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Molecular motors operating in a highly dissipative, noisy and subdiffusive interior of living cells:

How a highly efficient operation is possible?

Lessons from the fluctuation-dissipation theorem

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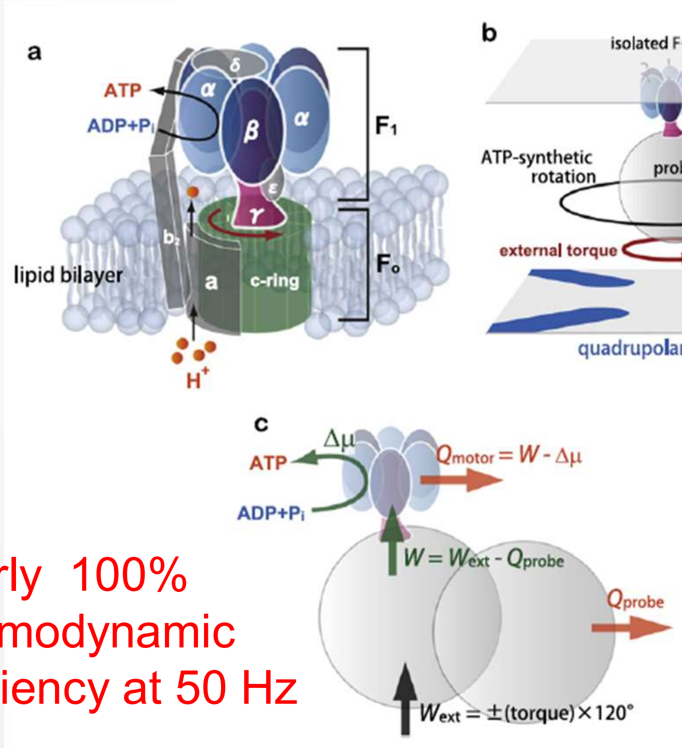
Review: Beilstein J. Nanotechnol. **7**, 328–350 (2016)

Motivation

Natural nanomachines

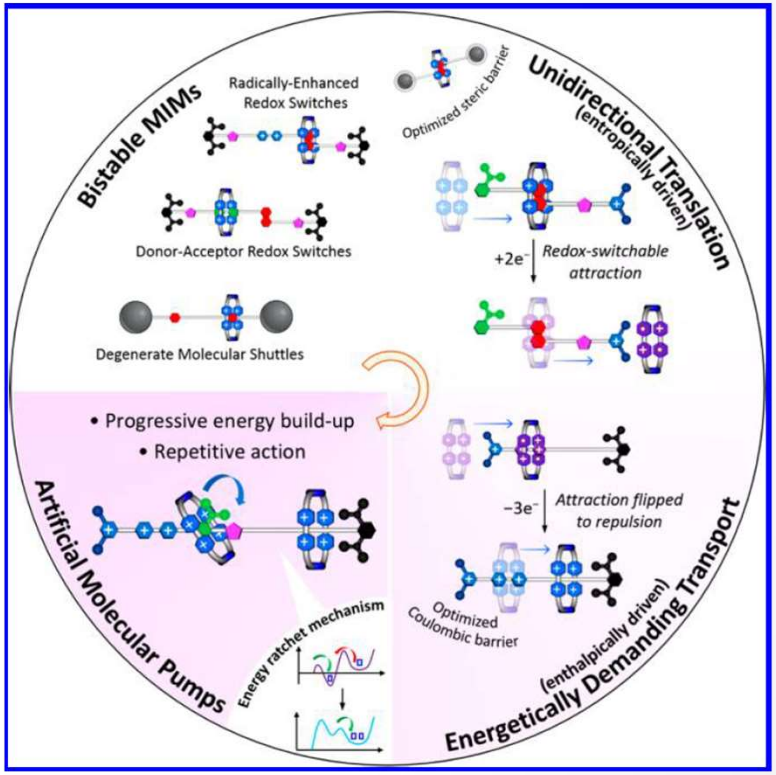
F_oF_1-ATP synthase



nearly 100% thermodynamic efficiency at 50 Hz

From: Toyabe, Mineyuki, *New J. Phys.* **17** , 015008 (2015)

Artificial nanomachines



From: Cheng, McGonigal, **Stoddart** Astumian, *ACS Nano* **9** , 8672 (2015)

Significance?

The Nobel Prize in Chemistry 2016
Jean-Pierre Sauvage, Sir J. Fraser Stoddart, Bernard L. Feringa

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The Nobel Prize in Chemistry 2016

Photo: A. Mahmoud
Jean-Pierre Sauvage
Prize share: 1/3

Photo: A. Mahmoud
Sir J. Fraser Stoddart
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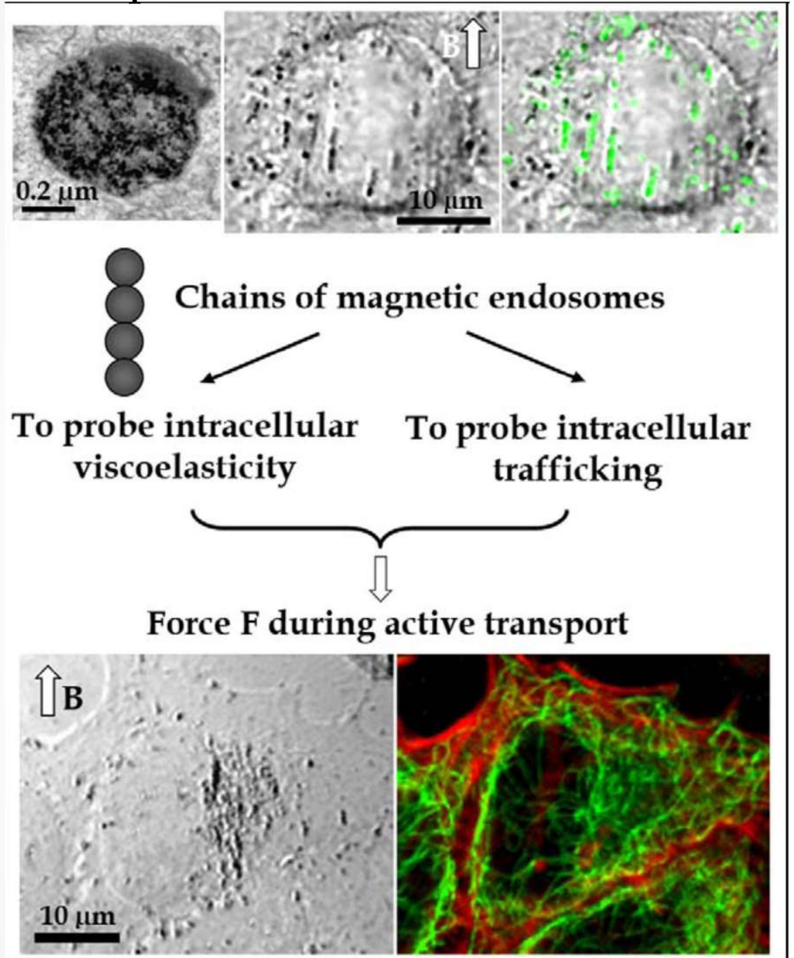
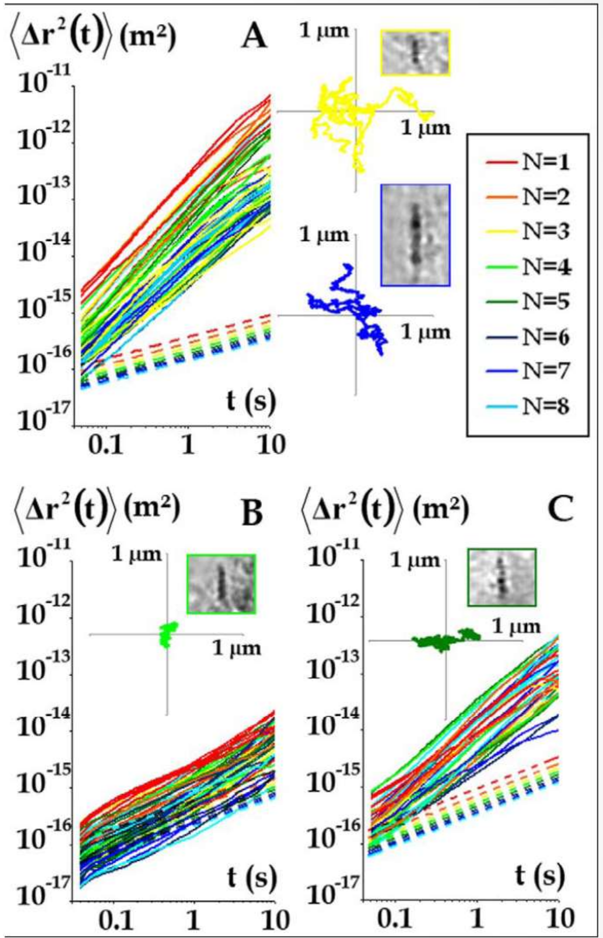
Photo: A. Mahmoud
Bernard L. Feringa
Prize share: 1/3

The Nobel Prize in Chemistry 2016 was awarded jointly to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa *"for the design and synthesis of molecular machines"*.

Occurrence of subdiffusion in living cells

Example from: Robert *et al.*, *PLoS ONE* **5**, e10046 (2010)





Passive subdiffusion $\langle \delta r^2(t) \rangle \propto t^\alpha$ with $\alpha \approx 0.4$ (intact cytoskeleton)
$\alpha \approx 0.49$ (actin filaments only),
$\alpha \approx 0.56$ (microtubuli only)
Active superdiffusion: $\alpha \to \beta \approx 1.2 - 1.3$

Major theory questions

Isothermal engines operating cyclically in highly dissipative environments. Need a free energy source. Do something useful (e.g. pump ions against electrochemical gradients or do mechanical work)

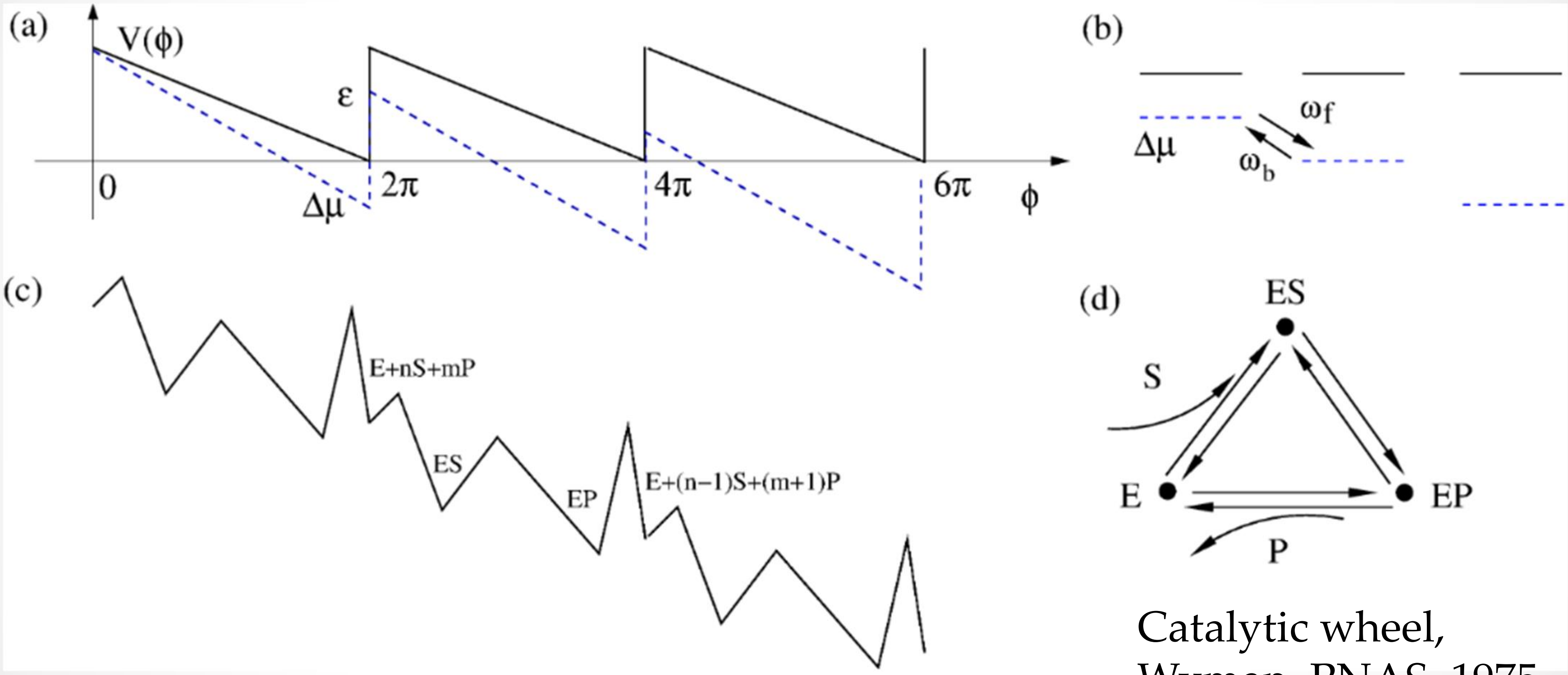
Terrell L. Hill, Free energy transduction and biochemical cycle kinetics, 1989

Stochastic thermodynamics

- Can they operate at nearly 100% thermodynamic efficiency?
- Can efficiency at maximum power exceed 50%?
- Do we need to minimize friction? Or how can molecular machines operate highly efficiently in viscoelastic cytosol?

Defeating some common fallacies…

Simplest model



Catalytic wheel,
Wyman, PNAS, 1975

Cyclic operation → periodic potential $V(\phi+2\pi)=V(\phi),\ f(\phi)=-\partial V(\phi)/\partial\phi$

Input energy → free energy bias $U(\phi)=V(\phi)-F\phi+f_L\phi$

$$\Delta\mu=-2\pi F$$

friction — periodic force — thermal noise (“stochastic lubricant”) provides energy to overcome barriers

$$\eta\dot{\phi} = f(\phi) + F - f_L + \xi(t)$$

driving force — load

fluctuation-dissipation relation

$$\langle \xi(t')\xi(t)\rangle = 2k_B T\eta\delta(|t-t'|)$$

stochastic dissipative force $F_d(t) = \eta\dot{\phi} - \xi(t)$

Net heat exchange = frictional loss - thermal noise gain

$$Q(t) = \int_0^t \langle F_d(t')\dot{\phi}(t')\rangle dt'$$

Fluctuation-dissipation theorem: at thermal equilibrium

$$\overline{Q} = \lim_{t\to\infty}\frac{1}{t}\int_0^t Q(t')dt = 0$$

Input energy $E_{\text{in}}(t) = F\int_0^t \langle\dot{\phi}(t')\rangle dt' = F\langle\phi(t) - \phi(0)\rangle$

Useful work $W(t) = f_L\int_0^t \langle\dot{\phi}(t')\rangle dt' = f_L\langle\phi(t) - \phi(0)\rangle$

Energy balance $Q(t) + W(t) = E_{\text{in}}(t)$ $t \to \infty$

Thermodynamic efficiency

$$R = \lim_{t\to\infty}\frac{W(t)}{E_{in}(t)} = \frac{f_L}{F}$$

can be nearly 100% for arbitrary strong friction

Efficiency at maximum power

trivial example: $f(\phi) = 0 \Longrightarrow \omega = \langle \dot{\phi} \rangle = (F - f_L)/\eta \rightarrow 0$, when $R \rightarrow 1$

100% efficiency at zero power (infinitesimally slow)

Efficiency at maximum power?

$$P_W = f_L \langle \dot{\phi}(t) \rangle = f_L (F - f_L)/\eta$$

P_W is maximal at $f_L = F/2$ and $R = 0.5$

Long-living fallacy:
efficiency at maximum power cannot exceed 50%
generally…

Nonlinear stochastic dynamics

$$\omega(\Delta\mu, f_L) = \omega_f(\Delta\mu, f_L)\left[1 - \exp\left(\beta(\Delta\mu + 2\pi f_L)\right)\right]$$
$$\equiv \omega_f(\Delta\mu, f_L) - \omega_b(\Delta\mu, f_L)$$

$$\Delta\mu = -2\pi F < 0$$

$$\beta = 1/(k_B T)$$

R.L. Stratonovich, *Radiotekh. Elektron.* **3**, 497 (1958, in a very different context)

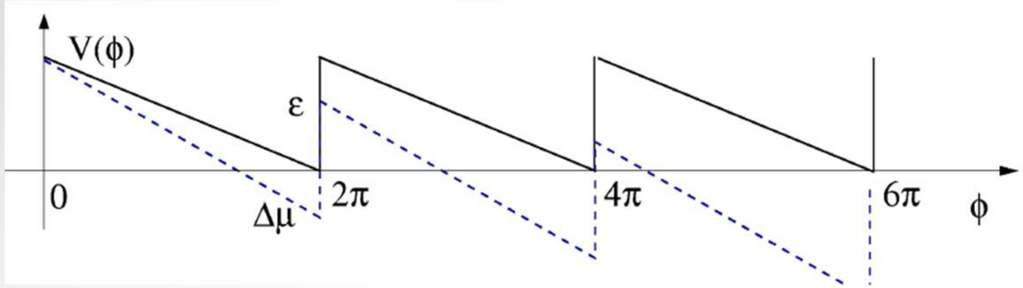
$$D = k_B T/\eta$$

$$\omega_f(\Delta\mu, f_L) = \frac{2\pi D}{\int_0^{2\pi} d\phi \int_\phi^{\phi+2\pi} e^{-\beta\left[U(\phi) - U(\phi')\right]} d\phi'}$$

$$P_W(f_L) = f_L \omega_f(\Delta\mu, f_L)[1 - \exp(\beta(\Delta\mu + 2\pi f_L))]$$

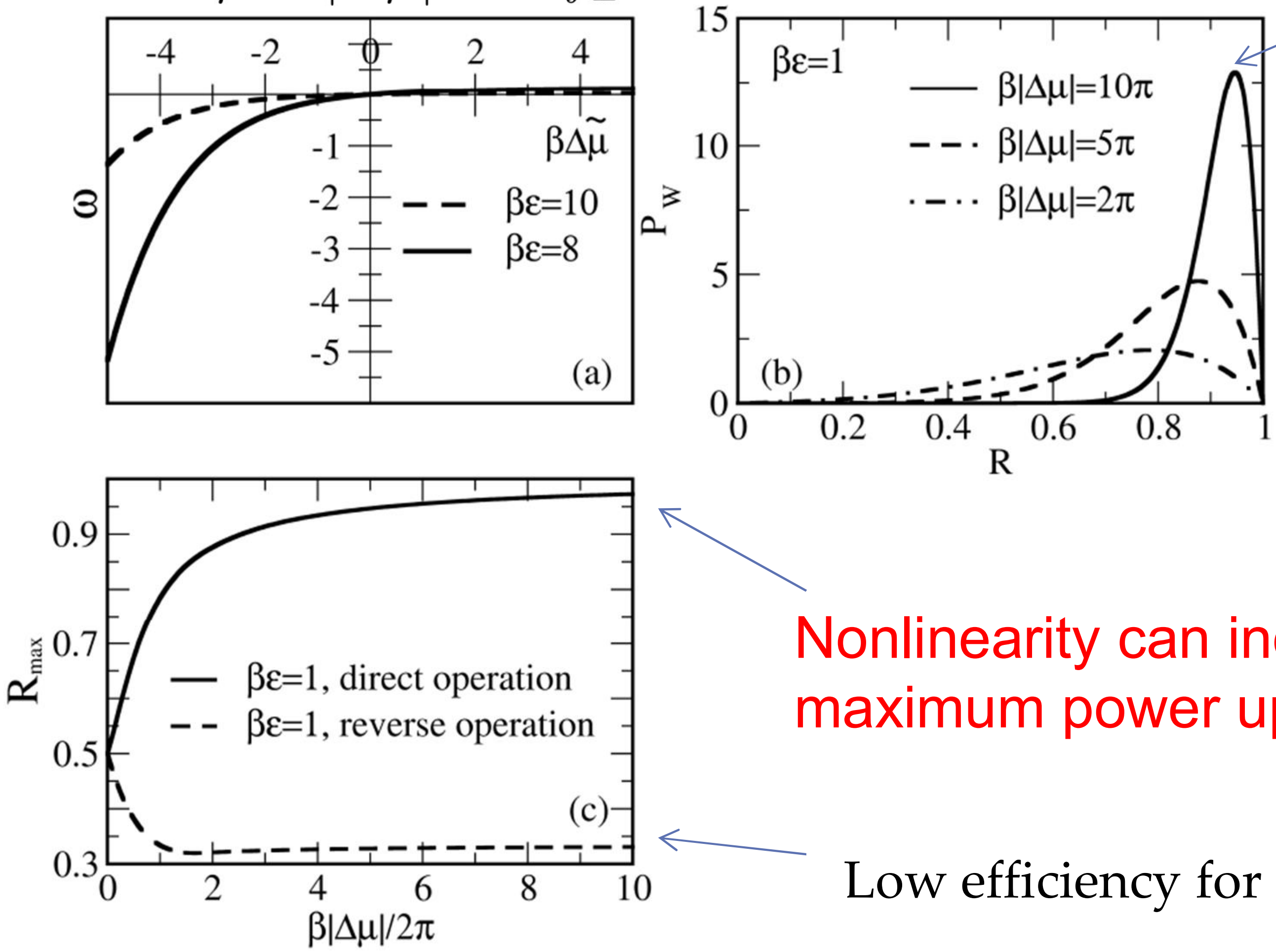
ratchet potential

From: Beilstein J. Nanotechnol. **7**, 328–350 (2016)



$$\omega_f(\Delta\mu, f_L) = \frac{D}{8\pi}\frac{\beta^2\varepsilon(\varepsilon-\Delta\mu-2\pi f_L)}{\sinh^2(\beta\varepsilon/2)-[\varepsilon/(\Delta\mu+2\pi f_L)]\sinh^2(\beta(\Delta\mu+2\pi f_L)/2)}$$

$$\widetilde{\Delta\mu} = |\Delta\mu| - 2\pi f_L$$

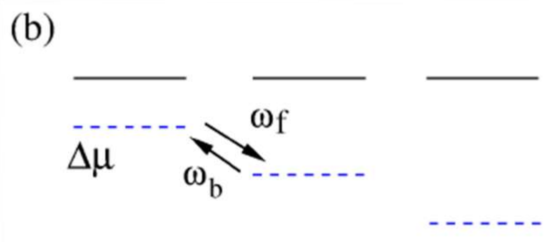


96% at maximum power

Nonlinearity can increase efficiency at maximum power up to 100%

Low efficiency for reverse operation

Discrete state models



$$\omega_f(\Delta\mu, f_L) = \omega_0 \exp[-\beta\delta(\Delta\mu + 2\pi f_L)]$$

$0 < \delta < 1$ describes asymmetry of potential drop

$$\exp\left[r\left(1 - R_{\max}\right)\right] = 1 + \frac{rR_{\max}}{1 + rbR_{\max}}$$

$$r = |\Delta\mu|/(k_B T),\ b = (k_B T/2\pi)\partial \ln \omega_f(\Delta\mu, f_L)/\partial f_L$$

$r << 1$

$$R_{\max} = \frac{1}{2} + \frac{1}{8}\left(\frac{b+1}{2}\right) r + o(r)$$

$$\approx \frac{1}{2} + \frac{1}{8}\left(\frac{1}{2} - \delta\right)\frac{|\Delta\mu|}{k_B T}.$$

asymmetry is important!

The same result as by U. Seifert, *Phys. Rev. Lett.* **106**, 020601 (2011), and
Ch. Van den Broeck, N. Kumar, K. Lindenberg, *Phys. Rev. Lett*. **108**, 210602 (2012)

Simplest model of quantum pump

From: Beilstein J. Nanotechnol. **7**, 328–350 (2016)

Toy model for electron-driven proton pump (like cytochrome c oxidase)

Marcus–Levich–Dogonadze rate $\omega_f\left(\Delta\mu,\Delta\mu_p=0\right)=\omega_0\exp\left[-(\Delta\mu+\lambda)^2/(4\lambda k_\mathrm{B}T)\right]$

$2\pi f_L \longrightarrow \Delta\mu_p$

$$\omega_0=(2\pi/\hbar)V_{tun}^2/\sqrt{4\pi\lambda k_\mathrm{B}T}$$

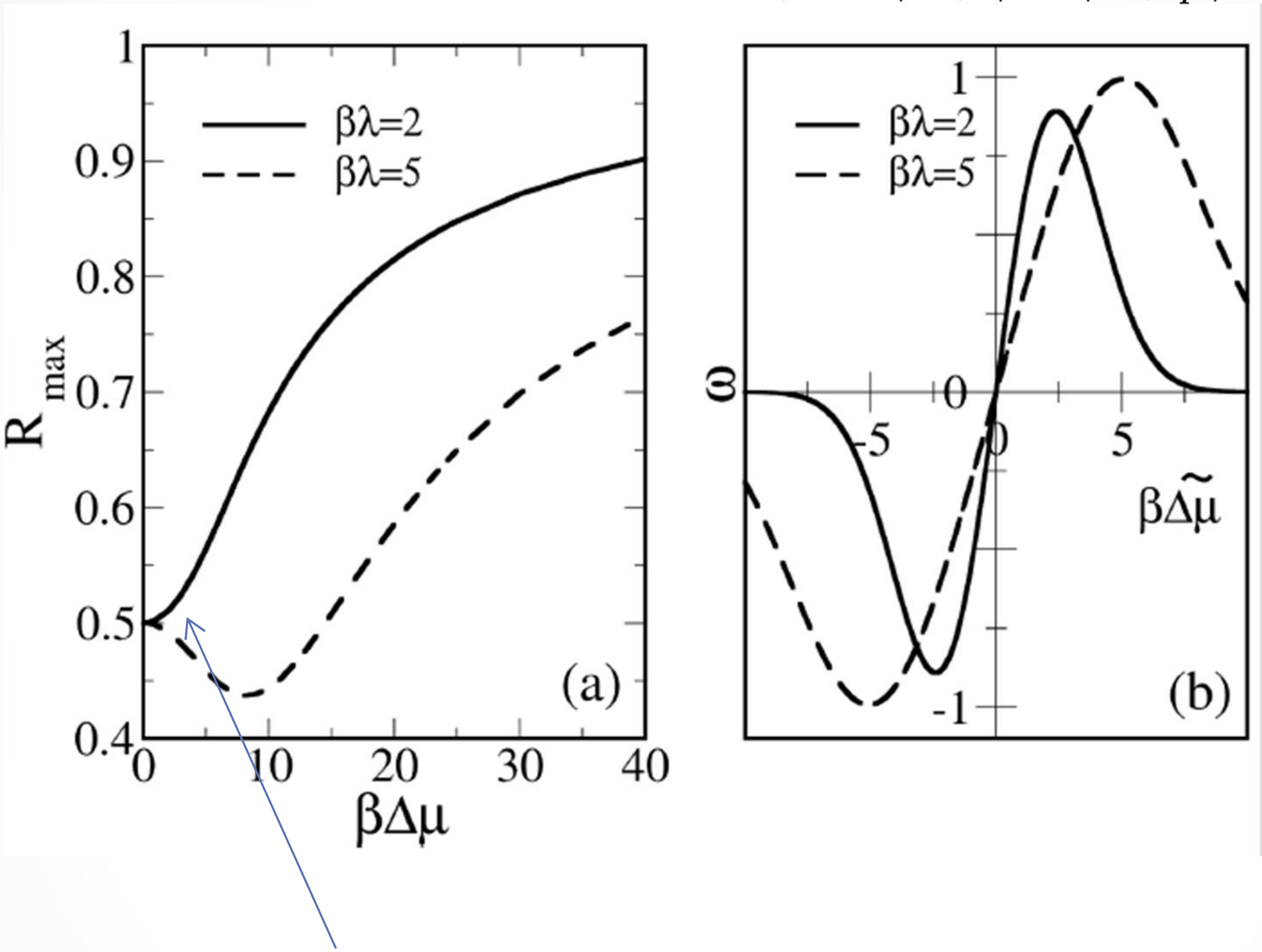
$$\exp\left[r\left(1-R_\mathrm{max}\right)\right]=\frac{1+r\left[-1/2+r\left(1-R_\mathrm{max}\right)/(4c)\right]R_\mathrm{max}}{1+r\left[1/2+r\left(1-R_\mathrm{max}\right)/(4c)\right]R_\mathrm{max}}$$

$$c=\lambda/(k_\mathrm{B}T) \qquad r=|\Delta\mu|/k_\mathrm{B}T$$

$r<<1$ $$R_\mathrm{max}\approx\frac{1}{2}+\frac{1}{192}\frac{(\Delta\mu)^2}{\lambda k_\mathrm{B}T}\left(3-\frac{\lambda}{k_\mathrm{B}T}\right)$$

$R_\mathrm{max}>1/2$ for $\lambda<3k_\mathrm{B}T$ in perturbative regime

$$\widetilde{\Delta\mu} = |\Delta\mu| - |\Delta\mu_p|$$



cannot be smaller than 50%!

Simplest model of anomalous motor

Kubo-Zwanzig Generalized Langevin Equation. Here, fractional GLE

$0 < \alpha < 1$

$$\eta_\alpha \frac{d^\alpha \phi}{dt^\alpha} = -\frac{\partial V(\phi)}{\partial \phi} + F - f_L + \xi_\alpha(t)$$

Caputo fractional derivative

$$\frac{d^\alpha \phi}{dt^\alpha} := \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{\dot{\phi}(t')dt'}{(t-t')^\alpha}$$

$$\langle \xi_\alpha(t)\xi_\alpha(t') \rangle = k_B T \, \eta_\alpha / |t-t'|^\alpha$$

In the potential-free case:

$$\langle \phi(t) \rangle = \frac{(F-f_L)t^\alpha}{\eta_\alpha \Gamma(1+\alpha)}$$

Fractional turnover velocity

$$\omega_\alpha = \frac{F-f_L}{\eta_\alpha}$$

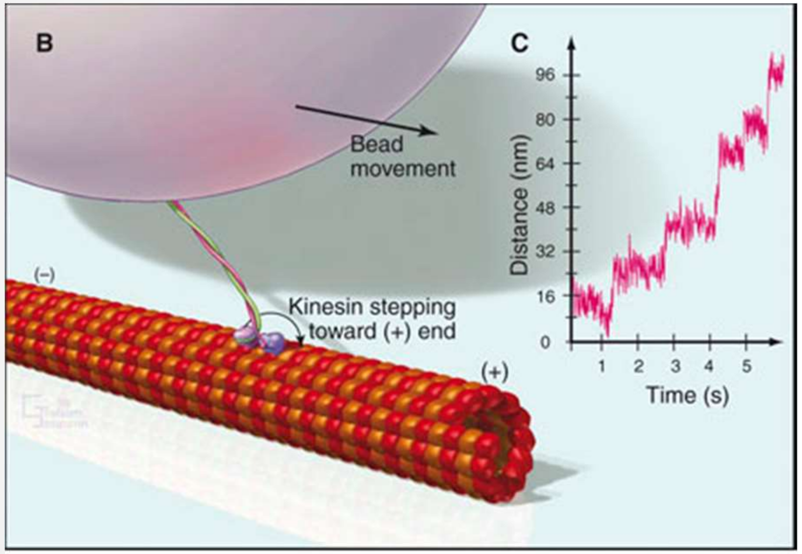
Notion of power is replaced by sub-power. However, thermodynamic efficiency is the same $R = f_L/F$. It can reach 100%. Optimal operation at maximum sub-power at $f_L = F/2$, with thermodynamic efficiency of 50%.

Phys. Rev. E 80, 046125 (2009), Adv. Chem. Phys. 150, 187 (2012) imply that these results are universally valid for any static potential, asymptotically

Flashing ratchet model for transport of subdiffusing cargos

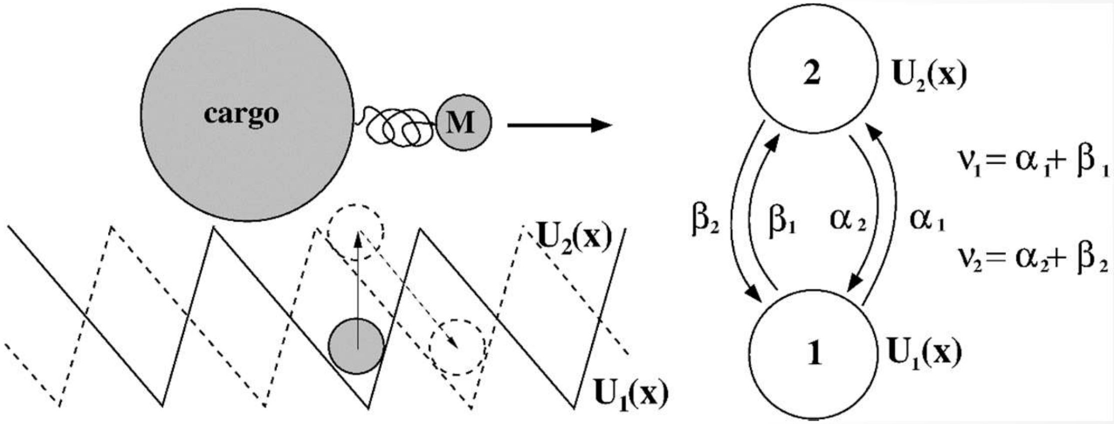
free cargo subdiffuses $\langle \delta y^2(t) \rangle \propto t^\alpha$ $\quad 0 < \alpha < 1$, e.g. $\alpha = 0.4$

Robert D, Nguyen T-H, Gallet F and Wilhelm C 2010 *PLoS One* 4 e10046



Aus: Pollard/Earnshaw, *Cell Biology*. © Spektrum Akademischer Verlag GmbH 2007

Physical Biology **12**, 016013 (2015)



T.L. Hill +

Can transport by motors be normal?

Generalization of model by Astumian & Bier, 1996, Jülicher, Ajdari & Prost, 1997, to include transport of subdiffusing cargo on FENE tether

Goychuk, Kharchenko , Metzler (2014) How Molecular Motors Work in the Crowded Environment of Living Cells: Co-existence and Efficiency of Normal and Anomalous Transport. *PLoS ONE* **9**(3): e91700, also *Phys. Chem. Chem. Phys.* **16**: 16524

Physical Biology **12**, 016013 (2015)

$$\eta_c \dot{y} = -\int_0^t \eta_{\text{mem}}(t-t')\dot{y}(t')dt' - \frac{k_L(y-x)}{1-(y-x)^2/r_{\text{max}}^2} + \xi_c(t) + \xi_{\text{mem}}(t)$$

$$\eta_m \dot{x} = \frac{k_L(y-x)}{1-(y-x)^2/r_{\text{max}}^2} - \frac{\partial}{\partial x}U(x,\zeta(t)) - f_0 + \xi_m(t)$$

$f_0 \equiv f_L$

$$\eta_{\text{mem}}(t) = \eta_\alpha t^{-\alpha}/\Gamma(1-\alpha),\ 0<\alpha<1$$

← viscoelastic fractional memory kernel, fractional GLE

Thermal FDR

$$\langle \xi_c(t)\xi_c(t')\rangle = 2k_B T \eta_c \delta(t-t')$$

$$\langle \xi_m(t)\xi_m(t')\rangle = 2k_B T \eta_m \delta(t-t')$$

$$\langle \xi_{\text{mem}}(t)\xi_{\text{mem}}(t')\rangle = k_B T \eta_{\text{mem}}(|t-t'|)$$

$$\frac{\alpha_1(x)\beta_2(x)}{\alpha_2(x)\beta_1(x)} = \exp\left[\Delta G_{\text{ATP}}/(k_B T)\right]$$

Thermal detailed balance for $\Delta G_{\text{ATP}} = 0$

$$\frac{\nu_1(x)}{\nu_2(x)} = \exp\left[(U_1(x)-U_2(x))/(k_B T)\right]$$

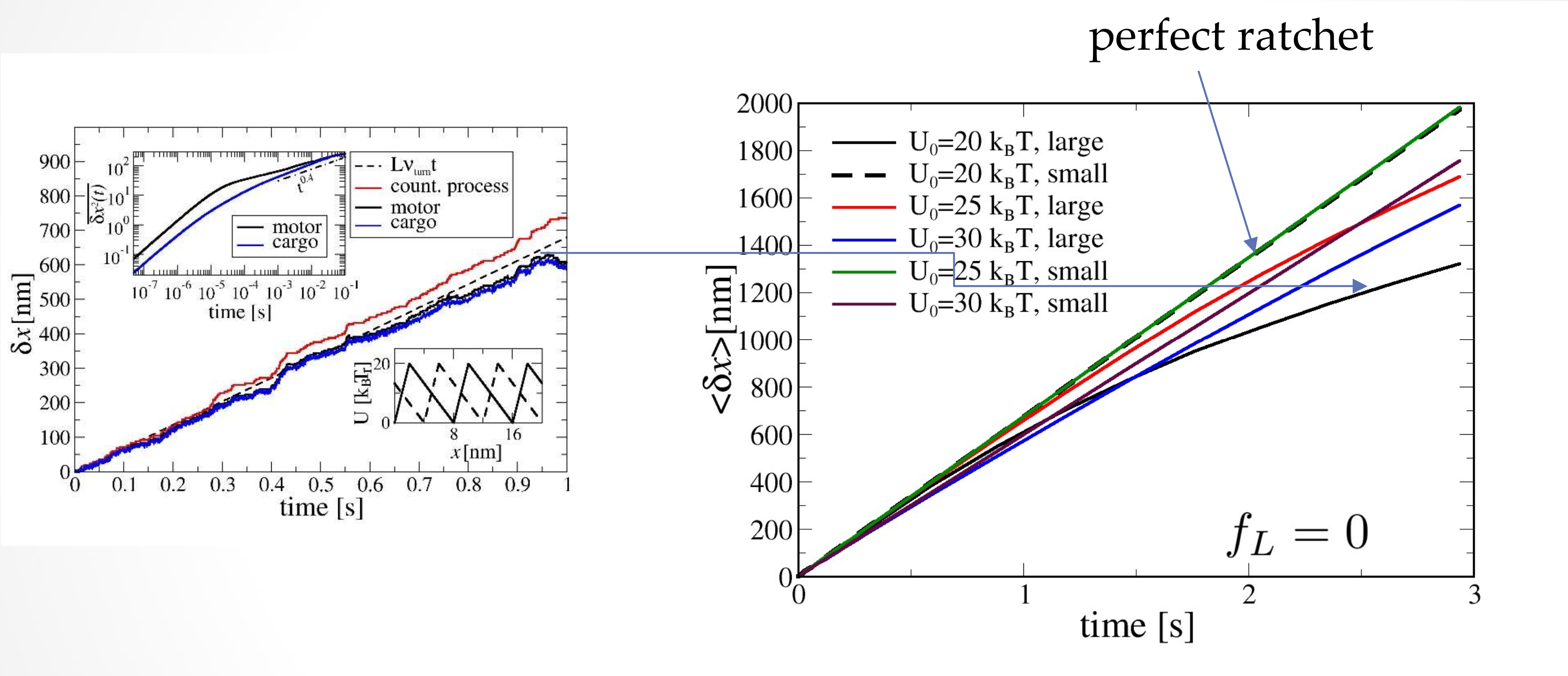
allostery seen in x-dependence ("information ratchets", a hype wording)

$$\nu_1(x) = \alpha_1(x) + \alpha_1(x+L/2)\exp[-(U_2(x)-U_1(x)+\Delta G_{\text{ATP}}/2)/(k_B T)]$$

$$\nu_2(x) = \alpha_1(x)\exp[-(U_1(x)-U_2(x)+\Delta G_{\text{ATP}}/2)/(k_B T)] + \alpha_1(x+L/2)$$

$\alpha_1(x) = \alpha_1 = const$ in a $\pm\delta/2$ neighborhood of $U_1(x)$ minimum

$\alpha = 0.4$, $|\Delta\mu| = \Delta G_{\mathrm{ATP}} = 20k_B T_r$, small $\sim$ 30 nm, large $\sim$ 300 nm



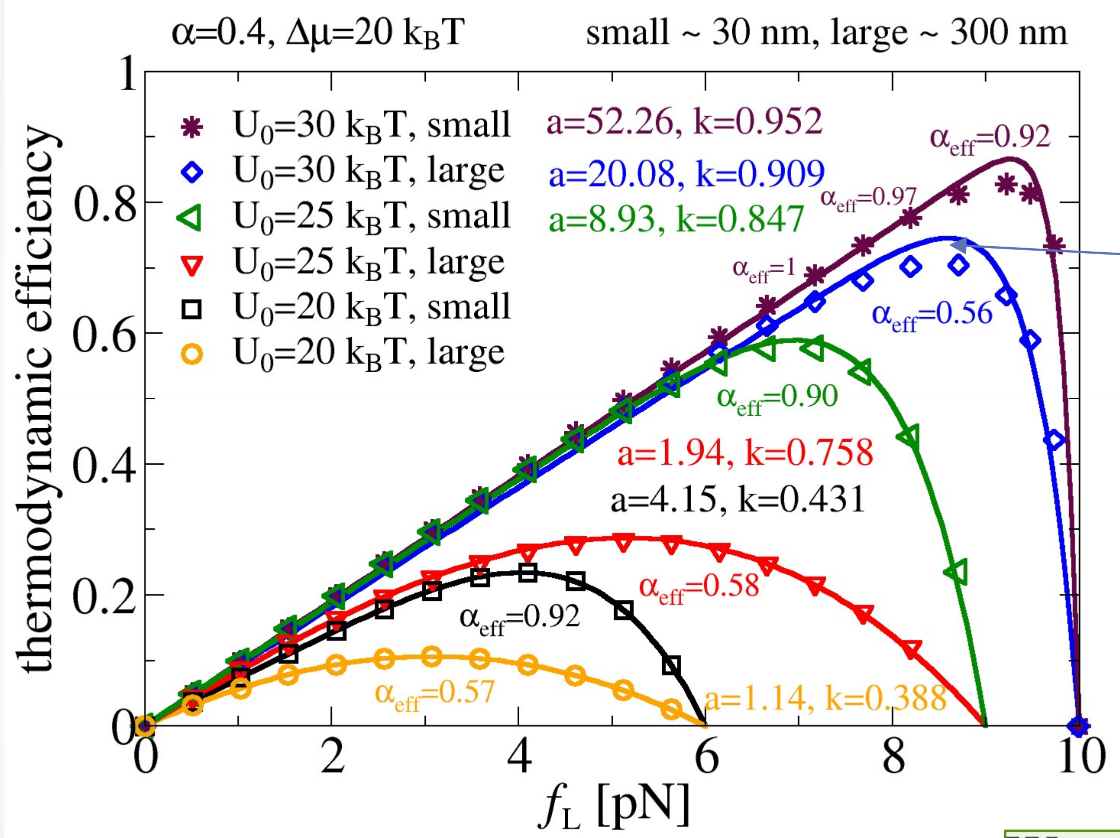
Stalling force $f_L^{\mathrm{stall}} \approx \frac{4}{3L} F_0(T, U_0, \nu_{\mathrm{turn}})$
with $F_0(T, U_0, \nu_{\mathrm{turn}}) = U_0 - TS_0(\nu_{\mathrm{turn}})$
For $F_0 > 0$, $TS_0 \approx 11.2 k_B T$ for $\alpha_1 = 170$ 1/sec and $\nu_{\mathrm{turn}} = 85$ Hz

From: Physical Biology 12, 016013 (2015)

Large cargo: $D_\alpha = 171\ \mathrm{nm}^2/\mathrm{sec}^{0.4}$

like for magnetosomes in:
Robert D, Nguyen T-H, Gallet F and Wilhelm C 2010
PLoS One 4 e10046

$$\langle \delta x(t) \rangle \propto t^{\alpha_{\mathrm{eff}}}$$



$U_0 = 30\ k_B T_r$
large cargo
$\langle N_{\mathrm{turn}}(t) \propto t^\gamma,\ \gamma \approx 0.62$
$\alpha_{\mathrm{eff}} \approx 0.556$

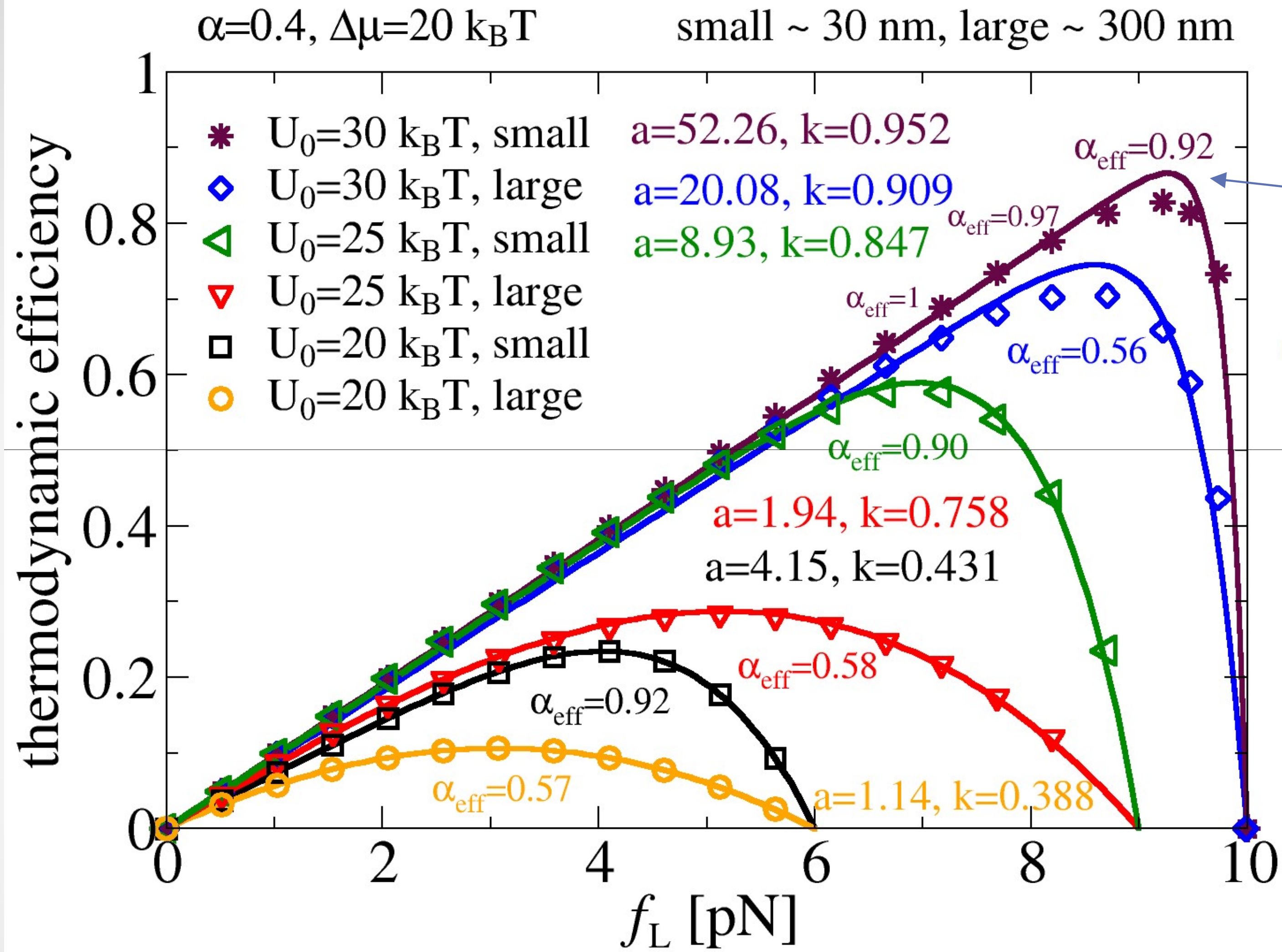
anomalous transport
anomalous kinetics

$$W_{\mathrm{use}}(t) = f_L \langle \delta x(t) \rangle \propto t^{\alpha_{\mathrm{eff}}}$$

$$R(t) = \frac{W_{\mathrm{use}}(t)}{E_{\mathrm{in}}(t)} \propto 1/t^{\gamma - \alpha_{\mathrm{eff}}}$$

$$E_{\mathrm{in}}(t) = \Delta G_{\mathrm{ATP}} \langle N_{\mathrm{turn}}(t) \rangle \propto t^\gamma$$

Mechano-chemical coupling can introduce anomalously slow enzyme turnovers, no turnover rate. Yet fast operation, in absolute terms!



$\alpha = 0.4$

$D_\alpha = 1710\ \mathrm{nm}^2/\mathrm{sec}^{0.4}$

10x larger than in:

Robert D, Nguyen T-H, Gallet F and Wilhelm C 2010 *PLoS One* 4 e10046

Linear motor: $a = 1,\ k = 1$

$$R = k(a)\left(\frac{f_L}{F}\right)\left[1 - \left(\frac{f_L}{F}\right)^a\right]$$

$$R_{max} = k(a)\, a/(1+a)^{1+1/a}$$

$$f_L = F/(1+a)^{1/a}$$

Summary

- Molecular machines can operate at nearly 100% thermodynamic efficiency in highly dissipative environments, even ones causing subdiffusion (cytosol)

- Efficiency at maximum power can exceed 50%, nonlinearity is vitally important

- Frictionless motors can have zero efficiency, be futile

see in: Beilstein J. Nanotechnol. **7**, 328–350 (2016)

- Design is crucial (alosteric interactions are important)

Thanks

- DFG for funding, grant GO 2052/3-1
- Vasyl Kharchenko and Ralf Metzler for collaboration on anomalous diffusion ratchet models

You for attention !

Read review in: *Beilstein J. Nanotechnol.* **7**, 328–350 (2016)
for further detail

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