Driving Molecules out of Thermodynamic Equilibrium

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Knowles group meeting
Nov. 10, 2018
Outline

- Introduction
- Molecular Motors and Pumps
- Dissipative Out-of Equilibrium Molecular Assembly
- Conclusion
God Loves Out-of-Equilibrium Systems

- Nature’s Molecular Pumps, Motors and supramolecular assembly

- Na\(^+\)/K\(^+\)-ATPase

- Kinesin

- Microtubule
God Loves Out-of-Equilibrium Systems

- Nature’s Molecular Pumps, Motors and supramolecular assembly

**Na\(^+\)/K\(^+\)-ATPase**

**Kinesin**

More about Kinesin:

- Molecular weight: \(\sim 200\text{kDa}\);
- Stall force: 7.2 pN;

The force a kinesin can exert on its cargo is \(2 \times 10^6\) times of its own gravitational weight, which means **45mg** of Kinesin can lift me.

Hulk can lift 100 tons when calm, which is **100** times of his body weight.
God Loves Out-of-Equilibrium Systems

- Mechanism of the Directional “Walk” of Kinesin
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Macroscopic vs. Molecular Machines

- World’s smallest electric motor

Richard Feynman’s Challenge (1959): $1000 for building a functional motor with 1/64-inch cube, which was claimed within a year by William McLellan, a graduate student at Caltech.
Macroscopic vs. Molecular Machines

- Brownian Motion — Bless or Curse?

In an ordinary motor, energy is used to cause motion. In molecular motors, energy is used to cause a cessation of motion.

Mean velocity at $t \sim 100$ m/s (225 miles/h)

Molecular Switch vs. Molecular Motors & Pumps

- **Molecular Switches:** switching between two (or more) different states responding to external environment change

  ![Molecular Switch Diagram]

  \[
  X = \text{C, N}
  \]

- **Molecular Motors & Pumps:** are able to drive chemical reactions uphill or chemical systems away from their “inherent” equilibria.
Frequently Used Photoswitches in Out-of-Equilibrium Systems

**Azobenzene**

\[
\begin{align*}
\text{X} &= \text{C, N} \\
X &= \text{N}
\end{align*}
\]

Associated with large structural change

**Spiropyran**

Dipole and acidity switch

**Diarylethene**

Switching induces little geometry change, but a large electronic change.

Thermodynamic and Photodynamic Equilibrium

Thermodynamic equilibrated state

Principle of microscopic reversibility & Principle of detailed balance

\[ K_{eq} = \frac{II}{I} = e^{\frac{\Delta G^\ominus}{RT}} \]


Thermodynamic and Photodynamic Equilibrium

Thermodynamic equilibrated state

**Principle of microscopic reversibility & Principle of detailed balance**

Photostationary state

**T-type: thermally bistable system**

**P-type: thermally labile system**

In the absence of thermo back reactions:


Mechanisms of Molecular Motors & Pumps

- Power Stroke vs. Brownian Ratchet

Selectivity or Accuracy? Out-compete Brownian motion?

J. Howard, Current Biology, 2006, 16, 518.
Mechanisms of Molecular Motors & Pumps

- Power Stroke vs. Brownian Ratchet

Selectivity or Accuracy? Out-compete Brownian motion?

Dominant mechanism for biological molecular motors and pumps. Spatial and temporal control of the potential surface.

Mechanisms of Molecular Motors & Pumps

- How to tell? — apply an external force (potential field)!

Power Stroke

Example of Kinesin — Brownian Ratchet

Force has little effect on the forward rate constant.

Brownian Ratchet

A load force will have a big effect on the forward rate constant. (Change the Boltzmann distribution)

How to tell? — apply an external force (potential field)!

Power Stroke

Force has little effect on the forward rate constant.

Brownian Ratchet

A load force will have a big effect on the forward rate constant. (Change the Boltzmann distribution)

Example of Kinesin — Brownian Ratchet

The directional bias can be reversed and the speed is force dependent suggest a diffusional search for its next step.

J. Howard, Current Biology, 2006, 16, 518.
**Mechanisms of Molecular Motors & Pumps**

- **Feymann’s Ratchet**

\[ T_1 = T_2, \text{ no moving} \]
\[ T_1 > T_2, \text{ counter-clockwise rotation} \]
\[ T_1 < T_2, \text{ clockwise rotation} \]
Feymann’s Ratchet

Three elements of ratcheting mechanism:

1. Random motion (Brownian);
2. Asymmetric gating;
3. Non-equilibrium driving force;

\[ T_1 = T_2, \text{ no moving} \]
\[ T_1 > T_2, \text{ counter-clockwise rotation} \]
\[ T_1 < T_2, \text{ clockwise rotation} \]
Mechanisms of Molecular Motors & Pumps

- **Energy Ratchet** — changing of potential surface is INDEPENDENT of position (configuration, status) of the particle

- **Information Ratchet** — changing of potential surface is DEPENDENT of position (configuration, status) of the particle

**Example**: driving uphill in a hailstorm with no gas!
Mechanisms of Molecular Motors & Pumps

- **Energy Ratchet** — changing of potential surface is INDEPENDENT of position (configuration, status) of the particle
- **Information Ratchet** — changing of potential surface is DEPENDENT of position (configuration, status) of the particle

**Example**: driving uphill in a hailstorm with no gas!

Move the brick as soon as your car going uphill!
Mechanisms of Molecular Motors & Pumps

- **Energy Ratchet** — changing of potential surface is INDEPENDENT of position (configuration, status) of the particle
- **Information Ratchet** — changing of potential surface is DEPENDENT of position (configuration, status) of the particle
Mechanisms of Molecular Motors & Pumps

**Example:** driving uphill in a hailstorm with no gas!

Plan B — replace the standard brake with a ratchet

Two Types of Energy Ratchet

- "Flashing" Ratchet — A fluctuating potential

- "Rocking" Ratchet — A fluctuating force

Particle drift to the left!

F_{\text{ext}} is too big!

R. D. Astumian, Science, 1997, 276, 917
Summary of Key Concepts

**Macroscopic motors**
External force to drive

**Molecular machines**
External force to outcompete or bias Brownian motion

**Molecular switch**
Switch between states

**Molecular motors**
Able to do work

**Power stroke**
Do work albeit Brownian motion

**Brownian Ratchet**
Do work because of Brownian motion

**Energy ratchet**
Potential surface independent of the position of particle

**Information ratchet**
Potential surface dependent of the position of particle

**“Flashing” ratchet**
Constant external force + “on” and “off” ratcheting potential

**“Rocking” ratchet**
Fluctuating external force + constant ratcheting potential

R. D. Astumian, Science, 1997, 276, 917
The First Molecular Ratchet

Calculated energy diagram for rotation

Asymmetric energy curve results from the helical chirality!

ΔH/kcal mol⁻¹

0 120

α/°
clockwise

counter-clockwise

There is no net directional rotation of the molecular ratchet from spin polarization transfer NMR technique (at 160°C).

\[ \Delta G^\neq = 24.5 \text{ kcal/mol} \]

The symmetry of the rotational energy curve in Figure 2 is thus deceptive: In contrast to mountain climbing, it is only the height of the summit, not the steepness of the terrain that matters. The chemical principle of microscopic reversibility prevails.

The First Molecular Ratchet

- Use chemical fuel to bias brownian motion

The First Molecular Ratchet

- Use chemical fuel to bias brownian motion

Clockwise Rotation

Rotation is significantly faster by shortening the chain!

However, not a motor yet …

First Molecular Motor

- Design principle

The diastereometric nature of two chiral elements determines the rotating direction.

Light-driven motor that achieves uni-directional continuous 360° rotation, with controllable speed.

First Molecular Motor

- Macroscopic contraction of a gel induced by the integrated motion of light-driven molecular motors — featuring continuous rotation
First Molecular Motor

- Dual-light control of nanomachines that integrate motor and modulator subunits — featuring continuous rotation

N. Giuseppone, Nat. nanotech., 2017, 12, 540
First Molecular Motor

- Dual-light control of nanomachines that integrate motor and modulator subunits — featuring continuous rotation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Modulator 2</th>
<th>Motor 3 (equiv.)</th>
<th>Motor 4 (equiv.)</th>
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<tr>
<td>Gel 50</td>
<td>1.00</td>
<td>1</td>
<td>0.00</td>
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<tr>
<td>Gel 25</td>
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<tr>
<td>Gel 12</td>
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<td>Gel 5</td>
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<tr>
<td>Gel 0</td>
<td>0.00</td>
<td>1</td>
<td>1.00</td>
</tr>
</tbody>
</table>

N. Giuseppone, *Nat. nanotech.*, 2017, 12, 540
Light-driven Transport of a Synthetic Molecular Walker in Either Direction along a Molecular Track

The key to achieve directionality lies in the isomerization of stilbene.

D.A. Leigh, Nat. Chem., 2010, 2, 96
Kinesin:
- takes 16.6 nm steps
- takes one step per molecule ATP hydrolysed
- mean 75-150 steps before dissociating
- 250 kD walker
- carries cargo
- autonomous
- walks up to 1 micron along microtubule supramolecular polymers

1st generation small-molecule walker:
- takes 1.4 nm steps
- takes one step per acid-base/redox oscillation
- mean 37 steps before dissociating
- 21 atom walker unit
- doesn’t carry cargo (yet)
- requires sequential change of conditions (at present)
- walks along four-footed track (so far)
An Artificial Molecular Pump

J. F. Stoddart, Nat. nanotech., 2015, 10, 547
An Artificial Molecular Pump

J. F. Stoddart, *Nat. nanotech.*, 2015, 10, 547
An Artificial Molecular Pump

Up to 11 CBPQT\(^{4+}\) can be transferred onto the rotaxane!
Rotary Molecular Motors Driven by Pulses of a Chemical Fuel

Rotary Molecular Motors Driven by Pulses of a Chemical Fuel

Molecular Rotary Motor
with a pulsed chemical fuel

Dynamic cationic charge

Blocking Unit 1 (Disulfide)

Blocking Unit 2 (Hydrazone)

Crown ether

Fuel pulse:

Static cationic charge

A Molecular Information Ratchet — No Change of the Relative Affinity

Step 1: Close form, slow movement

Step 2: the strong demon open the switch when close to it

Probabilities obey Boltzmann distribution

Fast thermodynamic equilibrium

Step 3: the weak demon close the switch when the strong demon is away

Out of equilibrium

A Molecular Information Ratchet — No Change of the Relative Affinity


Photostationary state: 59% Z, 41% E

Photostationary state: 80% Z, 20% E
A Molecular Information Ratchet — No Change of the Relative Affinity

\[
\Delta G = Nk_B T \left[ x_1 \ln \frac{x_1}{y_1} + (1 - x_1) \ln \frac{1 - x_1}{1 - y_1} \right]
\]

\[ x_1 = 0.45; \ y_1 = 0.65 \]

\[ \Delta G = 49 \text{ kcal/mol} \]

Light-driven information ratchet.

A Molecular Information Ratchet — No Change of the Relative Affinity

A Chemically-Driven Molecular Information Ratchet

Component 1: biased Fmoc attachment

Start from FumH$_2$-4:FumD$_2$-4 = 100:0

(F)-5

$FumH_2$-4:FumD$_2$-4

17:83

An Autonomous Chemically Fuelled Small Molecule Motor

**Step II: unbiased Fmoc cleavage**

Recovered protected rotaxane has same FumH$_2$-4:FumD$_2$-4 = 20:80
Step III: Connect to form [2]catenane
An Autonomous Chemically Fuelled Small Molecule Motor

Experimental observation

Net reaction (energy source — 2 molecule of Fmoc-Cl per 360°)

Estimated rotation time ~12h every 360°

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Equilibrium Assembly vs. Dissipative Assembly


B: Kinetically trapped assembly. Local minimum. Infinite lifetime.

C: Metastable assembly. Finite lifetime.

D: Dissipative assembly. Need to be coupled to a chemical reaction or other energy source.

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Out-of-Equilibrium Systems Chemistry

The photodynamic covalent bonds shift reaction networks using light energy

\[ \text{heat} \quad \rightarrow \quad \text{out-of-equilibrium} \]

\[ \text{reaction coordinate} \]

\[ \text{Gibbs free energy} \]

\[ \text{excited state} \]

\[ \text{light} \quad \rightarrow \quad \text{equilibrium} \]

\[ \text{reaction coordinate} \]

\[ \text{Gibbs free energy} \]

\[ \text{heat} \]

\[ \text{light} \]

\[ \text{Gibbs free energy} \]

XEt-TMIOX + PhEt-TMIO \xrightleftharpoons[\text{UV}]{\Delta} \text{XEt-TMIO} + PhEt-TMIOX

Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems

S. Hecht, Nat. Chem., 2018, 10, 1031
Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems

Crucial band separation of 70 nm of $\text{III}_{\text{A/H}}$ vs. $\text{II}

Quantum yield of ring opening of $\text{II}$ is five times higher than $\text{III}_{\text{A/H}}$

Photostationary state distribution:

$$K^\lambda_{eq} = \frac{II}{I} = \frac{\varepsilon_1^\lambda \cdot \Phi_{1\rightarrow II}^\lambda}{\varepsilon_{II}^\lambda \cdot \Phi_{II\rightarrow I}^\lambda}$$

S. Hecht, *Nat. Chem.*, 2018, 10, 1031
Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems

Ar = 3,5-bis(trifluoromethylphenyl); RNH₂ = octylamine; H⁺ source: benzoic acid

S. Hecht, Nat. Chem., 2018, 10, 1031
Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems

Ar = 3,5-bis(trifluoromethyl)phenyl;
RNH₂ = benzhydrazide
H⁺ source: trifluoroacetic acid

S. Hecht, *Nat. Chem.*, 2018, 10, 1031
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Light-Driven Bidirectional Manipulation of Dynamic Covalent Systems

Ar = 3,5-bis(trifluoromethyl)phenyl;
RNH₂ = benzhydrazide
H⁺ source: trifluoroacetic acid
Transient Assembly of Active Materials Fueled by a Chemical Reaction

\[ \text{Conditions: } \text{pH} = 11, [1a]_0 = 50 \text{ mM}, [\text{DMS}]_0 = 200 \text{ mM}, \text{ with } 1 \mu\text{M} \text{ fluorescein for coloring} \]

Transient Assembly of Active Materials Fueled by a Chemical Reaction

pH dependent kinetics and self-healing ability

Light-Controlled Self-assembly of Non-photoresponsive Nanoparticles

Electrostatic repulsion prevents aggregation

R. Klajn, Nat. Chem., 2015, 7, 646
Light-Controlled Self-assembly of Non-photoresponsive Nanoparticles

(a) Absorbance (a.u.) vs. Wavelength (nm) showing changes under light (hv) and thermal effects (k_B T).

(b) Absorbance (a.u.) vs. Wavelength (nm) with multiple time points indicated.

(c) Cycle number vs. λ_max (nm) showing the effect of light (hv) on the system.

(d) Three-dimensional graph showing size distribution over cycle number.

R. Klajn, Nat. Chem., 2015, 7, 646
Light-Controlled Self-assembly of Non-photoresponsive Nanoparticles

Writing self-erasing images with NPs in a photoresponsive gel

R. Klajn, Nat. Chem., 2015, 7, 646
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Conclusion

- Design molecular motors and pumps featuring unidirectional movement and capabilities to do effective work, with high fatigue-resistance and simple structures.

- Drive chemical reactions and dynamic mixtures of molecules out-of-equilibrium. New strategies for spatial-temporal control and are needed.

- Potential application of out-of-equilibrium systems include solar-to-chemical energy conversion and storage, more efficient communication and information transfer.

- Maxwell’s demon or angel?