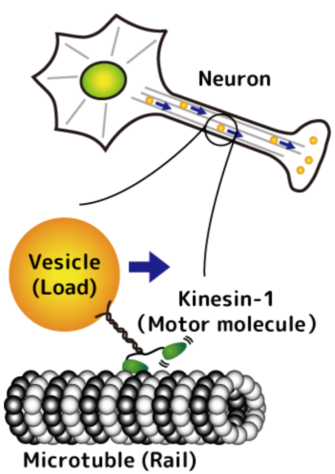
2023/03/16

Workshop OT 2023　最適輸送とその周辺
機械学習から熱力学的最適化について

非熱的にゆらぐ細胞内環境に最適化する生体分子モーター



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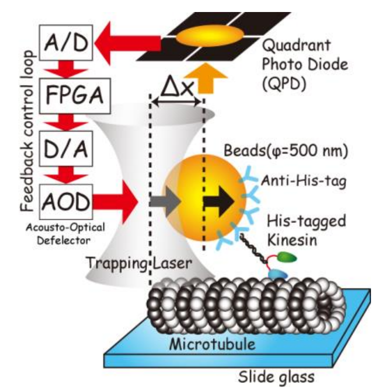
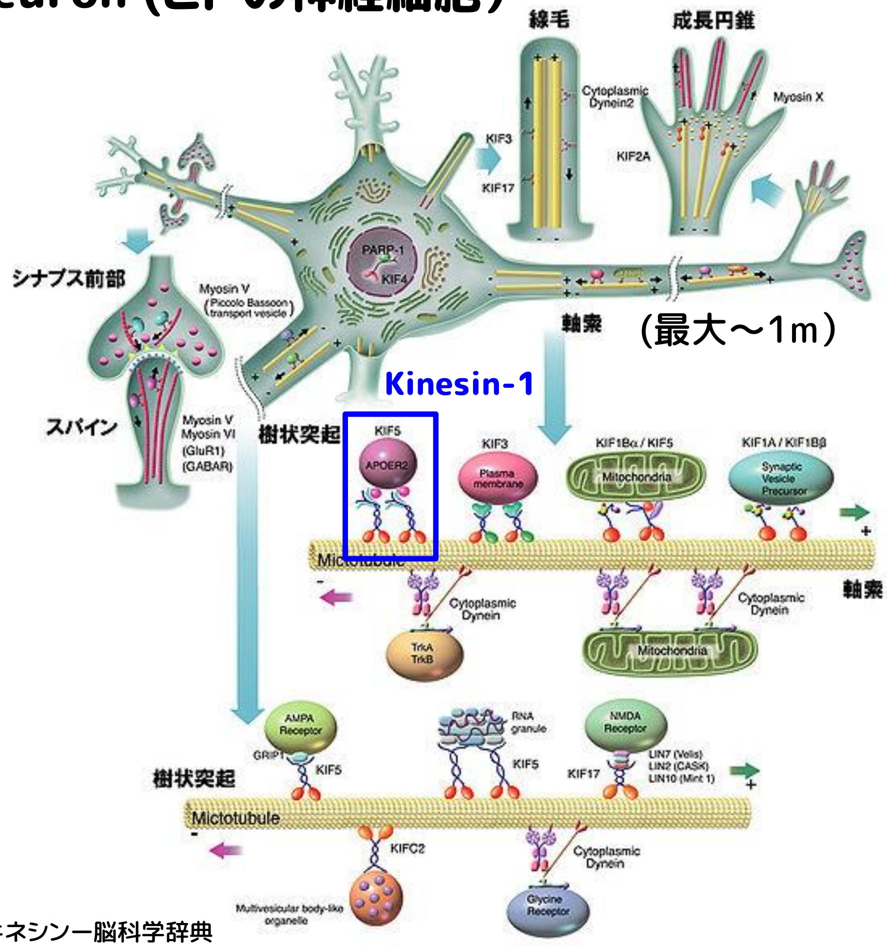
生命機能研究科
(4月から)



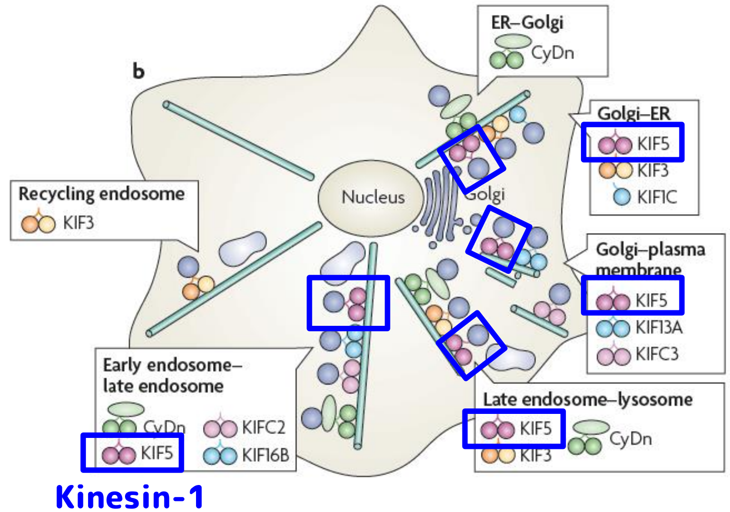
Molecular Transporters in Cells

Neuron (ヒトの神経細胞)



from キネシン一脳科学辞典
https://bsd.neuroinf.jp/wiki/%E3%82%AD%E3%83%8D%E3%82%B7%E3%83%B3

Non-Neuron Cell (普通の細胞)



[Hirokawa *Nat. Rev. Mol. Biol* 2009]

スケール感

分子~5 nm → 人間~1 m
小胞~0.1 μm→荷物~20 m
細胞~50 μm→ 山手線内~10 km
神経~1 m → 月まで~40万 km

What is the *optimal transport* for living beings?

生き物にとって最適な輸送とは?

Today’s contents

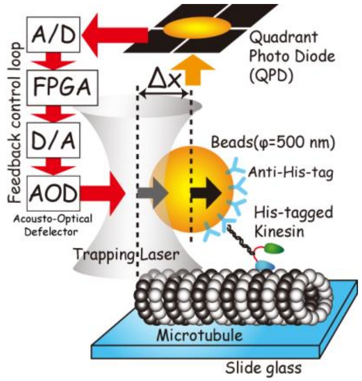
エネルギー効率の最適化(？)

① Optimization for energy efficiency (?)

I. Molecular motor: Kinesin 1

II. Nonequilibrium energetics of kinesin 1

[Ariga et al. *Phys. Rev. Lett.* **121**, 218101 (2018)]



環境への最適化(？)

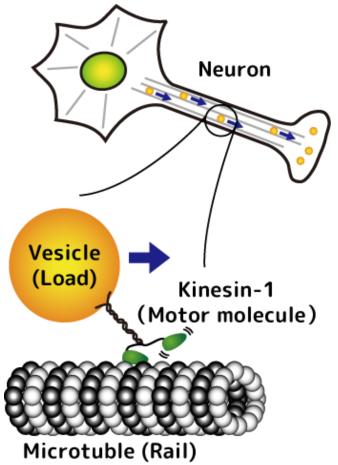
② Optimization for the environment (?)

III. Nonthermal fluctuation in living cells

[Nishizawa, TA, et al. *Sci. Adv.* **3**, e1700318 (2017)]

IV. Noise-induced acceleration of kinesin 1

[Ariga et al. *Phys. Rev. Lett.*, **127**, 178101 (2021)]



(前半を重点的に、後半は駆け足で)

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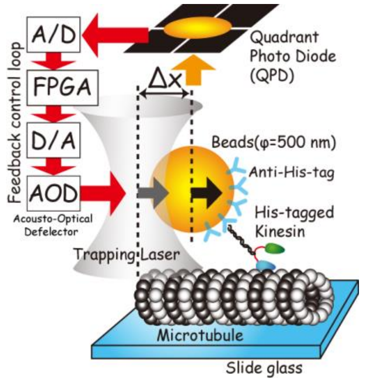

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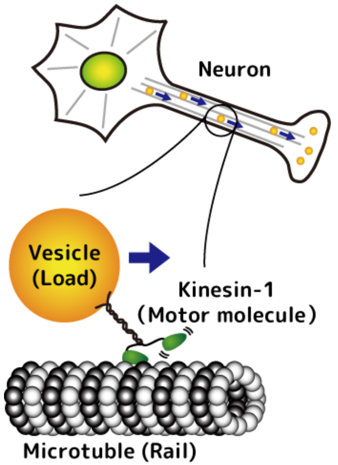
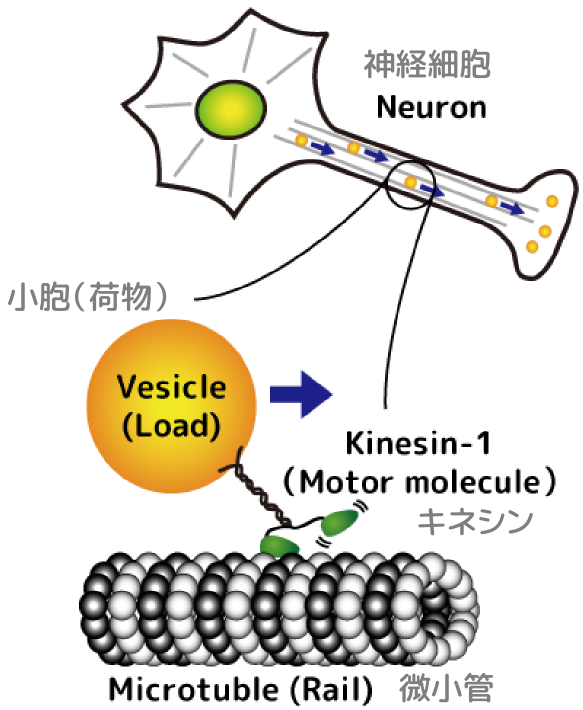


（前半を重点的に、後半は駆け足で）

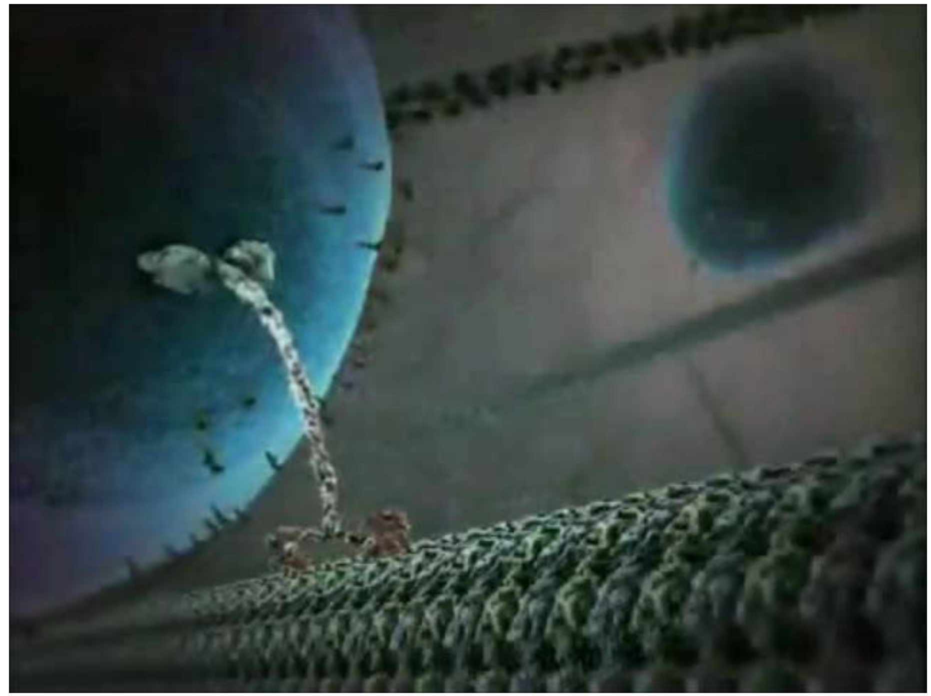
Molecular motor: kinesin-1



Kinesin-1 is a molecular motor that carries a cargo in cells by utilizing chemical free energy of ATP hydrolysis (Δμ).

ATP → ADP + Pi

$$\Delta\mu = \Delta\mu^0 + k_B T \ln \frac{[\mathrm{ATP}]}{[\mathrm{ADP}][\mathrm{Pi}]}$$



"The inner Life of the cell" from BioVisions at Harvard Univ.
https://www.youtube.com/watch?v=wJyUtbn0O5Y

There are two major* mistakes in this movie.

Question: What's wrong?

ふたつの大きな間違いとはなんでしょう?

*Trivial mistakes are also exist. (ex. colors)

Q: There are two major mistakes. What's wrong?

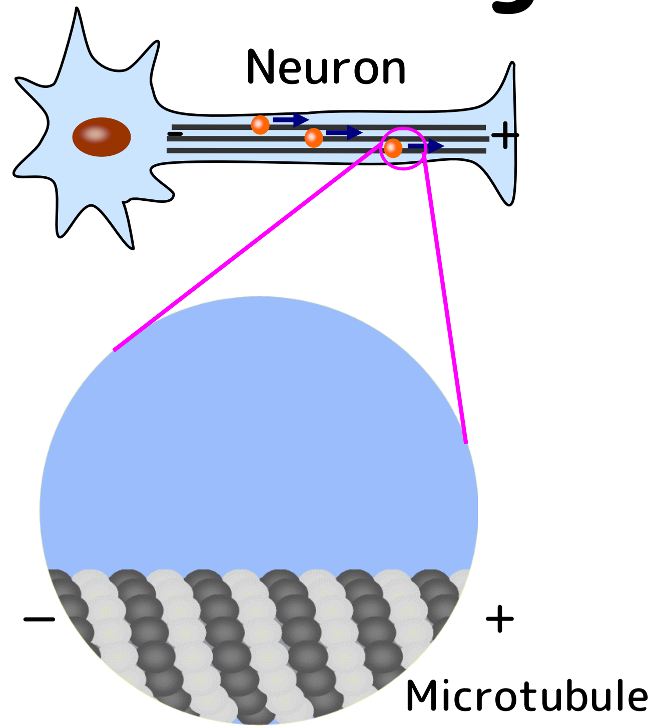
Answer 1: kinesin is fluctuating

Conventional kinesin model

"The Inner life of the cell" from BioVisions at Harvard Univ.

A floating foot is smoothly thrown forward like "Seoi-Nage." in judo.

[Rice et al. *Nature* 1999]



Brownian motion or thermal fluctuation is shaking their foot (head domain).

[Isojima et al. *NCB* 2016]

One can predict that:

"Kinesin walks ***efficiently*** by utilizing fluctuations."

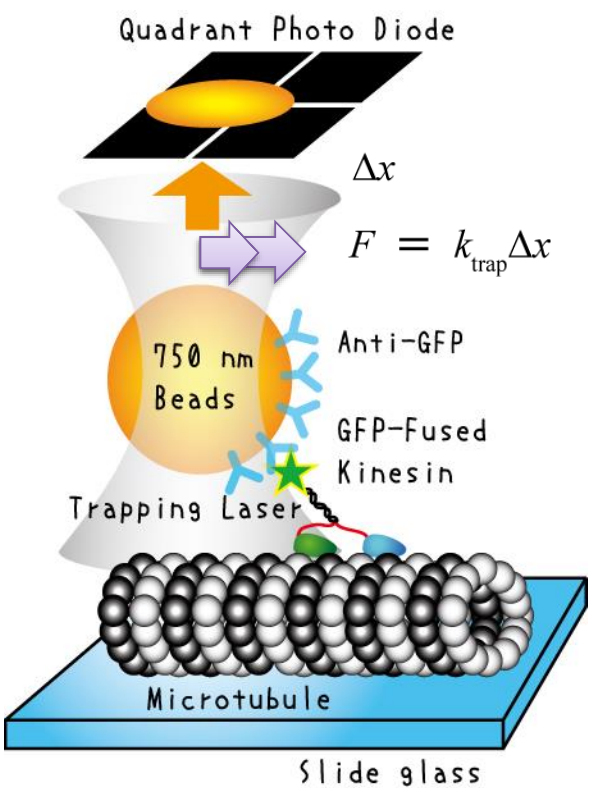
[Vale & Oosawa *Adv. Biophys.*1990] [有賀 *物性研究* 2011]

Fluctuation is actually observed. → How about the *efficiency*?

Conventional energetics of kinesin

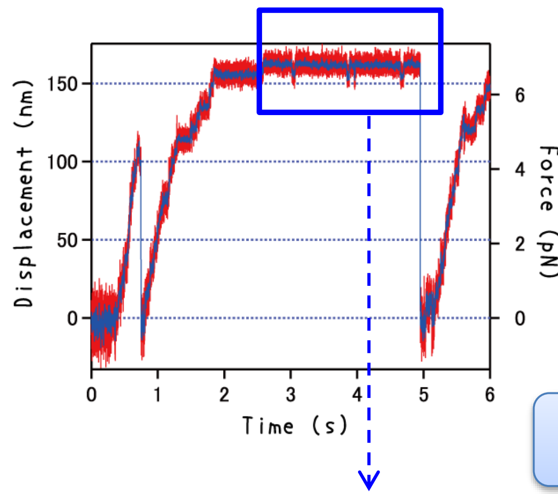
光ピンセット

Optical tweezers



Kinesin's movement (Δx～nm) and forces ($F=k_{trap}\Delta x$～pN) can be measured at once.

At Stall force condition (Maximum work)

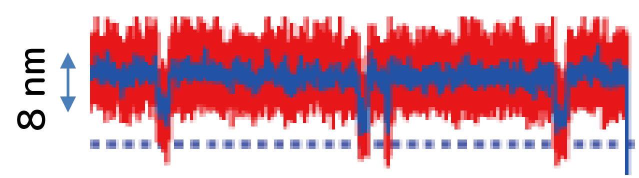


- ✓ F_{stall} ~ 7 pN (Max. force)
- ✓ Step size ~ 8 nm
- ✓ W_{stal} ~ 7 x 8 = 56 pNnm
- ✓ $\Delta\mu$ ~ 80～100 pNnm (Typical value in cell)

$$\eta_{stall} \equiv \frac{W_{stall}}{\Delta\mu}$$

Max. Eff. (η_{stall}) ~50%

[J. Howard 2001]



However!

Backsteps cannot synthesize ATP but hydrolyze ATP or slippage.

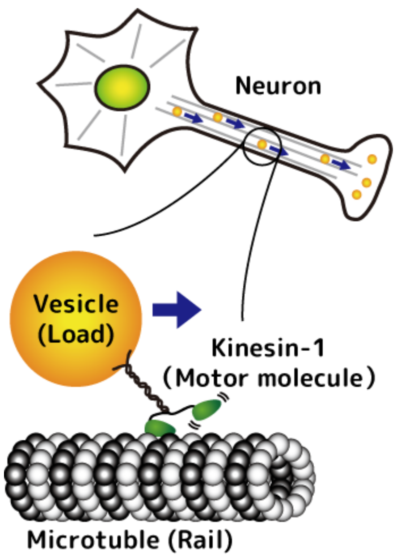
[Taniguchi *Nat. Chem. Biol.* 2005, Carter *Nature* 2005]

Realistic power efficiency (η_{real}) at stall force (v = 0) is **0 (zero)**

Kinesin Works but Energy Dissipates

The physiological role of kinesin is to carry vesicles against *viscous media*

キネシンの生理的役割は、細胞内の粘性に逆らって荷物を運ぶことにある



Kinesin works by pulling the vesicles
but we observed just vesicles as probe.

Output energy from the kinesin is observed as
"heat" dissipation rather than "work."

However,

Microscopic motor shows *fluctuation*

- Brownian motion
- Kinesin's steps

To evaluate the energy input/output balance,

Dissipations must be measured *separately*

エネルギー入出力を評価するためには、散逸を個別に計測する必要がある。

Using **Harada-Sasa equality**

$$J_x = \gamma \langle v \rangle^2 + \gamma \int_{-\infty}^{\infty} df \left[\tilde{C}(f) - 2k_B T \tilde{R}'(f) \right]$$

[Harada *PRL* 2005]

What's this?

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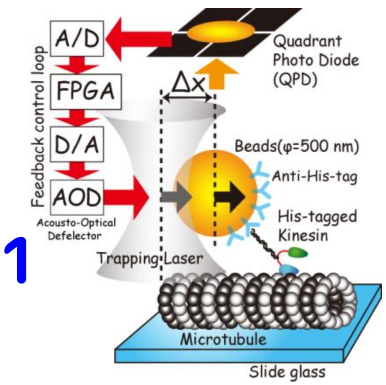

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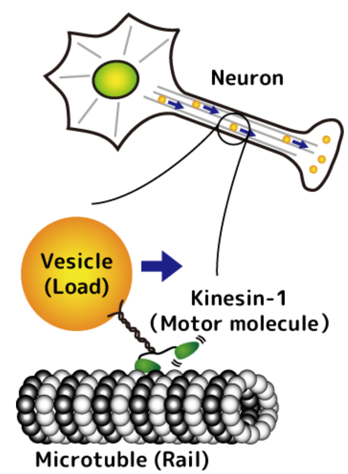

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$$J_x = \gamma \langle v \rangle^2 + \gamma \int_{-\infty}^{\infty} df \left[\tilde{C}(f) - 2k_B T \tilde{R}'(f) \right]$$

[Harada *PRL* 2005]

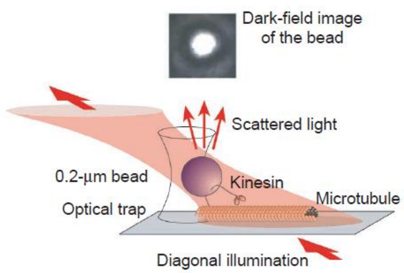
What's this?

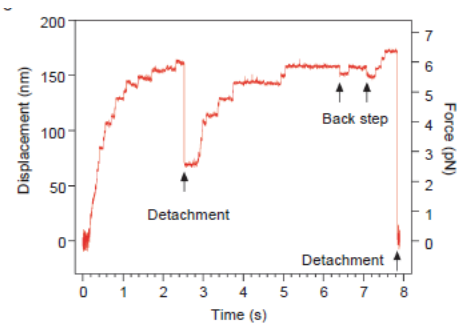
Initial motivation: Phenomenological energetics

T. Harada

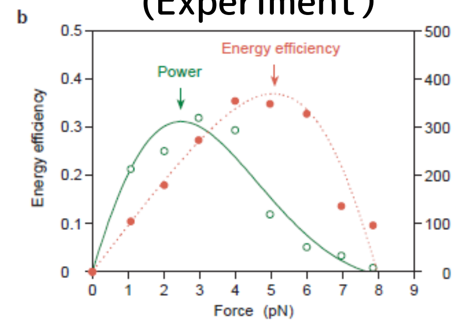
Harada-san said

"I want to describe the energetics of kinesin *theoretically*."





(Experiment)



[Nishiyama et al. *NCB* 2002]

He predicted that

Violation of the Fluctuation Dissipation Theorem (FDT) is somehow related to the dissipation of energy.

揺動散逸定理の破れがどうも関係してるっぽい。

EUROPHYSICS LETTERS 1 April 2005
Europhys. Lett., **70** (1), pp. 49–55 (2005)
DOI: 10.1209/epl/i2004-10456-2

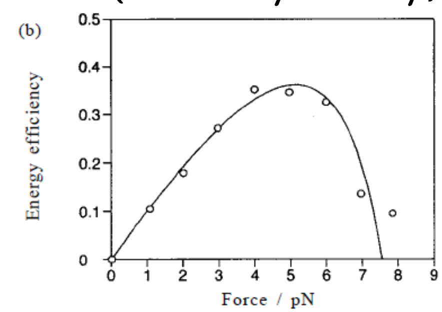
Phenomenological energetics for molecular motors

T. Harada

[Harada EPL (2005)]

$$\eta \approx \frac{f_{\rm L}\langle v\rangle}{F_0\langle v\rangle + (D/\mu - T_0)\,\tau^{-1}},$$

(Fitted by Theory)

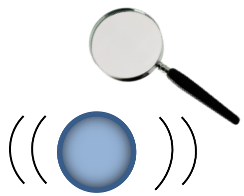


→What is FDT (violation)?

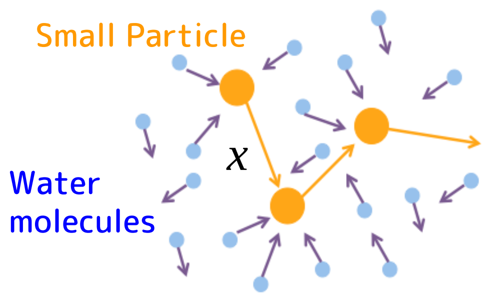
Fluctuation and Dissipation Theorem (FDT)

Issue: Measuring energy input/output is difficult in a small, fluctuating world.

Small molecules or particles in water are



Fluctuate thermally by Brownian motion.



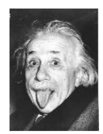
$$C = \langle x^2 \rangle = 2Dt$$

They are moving even without consuming energy.

Equilibrium

(No energy input/output)

Einstein relation



$$D = \frac{k_B T}{\gamma}$$

D: Diffusion constant; T: Temp.; γ: Viscous drag

[Einstein *Annalen der Physik.* 1905]

Generalization (Fourier transform)

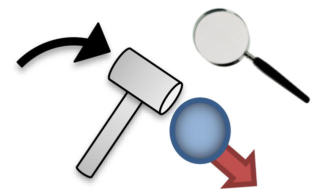
Fluctuation Dissipation Theorem (FDT / FRR)

$$\tilde{C}(f) = 2k_B T \tilde{R}'(f)$$

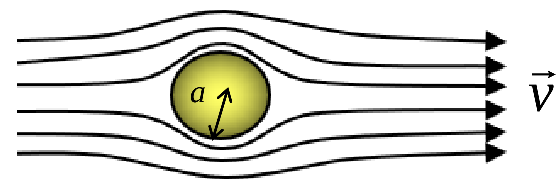
Fluctuation **Response**

[Kubo *JPSJ* 1957]

When a force is applied to a particle



Dissipate the energy by friction with water.



$$F = \gamma v \qquad \gamma = 6\pi\eta a$$

$$v = R \cdot F \qquad (R = 1/\gamma)$$

Response: How much speed changes when pushed

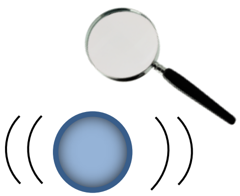
At equilibrium, the (thermal) fluctuation agree with the response

We cannot get the energy balance *just by observing the movement.*

Violation of FDT/FRR

Issue: Measuring energy input/output is difficult in a small, fluctuating world.

Small molecules or particles in water are

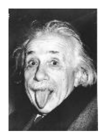


Further stirred.

Nonthermal fluctuations that utilize energy

Non-equilibrium
(Energy input/output exist)

Einstein relation



$$D = \frac{k_B T}{\gamma}$$

Diffusion constant — Temp. — Viscous drag

[Einstein *Annalen der Physik.* 1905]

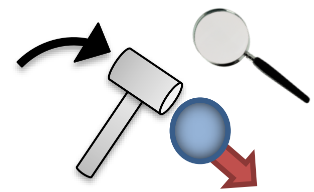
Generalization (Fourier transform)

FDT/FRR violation

$$\tilde{C}(f) \neq 2k_B T \tilde{R}'(f)$$

Fluctuation **Response**

When a force is applied to a particle



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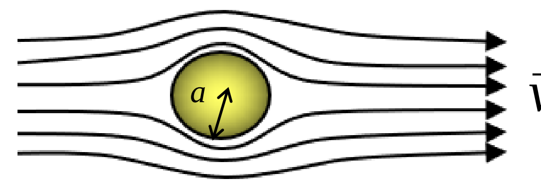


$F = \gamma v \qquad \gamma = 6\pi\eta a$

$v = R \cdot F \qquad (R = 1/\gamma)$

- ✓ At nonequilibrium, **fluctuations** do not agree with **responses** →**FDT violation**
- ✓ The **FDT violation** indicates active fluctuations excluding Brownian motion.

e.g. [Mizuno *Science* 2007]

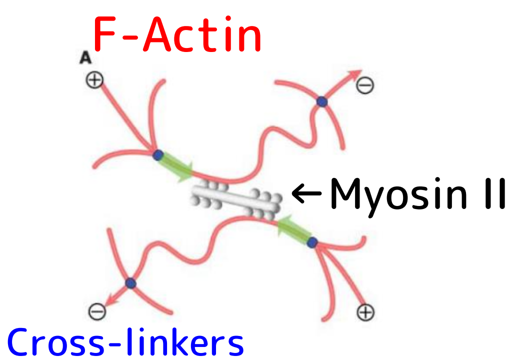
Violation of FDT/FRR

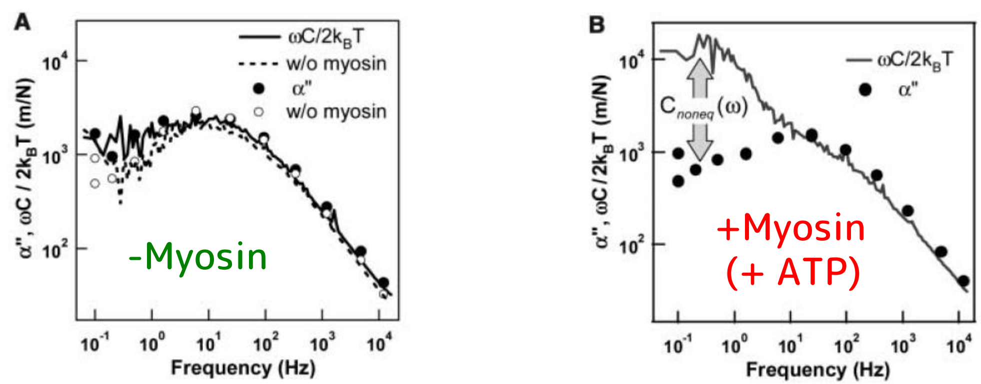
Equilibrium	**Nonequilibrium**
fluctuation, response	fluctuation, response
$\tilde{C}(f) = 2k_B T\tilde{R}'(f)$	$\tilde{C}(f) \neq 2k_B T\tilde{R}'(f)$
(Einstein relation or FDT/FRR)	(FRR violation)

The degree of "violation" of Fluctuation Response Relations has been used as **a measure of "nonequilibrium" conditions**.

For example...

D. Mizuno (Kyushu-U.)





[Mizuno et al. *Science* 315:370 2007]

Fluctuation – Response = **Active fluctuation** (excluding Brownian motion)

$\tilde{C}(f) - 2k_B T\tilde{R}'(f)$ by consuming energy!

T. Harada

Harada-Sasa equality

Equilibrium

fluctuation — response

$$\tilde{C}(f) = 2k_B T \tilde{R}'(f)$$

(Einstein relation or FDT/FRR)

Nonequilibrium

fluctuation — response

$$\tilde{C}(f) \neq 2k_B T \tilde{R}'(f)$$

(FRR violation)

The degree of "violation" of Fluctuation Response Relations relates the non-equilibrium dissipation of the system.

e.g. [Mizuno *Science* 2007]

Total energy dissipation — Viscous dissipation — Velocity fluctuation — Response function — (per unit time)

$$J_x = \gamma \langle v \rangle^2 + \gamma \int_{-\infty}^{\infty} df \left[\tilde{C}(f) - 2k_B T \tilde{R}'(f) \right]$$

Nonequilibrium dissipation

ALL parameters are measureable!!

Definitions

$$C(t) \equiv \langle [v(t) - v_s][v(0) - v_s] \rangle$$

$$v(t) = v_s + \int_{-\infty}^{t} R(t-s)\delta F(s) ds$$

$$J \equiv \langle [\gamma v - \xi(t)] \circ v \rangle$$

v_s : Average velocity
γ : Viscous drag
k_B : Boltzmann constant
T : Absolute temperature

Novel non-equilibrium equation as a new type measure of efficiency for molecular motors.

Aim: How about kinesin?

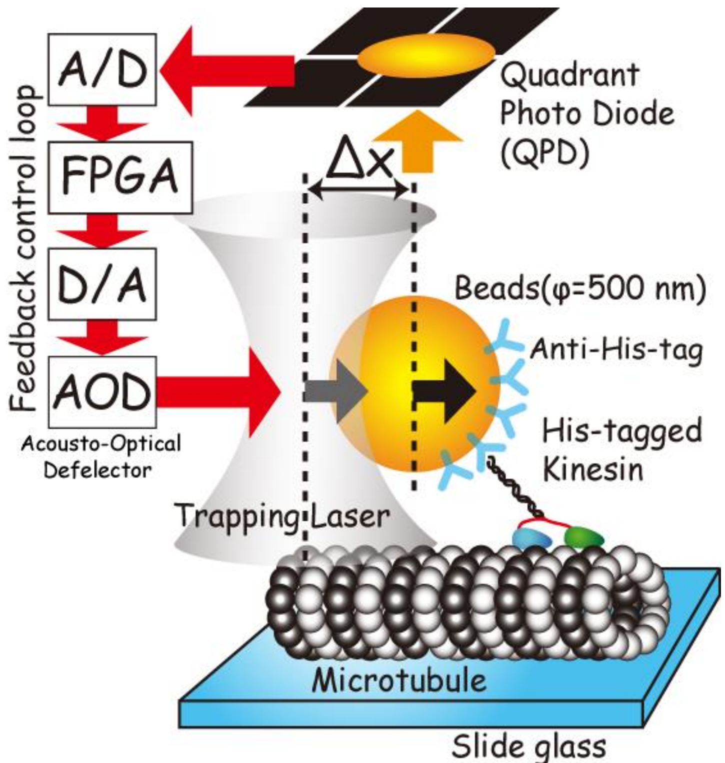
[Harada, Sasa *PRL*, **95**: 130602 (2005)]

実験方法

Field-Programmable Gate Array

Method: Force clamp with FPGA

Optical tweezers

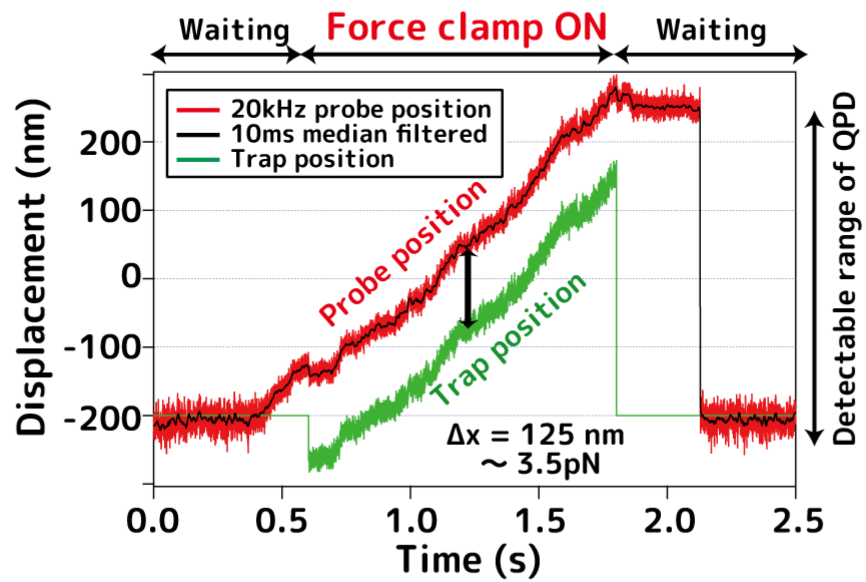


Sampling rate: 20 kHz
Feedback rate: 20 kHz

Electrical circuit on FPGA can be modified only by programming.

FPGA: Field Programable Gate Array

Force Clamp Measurement



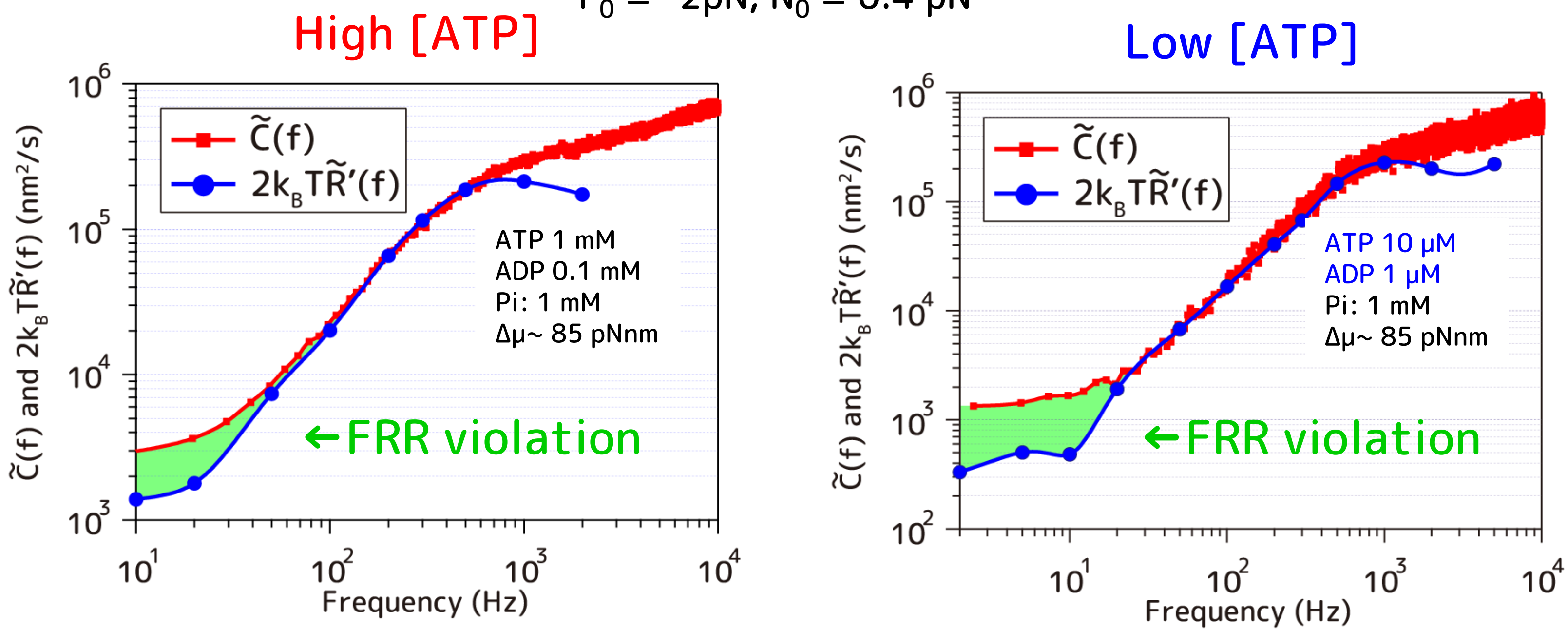
Real-time force clamp apparatus allows to apply *arbitrary forces*.

$$F_{ext} = F_0 + N_0 \sin(2\pi f_0 t) \rightarrow v = v_0 + A_0 \sin(2\pi f_0 + \phi)$$

By applying sine wave perturbations,
we got response function $\tilde{R}'(f) = A_0 / N_0 \bullet \cos(\phi)$
and velocity fluctuations $\tilde{C}(f) = \left\langle \left(\tilde{v} - \langle \tilde{v} \rangle \right)^2 \right\rangle$

FRR violation of kinesin

F_0 = -2pN, N_0 = 0.4 pN



Energy flows [pNnm/s]	High ATP Experiment	Low ATP Experiment
Input energy rate $(\Delta\mu/\tau)$	6160 ±560	2190 ±310
Output power $(-F_0\langle v\rangle)$	1150 ±1120	410 ±60
Viscous dissipation $(\gamma\langle v\rangle^2)$	10.6 ±1.9	1.35 ±0.37
Nonequilibrium dissipation $\left(2\gamma\int_0^{f_{max}} df\left[\tilde{C}(f)-2k_BT\tilde{R}'(f)\right]\right)$	53.4 ±41.4[a]	2.74 ±1.52[b]

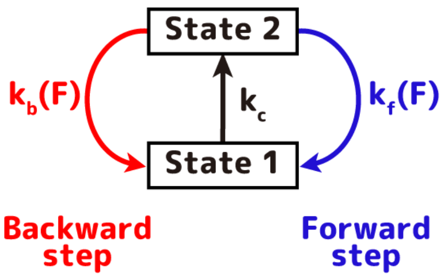
Power efficiency ~20%

Very small! << 1%

Dissipations are dramatically small → ~80% of the input energy is ***missing***.

Markov-Langevin model

① Kinesin model



Arrhenius-type force dependency

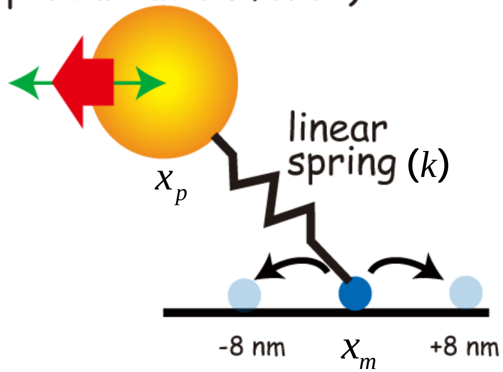
$$k_f(F) = k_f^0 \exp\left(\frac{Fd_f}{k_B T}\right)$$

$$k_b(F) = k_b^0 \exp\left(\frac{Fd_b}{k_B T}\right)$$

[Taniguchi *NCB* 2005]

② Probe's dynamics

External force: F
+ Thermal noise: ξ
(+ perturbation force)

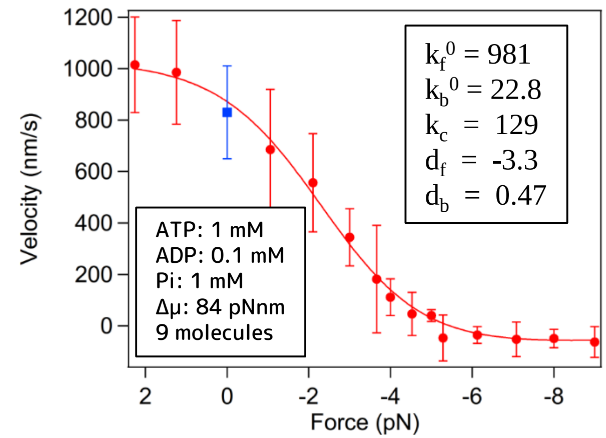


$$\gamma \frac{dx_p}{dt} = k\left(x_m - x_p\right) + F_p + \xi$$

$$\langle \xi \rangle = 0, \langle \xi(t)\xi(t') \rangle = 2k_B T \gamma \delta(t - t')$$

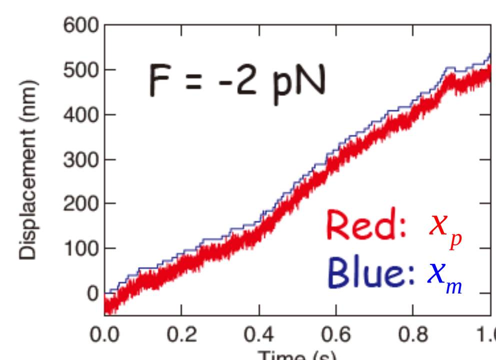
③ Parameter from experiments.

Force-velocity relationship



Fitting line: $\langle v \rangle = d \times \frac{(k_f - k_b)k_c}{k_f + k_b + k_c}$

Simulated traces

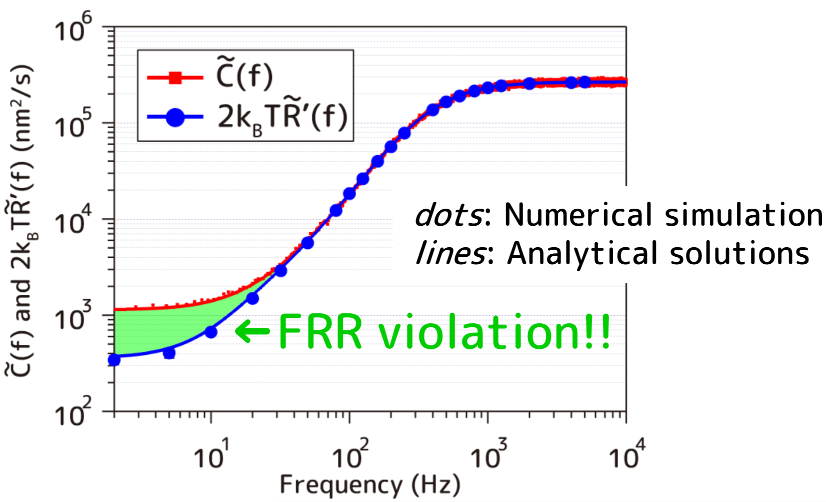


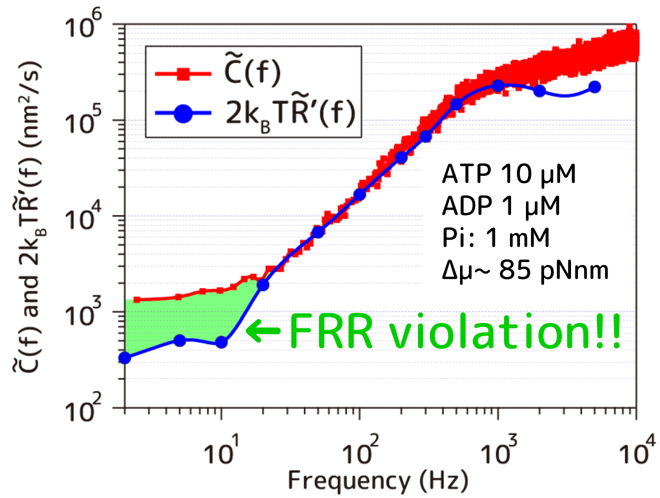
(d: 8 nm, γ: 3.1×10^{-5} pN/nm s, k= 0.075 pNnm, T: 25°C)

① Kinesin: two-state Markov stepper model
② Probe: Langevin dynamics connected with liner spring
③ All parameters can be experimentally determined.

FRR violation of kinesin

Most of the input energy dissipates without used to carry cargo.





Model reproduced the experimental results very well

Energy flows [pNnm/s]	High ATP Experiment	High ATP Model	Low ATP Experiment	Low ATP Model
①Input energy rate $(\Delta\mu/\tau)$	6160 ±560	6820	2190 ±310	2170
②Output power $(-F_0\langle v\rangle)$	1150 ±1120	1070	410 ±60	410
③Viscous dissipation $(\gamma\langle v\rangle^2)$	10.6 ±1.9	8.89	1.35 ±0.37	1.29
④Nonequilibrium dissipation	53.4 ±41.4[a]	50.7	2.74 ±1.52[b]	2.14

Power efficiency ~20%

Very small!! << 1%

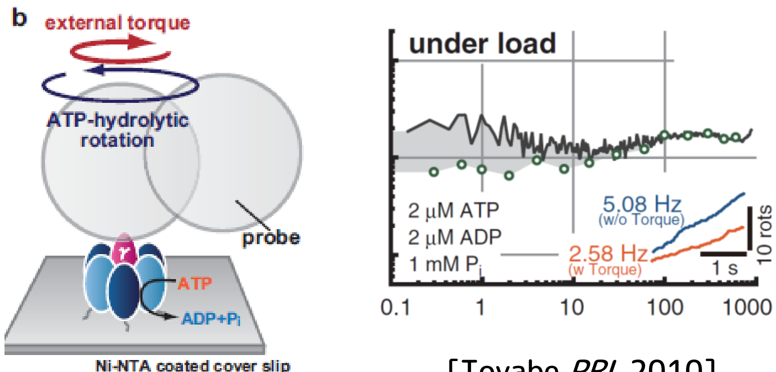
① ② ③+④ ???

$$\Delta\mu/\tau = -F_0\langle v\rangle + J_x + J_{Allothers}$$

~80% of the input energy is ***still missing***.

Comparison with F_1-ATPase

F_1-ATPase: A part of ATP synthesis

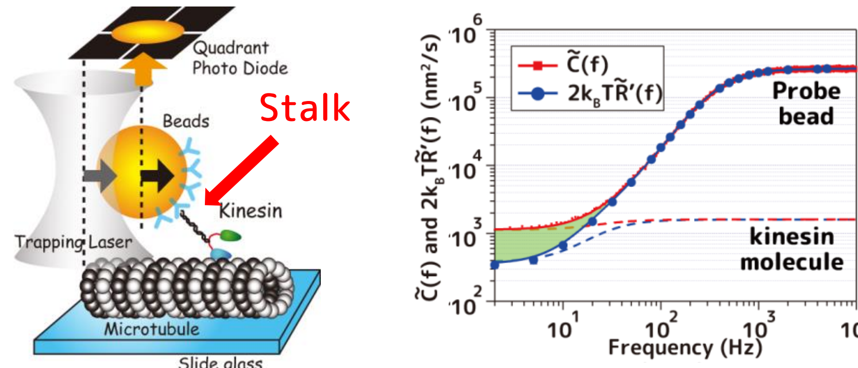


[Toyabe *PRL* 2010]

All (100%) dissipation is observed.

No internal dissipation

Kinesin: Vesicle transporter



[Ariga *PRL* 2018]

Most (~80%) dissipation is *hidden.*

Large (~80%) internal dissipation

内部散逸

Two candidate reasons for the discrepancy were evaluated.

I. Reversibility: Reversible rotary motor *vs* Irreversible translational motor.

→ At high Δμ & low load → only few % is dissipated via futile ATPase pathways.

II. Softness of linker: Probes cannot follow kinesin's rapid steps such that the observed dissipation might underestimate due to the long elastic Stalk.

→ By analyzing model → the *softness* is not affected to the observed dissipation.

Kinesin is *low efficiency* (?)

Most of the input energy dissipates without used to carry cargo.

[Ariga et al. *PRL* **121**, 218101 (2018)]
Editors' suggestion & *Featured in physics*

From American Physical Society

Physics
VIEWPOINT
Low Efficiency Spotted in a Molecular Motor
A detailed study of kinesin—a molecular motor responsible for transporting cellular cargo—shows that it loses 80% of input energy to heat.

by Adam G. Hendricks*

compared to other motor proteins that are much more effi-

[Hendrics *Physics* 2018]

From Russian web news

Физики не смогли объяснить энергетическую неэффективность кинезина

15:48 В израильской Кесарии нашли средневековые

Google translation:
"Physicists could not explain the energy inefficiency of kinesin"

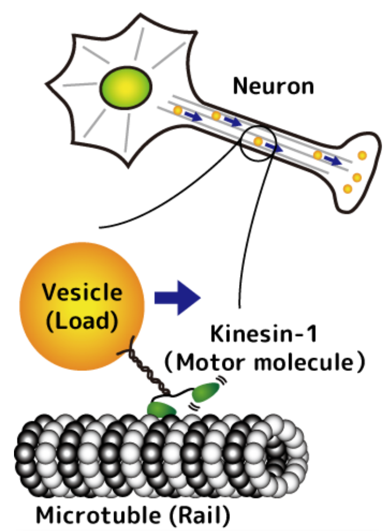
"Kinesin is low efficiency motor"

However,

It is hard to imagine that kinesin is so inefficient, because they have evolved over billions of years to carry vesicles in cells.

Instead, we hypothesized that:

Kinesin is <u>optimized inside living cells,</u> the environment that actually carries cargo.



What's the difference inside the cell?

[Ariga*, Tomishige, Mizuno, *Biophys. Rev.* **12**, 503-510 (2020)]
[有賀 *生物物理* (2019)]

Today's contents

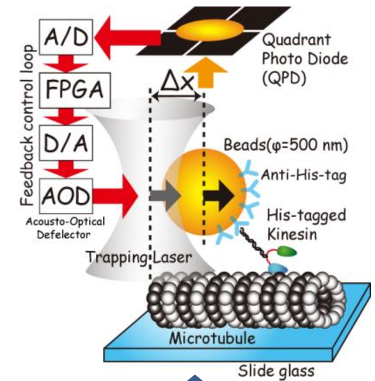
エネルギー効率の最適化(？)

① Optimization for energy efficiency (?)

I. Molecular motor: Kinesin 1

II. Nonequilibrium energetics of kinesin 1

[Ariga et al. *Phys. Rev. Lett.* **121**, 218101 (2018)]



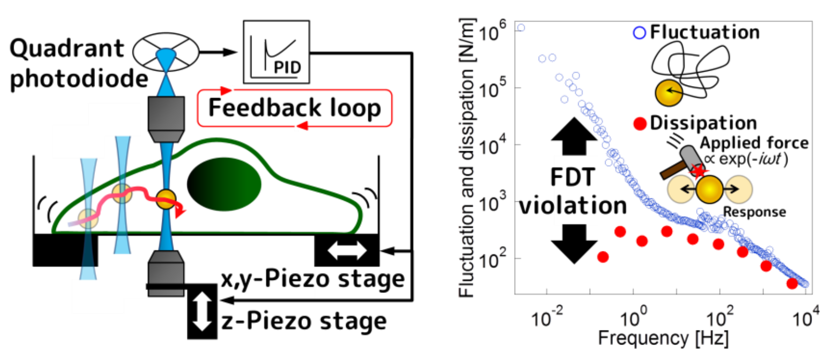
環境への最適化(？)

② Optimization for the environment (?)

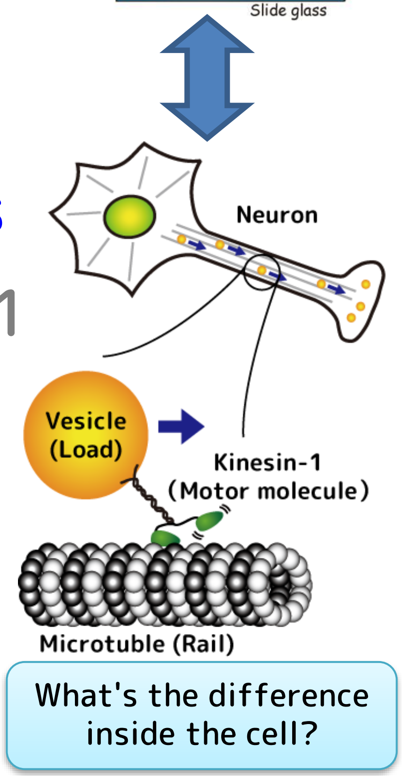
III. Nonthermal fluctuation in living cells

IV. Noise-induced acceleration of kinesin 1

[Ariga et al. *Phys. Rev. Lett.*, **127**, 178101 (2021)]



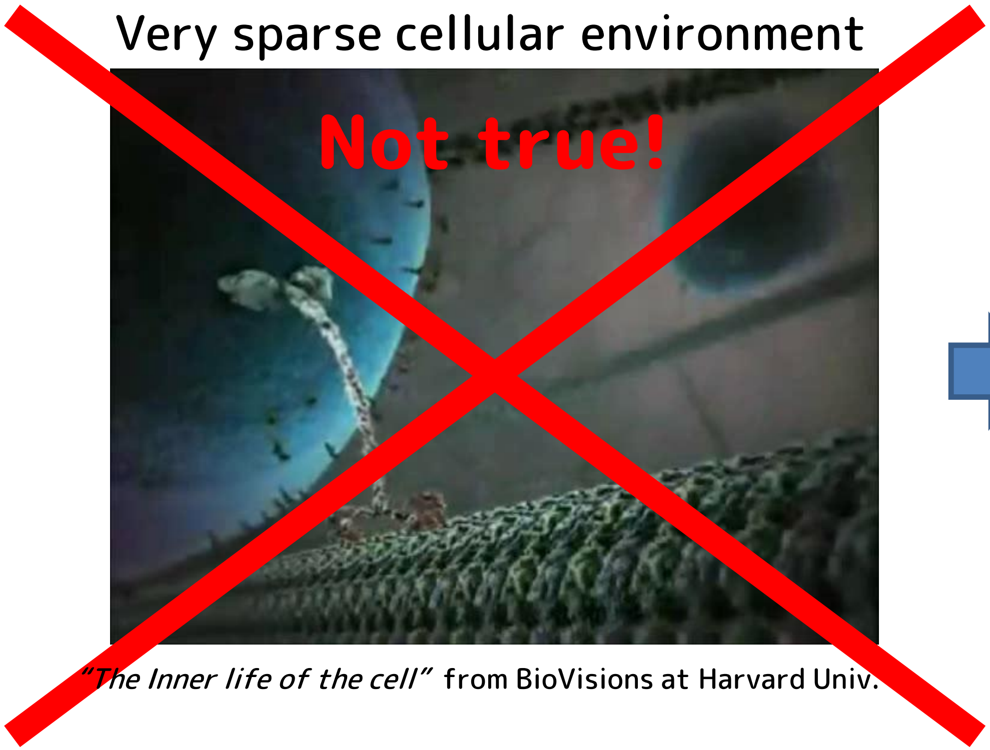
[Nishizawa, TA, et al. *Sci. Adv.* **3**, e1700318 (2017)]



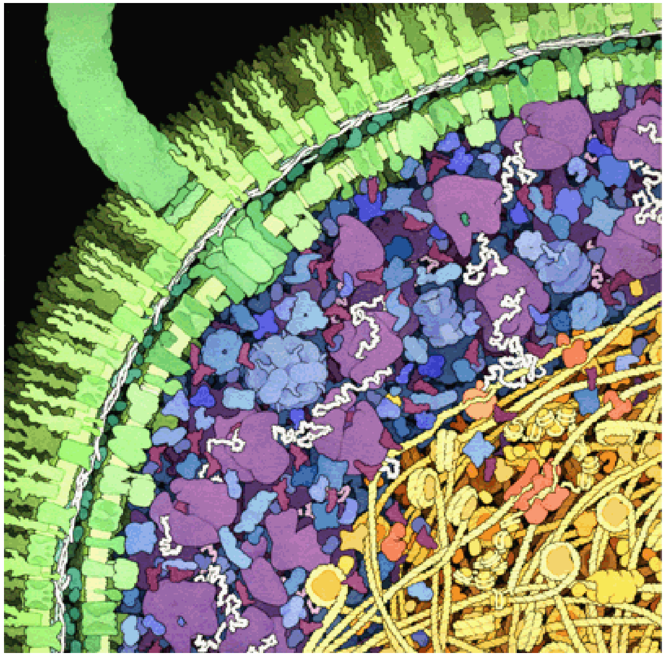
Q: There are two major mistakes. What’s wrong?

Answer 2: Cell is crowded

Very sparse cellular environment



“The Inner life of the cell” from BioVisions at Harvard Univ.



Escherichia coli

© David S. Goodsell 1999.

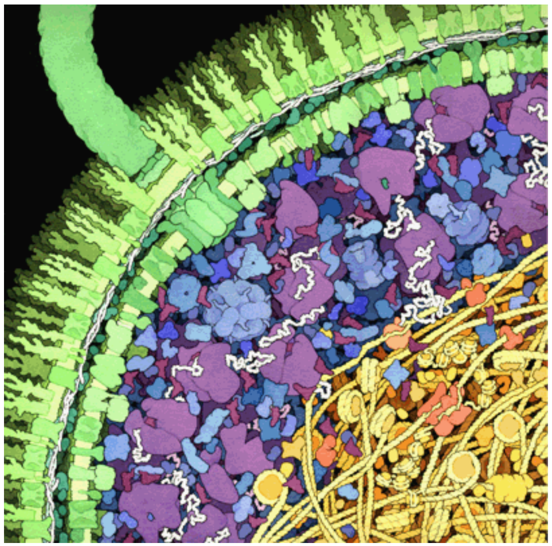
A: Intracellular environment is very crowded!!

How crowded?

どのくらい?

How much crowded in cells?

Intracellular environment filled with macromolecules

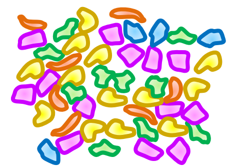


Escherichia coli

Concentrations ~ 0.3 g/ml

[Zimmerman *JMB* 1991]

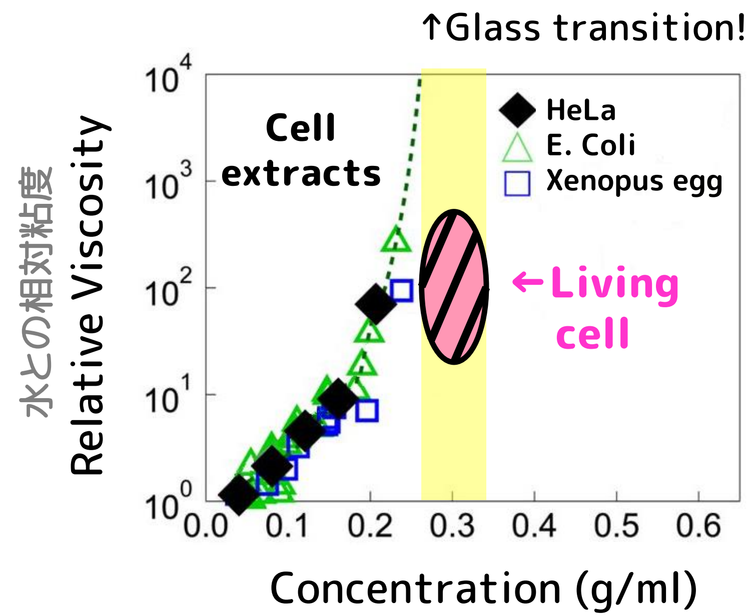
Cell extracts



Extract

K. Nishizawa
(Kyushu Univ.)
(IBDM, France)
@Mizuno-lab

Viscosity of the cell extracts



The viscosity goes to diverge

[Nishizawa *et al. Sci. Rep.* 2017]

Cell extracts at the cellular concentration is frozen, so that **the molecular motors *cannot* move in it!**

細胞内の分子は、分子モーターが動けないほどぎっしりと詰まっていた。

Active fluctuations *In living cell*

(Non-thermal)

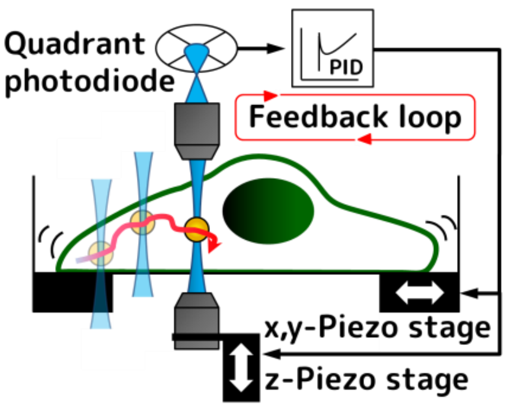
K. Nishizawa
(IBDM, France)

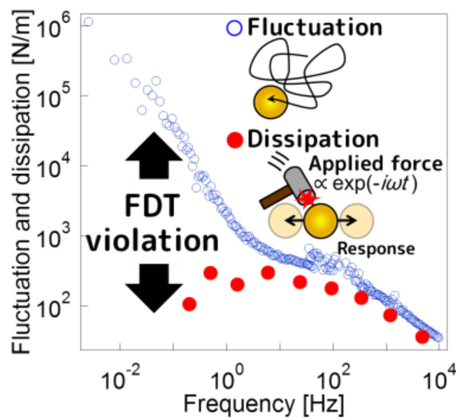
SCIENCE ADVANCES | RESEARCH ARTICLE

BIOMECHANICS

Feedback-tracking microrheology in living cells

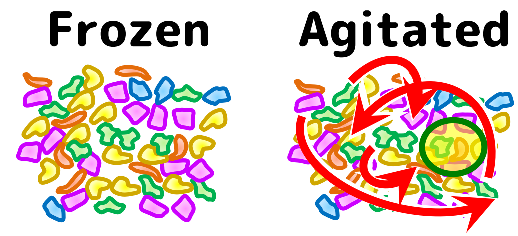
Kenji Nishizawa,[1]* Marcel Bremerich,[1]* Heev Ayade,[1] Christoph F. Schmidt,[2†] Takayuki Ariga,[1] Daisuke Mizuno[1‡]

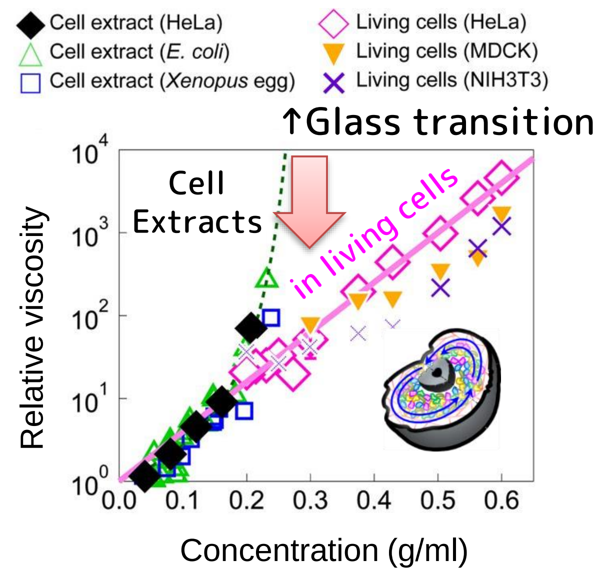




Fluctuation and responses of the cytoplasm in living cells were measured.

[Nishizawa,⋯, Ariga, Mizuno, *Sci. Adv.* **3**, e1700318 (2017)]





[Nishizawa *Sci. Rep.* **7**:15143 (2017)]

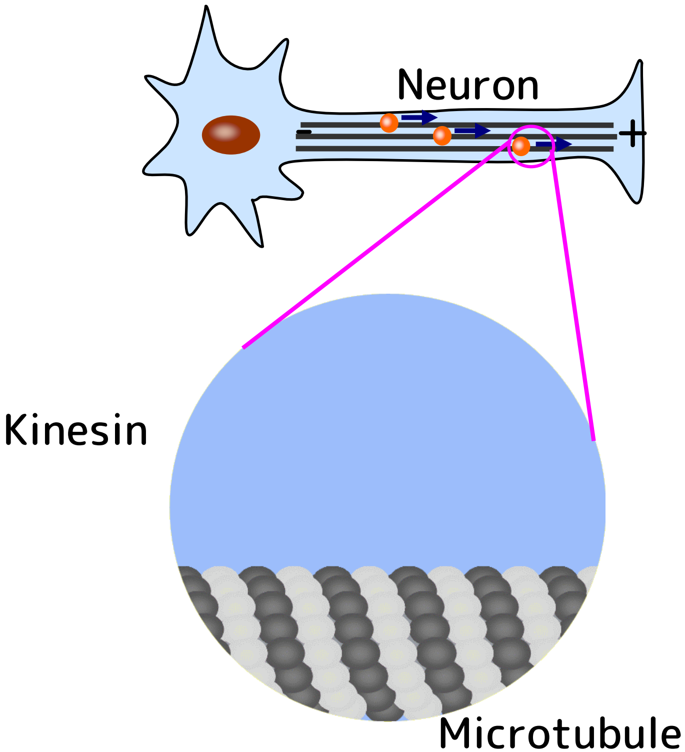
Actively (Non-thermally) fluctuated → Agitate → **Fluidize**

[Parry *Cell* 2014][Guo *Cell* 2014]

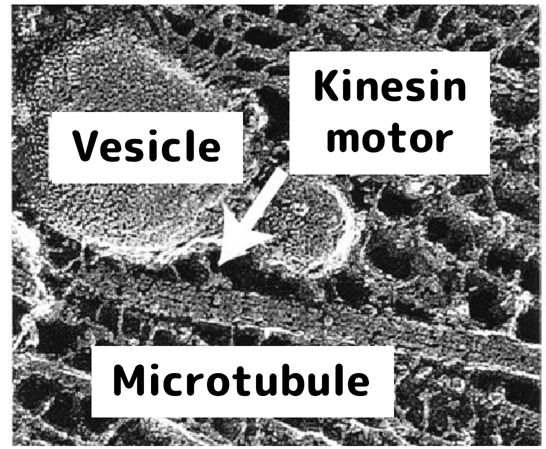
Violation of FDT: A new measure that quantifies the "***vitality of life***"

揺動散逸定理の破れ:「生き物の活きの良さ」を定量する新たな指標

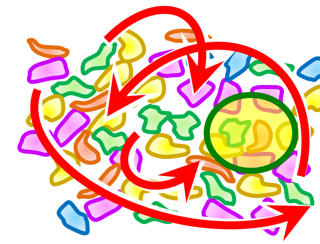
Cell: Active environment

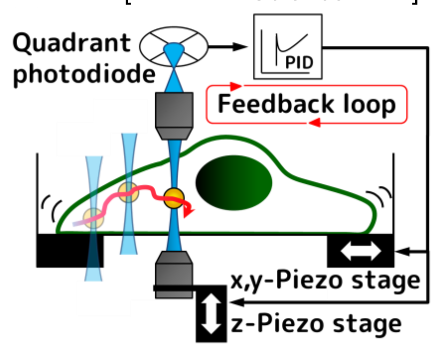


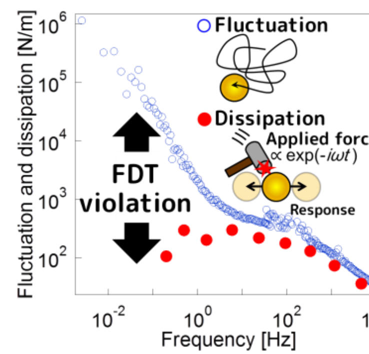
[Vale & Oosawa *Adv. Biophys.* **26**: 97 (1990)]
[Isojima *Nat. Chem. Biol.* **12**: 290 (2016)]
[有賀 物性研究 **96** 149 (2011)]



[Hirokawa *Science* 1998]







[Nishizawa,…, Ariga, Mizuno *Sci. Adv.* **3**: e1700318 (2017)]

Kinesin uses ***thermal*** fluctuations.

Cell has ***nonthermal*** active fluctuations.

Hypothesis: kinesin uses the active fluctuations *in cells*.

Confirm *in vitro*

[Ariga*, Tomishige, Mizuno, *Biophys. Rev.* **12**, 503-510 (2020)]

試験管内で確かめる

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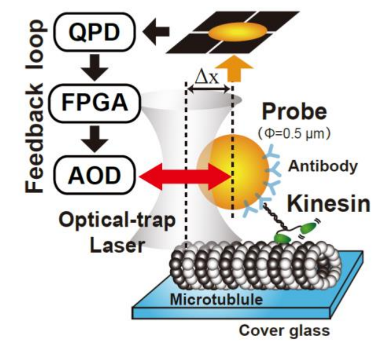
[Ariga et al. *Phys. Rev. Lett.* **121**, 218101 (2018)]



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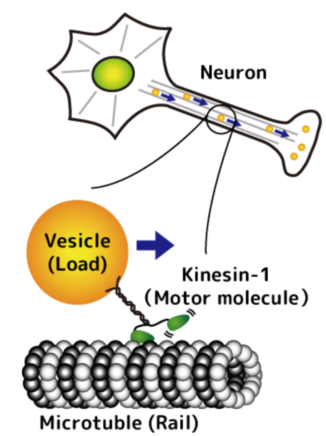
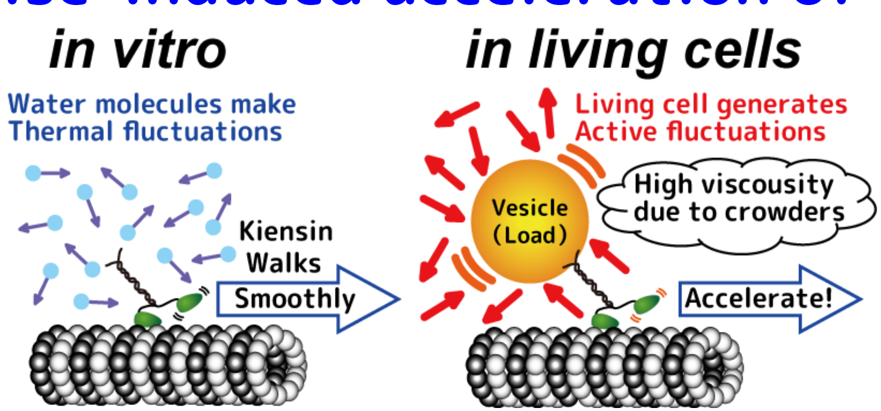




[Ariga et al. *Phys. Rev. Lett.*, **127**, 178101 (2021)]

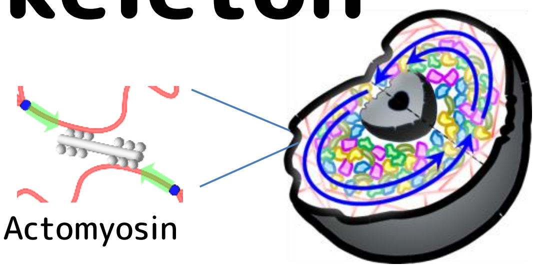
Confirm *in vitro*

試験管内で確かめる

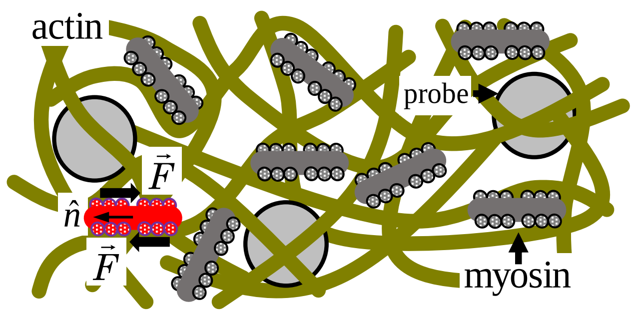
Nonthermal fluctuations generated by cytoskeleton

Active fluctuations *in* ***eukaryotic*** *cells* are mainly generated by the metabolic activity of actomyosin

[Guo et al. *Cell* 2014]



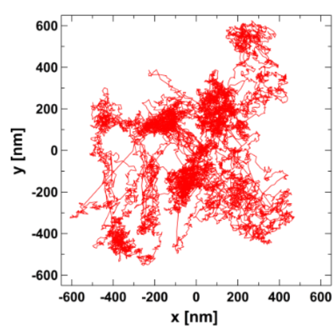
Artificial *in cell* environment



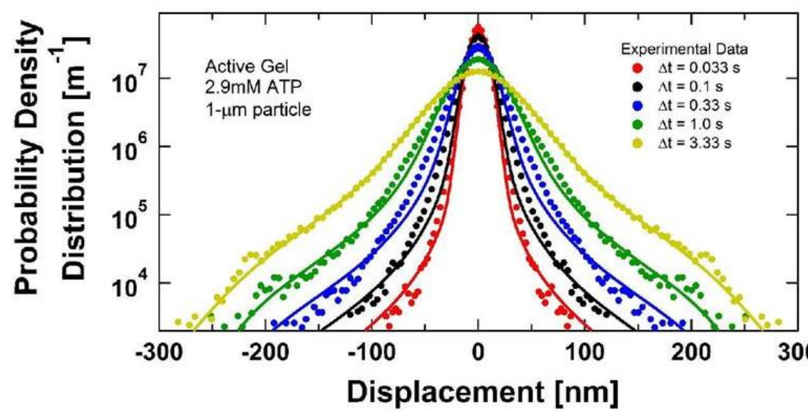
cytoskeletal network

H. Ayade
(Kyushu Univ.)
@Mizuno-lab

Probe's trajectory



Truncated Lévy distributions



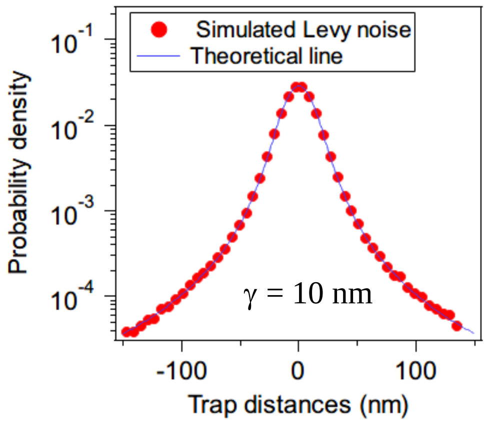
Displacement of the probe per time is proportional to the active fluctuating force

Cytoskeletal network generates non-Gaussian force fluctuations

[H. Ayade *unpublished*]

Mimicking intracellular environment *in vitro* experiments/simulation

Lévy stable distribution

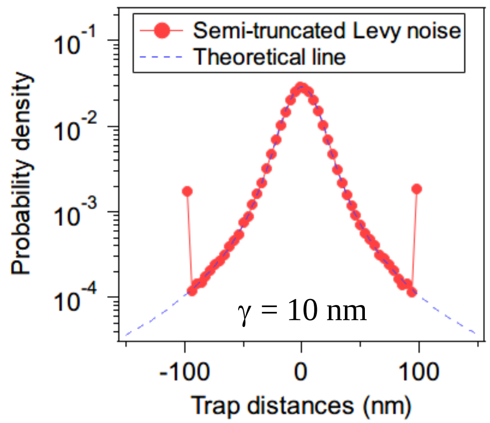


Non-Gaussian fluctuations are numerically generated

$$P(x) = \frac{1}{2\pi}\int_{-\infty}^{\infty} \phi(t) e^{-ixt} dt$$

$$\phi(t) = \exp\left[i\delta t - \gamma^{\alpha} |t|^{\alpha} \right]$$

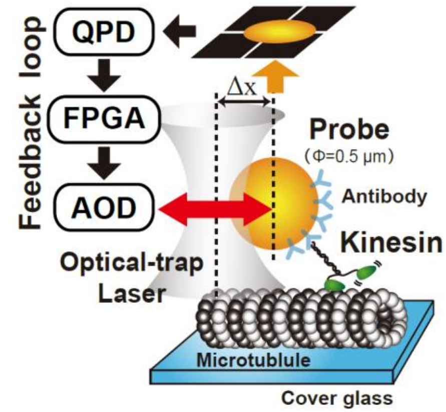
Semi-truncated Lévy noise



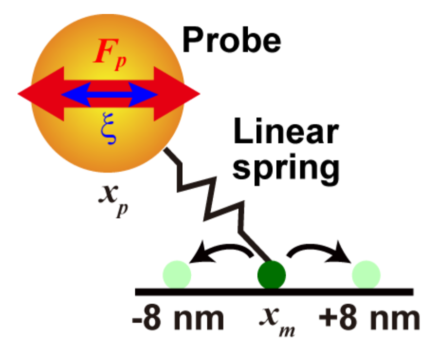
Truncated to the linear range of the optical tweezers (±100 nm)

α = 1.5 (characteristic exponent)
γ = 1 ~ 200 nm (scale parameter)
↑magnitude of noise.

Experimental setup



Mathematical model



$$F_p = F_0 + F_n$$

External force, loads, noise

Active non-Gaussian fluctuation is *artificially* generated and applied to a kinesin molecule as noisy external forces.

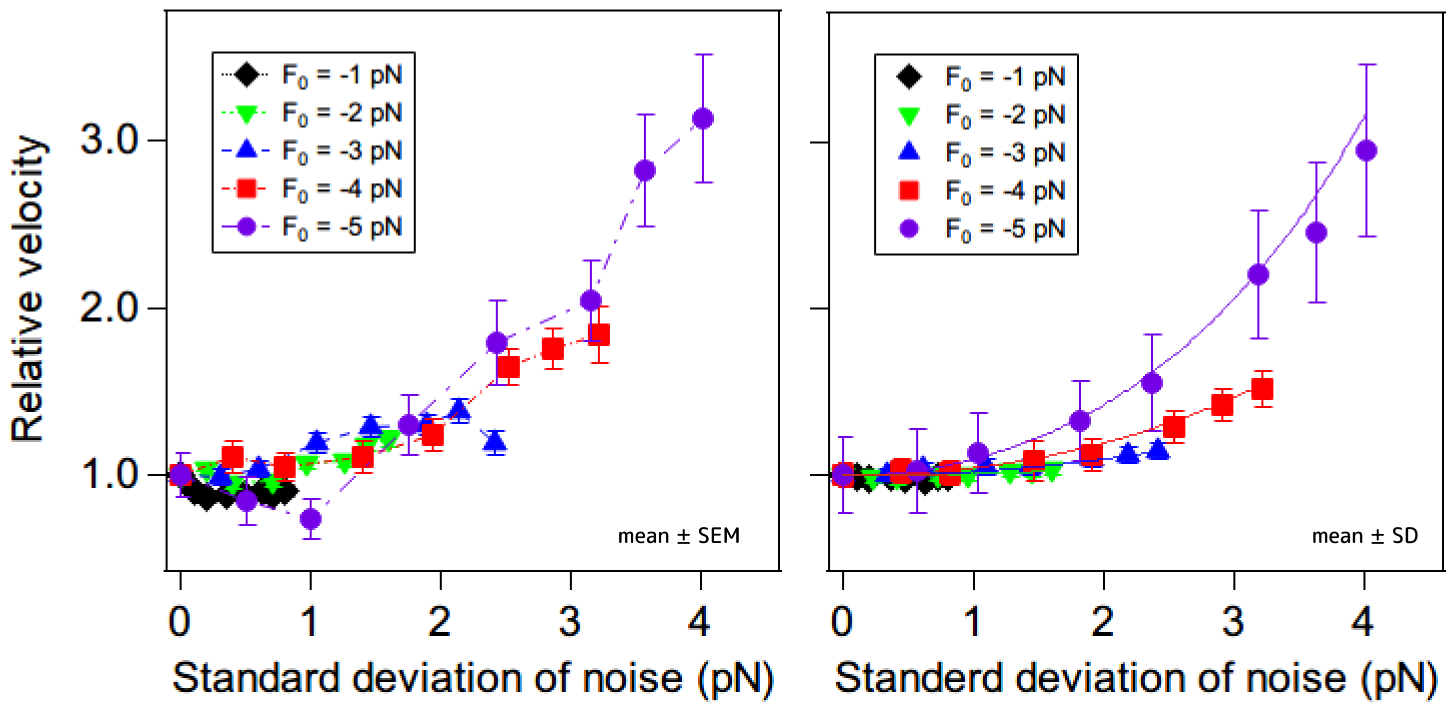
細胞内の非熱的なゆらぎを模倣した、人工的な外力ゆらぎをキネシンに加える

[T. Ariga, et al., *Phys. Rev. Lett.*, **127**, 178101 (2021)]

Active fluctuations

Noise-induced acceleration

Experimental results | **Model simulations**



※ Different markers indicate the average external force (loads) excluding fluctuations.

K. Tateishi
(Yamaguchi Univ.)

Kinesin *accelerates* under artificial fluctuations, especially at higher loads (constant forces) .

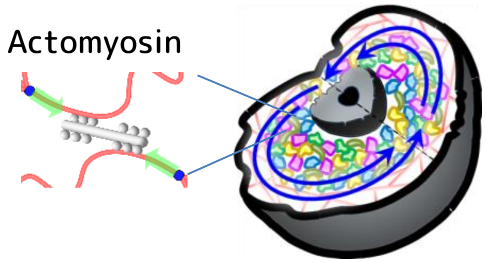
外力のゆらぎ(非熱ゆらぎ)によって(特に高負荷下で)キネシンが加速した!

[T. Ariga, K. Tateishi, M. Tomishige, D. Mizuno, *Phys. Rev. Lett.*, **127**, 178101 (2021)]

Editors' suggestion and *Featured in Physics*

Acceleration of kinesin under intracellular conditions

- Active fluctuations ***in eukaryotic cells*** are produced mainly by the metabolic activity of actomyosin. [Guo *Cell* 2014]
- Actomyosin can generate ***up to 30 pN*** of force. [Kaya *Nature comm.* 2017]

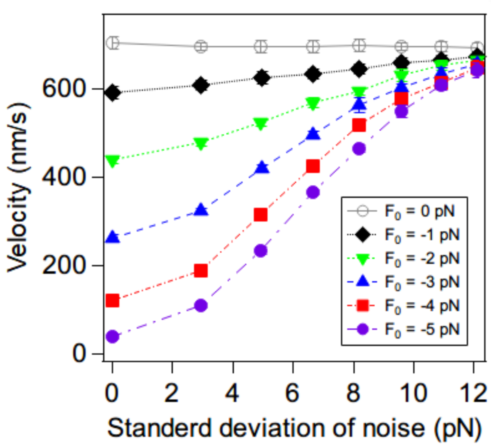


However, by using our measurement system,

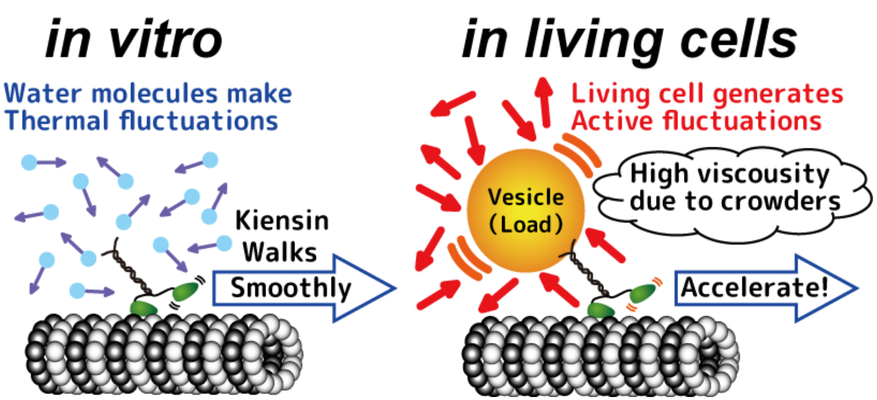
Large external force fluctuation can not be applied due to experimental constraints.

Mathematical models can do it!

Simulations



The high average load can be regarded as high viscous resistance in crowded cells.



Acceleration of Kinesin under physiologically plausible force fluctuations (up to ±30 pN)

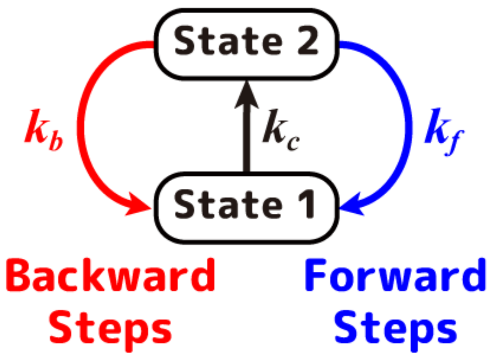
Kinesin can move smoothly even under intracellular high viscosity due to crowding.

[T. Ariga, K. Tateishi, M. Tomishige, D. Mizuno, *Phys. Rev. Lett.*, **127**, 178101 (2021)]

Editors' suggestion and *Featured in Physics*

Universality of the theory behind the kinesin model

Simplified kinetic model of kinesin



[Taniguchi *Nat. Cell Biol.* 2005]

Arrhenius-type force dependency

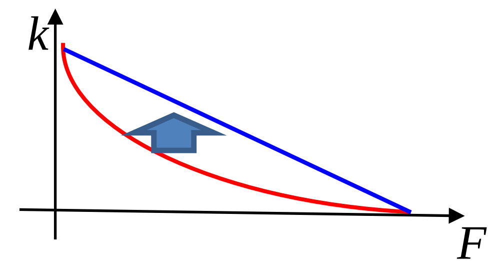
$$k_f = k_f^0 \exp\left(\frac{d_f F_m}{k_B T}\right)$$

$$k_b = k_b^0 \exp\left(\frac{d_b F_m}{k_B T}\right)$$

[Howard 2001]

Jensen's inequality

$$\langle k(F)\rangle \geq k(\langle F\rangle)$$



[Jensen *Acta Math.* 1906]

The noise-induced acceleration of kinesin can be explained by the Arrhenius-type rate constant and Jensen's inequality.

General enzymes in living cells undergo structural changes in their reactions and follow the same Arrhenius-type equation, suggesting that

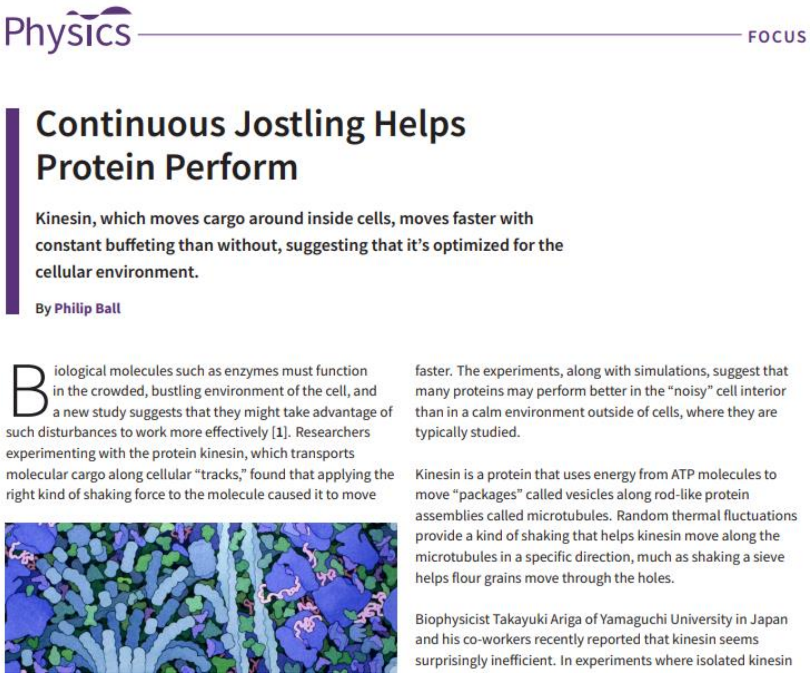
General enzymes can accelerate due to the intracellular fluctuations.

[T. Ariga, K. Tateishi, M. Tomishige, D. Mizuno, *Phys. Rev. Lett.*, **127**, 178101 (2021)]
Editors' suggestion and *Featured in Physics*

Biological Perspectives *in living cells*

Featured in Physics

News article in APS physics


Physics FOCUS

Continuous Jostling Helps Protein Perform

Kinesin, which moves cargo around inside cells, moves faster with constant buffeting than without, suggesting that it's optimized for the cellular environment.

By Philip Ball

Biological molecules such as enzymes must function in the crowded, bustling environment of the cell, and a new study suggests that they might take advantage of such disturbances to work more effectively [1]. Researchers experimenting with the protein kinesin, which transports molecular cargo along cellular "tracks," found that applying the right kind of shaking force to the molecule caused it to move faster. The experiments, along with simulations, suggest that many proteins may perform better in the "noisy" cell interior than in a calm environment outside of cells, where they are typically studied.

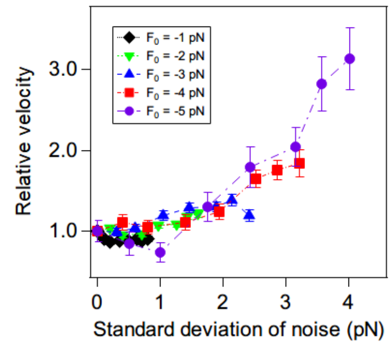
Kinesin is a protein that uses energy from ATP molecules to move "packages" called vesicles along rod-like protein assemblies called microtubules. Random thermal fluctuations provide a kind of shaking that helps kinesin move along the microtubules in a specific direction, much as shaking a sieve helps flour grains move through the holes.

Biophysicist Takayuki Ariga of Yamaguchi University in Japan and his co-workers recently reported that kinesin seems surprisingly inefficient. In experiments where isolated kinesin

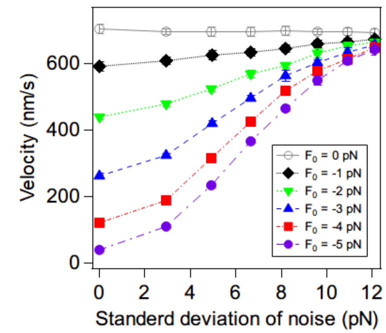
[P. Ball *Physics* **14**:149, 2021]

"*Ariga cautions that the relevance of the findings for biology* ***remains speculative***"

in vitro measurement

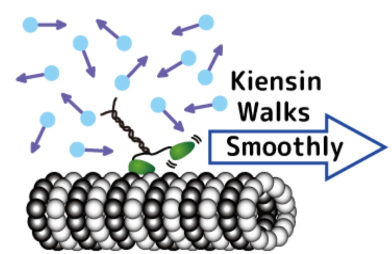


Theoretical prediction



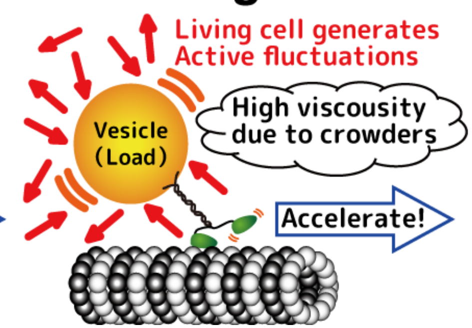
in vitro

Water molecules make Thermal fluctuations



in living cells

Living cell generates Active fluctuations



To clear whether nonthermal fluctuations in cells *actually* help protein perform,

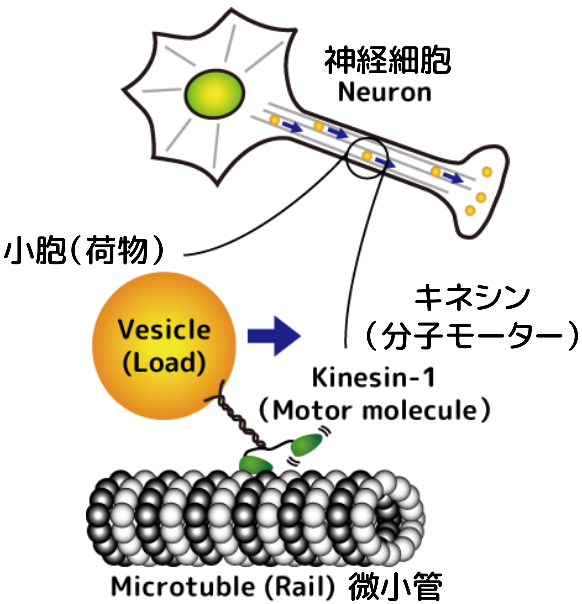
More direct evidence *in living cells* will be needed

What are kinesin optimizing?

Q:輸送する生体分子モーターは なにを最適化しているのか?

本日のまとめ

- ➢ キネシンは、あまり(化学)エネルギーを効率よく使っていないように見える。
  [Ariga et al. *Phys. Rev. Lett.* **121**, 218101 (2018)]
- ➢ 細胞の中は非常に混雑し、非熱的に激しくゆらぐ環境である。
  [Nishizawa, TA, et al. *Sci. Adv.* **3**, e1700318 (2017)]
- ➢ 生体分子モーターは非熱的なゆらぎも利用しつつ、荷物を輸送する(だろう)。
  [Ariga et al. *Phys. Rev. Lett.*, **127**, 178101 (2021)]



議論

- ✓ これ自体が、分子の運動により生み出されており、大量にエネルギーを消費している。
- ✓ キネシンもまた、非熱的なゆらぎの生成に関与するはずだが、その出力(=非平衡散逸)はとても小さい。
- ✓ 定常状態では輸送速度はあまり問題にならない。
- ✓ 一方、環境の変化(細胞分裂など)にはすばやく応答しなければならない。
- ✓ そもそも本当に、なにかを最適化しているのか?

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ご清聴ありがとうございました

Thank you for your attention.