Stochastic thermodynamics of biological systems

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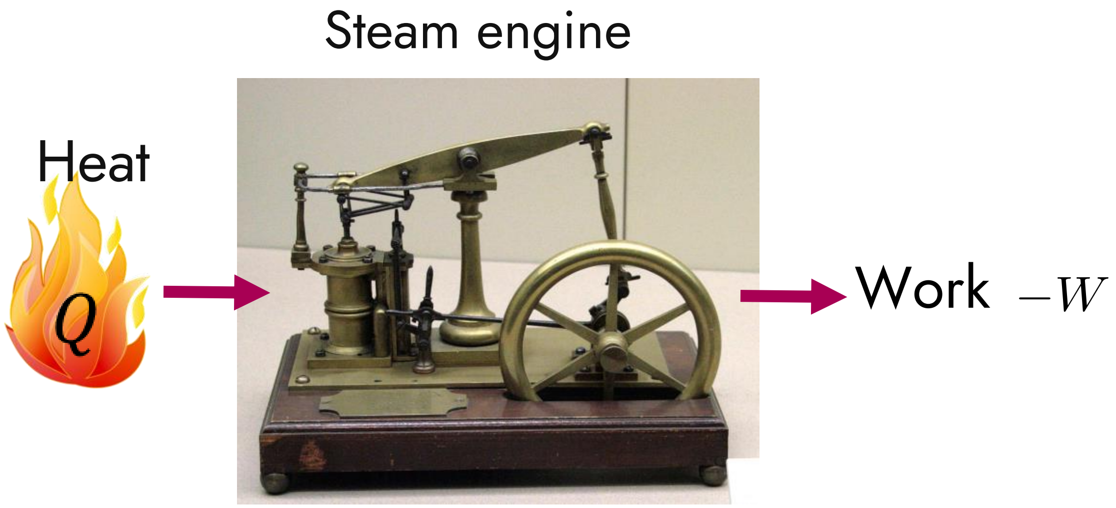
H.-T Han, J. S. Lee and J.-H. Jeon, Thermodynamic uncertainty relation for systems with active Ornstein-Uhlenbeck particles, PNAS nexus, (2025)

Classical thermodynamics

- Macroscopic $N \gg 10^{23}$
- Deterministic U, W, Q, S
- Equilibrium
- Laws

1) $\Delta U = W + Q$

2) $\Delta S \geq 0$

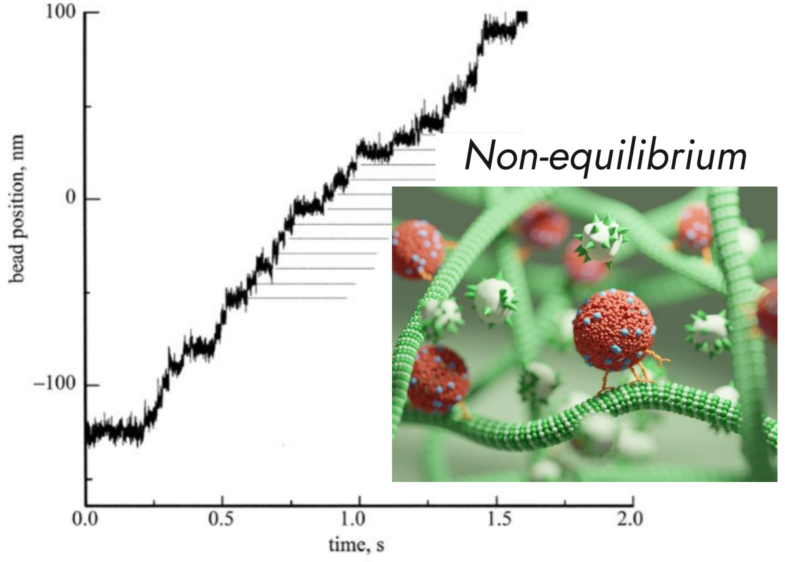


U. Seifert *Rep. Prog. Phys.* (2012)

Non-equilibrium thermodynamics

- Over the last 30 years, new approaches push the boundary into the non-equilibrium region
- Entropy s , heat q , work w , and energy u are defined from single trajectory

Kinesin



Novel discoveries

- **Fluctuation theorem** $\frac{P(-\Delta s)}{P(+\Delta s)} = e^{-\Delta s/k_\mathrm{B}}$

  D. Evans *et al.*, *PRL* (1993)

Entropy s
Heat q
Work w
Energy u

$$\langle e^{-\Delta s/k_\mathrm{B}} \rangle = \int e^{-\Delta s/k_\mathrm{B}} P(+\Delta s) d\Delta s = \int P(-\Delta s) d\Delta s = 1$$

$$\langle -\Delta s/k_\mathrm{B} \rangle \leq \log[\langle e^{-\Delta s/k_\mathrm{B}} \rangle] = 0$$

Jensen's inequality

$$\Rightarrow \Delta s \geq 0$$

***Beyond** thermodynamic second law*

Stochastic thermodynamics

U. Seifert, *PRL* (2005)
U. Seifert, *Eur. Phys. J. B* (2008)

1. The x is *observable slow and Markovian* degree of freedom
2. The *thermal bath* consist of *unobservable fast* degree of freedom
3. The system entropy is defined as $s_{\mathrm{sys}} = -k_{\mathrm{B}} \ln p(x)$

Langevin equation

$$\gamma \dot{x} = F(x) + \xi(t)$$

Friction coefficient γ | External force F | Thermal noise ξ

→Principle laws of stochastic thermodynamics

$$\langle \Delta u \rangle = \langle w \rangle + \langle q \rangle$$

$$\langle e^{-\Delta s / k_{\mathrm{B}}} \rangle = 1$$

Thermodynamic uncertainty relation (TUR)

cf. $\Delta s \geq 0$

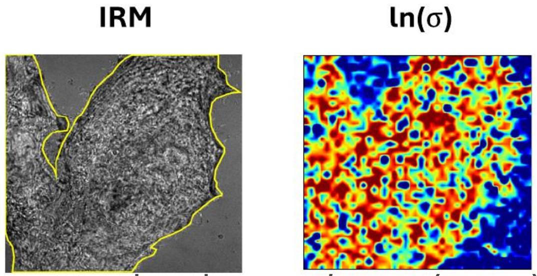
$$1 \leq \frac{\mathrm{Var}^{\mathrm{ss}}[\Theta(t)]}{[\langle\Theta(t)\rangle^{\mathrm{ss}}]^2} \frac{\langle\Delta s(t)\rangle^{\mathrm{ss}}}{2k_{\mathrm{B}}}$$

~ uncertainty ~ energy

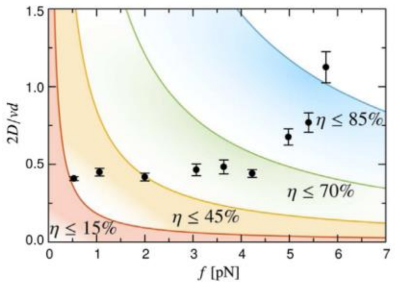
$$\Theta(t) = \int_0^t \boldsymbol{\Lambda}(\boldsymbol{x})^{\mathsf{T}} \circ \dot{\boldsymbol{x}}(t')\, dt'$$

A. Barato, *et al.*, *PRL* (2015)

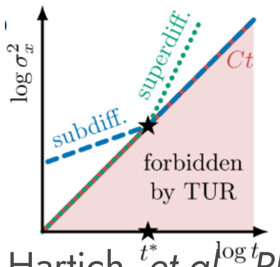
- Lower bound of entropy production
- Inference of the efficiency of motor proteins
- Limit the extent of anomalous diffusion



S. Manikandan *et al*, *PRR* (2024)



U. Seifert, *Phys. A* (2018)



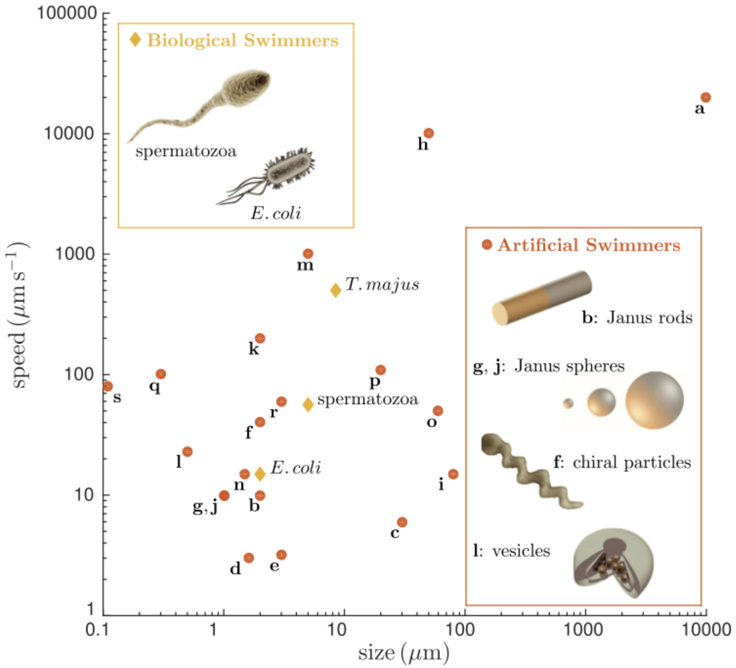
D. Hartich, *et al.*, *PRL* (2021)

Beyond the Markovian systems

- The TUR is validated in
  - Overdamped Langevin dynamics — Y. Hasegawa *et al*, *PRE* (2019)
  - Underdamped Langevin dynamics — J. Lee *et al.*, *PRE* (2021)
  - Countinous time Markov jump process — T. Gingrich *et al.*, *PRL* (2016)
  - Descrete time Markov jump process — K. Proesmans *et al.*, *EPL* (2017)

Non-Markovian biological systems

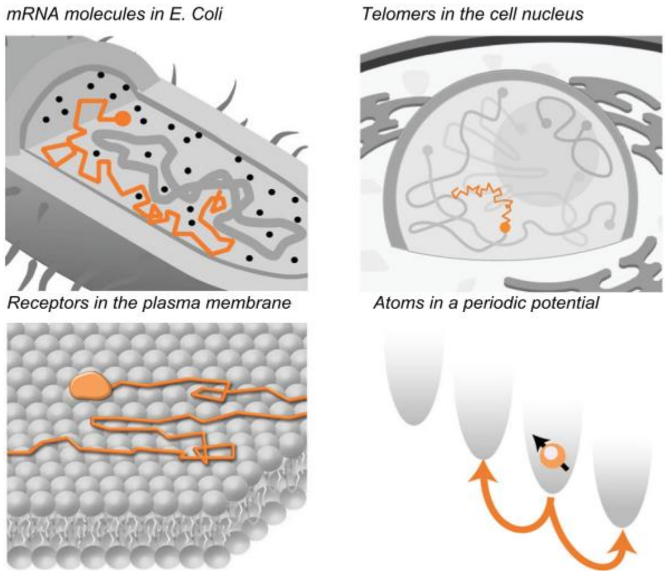
- Bio-activeness



B. Clemens *et al.*, *Rev. Mod. Phys.* (2016)

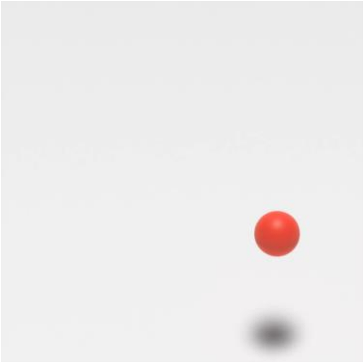
- Memory effect

(aging, non-ergodicity)



G. Muñoz-Gil *et al.*, *Nat. Commun.* (2021)

Active OU particle (AOUP)



Systems with **active** OU particle

- Non-equilibrium active systems

$$\gamma \dot{x}_i(t) = f_i^{\text{ex}}(\boldsymbol{x}, \boldsymbol{\eta}, t) - \nabla_{x_i} U^{\text{int}} + \eta_i(t) + \xi_i(t)$$
$$\tau_A \dot{\eta}_i(t) = -\eta_i + \zeta_i(t)$$

$\xi_i(t)$: thermal noise

$\eta_i(t)$: active Ornstein-Uhlenbeck noise

v_p Self-propulsion velocity

τ_A Directional correlation time

$$\langle \eta_i(t) \eta_j(t') \rangle = \gamma^2 \delta_{ij} {v_p}^2 e^{-|t-t'|/\tau_A}$$

B. Clemens *et al.*, *Rev. Mod. Phys.* (2016)

Derivation of modified TUR

- TUR can be driven from the *Cramér-Rao inequality*: Y. Hasegawa *et al.*, *PRE* (2019)

How much does the mean of observable change under **perturbation**

$$\gamma \dot{x}_i(t_\theta) = -\nabla_{x_k} U^{\mathrm{int}}(x) + f_i^{\mathrm{ex}} + (1-\alpha)\eta_i + h_\theta \alpha \eta_i + \xi_i(t_\theta)$$

$$\tau_A \dot{\eta}_i(t_\theta) = -\eta_i(t_\theta) + \zeta(t_\theta)$$

$$h_\theta = h/(1+\theta)$$

$$t_\theta = (1+\theta)t$$

$$\frac{\mathrm{Var}[\Delta\Theta(t)]}{\langle \Delta\Theta(t)\rangle^2}\left[\langle \Delta s_{\mathrm{sys}}\rangle + \frac{\langle \Delta q\rangle}{T} + \frac{\langle \Delta q_\eta(\alpha)\rangle}{T}\right] \geq 2k_B$$

Conventional *Modified*

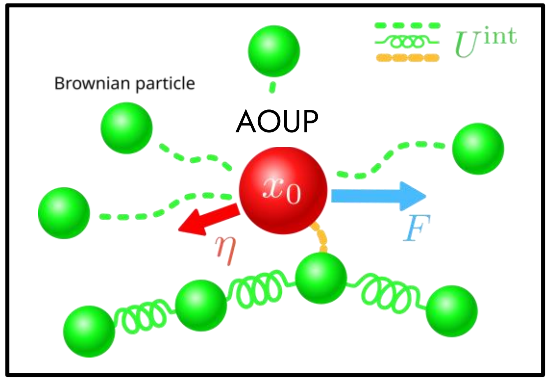
$$\langle \Delta q\rangle = -\Delta U^{\mathrm{int}} + \sum_i \int_0^t \langle f_i^{\mathrm{ex}} \circ \dot{x}_i\rangle dt$$

$$\langle \Delta q_\eta(\alpha)\rangle = \sum_i \int_0^t \frac{(1-2\alpha)\langle \eta_i \circ \dot{x}_i\rangle}{T} + \frac{\alpha^2 \langle \eta_i(t)^2\rangle}{T\gamma} dt$$

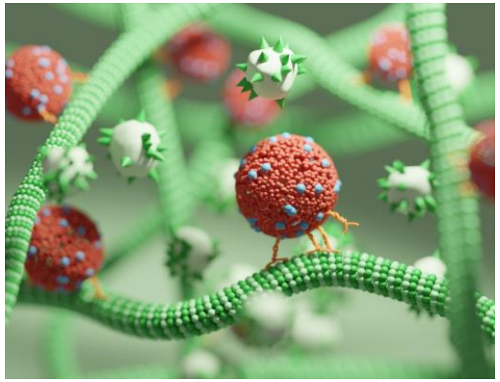
Application to the bound on MSD

- Non-equilibrium active systems like kinesin

$$\gamma \dot{x}_0(t) = -\nabla_{x_0} U^{\text{int}}(x) + \eta(t) + F + \xi_0(t)$$



Kinesin

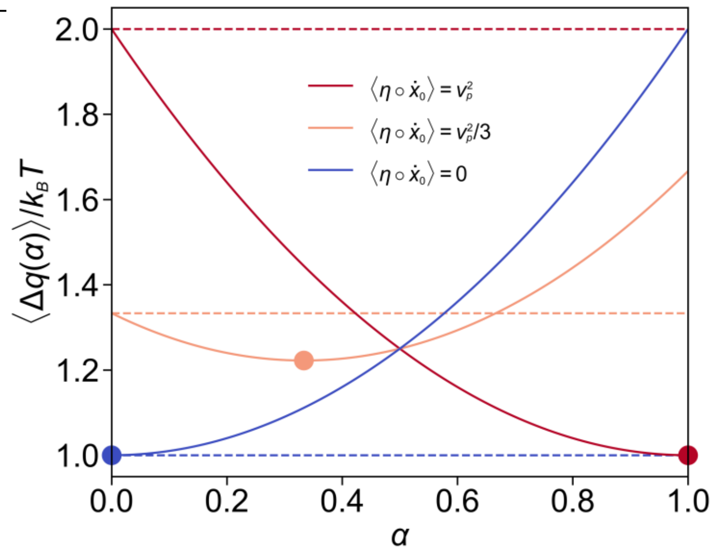


$$\frac{\text{Var}[\Delta x_0(t)]}{\langle \Delta x_0(t) \rangle^2} \left[\langle \Delta s_{\text{sys}} \rangle + \frac{\langle \Delta q \rangle}{T} + \frac{\langle \Delta q_\eta(\alpha) \rangle}{T} \right] \geq 2k_B$$

Optimized TUR bound

- We can optimize the TUR bound by taking optimized parameter α^* in the absence of in priori information of α values

$$\alpha^* = \frac{\langle \eta \circ \dot{x}_0 \rangle}{\gamma {v_p}^2}$$



$$\frac{\mathrm{Var}[\Delta x_0(t)]}{\langle \Delta x_0(t) \rangle^2} \left[\langle \Delta s_{\mathrm{sys}} \rangle + \frac{\langle \Delta q \rangle}{T} + \frac{\langle \Delta q_\eta(\alpha^*) \rangle}{T} \right] \geq 2k_B$$

independent of α

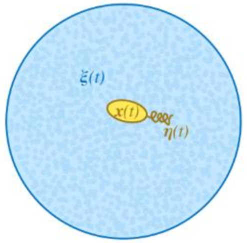
Physical interpretation of α

- The modified entropy is a heat dissipated by the active noise η with generalized parity α under time reversal symmetry (TRS)

$$\Delta q_\eta(\alpha) = [-\nabla_{x_0} U^{\mathrm{int}} + F + (1-\alpha)\eta] \circ [\dot{x}_0 - \alpha\eta/\gamma] - \Delta q$$

  - $q_\eta(\alpha = 0)$: heat dissipated with even parity under TRS

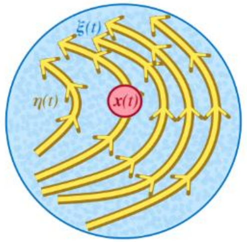
    e.g. Self-propelling particle



  - $q_\eta(\alpha = 1)$: heat dissipated with odd parity under TRS

    e.g. Active bath

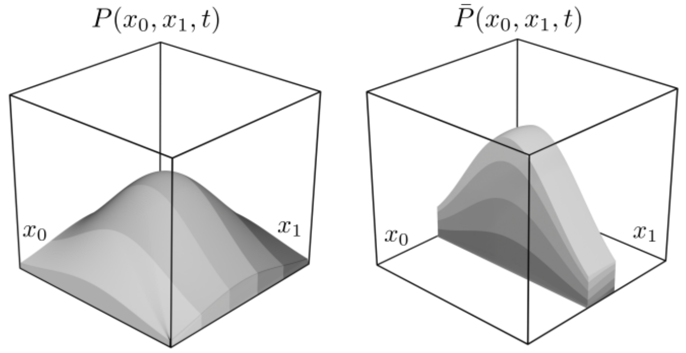
    L. Dabelow *et al.*, *PRX* (2019)



Mapping to a steady-state system

- Contracted PDF $\overline{P}$

$$\overline{P}(x_0, x_{\pm 1}, \cdots, x_{\pm M}, \eta, t) \equiv \sum_{n=-\infty}^{\infty} P(x_0 + nL, x_{\pm 1} + nL, \cdots, x_{\pm M} + nL, \eta, t)$$



▶ Contracted PDF will converge to the steady-state

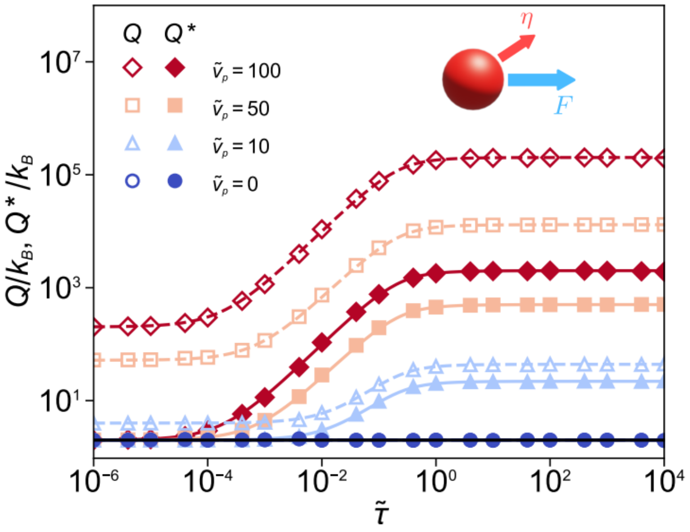
▶ Observable is equivalent with that of free-space by the translational symmetry

$$\frac{\mathrm{Var}[\Delta x_0(t)]}{\langle \Delta x_0(t) \rangle^2} \left[\frac{\langle \Delta q \rangle}{T} + \frac{\langle \Delta q_\eta(\alpha^*) \rangle}{T} \right] \geq 2k_B$$

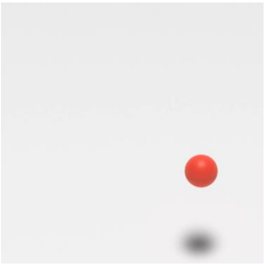
$$\int_0^t \langle \dot{x}(t') \rangle_{\bar{P}} dt = \int_0^t \langle \dot{x}(t') \rangle_P dt'$$

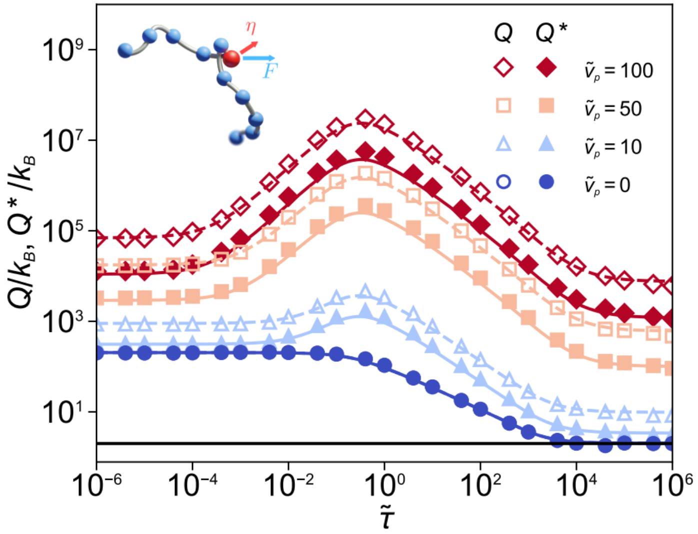
Simulation results

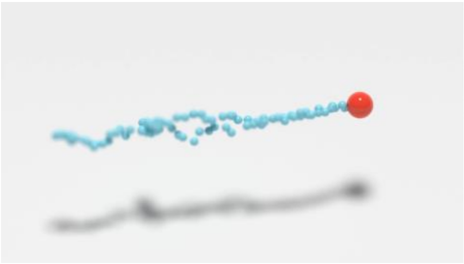
- The tight bound is reproduced in the absence of active noise, but we get a loose bound in the present of active noise



$$\tilde{v}_p \equiv \frac{\gamma v_p}{D}$$

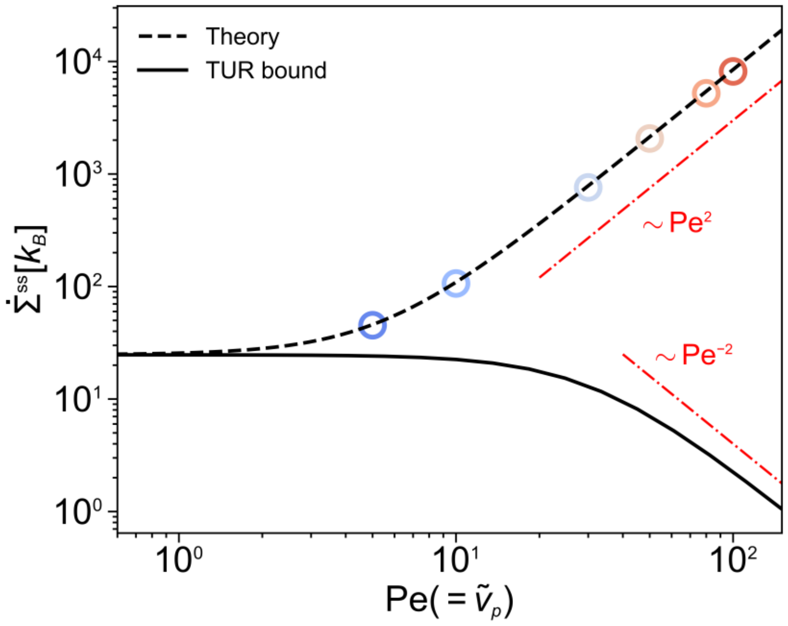






Simulation results

- Strong activity breaks down the energy-precision trade-off



$$\mathrm{Pe} \equiv \frac{\text{advective rate}}{\text{diffusive rate}} = \frac{\gamma v_p}{D}$$

Active-TUR



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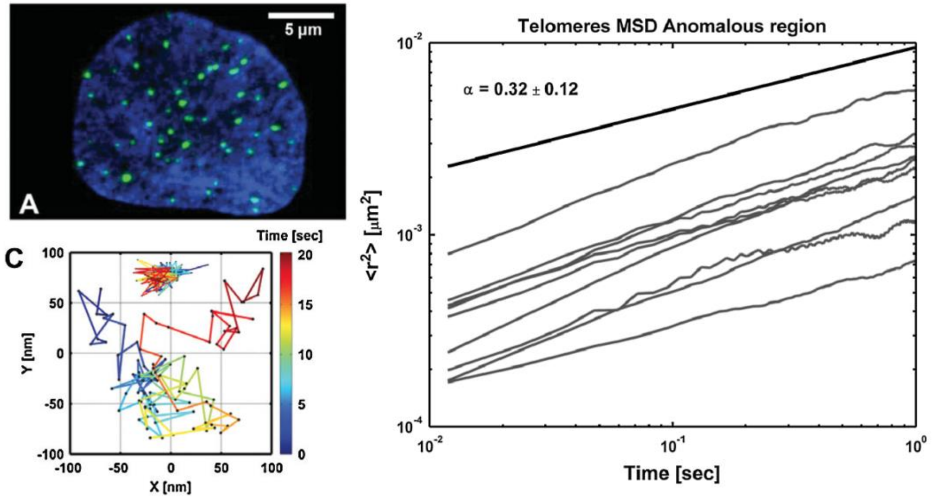
- We established the **TUR** for the active system where the **thermal and active noises are present**.
- We can interpret entropy as a **generalization** of two **heat contributions**, each corresponding to a component with either **even or odd parity**.
- We demonstrate that the **system entropy** can be **disregarded** in the case of free space diffusion with the **translational symmetry**.
- We also **simulated** various active systems to test our TUR.
- We found that in the **presence of active noise** the TUR **does not give a tight bound** for the anomalous diffusion.

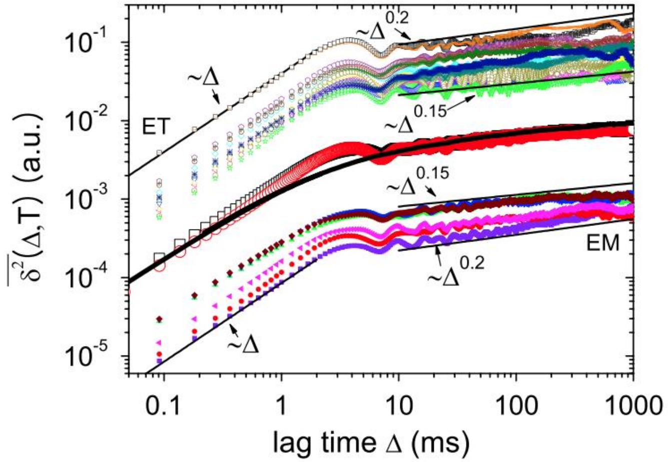
H.-T Han, J. S. Lee and J.-H. Jeon, Thermodynamic uncertainty relation for systems with active Ornstein-Uhlenbeck particles, arXiv

Memory effect and aging

- DNA and Chromatin Dynamics
- Intracellular Transport

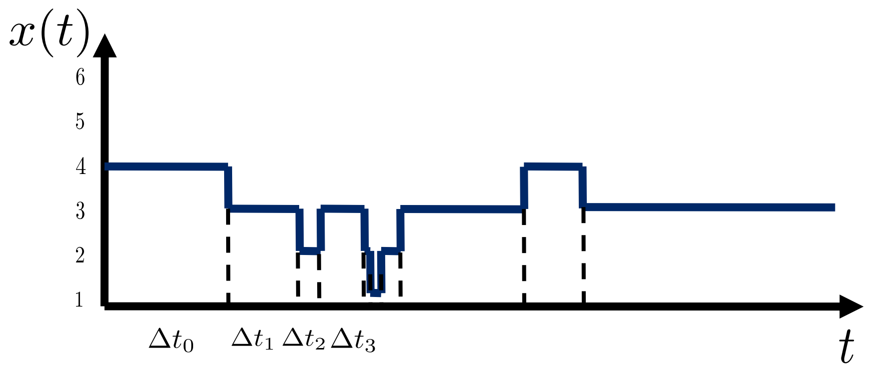


I. Bronstein *et al.*, *PRL* (2009)



J.-H. Jeon *et al.*, *PRL* (2011)

Trap model

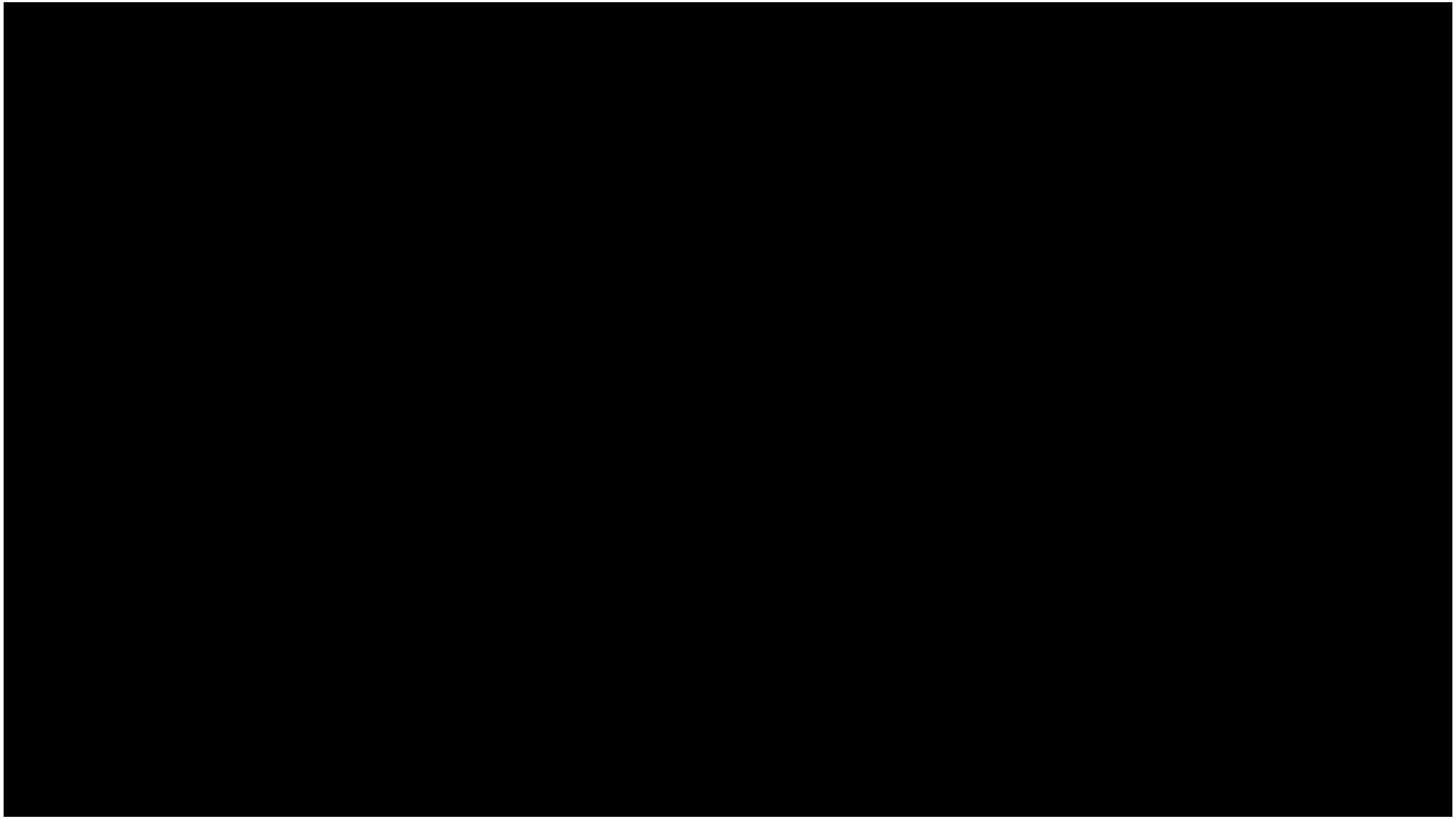


- The long-tail trap time $\Delta\, t_i$ captures the memory effect in complex systems

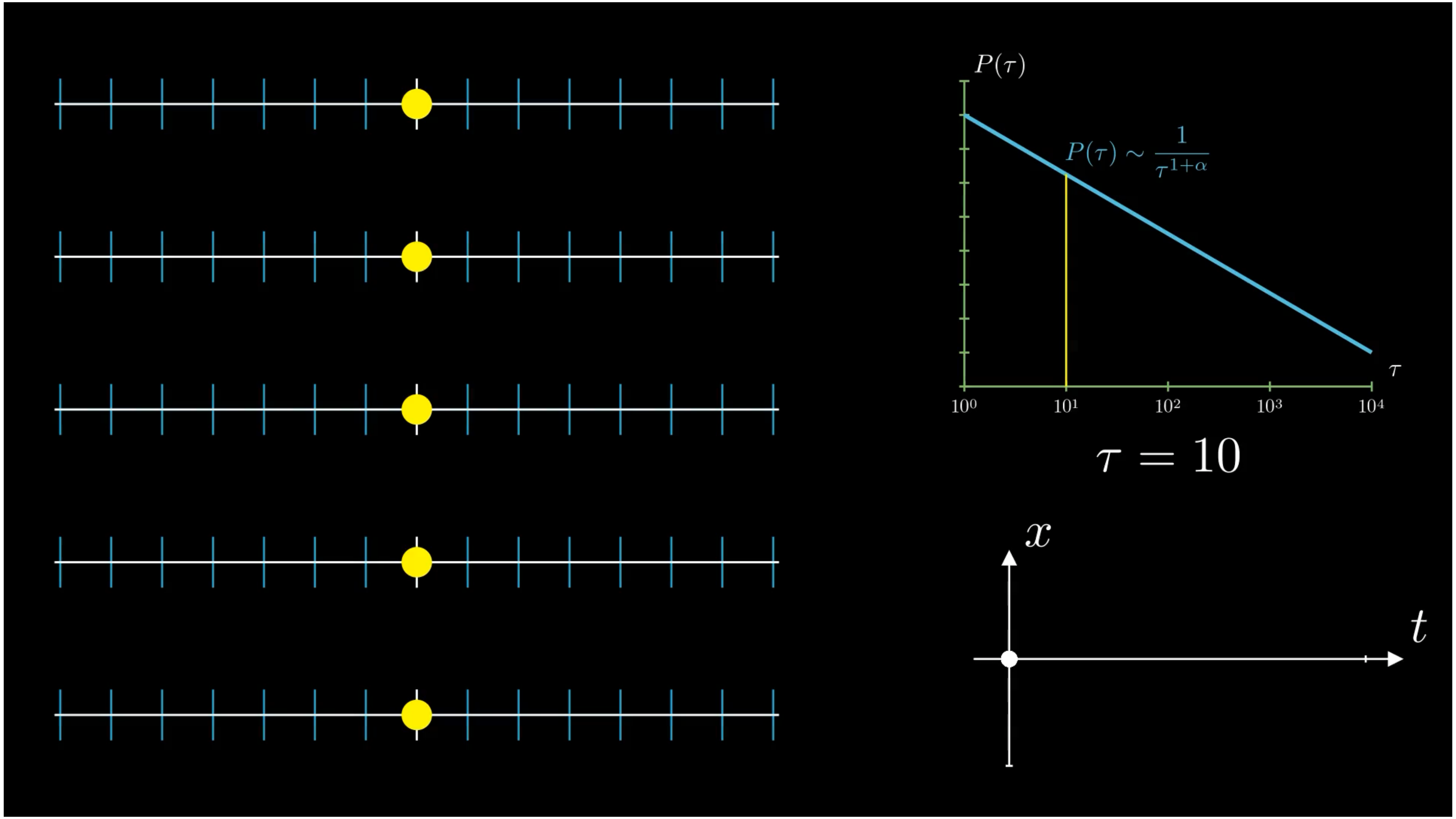
I. Sokolov, *Soft Matter* (2012)

- Non-Markov process
- Non-ergodicity
- Memory effect
- Aging effect

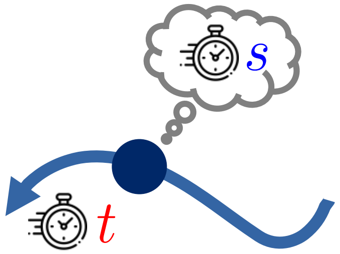
Continuous Time Random Walk (CTRW)



Quenched Trap Model (QTM)



Subordinated process



- A stochastic process governed by a stochastic time (subordinator)

$$x(t) = x(s(t))$$

- The probability density function is represented as weighted sum of pdfs

$$p(x|t) = \int_0^\infty f(x|s,t)g(s|t)ds$$

Law of total probability

$$= \int_0^\infty f(x|s)g(s|t)ds$$

Independence of x and t
(time t-homogeneous process)

Derivation of TUR for the subordinated process

$$\int \cdots g(s|t)ds \qquad \boxed{|\langle \Theta(s)\rangle_f^{\mathrm{ss}}| \le \frac{1}{\sqrt{2k_{\mathrm{B}}}}\sqrt{\mathrm{Var}_f^{\mathrm{ss}}[\Theta(s)]}\sqrt{\langle \Delta s(s)\rangle_f^{\mathrm{ss}}}}$$

$f(x|s)$: Pdf of Brownian particle after time s

$\geq$ Triangle inequality

$\leq$ Cauchy-Schwarz inequality

$$\left|\int \langle \Theta(s)\rangle_f^{\mathrm{ss}} g(s|t)ds\right| = \left|\langle \Theta(t)\rangle_p^{\mathrm{ss}}\right|$$

$$\frac{1}{\sqrt{2k_B}}\sqrt{\int \mathrm{Var}_f^{\mathrm{ss}}[\Theta](s)g(s|t)ds}\sqrt{\int \langle \Delta s(s)\rangle_f^{\mathrm{ss}} g(s|t)ds}$$

$\leq$ Concavity of variance

$$\frac{1}{\sqrt{2k_B}}\sqrt{\mathrm{Var}_p^{\mathrm{ss}}[\Theta](t)}\sqrt{\langle \Delta s(t)\rangle_p^{\mathrm{ss}}}$$

TUR for the subordinated process:

$$\boxed{1 \le \frac{\mathrm{Var}_p^{\mathrm{ss}}[\Theta(t)]}{[\langle \Theta(t)\rangle_p^{\mathrm{ss}}]^2}\frac{\langle \Delta s(t)\rangle_p^{\mathrm{ss}}}{2k_{\mathrm{B}}} \equiv Q}$$

$$\Delta s(t) = \frac{1}{T}[V(\boldsymbol{x}(t)) - V(\boldsymbol{x}(0))]$$

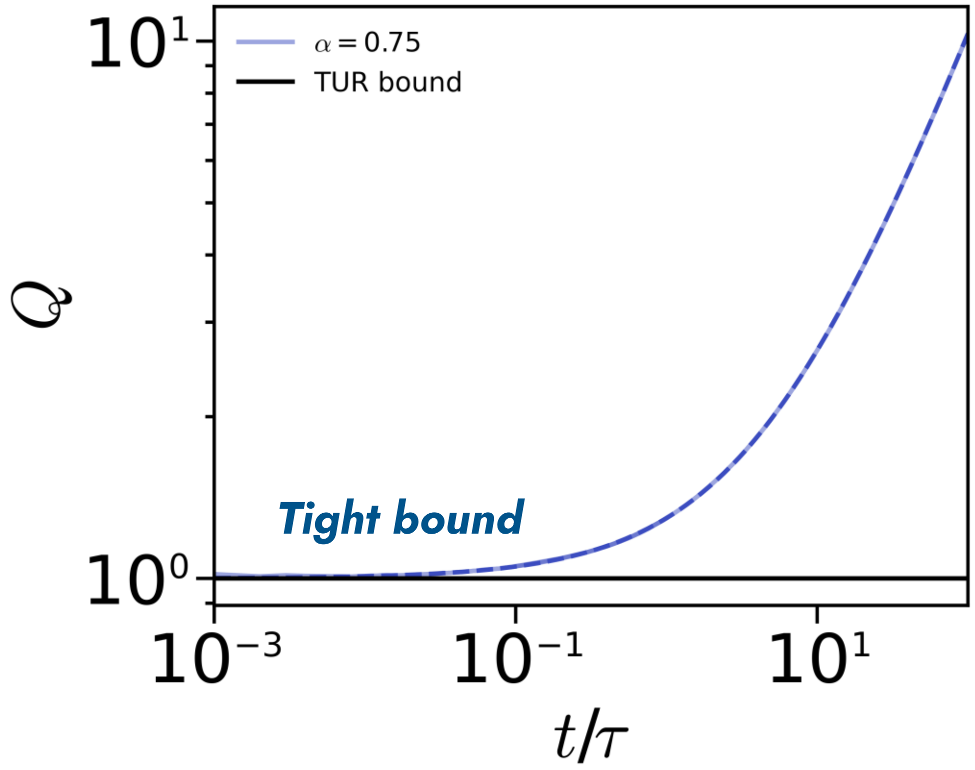
Example 1) Biased Continuous Time Random Walk

- TUR validated through simulations

$$\boldsymbol{\Lambda} = 1 \quad 1 \leq \frac{\mathsf{Var}_p^{\mathsf{ss}}[\Delta \boldsymbol{x}(t)]}{[\langle \Delta \boldsymbol{x}(t) \rangle_p^{\mathsf{ss}}]^2} \frac{\langle \Delta s(t) \rangle_p^{\mathsf{ss}}}{2k_{\mathrm{B}}} \equiv Q$$

- TUR provides a **tight bound in the short-time limit**

Force-induced dispersion



Generalized Einstein relation

Aging effects on TUR bound

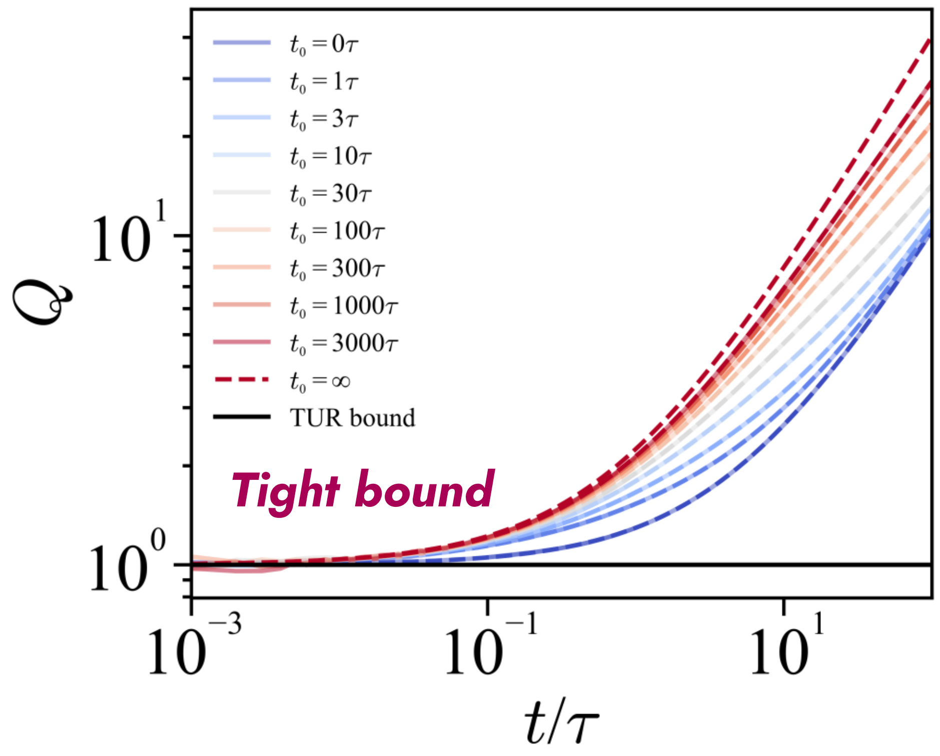
- PDF with aging time also follows subordination

$$p(x|t,t_a) = \int_0^\infty f(x|s)g(s|t,t_a)\,ds$$

E. Barkai *et al.*, *J. Chem. Phys.* (2003)

$$1 \le \frac{\mathrm{Var}_p^{\mathrm{ss}}[\Delta \boldsymbol{x}(t,t_a)]}{[\langle \Delta \boldsymbol{x}(t,t_a)\rangle_p^{\mathrm{ss}}]^2}\,\frac{\langle \Delta s(t,t_a)\rangle_p^{\mathrm{ss}}}{2k_{\mathrm{B}}} \equiv Q$$

- **Q curve converges** as $t_a \to \infty$

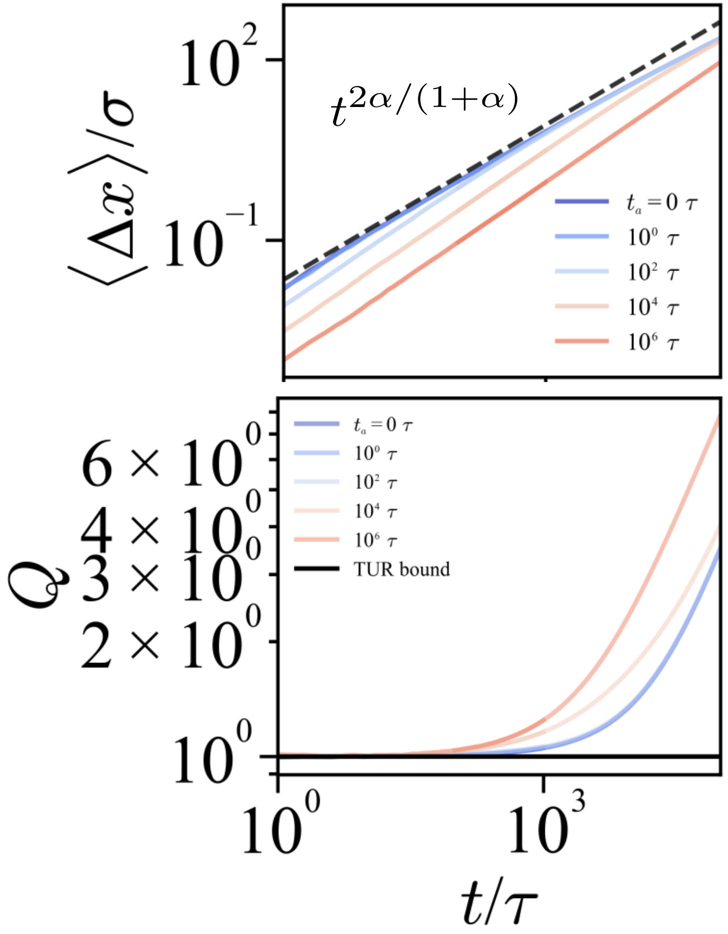


Example 2) Biased Quenched Trap Model

J. Bouchaud *et al.*, *Phys. Rep.* (1990)

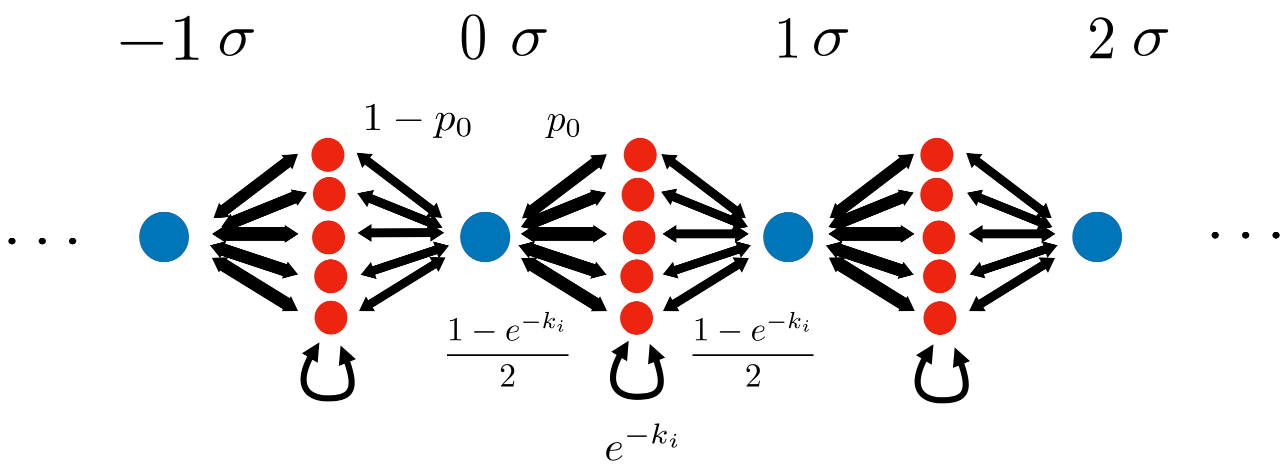
- Trap time distribution $\psi(\Delta t_i) \sim \Delta t_i^{-1-\alpha}$
- PDF of the quenched trap model follows the subordinated framework

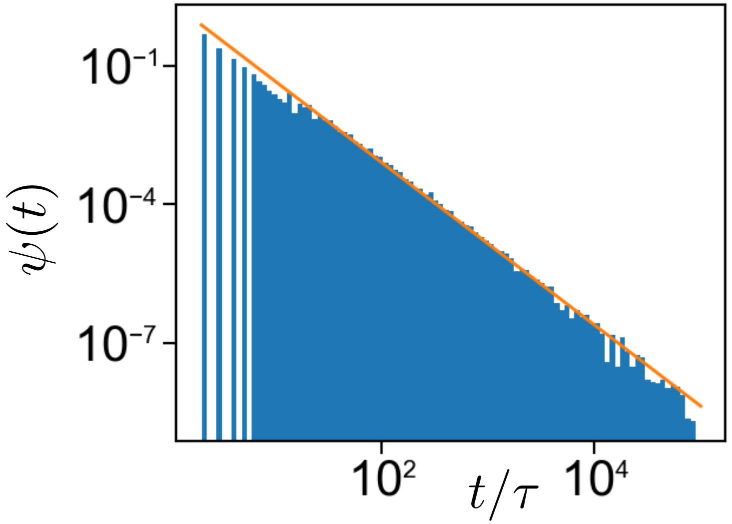
S. Burov *et al.*, *PRL* (2011)



Markovian approximation of CTRW

- We use the Markovian embedding for power law waiting time



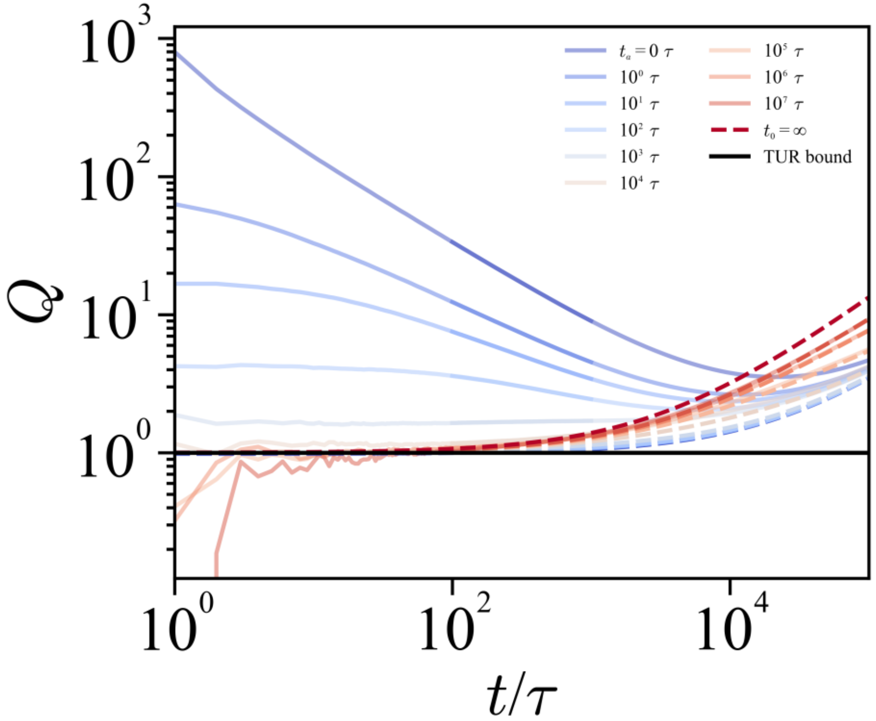


$$\Delta S_1 = k_B(p-q)\ln(p/q)$$

S. Park et al., *J. Phys. A:Math. Theor.* 2021

Markovian approximation of CTRW

- The aging helps to find the tightest bound.



Subordinated-TUR

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- **Trap model**, common in **biological systems**, exhibit strongly **non-Markovi an** behavior including **aging effects**.
- We developed the **TUR** for **trap** model.
- Various trap models were simulated to test our TUR.
- The TUR shows a **tight bound** in the short-time limit even for large $t_a \to \infty$. Ou r TUR framework can be applied to biological systems to **estimate entropy p roduction without prior knowledge of aging time t_a.**