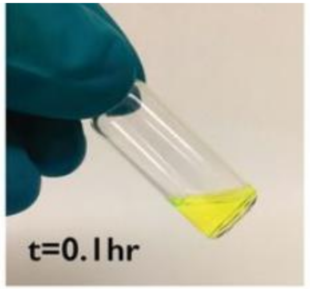
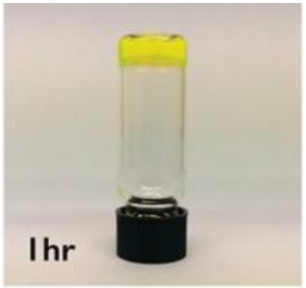
$$A \xrightarrow{\Delta G > 0} B$$

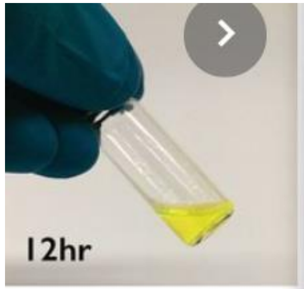
How can you make these reactions happen?

Chemically-driven non-equilibrium systems

Transient systems
(may NOT absorb energy)

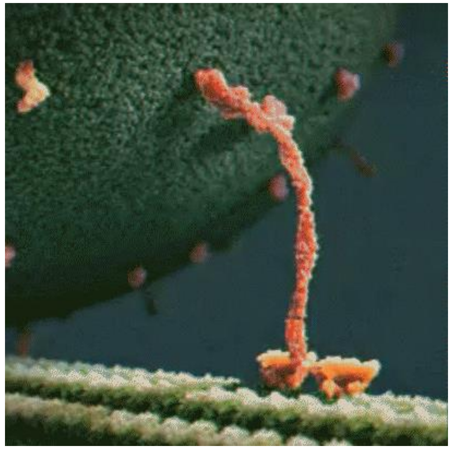


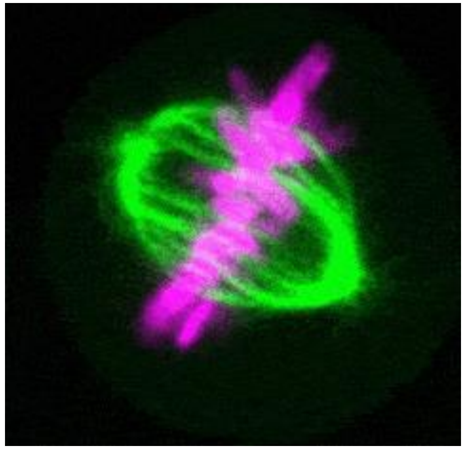


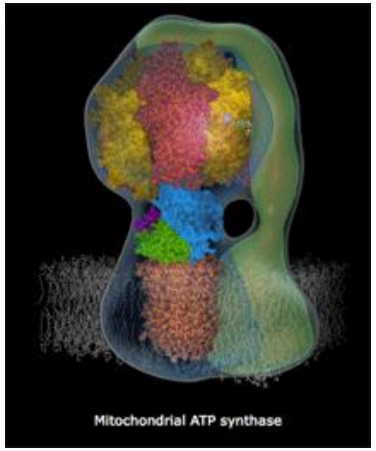


Kinetic asymmetry

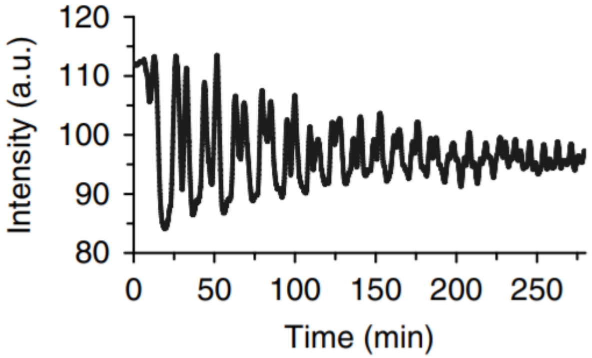
Driven systems
(DO absorb energy)

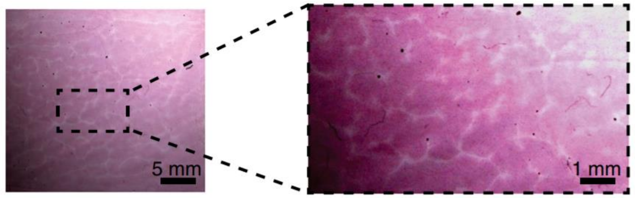






Oscillating systems
(DO absorb energy & are synchronized)





Bifurcation

Do not forget the big picture: alternating conditions, light, spatial differentiation..

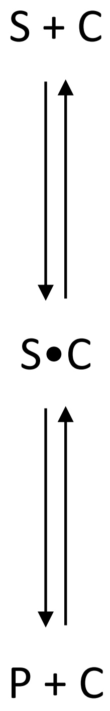
Notation used to describe these phenomena

Often used as interchangeable in this context:
F = Fuel or S = Substrate
W = Waste or P = Product

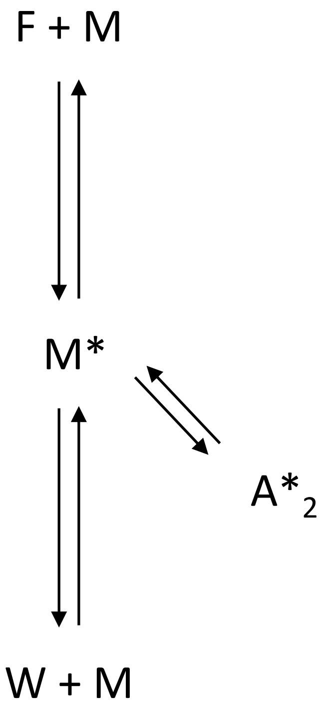
M = Monomer/Machine or C = Catalyst (or E = Enzyme)
M' or C' = other conformation of Monomer/Machine and Catalyst
[in some cases: M = L , M' = H, M* = L']

S•C or F•M or M* or P•C
= Substrate-Catalyst complex, Fuel-Monomer/Fuel-Machine complex, activated Monomer, Product-Catalyst complex (sometimes indicated as «bound state»)

M_2 or A_2= Dimer or Aggregate of M
M^*_2 or A^*_2= Dimer or Aggregate of M*



Standard enzymatic catalysis



Example of transient assembly

Notation used to describe these phenomena

Often used as interchangeable in this context:
F = Fuel or S = Substrate
W = Waste or P = Product

M = Monomer/Machine or C = Catalyst (or E = Enzyme)
M’ or C’ = other conformation of Monomer/Machine and Catalyst
[in some cases: M = L , M’ = H, M* = L’]

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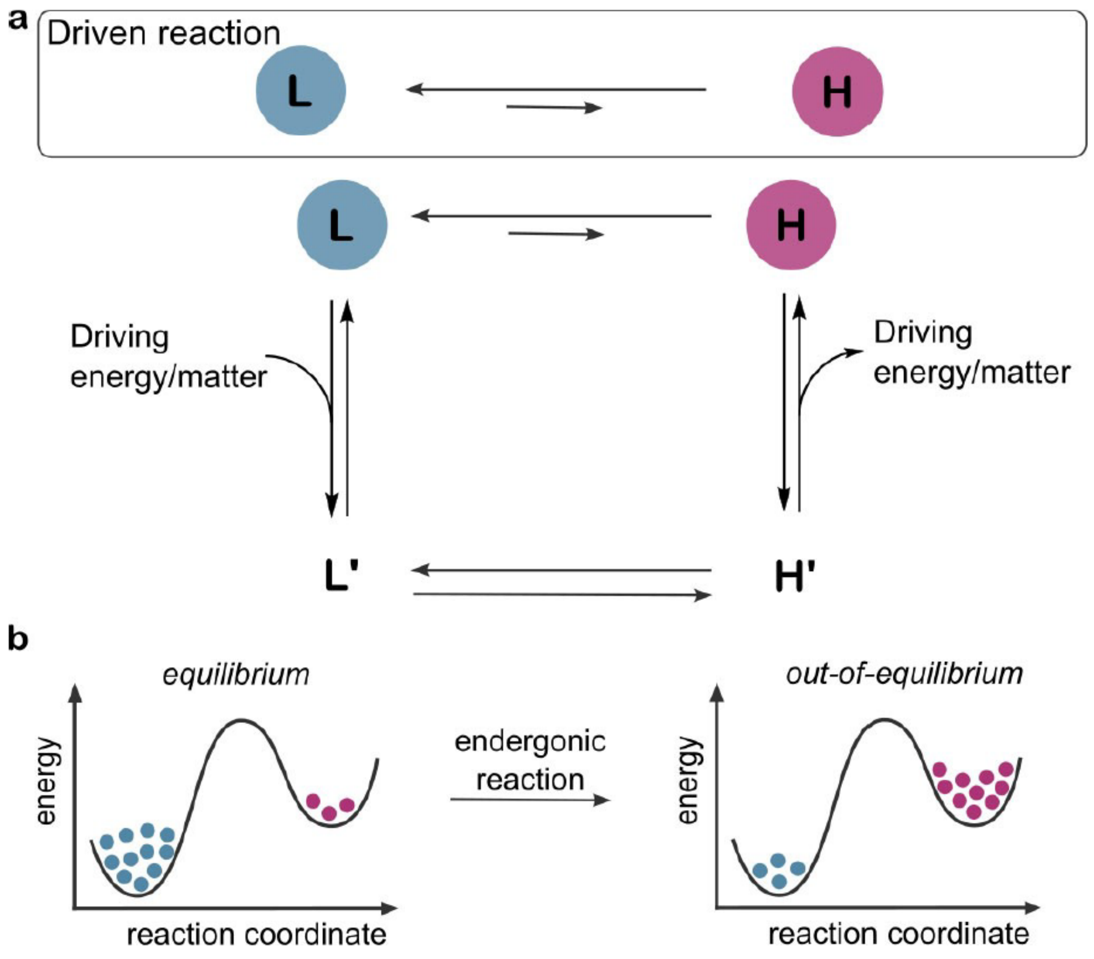

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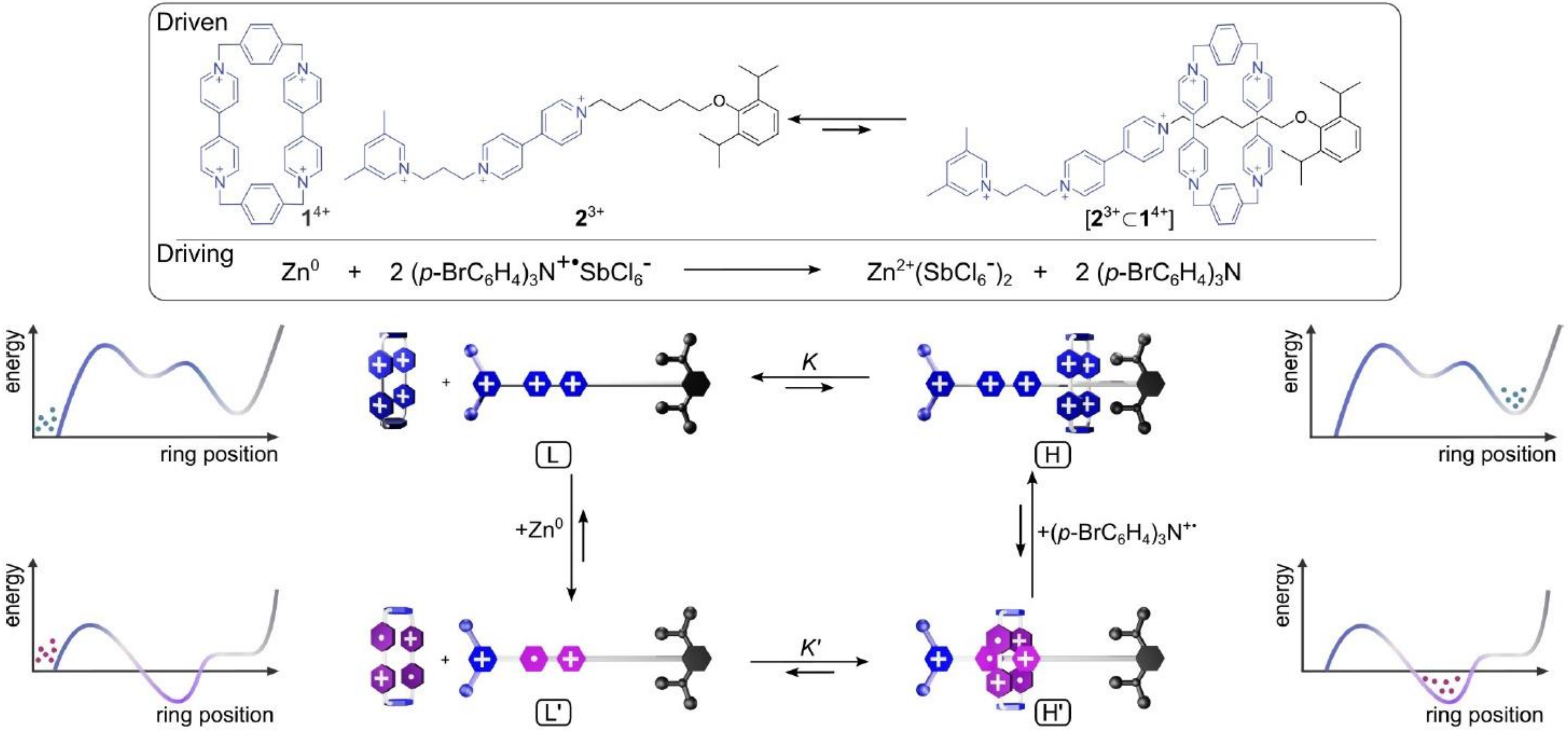
Alternating conditions: example



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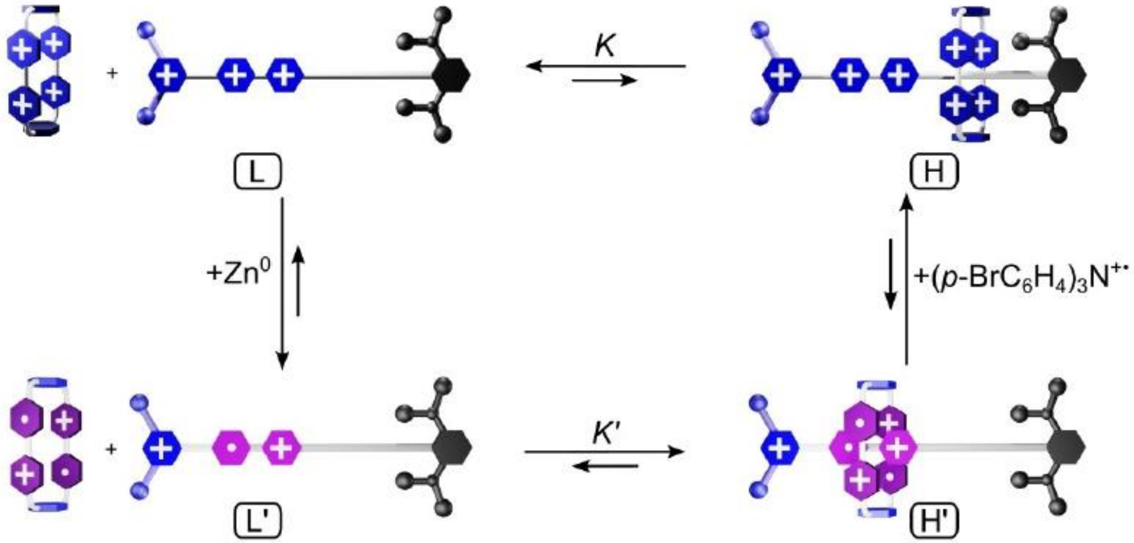
Outcomes of alternating conditions

Under appropriate kinetic & thermodynamic conditions:

- A cyclic reaction sequence is performed

- Concentrations are different from equilibrium values

- Energy is stored in the system



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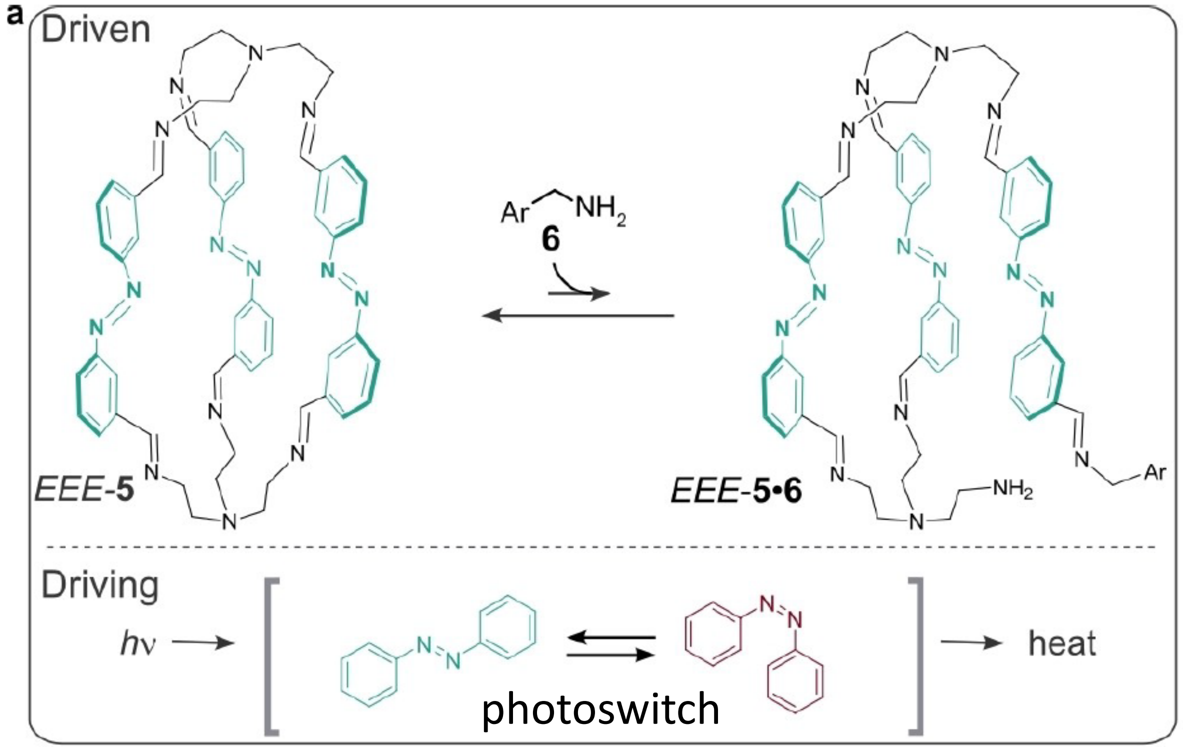
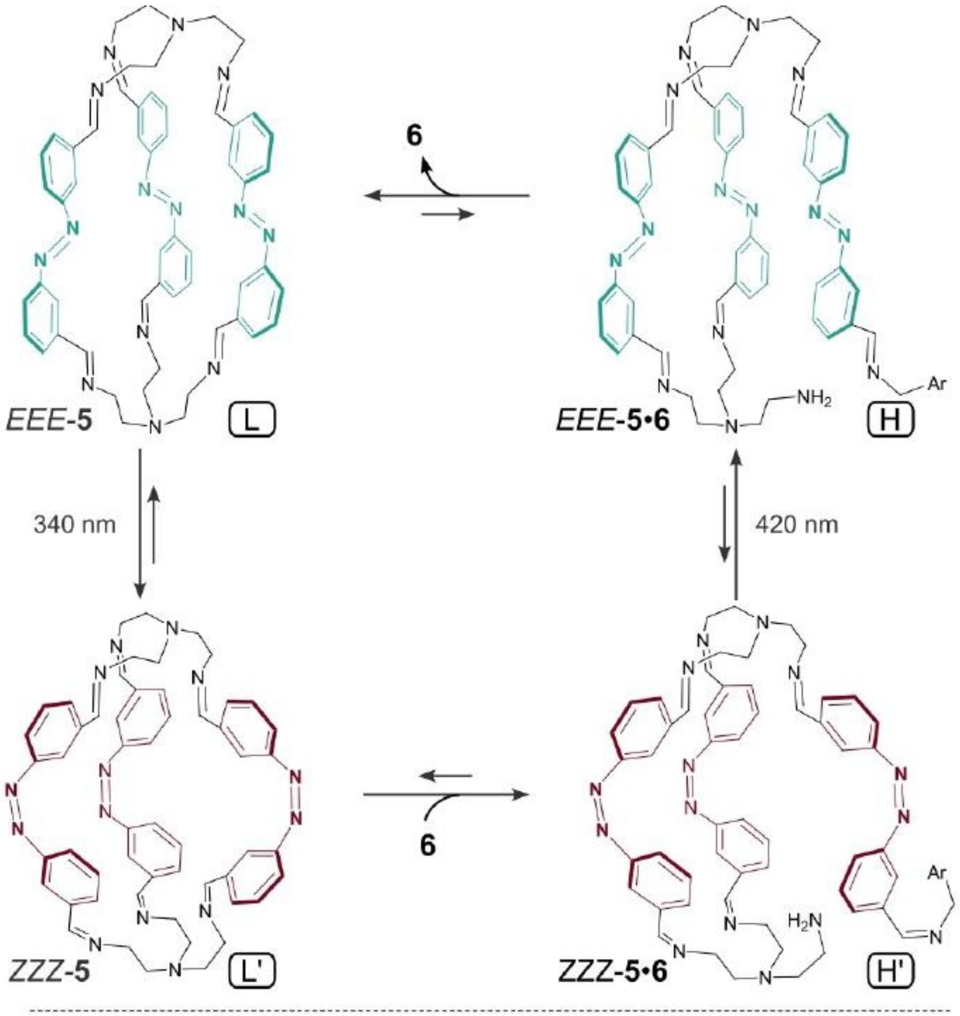
Alternating conditions with light: example





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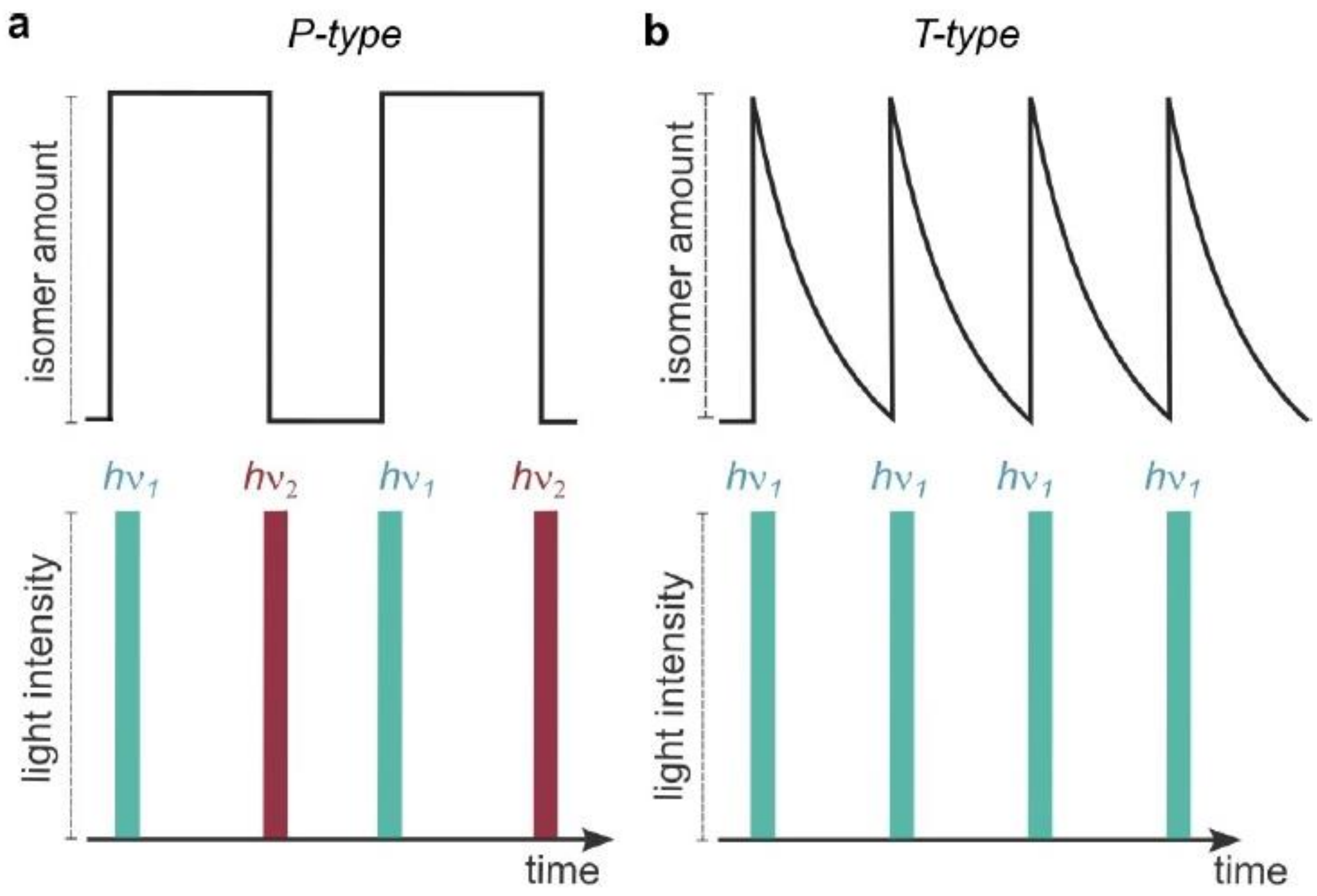
Alternating conditions with light



What happens if we keep the light «on»?

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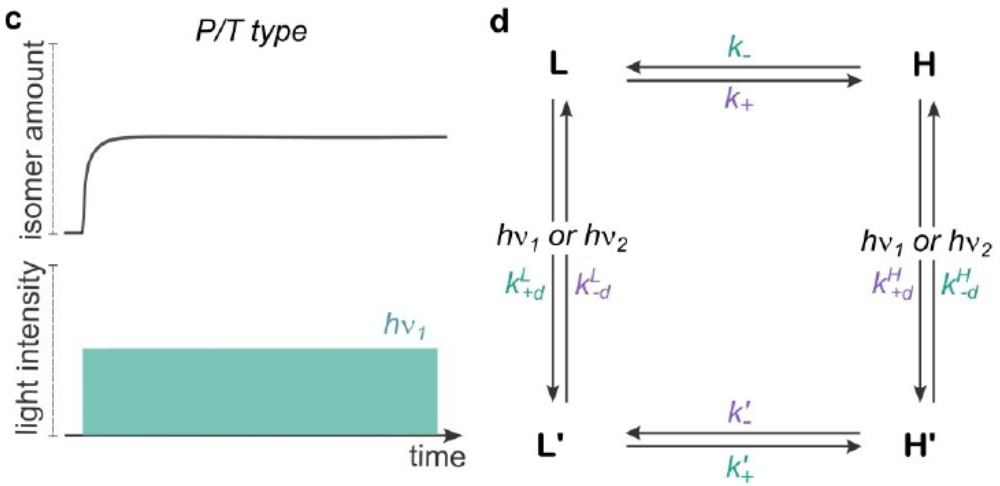
Alternating conditions with light



$$K_r = \frac{k_{+d}^{L} \times k_{+}^{\prime} \times k_{-d}^{H} \times k_{-}}{k_{-d}^{L} \times k_{-}^{\prime} \times k_{+d}^{H} \times k_{+}}$$

$$\frac{[L']_{PSS}}{[L]_{PSS}} = \frac{k_{+d}^{L}}{k_{-d}^{L}} = \frac{\epsilon_L \times QY_{L \to L'}}{\epsilon_{L'} \times QY_{L' \to L}} = K_{PSS(\lambda)}^{L}$$

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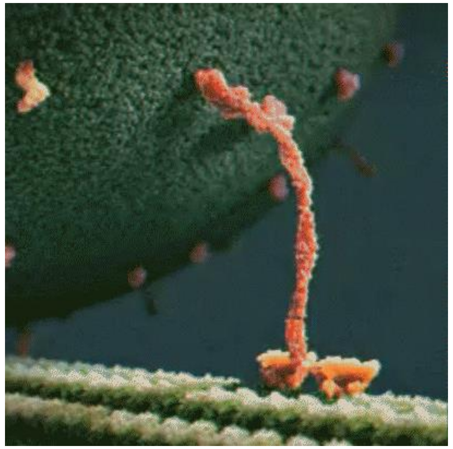
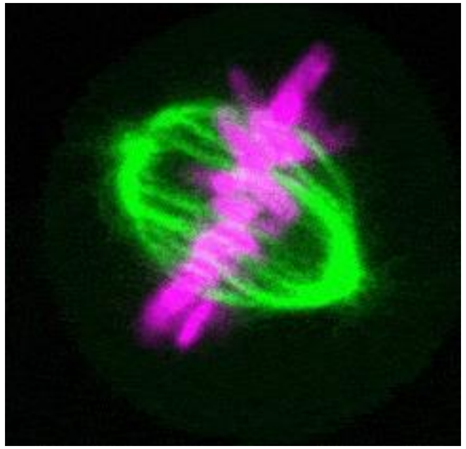
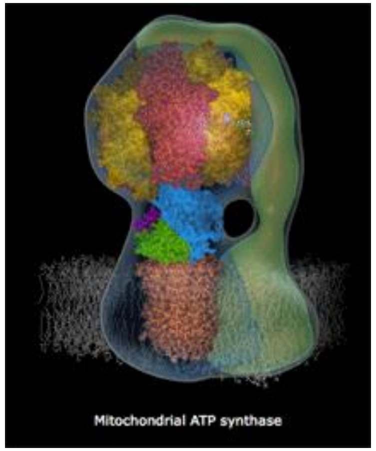
Chemically-driven non-equilibrium systems

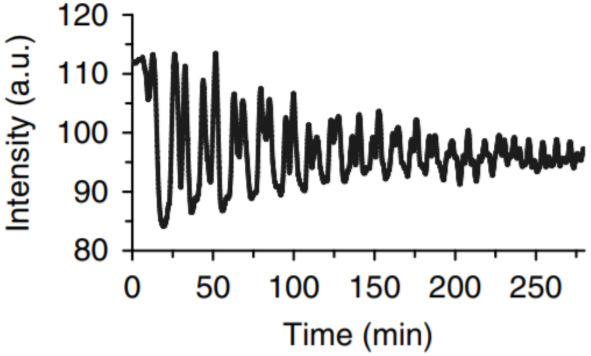
Transient systems (may NOT absorb energy)	Driven systems (DO absorb energy)	Oscillating systems (DO absorb energy & are synchronized)

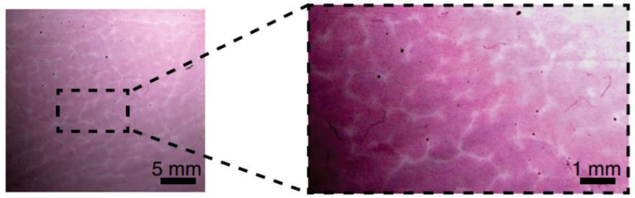
Kinetic asymmetry







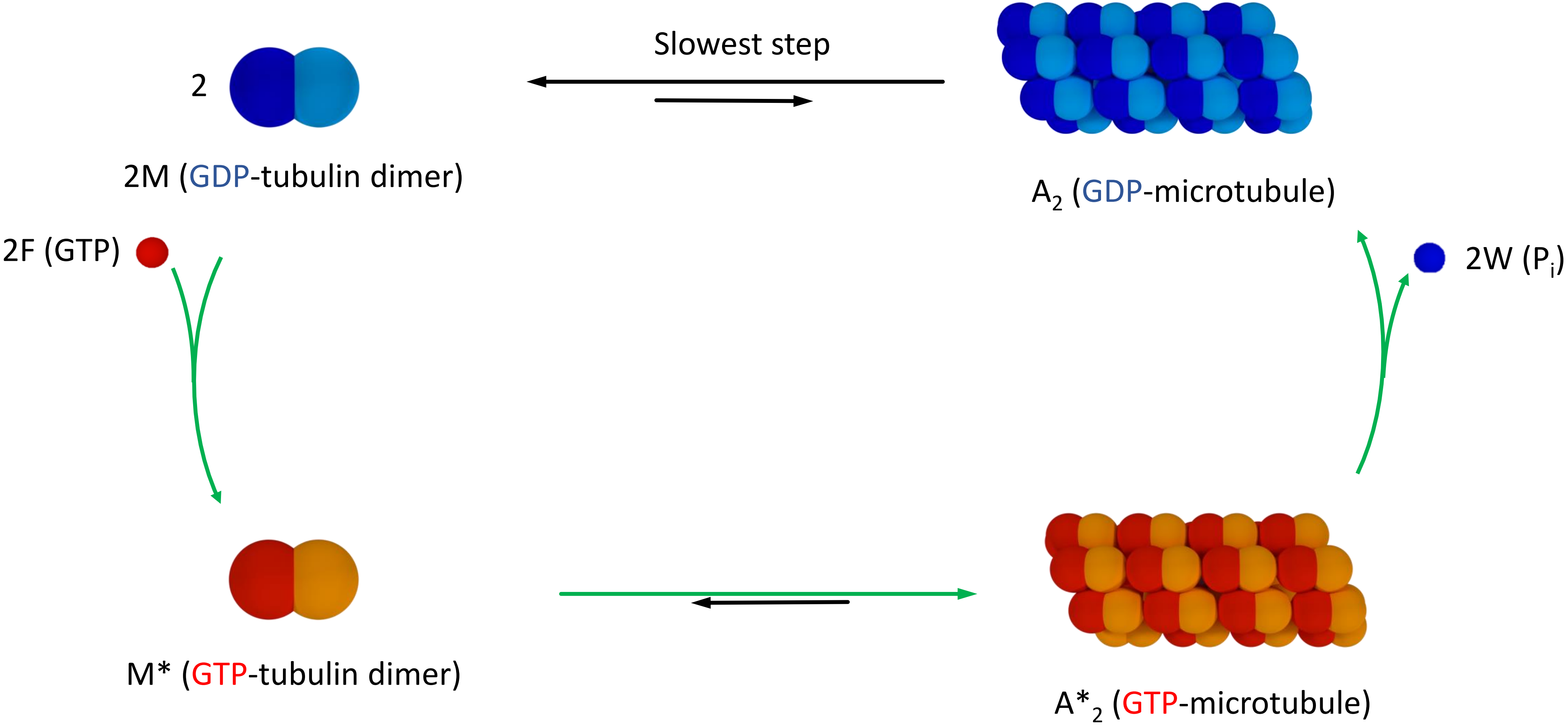




Bifurcation

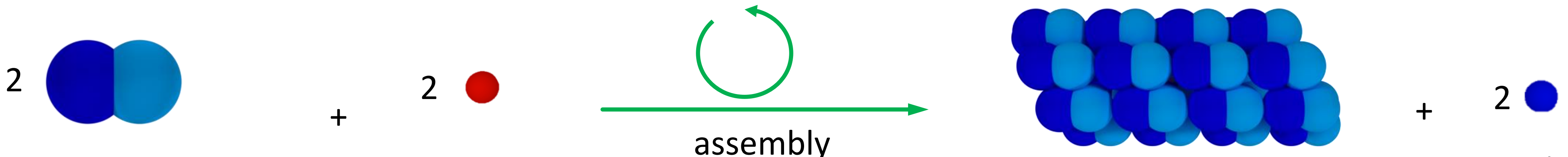
Do not forget the big picture: alternating conditions, light, spatial differentiation..

Epitomic example: assembly of a dimer



Nat. Nanotechnol. **2018**, 13, 882

Epitomic example: assembly of a dimer



2M (GDP-tubulin dimer) + F (GTP) → assembly → A_2 (GDP-microtubule) + W (P_i)

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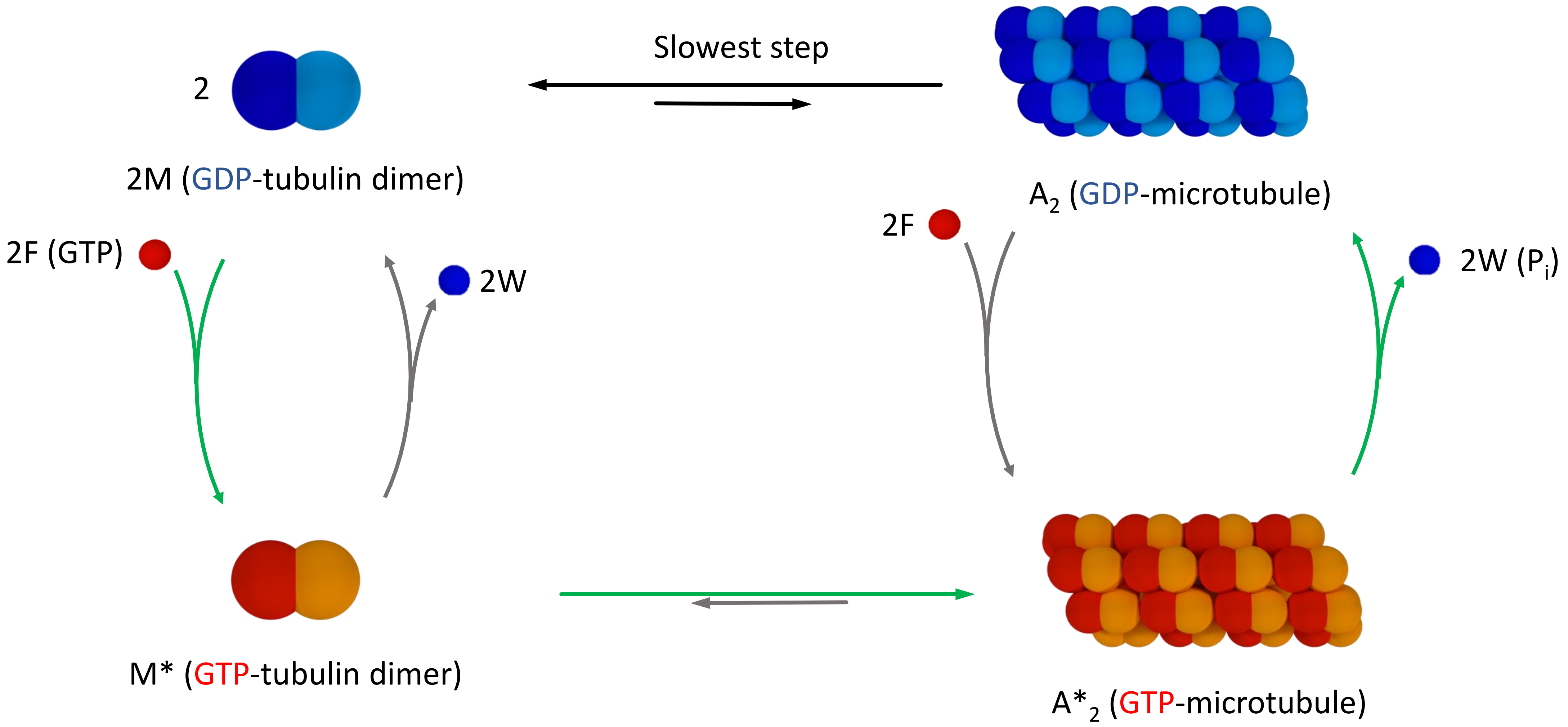
Epitomic example: assembly of a dimer



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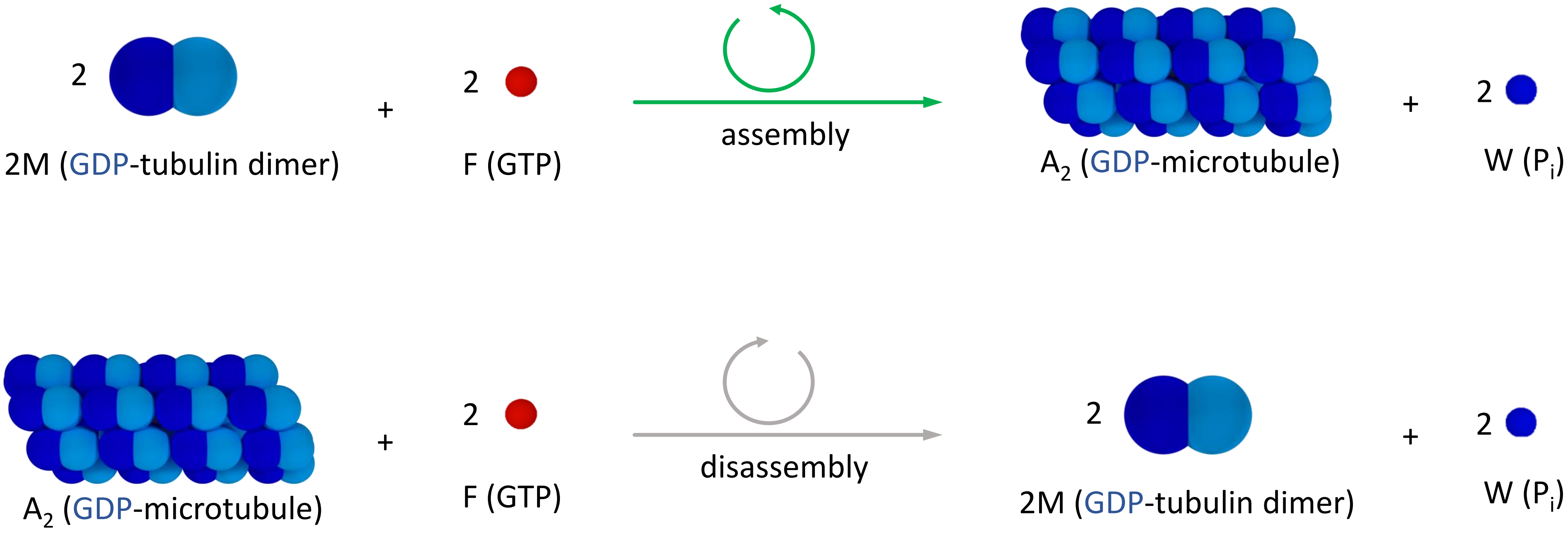
Epitomic example: assembly of a dimer



Both paths are thermodynamically allowed, kinetics dictates which one will prevail

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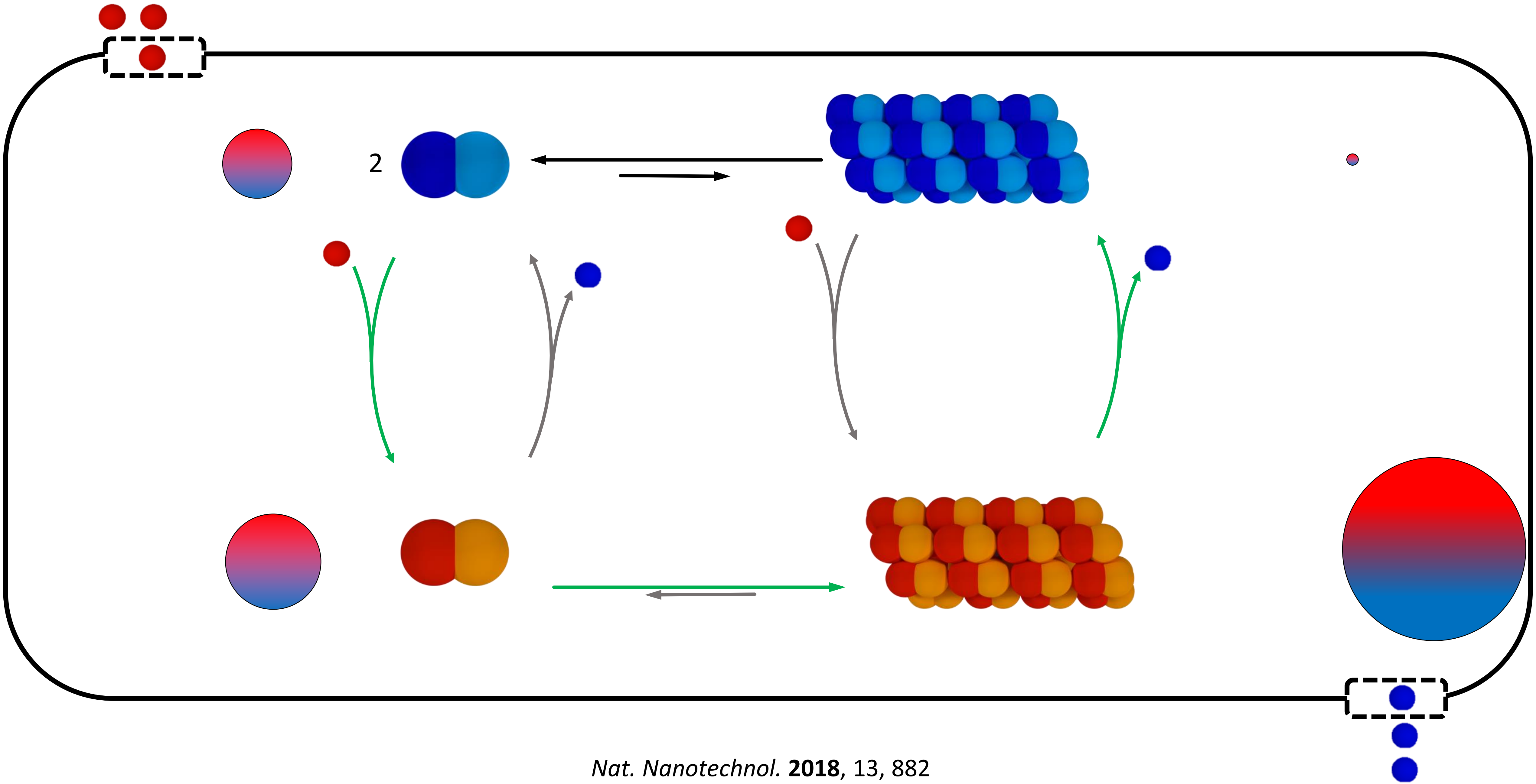
Distribution for a kinetically symmetric system



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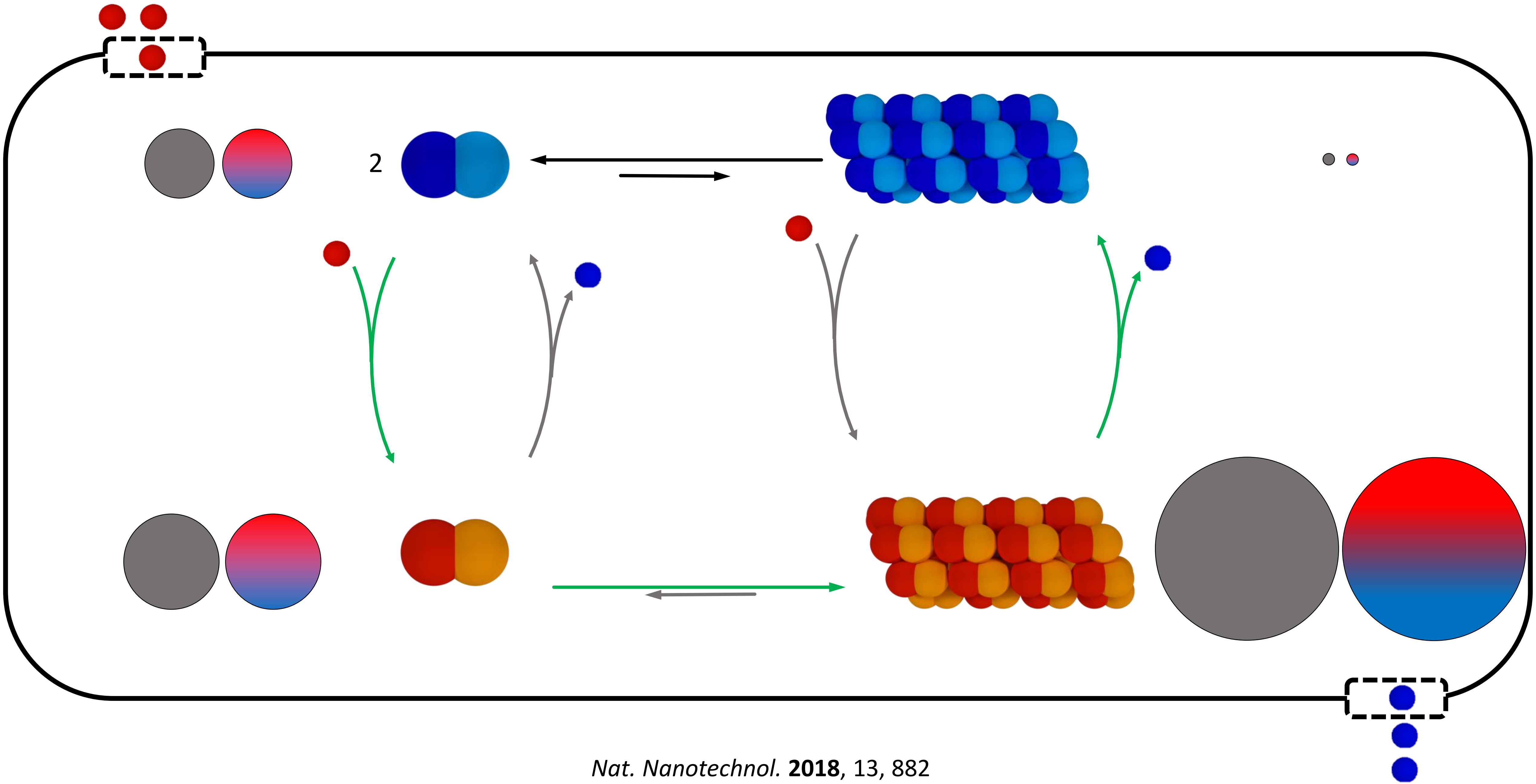

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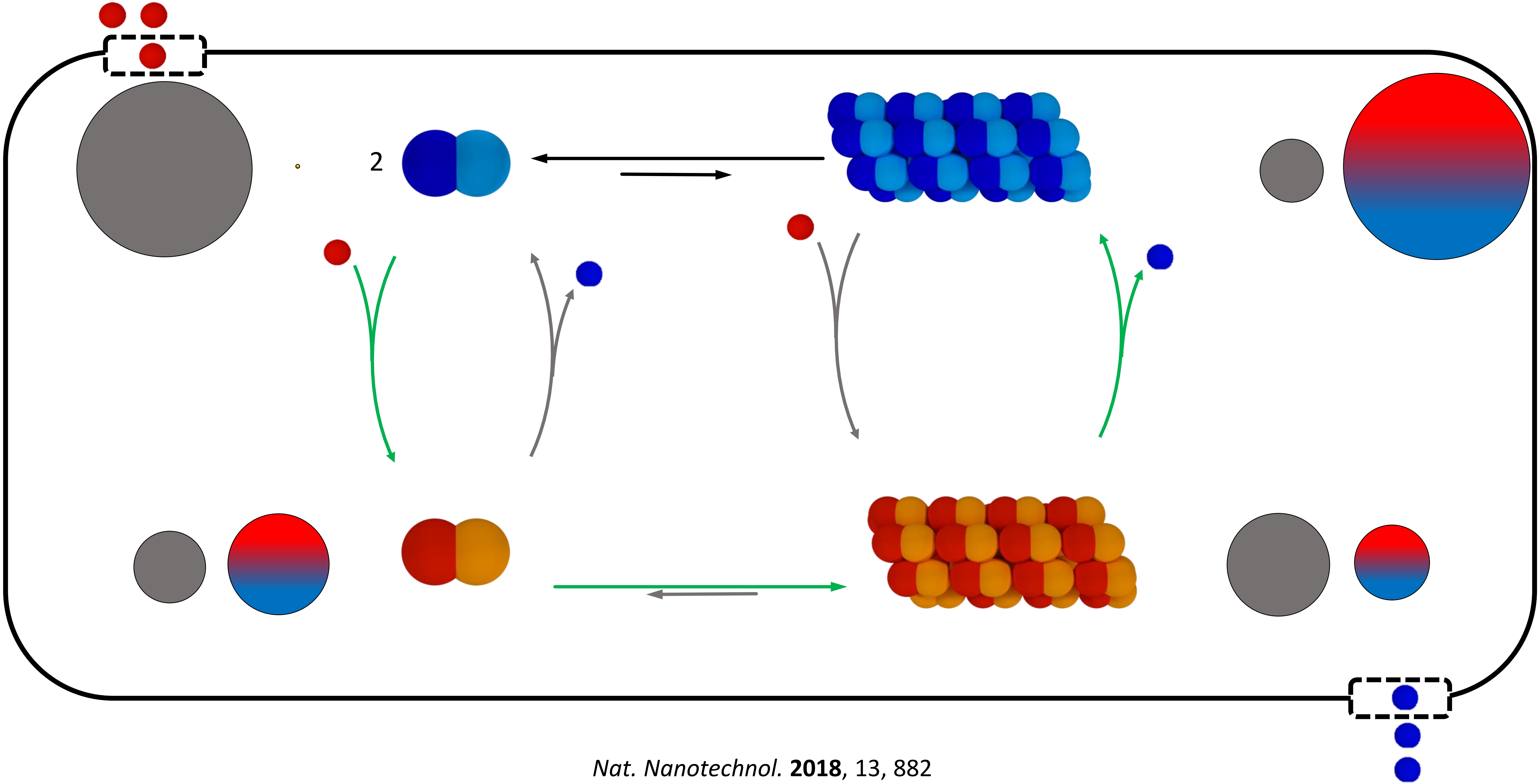
Distribution for a kinetically **a**symmetric system



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Outcomes of coupled reactions – at steady state

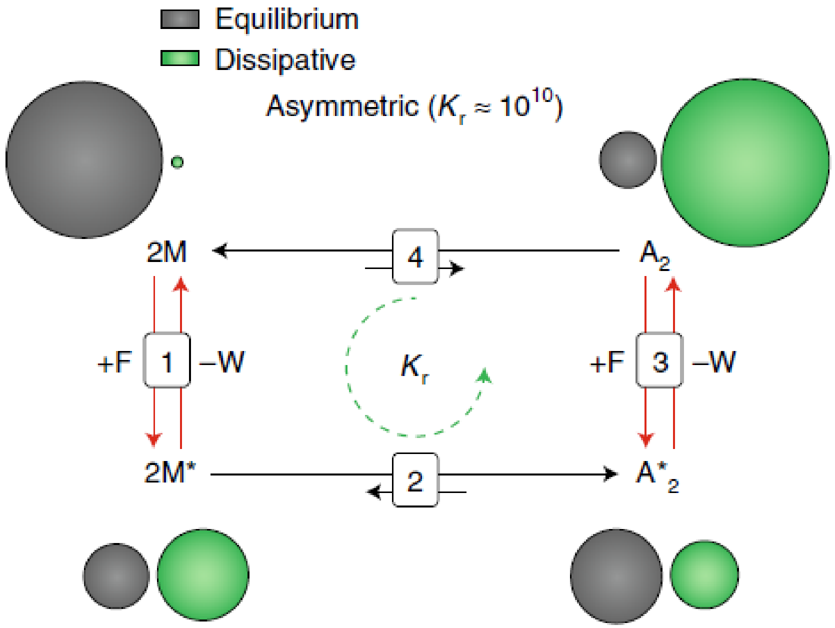
A cyclic current arises

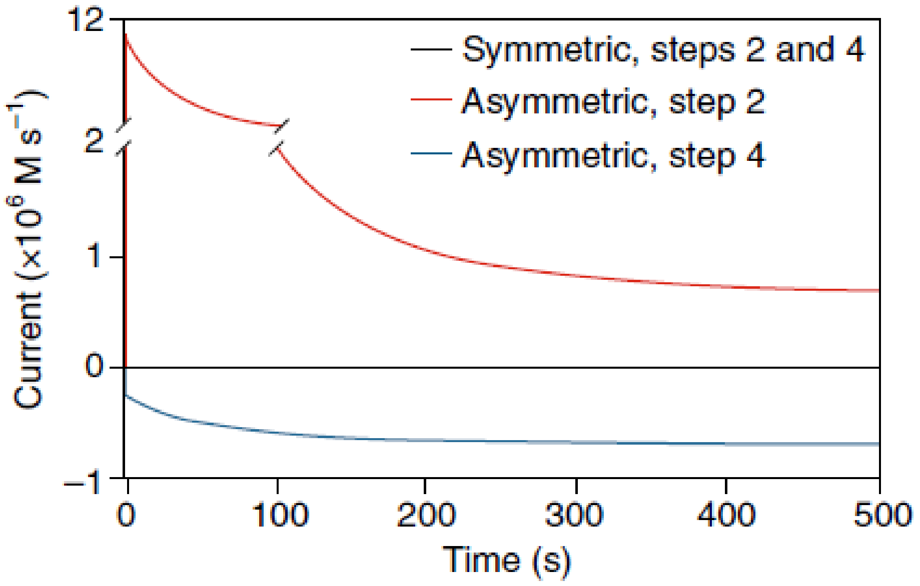
Concentrations are stationary, but differ from equilibrium values

Energy is stored in the system

Expression for step 2 net chemical current:

$v_2 = k_{2f} \times [M]^2 - k_{2b} \times [A^*_2]$





To consider when analyzing coupled reactions under stationary conditions

Key underlying phenomenon: different transition state depending on network position
i.e. chemical reactivity depends on target/mechanical state: *information*

Identify a self-standing reaction (mass/redox balance should be ok)

The self-standing reaction should take part in a cyclic reaction path

A branch of the cycle should afford the conversion of Substrate into Product

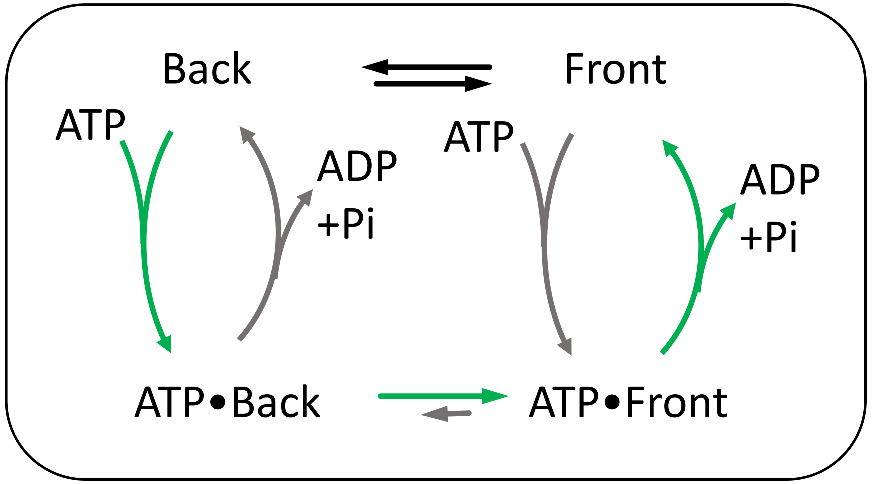
Design/evaluate kinetic asymmetry

Example 1: kinesin directional stepping

Back $$\mathrm{ATP} + \mathrm{E_b} \underset{k_{-\mathrm{T,b}}}{\overset{k_{+\mathrm{T,b}}}{\rightleftharpoons}} \mathrm{E[ATP \leftrightarrow ADP \bullet P_i]} \underset{k_{+\mathrm{D,b}}}{\overset{k_{-\mathrm{D,b}}}{\rightleftharpoons}} \mathrm{E_b} + \mathrm{ADP} + \mathrm{P_i}$$

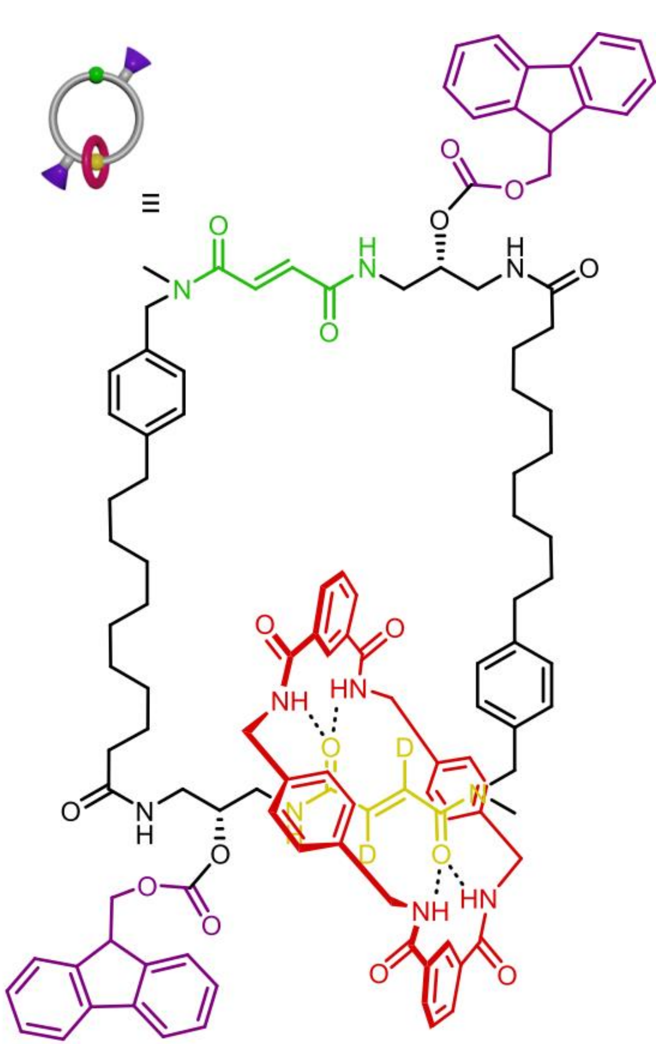
$$\downarrow\uparrow$$

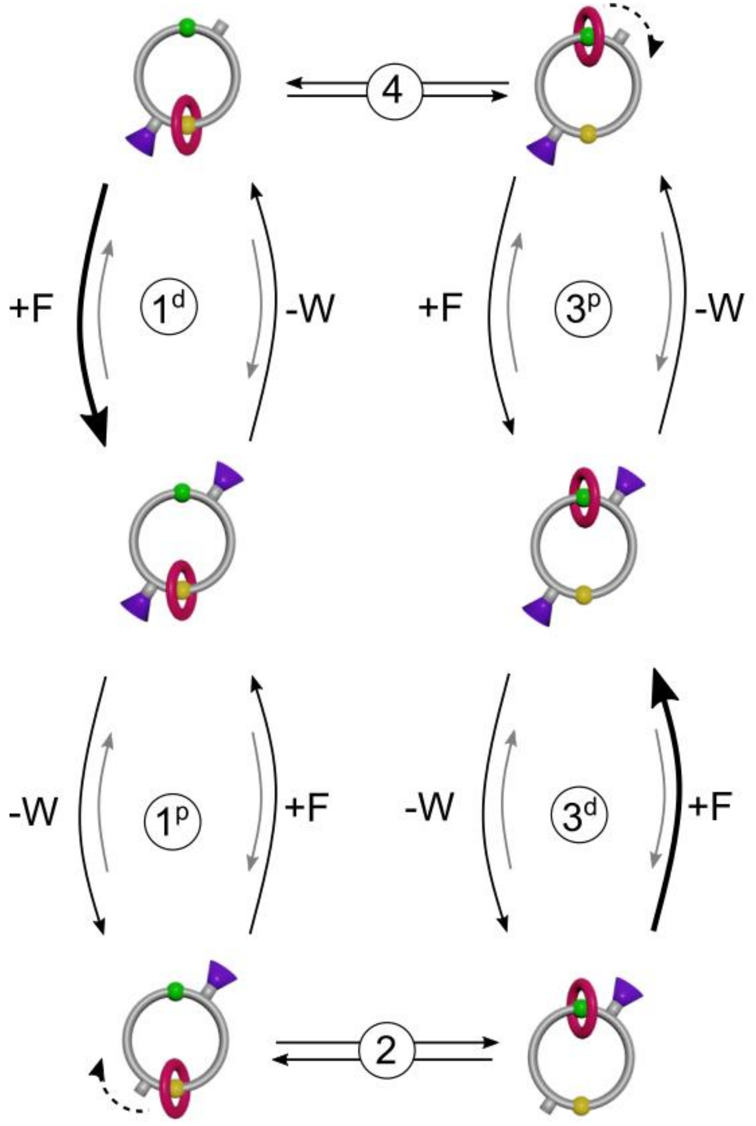
Front $$\mathrm{ATP} + \mathrm{E_f} \underset{k_{-\mathrm{T,f}}}{\overset{k_{+\mathrm{T,f}}}{\rightleftharpoons}} \mathrm{E[ATP \leftrightarrow ADP \bullet P_i]} \underset{k_{+\mathrm{D,f}}}{\overset{k_{-\mathrm{D,f}}}{\rightleftharpoons}} \mathrm{E_f} + \mathrm{ADP} + \mathrm{P_i}$$

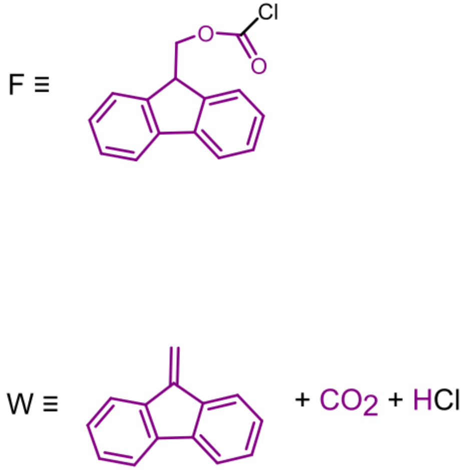


Nat. Nanotechnol. **2012**, 7, 684

Example 2: catenane rotary motor



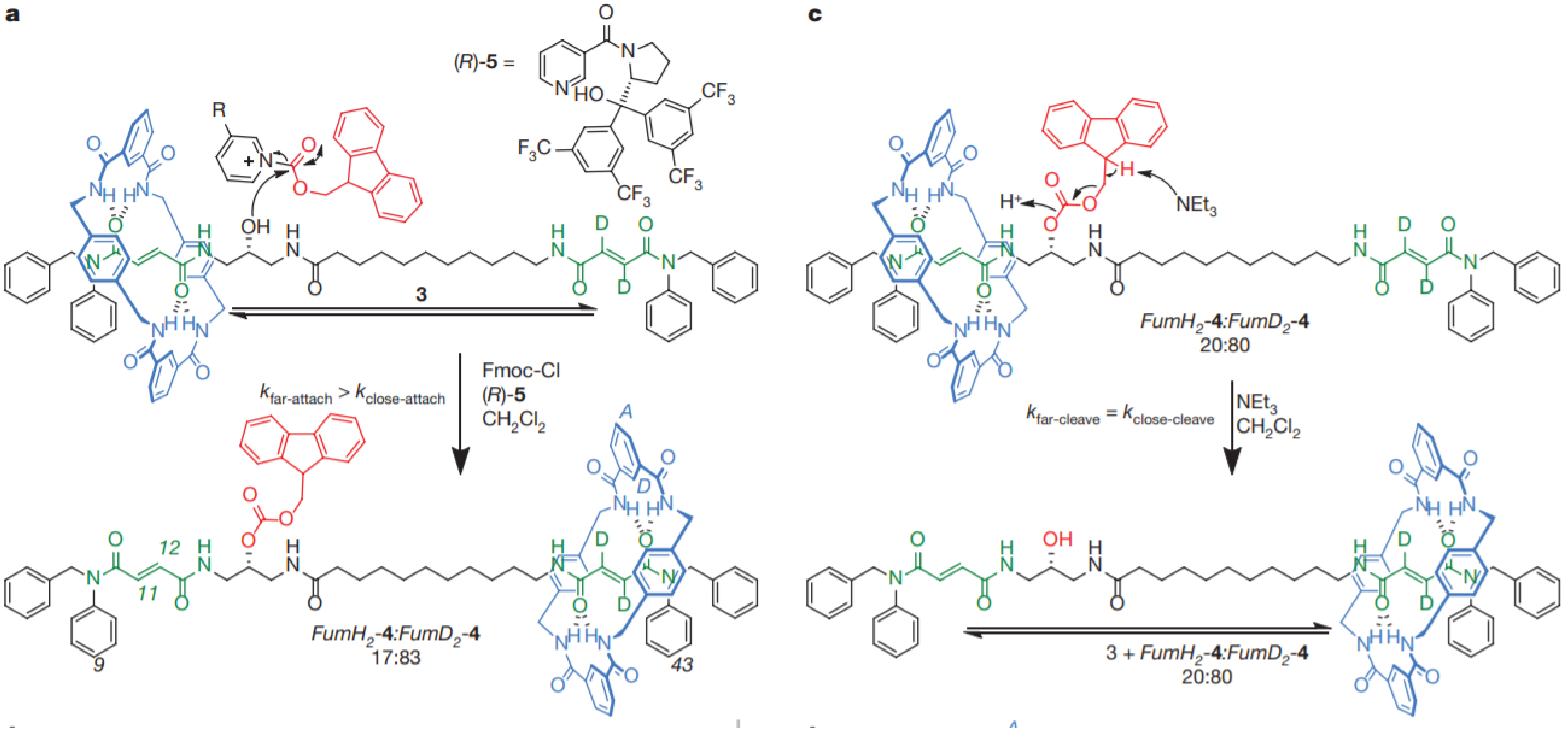




Cartoon credit: Elisabeth Kreidt

Nature **2016**, 7, 684

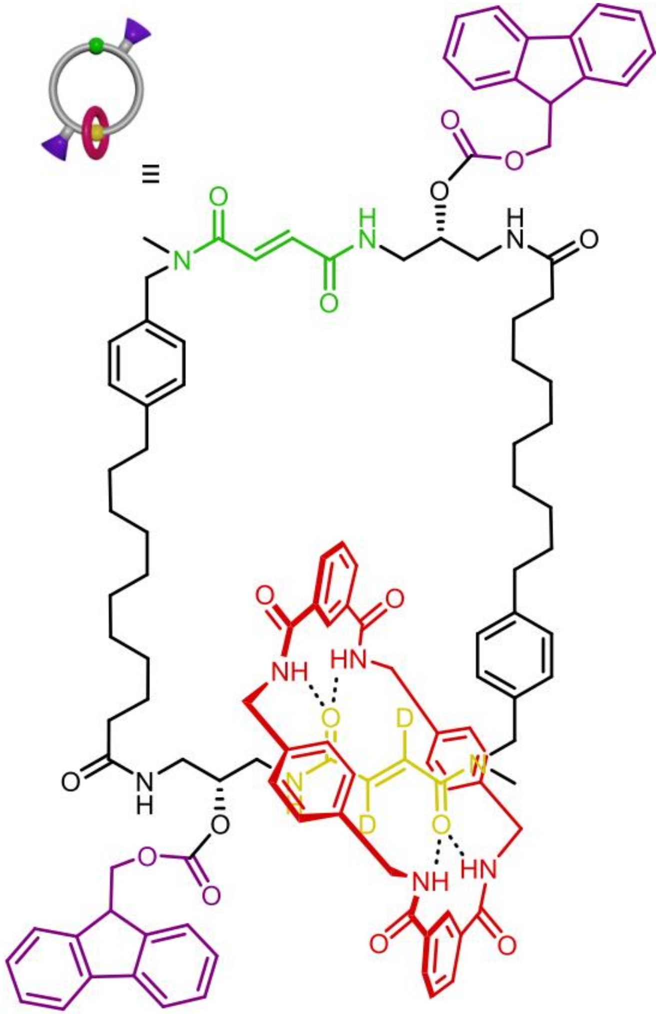
Example 2: catenane rotary motor

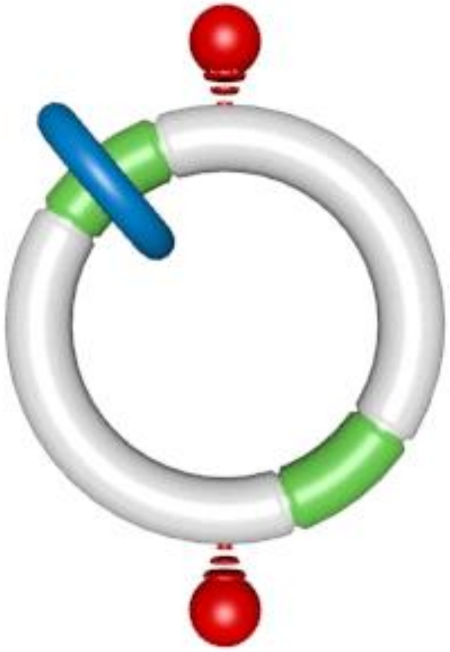


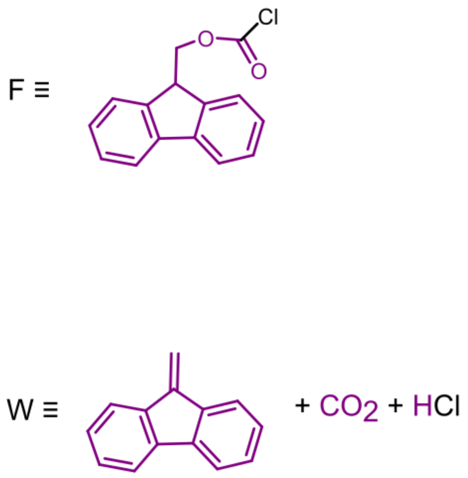
The molecular origin of kinetic asymmetry lies in the different mechanisms for attachment and detachment

Nature **2016**, 7, 684

Example 2: catenane rotary motor







Cartoon credit: Elisabeth Kreidt

Nature **2016**, 7, 684

Outcomes of coupled reactions – at steady state

A cyclic current arises – kinesin, catenane rotor

Concentrations are stationary, but differ from equilibrium values – microtubules, molecular pump

Energy is stored in the system

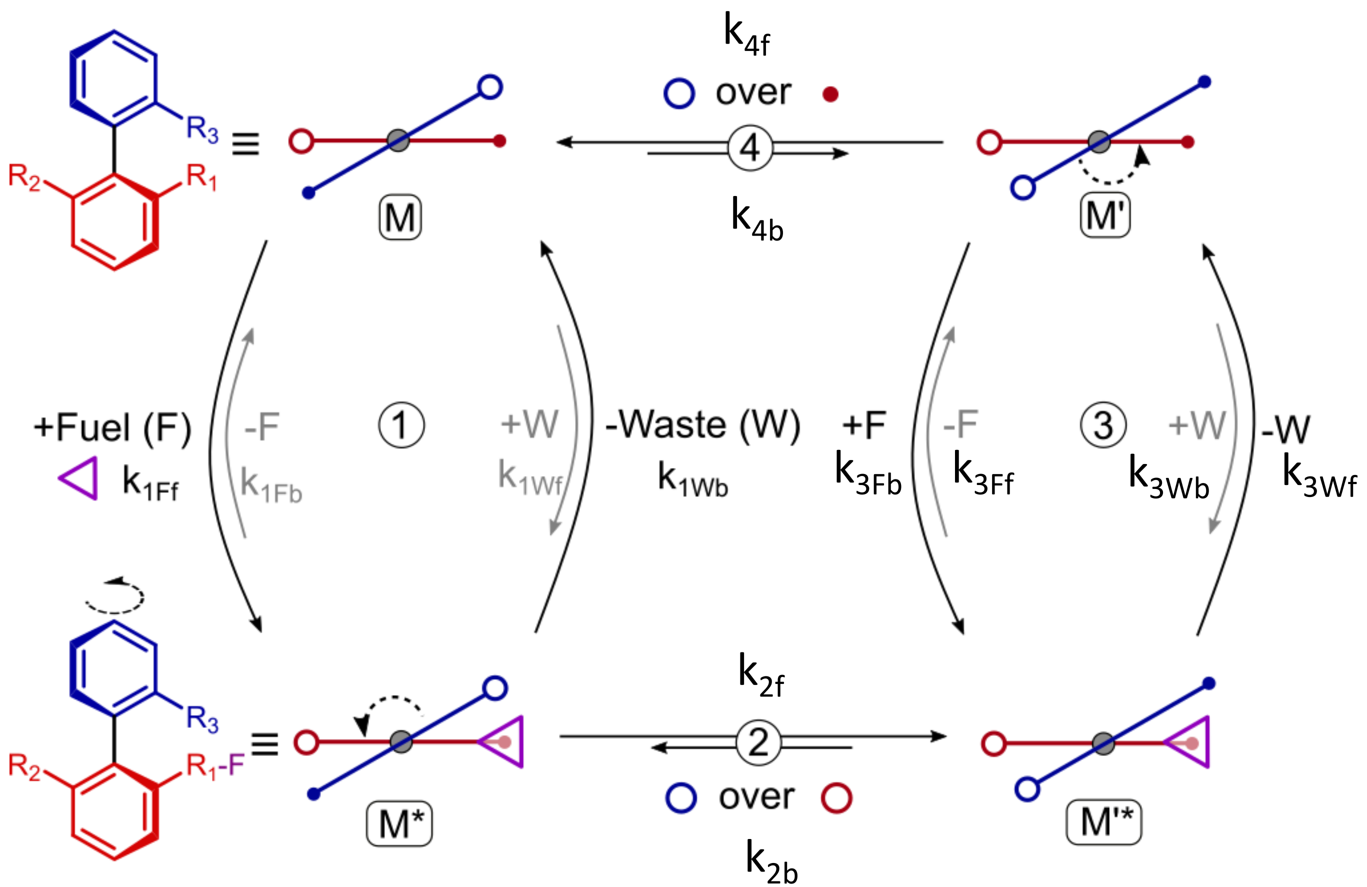
Exercise: kinetic asymmetry and energy

Consider the following scheme, which depicts a hypothetical chemically-driven rotary motor.

Is the motor rotating under the stationary condition [F] = 2 M, [W] = 0.02 M.

What is the upper bound for the work that the motor can do at room temperature (298 K)?

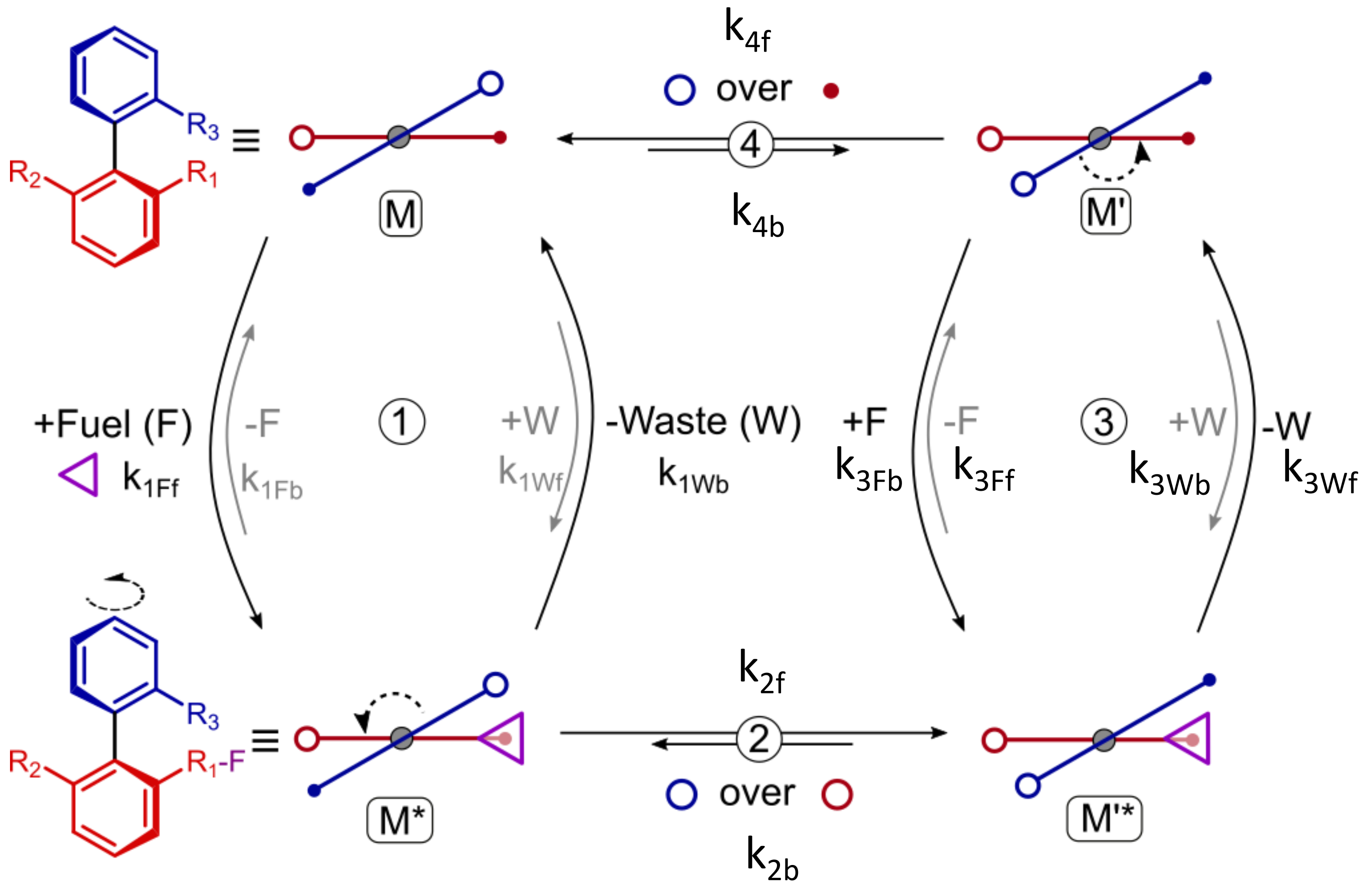
Use the available rate constants to answer these questions (see excel, with k1Ff = k0_1Ff*[S])



Forward reactions defined according to counterclockwise cycle

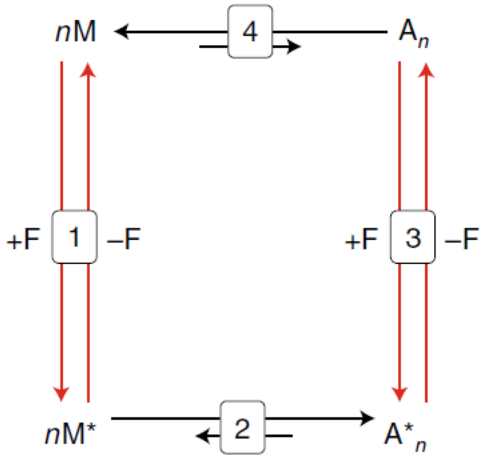
Exercise: kinetic asymmetry and energy

Thermodynamic relations remain valid, for any thermodynamic cycle: $\Pi\, k_f \,/\, \Pi\, k_b = 1$

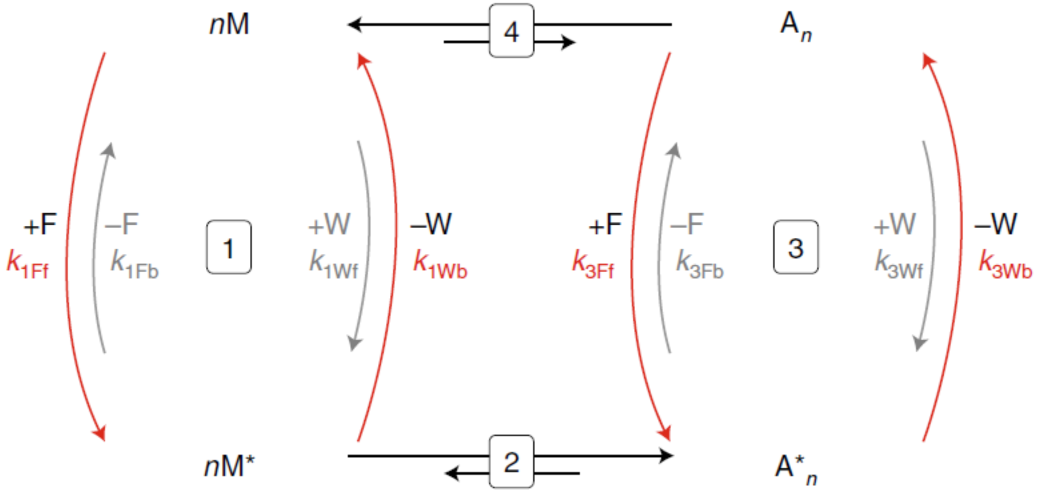


Forward reactions defined according to counterclockwise cycle

Energy storage: the ratcheting constant, K_r



$$K_1^n K_2 K_3^{-1} K_4^{-1} = 1$$



$$\left(\frac{k_{1Ff} + k_{1Wf}}{k_{1Wb} + k_{1Fb}}\right)^n K_2 \left(\frac{k_{3Ff} + k_{3Wf}}{k_{3Wb} + k_{3Fb}}\right)^{-1} K_4^{-1} = K_r$$

with: $k_{1Ff} = [F] \times k^0_{1Ff}$ $\quad k_{3Ff} = [F]^n \times k^0_{3Ff}$

$k_{1Wf} = [W] \times k^0_{1Wf}$ $\quad k_{3Wf} = [W]^n \times k^0_{3Wf}$

because: $v_{1Ff} = k^0_{1Ff} \times [F] \times [M]$

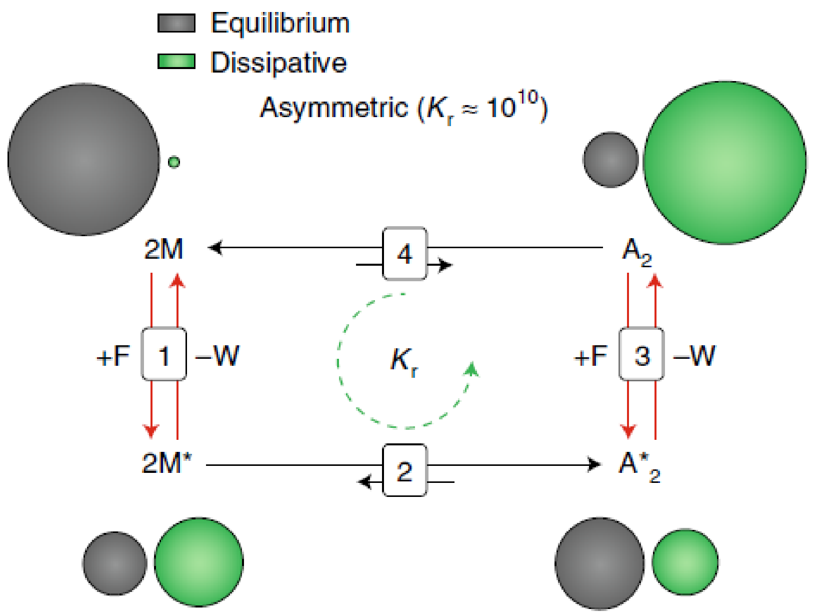
Probability of cycling counter clockwise / probability of cycling clockwise

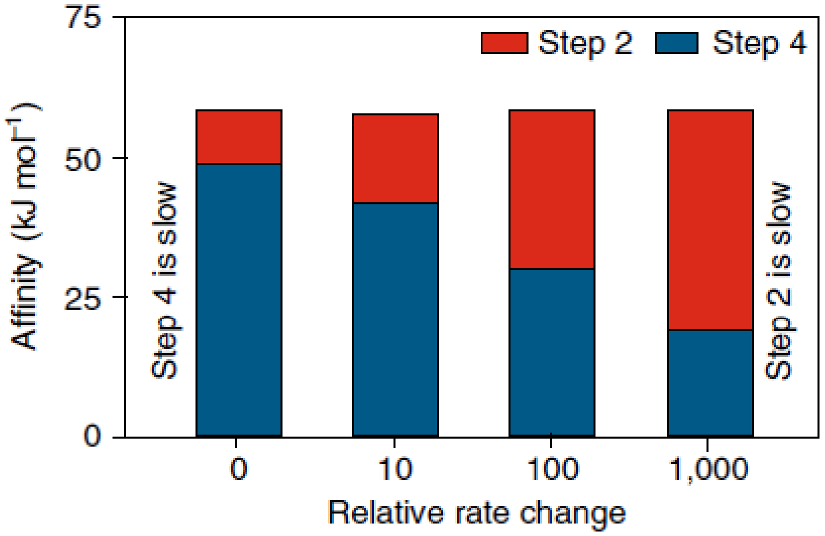
[Why brownian directionality emerges: because F to W conversion liberates energy, that is not any more available]

Origin of the name: brownian ratchets, popularized by Feynman https://www.youtube.com/watch?v=M3fYbCatKbA

Further readings: «Life's Ratchet: How Molecular Machines Extract Order from Chaos» by P. M. Hoffmann

Energy storage: the ratcheting constant, K_r





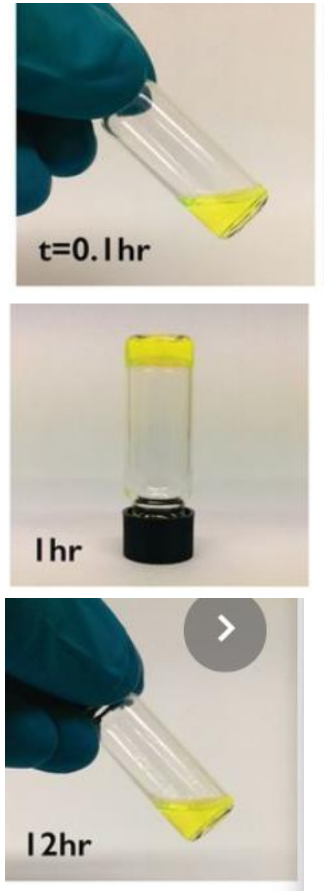
Δ = RT ln (K_r) is an upper bound for the energy stored in the system

Originates from affinity values: e.g. for step 2, $A = -RT \ln ([A^*_2]/[M]^2) + RT \ln [K_2]$

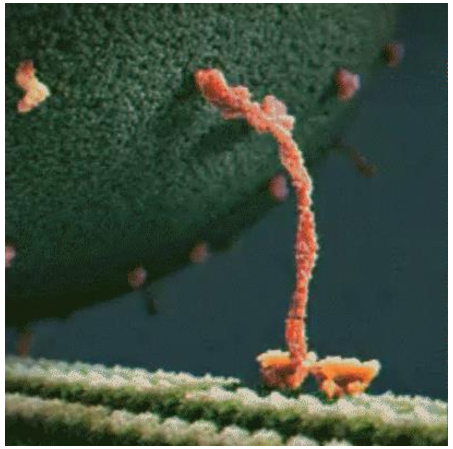
Université de Strasbourg

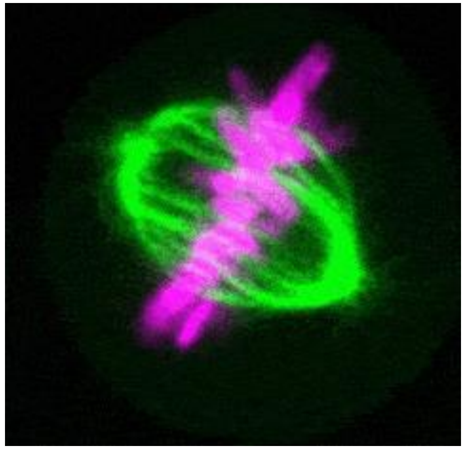
Chemically-driven non-equilibrium systems

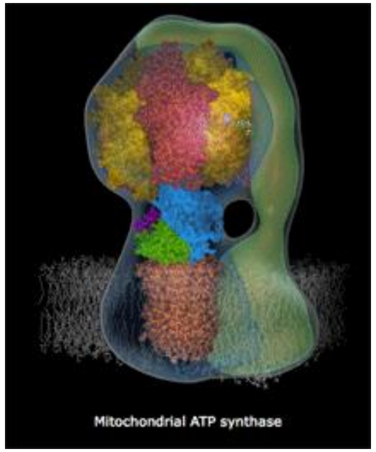
Transient systems (do NOT absorb energy)



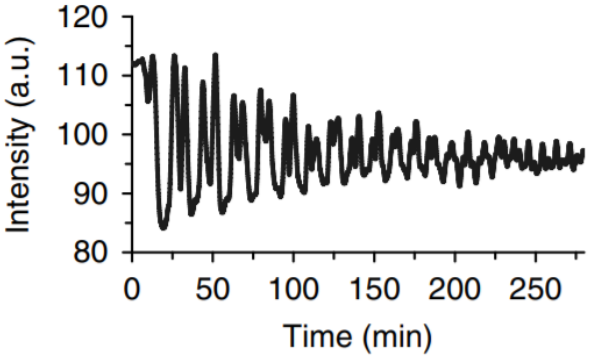
Driven systems (DO absorb energy)

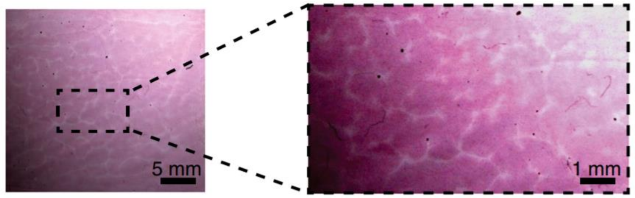






Oscillating systems (DO absorb energy & are synchronized)





Learning points: alternating conditions or light to drive endergonic reactions; what is kinetic asymmetry; how it underlies molecular machines & assembly of high-energy structures; how it's related to energy storage and energy transduction; how to calculate it

Topics & techniques: chemical reaction networks, non-equilibrium thermodynamics, organic chemistry, NMR & optical spectroscopies, kinetic modeling, microscopy, compartimentalization…

Kinetic asymmetry

Bifurcation