Introduction to Biomolecular nanomachines and related thermodynamics

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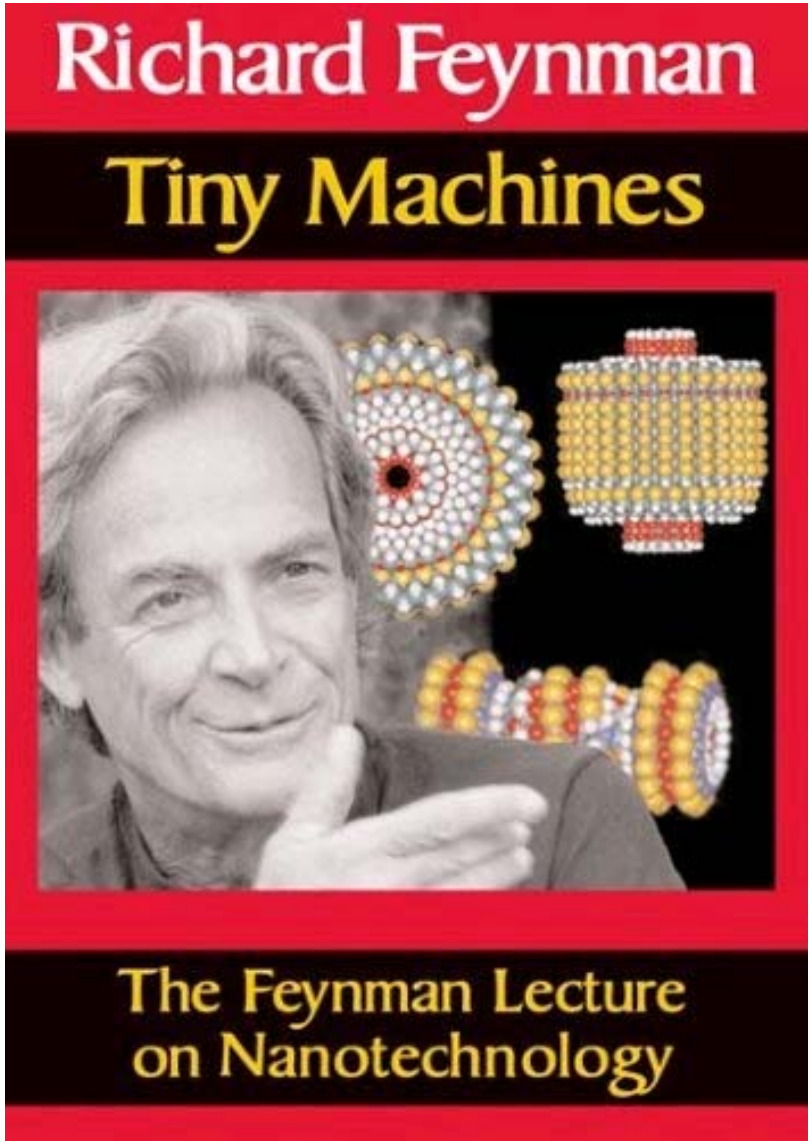


Richard Feynman, there's plenty of room at the bottom,1959

Kim Eric Drexler, Mr.Nanotechnology

A dreamer!

Engines of Creation: The Coming Era of Nanotechnology,1986

And a serious physicst?

Nanosystems Molecular Machinery Manufacturing and Computation,1992

Outline

I, what is biomolecular machinery

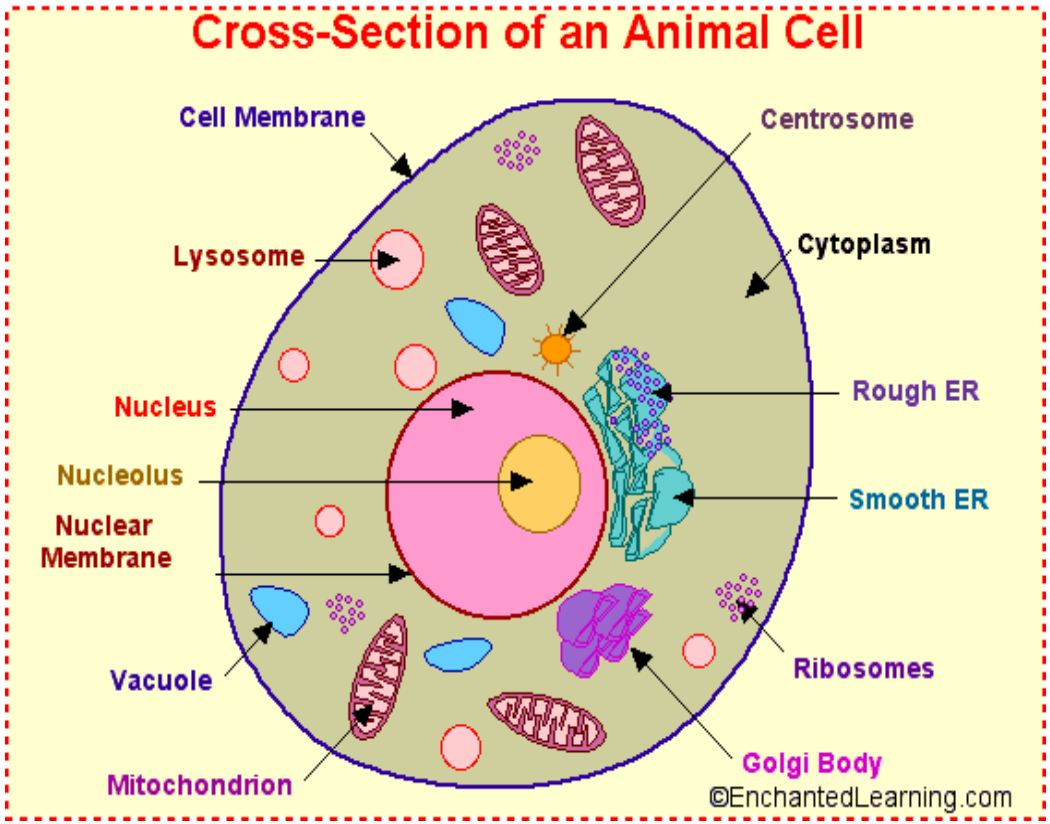
II, the working principle: Brownian Ratchet

III, thermodynamics of nanomachines

Part I
what is biomolecular machinery

Is ‘nanomachine’ a fundamental concept for biology?
--- one story: structural heterogeneity

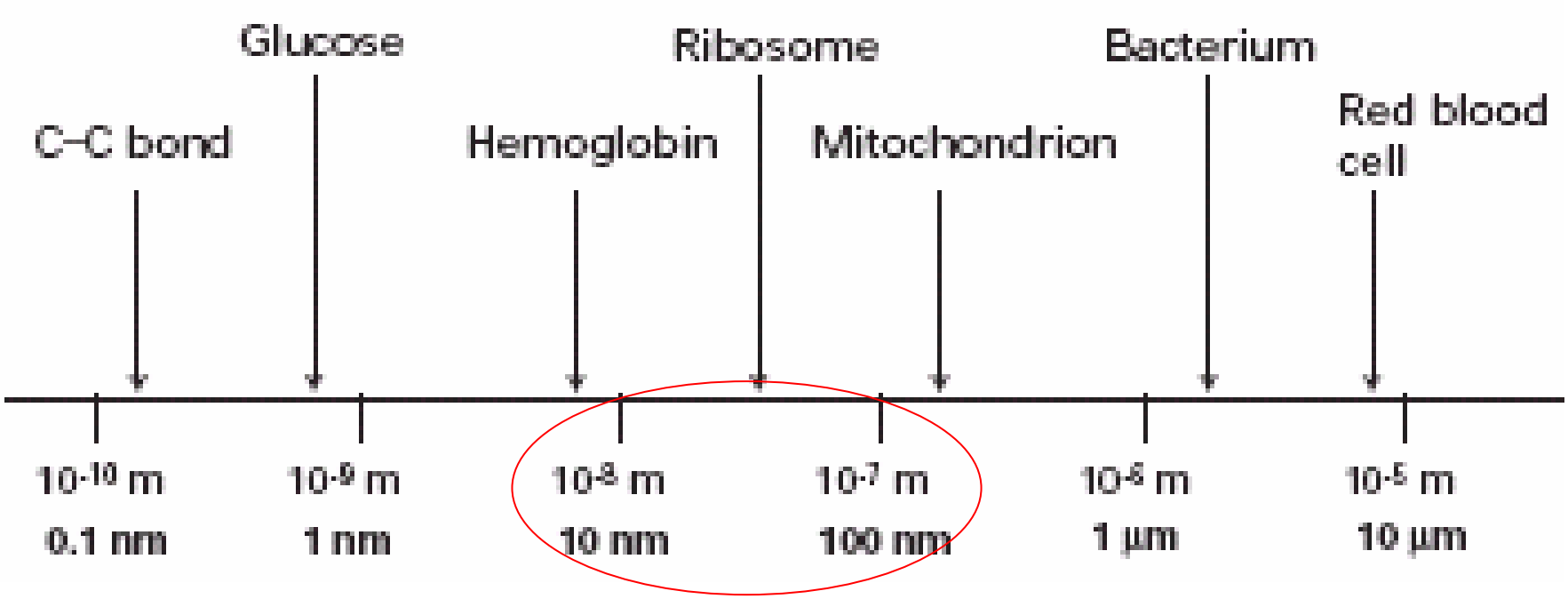
Cell is a extremely hierarchical system.
Cells not only do chemical things (synthesis and degradation), they also do physical things (ion translocation, vesicle transportation,…)



A reactor of homogeneous chemical solution?

A nano-factory?

The structural hierarchy spans from the scale of cell body all the way down to the scale of macromolecules,
i.e., **structural heterogeneity** exists even at macromolecule scales (e.g. ribosome, chromosome)



Biomolecular machines: macromolecules or their complex

Is ‘nanomachine’ a fundamental concept for biology? --- another story: dynamic heterogeneity

- an enzyme (or a protein assembly) often has very small number of copies (most < 10000, sometimes even <100) in a cell. By contrast, in *in vitro* biochemical experiments, the copy number can be ~10^10.

- Do they function as an ensemble, or as **individual machines?**

  the latter may be more reasonable, i.e., different copy can be in different working state at the same moment though they all have the same function (this is called **dynamic heterogeneity**).

- **Nanomachine, only a metaphor?**

  For a long time period, there was no way to identify the individualism by conventional biochemistry which only provides the ensemble-averaged information.

Nanomachine, not only a metaphor !

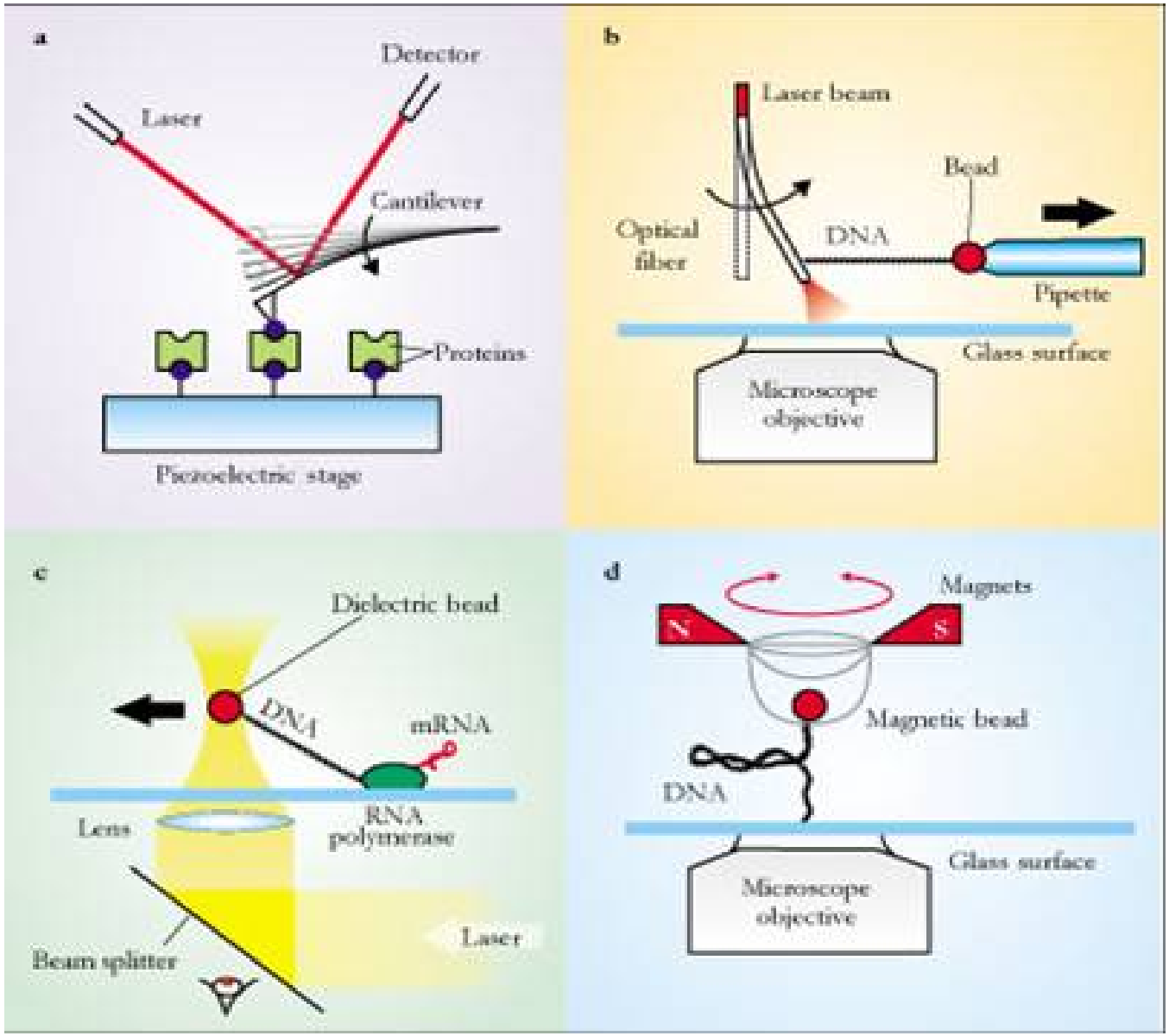
- Since 1990, rapid progress of techniques of single molecule manipulation (optical tweezer, magnetic tweezer, micro-pipette, etc) made it possible to observe and control the action of an individual protein molecule.

- Details have been revealed how some protein enzymes (motors) work. Indeed, they resemble their macro-counterparts either in the constructions or in the working cycles.

- A well-estabilished picture:

  cell is like a factory with workshops, assembly lines, transports, and hundreds of thousands of molecular machines performing different tasks to make the cell a self-sustaining system.

Some popular single-molecule manipulations



How does a biomolecular machine look like?
-- Miniature miracle resembling its macro-counterpart !

- **Containing highly coordinated moving parts;**
- **using chemical energy to do physical things;**
- **performing a series of ordered actions (conformation changes) , though not in a deterministic way (due to the unavoidable thermal fluctuation);**

➢ Natural biomolecular machines:

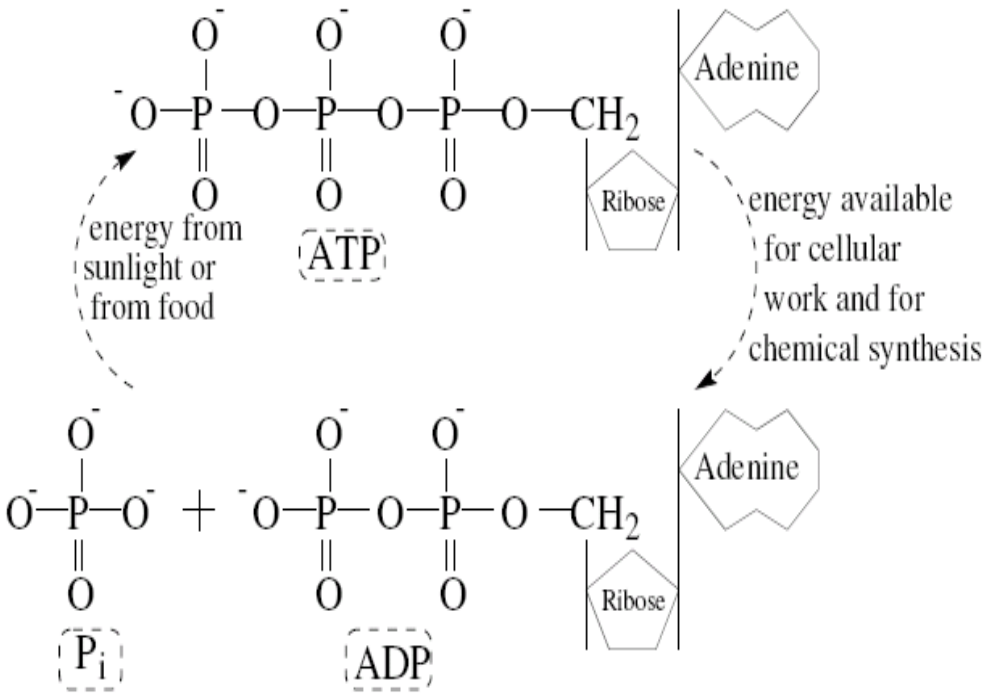
1, enzyme: scissor(restriction enzymes),
replicator (RNA/DNA polymerase) …

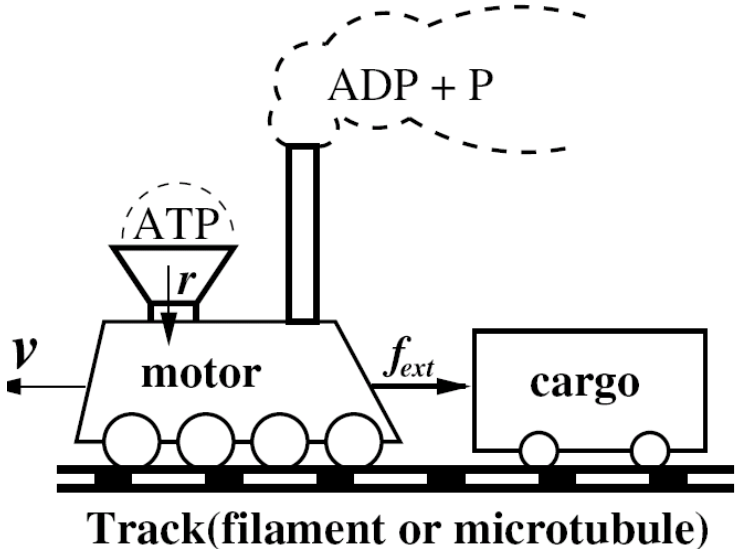
2, motor: transporter(kinesin), rotor(ATP synthase),
clamp (condensin), sweeper(helicase),
scissor-and-ligater (topoisomerse)…

➢ Biomimic soft-material nanomachines:
transporter, actuator, tweezer,…

- ATP is the universal energy currency used by most natural biomolecular motors.
- Biomimic nanomachines can use other kind of energy.

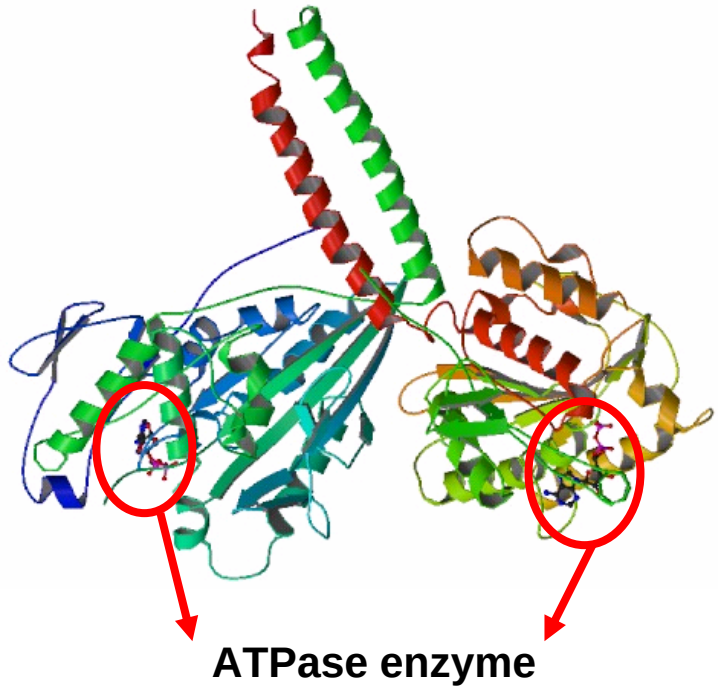
$$ATP^{4-} + H_2O \Rightarrow ADP^{3-} + H_2PO_4^- + 27.6\,\text{kJ/mol}$$

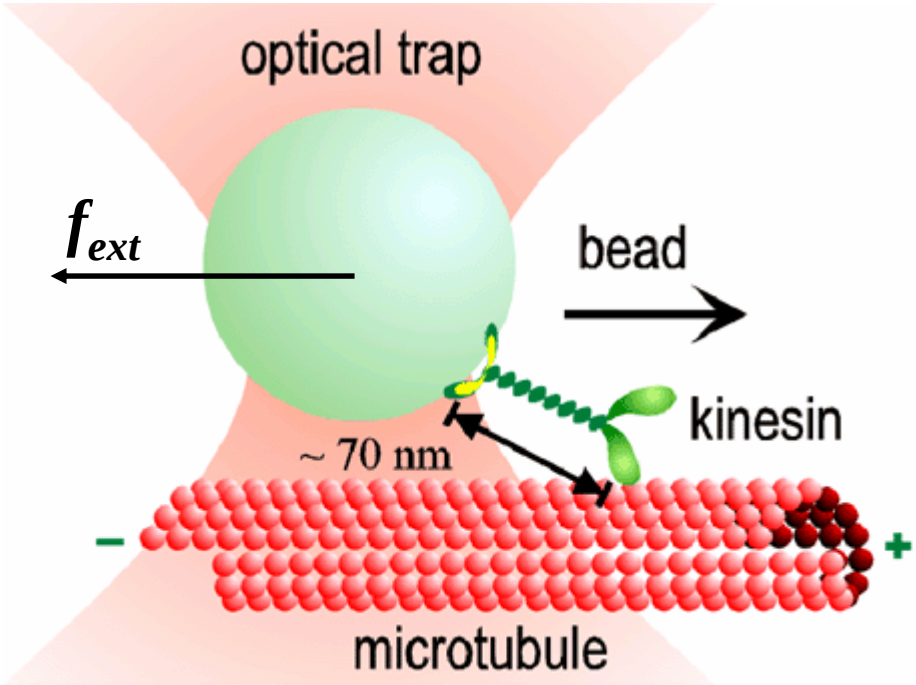




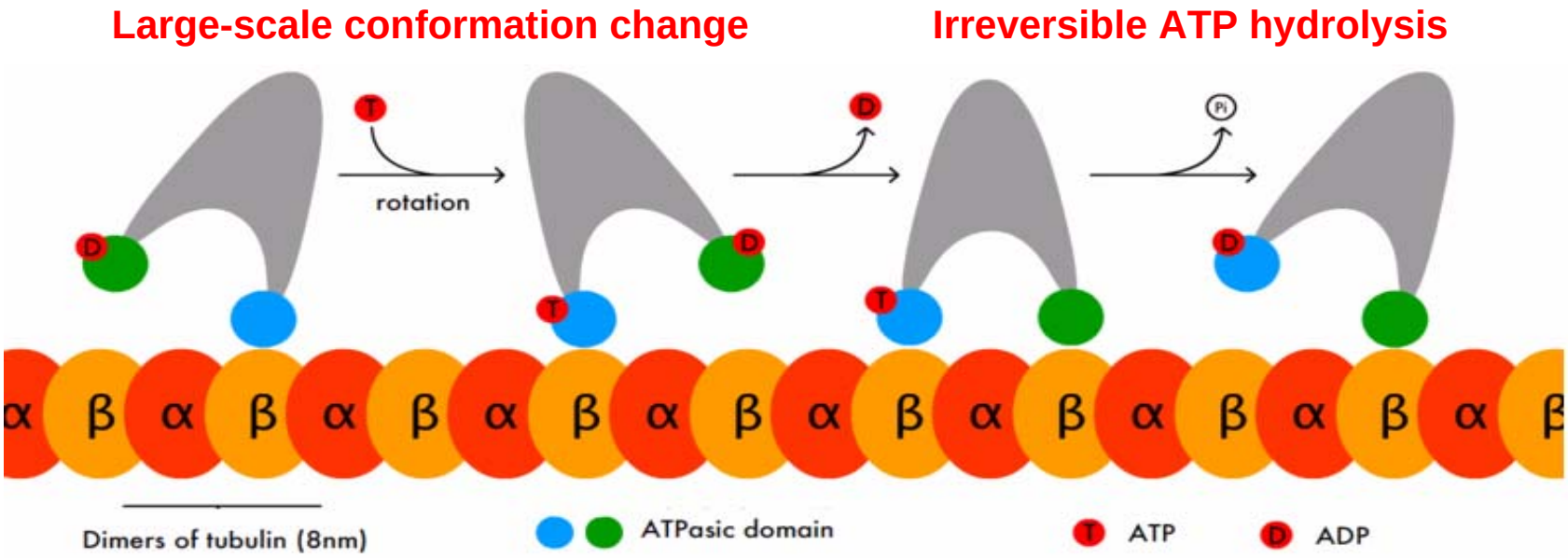
Example I : kinesin (porter)

- A two-head transporter: hand-over-hand walking on the **polarized** microtubule. Unidirected movement to plus-end.
- Two identical subunits (homodimer) with ATPase activity on their head (the gasoline tank!) ATP hydrolysis serves to **bias** the brownian motion.
- Kinesin can do mechanical work against a loading force (<7 pN). The conversion efficiency of chemical energy to mechanical work is very high (~60%).





A cartoon view of the baised motion



Kinesin differs essentially from their macro-counterpart:

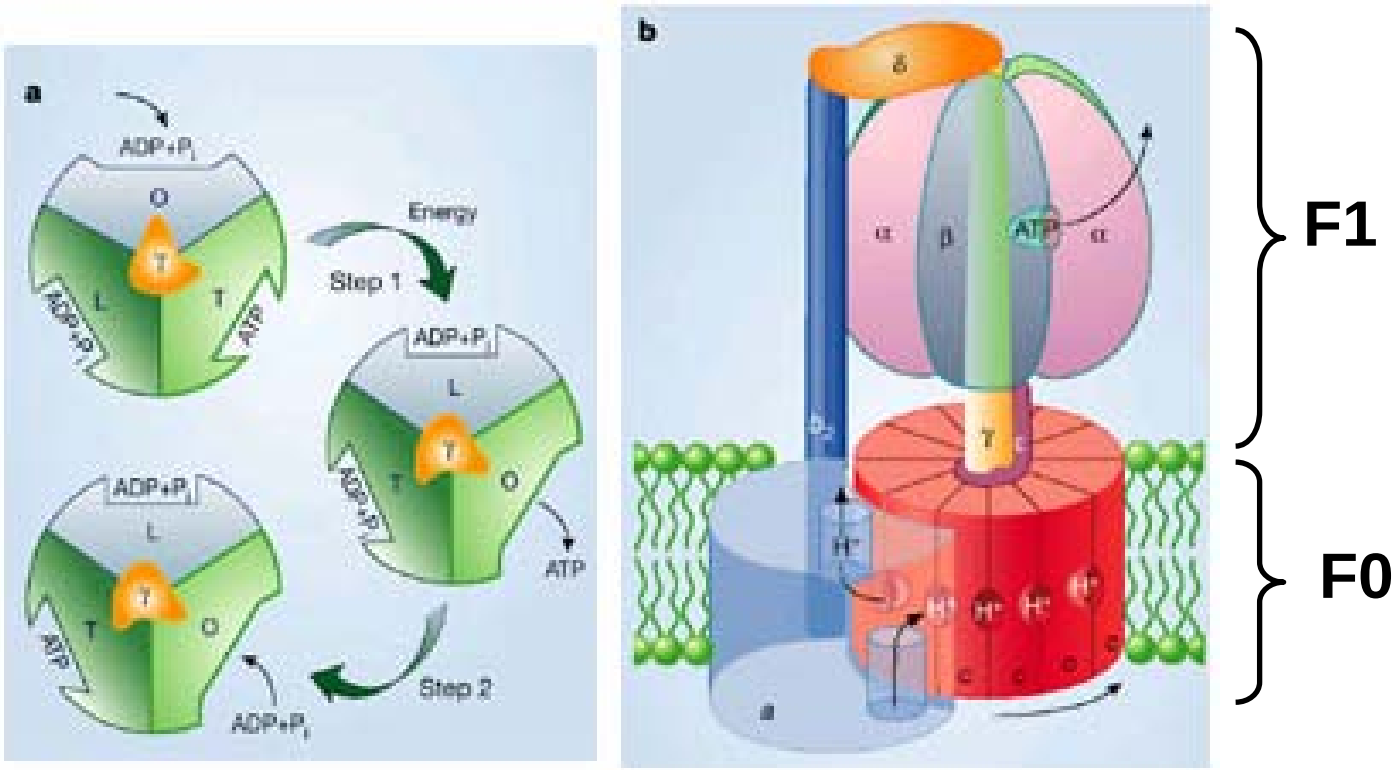
✓ ATP hydrolysis occurs after the motor steps forward.

It's the thermal fluctuation & substrate(ATP,ADP,Pi) binding/releasing that power the conformation changes, while the out-of-equilibrium chemical step (ATP hydrolysis) serves merely to rectify (bias) the brownian motion.

✓ the track (microtubule) is polarized. Or, the environment needs to be anisotropic.

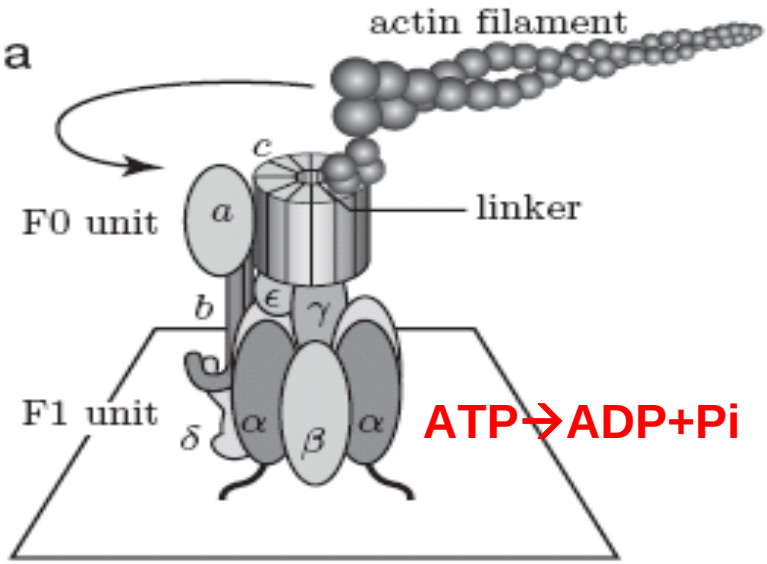
Example II : F0F1-ATP Synthase (rotor)

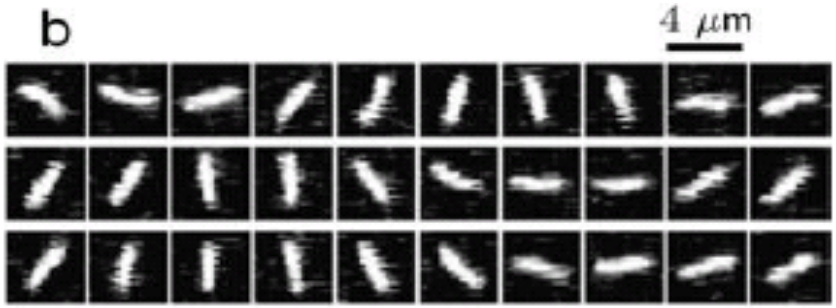
- A delicate machine with a micro-turbine (F0, rotor) and a micro power generator (F1, stator)
- The cation (H+,Na+, etc) flow rotates F0, which then makes F1 synthesize ATP from ADP and Pi.
- The electrochemical energy of the cation is converted into the chemical energy of the covalent bond in ATP.



- F1 also has ATPase activity. When F1 catalyzes ATP hydrolysis, F0 can rotate in the opposite direction and do mechanical work against an external torque.
- The efficiency of energy conversion is pretty high (~ 80%) !

  At stall, the efficiency can approach 100%.



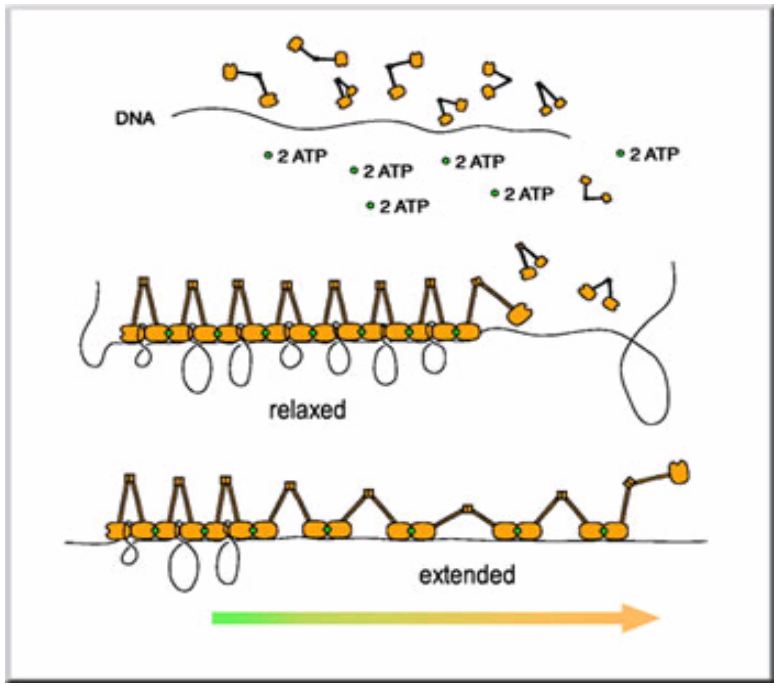


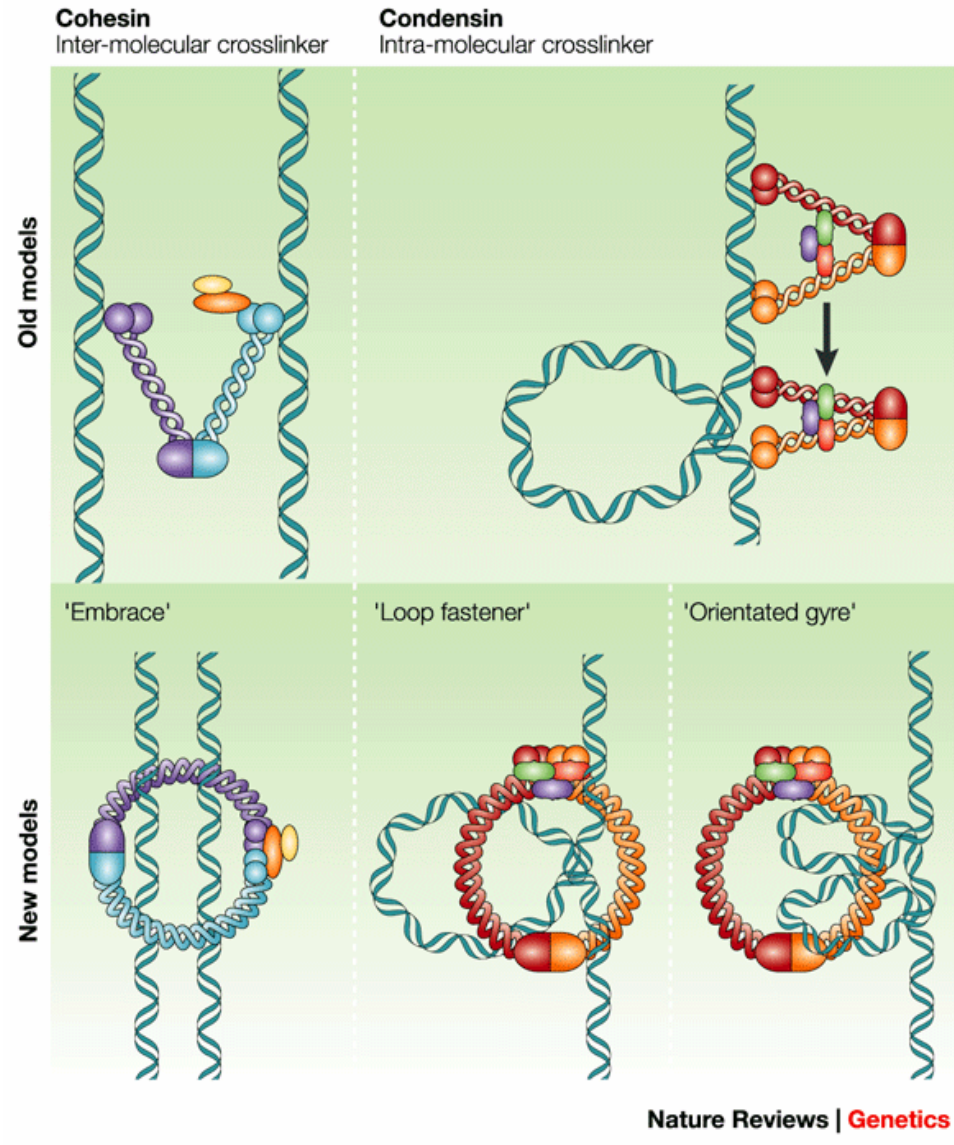
- Actin filament covered with fluorophore;
- as viscous drag;
- as indicator;

Noji,H, R.Yasuda, M.Yoshida, K,Kinosita,Jr, nature, 386:299-302(1997)

Example III: cohesin and condensin (clamp)

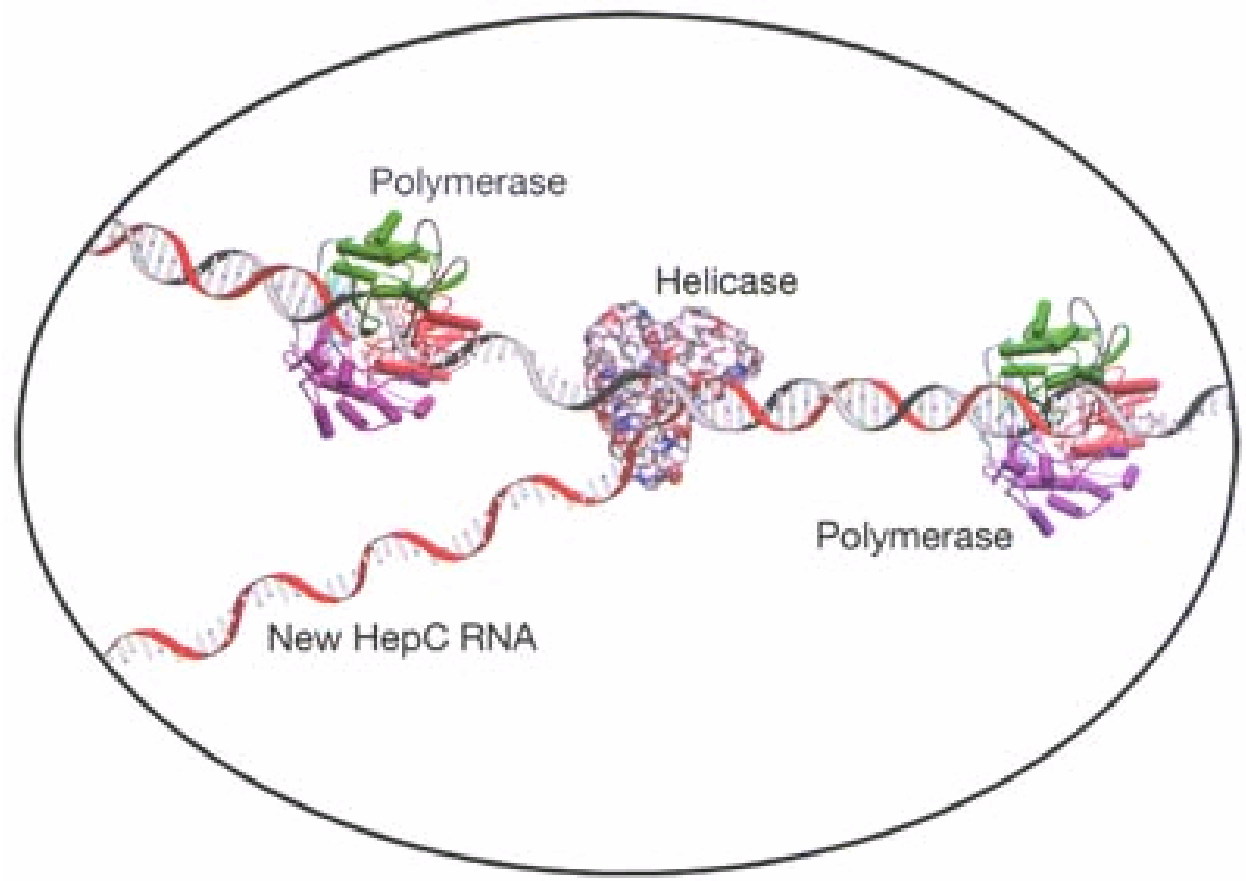
- Cohesin and condensin work in cooperation to condense genomic DNA into chromosome.
- ATP-dependent.





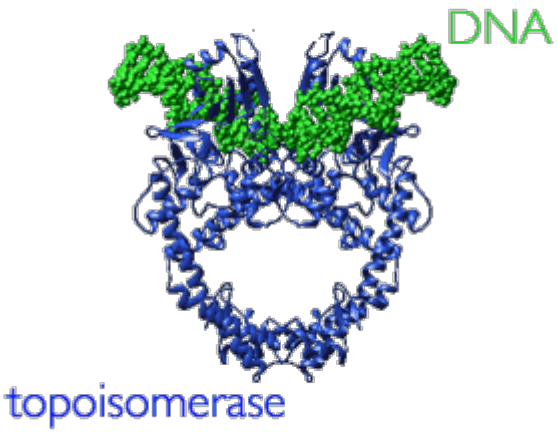
Example IV: DNA helicase (sweeper)

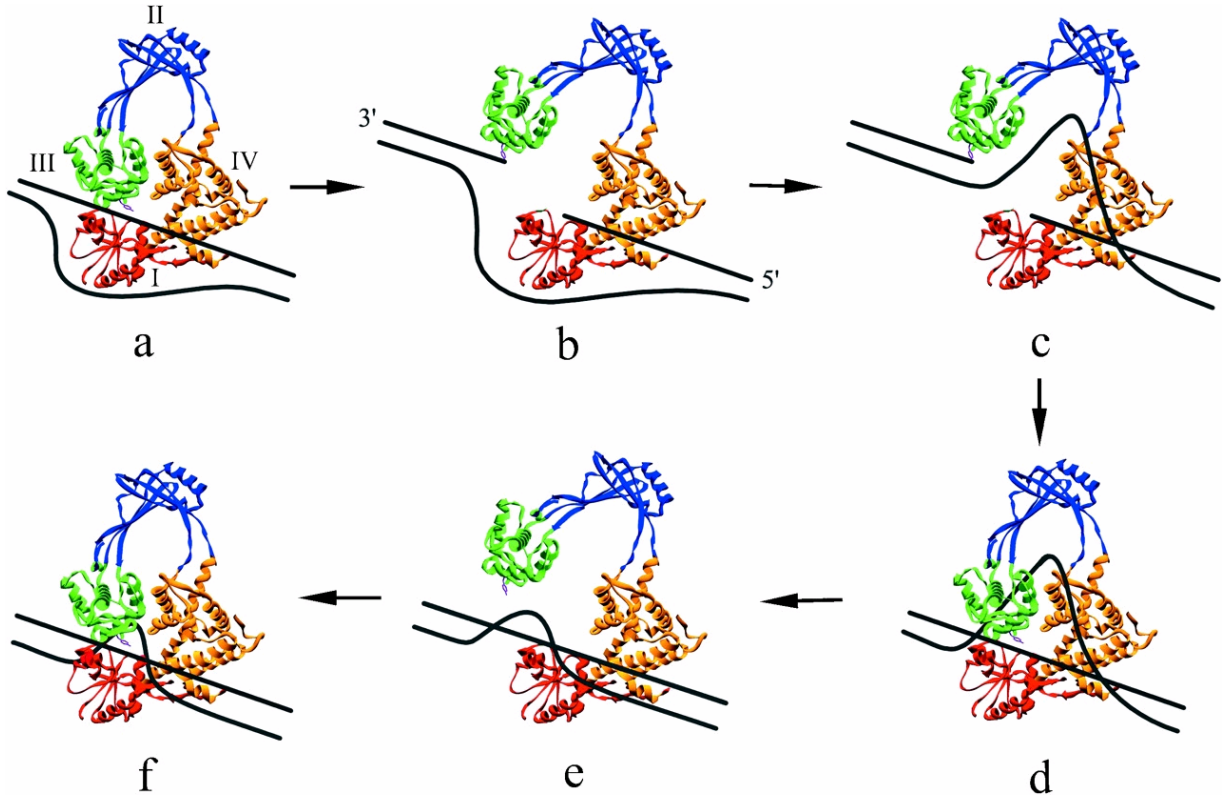
- Unzipping the double-strand DNA, as well as sweeping off proteins bound on single-strand DNA
- ATP hydrolysis-dependent



Example V: topoisomerase II (scissor-and-ligater)

- dsDNA is ready to get knotted or catenated in processes like replication, transcription.
- Topo II can unknot or decatenate DNA by using the energy released from ATP hydrolysis.

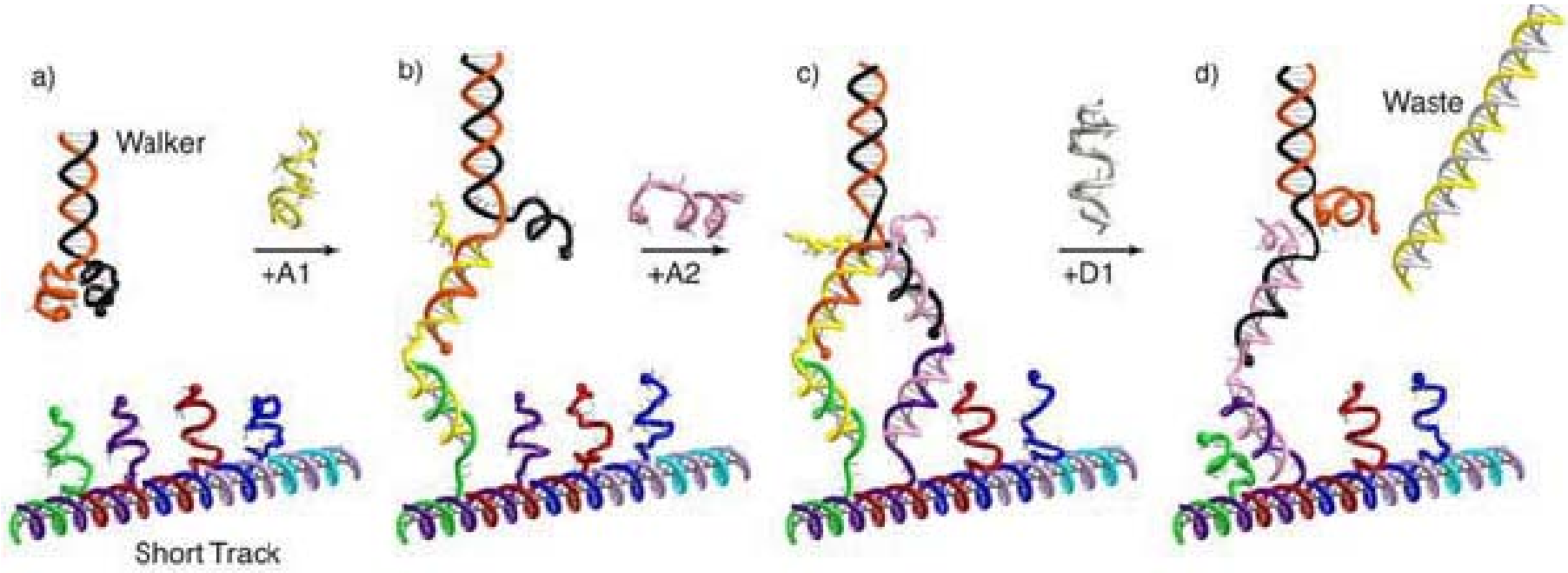




Biomimic nanomachines

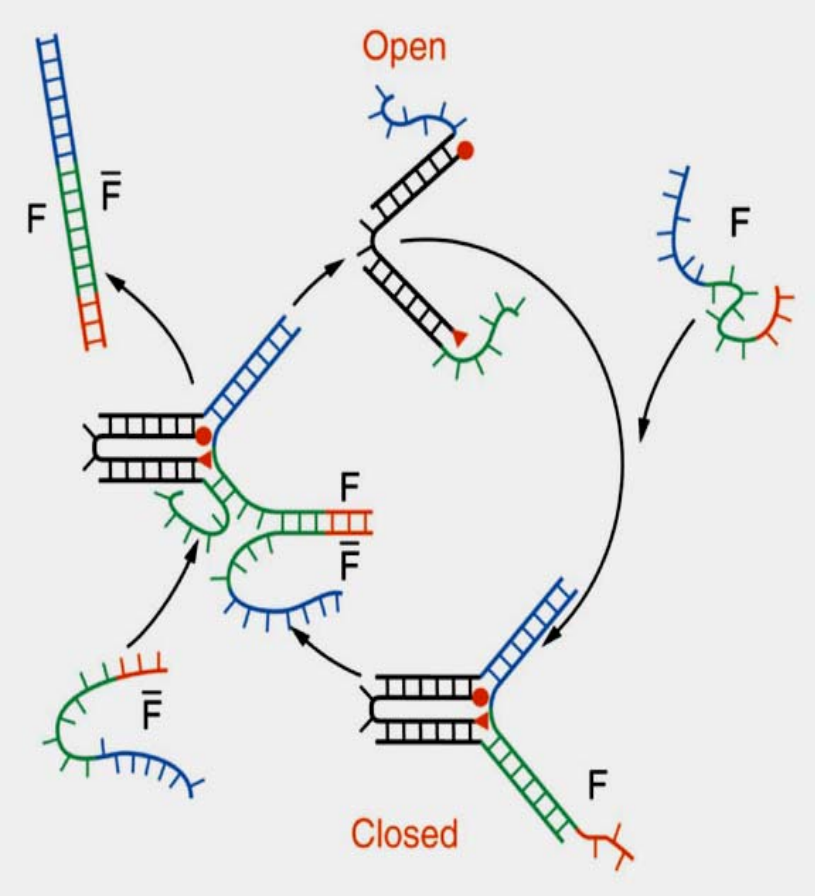
Kinesin-like DNA walker: hand-over-hand

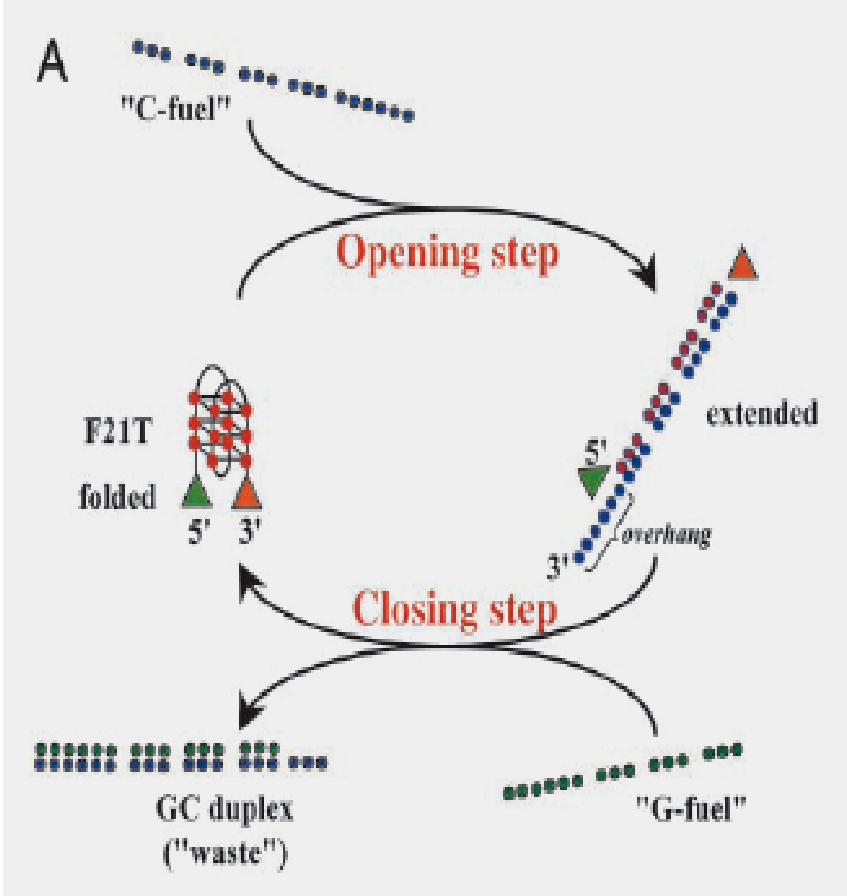
- **DNA is not only the carrier of genetic information. It's also perfect nanomaterial.**
- **It can even be used as fuel.**



***J. Am. Chem. Soc.*, 126 (35), 10834 (2004)**

- **DNA-tweezer**





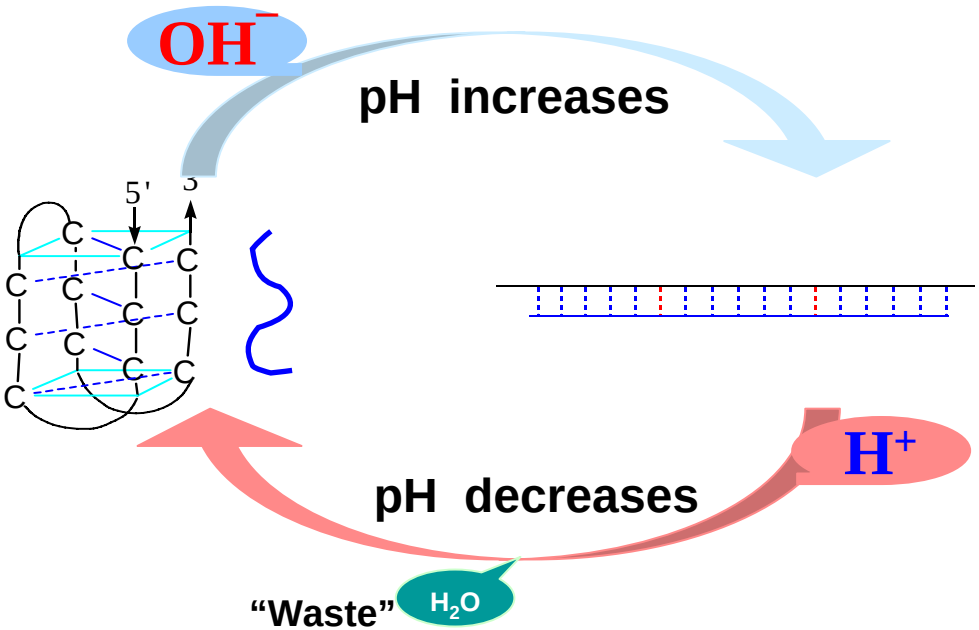
Nature 406, 605 (2000)

PNAS 100,1569 (2003)

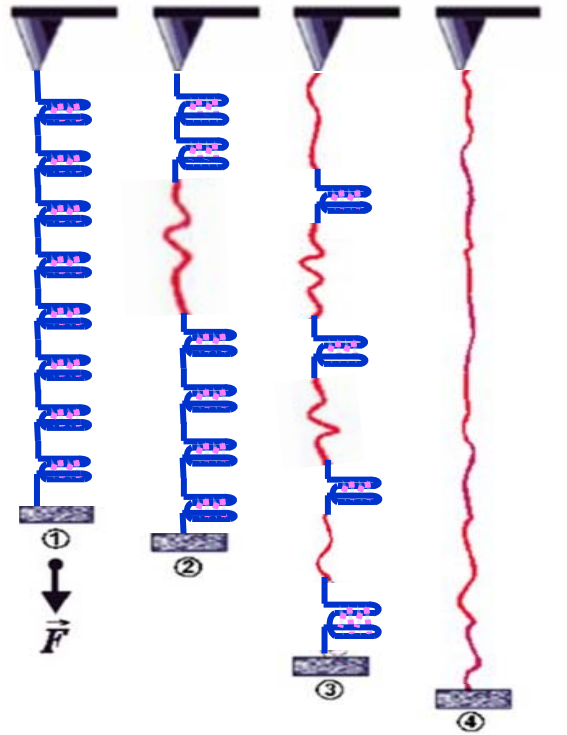
- **DNA actuator (i-motif)**

Other chemical reactions can also provide the energy

$$OH^- + H^+ \rightarrow H_2O$$



AFM cantilever



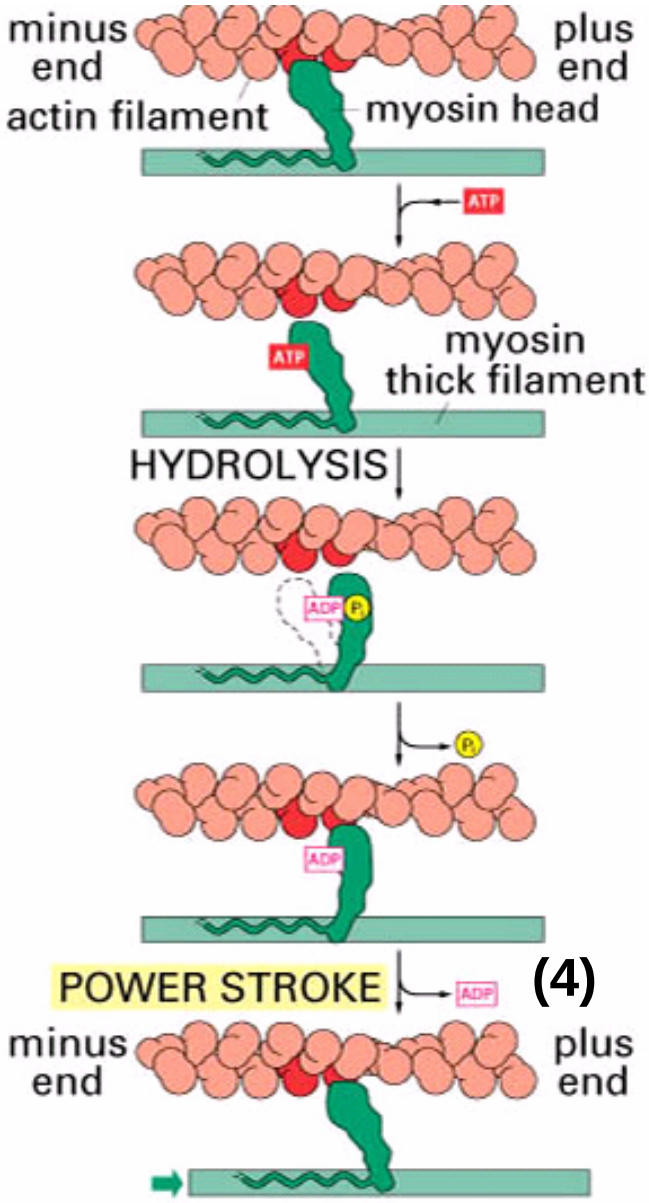
Contractile machinery to mimic muscle

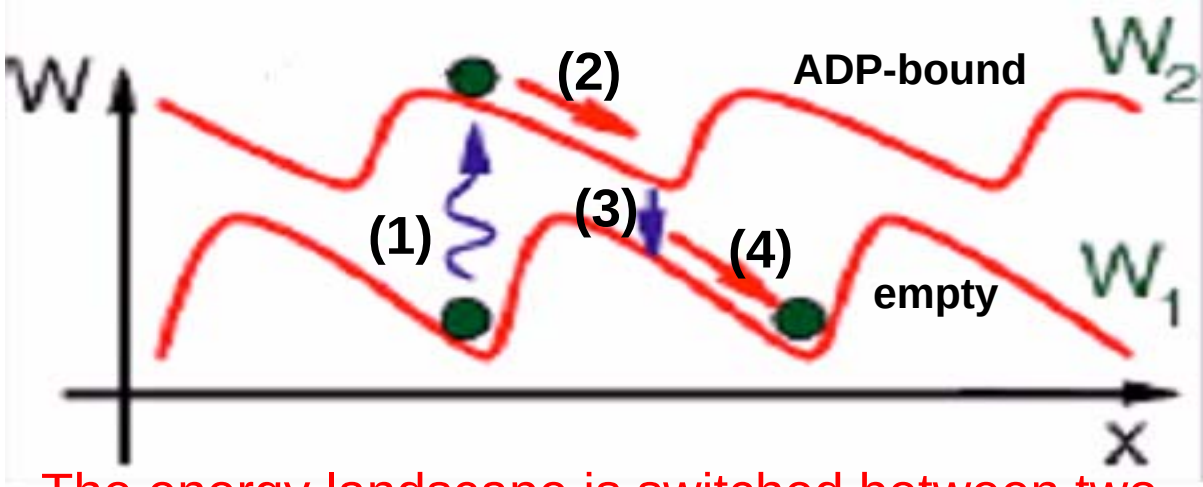
Part II

Conceptual framework of the Working Principle for soft-material nanomachines: Brownian Rachet

How can a rachet get a net motion (translation, rotation, etc) out of thermal fluctuation ?

Brownian Ratchet : Myosin as an example



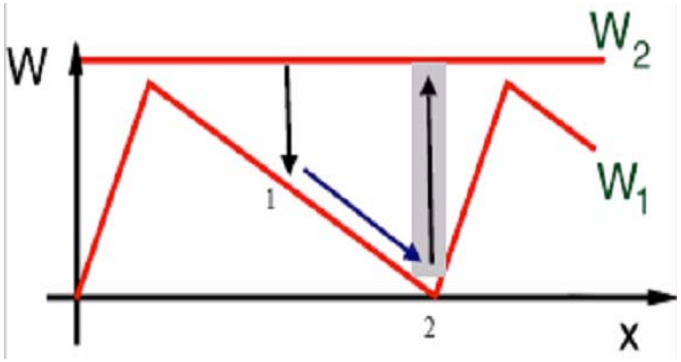


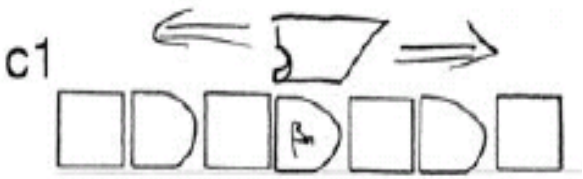
The energy landscape is switched between two states (head empty or ADP-bound) irreversibly and randomly by chemical reactions !

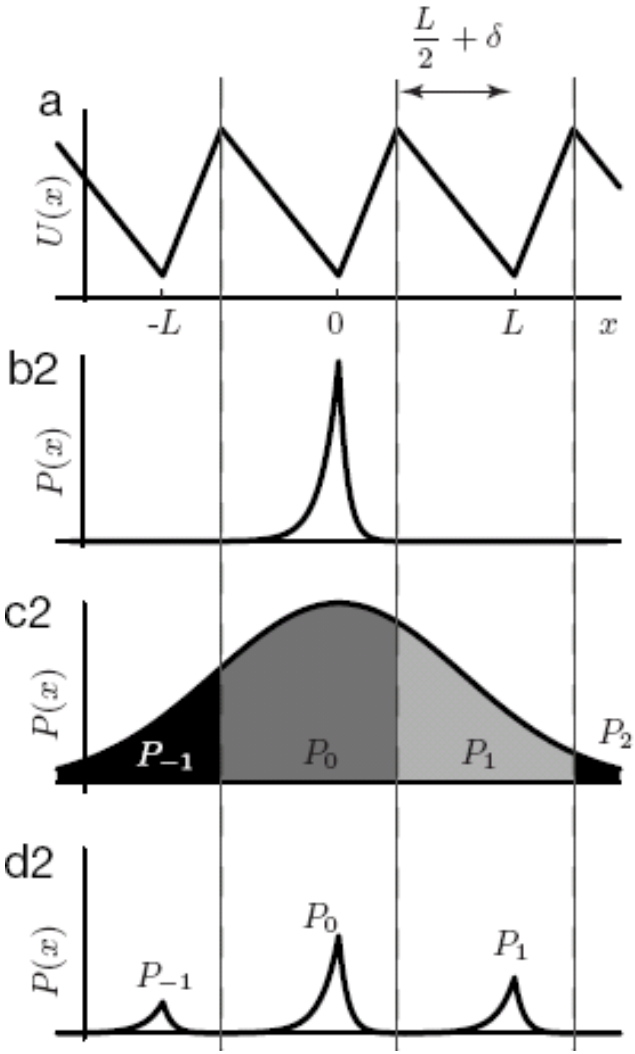
(1) ATP binding to the head. Head detached. ATP hydrolysis. Conformation change. Head displaced.
(2) Pi released. The ADP-bound head rebinding to a new site on actin.
(3) ADP released. myosin stressed
(4) recovery the original conformation. The thin filament sliding to the plus end of the thick filament..

Simpler case: one-head kinesin (KIF1A)

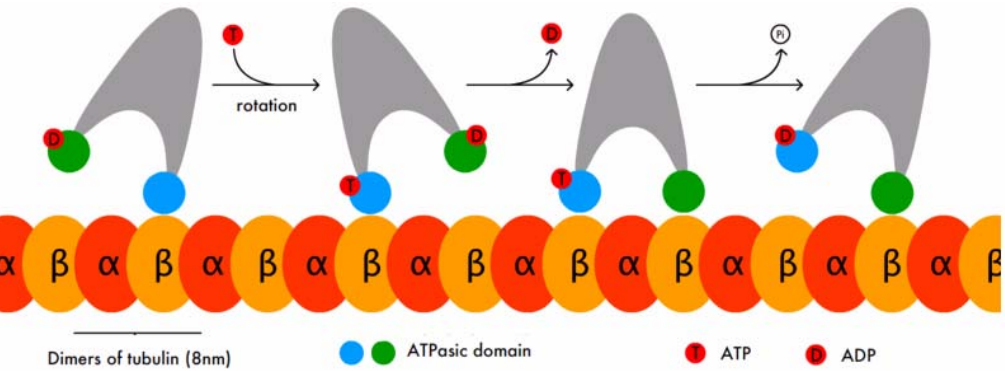
Landscape switching describes the fast steps of the chemical reaction.
These steps are not coupled directly to motor's translation.

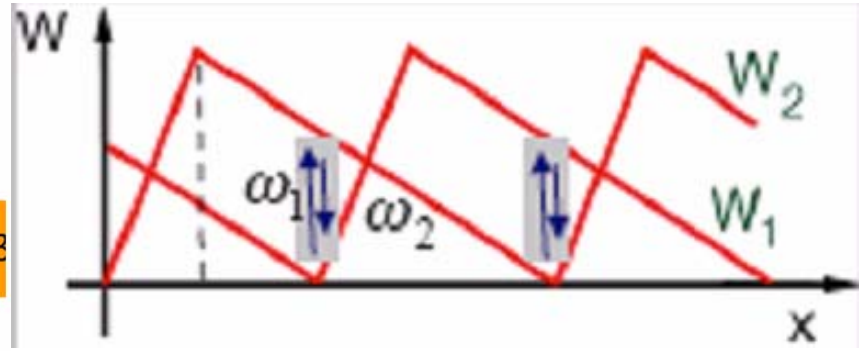




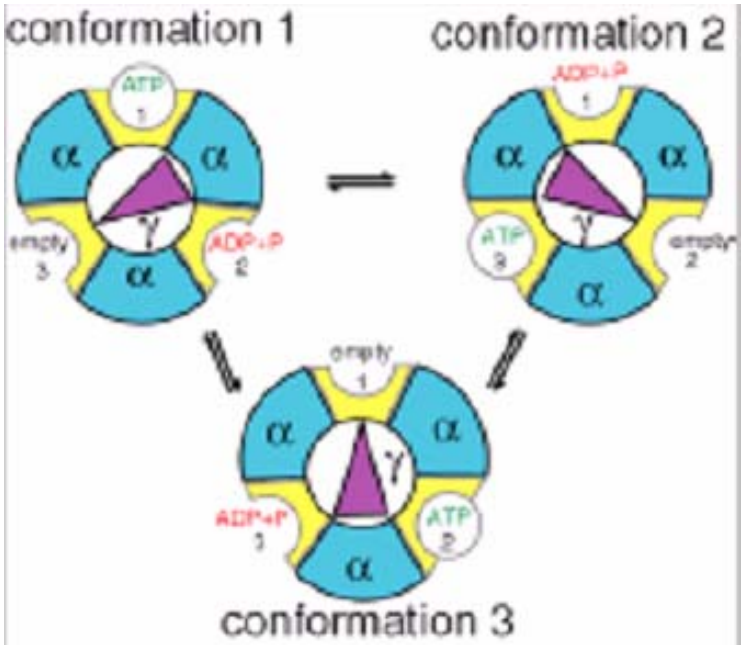


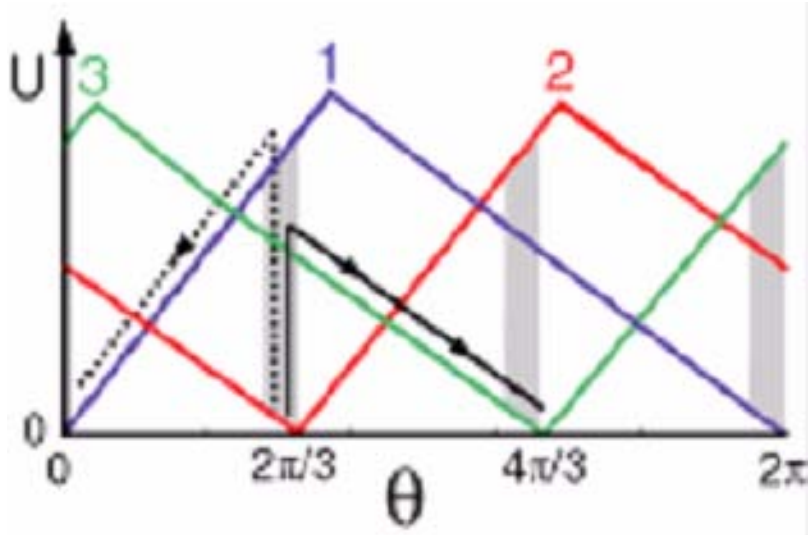
Kinesin: hand-over-hand. bi-state model





F0-F1 ATP synthase: tri-state model



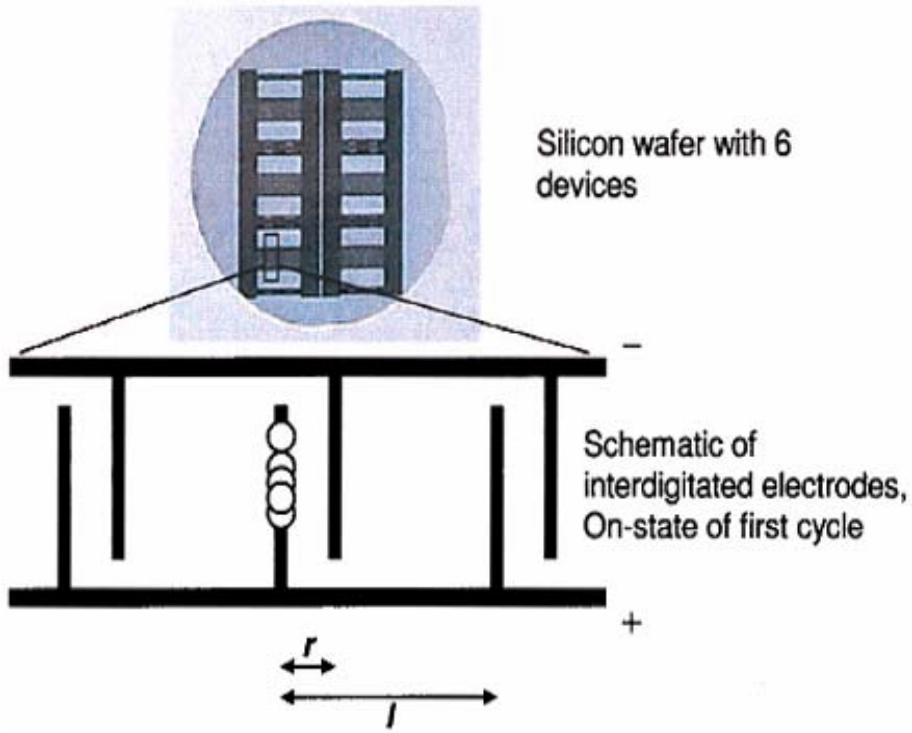


- Brownian ratchet model is only proposed and partially verified for certain biomachines (kinesin, myosin, ATP synthase, etc). But it’s still believed to apply to many other (though not all) biomachines powered by chemical reactions.

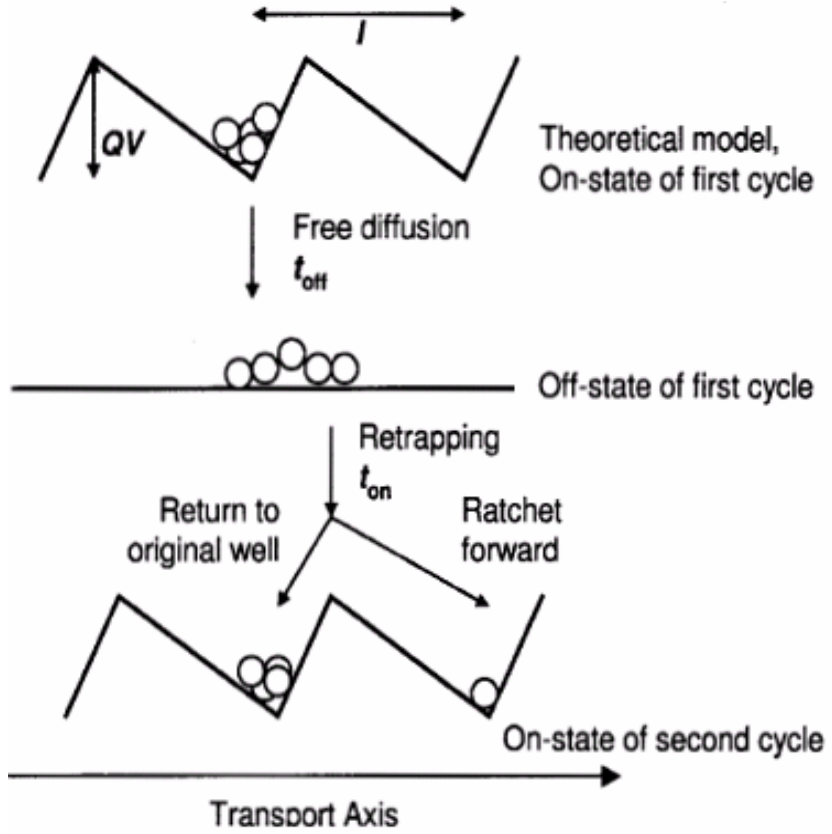
- Brownian ratchet can also serve as an universal principle for nano-manipulation.

Biomachine-inspired nano-engineering: brownian ratchet for DNA segregation

- landscape can also be switched manually in a deterministic way.
- landscape switching can be powered by means other than chemical reactions.



Micro-array of electrodes



Part III

thermodynamics of nanomachines:

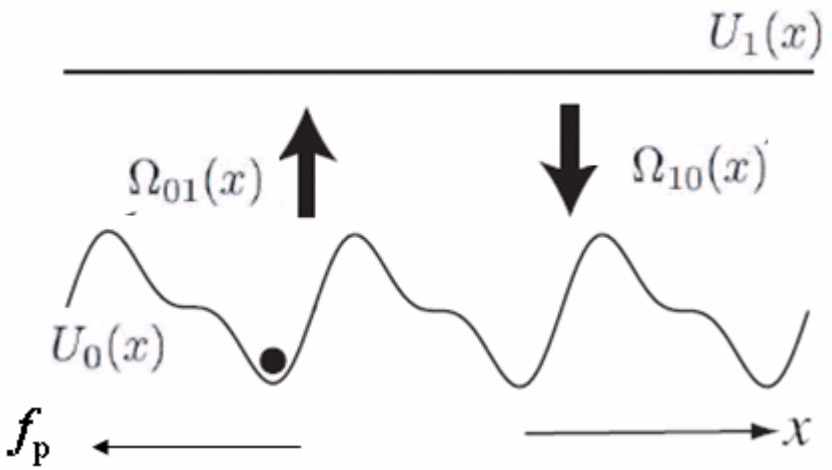
A theory still not well-established;

Some preliminary results presented

Why thermodynamics (or energetics)?

- Any machine (either macro- or micro) uptakes and dissipates energy when it performs its tasks.
- Energetics is the key information for optimal control or optimal design of a machine.
- Natural biomachines can achieve a high efficiency of energy conversion. This is a special interest for physicists and engineers.

I . Fokker-Planck Equations for mechano-chemical coupling of biomachines



Asymmetric and periodic energy landscapes;
Switched randomly by chemical reations.

$$\frac{\partial}{\partial t}\begin{pmatrix} P_0(x,t) \\ P_1(x,t) \end{pmatrix} = \begin{pmatrix} \mathcal{L}_0(t) - \Omega_{01}(x) & \Omega_{10}(x) \\ \Omega_{01}(x) & \mathcal{L}_1(t) - \Omega_{10}(x) \end{pmatrix} \begin{pmatrix} P_0(x,t) \\ P_1(x,t) \end{pmatrix}$$

$$\mathcal{L}_\sigma(t) \equiv \frac{1}{\gamma}\frac{\partial}{\partial x}\left[U'_\sigma(x) - \varepsilon f_{\rm p}(t) + k_{\rm B}T\frac{\partial}{\partial x}\right]$$

In equilirium, the spontaneous switching rates between the two states follows the principle of detailed balance, and the particle undergoes pure thermal motion and there can be no net movement.

$$\frac{\Omega_{10}(x)}{\Omega_{01}(x)} = \exp\left\{\left[U_1(x) - U_0(x)\right]/k_B T\right\}$$

To biased the thermal motion, the detailed balance should be broken (irreversibility comes in). Coupling to a chemical reaction can achieve this goal.

$$\frac{\Omega_{10}(x)}{\Omega_{01}(x)} = \exp\left\{\left[U_1(x) - U_0(x) + \Delta\mu\right]/k_B T\right\}$$

$\Delta\mu$: free energy released from the chemical reaction

Necessary and sufficient condition for a brownian ratchet to get a net motion:

- Asymmetric and periodic energy landscapes.
- An out-of-equilibrium process coupled to break the detailed balance.

Key features:

- chemical steps do not push the movement directly, i.e., only serve to rectify the thermal motion.
- the more intermediate states (i.e., more energy landscape), the slower the net motion, and the higher the energy conversion efficiency.

The chemical energy is fed into the nanomachine in a way essentially different from that in its macro-couterpart.

It’s difficult to carry out an energetics analysis for a mechano-chemical nanomachine, because the energy landscape is randomly switched back-and-forth.

Cases in which the energy landscape is deterministically switched are much easier to be analyzed. And Rigorous results can be obtained.

II. Fokker-Planck Equation for cases of deterministic landscape switching

$$\frac{\partial P(x,t)}{\partial t} = \frac{1}{\xi}\frac{\partial}{\partial x}\left(\frac{\partial U\left(\lambda(t)\right)}{\partial x}P + K_B T\frac{\partial P(x,t)}{\partial x}\right)$$

$\lambda(t)$: externally-controlled protocol

$$\text{internal energy}: \; E_{sys}(t) = \int P(x,t)U\left(\lambda(t),x\right)dx$$

First law of thermodynamics (energy conservation):

$$\mathrm{d}E_{sys} = \mathrm{d}Q_{exch} + \mathrm{d}W_{input}$$

Heat: energy exchanged with environment

???

Work: done on the system externally

$$dE_{sys} = \left[\int_x \frac{\partial P(x,t)}{\partial t}U(\lambda,x)dx\right]dt + \left[\int_x P(x,t)\frac{\partial U(\lambda,x)}{\partial \lambda}dx\right]d\lambda$$

- In manipulations on micro-systems with large thermal fluctuation, it's hard to distinguish between heat and work.
- Definitions of heat and work above seems reasonable because one can prove a second-law-like equality for such driven systems.

For a given protocol $(\lambda_i, t_i) = (\lambda_0, t_0) \to (\lambda_1, t_1) \ldots \to (\lambda_k, t_k) \to (\lambda_n, t_n) = (\lambda_f, t_f)$

$[t_i, t_f]$ is the given time interval in which λ varies from λ_i to λ_f

the 'work' done on the system and the 'heat' exchanged with environment are both trajectory - dependent.

For a stochastic trajectory $\Gamma = (x_0, t_0) \to (x_1, t_1) \ldots \to (x_k, t_k) \to (x_n, t_n)$,

work : $W_{input}(\Gamma) \equiv \sum_{k=1}^{n} \left[U(\lambda_k, x_k) - U(\lambda_{k-1}, x_k) \right]$

heat : $Q_{exch}(\Gamma) \equiv \sum_{k=0}^{n-1} \left[U(\lambda_k, x_{k+1}) - U(\lambda_k, x_k) \right]$

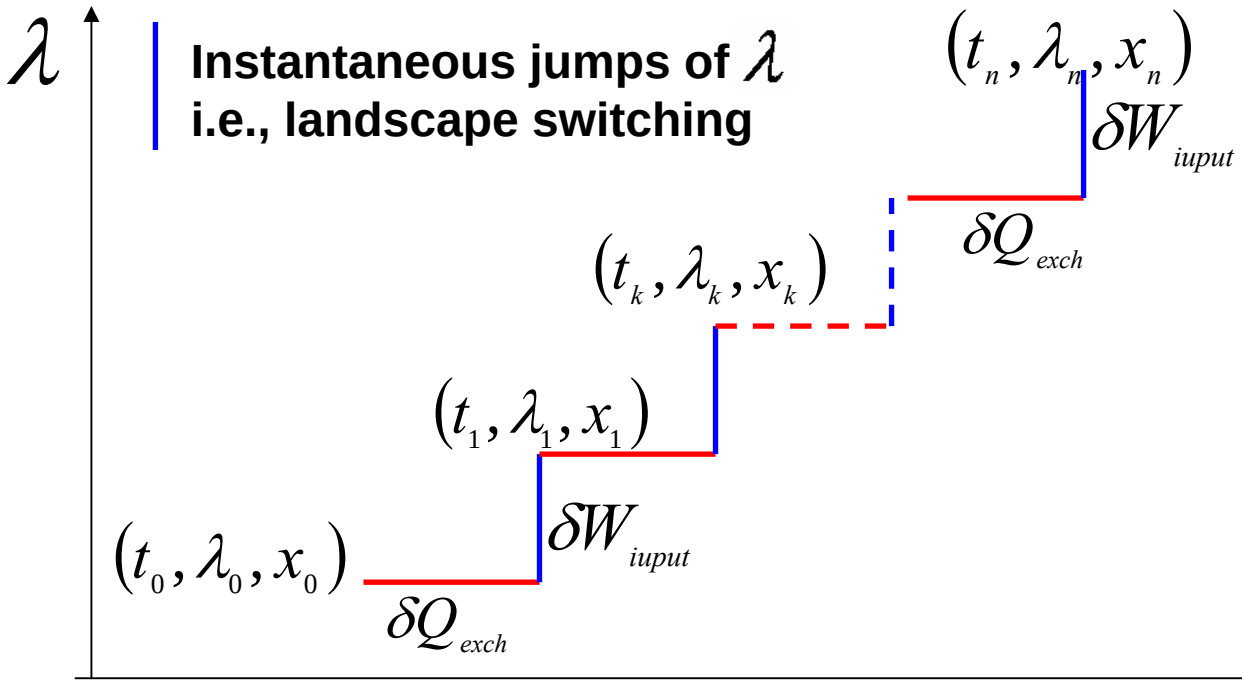
energy change : $\Delta U(\Gamma) \equiv W_{input}(\Gamma) + Q_{exch}(\Gamma) = U(\lambda_f, x_f) - U(\lambda_0, x_0)$

Second law of thermodynamics of small systems:

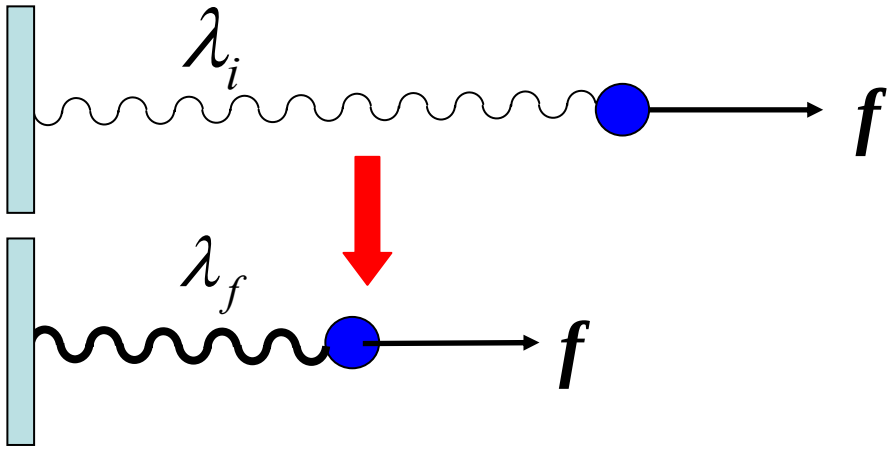
$$\left\langle \exp\left(-W_{input}/k_BT\right)\right\rangle_{\Gamma} = \exp\left(-\Delta F/k_BT\right)$$ Jarzynski equality

ΔF : equilibrium free energy difference between the intial and final states

$$\left\langle \exp\left(-x\right)\right\rangle_{\Gamma} \geq \exp\left(-\left\langle x\right\rangle_{\Gamma}\right) \Rightarrow \boxed{\left\langle W_{input}\right\rangle_{\Gamma} \geq \Delta F}$$



III, optimal control problems:
A toy model of actuator as an example



$$U = \frac{1}{2}\lambda x^2 - fx$$

$$\lambda_i \rightarrow \lambda_f$$

$$\delta = \int x^2 P(x,t)\,dx$$

$$\mu = \int x P(x,t)\,dx$$

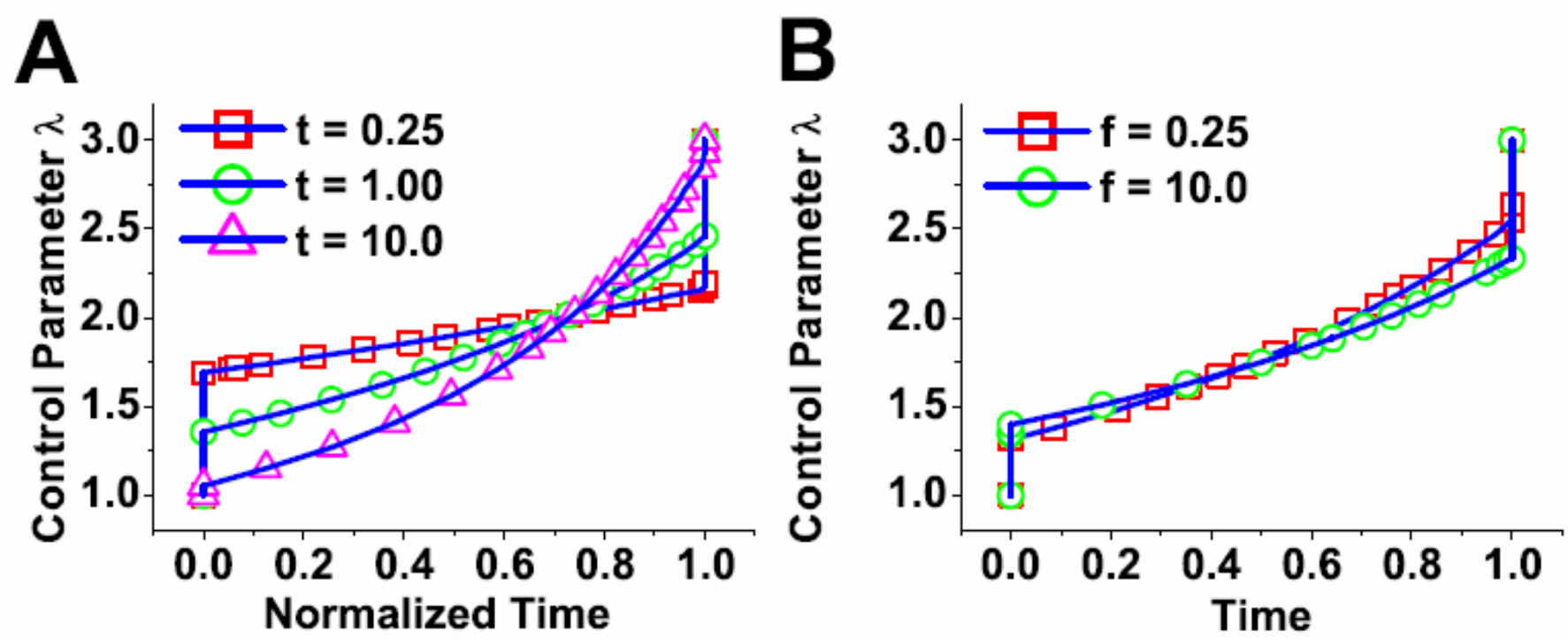
$$\dot{\delta} = 2 - 2\lambda\delta + 2f\mu$$

$$\dot{\mu} = f - \lambda\mu$$

Minimal input work problem:

1, What is the optimal protocol which minimizes the input work?

$$W_{input} = \int \left(\int P(x,t) \left(\frac{\partial U(\lambda,x)}{\partial \lambda} \right) dx \right) d\lambda = \int_{t_i}^{t_f} \frac{1}{2} \dot{\lambda} \delta \, dt$$

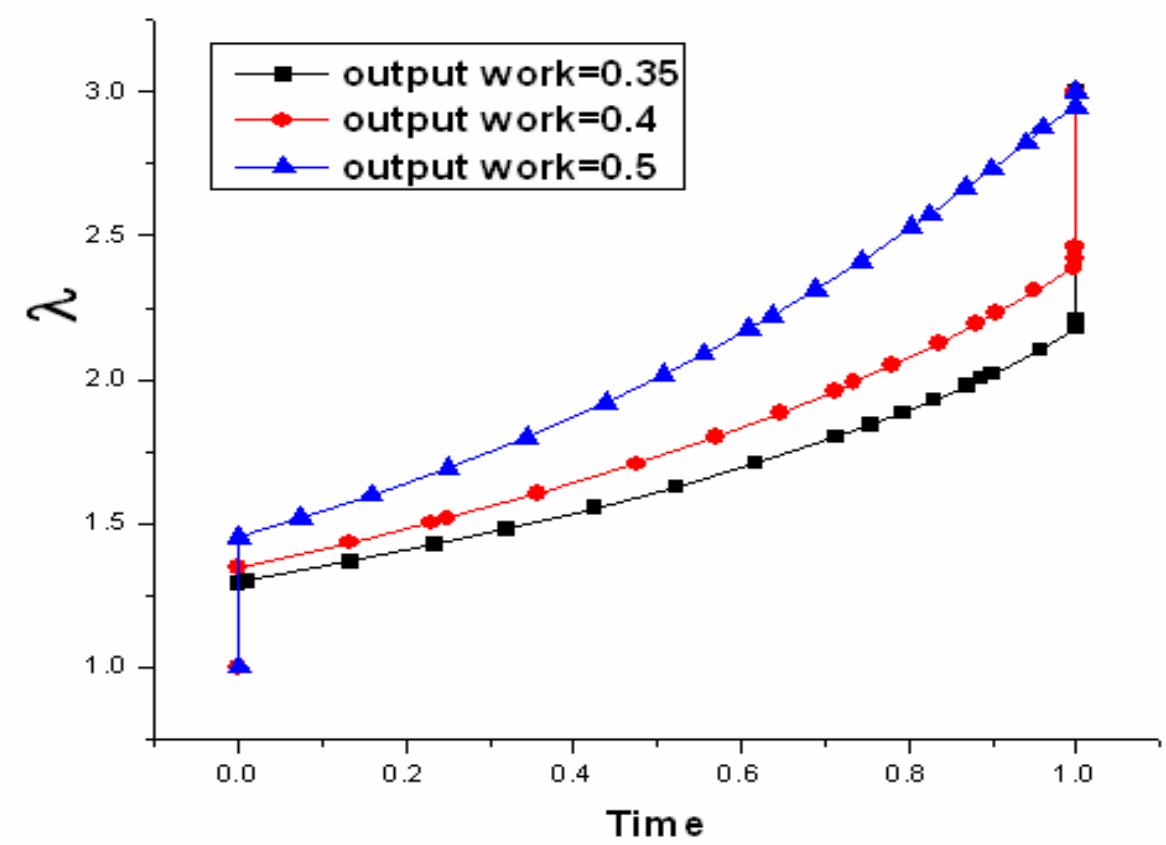


LC Gong, M Li, unpublished results

More constraints:

2, for rated output work, What is the optimal protocol which minimizes the input work?

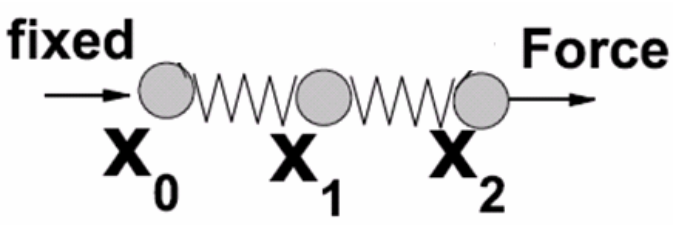
$$W_{output} = -f\left\langle \int_{t_i}^{t_f} \dot{\mu} dt \right\rangle = \left\langle f(\mu_i - \mu_f) \right\rangle = f\left\langle \mu \right\rangle_{\lambda_f} - f\left\langle \mu \right\rangle_{\lambda_f}$$



IV, optimal design problem

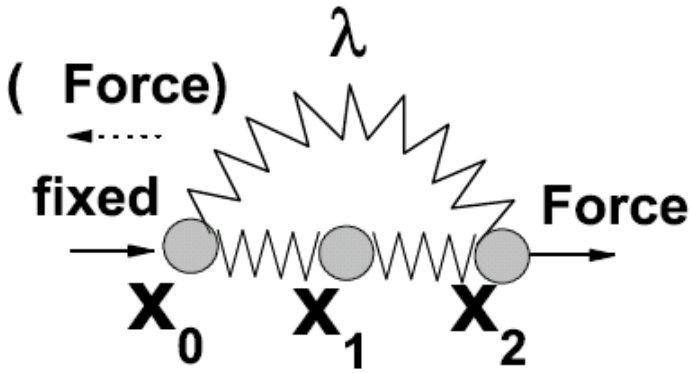
- More degrees of freedom:

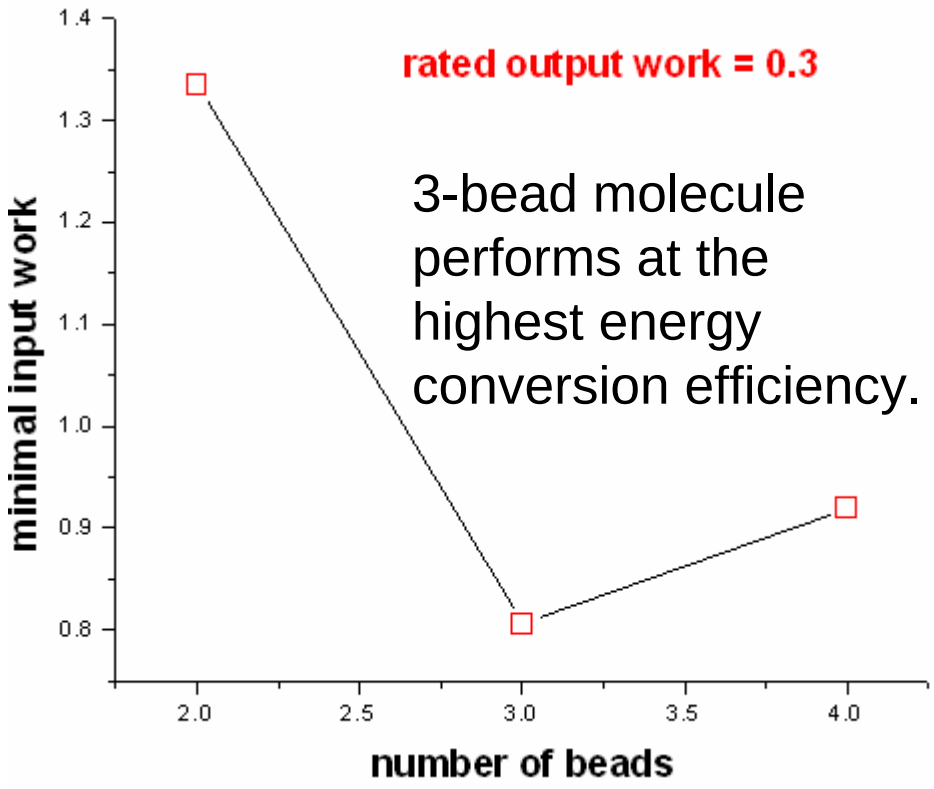
  Do structured molecules (with long-distance intramolecular interaction) perform better than simple polymers?



Simple polymers (with N beads) behave in exactly the same way as one-bead actuator

Structured molecule: interaction between two ending beads be externally-controlled





3-bead molecule performs at the highest energy conversion efficiency.

Further problems for machine design

- Are natural biomachines are optimized for their functions?

- If yes, what are the optimization function?

  in view of energetics: minimal input work, maximal output work, maximal entropy production(MEP),…

  or other physical / non-physical purposes ?

- how the structure and kinetics of the machine are evolved for the optimization?

Thanks for your attention!