Energetics of active fluctuations in living cells

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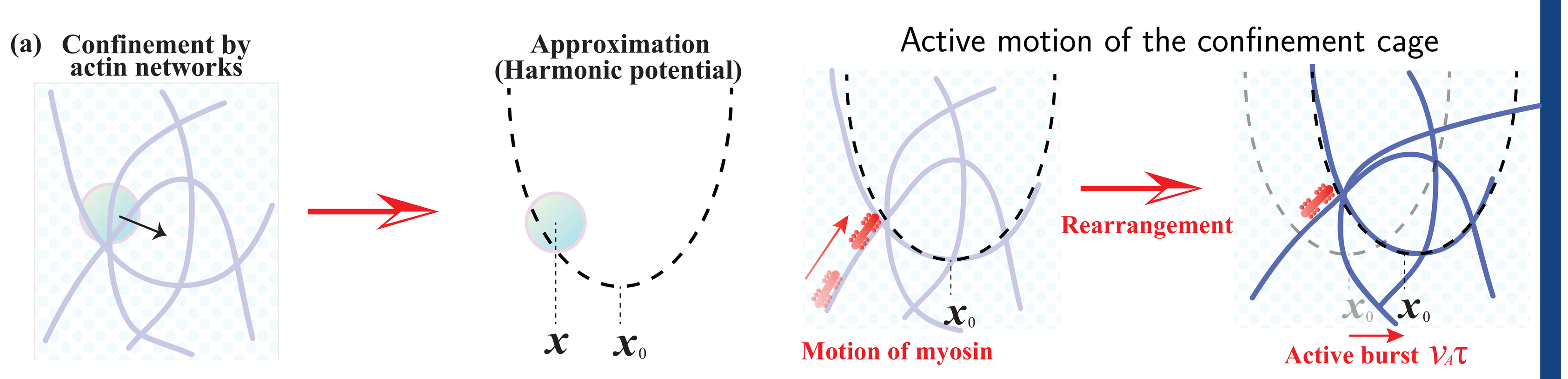
Can we gain information about nonequilibrium activity by applying external potentials/perturbations?

Tracer inside living cell/actin gel: thermal fluctuations and nonequilibrium activity



The tracer is trapped in a cage formed by the cytoskeletal filaments:

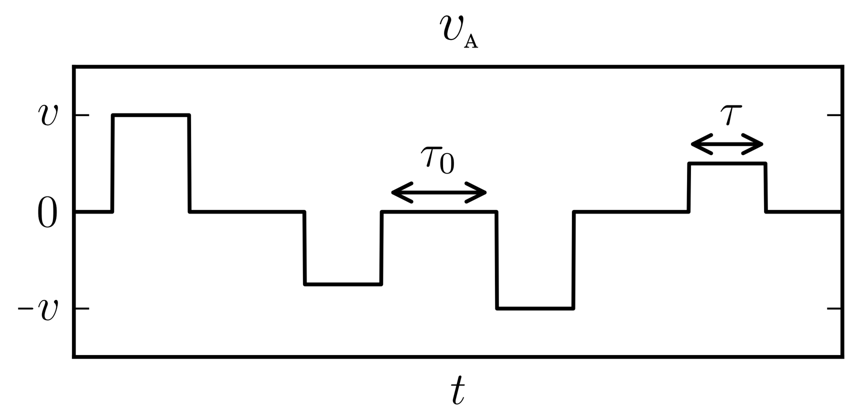
$$\frac{d\mathbf{r}}{dt} = \frac{1}{\gamma}\mathbf{F}_N(\mathbf{r},\mathbf{r}_0) + \sqrt{\frac{2T}{\gamma}}\xi$$

- $\mathbf{F}_N = -k(\mathbf{r}-\mathbf{r}_0)$ restoring force
- $\{\xi,\xi_0\}$ Gaussian white noises

Nonequilibrium activity induces local rearrangements of the network:

$$\frac{d\mathbf{r}_0}{dt} = \mathbf{v}_A - \frac{\varepsilon}{\gamma}\mathbf{F}_N(\mathbf{r},\mathbf{r}_0) + \sqrt{\frac{2\varepsilon T}{\gamma}}\xi_0$$

- $\mathbf{v}_A$ stochastic active burst
- $\varepsilon \ll 1$ back action strength



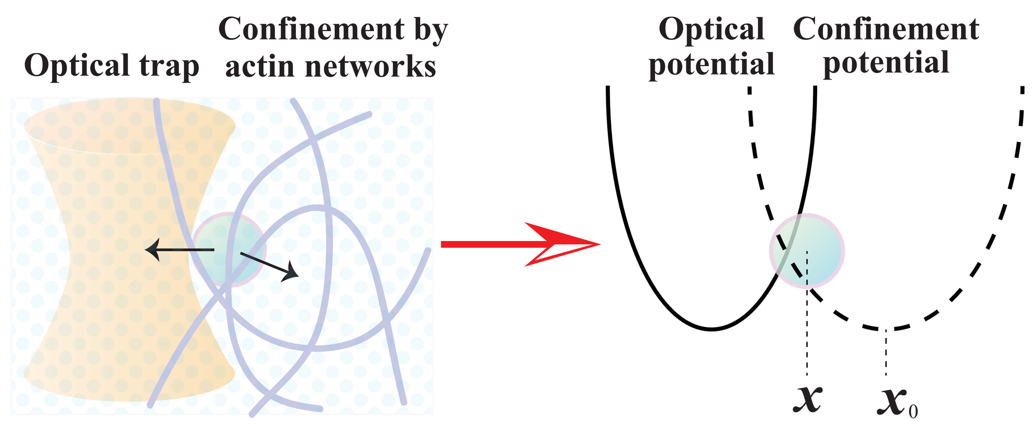
Stochastic active burst: non-Gaussian colored process

$$\langle v_A(t)v_A(0)\rangle = \underbrace{\frac{(v\tau)^2}{3(\tau+\tau_0)}}_{T_A/\gamma}\frac{e^{-|t|/\tau}}{\tau}$$

New experiments based on microrheology (MR)

External confinement potential

Design protocols where the potential parameters vary in time, and measure the corresponding extracted work.



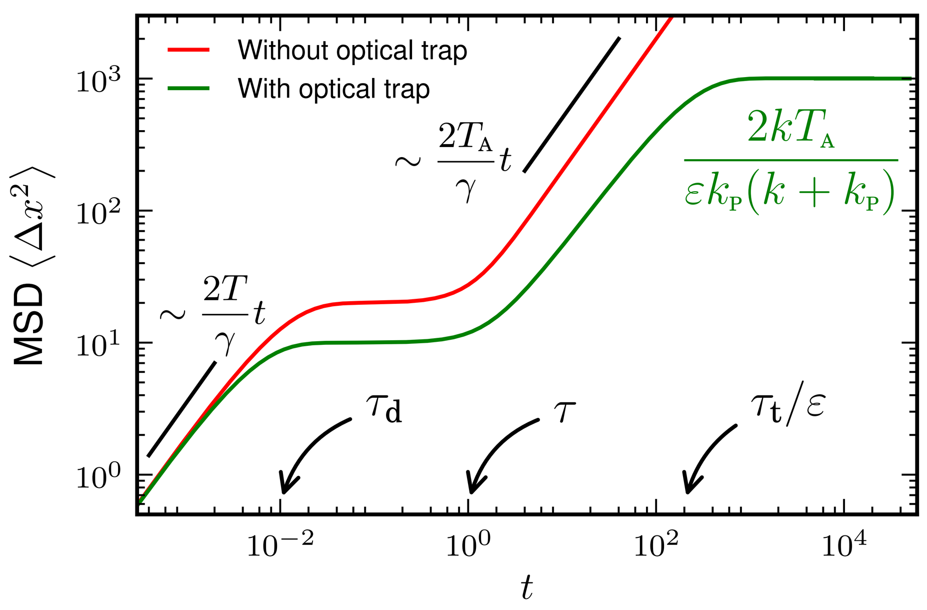
$U_P = U_P(x,\{a_i(t)\}) \quad \rightarrow \quad$ average work: $W = \sum_i \int da_i \left\langle \frac{\partial U_P}{\partial a_i}\right\rangle$

Varying the spring constant

$U_P = k_P x^2/2$

$$\begin{cases} t \ll \tau_d = \gamma/k & \text{thermal diffusion} \\ \tau_d < t < \tau_t/\varepsilon & \text{crossover regime} \\ \tau_t/\varepsilon \ll t & \text{steady state} \end{cases}$$

where $\tau_t = \tau_d(1 + k/k_P)$



- No optical trap. The MSD reaches the equilibrium plateau, and then a free diffusive regime sets in:

$$\text{MSD} \underset{t\gg\tau}{\sim} \frac{2T_A}{\gamma}t = \frac{2(v\tau)^2}{3(\tau+\tau_0)}t$$

- Optical trap. The MSD saturates to a plateau value within a relaxation time τ_t/ε:

$$\text{MSD} \underset{t\gg\tau_t/\varepsilon}{\longrightarrow} \frac{2kT_A}{\varepsilon k_P(k+k_P)} + \mathcal{O}(\varepsilon^0)$$

Quasistatic protocol $k_P = \{k_i \longrightarrow k_f\}$

$$W_H = \frac{1}{2}\int_{k_i}^{k_f} dk_P \langle x^2\rangle_{ss} = \frac{T_A}{2\varepsilon}\ln\left[\frac{k_f(k+k_i)}{k_i(k+k_f)}\right] + \mathcal{O}(\varepsilon^0)$$

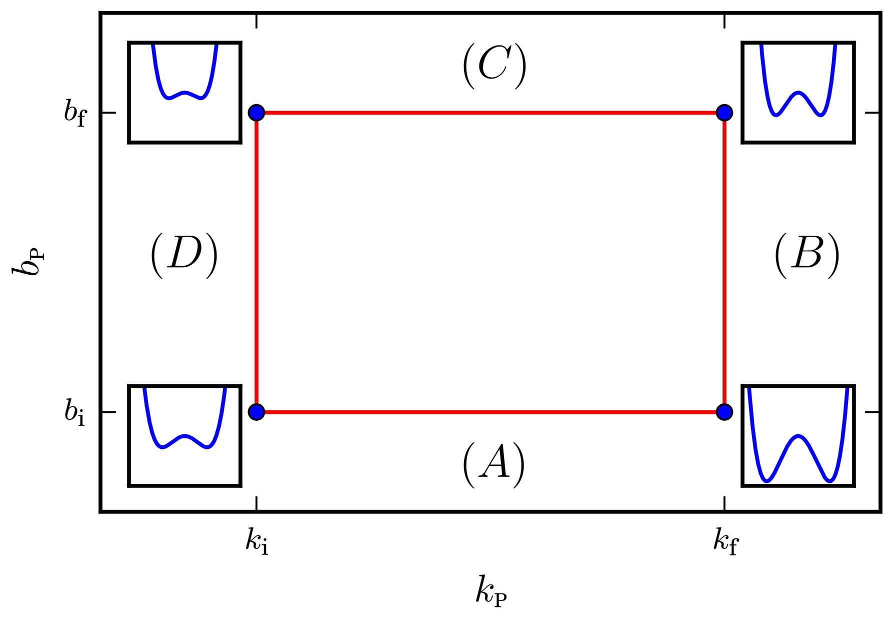
Thermodynamic cycle with quartic potentials

$U_P = k_P x^2/2 + b_P x^4/4$

Quasistatic protocol $k_P = \{k_i \longrightarrow k_f\}$

$$W_Q = \frac{1}{2}\int_{k_i}^{k_f} dk_P \langle x^2\rangle_{ss} = W_H + W_P + \mathcal{O}(b_P^2)$$

where $\frac{W_P}{b_P} = \left(\frac{T_A}{\varepsilon}\right)^2 f(k,\gamma,k_i,k_f,\tau) + \mathcal{O}(1/\varepsilon)$



Quasistatic cycle $\mathcal{C}$ in parameter space

$$W_{\mathcal{C}} = \frac{1}{2}\oint_{\mathcal{C}} dk_P \langle x^2\rangle_{ss} + \frac{1}{4}\oint_{\mathcal{C}} db_P \langle x^4\rangle_{ss} = \left(\frac{T_A}{\varepsilon}\right)^2 f_{\mathcal{C}}(k,\gamma,k_i,k_f,b_i,b_f,\tau) + \mathcal{O}(1/\varepsilon)$$

Nonequilibrium activity leads to a non-zero extracted work for a cycle.

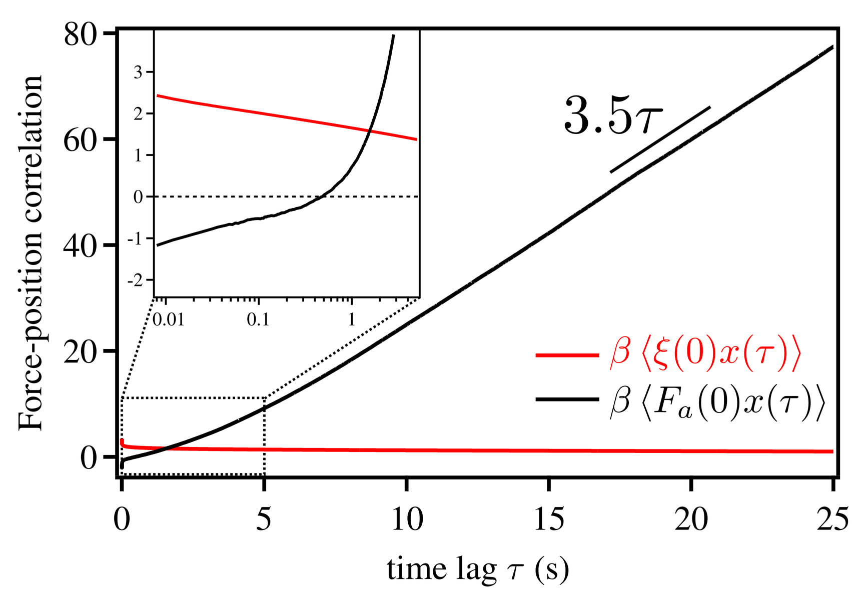
Extended fluctuation-dissipation relation

$$\begin{cases} \text{Position autocorrelation: } C(s,u) = \langle x(s)x(u)\rangle & \rightarrow \text{ passive MR} \\ \text{Response to perturbation } f_P\text{: } \chi(s,u) = \left.\frac{\delta\langle x(s)\rangle}{\delta f_P(u)}\right|_{f_P=0} & \rightarrow \text{ active MR} \end{cases}$$

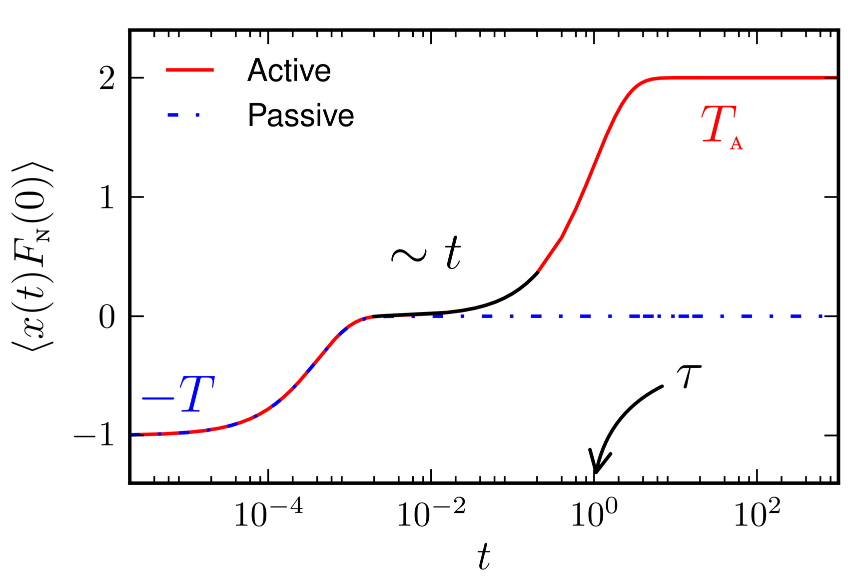
$$\chi(s,u) = \frac{1}{2\gamma T}\left[\gamma\frac{\partial C(s,u)}{\partial u} - \langle x(s)F_N(u)\rangle\right]$$

The force-position correlation $\langle x(s)F_N(u)\rangle$ is extracted from χ and C.

Experimental results [1]



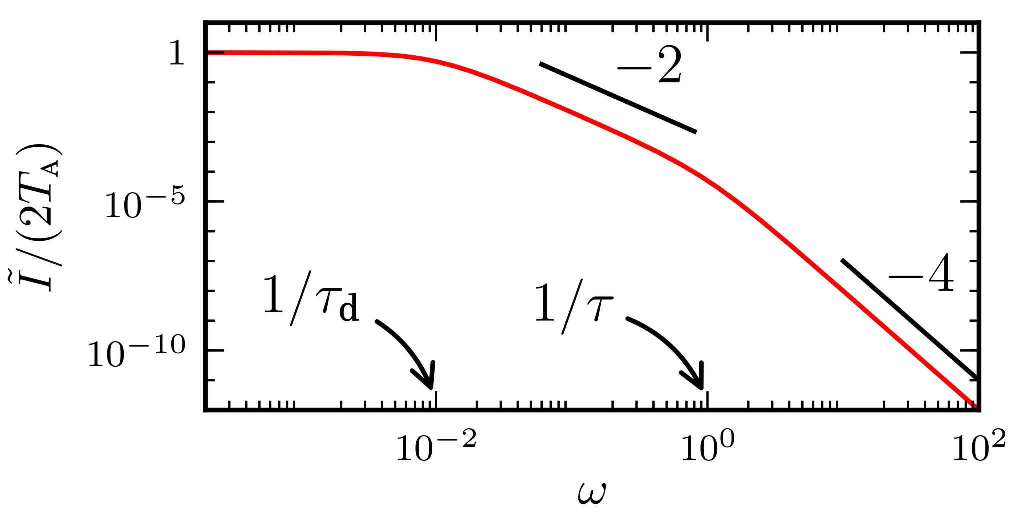
Analytic prediction



Nonequilibrium energy dissipation

Quantify the mean rate of energy dissipation from a combination of passive and active microrheology measurements.

Harada-Sasa relation: $J = \langle\dot{x}(\gamma\dot{x}-\xi)\rangle = \int\frac{d\omega}{2\pi}\gamma\omega\underbrace{\left[\omega\tilde{C}(\omega) + 2T\tilde{\chi}''(\omega)\right]}_{\text{spectral density } \tilde{I}(\omega)}$



$$\tilde{I}(\omega) = \frac{1}{1+(\omega\tau_d)^2}\frac{2T_A}{1+(\omega\tau)^2}$$

$$\rightarrow J = \frac{T_A}{\tau+\tau_d} + \mathcal{O}(\varepsilon)$$

Nonequilibrium activity generates some athermal energy dissipation.

Conclusion and outlook

- Alternative protocols to access observables which hold the signature of nonequilibrium activity.
- Characterize nonequilibrium fluctuations: **typical time of activity**, and **amplitude of active fluctuations**.
- Generalization to a more complex rheology: add memory effects.

[1] P. Bohec, F. Gallet, C. Maes, S. Safaverdi, P. Visco, and F. van Wijland, EPL, **102** (2013) 50005

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