Modeling Active Fluctuations in Living Matter

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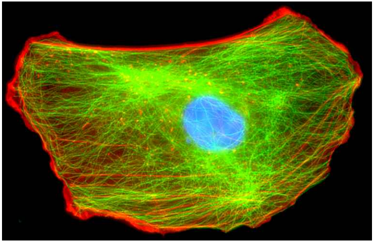
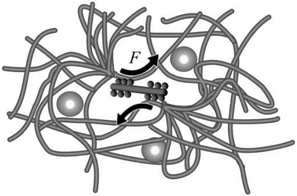
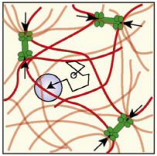
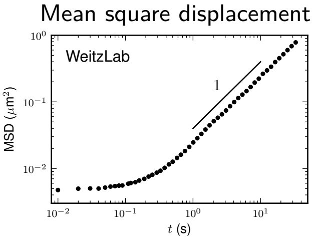


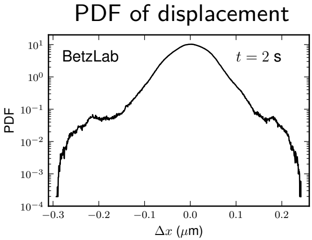
Cytoskeletal network



Molecular motors




Mean square displacement
WeitzLab
1
MSD (μm^2)
10^{0}
10^{-1}
10^{-2}
10^{-2}
10^{-1}
10^{0}
10^{1}
t (s)


PDF of displacement
BetzLab
$t = 2$ s
PDF
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
-0.3
-0.2
-0.1
0.0
0.1
0.2
Δx (μm)

Langevin dynamics - 1908

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -\nabla V + \boldsymbol{\xi}$$

Tracer in thermal bath

$$\gamma \frac{d\mathbf{r}}{dt} = -\nabla V + \boldsymbol{\xi} + \mathbf{f}_P \qquad \begin{cases} \text{Response function} & \chi(t) = \left.\dfrac{\delta \langle \mathbf{r}(t) \rangle}{\delta \mathbf{f}_P(0)}\right|_{\mathbf{f}_P = \mathbf{0}} \\ \text{Correlation function} & C(t) = \langle \mathbf{r}(t)\mathbf{r}(0) \rangle_{\mathbf{f}_P = \mathbf{0}} \end{cases}$$

Fluctuation-dissipation theorem (FDT)

1. $\chi(t) - \chi(-t) = -\dfrac{1}{T}\dfrac{dC}{dt} \quad \rightarrow \quad T = \dfrac{\omega \tilde{C}(\omega)}{2\tilde{\chi}''(\omega)}$
2. $\langle \xi(t)\xi(0) \rangle = 2\gamma T \delta(t)$

$$\int^{t} \mathrm{d}t' \gamma(t - t') \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t'} = -\boldsymbol{\nabla} V + \boldsymbol{\xi}$$

Fluctuation-dissipation theorem (FDT)

1. $\chi(t) - \chi(-t) = -\dfrac{1}{T}\dfrac{\mathrm{d}C}{\mathrm{d}t} \quad \rightarrow \quad T = \dfrac{\omega \tilde{C}(\omega)}{2\tilde{\chi}''(\omega)}$
2. $\langle \xi(t)\xi(0)\rangle = T\gamma\left(|t|\right)$

Nonequilibrium dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -\boldsymbol{\nabla} V + \boldsymbol{\xi} + \mathbf{F}_{\mathrm{A}}$$

Extended fluctuation-dissipation relations

Nonequilibrium dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -\nabla V + \boldsymbol{\xi} + \mathbf{F}_{\mathrm{A}}$$

Extended fluctuation-dissipation relations

$$\chi(t) = -\frac{1}{2\gamma T}\left[\gamma \frac{\mathrm{d}C}{\mathrm{d}t} + C_{\mathrm{FP}}(t)\right],$$

Nonequilibrium dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -\boldsymbol{\nabla} V + \boldsymbol{\xi} + \mathbf{F}_{\mathrm{A}}$$

Extended fluctuation-dissipation relations

$$\chi(t) = -\frac{1}{2\gamma T}\left[\gamma \frac{\mathrm{d}C}{\mathrm{d}t} + C_{\mathrm{FP}}(t)\right], \qquad T_{\mathrm{eff}}(\omega) = \frac{\omega \tilde{C}(\omega)}{2\tilde{\chi}''(\omega)},$$

Nonequilibrium dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -\boldsymbol{\nabla} V + \boldsymbol{\xi} + \mathbf{F}_{\mathrm{A}}$$

Extended fluctuation-dissipation relations

$$\chi(t) = -\frac{1}{2\gamma T}\left[\gamma \frac{\mathrm{d}C}{\mathrm{d}t} + C_{\mathrm{FP}}(t)\right], \qquad T_{\mathrm{eff}}(\omega) = \frac{\omega \tilde{C}(\omega)}{2\tilde{\chi}''(\omega)},$$

$$J_{\mathrm{diss}} = \left\langle \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t}\left(\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} - \boldsymbol{\xi}\right)\right\rangle$$

Outline

1. Experimental systems
    - Human melanoma cells
    - Mouse oocytes

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3. Comparison and prediction: information about the system
   - Amplitude and time scales of active fluctuations
   - Alternative protocols
   - Mean rate of active dissipation

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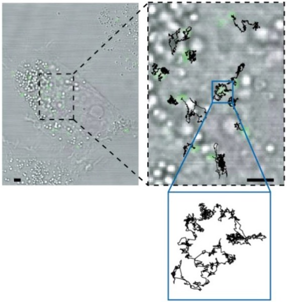
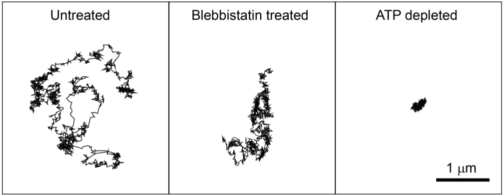
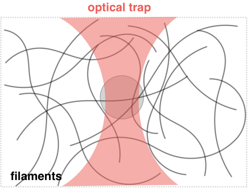




Melanoma = Skin cancer

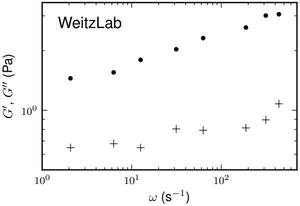
Tracers = Micro-size silica beads

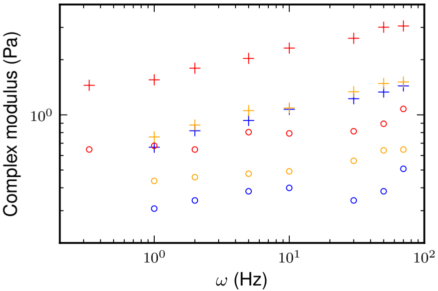


$$\tilde{\chi} = \frac{\Delta \tilde{x}}{\tilde{f}_{\mathrm{P}}} \propto \frac{1}{G^*}$$

$$G^* = G' + \mathrm{i}G''$$

Complex modulus





$$G^* = G' + \mathrm{i}G'' \propto 1/\tilde{\chi}$$

— Control — Blebb. treated
— ATP depleted

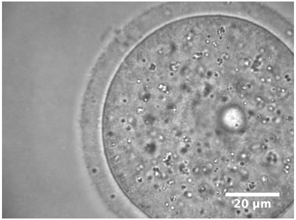
$+$ G' Elastic Modulus

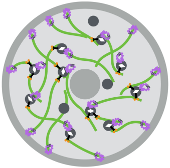
$\circ$ G'' Viscous Modulus

Experimental systems
Mouse oocytes

Wylie W. Ahmed[1], Maria Almonacid[2], Matthias Bussonnier[1],
Marie-Hélène Verlhac[2], Timo Betz[1]

1. Physico-Chimie Curie, Curie Institute 2. CIRB, Collège de France





WT

Oocyte = Immature egg

Tracers = Vesicles

Experimental systems

Mouse oocytes

Wylie W. Ahmed[1], Maria Almonacid[2], Matthias Bussonnier[1], Marie-Hélène Verlhac[2], Timo Betz[1]

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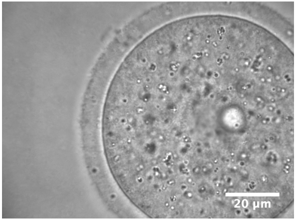
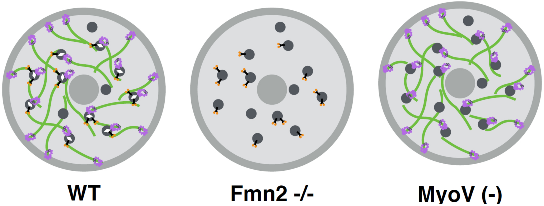
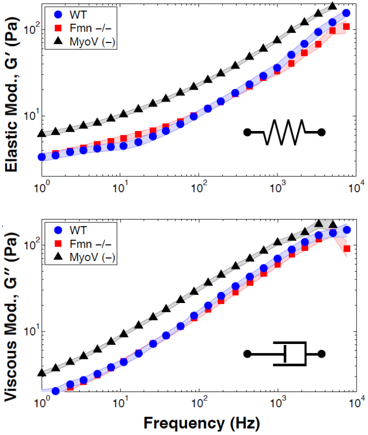






Complex modulus

$$G^* = G' + \mathrm{i}G'' \propto 1/\tilde{\chi}$$

$$G^*(\omega) = G_0\left[1 + (\mathrm{i}\omega\tau_\alpha)^\alpha\right]$$

where $\alpha \sim 0.6$

Experimental systems

Summary

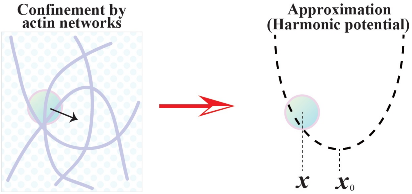
Two types of living cells

1. Human melanoma cells
   Silica beads, Simple rheology
   Two treatments: ATP depletion, Blebbistatin
2. Mouse oocytes
   Vesicles, Complex rheology
   Two mutants: Fmn -/-, MyoV (-)

Outline

Minimal model

Equation of motion

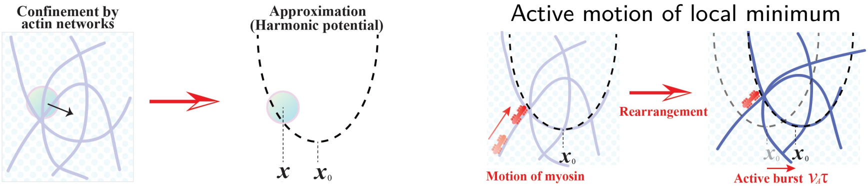


Tracer's dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -k(\mathbf{r} - \mathbf{r}_0) + \boldsymbol{\xi}$$

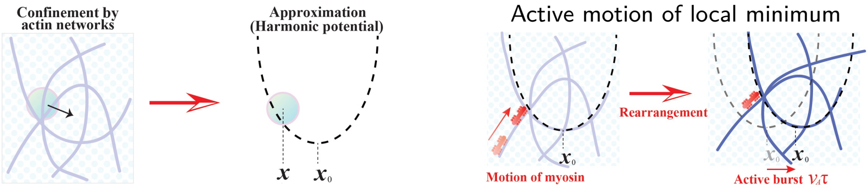
Minimal model

Equation of motion



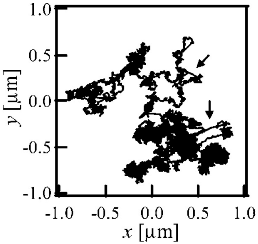
Tracer's dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -k(\mathbf{r} - \mathbf{r}_0) + \xi, \qquad \frac{\mathrm{d}\mathbf{r}_0}{\mathrm{d}t} = \mathbf{v}_\mathrm{A}$$

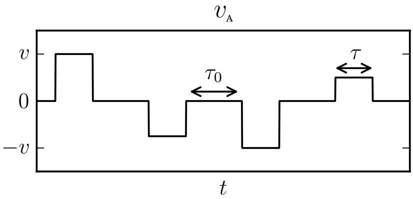


Tracer's dynamics

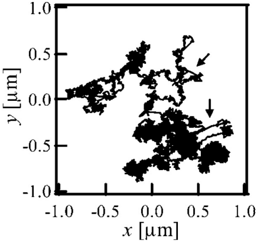
$$\int^t \mathrm{d}t'\gamma(t-t')\frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t'} = -k(\mathbf{r}-\mathbf{r}_0)+\boldsymbol{\xi}, \quad \int^t \mathrm{d}t'\gamma(t-t')\frac{\mathrm{d}\mathbf{r}_0}{\mathrm{d}t'} \propto \mathbf{v}_\mathrm{A}$$

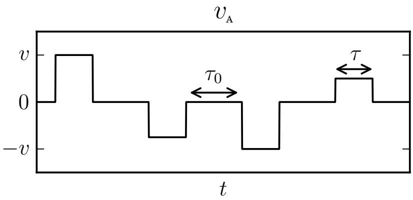


1.0
0.5
0.0
-0.5
-1.0
y [μm]
-1.0
-0.5
0.0
0.5
1.0
x [μm]



v_A
v
0
$-v$
τ_0
τ
t





2–time correlation function

$$\langle v_A(t) v_A(0) \rangle = \frac{D_A}{\tau} e^{-|t|/\tau} \ , \quad D_A = \frac{(v\tau)^2}{3(\tau + \tau_0)}$$

Minimal model

Tracer's statistics

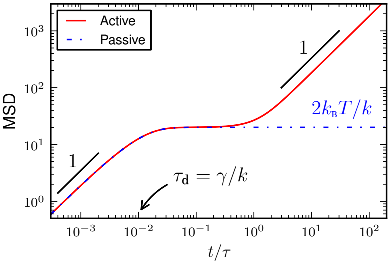
$$\text{MSD} = \left\langle [\mathbf{r}(t) - \mathbf{r}(0)]^2 \right\rangle$$

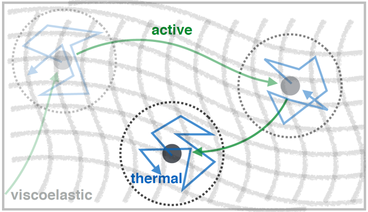
Short time Diffusion + Confinement

$\text{MSD} \sim 2D_\text{T}t$

Large time Free diffusion

$\text{MSD} \sim 2D_\text{A}t$





Outline

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   - Human melanoma cells
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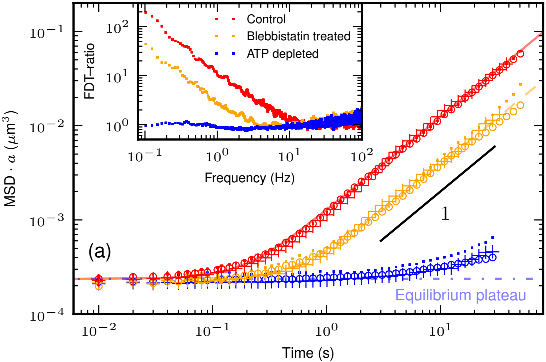
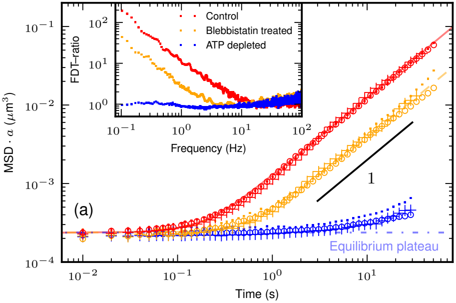
Melanoma cells



$$T_{\text{eff}}(\omega) = \frac{\omega \tilde{C}(\omega)}{2\tilde{\chi}''(\omega)}, \qquad \text{FDT–ratio} = \frac{T_{\text{eff}}(\omega)}{T}$$

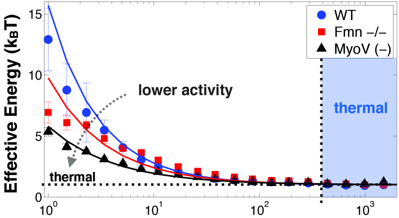
Comparison and prediction: information about the system

Amplitude and time scales of active fluctuations



Melanoma cells

	Control	Blebb.
D_A/D_T	2.8×10^{-3}	9×10^{-4}
τ (s)	0.16	0.39



Mouse oocytes

	WT	Fmn -/-	MyoV (-)
D_A/D_T	5.5	5.0	3.8

Comparison and prediction: information about the system

Amplitude and time scales of active fluctuations

Active force spectrum $S_{\mathrm{A}}(\omega) = \mathcal{F}\left[\langle F_{\mathrm{A}}(t) F_{\mathrm{A}}(0)\rangle\right]$

Tracer's dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -k\mathbf{r} + \boldsymbol{\xi} + \underbrace{\mathbf{F}_{\mathrm{A}}}_{k\mathbf{r}_0} \quad \rightarrow \quad \mathbf{r}(t) = \int^{t} \mathrm{d}t' \chi(t-t') \left[\boldsymbol{\xi}(t') + \mathbf{F}_{\mathrm{A}}(t')\right]$$

Comparison and prediction: information about the system

Amplitude and time scales of active fluctuations

Active force spectrum $S_{\text{A}}(\omega) = \mathcal{F}\left[\langle F_{\text{A}}(t) F_{\text{A}}(0)\rangle\right]$

Tracer's dynamics

$$\gamma \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} = -k\mathbf{r} + \boldsymbol{\xi} + \underbrace{\mathbf{F}_{\text{A}}}_{k\mathbf{r}_0} \quad \rightarrow \quad \mathbf{r}(t) = \int^{t} \mathrm{d}t' \chi(t-t')\left[\boldsymbol{\xi}(t') + \mathbf{F}_{\text{A}}(t')\right]$$

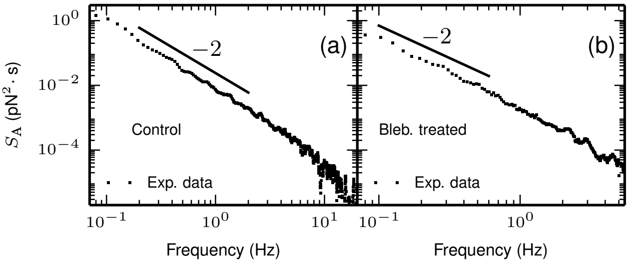
Spectrum of stochastic forces

$$S_{\text{cell}}(\omega) = \frac{\tilde{C}(\omega)}{|\tilde{\chi}(\omega)|^2} = S_{\text{th}}(\omega) + S_{\text{A}}(\omega)$$

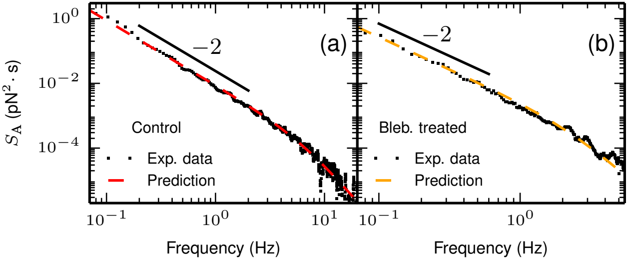
Comparison and prediction: information about the system

Amplitude and time scales of active fluctuations

Melanoma cells $\underbrace{S_{\text{cell}} = S_{\text{th}}}_{\text{ATP depleted}} + \cancel{S_A}$



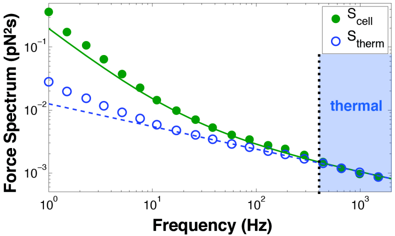
Melanoma cells $\underbrace{S_{\text{cell}} = S_{\text{th}}}_{\text{ATP depleted}} + \cancel{S_{\text{A}}}$



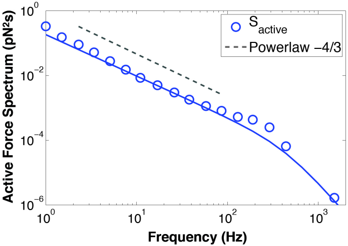
Mouse oocytes

$$\text{FDT} \quad S_{\text{th}}(\omega) \propto \frac{G''(\omega)}{\omega}$$

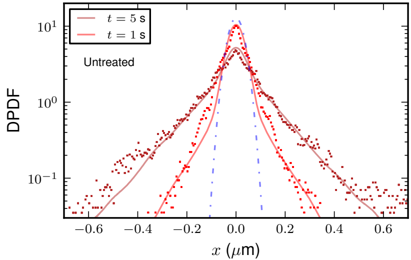
Wild type

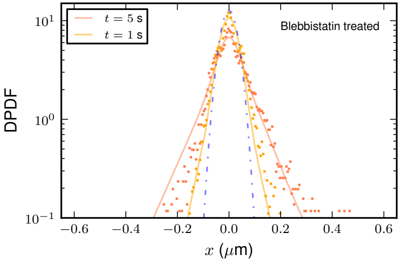


Wild type



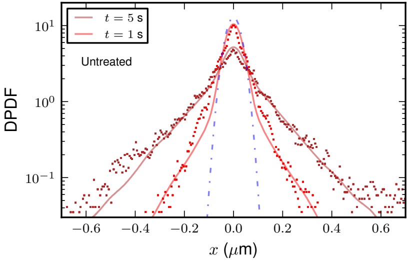
Melanoma cells PDF of displacement

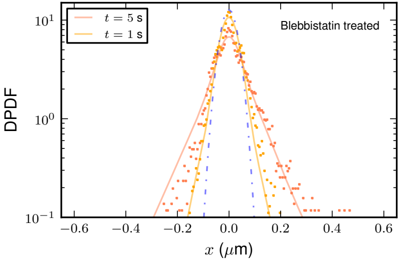




DPDF = histogram of displacement

Melanoma cells PDF of displacement

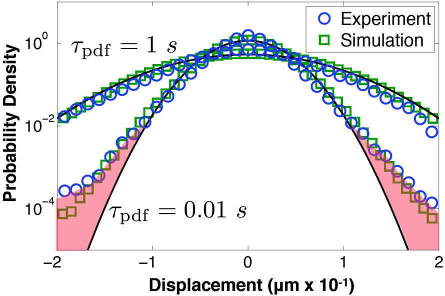




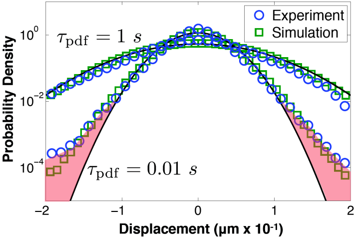
Numerical simulations

	Control	Blebb.
τ_0 (s)	2.5	2.8
v (nm/s)	860	220

Mouse oocytes PDF of displacement



Mouse oocytes PDF of displacement



Numerical simulations (Prony series)

	WT	Fmn -/-	MyoV (-)
τ (μs)	300	150	100
v (nm/s)	320	300	200

Comparison and prediction: information about the system

Amplitude and time scales of active fluctuations

Summary

Comparison with experimental results

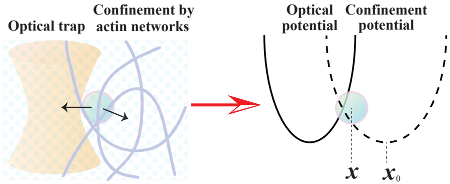
Minimal model $\rightarrow$ Extract D_{A}, τ, and τ_0

Consistent framework

effective temperature, active force spectrum

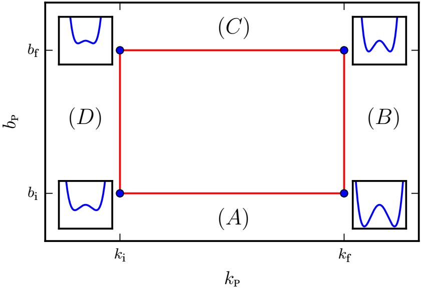
Kiyoshi Kanazawa, Hisao Hayakawa [PRE **90**, 042724 (2014)]

External potential $U_{\mathrm{P}} = U_{\mathrm{P}}\left[x, \{a_i(t)\}\right]$

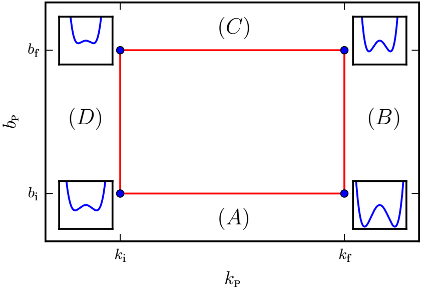


Average work $W = \sum_i \int \mathrm{d}a_i \left\langle \frac{\partial U_{\mathrm{P}}}{\partial a_i} \right\rangle$

External potential $U_{\mathrm{P}} = \frac{k_{\mathrm{P}}}{2}\mathbf{r}^2 + \frac{b_{\mathrm{P}}}{4}\mathbf{r}^4$



External potential $U_{\mathrm{P}} = \dfrac{k_{\mathrm{P}}}{2}\mathbf{r}^2 + \dfrac{b_{\mathrm{P}}}{4}\mathbf{r}^4$



Quasistatic protocol

$$W_{\mathcal{C}} = \oint_{\mathcal{C}} \frac{\mathrm{d}k_{\mathrm{P}}}{2}\left\langle \mathbf{r}^2 \right\rangle_{\mathrm{ss}} + \oint_{\mathcal{C}} \frac{\mathrm{d}b_{\mathrm{P}}}{4}\left\langle \mathbf{r}^4 \right\rangle_{\mathrm{ss}}$$

$$W_{\mathcal{C}} \propto D_{\mathrm{A}}^2$$

Extended fluctuation-dissipation relation

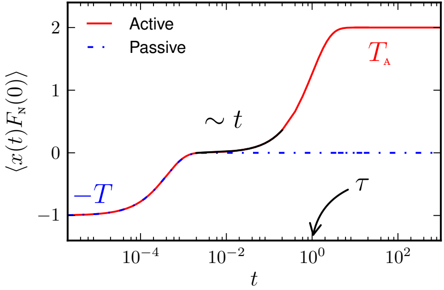
$$\chi(t) = -\frac{1}{2\gamma T}\left[\gamma \frac{\mathrm{d}C}{\mathrm{d}t} + C_{\mathrm{FP}}(t)\right]$$

$$C_{\mathrm{FP}}(t) = \langle \mathbf{r}(t) \times k\left[\mathbf{r}(0) - \mathbf{r}_0(0)\right]\rangle \equiv \langle x(t) F_{\mathrm{N}}(0)\rangle$$

Extended fluctuation-dissipation relation

$$\chi(t) = -\frac{1}{2\gamma T}\left[\gamma\frac{\mathrm{d}C}{\mathrm{d}t} + C_{\text{FP}}(t)\right]$$

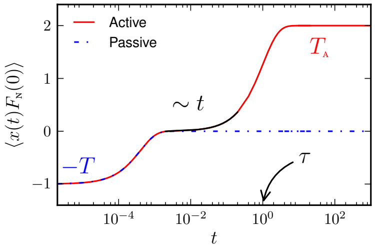
$$C_{\text{FP}}(t) = \langle \mathbf{r}(t) \times k\,[\mathbf{r}(0) - \mathbf{r}_0(0)]\rangle \equiv \langle x(t) F_{\text{N}}(0)\rangle$$



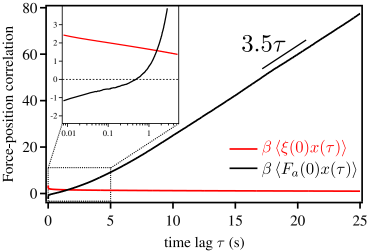
Comparison and prediction: information about the system

Alternative protocols

Analytic prediction



Experimental results [1]



[1] Bohec *et al.*, EPL **102** (2013) 50005

Comparison and prediction: information about the system

Mean rate of active dissipation

Mean rate of energy dissipation

$$
\begin{aligned}
J_{\text{diss}} &= \left\langle \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} \left[\gamma(t) * \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} - \boldsymbol{\xi} \right] \right\rangle \\
&= \int \frac{\mathrm{d}\omega}{2\pi} \underbrace{\left[\omega \tilde{C}(\omega) - 2T\tilde{\chi}''(\omega) \right] \omega \tilde{\gamma}'(\omega)}_{\text{spectral density} \quad I(\omega)} \qquad \text{Harada-Sasa relation}
\end{aligned}
$$

Comparison and prediction: information about the system

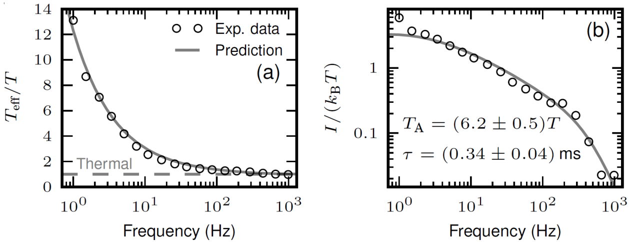
Mean rate of active dissipation

Mean rate of energy dissipation

$$\begin{aligned} J_{\text{diss}} &= \left\langle \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t}\left[\gamma(t) * \frac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} - \boldsymbol{\xi}\right]\right\rangle \\ &= \int \frac{\mathrm{d}\omega}{2\pi} \underbrace{\left[\omega\tilde{C}(\omega) - 2T\tilde{\chi}''(\omega)\right]\omega\tilde{\gamma}'(\omega)}_{\text{spectral density} \quad I(\omega)} \quad \text{Harada-Sasa relation} \end{aligned}$$

$$I(\omega) = 2\frac{T_{\text{eff}}(\omega) - T}{1 + [G'(\omega)/G''(\omega)]^2}$$

Mouse oocytes



Dissipation rate

$$J_{\rm diss} = 360\ k_{\rm B}T/s$$

Power injected by one motor $= 10^4\ k_{\rm B}T/s > J_{\rm diss}$

Mean rate of injected energy

Two levels of injection

1. Tracer's motion $J_{\text{tracer}} = \left\langle \dfrac{\mathrm{d}\mathbf{r}}{\mathrm{d}t} \mathbf{F}_{\text{A}} \right\rangle = J_{\text{diss}}$
2. Trap's motion $J_{\text{trap}} = \left\langle \dfrac{\mathrm{d}\mathbf{r}_0}{\mathrm{d}t} k \tau_\alpha \mathbf{v}_{\text{A}} \right\rangle = \dfrac{T_{\text{A}}}{\tau} \left(\dfrac{\tau_\alpha}{\tau} \right)^{\alpha - 1}$

Mean rate of injected energy

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Mouse oocytes

$$J_{\text{trap}} = 2 \times 10^5 \; k_{\text{B}} T/s = \text{power provided by 20 motors}$$

Conversion of energy from trap to tracer motion

$$\rho = J_{\text{tracer}}/J_{\text{trap}} = 10^{-3}$$

Conclusion

Dynamics in living cells

Short time	Thermal, equilibrium
Large time	Active, out-of-equilibrium

What have we learned about the system?

1. Amplitude of active fluctuations
2. Typical active time scales
3. Mean rate of active dissipation

Conclusion

Outlook

- Power-law statistics of active fluctuations
- Exact solution $\tau \to 0$
  Time dependent scaling of PDF tails
- Microscopic derivation of the dynamics
- Interaction between tracers
  Collective modes

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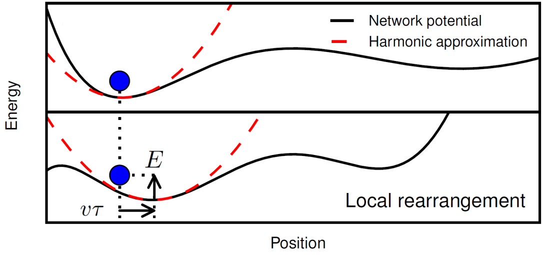
MSD scaling



$$E \sim k(v\tau)^2$$

$$k = 6\pi a G_0 \quad \rightarrow \quad D_{\mathrm{A}} = \frac{(v\tau)^2}{3(\tau + \tau_0)} \propto \frac{1}{a}$$