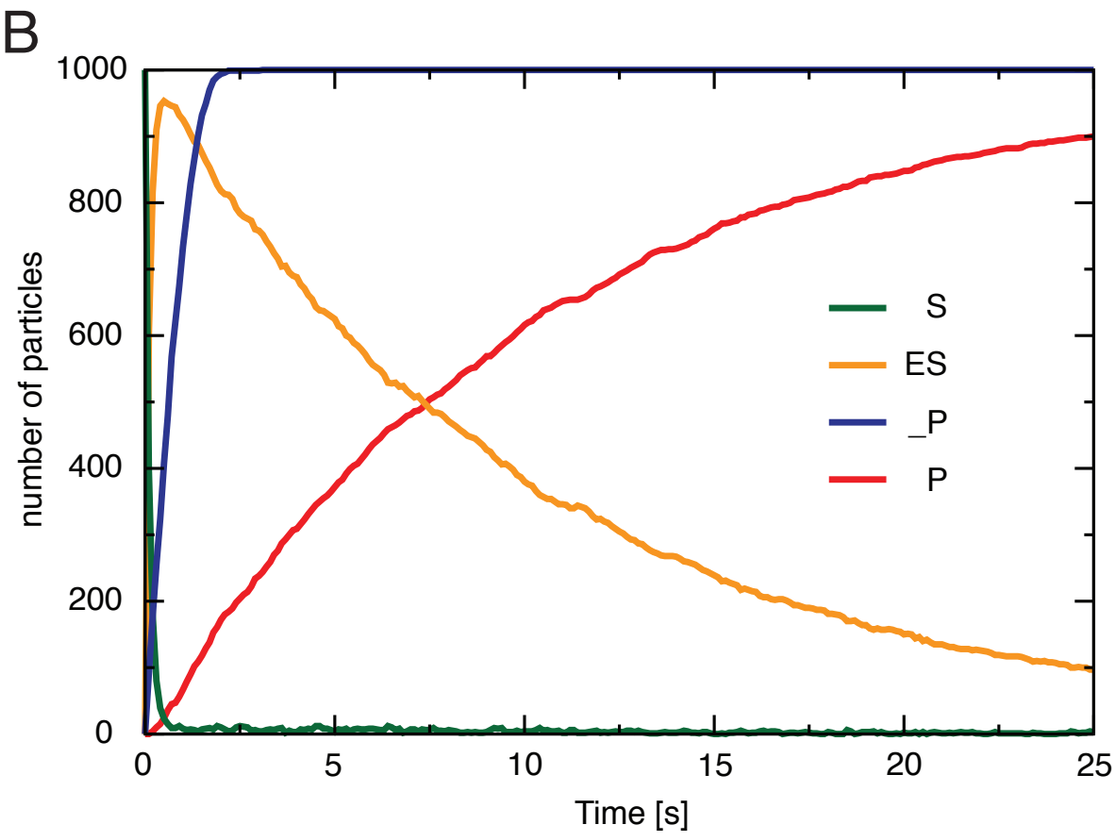
$$\frac{d[P]}{dt} = \frac{k_2 E_t [S]}{K_m + [S]}$$

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

$$E + S \xrightarrow{\frac{k_2}{K_m + [S]}} E + P$$

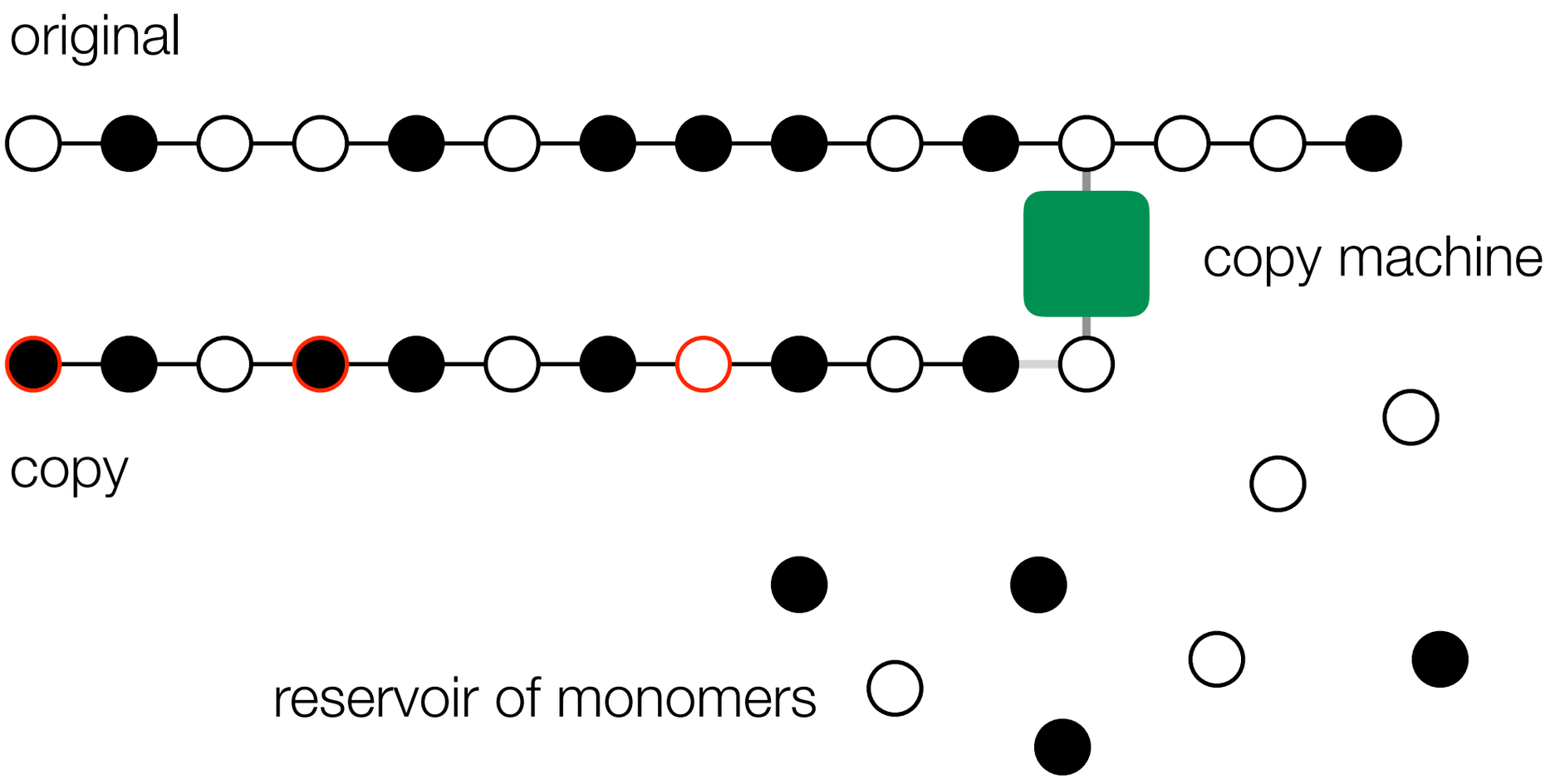


substrate in excess of enzyme



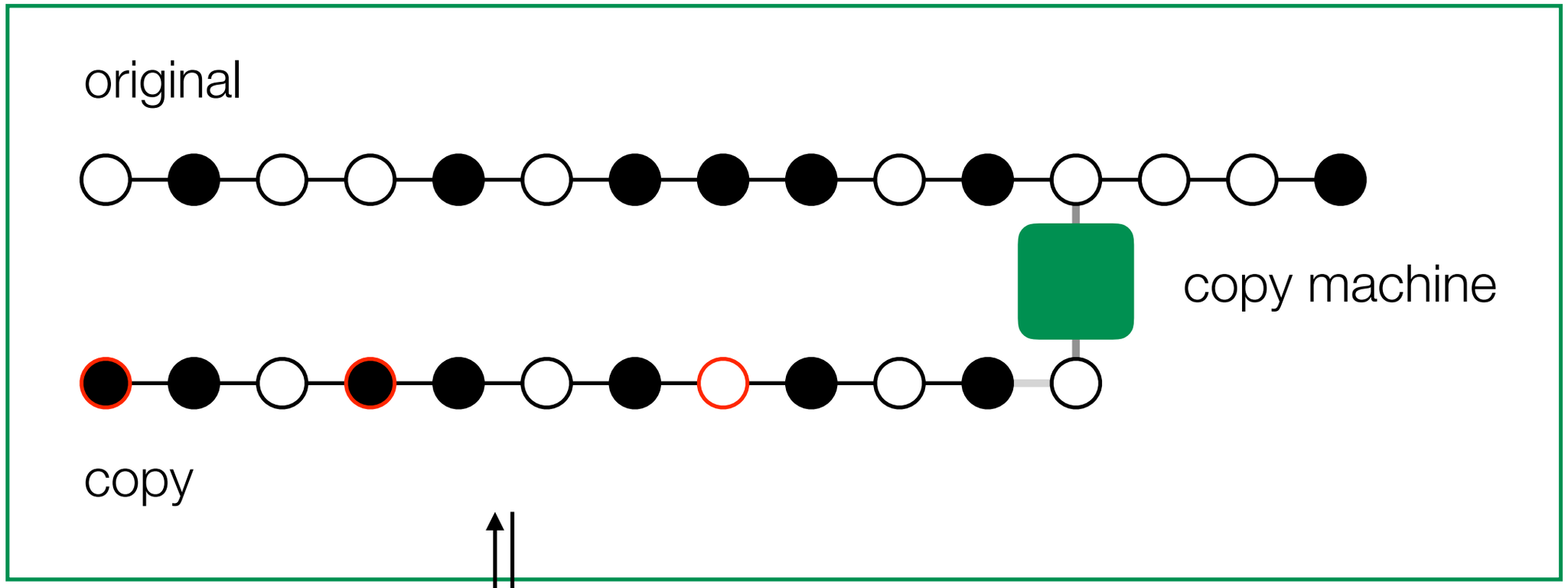
enzyme in excess of substrate

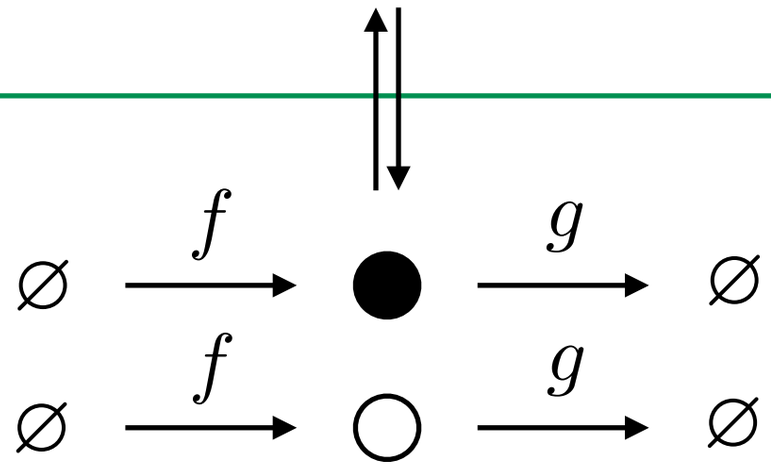
Copying a Polymer (Single-Step)



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

Copying a Polymer (Single-Step)





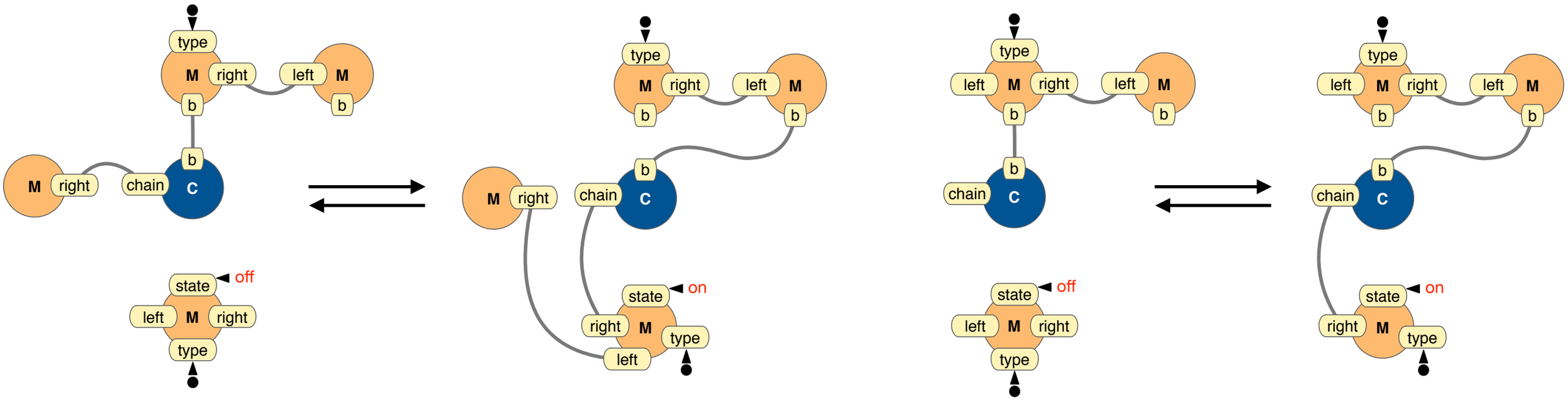
reservoir of monomers

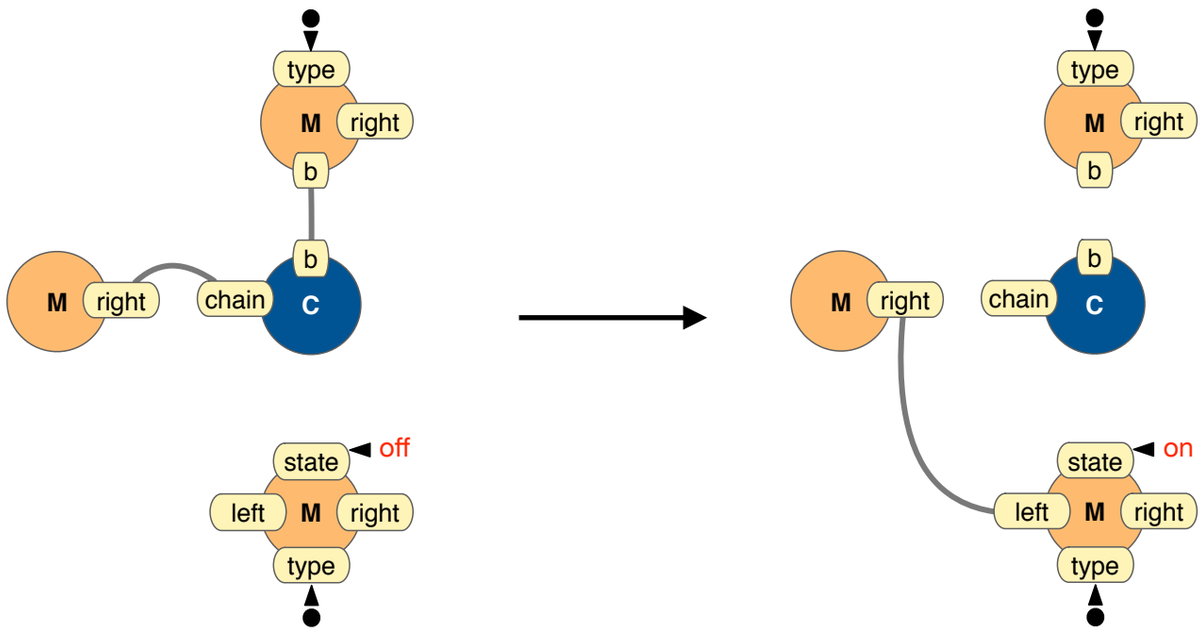
$$\varnothing \xrightarrow{f} X \xrightarrow{g} \varnothing$$

$$X(t) = \frac{f}{g}(1 - \exp(-g\,t))$$

$$\bar{X} = \frac{f}{g}$$

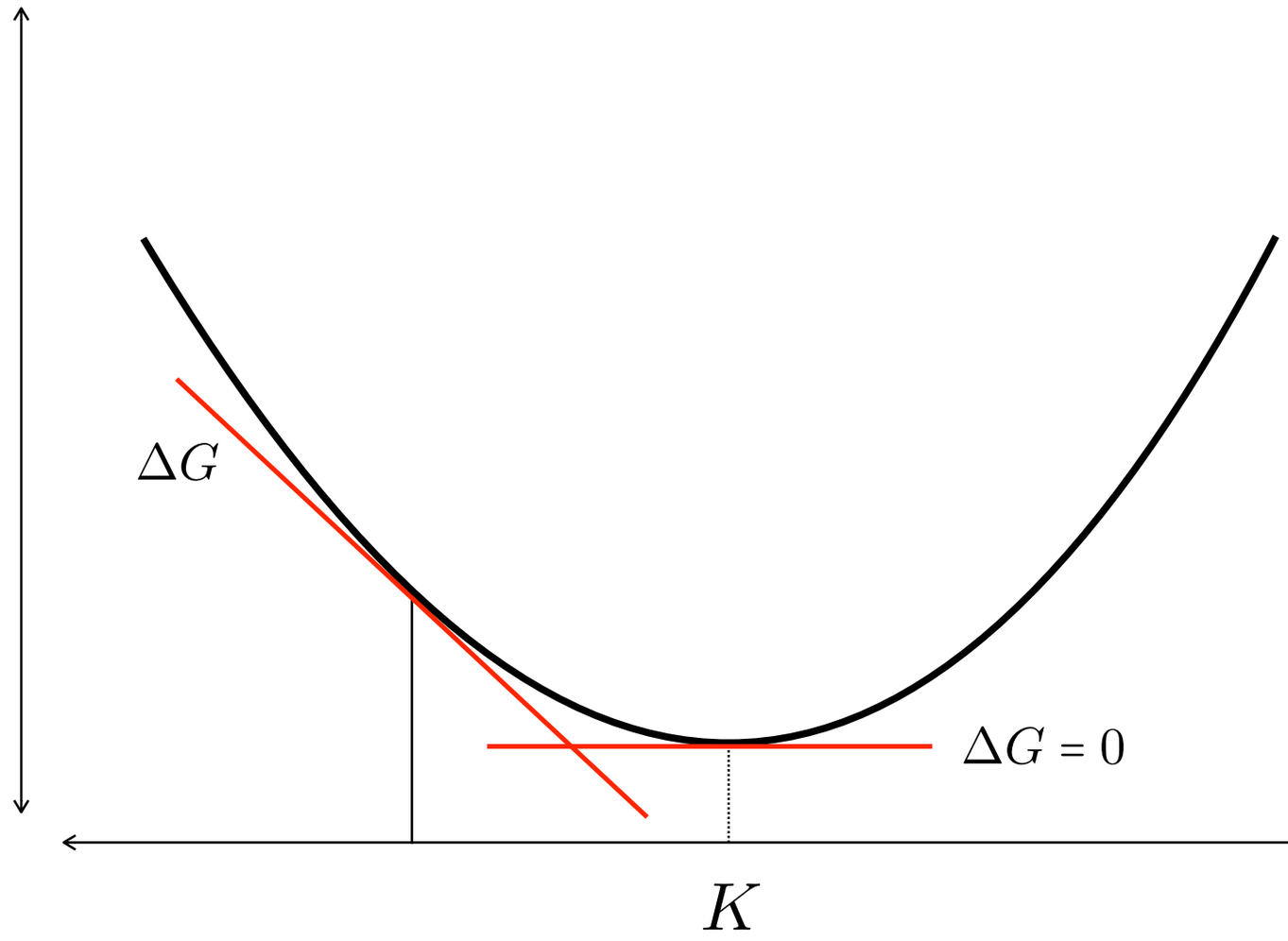
Copying a Polymer (Single-Step)





Free Energy Landscape in Composition Space

free energy

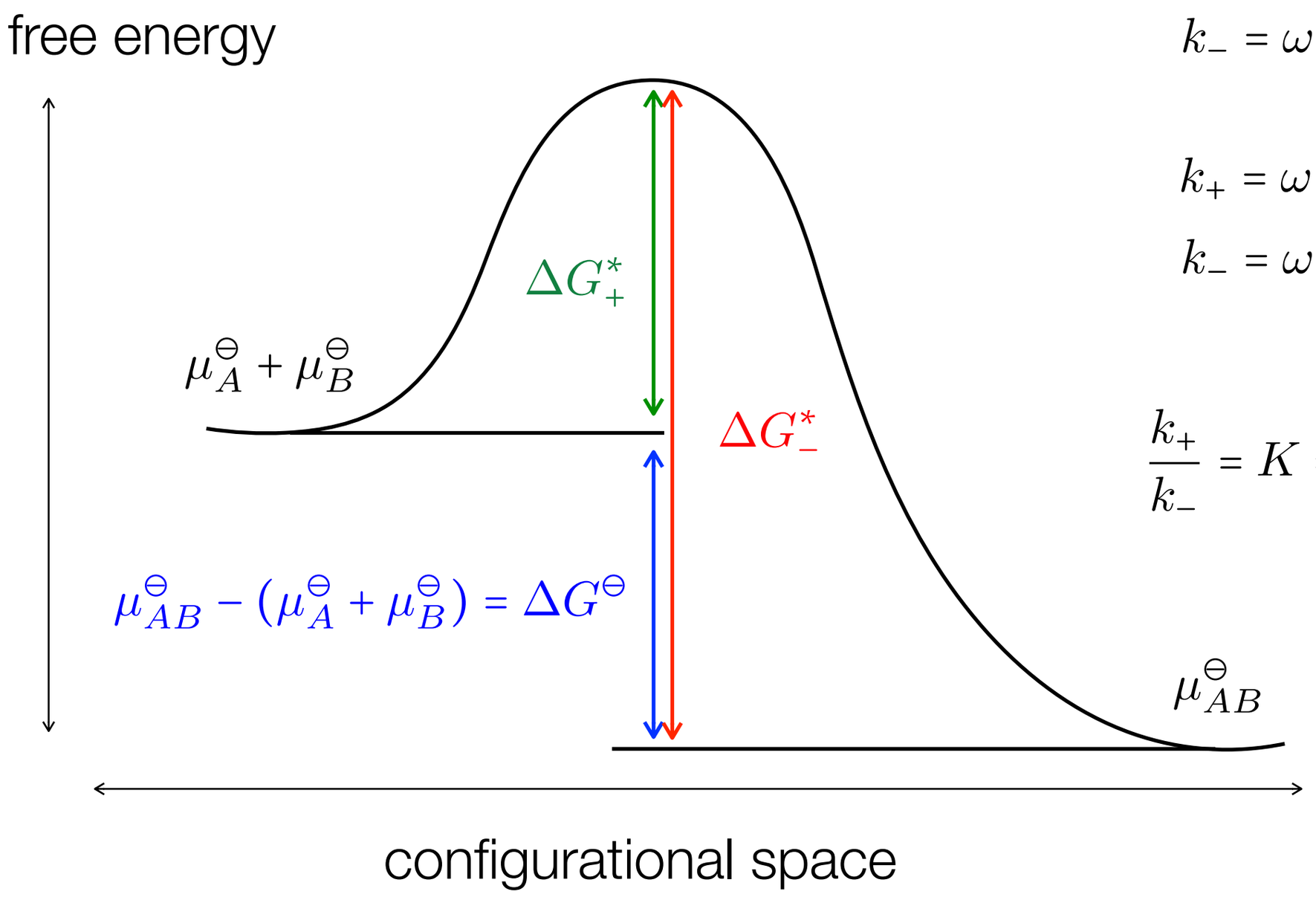


$$\Delta G_{T,P} = \sum_i \mu_i \nu_i$$
$$= \sum_i \left(\mu_i^{\ominus} + RT \ln n_i\right) \nu_i$$
$$= \sum_i \mu_i^{\ominus} \nu_i + RT \ln \Pi_i n_i^{\nu_i}$$
$$= \Delta G^{\ominus} + RT \ln Q$$

$$\Delta G_{T,P} = 0 \;\Rightarrow\; K = \exp\left(-\Delta G^{\ominus}/RT\right)$$

Free Energy Landscape in Configurational Space

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} AB$$



$$k_+ = \omega \ \exp\left(-\Delta G_+^*/RT\right)$$

$$k_- = \omega \ \exp\left(-\Delta G_-^*/RT\right)$$

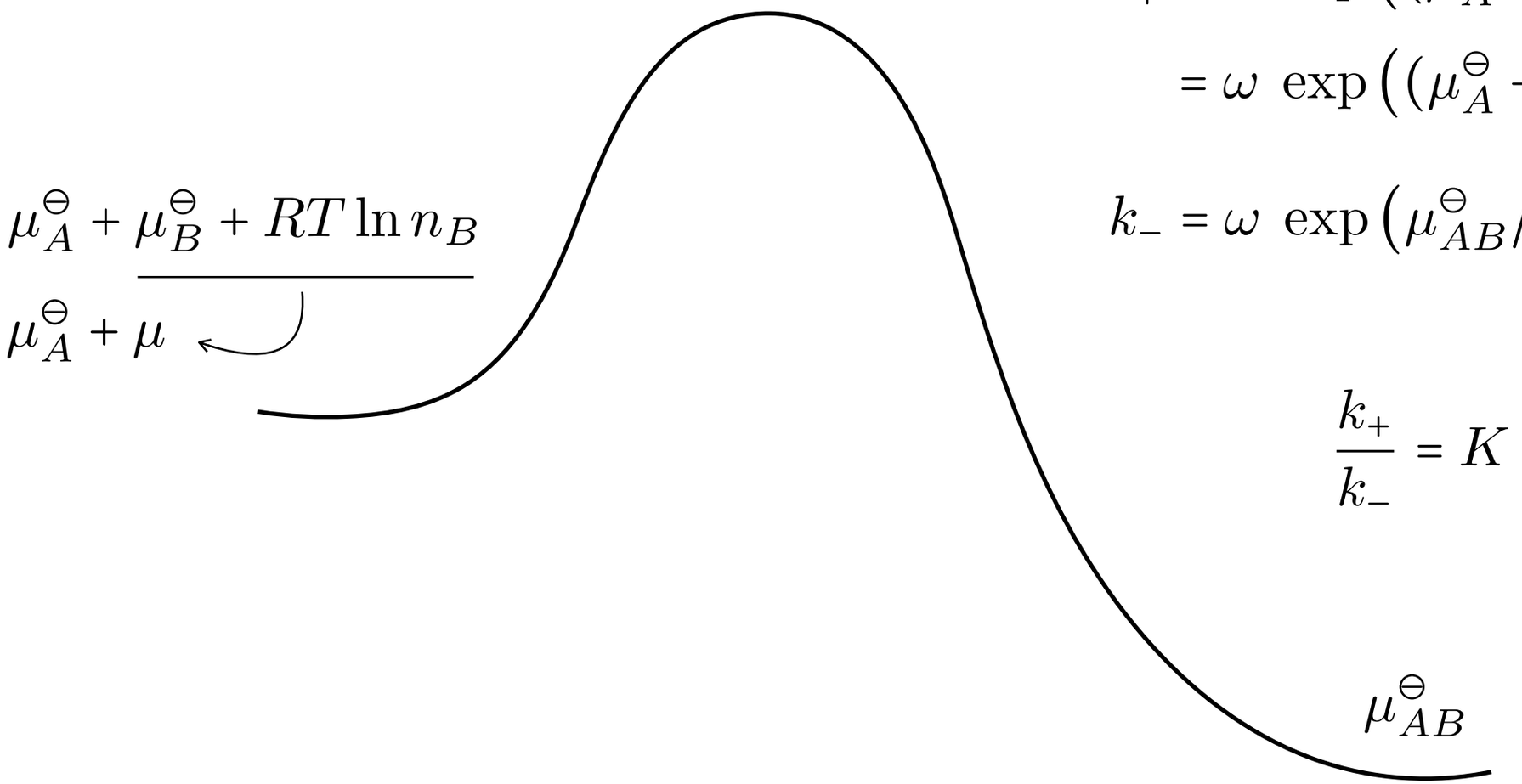
$$k_+ = \omega \ \exp\left((\mu_A^\ominus + \mu_B^\ominus)/RT\right)$$

$$k_- = \omega \ \exp\left(\mu_{AB}^\ominus/RT\right)$$

$$\frac{k_+}{k_-} = K = \exp\left(-\Delta G^\ominus/RT\right)$$

Rate Constants and Driving Potential

$$A \underset{k_-}{\overset{k_+ n_B}{\rightleftharpoons}} AB$$



$$k'_+ = \omega \ \exp\left((\mu_A^\ominus + \mu)/RT\right)$$

$$= \omega \ \exp\left((\mu_A^\ominus + \mu_B^\ominus)/RT\right) n_B = k_+ n_B$$

$$k_- = \omega \ \exp\left(\mu_{AB}^\ominus/RT\right)$$

$$\frac{k_+}{k_-} = K = \exp\left(-\Delta G^\ominus/RT\right)$$

Copying

difference in barrier for W and R

$$k^R_{0\to1} = \omega\ \exp\left((E^R_0 + \mu_{0\to1} + \delta_{0\leftrightarrow1})/RT\right)$$

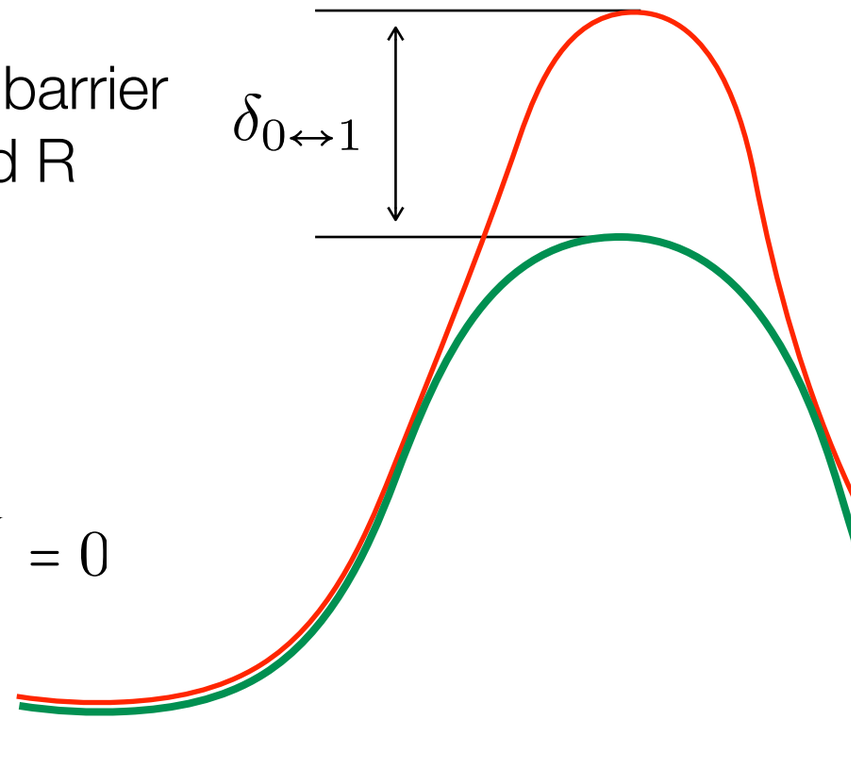
$$k^W_{0\to1} = \omega\ \exp\left((E^W_0 + \mu_{0\to1})/RT\right)$$

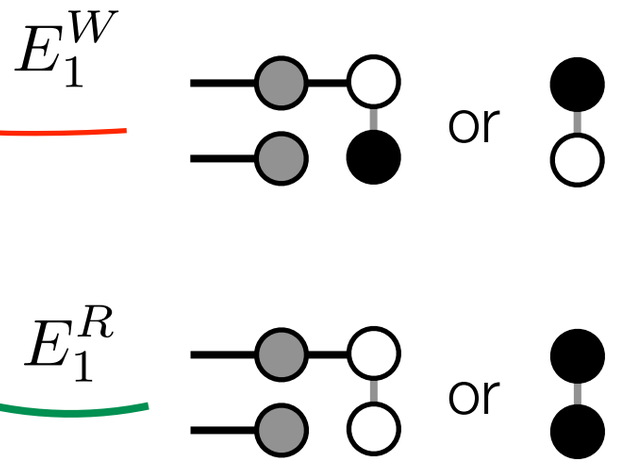
$$k^R_{1\to0} = \omega\ \exp\left((E^R_1 + \delta_{0\leftrightarrow1})/RT\right)$$

$$k^W_{1\to0} = \omega\ \exp\left(E^W_1/RT\right)$$

favors a direction

facilitates R over W





Error Rate

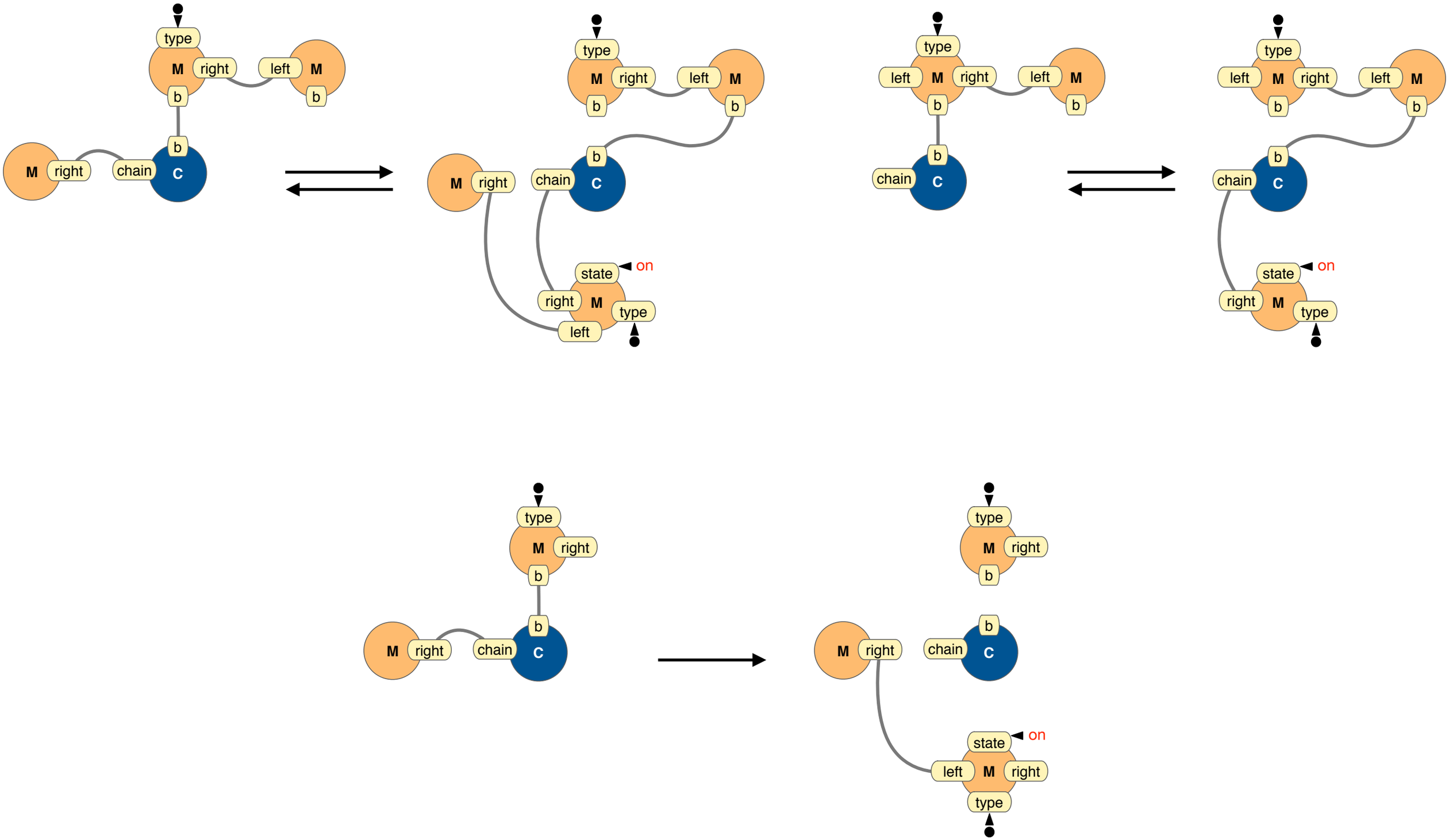
$$\eta' = \frac{p_W}{p_R}$$ error rate

$$\eta = \frac{p_W}{p_W + p_R} = \frac{1}{1 + \eta'^{-1}}$$ error probability

$$\eta'_{rev} = \exp\left(-(E^W - E^R)/RT\right)$$ (single step) error rate in the reversible limit

$$\eta'_{irr} = \exp\left(-\delta/RT\right)$$ (single step) error rate in the irreversible limit

Copying a Polymer (Single-Step)



Copying a Polymer (Contact Map)